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AN APPROACH TO A 2-HYDROXY-3-PHENYLDIBENZOFURAN SKELETON BASED ON Rh(PPh₃)₃Cl-CATALYZED [2+2+2] CYCLOADDITION BETWEEN A 1-ETHYNYL-2-(ETHYNYLOXY)BENZENE AND AN (ALKOXYETHYNYL)BENZENE

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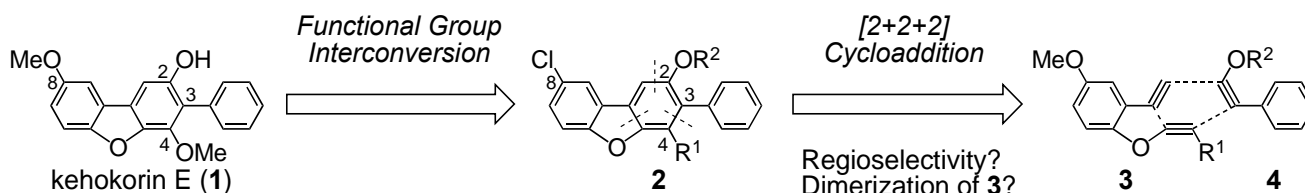
Dedicated to Prof. Dr. Kaoru Fuji on the occasion of his 80th Birthday

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Abstract – A Rh(PPh₃)₃Cl-catalyzed [2+2+2] cycloaddition of a 2-(trimethylsilylethynyl)-1-(ethynyloxy)benzene derivative (a 1,6-diyne unit) with an (alkoxyethynyl)benzene (an alkoxyacetylene unit) was studied for the construction of the 2-hydroxy-3-phenyldibenzofuran skeleton of kehokorin E. Although the dimerization of the 1,6-diyne unit was a serious problem in the initial trial, installation of a bulky substituent at the terminal of the ethynyloxy group of the 1,6-diyne unit was found to inhibit the dimerization to produce cycloadducts in good yield. It was also found that the use of a 2-hydroxypropan-2-yl group as the bulky group increased the ratio of the desired 2-alkoxy-3-phenyldibenzofuran isomer to a 3-alkoxy-2-phenyldibenzofuran isomer.

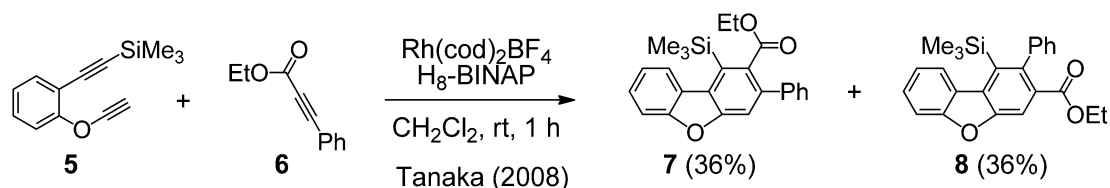
Naturally occurring 2-hydroxy-3-phenyldibenzofuran derivatives, such as kehokorins,¹ vialinin B,² and terrestrin E,³ are a rare class of natural products, of which the several members show bioactivity. Their characteristic structures attracted attention of chemists in view of the development of new synthetic strategies for them. The previous successful examples for the construction of the 2-hydroxy-3-phenyldibenzofuran skeleton were based on a common combination of Suzuki-Miyaura cross-coupling and Ullmann ether synthesis, which necessarily demanded three aryl components as starting materials.⁴ In the course of our project toward total synthesis of kehokorin E (**1**),^{1b} [2+2+2] cycloaddition between 1-ethynyl-2-(ethynyloxy)benzene and (alkoxyethynyl)benzene derivatives (**3** and **4**,

respectively) producing intermediate **2**, which would be converted to **1** by functional group interconversion, was designed as a key reaction for the two-component synthesis of the skeleton (Scheme 1). Here, the optimization of the [2+2+2] cycloaddition conditions to suppress undesired dimerization of **3** and to improve the yield of **2** is described.



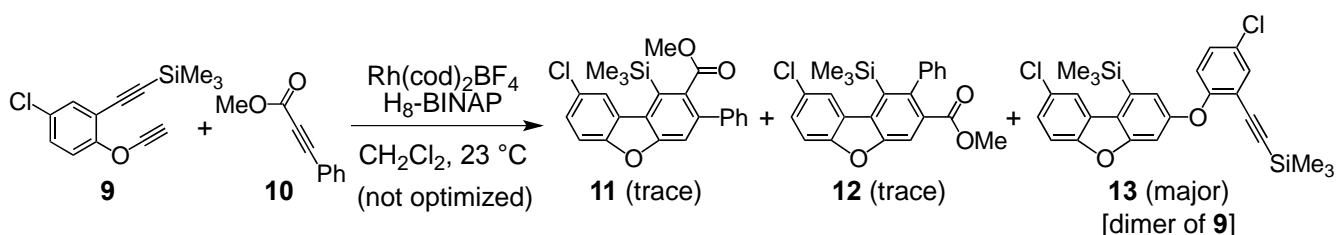
Scheme 1

For the synthesis of dibenzofuran by [2+2+2] cycloaddition, an effective, catalytic reaction with cationic Rh(I)/H₈-BINAP complex was reported by Tanaka (Scheme 2).⁵ Although low regioselectivity was shown, Tanaka's conditions were attractive in view of the facile synthesis of 3-phenyldibenzofurans.



Scheme 2

Initially, we applied the conditions to the reaction of **9**⁶ and **10** in a preliminary trial (Scheme 3). The desired products **11** and **12** were, however, obtained as minor components, while **13**, a dimer of **9**, was given as a major product. Although the failure may be due to our initial inexperience, which may cause insufficient complexation of Rh(cod)₂BF₄ with H₈-BINAP, it should be noted that the homo-[2+2+2] reaction of **9** was enhanced by such incomplete Rh-catalyst to produce **13**. This suggests that alkoxyacetylenes would be highly reactive in Rh-catalyzed [2+2+2] cycloaddition and that the [2+2+2] cycloaddition between a 3-oxahepta-1,6-diyne and an alkoxyacetylene would proceed even with a neutral Rh-catalyst such as Rh(PPh₃)₃Cl.⁷



Scheme 3

Accordingly, we designed the synthetic route to kehokorin E (**1**), having a 2-hydroxy-3-phenyldibenzofuran skeleton, from 1,6-diyne **3** and alkoxyacetylene **4**, as shown in Scheme 1. To realize the route, suppression of the dimerization of 1,6-diyne **3** was necessary, and, therefore, employment of a bulky group at the both ends of 1,6-diyne was planned for inhibiting the dimerization by steric congestion (Figure 1).

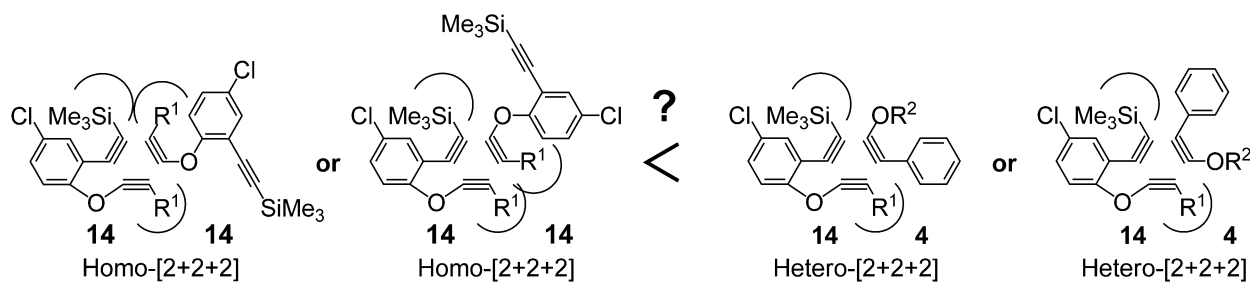
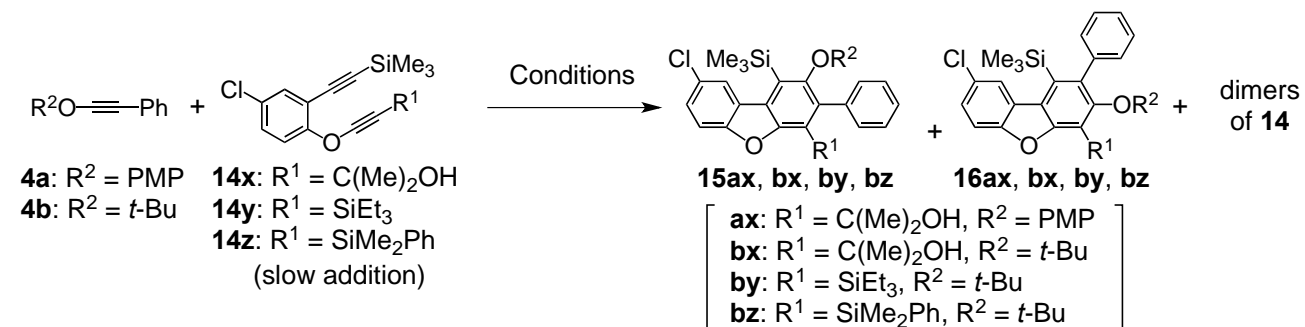


Figure 1

Consequently, 1,6-diyne **14**, having a trimethylsilyl group at the phenylacetylene moiety and a 2-hydroxypropan-2-yl group (**14x**) or a trialkylsilyl group (**14y** or **14z**) at the terminal of the alkoxyacetylene unit,⁸ was used for the optimization of the [2+2+2] cycloaddition with **4**. Selected results are shown in Table 1. First, the reaction of 4-methoxyphenoxyacetylene **4a**⁹ with 1,6-diyne **14x** was examined in the presence of Rh(PPh₃)₃Cl (14 mol%) in toluene under high dilution conditions by slow addition of **14x** using a syringe pump at ambient temperature (entry 1). Although the dimerization was inhibited, the hetero-[2+2+2] cycloaddition between **4a** and **14x** was slow and competed with the decomposition of substrates to give **15ax** and **16ax** in modest yields (13% and 7%, respectively). An increased amount of Rh(PPh₃)₃Cl (30 mol%) slightly improved the yields of **15ax** and **16ax** (entry 2). Heating to 40 °C also effected an enhancement of the reaction rate to give **15ax** and **16ax** in 20% and 11% yields, respectively (entry 3). When *tert*-butoxyacetylene **4b**¹⁰ was used instead of **4a**, the reactivity was significantly improved, and the reaction time was reduced to produce **15ax** and **16ax** in 25% and 8% yields, respectively (entry 4). The use of benzene as solvent gave the best result of yields and selectivity of cycloadducts (**15ax**: 52% and **16ax**: 14%) (entry 5).¹¹ Interestingly, the cycloaddition of 1,6-diyne **14y**, having a SiEt₃ group instead of the 2-hydroxypropan-2-yl group, with **4b** showed reverse regioselectivity under the same conditions to give **15by** and **16by** in 15% and 36% yields, respectively (entry 6). The reverse selectivity was also observed in the reaction of ethynyldimethylphenylsilane **14z** with **4b** affording **15bz** and **16bz** (16% and 36%, respectively) (entry 7). The effect of the substituents of the alkoxyacetylene unit of **14** on the regioselectivity is under investigation. Thus, Rh(PPh₃)₃Cl-catalyzed [2+2+2] cycloaddition between 1,6-diyne **14x**, having a 2-hydroxypropan-2-yl group at the terminal of

the alkoxyacetylene unit, and *tert*-butoxyacetylene **4b** under high dilution conditions successfully afforded 2-alkoxy-3-phenyldibenzofuran **15bx** as a major product without dimerization of **14x**.

Table 1. [2+2+2] Cycloaddition of 1,6-diynes with alkoxyacetylenes



Entry	4 (eq)	14	Rh(PPh ₃) ₃ Cl	Solvent	Temp.	Addition Period	Total Reaction Time	Yield 15	Yield 16	Dimers of 14
1	4a (1.0)	14x	14 mol%	toluene	22 °C	over 44 h	93 h	13% ^a	7% ^a	trace
2	4a (1.2)	14x	30 mol%	toluene	22 °C	over 17 h	66 h	17% ^a	12% ^a	trace
3	4a (1.4)	14x	15 mol%	toluene	40 °C	over 16 h	42 h	20% ^a	11% ^a	trace
4	4b (1.2)	14x	10 mol%	toluene	40 °C	over 5 h	15 h	27% ^b	8% ^b	trace
5	4b (1.6)	14x	12 mol%	benzene	40 °C	over 5 h	19 h	55% ^b	14% ^b	trace
6	4b (2.0)	14y	10 mol%	benzene	40 °C	over 8 h	16 h	15% ^c	36% ^c	trace
7	4b (3.8)	14z	15 mol%	benzene	40 °C	over 5 h	14 h	16% ^c	35% ^c	trace

(a) Isolated yield. (b) Calculated yield based on the result of the succeeding chemical conversion. (c) Calculated yield by NMR analysis.

In conclusion, a Rh(PPh₃)₃Cl-catalyzed [2+2+2] cycloaddition of a 2-(trimethylsilyloxy)-1-(ethynyl)benzene derivative (a 1,6-diyne unit) with an (alkoxyethynyl)benzene (an alkoxyacetylene unit) was studied for the construction of the 2-hydroxy-3-phenyldibenzofuran skeleton of kekokorin E (**1**). Although the dimerization of the 1,6-diyne unit was a serious problem in the initial trial, installation of a bulky substituent at the terminal of the ethynyloxy group of the 1,6-diyne unit was found to inhibit the dimerization to produce cycloadducts in good yield. It was also found that the use of a 2-hydroxypropan-2-yl group as the bulky group increased the ratio of the desired 2-alkoxy-3-phenyldibenzofuran isomer to a 3-alkoxy-2-phenyldibenzofuran isomer. Further studies toward the synthesis of kekokorin E (**1**) are in progress in this laboratory.

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11. A typical procedure for the [2+2+2] cycloaddition between **14** and **4**: To a mixture of **4b** (83.0 mg, 0.476 mmol) and Rh(PPh₃)₃Cl (33.2 mg, 0.0359 mmol) in anhydrous benzene (0.9 mL) was added a solution of **14x** (89.9 mg, 0.293 mmol) in anhydrous benzene (1.0 mL) dropwise by a syringe pump at 40 °C over 5 h under nitrogen atmosphere, and the mixture was additionally stirred for 14 h at 40 °C. The mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexane/EtOAc = 50) to give a 3.8:1 mixture of **15bx** and **16bx** (97.0 mg, 0.202 mmol, 69%) as a colorless oil. The ratio of **15bx** to **16bx** was determined from the isolated yields of products in the succeeding dehydration reaction of the mixture using MsCl and

Et₃N, which cleanly produced only 2-(*tert*-butoxy)-8-chloro-1-(trimethylsilyl)-3-phenyl-4-(prop-1-en-2-yl)dibenzofuran (**17**) (from **15bx**) and **16bx** remained unreacted. Spectral data of **14x**: IR (film) ν 3388, 2980, 2934, 2900, 2277, 2165, 1651, 1480, 1251, 1178, 1131, 903, 846 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.26 (9H, s), 1.60 (6H, s), 7.29 (1H, dd, $J = 2.5, 8.9$ Hz), 7.40 (1H, d, $J = 8.9$ Hz), 7.42 (1H, d, $J = 2.5$ Hz); ¹³C NMR (125 MHz, CDCl₃) δ -0.2 (CH₃ \times 3), 32.0 (CH₃ \times 2), 51.4 (C), 65.3 (C), 84.7 (C), 97.0 (C), 102.2 (C), 113.8 (C), 114.9 (CH), 129.1 (C), 129.6 (CH), 133.4 (CH), 154.8 (C); ESI-HRMS (neg.) m/z calcd for C₁₆H₁₈O₂Si³⁵Cl [M - H]⁻: 305.0770, found: 305.0762. Spectral data of **17**: IR (film) ν 3084, 3059, 2975, 2919, 1643, 1464, 1444, 1364, 1337, 1264, 1254, 1224, 1167, 1150, 1093, 861, 840, 806, 756, 729, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.57 (9H, s), 0.91 (9H, s), 1.76 (3H, s), 5.07 (1H, br-s), 5.37 (1H, br-s), 7.28 (1H, br-t, $J = 7.4$ Hz), 7.33 (2H, br-t, $J = 7.4$ Hz), 7.37 (1H, dd, $J = 2.1, 8.7$ Hz), 7.47 (2H, br-d, $J = 7.4$ Hz), 7.49 (1H, d, $J = 8.7$ Hz), 8.00 (1H, d, $J = 2.1$ Hz); ¹³C NMR (125 MHz, CDCl₃) δ 2.6 (CH₃ \times 3), 23.5 (CH₃), 28.9 (CH₃ \times 3), 81.1 (C), 112.7 (CH), 119.0 (CH₂), 123.9 (CH), 126.3 (CH), 126.6 (CH), 126.97 (C), 127.00 (C), 127.15 (CH \times 2), 127.17 (C), 128.6 (C), 129.5 (C), 132.4 (CH \times 2), 136.2 (C), 139.0 (C), 139.6 (C), 150.7 (C), 154.6 (C), 154.9 (C); ESI-HRMS (pos) m/z calcd for C₂₈H₃₁O₂Si³⁵ClNa [M + Na]⁺: 485.1674, found: 485.1682. Spectral data of **16bx**: IR (film) ν 3451, 3082, 3059, 3026, 2977, 2932, 1667, 1643, 1462, 1454, 1392, 1368, 1338, 1266, 1253, 1220, 1146, 1074, 1037, 1015, 838, 704, 691 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.05 (9H, s), 0.88 (9H, s), 1.90 (6H, s), 6.89 (1H, s, OH), 7.35-7.50 (5H, m), 7.38 (1H, dd, $J = 2.1, 8.7$ Hz), 7.50 (1H, d, $J = 8.7$ Hz), 7.96 (1H, d, $J = 2.1$ Hz); ¹³C NMR (125 MHz, CDCl₃) δ 1.5 (CH₃ \times 3), 29.1 (CH₃ \times 5), 73.6 (C), 85.6 (C), 112.3 (CH), 124.3 (CH), 125.1 (C), 126.1 (CH), 126.3 (C), 127.3 (C), 127.9 (CH), 128.0 (CH \times 2), 128.3 (C), 133.4 (CH \times 2), 133.7 (C), 141.7 (C), 142.3 (C), 150.0 (C), 153.2 (C), 154.4 (C); ESI-HRMS (pos.) m/z calcd for C₂₈H₃₃O₃Si³⁵ClNa [M + Na]⁺: 503.1780, found: 503.1764.