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Photochemical synthesis and NMR analysis of novel regiospecifically trifluoromethyl-substituted dibenzosemibullvalene

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Abstract

Preparation of the novel regiospecific bis(trifluoromethyl)-substituted dibenzobarrelene (**2**) and dibenzosemibullvalene (**3**) is described. The stereostructure of compounds **2** and **3** has been deduced on the basis of their ^{1}H, ^{19}F and ^{13}C 1D/2D NMR spectra. Three-bond C–F couplings were used as a structural probe while the longest C–F coupling observed was over four bonds.

Keywords: Photochemical synthesis; Trifluoromethyl-substituted dibenzosemibullvalene; Trifluoromethyl-substituted dibenzobarrelene; ^{1}H NMR; ^{13}C NMR; C–F couplings

1. Introduction

The group of agents all having a three-ring molecular core and producing therapeutic responses in most patients with major depression has the trivial name the tricyclic antidepressants [1]. Among these agents are the dibenzazepine derivative imipramine and other closely related drugs such as the secondary amine congener of imipramine, desipramine, and the cycloheptadiene derivative, amitriptyline [1,2]. Additional drugs that are commonly used in the treatment of depression are the so-called new generation antidepressants, e.g., the tetracyclic agent maprotiline [2]. Two additional classes of compounds, dibenzobarrelenes (dibenzobicyclo[2.2.2]octa-2,5,7-triene), and particularly dibenzosemibullvalenes (dibenzotricyclo[3.3.0.$0^{2,8}$]octa-3,6-diene), have been discovered to exert pharmacological effects on the central nervous system as antidepressive agents [3,4]. Furthermore, a number of fluorinated compounds have found application in medicine as drugs [5]. In the search for compounds chemically related to those classes of pharmacologically active compounds and in connection to our previous studies on dibenzobarrelenes and dibenzosemibullvalenes [6,7] we have prepared the novel regiospecifically bis(trifluoromethyl)-substituted dibenzobarrelene (**2**) and dibenzosemibullvalene (**3**) to evaluate their potential antidepressive activities. The synthesis and some details of NMR spectra relevant for the structural determination of **2** and **3** are reported here.

2. Results and discussion

2.1. Synthetic work

Regiospecifically trifluoromethyl-substituted dibenzobarrelene (**2**) was prepared by thermal Diels–Alder [4+2] cycloaddition of phenylacetylene to 9,10-bis(trifluoromethyl)-substituted anthracene (**1**) [8]. Irradiation of **2** in acetone as a sensitizer led to a racemic mixture of dibenzosemibullvalene (**3**) that can be designated by the relative position of the phenyl and trifluoromethyl groups on the semibullvalene ring as (1*R*,2*R*,5*S*,8*R*)- and (1*S*,2*S*,5*R*,8*S*)-(**3**) (Scheme 1). This is in agreement with data found earlier on the mechanism of the di-π-methane photorearrangement of dibenzobarrelenes in solution [9]. Our preliminary results regarding the resolution of enantiomers by liquid chromatography on triacetylcellulose clearly show the presence of two enantiomers in a racemic mixture of (±)-(**3**) [10].

Since the bridging carbon–carbon double bond in **2** is unsymmetrically substituted, irradiation of **2** could also give rise to another pair of racemic mixture of enantiomers (1*S*,2*S*,5*R*,8*S*)- and (1*R*,2*R*,5*S*,8*R*)-(**3a**) as shown in Fig. 1. The formation of a symmetrically-substituted trifluoromethyl molecule could also be possible (**3b** in Fig. 1).

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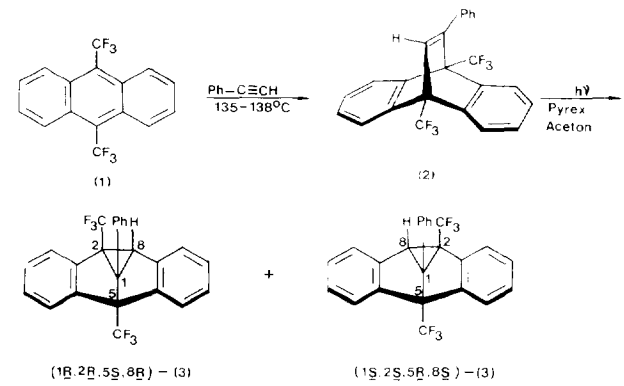


Scheme 1.

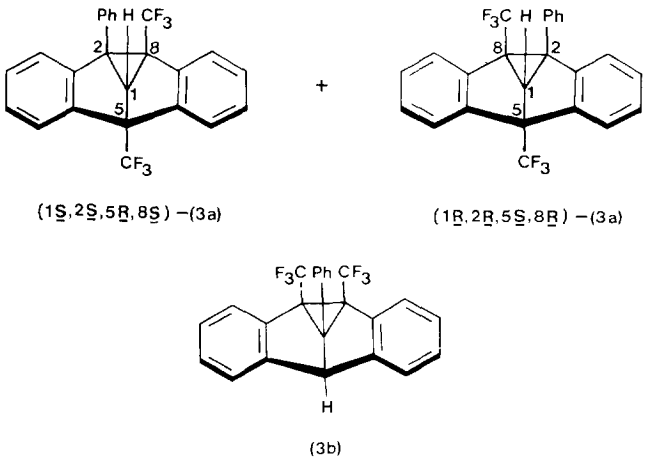


Fig. 1. Possible regioisomers (**3a** and **3b**) arising from the irradiation reaction of **2**.

2.2. NMR spectra

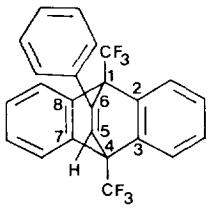
The ^{13}C spectrum of **2** exhibits 16 signals. Eight belong to quaternary carbons (four aliphatic, three aromatic and one olefinic) and eight to tertiary carbons (seven aromatic and one olefinic). The assignment of signals was performed on the basis of chemical shifts and signal intensities, multiplicity and the magnitude of the C–F and C–H spin–spin couplings, connectivity in HETCOR spectra and by comparison with the related mono trifluoromethyl-substituted compounds. Table 1 lists the chemical shifts and C–F coupling constants of the C atoms which are relevant for the structural determination of **2**. One can see that the C-1 atom is deshielded relative to C-4 due to the effect of the phenyl ring, while the two-bond C–F coupling leading to quartet splitting of these carbons is practically the same. The C-1 and C-4 atoms could also be mutually distinguished by comparison with the ^{13}C NMR data for the structurally-related mono trifluoromethyl-substituted dibenzobarrelene [7,11]. The C-2,8 and C-3,7 atoms have very similar chemical shifts, i.e. δ 141.10 and 141.40 ppm, respectively. Although both pairs of carbons are three bonds away from fluorine atoms, only the C-3,7 signal shows quartet splitting amounting to 2.20 Hz. Fluorine coupling with C-2,8 is most probably perturbed by the electronic effect of the neighbouring phenyl ring. The olefinic C-5 at δ 136.83 ppm is split into a quintet with a line separation of 2.62 Hz. Obviously this splitting pattern arises from C–F coupling with both CF_3 groups, which means that three- and four-bond C–F coupling constants have very similar or similar values. Four-bond C–F coupling, which is rarely observed in aliphatic molecules, was detected here since the coupling pathway incorporates an olefinic double bond. In fact the C-5 multiplet should be a septet but two lines (the first and the seventh) are unresolved due to their low intensity and small C–F coupling constant. Gated decoupled spectra allowed detection of one-bond C–H splitting equal to 178.3 Hz at C-5, while for other tertiary carbons in **2** this splitting was equal to 161–163 Hz. In the structurally related norbornadiene derivative, a $^1J_{CH}$ value of 175 Hz was observed at the olefinic carbon [12]. The chemical shifts of tertiary carbons range from δ 122 to 125 ppm in the barrelene moiety and from δ 127 to 129 ppm in the phenyl moiety. The olefinic quaternary C-6 resonates at 152.14 ppm, displaying doublet splitting of 5.6 Hz due to three-bond C–F coupling. The two remaining lines of the quartet are unresolved. The three-bond C–F coupling at C-6 was twice as great as the other $^3J_{CF}$ values found for **2**. This difference arises from the different coupling pathways and dihedral angles involved (Karplus relationship) but a through-space contribution to coupling has to be taken into account as well as far as C-6 is concerned [12]. The phenyl quaternary carbon at δ 135.70 ppm, showed no four-bond C–F coupling. The CF_3 groups resonate at δ 125.65 and 126.34 ppm, displaying quartet splitting of ca. 280 Hz due to one-bond C–F coupling.

As shown in Scheme 1 and Fig. 1, the three possible regioisomers of the irradiation reaction of **2** are **3**, **3a** and **3b**, respectively. Two signals in the ^{19}F NMR spectrum of the photoproduct discounted the presence of the symmetrically fluorinated molecule (**3b**). This was also confirmed from the 22 signals in ^{13}C NMR spectrum (a symmetrical structure would only exhibit 14 signals). Of these signals, 16 belong to the aromatic carbons (11 tertiary carbons and five quaternary) while six belong to the aliphatic carbons (two CF_3, three other quaternary and one tertiary, i.e., methine, carbon). In addition to this spectroscopic evidence, the hypothetical symmetrical structure (**3b**) is inconsistent with our chromatographic results which indicate the existence of two enantiomeric forms [10].

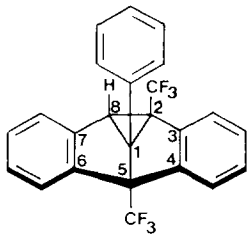
We have found that the structure of **3** can be deduced solely on the basis of the magnitude and multiplicity of the long-range C–F couplings observed in the proton-decoupled ^{13}C NMR spectra and in the ^1H inversion spectra with decoupling in the ^{13}C dimension.

It is well documented that the magnitude of the C–F coupling depends on the molecular geometry and that it decreases with an increasing number of bonds separating the C and F nuclei, e.g., $^1J_{CF} > {}^2J_{CF} > {}^3J_{CF}$, etc. In aromatic molecules, C–F couplings separated by up to 10 bonds have been observed [13]. However, in saturated systems this is not the case and

Table 1
^{13}C chemical shifts and C–F coupling constants in dibenzobarrelene (**2**) and in dibenzosemibullvalene (**3**)



(2)



(3)

C atom	Compound **2**			Compound **3**		
	δ (ppm) [a]	n [b]	J_{CF} (Hz) [c]	δ (ppm) [a]	n [b]	J_{CF} (Hz) [c]
C-1	64.27	2	27.05 (q) [d]	68.41	3,3	1.35 (qn)
C-2	141.10	3	–	51.30	2	32.98 (q)
C-3	141.40	3	2.20 (q)	146.35	3	1.23 (q)
C-4	60.03	2	28.76 (q)	121.77	3	2.46 (q)
C-5	136.83	3,4	2.62 (qn)	71.85	2	28.20 (q)
C-6	152.14	3	5.60 (d)	121.46	3	2.13 (q)
C-7	141.40	3	2.20 (q)	145.80	4	0.98 (q)
C-8	141.10	3	–	44.77	3	2.30 (q)

[a] In $CDCl_3$ solution, referred to TMS.
[b] Number of intervening bonds between C and F atom.
[c] Digital resolution for $n = 2$ was equal to ± 1.4 Hz and for $n > 2$ was equal to ± 0.25 Hz.
[d] Multiplicity of C–F coupling: d = doublet, q = quartet and qn = quintet.

it is only very rarely that C–F coupling through more than three bonds may be detected, although $^3J_{CF}$ often displays a dihedral angle dependence [12]. Similarly, the three-bond C–F coupling at the aliphatic carbons of dibenzobarrelenes and dibenzosemibullvalenes may act as a good structural probe. Thus, for instance, if structure **3a** in Fig. 1 were present, the methine carbon, C-1, would exhibit some form of complex multiplet caused by the three-bond C–F coupling arising from the two trifluoromethyl groups at C-5 and C-8. In addition, the aliphatic quaternary signal, C-2, would be split into a quartet because of the three-bond coupling to the neighbouring CF_3 group at C-8.

In fact, the quartet for the methine carbon (C-8) and an uncompletely resolved septet for the quaternary aliphatic carbon (C-1) were observed. This can only be explained by the presence of structure **3** as depicted in Scheme 1. The assignment of C-8 was demonstrated unambiguously by the ^1H inversion spectrum (H-8, 3.99 ppm; C-8, 44.77 ppm) which showed quartet splitting of 2.29 Hz (Fig. 2). The NOESY spectrum with a long mixing time (1.5 s) revealed two cross-peaks between the methine proton (H-8) and aromatic protons in agreement with molecular modelling [2] which showed two short H–H distances in **3**, i.e., H-8/H-2′ and H-8/H-7a of 2.423 Å and 2.783 Å, respectively. In contrast, in **3a**, only one short distance, i.e., H-1/H-2′, amounting to 2.522 Å, exists (Fig. 3).

[2] The results obtained were generated using the Quanta 4.0/CHARMm22 program. This program has been developed by Molecular Simulation Inc.

The chemical shifts and C–F coupling constants for selected C atoms (the remaining C atoms are in the aromatic region, δ 126–135 ppm) of **3** are displayed in Table 1. The C-8 and C-1 atoms were assigned on the basis of their chemical shifts and their multiplicity in coupled C–H (C-8, doublet; C-1, singlet) spectrum. The $^1J_{CH}$ value at C-8 amounted to 170.3 Hz, i.e. very close to the $^1J_{CH}$ value measured for the bridgehead carbon in structurally related tricyclo[3.1.0]hexane [12] which had a value of 166 Hz. The C-2 atom, at the bridgehead of the cyclopropane moiety, has lower chemical shift value than C-5, at the bridgehead of the cyclopentane moiety, as a consequence of the different ring size and hence the difference in hybridization of these two C atoms. From the same reason, the two-bond C–F coupling at C-2 is greater (32.98 Hz) than the $^2J_{CF}$ value at C-5 (28.80 Hz). This assignment has also been confirmed by comparison with related mono trifluoromethyl-substituted molecules [11]. The aromatic quaternary C-3 and C-7 which are close to the cyclopropane ring have similar chemical shifts, δ 146.35 and 145.80 ppm, respectively. Both signals displayed quartet splitting, that of C-3 being due to three-bond C–F coupling with the neighbouring CF_3 group and amounting to 1.23 Hz, while that of C-7 being due to four-bond coupling and amounting to 0.98 Hz. It is well known that aliphatic C–F coupling is greater if the coupling pathway includes a double or a triple bond. For this reason, we assume that the four-bond coupling at C-7 arises from a CF_3 group placed at the cyclopentane bridgehead since this coupling pathway includes one aromatic double bond, rather than from CF_3

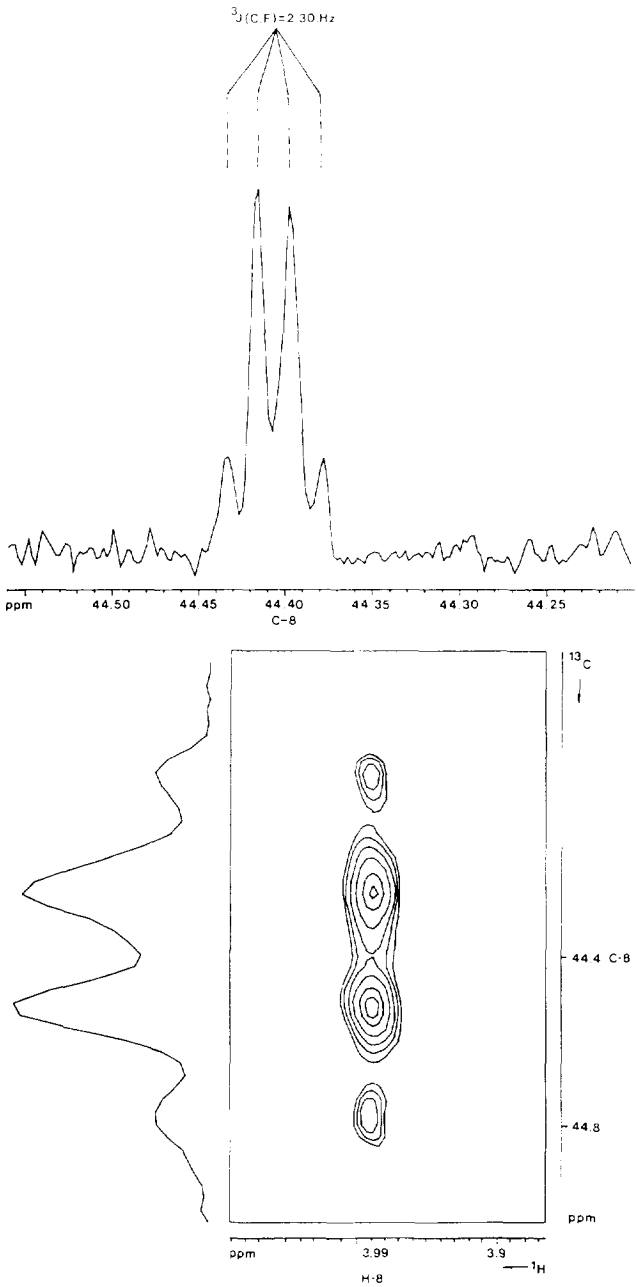


Fig. 2. The ^{1}H inversion spectrum of C-8 in compound **3** (cf. formula in Table 1). Projection on to the ^{13}C axis (top). Contour of quartet due to three-bond C–F coupling (bottom).

group placed at a cyclopropane moiety since this pathway is completely saturated. The second pair of aromatic quaternary carbons, C-4 and C-6, situated further from the cyclopropane moiety, have significantly lower chemical shift values (δ 121.77 and 121.46 ppm, respectively) than the quaternary carbons, C-3 and C-7, placed closer to this moiety (δ 146.35 and 145.80 ppm, respectively).

From Table 1 it will be seen that the three-bond C–F couplings range from 1.23 Hz to 5.6 Hz, depending on the stereostructure and the coupling pathway. If there is no double bond in the aliphatic pathway, $^3J_{CF}$ might be related to the dihedral angles. The $^4J_{CF}$ couplings at C-5 in **2** and at C-7 in **3** are the longest C–F coupling constants observed in molecules investigated here.

3. Experimental details

Melting points were determined on a Kofler micro hot-stage instrument (Reichert, Wien) and are not corrected. UV spectra were recorded on a Hitachi Perkin-Elmer 124 spectrometer. The 1D ^{1}H NMR spectra were recorded on a Varian Gemini 300 instrument while NOESY and ^{1}H inversion spectra were measured on a Bruker AMX-500 spectrometer. The ^{19}F NMR spectra were obtained with a Varian XL-300 spectrometer operating at 282.3 MHz for fluorine. The ^{13}C NMR spectra were recorded on Varian VXR-500S and Bruker AMX-500 instruments, operating at 125.70 and at 125.78 MHz, respectively. The sample concentrations were 0.1 M for ^{1}H and ^{19}F NMR spectra and 0.3 M for ^{13}C NMR measurements. Samples were dissolved in $CDCl_3$ and measured at 300 K (27 °C) in 5 mm NMR tubes. Digital resolution for C–F couplings through more than two bonds was 0.25 Hz per point, while for one- and two-bond couplings was 1.4 Hz per point. Molecular modelling was performed using a Quanta4.0/CHARMm22 program [2]. Electron impact (EI) mass spectra were recorded on a Varian MAT CH 7 spectrometer with an ionizing energy of 70 eV. Elemental analyses were performed by the Central Analytical Service, Ruđer Bošković Institute, Zagreb.

3.1. 6-Phenyl-1,4-bis(trifluoromethyl)dibenzobicyclo-[2.2.2]octa-2,5,7-triene (2)

A stirred mixture of **1** [8] (1 g, 0.0037 mol) and phenylacetylene (4.6 ml, 0.018 mol) was heated under nitrogen at 135–138 °C for 6 h. The crude oily product was then purified by column chromatography on silica gel (0.063–0.2 mm diameter) using light petroleum (40–70 °C)/carbon tetrachloride in a volume ratio of 3:1 as the solvent. Recrystallization of the separated solidified product from ethanol/H_2O (96:4) gave colourless crystals of **2**.

Compound **2**: Yield, 44%; m.p. 153–154 °C. MS (70 eV) *m/z*: 416 (M^+, 100); 417 (56); 348 (34); 347 (100); 338 (15); 327 (10); 314 (33); 279 (24); 278 (96); 277 (24); 276 (26); 270 (15); 269 (11); 246 (41); 245 (25); 225 (10); 139 (19); 138 (20); 102 (10); 51 (12). UV (abs. MeOH) λ_{max} (nm) (log ϵ): 262.5 (5.67); 270 (5.73); 277.7 (5.67). IR (KBr disc) ν (cm^{-1}): 1620 (C=C). ^{1}H NMR ($CDCl_3$, TMS) δ: 7.60; 6.83–7.28 ppm. ^{13}C NMR ($CDCl_3$, TMS) δ: 152.14; 141.40; 141.10; 136.83; 135.70; 129.25; 126.34; 127.93; 127.47; 125.58; 125.42; 125.65; 122.80; 122.14; 64.27; 60.03 ppm. Analysis: Calc. for $C_{24}H_{14}F_6$ (416.4): C, 69.23; H, 3.39%. Found: C, 69.1; H, 3.42%.

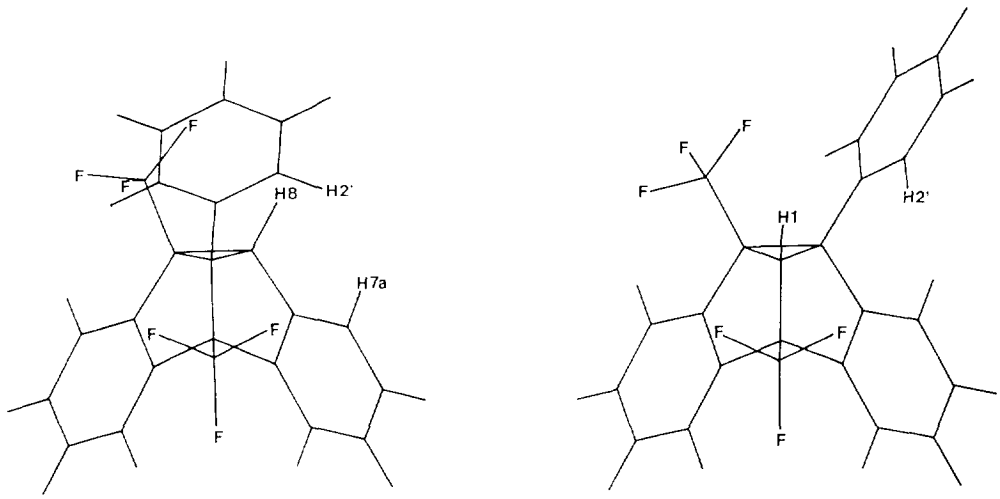


Fig. 3. The structures of two possible regioisomeric forms (**3** and **3a**) based on molecular modelling.

3.2. 1-Phenyl-2,5-bis(trifluoromethyl)dibenzotricyclo-[3.3.0.0^{2,8}]octa-3,6-diene (3)

A solution containing 0.2 g (0.0004 mol) of dibenzobarrelene (**2**) in 2000 ml of acetone as sensitizer was irradiated through Pyrex glass using a high-pressure mercury immersion lamp at 0 °C for 22 h. Oxygen was excluded during irradiation by bubbling nitrogen through the solution. After removing the solvent by evaporation under reduced pressure, an oily residue was obtained which was purified by liquid chromatography on silica gel using light petroleum (40–70 °C)/chloroform in a volume ratio of 1:3 as the solvent. The separated oily product crystallized from ethanol water (96:4) at low temperature. Recrystallization from ethyl acetate ethanol in a volume ratio of 1:5 gave colourless crystals of **3**.

Compound **3**: Yield 11%; m.p. 102–104 °C. MS (70 eV) *m/z*: 416 (M^+, 100); 417 (37); 348 (26); 347 (95); 279 (18); 278 (73); 277 (21); 276 (25); 270 (14); 269 (10); 246 (33); 139 (15); 138 (16); 51 (18). UV (abs. MeOH) λ_{max} (nm) (log ϵ): 253 (6.23); 268.5 (6.23); 276.5 (6.25). ^{1}H NMR ($CDCl_3$, TMS) δ: 3.99; 7.10–7.50 ppm. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: 20.48; 19.54 ppm. ^{13}C NMR ($CDCl_3$, TMS) δ: 146.35; 145.80; 135.54; 132.52; 131.88; 131.59; 130.51; 129.09; 128.76; 128.70; 128.41; 128.04; 126.09; 125.43; 125.24; 124.74; 121.77; 121.46; 71.85; 68.41; 51.30; 44.77. Analysis: Calc. for $C_{24}H_{14}F_6$ (416.4): C, 69.23; H, 3.39%. Found: C, 68.99; H, 3.47%.

4. Conclusions

Regiospecific trifluoromethyl-substituted dibenzobarrelene (**2**), and dibenzosemibullvalene (**3**) have been prepared by an elegant two-step reaction pathway including (i) the [4+2] cycloaddition of specifically trifluoromethylated anthracene with the corresponding alkyne and (ii) the subsequent di-π-methane photorearrangement of dibenzobarrelene (**2**). The magnitude and multiplicity of the three-bond C–F coupling constants observed in the corresponding NMR spectra proved to be a very useful probe for determining the stereostructure of these compounds.

Acknowledgements

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