



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/lcyc20>

L-ALANINE BENZYLESTER AS CHIRAL INDUCTOR: SYNTHESIS OF ENANTIOPURE PYRAZOLO[1,5-a]-[1,4]BENZODIAZEPINE-4-ONES VIA INTRAMOLECULAR NITRILIMINE CYCLOADDITIONS

Gianluigi Broggini^a, Luisa Garanti^b, Giorgio Molteni^b & Tullio Pilati^b

^a Dipartimento di Scienze Chimiche, Fisiche e Matematiche, Università dell'Insubria, via Lucini 3, Como, 22100, Italy

^b Dipartimento di Chimica Organica e Industriale, Università di Milano, via Golgi 19, Milano, 20133, Italy

Published online: 09 Nov 2006.

To cite this article: Gianluigi Broggini, Luisa Garanti, Giorgio Molteni & Tullio Pilati (2001) L-ALANINE BENZYLESTER AS CHIRAL INDUCTOR: SYNTHESIS OF ENANTIOPURE PYRAZOLO[1,5-a]-[1,4]BENZODIAZEPINE-4-ONES VIA INTRAMOLECULAR NITRILIMINE CYCLOADDITIONS, *Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry*, 31:17, 2649-2656, DOI: [10.1081/SCC-100105392](https://doi.org/10.1081/SCC-100105392)

To link to this article: <http://dx.doi.org/10.1081/SCC-100105392>

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <http://www.tandfonline.com/page/terms-and-conditions>

SYNTHETIC COMMUNICATIONS, 31(17), 2649–2656 (2001)

**L-ALANINE BENZYLESTER AS CHIRAL
INDUCTOR: SYNTHESIS OF
ENANTIOPURE PYRAZOLO[1,5-*a*]-
[1,4]BENZODIAZEPINE-4-ONES VIA
INTRAMOLECULAR NITRILIMINE
CYCLOADDITIONS**

**Gianluigi Broggini,² Luisa Garanti,^{1,*}
Giorgio Molteni,¹ and Tullio Pilati³**

¹Dipartimento di Chimica Organica e Industriale, Università di
Milano, via Golgi 19, 20133 Milano, Italy

²Dipartimento di Scienze Chimiche, Fisiche e Matematiche,
Università dell'Insubria, via Lucini 3, 22100 Como, Italy

³CNR-Centro per lo Studio delle Relazioni tra Struttura e
Reattività Chimica c/o, Università di Milano, via Golgi 19,
20133 Milano, Italy

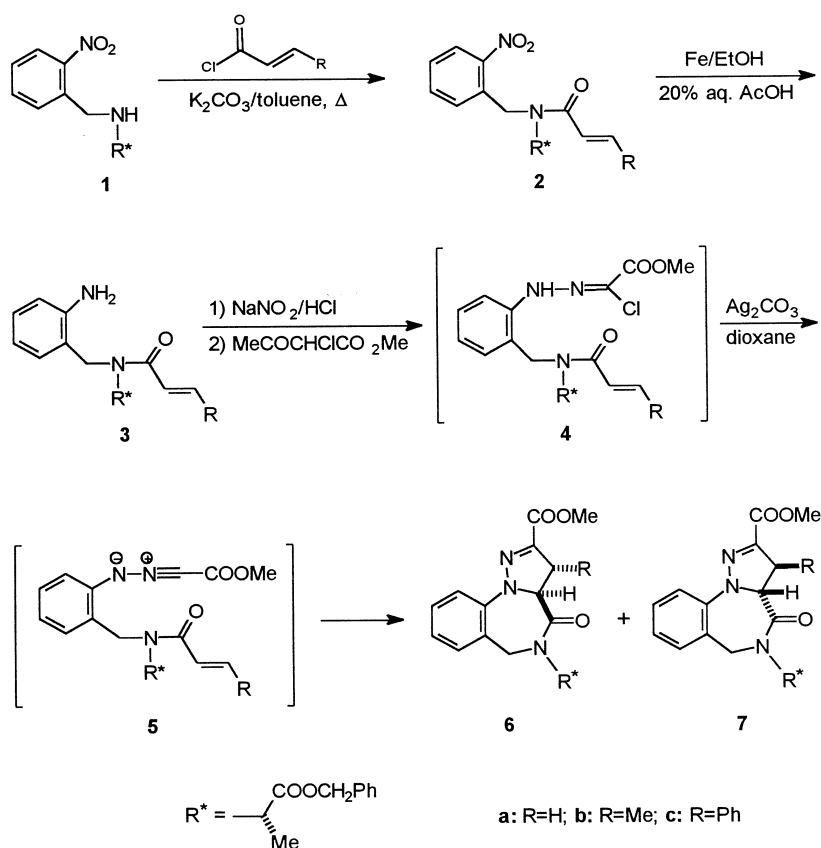
ABSTRACT

The title compounds, of potential pharmacological interest, have been obtained in the enantiopure form through a stereoselective intramolecular 1,3-dipolar cycloaddition of homo-chiral nitrilimines **5**.

*Corresponding author.

In the last years, we focussed our attention to stereoselective intramolecular cycloadditions of homochiral nitrilimines, which were proven to be of wide applicability in the synthesis of optically active heterocyclic systems.¹⁻⁵ Among them, some derivatives containing the pyrazolo[1,5-*a*]-[1,4]benzodiazepine skeleton⁴ were found endowed with biological activity against breast cancer.⁶ Encouraged by these results, we synthesized some new 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones by using the inexpensive L-alanine benzyl ester as the starting chiral unit.

Our synthetic route, which is outlined in the Scheme, starts with the reaction between L-alanine benzylester and 2-nitrobenzyl chloride in order to obtain benzyl *N*-(2-nitrophenyl)methyl-L-alaninate **1**. Subsequent steps involve *N*-acylation of **1** with the appropriate alkenoyl chloride, reduction



Scheme.



of the aromatic nitro group of **2**, and diazotization of the so formed amino group of **3** followed by coupling with methyl 2-chloroacetoacetate. Since hydrazonoyl chlorides **4** were found rather unstable, we felt advisable to use them as crude materials without full characterisation.⁷ The *in situ* generation of nitrilimines **5** was accomplished by treating a solution of crude **4** with a two fold molar excess of silver carbonate in dry dioxane at room temperature. Products, isolation yields, reaction times and eluents are collected in the Table.

The extent of the one-pot like conversion $3 \rightarrow 6 + 7$ was fully satisfactory, the ranging between 70 and 80%. It needs to be added that clean separation of enantiopure cycloadducts **6** and **7** was achieved through simple column chromatography. Structural assignment to the above

Table. Conversion of **3** into Cycloadducts **6** and **7**

Compd	Time (h)	Products and Yields (%) ^a		Product Ratio 6 : 7	Eluent ^b
		6	7		
3a	96	56	14	80:20	Et ₂ O-LP 3:1
3b	120	43	37	54:46	AcOEt- <i>n</i> -hexane 1:1
3c	120	42	28	60:40	Et ₂ O- <i>n</i> -hexane 2:3

^aIsolation yield of pure product. ^bLP = light petroleum, b.p. 40–60°C.

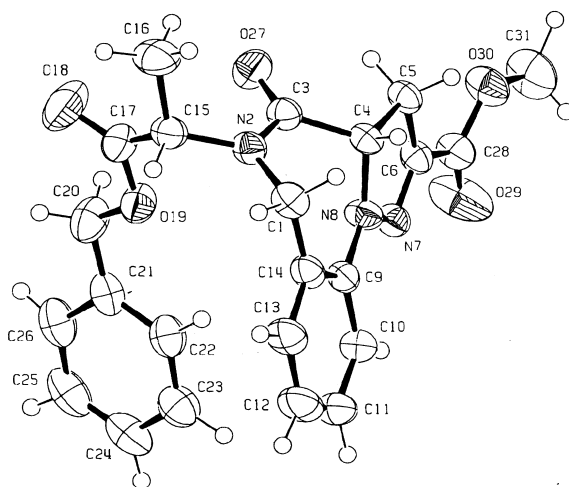


Figure. ORTEP projection of **6a** with the crystallographic numbering scheme. Ellipsoids are at 50% probability level. H atoms not to scale.



cycloadducts rely upon analytical and spectral data as well as upon the X-ray diffractometric analysis of **6a**, which proved the absolute (*S*) configuration to the pyrazolinic C-5 of major cycloadducts **6**.

Intramolecular cycloadditions of nitrilimines **5** display a diastereoselectivity degree ranging from low to good, as can be inferred from the ratio **6/7** (see Table). Furthermore, our synthetic approach was proven to be very efficient and hence valuable on a multi-gram preparative scale of enantiopure 3,3a-dihydropyrazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus and are not corrected. IR spectra were recorded with a Perkin-Elmer 1725 X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ¹H-NMR spectra (300 MHz) were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in CDCl₃ solutions). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. Optical rotations, [α]_D²⁵ were recorded on a Perkin-Elmer Model 241 polarimeter at the sodium D line.

Preparation of benzyl *N*-(2-nitrophenyl)methyl-L-alaninate (1**).** A solution of L-alanine benzylester (5.00 g, 27.9 mmol) in dry toluene (55 ml) was added with KI (0.46 g, 2.8 mmol). 2-Nitrobenzyl chloride (2.21 g, 13.0 mmol) in dry toluene (5 ml) was slowly added and the mixture was warmed to 75°C for 7 h under vigorous stirring. Toluene (35 ml) was added, the white precipitate was filtered off, and the solvent was evaporated under reduced pressure affording **1** (2.94 g, 73% yield) as undistillable oil; [α]_D²⁵ = −18.4 (MeOH, *c* = 0.14); IR (neat): 3340, 1740 (cm^{−1}); ¹H-NMR δ: 1.38 (3H, d, *J* = 7.1), 2.10 (1H, br s), 3.42 (1H, q, *J* = 7.1), 3.95 (1H, d, *J* = 14.6), 4.10 (1H, d, *J* = 14.6), 5.12 (2H, s), 7.20–7.95 (9H, m); MS: *m/z* 310 (M⁺).

General procedure for the preparation of benzyl *N*-(2-nitrophenyl)-methyl-*N*-(1-oxo-2-alkenyl)-L-alaninate (2**).** A solution of **1** (5.20 g, 16.6 mmol) in dry toluene (120 ml) was added with K₂CO₃ (4.58 g, 33.2 mmol). The appropriate alkenyl chloride (16.6 mmol) in dry toluene (6.0 ml) was added dropwise at 90°C. The mixture was refluxed for 5 h, then the undissolved material was filtered off. The organic layer was washed with water (50 ml) and dried (Na₂SO₄). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with hexane-ethyl acetate 1:1 affording **2a–c** as undistillable oils not analytically pure.

2a (4.46 g, 73%) as pale yellow oil; [α]_D²⁵ = −52.3 (MeOH, *c* = 0.24); IR (neat): 1660 (cm^{−1}); ¹H-NMR δ: 1.48 (3H, d, *J* = 7.2), 4.63 (1H, q, *J* = 7.2),



L-ALANINE BENZYLESTER

2653

4.90 (1H, d, $J=19.5$), 5.17 (2H, s), 5.18 (1H, d, $J=19.5$), 5.70 (1H, d, $J=10.4$), 6.24 (1H, dd, $J=16.5$, 10.4), 6.47 (1H, d, $J=16.5$), 7.25–8.20 (9H, m); MS: m/z 368 (M^+).

2b (4.76 g, 75%) as pale yellow oil; $[\alpha]_D^{25} = -35.5$ (MeOH, $c=0.50$); IR (neat): 1660 (cm^{-1}); $^1\text{H-NMR}$ δ : 1.46 (3H, d, $J=7.1$), 1.82 (3H, d, $J=6.7$), 4.57 (1H, q, $J=7.1$), 4.86 (1H, d, $J=19.5$), 5.13 (2H, s), 5.15 (1H, d, $J=15.0$), 5.17 (1H, d, $J=19.5$), 5.91 (1H, d, $J=15.0$), 7.00–8.10 (9H, m); MS: m/z 382 (M^+).

2c (6.12 g, 83%) as yellow oil; $[\alpha]_D^{25} = -42.3$ (MeOH, $c=0.28$); IR (neat): 1650 (cm^{-1}); $^1\text{H-NMR}$ δ : 1.50 (3H, d, $J=7.0$), 4.60 (1H, q, $J=7.0$), 4.95 (1H, d, $J=18.0$), 5.18 (2H, s), 5.22 (1H, d, $J=16.2$), 5.24 (1H, d, $J=18.0$), 6.50 (1H, d, $J=16.2$), 7.25–7.90 (14H, m); MS: m/z 444 (M^+).

General procedure for the preparation of benzyl *N*-(2-aminophenyl)-methyl-*N*-(1-oxo-2-alkenyl)-L-alaninate (3**).** A solution of **2** (10.0 mmol) in EtOH (40 ml) was treated with iron dust (4.80 g, 83.0 mmol) and 20% aqueous AcOH (1.7 ml), and then refluxed for 3 h under vigorous stirring. The mixture was taken up with AcOEt (50 ml) and filtered over celite. The organic layer was washed firstly with 5% aqueous NaHCO_3 (50 ml), then with water (2×50 ml), and dried Na_2SO_4 . Evaporation of the solvent gave **3** as undistillable oils not analytically pure.

3a (2.73 g, 81%) as yellow oil; $[\alpha]_D^{25} = -32.3$ (MeOH, $c=0.17$); IR (neat): 3430, 3360, 3240, 1645 (cm^{-1}); $^1\text{H-NMR}$ δ : 1.45 (3H, d, $J=7.0$), 3.58 (2H, br s), 4.25 (1H, q, $J=7.0$), 4.80 (1H, d, $J=18.0$), 5.20 (2H, s), 5.22 (1H, d, $J=18.0$), 5.60–6.40 (3H, m), 6.90–7.30 (9H, m); MS: m/z 338 (M^+).

3b (2.60 g, 74%) as yellow oil; $[\alpha]_D^{25} = -14.3$ (MeOH, $c=0.15$); IR (neat): 3430, 3360, 3235, 1660 (cm^{-1}); $^1\text{H-NMR}$ δ : 1.37 (3H, d, $J=7.2$), 1.80 (3H, d, $J=6.8$), 3.80 (2H, br s), 4.25 (1H, q, $J=7.2$), 4.70 (1H, d, $J=18.5$), 5.18 (2H, s), 5.20 (1H, d, $J=18.5$), 5.50–6.20 (2H, m), 6.80–7.45 (9H, m); MS: m/z 352 (M^+).

3c (3.02 g, 73%) as yellow oil; $[\alpha]_D^{25} = -10.8$ (MeOH, $c=0.12$); IR (neat): 3440, 3355, 3245, 1650 (cm^{-1}); $^1\text{H-NMR}$ δ : 1.48 (3H, d, $J=7.0$), 3.85 (2H, br s), 4.45 (1H, q, $J=7.0$), 4.68 (1H, d, $J=17.8$), 5.12 (2H, s), 5.18 (1H, d, $J=17.8$), 5.60–6.00 (2H, m), 6.90–97.40 (14H, m); MS: m/z 414 (M^+).

General procedure for the conversion of **3 into **6,7**.** A solution of **3** (5.0 mmol) in 6M aqueous hydrochloric acid (3.0 ml) and MeOH (2.5 ml) was cooled to 0°C . Sodium nitrite (0.69 g, 10.0 mmol) was added portion-wise keeping the temperature between 0 and 5°C . After 15 min, the pH was adjusted to 5 by adding sodium acetate, and a solution of methyl-2-chloro-acetoacetate (0.75 g, 5.0 mmol) in MeOH (1.5 ml) was added under vigorous



stirring and ice-cooling. The mixture was allowed to stand overnight under stirring at room temperature. The solvent was partly removed under reduced pressure and the resulting mixture was extracted with Et₂O (50 ml). The organic layer was washed firstly with 5% NaHCO₃ (15 ml), then with water (50 ml), and dried (Na₂SO₄). The solvent was removed under reduced pressure to give an oily residue that was dissolved in dry dioxane (225 ml). Silver carbonate (2.48 g, 9.0 mmol) was added and the mixture was stirred in the dark at room temperature for the time indicated in the Table. After evaporation of the solvent, the crude was chromatographed on a silica gel column with the eluents indicated in the Table affording the 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones **6** and **7**. Major diastereoisomers **6** was eluted first, followed by minor diastereoisomers **7**.

6a (1.18 g, 56%) m.p. 140°C (from hexane-CH₂Cl₂); $[\alpha]_D^{25} = +178.0$ (MeOH, *c* = 0.33); IR (nujol): 1730, 1645 (cm⁻¹); ¹H-NMR δ : 1.43 (3H, d, *J* = 7.4), 3.27 (3H, dd, *J* = 18.1, 13.5), 3.90 (3H, s), 4.02 (1H, d, *J* = 17.2), 4.13 (1H, dd, *J* = 18.1, 8.3), 5.18 (1H, d, *J* = 12.3), 5.23 (1H, d, *J* = 12.3), 5.38 (1H, d, *J* = 17.2), 5.47 (1H, q, *J* = 7.4), 5.66 (1H, dd, *J* = 13.5, 8.3), 6.90–7.60 (9H, m); MS: *m/z* 421 (M⁺) (30%). Anal. Calcd for C₂₃H₂₃N₃O₅: C, 65.55; H, 5.50; N, 9.97. Found: C, 65.61; H, 5.53; N, 10.04.

7a (0.29 g, 14%) m.p. 89°C (from diisopropyl ether); $[\alpha]_D^{25} = -54.2$ (MeOH, *c* = 0.05); IR (nujol): 1730, 1660 (cm⁻¹); δ_H : 1.48 (3H, d, *J* = 7.1), 3.26 (1H, dd, *J* = 18.1, 13.5), 3.90 (3H, s), 3.97 (1H, d, *J* = 16.8), 4.12 (1H, dd, *J* = 18.1, 8.5), 4.51 (1H, d, *J* = 12.3), 4.98 (1H, d, *J* = 12.3), 5.22 (1H, q, *J* = 7.1), 5.32 (1H, d, *J* = 16.8), 5.67 (1H, dd, *J* = 13.5, 8.5), 6.85–7.60 (9H, m); MS: *m/z* 421 (M⁺) (29%). Anal. Calcd for C₂₃H₂₃N₃O₅: C, 65.55; H, 5.50; N, 9.97. Found: C, 65.50; H, 5.53; N, 9.91.

6b (0.94 g, 43%) m.p. 150°C (from diisopropyl ether); $[\alpha]_D^{25} = +147.0$ (MeOH, *c* = 0.33); IR (nujol): 1740, 1670 (cm⁻¹); ¹H-NMR δ : 1.36 (3H, d, *J* = 7.4), 1.38 (3H, d, *J* = 7.1), 3.86 (3H, s), 4.01 (1H, d, *J* = 17.4), 4.37 (1H, dq, *J* = 7.1, 6.7), 5.17 (2H, s), 5.21 (1H, d, *J* = 6.7), 5.32 (1H, d, *J* = 17.4), 5.36 (1H, q, *J* = 7.4), 6.80–7.60 (9H, m); MS: *m/z* 435 (M⁺) (36%). Anal. Calcd for C₂₄H₂₅N₃O₅: C, 66.19; H, 5.79; N, 9.65. Found: C, 66.12; H, 5.74; N, 9.58.

7b (0.80 g, 37%) m.p. 125°C (from diisopropyl ether); $[\alpha]_D^{25} = -214.5$ (MeOH, *c* = 0.33); IR (nujol): 1740, 1660 (cm⁻¹); ¹H-NMR δ : 1.38 (3H, d, *J* = 7.2), 1.44 (3H, d, *J* = 7.1), 3.87 (3H, s), 4.01 (1H, d, *J* = 17.0), 4.38 (1H, dq, *J* = 7.1, 6.9), 4.47 (1H, d, *J* = 12.3), 4.92 (1H, d, *J* = 12.3), 5.15 (1H, d, *J* = 6.9), 5.18 (1H, d, *J* = 7.1), 5.25 (1H, d, *J* = 17.0), 6.80–7.60 (9H, m); MS: *m/z* 435 (M⁺) (30%). Anal. Calcd for C₂₄H₂₅N₃O₅: C, 66.19; H, 5.79; N, 9.65. Found: C, 66.24; H, 5.84; N, 9.60.



6c (1.04 g, 42%) m.p. 155°C (from diisopropyl ether); $[\alpha]_D^{25} = +217.0$ (MeOH, $c = 0.36$); IR (nujol): 1740, 1670 (cm^{-1}); $^1\text{H-NMR}$ δ : 1.35 (3H, d, $J = 7.3$), 3.73 (3H, s), 3.97 (1H, d, $J = 17.5$), 5.15 (2H, s), 5.21 (1H, d, $J = 17.5$), 5.38 (1H, q, $J = 7.3$), 5.49 (1H, d, $J = 6.3$), 5.54 (1H, d, $J = 6.3$), 6.80–7.50 (14H, m); MS: m/z 497 (M^+) (54%). Anal. Calcd for $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_5$: C, 73.77; H, 5.74; N, 9.57. Found: C, 73.83; H, 5.80; N, 9.66.

7c (0.70 g, 28%) m.p. 95°C (from diisopropyl ether); $[\alpha]_D^{25} = -445$ (MeOH, $c = 0.15$); IR (nujol): 1740, 1670 (cm^{-1}); $^1\text{H-NMR}$ δ : 1.42 (3H, d, $J = 7.2$), 3.93 (3H, s), 3.99 (1H, d, $J = 17.1$), 4.46 (1H, d, $J = 12.3$), 4.93 (1H, d, $J = 12.3$), 5.18 (1H, d, $J = 17.1$), 5.21 (1H, q, $J = 7.2$), 5.51 (2H, s), 6.90–7.80 (14H, m); MS: m/z 497 (M^+) (54%). Anal. Calcd for $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_5$: C, 73.77; H, 5.74; N, 9.57. Found: C, 73.80; H, 5.68; N, 9.53.

X-ray structure determination of 6a. Crystal data were collected using graphite monochromated Mo- $K\alpha$ radiation $\lambda = 0.71073 \text{ \AA}$. The structures was solved by *SIR92*,⁸ and refined on *F*² by full-matrix least-squares using *SHELX97*;⁹ heavy atoms were anisotropic, H atoms isotropic. Absolute configurations was based on the reactants knowledge. Data of 6a. $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_5$, $M_r = 421.44$, triclinic, space group *P*1, $a = 7.3469(6)$, $b = 8.6967(8)$, $c = 8.8671(9) \text{ \AA}$, $\alpha = 95.540(7)$, $\beta = 107.008(7)$, $\gamma = 98.187(7)^\circ$, $V = 530.51(8) \text{ \AA}^3$, $T = 291(1) \text{ K}$, $Z = 1$, $d_{\text{calc}} = 1.319 \text{ g cm}^{-3}$, $\mu(\text{Mo-K}\alpha) = 0.094 \text{ mm}^{-1}$; $\omega/2\theta$ scans, $4 < 2\theta < 60^\circ$; 6169 reflection collected, 3094 unique ($R_{\text{av}} = 0.0149$) used for all calculations. Final $R = 0.0350$ and $wR = 0.0859$, g.o.f. 0.926, $-0.14 < \Delta\rho < 0.23 \text{ e \AA}^{-3}$. Detailed crystallographic data were deposited (as CCDC 147229) with the Cambridge crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

ACKNOWLEDGMENTS

We are grateful to CNR and MURST for financial support.

REFERENCES

1. Broggin, G.; Garanti, L.; Molteni, G.; Zecchi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 487.
2. Broggin, G.; Garanti, L.; Molteni, G.; Pilati, T.; Ponti, A.; Zecchi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 2203.
3. Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **1999**, *10*, 3873.
4. Broggin, G.; Casalone, G.; Garanti, L.; Molteni, G.; Pilati, T.; Zecchi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 4447.



5. Broggin, G.; Molteni, G.; Pilati, T. *Tetrahedron: Asymmetry* **2000**, *11*, 1975.
6. Personal communication from the National Institute of Health (Bethesda, Maryland, USA) to the Senior Author.
7. The IR spectra of crude **4a-c** exhibited the typical N-H stretch band of hydrazoneyl chlorides at 3240–3250 cm⁻¹.
8. Altomare, A.; Cascarano, G.; Giacovazzo, G.; Guagliardi, A.; Burla, M.C.; Polidori, G.; Camalli, G. *J. Appl. Crystallogr.* **1994**, *27*, 435.
9. Sheldrick, G.M. *SHELX97. Program for the Refinement of Crystal Structures*, 1997, University of Goettingen Germany.

Received in the UK August 2, 2000



Request Permission or Order Reprints Instantly!

Interested in copying and sharing this article? In most cases, U.S. Copyright Law requires that you get permission from the article's rightsholder before using copyrighted content.

All information and materials found in this article, including but not limited to text, trademarks, patents, logos, graphics and images (the "Materials"), are the copyrighted works and other forms of intellectual property of Marcel Dekker, Inc., or its licensors. All rights not expressly granted are reserved.

Get permission to lawfully reproduce and distribute the Materials or order reprints quickly and painlessly. Simply click on the "Request Permission/Reprints Here" link below and follow the instructions. Visit the [U.S. Copyright Office](#) for information on Fair Use limitations of U.S. copyright law. Please refer to The Association of American Publishers' (AAP) website for guidelines on [Fair Use in the Classroom](#).

The Materials are for your personal use only and cannot be reformatted, reposted, resold or distributed by electronic means or otherwise without permission from Marcel Dekker, Inc. Marcel Dekker, Inc. grants you the limited right to display the Materials only on your personal computer or personal wireless device, and to copy and download single copies of such Materials provided that any copyright, trademark or other notice appearing on such Materials is also retained by, displayed, copied or downloaded as part of the Materials and is not removed or obscured, and provided you do not edit, modify, alter or enhance the Materials. Please refer to our [Website User Agreement](#) for more details.

[Order now!](#)

Reprints of this article can also be ordered at

<http://www.dekker.com/servlet/product/DOI/101081SCC100105392>