Rapid #: -24962752

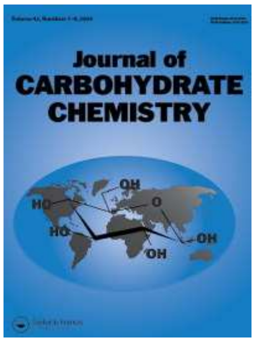
CROSS REF ID: **6112750**

LENDER: **LQ0 (Queensland University of Technology) :: Main Library**

BORROWER: **LUU (Louisiana State University) :: Main Library**

TYPE:	Article CC:CCG
JOURNAL TITLE:	Journal of carbohydrate chemistry
USER JOURNAL TITLE:	Journal of Carbohydrate Chemistry
ARTICLE TITLE:	On the relevance of glycosyl oxonium ions to 1,2-cis-selective O-glycosylation in ether solvents.
ARTICLE AUTHOR:	Agarkar, Varad,
VOLUME:	43
ISSUE:	7-9
MONTH:	
YEAR:	2024
PAGES:	302-322
ISSN:	0732-8303
OCLC #:	

Processed by RapidX: 7/29/2025 8:23:41 PM



Journal of Carbohydrate Chemistry

ISSN: 0732-8303 (Print) 1532-2327 (Online) Journal homepage: www.tandfonline.com/journals/lcar20

On the relevance of glycosyl oxonium ions to 1,2-*cis*-selective *O*-glycosylation in ether solvents

Varad Agarkar, Ava E. Hart & Justin R. Ragains

To cite this article: Varad Agarkar, Ava E. Hart & Justin R. Ragains (2024) On the relevance of glycosyl oxonium ions to 1,2-*cis*-selective *O*-glycosylation in ether solvents, Journal of Carbohydrate Chemistry, 43:7-9, 302-322, DOI: 10.1080/07328303.2024.2410800

To link to this article: https://doi.org/10.1080/07328303.2024.2410800

JOURNAL OF CARBOHYDRATE CHEMISTRY
2024, VOL. 43, NOS. 7–9, 302–322
https://doi.org/10.1080/07328303.2024.2410800

Taylor & Francis
Taylor & Francis Group

On the relevance of glycosyl oxonium ions to 1,2-*cis*-selective *O*-glycosylation in ether solvents

Varad Agarkar, Ava E. Hart, and Justin R. Ragains

Department of Chemistry, Louisiana State University, Baton Rouge, LA, USA

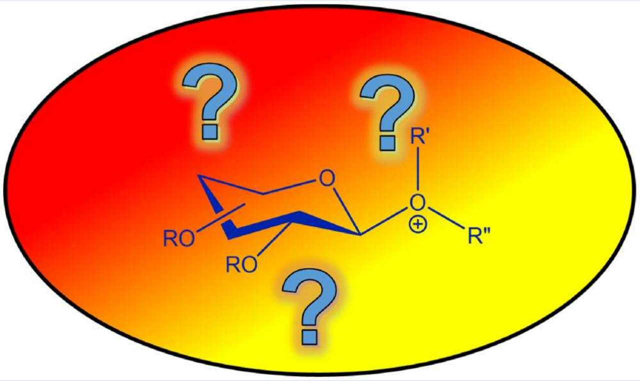
ABSTRACT

Since no later than the 1970s, organic chemists have speculated on the role of glycosyl oxonium ions in chemical *O*-glycosylation. Such species result from the attack of ethers on glycosyl oxocarbenium ions and are invoked to explain 1,2-*cis*-selectivity in ether solvents. However, a systematic study to probe this phenomenon appears to be lacking in the chemical literature. Herein, we study the effects of solvent, counteranion, protecting group electron-withdrawing effects, and acceptor on *O*-glycosylation stereoselectivity with D-glucosyl trichloroacetimidate donors. While many of these transformations proceed with 1,2-*cis*-selectivity, our results suggest that glycosyl oxonium ions play minimal, if any, role in *O*-glycosylation.

ARTICLE HISTORY
Received 1 June 2024
Accepted 18 September 2024

KEYWORDS
O-glycosylation; glycosyl oxonium ion; stereoselectivity; counterion effects

GRAPHICAL ABSTRACT



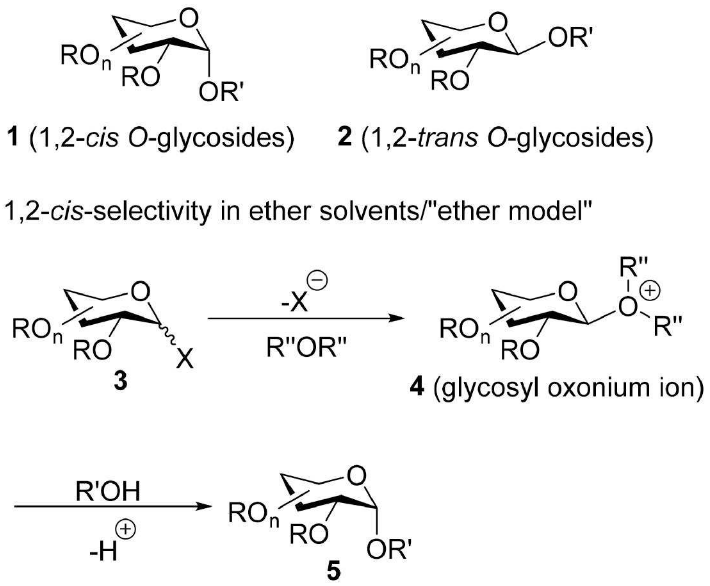
Introduction

Synthetic oligosaccharides and other *O*-glycosides are important molecules for the development of glycoconjugate vaccines,[1–3] glycan arrays,[4] and drugs.[5] Of the synthetic operations necessary for the production of oligosaccharides using chemical means, chemical *O*-glycosylation involving the

---

CONTACT Justin R. Ragains jragains@lsu.edu Department of Chemistry, Louisiana State University, 347 Chemistry and Materials Building, Baton Rouge, LA 70803, USA.

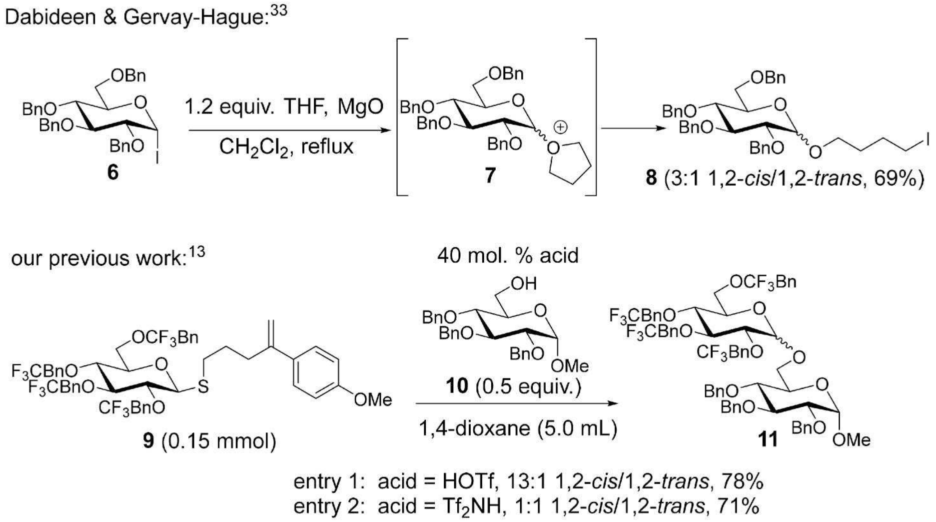
Supplemental data for this article can be accessed online at https://doi.org/10.1080/07328303.2024.2410800



Scheme 1. Background on 1,2-*cis* *O*-glycosides and the "ether model".

reaction of alcohol (acceptor) with glycosyl electrophile (donor) in the presence of an activating agent is perhaps the most important. However, all *O*-glycosylations with fully substituted donors can potentially produce both 1,2-*cis* and 1,2-*trans* *O*-glycosidic products (Sch. 1). While 1,2-*trans* linkages are readily accessed with high selectivity using neighboring-group participation from 2-position esters, carbonates, and carbamates, accessing 1,2-*cis* linkages with the same selectivity has proven to be a much more difficult problem. The myriad of solutions to the 1,2-*cis* problem, whether they involve use of nucleophilic additives,[6–9] ether solvents,[10–14] electron-withdrawing groups,[13,15–17] benzylidene protection,[18,19] remote/neighboring group participation,[20,21] and H-bonded directing groups[22,23] just to name a few, speaks both to the ingenuity of carbohydrate chemists and the difficulty associated with this problem.[24,25] Further, the paucity of automated syntheses of glycans rich in 1,2-*cis* linkages[26] suggests the need for highly 1,2-*cis*-selective methods.

One of the most simple solutions to 1,2-*cis*-selective *O*-glycosylation involves the implementation of ether solvents especially with relatively electron-rich glycosyl *O*-trichloroacetimidate or thioglycoside donors in the presence of acidic/electrophilic activators.[10–14] Investigators such as Seeberger, Boons, and especially Schmidt, as well as many others, have demonstrated the unmistakable positive effect that ether solvents have toward improving 1,2-*cis* selectivity. A common mechanistic proposal to explain this effect involves the formation of intermediate oxocarbenium ions from donor



Scheme 2. Indirect evidence for glycosyl oxonium ions and previous work.

substrates **3**, their interception of an ether molecule to generate an equatorial glycosyl oxonium ion (**4**, which is likely more stable than the axial diastereomer),[27] and subsequent backside attack of acceptor to generate 1,2-*cis* glycoside (**5**, Sch. 1). Indeed, organic chemists have speculated on the existence of **4** since a time no later than the 1970s.[12,28–30] Despite direct evidence of other highly reactive species such as glycosyloxyiminium[6] and sulfonium[9,21,31] ions in addition to glycosyl oxocarbenium ions,[32] we are not aware of any direct observation of species **4**.

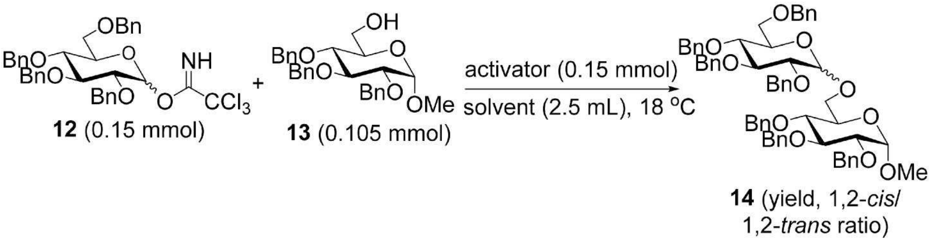
Perhaps the most compelling *indirect* evidence for **4** has been provided by Dabideen and Gervay-Hague who demonstrated that various epoxides, oxetane, and THF could give ring-opened products such as **8** (Sch. 2) via putative intermediate **7** upon reaction with glycosyl iodide substrates in the presence of MgO in CH_2Cl_2.[33] Curiously, these processes occur with relatively low stereoselectivity which contrasts with the often high stereoselectivity in the studies detailed by references.[10–14] In our opinion, these conditions differ dramatically from the aforementioned 1,2-*cis* selective methods in ether solvents[10–14] which occur, *almost without exception, not in the presence of halide anions but triflate and perchlorate.*

Our previous foray into this area (Sch. 2) involved the conversion of 4-trifluoromethylbenzyl-protected (CF_3Bn) glucosyl donor **9** which can be activated toward *O*-glycosylation with strong acids.[13] Activation with triflic acid in CH_2Cl_2 resulted in poor selectivity (data not shown), however, activation in 1,4-dioxane resulted in an encouraging selectivity of 13:1 in favor of 1,2-*cis* product **11** (our previous work, entry 1). During the study, we reasoned that replacement of triflic acid with similarly acidic trifluoromethanesulfonamide could be beneficial for a number of reasons.

First, glycosyl triflates are well-documented intermediates which can be generated under a host of conditions and which readily undergo reaction with acceptors to generate *O*-glycosides.[34] We believed that glycosyl triflates might serve to erode selectivity by competing with ether for the formation of glycosyl triflates at the expense of equatorial glycosyl oxonium ions **4**. Second, trifluoromethanesulfonamide anion does not form glycosyl trifluromethanesulfonamides with anything approaching the ease of glycosyl triflate formation.[35,36] Efforts by Nokami[35] as well as Wang & Pedersen[36] failed to produce any evidence for glycosyl trifluoromethanesulfonamides under conditions that readily produced the glycosyl triflate analogs. With this in mind, we performed an experiment (Sch. 2, our previous work, entry 2) identical to the previous, triflic-acid-promoted protocol save for the use of trifluoromethanesulfonamide in its place. We hypothesized that the presence of the apparently less-nucleophilic trifluoromethanesulfonamide anion would result in higher proportions of a 1,4-dioxane-derived glycosyl oxonium intermediate. *To our great surprise, this second experiment proceeded with total loss of stereoselectivity* (1:1 1,2-*cis*/1,2-*trans*). This observation was highly intriguing to us, and we elected to conduct a study using glucosyl *O*-trichloroacetimidate donors, a species with an especially rich history of 1,2-*cis* selectivity in the presence of ether solvents.[11] Herein, we provide details of this study. *While we cannot disprove the existence of glycosyl oxonium intermediates, we argue that these species bear little relevance to 1,2-cis selective processes in ether solvents and that the mechanistic picture may be far more complex than originally thought to be.*

Results and discussion

In our initial studies (Sch. 3), we employed relatively electron-rich benzyl-protected glucosyl *O*-trichloroacetimidate donor **12** with acceptor **13** under conditions similar to those at the bottom of Scheme 2 (Sch. 3). The D-glucose stereochemistry was chosen due to the lack of axial substituents which might bias selectivity as could be the case with the D-mannose or D-galactose analogs. The acceptor **13** was chosen due to its moderate reactivity and the relative ease of selectivity determination using integration of reducing-end methyl groups with ^{1}H NMR.[13,15] Reaction with HOTf in 1,4-dioxane gave a 70% yield of product **14** with a 1,2-*cis*/1,2-*trans* selectivity of 4.6:1 (entry 1). Likewise, implementation of Et_2O provided similar yield and a similar selectivity of 2.3:1 (entry 2). Replacing HOTf with TMSOTf under these same conditions resulted in a selectivity of 3.0:1 (entry 3). These selectivities are similar to those reported in our previous work.[13] The diminished selectivity relative to the CF_3Bn-protected

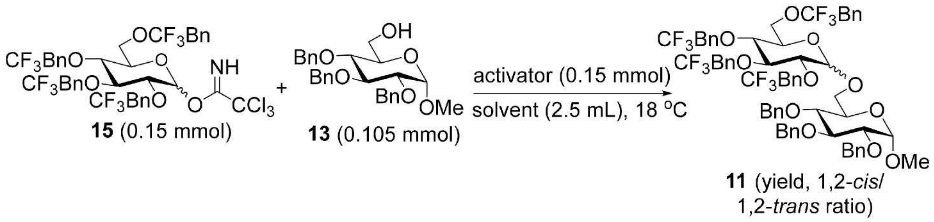


Entry	Solvent	Activator	Yield	1,2-*cis*/1,2-*trans*
1	1,4-dioxane	HOTf	70%	4.6:1
2	Et_2O	HOTf	78%	2.3:1
3	Et_2O	TMSOTf	75%	3.0:1
4	THF	HOTf	77%	1:1.3
5	1,4-dioxane	Tf_2NH	71%	1:1.2
6	Et_2O	Tf_2NH	72%	1:1.3
7	1,4-dioxane	$BF_3 \cdot OEt_2$	72%	1:1.4

Scheme 3. 1,2-*cis*-Selectivity with a benzyl-protected D-glucosyl trichloroacetimidate.

substrates from Scheme 2 is no cause for concern as we and others have shown that halogenation of benzyl protecting groups results in an increase in selectivity.[13,15–17] Interestingly, switching to THF as solvent resulted in a total loss of selectivity but a comparable yield of 77% (1:1.3 1,2-*cis*/1,2-*trans*, entry 4). Given the high Lewis basicity of THF relative to 1,4-dioxane and diethyl ether[37] as well as the previous results of Dabideen and Gervay-Hague, this is a surprising result. According to a mechanistic hypothesis like that shown in Scheme 1, one would expect glycosyl oxonium formation to be most relevant in the most Lewis-basic solvents. Just as interesting are the results of entries 5–7. Replacement of HOTf with Tf_2NH in 1,4-dioxane and diethyl ether resulted in near-total loss of 1,2-*cis* selectivity providing **14** with 1,2-*cis*/1,2-*trans* selectivities of 1:1.2 and 1:1.3, respectively (entries 5 and 6). Finally, we screened $BF_3 \bullet Et_2O$ as activator, and this resulted in a loss of 1,2-*cis* selectivity as well (entry 7, 1:1.4 1,2-*cis*/1,2-*trans*). These results are similar to those presented at the bottom of Scheme 2. Triflate appears to be essential for 1,2-*cis* selectivity while alternative activators result in loss or reversal of selectivity despite the implementation of various ether solvents. In addition, the most Lewis-basic solvent screened (THF)[37] provides the lowest selectivity under conditions otherwise identical to those in 1,4-dioxane and Et_2O.

As mentioned before, we and others have demonstrated that halogenation of benzyl groups results in an increase in 1,2-*cis* selectivity wherein we attribute this increase to electron withdrawing effects.[13,15–17] Thus, we elected to study solvent and activator parameters with CF_3Bn-protected donor **15** and acceptor **13** (Sch. 4). As with Scheme 3, we observed the highest selectivity (9.1:1 1,2-*cis*/1,2-*trans*) with 1,4-dioxane (entry 1).

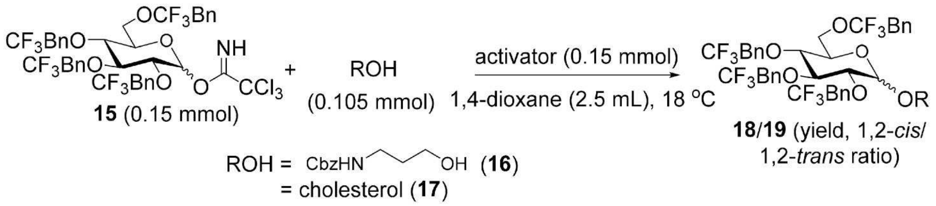


Entry	Solvent	Activator	Yield	1,2-*cis*/1,2-*trans*
1	1,4-dioxane	HOTf	90%	9.1:1
2	Et_2O	HOTf	89%	5.4:1
3	THF	HOTf	85%	1.6:1
4	THF	TMSOTf	60%	2:1
5	TBME	HOTf	75%	7.0:1
6	1,4-dioxane	Tf_2NH	70%	1.2:1
7	Et_2O	Tf_2NH	75%	1:1.1
8	TBME	Tf_2NH	80%	1:1
9	1,4-dioxane	$BF_3 \cdot OEt_2$	36%	1:2.6

Scheme 4. 1,2-*cis*-selectivity with a CF_3Bn-protected D-glucosyl trichloroacetimidate.

Diethyl ether also provided 1,2-*cis* selectivity using HOTf as activator (5.4:1, entry 2). Similar to our previous observations, implementation of THF results in a loss of selectivity relative to 1,4-dioxane and ether using HOTf (1.6:1) and TMSOTf (2:1) as activators (entries 3 and 4). These results further corroborate the notion that high Lewis basicity does not guarantee the high 1,2-*cis* selectivity expected with glycosyl oxonium intermediates. We were also interested in screening an alternative ether solvent chosen due to an expected poor propensity toward glycosyl oxonium formation. Thus, the implementation of *tert*-butyl methyl ether (TBME, entry 5) resulted in a respectable 1,2-*cis* selectivity of 7:1 despite the steric hindrance about the ether oxygen! This observation corroborates those previously made by Seeberger and coworkers in which TBME engendered high 1,2-*cis* selectivity under a multitude of conditions.[14] Further, we screened these same solvents using Tf_2NH as activator and observed dramatically reduced 1,2-*cis* selectivities with 1,4-dioxane (entry 6, 1.2:1), diethyl ether (entry 7, 1:1.1), and TBME (1:1, entry 8). Finally, the implementation of $BF_3 \bullet Et_2O$ (entry 9) resulted in a reversal of selectivity in favor of 1,2-*trans*.

We were then interested in screening other acceptors than **13** to assure that these results were not dependent on acceptor structure (Sch. 5). We elected to screen two acceptors with high reactivity (and thus low expected selectivity) relative to **13**. Reaction of CF_3Bn-protected **15** with the alcohols *N*-carbobenzyloxy-3-amino-propan-1-ol **16** and cholesterol **17** resulted in the expected 1,2-*cis* selectivity with HOTf as activator and a loss of selectivity with Tf_2NH.



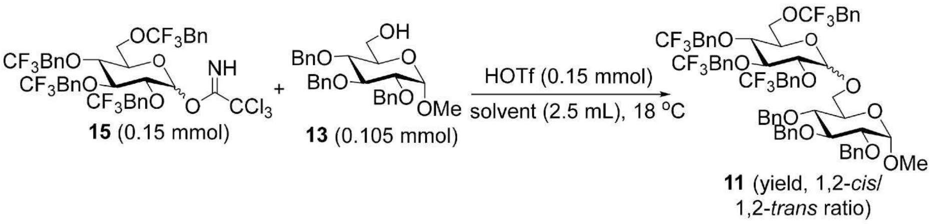
Entry	ROH	Activator	Yield	1,2-*cis*/1,2-*trans*
1	**16**	HOTf	73%	4.2:1
2	**16**	Tf_2NH	70%	1:1
3	**17**	HOTf	70%	6.9:1
4	**17**	Tf_2NH	76%	1.1:1

Scheme 5. Selectivity with additional acceptors.

Taken together, the results in Schemes 3–5 cast serious doubt on the "ether model" presented in Scheme 1. Particularly salient are the following three observations: 1. THF, the most Lewis-basic of the three solvents, consistently provides the poorest selectivity in the presence of activators such as HOTf and TMSOTf. 2. TBME, the most hindered of the four ether solvents screened, provides 1,2-*cis* selectivity comparable to 1,4-dioxane and diethyl ether and far superior to that observed with THF provided that the relevant counteranion is triflate. 3. Perhaps most compellingly, switching from activators such as HOTf and TMSOTf to Tf_2NH and $BF_3{\bullet}OEt_2$ results in loss of stereoselectivity even though we would expect trifluoromethanesulfonimide to interfere less than triflate with glycosyl oxonium formation. As suggested before, these results do not disprove the formation of glycosyl oxonium ions. But they do call into serious question the agency of such species in 1,2-*cis* selective processes as shown in Scheme 1.

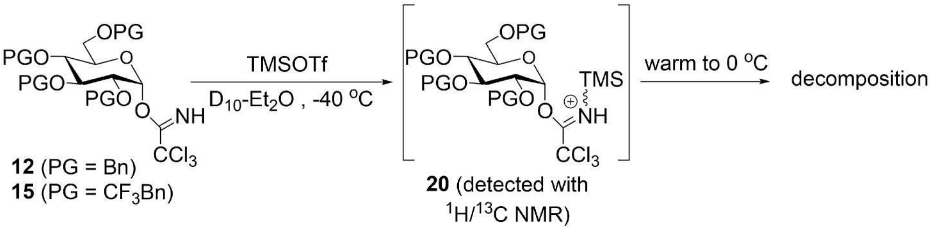
At this juncture, we conceived of alternative hypotheses. Given the loss of stereoselectivity observed with THF, we were interested in what, if any, effect solvent polarity might have on selectivity. We screened an additional 3 solvents (toluene, CH_2Cl_2, and α,α,α-trifluoromethylbenzene, Sch. 6) and compared the resulting selectivity to solvent dielectric constant (ε) with these new results and results from Sch. 4. However, no clear trends could be discerned in comparing either ε or solvent polarity index (P', not shown) to 1,2-*cis* selectivity (Sch. 6).

Given the relatively high selectivity engendered in the presence of triflate anion in this study and in numerous previous studies, we also hypothesized that glycosyl triflate intermediates might play a role in 1,2-*cis* selectivity as has been postulated elsewhere.[38] However, given the poor stability of glycosyl triflates at the temperature (18 °C) under which the reported *O*-glycosylations were studied herein, we elected to attempt observation of glycosyl triflates and other intermediates derived from **12** and **15** under reaction with TMSOTf in perdeuterated Et_2O at low temperature (−40 °C). Indeed,



Entry	Solvent	ε	Yield	1,2-*cis*/1,2-*trans*
1	1,4-dioxane	2.2	90%	9.1:1
2	toluene	2.4	75%	2.0:1
3	Et_2O	4.3	89%	5.4:1
4	TBME	4.5	75%	7.0:1
5	THF	7.6	85%	1.6:1
6	CH_2Cl_2	8.9	71%	3.6:1
7	$CF_3C_6H_5$	9.2	80%	4.0:1

Scheme 6. Solvent dielectric screen.



Scheme 7. NMR studies.

Wang & Pedersen had observed formation of glycosyl triflates from super-disarmed 2-benzyl-3,4,6-triacetyl-D-glucosyl trichloroacetimidate under similar conditions.[36] In the event, treatment of **12/15** with TMSOTf in D_{10}-Et_2O at −40 °C resulted in a clear conversion of trichloroacetimidate to silylated analogs **20** confirmed by comparison to the work of Wang & Pedersen (Sch. 7).[36] However, there was no obvious formation of glycosyl triflate derivatives of **12/15**, and slow warming toward 0 °C simply resulted in decomposition. Failure to observe glycosyl triflates under these conditions does not disprove the relevance of such intermediates to 1,2-*cis* selective *O*-glycosylation, and we deem these results inconclusive on the subject.

Conclusion

In conclusion, the results of this work paint a far more complicated picture than previous assumptions based on the "ether model" might predict. While observations made herein do not place us anywhere close to a full mechanistic understanding of the reasons for 1,2-*cis* selectivity in ether solvents, we believe that this work rules out ether-derived glycosyl oxonium ions as relevant intermediates. Previous mechanistic proposals that invoke these intermediates should be reconsidered. Continuing work that will shed further light onto the mechanistic underpinnings of these processes is underway in our lab and will be reported in due course.

Experimental section

General methods

All reactions were performed under N_2 atmosphere, which was achieved by vacuum purge backfill three times. Dried solvents (CH_2Cl_2, Et_2O, THF) were used directly from a PureSolv 400-5 solvent purification system. Dry 1,4-dioxane solvent was obtained through distillation from sodium-benzophenone ketyl. Dry *tert*-butyl methyl ether (TBME) and toluene were purchased from Acros Organics. Dry $CF_3C_6H_5$ was purchased from Sigma-Aldrich. Reagents were purchased from commercial sources (Alfa Aesar, Acros Organics, Matrix Scientific (4-trifluoromethyl benzyl bromide), Sigma Aldrich, TCI). Column chromatography was performed using silica gel (60 Å) purchased from SiliCycle. Analytical TLC was performed using 60 Å silica gel with F254 indicator on aluminum sheets (Sigma Aldrich). Compound visualization on TLC was performed using a hand-held UV hand lamp and/or staining with anisaldehyde. ^1H NMR and ^{13}C NMR experiments for intermediate compounds and anomeric ratio analysis were performed using a Bruker AVIII-400 MHz NMR spectrometer. Low-temperature NMR experiments were performed using a Bruker AVNEO 700 MHz spectrometer. $CDCl_3$ was purchased from Cambridge Isotope Laboratories. D_{10}-Et_2O was purchased from Thermo Fischer Scientific.

Determination of anomeric ratios

For ^1H NMR analysis of anomeric mixtures in both the crude and purified samples, the number of scans was set to 16, while relaxation delays were set to 20 seconds. For glycosylation reactions using acceptor **13** (methyl 2,3,4-tribenzyl-a-D-glucoside), anomeric ratios were determined according to the following set of commands using the GSD algorithm (deconvolution) in MestReNova:

1. Phase correction – Processing > Phase correction > Automatic
2. Baseline correction – Processing > Baseline > Full auto (Bernstein polynomials)
3. Analysis > Peak picking > options = Method – GSD, Refinement level – 5 fitting, Optimized for peaks – average. Then Ok.

4. Analysis > Integration > Options = Calculation method – Sum, Source – autodetect, Algorithm – peak picking, Minimum area – 3%. Then Ok.
5. Analysis > Peak picking > Automatic
6. View > Tables > Peaks.

A GSD table containing all the peaks with their respective height, width, and area was generated. The reducing-end aglycone methyl signals from both the 1,2-*cis* or *alpha* (3.35–3.36 ppm) and 1,2-*trans* or *beta* (3.32–3.33 ppm) products were analyzed. Areas of these signals were used to determine anomeric ratios in Schemes 3, 4, and 6. Anomeric ratios in Scheme 5 were determined through the integration of key signals in the ^{1}H NMR spectra of crude and purified samples.

Synthesis of phenyl-2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranose (23)

To 5.10 g of 1,2,3,4,6-penta-*O*-acetyl-α,β-D-glucopyranose (**21**) (13.1 mmol) in an R.B.F. with a magnetic stir bar, 25.0 mL of dichloromethane was added. The flask was capped with a septum, then three cycles of nitrogen purge backfill were performed, and the resulting solution was maintained under a N_2 blanket. After all solids dissolved, the flask was placed in an ice bath, and its contents were stirred for 30 min. 12.5 mL of 33% HBr in acetic acid was added in a dropwise fashion over a period of 5 min to the flask in an ice bath with continued stirring. The ice bath was removed after 1 h, and the reaction was monitored by TLC. The TLC showed complete conversion after 3 h. The reaction mixture was then added to 100 mL of ice-cold water in a beaker. The mixture from the beaker was then transferred to a separatory funnel and washed with 60 mL x2 of sat. aq. $NaHCO_3$ solution. The organic layer was then concentrated on the rotary evaporator to obtain a brown foam. To this brown foam in an R.B.F., a magnetic stir bar was added, and the flask was then subjected to high vacuum for 1 h. The flask was then backfilled with N_2, followed by three cycles of nitrogen purge backfill, and 25.0 mL of acetonitrile and 1.5 mL of thiophenol (15 mmol) were syringed into the flask. After a homogeneous mixture was obtained, the flask was placed in an ice bath and its contents were stirred for 30 min. 3.9 mL of triethylamine (28 mmol) was then added dropwise over a period of 5 min into the flask with continued stirring. The ice bath was removed after 1 h, and the reaction was monitored by TLC. The TLC showed complete conversion after 3 h. The reaction mixture was transferred to a separatory funnel, and 75 mL of dichloromethane was added to the funnel. The organic layer was then washed with 100 mL x2 of water followed by 30 mL x2 saturated brine solution. The organic layer was then dried using Na_2SO_4 and concentrated to give a crude product, which was purified using flash column chromatography (0-20% EtOAc/hexanes) to give 2.29 g (5.20 mmol) of **23** as a white solid (40% two steps).^{1}H NMR (400 MHz, Chloroform-d): δ 7.50 (m, 2H), 7.32 (m, 3H), 5.22 (t, $J = 9.3$ Hz, 1H), 5.04 (t, $J = 9.8$ Hz, 1H), 4.97 (t, $J = 9.3$ Hz, 1H), 4.71 (d, $J = 10$ Hz, 1H), 4.20 (m, 2H), 3.72 (m, 1H), 2.09–2.06 (m, 6H), 2.02 (s, 3H), 1.99 (s, 3H). The ^{1}H NMR matched the literature spectrum.[39]

Synthesis of phenyl-2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranose (25)

To 2.26 g of **23** (5.13 mmol) in an R.B.F. with a magnetic stir bar, 5 ml of methanol was added. The flask was capped with a septum. This was followed by three cycles of nitrogen purge backfill, and the resulting solution was maintained under a N_2 blanket. Then, 0.2 mL of 5 M NaOMe was added in a dropwise fashion to the flask with continued stirring. After 1 h, the spots on TLC converged onto a single, low-eluting compound. 6.00 g of Dowex® 50WX8, 200–400 mesh, ion exchange resin (Acros Organics) was then added to the reaction mixture to adjust the pH to 4. The reaction mixture was then filtered through a celite cake, and the filter cake was rinsed with 10.0 mL of methanol. The filtrate was concentrated using rotary evaporator and twice co-evaporated with 5.0 mL of toluene to give a white powder of phenyl-β-D-thioglucopyranoside (**24**). To this powder in an R.B.F. was added a magnetic stir bar, and the flask was then subjected to vacuum for 1 h. The flask was then backfilled with N_2. Then, 1.87 g (5.06 mmol) of tetrabutylammonium iodide was added, and the flask was capped with a septum. This was followed by three cycles of nitrogen purge backfill, and 15.0 mL of DMF was syringed into the flask. After dissolution of all solids, the flask was lowered into an ice bath, and the flask contents were stirred for 30 min. While the flask was still in the ice bath, excess NaH (3.0 g-60% in mineral oil, 75 mmol) was added carefully portion-wise over a period of 5 min to the reaction mixture with continued stirring. Then, 3.0 mL (25 mmol) of benzyl bromide was then syringed into the reaction mixture in a dropwise fashion over a period of 2 min with continued stirring. After 10 min, the flask was removed from the ice bath and the reaction contents were stirred at room temperature for 20 h. The reaction was quenched at 0 °C by the addition of water until gas evolution ceased. The reaction mixture was then transferred to a separatory funnel, and 300.0 mL of water was added. Then, 200.0 mL of EtOAc was added followed by vigorous shaking of the separatory funnel to get rid of DMF. The organic and aqueous layers were separated, and the organic layer was washed with 50 mL x2 of saturated brine solution. The organic layer was then dried using Na_2SO_4 and concentrated to give a crude product, which was purified using flash column chromatography (0–15% EtOAc/hexanes) to give 2.91 g (4.60 mmol) of **25** as a white solid (90% two steps). ^{1}H NMR (400 MHz, Chloroform-d): δ 7.60–7.55 (m, 2H), 7.40–7.26 (m, 18H), 7.23–7.16 (m, 5H), 4.88 (dd, *J* = 10.9 Hz, *J* = 2.6 Hz, 2H), 4.84 (d, *J* = 7.7 Hz, 1H), 4.81 (d, *J* = 7.6 Hz, 1H), 4.72 (d, *J* = 10.3 Hz, 1H), 4.67 (d, *J* = 9.7 Hz, 1H), 4.62–4.54 (m, 3H), 3.78 (dd, *J* = 10.9 Hz, *J* = 2.0 Hz, 1H), 3.73 (d, *J* = 4.7 Hz, 1H), 3.71–3.67 (m, 1H), 3.64 (t, *J* = 9.3 Hz, 1H), 3.54–3.47 (m, 2H). The ^{1}H NMR matched the literature spectrum.[40]

Synthesis of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (26)

To 3.04 g of **25** (4.80 mmol) in an R.B.F. with a magnetic stir bar, 12.7 mL of acetone was added followed by 1.6 mL of water. Then, 3.42 g (19.2 mmol) of NBS was added carefully to the reaction mixture with continued stirring. The flask was capped with a septum and three cycles of nitrogen purge refill were performed. After 3 h, the TLC showed complete consumption of the starting material. The reaction contents were concentrated on the rotary evaporator, and then 50.0 mL of dichloromethane was added to the flask. The solution was then transferred to a separatory funnel and washed with 50 mL x2 of water. The organic layer was then washed with 25 mL x2 of saturated brine solution. The organic layer was then dried using Na_2SO_4 and concentrated to give crude product, which was purified using flash column chromatography (10–40% EtOAc/hexanes) to give 1.31 g (2.42 mmol) of **26** as a white solid (50%). ^{1}H NMR (400 MHz, Chloroform-d): δ 7.37–7.27 (m, 23H), 7.16–7.11 (m, 2H), 5.23 (s,1H), 4.97–4.90 (m, 2H), 4.84 (d, *J* = 5.9 Hz, 1H), 4.82–4.80 (m, 1H), 4.79–4.77 (m, 1H), 4.75 (s, 1H), 4.71–4.66 (m, 1H), 4.61–4.54 (m, 2H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.47 (d, *J* = 7.3 Hz, 1H), 4.05–4.00 (m, 1H), 3.96 (t, *J* = 9.2 Hz, 1H), 3.73–3.68 (m, 1H), 3.66–3.61 (m, 2H), 3.59 (d, *J* = 3.4 Hz, 1H), 3.58–3.54 (m, 1H), 2.92 (d, *J* = 2.5 Hz, 1H). The ^{1}H NMR matched the literature spectrum.[41]

Synthesis of 2,3,4,6-tetra-O-benzyl-α-glucopyranosyl trichloroacetimidate (12)

To 1.17 g (2.16 mmol) of **26** in an R.B.F. with a magnetic stir bar, 20.0 mL of dichloromethane was added followed by 20.0 mL of trichloroacetonitrile. Then, 7.00 g (50.6 mmol) of K_2CO_3 was added to the flask. A reflux condenser was then attached to the flask, and the flask was then lowered into a temperature-controlled oil bath maintained at 45 °C with continued stirring. The reaction was refluxed for 4 h. After 4 h, the TLC showed complete conversion of the starting material. The reaction mixture was then filtered through a celite cake and washed with 10 mL x2 dichloromethane. The filtrate was then concentrated to obtain crude product, which was then purified using flash column chromatography (0–25% EtOAc/hexanes) to give 0.81 g (1.18 mmol) of **12** as a colorless sirup (55%). ^{1}H NMR (400 MHz, Chloroform-d): δ 8.57 (s, 1H), 7.35–7.24 (m, 18H), 7.17–7.11 (m, 2H), 6.52 (d, $J = 3.5$ Hz, 1H), 4.96 (d, $J = 10.9$ Hz, 1H), 4.85 (d, $J = 10.9$ Hz, 1H), 4.82 (d, $J = 11.2$ Hz, 1H), 4.74 (d, $J = 11.7$ Hz, 1H), 4.67 (d, $J = 11.8$ Hz, 1H), 4.59 (d, $J = 12.0$ Hz, 1H), 4.53 (d, $J = 10.7$ Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.05 (t, $J = 9.3$ Hz, 1H), 3.99 (d, $J = 9.9$ Hz, 1H), 3.81–3.73 (m, 3H), 3.67 (dd, $J = 11.0$ Hz, $J = 2.0$ Hz, 1H). The ^{1}H NMR matched the literature spectrum.[41]

Synthesis of phenyl-2,3,4,6-tetra-O-4′-trifluoromethylbenzyl-1-thio-β-D-glucopyranose (27)

To 1.47 g of **23** (3.34 mmol) in an R.B.F. with a magnetic stir bar, 5 mL of methanol was added. The flask was capped with a septum. This was followed by three cycles of nitrogen purge backfill, and the resulting solution was maintained under a N_2 blanket. Then, 0.2 mL of 5 M NaOMe was added in a dropwise fashion to the flask with continued stirring. After 1 h, the spots on TLC converged onto a single, low-eluting compound. Then, 7.00 g of Dowex® 50WX8, 200–400 mesh ion exchange resin (Acros Organics) was added to the reaction mixture to adjust the pH to 4. The reaction mixture was then filtered through a celite cake which was rinsed with 20.0 mL of methanol. The filtrate was concentrated using a rotary evaporator and twice co-evaporated with 5.0 mL of toluene to give a white powder **24**. To this powder in an R.B.F. was added a magnetic stir bar, and the flask was then subjected to vacuum for 1 h. The flask was then backfilled with N_2, 1.23 g (3.33 mmol) of tetrabutylammonium iodide, and 3.98 g (16.6 mmol) of *p*-trifluoromethylbenzyl bromide were added, and the flask was capped with a septum. This was followed by three cycles of nitrogen purge backfill, and 25.0 ml of DMF was syringed into the flask. After dissolution of all solids, the flask was lowered into an ice bath, and the flask contents were stirred for 30 min. While the flask was still in the ice bath, excess NaH (2.0 g-60% in mineral oil, 50 mmol) was added carefully to the reaction mixture with continued stirring. After 10 min, the flask was removed from the ice bath and the reaction contents were stirred at room temperature for 20 h. The reaction was quenched at 0 °C by the addition of water until gas evolution ceased. The reaction mixture was then transferred to a separatory funnel, and 300.0 mL of water was added. Then, 200.0 mL of EtOAc was added followed by vigorous shaking of the separatory funnel to get rid of DMF. The organic and aqueous layers were separated, and the organic layer was washed with 50 mL x3 of saturated brine solution. The organic layer was then dried using Na_2SO_4 and concentrated to give a crude product which was purified using flash column chromatography (0–15% EtOAc/hexanes) to give 1.98 g (2.19 mmol) of **27** as a white solid (66% two steps). ^{1}H NMR (400 MHz, Chloroform-d): δ 7.60–7.47 (m, 10H), 7.46–7.37 (m, 4H), 7.33–7.26 (m, 4H), 7.25–7.20 (m, 3H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.88–4.76 (m, 3H), 4.73–4.62 (m, 4H), 4.57 (d, *J* = 12.7 Hz, 1H), 3.81–3.71 (m, 2H), 3.70–3.62 (m, 2H), 3.55–3.47 (m, 2H). The ^{1}H NMR matched the literature spectrum.[15]

Synthesis of 2,3,4,6-tetra-O-4′-trifluoromethylbenzyl-D-glucopyranose (28)

To 2.19 g of **27** (2.42 mmol) in an R.B.F. with a magnetic stir bar, 20.0 mL of acetone was added followed by 2.0 mL of water. Then, 1.72 g (9.66 mmol) of NBS was added quickly to the reaction mixture with continued stirring. The flask was capped with a septum, and three cycles of nitrogen purge refill were performed. After 3 h, the TLC showed complete consumption of the starting material. The reaction contents were concentrated on the rotary evaporator, and then 50.0 mL of dichloromethane was added to the flask. The solution was then transferred to a separatory funnel and washed with 50 mL x2 of water. The organic layer was then washed with 25 mL x2 of saturated brine solution. The organic layer was then dried using Na_2SO_4 and concentrated to give crude product, which was purified using flash column chromatography (0–30% EtOAc/hexanes) to give 1.08 g (1.33 mmol) of **28** as a colorless gum (55%). ^{1}H NMR (400 MHz, Chloroform-d): δ 7.60–7.47 (m, 14H), 7.45–7.38 (m, 7H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.23–7.18 (m, 3H), 5.33 (t, *J* = 3.0 Hz, 1H), 5.02 (d, *J* = 11.9 Hz, 1H), 4.94 (d, *J* = 12.1 Hz, 1H),4.91 (d, *J* = 12.0 Hz, 1H), 4.84–4.70 (m, 7H), 4.64 (dd, *J* = 12.8 Hz, *J* = 3.2 Hz, 2H), 4.60–4.49 (m, 3H), 4.09–4.03 (m, 1H), 3.99 (t, *J* = 9.3 Hz, 1H), 3.76–3.69 (m, 2H), 3.66 (d, *J* = 2.2 Hz, 1H), 3.65–3.60 (m, 2H), 3.58 (dd, *J* = 9.5 Hz, *J* = 3.5 Hz, 1H), 3.43–3.37 (m, 1H), 3.35 (d, *J* = 5.0 Hz, 1H), 2.97 (d, *J* = 2.7 Hz, 1H). The ^{1}H NMR matched the literature spectrum.[15]

Synthesis of 2,3,4,6-tetra-O-4′-trifluoromethylbenzyl-α,β-glucopyranosyl trichloroacetimidate (15)

To 0.71 g (0.87 mmol) of **28** in an R.B.F. with a magnetic stir bar, 15.0 mL of dichloromethane was added followed by 5.0 mL of trichloroacetonitrile. Then, 4.50 g of K_2CO_3 (32.6 mmol) was added to the flask. A reflux condenser was then attached to the flask, and the flask was then lowered into a temperature-controlled oil bath maintained at 45 °C with continued stirring. The reaction was refluxed for 7 h. After 7 h, the TLC showed complete conversion of the starting material. The reaction mixture was then filtered through a celite cake which was washed with 20 mL x2 dichloromethane. The filtrate was then concentrated to obtain crude product which was then purified using flash column chromatography (0–25% EtOAc/hexanes) to give 0.46 g (0.48 mmol) of **15** as a colorless sirup (55%). ^{1}H NMR (400 MHz, Chloroform-d): δ 8.74 (s, 1H), 8.60 (s, 1H), 7.58–7.54 (m, 5H), 7.53–7.47 (m, 11H), 7.43–7.30 (m, 11H), 7.29–7.27 (m, 3H), 7.24–7.21 (m, 3H), 7.20–7.14 (m, 9H), 6.55 (d, $J = 3.4$ Hz, 1H), 5.82 (dd, $J = 5.3$ Hz, $J = 2.2$ Hz, 1H), 4.98 (d, $J = 11.8$ Hz, 1H), 4.93 (t, $J = 11.9$ Hz, 1H), 4.88–4.71 (m, 8H), 4.67 (d, $J = 4.9$ Hz, 1H), 4.65–4.56 (m, 5H), 4.51 (d, $J = 12.7$ Hz, 1H), 4.07–3.98 (m, 2H), 3.81–3.72 (m, 8H), 3.70 (d, $J = 1.9$ Hz, 1H), 3.68 (d, $J = 2.4$ Hz, 1H). The ^{1}H NMR matched the literature spectrum.[15]

General *procedure A* for glycosylation using TfOH or TMSOTf or $BF_3•OEt_2$ as activators

An oven dried vial was charged with 0.15 mmol of trichloroacetimidate donor and 0.105 mmol of alcohol acceptor (0.7 eq.) followed by a stir bar. The vial was capped with a septum, subjected to vacuum for 1 h, and then backfilled with N_2. Then, 2.5 mL of the specified solvent was syringed into the vial with the nitrogen line still attached. After obtaining a homogeneous mixture, 0.15 mmol (1 eq.) of activator was added using a micro-syringe, and the reaction was allowed to stir for 12 h at 18 °C. The reaction was quenched by addition of 0.05 mL of Et_3N. The reaction mixture was concentrated using a rotary evaporator and purified using flash column chromatography (0–30% EtOAc/hexanes).

General *procedure B* for glycosylation using Tf_2NH as activator

An oven dried vial was charged with 0.15 mmol of trichloroacetimidate donor and 0.105 mmol of alcohol acceptor (0.7 eq.) followed by a stir bar. The vial was capped with a septum, subjected to vacuum for 1 h, and then backfilled with N_2. The vial was then taken inside a glove box. Then, 42.2 mg (0.15 mmol) of Tf_2NH (1 eq.) was added to the vial, and the vial was recapped with the septum. Then, the vial was removed from the glove box, and a nitrogen line was attached to the vial. Following this, 2.5 mL of specified solvent was then added with vigorous stirring. The reaction was allowed to stir for 12 h at 18 °C. The reaction was then quenched by addition of 0.05 mL of Et_3N. The reaction mixture was concentrated using a rotary evaporator and purified using flash column chromatography (0–30% EtOAc/hexanes).

Glycosylation of acceptor 13 with donor 12

Compound **14** produced in the course of the Scheme 3 studies was analyzed for purity and anomeric ratios using ^{1}H NMR (see below). The ^{1}H NMR spectra matched those from the literature.[42]

Scheme 3, Entry 1: Following general procedure A, 2.5 mL of 1,4-dioxane, 100.0 mg (0.1460 mmol) of **12**, 51.1 mg (0.110 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 75.7 mg (0.076 mmol) of **14** was obtained in 70% yield. 1,2-*cis*: 1,2-*trans* = 4.6: 1.

Scheme 3, Entry 2: Following general procedure A, 2.5 mL of Et_2O, 102.0 mg (0.1490 mmol) of **12**, 52.9 mg (0.114 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 88.3 mg (0.089 mmol) of **14** was obtained in 78% yield. 1,2-*cis*: 1,2-*trans* = 2.3: 1.

Scheme 3, Entry 3: Following general procedure A, 2.5 mL of Et_2O, 103.2 mg (0.1506 mmol) of **12**, 46.5 mg (0.100 mmol) of **13**, and 27 µL (0.15 mmol) of TMSOTf were used. 73.9 mg (0.075 mmol) of **14** was obtained in 75% yield. 1,2-*cis*: 1,2-*trans* = 3: 1.

Scheme 3, Entry 4: Following general procedure A, 2.5 mL of THF, 101.9 mg (0.1487 mmol) of **12**, 51.6 mg (0.111 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 84.9 mg (0.086 mmol) of **14** was obtained in 77% yield. 1,2-*cis*: 1,2-*trans* = 1: 1.3.

Scheme 3, Entry 5: Following general procedure B, 2.5 mL of 1,4-dioxane, 108.1 mg (0.1578 mmol) of **12**, 49.1 mg (0.106 mmol) of **13**, and 42.2 mg (0.150 mmol) of Tf_2NH were used. 74.3 mg (0.075 mmol) of **14** was obtained in 71% yield. 1,2-*cis*: 1,2-*trans* = 1: 1.2.

Scheme 3, Entry 6: Following general procedure B, 2.5 mL of Et_2O, 101.8 mg (0.1486 mmol) of **12**, 46.7 mg (0.101 mmol) of **13**, and 43.1 mg (0.153 mmol) of Tf_2NH were used. 71.8 mg (0.073 mmol) of **14** was obtained in 72% yield. 1,2-*cis*: 1,2-*trans* = 1: 1.3.

Scheme 3, Entry 7: Following general procedure A, 2.5 mL of 1,4-dioxane, 104.4 mg (0.1524 mmol) of **12**, 48.4 mg (0.104 mmol) of **13**, and 19 µL (0.15 mmol) of $BF_3{\bullet}OEt_2$ were used. 74.4 mg (0.075 mmol) of **14** was obtained in 72% yield. 1,2-*cis*: 1,2-*trans* = 1: 1.4.

Compounds **11**, **18**, and **19** produced in the course of the Scheme 4, and Scheme 5 studies were analyzed for purity and anomeric ratios using ^{1}H NMR (see below). The ^{1}H NMR spectra matched those from the literature.[13]

Glycosylation of acceptor 13 with donor 15

Scheme 4, Entry 1: Following general procedure A, 2.5 mL of 1,4-dioxane, 140.9 mg (0.1472 mmol) of **15**, 52.9 mg (0.114 mmol) of **13**, and 13 µL

(0.15 mmol) of TfOH were used. 129.9 mg (0.1032 mmol) of **11** was obtained in 90% yield. 1,2-*cis*: 1,2-*trans* = 9.1: 1.

Scheme 4, Entry 2: Following general procedure A, 2.5 mL of Et_2O, 145.6 mg (0.1521 mmol) of **15**, 49.2 mg (0.106 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 119.2 mg (0.0947 mmol) of **11** was obtained in 89% yield. 1,2-*cis*: 1,2-*trans* = 5.4: 1.

Scheme 4, Entry 3: Following general procedure A, 2.5 mL of THF, 143.7 mg (0.1501 mmol) of **15**, 49.4 mg (0.106 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 113.5 mg (0.0901 mmol) of **11** was obtained in 85% yield. 1,2-*cis*: 1,2-*trans* = 1.6: 1.

Scheme 4, Entry 4: Following general procedure A, 2.5 mL of THF, 147.1 mg (0.1537 mmol) of **15**, 47.4 mg (0.102 mmol) of **13**, and 27 µL (0.15 mmol) of TMSOTf were used. 77.5 mg (0.0615 mmol) of **11** was obtained in 60% yield. 1,2-*cis*: 1,2-*trans* = 2: 1.

Scheme 4, Entry 5: Following general procedure A, 2.5 mL of TBME, 143.7 mg (0.1501 mmol) of **15**, 49.1 mg (0.106 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 100.1 mg (0.0794 mmol) of **11** was obtained in 75% yield. 1,2-*cis*: 1,2-*trans* = 7: 1.

Scheme 4, Entry 6: Following general procedure B, 2.5 mL of 1,4-dioxane, 141.3 mg (0.1476 mmol) of **15**, 48.5 mg (0.104 mmol) of **13**, and 42.4 mg (0.151 mmol) of Tf_2NH were used. 91.6 mg (0.073 mmol) of **11** was obtained in 70% yield. 1,2-*cis*: 1,2-*trans* = 1.2: 1.

Scheme 4, Entry 7: Following general procedure B, 2.5 mL of Et_2O, 142.5 mg (0.1489 mmol) of **15**, 47.2 mg (0.102 mmol) of **13**, and 42.2 mg (0.150 mmol) of Tf_2NH were used. 96.2 mg (0.076 mmol) of **11** was obtained in 75% yield. 1,2-*cis*: 1,2-*trans* = 1: 1.1.

Scheme 4, Entry 8: Following general procedure B, 2.5 mL of TBME, 145.6 mg (0.1521 mmol) of **15**, 47.9 mg (0.103 mmol) of **13**, and 43.1 mg (0.153 mmol) of Tf_2NH were used. 103.6 mg (0.0823 mmol) of **11** was obtained in 80% yield. 1,2-*cis*: 1,2-*trans* = 1.2: 1.

Scheme 4, Entry 9: Following general procedure A, 2.5 mL of 1,4-dioxane, 147.1 mg (0.1537 mmol) of **15**, 50.1 mg (0.107 mmol) of **13**, and 19 µL (0.15 mmol) of $BF_3•OEt_2$ were used. 47.9 mg (0.038 mmol) of **11** was obtained in 36% yield. 1,2-*cis*: 1,2-*trans* = 1: 2.6.

Glycosylation of acceptors 16 and 17 with donor 15

Scheme 5, Entry 1: Following general procedure A, 2.5 mL of 1,4-dioxane, 145.8 mg (0.1523 mmol) of **15**, 22.2 mg (0.106 mmol) of **16**, and 13 µL (0.15 mmol) of TfOH were used. 77.6 mg (0.077 mmol) of **18** was obtained in 73% yield. 1,2-*cis*: 1,2-*trans* = 4.2: 1.

Scheme 5, Entry 2: Following general procedure B, 2.5 mL of 1,4-dioxane, 146.3 mg (0.1529 mmol) of **15**, 23.6 mg (0.113 mmol) of **16**, and 42.2 mg (0.150 mmol) of Tf_2NH were used. 79.4 mg (0.079 mmol) of **18** was obtained in 70% yield. 1,2-*cis*: 1,2-*trans* = 1: 1.

Scheme 5, Entry 3: Following general procedure A, 2.5 mL of 1,4-dioxane, 145.5 mg (0.1520 mmol) of **15**, 42.6 mg (0.110 mmol) of **17**, and 13 µL (0.15 mmol) of TfOH were used. 89.7 mg (0.076 mmol) of **19** was obtained in 70% yield. 1,2-*cis*: 1,2-*trans* = 6.9: 1.

Scheme 5, Entry 4: Following general procedure B, 2.5 mL of 1,4-dioxane, 176.8 mg (0.1847 mmol) of **15**, 43.8 mg (0.113 mmol) of **17**, and 51.7 mg (0.184 mmol) of Tf_2NH were used. 100.2 mg (0.0858 mmol) of **19** was obtained in 76% yield. 1,2-*cis*: 1,2-*trans* = 1.1: 1.

Glycosylation of acceptor 13 with donor 15 (additional solvents)

Scheme 6, Entry 2: Following general procedure A, 2.5 mL of toluene, 148.1 mg (0.1547 mmol) of **15**, 48.1 mg (0.103 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 97.2 mg (0.077 mmol) of **11** was obtained in 75% yield. 1,2-*cis*: 1,2-*trans* = 2.0: 1.

Scheme 6, Entry 6: Following general procedure A, 2.5 mL of DCM, 139.5 mg (0.1458 mmol) of **15**, 48.5 mg (0.104 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 92.8 mg (0.074 mmol) of **11** was obtained in 71% yield. 1,2-*cis*: 1,2-*trans* = 3.6: 1.

Scheme 6, Entry 7: Following general procedure A, 2.5 mL of trifluorotoluene, 141.5 mg (0.1478 mmol) of **15**, 47.3 mg (0.102 mmol) of **13**, and 13 µL (0.15 mmol) of TfOH were used. 102.6 mg (0.0815 mmol) of **11** was obtained in 80% yield. 1,2-*cis*: 1,2-*trans* = 4.0: 1.

Acknowledgements

We thank Dr. Thomas Weldeghiorghis (LSU) for assistance with, and helpful conversations about, NMR.

Disclosure statement

The authors report that there are no competing interests to declare.

Funding

This work was supported by the National Science Foundation under Grant CHE-2101153.

References

[1] Del Bino, L.; Østerlid, K. E.; Wu, D.-Y.; Nonne, F.; Romano, M. R.; Codée, J.; Adamo, R. Synthetic Glycans to Improve Current Glycoconjugate Vaccines and

Fight Antimicrobial Resistance. *Chem. Rev.* **2022**, *122*(20), 15672–15716. DOI: 10.1021/acs.chemrev.2c00021.

[2] Adamo, R.; Nilo, A.; Castagner, B.; Boutureira, O.; Berti, F.; Bernardes, G. J. L. Synthetically Defined Glycoprotein Vaccines: Current Status and Future Directions. *Chem. Sci.* **2013**, *4*(8), 2995–3008. DOI: 10.1039/C3SC50862E.

[3] Anish, C.; Schumann, B.; Pereira, C. L.; Seeberger, P. H. Chemical Biology Approaches to Designing Defined Carbohydrate Vaccines. *Chem. Biol.* **2014**, *21*(1), 38–50. DOI: 10.1016/j.chembiol.2014.01.002.

[4] Horlacher, T.; Seeberger, P. H. Carbohydrate Arrays as Tools for Research and Diagnostics. *Chem. Soc. Rev.* **2008**, *37*(7), 1414–1422. DOI: 10.1039/B708016F.

[5] Chang, C.-H.; Lico, L. S.; Huang, T.-Y.; Lin, S.-Y.; Chang, C.-L.; Arco, S. D.; Hung, S.-C. Synthesis of the Heparin-Based Anticoagulant Drug Fondaparinux. *Angew. Chem. Int. Ed. Engl.* **2014**, *53*(37), 9876–9879. DOI: 10.1002/anie.201404154.

[6] Lu, S.-R.; Lai, Y.-H.; Chen, J.-H.; Liu, C.-Y.; Mong, K.-K. T. Dimethylformamide: An Unusual Glycosylation Modulator. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*(32), 7315–7320. DOI: 10.1002/anie.201100076.

[7] Mukaiyama, T.; Kobashi, Y. Highly α-Selective Synthesis of Disaccharide Using Glycosyl Bromide by the Promotion of Phosphine Oxide. *Chem. Lett.* **2004**, *33*(1), 10–11. DOI: 10.1246/cl.2004.10.

[8] Wang, L.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. Reagent Controlled Stereoselective Synthesis of α-Glucans. *J. Am. Chem. Soc.* **2018**, *140*(13), 4632–4638. DOI: 10.1021/jacs.8b00669.

[9] Park, J.; Kawatkar, S.; Kim, J.-H.; Boons, G.-J. “Stereoselective Glycosylations of 2-Azido-2-deoxy-glucosides Using Intermediate Sulfonium Ions.” *Org. Lett.* **2007**, *9*(10), 1959–1962. DOI: 10.1021/ol070513b.

[10] Wegmann, B.; Schmidt, R. The Application of the Trichloroacetimidate Method to the Synthesis of α-D-Gluco- and α-D-Galactopyranosides. *J. Carbohydr. Chem.* **1987**, *6*, 357–375. DOI: 10.1080/07328308708057926.

[11] Schmidt, R. R.; Jung, K.-H. Trichloroacetimidates. In *Carbohydrates in Chemistry and Biology*; Ernst, B.; Hart, G.W.; Sinaÿ, P., Eds. Wiley-VCH: Weinheim; 2000; pp 5–59.

[12] Demchenko, A.; Stauch, T.; Boons, G.-J. Solvent and Other Effects on the Stereoselectivity of Thioglycoside Glycosidations. *Synlett.* **1997**, *1997*(7), 818–820. DOI: 10.1055/s-1997-5762.

[13] Njeri, D. K.; Pertuit, C. J.; Ragains, J. R. 1,2-*cis*-Selective Glucosylation Enabled by Halogenated Benzyl Protecting Groups. *Org. Biomol. Chem.* **2020**, *18*(13), 2405–2409. DOI: 10.1039/D0OB00373E.

[14] Chatterjee, S.; Moon, S.; Hentschel, F.; Gilmore, K.; Seeberger, P. H. An Empirical Understanding of the Glycosylation Reaction. *J. Am. Chem. Soc.* **2018**, *140*(38), 11942–11953. DOI: 10.1021/jacs.8b04525.

[15] Njeri, D. K.; Valenzuela, E. A.; Ragains, J. R. Leveraging Trifluoromethylated Benzyl Groups toward the Highly 1,2-*cis*-Selective Glucosylation of Reactive Alcohols. *Org. Lett.* **2021**, *23*(21), 8214–8218. DOI: 10.1021/acs.orglett.1c02947.

[16] Moons, S. J.; Mensink, R. A.; Bruekers, J. P. J.; Vercammen, M. L. A.; Jansen, L. M.; Boltje, T. J. α-Selective Glycosylation with α-Glycosyl Sulfonium Ions Prepared via Intramolecular Alkylation. *J. Org. Chem.* **2019**, *84*(7), 4486–4500. DOI: 10.1021/acs.joc.9b00022.

[17] Zheng, Z.; Zhang, L. Gold-Catalyzed Synthesis of α-D-Glucosides Using an o-Ethynyl β-D-1-Thioglucoside Donor. *Carbohydr. Res.* **2019**, *471*, 56–63. DOI: 10.1016/j.carres.2018.10.010.

[18] Crich, D.; Sun, S. Direct Formation of β-Mannosides and Other Hindered Glycosides from Thioglycosides. *J. Am. Chem. Soc.* **1998**, *120*(2), 435–436. DOI: 10.1021/ja9734814.

[19] Crich, D.; Sun, S. Direct Synthesis of β-Mannopyranosides by the Sulfoxide Method. *J. Org. Chem.* **1997**, *62*(5), 1198–1199. DOI: 10.1021/jo962345z.

[20] Komarova, B. S.; Tsvetkov, Y. E.; Nifantiev, N. E. Design of α-Selective Glycopyranosyl Donors Relying on Remote Anchimeric Assistance. *Chem. Rec.* **2016**, *16*(1), 488–506. DOI: 10.1002/tcr.201500245.

[21] Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. A General Strategy for Stereoselective Glycosylations. *J. Am. Chem. Soc.* **2005**, *127*(34), 12090–12097. DOI: 10.1021/ja052548h.

[22] Yasomanee, J. P.; Demchenko, A. V. Effect of Remote Picolinyl and Picoloyl Substituents on the Stereoselectivity of Chemical Glycosylation. *J. Am. Chem. Soc.* **2012**, *134*(49), 20097–20102. DOI: 10.1021/ja307355n.

[23] Pistorio, S. G.; Yasomanee, J. P.; Demchenko, A. V. Hydrogen-Bond-Mediated Aglycone Delivery: Focus on β-Mannosylation. *Org. Lett.* **2014**, *16*(3), 716–719. DOI: 10.1021/ol403396j.

[24] Nigudkar, S. S.; Demchenko, A. V. Stereocontrolled 1,2-*cis* Glycosylation as the Driving Froce of Progress in Synthetic Carbohydrate Chemistry. *Chem. Sci.* **2015**, *6*(5), 2687–2704. DOI: 10.1039/C5SC00280J.

[25] Demchenko, A. V. Stereoselective Chemical 1,2-*cis* *O*-Glycosylation: From 'Sugar Ray' to Modern Techniques of the 21st Century. *Synlett.* **2003**, *2003*(09), 1225–1240. DOI: 10.1055/s-2003-40349.

[26] Hahm, H. S.; Hurevich, M.; Seeberger, P. H. Automated Assembly of Oligosaccharides Containing Multiple *cis*-Glycosidic Linkages. *Nat. Commun.* **2016**, *7*(1), 12482. DOI: 10.1038/ncomms12482.

[27] Filloux, C. M. The Problem of Origins and Origins of the Problem: Influence of Language on Studies Concerning the Anomeric Effect. *Angew. Chem. Int. Ed. Engl.* **2015**, *54*(31), 8880–8894. DOI: 10.1002/anie.201411185.

[28] Wulff, G.; Röhle, G. Results and Problems of *O*-Glycoside Synthesis. *Angew. Chem. Int. Ed. Engl.* **1974**, *13*(3), 157–170. DOI: 10.1002/anie.197401571.

[29] Wulff, G.; Schmidt, W. Uber die Orthoesterbildung als Konkurrenzreaktion zur Glykosylierung. *Carbohydr. Res.* **1977**, *53*(1), 33–46. DOI: 10.1016/S0008-6215(00)85452-X.

[30] Wulff, G.; Schröder, U.; Wilchelhaus, J. On the Stereochemical Control of Glycosylation Reactions by the Addition of Tetrahydrofuran. *Carbohydr. Res.* **1979**, *72*, 280–284. DOI: 10.1016/S0008-6215(00)83950-6.

[31] Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J-i Glycosyl Sulfonium Ions as Storable Intermediates for Glycosylations. *Org. Lett.* **2011**, *13*(6), 1544–1547. DOI: 10.1021/ol200242u.

[32] Martin, A.; Arda, A.; Désiré, J.; Martin-Mingot, A.; Probst, N.; Sinaÿ, P.; Jiménez-Barbero, J.; Thibaudeau, S.; Blériot, Y. Catching Elusive Glycosyl Cations in a Condensed Phase with HF/SbF_5 Superacid. *Nat. Chem.* **2016**, *8*(2), 186–191. DOI: 10.1038/nchem.2399.

[33] Dabideen, D. R.; Gervay-Hague, J. Unique Reactions of Glycosyl Iodides with Oxa- and Thiocycloalkane Acceptors. *Org. Lett.* **2004**, *6*(6), 973–975. DOI: 10.1021/ol049966w.

[34] Adero, P. O.; Amarasekara, H.; Wen, P.; Bohé, L.; Crich, D. The Experimental Evidence in Support of Glycosylation Mechanisms at the S_N1-S_N2 Interface. *Chem. Rev.* **2018**, *118*(17), 8242–8284. DOI: 10.1021/acs.chemrev.8b00083.

[35] Isoda, Y.; Kitamura, K.; Takahashi, S.; Nokami, T.; Itoh, T. Mixed-Electrolyte-Driven Stereoselective Electrochemical Glycosylation. *ChemElectroChem.* **2019**, *6*(16), 4149–4152. DOI: 10.1002/celc.201900215.

[36] Qiao, Y.; Ge, W.; Jia, L.; Hou, X.; Wang, Y.; Pedersen, C. M. Glycosylation Intermediates Studied Using Low Temperature ^{1}H and ^{19}F-DOSY NMR: New Insight into the Activation of Trichloroacetimidates. *Chem. Commun. (Camb).* **2016**, *52*(76), 11418–11421. DOI: 10.1039/C6CC05272J.

[37] Maria, P.-C.; Gal, J.-F. A Lewis Basicity Scale for Nonprotogenic Solvents: Enthalpies of Complex Formation with Boron Trifluoride in Dichloromethane. *J. Phys. Chem.* **1985**, *89*(7), 1296–1304. DOI: 10.1021/j100253a048.

[38] Van der Vorm, S.; Hansen, T.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. The Influence of Acceptor Nucleophilicity on the Glycosylation Reaction Mechanism. *Chem. Sci.* **2017**, *8*(3), 1867–1875. DOI: 10.1039/c6sc04638j.

[39] Kitowski, A.; Jiménez-Moreno, E.; Salvadó, M.; Mestre, J.; Castillón, S.; Jiménez-Osés, G.; Boutureira, O.; Bernardes, G. J. L. Oxidative Activation of C–S Bonds with an Electropositive Nitrogen Promoter Enables Orthogonal Glycosylation of Alkyl over Phenyl Thioglycosides. *Org. Lett.* **2017**, *19*(19), 5490–5493. DOI: 10.1021/acs.orglett.7b02886.

[40] Heuckendorff, M.; Poulsen, L. T.; Jensen, H. H. Remote Electronic Effects by Ether Protecting Groups Fine-Tune Glycosyl Donor Reactivity. *J. Org. Chem.* **2016**, *81*(12), 4988–5006. DOI: 10.1021/acs.joc.6b00528.

[41] van de Vrande, K. N. A.; Filippov, D. V.; Codée, J. D. C. Formation of Glycosyl Trichloroacetamides from Trichloroacetimidate Donors Occurs through an Intermolecular Aglycon Transfer Reaction. *Org. Lett.* **2023**, *25*(33), 6128–6132. DOI: 10.1021/acs.orglett.3c02196.

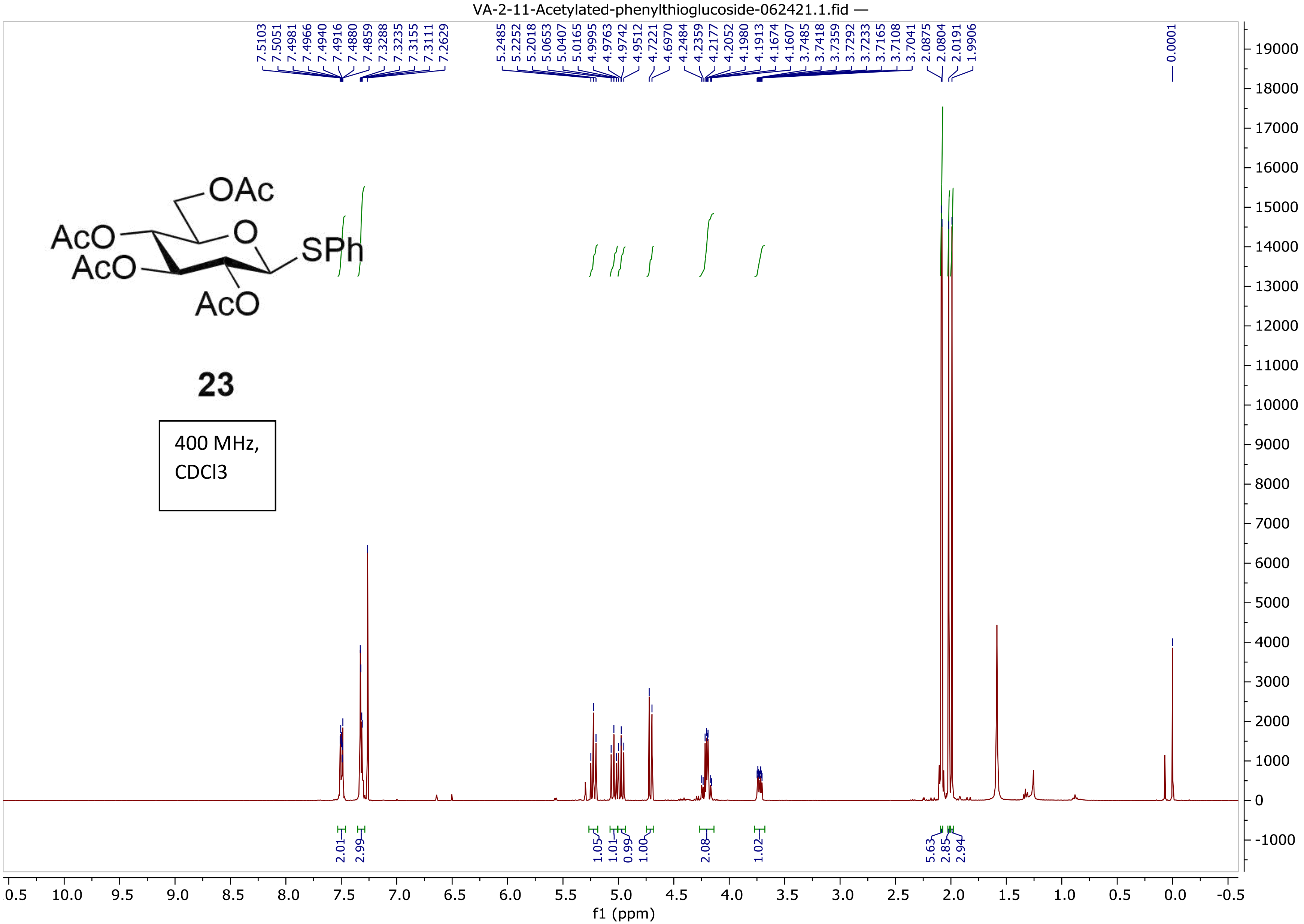
[42] Dieskau, A. P.; Plietker, B. A Mild Ligand-Free Iron-Catalyzed Liberation of Alcohols from Allylcarbonates. *Org. Lett.* **2011**, *13*(20), 5544–5547. DOI: 10.1021/ol202270g.

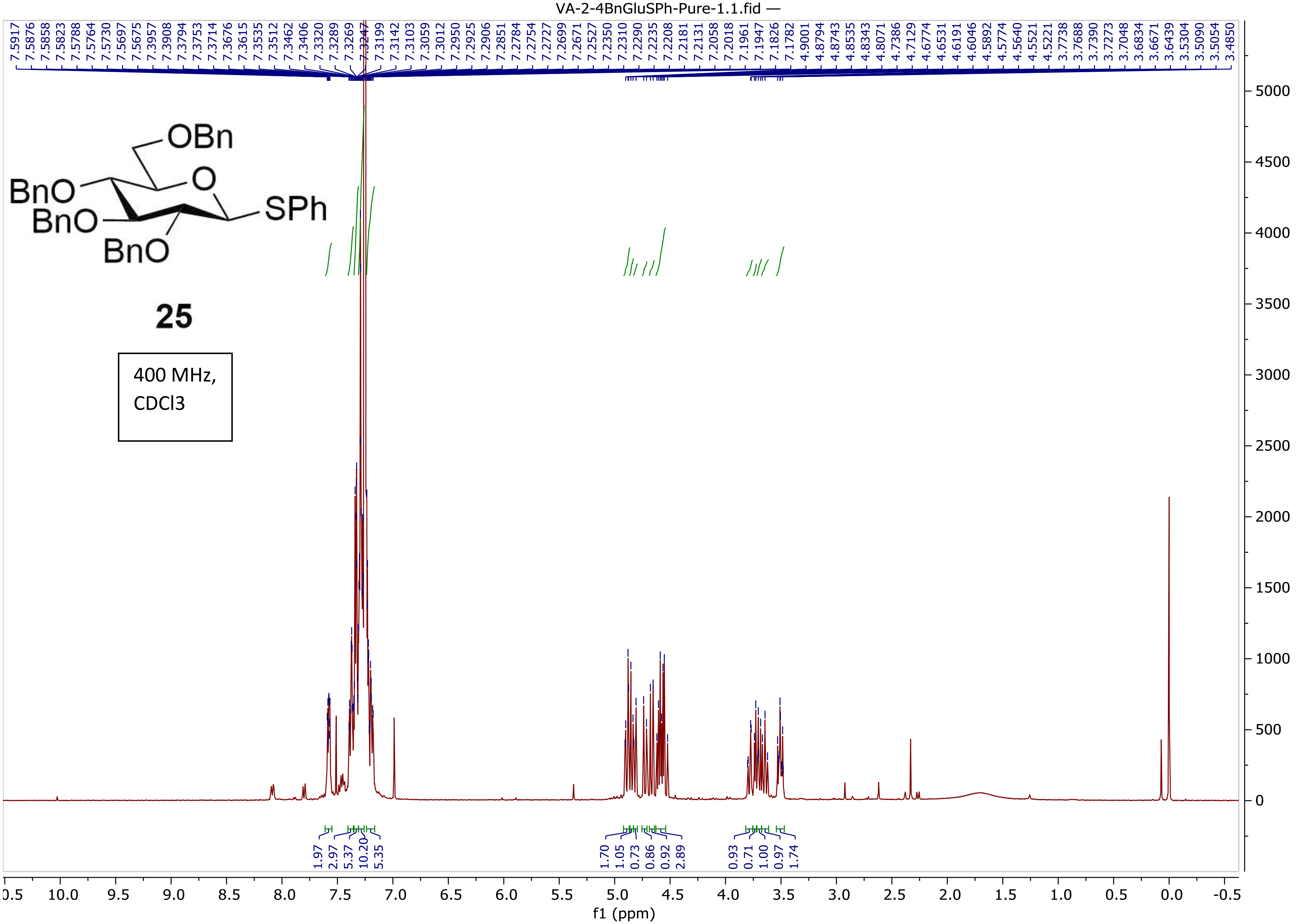
On the Relevance of Glycosyl Oxonium Ions to 1,2-*cis*-Selective *O*-Glycosylation in Ether Solvents

Varad Agarkar, Ava E. Hart, and Justin R. Ragains

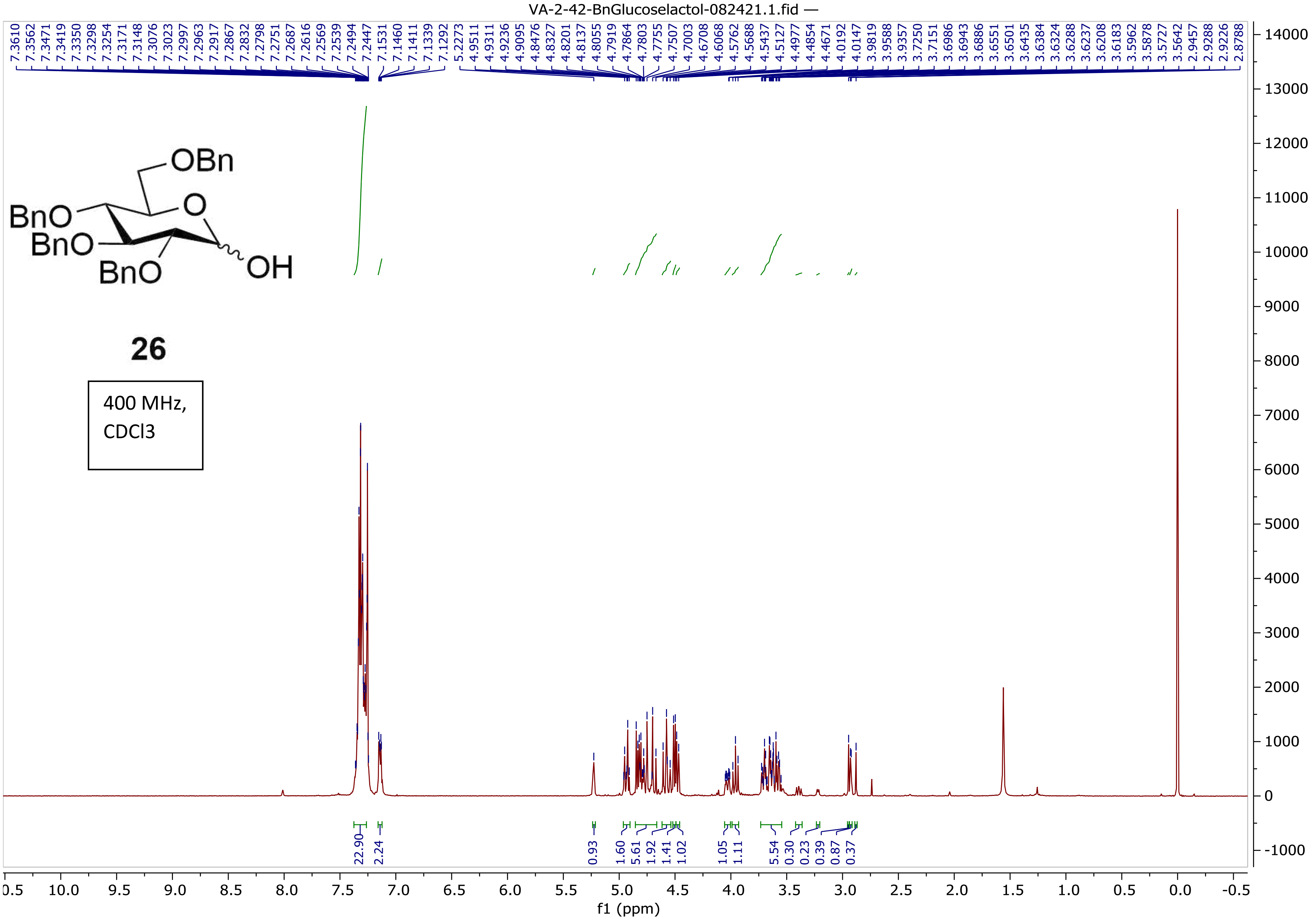
Supplementary Information

TABLE OF CONTENTS

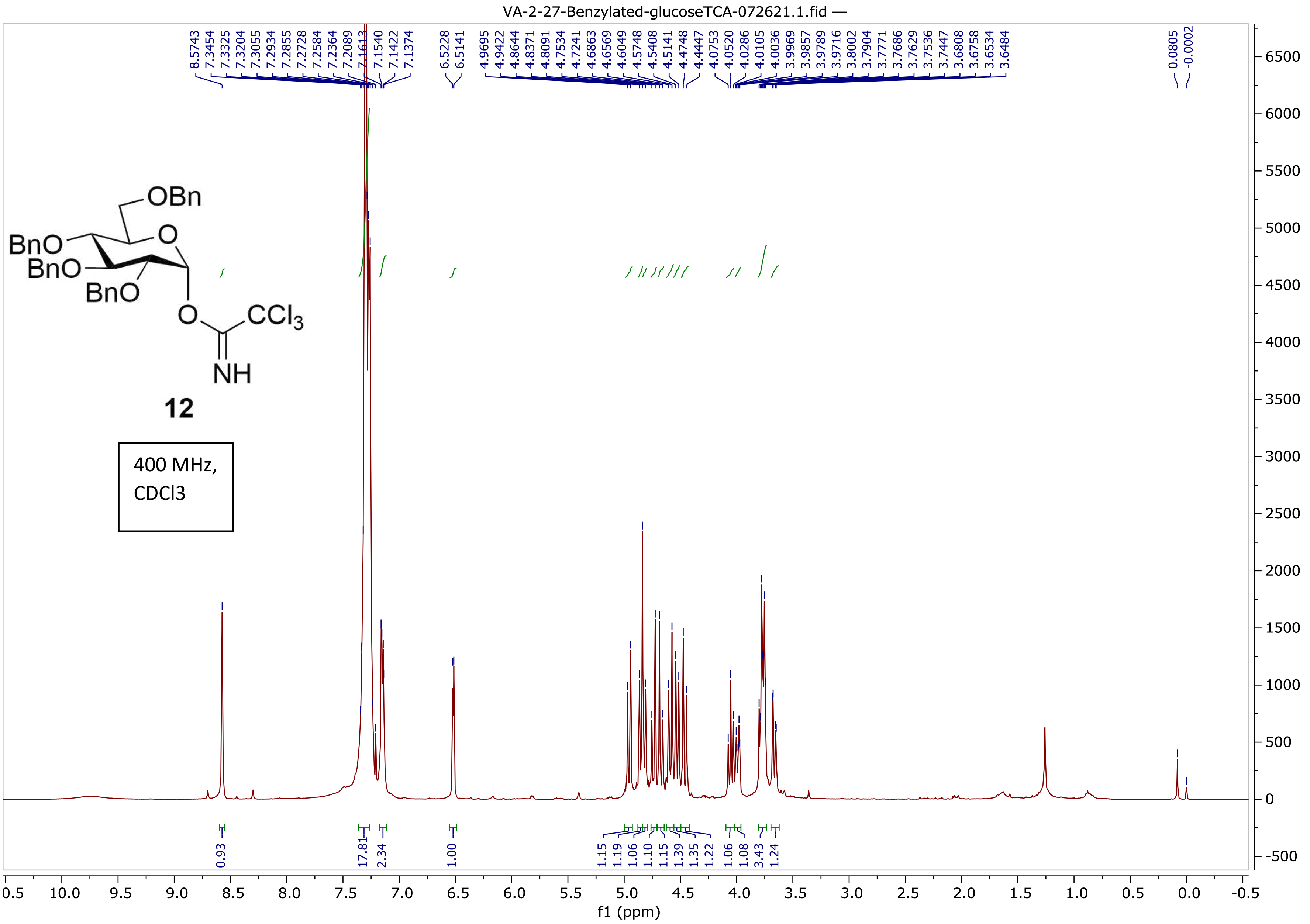

VA-2-11-Acetylated-phenylthioglucoside-062421.1.fid —
7.5103
7.5051
7.4981
7.4966
7.4940
7.4916
7.4880
7.4859
7.3288
7.3235
7.3155
7.3111
7.2629
5.2485
5.2252
5.2018
5.0653
5.0407
5.0165
4.9995
4.9763
4.9742
4.9512
4.7221
4.6970
4.2484
4.2359
4.2177
4.2052
4.1980
4.1913
4.1674
4.1607
3.7485
3.7418
3.7359
3.7292
3.7233
3.7165
3.7108
3.7041
2.0875
2.0804
2.0191
1.9906
0.0001
OAc
AcO
O
SPh
AcO
AcO
23
400 MHz,
CDCl3
2.01
2.99
1.05
1.01
0.99
1.00
2.08
1.02
5.63
2.85
2.94
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

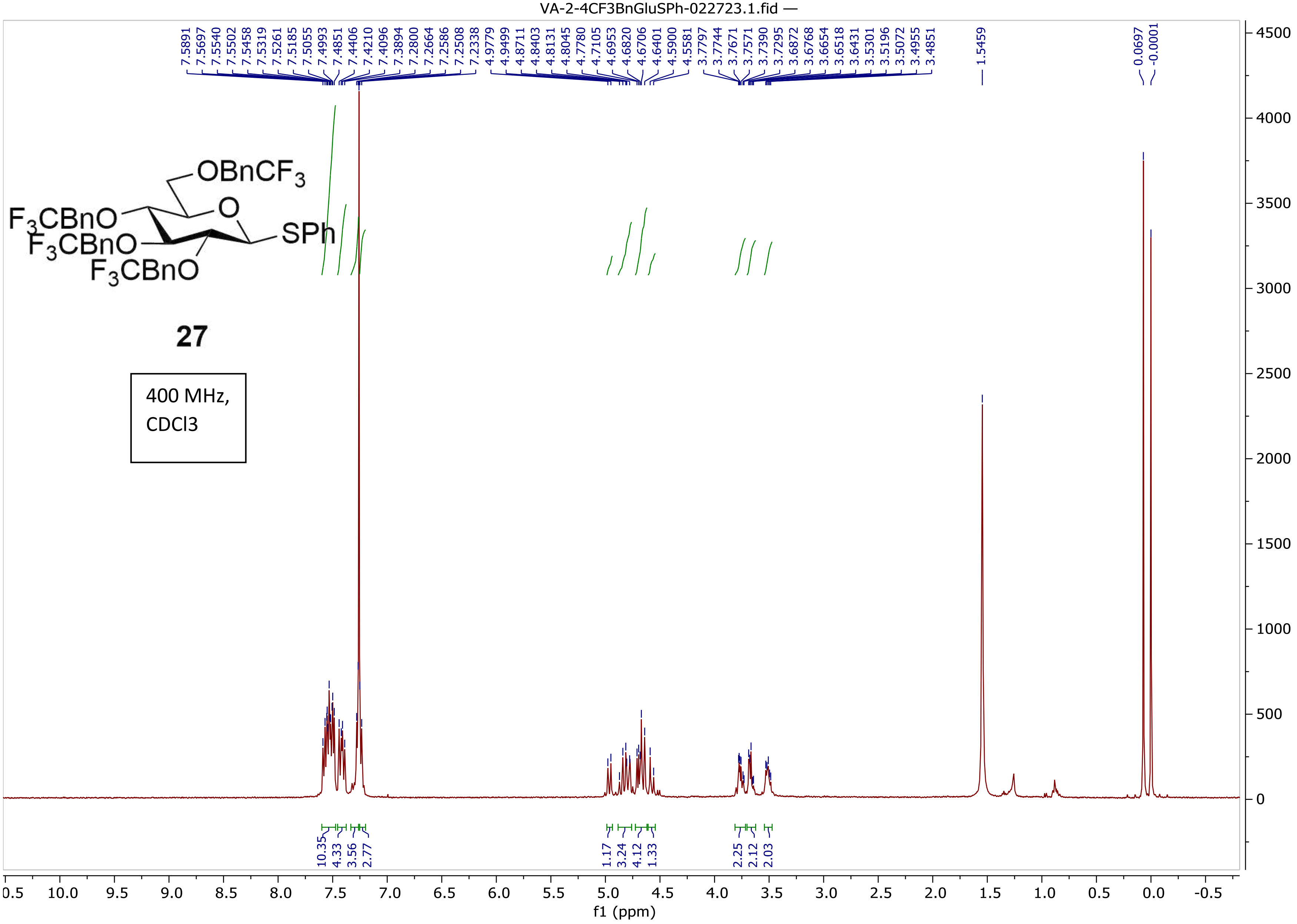

VA-2-4BnGluSPh-Pure-1.1.fid —
7.5917
7.5876
7.5858
7.5823
7.5788
7.5764
7.5730
7.5697
7.5675
7.3957
7.3908
7.3794
7.3753
7.3714
7.3676
7.3615
7.3535
7.3512
7.3462
7.3406
7.3320
7.3289
7.3269
7.3247
7.3199
7.3142
7.3103
7.3059
7.3012
7.2950
7.2925
7.2906
7.2851
7.2784
7.2754
7.2727
7.2699
7.2671
7.2527
7.2350
7.2310
7.2290
7.2235
7.2208
7.2181
7.2131
7.2058
7.2018
7.1961
7.1947
7.1826
7.1782
4.9001
4.8794
4.8743
4.8535
4.8343
4.8071
4.7386
4.7129
4.6774
4.6531
4.6191
4.6046
4.5892
4.5774
4.5640
4.5521
3.7738
3.7688
3.7390
3.7273
3.7048
3.6834
3.6671
3.6439
3.5304
3.5090
3.5054
3.4850
OBn
O
BnO
SPh
BnO
BnO
400 MHz,
CDCl3
1.97
2.97
5.37
10.20
5.35
1.70
1.05
0.73
0.86
0.92
2.89
0.93
0.71
1.00
0.97
1.74
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

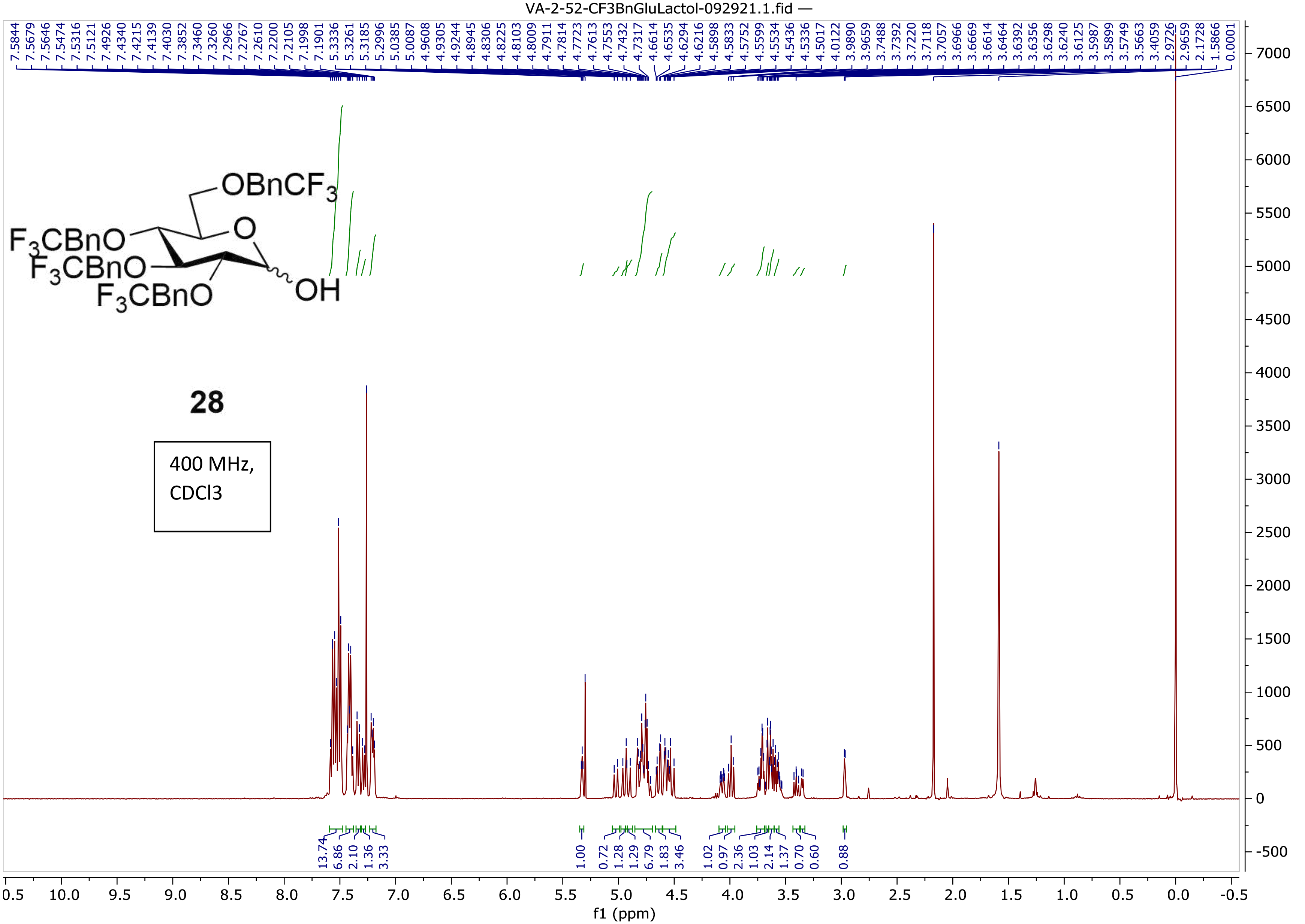
25

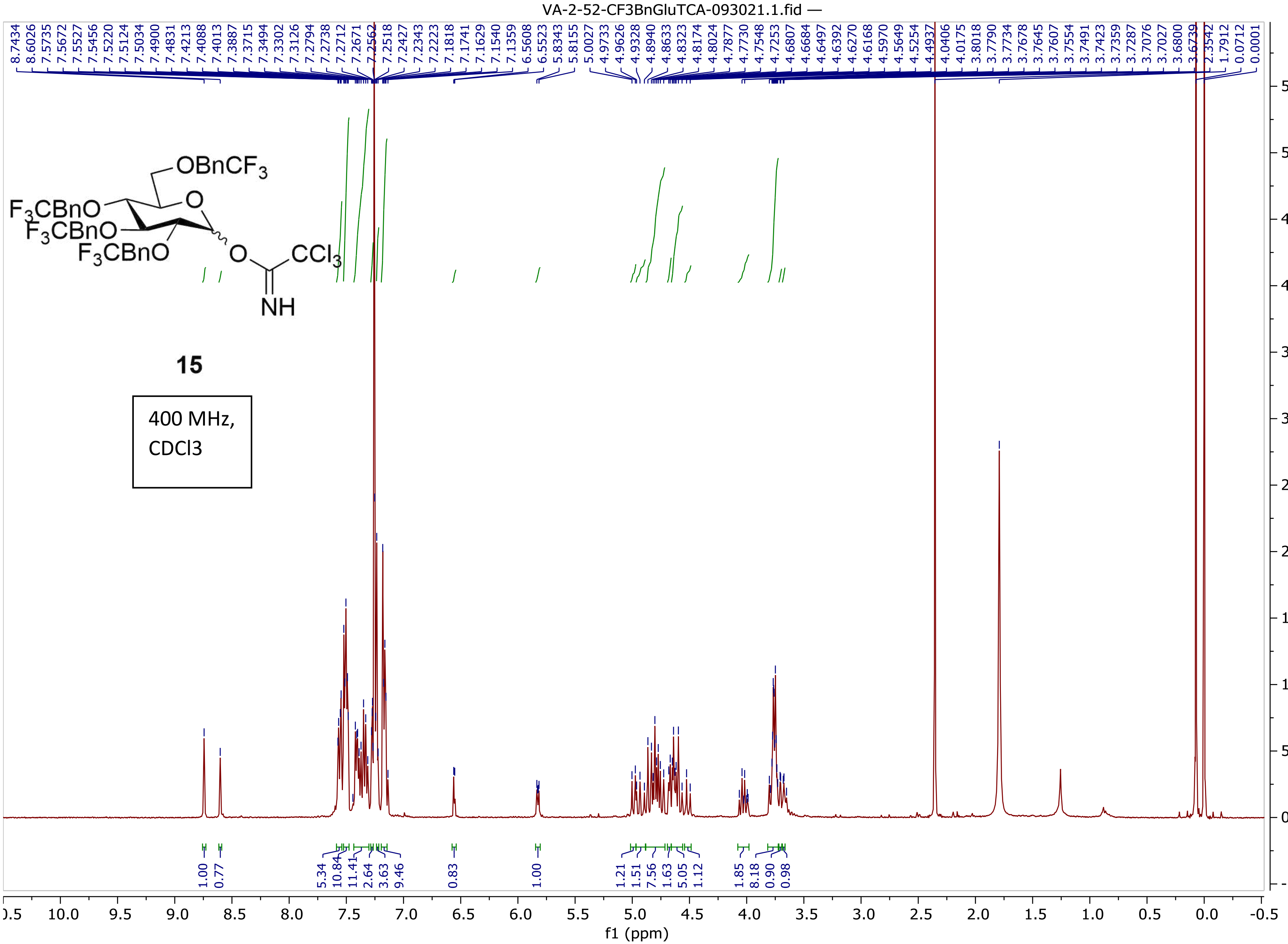

VA-2-42-BnGlucoselactol-082421.1.fid —
7.3610
7.3562
7.3471
7.3419
7.3350
7.3298
7.3254
7.3171
7.3148
7.3076
7.3023
7.2997
7.2963
7.2917
7.2867
7.2832
7.2798
7.2751
7.2687
7.2616
7.2569
7.2539
7.2494
7.2447
7.1531
7.1460
7.1411
7.1339
7.1292
5.2273
4.9511
4.9311
4.9236
4.9095
4.8476
4.8327
4.8201
4.8137
4.8055
4.7919
4.7864
4.7803
4.7755
4.7507
4.7003
4.6708
4.6068
4.5762
4.5688
4.5437
4.5127
4.4977
4.4854
4.4671
4.0192
4.0147
3.9819
3.9588
3.9357
3.7250
3.7151
3.6986
3.6943
3.6886
3.6551
3.6501
3.6435
3.6384
3.6324
3.6288
3.6237
3.6208
3.6183
3.5962
3.5878
3.5727
3.5642
2.9457
2.9288
2.9226
2.8788
OBn
BnO
O
BnO
BnO
OH
400 MHz,
CDCl3
22.90
2.24
0.93
1.60
5.61
1.92
1.41
1.02
1.05
1.11
5.54
0.30
0.23
0.39
0.87
0.37
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000

26

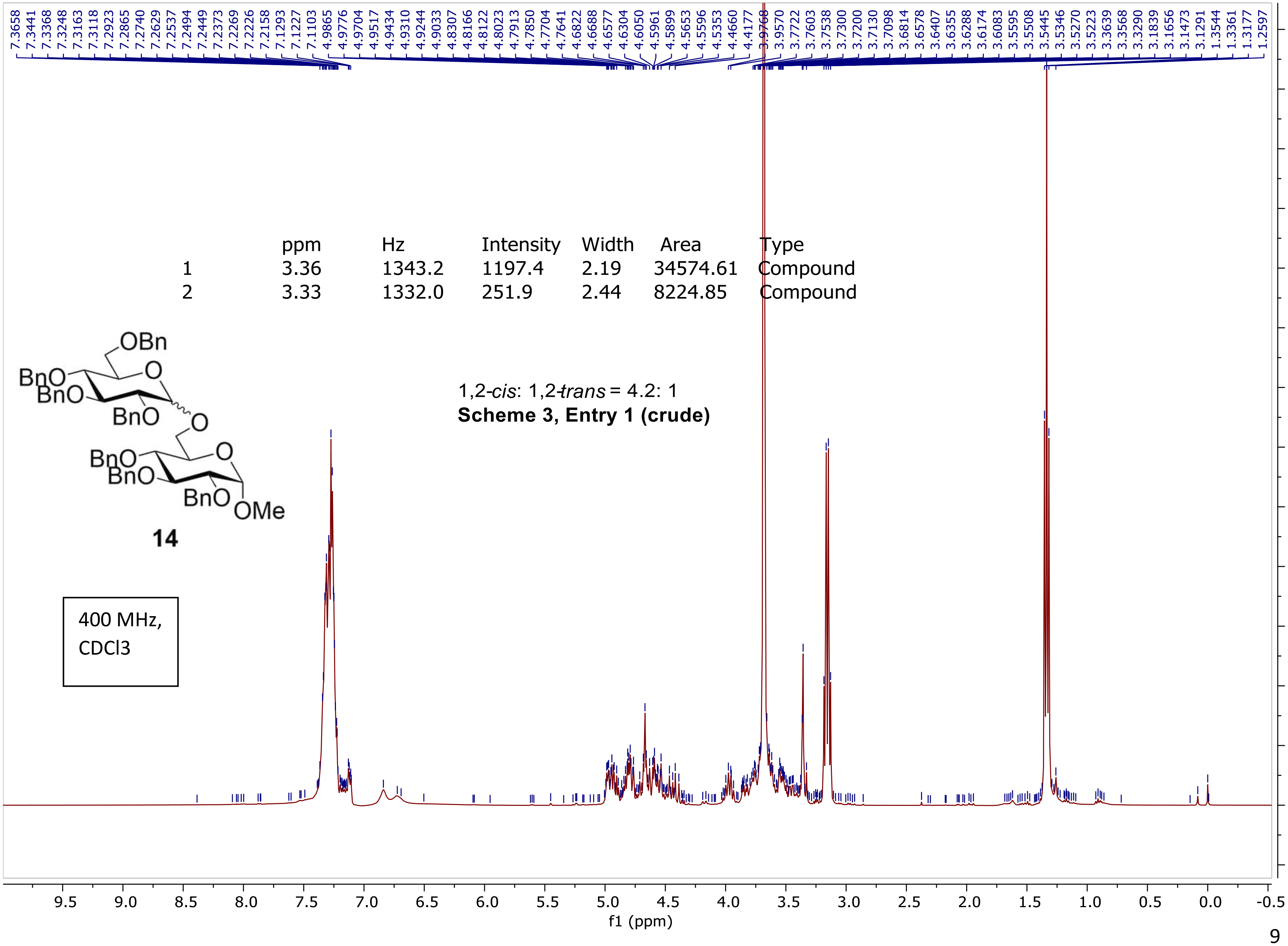

VA-2-27-Benzylated-glucoseTCA-072621.1.fid —
8.5743
7.3454
7.3325
7.3204
7.3055
7.2934
7.2855
7.2728
7.2584
7.2364
7.2089
7.1613
7.1540
7.1422
7.1374
6.5228
6.5141
4.9695
4.9422
4.8644
4.8371
4.8091
4.7534
4.7241
4.6863
4.6569
4.6049
4.5748
4.5408
4.5141
4.4748
4.4447
4.0753
4.0520
4.0286
4.0105
4.0036
3.9969
3.9857
3.9789
3.9716
3.8002
3.7904
3.7771
3.7686
3.7629
3.7536
3.7447
3.6808
3.6758
3.6534
3.6484
0.0805
-0.0002
OBn
O
BnO
BnO
BnO
O
CCl$_3$
NH
12
400 MHz,
CDCl3
0.93
17.81
2.34
1.00
1.15
1.19
1.06
1.10
1.15
1.39
1.35
1.22
1.06
1.08
3.43
1.24
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500


VA-2-4CF3BnGluSPh-022723.1.fid —
7.5891
7.5697
7.5540
7.5502
7.5458
7.5319
7.5261
7.5185
7.5055
7.4993
7.4851
7.4406
7.4210
7.4096
7.3894
7.2800
7.2664
7.2586
7.2508
7.2338
4.9779
4.9499
4.8711
4.8403
4.8131
4.8045
4.7780
4.7105
4.6953
4.6820
4.6706
4.6401
4.5900
4.5581
3.7797
3.7744
3.7671
3.7571
3.7390
3.7295
3.6872
3.6768
3.6654
3.6518
3.6431
3.5301
3.5196
3.5072
3.4955
3.4851
1.5459
0.0697
-0.0001
OBnCF3
F3CBnO
O
SPh
F3CBnO
F3CBnO
27
400 MHz,
CDCl3
10.35
4.33
3.56
2.77
1.17
3.24
4.12
1.33
2.25
2.12
2.03
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

VA-2-52-CF3BnGluLactol-092921.1.fid —
7.5844
7.5679
7.5646
7.5474
7.5316
7.5121
7.4926
7.4340
7.4215
7.4139
7.4030
7.3852
7.3460
7.3260
7.2966
7.2767
7.2610
7.2200
7.2105
7.1998
7.1901
5.3336
5.3261
5.3185
5.2996
5.0385
5.0087
4.9608
4.9305
4.9244
4.8945
4.8306
4.8225
4.8103
4.8009
4.7911
4.7814
4.7723
4.7613
4.7553
4.7432
4.7317
4.6614
4.6535
4.6294
4.6216
4.5898
4.5833
4.5752
4.5599
4.5534
4.5436
4.5336
4.5017
4.0122
3.9890
3.9659
3.7488
3.7392
3.7220
3.7118
3.7057
3.6966
3.6669
3.6614
3.6464
3.6392
3.6356
3.6298
3.6240
3.6125
3.5987
3.5899
3.5749
3.5663
3.4059
2.9726
2.9659
2.1728
1.5866
0.0001
$OBnCF_3$
O
F_3CBnO
F_3CBnO
F_3CBnO
OH
28
400 MHz,
CDCl3
13.74
6.86
2.10
1.36
3.33
1.00
0.72
1.28
1.29
6.79
1.83
3.46
1.02
0.97
2.36
1.03
2.14
1.37
0.70
0.60
0.88
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

VA-2-52-CF3BnGluTCA-093021.1.fid —
8.7434
8.6026
7.5735
7.5672
7.5527
7.5456
7.5220
7.5124
7.5034
7.4900
7.4831
7.4213
7.4088
7.4013
7.3887
7.3715
7.3494
7.3302
7.3126
7.2794
7.2738
7.2712
7.2671
7.2562
7.2518
7.2427
7.2343
7.2223
7.1818
7.1741
7.1629
7.1540
7.1359
6.5608
6.5523
5.8343
5.8155
5.0027
4.9733
4.9626
4.9328
4.8940
4.8633
4.8323
4.8174
4.8024
4.7877
4.7730
4.7548
4.7253
4.6807
4.6684
4.6497
4.6392
4.6270
4.6168
4.5970
4.5649
4.5254
4.4937
4.0406
4.0175
3.8018
3.7790
3.7734
3.7678
3.7645
3.7607
3.7554
3.7491
3.7423
3.7359
3.7287
3.7076
3.7027
3.6800
3.6739
2.3542
1.7912
0.0712
0.0001
OBnCF3
F3CBnO
O
F3CBnO
F3CBnO
O
CCl3
NH
15
400 MHz,
CDCl3
1.00
0.77
5.34
10.84
11.41
2.64
3.63
9.46
0.83
1.00
1.21
1.51
7.56
1.63
5.05
1.12
1.85
8.18
0.90
0.98
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

VA-2-28-Bndonorglycosylationmodel.1.fid — Crude-1



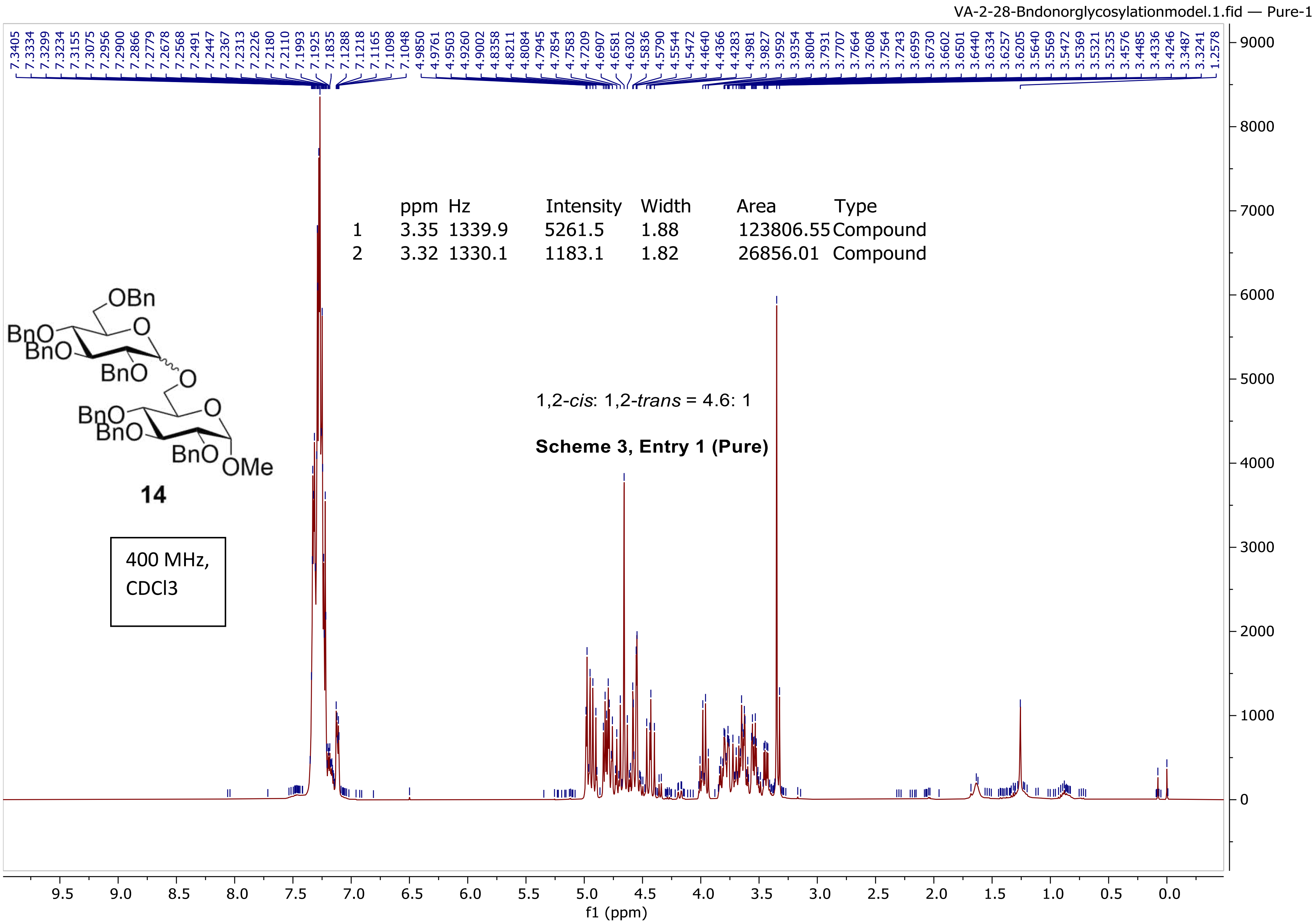
	ppm	Hz	Intensity	Width	Area	Type
1	3.36	1343.2	1197.4	2.19	34574.61	Compound
2	3.33	1332.0	251.9	2.44	8224.85	Compound

14

1,2-*cis*: 1,2-*trans* = 4.2: 1

Scheme 3, Entry 1 (crude)

400 MHz,
CDCl3



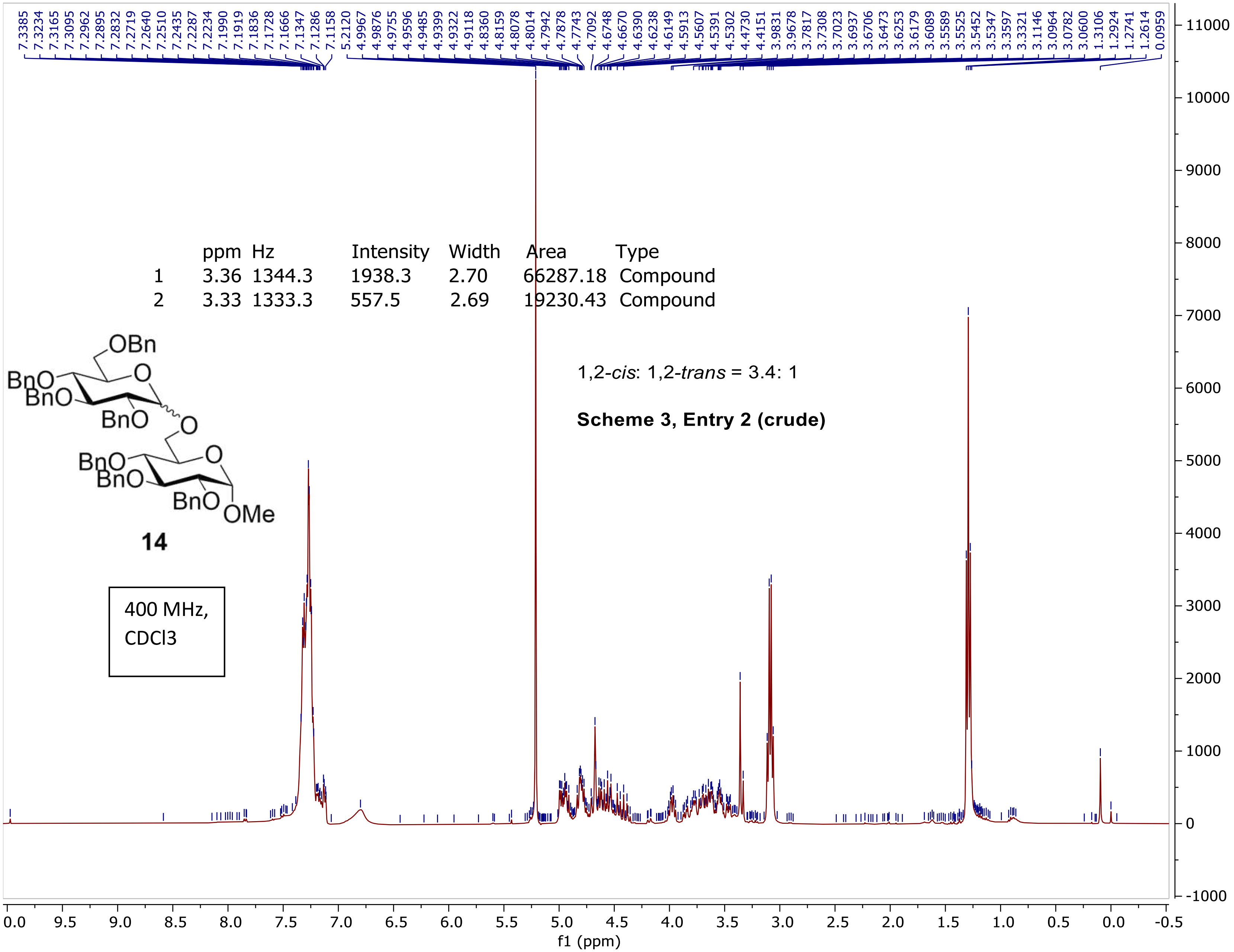
	ppm	Hz	Intensity	Width	Area	Type
1	3.35	1339.9	5261.5	1.88	123806.55	Compound
2	3.32	1330.1	1183.1	1.82	26856.01	Compound

14

1,2-*cis*: 1,2-*trans* = 4.6: 1

Scheme 3, Entry 1 (Pure)

VA-2-63-BnDonor+6acceptor+Et2O+TfOH.1.fid — crude-1



	ppm	Hz	Intensity	Width	Area	Type
1	3.36	1344.3	1938.3	2.70	66287.18	Compound
2	3.33	1333.3	557.5	2.69	19230.43	Compound

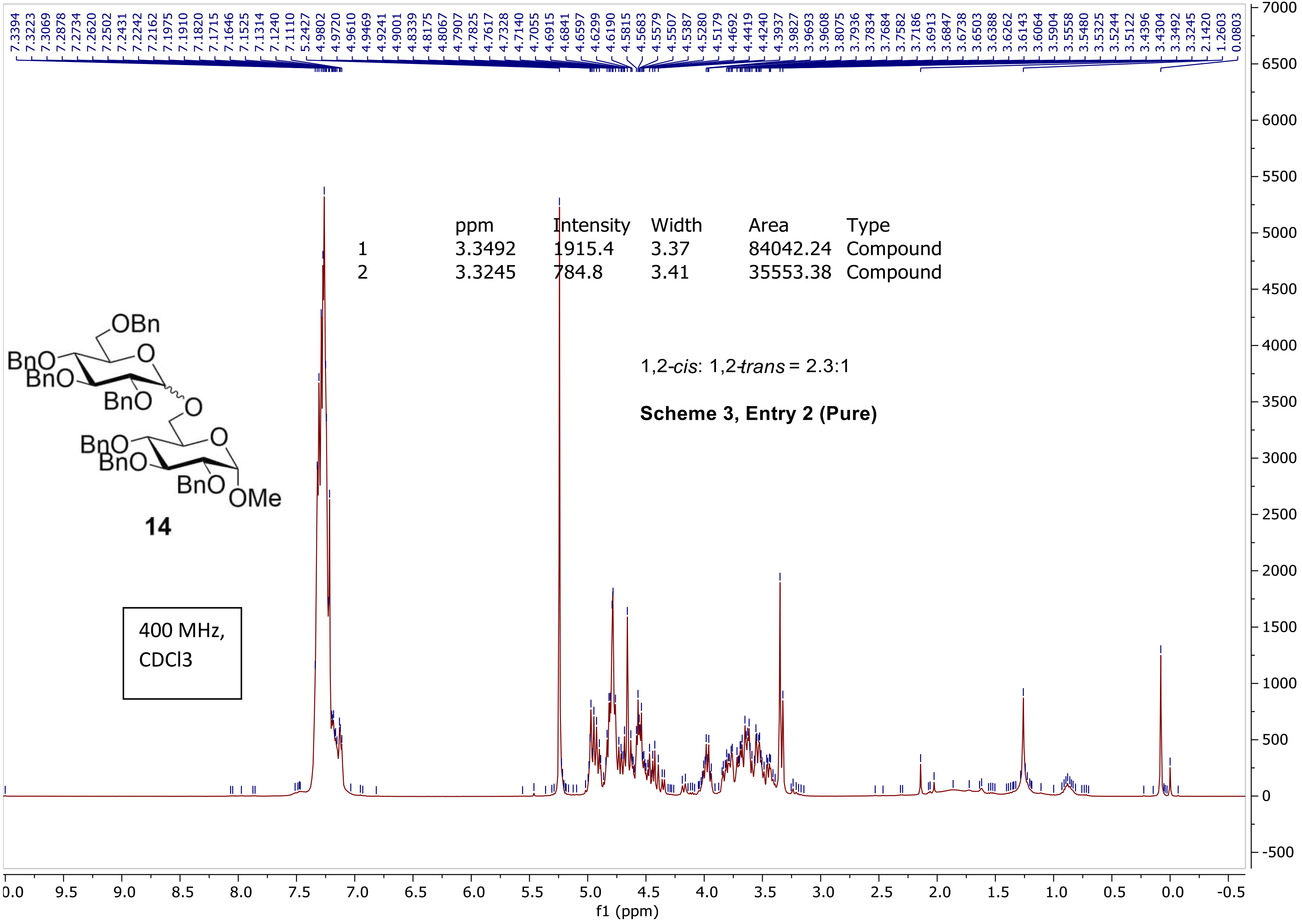
14

400 MHz,
CDCl3

1,2-*cis*: 1,2-*trans* = 3.4: 1

Scheme 3, Entry 2 (crude)

VA-2-BnDonor+6acceptor+Et2O+TfOH-Amideremoval-021723-Pure.1.fid —



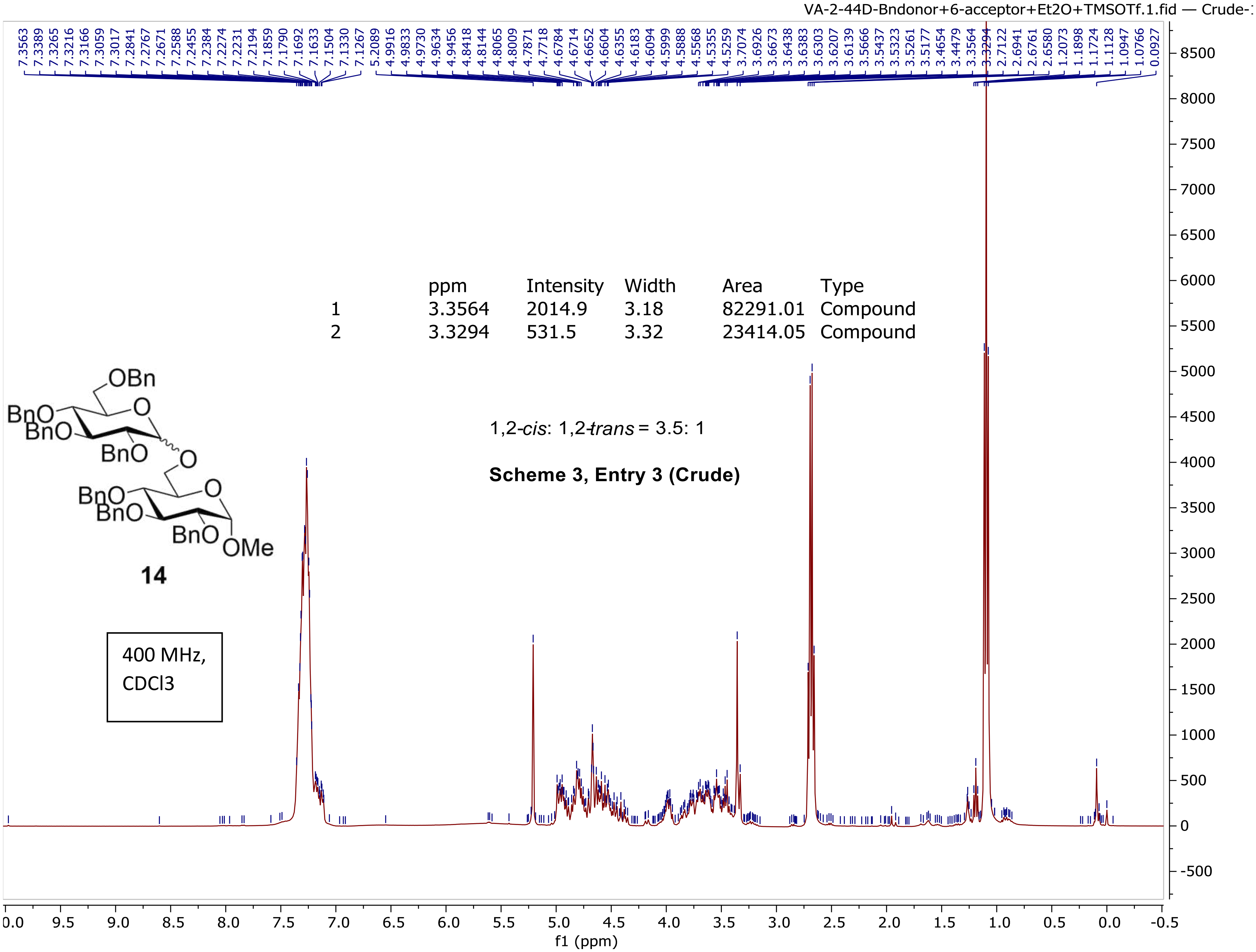
14

	ppm	Intensity	Width	Area	Type
1	3.3492	1915.4	3.37	84042.24	Compound
2	3.3245	784.8	3.41	35553.38	Compound

1,2-*cis*: 1,2-*trans* = 2.3:1

Scheme 3, Entry 2 (Pure)

400 MHz,
CDCl3



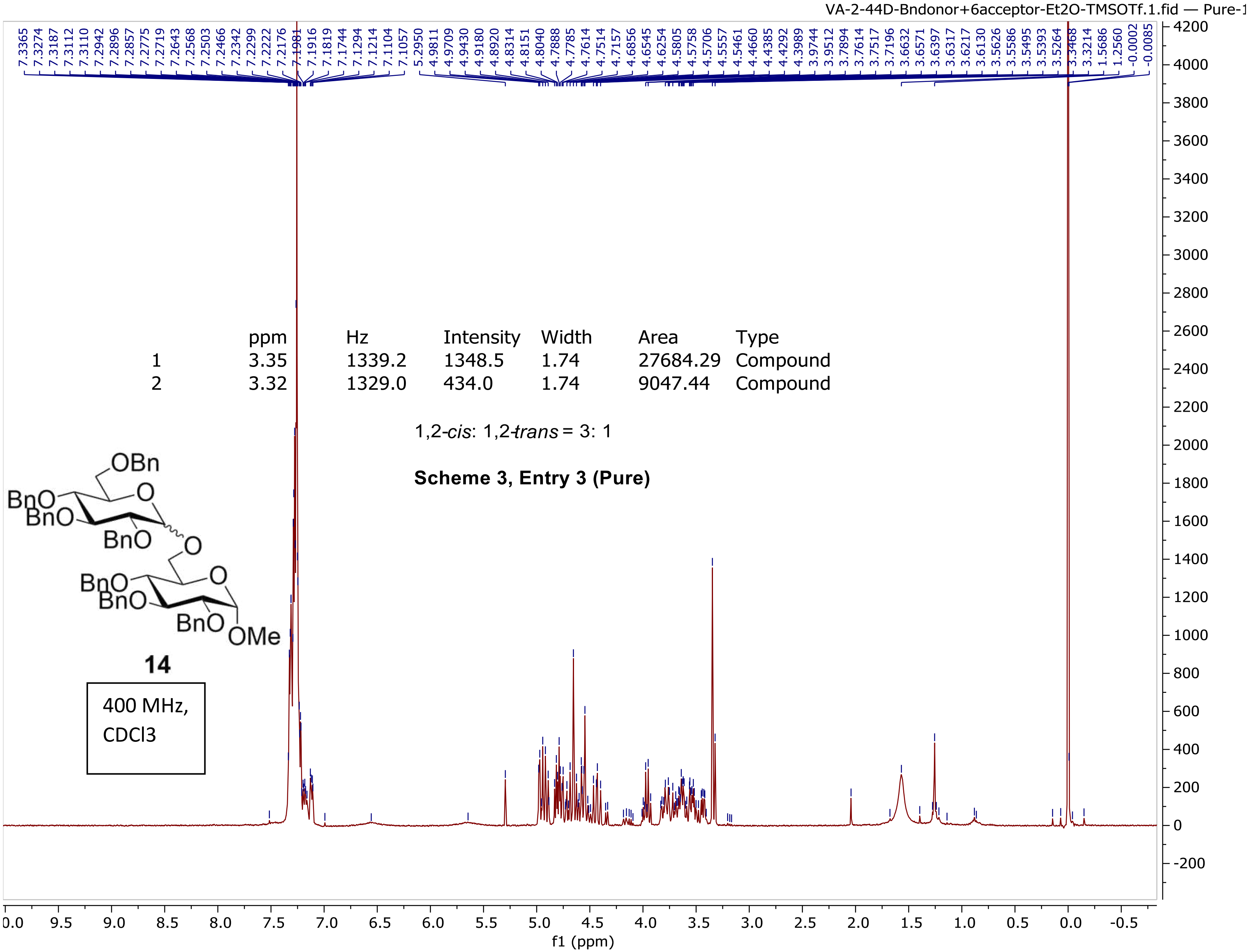
	ppm	Intensity	Width	Area	Type
1	3.3564	2014.9	3.18	82291.01	Compound
2	3.3294	531.5	3.32	23414.05	Compound

1,2-*cis*: 1,2-*trans* = 3.5: 1

Scheme 3, Entry 3 (Crude)

14

400 MHz, CDCl3



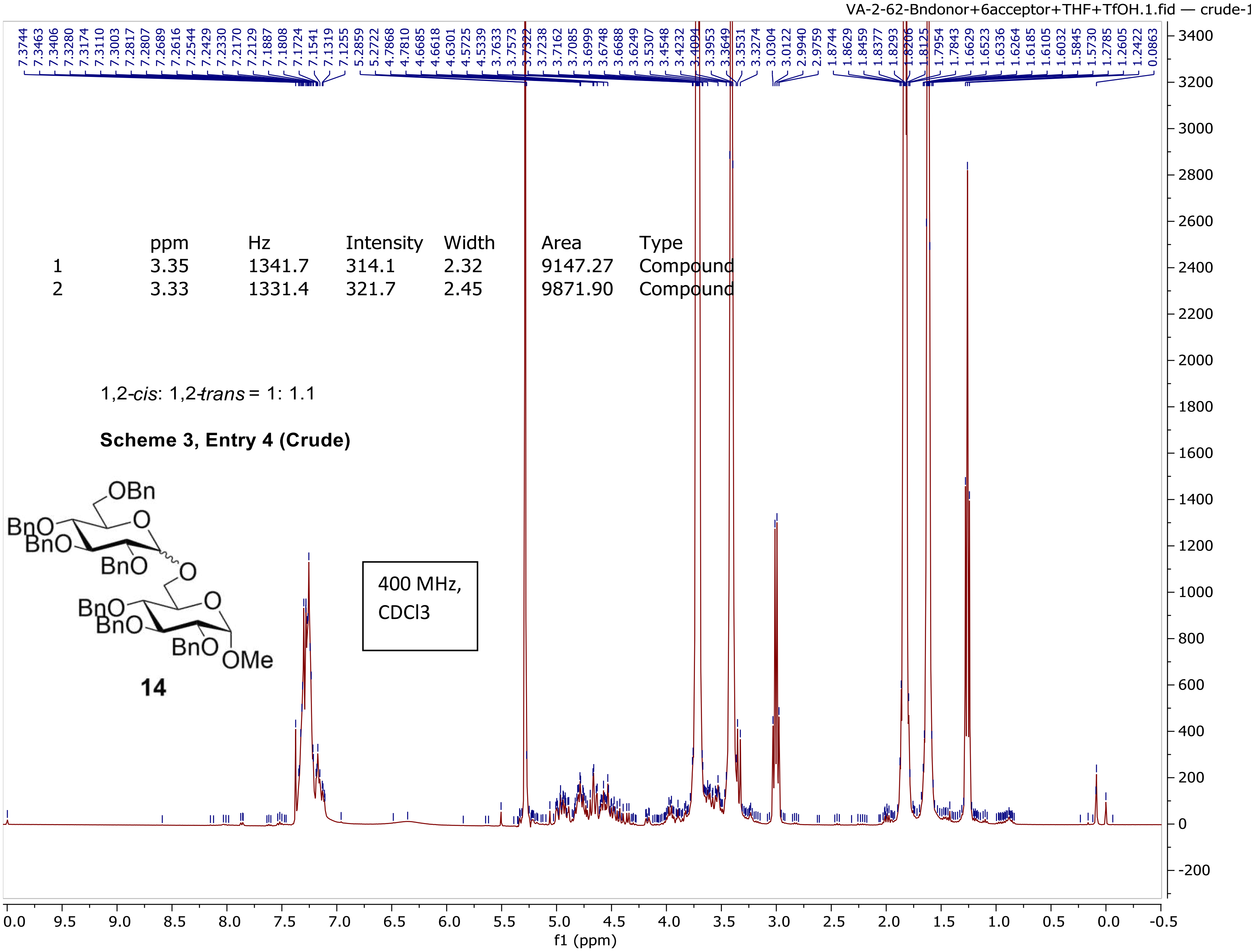
	ppm	Hz	Intensity	Width	Area	Type
1	3.35	1339.2	1348.5	1.74	27684.29	Compound
2	3.32	1329.0	434.0	1.74	9047.44	Compound

1,2-*cis*: 1,2-*trans* = 3: 1

Scheme 3, Entry 3 (Pure)

14

400 MHz,
CDCl3



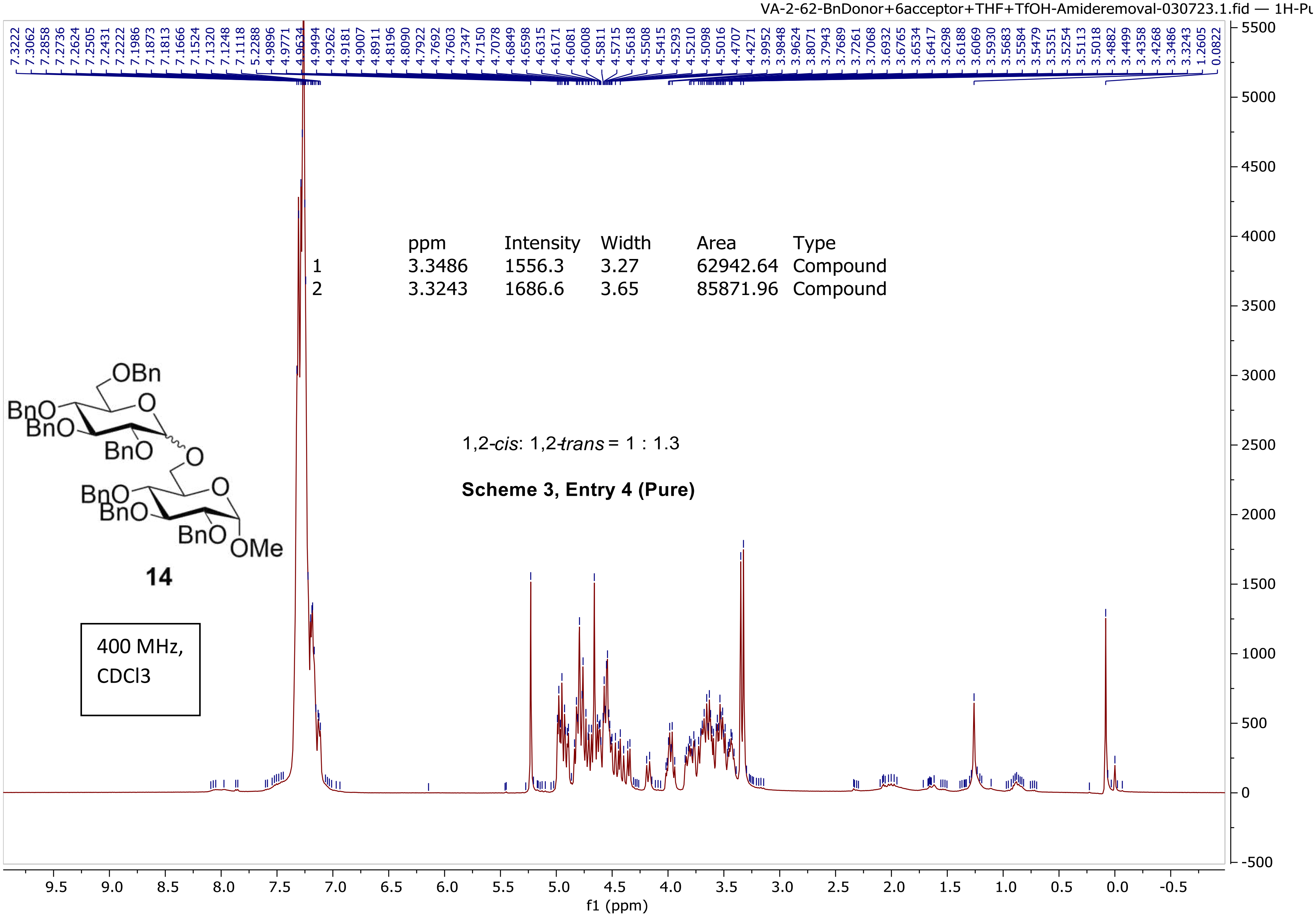
	ppm	Hz	Intensity	Width	Area	Type
1	3.35	1341.7	314.1	2.32	9147.27	Compound
2	3.33	1331.4	321.7	2.45	9871.90	Compound

1,2-*cis*: 1,2-*trans* = 1: 1.1

Scheme 3, Entry 4 (Crude)

14

400 MHz,
CDCl3



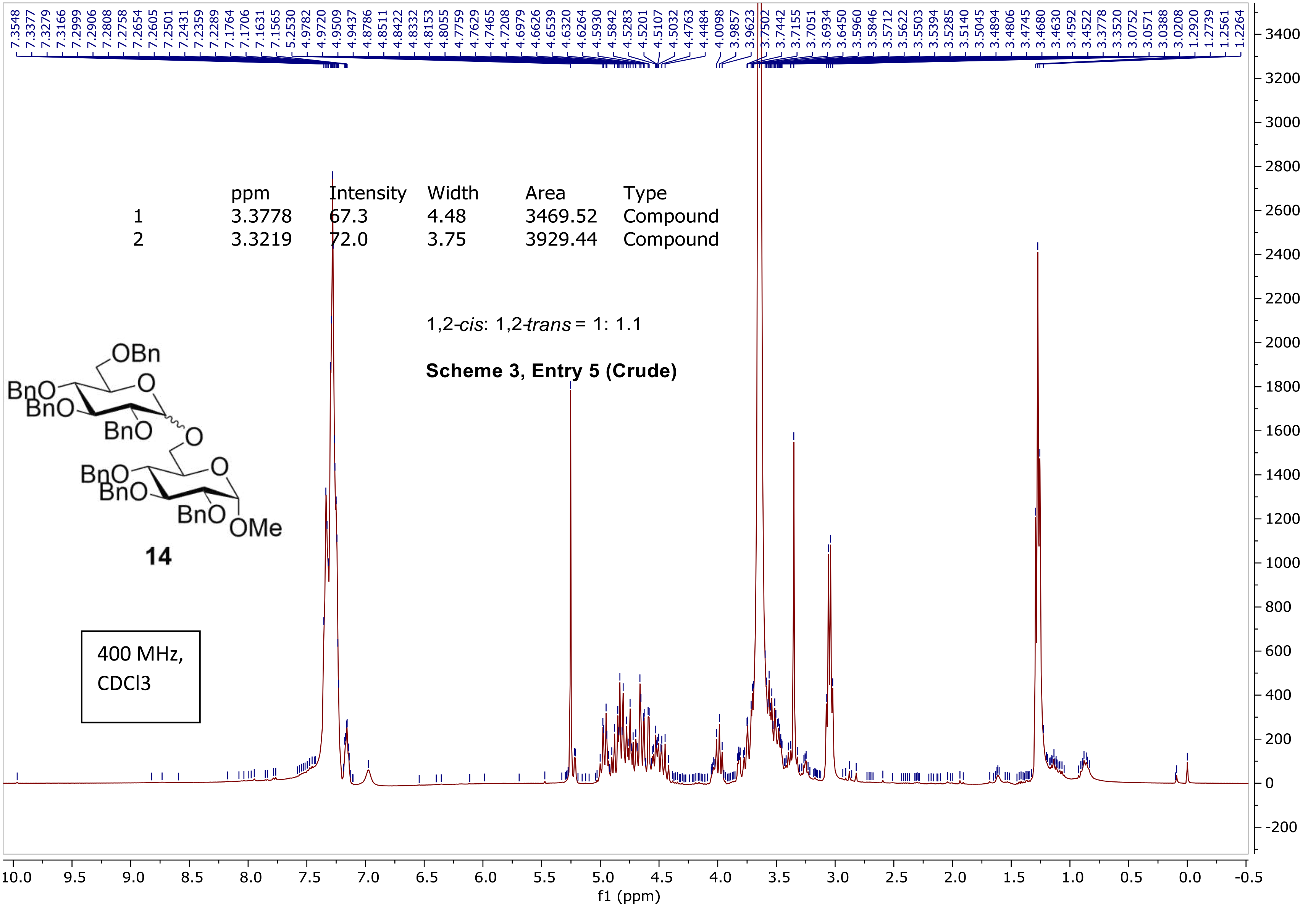
	ppm	Intensity	Width	Area	Type
1	3.3486	1556.3	3.27	62942.64	Compound
2	3.3243	1686.6	3.65	85871.96	Compound

1,2-*cis*: 1,2-*trans* = 1 : 1.3

Scheme 3, Entry 4 (Pure)

400 MHz,
CDCl3

VA-2-Bndonor+6acceptor+1,4-dioxane+Tf2NH.1.fid — Crude-



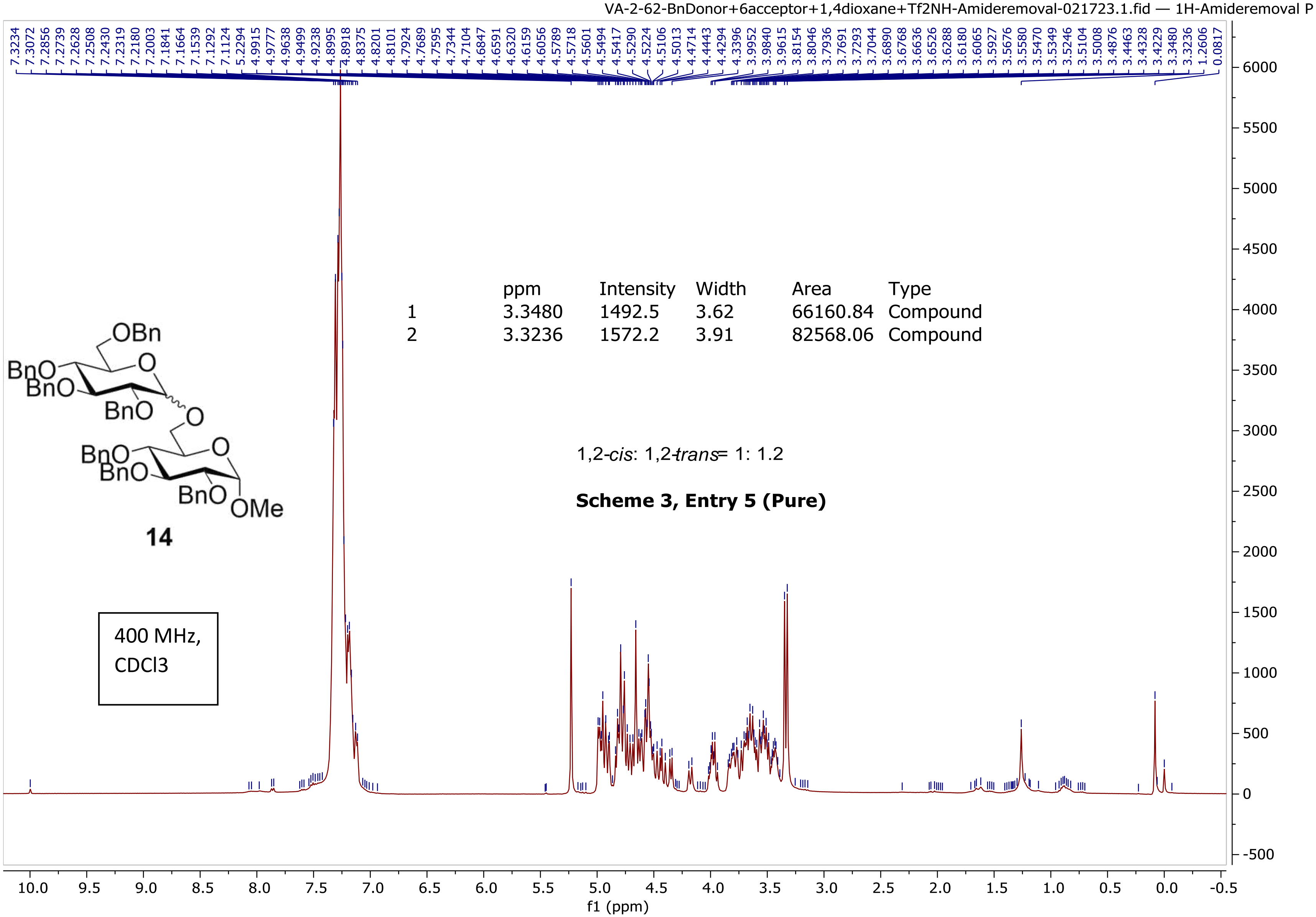
	ppm	Intensity	Width	Area	Type
1	3.3778	67.3	4.48	3469.52	Compound
2	3.3219	72.0	3.75	3929.44	Compound

1,2-*cis*: 1,2-*trans* = 1: 1.1

Scheme 3, Entry 5 (Crude)

14

400 MHz,
CDCl3



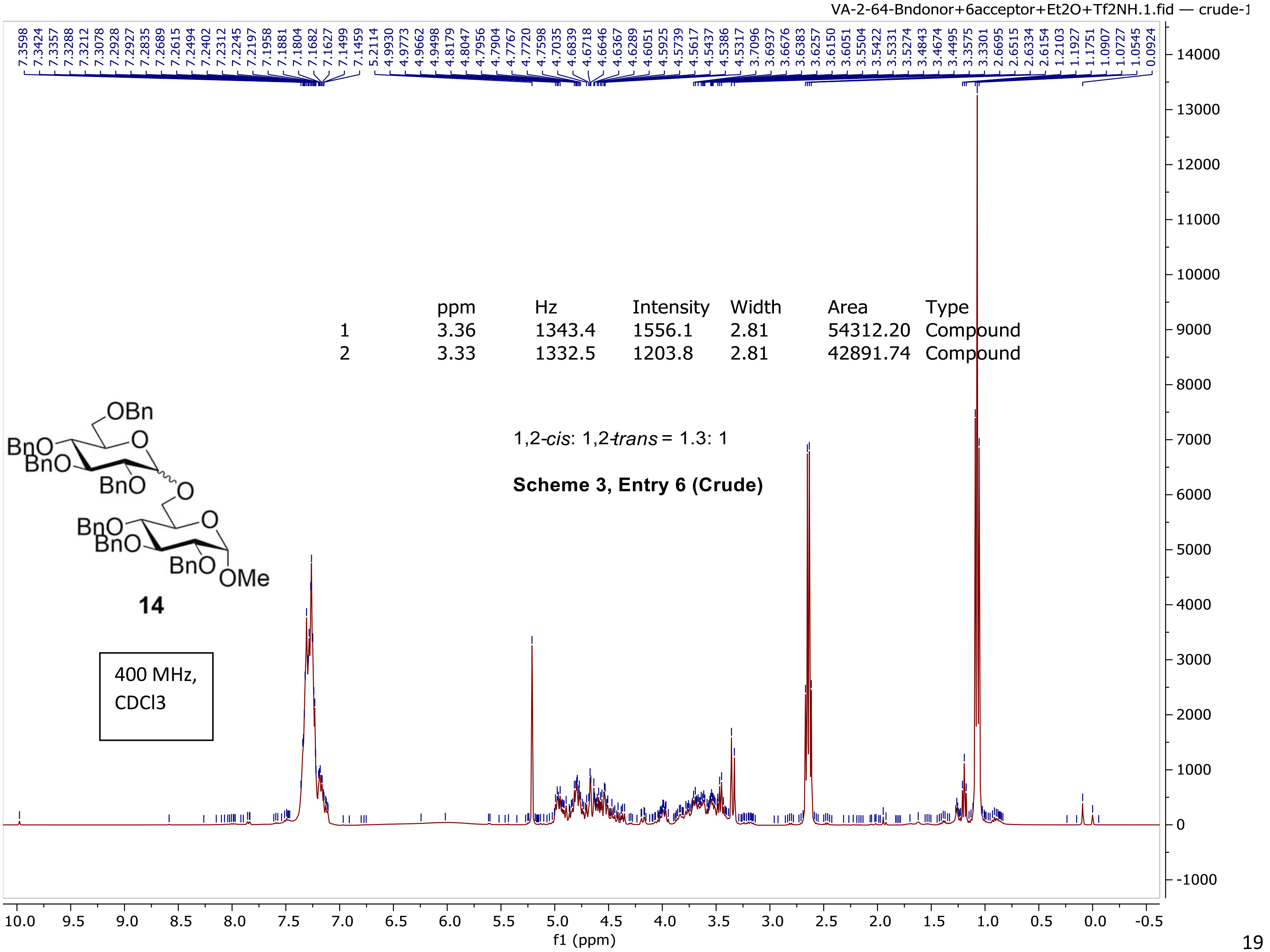
14

	ppm	Intensity	Width	Area	Type
1	3.3480	1492.5	3.62	66160.84	Compound
2	3.3236	1572.2	3.91	82568.06	Compound

1,2-*cis*: 1,2-*trans*= 1: 1.2

Scheme 3, Entry 5 (Pure)

400 MHz,
CDCl3



14

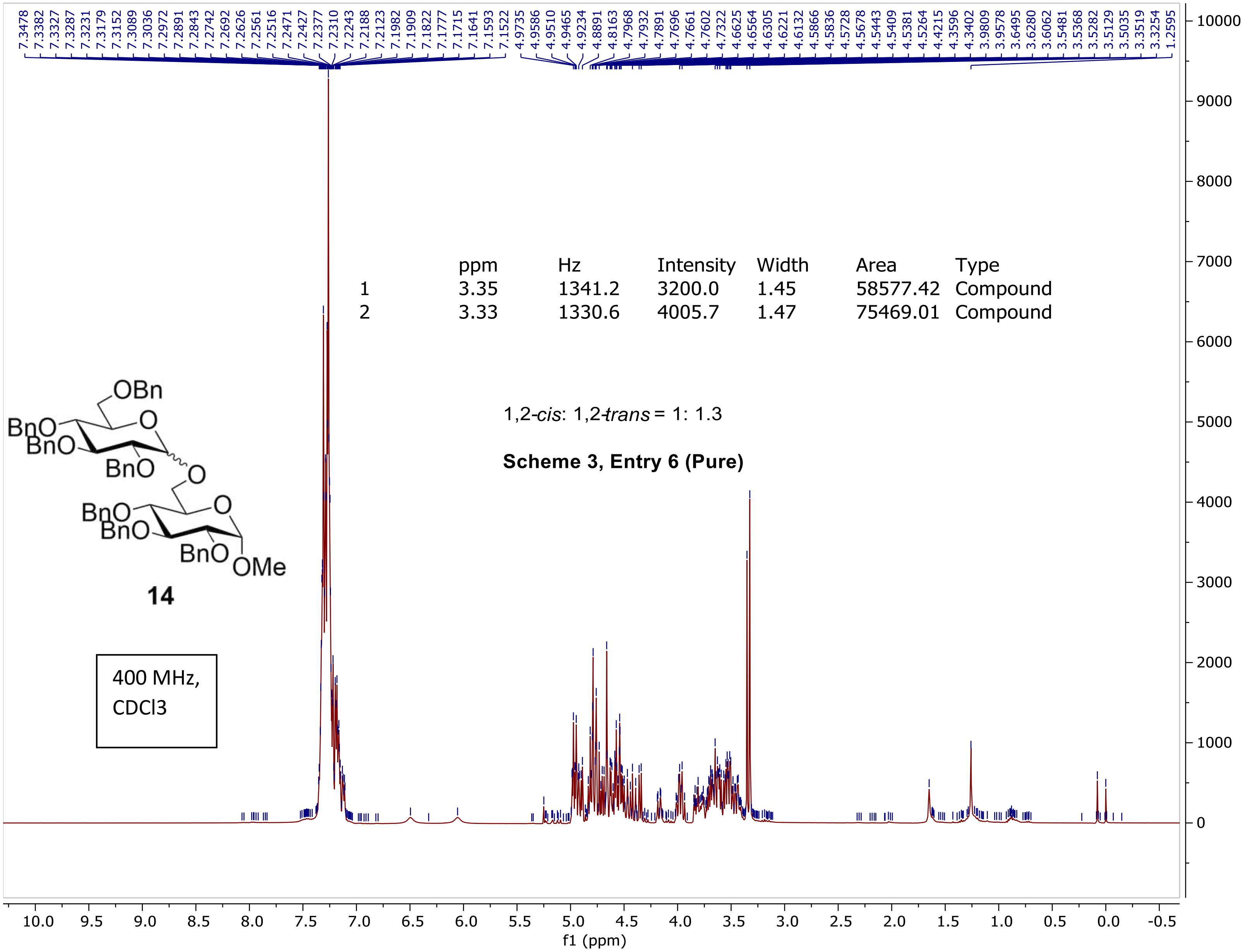
	ppm	Hz	Intensity	Width	Area	Type
1	3.36	1343.4	1556.1	2.81	54312.20	Compound
2	3.33	1332.5	1203.8	2.81	42891.74	Compound

1,2-*cis*: 1,2-*trans* = 1.3: 1

Scheme 3, Entry 6 (Crude)

400 MHz,
CDCl3

VA-2-64-BnDonor+6acceptor+Et2O+Tf2NH.1.fid — Pure-1



	ppm	Hz	Intensity	Width	Area	Type
1	3.35	1341.2	3200.0	1.45	58577.42	Compound
2	3.33	1330.6	4005.7	1.47	75469.01	Compound

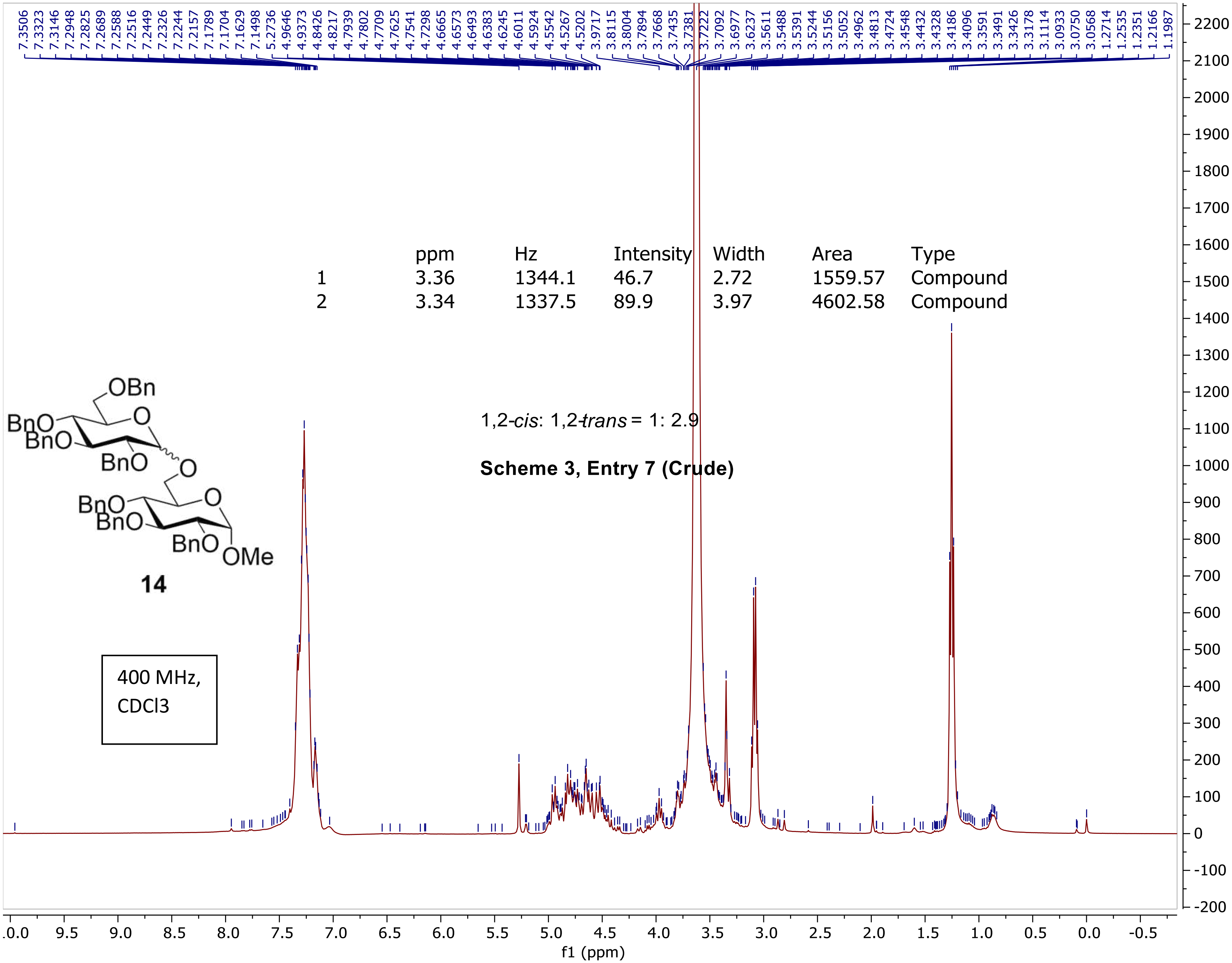
1,2-*cis*: 1,2-*trans* = 1: 1.3

Scheme 3, Entry 6 (Pure)

14

400 MHz,
CDCl3

VA-2-Bndonor+6acceptor+1,4dioxane+BF3OEt2.1.fid — Crude-



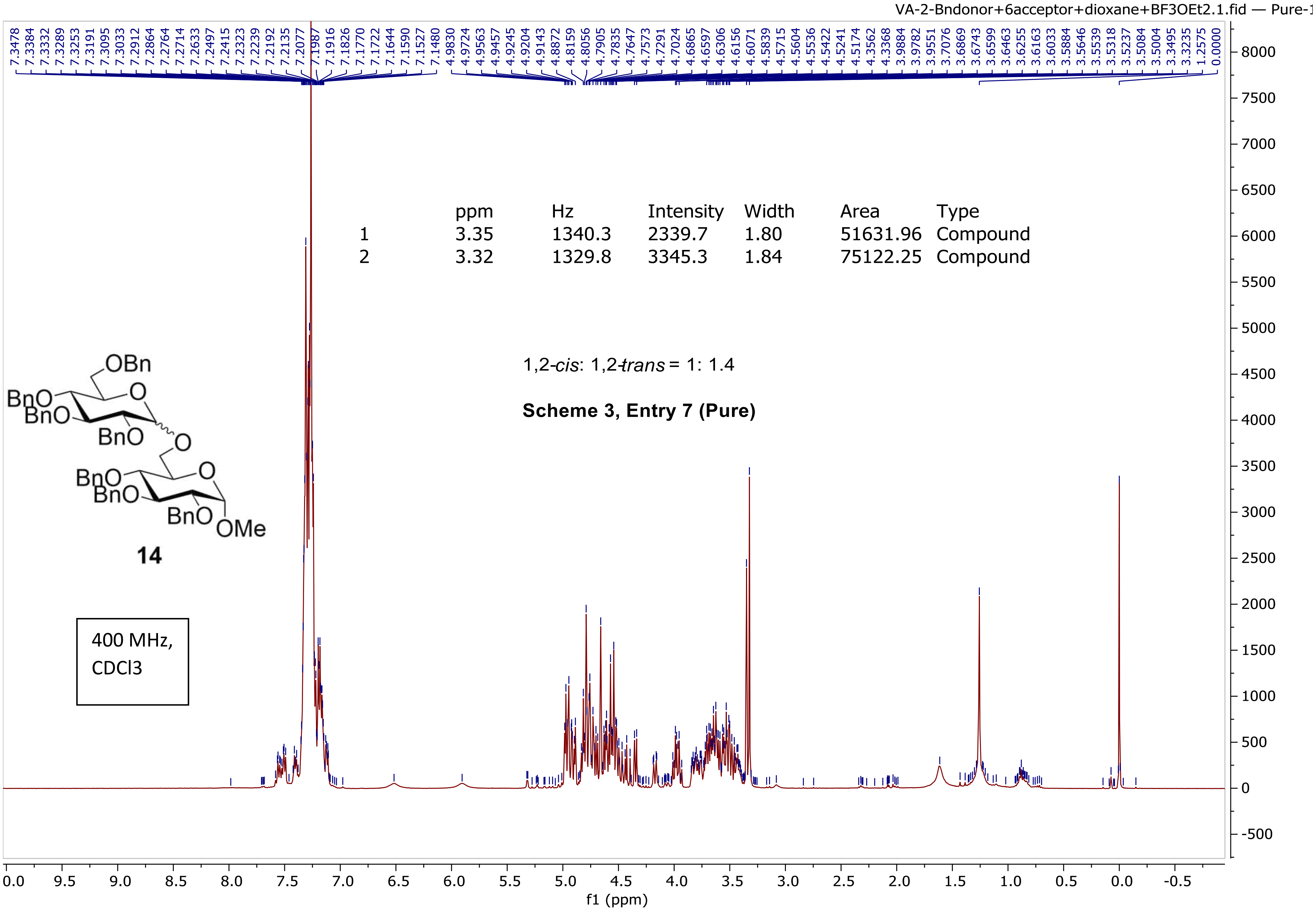
14

	ppm	Hz	Intensity	Width	Area	Type
1	3.36	1344.1	46.7	2.72	1559.57	Compound
2	3.34	1337.5	89.9	3.97	4602.58	Compound

1,2-*cis*: 1,2-*trans* = 1: 2.9

Scheme 3, Entry 7 (Crude)

400 MHz,
CDCl3

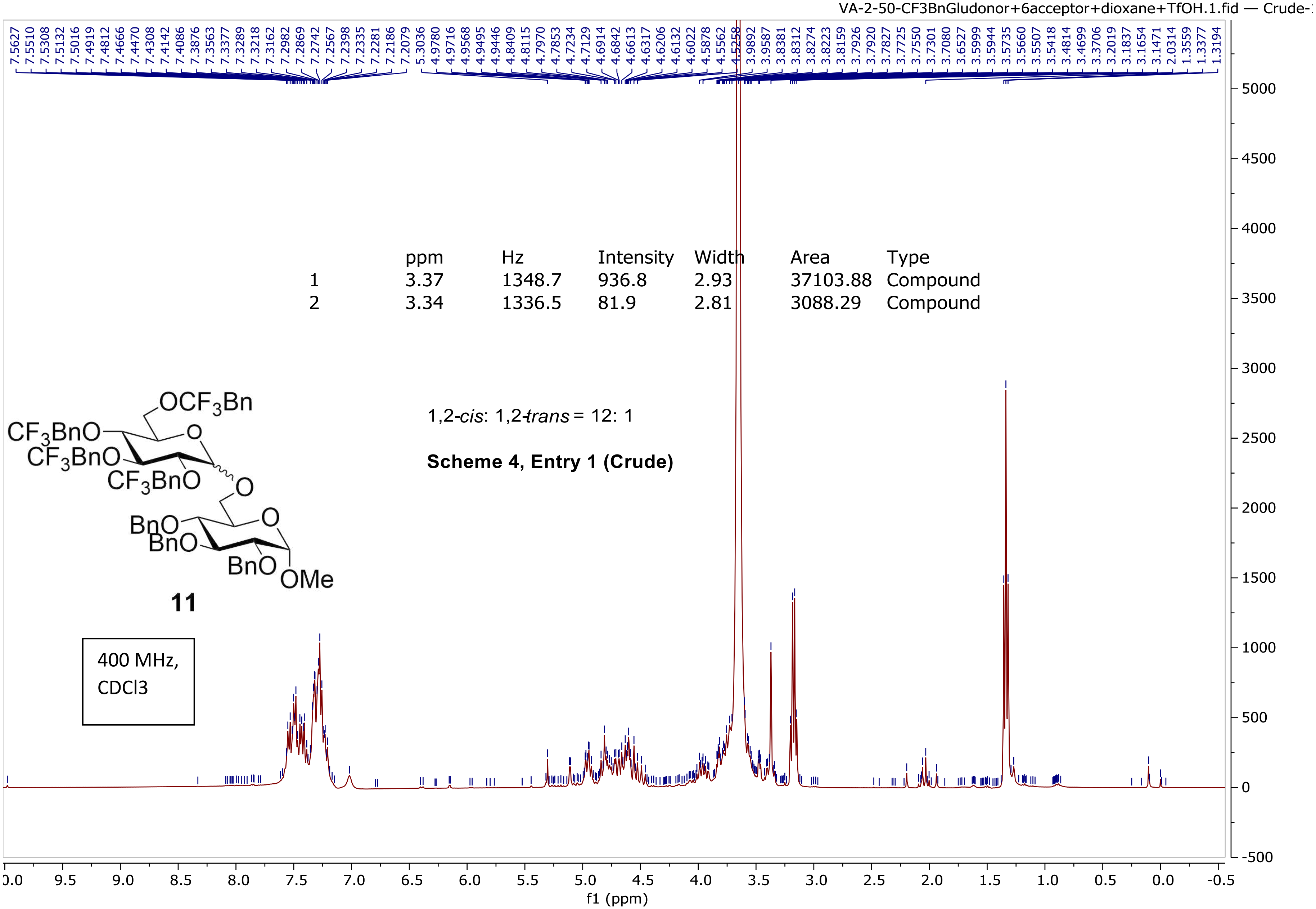


	ppm	Hz	Intensity	Width	Area	Type
1	3.35	1340.3	2339.7	1.80	51631.96	Compound
2	3.32	1329.8	3345.3	1.84	75122.25	Compound

1,2-*cis*: 1,2-*trans* = 1: 1.4

Scheme 3, Entry 7 (Pure)

400 MHz,
CDCl3



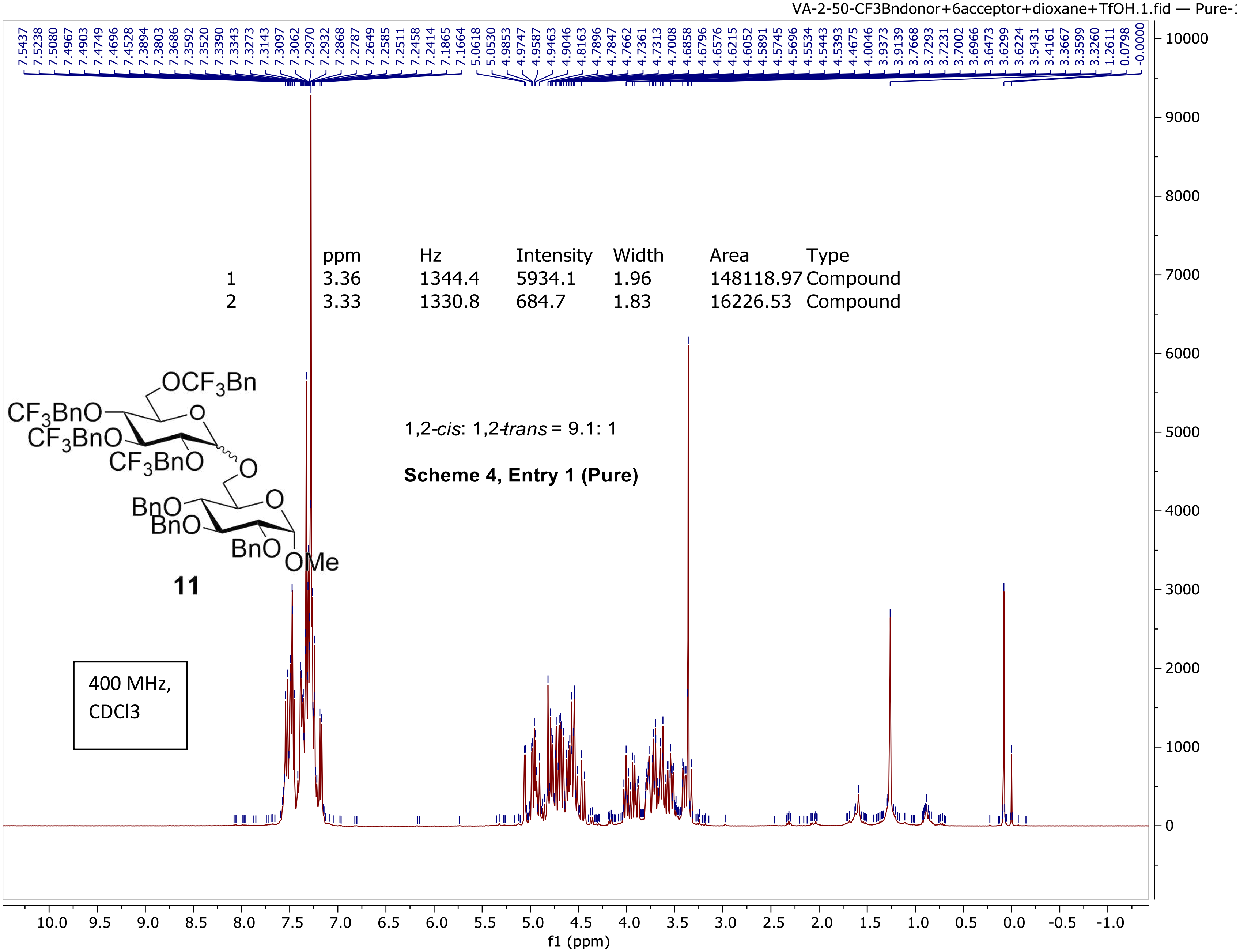
11

	ppm	Hz	Intensity	Width	Area	Type
1	3.37	1348.7	936.8	2.93	37103.88	Compound
2	3.34	1336.5	81.9	2.81	3088.29	Compound

1,2-*cis*: 1,2-*trans* = 12: 1

Scheme 4, Entry 1 (Crude)

400 MHz,
CDCl3



	ppm	Hz	Intensity	Width	Area	Type
1	3.36	1344.4	5934.1	1.96	148118.97	Compound
2	3.33	1330.8	684.7	1.83	16226.53	Compound

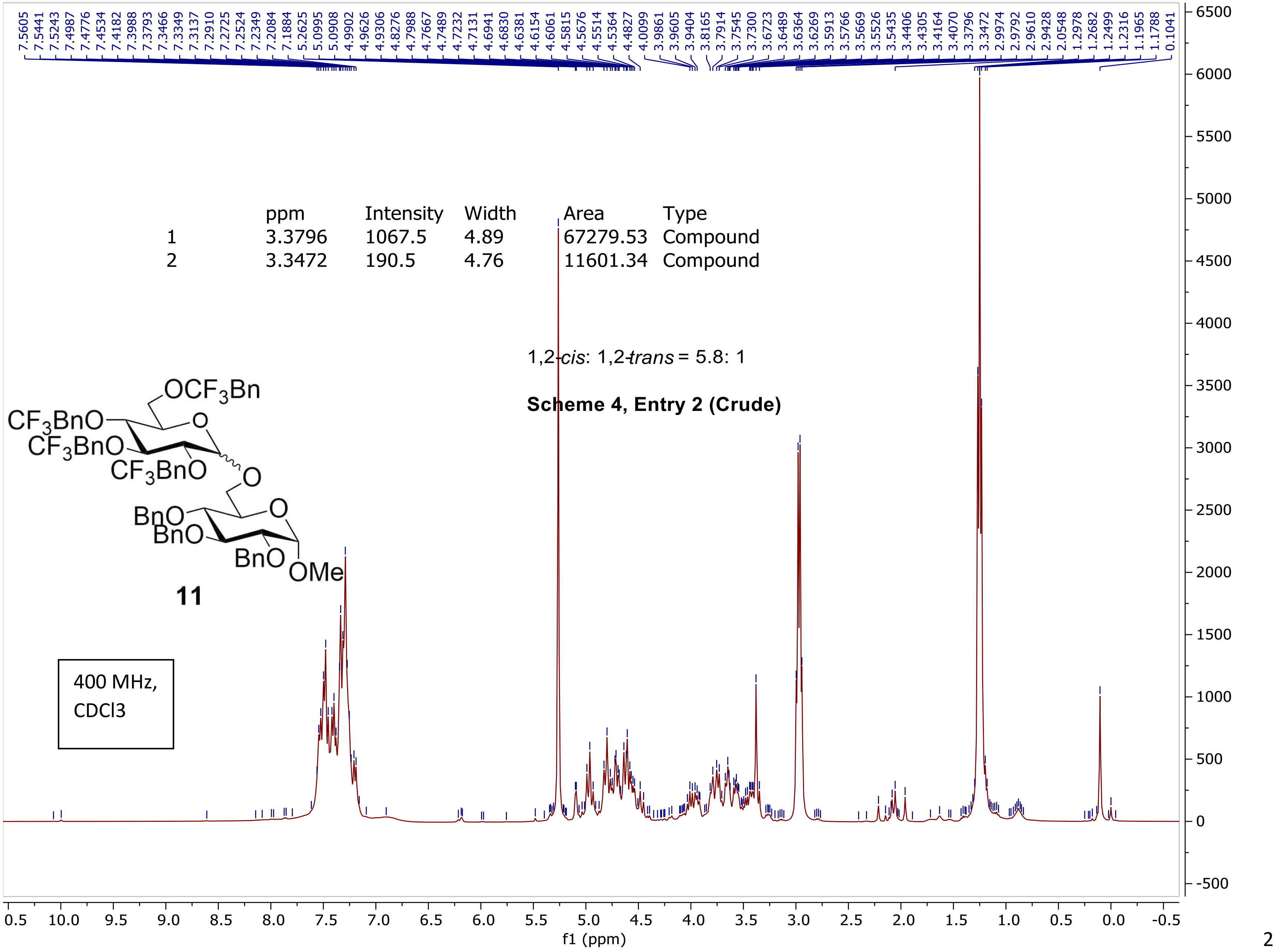
11

1,2-*cis*: 1,2-*trans* = 9.1: 1

Scheme 4, Entry 1 (Pure)

400 MHz,
CDCl3

VA-2-52-CF3BnGludonor+6acceptor+Et2O+TfOH.1.fid — Crude-



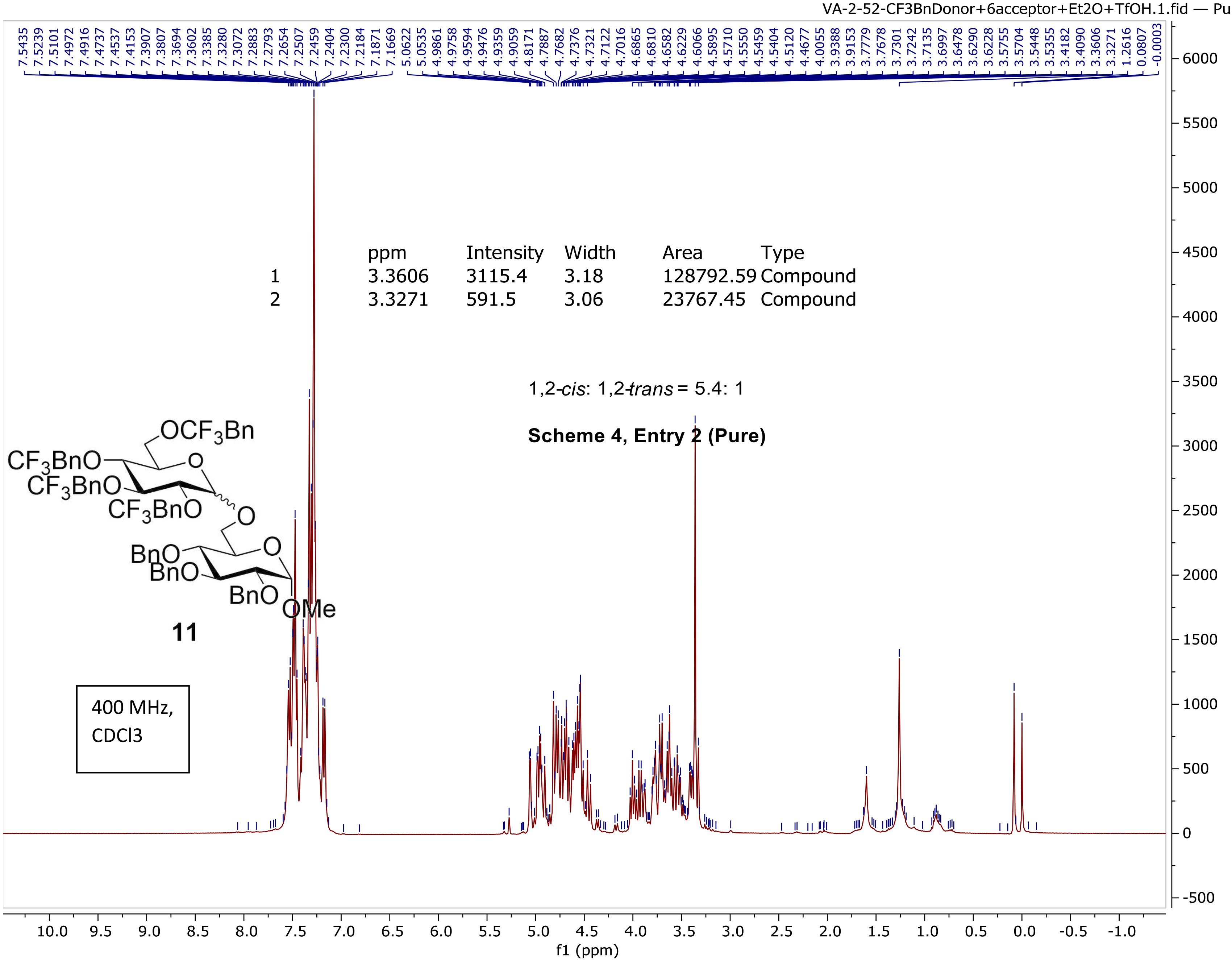
	ppm	Intensity	Width	Area	Type
1	3.3796	1067.5	4.89	67279.53	Compound
2	3.3472	190.5	4.76	11601.34	Compound

1,2-*cis*: 1,2-*trans* = 5.8: 1

Scheme 4, Entry 2 (Crude)

11

400 MHz,
CDCl3



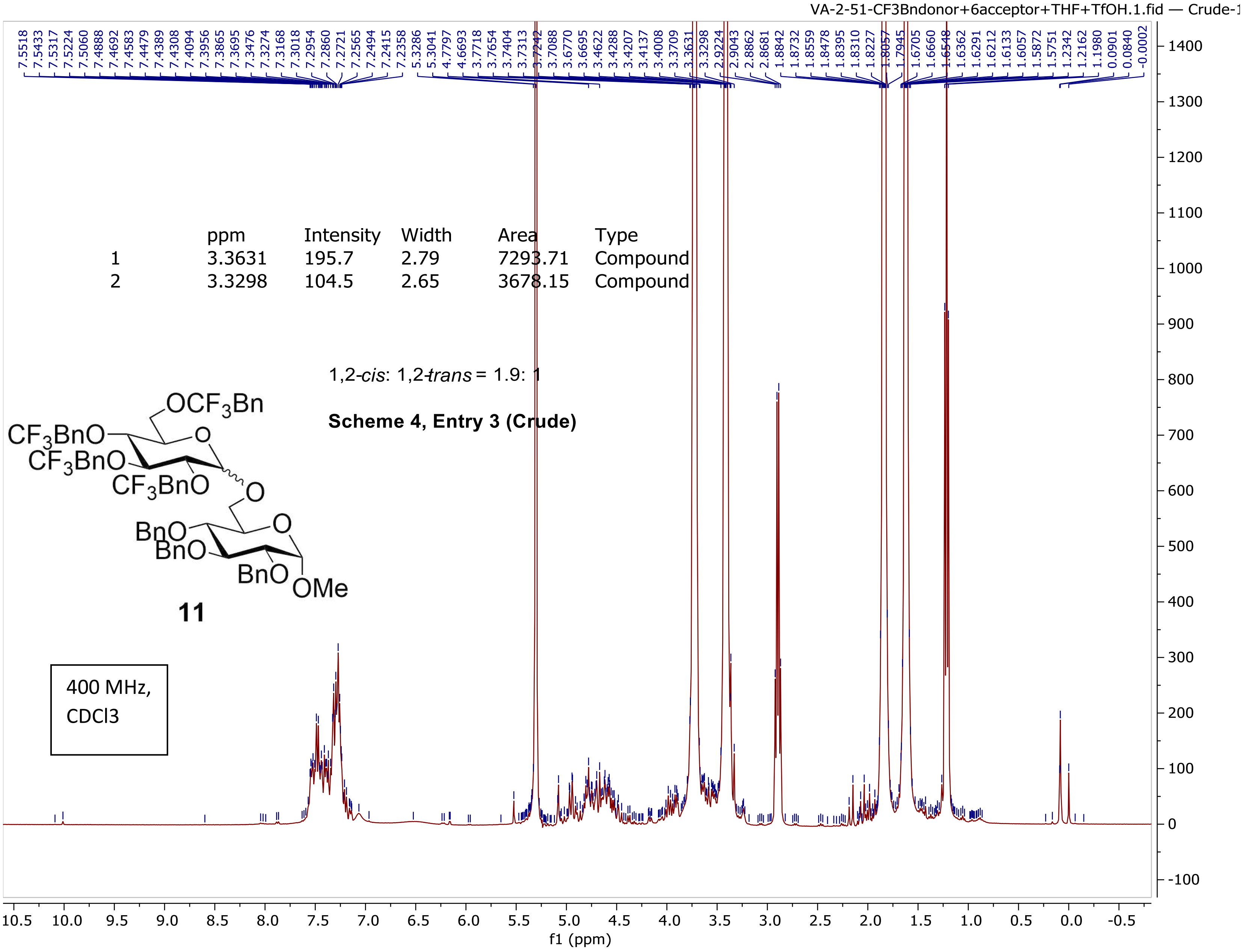
	ppm	Intensity	Width	Area	Type
1	3.3606	3115.4	3.18	128792.59	Compound
2	3.3271	591.5	3.06	23767.45	Compound

1,2-*cis*: 1,2-*trans* = 5.4: 1

Scheme 4, Entry 2 (Pure)

11

400 MHz,
CDCl3



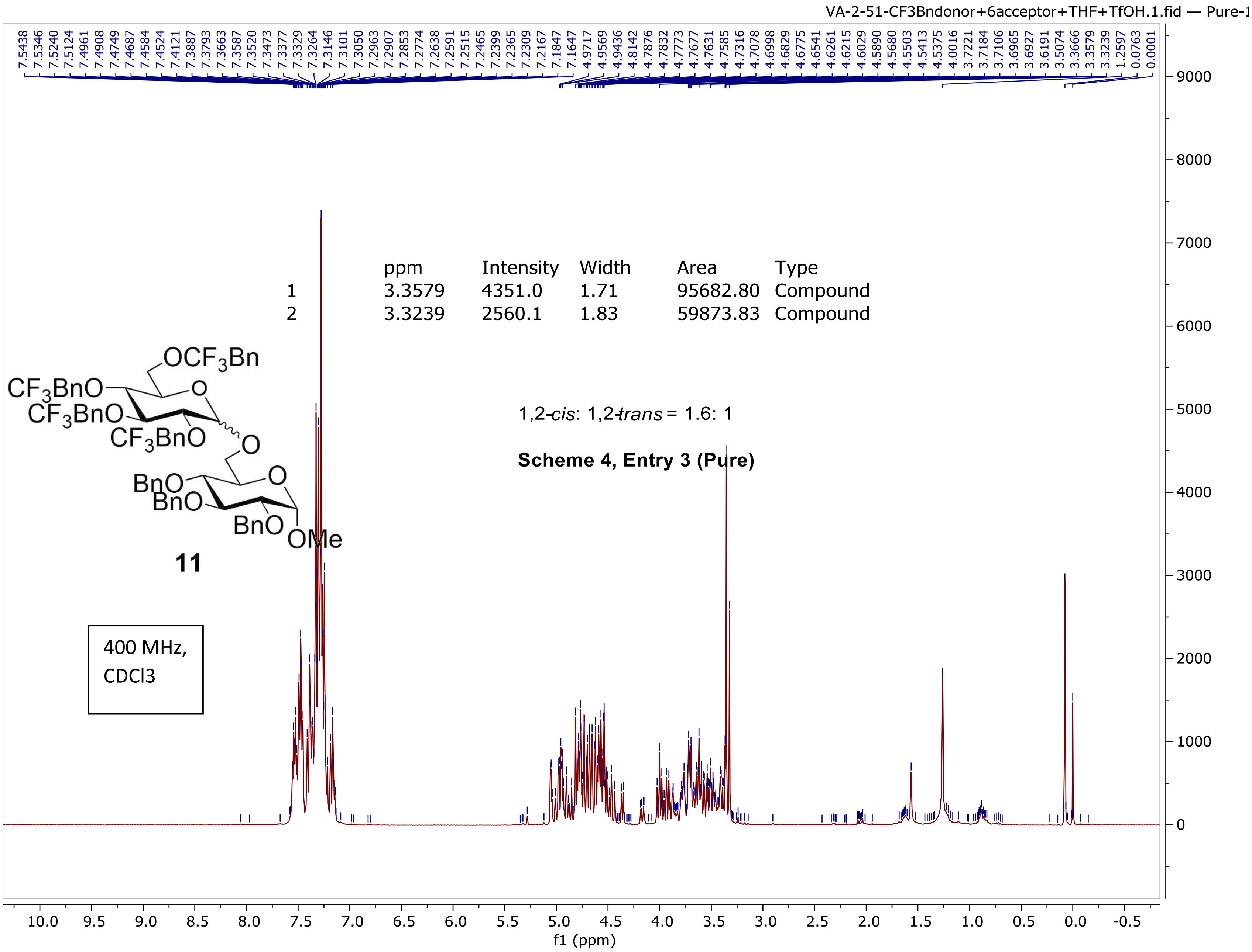
	ppm	Intensity	Width	Area	Type
1	3.3631	195.7	2.79	7293.71	Compound
2	3.3298	104.5	2.65	3678.15	Compound

1,2-*cis*: 1,2-*trans* = 1.9: 1

Scheme 4, Entry 3 (Crude)

11

400 MHz,
CDCl3



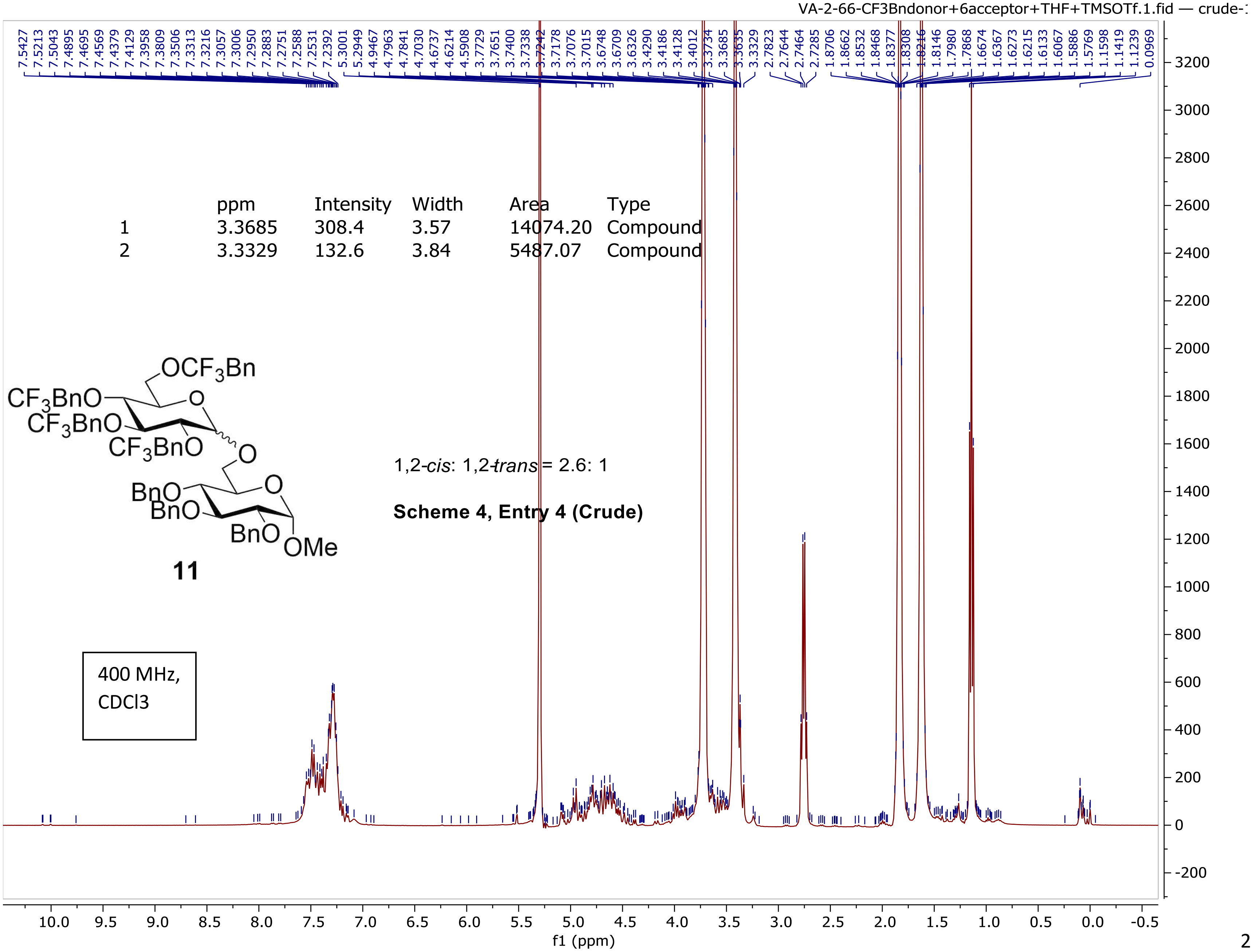
	ppm	Intensity	Width	Area	Type
1	3.3579	4351.0	1.71	95682.80	Compound
2	3.3239	2560.1	1.83	59873.83	Compound

11

1,2-*cis*: 1,2-*trans* = 1.6: 1

Scheme 4, Entry 3 (Pure)

400 MHz,
CDCl3

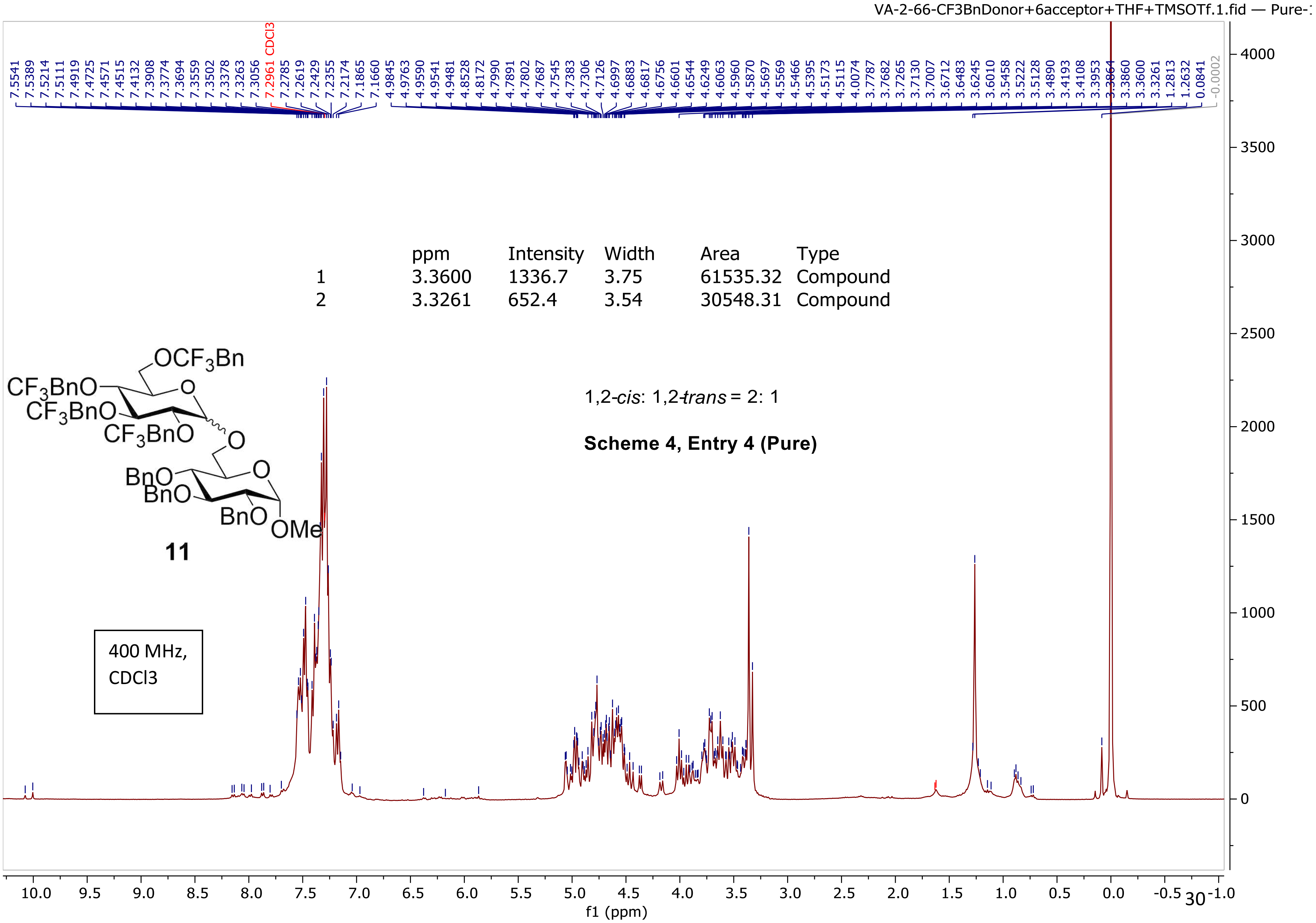


	ppm	Intensity	Width	Area	Type
1	3.3685	308.4	3.57	14074.20	Compound
2	3.3329	132.6	3.84	5487.07	Compound

1,2-*cis*: 1,2-*trans* = 2.6: 1

Scheme 4, Entry 4 (Crude)

400 MHz, CDCl3



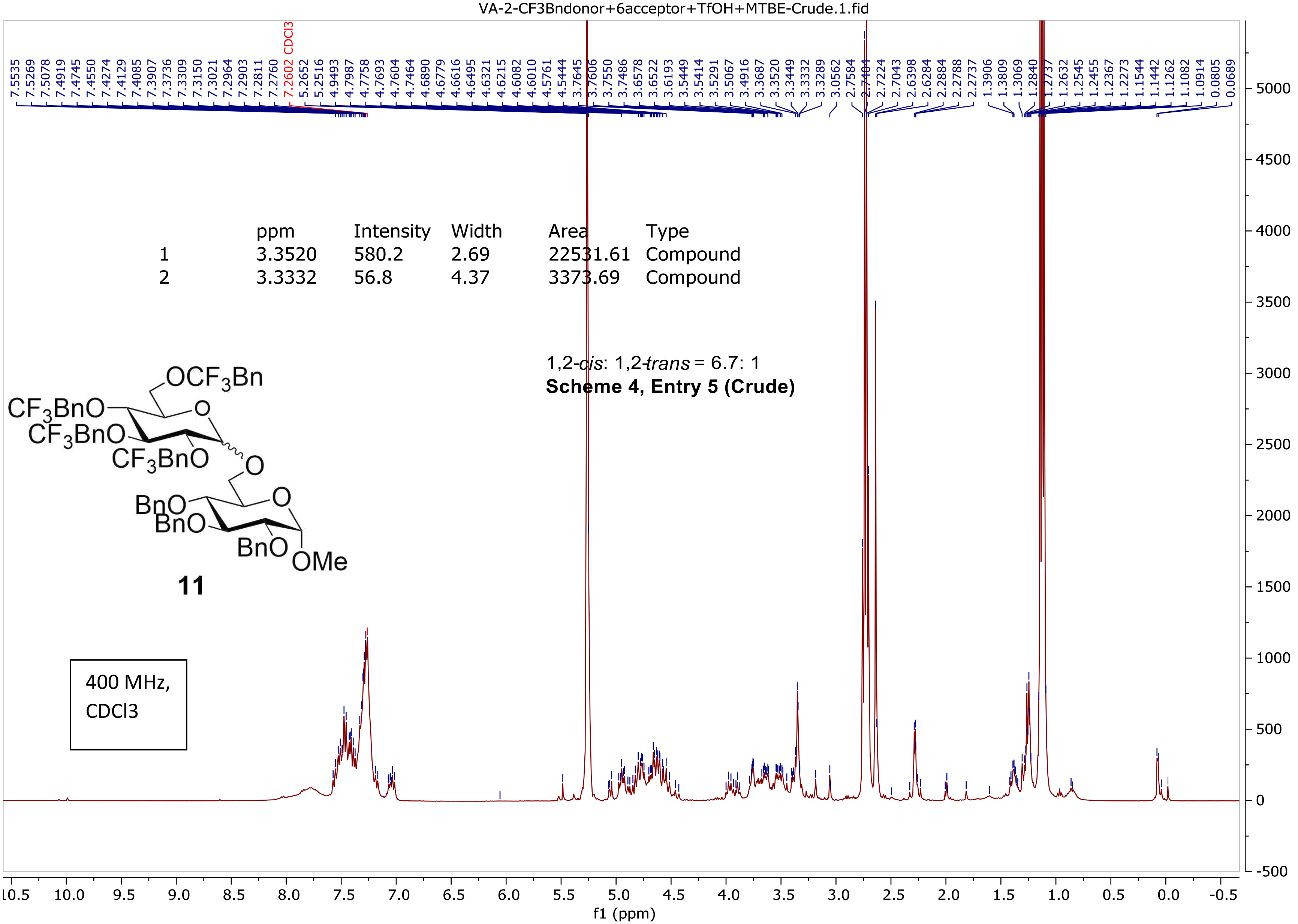
	ppm	Intensity	Width	Area	Type
1	3.3600	1336.7	3.75	61535.32	Compound
2	3.3261	652.4	3.54	30548.31	Compound

11

1,2-*cis*: 1,2-*trans* = 2: 1

Scheme 4, Entry 4 (Pure)

400 MHz,
CDCl3



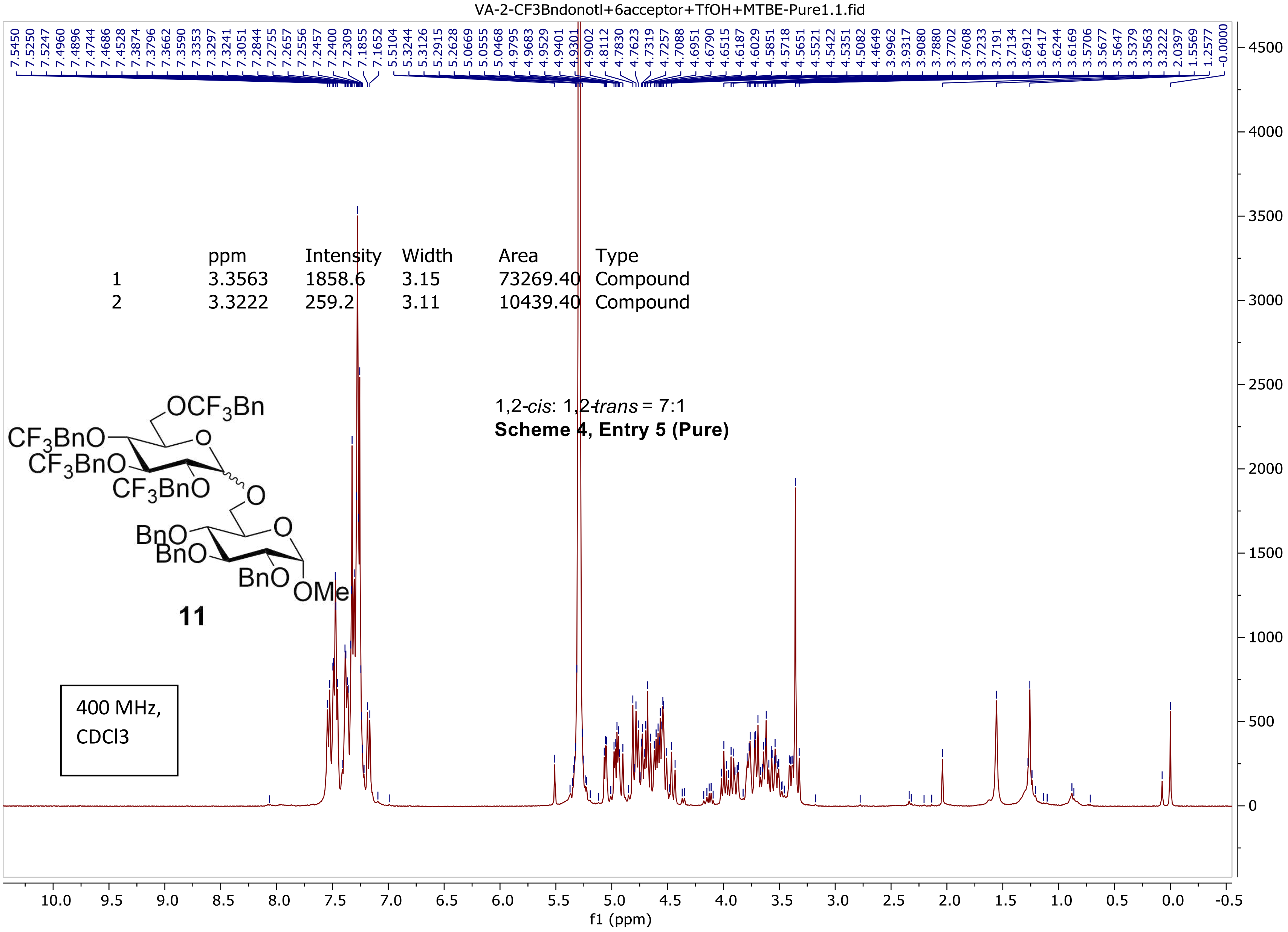
11

	ppm	Intensity	Width	Area	Type
1	3.3520	580.2	2.69	22531.61	Compound
2	3.3332	56.8	4.37	3373.69	Compound

1,2-*cis*: 1,2-*trans* = 6.7: 1

Scheme 4, Entry 5 (Crude)

400 MHz,
CDCl3



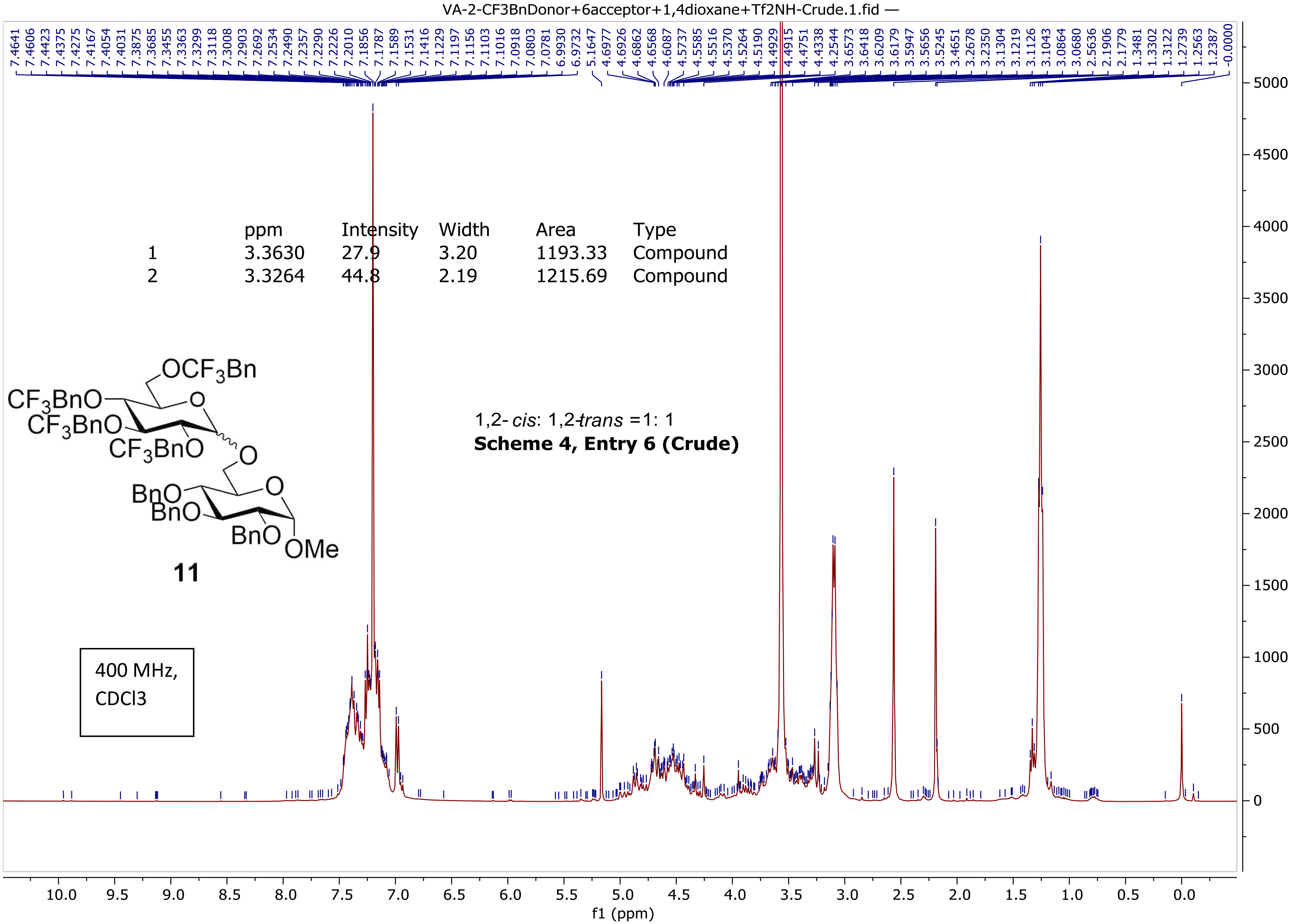
	ppm	Intensity	Width	Area	Type
1	3.3563	1858.6	3.15	73269.40	Compound
2	3.3222	259.2	3.11	10439.40	Compound

11

1,2-*cis*: 1,2-*trans* = 7:1

Scheme 4, Entry 5 (Pure)

400 MHz,
CDCl3



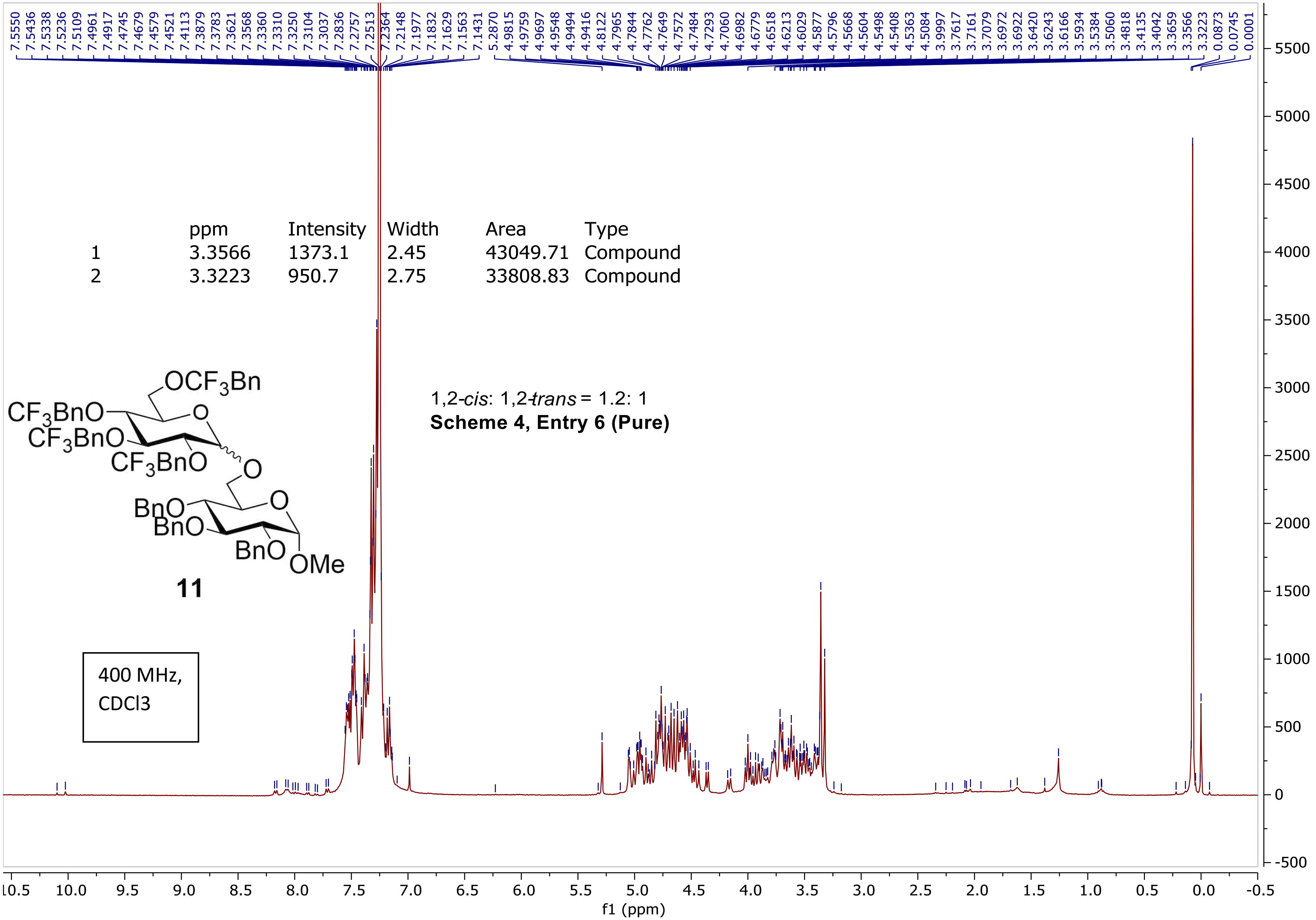
11

	ppm	Intensity	Width	Area	Type
1	3.3630	27.9	3.20	1193.33	Compound
2	3.3264	44.8	2.19	1215.69	Compound

1,2- *cis*: 1,2-*trans* =1: 1

Scheme 4, Entry 6 (Crude)

VA-2-CF3BnDonor+6acceptor+1,4-dioxane+Tf2NH-Pure



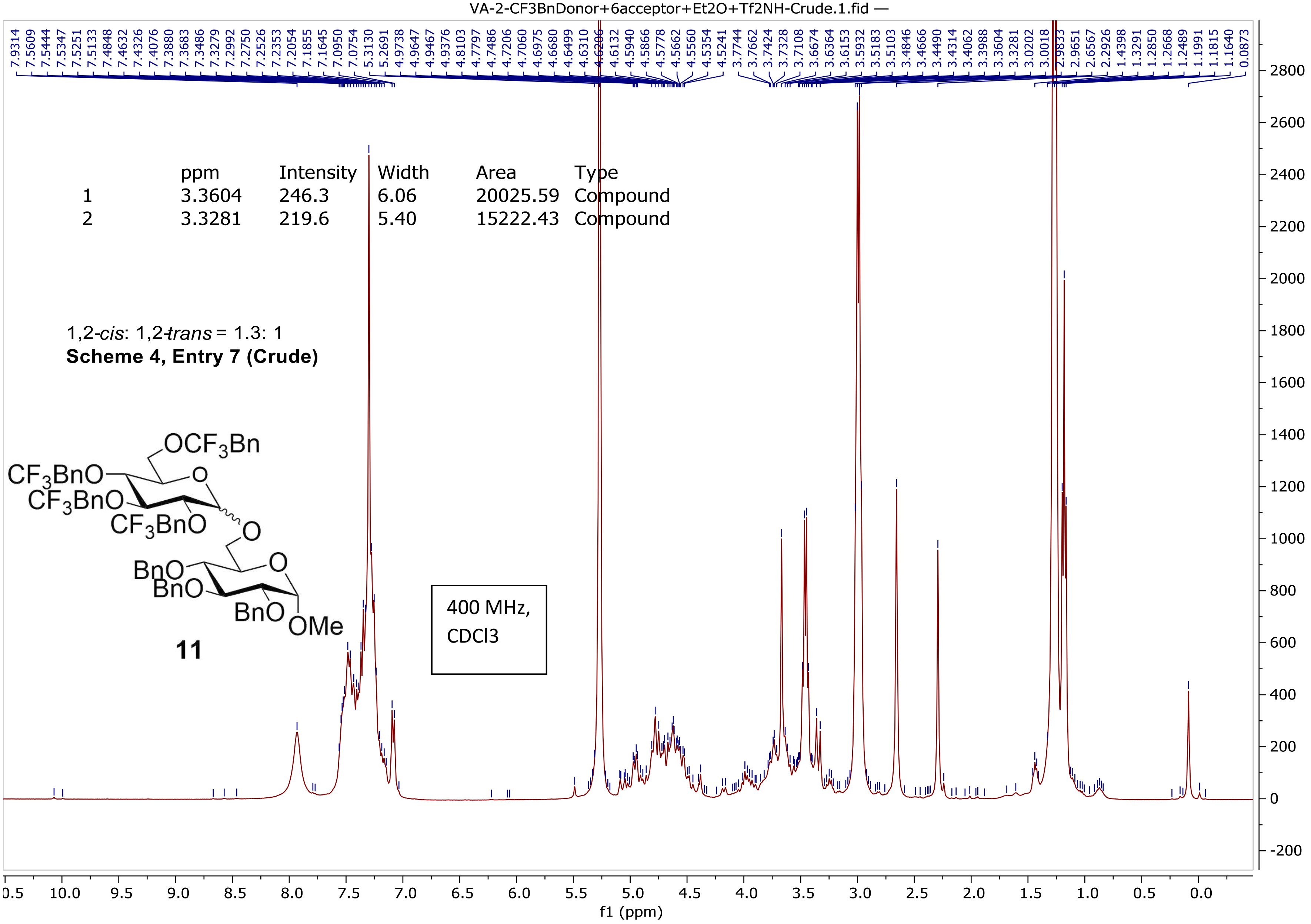
	ppm	Intensity	Width	Area	Type
1	3.3566	1373.1	2.45	43049.71	Compound
2	3.3223	950.7	2.75	33808.83	Compound

11

1,2-*cis*: 1,2-*trans* = 1.2: 1

Scheme 4, Entry 6 (Pure)

400 MHz,
CDCl3



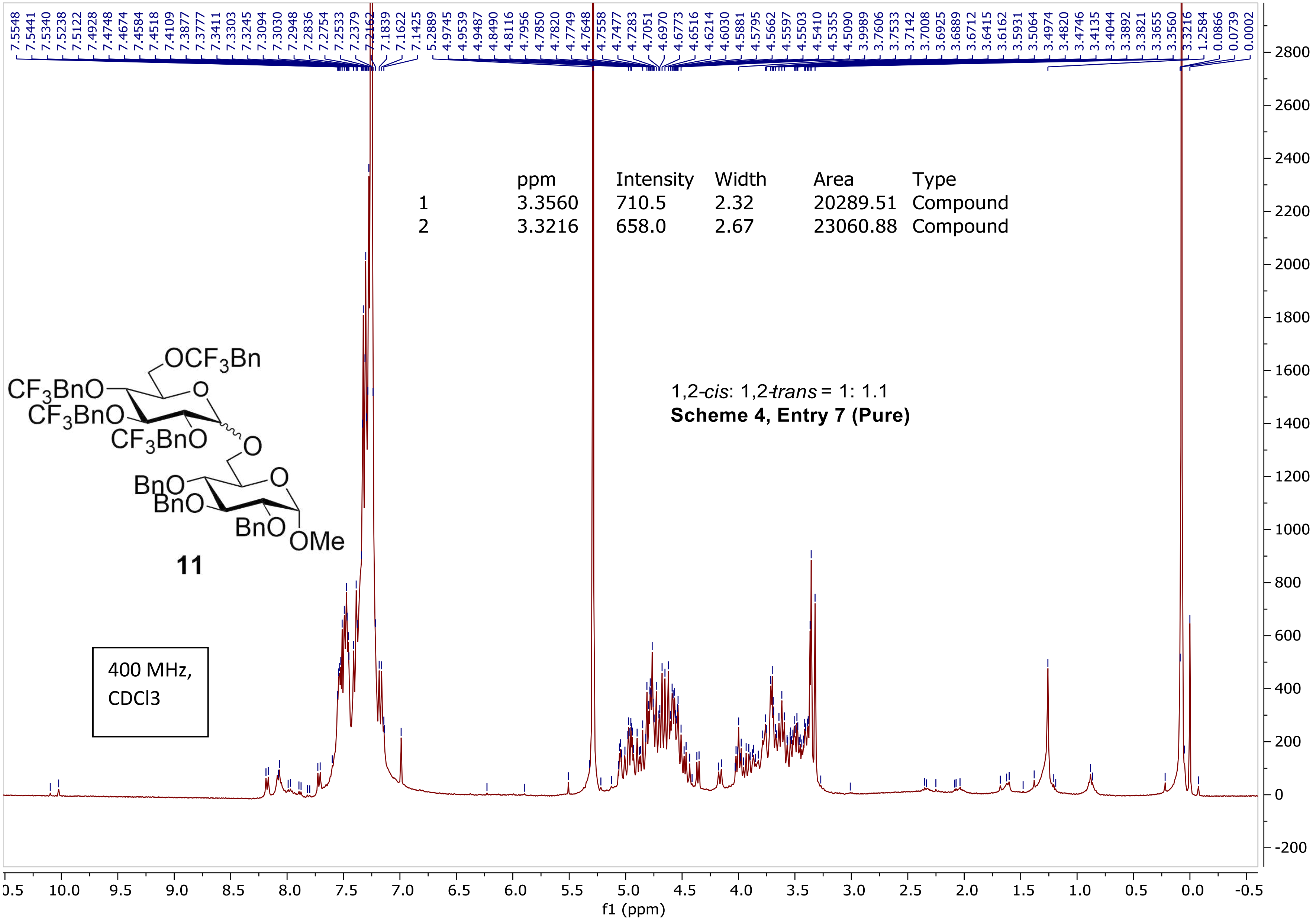
	ppm	Intensity	Width	Area	Type
1	3.3604	246.3	6.06	20025.59	Compound
2	3.3281	219.6	5.40	15222.43	Compound

1,2-*cis*: 1,2-*trans* = 1.3: 1

Scheme 4, Entry 7 (Crude)

11

VA-2-CF3Bndonor+6acceptor+Et2O+Tf2NH-Pure



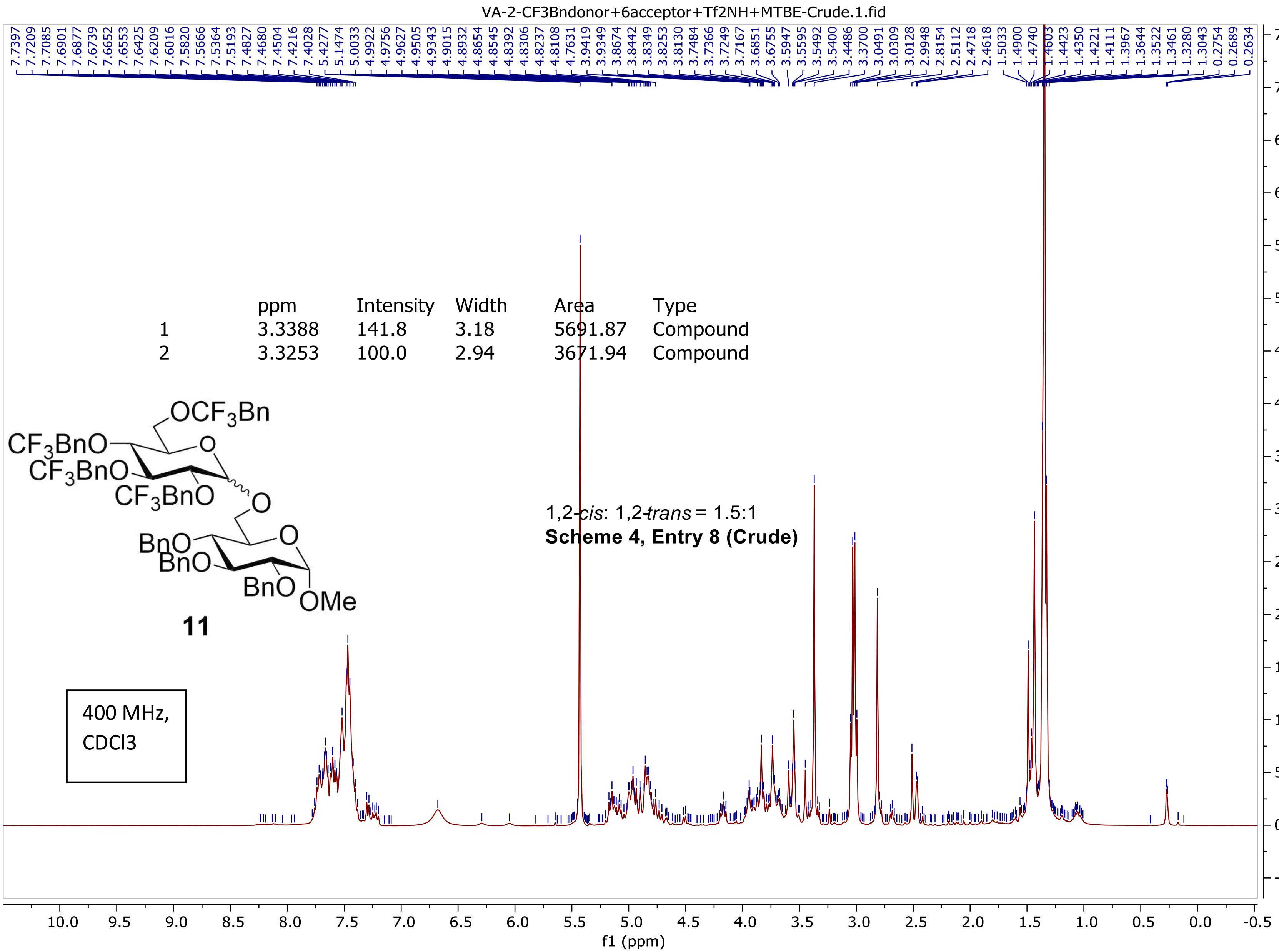
	ppm	Intensity	Width	Area	Type
1	3.3560	710.5	2.32	20289.51	Compound
2	3.3216	658.0	2.67	23060.88	Compound

11

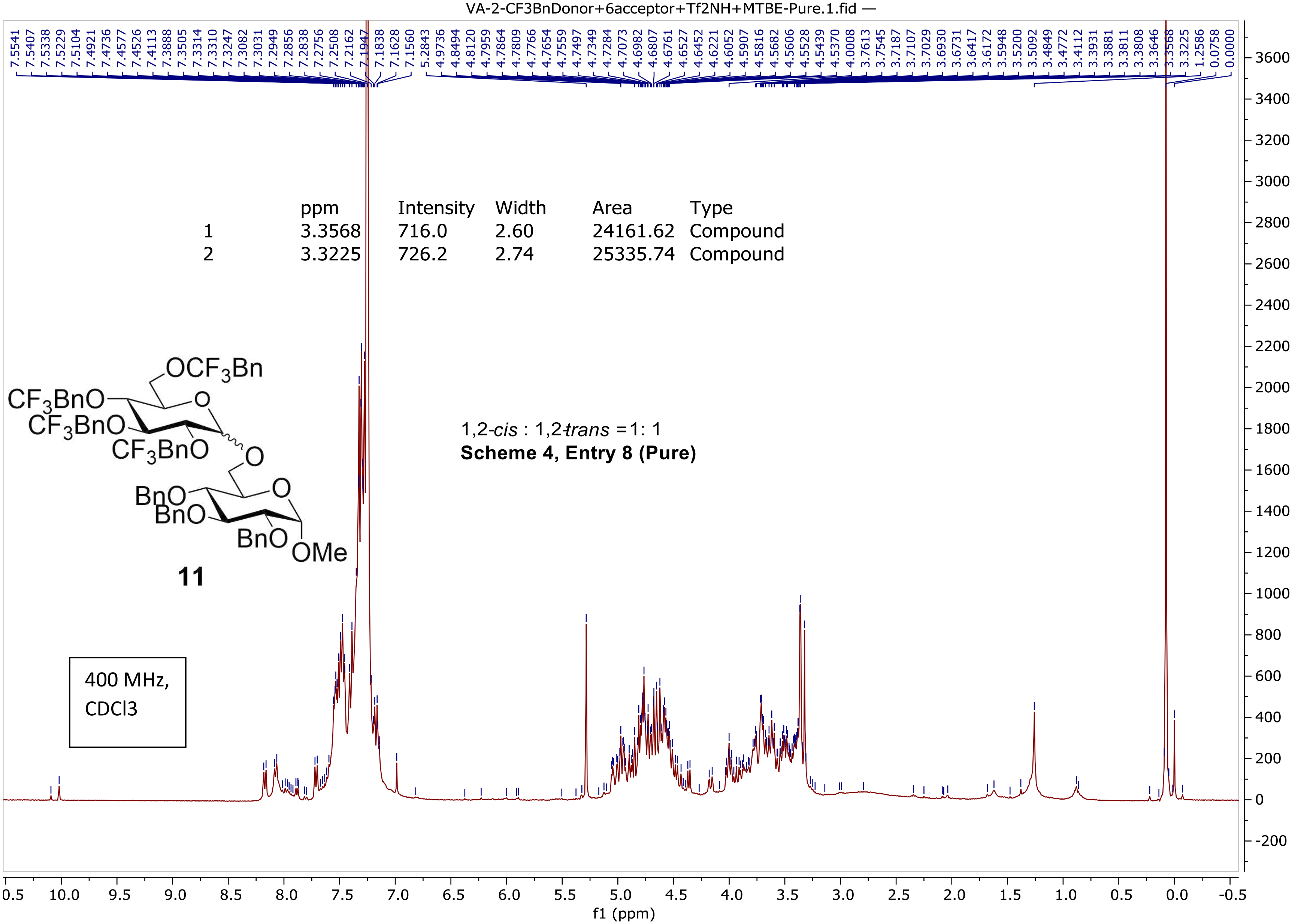
1,2-*cis*: 1,2-*trans* = 1: 1.1

Scheme 4, Entry 7 (Pure)

400 MHz,
CDCl3



	ppm	Intensity	Width	Area	Type
1	3.3388	141.8	3.18	5691.87	Compound
2	3.3253	100.0	2.94	3671.94	Compound

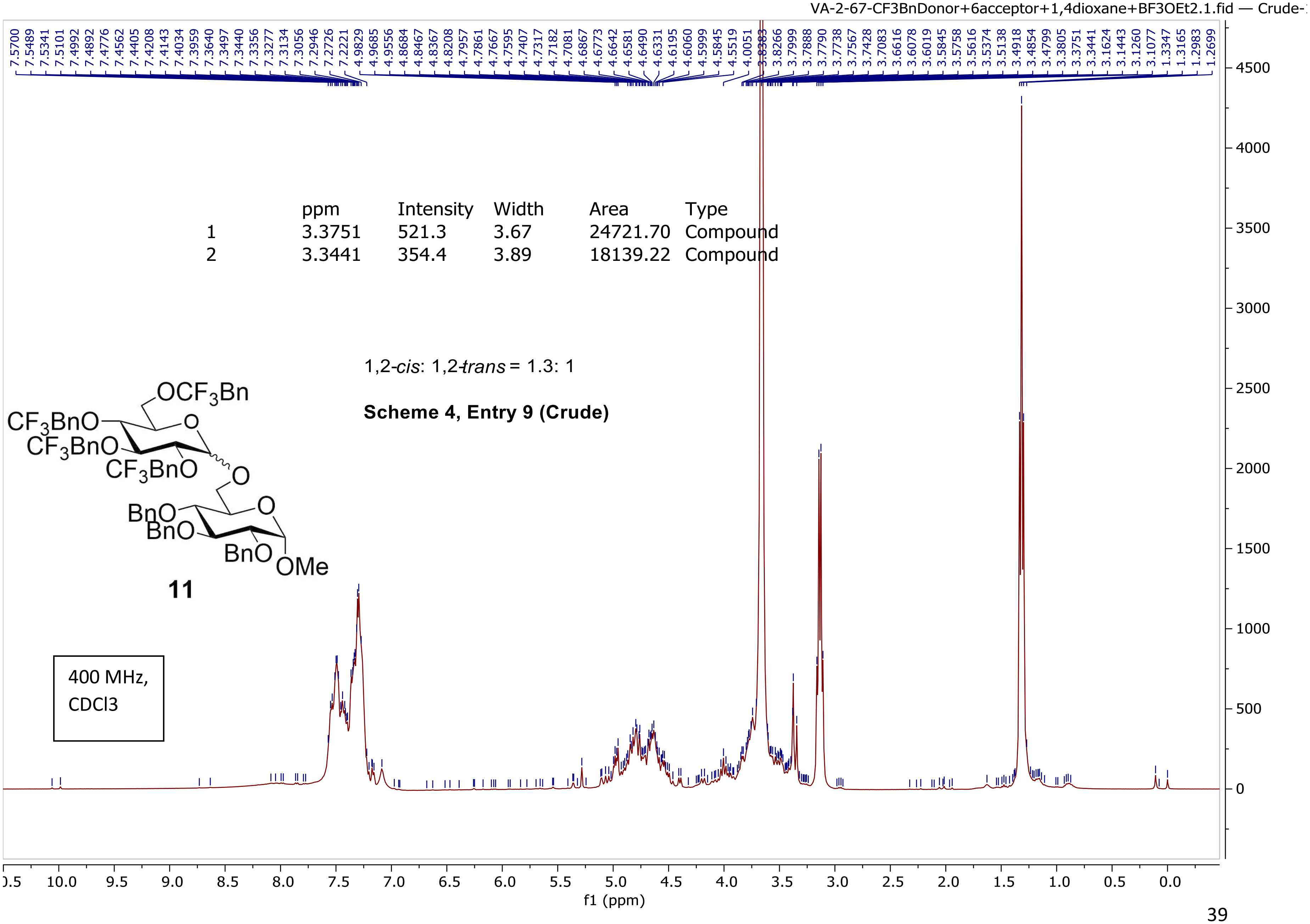


11

	ppm	Intensity	Width	Area	Type
1	3.3568	716.0	2.60	24161.62	Compound
2	3.3225	726.2	2.74	25335.74	Compound

1,2-*cis* : 1,2-*trans* = 1: 1

Scheme 4, Entry 8 (Pure)



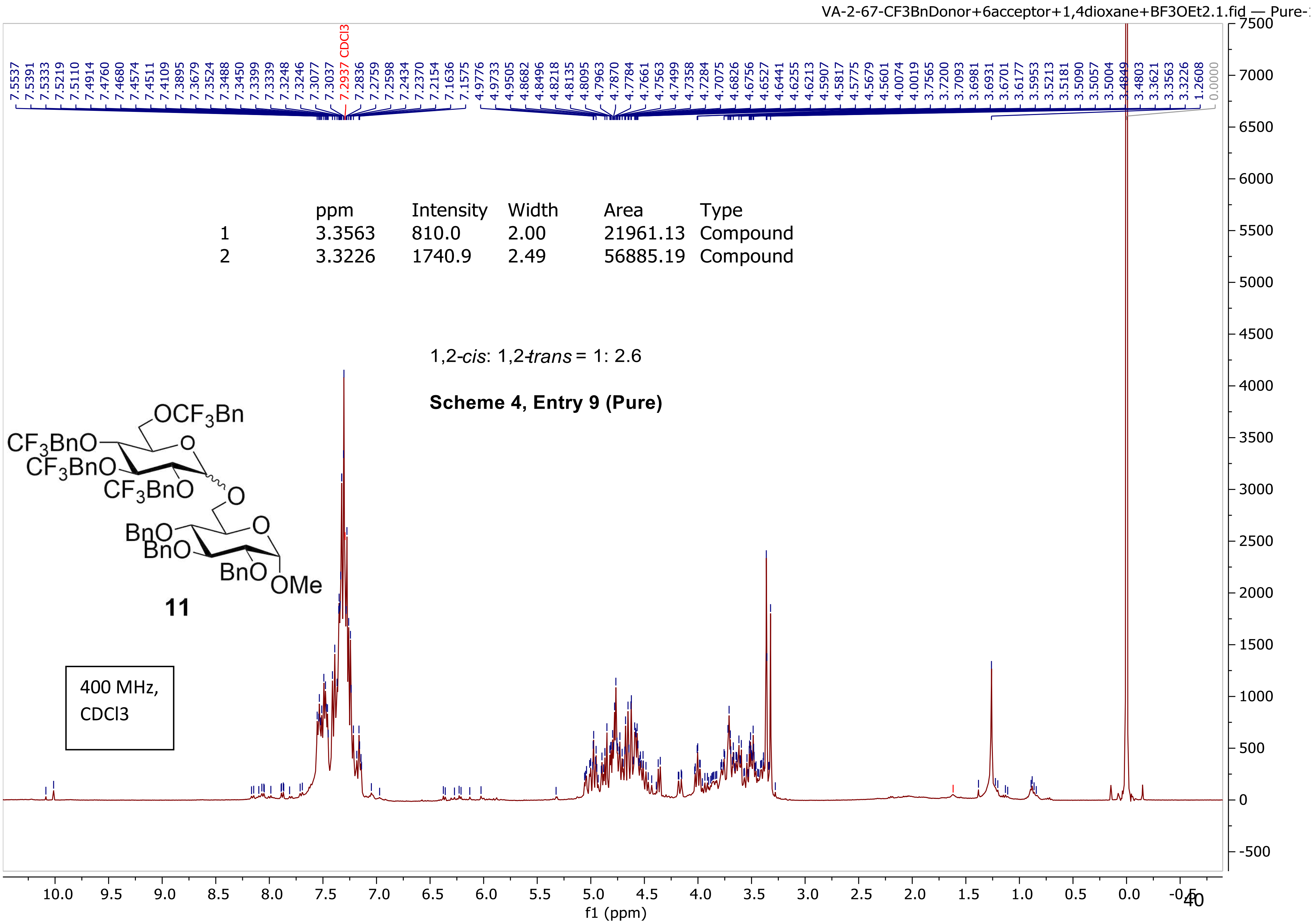
	ppm	Intensity	Width	Area	Type
1	3.3751	521.3	3.67	24721.70	Compound
2	3.3441	354.4	3.89	18139.22	Compound

1,2-*cis*: 1,2-*trans* = 1.3: 1

Scheme 4, Entry 9 (Crude)

11

400 MHz,
CDCl3



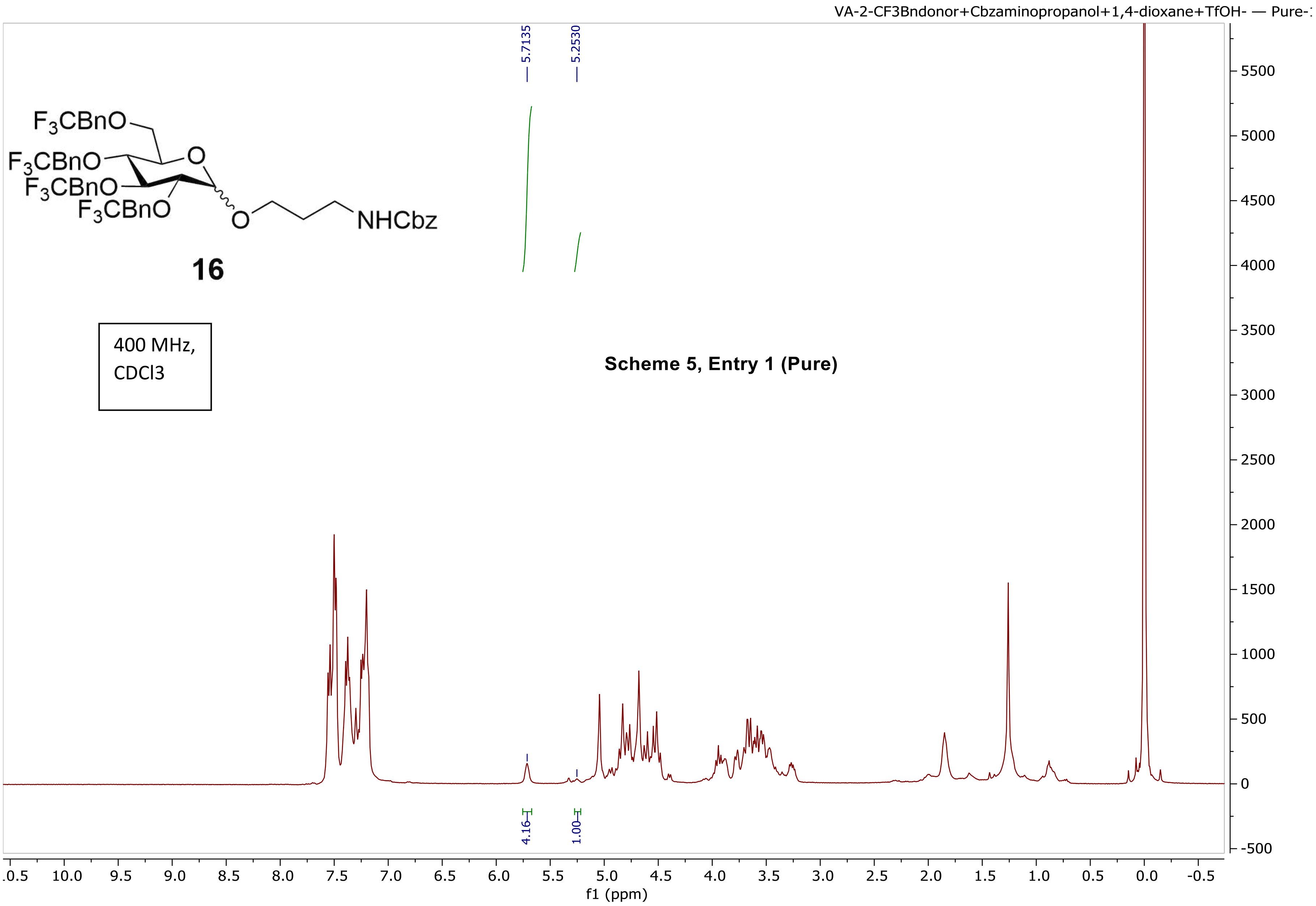
	ppm	Intensity	Width	Area	Type
1	3.3563	810.0	2.00	21961.13	Compound
2	3.3226	1740.9	2.49	56885.19	Compound

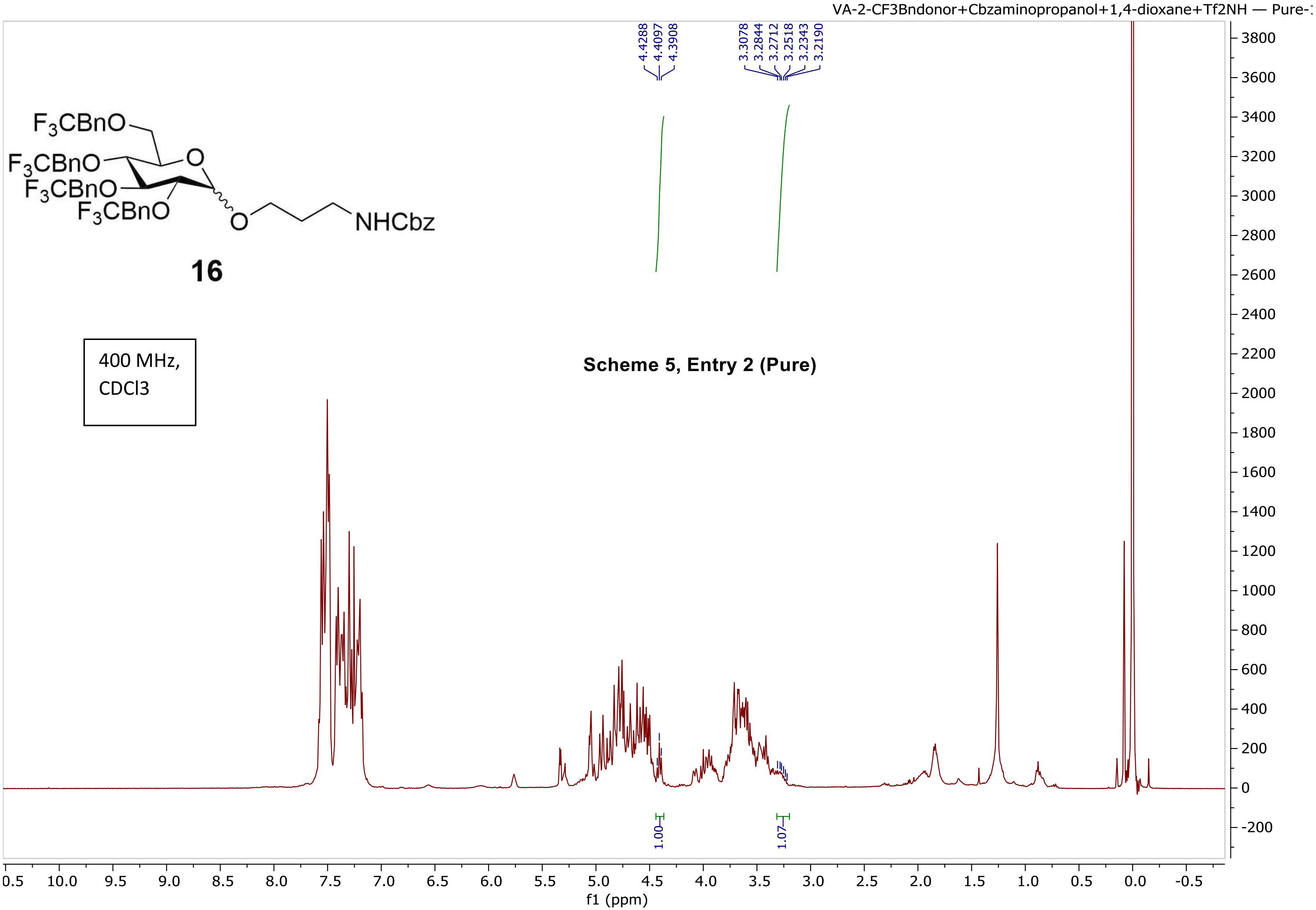
1,2-*cis*: 1,2-*trans* = 1: 2.6

Scheme 4, Entry 9 (Pure)

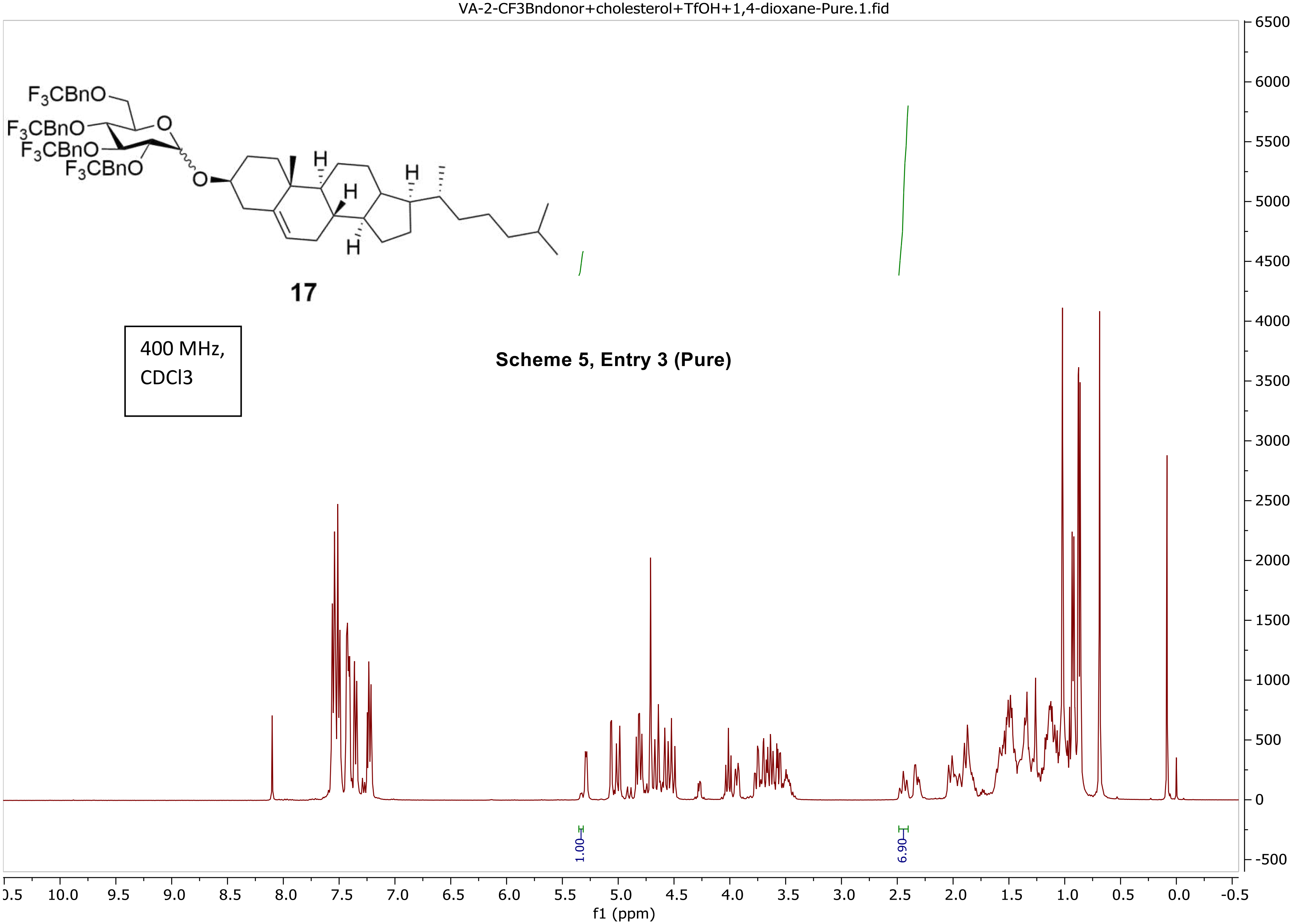
11

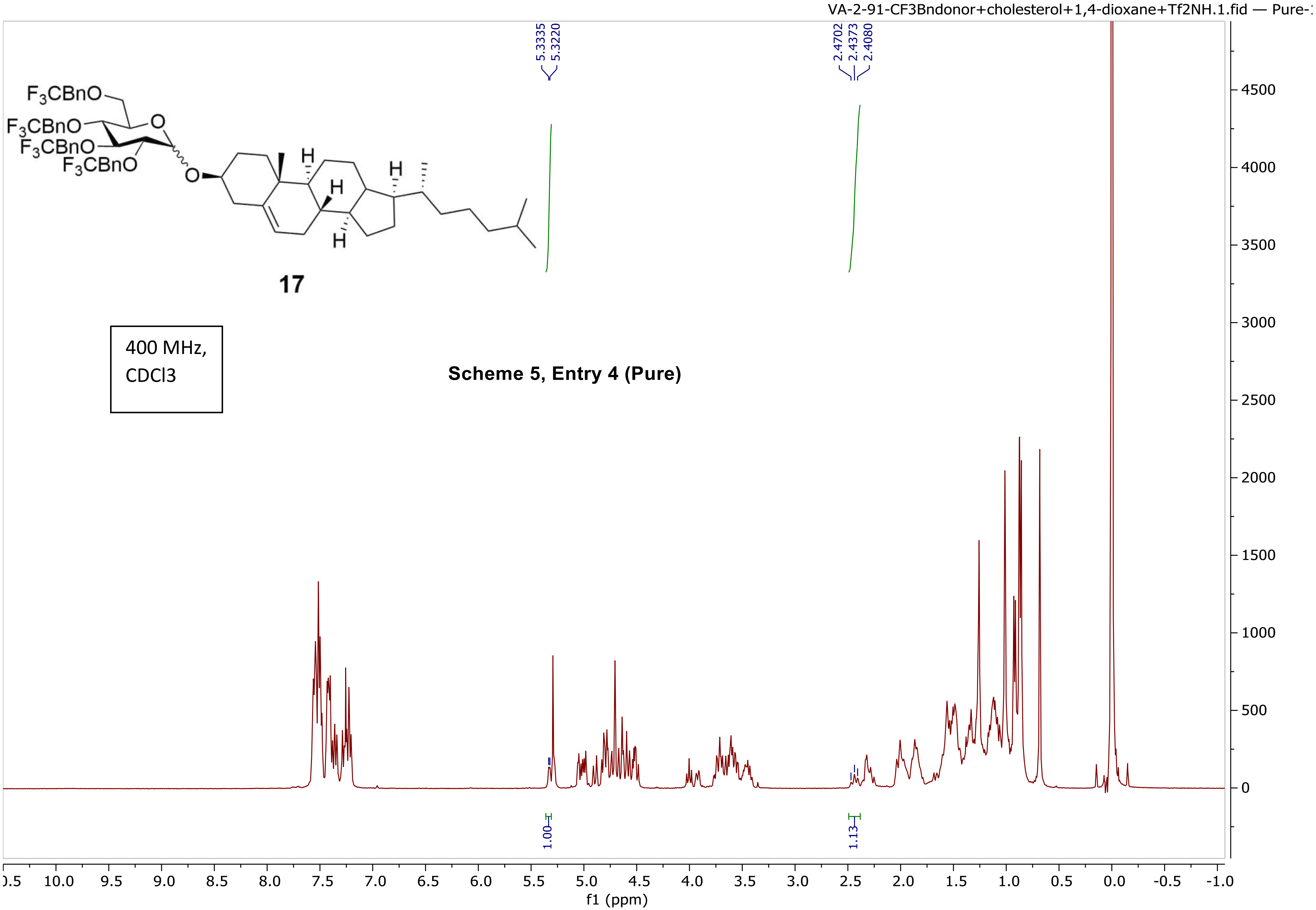
400 MHz,
CDCl3

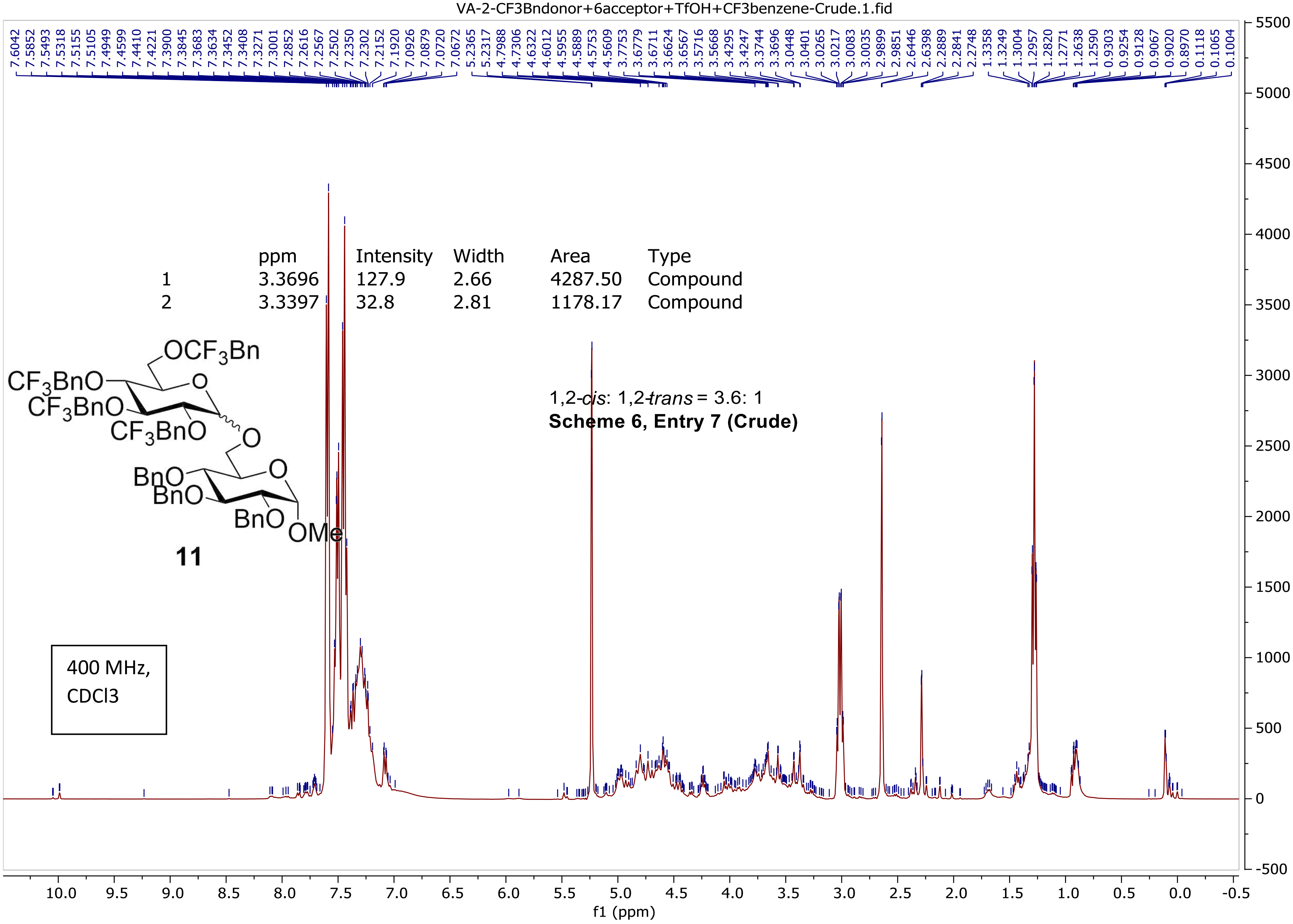

VA-2-CF3Bndonor+Cbzaminopropanol+1,4-dioxane+TfOH- — Pure-:
5.7135
5.2530
F3CBnO
F3CBnO
F3CBnO
F3CBnO
O
O
NHCbz
16
400 MHz,
CDCl3
Scheme 5, Entry 1 (Pure)
4.16
1.00
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
.0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


VA-2-CF3Bndonor+Cbzaminopropanol+1,4-dioxane+Tf2NH — Pure-
4.4288
4.4097
4.3908
3.3078
3.2844
3.2712
3.2518
3.2343
3.2190
F3CBnO
F3CBnO
F3CBnO
F3CBnO
O
O
NHCbz
16
400 MHz,
CDCl3
Scheme 5, Entry 2 (Pure)
1.00
1.07
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

VA-2-CF3Bndonor+cholesterol+TfOH+1,4-dioxane-Pure.1.fid




VA-2-91-CF3Bndonor+cholesterol+1,4-dioxane+Tf2NH.1.fid — Pure-
5.3335
5.3220
2.4702
2.4373
2.4080
F3CBnO
F3CBnO
F3CBnO
F3CBnO
O
O
H
H
H
H
17
400 MHz,
CDCl3
Scheme 5, Entry 4 (Pure)
1.00
1.13
4500
4000
3500
3000
2500
2000
1500
1000
500
0
.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

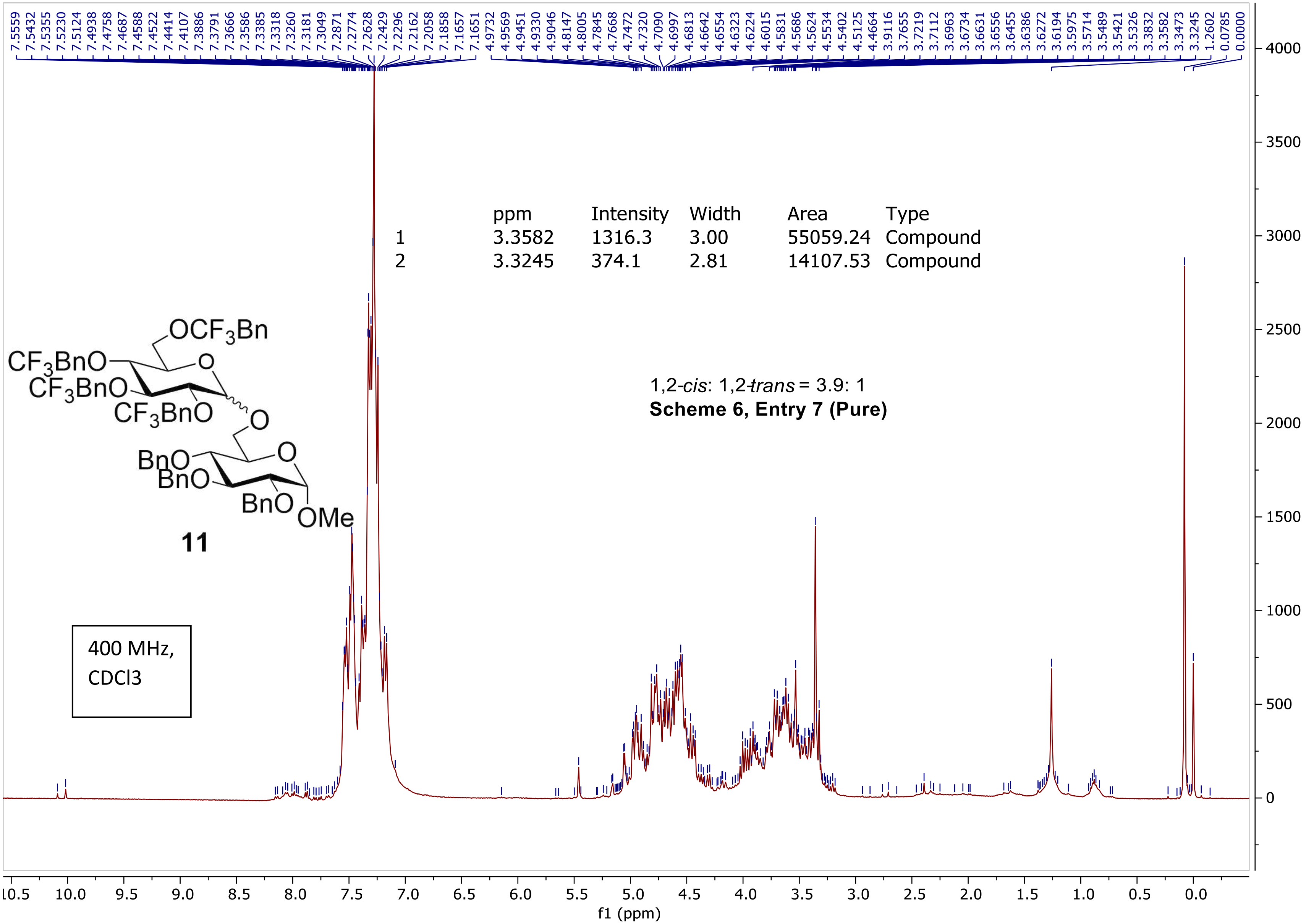


	ppm	Intensity	Width	Area	Type
1	3.3696	127.9	2.66	4287.50	Compound
2	3.3397	32.8	2.81	1178.17	Compound

1,2-*cis*: 1,2-*trans* = 3.6: 1

Scheme 6, Entry 7 (Crude)

VA-2-CF3Bndonor+6acceptor+TfOH+CF3Benzene-Pure.1.fid —



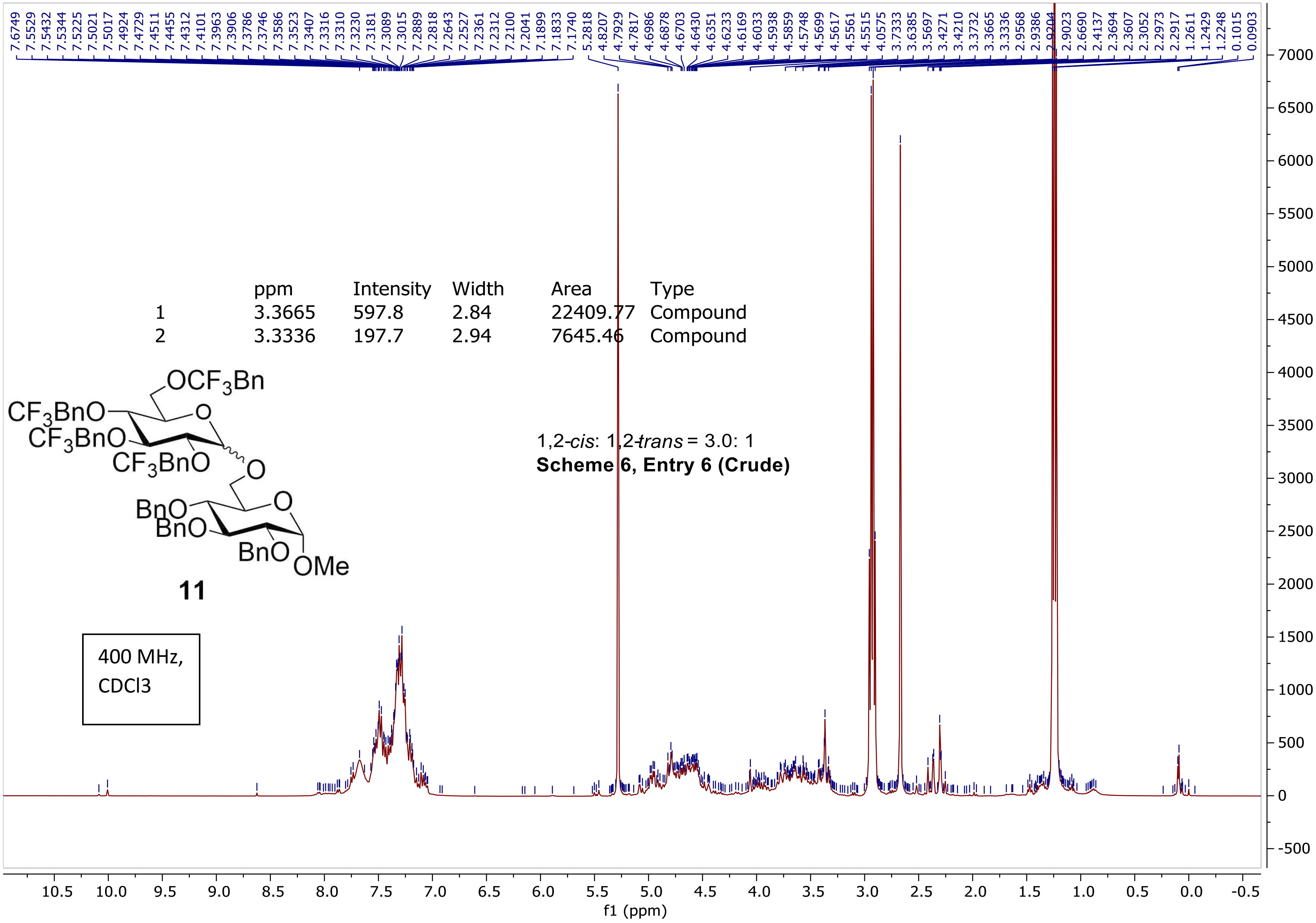
	ppm	Intensity	Width	Area	Type
1	3.3582	1316.3	3.00	55059.24	Compound
2	3.3245	374.1	2.81	14107.53	Compound

1,2-*cis*: 1,2-*trans* = 3.9: 1

Scheme 6, Entry 7 (Pure)

400 MHz,
CDCl3

VA-2-CF3Bndonor+6acceptor+TfOH+DCM-Crude.1.fid



	ppm	Intensity	Width	Area	Type
1	3.3665	597.8	2.84	22409.77	Compound
2	3.3336	197.7	2.94	7645.46	Compound

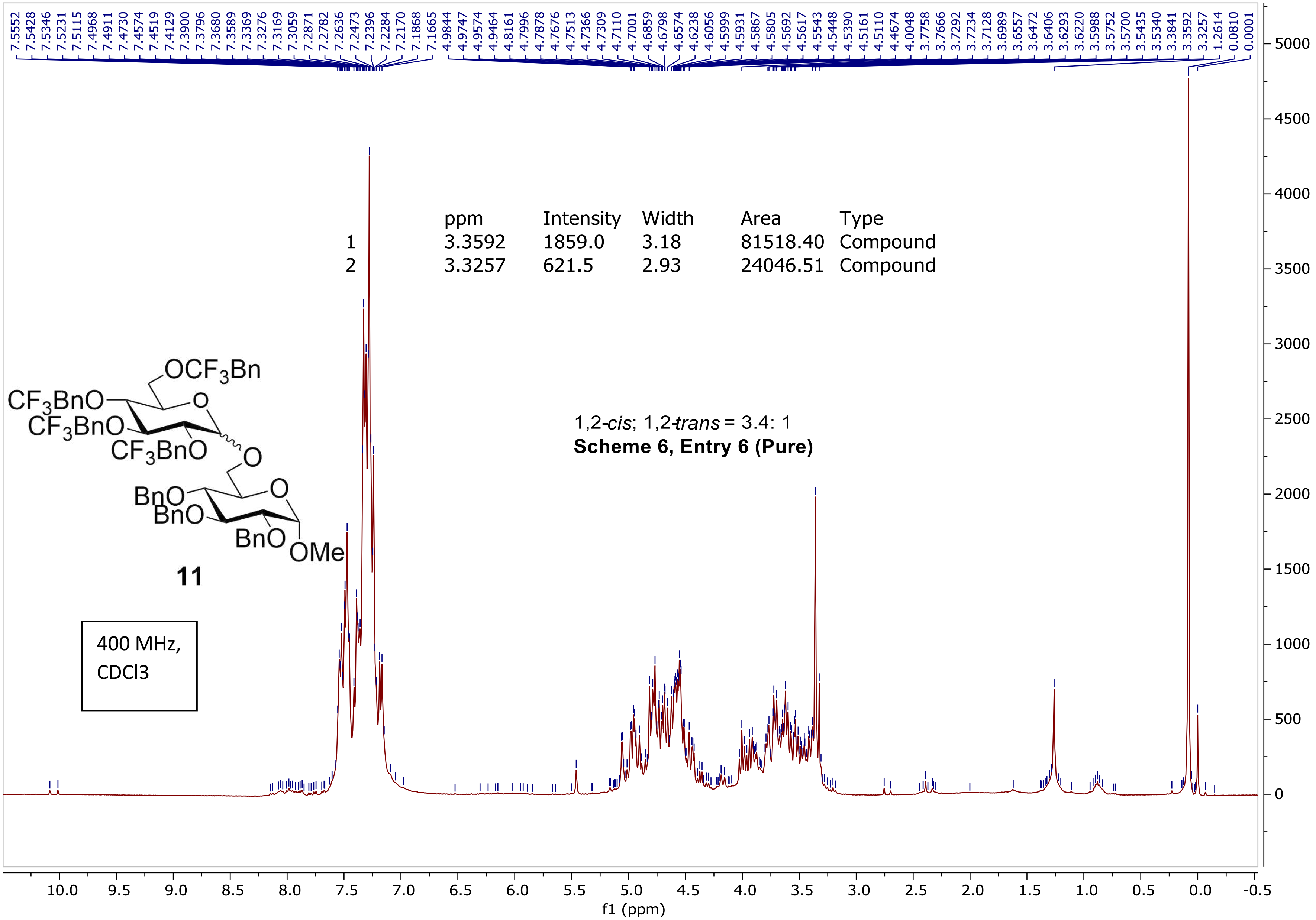
11

400 MHz, CDCl3

1,2-*cis*: 1,2-*trans* = 3.0: 1

Scheme 6, Entry 6 (Crude)

VA-2-CF3Bndonor+6acceptor+TfOH+DCM-Pure.1.fid



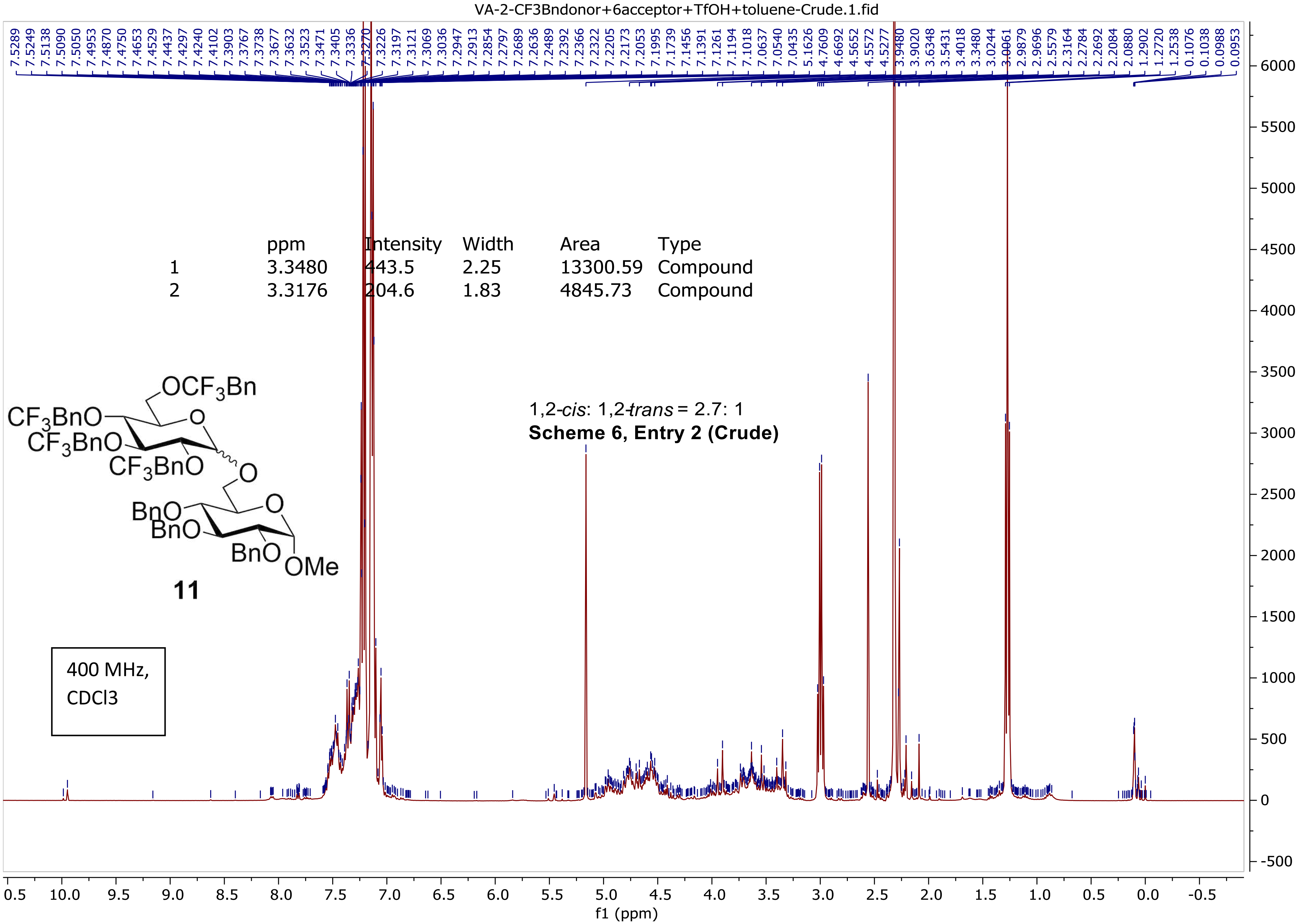
	ppm	Intensity	Width	Area	Type
1	3.3592	1859.0	3.18	81518.40	Compound
2	3.3257	621.5	2.93	24046.51	Compound

11

1,2-*cis*; 1,2-*trans* = 3.4: 1

Scheme 6, Entry 6 (Pure)

400 MHz,
CDCl3



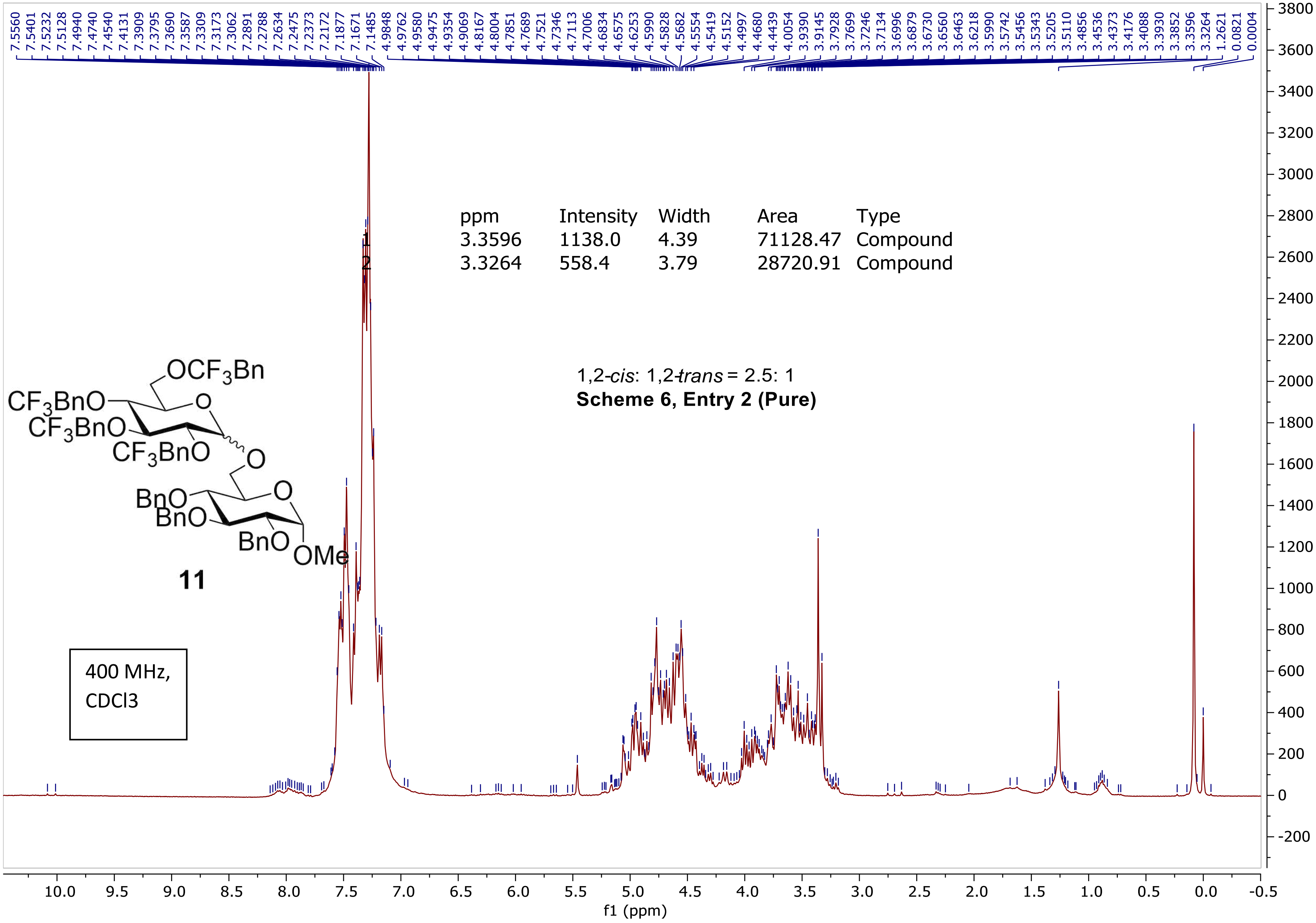
	ppm	Intensity	Width	Area	Type
1	3.3480	443.5	2.25	13300.59	Compound
2	3.3176	204.6	1.83	4845.73	Compound

11

1,2-*cis*: 1,2-*trans* = 2.7: 1

Scheme 6, Entry 2 (Crude)

VA-2-CF3Bndonor+6acceptor+TfOH+toluene-Pure.1.fid



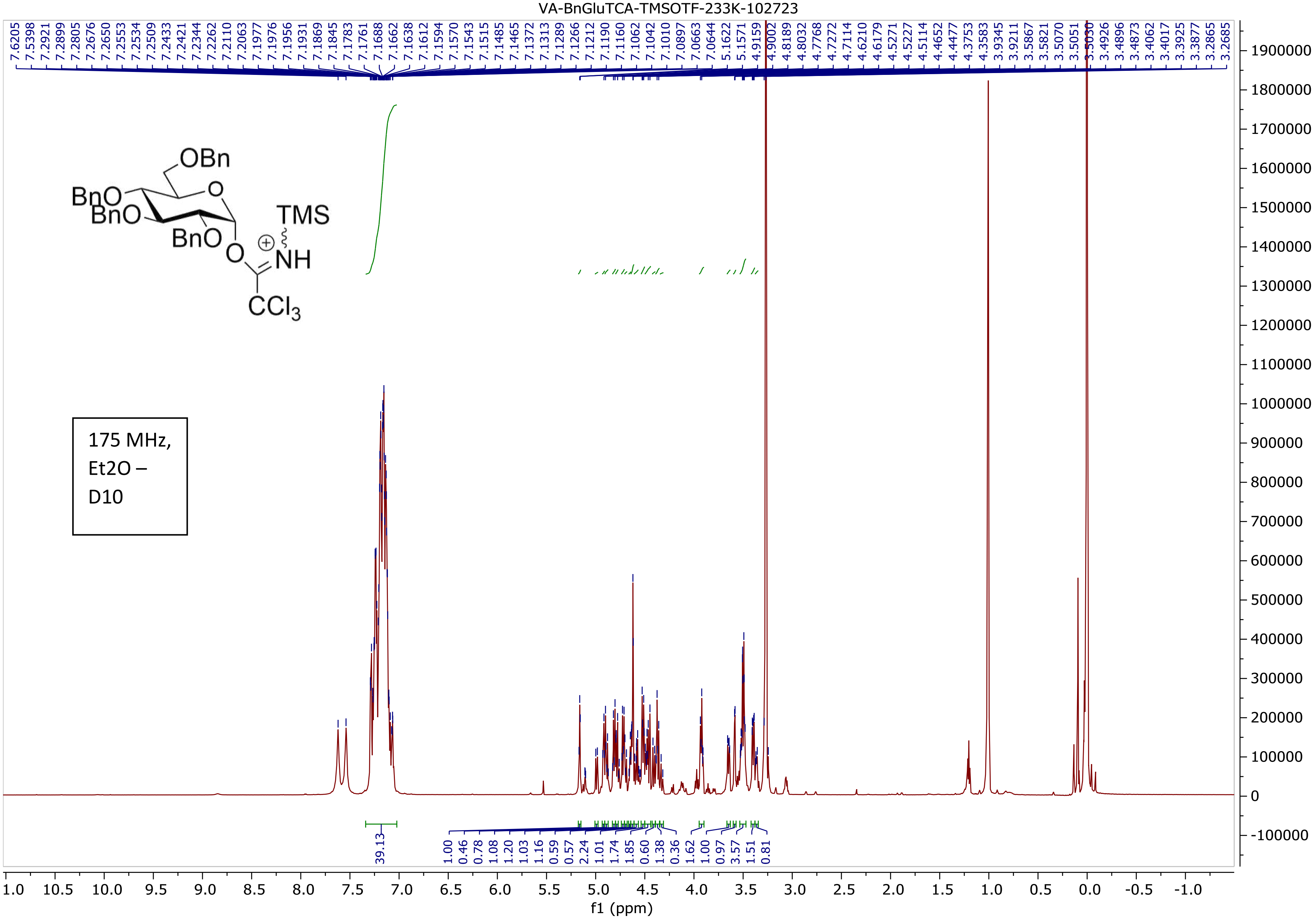
ppm	Intensity	Width	Area	Type
3.3596	1138.0	4.39	71128.47	Compound
3.3264	558.4	3.79	28720.91	Compound

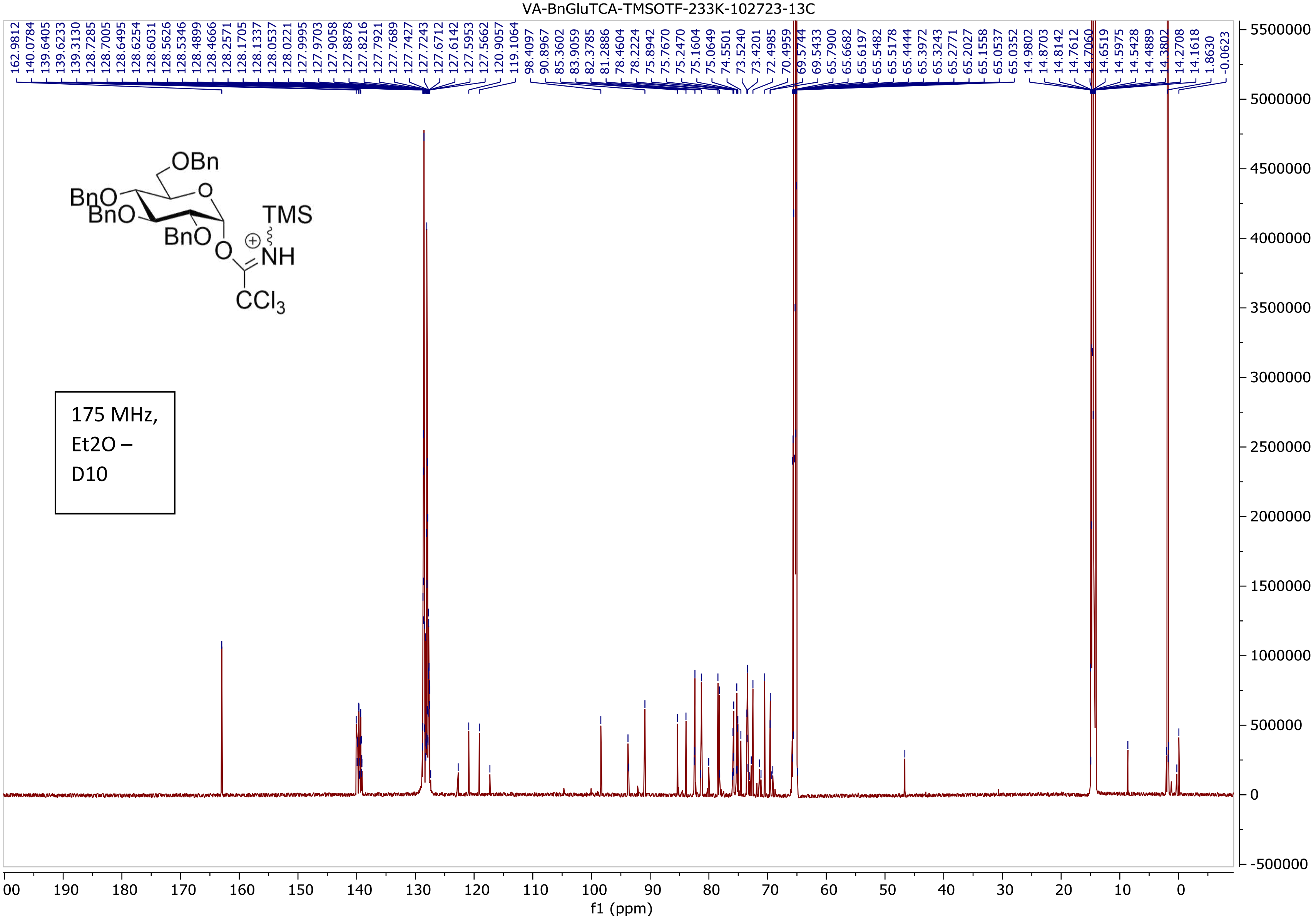
1,2-*cis*: 1,2-*trans* = 2.5: 1

Scheme 6, Entry 2 (Pure)

11

400 MHz,
CDCl3


VA-BnGluTCA-TMSOTF-233K-102723
7.6205
7.5398
7.2921
7.2899
7.2805
7.2676
7.2650
7.2553
7.2534
7.2509
7.2433
7.2421
7.2344
7.2262
7.2110
7.2063
7.1977
7.1976
7.1956
7.1931
7.1869
7.1845
7.1783
7.1761
7.1688
7.1662
7.1638
7.1612
7.1594
7.1570
7.1543
7.1515
7.1485
7.1465
7.1372
7.1313
7.1289
7.1266
7.1212
7.1190
7.1160
7.1062
7.1042
7.1010
7.0897
7.0663
7.0644
5.1622
5.1571
4.9159
4.9002
4.8189
4.8032
4.7768
4.7272
4.7114
4.6210
4.6179
4.5271
4.5227
4.5114
4.4652
4.4477
4.3753
4.3583
3.9345
3.9211
3.5867
3.5821
3.5070
3.5051
3.5030
3.4926
3.4896
3.4873
3.4062
3.4017
3.3925
3.3877
3.2865
3.2685
OBn
BnO
BnO
BnO
O
O
TMS
NH
CCl3
175 MHz,
Et2O –
D10
39.13
1.00
0.46
0.78
1.08
1.20
1.03
1.16
0.59
0.57
2.24
1.01
1.74
1.85
0.60
1.38
0.36
1.62
1.00
0.97
3.57
1.51
0.81
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


VA-BnGluTCA-TMSOTF-233K-102723-13C
162.9812
140.0784
139.6405
139.6233
139.3130
128.7285
128.7005
128.6495
128.6254
128.6031
128.5626
128.5346
128.4899
128.4666
128.2571
128.1705
128.1337
128.0537
128.0221
127.9995
127.9703
127.9058
127.8878
127.8216
127.7921
127.7689
127.7427
127.7243
127.6712
127.6142
127.5953
127.5662
120.9057
119.1064
98.4097
90.8967
85.3602
83.9059
82.3785
81.2886
78.4604
78.2224
75.8942
75.7670
75.2470
75.1604
75.0649
74.5501
73.5240
73.4201
72.4985
70.4959
69.5744
69.5433
65.7900
65.6682
65.6197
65.5482
65.5178
65.4444
65.3972
65.3243
65.2771
65.2027
65.1558
65.0537
65.0352
14.9802
14.8703
14.8142
14.7612
14.7060
14.6519
14.5975
14.5428
14.4889
14.3802
14.2708
14.1618
1.8630
-0.0623
OBn
BnO
BnO
O
BnO
O
TMS
⊕
NH
CCl3
175 MHz,
Et2O –
D10
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)