2010 *Russian Chemical Bulletin, International Edition, Vol. 60, No. 10, pp. 2010—2013, October, 2011*

Optically active diastereomers of *N*-methyl-1´-(–)-myrtenylpyrrolidino[3´,4´:1,9](C_{60}-J_h)[5,6]fullerenes: synthesis, electrochemical and chiroptical properties

N. V. Abramova, K. K. Babievskii, S. M. Peregudova, A. S. Peregudov, and V. I. Sokolov★

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
28 ul. Vavilova, 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5085. E-mail: stemos@ineos.ac.ru; sokol@ineos.ac.ru

Novel optically active diastereomers of *N*-methyl-1´-myrtenylpyrrolidino[3´,4´:1,9]-(C_{60}-J_h)[5,6]fullerenes were synthesized. Reaction of the latter with methyl iodide yielded the corresponding quaternary ammonium salts. Individual diastereomers were isolated, their chiroptical and electrochemical properties were studied.

Key words: pyrrolidinofullerenes, myrtenal, diastereomers, circular dichroism, the Cotton effect, electrochemistry, the Prato reaction.

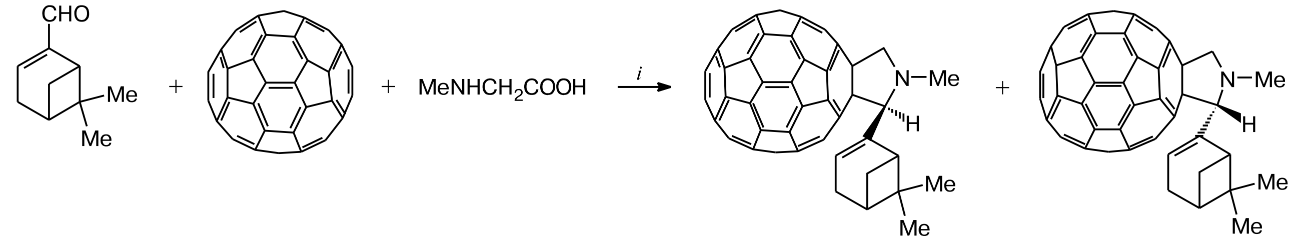
Biology and medicine are the potent area for the practical application of fullerene derivatives.[1–4] Due to this fact, synthetic approaches towards fullerenes covalently or supramolecularly bonded to natural products are of interest.

In continuation of our research on the synthesis of optically active fullerene derivatives by the Prato reaction,[5] in the present work we described reaction of [60]fullerene with commercially available natural terpenoid aldehyde (–)-1*R*-myrtenal ((–)-1*R*-6,6-dimethylbicyclo-[3.1.1]hept-2-ene-2-carboxaldehyde). Bicyclic core of the myrtenal molecule includes two rigidly bonded stereogenic centers which explained the existence of myrtenal as two (not four) isomers. Therefore, the reaction resulted in only two diastereomeric cycloadducts **1** (R_f = 0.68) and **2** (R_f = 0.47) in the ratio of 2 : 9 (Scheme 1) regardless of the formation of a new stereogenic center at the C(2) of the fuzed pyrrolidine ring. The diastereomers were isolated as individual compounds by two-step column chromatography (SiO_2, elution with toluene—hexane, 1 : 1). Structures of compounds **1** and **2** were established by ^{1}H NMR spectroscopy, mass spectrometry, circular dichroism (CD) spectroscopy, and confirmed by elemental analysis.

Heating of these compounds in the sealed ampule in the excess of MeI at 70—75 °C for 20—28 h afforded the corresponding methiodides **3** and **4** (Scheme 2). The structure evaluation of derivatives **3** and **4** were also accomplished using ^{1}H NMR spectra, mass spectra, CD spectra and elemental analysis data.

On the CD curves of diastereomers in the region 400—750 nm, several Cotton effects are observed, which are due to electron transitions of the fullerene framework as no other chromophores in the molecules are present (Figs 1 and 2). Comparison of the spectra of neutral molecules (bases) and their salts and estimation of the contribution of stereogenic centers on the positions and intensity of the Cotton effects are of interest. Comparison of the CD spectra of compounds **1** and **3**, **2** and **4** indicates that at quaternization the signs of the long wavelength Cotton effects (550—750 nm) retained, while their intensity changed. The CD spectra of compounds **1** and **2** in the

Scheme 1

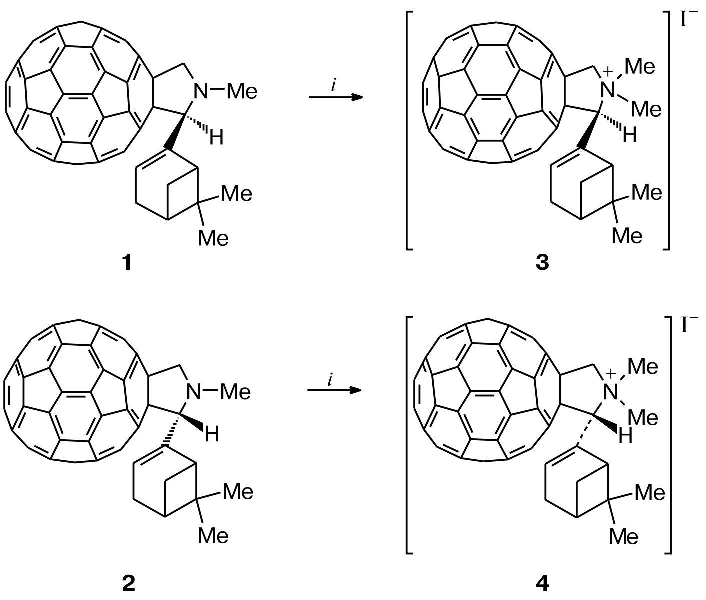


1 **2**

i. PhMe, reflux, 25 h.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 1974—1977, October, 2011.

Scheme 2



i. MeI, 70—75 °C, 20 h.

range of 500 nm are notably different. Thus, diastereomer **2** exhibited intense positive singlet Cotton effect (492.7 nm) and so much intense negative shifted couplet CD (537.1, 570.0 nm), whereas for diastereomer **1** several Cotton effects of low intensity nearby the zero line were observed. The CD spectra of methiodides **3** and **4** in the range of 450—500 nm are of almost perfect mirror symmetry: for **3** positive Cotton effect at 477.9 nm was observed and for **4** negative Cotton effect at 477.8 nm was found. Generally, it is believed that stereogenic center affects a remote chromophore stronger when it is closer. From a few publications on the CD spectra of 2-substituted derivatives of *N*-methylpyrrolidino[60]fullerene follows that the negative Cotton effect corresponds to *S*-configuration of center C(2), while the positive Cotton effect to *R*-configuration.[6—8] Based on this conclusion, we could suggest that diastereomer **1** has *R,R*-configuration and diastereomer **2** has *R,S*-configuration. However, no studies on the model comparing neutral molecule and cation were performed. Apparently, for the model studied by us, the pattern of the CD spectra reflects different configuration of the C(2) center for methiodides **3** and **4**, while in the case of pyrrolidines **1** and **2** the configuration of the C(2) center makes no contribution on the signs of the longest wavelength Cotton effects thus confirming their fullerene structure. Due to disagreement in the signs of the Cotton effects in the region of 450—500 nm between the neutral compound and the salt, the configuration of the C(2) center could reliably be assigned by the independent study.

From the comparison of the ^{1}H NMR spectra of diastereomers **1** and **2** it follows that in the case of the latter the signals shifted in the lower fields. This fact is in a good agreement with published data[8] according to which the protons of the diastereomer with *R*,*S*-configuration resonate in the lower fields compared with that of the other diastereomer. It is of note that the spectra of salts differ from those of neutral compounds. Thus, in the ^{1}H NMR spectra of methiodides **3** and **4**, the signals of the expected *R*,*S*-diastereomer shifted not in the lower fields as in the case of compounds **1** and **2**, but in the stronger fields.

In the mass spectra of compounds **1** and **2**, peaks of the molecular ions with *m*/*z* 898.3 were recorded as well as the peaks of the molecular ion of the bis-adduct with *m*/*z* 1075.3. The mass spectra of compounds **3** and **4** exhibit peaks of the ions with *m*/*z* 1039.2 and peaks correspond-

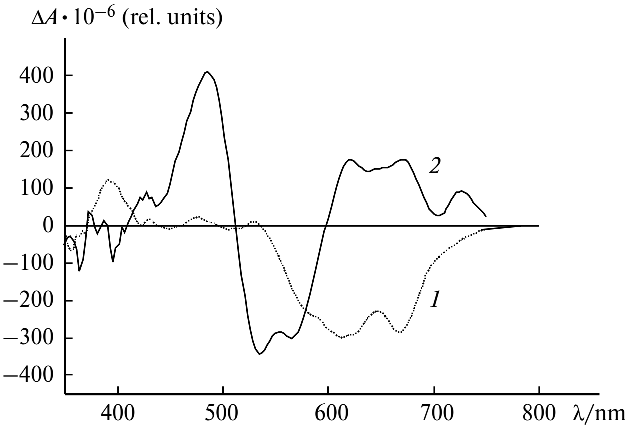


Fig. 1. The circular dichroism spectra of diastereomers **1** (*1*) and **2** (*2*) of *N*-methyl-1′′-(−)-myrtenylpyrrolidino[3′,4′:1,9](C_{60}-J_h)-[5,6]fullerene ($c = 4 \cdot 10^{-4}$ mol L^{-1}) in *o*-dichlorobenzene.

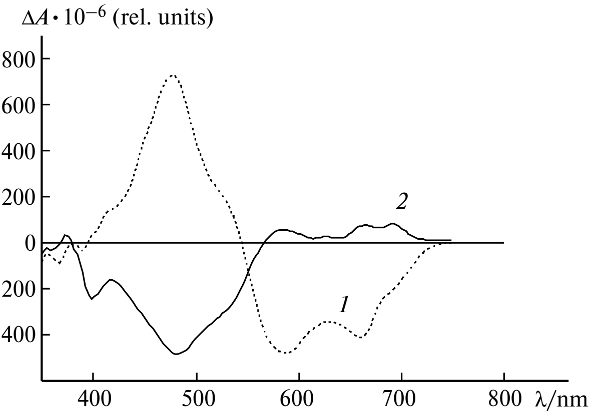


Fig. 2. The circular dichroism spectra of diastereomers **3** (*1*) and **4** (*2*) of *N*,*N*-dimethyl-1´-(−)-myrtenylpirrolidiniofullerene iodide ($c = 4 \cdot 10^{-4}$ mol L^{-1}) in *o*-dichlorobenzene.

Fig. 3. Cyclic voltammograms of the reduction of diastereomer **1** ($c = 5 \cdot 10^{-4}$ mol L^{-1}), carbon glassy electrode, *o*-$C_6H_4Cl_2$, 0.1 *M* Bu_4NPF_6, potential sweep rate 200 mV s^{-1}.

ing to the addition of iodine to the molecular ions $[M + I]^-$ with m/z 1166.5.

Electrochemical properties of **1** and the corresponding methiodide **3** were studied by cyclic voltammetry (CV) in the solution in *o*-dichlorobenzene in the presence of 0.1 *M* Bu_4NPF_6 using a glassy carbon electrode (GC). Potentials of the peaks measured relative to the saturated calomel electrode (s.c.e.) are listed in Table 1. For the comparison, the potentials of the reduction potentials for [60]fullerene and unsubstituted *N*-methylpyrrolidino[3´,4´:1,9]-(C_{60}-I_h)[5,6]fullerene (**5**) are also given.

The CV curves of compound **1** exhibit three single-electron reversible peaks of reduction (Fig. 3). In the anodic potential region in the reverse scan, only peaks of the oxidation of the corresponding anions were found which are in favor of the stability of anion radical, dianion, and trianion.

In the CV curve of compound **3** in the cathodic potential region, four peaks of reduction were observed. (Fig. 4). The first and second peaks are single-electron and reversible, *i.e.*, subsequent addition of two electrons resulted in the stable anion radicals and dianions; the third and fourth peaks are irreversible. In the anodic potentials in the reverse scan, no peaks characteristic of fullerene were observed which can indicate instability of the reduced form of the compound **3** after addition of the third electron. From Table 1 it follows that for compounds **1**, **3**, and their unsubstituted analog **5**, the differences between reduction potentials of the second and first peaks ($\Delta E_p{}' = 0.37$ V)

Table 1. Reduction potentials of compounds **1** and **3**, [60]fullerene, and *N*-methylpyrrolidino[60]fullerene **5**

Compound	$E_p{}^1$ ($\Delta E_p{}'$)*	$E_p{}^2$ ($\Delta E_p{}''$)**	$E_p{}^3$	$E_p{}^4$
	/V			
1	−1.03 (0.37)	−1.40 (0.52)	−1.92	—
3	−0.99 (0.37)	−1.36 (0.61)	−1.97	−2.23
C_{60}	−0.56 (0.44)	−1.00 (0.45)	−1.45	—
5	−0.65 (0.37)	−1.02 (0.51)	−1.53	—

* $\Delta E_p{}' = E_p{}^2 - E_p{}^1$. ** $\Delta E_p{}'' = E_p{}^3 - E_p{}^2$.

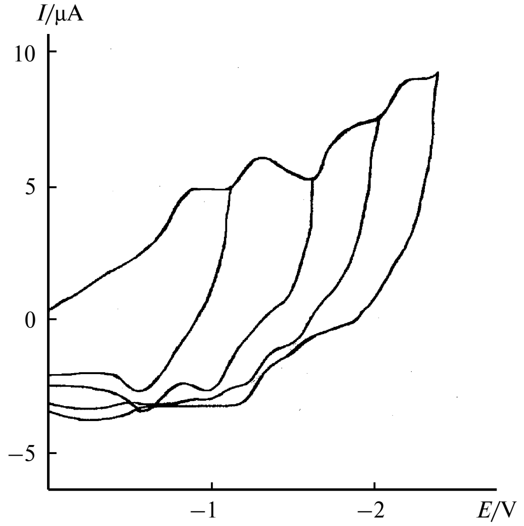


Fig. 4. Cyclic voltammograms of the reduction of diastereomer **3** ($c = 5 \cdot 10^{-4}$ mol L^{-1}), carbon glassy electrode, *o*-$C_6H_4Cl_2$, 0.1 *M* Bu_4NPF_6.

coincide; the differences between the third and second peaks ($\Delta E_p''$) for *N*-methyl[3´,4´:1,9]pyrrolidino[3´,4´:1,9]-(C_{60}-J_h)[5,6]fullerene (**5**) and compound **1** are nearly the same (0.51 and 0.52 V), but they altered from that for salt **3** (0.61 V) approximately by 0.1 V. From these facts, it is possible to suggest that upon the reduction of methiodide **3**, the first and second electrons are localized on a fullerene core, while next electrons compensate the charge of the nitrogen atom.

Experimental

Commercially available [60]fullerene (99.9%, G. A. Razuvaev Institute of Organometallic Chemistry, Nizhny Novgorod) was used. The CD spectra were recorded on the circular dichroism spectrometer SKD-2 (developed by Institute of Spectroscopy of the Russian Academy of Sciences and V. A. Engelhard Institute of Molecular Biology of the Russian Academy of Sciences) in *o*-dichlorobenzene. ^{1}H NMR spectra were run on a Bruker 400 HX instrument in $CDCl_3$ and DMSO-d_6. Electrochemical study by cyclic voltammetry were performed on a potentiostat PI-50-1 in the solution in *o*-dichlorobenzene using glassy carbon electrode (d = 2 mm^2), 0.1 *M* Bu_4NPF_6 was used as a supporting electrolyte, the potentials were measured relative to saturated calomel electrode (reference electrode). Mass spectra (electrospray ionization, ESI) were recorded on an Agilent 1100 Series LC/MSD Trap instrument in the positive and negative ion modes. Melting points of all synthesized compounds are above 300 °C.

***N*-Methyl-1´-(–)-myrtenylpyrrolidino[3´,4´:1,9](C_{60}-J_h)-[5,6]fullerene.** A mixture of [60]fullerene (0.216 g, 0.3 mmol), sarcosine (0.054 g, 0.6 mmol), and myrtenal (0.045 g, 0.3 mmol) in toluene was refluxed for 25 h. Two diastereomeric cycloadducts **1** and **2** were separated by two-step column chromatography (SiO_2, hexane—toluene, 1 : 1) in a ratio of 2 : 9. Total yield 41%.

***N*-Methyl-1´-(–)-myrtenylpyrrolidinofullerene (diastereomer 1).** ^{1}H NMR ($CDCl_3$), δ: 1.21—1.33 (m, 2 H, CH, myrt.); 1.27 (s, 6 H, Me, myrt.); 2.34—2.42 (m, 4 H, CH_2, myrt.); 2.78 (s, 3 H, NMe); 4.11 (d, 1 H, CH_2, pyrr., J = 9.4 Hz); 4.49 (s, 1 H, CH, pyrr.); 4.82 (d, 1 H, CH_2, pyrr., J = 9.4 Hz); 6.04 (m, 1 H, CH=C, myrt.). Found (%): C, 95.31; H, 2.44; N, 1.21. $C_{72}H_{19}N$. Calculated (%): C, 96.32; H, 2.12; N, 1.56. MS (ESI), *m/z*: 898.3 $[M]^+$. CD (*o*-dichlorobenzene), λ_{max} ($\Delta A \cdot 10^{-4}$): 393.2 (1.20), 473.8 (0.29), 528.5 (0.14), 616.9 (–3.00), 667.8 (–2.72).

***N*-Methyl-1´-(–)-myrtenylpyrrolidinofullerene (diastereomer 2).** ^{1}H NMR ($CDCl_3$), δ: 1.11—1.39 (m, 2 H, CH, myrt.); 1.35 (s, 6 H, Me, myrt.); 2.15—2.75 (m, 4H, CH_2, myrt.); 2.89 (s, 3 H, NMe); 4.10 (d, 1 H, CH_2, pyrr., J = 9.4 Hz); 4.30 (s, 1 H, CH, pyrr.); 4.87 (d, 1 H, CH_2, pyrr., J = 9.4 Hz); 6.13 (m, 1 H, CH=C, myrt.). Found (%): C, 92.81; H, 2.50; N, 1.41. $C_{72}H_{19}N$. Calculated (%): C, 96.32; H, 2.12; N, 1.56. MS (ESI), *m/z*: 898.3 $[M]^+$. CD (*o*-dichlorobenzene), λ_{max} ($\Delta A \cdot 10^{-4}$): 414.8 (4.15), 537. (–3.41), 570.0 (–2.96), 622.2 (1.67), 669.2 (1.67), 725.1 (1.02).

***N*,*N*-Dimethyl-1´-(–)myrtenylpyrrolidiniofullerene iodide (diastereomer 3).** A solution of diastereomer **1** (0.020 g) in the excess of MeI, which also served as a solvent, was heated in a sealed tube on a water bath at 70—75 °C for 20 h (until formation of the precipitate). The precipitate was filtered off, washed with toluene, and dried. Compound **3** was obtained in the yield of 0.021 g (90%). ^{1}H NMR (DMSO-d_6), δ: 1.15—1.37 (m, 6 H, Me, myrt.); 2.13—2.37 (m, 4 H, CH_2, myrt.); 3.01 (m, 2 H, CH, myrt.); 3.71 (s, 3 H, NMe); 4.01 (s, 3 H, NMe); 5.59 (d, 1 H, CH_2, pyrr., J = 12.3 Hz); 5.86 (d, 1 H, CH_2, pyrr., J = 12.3 Hz); 6.56 (s, 1 H, CH, pyrr.); 6.63 (m, 1 H, CH=C, myrt.). Found (%): C, 75.61; H, 2.02; N, 1.04. $C_{73}H_{22}NI$. Calculated for $C_{73}H_{22}IN \cdot CH_3I$ (%): C, 75.19; H, 2.12; N, 1.19. MS (ESI), *m/z*: 1039.2 $[M]^-$. CD (*o*-dichlorobenzene), λ_{max} ($\Delta A \cdot 10^{-4}$): 477.9 (7.22), 589.6 (–4.89), 654.4 (–4.05).

***N*,*N*-Dimethyl-1´-(–)-myrtenylpyrrolidiniofullerene iodide (diastereomer 4).** A solution of diastereomer **2** (0.055 g) in the excess of MeI was heated in a sealed tube on a water bath at 70—75 °C for 28 h (until formation of the precipitate). The precipitate was filtered off, washed with toluene, and dried. Compound **4** was obtained in the yield of 0.038 g (59%). ^{1}H NMR (DMSO-d_6), δ: 1.11—1.20 (m, 6 H, Me); 2.13 (m, 2 H, CH_2, myrt.); 2.26 (m, 2 H, CH_2, myrt.); 2.70, 2.86 (both s, 2 H, CH, myrt.); 3.70 (s, 3 H, NMe); 3.97 (s, 3 H, NMe); 5.49 (d, 1 H, CH_2, pyrr., J = 12.7 Hz); 5.76 (d, 1 H, CH_2, pyrr., J = 12.7 Hz); 6.49 (s, 1 H, CH, pyrr.); 6.64 (m, 1 H, CH=C). Found (%): C, 74.38; H, 2.67; N, 1.66. $C_{73}H_{22}IN$. Calculated for $C_{73}H_{22}NI \cdot CH_3I$ (%): C, 75.19; H, 2.12; N, 1.19. MS (ESI), *m/z*: 1039.2 $[M]^-$. CD (*o*-dichlorobenzene), λ_{max} ($\Delta A \cdot 10^{-4}$): 398.5 (–2.54), 477.8 (–4.71), 589.5 (0.55), 654.5 (0.82), 690.2 (0.96).

The authors are grateful to Prof. Cui Xiuling (Zhengzhou University, Public´s Republic of China) for the mass spectrometry.

This work was financially supported by the Russian Foundation for Basic Research (Project Nos 08-03-00169 and 11-03-00252) and the Department of Chemistry and Material Sciences of the Russian Academy of Sciences (Program OKh-1).

References

1. S. H. Friedman, D. L. DeCamp, R. P. Sijbesma, G. Srdanov, F. Wudl, G. L. Kenyon, *J. Am. Chem. Soc.*, 1993, **115**, 6506.
2. E. Nakamura, H. Isobe, *Acc. Chem. Res.*, 2003, **36**, 807.
3. L. B. Piotrovsky, *Fullereny v biologii i meditsyne: problemy i perspectivy* [*Fullerenes in Biology and Medicine: Problems and Prospects*] in *Fundamental´nye napravleniya molekulyarnoi meditsyny* [*Fundamental Trends of Molecular Medicine*], Ed. I. O. Kiselev, Izd-vo Rostok, St.-Petersburg, 2005, p. 195 (in Russian).
4. M. S. Bjelaković, D. M. Godjevac, D. R. Milić, *Carbon*, 2007, **45**, 2260.
5. M. Prato, M. Maggini, *Acc. Chem. Res.*, 1998, **31**, 519.
6. M. Maggini, G. Scorrano, A. Bianco, C. Toniolo, R. P. Sijbesma, F. Wudl, M. Prato, *J. Chem. Soc., Chem. Commun.*, 1994, 305.
7. A. Bianco, M. Maggini, G. Scorrano, C. Toniolo, G. Marconi, C. Villani, M. Prato, *J. Am. Chem. Soc.*, 1996, **118**, 4072.
8. S. Campidelli, P. Bourgun, B. Guintchin, J. Furrer, H. Stoeckli-Evans, I. M. Saez, J. W. Goodby, R. Deschenaux, *J. Am. Chem. Soc.*, 2010, **132**, 3574.

Received November 25, 2010;
fin revised form April 15, 2011