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Synthesis of Enantiomerically Pure *Trans* Aziridine-2-carboxylates by Diastereoselective Gabriel-Cromwell Reaction

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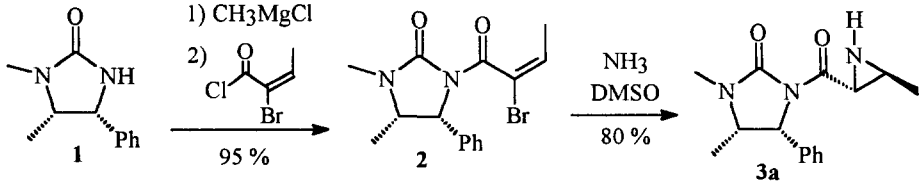
Abstract. Benzyl aziridine-2-carboxylates have been obtained in high yield and selectivity by conjugate addition of ammonia to α,β-unsaturated chiral imides followed by treatment with lithium benzyloxide. A ring-expansion of the aziridine to an oxazoline allowed the determination of the absolute stereochemistry for the newly formed stereogenic centres.

In recent years growing attention has been paid to the synthesis of homochiral aziridine-2-carboxylates[1] as suitable precursors of optically active α- or β-amino acids. The nucleophilic ring-opening of *N*-activated aziridines in the presence of Lewis acids affords regioselectively α-functionalised β-amino acid or β-functionalised α-amino acid[2] precursors, depending on the nature of the nucleophile, of the Lewis acid and of the three membered ring substituents. Furthermore, aziridine-2-carboxylates can also be used as chiral auxiliaries or ligands[3] or building blocks for the synthesis of biologically active compounds in which the aziridine ring remains intact.[4]

Among the several syntheses of chiral aziridine-2-carboxylate derivatives reported in the literature,[5] few examples are present on the diastereocontrolled Gabriel-Cromwell reaction of ammonia or amines with chiral α,β-unsaturated α-bromo carbonyl compounds.[6] Following this procedure Garner[7] described the asymmetric synthesis of C-3 unsubstituted aziridine-2-carboxylates using as chiral auxiliary the Oppolzer's camphor-derived sultam.[8] Unfortunately the reaction resulted in a 1 : 1 diastereomeric mixture when applied to the preparation of 3-methyl aziridines.

Recently our group dealt with the asymmetric 1,4-addition of nucleophiles to chiral α,β-unsaturated carbonyl compounds.[9] The asymmetric induction was controlled by means of (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one[10] as the chiral auxiliary.

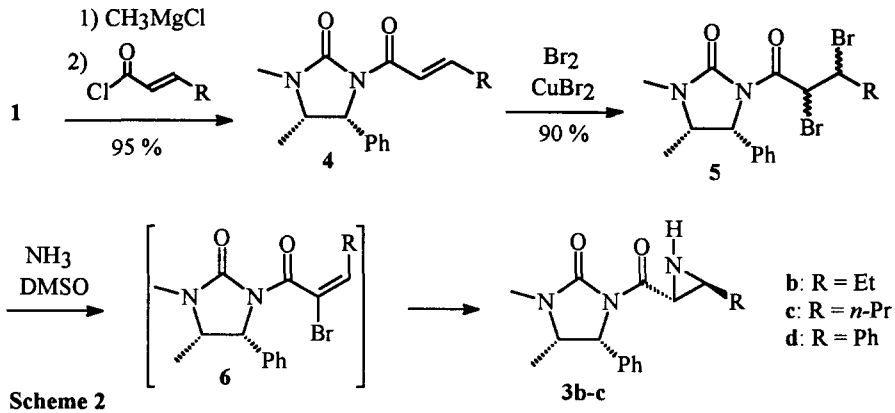


Scheme 1

On the basis of this experience we tested the Gabriel-Cromwell addition of ammonia in DMSO[11] at room temperature to the chiral α,β-unsaturated α-bromo imide **2**, readily obtained by reaction of the magnesium

salt of (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one **1**[10] with 2-bromocrotonyl chloride, as depicted in Scheme 1. Interestingly, the reaction turned out to be highly diastereoselective, affording in good yield the optically active *trans* aziridine **3a**.

The reaction was repeated on the α,β-unsaturated derivatives **4b** (R = Et), **4c** (R = *n*-Pr, $[\alpha]_D$ = -98 (*c* 2.5, $CHCl_3$)),[9a] **4d** (R = Ph) prepared by reaction of the magnesium salt of **1** with the corresponding α,β-unsaturated acid chlorides. By treatment with bromine in the presence of $CuBr_2$ (Scheme 2), a mixture of two diastereomeric dibromo compounds **5** was formed in a diastereomeric ratio ranging from 2 : 1 to 3 : 1.



Scheme 2

The selectivity of this reaction is worthless because it is well known that both dibromo compounds **5** are transformed into the (*E*)-α,β-unsaturated α-bromo intermediate **6** which undergoes the addition of gaseous ammonia. The reaction proceeds at room temperature in DMSO affording the corresponding *trans* aziridines **3b**, **3c** in high yield and good diastereoselectivity.

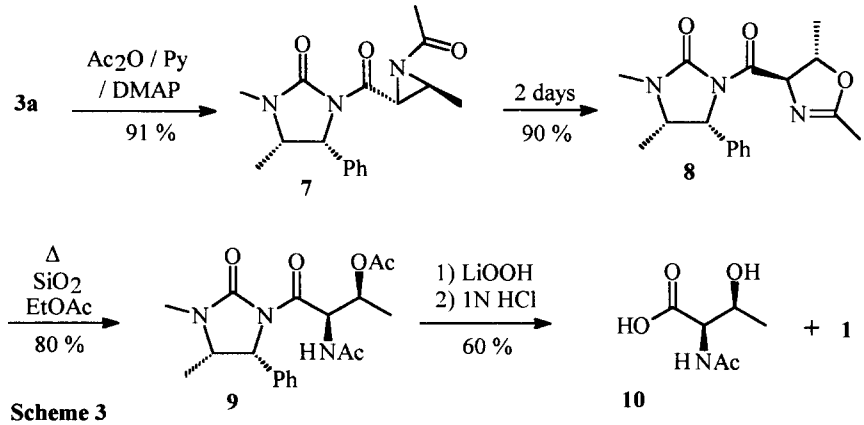
Table 1. Addition of Ammonia to the Imides **2**, **5b-d**.

Entry	R	Time (h)	Solvent	*R,S/S,R/cis* (%)[a]	Conversion (%)	Yield of isolate (2'*R*,3'*S*)-**3** (%)[f]
1	Me	1.5	DMSO	92/8/traces	95[b]	84
2	Me	1.5	MeOH	67/-/33	20[c]	-[g]
3	Et	2	DMSO	90/10/traces	86[d]	75
4	*n*-Pr	2.5	DMSO	90/10/-	88[d]	75
5	Ph	24	DMSO	-	3[e]	-[g]

[a] Determined according to NMR and HPLC analysis. [b] Calculated on the basis of the unreacted **2**. [c] Calculated on the basis of recovered **1**. [d] Determined on the basis of unreacted **5**. [e] Determined on the basis of recovered **4**. [f] After flash cromatography. [g] No purification attempted.

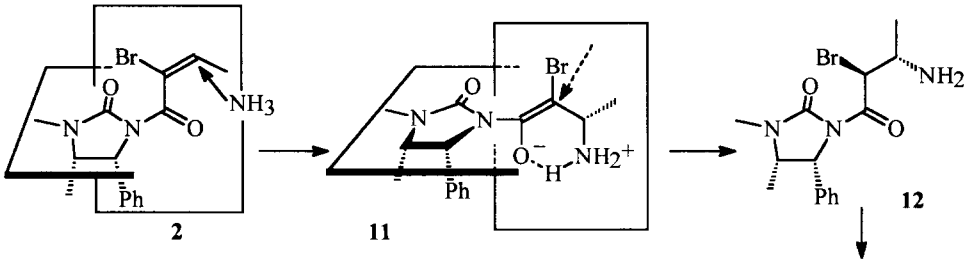
The aziridines **3a-c** were obtained diastereomerically pure after flash chromatography, the other isomers being present in small amounts, as revealed by NMR and HPLC analysis (Table 1). The use of MeOH as solvent under the same conditions was also considered (entry 2), but the reaction resulted mostly in the cleavage of the chiral auxiliary **1**, providing the 3-methyl aziridine **3a** in a rather low yield and a mixture of by-products. It is notable that the reaction proceed to a very low extent for R = Ph (entry 5), affording in large amount the product of debromination **4**.

The *trans* relative stereochemistry of **3** was assigned according to the coupling constant value for the $H_{2'}$ - $H_{3'}$ protons of the aziridine ring ($J_{2'-3'}$ = 2.2 - 2.4 Hz). The absolute configuration of the two newly formed aziridinic stereogenic centres was unambiguously determined to be (2*R*, 3*S*) through the sequence depicted in Scheme 3.



Scheme 3

Acetylation of aziridine **3a** with acetic anhydride in the presence of pyridine and a catalytic amount of DMAP gave the *N*-acetyl aziridine **7**. The three membered ring spontaneously rearranged in chloroform affording almost quantitatively the *trans* 2-methyl oxazoline **8** under perfect regio and stereochemical control. The *trans* stereochemistry was determined by comparison of the coupling constant value for the H_4 - H_5 protons of the oxazoline with the values reported in literature for similar compounds.[12] Heating **8** in the presence of sylica gel in EtOAc resulted in a clean and quantitative ring-opening reaction with formation of a mixture of the 2'-acetamido-3'-acetoxy compound **9** and of the corresponding 2'-acetamido-3'-hydroxy compound in the ratio 8 : 2. Hydrolysis under the conditions reported by Evans[13] ($LiOH/H_2O_2$ in THF/H_2O) afforded the chiral auxiliary **1** and *N*-acetyl threonine **10** $[\alpha]_D$ = -9 (*c* 2.6, MeOH). The absolute stereochemistry of **10** was definitively assigned to be (2*R*, 3*S*) by comparison with an authentic sample of *N*-acetyl threonine $[\alpha]_D$ = +12 (*c* 4.7, MeOH) obtained by acetylation with acetic anhydride of the commercially available (2*S*,3*R*)-(-)-threonine.[14] The stereochemistry of compounds **3b**, **3c** was assigned by comparison of the ^1H and ^{13}C NMR spectra of compounds **3a**, **3b**, **3c**.

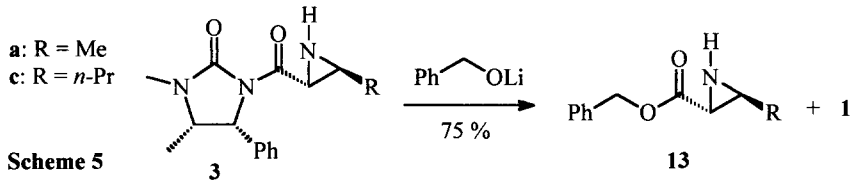


Scheme 4

The origin of the diastereoselectivity can be rationalized taking into account that the nucleophilic attack of ammonia would mainly occur from the Cβ - *si* face of the 2'-bromo derivative **2**, resulting in the formation of the corresponding chelate enolate **11** (Scheme 4).[15] The formation of a chelate is favoured in respect of an open intermediate by the use of the aprotic DMSO as a solvent.[6b] The stereocontrolled

protonation from the less hindered *re* face of the enolate affords the *erythro* derivative **12**, precursor of the *trans* aziridine **3a**.

Finally, the non-destructive removal of the chiral auxiliary **1** was accomplished using lithium benzyloxide[16] in THF. Under these conditions the aziridines **3a** and **3c** were transformed in the enantiomerically pure benzyl (2*R*,3*S*)-(-)-aziridine-2-carboxylates **13a**, **13c** in good yield (Scheme 5). Any attempt of performing the above hydrolysis using other alcoholates (NaOMe/MeOH, $(MeO)_2Mg$/MeOH, NaOBn/THF), gave the corresponding aziridine esters in poor yields.



Scheme 5 **3** **13**

In conclusion, 1,4-addition of ammonia to chiral imides **2** and **4** in DMSO is a diastereoselective and high yielding procedure to obtain the optically active *trans* aziridines **3**. The non-destructive cleavage of the chiral auxiliary **1** with lithium benzyloxide affords the corresponding chiral benzyl aziridine-2-carboxylate **13**. A quantitative regio- and stereo-controlled ring-expansion of the aziridine ring to oxazoline followed by mild ring opening reaction allows to determine the absolute stereochemistry of the aziridines, and suggests a simple procedure for the stereocontrolled synthesis of β-hydroxy α-amino acids.

EXPERIMENTAL SECTION

General methods. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively, and chemical shift are reported in ppm relative to the solvent peak of $CHCl_3$. IR spectra were recorded with a FT-IR spectrometer. Melting points are uncorrected and are determined in open capillaries. Flash cromatography was performad with Merck silica gel 60 (230-400 mesh). THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from P_2O_5. DMSO was distilled from molecular sieves. 2-Bromo-2-butenoic acid chloride was prepared by hydrolysis (1N NaOH) of the commercially available 2-bromo-2-butenoic acid methyl ester to 2-bromo-2-butenoic acid followed by treatment with thionyl chloride.

(4*R*,5*S*)-1,5-Dimethyl-3-alkenoyl-4-phenylimidazolidin-2-one 2, 4

To a stirred solution of **1** (6.5 g, 34.2 mmol) in anhydrous THF (30 mL), methylmagnesium chloride (3 M in THF, 37.6 mmol, 12.5 mL) is added dropwise at 0 °C under inert atmosphere. After 20 min a solution of alkenoyl chloride (40 mmol) in anhydrous THF (10 mL) is added within 5 min. After 3 h the reaction is quenched with water (20 mL), and THF is evaporated at reduced pressure. The mixture is extracted three times with EtOAc (3 x 50 mL) and the collected organic layers are dried over Na_2SO_4. Evaporation of the organic solution and purification of the residue by flash chromatography with silica gel (eluant EtOAc : cyclohexane = 1 : 9) gave the product (31 mmol, 95%).

2: IR (nujol) ν 1700, 1690, 1670, 1610, 1450, 1330, 1190, 1160, 1100, 1070, 990, 860, 830, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (d, 3H, *J* = 6.6 Hz, CH_3CHCHPh), 1.89 (d, 3H, *J* = 6.7 Hz, CH_3), 2.80 (s, 3H, NCH_3), 3.93 (dq, 1H, *J* = 6.6 Hz, 8.8 Hz, CH_3CHCHPh), 5.35 (d, 1H, *J* = 8.8 Hz, CH_3CHC*H*Ph), 6.39 (q, 1H, *J* = 6.7 Hz, =CH), 7.10-7.35 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.1, 16.6, 28.1, 53.9, 59.3, 117.2, 126.7, 128.4, 128.4, 132.5, 135.7, 153.9, 164.2; MS *m/z* 257(100), 226 (1), 217 (1), 189 (2), 173 (6), 160 (6), 132

(23), 117 (16), 91 (10), 77 (15); $[\alpha]_D$ = -69.2 (*c* 1.02, $CHCl_3$). Anal: Calcd. for $C_{15}H_{17}BrN_2O_2$: C, 53.4; H, 5.1; N, 8.3. Found: C, 53.2; H, 5.1; N, 8.4.

4b: IR (nujol) ν 1770, 1710, 1670, 1630, 1450, 1320, 1200, 1170, 1150, 1070, 990, 860, 830, 790, 760, 720, 620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, *J* = 6.6 Hz, CH_3CHCHPh), 1.08 (t, 3H, *J* = 7.4 Hz, CH_3), 2.25 (m, 2H, CH_2), 2.85 (s, 3H, NCH_3), 3.92 (dq, 1H, *J* = 6.6 Hz, 8.5 Hz, CH_3CHCHPh), 5.36 (d, 1H, *J* = 8.5 Hz, CH_3CHCHPh), 7.05 (dt, 1H, *J* = 6.4 Hz, 15.4 Hz, =CH_2), 7.15-7.35 (m, 5H, Ph), 7.46 (d, 1H, *J* = 15.4 Hz, COCH=); ^{13}C NMR ($CDCl_3$) δ 12.2, 14.9, 25.6, 28.1, 53.9, 59.4, 120.8, 126.9, 127.9, 128.4, 136.7, 150.6, 155.9, 164.9; MS *m/z* 272 (M^+, 100), 243 (24), 191 (21), 189 (48), 146 (5), 132 (64), 83 (64), 83 (43), 55 (21); $[\alpha]_D$ = -93.6 (*c* 1.15, $CHCl_3$); mp = 130-132 °C. Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.6; H,7.4; N, 10.3. Found: C, 70.7; H,7.3; N, 10.1.

4d: IR (nujol) ν 1710, 1665, 1610, 1455 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (d, 3H, *J* = 6.6 Hz, CH_3CHCHPh), 2.89 (s, 3H, NCH_3), 3.97 (dq, 1H, *J* = 6.6 Hz, 8.5 Hz, CH_3CHCHPh), 5.44 (d, 1H, *J* = 8.5 Hz, CH_3CHCHPh), 7.20-7.60 (m, 10H, Ph), 7.72 (d, 1H, *J* = 15.8 Hz, =CHPh), 8.19 (d, 1H, *J* = 15.8 Hz, =CHCO); ^{13}C NMR ($CDCl_3$) δ 14.9, 28.1, 53.9, 59.5, 118.8, 126.9, 127.9, 128.2, 128.4, 128.6, 128.8, 129.9, 130.5, 135.0, 136.5, 144.2, 155.9, 164.8; MS *m/z* 320 (M^+, 25), 189 (63), 132 (100), 103 (60), 77 (48); $[\alpha]_D$= -19.3 (*c* 1.1, $CHCl_3$); mp = 160 °C; Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 75.0; H, 6.3; N, 8.7. Found: C, 74.9; H, 7.2; N, 8.76.

(4*R*,5*S*)-1,5-Dimethyl-3-(2',3'-dibromoalkanoyl)-4-phenylimidazolidin-2-one 5

Bromine (0.18 mL, 3.6 mmol) and $CuBr_2$ (0.58 g, 2.6 mmol) are added under inert atmosphere at -70 °C to a stirred solution of **4** (2.4 mmol) in dry CH_2Cl_2 (15 mL). After 6 h the reaction is quenched with a saturated solution of Na_2SO_3 (20 mL) and extracted 3 times with EtOAc (3 x 40 mL). The collected organic layers are dried over Na_2SO_4 and concentrated at reduced pressure, affording the product as an oily mixture of two diastereoisomers, not needing further purification.

5b: ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, *J* =6.6 Hz, CH_3CHCHPh), 1.09 (t, 3H, *J* = 7.1 Hz, CH_3), 1.80-2.05 + 2.20-2.40 (m, 2H, CH_2), 2.88 (s, 3H, NCH_3), 4.00 (m, 1H, CH_3CHCHPh), 4.35-4.55 (m, 1H, CH_2CHBr), 5.35 + 5.39 (d, 1H, *J* = 8.3 Hz, CH_3CHCHPh), 6.34 + 6.45 (d, 1H, *J* = 11.3 Hz, COCHBr), 7.15-7.40 (m, 5H, Ph).

5c: ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, *J* =6.6 Hz, CH_3CHCHPh), 0.94 + 0.98 (t, 3H, *J* = 7.4 Hz, CH_3), 1.40-1.70 (m, 2H, CH_2), 1.80-2.26 (m, 2H, CH_2), 2.87 (s, 3H, NCH_3), 3.99 (dq, 1H, *J* = 6.6 Hz, 8.8 Hz, CH_3CHCHPh), 4.37-4.50 (m, 1H, CH_2CHBr), 5.35 + 5.38 (d, 1H, *J* = 8.8 Hz + 9.0 Hz, CH_3CHCHPh), 6.34 + 6.44 (d, 1H, *J* = 11.4 Hz + 11.1 Hz, COCHBr), 7.15-7.40 (m, 5H, Ph).

5d: ^1H NMR ($CDCl_3$) δ 0.86 (d, 3H, *J* = 6.6 Hz, CH_3CHCHPh), 2.93 (s, 3H, NCH_3), 4.05 (dq, 1H, *J* = 6.6 Hz, 8.7 Hz, CH_3CHCHPh), 5.15 + 5.46 (d, 1H, *J* = 8.7 Hz, CH_3CHCHPh), 5.32 + 5.49 (d, 1H, *J* = 11.6 Hz, BrCHPh), 6.85 + 6.98 (d, 1H, *J* = 11.6 Hz, COCHBr), 7.15-7.50 (m, 5H, Ph).

(4*R*,5*S*,2'*R*,3'*S*)-1,5-Dimethyl-3-[(3'-methyl-2'-aziridinyl)carbonyl]-4-phenylimidazolidin-2-one 3a

To a stirred solution of **2** (7.45 g, 22.1 mmol) in distilled DMSO (16 mL), gaseous ammonia is added at room temperature until solvent saturation. After 1 h the reaction is diluted with EtOAc (250 mL) and the solution is washed three times with small portions of water (3 x 10 mL). The organic phase is dried over Na_2SO_4 and concentrated at reduced pressure. Crystallisation of the residue by EtOAc or flash chromatography on silica gel (eluant EtOAc : cyclohexane = 1 : 1) affords 4.87 g of **3a** (84 %) as a solid. IR (nujol) ν 3280, 1720, 1650, 1420, 1370, 1230, 1070, 940, 870, 800, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, 3H, *J* = 6.6 Hz, CH_3CHCHPh), 1.29 (d, 3H, *J* = 5.4 Hz, CH_3), 1.70 (s, 1H, NH), 2.18 (dq, 1H, *J* = 2.4 Hz, 5.4 Hz, $HNCHCH_3$), 2.87 (s, 3H, NCH_3), 3.78 (d, 1H, *J* = 2.4 Hz, OCCHNH), 3.95 (dq, 1H, *J* = 6.6 Hz, 8.8 Hz,

$CH_3CHCHPh$), 5.32 (d, 1H, J = 8.8 Hz, $CH_3CHCHPh$), 7.16-7.36 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.1, 18.3, 28.3, 36.3, 36.7, 54.2, 59.4, 126.9, 128.3, 128.5, 136.1, 155. 7, 171.4; MS *m/z* 273 (M^+, 53), 231 (16), 217 (12), 191 (100), 175 (18), 148 (1), 132 (20), 113 (18), 105 (1), 91 (14), 70 (1), 56 (43); $[\alpha]_D$ = -115 (*c* 1.1, $CHCl_3$); mp = 169-171 °C. Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.9; H, 7.0; N, 15.4. Found: C, 66.1; H, 6.9; N, 15.4.

(4*R*,5*S*,2'*R*,3'*S*)-1,5-Dimethyl-3-[(3'-alkyl-2'-aziridinyl)carbonyl]-4-phenylimidazolidin-2-one 3

The addition of ammonia on **5** (3.5 mmol) in DMSO (5 mL) under the same conditions described for the preparation of **3a** affords, after flash chromatography on silica gel (eluant EtOAc : cyclohexane = 1 : 1) **3** (2.5 mmol, 71 %).

3b: IR (nujol): ν 3270, 1720, 1650, 1450, 1370, 1230, 1200, 1010, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.5 Hz, $CH_3CHCHPh$), 1.03 (t, 3H, J = 7.3 Hz, CH_3), 1.48-1.62 (m, 2H, CH_2), 1.81 (b.s, 1H, NH), 2.10 (dt, 1H, J = 2.3 Hz, 5.5 Hz, $HNCHCH_2$), 2.87 (s, 3H, NCH_3), 3.82 (d, 1H, J = 2.3 Hz, $OCCHNH$), 3.96 (dq, 1H, J = 6.5 Hz, 8.7 Hz, $CH_3CHCHPh$), 5.32 (d, 1H, J = 8.7 Hz, $CH_3CHCHPh$), 7.13-7.41 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 11.0, 15.1, 25.9, 28.3, 35.6, 42.5, 54.2, 59.4, 126.9, 128.3, 128.6, 136.1, 155.6, 171.5; MS *m/z* 287 (M^+, 22), 272 (3), 258 (4), 231 (15), 217 (5), 203 (4), 191 (100), 175 (12), 148 (7), 132 (24), 113 (21), 105 (11), 77 (19), 70 (23), 58 (15); $[\alpha]_D$ = -93 (*c* 1.0, $CHCl_3$); mp = 142-146 °C. Anal. Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.9; H, 7.4; N, 14.6. Found: C, 66.8; H, 7.5; N, 14.5.

3c: IR (nujol) ν 3270, 1740, 1660, 1470, 1450, 1360, 1240, 1150, 970, 950, 870, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (d, 3H, J = 6.6 Hz, $CH_3CHCHPh$), 0.94 (t, 3H, J = 6.6 Hz, CH_3), 1.45-1.52 (m, 4H, CH_2CH_2), 1.74 (s, 1H, NH), 2.09-2.15 (m, 1H, $HNCHCH_2$), 2.87 (s, 3H, NCH_3), 3.82 (d, 1H, J = 2.2 Hz, $OCCHNH$), 3.95 (dq, 1H, J = 6.6 Hz, 8.8 Hz, $CH_3CHCHPh$), 5.31 (d, 1H, J = 8.8 Hz, $CH_3CHCHPh$), 7.15-7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 13.1, 15.0, 20.3, 28.2, 34.9, 35.6, 41.0, 54.09, 50.4, 126.9, 128.2, 128.6, 136.1, 155.5, 171.5; MS *m/z* 301 (M^+, 13), 286 (8), 273 (5), 258 (5), 231 (18), 217 (6), 191 (100), 175 (13), 160 (3), 132 (27), 117 (21), 113 (27), 84 (29), 77 (18), 56 (21); $[\alpha]_D$ = -91 (*c* 0.77, $CHCl_3$). Anal. Calcd. for $C_{17}H_{23}N_3O_2$: C, 67.8; H, 7.7; N, 13.9. Found: C, 67.8; H, 7.7; N, 13.8.

(4*R*,5*S*,2'*R*,3'*S*)-1,5-Dimethyl-3-[(1'-acetyl-3'-methyl-2'-aziridinyl)carbonyl]-4-phenylimidazolidin-2-one 7

To a stirred solution of **3a** (0.2 g, 0.73 mmol), pyridine (0.12 mL, 14.8 mmol) and a catalytic amount of DMAP in dry CH_2Cl_2 (3 mL), acetic anhydride (0.11 mL, 1.1 mmol) is added at 0 °C under inert atmosphere. After 2 h the reaction is quenched with water (3 mL), and extracted three times with EtOAc (3 x 20 mL). The organic layers are dried over Na_2SO_4 and concentrated at reduced pressure, affording **7** (0.21 g, 91 %) as an oil. No further purification is attempted. ^1H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.6 Hz, $CH_3CHCHPh$), 1.38 (d, 3H, J = 5.5 Hz, CH_3), 1.75 (s, 3H, CH_3CO), 2.79-2.84 (m, 1H, $NCHCH_3$), 2.88 (s, 3H, NCH_3), 3.95 (dq, 1H, J = 6.6 Hz, 8.4 Hz, $CH_3CHCHPh$), 4.54 (d, 1H, J = 2.4 Hz, $OCCHN$), 5.30 (d, 1H, J = 8.4 Hz, $CH_3CHCHPh$), 7.10-7.35 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 15.0, 16.9, 24.1, 28.2, 40.3, 41.6, 54.1, 59.5, 126.9, 128.3, 128.5, 135.9, 155.3, 166.9, 180.3; MS *m/z* 315 (M^+, 25), 273 (35), 231 (14), 217 (8), 203 (5), 191 (100), 179 (18), 160 (5), 142 (5), 132 (26), 117 (21), 91 (19), 77 (19), 56 (53).

(4*R*,5*S*,4'*R*,5'*S*)-4,5-Dihydro-2,5-dimethyl-4-[(1',5'-dimethyl-4'-phenylimidazolidin-2'-on-3'-yl)carbonyl]oxazole 8

Compound **7** (0.21 g, 0.67 mmol) is stirred under inert atmosphere in anhydrous $CHCl_3$ (5 mL) at room temperature. After 2 days the reaction is concentrated at reduced pressure and the residue is purified by

flash chromatography over silica gel (eluent EtOAc : cyclohexane = 1 : 1), affording **8** (0.19 g, 90 %) as a waxy solid. IR (neat) ν 3020, 2960, 2920, 1720, 1680, 1420, 1385, 1030, 980, 760, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (d, 3H, *J* = 6.6 Hz, $CH_3CHCHPh$), 1.40 (d, 3H, *J* = 6.4 Hz, CH_3), 1.97 (s, 3H, $CH_3C{=}N$), 2.84 (s, 3H, NCH_3), 3.93 (dq, 1H, *J* = 6.6 Hz, 8.8 Hz, $CH_3CHCHPh$), 4.82-4.98 (m, 1H, $OCHCH_3$), 5.32 (d, 1H, *J* = 8.8 Hz, $CH_3CHCHPh$), 5.59 (d, 1H, *J* = 5.3 Hz, $OCCHN$), 7.10-7.30 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.2, 20.6, 28.2, 54.0, 59.3, 73.7, 78.2, 127.1, 128.0, 128.4, 135.9, 155.1, 166.5, 170.0; MS *m/z* 315 (M^+, 4), 300 (4), 272 (3), 217 (1), 198 (4), 191 (100), 179 (8), 160 (4), 148 (4), 132 (16), 98 (43), 91 (14), 77 (14), 57 (26); $[\alpha]_D$ = -195 (*c* 0.45, $CHCl_3$); Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.7; H, 6.7; N, 13.3. Found: C, 64.6; H, 6.6; N, 13.2.

(4*R*,5*S*,2'*R*,3'*S*)-1,5-Dimethyl-3-(2'-acetamido-3'-acetoxybutyryl)-4-phenylimidazolidin-2-one 9

A solution of **8** (0.19 g, 0.6 mmol) in EtOAc (5 mL) is refluxed in presence of silica gel 60, 230-400 mesh, (0.5 g). After 24 h the solution is filtrated and concentrated at reduced pressure. Purification of the residue by flash chromatography over silica gel (eluant EtOAc : cyclohexane = 1 : 1) gives **9** (0.18 g, 82 %). IR (neat) ν 3350, 3060, 3040, 2980, 2940, 1735, 1670, 1390, 1240, 1070, 770, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (d, 3H, *J* = 6.7 Hz, $CH_3CHCHPh$), 1.30 (d, 3H, *J* = 6.5 Hz, CH_3), 1.98 (s, 3H, CH_3COO), 2.02 (s, 3H, CH_3CON), 2.86 (s, 3H, NCH_3), 4.00 (dq, 1H, *J* = 6.7 Hz, 8.5 Hz, $CH_3CHCHPh$), 5.07 (d, 1H, *J* = 8.5 Hz, $CH_3CHCHPh$), 5.55 (dq, 1H, *J* = 1.3 Hz, 6.5 Hz, $OCHCH_3$), 6.12 (dd, 1H, *J* =1.3 Hz, 9.6 Hz, $OCCHN$), 6.27 (d, 1H, *J* = 9.6 Hz, NH), 7.10-7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.7, 17.4, 20.3, 23.2, 54.1, 54.8, 59.9, 70.7, 126.9, 128.1, 128.5, 136.1, 155.3, 169.2, 169.9, 170.5; MS *m/z* 315 (75), 289 (54), 246 (21), 191 (100), 132 (8), 98 (42), 74 (21), 58 (79) $[\alpha]_D$ = -94 (*c* 1.2, $CHCl_3$). Anal. Calcd. for $C_{19}H_{25}N_3O_5$: C, 60.8; H, 6.7; N, 11.2. Found: C, 60.7; H, 6.6; N, 11.2.

***N*-Acetyl-(2*R*,3*S*)- threonine 10**

H_2O_2 (30 %, 0.65 mL, 5.7 mmol) and LiOH (0.052 g, 2.2 mmol) are added to a solution of **9** (0.13 g, 0.35 mmol) in THF / H_2O (4 + 1 mL) at room temperature. After 12 h the excess of H_2O_2 is decomposed with Na_2SO_3 (0.63 g, 5 mmol) and THF is evaporated at reduced pressure. The residue is extracted three times with EtOAc (3 x 30 mL). The organic layers are dried with Na_2SO_4 and concentrated, affording **1** (0.062 g, 94 %), $[\alpha]_D$ = -43.2 (*c* 1.5, MeOH), mp = 175-176 °C (lit.[10] $[\alpha]_D$ = -44.5 (*c* 3, MeOH), mp = 177-179 °C). The water layer is treated with 1N HCl until pH is adjusted at 3 and extracted three times with EtOAc (5 x 15 mL). The collected organic layers are dried over Na_2SO_4 and concentrated et reduced pressure affording **10** as an oil (0.040 g, 60 %). IR (neat) ν 3350 (br.), 2980, 1729, 1645, 1553, 1377, 1258, 1166, 1082 cm^{-1}; ^1H NMR (CD_3OD) δ 1.18 (d, 3H, *J* = 6.5 Hz, CH_3), 2.05 (s, 3H, CH_3CON), 4.30 (dq, 1H, *J* = 3.2 Hz, 6.5 Hz, $HOCHCH_3$), 4.42 (d, 1H, *J* = 3.2 Hz, $OCCHN$); ^{13}C NMR (CD_3OD) δ 20.4, 22.4, 59.2, 68.3, 173.8, 173.9; $[\alpha]_D$ = -9 (*c* 2.6, MeOH).

Benzyl (2*R*,3*S*)-(-)-3-alkylaziridine-2-carboxylate 13

BuLi (1.6 M in THF, 2.4 mmol, 1.5 mL) is added under inert atmosphere at -10 °C to a stirred solution of benzylic alcohol (2.4 mmol) in anhydrous THF (5 mL). After 20 min a solution of **3** (1.2 mmol) in THF (3 mL) is added dropwise at -10 °C. The reaction is quenched after 30 min with water (5 mL) and THF is removed under reduced pressure. The residue is extracted three times with ether (3 x 30 mL) and the collected organic layers dried with Na_2SO_4. After evaporation of the solvent the resulting mixture is separated by flash chromatography on silica gel (eluant EtOAc : cyclohexane = 1 : 5) affording **13** (0.9 mmol, 75 %) as an oil and **1** (1.1 mmol, 90 %), $[\alpha]_D$ = -42.6 (*c* 1.5, MeOH),[10] mp = 176 °C.[10]

13a: IR (neat) ν 3280, 3040, 2960, 1730, 1500, 1450, 1410, 1200, 1080, 820, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (d, 3H, *J* = 5.2 Hz, CH_3), 1.54 (s, 1H, NH), 2.28-2.37 (m, 2H, C*H*C*H*), 5.16 (d, 1H, *J* = 12.1 Hz, OC*H*Ph), 5.21 (d, 1H, *J* = 12.1 Hz, OC*H*Ph), 7.30-7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) 18.0, 34.9, 36.1, 67.2, 128.3, 128.5, 128.6, 135.3, 172.5; MS *m/z* 176 (2), 147 (3), 131 (3), 117 (2), 100 (60), 91 (100), 77 (6), 65 (20); $[\alpha]_D$ = -50 (*c* 0.95, $CHCl_3$). Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.1; H,6.9; N, 7.3. Found: C, 69.0; H,7.0; N, 7.2.

13c: IR (neat) ν 3280, 3050, 2960, 1730, 1490, 1400 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, *J* = 7.0 Hz, CH_3), 1.36-1.70 (m, 5H, C*H*$_2$C*H*$_2$, NH), 2.21-2.32 (m, 1H, CHC*H*CH$_2$), 2.35 (d, 1H, *J* = 2.5 Hz, COC*H*CH), 5.16 (d, 1H, *J* = 12.3 Hz, OC*H*Ph), 5.22 (d, 1H, *J* = 12.3 Hz, OC*H*Ph), 7.34-7.45 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$); δ 13.6, 20.2, 34.3, 35.0, 39.5, 67.1, 128.0, 128.5, 128.8, 135.2, 172.3; MS *m/z* 218 (M^+-1, 2), 204 (1), 191 (2), 176 (3), 160 (3), 148 (4), 128 (80), 91 (100), 86 (25), 73 (20); $[\alpha]_D$ = -43 (*c* 0.7, $CHCl_3$). Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.8; N, 6.4. Found: C, 71.0; H, 7.8; N, 6.3.

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References and Notes

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