HETEROCYCLES, Vol. 101, No. 2, 2020, pp. 417 - 422. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 27th June, 2019, Accepted, 5th August, 2019, Published online, 25th September, 2019
DOI: 10.3987/COM-19-S(F)34

AN APPROACH TO A 2-HYDROXY-3-PHENYLDIBENZOFURAN SKELETON BASED ON $Rh(PPh_3)_3Cl$-CATALYZED [2+2+2] CYCLOADDITION BETWEEN A 1-ETHYNYL-2-(ETHYNYLOXY)BENZENE AND AN (ALKOXYETHYNYL)BENZENE

Daisuke Sato, Kenshu Fujiwara,* Yoshihiko Kondo, Uichi Akiba, and Tetsuo Tokiwano†

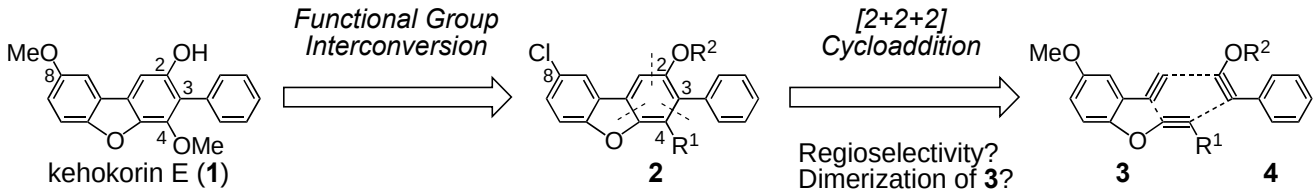
Dedicated to Prof. Dr. Kaoru Fuji on the occasion of his 80th Birthday

Department of Life Science, Graduate School of Engineering Science, Akita University, Akita 010-8502, Japan. †Department of Biotechnology, Faculty of Bioresource Sciences, Akita Prefectural University, Akita 010-0195, Japan.

Abstract – A $Rh(PPh_3)_3Cl$-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.

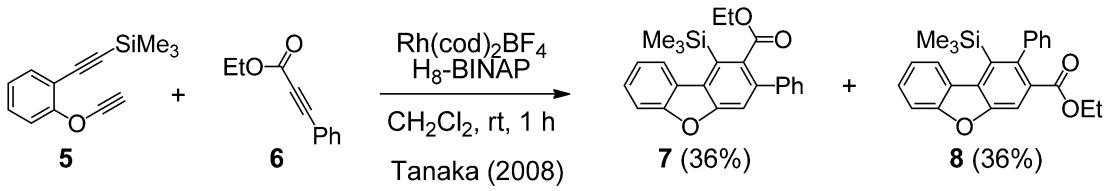
Naturally occurring 2-hydroxy-3-phenyldibenzofuran derivatives, such as kehokorins,[1] vialinin B,[2] and terrestrin E,[3] are a rare class of natural products, of which the several members show bioactivity. Their characteristic structures attracted attention of chemists in view of the development of 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.



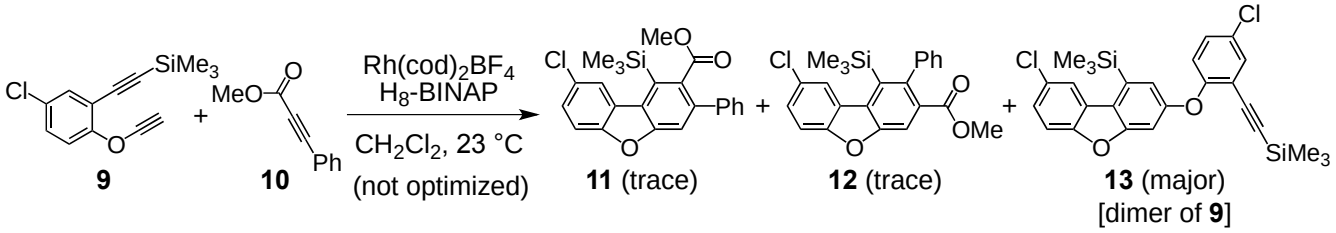
Scheme 1

For the synthesis of dibenzofuran by [2+2+2] cycloaddition, an effective, catalytic reaction with cationic Rh(I)/H_8-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 $Rh(cod)_2BF_4$ with H_8-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 $Rh(PPh_3)_3Cl$.[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).

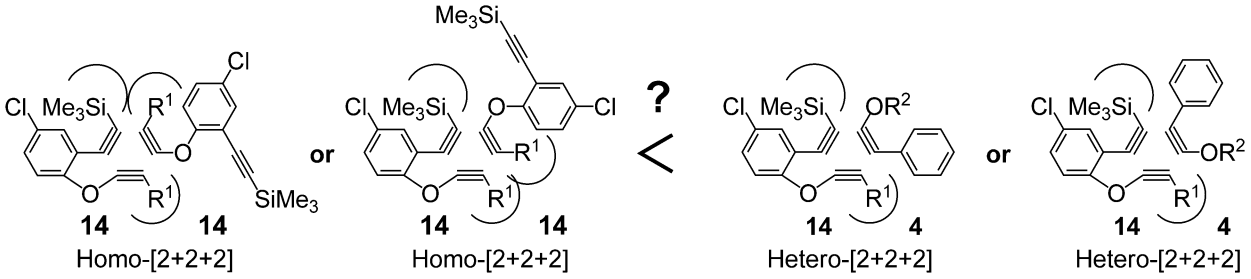
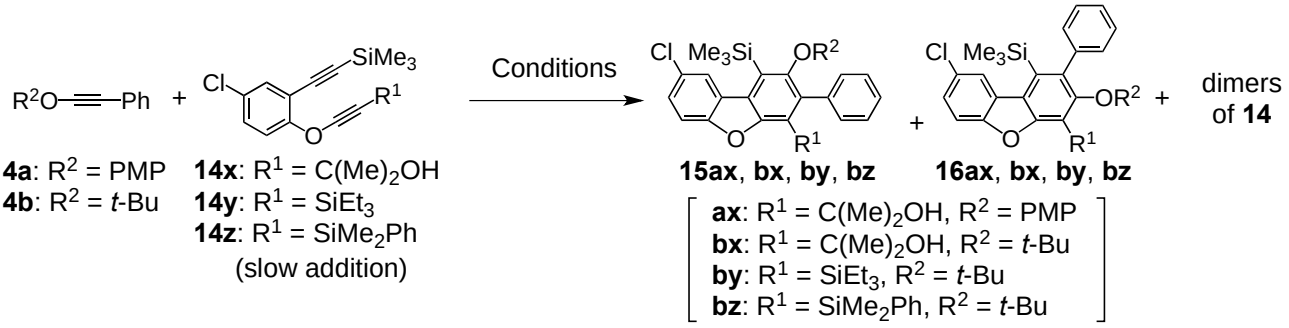


Figure 1

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-methoxyphenyloxyacetylene **4a**[9] with 1,6-diyne **14x** was examined in the presence of $Rh(PPh_3)_3Cl$ (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 $Rh(PPh_3)_3Cl$ (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 $SiEt_3$ 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, $Rh(PPh_3)_3Cl$-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



4a: R^2 = PMP
4b: R^2 = *t*-Bu

14x: R^1 = $C(Me)_2OH$
14y: R^1 = $SiEt_3$
14z: R^1 = $SiMe_2Ph$
(slow addition)

15ax, **bx**, **by**, **bz** **16ax**, **bx**, **by**, **bz**

ax: R^1 = $C(Me)_2OH$, R^2 = PMP
bx: R^1 = $C(Me)_2OH$, R^2 = *t*-Bu
by: R^1 = $SiEt_3$, R^2 = *t*-Bu
bz: R^1 = $SiMe_2Ph$, R^2 = *t*-Bu

Entry	**4** (eq)	**14**	$Rh(PPh_3)_3Cl$	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 $Rh(PPh_3)_3Cl$-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 (**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 kehokorin E (**1**) are in progress in this laboratory.

ACKNOWLEDGEMENTS

We thank Prof. Mitsutoshi Jikei and Prof. Kazuya Matsumoto (Department of Materials Science, Graduate School of Engineering Science, Akita University) for the measurements of NMR spectra. This work was supported by JSPS KAKENHI Grant Numbers JP15K01794, JP18K05450.

REFERENCES AND NOTES

1. (a) K. Kaniwa, T. Ohtsuki, Y. Yamamoto, and M. Ishibashi, *Tetrahedron Lett.*, 2006, **47**, 1505; (b) K. Watanabe, T. Ohtsuki, Y. Yamamoto, and M. Ishibashi, *Heterocycles*, 2007, **71**, 1807.
2. C. Xie, H. Koshino, Y. Esumi, J. Onose, K. Yoshikawa, and N. Abe, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5424.
3. N. Radulović, D. N. Quang, T. Hashimoto, M. Nukada, and Y. Asakawa, *Phytochemistry*, 2005, **66**, 1052.
4. (a) Y. Q. Ye, H. Koshino, J. Onose, K. Yoshikawa, N. Abe, and S. Takahashi, *Org. Lett.*, 2009, **11**, 5074; (b) S. Takahashi, Y. Suda, T. Nakamura, K. Matsuoka, and H. Koshino, *J. Org. Chem.*, 2017, **82**, 3159; (c) K. Fujiwara, R. Motousu, D. Sato, Y. Kondo, U. Akiba, T. Suzuki, and T. Tokiwano, *Tetrahedron Lett.*, 2019, **60**, 1299.
5. Y. Komina, A. Kamisawa, and K. Tanaka, *Org. Lett.*, 2009, **11**, 2361.
6. Diyne **9** was prepared from 4-chloro-2-iodophenol according to the procedure for diyne **5** reported by Tanaka.[5]
7. R. Grigg, R. Scott, and P. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1357.
8. Diyne **14x**, **14y**, or **14z** was obtained via a process including the lithiation of (*E*)-((5-chloro-2-((1,2-dichlorovinyl)oxy)phenyl)ethynyl)trimethylsilane, prepared from 4-chloro-2-iodophenol according to Tanaka's procedure,[5] with BuLi followed by the reaction with acetone, Et_3SiCl, or $Me_2PhSiCl$, respectively.
9. J. R. Sosa, A. A. Tudjarian, and T. G. Minehan, *Org. Lett.*, **10**, 5091.
10. L. Marzo, A. Parra, M. Frias, J. Alemán, and J. L. G. Ruano, *Eur. J. Org. Chem.*, 2013, 4405.
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 $Rh(PPh_3)_3Cl$ (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

Et_3N, 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) *v* 3388, 2980, 2934, 2900, 2277, 2165, 1651, 1480, 1251, 1178, 1131, 903, 846 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ –0.2 (CH_3 × 3), 32.0 (CH_3 × 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 $C_{16}H_{18}O_2Si^{35}Cl$ $[M - H]^-$: 305.0770, found: 305.0762. Spectral data of **17**: IR (film) *v* 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, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 2.6 (CH_3 × 3), 23.5 (CH_3), 28.9 (CH_3 × 3), 81.1 (C), 112.7 (CH), 119.0 (CH_2), 123.9 (CH), 126.3 (CH), 126.6 (CH), 126.97 (C), 127.00 (C), 127.15 (CH × 2), 127.17 (C), 128.6 (C), 129.5 (C), 132.4 (CH × 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 $C_{28}H_{31}O_2Si^{35}ClNa$ $[M + Na]^+$: 485.1674, found: 485.1682. Spectral data of **16bx**: IR (film) *v* 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, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.5 (CH_3 × 3), 29.1 (CH_3 × 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 × 2), 128.3 (C), 133.4 (CH × 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 $C_{28}H_{33}O_3Si^{35}ClNa$ $[M + Na]^+$: 503.1780, found: 503.1764.