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Stannylation and Stille Coupling of Base-Sensitive Tetrahydroxanthones to Heteromeric Biaryls

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Abstract: Herein, the synthesis of heteromeric tetrahydroxanthone biaryls is described, a widespread core structure of many natural products. The development of both stannylation and Stille coupling procedures of base-sensitive tetrahydroxanthones enabled their coupling with benzene derivatives as well as with xanthenes. These methods provide access to structures that are analogous to parnafungins as well as to dimeric compounds similar to secalonic acids or phomoxanthones.

Keywords: heteromeric biaryls; stannylation; Stille coupling; tetrahydroxanthones

Introduction

The tetrahydroxanthone moiety is a common scaffold of many mycotoxins that display a broad range of pharmacological and agrochemical activities.[1] Beside monomeric tetrahydroxanthone natural products like blennolides A–C, this unit is often connected to more complex structures. Among them the tetrahydroxanthone biaryls play an important role. A recently isolated fascinating subgroup, the parnafungins (such as **1a** and **1b**, Figure 1), comprises a tetrahydroxanthone unit linked to a benzoxazolidinone by a biaryl bond.[2] Moreover, a variety of homo- and heterodimeric tetrahydroxanthone biaryls have been identified, with

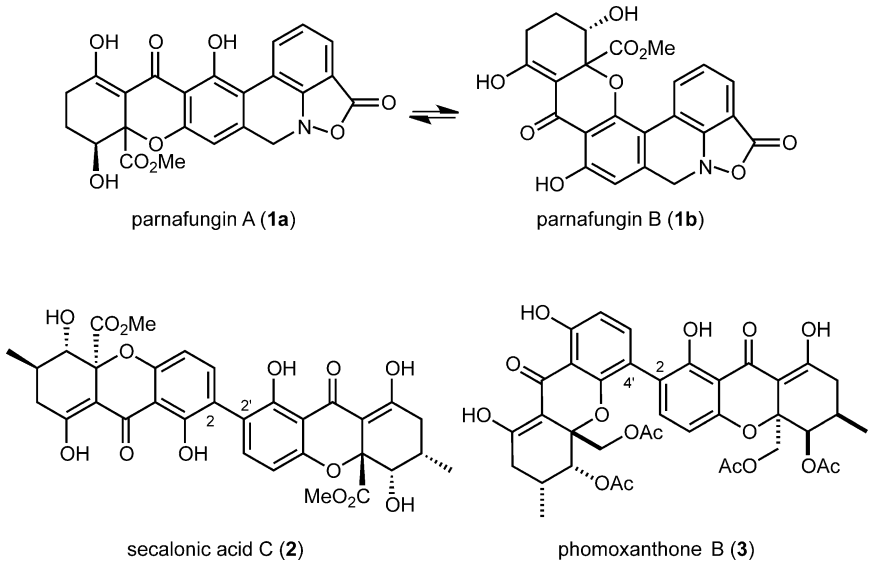


Figure 1. Selected natural products containing a heteromeric tetrahydroxanthone biaryl moiety.

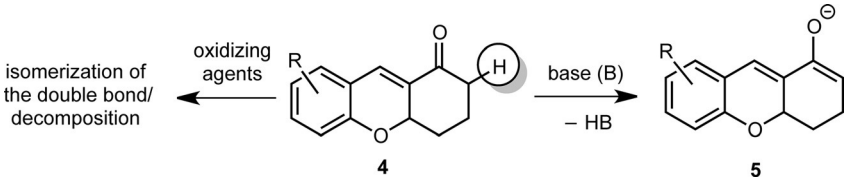
2,2-linked secalonic acids[3] (such as **2**) being the most famous representatives.

While various syntheses of monomeric tetrahydroxanthones have been described by our group[4] as well as by Nicolaou,[5] Porco[6] and Tietze,[7] the preparation of tetrahydroxanthone biaryls remains underexplored. Snider and co-workers reported on the synthesis of parnafungin A and C models *via* a Suzuki coupling reaction using a far less sensitive xanthone system.[8] Recently, Porco et al. accomplished the first total syntheses of three homodimeric natural products, the secalonic acids A and D, using a copper-catalyzed oxidative coupling of aryl stannane monomers[9] as well as the atropselective synthesis of rugulotrosin A.[10] Although this displays a milestone in the synthesis of tetrahydroxanthone biaryls,[11] heterodimers are not accessible by this method. Herein we report a flexible method for the synthesis of heteromeric tetrahydroxanthone biaryls *via* the Stille coupling reaction.[12]

Results and Discussion

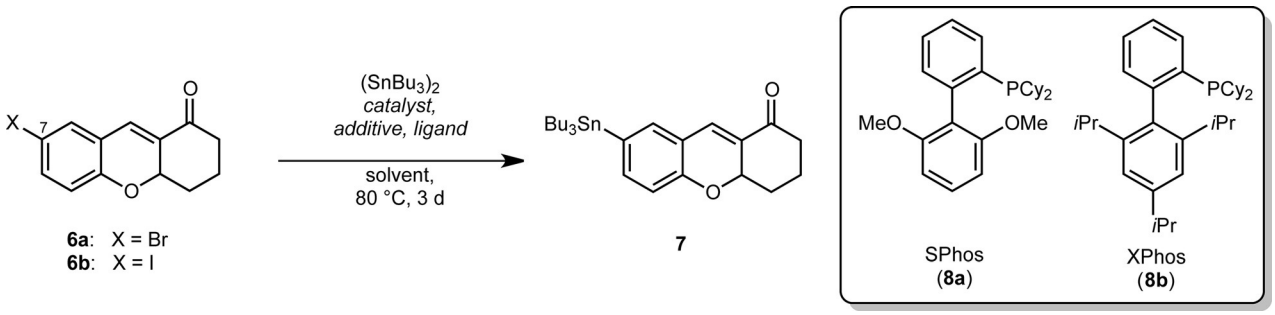
Since the tetrahydroxanthone core is sensitive to bases and oxidation, previous trials to apply Suzuki[13] or oxidative[14] couplings turned out to be problematic (Scheme 1).

Thus, we decided to investigate the stannylation and Stille cross-coupling of easily accessible tetrahydroxanthones. We developed a method for the palladium-catalyzed stannylation of tetrahydroxanthones, using bromide **6a**[13] as model substrate (Table 1). While similar results were obtained by replacing $PdCl_2(PPh_3)_2$ with $Pd(PPh_3)_4$ (entries 2 and 3), a remarkable optimization (up to 60% yield, entry 4) could be achieved by adding the Buchwald[15] ligands SPhos (**8a**) and XPhos (**8b**), respectively (entries 4 and 5). It has already been shown, that such electron-rich and bulky ligands have a positive effect on every step of the catalytic cycle.[12c] Furthermore, neither



Scheme 1. Sensitivity of the tetrahydroxanthone scaffold.

Table 1. Optimization of the synthesis of tetrahydroxanthone stannane **7**.

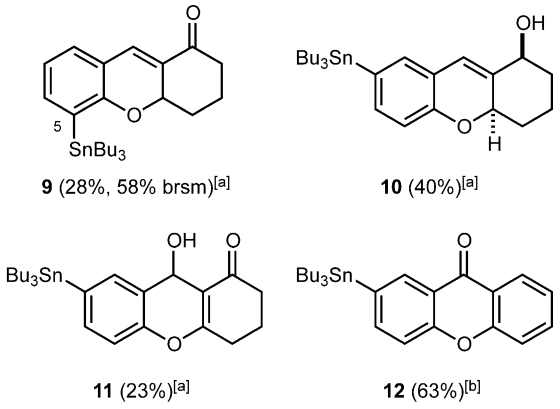


Entry	X	Catalyst	Additive/ligand	Equiv. [mol%] (cat./ligand)	Solvent	Isolated yield [%]
1	Br	$PdCl_2(PPh_3)_2$	DIPEA	2/–	toluene	19
2	Br	$PdCl_2(PPh_3)_2$	–	2/–	toluene	24
3	Br	$Pd(PPh_3)_4$	–	2/–	toluene	25
4	**Br**	**$Pd(PPh_3)_4$**	**SPhos**	**2/5**	**toluene**	**60**
5	Br	$Pd(PPh_3)_4$	XPhos	2/5	toluene	49
6	Br	$Pd(PPh_3)_4$	SPhos	2/5	dioxane	56
7	Br	$Pd(PPh_3)_4$	SPhos	2/5	NMP	traces
8	Br	$Pd(PPh_3)_4$	SPhos	1/2.5	toluene	49
9	Br	$Pd(PPh_3)_4$	SPhos	4/10	toluene	52
10	I	$Pd(PPh_3)_4$	SPhos	2/5	toluene	53[a]
11	Br	$Pd(PPh_3)_4$	SPhos, Bu_4NI	2/5	toluene	31[b]

[a] Reaction time: 2 d.
[b] Reaction time: 20 h.

the exchange of toluene as solvent (entries 6 and 7) nor varying the amount of the catalyst/ligand system (entries 8 and 9) led to enhanced yields. After completion of these studies, Porco et al.[9] reported on an alternative stannylation procedure of tetrahydroxanthones. Here, the formation of tin organyls was achieved using $Pd_2(dba)_3$ in combination with air sensitive P(*t*-Bu)$_3$ as ligand, whereby Bu_4NI was necessary to obtain full conversion. Therefore, we also tested the addition of Bu_4NI. However these attempts only led to decreased yield due to side reactions (entry 11). Thus, in our case the best conditions for the Pd-catalyzed stannylation of tetrahydroxanthone halides turned out to be the use of $Pd(PPh_3)_4$ as catalyst in combination with SPhos as ligand in toluene (entry 4).

The optimized stannylation conditions were applied to further xanthene halides, yielding the corresponding stannanes **9**–**12** (Figure 2).



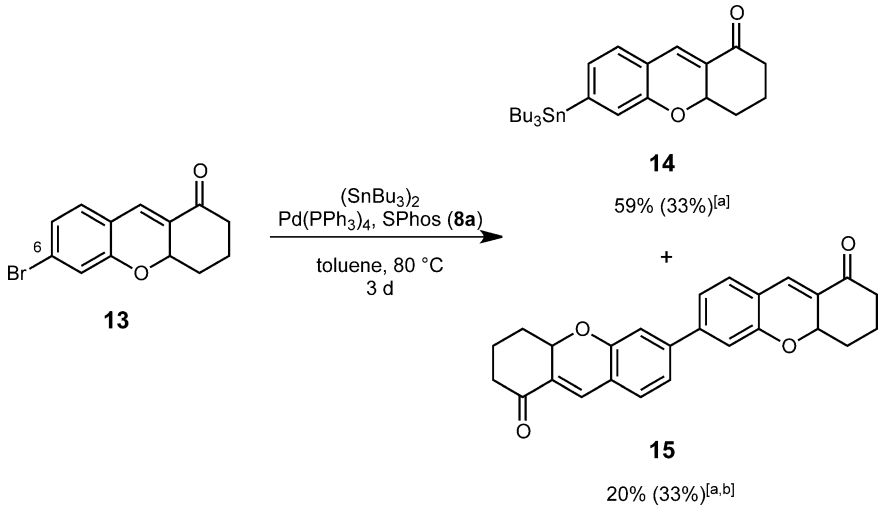
[a] From bromide.
[b] From iodide.

Figure 2. Successfully synthesized stannanes starting from the corresponding bromides or iodides.

Although this linkage does not exist in nature, the stannylation in the 6-position was performed. Interestingly, in contrast to the other positions, for the first time dimerization was observed leading to dimer **15** as a side product (Scheme 2). This might be explained by the increased nucleophilicity of the C–Sn bond due to the electron donor in the *meta* position, which facilitate transmetallation. The yield of the dimer, based on bromide **13**, could be increased by using lesser amounts of $(SnBu_3)_2$.

With tetrahydroxanthone stannanes in hand we proceeded with the synthesis of biaryls analogous to the parnafungin core (Table 2). Hereby, both building blocks were implemented as stannanes and as halides or triflates either way. In the case of the toluene derivative **18** the best result was obtained using stannane **16a** together with the tetrahydroxanthone halide **6a** (entry 1) while the other combination only led to 30% of the coupling product **18** (entries 2 and 3). However, starting from electron poor ester **17**, the biaryl only could be obtained using tetrahydroxanthone stannane **7** (entries 4–8). In doing so, the best results were reached with triflate as coupling partner in dioxane (entry 7). These conditions were also adapted to other benzene triflates, whereby the parnafungin B analogous linkage **20a** as well as other electron poor biaryls **20b** and **20c** could be obtained (Figure 3).

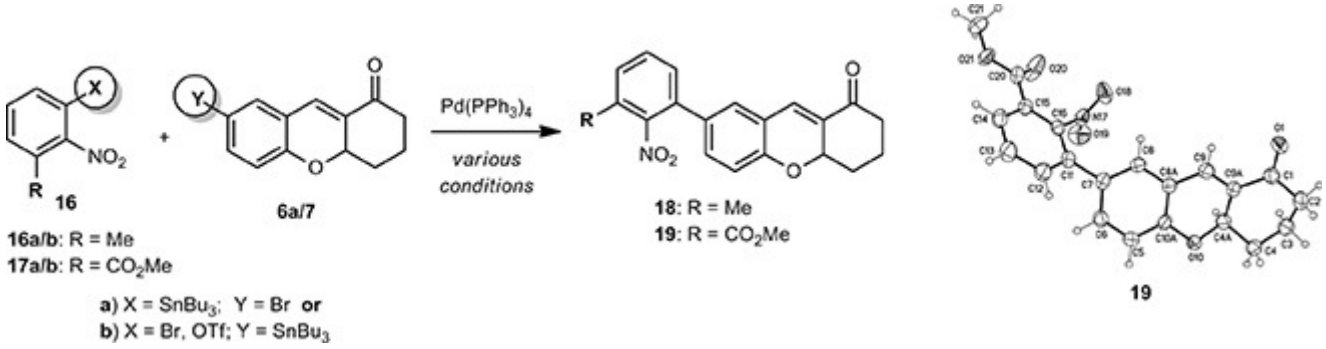
The formation of dimeric compounds was first explored on the synthesis of the homodimer of tetrahydroxanthone **6**, starting from stannane **7** and bromide



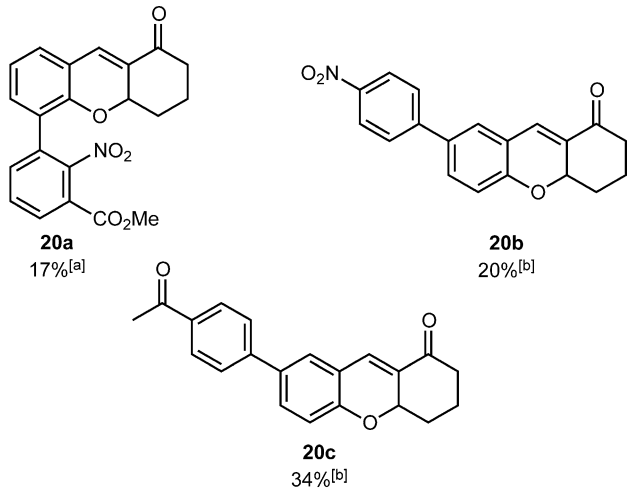
[a] Yield when using only 0.25 equiv. (instead of 1.5 equiv.) of $(SnBu_3)_2$ in brackets.
[b] In NMR spectra no different signals for diastereomers could be identified.

Scheme 2. Stannylation of bromide **13**. Yields are based on tetrahydroxanthone bromide **13**.

Table 2. Synthesis of tetrahydroxanthone biaryls similar to parnafungins and molecular structure of **19** (CCDC 1020439; displacement parameters are drawn at 50% probability level).



Entry	R	X	Y	Additive	Solvent/temperature	Time	Yield [%]
1	**Me**	**$Sn(Bu)_3$**	**Br**	**CuBr**	**THF/reflux**	**5 h**	**40**
2	Me	Br	$Sn(Bu)_3$	LiCl	toluene/80 °C	3 d	19
3	Me	Br	$Sn(Bu)_3$	LiCl, CuI	toluene/80 °C	40 h	30
4	CO_2Me	$Sn(Bu)_3$	Br	CuBr	THF/reflux	5 h	–
5	CO_2Me	$Sn(Bu)_3$	Br	LiCl, CuBr	dioxane	2 d	traces
6	CO_2Me	Br	$Sn(Bu)_3$	LiCl, CuI	dioxane/80 °C	3 d	18
7	CO_2Me	**OTf**	**$Sn(Bu)_3$**	**LiCl, CuI**	**dioxane/80 °C**	**3 d**	**52**
8	CO_2Me	OTf	$Sn(Bu)_3$	LiCl, CuI	toluene/80 °C	3 d	30



[a] Reaction temperature: 80 °C.
[b] Reaction temperature: 100 °C.

Figure 3. Synthesized tetrahydroxanthone biaryls.

6a or the corresponding triflate **6c** (**21k**, see Table 1 in the Supporting Information). Therefore, we tested various catalysts, ($Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(dba)_2$, $Pd(PPh_3)_2Cl_2$, $Ni(dppe)Cl_2$), in combination with special ligands such as $AsPh_3$ or bulky phosphines (SPhos, TFP) and additives like copper halides[16] or LiCl[17] in different solvents (toluene, DMF, dioxane, NMP, THF).[12c] The only successful coupling reaction was achieved using bromide **6a** as coupling partner catalyzed by $Pd(PPh_3)_4$ in combination with CuBr in THF at 60 °C. These conditions were subsequently applied to the coupling of the other synthesized xanthenes and the corresponding stannanes leading to a variety of heterodimers (Figure 4, for further examples see Figure 1 in the Supporting Information). Thus, dimeric xanthone biaryls with different linkages could be synthesized successfully in up to 61% yield. The 2,2- and 2,4-linkages (as in **21a**, **21b** and **21d**) correspond to the core structure of natural products like secalonic acid C (**2**) and phomoxanthone B (**3**), whilst the 2,3- and 3,4-linkage (as in **21c** and **21e**) represent new kinds of connections. The reason for the absence of these linkages in nature is based on the biaryl biosynthesis *via* oxidative coupling of phenols.

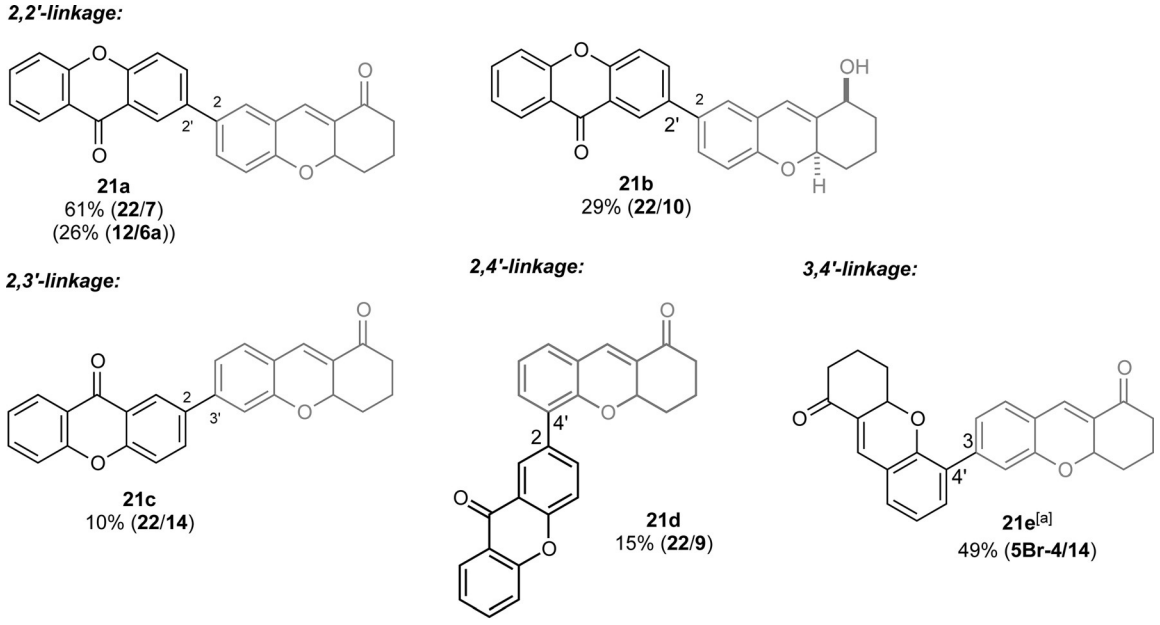
Conclusions

We have developed an approach to base-sensitive heteromeric tetrahydroxanthone biaryls, a widespread core structure of many natural products. The elaborated stannylation and Stille cross-coupling procedures that are reported herein provide access to versatile and complex tetrahydroxanthone biaryl structures.

Experimental Section

General Procedure for the Pd-Catalyzed Stannylation of Xanthenes (GP 1)

A vial equipped with a crimp top and a stirring bar was charged with the haloxanthenone (1.00 equiv.), $Pd(PPh_3)_4$



[a] In NMR spectra no different signals for diastereomers could be identified.

Figure 4. Selected synthesized dimeric tetrahydroxanthone biaryls. The part that was implemented as stannane is displayed in grey. Numbers of starting material are shown in brackets. *Reaction conditions:* $Pd(PPh_3)_4$ (10 mol%), CuBr (30 mol%), THF, 60 °C, 1–4 d.

(2 mol%) and SPhos (5 mol%, **8a**). The vial was closed and absolute and degassed toluene [c(haloxanthene) ≈ 200 mM) was added under an argon atmosphere. Hexabutyldistannane (1.50 equiv.) was added and the reaction mixture was heated to 80 °C for 3 d. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was diluted with dichloromethane. The mixture was displaced with an aqueous solution of KF (7 M, $c \approx 0.7$ mL mmol^{-1}) and stirred for 30–60 min. After filtration over Celite®, the solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

General Procedure for the Stille Coupling Reactions of Haloxanthenes with Xanthene Stannanes (GP 2)

A vial equipped with a crimp top and a stirring bar was charged with the stannane (1.00 equiv.), the halide (1.00 equiv.), $Pd(PPh_3)_4$ (10 mol%) and CuBr (0.300 equiv.). The vial was closed and absolute tetrahydrofuran [c(haloxanthene) ≈ 100 mM) was added under an argon atmosphere. The reaction mixture was heated to 60 °C for the appropriate time. After cooling, the reaction mixture was displaced with an aqueous solution of KF (7 M, $c \approx 0.7$ mL mmol^{-1}) and stirred for 60 min. After filtration over Celite®, the solution was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

Crystal Structure Determination

The crystal structures were determined on an Agilent SuperNova Diffractometer with EOS detector at 173(2) K (**19**) or a Bruker-Nonius Kappa CCD diffractometer at 123(2) K (**5Br-4**) using Mo-K_α radiation ($\lambda = 0.71073$ Å). Direct methods (SHELXS-97)[18] were used for structure solution. Refinement was carried out using SHELXL-2013 or SHELXL-97[18] (full-matrix least-squares on F^2), and hydrogen atoms were localized by difference Fourier synthesis and refined using a riding model. Semi-empirical absorption correction were applied.

19: yellow crystals, $C_{21}H_{17}NO_6$, $M_r = 379.36$, crystal size 0.15 × 0.10 × 0.06 mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 11.7991(6)$ Å, $b = 12.8236(10)$ Å, $c = 11.7731(8)$ Å, $\beta = 100.555(5)°$, $V = 1751.3(2)$ Å^3, $Z = 4$, $\rho = 1.439$ Mg/m^{-3}, μ(Mo-K_α) = 0.107 mm^{-1}, $F(000) = 792$, $2\theta_{max} = 50°$, 7475 reflections, of which 3082 were independent ($R_{int} = 0.037$), 254 parameters, $R_1 = 0.055$ [for 2138 $I > 2\sigma(I)$], $wR_2 = 0.133$ (all data), $S = 1.05$, largest diff. peak/hole = 0.323/−0.199 e Å^{-3}.

5Br-4: yellow crystals, $C_{13}H_{11}BrO_2$, $M_r = 279.13$, crystal size 0.50 × 0.40 × 0.30 mm, monoclinic, space group $P2_1/c$ (No. 14), $a = 8.822(1)$ Å, $b = 6.017(1)$ Å, $c = 20.660(2)$ Å, $\beta = 94.91(1)°$, $V = 1092.6(2)$ Å^3, $Z = 4$, $\rho = 1.697$ Mg/m^{-3}, μ(Mo-K_α) = 3.742 mm^{-1}, $F(000) = 560$, $2\theta_{max} = 55°$, 12650 reflections, of which 2500 were independent ($R_{int} = 0.021$), 145 parameters, $R_1 = 0.023$ [for 2196 $I > 2\sigma(I)$], $wR_2 = 0.054$ (all data), $S = 1.07$, largest diff. peak/hole = 0.388/−0.422 e Å^{-3}.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 1020439 (**19**) and CCDC 1061611 (**5Br-4**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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