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Supporting Information

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Highly Enantioselective Approach to Geminal Bisphosphonates by Organocatalyzed Michael-type Addition of ß-Ketoesters

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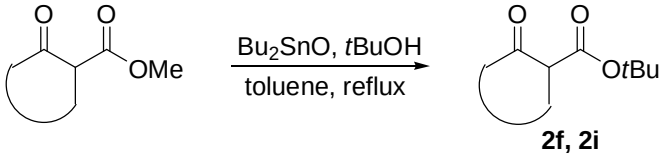
Contents

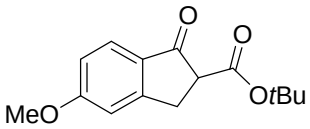
General procedure for the preparation of *tert*-butyl ß-ketoesters 2f and 2i by transesterification from the corresponding methyl esters.



2f, 2i

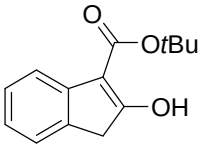
To a stirred solution of ß-keto methyl ester (5 mmol) in 60 mL of toluene, *t*BuOH (24 mL, 250 mmol) and Bu_2SnO (124 mg, 0.5 mmol) were added and the mixture was heated to reflux for 6 h employing a Dean Stark apparatus to remove MeOH formed. When the reaction was complete, the solvents were removed under reduced pressure and the residue was purified by FC (pentane/EtOAc 9:1) affording the desired ß-keto *tert*-butyl esters.

***tert*-Butyl 5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2f).**



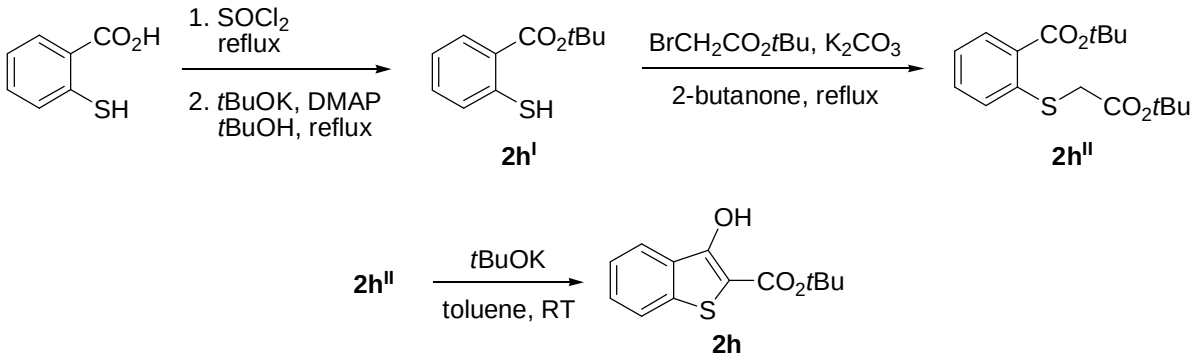
The title compound was obtained according to the general procedure, starting from methyl 5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate.[1] The product was isolated in 84% yield as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, *J* = 9.1 Hz, 1H), 6.89-6.87 (m, 2H), 3.87 (s, 3H), 3.56 (dd, *J* = 3.9 Hz, *J* = 8.1 Hz, 1H), 3.40 (A of AB system, *J* = 17.1 Hz, 1H), 3.22 (B of AB system, *J* = 8.1 Hz, *J* = 17.1 Hz, 1H), 1.47 (s, 9H) . ^{13}C NMR ($CDCl_3$) δ 197.3, 168.04, 165.1, 156.2, 127.8, 125.3, 115.2, 108.9, 80.9, 55.1, 53.9, 29.7, 27.3. HRMS: $C_{15}H_{18}NaO_4$ $[M+Na]^+$ calcd.: 285.1103, found: 285.1107.

***tert*-Butyl 2-hydroxy-1*H*-indene-3-carboxylate (2i).**



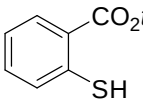
The title compound was obtained according to the general procedure, starting from the commercial available 2-oxo-1-indanecarboxylate. The product was isolated in 60% yield as a white solid. ^{1}H NMR ($CDCl_3$) (enolic form) δ 11.29 (bs, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.30-7.24 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 3.55 (s, 2H), 1.65 (s, 9H). ^{13}C NMR ($CDCl_3$) (enolic form) δ 180.3, 168.6, 139.8, 133.0, 126.8, 123.3, 119.9, 105.9, 81.8, 37.2, 28.2. $C_{14}H_{16}NaO_3$ $[M+Na]^+$ calcd.: 255.0997, found: 255.0997.

Procedure for the preparation of *tert*-butyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate (2h).



Thionyl chloride (6.0 mL, 81.7 mmol) was added to thiosalicylic acid (5.050 g, 32.7 mmol) and the mixture was heated to reflux for 1 h, then concentrated at atmospheric pressure. To the residue dissolved in *t*BuOH (20 mL), *t*-BuOK (11 g, 98.1 mmol) and *N*,*N*-dimethylaminopyridine (0.409 g, 3.35 mmol) were added at 0 °C, then the mixture was allowed to reflux for 24 h. The solvent was removed under reduced pressure and the resulting residue diluted with CH_2Cl_2 (10 mL), washed with a saturated aqueous solution of NH_4Cl (40 mL) and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude mixture by FC (pentane) afforded the *tert*-butyl thiosalicylate **2h^{I}** in 65% yield as a yellow oil.

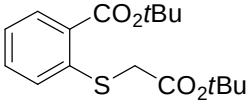
***tert*-Butyl 2-mercaptobenzoate (2h^{I}).**



^{1}H NMR ($CDCl_3$) δ 7.95-7.87 (m, 1H), 7.31-7.24 (m, 2H), 7.16-7.10 (m, 1H), 4.51 (s, 1H), 1.60 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 165.5, 137.2, 131.7, 131.3, 130.5, 124.2, 81.5, 27.9. HRMS: $C_{11}H_{44}NaO_2S$ $[M+Na]^+$ calcd.: 233.0612, found: 233.0617.

To a solution of *tert*-butyl thiosalicylate **2h^{I}** (1.102 g, 5.2 mmol) and K_2CO_3 (1.663 g, 12.0 mmol) in 2-butanone (2 mL) *tert*-butyl bromoacetate (1.7 mL, 11.5 mmol) was added and the mixture was refluxed for 4 h. The reaction was quenched with water and the mixture extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude mixture by FC (pentane/Et_2O 9:1) afforded the diester **2h^{II}** in 68% yield as colorless oil.

***tert*-Butyl 2-(2-*tert*-butoxy-2-oxoethylthio)benzoate (2h^{II}).**

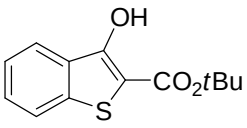


^{1}H NMR ($CDCl_3$) δ 7.89 (d, *J* = 7.7 Hz, 1H), 7.43-7.36 (m, 2H), 7.16 (t, *J* = 7.7 Hz, 1H), 3.61 (s, 2H), 1.60 (s, 9H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 168.0, 165.1, 139.2, 131.4, 130.5, 129.4, 125.6, 123.9, 81.2, 35.8, 27.7, 27.3. HRMS: $C_{17}H_{24}NaO_4S$ $[M+Na]^+$ calcd.: 347.1293, found: 347.1290.

To a suspension of *t*-BuOK (0.651 mg, 5.8 mmol) in toluene (6 mL) **2h^{II}** (0.878 g, 2.7 mmol) was added and the mixture was stirred for 1 h at rt. The reaction was quenched with a saturated aqueous solution of NH_4Cl (40 mL) and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over

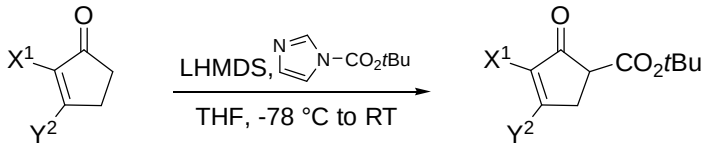
anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude mixture by FC (pentane/Et_2O 95:5) afforded the *tert*-butyloxycarbonyl benzothiophenone **2h** (enolic form) in 89% yield as a white solid.

***tert*-Butyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate (2h).**



^{1}H NMR ($CDCl_3$) (enolic form) δ 10.3 (bs, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 1.62 (s, 9H). ^{13}C NMR ($CDCl_3$) (enolic form) δ 166.7, 158.7, 138.2, 130.3, 128.2, 123.9, 122.7, 122.5, 103.0, 82.6, 28.0. HRMS: $C_{13}H_{14}NaO_3S$ $[M+Na]^+$ calcd.: 273.0561, found: 273.0569.

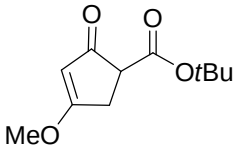
General procedure for the preparation of ß-keto *tert*-butyl esters 2j-l by acylation with 1-(*tert*-butoxycarbonyl)-imidazole .



2j-k

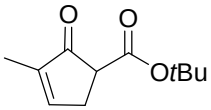
To a stirred cooled (-78 °C) solution of LHMDS in THF (12.5 mmol, 1.06 M) ketone (5 mmol) was slowly added under an argon atmosphere. The mixture was stirred at -78 °C for 10 min, then at rt for 15 min. After this period of time, to the re-cooled (-78 °C) enolate solution, 1-(*tert*-butoxycarbonyl)-imidazole (1.271 g, 7.5 mmol) was added and the resulting mixture was allowed to gradually reach to rt. After stirring for 30 min, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (40 mL) and the mixture extracted with CH_2Cl_2 (4 x 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. Purification of the crude mixture by FC afforded the desired ß-keto *tert*-butyl esters.

***tert*-Butyl 4-methoxy-2-oxocyclopent-3-enecarboxylate (2j).**



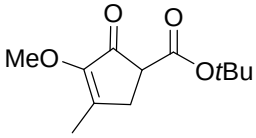
The title compound was obtained according to the general procedure of acylation, starting from the commercial available 3-methoxycyclopent-2-enone. The crude product was purified by FC on silica eluting with pentane/EtOAc 7:3 to give **2j** in 76% yield as a white solid. ^{1}H NMR ($CDCl_3$) δ 5.23 (s, 1H), 3.83 (s, 3H), 3.37 (dd, *J* = 7.6 Hz, J = 3.0 Hz), 2.92 (A of AB system, dd, *J* = 17.6 Hz, J = 3.0 Hz, 1H), 2.70 (B of AB system, dd, *J* = 17.6 Hz, *J* = 7.6 Hz), 1.43 (s, 9H).^{13}C NMR ($CDCl_3$) δ 198.5, 190.6, 168.3, 102.7, 81.9, 59.0, 52.5, 32.1, 27.9. HRMS: $C_{11}H_{16}NaO_4$ $[M+Na]^+$ calcd.: 235.0946, found: 235.0948.

***tert*-Butyl 3-methyl-2-oxocyclopent-3-enecarboxylate (2k).**



The title compound was obtained according to the general procedure of acylation, starting from the commercial available 2-methylcyclopent-2-enone. The crude product was purified by FC on silica eluting with pentane/EtOAc 95:5 to give **2k** in 94% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.37-7.34 (bs, 1H), 3.30 (dd, *J* = 6.8 Hz, *J* = 2.5 Hz, 1H), 2.90-2.83 (m, 1H), 2.77-2.69 (m, 1H), 1.79-1.77 (m, 3H), 1.46 (9H). ^{13}C NMR ($CDCl_3$) δ 202.9, 168.1, 157.4, 139.9, 83.5, 51.8, 30.5, 27.6, 9.9. HRMS: $C_{11}H_{16}NaO_3$ $[M+Na]^+$ calcd.: 219.0997, found: 219.0998.

***tert*-Butyl 3-methoxy-4-methyl-2-oxocyclopent-3-enecarboxylate (2l).**



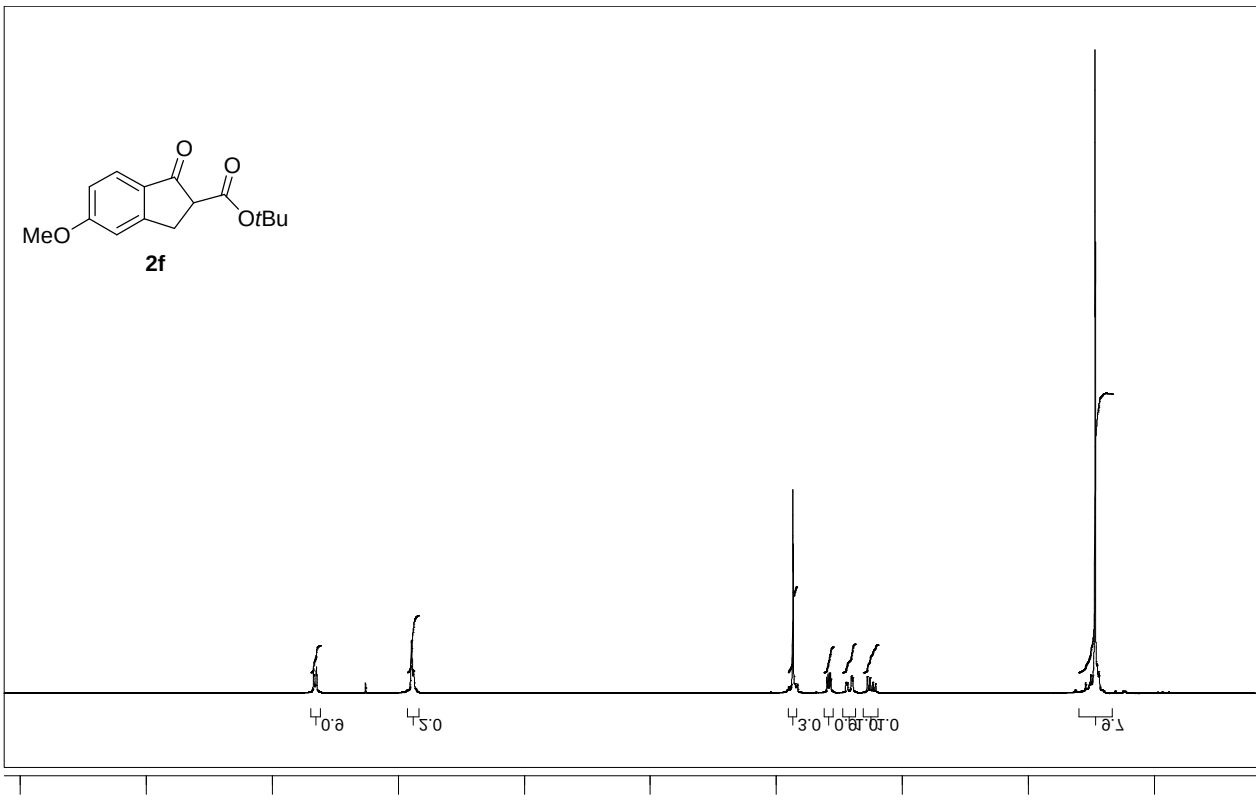
The title compound was obtained according to the general procedure of acylation, starting from 2-methoxy-3-methylcyclopent-2-enone.[2] The crude product was purified by FC on silica eluting with pentane/EtOAc 95:5 to give **2l** in 65% yield as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.85 (s, 3H), 3.26 (d, 6.8 Hz, 1H), 2.71 (d, *J* = 17.9 Hz, 1H), 2.57 (dd, *J* = 17.9 Hz, *J* = 6.8 Hz, 1H), 2.00 (s, 3H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 196.3, 168.0, 153.8, 150.7, 81.6, 58.1, 50.4, 31.0, 27.7, 14.6. HRMS: $C_{12}H_{12}NaO_4$ $[M+Na]^+$ calcd.: 249.1104, found: 299.1108.

.

References

1. S. Kobayashi, T. Gustafsson, Y. Shimizu, H. Kiyohara, R. Matsubara, *Org. Lett.* **2006**, *8*, 4923-4925.

2. B.-M. Kwon, C. S. Foote, *J. Org. Chem.* **1989**, *54*, 3878-3882.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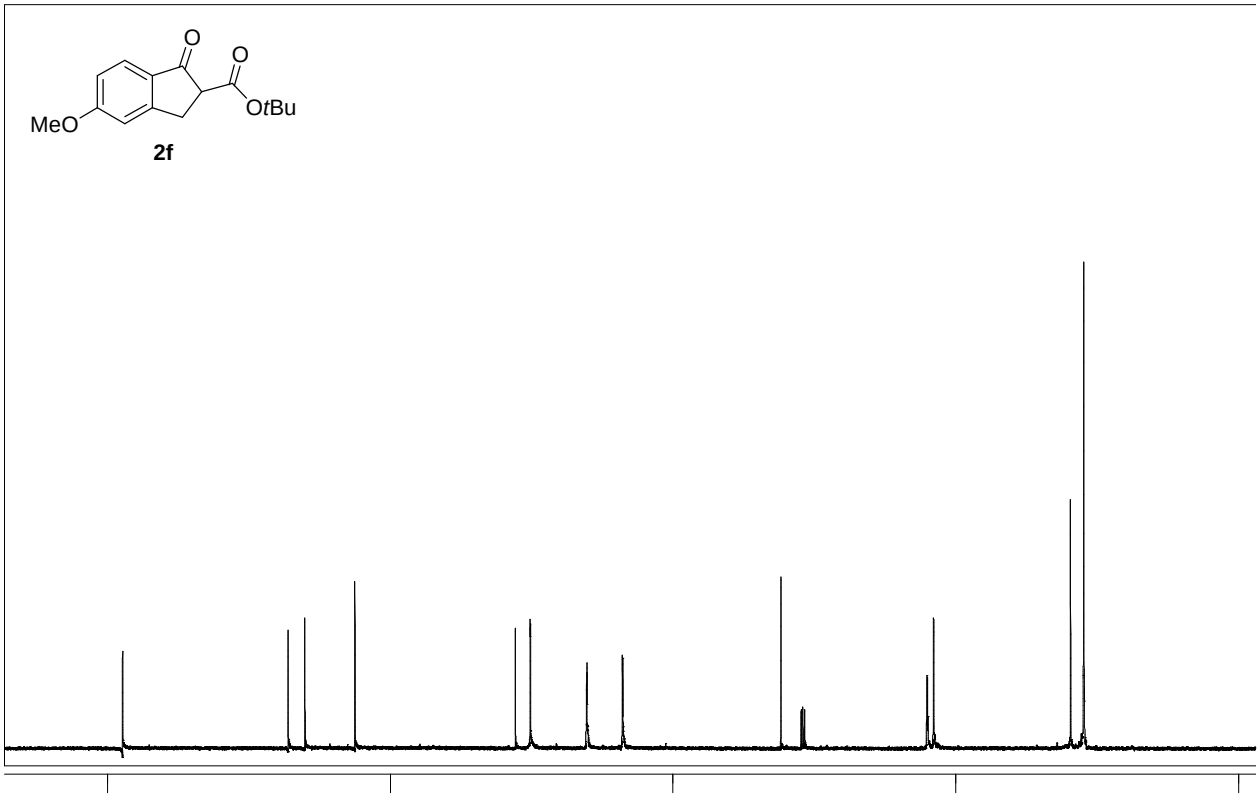
OtBu
2f

.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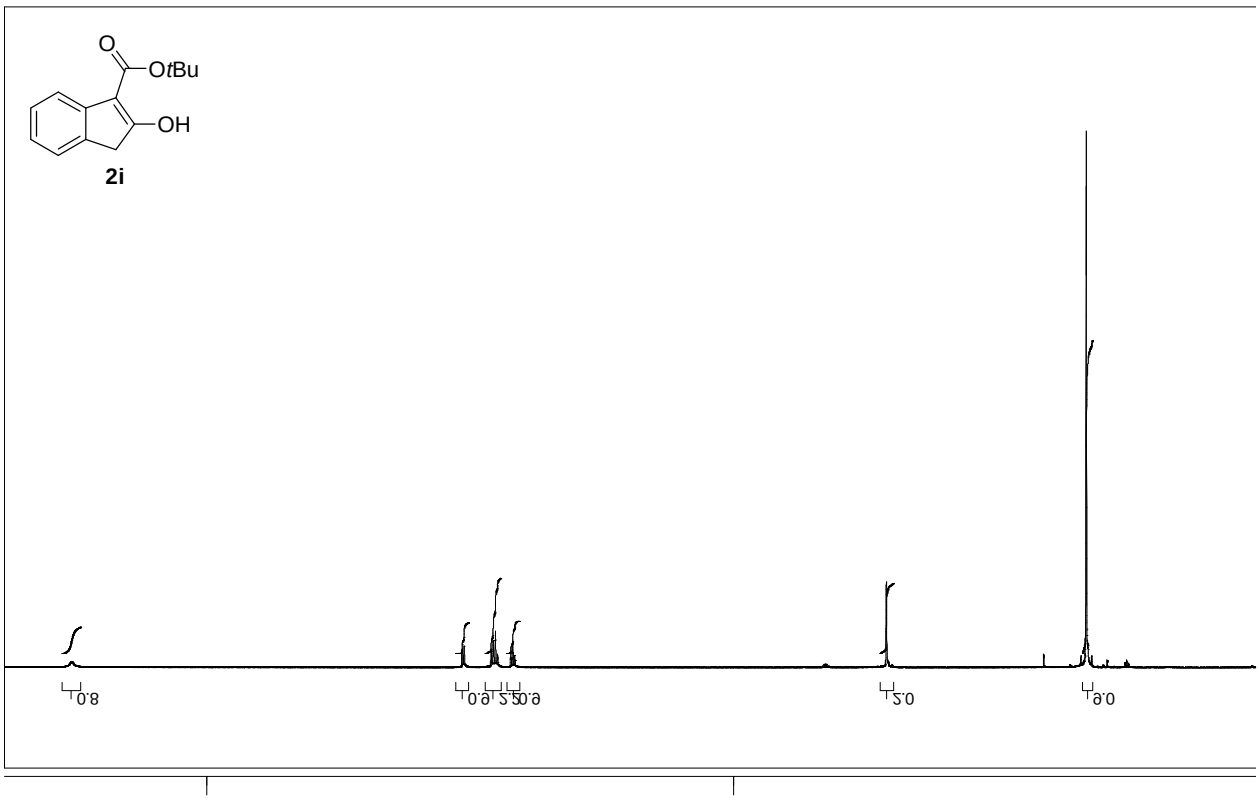
2f



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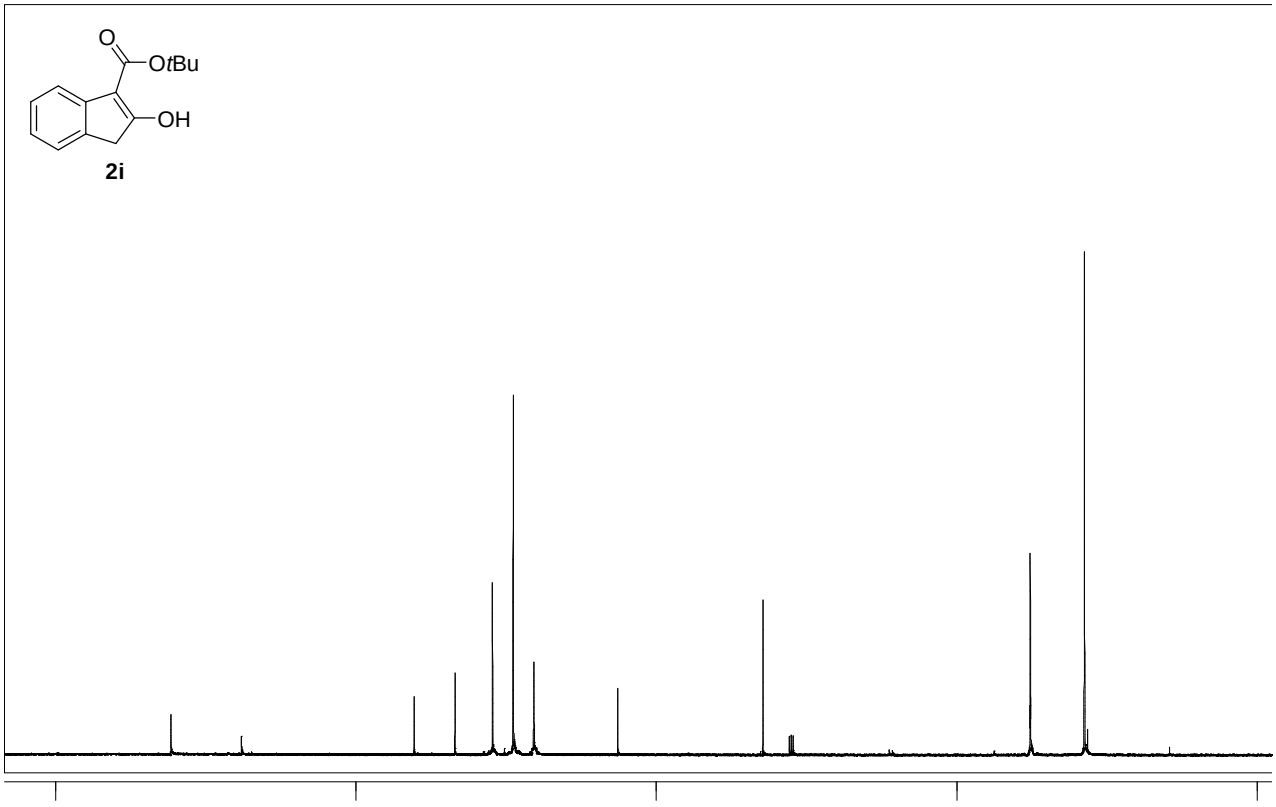

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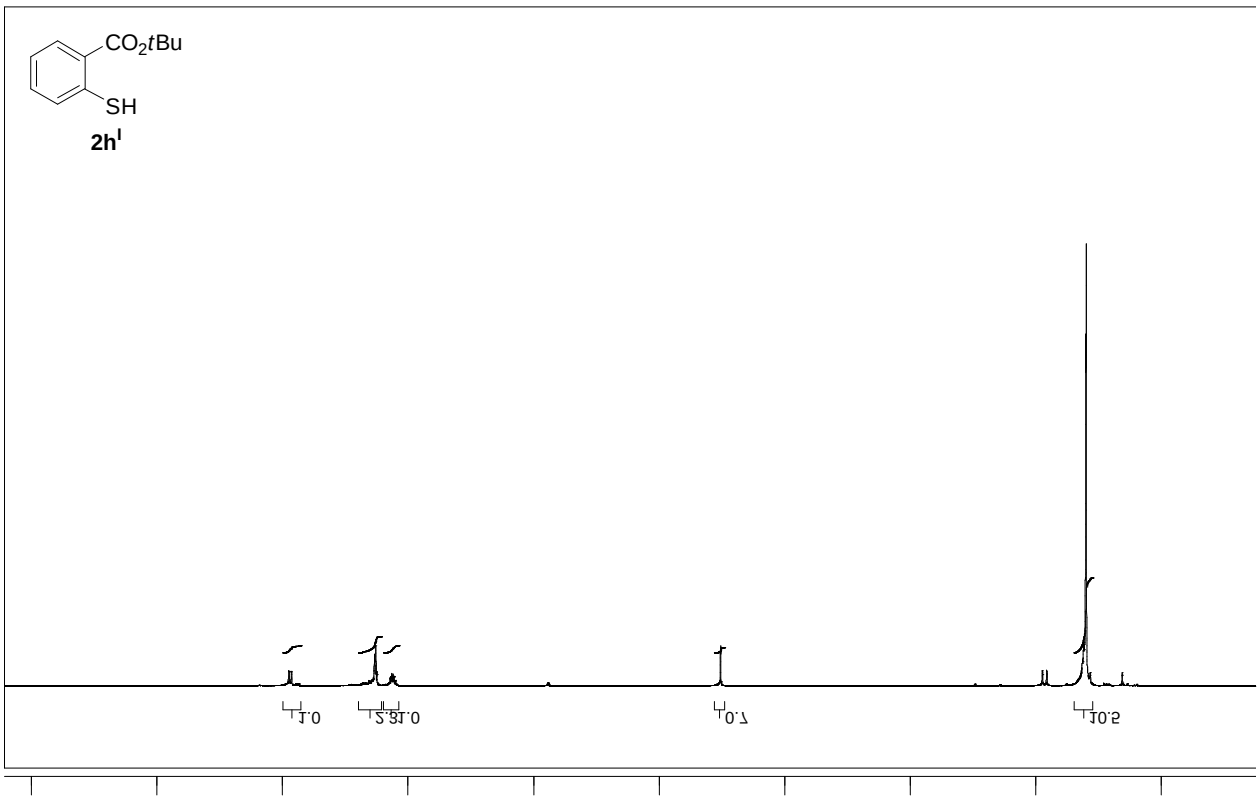
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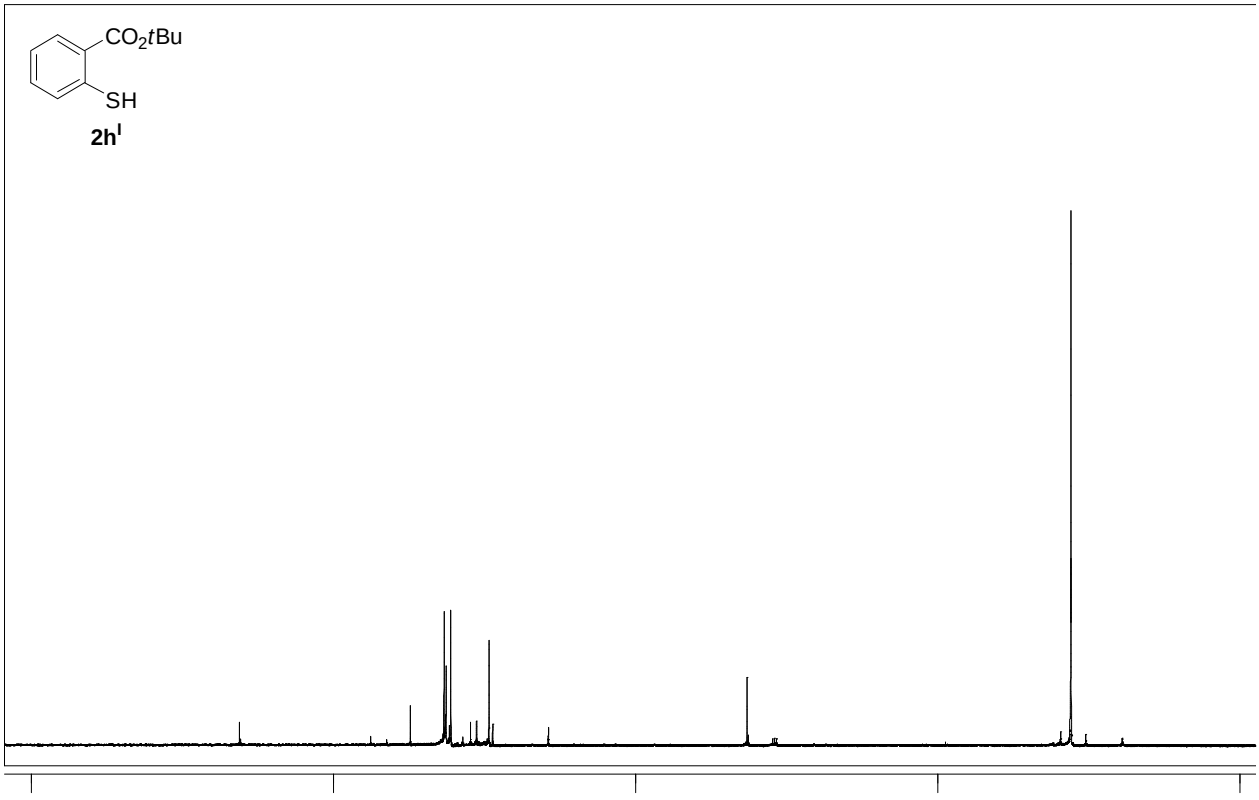
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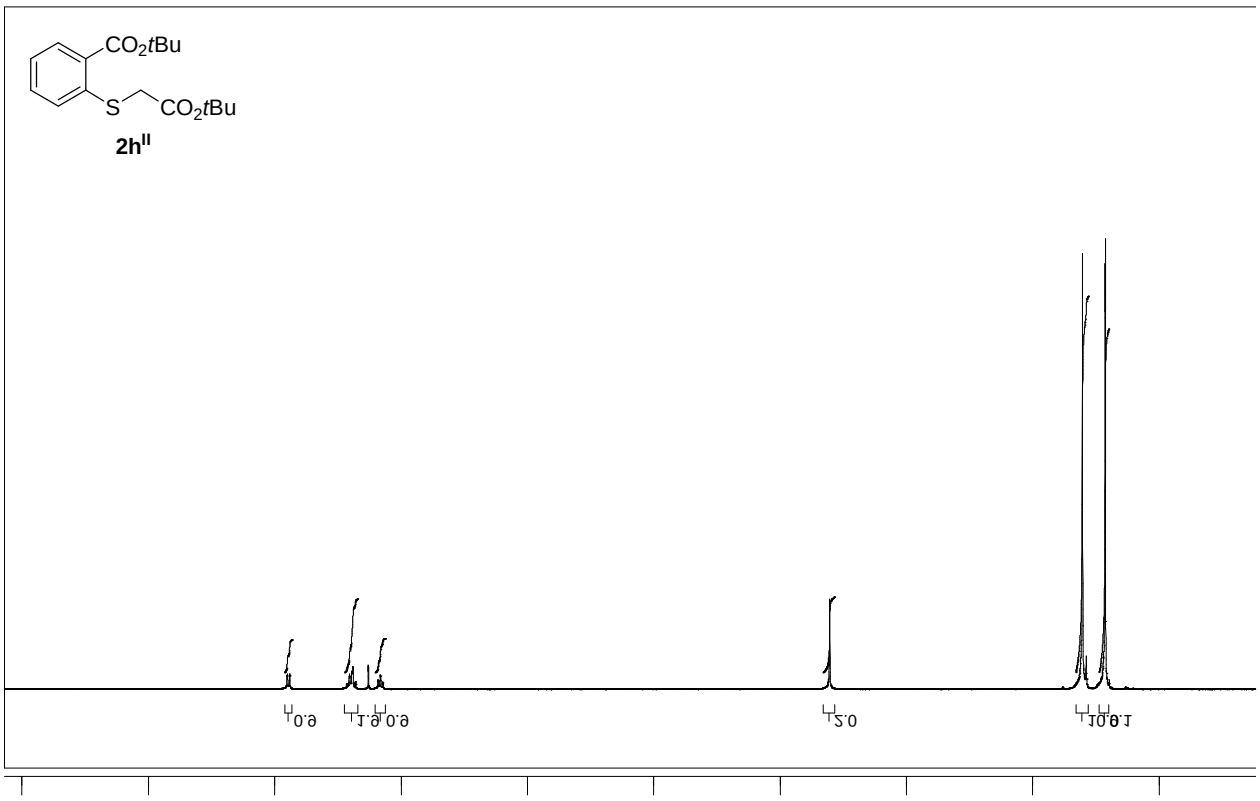
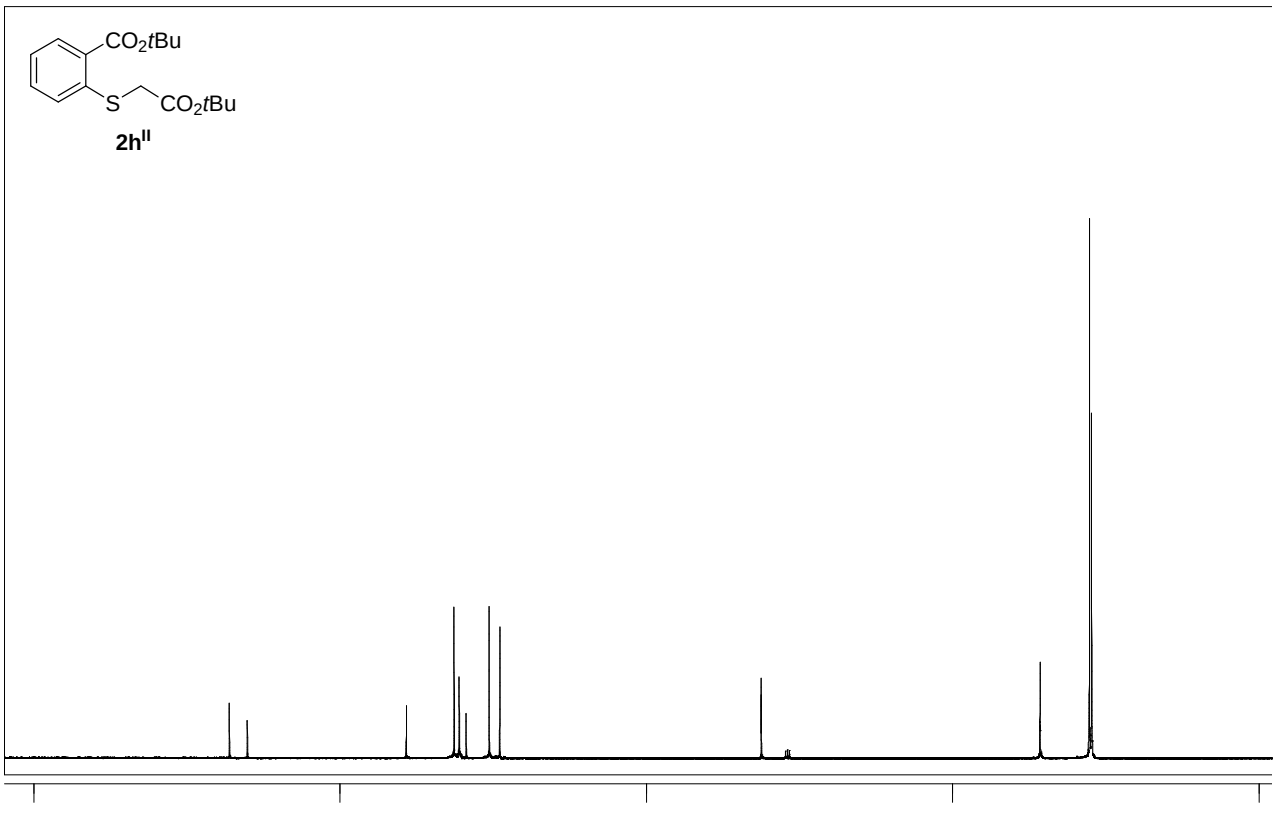


2h^{II}



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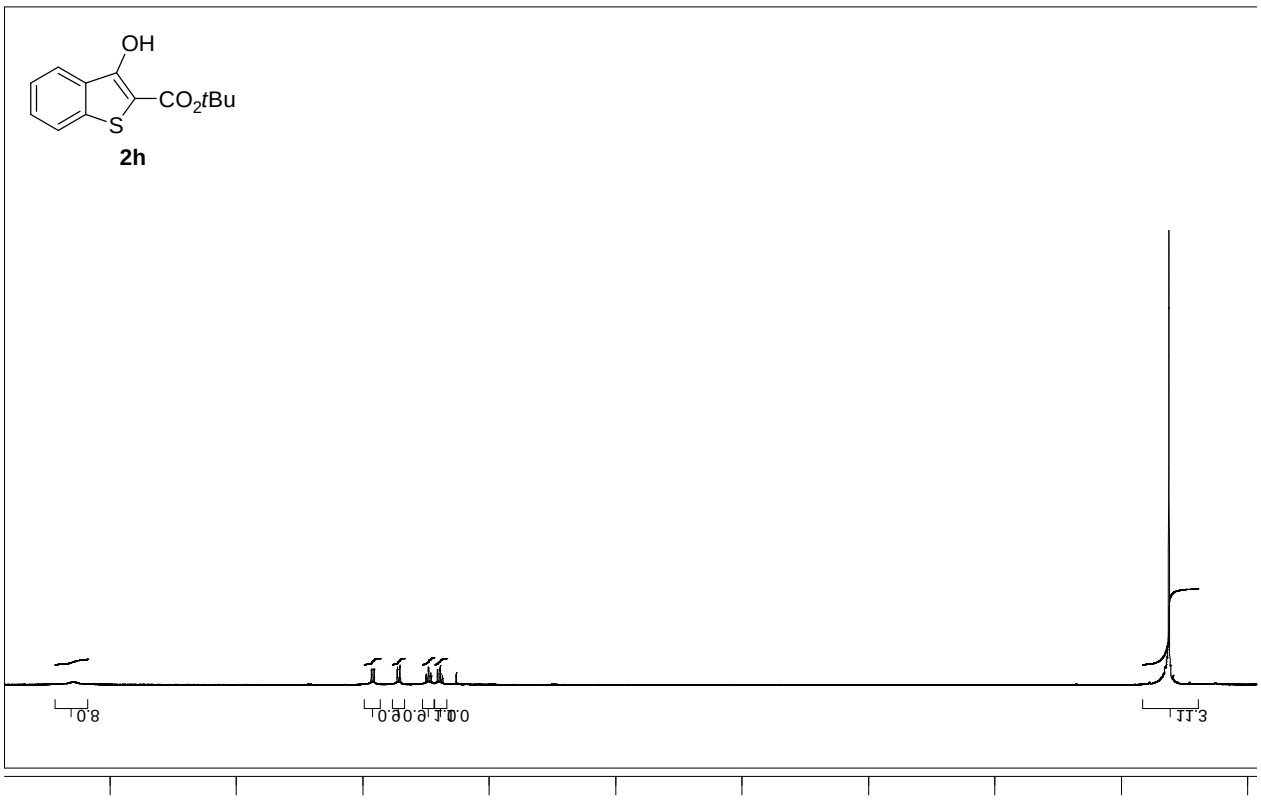
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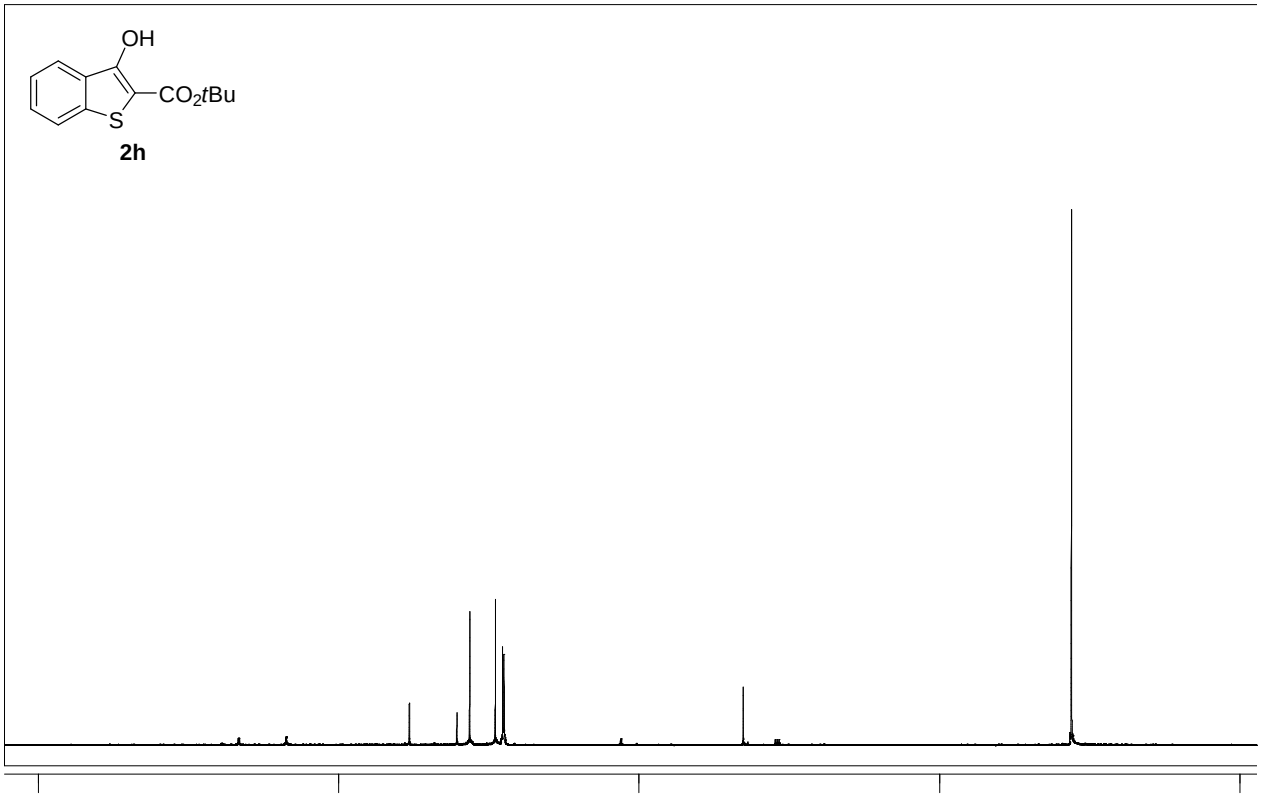
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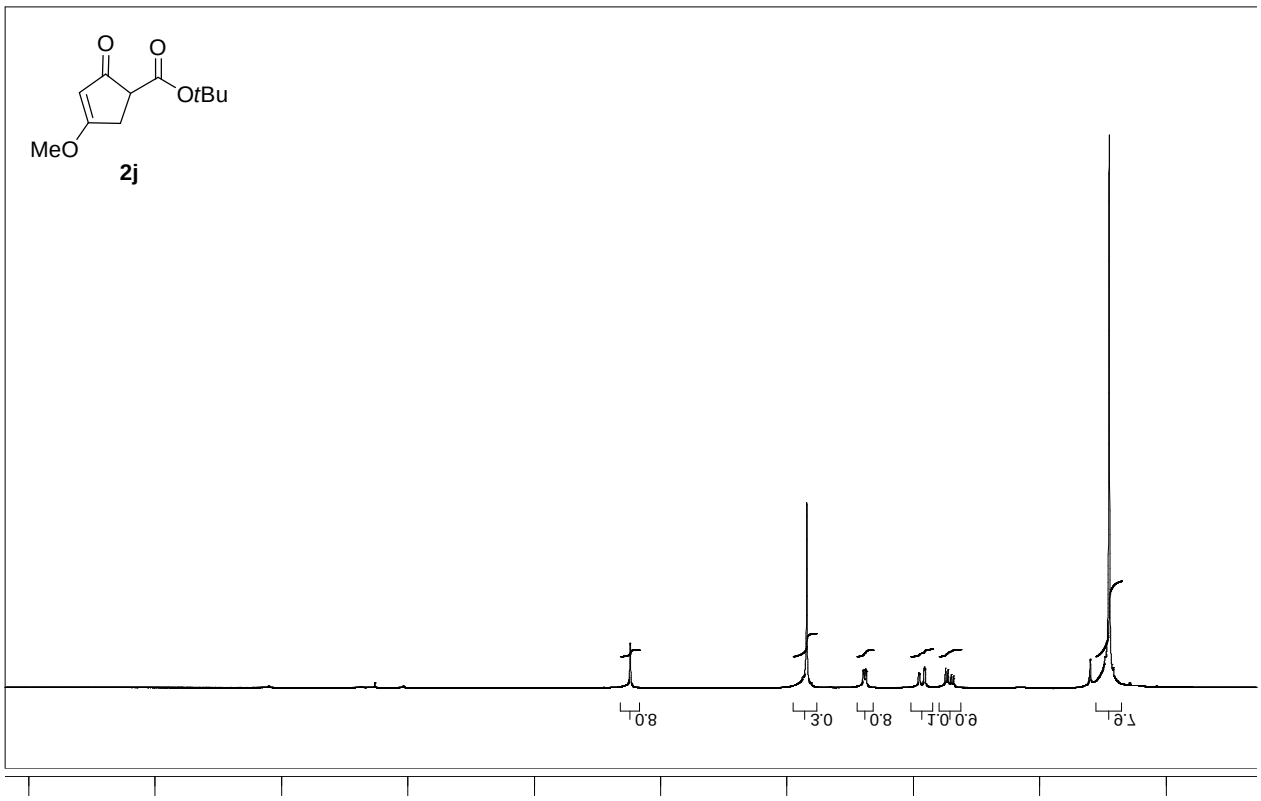
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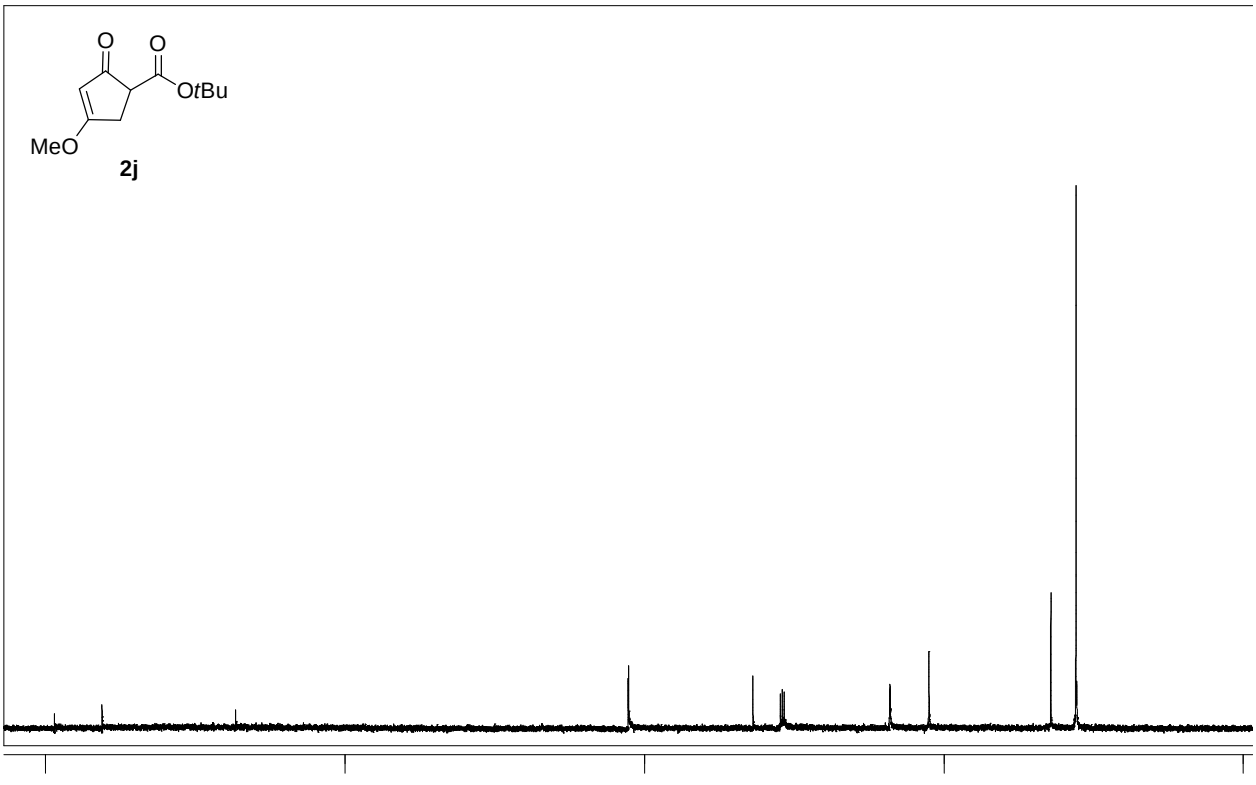
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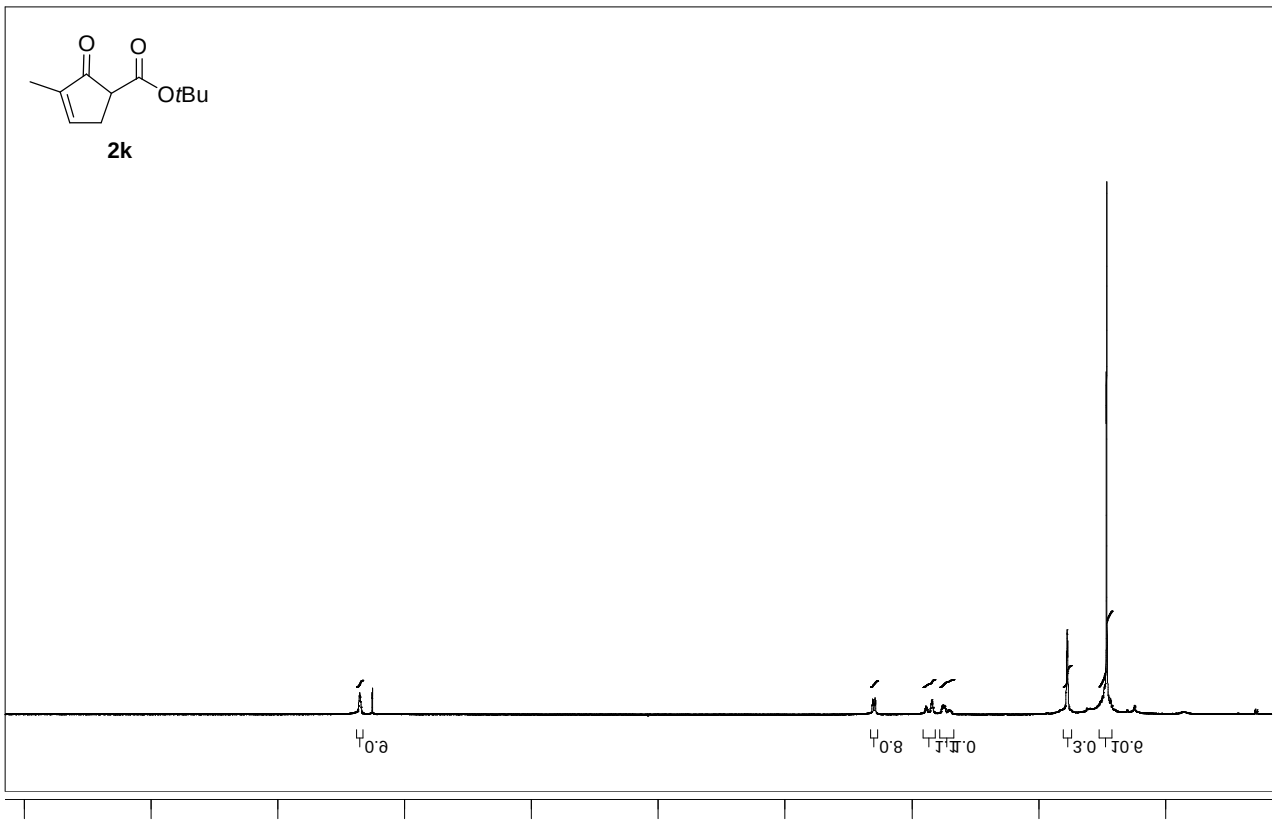

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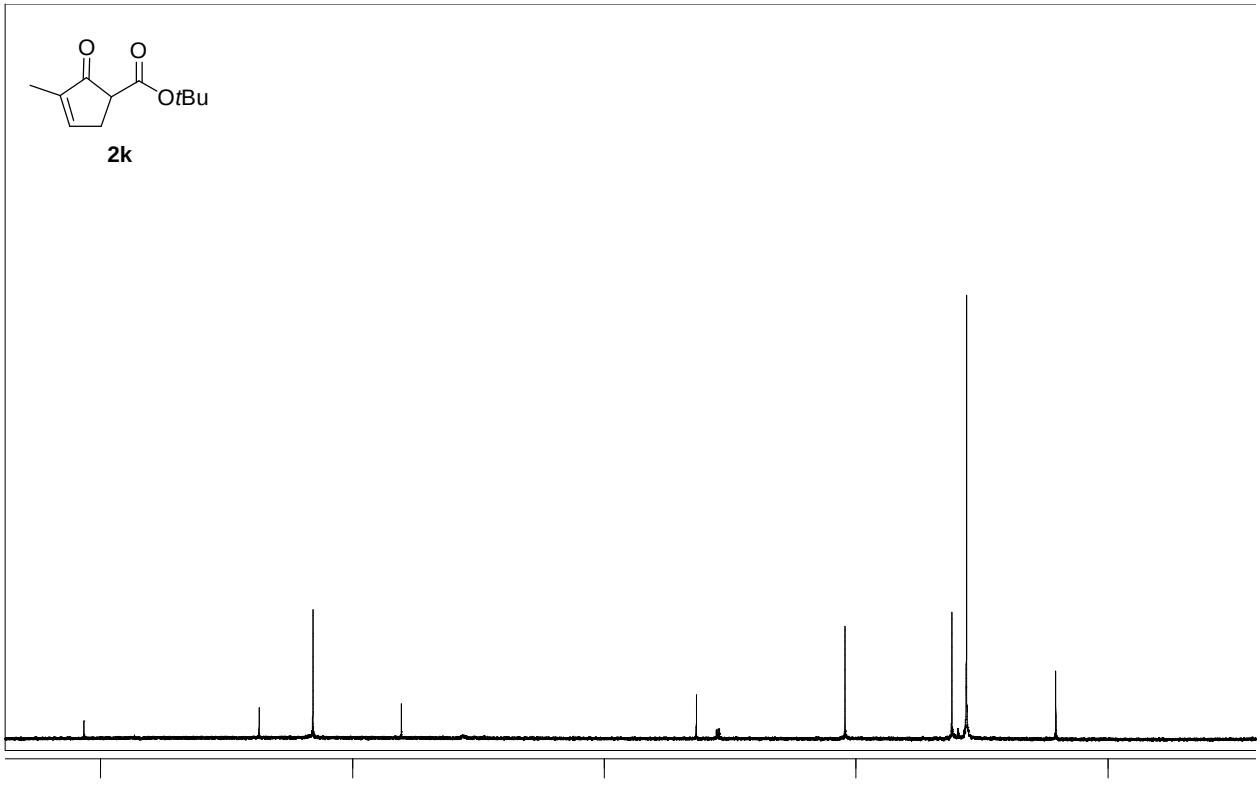

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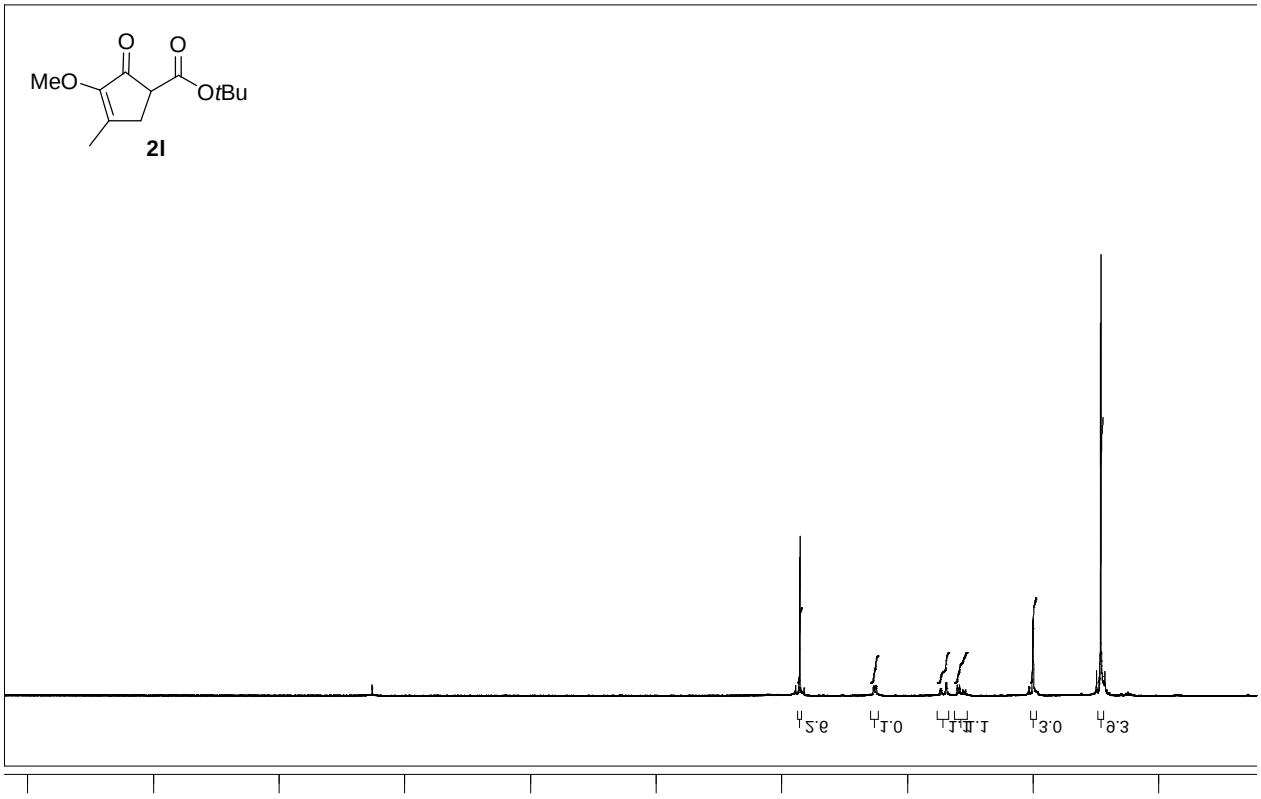

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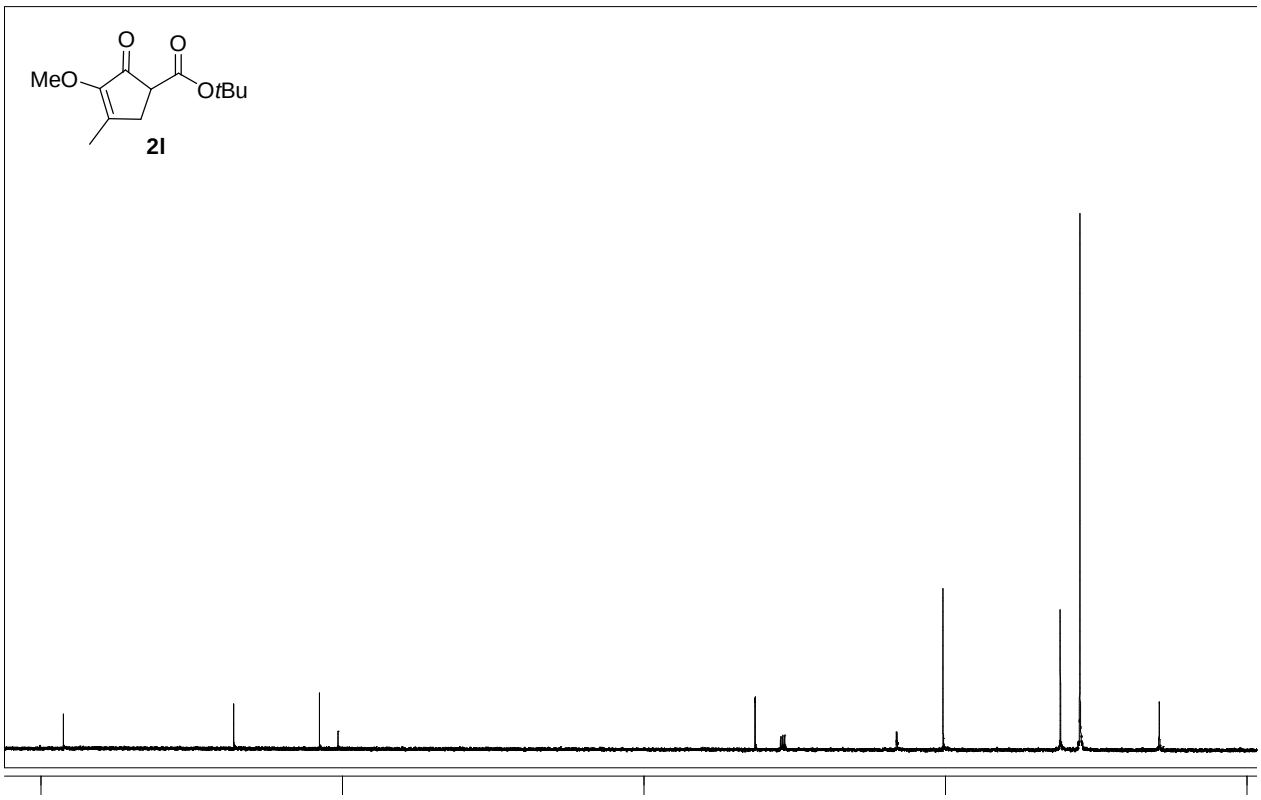

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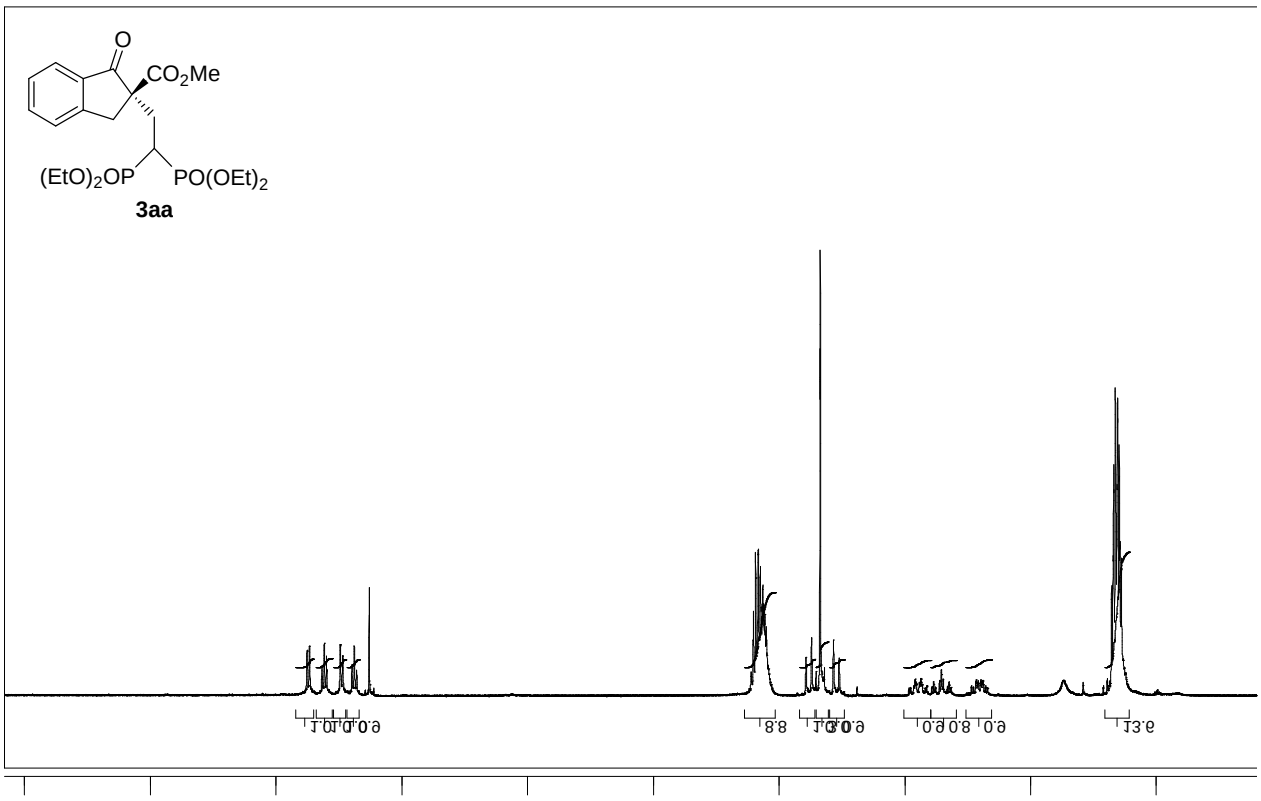

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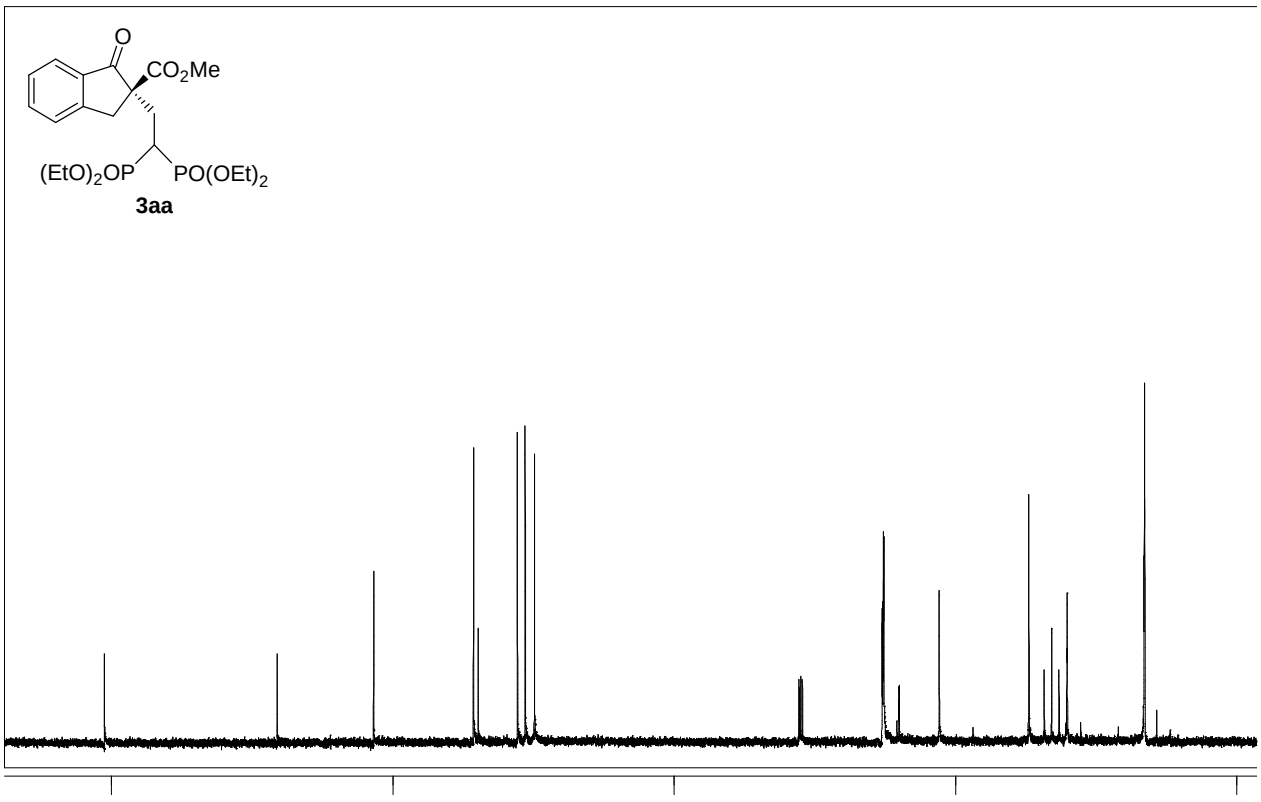

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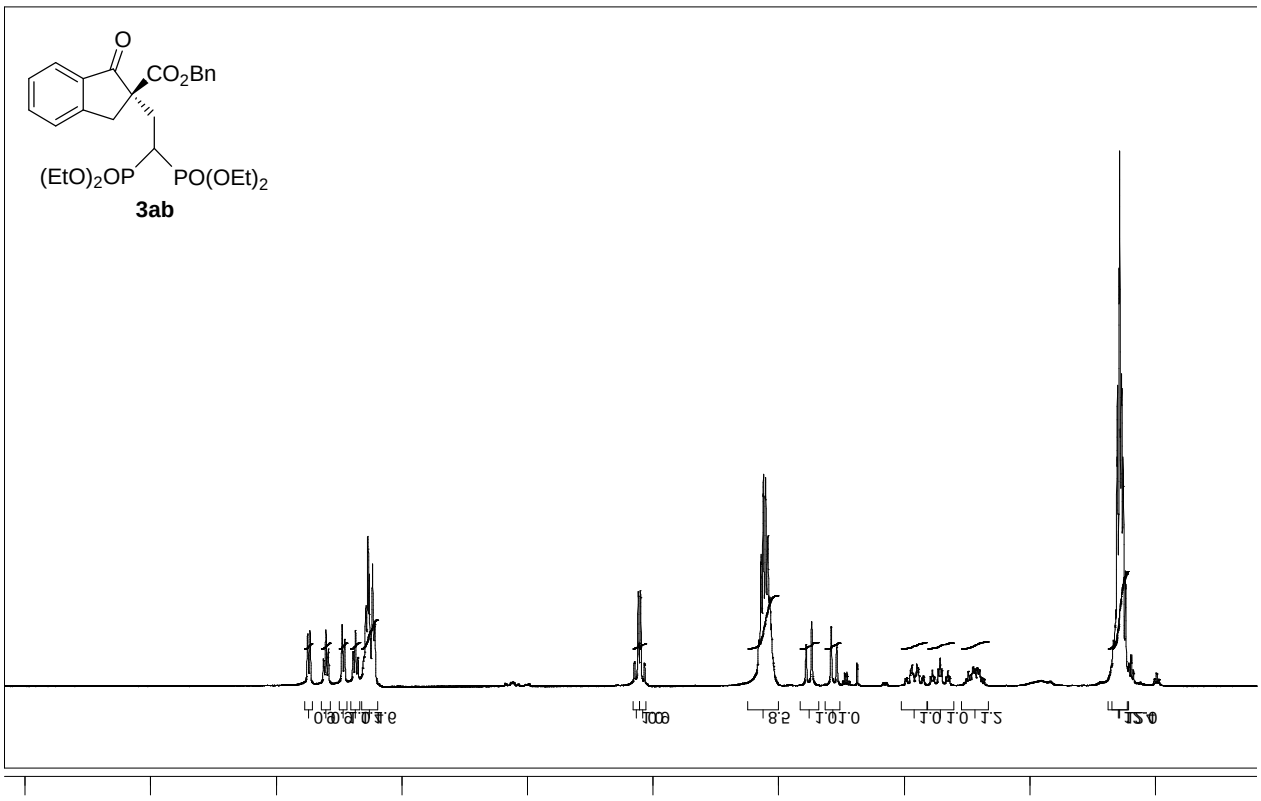
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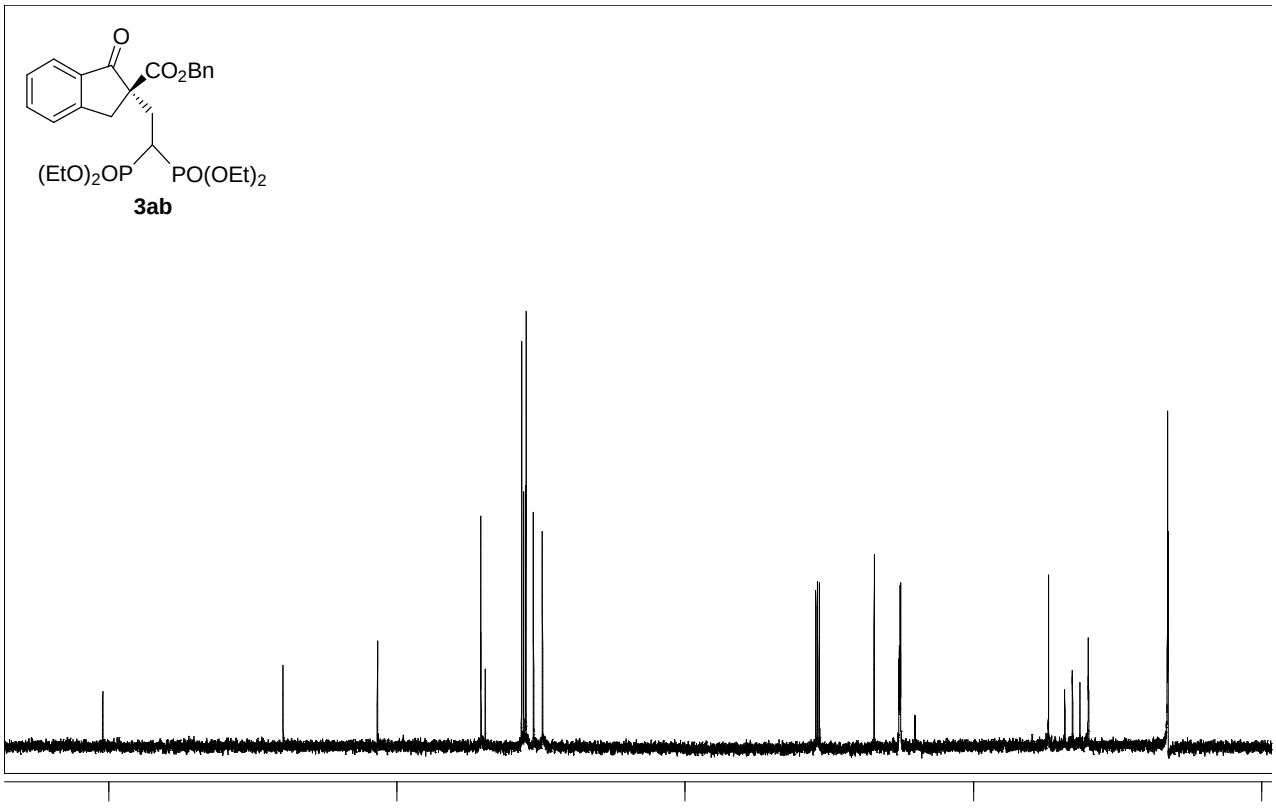
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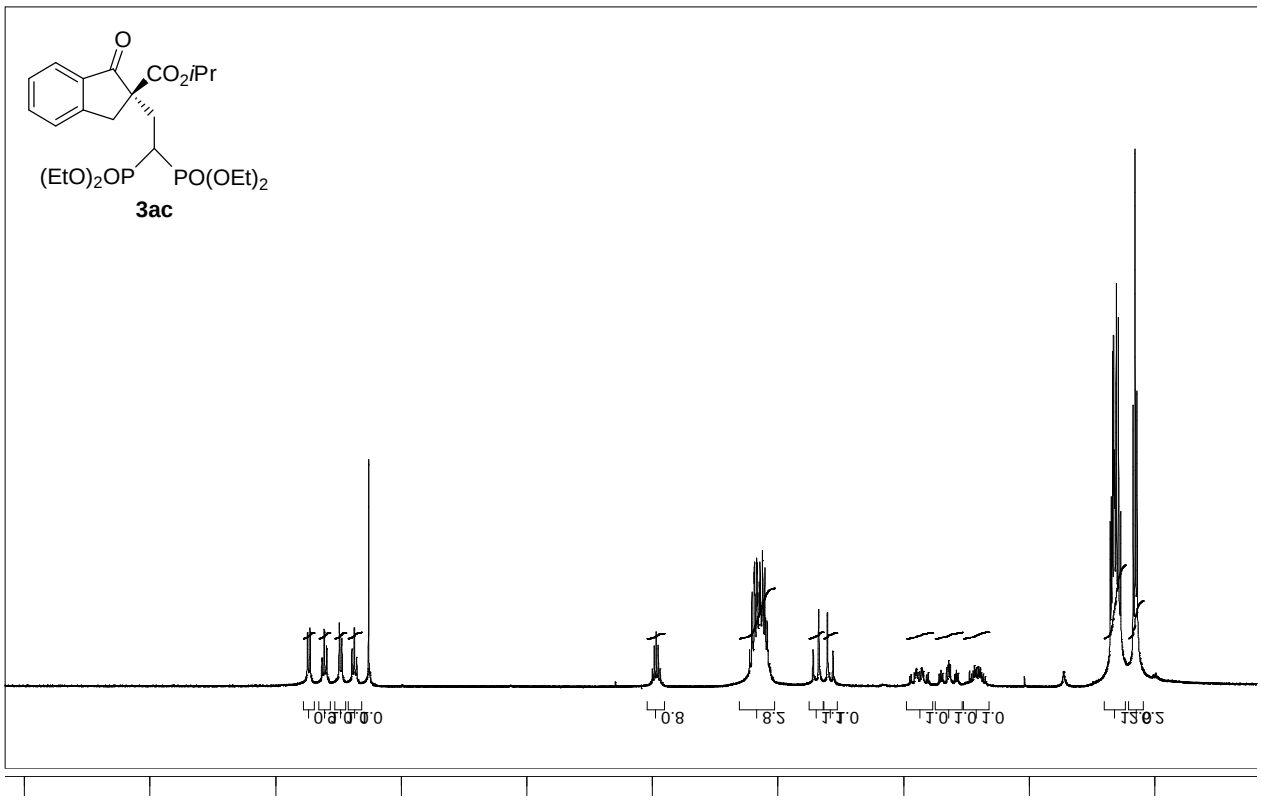
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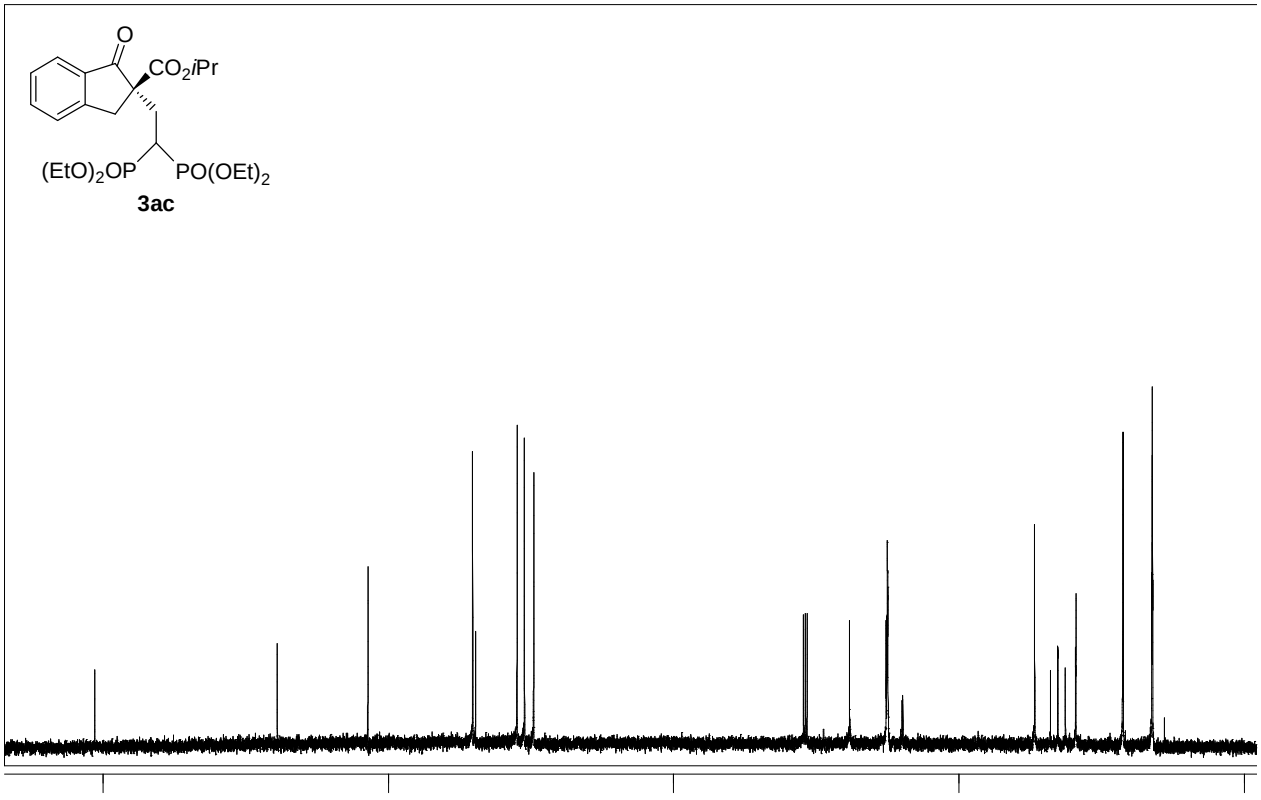
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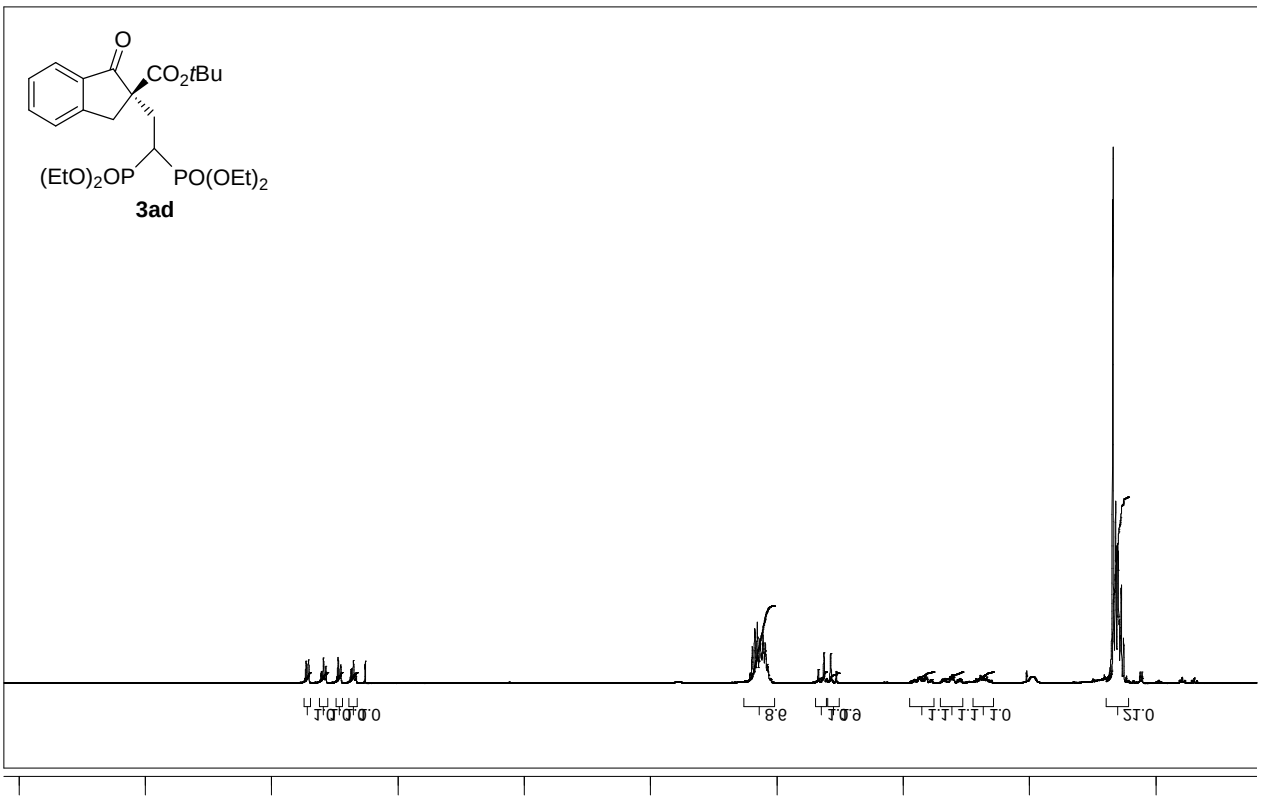
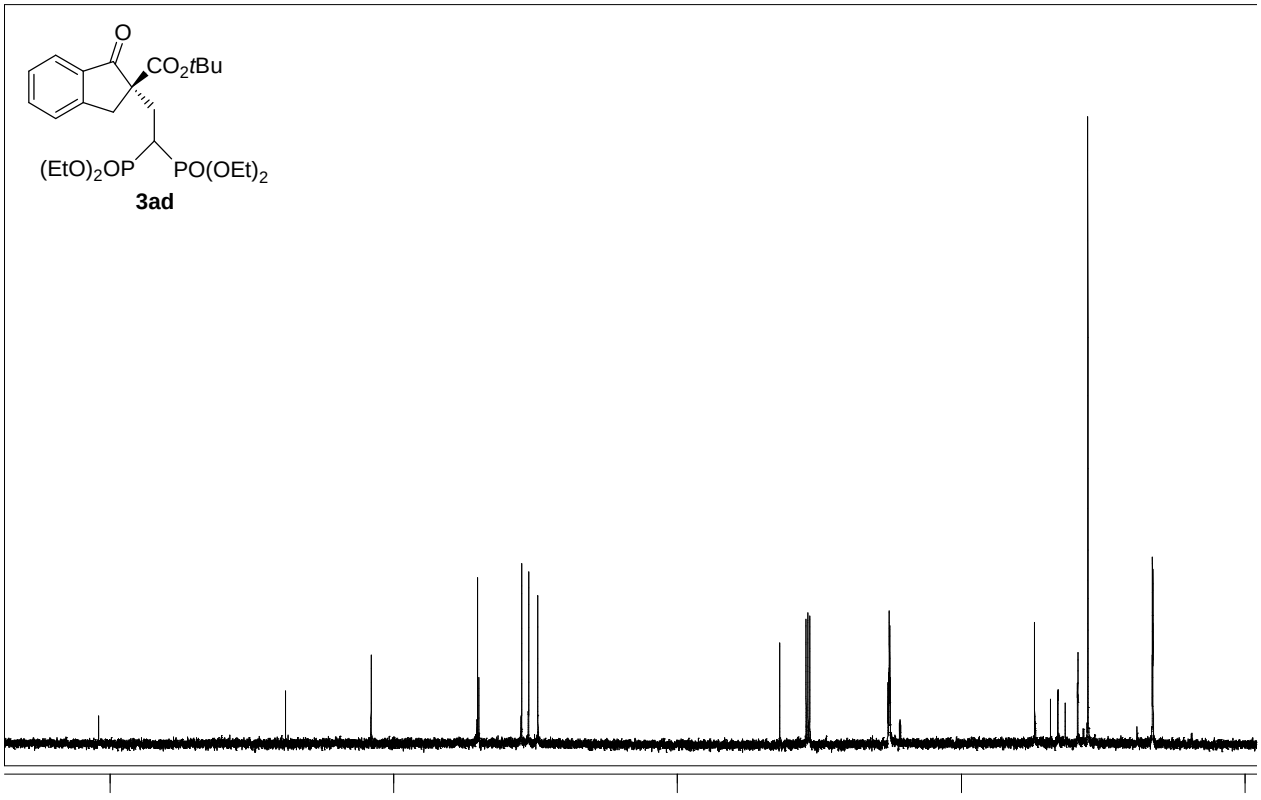
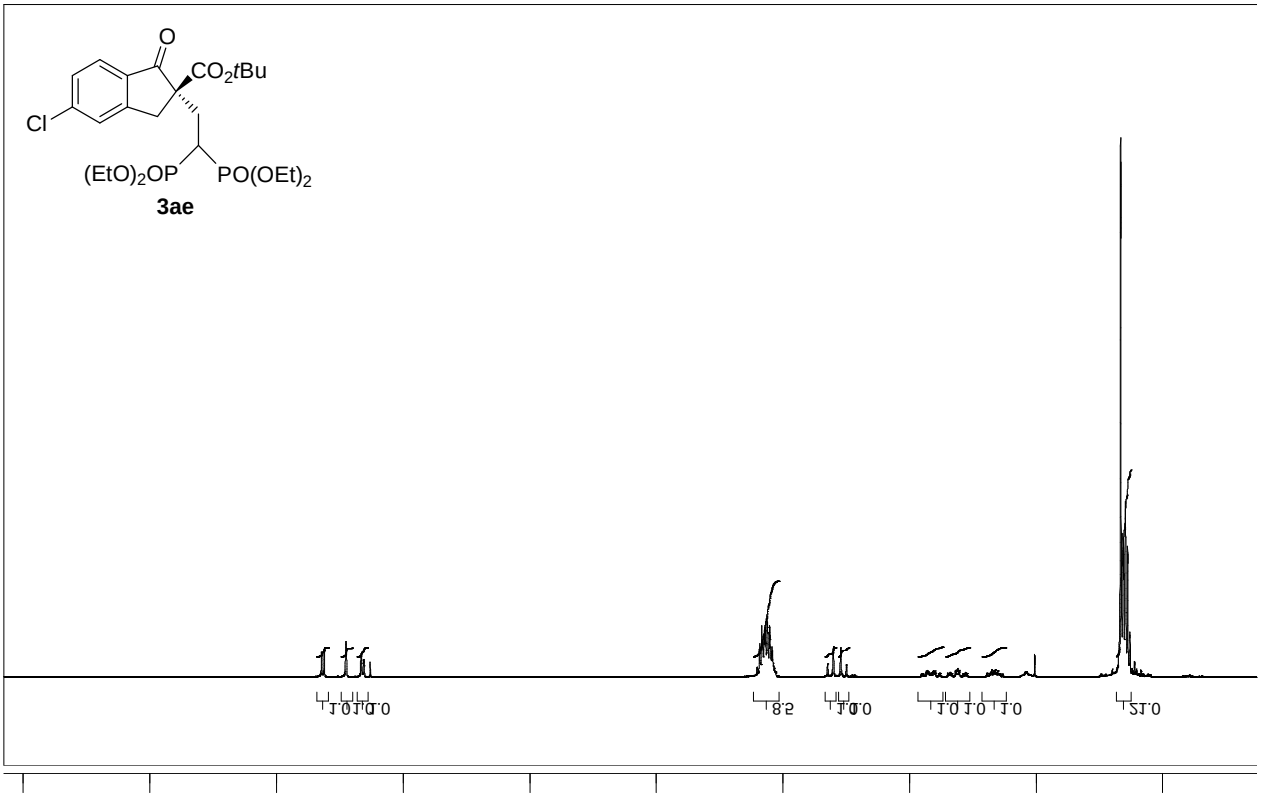
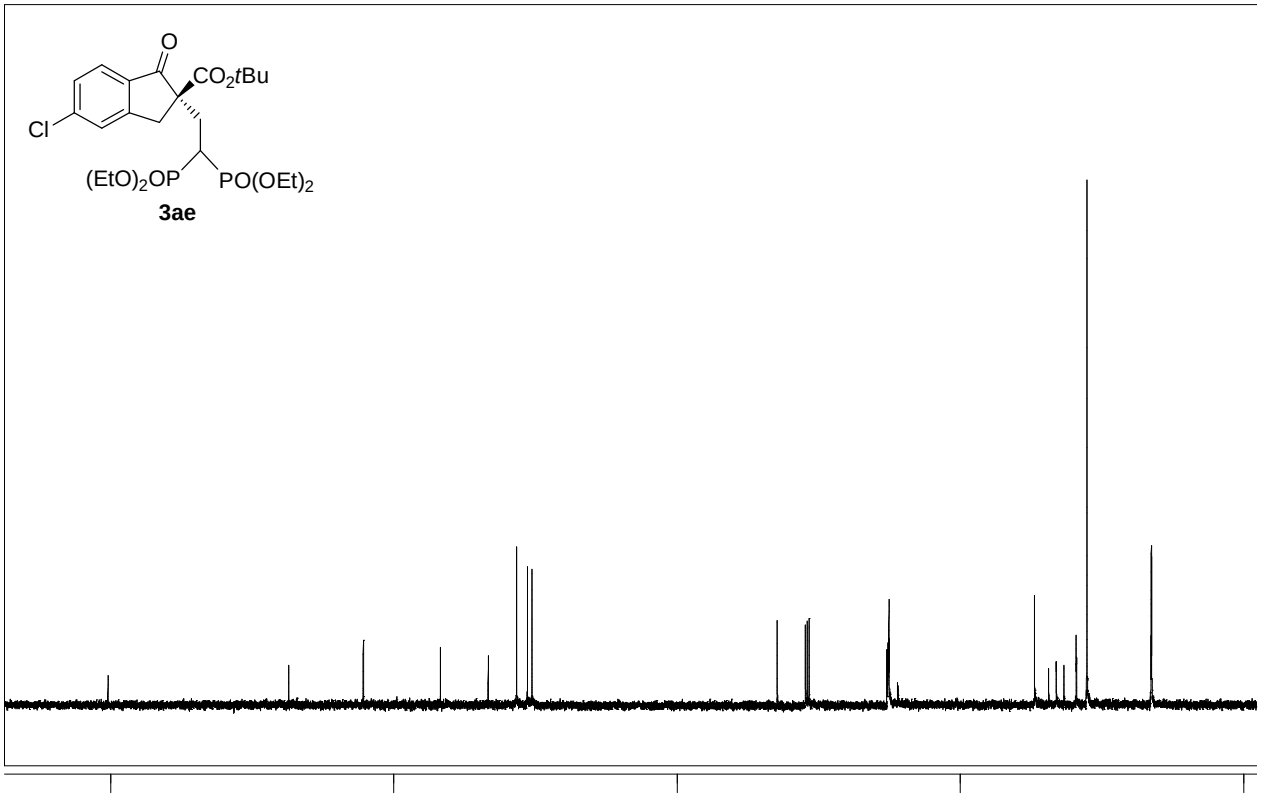
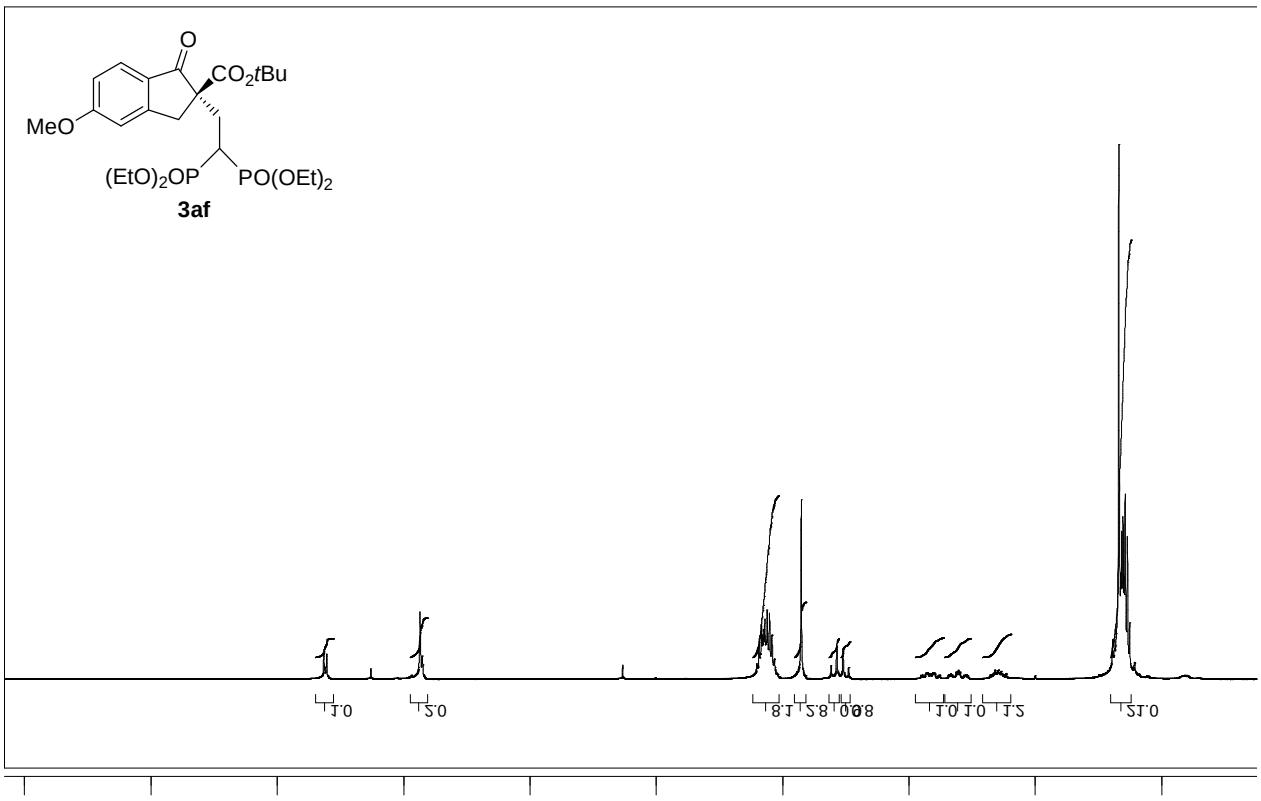
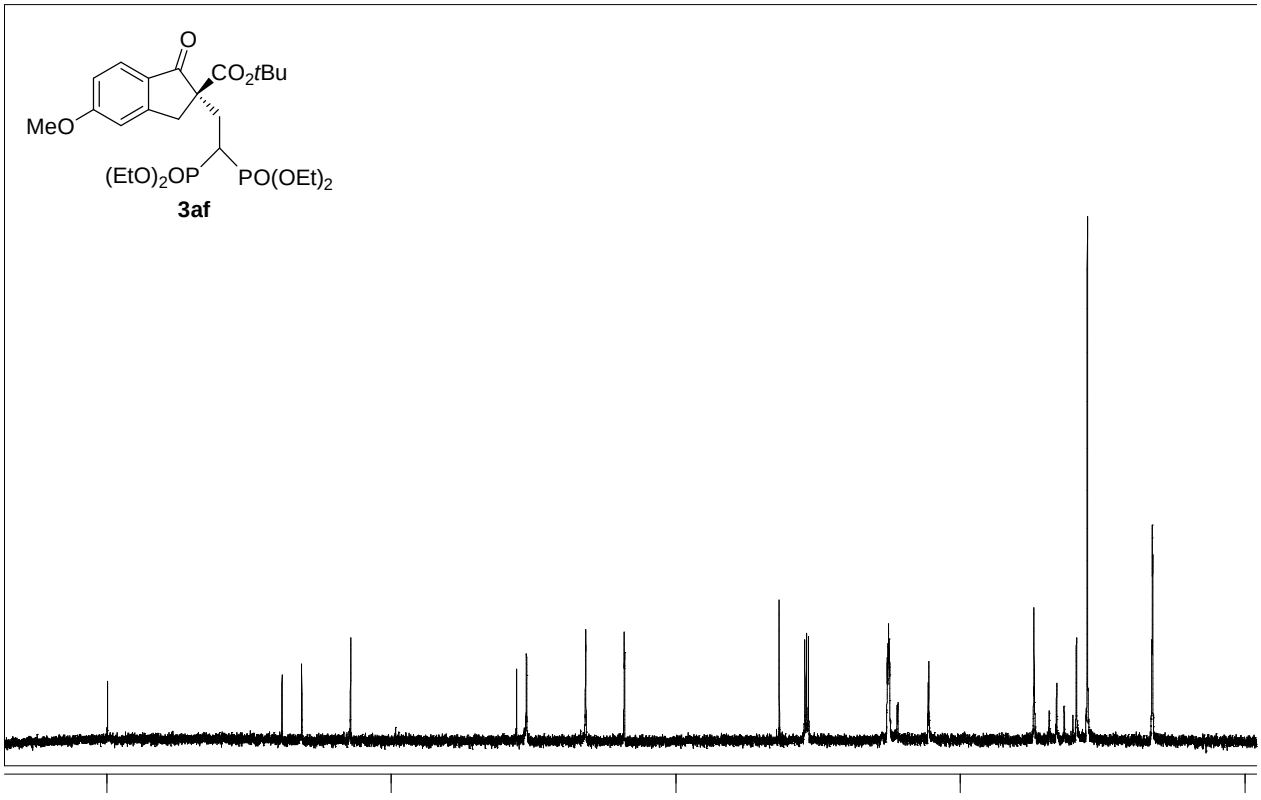

O
CO2tBu
(EtO)2OP
PO(OEt)2
3ad

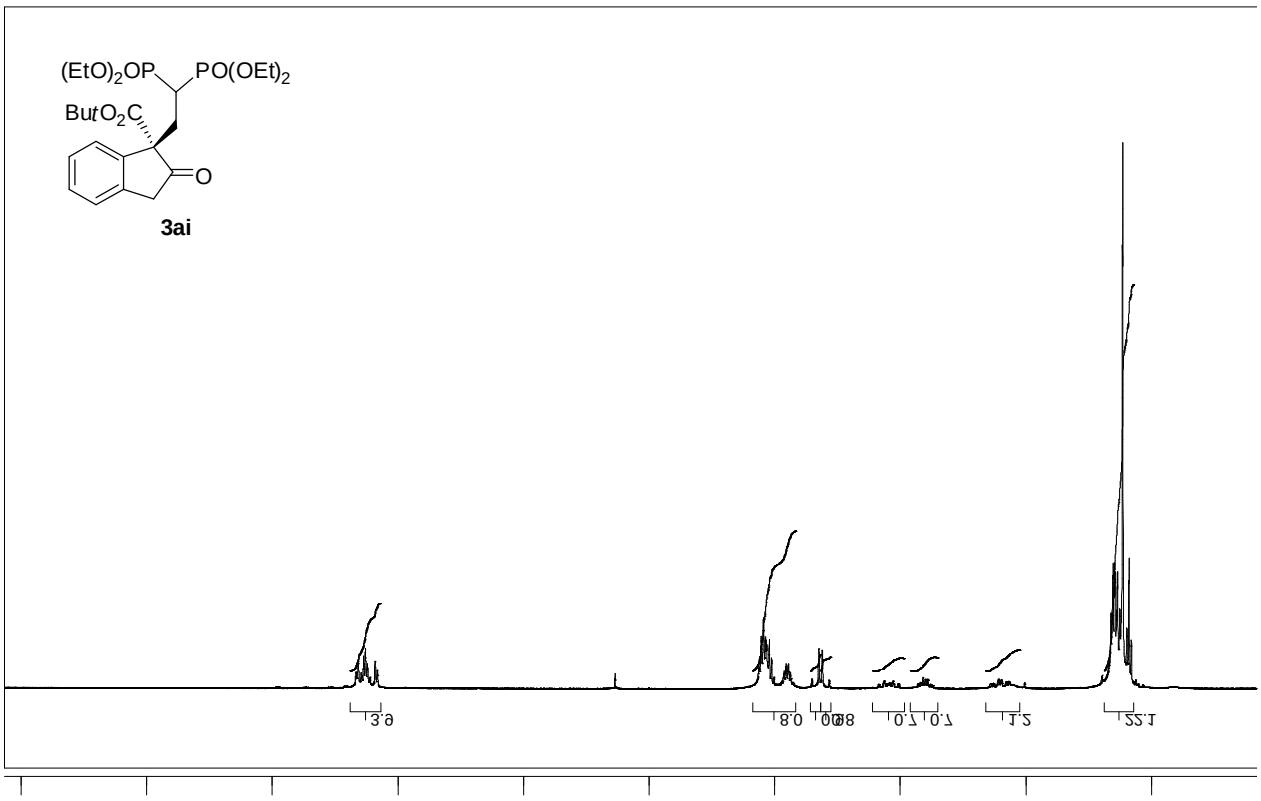

O
CO2tBu
(EtO)2OP
PO(OEt)2
3ad

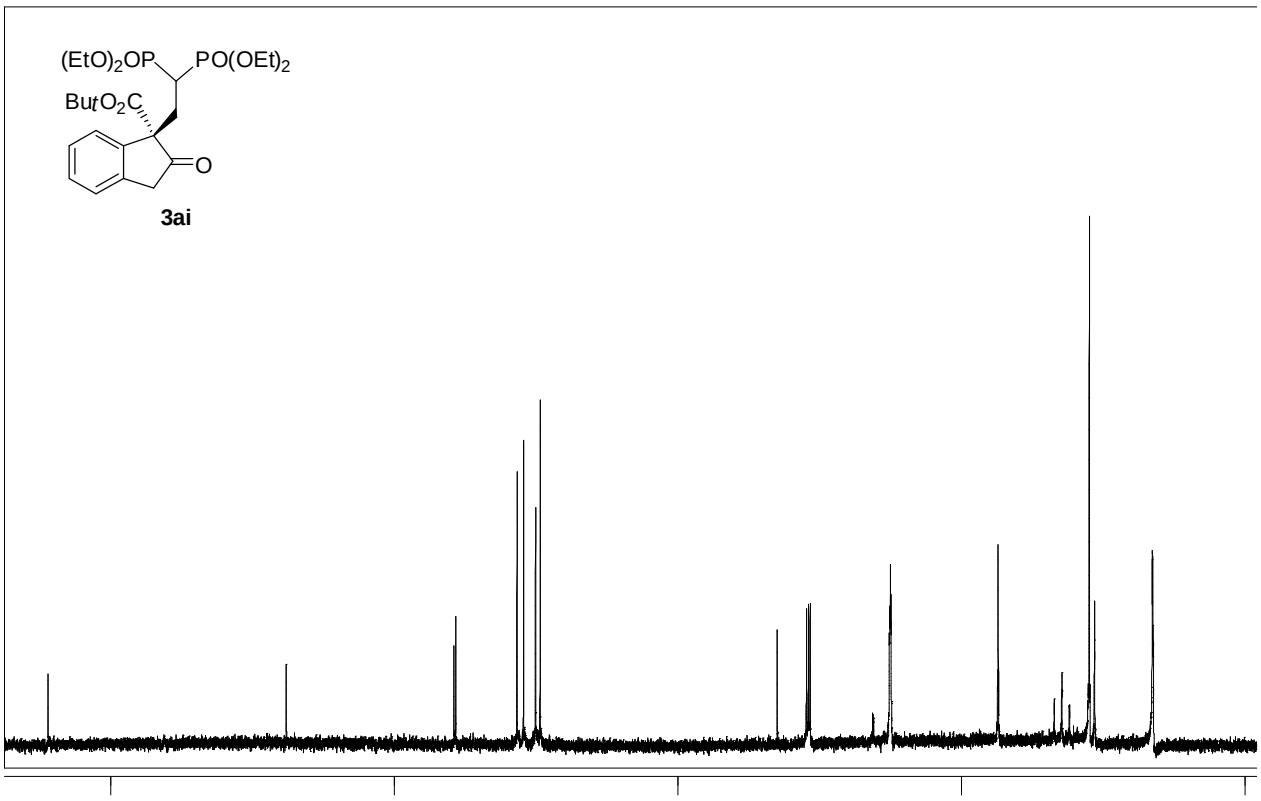

O
CO2tBu
Cl
(EtO)2OP
PO(OEt)2
3ae


O
CO2tBu
Cl
(EtO)2OP
PO(OEt)2
3ae


O
CO2tBu
MeO
(EtO)2OP
PO(OEt)2
3af


O
CO2tBu
MeO
(EtO)2OP
PO(OEt)2
3af


(EtO)2OP
PO(OEt)2
ButO2C
O
3ai



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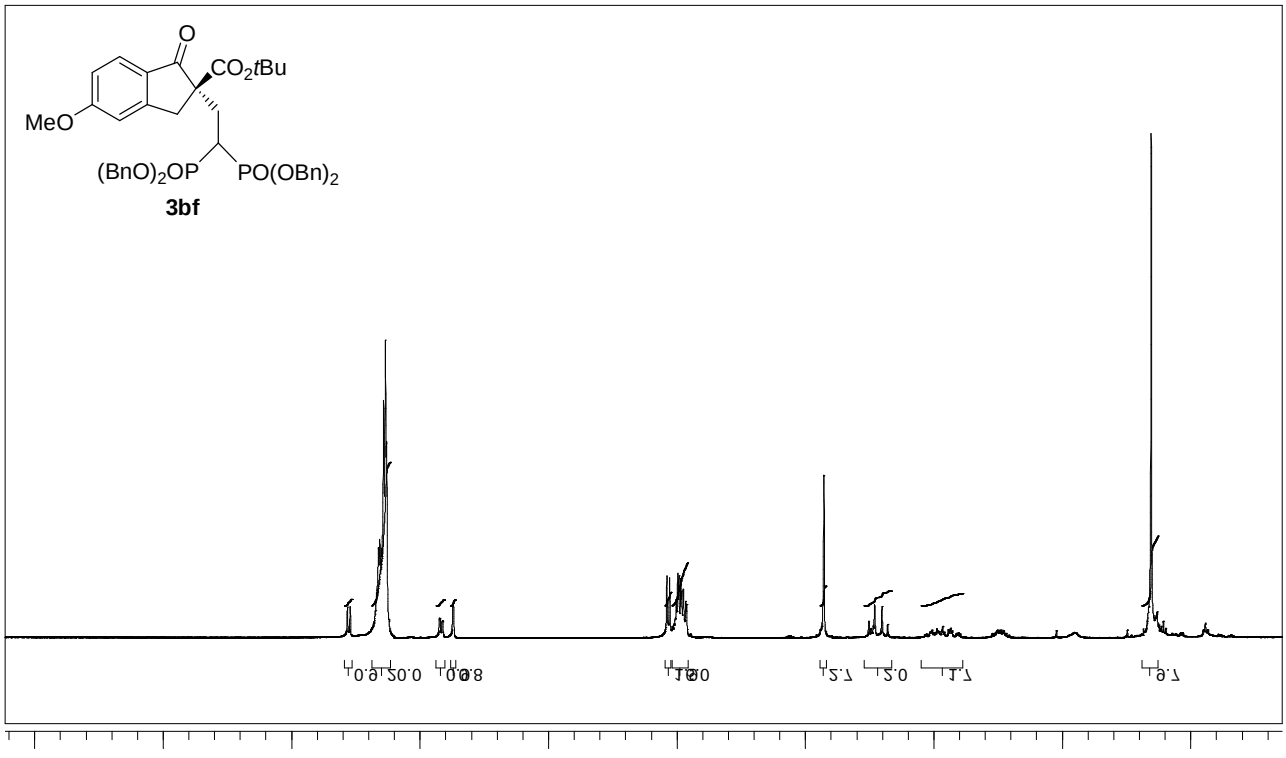

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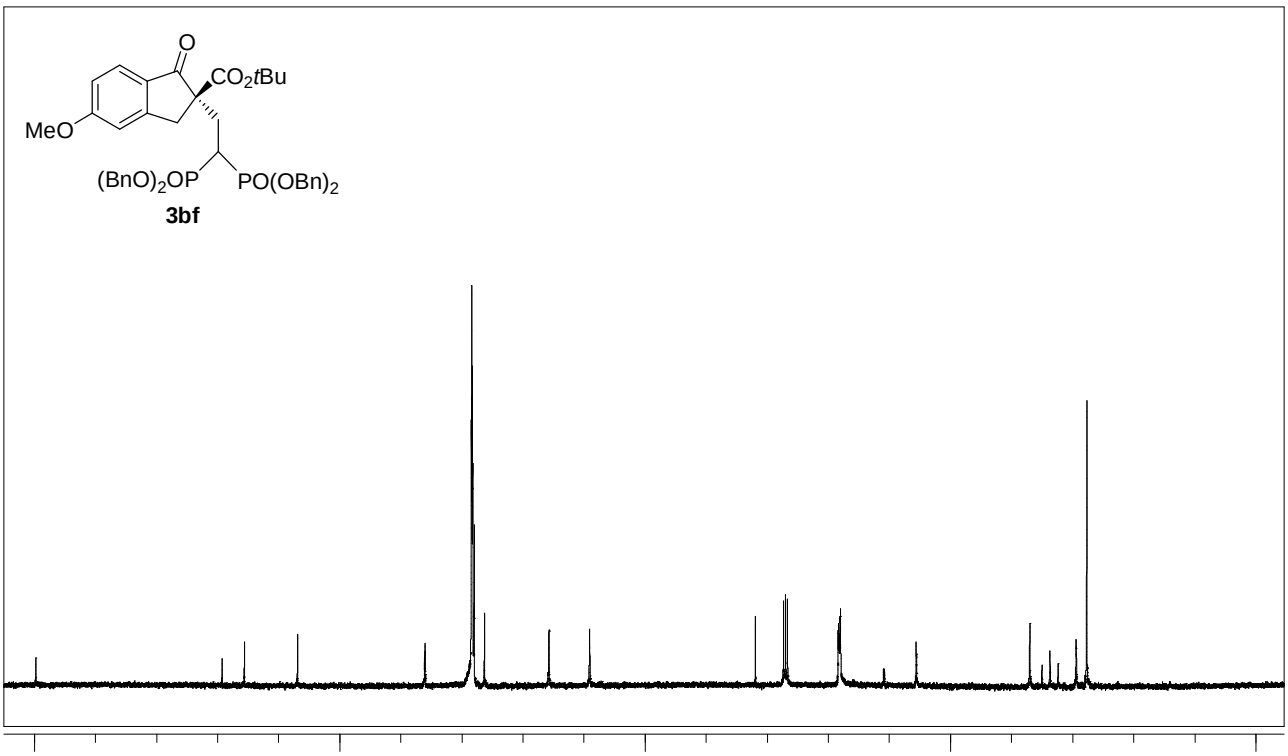

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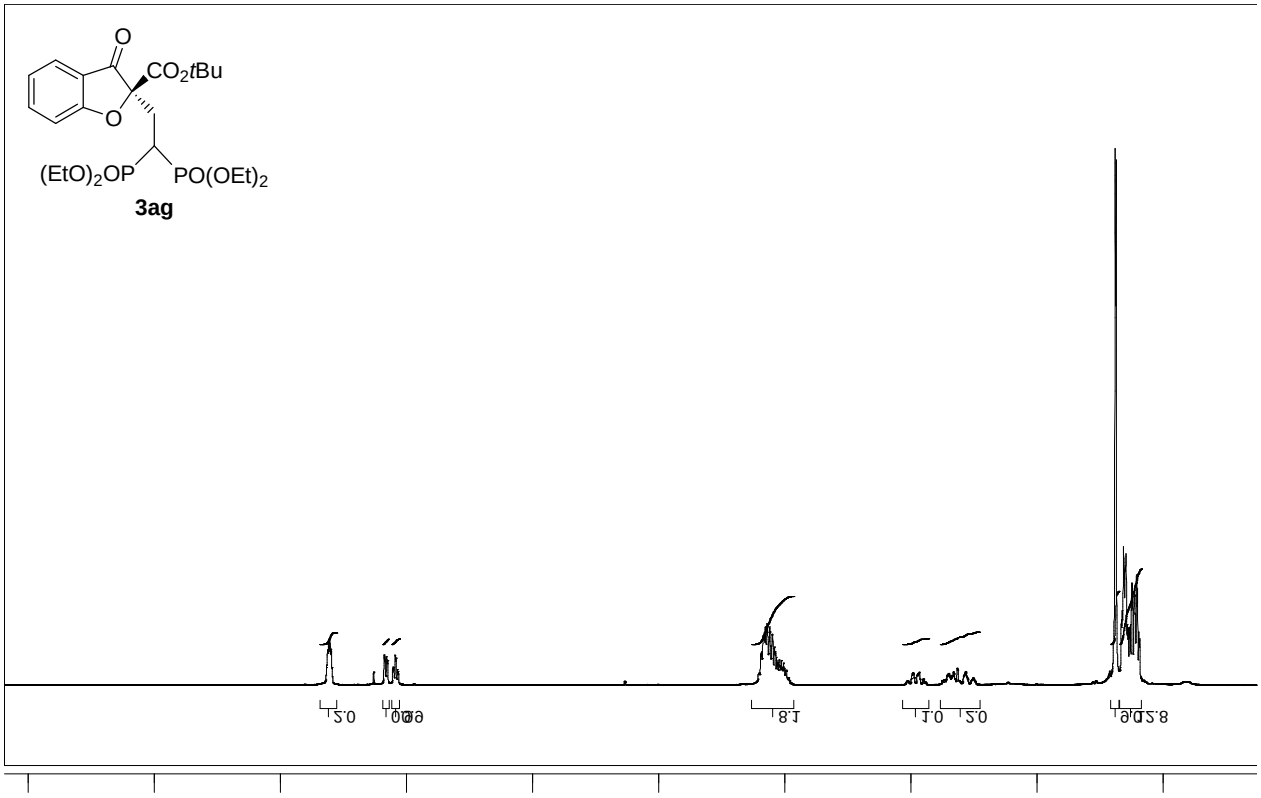

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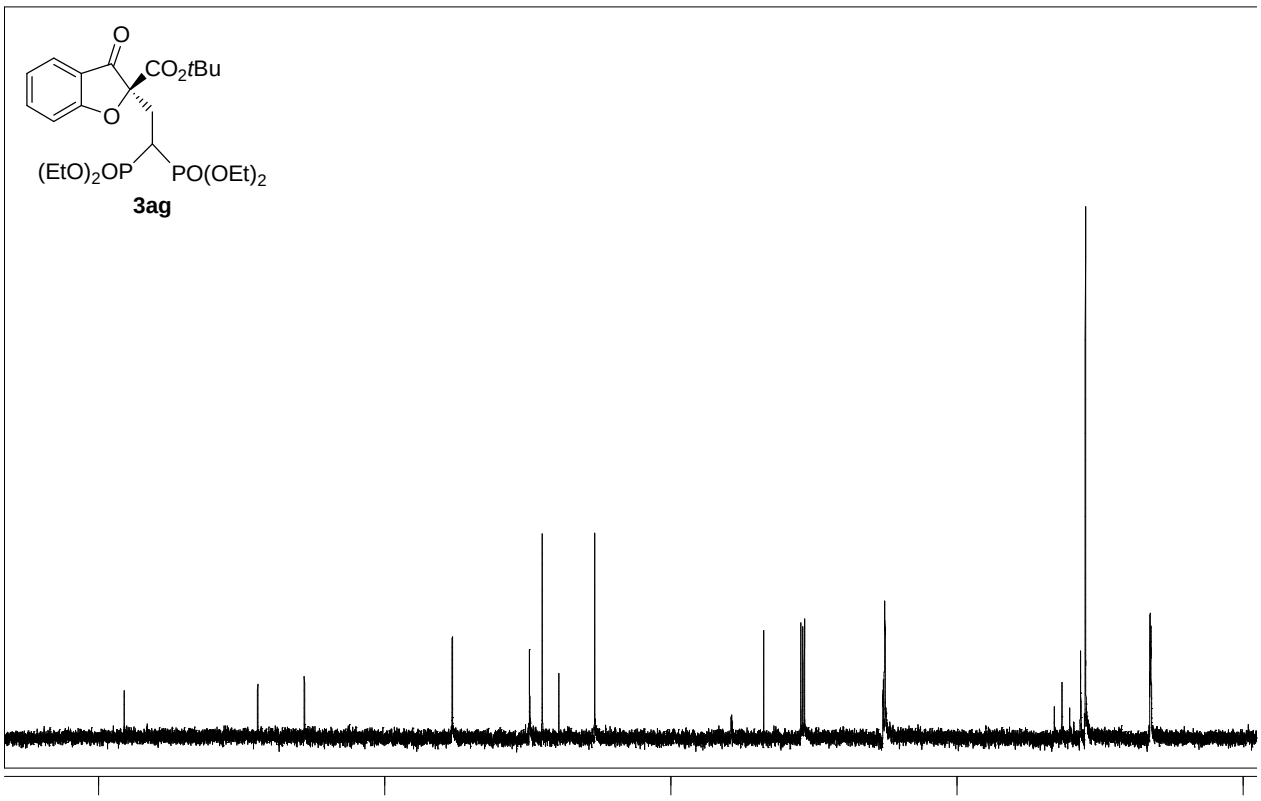

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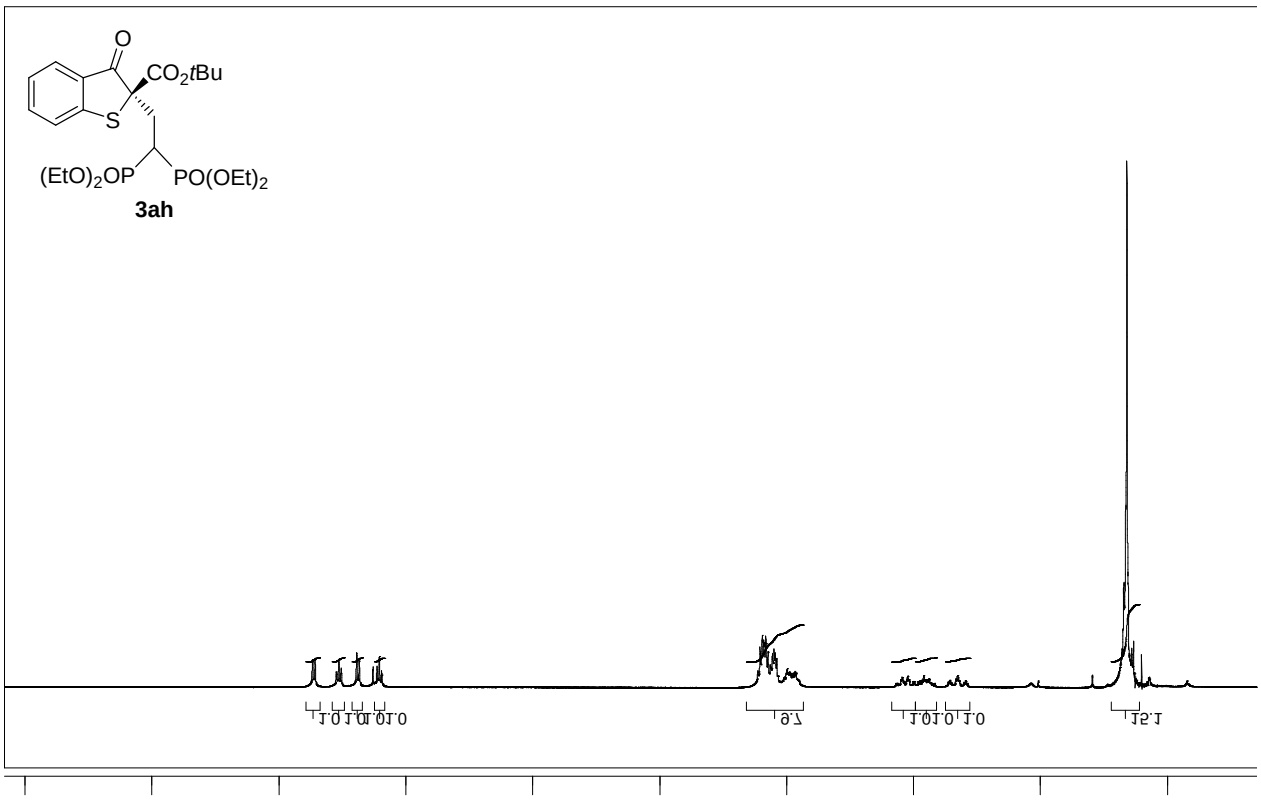

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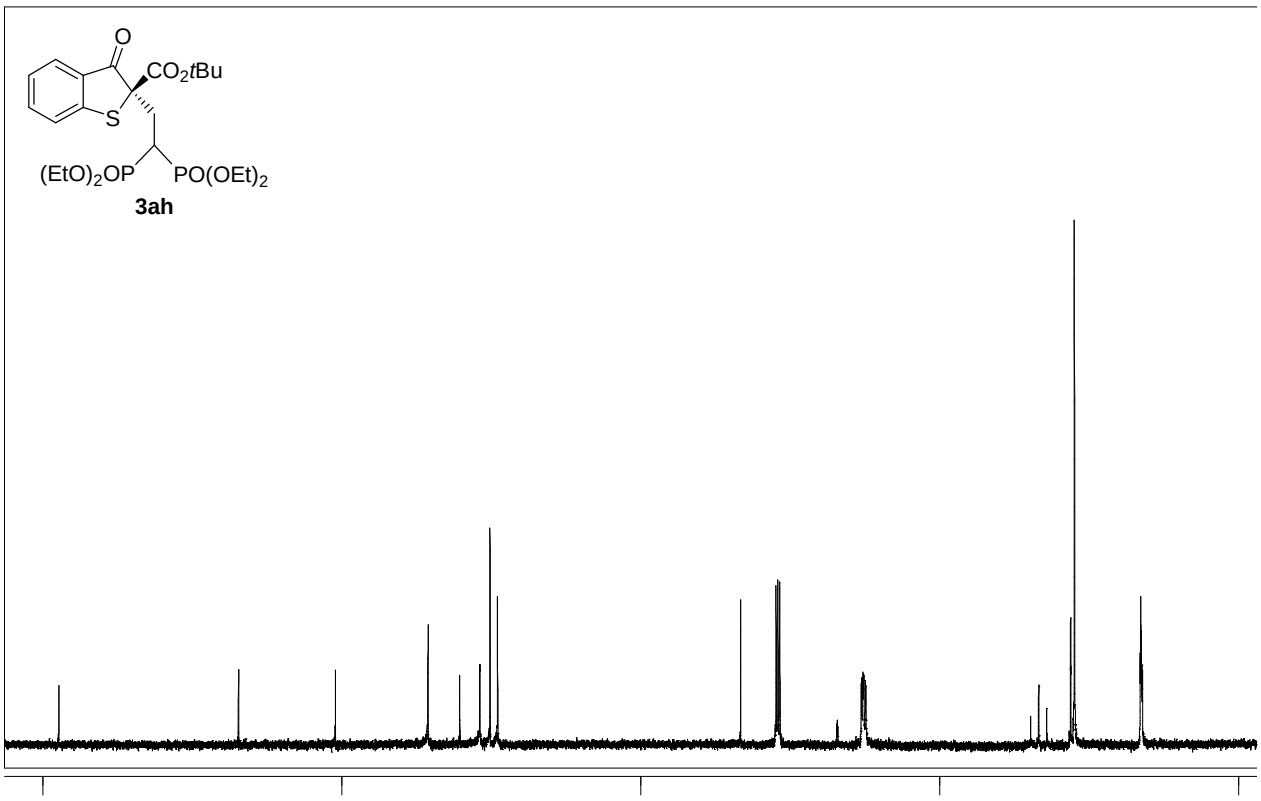

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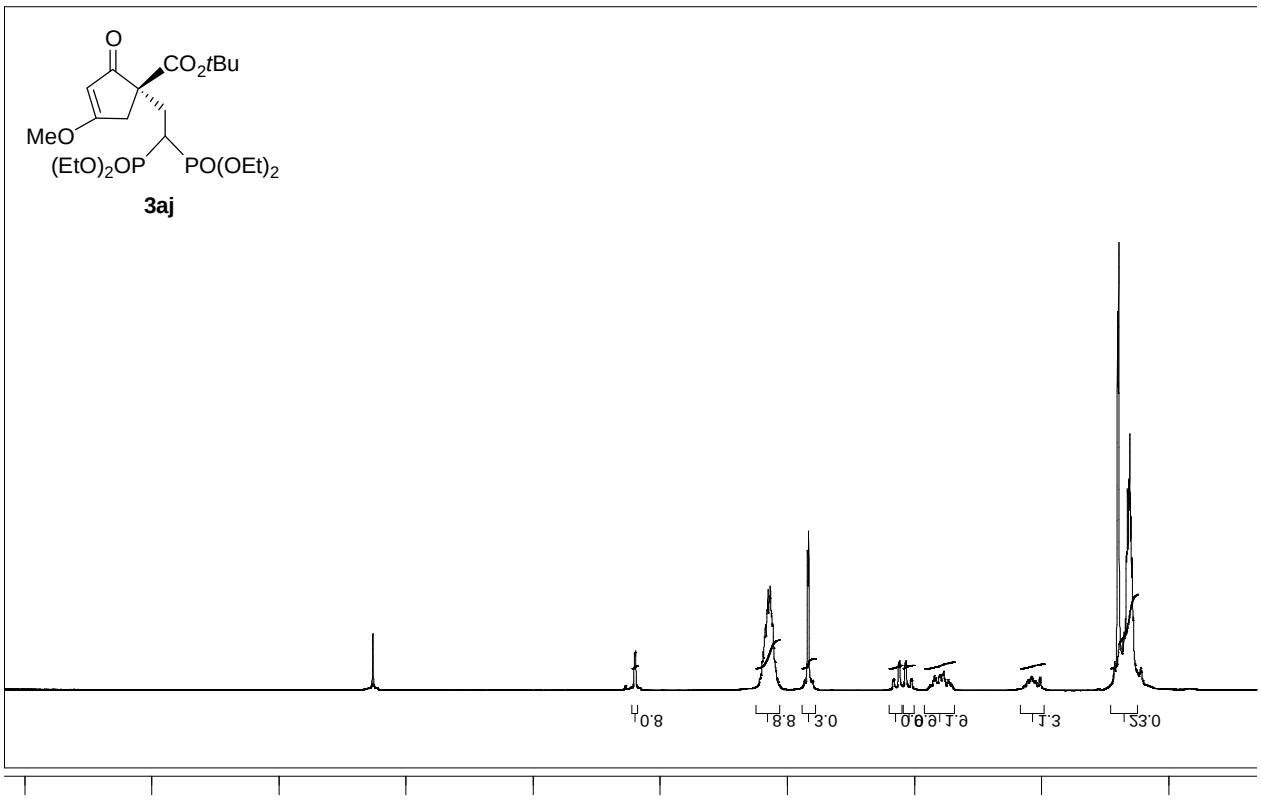

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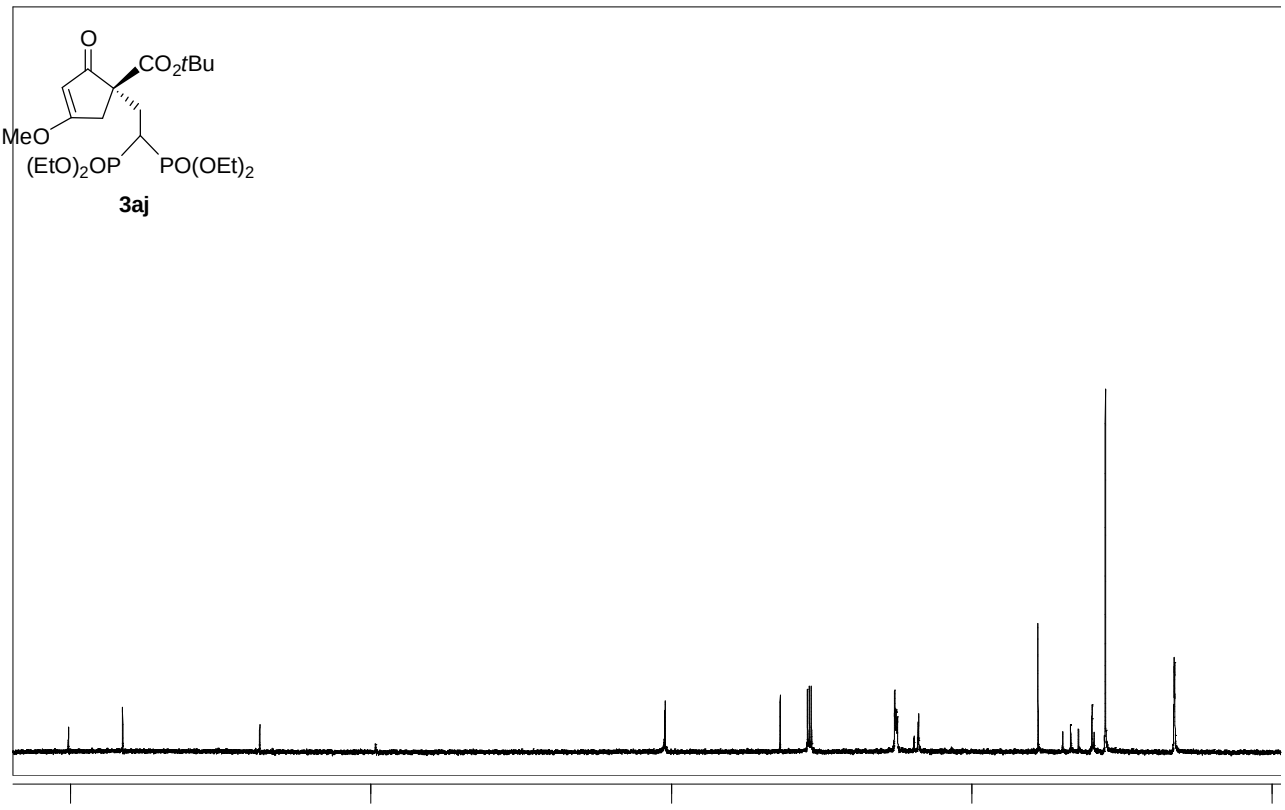
3aj



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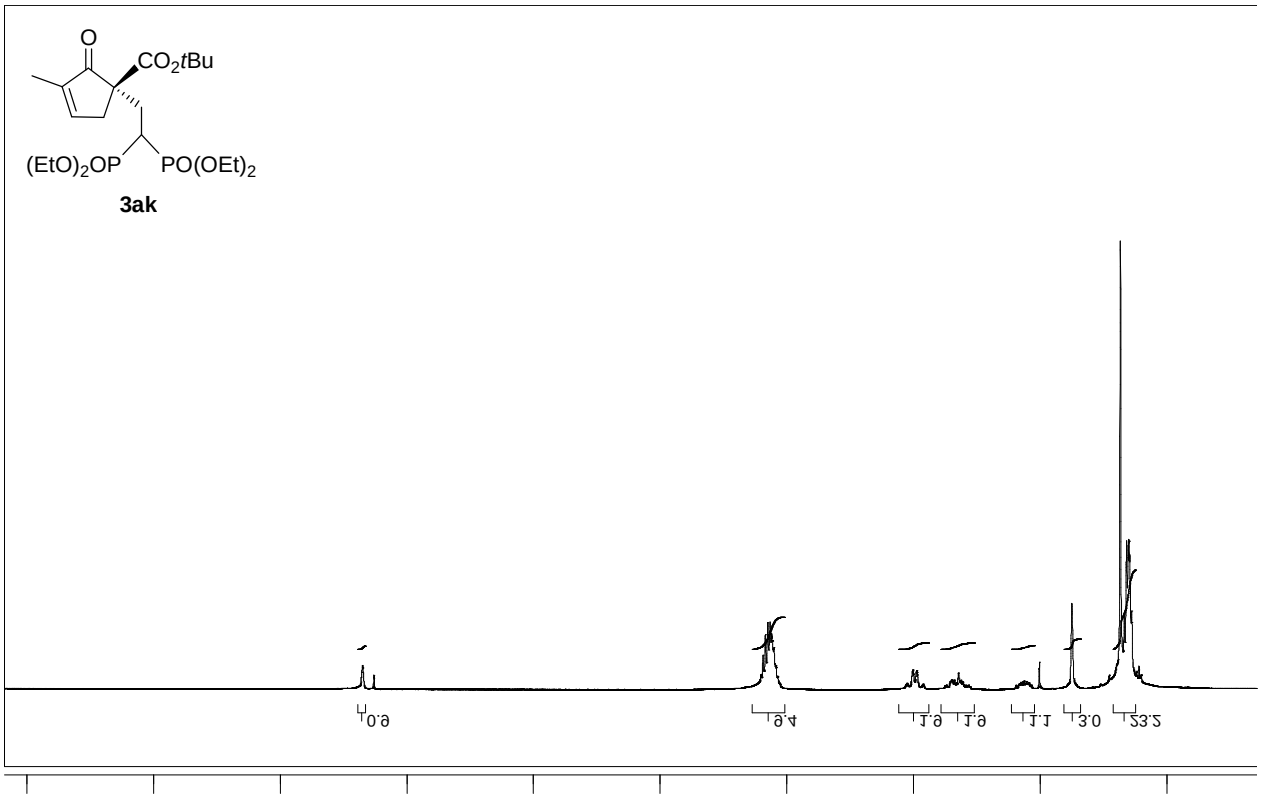

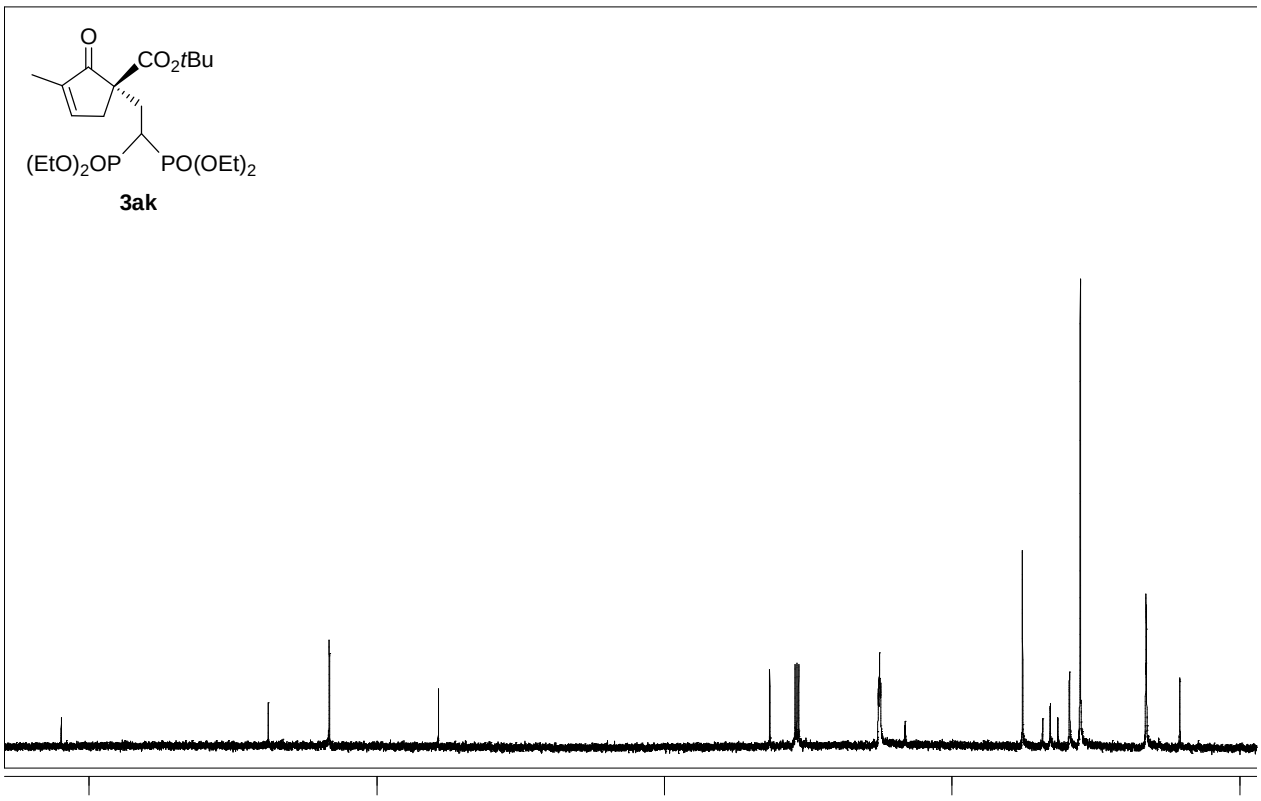

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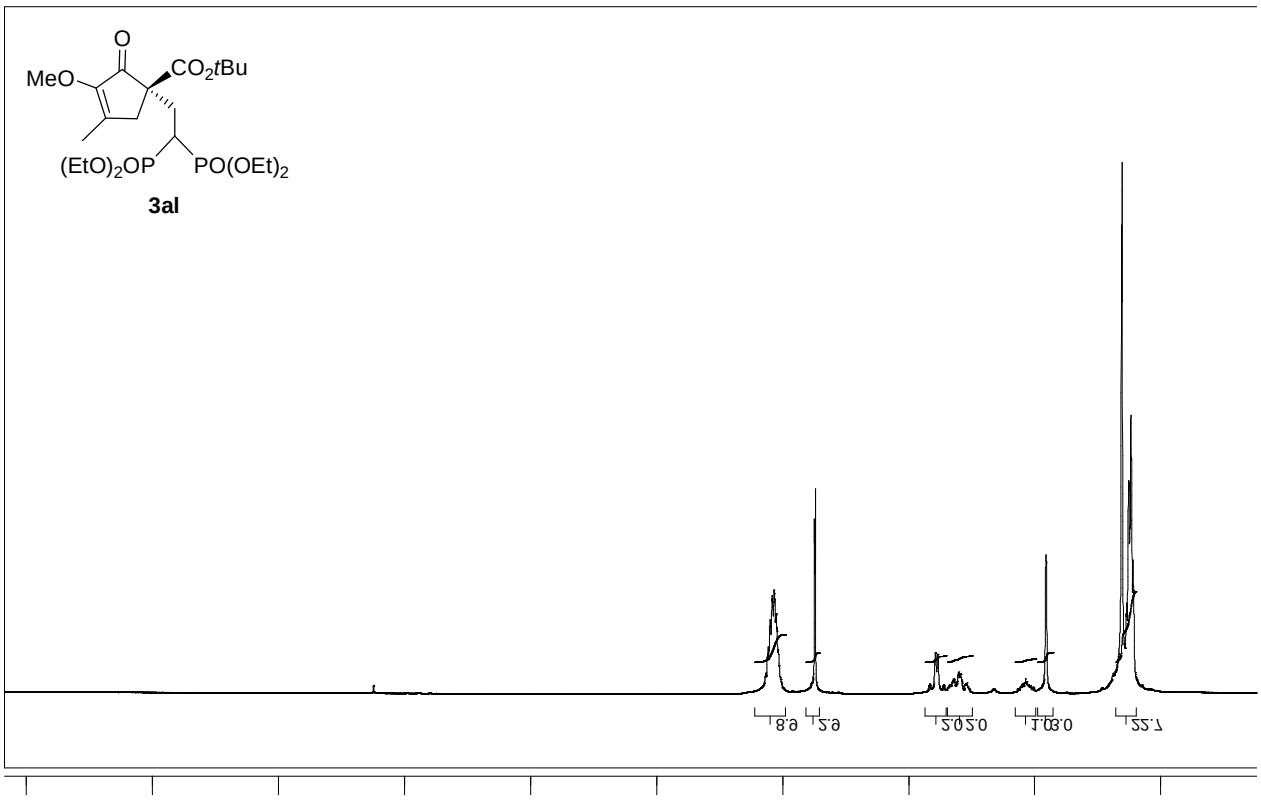

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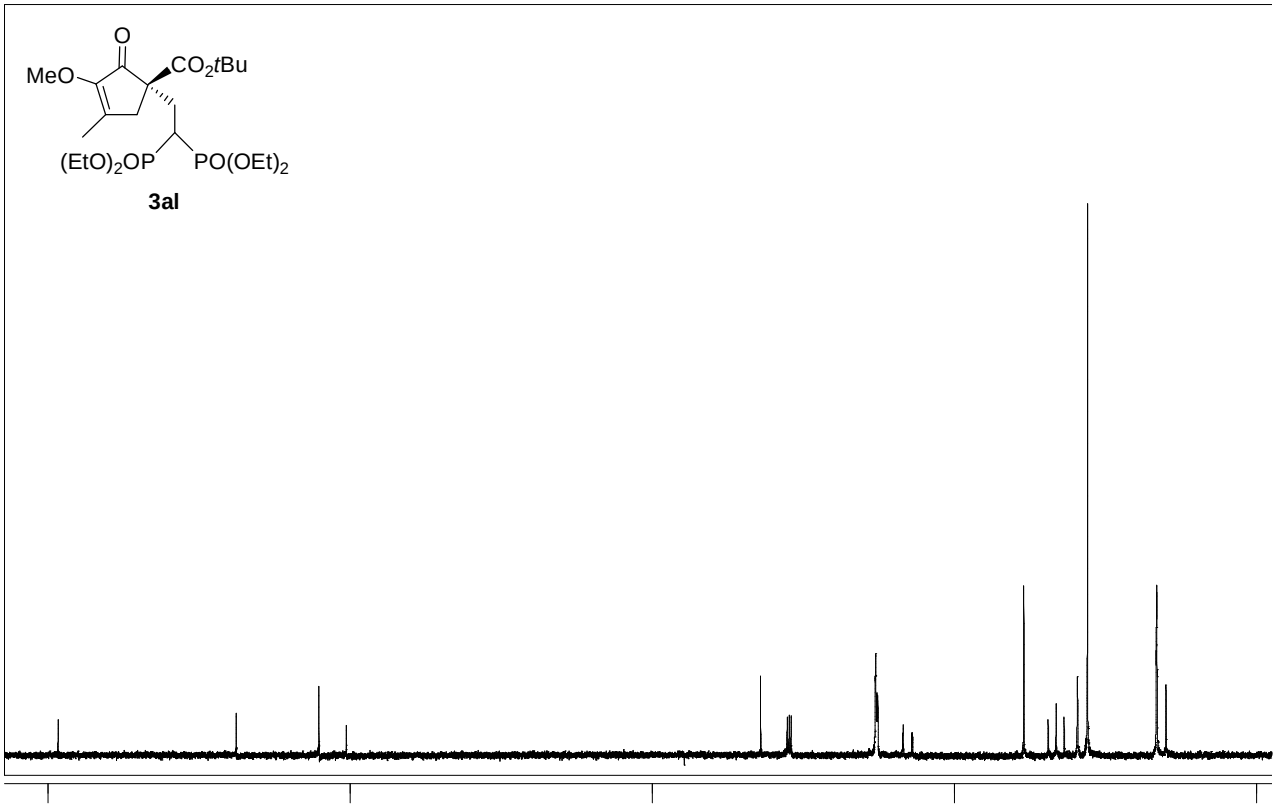
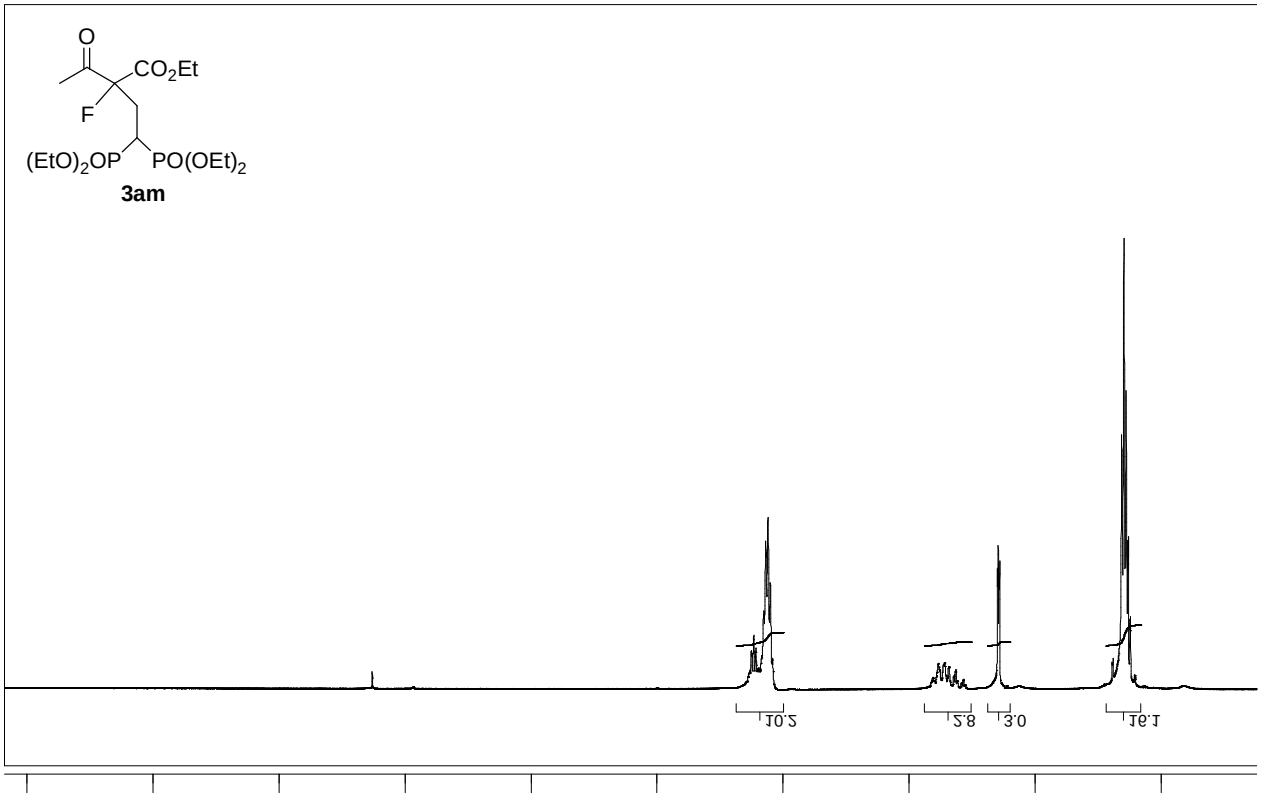
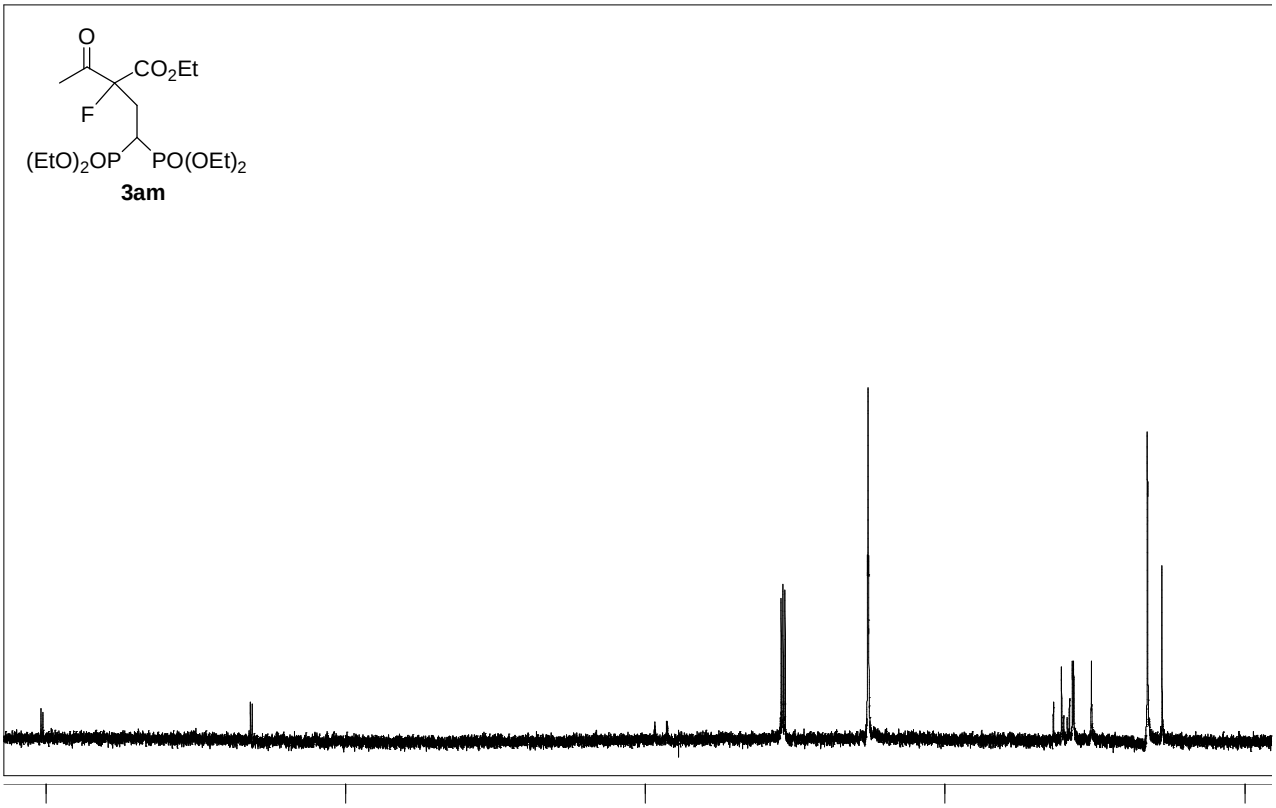

O
MeO
CO2tBu
(EtO)2OP
PO(OEt)2

3al


O
CO2Et
F
(EtO)2OP
PO(OEt)2
5.01
8.5
0.8
1.81

3am



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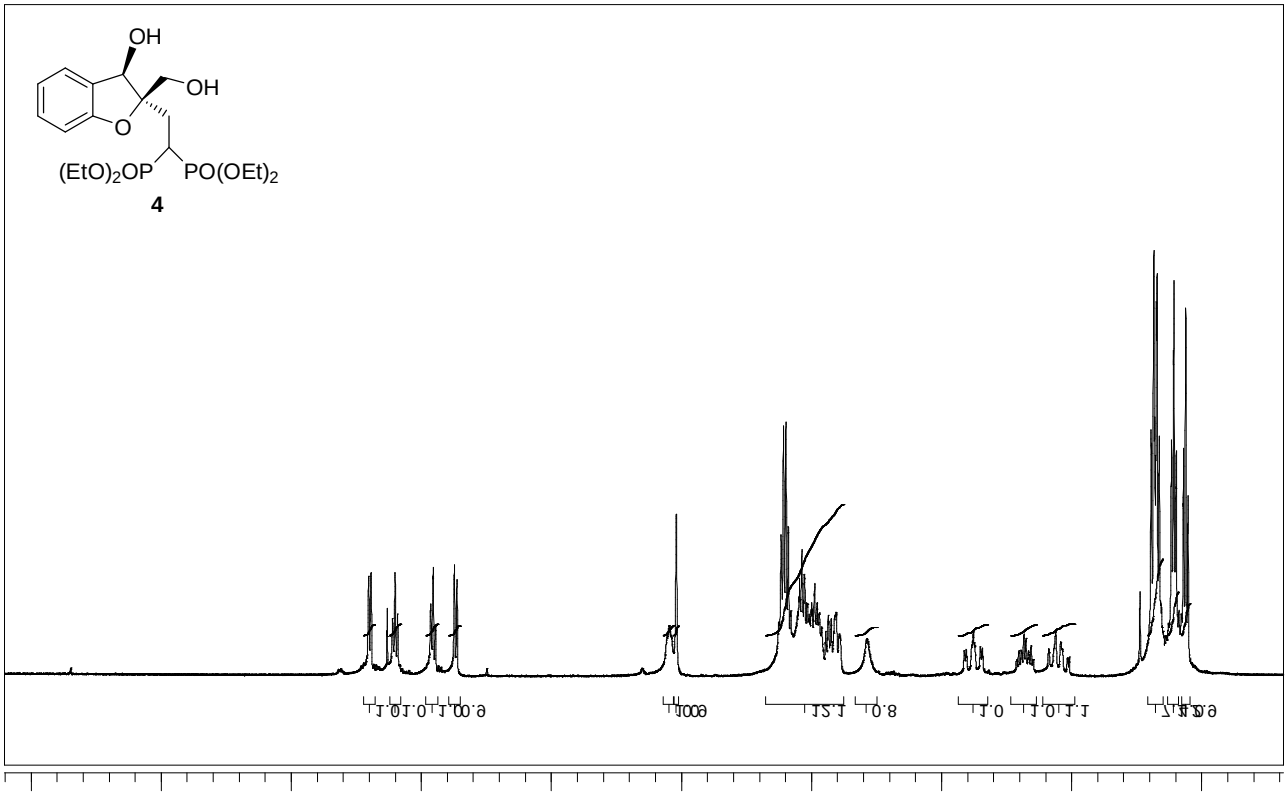

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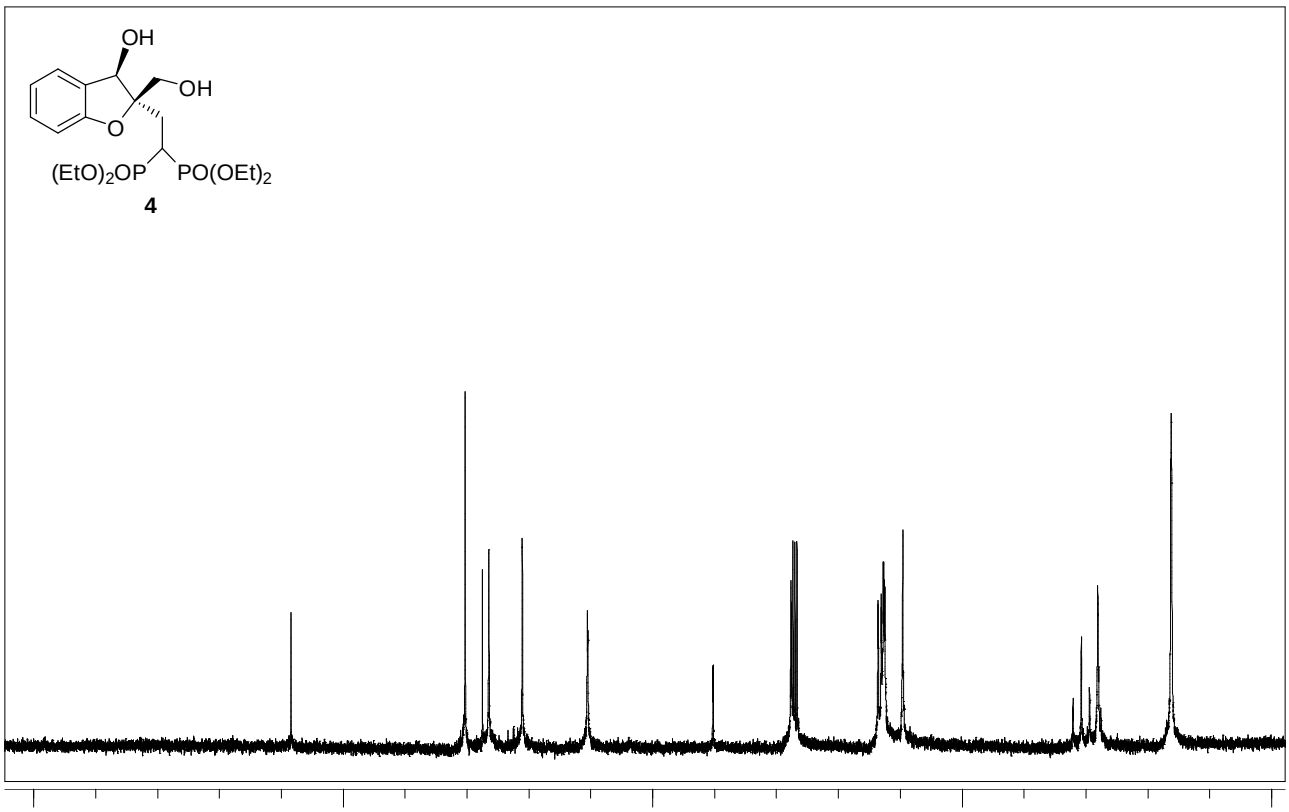

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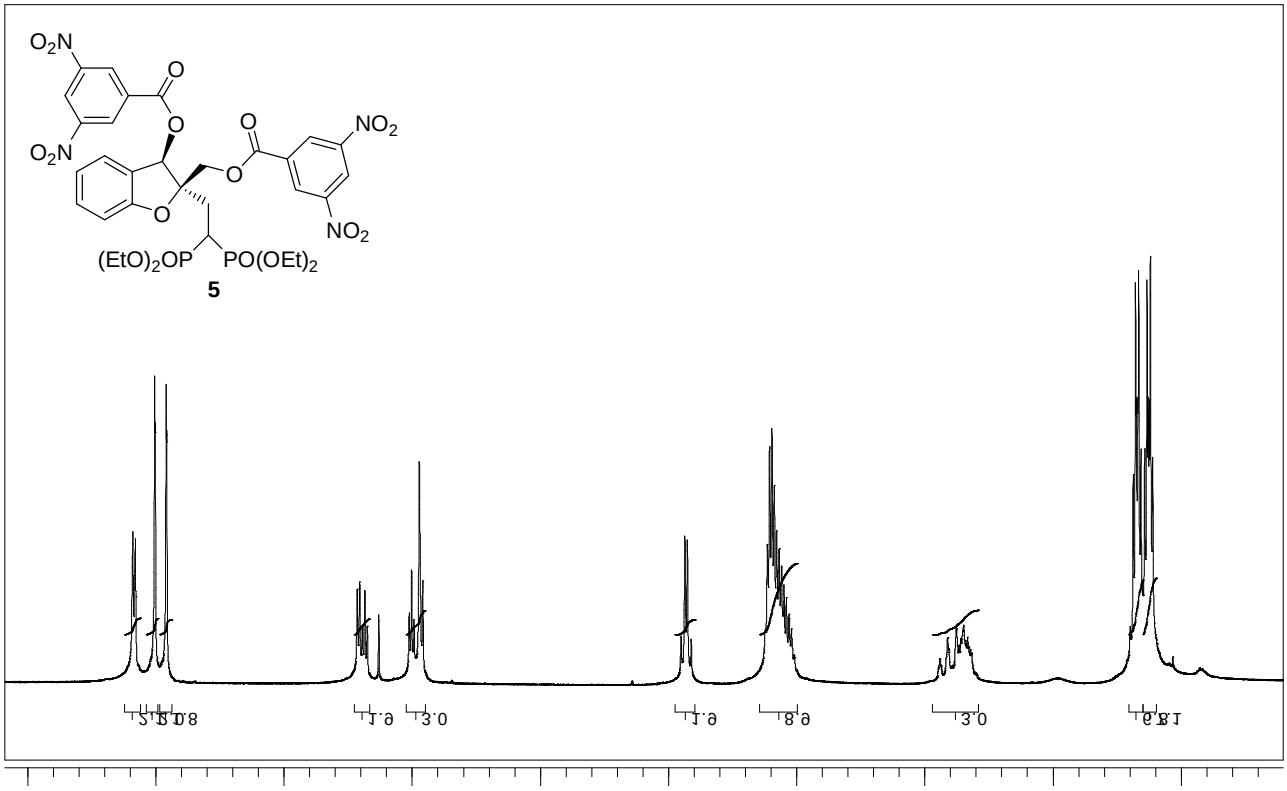

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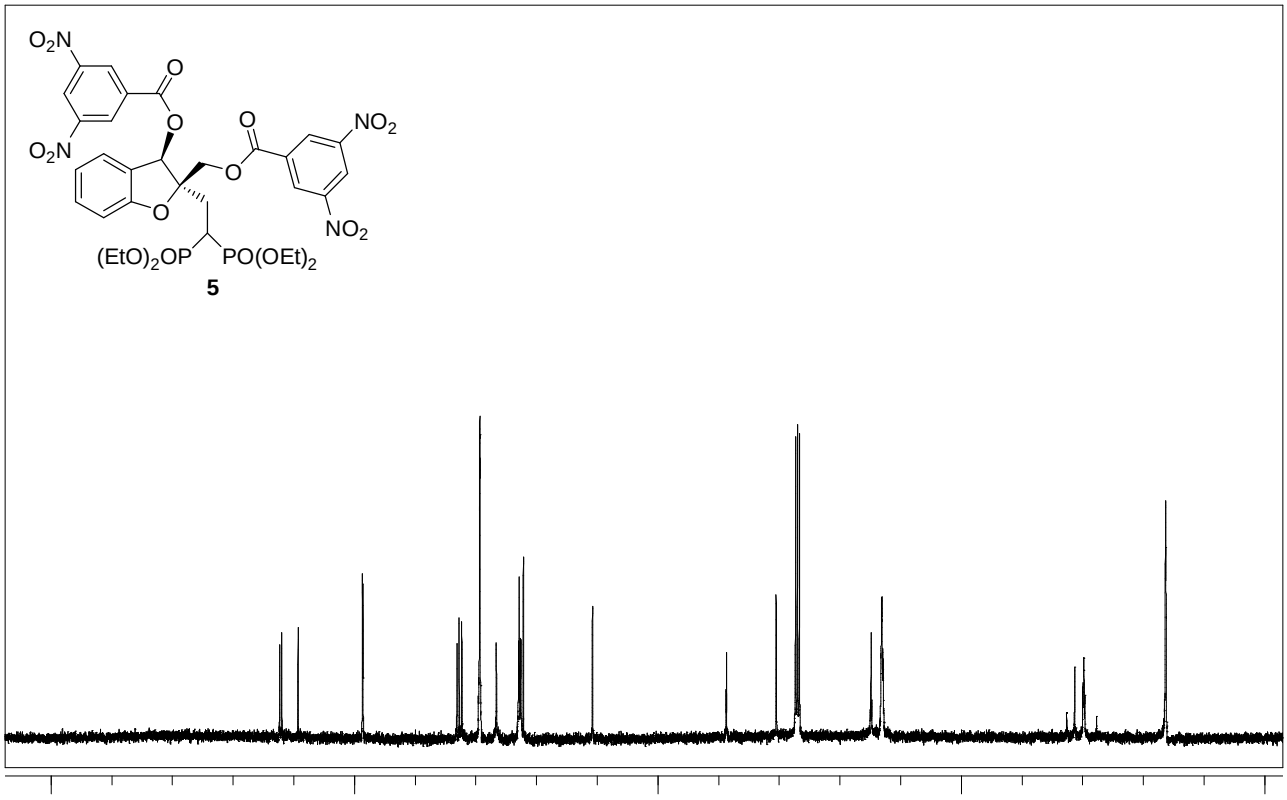

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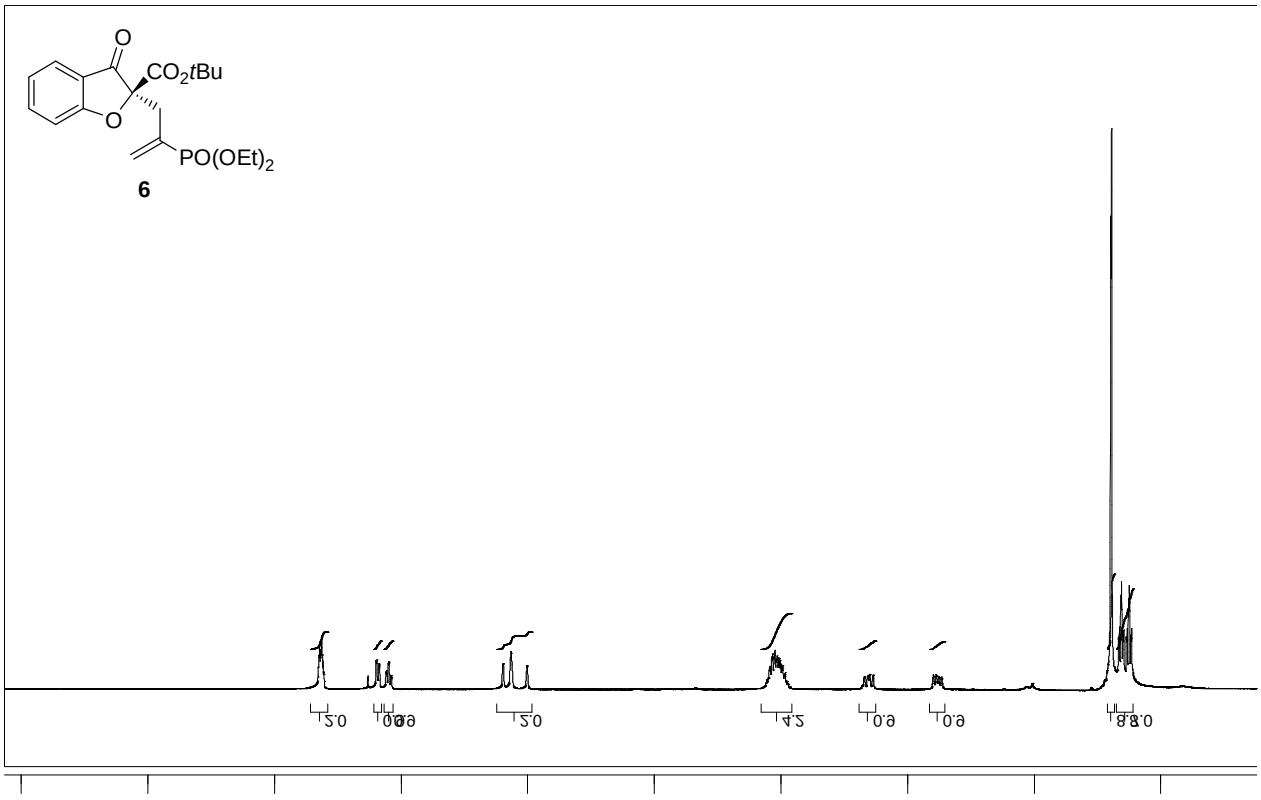

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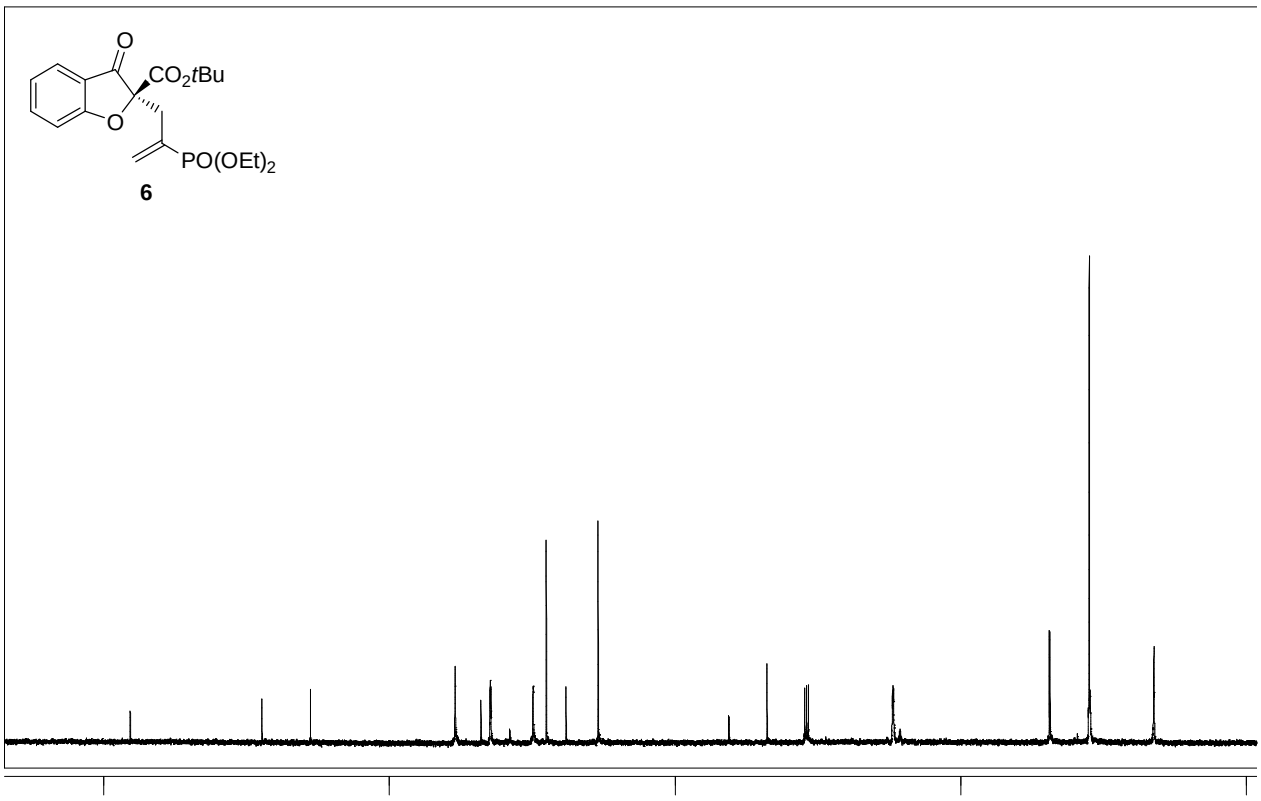

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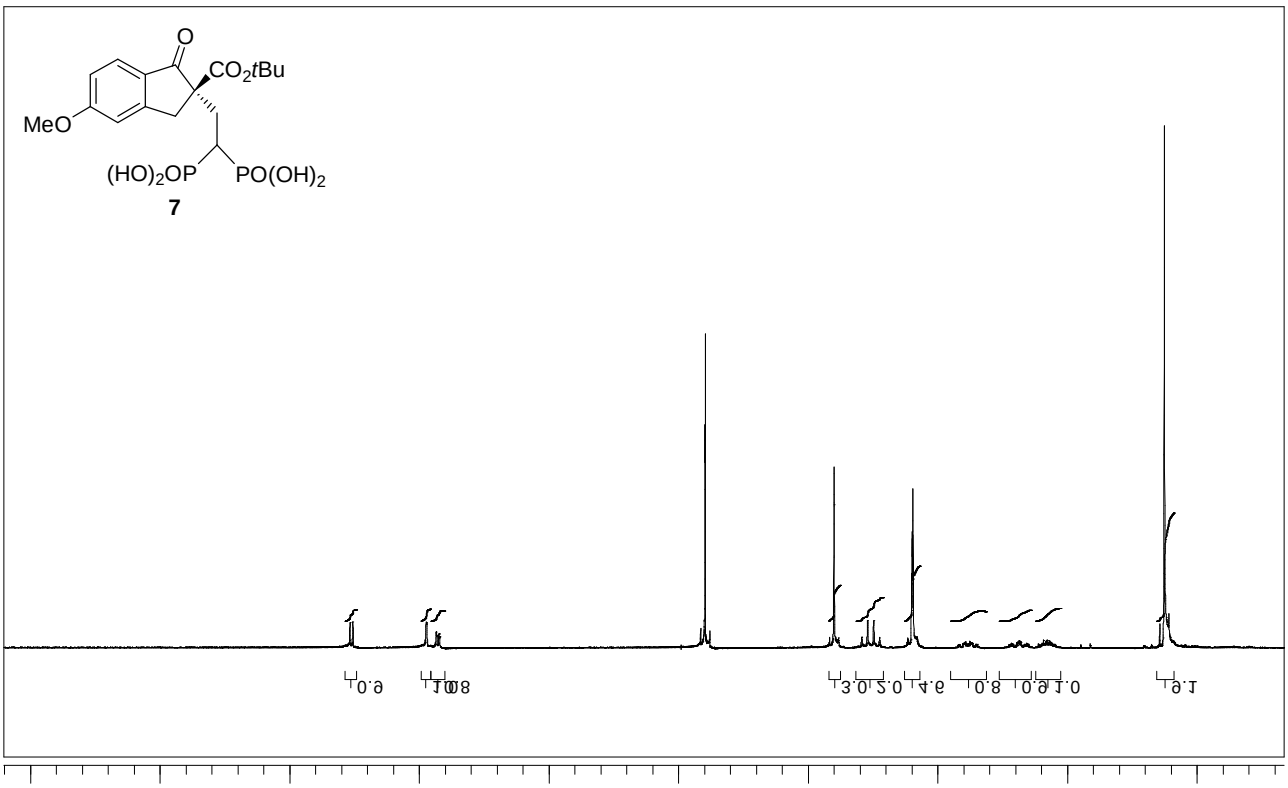

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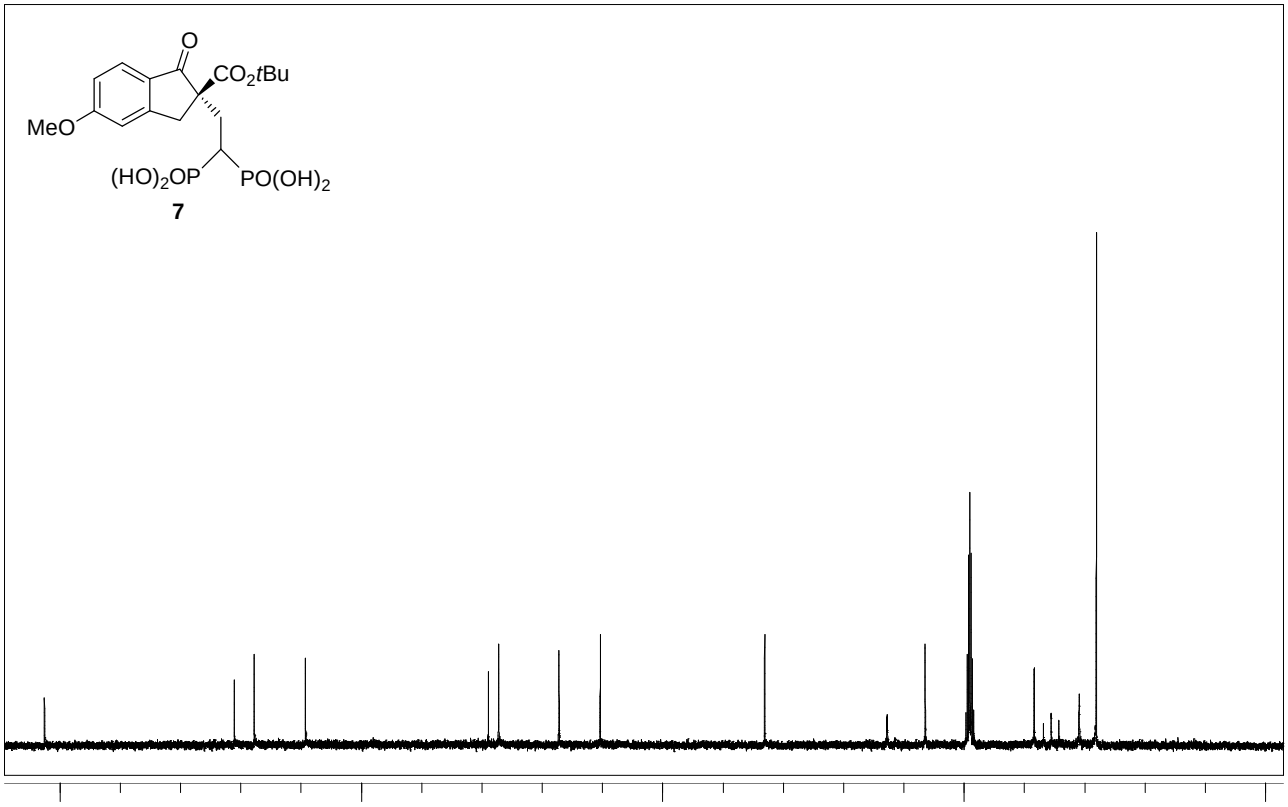

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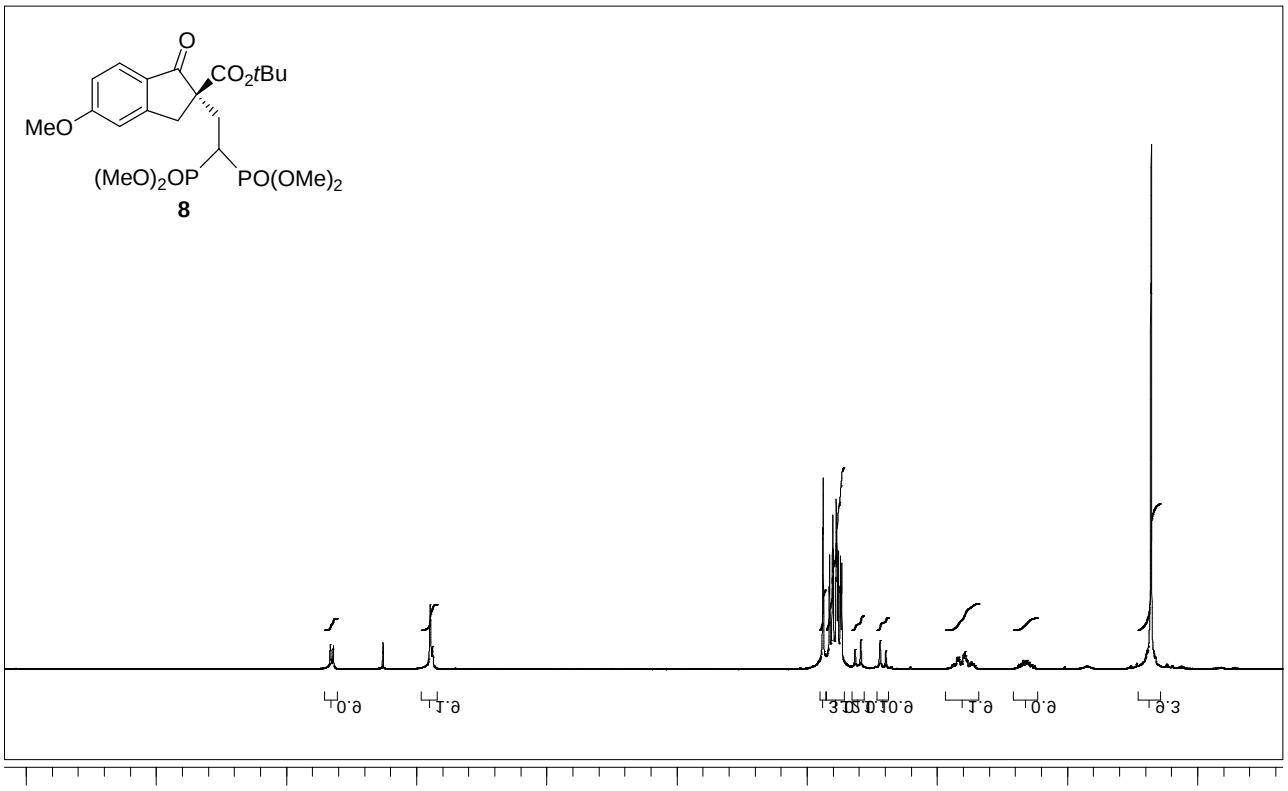

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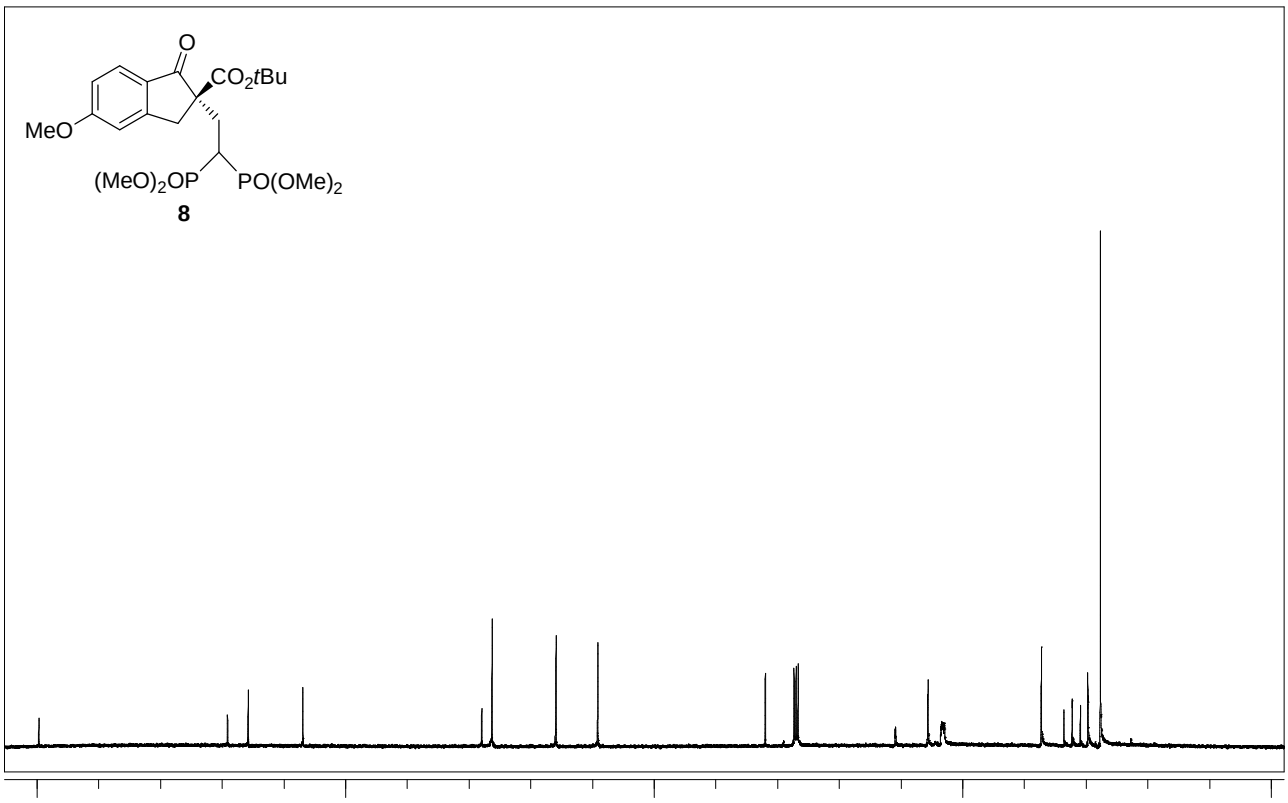
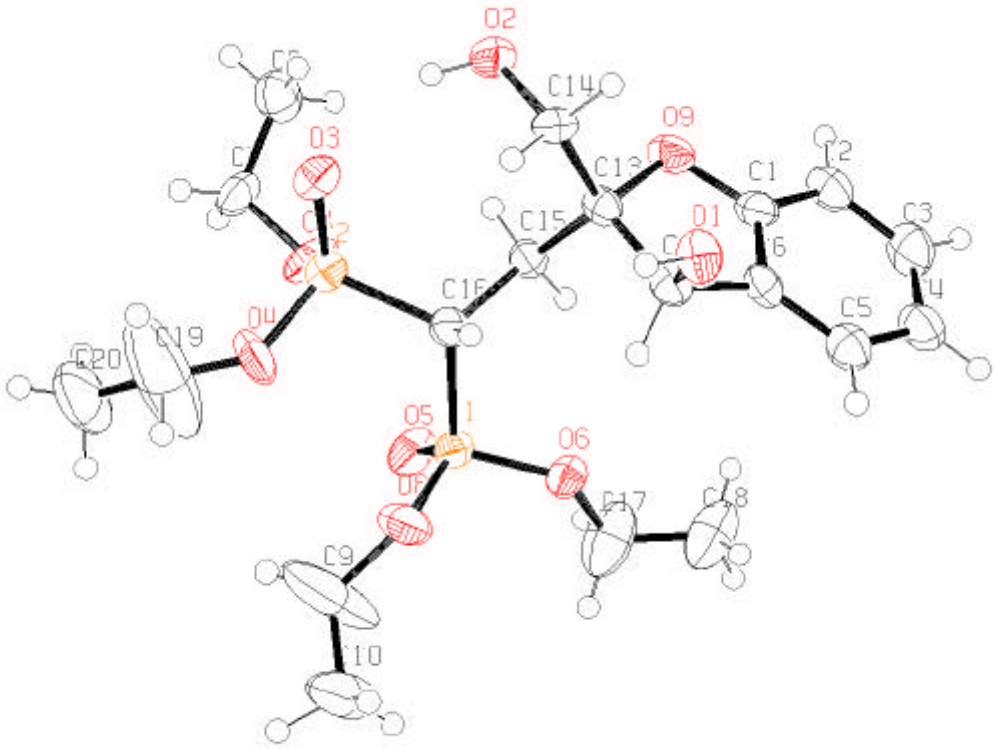


ORTEP of compound **4**


O2
C14
O9
O3
C13
C1
C12
C15
O1
C3
C16
C6
C4
C5
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C19
C20
O5
I1
O6
C17
C18
C9
C10