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FACILE CONSTRUCTION OF A FURAN-FUSED METHANO[11]ANNULENONE SKELETON BY SUCCESSIVE ALDOL CONDENSATIONS FROM 3,4-FURANDICARBALDEHYDES

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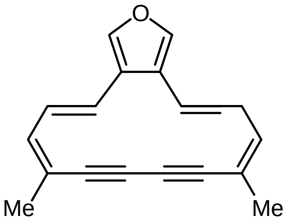
This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday

Abstract – Aldol condensation of furan-3,4-dicarbaldehyde with pentanedial in acetic acid gave 6*H*-cyclohepta[*c*]furan-5,7-dicarbaldehyde in a good yield. Then, successive condensation of 6*H*-cyclohepta[*c*]furan-5,7-dicarbaldehyde with dimethyl 1,3-acetonedicarboxylate under azeotropic conditions gave a diester derivative of furan-fused methano[11]annulenone also in a good yield. The hydrolysis of the diester groups and subsequent decarboxylation provided a non-substituted furan-fused methano[11]annulenone. A similar sequence starting from 2,5-dimethylfuran-3,4-dicarbaldehyde gave its dimethyl derivative. Cycloaddition and protonation of these furan-fused methano[11]annulenones were also studied.

INTRODUCTION

Various furan-fused annulenes,[1] including benzofuran as a typical example of [6]annulenofuran,[2] have been synthesized from the viewpoints of their aromatic character and synthetic utility. Sondheimer *et al*. synthesized two types of furan-fused dehydroannulenes, **1** and **2**, and reported that **1** has atropic nature for



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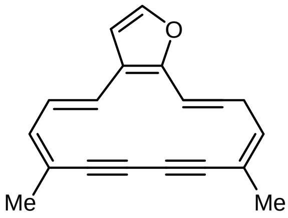

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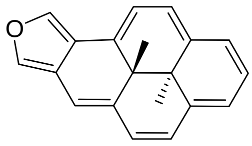
the annulene ring based on its ^{1}H NMR spectral data, whereas **2** is a diatropic compound.[3,4] They also indicated that the furan ring part of **1** could be used as a foothold for producing a carbon framework through the annulene-1,2-dicarbaldehyde in the synthesis of annulenoannulenes.[3] Annuleno[*c*]furan, a type of **1**, also serves as a good enophile in Diels–Alder reactions. For example, Mitchell *et al*. reported that bridged [14]annuleno[*c*]furan **3** reacts various arynes to form cycloadducts, which were transformed to arene-annulated bridged [14]annulenes by subsequent deoxygenation.[5] Meanwhile, such chemical behaviors of furan-fused annulenediones aroused our interest and we reported the synthesis and physical properties of **4**.[6] During the course of our continuing research on bridged annulenes,[7] we have also been interested in annulenoannulenones, towards which an effective short-step synthesis of furan-fused annulenones as a synthetic intermediate is required. Herein we disclose a facile method for synthesizing such an annulenone, 5,11-methano-8*H*-[11]annuleno[*c*]furan-8-one (**5**).



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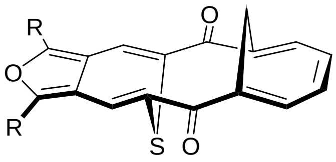

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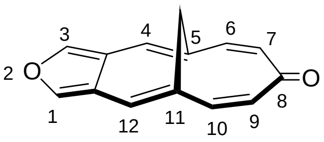

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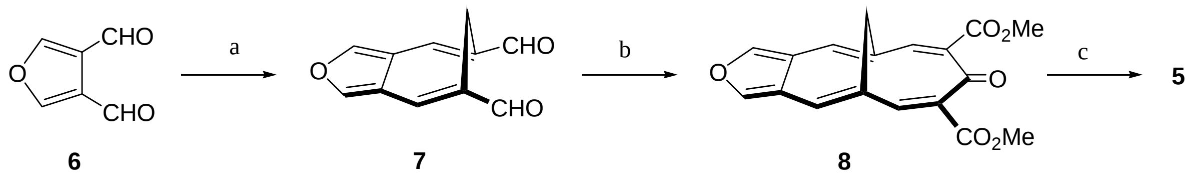
RESULTS AND DISCUSSION

The straightforward route to the title compound **5** is shown in Scheme **1**. Furan-3,4-dicarbaldehyde (**6**) reacts with pentanedial in the presence of piperidine in acetic acid at 120 °C for 4 h to give 6*H*-cyclohepta[*c*]furan-5,7-dicarbaldehyde (**7**) in 68% yield. The synthesis of **7** under similar reaction conditions in the presence of piperidine in refluxing acetic acid had been reported by Lepage *et al.*[8] However, the reported yield was as low as 22%. After extensive work on the reaction conditions, we found that the yield could be greatly improved by modifying the reaction conditions. It is worth noting that a short reaction time and using hydrated pentanedial instead of 2-methoxy-2,3,4-trihydropyrane are crucial for the improvement of the yield and that low substrate concentration and flash chromatography of the product are important to gain a constant yield. Having a large quantity of **7** available, we next examined the aldol condensation of **7** with dimethyl 1,3-acetonedicarboxylate to construct the carbon framework of the desired **5**. Although yields of similar condensations between arene-1,2-dicarbaldehyde and dimethyl 1,3-acetonedicarboxylate are moderate to good,[9] those of the 1,3-carbaldehyde are usually less than 50%.[10] After several reported reaction conditions were applied for the condensation of **7** to result in disappointing yields of **8**,[11] it was found that under azeotropic conditions with a Dean–Stark apparatus,



Scheme 1. A synthetic route to **5**. Reagents and conditions: a) aqueous pentanedial, piperidine (3 eq.), AcOH, reflux, 4 h. b) dimethyl 1,3-acetonedicarboxylate, piperidine (3 eq.), AcOH, toluene, reflux, 8 h. c) i: NaOH, EtOH, then 3N HCl, ii: Cu, 120 °C, DMF.

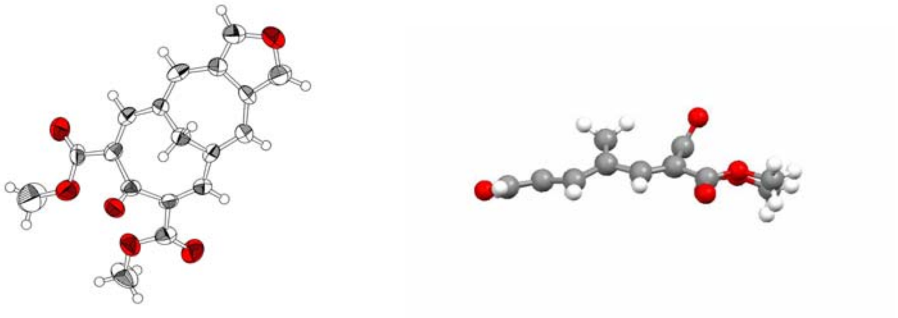
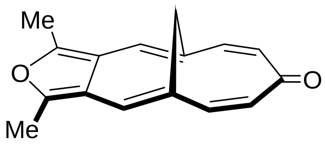


Figure 1. ORTEP drawings of **8**.

8 was produced in 69% yield. The structure of **8** was confirmed by spectroscopic analysis and also by X-ray crystallographic analysis (Figure 1).[12] The hydrolysis of **8** yielded the corresponding carboxylic acid, which was decarboxylated in the presence of copper powder at 120 °C in DMF to give the annulenone **5** as yellow oil in 73% yield. Thus, the facile and efficient construction of furan-fused [11]annulenone was accomplished. Using 2,5-dimethylfuran-3,4-dicarbaldehyde as a starting material, application of this protocol for synthesizing a derivative of **5** provided its 1,3-dimethyl derivative, **9**, in 20% total yield.[11]



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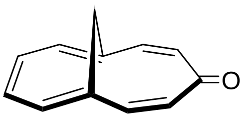

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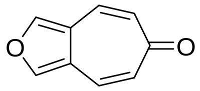

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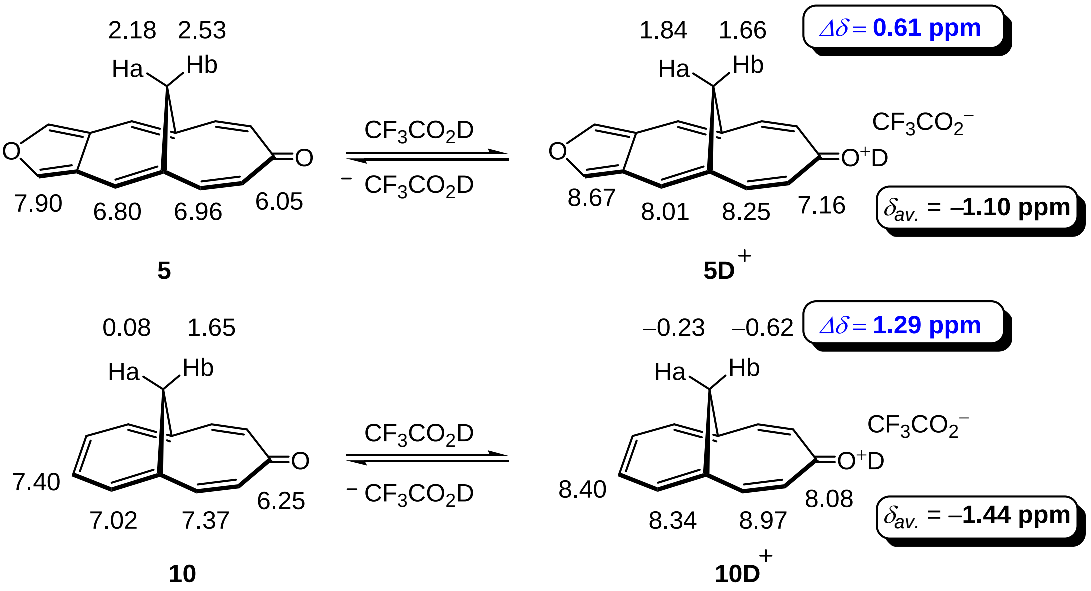
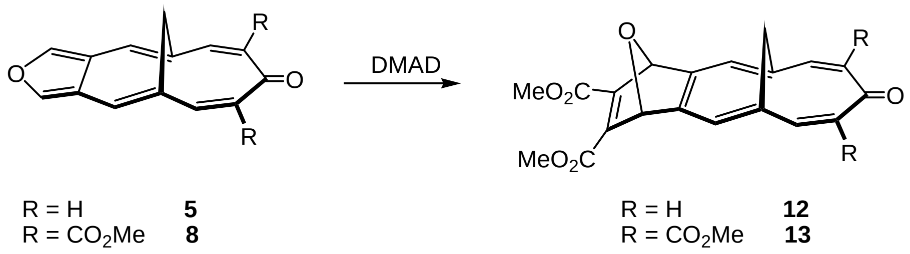
The title compound **5** was isolated as slightly acid- and air-sensitive yellow oil. Protonation of **5** in an acidic medium at room temperature resulted in decomposition of **5**, whereas the 4,9-methano[11]annulenone (**10**) and furo[*c*]tropone **11** were stable under similar conditions. Although monitoring a solution of **5** in CF_3CO_2D at –15 °C by ^1H NMR spectroscopy revealed the complete decomposition of **5** in 4 h, the transient protonated species $\mathbf{5D}^+$ could be observed (Scheme 2). The olefinic protons of $\mathbf{5D}^+$ resonate at a lower magnetic field by 1.10 ppm on average and the bridging methylene protons resonate at a higher magnetic field by 0.61 ppm on average, compared with those in $CDCl_3$ solution. At a glance, these shifts appear to indicate a deshielding effect on the olefinic protons and a shielding effect on the bridging methylene protons based on the diamagnetic ring current induced by the peripheral 14π-electorn aromatic system in the protonated species. Since the magnitude of these shifts is less than those observed in **10** upon protonation, the protonated species **5D**$^+$ is thought to be weakly diatropic. In other words, the contribution of the peripheral 14π-electorn aromatic system in the protonated species is very small.



Scheme 2. Chemical shifts (δ_{ppm}) of **5** and **1a0** in $CDCl_3$ and CF_3CO_2D and their differences.

The furan ring of [11]annulenones, **5** and **8**, serves as a 4π-component for the Diels–Alder reaction. On heating **5** and **8** with dimethyl acetylenedicarboxylate (DMAD) in toluene, cycloadducts **12** and **13** were obtained in 87% and 89% yields, respectively. The structure of **13** was determined by X-ray crystallography analysis (Figure 2) to reveal the *syn*-configuration between oxa- and methano-bridges in the product. The stereochemistry of **12** was deduced to have the same configuration as **13** by comparison of the spectroscopic data of **12** and **13**. Thus, in these reactions, DMAD approaches the furan ring from the rear side of the methylene bridge.



Scheme 3. Cycloaddition reactions of **5** and **8**.

In summary, the facile and efficient synthesis of furan-fused [11]annulenones has been accomplished by a four-step sequence starting from furan-dicarbaldehydes. The 11-membered ring of the protonated species of [11]annulenone **5** is weakly diatropic in nature. The furan ring of annulenones **5** and **8** indicated sufficient reactivity for DMAD. Such reactivity of these compounds gives the prospect of constructing a new framework towards annulenoannulenones by cycloaddition with suitable arynes. Further transformation of **5** along these lines is now in progress.

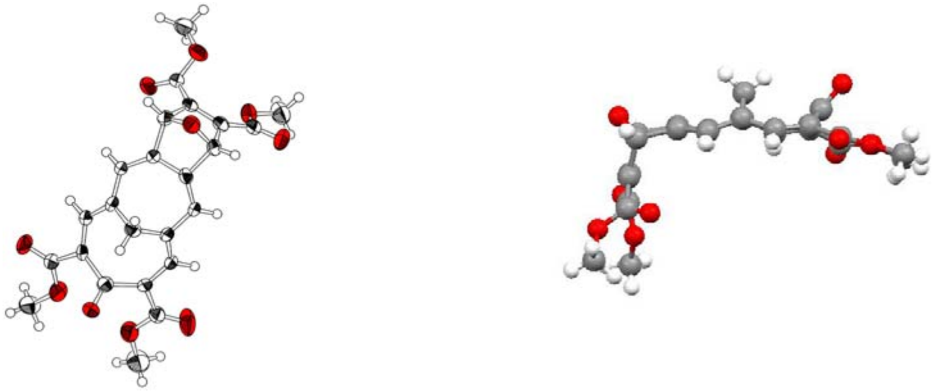


Figure 2. ORTEP drawings of **13**.

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11. Selected data of new compounds are as follows; **8**: Yellow crystals, mp 198–200 °C, ^{1}H-NMR (CDCl$_3$) δ = 2.22 (d, J =14.0 Hz, 1H), 2.78 (d, J = 14.0 Hz, 1H), 3.83 (s, 6H), 7.01 (s, 2H), 7.80 (s, 2H), 7.95 (s, 2H) ppm; ^{13}C-NMR (CDCl$_3$) δ = 30.2, 52.7, 123.2, 125.5, 128.8, 131.5, 141.5, 141.9, 164.9, 196.0 ppm; IR (KBr) $\nu_{\max}$ = 1704s, 1685m, 1510m, 1435m, 1254s, 1190m cm^{-1}; UV (MeOH) $\lambda_{\max}$ = 217 (logε = 3.99), 242 (4.18), 302 (4.67), 377sh (3.47) nm; HRMS: Calcd for $C_{18}H_{14}O_6$ 326.0790; Found 326.0781. **5**: yellow oil, ^{1}H-NMR (CDCl$_3$) δ = 2.18 (d, J = 13.2 Hz, 1H), 2.53 (d, J = 13.2 Hz, 1H), 6.05 (dm as a part of AA'BB', J = 12.0 Hz , 2H), 6.80 (s, 2 H), 6.96 (dm as a part of AA'BB', J = 12.0 Hz, 2H), 7.90 (s, 2H) ppm; ^{13}C-NMR (CDCl$_3$) δ = 32.4, 119.5, 123.4, 127.8, 133.9, 137.3, 140.8, 196.2 ppm; IR (KBr) $\nu_{\max}$ = 2926s, 2854m, 1745m, 1608m, 1149m, 1089m cm^{-1}; UV (MeOH) $\lambda_{\max}$ = 229 (logε =3.92), 292 (3.90), 346sh (3.47), 410sh (3.03) nm; HRMS: Calcd for $C_{14}H_{10}O_2$ 210.0681; Found 210.0649.

7,9-Bis(methoxycarbonyl)-1,3-dimethyl-5,11-methano[*c*]furan-8-one: Yellow crystals, mp 213–215 °C, ^{1}H-NMR (CD$_2$Cl$_2$) δ = 2.28 (d, J =14.0 Hz, 1H), 2.45 (s, 6H), 2.76 (d, J = 14.0 Hz, 1H), 3.75 (s, 6H), 6.86 (s, 2H), 7.72 (s, 2H) ppm; ^{13}C-NMR (CD$_2$Cl$_2$) δ = 12.4, 30.7, 52.3, 119.4, 127.3, 128.5, 130.8, 141.5, 149.8, 165.0, 196.0 ppm; IR (KBr) $\nu_{\max}$ = 1713s, 1660m, 1580m, 1434m, 1265s, 1245s, 1216s, 766w cm^{-1}; UV (MeOH) $\lambda_{\max}$ = 254 (logε = 4.21), 318 (4.54), 376 (4.96) nm; **9**: Yellow crystals, mp 95–97 °C, ^{1}H-NMR (CDCl$_3$) δ = 2.28 (d, J =12.4 Hz, 1H), 2.48 (s, 6H), 2.58 (d, J = 12.4 Hz, 1H), 5.99 (dm as a part of AA'BB', J = 12.2 Hz, 2H), 6.62 (s, 2H), 6.92 (dm as a part of AA'BB', J = 12.2 Hz, 2H) ppm; ^{13}C-NMR (CDCl$_3$) δ = 12.5, 32.8, 119.4, 121.1, 127.2, 133.0, 137.7, 147.9, 196.2 ppm; IR (KBr) $\nu_{\max}$ = 1608s, 1573s, 1396m, 1261s, 1151m, 1084s, 929w, 886m cm^{-1}; UV (MeOH) $\lambda_{\max}$ = 231 (logε = 4.11), 302 (4.42), 411 (3.17) nm; **12**: yellow powder, mp 90–91 °C, ^{1}H-NMR (CDCl$_3$) δ = 0.08 (d, J = 11.2 Hz, 1H), 1.36 (d, J = 11.2 Hz, 1H), 3.84 (s, 6 H), 6.13 (s, 2H), 6.35 (d, J = 11.2 Hz , 2H), 7.39 (d, J = 11.2 Hz, 2H), 7.41 (s, 2H) ppm; ^{13}C-NMR (CDCl$_3$) δ = 36.1, 52.6, 86.2, 120.4, 124.8, 126.9, 137.2, 150.3, 150.7, 163.0, 192.1 ppm; IR (KBr) $\nu_{\max}$ = 2927m, 2854w, 1736s, 1719s, 1706s, 1655m, 1637s, 1596s, 1438m, 1300s, 1259s, 1216s, 1112m cm^{-1}; UV

(MeOH) λ_{max} = 241 (logε = 3.82), 309(4.08), 383 (3.11) nm; HRMS: Calcd for $C_{20}H_{16}O_6$ 352.0947; Found 352.0949. **13**: Yellow crystals, mp 235–237 °C, ^{1}H-NMR ($CDCl_3$) δ = 0.16 (d, *J* =13.2 Hz, 1H), 1.92 (d, *J* = 13.2 Hz, 1H), 3.85 (s, 6H), 3.86 (s, 6H), 6.13 (s, 2H), 7.52 (s, 2H), 8.07 (s, 2H) ppm; ^{13}C-NMR ($CDCl_3$) δ = 33.3, 52.7, 52.9, 86.2, 117.5, 122.7, 128.3, 139.7, 150.6, 151.7, 162.7, 164.7, 191.9 ppm; IR (KBr) ν_{max} = 1716s, 1699s, 1663m, 1638m, 1437m, 1307m, 1273s, 1226s cm^{-1}; UV (MeOH) λ_{max} = 216 (logε = 3.98), 265 (4.30), 311 (4.51), 391 (3.47) nm; HRMS: Calcd for $C_{24}H_{20}O_{10}$ 468.1056; Found 468.1092.

12. The X-ray data for **8**: $C_{18}H_{14}O_6$, Mw = 326.30, monoclinic, space group *P2₁/c* (#14), *a* = 11.574(5), *b* =7.529(3), *c* = 17.605(4) Å, β = 100.06(2) deg, *V* = 1510.4(9) Å^3, *Z* = 4, D_{calc} = 1.435 g cm^{-3}, μ(Mo-*K*α) = 1.09 cm^{-1}, 5352 independent reflections, 217 parameters, *R* = 0.050, *Rw* = 0.116, T = 298 K. Those for **13**: $C_{24}H_{20}O_{10}$, Mw = 468.42, triclinic, space group *P1 /* (#2), *a* = 9.788(3), *b* = 14.132(4), *c* = 9.179(3) Å, β = 116.27(2) deg, *V* = 1071.2(6) Å^3, *Z* = 2, D_{calc} = 1.452 g cm^{-3}, μ(Mo-*K*α) = 1.14 cm^{-1}, 5344 independent reflections, 387 parameters, *R* = 0.053, *Rw* = 0.135, T = 298 K. Estimated standard deviations for the bond lengths and angles are 0.004–0.007 (ang) and 0.2–0.4 (deg), respectively, for the non-hydrogen atoms. Crystallographic data excluding structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 695660 for **8** and CCDC 695659 for **13**. A copy of the data can be obtained free of charge from CCDC, 12 Union road, Cambridge CB2 1EZ. UK [DIRECT LINE: +44 1223 762910, Fax: +44 (0) 1223-336033 or e-mail: linstead@ccdc.cam.ac.uk; deposit@ccdc.cam.ac.uk.