Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2093–2099

TETRAHEDRON: *ASYMMETRY*

Application of phosphorylated reagents derived from *N,N'*-di-[(*S*)-α-phenylethyl]-cyclohexane-1,2-diamines in the determination of the enantiomeric purity of chiral alcohols

Cecilia Anaya de Parrodi,[a,*] Gloria E. Moreno,[b] Leticia Quintero[b,*] and Eusebio Juaristi[c,*]

[a]*Departamento de Química y Biología, Universidad de las Américas-Puebla, Santa Catarina Mártir, Cholula, 72820 Puebla, México*

[b]*Centro de Investigación de la Facultad de Ciencias Químicas, Universidad Autónoma de Puebla, Puebla, 72570 Puebla, México*

[c]*Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, 07000 México D. F.*

Received 15 April 1998; accepted 21 May 1998

Abstract

The synthesis of two new *N*-[(*S*)-α-phenylethyl] substituted *P*-chloro-1,3-diazaphospholidines derived from C_2-symmetric *trans*-1,2-diaminocyclohexanes, and their application as chiral derivatizing agents in the determination of enantiomeric purities of chiral alcohols by means of ^{31}P NMR spectroscopy is described.

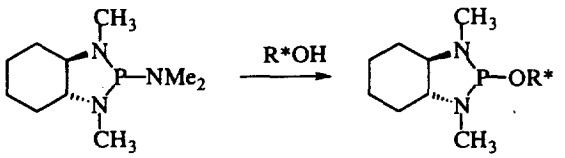
1. Introduction

trans-1,2-Diaminocyclohexane derivatives have been shown to be useful chiral reagents and ligands for catalysis, with applications in asymmetric synthesis.[1] By the same token, (*R*)- and (*S*)-α-phenylethylamine are simple, yet powerful stereodifferentiating auxiliaries in organic transformations.[2]

In view of the continuing need for the development of chiral derivatizing agents for the determination of enantiomeric purities,[3] and with consideration of the high sensitivity provided by ^{31}P NMR spectroscopic methods in this endeavour,[4] we were attracted by the report of Alexakis and coworkers,[5] who presented convincing evidence for diazaphospholidine **A**, prepared from (*R,R*)-*N,N'*-dimethylcyclohexane-1,2-diamine and hexamethylphosphorous triamide, as an excellent reagent for the determination of the enantiomeric excess of chiral alcohols.[6] (Eq. 1).

* Corresponding authors. E-mail: anaya@mail.pue.udlap.mx, lquintero@siu.cen.buap.mx and juaristi@chem.cinvestav.mx

0957-4166/98/$19.00
PII: S0957-4166(98)00219-5



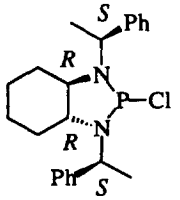
A

diastereoisomeric phosphonamides

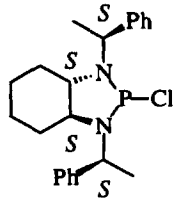
(1)

Among the most useful characteristics of reagent **A** are its very rapid reaction with most alcohols, and the substantial differences in ^{31}P NMR chemical shifts ($\Delta\delta$) exhibited by the resulting diastereoisomeric phosphonamides.[5]

The present paper describes the preparation and examination of the related *P*-chloro-1,3-diazaphospholidines (1*R*,2*R*,1′*S*,1″*S*)-**1** and (1*S*,2*S*,1′*S*,1″*S*)-**1** as chiral derivatizing agents in the determination of enantiomeric purity. It was anticipated that the presence of the α-phenylethyl substituents in these reagents could lead to even larger ($\Delta\delta$) values in the ^{31}P NMR spectra of the derived phosphonamides.



(1*R*,2*R*,1′*S*,1″*S*)-**1**



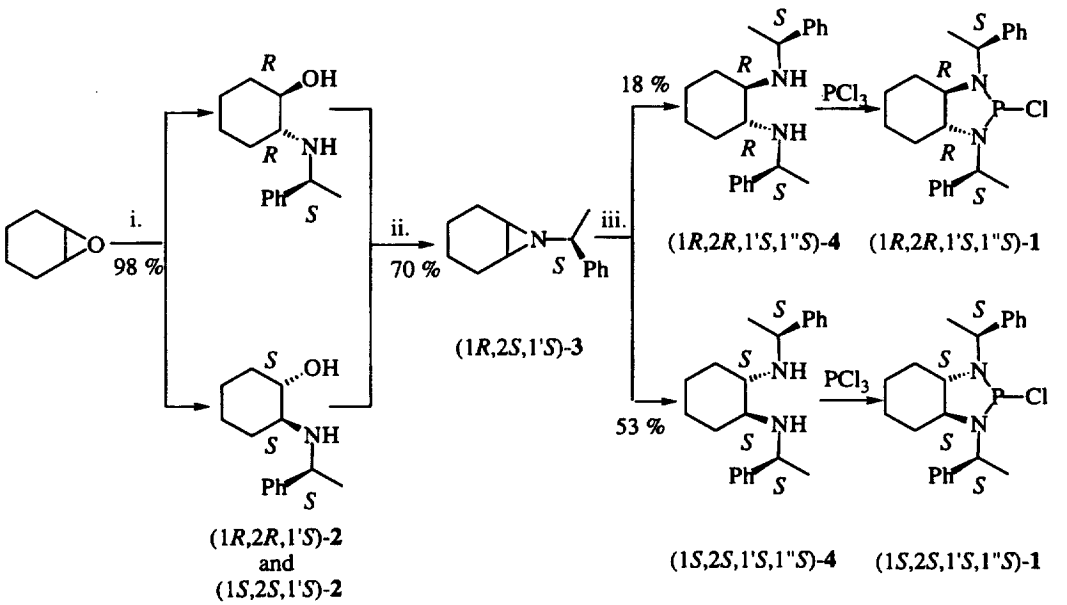
(1*S*,2*S*,1′*S*,1″*S*)-**1**

2. Results and discussion

The preparation of diastereoisomeric diazaphospholidines **1** was accomplished according to the synthetic route outlined in Scheme 1. (1*R*,2*R*,1′*S*)- and (1*S*,2*S*,1′*S*)-2-[*N*-(α-Phenylethyl)-amino]cyclohexanols **2** were prepared by aminolysis of cyclohexene oxide according to the literature procedure.[7,8] The resulting diastereoisomeric mixture of (1*R*,2*R*,1′*S*)- and (1*S*,2*S*,1′*S*)-**2** was mesylated according to standard procedures,[9] to furnish the expected *N*-[(*S*)-α-phenylethyl]cyclohexene aziridine (1*R*,2*S*,1′*S*)-**3** as generated via spontaneous intramolecular mesylate displacement.[10] *trans*-Cyclohexane-1,2-diamines (1*R*,2*R*,1′*S*,1″*S*)- and (1*S*,2*S*,1′*S*,1″*S*)-**4** were then prepared via the opening of aziridine **3** with (*S*)-α-phenylethylamine,[11] catalyzed with lithium perchlorate.[12,13] The separation of diastereomeric diamines **4** was accomplished by fractional crystallization, and assignment of the absolute configuration at the cyclohexane stereogenic centers was possible from an X-ray diffraction analysis carried out on the (1*S*,2*S*,1′*S*,1″*S*)-isomer.[14]

Once separated, (1*R*,2*R*,1′*S*,1″*S*)-**1** and (1*S*,2*S*,1′*S*,1″*S*)-**1** were examined as chiral derivatizing agents via their corresponding *P*-chloro-1,3-diazaphospholidines, which were formed directly in the NMR tube employed for ^{31}P NMR analysis. To this end, 1,2-diamine **4** in $CDCl_3$ solvent (lock signal) was treated with one equivalent of PCl_3 in CH_2Cl_2 to give the required phospholidine **1**. The exocyclic *P*–Cl bond is readily cleaved,[5] so derivatization is carried out by addition of 0.8 equivalents of the racemic alcohol to afford phosphonamides **5**, whose ^{31}P NMR spectra were then recorded (Tables 1 and 2).

The NMR spectroscopic observations summarized in Tables 1 and 2 reveal the effectiveness of chlorophospholidines **1** for the determination of enantiomeric ratios in mixtures of chiral alcohols. Indeed, with one exception (entry 2 in Table 1) the diastereomeric pair of derivatives **5** was always



Conditions: (i) (*S*)-α-Phenylethylamine/$LiClO_4$/CH_3CN, reflux, 18 h. (ii) MsCl, Et_3N/CH_2Cl_2, 24 h, 0°C → r.t., 12 h. (iii) 1. (*S*)-α-Phenylethylamine/$LiClO_4$/CH_3CN, reflux, 30 h. 2. HCl/ether, fractional crystallization. 3. NaOH/CH_2Cl_2.

Scheme 1.

observed, and integration of the signals corresponded to the expected 50:50±2% ratio; i.e., no kinetic resolution takes place.

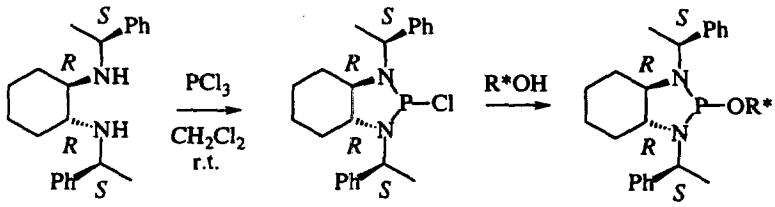
P-Alkoxy-1,3-diazaphosphonamides **5**, in particular those derived from the all-(*S*)-isomer (Table 2), generally gave larger values of the difference of chemical shifts (Δδ) than those observed with the *N*-methyl analogues developed by Alexakis and coworkers.[5] For example, with 2-butanol (entries 1 in Tables 1 and 2) diastereomeric phosphonamides derived from **A** (Eq. 1) gave Δδ=0.27 ppm, while the corresponding Δδ values in diastereomeric **5** are 0.38 and 1.07 ppm. Furthermore, the largest value of the difference of chemical shift (Δδ 3.7 ppm) obtained with **A**,[5] can be compared with the largest value obtained with (1*S*,2*S*,1′*S*,1″*S*)-**1**, Δδ 6.34 ppm (entry 5, Table 2).

In our hands, ^1H and ^{13}C NMR spectra of diastereomeric phosphonamides **5** were not useful for the determination of the isomeric composition, owing to insufficient differences in chemical shifts with these nuclei (^1H and ^{13}C). In this regard, the half-height line width of ^{31}P signals in the NMR spectra of **5** is 26.5±0.5 Hz.

Diastereomeric phosphonamides **5** can be detected by TLC (eluent: petroleum ether:EtOAc=95:5) but have not been isolated and purified. Treatment with sulfur powder affords the corresponding thiophosphonamides, which are known to be stable derivatives.[5]

In summary, reagents **1** incorporating *N*-(α-phenylethyl) substituents, are convenient chiral derivatizing agents for the determination of the enantiomeric purity of chiral alcohols. The quantitative and fast *P*–Cl bond cleavage upon alcoholysis allows phosphonamide formation directly in the NMR tube prior to measurement. Very large differences in the ^{31}P NMR chemical shifts (Δδ) for the diastereoisomeric phosphonamides were observed, allowing accurate integration and quantitative determination of the diastereoisomeric ratios.

Table 1
Evaluation of chiral derivatizing agent (1*R*,2*R*,1′*S*,1″*S*)-**1** with various chiral alcohols



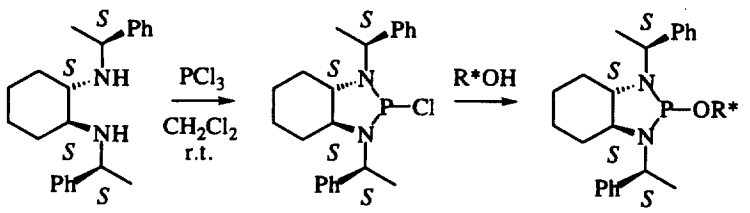
(1*R*,2*R*,1′*S*,1″*S*)-**4** (1*R*,2*R*,1′*S*,1″*S*)-**1** (1*R*,2*R*,1′*S*,1″*S*)-**5**

entry	alcohol	δ(ppm) ^{31}P of diastereoisomeric **5**	Δδ	lit.[5a] Δδ
1	2-butanol	131.56 and 131.18	0.38	0.27
2	2-ethylhexanol	129.90	0.00	—
3	2-octanol	131.86 and 131.55	0.31	0.27
4	1-phenyl-1-ethanol	131.35 and 130.77	0.58	0.40
5	1-phenyl-1-propanol	132.52 and 131.51	1.01	—
6	2-(*N*-methylamino)-1-phenyl-1-ethanol	137.77 and 137.65	0.12	—

3. Experimental section

Melting points were taken using a Mel-Temp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 200 MHz on a Varian Gemini-200 spectrometer, with tetramethylsilane (TMS) as an internal standard. ^{31}P NMR were recorded on a 400 MHz JEOL spectrometer. Chemical shifts are given as δ values (ppm) and coupling constants *J* are given in Hz. Optical rotations $[\alpha]_D$ were measured at ambient temperature in 0.1 dm cells, using a Perkin–Elmer 241 spectrophotometer. FT-IR spectra were recorded on a GBC instrument. Mass spectra were recorded on a Hewlett Packard 5989A spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. All reagents were purchased from Aldrich Chemical Co.

Table 2
Evaluation of chiral derivatizing agent (1*S*,2*S*,1′*S*,1″*S*)-**1** with various chiral alcohols



(1*S*,2*S*,1′*S*,1″*S*)-**4** (1*S*,2*S*,1′*S*,1″*S*)-**1** (1*S*,2*S*,1′*S*,1″*S*)-**5**

entry	alcohol	δ_1 (ppm) ^{31}P of diastereoisomeric **5**	Δδ	lit.[5a] Δδ
1	2-butanol	127.90 and 126.82	1.07	0.27
2	2-ethylhexanol	124.31 and 124.06	0.25	——
3	2-octanol	127.89 and 126.91	0.98	0.27
4	1-phenyl-1-ethanol	128.58 and 123.87	4.71	0.40
5	1-phenyl-1-propanol	130.10 and 123.76	6.34	——
6	2-(*N*-methylamino)-1-phenyl-1-ethanol	131.98 and 131.75	0.23	——

3.1. N-*[(S)-α-Phenylethyl]cyclohexene aziridine, (1R,2S,1′S)-3*

In a two-necked flask provided with an addition funnel, condenser and a magnetic stirrer, under argon, the diastereoisomeric mixture of (1*R*,2*R*,1′*S*)- and (1*S*,2*S*,1′*S*)-**2** (2.2 g, 10.0 mmol)[7] and dry triethylamine (5 ml) were dissolved in dry CH_2Cl_2 (20 ml). To the ice-cooled mixture was added dropwise a mixture of methanesulfonyl chloride (1.1 g, 10.0 mmol) in dry CH_2Cl_2 (5 ml). The reaction mixture was stirred at 0°C until no more β-aminoalcohols (1*R*,2*R*,1′*S*)- and (1*S*,2*S*,1′*S*)-**2** were detected by TLC (ca. 24 h), and then the in situ mesylated compounds were allowed to warm to rt for 8 h to give the desired product. The cool reaction mixture was poured over ice cooled 1 N HCl (30 ml) and the organic layer was extracted with CH_2Cl_2 (3×25 ml). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude products were purified by flash chromatography (petroleum ether:ethyl acetate=30:1) to provide aziridine (1*R*,2*S*,1′*S*)-**3**, as a yellow liquid. Vacuum distillation (5

mmHg, 80°C) afforded pure (1*R*,2*S*,1′*S*)-**3** (1.4 g, 70.0% yield) as a colorless liquid, $[\alpha]_D=-42.4$ (c=1.4, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.2 (m, 2H), 1.4 (d, 3H, *J*=7), 1.5 (m, 3H), 1.8 (m, 5H, *J*=7), 2.5 (q, 1H, *J*=7), 7.2–7.5 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 21.1, 21.2, 24.1, 25.1, 25.4, 38.4, 38.7, 70.4, 127.0, 127.2, 128.6, 146.1. Anal. calcd $C_{14}H_{19}N$ (201.3) C 83.54%, H 9.51%; found C 83.32%, H 9.75%.

3.2. (1R,2R,1′S,1″S)- and (1S,2S,1′S,1″S)-N,N′-Di(α-phenylethyl)-1,2-cyclohexanediamine, (1R,2R,1′S,1″S)- and (1S,2S,1′S,1″S)-4

In a dry two-necked flask provided with an addition funnel, condenser and magnetic stirrer, was placed with stirring and under argon an equimolar mixture of *N*-[(*S*)-α-phenylethyl]cyclohexene aziridine (1*R*,2*S*,1′*S*)-**3** (2.0 g, 10 mmol) and anhydrous lithium perchlorate (1.1 g, 10 mmol) in freshly dried acetonitrile (ca. 10 ml) until complete dissolution of the lithium salt. The reaction mixture was cooled in an ice–water bath to 0°C before the dropwise addition of (*S*)-α-phenylethylamine (10 mmol). The resulting solution was then heated to reflux until the reaction was complete, ca. 30 h. Water (25 ml) was added to the reaction mixture and the organic phase was extracted with CH_2Cl_2 (3×25 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* affording a mixture of the 1,2-diamines, (1*R*,2*R*,1′*S*,1″*S*)- and (1*S*,2*S*,1′*S*,1″*S*)-**4**, in a 1:2 ratio. The mixture of 1,2-diamines was treated with an ethereal solution of hydrochloric acid. (1*R*,2*R*,1′*S*,1″*S*)-**4** Dihydrochloride was separated by fractional crystallization from AcOEt:MeOH (3:1). (1*S*,2*S*,1′*S*,1″*S*)-**4** Dihydrochloride was crystallized from petroleum ether:CH_2Cl_2 (3:1).

3.3. 1,2-Diamine (1R,2R,1′S,1″S)-4 dihydrochloride

White crystals, mp 205.0°C, $[\alpha]_D=-80.5$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.1 (m, 2H); 1.2 (m, 2H), 1.6 (d, 6H), 1.7 (m, 2H), 2.1 (m, 2H), 2.5 (m, 2H), 4.1 (q, 2H), 5.9 (broad, 4H), 7.3–7.5 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 23.6, 24.6, 29.8, 55.0, 58.0, 127.1, 128.4, 129.2, 141.3. Anal. calcd $C_{22}H_{30}N_2 \cdot 2HCl \cdot MeOH$ (427.4): C 64.63%, H 8.48%; found C 64.98%, H 8.70%.

Free 1,2-diamine (1*R*,2*R*,1′*S*,1″*S*)-**4**, colorless liquid, 0.58 g (18.0% yield), $[\alpha]_D=-120.0$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.8 (m, 2H), 1.0 (t, 2H), 1.3 (d, 6H, *J*=6), 1.6 (d, 2H), 1.8 (broad, 2H), 1.9 (m, 2H), 2.0 (m, 2H), 3.9 (q, 2H, *J*=6), 7.2–7.5 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 25.3, 26.1, 31.8, 54.8, 58.5, 127.2, 128.8, 128.9, 146.4.

3.4. 1,2-Diamine (1S,2S,1′S,1″S)-4 dihydrochloride

White crystals mp 198–200°C, $[\alpha]_D=+45.0$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.1 (m, 2H), 1.2 (m, 2H), 1.4 (m, 2H), 1.5 (m, 2H), 1.6 (d, 6H), 2.6 (m, 2H), 3.9 (q, 2H), 5.0 (broad, 4H), 7.3–7.4 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 22.5, 24.1, 30.0, 57.4, 60.1, 127.1, 129.1, 129.2, 141.0. Anal. calcd $C_{22}H_{30}N_2 \cdot 2HCl \cdot H_2O$ (413.4): C 63.91%, H 8.28%; found C 64.05%, H 8.29%.

Free 1,2-diamine (1*S*,2*S*,1′*S*,1″*S*)-**4**, colorless liquid, 1.7 g (53.0% yield), $[\alpha]_D=+40.5$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.9 (m, 2H), 1.1 (t, 2H), 1.3 (d, 6H, *J*=6), 1.6 (d, 2H), 1.8 (m, 2H), 1.9 (broad, 2H), 2.3 (m, 2H), 3.8 (q, 2H, *J*=6), 7.2–7.5 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 24.5, 25.5, 33.1, 56.6, 60.9, 127.0, 127.1, 128.9, 148.0.

3.5. Procedure for chiral alcohol derivatization with (1R,2R,1′S,1″S)- and (1S,2S,1′S,1″S)-4 to give diastereomeric 5

In an NMR tube are placed with vigorous stirring 51 mg (0.16 mmol) of free 1,2-diamine (1*R*,2*R*,1′*S*,1″*S*)- or (1*S*,2*S*,1′*S*,1″*S*)-**4**, 0.5 ml of $CDCl_3$, 119 mg (0.80 mmol) of diethylaniline, and 23 mg (0.16 mmol) of PCl_3 previously dissolved in 50 μl of CH_2Cl_2, affording the chlorodiazaphospholidine (1*R*,2*R*,1′*S*,1″*S*)- or (1*S*,2*S*,1′*S*,1″*S*)-**1**. (1*R*,2*R*,1′*S*,1″*S*)-**1** ^{31}P NMR ($CDCl_3$): δ 176.7. (1*S*,2*S*,1′*S*,1″*S*)-**1** ^{31}P NMR ($CDCl_3$): δ 179.5. Immediately after 0.13 mmol of racemic secondary alcohol is added (Tables 1 and 2) and the resulting mixture is stirred for 30 minutes before ^{31}P NMR spectra are recorded at rt.

Acknowledgements

We thank CONACYT for financial support (Projects No. L0006E and 3983-E and Grant No. 91276).

References

1. For an excellent review, see: Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.
2. (a) Jaen, J. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed.; Wiley: New York, 1995, Vol. 5, p. 3427. (b) Juaristi, E.; Escalante, J.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715–740.
3. (a) For a detailed recent review, see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441. See, also: (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335. (d) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263. (e) Jursic, B. S.; Zdravkovski, Z.; Zuanic, M. *Tetrahedron: Asymmetry* **1995**, *5*, 1711.
4. (a) Verkade, L. D.; Quin, L. D. *Phosphorus-31 NMR Spectroscopy in Stereochemical Analysis*; VCH Publishers: Deerfield Beach, 1987. (b) See, also: Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; p. 137. (c) Johnson, C. R.; Elliott, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019. (d) Kato, N. *J. Am. Chem. Soc.* **1990**, *112*, 254. (e) Anderson, R. C.; Shapiro, M. J. *J. Org. Chem.* **1984**, *49*, 1304. (f) Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Rec. Trav. Chim. Pays-Bas* **1995**, *114*, 115.
5. (a) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224. (b) Alexakis, A.; Frutos, J. C.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1994**, *59*, 3326.
6. For other chiral derivatizing agents based on enantiopure *trans*-1,2-diaminocyclohexane, see: (a) Resch, J. F.; Meinwald, J. *Tetrahedron Lett.* **1981**, *22*, 3159. (b) Staubach, B.; Buddrus, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1344.
7. Anaya de Parrodi, C.; Juaristi, E.; Quintero, L. *An. Quím. Int. Ed.* **1996**, *92*, 400.
8. See, also: (a) Pracejus, H.; Pracejus, G.; Costisella, B. *J. Prak. Chem.* **1987**, *329*, 235. (b) Overman, L. E.; Sugai, S. *J. Org. Chem.* **1985**, *50*, 4154. (c) Barbaro, P.; Bianchini, C.; Sernau, V. *Tetrahedron: Asymmetry* **1996**, *7*, 843.
9. Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, pp. 1179–1181.
10. For an authoritative review on aziridine formation, see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
11. For a general discussion on aziridine conversion to 1,2-diamines, see: Kemp, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 7, p. 469.
12. The use of $LiClO_4$ as a catalyst in a nucleophilic epoxide ring opening has been developed by Chini, et al.[13] The present application to aziridine ring opening may prove to be a valuable synthetic method.
13. (a) Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *Synlett* **1992**, 673. (b) Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939. (c) Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661.
14. Juaristi, E.; Anaya de Parrodi, C.; Quintero-Cortés, L.; Ramírez-Quirós, Y. Unpublished results.