GEOMETRICAL ISOMERISM IN *β*-NITROSTYRENES: PREFERRED CONFORMATIONS OF (*E*)- AND (*Z*)- 1-(4-METHYLTHIOPHENYL)-2-NITROBUTENES

CLAUDIO HURTADO-GUZMÁN, PATRICIO ITURRIAGA-VÁSQUEZ, GERALD ZAPATA-TORRES AND BRUCE K. CASSELS*

Millennium Institute for Advanced Studies in Cell Biology and Biotechnology, and Department of Chemistry, Faculty of Sciences, University of Chile, Santiago, Chile. E-mail:bcassels@uchile.cl.

ABSTRACT

Condensation of 4-methylthiobenzaldehyde with 1-nitropropane unexpectedly afforded separable amounts of both (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitrobutene. The ^{1}H and ^{13}C NMR spectra allowed the unequivocal assignment of all signals and their correlation with the preferred conformations adopted by these compounds as determined by NOESY experiments. Hartree Fock theory optimizations at the 6-311G(d,p) level were carried out for the stereoisomeric 4-methylthionitroethene, -nitropropene, and -nitrobutene pairs, and the relative energy differences between isomers were calculated in order to estimate approximate *E/Z* equilibrium constants. These energy differences decrease with the increasing number of side chain carbon atoms, explaining the possibility of separating (*E*)- and (*Z*)-nitrobutenes and the failure to isolate the (*Z*) isomers of the lower homologues under the usual thermodynamically controlled reaction conditions.

Keywords: *β*-nitrostyrene geometrical isomers; preferred conformations; NMR studies; RHF/6-311G(d,p) calculations.

INTRODUCTION

β-Nitroolefins are widely used as substrates for nucleophilic additions.[1,2] *β*-Nitrostyrenes are commonly prepared en route to *β*-phenylalkylamines, and nitro cycloalkenes have been reviewed as very versatile synthetic intermediates.[3,4] The steric outcome of nucleophilic additions to these compounds depends on the configuration of the starting material, but both stereoisomers are seldom readily available, and *β*-nitrostyrenes and 1-nitroprop-2-enes obtained by the usual Knoevenagel sequence show a strong predominance of the (*E*)-isomer which is generally the sole isolated product. Only one literature reference reports obtaining (*Z*)-*β*-nitroolefins in good yield by dehydration of the corresponding nitro alcohol when the reaction is carried out at a very low temperature.[5] A related example reports the elimination reaction of a 2-alkylthio-1-nitropropane with potassium fluoride to produce a mixture of both isomers with the (*Z*)-isomer predominating.[6]

We now report the separation and complete NMR spectroscopic characterization of both α-ethyl-*β*-nitrostyrene isomers, (*E*)-1a and (*Z*)-1a (Figure 1), obtained by Knoevenagel condensation of 4-methylthiobenzaldehyde and 1-nitropropane as an approach to novel monoamine oxidase inhibitors and possible serotonin releasers.[7] NOESY experiments provided evidence for the preferred conformations of the products. In addition, we computed the relative energy differences at the RHF/6-311G(d,p) level for this (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitrobutene pair and the corresponding nitropropenes (1b) and ethenes (1c).

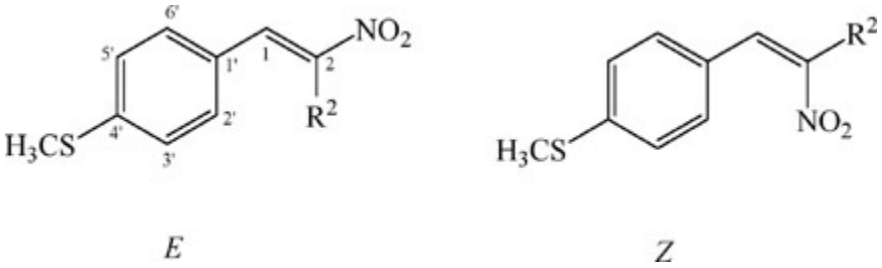

Fig. 1. Structures and numbering of the (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitroalkenes mentioned in this study: 1a, $R^2 = CH_2CH_3$; 1b, $R^2 = CH_3$; 1c, $R^2 = H$.

RESULTS AND DISCUSSION

The (*E*) and (*Z*) isomers of 1-(4-methylthiophenyl)-2-nitrobutene were formed in the reaction mixture of 4-methylthiobenzaldehyde and 1-nitropropane in refluxing toluene, using N,N-dimethylethylenediamine as catalyst, in an approximately 92:8 molar ratio, judging from the ^{1}H NMR spectrum of the crude product. Both products [(*E*)-1a and (*Z*)-1a, respectively] were separated chromatographically and fully characterized by ^{1}H- and ^{13}C-NMR spectroscopy, using HMBC, HMQC and NOESY experiments for complete assignment of the signals. Tables 1 and 2 allow direct comparison of the ^{1}H and ^{13}C chemical shifts of stereoisomers (*E*)-1a and (*Z*)-1a.

Table 1. ^{1}H-NMR chemical shifts of (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitrobutenes [(*E*)- 1a and (*Z*)- 1a] ($CDCl_3$).

	(E)-1[a]	(Z)-1a
CH_2CH_3	1.38 (3H, t, J = 7.4 Hz)	1.20 (3H, t, J = 7.4 Hz)
SCH_3	2.52 (3H, s)	2.46 (3H, s)
CH_3CH_2C=CH	2.88 (2H, q, J = 7.4 Hz)	2.67 (2H, q, J = 7.4 Hz)
ArCH=C	7.98 (1H, s)	6.29 (1H, s)
H3'; H5'	7.29 (2H, d, J = 8.5 Hz)	7.16 (4H, s*)
H2'; H6'	7.36 (2H, d, J = 8.5 Hz)	7.16 (4H, s*)

* = apparent singlet

Table 2. ^{13}C-NMR chemical shifts of (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitrobutenes [(*E*)-1a and (*Z*)-1a] ($CDCl_3$).

	(E)-1[a]	(Z)-1a
CH_2CH_3	12.42	11.49
SCH_3	15.04	15.25
CH_3CH_2C=CH	20.88	27.27
ArCH=C	132.9	122.4
ArCH=C	152.5	151.8
C1'	128.5	128.3
C4'	142.3	140.3
C3' and C5'	125.3	126.1
C2' and C6'	130.3	128.4

The ^{1}H-NMR spectrum of (*E*)-1-(4-methylthiophenyl)-2-nitrobutene [(*E*)-1a] (Figure 2a) shows the H1 resonance shifted further downfield (7.98 ppm) than either of the aromatic ring proton resonances (7.29 and 7.36 ppm), while in the (*Z*) isomer [(*Z*)-1a] (Figure 2b) the H1 nucleus resonates upfield (6.29 ppm) from the aromatic ring protons (7.16 ppm). This striking difference prompted us to study the two isomers in detail.

This initial observation might be attributed to the different side chain conformations in both molecules, and/or to the resulting difference in conjugation. The (*E*) isomer might be expected to present a coplanar extended conjugated π system from the nitro group to the aromatic ring in which only a relatively weak steric compression of the C3 methylene hydrogen atoms and H2'/6' might destabilize the planar conformation. Thus, H1 of the (*E*) isomer would be expected to lie close to the ring plane and be strongly deshielded by the ring current as well as by the resonance effect of the nitro group. On the contrary, the high field resonance of H1 in the (*Z*) isomer suggests either a loss of coplanarity between the side chain and the ring, with concomitantly weaker conjugation between both π systems, or poor conjugation of the side chain double bond with the nitro group, or both conformational effects acting in conjunction. Clearly, the nitro group cannot lie near the ring plane and the side chain must

relieve the steric compression due to the proximity of a nitro oxygen atom to H2'/6'. This could occur by twisting around either the C1-C1' bond or the C2-N bond, or by both effects simultaneously. These possibilities are discussed below, on the basis of RHF/6-311G(d,p) calculations.

Another interesting aspect of the magnetic behavior of the (*Z*) isomer is the disappearance of the well resolved AA'BB' system which is seen in the ^{1}H-NMR spectrum of the (*E*) isomer and is characteristic of asymmetrically 1,4-disubstituted aromatic rings. In the ^{1}H-NMR spectrum of the (*Z*) isomer a second-order splitting pattern resembling a singlet can be seen at 7.16 ppm, with very small side peaks, at a higher field than either aromatic ring proton doublet of the (*E*) isomer (see Figures 2a and 2b). The upfield shift and the decreased difference in the chemical shifts of H2'/6' and H3'/5' could be taken as indications of different degrees of conjugation between the ring and the side chain, although the magnetic anisotropic effect of the nitro group cannot be disregarded.

The complete and unequivocal assignment of all the ^{13}C-NMR signals leads to the observation that the chemical shifts of the ring carbon nuclei do not change by more than 2 ppm on going from the (*E*) to the (*Z*) isomer, in contrast with the behavior of the attached proton resonances. As chemical shift is a function of the electronic environment, it could be surmised that a similar degree of conjugation between the aromatic ring and the unsaturated side chain in both cases leads to these very similar values. Nevertheless, the chemical shift of the side chain carbon nucleus directly attached to the ring (C1) in the (*E*) isomer lies 10.5 ppm below that of the (*Z*) isomer, suggesting that conjugation with the nitro group may be lost in the latter isomer. An opposite effect, but now attributable to the magnetic anisotropy of the nitro group, is seen for the C3 signals: this nucleus is deshielded in the (*Z*) isomer by 6.4 ppm relative to the (*E*) isomer. This supports the idea that the nitro group may be twisted out of the plane of the C=C double bond in the (*Z*)-nitrobutene.

Table 3 shows the NOE's observed for each of the isomers in NOESY experiments (Figures 2a and 2b). The expected through-space interactions confirm the structure assignments. In particular, the cis relationship of the hydrogen atom and the ethyl group bound to the side-chain ethylene moiety of the (*Z*) isomer is demonstrated by the reciprocal NOE between H1 and H3-H4. Such an interaction is absent in the spectrum of the (*E*) isomer, but here the ethyl group protons interact with H2' and H6', showing their proximity.

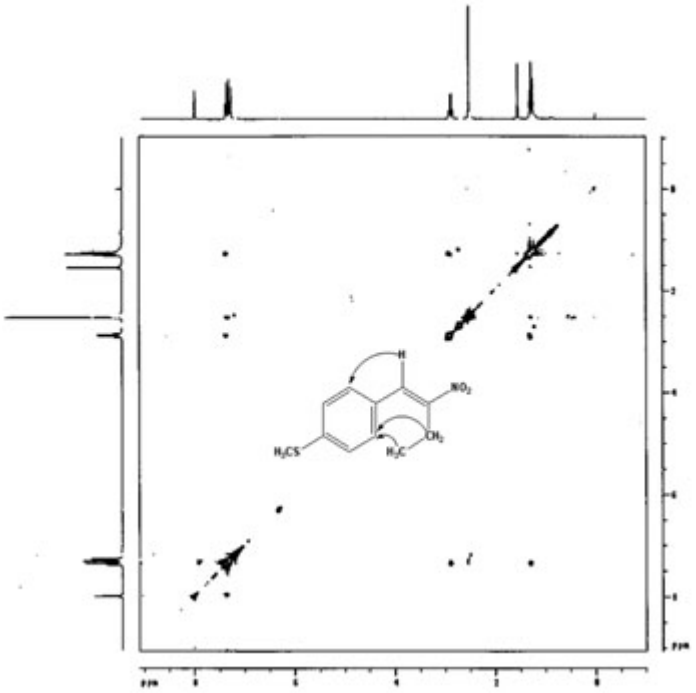

Fig. 2a. NOESY spectrum of (E)-1-(4-methylthiophenyl)-2-nitrobutene [(E)-1a] ($CDCl_3$).

Fig. 2b. NOESY spectrum of (*Z*)-1-(4-methylthiophenyl)-2-nitrobutene [(*Z*)-1b] ($CDCl_3$).

Table 3. ^{1}H-NOESY correlations of (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitrobutenes [(*E*)-1a and (*Z*)-1a] ($CDCl_3$).

	(E)-1[a]	(Z)-1a
CH_2CH_3	H2', H6'; H4	H1, H3
SCH_3	H3', H5'	H-Ar
$CH_3CH_2C{=}CH$	H2', H6'; H4	H1; H4
$ArCH{=}C$	H2', H6'	H-Ar; H3; H4
H3'; H5' (Ar-H)	SCH_3	SCH_3
H2'; H6' (Ar-H)	H3; H4; H1	H1

In order to analyze the conformational differences revealed by the NMR spectra using theoretical tools, the structures of both isomers were optimized at the RHF/6-311G(d,p) level. In both cases, the side chain and the ring were found to be far from coplanarity and therefore only weakly conjugated in the minimum energy conformation. In (*E*)-1a, dihedral angle C2'-C1'-C1-C2 (θ) is 46°, reflecting the relief of steric compression between H2'/6' and the α-ethyl side chain. In the (*Z*) isomer, the corresponding angle is 50°, showing a similar interaction between H2'/6' and the nitro group.

In the (*E*) isomer, an O-N-C2-C3 dihedral angle of 6° shows that the nitro group is almost coplanar with regard to the C=C double bond, consistent with an almost completely conjugated side chain, although interacting only weakly with the aromatic π system. On the contrary, in the (*Z*) isomer this angle is 71°, as a result of the repulsion between the nitro group and H2'/6'. Figure 3 shows the optimized conformations of both isomers. Consequently,

the low field (7.98 ppm) at which H1 resonates in the (*E*) isomer should not be attributed to deshielding of this proton by the aromatic ring current, but only to the electron-withdrawing effect of the nitro group, which in this isomer (and not in the other) is strongly conjugated with the alkene double bond. The rotational barriers around the C1-C1' bond differ slightly between both isomers, but in neither case do they exceed 2.2 kcal mol^{-1} (Figure 4), suggesting that this rotation is relatively unhindered. It should be pointed out that in the (*Z*) isomer the nitro group remains almost perpendicular to the C=C double bond regardless of the θ angle.

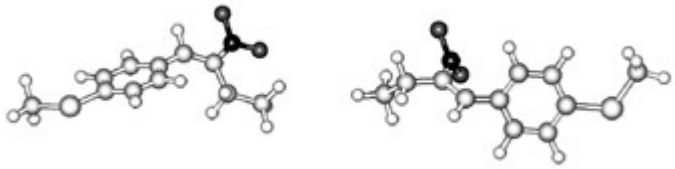

Fig. 3. Optimized conformations of (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitrobutenes [(*E*)-1a and (*Z*)-1a].

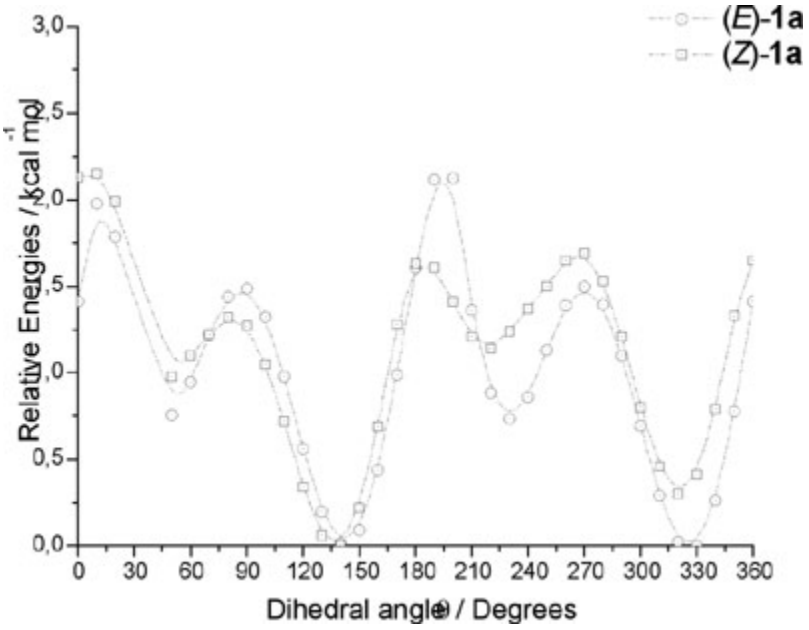

Fig. 4. Relative rotational energies of (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitrobutenes [(*E*)-1a and (*Z*)-1a] around the C1'-C1 bond.

The structures of the corresponding isomeric nitroethenes and nitropropenes [1c: R^1 = H or 1b: R^1 = CH_3, respectively (Figure 1)] were also optimized using RHF at the 6-311G(d,p) level of calculation. The (*E*) nitroethene molecule was found to be almost flat with dihedral angle C2'-C1'-C1-C2 amounting to 10° and no steric interaction between H2 and H2'/6', but in the (*Z*) isomer this angle was 49°, due to the relief of steric strain between H2'/H6' and the nitro group. In the case of the nitropropenes, both molecules were considerably twisted, like the nitrobutenes, with dihedral angles of 42° and 50° for the (*E*) and (*Z*) isomer, respectively.

In order to predict the relative stabilities of both 1-(4-methylthiophenyl)-2-nitrobutene isomers, it was necessary to compute the absolute enthalpy for each molecule and then compare these two values. This involved first performing a geometry optimization on each isomer in order to determine the minimum energy structure, followed by a frequency calculation at the optimized geometry during which various termochemical quantities were also computed. Comparison of these absolute entalphies of both 1-(4-methylthiophenyl)-2-

nitrobutene isomers gave a difference of 3.04 kcal mol^{-1}. A similar theoretical comparison of the absolute enthalpies of the (*E*)- and (*Z*)-1-(4-methylthiophenyl)-2-nitropropenes and -ethenes gave differences of 4.49 and 7.23 kcal mol^{-1}, respectively. According to the values obtained including the thermal and entropic corrections appropriate for 298.15 K and 1 atm, the computed ΔG for these pairs always indicate that the *E*-isomers are more stable than the *Z*-isomers. Plugging these numbers into the free energy relationship allows us to estimate equilibrium constants (K_{eq}) for the (*E*) to (*Z*) interconversion as shown in table 4. The calculated K_{eq} for the nitrobutenes corresponds to an approximately 98:2 isomer ratio in the equilibrium mixture. Nevertheless, the fact that it was possible to isolate both isomers formed under the usual thermodynamically controlled conditions and that the isomer ratio in the crude reaction mixture was close to 92:8 indicates that our RHF6-311G(d,p) calculations in vacuo overestimate their free energy difference. In the lower homologues, the relative stability of the (*E*) isomer is sufficient to predict its formation to almost complete exclusion of the (*Z*) isomer. The results of this theoretical approach are in agreement with the ^{1}H-NMR spectrum of the crude 1-(4-methylthiophenyl)-2-nitropropene, which suggests the presence of a small amount of the (*Z*) isomer, judging from the appearance of a very weak singlet at 7.17 ppm which may be attributed to H1. The strong H1 signal for the (*E*) isomer occurs at 8.04 ppm.[7] In the spectrum of the crude 2-(4-methylthiophenyl)-1-nitroethene, only one signal (a doublet) correspondingly assigned to H2, was visible at 7.96 ppm.

Table 4. Differences in absolute enthalpies and free energies and calculated equilibrium constants of (*E*)- and (*Z*)-4-methylthiophenylnitrobutenes (1a), -propenes (1b), and –ethenes (1c).

	$\Delta H_{(E/Z)}^{298}$ [kcal mol^{-1}]	$\Delta G_{(E/Z)}^{298}$ [kcal mol^{-1}]	K_{eq}
(E)- and (Z)-1a	-3,04	-2,37	0,018
(E)- and (Z)-1b	-4,49	-3,80	0,0016
(E)- and (Z)-1c	-7,23	-7,21	0,0000052

In conclusion, the Knoevenagel condensation of benzaldehydes with nitroalkanes as bulky as or more so than nitropropane under thermodynamic control may be expected to afford isolable amounts of the (*Z*)-arylnitroalkenes. The ^{1}H-NMR spectra of the stereoisomeric arylnitrobutenes (1a) exhibit marked differences which have now been interpreted on the basis of RHF/6-311G(d,p) calculations. In particular, the side chain of the (*E*)-arylnitrobutenes is practically flat, while in the (*Z*) isomers the nitro group is twisted by about 70 with regard to the ethylene double bond and this torsion angle is preserved when the side chain is rotated with regard to the ring. Interestingly, the calculated optimal conformations of the (*E*)- and (*Z*)-arylnitrobutenes and -propenes *in vacuo* incorporate similar torsion angles of the side chain with regard to the ring of about 45-50. Therefore, the considerable deshielding of the side chain hydrogen nucleus next to the aromatic ring in the (*E*) isomers is due mainly to the electronic effect of the strongly conjugated nitro group, and not to the magnetic anisotropy of the ring.

EXPERIMENTAL

NMR Studies

The NMR spectra were recorded using a Bruker Avance DRX 300 instrument operating at a ^{1}H frequency of 300.13 MHz and a ^{13}C frequency of 75.47 MHz. All measurements were performed at a probe temperature of 300 K, using solutions of the compounds in $CDCl_3$ (25-30

mg ml^{-1}) containing tetramethylsilane (TMS) as an internal standard. The two-dimensional spectra were acquired with a Bruker inverse 5 mm Z-gradient probe. The one-dimensional carbon spectra were obtained with a spectral width of 18,000 Hz with 3 s between transients and the 90° pulse was 10 µs. The NOESY spectra were acquired using standard Bruker software (noesytp). The spectra were collected as 512 x 512 blocks of data and were processed by sinusoidal multiplication in each dimension. Other parameters were as follows: 256 increments in t_1; 4 scans; and relaxation delay, 1s.

(*E*)-1-(4-Methylthiophenyl)-2-nitrobutene [(*E*)-1a] and (*Z*)-1-(4-Methylthiophenyl)-2-nitrobutene [(*Z*)-1a].

A mixture of 4-methylthiobenzaldehyde (1.3 ml, 0.010 mol), N,N-dimethylethylenediamine (1.3 ml, 0.010 mol), 1-nitropropane (4.5 ml, 0.041 mol) and toluene (10 ml) was refluxed for 24 h with continuous water removal under a Dean-Stark trap. All volatiles were removed under reduced pressure and the residue was fractionated chromatographically over silica gel, eluting with $CHCl_3$, to afford the E [(*E*)-1a] (1.08 g, 92% in the mixture) and *Z* isomers [(*Z*)-1a] (0.096 g, 8% in the mixture) as viscous orange colored liquids.

(*E*)-1a: ^{1}H-NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.52 (s, 3H, S-CH_3), 2.88 (q, 2H, J = 7.4 Hz, CH_3CH_2C=CH), 7.29 (d, 2H, J = 8.5 Hz, H3' and H5'), 7.36 (d, 2H, J = 8.5 Hz, H2' and H6'), 7.98 (s, 1H, Ar-CH=C). HREIMS m/z (M^+) = 223.06621; calc. for $C_{11}H_{13}NO_2S$ = 223.06670.

(*Z*)-1a: ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 7.4 Hz, CH_2CH_3), 2.46 (s, 3H, S-CH_3), 2.67 (q, 2H, J = 7.4 Hz, CH_3CH_2C=CH), 6.29 (s, 1H, Ar-CH=C), 7.16 (apparent s, 4H, J = 9.2 Hz, Ar-H). HREIMS m/z (M^+) = 223.06622; calc. for $C_{11}H_{13}NO_2S$ = 223.06670.

Computational Details

The *ab initio* calculations were performed using the Gaussian 98 suite of quantum chemistry programs.[8] The computations were carried out on an SGI Octane R10000 workstation. The calculations presented here involved geometry optimizations using the RHF/6-311G(d,p) basis set followed by calculation of the vibrational frequencies. All geometry optimizations as well as partially relaxed potential energy surface (PES) scan calculations for the compounds were calculated under tight optimization conditions at the RHF/6-311G(d,p) level of theory using Berny Optimization (Opt = Z-matrix, Tight). In the scan calculations, the θ angle was fixed by specifying its torsional value while all other parameters were optimized at 10° intervals. The relative energies were calculated from the difference between the total energy for each rotamer with respect to the lowest minimum found for each compound in the PES scan calculation.

ACKNOWLEDGEMENTS

This work was supported by ICM grant N° P99-031-F and FONDECYT grant N° 1000776. The authors are grateful to Dr. J. A. Hueso for the HRMS measurements.

REFERENCES

1. A. Yoshikoshi and M. Miyashita, Acc. Chem. Res. 18, 284-290 (1985).

2. M. Miyashita, T. Kumazawa and A. Yoshikoshi, J. Org. Chem. 45, 2945-2950 (1980).

3. A. G. Barrett and G. G. Graboski, Chem. Rev. 86, 751-762 (1986).

4. E. J. Corey and H. Streicher, J. Am. Chem. Soc. 100, 6294-6295 (1978).

5. Y. V. Baskov, T. Urbanski, M. Witanowski and L. Stefaniac, Tetra hedron 20, 1519-1526 (1964).

6. M. Node, T. Kawabata, M. Fujimoto and K. Fuji, Synthesis 1984, 234-236.

7. C. Hurtado-Guzmán, A. Fierro, P. Iturriaga-Vásquez, S. Sepúlveda- Boza, B.K. Cassels and M. Reyes-Parada, J. Enzyme Inhib. Med. Chem. 18, 339-347 (2003).

8. C. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople. Gaussian98; Gaussian Inc; Pittsburgh, PA, (1998).