Efficient Synthesis and Functionalization of 3-Bromo Naphtho[2,3*b*]thiophene

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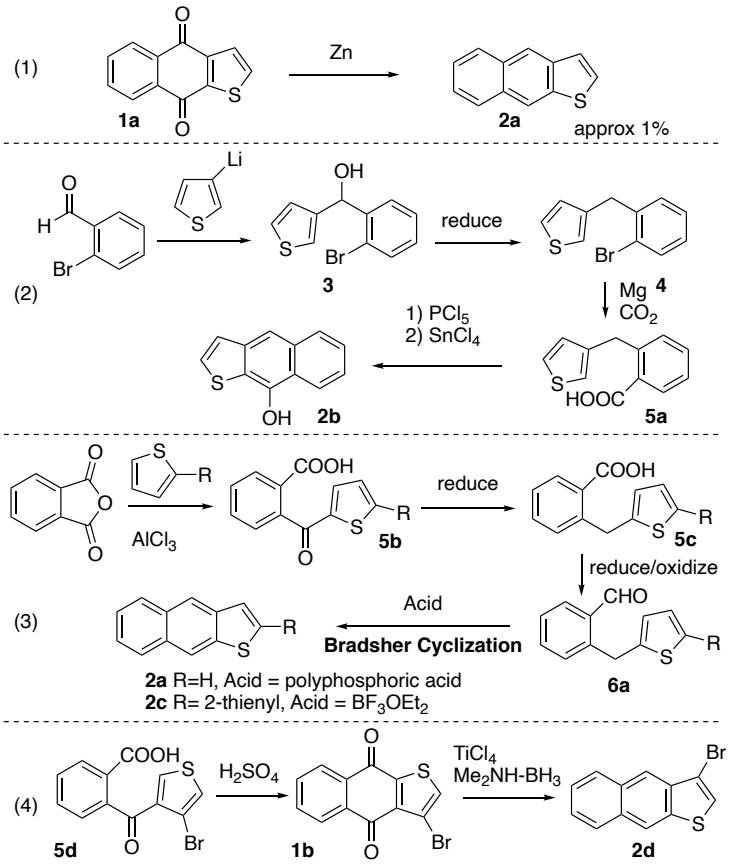
Abstract Naphtho[2,3*b*]thiophene is a linear sulfur containing polycyclic aromatic hydrocarbon. Naphtho[2,3*b*]thiophene and its derivatives are commonly accessed by a Bradsher cyclization. Synthesis of the Bradsher cyclization substrate typically requires harsh conditions, including several oxidation state changes. Here we report an improved, multigram synthesis of 3-bromonaphtho[2,3*b*]thiophene, exploiting a copper-catalyzed cross coupling to prepare the Bradsher substrate in 3 steps from commercial materials while minimizing redox reactions. Modification of the naphthothiophene scaffold in the 3-position has not previously been reported. In this work, the 3-bromonaphthothiophene is further functionalized via lithium-halogen exchange, with the key finding being a specific order of addition in lithiation is required to avoid undesired rearrangement reactions. A small yet versatile set of derivatives, including a naphthothiophene-containing chiral amine are prepared.

Introduction

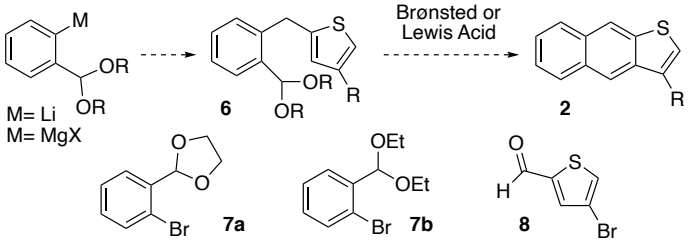
In the course of our research program involving chiral amines, we wished to synthesize amines containing a naphtho[2,3*b*]thiophene group. Naphthothiophenes are isomers of dibenzothiophene, and have found use in molecular electronic applications, including field-effect transistors,[1] and medicinal chemistry.[2] The linear isomer, naphtho[2,3*b*]thiophene (hereafter abbreviated naphthothiophene) is not currently commercially available. The first synthesis of naphthothiophene was reported by Carruthers (Scheme 1, equation 1).[3] The key step involved zinc mediated reduction of quinone **1a**, with a yield of naphthothiophene **2a** on the order of 1%. Carruthers pointed out that naophthothiophene is more stable than anthracene towards dearomatization of the central ring, by either Diels-Alder reaction, or oxidation, implying replacement of anthracenyl groups with naphthothienyl groups may impart added stability to molecules.[4] A similar route by MacDowell and co-workers involved access to the naphthothiophene core by Friedel-Crafts acylation (Scheme 1 equation 2).[5] MacDowell's synthesis began by addition of 3-thienyllithium to 2-bromobenzaldehyde, followed by reduction of the doubly-benzylic alcohol product **3** to afford benzyl-thiophene derivative **4.** Carbonation of the Grignard reagent derived from **4** afforded acid **5a**, which was cyclized via intramolecular Friedel-Crafts acylation with the corresponding acyl chloride, affording hydroxy naphthothiophene **2b**. Castle and co-workers developed a similar route to **2a** , avoiding formation of a hydroxy-naphthothiophene by changing the oxidation state of the cyclization partner to an aldehyde in **6a** (Scheme 1, equation 3).[6] Such intramolecular Friedel-Crafts cyclizations with carbonyls are commonly termed Bradsher cyclizations.[7]



Scheme 1. Pertinent Synthetic Routes to Naphthothiophene and Derivatives

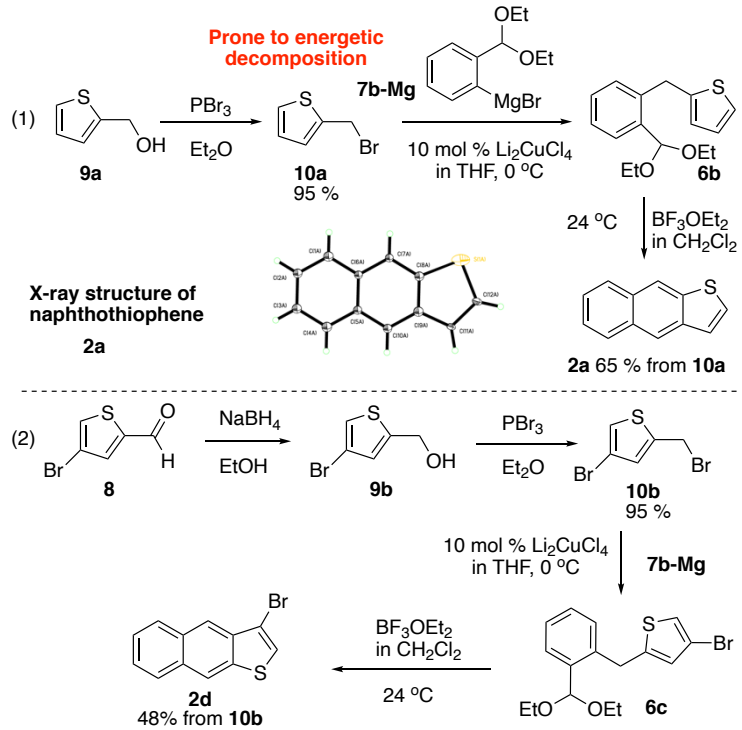
In Castle's Bradsher substrate, the cyclization occurred on the 3-position of thiophenes **6a**. Related intermediates were also accessed by Mohanakrishnan and co-workers.[8] Both groups used a similar strategy to access that substrate, which was different than that of MacDowell, and reminiscent of Carruthers' earlier work.[3B] Friedel-Crafts reaction between a thiophene and phthalic anhydride afforded keto-acid **5b** (Scheme 1, equation 3). The ketone could be selectively reduced via Clemmensen reduction to afford acid **5c**. Transformation of **5c** to **6a** was accomplished by reduction to the alcohol, and reoxidation to the aldehyde. Castle and co-workers employed poly-phosphoric acid for the Bradsher reaction to afford naphthothiophene **2a**, while Mohanakrishnan and co-workers subsequently employed more conveniently handled BF_3 etherate in the Bradsher cyclization.[8] In this work a 2-thienyl substituent in the 2-position of the thiophene withstood the synthesis to afford 2-(2-thienyl)-naphthothiophene **2c**. Mohanakrishnan subsequently showed HI/red phosphorus could effect both the reduction and cyclization step.[9] Further studies by Mohanakrishnan and co-workers also showed that malonylidene units could be used as an aldehyde surrogate in comparable chemistry with very electron rich arenes, leading to elimination of a malonate rather than water.[10] In another approach, Steinmetz and co-workers accessed 3-bromonaphthothiophene **2d** via a more successful modification of the Carruthers method (Scheme 1, equation 4).[11] Keto-acid **5d** was accessed by Friedel-Crafts chemistry and thiophene bromination, and subsequently cyclized to quinone **1b** employing sulfuric acid. Reduction of quinone **1b** to **2d** in the presence of a titanium tetrachloride/amine-borane mixture occurred with a synthetically useful yield. While overreduction did occur, the overreduction product could be converted to **2d** with DDQ. Loss of the bromide was not reported under these conditions. A completely different approach to 3-iodonaphthothiophene that did not involve Bradsher cyclization was reported by Tovar and co-workers,[12] employing methodology developed by Larock and co-workers,[13] and elaborated by Takimiya and co-workers.[14] While this synthesis was relatively efficient it used high loadings of palladium, rendering scale-up expensive.

Results and discussion



Scheme 2. Envisioned Bradsher approach to 3-bromonaphthothiophene, and key starting materials

We wished to synthesize either parent naphthothiophene **2a** or 3-bromonaphthothiophene **2d** as substrates for further derivatization. In considering practical scale-up of the reaction, we wished to avoid the phthalic anhydride Friedel-Crafts step used in earlier routes because of negative experiences with copious amounts of aluminate waste necessitating a difficult filtration. The subsequent ketone reduction also presented practicality or safety issues. The harsh Clemmensen conditions required amalgamation, and the use of I_2/red phosphorus presented supply/regulatory issues in our jurisdiction. The Bradsher cyclizations reported by Castle and Mohanakrishnan to prepare thiophene-containing acenes were particularly effective, because of the electron-rich nature of thiophenes. We wished to keep the efficient Bradsher reaction as a key step. Since Steinmetz did not employ a Bradsher cyclization with an aldehyde to access **2d**,[11] we remained uncertain if bromo-substitution on the thiophene, which may withdraw electron density would perturb the outcome of the reaction. We recognized that MacDowell's approach would represent a more efficient way of accessing the Bradsher cyclization substrate than the thiophene phthaloylation used by Castle and Mohanakrishnan, if oxidation state changes could be minimized. Accordingly, we targeted preparation of Bradsher substrates from an organometallic already containing a latent aldehyde, so that the carbonation and the two subsequent oxidation state changes originally used by MacDowell could be avoided (Scheme 2). Bromo-acetal **7a** can be prepared in one step from 2-bromobenzaldehyde, while bromo-acetal **7b** and bromo-thiophenecarbaldehyde **8** are commercially available. We recognized the potential of these key starting materials for an improved route. Literature precedent suggests that Bradsher cyclization can directly occur from acetals, meaning that hydrolysis of the acetal may be unnecessary, further improving efficiency.[15]



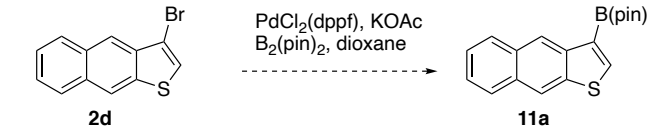
Scheme 3. Realized Bradsher routes to naphthothiophene and 3-bromonaphthothiophene

We decided to prepare a Bradsher cyclization substrate via direct alkylation of the Grignard reagent derived from commercially available bromoacetal **7b** with thienylmethyl bromide **10a**, rather than making **7a** (Scheme 3, equation 1).[16] Bromide **10a** is accessible in 1 step from commercial flavoring ingredient thienylmethanol **9a**.[17] This alkylation procedure avoids the oxidation state changes shown in previous routes to naphthothiophenes shown in Scheme 1. Grignard reagent **7b-Mg** was formed from **7b**

and magnesium turnings. This Grignard reagent was added to a mixture of thienylmethyl bromide **10a** and 10 mol % lithium tetrachlorocuprate in THF at 0 °C to afford coupling product **6b**.[18] Addition of BF_3-OEt_2 to a dichloromethane solution of unpurified **6b** resulted in Bradsher cyclization to naphthothiophene **2a** directly from the acetal. Naphthothiophene **2a** was readily purified by column chromatography. Crystals of **2a** were grown by evaporation from an ethereal solution, and while somewhat disordered, allowed satisfactory X-ray analysis, providing the first crystal structure of **2a**. This sequence afforded naphthothiophene **2a** on gram scale in 65% yield over three steps from 2-thienylmethanol **9a** with only one purification. This result showed that direct alkylation of an acetal-containing Grignard reagent was more efficient than McDowell's approach involving addition to an aldehyde, reduction, organometallic carbonation, and redox reactions of the resulting acid. The reaction directly afforded the methylene connection in the correct oxidation state between the aryl group and thiophene, with the latent aldehyde already in place, meaning that carbonation and redox state changes could be avoided. While this procedure represents a more efficient synthesis in terms of step and purification count than existing syntheses of **2a**, a practical safety issue became apparent during scale-up when we observed that intermediate **10a** was not a stable compound. A five-gram sample of **10a** underwent vigorous decomposition at room temperature. The unobserved decomposition ejected the stopper and charred material from the flask. The remaining black solid was not soluble in any common laboratory solvents, precluding further analysis. Many electron-rich alkoxybenzyl halides are unstable or are only stable in solution.[19] We assume the decomposition noted in our sample of **10a** was a consequence of an exothermic ring-alkylation polymerization, undergoing autocatalysis with release of HBr. Due to this potential safety issue, we discontinued studies toward naphthothiophene **2a** by this route.

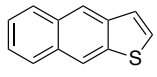
We returned to a synthesis of derivative **2d** via an analogous route to that employed for **2a**, but where the bromine was pre-installed on the desired position of the thiophene with the anticipation that the bromide would stabilize the corresponding intermediate by slowing ring-alkylation polymerization (Scheme 3, Equation 2). Alcohol **9b**, prepared by sodium borohydride reduction of **8**, was brominated with PBr_3 in diethyl ether. Thienyl bromide **10b** solidified upon cooling, and we never observed decomposition of this compound in the solid state, though we were cautious to avoid heating the compound during its preparation. In analogy to **10a** lithium tetrachlorocuprate-mediated coupling with Grignard reagent **7b-Mg** gave **6c**. Attempts to purify **6c** by column chromatography before the Bradsher cyclization did not result in improved purity and only detracted from the yield in the subsequent step. Unpurified **6c** underwent Bradsher cyclization mediated by boron trifluoride etherate to form **2d** in 48% yield from **10b**, indicating minimal perturbation from the bromide to the cyclization reaction. Use of an excess of Grignard reagent in the previous step is important to ensure complete consumption of **10b** since **10b** is challenging to separate from naphthothiophene **2d** by column chromatography, and was observed to release HBr, which decomposed impure samples of **2d**. Only one positional isomer of bromide **2d** was observed after the Bradsher cyclization. Bromonaphthothiophene **2d** was prepared on a 2.5 gram scale over four steps from aldehyde **8** by this route, with only one chromatographic purification required. For our purposes, this result compared favourably in terms of yield, ease of work-up, and reagent availability to the existing route to **2d**.[11]

With an improved route to 3-bromonaphthothiophene in place, a family of derivatives of naphthothiophene were prepared. Reports of functionalization of naphthothiophenes are sparse, with Castle and co-workers having reported acylation in the 2 position,[6] and Steinmetz and co-workers reporting lithiation of the 2 position.[11] None of these reports involve functionalization of the more hindered and less-acidic 3-position.[20] We initially targeted a boronic ester (**11a**, Scheme 4), which represents a versatile handle for further functionalization.

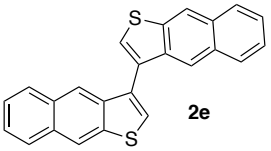


2d **11a**

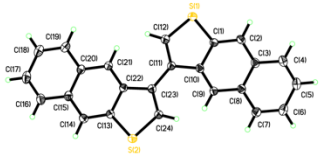
Observed products (other unidentified products were also present)



2a



2e

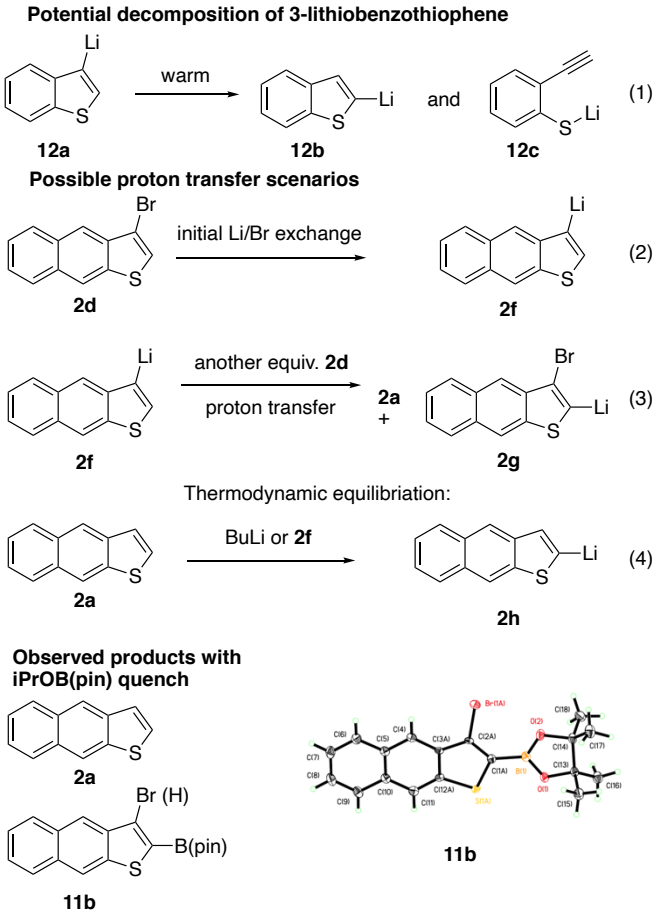


Structure of 2e

Scheme 4. Attempted Miyaura Borylation

We initially attempted a Miyaura borylation due to the mildness of the reported conditions (Scheme 4). Unfortunately, exposure of the bromide to $PdCl_2$(dppf), sodium acetate, and $B_2(pin)_2$ in refluxing dioxane gave a complex mixture of products. Two products were identified. Naphthothiophene **2a** was recovered. Another highly UV active product was observed by TLC and was separated by chromatography. Crystallization and X-ray analysis showed it was the 3,3' bi-naphthothiophene (Scheme 4, compound **2e**). Interestingly, Miyaura borylation on 3-bromobenzothiophene proceeded uneventfully in our hands under the same conditions,[21] implying that the dimerization reactivity might be a property of the specific heterocycle.

We instead decided to target functionalization by lithiation/quench.[22] We had some trepidation about the stability of 3-lithionaphthothiophene **2f** (Scheme 5).[23] To the best of our knowledge, lithiation of naphthothiophene has not been previously reported. As the best approximation found in literature, 3-lithiobenzothiophene **12a** has been reported to undergo both isomerization to more stable 2-lithiobenzothiophene **12b** and ring opening to **12c** upon warming (Scheme 5, equation 1). Upon adding n-BuLi to a solution of **2d** at –78 °C in THF, an immediate colour change was observed. Isopropoxy B(pin) was added after 10 minutes. Unfortunately, this reaction resulted in a relatively complex mixture of products that could not be completely analyzed.

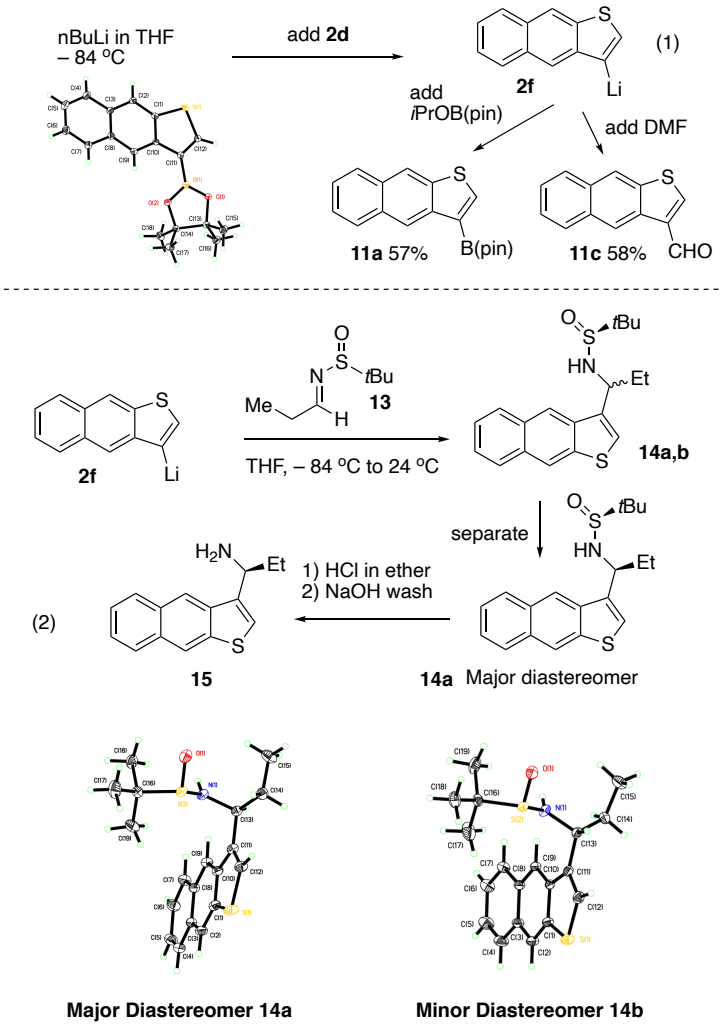


Scheme 5. Initial Lithiation Attempt of 3-bromonaphthothiophene

Both parent naphthothiophene **2a**, and multiple boron containing compounds were observed, however chromatographic separation was not possible in our hands precluding complete characterization. A hint as to what happened was obtained when a single crystal was serendipitously obtained by evaporation of a solution of the product mixture. While the crystal was highly disordered, X-ray crystallography revealed the presence of a bromine in the 3 position and HB(pin) group in the 2-position corresponding to structure **11b**. Furthermore, occupancy of less than 100% was observed for the Br, suggesting the presence of some material with a B(pin) at the 2 position, and a H at the 3 position. Coupled with the presence of parent naphthothiophene **2a**, we speculated that the order of addition meant that in addition to the expected lithiation (Equation 2) rapid proton transfer occurred between organolithium and non-lithiated **2d** (Equation 3), during the course of the addition of the n-BuLi. Also as **2a** was formed, it could undergo lithiation in the most acidic 2-position, either from n-BuLi or organolithium **2f** (Equation 4). Such equilibration phenomena have been reported for the lithiation of 3-bromothiophenes.[24] While a complete scenario of the reactions occurring upon addition of n-butyllithium to 3-bromonaphthothiophene **2d** could not be detailed due to a paucity of data, it was evident this set of conditions would not lead to a viable functionalization reaction. A possible solution was envisioned in the form of inverting the order of addition. We added a solution of bromide **2d** in THF to an excess of n-BuLi in solution in THF at –84 °C, followed by boron

quench in an attempt to circumvent this problem (Scheme 6, Equation 1). Upon following this procedure, arylpinacolboronate **11a** was obtained in 57% yield as one regioisomer after quench and purification. The connectivity was confirmed by X-ray crystallography of a single crystal of **11a** grown by evaporation of a diethyl ether solution. A similar procedure where DMF was employed to quench the organolithium afforded aldehyde **11c** in comparable yield (58%), however minor inseparable impurities (<10% by NMR) were observed in this product.

We then turned our attention to the preparation of chiral amines containing the naphthothiophene moiety. Imine **13**, derived from propionaldehyde and Ellman auxiliary was added to freshly prepared 3-lithionaphthothiophene **2f**.[25] This protocol cleanly afforded **14** as a separable mixture of diastereomers. X-ray quality crystals of both diastereomers **14a** and **14b** were grown by cooling saturated diethyl ether solutions of the isolated diasteromers. In addition to correlating relative configuration to NMR spectra, which will be of use to anyone working in this field, these structures, shown in Scheme 6, confirmed that the products of the Ellman addition were epimers at the newly created stereocentre, rather than regioisomers arising from rearrangement of the lithiated heterocycles. Deprotection of the major diastereomer with ethereal HCl followed by basification afforded chiral amine **15**. We will note to anybody interested in pursuing work with these compounds that an alternate bond connection order, where an Ellman auxiliary was condensed with aldehyde **11c** was less convergent and provided less clean material upon both condensation of the auxiliary, and addition of ethyl Grignards. Other attempts to perform the Ellman chemistry with a methyl rather than ethyl sidechain resulted in inseparable diastereomers, an observation also made in our earlier work with a dibenzothiophene-containing chiral amine, where ethyl sidechains were more tractable than methyl sidechains.[26]



Scheme 6. Successful functionalization of 3-bromonaphthothiophene

Conclusions

In conclusion, we developed an approach to naphthothiophenes using an efficient Bradsher cyclization, while improving the synthesis of the Bradsher substrate versus previous routes by leveraging copper-mediated coupling of a Grignard reagent containing a latent aldehyde to minimize oxidation state changes. This strategy avoids harsh reagents and is the first use of this variety of

organo-copper coupling in naphthothiophene synthesis. This has resulted in an efficient route to 3-bromonaphthothiophene **2d**. Functionalization of the naphthothiophene proved challenging, with a Miyura borylation giving an undesired outcome, however we show that lithiation of 3-bromonaphthothiophene **2d** is feasible. Care regarding the addition order was needed, with addition of the aryl bromide to the alkyllithium being required to avoid undesirable isomerization. We showed how 3-bromonaphthothiophene **2d** can be transformed into an enantiopure amine **15** using Ellman auxiliary methodology. A specific ethyl side-chain, and addition of the lithiated arene to the imine of propionaldehyde were required for clean reaction outcome, and practical separation of diastereomers. Further exploration of the applications of naphthothiophene containing molecules are in progress and will be reported in due course.[27]

Conflicts of interest

There are no conflicts to declare

Acknowledgements

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Dr. Michael Lumsden and Mr. Xiao Feng (Dalhousie University) are thanked for assistance with NMR spectroscopy and mass spectrometry, respectively. Dr. Travis Lundrigan is thanked for the preparation of a batch of **9b** and **14**.

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[27] Preliminary aspects of this work, including the preparation of **2a**, **2d**, **11a** and **11c** were reported in E. N. Welsh, E. K. Burke, K. N. Robertson, A. W. H. Speed, *ChemRxiv*. 2019

Efficient Synthesis and Functionalization of 3-Bromo Naphtho[2,3*b*]thiophene

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General Experimental Considerations

Reactions were run under nitrogen, using oven-dried glassware unless otherwise specified. ^{1}H, ^{13}C, and ^{11}B NMR data were collected at 300K on a Bruker AV-500 NMR spectrometer. ^{1}H NMR spectra are referenced to residual non-deuterated NMR solvent ($CHCl_3$ =7.26 ppm). ^{13}C NMR spectra are referenced to the central $CDCl_3$ peak (77.16 ppm). Mass spectrometric data were acquired by Mr. Xiao Feng (Mass Spectrometry Laboratory, Dalhousie University).

Solvents

Diethyl ether was purchased as anhydrous ACS reagent grade, >99.0% stabilized by BHT in 1L metal cans from Aldrich.

Dichloromethane (ACS grade) was purchased from Fisher. Dichloromethane for reactions was distilled from calcium hydride immediately before use, while no purification was carried out on dichloromethane used for extractive work-ups.

Deuterochloroform for NMR of complexes was stored over activated 3 Å molecular sieves, but otherwise used as received. Deuterochloroform for substrates and products was used as received.

Tetrahydrofuran was purchased from Aldrich in a Sure/seal® bottle (anhydrous, >99.9%, inhibitor free, catalogue number 401757). Tetrahydrofuran was used directly from this bottle for Grignard reactions and lithiations.

Reagents

2-Bromobenzaldehyde diethyl acetal, n-Butyllithium, dimethyl formamide, magnesium turnings, phosphorus tribromide, and propionaldehyde were purchased from Aldrich and used directly as received.

4-Bromothiophene-2-carboxaldehyde and isopropoxy B(pin) were purchased from Oakwood Chemical and used directly as received.

Ellman Sulfinimide Auxiliary was purchased from Oakwood Chemical and configuration was verified by measurement of optical rotation.

X-Ray Crystallography Data

The crystal chosen was attached to the tip of a MicroLoop with Paratone-N oil. Measurements were made on a Bruker D8 VENTURE diffractometer equipped with a PHOTON III CMOS detector using monochromated Mo Kα radiation (λ = 0.71073 Å) from an Incoatec micro-focus sealed tube at the temperature indicated, 100 to 150 K [1]. The initial orientation and unit cell were indexed using a least-squares analysis of the reflections collected from a 180° phi-scan, 2 seconds per frame and 1° per frame. For data collection, a strategy was calculated to maximize data completeness and multiplicity, in a reasonable amount of time, and then implemented using the Bruker Apex 3 software suite [1]. The crystal to detector distance was set to 4 cm and 15 second frames were collected unless otherwise stated. Cell refinement and data reduction were performed with the Bruker SAINT [2] software, which corrects for beam inhomogeneity, possible crystal decay, Lorentz and polarisation effects. A multi-scan absorption correction was applied (SADABS [3]). The structure was solved using SHELXT-2014 [4] and was refined using a full-matrix least-squares method on F^2 with SHELXL-2018 [4]. The non-hydrogen atoms were refined either as part of a rigid group (see below) or anisotropically. The hydrogen atoms bonded to carbon were included at geometrically idealized positions and were not refined. The isotropic thermal parameters of these hydrogen atoms were fixed at $1.2U_{eq}$ of the parent carbon atom or $1.5U_{eq}$ for methyl hydrogens. All H(N) hydrogen atom positions were located in near final Fourier difference maps. They were allowed to refine isotropically and were not restrained in any way.

Compound **2a**

The crystals supplied for this compound were in the form of very thin sheets. They did not diffract well at all, and it was very difficult to obtain a useable data set; many crystals were attempted with little success. Even with the chosen long frame times (20 sec), very few reflections were obtained. These were weak and the resolution of the data set as a whole was poor. The data was cut off at a resolution of 0.83 Å by adding a SHEL instruction to the refinement. This resulted in a number of checkcif alerts once the final refinement had been carried out. Level C alerts were obtained because of the High R1 Value, High wR2 Value and Poor Data / Parameter Ratio. The poor quality of the data set also resulted in the absolute structure not being reliably determined.

Because of the lack of data, a rigid group refinement was carried out for the naphthyl groups. This helped to increase the final data/parameter ratio to a barely acceptable 6.83. The remaining atoms of the 5-membered rings containing the sulfur atoms were freely refined, but 1,2 and 1,3 distances were restrained to be equal using SADI commands. All of the carbon atoms were restrained to have similar thermal parameters, while C11 and C12 (individually) were restrained to have identical thermal parameters in each component of the disorder. The sulfur atoms in each part of the disorder were restrained to have similar thermal parameters and these were also restrained to have more isotropic geometries. After all of this the final data / restraints / parameters ratio was still poor (1597 / 715 / 141) but there were no level A or B checkcif alerts.

The final model refined for this structure included a four part disorder of the entire molecule. In essence, the molecule could crystallize with the 5-membered ring containing the sulfur on either side of the central naphthyl rings, and in that 5-membered ring, the sulfur atom could be either up or down (bonded to different atoms of the naphthyl ring). The occupancies of these four

components of the disorder were modelled and they refined to a ratio of 45.2 : 18.7 : 19.0 : 17.1% with errors of roughly 1.5%. The main component of the disorder is favoured (and it is shown in the figure in the main manuscript), while the other three components have a roughly equal distribution.

Compound **2e**

Data collection with 30 second frames resulted in a data set that could be integrated to a resolution of 0.65 Å resolution. All of this data was used in the final refinement.

Compound **11a**

One reflection (3 3 6) was found to have poor agreement between F_{obs}^2 and F_{calc}^2 and was removed from the final refinement using an OMIT instruction. The data was integrated to θ_{max} = 39.66° (0.56 Å resolution).

Compound **11b**

The final model refined for this structure included a two part disorder of the 5-membered C_4SBr ring. In essence, the molecule could crystallize with the sulfur center on either side of the ring, and the C-Br group on the opposite side of the ring in each component. The occupancies of the two components of the disorder were modelled and they refined to a ratio of 91.88 and 8.12 % with errors of 0.14%. The main component of the disorder is favoured (and it is shown in the figure in the main manuscript). During the refinement, the disordered region of the molecule had to be heavily restrained. A SAME instruction was used to make the two 5-membered ring geometries similar. Additional 1,3 bond length restraints were added, as were restraints to make the thermal parameters of the ring atoms more similar.

A SHEL instruction was added to cut the data used in the refinement off at θ_{max} = 28.28°. Above this resolution (0.83 Å) the data collected was mostly noise.

Compound **14a** (major product)

The crystal used for the data collection was not cut. When other crystals were cut, they shredded into long shards that were not suitable for data collection. To avoid this, a long needle/plate crystal was used without cutting it to fit it into the beam. However, this did result in a level C checkcif alert for the crystal being too long for the beam size. The other two dimensions were suitable.

The molecule was found to crystallize in the chiral space group $P2_1$, with an S configuration at C13. The absolute structure of the molecule was reliably determined. Using the program Platon [5] the refined structure was calculated to have a Flack parameter of –0.012(16), a Parsons

parameter of –0.003(16) and a Hooft parameter of 0.012(15). These values agree with the Parson's value calculated by the program SHELXL, –0.012(16) from 3921 selected quotients.

Compound **14b** (minor product)

The molecule was found to crystallize in the chiral space group $P2_12_12_1$, with an R configuration at C13. The absolute structure of the molecule was reliably determined. Using the program Platon [5] the refined structure was calculated to have a Flack parameter of –0.002(8), a Parsons parameter of -0.001(7) and a Hooft parameter of –0.007(7). These values agree with the Parson's value calculated by the program SHELXL, –0.002(8) from 4386 selected quotients.

References

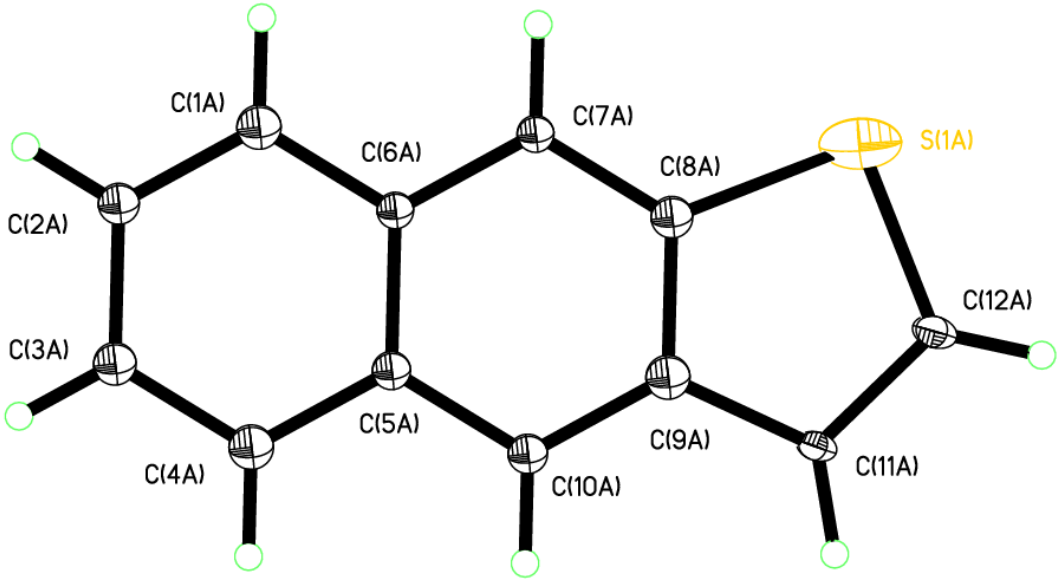
[1] APEX 3 (Bruker, 2018) Bruker AXS Inc., Madison, Wisconsin, USA.
[2] SAINT (Bruker, 2016) Bruker AXS Inc., Madison, Wisconsin, USA.
[3] SADABS (Bruker, 2016) Bruker AXS Inc., Madison, Wisconsin, USA.
[4] Sheldrick, G.M. (2015) *Acta Cryst*., A71, 3-8; Sheldrick, G.M. (2015) *Acta Cryst*., C71, 3-8.
[5] Spek, A.L. (2009) *Acta Cryst*., D65, 148-155.

Table Sx: Crystal data and structure refinement details.

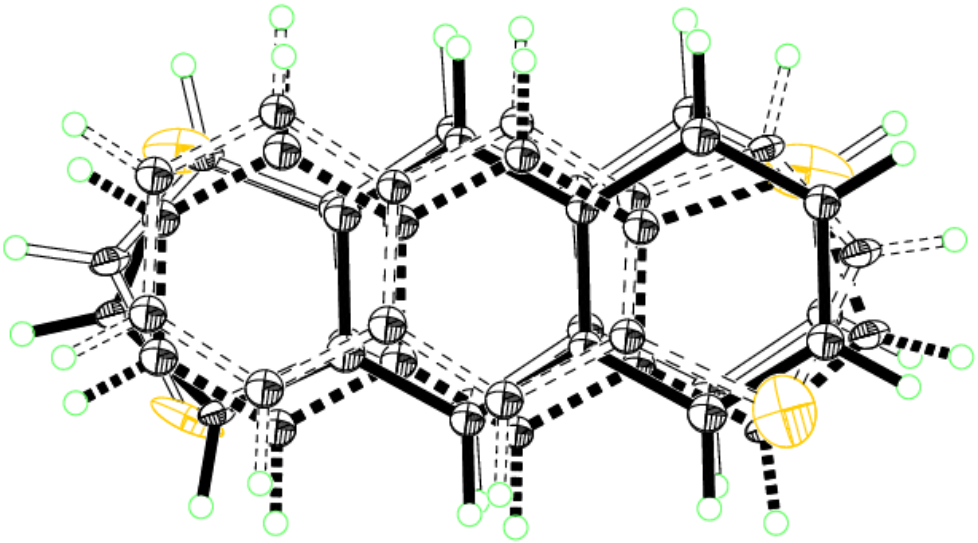
Identification code	**2a**	**2e**	**11a**
CCDC deposit number	1958922	2116338	1999813
Temperature (K)	100	150	100
Empirical formula	$C_{12}H_8S$	$C_{24}H_{14}S_2$	$C_{18}H_{19}BO_2S$
Formula weight	184.24	366.47	310.20
Crystal system	Orthorhombic	Triclinic	Monoclinic
Space group	$P2_12_12_1$	P-1	$P2_1/c$
Unit cell dimensions (Å and º)	a = 5.8206(13)	a = 3.8894(4)	a = 5.9637(3)
	b = 7.6166(16)	b = 14.4863(12)	b = 8.7167(4)
	c = 19.769(4)	c = 15.6726(14)	c = 30.1381(15)
	α = 90	α= 69.643(3)	α = 90
	β = 90	β= 86.726(3)	β = 90.395(2)
	γ = 90	γ = 86.545(3)	γ = 90
Volume (Å^3)	876.4(3)	825.77(13)	1566.66(13)
Z	4	2	4
Density (calculated, Mg/m^3)	1.396	1.474	1.315
Absorption coefficient (mm^{-1})	0.308	0.327	0.210
F(000)	384	380	656
Crystal size (mm^3)	0.296x0.226x0.029	0.202x0.024x0.019	0.377x0.344x0.043
Theta range of data (º)	2.866 to 25.341	2.370 to 33.164	2.432 to 36.317
Index ranges (h, k, l)	-7/6, -9/9, -23/23	-5/5, -22/22, -24/24	-9/9, -14/14, -50/50
Reflections collected	19632	64074	60760
Independent reflections	1597	6266	7579
R(int)	0.1073	0.0568	0.0629
Completeness to 25.242º (%)	99.9	99.99	99.8
Max. and min. transmission	0.7477 and 0.5483	0.7465 and 0.7068	0.7478 and 0.5934
Data / restrains / parameters	1597 / 715 / 141	6266 / 0 / 235	7579 / 0 / 203
Goodness-of-fit on F^2	1.160	1.195	1.153
Final R indices [I>2sigma(I)]	R1 = 0.1360	R1 = 0.0475	R1 = 0.0586
	wR2 = 0.2796	wR2 = 0.1034	wR2 = 0.1216
R indices (all data)	R1 = 0.1511	R1 = 0.0838	R1 = 0.0721
	wR2 = 0.2871	wR2 = 0.1350	wR2 = 0.1270
Absolute structure parameter	0.41(12)	n.a.	n.a.
Largest diff. peak and hole (e.Å^{-3})	0.475 and -0.624	0.587 and -0.477	0.586 and -0.463

Table Sx: Crystal data and structure refinement details (continued).

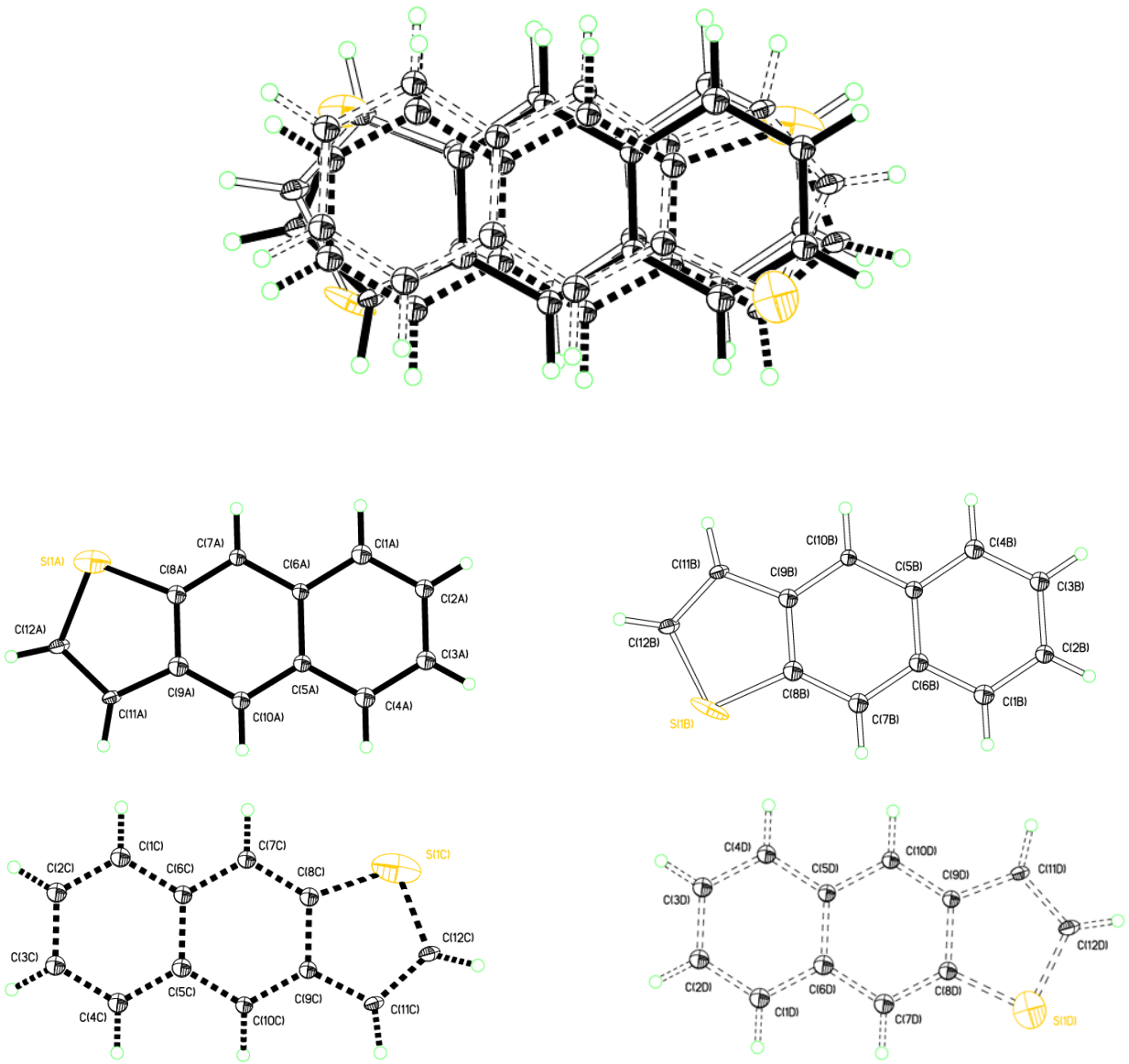
Identification code	**11b**	**14a - major**	**14b - minor**
CCDC deposit number	1999814	1999812	1999815
Temperature (K)	100	125	125
Empirical formula	$C_{18}H_{18}BBrO_2S$	$C_{19}H_{23}NOS_2$	$C_{19}H_{23}NOS_2$
Formula weight	389.10	345.50	345.50
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1$	$P2_12_12_1$
Unit cell dimensions (Å and º)	a = 9.4189(4)	a = 8.9768(4)	a = 8.9317(4)
	b = 10.6805(5)	b = 9.4961(4)	b = 9.4815(4)
	c = 16.5959(7)	c = 11.1085(5)	c = 21.8980(10)
	α = 90	α = 90	α = 90
	β = 91.771(2)	β = 102.289(2)	β = 90
	γ = 90	γ = 90	γ = 90
Volume (Å^3)	1668.73(13)	925.24(7)	1854.45(14)
Z	4	2	4
Density (calculated, Mg/m^3)	1.549	1.240	1.237
Absorption coefficient (mm^{-1})	2.594	0.292	0.291
F(000)	792	368	736
Crystal size (mm^3)	0.180x0.106x0.075	0.651x0.103x0.032	0.374x0.152x0.098
Theta range of data (º)	2.268 to 28.282	2.657 to 39.384	2.341 to 39.380
Index ranges (h, k, l)	-12/12, -14/14, -22/22	-15/15, -16/16, -19/19	-15/15, -16/16, -37/38
Reflections collected	64929	41764	105907
Independent reflections	4134	10545	10795
R(int)	0.0414	0.0375	0.0335
Completeness to 25.242º (%)	99.8	99.3	98.1
Max. and min. transmission	0.7478 and 0.6629	0.7478 and 0.7004	0.7478 and 0.6954
Data / restrains / parameters	4134 / 158 / 267	10545 / 1 / 216	10795 / 0 / 216
Goodness-of-fit on F^2	1.081	1.049	1.063
Final R indices [I>2sigma(I)]	R1 = 0.0315	R1 = 0.0342	R1 = 0.0276
	wR2 = 0.0883	wR2 = 0.0774	wR2 = 0.0718
R indices (all data)	R1 = 0.0325	R1 = 0.0445	R1 = 0.0305
	wR2 = 0.0889	wR2 = 0.0839	wR2 = 0.0736
Absolute structure parameter	n.a.	-0.012(16)	-0.002(8)
Largest diff. peak and hole (e.Å^{-3})	0.627 and -0.858	0.370 and -0.376	0.318 and -0.269



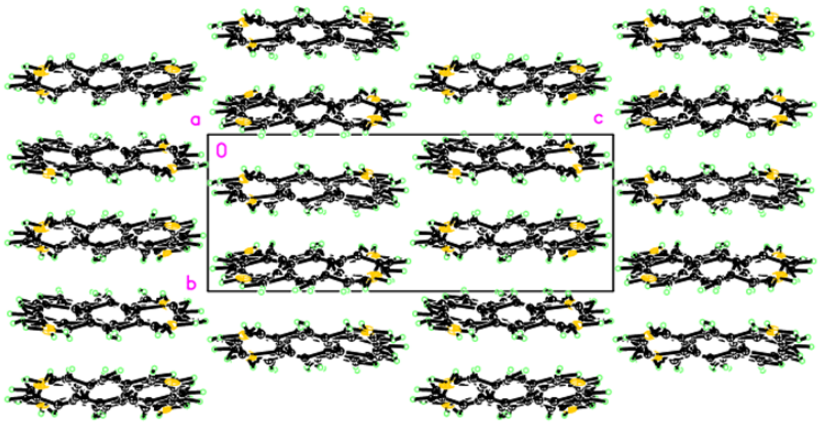
Structure of compound **2a** showing only the main component of the 4-part disordered model. Thermal ellipsoids have been drawn at the 50% probability level. Hydrogen atoms have not been labelled.



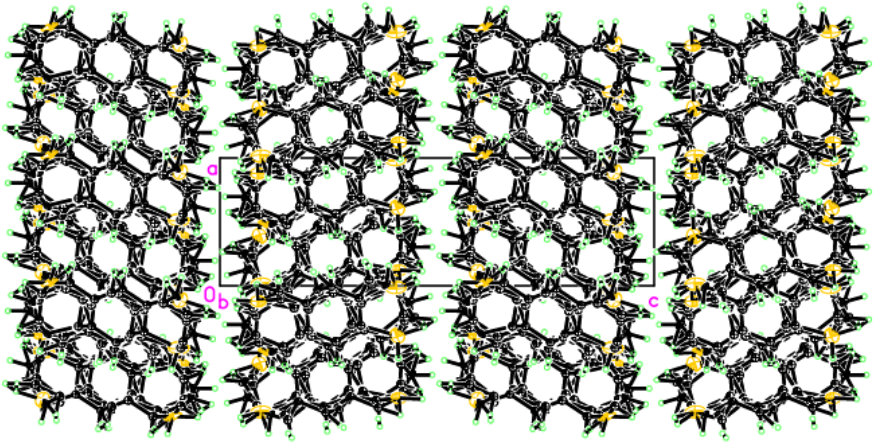
Structure of compound **2a** showing all components of the 4-part disordered model. Thermal ellipsoids have been drawn at the 50% probability level.



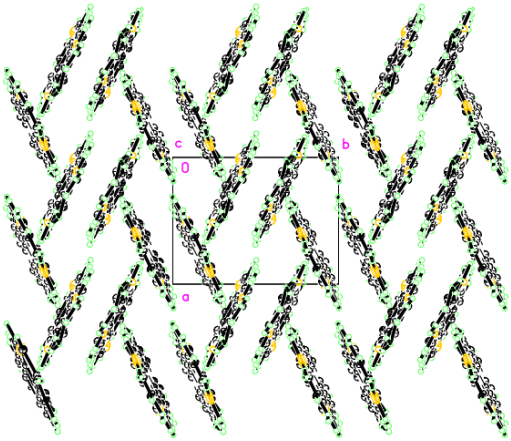
Structure of compound **2a** showing all components of the 4-part disordered model (top). In the four lower diagrams each of the four individual components are shown. Thermal ellipsoids have been drawn at the 50% probability level. The heavy atoms have been labelled in the individual diagrams.



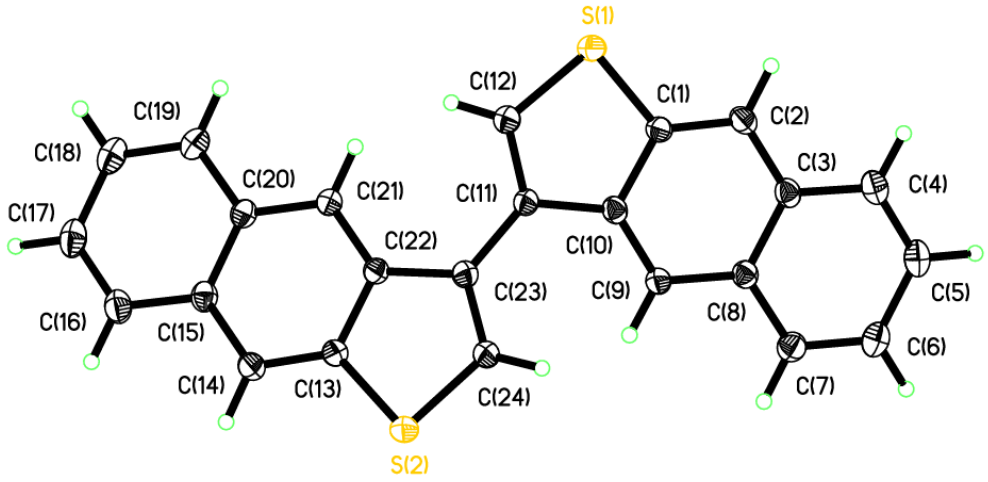
Packing diagram of compound **2a** viewed down the *X*-axis.



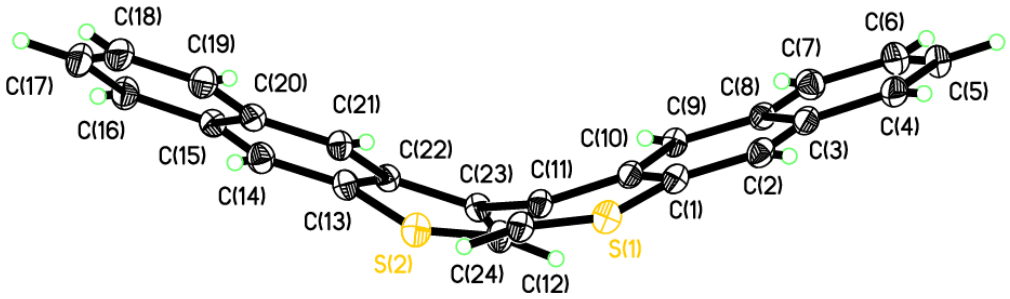
Packing diagram of compound **2a** viewed down the *Y*-axis.



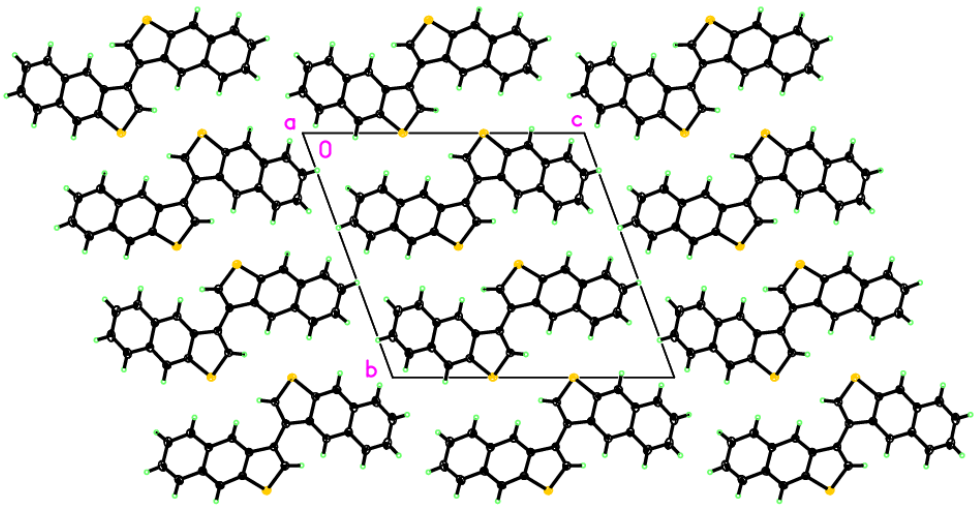
Packing diagram of compound **2a** viewed down the *Z*-axis.



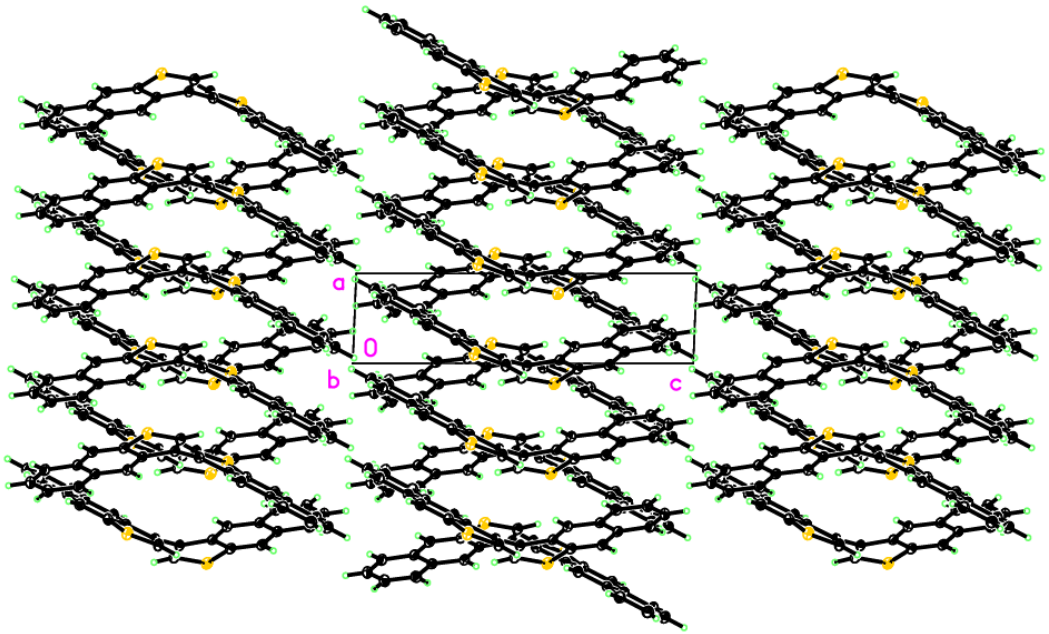
Structure of compound **2e**. Thermal ellipsoids are drawn at the 50 % probability level. Hydrogen atoms have not been labelled.



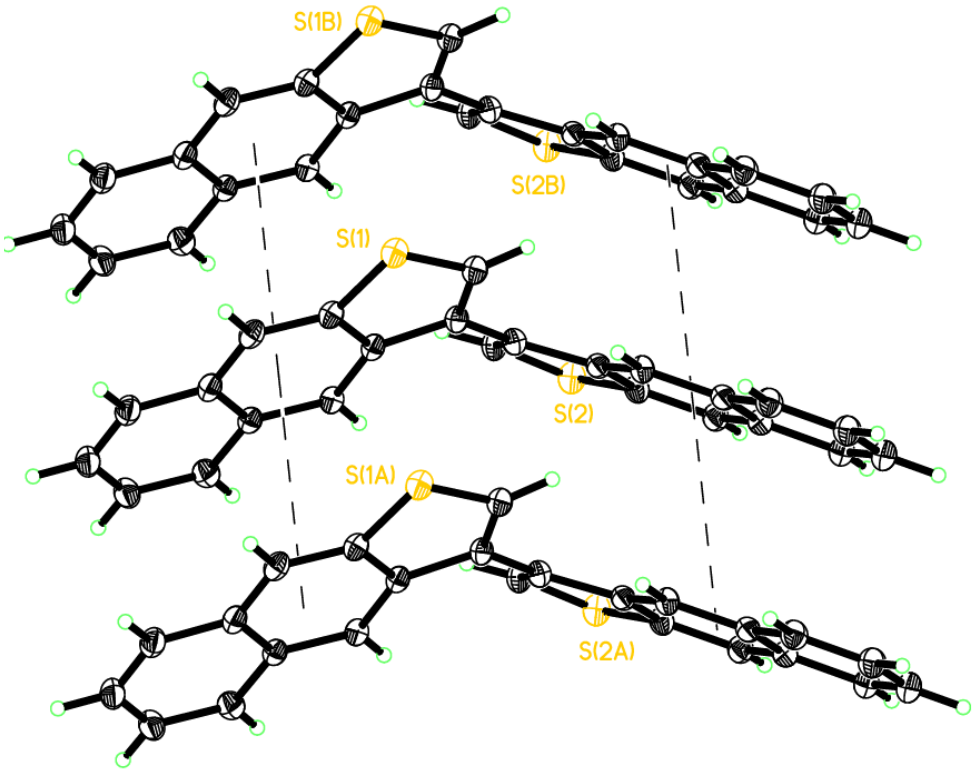
Side view of the structure of compound **2e**, rotated by 90° relative to the first view above. Thermal ellipsoids are drawn at the 50 % probability level. Hydrogen atoms have not been labelled.



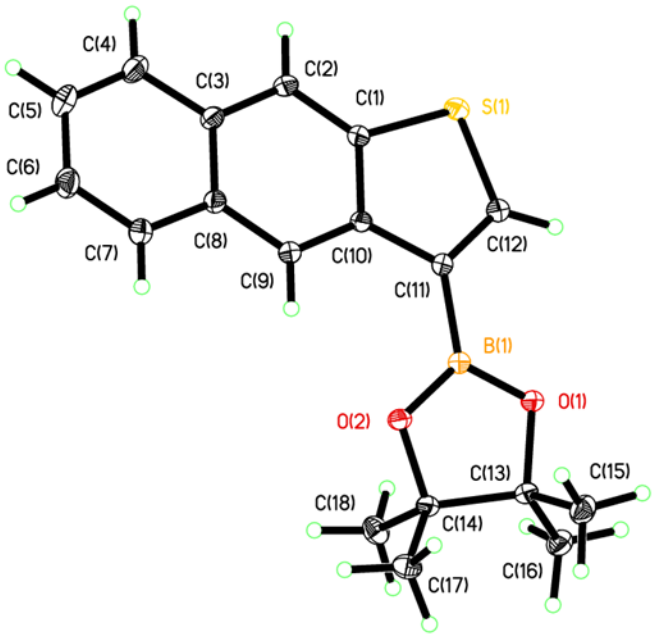
Packing diagram for compound **2e** viewed down the *X*-axis.



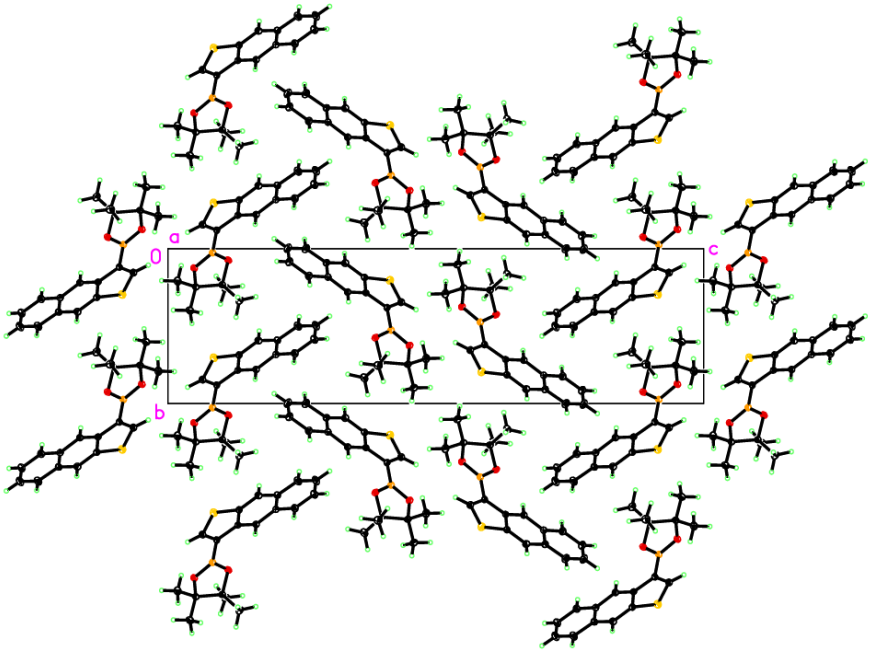
Packing diagram for compound **2e** viewed down the *Y*-axis.



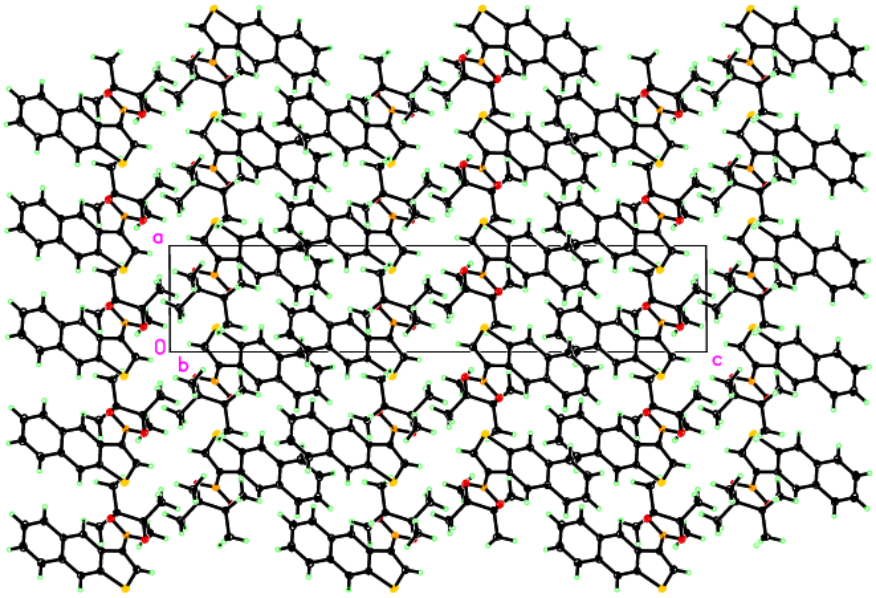
Stacking contacts in the compound **2e**. Dashed lines join the centroids of the naphthothiophene groups. The molecules above and below the central molecule are generated by the symmetry operations (*x*+1, *y*, *z*) and (*x*-1, *y*, *z*) respectively.



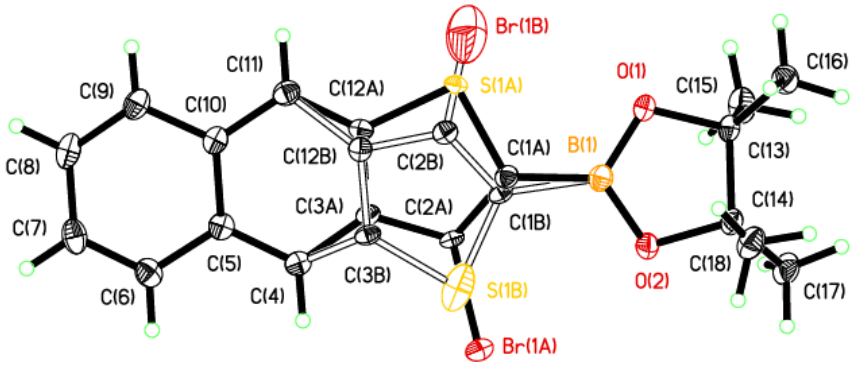
Structure of compound **11a**. Thermal ellipsoids have been drawn at the 50% probability level. Hydrogen atoms have not been labelled.



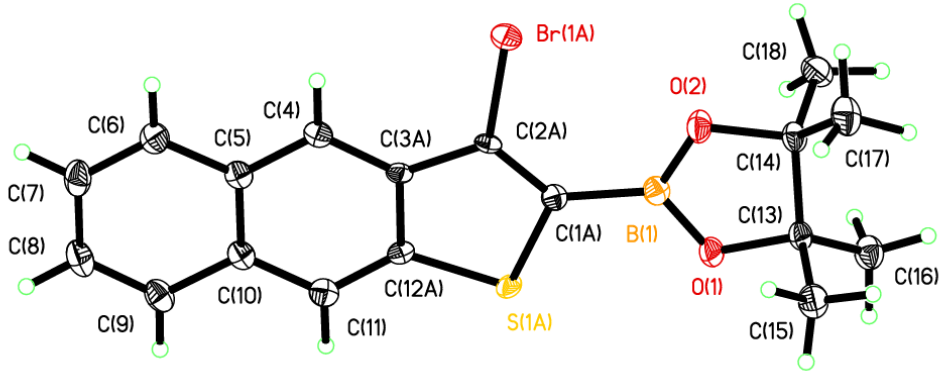
Packing diagram for compound **11a** viewed down the *X*-axis.



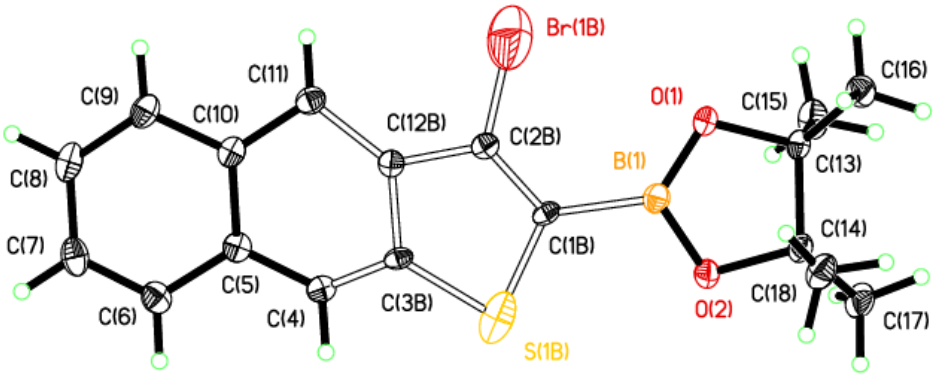
Packing diagram for compound **11a** viewed down the *Y*-axis.



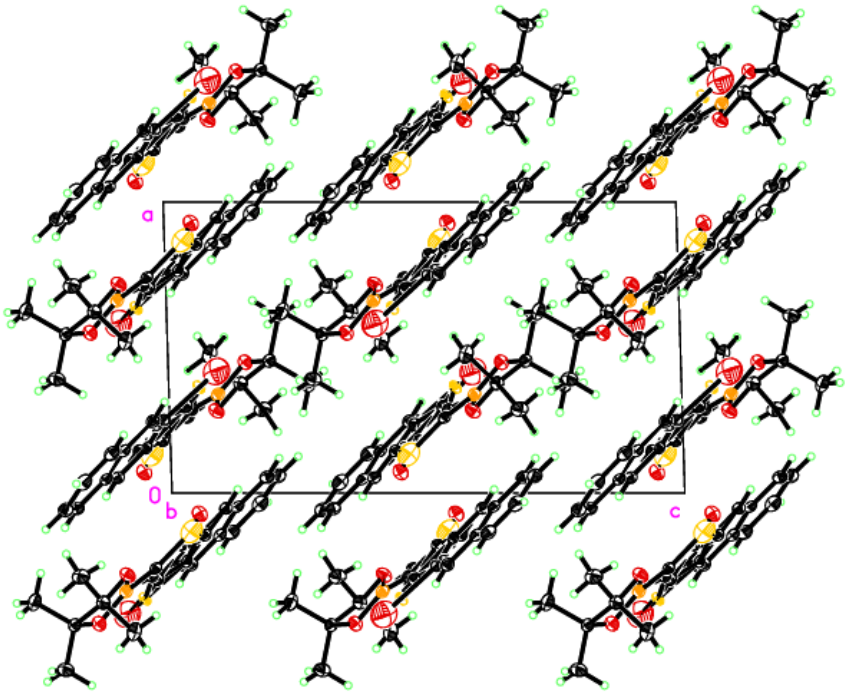
Structure of compound **11b** showing both parts of the disordered model. Thermal ellipsoids have been drawn at the 50% probability level. The hydrogen atoms have not been labelled.



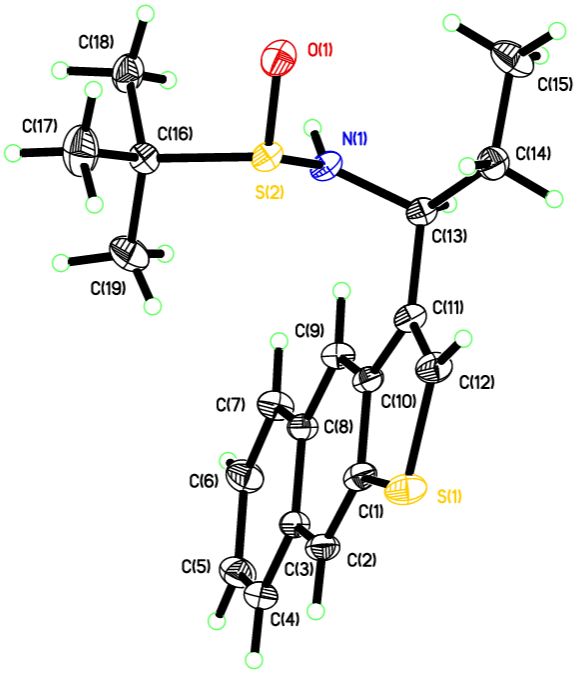
Structure of compound **11b** showing only the main component of the disordered model. Thermal ellipsoids have been drawn at the 50% probability level. The hydrogen atoms have not been labelled.



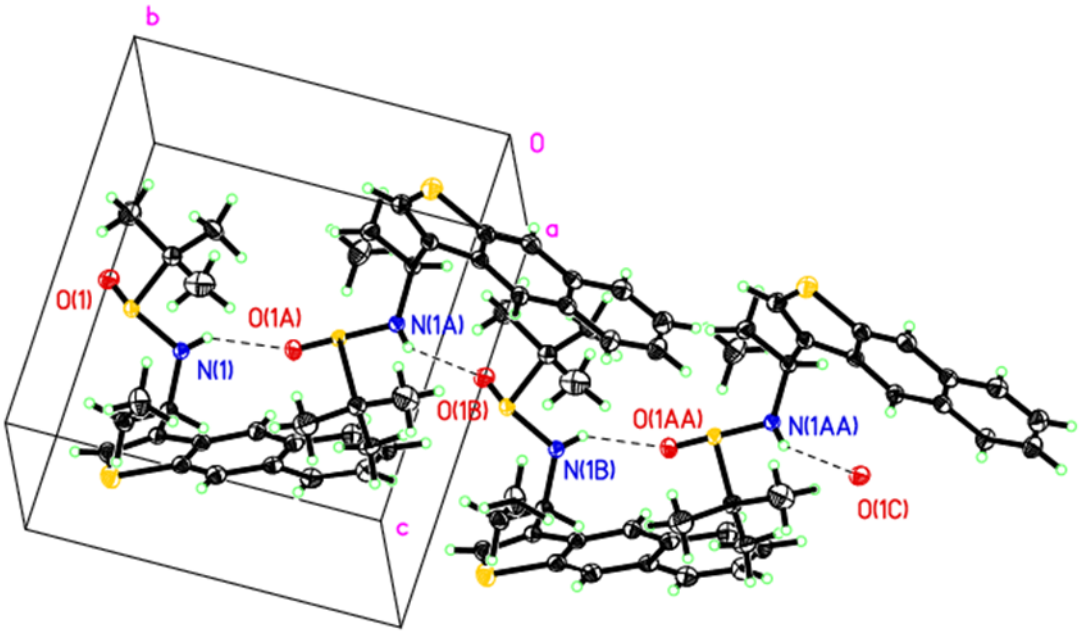
Structure of compound **13a** showing only the minor component of the disordered model. Thermal ellipsoids have been drawn at the 50% probability level. The hydrogen atoms have not been labelled.



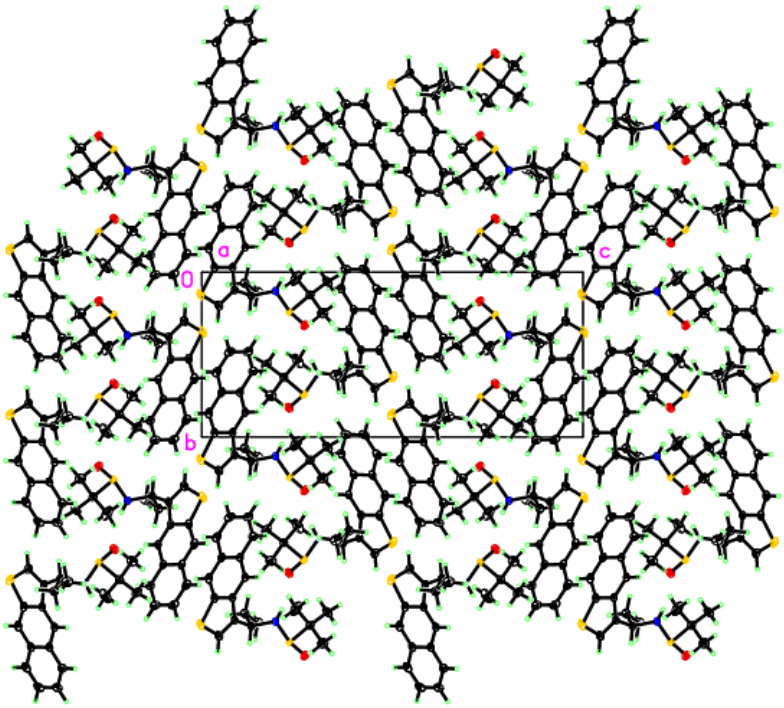
Packing diagram for compound **13a** viewed down the *Y*-axis.



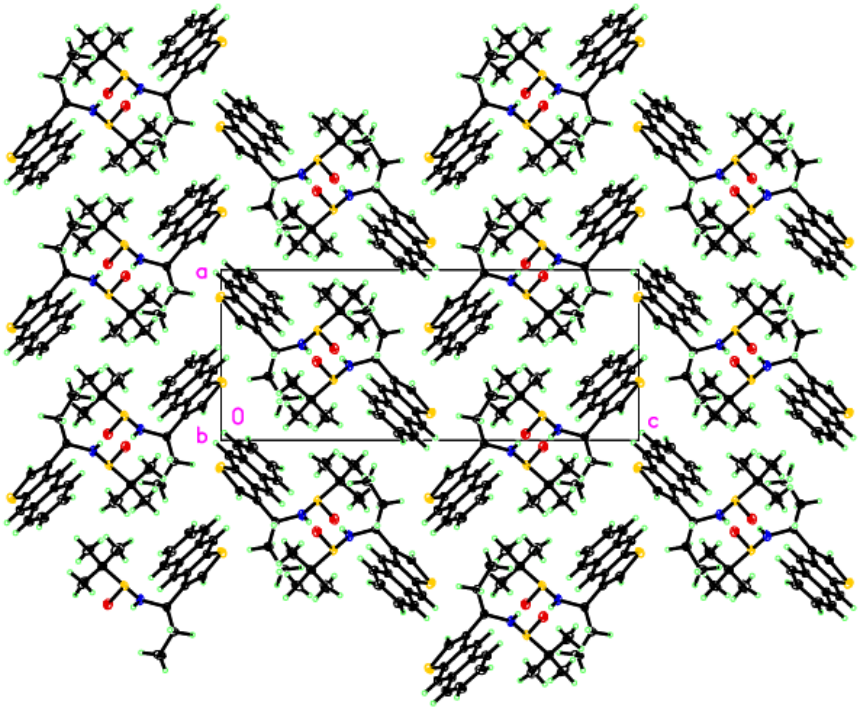
Structural diagram of compound compound **14a**. Thermal ellipsoids have been drawn at the 50% probability level. Hydrogen atoms have not been labelled.



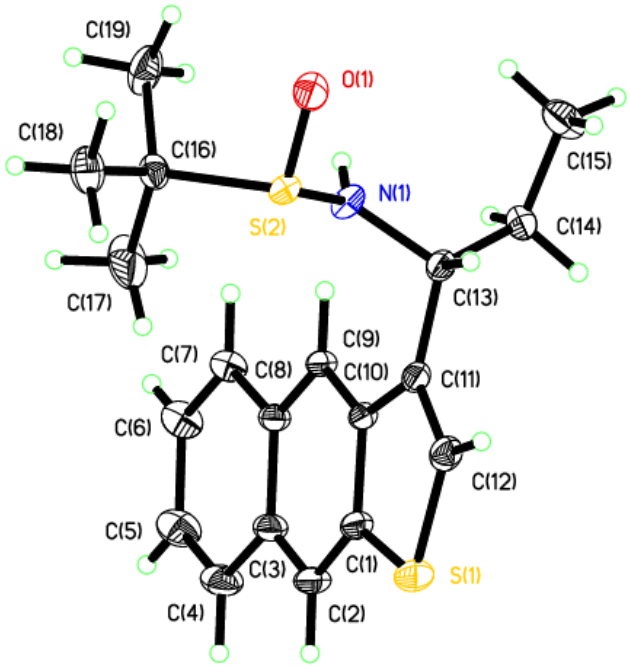
Structural diagram of the hydrogen bonded chain found in compound **14a**. Thermal ellipsoids have been drawn at the 50% probability level. Hydrogen atoms have not been labelled.



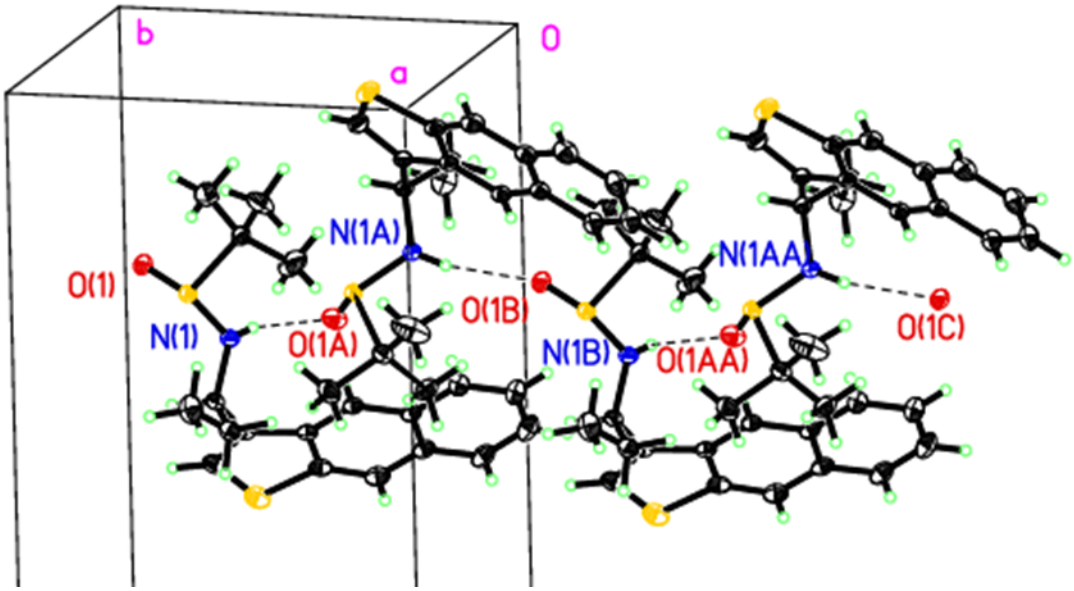
Packing diagram for compound **14a** viewed down the *X*-axis.



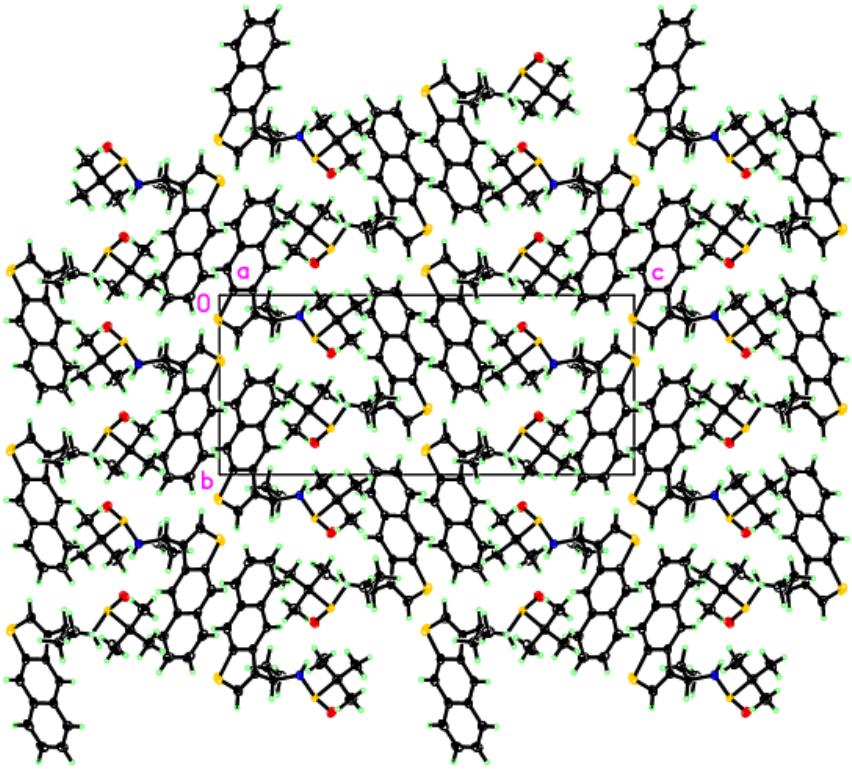
Packing diagram for compound **14a** viewed down the *Y*-axis.



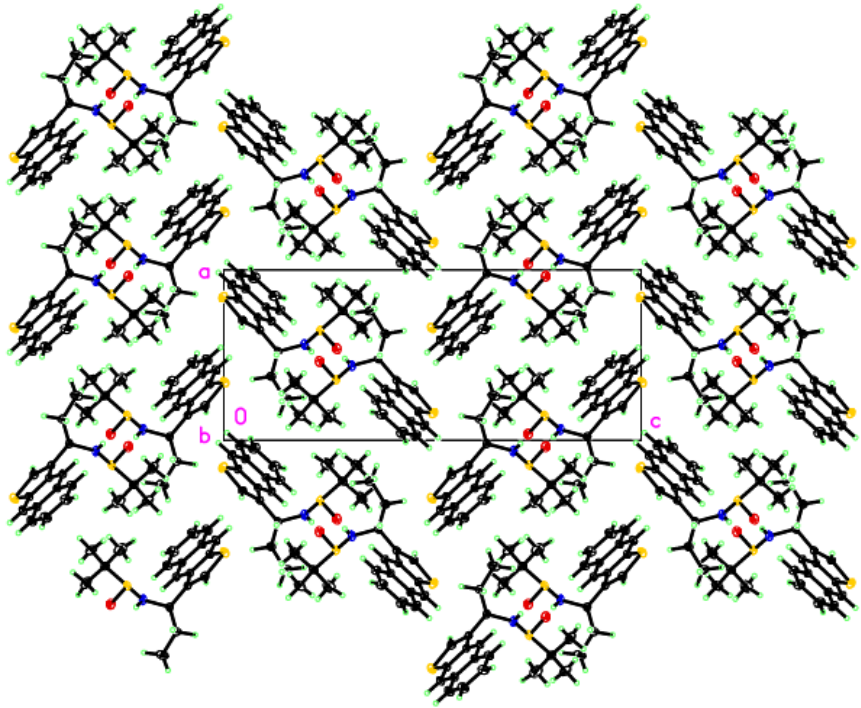
Structural diagram of compound compound **14b**. Thermal ellipsoids have been drawn at the 50% probability level. Hydrogen atoms have not been labelled.



Structural diagram of the hydrogen bonded chains found in compound **14b**. Thermal ellipsoids have been drawn at the 50% probability level. Hydrogen atoms have not been labelled.

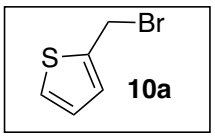


Packing diagram for compound **14b** viewed down the *X*-axis.



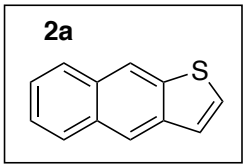
Packing diagram for compound **14b** viewed down the *Y*-axis.

Experimental Procedures and Tabulated Data



2-bromomethylthiophene (10a): The following reaction was not conducted under nitrogen to avoid contamination of the manifold with HBr. Alcohol **9a** (1.66 mL, 17.5 mmol, 1 equiv) was dissolved in 15 mL of diethyl ether, cooled to 0 °C, and PBr_3 (1.66 mL, 17.5 mmol, 1 equiv) was added. The cooling bath was allowed to decay, and the reaction was stirred for 16 hours. The reaction was recooled and quenched by the dropwise addition of 30 mL of water. When HBr evolution ceased, the layers were separated, and the aqueous layer was extracted with a further 45 mL of ether. The combined organic layers were cautiously washed with saturated $NaHCO_3$, then brine, then dried over Na_2SO_4. Concentration gave **10a** as a yellow oil (2.94 g, 16.6 mmol, 95% yield), which was prone to decomposition as mentioned in the text and was used without further purification. ref

Lithium tetrachlorocuprate (0.5 M): Solid LiCl (1.26 g, 29.7 mmol, 2 equiv) and $CuCl_2$ (2.00 g, 14.9 mmol, 1 equiv) were placed in a 50 mL Schlenk storage tube under nitrogen. THF (30 mL) was added, and the dark red/brown reaction was stirred until all solids were dissolved. The dark red solution was stored under nitrogen at room temperature. A 0.1 M solution of Li_2CuCl_4 in THF was also prepared in the same fashion.

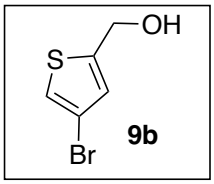


Naphthothiophene (2a): Magnesium turnings (0.315 g, 13.0 mmol, 1.65 equiv) were placed in a 3-neck flask equipped with a reflux condenser under nitrogen. Syringes with halide **7b** (2.38 mL, 11.8 mmol, 1.5 equiv) and THF (15 mL) were placed in the other septa. THF (5 mL) and halide **7b** (0.3 mL) were added, and the reaction was heated in an oil bath at 80 °C. A crystal of iodine, and 0.1 mL of dibromoethane were added. After several minutes, the color of the iodine disappeared, and THF and halide **10a** were gradually added at a rate to maintain reflux. When the addition was complete, the light brown solution of Grignard reagent was stirred at reflux for a further hour, until only very small pieces of magnesium remained. It was then allowed to cool. Separately, lithium tetrachlorocuprate (0.1 M in THF, 7.85 mL, 0.785 mmol, 0.1 equiv) was added to a solution of bromide **10a** (1.39 g, 7.85 mmol, 1 equiv) in 8 mL THF. This bright orange mixture was cooled to 0 C. The Grignard solution **7b-Mg** was transferred into this solution with a syringe and stainless steel needle. The red solution darkened during the addition, then suddenly turned very pale yellow. After completion of the addition, the solution remained yellow, but gradually became cloudy. The solution was stirred for 16 hours. The reaction was quenched with saturated NH_4Cl, and 10 mL aqueous ammonia was added. Diethyl ether 100 mL was added, and the mixture was vigorously shaken in a separatory funnel until it turned bright blue. The layers were separated, and the aqueous layer was extracted with another 100 mL of diethyl ether. The combined organic layers were washed with brine, and dried over Na_2SO_4, then concentrated. The resulting orange oil was used directly in the next step without further purification.

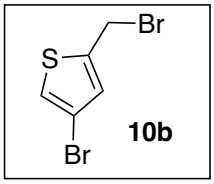
The orange oil was dissolved in 20 mL DCM and cooled to 0 °C. Boron trifluoride etherate (3.37 mL, 27.3 mmol, 3.5 equiv) was added, and the reaction immediately turned deep black. The cooling bath was allowed to decay, and the reaction was stirred for 16 hours. The reaction was quenched by the addition of saturated $NaHCO_3$. When bubbling ceased, layers were separated, and the aqueous layer was extracted with a further 50 mL DCM. The combined organic layers were dried over Na_2SO_4, and concentrated. The brown residue purified by flash chromatography on silica gel (1% ethyl acetate/ hexanes). Combination of the product containing fractions yielded compound **2a** as a white solid (0.936 g, 5.08 mmol, 65% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.33 (s, 1H), 7.99–7.97 (m, 1H), 7.93–7.92 (m, 1H), 7.52–7.47 (m, 3H), 7.43 (ap. d, *J*= 5.64 Hz).

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 139.0, 138.4, 131.1, 131.0, 128.4, 128.3, 127.4, 125.4, 125.1, 123.6, 122.0, 120.8.

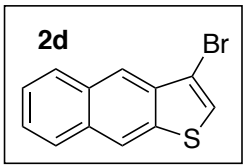


2-(4-bromothiophene)methanol (9b): The following reaction was conducted under air in an open flask. Commercially available 4-bromo-2-thiophenecarboxaldehyde **8** (10.0 g, 52 mmol, 1 equiv) was dissolved in 100 mL ethanol and cooled to 0 °C. Sodium borohydride (2.0 g, 53 mmol, 1 equiv) was cautiously added. The reaction was stirred for 2 hours, at which time an NMR aliquot showed complete consumption of the aldehyde. The reaction was cautiously quenched with 1.0 M aqueous HCl. When gas evolution ceased, volatiles were removed in vacuo. The residue was diluted with 100 mL water, and extracted with 100 mL diethyl ether, and a further 50 mL diethyl ether. The combined organic layers were dried with Na_2SO_4, and concentrated to yield alcohol **9b** (10.1 g, 52 mmol, quant) as a light brown liquid, which was used in the next step without further purification. Ref, NMR Data?



2-bromomethyl-4-bromothiophene (10b): The following reaction conducted under air, in a flask equipped with a septum, and 22 gauge needle for pressure release to avoid contamination of the manifold with HBr. Alcohol **9b** (3.80 g, 19.6 mmol, 1 equiv) was dissolved in 20 mL of diethyl ether, cooled to 0 °C, and PBr_3 (2.00 mL, 21.6 mmol, 1.1 equiv) was added. The cooling bath was allowed to decay, and the reaction was stirred for 16 hours. The reaction was recooled and quenched by the dropwise addition of 30 mL of water. When HBr evolution ceased, the layers were separated, and the aqueous layer was extracted with a further 40 mL of ether. The combined organic layers were cautiously washed with saturated $NaHCO_3$, then brine, then dried over Na_2SO_4. Concentration with a non-heated rotavap bath gave **10b** as a yellow oil, which was dried under vacuum in a flask placed in an ice bath, which caused the compound solidify (4.8 g, 18.8 mmol, 95% yield). Decomposition was not observed with this compound in the solid state at this scale. An attempt to filter a highly concentrated ethereal solution of bromide **10b** through basic alumina did result in darkening and exothermic decomposition, indicating this compound should be treated cautiously.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.03 (s, 1H), 4.65 (s, 2H).
$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.8, 130.5, 124.2, 109.7, 25.5.
HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_5H_5Br^{79}Br^{81}S$ 256.8453 found 256.8455.



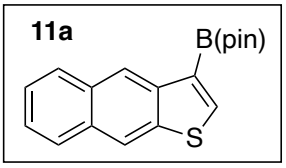
3-bromonaphthothiophene (2d): Magnesium turnings (0.729 g, 30.0 mmol, 1.6 equiv) were placed in a 3-neck flask equipped with a reflux condenser under nitrogen. Syringes with halide **7b** (6.05 mL, 30.0 mmol, 1.6 equiv) and THF (30 mL) were placed in the other septa. THF (5 mL) and halide **7b** (0.5 mL) were added, and the reaction was heated in an oil bath at 70 °C. A crystal of iodine, and 0.1 mL of dibromoethane were added. After several minutes, the color of the iodine disappeared, and THF and halide **7b** were gradually added at a rate to maintain reflux. When the addition was complete, the light brown solution of Grignard reagent **7b-Mg** was stirred for a further hour, until only very small pieces of magnesium remained. It was then allowed to cool. Separately, lithium tetrachlorocuprate (0.5 M in THF, 6 mL, 3.0 mmol, 0.16 equiv) was added to a solution of bromide **10b** (4.8 g, 18.8 mmol, 1 equiv) in 15 mL THF. This bright orange mixture was cooled to 0 °C. The Grignard solution **10b** was transferred into this solution with a syringe and stainless needle. The red solution darkened during the addition, then suddenly turned very pale yellow. After completion of the addition, the solution remained yellow, but gradually became cloudy. The solution was stirred for 16 hours. The reaction was quenched with saturated $NH_4Cl_{(aq)}$, and 10 mL aqueous ammonia was added. Diethyl ether 100 mL was added, and the mixture was vigorously shaken in a separatory funnel until it turned bright blue. The layers were separated, and the aqueous layer was extracted with another 100 mL of diethyl ether. The combined organic layers were washed with brine, and dried over Na_2SO_4, then concentrated. The resulting orange oil was used directly in the next step without further purification.

The orange oil (18.8 mmol maximum theoretical amount) was dissolved in 60 mL DCM and cooled to 0 °C. Boron trifluoride etherate (3.70 mL, 30.1 mmol, 1.6 equiv) was added, and the reaction immediately turned deep black. The cooling bath was allowed to decay, and the reaction was stirred for 16 hours. The reaction was quenched by the addition of saturated $NaHCO_3$. When bubbling ceased, layers were separated, and the aqueous layer was extracted with a further 50 mL DCM. The combined organic layers were dried over Na_2SO_4, and concentrated. The brown residue was redissolved in DCM, and several scoops of celite were added, and solvent was removed in vacuo. This was added on top of a pre-wetted silica-gel column, and elution was carried out with 1% ethyl acetate/ hexanes. Combination of the product containing fractions yielded compound **2d** as a white solid (2.40 g, 9.12 mmol, 48% yield over 2 steps). Spectral data were in accordance with literature values. **Error! Bookmark not defined.**

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.30 (s, 1H), 8.05–8.03 (m, 1H), 7.92–7.90 (m, 1H), 7.53–7.50 (m, 2H), 7.52 (s, 1H).

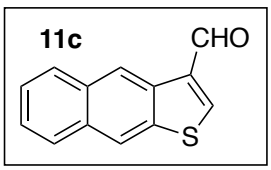
$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 136.5, 136.2, 131.5, 131.2, 128.6, 127.3, 126.1, 125.6, 125.3, 121.9, 121.3, 107.4.

HRMS (APCI) *m/z* $[M + H]^+$ calcd for $C_{12}H_8Br^{79}S$ 262.9525 found 262.9516.



3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan2-yl)-naphthothiophene (11a): In a recovery flask, 3-bromonaphthothiophene **2d** (500 mg, 1.9 mmol, 1 equiv) was dissolved in 3 mL THF. Separately 6 mL of THF was placed in a Schlenk flask and cooled to –84 °C (liquid nitrogen/ethyl acetate). N-butyllithium (2.5 M in hexanes, 0.87 mL, 2.2 mmol, 1.1 equiv) was added to the Schlenk flask, and the solution was allowed to stir at –84 °C for another 10 minutes. The solution of 3-naphthothiophene was added over 1 minute, running the solution down the inside of the flask to facilitate pre-cooling. The solution became inky blue in colour, and occasionally a greyish precipitate formed. The reaction was stirred at –84 °C for 5 minutes, then *i*PrOB(pin) (0.47 mL, 2.3 mmol, 1.2 equiv) was added. The dark greenish reaction was stirred for 10 minutes, warmed to 0 °C for 5 minutes, then quenched with 10 mL of 2 M HCl. To the solution was added 25 mL of dichloromethane, and the mixture was vigorously stirred for 5 minutes. The layers were separated. The aqueous layer washed with an additional 25 mL dichloromethane, and the combined residues were dried over Na_2SO_4 and concentrated. The brown residue was purified by flash chromatography (1% ethyl acetate/hexanes) to afford boronic ester **11a** as a white solid (338 mg, 1.09 mmol, 57% yield). S

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.39 (s, 1H), 8.18 (s, 1H), 8.09–8.07 (m, 1H), 7.92–7.90 (m, 1H), 7.50–7.46 (m, 2H), 1.44 (s, 12H).
$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.8, 141.5, 139.6, 131.2, 130.9, 128.9, 127.3, 125.3, 124.8, 123.9, 120.4, 83.9, 25.1.
^{11}B NMR (160 MHz, $CDCl_3$): δ 29.1 (br. s).
HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{19}BNaO_2$ 333.1091 found 333.1082.



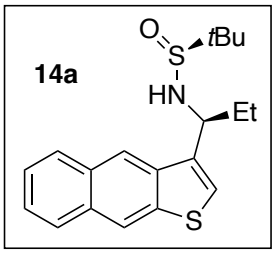
3-naphthothiophenecarboxaldehyde (11c): In a recovery flask, 3-bromonaphthothiophene **2d** (1.60 g, 6.08 mmol, 1 equiv) was dissolved in 4 mL THF. Separately 6 mL of THF was placed in a Schlenk flask and cooled to –84 °C (liquid nitrogen/ethyl acetate). N-butyllithium 2.5 M in hexanes (3.89 mL, 9.72 mmol, 1.6 equiv) was added to the Schlenk, and the solution was allowed to stir at –84 °C for another 10 minutes. The solution of 3-bromonaphthothiophene **2d** was added over 1 minute, running the solution down the inside of the flask to facilitate pre-cooling, with a further 2 mL THF used to quantitiate the transfer. The solution became inky blue in colour, and occasionally a greyish precipitate formed. The reaction was stirred at –84 °C for 10 minutes, then DMF (0.94 mL, 12 mmol, 2 equiv) was added. The dark greenish reaction was stirred for 10 minutes, warmed to 0 °C for 5 minutes, then quenched with 10 mL $NH_4Cl_{(aq)}$ and 10 mL 2 M HCl. To the solution was added 25 mL of dichloromethane, and the mixture was vigorously

stirred for 5 minutes. The layers were separated. The aqueous layer washed with an additional 25 mL dichloromethane, and the combined residues were dried over Na_2SO_4 and concentrated. The brown residue was purified by flash chromatography (5%–10% ethyl acetate/hexanes) to afford aldehyde **11c** as an orange/yellow solid (749 mg, 3.52 mmol, 58% yield). Minor, inseparable impurities were noted in the NMR spectra.

^{1}H NMR (500 MHz, $CDCl_3$): 10.15 (s, 1H), 9.21 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 8.08–8.03 (m, 1H), 7.92–7.88 (m, 1H), 7.57–7.50 (m, 2H).

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): 185.1, 146.3, 138.2, 136.1, 133.2, 131.7, 131.6, 128.9, 127.2, 126.3, 125.7, 123.9, 120.8.

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{13}H_8NaOS$ 235.0188 found 235.0197.

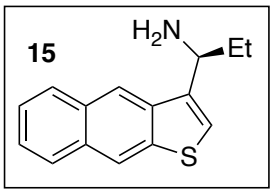


Sulfinamides (14a and b): In a recovery flask, 3-bromonaphthothiophene **2d** (1.00 g, 3.80 mmol, 1 equiv) was dissolved in 5 mL THF. Separately 7 mL of THF was placed in a Schlenk flask and cooled to –84 °C (liquid nitrogen/ethyl acetate). N-butyllithium 2.5 M in hexanes (1.98 mL, 4.94 mmol, 1.3 equiv) was added to the Schlenk, and the solution was allowed to stir at –84 °C for another 10 minutes. The solution of 3-bromonaphthothiophene **2d** was added over 1 minute, running the solution down the inside of the flask to facilitate pre-cooling, with a further 2 mL THF used to quantitiate the transfer. The solution became inky blue in colour. The reaction was stirred at –84 °C for 5 minutes, then a solution of imine **13** (0.88 g, xx mmol, xx equiv) in 3 mL THF was added. The resulting clear orange reaction mixture was stirred for 2 hours, then allowed to warm to room temperature. The mixture was then quenched with 10 mL $NH_4Cl_{(aq)}$. The reaction was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, and concentrated. The resulting residue was purified by flash chromatography (40% ethyl acetate/hexanes moving to 50% when the first diastereomer eluted). The less polar diastereomer **14a** was the major one. Compound **14a** was obtained as a yellow tacky solid (631 mg, xx mmol, xx% yield). Minor diastereomer **14b** was obtained as a colourless tacky solid (263 mg, xx mmol, xx% yield). X-Ray quality crystals of both diastereomers were obtained by slow evaporation of diethyl ether solutions of the products.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.35 (s, 1H), 8.00–7.88 (m, 2H), 7.49–7.46 (m, 3H), 4.89–4.86 (m, 1H), 2.22–2.17 (m, 2H), 1.24 (s, 9H), 0.94 (ap. t, *J*= 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 136.7, 136.0, 131.1, 130.7, 128.7, 127.2, 125.8, 125.7, 125.2, 121.3, 120.9, 55.9, 55.0, 27.9, 27.7, 10.4.

HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{32}H_{28}N_2NaS_2$ 527.1586 found 527.1586



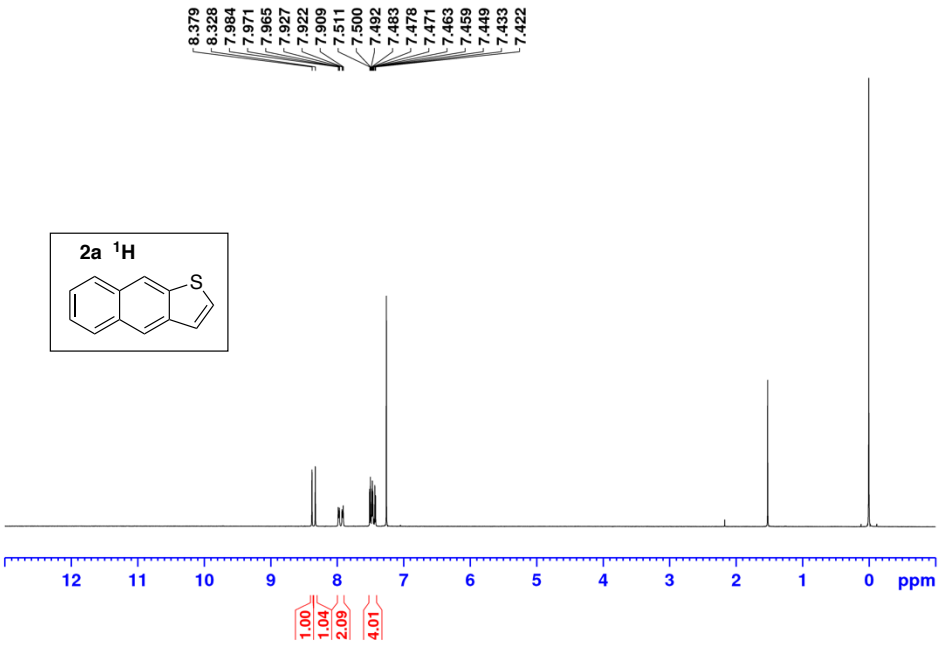
Chiral Amine 15a: In a 30 mL round-bottom flask, compound **14a** (500 mg, xx mmol, 1 equiv) was dissolved in 10 mL of a 1:1 mixture of diethyl ether and dichloromethane. To the mixture was added 2M HCl in diethyl ether (2.89 mL, 5.79 mmol, 4 equiv). The resulting tan suspension was stirred for 12 hours. The product was collected by filtration, and washed with additional diethyl ether. The HCl salt was collected as a beige solid (362 mg, xx mmol, xx% yield). Due to low solubility, the HCl salt was characterized as the free-base. A portion was suspended in dichloromethane, and washed with 1 M $NaOH_{(aq)}$. The organic layer was dried over Na_2SO_4, and concentrated to give the freebase as a beige oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (ap. d, *J*= 7.2 Hz, 2H), 8.00–7.89 (m, 2H), 7.49–7.45 (m, 2H), 7.38 (s, 1H), 4.43–4.41 (m, 1H), 2.10–2.02 (m, 1H), 1.91–1.82 (m, 1H), 1.03 (ap. t, *J*= 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.6, 137.5, 131.1, 130.7, 128.6, 127.3, 125.5, 125.1, 122.9, 121.2, 120.4, 52.3, 30.8, 11.0.

HRMS (ESI) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{15}NNaS$ 264.081741 found 264.0822

NMR Data: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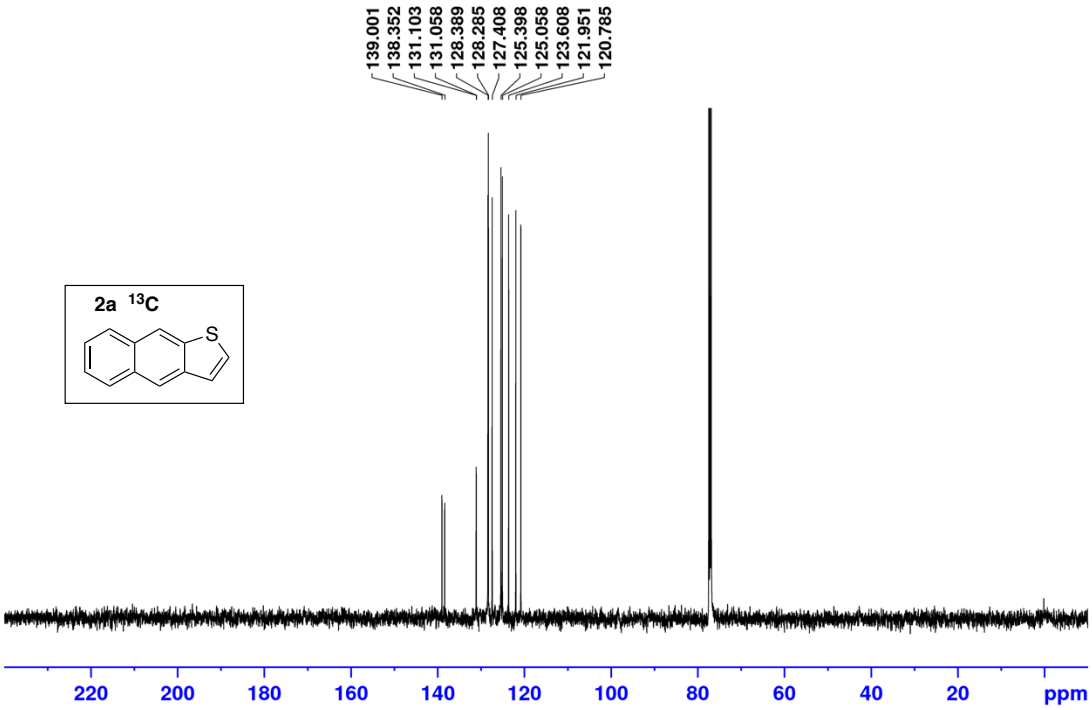
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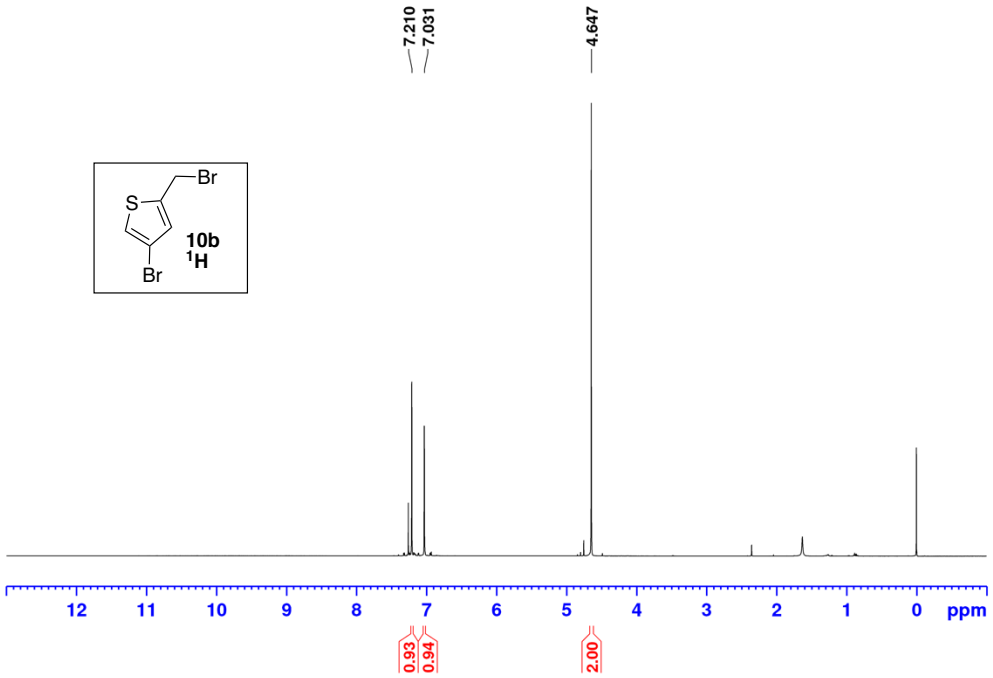
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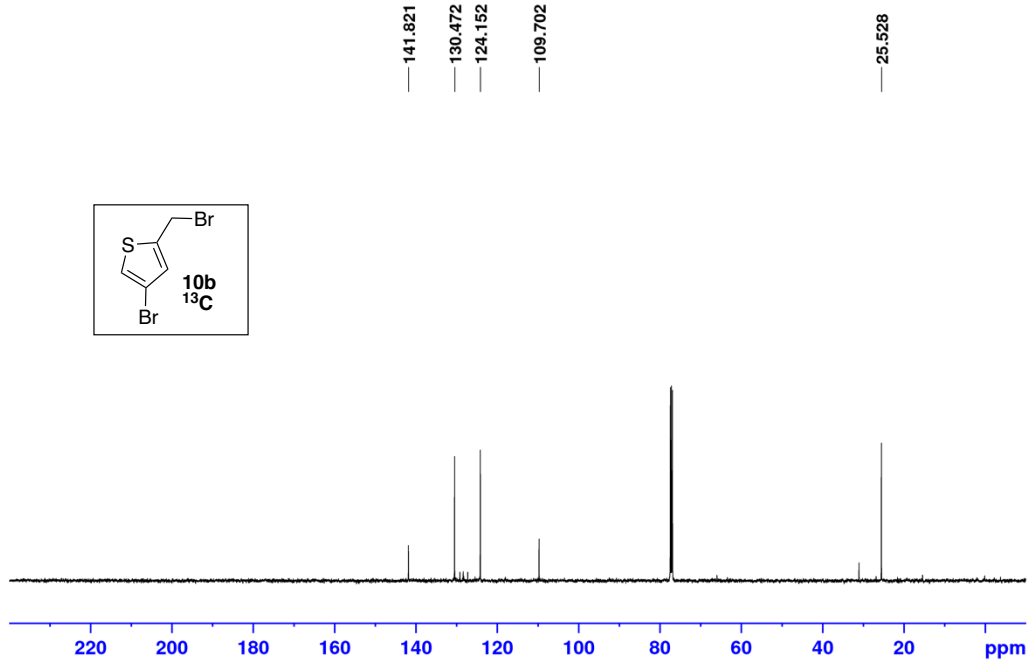
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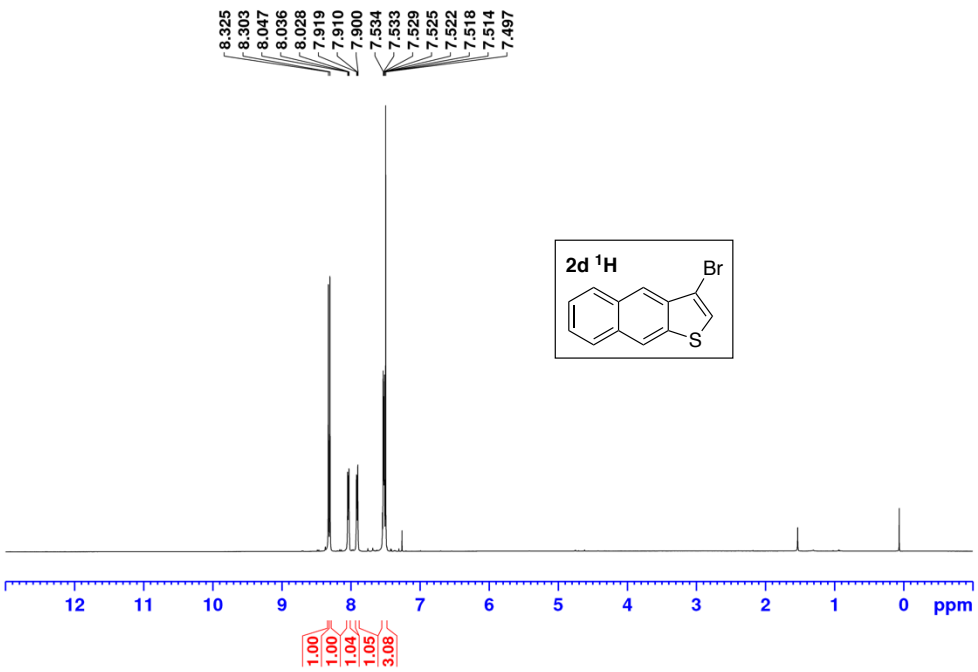
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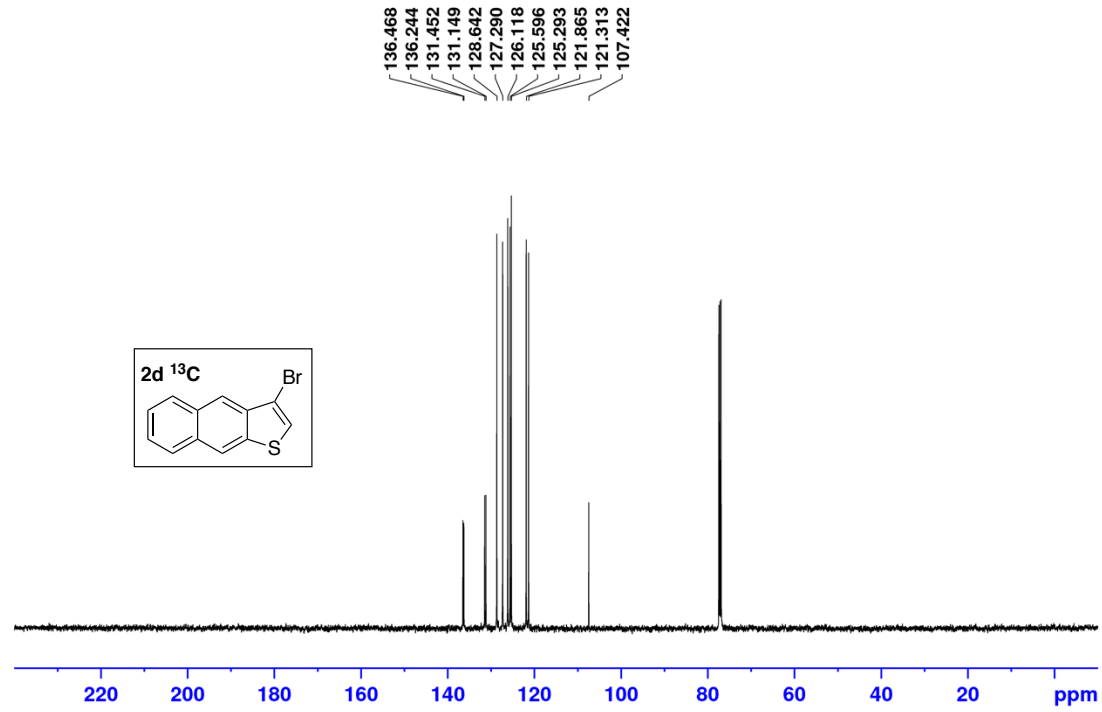
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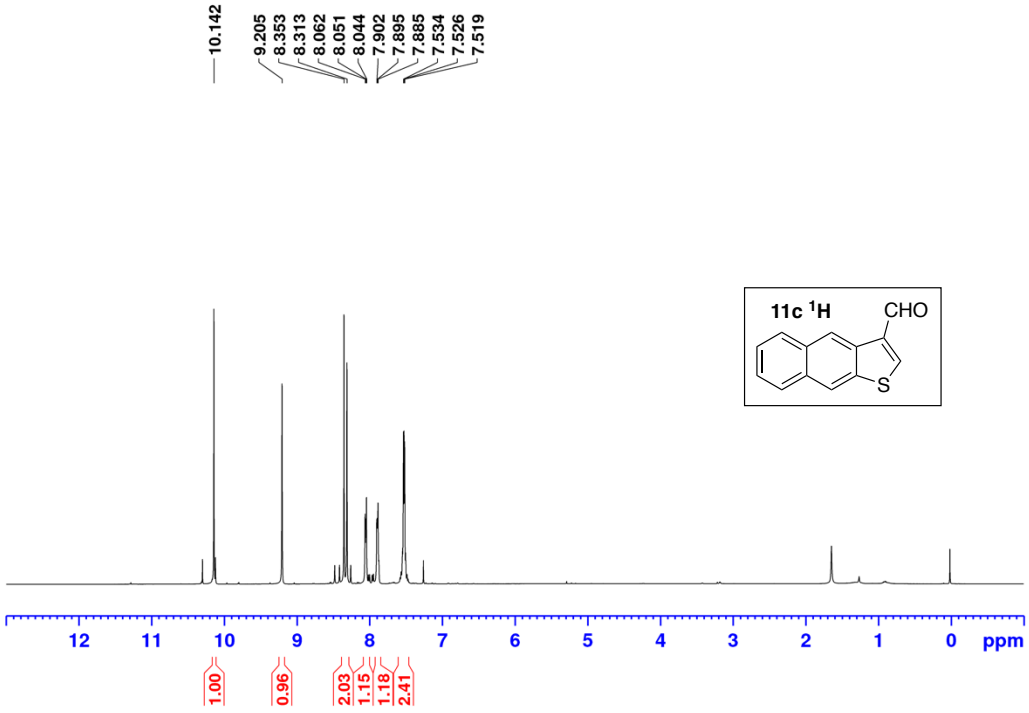
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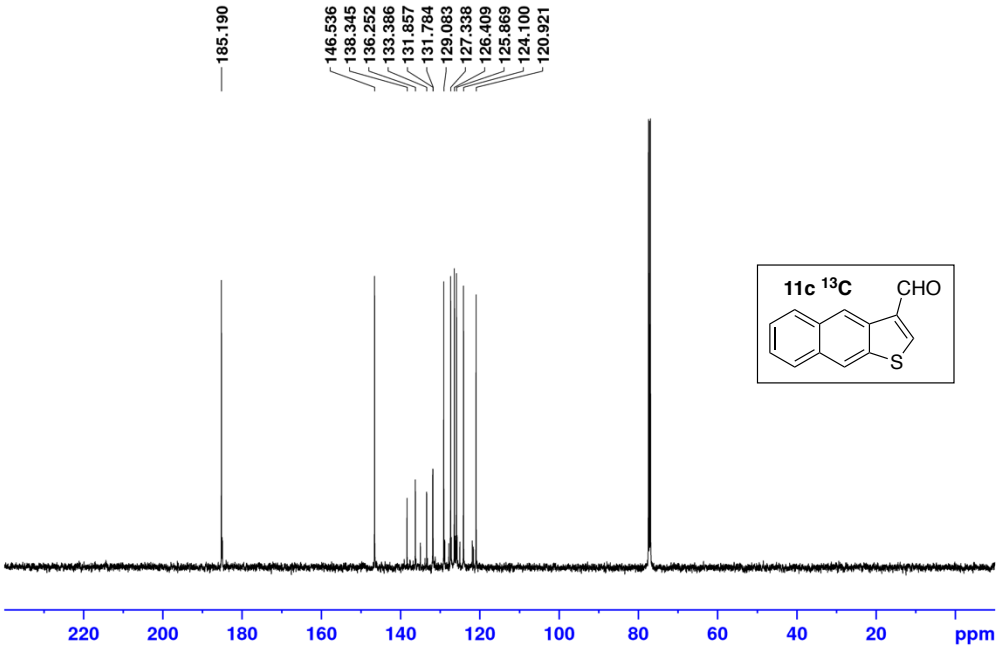
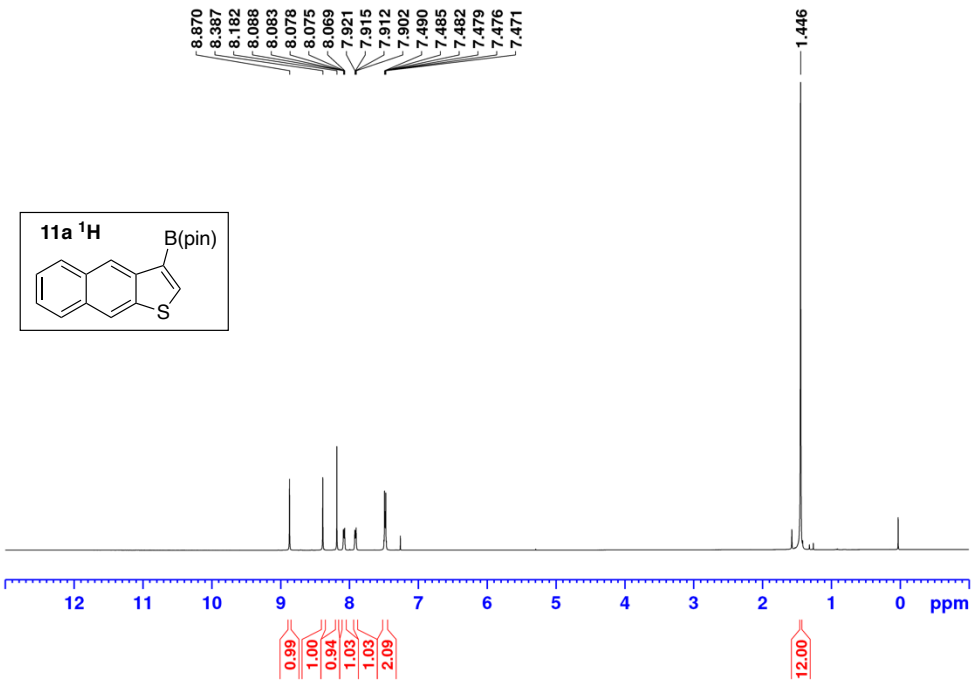
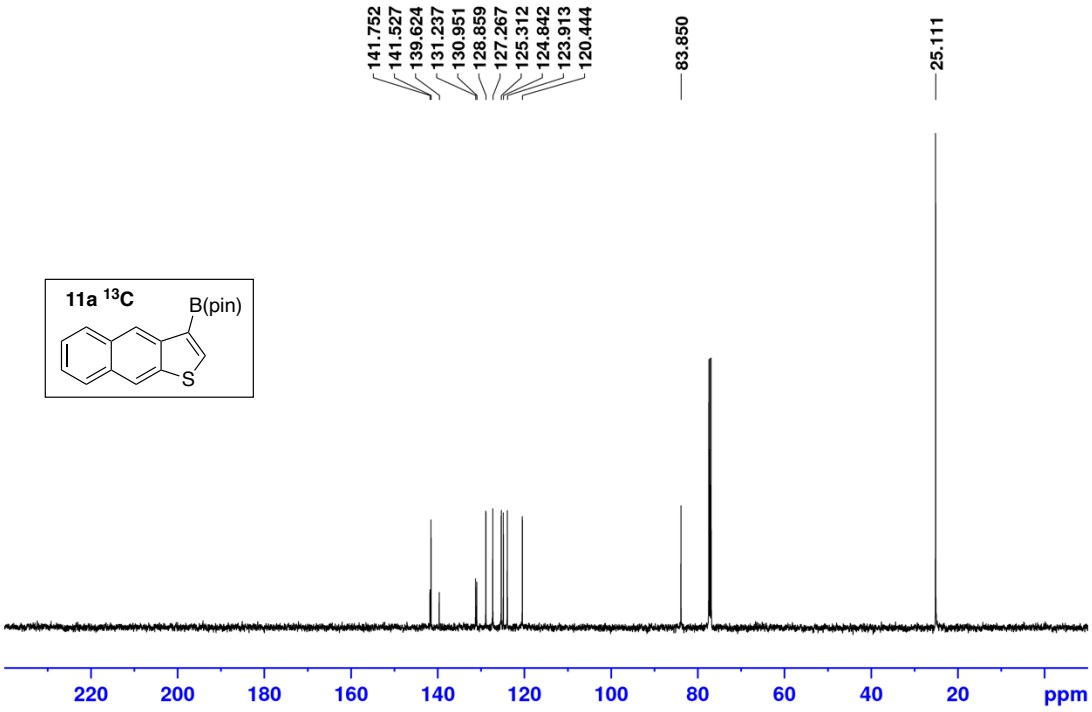
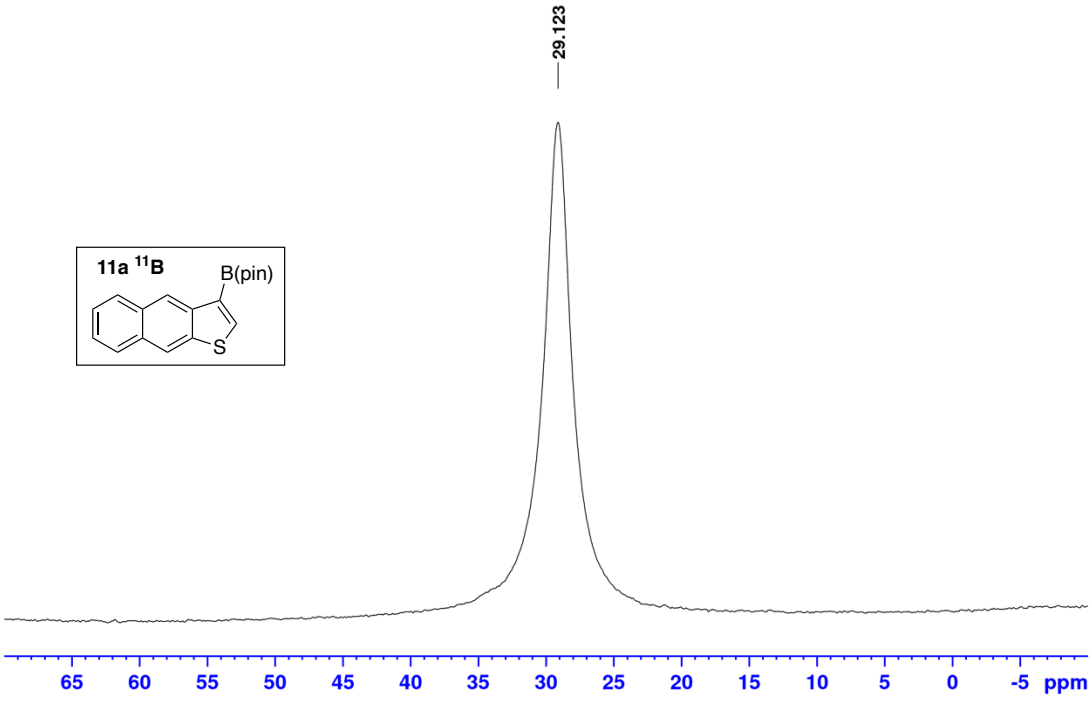
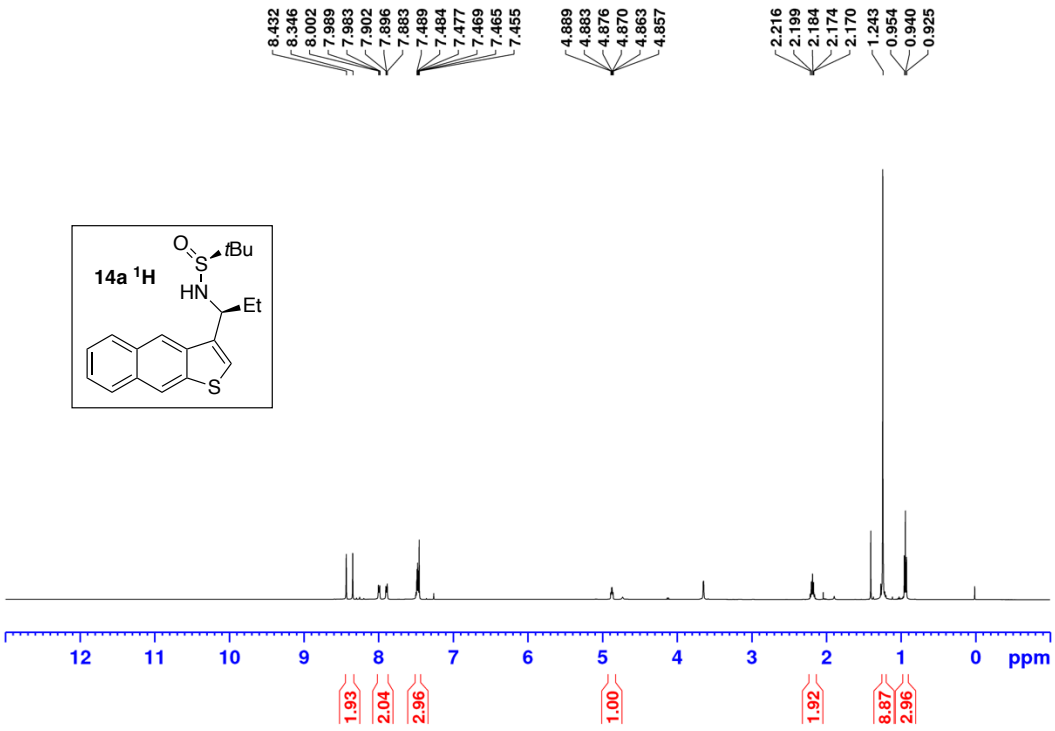
2.41

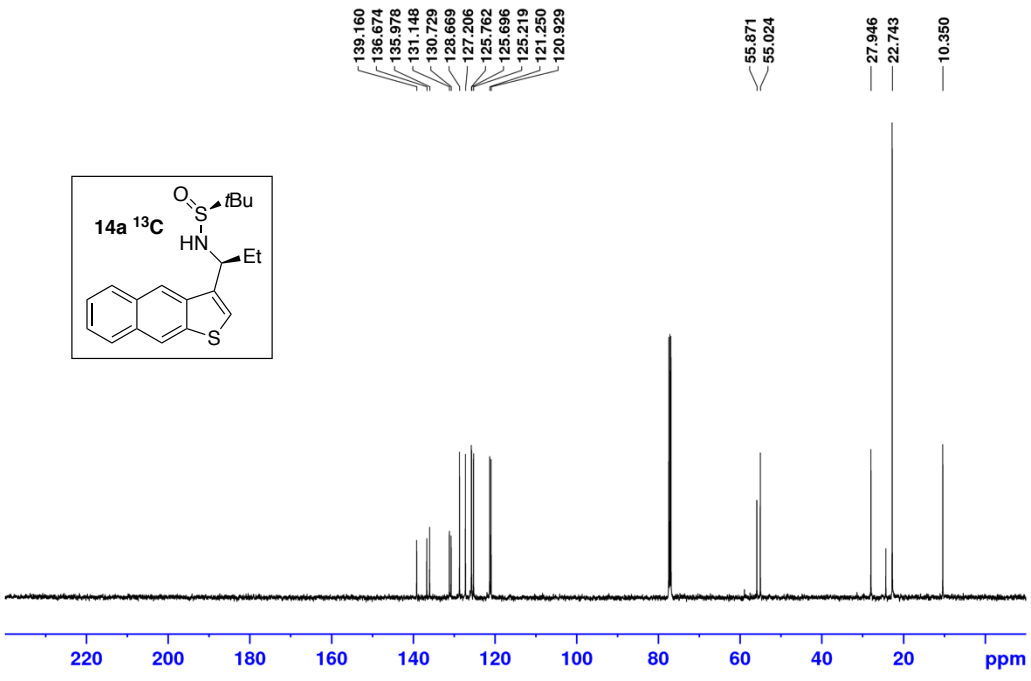

185.190
146.536
138.345
136.252
133.386
131.857
131.784
129.083
127.338
126.409
125.869
124.100
120.921
11c ^{13}C
CHO
S
220
200
180
160
140
120
100
80
60
40
20
ppm

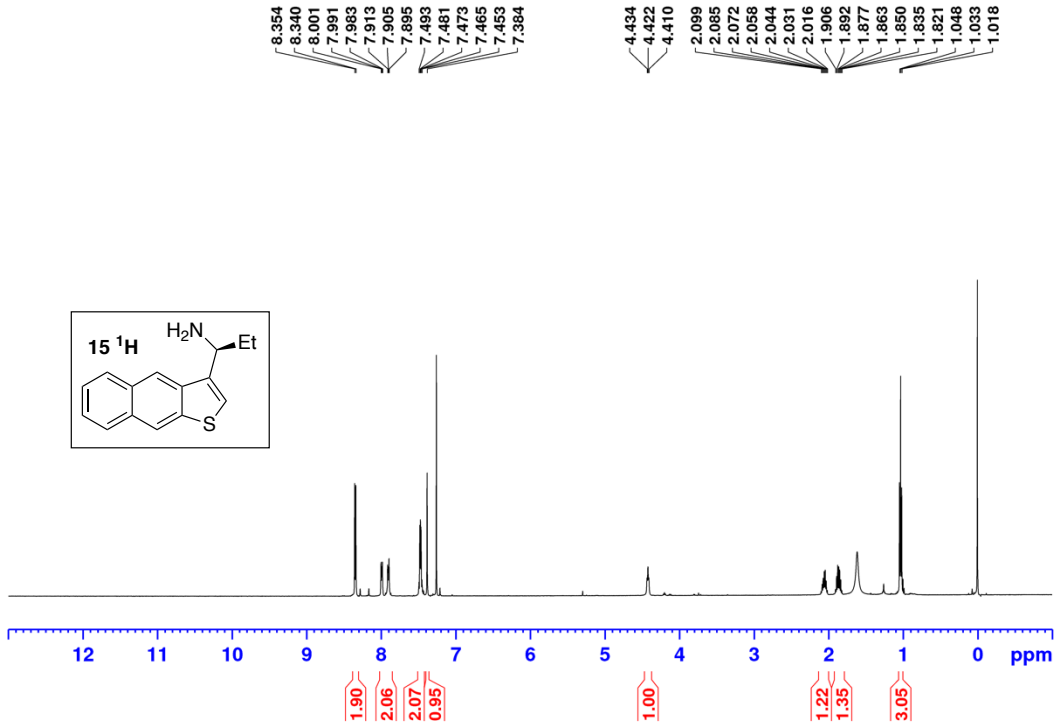

8.870
8.387
8.182
8.088
8.083
8.078
8.075
8.069
7.921
7.915
7.912
7.902
7.490
7.485
7.482
7.479
7.476
7.471
1.446
11a 1H
B(pin)
S
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.00
0.94
1.03
1.03
2.09
12.00

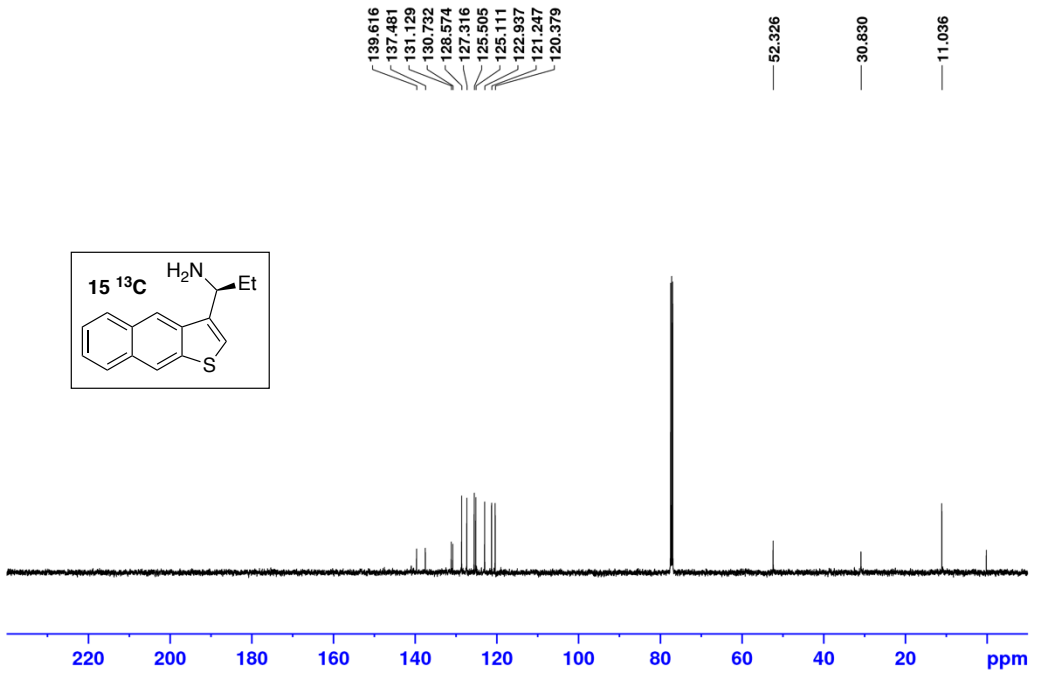

141.752
141.527
139.624
131.237
130.951
128.859
127.267
125.312
124.842
123.913
120.444
83.850
25.111
11a 13C
B(pin)
S
220
200
180
160
140
120
100
80
60
40
20
ppm


29.123
11a ^{11}B
B(pin)
S
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
ppm


8.432
8.346
8.002
7.989
7.983
7.902
7.896
7.883
7.489
7.484
7.477
7.469
7.465
7.455
4.889
4.883
4.876
4.870
4.863
4.857
2.216
2.199
2.184
2.174
2.170
1.243
0.954
0.940
0.925
14a 1H
tBu
Et
HN
S
O
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.93
2.04
2.96
1.00
1.92
8.87
2.96


139.160
136.674
135.978
131.148
130.729
128.669
127.206
125.762
125.696
125.219
121.250
120.929
55.871
55.024
27.946
22.743
10.350
14a 13C
tBu
Et
HN
S
O
220
200
180
160
140
120
100
80
60
40
20
ppm


8.354
8.340
8.001
7.991
7.983
7.913
7.905
7.895
7.493
7.481
7.473
7.465
7.453
7.384
4.434
4.422
4.410
2.099
2.085
2.072
2.058
2.044
2.031
2.016
1.906
1.892
1.877
1.863
1.850
1.835
1.821
1.048
1.033
1.018
15 1H
H2N
Et
S
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.90
2.06
2.07
0.95
1.00
1.22
1.35
3.05


139.616
137.481
131.129
130.732
128.574
127.316
125.505
125.111
122.937
121.247
120.379
52.326
30.830
11.036
15 13C
H2N
Et
S
220
200
180
160
140
120
100
80
60
40
20
ppm