Pergamon

Tetrahedron 56 (2000) 7299–7304

TETRAHEDRON

Synthesis of Chiral *cis*-1,2,3-Trisubstituted Aziridines

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Received 7 April 2000; revised 23 June 2000; accepted 6 July 2000

Abstract—Chiral *cis*-1,2,3-trisubstituted aziridines were conveniently synthesized from (1*R*,2*S*)-(−)- or (1*S*,2*R*)-(+)-norephedrine via the corresponding chiral *N*-(arylidene)-β-chloroamines. The enantiomeric purity of the chiral aziridines (e.e. >98%) was established by NMR spectroscopy utilizing (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol.

Introduction

The ability of aziridines to undergo highly regio and stereoselective ring opening reactions gives them great value in organic synthesis.[1] In addition, it has been shown that a number of naturally occurring and synthetic aziridines have potent biological activity. For this reason, aziridines have been frequently target compounds in synthetic organic chemistry.

Classical methods for the synthesis of chiral aziridines are the ring closure of chiral amino alcohols[1] and the ring opening of chiral epoxides with azide[1,2] and subsequent ring closure.

Racemic 1,2,3-trisubstituted aziridines have been previously synthesized by the Wenker procedure, involving ring closure of β-aminoalcohols[3–5] or β-chloroamines[6] or by reductive ring closure of α,α-dichloroketimines.[7] Another synthesis of racemic 1,2,3-trisubstituted aziridines was achieved by *N*-alkylation of *N*-unsubstituted aziridines under phase transfer catalytic conditions, but this method has limited generality.[8]

We report here a convenient synthesis of chiral 1,2,3-trisubstituted aziridines **4** and **9** from (1*R*,2*S*)-(−)-norephedrine **1** and (1*S*,2*R*)-(+)-norephedrine **11** via the corresponding *N*-(arylidene)-β-chloroamines. In addition, we report on an NMR method, employing (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol (Pirkle alcohol) as the chiral solvating agent, for the rapid and convenient determination of the enantiomeric composition of chiral 1,2,3-trisubstituted aziridines.

Keywords: chiral aziridines; *N*-(arylidene)-β-chloroamines; e.e. determination; NMR.

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Results and Discussion

As shown in Scheme 1, (1*R*,2*S*)-(−)-norephedrine **1** was chlorinated with PCl_5 in dry chloroform under reflux to give (1*S*,2*S*)-(+)-1-chloro-1-phenyl-2-propylamine hydrochloride **2** in 81% yield.[9] (1*S*,2*S*)-(+)-1-Chloro-1-phenyl-2-propylamine hydrochloride **2** was then treated with different 4-substituted benzaldehydes in dichloromethane in the presence of triethylamine and magnesium sulfate to afford (1*S*,2*S*)-(+)-*N*-(arylidene)-1-chloro-1-phenyl-2-propylamines **3a**–**d** in 88–97% yield.

The reaction of the chiral *N*-(β-chloroalkyl)aldimines **3a**–**d** with excess sodium borohydride in methanol under reflux gave rise to a series of (2*S*,3*R*)-(−)-1-benzyl-2-methyl-3-phenylaziridines **4a**–**d** in 96–99% yield. The reaction products are formed by nucleophilic addition of hydride across the imino bond and subsequent intramolecular nucleophilic substitution, which occurs by a Walden inversion (Scheme 1).[9] The reaction products were attributed the *cis*-configuration, based on the reaction mechanism and clearly confirmed by the coupling constant of the vicinal hydrogens H-2 and H-3 of the aziridines **4** of 6.4–7.2 Hz.[10]

In order to establish the enantiomeric purity of the aziridines **4**, an NMR technique employing a chiral solvating agent (CSA) **5** was utilized. Chiral aryltrifluoromethyl carbinols are known to be most useful in NMR analyses, which induce a spectral nonequivalence in lactones, amines and alcohols, probably due to the fact that both the hydroxyl and carbinyl hydrogens of **5** are capable of giving bonding interactions with basic sites.[10–13]

It was found that (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol **5** has the ability to induce a spectral nonequivalence in the racemic mixture of *cis*-aziridines **4a** and **9a** in deuterated chloroform. In the present case of aziridines,

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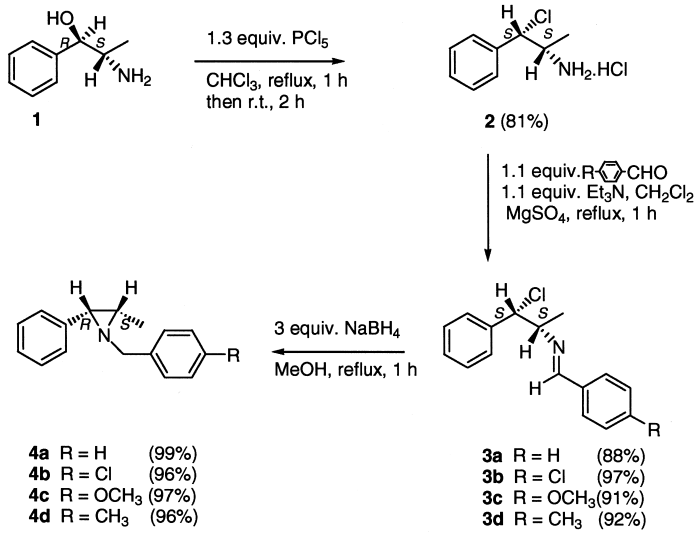

Scheme 1.

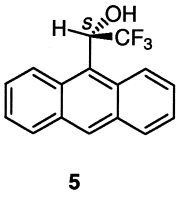

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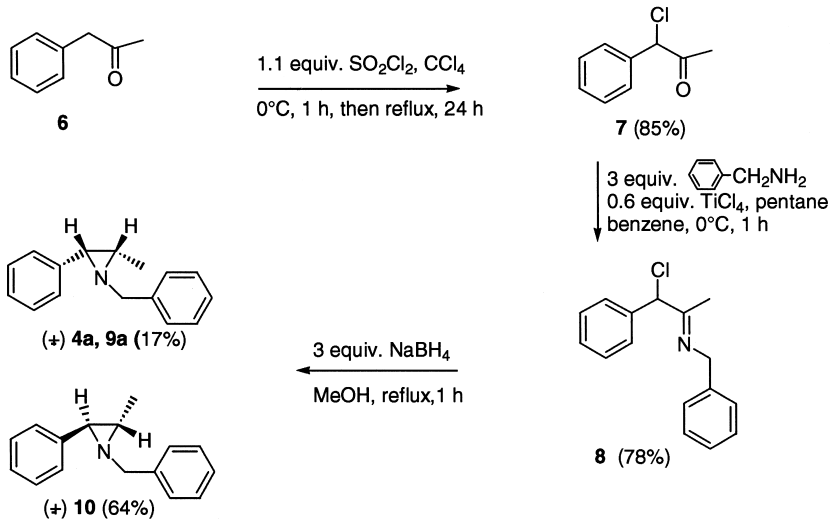
Figure 1.

the interaction of **5** induced a nonequivalence in the magnetic environment, probably by the bonding interaction between the hydroxyl and the carbinyl hydrogens of CSA **5** with the aziridine nitrogen atom and the aromatic ring of the aziridine, respectively. In addition, π-stacking of the aromatic nucleus of **5** with the *N*-benzyl group will also play a role (see Fig. 1).

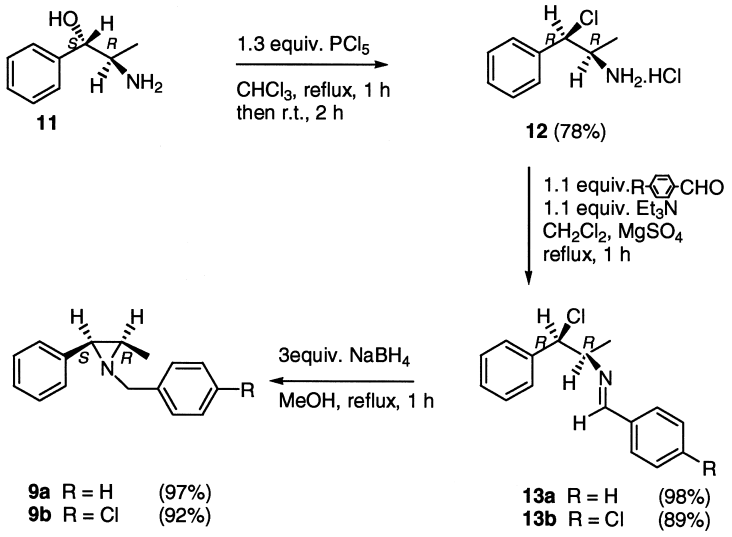
The racemic 1-benzyl-2-methyl-3-phenylaziridine (composed of **4a** and **9a**) was synthesized by α-chlorination of 1-phenyl-2-propanone **6** with sulfuryl chloride in carbon tetrachloride, followed by imination of α-chloroketone **7** with benzylamine in benzene in the presence of titanium-(IV) chloride. Sodium borohydride reduction of α-chloroketimine **8** in methanol under reflux afforded a mixture of the racemic *cis*-aziridine (composed of **4a** and **9a**) (17%) and the racemic *trans*-aziridine **10** (64%).[14]

The 1:1 mixture of the enantiomers **4a** and **9a** showed a good separation in many of the corresponding signals for the two components in the ^{1}H NMR spectrum (270 MHz; $CDCl_3$) on addition of 30 mol% of the chiral aryltrifluoromethylcarbinol **5**. In these spectra, two well-resolved signals for each methyl group at C-2 and two different signals for the proton at C-4 of the two enantiomers were observed, allowing discrimination of the *cis*-aziridine enantiomers.

Application of the same protocol with the chiral (*S*)-aryltrifluoromethylcarbinol **5** to the (−)-*cis*-aziridine **4a**, obtained according to the procedure outlined in Scheme 1, showed no signals resulting from the enantiomer **9a**. To ascertain that



Scheme 2.



Scheme 3.

this aziridine **4a** is enantiomerically pure, the ^{1}H NMR spectrum of the mixture of compound **4a**, the racemic mixture of *cis*-aziridines **4a** and **9a** and the chiral solvating agent **5** (molar ratio 1:1:0.3) was recorded. In this case, there is a clear visible separation of the signals of both the enantiomers in a 3:1 ratio. These experiments established unambiguously that *cis*-aziridine **4a** was optically pure (e.e. >98%) within the limits of the NMR technique.

Similar NMR experiments on the determination of the enantiomeric excess were also carried out with the chiral aziridines **4b**–**d**. It was confirmed as well that these aziridine **4b**–**d** were enantiomerically pure (e.e. >98%) (Scheme 2).

The opposite enantiomers of the former aziridines **9a**,**b** were synthesized from (1*S*,2*R*)-(+)-norephedrine **11** in good yield (Scheme 3). After conversion of (1*S*,2*R*)-(+)-norephedrine **11** into (1*R*,2*R*)-(−)-1-chloro-1-phenyl-2-propylamine hydrochloride **12**, the latter was reacted with benzaldehyde or 4-chlorobenzaldehyde in dichloromethane in the presence of triethylamine and magnesium sulfate to afford the chiral imines **13a,b** in 89–98% yield. Reduction of these *N*-(β-chloroaryl)imines **13a,b** with sodium borohydride in methanol under reflux gave (2*R*,3*S*)-1-benzyl-2-methyl-3-phenylaziridines **9a,b** in 92–97% yield. Also in this case, the enantiomeric purity of aziridines **9a** and **9b** was determined by the above NMR technique utilizing the chiral solvating agent **5**. By this way it was shown that also (+)-*cis*-aziridines **9a** and **9b** were enantiomerically pure (e.e. >98%).

In conclusion, the chiral 1,2,3-trisubstituted aziridines (−)-**4a**–**d** and (+)-**9a**–**b** were synthesized conveniently in high yield and high enantiomeric excess (>98%) from (1*R*,2*S*)-(−)-norephedrine **1** and (1*S*,2*R*)-(+)-norephedrine **11** via the corresponding *N*-(arylidene)-β-chloroamines.

Pirkle alcohol **5** was used as the chiral solvating agent for the rapid and convenient determination of the enantiomeric composition of 1,2,3-trisubstituted aziridines.

Experimental

Melting points were determined on a Buchi 535 apparatus. ^{1}H NMR spectra (270 MHz) and ^{13}C NMR (67 MHz) were recorded with a Jeol JNM-EX 270 NMR spectrometer. IR spectra were measured with a Perkin Elmer model 983 spectrophotometer. Mass spectra were recorded with a Varian-MAT 112 mass spectrometer (70 eV). Optical rotations were determined with a AA-10 automatic polarimeter.

(1*S*,2*S*)-(+)-1-Chloro-1-phenyl-2-propylamine hydrochloride 2 and (1*R*,2*R*)-(−)-1-chloro-1-phenyl-2-propylamine hydrochloride 12.[9] To a solution of 1.0 g (6.6 mmol) of (1*R*,2*S*)-(−)-norephedrine **1** or (1*S*,2*R*)-(−)-norephedrine **11** in 20 ml of dry chloroform was added 8.6 mmol of PCl_5. The mixture was stirred and refluxed for 1 h, after which the reaction mixture was kept at room temperature for 2 h. The excess of PCl_5 was decomposed cautiously with 5 ml of methanol. Finally, the solvent was removed in vacuo and the reaction mixture was stirred with 30 ml of dry diethyl ether. The white crystalline hydrochloride was separated by filtration. The crude product was recrystallized from a mixture of methanol and ether (1/5) to give the pure compound **2** or **12**, respectively.

(1*S*,2*S*)-(+)-1-Chloro-1-phenyl-2-propylamine hydrochloride 2. Compound **2** was obtained from (1*R*,2*S*)-(−)-norephedrine **1** as white crystals in 81% yield. mp 178–179°C (MeOH); $[\alpha]_D^{22}$=+81 (*c*=0.5; MeOH) [Lit[9] mp 167°C, Lit[15] mp 198–203°C; [α]=+76 (*c*=6; EtOH)]. ^{1}H NMR (D_2O): 1.21 (3H, d, *J*=6.7 Hz, CH_3), 3.96–4.04 (1H, m, H-2), 5.13 (1H, d, *J*=9.7 Hz, H-1), 7.47–7.56 (5H, m, C_6H_5); ^{13}C NMR: 16.9 (CH_3), 54.4 (C-2), 65.1 (C-1), 128.6 (C-3′ and C-5′), 130.3 (C-2′ and C-6′), 130.7 (C-4′), 137.8 (C-1′); IR (KBr): 3440 (NH_3^+), 1599, 1575, 1492, 1450, 1194, 1146, 1005, 712 cm^{-1}.

(1*R*,2*R*)-(−)-1-Chloro-1-phenyl-2-propylamine hydrochloride 12. Compound **12** was obtained from (1*S*,2*R*)-(+)-norephedrine **11** as white crystals in 78% yield. Mp 168–170°C (MeOH); $[\alpha]_D^{22}$=−91 (*c*=0.93; MeOH). ^{1}H

NMR (D_2O): 1.21 (3H, d, J=6.7 Hz, CH_3), 3.96–4.04 (1H, m, H-2), 5.13 (1H, d, J=9.7 Hz, H-1), 7.48–7.56 (5H, m, C_6H_5); ^{13}C NMR: 16.9 (CH_3), 54.4 (C-2), 65.1 (C-1), 128.7 (C-3′ and C-5′), 130.3 (C-2′ and C-6′), 130.7 (C-4′), 137.8 (C-1′); IR (KBr): 3430 (NH_3^+), 1599, 1575, 1494, 1450, 1390, 1244, 1195, 1147, 1030, 1006, 987, 837, 698 cm^{-1}.

(1*S*,2*S*)-(+)-(*E*)-*N*-(Benzylidene)-1-chloro-1-phenyl-2-propylamine 3 and 13. A solution of 333 mg (1.624 mmol) of 1-chloro-1-phenyl-2-propylamine hydrochloride **2** or **12**, 188 mg (1.78 mmol) of benzaldehyde, 179 mg (1.78 mmol) of triethylamine and 303 mg (2.528 mmol) of $MgSO_4$ in 15 ml of dichloromethane was refluxed for 1 h. The reaction mixture was filtered and then evaporated in vacuo. The reaction product was dissolved in 10 ml of dry diethyl ether and filtered, then washed with $NaHCO_3$ (5N), water and dried (K_2CO_3). The filtered solution was evaporated in vacuo to afford the crude product.

(1*S*,2*S*)-(+)-(*E*)-*N*-(Benzylidene)-1-chloro-1-phenyl-2-propylamine 3a. This compound was synthesized from (1*S*,2*S*)-1-chloro-1-phenyl-2-propylamine hydrochloride **2**, as described above, to give compound **3a** in 88% yield. The crude product was recrystallized from hexane. Mp 85–87°C (hexane); $[\alpha]_D^{22}$=+225 (c=0.32; MeOH). ^1H NMR ($CDCl_3$): 1.08 (3H, d, J=6.6 Hz, CH_3), 3.74–3.80 (1H, m, H-2), 4.95 (1H, d, J=8.5 Hz, H-1), 7.30–7.42 (8 H, m, =CH), 7.77–7.80 (2H, m, =CH), 8.34 (1H, s, CH=N); ^{13}C NMR ($CDCl_3$): 20.2 (CH_3), 67.9 (C-2), 72.3 (C-1), 127.9 (2× =CH), 128.3 (2× =CH), 128.5 (4× =CH), 129.5 (=Cquat), 130.7 (=Cquat), 135.9 (=CH), 139.4 (=CH), 161.4 (C=N); IR (KBr): 1643 (C=N), 1445, 1366, 1121, 1069, 970, 757, 718 cm^{-1}; MS m/z: no M^+, 133 (11), 132 (100, $MeCH{=}N^+{=}CH{-}C_6H_5$). Anal. $C_{16}H_{16}ClN$, Calcd C 74.55%, H 6.26%, N 5.43%; Found C 74.72%, H 6.35%, N 5.29%.

(1*S*,2*S*)-(+)-(*E*)-1-Chloro-*N*-(4-chlorobenzylidene)-1-phenyl-2-propylamine 3b. The synthesis of compound **3b** (97% yield) was carried out according to the general procedure given above. The crude product was crystallized from hexane to give white crystals. Mp 88–90°C (hexane); $[\alpha]_D^{20}$=+189.8 (c=0.59; MeOH). ^1H NMR ($CDCl_3$): 1.07 (3H, d, J=6.7 Hz, CH_3), 3.72–3.77 (1H, m, H-2), 4.93 (1H, d, J=8.6 Hz, H-1), 7.29 (2H, d, J=8.0 Hz, =CH, A_2B_2 system), 7.30–7.43 (5H, m, =CH), 7.68 (2H, d, J=8.0 Hz, =CH, A_2B_2 system), 8.26 (1H, s, CH=N); ^{13}C NMR ($CDCl_3$): 20.2 (CH_3), 67.8 (C-2), 72.3 (C-1), 127.2 (2× =CH), 128.5 (=CH), 128.5 (2× =CH), 128.7 (2× =CH), 129.5 (2× =CH), 134.4 (=Cquat), 136.7 (=Cquat), 139.2 (=Cquat), 160.0 (C=N); IR (KBr): 1640 (C=N), 1590, 1485, 1380, 837, 826, 723 cm^{-1}; MS m/z: no M^+, 256/258 (1, M^+-Cl), 166/168 (100, $MeCH{=}N^+{=}CH{-}C_6H_4Cl$). Anal. $C_{16}H_{15}Cl_2N$, calcd C 65.77%, H 5.17%, N 4.79%; Found C 65.61%, H 5.30%, N 4.66%.

(1*S*,2*S*)-(+)-(*E*)-1-Chloro-*N*-(4-methoxybenzylidene)-1-phenyl-2-propylamine 3c. The synthesis of compound **3c** was carried out according to the general procedure to afford the crude product, which was crystallized from hexane to give white crystals in 91% yield. Mp 78–80°C (hexane); $[\alpha]_D^{20}$=+236 (c=1.31; MeOH); ^1H NMR ($CDCl_3$): 1.08 (3H, d, J=6.6 Hz, CH_3), 3.73–3.77 (1H, m, H-2), 3.85 (3H, s, OCH_3), 4.94 (1H, d, J=8.4 Hz, H-1), 6.94 (2H, d, J=8.4 Hz, =CH, A_2B_2 system), 7.30–7.40 (5H, m, =CH), 7.73 (2H, d, J=8.4 Hz, =CH, A_2B_2 system), 8.28 (1H, s, CH=N); ^{13}C NMR ($CDCl_3$): 20.2 (CH_3), 55.2 (OCH_3), 68.1 (C-2), 72.2 (C-1), 113.9 (2× =CH), 127.9 (2× =CH), 128.3 (=CH), 128.4 (2× =CH), 128.9 (=Cquat), 129.8 (2× =CH), 139.5 (=Cquat), 160.7 (C=N), 161.8 (=Cquat); IR (KBr): 1639 (C=N), 1604, 1574, 1449, 1250, 1168, 1029, 831, 819, 706 cm^{-1}; MS m/z: no M^+, 252 (1, M^+-Cl), 163 (16), 162 (100, $MeCH{=}N^+{=}CH{-}C_6H_4OCH_3$), 135 (19). Anal. $C_{17}H_{18}ClNO$, calcd C 70.95%, H 6.30%, N 4.87%; Found C 70.86%, H 6.15%, N 5.09%.

(1*S*,2*S*)-(+)-(*E*)-1-Chloro-*N*-(4-methylbenzylidene)-1-phenyl-2-propylamine 3d. The synthesis of compound **3d** was carried out according to the general procedure to afford the crude product. This product was crystallized from hexane to give white crystals in 92% yield. Mp 104–105°C (hexane); $[\alpha]_D^{20}$=+252 (c=0.75; MeOH); ^1H NMR ($CDCl_3$): 1.09 (3H, d, J=6.2 Hz, CH_3), 2.40 (3H, s, Ar–CH_3), 3.73–3.79 (1H, m, H-2), 4.95 (1H, d, J=8.6 Hz, H-1), 7.23 (2H, d, J=7.8 Hz, =CH, A_2B_2 system), 7.31–7.39 (5H, m, =CH), 7.68 (2H, d, J=7.8 Hz, =CH, A_2B_2 system), 8.32 (1H, s, CH=N); ^{13}C NMR ($CDCl_3$): 20.2 (CH_3), 21.4 (Ar–CH_3), 68.0 (C-2), 72.3 (C-1), 127.9 (2× =CH), 128.3 (3× =CH), 129.5 (2× =CH), 129.2 (2× =CH), 133.4 (=Cquat), 139.5 (=Cquat), 140.9 (=Cquat), 161.3 (C=N); IR (KBr): 1639 (C=N), 1607, 1449, 1381, 1106, 975, 838, 818, 778, 723, 698 cm^{-1}; MS m/z: no M^+, 236 (1, M^+-Cl), 146 (22, $MeCH{=}N^+{=}CH{-}C_6H_4Me$), 132 (100). Anal. $C_{17}H_{18}ClN$, calcd C 75.13%, H 6.68%, N 5.15%; Found C 75.24%, H 6.80%, N 5.01%.

(1*R*,2*R*)-(+)-(*E*)-*N*-(Benzylidene)-1-chloro-1-phenyl-2-propylamine 13a. The synthesis of compound **13a** was carried out according to the general procedure to afford the crude product. This product was crystallized from hexane to give white crystals in 98% yield. Mp 79–81°C (hexane); $[\alpha]_D^{22}$=−246 (c=0.86; MeOH); ^1H NMR ($CDCl_3$): 1.08 (3H, d, J=6.6 Hz, CH_3), 3.74–3.80 (1H, m, H-2), 4.96 (1H, d, J=8.5 Hz, H-1), 7.30–7.42 (8 H, m, =CH), 7.77–7.80 (2H, m, =CH), 8.33 (1H, s, CH=N); ^{13}C NMR ($CDCl_3$): 20.2 (CH_3), 67.9 (C-2), 72.4 (C-1), 128.0 (2× =CH), 128.4 (2× =CH), 128.5 (2× =CH), 128.6 (2× =CH), 129.6 (=Cquat), 130.8 (=Cquat), 136.0 (=CH), 139.5 (=CH), 161.5 (C=N); IR (KBr): 1640 (C=N), 1449, 1371, 1088, 1013, 825, 723 cm^{-1}; MS m/z: no M^+, 222 (1, M^+-Cl), 133 (10), 132 (100, $MeCH{=}N^+{=}CH{-}C_6H_5$). Anal. $C_{16}H_{16}ClN$, calcd C 74.55%, H 6.26%, N 5.43%; Found C 74.41%, H 6.34%, N 5.35%.

(1*R*,2*R*)-(+)-(*E*)-1-Chloro-*N*-(4-chlorobenzylidene)-1-phenyl-2-propylamine 13b. The synthesis of compound **13b** was carried out according to the general procedure to afford the crude product. This product was crystallized from hexane to give white crystals in 89% yield. Mp 96–98°C (hexane); $[\alpha]_D^{22}$=−250 (c=0.54; MeOH); ^1H NMR ($CDCl_3$): 1.07 (3H, d, J=6.7 Hz, CH_3), 3.72–3.77 (1H, m, H-2), 4.93 (1H, d, J=8.6 Hz, H-1), 7.29 (2H, d, J=8.0 Hz, =CH, A_2B_2 system), 7.30–7.43 (5H, m, =CH), 7.69 (2H,

d, J=8.0 Hz, =CH, A_2B_2 system), 8.27 (1H, s, CH=N); ^{13}C NMR ($CDCl_3$): 20.2 (CH_3), 67.9 (C-2), 72.3 (C-1), 127.2 (2× =CH), 128.4 (=CH), 128.5 (2× =CH), 128.8 (2× =CH), 129.5 (2× =CH), 134.4 (=Cquat), 136.7 (=Cquat), 139.3 (=Cquat), 160.10 (C=N); IR (KBr): 1640 (C=N), 1590, 1482, 1379, 1088, 1013, 974, 825, 723, 725 cm^{-1}; MS *m/z*: 291/293/295 (M^+, 1), 261 (3), 221 (7), 168 (26), 166 (100). Anal. $C_{16}H_{15}Cl_2N$, calcd C 65.77%, H 5.17%, N 4.79%; Found C 65.87%, H 5.30%, N 4.63%.

Chiral 1,2,3-trisubstituted aziridines 4 and 9. To a solution of 330 mg (1.28 mmol) of benzaldimine **3** or **13** in 20 ml of absolute methanol was added 145 mg (3.85 mmol) of sodium borohydride. The reaction mixture was refluxed for 1 h, then MeOH was evaporated in vacuo. The residue was treated with water, then extracted with CH_2Cl_2. The combined extracts were washed with water, dried (K_2CO_3) and evaporated in vacuo to give the crude product, which was purified by flash chromatography on silica gel column with ethyl acetate/hexane (10/90) to afford the pure aziridines **4** and **9**.

(2*S*,3*R*)-(−)-1-Benzyl-2-methyl-3-phenylaziridine 4a. The synthesis of aziridine **4a** was carried out according to the general procedure to give the pure aziridine **4a** in 99% yield. $[\alpha]_D^{22}$=−60 (c=0.9; MeOH); ^{1}H NMR ($CDCl_3$): 0.95 (3H, d, J=5.7 Hz, CH_3), 1.80–1.85 (1H, m, H-2), 2.59 (1H, d, J=6.9 Hz, H-3), 3.50 (1H, d, J=13.8 Hz, H-4), 3.70 (1H, d, J=13.8 Hz, H-4), 7.15–7.37 (10H, m, =CH); ^{13}C NMR ($CDCl_3$): 12.8 (CH_3), 41.8 (C-2), 46.3 (C-3), 64.5 (C-4), 126.4 (=CH), 126.7 (=CH), 127.7 (2× =CH), 127.8 (4× =CH), 128.3 (2× =CH), 137.5 (=Cquat), 139.4 (=Cquat); IR (NaCl): 1599, 1491, 1374, 1119, 732, 698 cm^{-1}; MS *m/z*: 223 (M^+, 2), 222 (1), 133 (10), 132 (100). Anal. $C_{16}H_{17}N$, calcd C 86.05%, H 7.67%, N 6.27%; Found C 85.94%, H 7.80%, N 6.23%.

(2*S*,3*R*)-(−)-1-(4-Chlorobenzyl)-2-methyl-3-phenylaziridine 4b. The synthesis of aziridine **4b** was carried out according to the general procedure to give the pure aziridine **4b** in 96% yield. $[\alpha]_D^{20}$=−76 (c=0.54; MeOH); ^{1}H NMR ($CDCl_3$): 0.94 (3H, d, J=5.7 Hz, CH_3), 1.84–1.89 (1H, m, H-2), 2.61 (1H, d, J=6.5 Hz, H-3), 3.47 (1H, d, J=14.0 Hz, H-4), 3.69 (1H, d, J=14.0 Hz, H-4), 7.23–7.35 (9H, m, =CH); ^{13}C NMR ($CDCl_3$), 12.7 (CH_3), 41.8 (C-2); 46.3 (C3), 63.6 (C-4); 126.5 (=CH), 126.7 (2× =CH), 127.8 (2× =CH), 128.3 (2× =CH), 128.9 (2× =CH), 132.4 (=Cquat), 137.2 (=Cquat), 137.9 (=Cquat); IR (NaCl): 1601, 1486, 1347, 1121, 733, 699 cm^{-1}; MS *m/z*: 257/259 (M^+, 1), 133 (10), 132 (100). Anal. $C_{16}H_{16}ClN$, calcd C 74.55%, H 6.26%, N 5.43%; Found C 74.63%, H 6.14%, N 5.37%.

(2*S*,3*R*)-(−)-2-Methyl-1-(4-methoxybenzyl)-3-phenylaziridine 4c. The synthesis of aziridine **4c** was carried out according to the general procedure to give the pure aziridine **4c** in 97% yield. $[\alpha]_D^{20}$=−91 (c=0.99; MeOH); ^{1}H NMR ($CDCl_3$): 0.94 (3H, d, J=5.7 Hz, CH_3), 1.87–1.91 (1H, m, H-2), 2.63 (1H, d, J=6.7 Hz, H-3), 3.45 (1H, d, J=13.5 Hz, H-4), 3.72 (1H, d, J=13.5 Hz, H-4), 3.75 (3H, s, OCH_3), 6.84 (2H, d, J=8.9 Hz, =CH, A_2B_2 system), 7.20–7.28 (5H, m, C_6H_5), 7.3 (2 H, d, J=8.9 Hz, =CH, A_2B_2 system, overl.); ^{13}C NMR ($CDCl_3$): 12.8 (CH_3), 41.6 (C-2), 46.1 (C-3), 55.0 (OCH_3), 63.8 (C-4), 113.6 (2× =CH), 126.3 (=CH), 127.7 (2× =CH), 127.8 (2× =CH), 128.8 (2× =CH), 131.5 (=Cquat), 137.5 (=Cquat), 158.5 (=Cquat); IR (NaCl): 1608, 1508, 1245, 1035, 739 cm^{-1}; MS *m/z*: 253 (M^+, 1), 133 (11), 132 (100), 121 (19), 105 (27), 86 (19), 84 (31), 49 (63). Anal. $C_{17}H_{19}NO$, calcd C 80.60%, H 7.56%, N 5.53%; Found C 80.69%, H 7.50%, N 5.39%.

(2*S*,3*R*)-(−)-2-Methyl-1-(4-methylbenzyl)-3-phenylaziridine 4d. The synthesis of aziridine **4d** was carried out according to the general procedure to give the pure aziridine **4d** in 96% yield. $[\alpha]_D^{20}$=−89 (c=1.27; MeOH); ^{1}H NMR ($CDCl_3$): 0.95 (3H, d, J=5.7 Hz, CH_3), 1.88–1.93 (1H, m, H-2), 2.32 (3H, s, Ar–CH_3), 2.65 (1H, d, J=6.5 Hz, H-3), 3.51 (1H, d, J=13.8 Hz, H-4), 3.75 (1H, d, J=13.8 Hz, H-4), 7.22–7.32 (9H, m, =CH); ^{13}C NMR ($CDCl_3$): 12.8 (CH_3), 21.0 (Ar–CH_3), 41.7 (C-2), 46.1 (C-3), 64.2 (C-4), 126.3 (=CH), 127.7 (3× =CH), 127.8 (3× =CH), 128.9 (2× =CH), 136.3 (2× =Cquat), 137.5 (=Cquat); IR (NaCl): 1601, 1448, 1346, 1117, 795 cm^{-1}; MS *m/z*: 237 (M^+, 2), 133 (10), 132 (100). Anal. $C_{17}H_{19}N$, calcd C 86.03%, H 8.07%, N 5.90%; Found C 86.19%, H 8.15%, N 5.78%.

(2*R*,3*S*)-(+)-1-Benzyl-2-methyl-3-phenylaziridine 9a. The synthesis of aziridine **9a** was carried out according to the general procedure to give the pure aziridine **9a** in 97% yield. $[\alpha]_D^{22}$=+116 (c=1.2; MeOH); ^{1}H NMR ($CDCl_3$): 0.95 (3H, d, J=5.7 Hz, CH_3), 1.80–1.85 (1H, m, H-2), 2.59 (1H, d, J=6.9 Hz, H-3), 3.50 (1H, d, J=13.8 Hz, H-4), 3.69 (1H, d, J=13.8 Hz, H-4), 7.15–7.37 (10H, m, =CH); ^{13}C NMR ($CDCl_3$): 12.8 (CH_3), 41.7 (C-2), 46.2 (C-3), 64.4 (C-4), 126.4 (=CH), 127.7 (=CH), 127.6 (2× =CH), 127.8 (4× =CH), 128.2 (2× =CH), 137.4 (=Cquat), 139.4 (=Cquat); IR (NaCl): 1601, 1492, 1449, 1348, 1027, 733, 698 cm^{-1}; MS *m/z*: 223 (M^+, 2), 133 (12), 132 (100), 99 (23), 91 (17).

(2*R*,3*S*)-(+)-1-(4-Chlorobenzyl)-2-methyl-3-phenylaziridine 9b. The synthesis of aziridine **9b** was carried out according to the general procedure to give the pure aziridine **9b** in 92% yield. $[\alpha]_D^{22}$=+92.8 (c=0.98; MeOH); ^{1}H NMR ($CDCl_3$): 0.94 (3H, d, J=5.7 Hz, CH_3), 1.84–1.89 (1H, m, H-2), 2.61 (1H, d, J=6.5 Hz, H-3), 3.47 (1H, d, J=14.0 Hz, H-4), 3.69 (1H, d, J=14.0 Hz, H-4), 7.23–7.35 (10H, m, =CH); ^{13}C NMR ($CDCl_3$): 12.8 (CH_3), 41.9 (C-2), 46.4 (C-3), 63.8 (C-4), 126.5 (=CH), 127.8 (2× =CH), 127.9 (2× =CH), 128.4 (2× =CH), 129.1 (2× =CH), 132.5 (=Cquat), 137.2 (=Cquat), 137.9 (=Cquat); IR (NaCl): 1601, 1487, 1404, 1088, 1014, 813, 738, 700 cm^{-1}; MS *m/z*: 257/259 (M^+, 1), 179 (1), 164 (1), 133 (9), 132 (100).

1-Chloro-1-phenyl-2-propanone 7. To solution of 10.0 g (7.46 mmol) of ketone **6** in 20 ml of carbon tetrachloride was added 11.0 g (8.2 mmol) of sulfuryl chloride over a period of 1 h at 0°C, after which the reaction mixture was refluxed for 24 h. Then, the reaction mixture was poured in the same amount of cold water, and was extracted with dichloromethane. The extracts were washed with saturated $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was removed in vacuo to give a residue, which was distilled to give 10.68 g of pure α-chloroketone **7** in 85% yield; b.p.

120–121°C/12 mmHg; ^{1}H NMR ($CDCl_3$): 2.2 (3H, s, CH_3), 5.39 (1H, s, H-1), 7.25–7.43 (5H, m, =CH); ^{13}C NMR ($CDCl_3$): 25.6 (CH_3), 66.4 (C-1), 127.7 (2× =CH), 128.9 (2× =CH), 129.0 (=CH), 134.9 (=Cquat), 199.7 (C=O); IR (NaCl): 1719 (C=O), 1597, 774, 697 cm^{-1}; MS *m/z*: 168/170 (M^+, 6), 132 (8), 125 (23), 89 (11), 43 (100).

***N*-(1-Chloro-1-phenyl-2-propylidene)benzylamine 8.** To a solution of 500 mg (2.97 mmol) of α-chloroketone **7** and 963 mg (9.0 mmol) of benzylamine in 20 ml of dry benzene was added dropwise a solution of 336 mg of $TiCl_4$ (1.78 mmol) in 10 ml of pentane at 0°C over a period of 15 min. The solution was stirred for 45 min at this temperature, then the mixture was poured in cold water. The reaction product was extracted with ether, the combined extracts were washed with $NaHCO_3$ (5N), water and dried (K_2CO_3) then evaporated under vacuum to give 590 mg of α-chloroketimine **8** in 78% yield (purity >95%). ^{1}H NMR ($CDCl_3$): 1.89 (3H, s, CH_3), 4.5 (2H, d, *J*=3.2 Hz, CH_2–Ar), 5.68 (1H, s, H-1), 7.36 (8H, m, =CH), 7.52 (2H, dd, *J*=8.1 Hz and *J*=2.1 Hz, =CH); ^{13}C NMR ($CDCl_3$): 13.4 (CH_3), 55.1 (CH_2–Ar), 68.5 (CH–Cl), 126.6 (=CH), 127.0 (2× =CH), 127.5 (2× =CH), 128.1 (=CH); 128.3 (2× =CH), 128.4 (2× =CH), 136.9 (=Cquat), 139.4 (=Cquat), 167.5 (C=N); IR (NaCl): 1654 (C=N), 1489, 1449, 733, 696 cm^{-1}; MS *m/z*: 257/259 (M^+, 1), 168 (8), 125 (23), 91 (33), 43 (100).

(±)-*cis*-1-Benzyl-2-methyl-3-phenylaziridine. To a solution of 257 mg (1 mmol) of compound **8** in 10 ml of methanol was added 113 mg (3 mmol) of sodium borohydride. The mixture was refluxed for 1 h, then MeOH was removed by evaporation in vacuo. The product was treated with cold water, then extracted with CH_2Cl_2, the combined extracts were washed with water, dried (K_2CO_3) and the solvent was evaporated in vacuo to give 210 mg of a mixture of *cis*- and *trans*-aziridines (**4a**, **9a**) and (**10**). The product was isolated by flash chromatography on a silica gel column with the solvent system hexane/ethyl acetate (1/9) to give 40 mg of (±)-*cis*-aziridine (17%) and 150 mg of (±)-*trans*-aziridine (64%).

(±)-*cis*-Aziridine 4a (9a). ^{1}H NMR ($CDCl_3$): 0.94 (3H, d, *J*=5.7 Hz, CH_3), 1.80–1.85 (1H, m, H-2), 2.59 (1H, d, *J*=6.8 Hz, H-3), 3.50 (1H, d, *J*=13.8 Hz, H-4), 3.70 (1H, d, *J*=13.8 Hz, H-4), 7.15–7.37 (10H, m, =CH); ^{13}C NMR ($CDCl_3$): 12.9 (CH_3), 41.9 (C-2), 46.3 (C-3), 64.6 (C-4), 126.4 (=CH), 126.8 (=CH), 127.8 (2× =CH), 127.8 (2× =CH), 127.9 (2× =CH), 128.3 (2× =CH), 137.5 (=Cquat), 139.4 (=Cquat); IR (NaCl): 1601, 1492, 1449, 1348, 1027, 733, 698 cm^{-1}; MS *m/z*: 223 (M^+, 2), 72 (10), 71 (100), 41 (20).

(±)-*trans*-Aziridine 10. ^{1}H NMR ($CDCl_3$): 1.40 (3H, d, *J*=5.6 Hz, CH_3), 1.18–2.30 (1H, m, H-2), 2.30 (1H, d, *J*=3.2 Hz, H-3), 3.78 (1H, d, *J*=14.5 Hz, H-4), 3.89 (1H, d, *J*=14.5 Hz, H-4), 7.21–7.44 (10 H, m, =CH); ^{13}C NMR ($CDCl_3$): 11.5 (CH_3), 42.9 (C-2), 48.5 (C-3), 55.4 (C-4), 126.0 (2× =CH), 126.6 (2× =CH), 126.6 (=CH), 127.6 (2× =CH), 128.2 (3× =CH), 130.2 (=CH), 140.1 (=Cquat), 140.7 (=Cquat); IR (NaCl): 1600, 1492, 1449, 1090, 730, 697 cm^{-1}; MS *m/z*: 223 (M^+, 2), 133 (10), 132 (100), 105 (28), 99 (23).

Measurement of the enantiomeric excess of aziridines 4 and 9. The measurement of the enantiomeric excess of aziridines **4a**–**d** and **9a**–**b** was performed by NMR utilizing the solvating agent **5** in $CDCl_3$. It was shown that aziridines **4a**–**b** and **9a**–**b** were enantiomeric pure (e.e. >98%). For this purpose, 0.03 mmol of aziridine **4** or **9** was dissolved in 0.5 ml of $CDCl_3$. To this solution was added 2.73 mg (0.0099 mmol) of Pirkle alcohol **5**. The ^{1}H NMR spectrum of this mixture was run in order to determine the e.e. A similar analysis was performed on racemic mixture **4a** and **9a**.

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