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ACID-CATALYZED CYCLOAROMATIZATION OF ENEDIYNE MODEL COMPOUNDS *VIA* ENYNE-ALLENE INTERMEDIATES

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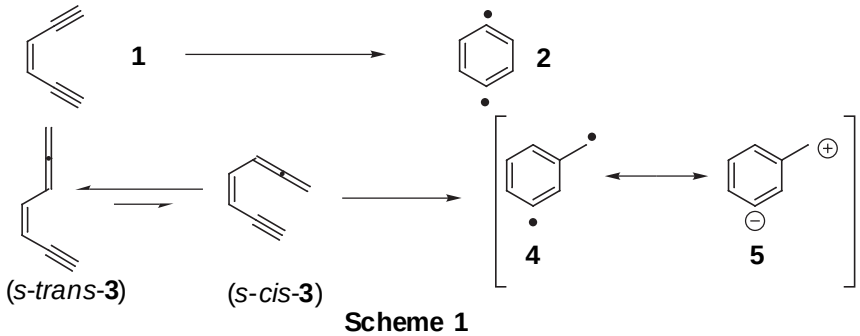
This paper is dedicated to Professor Shô Itô on the occasion of his 77th birthday.

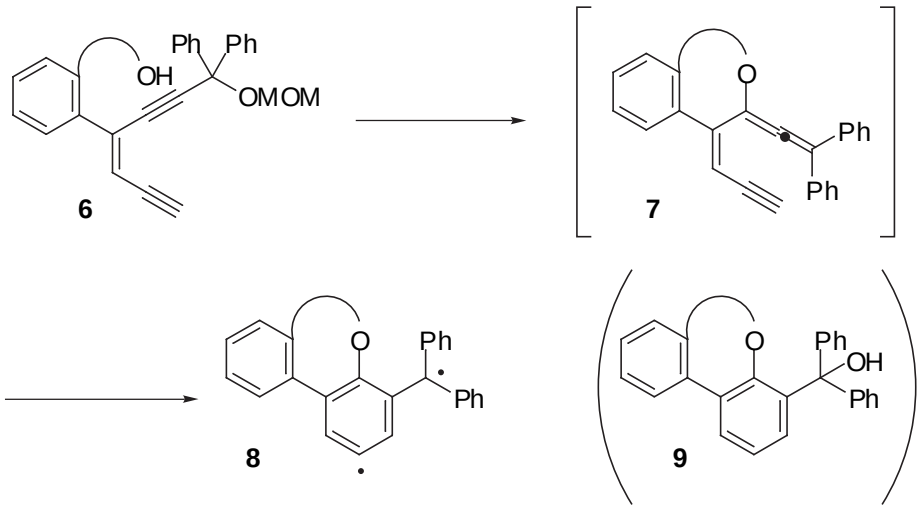
Abstract- The synthesis of enediyne models which produce dehydrotoluene diradicals preferentially under acidic conditions by means of intramolecular participation of the carboxylic acid is described. To diminish an ionic character of diradicals, an electron-withdrawing group was introduced into the radical-forming carbon of the substrate.

Since a number of natural products incorporating a (*Z*)-hex-3-ene-1,5-diyne and possessing anticancer activity were discovered, the synthesis of the natural products and the simplified analogues has been pursued.[1] Simple (*Z*)-1,2,4-heptatriene-6-ynes, which undergo cycloaromatization to produce reactive dehydrotoluene diradicals (Myers-Saito-type cyclization, Scheme 1, **3** → **4**),[2] have also been investigated as chemical models of the potent antitumor antibiotics neocarzinostatin and related drugs.[1] While the rearrangement of an acyclic (*Z*)-hex-3-ene-1,5-diyne (**1**) to a 1,4-didehydrobenzene diradical (**2**) (Bergman-Masamune-type cyclization, Scheme 1, **1** → **2**) requires thermal activation, the cycloaromatization of (*Z*)-1,2,4-heptatrien-6-yne (**3**) derivatives proceeds under relatively mild conditions.[2] However, the reaction of acyclic enyne-allene derivatives requires higher temperature,[2] because the *s-trans* conformer is generally more stable than the *s-cis* conformer which is indispensable for this reaction (Scheme 1).[3]



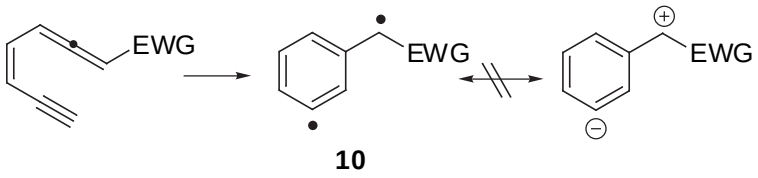
Scheme 1

In the previous paper, we reported that the *cis*-enediyne derivative (**6**) generates the dehydrotoluene diradical (**8**) *via* the fixed *s-cis*-enyne-allene intermediate (**7**) by means of intramolecular triggering action of the hydroxy group under acidic conditions (Scheme 2).[4]



Scheme 2

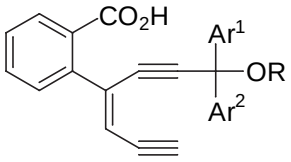
After the publication of the above report, we isolated a small amount of by-product (**9**) from the reaction mixture. The production of **9** suggested the ionic character of the diradical (**8**).[5] In contrast to diradicals such as **2**, the diradicals such as **4** are known to have an ionic character in a protic solvent. This nature is thought to reduce their DNA damaging ability.[6] In this communication, we describe the synthesis and evaluation of enediyne models which produce dehydrotoluene diradicals (**10**) having electron-withdrawing groups in benzylic position to enhance the diradical character of **8** (Scheme 3).



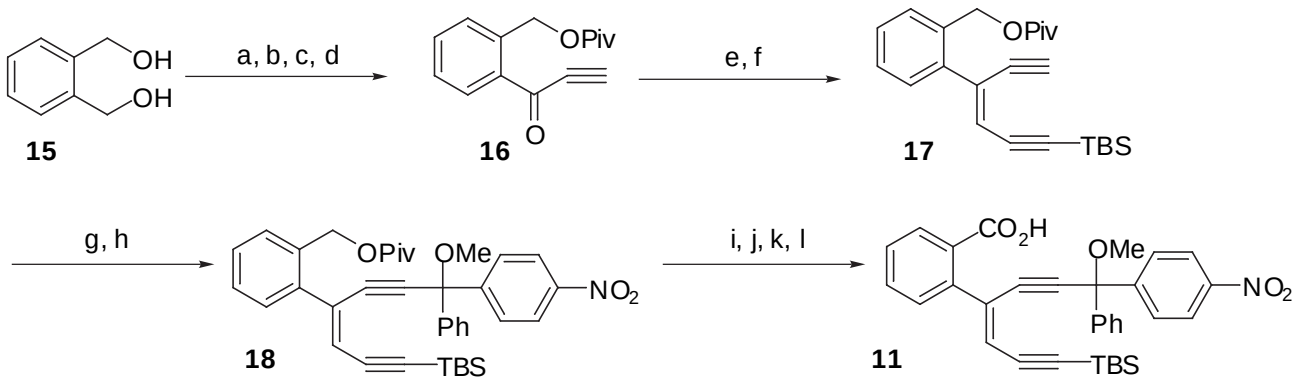
Scheme 3

For this purpose, the *p*-nitrophenyl derivatives (**11**) and (**12**), and compounds (**13**) and (**14**) as reference for the evaluation, were prepared. Typically, the synthesis of **11** is described (Scheme 4). Commercially available 1,2-benzenedimethanol (**15**) was converted into a monopivaloyl ester and then oxidized to give the aldehyde. Condensation of the aldehyde with acetylenemagnesium bromide followed by oxidation of the resulting alcohol gave the ethynyl ketone (**16**). The ketone (**16**) was condensed with 3-bromo-1-*tert*-butyldimethylsilyl-1-propyne[7] in the presence of zinc to provide the *tert* alcohol, which upon dehydration afforded enediyne (**17**) as a single isomer. The acetylide produced from **17** was reacted with *p*-

nitrobenzophenone to afford the alcohol, which was methylated to give **18**. Transformation of **18** into **11** was effected by a four-step sequence: (1) reduction of the pivaloyl ester; (2) oxidation of the alcohol to aldehyde; (3) oxidation of the aldehyde to carboxylic acid; (4) desilylation. The resulting enediynes are found to be relatively unstable at room temperature.



11: Ar^1 = phenyl, Ar^2 = *p*-nitrophenyl, R = methyl
12: Ar^1 = phenyl, Ar^2 = *p*-nitrophenyl, R = acetyl
13: Ar^1 = Ar^2 = phenyl, R = methyl
14: Ar^1 = phenyl, Ar^2 = *p*-methoxyphenyl, R = methyl



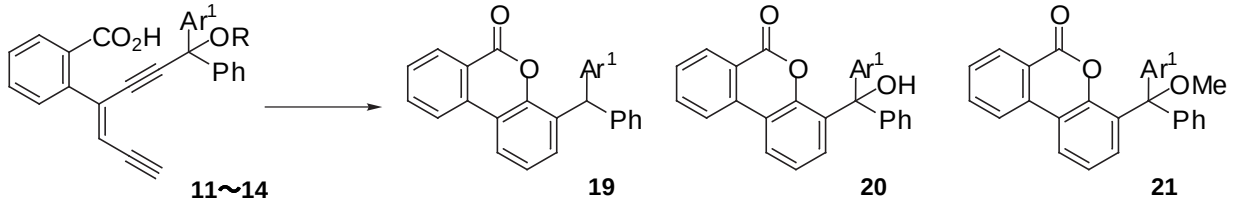
(a) NaH, PivCl, THF, 65%; (b) PDC, CH_2Cl_2, 79%; (c) HC≡CMgBr, THF; (d) CrO_3 , H_2SO_4, acetone, 60% (2 Steps); (e) TBSC≡CCH_2Br, Zn, THF, 45%; (f) MsCl, Et_3N, CH_2Cl_2, 74%; (g) EtMgBr, 4-nitrobenzophenone, 45%; (h) Me_2SO_4, NaOH, tetrabutylammonium iodide, C_6H_6-H_2O, 78%; (i) $LiEt_3BH$, THF, 72%; (j) PDC, CH_2Cl_2, 85%; (k) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *tert*-BuOH-H_2O, 60%; (l) TBAF, THF, 94%.

Scheme 4

Cycloaromatization reactions of the synthesized enediynes (**11**-**14**) were performed in the presence of trifluoroacetic acid (TFA) and 1,4-cyclohexadiene (1,4-CHD) (50 equiv.) at 37˚C, and the results are summarized in Table. The products isolated from the crude reaction mixture were fully characterized as **19**-**21** by means of the spectroscopic analysis. During the reaction time, the substrate, products (**19**-**21**), and polar substances (probably polymerized products) were detected on TLC, and the intermediate corresponding to enyne-allene could not be detected by ^{1}H NMR. Therefore the rate of reaction is most likely dependent on the δ-lactone formation step. Because of the slow reaction of *p*-nitrophenyl derivative (**11**) (entries 1, 5), the reaction of compounds (**12**) having an acetoxy leaving group was also examined (entries 2, 6). Among the products, **19** is apparently formed from the diradical intermediate (**4**) by the abstraction of the hydrogen radical from 1,4-CHD. Products (**20**) and (**21**) must be formed by ionic trapping of diradicals by the solvent MeOH (MeOH cleaved from the substrate for entry 3) or water adventitiously contaminated in the solvent. As the tendency of electron-withdrawing of the Ar group increases, the zwitterionic character of diradicals is expected to be diminished, even in MeOH solution.

In fact, the product ratio of **19** compared with **20** and **21** was in the order of **11**, **12**>**13**>**14** for the reaction both in the benzene and MeOH.

Table Cycloaromatization of enediynes under acidic conditions by means of intramolecular participation of the carboxylic acid.[a]



11∼**14** **19** **20** **21**

entry	Substrate	Ar^1	R	Solvent	Additive	Reaction time	Yield (%)	Product ratio (**19:20:21**)		
1	**11**	*p*-NO_2-C_6H_4	Me	Benzene	3.0%(V/V) TFA	2 h	48	85	15	0
2	**12**	*p*-NO_2-C_6H_4	Ac	Benzene	0.3%(V/V) TFA	15 h	43	91	9	0
3	**13**	Ph	Me	Benzene	0.3%(V/V) TFA	25 min	54	78	14	8
4	**14**	*p*-MeO-C_6H_4	Me	Benzene	0.3%(V/V) TFA	15 min	54	44	37	21
5	**11**	*p*-NO_2-C_6H_4	Me	MeOH	3.0%(V/V) TFA	9 h	0 [b]	-	-	-
6	**12**	*p*-NO_2-C_6H_4	Ac	MeOH	3.0%(V/V) TFA	9 h	22	83	0	17
7	**13**	Ph	Me	MeOH	0.3%(V/V) TFA	4 h	45	15	0	85
8	**14**	*p*-MeO-C_6H_4	Me	MeOH	0.3%(V/V) TFA	9 h	67	10	86	4

a) Each experiment was performed at 37˚C in the presence of 1,4-cyclohexadiene. b) 60% recovery of substrate.

In conclusion, we demonstrate the synthesis of enediyne models, which produce dehydrotoluene diradicals (Type-**4**) preferentially, by means of introduction of an electron-withdrawing group into the benzylic position (Type-**10**) to suppress the zwitterionic contribution (Type-**5**). The design of molecules having a proper combination of an electron-withdrawing group and a leaving group is necessary for further development. Studies on the analogues of this class of compounds and development of bio-active enediynes are continuing.

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8. Selected data; **19** (Ar^1=Ph, Ar^2=*p*-NO_2-C_6H_4): Yellow needles; mp 179-183 ˚C(hexane-ether); ^{1}H-NMR (300 MHz, $CDCl_3$): 8.37 (1H, dd, *J*=8.0 and 1.0), 8.16 (1H, t, *J* =7.5), 8.15 (2H, d, *J* =8.0), 8.03 (1H, dd, *J* =8.0 and 1.0), 7.83 (1H, ddd, *J* =8.0, 7.5, and 1.0), 7.59 (1H, ddd, *J* =8.0, 7.5, and 1.0), 7.40-7.25 (6H, m), 7.15 (2H, d, *J* =8.0), 7.07 (1H, dd, *J* =7.5 and 1.0), 6.35 (1H, s); IR ($CHCl_3$) 3019, 1738, and 1606 cm^{-1}; MS(EI): m/z calcd for $C_{26}H_{17}NO_4$ (M^+): 407.1157. found: 407.1140. **20** (Ar^1=Ph, Ar^2=*p*-NO_2- C_6H_4): Yellow powder; mp 118 ˚C (hexane-ether); ^{1}H-NMR (400 MHz, $CDCl_3$): 8.31 (1H, d, *J* =8.0), 8.19 (2H, d, *J* =8.8), 8.18 (1H, d, *J* =8.0), 8.11 (1H, d, *J* =8.0), 7.86 (1H, t, *J* =8.0), 7.60 (1H, t, J=8.0), 7.54 (2H, d, *J* =8.8), 7.45-7.20 (6H, m), 6.80 (1H, d, *J* =8.0), 4.80 (1H, br s); IR ($CHCl_3$) 3579, 2928, and 1742cm^{-1}; MS(EI): calcd for $C_{26}H_{17}NO_5$ (M^+): 423.1106. found: 423.1072. **21** (Ar^1=Ph, Ar^2=*p*-NO_2-C_6H_4): Yellow powder; mp 210 ˚C (decomp, hexane-ether), ^{1}H-NMR (300 MHz, $CDCl_3$): 8.24 (1H, dd, *J* =8.0 and 0.5), 8.16 (2H, d, *J* =9.0), 8.12 (1H, dd, *J* =8.0 and 1.0), 8.10 (1H, dd, *J* =8.0 and 1.0), 8.07 (1H, dd, *J* =8.0 and 0.5), 7.87 (2H, d, *J* =9.0), 7.79 (1H, dt, *J* =8.0 and 0.5), 7.53-7.54 (2H, m), 7.45 (1H, t, *J* =8.0), 7.40-7.30 (3H, m), 3.06 (3H, s); IR ($CHCl_3$) 2984, 1745, and 1474 cm^{-1}; MS(EI): m/z calcd for $C_{27}H_{19}NO_5$(M^+): 437.1263. found: 437.1272. **19** (Ar^1=Ar^2=Ph): Analytical data cited in reference 4 were found to be incorrect. The correct data are as follows; Colorless needles; mp 174-176 ˚C (hexane-ether); ^{1}H-NMR (400 MHz, $CDCl_3$): 8.35 (1H, dd, *J* =8.0 and 1.0), 8.11 (1H, d, *J* =8.0), 7.96 (1H, dd, *J* =8.0 and 1.0), 7.78 (1H, dt, *J* =8.0 and 1.0), 7.54 (1H, t, *J* =8.0), 7.40-7.16 (11H, m), 7.12 (1H, dd, *J* =7.0 and 1.0), 6.29 (1H, s); IR ($CHCl_3$): 3020, 1736, and 1614 cm^{-1}; MS(EI): m/z calcd for $C_{26}H_{18}O_2$: 362.1207(M^+). found: 362.1392. **20 (**Ar^1=Ar^2=Ph**):** Yellow needles; mp 220 ˚C (decomp, hexane-ether); ^{1}H-NMR (300 MHz, $CDCl_3$): 8.31 (1H, dd, *J* =8.0 and 1.0), 8.15 (1H, d, *J* =8.0), 8.06 (1H, dd, *J* =8.0 and 1.5), 7.83 (1H, ddd, *J* =8.5, 8.0, and 1.5), 7.57 (1H, ddd, *J* =8.5, 8.0, and 1.0), 7.40-7.25 (10H, m), 7.19 (1H, t, *J* =8.0), 6.82 (1H, dd, *J* =8.0 and 1.5), 4.74 (1H, br s); IR (KBr): 3652, 3524, 3020, and 1729 cm^{-1}; MS (EI): m/z calcd for $C_{26}H_{18}O_3$ (M^+): 378.1256. found: 378.1266. **21** (Ar^1=Ar^2=Ph): Colorless needles; mp 215 ˚C (decomp, hexane-ether); ^{1}H-NMR (300 MHz, $CDCl_3$): 8.22 (1H, dd, *J* =8.0 and 1.0), 8.18 (1H, dd, *J* =7.5 and 1.0), 8.07 (1H, dd, *J* =8.0 and 1.0), 8.01 (1H, dd, *J* =8.0 and 1.0), 7.75 (1H, ddd, *J* =8.0, 7.5, and 1.0), 7.65-7.55 (3H, m), 7.48 (1H, dt, *J* =7.5 and 1.0), 7.42 (1H, t, *J* =8.0), 7.37-7.20 (7H, m), 3.04 (3H, s); IR

($CHCl_3$): 3033, 2932, 1735, 1613, and 1222 cm^{-1}; MS (EI): calcd for $C_{27}H_{20}O_3$ (M^+): 392.1412. found: 392.1415. **19** (Ar^1=Ph, Ar^2=*p*-MeO-C_6H_4): Colorless needles; mp 178-180 ˚C (hexane-ether); ^{1}H-NMR (300 MHz, $CDCl_3$): 8.37 (1H, d, *J* =8.0), 8.14 (1H, d, *J* =8.0), 7.98 (1H, d, *J* =8.0), 7.81 (1H, t, *J* =8.0), 7.56 (1H, t, *J* =8.0), 7.26 (1H, t, *J* =8.0), 7.40-7.12 (9H, m) 7.08 (4H, d, *J* =8.4), 6.83 (2H, d, *J* =9.0), 6.24 (1H, s), 3.78 (3H, s); IR (CCl_4): 3019, 1746, and 1510 cm^{-1}; MS (EI): m/z calcd for $C_{27}H_{20}O_3$(M^+): 392.1412. found: 392.1424. **20** (Ar^1=Ph, Ar^2=*p*-MeO-C_6H_4): colorless needles; mp 219-220 ˚C (hexane-ether); ^{1}H-NMR (300 MHz, $CDCl_3$): 8.31 (1H, d, *J* =8.0), 8.15 (1H, d, *J* =8.0), 8.05 (1H, d, *J* =8.0), 7.83 (1H, t, *J* =8.0), 7.57 (1H, t, *J* =8.0), 7.30-7.10 (8H, m), 6.85 (3H, m), 4.70 (1H, br s), 3.81 (3H, s); IR (CCl_4): 3577, 2935, and 1752cm^{-1}; MS (EI): m/z calcd for $C_{27}H_{20}O_4$(M^+): 408.1361. found: 408.1379. **21** (Ar^1=Ph, Ar^2=*p*-MeO-C_6H_4) Colorless needles; mp 131 ˚C (hexane-ether); ^{1}H-NMR(300 MHz, $CDCl_3$): 8.23 (1H, d, *J* =8.0), 8.18 (1H, dd, *J* =8.0 and 1.0), 8.08 (1H, d, *J* =8.0), 8.01 (1H, dd, *J* =8.0 and 1.0), 7.75 (1H, dt, *J* =8.0 and 1.0), 7.61 (2H, d, *J* =8.5), 7.51 (3H, m), 7.41 (1H, t, *J* =8.0), 7.40-7.21 (3H, m), 6.84 (2H, d, *J* =8.5), 3.78 (3H, s), 3.02 (3H, s); IR (CCl_4): 2912, 1746, and 1510 cm^{-1}; MS(EI): m/z calcd for $C_{28}H_{22}O_4$(M^+): 422.1518. found: 422.1512.