B

Trioxypentafulvenes, 2[1]

Synthesis of 1-Substituted 2,3,6-Trioxypentafulvenes

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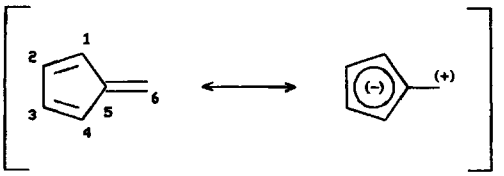
Syntheses of 2,3,6-trioxypentafulvenes with a free position at the ring are described, in which the protection of the C-3 hydroxy group as methoxy or acetoxy derivative has been required. The difference in the behavior of the title compounds in relation to the previously reported 1,4-disubstituted 2,3,6-trihydroxypentafulvenes **2a–e**, which only exhibit enol forms, is discussed and attributed to the disappearance of the push-pull system formed by the C-3 enol group and the C-4 electron-withdrawing substituent.

Pentafulvenes are an interesting group of products whose properties lie between those of polyenes and benzenoid compounds[2]. Their behavior depends on the contribution of each canonical form to the real structure. Thus, if **1b** predominates, the pentafulvene has an aromatic character because of the presence of 6 π-electrons delocalized on the ring. On the other hand, if **1a** is the predominant one, the molecule exhibits polyenic character. The contribution of each canonical form is strongly determined by the nature of the substituents. In particular, the presence of electron-donating substituents at C-6 enhances the relative contribution of the polar form **1b**.



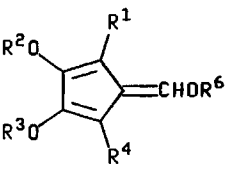
1a **1b**

Our group has reported on the synthesis of 1,4-disubstituted 2,3,6-trioxypentafulvenes **2a–m**[1]. These compounds are the first known pentafulvenes with three electron-donating groups. Their presence should increase the electron density in the ring.

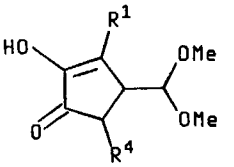
In this paper we describe the synthesis of 2,3,6-trioxypentafulvenes with a free position at the ring. The interest in such pentafulvenes lies in the fact that they maintain the three electron-donating groups at the ring, whose effect is to be counterbalanced by a sole electron-withdrawing group.

Results and Discussion

Two strategies were planned for the synthesis of 2,3,6-trioxypentafulvenes with a free C-4 position; the first one starts from the previously obtained pentafulvenes **2a–m** and involves the elimination of one of the groups present at C-1 or C-4 (Route A). The second approach starts from the cyclic precursors **3a,b,d** and comprises the elimination of the substituent before the introduction of the exocyclic double bond (Route B).



2a–m



3a, b, d

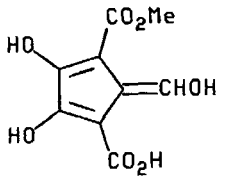
	R^1	R^4	R^2	R^3	R^6
a	CO_2Me	CO_2Me	H	H	H
b	CN	CO_2Me	H	H	H
c	CN	CN	H	H	H
d	CO_2Me	Tos	H	H	H
e	CO_2Me	NO_2	H	H	H
f	CO_2Me	CO_2Me	H	H	Me
g	CN	CO_2Me	H	H	Me
h	CN	CN	H	H	Me
i	CO_2Me	CO_2Me	Me	Me	Me
j	CN	CO_2Me	Me	Me	Me
k	CN	CN	Me	Me	Me
l	CO_2Me	CO_2Me	Me	Me	H
m	CN	CO_2Me	Me	Me	H

  0009–2940/91/0101–207 $ 3.50+.25/0

Route A: Attempts carried out from the pentafulvenes **2**: None of the attempts to saponify and subsequently decarboxylate the ester groups of **2a** or their hydroxy-protected derivatives **2f** and **2l** were successful. All experimental conditions tried gave multicomponent mixtures, probably due to the instability of the carbonyl intermediates involved.

Route B: From the cyclic precursors **3**: When the saponification of **3a** was performed, the reaction conditions were found to be critical. Thus, treatment of **3a** with a 1.8 M KOH solution at −10°C afforded an equimolar mixture of the (*Z*) and (*E*) isomers of the monocarboxylic acid **4**, but when the reaction was carried out in 0.1 M NaOH (NaOH:**3a** = 3:1) at 25°C for 24 h, the desired monoester **5a** was obtained in 99% yield. Still, if the treatment of **3a** was performed at 30°C for 26 h the fairly stable by-product **6** was obtained.

Analogously, the saponification of the cyano-substituted compound **3b** in refluxing 0.1 M NaOH for 15 min afforded the corresponding demethoxycarbonylated product **5b** in good yield.



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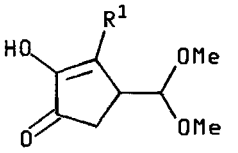
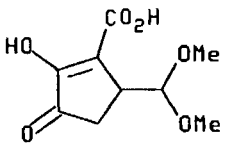


5a–b **a:** R^1 = CO_2Me **b:** R^1 = CN



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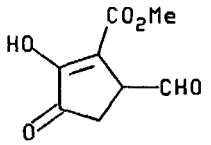

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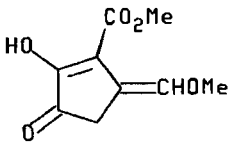

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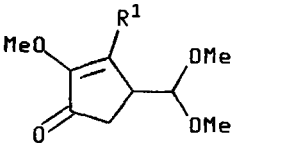
Compound **5a** was also obtained by reductive elimination of the *p*-toluenesulfonyl group of **3d** with aluminum amalgam in THF. Although the yield was satisfactory, the procedure was not optimized, because **5a** was more readily obtained by dealkoxycarbonylation of the diester **3a**.

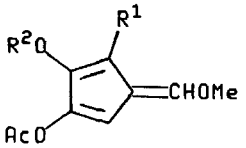
When the hydrolysis of the acetal group of **5a** was carried out under the same conditions that provided the pentafulvenes **2a–e**, the highly unstable aldehyde **7** was obtained. Treatment of **5a** under methanol-eliminating conditions gave the also unstable enol ether **8**.

Both compounds **7** and **8** exist in the carbonyl forms instead of the tautomeric fulvenic structure; this fact forced us to consider an alternative strategy to synthesize the desired 2,3,6-trioxypentafulvenes, with protection of the enol forms of the carbonyl groups at C-2 and C-3 before the introduction of the exocyclic double bond.

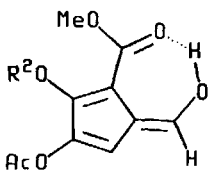
While the protection of the hydroxy groups of **5a** and **5b** was easily achieved by methylation with diazomethane, and the monomethoxy derivatives **9a** and **9b** were formed in quantitative yield, in no case was it possible to obtain the 2,3-dimethoxy derivatives. This reluctant enolization of the C-3 carbonyl group was finally overcome by treatment of **9a,b** and **5a,b** with isopropenyl acetate or by treatment of **9a,b** with trimethyl orthoformate.



9a–b **a:** R^1 = CO_2Me **b:** R^1 = CN



10a–b, 12a



11a, 13a

R^1 \ R^2	Me	Ac
CO_2Me	**10a, 11a**	**12a, 13a**
CN	**10b**	

When the ester **9a** was treated with isopropenyl acetate using sulfuric acid as a catalyst, the crude 3-acetoxy-2,6-dimethoxypentafulvene **10a** was obtained directly. This unexpected result may be explained in terms of the anhydrous acid conditions involved, which cause the *O*-acylation at C-3 and the subsequent elimination of methanol from the acetal group. No attempt was made to purify the crude material due to its high instability: furthermore, its treatment with sulfuric acid adsorbed on silica gel in CH_2Cl_2 yielded the stable (*Z*)-3-acetoxy-6-hydroxy-2-methoxypentafulvene **11a**.

This compound possesses an intramolecular hydrogen bond between the C-6 hydroxy group and the ester carbonyl group at C-1 as shown in the IR spectrum by the presence of the carbonyl group stretching band at $\tilde{\nu}$ = 1640 cm^{-1} and by the absence of a clear O–H absorption. On the other hand, the ^{1}H-NMR spectrum exhibits two doublets (J = 12 Hz) at δ = 7.40 and 14.5 which correspond to

6-H and the hydroxy proton, respectively. The addition of D_2O causes the disappearance of the signal at the lowest field and the collapsing to a singlet of the 6-H signal. This proton coupling across the hydroxy oxygen atom was previously observed in the 1,4-disubstituted 2,3,6-trihydroxypentafulvenes **2a,b,d,e,l,m** when the C-6 hydroxy group is (*Z*) in relation to an ester group at C-1[1].

When the cyano compound **9b** was treated under the same reaction conditions that yield **10a**, a 70:30 mixture of the (*E*)- and (*Z*)-1-cyano-2,6-dimethoxypentafulven-3-yl acetates **10b** was obtained. Its structure was assigned by comparison of the ^1H- and ^{13}C-NMR spectra of both isomers, previously separated by column chromatography, and confirmed by the X-ray diffraction study of the (*E*) isomer[3].

A spontaneous irreversible isomerization of the (*Z*) to the (*E*) isomer has been observed in $CHCl_3$ solution. This kind of isomerization by rotation of the exocyclic "ethylenic" bond has been previously described for 6-hetero- and 6,6-dihetero-substituted pentafulvenes, and the rotational barriers have been determined (40–100 kJ mol^{-1})[4].

Although the hydrolysis of the C-6 methoxy group of both isomers of **10b** was attempted under a variety of conditions, in no case was it possible to obtain the corresponding 6-hydroxypentafulvene, starting material being recovered in all the attempts.

Like **9a**, the hydroxy derivative **5a** also reacts with isopropenyl acetate by *O*-acetylation yielding the 2,3-diacetoxy-6-methoxypentafulvene **12a**. Subsequent treatment with sulfuric acid adsorbed on silica gel in chloroform afforded the (*Z*)-2,3-diacetoxy-6-hydroxypentafulvene **13a** which shows a hydrogen bond similar to the one present in **11a**.

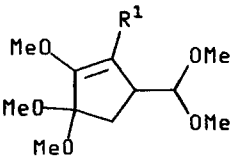
In contrast, all efforts with the cyano-substituted compound **5b** were futile; no diacetoxypentafulvene could be obtained.

Treatment of **9a** with trimethyl orthoformate and Amberlyst 15 in methanol (55°C, 12 h) or Montmorillonite clay in CCl_4 (room temp., 24 h) led to crude materials, mainly composed out of the acetalized compound **14a** and the bis-enol ether **15a**. In some experiments, however, the monoprotected product **16a** was found, which could not be converted into a pentafulvene.

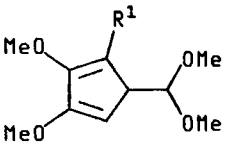
When the reaction mixture of the H_3O^+-sensitive compounds **14a** and **15a** was treated with freshly melted $KHSO_4$ at 130–140°C under reduced pressure, only a geometric isomer of the 2,3,6-trimethoxypentafulvene **17a** was obtained.

Likewise, the treatment of the cyano derivative **9b** with trimethyl orthoformate and Montmorillonite in methanol (room temp., 12 h) produced a mixture of **14b** and **15b**. When the reaction was carried out in the presence of Amberlyst 15 (room temp., 24 h), the bis-enol **15b** was obtained in quantitative yield. The (*Z*) and (*E*) isomers of the 2,3,6-trimethoxypentafulvene **17b** were obtained by heating **15b** or the mixture **14b**/**15b** with $KHSO_4$ at reduced pressure.

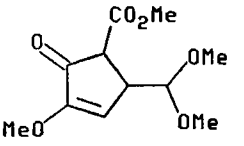
The alternative approach, which involves the introduction of the exocyclic double bond before the enolization of the C-3 carbonyl group, also allowed the preparation of the pentafulvenes **17a** and **17b**. Thus, the 6-methoxy derivative **18a** was obtained by heating **9a** with $KHSO_4$. The subsequent treatment of **18a** with trimethyl orthoformate and Amberlyst 15 in methanol (room temp., 12 h) afforded compound **17a**. Similarly, the cyanopentafulvene **17b** was synthesized by the sequence **9b** → **18b** → **17b**.



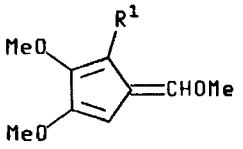
14a-b



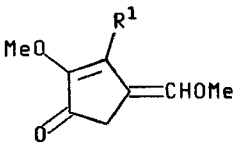
15a-b



16a



17a-b



18a-b

a: R^1 = CO_2Me
b: R^1 = CN

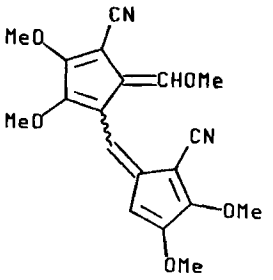
The comparison of the results obtained by both synthetic procedures clearly illustrates the higher efficiency of the former. Thus, the yields of **17a** and **17b** reached 64 and 72%, respectively, when the exocyclic double bond was introduced in the last step. When the operations were reversed they decreased to 35 and 19%, respectively.

Although the selective hydrolysis of the C-6 methoxy group of **17a** and **17b** was attempted under a variety of reaction conditions, in no case was it possible to obtain the corresponding 6-hydroxypentafulvenes. Instead, only the hydrolysis of the C-3 enol ether afforded the previously known compounds **18a** and **18b**.

In order to obtain the desired 6-hydroxy-1-cyano-2,3-dimethoxypentafulvenes an indirect way was tested. Compound **15b** was treated with acetyl chloride at room temperature to convert the acetal group into an intermediate chloroether, whose hydrolysis might yield the corresponding 6-hydroxypentafulvene. However, the reaction yielded a mixture of two of the four possible isomers of the 4-(1-cyano-2,3-dimethoxypentafulven-6-yl)-2,3,6-trimethoxypentafulvene-1-carbonitrile (**19**), as is shown by their spectroscopic and analytical data, and small amounts of the pentafulvene **17b**. Some similar condensation products have already been described in 6-hetero-substituted pentafulvenes[5].

Mechanistic considerations support the formation of **19** through an electrophilic substitution of the pentafulvene **17b**

by an intermediate C-6 cation, formed during the chloroether synthesis.



19

Although the synthesis of the desired 2,3,6-trioxypentafulvenes has been achieved, it is noteworthy to point out the difficulties observed in the enolization of the C-3 carbonyl group. This fact seems to indicate that the expected resonance energy of the pentafulvene structure is lower than the energy difference between the carbonyl group and its enol form. In contrast, the previously described pentafulvenes **2a**–**e** always exist as the tris-enol tautomer. The difference in the behavior of such pentafulvenes and the ones described in the present work may be attributed to the disappearance of the push-pull system formed by the C-3 hydroxy group and the C-4 electron-withdrawing substituent through the endocyclic double bond. The subsequent tautomerism of the enol group compels the observed monoketo tautomers.

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Experimental

All melting points, determined with a Büchi capillary apparatus, and boiling points, determined during distillation, are uncorrected. – IR and UV: Perkin-Elmer 683 and Hewlett-Packard 8450 A spectrometers, respectively. – ^{1}H NMR: Perkin-Elmer R-24 and Bruker AC-80 instruments at 60 and 80 MHz, respectively, using tetramethylsilane as the internal standard. – ^{13}C NMR: Varian XL-200 instrument at 50.3 MHz, using the frequency of the solvent for calibration. – MS: Hewlett-Packard 5995 A instrument (electron impact at 70 eV). – Column chromatography was performed on silica gel, Merck 60 (70–230 mesh), the eluents being indicated in the text of the individual procedures. – Elemental analyses were performed at Consejo Superior de Investigaciones Científicas, Barcelona.

Methyl 5-(Dimethoxymethyl)-2-hydroxy-3-oxo-1-cyclopentene-1-carboxylate (**5a**). – a) *Saponification of Dimethyl 2-(Dimethoxymethyl)-4-hydroxy-5-oxo-3-cyclopentene-1,3-dicarboxylate* (**3a**): A mixture of 15.00 g (52.00 mmol) of **3a**[1] and 1.6 l of 0.1 N NaOH was stirred until a clear solution was obtained. The solution was thermostated at 25°C for 24 h, then acidified (to pH = 2–3) with 3 N hydrochloric acid, extracted with chloroform (3 × 500 ml), and dried with $MgSO_4$. After removal of the solvent, recrystallization from AcOEt/hexane gave 11.38 g (95%) of **5a**, m.p. 77°C. – IR (KBr): $\tilde{\nu}$ = 3280 cm^{-1} (O–H), 1730 and 1680 (C=O), 1630 (C=C). – UV (ethanol): λ_{max} (lg ε) = 210 (3.699), 280 (4.000), 333 (3.699). – ^{1}H NMR ($CDCl_3$): δ = 8.50 (br. s, 1H, OH), 4.60 [d, *J* = 2 Hz, 1H, C*H*(OMe)$_2$], 3.95 (s, 3H, CO_2CH_3), 3.45 (s, 3H, acetal OMe), 3.35 (s + m, 3H + 1H, acetal OMe + 5-H), AB system (δ_A = 2.65, δ_B = 2.35, J_{AB} = 18 Hz, $J_{A,5}$ = 2 Hz, $J_{B,5}$ = 6 Hz, 2H at C-4). – MS (70 eV): *m/z* (%) = 230 (0.8) [M$^+$].

$C_{10}H_{14}O_6$ (230.2) Calcd. C 52.17 H 6.13
Found C 52.11 H 6.11

b) *Reductive Elimination of the Tosyl Group of Methyl 5-(Dimethoxymethyl)-2-hydroxy-3-oxo-4-tosyl-1-cyclopentene-1-carboxylate* (**3d**): 2.13 g of aluminium foil cut into 2 × 2 cm portions was immersed for 15 s each in ethanol, Et_2O, 2% $HgCl_2$ solution, water, ethanol, and Et_2O. The amalgam was added to a solution of 3.00 g (7.80 mmol) of **3d**[1] in 37 ml of THF and 4 ml of water. The mixture was heated at reflux for 3 h with stirring. After cooling, filtration and removal of the solvent, 50 ml of water was added and the mixture extracted with Et_2O (3 × 50 ml). The combined extracts were dried and the solvent evaporated in vacuo to give 1.43 g (80%) of crude **5a**.

5-(Dimethoxymethyl)-2-hydroxy-3-oxo-1-cyclopentene-1-carbonitrile (**5b**): A mixture of 20.00 g (78.40 mmol) of **3b**[1] and 2.4 l of 0.1 N NaOH was stirred until a clear solution was obtained. The solution was heated at reflux for 15 min, then acidified (to pH = 1) with 3 N hydrochloric acid, extracted with chloroform (10 × 400 ml), and dried with $MgSO_4$. After removal of the solvent, recrystallization from Et_2O/hexane gave 12.82 g (83%) of **5b**, m.p. 76°C. – IR (KBr): $\tilde{\nu}$ = 3420 cm^{-1} (O–H), 2210 (C≡N), 1720 (C=O), 1650 (C=C). – UV (ethanol): λ_{max} (lg ε) = 275 (3.960), 325 (3.545). – ^{1}H NMR ($CDCl_3$): δ = 6.30 (br. s, 1H, OH), 4.40 [d, *J* = 5 Hz, 1H, C*H*(OMe)$_2$], 3.50 (s, 3H, acetal OMe), 3.45 (s, 3H, acetal OMe), 3.30 (dt, *J* = 5 Hz, 1H, 5-H), 2.50 (d, *J* = 5 Hz, 2H at C-4). – MS (70 eV): *m/z* (%) = 198 (0.2) [M$^+$ + 1], 196 (0.2) [M$^+$ – 1].

$C_9H_{11}NO_4 \cdot H_2O$ (215.2) Calcd. C 50.23 H 6.09 N 6.51
Found C 50.39 H 6.04 N 6.45

Methyl 5-(Dimethoxymethyl)-2-methoxy-3-oxo-1-cyclopentene-1-carboxylate (**9a**): A solution of 23.92 g (0.10 mol) of **5a** in 150 ml of Et_2O at 0°C was treated with an ethereal diazomethane solution[6] (0.14 mol). The mixture was allowed to stand at room temp. for 12 h and was then evaporated in vacuo. That afforded 25.28 g (100%) of **9a** as an oily material. – IR (film): $\tilde{\nu}$ = 1730 cm^{-1} (C=O), 1635 (C=C). – ^{1}H NMR ($CDCl_3$): δ = 4.45 [d, *J* = 4 Hz, 1H, C*H*(OMe)$_2$], 4.10 (s, 3H, 2-OMe), 3.85 (s, 3H, CO_2CH_3), 3.45 (s, 3H, acetal OMe), 3.40 (s + m, 3H + 1H, acetal OMe + 5-H), 2.50 (m, 2H at C-4). – ^{13}C NMR ($CDCl_3$): δ = 202.8 (C-3), 157.3 (C-2), 165.6 (CO_2Me), 131.5 (C-1), 105.7 (C-6), 58.9 (2-OMe), 56.2 and 55.8 [CH(O*Me*)$_2$], 52.0 (CO_2*Me*), 39.1 (C-5), 34.8 (C-4). – MS (70 eV): *m/z* (%) = 244 (0.5) [M$^+$], 75 (100).

$C_{11}H_{16}O_6$ (244.2) Calcd. C 54.09 H 6.60
Found C 53.82 H 6.51

5-(Dimethoxymethyl)-2-methoxy-3-oxo-1-cyclopentene-1-carbonitrile (**9b**): The same procedure as described above starting with **5b** (32.64 g, 0.17 mol) in 200 ml of Et_2O at 0°C and an ethereal diazomethane solution[6] (0.18 mol) gave 34.90 g (100%) of **9b** as an oil. – IR (film): $\tilde{\nu}$ = 2215 cm^{-1} (C≡N), 1735 (C=O), 1625 (C=C). – ^{1}H NMR ($CDCl_3$): δ = 4.32 [d, *J* = 5 Hz, 1H, C*H*(OMe)$_2$], 4.16 (s, 3H, 2-OMe), 3.42 (s, 3H, acetal OMe), 3.39 (s, 3H, acetal OMe), 3.18 (dt, *J* = 5 Hz, 1H, 5-H), 2.46 (d, *J* = 5 Hz, 2H at C-4). – ^{13}C NMR ($CDCl_3$): δ = 199.4 (C-3), 162.3 (C-2), 115.3 (C≡N), 106.2 (C-1), 105.2 (C-6), 59.1 (2-OMe), 55.9 and 55.9

[$CH(OMe)_2$], 39.7 (C-5), 34.3 (C-4). – MS (70 eV): *m/z* (%) = 211 (0.7) [M^+].

$C_{10}H_{13}NO_4$ (211.2) Calcd. C 56.87 H 6.20 N 6.63
Found C 56.37 H 6.48 N 6.45

Methyl (Z)-3-Acetoxy-6-hydroxy-2-methoxypentafulvene-1-carboxylate (**11a**): A solution of 26.30 g (0.10 mol) of **9a** and 98% sulfuric acid (2.00 ml) in 1000 ml of isopropenyl acetate was heated at reflux for 4 h. After cooling, neutralization with solid sodium carbonate, filtration, and solvent removal under reduced pressure, 25.00 g of crude product was obtained. Purification by column chromatography (CH_2Cl_2) afforded 21.80 g (80%) of pure *methyl (Z)-3-acetoxy-2,6-dimethoxypentafulvene-1-carboxylate* [(*Z*)-**10a**] as an oily material that decomposes on standing. – IR (film): $\tilde{\nu}$ = 1770 and 1695 cm^{-1} (C=O), 1635 (C=C). – ^1H NMR ($CDCl_3$): δ = 7.85 (s, 1H, 6-H), 6.65 (s, 1H, 4-H), 4.00 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.80 (s, 3H, OMe), 2.25 (s, 3H, AcO). – The crude material was immediately dissolved in 1200 ml of CH_2Cl_2 and treated with 13 ml of 75% sulfuric acid adsorbed on silica gel (188 g) for 1 h at room temp. with efficient magnetic stirring. The solid was filtered off and washed with 200 ml of CH_2Cl_2. After solvent removal under reduced pressure, the crude product was purified by column chromatography [hexane/ethyl acetate (4:1)] affording 11.26 g (49%) of pure **11a**, m.p. 66°C. – IR (film): $\tilde{\nu}$ = 1765 cm^{-1} (C=O), 1640 (C=C + C=O). – UV (ethanol): λ_{max} (lg ε) = 230 (4.413), 317 (4.190), 369 sh (3.539). – ^1H NMR ($CDCl_3$): δ = 14.25 (d, *J* = 13 Hz, 1H, 6-OH), 7.30 (d, *J* = 13 Hz, 1H, 6-H), 6.50 (s, 1H, 4-H), 3.90 (s, 3H, OMe), 3.80 (s, 3H, OMe), 2.25 (s, 3H, AcO). – ^{13}C NMR ($CDCl_3$): δ = 168.17 (3-*O*COMe), 168.92 (1-*C*O_2Me), 160.78 (C-6), 159.60 (C-2), 138.52 (C-3), 119.85 (C-4), 112.84 (C-5), 100.92 (C-1), 60.95 (2-OMe), 52.65 (1-CO_2*Me*), 21.02 (3-OCO*Me*). – MS (70 eV): *m/z* (%) = 240 (12.7) [M^+], 43 (100).

$C_{11}H_{12}O_6$ (240.2) Calcd. C 55.00 H 5.04
Found C 55.00 H 5.18

(Z)- and (E)-1-Cyano-2,6-dimethoxypentafulven-6-yl Acetate [(*Z*)-**10b** and (*E*)-**10b**]: A solution of 2.00 g (9.50 mmol) of **9b** and 98% sulfuric acid (0.50 ml) in 80 ml of isopropenyl acetate was heated at reflux for 4 h. After cooling and neutralization with solid sodium carbonate, the suspension was filtered, the solvent removed under reduced pressure, and the residue purified by column chromatography (Cl_2CH_2) to give 0.53 g (25%) of (*E*)-**10b** (R_f = 0.24) and 0.23 g (11%) of (*Z*)-**10b** (R_f = 0.18).

$C_{11}H_{11}NO_4$ (221.2) Calcd. C 59.73 H 5.01 N 6.33
Found C 59.81 H 4.95 N 6.31

(*E*)-**10b**: Yellow crystals, m.p. 126°C. – IR (film): $\tilde{\nu}$ = 2200 cm^{-1} (C≡N), 1760 (C=O), 1650 (C=C). – UV (ethanol): λ_{max} (lg ε) = 204 (4.009), 309 (4.274). – ^1H NMR ($CDCl_3$): δ = 6.90 (s, 1H, 6-H), 6.50 (s, 1H, 4-H), 4.15 (s, 3H, 2-OMe), 3.93 (s, 3H, 6-OMe), 2.20 (s, 3H, AcO). – ^{13}C NMR ($CDCl_3$): δ = 167.61 (3-*O*COMe), 158.40 (C-2), 154.25 (C-6), 141.50 (C-3), 115.80 (C-5), 115.73 (1-CN), 108.40 (C-4), 76.00 (C-1), 62.38 (6-OMe), 59.18 (2-OMe), 20.82 (3-OCO*Me*). – MS (70 eV): *m/z* (%) = 221 (23.2) [M^+], 179 (100).

(*Z*)-**10b**: Yellow crystals, m.p. 141°C. – IR (film): $\tilde{\nu}$ = 2200 cm^{-1} (C≡N), 1760 (C=O), 1650 (C=C). – UV (ethanol): λ_{max} (lg ε) = 205 (4.180), 309 (4.280). – ^1H NMR ($CDCl_3$): δ = 6.80 (s, 1H, 6-H), 6.20 (s, 1H, 4-H), 4.20 (s, 3H, 2-OMe), 3.95 (s, 3H, 6-OMe), 2.20 (s, 3H, AcO). – ^{13}C NMR ($CDCl_3$): δ = 167.82 (3-*O*COMe), 161.84 (C-2), 155.78 (C-6), 139.68 (C-3), 117.23 (1-CN), 114.94 (C-5), 114.34 (C-4), 72.77 (C-1), 62.88 (6-OMe), 59.33 (2-OMe), 20.80 (3-OCO*Me*). – MS (70 eV): *m/z* (%) = 221 (21.2) [M^+], 179 (100).

Methyl (Z)-2,3-Diacetoxy-6-hydroxypentafulvene-1-carboxylate (**13a**): The same procedure as described for **10a** starting with **5a** (2.00 g, 8.70 mol) and 98% sulfuric acid (0.60 ml) in 80 ml of isopropenyl acetate gave crude **12a**. Purification by column chromatography [$CHCl_3/Et_2O$ (9:1)] afforded 0.98 g (40%) of pure *methyl 2,3-diacetoxy-6-methoxypentafulvene-1-carboxylate* (**12a**) as an oily material that rapidly decomposes on standing. – IR (film): $\tilde{\nu}$ = 1775 and 1700 cm^{-1} (C=O), 1630 (C=C). – ^1H NMR ($CDCl_3$): δ = 8.05 (s, 1H, 6-H), 6.73 (s, 1H, 4-H), 4.00 (s, 3H, OMe), 3.80 (s, 3H, OMe), 2.25 (s, 3H, AcO), 2.20 (s, 3H, AcO). – Crude **12a** was dissolved in 100 ml of CH_2Cl_2 and treated with 1 ml of 50% sulfuric acid adsorbed on silica gel (16 g) for 1 h at room temp. with efficient magnetic stirring. The solid was filtered off and washed with 50 ml of CH_2Cl_2. The combined organic solutions were neutralized with solid $NaHCO_3$, filtered and dried. After solvent removal under reduced pressure, the crude product was purified by column chromatography [$CHCl_3/Et_2O$ (9:1)] affording 0.70 g (30%) of pure **13a** as an unstable crystalline solid, m.p. 77°C. – IR (film): $\tilde{\nu}$ = 1765 cm^{-1} (C=O), 1640 (C=C + C=O). – UV (ethanol): λ_{max} (lg ε) = 227 (4.093), 315 (4.103), 370 sh (3.466). – ^1H NMR ($CDCl_3$): δ = 14.35 (d, *J* = 14 Hz, 1H, 6-OH), 7.60 (d, *J* = 14 Hz, 1H, 6-H), 6.70 (s, 1H, 4-H), 3.85 (s, 3H, OMe), 2.25 (s, 3H, AcO), 2.20 (s, 3H, AcO).

Methyl 2,3,6-Trimethoxypentafulvene-1-carboxylate (**17a**): (i) A mixture of 5.00 g (0.20 mol) of **9a**, Amberlyst 15 resin (1.25 g), trimethyl orthoformate (100 ml), and methanol (100 ml) was stirred under nitrogen for 12 h at 55°C. After cooling, the resin was filtered off, washed with methanol, and the solution concentrated in vacuo to give a crude material consisting of **14a** and **15a**. The mixture of **14a** and **15a** and powdered, freshly melted $KHSO_4$ (0.80 g, 5.90 mmol) was vigorously stirred in vacuo and heated to 130–140°C for 45 min. The crude product was extracted with CH_2Cl_2 and purified by column chromatography ($CHCl_3$) to give 3.30 g (72%) of pure **17a**, m.p. 30°C. – IR (film): $\tilde{\nu}$ = 1690 cm^{-1} (C=O), 1640 (C=C). – UV (methanol): λ_{max} (lg ε) = 231 (4.110), 317 (4.170). – ^1H NMR ($CDCl_3$): δ = 7.55 (s, 1H, 6-H), 5.90 (s, 1H, 4-H), 4.05 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.75 (s, 3H, OMe). – ^{13}C NMR ($CDCl_3$): δ = 163.9 (*C*O_2Me), 157.8 (C-2), 154.1 (C-3), 153.2 (C-6), 115.6 (C-5), 103.6 (C-1), 93.9 (C-4), 61.2 (OMe), 60.5 (OMe), 56.9 (OMe), 50.5 (CO_2*Me*). – MS (70 eV): *m/z* (%) = 226 (100) [M^+], 215 (69) [M^+ – 15].

$C_{11}H_{14}O_5$ (226.2) Calcd. C 58.40 H 6.24
Found C 58.17 H 5.93

(ii) As above, but using 5.00 g (0.20 mol) of **9a**, Montmorillonite K-10/trimethyl orthoformate[7] (25 g) in CCl_4 (50 ml) for 24 h at room temp. for the synthesis of crude **14a/15a**.

(iii) A mixture of 500 mg (2.00 mmol) of **9a** and powdered, freshly melted $KHSO_4$ (100 mg, 0.74 mmol) was vigorously stirred in vacuo and heated to 130–140°C for 1 h. The crude product was extracted with CH_2Cl_2 and purified by column chromatography ($CHCl_3$) to give 95 mg (22%) of *methyl 2-methoxy-5-(methoxymethylene)-3-oxo-1-cyclopentene-1-carboxylate* (**18a**). – IR (film): $\tilde{\nu}$ = 1730 and 1710 cm^{-1} (C=O). – ^1H NMR ($CDCl_3$): δ = 6.55 (t, *J* = 1 Hz, 1H, 6-H), 4.05 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.00 (d, *J* = 1 Hz, 2H at C-4). – A mixture of 95 mg (0.45 mmol) of **18a**, Amberlyst 15 resin (20 mg), trimethyl orthoformate (0.15 ml), and methanol (1 ml) was stirred for 12 h at room temp. After filtration, concentration in vacuo, and purification by column chromatography ($CHCl_3$), 71 mg (70%) of **17a** was obtained.

(Z)- and (E)-2,3,6-Trimethoxypentafulvene-1-carbonitrile [(*Z*)-**17b** and (*E*)-**17b**]: (i) The same procedure as described for **17a** starting with **9b** (5.00 g, 23.70 mmol), Amberlyst 15 resin (1.25 g), trimethyl orthoformate (100 ml) and methanol (100 ml) for 24 h at room temp. gave 5.30 g (100%) of *2,3-dimethoxy-5-(dimethoxy-*

methyl)-1,3-cyclopentadiene-1-carbonitrile (**15b**) as an oily material. – IR (film): $\tilde{\nu}$ = 2205 cm^{-1} (C≡N). – ^1H NMR ($CDCl_3$): δ = 5.30 (d, *J* = 2.0 Hz, 1H, 4-H), 4.25 (s, 3H, 2-OMe), 4.10 (d, *J* = 7.5 Hz, 1H, 6-H), 3.75 (s, 3H, 3-OMe), 3.50 (s, 3H, acetal OMe), 3.45 (s, 3H, acetal OMe). – The subsequent treatment with powdered, freshly melted $KHSO_4$ (0.80 g, 5.90 mmol) afforded a mixture of (*Z*)-**17b** and (*E*)-**17b**. Purification by column chromatography ($CHCl_3$) gave 1.87 g (41%) of (*E*)-**17b** (R_f = 0.31) and 1.05 g (23%) of (*Z*)-**17b** (R_f = 0.26).

$C_{10}H_{11}NO_3$ (193.2) Calcd. C 62.17 H 5.74 N 7.25
Found C 62.23 H 5.96 N 6.97

(*E*)-**17b**: Yellow crystals, m.p. 103°C. – IR (film): $\tilde{\nu}$ = 2195 cm^{-1} (C≡N), 1645 (C=C). – UV (methanol): λ_{max} (lg ε) = 211 (4.170), 309 (4.350). – ^1H NMR ($CDCl_3$): δ = 6.75 (s, 1H, 6-H), 5.80 (s, 1H, 4-H), 4.20 (s, 3H, 2-OMe), 3.90 (s, 3H, 6-OMe), 3.75 (s, 3H, 3-OMe). – ^{13}C NMR ($CDCl_3$): δ = 158.30 (C-2), 152.80 (C-3), 149.20 (C-6), 115.80 (C-5), 115.30 (1-CN), 93.00 (C-4), 76.80 (C-1), 61.20 (6-OMe), 58.60 (2-OMe), 56.80 (3-OMe). – MS (70 eV): *m/z* (%) = 193 (100) [M^+], 178 (87) [M^+ – 15].

(*Z*)-**17b**: Yellow crystals, m.p. 130°C. – IR (film): $\tilde{\nu}$ = 2205 cm^{-1} (C≡N), 1650 (C=C). – UV (methanol): λ_{max} (lg ε) = 2095 (4.090), 306 (4.290). – ^1H NMR ($CDCl_3$): δ = 6.70 (s, 1H, 6-H), 5.45 (s, 1H, 4-H), 4.20 (s, 3H, 2-OMe), 3.85 (s, 3H, 6-OMe), 3.70 (s, 3H, 3-OMe). – ^{13}C NMR ($CDCl_3$): δ = 161.40 (C-2), 150.50 (C-3), 151.40 (C-6), 116.80 (1-CN), 114.60 (C-5), 98.50 (C-4), 73.70 (C-1), 61.60 (6-OMe), 58.80 (2-OMe), 56.90 (3-OMe). – MS (70 eV): *m/z* (%) = 193 (100) [M^+], 178 (91) [M^+ – 15].

(ii) As above, but starting from 5.00 g (0.20 mol) of **9b**, Montmorillonite K-10/trimethyl orthoformate[7] (25 g) in CCl_4 (50 ml) for 12 h at room temp. gave a 33:67 mixture of **14b**:**15b**. The treatment with $KHSO_4$ afforded (*Z*)-**17b** and (*E*)-**17b**.

(iii) A mixture of 0.50 g (2.50 mmol) of **9b** and powdered, freshly melted $KHSO_4$ (100 mg, 0.74 mmol) was vigorously stirred in vacuo and heated to 110–120°C for 30 min. The crude product was extracted with CH_2Cl_2 and purified by column chromatography ($CHCl_3$) to give 105 mg (25%) of *2-methoxy-5-(methoxymethylene)-3-oxo-1-cyclopentene-1-carbonitrile* (**18b**), m.p. 129 (dec.). – IR (film): $\tilde{\nu}$ = 2220 cm^{-1} (C≡N), 1720 (C=O). – ^1H NMR ($CDCl_3$): δ = 6.45 (t, *J* = 2 Hz, 1H, 6-H), 4.20 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.00 (d, *J* = 2 Hz, 2H at C-4). – ^{13}C NMR ($CDCl_3$): δ = 196.10 (C-3), 158.20 (C-2), 143.00 (C-6), 112.70 (1-CN), 108.7 (C-5), 105.20 (C-1), 61.10 (6-OMe), 59.20 (2-OMe), 34.90 (C-4). – MS (70 eV): *m/z* (%) = 179 (100) [M^+], 164 (21) [M^+ – 15].

$C_9H_9NO_3$ (179.2) Calcd. C 60.33 H 5.06 N 7.82
Found C 60.19 H 5.08 N 7.84

A mixture of 98 mg (0.55 mmol) of **18b**, Amberlyst 15 resin (21 mg), trimethyl orthoformate (0.15 ml), and methanol (1 ml) was stirred for 12 h at room temp. After filtration, concentration in vacuo, and purification by column chromatography ($CHCl_3$), 94 mg (89%) of (*E*)-**17b** was obtained.

4-(1-Cyano-2,3-dimethoxypentafulven-6-yl)-2,3,6-trimethoxypentafulvene-1-carbonitrile (**19**): Crude **18b** obtained starting from 250 mg (1.18 mmol) of **9b** was dissolved in acetyl chloride (0.5 ml, 7.0 mmol) and stirred for 6 h at room temp. After concentration in vacuo, the residue was purified by column chromatography ($CHCl_3$) affording 54 mg (13%) of isomer **19-1** (R_f = 0.54) and 38 mg (9%) of isomer **19-2** (R_f = 0.44).

$C_{19}H_{18}N_2O_5$ (354.2) Calcd. C 64.40 H 5.12 N 7.91
Found C 64.22 H 5.09 N 7.67

19-1: Yellow crystals, m.p. 202°C. – IR (KBr): $\tilde{\nu}$ = 2205 cm^{-1} (C≡N), 1640 (C=C). – UV (methanol): λ_{max} (lg ε) = 210 (4.350), 306 (4.390). – ^1H NMR ($CDCl_3$): δ = 6.90 (s, 1H), 6.85 (s, 1H), 6.35 (s, 1H), 4.25 (s, 6H, 2-OMe and 2′-OMe), 4.00 (s, 3H, 3-OMe), 3.80 (s, 3H, 3′-OMe), 3.70 (s, 3H, 6-OMe). – MS (70 eV): *m/z* (%) = 354 (60) [M^+], 44 (100).

19-2: Yellow crystals, m.p. 227°C. – IR (KBr): $\tilde{\nu}$ = 2205 cm^{-1} (C≡N), 1640 (C=C). – UV (methanol): λ_{max} (lg ε) = 209 (4.350), 311 (4.410). – ^1H NMR ($CDCl_3$): δ = 6.95 (s, 1H), 6.50 (s, 1H), 6.30 (s, 1H), 4.25 (s, 3H, 2′-OMe), 4.20 (s, 3H, 2-OMe), 4.00 (s, 3H, 3-OMe), 3.85 (s, 3H, 3′-OMe), 3.65 (s, 3H, 6-OMe). – MS (70 eV): *m/z* (%) = 354 (90) [M^+], 44 (100).

CAS Registry Numbers

3a: 124693-34-1 / **3d**: 124693-36-3 / **5a**: 129064-59-1 / **5b**: 129064-60-4 / **9a**: 129064-61-5 / **9b**: 129064-62-6 / (*Z*)-**10a**: 129102-67-4 / (*Z*)-**10b**: 129064-64-8 / (*E*)-**10b**: 124521-78-4 / (*Z*)-**11a**: 129064-63-7 / **12a**: 129064-66-0 / (*Z*)-**13a**: 129064-65-9 / **14a**: 129064-68-2 / **14b**: 129064-74-0 / **15a**: 129064-69-3 / **15b**: 129064-73-9 / **17a**: 129064-67-1 / (*Z*)-**17b**: 129064-71-7 / (*E*)-**17b**: 129064-72-8 / **18a**: 129064-70-6 / **18b**: 129064-75-1 / (*X,E*)-**19-1**: 129064-76-2 / (*X,Z*)-**19-2**: 129064-77-3

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