Organic Syntheses

Enantioselective Synthesis of *(S)*-Ethyl 2-((*tert*-butoxycarbonyl)((*tert*-butyldimethylsilyl)oxy)amino)-4-oxobutanoate

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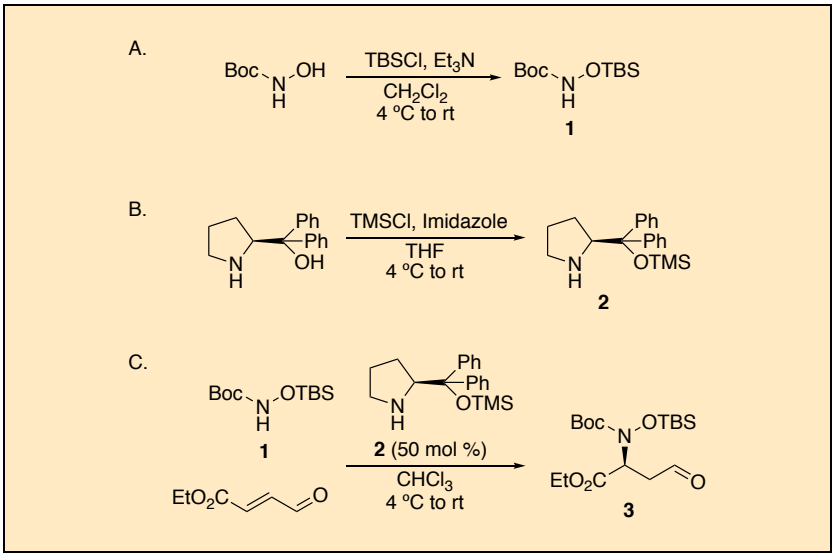

Procedure (Note 1)

A. *tert-Butyl (tert-butyldimethylsilyl)oxycarbamate (**1**).* *N*-Boc hydroxylamine (44.0 g, 330 mmol, 1.0 equiv) (Note 2) is introduced into a 2-L round-bottomed flask equipped with a 4-cm oval Teflon-coated stir-bar and is dissolved with CH_2Cl_2 (1.10 L). The reaction mixture is cooled to 4 °C

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in an ice-water bath after which a 250-mL addition funnel is attached. Triethylamine (49.0 mL, 363 mmol, 1.10 equiv) is transferred into the addition funnel *via* a graduated cylinder, and added dropwise over 15 min. Dichloromethane (20 mL) is used to ensure that no reagents are left on the side. *tert*-Butyldimethylsilylchloride (49.7 g, 330 mmol, 1.0 equiv) is dissolved in CH_2Cl_2 (150 mL) and added dropwise over 60 min *via* the addition funnel at 4 ºC. Dichloromethane (50 mL) is used to ensure that no reagent is left on the side of the addition funnel (final concentration of substrate is 0.25 M). The addition funnel is removed, the flask is equipped with a nitrogen inlet, and the reaction is stirred for 16 h at 23 °C under nitrogen (Note 3). Water (250 mL) is added and the mixture is poured into a 2-L separatory funnel. The reaction flask is rinsed with CH_2Cl_2 (50 mL) and the combined organic layer is separated and washed with saturated aqueous NaCl (250 mL). The organic layer is dried over $MgSO_4$ (20 g) and filtered by suction using a fritted funnel. Dichloromethane (50 mL) is used to wash the $MgSO_4$ and the filtrate is concentrated by rotary evaporation in a 2-L round-bottomed flask (40 °C bath, 425–30 mmHg). The resulting oil, which contains *tert*-butyl (*tert*-butyldimethylsilyl)oxycarbamate, is transferred to a 500-mL round-bottomed flask using CH_2Cl_2, which is then evaporated (40 °C bath, 425–30 mmHg). The product is dried on the vacuum pump (0.5 mmHg) for 48 h affording the desired compound (81.3 g, 329 mmol, 99.5% yield, 97.5% purity) as a white solid (Notes 4 and 5).

B. *(S)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether* (**2**). (S)-(-)-α,α-Diphenyl-2-pyrrolidinylmethanol (25.0 g, 98.8 mmol, 1.0 equiv) (Note 6) is introduced in a 1-L three-necked round-bottomed flask (equipped with a 4-cm oval Teflon-coated stir-bar, an internal thermometer, and a glass stopper) and is dissolved with THF (220 mL). To the resulting solution, imidazole (20.0 g, 294 mmmol, 3.0 equiv) is added in one portion. After complete dissolution of the imidazole, the reaction mixture is cooled to 4 ºC in an ice-water bath. A 250-mL addition funnel is attached and then charged with trimethylchlorosilane (31.3 mL, 247 mmol, 2.50 equiv) *via* a 50 mL syringe. The TMSCl is added dropwise via the addition funnel over 20 min (Figure 1). Tetrahydrofuran (50 mL) is used to rinse the addition funnel and ensure that no reagent is left on the side of the addition funnel. The addition funnel is removed, the flask is equipped with a nitrogen inlet, and the reaction is stirred for 15 h at 23 °C under nitrogen. Methyl *tert*-butyl ether (MTBE) (150 mL) is added and the reaction stirred for an additional 15 min. The resultant heterogeneous mixture is filtered through a

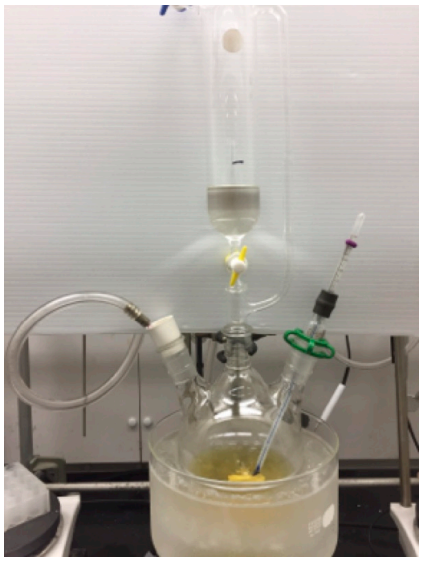


Figure 1. Addition of trimethylchlorosilane in Step B

10 cm diameter fritted funnel packed with Celite, and MTBE (3 x 50 mL) is used to wash the precipitate. The filtrate is poured into a 2-L separatory funnel. MTBE (50 mL) is used to rinse the flask and ensure that no reagents are left on the side of the flask. The organic layer is separated and washed with H_2O (3 x 150 mL) and saturated aqueous NaCl (2 x 250 mL). The organic layer is dried over $MgSO_4$ (10 g) and filtered by suction using a fritted funnel. Methyl *tert*-butyl ether (MTBE) (50 mL) is used to wash the $MgSO_4$ and the filtrate is concentrated by rotary evaporation into a 2-L round-bottomed flask (40 °C bath, 425–30 mmHg). The resulting oil containing **2** is transferred to a 250-mL round-bottomed flask using MTBE (10 mL), which is evaporated (40 °C bath, 425–30 mmHg) to provide the crude product (29.24 g, 89.8 mmol, 90.9%, purity <85%) (Note 7). The material is further purified by column chromatography to provide the desired compound (22.7 g, 69.8 mmol, 70.6% yield, 97.7% purity) as a pale yellow oil (Note 8 and 9).

C. *(S)-Ethyl 2-((tert-butoxycarbonyl)((tert-butyldimethylsilyl)oxy)amino)-4-oxobutanoate* (***3***)**.** A solution of (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **2** (19.0 g, 58.6 mmol, 0.50 equiv) in chloroform (120 mL) is transferred to a 1-L, three-necked, round-bottomed flask equipped with a 4-cm Teflon-coated magnetic stir-bar, a 250-mL addition funnel, a thermometer fitted with a glass adaptor, and a rubber septum through

which nitrogen atmosphere is ensured (Figure 2). The flask is cooled to 4 ºC using an ice-water bath. Using a 20 mL syringe, ethyl (2*E*)-4-oxo-2-butenoate (14.1 mL, 117 mmol, 1.0 equiv) (Note 10) is added to the addition

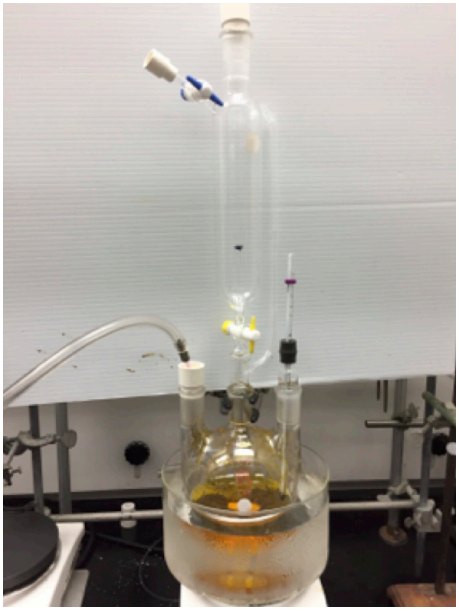


Figure 2. Reaction Assembly for Step C

funnel. The enoate is then added to the flask dropwise via the addition funnel over 15 min, maintaining the internal temperature at 4 ºC. Chloroform (10 mL) is used to rinse the additional funnel. *tert*-Butyl (*tert*-butyldimethylsilyl)oxycarbamate **1** (34.8 g, 141 mmol, 1.20 equiv) is dissolved in chloroform (60 mL), placed in the addition funnel, and added dropwise over 1 h. The internal temperature is maintained at 4 ºC throughout the course of the addition. Chloroform (10 mL) is used to wash both the flask that contained the *tert*-butyl (*tert*-butyldimethylsilyl)oxycarbamate and the addition funnel. The final concentration of the substrate is 0.6 M. The reaction is stirred for 12 h under nitrogen at 23 °C, and the reaction is monitored by TLC (Note 11). The reaction mixture is transferred to a 1-L round-bottomed flask and concentrated by rotary evaporation (40 °C bath, 325–30 mmHg). The residue is dried on the vacuum pump (0.5 mmHg) for 5 h, after which the crude compound is purified by column chromatography (Note 12). The desired

fractions are collected and concentrated by rotary evaporation (40 °C bath, 325–30 mmHg) to provide 13.3 g (30.1%) of the desired product. Impure fractions from the initial column are combined and further purified by column chromatography (Note 13). The desired fractions are collected and concentrated by rotary evaporation (40 °C bath, 325–30 mmHg) to provide 3.4 g (7.7%) of the product. The residual oils are further dried for 5 h under vacuum pump (0.5 mmHg) to afford the desired compound as a pale yellow oil (combined yield of 16.7 g, 37.8%, >98.5% purity, 94% ee) (Notes 14, 15, 16, and 17).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical). See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with *N*-Boc hydroxylamine, triethylamine, dichloromethane, *tert*-butyldimethylsilyl chloride, ninhydrin, ethyl acetate, hexanes, sodium chloride, magnesium sulfate, (*S*)-(–)-α, α-Diphenyl-2-pyrrolidinylmethanol, tetrahydrofuran, imidazole, trimethylchlorosilane, methyl *tert*-butylether, Celite, ethyl (2*E*)-4-oxo-2-butenoate, chloroform, and potassium permanganate.
2. *N*-Boc-Hydroxylamine was obtained from Chem-Impex International, Inc (catalog number 29751) and used without further purification. The

following reagents and solvents are used as received: methanol (Sigma-Aldrich, chromasolv, ≥99.9%), chloroform (Sigma-Aldrich, chromasolv, ≥99.8%), and tetrahydrofuran (Merck, ACS, reag ≥99.8%). The checkers purchased THF from Fisher Scientific (HPLC, >99.9%). The submitters purchased dichloromethane from Sigma-Aldrich (chromasolv, ≥99.5%), and the checkers purchased DCM from VWR (J.T. Baker, >99.5%). The submitters purchased *tert*-butyl methyl ether from Fluka (≥99%), and the checkers purchased MTBE from Fisher Scientific, (>99%). Triethylamine (Sigma-Aldrich, ≥99.5%) and imidazole (Sigma-Aldrich) were purchased and used as received. The submitters purchased *tert*-butyldimethylchlorosilane (TBDMSCl) from Fluorochem Ltd, and the checkers purchased TBDMSCl from Oakwood Chemical (99%). Trimethylchlorosilane was purchased from Sigma-Aldrich, and magnesium sulfate was purchased from Fisher Chemical. The submitters used silica gel (Fluka, high purity grade, pore size 60 Å, 230-400 mesh), and the checkers purchased silica gel from Silicycle, pore size 60 Å, 230-400 mesh particle size). Chloroform-D was purchased from (Armar, 99.8 atom%, submitters) and from Sigma-Aldrich (99.8 atom% D, checkers). The submitters purchased 1,3,5-trimethoxybenzene from ABCR (99%), and the checkers purchased that material from Sigma-Aldrich (99%). Deionized water is used throughout the procedure. The submitters purchased glass-backed, extra-hard layer TLC plates (60 Å, 250 μm thickness containing F-254 indicator) from Silicycle, and the checkers purchased identical TLC plates from EMD Millipore.

3. TLC analysis was performed on silica: Compound **1** has an R_f = 0.8 in 40% EtOAc in hexanes using ninhydrin as stain (product color is fuschia).
4. The identity of the product (**1**) was established with the following characterization data. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.14 (s, 6H), 0.93 (s, 9H), 1.45 (s, 9H), 6.68 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: –5.80, 18.01, 25.87, 28.15, 81.55, 157.89; HRMS (ESI+) calc. for $C_{11}H_{25}NO_3Si$ $[M+Na]^+$ 270.1496, found 270.1498. The purity of the compound was calculated by qNMR with a delay of relaxation of 30 seconds using 15.6 mg of 1,3,5-trimethoxybenzene (purity 99%) and 20.9 mg of the compound **1**.
5. A second run on full scale provided 79.3 g (97%) of the same product.
6. (*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol was obtained from Combi-Blocks and used without further purification.

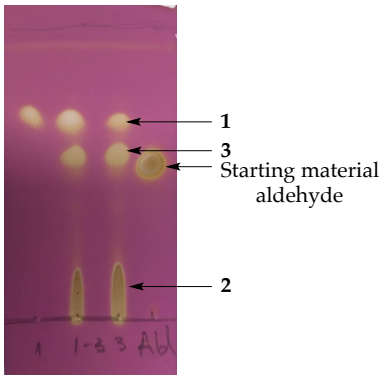
7. The crude compound **2** obtained by the checkers contained impurities that could be seen in the ^{1}H NMR spectrum. Purification was performed by silica gel column chromatography (9 x 55 cm) with 500 g of silica gel packed with 2 L of 30% diethyl ether/hexanes. Fraction collection (500 mL per fraction) begins immediately with 3 L of 30% diethyl ether/hexanes, then 2 L of 60% diethyl ether/hexanes. Fractions 4-16 contain the desired compound (**2**) and are collected. The combined fractions are concentrated by rotary evaporation (40 °C bath, 325–30 mmHg) and then dried on the vacuum pump for 10 h.
8. The identity of the product (**2**) was established with the following characterization data. ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.06 (s, 9H), 1.38–1.47 (m, 1H), 1.47–1.65 (m, 2H), 1.73 (bs, 1H), 2.79–2.91 (m, 1H), 4.06 (t, *J* = 7.2 Hz, 1H), 7.22–7.32 (m, 6H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 2.2, 25.0, 27.5, 47.1, 65.4, 83.2, 126.7, 126.9, 127.5, 127.5, 127.6, 128.4, 145.8, 146.8. HRMS (ESI+) calc. for $C_{20}H_{28}NOSi$ $[M+H]^+$ 326.1940, found 326.1938. The purity of the compound was calculated by qNMR with a delay of relaxation of 30 seconds using 18.56 mg of 1,3,5-trimethoxybenzene (purity 99%) and 33.19 mg of the compound **2**.
9. A second run on full scale provided 31.6 g (98%) of **2** with purity sufficient to avoid chromatography.
10. Ethyl *trans*-4-oxo-2-butenoate was obtained from ABCR-Chemicals (96%) and must be purified prior to use. Purification can be performed by either column chromatography or by distillation under reduced pressure.

    Purification by column chromatography: A column (5 x 35 cm) is packed with 75 g of silica gel in 5% EtOAc:hexanes (200 mL). Ethyl *trans*-4-oxo-2-butenoate (20 mL) is directly loaded on the column. The elution is performed with 5% EtOAc:hexanes and fractions are collected in 200 mL Erlenmeyer flasks. The first 100 mL are discarded. The collection is started and the desired product is generally obtained in fractions 2-9, which are concentrated by rotatory evaporation and (40 °C bath, 325–30 mmHg) and high vacuum. The recovery yield is generally >90 %.

    Purification by distillation: Ethyl *trans*-4-oxo-2-butenoate is placed in a 100 mL flask with a 2.5–cm Teflon-coated magnetic stir bar. The flask is equipped with a Vigreux column containing a thermometer on its top, a

water condenser on the side to collect the distillate, and attached to a vacuum source. The purified product distills at 35 °C at 6.10^{-2} mmHg.

11. TLC analysis is performed with 25% EtOAc in hexanes using $KMnO_4$ as stain. The product **3** has an R_f = 0.6, the starting material **1** has an R_f = 0.7, and the aldehyde starting material has an R_f = 0.5.



12. A column (15 x 45 cm) is packed with 1.5 kg of silica gel with 5% EtOAc:hexanes (~3 L). The crude material is dissolved in 20 mL eluent (heating at 35° C is required to fully dissolve) and loaded onto the silica gel. The flask is washed with 30 mL eluent in order to ensure that no products are left on the side of the flask. Sand (600 g) is added to the top of the silica gel and provides a layer of 2 cm. Elution is performed with 5% EtOAc:hexanes and collected in 250-mL Erlenmeyer flasks, from which the first 5.0 L are discarded. The eluent is increased to 10% EtOAc:hexanes and collection with 250-mL fractions is started. After elution with 5 L, fractions 6–18 contain compound **1** whereas fractions 19–20 contain mixture of compounds **1** and **3**. Elution is then performed with 15% EtOAc:hexanes until the product (**3**) has fully eluted. No pressure is applied. Fractions 1-3, obtained from the 15% EtOAc:hexanes elution, contain a mixture of **1** and **3**. The desired product is obtained in fractions 4–20, which are concentrated by rotary evaporation (40 °C bath, 325–30 mmHg).
13. The remaining impure fractions were combined, concentrated and purified again with a second column (9 x 55 cm) packed with 750 g of silica gel. The silica gel is loaded in 5% EtOAc:hexanes (~3 L), and the crude material is loaded on the silica gel. The flask is washed with 5 mL

eluent in order to ensure that no products are left on the side of the flask. Sand (200 g, ~2 cm) is added to the top of the silica gel. The elution is performed with 5% EtOAc:hexanes, in 250-mL Erlenmeyer flasks and the first 4.0 L are discarded. Elution with 5% EtOAc:hexanes is continued for another 5 L, and 150-mL fractions are collected. These fractions (1-39) contain compound **1**. The eluent is increased to 10% EtOAc:hexanes and collection of 150-mL fractions is performed. Fractions 9-12 contain desired compound **3,** and the eluent is increased to 20% EtOAc:hexanes (~1.5 L) to flush out the remaining compound **3**. No pressure is applied before 20% EtOAc:hexanes is added. The desired fractions are collected and concentrated by rotary evaporation (40 °C bath, 325–30 mmHg).

14. The identity of the product (**3**) was established with the following characterization data. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.15 (d, J = 7.2 Hz, 6H), 0.90 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H), 1.47 (s, 9H), 2.78 (dd, J = 17.6, 5.2 Hz, 1H), 3.21 (dd, J = 17.6, 8.0 Hz, 1H), 4.11-4.25 (m, 1H), 4.89 (dd, J = 8.0, 5.2 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: –4.8, –4.7, 14.1, 17.9, 25.8, 28.1, 42.8, 60.5, 61.6, 82.5, 157.9, 169.0, 198.7; HRMS (ESI+) calc. for $C_{17}H_{33}NO_6Si$ $[M+Na]^+$ 398.1975, found 398.1973. IR (thin film): 3393, 3187, 3029, 2953, 2982, 2895, 2656, 1735, 1617, 1462, 1252, 1091, 836, 775 cm^{-1} . The purity of the compound was calculated by qNMR with a delay of relaxation of 30 seconds using 16.40 mg of 1,3,5-trimethoxybenzene (purity 99%) and 31.09 mg of compound **3**.
15. A second run on full scale provided 15.7 g (35.5%) of the same product.
16. Procedure for preparing the racemic product: To a solution of ethyl *trans*-4-oxo-2-butenoate (2.0 L, 16.6 mmol, 1.0 equiv) in $CHCl_3$ (24 mL, 0.75 M), pyrrolidine (0.27 L, 3.3 μmol, 0.2 equiv) was added. The solution was stirred for 5 min and **1** (4.9 g, 19.8 mmol, 1.2 equiv) was added. The mixture was stirred at rt for 16 h, after which it was concentrated to a brown-orange oil. Purification by silica gel chromatography (gradient of 5–15% Et_2O:pentane) gave the racemic material as a colorless oil (0.93 mg, 2.5 μmol, 15% yield).
17. The checkers determine the enantiomeric excess to be 94% by chiral the HPLC on Chiralcel IA column using hexanes/isopropyl alcohol (98:2) at a flow rate of 0.8 mL/min, while monitoring at 210 nm. Retention time (t_R) of the major enantiomer = 7.3 min, and retention time (t_R) of the minor enantiomer = 8.0 min.

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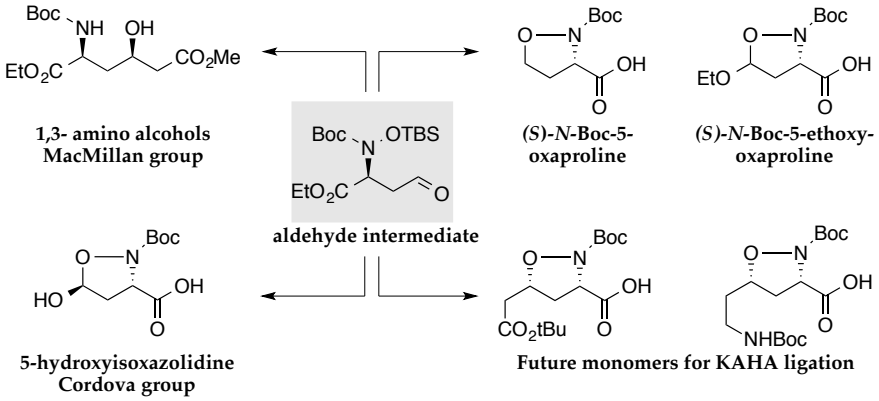
Discussion

Enantioenriched β-amino aldehydes are important chiral building blocks that are readily converted into the corresponding amino alcohols and β-amino acids. β-amino carbonyls have broad utility and they are constituents of natural products and pharmaceutical agents. Asymmetric methods have been well documented for their preparation by MacMillan

and Cordova via conjugate addition reactions involving *N*-centered nucleophiles and chiral amine catalysts.[3]

In the context of expanding the α-ketoacid–hydroxylamine (KAHA)[4] ligation monomers we have recently published the synthesis of a modified cyclic hydroxylamine by organocatalytic synthesis.[5] We were intrigued by the key intermediate *(S)-ethyl 2-((tert-butoxycarbonyl)((tert-butyldimethylsilyl)oxy)amino)-4-oxobutanoate* obtained via conjugate addition between the *N*-Boc-protected hydroxylamine and ethyl *trans*-4-oxo-2-butenoate. We were pleased to find that this intermediate proved to be extremely useful in the synthesis of several other cyclic hydroxylamines and more importantly to (*S*)-*N*-Boc-5-oxaproline, which is our preferred building block for KAHA ligation (Scheme 1).



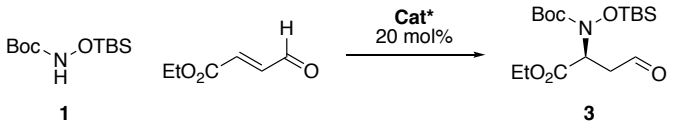
Scheme 1. General use of the β-amino aldehyde intermediate for the synthesis of various hydroxylamines for KAHA ligation or amino-acid analogues[1,3]

This encouraged us to enable an efficient, practical route that could be easily scaled up to provide enantiopure *(S)-ethyl 2-((tert-butoxycarbonyl)((tert-butyldimethylsilyl)oxy)amino)-4-oxobutanoate* based on an enantioselective, organomediated addition reaction between *tert-butyl (tert-butyldimethylsilyl)oxycarbamate* and ethyl *trans*-4-oxo-2-butenoate.

For these two reaction partners we have screened three different diphenylprolinol catalysts. We noticed that TBS protected diphenylprolinol **4** proceeded with slightly higher enantioselectivity[6a] yet the addition yield was lower than the TMS protected catalyst **2**.[6b] Unfortunately we could not

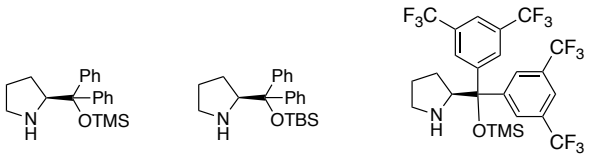
obtain a satisfying result when using catalyst **5**.[6c] In order to make the route suitable for a larger scale synthesis we chose the TMS protected diphenylprolinol as the catalyst of choice (Table 1).

Table 1. Screening of catalysts for the addition reaction



1 **3**

Cat*



2 **4** **5**

Entry	Catalyst	T (°C)	Yield (%)	ee (%)
1	**2**	4	23	96
2	**2**	25	29	94–95
3	**4**	4	20	98
4	**5**	4	n.d.[a]	n.d.[a]

[a] n.d. refers to 'not determined' values, the enantiomeric excess was poorer than with the other catalysts.

The synthesis of the TMS protected diphenylprolinol catalyst was straightforward starting from the commercially available, affordable intermediate (*S*)-diphenyl(pyrrolidin-2-yl)methanol. Screening of different acid additives as benzoic acid, acetic acid or dimethylhydrogen phosphate did not improve the outcome of the reaction. Stronger acids such as p-toluene sulfonic acid or 2,4-dinitrobenzenesulfonic acid led to equivalent yield. Further evaluation of the conditions for the conjugate addition revealed that using 50% of the organic catalyst and the purification of the commercially available 1,4-unsaturated aldehyde improved the addition yield to 48%. Surprisingly, increasing the quantity of the TMS protected diphenylprolinol to 75% and to an equimolar ratio did not show any yield

improvement. Despite all of our attempts to optimize it we were not able to make this process catalytic.

The present synthesis of *(S)-ethyl 2-((tert-butoxycarbonyl)((tert-butyldimethylsilyl)oxy)amino)-4-oxobutanoate* provides a convenient route to the synthesis of unnatural amino acids and hydroxylamine building blocks for the KAHA ligation. This synthesis will be the starting point for the design and synthesis of a large number of cyclic hydroxylamines as new monomers for KAHA ligation.

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Appendix
Chemical Abstracts Nomenclature (Registry Number)

N-Boc hydroxylamine; (36016-38-3)
tert-Butyldimethylsilyl chloride; (18162-48-6)
Triethylamine; (121-44-8)
(*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol; (112068-01-6)
Ethyl (2*E*)-4-oxo-2-butenoate; (2960-66-9)

Thibault Harmand studied Chemistry at the University of Nantes and Lyon (France). After his master thesis with Prof. George Fleet at the University of Oxford, he joined the group of Prof. Jeffrey Bode at ETH Zurich. His research focuses on the total chemical synthesis of proteins such as the hormone protein betatrophin and the antiviral membrane protein IFITM3 as well as the development of amino acids building blocks for chemical ligation.

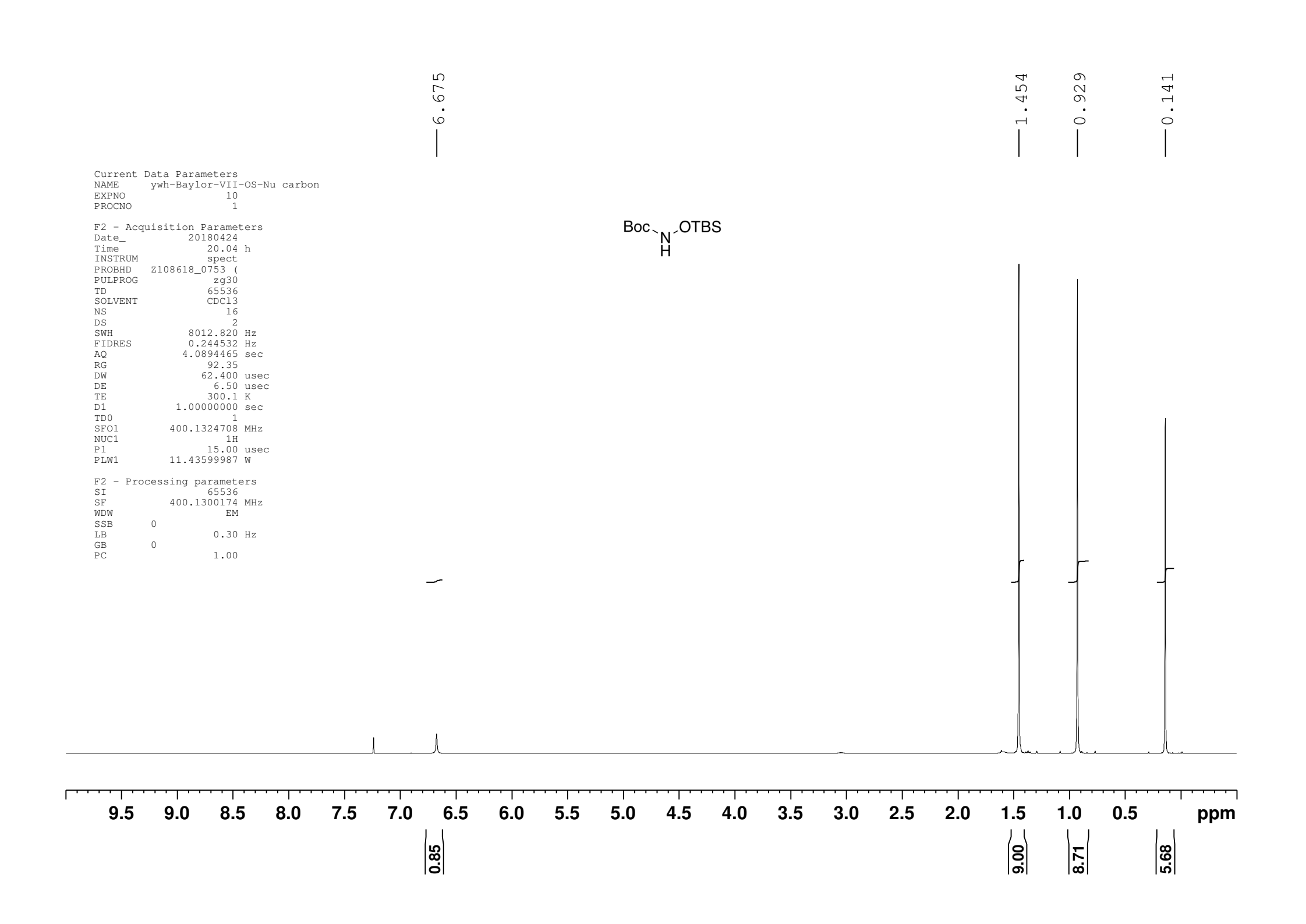
Claudia Murar was born in Deva, Romania in 1988. She moved for her studies to France where she studied chemistry at the National Institute of Applied Sciences (INSA), Rouen (France). She worked for one year at GSK, King of Prussia (USA) after which she completed her master thesis at Novartis, Basel (Switzerland). She joined the group of Prof. Jeffrey Bode at ETH Zurich in 2012 for her Ph.D. Her research focuses on the total chemical synthesis of hormone proteins and therapeutic proteins, development of new building blocks for chemical ligation and synthesis of unnatural amino acids.

Hikaru Takano was born in Nagasaki, Japan in 1989. He received his B.Eng. degree in 2012 from Saitama University (Prof. Katsukiyo Miura). He then moved to Tokyo Medical and Dental University and is currently pursuing his Ph.D. degree under the supervision of Prof. Hirokazu Tamamura (2012-present). His current research focuses on the development of chemical probes, especially fluorescent dyes, photolabile protecting groups and caged compounds.

Jeffrey Bode is Professor of Synthetic Organic Chemistry at ETH Zürich. In addition, he serves as an Executive Editor for the *Encyclopedia of Reagents for Organic Synthesis*, co-Editor in Chief of *Helvetica Chimica Acta*, and a Principal Investigator at the *Institute of Transformative bio-Molecules (ITbM)* at Nagoya University in Japan. His research group focuses on the development of new reactions, including methods for *N*-heterocycles, chemical protein synthesis, bioconjugation, and chemical biology.

Jacob C. Timmerman graduated from the University of North Carolina at Chapel Hill in 2012 with a B.A. in Chemistry. Later in 2012, Jacob began his graduate studies at Duke University under the advisement of Professor Ross A. Widenhoefer where his research focused on the development and mechanistic studies of gold(I)-catalyzed hydrofunctionalization reactions of alkenes. After completing his Ph.D. in 2017, Jacob joined the laboratories of Professor John L. Wood as a postdoctoral research associate where his research focuses on the total synthesis of natural products.

Yu-Wen Huang was born in Hsinchu, Taiwan (R.O.C.) in 1982. He received his bachelor's degree from National Cheng Kung University in 2005. He then joined the M.S. program at the National Tsing Hua University working under the supervision of Professor Shang-Cheng Hung on carbohydrate synthesis. In 2016, he received his Ph.D. degree from the University of Rochester where he worked with Professor Alison J. Frontier on 1,6-conjugate addition initiated Nazarov reactions and sequential 1,5-hydride transfer chemistry. He is currently a post-doctoral fellow in the CPRIT lab (Baylor University) with Professor John L. Wood working on the total synthesis of natural products.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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 92.35
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DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324708 MHz
NUC1 1H
P1 15.00 usec
PLW1 11.43599987 W
F2 - Processing parameters
SI 65536
SF 400.1300174 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Boc
N
H
OTBS
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 ppm
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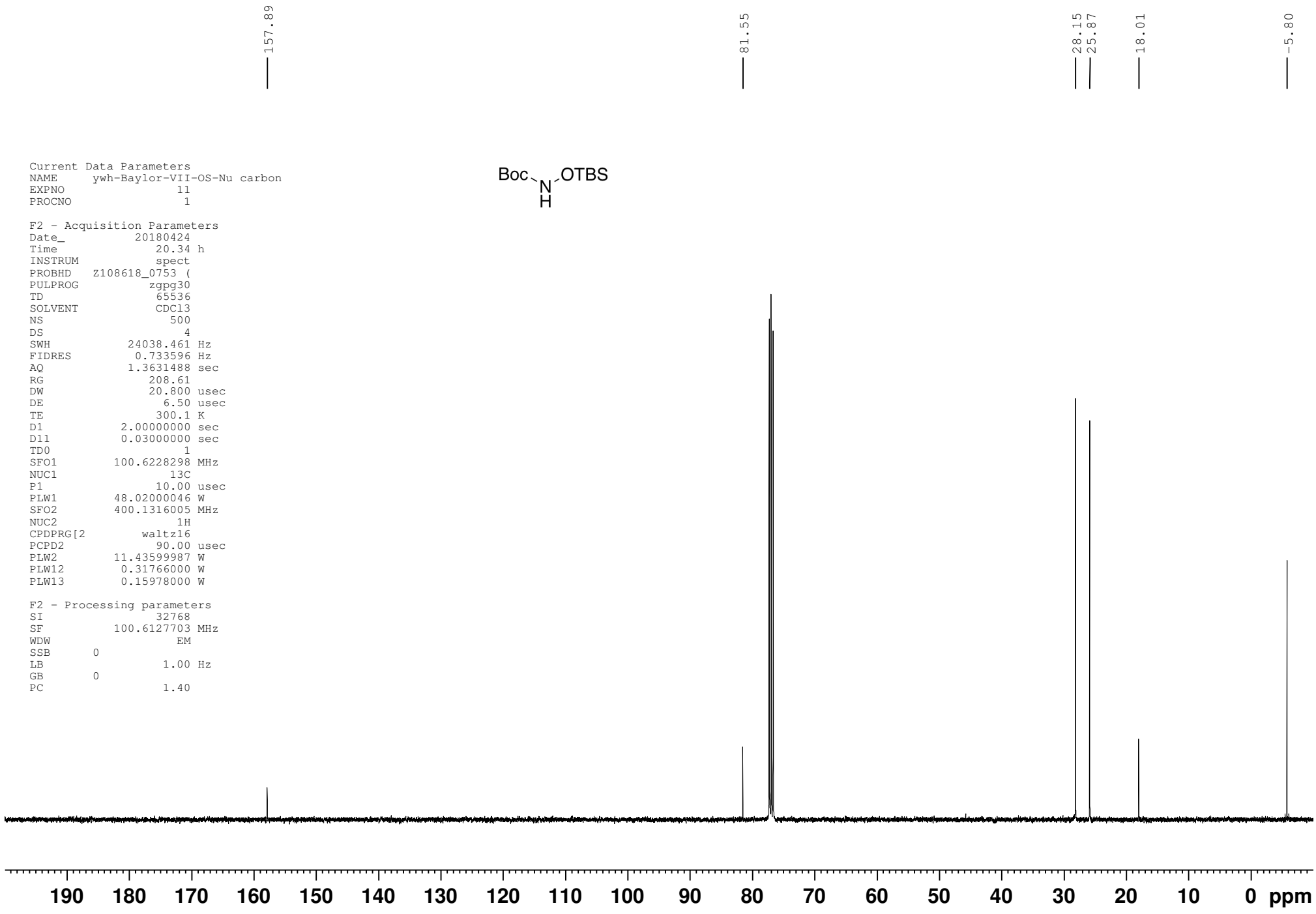
9.00
8.71
5.68

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EXPNO                 11
PROCNO                 1

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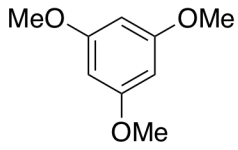
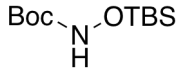
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  500
DS                    4
SWH           24038.461 Hz
FIDRES         0.733596 Hz
AQ            1.3631488 sec
RG               208.61
DW               20.800 usec
DE                6.50 usec
TE               300.1 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1
SFO1        100.6228298 MHz
NUC1                13C
P1                10.00 usec
PLW1        48.02000046 W
SFO2        400.1316005 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             90.00 usec
PLW2        11.43599987 W
PLW12        0.31766000 W
PLW13        0.15978000 W

F2 - Processing parameters
SI                32768
SF          100.6127703 MHz
WDW                 EM
SSB      0
LB                1.00 Hz
GB       0
PC                1.40
```

$$wt\% = \frac{15.6\ mg\ x\ 247.4100\ x\ 0.99}{20.9\ mg\ \text{x}\ 168.19}\ x\ \frac{(8.2707+7.8898)/18}{(3.0000+9.0080)/12} = 97.53\%$$



internal standard
(99% purity)

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PROCNO                 1

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TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH             8012.820 Hz
FIDRES          0.244532 Hz
AQ              4.0894465 sec
RG                  66.8
DW                62.400 usec
DE                 6.50 usec
TE                300.1 K
D1          30.00000000 sec
TD0                    1
SFO1        400.1324708 MHz
NUC1                  1H
P1                15.00 usec
PLW1        11.43599987 W

F2 - Processing parameters
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SF          400.1300745 MHz
WDW                   EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
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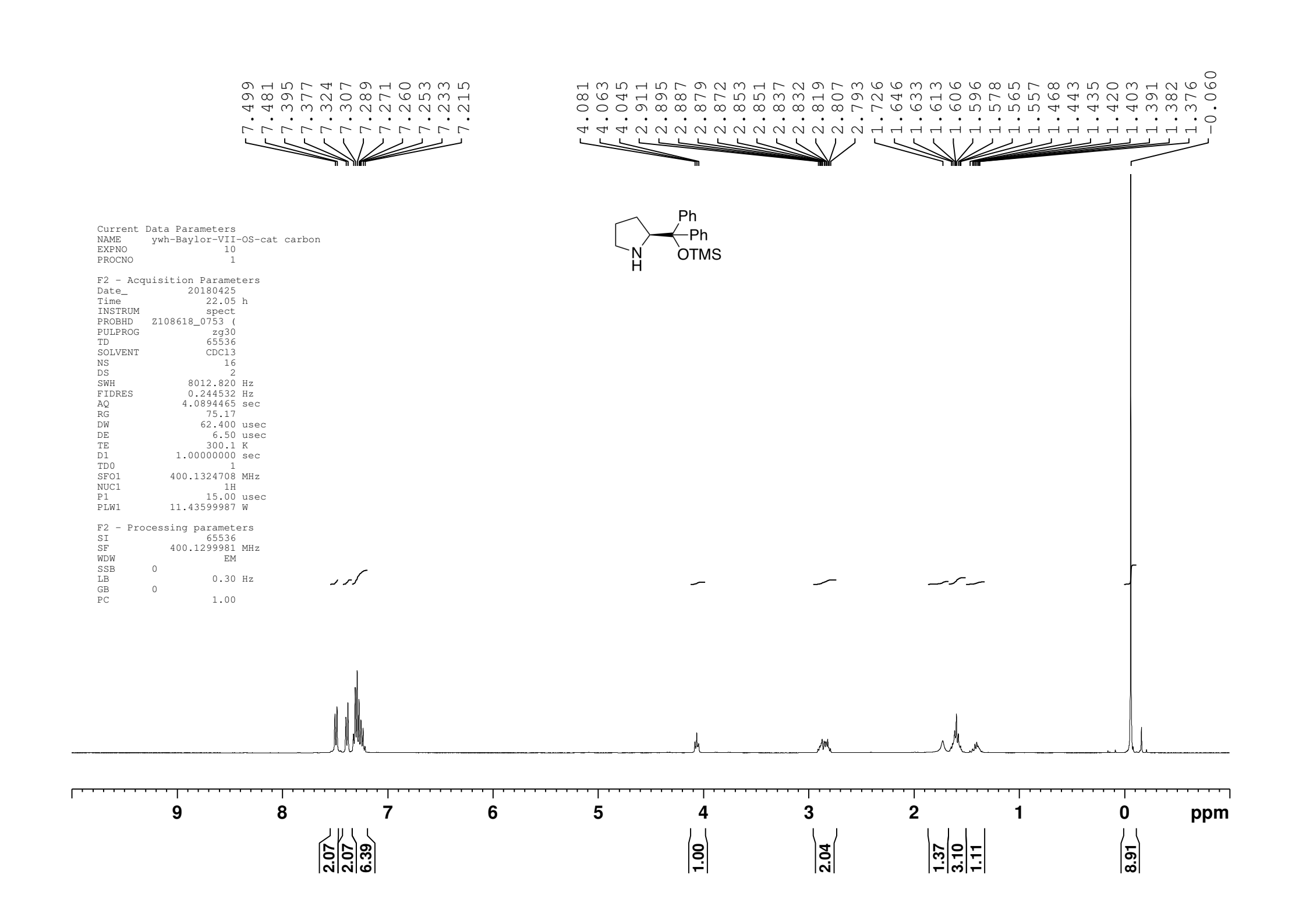
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7.271
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7.253
7.233
7.215
4.081
4.063
4.045
2.911
2.895
2.887
2.879
2.872
2.853
2.851
2.837
2.832
2.819
2.807
2.793
1.726
1.646
1.633
1.613
1.606
1.596
1.578
1.565
1.557
1.468
1.443
1.435
1.420
1.403
1.391
1.382
1.376
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Ph
Ph
OTMS
N
H
Current Data Parameters
NAME ywh-Baylor-VII-OS-cat carbon
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180425
Time 22.05 h
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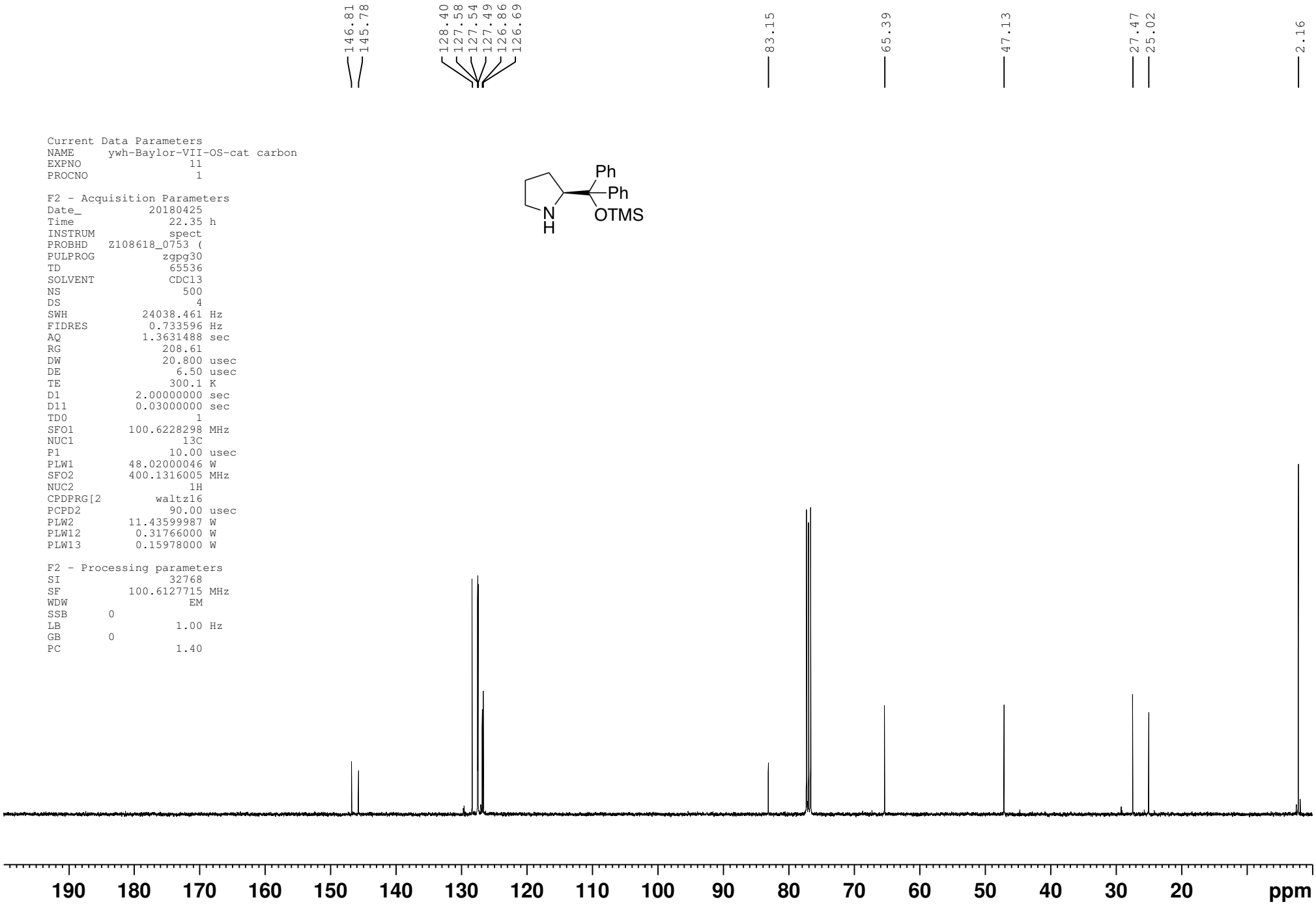
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 75.17
DW 62.400 usec
DE 6.50 usec
TE 300.1 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324708 MHz
NUC1 1H
P1 15.00 usec
PLW1 11.43599987 W
F2 - Processing parameters
SI 65536
SF 400.1299981 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9
8
7
6
5
4
3
2
1
0
ppm
2.07
2.07
6.39
1.00
2.04
1.37
3.10
1.11
8.91


146.81
145.78
128.40
127.58
127.54
127.49
126.86
126.69
83.15
65.39
47.13
27.47
25.02
2.16
Current Data Parameters
NAME ywh-Baylor-VII-OS-cat carbon
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180425
Time 22.35 h
INSTRUM spect
PROBHD Z108618_0753 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 500
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 208.61
DW 20.800 usec
DE 6.50 usec
TE 300.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6228298 MHz
NUC1 13C
P1 10.00 usec
PLW1 48.02000046 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 90.00 usec
PLW2 11.43599987 W
PLW12 0.31766000 W
PLW13 0.15978000 W
F2 - Processing parameters
SI 32768
SF 100.6127715 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
Ph
Ph
OTMS
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H
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180
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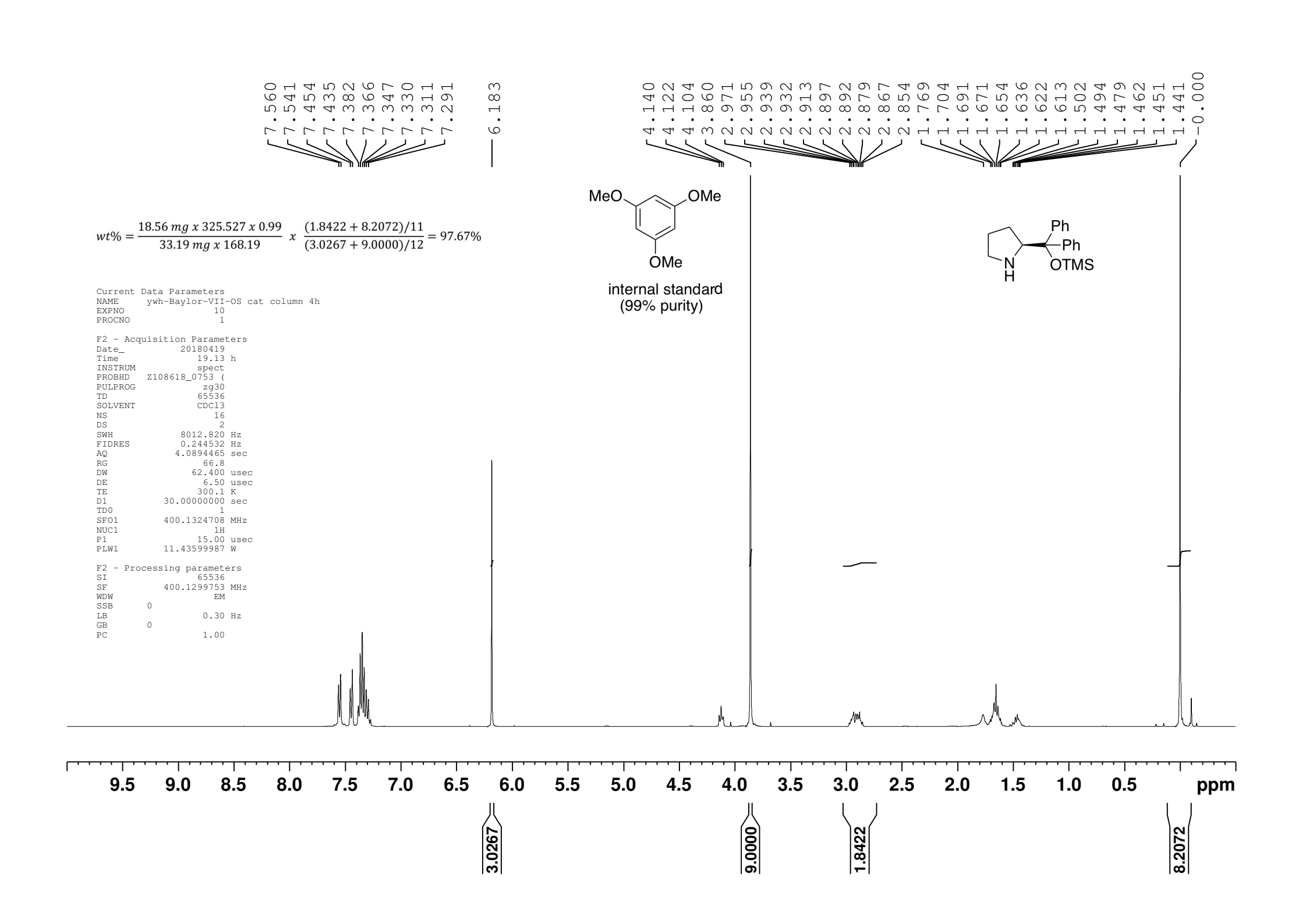
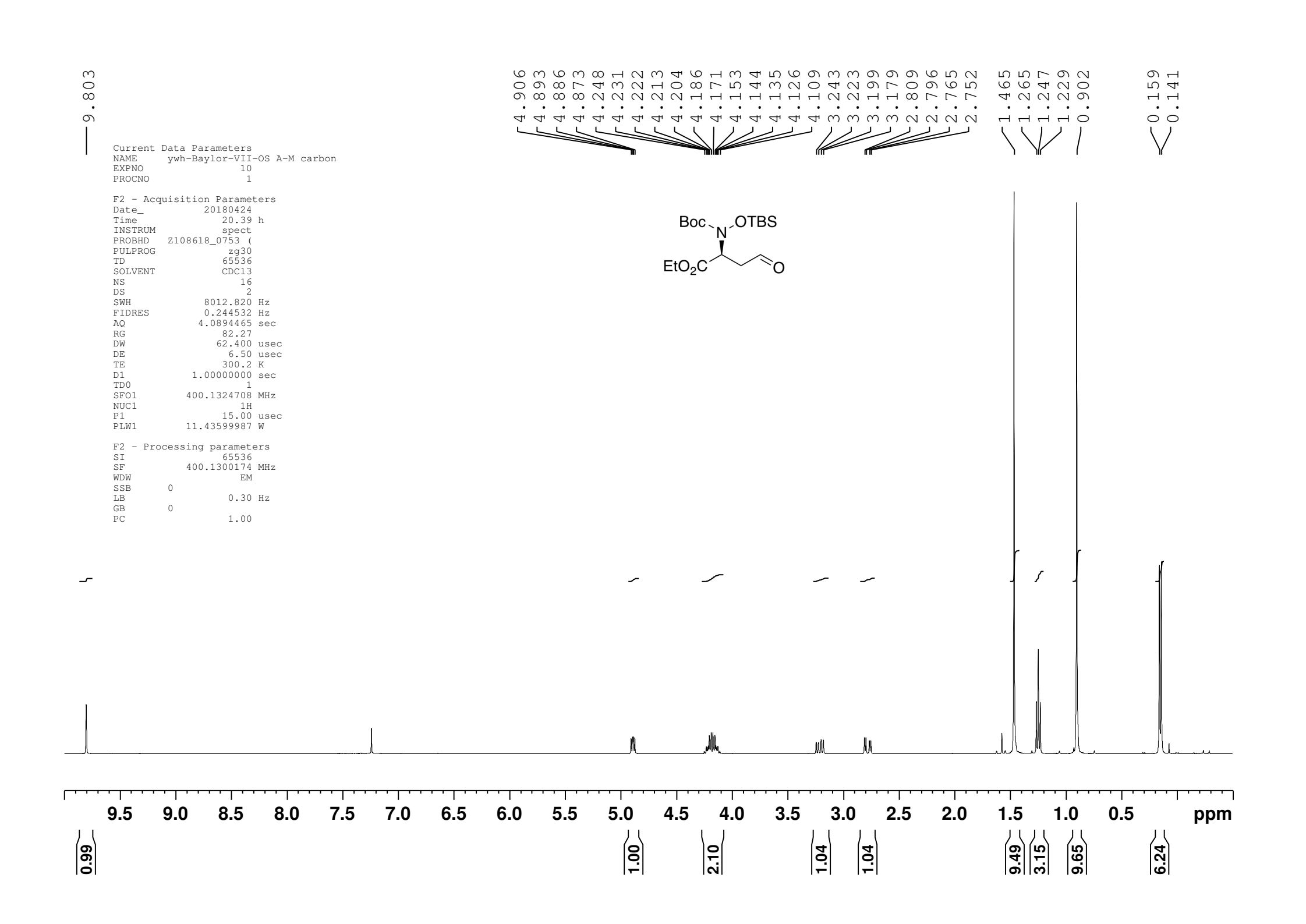
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.560
7.541
7.454
7.435
7.382
7.366
7.347
7.330
7.311
7.291
6.183
4.140
4.122
4.104
3.860
2.971
2.955
2.939
2.932
2.913
2.897
2.892
2.879
2.867
2.854
1.769
1.704
1.691
1.671
1.654
1.636
1.622
1.613
1.502
1.494
1.479
1.462
1.451
1.441
0.000
$wt\% = \frac{18.56\ mg\ x\ 325.527\ x\ 0.99}{33.19\ mg\ x\ 168.19}\ x\ \frac{(1.8422 + 8.2072)/11}{(3.0267 + 9.0000)/12} = 97.67\%$
MeO
OMe
OMe
internal standard
(99% purity)
Ph
Ph
OTMS
N
H
Current Data Parameters
NAME ywh-Baylor-VII-OS cat column 4h
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180419
Time 19.13 h
INSTRUM spect
PROBHD Z108618_0753 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 66.8
DW 62.400 usec
DE 6.50 usec
TE 300.1 K
D1 30.00000000 sec
TD0 1
SFO1 400.1324708 MHz
NUC1 1H
P1 15.00 usec
PLW1 11.43599987 W
F2 - Processing parameters
SI 65536
SF 400.1299753 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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
ppm
3.0267
9.0000
1.8422
8.2072


9.803
4.906
4.893
4.886
4.873
4.248
4.231
4.222
4.213
4.204
4.186
4.171
4.153
4.144
4.135
4.126
4.109
3.243
3.223
3.199
3.179
2.809
2.796
2.765
2.752
1.465
1.265
1.247
1.229
0.902
0.159
0.141
Current Data Parameters
NAME ywh-Baylor-VII-OS A-M carbon
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180424
Time 20.39 h
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PROBHD Z108618_0753 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 4.0894465 sec
RG 82.27
DW 62.400 usec
DE 6.50 usec
TE 300.2 K
D1 1.00000000 sec
TD0 1
SFO1 400.1324708 MHz
NUC1 1H
P1 15.00 usec
PLW1 11.43599987 W
F2 - Processing parameters
SI 65536
SF 400.1300174 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Boc
N
OTBS
EtO2C
O
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 ppm
0.99
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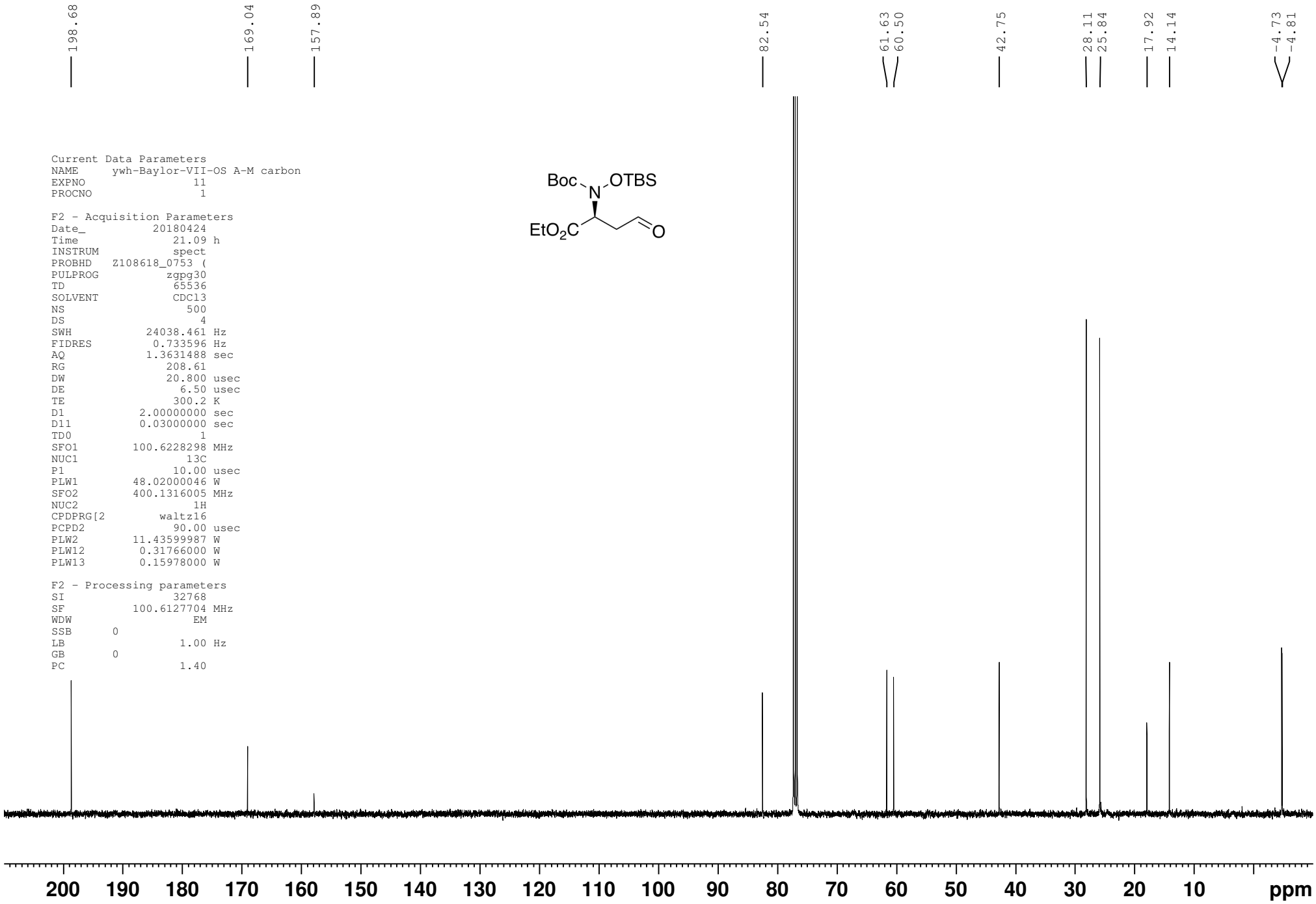
2.10
1.04
1.04
9.49
3.15
9.65
6.24

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PROCNO                  1

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PULPROG           zgpg30
TD                 65536
SOLVENT             CDCl3
NS                    500
DS                      4
SWH            24038.461 Hz
FIDRES          0.733596 Hz
AQ             1.3631488 sec
RG                208.61
DW                20.800 usec
DE                 6.50 usec
TE                300.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                     1
SFO1         100.6228298 MHz
NUC1                 13C
P1                 10.00 usec
PLW1         48.02000046 W
SFO2         400.1316005 MHz
NUC2                 1H
CPDPRG[2         waltz16
PCPD2              90.00 usec
PLW2         11.43599987 W
PLW12         0.31766000 W
PLW13         0.15978000 W

F2 - Processing parameters
SI                 32768
SF           100.6127704 MHz
WDW                  EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
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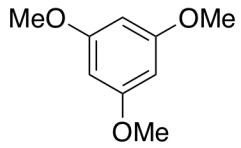
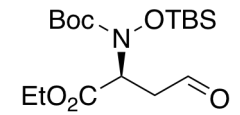
$$wt\% = \frac{16.40\ \text{mg} \times 375.54 \times 0.99}{31.09\ \text{mg} \times 168.19} \times \frac{(7.4562+7.7382)/18}{(3.0000+8.9929)/12} = 98.49\%$$



internal standard
(99% purity)

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EXPNO                   10
PROCNO                   1

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PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      16
DS                       2
SWH              8012.820 Hz
FIDRES           0.244532 Hz
AQ               4.0894465 sec
RG                   50.62
DW                 62.400 usec
DE                  6.50 usec
TE                  300.1 K
D1           30.00000000 sec
TD0                      1
SFO1         400.1324708 MHz
NUC1                   1H
P1                 15.00 usec
PLW1         11.43599987 W

F2 - Processing parameters
SI                   65536
SF           400.1300174 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```