

Regioselective Mono and Homo/hetero Dihalogenation of the Benzothioxanthene Monoimide

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Through the preparation and characterization of five new derivatives, the regioselective mono and di, homo and hetero, halogenation of the benzothioxanthene (BTXI) core is demonstrated herein. All structurally solved by X-ray crystallography, these complementary functionalized building blocks open doors to the design of new symmetrical and asymmetrical π -conjugated systems based on this promising but still under-explored rylene.

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Regioselective mono and homo/hetero dihalogenation of the benzothioxanthene monoimide

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Abstract: Through the preparation and characterization of five new derivatives, the regioselective mono and di, homo and hetero, halogenation of the benzothioxanthene (**BTXI**) core is demonstrated herein. All structurally solved by X-ray crystallography, these complementary functionalized building blocks open doors to the design of new symmetrical and asymmetrical π -conjugated systems based on this promising but still under-explored rylene.

Introduction

Over the past decades, the naphthalene (**NDI**) and perylene (**PDI**) diimides have emerged as reference building blocks in the field of organic electronics due to their excellent thermal and photochemical stability, synthetic tunability as well as specific electrochemical and high charge transport properties (Figure 1).¹⁻⁶ Although belonging to the imide-containing rylene family, the benzothioxanthene monoimide (**BTXI**) has not triggered such research interest, until recently.⁷

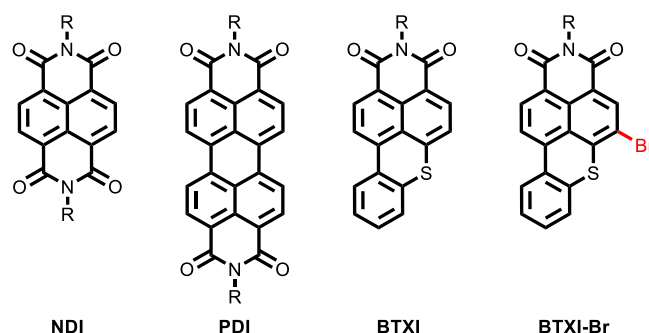


Figure 1. Structures of naphthalene diimide (**NDI**), perylene diimide (**PDI**), benzothioxanthene monoimide (**BTXI**) and the brominated derivative **BTXI-Br**.

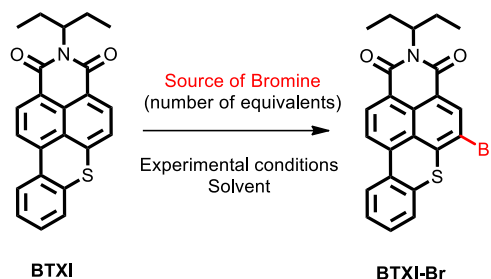
Synthesized in the 70's and solely functionalized on the *N*-position for post-grafting and/or solubility purposes,⁸⁻¹² we indeed recently demonstrated the selective mono-bromination (Figure 1, **BTXI-Br**) and use of this new promising block to prepare new π -conjugated systems *via* conventional palladium catalyzed cross-coupling reactions for organic photovoltaic applications.¹³⁻¹⁵ As a step towards new design principles, and therefore potential applications, we report herein a systematic halogenation study of the **BTXI** block to afford complementary mono- and di-halogenated derivatives.

Results and Discussion

Hence, and from our early reported procedure,¹³ where the **BTXI** was efficiently mono-brominated in the presence of 1.1 equivalents of bromine (Table 1, entry 1), we started to investigate the reactivity of additional and safer sources of bromine atoms.

To that end, the reactivity of the cheap and well-known *N*-bromosuccinimide (NBS) was first evaluated. It turned out that regardless of the reaction time (from few minutes to hours), temperature (room temperature or reflux) and nature of the solvent (chloroform or *N,N*-dimethylformamide), the entirety of the starting material was systematically recovered (Table 1, entries 2-5). However, while activating the NBS with *p*-toluenesulfonic acid in ethanol barely improved the conversion (Table 1, entry 6),¹⁶ it was found that mechanochemistry can be an interesting tool to prepare the target **BTXI-Br** in high yield (Table 1, entry 7).¹⁷ However, this solvent-free method requires a large excess of reactant (12 equivalents) to reach a full conversion of the starting material (Table 1, entry 9).

Table 1. Experimental conditions evaluated in this study to mono-brominate the **BTXI**. R.T. = room temperature.



Entry	Source of Bromine atom	Number of equivalents	Solvent	Experimental conditions	Synthetic Yield of isolated BTXI-Br
1	Bromine (Br ₂)	1.1	dichloromethane	R.T.; overnight	93%
2	<i>N</i> -bromosuccinimide	4.0	<i>N,N</i> -dimethylformamide	R.T.; overnight	0%
3	<i>N</i> -bromosuccinimide	4.0	chloroform	R.T.; overnight	0%
4	<i>N</i> -bromosuccinimide	4.0	<i>N,N</i> -dimethylformamide	reflux; overnight	0%
5	<i>N</i> -bromosuccinimide	4.0	chloroform	reflux; overnight	0%
6	<i>N</i> -bromosuccinimide	4.0	ethanol	<i>p</i> -toluenesulfonic acid; microwave; 100 °C 15 minutes	11%
7	<i>N</i> -bromosuccinimide	3	no solvent	ball-milling; 1 hour	33%
8	<i>N</i> -bromosuccinimide	6	no solvent	ball-milling; 1 hour	60%
9	<i>N</i> -bromosuccinimide	12	no solvent	ball-milling; 1 hour	99%
10	Dibromoisocyanuric acid	1.1	<i>N,N</i> -dimethylformamide	R.T.; overnight	95%
11	Pyridinium tribromide	1.1	dichloromethane	R.T.; overnight	47%
12	Pyridinium tribromide	1.1	dichloromethane	microwaves, 100 °C; 1 hour	52%
13	Pyridinium tribromide	2.2	dichloromethane	microwaves, 100 °C; 1 hour	94%

In contrast, this was not the case for the dibromoisocyanuric acid since only 1.1 molar equivalents of this strong bromine source were indeed necessary to efficiently convert the **BTXI** into the target compound. Moreover, it is important to note that the reaction occurs under very mild conditions, *i.e.*, at room temperature and overnight (Table 1, entry 10). However, considering the relative high price of this reagent, the use of a cheaper one but still known to be a strong and solid source of bromine was finally assessed, namely the pyridinium tribromide. When engaged under the previously described mild conditions, *i.e.*, 1.1 equivalents at room temperature and overnight (Table 1, entry 11), a maximum conversion of 50% was reached (47% isolated), corresponding to a mixture of the target **BTXI-Br** and the starting material (**BTXI**). In an attempt to improve the reactivity, the conventional oil bath was directly replaced by microwave irradiations (Table 1, entry 12). Unfortunately, a well-balanced blend of **BTXI-Br** and **BTXI** was once

again recovered even after one hour of stirring at 100 °C. According to these observations, it was decided to double the amount of brominating agent (Table 1, entry 13) resulting in a full conversion, thus suggesting that the quantity of the pyridinium tribromide was the limiting parameter.

On the other hand, characterization of the crude by mass spectrometry also revealed the presence of a minor product attributed to a dibrominated species. As an important building block for a multi functionalization of the **BTXI** core, the second insertion of a bromine atom was naturally investigated. To do so, the amount of pyridinium tribromide was significantly increased to 5, 10 and even 20 equivalents under the same heating conditions (Table 2, entries 1-3). It turned out that using a large excess of this brominating agent indeed generated a dibrominated species but with a maximum yield of 12%, the major product still being in these conditions the mono derivative, ie, the **BTXI-Br**.

Hence, owing to its high reactivity, 2.2 equivalents of dibromoisocyanuric acid were subsequently added to a solution of **BTXI** (Table 2, entry 4). After 16 hours under reflux and the total consumption of the starting material, only one spot migrated on the thin layer chromatography (TLC), corresponding, after purification, to a dibrominated compound. With a resulting yield of *ca.* 32%, the quantity of brominated agent was increased to 5.0 equivalents (Table 2, entry 5). In these conditions, although only a single dibrominated derivative was recovered from the purification, the synthetic yield dropped to 18%, resulting from the higher amount of polar by-products stuck at the start of the chromatography column.

Consequently, the **BTXI** was finally exposed to an increasing quantity of bromine and the solutions were refluxed overnight (Table 2, entries 6-8). While, in all cases, the starting material was systematically consumed, the full conversion into a dibrominated derivative was only reached with 20 equivalents (Table 2, entry 8).

All isolated **Br-BTXI-Br** products were analyzed by ^1H NMR revealing a perfect superimposition of their spectra, thus confirming, in consistency with the TLC (same $R_f = 0.6$ in toluene), the generation of the same and unique dibrominated compound regardless of the nature of the brominating agent. Luckily, single crystals were successfully grown revealing the exact grafting of the second bromine atom at the 11 position as depicted in Figure 2.

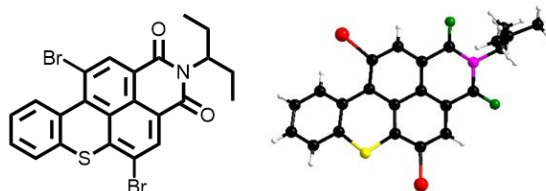
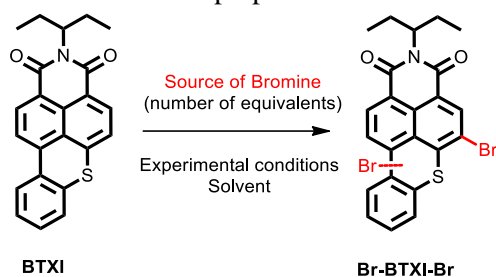


Figure 2. Molecular structure of the **Br-BTXI-Br** obtained by X-ray diffraction.

In parallel, the iodination of the **BTXI** was also investigated to extend the range of functionalization and reactivity (Table 3).

Table 2. Experimental conditions evaluated for the preparation of a dibrominated **BTXI**.

Entry	Source of Bromine atom	Number of equivalents	Solvent	Experimental conditions	Synthetic yield of BTXI/BTXI-Br and Br-BTXI-Br
1	Pyridinium tribromide	5.0	dichloromethane	microwaves, 100 °C; 1 hour	0%/93%/5%
2	Pyridinium tribromide	10.0	dichloromethane	microwaves, 100 °C; 1 hour	0%/85%/11%
3	Pyridinium tribromide	20.0	dichloromethane	microwaves, 100 °C; 1 hour	0%/83%/12%
4	Dibromoisocyanuric acid	2.2	<i>N,N</i> -dimethylformamide	reflux.; overnight	0%/0%/32%
5	Dibromoisocyanuric acid	5.0	<i>N,N</i> -dimethylformamide	reflux.; overnight	0%/0%/18%
6	Bromine	5.0	dichloromethane	reflux; overnight	0%/78%/19%
7	Bromine	10.0	dichloromethane	reflux; overnight	0%/23%/73%
8	Bromine	20.0	dichloromethane	reflux; overnight	0%/0%/98%

Mild and green conditions, reported by Gohier and coworkers,¹⁶ using *N*-iodosuccinimide in ethanol with a catalytic amount of *p*-toluenesulfonic acid, were first investigated (Table 3, entry 1). Stirring the reaction mixture overnight at 60 °C successfully led to the formation of a new compound. Once isolated in good yield by column chromatography, the latter was subsequently analyzed by mass spectrometry and NMR experiments revealing the presence of a single iodine atom grafted on the constituting naphthyl moiety of **BTXI**, the exact position of which was, once again, solved by single crystal X-ray diffraction (Figure 3).

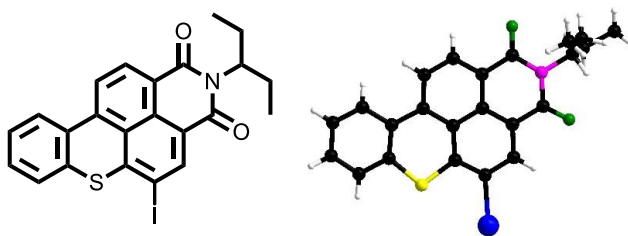
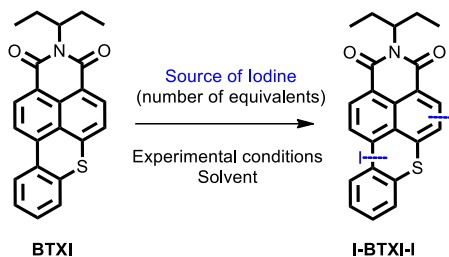
**Figure 3.** Molecular structure of the **BTXI-I** obtained by X-ray diffraction.

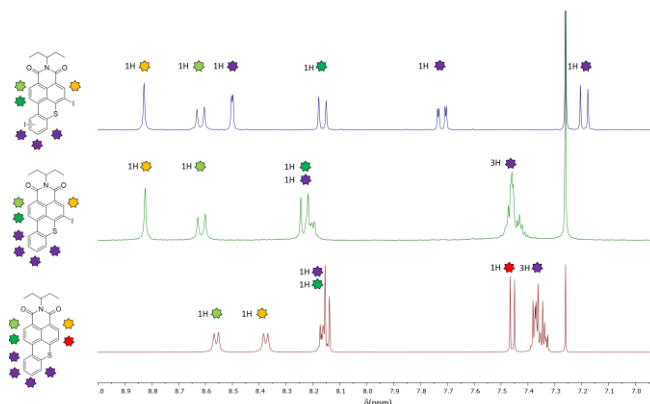
Table 3. Experimental conditions for the synthesis of the mono- and di-iodinated **BTXI** based derivatives (**BTXI-I** and **I-BTXI-I**). R.T. = room temperature.



Entry	Source of Iodine atom	Number of equivalents	Solvent	Experimental conditions	Synthetic yield of BTXI/BTXI-I and I-BTXI-I
1	<i>N</i> -iodosuccinimide	2.0	ethanol	<i>p</i> -toluenesulfonic acid; 60 °C.; overnight	30%/67%/0%
2	<i>N</i> -iodosuccinimide	2.0	ethanol	<i>p</i> -toluenesulfonic acid; microwave, 100 °C; 1 hour	12%/80%/0%
3	<i>N</i> -iodosuccinimide	4.0	ethanol	<i>p</i> -toluenesulfonic acid; microwave, 100 °C; 1 hour	0%/100%/0%
4	Iodine/Iodic acid	2.5/cat.	acetic acid:sulfuric acid:water:CHCl ₃ (1:0.02:0.2:0.08 /v:v:v:v)	R.T.; overnight	0%/67%/3%
5	Iodine/Iodic acid	2.5/cat.	acetic acid:sulfuric acid:water:CHCl ₃ (1:0.02:0.2:0.08 /v:v:v:v)	90 °C; overnight	0%/38%/19%

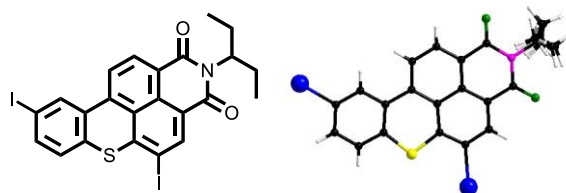
As for **BTXI-Br**, the iodination occurs on the naphthalene core at the β -position with regards to the sulfur atom. In addition to changing the heating method (Table 3, entry 2), the full conversion of the **BTXI** in this new derivative, namely **BTXI-I**, was only achieved by increasing the quantity of *N*-iodosuccinimide (Table 3, entry 3). Interestingly, though a large excess of this reagent was used, no multi-halogenated compound was detected in the crude. In an attempt to generate such species, a stronger method based on the use of the iodic acid/iodine couple in a mixture of acetic and sulfuric acid, water and chloroform was considered and evaluated. After 16 hours of stirring at room temperature, TLCs highlighted the formation of two compounds (Table 3, entry 4). Once purified by simple column chromatography, the major product was found to be the above mentioned mono-iodinated **BTXI** (**BTXI-I**) while the second, isolated with a low yield, corresponds to a di-iodinated derivative. In stark contrast with **Br-BTXI-Br** where both bromine atoms are localized on the naphthyl ring, ¹H NMR experiments of the new **I-BTXI-I** suggested a functionalization of the constituting phenyl ring (Figure 4, purple tagged protons).

Figure 4. Comparison of **BTXI**, **BTXI-I** and **I-BTXI-I** ^1H NMR spectra recorded at room temperature in deuterated chloroform.



While the integrity of the naphthyl constituting protons were recovered when comparing the spectra of both **BTXI-I** and **I-BTXI-I**, the multiplet centered at ca. 7.45 ppm, that comprises three hydrogen atoms, splits into a doublet (at 7.19 ppm) and a doublet of doublets (at 7.72 ppm) of one proton each. Moreover, the characteristic doublet centered at 8.5 ppm of **I-BTXI-I**, also attributed to a phenyl proton, appears significantly deshielded (compared to its **BTXI-I** analogue) thus supporting a close-by halogenation. Single crystal X-ray diffraction later confirmed these suppositions, thus revealing the exact position of the second iodine atom, corresponding to a functionalization in *para* of the sulfur atom (Figure 5).

Figure 5. Molecular structure of the **I-BTXI-I** obtained by X-ray diffraction



In a further attempt to improve the conversion into this new bis-functionalized derivative, the temperature of the reaction was increased to 90 °C for 24 h (Table 3, entry 5). While a larger amount of **I-BTX-I** was indeed isolated, these conditions also led to more unidentified and mostly insoluble by-products. Hence, to take it to the next level, these reactions were finally complementarily combined to afford hetero- and regiospecific dihalogenated derivatives (Scheme 1).

To do so, **BTXI-Br** was successfully iodinated in acidic conditions in the presence of iodic acid and iodine. As for **I-BTXI-I**, the iodine atom was found to be localized on the phenyl ring in *para* position with respect to the sulfur atom as evidenced by ^1H NMR and single crystal X-ray diffraction (**I-BTXI-Br**, Figure 6). In parallel, **BTXI-I** was first exposed to 20 equivalents of bromine. After reflux overnight, TLCs revealed the total consumption of the starting compound and generation of a single compound. However, once isolated and characterized, the latter turned out to be the dibrominated **Br-BTXI-Br**. Consequently, to avoid the halogen exchange reaction, the excess of bromine was replaced by only 1.1 equivalents of dibromoisocyanuric acid. First highlighted by TLCs, a new compound, whose R_f was found to be different from that of the **Br-BTXI-Br**, was successfully isolated in good yield after the total consumption of the starting material and purification of the crude. Mass spectrometry confirmed the presence of both a bromine and an iodine atom on this new **BTXI** derivative and ^1H NMR suggested a functionalization on the naphthyl

ring as for **Br-BTXI-Br** (see SI). Luckily, crystals of good quality were successfully grown and analyzed by X-ray diffraction confirming both hypothesized structures (Figure 6).

Scheme 1. Regioselective hetero dihalogenated derivatives reported herein.

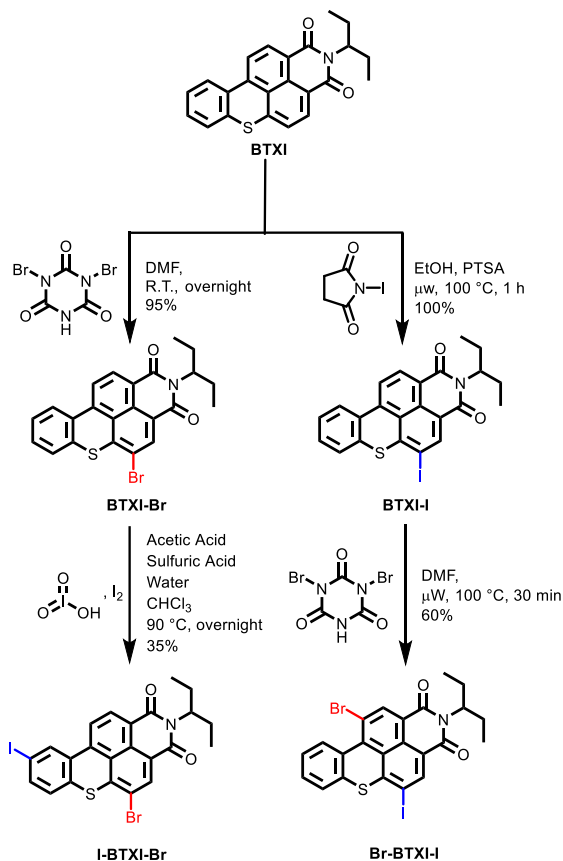
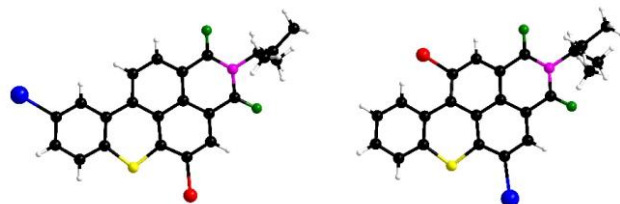


Figure 6. X-ray structures of **I-BTXI-Br** (left) and **Br-BTXI-I** (right).



Conclusion

In conclusion, the regioselective dihalogenation of the **BTXI** core is demonstrated herein. As a result, five new derivatives were successfully prepared, isolated and characterized. Depending on the nature and source of the halogen atom, different positions on the rylene core are now fully and, above all, selectively accessible for post grafting purposes, thus opening doors to new designs of functional π -conjugated BTXI based molecules and polymers.

Experimental Section

Supporting Information

Acknowledgements

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Keywords: selective halogenation • benzothioxanthene • organic chemistry • rylene

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Supplementary Information

Regioselective mono and homo/hetero dihalogenation of the benzothioxanthene monoimide

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General methods

All reagents and solvents were purchased from commercial sources and used without further purification. Purifications by chromatography were performed with analytical-grade solvents using Aldrich silica gel (technical grade, pore size 60 Å, 230–400 mesh particle size). Flexible plates ALUGRAM® XtraSIL G UV254 from MACHEREY-NAGEL were used for thin layer chromatography (TLC). ^1H and ^{13}C nuclear magnetic resonance (NMR) were recorded on a Bruker AVANCE III 300 (^1H , 300 MHz ; ^{13}C , 75 MHz) or a Bruker AVANCE DRX500 (^1H , 500 MHz ; ^{13}C , 125 MHz). Chemical shifts are given in ppm relative to tetramethylsilane (TMS) and coupling constants J in Hertz (Hz). Matrix Assisted Laser Desorption/Ionization was performed on MALDI-TOF MS BIFLEX III Bruker Daltonics spectrometer or with a JEOL Spiral-TOF JMS3000. Microwave assisted reactions were performed with a biotage initiator⁺ system. Ball-milling technique was performed with a RETSCH MM400 with a frequency of 30 Hz.s⁻¹. X-ray single-crystal diffraction data were collected on a Rigaku Oxford Diffraction SuperNova diffractometer equipped with Atlas CCD detector and micro-focus Cu-K α radiation (1.54184 Å). The structures were solved by direct methods and refined on F2 by full matrix least-squares techniques using SHELX programs (G. M. Sheldrick, 2018). All non-H atoms were refined anisotropically and multiscan empirical absorption was corrected using CrysAlisPro program (CrysAlisPro, Agilent Technologies, V 1.171.40.45a, 2019). The H atoms were included in the calculation without refinement.

Synthetic procedures

5-bromo-2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI-Br**)

Entry 1, Table 1: To a solution of 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (700 mg, 1.87 mmol) in CH₂Cl₂ (100 mL) was added dropwise a solution of bromine (1.1 eq, 94 mmL, 2.06 mmol) in CH₂Cl₂ (40 mL). The reaction mixture was stirred overnight at room temperature before being subsequently washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subsequently subjected to silica gel column chromatography using toluene as eluent to give the target compound as an orange solid in 93% yield (784 mg).**REF**

Entries 2-3, Table 1: *N*-bromosuccinimide (95 mg, 535 μmol) was added to a solution of 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (50 mg, 133 μmol) in either chloroform or *N,N*-dimethylformamide (20 mL) at room temperature. After a night of stirring, the crude was analyzed mass spectrometry revealing the absence of reactivity since only the starting material (**BTXI**) was detected.

Entries 4-5, Table 1: *N*-bromosuccinimide (95 mg, 535 μmol) was added to a solution of 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (50 mg, 133 μmol) in either chloroform or *N,N*-dimethylformamide (20 mL) at room temperature. After a night under reflux, the crude was analyzed mass spectrometry once again revealing the absence of reactivity since only the starting material (**BTXI**) was detected.

Entry 6, Table 1: In a 20 mL microwave vial with a stir-bar 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (50 mg, 133 μmol) and *N*-bromosuccinimide (NBS, 4.0 eq, 95 mg, 535 μmol) were suspended in EtOH (10 mL). The vial was sealed with a cap and the mixture was heated under microwave irradiation for 15 min at a pre-selected temperature of 100 °C. Then, the crude was then poured into CH₂Cl₂ and the organic layer was subsequently washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent to give the target compound as an orange solid in 11% yield (7 mg).

General procedure for entries 7-9, Table 1: 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (100 mg, 267 μmol) and *N*-bromosuccinimide were transferred into a milling vessel (5 mL, stainless steel). Once the 5 mm stainless steel ball added, the ball-milling process was carried out over an hour. Thereafter, the milling vessel was washed with crude CH₂Cl₂ and the resulting organic layer was washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent to give the target compound as an orange solid. Entry 7: 42 mg, 33%. Entry 8: 76 mg, 60%. Entry 9: 126mg, 99%

Entry 10, Table 1: 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (20 mg, 53 μ mol) and dibromoisocyanuric acid (1.1 eq, 17 mg, 59 μ mol) were suspended in DMF (4 mL). The reaction mixture was stirred overnight at room temperature. Then the crude was poured into EtOAc and the organic layer was washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent to give the target compound as an orange solid in 95% yield (23 mg).

Entry 11, Table 1: 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (100 mg, 267 μ mol) and pyridinium tribromide (1.1 eq, 94 mg, 294 μ mol) were solubilized in CH₂Cl₂ (10 mL). The reaction mixture was stirred overnight at room temperature before being washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent to give the target compound as an orange solid in 47% yield (57 mg).

General procedure for entries 12-13, Table 1: 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (100 mg, 267 μ mol) and pyridinium tribromide (1.1 eq or 2.2 eq) were transferred in a 20 mL microwave vial before being solubilized in CH₂Cl₂ (10 mL). The mixture was heated under microwave irradiation for 1 hour at a pre-selected temperature of 100 °C. Upon completion, the organic layer was removed by rotary evaporation and the crude was directly subjected to silica gel column chromatography using toluene as eluent to afford the target compound (**BTXI-Br**) as an orange solid. Entry 10: 52%, 63 mg, 139 μ mol. Entry 11: 94%, 115 mg, 254 μ mol.

¹H NMR (300 MHz, Chloroform-*d*): δ 8.62 (m, 2H), 8.29 – 8.22 (m, 2H), 7.52-7.43 (m, 3H), 5.09 – 4.99 (m, 1H), 2.32 – 2.17 (m, 2H), 1.97 – 1.84 (m, 2H), 0.89 (t, *J*=7.5, 6H). ¹³C NMR (125 MHz, Chloroform-*d*): δ 140.0, 135.9, 134.6, 132.1, 131.6, 130.1, 129.1, 128.0, 127.4, 127.8, 126.6, 125.7, 121.7, 119.8, 119.0, 114.5, 57.7, 25.0, 11.5. HRMS (EI): calculated for C₂₃H₁₈BrNO₂S 451.0242, found 451.0246.

5,11-dibromo-2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (Br-BTXI-Br)

General procedure for entries 1-3, Table 2: 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (100 mg, 267 μ mol) and pyridinium tribromide (5.0 eq, 10.0 eq or 20.0 eq) were transferred in a 20 mL microwave vial before being solubilized in CH₂Cl₂ (10 mL). The mixture was then heated under microwave irradiation for 1 hour at a pre-selected temperature of 100 °C. Upon completion, the organic layer was removed by rotary evaporation and the crude was directly subjected to silica gel column chromatography using toluene as eluent. Entry 1: 5%, 7 mg, 13 μ mol. Entry 2: 11%, 16 mg, 30 μ mol. Entry 3: 12%, 17 mg, 32 μ mol.

General procedure for entries 4-5, Table 2: 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (50 mg, 133 μ mol) and dibromoisocyanuric acid (2.2 eq or 5 eq) were suspended in DMF (10 mL). The reaction mixture was stirred overnight at 150 °C. Then, the crude was poured into EtOAc and the organic layer was washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using CH₂Cl₂ as eluent. Entry 4: 32%, 23 mg, 43 μ mol. Entry 5: 18%, 13 mg, 24 μ mol.

General procedure for entries 6-8, Table 2: Bromine (5.0 eq, 10.0 eq or 20.0 eq) was directly added to a solution of 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) in CH₂Cl₂ (4 mL). The reaction mixture was refluxed overnight before being washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent. Entry 6: 19%, 14 mg, 26 μ mol. Entry 7: 73%, 52 mg, 98 μ mol. Entry 8: 98%, 70 mg, 131 μ mol.

¹H NMR (500 MHz, Chloroform-*d*): δ 8.85 (s, 1H), 8.70 (dd, *J* = 8.2, 1.4 Hz, 1H), 8.63 (s, 1H), 7.57 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.42 (td, *J* = 7.9, 7.5, 1.5 Hz, 1H), 5.01 (m, 1H), 2.22 (m, 2H), 1.95 – 1.83 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 6H). ¹³C NMR (125 MHz, Chloroform-*d*): δ 139.2, 136.8, 133.1, 131.2, 130.7, 130.3, 128.3, 127.3, 127.1, 126.8, 117.9, 116.1, 58.0, 25.0, 11.4. HRMS (EI): calculated for C₂₃H₁₇Br₂NO₂S: 528.9347, found 528.9352. Monocrystal was obtained by slow evaporation of toluene.

5-iodo-2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI-I**)

Entry 1, Table 3: 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (20 mg, 53 μ mol), *p*-toluenesulfonic acid (922 μ g, 5.36 μ mol) and *N*-iodosuccinimide (NIS, 2.0 eq, 24 mg, 107 μ mol) were suspended in EtOH (10 mL). The reaction mixture was stirred overnight at 60 °C. Then, the crude product was poured into CH₂Cl₂ and washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent to afford the target compound (**BTXI-I**) as an orange solid in 67% yield (18 mg).

General procedure for entries 2-3, Table 3: 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) (50 mg, 133 μ mol), *p*-toluenesulfonic acid (2.31 mg, 13 μ mol) and *N*-iodosuccinimide (NIS, 2.0 eq or 4.0 eq) were transferred in a 20 mL microwave vial before being suspended in 10 mL of EtOH. The reaction mixture was then heated under microwave irradiation for 1 hour at a pre-selected temperature of 100 °C. Upon completion, the organic layer was removed by rotary evaporation and the crude was directly subjected to silica gel column chromatography using toluene as eluent to afford the target compound (**BTXI-I**) as an orange solid. Entry 2: 80%, 54 mg. Entry 3: 100% yield, 67 mg.

¹H NMR (300 MHz, Chloroform-*d*): δ 8.82 (s, 1H), 8.61 (d, *J* = 8.2 Hz, 1H), 8.26 – 8.19 (m, 2H), 7.53 – 7.37 (m, 3H), 5.04 (m, 1H), 2.24 (m, 2H), 1.91 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 6H). **¹³C NMR** (76 MHz, Chloroform-*d*): δ 143.9, 136.6, 132.8, 130.3, 129.8, 128.2, 128.0, 126.9, 126.8, 126.0, 120.0, 88.7, 57.7, 25.0, 11.5. **HRMS (EI)**: calculated for C₂₃H₁₈INO₂S: 499.0103, found 499.0096. Monocrystal was obtained by slow evaporation of toluene.

5,9-diiodo-2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (I-BTXI-I)

General procedure for entries 4-5, Table 3: To a stirred suspension of 2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI**) in a mixture of acetic acid, concentrated sulphuric acid, water and CHCl₃ (v/v 100/5/20/8 respectively) were added iodine (2.5 eq, 169 mg, 669 μmol) and iodic acid (0.5 eq, 59 mg, 334 μmol). The mixture was either stirred at room temperature (entry 4) or refluxed (entry 5) overnight. Then the mixture was cooled to room temperature and was poured into iced water, washed with a saturated aqueous solution of Na₂S₂O₃ and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent. **Entry 4:** 5 mg, 8 μmol, 3%. **Entry 5:** 130 mg, 208 μmol, 19%.

¹H NMR (300 MHz, Chloroform-*d*): δ 8.83 (s, 1H), 8.62 (d, *J* = 8.2 Hz, 1H), 8.50 (d, *J* = 1.7 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.72 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 5.03 (s, 1H), 2.21 (dd, *J* = 9.6, 7.4 Hz, 2H), 2.01 – 1.83 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 6H). **¹³C NMR** (75 MHz, Chloroform-*d*): δ 138.8, 134.9, 134.8, 132.5, 130.0, 128.0, 126.9, 120.3, 92.8, 89.1, 57.8, 25.01, 11.4. **HRMS (EI)**: calculated for C₂₃H₁₇I₂NO₂S: 624.9069, found 624.9046. Monocrystal was obtained by slow evaporation of toluene.

11-bromo-5-iodo-2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline 1,3(2*H*)-dione (Br-BTXI-I).

5-iodo-2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (**BTXI-I**) (30 mg, 60 μmol) and dibromoisocyanuric acid (68 mg, 240 μmol) were transferred in a 10 mL microwave vial before being suspended in 5 mL of F. The mixture was subsequently heated under microwave irradiation for 30 min at a pre-selected temperature of 100 °C. Then the crude was poured into EtOAc and the organic layer was washed with a saturated aqueous solution of Na₂S₂O₃, water and brine. Once dried over MgSO₄, the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent to give the target compound as an orange solid in 60% yield (21 mg).

¹H NMR (300 MHz, Chloroform-*d*): δ 8.85 (s, 1H), 8.83 (s, 1H), 8.67 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.54 – 7.36 (m, 2H), 5.00 (m, 1H), 2.32 – 2.11 (m, 2H), 1.99 – 1.79 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 6H). **¹³C NMR** (76 MHz, Chloroform-*d*): δ 142.8, 140.6, 138.7, 137.0, 133.9, 131.1, 130.3, 130.2, 128.5, 127.8, 126.0, 126.8, 117.6, 90.4, 58.0, 25.0, 11.4. **HRMS (EI)**: calculated for C₂₃H₁₇BrINO₂S: 576.9208, found 576.9196. Monocrystal was obtained by slow evaporation of toluene.

5-bromo-11-iodo-2-(pentan-3-yl)-1*H*-thioxantheno[2,1,9-*def*]isoquinoline-1,3(2*H*)-dione (I-BTXI-Br).

To a stirred suspension of **BTXT-Br** (100.0 mg, 221 μmol) in a mixture of acetic acid (20 mL), concentrated sulphuric acid (1 mL), water (4 mL) and CHCl₃ were added iodine (78.5 mg, 309 μmol) and iodic acid (54.4 mg, 309 μmol). After a night of stirring at 90 °C, the reaction

mixture was cooled down to room temperature and poured into iced water, washed with a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ and brine. Once dried over MgSO_4 , the solvent was removed by rotary evaporation and the crude was subjected to silica gel column chromatography using toluene as eluent to afford **I-BTXI-Br** as an orange solid in 35% yield (45 mg).

^1H NMR (300 MHz, Chloroform-*d*): δ 8.63 (m, 2H), 8.53 (d, J = 1.7 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 7.73 (dd, J = 8.4, 1.7 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 5.03 (m, 1H), 2.35 – 2.13 (m, 2H), 2.00 – 1.80 (m, 2H), 0.89 (t, J = 7.5 Hz, 6H). **^{13}C NMR** (76 MHz, Chloroform-*d*): δ 138.8, 134.9, 134.7, 131.6, 129.7, 129.3, 128.3, 127.1, 120.4, 115.0, 92.8, 57.8, 25.0, 11.4. **HRMS (FAB-neg)**: calc. for $\text{C}_{23}\text{H}_{17}\text{BrINO}_2\text{S}$: 576.9208, found 576.9205. Monocrystal was obtained by slow evaporation of toluene.

NMR Spectra

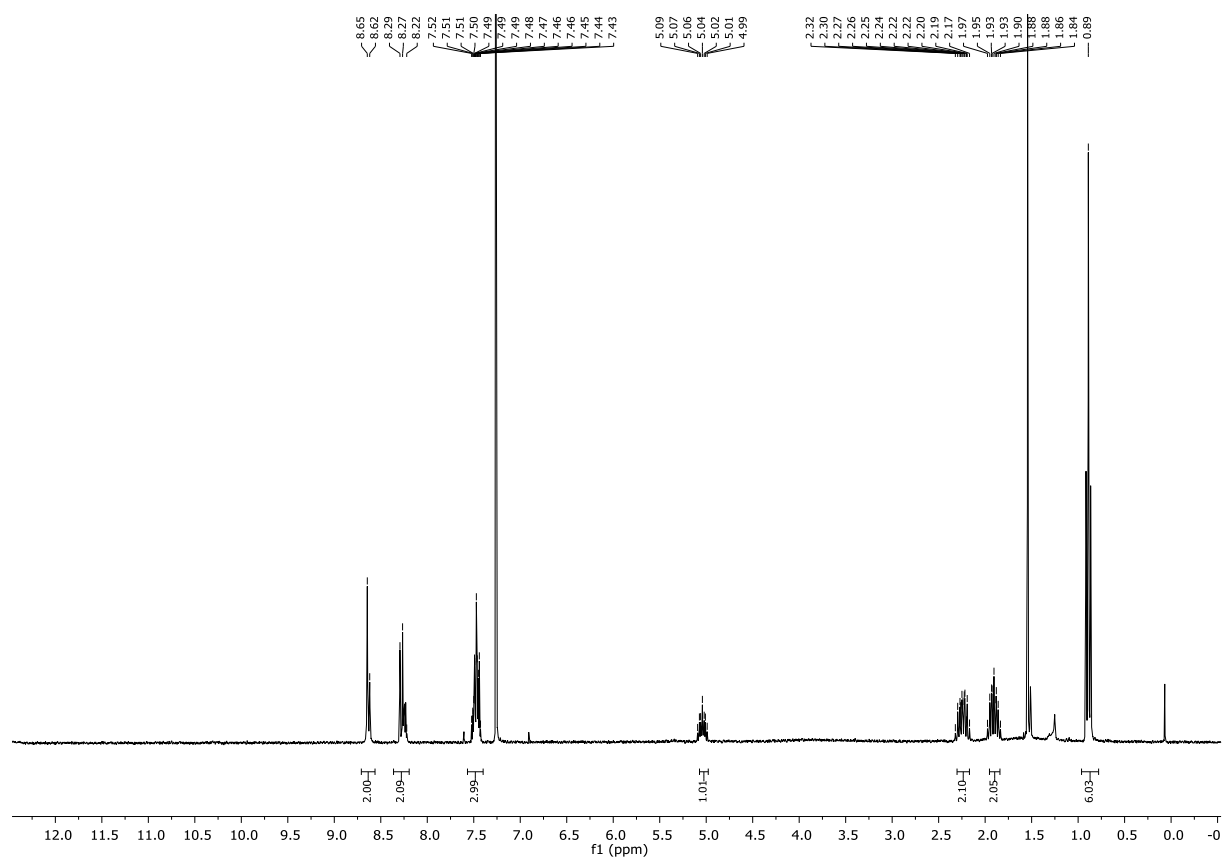


Figure 1: ¹H NMR BTXI-Br

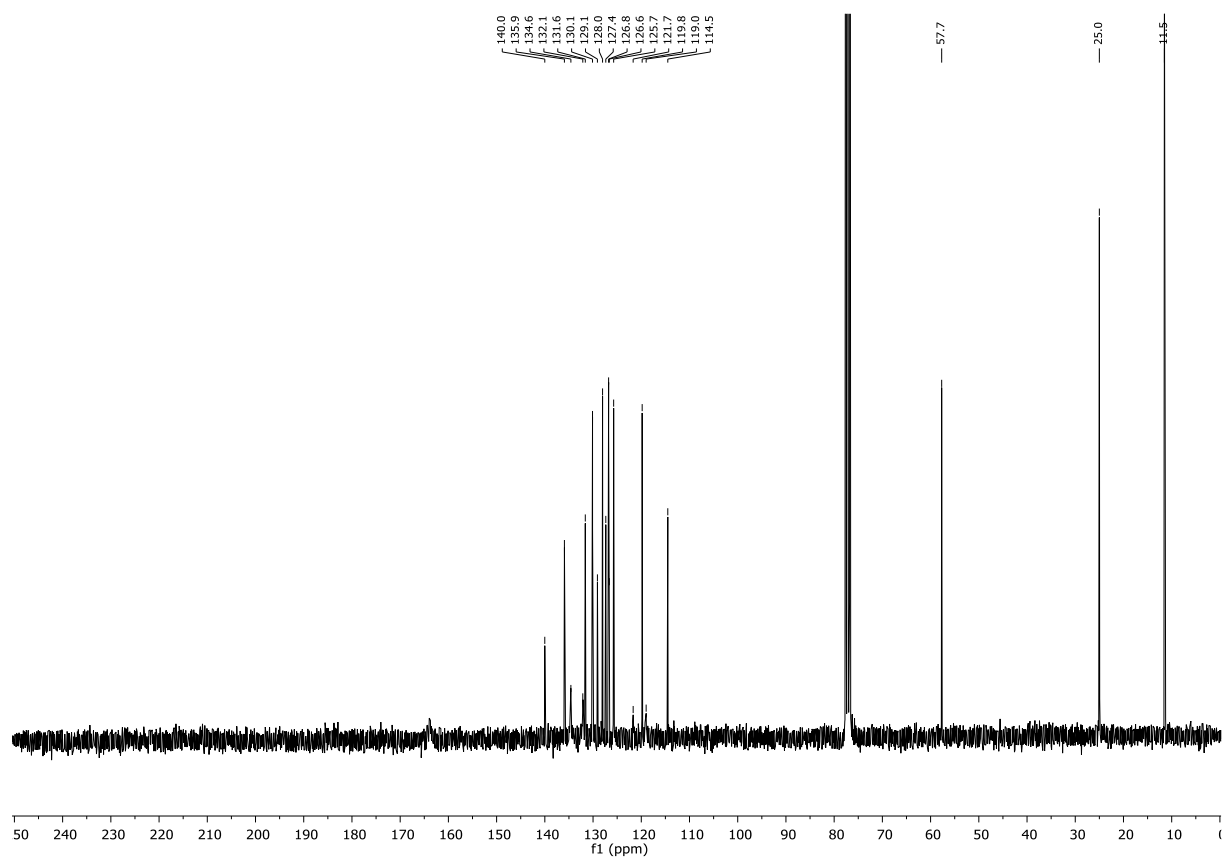


Figure 2: ¹³C NMR BTXI-Br

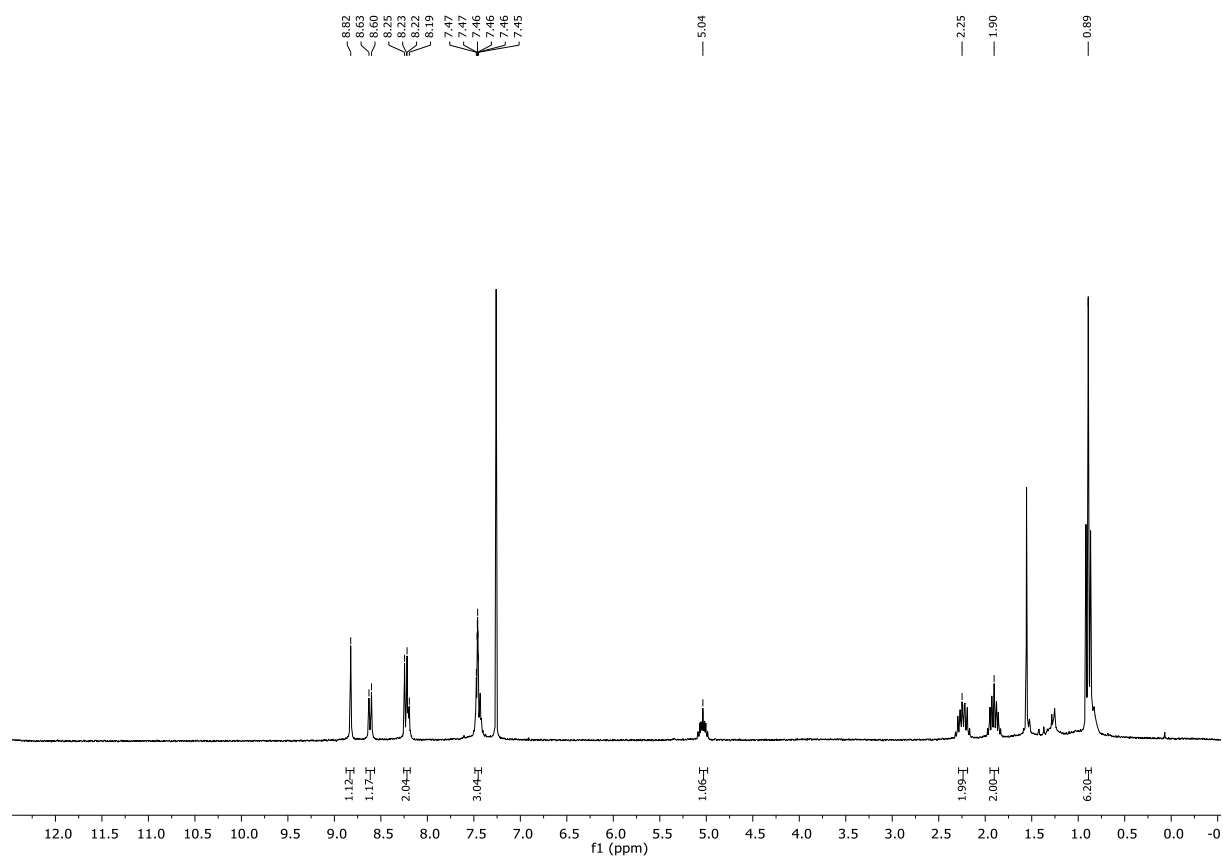


Figure 3: ¹H NMR BTXI-I

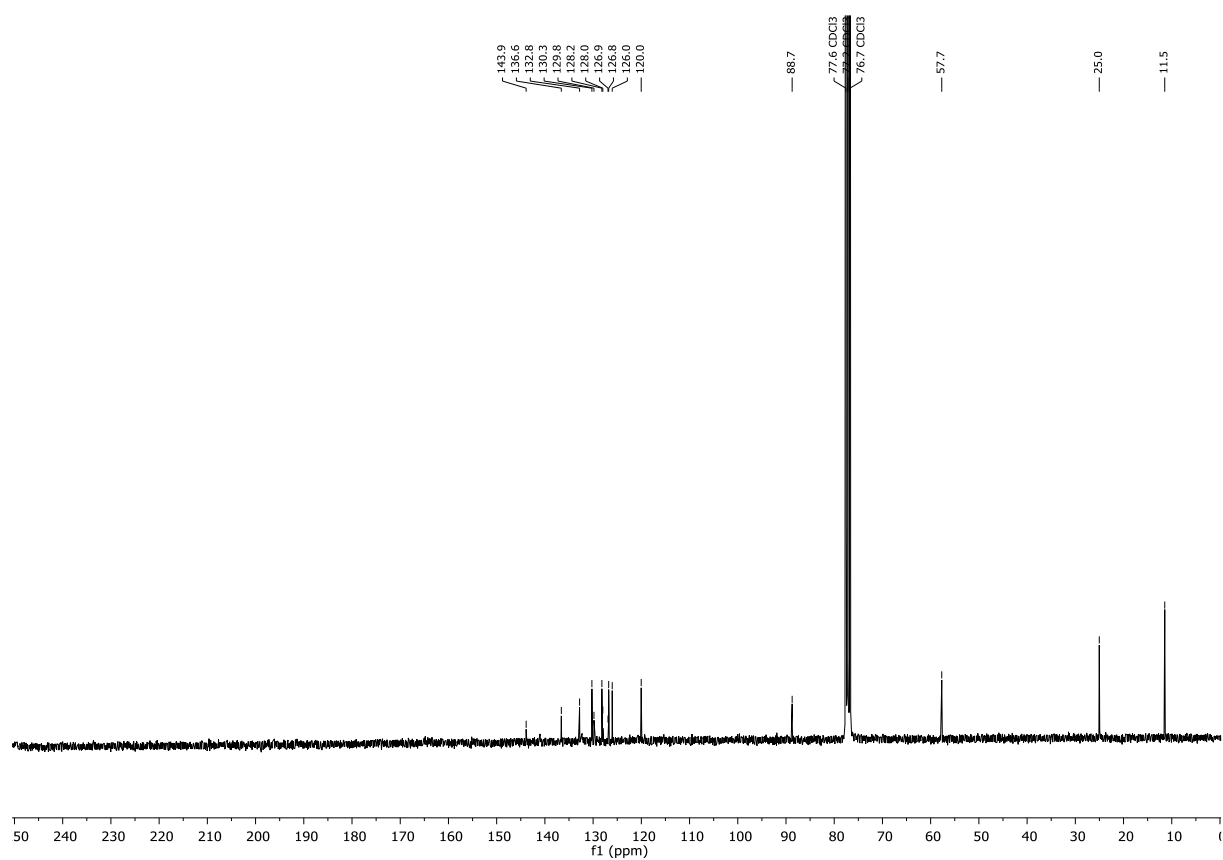


Figure 4: ¹³C NMR BTXI-I

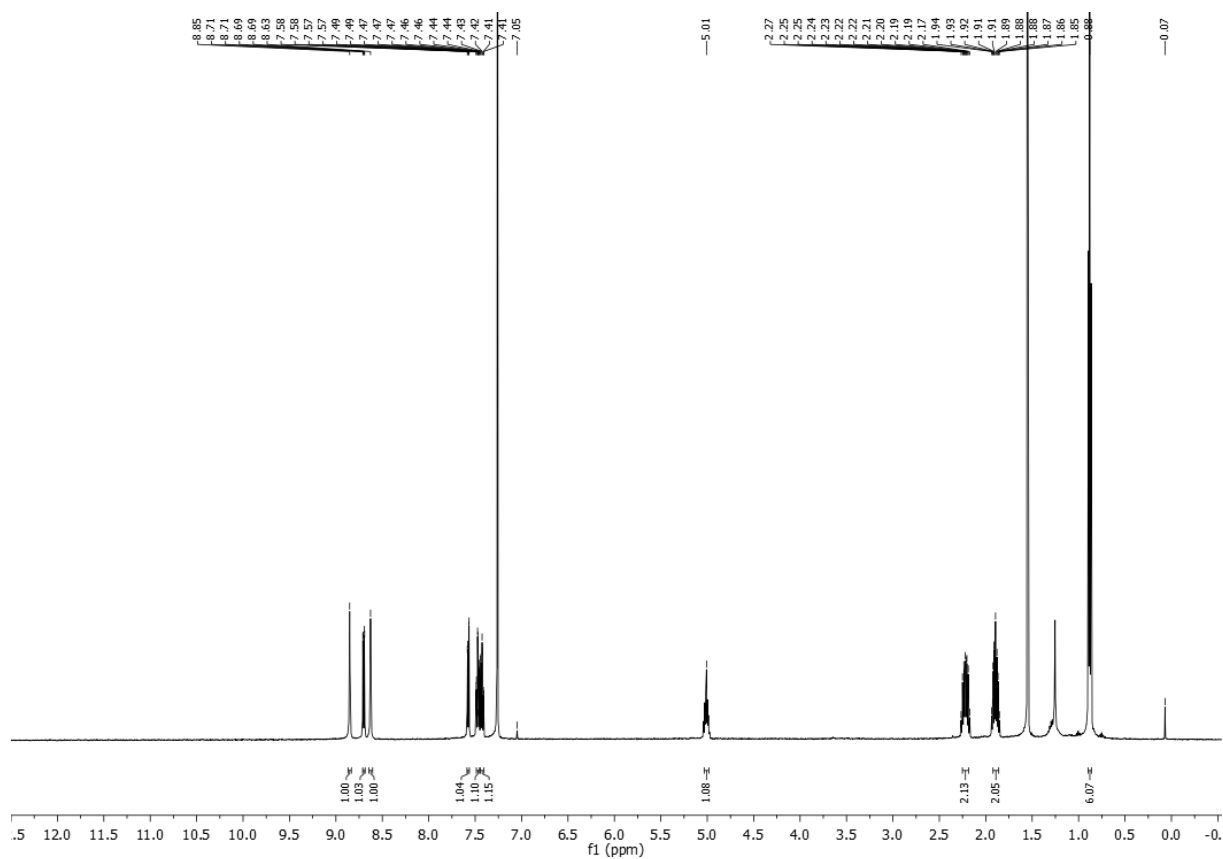


Figure 5: ¹H NMR Br-BTXI-Br

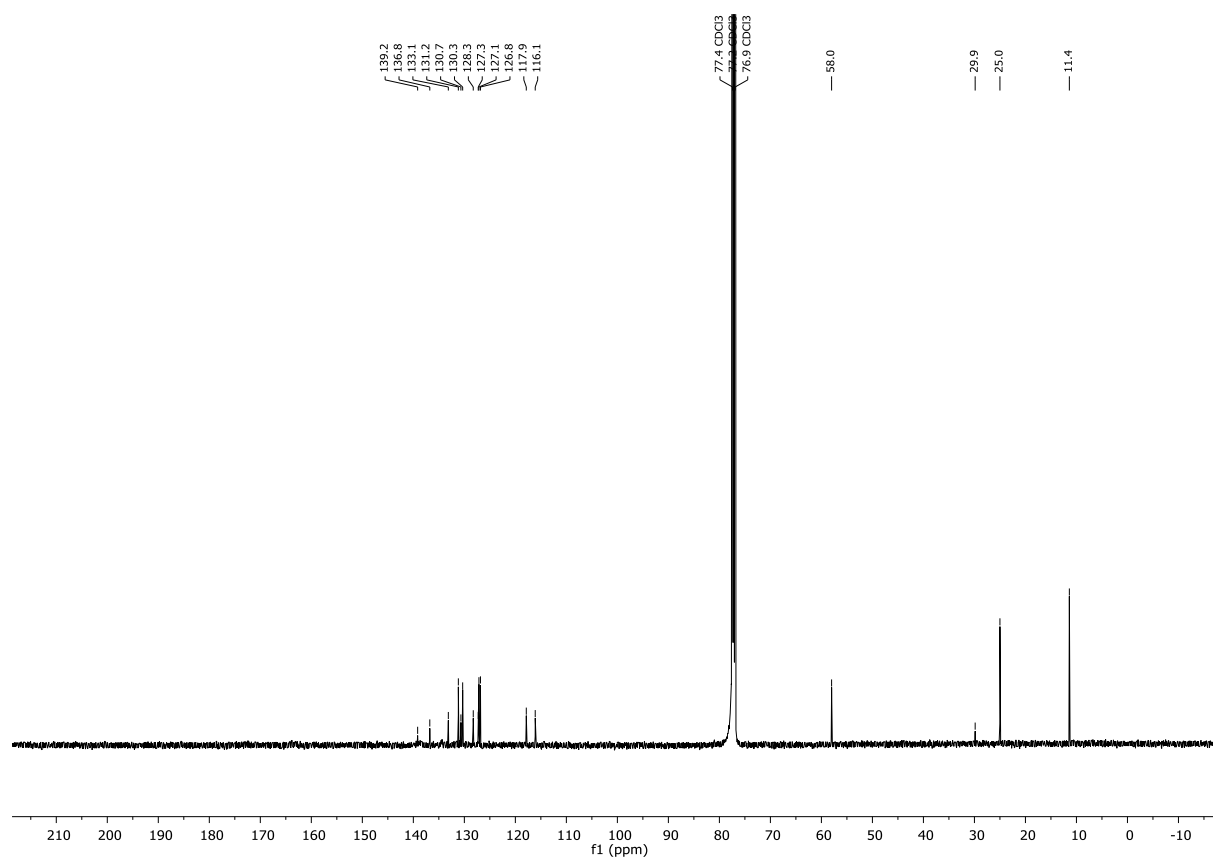


Figure 6: ¹³C NMR Br-BTXI-Br

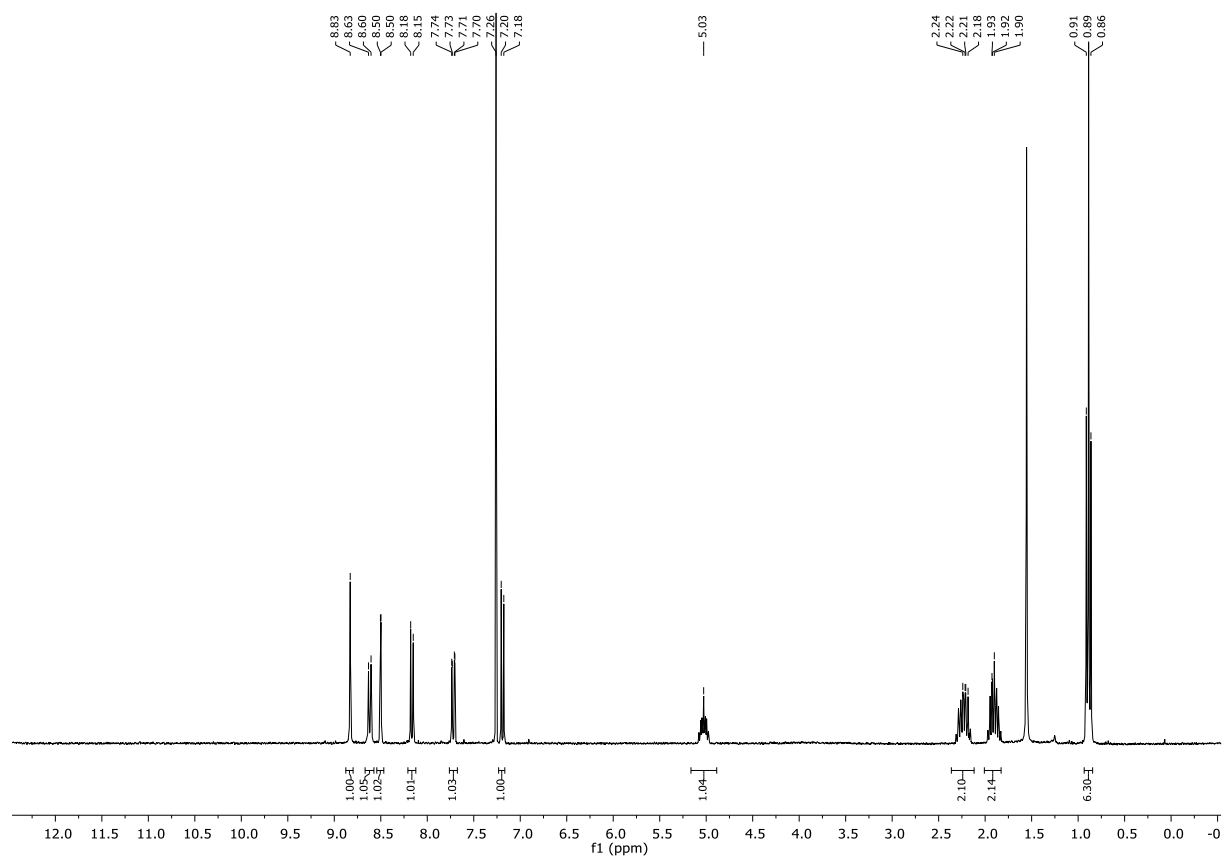


Figure 7: ¹H NMR I-BTXI-I

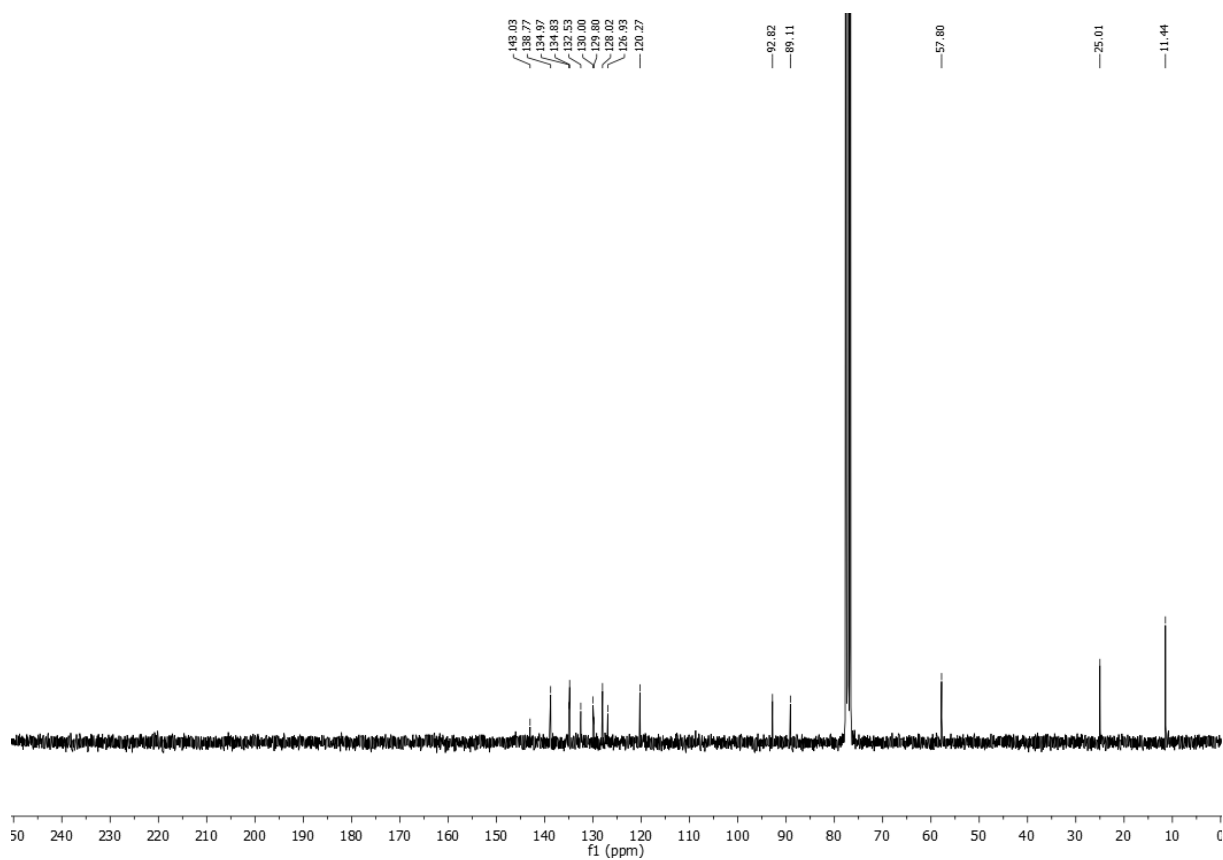


Figure 8: ¹³C NMR I-BTXI-I

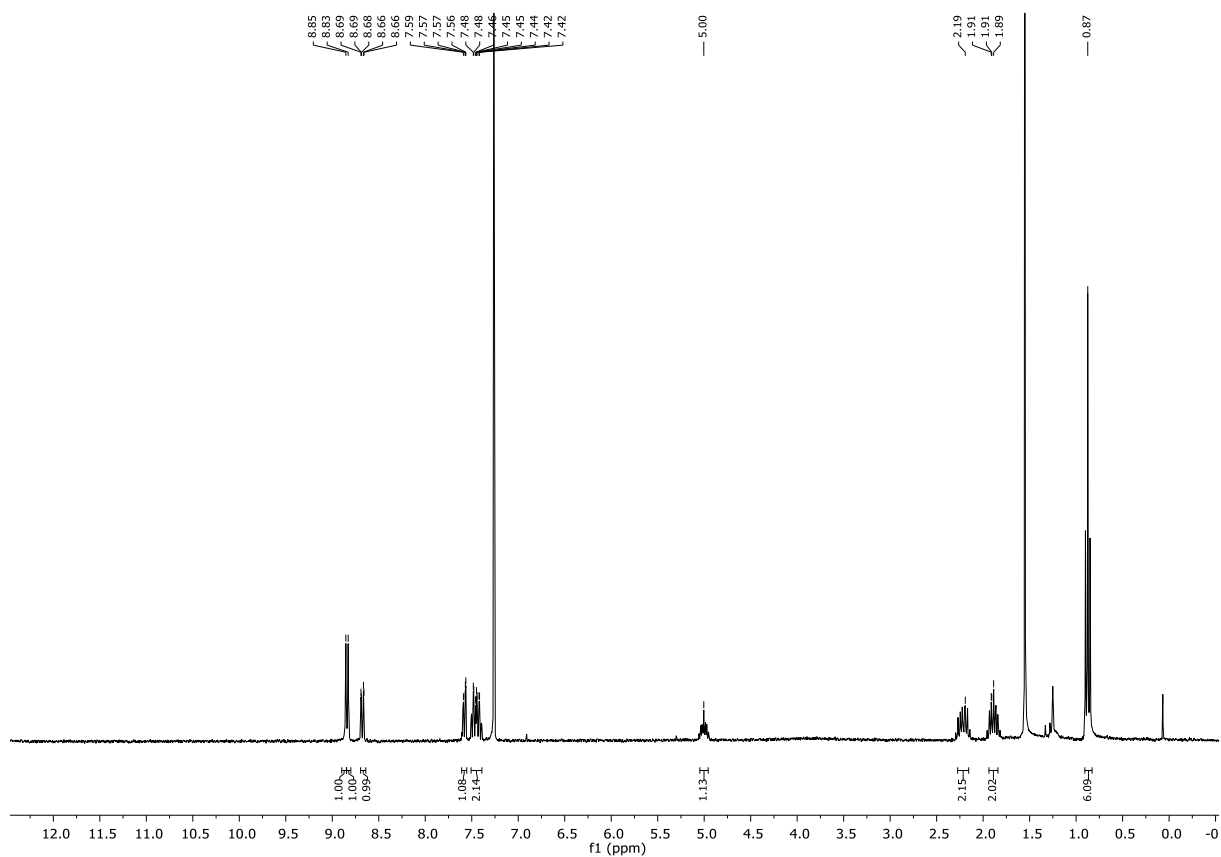


Figure 9: ¹H NMR Br-BTXI-I

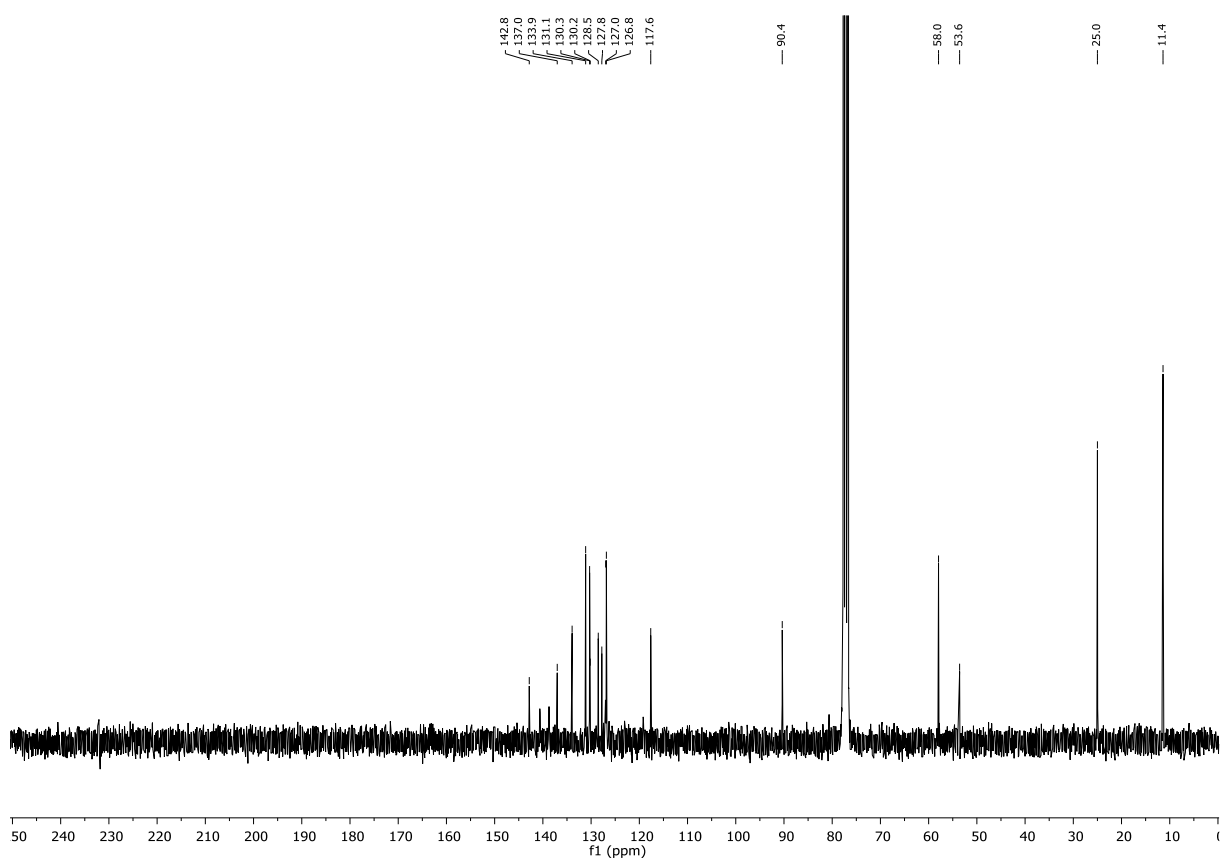


Figure 10: ¹³C NMR Br-BTXI-I

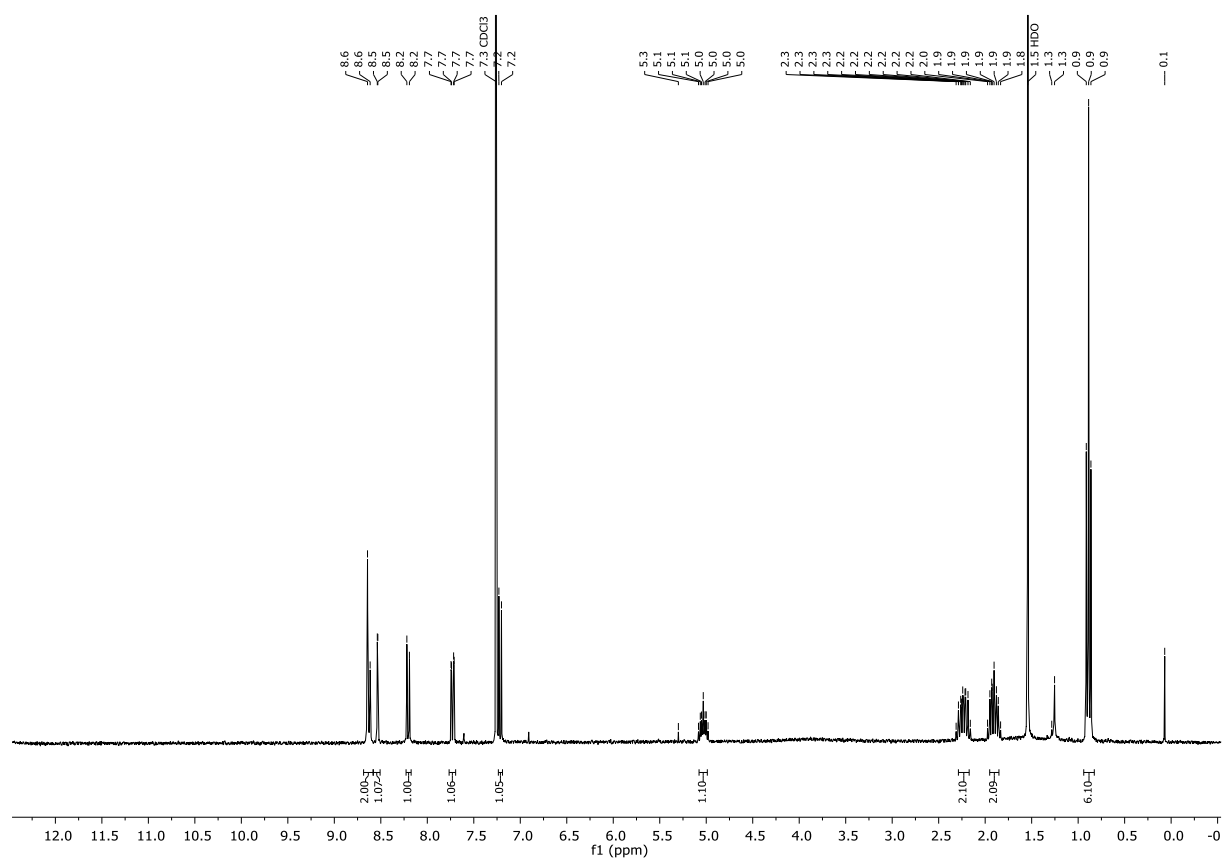


Figure 11: ¹H NMR I-BTXI-Br

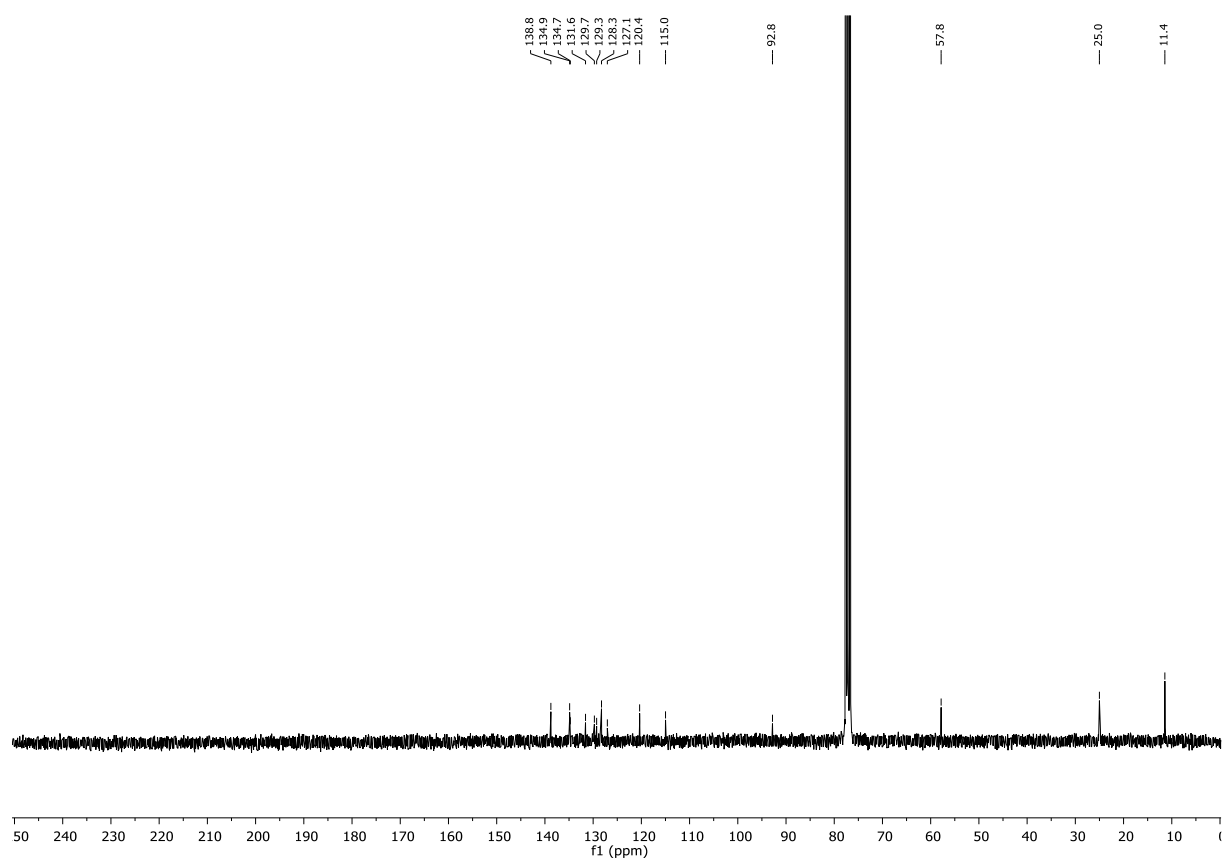
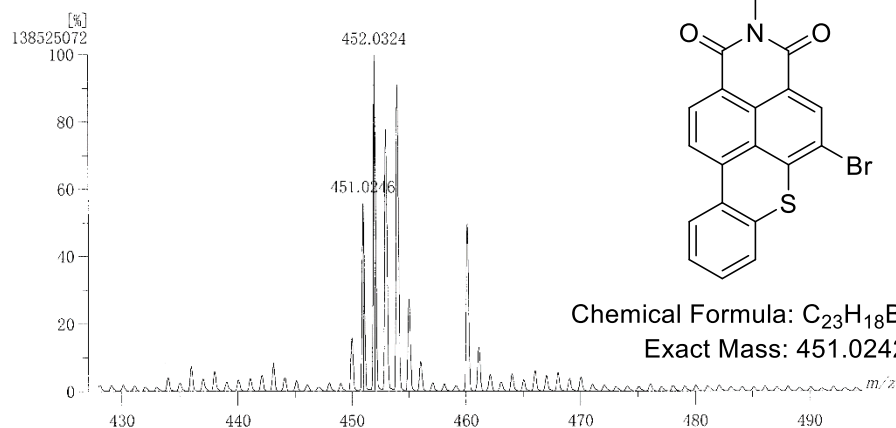


Figure 12: ¹³C NMR I-BTXI-Br

Mass Spectra

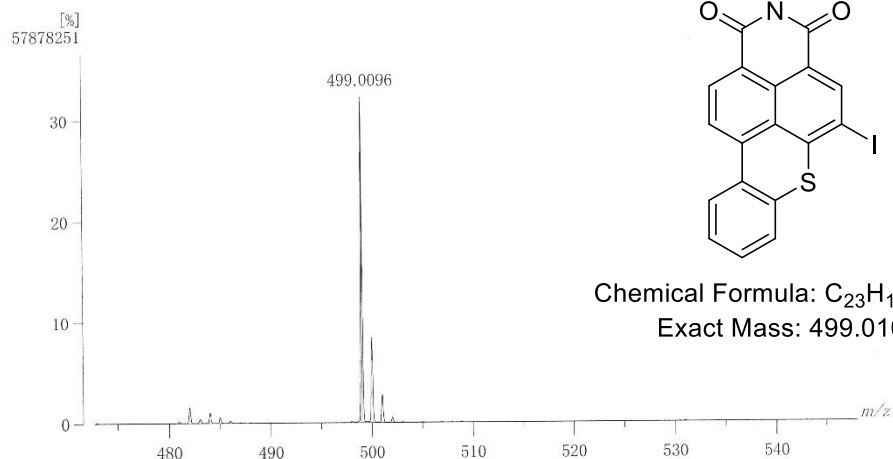
[Mass Spectrum]
 Data : CL21-FAB+Xe001 Date : 28-Feb-2019 09:49
 RT : 1.51 min Scan# : (310,407)
 Elements : C 24/0, H 49/0, Br 1/0, N 1/0, O 2/0, S 1/0
 Mass Tolerance : 1mmu
 Unsaturation (U.S.) : -0.5 - 30.0



	Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
1	451.0246	55.82	+1.0 / +0.4	16.0	C23 H18 Br N O2 S
2	452.0324	100.00	+0.9 / +0.4	15.5	C23 H19 Br N O2 S

Figure 13: HRMS BTXI-Br

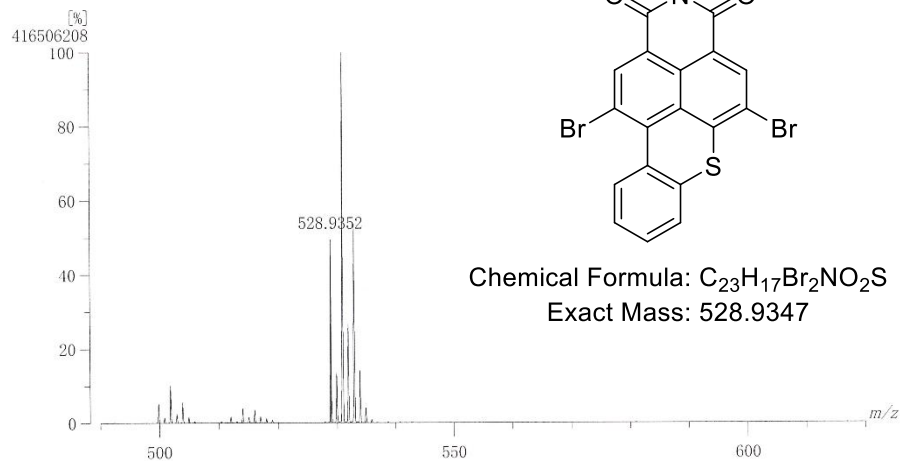
[Mass Spectrum]
 Data : spiro8-01-isobutylane006 Date : 29-Jan-2019 15:37
 RT : 8.56 min Scan# : (2263,2376)
 Elements : C 24/0, H 49/0, N 1/0, O 2/0, S 1/0, I 1/0
 Mass Tolerance : 1000ppm, 1mmu if m/z > 1
 Unsaturation (U.S.) : -0.5 - 30.0



	Observed m/z	Int%	Err [ppm / mmu]	U.S.	Composition
1	499.0096	32.32	-1.4 / -0.7	16.0	C23 H18 N O2 S I

Figure 14: HRMS BTXI-I

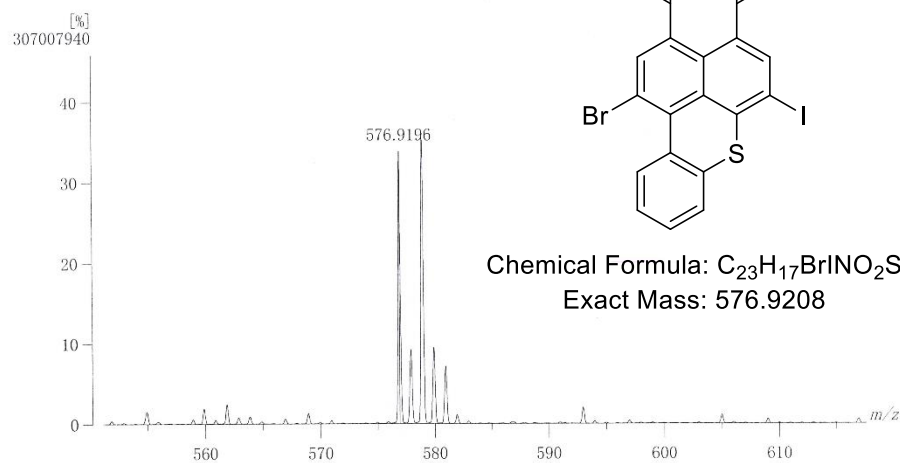
[Mass Spectrum]
 Data : Spiro05-EI003 Date : 24-Jan-2019 10:52
 RT : 3.12 min Scan# : (1016.1093)
 Elements : C 24/0, H 49/0, Br 2/0, N 1/0, O 2/0, S 1/0
 Mass Tolerance : 1000ppm, 1mmu if m/z > 1
 Unsaturation (U.S.) : -0.5 - 50.0



Observed m/z	Int%	Err [ppm / mmu]	U.S. Composition
1 528.9352	49.41	+1.0 / +0.5	16.0 C23 H17 Br2 N O2 S

Figure 15: HRMS Br-BTXI-Br

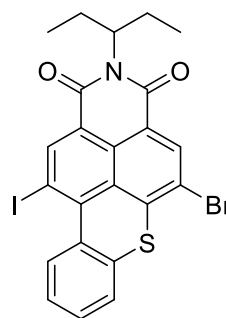
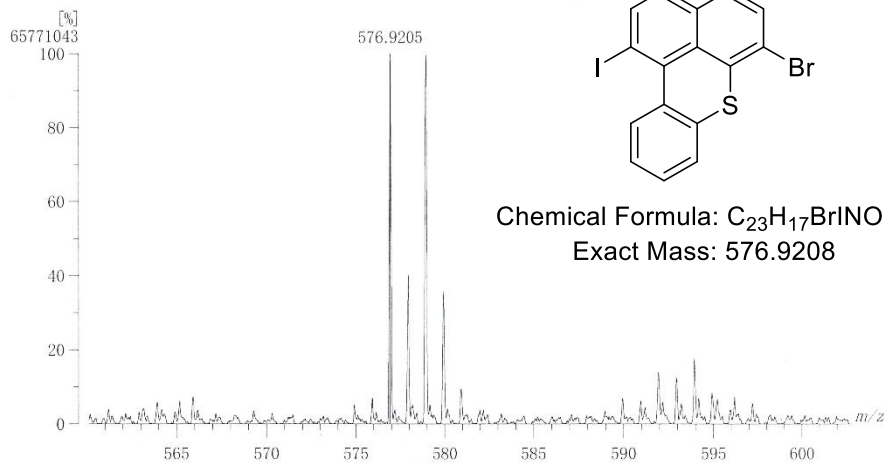
[Mass Spectrum]
 Data : spiro67-EI001 Date : 09-Apr-2019 10:56
 RT : 14.65 min Scan# : (4531.4817)
 Elements : C 24/0, H 49/0, Br 1/0, N 1/0, O 2/0, S 1/0, I 1/0
 Mass Tolerance : 2mmu
 Unsaturation (U.S.) : -0.5 - 30.0



Observed m/z	Int%	Err [ppm / mmu]	U.S. Composition
1 576.9196	33.88	-2.1 / -1.2	16.0 C23 H17 Br N O2 S I

Figure 16: HRMS Br-BTXI-I

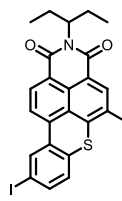
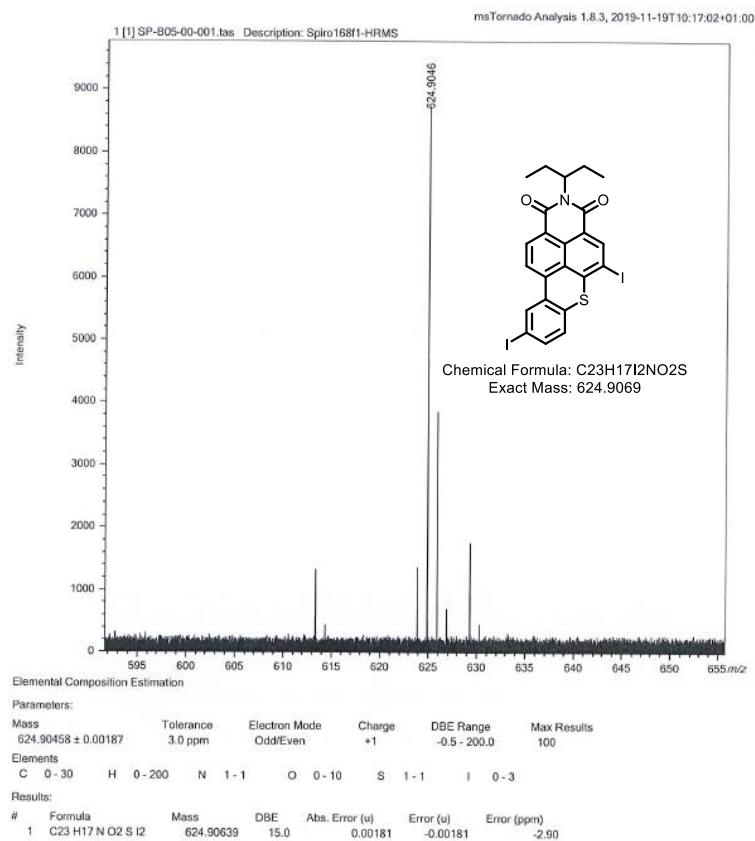
[Mass Spectrum]
 Data : spiro69-FABnegXe001 Date : 11-Apr-2019 15:27
 RT : 7.87 min Scan# : (987,1104)
 Elements : C 24/0, H 49/0, Br 1/0, N 1/0, O 2/0, S 1/0, I 1/0
 Mass Tolerance : 1000ppm, 1mmu if m/z > 1
 Unsaturation (U.S.) : -0.5 - 30.0



Chemical Formula: $C_{23}H_{17}BrINO_2S$
 Exact Mass: 576.9208

Observed m/z	Int%	Err [ppm / mmu]	U.S. Composition
1 576.9205	100.00	-0.5 / -0.3	16.0 C23 H17 Br N O2 S I

Figure 17: HRMS I-BTXI-Br



Chemical Formula: $C_{23}H_{17}I_2NO_2S$
 Exact Mass: 624.9069

Elemental Composition Estimation

Parameters:

Mass	Tolerance	Electron Mode	Charge	DBE Range	Max Results
624.90458 ± 0.00187	3.0 ppm	Odd/Even	+1	-0.5 - 200.0	100

Elements

C	H	N	O	S	I
0 - 30	0 - 200	1 - 1	0 - 10	1 - 1	0 - 3

Results:

#	Formula	Mass	DBE	Abs. Error (u)	Error (u)	Error (ppm)
1	C23 H17 N O2 S I2	624.90639	15.0	0.00181	-0.00181	-2.90

Figure 18: HRMS I-BTXI-I

Crystallographic data

The **I-BTXI-I** structure showed disordered electron density which could not be reliably modeled and the program PLATON/SQUEEZE (A.L. Spek V270519 (1980-2019)) was used to remove the corresponding scattering contribution from the intensity data. This electron density can be attributed to toluene molecules and the assumed solvent composition was used in the calculation of the empirical formula, formula weight, density, linear absorption coefficient, and F(000).

Crystal	2(Br-BTXI-Br), PhMe	BTXI-I	3(I-BTXI-I), PhMe	I-BTXI-Br	Br-BTXI-I
Formula	C ₅₃ H ₄₂ Br ₄ N ₂ O ₄ S ₂	C ₂₃ H ₁₈ INO ₂ S	C ₇₆ H ₅₉ I ₆ N ₃ O ₆ S ₃	C ₂₃ H ₁₇ BrINO ₂ S	C ₂₃ H ₁₇ BrINO ₂ S
Molecular Weight	1154.64	499.34	1967.84	578.24	578.24
Temperature (K)	200	293	150	295	295
Crystal system	Monoclinic	Monoclinic	Trigonal	Monoclinic	Orthorhombic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> -3	<i>P</i> 2 ₁ / <i>c</i>	<i>Pbcn</i>
a (Å)	20.8497(3)	14.1742(4)	23.5066(2)	7.4020(2)	22.5232(7)
b (Å)	7.4879(1)	12.1233(3)	23.5066(2)	17.7593(3)	7.4885(3)
c (Å)	29.7763(5)	22.8334(5)	7.3117(1)	31.1827(5)	24.3955(9)
α (°)	90	90	90	90	90
β (°)	94.603(1)	90.112(2)	90	91.047(2)	90
γ (°)	90	90	120	90	90
V (Å ³)	4633.7(1)	3923.6(2)	3498.88(8)	4098.4(1)	4114.7(3)
Z	4	8	2	8	8
Crystal color	Orange	Orange	Orange	Orange	Orange
Crystal size (mm ³)	0.37x0.076x0.04	0.31x0.039x0.028	0.148x0.04x0.034	0.253x0.12x0.042	0.278x0.058x0.02
D _c (g cm ⁻³)	1.655	1.691	1.868	1.874	1.867
F(000)	2312	1984	1900	2256	2256
μ (mm ⁻¹)	5.481	13.973	22.197	15.680	15.618
Trans (min/max)	0.50637/1.000	0.54479/1.000	0.49257/1.000	0.24965/1.000	0.58802/1.000
θ (min/max) (°)	2.978/72.067	3.667/72.186	3.761/74.066	2.835/73.549	3.624/73.982
Data collected	16509	15962	16286	18110	10332
Data unique	8756	7511	4650	8065	4073
Data observed	7551	6434	4370	7295	3575
R (int)	0.0293	0.0328	0.0233	0.0313	0.0310
Parameters	599	509	283	527	264
R ₁ [I > 2σ(I)]	0.0389	0.0365	0.0193	0.0383	0.0295
wR ₂ [I > 2σ(I)]	0.0982	0.0920	0.0523	0.1101	0.0725
R ₁ [all data]	0.0461	0.0441	0.0211	0.0416	0.0344
wR ₂ [all data]	0.1039	0.0987	0.0536	0.1143	0.0766
GOF	1.031	1.014	0.899	1.025	1.029
Largest diff. peak and hole (e.Å ⁻³)	1.305 /-0.415	0.781/-0.750	0.659/-0.856	1.197 /-0.722	0.554/-0.546
CCDC number	1970428	1970429	1970430	1970431	1970434

Regioselective mono and homohetero dihalogenation of th... (2.21 MiB)

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