J. Braz. Chem. Soc., Vol. 21, No. 10, 1896-1904, 2010.
Printed in Brazil - ©2010 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

Synthesis of Some Fenchyl-Substituted Alkenes and Enol-Ethers Containing 3-Oxyphenyl Substituents by the Barton-Kellogg Reaction

Luiz Francisco M. L. Ciscato,[a,c] Erick L. Bastos,[b] Fernando H. Bartoloni,[a] Wolfgang Günther,[c] Dieter Weiss,[c] Rainer Beckert[c] and Wilhelm Josef Baader*[,a]

[a]*Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo, 05508-000 São Paulo-SP, Brazil*

[b]*Centro de Ciências Naturais e Humanas, Universidade Federal do ABC, 09210-170 Santo André-SP, Brazil*

[c]*Institut für Organische Chemie und Makromolekulare Chemie, Friedrich-Schiller Universität Jena, 07737 Jena, Germany*

Usando-se a reação de Barton-Kellogg, foram sintetizados um alceno e dois enóis-éteres fenchyl-substituídos, contendo grupos 3-oxifenila como substituintes. O fenchil-alceno aromático tri-substituído **1a** foi preparado com rendimento de 53% a partir de tiofenchona e um diazoanisol. A abordagem inversa, baseada no acoplamento entre diazofenchona e tionoésteres aromáticos, foi utilizada para produzir os enóis-éteres **1b** e **1c** (rendimentos 95 e 75%, respectivamente). Em todos os casos foi obtida uma mistura dos isômeros *E* e *Z*; a atribuição e quantificação destes isômeros foram realizadas pela análise dos dados de espectroscopia de RMN assistida por cálculos teóricos (relação *E*/*Z* **1a** = 0,72, **1b** = 2,2, **1c** = 1,8). A reação ocorre com baixa estereosseletividade, levando à formação preferencial dos diastereoisômeros das olefinas e enóis-éteres, nos quais o substituinte aromático está localizado ao lado dos dois grupos metila da porção fenchila.

The synthesis of one fenchyl-substituted alkene and two enol-ethers, containing 3-oxyphenyl substituents by the Barton-Kellogg reaction is described. The tri-substituted aromatic fenchyl-alkene **1a** was prepared in 53% yield from thiofenchone and a diazoanisole; whereas enol-ethers **1b** and **1c** were obtained (95 and 75% yield, respectively) using an inverse approach based on diazofenchone and aromatic thionoesters. A mixture of *Z* and *E* isomers was obtained in all cases; isomer attribution and quantification has been carried out by analysis of NMR spectroscopic data assisted by theoretical calculations (*E*/*Z* ratio: **1a** = 0.72, **1b** = 2.2, **1c** = 1.8). Reaction proceeds with low stereoselectivity leading to the preferential formation of diastereoisomeric olefins and enol-ethers where the aromatic substituent resides at the side of the two fenchyl methyl groups.

Keywords: Barton-Kellogg olefination, hindered alkenes, diazo compounds, thioketone, fenchone

Introduction

The chemistry of hindered olefins is a challenging topic for both synthetic and theoretical chemists.[1,2] Strained alkenes containing the fenchone-type skeleton are chiral elements in asymmetric synthesis[3-5] and model compounds in the study of structural deformations on double bonds.[6] The Barton-Kellogg (BK) reaction, or Barton-Kellogg (BK) olefination,[7-9] is the method of choice for the efficient preparation of such alkenes. The synthesis of 2-diphenylmethylenefenchane, 2-cyclohexylidenefenchane and bis-fenchylidene, one of the most hindered olefin yet synthesized, were accomplished with this method.[6,10,11] The reaction consists of the 1,3-dipolar cycloaddition between a diazo and a thio or selenocarbonyl compound, furnishing the target alkene after two-fold extrusion of nitrogen and sulfur/selenium from Δ^3-1,3,4-thia- or selenodiazolines.[9] The synthesis of enol-ethers by the BK method has been scarcely investigated,[12,13] and derivatives bearing the fenchyl group have not yet been described.

The stabilization provided by the fenchyl group to these alkenes and enol-ethers, can bring new knowledge and possibilities to areas like organic synthesis and material science, as well as to chemiluminescence research, where

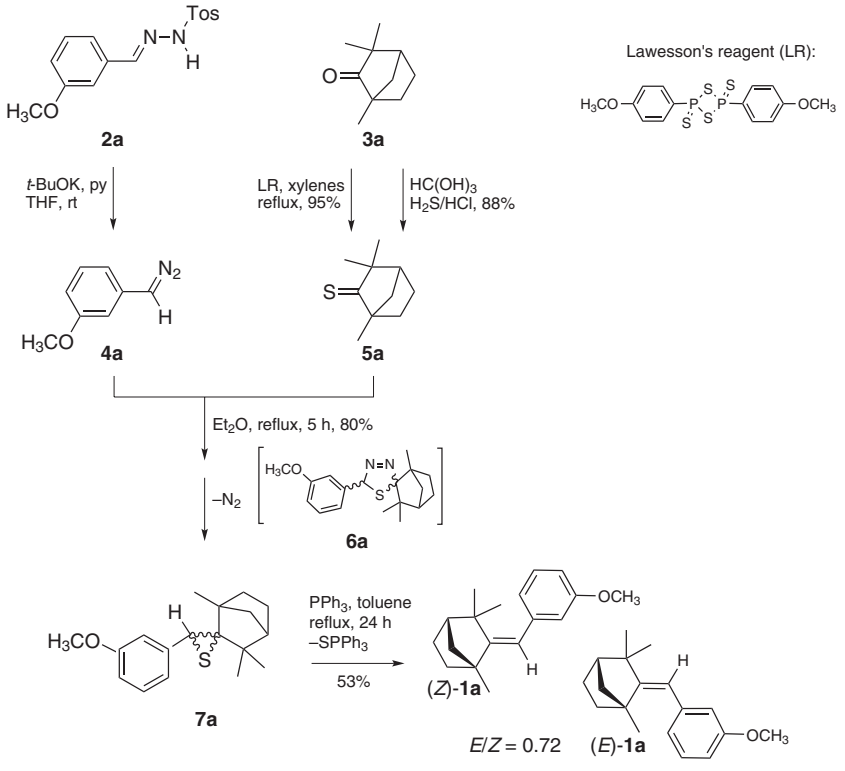
*e-mail: wjbaader@iq.usp.br

they can be used as affordable starting materials for the synthesis of thermally stable 1,2-dioxetane derivatives.[14-16] Therefore, herein we present: (*i*) the synthesis of the tri-substituted alkene **1a** by conventional BK reaction from thiofenchone (**5a**) and diazoalkane **4a**, and (*ii*) the synthesis of enol-ethers **1b** and **1c** using the inverse approach for the BK reaction, *i.e.*, from diazofenchane (**4b**) and thionoesters **5b** and **5c** (Schemes 1 and 2).

Results and Discussion

Treatment of (−)-fenchone (**3a**) with Lawesson's reagent in refluxing xylene afforded (−)-thiofenchone (**5a**) in 95% yield (Scheme 1).[17] Alternatively, **5a** was prepared by the reaction of **3a** with a mixture of H_2S/HCl gas in trimethyl orthoformate (88% yield, orange crystals). The diazo compound **4a** was prepared by the Bamford-Stevens route from the corresponding tosylhydrazone **2a**, using potassium *tert*-butoxide and pyridine in THF.[18] This compound is highly unstable and therefore it was not isolated or characterized. Reaction yield was estimated in 75% from the stoichiometry of the subsequent reaction with thiofenchone (Scheme 1). The reaction of **5a** with the deep red diazo compound **4a** occurred immediately at room temperature affording a diastereoisomeric mixture of Δ^3-1,3,4-thiadiazolinic intermediates **6a**, as indicated by discoloration of the mixture and TLC analysis (Scheme 1). Warming up of the reaction mixture leads to nitrogen liberation and formation of thiirane **7a** as a colorless solid. A solution of **7a** in toluene was treated with triphenylphosphine and refluxed for 24 h, resulting, after sulfur extrusion, in a mixture of *E*/*Z* isomers of the alkene **1a** (overall yield: 53% from **5a**). The products were isolated and characterized by spectroscopic analysis.

Enol-ethers **1b** and **1c** were prepared by the coupling of diazofenchane (**4b**) with thionoesters **3b** and **3c** (Scheme 2).[12,13] This inverse approach is required because the conventional BK reaction would require the difficult preparation of a methoxy-substituted diazomethane derivative.[19] The Bamford-Stevens method was unsuccessful to convert the corresponding tosylhydrazone to diazofenchane (**4b**). Thus, **4b** was prepared by oxidation of fenchylhydrazone (**2b**) with nickel peroxide and calcium oxide in dimethoxyethane at −78 °C.[20,21] Again, due to the highly unstable nature of **4b**, the yield of this transformation could only be estimated to be as high as 90% based on the stoichiometry of the subsequent reaction with the thionoesters. Thionoesters **5b** and **5c** were prepared from the corresponding esters with Lawesson's reagent in 84% (R = Me) and 45% (R = TBDMS) yields,[17,22] and stored at −20 °C after purification by column chromatography, to avoid polymerization.[23] The reaction

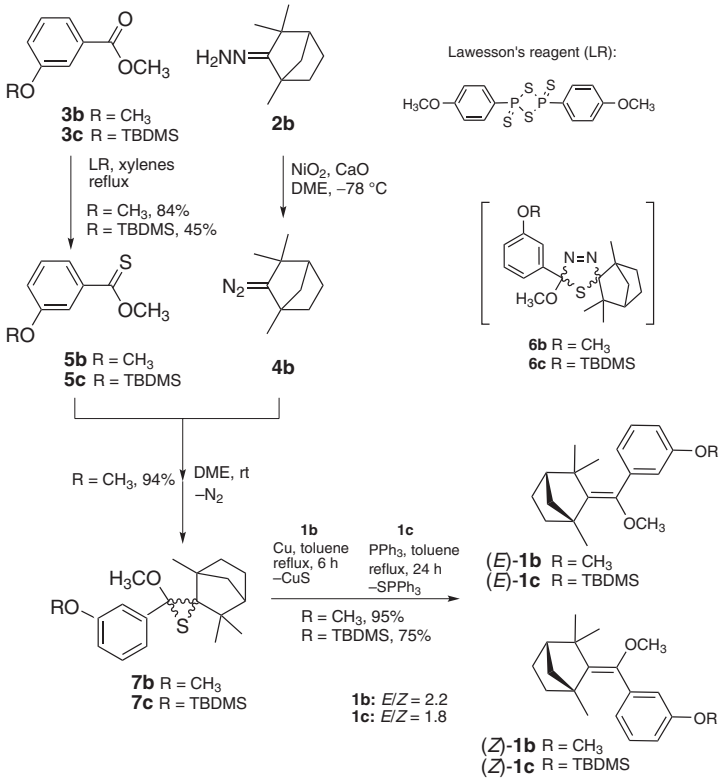


Scheme 1. Synthesis of fenchyl-substituted olefin **1a** by the Barton-Kellogg reaction.

between diazofenchane (**4b**) and thionoesters **5b** or **5c** was carried out in a similar manner as described previously for diazo compound **4a**, except that the solution of **6c** in toluene was refluxed with copper-bronze for 6 h after nitrogen extrusion (Scheme 2). Enol-ethers **1b** and **1c** were obtained as mixtures of isomers, with overall yields of 95 and 75%, respectively.

The fenchyl-substituted alkene **1a** and enol-ethers **1b** and **1c** were obtained in better yields with the BK method that by other classical methods of carbon-carbon double-bond formation. For example, the methylenation of fenchone by an optimized Wittig reaction was reported to afford a yield of 5%.[24] The same reaction using the very expensive Tebbe's reagent gives a yield of only 16%, showing that the preparation of fenchone-derived olefins generally occurs with low yields.[24] Our own attempts to prepare these compounds using Wittig and Horner-Wadsworth-Emmons (HWE) methods failed or resulted in very poor yields. (−)-Fenchone showed to be not reactive in HWE conditions, independent of the base used (NaH, *n*-BuLi, *sec*-BuLi, LDA, LiHMDS), with no product formation detected at all, even after a 24 h reaction time. Also, the intermolecular McMurry cross-coupling[15,25] of methyl 3-methoxybenzoate and (−)-fenchone, in the presence of either $TiCl_3$/$LiAlH_4$/TEA or $TiCl_4$/Zn, did not produce reproducible results.[26]

The attribution of NMR signals and quantification of the *E* and *Z* isomers of **1a** and **1b** was performed as follows. The ^{1}H NMR spectra of **1a** featured two singlet signals at 6.15 and 6.16 ppm, which clearly indicate the existence of two different olefinic hydrogen atoms. The HSQC experiment (see Figure S1) shows that there are two different sets of signals corresponding to three methyl groups each: one group with ^{1}H shifts of 1.27, 1.04 and 0.98 ppm, and another group at 1.15, 1.14 and 0.95 ppm (Figure S2 and Figure S3). The integration of the corresponding carbon peaks in the ^{13}C spectrum showed a slight majority of the first set of methyl groups. The attribution of *E* and *Z* isomers could not be done by means of a straightforward 1D NOESY spectrum, because the irradiation intensity at the olefinic hydrogen had to be very high to produce any detectable nOe signal for the adjacent methyl groups, causing a broadening of the signal that prevented the selective excitation of just one hydrogen atom. The 2D NOESY experiments (see Figure S4) showed that the hydrogen atom at 6.15 ppm is located in the proximity of the region of the two methyl groups with signals at 1.15 and 1.14 ppm, an indication that these signals correspond to the *E* isomer. Contrarily, the hydrogen atom at 6.16 ppm is located in the proximity of only one methyl group at 1.27 ppm, therefore corresponding to the *Z* isomer (see spatial structures in Scheme 1). Consequently, the signals at 6.15 and 6.16 ppm were attributed to the



Scheme 2. Synthesis of fenchyl-substituted enol-ethers **1b** and **1c** by the inverse Barton-Kellogg reaction.

olefinic hydrogen atoms of isomers *E* and *Z*, respectively (*E*/*Z* ratio = 0.72). NMR spectra (HMBC, HSQC, NOESY, HSQC/HMBC) are given in Supplementary Information.

The evaluation of the ^{1}H NMR spectrum of **1b** also suggests the presence of two isomers, because there are two different olefinic methoxy group signals at 3.09 and 3.08 ppm, but only one signal at 3.73 ppm, corresponding to the aromatic methoxy group of both isomers. The HSQC spectra (see Figure S5) also corroborate the presence of two isomers: methyl groups of the fenchyl moiety are observed at 1.45, 1.01 and 0.52 ppm for one isomer, and 1.23 (two signals together) and 0.56 ppm for the other isomer (Figure S2). With the methyl groups of different isomers localized, selective excitation 2D- and 1D-NOESY experiments were carried out to assert the attribution of *E* and *Z* isomers of **1b** (see Figures S5 and S6). Selective excitation of the single methyl group at 1.45 resulted in the nOe enhancement of the methoxy group signal at 3.09 ppm, identifying it as belonging to the *E* isomer (Figure S7). Excitation of the two methyl groups at 1.23 ppm resulted in the NOE enhancement of the signal at 3.08 ppm, therefore belonging to the *Z* isomer (see structures in Scheme 2). The integration of the carbon peaks in the INVGATE ^{13}C NMR spectrum[27] revealed an *E*/*Z* ratio of 2.2.

The spectrum of **1c** showed to be very similar to that of **1b**, so *E*/*Z* attribution could be performed in analogy to the former compound. Two sets of three methyl groups could also be observed in the ^{1}H NMR spectrum, one set with peaks at 1.50, 1.06 and 0.60 ppm, and another one with two peaks together at 1.29 and one at 0.63 ppm. For **1b**, the two CH_3 signals together correspond to the *Z* isomer; therefore it is assumed that this is also the case for **1c**. An *E*/*Z* ratio of 1.8 could be obtained from the integration of these ^{1}H signals.

A quantum chemistry study was carried out in order to provide further structural evidence on *E*/*Z* attribution of **1a** and **1b** isomers from spectroscopic data. The equilibrium geometries, vibrational frequencies and thermochemical data were obtained using the hybrid generalized gradient approximation functional PBE1PBE[28] with the 6-311+G(d,p) basis set (see Supplementary Information).[29] This functional was used because it produced excellent results in the calculation of bond angles in a dataset of 27 small organic molecules, when compared with other 37 density functionals, including the popular B3LYP.[30] Also, structural parameters of *E*/*Z* isomers of bis-fenchylidene obtained at the PBE1PBE/6-311+G(d,p) level are in good agreement with both X-ray data as well as theoretical calculations (see Supplementary Information).[31-35] The optimized structures of *E*/*Z* , **1a** and **1b** are depicted in Figure 1 and relevant geometry parameters are given in Table S1 (see Supplementary Information). The isotropic chemical shielding at H and C nuclei of **1a**, **1b** and TMS were calculated at the GIAO/IEFPCM/W04P/cc-pVDZ//pbe1pbe/6-311+G(d,p) level.[34] This approach allowed us to calculate ^{1}H and ^{13}C chemical shifts of **1a** and **1b,** which were compared to the experimental data (Figure S8).[35] The adjusted coefficients of determination (adj-$R^2 > 0.99$) indicate that the predicted d values for both ^{1}H and ^{13}C nuclei are in excellent agreement with experimental data.

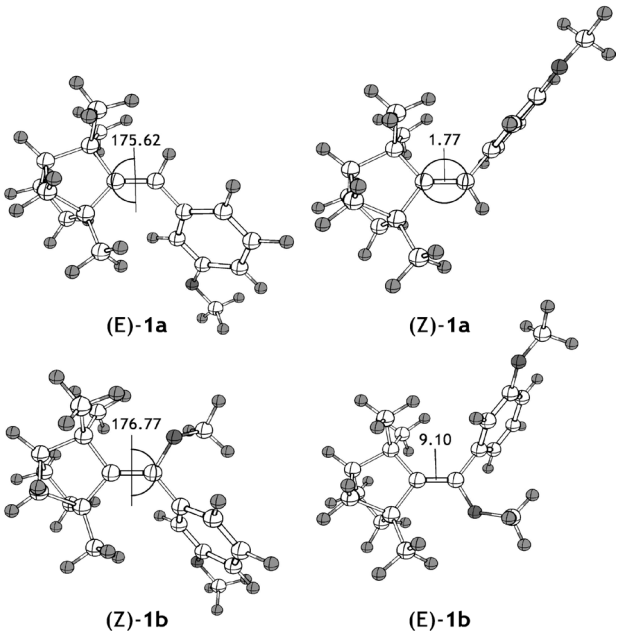


Figure 1. Optimized structures of *E*/*Z* isomers of **1a** and **1b**.

Conclusions

Sterically-hindered fenchyl-substituted aromatic alkene **1a** can be prepared using the Barton-Kellogg method from thiofenchone and a diazoanisole; whereas enol-ethers **1b** and **1c** can be obtained from diazofenchane and aromatic thionoesters. This approach results in product formation in better yields than those obtained by classical methods and can be useful for the synthesis of encumbered alkenes. Reaction proceeds with low stereoselectivity leading to the preferential formation of diastereoisomeric olefins and enol-ethers where the aromatic substituent resides at the side of the two fenchyl methyl groups.

Experimental

All reactants were purchased at highest commercial quality and used without purification, except otherwise mentioned. Solvents were purified and dried as described by Armarengo and Perrin.[36] Bulb-to-bulb distillations were made using a Kugelrohr apparatus (Büchi Glass Oven B-580). Melting points (°C) were determined in a Kofler hot-stage apparatus

and uncorrected. NMR spectra were acquired on a Bruker spectrometer AC-250, DRX-400, or DRX-500 (25 °C, $CDCl_3$, tetramethylsilane (TMS) as internal reference). Mass spectra were obtained on a CG-MS Hewlett-Packard 5890/5988, MAZ 95 XL or Finnigan MAT SSQ 710.

CAUTION: Although no accident occurred during the progress of this work, diazo compounds are known to decompose explosively.[37] Therefore, all caution should be taken.

*(1R)-2-Thione-1,3,3-trimethylbicyclo[2.2.1]heptane ((−)-thiofenchone, **5a**)*

Method A: A mixture of (−)-fenchone **3a** (1.5 g, 10 mmol) and Lawesson's Reagent (8.1 g, 20 mmol) was refluxed in xylene (20 mL) under inert atmosphere for 3 h and filtered over silica gel (5 cm, heptane). The resulting orange solution was evaporated in vacuo (0.3 mbar, rt) until **5a** starts to distillate. Xylene was mostly removed by stirring the solution at temperatures between −50 °C and room temperature at 0.3 mbar. The product was obtained in 95% yield (1.6 g, 0.95 mmol) containing small amounts of residual xylene.

Method B: A mixture of (−)-fenchone (4.0 g, 27 mmol) and Lawesson's reagent (6.5 g, 16 mmol) was refluxed under inert atmosphere for 1 h until it becomes a homogeneous solution. Thereafter, the mixture was allowed to reach room temperature and the resulting oil was purified by column chromatography (SiO_2, hexanes/ethyl acetate 9:1), resulting in **5a** (3.1 g, 21 mmol, 78% yield).

Method C: A solution of (−)-fenchone (1.5 g, 10 mmol) and trimethylorthoformate (12 g, 94 mmol) in dry methanol (10 mL) was simultaneously bubbled at 0 °C with gaseous HCl and H_2S for 2 h. Ethyl ether (25 mL) was added and the resulting orange solution washed with water until the aqueous phase became neutral. The organic layer was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The resulting orange oil was purified by column chromatography (SiO_2, hexanes), resulting in pure **5a** (1.48 g, 8.8 mmol, 88%).

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 1.9-1.6 (m, 4H, fenchyl H), 1.4-1.2 (m, 3H, fenchyl H), 1.28 (s, 3H, 1-CH_3), 1.14 (s, 3H, 3-CH_3), 1.10 (s, 3H, 3-CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 279.8 (C=S), 66.2 (1-C), 57.7 (3-C), 46.9 (4-C), 43.7 (7-C), 35.4 (6-C), 28.6 (5-C), 26.4 (3-$\underline{C}H_3$), 25.0 (3-$\underline{C}H_3$), 19.2 (1-$\underline{C}H_3$) ppm. mp 22-24 ºC (reported: 22-24 °C)[7-9]

*(1R)-2-Diazo-1,3,3-trimethylbicyclo[2.2.1]heptane (diazofenchane, **4b**)*

A solution of (−)-fenchone **3a** (3.0 g, 20 mmol), hydrazine hydrate 100% (4.5 g, 20 mmol), and acetic acid (1.2 mL) in ethanol (8 mL) was refluxed for 8 h.[38] After reaching room temperature, the solution was evaporated *in vacuo* and Et_2O (30 mL) was added to the residue. The solution was washed with aqueous solutions of NaOH (10%, 30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and evaporated in vacuo, resulting in fenchylhydrazone (3.0 g, 18 mmol, 89% yield), which was recrystallized from heptane at −20 ºC. A solution of fenchylhydrazone (2.0 g, 12 mmol) in dry dimethoxyethane (60 mL) was cooled to −78 °C and a mixture of NiO_2 (4 g, 44 mmol) and CaO (1 g, 18 mmol) was added slowly. The resulting suspension was stirred for 30 min and the temperature was allowed to reach 0 °C. The suspension containing **4b** was filtered under inert atmosphere and used immediately.

*1-(Diazomethyl)-3-methoxybenzene (**4a**)*

A solution of 3-methoxybenzaldehyde (1.0 g, 7.3 mmol) and *N*-tosylhydrazide (1.4 g, 7.3 mmol) in ethanol (15 mL) was refluxed for 8 h. After this period, the resulting solution was evaporated and the residue was purified by column chromatography (SiO_2, hexanes/ethyl acetate 1:1) resulting in *N*'-(3-methoxybenzylidene)-4-methylbenzenesulfonohydrazide **2a** (2.2 g, 7.3mmol, 100%). To a solution of **2a** (2.2 g, 7.3 mmol) in pyridine (15 mL) was added *t*-BuOK (0.8 g, 7.5 mmol). The mixture was warmed to 60 ºC under stirring, resulting in a red solution, which was poured into water (100 mL). The mixture was extracted with Et_2O (3 × 30 mL) and the unified organic layers were dried ($MgSO_4$, 0 °C, 15 min). After filtration, the deep red solution of 1-(diazomethyl)-3-methoxybenzene (**4a**) was used immediately.

*O-Methyl 3-methoxybenzothioate (**5b**)*

A mixture of methyl 3-methoxybenzoate (**3b**, 1.0 g, 6.0 mmol) and Lawesson's reagent (3.3 g, 8.1 mmol) in dry xylene (10 mL) was refluxed for 12 hours. The suspension was filtered in silica gel (5 cm) and the solution evaporated *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2, hexanes/ethyl acetate 5:1), yielding **5b** (0.92 g, 5.0 mmol, 84%) as a bright yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$, 25 ºC): δ 7.81 (dd, $^3J_{H,H}$ 5 Hz, $^4J_{H,H}$ 2.5 Hz, 1H, Ar, 4-H), 7.76 (t, $^4J_{H,H}$ 2.5 Hz, 1H, Ar, 2-H), 7.31 (t, $^3J_{H,H}$ 5 Hz, 1H, Ar, 5-H), 7.11 (dd, $^3J_{H,H}$ 5 Hz, $^4J_{H,H}$ 2.5 Hz, 1H, Ar, 6-H), 4.31 (s, 3H, C(S)OCH_3), 3.87 (s, 3H, ArOCH_3) . ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 ºC): δ 211.9 (C=S), 159.3 (Ar, 3-C), 139.5 (Ar, 1-C), 129.0 (Ar, 5-C), 121.2 (Ar, 6-C), 119.1 (Ar, 4-C), 113.6 (Ar, 2-C), 59.3 (Ar$O\underline{C}H_3$), 55.4 (C(S)$O\underline{C}H_3$). Anal. calc. for $C_9H_{10}O_2S$: C 59.32, H 5.53, S 17.59, found: C 59.22, H 5.53, S 17.53%.

*O-Methyl 3-(tert-butyldimethylsilyloxy)benzothioate (**5c**)*

Methyl 3-(*tert*-butyldimethylsilyloxy)benzoate (**3c**) was prepared through microwave irradiation as described previously.[39] To a solution of **3c** (3.0 g, 11 mmol) in dry xylene (50 mL), Lawesson's reagent (6.1 g, 15 mmol) was added and the resulting suspension was refluxed for 24 h. The suspension was filtered in silica gel (5 cm) and the solution evaporated *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2, hexanes/ethyl acetate 9:1), yielding **5c** (1.4 g, 5.9 mmol, 45%) as a bright yellow oil.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 7.80 (dt, $^3J_{H,H}$ 7.8 Hz, $^4J_{H,H}$ 2.5 Hz, 1H, Ar, 4-H), 7.68 (t, $^4J_{H,H}$ 2.0 Hz, 1H, Ar, 2-H), 7.26 (t, $^3J_{H,H}$ 7.9 Hz, 1H, Ar, 5-H), 7.02 (ddd, $^3J_{H,H}$ 8.0 Hz, $^4J_{H,H}$ 2.5 Hz, $^5J_{H,H}$ 1.0 Hz, 1H, Ar, 6-H), 4.29 (s, 3H, C(S)OCH_3), 1.01 (s, 9H, $SiC(CH_3)_3$), 0.24 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 211.9 (C=S), 155.4 (Ar, 3-C), 139.6 (Ar, 1-C), 128.5 (Ar, 5-C), 124.5 (Ar, 6-C), 121.8 (Ar, 4-C), 120.3 (Ar, 2-C), 59.3 (OCH_3), 25.4 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), −5.0 ($Si(CH_3)_2$). MS (*m/z*): 282 (M^+), 266, 251, 225, 209, 193, 177, 89. HRMS (Micro-ESI): *m/z* calc. for $C_{14}H_{23}O_2SSi$: 283.1188 $(M-H)^+$; found: 283.1193.

*3'-(3-Methoxyphenyl)-1,3,3-trimethylspiro[bicyclo[2.2.1]heptane-2,2'-thiirane] (**7a**)*

Thiofenchone **5a** (0.5 g, 3 mmol) was added to a solution of 1-diazomethyl-3-methoxybenzene (**4a**) (generated from 7.3 mmol of **2a)** in diethyl ether. The reaction was refluxed for 5 h, the solvent evaporated in vacuo and the residue purified by column chromatography (SiO_2, heptane/ethyl acetate 9:1), yielding **7a** (0.69 g, 2.4 mmol, 80%) as a clear oil containing a complex mixture of isomers.

In the attributions of the ^{1}H and ^{13}C NMR spectra below, more than one chemical shift values have been assigned to several of the atoms, since a mixture of diastereoisomers has been obtained in the synthesis.

^{1}H NMR (250 MHz, $CDCl_3$, 25 ºC): δ 7.14-7.19 (m, 1H, Ar, 4-H), 7.01-7.03 (m, 1H, Ar, 2-H), 6.97-7.00 (m, 1H, Ar, 5-H), 6.73-6.77 (m, 1H, Ar, 6-H), 4.26, 4.08, 3.87 (s, 1H, thiirane H), 3.785, 3.783, 3.780, 3.776 (s, 3H, OCH_3), 1.88-1.69, 1.66-1.42 (m, 7H, fenchyl H), 1.318, 1.223, 1.172, 1.142, 1.132, 1.128, 1.097, 1.034, 1.022, 1.002, 0.998, 0.953 (s, 9H, fenchyl CH_3) . ^{13}C NMR (125 MHz, $CDCl_3$, 25 ºC): δ 159.45, 159.32, 158.98 (Ar, 3-C), 140.06, 139.69, 138.79, 138.00 (Ar, 1-C), 128.81, 128.71, 128.68, 128.39 (Ar, 5-C), 122.49, 121.95, 121.54 (Ar, 6-C), 116.00, 115.06, 114.87, (Ar, 2-C), 112.56, 112.31, 112.21, 112.17 (Ar, 4-C), 75.82, 75.21, 74.91, 74.78 (fenchyl C-S), 43.66, 43.30, 42.92, 42.75 (HC-S), 52.31, 51.39, 51.06, 50.83, 50.46, 49.31, 49.21, 49.06, 48.28, 46.90, 45.79, 45.50, 43.27, 42.70, 42.08, 42.06, 35.43, 34.51, 33.77, 32.07, 29.43, 28.97, 28.63, 27.61 (fenchyl CH and CH_2), 26.89, 26.73, 26.41, 26.34, 26.18, 25.94, 25.76, 25.09, 21.06, 19.15, 18.26, 18.10 (fenchyl CH_3) . MS (*m/z*): 288 (M^+), 256, 213, 173, 121.

*(E,Z)-2-[1-(3-Methoxyphenyl)-methylyliden]-1,3,3-trimethylbicyclo[2.2.1]heptane (**1a**)*

Triphenylphosphine (0.52 g, 2.0 mmol) was added to a solution of **7a** (5.2 g, 1.8 mmol) in dry toluene (5 mL) and the resulting mixture refluxed for 24 h. The solution was cooled to room temperature and 1 mL of methyl iodide was added, and the resulting suspension kept at 50 °C for 1 h, filtered and the solvent removed *in vacuo*. The oily liquid obtained was purified by column chromatography (Al_2O_3, heptane), yielding **1a** (0.24 g, 53%) as a clear oil.

In the attributions of the ^{1}H and ^{13}C NMR spectra below, two chemical shift values have been assigned to several of the atoms, since a mixture of two diastereoisomers has been obtained in the synthesis.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC): δ 7.19-7.13 (m, 1H, Ar, 5-H), 6.79-6.69 (m, 3H, Ar, 2-H, 4-H, 6-H), 6.16 (*Z*), 6.15 (*E*) (s, 1H, HC=C), 3.79 (s, 3H, $ArOCH_3$), 1.88-1.63, 1.58-1.43, 1.38-1.18 (m, 7H, fenchyl H), 1.27, 1.15, 1.14, 1.04, 0.98, 0.95 (s, 9H, fenchyl CH_3) . ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC): δ 160.57, 160.52 (Ar, 3-C), 158.96, 158.83 (olefin fenchyl C), 141.09, 140.78 (Ar, 1-C), 128.41, 128.20 (olefin CH), 122.11, 122.07 (Ar, 5-C), 117.00, 116.46 (Ar, 6-C), 115.11, 114.95 (Ar, 4-C), 111.42, 111.30 (Ar, 2-C), 55.14 ($ArOCH_3$), 55.14, 51.09, 50.64, 49.95, 46.88, 45.20, 43.97, 43.48, 36.40, 36.12, 29.58, 28.64 (fenchyl CH and CH_2), 27.23, 26.25, 25.74, 25.58, 20.32, 19.30 (fenchyl CH_3) . MS (*m/z*): 256 (M^+), 213, 173, 159, 121, 115. Anal. Calc. for $C_{18}H_{24}O$: C 84.32, H 9.44; found: C 84.41, H 9.51%.

*1-Spiro(1,3,3-trimetilbiciclo[2.2.1]heptyl)-2-methoxy-2-(3-methoxyphenyl)thiirane (**7b**)*

A solution of diazofenchane **4b** (obtained from 2.0 g fenchylhydrazone, 12 mmol) in DME (10 mL) was added in small portions at room temperature to *O*-methyl 3-methoxythiobenzoate **5b** (1.1 g, 6.0 mmol). The reaction was stirred for 20 h and the consumption of the thionoester was monitored by TLC (Al_2O_3, heptane/EtAc 20:1). Afterwards, the solvent was evaporated *in vacuo* and the residue purified by column chromatography (Al_2O_3, heptane/ethyl acetate 20:1), furnishing **7b** (1.8 g, 5.6 mmol, 94%) as a pale yellow oil.

In the attributions of the ^{1}H and ^{13}C NMR spectra below, more than one chemical shift values have been assigned to

several of the atoms, since a mixture of diastereoisomers has been obtained in the synthesis.

^{1}H NMR (250 MHz, $CDCl_3$, 25 ºC): δ 7.31-7.05 (m, 3H, Ar, 2-H, 4-H, 5-H), 6.88-6.82 (m, 1H, Ar, 6-H), 3.851, 3.842, 3.836, 3.823 (s, 3H, $ArOCH_3$), 3.177, 3.153, 3.080, 3.052 (s, 3H, S-C-OCH_3), 2.00-0.75 (m, 7H, fenchyl H), 1.48, 1.37, 1.21, 1.19, 1.08, 1.00, 0.99, 0.95, 0.94 (s, 9H, fenchyl CH_3) . ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 ºC): δ 159.44, 159.38, 159.23, 156.70 (Ar, 3-C), 141.24, 140.84, 139.28, 138.60 (Ar, 1-C), 128.96, 128.75, 128.61, 128.28 (Ar, 5-C), 124.00, 123.28, 121.98, 121.42 (Ar, 6-C), 117.28, 116.56, 114.90, 114.44 (Ar, 2-C), 113.52, 113.25, 113.18 (Ar, 4-C), 95.50, 94.96 (S-C-OCH_3), 81.22, 80.62, 80.32, 80.18 (fenchyl C-S), 55.30, 55.23, 55.03, 54.74 ($ArOCH_3$), 53.47, 51.98, 50.95, 50.39 (S-C-OCH_3), 45.64, 44.86, 44.44, 43.91, 43.26, 42.77, 41.31, 41.00, 37.48, 37.40, 32.77, 32.09, 32.01, 31.87, 31.72, 31.45, 31.41, 29.50, 28.97, 28.75, 28.52 (fenchyl CH and CH_2), 27.01, 26.60, 25.91, 25.77, 25.65, 24.97, 24.18, 23.01, 22.68, 21.93, 21.71, 20.70 (fenchyl CH_3). MS (*m/z*): 318 (M^+), 303, 286, 271, 257, 237, 217.

*(E,Z)-2-[1-Methoxy-(3-methoxyphenyl)-methylyliden]-1,3,3-trimethylbicyclo[2.2.1]heptane (**1b**)*

To a solution of **7b** (1.1 g, 6.0 mmol) in dry toluene (20 mL) was added copper powder (3.0 g) and this suspension was stirred and refluxed for 6 hours. After filtration and concentration, the oily liquid obtained was purified by column chromatography (SiO_2, heptane/ethyl acetate 5:1) yielding **1b** (1.6 g, 5.7 mmol, 95%) as a clear oil, which was formed by a mixture of *E* and *Z* isomers.

In the attributions of the ^{1}H and ^{13}C NMR spectra below, two chemical shift values have been assigned to several of the atoms, since a mixture of two diastereoisomers has been obtained in the synthesis.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 7.15-7.09 (m, 1H, Ar, 5-H), 6.80-6.72 (m, 3H, Ar, 2-H, 4-H, 6-H), 3.73 (s, 3H, $ArOCH_3$), 3.09, 3.08 (s, 3H, C=COCH_3), 1.82-1.53, 1.52-1.27 (m, 7H, fenchyl H), 1.45, 1.23, 1.01, 0.56, 0.52 (s, 9H, fenchyl CH_3) . ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 158.92, 158.86 (Ar, 3-C), 147.43, 146.13 (olefin COCH_3), 138.68, 138.54 (Ar, 1-C), 137.92, 137.79 (Ar, 5-C), 128.32, 128.27 (Ar, 6-C), 123.54 (Ar, 4-C), 116.18 (Ar, 2-C), 113.46 (olefin fenchyl C), 56.20, 55.89 (olefin OCH_3), 55.15 ($ArOCH_3$), 51.15, 50.40, 48.66, 48.48, 47.04, 45.70, 45.29, 43.18, 37.33, 36.16, 30.17, 26.53 (fenchyl CH and CH_2), 25.76, 25.72, 25.35, 25.08, 21.19, 20.92 (fenchyl CH_3) . MS (*m/z*): 286 (M^+), 271, 257, 243, 217, 135. Anal. calc. for $C_{19}H_{26}O_2$: C 79.68, H 9.15; found: C 79.17, H 9.26%.

*(E,Z)-tert-Butyl-(3-[methoxy-[1,3,3-trimethyl-bicyclo[2.2.1]-yliden]-methyl]-phenoxy)dimethylsilane (**1c**)*

A solution of diazofenchane **4b** (obtained from 0.70 g fenchylhydrazone, 4.2 mmol) in DME (10 mL) was added in small portions at room temperature to *O*-methyl 3-(tert-butyldimethylsilyloxy)-benzothioate **5c** (0.95 g, 3.4 mmol). The reaction mixture was stirred for 12 h and the consumption of the thionoester was monitored by TLC (Al_2O_3, heptane/EtAc 20:1). The solvent was evaporated and the oily residue obtained dissolved in dry toluene (30 mL), added 2.5 g (9.5 mmol) of triphenylphosphine and the mixture refluxed for 10 h. After cooling to rt, addition of 3 mL of methyl iodide, filtration and evaporation, the residue was purified by column chromatography (Al_2O_3, heptane/ethyl acetate 20:1) yielding **1c** (0.68 g, 2.4 mmol, 75%) as a clear oil containing a mixture of the *E* and *Z* isomers.

In the attributions of the ^{1}H and ^{13}C NMR spectra below, two chemical shift values have been assigned to several of the atoms, since a mixture of two diastereoisomers has been obtained in the synthesis.

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ 7.18-7.14 (m, 1H, Ar, 5-H), 6.88-6.75 (m, 3H, Ar, 2-H, 4-H, 6-H), 3.155, 3.152 (s, 3H, OCH_3), 1.90-1.00 (m, 7H, fenchyl H), 1.50, 1.29, 1.06, 0.63, 0.60 (s, 9H, fenchyl CH_3), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 6H, $Si(CH_3)_2$) . ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 154.92 (Ar, 3-C), 147.31, 146.05 (olefin COCH_3), 138.37, 138.28 (Ar, 1-C), 137.97, 137.80 (Ar, 5-C), 128.27 (Ar, 4-C), 124.43, 124.17 (Ar, 6-C), 122.58 (Ar, 2-C), 119.70 (olefin fenchyl C), 56.12, 55.81 (OCH_3), 51.10, 50.37, 48.64, 48.47, 47.04, 45.71, 45.25, 43.16, 37.32, 36.14, 31.86, 30.13 (fenchyl CH and CH_2), 29.00 ($SiC(CH_3)_3$), 26.54, 25.34, 25.06, 21.18, 20.98, 18.18 (fenchyl CH_3), 25.67 ($SiC(CH_3)_3$), −5.0 ($Si(CH_3)_2$). MS (*m/z*): 386 (M^+), 371, 317, 235, 73. Anal. calc. for $C_{24}H_{38}O_2Si$: C 74.55, H 9.91; found: C 74.70, H 9.97%.

Computational details

Gaussian03 was used for all calculations.[40] All geometries were optimized at the pbe1pbe/6-311+G(d,p) theoretical level.[28] To model the solvent effect (chloroform), CPCM-SCRF (self-consistent reaction field) procedure was employed.[41] Stationary points were characterized as minima by vibrational analysis. All reported energies include zero-point energy (ZPE) as well as thermal corrections (T = 298.15 K) from frequency calculations. Gauge invariant atomic orbitals (GIAO) method was used to calculate isotropic chemical shielding.[42,43] Calculations were carried out using the WP04 functional, a version

of the B3LYP functional explicitly reparameterized for the calculation of chemical shifts in chloroform,[44] with Dunning's cc-pVDZ basis.[34] WP04 functional was invoked by specifying the BLYP keyword and adding iop (3/76 = 1000001189, 3/77 = 0961409999, 3/78 = 0000109999) to the keyword line. The theoretical NMR chemical shifts were calculated as the difference isotropic shielding constants with respect to tetramethylsilane (GIAO/WP04/cc-pVDZ//pbe1pbe/6-311+G(d,p)) ^{1}H shielding = 31.79, ^{13}C shielding = 188.78). Solvent effects in GIAO calculations were modeled by the IEFPCM-SCRF method.[45] The IEFPCM-SCRF method was used to model solvent (chloroform) effects, which are known to be of great importance in such calculations.[34] The IEFPCM was used because it has been successfully used in association with the W04P functional in the accurate prediction of ^{1}H and ^{13}C chemical shifts in chloroform.[34]

Supplementary Information

HSQC, HMBC and NOESY NMR spectra, theoretical coordinates for the equilibrium geometries and vibrational frequencies of **1a** and **1b** are available free of charge at http://jbcs.sbq.org.br, as PDF file.

Acknowledgments

We thank Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for research grants (W. J. B. 2006/03420-7, E. L. B. 2007/00684-6) and for a PhD fellowship (F. H. B. 2005/58320-4), Conselho Nacional de Pesquisa e Desenvolvimento (CNPq) for a PhD fellowship for L. F. M. L. C., as well as, Deutscher Akademischer Austauschdienst (DAAD) and Coordenadoria de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES) for an international fellowship for L. F. M. L. C. (BEX 1132/04-0).

References

1. Klein, O.; Hopf, H.; Grunenberg, J.; *Eur. J. Org. Chem.* **2009**, 2141.
2. Lenoir, D.; Wattenbach, C.; Liebman, J. F.; *Struct. Chem.* **2006**, *17*, 419.
3. Garcia Martinez, A.; Teso Vilar, E.; Garcia Fraile, A.; de la Moya Cerero, S.; Lora Maroto, B.; *Tetrahedron Lett.* **2002**, *43*, 1183.
4. Yang, T.-F.; Chao, H.-H.; Lu, Y.-H.; Tsai, C.-J.; *Tetrahedron* **2003**, *59*, 8827.
5. Kido, F.; Uda, H.; Yoshikoshi, A.; *J. Chem. Soc., Perkin Trans. 1* **1972**, 1755.
6. Brooks, P. R.; Bishop, R.; Counter, J. A.; Tiekink, E. R. T.; *J. Org. Chem.* **1994**, *59*, 1365.
7. Barton, D. H. R.; Smith, E. H.; Willis, B. J.; *J. Chem. Soc. D* **1970**, 1226.
8. Kellogg, R. M.; *Tetrahedron* **1976**, *32*, 2165.
9. Buter, J.; Wassenaar, S.; Kellogg, R. M.; *J. Org. Chem.* **1972**, *37*, 4045.
10. Cullen, E. R.; Guziec, F. S., Jr.; Hollander, M. I.; Murphy, C. J.; *Tetrahedron Lett.* **1981**, *22*, 4563.
11. Back, T. G.; Barton, D. H. R.; Britten-Kelly, M. R.; Guziec, F. S., Jr.; *J. Chem. Soc., Perkin Trans. 1* **1976**, 2079.
12. Schmidt, U.; Kabitzke, K.; Boie, I.; Osterroht, C.; *Chem. Ber.* **1965**, *98*, 3819.
13. Hartke, K.; Kumar, A.; Koester, J.; Henssen, G.; Kissel, T.; Kaempchen, T.; *Chem. Ber.* **1982**, *115*, 3096.
14. Baader, W. J.; Bastos, E. L. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Berkessel, A., ed.; Thieme-Chemistry: Stuttgart, 2008, Vol. 38, p. 323.
15. Bastos, E. L.; Ciscato, L. F. M. L.; Weiss, D.; Beckert, R.; Baader, W. J.; *Synthesis* **2006**, 1781.
16. Baader, W. J.; Stevani, C. V.; Bastos, E. L. In *The Chemistry of Peroxides*; Rappoport, Z., ed.; Wiley: Chichester, 2006, p. 1211.
17. Ozturk, T.; Ertas, E.; Mert, O.; *Chem. Rev.* **2007**, *107*, 5210.
18. Farnum, D. G.; *J. Org. Chem.* **1963**, *28*, 870.
19. Pezacki, J. P.; Wood, P. D.; Gadosy, T. A.; Lusztyk, J.; Warkentin, J.; *J. Am. Chem. Soc.* **1998**, *120*, 8681.
20. Krebs, A.; Rueger, W.; Nickel, W. U.; *Tetrahedron Lett.* **1981**, *22*, 4937.
21. Okazaki, R.; Inoue, K.; Inamoto, N.; *Tetrahedron Lett.* **1979**, *20*, 3673.
22. Weiss, D.; Gaudig, U.; Beckert, R.; *Synthesis* **1992**, 751.
23. Greidanus, J. W.; *Can. J. Chem.* **1970**, *48*, 3530.
24. Pine, S. H.; Shen, G. S.; Hoang, H.; *Synthesis* **1991**, 165.
25. Sabelle, S. P.; Hydrio, J.; Leclerc, E.; Mioskowski, C.; Renard, P. Y.; *Tetrahedron Lett.* **2002**, *43*, 3645.
26. Bastos, E. L.; PhD Thesis, Universidade de São Paulo, Brazil, 2004, available in: http://capesdw.capes.gov.br/capesdw/resumo.html?idtese=20042723300201019lP0.
27. Sanders, S. K. M.; Hunter, B. K. In *Modern NMR Spectroscopy*; Oxford University Press: Oxford, 1987, pp. 180-190.
28. Perdew, J. P.; Burke, K.; Ernzerhof, M.; *Phys. Rev. Lett.* **1996**, *77*, 3865.
29. Sousa, S. F.; Fernandes, P. A.; Ramos, M. J.; *J. Phys. Chem. A* **2007**, *111*, 10439.
30. Riley, K. E.; Op't Holt, B. T.; Merz, K. M., Jr.; *J. Chem. Theory Comput.* **2007**, *3*, 407.
31. McCann, D. M.; Stephens, P. J.; *J. Org. Chem.* **2006**, *71*, 6074.
32. Brooks, P. R.; Bishop, R.; Counter, J. A.; Tiekink, E. R. T.; *Z. Kristallogr.* **1993**, *208*, 319.
33. Pilati, T.; Simonetta, M.; *J. Chem. Soc., Perkin Trans. 2* **1977**, 1435.
34. Jain, R.; Bally, T.; Rablen, P. R.; *J. Org. Chem.* **2009**, *74*, 4017.
35. Oliveira, C. S.; Bastos, E. L.; Duarte, E. L.; Itri, R.; Baptista, M. S.; *Langmuir* **2006**, *22*, 8718.

36. Armarego, W. L. F.; Perrin, D. D.; *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1998.
37. Phillips, D. D.; Champion, W. C.; *J. Am. Chem. Soc.* **1956**, *78*, 5452.
38. Bonacorso, H. G.; Paim, G. R.; Guerra, C. Z.; Sehnem, R. C.; Cechinel, C. A.; Porte, L. M. F.; Martins, M. A. P.; Zanatta, N.; *J. Braz. Chem. Soc.* **2009**, *20*, 509.
39. Bastos, E. L.; Ciscato, L. F. M. L.; Baader, W. J.; *Synth. Commun.* **2005**, *35*, 1501.
40. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; *Gaussian 03,* Gaussian, Inc.: Wallingford CT, 2004.
41. Barone, V.; Cossi, M.; *J. Phys. Chem. A* **1998**, *102*, 1995.
42. Wolinski, K.; Hinton, J. F.; Pulay, P.; *J. Am. Chem. Soc.* **1990**, *112*, 8251.
43. Ruud, K.; Helgaker, T.; Bak, K. L.; Joergensen, P.; Jensen, H. J. A.; *J. Chem. Phys.* **1993**, *99*, 3847.
44. Wiitala, K. W.; Hoye, T. R.; Cramer, C. J.; *J. Chem. Theory Comput.* **2006**, *2*, 1085.
45. Cances, E.; Mennucci, B.; Tomasi, J.; *J. Chem. Phys.* **1997**, *107*, 3032.

Submitted: April 14, 2010
Published online: June 23, 2010

FAPESP helped in meeting the publication costs of this article.