Synthesis of Macrocyclic Fulvalene Derivatives[1]

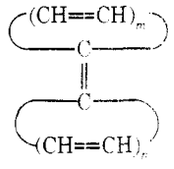
Peter D. Howes and Franz Sondheimer*

Department of Chemistry, University College, London WC1H OAJ, England

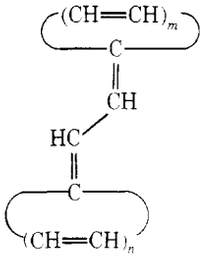
Received December 15, 1977

Reactions of the bis(cyclohexene)-annelated bisdehydro[13]annulenone **5** are described, which led to the pentatridecafulvalene **7**, the tridecatridecafulvalene **12**, and the vinylogous pentatridecafulvalene **19**. The attempted electrocyclization of **19** to **22** did not succeed.

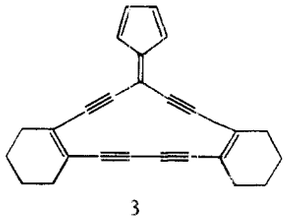
Bicyclic polyenes containing a cyclic cross-conjugated π-electron system of the fulvalene type (**1**) have been extensively investigated.[2] More recently, a number of vinylogous fulvalenes (compounds of type **2**) have been studied.[3] Nearly all of these compounds contained three-, five-, or seven-membered rings, the only macrocyclic fulvalene derivatives prepared previously being the pentatridecafulvalene **3**[4] and the tridecatridecafulvalene **4**[5] containing a cumulated triene



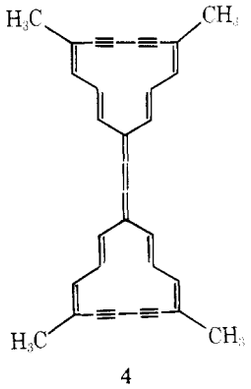
1



2

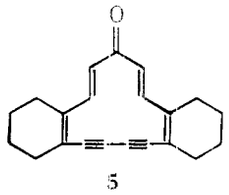


3

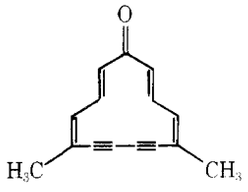


4

between the two macrocyclic rings.[6] The convenient syntheses of the bisdehydro[13]annulenones **5**[7] and **6**[1] in satisfactory yield made it desirable to utilize these compounds for the syntheses of other fulvalene derivatives of type **1** and **2**, in which one or both rings are 13 membered. We now describe this objective, the derivatives prepared being the pentatridecafulvalene **7**, the tridecatridecafulvalene **12**, and the vinylogous pentatridecafulvalene **19**.

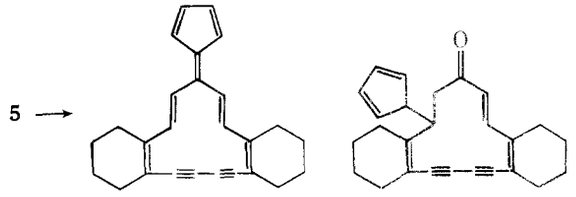


5



6

The Pentatridecafulvalene 7. The pentatridecafulvalene **7** was prepared as red crystals in 16% yield by treatment of the bisdehydro[13]annulenone **5** with a large excess of sodium cyclopentadienide (prepared from cyclopentadiene and sodium methoxide). The structure[8] of **7** was established by spectral means. As in other cases,[4,9] the cyclopentadiene ole-

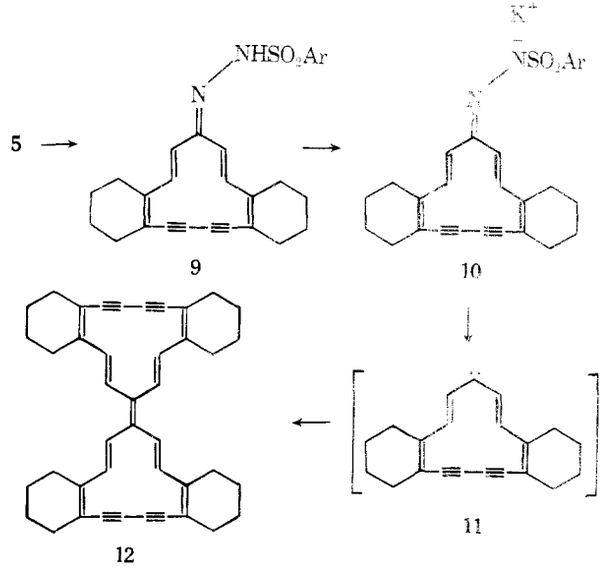


7 8

finic resonances in the ^{1}H-NMR spectrum of the fulvalene **7** resonated as a singlet (τ 3.40), and there was no evidence for a ring current. Comparison of the electronic spectrum of the fulvalene **7** [main λ_{max} 390 nm (ϵ 16400)] with that of the tetradehydro derivative **3**[4] [main λ_{max} 401 nm (ϵ 43500)] indicates that the conjugated 13-membered ring system in **7** is less planar than that in **3**.

A yellow oily by-product was obtained in the synthesis of the pentatridecafulvalene **7**, and this was the main product when a smaller excess of sodium cyclopentadienide was used in the reaction with **5**. The spectral properties of this material are consistent with a structure such as **8**, arising from conjugate addition.

The Tridecatridecafulvalene 12. After several routes designed to convert the bisdehydro[13]annulenone **5** to the tridecatridecafulvalene **12** failed, the following sequence led to success. Substance **5** was first converted to the *p*-toluenesulfonylhydrazone **9** (92% yield), which was then transformed to the potassium salt **10** by means of potassium *tert*-butoxide. This type of species has been shown to be convertible to products derived from the corresponding carbene (type **11**,



9 10 11 12

formed via the diazo compound), either by pyrolysis[6b,10] or photolysis.[11]

In practice, pyrolysis of **10** under various conditions led to no new conjugated macrocyclic products. On the other hand, irradiation of **10** at 0°C with a Hanovia high-pressure lamp gave the required tridecatridecafulvalene **12** relatively rapidly,

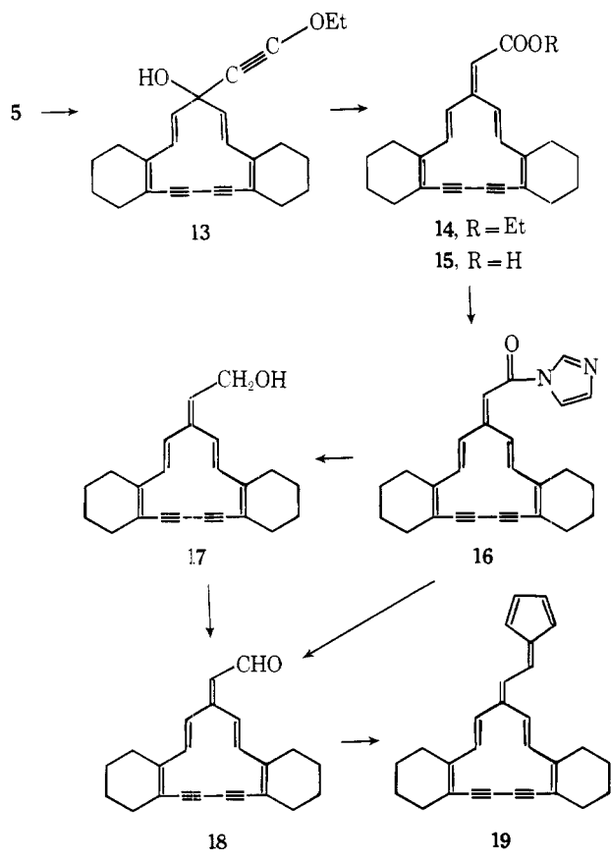
0022-3263/78/1943-2158$01.00/0

although only in poor yield (1.3%). The deep red fulvalene **12** proved to be rather unstable and underwent considerable decomposition on evaporation to dryness. Its structure was confirmed by the ^{1}H-NMR and electronic spectra given in the Experimental Section. As expected, the ^{1}H-NMR spectrum showed the compound to possess no appreciable ring current. It is of interest that both types of olefinic protons in the ^{1}H-NMR spectrum of **12** appear as a singlet (τ 2.87) and no separation could be observed by changing solvent. In the electronic spectrum of **12**, the main maximum occurred at 446 nm, the expansion of the 5-membered ring in **7** to a 13-membered ring in **12** resulting in a bathochromic shift of 56 nm.

The molecular weight of the fulvalene **12** could not be determined by the mass spectrum, in view of its involatility and relative instability. It was therefore hydrogenated in acetic acid over a platinum catalyst to the corresponding perhydro derivative, the mass spectrum of which showed it to possess the expected molecular formula.

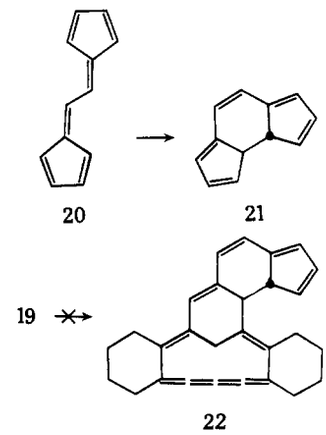
The Vinylogous Pentatridecafulvalene 19. A suitable intermediate in the conversion of the bisdehydro[13]annulenone **5** to the vinylogous pentatridecafulvalene **19** appeared to be the α,β-unsaturated aldehyde **18**. The transformation of **5** to **18** at first presented some difficulty (e.g., **5** did not undergo the normal Wittig reaction with carbethoxymethylenetriphenylphosphorane[12] to give the ester **14**). After some experimentation, the following route to **18** proved to be successful.

Treatment of the bisdehydro[13]annulenone **5** with excess lithium ethoxyacetylide led to the ethoxyacetylenic carbinol **13**, which on direct rearrangement with aqueous sulfuric acid[13] yielded 75% (based on **5**) of the α,β-unsaturated ester **14**, mp 137–138 °C. Saponification of **14** with potassium carbonate gave the corresponding acid **15**, which was converted to the imidazolide **16** with excess *N,N'*-carbonyldiimidazole in boiling tetrahydrofuran. Reduction of **16** with excess lithium tri-*tert*-butoxyaluminum hydride[14] led to a mixture of the alcohol **17** and the aldehyde **18**, which was then treated with activated manganese dioxide[15] in order to convert **17** to **18**. This procedure resulted in the aldehyde **18**, mp ~135 °C, in 48% yield (based on the ester **14**). Finally, reaction of **18** with an excess of sodium cyclopentadienide (prepared from cyclopentadiene and sodium methoxide) gave 19% of the desired vinylogous pentatridecafulvalene **19** as dark red crystals, which decomposed on attempted melting point determination.



The structure of **19** follows from the mass, ^{1}H-NMR, and electronic spectra, given in the Experimental Section. In the ^{1}H-NMR spectrum the olefinic protons resonated in the region τ 2.15–4.05, showing the absence of a ring current. In the electronic spectrum, the main maximum was at 416 nm; the bathochromic shift of 26 nm compared with the main maximum of the pentatridecafulvalene **7** (390 nm) is due to the extra double bond.

It has been shown by Sauter, Gallenkamp, and Prinzbach[3] that the vinylogous pentapentafulvalene **20** readily undergoes conrotatory electrocyclization to the trans dihydro-*as*-indacene **21** at room temperature. By contrast, the vinylogous pentatridecafulvalene **19** was stable in organic solvents at room temperature. On boiling in solvents such as benzene or ethyl acetate, **19** gradually formed an insoluble polymer. It is possible that this is derived from the cumulene **22** (the conrotatory electrocyclization product of **19**), but all attempts to isolate this compound failed.



Experimental Section

General Procedures. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were measured on a Unicam SP 200 spectrophotometer (s = strong, m = medium, w = weak); only significant maximum are reported. Electronic spectra were determined on a Unicam SP 800 spectrophotometer (sh = shoulder). ^{1}H-NMR spectra were recorded on a Varian T-60 spectrometer, tetramethylsilane being used as internal standard. Mass spectra were determined on an AEI MS-902 spectrometer operating at 70 eV. All reactions were carried out under prepurified nitrogen.

The Pentatridecafulvalene 7. Freshly distilled cyclopentadiene (150 mL) was added during 10 min to an ice-cooled solution of sodium methoxide [from sodium (4.0 g)] in methanol (250 mL) under nitrogen, and the solution was stirred at 0 °C for a further 10 min. A solution of the [13]annulenone **5**[7] (480 mg) in dry ether (150 mL) was then added at 0 °C during 10 min, and the mixture was stirred at this temperature for a further 3 h. Water (500 mL) was added, and the organic layer was separated. The aqueous layer was washed with ether (2 × 500 mL) and the combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was evaporated and the residue was chromatographed on silica gel. Elution with petroleum ether (49:1) and crystallization from ether gave the fulvalene **7** (90 mg, 16%) as red crystals, which decomposed at ~150 °C on attempted melting point determination: MS *m/e* 336.1871 (M^+, calcd 336.1877); UV (Et_2O) λ_{max} 260 nm (ϵ 14700), 274 (13800), 318 (14900), 390 (16400); IR (KBr) 2170 w (C≡C), 970 cm^{-1} m (*trans*-HC=CH); ^{1}H NMR (60 MHz, $CDCl_3$) τ 2.08 (d, J = 16 Hz, 2 H, olefinic H), 3.15 (d, J = 16 Hz, 2 H, olefinic H), 3.40 (s, 4 H, cyclopentadiene H), 7.4–8.0 (m, 8 H, allylic CH_2), 8.05–8.55 (m, 8 H, nonallylic CH_2).

Further elution with ether gave a yellow oily material: MS *m/e* 354; UV (Et_2O) main λ_{max} 269, 281 nm; IR (CCl_4) 1670 cm^{-1} (s, C=C-C=O); ^1H NMR (60 MHz, CCl_4, olefinic:aliphatic H = 6:20). This material, which may have structure **8**, was the main product when a much smaller excess of sodium cyclopentadienide was used in the reaction with **5**.

The Tridecatridecafulvalene 12. A solution of the [13]annulenone **5** (500 mg, 1.74 mmoles) in benzene (100 mL) and ethanol (100 mL) was treated with *p*-toluenesulfonylhydrazide (330 mg, 1.77 mmol) and then with 5 drops of concentrated hydrochloric acid at room temperature. The resulting insoluble *p*-toluenesulfonylhydrazone **9** (733 mg, 92%) formed orange crystals, mp >230 °C dec: UV λ_{max} ($CHCl_3$, qualitative) ~270 (sh), 295, ~350 nm (sh); IR (KBr) 2170 (w, C≡C), 1345 (m), 1165 cm^{-1} (s, SO_2). Substance **9** was too insoluble in the usual solvents for a ^1H-NMR spectrum to be obtained. The yield of **9** was only 64% when the reaction was carried out in boiling ethanol for 3 h.

A solution of potassium *tert*-butoxide (300 mg, 2.68 mmol) in tetrahydrofuran (150 mL) was added during 10 min to the *p*-toluenesulfonylhydrazone **9** (1.00 g, 2.19 mmol) in tetrahydrofuran (400 mL) at 0 °C under nitrogen. The resulting potassium salt **10** (deep red solution) was then irradiated at 0 °C under N_2 with a Hanovia high-pressure lamp. Aliquots were removed at intervals and analyzed by TLC (silica plates). The reaction was found to be complete after 30 min, and irradiation was terminated (irradiation for 90–120 min was found to result in a reduced yield of **12**). The photolysate was poured into ice (~500 g), and benzene (500 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 500 mL). The combined organic extracts were dried over magnesium sulfate.

One-half of the extract was concentrated to ~5 mL (external temperature not greater than 40 °C), carbon tetrachloride (250 mL) was added, and the solution was again concentrated to ~5 mL. The concentrate was chromatographed on silicic acid (50 g, Mallinckrodt), with carbon tetrachloride as eluent. The same procedure was employed with the other half of the extract, giving a total of 8 mg (1.3%) of the fulvalene **12** as a deep red solution, which underwent substantial decomposition on evaporation to dryness: UV λ_{max} (Et_2O) 253 (ϵ 36600),[16] ~265 (sh, ϵ 32800), ~295 (sh, ϵ 25700), ~340 (sh, ϵ 13600), 446 nm (11300); IR (CCl_4) 2180 (w, C≡C), 975 cm^{-1} (m, *trans*-HC=CH); ^1H NMR (60 MHz, CCl_4) τ 2.87 (s, 8 H, olefinic H), 7.5–8.0 (m, 16 H, allylic CH_2), 8.1–8.5 (m, 16 H, nonallylic CH_2); the olefinic protons remained as a singlet in acetone-d_6 or in benzene-d_6. No mass spectrum could be obtained at probe temperatures up to 215 °C, presumably due to the involatility and relative instability of **12**.

Catalytic Hydrogenation of the Tridecatridecafulvalene 12 to the Perhydro Derivative. The fulvalene **12** (~4 mg) in glacial acetic acid (5 mL) was stirred under hydrogen in the presence of a prereduced platinum catalyst (from ~10 mg of PtO_2) until uptake of hydrogen had ceased. The mixture was diluted with ether (100 mL), filtered, and washed well with sodium bicarbonate solution. The ether solution was dried over magnesium sulfate and evaporated to give the perhydro derivative of **12** as a colorless oil. The mass spectrum showed a base peak at 578.5771 (M^+, calcd 578.5787).

The α,β-Unsaturated Ester 14. A solution of methyllithium (2.2 mmol) in ether was added to a stirred solution of ethoxyacetylene (250 mg, 3.5 mmol) in ether (20 mL) at −78 °C under nitrogen. The mixture was stirred at this temperature for 10 min, and a solution of the [13]annulenone **5** (100 mg, 0.35 mmol) in ether (25 mL) was then added. The cooling bath was removed, and the mixture was stirred for a further 15 min. Saturated aqueous sodium chloride was then added; the organic layer was washed with water and was dried over magnesium sulfate. Removal of solvent yielded the crude alcohol **13**, which was used directly for the next step.

The crude alcohol **13** was dissolved in ether (25 mL) and ethanol (3 mL) and shaken vigorously with 10% aqueous sulfuric acid (25 mL) at room temperature for 10 h. The organic layer became deep orange during this time. The organic layer was washed with water, dried over magnesium sulfate, and evaporated. Chromatography on silica gel and elution with pentane–ether (19:1) yielded the α,β-unsaturated ester **14** (60 mg, 48% based on **5**) as orange crystals: mp 137–138 °C; MS *m/e* 358.1924 (M^+, calcd 358.1933); UV (Et_2O) λ_{max} 255 (ϵ 15200), 268 (sh, ϵ 18000), 297 (27800), 343 nm (sh, ϵ 14800); IR (KBr) 2190 (w, C≡C), 1705 (s, ester), 975 cm^{-1} (s, *trans*-HC=CH); ^1H NMR (60 MHz, $CDCl_3$) τ 1.78 (d, J = 16 Hz, 1 H, ring olefinic H), 2.18 (d, J = 16 Hz, 1 H, ring olefinic H), 2.53 (d, J = 16 Hz, 1 H, ring olefinic H), 3.73 (d, J = 16 Hz, 1 H, ring olefinic H), 4.12 (s, 1 H, α-olefinic H), 5.81 (q, J = 7 Hz, 2 H, CH_2CH_3), 7.4–8.05 (m, 8 H, allylic CH_2), 8.1–8.55 (m, 8 H, nonallylic CH_2), 8.73 (t, J = 7 Hz, 3 H, CH_2CH_3).

Subsequently it was found that the yield of **14** from **5** could be improved to 75%, and the transformation of **13** to **14** could be completed in 2–3 h, by increasing the amount of ethanol used for the conversion of **13** to **14**.

The α,β-Unsaturated Acid 15. The ester **14** (75 mg) in methanol (50 mL) was saponified by being boiled under reflux with a solution of potassium carbonate (2 g) in water (10 mL) and methanol (50 mL) for 4 h. The solution was cooled, acidified with 10% sulfuric acid, and thoroughly extracted with ether. The organic extracts were washed with brine, dried over magnesium sulfate, and evaporated. Purification of the residue by preparative LC on silica gave the acid **15** (60 mg, 87%) as an orange solid: mp >300 °C: MS *m/e* 330.1612 (M^+, calcd 330.1620); UV (Et_2O, qualitative) λ_{max} 255 (sh), 268 (sh), 296, ~340 nm (sh); IR (KBr) 3400–2400 (b, COOH), 2190 (w, C≡C), 1665 (s, COOH), 975 cm^{-1} (s, *trans*-HC=CH); ^1H NMR (60 MHz, THF) 1.85 (d, J = 17 Hz, 1 H, ring olefinic H), 2.20 (d, J = 16 Hz, 1 H, ring olefinic H), 2.41 (d, J = 17 Hz, 1 H, ring olefinic H), 3.67 (d, J = 16 Hz, 1 H, ring olefinic H), 4.06 (s, 1 H, α-olefinic H).

The α,β-Unsaturated Aldehyde 18. A solution of the acid **15** (60 mg, 0.19 mmol) in dry tetrahydrofuran (10 mL) was treated with a solution of *N,N'*-carbonyldiimidazole (200 mg, 1.23 mmol) in tetrahydrofuran (100 mL), and the solution was boiled under reflux for 4 h, moisture being excluded. The solvent was evaporated; the residue was dissolved in the minimum amount of chloroform and chromatographed on silica gel. Elution with chloroform yielded the imidazolide **16** (65 mg, 91%) as a red solid, which was used directly in the next step.

A slurry of lithium tri-*tert*-butoxyaluminum hydride (prepared by the addition of 3 molar equiv of *tert*-butyl alcohol to lithium aluminum hydride in ether) in ether was added in small portions to a stirred solution of the imidazolide **16** (65 mg) in tetrahydrofuran (10 mL) at room temperature, until no **16** could be detected by TLC. Water and ether were added; the organic layer was washed with water, dried over magnesium sulfate, and evaporated. TLC examination of the residue indicated it to consist of the alcohol **17** and the aldehyde **18**. The residue in ether (10 mL) was therefore shaken with activated manganese dioxide[15] (1 g) for 10 min, when oxidation of **17** to **18** appeared to be complete (TLC). The solid was removed by filtration and washed well with ether, and the combined filtrates were evaporated. Preparative LC of the residue on silica (elution with 50% ether–pentane) yielded the α,β-unsaturated aldehyde **18** (35 mg, 61%) as a red solid, mp 135 °C dec (rapid heating): MS *m/e* 314.1665 (M^+, calcd 314.1671); UV (Et_2O) λ_{max} 263 (ϵ 16300), ~ 280 (sh, 18000), 302 (ϵ 21300), ~345 nm (sh, ϵ11800); IR (KBr) 2180 (w, C≡C), 1660 (s, unsaturated CHO), 965 cm^{-1} (s, *trans*-HC=CH); ^1H NMR (60 MHz, $CDCl_3$) τ 0.03 (d, J = 7.5 Hz, 1 H, CHO), 2.05 (d, J = 16 Hz, 1 H, ring olefinic H), 2.57 (d, J = 16 Hz, 1 H, ring olefinic H), 3.20 (d, J = 16 Hz, 1 H, ring olefinic H), 3.65 (d, J = 16 Hz, 1 H, ring olefinic H), 3.98 (d, J = 7.5 Hz, 1 H, α-olefinic H), 7.5–8.0 (m, 8 H, allylic CH_2), 8.1–8.5 (m, 8 H, nonallylic CH_2).

The Vinylogous Pentatridecafulvalene 19. Freshly distilled cyclopentadiene (10 g) was added during 5 min to an ice-cooled solution of sodium methoxide [from sodium (0.23 g)] in methanol (50 mL) under nitrogen, and the solution was stirred at 0 °C for a further 10 min. A solution of the aldehyde **18** (50 mg) in dry ether (50 mL) was added, and the resulting deep orange mixture was stirred at 0 °C under N_2 for 15 min (TLC examination at this stage showed the reaction to be terminated). Water (100 mL) was added, and the organic layer was separated. The aqueous layer was washed with ether (2 × 100 mL); the combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was evaporated and the residue was subjected to preparative LC on silica. Elution with 5% ether–pentane yielded the vinylogous fulvalene **19** (11 mg, 19%) as dark red crystals, which decomposed on attempted melting point determination: MS *m/e* 362.2025 (M^+, calcd 362.2034); UV λ_{max} 274 (ϵ 26100), 334 (ϵ 24600), 416 (ϵ 47800), ~435 nm (sh, ϵ 42700); IR (KBr) 2180 (m, C≡C), 975 cm^{-1} (s, *trans*-HC=CH); ^1H NMR (60 MHz, CCl_4) τ 2.15–4.05 (m, 10 H, olefinic H), 7.4–8.0 (m, 8 H, allylic CH_2), 8.1–8.5 (m, 8 H, nonallylic CH_2).

Acknowledgment. Financial support from the Science Research Council and the Royal Society is gratefully acknowledged.

Registry No.—**5**, 39694,95-6; **7**, 65682-12-4; **8**, 65682-13-5; **9**, 65682-14-6; **10**, 65682-15-7; **12**, 65682-16-8; **12** perhydro derivative, 65682-17-9; **13**, 65682-18-0; **14**, 65682-19-1; **15**, 65682-20-4; **16**, 65682-21-5; **17**, 65682-22-6; **18**, 65682-23-7; **19**, 65682-24-8; sodium cyclopentadienide, 4984-82-1; ethoxyacetylene, 927-80-0; *N,N*-carbonyldiimidazole, 530-62-1.

References and Notes

(1) Unsaturated Macrocyclic Compounds. 123. For part 122, see T. M. Cresp, J. Ojima, and F. Sondheimer, *J. Org. Chem.*, **42**, 2130 (1977).
(2) For a review, see E. D. Bergmann, *Chem. Rev.*, **68**, 41 (1968).
(3) See H. Sauter, B. Gallenkamp, and H. Prinzbach, *Chem. Ber.*, **110**, 1382 (1977); H. Babsch and H. Prinzbach, *Angew. Chem.*, in press, and references cited therein.
(4) G. W. Pilling and F. Sondheimer, *J. Am. Chem. Soc.*, **90**, 5611 (1968); **93**, 1977 (1971).
(5) L. Lombardo and F. Sondheimer, *Tetrahedron Lett.*, 3631 (1976).
(6) For the synthesis of fulvalenes containing bridged 11-membered rings, see (a) H. Prinzbach and L. Knothe, *Angew. Chem.*, **79**, 620 (1967); **80**, 698 (1968); (b) R. A. LaBar and W. M. Jones, *J. Am. Chem. Soc.*, **95**, 2359 (1973).
(7) P. D. Howes, E. LeGoff, and F. Sondheimer, *Tetrahedron Lett.*, 3691 (1972).
(8) No proof was obtained for the conformation of the 13-membered ring of **7** and related compounds described in this paper. The indicated conformation is assumed by analogy with that of the bisdehydro[13]annulenone **5**.[7]
(9) See K. V. Scherer, *J. Am. Chem. Soc.*, **85**, 1550 (1963).
(10) Inter alia, see W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959); L. Friedman and H. Shechter, *J. Am. Chem. Soc.*, **81**, 5512 (1959); G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Schechter, *ibid.*, **87**, 936 (1965); R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *ibid.*, **89**, 471 1442 (1967); P. H. Gebert, R. W. King, R. A. LaBar, and W. M. Jones, *ibid.*, **95**, 2357 (1973); R. A. LaBar and W. M. Jones, *ibid.*, **96**, 3645 (1974).
(11) Inter alia, see W. G. Dauben and F. G. Willey, *J. Am. Chem. Soc.*, **84**, 1497 (1962); P. K. Freeman and R. C. Johnson, *J. Org. Chem.*, **34**, 1746 (1969); H. Dürr, *Chem. Ber.*, **103**, 369 (1970).
(12) O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).
(13) See J. F. Arens, "Advances in Organic Chemistry, Methods and Results", Vol. II, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience, New York, N.Y., 1960, pp 159–160, and references cited there.
(14) Modification of the method of Staab: inter alia, see H. A. Staab, and H. Bräunling, *Justus Liebigs Ann. Chem.*, **654**, 119 (1962); F. Sondheimer, W. McCrae, and W. G. Salmond, *J. Am. Chem. Soc.*, **91**, 1228 (1969); T. C. McMorris, *J. Org. Chem.*, **35**, 458 (1970).
(15) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).
(16) The ϵ values are minimum ones, due to the instability of the substance.

Rate Acceleration of the Intramolecular Ene Reactions of 1,6- and 1,7-Enynes by Electron-Withdrawing Substituents

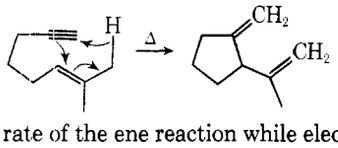
Barry B. Snider* and Thomas A. Killinger

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

Received December 5, 1977

The intramolecular ene reactions of 1,6- and 1,7-enynes containing a hydrogen, methyl, or carbomethoxy substituent of the acetylene have been investigated. Since the acetylene is acting as the enophile, the methyl substituent retards the reaction while the carbomethoxy group significantly accelerates it. A terminal 1,6-enyne, **1**, cyclizes at 210 °C while the carbomethoxy enyne **2** cyclizes at 135 °C. The cyclization of 1,7-enynes has been shown to be slow, typically requiring temperatures 100 °C higher than the corresponding 1,6-enyne. The acetylene **10** activated by both ketone and a carbomethoxy group cyclizes cleanly at 90 °C.

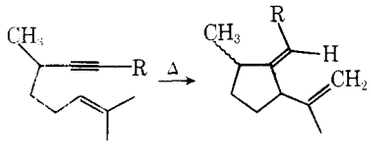
The intramolecular ene reaction of 1,6-enynes (eq 1) has recently been shown to be a useful method for the synthesis of complex molecules,[1] including chiral acetic acid[1h] and prostaglandins.[1i] For terminal acetylenes this reaction typically takes place in 1–5 h at 220 °C. In this intramolecular ene reaction the triple bond is functioning as the enophile so that electron-withdrawing substituents on the acetylene should



(1)

accelerate the rate of the ene reaction while electron-donating or bulky substituents on the acetylene should retard the reaction. We were interested in examining the magnitude of these effects and the extension of this ene reaction to 1,7- and 1,8-enynes. We report here that the addition of electron-withdrawing substituents to 1,6- and 1,7-enynes drastically lowers the temperature required for the intramolecular ene reaction and makes it a mild, general route for the formation of both five- and six-membered rings.

Enynes **1**–**3** were chosen for initial study because of their accessibility from the noraldehyde using the procedure of



1, R = H
2, R = CO_2CH_3
3, R = CH_3

4, R = H
5, R = CO_2CH_3
6, R = CH_3

Corey and Fuchs.[2] Reaction of 2,6-dimethyl-5-heptenal[3] with dibromomethylenetriphenylphosphorane affords 1,1-dibromo-3,7-dimethyl-1,6-octadiene. Treatment of this dibromide with 2 equiv of butyllithium yields the lithium salt of 3,7-dimethyl-6-octen-1-yne.[2] Addition of water, methyl chloroformate, or methyl iodide yields **1**,[4] **2**, or **3**, respectively. Pyrolysis of **1** in toluene for 62 h at 210 °C gives the ene adduct **4** in greater than 95% yield as a ca. 1:1 mixture of diastereomers. These conditions are similar to those reported for similar systems.[1] Adduct **4** contains the skeleton of the iridoid monoterpenes with appropriate functionality for conversion to a variety of iridodiols.[5] Enyne **3**, a methyl acetylene, cyclizes more slowly than **1**. Pyrolysis of **3** for 48 h at 225 °C gives 15% conversion to **6**. At higher temperatures or longer reaction times a variety of unidentified products are formed. A previous study has shown that *trans*-6-octen-1-yne (**7**) cyclizes 5.7 times faster than the homologous methylacetylene, *trans*-7-nonen-2-yne (**8**), at 382 °C in the vapor phase.[1b,1c] While these results are not strictly comparable to our solution studies, they are consistent with our results. Huntsman found that the terminal acetylene **7** cyclizes cleanly to the expected ene adduct, while the methyl acetylene **8** gives two products. The expected ene adduct is obtained in 80% yield and 2-ethyl-1-vinylidenecyclopentane (**9**) is formed in 10% yield. The allene **9** is derived from the double bond functioning as the enophile. *cis*-7-Nonen-2-yne gives only **9** and recovered starting material.[1b,cc]

Substitution of the terminal hydrogen of **1** with a carbomethoxy group was expected to lower the temperature required for the ene reaction. Pyrolysis of the alkenynoate **2** for 24 h at 135 °C results in conversion to the ene adduct **5** in

0022-3263/78/1943-2161$01.00/0