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Cycloaromatization of a Non-Conjugated Polyenyne System: Synthesis of 5*H*-Benzo[*d*]fluoreno[3,2-*b*]pyrans via Diradicals Generated from 1-[2-{4-(2-Alkoxymethylphenyl)butan-1,3-diynyl}]phenylpentan-2,4-diyn-1-ols and Trapping Evidence for the 1,2-Didehydrobenzene Diradical

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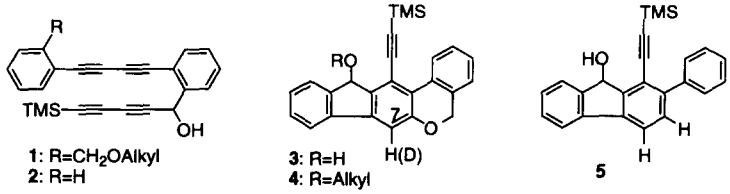
Abstract: Non-conjugated tetraynes **1** undergo thermal intramolecular cyclization to non-benzenoid diradicals (**23**) followed by radical cycloaromatization at 25 ℃ to provide 7-dehydro-5*H*-benzo[*d*]fluoreno[3,2-*b*]pyran monoradical (**24**) and alkyl radicals (**25**). Hydrogen abstraction of **24** gives 5*H*-benzo[*d*]fluoreno[3,2-*b*]pyrans (**3**) which are converted to **4** by reaction with **25**. On the other hand, **2** gives 5*H*-fluorenol (**5**), indicating the formation of 1,2-didehydrobenzene diradical intermediates (**28** and **29**). These radicals are trapped as the corresponding Diels-Alder-type products by reaction with an aromatic diene, anthracene. © 1997 Elsevier Science Ltd.

The cyclization of conjugated polyenyne systems such as enediyne (the Bergman cyclization), enyne-allene (the Saito-Myers cyclization) and enyne-ketene (the Moore cyclization) forms arene diradicals with DNA-cleaving activity.[1] While much effort and the main emphasis of recent investigation have been focused on using these diradical-forming methods for DNA cleavage,[2] Grissom and Calkins first utilized the Bergman cycloaromatization of 1,2-diethynylbenzene derivatives as a means of generating a radical for carrying out a subsequent radical ring annulation reaction to give 3,4-dihydrobenz[*e*]indenes.[3,4] Since then, there have been reported many examples using the resulting carbon radicals for the construction of multicyclic systems.[1] We herein report synthesis of 5*H*-fluorenol derivatives (**3**, **4** and **5**) by the tandem radical cyclization of non-conjugated acyclic tetraynes, 1-[2-(butan-1,3-diynyl)phenyl]pentan-2,4-diyn-1-ols (**1** and **2**) having the (*Z*)-4-hepten-1,6-diyn-3-ol subunit[5] as a blocking device. Furthermore, we have obtained evidence that 1,2-didehydrobenzene diradicals (**28** and **29**) are true intermediates with a lifetime long enough to allow trapping by external reagents.



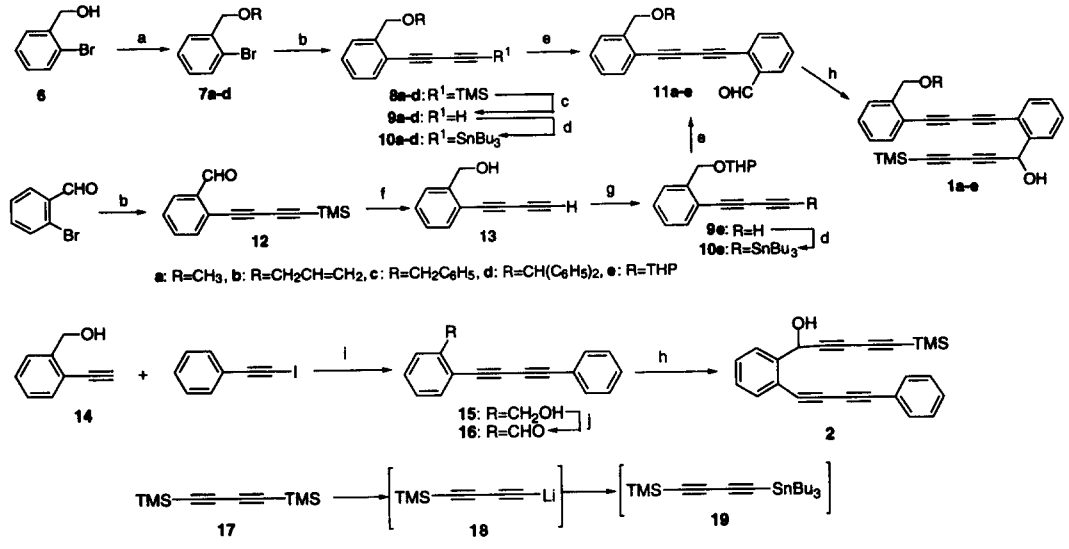
1: R=$CH_2OAlkyl$
2: R=H

3: R=H
4: R=Alkyl
H(D)

5

Scheme 1 shows an outline for preparation of the key alcohol derivatives **1** and **2**. Intermediates (**11** and **16**) were easily accessed in several high-yielding steps using commercially available starting materials according to the methods described in the literature. Compounds (**11** and **16**) were allowed to react with **18** prepared by the method described in the literature[6] to give the corresponding alcohol derivatives (**1** and **2**)[7] in good yields. However, as **1** and **2** are cyclized gradually to the corresponding 5*H*-fluorenol derivatives (**3**, **4** and **5**) at room temperature, isolation, purification and storage of these compounds should be done with care keeping the temperature below 0 ℃ to avoid the following cyclization.

Scheme 1.



Reaction conditions and Reagents: a) NaH or KO^{t}Bu, RBr (or RI), Bu_4NI, C_6H_6 or THF, r.t., 0.5-1 h; b) **19**, $PdCl_2(PPh_3)_2$, Toluene, 80-110 °C; c) K_2CO_3, MeOH, 0 °C, 30 min; d) Bu_3SnCl, $[(CH_3)_2CH]_2NH$, 0 °C, 30 min, then added **9**, r.t., 24 h; e) 2-Bromobenzaldehyde, $PdCl_2(PPh_3)_2$, Toluene, 80-110 °C, 2h; f) $NaBH_4$, MeOH, 0 °C,10 min, then added K_2CO_3, 0 °C, 30 min; g) DHP, *p*-TosOH, CH_2Cl_2, r.t., 1 h; h) **18**, Ether, r.t 30 min; i) CuI, Pyrrolidine, -20 °C; j) IBX, DMSO, r.t.

Compound **1e** in dry benzene was allowed to stand for 48 h at 25 ℃ with stirring. Removal of the solvent gave a yellow oily residue which was purified by silica gel chromatography with benzene as an eluent to give 5*H*-benzo[*d*]fluoreno[3,2-*b*]pyran (**3**). Reaction of **1e** in *iso*propanol-d_8 solution gave the compound deuterated at the 7 position of **3** in 17% yield. Treatment of **1a**, **1b** and **1c** in benzene solution under similar conditions gave **3** along with **4a**, **4b**, **4c**. Reaction of **1d** under similar conditions gave **3** and **4d** along with a small amount of benzophenone. Results are shown in Table 1.

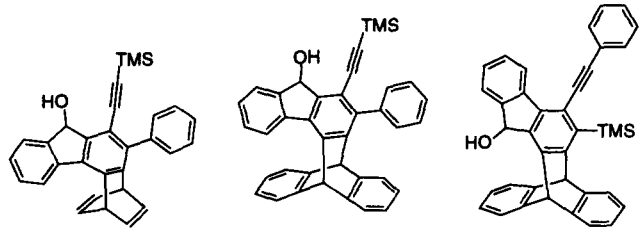
Table 1. Reaction of **1**

Substrate	Conditions[a] Time (h)	Product (%)[b] **3**		
1a	48	45	**4a**: 38	
1b	72	66	**4b**: 6.3	
1c	72	53	**4c**: 14	
1d	72	40	**4d**: 3.3	benzophenone: 6.0
1e	48	52	**4e**: nd[c]	

a) Reaction was carried out in benzene at 25 °C with stirring.
b) Isolated yield. c) nd: not detected

When a solution of **2** in benzene was stirred for 72 h at 25 ℃ under argon atmosphere until **2** disappeared on silica gel TLC, **5**, after purification using the technique of gradient elution on silica gel with benzene and hexane, was obtained in 7% yield along with a Diels-Alder-product (**20**) in 6% yield, indicating that a 1,2-didehydrobenzene diradical will be formed. In order to confirm the formation of the radical, **2** in a (1:1) mixture of ether and THF was treated in the presence of ten equivalents of anthracene as a trapping reagent of

1,2-didehydrobenzene diradical for 72 h at 25 ℃ with vigorous stirring to give **21** in 72% yield along with its isomer **22** in 8% yield.

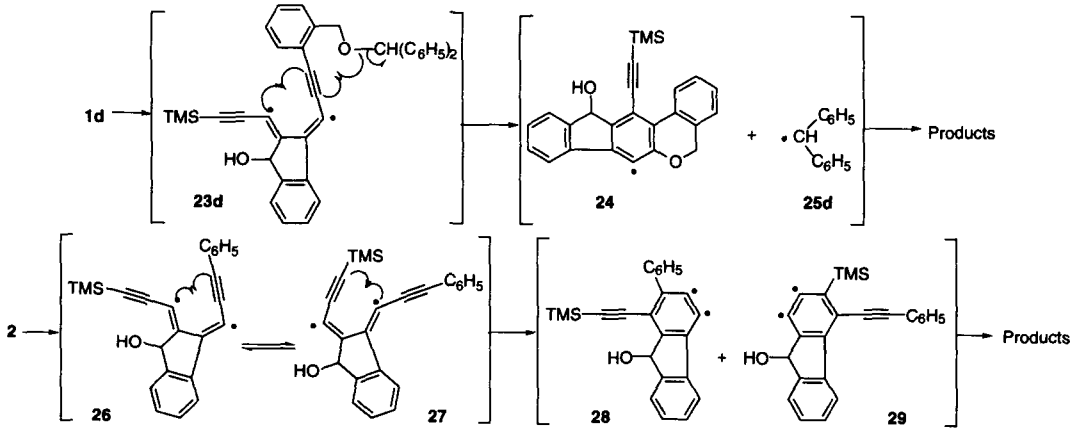


20 **21** **22**

The structure of **3**, **4**, **5** and the Diels-Alder products (**20**, **21**, **22**) was determined on the basis of spectral data and elementary analyses. Recrystallization of **3** from dichloromethane and *n*-hexane yielded yellow prisms with a monoclinic form, the structure of which was also confirmed by single crystal X-ray analysis.[8]

A plausible mechanism of the overall transformation is outlined in Scheme 2 for **1d** as a typical example. First, **1d** gives an outer-ring diradical, one of four configurational isomers (**23d**) generated by intramolecular cyclization. The diradical **23d** is transformed to 7-dehydro-5*H*-benzo[*d*]fluoreno[3,2-*b*]pyran monoradical (**24**) and diphenylmethyl radical (**25d**). The monoradical **24** abstracts the hydrogen atom from its donor to give **3** which is converted to **4d** by reaction with the radical **25d**. Reaction of **25d** with oxygen gives benzophenone. On the other hand, **2** gives two configurational isomers (**26** and **27**) which are transformed to 1,2-didehydrobenzene diradicals (**28** and **29**). These diradicals are converted to the final products.

Scheme 2.



In conclusion, we have introduced the tandem radical cyclization of non-conjugated tetrayne derivatives (**1** and **2**) having the (*Z*)-4-hepten-1,6-diyn-3-ol subunit as a blocking device which can be readily synthesized from commercially available starting materials. In contrast to the tandem enediyne- and enyne allene-radical cyclizations via the formation of the respective 1,4-didehydrobenzene diradical and 3,α-didehydrotoluene diradical, the tandem radical cyclization of **1** occurs at room temperature, forming a radical pair of monodehydrobenzene radical and alkyl radical. Compound **2** gives 1,2-didehydrobenzene diradicals. Results

from this work provide guidelines for the design of potential DNA damaging agents, and the advantage of permitting synthesis of polycyclic heterocycles. Additionally, the question why **2** easily generates the reactive 1,2-didehydrobenzene diradical species (**28** and **29**) of high energy level reamins to be solved. Further studies on the mechanism and application of this novel radical-forming reaction are underway.

Acknowledgments

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7. All new compounds in this paper gave satisfactory IR, NMR, Mass spectra and elementary analyses. Selected physical data are as follows. **1d**: Yellow viscous oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72-7.69 (m, 1 H), 7.57-7.51(m, 3 H), 7.45-7.24 (m, 4 H), 5.95 (d, *J*=5.4 Hz, 1 H), 4.96 (d, *J*=12.9 Hz, 1 H), 4.83 (t, *J*=3.4 Hz, 1 H), 4.72 (d, *J*=12.9 Hz, 1 H), 4.01-3.95 (m, 1 H), 3.64-3.59 (m, 1 H), 2.77 (d, *J*=5.6 Hz, 1 H), 1.96-1.56 (m, 6 H), 0.19 (s, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.44 , 141.95, 133.52, 133.19, 129.83, 129.52 (x3), 127.75, 127.32, 127.00, 120.27, 120.13, 98.58, 88.65, 87.17, 81.02, 79.21, 79.07, 77.72, 76.33, 71.50, 67.35, 63.07, 62.15, 30.52, 25.47, 19.30, -0.53. MS (FAB) m/z 353 [(M+H) $^+$]. **3**: Yellow prisms, mp 63.6 °C (CH_2Cl_2-*n*-hexane). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.78-8.76 (m, 1 H), 7.70-7.68 (m, 1 H), 7.63-7.61 (m, 1 H), 7.43-7.31 (m, 5 H), 7.30 (s, 1 H), 7.23-7.21 (m, 1 H), 5.84 (d, *J*= 3.3 Hz, 1 H), 5.05 (d, *J*= 12.9 Hz, 1 H), 5.04 (d, *J*= 12.9 Hz, 1 H), 3.38 (d, *J*= 3.4 Hz, 1 H), 0.36 (s, 9 H); ^{13}C-NMR (100 MHz, $CDCl_3$) d. 156.80, 145.11, 143.62, 140.94, 138.91, 132.43, 129.67, 129.04, 128.38, 127.88, 127.65, 125.40, 125.24, 124.45, 123.25, 120.25, 115.46, 110.09, 104.44, 102.78, 74.46,69.01, -0.36. MS (FAB) m/z 382 (M^+), 365 [(M-OH) $^+$]. *Anal.* Calcd. for $C_{25}H_{22}O_2Si$: C, 78.43; H, 5.79%. Found: C, 78.47; H, 5.52 %.
8. Crystallographic parameters of **3**: Crystal system monoclinic; Cell parameter a=33.367(2)Å, b=6.419(5)Å, c=20.164(2)Å, β=105.045(7)°, V=4170(2)Å^3; Space group C2/c (#15); Z value 8 ; D_{calc} 1.218 g/cm^3; R;R_w 0.094 ; 0.095.

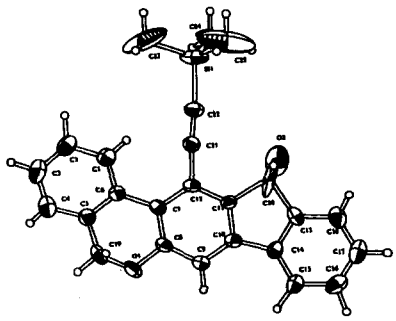

Fig. 1. Molecular structure of **3**

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