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Stereoselectivity in the Amination of Chiral Cyclohex-3-en-1-one Ketals

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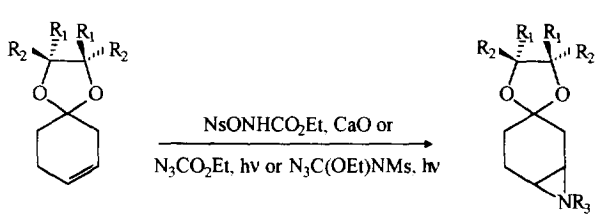
Abstract: Optically active cyclohex-3-en-1-one ketals by photolysis of N_3CO_2Et or $N_3C(OEt)NMs$ or by CaO induced α-elimination of $NsONHCO_2Et$ give diastereomeric aziridines (up to 72% yields, up to 60% d.e.). A simple HPLC separation allows to obtain practically pure aziridines. The conversion of the main product to the ketal of (*R*)-*N*-(ethoxycarbonyl)-β-aminocyclohexanone is also reported and a further oxidation directly gives a derivative of (*R*)-2-aminoadipic acid. © 1997 Elsevier Science Ltd.

We have recently proposed an improved amination methodology, based on the use of solid bases to deprotonate sulphonyloxycarbamates,[1-3] and we have shown that homoallylic cyclic ketals were promising substrates.[1,4]

We now report on results obtained with optically active cyclohex-3-en-1-one ketals **1a-e** upon reaction with ethyl {[(4-nitrobenzene)sulphonyl]oxy}carbamate ($NsONHCO_2Et$)[5] and in the photolysis of ethyl azidoformate (N_3CO_2Et)[6] and of a related imidoyl azide, ethyl *N*-(methanesulphonyl)azidoformimidate [N_3-$C(OEt)NMs$].[7,8] All reactions were performed at room temperature in dichloromethane.



1a-e

2 a-e $R_3 = CO_2Et$
2'a-e $R_3 = C(OEt)NMs$

Scheme 1

Isolated yields and diastereomeric excesses of the aziridination products are collected in the Table. Reactions run with $NsONHCO_2Et$ are simpler and faster ($\leq$ 1 h) and the reagent is easier to prepare and to handle with respect to the azides.[9]

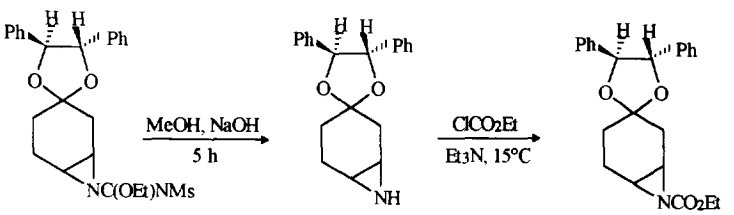
Table. Aziridines **2** and **2'** from Cyclohex-3-en-1-one Ketals **1**.

1 / 2 / 2'	R_1	R_2	$NsONHCO_2Et$		N_3CO_2Et		$N_3C(OEt)NMs$	
			% Yield	% d. e.	% Yield	% d. e.	% Yield	% d. e.
a	H	H	62[a]		40		75	
b	CH_2OMe	H	54	8	22	4	23	8
c	Me	H	33	16	67	17	72	22
d	[b]	H	43	25				
e	H	Ph	13	51	30	57	50	60

[a] See reference 1. [b] R_1 - R_1 = -$(CH_2)_4$-

The yields of **2'** are usually higher than those of **2**. The reactions performed with $NsONHCO_2Et$ or $N_3C(OEt)NMs$ appear nearly quantitative, by inspection of ^{13}C NMR spectra of the crude reaction mixtures. However the isolated yields result lower than those expected, very likely due to chromatographic instability of aziridines, as observed in other occasions. As the diastereomeric excesses are concerned the three methods appear equivalent: in all cases the best selectivity has been achieved when phenyl groups are the substituents in the stereogenic centres. Nevertheless the diastereomers **2c-e** and **2'c** were easily and completely separated by HPLC.

In order to chemically correlate the different aziridines, a mixture of diastereomeric **2'e** was converted into diastereomeric **2e**, by subsequent methanolysis[8] and chloroformylation.



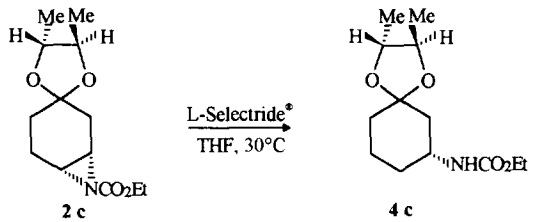
2'e **3e** **2e**

Scheme 2

The comparison by GC-MS and HPLC analyses has shown that the three aminating agents lead to the same major diastereomer. In all three procedures here reported the attack of the reagent always happened mainly from the same face of the chiral homoallylic ketals.

The optically active aziridines so obtained are versatile synthetic intermediates. By reductive ring cleavage[10] we were able to cleanly transform a single diastereomer **2c** into **4c** by using L-Selectride® with

complete regioselectivity,[11] while both $LiAlH_4$ and $NaBH_4$ failed to react. We obtained the optically pure *N*-(ethoxycarbonyl) β-amino ketal **4c** with a 69% yield, after a HPLC purification.

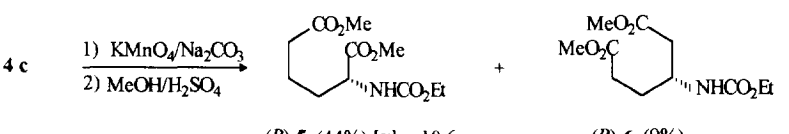


2 c **4 c**

Scheme 3

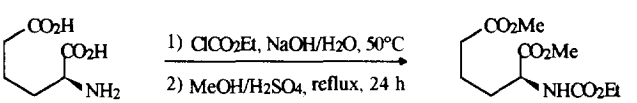
This clean ring scission after the aziridination step would provide a useful access to β-amino carbonyl compounds,[12] that are interesting building blocks for synthesis.

Next, aiming to know the absolute configuration of the carbon atom carrying the carbamate function, compound **4c** has been submitted to oxidation. Thus, the treatment[13] with $KMnO_4$ and Na_2CO_3 in water at 60°C for 24 h, followed by $MeOH/H_2SO_4$ esterification, allowed the formation of dimethyl 2-[(ethoxycarbonyl)amino]adipate **5** in 44% yield, in addition to a 9% of 3-isomer **6**. The two isomers were easily separated by HPLC.



(*R*)-**5** (44%) $[\alpha]_D$ -10.6 (*R*)-**6** (9%)

Scheme 4



(*S*)-**5** $[\alpha]_D$ +9.8

Scheme 5

By comparison with the optical properties of the enantiomer prepared from commercially available (*S*)-2-aminoadipic acid, we were able to assign the (*R*) configuration to **4c** and consequently the (*S,R*) configuration to the newly created chiral carbon atoms of the major aziridines **2** and **2'**.

We would like to emphasise the synthetic potential of the above one-step oxidative cleavage.

EXPERIMENTAL SECTION

GC analyses were performed on a HP 5890 Series II gas chromatograph with a capillary column (methyl silicone, 12.5 m x 0.2 mm). GC-MS were done on a HP G1800A GCD System with a capillary column (phenyl methyl silicone, 30 m x 0.25 mm). ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Varian XL-300 spectrometer, with $CHCl_3$ as an internal standard. IR spectra in CCl_4 were done with a Perkin-Elmer 1600 Series FTIR spectrometer. The separations by HPLC were done with a Varian 9001 instrument equipped with a Varian RI-4 differential refractrometer. Solvents were HPLC-grade. Optical rotations were recorded at the Sodium D line with a Perkin-Elmer 457 polarimeter (1-cm cell).

Synthesis of ketals ***1a-e.*** A solution of cyclohex-2-en-1-one (12 mmol), the appropriate commercial diol (10 mmol), benzene (toluene for **1d**) and 0.1 g of TsOH was refluxed under azeotropic conditions. Progress of the reaction was monitored by GC-MS (3-6 h). When the reaction was complete, the mixture was concentrated *in vacuo* and the residue diluted with CH_2Cl_2, washed with an 8% solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography on silica gel (hexane/ethyl acetate, 9:1).

1b: $[\alpha]_D$ +13.7 (CH_2Cl_2); IR 1687, 1114 cm^{-1}; ^{1}H NMR δ 1.7 (*t*, 2 H, CH_2), 2.16-2.32 (*m*, 4 H, CH_2), 3.36 (*s*, 6 H, CH_3), 3.50 (*d*, 2 H, OCH_2), 3.51 (*d*, 2 H, OCH_2), 3.91-3.97 (*dt*, 1 H, OCH), 3.98-4.05 (*dt*, 1 H OCH), 5.50-5.68 (*m*, 2 H, HC=CH); ^{13}C NMR δ 24.37, 23.13, 36.83 (CH_2), 59.33, 59.37 (CH_3), 73.26, 73.36 (OCH_2), 77.00, 77.05 (OCH), 108.95 (C), 124.12, 126.37 (HC=CH); MS *m/z* 228 (M$^+$, 27), 174 (50), 115 (56), 112 (15), 102 (15), 100 (12), 96 (12), 87 (18), 85 (39), 84 (68), 81 (21), 79 (15), 77 (10), 71 (16), 70 (30), 69 (16), 68 (24), 67 (20), 59 (28), 58 (16), 55 (32), 54 (29), 53 (17), 45 (100), 43 (29), 42 (10), 41 (33).

1c: $[\alpha]_D$ -3.1 (CH_2Cl_2); IR 1652, 1110 cm^{-1}; ^{1}H NMR δ 1.24 (*d*, 3 H, CH_3), 126 (*d*, 3 H, CH_3), 1.75 (*t*, 2 H, CH_2), 2.20-2.27 (*m*, 4 H, CH_2), 3.60-3.69 (*m*, 2 H, OCH), 5.56-5.72 (*m*, 2 H, HC=CH); ^{13}C NMR δ 16.82, 17.00 (CH_3), 24.45, 32.56, 37.18 (CH_2), 77.97, 78.15 (OCH), 106.90 (C), 124.36, 126.54 (HC=CH); MS *m/z* 168 (M$^+$, 25), 114 (100), 96 (26), 81 (22), 79 (20), 72 (18), 68 (11), 67 (12), 57 (11), 55 (24), 54 (11), 43 (51), 42 (16), 41 (16).

1d: $[\alpha]_D$ -5.1 (CH_2Cl_2); IR 1444, 1118 cm^{-1}; ^{1}H NMR δ 1.16-1.50 (*m*, 4 H, CH_2), 1.68-1.88 (*m*, 4 H, CH_2), 2.05-2.34 (*m*, 6 H, CH_2), 3.21-3.38 (*m*, 2 H, OCH), 5.53-5.76 (*m*, 2 H, HC=CH); ^{13}C NMR δ 23.62, 24.31, 28.87, 32.22, 36.83 (CH_2), 79.93, 80.11 (CHO), 107.93 (C), 124.52, 126.84 (HC=CH); MS *m/z* 194 (M$^+$, 48), 140 (100), 112 (13), 99 (12), 98 (41), 97 (22), 96 (56), 81 (62), 80 (29), 79 (28), 77 (18), 71 (12), 69 (39), 68 (76), 67 (41), 57 (12), 55 (27), 54 (78), 53 (21), 43 (24), 42 (18), 41 (66).

1e: $[\alpha]_D$ -67.7 (CH_2Cl_2); IR 3033, 1496, 1135 cm^{-1}; ^{1}H NMR δ 1.93-2.09 (*m*, 2 H, CH_2), 2.29-2.63 (*m*, 4 H, CH_2), 4.72 (*s*, 2 H, CH), 5.59-5.72 (*m*, 2 H, HC=CH), 7.13-7.28 (*m*, 10 H, aromatic H); ^{13}C NMR δ 24.54, 32.59, 37.11 (CH_2), 85.25 (CHPh), 108.67 (OCO), 124.20, 129.79 (HC=CH), 126.70, 126.81, 128.20, 128.29, 128.35, 128.41 (aromatic CH), 136.63, 136.88 (aromatic C); MS *m/z* 292 (M$^+$, 2), 187 (15), 186 (100), 180 (19), 179 (20), 178 (14), 168 (15), 167 (50), 165 (18), 105 (27), 96 (20), 91 (90), 90 (15), 89 (19), 81 (13), 80 (77), 79 (44), 77 (33), 68 (13), 54 (13).

Reaction of ***1*** *with* $NsONHCO_2Et$. To a stirred solution of the substrate (0.6 mmol) in 6 ml of CH_2Cl_2 at room temperature, CaO and $NsONHCO_2Et$ were added portionwise, in the molar ratios

substrate:$NsONHCO_2Et$:CaO=1:5:5 for **1b** and **1d**, 1:4:4 for **1c** and 1:7:7 for **1e**. After 1 h of stirring, 20 ml of CH_2Cl_2 and 200 ml of petroleum ether (bp 30-50 °C) were added. After filtration, the liquid phase was concentrated *in vacuo*. The aziridines **2b** were separated, as a diastereomeric mixture, by flash chromatography on silica gel (hexane/ethyl acetate, 1:1), while **2c**, **2d** and **2e** were obtained as pure diastereomers by HPLC (hexane/ethyl acetate, 8:2 for **2c** and **2e**; 7:3 for **2d**).

2b: IR 1720, 1098 cm^{-1}; ^1H NMR δ 1.23 (*t*, 3 H, CH_2CH_3), 1.32 (*t*, 2 H, CH_2), 2.00-2.11 (*m*, 4 H, CH_2) 2.58-2.65 (*m*, 2 H, NCH), 3.36 (*s*, 6 H, OCH_3), 3.43-3.50 (*m*, 4 H, CH_2CH), 3.85-3.92 (*m*, 2 H, OCH), 4.16 (*q*, 2 H, CH_2CH_3); ^{13}C NMR δ 14.28 (CH_3), 21.89, 28.40, 28.90, 34.63, 35.26 (CH_2), 35.58, 35.61, 37.14, 37.22 (NCH), 59.37 (OCH_3), 62.30 (CH_2CH_3), 72.99, 73.20 (CH_2CH), 77.01, 77.16 (OCH), 107.78, 107.89 (C), 163.86 (CO); MS *m/z* 315 (M^+, 0.4), 270 (12), 242 (10), 174 (24), 115 (73), 112 (17), 110 (17), 102 (15), 100 (13), 85 (39), 84 (72), 83 (11), 82 (18), 71 (17), 70 (33), 69 (20), 68 (25), 67 (13), 62 (11), 59 (14), 58 (13), 56 (13), 55 (34), 54 (20), 45 (100), 43 (25), 42 (12), 41 (30).

2c. Major diastereomer: $[\alpha]_D$ + 3.7 (CH_2Cl_2); IR 1721, 1214 cm^{-1}; ^1H NMR δ 1.19 (2d, 6 H, $CHCH_3$), 1.24 (*t*, 3 H, CH_2CH_3), 1.55-1.69 (*m*, 2 H, CH_2), 1.96-2.19 (*m*, 4 H, CH_2), 2.58-2.70 (*m*, 2 H, NCH), 3.45-3.60 (*m*, 2 H, OCH), 4.10 (*q*, 2 H, OCH_2); ^{13}C NMR δ 14.30 (CH_2CH_3), 16.57 ($CHCH_3$), 22.00, 29.33, 34.85 (CH_2), 35.77, 37.25 (NCH), 62.32 (OCH_2), 77.69, 77.78 (OCH), 105.83 (C), 164.00 (CO); MS *m/z* 255 (M^+, 0.4) 184 (12), 182 (13), 114 (100), 110 (13), 72 (11), 68 (11), 56 (16), 55 (23), 43 (22), 41 (13). Minor diastereomer: $[\alpha]_D$ -3.0 (CH_2Cl_2); ^{13}C NMR δ 14.27 (CH_2CH_3), 16.89 ($CHCH_3$), 22.11, 28.73, 35.62 (CH_2), 35.90, 37.11 (NCH), 62.32 (OCH_2), 78.14, 78.55 (OCH), 105.63 (C), 164.00 (CO).

2d. Major diastereomer: $[\alpha]_D$ + 6.1 (CH_2Cl_2); IR 1723, 1097 cm^{-1}; ^1H NMR δ 1.07 (*t*, 3 H, CH_2CH_3), 1.15-2.20 (*m*, 14 H, CH_2), 2.59-2.68 (*m*, 2 H, NCH), 3.10-3.30 (*m*, 2 H, OCH), 4.10 (*q*, 2 H, CH_2CH_3); ^{13}C NMR δ 14.31 (CH_2CH_3), 21.91, 23.73, 28.77, 29.03, 34.59 (CH_2), 35.85, 37.41 (NCH), 62.39 (OCH_2), 79.61, 80.56 (OCH), 106.57 (C), 169.78 (CO); MS *m/z* 281 (M^+, 0.7), 184 (40), 141 (16), 149 (100), 138 (19), 112 (14), 110 (31), 99 (17), 98 (48), 97 (20), 96 (20), 95 (14), 94 (11), 83 (11), 82 (21), 81 (43), 80 (32), 71 (13), 70 (11), 69 (48), 68 (28), 67 (27), 57 (13), 56 (27), 55 (41), 54 (26), 43 (27), 42 (20), 41 (46). Minor diastereomer: $[\alpha]_D$ -2.7 (CH_2Cl_2); ^{13}C NMR δ 14.35 (CH_2CH_3), 22.21, 23.67, 28.95, 29.16, 35.59 (CH_2), 35.80, 37.17 (NCH), 62.39 (OCH_2), 79.43, 80.18 (OCH), 106.73 (C), 169.78 (CO).

2e. Major diastereomer: $[\alpha]_D$ -10.3 (CH_2Cl_2); IR 1725 cm^{-1}; ^1H NMR δ 1.28 (*t*, 3 H, CH_2CH_3), 1.50-2.37 (*m*, 6 H, CH_2), 2.68-2.74 (*m*, 2 H, NCH), 4.14 (*q*, 2 H, CH_2CH_3), 4.66 (*s*, 2 H, OCH), 7.13-7.32 (*m*, 10 H, aromatic CH); ^{13}C NMR δ 14.37 (CH_2CH_3), 22.10, 29.46, 34.91 (CH_2), 35.77, 37.29 (NCH), 62.44 (OCH_2), 84.88, 84.95 (OCH), 107.38 (OCO), 126.41, 126.58, 126.82, 126.93, 128.21, 128.34, 128.41, 128.48, 128.56 (aromatic CH), 136.13, 136.25 (aromatic C), 163.91 (CO); MS *m/z* 273 (M^+-106, 35), 207 (29), 196 (15), 184 (44), 183 (10), 181 (17), 180 (100), 179 (39), 178 (23), 168 (18), 167 (78), 166 (10), 165 (26), 152 (10), 138 (19), 118 (11), 110 (12), 107 (15), 105 (43), 96 (18), 95 (12), 94 (27), 92 (12), 91 (93), 90 (29), 89 (19), 82 (15), 80 (11), 79 (20), 78 (25), 77 (35), 69 (11), 68 (16), 67 (33), 65 (13), 62 (15), 56 (14), 55 (23), 54 (26), 44 (16), 41 (27). Minor diastereomer: $[\alpha]_D$ +12.3 (CH_2Cl_2); ^{13}C NMR δ 14.34 (CH_2CH_3), 22.18, 28.72, 34.91 (CH_2), 35.64, 37.10 (NCH), 62.44 (OCH_2), 85.36, 85.56 (OCH), 107.76 (OCO), 126.41, 126.58, 126.82, 126.93, 128.21, 128.34, 128.41, 128.48, 128.56 (aromatic CH), 136.43, 137.00 (aromatic C), 163.91 (CO).

Photolysis of N_3CO_2Et or $N_3C(OEt)NMs$ with 1. The azide (12 mmol) and the ketal (10 mmol) in 1 ml of CH_2Cl_2 were photolysed in a quarz vessel under an atmosphere of nitrogen at room temperature, using a

medium pressure Hanovia PCR lamp (100 W). When the azide band disappeared in the IR spectrum [2-35 h for N_3CO_2Et, 4-30 h for $N_3C(OEt)NMs$] the solvent was evaporated *in vacuo*. The aziridines **2b** were separated, as a diastereomeric mixture, by flash chromatography on silica gel (hexane/ethyl acetate, 1:1), while **2c** and **2e** were obtained as pure diastereomers by HPLC. The aziridines **2'a**, **2'b** and **2'e** were separated, as diastereomeric mixtures, by flash chromatography on silica gel (hexane/ethyl acetate, 1:1), **2'c** were obtained as pure diastereomers by HPLC (hexane/ethyl acetate, 8:2).

2'a: IR 1320, 1110 cm^{-1}; ^1H NMR δ 1.26 (*t*, 3 H, CH_2CH_3), 1.40-1.50 (*m*, 2 H, CH_2), 1.60-2.20 (*m*, 4 H, CH_2), 2.40-2.60 (*m*, 2 H, NCH), 3.12 (*s*, 3 H, SCH_3), 3.78 (*m*, 4 H, CH_2O), 4.15 (*q*, 2 H, CH_2CH_3); ^{13}C NMR δ 13.65 (CH_2CH_3), 21.70, 27.43, 33.13 (CH_2), 38.91, 40.62 (NCH), 42.06 (SCH_3), 63.88, 64.34 (CH_2O), 65.50 (CH_2CH_3), 106.72 (C), 164.71 (C=N); MS *m/z* 304 (M^+, 0.2), 225 (38), 218 (37), 179 (10), 154 (51), 140 (12), 139 (88), 138 (61), 137 (15), 125 (21), 121 (37), 112 (15), 111 (82), 110 (20), 100 (19), 99 (100), 95 (19), 94 (12), 93 (16), 87 (39), 86 (91), 82 (27), 80 (11), 79 (40), 69 (15), 68 (36), 67 (31), 66 (12), 65 (12), 56 (11), 55 (20), 54 (13), 43 (18), 42 (25), 41 (22), 29 (24), 28 (14), 27 (10).

2'b: IR 1590, 1110 cm^{-1}; ^1H NMR δ 1.25 (*t*, 3 H, CH_2CH_3), 1.41-1.83 (*m*, 4 H, CH_2), 2.00-2.42 (*m*, 2 H, NCH), 2.98 (*s*, 3 H, SCH_3), 3.34 (*s*, 3 H, CH_3O), 3.36 (*s*, 3 H, CH_3O), 3.43 (*d*, 2 H, CH_2O), 3.46 (*d*, 2 H, CH_2O), 3.86-3.91 (*dt*, 2 H, OCH), 4.14 (*q*, 4 H, CH_2CH_3); ^{13}C NMR δ 13.61 (CH_2CH_3), 21.50, 28.45, 28.85, 34.11, 34.73 (CH_2), 39.01, 39.13, 40.72, 40.88 (NCH), 41.91 (SCH_3), 59.32 (OCH_3), 65.46 (CH_2CH_3), 72.96, 73.15 (CH_2), 77.09, 77.19 (OCH), 107.77, 107.83 (C), 164.75 (C=N); MS *m/z* 392 (M^+, 0.3), 313 (14), 226 (58), 218 (11), 213 (13), 187 (23), 175 (26), 174 (13), 167 (21), 139 (21), 121 (15), 115 (95), 112 (13), 111 (18), 110 (16), 100 (10), 95 (10), 94 (12), 93 (11), 85 (37), 84 (53), 82 (15), 79 (27), 71 (13), 70 (24), 69 (18), 68 (25), 67 (32), 66 (11), 58 (11), 55 (24), 45 (100), 43 (30), 41 (26).

2'c. Major diastereomer: $[\alpha]_D$ +1.0 (CH_2Cl_2); IR 1310, 1110 cm^{-1}; ^1H NMR δ 1.15 (*m*, 6 H, CH_3), 1.23 (*t*, 3 H, CH_2CH_3), 1.40-1.82 (*m*, 6 H, CH_2), 2.09-2.41 (*m*, 2 H, NCH), 2.97 (*s*, 3 H, SCH_3), 3.45-3.65 (*m*, 2 H, CH), 4.13 (*q*, 2 H, CH_2CH_3); ^{13}C NMR δ 13.91 (CH_2CH_3), 16.30, 16.41 (CH_3CH), 21.50, 29.22, 34.29 (CH_2), 39.18, 40.74 (NCH), 41.90 (SCH_3), 65.47 (CH_2CH_3), 78.14, 78.51 (OCH), 105.60 (C), 164.83 (C=N); MS *m/z* 332 (M^+, 3), 253 (13), 182 (20), 166 (26), 153 (10), 140 (15), 139 (13), 128 (15), 127 (69), 122 (22), 115 (18), 114 (100), 111 (17), 110 (23), 95 (11), 94 (11), 82 (13), 79 (26), 68 (14), 67 (22), 56 (18), 55 (36), 54 (13), 43 (25), 42 (11), 41 (17). Minor diastereomer: $[\alpha]_D$ -1.5 (CH_2Cl_2); ^{13}C NMR δ 13.62 (CH_2CH_3), 16.70, 16.93 (CH_3CH), 21.60, 28.70, 35.32 (CH_2), 39.10, 40.60 (NCH), 41.76 (CH_3S), 65.47 (CH_2CH_3), 78.14, 78.51 (OCH), 105.78 (C), 164.83 (C=N).

2'e. Major diastereomer: IR 1575, 1310, 1120 cm^{-1}; ^1H NMR δ 1.32 (*t*, 3 H, CH_2CH_3), 1.78-2.43 (m, 6 H, CH_2), 2.41-2.85 (*m*, 2 H, NCH), 3.06 (*s*, 3 H, SCH_3), 4.22 (*q*, 2 H, CH_2CH_3), 4.67 (*2d*, 2 H, OCH), 7.16-7.23 (*m*, 5 H, aromatic CH), 7.26-7.33 (*m*, 5 H, aromatic CH); ^{13}C NMR δ 13.90 (CH_2CH_3), 21.80, 29.47, 34.46 (CH_2), 39.45, 40.66 (NCH), 42.28 (SCH_3), 65.60 (CH_2CH_3), 84.86, 85.04 (OCH), 107.30 (OCO) 126.60, 128.53 (aromatic CH), 136.00, 136.18 (aromatic C), 164.05 (C=N). Minor diastereomer: ^{13}C NMR δ 13.90 (CH_2CH_3), 21.80, 28.84, 35.35 (CH_2), 39.19, 40.76 (NCH), 42.28 (SCH_3), 65.60 (CH_2CH_3), 85.33, 85.51 (OCH), 107.66 (OCO), 126.60, 128.53 (aromatic CH), 136.00, 138.18 (aromatic C), 164.05 (C=N).

Conversion of 2'e into 2e. The methanolysis of **2'e** was performed according to a reported procedure,[8] giving **3e**: IR 3300, 3035, 1100 cm^{-1}; ^1H NMR δ 1.30-1.50 (*m*, 2 H, CH_2), 1.70-1.90 (*m*, 2 H, NCH), 2.10-2.40 (*m*, 4 H, CH_2), 2.40 (*br*, 1 H, NH), 4.63-4.81 (*m*, 2 H, OCH), 7.10-7.25 (*m*, 5 H, aromatic CH), 7.27-7.43 (*m*,

5 H, aromatic CH); ^{13}C NMR δ 15.06, 22.43, 29.10, 29.34, 35.74 (CH_2), 84.92, 85.11 (OCH), 108.44 (OCO), 126.62, 126.80, 126.92, 126.99, 127.03, 128.33, 128.42, 128.51, 128.62, 128.71 (aromatic CH), 136.61 (aromatic C); MS *m/z* 307 (M^+, 0.01), 202 (15), 201 (100), 181 (11), 180 (72), 179 (50), 178 (24), 167 (45), 165 (31), 152 (12), 146 (21), 132 (66), 110 (13), 108 (11), 107 (41), 106 (22), 105 (35), 96 (14), 95 (27), 94 (60), 92 (11), 91 (32), 90 (13), 89 (21), 82 (19), 80 (22), 79 (20), 77 (37), 69 (14), 68 (32), 67 (27), 65 (12), 56 (49), 55 (24), 54 (22), 51 (12), 43 (20), 42 (13), 41 (28). The obtained aziridine **3e** underwent chloroformylation and **2e** was isolated and characterised.

Reduction of **2c**. To a stirred solution of the major diastereomer of **2c** (3 mmol) in 10 ml of anhydrous THF, 6.5 ml (6.2 mmol) of 1 M L-Selectride® in THF were added dropwise at room temperature. After 15 min, H_2O was added and the crude mixture was extracted with ethyl ether, dried over Na_2SO_4, filtered and concentrated. The product **4c** was purified by HPLC (hexane/ethyl acetate, 8:2): $[\alpha]_D$ +11.9 (CH_2Cl_2); IR 3400, 1750, 1100 cm^{-1}; ^{1}H NMR δ 1.19 (*m*, 9 H, CH_3), 1.70-2.00 (*m*, 8 H, CH_2), 3.54-3.64 (*m*, 2 H, $CHCH_3$), 3.90 (*m*, 1 H, NCH), 4.07 (*q*, 2 H, CH_2CH_3), 5.40 (*br* 1 H, NH); ^{13}C NMR δ 14.48 (CH_2CH_3), 16.60, 16.74 (CH_3), 19.52, 30.70, 36.08, 41.24 (CH_2), 47.32 (CHN), 60.30 (CH_2CH_3), 77.90, 78.06 ($CHCH_3$), 107.91 (C), 156.02 (CO); MS *m/z* 257 (M^+, 1), 215 (11), 169 (12), 142 (17), 141 (30), 129 (14), 128 (24), 127 (57), 116 (10), 115 (15), 113 (66), 112 (15), 97 (17), 96 (19), 73 (13), 70 (12), 69 (19), 56 (20), 55 (48), 43 (36), 42 (15), 41 (22).

Synthesis of (R)-***5*** *and* (R)-***6***. To a stirred solution of 69.0 mg (0.27 mmol) of **4c**, 0.31 ml of H_2O and 53 mg (0.5 mmol) of Na_2CO_3, 84.16 mg (0.5 mmol) of $KMnO_4$ in 2.7 ml of H_2O were added during 24 h at 60 °C. After 30 min, the crude mixture was filtered, acidified with concentrated HCl and concentrated. Then, 10 ml of MeOH and 0.08 ml of concentrated H_2SO_4 were added and the mixture was refluxed for 24 h. After cooling at room temperature, a saturated solution of NaOH was added. After concentration, the residue was diluted with H_2O, extracted with CH_2Cl_2, dried over Na_2SO_4 and the products were separated by HPLC (hexane/ethyl acetate, 7:3).

***(R)*-5**: $[\alpha]_D$ -10.6 (CH_2Cl_2); IR 3438, 1749, 1700, 1511 cm^{-1}, ^{1}H NMR δ 1.18 (*t*, 3 H, CH_2CH_3), 1.58-1.86 (*m*, 4 H, CH_2), 2.28 (*t*, 2 H, CH_2), 3.61 (*s*, 3 H, CH_3), 3.68 (*s*, 3 H, CH_3), 4.06 (*q*, 2 H, CH_2CH_3), 4.31 (*m*, 1 H, CH), 5.30 (*br*, 1 H, NH); ^{13}C NMR δ 14.22 (CH_2CH_3), 20.37, 31.69, 33.06 (CH_2), 51.40, 52.19, 53.27, 61.01 (CH_2CH_3), 156.30 (NCO), 173.01, 173.62 (CO); MS *m/z* 261 (M^+, 0.02), 230 (11), 203 (11), 202 (100), 170 (21), 156 (50), 128 (49), 124 (20), 115 (10), 98 (68), 88 (11), 84 (10), 59 (12), 56 (30), 55 (27), 43 (11).

***(R)*-6**: $[\alpha]_D$ +14.0 (CH_2Cl_2); IR 3438, 1749, 1700, 1511 cm^{-1}; ^{1}H NMR δ 1.21 (*t*, 3 H, CH_2CH_3), 1.85 (*q*, 2 H, CH_2), 2.38 (*t*, 2 H, CH_2), 2.54 (*d*, 2 H, CH_2), 3.65 (*s*, 1 H, CH_3), 3.66 (*s*, 1 H, CH_3), 3.95 (*m*, 1 H, CH), 4.07 (*q*, 2 H, CH_2CH_3), 5.22 (*br*, 1 H, NH); MS *m/z* 261 (M^+, 0.01), 230 (13), 188 (100), 174 (47), 156 (43), 142 (32), 128 (30), 102 (24), 84 (48), 71 (14), 70 (33), 60 (35), 59 (23), 56 (46), 55 (14), 43 (29), 42 (16), 41 (21).

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