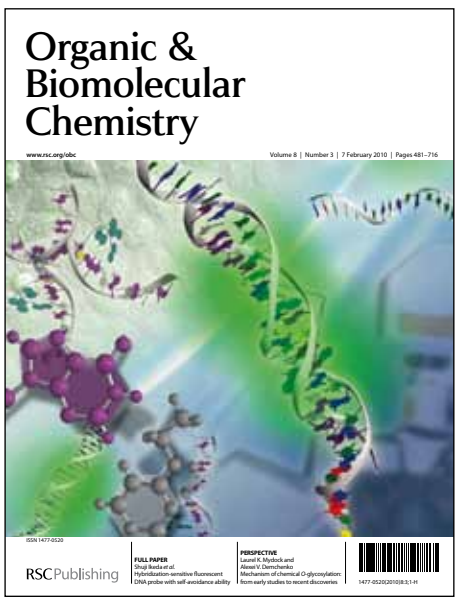
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Fang and C. Chen, *Org. Biomol. Chem.*, 2013, DOI: 10.1039/C3OB41622D.



This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

View Article Online
DOI: 10.1039/C3OB41622D

Synthesis of Oseltamivir and Tamiphosphor from *N*-Acetyl-D-glucosamine

Chih-An Chen[a] and Jim-Min Fang*[ab]

[a]*Department of Chemistry, National Taiwan University, Taipei 106, Taiwan. E-mail*: jmfang@ntu.edu.tw; *Fax: (8862) 23637812; Tel: (8862) 33661663*

[b]*The Genomics Research Center, Academia Sinica, Taipei, 115, Taiwan.*

† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C, ^{31}P and 2D NMR spectra. See DOI:

View Article Online
DOI: 10.1039/C3OB41622D

Abstract

Using *N*-acetyl-D-glucosamine as a starting material, the anti-influenza drugs oseltamivir and tamiphosphor were synthesized via a pivotal intermediate of aldehyde **8**. An intramolecular Horner–Wadsworth–Emmons reaction was utilized to construct the highly functionalized cyclohexene ring. The existing *N*-acetyl group was transformed into an azido group for the subsequent aziridination, followed by implantation of a 3-pentoxy group in the desired stereochemistry.

View Article Online
DOI: 10.1039/C3OB41622D

Introduction

Influenza has been a long-standing health threat to human. In addition to season's influenza epidemics, emergence of new influenza strains may become global pandemics and claims enormous number of lives as that occurred in Spanish flu (H1N1, 1918), Asian flu (H2N2, 1957), Hong Kong flu (H3N2, 1968), bird flu (H5N1, 2003), swine flu (H1N1, 2009), and the recent flu transmission from avian to human (H7N9, 2013). Influenza virus is a negative-sense single-strain RNA virus of the Orthomyxoviridae family.[1] There are 8 pieces of segmented RNA in influenza virus for production of 11 proteins, among which hemagglutinin (HA), neuraminidase (NA) and M2 channel proteins are located on the surface of virus.[2, 3] Use of amantadine and rimantadine in treatment of influenza infection is limited due to the high drug resistance of these M2 channel blockers.[4–6] At present, the most effective anti-influenza drugs are NA inhibitors[7–10] including zanamivir,[11, 12] oseltamivir (**1** in Figure 1),[13, 14] peramivir[15, 16] and laninamivir[17, 18]. Tamiflu®, the phosphate salt of oseltamivir, is currently the most popular orally available drug for influenza treatment. However, oseltamivir-resistant viruses have emerged over the years due to the extensive use of oseltamivir in influenza therapy. Oseltamivir is converted by endogenous esterase to the active carboxylate, which with three arginine residues (Arg118, Arg292 and Arg371) in the active site of NA.[19–21] We

View Article Online
DOI: 10.1039/C3OB41622D

have previously found that tamiphosphor[22, 23] (**2** in Figure 1), designed by replacement of the carboxylate group in oseltamivir with a phosphonate group, showed better NA inhibition, presumably due to the stronger electrostatic interactions of the phosphonate group with the three arginine residues in the active site of influenza NA. The cell-based assays and mouse tests[23] further indicate that tamiphosphor is a potent anti-influenza agent to improve the survival rate of mice challenged by lethal doses of avian (H5N1) and human (H1N1) viruses including the oseltamivir-resistant strain.

The current industrial synthesis of oseltamivir is originally designed by Kim and coworkers in Gilead,[24] and then developed by the research teams in Roche using naturally occurring shikimic acid as a starting material.[25, 26] This industrial process was further by Karpf and coworkers.[27, 28] To cope with the potential need of large quantity of oseltamivir during influenza pandemics, chemists have also devised various methods for the synthesis of oseltamivir without using shikimic acid.[29, 30] In contrast, only a few methods are reported for the synthesis of tamiphosphor.[22, 31–33] Carbohydrates are abundant and inexpensive natural source of chiral molecules suitable for construction of the scaffold of highly functionalized cyclohexene ring in oseltamivir and tamiphosphor. For example, the total synthesis of oseltamivir has been achieved by using D-glucose,[34] D-glucal,[35] D-mannose,[36, 37] D-mannitol,[38]

View Article Online
DOI: 10.1039/C3OB41622D

and D-ribose[39] as the starting materials, and we have utilized D-xylose as a starting material the synthesis of both oseltamivir and tamiphosphor.[22] In a different approach to tamiphosphor, Streicher's group[32] and Gunasekera[33] have converted the carboxylic acid group in oseltamivir derivatives to iodine and bromine atoms by Hunsdiecker–Barton halodecarboxylation, and subsequently carried out the palladium-catalyzed phosphonylation[31, 40] to furnish tamiphosphor.

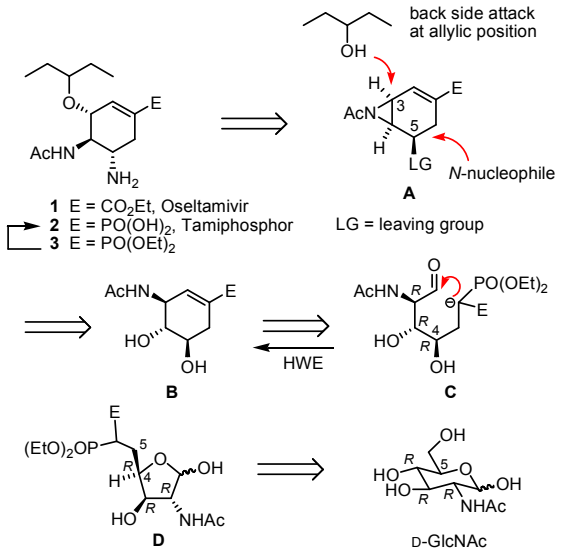


Figure 1 Retrosynthetic analysis of oseltamivir (**1**) and tamiphosphor (**2**)

We report herein the syntheses of oseltamivir and tamiphosphor using D-GlcNAc as a starting material (Figure 1). Our retrosynthetic analysis shows that aziridine **A** can be a good

View Article Online
DOI: 10.1039/C3OB41622D

candidate for implantation of pentan-3-ol and amino groups in the desired stereochemistry at the 3- and 5-positions, respectively. Intermediate **B** having three substituents in all-*trans* configuration on the cyclohexene core structure can be constructed by an intramolecular Horner–Wadsworth–Emmons (HWE) reaction[41] of compound **C**, which can exist as a furanoside tautomer **D**. Thus, D-GlcNAc appears to be an appropriate chiral-pool precursor for the synthesis of oseltamivir and tamiphosphor. This approach is evolved from an idea using the existing acetamido group of D-GlcNAc to construct aziridine **A** in the desired stereochemistry, and to avoid extra steps for introduction of acetamido group in our previous synthesis using D-xylose.[22] Thus, the syntheses of oseltamivir and tamiphosphor are expected to be accomplished in a straightforward manner with reduced synthetic steps.

Results and discussion

Scheme 1 shows a synthesis of oseltamivir from D-GlcNAc. The reaction of D-GlcNAc with acetone in the presence of $Et_2O{:}BF_3$ gave oxazolidine **4**.[42] This reaction was considered to proceed with an initial acetalization of the terminal 5,6-diol to form a furanose derivative, which was then promoted by Lewis acid to give an oxonium ion intermediate **E** for the intramolecular reaction with the adjacent acetamide group. Compound **4** was treated with

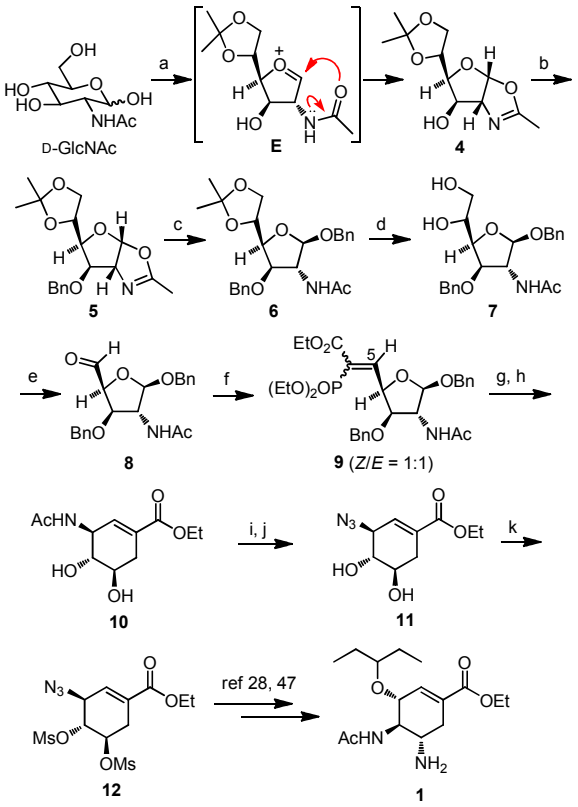
View Article Online
DOI: 10.1039/C3OB41622D

BnBr under basic condition to give the benzyl ether **5**.[43] Treatment of **5** with benzyl alcohol in the presence of a TFA catalyst afforded the β-anomer of benzyl furanoside **6** as the exclusive product in 80% yield. After deacetalization, the NOESY spectrum of diol product **7** showed the correlation of β-anomeric proton (H-1) with the adjacent acetamido proton (AcNH). Diol **7** was subjected to an oxidative cleavage by $NaIO_4$ to give aldehyde **8**, which underwent Knoevenagel condensation with triethyl phosphonoacetate in the presence of $TiCl_4$ and Et_3N to give compound **9**.[44, 45] Such Knoevenagel condensation could not be realized in conventional conditions using piperidine/HOAc, NH_4OAc or NaH, presumably due to the low nucleophilicity of the anion of triethyl phosphonoacetate. Compound **9** contained the *E*- and *Z*-isomers in a ratio of 1:1. As shown in ^1H–^1H COSY spectrum, the *E*-isomer having H-5 on the same side of phosphonate group occurred at δ_H 7.67 with a relatively small coupling constant ($J_{H–P}$ = 14.5 Hz), whereas the *Z*-isomer having H-5 on the opposite side of phosphonate group appeared at δ_H 7.23 with a large coupling constant ($J_{H–P}$ = 46.0 Hz).[45] Catalytic hydrogenation of **9** rendered a simultaneous debenzylation and saturation of the C=C bond to provide a lactol (structure **D** in Scheme 1, E = CO_2Et), which readily tautomerized in basic conditions to form an aldehyde intermediate for intramolecular HWE reaction,[41] giving the product of cyclohex-1-enecarboxylate **10**. As the scaffold of

View Article Online
DOI: 10.1039/C3OB41622D

polysubstituted cyclohexene ring was constructed, elaboration of substituents by functional-group transformations was executed. The acetamido group in **10** was first hydrolyzed in refluxing HCl–EtOH solution (1 M), and the intermediate product of amine was subsequently treated with imidazole-1-sulfonyl azide[46] in the presence of $CuSO_4$ and K_2CO_3 to give an azide **11** in 81% yield. Diol **11** was smoothly converted to the dimesylated derivative **12**, which has been transformed into aziridine **A** (LG = MsO and E = CO_2Et) for the synthesis of (–)-oseltamivir.[28, 47] We thus accomplished a formal synthesis of oseltamivir from D-GlcNAc.

View Article Online
DOI: 10.1039/C3OB41622D



Scheme 1 Synthesis of (–)-Oseltamivir from D-GlcNAc. *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, acetone, reflux, 20 min; 59%; (b) BnBr, NaH, DMF, 0 °C to rt, 2 h; 91%; (c) cat. TFA, BnOH, rt, 12 h; 80%; (d) 70% HOAc–H_2O, rt, 12 h; 95%; (e) $NaIO_4$, acetone, H_2O, 0 °C, 3 h, 96%; (f) $EtO_2CCH_2PO(OEt)_2$, $TiCl_4$, NEt_3, THF, 0 °C, 1 h; 76%; (g) Pd/C, H_2, EtOH, rt, 24 h; (h) NaH, THF, 0 °C, 1 h; 62% yield of **10** (from **9**); (i) HCl–EtOH (1 M), reflux, 12 h; (j) imidazole-1-sulfonyl azide, K_2CO_3, $CuSO_4{\cdot}5H_2O$, EtOH, rt, 2 h; 81% yield of **11** (from **10**); (k) MsCl, NEt_3, EtOAc, 0 °C, 2 h; 85%.

During this study, we have encountered several unexpected hurdles. In the beginning, we

View Article Online
DOI: 10.1039/C3OB41622D

planned to introduce triethyl phosphonoacetate moiety via the substitution reaction of mesylate **15** (Figure 2). Thus, compound **13** was subjected to an oxidative cleavage with $NaIO_4$, followed by reduction with $NaBH_4$, to give **14**. The selective mono-mesylation of the primary hydroxyl group in **14** was accomplished by using a stoichiometric amount of MsCl at 0 ^oC in the presence of Et_3N to provide mesylate **15**. However, several attempts to substitute the mesyl group of **15** with the anion of triethyl phosphonoacetate in THF solution failed, even in the presence of 15-crown-5.[41] Under such conditions, an intramolecular S_N2 reaction by the adjacent 3-OH group might occur to give an oxetane product, of which structure was inferred from the ^1H NMR and MS spectra of the crude reaction mixture. Alternatively, the mesylate **17** and its triflate analog with the 3-OH protected as benzyl ether were prepared from alcohol **16**. However, the nucleophilic substitution reactions with triethyl phosphonoacetate also failed in various reaction conditions (in THF or DMF solution with or without 15-crown-5, 25–70 ^oC, 12–24 h).[22, 48]

Our initial plan was to take advantage of the existing acetamido group to transform D-GlcNAc into aziridine **A** for an azide-free synthesis of oseltamivir. Thus, diol **10** was activated as the dimesylate derivative **18**, and treated with base (e.g., NaH, LDA, KHMDS and DMAP) in attempt to render the intramolecular substitution reactions to generate the

View Article Online
DOI: 10.1039/C3OB41622D

N-acetylaziridine product. Instead, we obtained ethyl 3-acetamidobenzoate (**19**)[47, 49] in such basic conditions due to elimination of two MsOH molecules from **18**. Alternatively, dimesylate **23** having *t*-BocNH substituent at the C-3 position was prepared from compound **9** via a five-step sequence: (i) treatment of **9** with Boc_2O to give **20**, (ii) Michael-type reduction of **20** with $NaBH_4$ to give **21**, (iii) debenzylation of **21** by catalytic hydrogenation to give a lactol, (iv) intramolecular HWE reaction of the lactol to afford cyclohexene-1-carboxylate **22**, and (v) dimesylation with excess MsCl to give **23**. After removal of the *t*-Boc group from **23**, the amine intermediate in THF solution was treated with Et_3N in order to form the desired aziridine product. Again, only ethyl 3-acetamidobenzoate (**19**) was obtained by elimination reactions. It was interesting to note that an unexpected product of cyclic carbamate **24** was obtained when the reaction was performed in aqueous media (e.g., EtOH–H_2O or CH_3CN–H_2O solution) with excess $NaHCO_3$ instead of Et_3N.

View Article Online
DOI: 10.1039/C3OB41622D

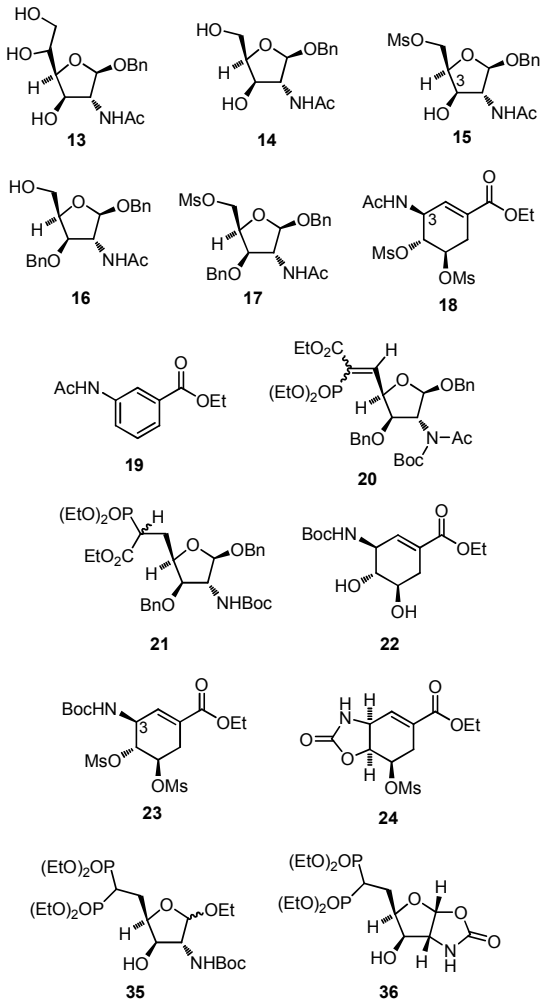


Figure 2 Chemical structures of side products **13**–**24**, **35** and **36**.

For the synthesis of tamiphosphor, aldehyde **8** was reacted with tetraethyl methylenediphosphonate in the presence of $TiCl_4$ and Et_3N to give the condensation product **25** (Scheme 2).[44, 45] By a procedure similar to that for cyclohexene-1-carboxylate **10**, diphosphonate **25** was subjected to catalytic hydrogenation, followed by treatment with NaH to furnish the intramolecular HWE reaction, giving cyclohexene-1-phosphonate **28a**.

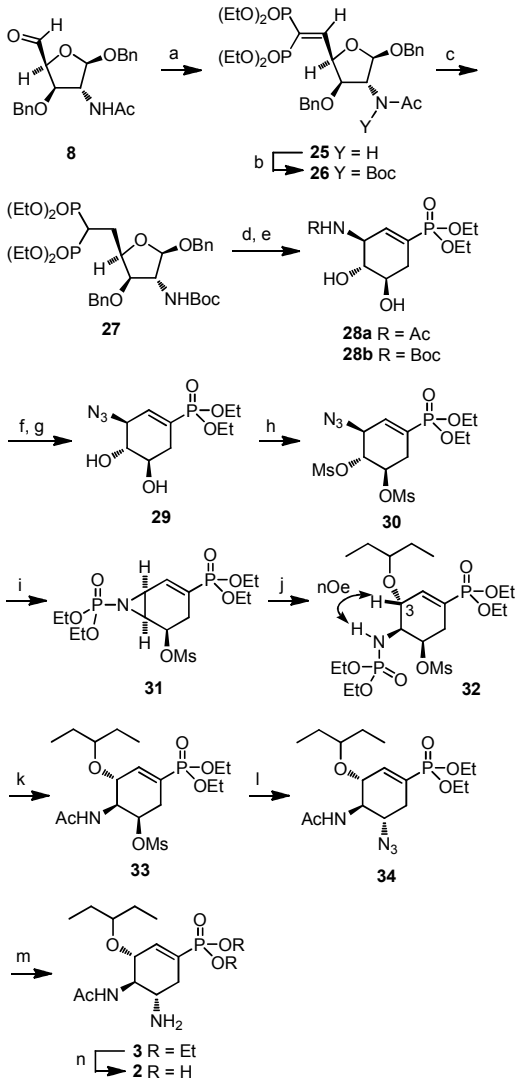
View Article Online
DOI: 10.1039/C3OB41622D

However, this transformation also yielded an unidentified side product, which could not be separated from **28a**. Attempts to improve the HWE reaction by using different bases (e.g., K_2CO_3, NaOEt and $Et_3N/MgBr_2$) in various conditions failed to give a clean cyclization product **28a**. Alternatively, we treated **25** with Boc_2O in the presence of DMAP to give the derivative **26**. Because saponification of **26** with K_2CO_3 in EtOH often caused undesired double bond migration, we thus utilized $NaBH_4$ reduction to remove the acetyl group, giving **27** by concurrent saturation of the C=C double bond in aqueous EtOH solution. In an attempt to remove benzyl groups by catalytic hydrogenation in EtOH solution, we unexpectedly obtained appreciable amounts of ethyl glycoside **35** and cyclic carbamate **36** (Figure 2) in addition to the desired lactol product. Fortunately, the catalytic hydrogenation was successfully conducted in THF solution to remove both benzyl groups. Thus, the subsequent intramolecular HWE reaction was carried out to give a pure cyclization product **28b** (53% yield from **27**) after chromatography on a silica gel column. The *t*-Boc group in **28b** was removed by TFA, and azide **29** was prepared by reaction with imidazole-1-sulfonyl azide. Compound **29** was subjected to mesylations with excess MsCl, and the dimesylated product **30** was treated with a freshly distilled $(EtO)_3P$ in anhydrous toluene solution to give a phosphoryl aziridine **31**.[28] If the purchased $(EtO)_3P$ reagent was used without prior distillation,

View Article Online
DOI: 10.1039/C3OB41622D

the reaction with azide **30** would afford a phosphonamide product.[50] Attempt to convert **30** by using Staudinger reaction[47] with Ph_3P to an unprotected aziridine product failed. The phosphoryl aziridine **31** was selectively attacked at the allylic position by pentan-3-ol in the presence of $BF_3{\cdot}Et_2O$ to furnish phosphonamide **32**, which was heated in H_2SO_4–EtOH solution (3 M) under reflux for 4 h to give the corresponding amine product. The NOESY spectrum of **32** supported the correlation of H-3 with NH on the same face. The amino group was subjected to acetylation, and the product **33** underwent an S_N2 reaction with sodium azide to replace the mesyloxy group at the C-5 position, giving compound **34**. Reduction of the azido group, followed by treatment with trimethylsilyl bromide, culminated in the synthesis of (–)-tamiphosphor.[22]

View Article Online
DOI: 10.1039/C3OB41622D



Scheme 2 Synthesis of (–)-tamiphosphor from D-GlcNAc. *Reagents and conditions*: (a) $H_2C[PO(OEt)_2]_2$, $TiCl_4$, NEt_3, 0 °C, 1 h; (b) Boc_2O, DMAP, reflux, 3 h; 32% yield of **26** (from aldehyde **8**); (c) $NaBH_4$, EtOH, H_2O, 0 °C to rt, 12 h; quantitative; (d) Pd/C, H_2, THF, rt, 24 h; (e) NaH, THF, 0 °C, 1 h; 53% of **28b** from **27**; (f) for **28a**, HCl–EtOH (1 M), reflux, 12 h; for **28b**, TFA, CH_2Cl_2, rt, 2 h; (g) imidazole-1-sulfonyl azide, K_2CO_3, $CuSO_4{\cdot}5H_2O$, EtOH, rt, 2 h; 58% yield of **29** (from **28b**); (h) MsCl, NEt_3, EtOAc, 0 °C, 2 h; 84%; (i) $P(OEt)_3$,

View Article Online
DOI: 10.1039/C3OB41622D

anhydrous toluene, reflux, 1 h; 77%; (j) $BF_3 \cdot Et_2O$, 3-pentanol, rt, 16 h; 87%; (k) H_2SO_4–EtOH (3 M), 70 ^oC, 4 h; then pyridine, Ac_2O, 0 ^oC, 15 min; 80%; (l) NaN_3, DMF, 100 ^oC, 2 h; 85%; (m) H_2, Lindlar catalyst, EtOH, rt, 16 h; 85%; (n) TMSBr, $CHCl_3$, rt, 24 h; 85%.

Conclusion

Even though the syntheses of oseltamivir and tamiphosphor from D-GlcNAc were not as straightforward as shown in our initial plan (Figure 1), we have finally overcome hurdles to complete the target syntheses. The intramolecular HWE reaction was applied to construct the scaffold of polysubstituted cyclohexenes. It was not reliable to introduce phosphonoacetate and diphosphorylmethyl moieties by the substitution reactions of triflate or mesylate compounds (e.g., **15**). The better resolution was to perform Knoevenagel reactions of aldehyde **8** followed by Michael-type reduction with $NaBH_4$. In the previous routes to oseltamivir and tamiphosphor from D-xylose[22] or D-glucose[34], extra steps are needed to introduce acetamido group and to invert some chiral centers. We thought that D-GlcNAc might be a better starting material because its absolute configuration is preset to manipulate the required stereochemistry in oseltamivir and tamiphosphor. Unfortunately, our experiments

View Article Online
DOI: 10.1039/C3OB41622D

revealed that the devised direct aziridination of dimesylated compounds (e.g., **18** and **23**) with the adjacent NHAc, NHBoc or NH_2 groups could not be realized as our anticipation for azide-free synthesis. In the long run, we still needed to prepare the dimesylated compounds **12** and **30** with an adjacent azido group for the subsequent aziridination. The problems and resolutions encountered in our study may be learned when one will design new methods for the synthesis of oseltamivir and tamiphosphor bearing the highly functionalized cyclohexene ring.

Experimental

General

All the reagents and solvents were reagent grade and were used without further purification unless otherwise specified. All solvents were anhydrous grade unless indicated otherwise. CH_2Cl_2 was distilled from CaH_2. All non-aqueous reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Reactions were magnetically stirred and monitored by thin-layer chromatography on silica gel using aqueous *p*-anisaldehyde and phosphomolybdic acid as visualizing agents. Silica gel (0.040–0.063 mm particle sizes) and reversed-phase RP-18 (0.040–0.063 mm particle sizes)

View Article Online
DOI: 10.1039/C3OB41622D

were used for column chromatography. Flash chromatography was performed on silica gel of 60–200 μm particle size. Molecular sieves were activated under high vacuum at 220 ^{o}C over 6 h.

Melting points were recorded in open capillaries and are not corrected. Optical rotations were measured on digital polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Nuclear magnetic resonance (NMR) spectra were obtained on 400 MHz spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to δ_H 7.24 / δ_C 77.0 (central line of t) for $CHCl_3/CDCl_3$, δ_H 4.80 for H_2O/D_2O, δ_H 3.31 / δ_C 48.2 for CD_3OD, or δ_H 2.49 / δ_C 39.5 for DMSO-d_6. The splitting patterns are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double of doublets) and br (broad). Coupling constants (*J*) are given in Hz. Distortionless enhancement polarization transfer (DEPT) spectra were taken to determine the types of carbon signals. The ESI–MS experiments were conducted on a high-resolution mass spectrometer.

2-Methyl-(1,2-dideoxy-5,6-*O*-isopropylidene-[2,1-*d*]-2-oxazoline) (4). Compounds **4** was prepared from D-GlcNAc according to the previously reported method.[42] To a suspension of 2-acetamido-2-deoxy-D-glucopyranose (GlcNAc, 21.0 g, 95 mmol) in anhydrous acetone

View Article Online
DOI: 10.1039/C3OB41622D

(300 mL) was added $BF_3{\cdot}Et_2O$ (37.8 mL, 285 mmol). The mixture was stirred at reflux for 20 min under an atmosphere of nitrogen, cooled in an ice-bath, and treated with triethylamine (140 mL). The mixture was added into a cold solution of sodium carbonate (60 g) in water (400 mL) with stirring. Acetone, triethylamine and some water were removed by rotary evaporation while the temperature of water bath was kept below 40 ^oC. The residue was extracted with Et_2O (300 mL × 4). The combined extracts were dried ($MgSO_4$) and concentrated by rotary evaporation while the temperature of water bath was kept below 40 ^oC to give compound **4** (13.7 g, 59% yield). $C_{11}H_{17}NO_5$; brownish syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.4; $[\alpha]^{25}_D$ –28.7 (*c* 4.2, EtOAc); IR ν_{max} (neat) 3377, 2987, 1666 (C=N), 1383, 1211, 1068, 918 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 6.11 (1 H, d, *J* = 4.8 Hz), 4.37 (1 H, d, *J* = 4.8 Hz), 4.31–4.25 (2 H, m), 4.07 (1 H, dd, *J* = 8.4, 6.4 Hz), 3.96 (1 H, dd, *J* = 8.8, 4.8 Hz), 3.68 (1 H, dd, *J* = 7.6, 2.0 Hz), 1.97 (3 H, s), 1.36 (3H , s), 1.29 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 109.4, 107.2, 81.8, 78.2, 74.3, 72.7, 67.3, 26.8, 25.1, 14.1; HRMS (ESI) calcd for $C_{11}H_{18}NO_5$: 244.1185, found: *m*/*z* 244.1185 $[M + H]^+$.

2-Methyl-(1,2-dideoxy-3-*O*-benzyl-5,6-*O*-isopropylidene-[2,1-*d*]-2-oxazoline) (5).

Compound **5** was prepared according to the previously reported method.[43] NaH (840 mg, 20.9

View Article Online
DOI: 10.1039/C3OB41622D

mmol; 60% dispersion in oil) was washed with hexane (2 ×) under an atmosphere of nitrogen, then compound **4** (3.38 g, 13.9 mmol) in anhydrous DMF (30 mL) was added dropwise at 0 ^{o}C. After 10 min, BnBr (1.83 mL, 15.3 mmol) was added dropwise into the suspension at 0 ^{o}C. The ice-bath was removed, and the mixture was stirred for 2 h at room temperature to give a pale yellow clear solution. MeOH was added to quench excess NaH, and the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 and water, dried ($MgSO_4$), filtered, and concentrated to give compound **5**, which was used in the next step without further purification. An analytical sample of **5** (4.22 g, 91%) was obtained by chromatography on a silica gel column (packed in EtOAc/hexane (1:3) containing 10% NEt_3) with elution of EtOAc/hexane (1:1) containing 3% NEt_3. $C_{18}H_{23}NO_5$; pale yellow syrup; TLC (EtOAc/hexane, 2:1) R_f = 0.5, $[\alpha]^{24}_{D}$ –32.7 (*c* 4.0, EtOAc); IR ν_{max} (neat) 2986, 1669 (C=N), 1381, 1210, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.26 (5 H, m), 6.10 (1 H, d, *J* = 5.2 Hz), 4.70 (1 H, d, *J* = 12.0 Hz), 4.63 (1 H, d, *J* = 11.6 Hz), 4.50 (1 H, d, *J* = 4.8 Hz), 4.35 (1 H, dd, *J* = 12.4, 6.0 Hz), 4.10–4.06 (2 H, m), 4.00 (1 H, dd, *J* = 8.4, 5.6 Hz), 3.82 (1 H, dd, *J* = 6.8, 2.4 Hz), 2.00 (3 H, s), 1.39 (3 H, s), 1.35 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 137.8, 128.6 (2 ×), 128.0, 127.9 (2 ×), 109.2, 107. 2, 81.8, 81.7, 75.6, 72.8, 72.3, 67.2, 26.9, 25.5, 14.3; HRMS (ESI) calcd for $C_{18}H_{24}NO_5$: 334.1654, found: *m*/*z* 334.1660 [M +

View Article Online
DOI: 10.1039/C3OB41622D

H]$^+$.

2-Acetamido-1,3-di-*O*-benzyl-2-deoxy-5,6-*O*-isopropylidene-β-D-glucofuranose (6). Oxazolidine **5** (4.22 g, 12.67 mmol) was dissolved in BnOH (16 mL), and a catalytic amount of TFA (56 μL) was added. The mixture was stirred for 12 h at room temperature until disappearance of the starting material based on TLC analysis. The mixture was subjected to silica column chromatography (EtOAc/hexane, 1:3) to remove excess BnOH, and then eluted with EtOAc/hexane (1:1) to give the desired product **6** (4.46 g, 80%). $C_{25}H_{31}NO_6$; pale yellow solid, mp 145.2–146.8 °C; TLC (EtOAc/hexane, 2:1) R_f = 0.4; $[\alpha]^{25}_D$ –90.1 (*c* 4.7, EtOAc); IR ν_{max} (neat) 1651, 1548, 1371, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.26 (10 H, m), 5.88 (1 H, d, *J* = 7.2 Hz, NH), 5.04 (1 H, s, anomeric), 4.87–4.81 (2 H, m), 4.62 (1 H, d, *J* = 12.0 Hz), 4.55–4.50 (2 H, m), 4.44–4.37 (2 H, m), 4.12 (1 H, dd, *J* = 8.4, 5.6 Hz), 4.06 (1 H, dd, *J* = 8.4, 6.4 Hz), 3.99 (1 H, d, *J* = 5.2 Hz), 1.97 (3 H, s), 1.47 (3 H, s), 1.38 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 138.2, 137.5, 128.5 (2 ×), 128.4 (2 ×), 128.0 (2 ×), 127.8 (2 ×), 127.6 (2 ×), 108.7, 105.9, 82.9, 81.8, 74.5, 71.7, 69.6, 66.7, 60.0, 26.8, 25.4, 23.3; HRMS (ESI) calcd for $C_{25}H_{30}NO_6$: 440.2073, found: *m*/*z* 440.2064 [M – H]$^-$.

View Article Online
DOI: 10.1039/C3OB41622D

2-Acetamido-1,3-di-*O*-benzyl-2-deoxy-β-D-glucofuranose (7). Compound **6** (7.5 g, 17 mmol) was dissolved in 70% aqueous HOAc (80 mL), and stirred for 12 h at room temperature. After disappearance of the starting material based on TLC analysis, the mixture was added to saturated $NaHCO_{3(aq)}$ cooled in an ice-bath. The mixture was extracted with CH_2Cl_2 and H_2O, dried ($MgSO_4$), filtered, and concentrated to give diol **7** (6.45 g, 95%), which was used in the next step without further purification. $C_{22}H_{27}NO_6$; pale yellow syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.3; $[\alpha]^{25}_D$ –118.4 (*c* 4.6, EtOAc); IR ν_{max} (neat) 3399, 3283, 1651, 1550, 1372, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.29 (10 H, m), 6.95 (1 H, d, *J* = 7.6 Hz, NH), 5.05 (1 H, s, anomeric), 4.92 (1 H, d, *J* = 11.6 Hz), 4.75 (1 H, d, *J* = 11.6 Hz), 4.64 (1 H, d, *J* = 7.6 Hz, 2-CH), 4.60 (1 H, d, *J* = 12.0 Hz), 4.48 (1 H, d, *J* = 12.0 Hz), 4.34 (1 H, dd, *J* = 8.8, 6.0 Hz, 4-CH), 4.14–4.08 (2 H, m), 3.83 (1 H, d, *J* = 11.2 Hz, 6-CH), 3.75 (1 H, d, *J* = 10.8 Hz, 6'-CH), 3.44 (1 H, d, *J* = 4.0 Hz, 5-OH), 3.39 (1 H, br s, 6-OH), 1.96 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 137.5, 137.4, 128.6 (2 ×), 128.4 (2 ×), 128.0, 127.9 (2 ×), 127.8, 127.7 (2 ×), 106.0, 82.8, 80.1, 71.7, 70.7, 69.3, 63.9, 59.3, 22.9; HRMS (ESI) calcd for $C_{22}H_{26}NO_6$: 400.1760, found: *m*/*z* 400.1768 $[M - H]^-$.

2-Acetamido-5-oxo-1,3-di-*O*-benzyl-2,5-deoxy-β-D-xylofuranose (8). Diol **7** (6.45 g,

View Article Online
DOI: 10.1039/C3OB41622D

16.1 mmol) was dissolved in acetone (200 mL), then $NaIO_4$ (5.17 g, 24.1 mmol) in water (40 mL) was added at 0 °C. The mixture was stirred for 3 h at 0 °C to give a white suspension. Acetone was removed by rotary evaporation. The residue was extracted with Et_2O and water, dried ($MgSO_4$), filtered, and concentrated to give aldehyde **8** (5.73 g, 96%), which was used in the next step without further purification. $C_{21}H_{23}NO_5$; colorless syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.4; $[\alpha]^{25}_D$ –121 (*c* 9.6 , EtOAc); IR ν_{max} (neat) 3281, 1734, 1655, 1547, 1373, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.64 (1 H, s), 7.37–7.27 (10 H, m), 6.20 (1 H, br, NH), 5.20 (1 H, s, anomeric), 4.96 (1 H, d, *J* = 12.0 Hz), 4.83 (1 H, d, *J* = 12.0 Hz), 4.65–4.57 (4 H, m), 4.33 (1 H, d, *J* = 7.2 Hz), 1.95 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.8, 170.1, 137.4, 137.1, 128.6 (2 ×), 128.5 (2 ×), 128.0 (2 ×), 127.95, 127.9, 127.8 (2 ×), 106.6, 85.6, 84.6, 72.1, 69.5, 59.8, 23.1; HRMS (ESI) calcd for $C_{21}H_{22}NO_5$: 368.1498, found: *m*/*z* 368.1498 $[M - H]^-$.

Ethyl 2-acetamido-1,3-di-*O*-benzyl-2,5,6-trideoxy-6-diethoxyphosphoryl-β-D-xylo-hept-5-ene-furanuronate (9). Aldehyde **8** (356 mg, 0.96 mmol) was dissolved in anhydrous THF (20 mL) at 0 °C, and $TiCl_4$ (1 M in CH_2Cl_2, 1.06 mL) was added dropwise. The mixture was stirred for

View Article Online
DOI: 10.1039/C3OB41622D

5 min at 0 °C, and a solution of triethyl phosphonoacetate (238 mg, 1.06 mmol) and triethylamine (585 mg, 5.8 mmol) in anhydrous THF (5 mL) was added dropwise. The resulting brownish red suspension was stirred for 1 h at 0 °C, diluted with Et_2O (80 mL), and quenched with 1 M $HCl_{(aq)}$ (10 mL). The mixture was extracted with Et_2O and 1 M $HCl_{(aq)}$, dried ($MgSO_4$), filtered, and concentrated to give pale yellow syrup. Purification by silica gel column chromatography (EtOAc/hexane gradients, 1:1 to 3:1, then CH_2Cl_2/MeOH, 15:1) gave the alkene product **9** as a mixture of *Z*/*E* isomers (1:1, 421 mg, 76%). $C_{29}H_{38}NO_9P$; colorless syrup, TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.5; IR ν_{max} (neat) 1724, 1656, 1550, 1453, 1239, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67 (0.5 H, dd, *J* = 46.0, 8.0 Hz, vinyl H of *Z*-isomer), 7.34–7.19 (10.5 H, m), 6.24 (0.5 H, d, *J* = 7.6 Hz, NH), 5.99–5.95 (0.5 H, m), 5.90 (0.5 H, d, *J* = 7.6 Hz, NH), 5.58–5.54 (0.5 H, m), 5.06 (0.5 H, s, anomeric), 5.05 (0.5 H, s, anomeric), 4.86–4.76 (2 H, m), 4.61–4.43 (3 H, m), 4.25–4.07 (4 H, m), 4.03–3.85 (3 H, m), 1.95 (1.5 H, s), 1.93 (1.5 H, s), 1.31–1.09 (9 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2/170.0, 164.6 (d, $J^2_{C–P}$ = 15.3 Hz)/164.3 (d, $J^2_{C–P}$ = 14.5 Hz), 161.1 (d, $J^2_{C–P}$ = 6.4 Hz)/159.6 (d, $J^2_{C–P}$ = 5.9 Hz), 138.2/137.7, 138.0/137.4, 128.6–127.5 (10 ×), 124.7 (d, $J^1_{C–P}$ = 182.0 Hz)/124.2 (d, $J^1_{C–P}$ = 183.3 Hz), 107.2/106.3, 85.4/84.7, 80.8 (d, $J^3_{C–P}$ = 18.0 Hz)/79.4 (d, $J^3_{C–P}$ = 4.8 Hz), 72.2/71.9, 69.3, 63.1–62.9 (2 ×), 61.7/61.6, 59.8/59.7, 23.3/23.2,

View Article Online
DOI: 10.1039/C3OB41622D

16.5–16.3 (2 ×), 14.3/14.2; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 12.70/11.07; HRMS (ESI) calcd for $C_{29}H_{37}NO_9P$: 574.2206, found: *m*/*z* 574.2203 $[M - H]^-$.

Ethyl (3*S*,4*R*,5*R*)-3-acetamido-4,5-dihydroxycyclohex-1-ene-1-carboxylate (10). Compound **9** (2.31 g, 4.02 mmol) was treated with Pd/C (300 mg) in EtOH (50 mL) at room temperature for 24 h under an atmosphere of hydrogen. After disappearance of the starting material based on TLC analysis, the mixture was filtered through a pad of Celite. The filtrate was concentrated by rotary evaporation to give the desired lactol (1.55 g) as colorless syrup.

NaH (177 mg, 4.42 mmol; 60% dispersion in oil) was washed with hexane (2 ×) under an atmosphere of nitrogen, and then the above-prepared lactol (1.55 g) in anhydrous THF (40 mL) was added dropwise at 0 °C. The mixture was stirred for 1 h at 0 °C, and quenched with $NH_4Cl_{(aq)}$. THF and H_2O were removed by rotary evaporation. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1 to 10:1) to give the product **10** (603 mg, 62%). $C_{11}H_{17}NO_5$; white solid, mp 183.6–184.3 °C; TLC ($CHCl_3$/MeOH, 5:1) R_f = 0.4; $[\alpha]^{21}_D$ +58.0 (*c* 2.2, MeOH); IR ν_{max} (KBr) 3478, 3391, 3302, 2977, 2925, 1709, 1634, 1549, 1376, 1329, 1278, 1231 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 6.56 (1 H, s), 4.50 (1 H, br s), 4.20 (2 H, br d, *J* = 6.4 Hz), 3.77 (1 H, br s), 3.52 (1 H, br s), 2.79 (1 H, br d, *J* = 17.2 Hz),

View Article Online
DOI: 10.1039/C3OB41622D

2.22 (1 H, br s), 2.02 (3 H, s), 1.29 (3 H, br s); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.4, 167.5, 138.4, 130.1, 75.3, 70.7, 61.9, 54.0, 32.9, 22.7, 14.5; HRMS (ESI) calcd for $C_{11}H_{16}NO_5$: 242.1028, found: *m*/*z* 242.1030 $[M - H]^-$.

Ethyl (3*S*,4*R*,5*R*)-3-azido-4,5-dihydroxycyclohex-1-ene-1-carboxylate (11). Compound **10** (210 mg, 0.87 mmol) was dissolved in EtOH (99.5%, 6.7 mL), and 12 M HCl (0.7 mL) was added. The mixture was stirred at reflux for 12 h under an atmosphere of nitrogen. After disappearance of the starting material based on TLC analysis, the mixture was concentrated by rotary evaporation to give an amine product (174 mg).

A mixture of the above-prepared amine product (174 mg), $CuSO_4 \cdot 5H_2O$ (22 mg, 0.09 mmol) and K_2CO_3 (360 mg, 2.61 mmol) in EtOH (4 mL) was treated with imidazole-1-sulfonyl azide (300 mg, 1.74 mmol) in EtOH (1 mL). The mixture was stirred for 2 h at room temperature. After disappearance of the amine starting material based on TLC analysis, the mixture was neutralized with $NH_4Cl_{(aq)}$, and concentrated by rotary evaporation. The residue was extracted with CH_2Cl_2 and H_2O, dried ($MgSO_4$), filtered, and concentrated to give an azide product **11** (160 mg, 81% yield from acetamide **10**), which was used in the next step without further purification. $C_9H_{13}N_3O_4$; pale yellow syrup, TLC (EtOAc/hexane, 1:1) R_f

View Article Online
DOI: 10.1039/C3OB41622D

= 0.3; $[\alpha]^{19}_{D}$ +6.4 (*c* 2.2, EtOAc); IR ν_{max} (neat) 3415, 2100 (N_3), 1714, 1654, 1248, 1098, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.59 (1 H, t, *J* = 2.4 Hz), 4.18 (2 H, q, *J* = 7.2 Hz), 4.09–4.06 (1 H, m), 3.79–3.73 (1 H, m), 3.57 (1 H, m), 2.87 (1 H, dd, *J* = 18.0, 5.2 Hz), 2.27–2.18 (1 H, m), 1.26 (3 H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 134.1, 130.8, 75.9, 69.7, 63.7, 61.5, 32.3, 14.3; HRMS (ESI) calcd for $C_{18}H_{27}N_6O_8$: 455.1890, found: *m*/*z* 455.1886 $[2M + H]^+$.

Ethyl (3*S*,4*R*,5*R*)-3-azido-4,5-di(methanesulfonyloxy)cyclohex-1-ene-1-carboxylate (12).[28, 47] Diol **11** (59 mg, 0.26 mmol) and methanesulfonyl chloride (89 mg, 0.78 mmol) were dissolved in anhydrous EtOAc (5 mL) at 0 °C. NEt_3 (108 μL, 0.78 mmol) was added dropwise at 0 °C. The mixture was stirred for 2 h at 0 °C. H_2O was added to quench the excess methanesulfonyl chloride. The mixture was extracted with EtOAc and 1 M $HCl_{(aq)}$. The organic layer was washed with saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (EtOAc/hexane gradients, 1:2 to 1:1) to give the dimesylated product **12** (85 mg, 85 %). $C_{11}H_{17}N_3O_8S_2$; colorless syrup; TLC (EtOAc/hexane, 1:1) R_f = 0.4; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70 (1 H, s), 4.88–4.82 (1 H, m), 4.74–4.70 (1 H, m), 4.32–4.30 (1 H, m), 4.20 (2 H, q, *J* = 7.2 Hz), 3.17 (3 H, s),

View Article Online
DOI: 10.1039/C3OB41622D

3.14–3.07 (1 H, m), 3.11 (3 H, s), 2.67–2.59 (1 H, m), 1.27 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 132.1, 130.5, 79.2, 74.0, 61.9, 61.3, 39.6, 39.2, 31.3, 14.3; HRMS (ESI) calcd for $C_{11}H_{17}N_3O_8NaS_2$: 406.0355, found: m/z 406.0359 $[M + Na]^+$.

2-Acetamido-1-*O*-benzyl-2-deoxy-β-D-glucofuranose (13). Oxazolidine **4** (100 mg, 0.41 mmol) was dissolved in BnOH (3 mL), and a catalytic amount of TFA (50 μL) was added. The mixture was stirred for 24 h at room temperature until disappearance of the starting material based on TLC analysis. The mixture was subjected to silica column chromatography (EtOAc/hexane, 1:3) to remove excess BnOH, followed by elution with CH_2Cl_2/MeOH (10:1) to give the desired product **13** (83 mg, 65%). $C_{15}H_{21}NO_6$; TLC (CH_2Cl_2/MeOH, 10:1) R_f = 0.3; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.36–7.24 (5 H, m), 4.96 (1 H, s, anomeric), 4.73 (1 H, d, J = 12.0 Hz), 4.53 (1 H, d, J = 12.0 Hz), 4.23–4.21 (2 H, m), 4.11–4.07 (1 H, m), 4.03–3.98 (1 H, m), 3.83 (1 H, dd, J = 11.2, 3.2 Hz), 3.65 (1 H, dd, J = 11.2, 5.6 Hz), 1.95 (3 H, s); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.0, 138.9, 129.3 (2 ×), 129.0 (2 ×), 128.7, 107.3, 82.6, 76.2, 71.9, 70.7, 65.2, 64.3, 22.6; HRMS (ESI) calcd for $C_{15}H_{20}NO_6$: 310.1291, found: m/z 310.1295 $[M - H]^-$.

View Article Online
DOI: 10.1039/C3OB41622D

2-Acetamido-1-*O*-benzyl-2-deoxy-β-D-xylofuranose (14). Compound **13** (100 mg, 0.32 mmol) was dissolved in EtOH (4 mL), and $NaIO_4$ (110 mg, 0.48 mmol) in water (2 mL) was added at 0 °C. The mixture was stirred for 3 h at 0 °C to give a white suspension, then $NaBH_4$ (27 mg, 0.48 mmol) was added. After stirring for 12 h at room temperature, the mixture was concentrated by rotary evaporation. The residue was extracted with CH_2Cl_2 and water. The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1) to give product **14** (54 mg, 60%). $C_{14}H_{19}NO_5$; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.3; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.27 (5 H, m), 5.91 (1 H, br s, NH), 4.99 (1 H, s, anomeric), 4.77 (1 H, d, J = 11.6 Hz), 4.54 (1 H, d, J = 12.0 Hz), 4.33–4.28 (3 H, m), 4.16–4.14 (1 H, m), 3.91–3.87 (1 H, m), 3.83–3.80 (1 H, m), 2.81 (1 H, br s, OH), 1.98 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 136.7, 128.7 (2 ×), 128.3, 128.2 (2 ×), 105.2, 81.8, 76.8, 70.2, 63.6, 62.5, 23.4; HRMS (ESI) calcd for $C_{14}H_{18}NO_5^-$: 280.1185, found: m/z 280.1188 $[M - H]^-$.

2-Acetamido-1-*O*-benzyl-2-deoxy-5-methanesulfonyl-β-D-xylofuranose (15). Compound **14** (53 mg, 0.19 mmol) and methanesulfonyl chloride (26 mg, 0.23 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL) at 0 °C. NEt_3 (78 μL, 0.57 mmol) was added dropwise

View Article Online
DOI: 10.1039/C3OB41622D

at 0 °C, and the mixture was stirred for 2 h at room temperature. After disappearance of the starting material based on TLC analysis, H_2O was added to quench the excess methanesulfonyl chloride. The mixture was diluted with CH_2Cl_2 (15 mL), and extracted with CH_2Cl_2 and 1 M $HCl_{(aq)}$. The organic phase was washed with saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (CH_2Cl_2/MeOH, 25:1) to give the mono-mesylated product **15** (56 mg, 82%). $C_{15}H_{21}NO_7S$; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.4; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.28 (5 H, m), 5.61 (1 H, d, J = 5.2 Hz, NH), 5.04 (1 H, s), 4.82 (1 H, d, J = 11.6 Hz), 4.56 (1 H, d, J = 11.6 Hz), 4.53–4.40 (3 H, m), 4.34–4.31 (1 H, m), 4.27–4.24 (1 H, m), 3.66 (1 H, d, J = 8.0 Hz), 3.04 (3 H, s), 1.99 (3 H, s); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.1, 138.8, 129.3 (2 ×), 129.0 (2 ×), 128.7, 107.3, 81.2, 76.2, 71.7, 70.7, 64.5, 37.5, 22.7; HRMS (ESI) calcd for $C_{15}H_{20}NO_7S$: 358.0960, found: m/z 358.0967 $[M - H]^-$.

2-Acetamido-1,3-di-*O*-benzyl-2-deoxy-β-D-xylofuranose (16). Diol **7** (733 mg, 1.83 mmol) was dissolved in EtOH (10 mL), and $NaIO_4$ (600 mg, 2.8 mmol) in water (5 mL) was added at 0 °C. The mixture was stirred for 3 h at 0 °C to give a white suspension, then $NaBH_4$ (110 mg, 2.8 mmol) was added. The mixture was stirred for 12 h at room temperature, and

View Article Online
DOI: 10.1039/C3OB41622D

concentrated by rotary evaporation. The residue was extracted with CH_2Cl_2 and water, dried ($MgSO_4$), filtered, and concentrated to give white solids of **16** (quantitative yield), which were used in the next step without further purification. An analytical sample of **16** (640 mg, 94%) was obtained by silica gel column chromatography (CH_2Cl_2/MeOH, 20:1). $C_{21}H_{25}NO_5$; white solid, mp 147.5–148.1 °C; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.4; $[\alpha]^{23}_D$ –149.5 (*c* 3.4, $CHCl_3$); IR ν_{max} (neat) 3276, 1650, 1560, 1374, 1139, 1057 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.28 (10 H, m), 5.93 (1 H, d, *J* = 7.2 Hz, NH), 5.04 (1 H, s, anomeric), 4.87 (1 H, d, *J* = 12.0 Hz), 4.83 (1 H, d, *J* = 12.0 Hz), 4.60 (1 H, d, *J* = 12.0 Hz), 4.55–4.52 (2 H, m), 4.36 (1 H, dd, *J* = 11.2, 5.2 Hz), 4.11 (1 H, dd, *J* = 6.4, 1.6 Hz), 3.93–3.82 (2 H, m), 2.59 (1 H, t, *J* = 6.0 Hz, OH), 1.96 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 137.8, 137.5, 128.63 (2 ×), 128.6 (2 ×), 128.1 (2 ×), 128.02, 128.0 (2 ×), 127.9, 105.4, 83.3, 81.4, 72.1, 69.4, 62.4, 60.4, 23.3; HRMS (ESI) calcd for $C_{21}H_{24}NO_5$: 370.1654, found: *m*/*z* 370.1645 $[M - H]^-$.

2-Acetamido-1,3-di-*O*-benzyl-2-deoxy-5-methanesulfonyl-β-D-xylofuranose (17). Alcohol **16** (64 mg, 0.17 mmol) and methanesulfonyl chloride (30 mg, 0.26 mmol) were dissolved in anhydrous CH_2Cl_2 (5 mL) at 0 °C. NEt_3 (36 μL, 0.26 mmol) was added dropwise at 0 °C, and the mixture was stirred for 2 h at room temperature. After disappearance of the

View Article Online
DOI: 10.1039/C3OB41622D

starting material based on TLC analysis, H_2O was added to quench the excess methanesulfonyl chloride. The mixture was diluted with CH_2Cl_2 (15 mL), and extracted with CH_2Cl_2 and 1 M $HCl_{(aq)}$. The organic phase was washed with saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (EtOAc/hexane, 2:1) to give the mesylated product **17** (60 mg, 78%). $C_{22}H_{27}NO_7S$; white solid, mp 140.2–140.9 °C; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.5; $[\alpha]^{22}_D$ –87.8 (*c* 1.0, EtOAc); IR ν_{max} (neat) 1653, 1554, 1454, 1352, 1175, 1056, 958 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.25 (10 H, m), 5.84 (1 H, d, *J* = 7.6 Hz, NH), 5.03 (1 H, s, anomeric), 4.84–4.78 (2 H, m), 4.55–4.51 (4 H, m), 4.43–4.42 (2 H, m), 4.07 (1 H, dd, *J* = 6.4, 0.8 Hz), 2.89 (3 H, s), 1.95 (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 137.7, 137.4, 128.62 (2 ×), 128.6 (2 ×), 128.1 (2 ×), 128.0, 127.94, 127.9 (2 ×), 106.0, 82.4, 79.4, 72.1, 70.5, 69.5, 60.0, 37.4, 23.3; HRMS (ESI) calcd for $C_{22}H_{26}NO_7S$: 448.1430, found: *m*/*z* 448.1426 $[M - H]^-$.

Ethyl (3*S*,4*R*,5*R*)-3-acetamido-4,5-di(methylsulfonyloxy)cyclohex-1-ene-1-carboxylate (18).

Diol **10** (12 mg, 0.05 mmol) in anhydrous pyridine (2 mL) at 0 °C was added methanesulfonyl chloride (12 μL, 0.15 mmol). The mixture was stirred for 2 h at 0 °C, diluted with CH_2Cl_2 (20

View Article Online
DOI: 10.1039/C3OB41622D

mL), and washed with 1 M $HCl_{(aq)}$ (2 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (EtOAc/hexane gradients, 1:1 to 3:1) to give the dimesylated product **18** (15 mg, 75%). $C_{13}H_{21}NO_9S_2$; white solid, mp 64.3–65.2 °C; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.5; $[\alpha]^{20}_D$ +24.6 (*c* 1.1, EtOAc); IR ν_{max} (neat) 1714, 1661, 1540, 1354, 1253, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70 (1 H, s), 5.93 (1 H, d, *J* = 7.6 Hz, NH), 4.99 (1 H, dd, *J* = 13.6, 7.6 Hz), 4.86–4.79 (2 H, m), 4.21 (2 H, q, *J* = 7.2 Hz), 3.15 (3 H, s), 3.11–3.05 (1 H, m), 3.09 (3 H, s), 2.74–2.68 (1 H, m), 2.02 (3 H, s), 1.29 (3 H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 165.0, 135.4, 128.3, 77.6, 75.1, 61.7, 50.1, 39.2, 39.0, 29.8, 23.3, 14.4; HRMS (ESI) calcd for $C_{13}H_{20}NO_9S_2$: 398.0580, found: *m*/*z* 398.0584 $[M - H]^-$.

Ethyl 2-(*N*-acetyl-*tert*-butoxycarbonylamino)-1,3-di-*O*-benzyl-2,5,6-trideoxy-6-diethoxyphosphoryl-β-D-xylo-hept-5-ene-furanuronate (20). Compound **9** (4.6 g) prepared from aldehyde **8** (2.9 g, 7.8 mmol), was treated with a solution of Boc_2O (5.3 g, 24.3 mmol) and DMAP (200 mg, 1.6 mmol) in anhydrous THF (100 mL). The mixture was heated at reflux for 3 h, and then concentrated by rotary evaporation. The residue was extracted with CH_2Cl_2 and 1 M

View Article Online
DOI: 10.1039/C3OB41622D

$HCl_{(aq)}$. The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (EtOAc/hexane gradients, 1:2 to 1:1) to give the *E*-isomer (3.0 g) of compound **20** and the *Z*-isomer (0.3 g). The overall yield of **20** was 63% (from aldehyde **8**).

E-isomer: $C_{34}H_{46}NO_{11}P$; pale yellow syrup; TLC (EtOAc/hexane, 1:1) R_f = 0.2; $[\alpha]^{24}_D$ –78.2 (*c* 1.1, EtOAc); IR ν_{max} (neat) 1737, 1693, 1370, 1253, 1222, 1149, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.22 (11 H, m), 5.61–5.57 (1 H, m), 5.21/5.20 (1 H, s, anomeric), 5.11 (1 H, t, *J* = 4.4 Hz), 4.86 (1 H, d, *J* = 12.0 Hz), 4.57–4.50 (3 H, m), 4.39 (1 H, d, *J* = 12.0 Hz), 4.30–4.22 (2 H, m), 4.13–4.02 (4 H, m), 2.39 (3 H, s), 1.49 (9 H, s), 1.32–1.24 (9 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 164.4 (d, $J^2_{C–P}$ = 14.6 Hz), 156.5 (d, $J^2_{C–P}$ = 5.8 Hz), 152.6, 137.84, 137.8, 128.5 (2 ×), 128.4 (2 ×), 128.0 (2 ×), 127.84, 127.8, 127.75 (2 ×), 125.8 (d, $J^1_{C–P}$ = 181.2 Hz), 104.5, 84.7, 82.2, 78.7 (d, $J^3_{C–P}$ = 18.0 Hz), 72.0, 70.6, 67.4, 62.9–62.8 (2 ×), 61.6, 28.1 (3 ×), 27.2, 16.5–16.4 (2 ×), 14.2; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 12.72; HRMS (ESI) calcd for $C_{34}H_{46}NO_{11}NaP$: 698.2706, found: *m*/*z* 698.2702 $[M + Na]^+$.

Z-isomer: $C_{34}H_{46}NO_{11}P$; pale yellow syrup; TLC (EtOAc/hexane, 1:1) R_f = 0.3; $[\alpha]^{23}_D$ –47.7 (*c* 2.8, EtOAc); IR ν_{max} (neat) 1737, 1454, 1369, 1244, 1149, 1024 cm^{-1}; ^1H

View Article Online
DOI: 10.1039/C3OB41622D

NMR ($CDCl_3$, 400 MHz) δ 7.78 (1 H, dd, J = 45.2, 8.4 Hz), 7.32–7.24 (10 H, m), 6.10–6.06 (1 H, m), 5.24 (1 H, t, J = 4.8 Hz), 5.21/5.20 (1 H, s, anomeric), 4.84 (1 H, d, J = 12.4 Hz), 4.61–4.57 (1 H, m), 4.55–4.51 (2 H, m), 4.3 (2 H, q, J = 14.4, 7.2 Hz), 4.21–4.05 (5 H, m), 2.38 (3 H, s), 1.46 (9 H, s), 1.34 (3 H, t, J = 6.8 Hz), 1.29 (3 H, t, J = 6.8 Hz), 1.23 (3 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 164.8 (d, $J^2_{C–P}$ = 15.5 Hz), 159.0 (d, $J^2_{C–P}$ = 6.3 Hz), 152.5, 138.0, 137.9, 128.4 (2 ×), 128.4 (2 ×), 127.7 (4 ×), 127.7 (2 ×), 125.5 (d, $J^1_{C–P}$ = 183.3 Hz), 104.8, 84.6, 82.4, 77.6 (d, $J^3_{C–P}$ = 4.4 Hz), 72.0, 70.3, 67.0, 62.7–62.6 (2 ×), 61.6, 28.0 (3 ×), 27.2, 16.5–16.3 (2 ×), 14.2; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 11.26; HRMS (ESI) calcd for $C_{34}H_{46}NO_{11}NaP$: 698.2706, found: m/z 698.2702 $[M + Na]^+$.

Ethyl 2-(*tert*-butoxycarbonylamino)-1,3-di-*O*-benzyl-2,5,6-trideoxy-6-diethoxyphosphoryl-β-D-xylo-heptofuranuronate (21). Compound **20** (163 mg, 0.24 mmol; *Z*/*E* mixture, 1:10) was dissolved in EtOH/THF (4 mL/4 mL), and $NaBH_4$ (55 mg, 1.45 mmol) in H_2O was added. The mixture was stirred for 3 h at room temperature, added saturated $NH_4Cl_{(aq)}$, and then concentrated by rotary evaporation. The residue was extracted with CH_2Cl_2 and H_2O. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give a crude product **21** (140

View Article Online
DOI: 10.1039/C3OB41622D

mg, 92%), which was used in the next step without further purification. $C_{32}H_{46}NO_{10}P$; colorless syrup, TLC (EtOAc/hexane, 1:1) R_f = 0.3; IR ν_{max} (neat) 1730, 1710, 1529, 1366, 1246, 1167, 1047, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.28 (10 H, m), 4.94 (1 H, s, anomeric), 4.81 (2 H, d, J = 12.0 Hz), 4.62–4.47 (3 H, m), 4.36–4.01 (8 H, m), 3.92 (1 H, dd, J = 14.0, 5.6 Hz), 3.36 (0.6 H, ddd, J = 23.2, 10.8, 4.0 Hz), 3.16 (0.4 H, dt, J = 22.4, 7.2 Hz), 2.52–2.23 (2 H, m), 1.46 (9 H, s), 1.30–1.24 (9 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 叨 169.4–169.3 (1 ×), 155.0, 138.2/138.1, 137.8/137.76, 128.4 (2 ×), 128.42 (2 ×), 128.0 (2 ×), 127.9 (2 ×), 127.7, 127.66, 105.7/105.6, 82.4/82.2, 80.2, 80.0 (d, $J^3_{C–P}$ = 13.1 Hz)/78.9 (d, $J^3_{C–P}$ = 13.9 Hz), 71.6/71.5, 69.3/69.2, 63.0–62.7 (2 ×), 61.6/61.5, 61.3/61.0, 43.0 (d, $J^1_{C–P}$ = 130.4 Hz)/42.5 (d, $J^1_{C–P}$ = 130.9 Hz), 28.5 (3 ×), 28.3 (d, $J^2_{C–P}$ = 3.7 Hz), 16.5/16.4 (2 ×), 14.3/14.2; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 22.89/22.47; HRMS (ESI) calcd for $C_{32}H_{46}NO_{10}NaP$: 658.2757, found: m/z 658.2764 $[M + Na]^+$.

Ethyl (3*S*,4*R*,5*R*)-3-(*tert*-butoxycarbonylamino)-4,5-dihydroxycyclohex-1-enecarboxylate (22). Compound **21** (300 mg, 0.47 mmol) was treated with Pd/C (100 mg) in EtOH (15 mL) at room temperature for 24 h under an atmosphere of hydrogen. After disappearance of the

View Article Online
DOI: 10.1039/C3OB41622D

starting material based on TLC analysis, the mixture was filtered through a pad of Celite. The filtrate was concentrated by rotary evaporation to give the desired lactol (200 mg) as colorless syrup.

NaH (10 mg, 0.26 mmol; 60% dispersion in oil) was washed with hexane (2 ×) under an atmosphere of nitrogen, and then the above-prepared lactol (97 mg, 0.21 mmol) in anhydrous THF (6 mL) was added dropwise at 0 ^{o}C. The mixture was stirred for 1 h at 0 ^{o}C, quenched with $NH_4Cl_{(aq)}$, and concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 30:1 to 20:1) to give the product **22** (35 mg, 55% from lactol). $C_{14}H_{23}NO_6$; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.3; IR ν_{max} (neat) 3363, 2979, 1713, 1521, 1367, 1244, 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.56 (1 H, s), 4.88 (1 H, br s), 4.28 (1 H, br s), 4.18 (2 H, q, J = 7.2 Hz), 3.84–3.77 (1 H, m), 3.48 (1 H, t, J = 8.8 Hz), 2.87 (1 H, dd, J = 17.6, 4.4 Hz), 2.25–2.17 (1 H, m), 1.44 (9 H, s), 1.27 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 157.2, 136.0, 130.7, 81.1, 77.4, 70.4, 61.3, 54.6, 31.4, 28.5 (3 ×), 14.4; HRMS (ESI) calcd for $C_{14}H_{22}NO_6$: 300.1447, found: m/z 300.1448 $[M - H]^-$.

Ethyl (3*S*,4*R*,5*R*)-3-(*tert*-butoxycarbonylamino)-4,5-di(methylsulfonyloxy)cyclohex-1-enecarboxylate (23). Diol **22** (94 mg, 0.31 mmol) and methanesulfonyl chloride (214

View Article Online
DOI: 10.1039/C3OB41622D

mg, 1.87 mmol) were dissolved in anhydrous CH_2Cl_2 (6 mL) at 0 ^oC, and triethylamine (260 μL, 1.87 mmol) was added. The mixture was stirred for 2 h at 0 ^oC. H_2O (0.5 mL) was added to quench the excess methanesulfonyl chloride. The mixture was extracted with CH_2Cl_2 and 1 M $HCl_{(aq)}$. The organic layer was washed with saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (EtOAc/hexane gradients, 1:2 to 1:1) to give the dimesylated product **23** (100 mg, 71%). $C_{16}H_{27}NO_{10}S_2$; white solid, mp 162.6–163.6 ^oC; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.5; $[\alpha]^{24}_D$ +29.9 (*c* 2.0, EtOAc); IR ν_{max} (neat) 1712, 1517, 1356, 1247, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68 (1 H, s), 4.98 (1 H, d, *J* = 8.8 Hz), 4.95–4.90 (1 H, m), 4.83 (1 H, m), 4.52 (1 H, br), 4.20 (2 H, q, *J* = 7.2 Hz), 3.15–3.10 (1 H, m), 3.12 (3 H, s), 3.10 (3 H, s), 2.69–2.63 (1 H, m), 1.43 (9 H, s), 1.28 (3 H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9, 155.2, 136.3, 128.2, 81.1, 78.8, 75.2, 61.7, 51.8, 39.2, 39.16, 30.5, 28.5 (3 ×), 14.4; HRMS (ESI) calcd for $C_{16}H_{27}NO_{10}NaS_2$: 480.0974, found: *m*/*z* 480.0983 $[M + Na]^+$.

Ethyl (3a*S*,7*R*,7a*S*)-7-(methylsulfonyloxy)-2-oxo-2,3,3a,6,7,7a-hexahydrobenzo[*d*]oxazole-5-carboxylate (24). Compound **23** (4 mg, 0.009 mmol) was dissolved in CH_2Cl_2 (1 mL), and TFA

View Article Online
DOI: 10.1039/C3OB41622D

(0.5 mL) was added. The mixture was stirred for 2 h at room temperature. After disappearance of the starting material based on TLC analysis, the mixture was concentrated by rotary evaporation to give an amine product.

The above-prepared compound and excess $NaHCO_3$ (15 mg, 0.18 mmol) were dissolved in EtOH/H_2O (1.5 mL/0.5 mL). The mixture was stirred for 18 h at room temperature, added saturated $NH_4Cl_{(aq)}$, and concentrated by rotary evaporation. The residue was extracted with EtOAc and H_2O. The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (EtOAc/hexane, 4:1) to give product **24** (2 mg, 73%). $C_{11}H_{15}NO_7S$; TLC (EtOAc/hexane, 3:1) R_f = 0.2; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.73 (1 H, s), 5.40 (1 H, s, NH), 5.03–4.99 (2 H, m), 4.49–4.47 (1 H, m), 4.23 (2 H, q, J = 7.2 Hz), 3.12 (3 H, s), 2.85–2.83 (2 H, m), 1.30 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.1, 157.7, 132.2, 130.2, 74.5, 73.7, 61.9, 51.1, 39.2, 25.8, 14.4; HRMS (ESI) calcd for $C_{11}H_{14}NO_7S$: 304.0491, found: m/z 304.0493 $[M - H]^-$.

2-Acetamido-1,3-di-*O*-benzyl-2,5,6-trideoxy-6,6-bis(diethoxyphosphoryl)-β-D-xylo-hex-5-ene-furanose (25). Aldehyde **8** (4.0 g, 11.0 mmol) was dissolved in anhydrous THF (100 mL) at 0 ^{o}C, and $TiCl_4$ (1 M in CH_2Cl_2, 12.2 mL) was added dropwise. The mixture was

View Article Online
DOI: 10.1039/C3OB41622D

stirred for 5 min at 0 °C, and a solution of tetraethyl methylenediphosphonate (3.5 g, 12.2 mmol) and triethylamine (6.7 g, 66.3 mmol) in anhydrous THF (20 mL) was added dropwise. The resulting brownish red suspension was stirred for 1 h at 0 °C, diluted with Et_2O (400 mL), and quenched with 1 M $HCl_{(aq)}$ (50 mL). The mixture was extracted with Et_2O and 1 M $HCl_{(aq)}$. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give product **25** (6.2 g). $C_{30}H_{43}NO_{10}P_2$; pale yellow syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.5; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (1 H, ddd, J = 49.6, 28.0, 8.0 Hz), 7.39–7.21 (10 H, m), 6.37 (1 H, d, J = 7.6 Hz, NH), 5.92–5.88 (1 H, m), 5.12 (1 H, s, anomeric), 4.89–4.84 (2 H, m), 4.66 (1 H, d, J = 7.6 Hz), 4.56 (1 H, d, J = 12.0 Hz), 4.47 (1 H, d, J = 11.6 Hz), 4.28 (1 H, d, J = 6.0 Hz), 4.22–3.87 (8 H, m), 1.97 (3 H, s), 1.34 (3 H, t, J = 7.2 Hz), 1.28 (3 H, t, J = 7.2 Hz), 1.17 (3 H, t, J = 7.2 Hz), 1.11 (3 H, t, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 165.5, 138.0, 137.5, 128.5 (2 ×), 128.2 (2 ×), 127.9 (2 ×), 127.7 (2 ×), 127.5 (2 ×), 122.2 (dd, J^1_{C-P} = 165.1, 164.0 Hz), 106.9, 85.6, 80.7–80.4 (1 ×), 72.0, 69.3, 62.9–62.6 (4 ×), 59.5, 23.2, 16.5–16.2 (4 ×); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 13.89 (d, J^2_{P-P} = 49.7 Hz), 11.73 (d, J^2_{P-P} = 49.7 Hz); HRMS (ESI) calcd for $C_{30}H_{42}NO_{10}P_2$: 638.2284, found: m/z 638.2278 $[M - H]^-$.

2-(*N*-Acetyl-*tert*-butoxycarbonylamino)-1,3-di-*O*-benzyl-2,5,6-trideoxy-6,6-bis(diethо

View Article Online
DOI: 10.1039/C3OB41622D

xyphosphoryl)-β-D-xylo-hex-5-ene-furanose (26). To the above-prepared condensation product **25** (6.2 g) was added a solution of Boc_2O (4.6 g, 20.9 mmol) and DMAP (170 mg, 1.4 mmol) in anhydrous THF (100 mL). The mixture was heated at reflux for 3 h, and then THF was removed by rotary evaporation. The residue was extracted with CH_2Cl_2 and 1 M $HCl_{(aq)}$. The organic phase was dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (EtOAc/hexane gradients, 1:1 to 3:1) to give the product **26** (2.6 g, 32% from aldehyde **8**). $C_{35}H_{51}NO_{12}P_2$; pale yellow syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.4; $[\alpha]^{24}_D$ –49.0 (*c* 2.0, EtOAc); IR ν_{max} (neat) 2981, 1739, 1696, 1604, 1370, 1247, 1150, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62 (1 H, ddd, *J* = 48.4, 27.6, 8.4 Hz), 7.31–7.22 (10 H, m), 5.93–5.90 (1 H, m), 5.23–5.19 (2 H, m), 4.82 (1 H, d, *J* = 12.0 Hz), 4.58–4.51 (3 H, m), 4.42 (1 H, d, *J* = 11.6 Hz), 4.20–4.08 (4 H, m), 4.07–3.97 (3 H, m), 3.95–3.93 (1 H, m), 2.38 (3 H, s), 1.45 (9 H, s), 1.35–1.18 (12 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 163.4, 152.5, 137.8, 137.75, 128.4 (2 ×), 128.3 (2 ×), 127.9 (2 ×), 127.7 (2 ×), 127.68 (2 ×), 123.3 (dd, $J^1_{C–P}$ = 165.7, 163.5 Hz), 104.8, 84.6, 82.7, 78.6–78.4 (1 ×), 71.9, 70.3, 67.1, 62.8–62.5 (4 ×), 27.9 (3 ×), 27.1, 16.4–16.3 (4 ×); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 14.13 (d, $J^2_{P–P}$ = 51.2 Hz), 11.66 (d, $J^2_{P–P}$ = 51.2 Hz); HRMS (ESI) calcd for $C_{35}H_{52}NO_{12}P_2$: 740.2965, found: *m*/*z* 740.2963 $[M + H]^+$.

View Article Online
DOI: 10.1039/C3OB41622D

2-(*Tert*-butoxycarbonylamino)-1,3-di-*O*-benzyl-2,5,6-trideoxy-6,6-bis(diethoxyphosphoryl)-β-D-xylo-hexofuranose (27). Compound **26** (2.6 g, 3.56 mmol) was dissolved in EtOH (30 mL), and $NaBH_4$ (807 mg, 21.35 mmol) in H_2O (10 mL) was added at 0 °C. The mixture was stirred for 12 h at room temperature, added saturated $NH_4Cl_{(aq)}$, and then concentrated by rotary evaporation. The residue was extracted with CH_2Cl_2 and H_2O. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give a crude product **27** (2.4 g, quantitative yield), which was used in the next step without further purification. $C_{33}H_{51}NO_{11}P_2$; colorless syrup; TLC (EtOAc/hexane, 6:1) R_f = 0.2; $[\alpha]^{22}_D$ –60.1 (*c* 3.5, EtOAc); IR ν_{max} (neat) 2979, 1707, 1531, 1454, 1391, 1365, 1246, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.22 (10 H, m), 4.93 (1 H, s), 4.83–4.77 (3 H, m), 4.73–4.68 (1 H, m), 4.53 (1 H, d, *J* = 12.0 Hz), 4.47 (1 H, d, *J* = 12.0 Hz), 4.28 (1 H, d, *J* = 6.4 Hz), 4.11–4.04 (8 H, m), 3.92 (1 H, d, *J* = 4.8 Hz), 2.77–2.62 (1 H, m), 2.48–2.33 (1 H, m), 2.31–2.15 (1 H, m), 1.43 (9 H, s), 1.27–1.21 (12 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 138.1, 137.8, 128.2 (3 ×), 128.21 (2 ×), 128.0, 127.7 (2 ×), 127.5, 127.4, 105.5, 82.0, 79.9, 79.1, 71.3, 68.9, 62.7–62.4 (4 ×), 60.8, 33.4 (t, J^1_{C-P} = 132.3 Hz), 28.4 (3 ×), 26.9, 16.4–16.3 (4 ×); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 23.51/23.29; HRMS (ESI) calcd for $C_{33}H_{50}NO_{11}P_2$: 698.2859, found:

View Article Online
DOI: 10.1039/C3OB41622D

m/*z* 698.2845 $[M - H]^-$.

Diethyl (3*S*,4*R*,5*R*)-3-(*tert*-butoxycarbonylamino)-4,5-dihydroxycyclohex-1-ene-1-phosphonate (28b). Compound **27** (832 mg, 1.19 mmol) was treated with Pd/C (120 mg) in THF (20 mL) at room temperature for 24 h under an atmosphere of hydrogen. After disappearance of the starting material based on TLC analysis, the mixture was filtered through a pad of Celite. The filtrate was concentrated by rotary evaporation to give the desired lactol (615 mg) as colorless syrup.

NaH (54 mg, 1.36 mmol; 60% dispersion in oil) was washed with hexane (2 ×) under an atmosphere of nitrogen, and then the above-prepared lactol (615 mg) in anhydrous THF (20 mL) was added dropwise at 0 °C. The mixture was stirred for 1 h at 0 °C, and quenched with $NH_4Cl_{(aq)}$. The mixture was concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 20:1 to 15:1) to give the product **28b** (230 mg, 53%). $C_{15}H_{28}NO_7P$; colorless foam; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.3; $[\alpha]^{25}_D$ +61.5 (*c* 2.0, EtOAc); IR ν_{max} (neat) 3365, 2980, 1697, 1522, 1393, 1367, 1226, 1165, 1052, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.36 (1 H, d, *J* = 21.2 Hz), 5.44 (1 H, d, *J* = 6.0 Hz, NH), 4.49 (1 H, br s, OH), 4.18 (1 H, br s), 4.07–3.97 (4 H, m), 3.80–3.74 (1 H, m), 3.47 (1 H, t, *J* = 8.8

View Article Online
DOI: 10.1039/C3OB41622D

Hz), 2.65–2.58 (2 H, m, mixed with OH), 2.18–2.11 (1 H, m), 1.40 (9 H, s), 1.27 (6 H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 141.1, 127.4 (d, $J^1_{C–P}$ = 182.7 Hz), 80.5, 75.7, 70.0 (d, $J^3_{C–P}$ = 14.8 Hz), 62.5–62.4 (2 ×), 54.8 (d, $J^3_{C–P}$ = 22.0 Hz), 31.8 (d, $J^2_{C–P}$ = 7.5 Hz), 28.5 (3 ×), 16.5 (2 ×, d, $J^3_{C–P}$ = 6.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 17.25; HRMS (ESI) calcd for $C_{15}H_{29}NO_7P$: 366.1682, found: m/z 366.1678 $[M + H]^+$.

Diethyl (3*S*,4*R*,5*R*)-3-azido-4,5-dihydroxycyclohex-1-ene-1-phosphonate (29). Compound **28b** (140 mg, 0.38 mmol) was dissolved in CH_2Cl_2 (4 mL), and TFA (2 mL) was added. The mixture was stirred for 2 h at room temperature. After disappearance of the starting material based on TLC analysis, the mixture was concentrated by rotary evaporation to give an amine product.

A mixture of the above-prepared amine product, $CuSO_4·5H_2O$ (10 mg, 0.04 mmol) and K_2CO_3 (159 mg, 1.15 mmol) in EtOH (5 mL) was treated with imidazole-1-sulfonyl azide (132 mg, 0.77 mmol) in EtOH (1 mL). The mixture was stirred for 2 h at room temperature. After disappearance of the amine compound based on TLC analysis, the mixture was neutralized with $NH_4Cl_{(aq)}$. EtOH was removed by rotary evaporation. The residue was extracted with CH_2Cl_2 and H_2O. The organic phase was dried ($MgSO_4$), filtered, and

View Article Online
DOI: 10.1039/C3OB41622D

concentrated to give a crude product, which was purified by silica gel column chromatography (CH_2Cl_2/MeOH gradients, 20:1 to 15:1) to give azide **29** (65 mg, 58% from **28b**). $C_{10}H_{18}N_3O_5P$; pale yellow syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.3; $[\alpha]^{26}_D$ +38.7 (*c* 1.7, EtOAc); IR ν_{max} (neat) 3369, 2984, 2098 (N_3), 1441, 1225, 1051, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.32 (1 H, d, *J* = 21.2 Hz), 4.52 (1 H, s, OH), 4.15 (1 H, s), 4.09–4.02 (4 H, m), 3.77–3.71 (1 H, m), 3.56 (1 H, t, *J* = 8.8 Hz), 2.72–2.64 (1 H, m), 2.45 (1 H, br s, OH), 2.20–2.12 (1 H, m), 1.30 (6 H, t, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.0 (d, J^2_{C-P} = 9.1 Hz), 129.0 (d, J^1_{C-P} = 182.5 Hz), 75.9 (d, J^4_{C-P} = 2.5 Hz), 69.7 (d, J^3_{C-P} = 14.9 Hz), 64.2 (d, J^3_{C-P} = 22.8 Hz), 62.9–62.8 (2 ×), 32.4 (d, J^2_{C-P} = 8.7 Hz), 16.5 (2 ×, d, J^3_{C-P} = 6.1 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 16.24; HRMS (ESI) calcd for $C_{10}H_{19}N_3O_5P$: 292.1062, found: *m*/*z* 292.1058 $[M + H]^+$.

Diethyl (3*S*,4*R*,5*R*)-3-azido-4,5-di(methanesulfonyloxy)cyclohex-1-ene-1-phosphonate (30). Diol **29** (50 mg, 0.17 mmol) and methanesulfonyl chloride (60 mg, 0.52 mmol) were dissolved in anhydrous EtOAc (5 mL) at 0 °C. NEt_3 (72 μL, 0.52 mmol) was added dropwise at 0 °C. The mixture was stirred for 2 h at 0 °C. H_2O was added to quench excess methanesulfonyl chloride. The mixture was extracted with EtOAc and 1 M HCl. The organic

View Article Online
DOI: 10.1039/C3OB41622D

layer was washed with saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$), filtered, concentrated, and purified by silica gel column chromatography (EtOAc/hexane gradients, 1:1 to 3:1) to give the dimesylated product **30** (65 mg, 84%). $C_{12}H_{22}N_3O_9PS_2$; colorless syrup; TLC (EtOAc/hexane, 3:1) R_f = 0.3; $[\alpha]^{25}_D$ +66.3 (*c* 1.2, EtOAc); IR ν_{max} (neat) 2924, 2104 (N_3), 1356, 1245, 1175, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.51 (1 H, dt, *J* = 20.0, 2.4 Hz), 4.89–4.83 (1 H, m), 4.74–4.70 (1 H, m), 4.27–4.24 (1 H, m), 4.13–4.06 (4 H, m), 3.18 (3 H, s), 3.12 (3 H, s), 3.05–2.98 (1 H, m), 2.64–2.55 (1 H, m), 1.32 (6 H, t, *J* = 14.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.5 (d, $J^2_{C–P}$ = 9.3 Hz), 130.0 (d, $J^1_{C–P}$ = 183.7 Hz), 79.13 (d, $J^4_{C–P}$ = 2.4 Hz), 73.8 (d, $J^3_{C–P}$ = 15.5 Hz), 62.9 (2 ×, d, $J^2_{C–P}$ = 5.7 Hz), 61.8 (d, $J^3_{C–P}$ = 22.3 Hz), 39.6, 39.2, 31.8 (d, $J^2_{C–P}$ = 9.2 Hz), 16.5 (2 ×, d, $J^3_{C–P}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 13.66; HRMS (ESI) calcd for $C_{12}H_{23}N_3O_9PS_2$: 448.0613, found: *m*/*z* 448.0615 $[M + H]^+$.

Diethyl (1*S*,5*R*,6*S*)-7-(diethoxy-phosphoryl)-5-methanesulfonyloxy-7-aza-bicyclo[4.1.0] hept-2-ene-3-phosphonate (31). Azide **30** (48 mg, 0.11 mmol) was dissolved in anhydrous toluene (10 mL), and triethyl phosphite (20.2 μL, 0.12 mmol) was added. The mixture was stirred for 0.5 h at room temperature, and then heated at reflux for 1 h. After disappearance of the starting material based on TLC analysis, the mixture was concentrated

View Article Online
DOI: 10.1039/C3OB41622D

by rotary evaporation to give a crude product. The crude product was purified on a silica gel column by elution with EtOAc/hexane (4:1) to remove excess $P(OEt)_3$, followed by elution with CH_2Cl_2/MeOH (30:1 to 20:1) to give the desired product **31** (38 mg, 77%). $C_{15}H_{29}NO_9P_2S$; colorless syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.4; $[\alpha]^{25}_D$ +33.7 (*c* 1.2, EtOAc); IR ν_{max} (neat) 1358, 1252, 1175, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.80 (1 H, dt, *J* = 19.6, 4.0 Hz), 5.00–4.95 (1 H, m), 4.17–4.05 (4 H, m), 4.04–3.98 (4 H, m), 3.32–3.27 (1 H, m), 3.17–3.10 (1 H, m), 3.08 (3 H, s), 2.73–2.64 (1 H, m), 2.46–2.37 (1 H, m), 1.32–1.26 (12 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.5–136.3 (1 ×), 130.4 (d, $J^1_{C–P}$ = 187.2 Hz), 75.8–75.6 (1 ×), 64.3–64.1 (2 ×), 62.5–62.4 (2 ×), 39.7–39.6 (1 ×), 39.2, 35.1 (dd, $J^3_{C–P}$ = 22.6 Hz, $J^2_{C–P}$ = 5.9 Hz), 27.4 (d, $J^2_{C–P}$ = 9.1 Hz), 16.6–16.4 (4 ×); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 15.34, 10.52; HRMS (ESI) calcd for $C_{15}H_{30}NO_9P_2S$: 462.1117, found: *m*/*z* 462.1117 $[M + H]^+$.

Diethyl (3*R*,4*S*,5*R*)-4-(diethoxy-phosphorylamino)-3-(1-ethyl-propoxy)-5-methane sulfonyloxy-cyclohexene-1-phosphonate (32). Compound **31** (31 mg, 0.07 mmol) was dissolved in 3-pentanol (2 mL), and 48% $BF_3{\cdot}Et_2O$ (27 μL in Et_2O, 0.10 mmol) was added. The mixture was stirred for 16 h at room temperature. After disappearance of the starting

View Article Online
DOI: 10.1039/C3OB41622D

material based on TLC analysis, the mixture was concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH gradients, 50:1 to 30:1) to give the product **32** (32 mg, 87%). $C_{20}H_{41}NO_{10}P_2S$; colorless syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.5; $[\alpha]^{25}_D$ –81.5 (*c* 1.5, EtOAc); IR ν_{max} (neat) 3208, 2979, 1461, 1356, 1236, 1175, 1096, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.62 (1 H, d, *J* = 21.2 Hz), 5.07 (1 H, s), 4.11–4.01 (8 H, m), 3.95 (1 H, s), 3.48–3.42 (1 H, m), 3.35 (1 H, quin, *J* = 5.6 Hz), 3.06 (3 H, s), 2.98 (1 H, t, *J* = 9.2 Hz, NH), 2.63 (2 H, s), 1.58–1.39 (4 H, m), 1.31–1.27 (12 H, m), 0.89–0.84 (6 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.5 (d, $J^2_{C–P}$ = 7.1 Hz), 126.8 (d, $J^1_{C–P}$ = 182.9 Hz), 81.6, 78.3 (d, $J^3_{C–P}$ = 11.7 Hz), 73.9 (dd, $J^3_{C–P}$ = 19.8, 6.4 Hz), 63.1–62.9 (2 ×), 62.4–62.3 (2 ×), 54.0 (d, $J^2_{C–P}$ = 2.0 Hz), 38.7, 29.4 (d, $J^2_{C–P}$ = 9.5 Hz), 26.4, 25.9, 16.5–16.3 (4 ×), 9.8, 9.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 16.18, 7.52; HRMS (ESI) calcd for $C_{20}H_{42}NO_{10}P_2S$: 550.2005, found: *m*/*z* 550.2007 $[M + H]^+$.

Diethyl (3*R*,4*S*,5*R*)-4-acetamido-3-(1-ethyl-propoxy)-5-methanesulfonyloxy-cyclohexene-1-phosphonate (33). Compound **32** (3 mg, 0.005 mmol) was dissolved in concentrated H_2SO_4 (0.4 mL) and EtOH (2 mL). The mixture was heated at 70 °C for 4 h. After disappearance of the starting material based on TLC analysis, pyridine (3 mL) and

View Article Online
DOI: 10.1039/C3OB41622D

Ac_2O (3 mL) were added at 0 °C. The mixture was stirred at 0 °C for 15 min, and then H_2O (3 mL) was added to quench excess Ac_2O. The mixture was extracted with EtOAc and 1 M $HCl_{(aq)}$. The organic layer was washed with saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$), filtered, and concentrated to give a crude product. The crude product was purified on a silica gel column by elution with EtOAc/hexane (6:1) to remove impurity, followed by elution with CH_2Cl_2/MeOH (15:1) to give the desired product **33** (2 mg, 80%). $C_{18}H_{34}NO_8PS$; colorless syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.4; $[\alpha]^{22}_D$ –102.5 (*c* 0.4, EtOAc); IR ν_{max} (neat) 1659, 1549, 1354, 1234, 1175, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.64 (1 H, dd, *J* = 21.6, 1.6 Hz), 5.85 (1 H, d, *J* = 8.0 Hz, NH), 5.19 (1 H, m), 4.29 (1 H, ddd, *J* = 8.4, 8.4, 2.4 Hz), 4.12–4.02 (4 H, m), 4.00–3.98 (1 H, m), 3.34 (1 H, quin, *J* = 5.6 Hz), 3.02 (3 H, s), 2.74–2.67 (1 H, m), 2.66–2.58 (1 H, m), 2.00 (3 H, s), 1.51–1.47 (4 H, m), 1.33–1.29 (6 H, m), 0.90–0.86 (6 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 140.8 (d, $J^2_{C–P}$ = 7.1 Hz), 126.0 (d, $J^1_{C–P}$ = 183.4 Hz), 82.5, 78.3 (d, $J^3_{C–P}$ = 12.6 Hz), 73.0 (d, $J^3_{C–P}$ = 19.8 Hz), 62.6–62.3 (2 ×), 51.8 (d, $J^4_{C–P}$ = 2.2 Hz), 39.0, 30.1 (d, $J^2_{C–P}$ = 9.9 Hz), 26.5, 26.0, 23.5, 16.6 (2 ×, d, $J^3_{C–P}$ = 6.1 Hz), 9.7, 9.6; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 16.26; HRMS (ESI) calcd for $C_{18}H_{35}NO_8PS$: 456.1821, found: *m*/*z* 456.1818 $[M + H]^+$.

View Article Online
DOI: 10.1039/C3OB41622D

Diethyl (3*R*,4*S*,5*S*)-5-azido-4-acetamido-3-(1-ethyl-propoxy)-cyclohexene-1-phosphonate (34).[31] Compound **33** (2 mg, 0.004 mmol) and NaN_3 (0.6 mg, 0.009 mmol) were dissolved in DMF (0.5 mL). The mixture was stirred at 100 ^oC for 2 h. After disappearance of the starting material based on TLC analysis, DMF was removed under reduced pressure. The residue was extracted with EtOAc and H_2O. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give a crude product. The crude product was purified on a silica gel column by elution with EtOAc/hexane (6:1) to remove impurity, followed by elution with CH_2Cl_2/MeOH (25:1) to give the desired product **34** (1.5 mg, 85%). $C_{17}H_{31}N_4O_5P$; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.5; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.56 (1 H, d, J = 21.6 Hz), 5.73 (1 H, d, J = 7.2 Hz, NH), 4.52 (1 H, d, J = 8.8 Hz), 4.32 (1 H, td, J = 10.8, 6.0 Hz), 4.12–4.01 (4 H, m), 3.32–3.23 (2 H, m), 2.71–2.63 (1 H, m), 2.18–2.10 (1 H, m), 2.02 (3 H, s), 1.52–1.44 (4 H, m), 1.33–1.29 (6 H, m), 0.89–0.85 (6 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 141.9 (d, $J^2_{C–P}$ = 7.2 Hz), 126.5 (d, $J^1_{C–P}$ = 181.7 Hz), 82.2, 74.0 (d, $J^3_{C–P}$ = 21.5 Hz), 62.3 (2 ×, d, $J^2_{C–P}$ = 5.8 Hz), 58.6, 57.4 (d, $J^3_{C–P}$ = 14.8 Hz), 31.2 (d, $J^2_{C–P}$ = 9.4 Hz), 26.5, 25.7, 23.8, 16.6–16.5 (2 ×), 9.8, 9.5; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 16.58; HRMS (ESI) calcd for $C_{17}H_{32}N_4O_5P$: 403.2110, found: m/z 403.2107 $[M + H]^+$.

View Article Online
DOI: 10.1039/C3OB41622D

2-(*Tert*-butoxycarbonylamino)-1-ethoxy-3-hydroxy-2,5,6-trideoxy-6,6-bis(diethoxyphosphoryl)-D-xylo-hexofuranose (35) and tetraethyl 2-((3a*R*,5*R*,6*R*,6a*R*)-4-hydroxy-2-oxohexahydrofuro[3,2-*d*]oxazol-5-yl)ethane-1,1-diphosphonate (36). Compound **27** (1.04 g, 1.49 mmol) was treated with Pd/C (180 mg) in EtOH (16 mL) at room temperature for 24 h under an atmosphere of hydrogen. After disappearance of the starting material based on TLC analysis, the mixture was filtered through a pad of Celite. The filtrate was concentrated by rotary evaporation and purified by silica gel column chromatography (CH_2Cl_2/MeOH gradients, 25:1 to 10:1) to give compound **35** (285 mg, 35%) and compound **36** (232 mg, 35%).

Compound **35**: $C_{21}H_{43}NO_{11}P_2$; pale yellow syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.5; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.19 (1 H, d, J = 5.2 Hz), 4.99–4.98 (1 H, m), 4.35 (1 H, br s), 4.14–4.09 (10 H, m), 3.90 (1 H, br s), 3.72–3.68 (1 H, m), 3.43–3.39 (1 H, m), 2.58 (1 H, t, J = 24.0 Hz), 2.21–2.17 (2 H, m), 1.39 (9 H, s), 1.29–1.25 (12 H, m), 1.15–1.12 (3 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8, 105.9, 99.5, 80.1, 75.5, 63.6, 63.4–62.7 (4 ×), 62.2, 32.9 (t, $J^1_{C–P}$ = 132.9 Hz), 28.5 (3 ×), 25.4, 16.5–16.4 (4 ×), 15.2; ^{31}P NMR ($CDCl_3$, 162 MHz) δ 23.88/23.65, 23.43/23.27; HRMS (ESI) calcd for $C_{21}H_{43}NO_{11}P_2Na$: 570.2204, found: m/z 570.2197 $[M + Na]^+$.

View Article Online
DOI: 10.1039/C3OB41622D

Compound **36**: $C_{15}H_{29}NO_{10}P_2$; pale yellow syrup; TLC ($CHCl_3$/MeOH, 10:1) R_f = 0.2; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (1 H, br s), 6.09 (1 H, d, J = 4.4 Hz), 4.35–4.32 (1 H, m), 4.22 (1 H, s), 4.14–4.09 (9 H, m), 2.58–2.20 (4 H, m), 1.31–1.29 (12 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.5, 103.3, 79.9, 74.5, 65.0, 63.7–63.2 (4 ×), 32.8 (t, J^1_{C-P} = 133.6 Hz), 23.8, 16.5 (4 ×); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 23.55/22.98; HRMS (ESI) calcd for $C_{15}H_{30}NO_{10}P_2$: 446.1339, found: m/z 446.1330 $[M + H]^+$.

Acknowledgements

We thank National Science Council and Academia Sinica for financial support.

Supplementary data

Supplementary data (^{1}H, ^{13}C, ^{31}P NMR spectra) associated with this article can be found, in the online version.

Notes and references

1. A. C. Lowen and P. Palese, *Infect. Disord. Drug Targets*, 2007, **7**, 318–328.

2. K. Subbarao and T. Joseph, *Nat. Rev. Immunol.*, 2007, **7**, 267–278.

View Article Online
DOI: 10.1039/C3OB41622D

3. R. G. Webster, W. J. Bean, O. T. Gorman, T. M. Chambers and Y. Kawaoka, *Microbiol. Rev.*, 1992, **56**, 152–179.

4. W. L. Davies, C. E. Hoffmann, M. Paulshock, T. R. Wood, R. F. Haff, R. R. Grunert, J. C. Watts, E. C. Hermann, E. M. Neumayer and J. W. Mcgahen, *Science*, 1964, **144**, 862–863.

5. J. R. Schnell and J. J. Chou, *Nature*, 2008, **451**, 591–595.

6. A. L. Stouffer, R. Acharya, D. Salom, A. S. Levine, L. Di Costanzo, C. S. Soto, V. Tereshko, V. Nanda, S. Stayrook and W. F. DeGrado, *Nature*, 2008, **451**, 596–599.

7. A. C. Schmidt, *Drugs*, 2004, **64**, 2031–2046.

8. A. Moscona, *New Engl. J. Med.*, 2005, **353**, 1363–1373.

9. E. De Clercq, *Nat. Rev. Drug Discov.*, 2006, **5**, 1015–1025.

10. E. G. Feng, D. J. Ye, J. Li, D. Y. Zhang, J. F. Wang, F. Zhao, R. Hilgenfeld, M. Y. Zheng, H. L. Jiang and H. Liu, *ChemMedChem*, 2012, **7**, 1527–1536.

11. J. M. Woods, R. C. Bethell, J. A. V. Coates, N. Healy, S. A. Hiscox, B. A. Pearson, D. M. Ryan, J. Ticehurst, J. Tilling, S. M. Walcott and C. R. Penn, *Antimicrob. Agents Chemother.*, 1993, **37**, 1473–1479.

12. C. J. Dunn and K. L. Goa, *Drugs*, 1999, **58**, 761–784.

View Article Online
DOI: 10.1039/C3OB41622D

13. C. U. Kim, W. Lew, M. A. Williams, H. W. Wu, L. J. Zhang, X. W. Chen, P. A. Escarpe, D. B. Mendel, W. G. Laver and R. C. Stevens, *J. Med. Chem.*, 1998, **41**, 2451–2460.

14. K. McClellan and C. M. Perry, *Drugs*, 2001, **61**, 263–283.

15. R. W. Sidwell and D. F. Smee, *Expert Opin. Invest. Drugs*, 2002, **11**, 859–869.

16. S. Jain and A. M. Fry, *Clin. Infect. Dis.*, 2011, **52**, 707–709.

17. S. Kubo, T. Tomozawa, M. Kakuta, A. Tokumitsu and M. Yamashita, *Antimicrob. Agents Chemother.*, 2010, **54**, 1256–1264.

18. H. Ikematsu and N. Kawai, *Expert Rev. Anti-Infect. Ther.*, 2011, **9**, 851–857.

19. M. von Itzstein, W. Y. Wu, G. B. Kok, M. S. Pegg, J. C. Dyason, B. Jin, T. V. Phan, M. L. Smythe, H. F. White, S. W. Oliver, P. M. Colman, J. N. Varghese, D. M. Ryan, J. M. Woods, R. C. Bethell, V. J. Hotham, J. M. Cameron and C. R. Penn, *Nature*, 1993, **363**, 418–423.

20. W. Lew, X. W. Chen and C. U. Kim, *Curr. Med. Chem.*, 2000, **7**, 663–672.

21. R. J. Russell, L. F. Haire, D. J. Stevens, P. J. Collins, Y. P. Lin, G. M. Blackburn, A. J. Hay, S. J. Gamblin and J. J. Skehel, *Nature*, 2006, **443**, 45–49.

22. J.-J. Shie, J.-M. Fang, S.-Y. Wang, K.-C. Tsai, Y.-S. E. Cheng, A.-S. Yang, S.-C. Hsiao, C.-Y. Su and C.-H. Wong, *J. Am. Chem. Soc.*, 2007, **129**, 11892–11893.

View Article Online
DOI: 10.1039/C3OB41622D

23. T.-J. R. Cheng, S. Weinheimer, E. B. Tarbet, J.-T. Jan, Y.-S. E. Cheng, J.-J. Shie, C.-L. Chen, C.-A. Chen, W.-C. Hsieh, P.-W. Huang, W.-H. Lin, S.-Y. Wang, J.-M. Fang, O. Y.-P. Hu and C.-H. Wong, *J. Med. Chem.*, 2012, **55**, 8657–8670.

24. C. U. Kim, W. Lew, M. A. Williams, H. T. Liu, L. J. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendel, C. Y. Tai, W. G. Laver and R. C. Stevens, *J. Am. Chem. Soc.*, 1997, **119**, 681–690.

25. J. C. Rohloff, K. M. Kent, M. J. Postich, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, E. J. Prisbe, L. M. Schultze, R. H. Yu and L. J. Zhang, *J. Org. Chem.*, 1998, **63**, 4545–4550.

26. M. Federspiel, R. Fischer, M. Hennig, H. J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Gockel, S. Gotzo, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Rockel-Stabler, R. Trussardi and A. G. Zwahlen, *Org. Process Res. Dev.*, 1999, **3**, 266–274.

27. M. Karpf and R. Trussardi, *J. Org. Chem.*, 2001, **66**, 2044–2051.

28. M. Karpf and R. Trussardi, *Angew. Chem. Int. Ed.*, 2009, **48**, 5760–5762.

29. J. Magano, *Chem. Rev.*, 2009, **109**, 4398–4438.

30. M. Shibasaki, M. Kanai and K. Yamatsugu, *Isr. J. Chem.*, 2011, **51**, 316–328.

View Article Online
DOI: 10.1039/C3OB41622D

31. J.-J. Shie, J.-M. Fang and C.-H. Wong, *Angew. Chem. Int. Ed.*, 2008, **47**, 5788–5791.

32. B. Carbain, P. J. Collins, L. Callum, S. R. Martin, A. J. Hay, J. McCauley and H. Streicher, *ChemMedChem*, 2009, **4**, 335–337.

33. D. S. Gunasekera, *Synlett*, 2012, 573–576.

34. B. K. Radatus, K. S. K. Murthy, G. Weeratunga, S. E. Horne, K. K. Kothakonda, E. C. G. Wolf and Z. Wang, US patent 2008/0009639 A1.

35. J. Ma, Y. Zhao, S. Ng, J. Zhang, J. Zeng, A. Than, P. Chen and X. W. Liu, *Chem. Eur. J.*, 2010, **16**, 4533–4540.

36. N. Chuanopparat, N. Kongkathip and B. Kongkathip, *Tetrahedron Lett.*, 2012, **53**, 6209–6211.

37. N. Chuanopparat, N. Kongkathip and B. Kongkathip, *Tetrahedron*, 2012, **68**, 6803–6809.

38. J. S. Ko, J. E. Keum and S. Y. Ko, *J. Org. Chem.*, 2010, **75**, 7006–7009.

39. H. Osato, I. L. Jones, A. Q. Chen and C. L. L. Chai, *Org. Lett.*, 2010, **12**, 60–63.

40. B. Bessieres, A. Schoenfelder, C. Verrat, A. Mann, P. Ornstein and C. Pedregal, *Tetrahedron Lett.*, 2002, **43**, 7659–7662.

41. J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247–258.

View Article Online
DOI: 10.1039/C3OB41622D

42. X. Eric Hu, *Tetrahedron*, 2004, **60**, 2701–2743.

43. S. Stanković, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe, and H.-J. Ha, *Chem. Soc. Rev.*, 2012, **41**, 643–665.

44. G. W. J. Fleet and T. K. M. Shing, *J. Chem. Soc., Chem. Commun.*, 1983, 849–850.

45. H. Mack, J. V. Basabe and R. Brossmer, *Carbohydr. Res.*, 1988, **175**, 311–316.

46. Y. Cai, C. C. Ling and D. R. Bundle, *J. Org. Chem.*, 2009, **74**, 580–589.

47. M. T. Reetz, R. Peter and M. von Itzstein, *Chem. Ber.*, 1987, **120**, 121–122.

48. S. Mirza and J. Harvey, *Tetrahedron Lett.*, 1991, **32**, 4111–4114.

49. E. D. Goddard-Borger and R. V. Stick, *Org. Lett.*, 2007, **9**, 3797–3800.

50. L. D. Nie, X. X. Shi, K. H. Ko and W. D. Lu, *J. Org. Chem.*, 2009, **74**, 3970–3973.

51. G. W. J. Fleet, T. K. M. Shing and S. M. Warr, *J. Chem. Soc.*, *Perkin Trans. 1*, 1984, 905–908.

52. H. K. Ulbrich, A. Luxenburger, P. Prech, E. E. Eriksson, O. Soehnlein, P. Rotzius, L. Lindbom and G. Dannhardt, *J. Med. Chem.*, 2006, **49**, 5988–5999.

53. E. Öhler and S. Kotzinger, *Liebigs Ann. Chem.*, 1993, 269–280.

Electronic Supplementary Information

View Article Online
DOI: 10.1039/C3OB41622D

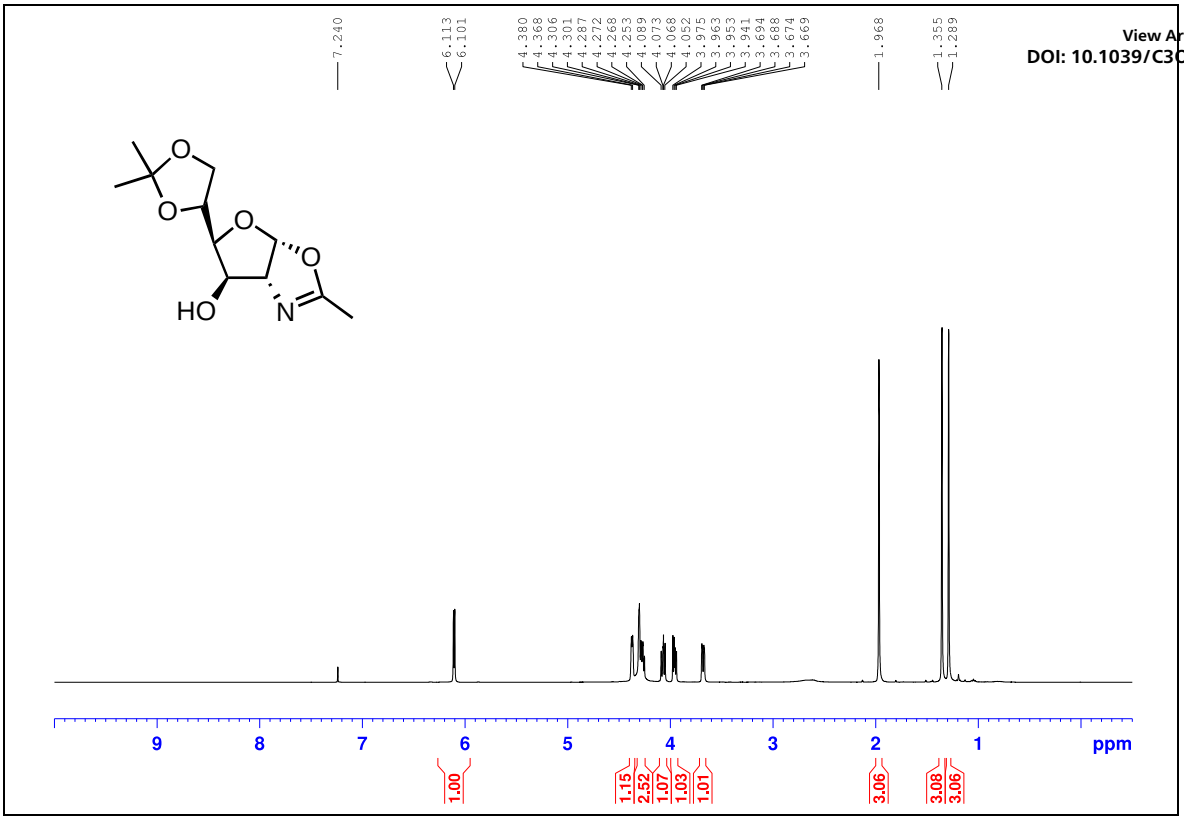
Synthesis of Oseltamivir and Tamiphosphor from *N*-Acetyl-D-glucosamine

Chih-An Chen[a] and Jim-Min Fang*[ab]

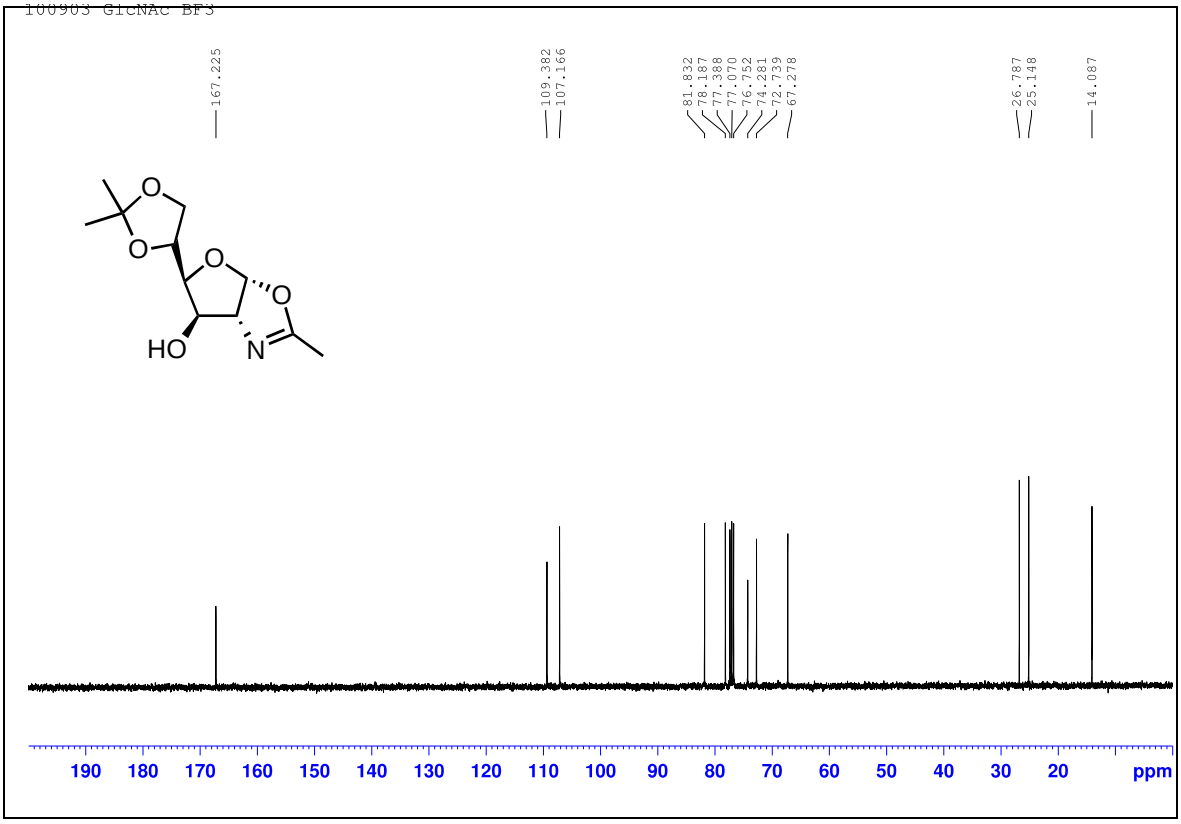
[a]*Department of Chemistry, National Taiwan University, Taipei 106, Taiwan. E-mail*: jmfang@ntu.edu.tw; *Fax: (8862) 23637812; Tel: (8862) 33661663*

[b]*The Genomics Research Center, Academia Sinica, Taipei, 115, Taiwan.*

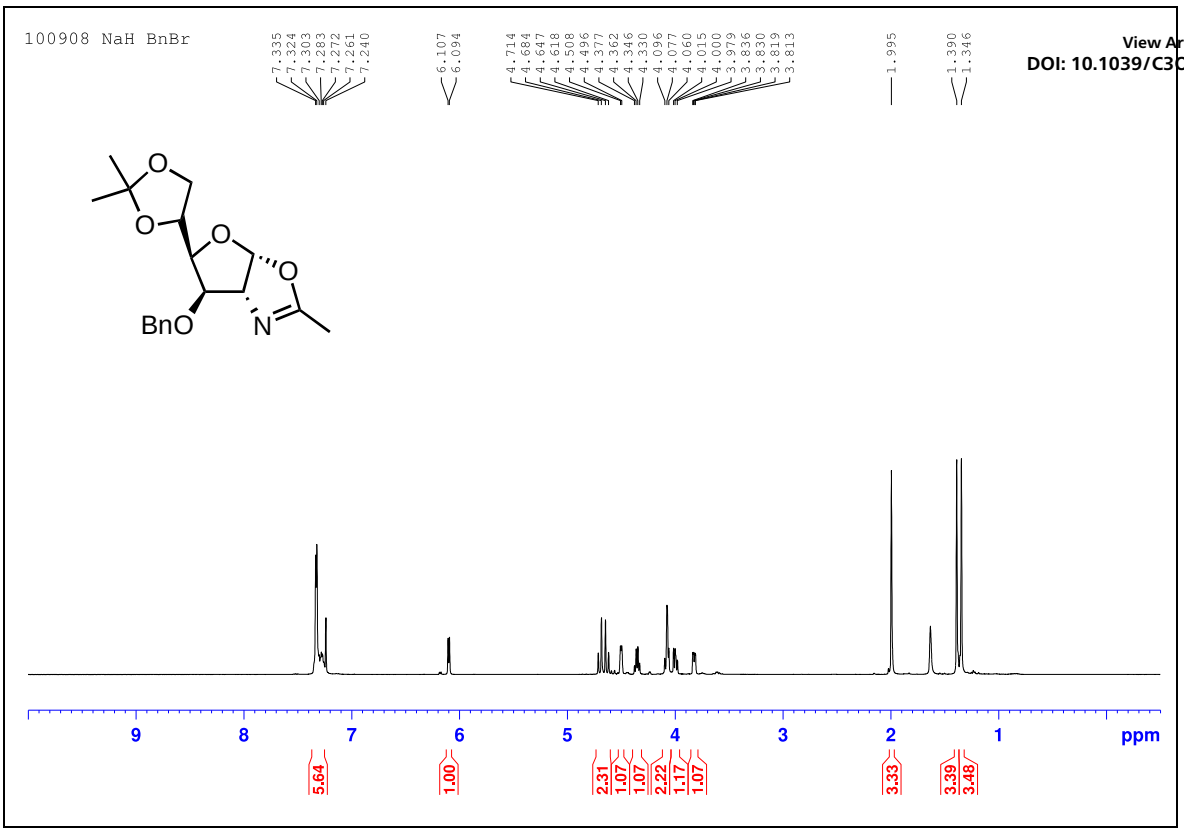
Contents	**Page number**



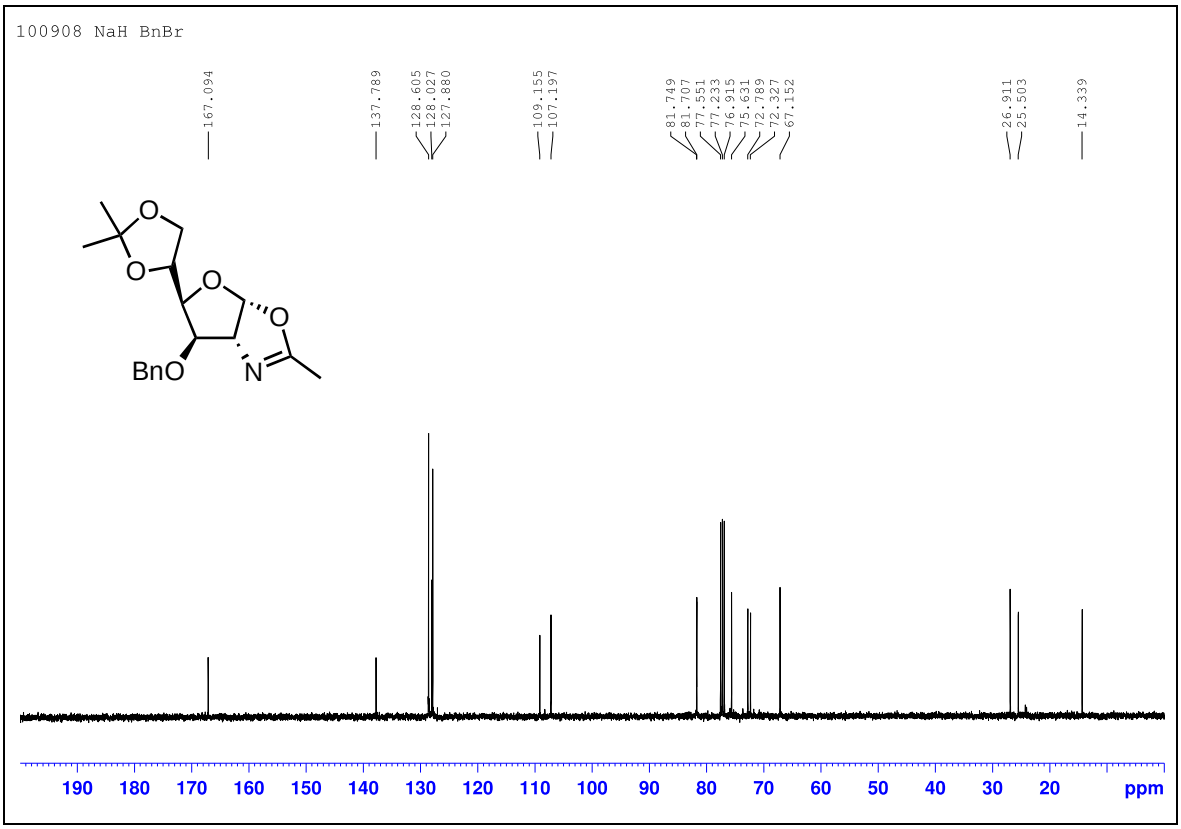
^{1}H NMR spectrum of compound **4** ($CDCl_3$, 400 MHz)



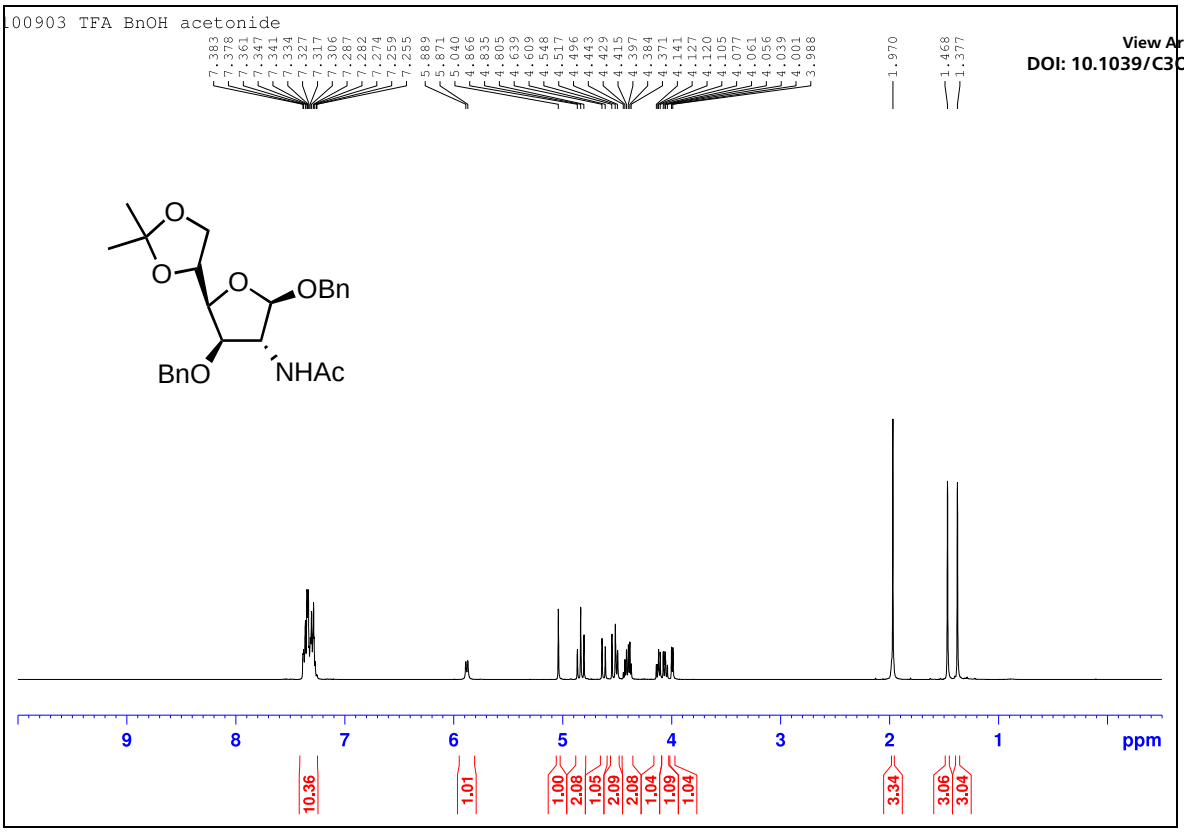
^{13}C NMR spectrum of compound **4** ($CDCl_3$, 100 MHz)



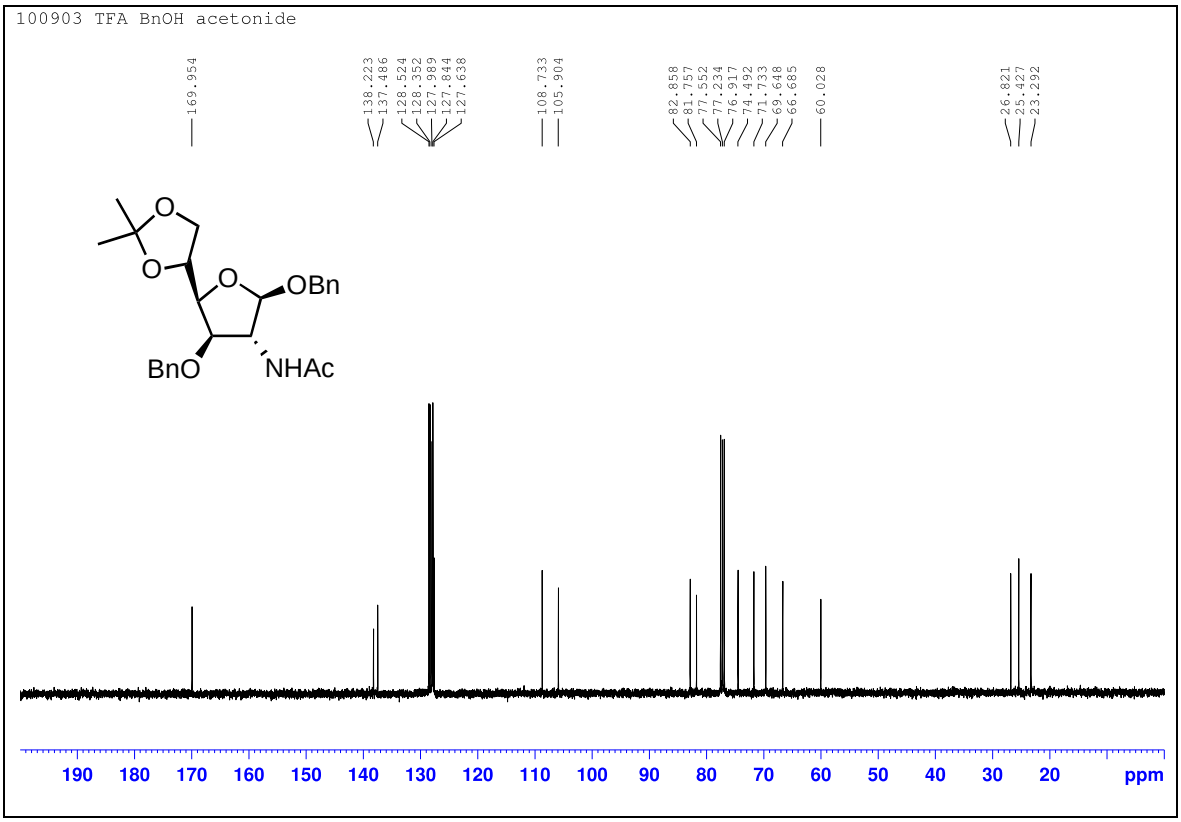
^{1}H NMR spectrum of compound **5** ($CDCl_3$, 400 MHz)



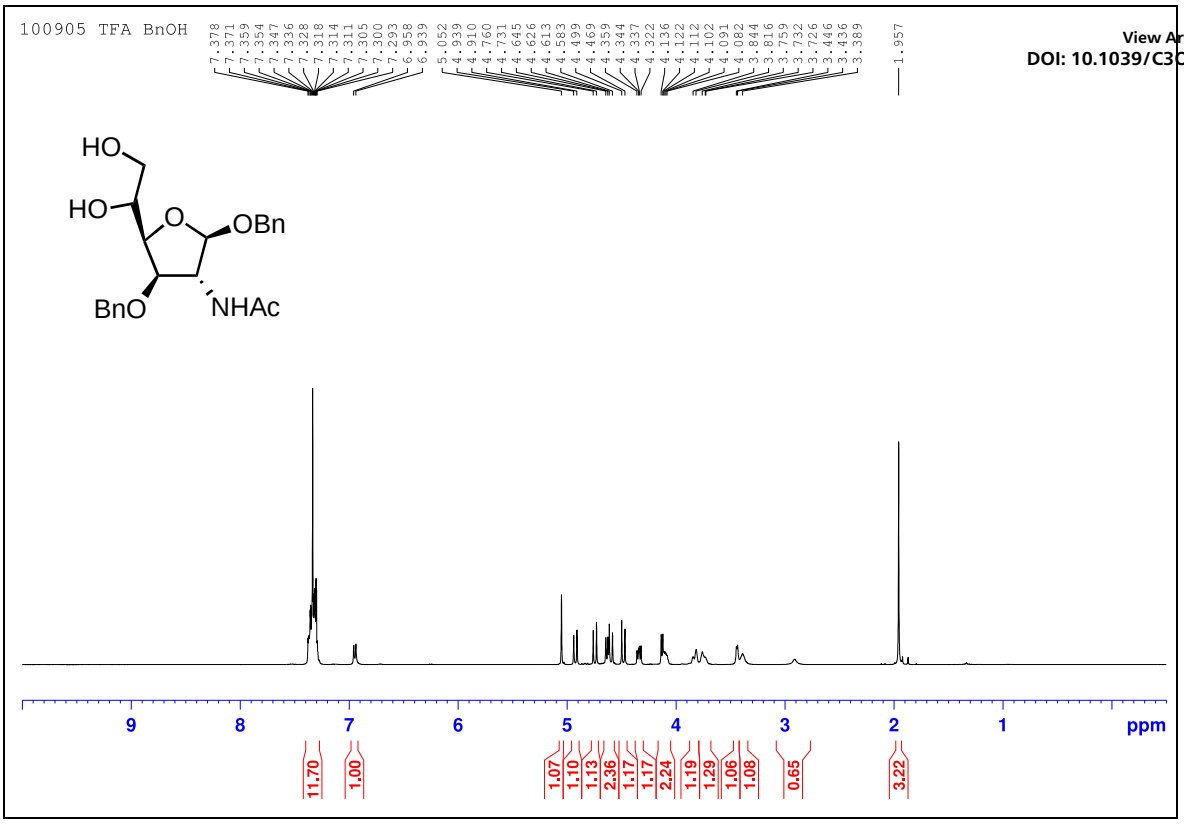
^{13}C NMR spectrum of compound **5** ($CDCl_3$, 100 MHz)



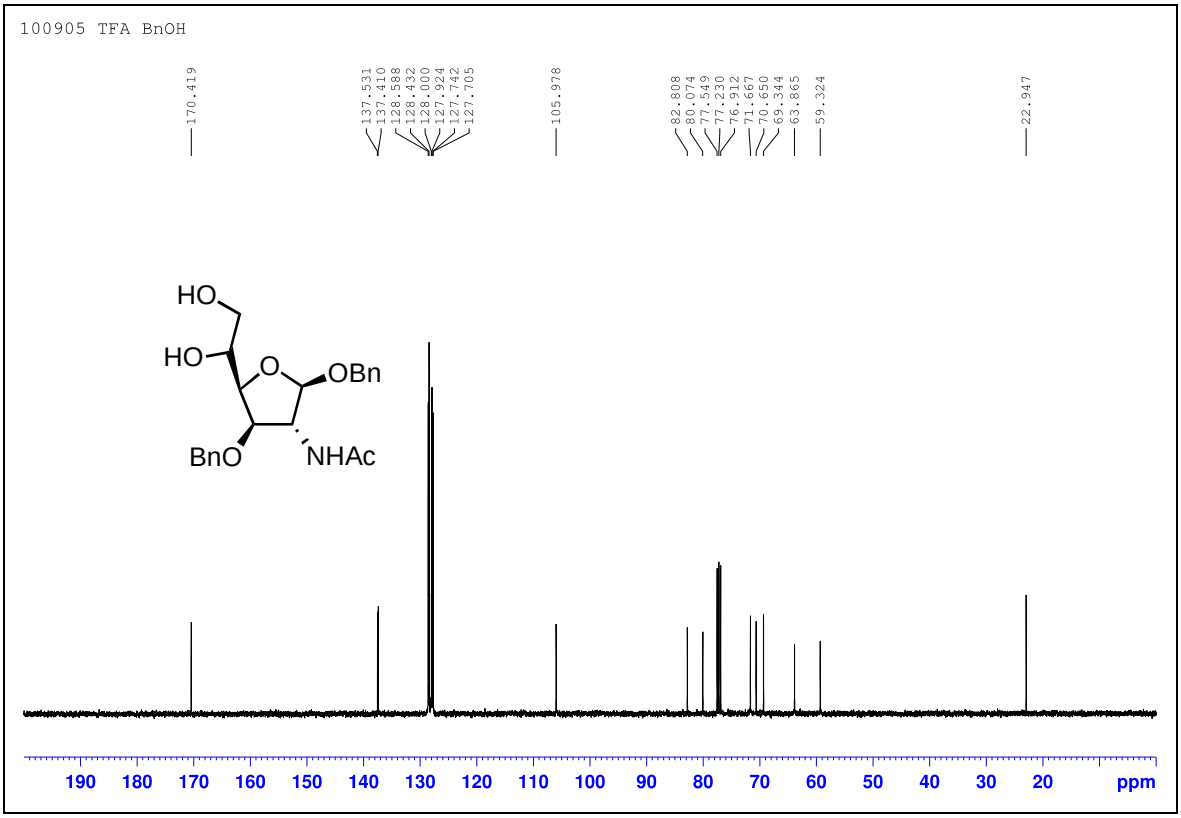
^{1}H NMR spectrum of compound **6** ($CDCl_3$, 400 MHz)



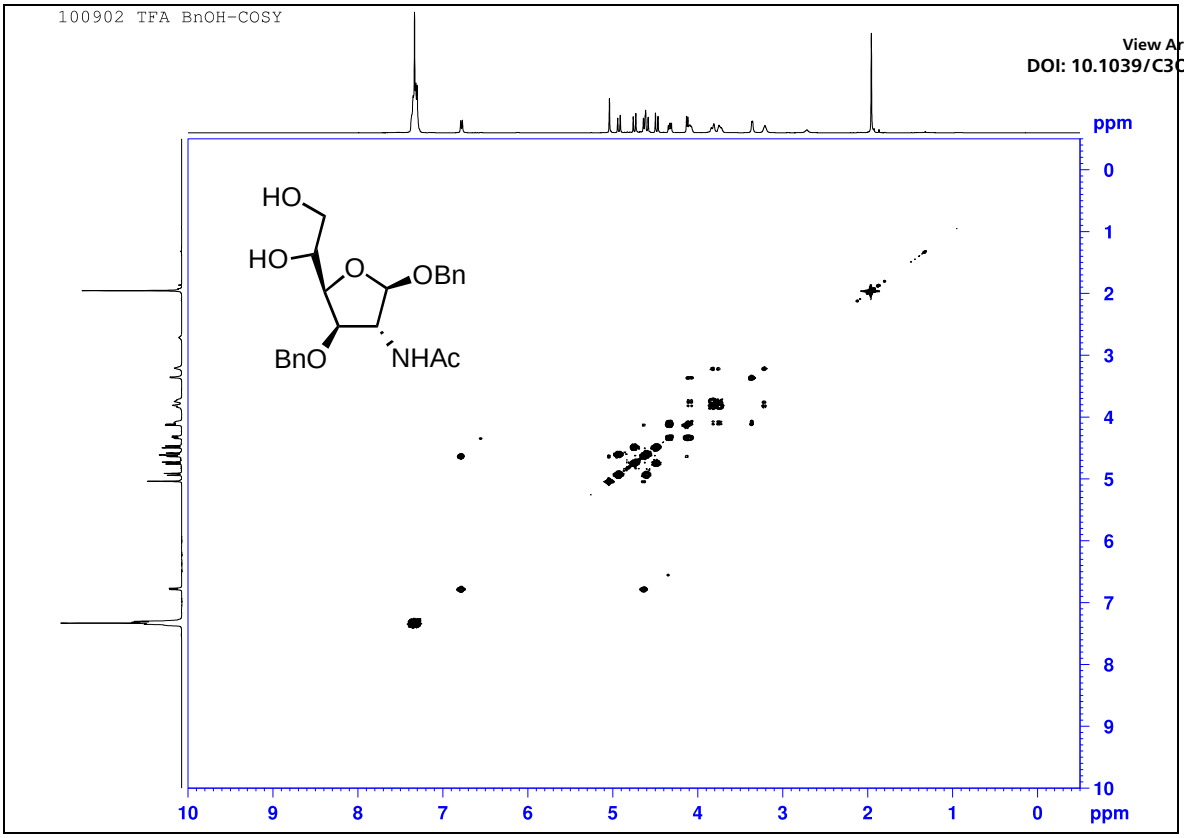
^{13}C NMR spectrum of compound **6** ($CDCl_3$, 100 MHz)



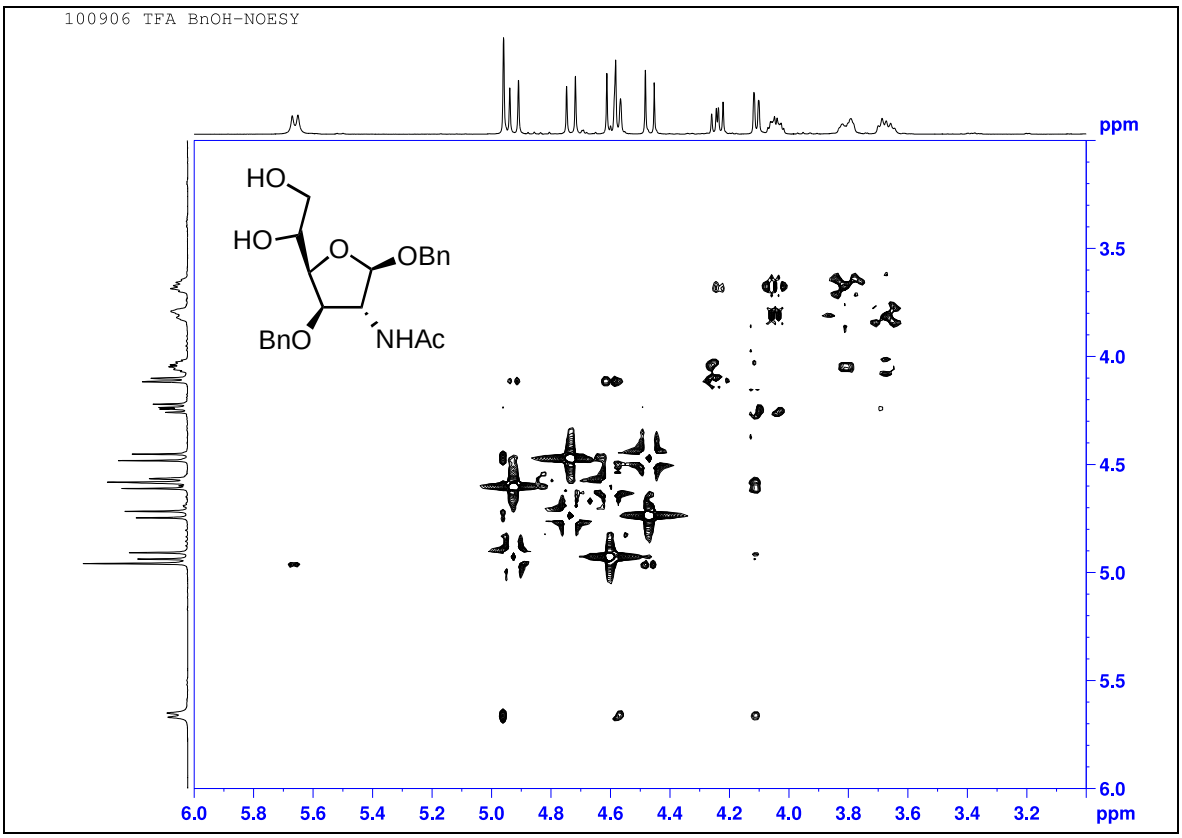
^{1}H NMR spectrum of compound **7** ($CDCl_3$, 400 MHz)



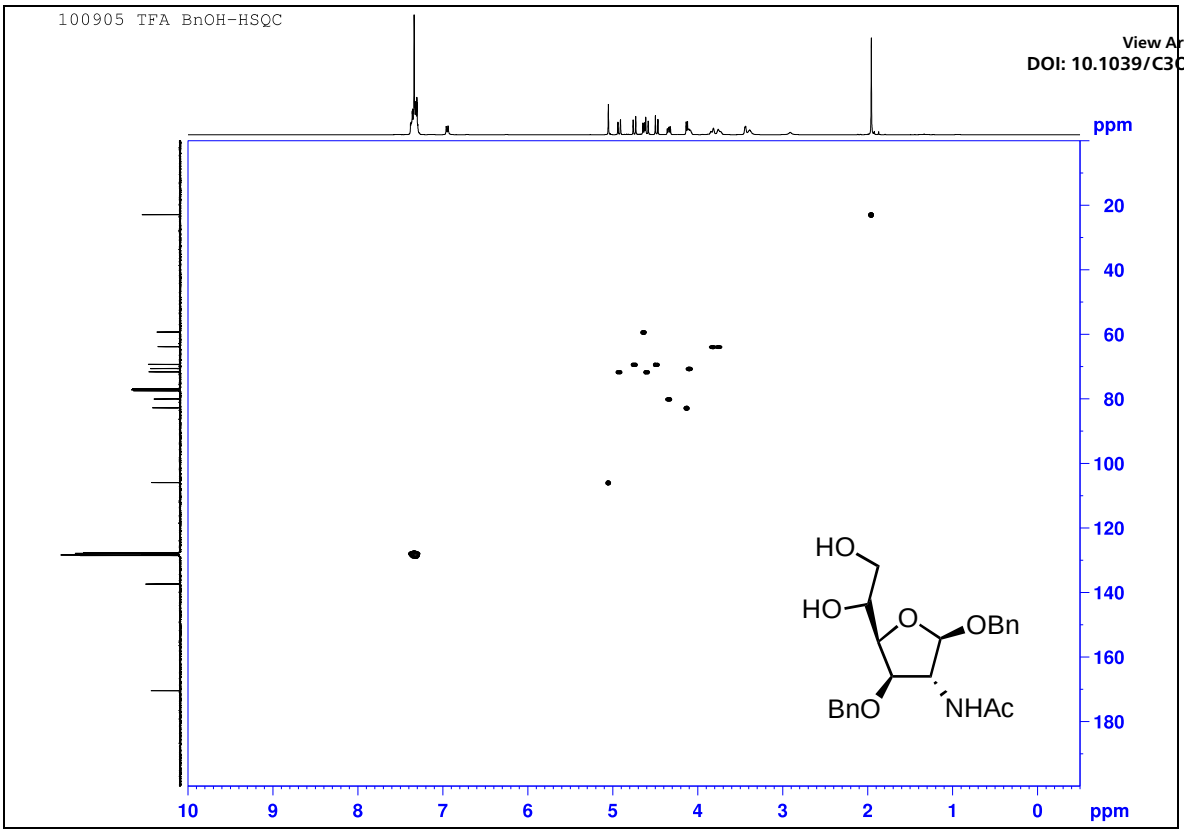
^{13}C NMR spectrum of compound **7** ($CDCl_3$, 100 MHz)



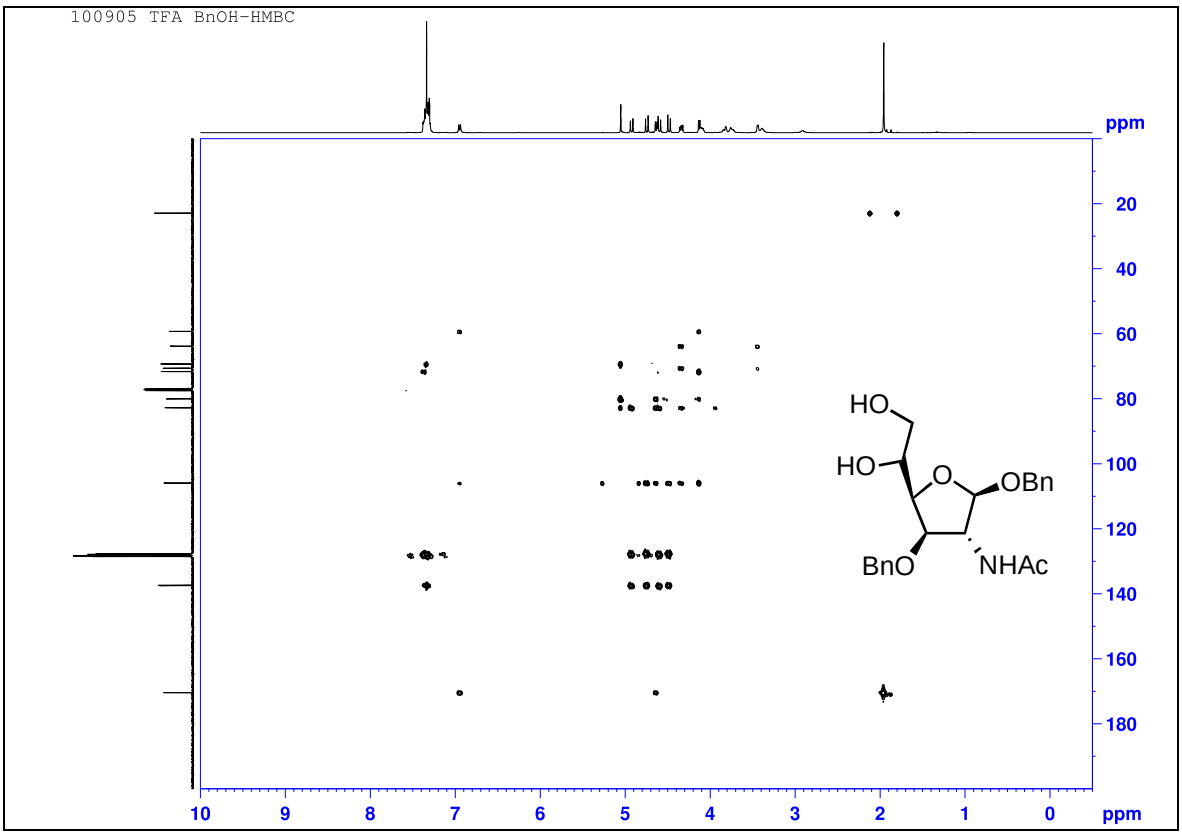
^{1}H–^{1}H COSY NMR spectrum of compound **7** ($CDCl_3$, 400 MHz)



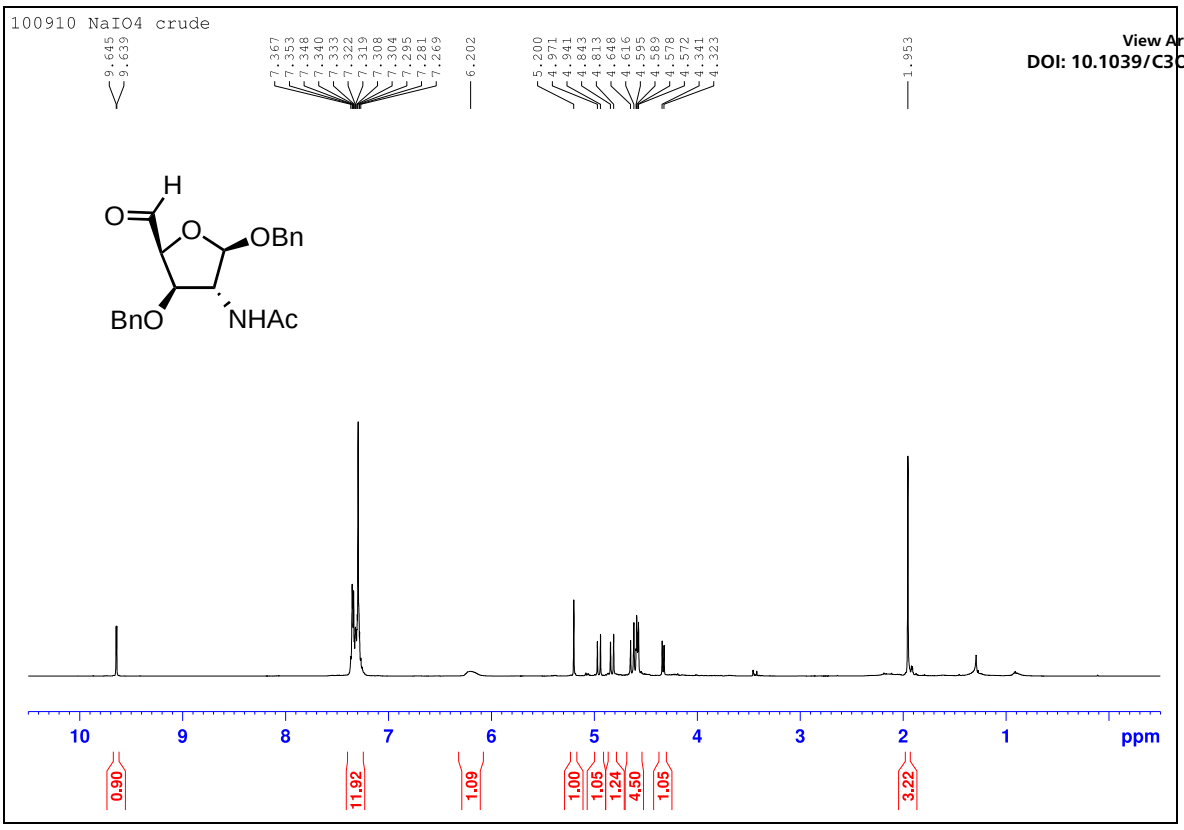
NOESY NMR spectrum of compound **7** ($CDCl_3$, 400 MHz)



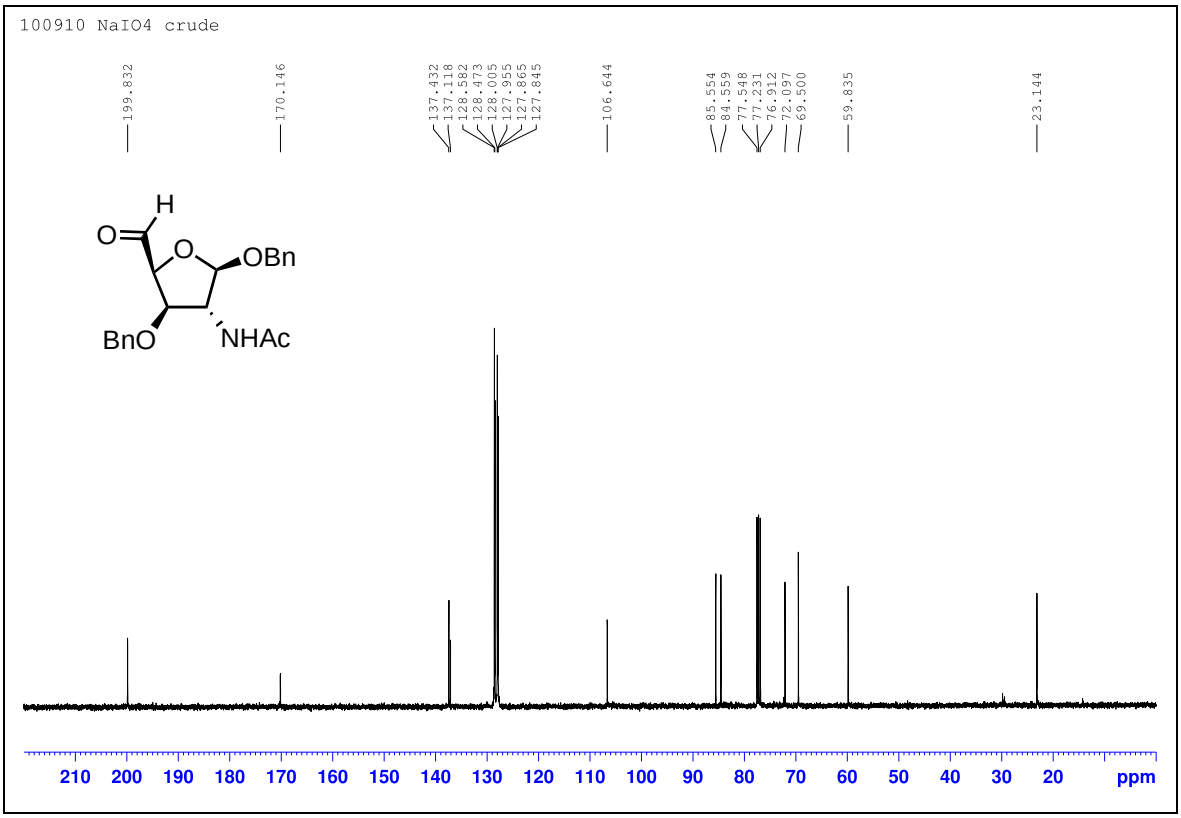
^{1}H–^{13}C HSQC NMR spectrum of compound **7** ($CDCl_3$, 400 MHz)



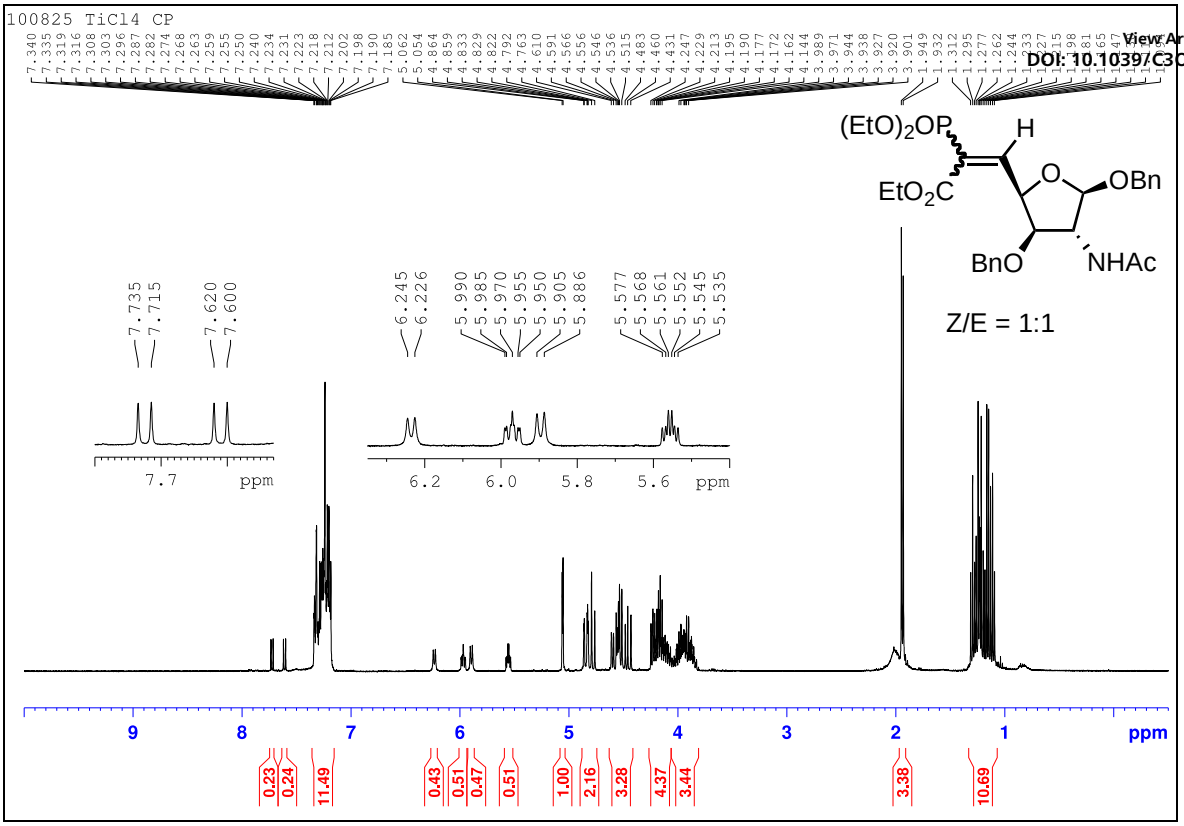
^{1}H–^{13}C HMBC NMR spectrum of compound **7** ($CDCl_3$, 400 MHz)



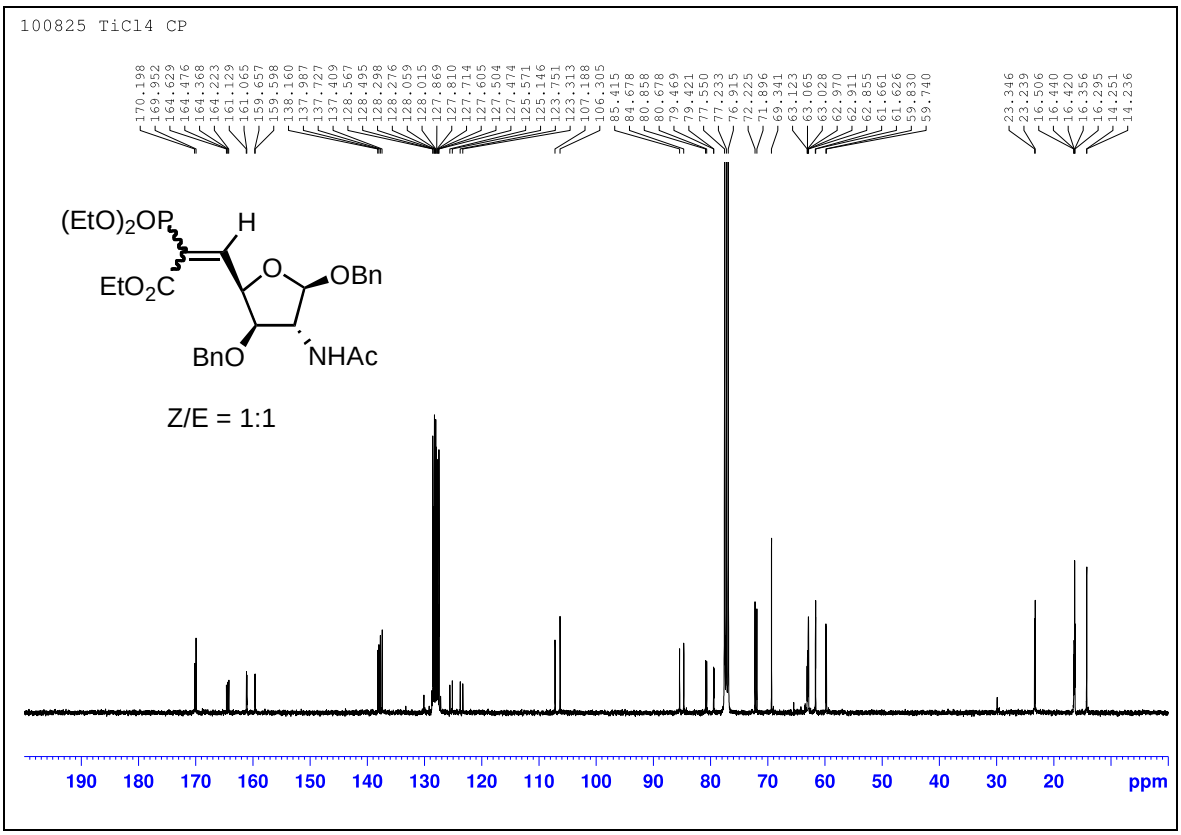
^{1}H NMR spectrum of compound **8** ($CDCl_3$, 400 MHz)



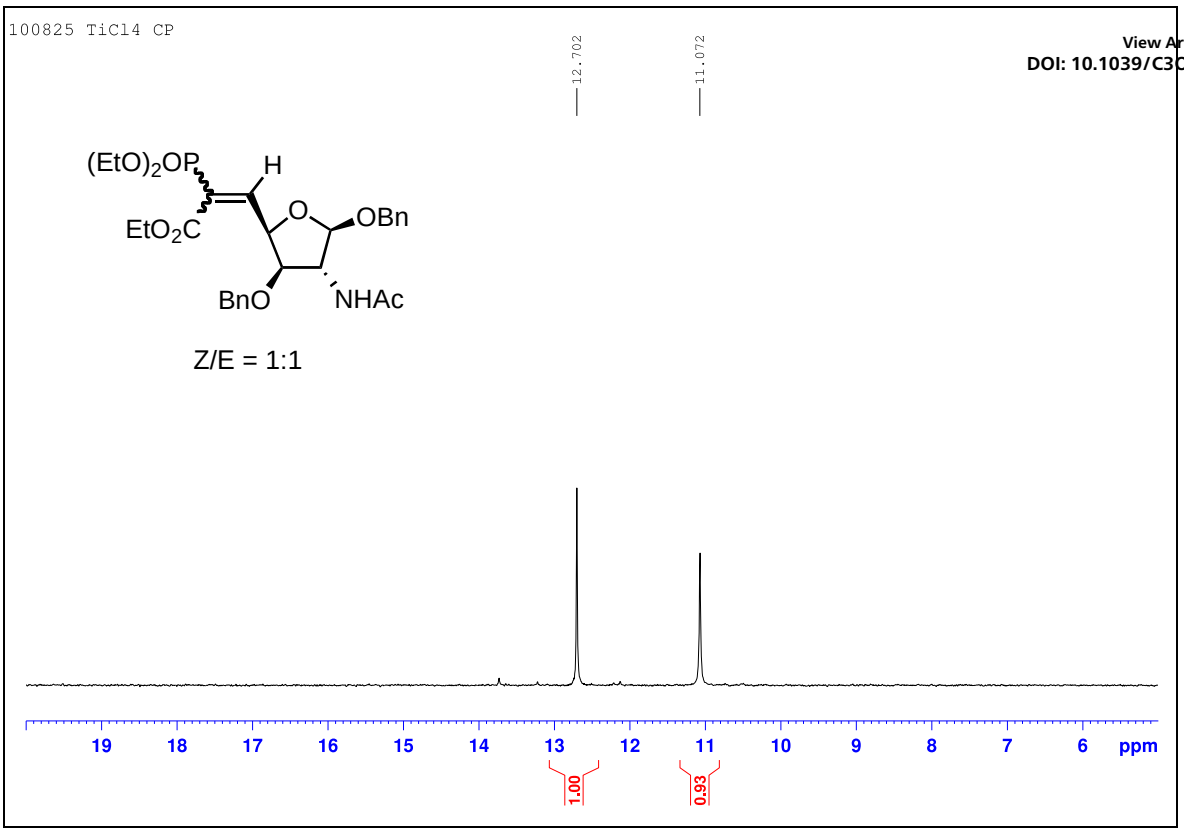
^{13}C NMR spectrum of compound **8** ($CDCl_3$, 100 MHz)



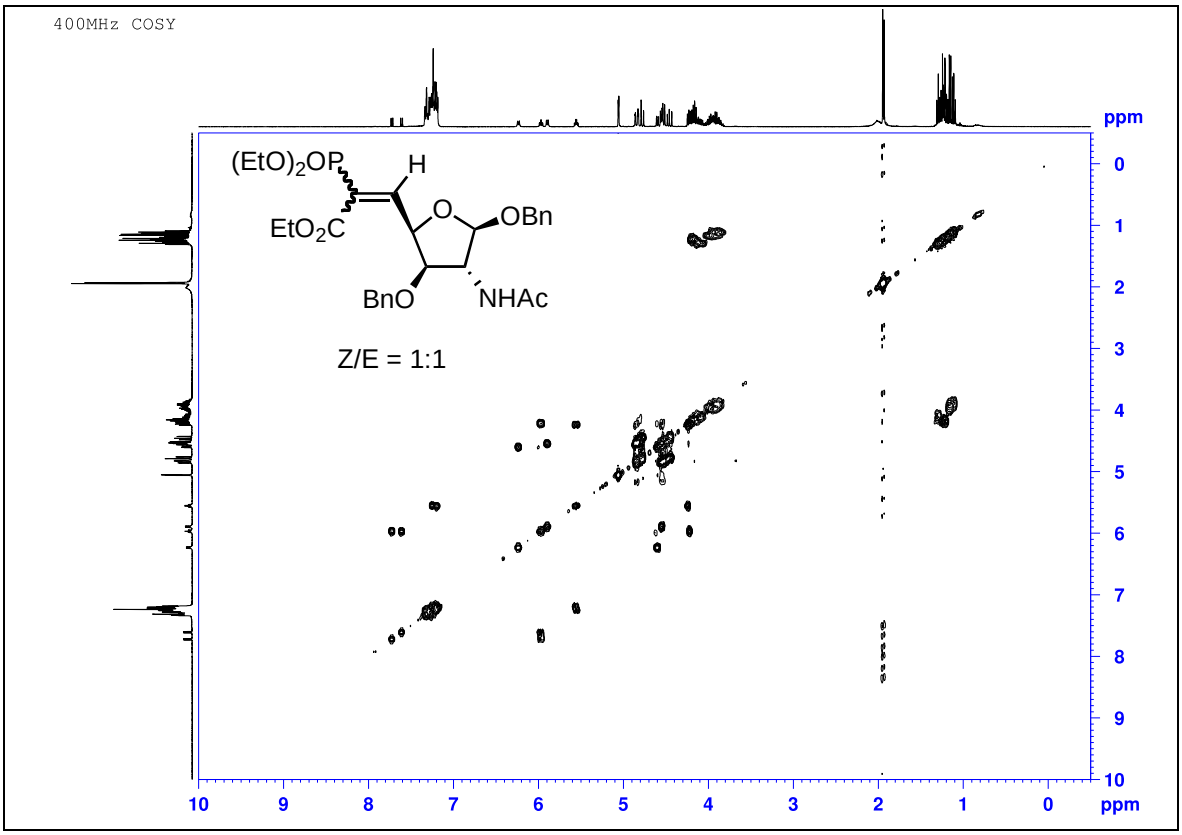
^{1}H NMR spectrum of compound **9** ($CDCl_3$, 400 MHz)



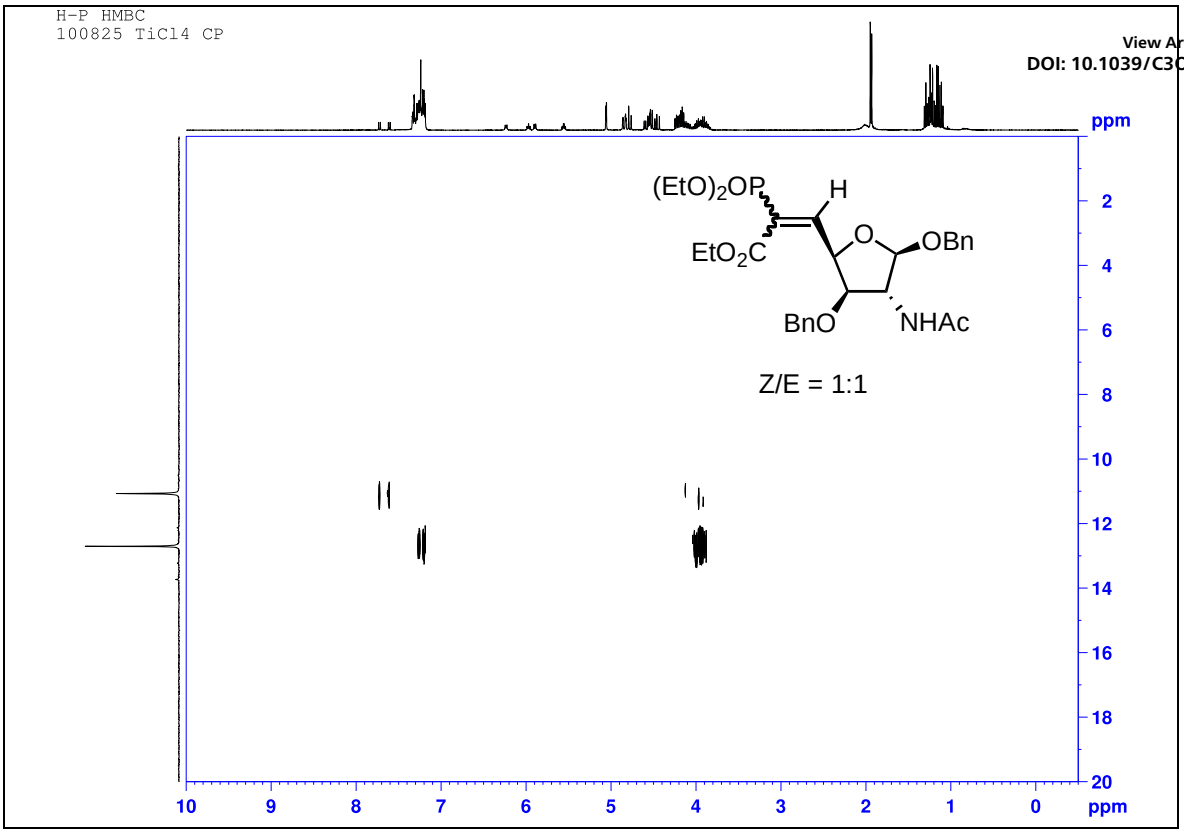
^{13}C NMR spectrum of compound **9** ($CDCl_3$, 100 MHz)



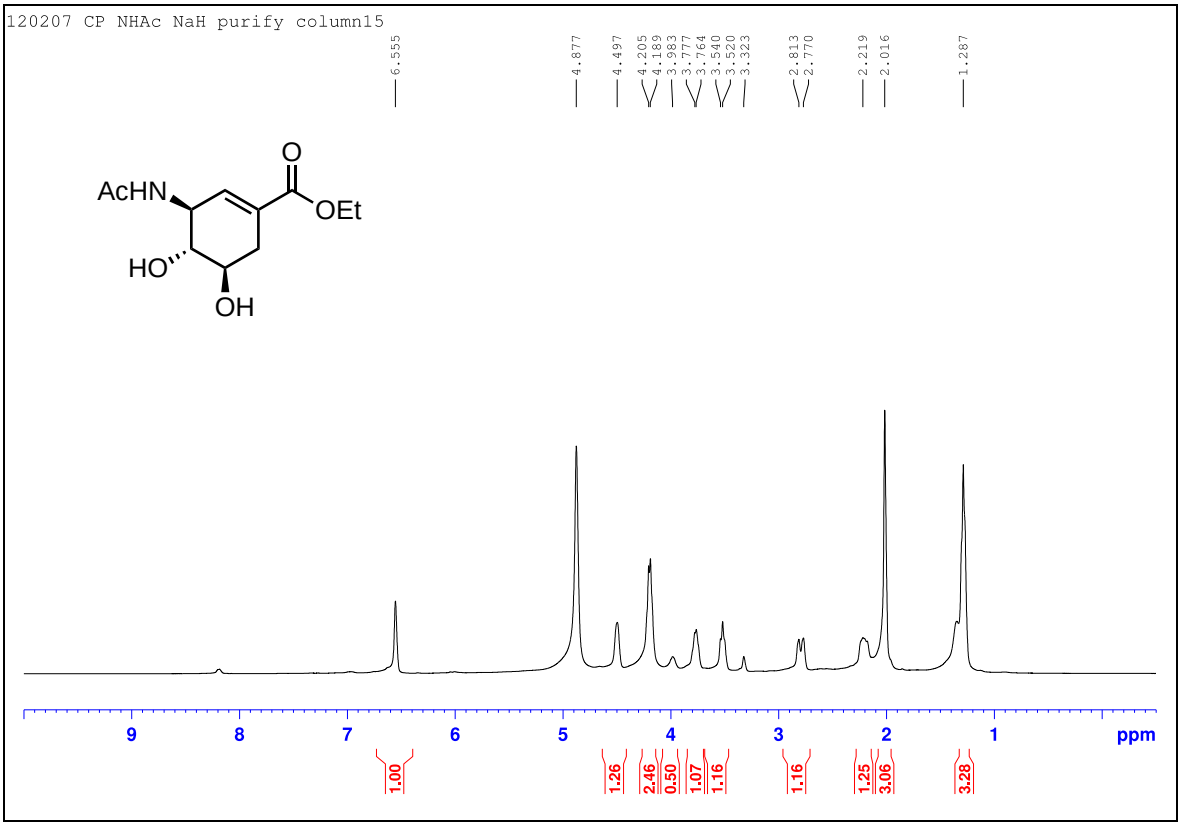
^{31}P NMR spectrum of compound **9** ($CDCl_3$, 162 MHz)



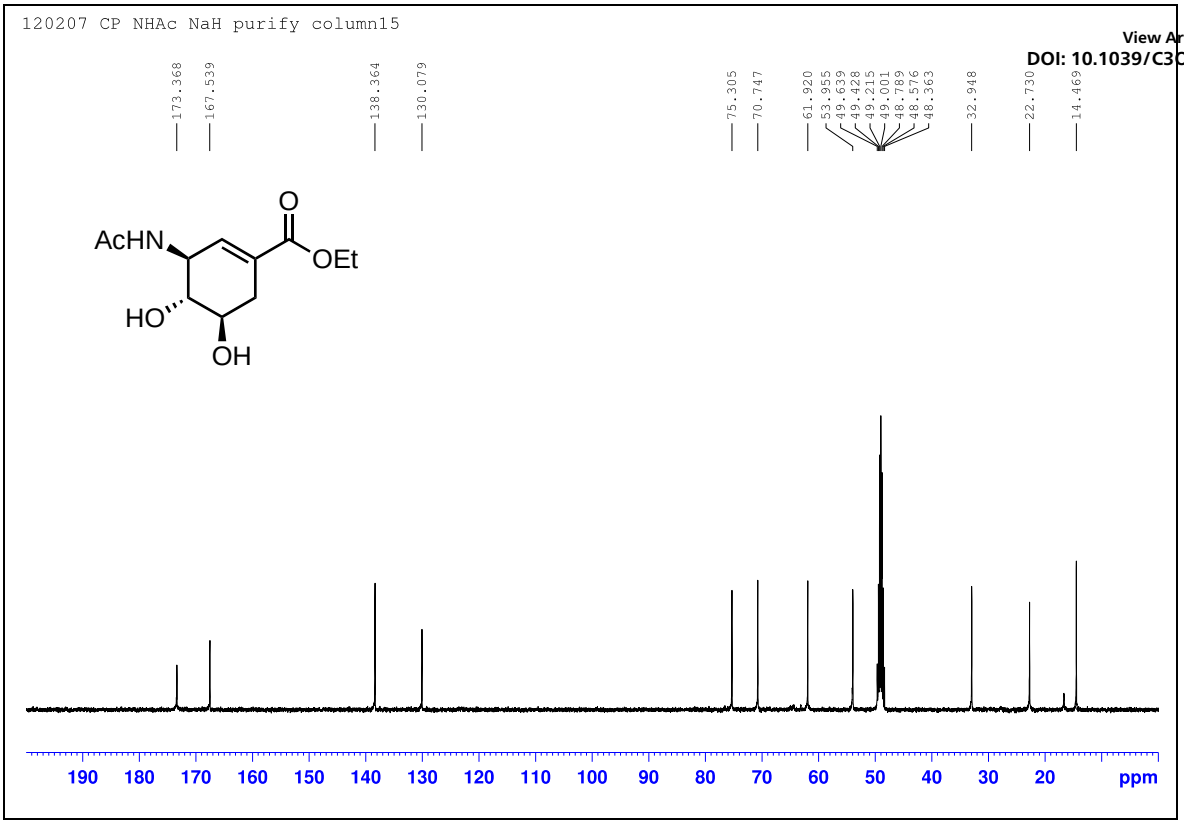
^{1}H–^{1}H COSY NMR spectrum of compound **9** ($CDCl_3$, 400 MHz)



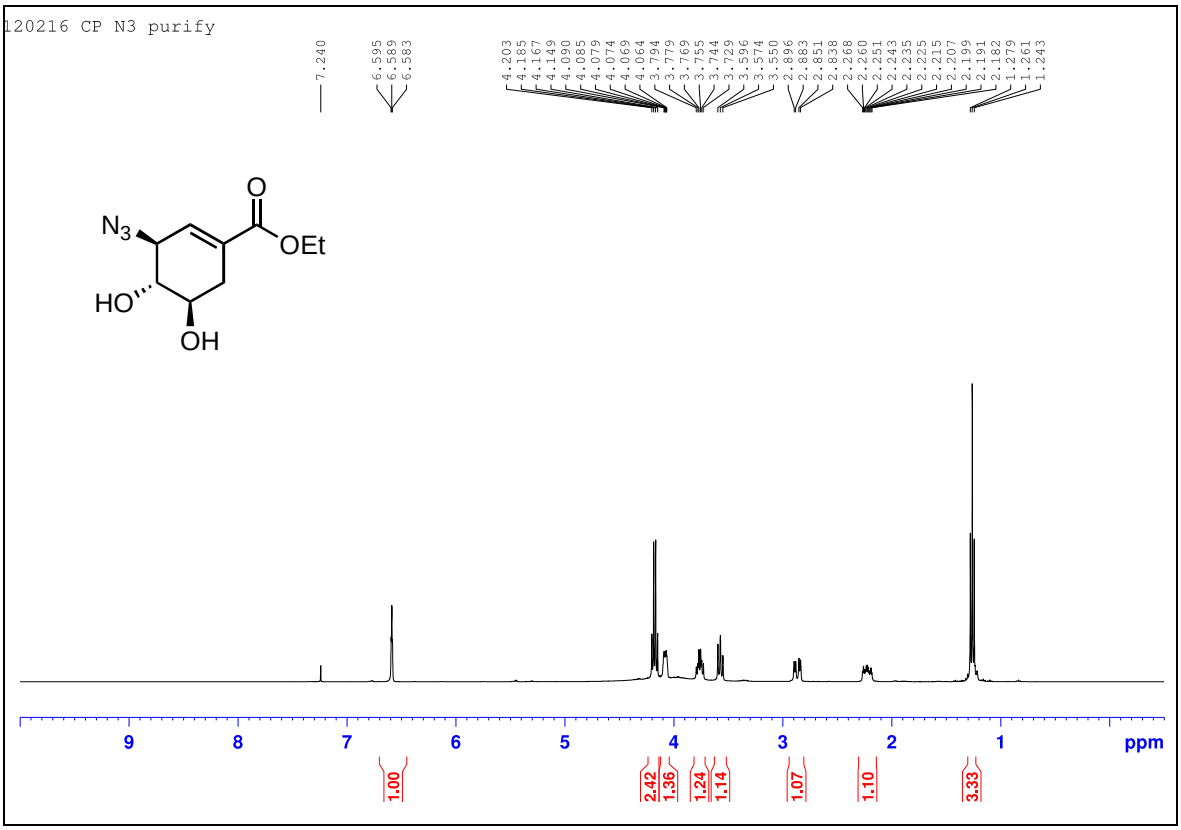
^{1}H–^{31}P HMBC NMR spectrum of compound **9** ($CDCl_3$, 400 MHz)



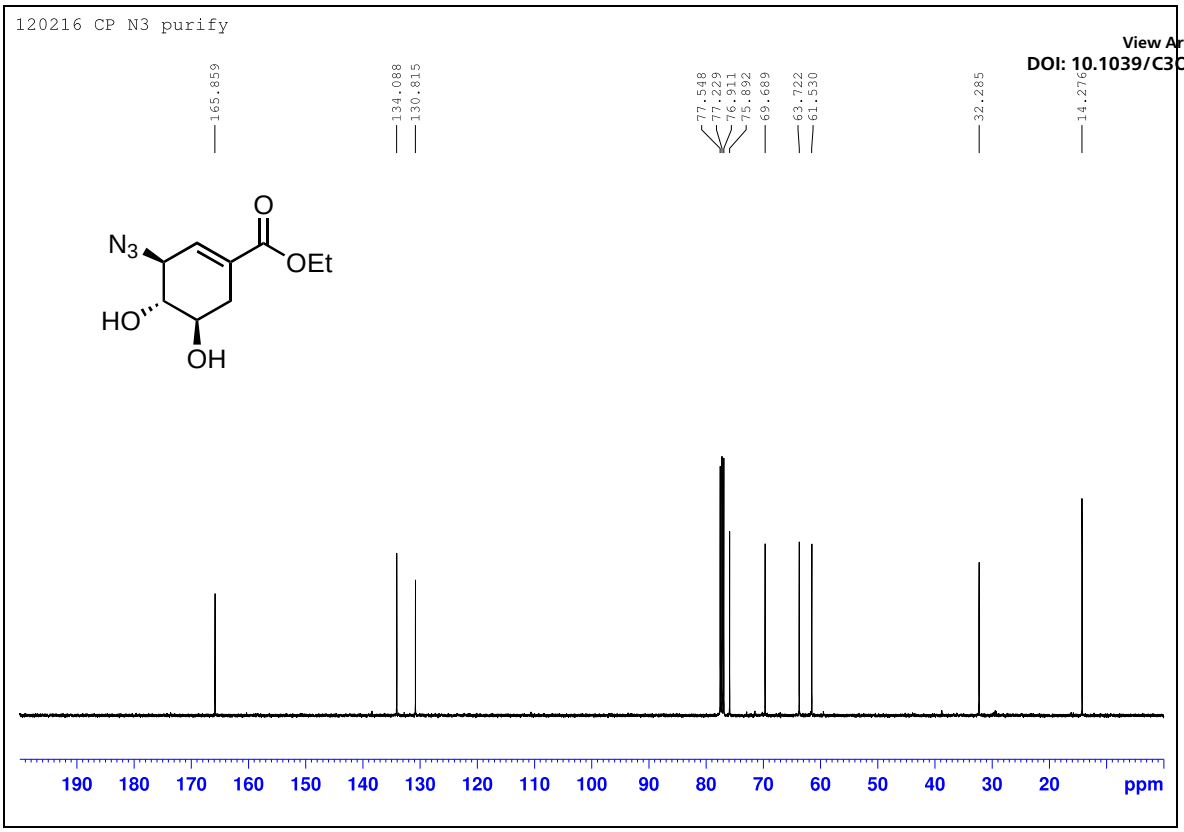
^{1}H NMR spectrum of compound **10** (CD_3OD, 400 MHz)



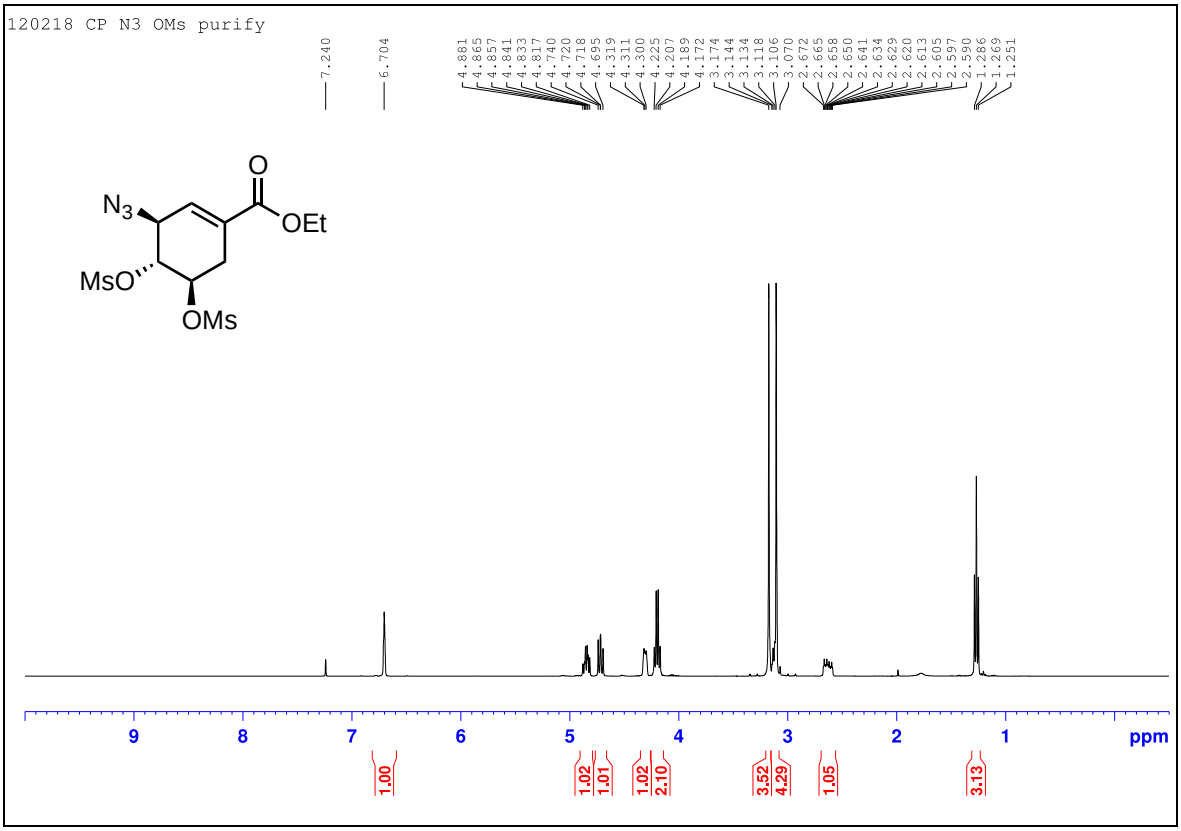
^{13}C NMR spectrum of compound **10** (CD_3OD, 100 MHz)



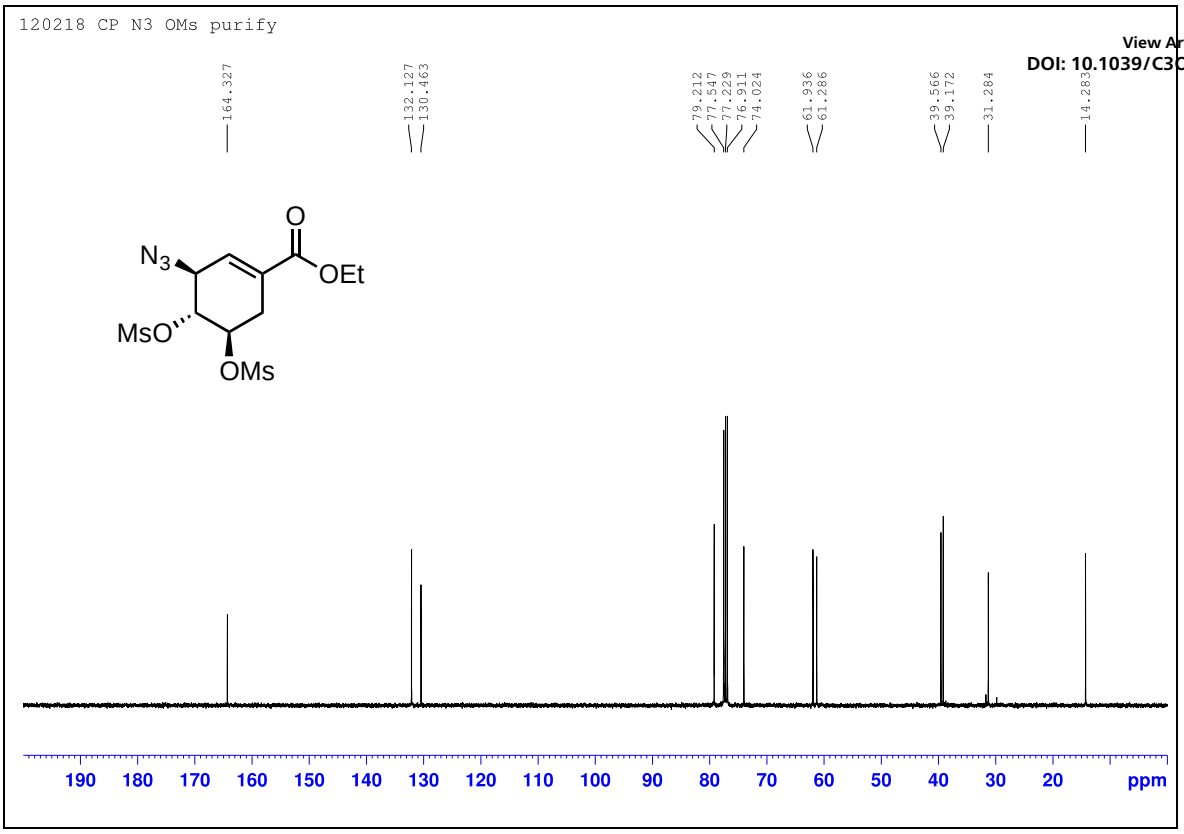
^{1}H NMR spectrum of compound **11** ($CDCl_3$, 400 MHz)



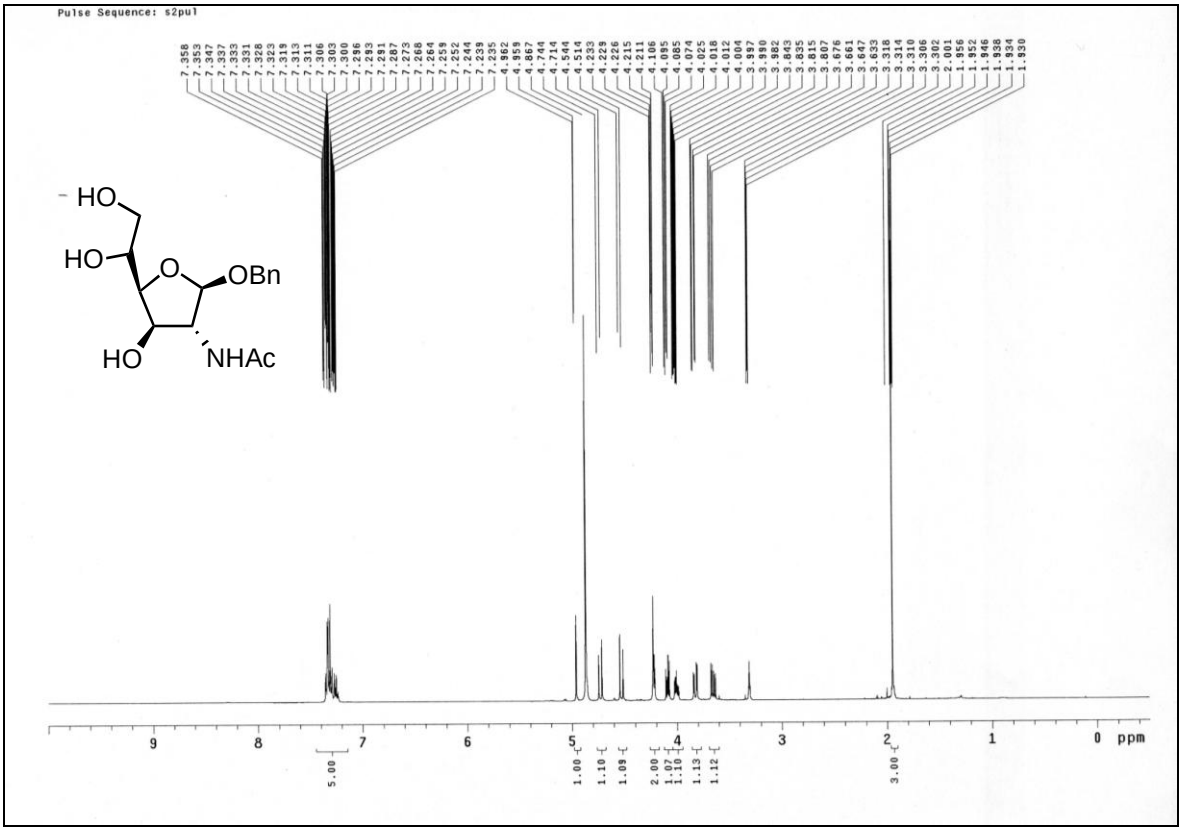
^{13}C NMR spectrum of compound **11** ($CDCl_3$, 100 MHz)



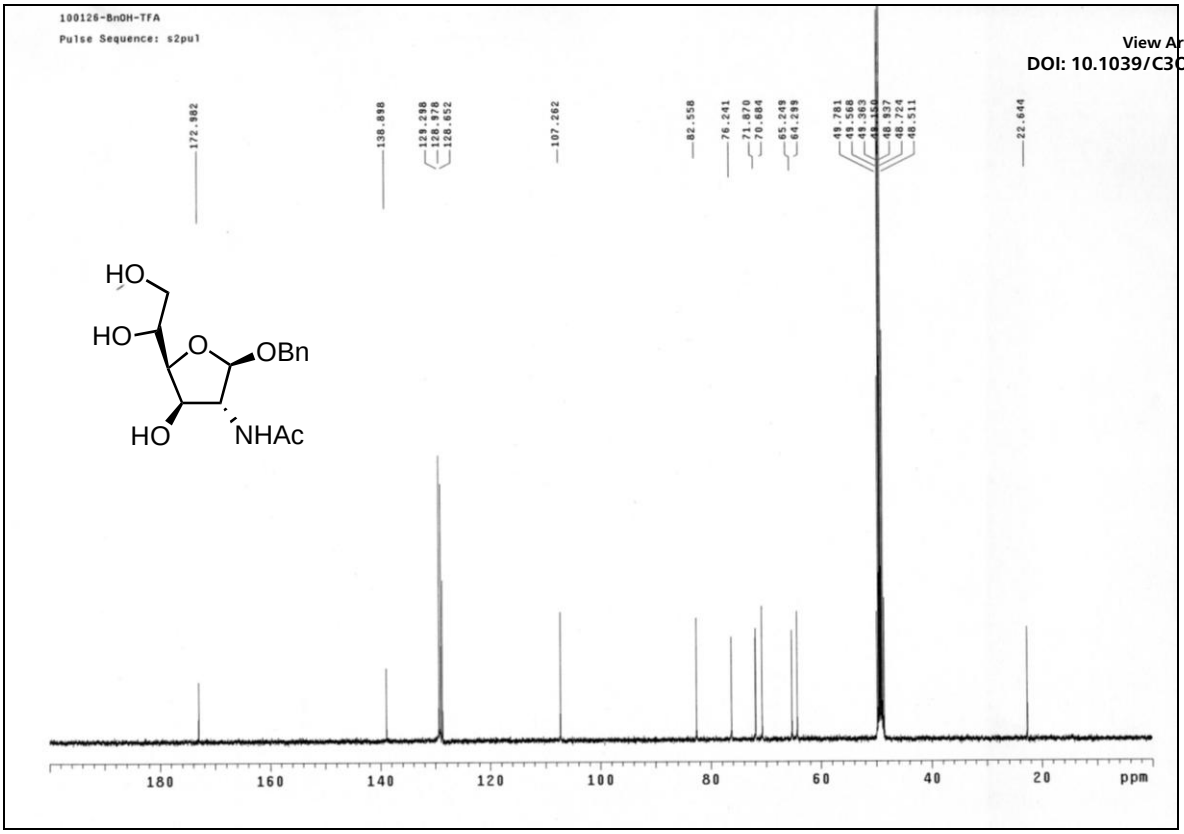
^{1}H NMR spectrum of compound **12** ($CDCl_3$, 400 MHz)



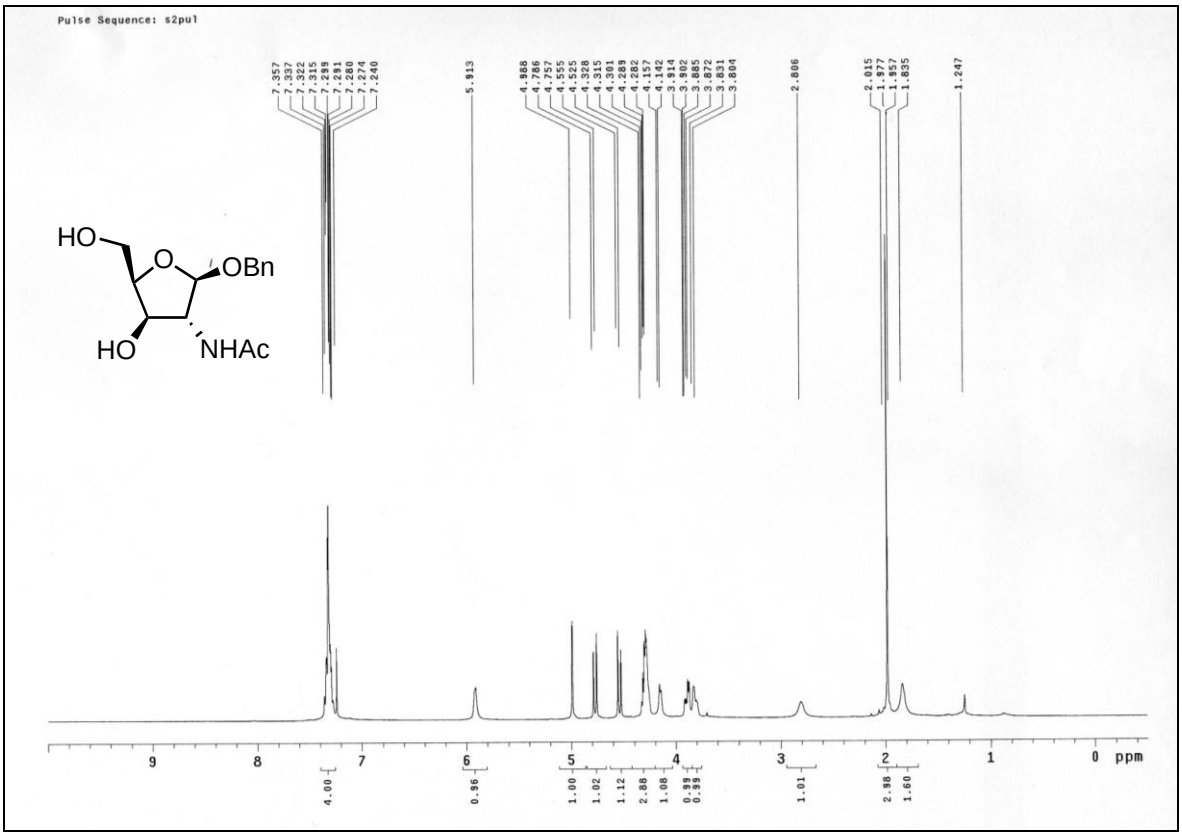
^{13}C NMR spectrum of compound **12** ($CDCl_3$, 100 MHz)



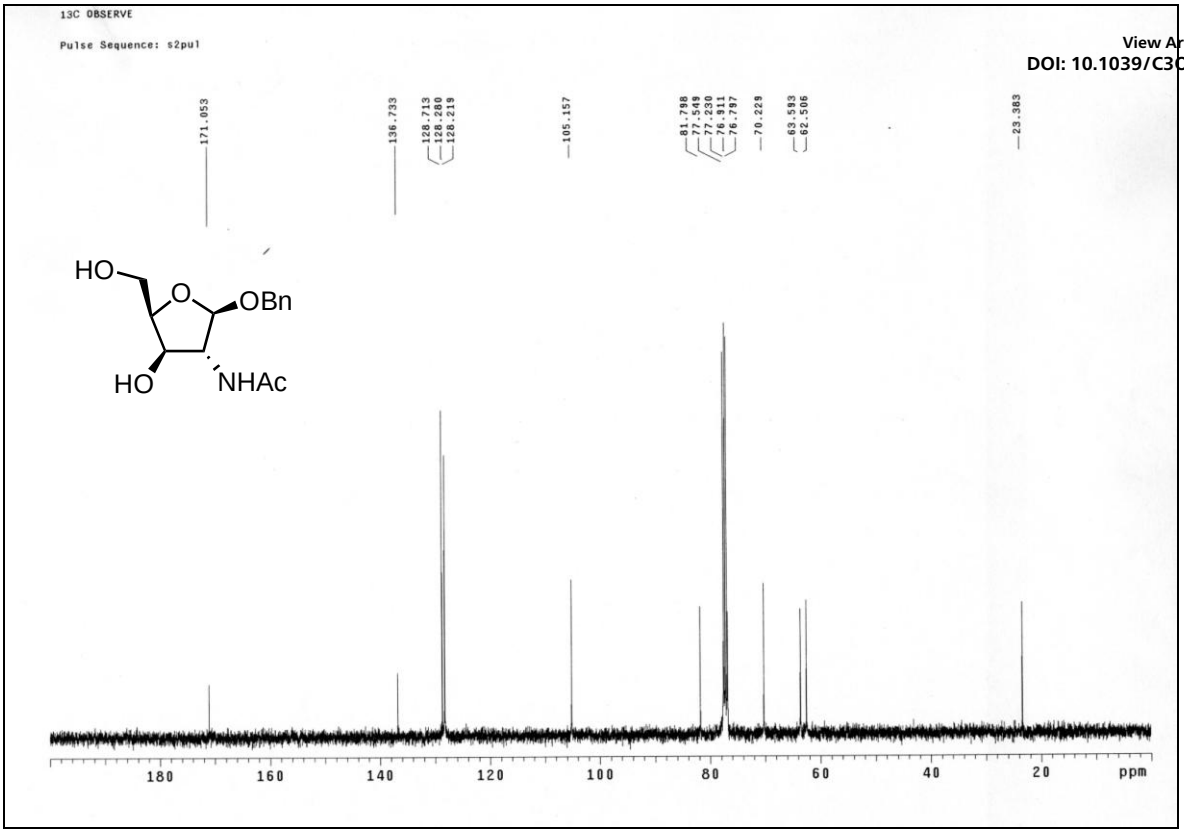
^{1}H NMR spectrum of compound **13** (CD_3OD, 400 MHz)



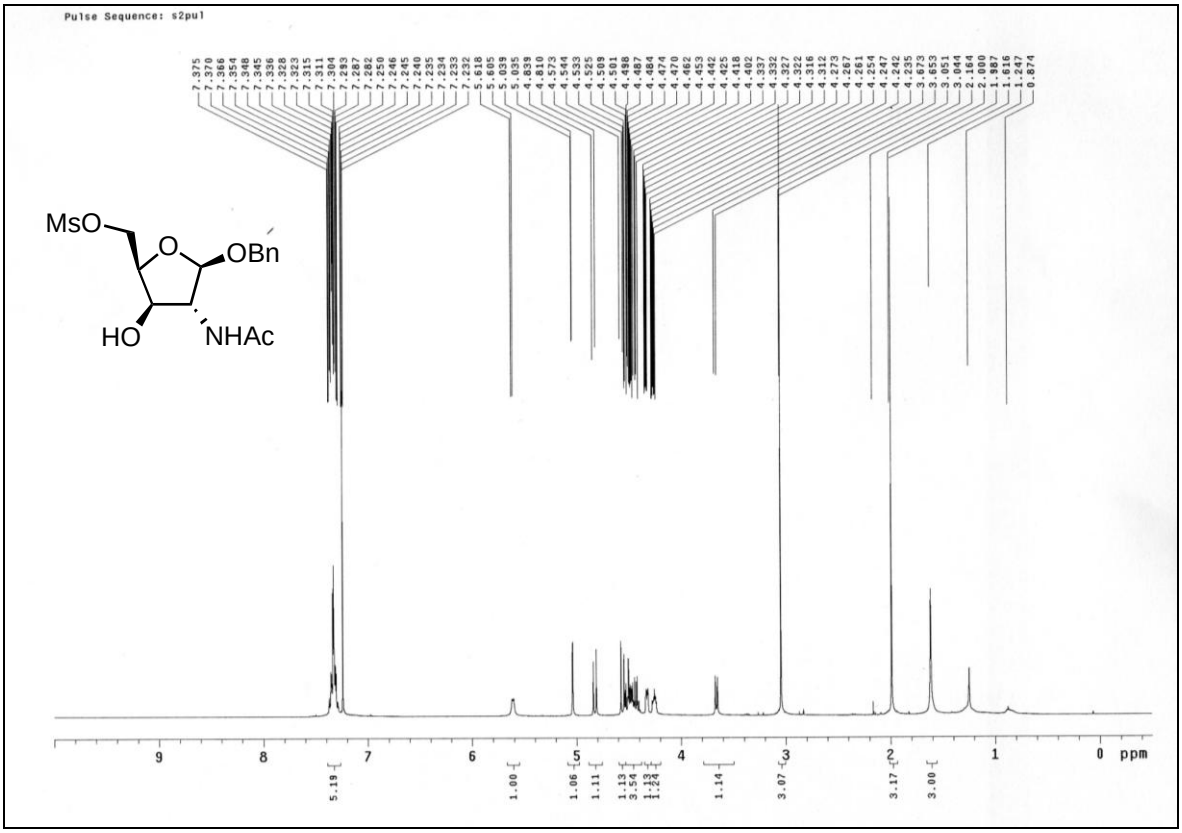
^{13}C NMR spectrum of compound **13** (CD_3OD, 100 MHz)



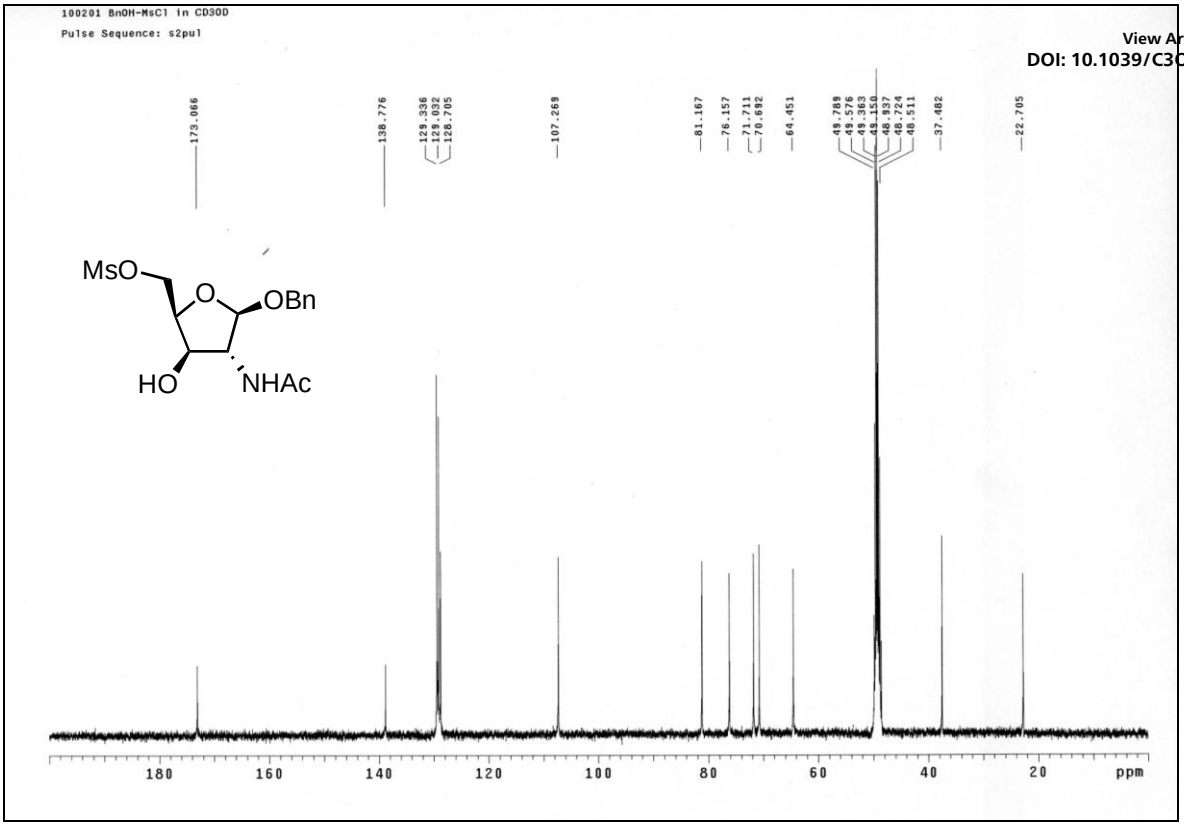
^{1}H NMR spectrum of compound **14** ($CDCl_3$, 400 MHz)



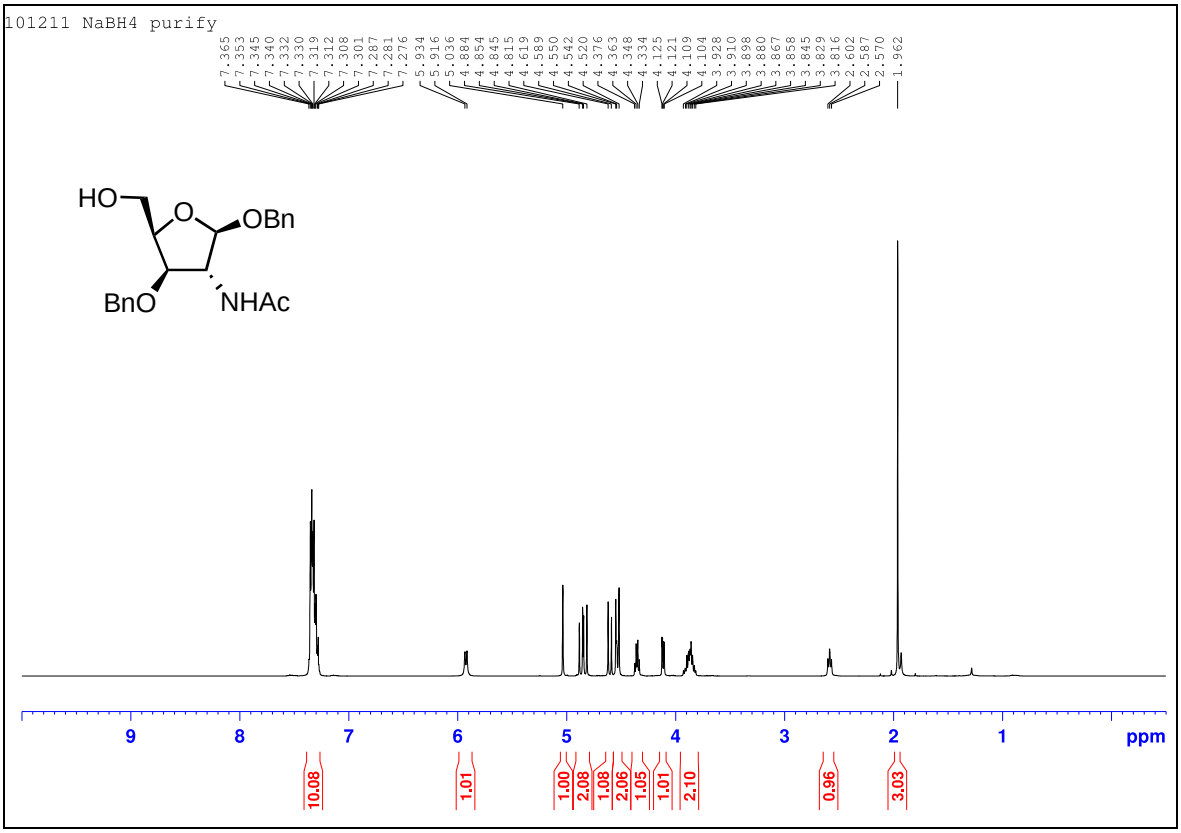
^{13}C NMR spectrum of compound **14** ($CDCl_3$, 100 MHz)



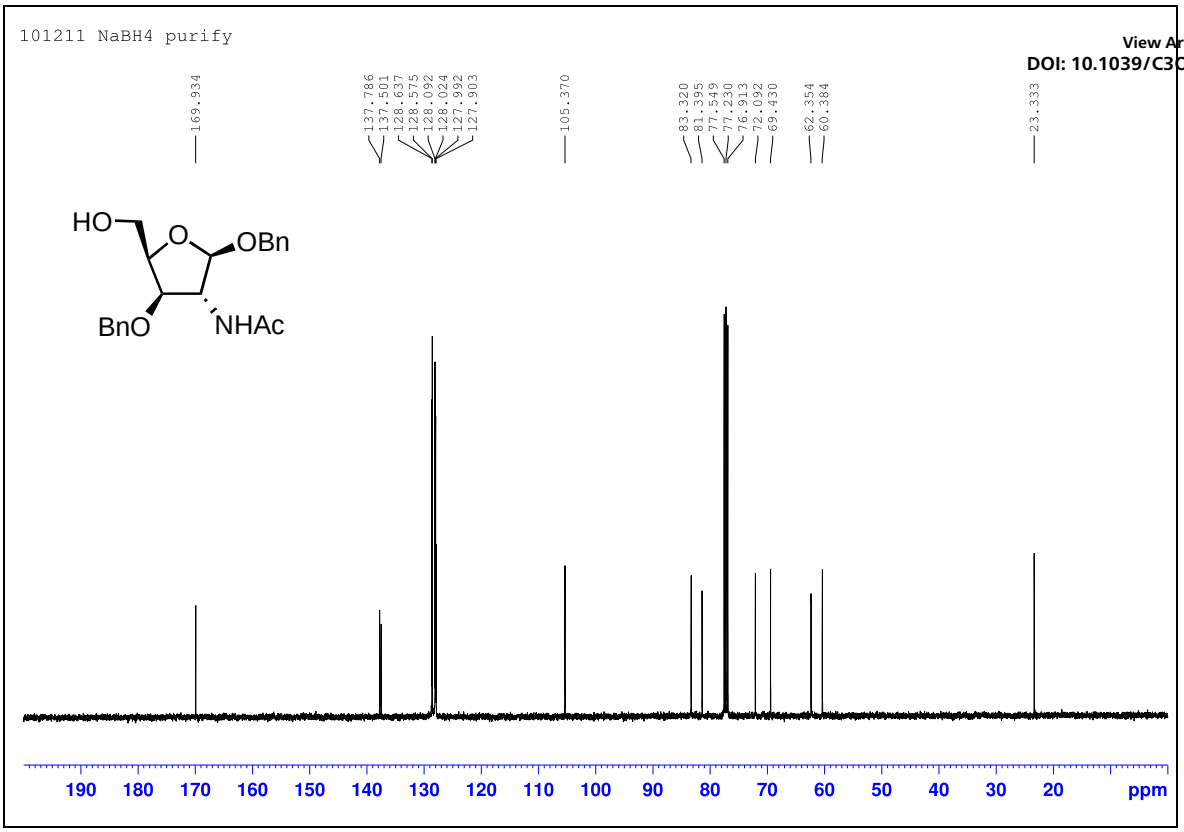
^{1}H NMR spectrum of compound **15** ($CDCl_3$, 400 MHz)



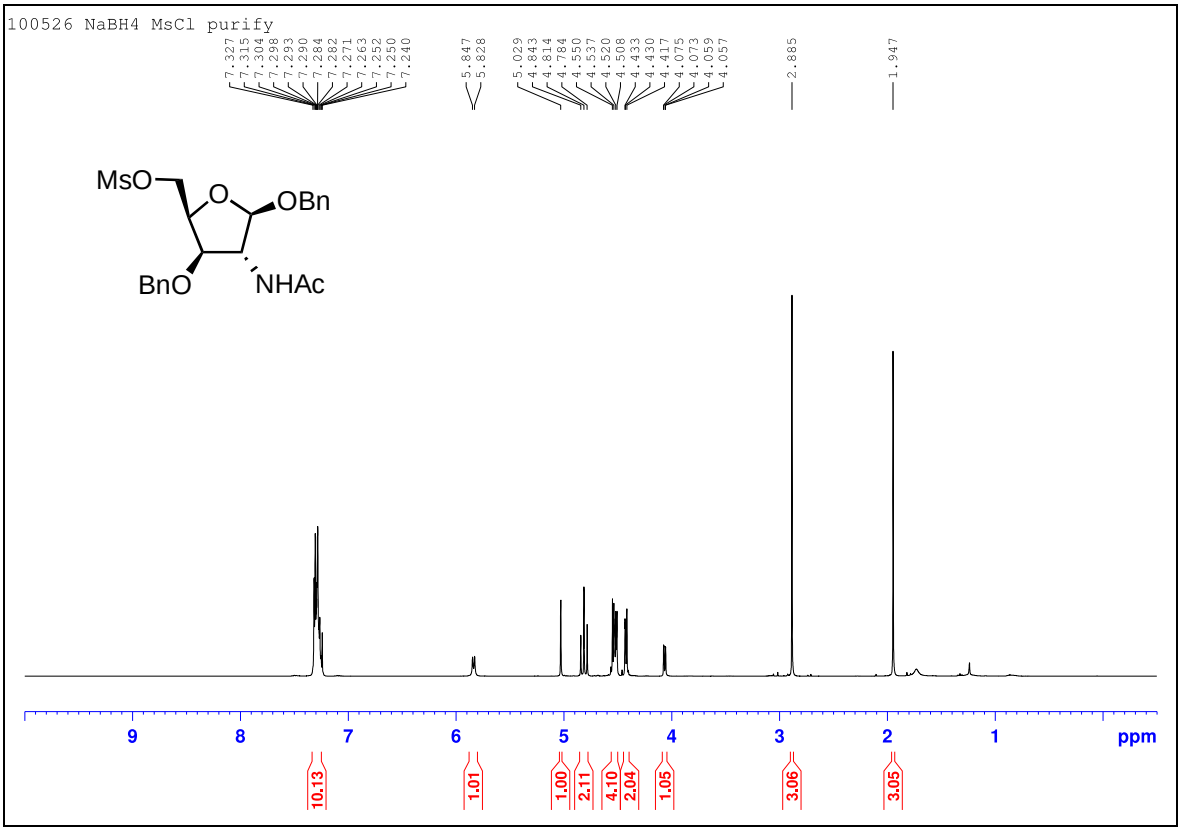
^{13}C NMR spectrum of compound **15** (CD_3OD, 100 MHz)



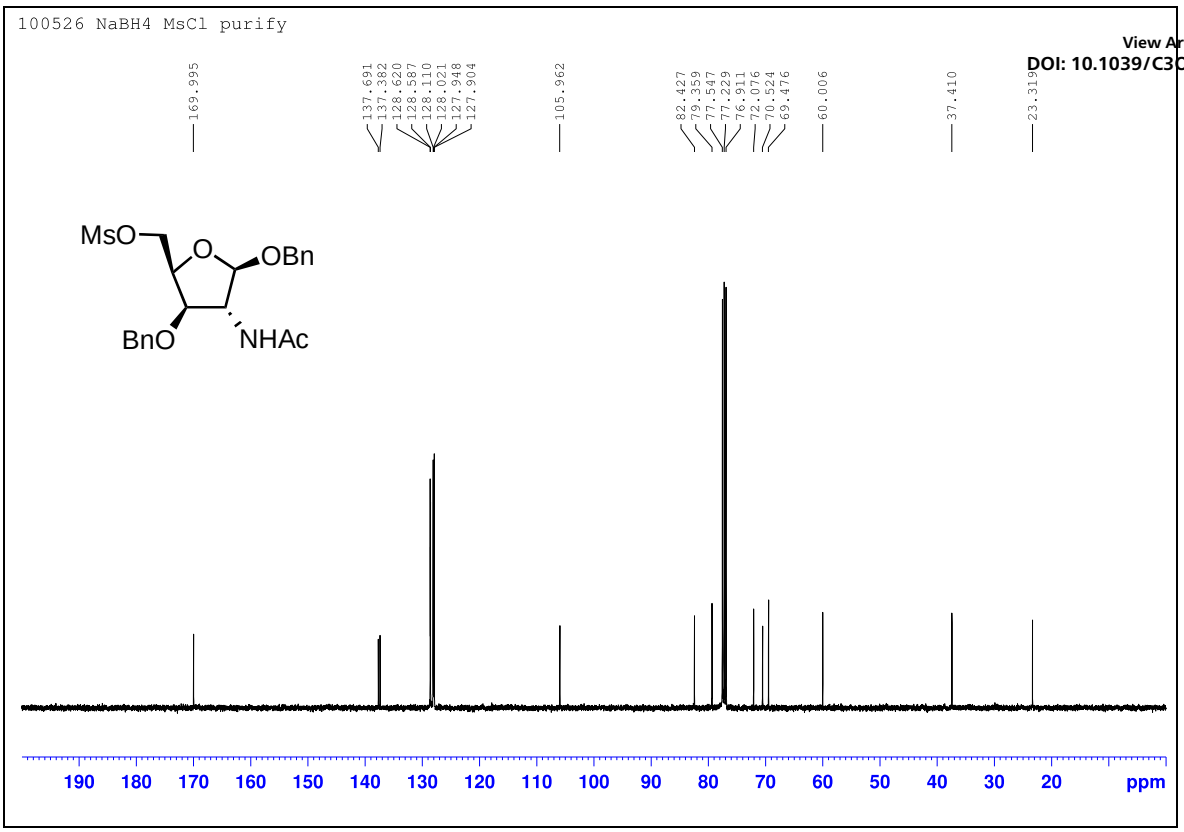
^{1}H NMR spectrum of compound **16** ($CDCl_3$, 400 MHz)



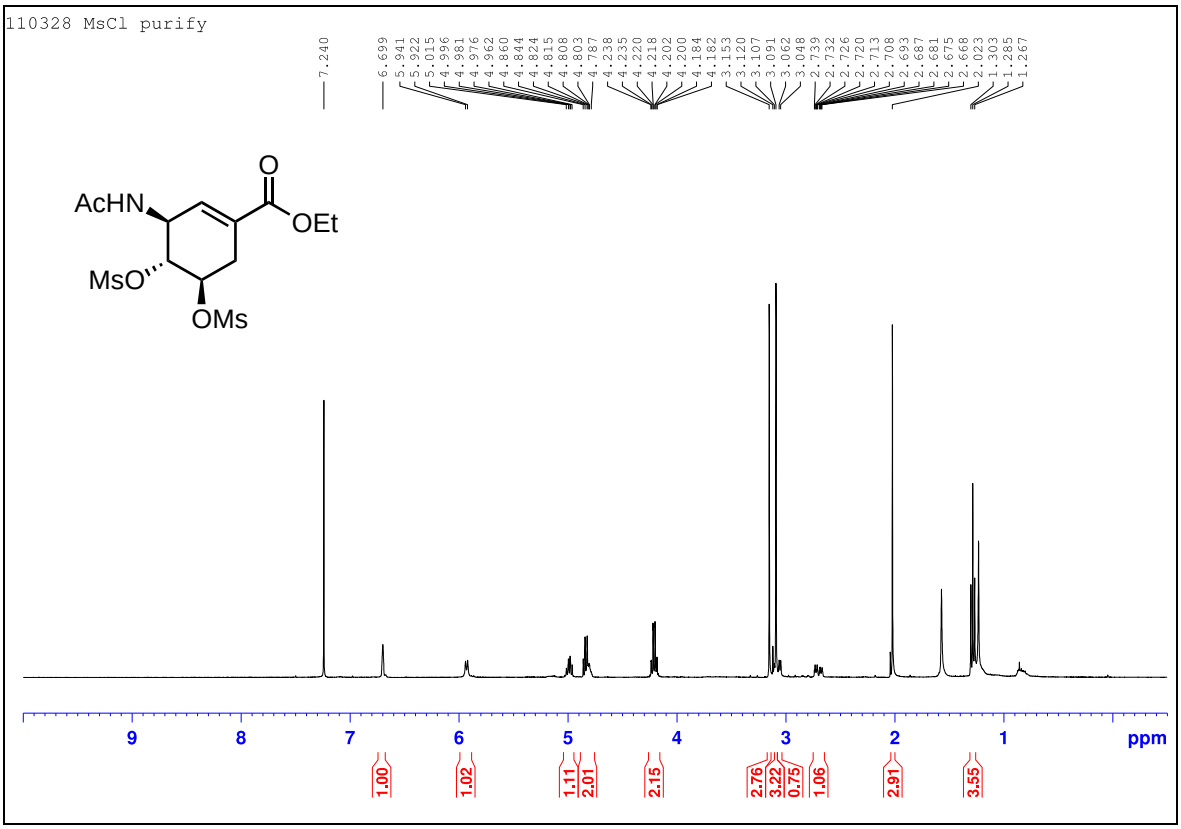
^{13}C NMR spectrum of compound **16** ($CDCl_3$, 100 MHz)



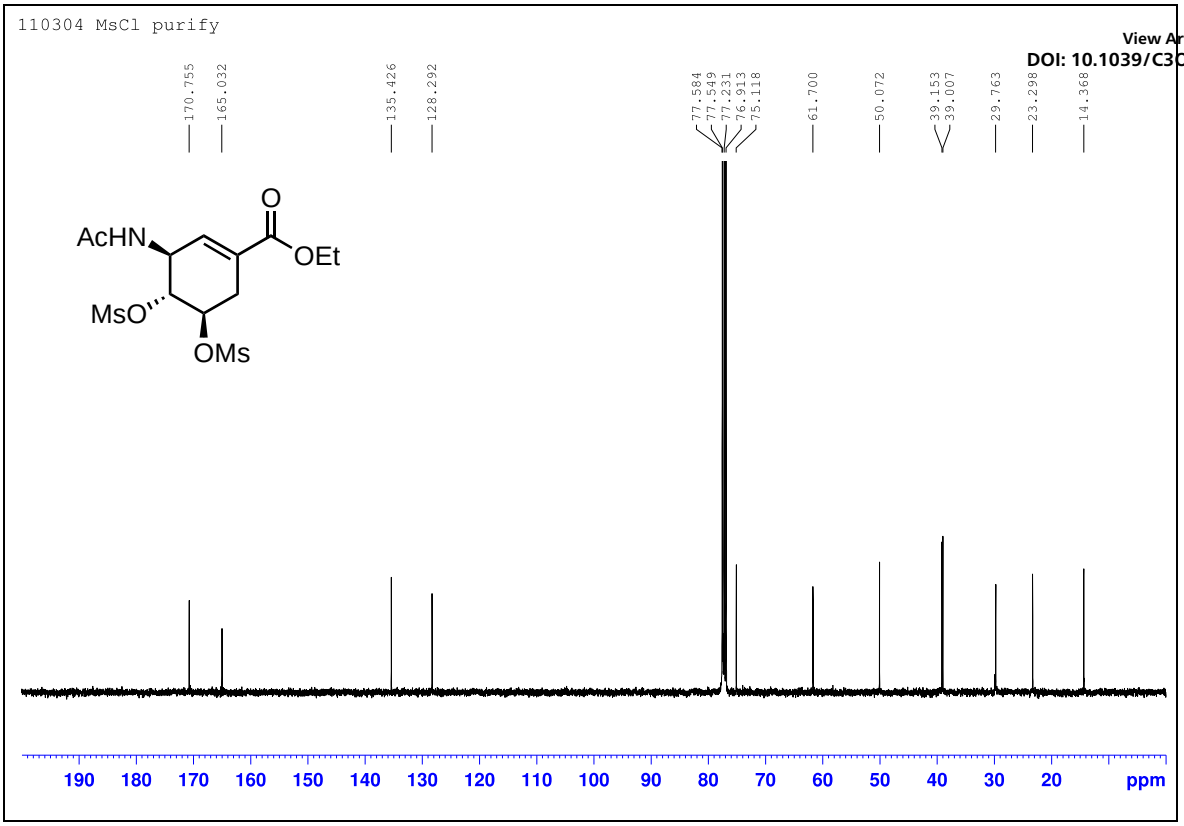
^{1}H NMR spectrum of compound **17** ($CDCl_3$, 400 MHz)



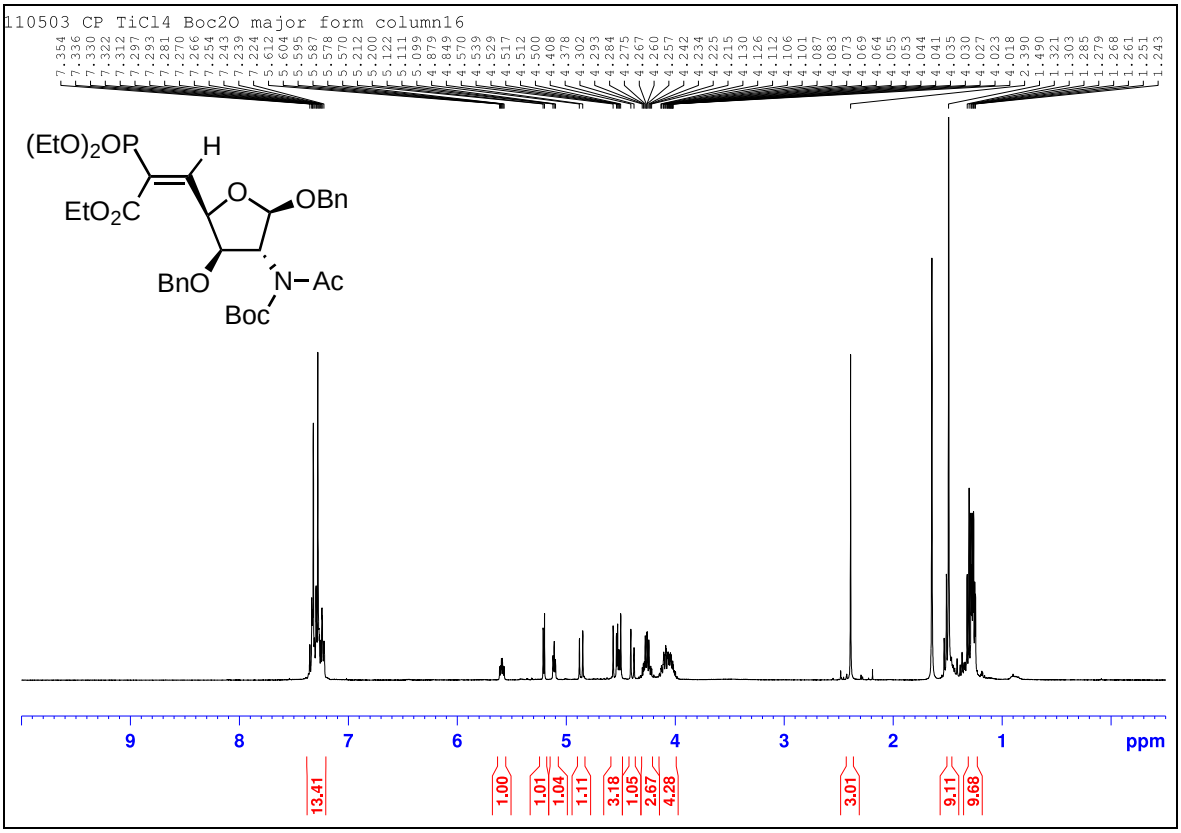
^{13}C NMR spectrum of compound **17** ($CDCl_3$, 100 MHz)



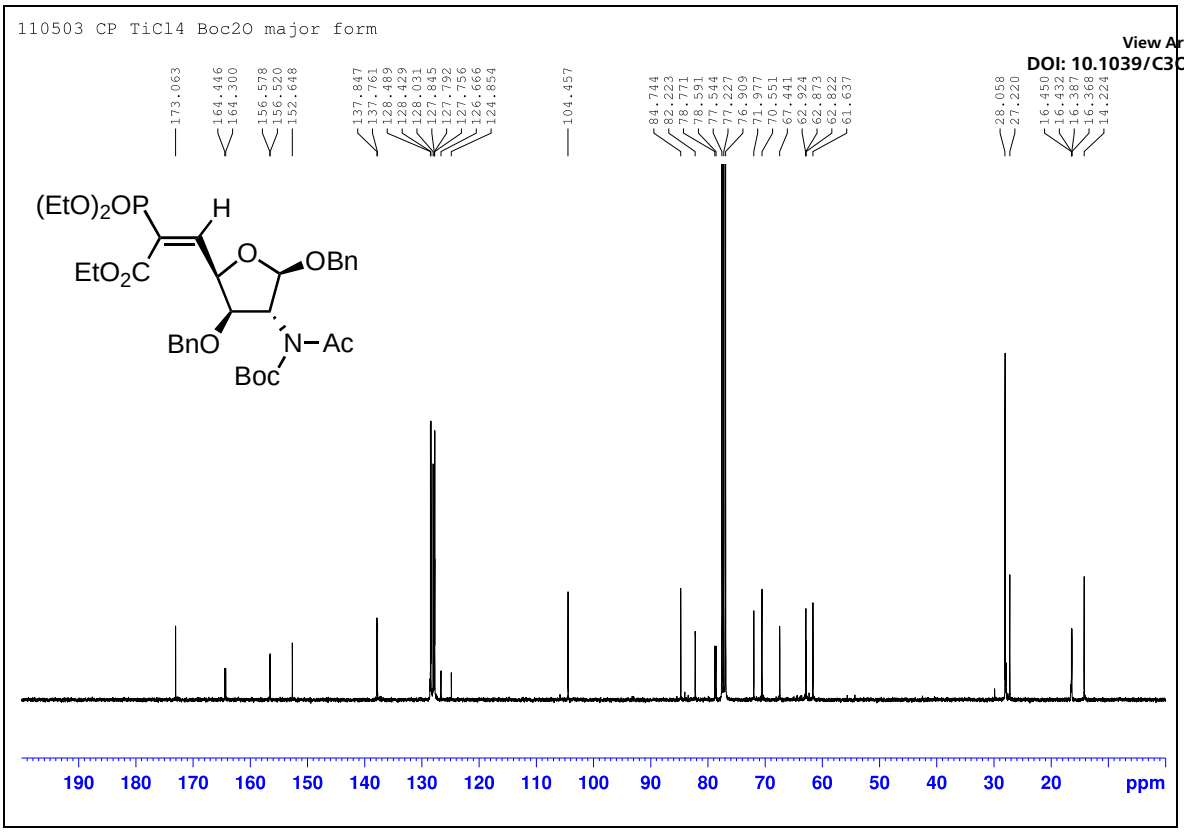
^{1}H NMR spectrum of compound **18** ($CDCl_3$, 400 MHz)



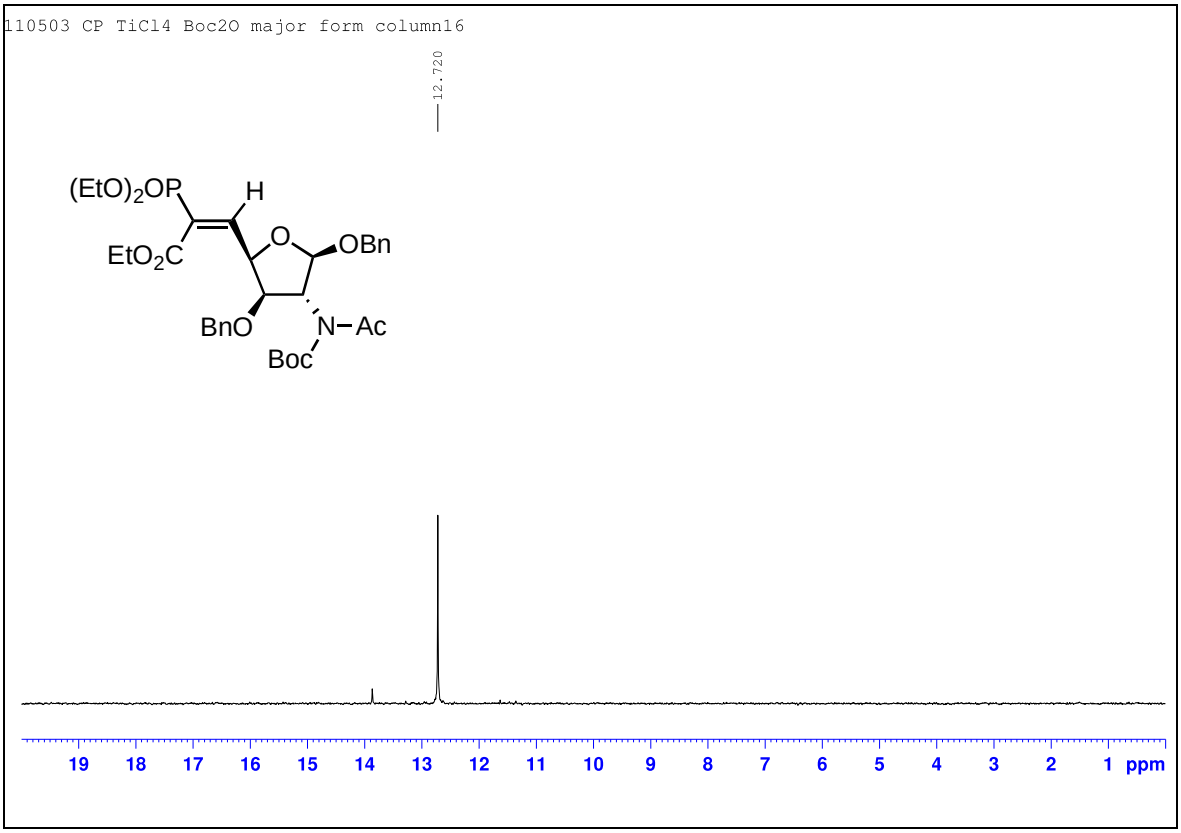
^{13}C NMR spectrum of compound **18** ($CDCl_3$, 100 MHz)



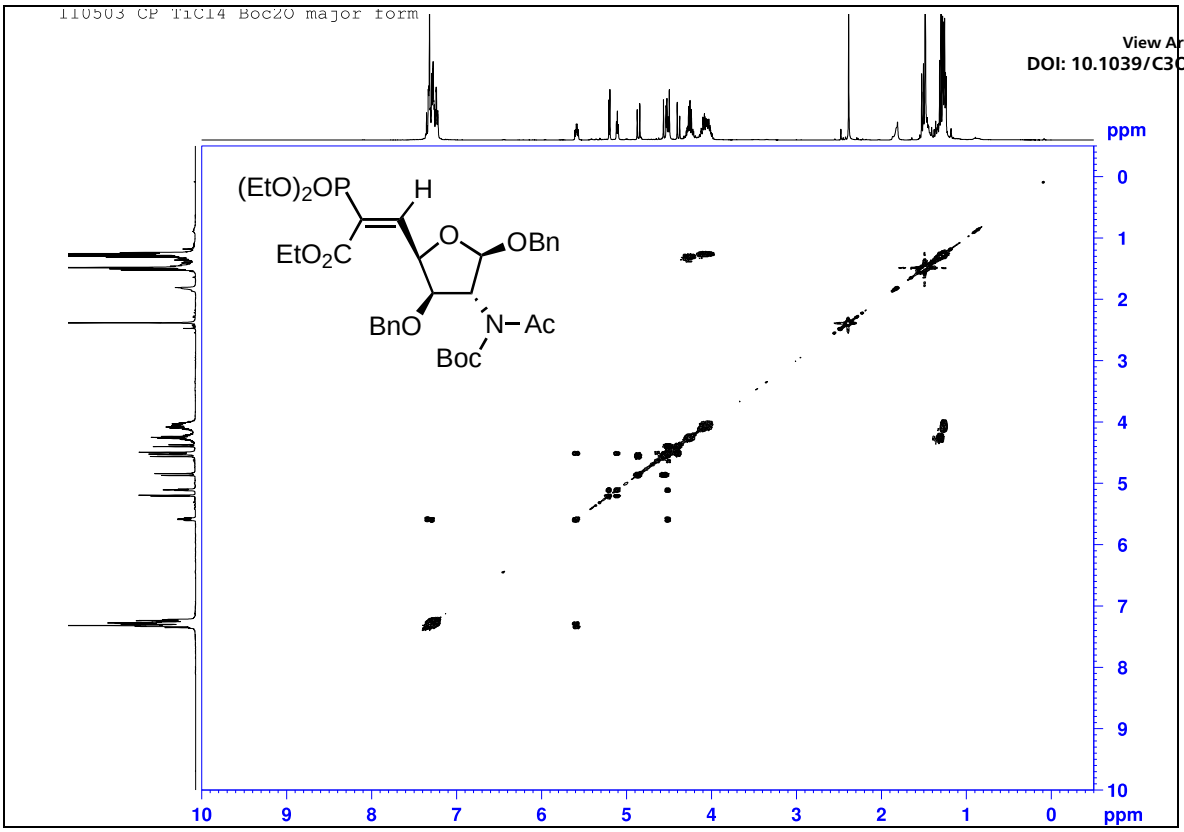
^{1}H NMR spectrum of compound (*E*)-**20** ($CDCl_3$, 400 MHz)



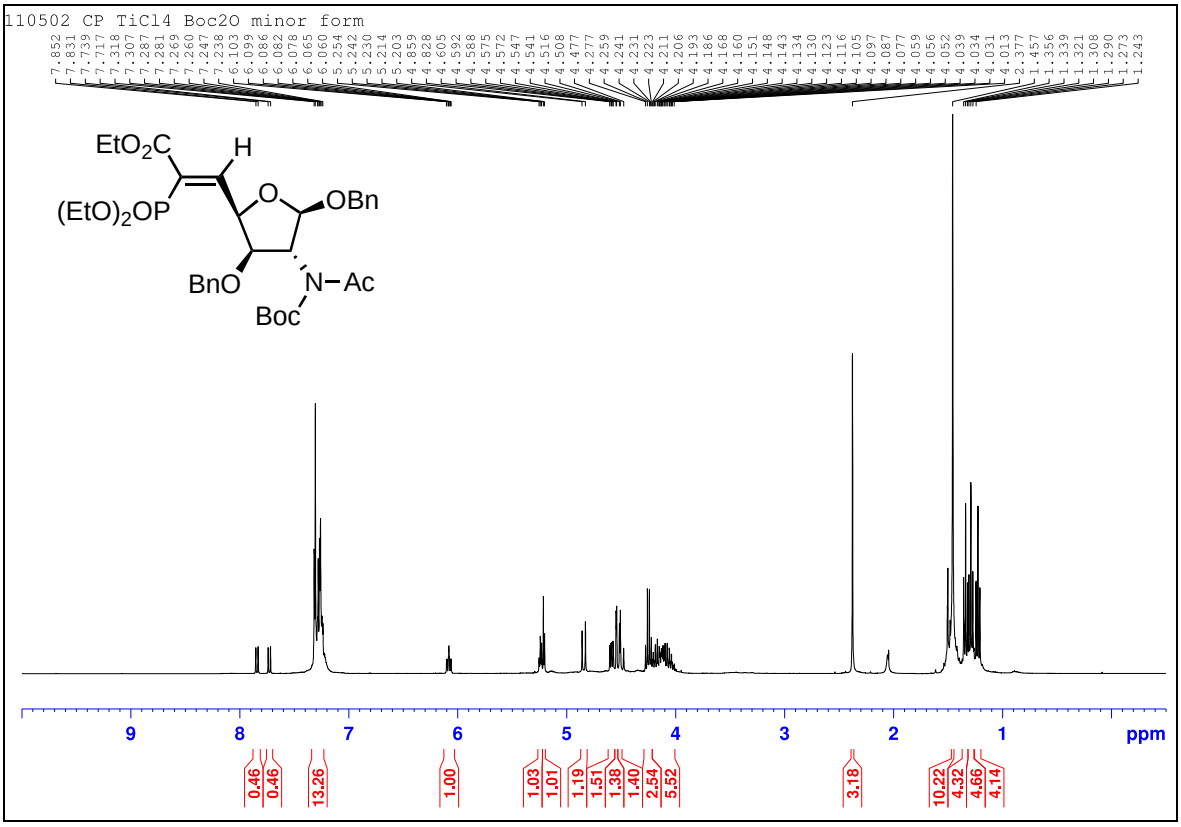
^{13}C NMR spectrum of compound (*E*)-**20** ($CDCl_3$, 100 MHz)



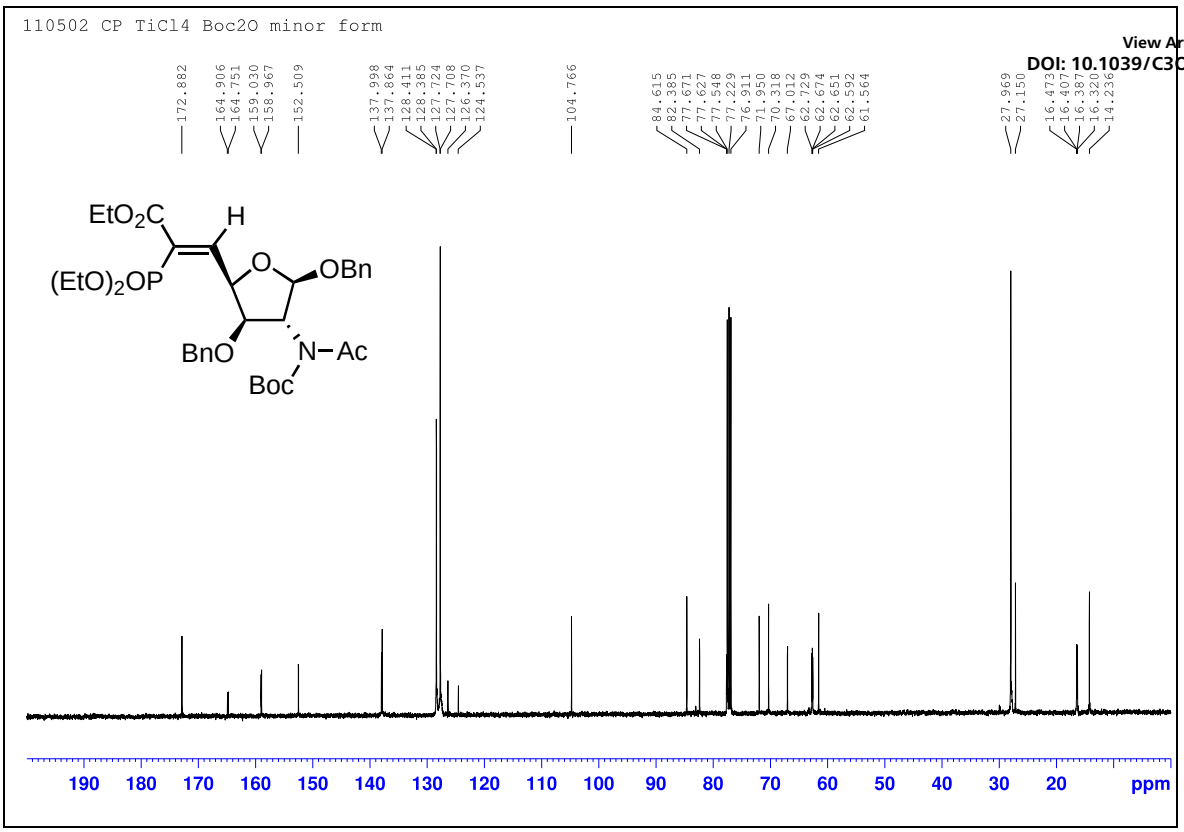
^{31}P NMR spectrum of compound (*E*)-**20** ($CDCl_3$, 162 MHz)



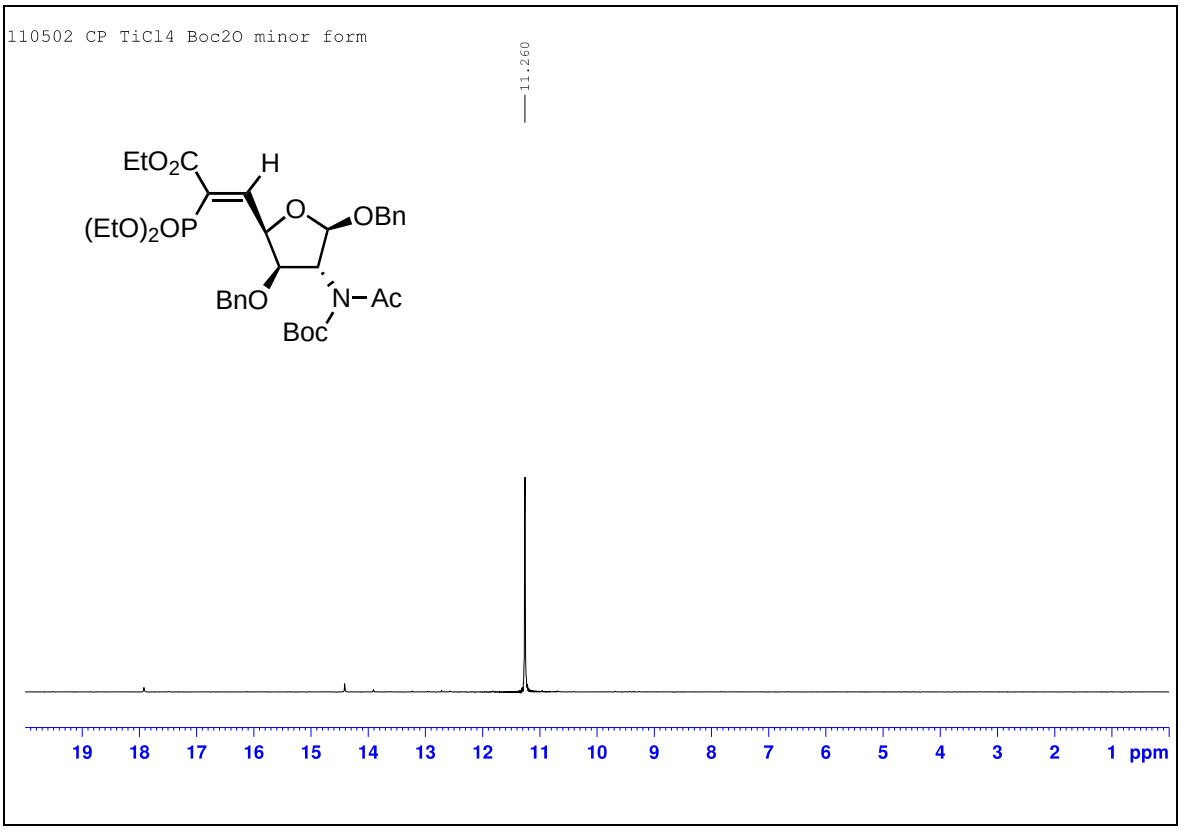
^{1}H–^{1}H COSY NMR spectrum of compound (*E*)-**20** ($CDCl_3$, 400 MHz)



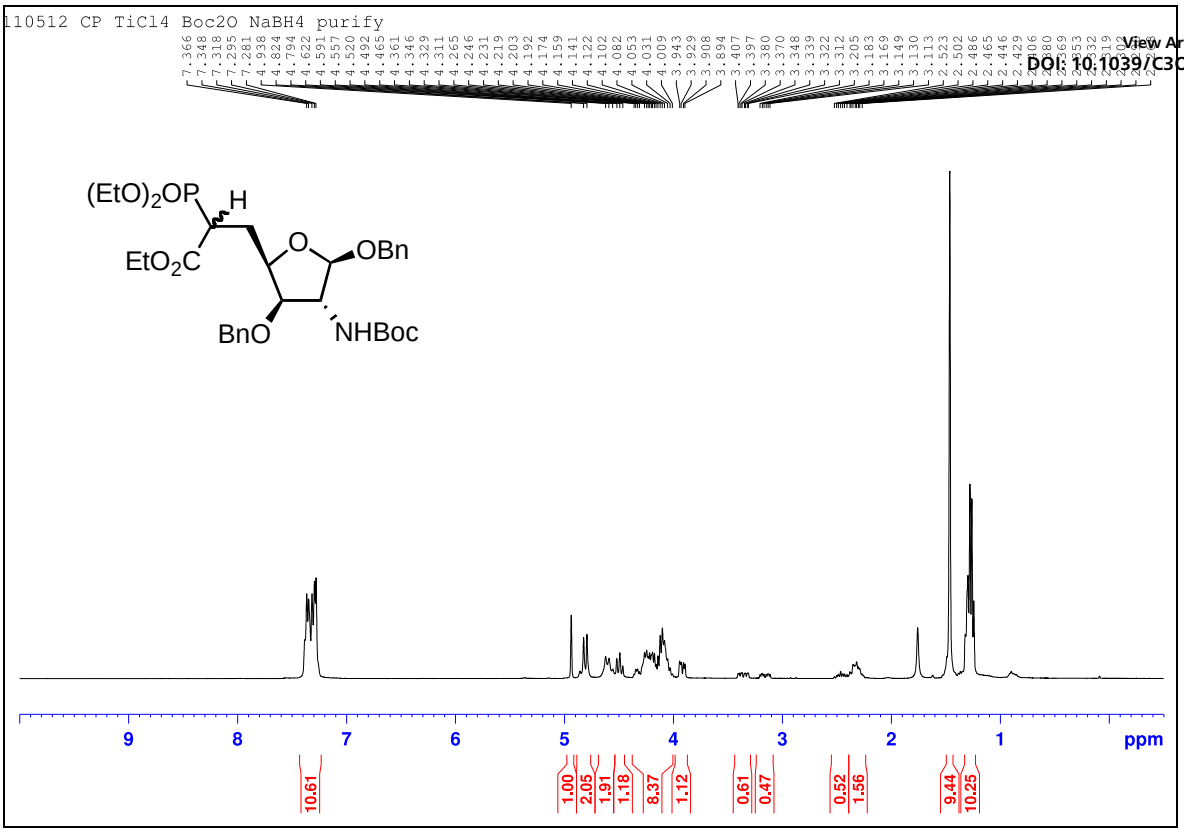
^{1}H NMR spectrum of compound (*Z*)-**20** ($CDCl_3$, 400 MHz)



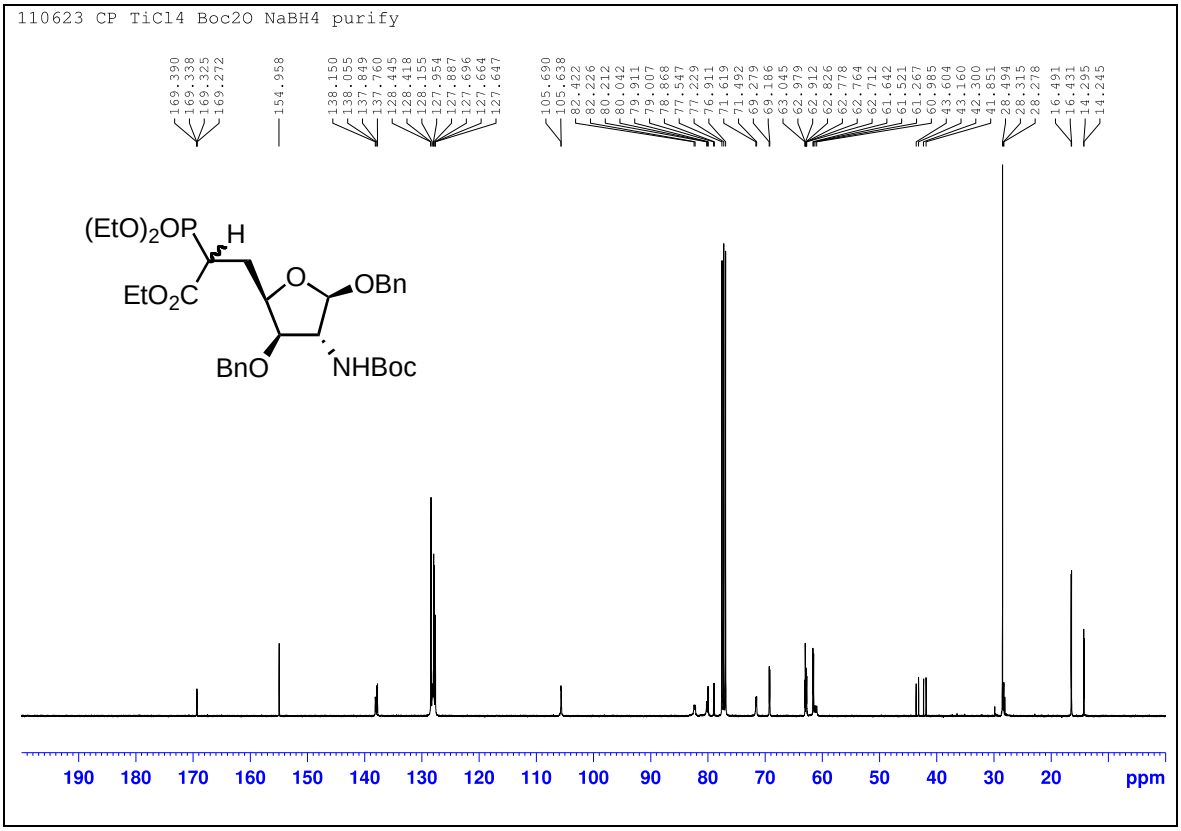
^{13}C NMR spectrum of compound (*Z*)-**20** ($CDCl_3$, 100 MHz)



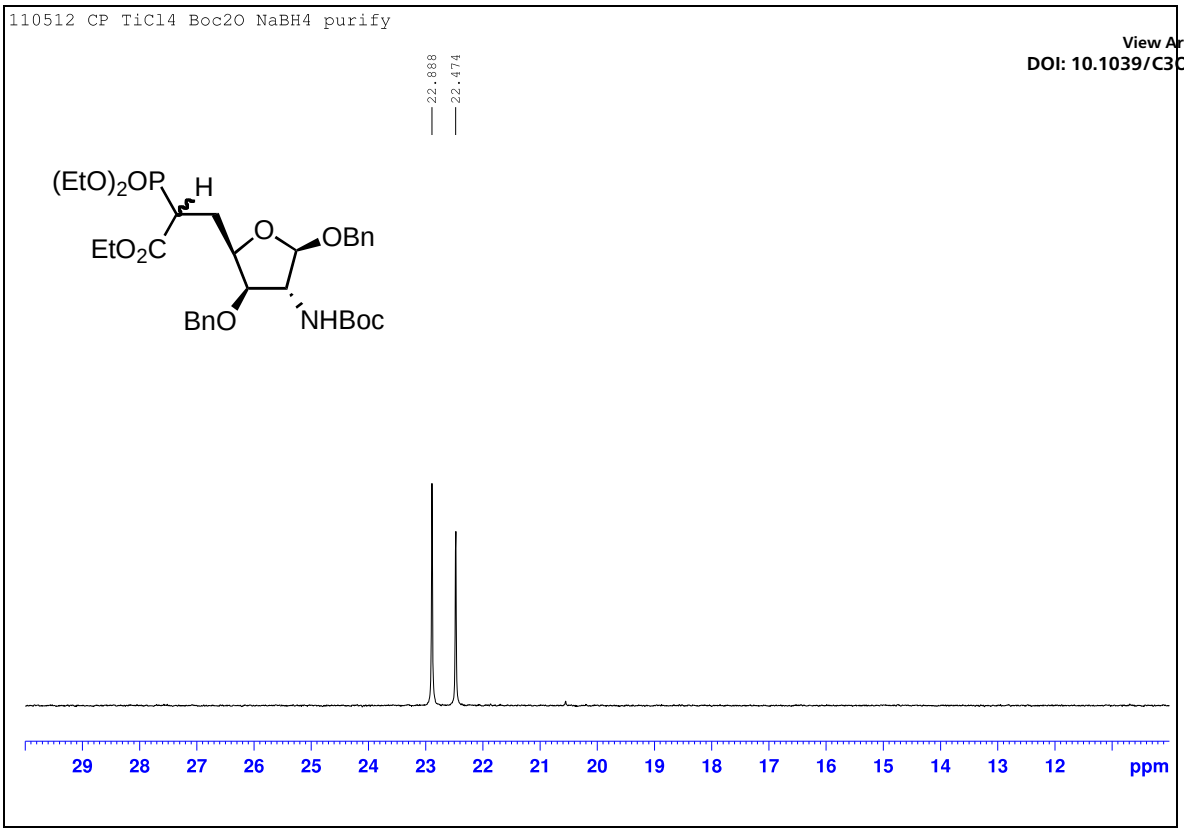
^{31}P NMR spectrum of compound (*Z*)-**20** ($CDCl_3$, 162 MHz)



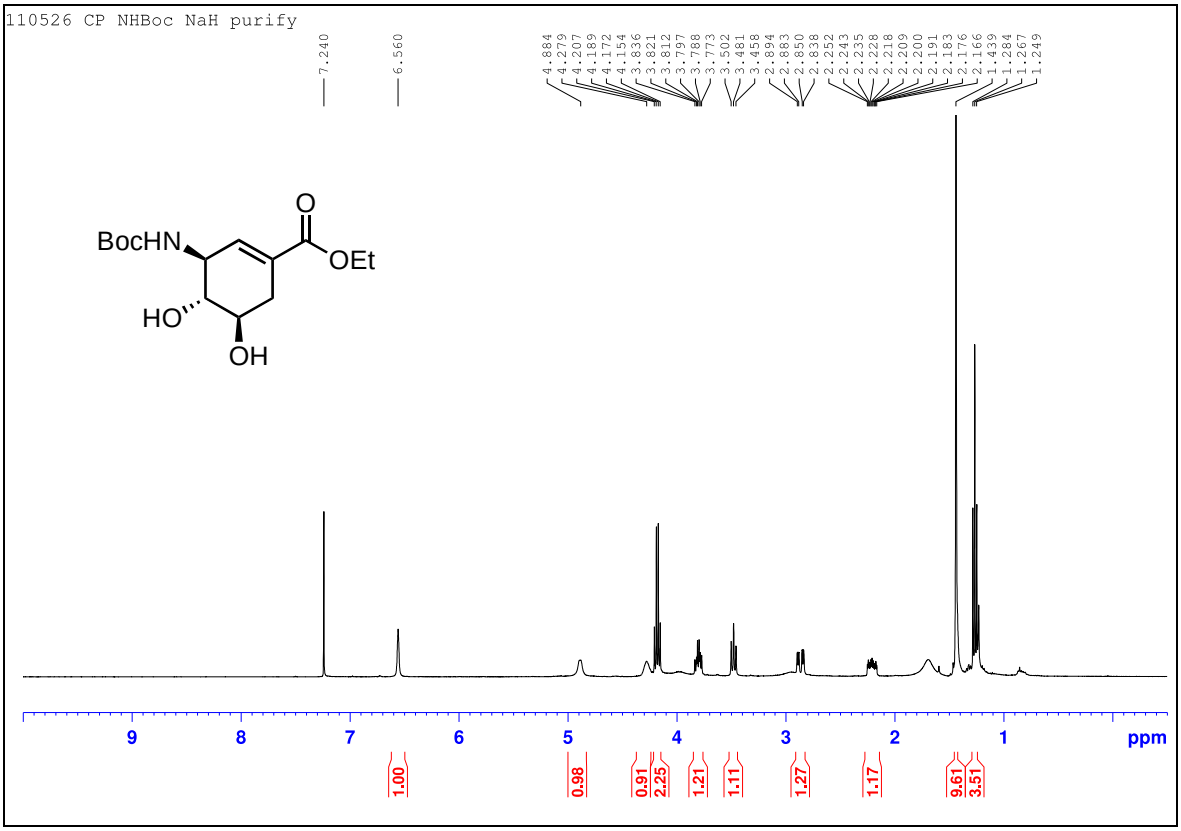
^{1}H NMR spectrum of compound **21** ($CDCl_3$, 400 MHz)



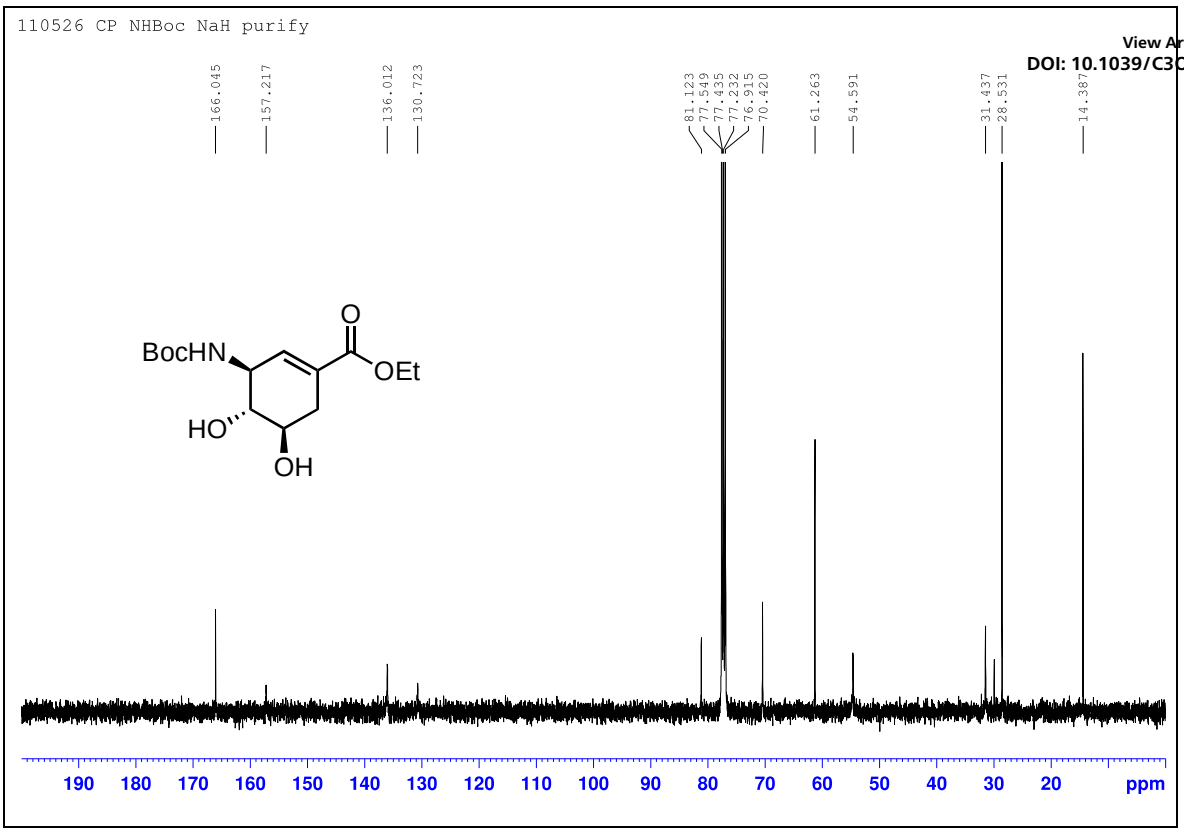
^{13}C NMR spectrum of compound **21** ($CDCl_3$, 100 MHz)



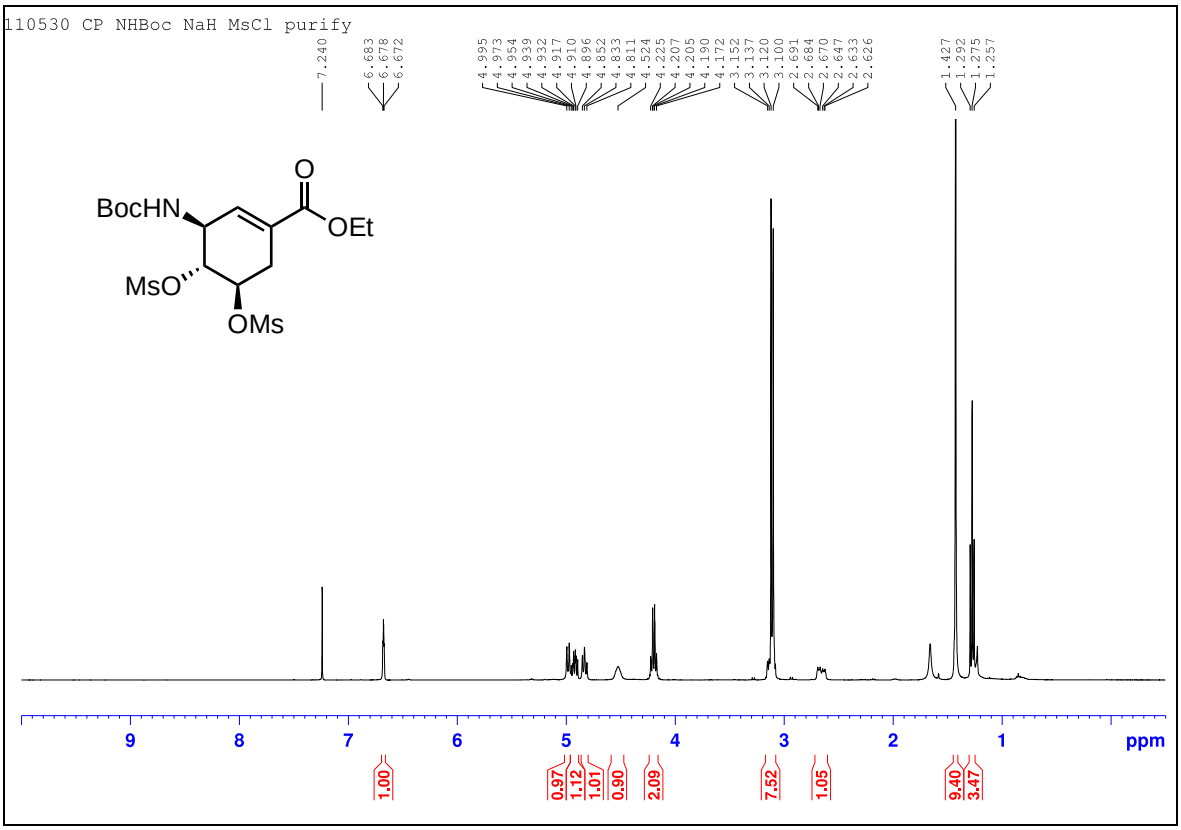
^{31}P NMR spectrum of compound **21** ($CDCl_3$, 162 MHz)



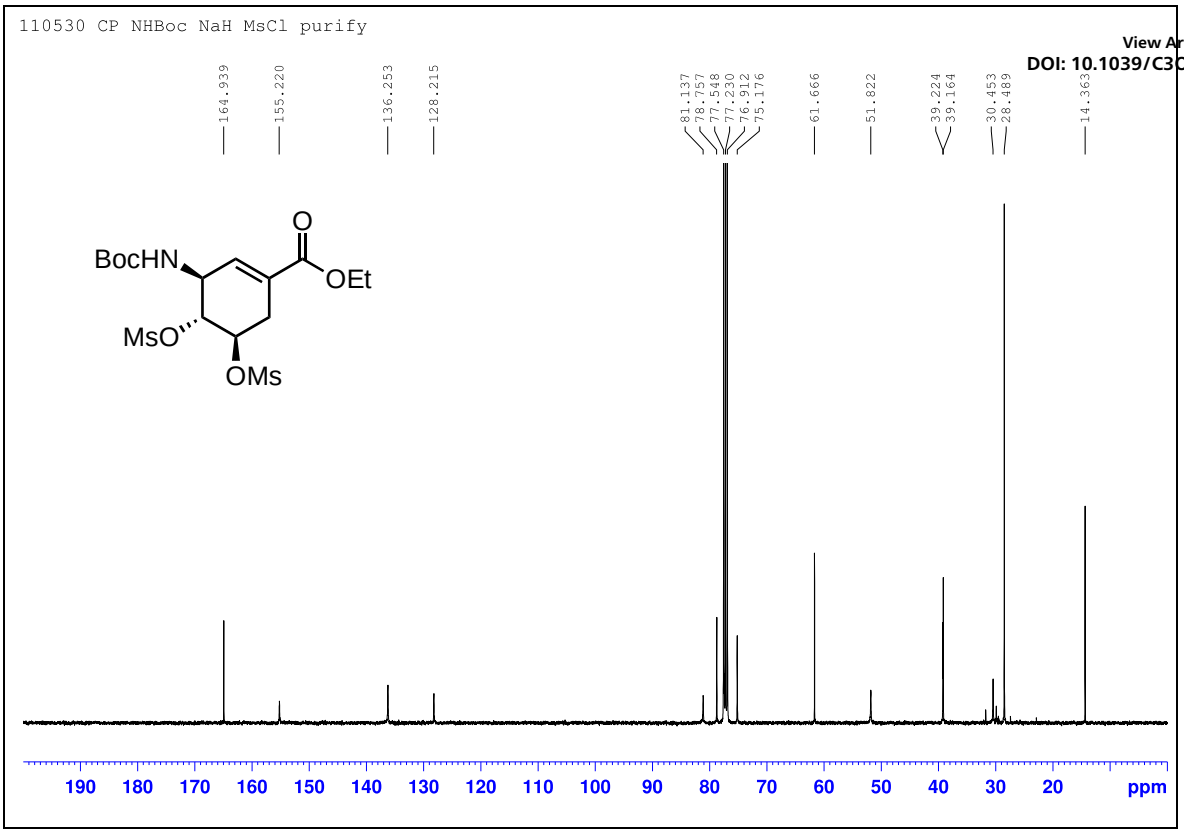
^{1}H NMR spectrum of compound **22** ($CDCl_3$, 400 MHz)



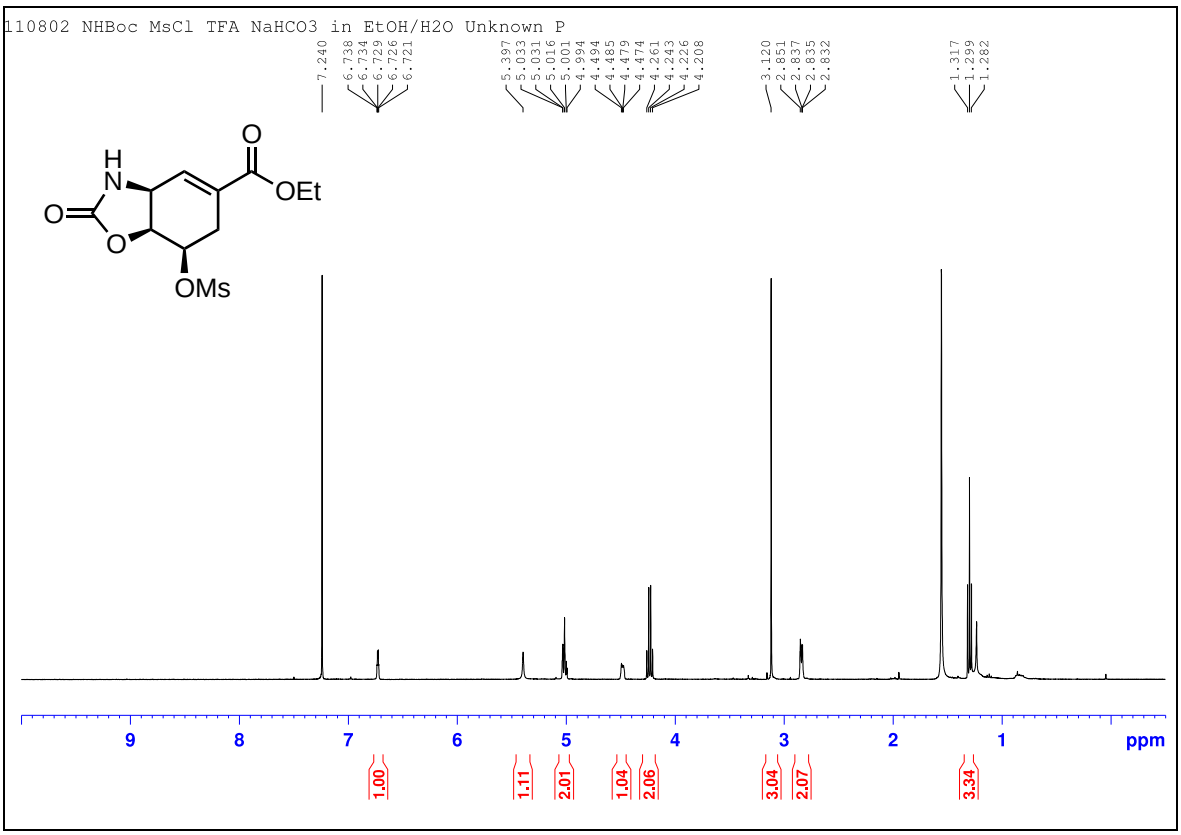
^{13}C NMR spectrum of compound **22** ($CDCl_3$, 100 MHz)



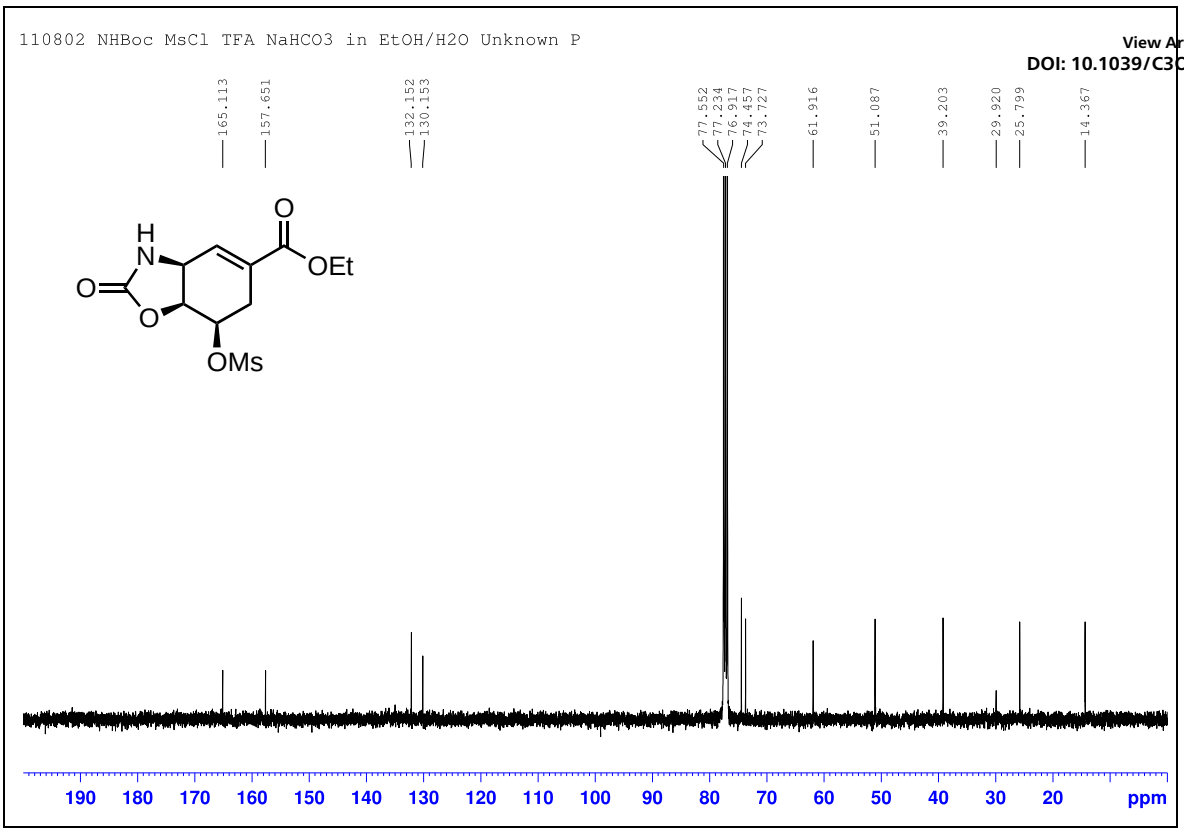
^{1}H NMR spectrum of compound **23** ($CDCl_3$, 400 MHz)



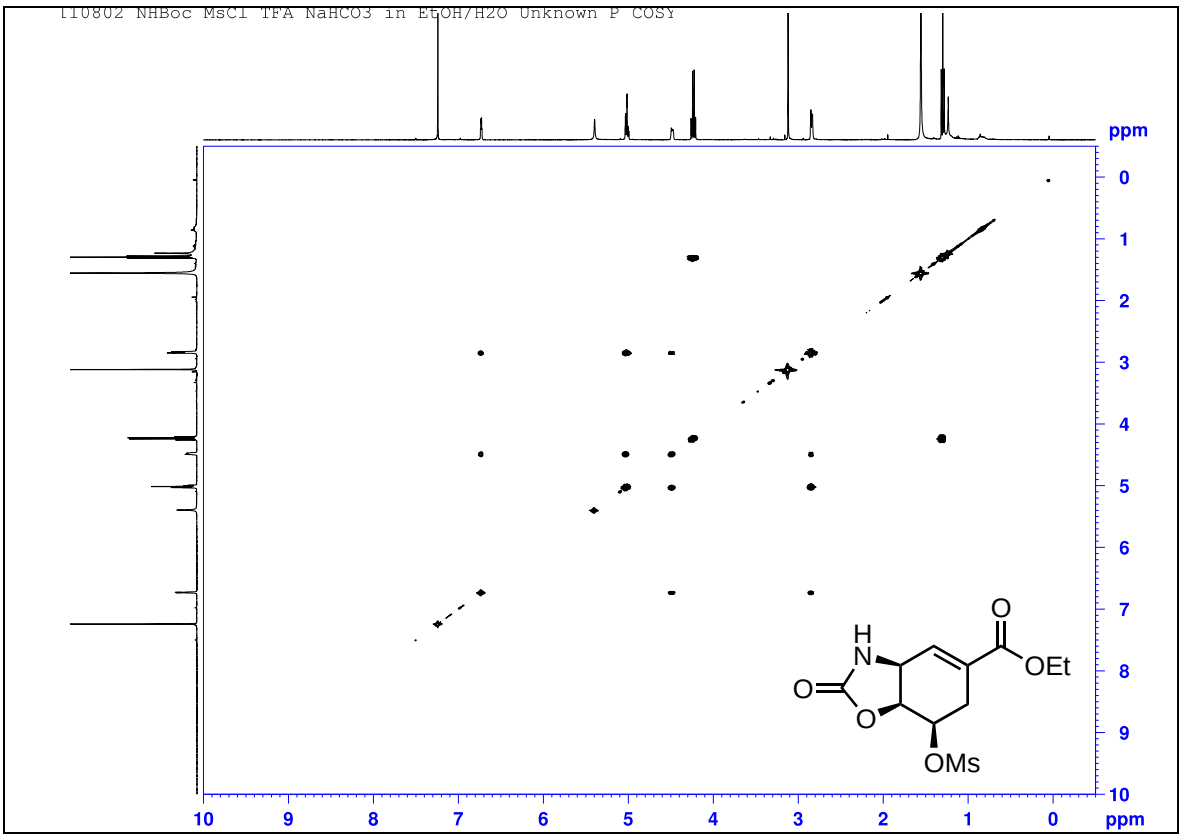
^{13}C NMR spectrum of compound **23** ($CDCl_3$, 100 MHz)



^{1}H NMR spectrum of compound **24** ($CDCl_3$, 400 MHz)

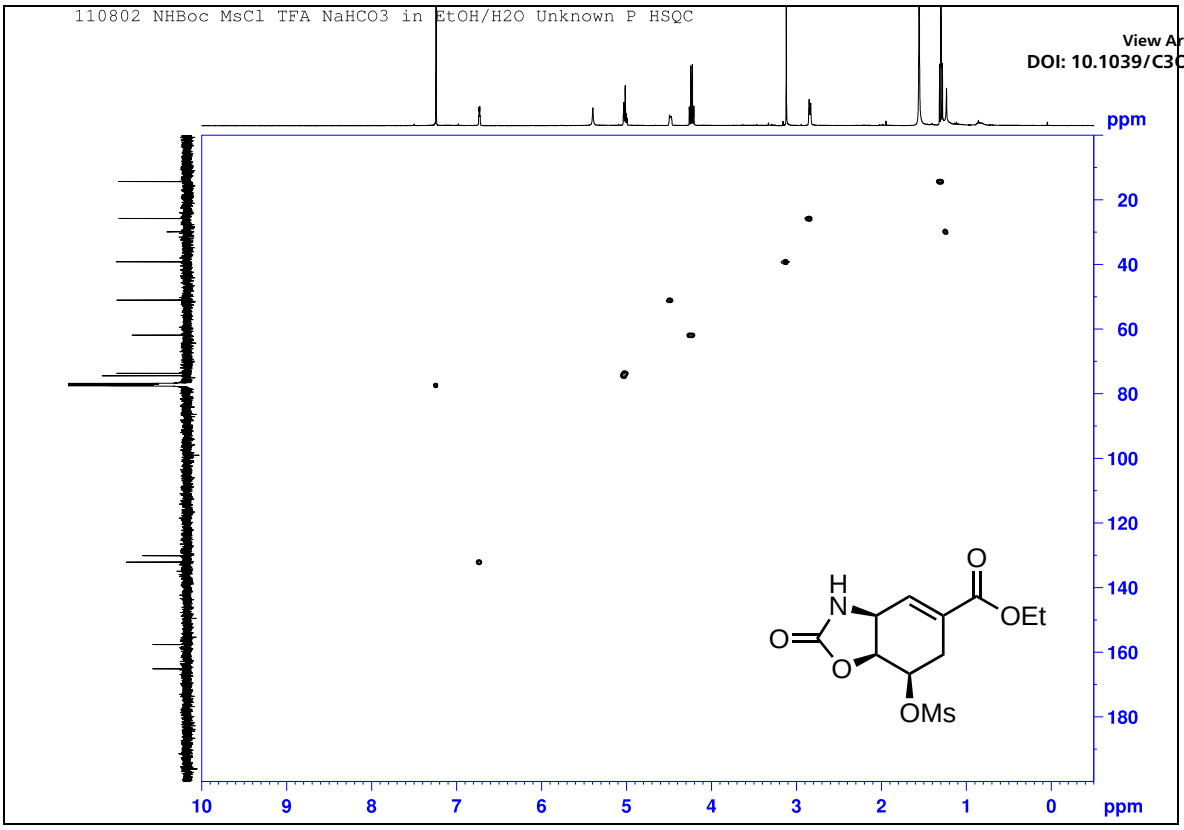


^{13}C NMR spectrum of compound **24** ($CDCl_3$, 100 MHz)

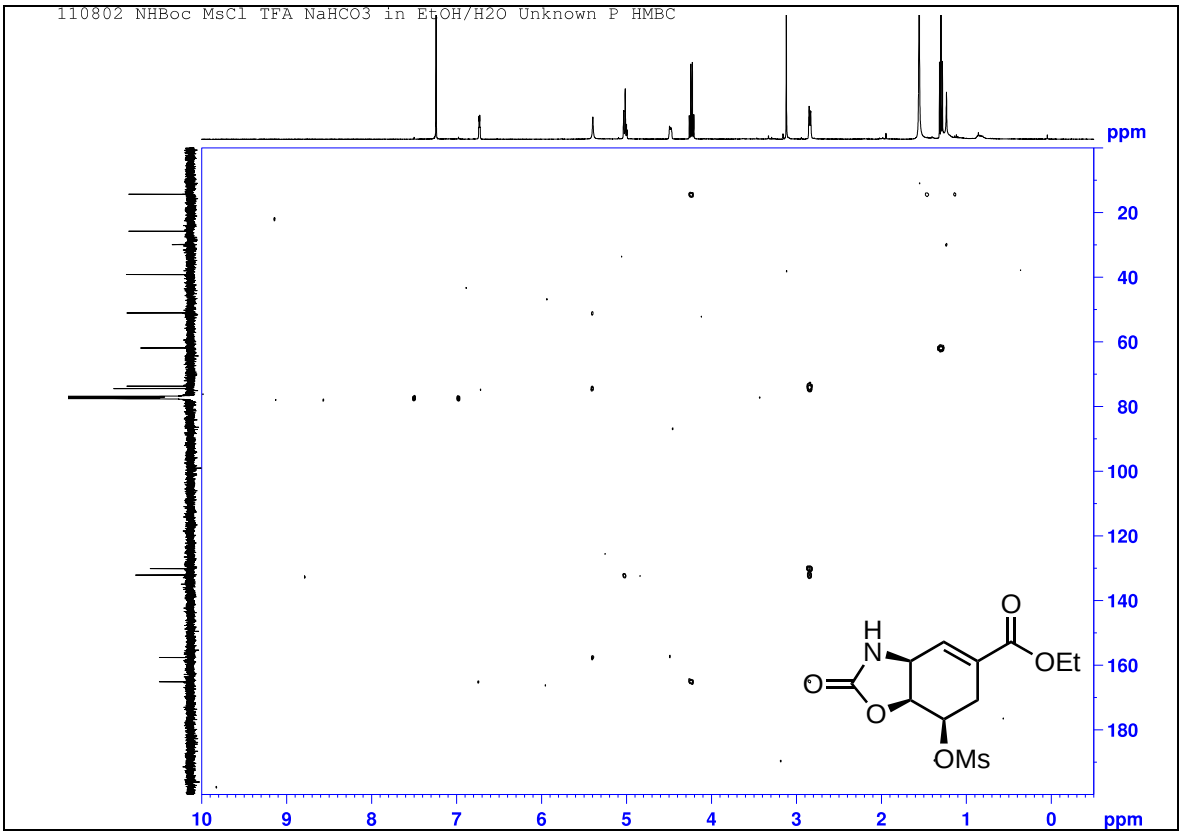


^{1}H–^{1}H COSY NMR spectrum of compound **24** ($CDCl_3$, 400 MHz)

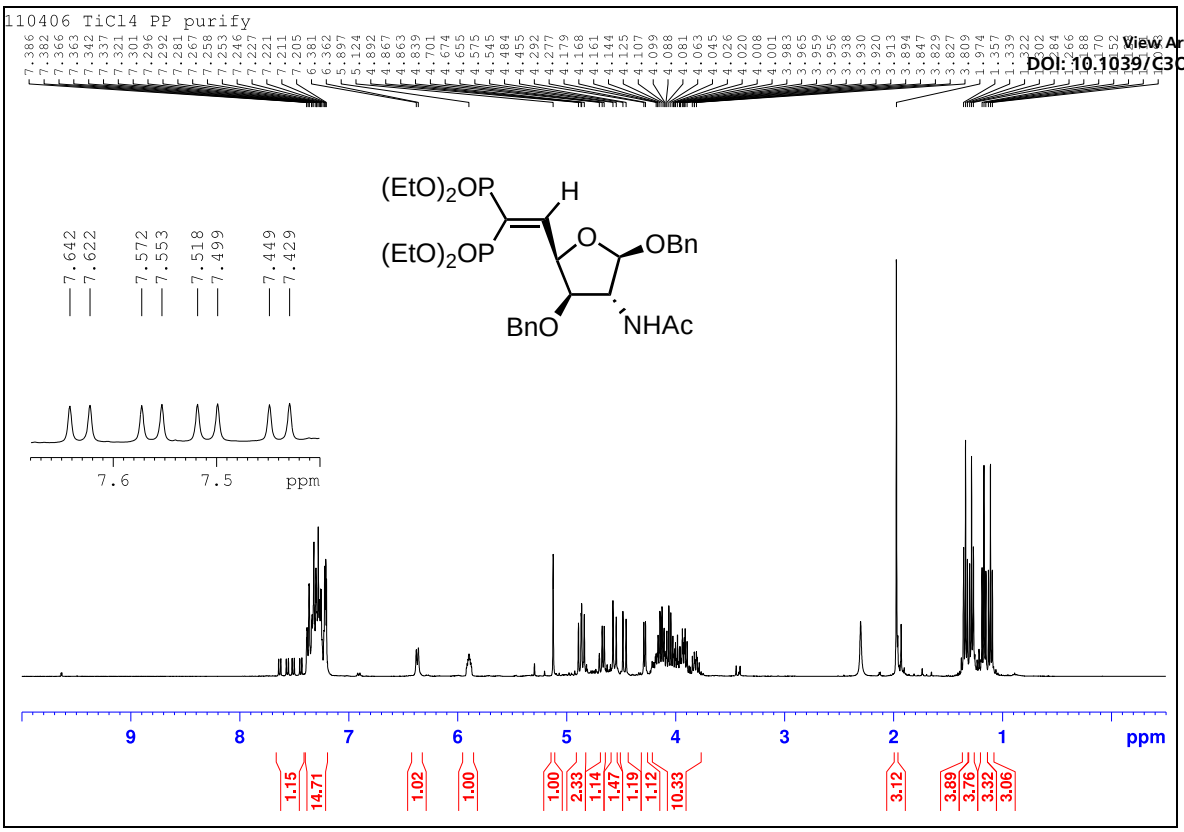
View Article Online
DOI: 10.1039/C3OB41622D



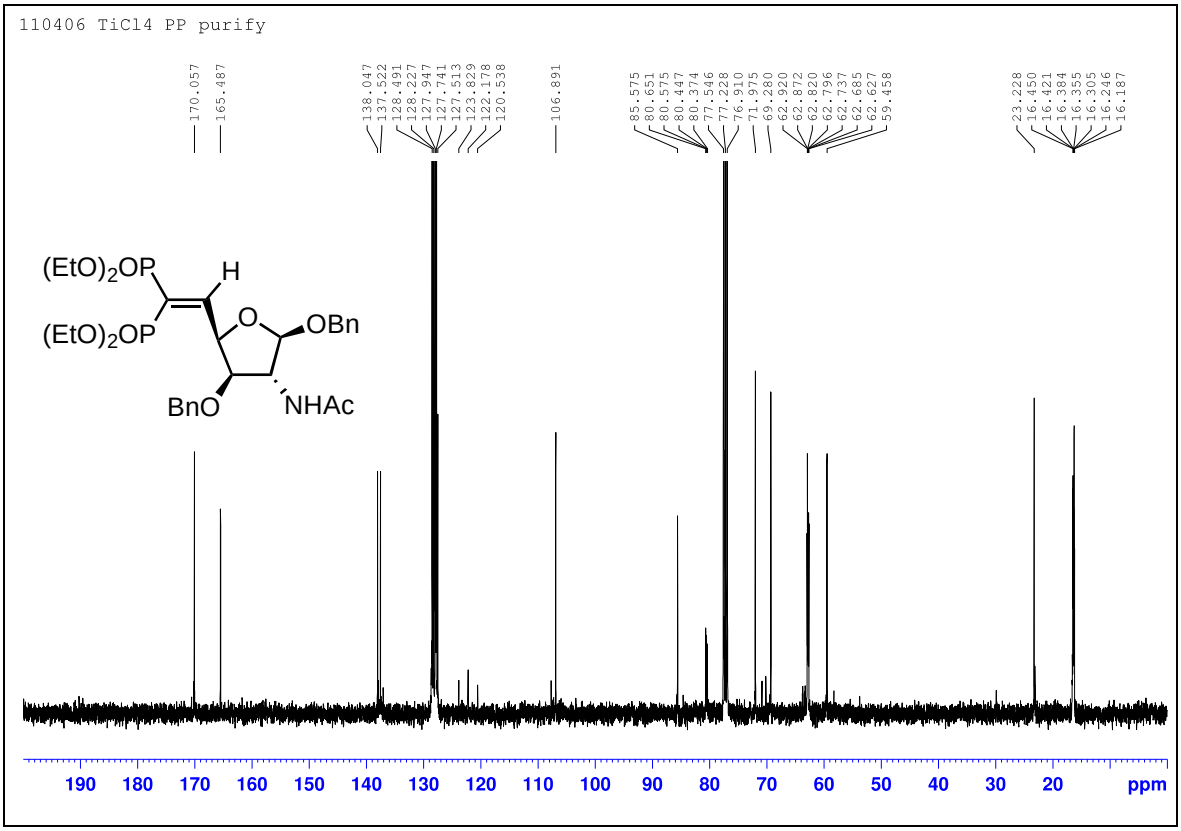
^{1}H–^{13}C HSQC NMR spectrum of compound **24** ($CDCl_3$, 400 MHz)



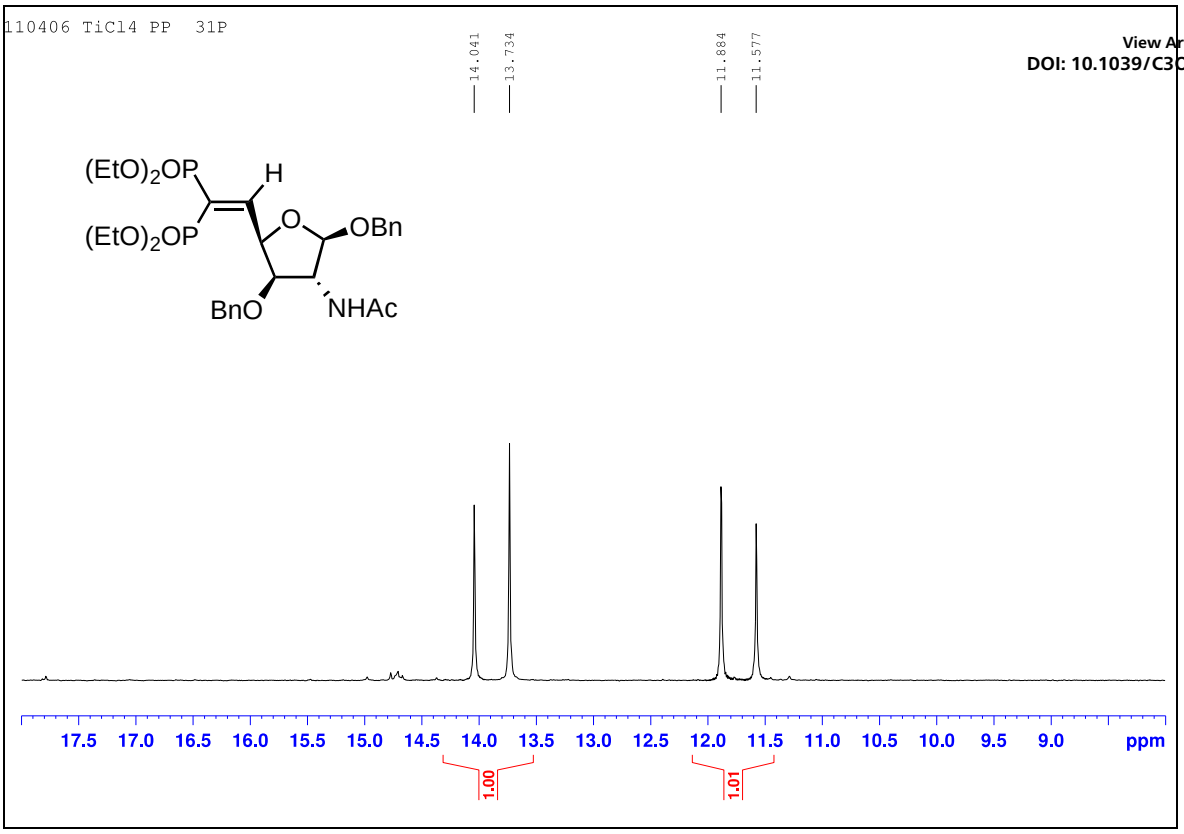
^{1}H–^{13}C HMBC NMR spectrum of compound **24** ($CDCl_3$, 400 MHz)



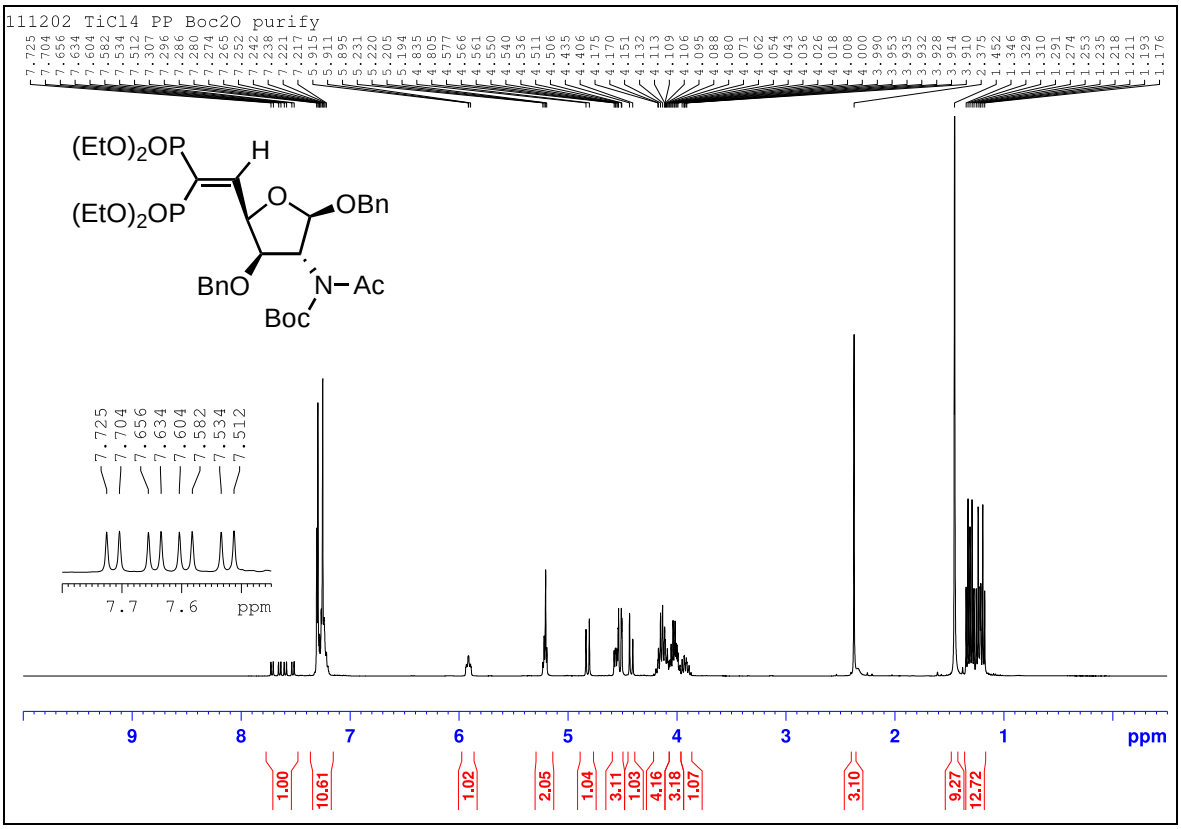
^{1}H NMR spectrum of compound **25** ($CDCl_3$, 400 MHz)



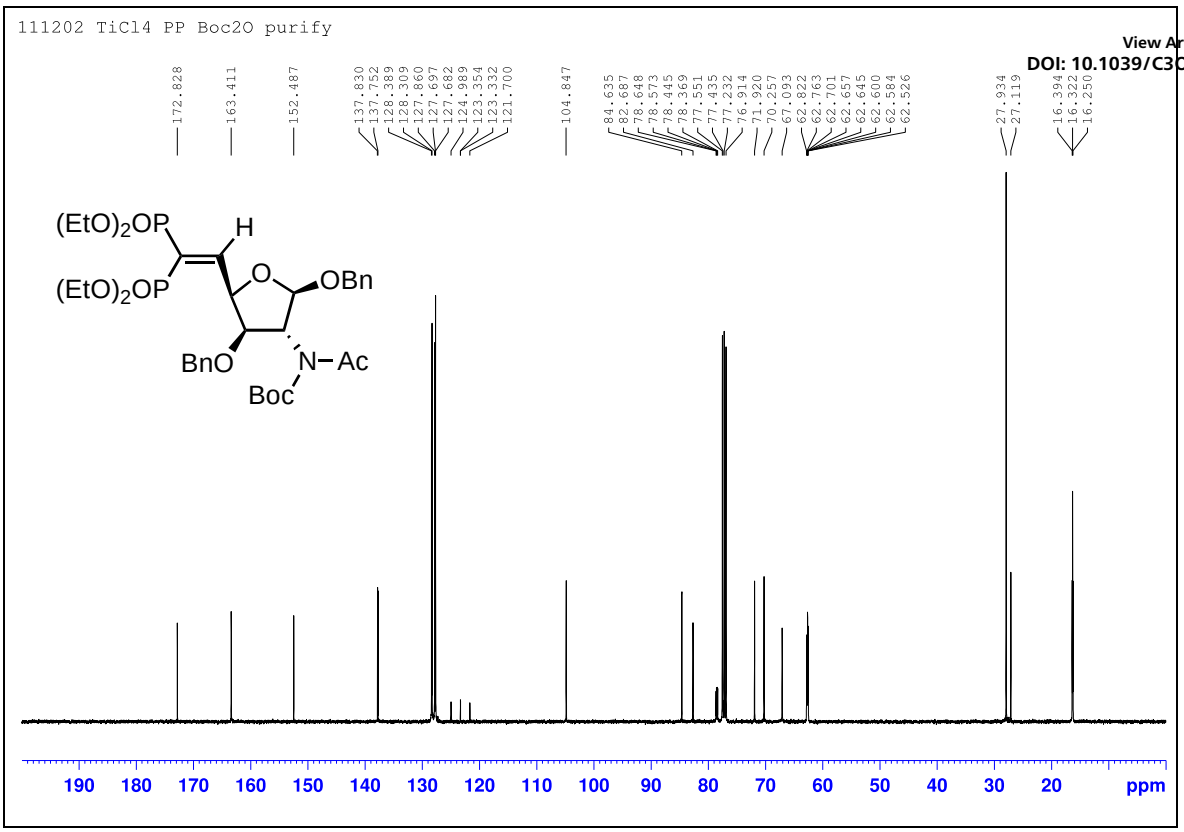
^{13}C NMR spectrum of compound **25** ($CDCl_3$, 100 MHz)



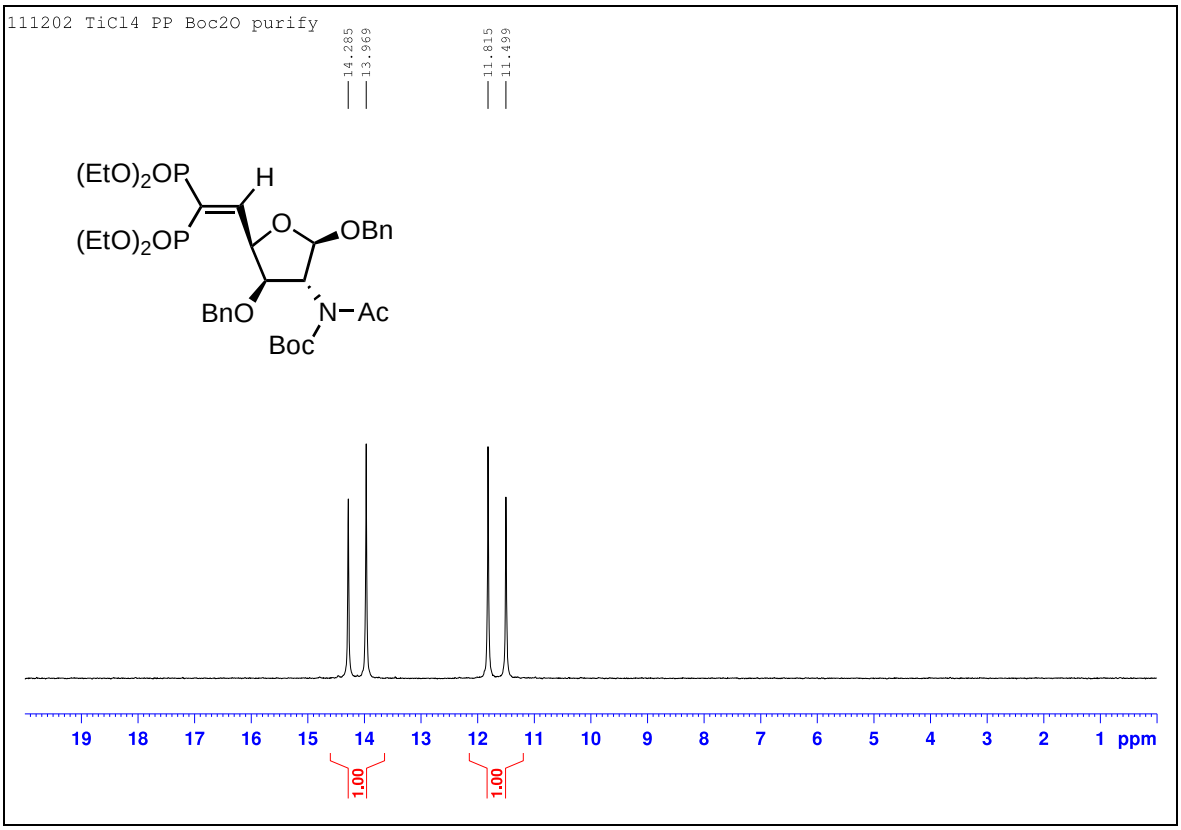
^{31}P NMR spectrum of compound **25** ($CDCl_3$, 162 MHz)



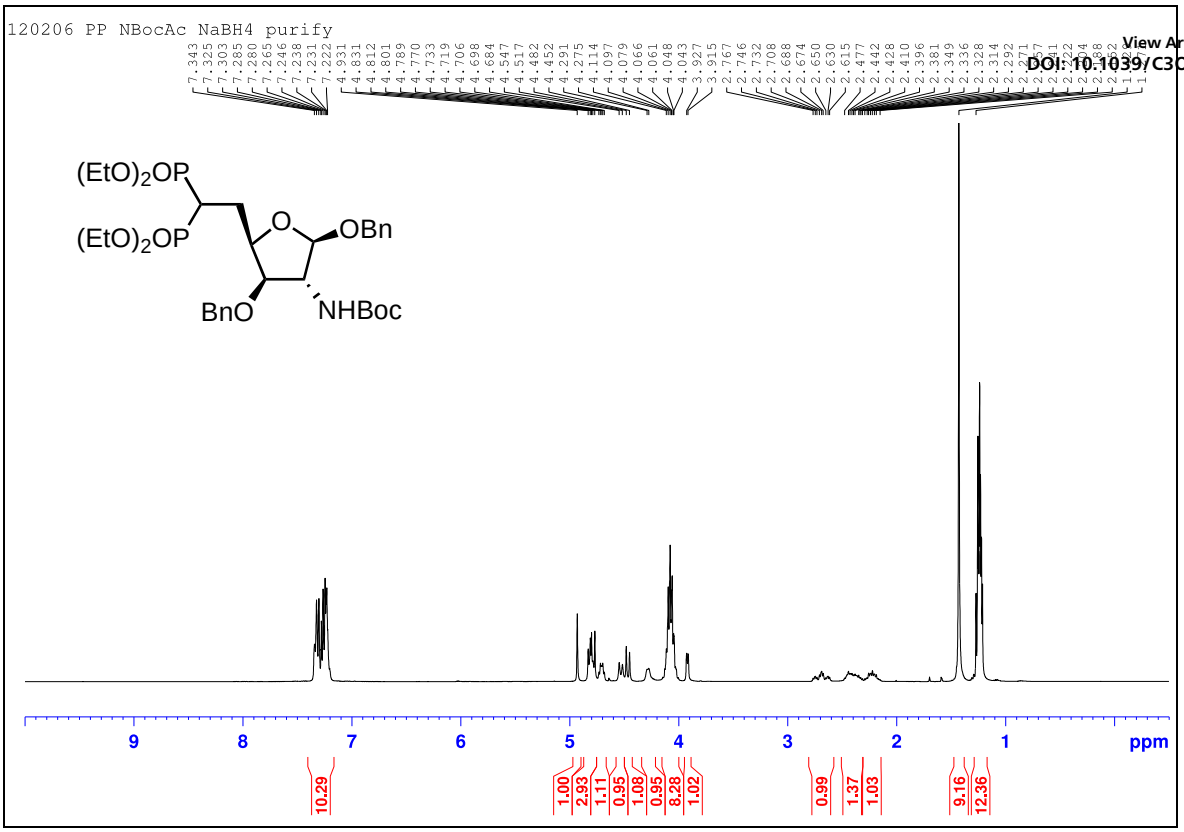
^{1}H NMR spectrum of compound **26** ($CDCl_3$, 400 MHz)



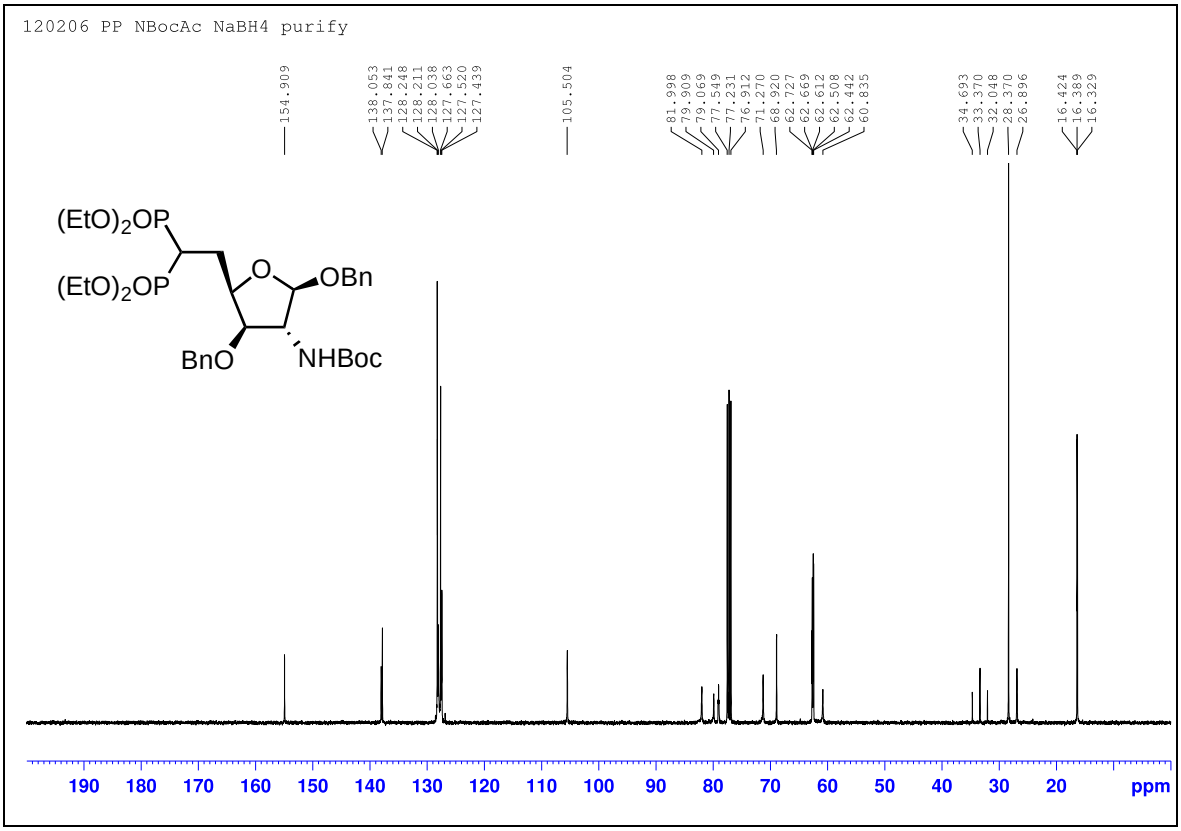
^{13}C NMR spectrum of compound **26** ($CDCl_3$, 100 MHz)



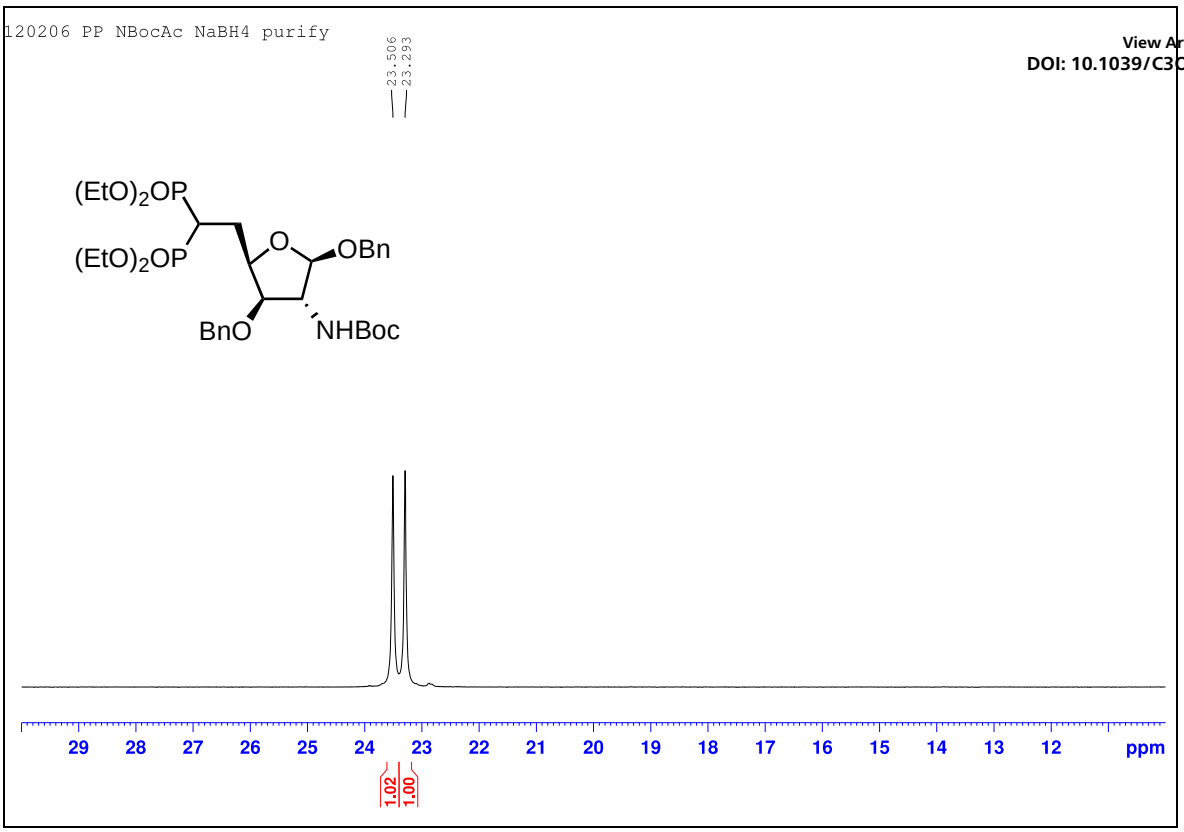
^{31}P NMR spectrum of compound **26** ($CDCl_3$, 162 MHz)



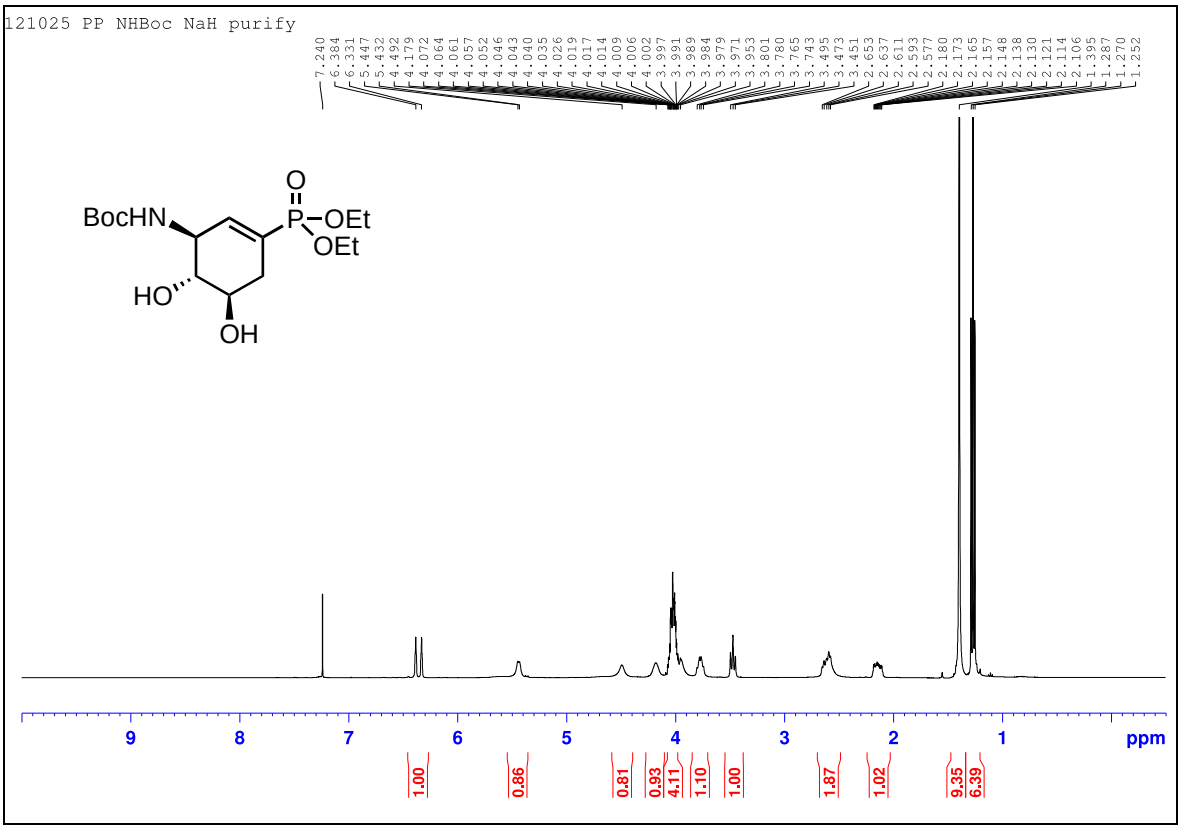
^{1}H NMR spectrum of compound **27** ($CDCl_3$, 400 MHz)



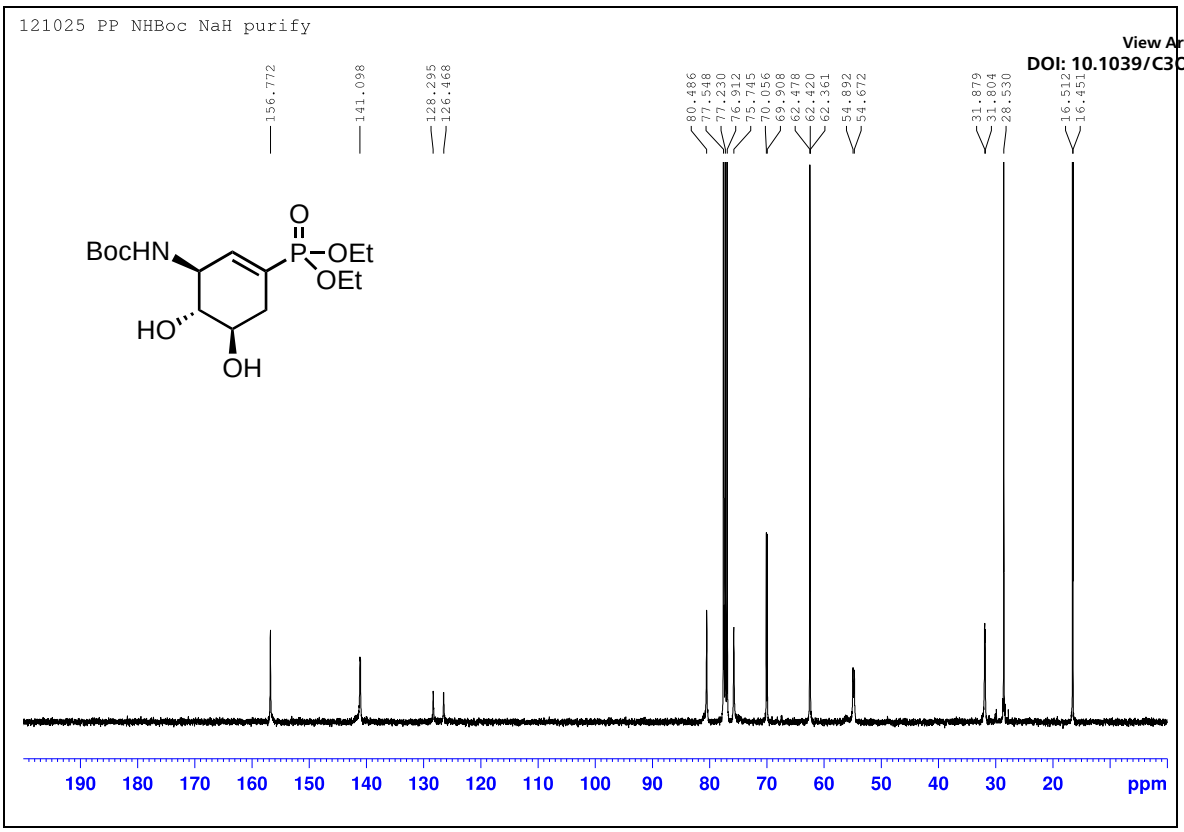
^{13}C NMR spectrum of compound **27** ($CDCl_3$, 100 MHz)



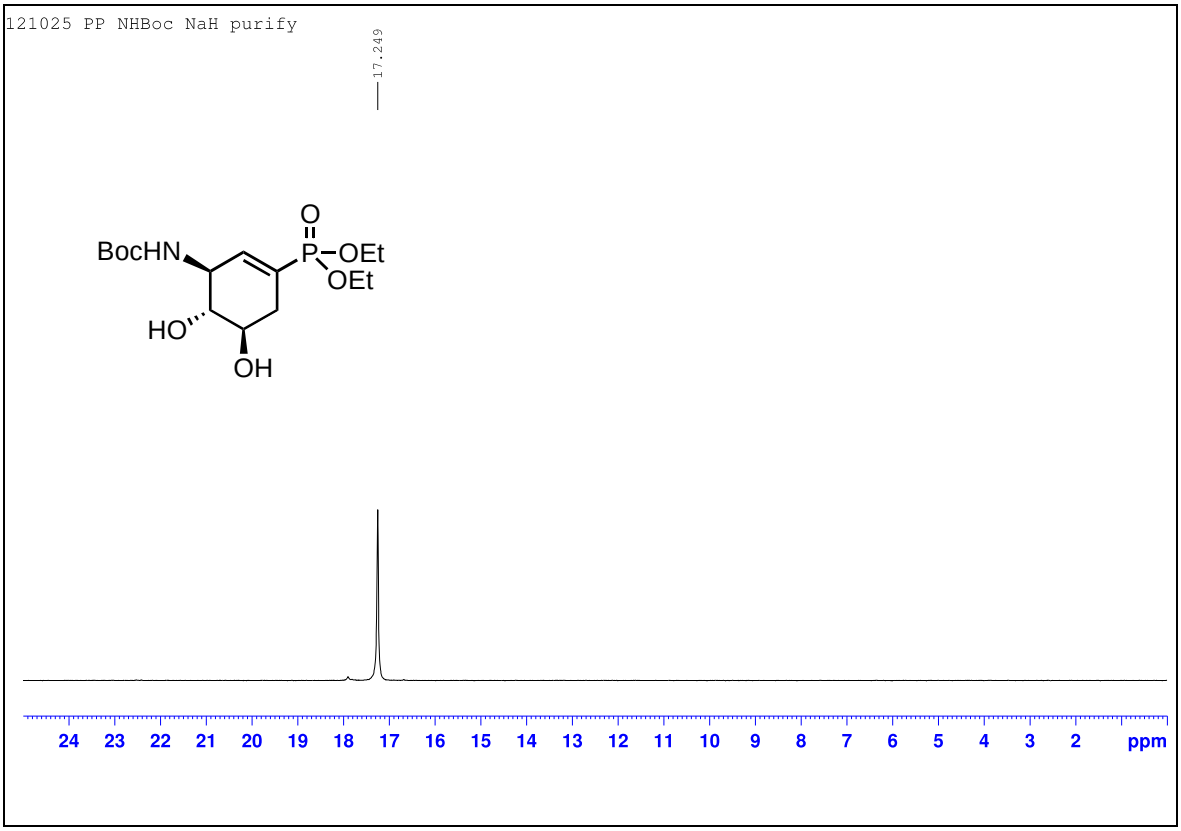
^{31}P NMR spectrum of compound **27** ($CDCl_3$, 162 MHz)



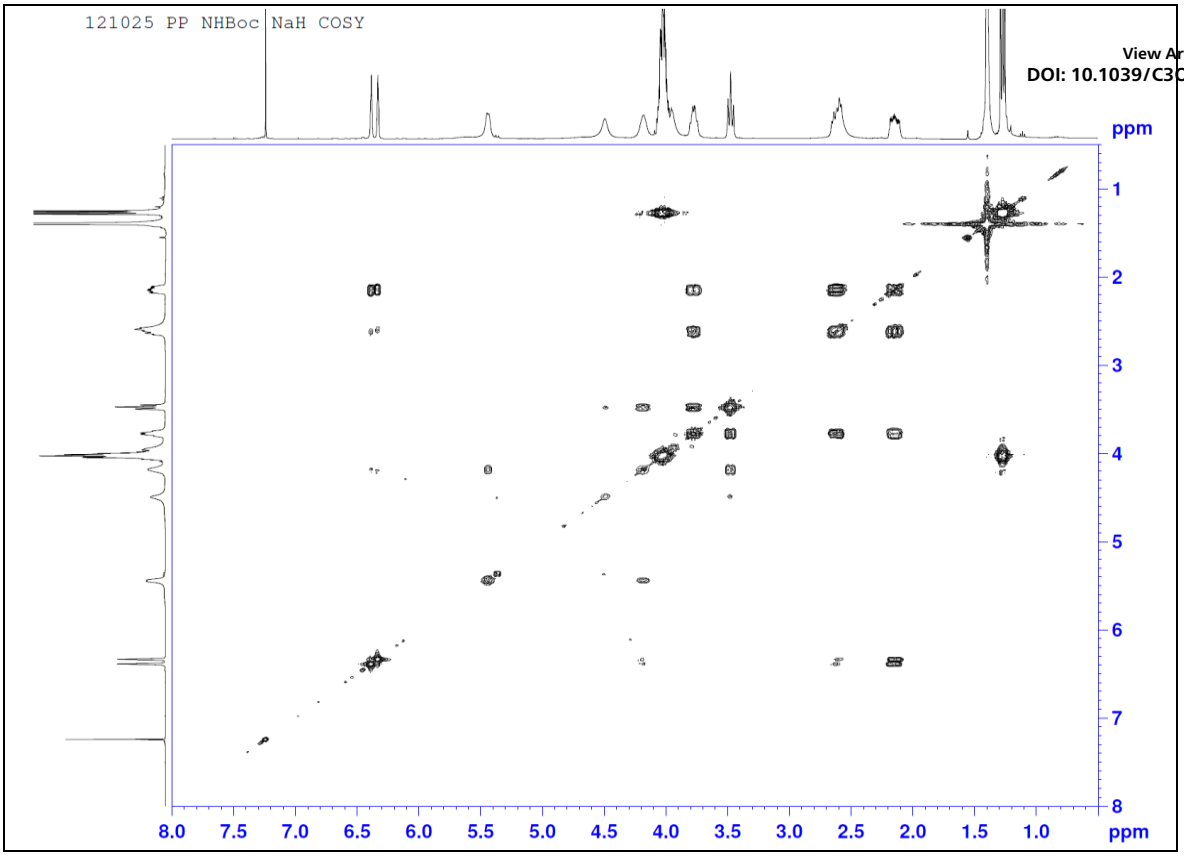
^{1}H NMR spectrum of compound **28b** ($CDCl_3$, 400 MHz)



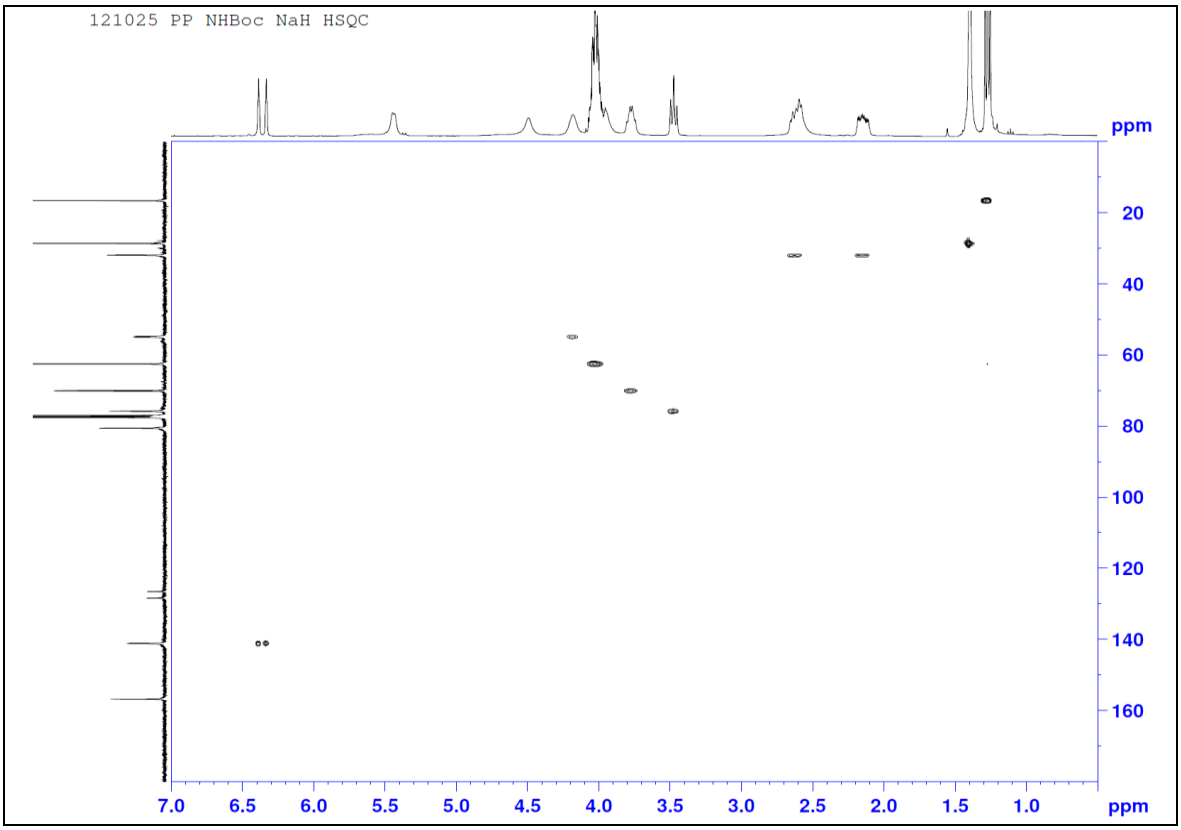
^{13}C NMR spectrum of compound **28b** ($CDCl_3$, 100 MHz)



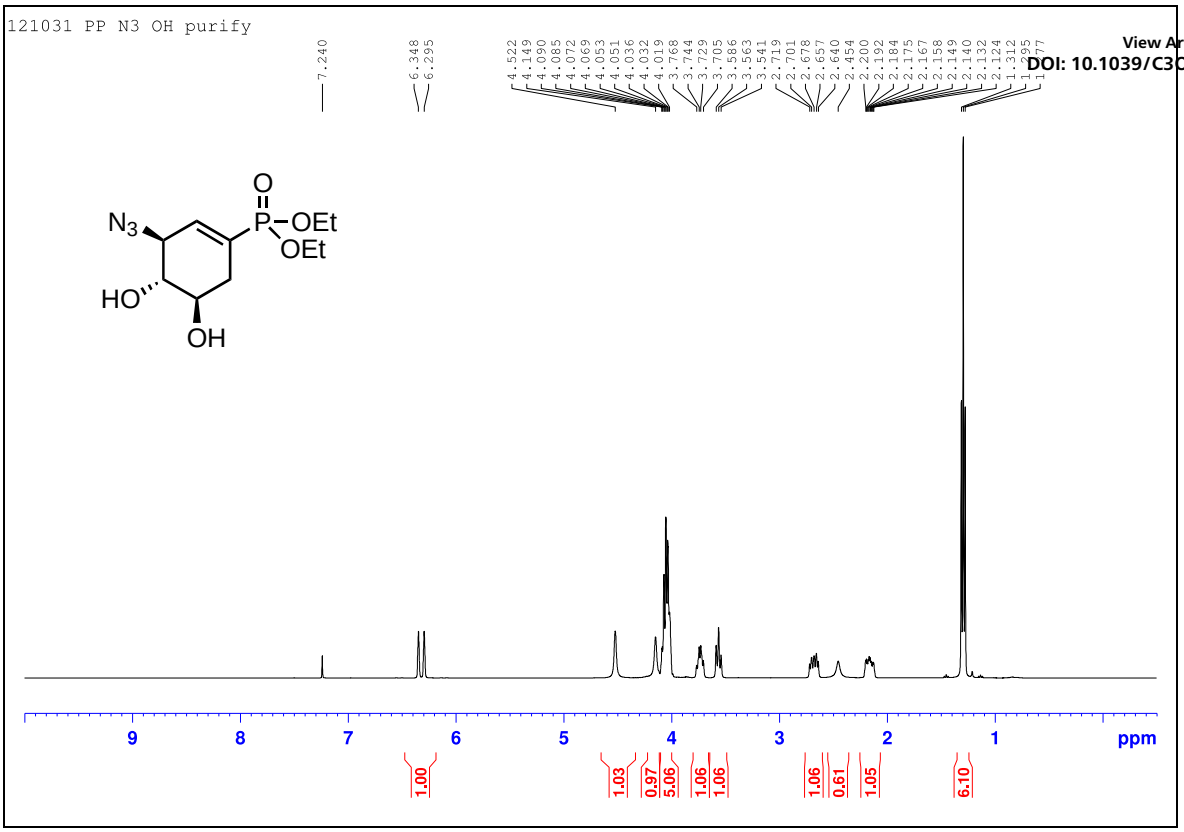
^{31}P NMR spectrum of compound **28b** ($CDCl_3$, 162 MHz)



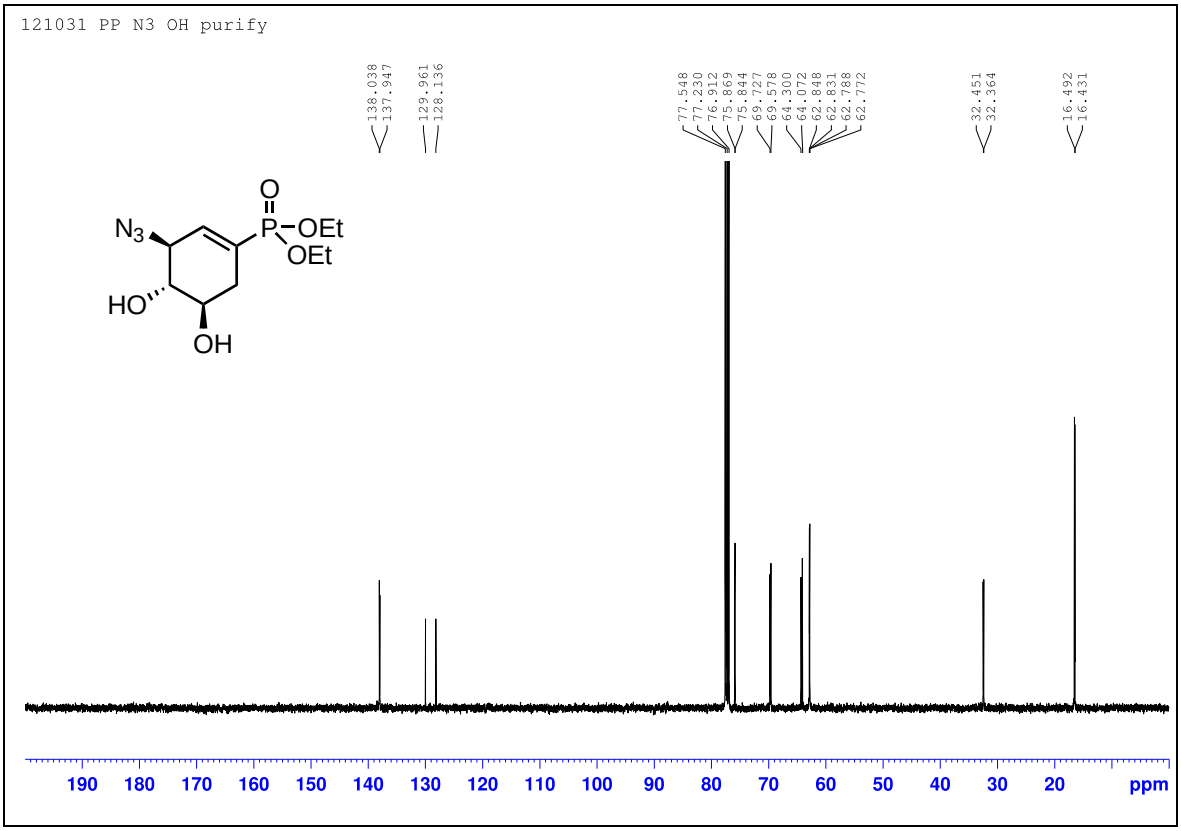
^{1}H–^{1}H COSY NMR spectrum of compound **28b** ($CDCl_3$, 400 MHz)



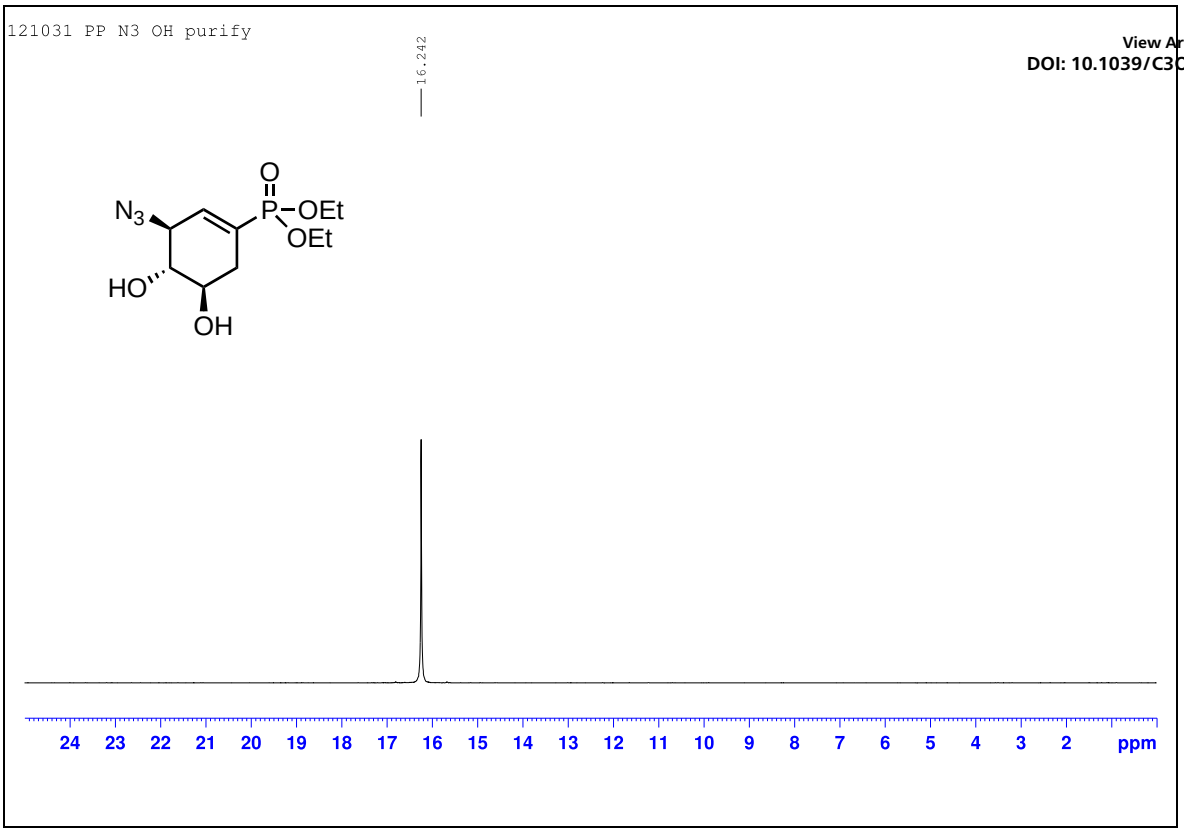
^{1}H–^{13}C HSQC NMR spectrum of compound **28b** ($CDCl_3$, 400 MHz)



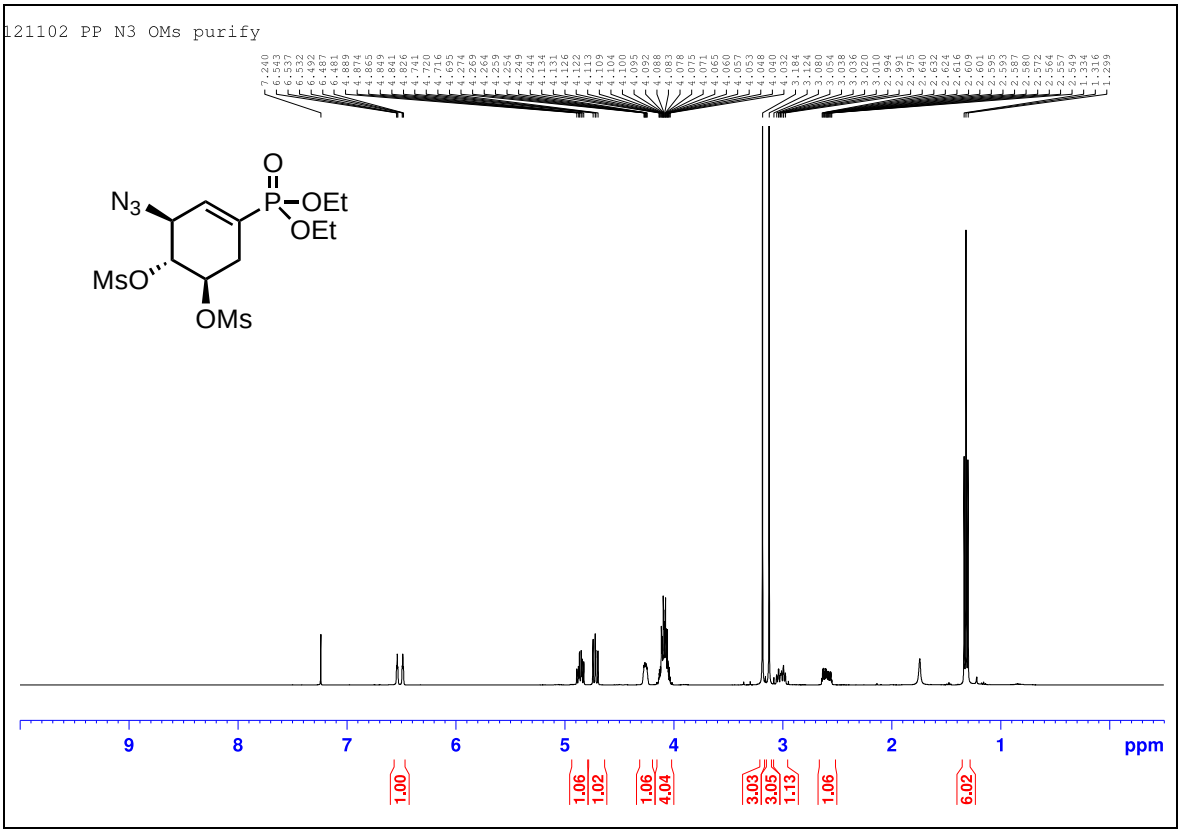
^{1}H NMR spectrum of compound **29** ($CDCl_3$, 400 MHz)



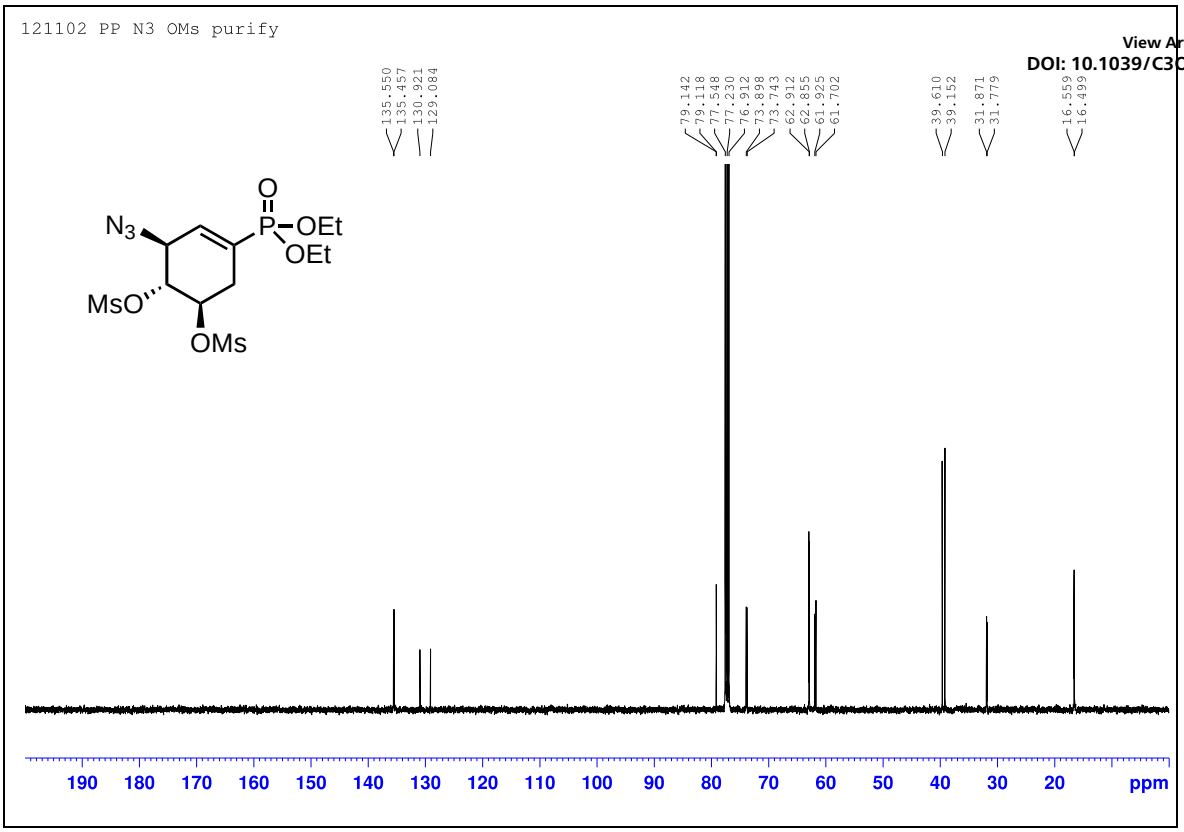
^{13}C NMR spectrum of compound **29** ($CDCl_3$, 100 MHz)



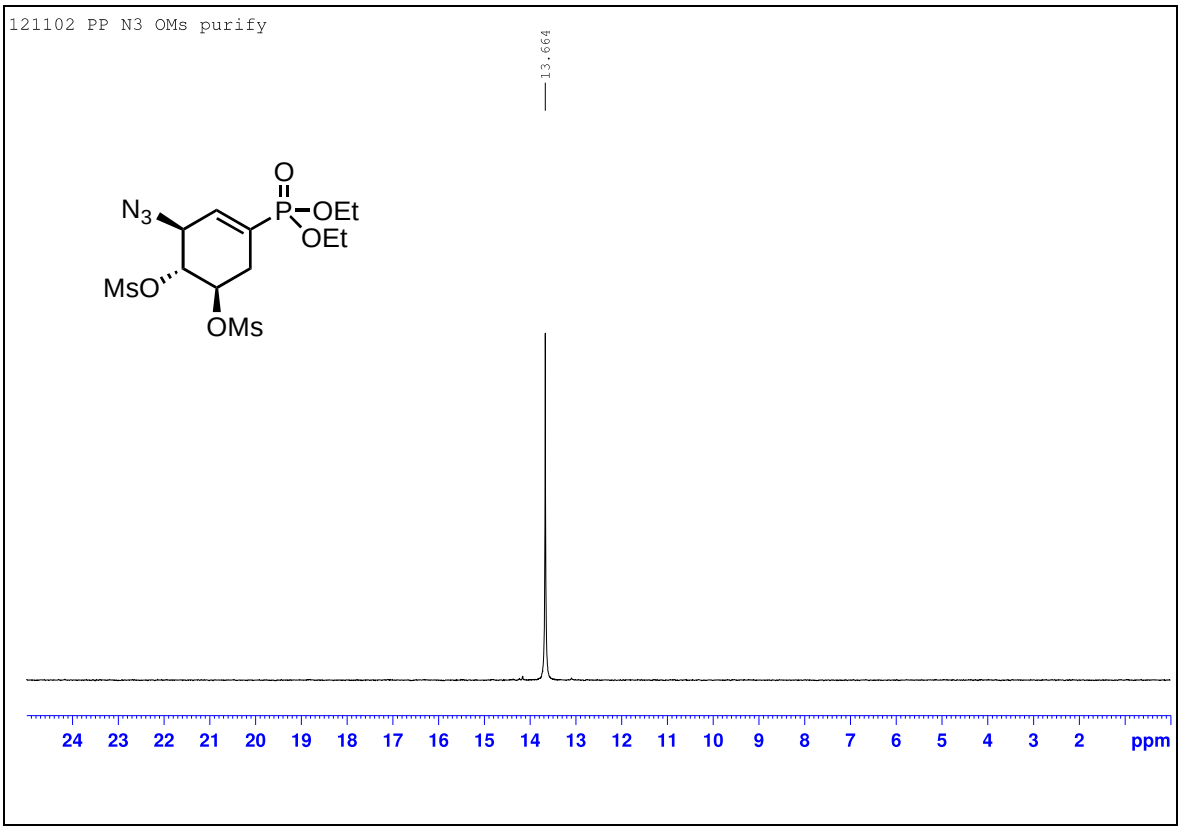
^{31}P NMR spectrum of compound **29** ($CDCl_3$, 162 MHz)



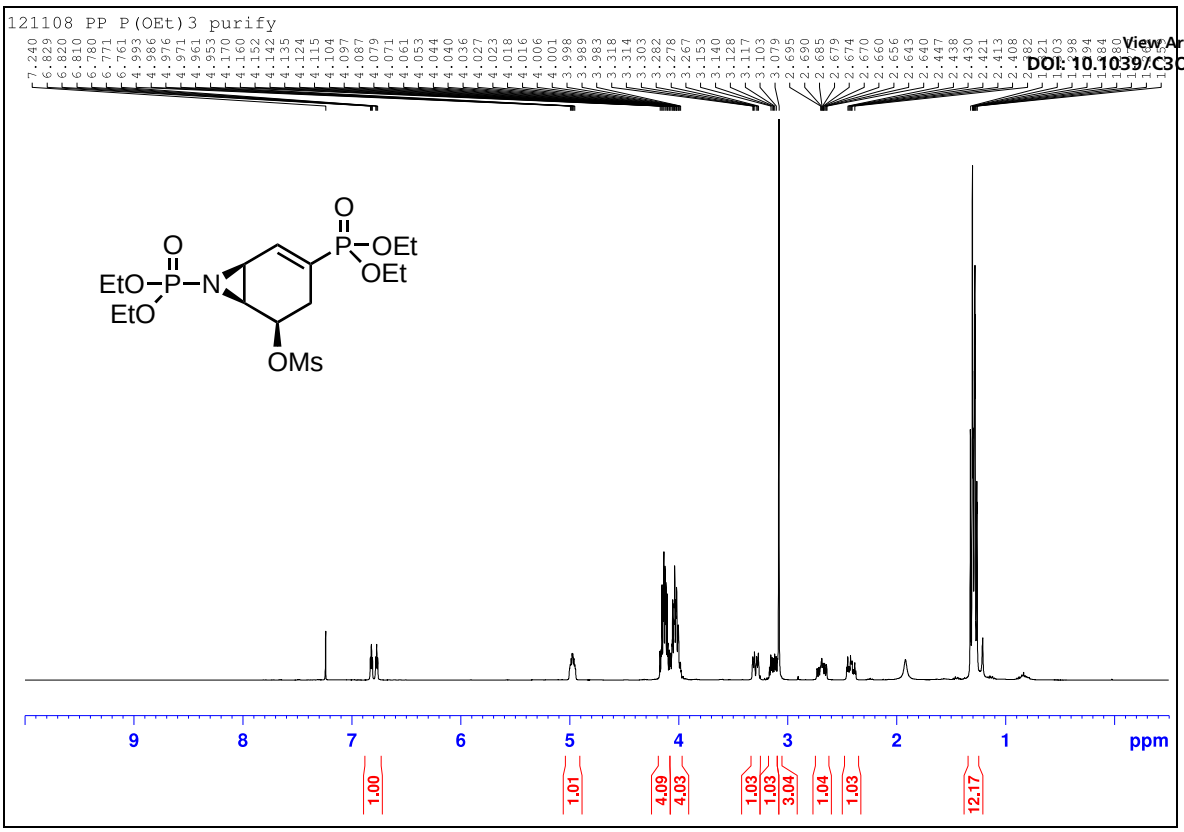
^{1}H NMR spectrum of compound **30** ($CDCl_3$, 400 MHz)



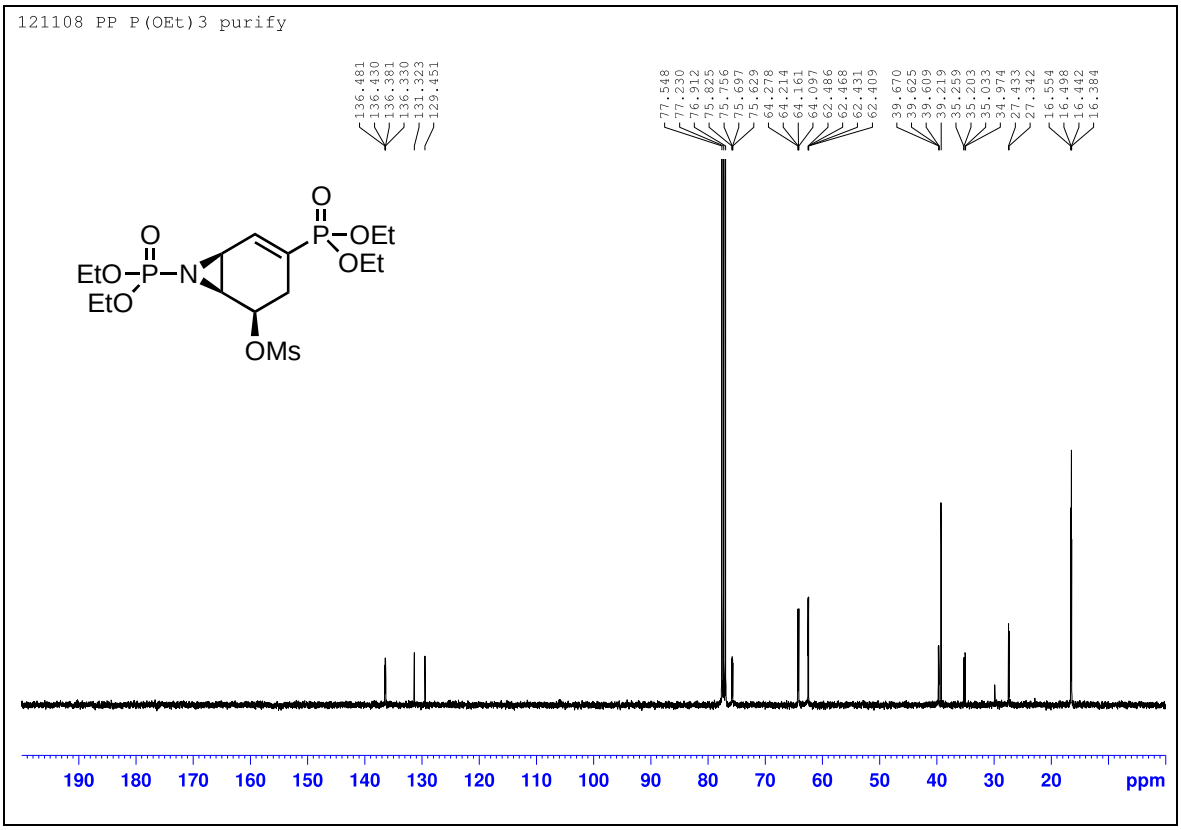
^{13}C NMR spectrum of compound **30** ($CDCl_3$, 100 MHz)



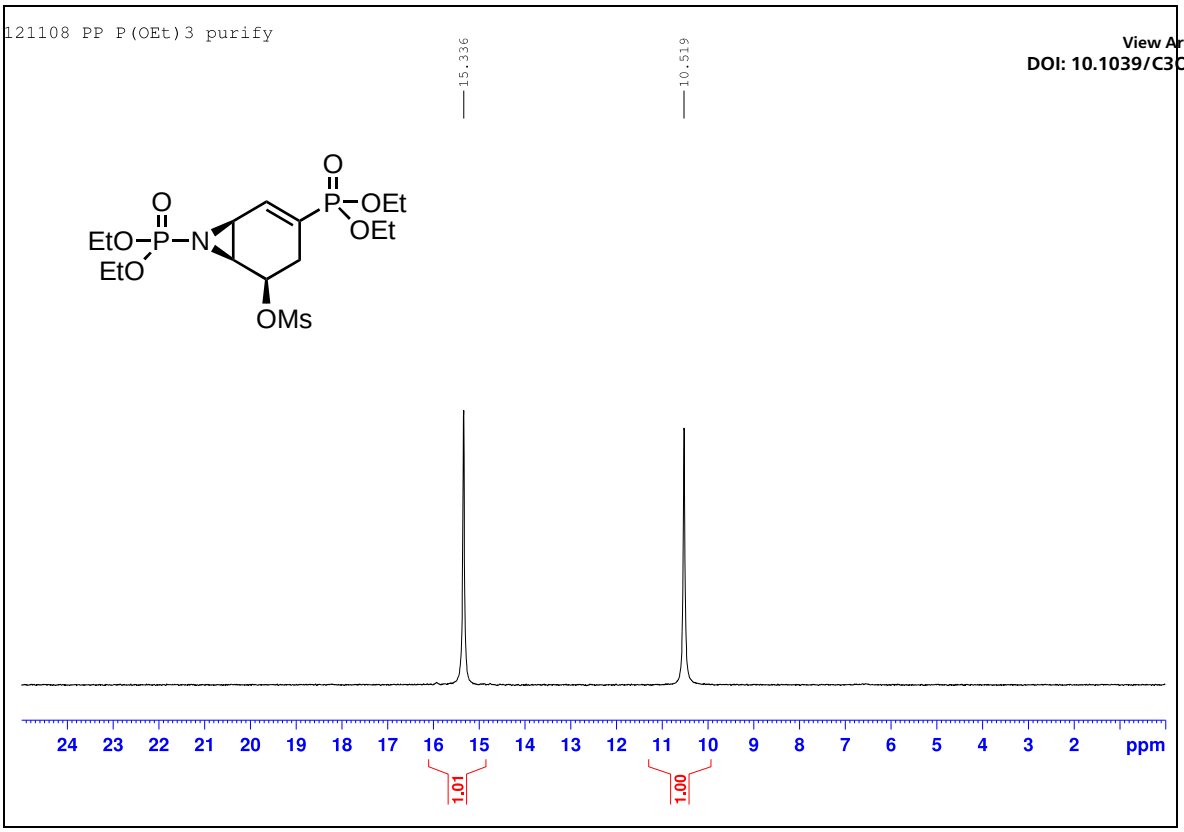
^{31}P NMR spectrum of compound **30** ($CDCl_3$, 162 MHz)



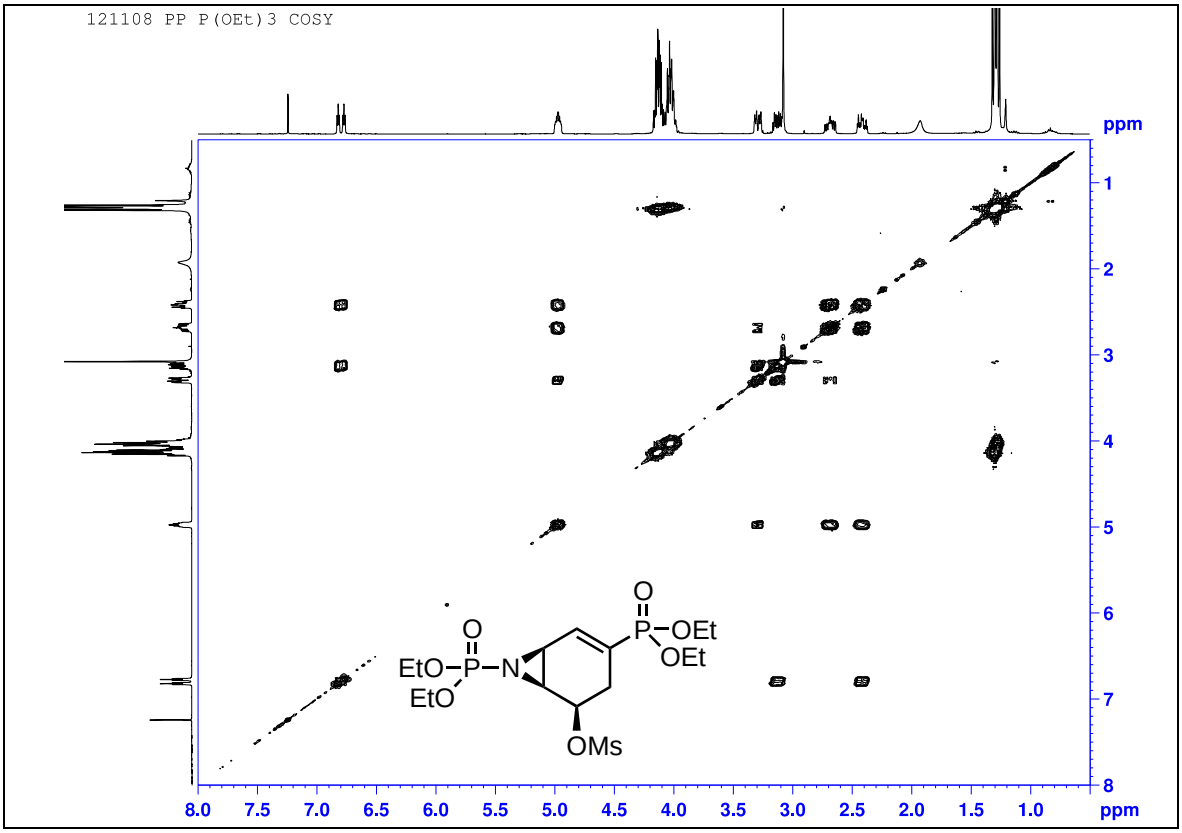
^{1}H NMR spectrum of compound **31** ($CDCl_3$, 400 MHz)



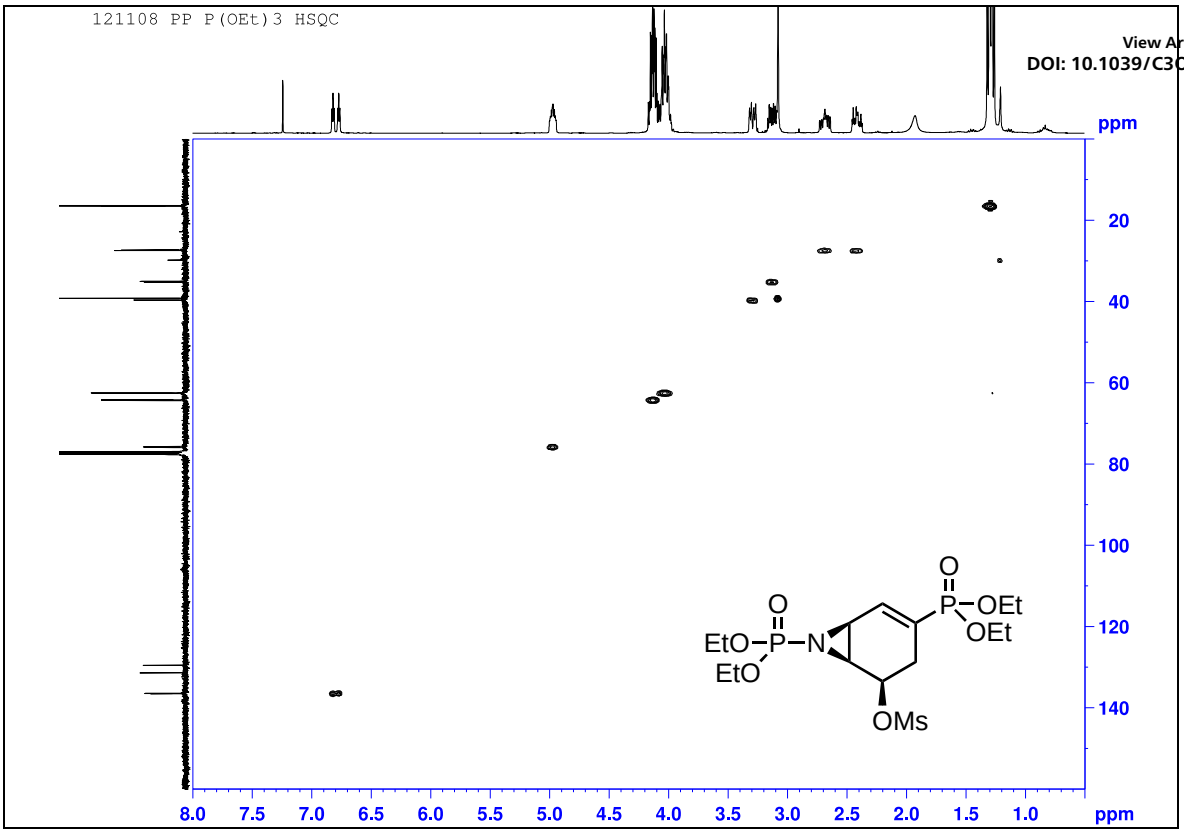
^{13}C NMR spectrum of compound **31** ($CDCl_3$, 100 MHz)



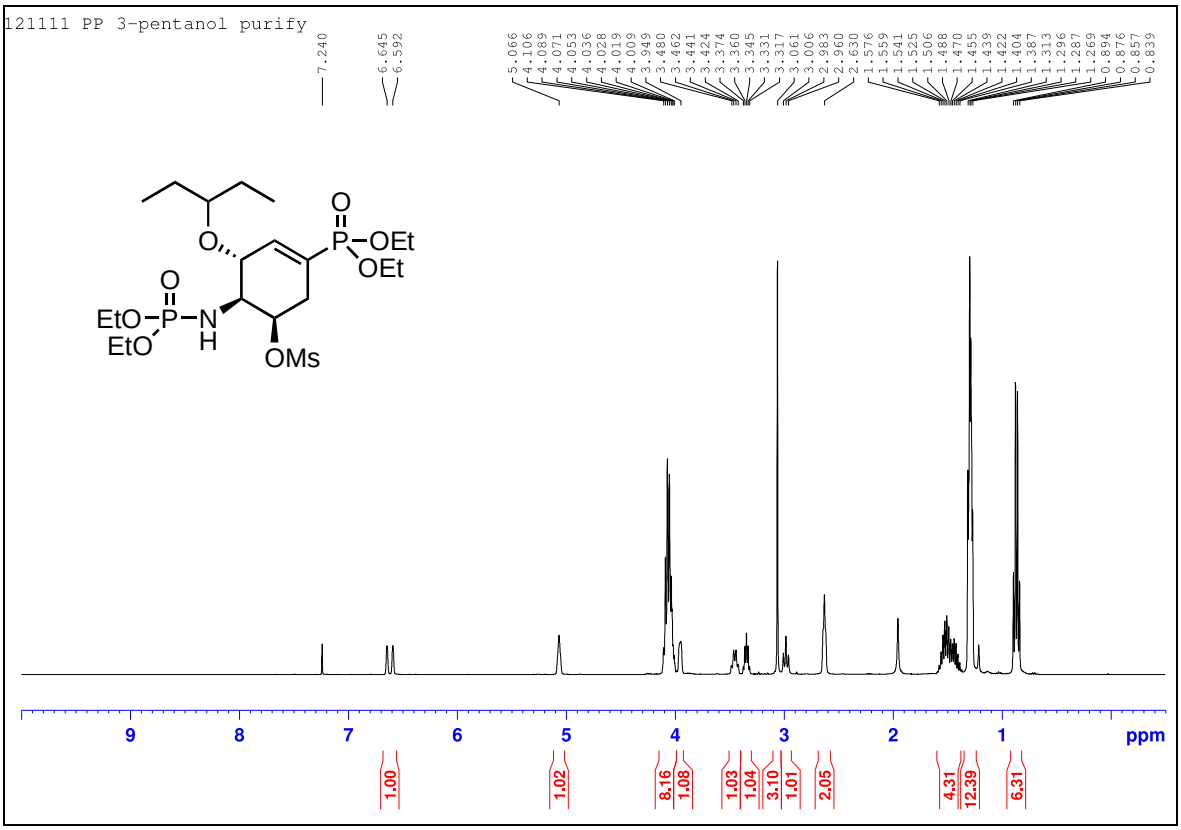
^{31}P NMR spectrum of compound **31** ($CDCl_3$, 162 MHz)



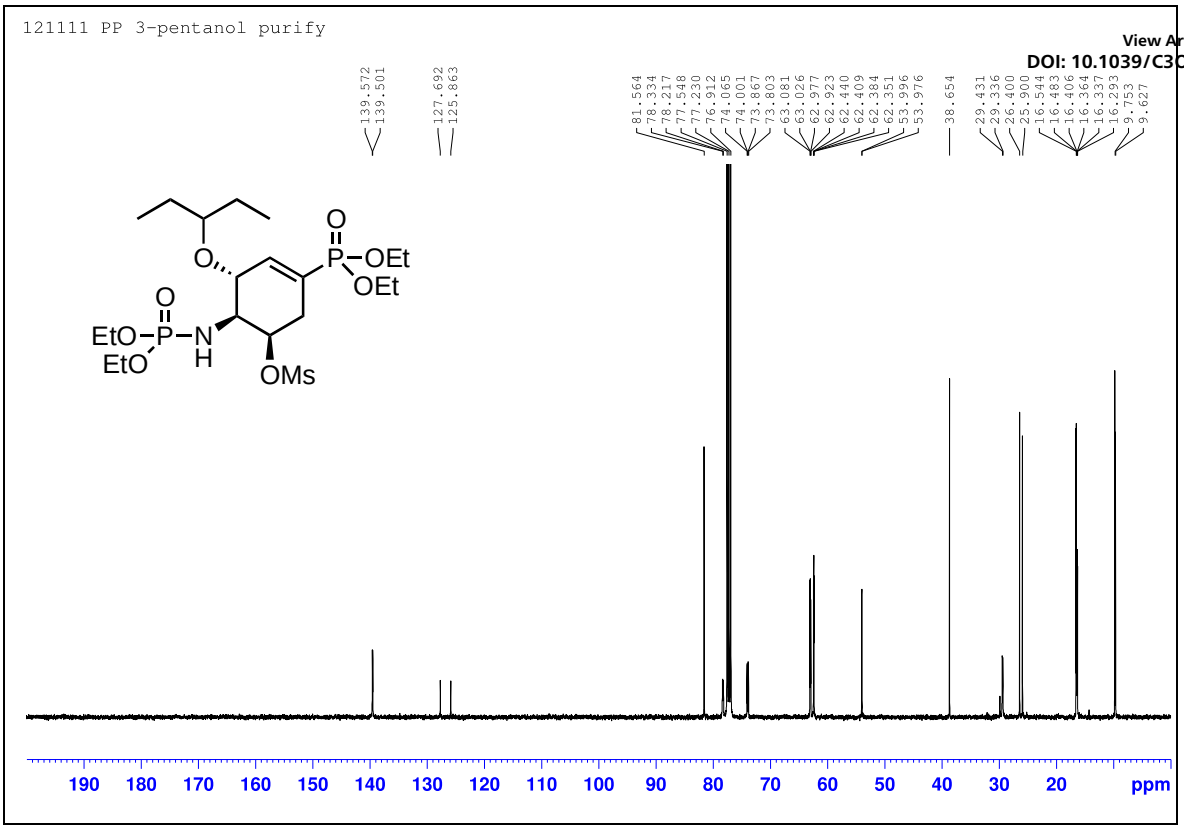
^{1}H–^{1}H COSY NMR spectrum of compound **31** ($CDCl_3$, 400 MHz)



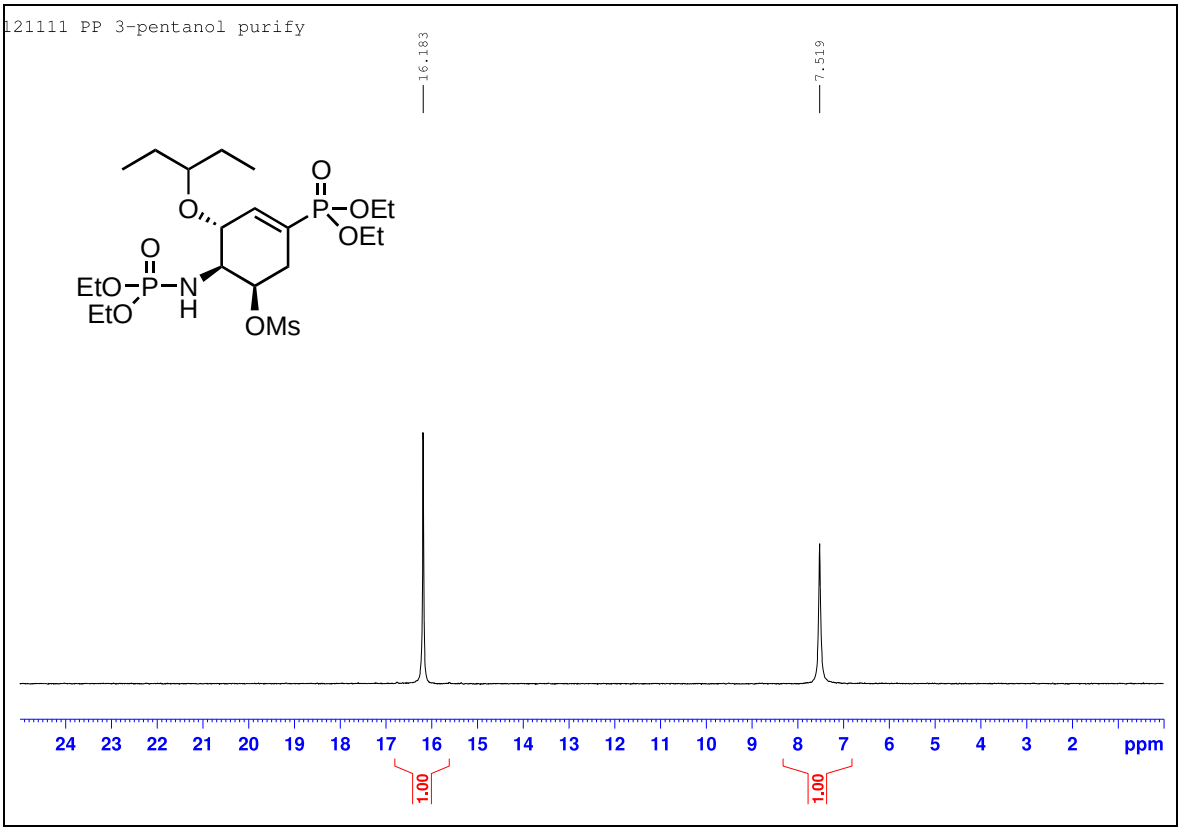
^{1}H–^{13}C HSQC NMR spectrum of compound **31** ($CDCl_3$, 400 MHz)



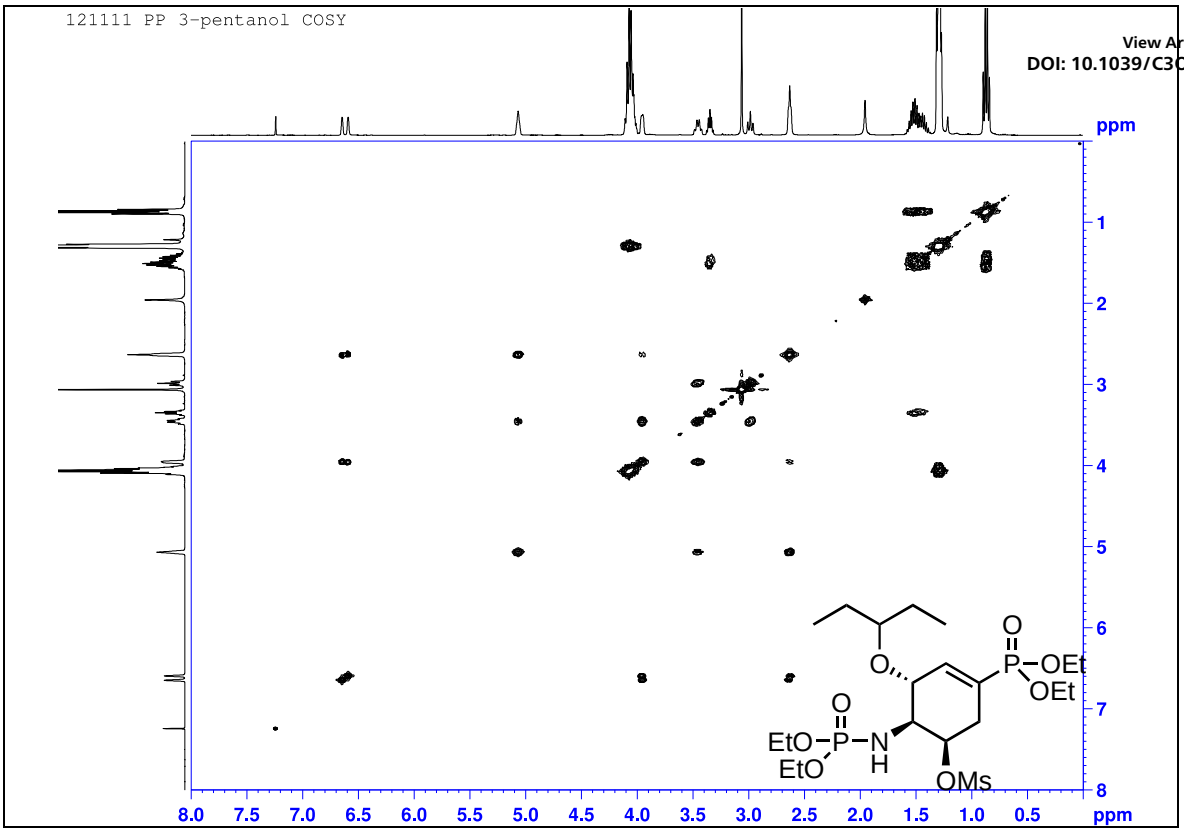
^{1}H NMR spectrum of compound **32** ($CDCl_3$, 400 MHz)



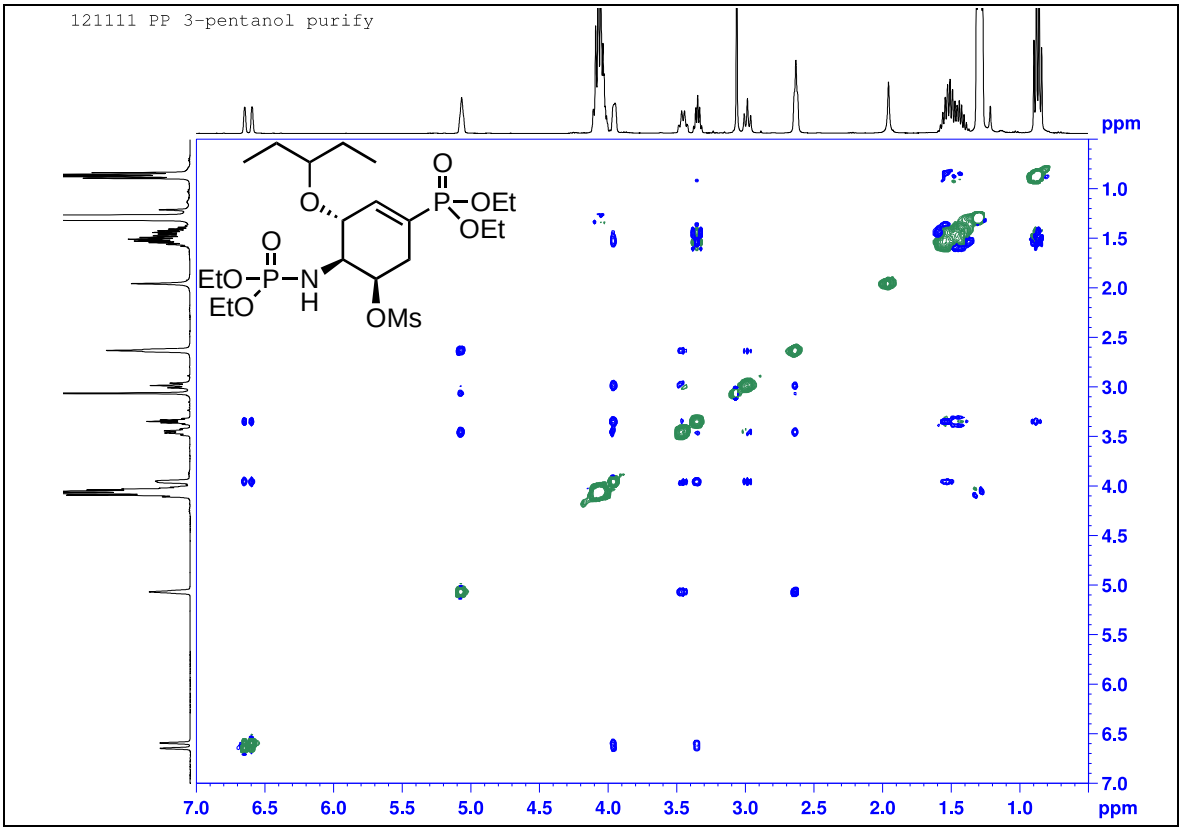
^{13}C NMR spectrum of compound **32** ($CDCl_3$, 100 MHz)



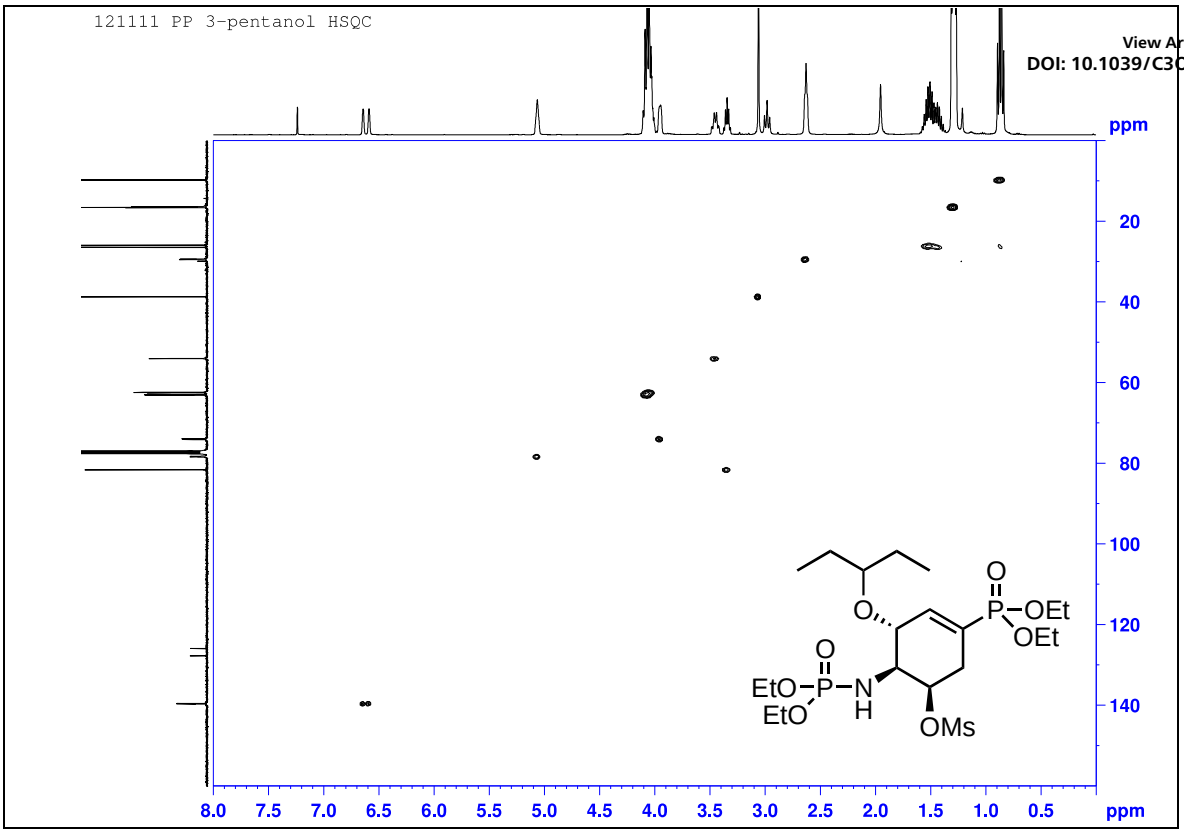
^{31}P NMR spectrum of compound **32** ($CDCl_3$, 162 MHz)



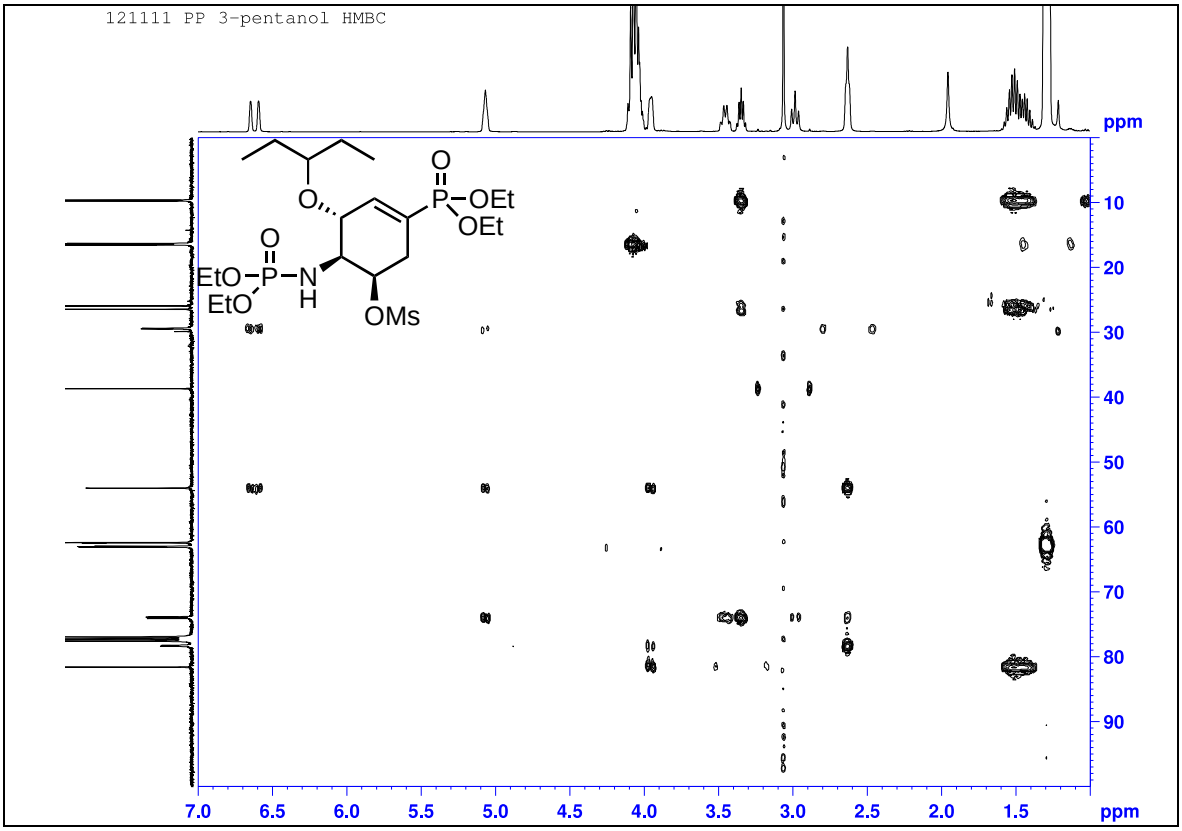
^{1}H–^{1}H COSY NMR spectrum of compound **32** ($CDCl_3$, 400 MHz)



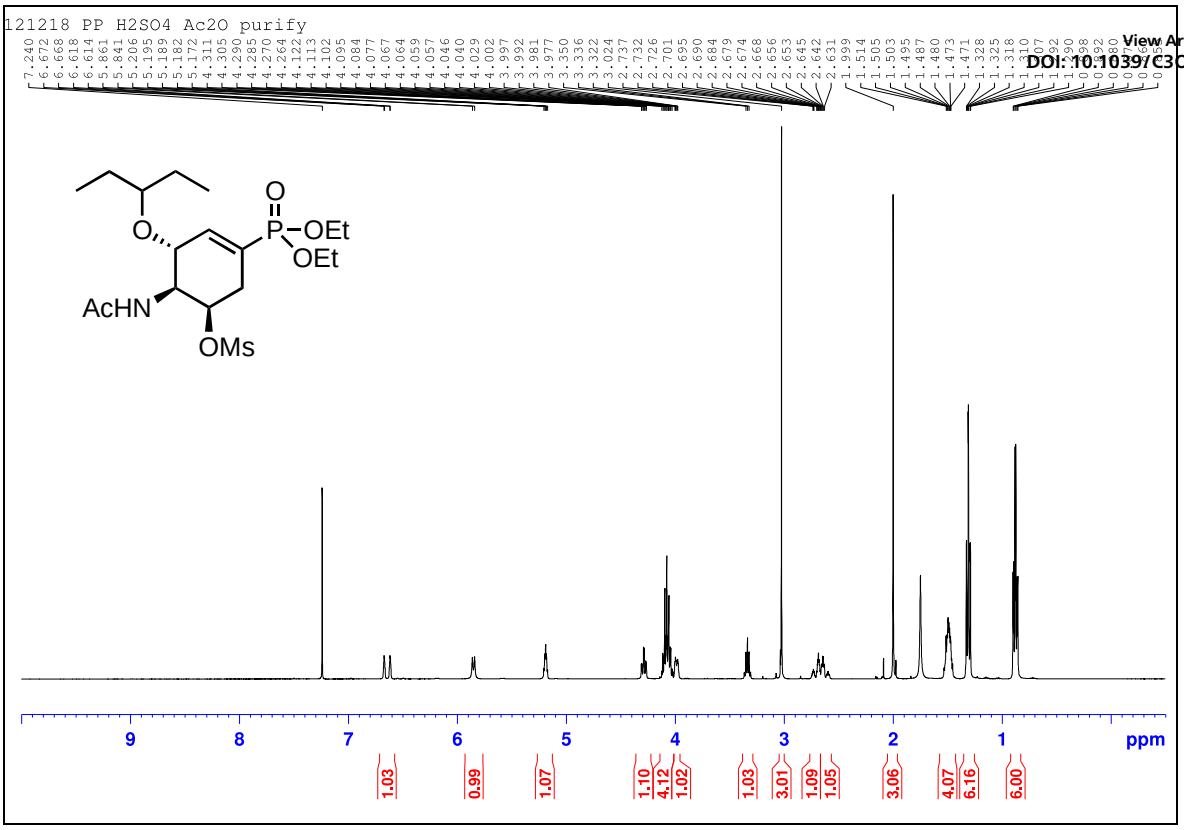
NOESY NMR spectrum of compound **32** ($CDCl_3$, 400 MHz)



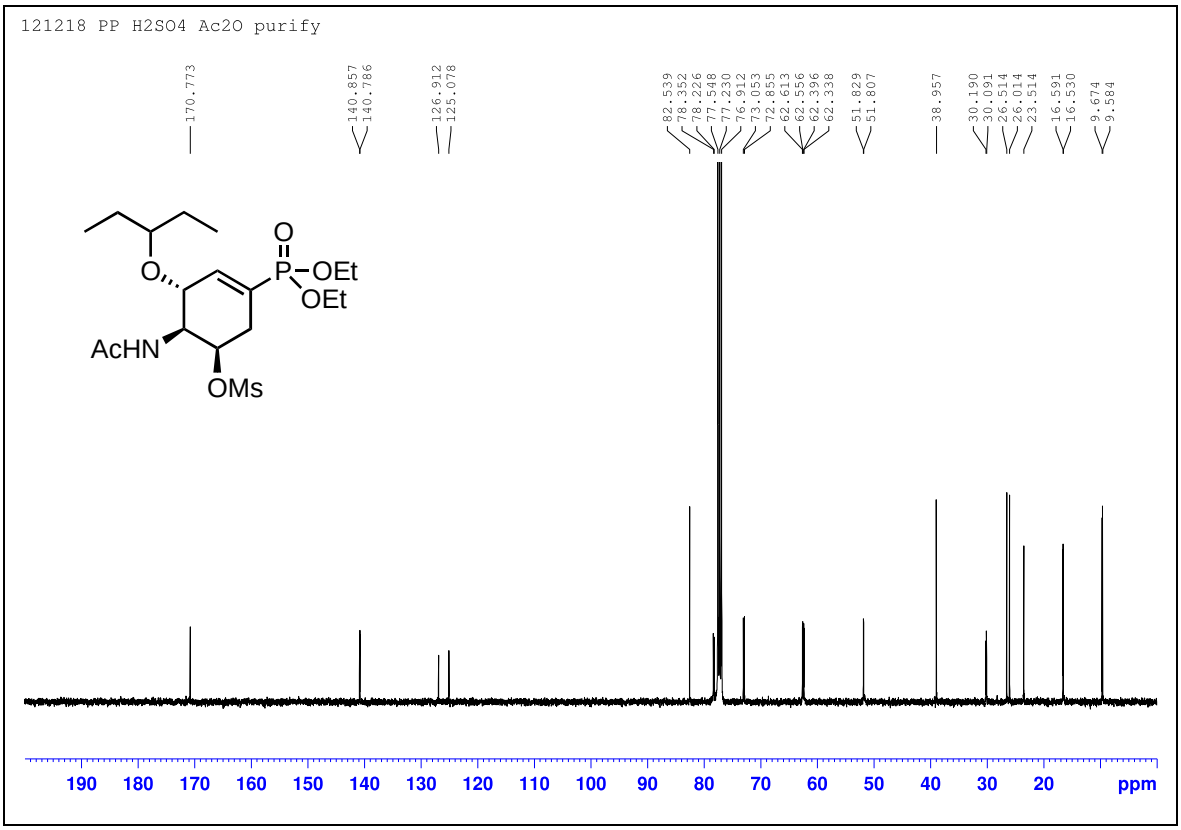
$^{1}H–^{13}C$ HSQC NMR spectrum of compound **32** ($CDCl_3$, 400 MHz)



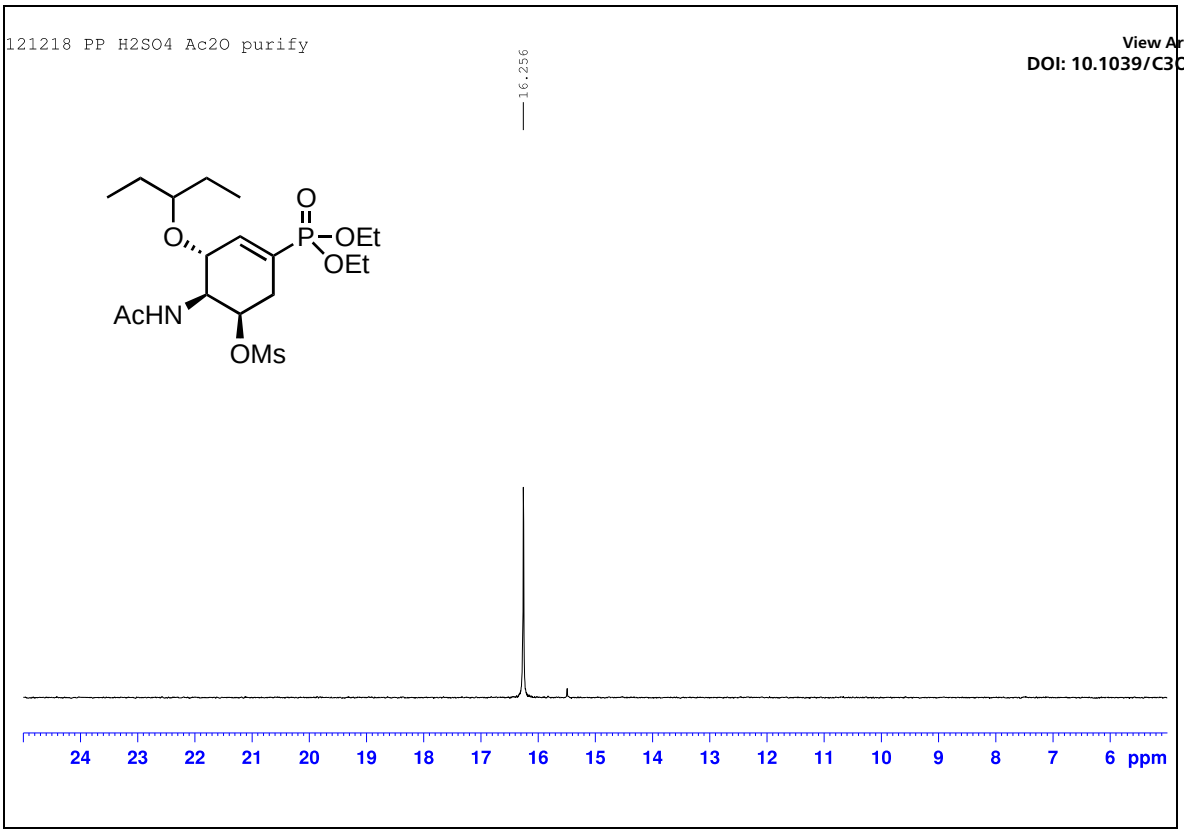
$^{1}H–^{13}C$ HMBC NMR spectrum of compound **32** ($CDCl_3$, 400 MHz)



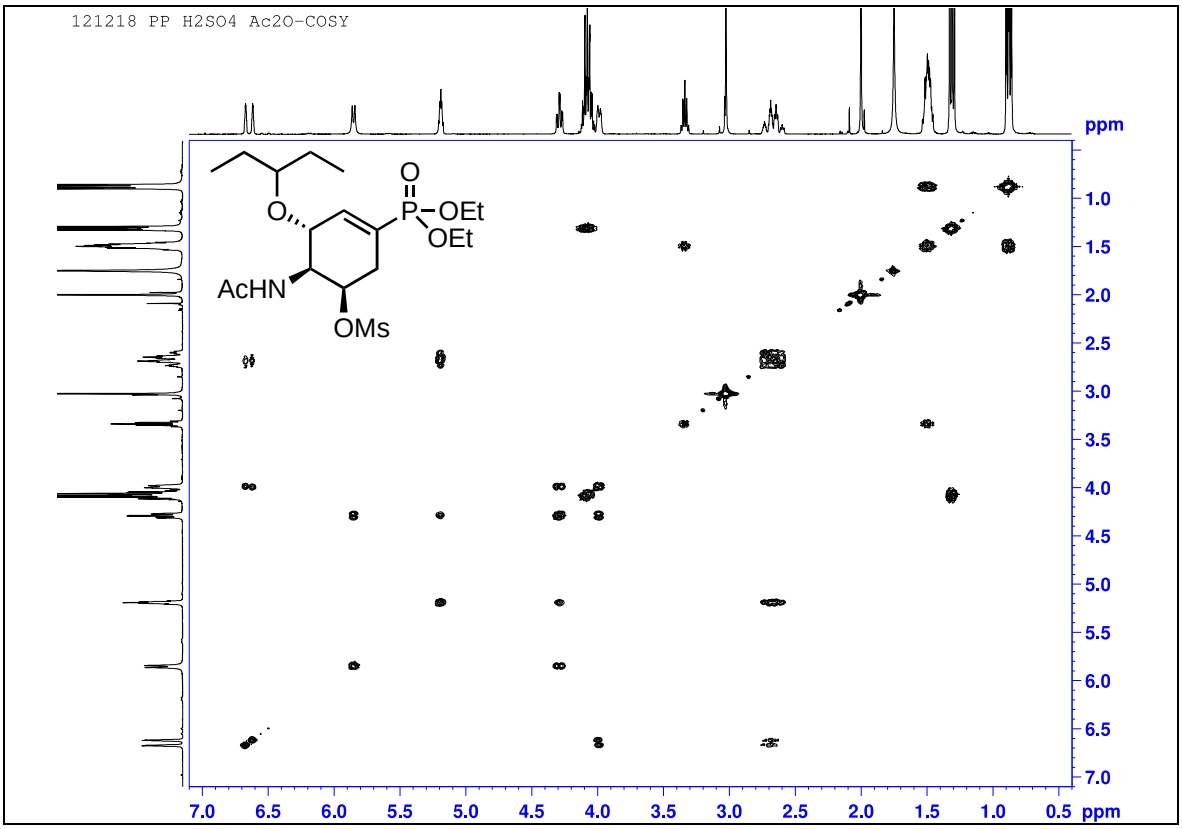
^{1}H NMR spectrum of compound **33** ($CDCl_3$, 400 MHz)



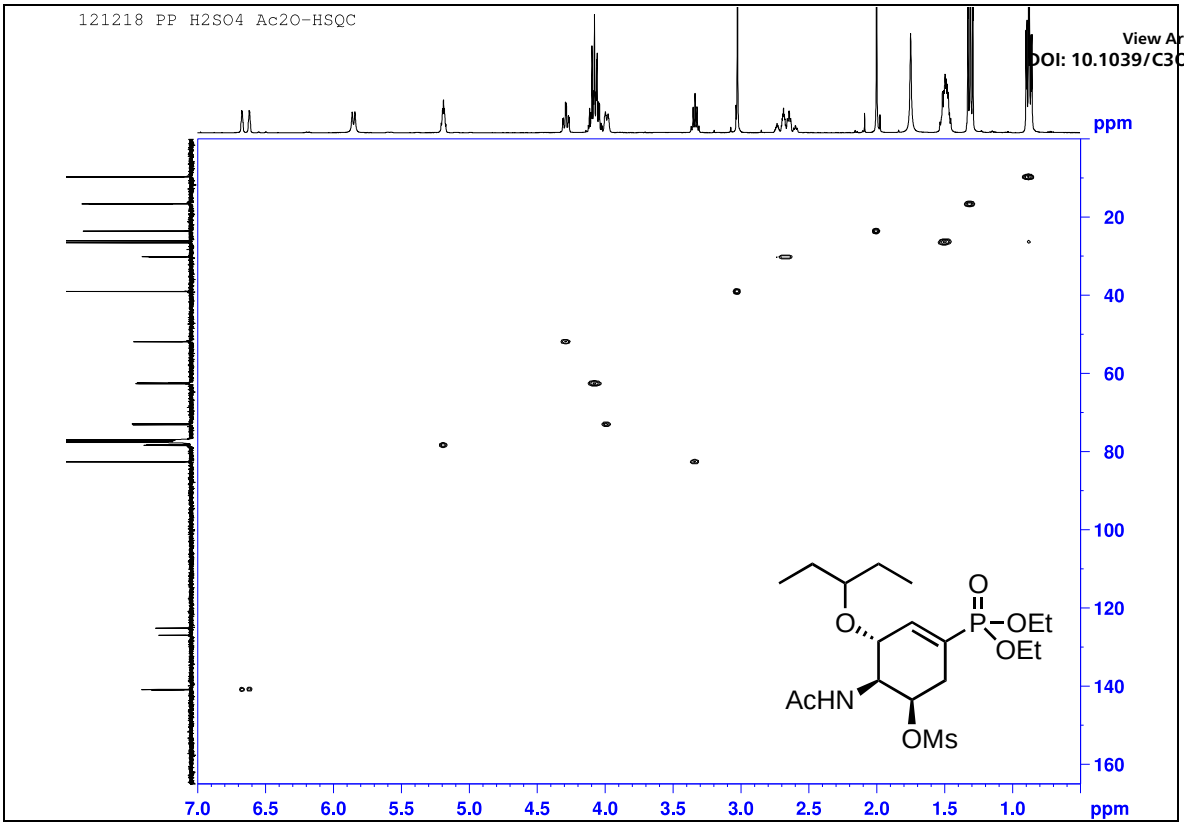
^{13}C NMR spectrum of compound **33** ($CDCl_3$, 100 MHz)



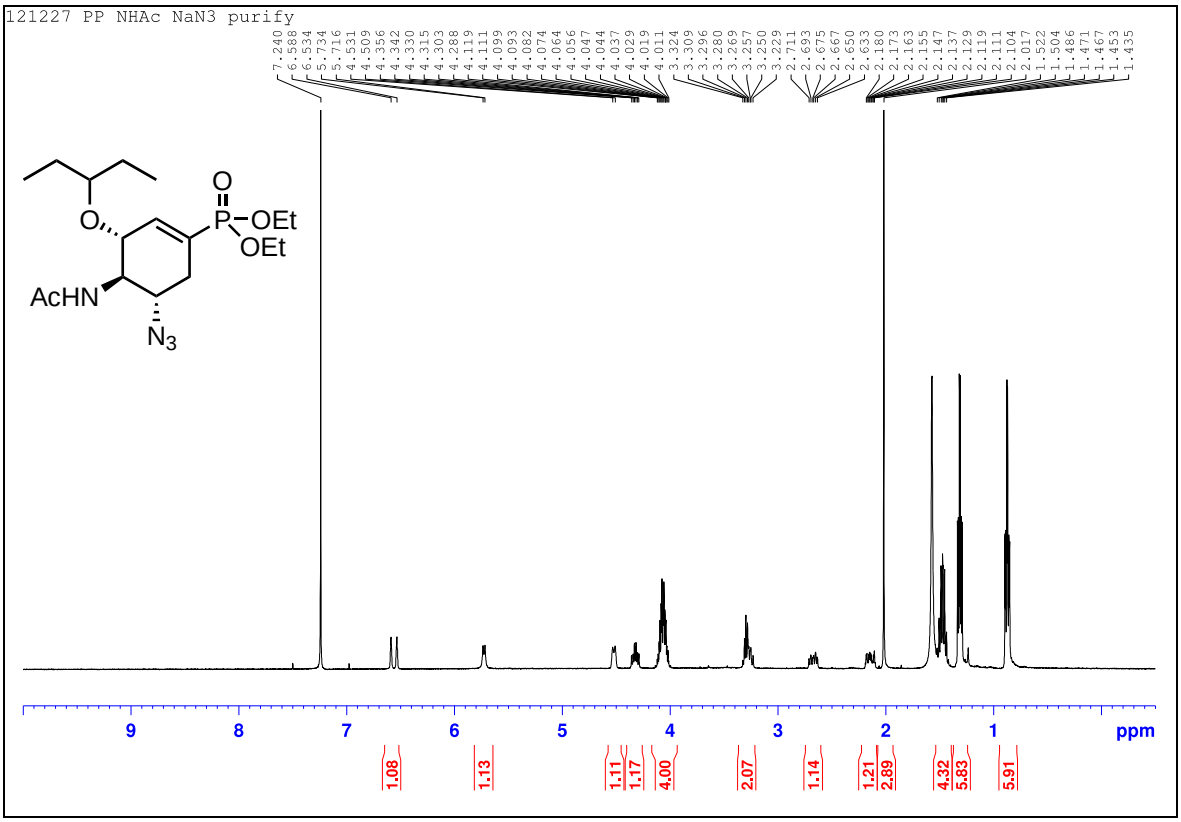
^{31}P NMR spectrum of compound **33** ($CDCl_3$, 162 MHz)



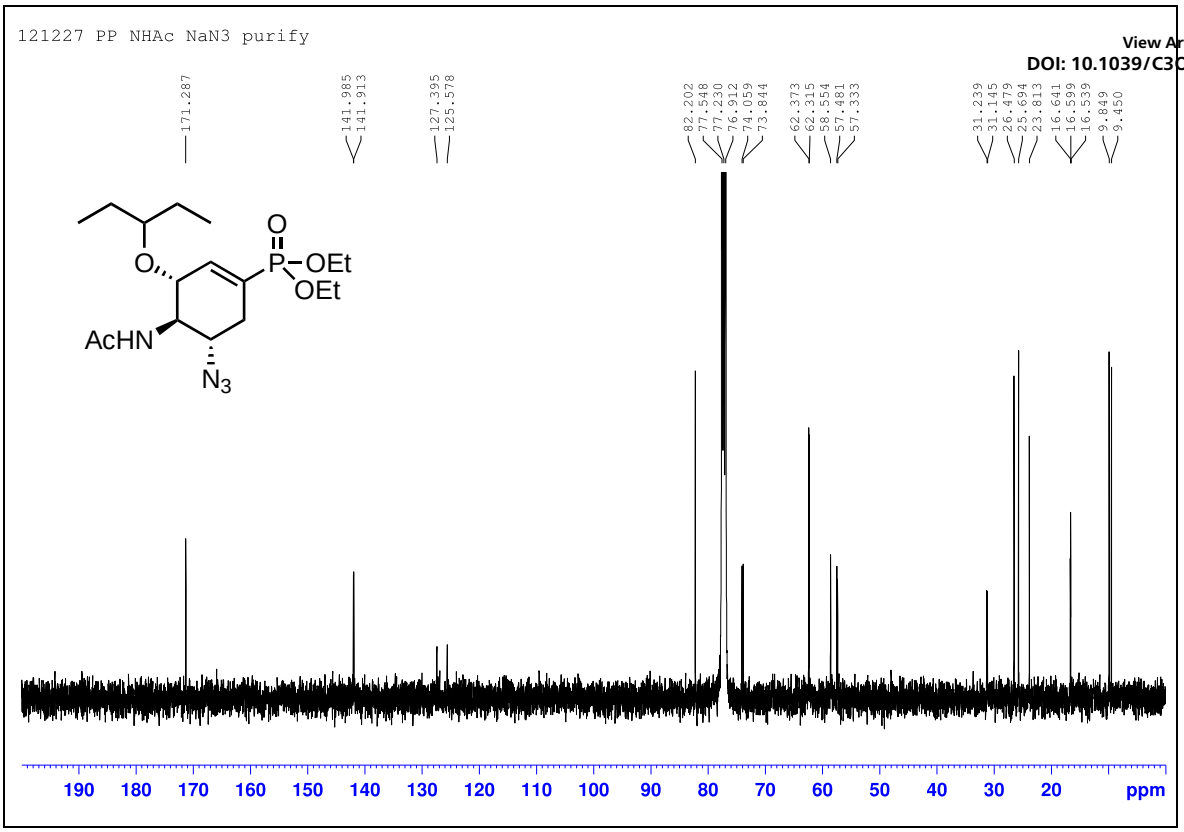
^{1}H–^{1}H COSY NMR spectrum of compound **33** ($CDCl_3$, 400 MHz)



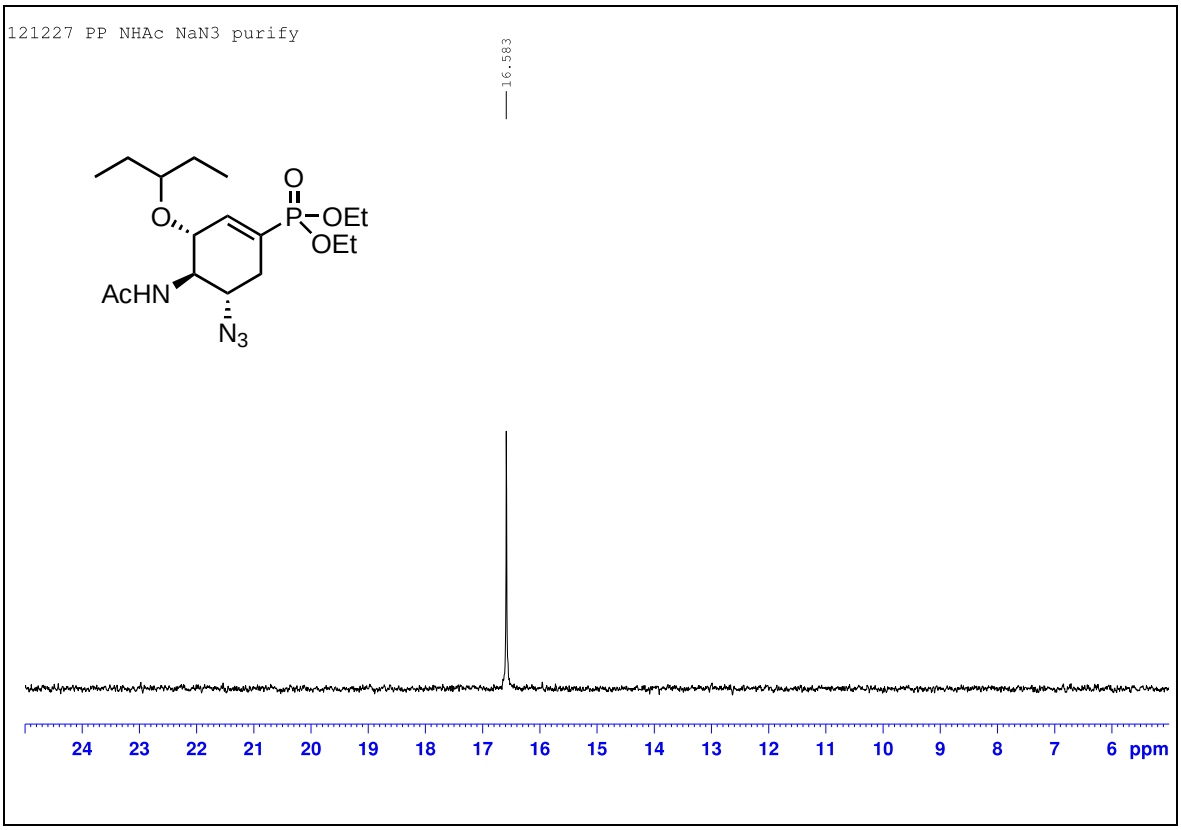
^{1}H–^{13}C HSQC NMR spectrum of compound **33** ($CDCl_3$, 400 MHz)



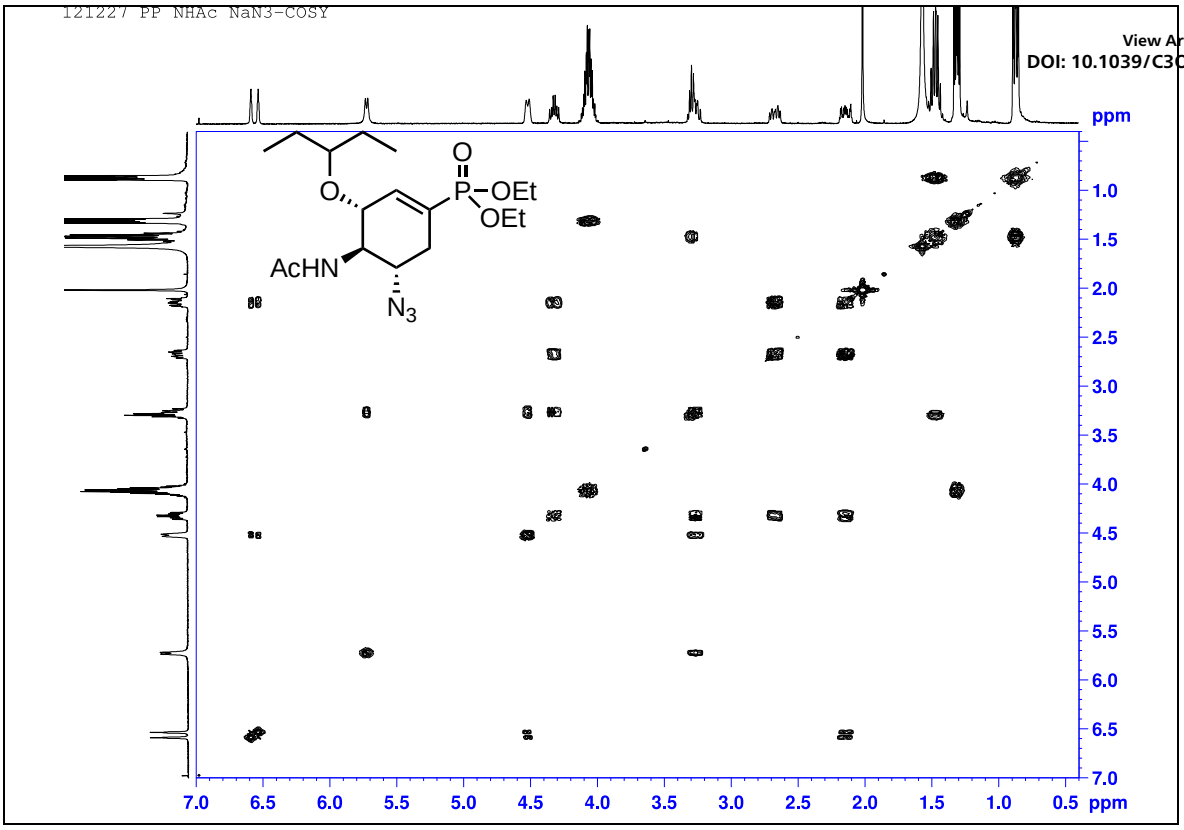
^{1}H NMR spectrum of compound **34** ($CDCl_3$, 400 MHz)



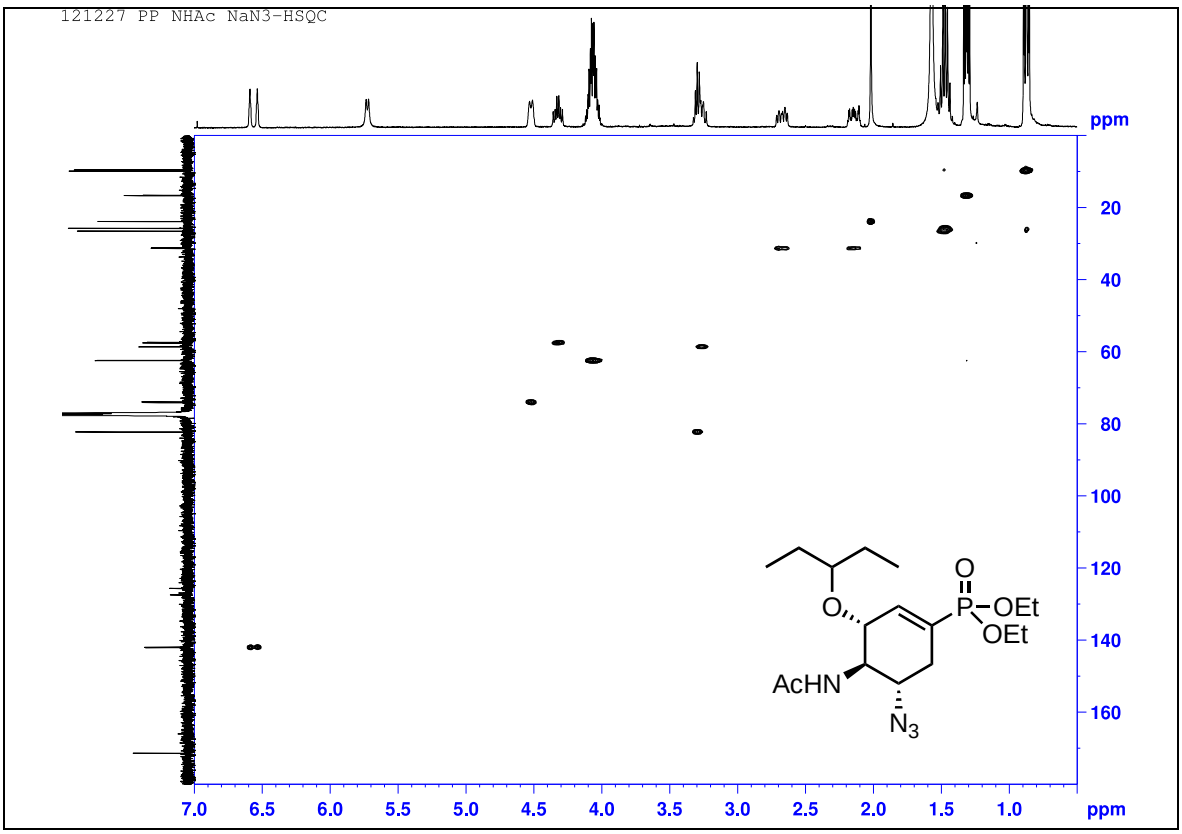
^{13}C NMR spectrum of compound **34** ($CDCl_3$, 100 MHz)



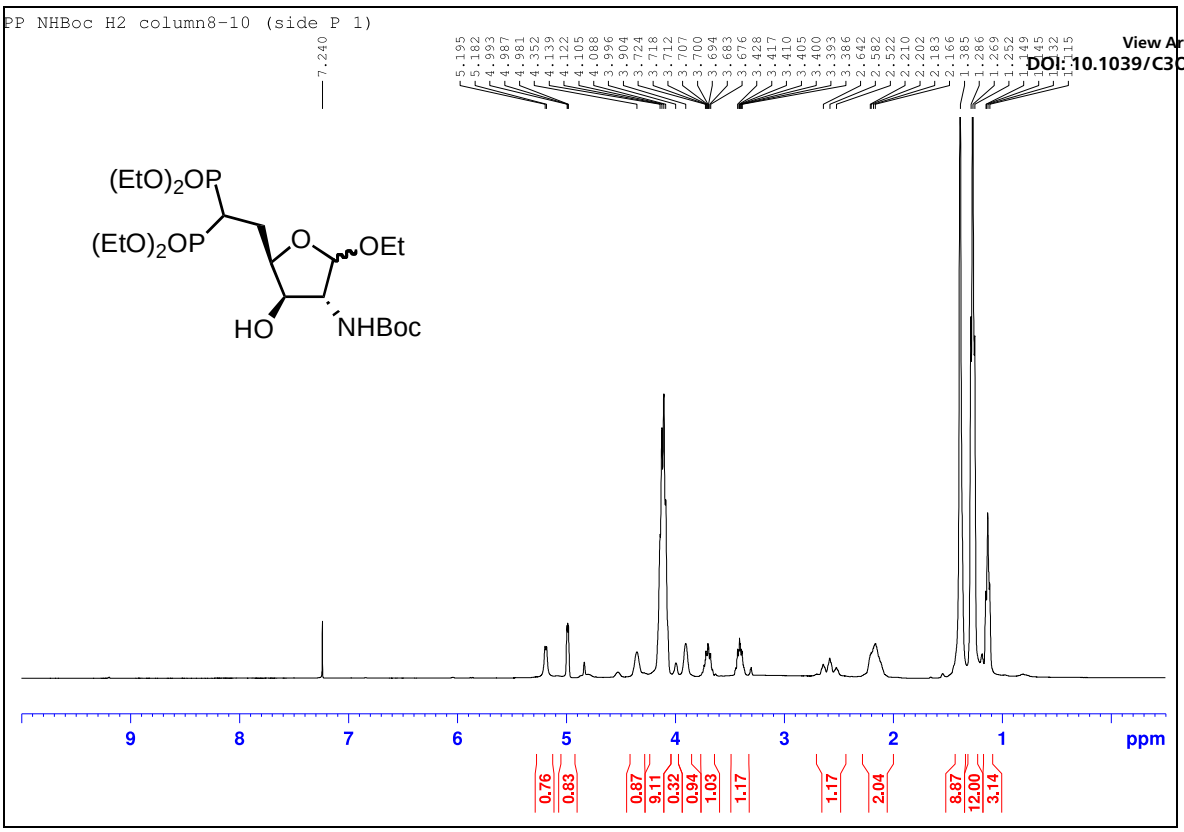
^{31}P NMR spectrum of compound **34** ($CDCl_3$, 162 MHz)



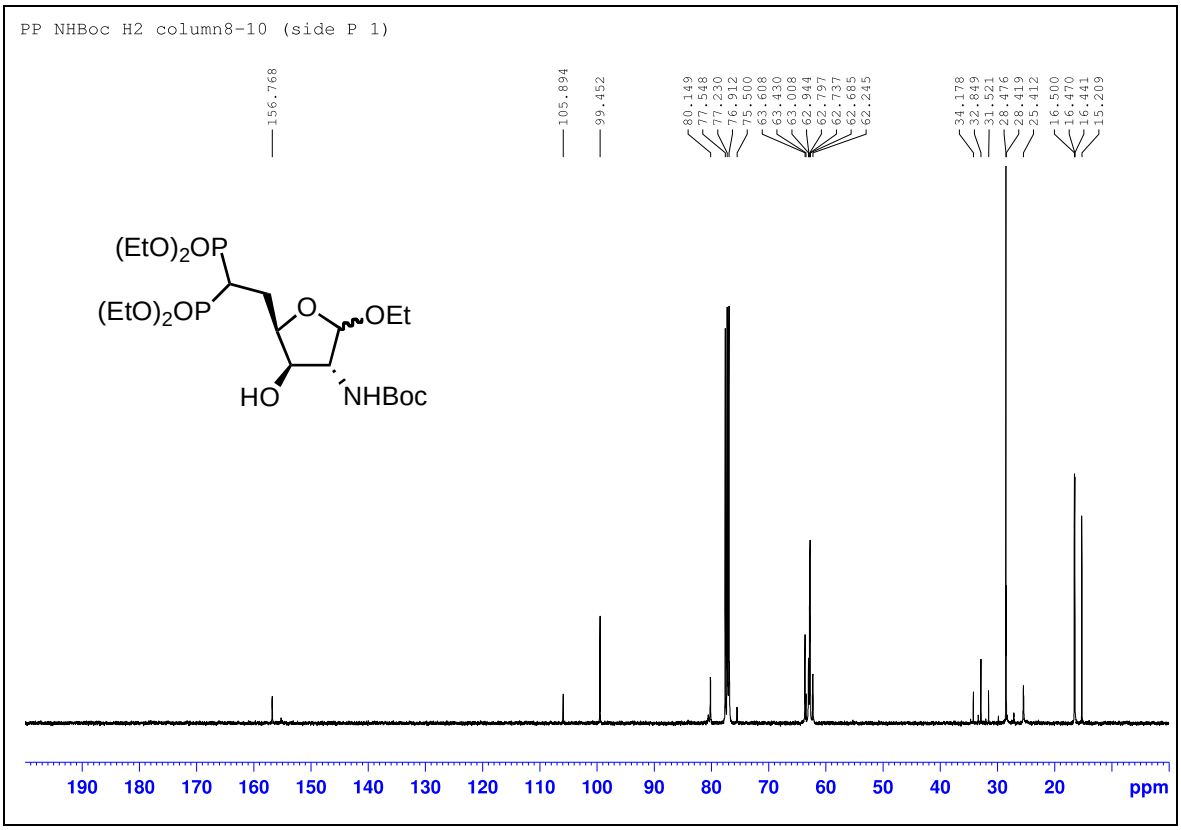
$^{1}H–^{1}H$ COSY NMR spectrum of compound **34** ($CDCl_3$, 400 MHz)



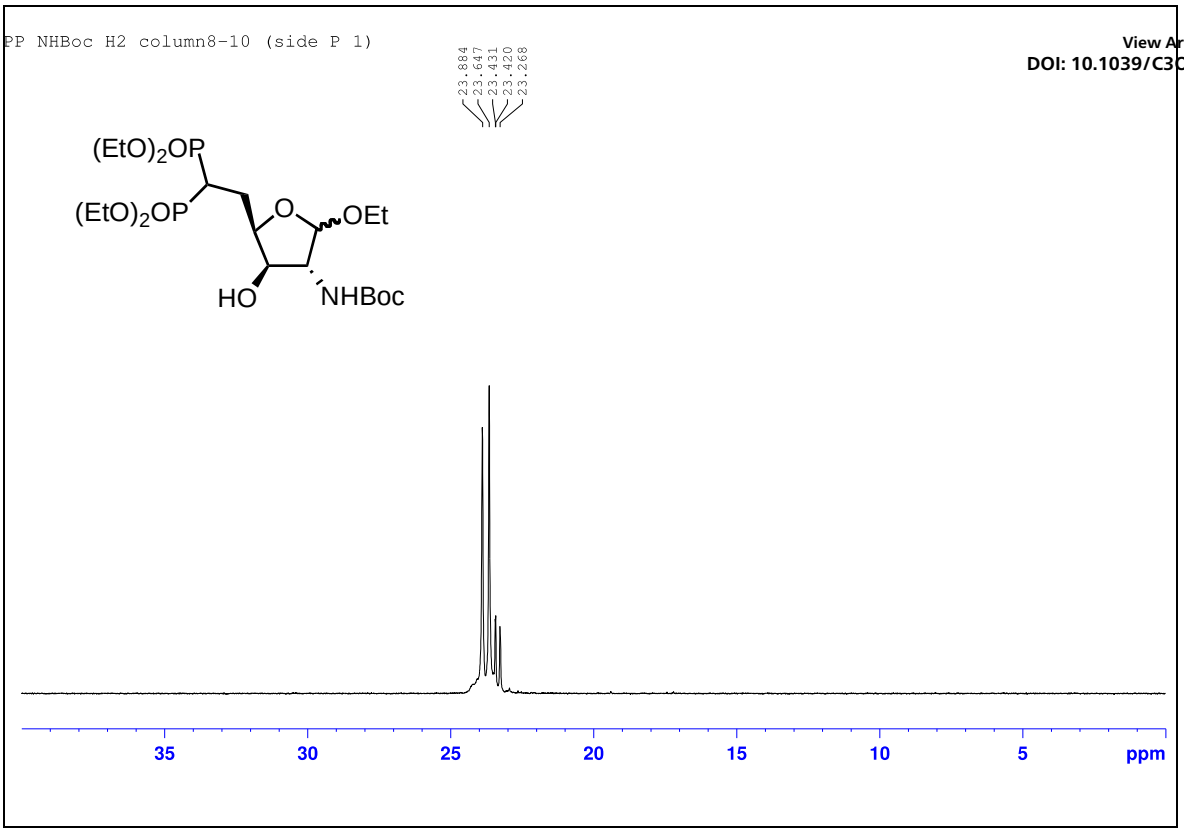
$^{1}H–^{13}C$ HSQC NMR spectrum of compound **34** ($CDCl_3$, 400 MHz)



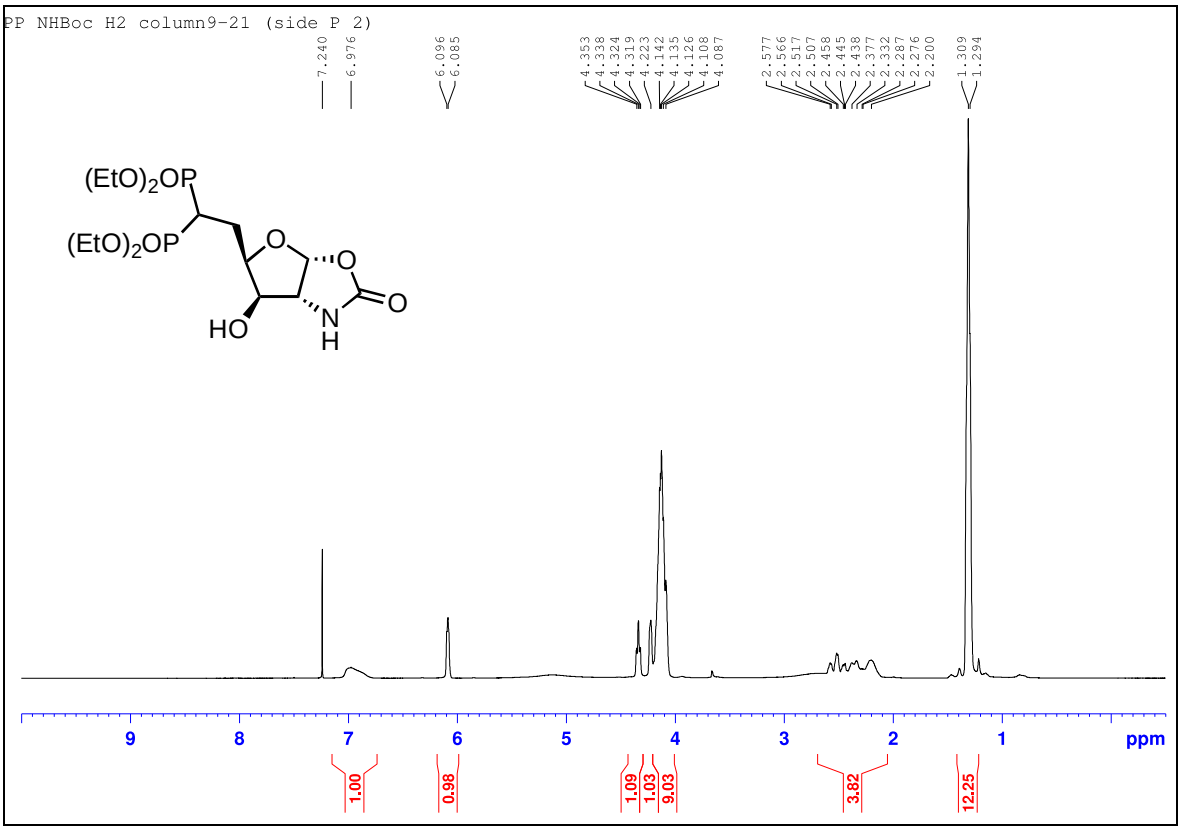
^{1}H NMR spectrum of compound **35** ($CDCl_3$, 400 MHz)



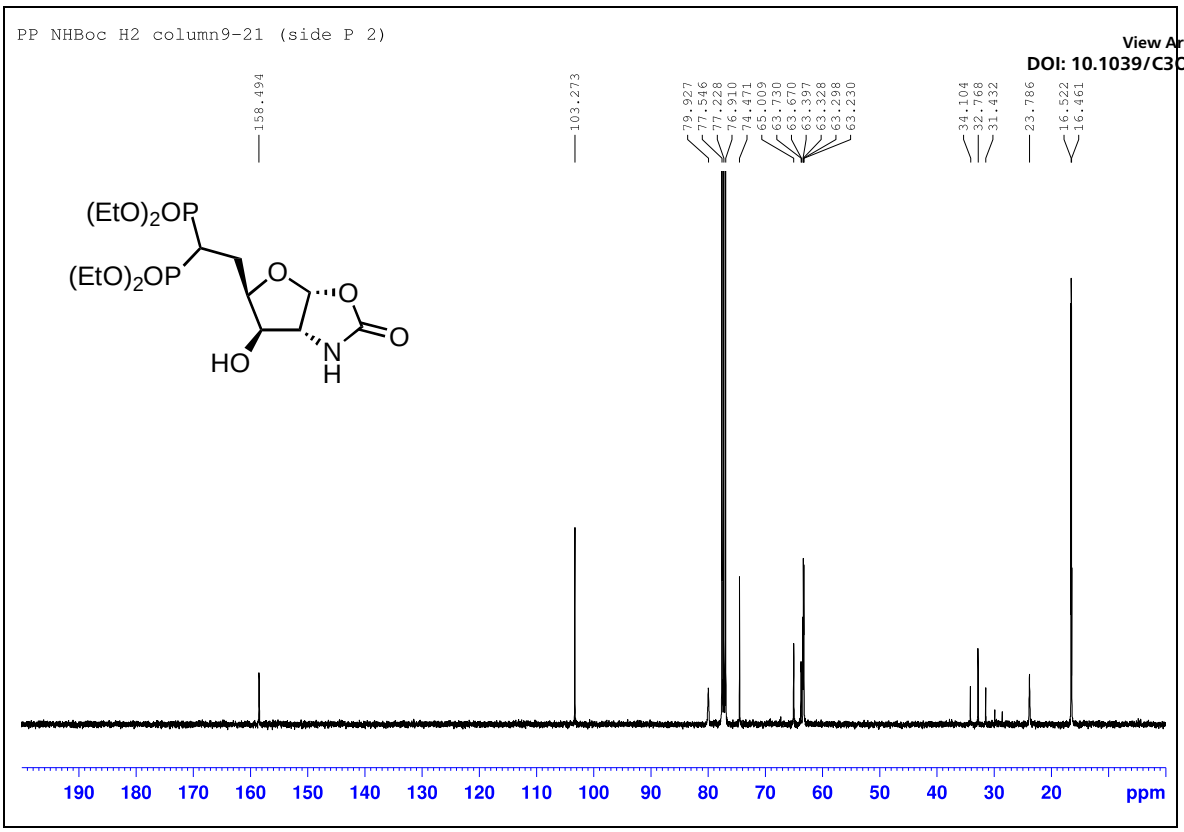
^{13}C NMR spectrum of compound **35** ($CDCl_3$, 100 MHz)



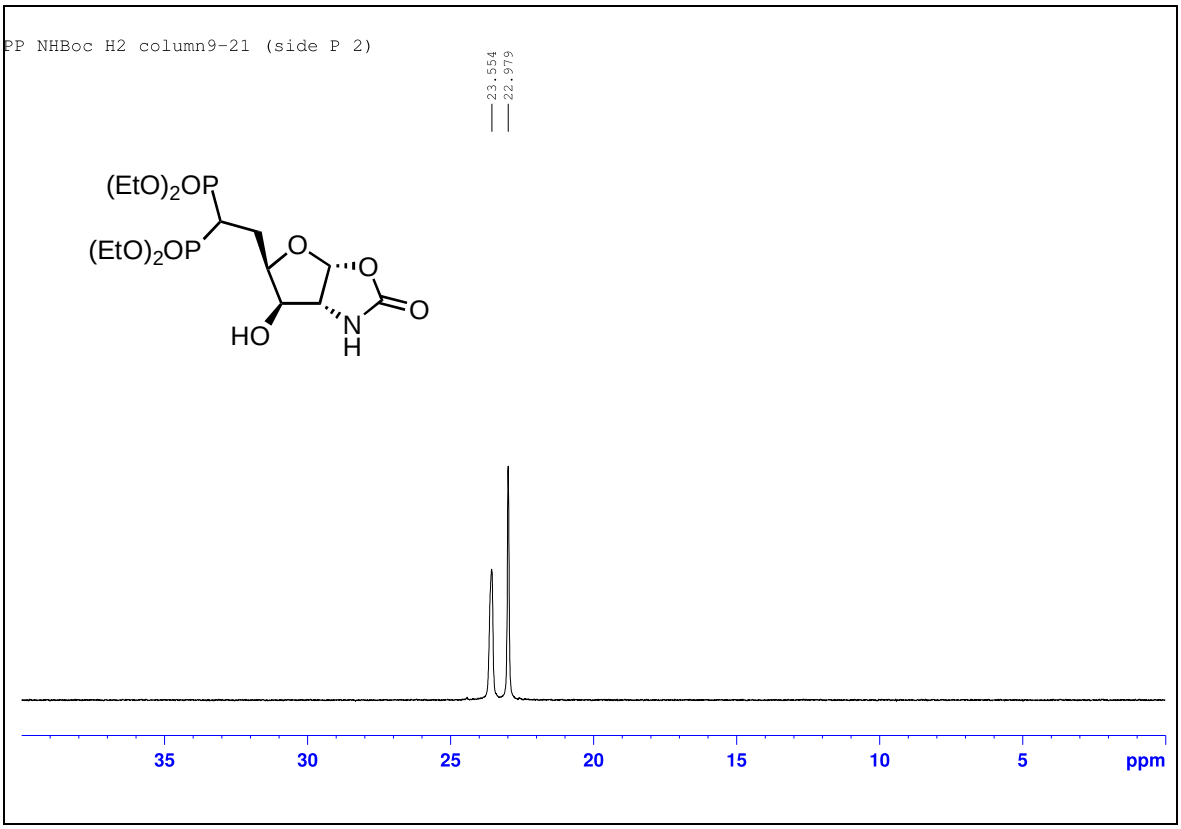
^{31}P NMR spectrum of compound **35** ($CDCl_3$, 162 MHz)



^{1}H NMR spectrum of compound **36** ($CDCl_3$, 400 MHz)



^{13}C NMR spectrum of compound **36** ($CDCl_3$, 100 MHz)

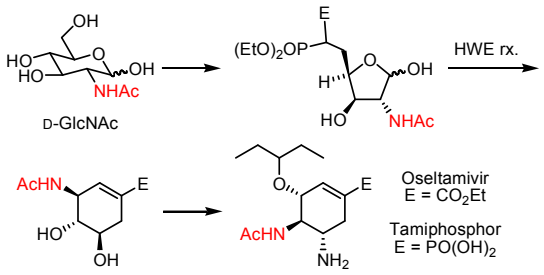


^{31}P NMR spectrum of compound **36** ($CDCl_3$, 162 MHz)

View Article Online
DOI: 10.1039/C3OB41622D

Synthesis of Oseltamivir and Tamiphosphor from *N*-Acetyl-D-glucosamine

Graphical Contents



Anti-influenza drugs oseltamivir and tamiphosphor were synthesized from *N*-acetyl-D-glucosamine via intramolecular Horner–Wadsworth–Emmons reaction to construct the highly functionalized cyclohexene ring.