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Regiospecific Synthesis and X-ray Structural Study of Trifluoromethyl Substituted Dibenzosemibullvalene

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Preparation of the novel regiospecifically trifluoromethyl substituted dibenzobarrelene **5** and dibenzosemibullvalene **6** is described. Unequivocal proof for the stereostructure of **6** was obtained by its X-ray crystallographic analysis. Geometrical data from X-ray structural analysis showed that the ester carbonyl groups adopt unfavorable conformations for conjugative interactions with respect to the cyclopropane ring involved in the skeleton of **6**.

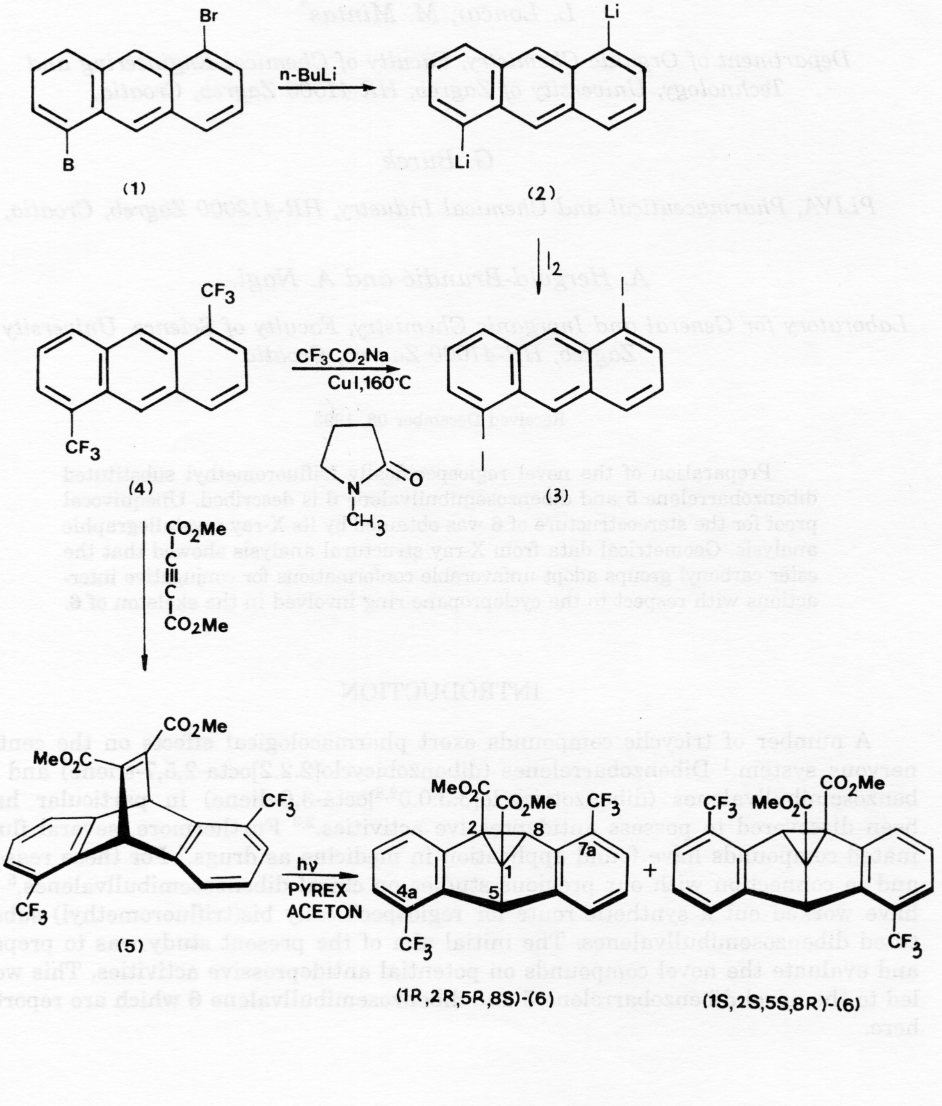
INTRODUCTION

A number of tricyclic compounds exert pharmacological effects on the central nervous system.[1] Dibenzobarrelenes (dibenzobicyclo[2.2.2]octa-2,5,7-triene) and dibenzosemibullvalenes (dibenzotricyclo[3.3.0.0^{2,8}]octa-3,6-diene) in particular have been discovered to possess antidepressive activities.[2,3] Furthermore, several fluorinated compounds have found application in medicine as drugs.[4] For these reasons and in connection with our previous studies on chiral dibenzosemibullvalenes,[5] we have worked out a synthetic route for regiospecifically bis(trifluoromethyl) substituted dibenzosemibullvalenes. The initial aim of the present study was to prepare and evaluate the novel compounds on potential antidepressive activities. This work led to the novel dibenzobarrelene **5** and dibenzosemibullvalene **6** which are reported here.

RESULTS AND DISCUSSION

Synthetic work

Regiospecifically trifluoromethyl substituted anthracene **4** was prepared by heating the corresponding iodo substituted anthracene **3** with sodium trifluoroacetate and copper(I)-iodide as catalyst in *N*-methylpyrrolidone as dipolar aprotic solvent using an analogous procedure described for 9-trifluoromethylanthracene.[6] Thermal Diels-Alder [4+2] cycloaddition of dimethylacetylene dicarboxylate to trifluoromethyl substituted anthracenes **3** gave the dibenzobarrelene **5**. Irradiation of **5** in acetone as sensitizer led to the racemic mixture of dibenzosemibullvalene (±)-**6** (Scheme). This is in accord with what was found earlier on the di-Π-methane photorearrangement



of dibenzobarrelenes in solution.[7] This is also in agreement with our preliminary results of resolution of enantiomers by liquid chromatography on triacetylcellulose, which clearly show the presence of two enantiomers in the racemic mixture of (±)-**6**.[8]

X-Ray Crystallographic Study

Single crystals of **6** suitable for X-ray structure analysis were prepared by growth under slow evaporation at room temperature of a very dilute solution of ethyl acetate ethanol mixture (1:5). A perspective view of the molecule with atom numbering is shown in Figure 1. Analysis of the structural data shows that the dihedral angles between the plane C(7)-C(9)-C(10) and the least square (l. s.) plane defined by atoms C(5)-C(6)-C(7)-C(10) and between the plane C(8)-C(9)-C(10) and l. s. plane C(8)-C(10)-C(11)-C(12) are 160.8 (4)° and 156.5 (4),° respectively. These values are in good agreement with those of the related dibenzosemibullvalene derivatives.[5] The bond lengths of the cyclopropane ring C(7)-C(9), C(7)-C(8) and C(8)-C(9) are very similar (the mean value is 1.539 Å, Table II), *i.e.* there is no evidence for the bond length asymmetry of the cyclopropane ring. However, such asymmetry has been found in cyclopropanes with Π-acceptor substituents possessing a favorable conformation for conjugative interaction with respect to the cyclopropane ring[9] and trifluoromethyl substituted dibenzosemibullvenes.[5] The torsional angles τ_1 [M(8)-C(8)-C(20)-O(3)] and τ_2 [M(9)-C(9)-C(18)-((18)-O(1)] amount to 119.8 (8)° and −165.1 (8)°, respectively (Figure 2), *i.e.* the carbonyl groups and the cyclopropane ring are *anti* disposed.

Trifluoromethyl groups on the benzene rings show, as expected, not influence on the conformation of the semibullvalene skeleton. Compound **6** crystallized in the centrosymmetric space group $P2_1/n$, *i.e.*, both enantiomers are present. In conclusion, the X-ray data indicate that the conformation of carbonyl groups are not effective enough for interaction with 3e'orbitals[10] of the cyclopropane ring.

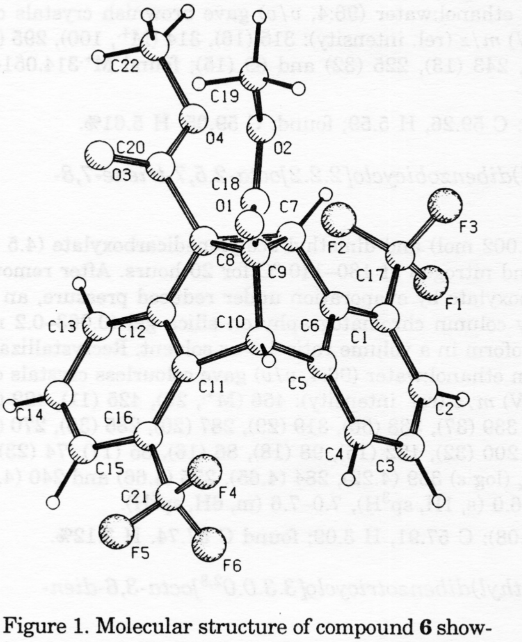


Figure 1. Molecular structure of compound **6** showing the crystallographic numbering scheme (Spek, 1991)

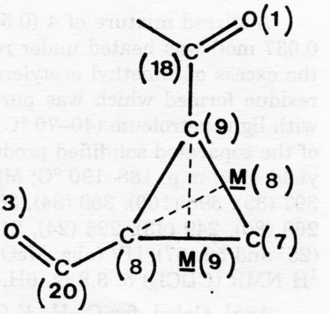


Figure 2. Geometry of the cyclopropane substructure in **6** (M_i are the midpoints of the cyclopropane ring bond opposite atoms C_i).

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage (Reichert, Wien) and are not corrected. UV spectra were recorded on a Hitachi Perkin-Elmer 124 spectrometer. The ^{1}H NMR spectra were recorded on a Varian XL GEM 300 (PFT mode, 300 MHz) spectrometer. The electron impact mass spectra were recorded on Extrel FT MS 2001. The exact mass measurements of the molecular ions of **4** and **6** were performed using the same instrument. Elemental analyses were performed by the Central Analytical Service, Rudjer Bošković Institute, Zagreb.

1,5-Diodoanthracene (**3**)

Prepared by the reaction of 1,5-dilithioanthracene (**2**) with iodine by the procedure analogous to that for 9,10-diiodoanthracene.[11] The 1,5-dilithioanthracene itself was made by the halogen-metal exchange in 1,5-dibromoanthracene (**1**) by analogy to the procedure reported for the 9,10-dilithioanthracene.[11] The compound **1** was made by the reaction route starting from the 1,5-dibromoanthraquinone.[12] The isolation procedure for **3** was modified as follows: Purification of the crude oily product was effected by column chromatography on silica gel (0.063–0.2 mm) with light petroleum (40–70 °C) : chloroform in a volume ratio 5:2 as solvent. Recrystallization of the separated solidified product from ethanol:water (96:4) gave yellow crystals of **3**: yield 7%; m.p. 225–226 °C; MS (70 eV) *m/z* (rel. intensity) 430 ($M^{+\cdot}$, 100), 431 (22), 340 (20), 338 (57), 303 (169), 211 (24), 177 (17), 176 (87), 175 (21), 174 (21), 150 (19), 88 (55), 87 (24), 75 (21) and 74 (159); UV (abs. MeOH) λ_{max} (log ε) 392 (4.53), 372 (4.54), 353 (4.53) and 256 (4.50).

1,5-bis(Trifluoromethyl)anthracene (**4**)

Prepared by the procedure analogous to that for 9-trifluoromethlanthracene.[6] After purification of the crude oily product by column chromatography on silica gel (0,063–0.2 mm) with light petroleum:chloroform in a volume ratio 3:2 as solvent, a solidified product was isolated. Recrystallization of this product from ethanol:water (96:4, *v*/*v*) gave brownish crystals of **4**: yield 34%; m.p. 165–166 °C; MS (70 eV) *m/z* (rel. intensity): 315 (16), 314 ($M^{+\cdot}$, 100), 295 (13), 282 (10), 280 (35), 264 (26), 245 (33), 243 (13), 225 (32) and 69 (15); found $M^{+\cdot}$314.051448; calcd. for $C_{16}H_8F_6$: 314.052469.

Anal. Calcd. for $C_{16}H_8F_6$ (314.05): C 59.26, H 5.59; found: C 59,05, H 5.61%.

Dimethyl-5a,7a-bis(trifluoromethyl)dibenzobicyclo[2.2.2]octa-2,5,7-triene-7,8-dicarboxylate (**5**)

A stirred mixture of **4** (0.533 g, 0.002 mol) and dimethyl acetylenedicarboxylate (4.5 mL, 0.037 mol) was heated under reflux and nitrogen at 130–140 °C for 20 hours. After removing the excess of dimethyl acetylenedicarboxylate by evaporation under reduced pressure, an oily residue formed which was purified by column chromatography on silica gel (0.063–0.2 mm) with light petroleum (40–70 °C) : chloroform in a volume ratio 1:3 as solvent. Recrystallization of the separated solidified product from ethanol:water (96:4, *v*/*v*) gave colourless crystals of **5**: yield 47%; m.p. 188–190 °C; MS (70 eV) *m/z* (rel. intensity): 456 ($M^{+\cdot}$, 26), 425 (11), 422 (16), 397 (39), 396 (100), 369 (34), 362 (54), 339 (37), 338 (56), 319 (29), 287 (20), 285 (36), 270 (51), 269 (80), 249 (43), 225 (24), 218 (32), 200 (32), 122 (15), 98 (18), 86 (16), 85 (17). 74 (23), 69 (25) and 59 (67); UV (abs. MeOH) λ_{max} (log ε) 339 (4.22), 284 (4.65), 275 (4.66) and 240 (4,67); ^{1}H NMR ($CDCl_3$) δ: 3.8 (s, 6H, CH_3), 6.0 (s, 1H, sp^{3}H), 7.0–7.6 (m, 6H, sp^{2}H).

Anal. Calcd. for $C_{22}H_{14}F_6O_4$ (456.08): C 57.91, H 3.09; found C 57.74. H 3.12%.

1,2-Dimethyl-4a,7a-bis(trifluoromethyl)dibenzotricyclo[3.3.0.0^{2,8}]octa-3,6-dien-1,2-dicarboxylate (**6**)

A 2.10–4 molar solution of **5** was degassed with nitrogen and irradiated through a pyrex glass with a high pressure mercury immersion lamp at 0 °C for 22 hours. After evaporation of acetone, an oily residue formed, which was purified by column chromatography on silica gel (0.063–0.2 mm) using light petroleum (40–70 °C):chloroform in a volume ratio 1:3 as solvent. Recrystallization of the separated solidified product from methanol gave colourless crystals of **6**: yield 24%; m.p. 124–126 °C;. MS (70 eV) *m/z* (rel. intensity): 456 ($M^{+\cdot}$, 32), 398 (13), 397 (73), 396 (100), 369 (32), 365 (13), 362 (11), 354 (12), 353 (13), 339 (35), 338 (52), 337 (20), 319 (14), 285 (16), 283 (18), 270 (16), 269 (29), 268 (12), 249 (13), 213 (16), 125 (12), 123 (11), 111 (18), 109 (15), 97 (24), 95 (18), 85 (17), 83 (20), 81 (19), 71 (21), 69 (26), 67 (12), and 57 (30); found $M^{+\cdot}$. 456,08068; calcd. for $C_{22}H_{14}F_6O_4$ 456,07963. ^1H NMR ($CDCl_3$) δ: 3.8 (s, 6H, CH_3), 4.8 (s, 1H, cyclopropane sp^{3}H), 5.5 (s, 1H, bridgehead-sp^{3}H), 7.1–7.6 (m, 6H, sp^{2}H).

Anal. Calcd. for $C_{22}H_{14}F_6O_4$ (456.08); C 57.91, H 3.09; found C 57.78, H 3.15%.

TABLE I

Atomic coordinates and equivalent isotropic thermal parameters (× 10^3) with e.s.d.'s in parentheses in the structure of $C_{22}H_{14}F_6O_4$

Atom	*x*	*y*	z	U_{eq}
C1	0.5730(5)	–0.2125(7)	0.6079(5)	50(3)
C2	0.5337(6)	–9.2957(8)	0.5238(5)	66(4)
C3	0.4391(6)	–0.2733(9)	0.4615(5)	69(4)
C4	0.3822(5)	–0.1719(8)	0.4803(4)	57(3)
C5	0.4214(4)	–0.0883(7)	0.5625(4)	44(3)
C6	0.5159(4)	–0.1090(7)	0.6257(4)	41(3)
C7	0.5423(4)	–0.0048(7)	0.7059(4)	41(2)
C10	0.3722(4)	0.0168(7)	0.6021(4)	43(2)
C18	0.4554(5)	0.2601(8)	0.6902(5)	51(3)
C19	0.5356(7)	0.4715(10)	0.7687(7)	105(6)
O1	0.3889(4)	0.3369(6)	0.6450(4)	74(2)
O2	0.5366(3)	0.3116(5)	0.7540(3)	64(2)
C17	0.6753(6)	–0.2346(10)	0.6738(8)	67(4)
F1	0.7101(4)	–0.3584(8)	0.6595(5)	146(4)
F2	0.6884(4)	–0.2385(8)	0.7605(4)	127(3)
F3	0.7264(4)	–0.1271(9)	0.6670(6)	163(5)
C8	0.4854(4)	–0.0101(7)	0.7662(4)	36(2)
C9	0.4563(4)	0.0962(7)	0.6820(4)	38(2)
C11	0.3321(4)	–0.0837(7)	0.6555(4)	40(2)
C12	0.4022(4)	–0.1074(7)	0.7450(4)	39(2)
C13	0.3875(5)	–0.2059(8)	0.8063(4)	53(3)
C14	0.3003(5)	–0.2758(10)	0.7771(5)	70(4)
C15	0.2301(5)	–0.2502(9)	0.6885(5)	63(3)
C16	0.2454(4)	–0.1542(8)	0.6258(5)	48(3)
C21	0.1648(5)	–0.1259(10)	0.5326(5)	54(3)
O3	0.4917(3)	0.1012(7)	0.9050(3)	80(3)
O4	0.6260(3)	0.0342(6)	0.8998(3)	62(2)
C22	0.6789(6)	0.0879(12)	0.9950(5)	91(4)
C20	0.5344(4)	0.0513(7)	0.8644(4)	45(3)
F4	0.1675(6)	–0.0062(11)	0.4985(6)	238(6)
F5	0.0857(5)	–0.1266(17)	0.5312(6)	258(7)
F6	0.1579(8)	–0.2122(13)	0.4740(6)	258(7)

$$U_{eq} = \frac{1}{3}\sum_i \sum_j U_{ij}\, a_i^*\, a_j^*\, a_i\, a_j$$

X-Ray Crystal Structure Study

A colourless crystal of compound **6** dimensions 0.5×0.57×0.51 mm was mounted on a Phillips PW 1100 diffractometer, upgraded by Stoe; data were collected in the ω-2θ scan mode (2-θ-30°), graphite-monochromated Mo Kα radiation; lattice parameters from a least-squares refinement of 19 reflections (16.57-2θ-35.83°); monitored reflections (0,–2,4; –4,–3,2 and 2,–2,2) showed only statistical variations in intensities; 5800 independent reflections were measured (h=22,22; k=0.13; l=0.22), 2619 $\geq 3\sigma(I)$; Lorentz-polarization corrections were applied; the structure was solved by direct methods, block-cascade least squares refinement, H atoms were located in the difference map but were allowed to ride at fixed distances from attached atoms, isotropic thermal parameters were refined for two groupings of H atoms; R=0.0865 and ωR=0.0888 for 294 parameters and 2619 reflections, S = 1.840; $(\Delta/\sigma)_{\max}$ = 0.006; largest peaks in the final difference map +0.59 and –0.60 e Å^{-3}. All calculations were performed with the SHELXS 86[13] and CRYSRULER package[14] on an IBM PC/AT compatible microcomputer. Atomic coordinates with equivalent isotropic thermal parameters and bond distances with bond angles are given in Tables I and II. Crystal data for $C_{22}H_{14}O_4F_6$; space group $P2_1/n$ with a=15.534 (3), b=8.988 (3), c=15.789 (3) Å, β=114.99 (1)°, V=1998.1 (9) Å^3, Z=4, D_{calc} = 1.517 g cm^{-3} and μ (Mo Kα)=1.332 cm^{-1} Additional X-ray crystallographic data: full tables of bond distances and bond angles, tables of anisotropic thermal parameters, hydrogen atomic coordinates with isotropic thermal parameters, as well as the observed and calculated structure factors (7 pages) are given as deposit.

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TABLE II

Selected bond distances (Å) and bond angles (°) in the structure of $C_{22}H_{14}F_6O_4$

C5 – C6	1.396(7)	C18 – C9	1.479(10)
C5 – C10	1.507(10)	C19 – 02	1.457(10)
C6 – C7	1.487(9)	C8 – C9	1.542(9)
C7 – C8	1.550(11)	C8 – C12	1.477(9)
C7 – C9	1.525(9)	C8 – C20	1.514(8)
C10 – C9	1.554(7)	C11 – C12	1.389(7)
C10 – C11	1.538(10)	O3 – C20	1.188(9)
C18 – O1	1.198(8)	O4 – C22	1.457(8)
C18 – O2	1.322(7)	O4 – C20	1.300(7)
C6 – C5 – C10	110.6(5)	C12 – C8 – C20	117.5(5)
C5 – C6 – C7	110.7(6)	C9 – C8 – C20	119.7(5)
C6 – C7 – C9	105.5(5)	C9 – C8 – C12	105.2(5)
C6 – C7 – C8	118.7(5)	C18 – C9 – C8	123.5(5)
C8 – C7 – C9	60.2(4)	C10 – C9 – C8	104.8(5)
C5 – C10 – C11	104.7(5)	C10 – C9 – C18	119.5(5)
C5 – C10 – C9	103.0(5)	C7 – C9 – C8	60.7(4)
C9 – C10 – C11	102.8(5)	C7 – C9 – C18	127.7(6)
O2 – C18 – C9	112.0(6)	C7 – C9 – C10	106.0(5)
O1 – C18 – C9	124.1(7)	C10 – C11 – C12	108.9(6)
O1 – C18 – 02	124.0(7)	C8 – C12 – C11	112.0(6)
C18 – 02 – C19	113.3(6)	C22 – O4 – C20	116.3(6)
C7 – C8 – C20	116.6(5)	O3 – C20 – O4	124.9(6)
C7 – C8 – C12	123.4(5)	C8 – C20 – O4	112.5(5)
C7 – C8 – C9	59.1(4)	C8 – C20 – O3	122.5(6)

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SAŽETAK

Regiospecifična sinteza i rentgensko strukturno istraživanje trifluorometil-supstituiranog dibenzosemibulvalena

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Opisana je priprava novoga regiospecifično trifluorometil-supstituiranog dibenzobarilena **5** i dibenzosemibulvalena **6**. Nedvojben dokaz stereostrukture spoja **6** dobiven je rentgenskom strukturnom analizom. Geometrijski podaci iz rentgenske strukturne analize pokazali su da esterske karbonilne skupine imaju nepovolljnu konformaciju za konjugativnu interakciju s ciklopropanskim prstenom u strukturi spoja **6**.