The Ring Expansions of Glyceraldehyde-Derived Aziridine-2-carboxylates to Oxazolines Take Place with an Uncommon Regiochemistry

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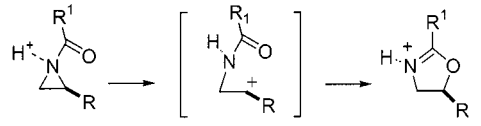
The ring expansion of the D-glyceraldehyde-derived ethyl *trans*-*N*-benzoylaziridine-2-carboxylate **9** occurs with retention of configuration, giving the ethyl *trans*-oxazoline-5-carboxylate **10** as the only product. The observed regioselectivity is rather unusual, since aziridine-2-carboxylates generally rearrange to give oxazoline-4-carboxylates. Conversely, the ring expansion of the *cis*-*N*-benzoyl compound **11** under the same reaction conditions is much slower and less stereoselective, giving a mixture of *cis*- and *trans*-oxazolines, but with the same regioselectivity. The hydrolysis of **10** under mild conditions permits the synthesis of the 3-amino-3-deoxy-D-xylonic acid derivative **13**.

Introduction

Aziridine-2-carboxylates are well known as useful reagents for the synthesis of many categories of nitrogen-containing compounds, in particular α- or β-amino acids, by way of nucleophilic ring opening with reversal of configuration.[1,2] Among the synthetic applications of these compounds, the rearrangement of *N*-activated aziridines has become the object of attention only very recently.[3] The ring expansion of *N*-acylaziridines to oxazolines can be promoted by thermal, acidic or nucleophilic conditions,[3] and generally takes place with good regiocontrol and with retention of the pre-existing configuration. By means of this reaction, we were able to obtain unusual hydroxy amino acid derivatives in optically pure form.[4−6] It was suggested that the Lewis acid promoted ring expansion of *N*-acylaziridines occurs through an S_N1' mechanism,[7] consisting of an initial C−N bond rupture resulting in a carbocationic-like transition state or a carbocationic intermediate,[8] followed by ring closure to the oxazoline (Scheme 1).

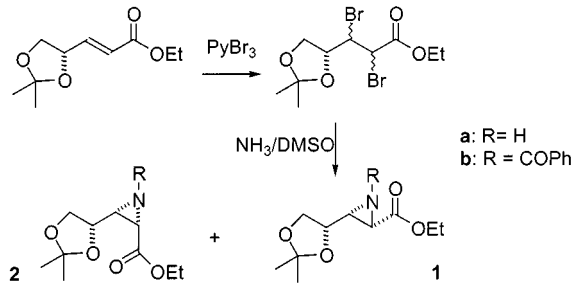


Scheme 1

Polyhydroxylated amino acids are compounds of particular interest thanks to their utility as alkaloid and azasugar precursors.[9] An example is polyoxamic acid,[10,11] a five-carbon α-amino acid present in some members of the potent antifungal polyoxins. Polyhydroxylated β-amino acids are much less well known, and to the best of our knowledge only 3-amino-3-deoxy-D-arabinonic acid has so far been synthesized from the five-carbon series.[12] For these reasons, we decided to look for new ways to synthesise polyhydroxylated amino acids from aziridine starting materials, as only a few examples from this field have been reported in the literature.[13]

Results and Discussion

In the course of our studies concerning Lewis acid promoted ring expansion of optically pure *trans*-aziridine-2-carboxylates or -2-imides, we decided to experiment with the use of *trans*-*N*-acylaziridine-2-carboxylates derived from D-glyceraldehyde as polyhydroxylated aminopentanoic acid precursors. For this reason we prepared the aziridines **1** and **2**[14] by a procedure similar to, although slightly modified from, that reported by Jähnisch.[14−16] Of the various aziridine-2-carboxylate syntheses,[1,2] the diastereoselective Gabriel−Cromwell reaction, consisting of the addition of ammonia to an α,β-dibromo compound, is a very simple and practical one. The α,β-dibromo precursors can easily be prepared by bromination of the corresponding α,β-unsaturated compounds. The diastereoselectivity can be controlled either by means of a chiral auxiliary substituent,[17,18] or by starting from an α,β-unsaturated compound derived from a naturally occurring optically active compound.[1] Ethyl (*E*)-4,5-isopropylidenedioxy-2-pentenoate was prepared according to the literature.[19] As direct treatment with Br_2 is known to cause diol deprotection,[20] the



Scheme 2

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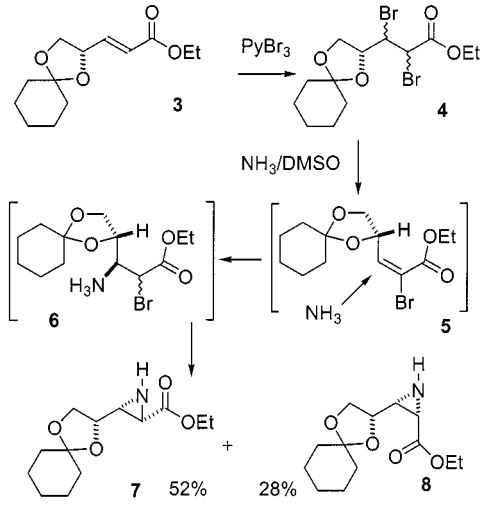
protected pentenoate was instead treated with pyridinium tribromide in water,[21] to give the corresponding dibromo derivative. Gabriel−Cromwell addition of NH_3 in DMSO at 0 °C furnished a mixture of *trans*-**1a** and *cis*-**2a** aziridines,[14] easily separated by flash chromatography, in a 62:38 ratio. Finally, **1a** and **2a** were derivatized with benzoyl chloride to produce *trans*-**1b** and *cis*-**2b** (Scheme 2).

The ring expansion of **1b** and **2b** to oxazolines was attempted in the presence of several Lewis acids and in different solvents. However, the acetonide protecting group was partially or totally removed in all cases. For this reason we decided to prepare aziridine-2-carboxylates derived from D-glyceraldehyde protected with the cyclohexylidene diol group.

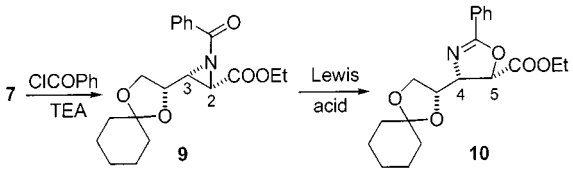
The cyclohexylidene-protected D-glyceraldehyde was prepared by oxidation of di-*O*-cyclohexylidene-D-mannitol,[22] and a Wittig olefination reaction with triethyl phosphonoacetate allowed us to obtain the α,β-unsaturated ethyl (*E*)-4,5-*O*,*O*-cyclohexylidenedioxy-2-pentenoate **3**.[23] Treatment of **3** with pyridinium tribromide[21] in water gave the dibromo derivative **4** as a mixture of diastereoisomers, which were used without separation. Ammonia was bubbled through a solution of these in DMSO at 0 °C, giving *trans*- and *cis*-aziridine **7** and **8** in a 65:35 diastereomeric ratio and good yield after separation by flash chromatography. The other two isomers represented less than 10% altogether, as determined by GC-MS analysis of the crude reaction mixture (Scheme 3).

The reaction goes through the α,β-unsaturated α-bromo intermediate **5**, the preferred conformation of which, shown in Scheme 3, was determined by means of semiempirical PM3 computations,[24] performed on geometries generated by a Monte Carlo procedure.[25] The ammonia attack is likely to occur from the less hindered face, which provides an explanation for the high diastereoselectivity observed experimentally in the formation of the C-3−N bond. Conversely, subsequent protonation of the resulting enolate, giving intermediate **6**, is responsible for the formation of the *cis*/*trans* mixture.



Scheme 3

The relative and absolute configurations of **7** and **8** were determined by comparison of their ^1H and ^{13}C NMR spectra with those of **1a** and **2a** respectively. The *trans*-aziridine **7** was derivatized with benzoyl chloride and the resulting *N*-benzoylaziridine **9** was subjected to ring expansion in the presence of a Lewis acid (Scheme 4 and Table 1).



Scheme 4

The ring expansion of *trans*-**9** in the presence of 1 equiv. of $BF_3{\cdot}Et_2O$ complex was performed at room temperature in $CHCl_3$. After 18 h, the reagent had almost disappeared, as indicated by ^1H NMR and GC-MS analysis of the crude reaction mixture, showing the presence of *trans*-oxazoline **10** (Table 1, Entry 1), accompanied by a complex mixture of deprotected compounds. The reaction was repeated at reflux, and was judged complete after 2 h. Again, a mixture of deprotected compounds was found to be present in the reaction mixture (Entry 2).

Much better results were obtained on treatment of **9** with 1 equiv. of $MgBr_2{\cdot}Et_2O$ complex in THF at reflux, which in 2 h gave the *trans*-oxazoline-5-carboxylate **10** in excellent yield (Table 1, Entry 3). No traces of any product resulting from bromine ring opening were detected.[26,27]

The aziridine **9** was found to be rather reactive towards ring expansion, even in the absence of a Lewis acid. Indeed, a slow, spontaneous conversion was observed when it was left to stand neat at room temperature, and after 4 d a certain quantity of *trans*-oxazoline **10** was present (Entry 4), as shown by ^1H NMR, the rest being unchanged **9**. In addition, *trans*-**9** exclusively underwent ring expansion, even at reflux for 2 h in acetic acid, without any trace of products originating from nucleophilic ring opening (Entry 5).[28]

These data indicate that the ring expansion of *trans*-**9** takes place with complete control over the regioselectivity, giving a single stereoisomer and retention of absolute configuration. The *trans* relative stereochemistry of **10** was determined on the basis of the 4-H−5-H ^1H NMR coupling constants, and the absolute stereochemistry could be definitively assigned as (4*S*,5*R*) since only the aziridine C-2−N bond had been broken during the ring-expansion reaction.

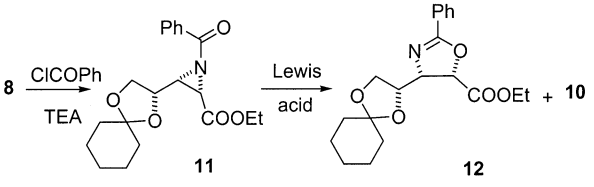
The *cis*-aziridine **8** was derivatized with benzoyl chloride and the resulting *cis*-*N*-benzoylaziridine **11** was subjected to ring-expansion conditions in the presence of a Lewis acid (Scheme 5). The reaction was observed to be much slower and less straightforward than the ring expansion of *trans*-**9** (Table 1). Indeed, after 2 h at reflux in THF in the presence of 1 equiv. of $MgBr_2$, the degree of conversion into *cis*-oxazoline **12** was around 15%, as determined by ^1H NMR and GC-MS analysis of the reaction mixture, the rest still being **11** (Table 1, Entry 6). After 4 h, the degree of conver-

Table 1. Ring expansions of *trans*-**9** and *cis*-**11** in the presence of 1 equiv. of Lewis acid

Entry	Aziridine	Lewis acid (1 equiv.)	Solvent	Temp. [°C]	Time [h]	**10** (%)	**12** (%)
1	**9**	BF_3	$CHCl_3$	room temp.	18	40[a]	–
2	**9**	BF_3	$CHCl_3$	reflux	2	60[a]	–
3	**9**	$MgBr_2$	THF	reflux	2	85[b]	–
4	**9**	–	–	room temp.	96	25[c]	
5	**9**	–	AcOH	reflux	2	55[c]	
6	**11**	$MgBr_2$	THF	reflux	2	–	15[a]
7	**11**	$MgBr_2$	THF	reflux	8	45[a]	30[a]
8	**11**	BF_3	$CHCl_3$	room temp.	18	–	traces

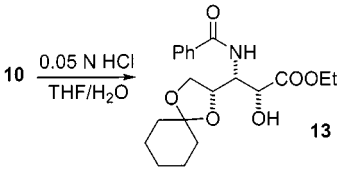
[a] Calculated on the basis of ^{1}H NMR and GC-MS analysis of the crude reaction mixture. – [b] Calculated after purification by flash chromatography, the rest being **9**. – [c] Calculated on the basis of ^{1}H NMR and GC-MS analysis of the crude reaction mixture, the rest being **9**.

sion was 60%, but by then we were able to detect a mixture of *cis*-oxazoline **12** and *trans*-oxazoline **10** in a 65:35 ratio, the latter probably deriving from *cis*/*trans* isomerization. After prolonged reaction times, the degree of conversion reached 75%, with a final **12**/**10** ratio of 40:60 (Entry 7), and a significant presence of bromo derivatives, probably originating from nucleophilic bromide ring opening.[25,26] The same bromo derivatives were also obtained when the reaction was performed in toluene, both at room temperature and at reflux. When the reaction was run for 18 h in the presence of BF_3·Et_2O in $CHCl_3$ at room temperature, we were able to detect only traces of **12**, together with deprotected compounds (Entry 8).



Scheme 5

The final ring opening of **10** was performed under mild acidic conditions, giving the β-amino acid **13** (Scheme 6). The regiochemistry of the ring expansion of **9** to **10** was definitively assigned by ^{1}H NMR decoupling experiments performed on **13**.



Scheme 6

The regioselectivity of the ring expansions of aziridine **9** and **11** in favour of the C-2 positions, and the high reactivity of **9**, were rather unexpected, and contrasted with the experimentally observed behaviour of activated aziridine-2-carboxylates.[3] Moreover, it is to be assumed that the regioselectivity is driven by the stability of the carbocationic intermediate or carbocationic-like transition state.[7,8] For this reason, it was to have been anticipated that the ring expansion of both of the aziridines was likely to take place in favour of the C-3 positions, which seem more capable of stabilizing the incipient positive charge (Scheme 1). This observed regioselectivity might be caused by the operation of a neighbouring-group effect,[6] as suggested by a study of the Lewis acid·**9** complex that we carried out using semiempirical computations.

To calculate the more stable $MgBr_2$·**9** structure, we considered $MgBr_2$ chelation at different positions, to simulate the existence of tautomeric complexes in equilibrium. Indeed, the aziridine N atom is pyramidalized by ring strain, making it more prone to complexation than the nitrogen atom of planar amides.[7,8,29] We performed PM3 semiempirical energy minimization[24] of a conformation set generated by a Monte Carlo procedure.[25] In a similar way, we calculated the more stable PM3 conformation of uncomplexed **9**. In the more stable $MgBr_2$·**9** structure, Mg coordinates both the benzoyl and the ester carbonyl O (Figure 1).

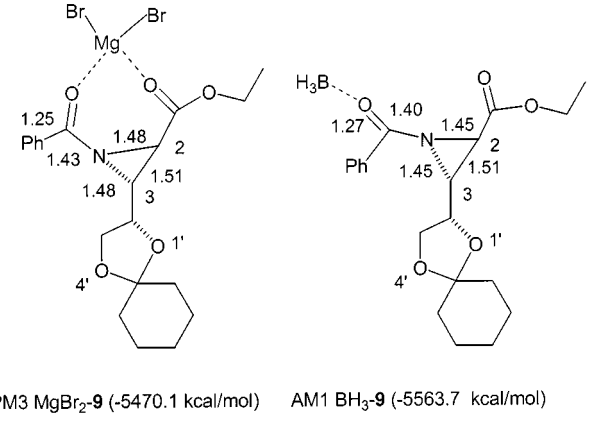
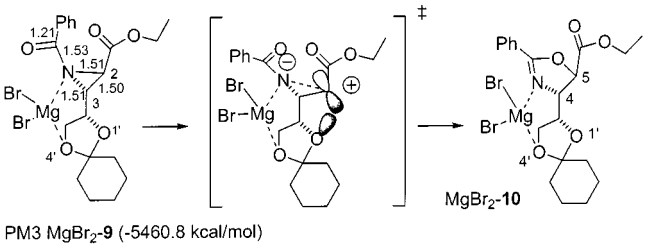


Figure 1. $MgBr_2$·**9** and BH_3·**9** structures calculated by semiempirical energy minimization

In this complex, however, there are only small or even no changes in the aziridine interatomic distances relative to those in **9**.[30] This situation reflects only slight aziridine activation towards ring opening, and in addition the complexation reduces the benzoyl O nucleophilicity,[7,8,29] and

so is generally considered not to be productive in the rearrangement to oxazoline.[7,8]

The next most stable $MgBr_2$·**9** structure, 9.3 kcal/mol higher in energy, shows Mg chelating both N and dioxolanic O-4′ (Scheme 7). The aziridine interatomic distances are lengthened with respect to **9**, and this bond weakening can activate ring expansion.[7,8] In this structural and conformational situation, the dioxolanic O-1′ is forced to point towards C-2, allowing the possibility that in the course of ring expansion to *trans*-oxazoline-5-carboxylate **10**, the C-2 carbocationic transition state might be stabilized by an O-1′ lone pair (Scheme 7). This stabilization does not appear to be possible for the alternative (not observed experimentally) ring expansion to the oxazoline-4-carboxylate by way of an aziridine C-3 carbocation. All the other complexes resulting from different modes of magnesium chelation were found to be higher in energy.



Scheme 7

Because of the impossibility of obtaining energy minima with BF_3 we substituted it with BH_3 and performed AM1 semiempirical computations for the complex BH_3·**9**. We considered both *N*- and *O*-boron coordination,[7,8,29] minimizing geometries furnished by the Monte Carlo procedure.[24,25] We also calculated the preferred AM1 conformation of uncomplexed **9**.[31] The *N*-boron-coordinated BH_3·**9** structure, computed to be more stable (Figure 2), shows interatomic distances longer than those in **9**, indicating strong activation towards ring expansion.[7,8] The dioxolane O-1′ is directed towards C-2, and so the carbocationic transition-state stabilization at C-2 by an O-1′ lone pair, as described above, still seems possible. The complex with B coordinated to the benzoyl O is only 1.1 kcal/mol higher in energy than the *N*-boron complex (Figure 1), but the interatomic distances are scarcely modified from those of **9**, and this structural feature provides grounds for considering this situation unreactive towards ring expansion.

The decision to exchange BF_3 with BH_3 for semiempirical computations has some consequences. Indeed, it seems extremely probable that the weaker BH_3 should influence the aziridine electron-density distribution in a less marked way than BF_3. It is generally accepted that BF_3 may be substituted by H^+ to simplify computations,[7,29] and so we also performed AM1 computations on protonated aziridines. A comparison between *N*-coordinated H^+-**9** and *N*-coordinated BH_3·**9** structures found excellent agreement, in terms both of interatomic distances and of interatomic angles. Comparison between *O*-coordinated H^+-**9** and *O*-coordinated BH_3·**9** found a difference in N geometry, the

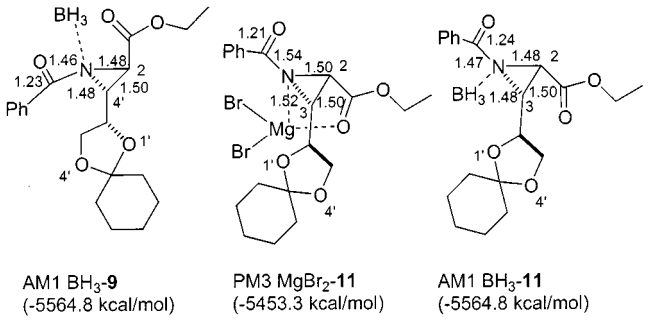


Figure 2. BH_3·**9**, $MgBr_2$·**11**, and BH_3·**11** structures calculated by semiempirical energy minimization

first being almost planar and the second slightly pyramidalized, probably due to the more weakly electron-withdrawing nature of BH_3 relative to H^+. The interatomic distances are in good agreement. Moreover, while *O*-coordinated BH_3·**9** is found to be 1.1 kcal/mol higher in energy than *N*-coordinated BH_3·**9**, *O*-coordinated H^+-**9** proves to be 4.2 kcal/mol lower in energy than *N*-coordinated H^+-**9**, confirming the trend observed for $MgBr_2$·**9**. These computations moved us to believe that the substitution of BF_3 for BH_3 may confidently be accepted in the *N*-coordinated species, and should offer good indications of the preferred conformations assumed by the BF_3·aziridine complex, from the similar dimensions of the two boron derivatives.

Repeating the PM3 computations for $MgBr_2$·**11** and the AM1 computations for BH_3·**11** similarly, we again considered coordination at different positions and performed calculations for different complexes. For the same structural reasons as discussed above for the *trans* isomer, we considered that Lewis acid *O*-coordination was unlikely to be productive.[7,8,29] The more stable *N*-coordinated $MgBr_2$·**11** structure, featuring *N*− and ester carbonyl *O*−Mg chelation, and the more stable *N*-coordinated BH_3·**11**, (Figure 2) may be regarded as the active structures as far as aziridine ring expansion is concerned.[7,8] Apparently, the *cis* dispositions of the aziridine substituents turn the dioxolane groups away from the aziridine moieties in both complexes. Conformations showing O-1′ directed towards C-2 or -3 can still be calculated, but are higher in energy. This renders the activation rather more difficult, and might be responsible for the slower ring-expansion reaction times observed with the *cis*-aziridines.

Conclusion

We have studied the acid-promoted ring expansion of D-glyceraldehyde-derived *N*-benzoylaziridine-2-carboxylates *trans*-**9** and *cis*-**11** to oxazolines, as potential polyhydroxylated amino acid precursors. For *trans*-**9** we observed a fast and regioselective rearrangement to the *trans*-oxazoline-5-carboxylate **10** with retention of configuration, while for *cis*-**11** we observed slow but still regioselective formation of both *cis*- and *trans*-oxazoline-5-carboxylates. The regiochemistry of the expansion displayed by *trans*-**9**, as well as

its high reaction rate, can be explained by allowing for the existence of a neighbouring group participation effect, as suggested by semiempirical computations. The *trans*-oxazoline-5-carboxylate **10** was hydrolysed under mild conditions to the α-hydroxy β-amino acid **13**, which is a protected form of the unnatural 3-amino-3-deoxy-D-xylonic acid in an optically pure state.

Experimental Section

General Remarks: Unless stated otherwise, chemicals were obtained from commercial sources and used without further purification. CH_2Cl_2 was distilled from P_2O_5. Toluene was distilled from molecular sieves. THF was distilled from sodium benzophenone ketyl. − Flash chromatography was performed on Merck silica gel 60 (230−400 mesh), and solvents were simply distilled. − TLC was performed on Merck fluorescent silica gel plates. − NMR spectra were recorded with a Gemini Varian spectrometer at 300 (^{1}H NMR) and 75 (^{13}C NMR) MHz. Chemical shifts are reported as δ values relative to the solvent peak of $CDCl_3$, defined at δ = 7.27 (^{1}H NMR) or δ = 77.0 (^{13}C NMR). − Infrared spectra were recorded with an FT-IR Nicolet 210 spectrometer. − Optical activity measurements were performed with a Perkin−Elmer 343 polarimeter. − GC-MS analysis was performed with a HP-5890 GC coupled with a HP-5971 MS.

Computational Methods: For $MgBr_2$·**9** and $MgBr_2$·**11** we assumed a number of alternative chelation possibilities: N and O-1′; N and O-4′; N and ester carbonyl O; benzoyl O and O-1′; benzoyl O and O-4′; benzoyl O and ester carbonyl O. We disregarded coordinations not involving the acyl aziridine portion. For each complex we generated a set of 200 random conformations by use of a Monte Carlo procedure,[25] and each conformation energy was minimized by means of semiempirical PM3 computations.[24] To perform semiempirical computations for BF_3·**9** and BF_3·**11**, we substituted BF_3 with BH_3, due to the impossibility of obtaining energy minima. We assumed benzoyl O or N coordination. We generated two sets of Monte Carlo[25] conformations and minimized energies by means of AM1 computations.[24] We calculated H^+·**9** in a similar way, taking account both of benzoyl O and N protonation. In the Monte Carlo procedure, we fixed a range for acyclic torsion variation of 45−180° and a range for ring torsion flexing of 15−90°. All the torsion angles were simultaneously varied in a random manner. For energy minimization we used PM3 or AM1 RHF calculations, fixing the Polak−Ribiere algorithm and a gradient of less than 0.001 kcal/Å mol as the termination condition.

Ethyl (2*R*)-2,3-Dibromo-3-(1′,4′-dioxaspiro[4,5]dec-2′-yl)propanoate (4): The α,β-unsaturated ester **3** (0.29 g, 1.2 mmol) was mechanically stirred at room temperature in water (5 mL) with pyridinium tribromide (90%, 0.51 g, 1.4 mmol), with exclusion of light. After 1 h, a saturated solution of Na_2SO_3 was added until the brown colour disappeared. The reaction mixture was extracted three times with Et_2O (10 mL) and the collected organic layers were dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was used without further purification (0.49 g, 100%, two diastereoisomers according to analysis of the crude reaction mixture). − ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, 3 H, CH_3), 1.30−1.40 (m, 4 H, CH_2), 1.40−1.80 (m, 6 H, CH_2), 3.70 + 3.95 (dd, 1 H, OCH_2), 3.83 + 4.12 (dd, 1 H, OCH_2), 4.26 (q, 2 H, CH_2CH$_3$), 4.36 + 4.52 (d, 1 H, CHBr), 4.52 + 4.75 (m, 2 H, OCH + CHBr). − GC-MS: *m*/*z* (%) = 400 (5) [M$^+$], 357 (55), 257 (20), 177 (13), 141 (13), 125 (38), 97 (39), 55 (100).

Ethyl (2′*S*)-3-(1′,4′-Dioxaspiro[4,5]dec-2′-yl)aziridine-2-carboxylate (7, 8): Ammonia was bubbled at 0 °C through a stirred solution of crude **4** (0.49 g, 1.2 mmol) in DMSO (8 mL) for 25 min. After a further 1 h, the solution was diluted with EtOAc (50 mL) and the solution was washed three times with water (5 mL). The organic layer was dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/cyclohexane, 50:50) to give *trans*-**7** (0.16 g, 52%) and *cis*-**8** (0.087 g, 28%) as waxy solids. − **(2*R*,3*R*)-7:** IR: ṽ = 1740, 1640, 1438, 1234, 1160, 1110, 1043 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.40−1.50 (m, 2 H, CH_2), 1.50−1.75 (m, 9 H, NH + CH_2), 2.36−2.57 (m, 2 H, CHN + CHC=O), 3.78 (dd, *J* = 6.6, 8.3 Hz, 1 H, OCH_2), 3.85−4.00 (m, 1 H, OCH_2), 4.00−4.20 (m, 1 H, OCH), 4.22 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$). − ^{13}C NMR ($CDCl_3$): δ = 14.0, 23.9, 25.0, 29.7, 32.0, 35.1, 36.0, 39.7, 61.8, 67.5, 73.2, 110.6, 169.0. − GC-MS: *m*/*z* (%) = 255 (25) [M$^+$], 212 (80), 140 (75), 112 (90), 68 (100). − $[\alpha]_D^{20}$ = −37.9 (*c* = 0.3, $CHCl_3$). − $C_{13}H_{21}NO_4$ (255.31): calcd. C 61.16, H 8.29, N 5.49; found C 61.20, H 8.31, N 5.50. − **(2*S*,3*R*)-8:** IR: ṽ = 1743, 1645, 1445, 1254, 1162, 1110, 1040 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.37−1.50 (m, 2 H, CH_2), 1.50−1.75 (m, 9 H, NH + CH_2), 2.34 (br. dd, 1 H, CHN), 2.69 (br. d, 1 H, CHC=O), 3.67−3.81 (m, 1 H, OCH_2), 3.88−4.08 (m, 2 H, OCH_2 + OCH), 4.23 (q, *J* = 7.4 Hz, 2 H, CH_2CH$_3$). − ^{13}C NMR ($CDCl_3$): δ = 14.0, 24.0, 25.0, 30.0, 33.3, 35.0, 36.5, 40.0, 61.9, 66.4, 74.3, 110.9, 168.8. − GC-MS: *m*/*z* (%) = 255 (25) [M$^+$], 212 (80), 140 (75), 112 (90), 68 (100). − $[\alpha]_D^{20}$ = +18.0 (*c* = 0.2, $CHCl_3$). − $C_{13}H_{21}NO_4$ (255.31): calcd. C 61.16, H 8.29, N 5.49; found C 61.21, H 8.27, N 5.47.

Ethyl (2*R*,3*R*)-1-Benzoyl-3-{(2′*S*)-1′,4′-dioxaspiro[4,5]dec-2′-yl}-aziridine-2-carboxylate (9): A solution of **7** (0.16 g, 0.63 mmol) in CH_2Cl_2 (8 mL) was treated at room temperature with triethylamine (0.10 mL, 0.75 mmol) and benzoyl chloride (0.065 mL, 0.75 mmol), and the mixture was stirred for 2 h under an inert gas. Water was then added and the mixture was extracted three times with CH_2Cl_2 (15 mL). The organic layers were collected and dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. Compound **9** was obtained pure after flash chromatography (EtOAc/cyclohexane, 20:80) in quantitative yield, as an oil that slowly tended to solidify (0.22 g, 97%). − IR: ṽ = 1735, 1650, 1438, 1229, 1160, 1111, 1040 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.05 (t, *J* = 7.6 Hz, 3 H, CH_3), 1.19−1.50 (m, 4 H, CH_2), 1.50−1.82 (m, 6 H, CH_2), 3.19 (dd, *J* = 2.4, 4.0 Hz, 1 H, CHN), 3.43 (d, *J* = 2.4 Hz, 1 H, CHC=O), 3.97 (q, *J* = 7.6 Hz, 2 H, CH_2CH$_3$), 3.98−4.10 (m, 1 H, OCH_2), 4.20 (dd, *J* = 6.6, 8.4 Hz, 1 H, OCH_2), 4.26−4.37 (m, 1 H, OCH), 7.38−7.59 (m, 3 H, ArH), 7.92−8.10 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 13.8, 23.9, 25.1, 29.7, 35.1, 35.9, 39.7, 43.5, 61.8, 67.6, 73.4, 110.7, 128.3, 128.5, 130.5, 132.6, 167.1, 175.4. − GC-MS: *m*/*z* (%) = 359 (5) [M$^+$], 330 (4), 316 (8), 244 (6), 216 (3), 188 (7), 172 (4), 140 (8), 105 (100). − $[\alpha]_D^{20}$ = +14.2 (*c* = 0.6, $CHCl_3$). − $C_{20}H_{25}NO_5$ (359.42): calcd. C 66.84, H 7.01, N 3.90; found C 66.80, H 6.99, N 3.92.

Lewis Acid Promoted Ring Expansion of *trans*-9

Ethyl (4*S*,5*R*)-4-{(2′*S*)-1′,4′-Dioxaspiro[4,5]dec-2′-yl}-2-phenyl-4,5-dihydro-1,3-oxazole-5-carboxylate (10): $MgBr_2$·Et_2O (0.16 g, 0.61 mmol) was added under an inert gas to a solution of **9** (0.22 g, 0.61 mmol) in THF (5 mL), and the mixture was refluxed for 2 h. The solvent was removed under reduced pressure, a saturated solution of $NaHCO_3$ (5 mL) was then added, and the mixture was extracted three times with CH_2Cl_2 (15 mL). The collected organic layers were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The mixture was purified by flash chroma-

tography on silica gel (cyclohexane/EtOAc, 80:20) to afford **10** (0.19 g, 85%) and unchanged **9** (0.028 g, 15%). − **Compound 10:** IR: $\tilde{\nu}$ = 1744, 1650, 1438, 1229, 1166, 1110, 1043 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.30−1.42 (m, 2 H, CH_2), 1.42−1.78 (m, 8 H, CH_2), 4.00 (dd, *J* = 6.3, 7.3 Hz, 1 H, OC*H*$_2$), 4.10 (dd, *J* = 6.3, 6.9 Hz, 1 H, OC*H*$_2$), 4.27 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 4.42−4.59 (m, 2 H, OCH + CHN), 5.03 (d, *J* = 5.7 Hz, 1 H, CHC=O), 7.40−7.58 (m, 3 H, ArH), 7.97−8.10 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.2, 23.8, 25.2, 29.7, 34.8, 35.6, 61.7, 65.0, 73.0, 76.2, 77.7, 108.6, 128.4, 131.7, 169.3, 180.7. − GC-MS: *m*/*z* (%) = 359 (6) [M^+], 330 (5), 316 (10), 262 (3), 244 (7), 216 (11), 200 (8), 172 (12), 141 (100), 105 (36). − $[\alpha]_D^{20}$ = +13.7 (*c* = 1.0, $CHCl_3$). − $C_{20}H_{25}NO_5$ (359.42): calcd. C 66.84, H 7.01, N 3.90; found C 66.82, H 7.00, N 3.92.

Ethyl (2*S*,3*R*)-1-Benzoyl-3-{(2′*S*)-1′,4′-dioxaspiro[4,5]dec-2′-yl}-aziridine-2-carboxylate(11): According to the same procedure as described for the synthesis of **9**, a solution of **8** (0.087 g, 0.34 mmol) in CH_2Cl_2 (4 mL) was treated with triethylamine (0.056 mL, 0.41 mmol) and benzoyl chloride (0.036 mL, 0.41 mmol). After the usual workup, **11** was obtained pure after flash chromatography (cyclohexane/EtOAc, 90:10) in quantitative yield as a oil that slowly tended to solidify (0.12 g, 99%). − IR: $\tilde{\nu}$ = 1748, 1653, 1441, 1229, 1166, 1110, 1033 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.56−1.83 (m, 10 H, CH_2), 2.92 (dd, *J* = 6.7, 8.2 Hz, 1 H, CHN), 3.68 (d, *J* = 6.7 Hz, 1 H, CHC=O), 3.80 (dd, *J* = 6.2, 8.4 Hz, 1 H, OC*H*$_2$), 4.05 (dd, *J* = 6.6, 8.4 Hz, 1 H, OC*H*$_2$), 4.28 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 4.25−4.45 (m, 1 H, OCH), 7.39−7.67 (m, 3 H, ArH), 8.20−8.40 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.2, 24.0, 25.1, 29.7, 34.9, 36.5, 37.7, 45.0, 61.9, 66.4, 74.3, 110.9, 128.2, 130.0, 133.3, 167.2, 176.1. − GC-MS: *m*/*z* (%) = 359 (3) [M^+], 330 (2), 316 (10), 286 (2), 262 (5), 216 (4), 188 (7), 172 (4), 140 (6), 105 (100). − $[\alpha]_D^{20}$ = −33.2 (*c* = 1.2, $CHCl_3$). − $C_{20}H_{25}NO_5$ (359.42): calcd. C 66.84, H 7.01, N 3.90; found C 66.82, H 7.03, N 3.88.

Lewis Acid Promoted Ring Expansion of *cis*-11

Ethyl (4*S*,5*S*)-4-{(2′*S*)-1′,4′-Dioxaspiro[4,5]dec-2′-yl}-2-phenyl-4,5-dihydro-1,3-oxazole-5-carboxylate (12): $MgBr_2{\cdot}Et_2O$ (0.086 g, 0.33 mmol) was added under an inert gas to a solution of **11** (0.12 g, 0.33 mmol) in THF (5 mL), and the mixture was refluxed for 8 h. The solvent was removed under reduced pressure, a saturated solution of $NaHCO_3$ (5 mL) was added, and the mixture was extracted three times with CH_2Cl_2 (5 mL). The collected organic layers were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The mixture was purified by flash chromatography on silica gel (cyclohexane/EtOAc, 80:20) to afford **10** (0.054 g, 45%) and an inseparable mixture of bromo derivatives and **12** (30%, according to the reaction mixture analysis). − **Compound 12:** ^1H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.30−1.75 (m, 10 H, CH_2), 4.10 (dd, *J* = 6.3, 7.3 Hz, 1 H, OC*H*$_2$), 4.20 (dd, *J* = 6.3, 7.0 Hz, 1 H, OC*H*$_2$), 4.24 (q, *J* = 7.1 Hz, 2 H, C*H*$_2$CH$_3$), 4.42−4.57 (m, 1 H, OCH), 4.61 (dd, *J* = 3.3, 10.8 Hz, 1 H, CHN), 5.15 (d, *J* = 10.8 Hz, 1 H, CHC=O), 7.40−7.58 (m, 3 H, ArH), 7.97−8.10 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.0, 24.0, 25.5, 29.7, 34.5, 35.6, 62.0, 65.0, 71.5.0, 76.0, 77.7, 108.6, 128.7, 130.8, 169.3, 180.4. − GC-MS: *m*/*z* (%) = 359 (5) [M^+], 330 (2), 316 (8), 244 (5), 216 (6), 172 (78), 141 (100), 117 (6), 105 (24).

Ethyl (2*R*,3*S*) 3-Benzoylamino-3-{(2′*S*)-1′,4′-dioxaspiro[4,5]dec-2′-yl}-2-hydroxypropanoate: *trans*-Oxazoline **10** (0.19 g, 0.53 mmol) was dissolved in THF (5 mL) at 0 °C and treated with 0.05 N HCl (3 mL). After this had stirred for 4 h, the mixture was neutralized with sat. $NaHCO_3$, and the THF was evaporated under reduced pressure. The residue was extracted three times with CH_2Cl_2 (5 mL), and the collected organic layers were dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (cyclohexane/EtOAc, 40:60) to give **13** as a viscous oil (0.18 g, 89%). − IR: $\tilde{\nu}$ = 3416, 3065, 1733, 1719, 1653, 1646, 1527, 1281, 1096, 1017 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.30 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.30−1.45 (m, 2 H, CH_2), 1.45−1.65 (m, 9 H, OH + CH_2), 3.77 (dd, *J* = 6.2, 8.4 Hz, 1 H, OC*H*$_2$), 4.17 (dd, *J* = 6.6, 8.4 Hz, 1 H, OC*H*$_2$), 4.26 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$CH$_3$), 4.45 (d, *J* = 2.7 Hz, 1 H, C*H*OH), 4.54 (dt, *J* = 2.7, 6.9 Hz, 1 H, OCH), 4.66 (dt, *J* = 3.3, 9.3 Hz, 1 H, CHN), 6.85 (br. d, *J* = 9.3 Hz, 1 H, NH), 7.35−7.60 (m, 3 H, ArH), 7.75−7.84 (m, 2 H, ArH). − ^{13}C NMR ($CDCl_3$): δ = 14.1, 23.7, 24.0, 25.1, 34.5, 36.0, 51.6, 62.4, 66.1, 71.1, 74.3, 110.3, 126.9, 127.2, 128.4, 128.6, 133.5, 167.3, 172.5. − GC-MS: *m*/*z* (%) = 377 (9) [M^+], 334 (28), 274 (7), 218 (6), 176 (21), 141 (11), 105 (100). − $[\alpha]_D^{20}$ = −3.5 (*c* = 0.3, $CHCl_3$). − $C_{20}H_{27}NO_6$ (377.44): calcd. C 63.64, H 7.21, N 3.71; found C 63.59, H 7.19, N 3.75.

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[1] D. Tanner, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599−619.
[2] H. M. I. Osborn, J. Sweeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1693−1715.
[3] W. McCoull, F. A. Davis, *Synthesis* **2000**, *10*, 1347−1365.
[4] G. Cardillo, L. Gentilucci, A. Tolomelli, C. Tomasini, *Tetrahedron Lett.* **1997**, *38*, 6953−6956.
[5] G. Cardillo, L. Gentilucci, A. Tolomelli, *Tetrahedron Lett.* **1999**, *40*, 8261−8264.
[6] S. Armaroli, G. Cardillo, L. Gentilucci, M. Gianotti, A. Tolomelli, *Org. Lett.* **2000**, *2*, 1105−1107 and references therein.
[7] K. Hori, T. Nishiguchi, A. Nabeja, *J. Org. Chem.* **1997**, *62*, 3081−3088.
[8] F. Ferraris, W. J. Drury III, C. Cox, T. Lectka, *J. Org. Chem.* **1998**, *63*, 4568−4569 and references therein.
[9] G. Casiraghi, F. Zanardi, *Chem. Rev.* **1995**, *95*, 1677−1716.
[10] C. Palomo, M. Oirbiade, A. Esnal, A. Landa, J. I. Mirando, A. Linden, *J. Org. Chem.* **1998**, *63*, 5838−5856.
[11] A. K. Ghosh, Y. Wang, *J. Org. Chem.* **1999**, *64*, 2789−2795 and references therein.
[12] M. Bols, I. Lundt, *Acta Chem. Scand.* **1991**, *45*, 280−284.
[13] A. Dureault, F. Carreaux, J. C. Depezay, *Synthesis* **1991**, *2*, 150−155.
[14] K. Jähnish, *Liebigs Ann./Recueil* **1997**, 757−760.
[15] H.-D. Ambrosi, W. Duczek, M. Ramm, E. Gründemann, B. Schulz, K. Jähnish, *Liebigs Ann. Chem.* **1994**, 1013−1018.
[16] K. Jähnish, F. Tittelbach, E. Gründemann, M. Schneider, *Eur. J. Org. Chem.* **2000**, 3957−3960.
[17] P. Garner, O. Dogan, S. Pillai, *Tetrahedron Lett.* **1994**, *35*, 1653−1656.
[18] G. Cardillo, L. Gentilucci, C. Tomasini, M. P. V. Castejon-Bordas, *Tetrahedron: Asymmetry* **1996**, *7*, 755−762.
[19] J. A. Marshall, J. D. Trometer, D. G. Cleary, *Tetrahedron* **1989**, *45*, 391−402.
[20] T. W. Greene, P. G. M. Wuts, in *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, Chichester, Brisbane, Toronto, Singapore, **1991**, pp. 123−127.
[21] P. G. Baraldi, R. Bazzani, S. Manfredini, D. Simoni, M. J. Robins, *Tetrahedron Lett.* **1993**, *34*, 3177−3180.
[22] T. Sugiyama, H. Sugawara, M. Watanabe, K. Yamashita, *Agric. Biol. Chem.* **1984**, *48*, 1841−1844.

[23] R. Annunziata, M. Cinquini, F. Cozzi, G. Dondio, L. Raimondi, *Tetrahedron* **1987**, *43*, 2369−2380.
[24] HYPERCHEM 5.1 Release Pro for Windows Molecular Modeling System, Hypercube Inc, Copyright, **1999**.
[25] CHEMPLUS™ Release, Hypercube Inc, Copyright, **1993−1997**).
[26] G. Righi, R. D'Achille, C. Bonini, *Tetrahedron Lett.* **1996**, *37*, 6893−6896.
[27] D. Tanner, C. Birgersson, H. K. Dhaliwal, *Tetrahedron Lett.* **1990**, *31*, 1903−1906.
[28] J. Legters, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pais-Bas* **1992**, *111*, 59−68.
[29] L. Dubius, A. Meth, E. Tourette, R. H. Dodd, *J. Org. Chem.* **1994**, *59*, 434−441.
[30] N−C-2 and N−C-3: 1.48 Å; benzoyl C−O: 1.21 Å; benzoyl C−N: 1.44 Å; C-2−C-3: 1.51 Å.
[31] N−C-2 and N−C-3: 1.45 Å; benzoyl C−O: 1.27 Å; benzoyl C−N: 1.40 Å; C-2−C-3: 1.51 Å.

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