1,4-Dimethyl-2,5-dioxabicyclo[2.2.1]heptane-3,6-dione: optical resolution, absolute configuration and circular dichroism

Igor V. Vystorop,*[a] Andrei N. Utienyshev,[a] Victor M. Anisimov[a] and Remir G. Kostyanovsky*[b]

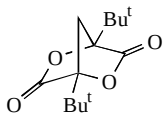
[a] *Institute for Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: +7 096 515 3588; e-mail: vystorop@icp.ac.ru*

[b] *N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 117977 Moscow, Russian Federation. Fax: +7 095 938 2156; e-mail: kost@center.chph.ras.ru*

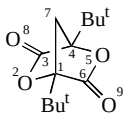
The title dilactone has been resolved into its enantiomers (+)-(*S*,*S*)-1 and (–)-(*R*,*R*)-1, whose absolute configurations were found by X-ray diffraction analysis of intermediate lactonic amide 2a; the magnitude of the *n*–π* Cotton effect increased with an increase in folding or a diminution in twist of the boat conformation of a dilactone ring.

Optically active α,α′-dihydroxyglutaric acid dilactones are of interest as conformationally rigid model systems of C_2 symmetry,[1] which provide an opportunity to perform a detailed analysis of the structure–chiroptical properties relationship in these compounds in order to reveal the structural characteristics that are responsible not only for the observed optical rotation sign, but also for the magnitude of the Cotton effect.

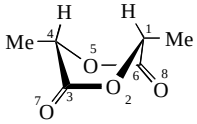
Previously, we have developed a procedure[2,3] for optical resolution of 1,4-di-*tert*-butyl dilactone (±)-**3** and examined chiroptical properties of its enantiomers by the electronic (CD)[2,3] and vibrational (VCD)[4] circular dichroism methods.



(+)-(1*R*,4*R*)-**3**, (B_N)



(–)-(1*S*,4*S*)-**3**, (B_S)



(+)-(1*S*,4*S*)-**4**, (B_S)

In this work, we have resolved dilactone of (±)-α,α′-dihydroxy-α,α′-dimethylglutaric acid (±)-**1** (Zelinsky's dilactone[5,6]) into its antipodes (Scheme 1)† by a modified procedure. The difference between this procedure and that described earlier[2,3] for the resolution of dilactone (±)-**3** consists in the ring opening in bicycle (±)-**1** under the action of (*S*)-α-methylbenzylamine (MBA) to form acyclic diastereomers, which were converted into a mixture of monocyclic diastereomers **2a**,**b** using an Amberlyst 15 cation exchanger. Diastereomerically pure lactonic amides **2a** and **2b** (*d.e.* > 98%, ^{1}H NMR data) were separated by column chromatography (Scheme 1) followed by acid-catalysed cyclization into enantiomeric dilactones (+)-**1** and (–)-**1** (*e.e.* > 96%, Pirkle's reagent[7]), respectively. The cyclization resulted in lower yields‡ as compared with the formation of di-*tert*-butyl antipodes (+)-**3** (61%) and (–)-**3** (64%) under similar conditions.[3]

The absolute configurations of all optically active compounds were determined from X-ray diffraction analysis data§ for high-melting isomer **2a** (Figure 1), which possesses an asymmetric carbon atom C(8) with the known (*S*)-configuration.

The characteristic feature of a molecule of **2a** in a crystal (Figure 1) is that the γ-lactone ring (phase angle[10] ψ_2 = 198.6°) has the shape of an almost ideal envelope ($_3E$, ψ_2 = 198°)[11] stabilised by intermolecular H-bonds of the C(7)=O(4)···H(3)–O(3) type [the O(4)···H(3) and O(4)···O(3) distances are equal to 1.91 and 2.78 Å, respectively].

The experimental long-wave Cotton effect for (–)-**1** (Figure 2), associated with the dilactone *n*–π* transition,[3] is negative; this fact is consisted with the optical activity calculations for (1*R*,4*R*)-**1** (RHF/6-31G*//6-31+G*, Gaussian 92).[2]

Thus, we experimentally supported a correlation, which was suggested previously[2,3] for bridging 1,4-dialkyl dilactones, between the sign of the *n*–π* Cotton effect and the inherent dilactone ring chirality of the boat enantiomeric form of the S-type[11] [B_S, (+)-φ_1 (O–CO–C–O), (–)-*n*–π* Cotton effect] or N-type[11] [B_N, (–)-φ_1, (+)-n–π* Cotton effect]. The CD spectra[12] of conformationally flexible (*S*,*S*)-lactide **4** {$\Delta\varepsilon_{221}$ = –5.7 [(MeO)$_3$P=O], $\Delta\varepsilon_{218}$ = –5.9 [(CF$_3$)$_2$CHOH)]} stabilised[12] in the boat conformation (B_S) by equatorial methyl groups are also consistent with this correlation.

According to the octant projection of Klyne's sector rule[13] applied to either of the homotopic lactone groups of dilactones,[3] the perturbation effects caused by the 1,4-dialkyl substituents, which are close to the symmetry plane of lactone chromophore [φ(C$_{Alk}$–C–C=O) = 10.4, 10.0 or –18.1° for **1**, **3** or **4**, respectively],§ are generally small and mutually compensated. Moreover, the contribution of dilactone bridging bonds to the optical rotation is opposite to the observed sign of the *n*–π* Cotton effect. Therefore, not only the sign, but also the magnitude of the *n*–π*

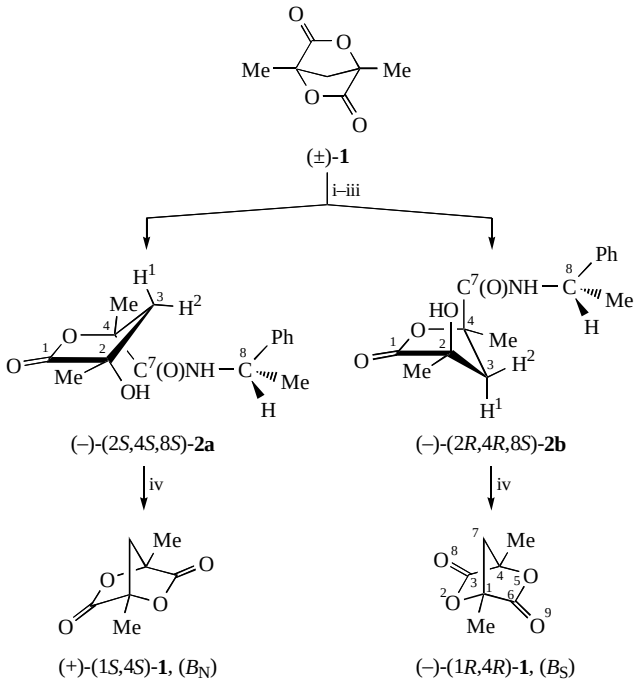
† *Characteristics and spectroscopic data*. IR spectra were measured on a Specord-80M spectrometer. NMR spectra were recorded on a Bruker WM-400 spectrometer (using TMS as an internal standard) at 400.13 (^{1}H) and 100.62 MHz (^{13}C) (data in square brackets were obtained under conditions of {2,4-Me}). Optical rotations were measured on a Polamat A polarimeter. CD spectra were taken on a Jasco J-500A spectropolarimeter with a DP-500N data processor.

(1*S*,4*S*)-(+)-**1**: yield 28%, mp 97–98 °C. [*cf.* ref. 6 for (±)-**1**, mp 102–104 °C], $[\alpha]_D^{18}$ = +130.0° (*c* 0.30, CHCl$_3$), $\Delta\varepsilon$ = +9.895 (228 nm) (*c* 2.94×10^{-3} mol dm^{-3}, MeOH). ^{1}H NMR (CD$_3$OD) δ: 1.64 (s, 6H, 2Me), 2.63 (s, 2H, CH$_2$). ^{1}H NMR (C$_6$D$_6$) δ: 0.94 (s, 2H, CH$_2$), 1.07 (s, 6H, 2Me).

(1*R*,4*R*)-(–)-**1**: yield 30%, mp 96–97 °C, $[\alpha]_D^{18}$ = –130.6° (*c* 0.31, CHCl$_3$), $\Delta\varepsilon$ = –10.441 (228 nm) (*c* 2.67×10^{-3} mol dm^{-3}, MeOH). ^{1}H NMR spectral data for (+)-**1** and (–)-**1** in CDCl$_3$ were identical to those for (±)-**1** in ref. 6.

(2*S*,4*S*,8*S*)-(–)-**2a**: yield 27.3%, mp 150–152 °C (benzene–hexane), R_f 0.30 (acetone–benzene, 1:3), $[\alpha]_D^{20}$ = –30.1° (*c* 0.73, CHCl$_3$), $\Delta\varepsilon$ = +1.748 (228 nm), $\Delta\varepsilon$ = –2.817 (216 nm) (*c* 15.6×10^{-3} mol dm^{-3}, MeOH). ^{1}H NMR (CDCl$_3$) δ: 1.48 (d, 3H, *Me*CH, ^3J 6.9 Hz), 1.55 (s, 3H, Me-2), 1.60 (s, 3H, Me-4), 2.09 and 3.00 (dd, 2H, CH$_2$, $^2J_{AB}$ –14.1 Hz), 2.60 (br. s, 1H, OH), 5.09 (m, 1H, MeC*H*), 6.78 (br. d, 1H, NH, ^3J 8.1 Hz), 7.29–7.35 (m, 5H, Ph). ^{13}C NMR (CDCl$_3$) δ: 21.39 (dq, *Me*CH, ^1J 127.9 Hz, ^2J 3.6 Hz), 24.07 (dq, Me-2, ^1J 129.3 Hz, $^3J_{H(1)}$ 4.4 Hz), 25.38 (dq, Me-4, ^1J 129.3 Hz, $^3J_{H(1)}$ 4.4 Hz), 46.71 [ddm, CH$_2$, $^1J_{H(1)}$ 130.8 Hz, $^1J_{H(2)}$ 138.1 Hz], 48.88 (dm, *C*HPh, ^1J 141.0 Hz, J 2.9 Hz), 73.59 [br. d, C(2), J 5.8 Hz], 83.11 [m, C(4)], 125.99 (dm, *o*-C$_{Ph}$, ^1J 159.0 Hz), 127.41 (dt, *p*-C$_{Ph}$, ^1J 160.1 Hz), 128.63 (dd, *m*-C$_{Ph}$, ^1J 160.2 Hz), 142.46 (m, *i*-C$_{Ph}$), 171.37 (m, CONH, $^3J_{H(1)}$ 6.0 Hz, J 5.0 and 3.5 Hz), 176.60 (m, ring C=O, [br. d, $^3J_{H(2)}$ 5.8 Hz, $^3J_{H(1)}$ 0.5 Hz]). IR (CH$_2$Cl$_2$, ν/cm^{-1}): 3680 (OH), 3424 (NH), 1788 (ring C=O), 1678 (C=O, amide I), 1520 (δ, NH, amide II), 1184, 1126, 1054, 964, 860.

(2*R*,4*R*,8*S*)-(–)-**2b**: yield 15.3%, mp 72–74 °C (hexane), (R_f 0.48), $[\alpha]_D^{20}$ = –31.8° (*c* 0.54, CHCl$_3$), $\Delta\varepsilon$ = –9.848 (216 nm) (*c* 0.024 mol dm^{-3}, MeOH). ^{1}H NMR (CDCl$_3$) δ: 1.39 (s, 3H, Me-2), 1.47 (d, 3H, *Me*CH, ^3J 6.9 Hz), 1.61 (s, 3H, Me-4), 1.98 and 2.88 (dd, 2H, CH$_2$, $^2J_{AB}$ –14.1 Hz), 3.60 (br. s, 1H, OH), 5.07 (m, 1H, MeC*H*), 6.69 (br. d, 1H, NH, ^3J 7.8 Hz), 7.20–7.29 (m, 5H, Ph). ^{13}C NMR (CDCl$_3$) δ: 21.63 (dq, *Me*CH, ^1J 128.2 Hz, ^2J 3.6 Hz), 23.91 (dq, Me-2, ^1J 128.1 Hz, $^3J_{H(1)}$ 2.9 Hz), 25.64 (dq, Me-4, ^1J 129.4 Hz, $^3J_{H(1)}$ 5.2 Hz), 46.46 (ddm, CH$_2$, $^1J_{H(1)}$ 132.7 Hz, $^1J_{H(2)}$ 137.2 Hz, $^3J_{Me}$ 3.5 Hz), 48.79 (dm, *C*HPh, ^1J 140.8 Hz), 73.53 (m, C^2, ^2J 5.2 Hz, ^2J 5.0 Hz), 83.15 (dm, C^4, ^2J 4.9 Hz), 126.02 (dm, *o*-C$_{Ph}$, ^1J 158.0 Hz, J 3.8 Hz), 127.29 (dt, *p*-C$_{Ph}$, ^1J 160.2 Hz, J 3.2 Hz), 128.53 (dd, *m*-C$_{Ph}$, ^1J 160.6 Hz, J 4.7 Hz), 142.35 (m, *i*-C$_{Ph}$), 171.32 (m, CONH), 176.64 (m, ring C=O). IR (CH$_2$Cl$_2$, ν/cm^{-1}): 3680 (OH), 3428 (NH), 1786 (ring C=O), 1678 (C=O, amide I), 1522 (δ, NH, amide II), 1186, 1128, 1054, 964, 860.



Scheme 1 *Reagents and conditions*: i, (*S*)-α-MBA, room temperature, 120 h, 74.5%; ii, Amberlyst 15 (H^+ form, Fluka)/$CHCl_3$, room temperature, 48 h, 79.5%; iii, column chromatography, silica gel (60 Å, 200–125 mesh, Aldrich), acetone–benzene (1:3); iv, TsOH–toluene, reflux, 5 h, then sublimation (50–60 °C/15 Torr).

Cotton effect are probably related to the stereochemistry of the dissymmetric dilactone chromophore.

In contrast to the experimental VCD spectra[4] of dilactones (–)-**1** and (–)-**3**, the similarity of their CD spectra (Figure 2), as well as the spectra of (*S*,*S*)-**4**,[12] allowed us to analyse the influence of structural features of their monocyclic dilactone rings upon the magnitude of the Cotton effect. The latter is proportional to the rotatory strength for the CD bands having almost Gaussian shapes (Figure 2).

A comparison of the geometric models§ of homochiral bicyclic dilactones (*R*,*R*)-**1** and (*S*,*S*)-**3** and slightly distorted monocyclic dilactone (*S*,*S*)-**4** demonstrates that the enantiomeric boat form (B_S) of a dilactone ring for these molecules (ψ_2 = 270.4, 271.1 or 277.7° for **1**, **3** or **4**, respectively) is similar to the canonical boat shape (ψ_2 = 270°).[11]

As follow from a comparison of the molecular structures of dimethyl dilactones (*R*,*R*)-**1** and (*S*,*S*)-**4**, the introduction of a bridge is accompanied by a close approach of C(1) and C(4) atoms to each other [distances of (**1**) 2.20 and (**4**) 2.66 Å], and by a decrease in the angle between the planes of O(2)C(1)C(6) and O(5)C(4)C(3) groups [ω_1 = (**1**) 52.3 or (**4**) 81.3°] or ester groups (O–C=O) [ω_2 = (**1**) 109.8 or (**4**) 137.3°]. Therefore, in general, this leads to an increase in the dilactone ring folding {folding amplitude[10] S_2 = (**1**) 1.132 or (**4**) 0.795; φ_1 [O–C(=O)–C–O] = (**1**) 69.2 or (**4**) 42.8°}, and also to an approach of carbonyl groups to each other [the C(3)···C(6) distance is (**1**) 2.73 or (**4**) 2.82 Å; the O(8)···O(9) distance is 4.84 Å (**1**) and the O(7)···O(8) distance is 5.14 Å (**4**)].

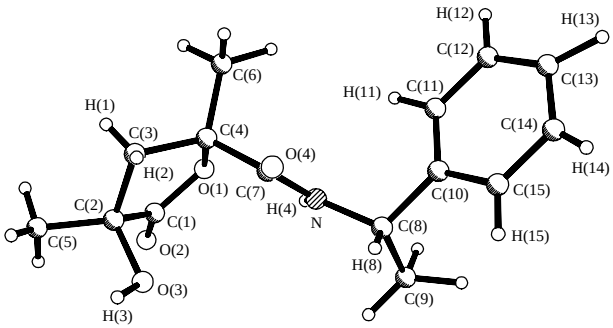


Figure 1 Molecular structure of lactonic amide **2a**. Selected bond lengths (Å): O(1)–C(1) 1.351(5), O(1)–C(4) 1.461(4), C(1)–C(2) 1.519(5), O(2)–C(1) 1.199(4), O(4)–C(7) 1.228(4), N–C(7) 1.332(5) C(4)–C(7) 1.524(6); selected bond and dihedral angles (°): O(1)–C(1)–O(2) 120.7(4), O(1)–C(1)–C(2) 111.0(3), O(2)–C(1)–C(2) 128.3(4), N–C(7)–O(4) 122.9(4), N–C(7)–C(4) 116.6(3), O(4)–C(7)–C(4) 120.4(3), C(2)–C(1)–O(1)–C(4) –0.1 (φ_0), O(1)–C(1)–C(2)–C(3) 17.1, C(1)–C(2)–C(3)–C(4) –26.4, C(2)–C(3)–C(4)–O(1) 27.3, C(3)–C(4)–O(1)–C(1) –17.2.

However, an increase in the volume of 1,4-alkyl substituents in the conformationally rigid bridged dilactone structure leads to a negligible decrease of the dilactone ring folding in (*S*,*S*)-**3** [S_2 = 1.128, φ_1 = 68.2°, the C(1)···C(4) distance is 2.22 Å, the C(3)···C(6) distance is 2.74 Å, the O(8)···O(9) distance is 4.86 Å, ω_1 = 53.2° and ω_2 = 110.4°], as compared with that in **1**. Moreover, an increase in the twist angle of the dilactone ring for **3** {φ_0[C–O–C(=O)–C] = 1.8°} and **4** (φ_0 = 7.3°), as compared with that for **1** (φ_0 = 0.9°), is probably responsible for a noticeable change in the relative orientation of carbonyls [the projected dihedral angle φ_2 (O=C···C=O) = (**1**) –34.5, (**3**) –27.6 or (**4**) –20.0°].

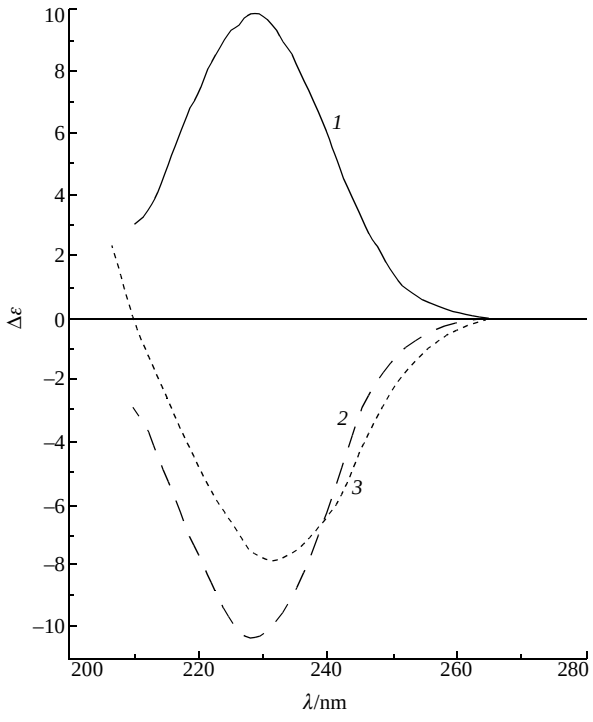


Figure 2 CD spectra of enantiomers (*1*) (+)-(*S*,*S*)-**1**, (*2*) (–)-(*R*,*R*)-**1** and (*3*) (–)-(*S*,*S*)-**3** ($\Delta\varepsilon$ = –7.861, λ_{max} = 231 nm) in MeOH.

‡ *Crystallographic data for* **2a**: $C_{15}H_{19}NO_4$, M = 277.31, orthorhombic crystals, space group $P2_12_12_1$, 293(2) K, a = 19.368(4), b = 9.889(2), c = 7.944(2) Å, V = 1521.5(6) Å^3, d_{calc} = 1.211 g cm^{-3}, Z = 4. Intensities of 1891 reflections were measured on an automatic KM-4 four-circle diffractometer (λMoKα radiation, 2.10° < θ < 97.02°). The structure was solved by a direct method (SHELXS-86[8]) and refined using the full-matrix least-squares procedure (SHELXL-93[9]) in the anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms were located from the difference Fourier synthesis with the exception of the hydrogens of the methyl groups, the positions of which were calculated and included in the further refinement using a riding motion model. The refinement is converged to wR_2 = 0.1053 and GOF = 1.024 for all independent reflections [R_1 = 0.040 is calculated against F for 1001 observed reflections with $I > 2\sigma(I)$]. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, 1999, Issue 1. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/56.

§ The geometry of dilactones (*R*,*R*)-**1**, (*S*,*S*)-**3** and (*S*,*S*)-**4** was completely optimised at the *ab initio* theoretical level of the second-order Møller–Plesset (MP2) theory with the conventional 6-31G* basis set using procedures implemented in the Gaussian 94 program package.[14] Convergence criteria for the density matrix were set to 1×10^{-8}. All calculations were performed on an SGI Power Challenge computer. The calculated energies (in hartrees) and dipole moments (in debyes) are (**1**) –570.80912 and 5.622, (**3**) –805.82048 and 5.175, or (**4**) –532.80678 and 3.362, respectively.

Therefore, both an increase in the folding and a decrease in the twist angle of the boat conformation of a dilactone ring, which decrease the distance and increase the skew angle between carbonyl groups, respectively, can be considered as the geometric factors responsible for increasing magnitude of the n–π^* Cotton effect. The calculations (CNDO–SCFMO)[15] of the optical activity of a glyoxal molecule resulted in a similar relationship between the relative disposition of equivalent carbonyl groups and the calculated rotatory strength of the ketone n–π^* transition.

In summary, we conclude that both the sign and the magnitude of the n–π^* Cotton effect of the dilactones reflect inherent dissymmetry springing in chiral distortions of the dilactone ring, which, therefore, can be considered as an inherently dissymmetric chromophore.[16]

Note that the observed relations between the sign or magnitude of the n–π^* Cotton effect and the spatial arrangement of the lactone group [*i.e.*, the sign or magnitude of the twist angle (φ_0), respectively] are opposite to the corresponding relations for the lactam chromophore [(–)-φ_0, (–)-n–π^* Cotton effect and *vice versa*],[17] for which the enforced n–π^* Cotton effect is observed with increasing the twist angle (φ_0).

This work was supported by the Russian Foundation for Basic Research (grant nos. 97-03-33021 and 98-07-90290).

References

1 W. Hug and G. Wagniere, *Tetrahedron*, 1972, **28**, 1241.
2 I. V. Vystorop, G. V. Shustov, A. Rauk and R. G. Kostyanovsky, *Mendeleev Commun*., 1994, 97.
3 I. V. Vystorop and R. G. Kostyanovsky, *Izv. Akad. Nauk, Ser. Khim*., 1998, 108 (*Russ. Chem. Bull*., 1998, **47**, 107).
4 A. Rauk, J. L. McCann, H. Wieser, P. Bour, I. V. Vystorop, Yu. I. El'natanov and R. G. Kostyanovsky, *Can. J. Chem*., 1998, **76**, 717; Correction: *Can. J. Chem*., 1998, **76**, 1931.
5 N. D. Zelinsky, *Ber*., 1891, **24**, 4006.
6 R. G. Kostyanovsky, V. P. Leshchinskaya, Yu. I. El'natanov, A. E. Aliev and I. I. Chervin, *Izv. Akad. Nauk SSSR, Ser. Khim*., 1989, 408 (*Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1989, **38**, 355).
7 W. H. Pirkle, D. L. Sikkenga and M. S. Pavlin, *J. Org. Chem*., 1977, **42**, 384.
8 G. M. Sheldrick, *Acta Crystallogr*., 1990, **A46**, 467.
9 G. M. Sheldrick, *SHELXL-93, Program for Crystal Structure Refinement*, University of Göttingen, D-37077, Germany, 1993.
10 N. S. Zefirov and V. A. Palyulin, *Dokl. Akad. Nauk SSSR*, 1980, **252**, 111 [*Dokl. Chem*. (*Engl. Transl.*), 1980, **252**, 207].
11 I. V. Vystorop, A. Rauk, C. Jaime, I. Dinares and R. G. Kostyanovsky, *Khim. Geterotsikl. Soedin*., 1995, 1479 [*Chem. Heterocycl. Compd*. (*Engl. Transl.*), 1995, **31**, 1280].
12 C. Toniolo, V. Perciaccante, J. Falcetta, R. Rupp and M. Goodman, *J. Org. Chem*., 1970, **35**, 6.
13 J. P. Jennings, W. Klyne and P. M. Scopes, *J. Chem. Soc*., 1965, 7211, 7229.
14 M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Manayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, *Gaussian 94, Revision D.1*, Gaussian, Inc., Pittsburgh PA, 1995.
15 W. Hug and G. Wagniere, *Theor. Chim. Acta*, 1970, **18**, 57.
16 C. W. Deutsche, D. A. Lightner, R. W. Woody and A. Moscowitz, *Ann. Rev. Phys. Chem*., 1969, **20**, 407.
17 D. N. Kirk, *Tetrahedron*, 1986, **42**, 777.

Received: 21st July 1999; Com. 99/1520