DOI: 10.1002/ejoc.200901169

Synthesis and Spectroscopic Characterization of the First Symmetrically and Nonsymmetrically Substituted Fluorinated Emerald-Green Trannulenes $C_{60}F_{15}R_3$ Soluble in Polar Media and Water

Pavel A. Troshin,*[a] Ekaterina A. Khakina,[a] Alexander V. Zhilenkov,[a] Alexander S. Peregudov,[b] Olesya A. Troshina,[a] Viacheslav I. Kozlovskii,[c] Natalya V. Polyakova,[d] and Rimma N. Lyubovskaya[a]

Keywords: Fullerenes / Fluorine / Annulenes / Bioorganic chemistry

The first water-soluble C_{3v}-symmetrical trannulene derivatives of fluorofullerene $C_{60}F_{18}$ possessing six carboxylic or ammonium ion groups have been synthesized and spectrally characterized. The stability of emerald-green aqueous solutions of these compounds was investigated. A novel synthetic route was developed for a step-by-step derivatization of $C_{60}F_{18}$ with different organic C–H acids that yielded nonsymmetrically substituted $C_{60}F_{15}R_2R'$ trannulenes. The synthesized trannulenes were loaded with polar carboxylic groups that improved greatly the solubility of these compounds in aqueous media. We showed that four solubilizing COOH groups could be introduced onto the fullerene cage of $C_{60}F_{15}R_2R'$ trannulenes with R substituents and then some additional organic functionality could be attached independently with R′. The R′ substituent might potentially comprise a ligand responsible for selective targeting of the whole trannulene molecule to some specific tissues or intracellular structures. The demonstrated loading of the fluorofullerene core with polar carboxylic or ammonium groups might be considered as an important step towards the design of sophisticated water-soluble trannulene-based assembles for biomedical applications.

Introduction

Trannulenes are nonconventional aromatic compounds that were predicted in 1979 by Schleyer et al.[1] Trannulene rings comprise alternating double bonds exclusively with the *trans*-configuration and have all their π orbitals lying parallel to the ring plane and overlapped inside and outside the ring. Such overlapping was called "in plane aromaticity" and the compounds exhibiting such aromaticity were called trannulenes.[2] The first experimental evidence for the existence of trannulenes was serendipitously obtained in 2001 by Taylor et al. who was studying the derivatization of fluorinated fullerene $C_{60}F_{18}$. It was found that carbon anions $^{-}CX(COOR)_2$ in reactions with $C_{60}F_{18}$ attach at the δ positions with respect to the carbon atoms bearing the leaving fluorine atoms, thus forming fluorinated trannulenes $C_{60}F_{15}R_3$.[3] Such remote fluorine displacement termed as S_N2'' or extended S_N' results in the formation of equatorial 18-memebered *all-trans* annulene rings in the fullerene cage that were shown to be truly aromatic. Other known examples of trannulenes include $C_{60}Cl_{30}$ that was prepared by exhausting chlorination of C_{60} and $C_{60}[C(Me)(COOR)_2]_6$ synthesized by alkylation of the fullerene hexaanion C_{60}^{6-}.[4] An appearance of trannulene rings integrated in the cages of fullerene derivatives brings some new electronic properties to these compounds, particularly, it lowers their band gaps and leads to strong visible absorptions at long wavelengths (500–950 nm).[3,4] Therefore, trannulenes show remarkable emerald-green colours so unusual for fullerenes and their derivatives.

Trannulenes demonstrated interesting electronic and photochemical properties that open prospects for their practical applications.[3,5] At the same time, trannulenes were reported to be fairly stable,[3] particularly towards moisture in contrast to all other known fluorinated fullerenes that undergo facile hydrolysis with the formation of oxygen-containing species: fullerenols, epoxyfullerenes and oxahomofullerenes.[6] Such improved stability of trannulenes inspired us to design their water-soluble derivatives that might find some interesting medicinal implementations.

[a] Institute of Problems of Chemical Physics of Russian Academy of Sciences,
Semenov Prospect 1, Chernogolovka, Moscow region 142432, Russian Federation
E-mail: troshin@cat.icp.ac.ru
[b] A. N. Nesmeyanov Institute of Organoelement Compounds, 1 Vavylova St. 28, B-334, Moscow 119991, Russia
[c] Institute for Energy Problems of Chemical Physics of Russian Academy of Science (Branch),
Semenov Prospect 1/10, Chernogolovka, Moscow Region 142432, Russia
[d] Research Institute of Electrocarbon Products,
1 per. Gorki, Electrougly, Moscow 142490, Russia
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200901169.

On the one hand, fullerenes and their derivatives are known as excellent photosensitizers that convert triplet oxygen into a very reactive singlet form with almost 100% quantum yield.[7] At the same time, fullerenes are selectively accumulated in tumour tissues.[8] The combination of these two effects makes the prospect of the application of these fullerenes in photodynamic therapy of cancer very promising. The only drawback is that ordinary fullerene derivatives absorb only at short wavelengths that do not penetrate deeply into living tissues. This problem might be overcome by using trannulene derivatives of fullerenes as photosensitizers. The fact that trannulenes have very strong absorptions in the red and near-infrared spectral regions is their strongest advantage over conventional fullerene derivatives.[9] The idea to use trannulenes for photodynamic therapy is also supported by previously reported studies that showed that trannulenes formed long-living excited triplet states that were quenched by molecular oxygen.[5]

On the other hand, it was reported that some water-soluble fullerene derivatives demonstrated strong tendency for accumulation in bone tissues.[10] It seems to be very promising to use this bone-vectoring effect of fullerenes to deliver selectively some drugs to bone. Particularly, this might be labile fluorine that could be applied to bone tissue to fight osteoporosis.[11] Here again, water-soluble fluorinated trannulenes might be considered as superior carriers for labile fluorine atoms that are already attached to their carbon cages.

The development of biomedical applications of trannulenes was restricted by their poor availability, especially in the case of fluorinated $C_{60}F_{15}R_3$ compounds. We have recently solved the problem of availability of precursor fluorofullerene $C_{60}F_{18}$ and developed efficient synthetic procedures that allowed us to obtain gram quantities of substituted $C_{60}F_{15}R_3$ trannulenes.[12] For some practical needs it might be critical to load the fluorinated trannulene core with different functional groups. It can be envisioned that one group in $C_{60}F_{15}R_2R'$ trannulenes might be responsible for specific targeting of the trannulene molecule, whereas two others should provide sufficient solubility in aqueous media.

Here we report the synthesis of the first symmetrically and nonsymmetrically substituted water-soluble trannulenes via simple procedures starting from $C_{60}F_{18}$.

Results and Discussion

Synthesis of C_{3v}-Symmetrical Water-Soluble Trannulenes

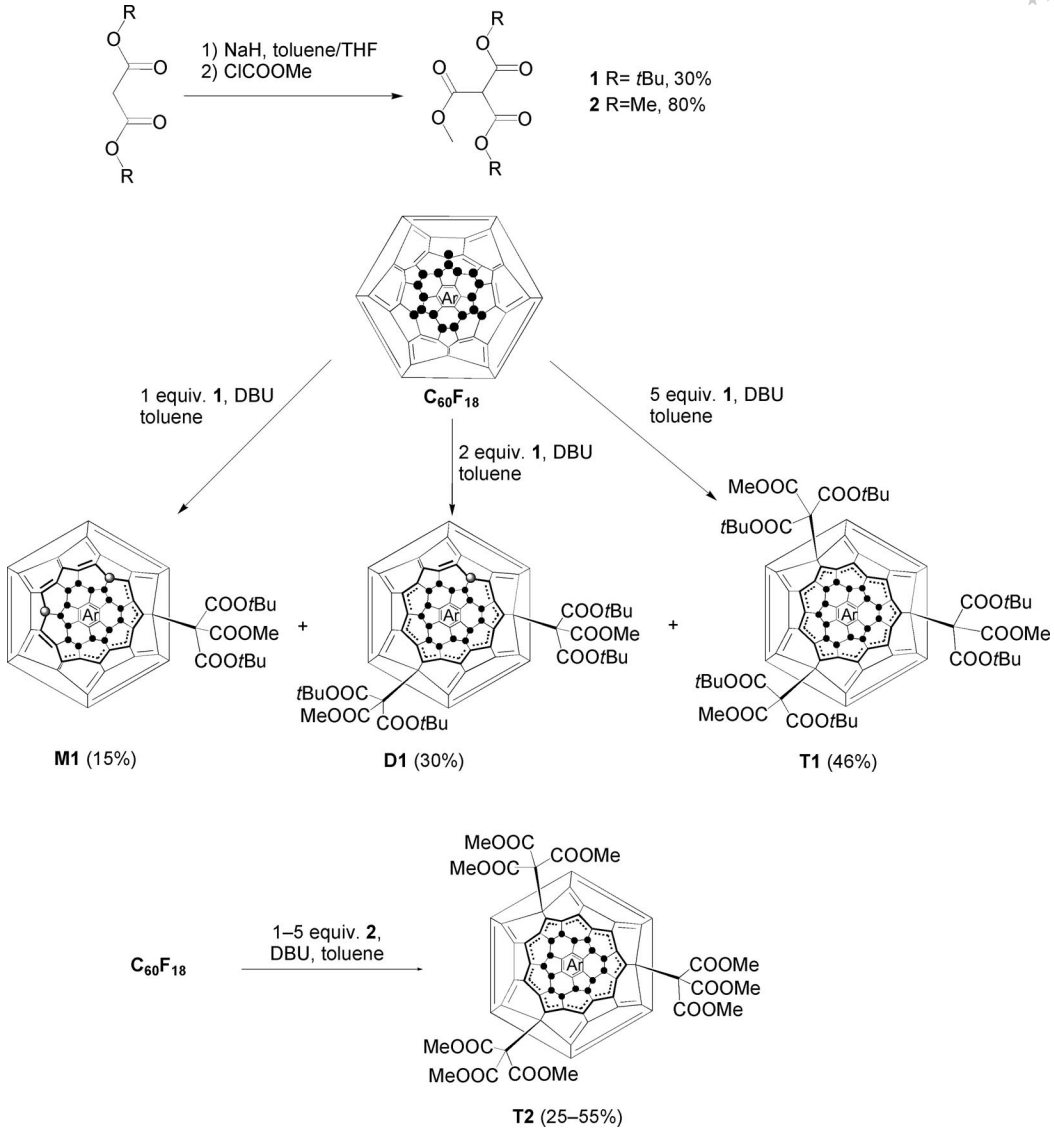
Reasonable solubility of trannulenes in aqueous media might be attained by attachment of highly polar carboxylic groups to the fullerene core. *tert*-Butyl esters of some acids are ideally suited for this purpose.[13] Therefore, we prepared C–H acid precursor **1** by acidification of bis(*tert*-butyl)malonate with methyl chloroformate. A reaction of $C_{60}F_{18}$ with 1.0 equiv. of **1** yielded monosubstitution product **M1** (≈15%) with a small amount (5%) of disubstitution product **D1**, whereas trisubstition product trannulene **T1** was not formed at all. The use of 2 equiv. of **1** per 1 equiv. of $C_{60}F_{18}$ produced mainly **D1** (30%) with trace amounts of **M1** and **T1**. Further increase in the amount of **1** introduced in the reaction to 5–8 equiv. yielded **T1** (46%) with just trace amounts of **D1** (Scheme 1). Such unusual behaviour of $C_{60}F_{18}$ in reactions with **1** does not fit well to previous reports where it was shown that the use of 1:1 reagent ratios affords the highest yields of trannulenes.[3] This contradiction between our results and the literature data can be tentatively explained by the bulkiness of –C(COOMe)-(COO*t*Bu)$_2$ addends, whose steric repulsion on the fullerene cage makes substitution of each next fluorine atom in $C_{60}F_{18}$ less energetically favourable. Therefore, three outlying fluorine atoms in $C_{60}F_{18}$ can be replaced successively one by one with bulky organic groups. At the same time, reactions with less bulky nucleophiles proceed in one stage with simultaneous substitution of three labile fluorine atoms. For instance, a similar reaction of the fluorofullerene with less bulky C–H acid **2** does not depend on the reagent ratios and produces almost exclusively trannulene **T2** in high yields (55%, Scheme 1).

The existence of considerable steric repulsion between the bulky organic addends and the fullerene cage in **M1**, **D1** and **T1** is evidenced in the NMR spectra of these compounds (Figure 1). First, it was revealed that rotation of the –C(COOMe)(COO*t*Bu)$_2$ addend is already frozen even in simplest derivative **M1**, as its ^{1}H NMR spectrum shows signals for two nonequivalent *tert*-butyl groups. Both ^{19}F and ^{13}C NMR spectra of this compound evidenced its C_1 molecular symmetry. Due to restricted addend rotation, compound **D1** exists as a mixture of atropoisomers as can be concluded from its quite complicated NMR spectra.

Surprisingly, the NMR spectra of symmetrical trannulene **T1** show sets of signals typical for trannulenes. Most probably, rotation of the organic addends in **T1** is also frozen like in the case of **M1** and **D1**. However, all three organic addends attain the most energetically favourable conformation in **T1**, which does not break the C_{3v} molecular symmetry of this trannulene. The absorption spectra of synthesized compounds **M1**, **D1** and **T1** are shown in Figure 2. These spectra differ significantly from each other, thus suggesting that a degree of organic substitution in $C_{60}F_{18}$ affects strongly the electronic structure of the entire molecule.

Heating **T1** at reflux in neat trifluoroacetic acid for 2 h resulted in cleavage of the *tert*-butyl ester groups and formation of trannulene **T3** with almost quantitative yields. It is notable that hydrolysis performed under milder conditions produced mixtures of partially hydrolyzed species instead of **T3**, which points to the unusual stability of the ester groups in trannulene **T1** (Scheme 2).

The compositions and molecular structures of synthesized trannulenes **T1** and **T3** were proved by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy. Chemical analyses of the trannulenes were complicated by the presence of fluorine in their molecular frameworks; therefore, mass spectrometry was applied for determination of the molecular compositions of all key compounds. The NMR spectra are shown in Figure 3 for trannulene **T3** and in the Supporting Information



Scheme 1.

for trannulene **T1**. The ^{1}H NMR spectrum of **T1** (in $CDCl_3$) consisted of two singlet lines at δ = 1.67 (O*t*Bu) and 4.05 ppm (OMe) with integral intensities ratio of 1:6. The ^{1}H NMR spectrum of **T3** (in DCOOD) showed only one singlet at δ = 3.31 ppm due to the COOMe protons that evidenced selective cleavage of all *tert*-butyl ester functions. The ^{13}C NMR spectra of both compounds were also very similar and evidenced their C_{3v} symmetrical trannulene-type structures; the only difference was that resonances corresponding to *tert*-butyl groups (δ = 27.96 and 85.89 ppm) appeared only in the spectrum of **T1**. The ^{19}F NMR spectra of **T1** and **T3** showed three singlets with integral intensity ratios of 3:6:6, which is very typical for trannulenes.

A multistep synthesis of water-soluble trannulene **T5** (Scheme 3) was started with Boc protection of 3-aminopropanol-1 and treatment of resulting product **3** with malonic acid that led to ester **4** with two masked amine groups. Acidification of this ester with methyl chloroformate in DMF afforded key precursor **5**. Reaction of an excess amount of **5** (15 equiv.) with $C_{60}F_{18}$ yielded trannulene **T4** bearing six Boc-protected amine groups. Removal of the protecting groups was easily achieved by stirring **T4** with neat trifluoroacetic acid at room temperature for 5–10 min. Evaporation of the excess amount of trifluoroacetic acid in vacuo, washing the residue with dichloromethane and drying yielded emerald-green solid **T5**, the first trannulene modified with ionic groups. Trannulenes **T4** and **T5** were characterized by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy. Splitting of some signals in the NMR spectra of compounds **T4** and **T5** suggested restricted rotation of bulky organic groups in these molecules. As a consequence, the molecular symmetry of trannulenes **T4** and **T5** is lowered to C_s or even to C_1 in contrast to C_{3v}-symmetrical **T1** and **T3**.

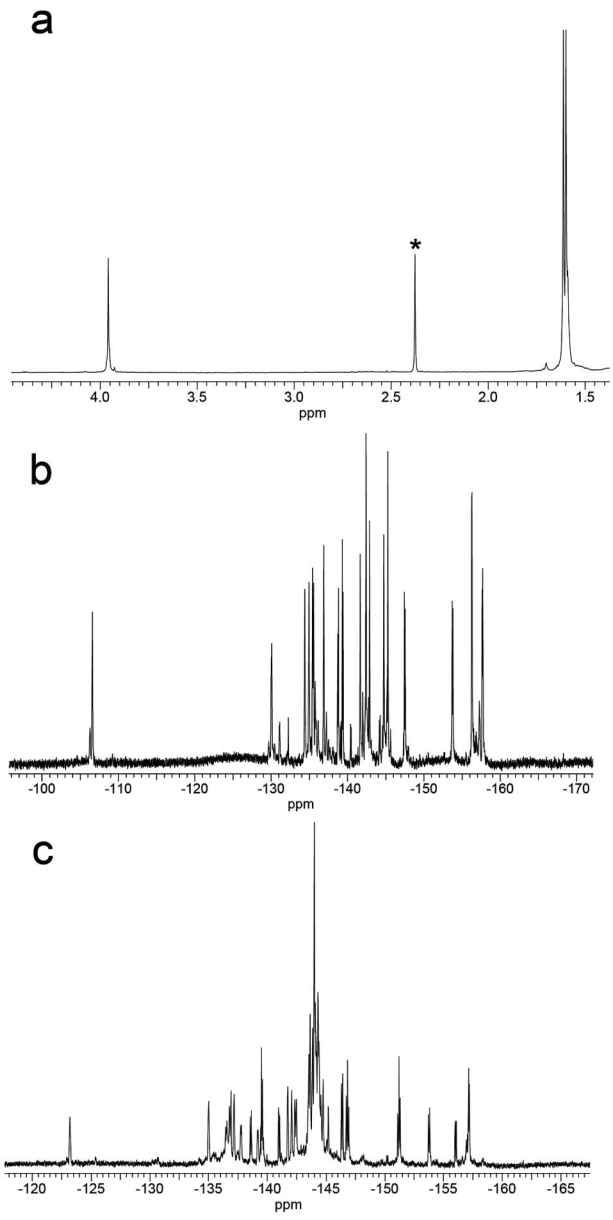


Figure 1. ^{1}H NMR spectrum of **M1** (a) and ^{19}F NMR spectra of **M1** (b) and **D1** (c). Symbol "*" denotes signal of the toluene impurity in the sample of **M1**.

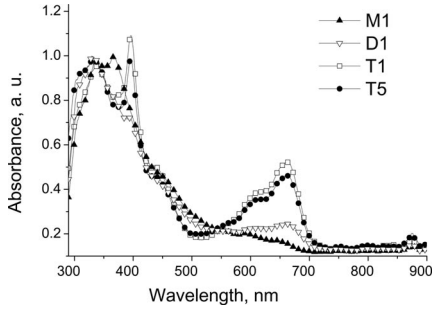
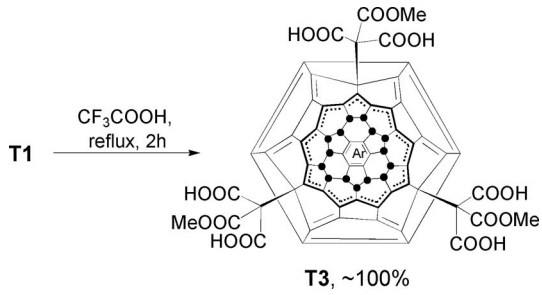


Figure 2. Absorption spectra of **M1**, **D1**, **T1** and **T5**.



Scheme 2.

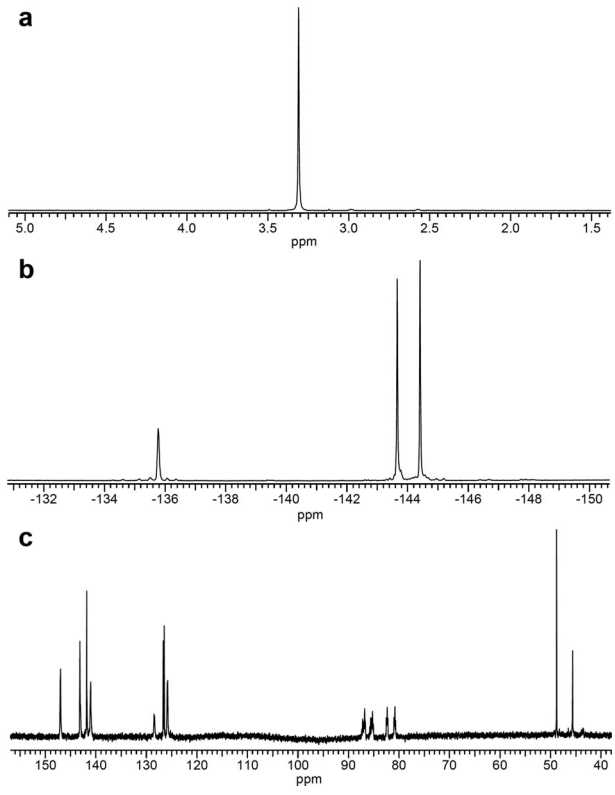
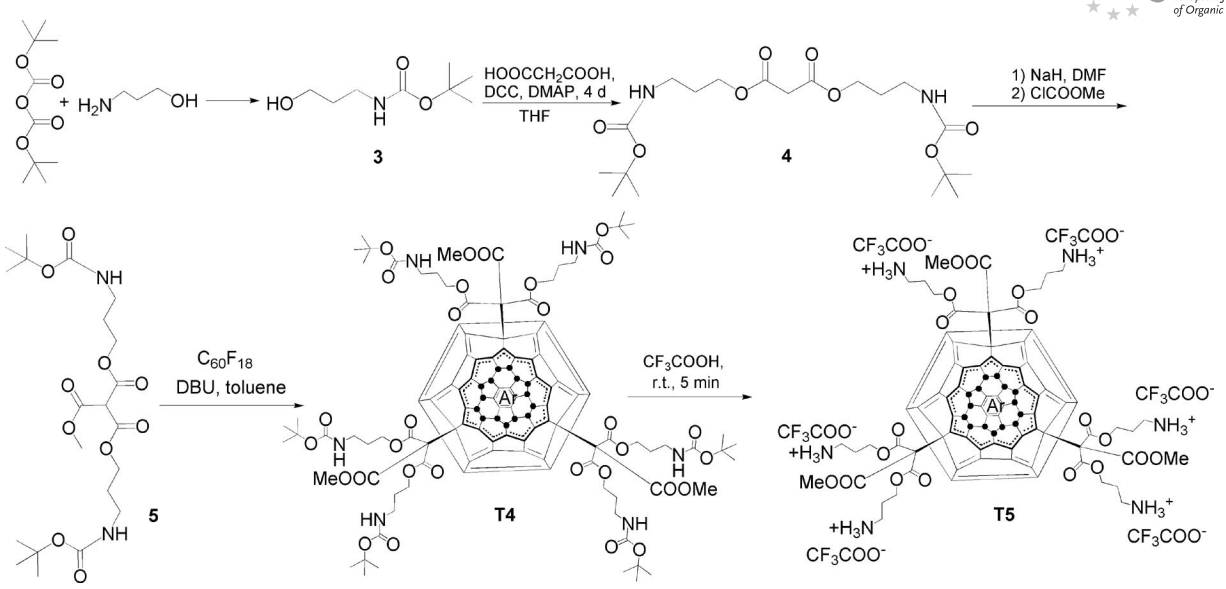


Figure 3. ^{1}H (a), ^{19}F (b) and ^{13}C (c) NMR spectra of trannulene **T3** dissolved in DCOOD.

Solubility of Trannulenes T3 and T5 in Water and Stability of Their Aqueous Solutions

The solubilities of trannulenes **T3** and **T5** in water were sharply different. Compound **T3** was quite hydrophobic despite the presence of six highly polar carboxylic groups in its molecular framework. However, it was readily soluble in organic acids such as acetic, formic and trifluoroacetic acid and polar organic solvents like THF and 1,4-dioxane. Therefore, solutions of **T3** in aqueous media were easily obtained by dissolving this compound in a minimal amount of appropriate organic solvent and following dilution with 10–100 volumes of deionized water. In contrast to **T3**, trannulene **T5** was extremely hydrophilic: 15 mg of this compound could be easily dissolved in just one drop of pure water. Figure 4 shows the absorption spectra of aqueous solutions of **T3** and **T5** in comparison with the spectra of



Scheme 3.

precursor trannulenes **T1** and **T4** dissolved in toluene. One can see that these spectra are virtually identical. Most importantly, the spectra of **T3** and **T5** are not broadened relative to the spectra of precursor trannulenes. This suggests that water-soluble trannulenes do not undergo strong aggregation in aqueous solutions, which distinguishes them from the most conventional fullerene derivatives that form large clusters upon dissolving in water.

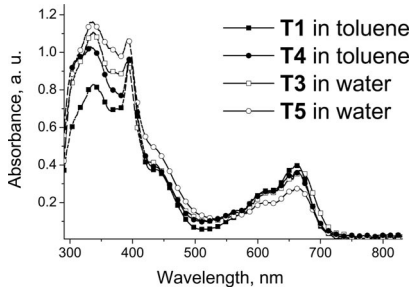


Figure 4. Absorption spectra of aqueous solutions of trannulenes **T3** and **T5** in comparison with the spectra of precursors **T1** and **T4** dissolved in toluene.

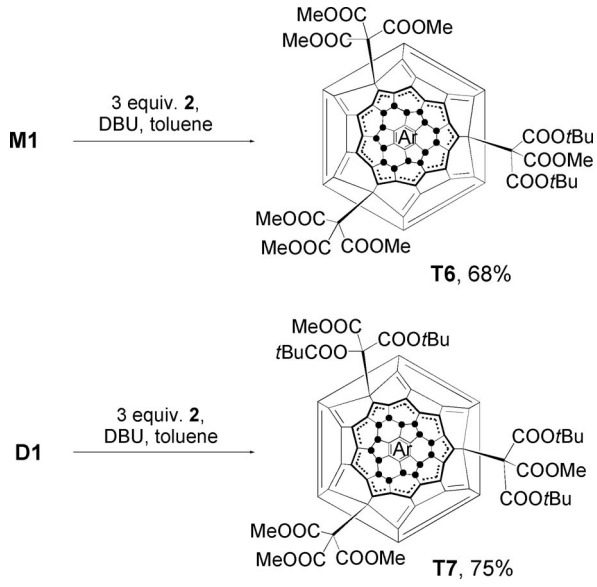
Unfortunately, the successful preparation of water-soluble trannulenes **T3** and **T5** was overshadowed by the poor stability of their aqueous solutions. Weakly concentrated (ca. 10^{-6} M) solutions of these trannulenes in water lose their green colours completely in 24 h. Moreover, such degradation occurs in a few minutes when small amounts of water are added to solutions of the trannulenes in dimethyl sulfoxide. Monitoring this process with the use of an optical fibre spectrometer (Avantes BV) allowed us to detect short-lived anion radicals of trannulenes ($\mathbf{T3}^{\bullet-}$ and $\mathbf{T5}^{\bullet-}$ or some of their derivatives). Characteristic absorptions of these anion–radical species at 900–1100 nm appeared immediately after addition of water and then vanished together with trannulene bands at 500–730 nm in 1–2 min. The formation of transient anion–radicals suggests a SET mechanism of degradation of trannulenes in water. We are currently investigating products that are formed after long exposure of trannulenes to water.

We believe that the instability of emerald-green trannulenes in water is not so ultimate. Particularly encouraging is an observation that solutions of trannulenes **T3** and **T5** in aqueous acids and even in slightly acidified water are stable for at least 3 months and do not show any signs of degradation. This funding allows us to expect that the problem of poor stability of aqueous solutions of trannulenes will soon be overcome and these compounds will become available for medicinal studies as novel photosensitizers potentially very useful for photodynamic therapy of cancer.

Delivery of fluorine to bone tissues is another field for possible medicinal implementation of water-soluble fluorinated fullerenes.[7,8] This application, however, does not rely on electronic properties of trannulenes; therefore, water-soluble fluorine-loaded products of partial degradation of **T3** and **T5** might be very promising as bone-vectored fluorine carriers. Isolation and spectroscopic characterization of these species is now in progress.

Synthesis of Unsymmetrically Substituted Trannulenes

Readily available compounds **M1** and **D1** also possess masked COOH groups and thus they might be considered as good precursors for the design of some sophisticated water-soluble trannulene-core-based assembles. This could be achieved by replacing the remaining labile fluorine atoms in **M1** and **D1** with appropriate functional groups. To prove the feasibility of this concept, we introduced **M1** and **D1** in reactions with C–H acid **2** that yielded first nonsymmetrically substituted trannulenes **T6** and **T7**, respectively (Scheme 4).



Scheme 4.

The compositions and molecular structures of trannulenes **T6** and **T7** were confirmed by MALDI-TOF mass spectrometry and ^{1}H, ^{19}F and ^{13}C NMR spectroscopy. Lowering the molecular symmetry from C_{3v} characteristic for conventional trannulenes to C_s should result in more complicated NMR spectra of compounds **T6** and **T7**. The ^{19}F NMR spectra of **T6** and **T7** comprised only sets of two signals at ≈137 ppm and one more group of 5 or 6 peaks at 144.5–145 ppm (Figure 5) instead of 8 separate resonances that could be expected for their C_s symmetrical structures. Such ^{19}F NMR spectra of these nonsymmetrical trannulenes resembled closely the spectra of symmetrical compounds such as **T1** and **T2** that showed a singlet resonance at δ = 137.1 ppm and two more peaks at 143–145 ppm. The ^{13}C NMR spectrum of **T7** was also quite similar to the ^{13}C NMR spectra of **T1** and **T2** with only difference that it showed more signals in the ranges of 146–151 ppm (fullerene cage carbon atoms) and 162–166 ppm (C=O groups). It is also notable that four *tert*-butyl groups in **T7** give two separate resonances in the ^{1}H NMR spectrum, which suggests that their rotations are completely frozen in this compound. Absorption spectra of nonsymmetrically substituted trannulenes **T6** and **T7** were virtually identical to the spectra of conventional trannulenes **T1** and **T2** (Figure 3). This observation suggests that nonsymmetrical substitution of trannulenes with different organic addends does not change significantly their electronic properties.

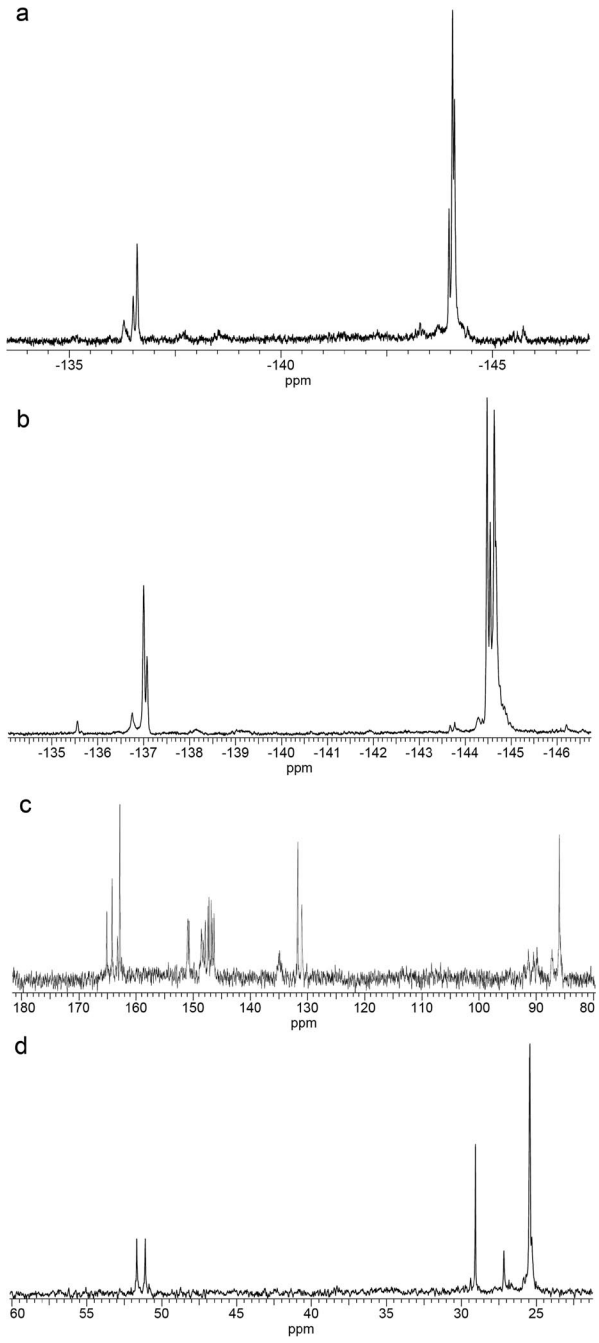
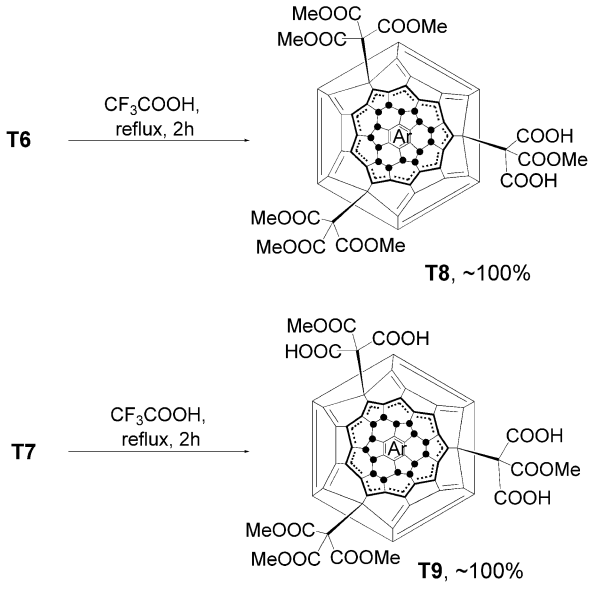


Figure 5. ^{19}F NMR spectra of **T6** (a) and **T7** (b); low-field (c) and high-field (d) parts of ^{13}C NMR spectrum of **T7**.

Deprotection of COOH groups in trannulenes **T6** and **T7** was achieved quantitatively by their treatment with trifluoroacetic acid that yielded highly polar emerald-green trannulene acids **T8** and **T9** (Scheme 5). These acids were characterized by ^{1}H, ^{19}F and ^{13}C NMR spectroscopy (^{13}C NMR spectrum was not obtained for **T9** because of low solubility) and mass spectrometry that evidenced their compositions and structures. In particular, the ^{19}F NMR spectra of these compounds were virtually identical to the spectra of parent trannulenes **T6** and **T7**. The presence of only two polar COOH groups in the molecular framework of trannulene **T8** was not sufficient for attaining any measurable solubility in aqueous media. However, this compound might be further derivatized with appropriate peptides or glycosides that could improve significantly its solubility in water and even make possible selective delivery of the whole molecule to some specific biological targets. For example, lactose appendages are used for targeting tumour cells.[14]



Scheme 5.

In contrast to **T8**, trannulene acid **T9** exhibited more or less the same behaviour with respect to water and polar organic solvents as symmetrical compound **T3** and, therefore, seems to be suitable for biological tests. This result allows us to anticipate that precursor **D1** can be derivatized with a variety of pharmacophores by using appropriately substituted C–H acids instead of **2** in Scheme 2. In the next step, resulting unsymmetrical trannulenes could be easily converted into water-soluble, emerald-green fullerene acids such as **T9**.

Conclusions

The first highly polar C_{3v}-symmetrical trannulene derivatives of fluorofullerene $C_{60}F_{18}$ possessing six carboxylic (**T3**) or six ammonium ion (**T5**) groups have been synthesized and spectrally characterized. It was shown that these compounds indeed can be dissolved in water; however, the resulting solutions slowly degrade with time. This degradation is inhibited by the presence of acidic additives that make aqueous solutions of **T3** stable for months.

A preparation and spectroscopic characterization of unsymmetrically substituted trannulenes **T6**–**T9** possessing the composition $C_{60}F_{15}R_2R'$ have been achieved for the first time. The developed synthetic route demonstrated the possibility of loading the trannulene core step-by-step with appropriate functionalities. This is particularly valuable for the design of trannulene-based compounds for biomedical implementations that should have a number of polar solubilizing groups in combination with a functionality responsible for specific targeting of the molecule to some specific tissues or intracellular structures. The feasibility of this concept was evidenced by the preparation of trannulene **T9**, which possesses four COOH groups that make it reasonably soluble in aqueous media and one more independently introduced organic functionality, which in perspective, could be some pharmacophore group.

We believe that deeper exploration of the developed synthetic methods will result in the preparation of a large variety of novel water-soluble symmetrically and unsymmetrically substituted emerald-green trannulenes with balanced physical properties (good solubility, long-term stability in aqueous media) and interesting biological activities.

Experimental Section

Synthesis of M1, D1, T1 and T2: Fluorinated fullerene $C_{60}F_{18}$ (200 mg, 0.19 mmol) was dissolved in dried toluene (200 mL, dried with metal sodium) and then an appropriate amount of the corresponding C–H acid was added (0.193 mmol of **1** for the preparation of **M1**; 0.39 mmol of **1** for **D1**; 0.95 mmol of **1** for **T1** and 0.6 mmol of **2** for **T2**) in one portion. The resulting solution and the whole reaction setup was degassed and then filled with argon. Afterwards, a solution of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in dry toluene (50 mL) was added dropwise within 15–30 min to a intensely stirred reaction mixture. Molar ratio between DBU and the corresponding C–H acid was nearly 1:2. The use of larger amounts of DBU resulted in strong degradation of $C_{60}F_{18}$ and the formation of an insoluble black precipitate. After the addition of DBU, the reaction mixture was stirred for an additional 30 min and then poured on top of a silica gel column (Acros organics, 40–60 μ, 60 Å). Elution with mixtures of toluene and ethyl acetate in variable ratios (volume concentration of EtOAc was varied in between 0.5 and 4%) yielded separate fractions of **M1**, **D1** and **T1** or only one product fraction in the synthesis of **T2**. These solutions were concentrated in vacuo (rotary evaporator), residues were washed with hexane and dried in air. Compounds **T1** and **T2** were obtained as dark-green solids, **D1** was obtained as a dark-olive powder and **M1** was obtained as a dark-brown, almost black, powder.

M1: Yield: 5–15% (12–37 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.60 (s, 9 H), 1.61 (s, 9 H) 3.96 (s, 3 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –107.69 (s, 1 F), –131.11 (d, J = 18.7 Hz, 1 F), –135.51 (m, 1 F), –136.06 (m, 1 F), –136.60 (d, J = 35.0 Hz, 1 F), –137.98 (t, J = 5.8 Hz, 1 F), –139.92 (dt, J = 26.6, 4.5 Hz, 1 F), –140.42 (m, 1 F), –142.77 (br. s, 1 F), –143.51 (br. s, 1 F), –143.99 (s, 1 F), –145.86 (br. s, 1 F), –146.37 (s, 1 F), –148.60 (d, J = 27.2 Hz, 1 F), –154.85 (dt, J = 27.8, 6.5 Hz, 1 F), –157.38 (m, 1 F), –158.74 (m, 1 F) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.78 (*t*Bu), 29.72 [*C*(COO*t*Bu)$_2$COOMe], 53.55 (OMe), 70.98 (cage sp^3 C), 86.63 (*t*Bu), 86.69 (*t*Bu), 88.9 (*C*F), 89.11 (*C*F), 89.26 (*C*F), 89.42 (*C*F), 89.65 (*C*F), 90.65 (*C*F), 90.81 (*C*F), 91.06 (*C*F), 93.85 (*C*F), 94.08 (*C*F), 95.63 (*C*F), 128.18, 128.31, 128.98, 129.13, 131.76, 131.9, 132.31, 132.47, 134.73, 137.9, 141.04, 141.35, 142.53, 143.09, 143.71, 143.74, 144.16, 145.62, 146.67, 146.91, 147.16, 147.97, 148.12, 148.17, 148.5, 149.01, 149.19, 149.25, 149.32, 149.49, 150.57, 150.83, 151.43, 151.85, 152.66, 157.53, 162.86, 162.91, 164.7, 165.21 ppm. UV/Vis (toluene, ε/M^{-1}cm^{-1}): λ = 339 (25.9×10^3), 367 (27.0×10^3), 442 (11.4×10^3), 553 (3.7×10^3), 592 (3.0×10^3), 647 (2.1×10^3) nm. MS (MALDI TOF): m/z = 1316 [M$^+$].

D1: Yield: 12–30% (35–89 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.61 (br. s, 36 H) 3.97 (s, 6 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –123.73 (s, 0.25 F), –135.59 (s, 0.25 F), –137.25 (m, 1 F), –137.73 (br. s., 0.5 F), –138.24 (m, 0.25 F), –139.15 (d, J = 25.9 Hz, 0.25 F), –139.73 (m, 0.25 F), –140.14 (m, 1 F), –141.59 (dd, J = 25.9, 6.5 Hz, 0.5 F), –142.23 (s, 0.5 F), –142.54 (s, 0.5 F), -142.95

(d, J = 35.0 Hz, 1 F), –144.56 (m, 7.25 F), –146.94 (d, J = 28.5 Hz, 0.5 F), –147.4 (t, J = 30.5 Hz, 0.5 F), –151.77 (t, J = 29.8 Hz, 0.5 F), –154.35 (dt, J = 27.2, 7.1 Hz, 0.25 F), –156.63 (dd, J = 28.2, 7.5 Hz, 0.25 F), –157.70 (m, 0.5 F) ppm. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) consisted of numerous badly overlapped peaks because of the atropoisomerism discussed in the text. UV/Vis (toluene, ε/M^{-1}cm^{-1}): λ = 332 (27.1×10^3), 363 (23.0×10^3), 396 (18.7×10^3), 443 (10.0×10^3), 606 (3.8×10^3), 661 (4.2×10^3) nm. MS (MALDI TOF): m/z = 1570 [M$^+$].

T1: Yield: 25–46% (80–160 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.67 (s, 54 H) 4.06 (s, 9 H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –137.05 (s, 3 F), –144.56 (s, 6 F), –144.78 (s, 6 F) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.96 (tBu), 31.6 [C(COOtBu)$_2$COOMe], 53.61 (OMe), 71.87 (cage sp^3 C), 85.75 (Me$_3$$C$O), 85.89 ($C$F), 87.23 ($C$F), 89.89 ($C$F), 90.48 ($C$F), 91.41 ($C$F), 92.07 ($C$F), 125.31, 128.24, 129.05, 130.94, 131.76, 146.85, 147.46, 148.42, 150.99, 162.83, 163.24, 165.14 ppm. UV/Vis (toluene, ε/M^{-1}cm^{-1}): λ = 338 (23.8×10^3), 397 (27.5×10^3), 438 (10.9×10^3), 565 (4.0×10^3), 617 (7.9×10^3), 661 (11.6×10^3) nm. MS (MALDI TOF): m/z = 1824 [M$^+$]. FTIR (KBr pellet): $\tilde{\nu}$ = 473 (w), 562 (w), 668 (w), 729 (w), 816 (w), 836 (w), 842 (w), 1078 (s), 1120 (vs), 1147 (vs), 1252 (s), 1295 (s), 1372 (m), 1396 (w), 1436 (w), 1462 (w), 1739 (s), 2334 (vw), 2359 (w), 2981 (w) cm^{-1}.

T2: Yield: 54% (160 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.06 (s, 27 H, OMe) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –137.14 (s, 3 F), –144.58 (s, 12 F) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 29.68 [C(COOMe)$_3$], 54.3 (OMe), 70.99 (cage sp^3 C), 85.69 (CF), 87.23 (CF), 89.72 (CF), 90.39 (CF), 91.3 (CF), 91.99 (CF), 125.26, 128.19, 129, 130.96, 131.71, 135.45, 135.58, 137.84, 146.8, 146.94, 148.3, 150.62, 162.54, 164.13 ppm. UV/Vis (toluene, ε/M^{-1}cm^{-1}): λ = 335 (24.2 10^3), 397 (26.8×10^3), 438 (11.3×10^3), 567 (4.2×10^3), 611 (7.7×10^3), 661 (12.5×10^3) nm. MS (MALDI TOF): m/z = 1572 [M$^+$]. FTIR (KBr pellet): $\tilde{\nu}$ = 465 (vw), 540 (vw), 562 (w), 584 (w), 658 (w), 671 (w), 688 (w), 732 (w), 764 (vw), 814 (m), 861 (vw), 935 (w), 946 (w), 968 (w), 1008 (w), 1026 (m), 1034 (m), 1056 (m), 1078 (vs), 1119 (vs), 1147 (s), 1168 (m), 1184 (m), 1244 (s), 1281 (vs), 1363 (vw), 1400 (w), 1437 (m), 1459 (m), 1630 (w), 1748 (vs), 2957 (w) cm^{-1}.

Synthesis of T4 and T5: Trannulene **T4** was synthesized from $C_{60}F_{18}$ (200 mg, 0.19 mmol) and C–H acid **5** (1360 mg, 2.85 mmol) in accordance with the procedure described above for the preparation of **T1** and **T2**. Isolation and purification of **T4** was performed by using silica gel column chromatography (Acros organics, 40–60 μ, 60 Å) and mixtures of toluene and ethyl acetate in variable ratios as eluent (volume concentration of EtOAc was gradually increased from 5 and 65%). **T4** was obtained as a dark-green solid after concentration of the eluate, washing the residue with hexane and drying in air.

For preparation of trannulene **T5**, precursor **T4** (50 mg) was first dissolved in neat trifluoroacetic acid (5 mL). Afterwards, this solution was stirred at room temperature for 5 min and then concentrated to dryness in vacuo. The residue was washed with dichloromethane and dried in air. Trannulene **T5** was obtained as a hygroscopic green solid highly soluble in water.

T4: Yield: 31% (142 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.50 (s, 18 H, tBu), 1.52 (s, 36 H, tBu), 1.75 (m, 12 H, CH_2), 2.09 (m, 12 H, CH_2), 3.33 (m, 12 H, CH_2), 4.59 (m, 9 H, COOMe), 5.07 (br. s., 6 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –136.27 (s, 3 F), –143.58 (m, 12 F) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.45 (tBu), 29.01 (CH_2-CH$_2$-CH$_2$), 33.87 [C(COOR)$_2$COOMe], 37.3 (CH$_2$NHBoc), 53.48 (OMe), 54.32 (OMe), 65.64 (COO-CH$_2$-), 79.47 [C(CH$_3$)$_3$], 79.51 [C(CH$_3$)$_3$], 83.36 (CF), 85.68 (CF), 87.23 (CF), 89.82 (CF), 91.39 (CF), 92.03 (CF), 125.3, 127.72, 128.23, 129.04, 130.54, 130.91, 131.02, 131.7, 131.77, 137.88, 146.8, 146.88, 148.26, 150.8, 156, 156.09, 156.17, 163.79, 164.19, 165.1 ppm. UV/Vis (toluene, ε/M^{-1}cm^{-1}): λ = 335 (27.2×10^3), 396 (29.6×10^3), 438 (12.0×10^3), 571 (5.3×10^3), 613 (7.8×10^3), 662 (10.7×10^3) nm. MS (MALDI TOF): m/z = 2430 [M$^+$], 1955 {M – C(COOMe)-[COO(CH$_2$)$_3$NHC(O)OtBu]$_2$}$^+$. FTIR (KBr pellet): $\tilde{\nu}$ = 555 (w), 668 (w), 781 (w), 815 (m), 861 (m), 970 (m), 1034 (m), 1076 (s), 1119 (vs), 1147 (s), 1168 (s), 1218 (s), 1252 (s), 1275 (s), 1368 (m), 1393 (m), 1436 (w), 1455 (m), 1462 (m), 1506 (m), 1520 (m), 1538 (m), 1698 (m), 1713 (m), 1746 (m), 2869 (w), 2933 (m), 2975 (m) cm^{-1}.

T5: Yield: 93% (48 mg). ^{1}H NMR (600 MHz, DCOOD): δ = 2.88 (m, 12 H, CH_2), 2.95 (m, 12 H, CH_2), 3.86 (m, 12 H, CH_2), 4.84 (m, 9 H, COOMe), 5.24 (br. s., 6 H, NH) ppm. ^{13}C NMR spectrum was not obtained due to low solubility of this compound in organic solvents including organic acids and its insufficient stability in aqueous media. ^{19}F NMR (282 MHz, DCOOD): δ = –76.06 (CF_3COO^-, 18 F), –136.14 (m, 3 F), –143.32 (m, 6 F), –143.96 (m, 6 F) ppm. UV/Vis (AcOH/water, 1:1; ε/M^{-1}cm^{-1}): λ = 338 (22.1×10^3), 369 (19.2×10^3), 393 (20.1×10^3), 436 (9.4×10^3), 606 (4.7×10^3), 665 (7.4×10^3). MS (ESI): m/z = 1831 [M + H]$^+$, 916 [M + 2H]$^{2+}$. FTIR (KBr pellet): $\tilde{\nu}$ = 483 (m), 604 (m), 659 (m), 723 (m), 760 (m), 801 (s), 839 (s), 890 (s), 1062 (vs), 1124 (vs), 1203 (vs), 1270 (s), 1688 (m), 1732 (m), 1736 (m), 2949 (s), 3108 (s) cm^{-1}.

Synthesis of T6 and T7: Precursor compound **M1** or **D1** (0.02 mmol) was dissolved in toluene together with a large excess of **2** (0.06 mmol). Afterwards, a solution of DBU (0.014 mmol) in toluene (10 mL) was added dropwise. At the end of the addition, the reaction mixture attained an emerald-green colour characteristic for trannulenes. Chromatography separation on silica using toluene/EtOAc mixtures as the eluent yielded trannulenes **T6** and **T7**. Further workup was done analogously to procedure reported for **T1** and **T2** above.

T6: Yield: 68% (22.5 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.69 (s, 18 H, tBu), 3.85 (s, 3 H, OMe), 4.05 (s, 18 H, OMe) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –137.05 (s, 1 F), –137.14 (s, 2 F), –144.51 (s, 2 F), –144.59 (m, 6 F), –144.64 (m, 4 F) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 28.03 (tBu), 29.44 [C(COOR)$_3$], 29.70 [C(COOR)$_3$], 53.37 (OMe), 54.26 (OMe), 86.17 (Me$_3$$C$O), 87.35 ($C$F), 128.63, 128.96, 131.72, 131.75, 135.21, 135.77, 141.06, 146.47, 146.59, 146.67, 146.79, 146.93, 146.96, 147.23, 147.86, 148.18, 148.2, 148.25, 148.28, 148.31, 150.63, 150.66, 150.69, 150.75, 150.86, 150.89, 162.87 (C=O), 164.15 (C=O), 164.2 (C=O) ppm. UV/Vis (toluene, ε/M^{-1}cm^{-1}): λ = 334 (23.0×10^3), 396 (24.3×10^3), 441 (9.1×10^3), 565 (3.6×10^3), 617 (6.6×10^3), 660 (9.5×10^3). MS (MALDI TOF): m/z = 1656 [M$^+$]. FTIR (KBr pellet): $\tilde{\nu}$ = 466 (w), 674 (w), 736 (m), 816 (m), 974 (m), 1029 (s), 1076 (vs), 1118 (vs), 1143 (s), 1247 (s), 1278 (s), 1436 (m), 1747 (s), 2851 (s), 2924 (s), 2957 (s) cm^{-1}.

T7: Yield: 75% (26 mg). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.64 (s, 18 H, tBu), 1.67 (s, 18 H, tBu), 3.99 (s, 6 H, OMe), 4.04 (s, 9 H, OMe) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –137.06 (s, 2 F), –137.13 (s, 1 F), –144.54 (m, 4 F), –144.61 (s, 2 F), –144.69 (m, 6 F) ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 25.42 (tBu), 25.45 (tBu), 27.17 [C(COOR)$_3$], 29.06 [C(COOR)$_3$], 51.1 (OMe), 51.66 (OMe), 83.45 (Me$_3$$C$O), 87.35 ($C$F), 89.86 ($C$F), 90.33 ($C$F), 91.42 ($C$F), 130.97, 131.7, 131.79, 146.37, 146.61, 146.87, 147.25, 147.41, 147.89, 148.15, 148.57, 150.71, 150.89, 162.85 (C=O), 164.16 (C=O), 165.1 (C=O) ppm. UV/Vis (toluene, ε/M^{-1}cm^{-1}): λ = 334 (22.2 10^3), 396 (23.5×10^3), 441 (8.4×10^3), 565 (3.0×10^3), 617 (4.9×10^3), 660 (8.8×10^3). MS (MALDI TOF): m/z = 1740 [M$^+$].

FTIR (KBr pellet): $\tilde{\nu}$ = 483 (m), 604 (m), 659 (m), 723 (m), 760 (m), 801 (s), 839 (s), 890 (s), 1062 (vs), 1124 (vs), 1203 (vs), 1270 (s), 1688 (m), 1732 (m), 1736 (m), 2949 (s), 3108 (s) cm^{-1}.

Synthesis of T3, T8 and T9: Precursor trannulene **T1**, **T6** or **T7** was dissolved in trifluoroacetic acid (to achieve concentration of ca. 4 $mg\,mL^{-1}$), and the resulting solution was heated at reflux for 2 h. Afterwards, an excess amount of CF_3COOH was removed in vacuo; the residue was washed two times with dichloromethane and then dried in air. Trannulenes **T3**, **T8** and **T9** were obtained as emerald-green powders highly soluble in organic and aqueous inorganic acids and polar organic solvents.

T3: Yield: ca. 100%. ^1H NMR (600 MHz, DCOOD): δ = 3.31 (s, 9 H, OMe) ppm. ^{19}F NMR (282 MHz, DCOOD), δ = –135.97 (s, 3 F), –143.86 (s, 6 F), –144.61 (s, 6 F) ppm. ^{13}C NMR (200 MHz, DCOOD): δ = 45.62 [*C*$(COOH)_2$(COOMe)], 48.81 (OMe), 80.84 (*C*F), 82.36 (*C*F), 85.24 (*C*F), 86.81 (*C*F), 125.78, 125.89, 126.47, 126.66, 128.37, 128.51, 141.02, 141.11, 141.79, 141.82, 143.05, 143.13, 143.16, 146.97, 147.06 ppm. UV/Vis (AcOH/water, 1:1; $\varepsilon/M^{-1}\,cm^{-1}$): λ = 338 (25.1 10^3), 373 (22.8 10^3), 391 (24.5×10^3), 433 (10.7×10^3), 569 (4.6×10^3), 610 (7.7×10^3), 663 (10.9×10^3) nm. MS (ESI): *m*/*z* = 1471.074 $[M - OH]^-$, 1427.089 $[M - COO - OH]^-$. FTIR (KBr pellet): $\tilde{\nu}$ = 478 (w), 562 (w), 663 (w), 728 (w), 816 (w), 1032 (m), 1069 (s), 1116 (vs), 1142 (s), 1166 (m), 1230 (m), 1327 (m), 1400 (w), 1732 (m), 1738 (m), 2855 (w), 2925 (w), 2956 (w), 3426 (m) cm^{-1}.

T8: Yield: ca. 100%. ^1H NMR (600 MHz, $CDCl_3$): δ = 4.05 (s, 18 H, OMe), 4.14 (s, 3 H, OMe) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –136.33 (s, 3 F), –143.62 (s, 2 F), –143.79 (m, 8 F), –142.88 (s, 2 F), ppm. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 54.29 (OMe), 54.89 (OMe), 120.8, 122.33, 129.76, 131.24, 131.43, 132.69, 137.88, 138.39, 143.02, 144.83, 144.93, 146.5, 146.52, 146.56, 147.09, 147.19, 147.84, 147.86, 147.95, 147.96, 147.99, 148.02, 148.06, 148.1, 148.2, 148.46, 148.58, 148.64, 148.67, 148.92, 148.95, 148.97 ppm. UV/Vis (AcOH/water, 1:1; $\varepsilon/M^{-1}\,cm^{-1}$): λ = 337 (24.8×10^3), 373 (22.5×10^3), 393 (23.7×10^3), 432 (11.4×10^3), 569 (4.2×10^3), 611 (8.0×10^3), 663 (10.5×10^3). MS (MALDI TOF): *m*/*z* = 1500 $[M - CO_2]^+$.

T9: Yield: ca. 100%. ^1H NMR (600 MHz, DCOOD): δ = 4.59 (m, 15 H, OMe) ppm. ^{19}F NMR (282 MHz, $CDCl_3$), δ = –137.06 (s, 2 F), –137.13 (s, 1 F), –144.54 (m, 4 F), –144.61 (s, 2 F), –144.69 (m, 6 F) ppm. ^{13}C NMR spectrum was not obtained due to low solubility of the compound in common organic solvents. UV/Vis (AcOH/water, 1:1; $\varepsilon/M^{-1}\,cm^{-1}$): λ = 335 (25.6×10^3), 375 (23.4 10^3), 392 (24.4×10^3), 431 (12.0×10^3), 572 (3.8×10^3), 613 (9.1×10^3), 662 (12.2×10^3) nm. MS (MALDI TOF): *m*/*z* = 1472 $[M - CO_2]^+$.

Supporting Information (see footnote on the first page of this article): ^1H, ^{19}F and ^{13}C NMR spectra of trannulene **T1** and ESI mass spectrum of trannulene **T3**

Acknowledgments

Financial support was provided by Russian Foundation for Basic Research (RFBR grants 07-03-01078-a and 06-03-39007 GFEN), Federal Agency for Science and Innovations (FASI contract 02.513.12.3103, code 2009-03-1.3-07-50-002), Research Program of Russian Academy of Sciences (OXHM - 01) and Russian President Foundation (MK-4305.2009.3).

[1] a) J. Chandrasekhar, E. D. Jemmis, P. von Rague Schleyer, *Tetrahedron Lett.* **1979**, *39*, 3707; b) P. von Rague Schleyer, H. Jiao, M. N. Glukhovtsev, J. Chandrasekhar, E. Kraka, *J. Am. Chem. Soc.* **1994**, *116*, 10129; c) A. A. Fokin, H. Jiao, P. von Rague Schleyer, *J. Am. Chem. Soc.* **1998**, *120*, 9364.
[2] G. A. Burley, *Angew. Chem. Int. Ed.* **2005**, *44*, 3176.
[3] a) X. W. Wei, A. D. Darwish, O. Boltalina, P. B. Hitchcock, J. M. Street, R. Taylor, *Angew. Chem. Int. Ed.* **2001**, *40*, 2989; b) G. A. Burley, A. G. Avent, O. V. Boltalina, T. Drewello, I. V. Gol′t, M. Marcaccio, F. Paolucci, D. Paolucci, J. M. Street, R. Taylor, *Org. Biomol. Chem.* **2003**, *1*, 2015; c) G. A. Burley, A. G. Avent, I. V. Gol′dt, P. B. Hitchcock, H. Al-Matar, D. Paolucci, F. Paolucci, P. W. Fowler, A. Soncini, J. M. Street, R. Taylor, *Org. Biomol. Chem.* **2004**, *2*, 319; d) A. D. Darwish, I. V. Kuvytchko, X.-W. Wei, O. V. Boltalina, I. V. Gol′dt, J. M. Street, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **2002**, 1118; e) X. W. Wei, A. Avent, O. Boltalina, A. D. Darwish, P. W. Fowler, J. P. B. Sandall, J. M. Street, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **2002**, 41.
[4] a) P. Troshin, R. N. Lyubovskaya, I. N. Ioffe, N. B. Shustova, E. Kemnitz, S. I. Troyanov, *Angew. Chem.* **2005**, *117*, 238; *Angew. Chem. Int. Ed.* **2005**, *44*, 234; b) T. Canteenwala, P. A. Padmawar, L. Y. Chiang, *J. Am. Chem. Soc.* **2005**, *127*, 26.
[5] a) G. A. Burley, A. G. Avent, O. V. Boltalina, I. V. Gol′dt, D. M. Guldi, M. Marcaccio, F. Paolucci, D. Paolucci, R. Taylor, *Chem. Commun.* **2003**, 148; b) D. M. Guldi, M. Marcaccio, F. Paolucci, D. Paolucci, J. Ramey, R. Taylor, G. A. Burley, *J. Phys. Chem. A* **2005**, *109*, 9723.
[6] O. V. Boltalina, B. de La Vaissière, A. Yu. Lukonin, P. W. Fowler, A. K. Abdul-Sada, J. M. Street, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **2001**, 550; O. Boltalina, J. H. Holloway, E. G. Hope, J. M. Street, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1998**, 1845; B. W. Clare, D. L. Kepert, R. Taylor, *Org. Biomol. Chem.* **2003**, *1*, 3618.
[7] J. W. Aborgast, C. S. Foote, *J. Am. Chem. Soc.* **1991**, *113*, 8886.
[8] Y. Tabata, Y. Murakami, Y. Ikada, *Fullerene. Sci. Technol.* **1997**, *5*, 989.
[9] a) D. M. Guldi, G. M. A. Rahman, V. Sgobba, C. Ehli, *Chem. Soc. Rev.* **2006**, *35*, 471; b) D. Bonifazi, O. Enger, F. Diederich, *Chem. Soc. Rev.* **2007**, *36*, 390; c) A. Mateo-Alonso, C. Sooambar, M. Prato, *Org. Biomol. Chem.* **2006**, *4*, 1629.
[10] L. J. Wilson, *Interface* **1999**, *8*, 24; K. A. Gonzales, L. J. Wilson, W. Wu, G. H. Nancollas, *Bioorg. Med. Chem.* **2002**, *10*, 1997.
[11] P. Pitt, H. Berry, *Postgrad. Med. J.* **1991**, *67*, 323.
[12] a) P. A. Troshin, A. B. Kornev, A. S. Peregudov, S. A. Baskakov, R. N. Lyubovskaya, *J. Fluorine Chem.* **2005**, *126*, 1559; b) A. B. Kornev, P. A. Troshin, A. S. Peregudov, Z. I. Klinkina, N. V. Polyakova, R. N. Lyubovskaya, *Mendeleev Commun.* **2006**, 157.
[13] M. Brettreich, A. Hirsch, *Tetrahedron Lett.* **1998**, *39*, 2731.
[14] M. Yamamoto, K. Ichinose, N. Ishii, T. Khoji, K. Akiyoshi, N. Moriguchi, J. Sunamoto, T. Kanematsu, *Oncol. Rep.* **2000**, *7*, 107.

Received: October 15, 2009
Published Online: January 12, 2010

