Synthesis of Enantiomerically Pure Aziridine-2-imides by Cyclization of Chiral 3′-Benzyloxyamino Imide Enolates

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Aziridine-2-imides are prepared both in high yield and high diastereoselectivity from chiral 3′-benzyloxyamino imides **2**, **3**, and **8** by treatment with triethylamine in the presence of either $TiCl_4$ or $AlMe_2Cl$. **2** and **3** are easily obtained by a diastereoselective conjugate addition of *O*-benzylhydroxylamine promoted by Lewis acids to α,β-unsaturated imides **1**. The synthesis of 3′-(benzyloxyamino)propanoyl **8** is performed by addition to the acryloyl compound **6** of *N*-BOC *O*-benzylhydroxylamine followed by deprotection. The cyclization of **2** and **3** affords complete trans selectivity and yields up to 97% of the corresponding 3′-alkyl aziridines **4** and **5**, while the cyclization of **8** affords a mixture of diasteroisomers **11**, **12** in 86/14 ratio and a 95% yield. A mechanistic study has been made to rationalize the trans selectivity observed in the cyclization of **2** and **3**. AM1 computations allow us to deduce that the reaction proceeds through cyclic titanium or aluminum enolate formation, and they reveal that enolates leading to trans aziridines are more stable than those leading to cis.

Aziridines[1] are very interesting heterocyclic compounds present in nature in unusual natural products that display strong biological activity. Azinomycines A and B[2] for instance are potent antitumor antibiotics isolated from the fermentation broth of *Streptomyces griseofuscus* and (+)-FR900482[3] from the culture broth of *Streptomyces sandaensis*. They exhibit exceptionally potent antitumor activity against various types of mammalian solid tumors.

Since their discovery in 1888 by Gabriel, aziridines have attracted much attention as starting material to further transformations. The ring strain renders these compounds susceptible to ring opening, and for this aspect they have received great interest as precursors for a variety of nitrogen-containing compounds. A number of synthetic approaches have been reported,[1b] most of which start from easily available enantiomerically pure compounds. Chiral nonracemic aziridines have been prepared by enzymatic separation of racemic mixtures,[4] from chiral oxiranes,[5] chiral diols,[6] β-hydroxy α-amino acids,[7] hydroxy acids,[8] or addition of ammonia to a suitable 2-haloacrylic acid derivative.[9]

Attention has recently been paid to the use of aziridine-2-carboxylates as intermediates of substituted α- and β-amino acids.[10] We have described the preliminary results in which enantiomerically pure *trans*-3-alkylaziridine-2-carboxylates have been obtained from chiral 3′-benzyloxyamino imides through a cyclization reaction.[11] While a variety of methods for the preparation of 3-alkyl- or 3-arylaziridines has been reported, the synthesis of chiral 3-unsubstituted aziridine-2-carboxylates seems to be limited to the use of natural serine from which (*S*)-aziridine can be exclusively obtained.[7a,12] Recently, 3-unsubstituted aziridine-2-carboxylates have been prepared from the reaction of chiral 1,3,5-triazine with alkyldiazoacetates in the presence of a Lewis acid as catalyst.[13]

In this work we supply the data relative to the preparation of 3-alkyl aziridine-2-carboxylates,[11] and we report the synthesis of 3-unsubstituted aziridine-2-carboxylates; furthermore we wish to give a rationale to the mechanism of the cyclization reaction.

Results

It has been reported[14] that treatment of 3-methoxyamino ketones with 2 equiv of sodium methoxide in methanol give rise to 2-ketoaziridines in good yields and trans selectivity probably via an intermediate enolate. On the basis of these results we have reported a new few steps synthesis[11] of trans chiral aziridines, starting from chiral 3-benzyloxyamino imides **2** and **3**, easily prepared in turn by the 1,4-addition of *O*-benzylhydroxylamine to **1** promoted by a Lewis acid[15] (Scheme 1).

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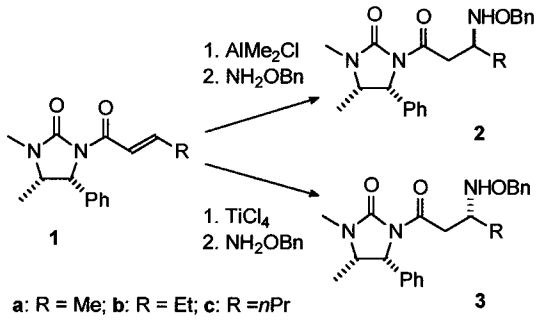
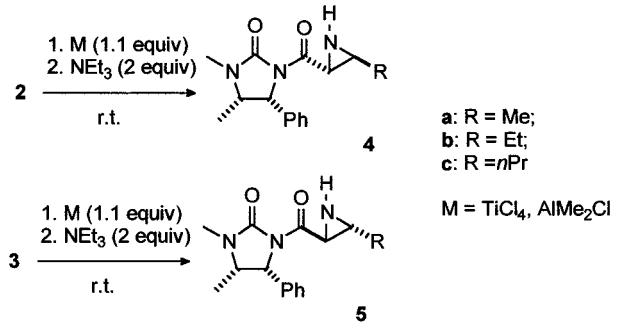
Scheme 1



Scheme 2



The interest of this addition reaction rests in the fact that a predominant (*S*) or (*R*) configuration of the newly introduced stereogenic center depends on the Lewis acid selected, thus a unique substrate **1** makes it possible to obtain the desired diasteroisomer in an enriched form.

At first we unsuccessfully tried to perform the cyclization of these compounds using sodium methoxide. Subsequently, considering the high tolerance of our substrates to Lewis acids, we thought enolates could be prepared under the conditions reported by Evans.[16] Addition of the complex formed by **2** or **3** with 1 equiv of $TiCl_4$ to a solution of triethylamine in CH_2Cl_2 under nitrogen at room temperature turned the reaction mixture red, thus showing the formation of an intermediate enolate.[16] After 30 min pure aziridines **4** and **5** were obtained by flash chromatography in high yield and complete trans diastereoselectivity (Scheme 2). No trace of the cis isomer was observed in the crude reaction mixture. The yield of this procedure was strongly sensitive to the reaction conditions. In particular it was observed that the presence of quite small moisture traces caused a fast enolate quench, giving poor yields of cyclization products. The possibility of utilizing boron enolates as useful intermediates to aziridines was also exploited. Nevertheless, any attempt to obtain boron enolates by means of the commercially available Bu_2-BOTf[17] has at the moment failed.

In contrast, when 1.1 equiv of $AlMe_2Cl$ was used as a Lewis acid under the same conditions as above, a clean and mild reaction took place, and aziridine-2-carboxylates were obtained again in high yield in complete trans diastereoselectivity without any reproducibility problem. To our knowledge, only a few examples of optically active aluminum enolates prepared under these conditions are reported.[18]

Scheme 3

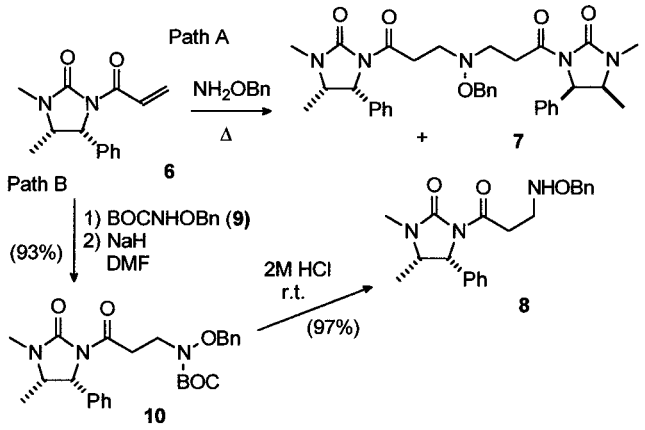


Table 1. 1,4-Addition of *O*-Benzylhydroxylamine to 6

entry	Lewis acid	solvent	time (h)	temp (°C)	**7**[a] (%)	**8**[a] (%)
1	$TiCl_4$	CH_2Cl_2	0.2	0	75	15
2	$AlMe_2Cl$	CH_2Cl_2	0.2	0	51	49
3	–	CH_2Cl_2	72	Δ	30	45
4	–	THF	72	Δ	25	45
5	–	PhMe	24	Δ	18	68

[a] Calculated after purification by flash cromatography on the basis of recovered **6**.

The cyclization to 3′-alkylaziridines easily occurs from the enantiomerically pure reagents **2** and **3**, while 3′-benzyloxyamino-3′-aryl derivatives are not accessible throughtout the 1,4-addition of *O*-benzylhydroxylamine to cinnamoyl derivatives promoted by Lewis acids.

The preparation of 3′-unsubstituted aziridines required as a first approach the preparation of acryloylimidazolidin-2-one **6**, which was carried out under the conditions reported above.[15] The magnesium salt of (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one[19] was treated with acryloyl chloride in dry THF to give **6** in 80% yield. Better yields were obtained in the preparation of **6** when diisopropyl ethylamine was used as base in the presence of catalytic amounts of CuCl, which avoids the polymerization of acryloyl chloride.[20] The direct addition of *O*-benzyl hydroxylamine to **6** was troublesome. Indeed, in the presence of $AlMe_2Cl$, the addition took place smootly. Unfortunately, however, the reaction afforded almost completely an undesired product, **7**, which was isolated and identified as the result of a further 1,4-addition of the desired 3′-(benzyloxyamino)propanoyl derivative **8** to the reagent **6**. To obtain high conversion of the starting material to **8**, the addition of *O*-benzylhydroxylamine was performed under a variety of conditions (Scheme 3, path A).

An improvement was observed simply reversing the order of reagent addition by transferring the complex Lewis acid−**6** to a solution of *O*-benzyhydroxylamine (Table 1, entries 1 and 2). Better results were obtained in different solvents at reflux in the absence of Lewis acids and in the presence of 1 equiv of triethylamine (entries 3−5). Carrying out the reaction in toluene at reflux the amount of **7** was reduced and **8** was obtained in a 68% yield (entry 5).

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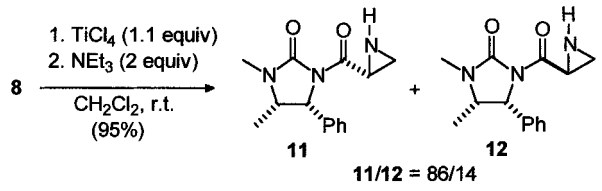
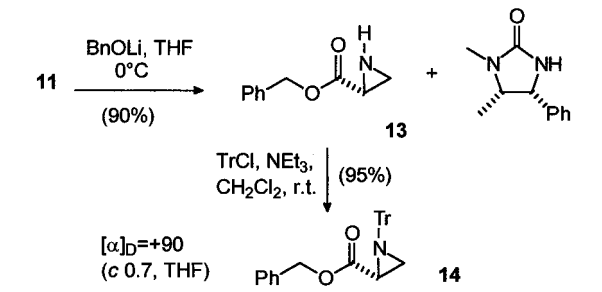
Scheme 4



Scheme 5



Since the direct addition of *O*-benzylhydroxylamine to **6** did not yield adequate amounts of product **8**, a two-step procedure was finally followed which allowed us to obtain **8** in an almost quantitative yield (Scheme 3, path B). *O*-Benzylhydroxylamine was first transformed into the *N*-BOC derivative **9** by means of di-*tert*-butyl dicarbonate. Treatment of a mixture of **6** and **9** with 0.3 equiv of NaH in DMF[15a] and subsequent acid deprotection of the resulting **10**[21] afforded the desired 3′-benzyloxyamino imide **8**.

The cyclization of **8** to aziridine was attempted in the same conditions described above. The titanium tetrachloride complex of **8** was treated with an excess of triethylamine in CH_2Cl_2 at room temperature, and in 30 min a mixture of two isomeric aziridines, **11** and **12**, was obtained in a 86/14 diastereomeric ratio, respectively, and 95% overall yield (Scheme 4). Using 1.1 equiv of $AlMe_2Cl$ instead of $TiCl_4$, the reaction was inefficient, with a cyclization yield of **8** to **11** and **12** less of 10%.

To determine the absolute stereochemistry of the two diastereoisomers the major product was isolated and treated with lithium benzyloxide,[9b,22] in THF at −10 °C (Scheme 5). Under these conditions, **11** was converted into the corresponding benzyl aziridine-2-carboxylate **13** in excellent yield. At the same time the chiral auxiliary (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one was removed without racemization and quantitatively recovered after flash chromatography.

The aziridine-2-ester **13** was subsequently derivatized with trityl chloride in the presence of triethylamine, and the absolute stereochemistry of the resulting *N*-trityl benzyl aziridine-2-carboxylate **14** proved to be (2*R*) by evaluation of its specific rotation power (for **14**: $[\alpha]_D = +90$ (*c* 0.7, THF); lit.[7a] (2*S*) isomer: $[\alpha]_D = -95.5$ (*c* 1.0, THF)).

Discussion

In the formation of trans 3-keto aziridine reported by Blatt and elucidated by Nagel,[14] it is reasonable to assume that an intermediate enolate will form and develop into ring closure. Delocalization of electrons can affect the geometry of the nearby centers toward a preferential *semi*-W transition state that induces a trans relationship between the substituents in the final aziridines[23] (Figure 1).

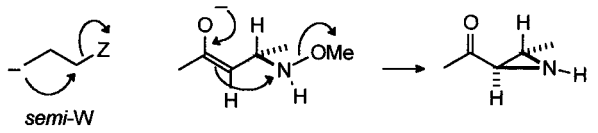


Figure 1.

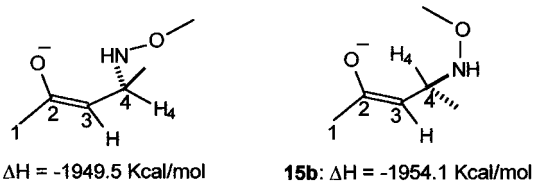


Figure 2.

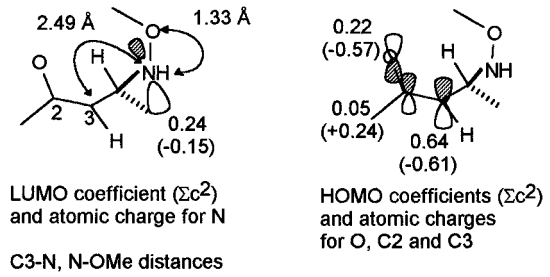


Figure 3.

To obtain additional information about the preferential structure of the transition state, we carried out some semiempirical AM1 calculations[24] on the *Z* enolate anion[25] of the (4*S*)-4-(methoxyamino)pentan-2-one. This species was able to reproduce the reliable model of the reactant in Blatt's reaction, which occurred when sodium methoxide was used. After minimization of several conformations affording by cyclization cis or trans aziridines, the more stable ones resulted to be **15a** and **15b**, respectively (Figure 2).

Conformation **15b**, having H4 almost eclipsed to the enolate oxygen, resulted to be the more stable one. The HOMO coefficient is very high in C3 of the enolate and presents a proper geometry and phase with respect to the LUMO that is located on the nitrogen carrying the leaving group (Figure 3). This structure shows a C3−N distance of 2.49 Å, an N−OMe distance of 1.33 Å, and a C3−C4−N angle of 113.49°. On the contrary, the conformation **15a** is so high in energy that it corresponds to less than 1% of the population.

To simulate a qualitative reaction pathway for the ring closure of enolate **15b** through a model transition state, different kinds of distance variations were examined. The C3−N distance was shortened to 1.83 Å, and the N−O bond was slightly broken by imposition of a N−OMe distance of 1.81 Å (Figure 4). Minimization by AM1 of this structure **15c** caused it to collapse to a **15d** structure that presents a C3−N distance of 1.43 Å, N−OMe distance of 4.5 Å, and C3−C4−N, C4−N−C3, and N−C3−C4 angles close to 60°. At the same time C3 looses its

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(24) Design and distributed by Hypercube Inc., 419 Phillip Street, Waterloo, Ont., N2L 3X2, Canada.

(25) *E* enolates have been also considered and calculated but always resulted in much less stability.

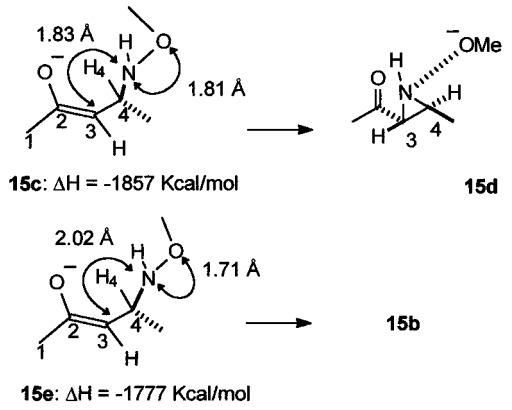

Figure 4.

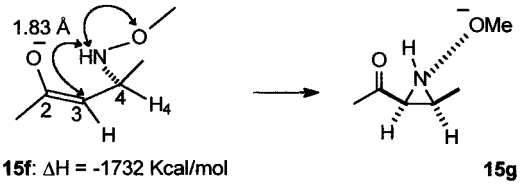

Figure 5.

sp^2 character and acquires an (*R*) configuration, while the carbonyl function is restored. This structure **15d** is substantially coincident with the probable structure of the trans 3-keto aziridine experimentally obtained in the cyclization of 4-(methoxyamino)pentan-2-one.

On the contrary, when C3−N and N−OMe distances are imposed at 2.02 and 1.71 Å, respectively, the structure obtained, **15e**, collapses after AM1 minimization to the reagent structure **15b**. This leads us to suppose that the transition state structure must be an average structure somewhere between **15c** and **15e**.

This procedure was repeated for the less stable enolate conformation **15a**. AM1 minimization of a slightly distorted **15f** structure by imposition of the same distances of 1.83 Å for C3−N and of 1.81 Å for N−O afforded a **15g** structure corresponding to the cis 3-keto aziridine, but the energy of the modelistic **15f** transition structure results considerably higher (Figure 5) than **15c**.

On the basis of these considerations it is possible to suggest that the high diastereoselectivity experimentally observed[14] is due not only to the lower energy of the reagent in anti conformation, but presumably also to the lower energy of the transition state that leads to the formation of trans aziridines.

To evaluate the effect of the presence of a chelating cation on the cyclization stereoselectivity, we introduced, in the 4-(methoxyamino)pentan-2-one enolate, a lithium cation complexed with two molecules of water. The energy of a number of cyclic and acyclic enolate structures were calculated by AM1, and the more stable one resulted to be the conformation **15h**. In this structure the HOMO and LUMO are properly disposed to yield trans 3-keto aziridine by way of cyclization (Figure 6).

The high trans selectivity observed in the ring closure of 3-benzyloxyamino imides **2** and **3** performed with $AlMe_2Cl$ or $TiCl_4$ can be justified by the formation of a cyclic titanium or aluminum complex that may be converted into the corresponding enolate by addition of

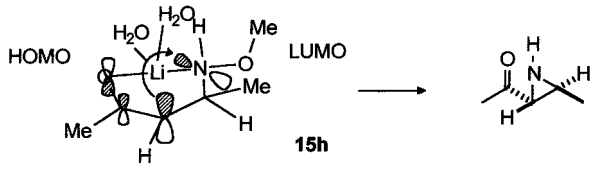

Figure 6.

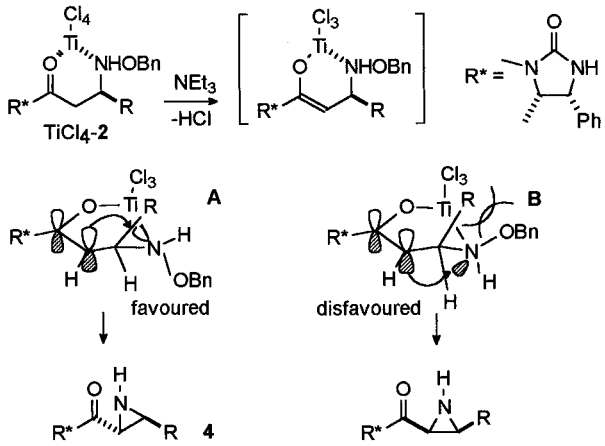

Figure 7.

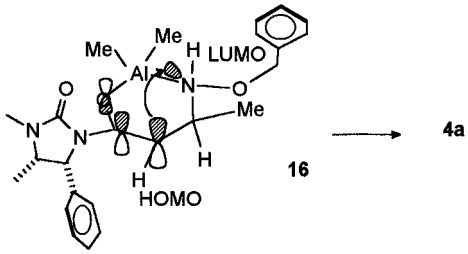

Figure 8.

a base. The enolate obtained from **2** can in principle assume two possible kinds of conformations, A and B (Figure 7). A shows R and the leaving group trans to each other, while B shows R and the leaving group cis. B seems disfavored because of the substituents interaction. The favored conformation, A, leads, by cyclization, to the experimentally observed trans aziridine, obtained as the sole isomer.

Encouraged by these coherent results, we calculated the preferential conformation of the aluminum enolate,[26] the likely intermediate in the synthesis of trans alkyl aziridine **4a**, obtained by treatment of **2a** with triethylamine in the presence of $AlMe_2Cl$. After minimization by means of AM1 calculations of several conformations that could afford cis or trans aziridines by cyclization, structure **16** (Figure 8) was found to be the most stable one.[27] Moreover, because of the proper reciprocal position and phase displayed by HOMO and LUMO, **16** seems to be the most likely arrangement for the anti nucleophilic substitution that is to afford the trans aziridine **4a**.

The proposed qualitative model just proposed provides a rationalization of the observation that only the trans configuration is obtained in the cyclization of **2** and **3** to aziridines **4** and **5**, respectively, as a consequence of the cyclic enolate formation.

(26) Minimization of the corresponding titanium enolate was also attempted by means of ZINDO Hamiltonian in HYPERCHEM package, but the results were unsatisfactory.

(27) An alternative conformation collection, showing aluminum chelating both the enolate oxigen and the heterocyclic carbonyl oxygen, was also considered, but the energy was always higher than in the case of **16**.

In conclusion, chiral 3′-benzyloxyamino imides are suitable precursors of 3′-alkylaziridine-2-carboxylates, which are obtained via chiral titanium or aluminum enolates. A mechanicistic study by AM1 calculations suggests that the complete trans diastereoselectivity can be attributed to the preferred conformation displayed by the intermediate cyclic enolate, which shows the alkyl group and the leaving group trans to each other. In the synthesis of 3′-unsubstituted aziridines, diastereoselectivity is lower, probably owing to the absence of the substituent in position 3′.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and chemical shifts were reported in ppm relative to the solvent peak of $CHCl_3$. IR spectra were recorded using a FT-IR spectrometer. Melting points are uncorrected and are determined in open capillaries. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). Solvents for flash chromatograpy were simply distilled. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from P_2O_5. DMF was distilled from activated molecular sieves. *O*-Benzylhydroxylamine was used as a 0.5 M solution in CH_2Cl_2. This solution was obtained by treatment of *O*-benzylhydroxylamine hydrochloride (2.0 g, 12.5 mmol) with NaOH (0.75 g, 18.8 mmol) in water (5 mL) followed by extraction with CH_2Cl_2 (4 × 10 mL). The organic layers were dried over Na_2SO_4 and partially evaporated at reduced pressure. Finally the solution volume was adjusted to 25 mL with dry CH_2Cl_2. $AlMe_2Cl$ was used as a 1 M solution in cyclohexane.

Molecular mechanics MM^+ and semiempirical AM1 calculations were achieved on the HYPERCHEM calculation package.[24] MM^+ was set on a dipole−dipole electrostatic force field. Geometry optimizations were performed using a Polak-Ribiere conjugate gradient algorithm until a gradient of 0.01 kcal/mol was reached. The Monte Carlo method is available on the CHEMPLUS[24] package. The preferential geometry of chelate and nonchelate *Z* enolate for (4*S*)-4-(methoxyamino)pentan-2-one was fully optimized with semiempirical AM1 calculations. The AM1 optimization was performed over a collection of stable conformations obtained with the Monte Carlo method and minimized with MM^+. The Monte Carlo method provided 100 random conformations by varying C3−C4, C4−N, and N−O torsion angles. The result of HYPERCHEM/AM1 full optimization was confirmed by MOPAC 6.0[28] AM1 calculations. The preferential conformation of the aluminum complex **16** was fully optimized by means of AM1 calculations performed on stable conformations obtained with a Monte Carlo method and minimized with MM^+. 300 Random conformations were considered varying O−Ti, C4−Ph, N3−C1′, C1′−C2′, C2′−C3′, C3′−N′, N′−O′, O′−CH_2Ph, and CH_2−Ph torsion angles.

(4*R*,5*S*)-1,5-Dimethyl-3-[(3′-alkyl-2′-aziridinyl)carbonyl]-4-phenylimidazolidin-2-one (4, 5). To a stirred solution of **2** or **3** (1 mmol) in dry CH_2Cl_2 (5 mL) under an inert atmosphere either $AlMe_2Cl$ (1 M in cyclohexane, 1.1 mL, 1.1 mmol) or $TiCl_4$ (0.12 mL, 1.1 mmol) was added at rt. After 15 min, the solution was transferred dropwise over 1 min at rt and under an inert atmosphere by means of a Teflon cannula to a solution of triethylamine (0.28 mL, 2 mmol) in CH_2Cl_2 (5 mL). The reaction was quenched with water after 30 min (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried over Na_2SO_4, and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography on silica gel (for **4** cyclohexane/ethyl acetate 1/1, for **5** cyclohexane/EtOAc 1/2) yielding **4** or **5** as a solid (70−97%).

References 9b and 11 include characterization data for (2′*R*,3′*S*)-**4**, and (2′*S*,3′*R*)-**5a**, respectively.

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(2′*S*,3′*R*)-5b: IR (Nujol) ν 3260, 1720, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.81 (d, 3H, J = 6.6 Hz), 1.02 (t, 3H, J = 7.4 Hz), 1.45−1.62 (m, 2H), 1.87 (br.s, 1H), 1.94 (dt, 1H, J = 2.5 Hz, 5.9 Hz), 2.86 (s, 3H), 3.76 (d, 1H, J = 2.5 Hz), 3.98 (dq, 1H, J = 6.6 Hz, 8.4 Hz), 5.25 (d, 1H, J = 8.4 Hz), 7.09−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 10.9, 14.7, 25.8, 27.9, 35.8, 42.0, 54.2, 59.6, 126.5, 128.1, 128.5, 136.1, 155.5, 171.1; MS *m*/*z* 287 (M^+, 25), 272 (15), 258 (3), 231 (16), 217 (4), 191 (100), 175 (18), 132 (30); $[\alpha]_D$ = −75 (*c* 1.2, $CHCl_3$); mp = 140−145 °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, 7.4; N. 14.5.

(2′*S*,3′*R*)-5c: IR (Nujol) ν 3270, 1720, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.6 Hz), 0.95 (t, 3H, J = 7.3 Hz), 1.46−1.56 (m, 4H), 1.72 (br.s, 1H), 2.00 (m, 1H), 2.89 (s, 3H), 3.80 (d, 1H, J = 2.7 Hz), 4.00 (dq, 1H, J = 6.6 Hz, 8.3 Hz), 5.26 (d, 1H, J = 8.3 Hz), 7.10−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.8, 20.2, 28.0, 34.8, 35.8, 40.6, 54.2, 59.7, 126.5, 127.1, 128.4, 128.5, 136.2, 155.5, 171.1; MS *m*/*z* 301 (M^+, 10), 286 (6), 258 (3), 231 (15), 217 (6), 191 (100), 175 (10), 132 (24), 113 (26), 84 (27), 77 (13); $[\alpha]_D$ = −54 (*c* 1.4, $CHCl_3$); mp = 112−116 °C. Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.8; H, 7.7; N, 13.9. Found: C, 67.9; H, 7.7; N. 14.0.

(4*R*,5*S*)-1,5-Dimethyl-3-acryloyl-4-phenylimidazolidin-2-one (6). To a stirred solution of (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (0.7 g, 3.7 mmol) in anhydrous CH_2Cl_2 (3 mL), were added diisopropylethylamine (0.95 mL, 5.5 mmol), acryloyl chloride (0.45 mL, 5.5 mmol) and catalytic CuCl under an inert athmosphere at rt. The reaction was refluxed for 2 h and then was quenched with 1 M NH_4OH and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were dried over Na_2SO_4, and the solvent was evaporated at reduced pressure. The residue was purified by crystallization from EtOAc/cyclohexane affording **6** (0.87 g, 97%) as a solid. IR (Nujol) 1710, 1670, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (d, 3H, J = 6.6 Hz), 2.86 (s, 3H), 3.94 (dq, 1H, J = 6.6 Hz, 8.5 Hz), 5.37 (d, 1H, J = 8.5 Hz), 5.77 (dd, 1H, J = 10.4 Hz, 2.0 Hz), 6.40 (dd, 1H, J = 17.0 Hz, 2.0 Hz), 7.40−7.15 (m, 5H), 7.72 (dd, 1H, J = 10.4 Hz, 17.0 Hz); ^{13}C NMR ($CDCl_3$) δ 14.8, 28.1, 53.8, 59.3, 126.8, 127.9, 128.4, 128.6, 128.7, 128.8, 129.7, 136.3, 155.5, 164.4; MS *m*/*z* 244 (M^+, 24), 229 (3), 189 (44), 175 (13), 143 (5), 132 (100), 105 (10), 91 (8), 77 (27), 58 (13), 55 (30); $[\alpha]_D$ = −100.6° (*c* 1.0, $CHCl_3$); mp 135−140 °C. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6; N, 11.5. Found: C, 69.0; H, 6.6; N. 11.5.

***N*-(*tert*-Butoxycarbonyl)-*O*-benzylhydroxylamine (9).** To a mechanically stirred solution of *O*-benzylhydroxylamine hydrochloride (0.15 g, 0.94 mmol) in water (2 mL) and CH_2Cl_2 (2 mL) was added $NaHCO_3$ (0.174 g, 2 mmol) in small portions at 0 °C. When foaming ceased, di-*tert*-butyl dicarbonate (0.25 g, 1.1 mmol) was added at 0 °C and strirring was continued for 3 h. The reaction was stopped by addition of 3 mL of a saturated solution of $NaHCO_3$ and extracted three times with CH_2Cl_2. The organic layers were dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, **9** (0.21 g, 99%) was obtained without further purification. ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 4.86 (s, 2H), 7.11−7.48 (m, 6H).

(4*R*,5*S*)-1,5-Dimethyl-3-[3′-[(*tert*-butoxycarbonyl)(benzyloxy)amino]propanoyl]-4-phenylimidazolidin-2-one (10). To a suspension of NaH (0.002 g, 0.08 mmol) in dry DMF (1.5 m) was added **9** (0.055 g, 0.25 mmol) under an inert athmosphere at rt. After 15 min, **6** (0.050 g, 0.2 mmol) was added, and stirring was continued for 3 h. The reaction was diluted with 30 mL of CH_2Cl_2 and washed four times with small portions of water. The organic solvent was dried over Na_2SO_4 and evaporated at reduced pressure. The residue was purified by flash chromatography on silica gel with cyclohexane/EtOAc 70/30 affording **10** (0.090 g, 96%) as an oil. IR (Nujol) 1730, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (d, 3H, J = 6.6 Hz), 1.49 (s, 9H), 2.80 (s, 3H), 3.23 (dt, 1H, J = 7.1 Hz, 16.9 Hz), 3.43 (dt, 1H, J = 6.9 Hz, 16.9 Hz), 3.70−3.87 (m, 3H), 4.80 (s, 2H), 5.18 (d, 1H, J = 8.5 Hz), 7.09−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.8, 28.2, 33.5, 45.2, 53.8, 59.2, 81.2, 126.8, 127.9, 128.2, 128.3, 129.3, 135.5, 136.5, 155.6, 156.3, 170.5; MS *m*/*z* 244 (19), 189 (34), 175 (13), 149 (9), 132 (100), 117 (6),

105 (7); $[\alpha]_D = -32°$ (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{26}H_{33}N_3O_5$: C, 66.8; H, 7.1; N, 9.0. Found: C, 66.6; H, 7.1; N. 9.1.

(4*R*,5*S*)-1,5-Dimethyl-3-[3′-(benzyloxyamino)propanoyl]-4-phenylimidazolidin-2-one (8). Pathway A. To a stirred solution of **6** (3.66 g, 15 mmol) in dry toluene (30 mL) were added triethylamine (1.04 mL, 7.5 mmol) and *O*-benzylhydroxylamine (54 mL, 0.5 M in CH_2Cl_2, 27 mmol) at rt under a nitrogen atmosphere. The solution was warmed at 50 °C, CH_2Cl_2 was completely removed under a nitrogen current, and then the solution was refluxed for 20 h. After cooling at rt, the reaction was quenched with water and extracted with EtOAc (3 × 30 mL). The organic layers were dried over Na_2SO_4, and the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography on silica gel with cyclohexane/EtOAc 70/30 affording **8** (3.74 g, 68%) as a waxy solid and **7** (0.82 g, 18%) as a major byproduct.

7: IR (Nujol) *ν* 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, 6H, $J = 6.6$ Hz), 2.79 (s, 6H), 3.00−3.50 (m, 8H), 3.86 (dq, 2H, $J = 6.6$ Hz, 8.5 Hz), 4.71 (s, 2H), 5.22 (d, 2H, $J = 8.5$ Hz), 7.10−7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 14.6, 27.8, 33.1, 53.3, 53.5, 58.9, 74.8, 126.6, 127.2, 127.5, 127.6, 127.8, 127.9, 128.1, 128.8, 136.5, 137.1, 155.5, 170.8; MS *m*/*z* 367 (6), 244 (46), 189 (50), 175 (41), 132 (100), 91 (80), 77 (26), 58 (75).

Pathway B. To a stirred solution of **10** (0.09 g, 0.19 mmol) in EtOAc (3 mL) was added 3 M HCl (2 mL) at rt. After 30 min, water (3 mL) and solid $NaHCO_3$ were added until basicity was reached. The mixture was extracted with EtOAc (3 × 15 mL), and the organic layers were dried over Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was purified by flash cromatography on silica gel with cyclohexane/EtOAc 70/30 affording **8** (0.068 g, 97%) as a waxy solid.

8: IR (Nujol) 1730, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (d, 3H, $J = 6.6$ Hz), 2.83 (s, 3H), 3.18−3.40 (m, 4H), 3.86 (dq, 1H, $J = 6.6$ Hz, 8.5 Hz), 4.66 (s, 2H), 5.25 (d, 1H, $J = 8.5$ Hz), 7.05−7.50 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.9, 28.1, 33.5, 47.1, 54.0, 59.3, 75.8, 126.9, 127.6, 128.3, 128.5, 136.5, 138.0, 171.6, 180.6; MS *m*/*z* 244 (19), 189 (34), 175 (13), 149 (9), 132 (100), 117 (6), 105 (7); $[\alpha]_D = -77$ (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.6; H, 6.9; N, 11.4. Found: C, 68.5; H, 7.0; N, 11.4.

(4*R*,5*S*)-1,5-Dimethyl-3-(2′-aziridinylcarbonyl)-4-phenylimidazolidin-2-one (11, 12). A solution of **8** (5 mmol, 1.84 g) and $TiCl_4$ (5.5 mmol, 0.6 mL) in CH_2Cl_2 (15 mL) was added dropwise at rt and under an inert atmosphere by means of a Teflon cannula to a solution of triethylamine (1.4 mL, 10 mmol) in CH_2Cl_2 (15 mL). After 30 min, the reaction was quenched with water and extracted three times with CH_2Cl_2. The organic layers were dried over Na_2SO_4, and the solvent was removed at reduced pressure. The residue was purified by flash chromatography on silica gel with cyclohexane/EtOAc 50/50, and **11** (1.05 g, 81%) and **12** (0.18 g, 14%) were obtained as waxy solids.

(2′*R*)-11: IR (Nujol) 1710, 1660, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (d, 3H, $J = 6.6$ Hz), 1.75 (s, 1H), 1.82−1.98 (m, 2H), 2.88 (s, 3H), 3.96 (dq, 1H, $J = 6.6$ Hz, 8.8 Hz), 4.07 (dd, 1H, $J = 2.9$ Hz, 5.7 Hz), 5.33 (d, 1H, $J = 8.8$ Hz), 7.15−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.1, 28.3, 28.7, 29.7, 54.2, 59.5, 127.0, 127.8, 128.7, 136.0, 155.6, 171.8; MS *m*/*z* 259 (M^+, 40), 243 (15), 231 (9), 217 (5), 203 (3), 189 (100), 175 (28), 148 (11), 133 (16), 132 (75), 117 (45), 91 (36); $[\alpha]_D = -68°$ (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.9; H, 6.6; N, 16.2. Found: C, 65.0; H, 6.6; N, 16.0.

(2′*S*)-12: IR (Nujol) 1710, 1660, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (d, 3H, $J = 6.6$ Hz), 1.77 (s, 1H), 1.85−1.98 (m, 2H), 2.88 (s, 3H), 3.90−4.11 (m, 2H), 5.27 (d, 1H, $J = 8.6$ Hz), 7.10−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.8, 28.0, 28.4, 29.5, 54.3, 59.8, 126.7, 128.4, 128.5, 128.6, 136.1, 155.6, 171.6; MS *m*/*z* 259 (M^+, 15), 244 (18), 191 (29), 189 (83), 175 (28), 132 (100), 117 (25), 91 (26); $[\alpha]_D = -140.7°$ (*c* 0.2, $CHCl_3$). Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.9; H, 6.6; N, 16.2. Found: C, 64.8; H, 6.7; N, 16.2.

Benzyl (2*R*)-Aziridine-2-carboxylate (13). To a stirred solution of BnOH (6 mmol, 0.65 g) in dry THF (10 mL) under an inert atmosphere, was added *n*-BuLi (4.5 mmol, 1.6 M in hexane, 2.8 mL) was added dropwise at −10 °C. After 20 min, this solution was added dropwise at −10 °C to a solution of **11** (3 mmol, 0.78 g) in anhyd THF (10 mL). The reaction was quenched after 30 min with 1 M NH_4Cl, THF was removed at reduced pressure, and the residue was extracted three times with Et_2O. The organic layers were dried over Na_2SO_4, and solvent was evaporated at reduced pressure, affording directly **13** (0.48 g, 90%) as an oil, not further purified. ^1H NMR ($CDCl_3$) δ 1.82−1.96 (m, 1H), 2.00−2.10 (m, 1H) 2.59 (dd, 1H, $J = 2.8$ Hz, 5.0 Hz), 5.18 (d, 1H, $J = 12.2$ Hz), 5.23 (d, 1H, $J = 12.2$ Hz), 7.10−7.40 (m, 5H); MS *m*/*z* 177 (M^+, 5), 162 (7), 132 (9), 91 (100), 65 (33).

Benzyl (2*R*)-1-Tritylaziridine-2-carboxylate (14). To a stirred solution of **16** (2 mmol, 0.35 g) in dry CH_2Cl_2 (10 mL) under an inert atmosphere were added triethylamine (4 mmol, 0.55 mL) and TrCl (2 mmol, 0.56 g) at 0 °C. The reaction was quenched after 20 h with water and extracted three times with CH_2Cl_2. The organic layers were dried over Na_2SO_4, and solvent was evaporated at reduced pressure. The residue was purified by flash chromatography over silica gel with cyclohexane/EtOAc 90/10 affording **14** (0.80 g, 95%) as a solid. ^1H NMR ($CDCl_3$) δ 1.43 (dd, 1H, $J = 1.6$ Hz, 6.1 Hz), 1.95 (dd, 1H, $J = 2.8$ Hz, 6.1 Hz), 2.30 (dd, 1H, $J = 1.6$ Hz, 2.8 Hz), 5.21 (d, 1H, $J = 12.2$ Hz), 5.27 (d, 1H, $J = 12.2$ Hz), 7.10−7.40 (m, 20H); MS *m*/*z* 341 (5), 281 (5), 260 (22), 183 (74), 154 (30), 105 (100), 77 (66), 51 (13); $[\alpha]_D = +90°$ (*c* 0.7, THF).[7a] Anal. Calcd for $C_{29}H_{25}NO_2$: C, 83.0; H, 6.0; N, 3.3. Found C, 83.2; H, 6.0; N, 3.3.

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