Synthesis and Inclusion Properties of 6,6′-Bi(benzo[*b*]fluoren-5-ol) Derivative by Cycloaromatization

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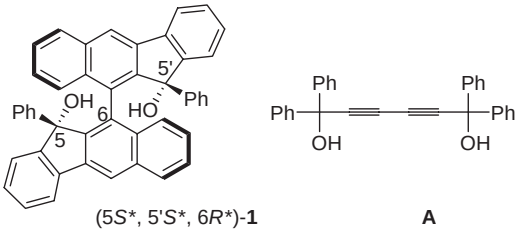
Aromatic non-conjugated tetraynes underwent step-by-step cycloaromatization to yield 6,6′-bi(benzo[*b*]fluoren-5-ol) derivative **1** via benzo[*b*]fluoren-5-ol derivatives. Treatment of compound **1** with a kind of organic guest compounds afforded crystalline inclusion compounds (clathrates).

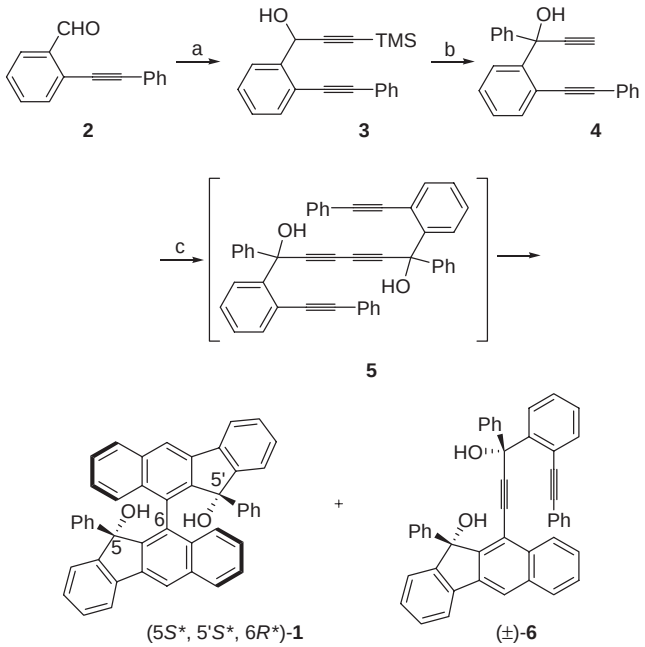
Benzo[*b*]fluorenes (BFs) have received considerable attention in the field of organic chemistry and medicinal chemistry. They are among the most fundamental intermediates for the synthesis of natural products possessing a tetracycline core such as kinobscurinone, stealthin C, kinamycin, and cysfluoretin.[1] A number of these natural products show Gram-positive and -negative antibacterial properties, and antitumor activity.[2] Recently, preparations of BFs as estrogen receptor antagonists have also been reported.[3] We have reported the synthesis of a series of polycyclic aromatic compounds, including BFs, by cycloaromatization of non-conjugated polyyne derivatives since 1997.[4] Two research groups reported the preparation of a benzo[*b*]fluorene core by cycloaromatization of non-conjugated benzodiynes[5] and benzotriynes[6] using our cyclization procedure. In the hope of further developing our procedure and discovering a new class of BFs, we newly designed 6,6′-bi(5-phenylbenzo-[*b*]fluoren-5-ol) derivative **1** in this study. Compound **1** was expected to possess inclusion properties because it possesses a double "diarylmethanol unit," which is characteristic of a series of wheel-and-axle-type host compounds with inclusion properties, such as **A** (Chart 1).[7] We herein describe the first synthesis of **1** by cycloaromatization of non-conjugated novel tetraynes, along with the inclusion properties.

In the first place, we planned to synthesize the target compound **1** by double cycloaromatization of tetrayne **5** (Scheme 1). Reaction of aldehyde **2**[8] with lithium salt of (trimethylsilyl)acetylene, obtained by treatment of (trimethylsilyl)-acetylene with *n*-butyllithium, gave alcohol **3** in a quantitative yield. *o*-Iodoxybenzoic acid (IBX) oxidation of **3** led to the formation of ketone derivative, followed by Grignard reaction of the resulting ketone with phenylmagnesium bromide (PhMgBr), and subsequent deprotection of the trimethylsilyl group gave non-conjugated diyne **4** in 98% yield in three steps. Dimerization of **4** for the synthesis of tetrayne **5**, which is a precursor of target compound **1**, under Hay's conditions yielded interesting results. The Hay's coupling[9] of **4** in the presence of tetramethylethylenediamine (TMEDA) and copper(I) iodide (CuI) in acetone under an oxygen atmosphere gave 6,6′-bi-(5-phenylbenzo[*b*]fluoren-5-ol) derivative **1** directly and mono-cycloaromatized product **6** in 23 and 18% yields, respectively, along with unchanged **4** in a recovery yield of 45%, without isolating tetrayne **5**. It is noteworthy that cycloaromatization of **6** gave a diastereomer of **1**, (5*S**, 5′*R**, 6*R**)-**1**, in 30% yield.



(5*S**, 5′*S**, 6*R**)-**1** **A**

Chart 1.



(5*S**, 5′*S**, 6*R**)-**1** (±)-**6**

Scheme 1. Cycloaromatization of non-conjugated tetraynes. *Reagents and conditions*: (a) *n*-BuLi, (trimethylsilyl)acetylene, THF, −78 °C. (b) (1) IBX, DMSO, rt; (2) PhMgBr, THF, 0 °C; (3) K_2CO_3, MeOH, 0 °C. (c) TMEDA, CuI, O_2, acetone, 45 °C.

We then examined the synthesis of **1** by the step-by-step cycloaromatization approach as shown in Scheme 2. Treatment of **3** with K_2CO_3 gave **8** in a quantitative yield. Protection of alcohol group of **8** with dihydropyran and subsequent iodonation of the acetylene terminus, followed by deprotection of tetrahydropyranyl group afforded **9** in 88% yield by three steps. Cross coupling reaction of **4** with **9** in the presence of CuI in pyrrolidine gave asymmetrical tetrayne **10** in 85% yield, along with 3% yield of the homo-coupling product of **4**. Cycloaromatization of **10** in acetone gave mono-benzo[*b*]fluoren-5-ol **11** in 55% yield as a mixture of diastereomers. IBX oxidation of **11** afforded ketone **12** in 88% yield. Grignard reaction of **12** with PhMgBr gave selectively alcohol **13** in 47% yield, which was found to be a diastereomer of **6** on the basis of ^{1}H NMR. This selectivity

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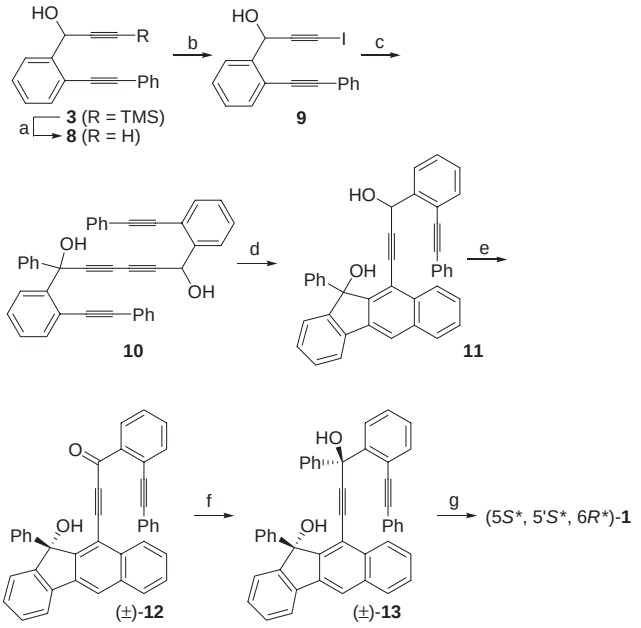

Scheme 2. Step-by-step cycloaromatization of non-conjugated tetrayne. *Reagents and conditions*: (a) K_2CO_3, MeOH, 0 °C. (b) (1) DHP, PPTS, CH_2Cl_2, rt; (2) MeLi, I_2, THF, −23 °C; (3) PPTS, MeOH, 55 °C. (c) **4**, CuI, O_2, pyrrolidine, −23 °C. (d) Acetone, −45 °C. (e) IBX, DMSO, rt. (f) PhMgBr, THF, 0 °C. (g) Benzene, 80 °C.

would be caused by chelation-control in the Grignard reaction of **12**. Finally, cycloaromatization of **13** in benzene led to the formation of **1** in 67% yield. All compounds obtained in this study were characterized by spectroscopy (NMR, IR, and FABMS) and elemental analysis.[10]

Among the many species of wheel-and-axle-type host compounds, molecules containing the hydroxyl group, especially the "diarylmethanol unit," are known to be effective for the formation of crystalline inclusion compounds (clathrates).[11] The inclusion behavior of compound **1** bearing a double diarylmethanol unit was estimated using a broad variety of guest compounds (Table 1). The results showed that compound **1** mainly favored clathrates in the 1:2 host/guest stoichiometric ratio, though a few examples of the formation of clathrates in the 1:1 ratio or 2:1 ratio were observed.[12]

In conclusion, we have demonstrated that step-by-step cycloaromatization of non-conjugated tetraynes proceeded smoothly to produce 6,6′-bi(5-phenylbenzo[*b*]fluoren-5-ol) derivative with inclusion properties. Further studies for the synthesis of a series of BFs and their detailed inclusion properties, including determination of crystal structure, are now in progress.

Table 1. Crystalline inclusion compounds of **1**[a]

CH_2Cl_2	DMSO	DMF	Et_3N	Pyridine	PhCHO
1:1	1:2	1:2	1:1	1:2	1:2
Acetone	Butan-2-one		CP[b]	Acetophenone	BP[c]
1:2	NT[d]		NT	1:2[e]	2:1[e]

[a]Host/guest stoichiometric ratios, which were determined by ^{1}H NMR. [b]Cyclopentanone. [c]Benzophenone. [d]Not detected. [e]Binding constants of acetophenone and BP were 3.64×10^3 and 4.29×10^3 M^{-1}, respectively.

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References and Notes

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10 Selected physical data are as follows. Compound **1**: Colorless prisms, mp 302.5–303.0 °C (from benzene–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 2H), 6.10 (d, 2H, $J = 8.3$ Hz), 6.44–6.52 (m, 10H), 6.59–6.62 (m, 2H), 7.04 (d, 2H, $J = 7.6$ Hz), 7.11–7.14 (m, 2H), 7.22–7.26 (m, 2H), 7.46 (d, 2H, $J = 7.6$ Hz), 7.71 (d, 2H, $J = 8.3$ Hz), 7.97 (d, 2H, $J = 7.6$ Hz), 8.24 (s, 2H) ppm. IR (KBr) ν 3270, 3045, 3020 cm^{-1}. FABMS (NBA) m/z 615 $[M + H]^+$. Anal. Calcd for $C_{46}H_{30}O_2$: C, 89.88; H, 4.92%. Found: C, 89.64; H, 5.11%. Compound **6**: Colorless powder, mp 153.5–154.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 1H), 3.51 (s, 1H), 7.11–7.29 (m, 15H), 7.33–7.51 (m, 7H), 7.64 (d, 1H, $J = 7.3$ Hz), 7.81 (d, 1H, $J = 7.6$ Hz), 7.89–7.94 (m, 2H), 8.14 (s, 1H), 8.29 (d, 1H, $J = 8.3$ Hz) ppm. IR (KBr) ν 3545, 3470, 3060, 3035, 2235, 2195 cm^{-1}. FABMS (NBA) m/z 615 $[M + H]^+$. Anal. Calcd for $C_{46}H_{30}O_2 \cdot 1/2H_2O$: C, 88.58; H, 5.01%. Found: C, 88.77; H, 4.78%.
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12 A typical method for the formation of clathrates: (Method A) A mixture of **1** and an excess amount of guest compound in ether was stirred at room temperature for 24 h. After addition of petroleum ether, the precipitates were collected and dried in vacuo. (Method B) Compound **1** was dissolved under heating in a minimum amount of guest compound. The resulting solution was allowed to stand overnight at room temperature, the precipitates which formed were collected and dried in vacuo. Selected physical data are as follows. Clathrate **1**·2DMSO: Colorless prisms. mp 300.0–301.0 °C (from DMSO). Anal. Calcd for $C_{50}H_{42}O_4S_2$: C, 77.89; H, 5.49%. Found: C, 77.88; H, 5.41%.

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