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Enantioselective synthesis of aziridine 2,2-dicarboxylates. Part 2: Determination of the absolute configuration

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Abstract—The absolute configuration of aziridine-2,2-dicarboxylates was determined through their transformation into the corresponding diastereomeric (*S*)-(−)-α-methylbenzylamido derivatives. The data obtained allows establishment of the stereochemistry of the first step of the conjugate addition reaction catalyzed by chiral bisoxazoline–Cu complex.

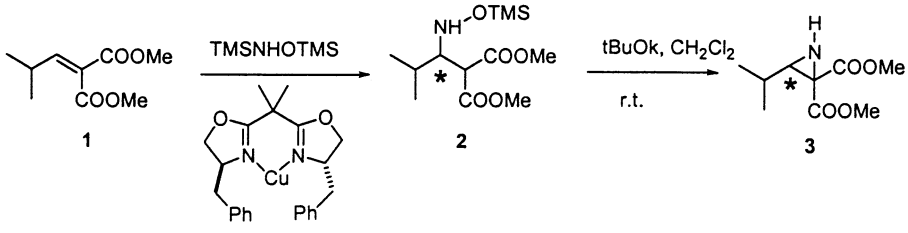
1. Introduction

The conjugate addition of hydroxylamine derivatives to chiral imide acceptors promoted by Lewis acids is of particular interest within our laboratory.[1] The 1,4-adduct is a useful intermediate for the synthesis of chiral non-racemic aziridines.[2] Recently we turned our attention to alkylidene malonates as good Michael acceptors.[3] In the previous work we reported the addition of *N*,*O*-bis (trimethylsilyl)hydroxylamine to an α,β-unsaturated malonate in the presence of a chiral Lewis acid[3] and the conversion of the 1,4-adduct to the corresponding aziridine-2,2-dicarboxylate.[4]

The procedure is exemplified by the reactions outlined in Scheme 1 and involves the conjugate addition of commercially available *N*,*O*-bis(trimethylsilyl) hydroxylamine to a substrate in the presence of a catalytic amount of $Cu(OTf)_2$ and chiral bisoxazoline ligand.[4] The subsequent cyclization occurs under very mild basic conditions. The conjugate addition performed in CH_2Cl_2 at −10°C gives the adduct **2** in 50–80% yield with enantioselectivity that strongly depends upon the alkyl substituent attached to the double bond. In all cases, cyclization to aziridine **3** occurs in good yield. When the addition was performed on isobutylidene malonate, good conversion and 80% e.e. were observed. Herein, we report the results obtained in the separation of the product enantiomers. The absolute configuration of the major isomer of 3-isopropylaziridine-2,2-dicarboxylate was determined through its transformation into the corresponding (*S*)-phenylethylamido derivative.

2. Results and discussion

For our investigation an uncatalyzed reaction was carried out and the racemic mixture was submitted to



Scheme 1. Synthesis of chiral aziridine-2,2-dicarboxylate.

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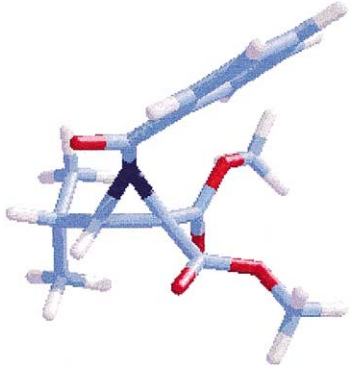
resolution. This separation could be carried out according to the observation that the regiospecific hydrolysis of benzoylamido diester **4** may be performed under very mild basic conditions.[5]

The monoester **5** is a useful intermediate that can be easily transformed in the diastereomeric appropriate amide utilizing chiral (*S*)-(−)-α-methylbenzylamine. For this purpose, the racemic compound **3** was prepared and the nitrogen atom of the aziridine was protected by treatment with benzoyl chloride in CH_2Cl_2 in the presence of TEA and DMAP. The benzamide **4** was obtained in quantitative yield. In the NMR spectrum of **4** recorded in $CDCl_3$ the signal of a methyl ester that resonates at 3.9 ppm can be seen, almost unchanged with respect to the starting compound **3**, and the other ester group at 3.3 ppm, strongly shielded by the protecting benzoyl group (Fig. 1). The amide **4** is a very stable molecule and regioselective hydrolysis of the more shielded methyl ester was effected by treatment with 1 equiv. of KOH in MeOH over 5 days at room temperature (Scheme 2).

This unexpected result may be rationalised on the basis of the structure of **4**, minimized with AM1 semiempirical calculation.[6] The structure shows, for a stable conformation, the *trans* relationship between the isopropyl group and the more shielded methyl ester resonating at 3.3 ppm. The ^{1}H NMR spectra of aziridine **3**, the diester **4** and the monoester **5** are reported in Fig. 1. From analysis of the ^{1}H NMR spectra of **4** and **5** it can be seen that the more shielded methyl ester is exclusively hydrolyzed (being the less sterically hindered one), while the methyl ester resonating at 3.9 ppm is resistant to the basic hydrolytic conditions. Transformation into the chiral amide was obtained through the formation of the intermediate acid chloride of **5**, prepared by reaction with oxalyl chloride and an equimolar amount of DMF in dry benzene.[7] The moisture-sensitive acid chloride, used without further purification in the coupling with (*S*)-(−)-α-methylbenzylamine, furnished the chiral amide **6** as a diastereomeric mixture in 70% yield.

A slurry of the diastereomeric mixture of amides **6** was then submitted to slow crystallization in MeOH/water (9:1). After 2 days, complete diastereomeric separation was obtained, since the diastereoisomer **6a** crystallised (>99% d.e.), with **6b** remaining in solution (84% d.e.). The diastereomeric excess of each derivative was determined by HPLC analysis.

The structure of **6a** has been determined by single crystal X-ray diffraction. The configuration and the conformation of **6a** in the crystal lattice, shown in Fig. 2, show that the asymmetric carbons of the aziridine ring possess 2*R* and 3*S* configuration respectively. Furthermore, the distance between (O)3 and (H)2 (2.34 Å) suggests the presence of an electrostatic interaction between the methyl ester carbonyl group and the amide NH. The (O)3–(H)2–(N)2 angle (124.76°) prevents the confirmation of a classical hydrogen bond. Selected bond lengths and angles are reported in Table 1. The synthetic pathway leading from aziridine **3** to amide **6**, was performed even on the enantiomerically enriched compound obtained from the chiral Lewis acid-catalyzed 1,4-addition, followed by cyclization to the aziridine. The ratio of **6a** and **6b** was determined by HPLC analysis. The most abundant isomer turned out



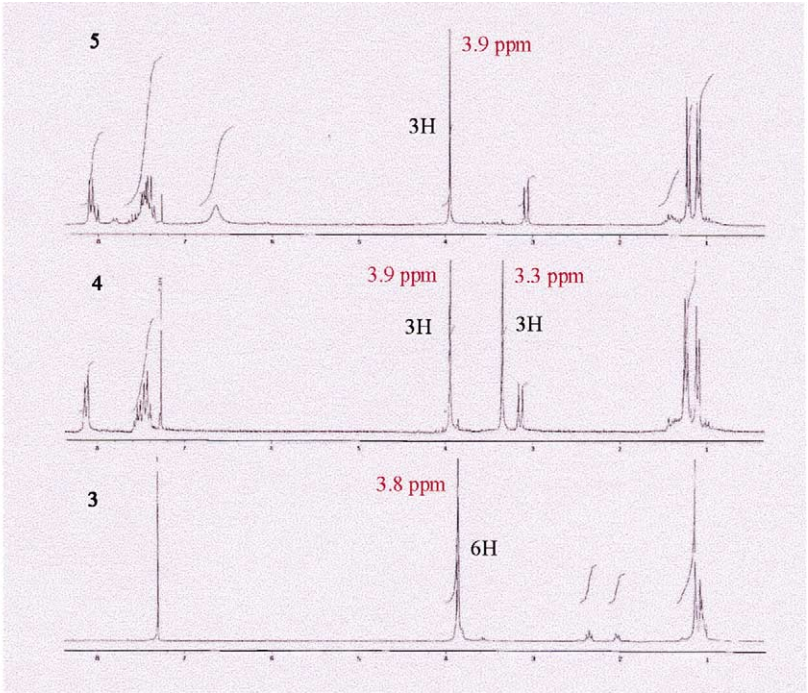
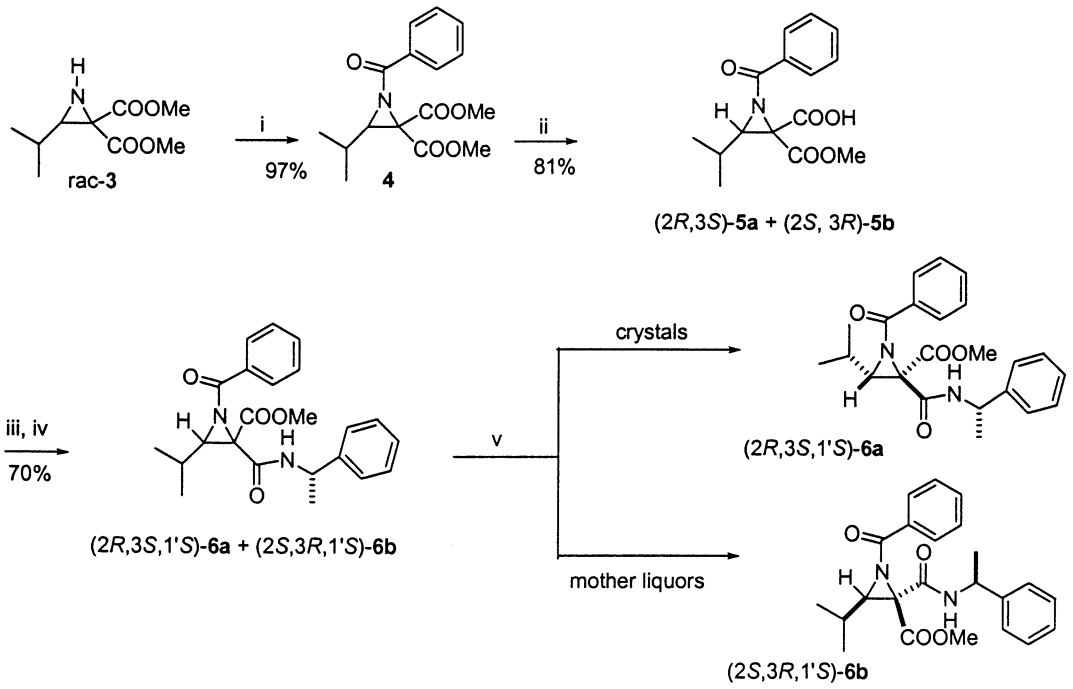


Figure 1. Semiempirical calculated (AM1) structure of aziridine **4** and ^{1}H NMR spectra of **3**–**5**.



Scheme 2. Regioselective hydrolysis of aziridine diester **4** and synthesis of diastereomers **6**. *Reagents and conditions*: (i) PhCOCl, TEA, CH_2Cl_2, rt; (ii) KOH (1 equiv.), MeOH, rt, 4 days; (iii) $COCl_2$, DMF, benzene; (iv) TEA, (*S*)-(−)-α-methylbenzylamine.

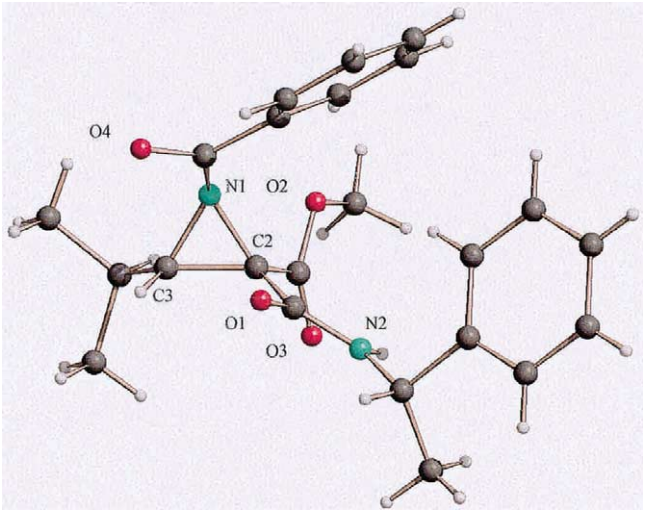


Figure 2. X-Ray structure of aziridine **6a**.

to be **6a**, allowing to deduce that the first step of the 1,4-addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine to isobutylidene malonate furnished (3*S*)-**2** as major isomer.

3. Conclusion

The absolute configuration of aziridine-2,2-dicarboxylates was determined through their transformation into the corresponding diastereomeric (*S*)-(−)-α-methylbenzylamido derivatives. The data obtained allows us to establish the stereochemical course of the conjugate addition reaction catalyzed by chiral bisoxazoline–Cu complex. The addition is the key step of the synthesis of aziridine-2,2-dicarboxylate since it is responsible for the final stereochemistry of the heterocylic product.

4. Experimental

4.1. General procedures

Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. CH_2Cl_2 was distilled from P_2O_5. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). NMR Spectra were recorded with a INOVA Varian spectrometer 300 MHz or with a Gemini Varian spectrometer 200 MHz. Chemical shifts were reported as δ values relative to the solvent peak of $CDCl_3$ set at δ 7.27 (^{1}H NMR) or δ 77.0 (^{13}C NMR). Infrared spectra were recorded with an FT-IR Nicolet 205 spectrometer. GC–MS analyses were performed on HP5890 series II cromatograph with HP5971 mass detector. Optical rotation powers were recorded with Perkin–Elmer polarimeter 343. HPLC analyses were performed on HP1090 liquid chromatograph equipped with UV detector. CHIRALCEL-OD chiral column, isocratic analysis with 90:10 hexane/isopropanol as eluent, 0.5 mL/min solvent flow, UV detector at 214.4 and 220.4 nm. MS analyses were performed with a HP 1100 series mass spectrometer single quadrupole electrospray ionization interface (ESI). Compounds **1**–**3** have been prepared following the procedure reported in the previous paper.

Table 1. Selected bond lengths (Å) and angles (°) for **6a**

Bond	(Å)	Bond	(Å)
N(1)–C(2)	1.456(2)	O(3)–C(7)	1.185(2)
N(1)–C(3)	1.439(3)	O(4)–C(17)	1.211(2)
N(1)–C(17)	1.411(2)	C(1)–C(2)	1.525(2)
N(2)–C(1)	1.332(2)	C(2)–C(3)	1.518(2)
N(2)–C(9)	1.467(2)	C(2)–C(7)	1.505(2)
N(2)–H(2)	0.93(3)	C(17)–C(18)	1.483(2)
O(1)–C(1)	1.217(2)		
Angle	(°)	Angle	(°)
C(2)–N(1)–C(3)	63.2(1)	O(1)–C(1)–C(2)	118.6(2)
N(1)–C(2)–C(3)	57.8(1)	N(2)–C(1)–C(2)	117.0(1)
N(1)–C(3)–C(2)	58.9(1)	O(4)–C(17)–N(1)	120.2(2)
C(1)–N(2)–C(9)	122.0(2)	O(4)–C(17)–C(18)	123.7(2)
C(1)–N(2)–H(2)	121(2)	N(1)–C(17)–C(18)	115.7(1)
C(9)–N(2)–H(2)	117(2)	C(17)–N(1)–C(2)	124.1(1)
O(1)–C(1)–N(2)	124.4(2)	C(17)–N(1)–C(3)	121.5(1)

4.2. Synthesis of *N*-benzoylaziridine 4

Benzoyl chloride (1.1. mmol, 0.127 mL) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of aziridine **3** (1 mmol) and TEA (1.2 mmol, 0.167 mL) in CH_2Cl_2 (5 mL). The reaction was allowed to stir for 2 h and then quenched with water. After diluting with CH_2Cl_2 (20 mL) and washing with water, the organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure. Compound **4** was obtained in 97% yield after flash chromatography on silica gel as a white solid (cyclohexane/Et_2O, 8/2). Compound **4**: mp 81–84°C; IR (film): 3059, 2972, 1739, 1693, 1428, 1242 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (d, 3H, $J=6.6$ Hz), 1.23 (d, 3H, $J=6.3$ Hz), 1.30–1.41 (m, 1H), 3.14 (d, 1H, $J=9.6$ Hz), 3.34 (s, 3H), 3.94 (s, 3H), 7.38–7.60 (m, 3H), 8.10–8.14 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 18.8, 20.8, 29.7, 52.7, 52.9, 53.0, 128.3, 128.6, 130.0, 132.9, 165.0, 165.3, 175.6; MS m/z 305 (6), 290 (11), 200 (13), 105 (100), 77 (33).

4.3. Partial hydrolysis of aziridine 4

To a stirred solution of aziridine **4** (0.5 mmol, 150 mg) in MeOH (5 mL) at rt, KOH (1 equiv., 2 mL of 0.25 M solution in MeOH) was added in one portion. The mixture was left stirring at rt for 4 days, quenched with diluted HCl and then solvent removed under reduced pressure. The residue was diluted with EtOAc and washed twice with water. The organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure to give aziridine **5** in 81% yield. Compound **5**: IR (film): 3131, 2965, 1752, 1706, 1283 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.09 (d, 3H, $J=6.6$ Hz), 1.21 (d, 3H, $J=6.6$ Hz), 1.31–1.51 (m, 1H), 3.07 (d, 1H, $J=9.02$ Hz), 3.94 (s, 3H), 6.51–6.82 (bs, 1H), 7.35–7.51 (m, 3H), 8.04–8.11 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 18.6, 20.6, 29.7, 52.6, 52.9, 53.2, 128.2, 128.5, 132.7, 133.6, 165.6, 167.3, 175.8; MS m/z 291 (2), 248 (7), 142 (4), 105 (100), 77 (24).

4.4. Synthesis of amide 6

To a stirred solution of aziridine **5** (1 mmol, 0.291 g) in dry benzene (10 mL), DMF (2 mmol, 0.15 mL) and oxalyl chloride (2 mmol, 0.128 mL) were added at rt under an inert atmosphere. After 1 h, the solvent was reduced to 5 mL under vacuum and another portion of dry benzene (5 mL) was added. To this solution, under a nitrogen atmosphere, (*S*)-(−)-α-methylbenzylamine (1.1 mmol, 0.141 mL) and TEA (1.1 equiv., 0.153 mL) were added. After 1 h the reaction was quenched with water (5 mL), diluted with EtOAc (10 mL) and washed with 0.1 M HCl (10 mL), 0.1 M $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and solvent removed under reduced pressure. Compound **6** was obtained as a yellow oil in 70% yield, after flash chromatography on silica gel (toluene/acetone, 9/1). Crystallization performed in MeOH/H_2O (10/1) allowed separation of **6a** and **6b**.

Compound **6a**: mp 123–125°C; IR (film): 3370, 3071, 2959, 2872, 1726, 1679, 1600, 1533, 1447 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (d, 3H, $J=7.0$ Hz), 1.27 (d, 3H, $J=6.2$ Hz), 1.46 (d, 3H, $J=7.0$ Hz), 1.40–1.60 (m, 1H), 3.06 (d, 1H, $J=9.8$ Hz), 3.98 (s, 3H), 4.80–4.94 (m, 1H), 6.86–6.91 (m, 2H), 7.16–7.19 (m, 3H), 7.28–7.52 (m, 3H), 7.83–7.93 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 19.2, 21.0, 21.3, 29.1, 49.3, 52.5, 53.6, 55.3, 125.8, 127.2, 127.9, 128.4, 128.5, 132.2, 134.3, 142.1, 161.8, 169.1, 175.8; MS-ESI m/z 395 (M+1); $[\alpha]_D^{20}=-151.0$ (c 1.2, $CHCl_3$).

Compound **6b**: IR (film): 3373, 3070, 2961, 2871, 1724, 1686, 1609, 1531, 1440 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01 (d, 3H, $J=6.6$ Hz), 1.10 (d, 3H, $J=6.8$ Hz), 1.25 (d, 3H, $J=5.2$ Hz), 1.40–1.60 (m, 1H), 2.99 (d, 1H, $J=9.6$ Hz), 4.01 (s, 3H), 4.80–4.94 (m, 1H), 7.18–7.58 (m, 8H), 7.80–8.02 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 18.9, 20.8, 21.8, 28.9, 49.5, 52.3, 53.4, 55.0, 125.6, 127.3, 127.8, 128.2, 128.6, 132.0, 134.1, 142.0, 161.6, 169.0, 175.7; MS-ESI m/z 395 (M+1); $[\alpha]_D^{20}=+75.0$ (c 0.9, $CHCl_3$).

4.5. X-Ray data collection and structure refinement

A suitable crystal of compound **6a** was mounted on a glass fiber in air on a Bruker-AXS SMART CCD area detector diffractometer. The detector to crystal distance was 5 cm. The diffraction experiment was carried out at rt. The initial cell parameters and an orientation matrix were obtained from least-squares refinement on reflections measured in three different sets of 20 frames each, in the range $-15<\theta<15°$. The intensity data comprising a hemisphere were collected using the ω-scan technique with frame width set at 0.3°. The first 50 frames were remeasured at the end of data collection to monitor decay. The collected frames were then processed for integration by software SAINT and an empirical absorption correction was applied by SADABS.[8] The structure was solved by direct methods (SIR-97)[9] and refined by full-matrix least-squares on F_o^2 using SHELXTL.[10] Anisotropic displacement parameters were assigned to all non-hydrogen atoms in the structure. Hydrogen atom on nitrogen was experimentally

located while the others were placed on idealized positions.

Crystallographic studies of 6a: $C_{23}H_{26}N_2O_4$, $M=394.46$, monoclinic, space group $P2_1$ (No. 4), $a=7.6491(5)$, $b=15.960(1)$, $c=9.1966(6)$ Å, $\beta=109.950(2)°$, $V=1055.4(1)$ Å^3, $T=293(2)$ K, $Z=2$, $D_{calcd}=1.241$ mg/m^3, μ(Mo Kα)$=0.085$ mm^{-1}, 9861 reflections collected, 5620 unique ($R_{int}=0.0186$) which were used in all calculations. The value of the goodness-of-fit indicator was 1.047. Final $R_1(F)=0.0495$ [$I>2\sigma(I)$] and $wR_2(F^2)=0.1449$ (all data).

Least-squares planes (x,y,z in crystal coordinates) and deviations from them (* indicates atom used to define plane)

$-0.3755\ (0.0299)\ x+15.7968\ (0.0232)\ y-1.0063\ (0.1140)\ z=9.6896\ (0.0404)$

* 0.0065 (0.0065) C1
* −0.0062 (0.0061) O1
* 0.0073 (0.0073) N2
* −0.0077 (0.0077) H2

Rms deviation of fitted atoms = 0.0070

The crystallographic data for **6a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 186973. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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