

Synthesis of Geminal Bisphosphonates via Organocatalyzed Enantioselective Michael Additions of Cyclic Ketones and 4-Piperidones

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Experimental Procedures

General procedures:

The reactions were performed under an argon atmosphere. The reagents were obtained from commercial suppliers and used without further purification. The synthesis and characterization of compounds **3a-c**, **6**, **9** and **10** has been previously described by us^[1]. The solvents used were purified by standard methods and distilled. For column chromatography, Merck silica gel 60 (230–400 mesh) or Mackerey-Nagel GmbH & Co silica gel was used. Thin layer chromatography was performed on silica gel plates Merck 60 F₂₅₄. Optical rotations were measured with an AA-1000 Polarimeter from Optical Activity Ltd, with 1 mL, 0.5 dm cells. NMR spectra were obtained with a Bruker AR X400 NMR spectrometer or a Bruker Avance 400 MHz spectrometer. Chemical shifts are relative to TMS. ³¹P NMR chemical shifts are relative to phosphoric acid, used as external standard. The multiplicity of signals in ¹³C NMR spectra was determined with DEPT experiments. When necessary, two-dimensional spectra (COSY 45, HMQC, HMBC, NOESY) and decoupling experiments were used to help with structural determinations. Mass spectra were recorded with a Micromass GCT spectrometer, operating in the electron impact mode, and were supplied by the Mass Spectrometry Services of the Chemistry Department/REQUIMTE, FCT, UNL. Elemental analyses were carried on a Thermo Finnigan Elemental Analyser 1112 series, by the Laboratory for External Services of CQFB-Lab Associado / REQUIMTE, of the Department of Chemistry, FCT, UNL. For HPLC analysis, a Merck Hitachi instrument equipped with a Chiralpak AD-H column from Daicel, and a Merck-Hitachi-4250 UV/Vis detector were used.

General procedure for the asymmetric Michael addition reaction: To vinyl *gem*-bisphosphonate (1.0 mmol) in dry dichloromethane (1.0 mL) was added the ketone (10.0 mmol), (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.1 mmol) and benzoic acid (0.1 mmol). The solution was stirred at room temperature, under argon, for the times specified. The reaction was then quenched with a concentrated solution of ammonium chloride, and the products were extracted with dichloromethane. The combined extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel. In some cases, as specified for each compound in the supporting information, the presence of benzoic acid in the crude product interfered with product isolation during chromatography. The work-up procedure was then modified to resolve this problem as follows: when the reaction was

complete, water was added, the mixture was treated with a saturated solution of NaHCO_3 and the product was extracted with dichloromethane. The organic phase was then washed successively with a 1 M HCl solution and with water, filtered through anhydrous Na_2SO_4 , and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel.

General procedure for the Michael addition reaction catalyzed by DBU: This procedure, used for the preparation of racemic standards, is a modification of the method described by Nugent *et al*^[2]. To vinyl *gem*-bisphosphonate (1.0 mmol) in dry dichloromethane (1.0 mL) was added the ketone (1.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.0 mmol). The solution was stirred at room temperature, under argon, for one hour. Water was then added, and the products were extracted with dichloromethane. The combined organic extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated off on a rotary evaporator to give the crude product, which was purified by column chromatography on silica gel.

Tetraethyl [2-(5'-ethyl-2'-oxocyclohexyl)ethylidene]bisphosphonate (3e): Prepared from ethylidene bisphosphonate **2** and 4-ethylcyclohexanone, according to the General procedure, modified to remove benzoic acid prior to chromatography. The product was obtained as a 70:30 (*trans/cis*) mixture of diastereoisomers as determined by ^{31}P NMR spectroscopy. The crude product was purified by column chromatography on silica gel with 2:3 acetone/ CHCl_3 to give product **3e** as an inseparable mixture of two diastereoisomers, in the form of a colourless viscous liquid (61 mg, 72%). δ_{H} (400 MHz; CDCl_3) 0.75–1.05 (m, $2 \times \text{CH}_3$), 1.14–1.40 (m, $4 \times \text{POCCH}_3$), 1.52–1.94 (m), 1.94–2.02 (m), 2.02–2.39 (m), 2.39–2.61 (tdd, J 5.4, 8.9, 23.8 Hz, PCH, major), 2.61–2.81 (tdd, J 4.5, 8.1, 24.0 Hz, PCH, minor), 2.81–3.00 (m), 4.00–4.25 (m, $4 \times \text{POCH}_2$) ppm; δ_{C} (100 MHz; CDCl_3) 11.57 (CH_3 , minor), 11.95 (CH_3 , major), 16.23 ($4 \times \text{POCCH}_3$, major + minor), 25.75 (CH_2 of Et, major), 25.94 (PCCH_2 , minor), 26.55 (PCCH_2 , major), 28.42 (CH_2 of Et, minor), 31.22 (CH_2 , C-4', major), 33.56 (CH_2 , C-4', minor), 33.66 (CHEt , minor), 33.85 (CH , d, J_{CP} 133.0 Hz, PCH, major + minor), 37.63 (CH_2 , C-6', major), 37.87 (CH_2 , C-3', major), 38.32 (CHEt , major), 40.43 (CH_2 , C-6', minor), 41.42 (CH_2 , C-3', minor), 45.06 (CH , C-1', major), 47.18 (CH , C-1', minor), 62.31–62.55 (CH_2 , $4 \times \text{POCH}_2$, major + minor), 213.0 (Cq, C=O, minor), 213.6 (Cq, C=O, major); δ_{P} (162 MHz; CDCl_3) 23.47 (minor), 23.53 (major), 24.09 (major), 24.17 (minor);

m/z 427 (M+1, 4), 426 (M⁺, 21), 397 (7), 381 (5), 302 (5), 301 (30), 290 (5), 289 (38), 288 (100), 273 (6), 261 (30), 260 (10), 244 (6), 243 (7), 233 (14), 215 (8), 204 (6), 177 (5), 165 (6), 159 (7), 152 (21), 138 (5), 109 (8), 105 (6), 97 (8), 96 (5), 95 (10), 83 (7), 82 (6), 81 (14), 72 (5), 71 (5), 70 (5), 69 (10), 67 (7), 59 (6), 57 (7), 56 (5), 55 (13), 45 (5) (Found C, 50.45; H, 8.75. Calcd for C₁₈H₃₆O₇P₂: C, 50.70; H, 8.51). The enantiomeric excesses were determined by HPLC on a chiral column after conversion of the diastereoisomers into their 2,4-dinitrophenylhydrazones, (Chiralpak AD-H, 25% *i*-PrOH in hexane, 1.0 mL min⁻¹, 365 nm): t_R = 9.00 (*cis*, major), 12.6 (*trans*, major), 14.0 (*trans*, minor), 15.8 (*cis*, minor) min, relative to the racemic sample prepared with DBU as base.

Tetraethyl [2-(8'-oxo-1',4'-dioxaspiro[4.5]dec-7'-yl)-ethane-1,1-diyl]bisphosphonate (3f): Prepared from ethylidene bisphosphonate **2** and 1,4-cyclohexanedione monoethylene acetal, according to the General procedure, but the ratio of ketone to bisphosphonate used was only 4:1. The crude product was purified by chromatography on silica gel with 2:1 EtOAc/hexane, followed by 1:1 acetone/CHCl₃ to give product **3f** in the form of a white solid (29 mg, 62%). δ_H (400 MHz; CDCl₃) 1.17–1.50 (m, 8 H, POCH₂), 1.56–1.77 (m + t, J 13.0 Hz, 2 H, PCCH + H-6'), 1.95 (td, J 5.0, 13.5 Hz, 1 H, H-10'), 2.00–2.06 (m, 1 H, H-10'), 2.11 (ddd, J 3.5, 5.6, 12.9 Hz, 1 H, H-6'), 2.25–2.50 (ddd + m, J 3.0, 5.0, 13.9 Hz, H-9' + PCCH), 2.56–2.85 (m, 2 H, PCH + H-3'), 3.20–3.35 (m, 1 H, C-7'), 3.94–4.10 (m, 4 H, 2 × acetal-CH₂), 4.10–4.36 (m, 8 H, POCH₂); δ_C (100 MHz; CDCl₃) 16.34 (4 × CH₃), 25.80 (CH₂, PCCH₂), 34.10 (CH, J 130.5 Hz, PCHP), 34.94 (CH₂, C-10'), 38.31 (CH₂, C-9'), 41.41 (CH₂, C-6'), 44.36 (CH, C-7'), 62.70 (CH₂, m, 4 × OCH₂), 64.58 (CH₂, acetal-CH₂), 64.78 (CH₂, acetal-CH₂), 107.2 (Cq, acetal), 211.3 (Cq, C=O); δ_P (162 MHz; CDCl₃) 23.39, 24.07; m/z 457 (M+1, 5), 456 (M⁺, 23), 412 (5), 411 (26), 410 (8), 399 (5), 319 (8), 301 (19), 288 (22), 281 (11), 273 (7), 264 (7), 261 (16), 233 (11), 220 (6), 205 (5), 192 (5), 178 (5), 169 (8), 167 (6), 166 (5), 165 (7), 164 (5), 159 (5), 154 (6), 152 (12), 151 (6), 150 (8), 149 (13), 140 (6), 138 (7), 137 (9), 136 (18), 135 (5), 128 (10), 126 (15), 125 (7), 124 (9), 105 (5), 101 (5), 100 (13), 99 (21), 98 (20), 97 (27), 96 (16), 95 (19), 94 (7), 93 (7), 91 (7), 86 (16), 85 (7), 84 (13), 83 (30), 82 (14), 81 (24), 80 (6), 79 (12), 77 (5), 73 (11), 72 (13), 71 (13), 70 (15), 69 (40), 68 (11), 67 (26), 60 (11), 59 (100), 57 (28), 56 (17), 55 (61), 54 (15), 53 (8) (Found C, 47.11; H, 7.72. Calcd for C₁₈H₃₄O₉P₂: C, 47.37; H, 7.51). The enantiomeric excesses were determined by HPLC on a chiral column after conversion of the diastereoisomers into their 2,4-dinitrophenylhydrazones, (Chiralpak AD-H, 25% *i*-PrOH in hexane, 1.0 mL min⁻¹, 365

nm): t_R = 15.2 (major), 17.2 (minor), relative to the racemic sample prepared with DBU as base.

Tetraethyl [2-(2',3'-dihydro-1'-oxo-indene-2'-yl)ethylidene]bisphosphonate (12): Prepared from ethylidene bisphosphonate **2** and 1-indanone, according to the General procedure. However, a concentration of phosphonate of 0.5 mmol / mL was used, and the reaction mixture was refluxed for 46 h. The crude product, which consisted of a 92:8 mixture of 2-mono to 2,2-disubstituted 1-indanone as determined by ^1H NMR spectroscopy, was purified by column chromatography on silica gel with 2:1 acetone/toluene or on neutral alumina with 1:100 *i*PrOH/ CHCl_3 , to give the product **12** in the form of a colourless oil (60 mg, 81%). δ_{H} (400 MHz; CDCl_3) 1.20–1.35 (m, 12 H, CH_3 of POEt), 1.90–2.11 (m, 1 H, PCCH), 2.25–2.50 (m, 1 H, PCCH), 2.72 (dd, 1 H, J 3.8, 17.0 Hz, ring CHH), 2.94 (tt, 1 H, J 6.3, 24.0 Hz, PCH), 3.09–3.20 (m, 1 H, ring CH), 3.35 (dd, 1 H, J 7.8, 17.0 Hz, ring CHH), 4.06–4.23 (m, 8 H, CH_2 of POEt), 7.30 (t, 1 H, J 7.4 Hz, H-6'), 7.38 (d, 1 H, J 7.6 Hz, H-4'), 7.52 (t, 1 H, J 7.2 Hz, H-5'), 7.67 (d, J 7.6 Hz, H-7'); δ_{C} (100 MHz; CDCl_3) 16.36 ($4 \times \text{CH}_3$ of POEt), 27.62 (CH_2 , $2 \times \text{PCCH}_2$), 33.18 (CH_2 , ring- CH_2), 34.13 (CH, t, J_{CP} 133.1 Hz, PCH), 45.26 (CH, t, J_{CP} 6.4 Hz, ring-CH), 62.61 (CH_2 , d, J_{CP} 6.2 Hz, $4 \times \text{CH}_2$ of POEt), 123.9 (CH, C-6'), 126.5 (CH, C-4'), 127.5 (CH, C-7'), 134.8 (CH, C-5'), 136.5 (Cq, C-7'a), 153.1 (Cq, C-3'a), 207.8 (Cq, C=O); δ_{P} (162 MHz; CDCl_3) 23.40, 23.83; m/z 433 ($\text{M}+1$, 3), 432 (M^+ , 14), 301 (40), 295 (67), 288 (100), 261 (44), 248 (19), 233 (27), 221 (26), 205 (14), 202 (16), 159 (19), 152 (43), 145 (25), 124 (19), 115 (44), 109 (19), 57 (10) (Found C, 52.62; H, 6.83. Calcd for $\text{C}_{19}\text{H}_{30}\text{O}_7\text{P}_2$: C, 52.77; H, 6.70). The enantiomeric excesses were determined by HPLC on a chiral column (Chiralpak AD-H, 6% *i*-PrOH in hexane, 1.1 mL min^{-1} , 254 nm): t_R = 43.8, 47.2. The proton NMR data of this compound corresponds to that described previously in ref. 2.

Octaethyl [(2',3'-dihydro-1'-oxo-inden-2',2'-diyl)diethane-2,1,1-triyl]tetrakisphosphonate (13): The title compound was prepared via the reaction of ethylidene bisphosphonate **2** and 1-indanone according to the General procedure using DBU catalysis. The crude product, which consisted of a 1:2 mixture of monosubstituted : disubstituted 2-indanone as determined by ^1H NMR spectroscopy, was purified by chromatography on silica gel, with 1:1 CHCl_3 /acetone. Disubstituted 1-indanone **13** (20.3 mg) and monosubstituted 1-indanone **12** (14.0 mg) were obtained from the reaction of 27 mg of 1-

indanone with 61 mg of bisphosphonate. δ_{H} (400 MHz; CDCl_3) 1.00–1.50 (m, 24 H, 8 \times CH_3), 2.26–2.50 (m, 6 H, 2 \times PCCH_2 + 2 \times PCH), 3.45 (s, 2 H, ring CH_2), 4.00–4.32 (m, 8 H, POCH_2), 7.35 (t, J 7.2 Hz, H-6'), 7.44 (d, J 7.3 Hz, H-4'), 7.58 (t, J 7.2 Hz, H-5'), 7.71 (d, J 7.5 Hz, H-7'); δ_{C} (100 MHz; CDCl_3) 16.27 (m, 8 \times CH_3), 31.49 (CH_2 , 4 \times PCCH_2), 32.57 (CH , J_{CP} 132.4 Hz, 2 \times PCH), 35.58 (CH_2 , ring CH_2), 52.08 (CH , ring CH), 62.72 (m, CH_2 , 4 \times OCH_2), 124.0 (CH , C-6'), 126.4 (CH , C-4'), 127.4 (CH , C-7'), 135.0 (CH , C-5'), 137.0 (Cq, C-7'a), 153.3 (Cq, C-3'a), 207.4 (Cq, C=O); δ_{P} (162 MHz; CDCl_3) 23.97, 24.67; m/z 732 (M^+ , 0.1), 687 (0.2), 595 (0.3), 445 (5), 444 (4), 432 (19), 431 (4), 301 (13), 295 (16), 288 (29), 261 (12), 245 (11), 221 (10), 217 (15), 189 (12), 171 (29), 164 (12), 163 (20), 158 (11), 152 (12), 145 (11), 144 (60), 137 (13), 136 (13), 135 (16), 116 (57), 115 (100), 109 (17), 89 (15), 81 (11), 63 (11), 45 (23) (Found C, 47.50; H, 7.18. Calcd for $\text{C}_{29}\text{H}_{52}\text{O}_{13}\text{P}_4$: C, 47.54; H, 7.16).

Tetraethyl [2-(2,3-dihydro-2-oxo-inden-1-yl)ethylidene]bisphosphonate (15): Prepared from ethylidene bisphosphonate **2** (0.533 mmol) and 2-indanone (1.52 mmol), according to the General procedure modified to remove benzoic acid prior to chromatography. The crude product, which consisted of a 70:30 monosubstituted to disubstituted 2-indanone mixture as determined by ^1H NMR spectroscopy, was purified by column chromatography on silica gel with 3:2 acetone/ CHCl_3 , to give the product **15** (102 mg, 44%) as a colourless oil, approx. 90% pure. δ_{H} (400 MHz; CDCl_3) 1.20–1.40 (m, 12 H, 4 \times OCCH_3), 2.13–2.40 (m, 2 H, PCCH_2), 3.26 (tdd, J 3.2, 8.8, 27.2 Hz, 1 H, PCH), 3.54 (s, 2 H, ring- CH_2), 3.82–3.95 (m, 1 H, PCCH), 4.13–4.28 (m, 8 H, 4 \times OCH_2), 7.20–7.40 (m, 4 H, 4 \times Ar-H); δ_{P} (162 MHz; CDCl_3) 23.30, 23.91.

Octaethyl [(2,3-dihydro-2-oxo-inden-1,1-diyl)diethane-2,1,1-triyl]tetrakisphosphonate (16): To vinyl *gem*-bisphosphonate **2** (0.13 mmol) in dry dichloromethane (0.6 mL) was added 2-indanone (0.13 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 mmol). The solution was stirred for 2 h in an ice bath, under argon. Water was then added, and the products were extracted with dichloromethane. The combined organic extracts were dried with anhydrous sodium sulfate, and the solvent was evaporated off on a rotary evaporator. The crude product, which consisted of a 12:82 monosubstituted to disubstituted 2-indanone mixture as determined by ^1H NMR spectroscopy, was purified by column chromatography on silica gel with 2:1 acetone/ CHCl_3 , to give the product **16** as an oil (11 mg, 22%). δ_{H} (400

MHz; CDCl₃) 0.93–1.47 (m, 24 H, 8 × CH₃), 2.32–2.65 (m, 6 H, 2 × PCH + 2 × PCCH₂), 3.59 (s, 2 H, ring CH₂), 3.93–4.29 (m, 16 H, 8 × OCH₂), 7.26–7.32 (m, 4 H, Ar-H); δ_C (100 MHz; CDCl₃) 16.29 (8 × CH₃), 32.38 (t, *J*_{CP} 133.2 Hz, 2 × PCHP), 33.09 (CH₂, 2 × PCCH₂), 42.85 (CH₂, ring CH₂), 56.17 (Cq), 62.54–62.69 (m, 8 × OCH₂), 125.1 (2 × CH, C-5 and C-6), 127.1 (CH, C-7), 127.8 (CH, C-4), 137.9 (Cq, C-3a), 142.7 (Cq, C-7a), 215.5 (Cq, C=O); δ_P (162 MHz; CDCl₃) 23.51, 24.56; *m/z* 734 (M+2, 1), 733 (M+1, 9), 732 (M⁺, 28), 432 (43), 386 (11), 301 (28), 288 (37), 273 (18), 261 (25), 260 (12), 249 (12), 245 (22), 233 (24), 221 (17), 220 (13), 217 (27), 205 (19), 199 (14), 192 (15), 189 (21), 177 (15), 171 (51), 165 (12), 164 (26), 163 (43), 159 (18), 153 (12), 152 (28), 145 (11), 144 (53), 137 (23), 136 (26), 135 (33), 129 (15), 128 (13), 127 (10), 125 (14), 116 (56), 115 (100), 109 (30), 107 (13), 102 (16), 99 (15), 91 (11), 89 (14), 82 (10), 81 (20), 65 (17), 63 (12), 45 (15).

Tetraethyl [2-(1'-methyl-4'-oxopiperidin-3'-yl)ethane-1,1-diyl]bisphosphonate (18a): Prepared from ethylidene bisphosphonate **2** and 1-methyl-4-piperidone **17a**, according to the General procedure, but the reaction was quenched with water only. The crude product was then purified by preparative chromatography on silica gel with 3:1 MeOH/EtOAc to give product **18a** in the form of a colourless viscous liquid (84 mg, 58%). δ_H (400 MHz; CDCl₃) 1.22–1.47 (m, 12 H, 4 × CH₃, POCCH₃), 1.60–1.78 (m, 1 H, PCCH), 2.10 (t, 1 H, *J* 10.8 Hz, H-2'), 2.27–2.50 (m + s, 6 H, PCCH + H-5' + H-6' + N-CH₃), 2.62–2.79 (m, 2 H, H-5' + PCH), 2.98–3.22 (m, 3 H, H-2' + H-3' + H-6'), 4.08–4.33 (m, 8 H, POCH₂); δ_C (100 MHz; CDCl₃) 16.34 (CH₃, 4 × CH₃, POCCH₃), 23.72 (CH₂, PCCH₂), 34.08 (CH, t, *J*_{CP} 133.9 Hz, PCH), 41.06 (CH₂, C-5'), 45.10 (CH₃, N-CH₃), 47.47 (CH₂, PCCH), 56.19 (CH₂, C-6'), 61.68 (CH₂, C-2'), 62.49–62.73 (m, 4 × CH₂, POCH₂), 210.0 (Cq, C=O); δ_P (162 MHz; CDCl₃) 23.31, 23.80; *m/z* 414 (M⁺ + 1, 1), 413 (M⁺, 4), 395 (17), 325 (7), 302 (15), 301 (10), 288 (5), 276 (7), 275 (5), 274 (6), 273 (5), 261 (8), 259 (8), 258 (64), 245 (10), 233 (9), 217 (7), 215 (5), 205 (6), 188 (5), 177 (6), 171 (8), 166 (12), 165 (74), 163 (6), 161 (9), 159 (9), 153 (5), 152 (7), 138 (11), 137 (15), 136 (7), 135 (7), 127 (7), 126 (100), 125 (6), 124 (19), 113 (10), 112 (41), 111 (8), 110 (12), 109 (14), 99 (5), 96 (5), 95 (5), 94 (14), 83 (6), 82 (7), 70 (7), 55 (9), 45 (6) (Found C, 44.92; H, 8.02; N, 3.17. Calcd for C₁₆H₃₃NO₇P₂: C, 46.49; H, 8.05; N, 3.39). The enantiomeric excesses were determined by HPLC on a chiral column (Chiralpak AD-H, *i*-PrOH : hexane : DEA 100/10/0.1, 1.0 mL min⁻¹, 254 nm): *t*_R = 18.8 (minor), 20.6 (major) min, relative to the racemic sample prepared with DBU as base.

Tetraethyl [2-(1'-benzyl-4'-oxopiperidin-3'-yl)ethane-1,1-diyl]bisphosphonate (18b): Prepared from ethylidene bisphosphonate **2** and 1-benzyl-4-piperidone **17b**, according to the General procedure. The crude product was then purified by chromatography on silica gel with 1:1 CHCl₃/acetone to give the product **18b** in the form of a colourless viscous liquid (46 mg, 61%). δ_{H} (400 MHz; CDCl₃) 1.23–1.33 (m, 12 H, 4 × CH₃), 1.53–1.75 (m, 1 H, PCCH), 2.12 (t, 1 H, *J* 10.4 Hz, H-2'), 2.19–2.50 (m, 3 H, PCCH + H-5' + H-6'), 2.50–2.72 (m, 2 H, PCHP + H-5'), 2.94–3.19 (m, 3 H, H-3' + H-6' + H-2'), 3.57 (d, AB system, 1 H, *J* 13.2 Hz, CH₂Ph), 3.61 (d, AB system, 1 H, *J* 13.2 Hz, CH₂Ph), 4.00–4.25 (m, 8 H, 4 × OCH₂), 7.14–7.41 (m, 5 H, Ph-H); δ_{C} (100 MHz; CDCl₃) 16.31 (4 × CH₃), 23.77 (CH₂, PCCH₂), 34.01 (CH, t, *J*_{CP} 132.8 Hz, PCHP), 41.09 (CH₂, C-5'), 47.65 (CH, C-3'), 53.58 (CH₂, C-6'), 59.61 (CH₂, C-2'), 61.49 (CH₂, CH₂Ph), 62.43–62.65 (CH₂, m, 4 × OCH₂), 127.3 (CH, *p*CH-Ar), 128.3 (CH, 2 × CH-Ar), 128.8 (CH, 2 × CH-Ar), 138.0 (Cq, Ar), 210.4 (Cq, C=O); δ_{P} (162 MHz; CDCl₃) 23.35, 23.91; *m/z* 489 (M⁺, 1), 399 (9), 398 (66), 353 (6), 352 (43), 334 (16), 325 (5), 302 (6), 261 (6), 245 (10), 233 (9), 215 (5), 205 (5), 202 (14), 189 (13), 188 (32), 177 (7), 171 (8), 165 (16), 159 (9), 137 (5), 119 (5), 109 (8), 107 (10), 106 (18), 104 (7), 92 (11), 91 (100), 79 (6), 77 (8), 65 (8) (Found C, 53.73; H, 7.80; N, 2.84. Calcd for C₂₂H₃₇NO₇P₂: C, 53.98; H, 7.62; N, 2.87). The enantiomeric excesses were determined by HPLC on a chiral column (Chiralpak AD-H, 18% *i*-PrOH in hexane, 1.0 mL min⁻¹, 254 nm): *t*_R = 8.0 (minor), 8.6 (major) min, relative to the racemic sample prepared with DBU as base.

Tetraethyl [2-(4'-oxotetrahydro-2*H*-pyran-3'-yl)ethane-1,1-diyl]bisphosphonate (20): Prepared from ethylidene bisphosphonate **2** and tetrahydropyran-4-one **19**, according to the General procedure modified to remove benzoic acid prior to chromatography. The crude product was purified by column chromatography on silica gel with 2:1 CHCl₃/acetone to give the product **20** in the form of a colourless liquid (104 mg, 88%). δ_{H} (400 MHz; CDCl₃) 1.26–1.40 (m, 12 H, 4 × CH₃), 1.55–1.62 (m, 1 H, PCCH), 2.23–2.43 (m, 2 H, H-5' + PCCH), 2.56–2.78 (m, 2 H, PCH + H-5'), 3.10–3.25 (m, 1 H, H-3'), 3.33 (t, 1 H, *J* 10.6 Hz, H-2'), 3.69 (td, 1 H, *J* 2.8, 11.3 Hz, H-6'), 4.08–4.28 (m, 10 H, 4 × OCH₂CH₃ + H-2' + H-6'); δ_{C} (100 MHz; CDCl₃) 16.27 (4 × CH₃), 21.89 (CH₂, PCCH₂), 33.97 (t, CH, *J*_{CP} 134.1 Hz, PCP), 42.66 (CH₂, C-5'), 49.53 (CH, d, *J*_{CP} 5.6 Hz, C-3'), 62.62 (m, 4 × OCH₂CH₃), 68.78 (CH₂, C-6'), 72.84 (CH₂, C-2'), 208.0 (Cq, C=O); δ_{P} (162 MHz; CDCl₃) 23.13, 23.61; *m/z* 401 (M+1, 2), 400 (M⁺, 14), 355 (5), 344 (11), 302 (25), 301 (64), 289 (10), 288 (100), 273 (19), 263 (37), 261 (53), 260 (14), 245 (45), 235 (23), 233 (38), 217 (18), 214 (12), 207 (13),

205 (18), 199 (10), 191 (15), 189 (10), 177 (12), 171 (10), 165 (37), 163 (10), 161 (24), 159 (20), 152 (41), 137 (10), 135 (24), 133 (10), 125 (12), 109 (26), 99 (19), 91 (12), 81 (14), 65 (11) (Found C, 44.77; H, 7.76. Calcd for C₁₅H₃₀O₈P₂: C, 45.00; H, 7.55). The enantiomeric excess was determined by ¹³C NMR analysis of the diastereoisomers obtained after reaction with optically pure (*S,S*)-2,3-butanediol in the presence of *p*-TsOH^[3]. Hence, for tetraethyl [2-(2',3'-dimethyl-1',4',8'-trioxa-spiro[4',5']dec-6'-yl)-ethane-1,1-diyl]bisphosphonate (21), major diastereoisomer: δ_C (100 MHz; CDCl₃) 16.40 (POCCH₃), 17.57 (C_qOCCH₃), 21.58 (PCCH₂), 35.03 (PCH), 36.77 (C-10'), 42.78 (C-6'), 62.45–62.53 (4 × POCH₂), 65.87 (C-9'), 69.08 (C-7'), 77.69 (C-2' or C-3'), 79.00 (C-2' or C-3'), 107.20 (C_q); minor diastereoisomer: 16.20 (POCCH₃), 17.73 (C_qOCCH₃), 21.41 (PCCH₂), 33.70 (PCH), 36.41 (C-10'), 43.50 (C-6'), 62.45–62.53 (4 × POCH₂), 65.97 (C-9'), 69.02 (C-7'), 78.09 (C-2' or C-3'), 78.87 (C-2' or C-3'), 107.22 (C_q).

General procedure for the synthesis of 2,4-dinitrophenylhydrazine adducts^[4]: The bisphosphonate (0.20 mmol) was dissolved in ethanol (1.0 mL) and 2,4-dinitrophenylhydrazine (0.20 mmol) was added, followed by a catalytic amount of *para*-toluenesulfonic acid. The mixture was stirred at room temperature for 17 h. An aqueous saturated solution of sodium bicarbonate was added, and the compound was extracted with dichloromethane. The combined organic extracts were washed with water, filtered through anhydrous sodium sulfate, and the solvent was then removed in a rotary evaporator, to give a yellow-orange solid.

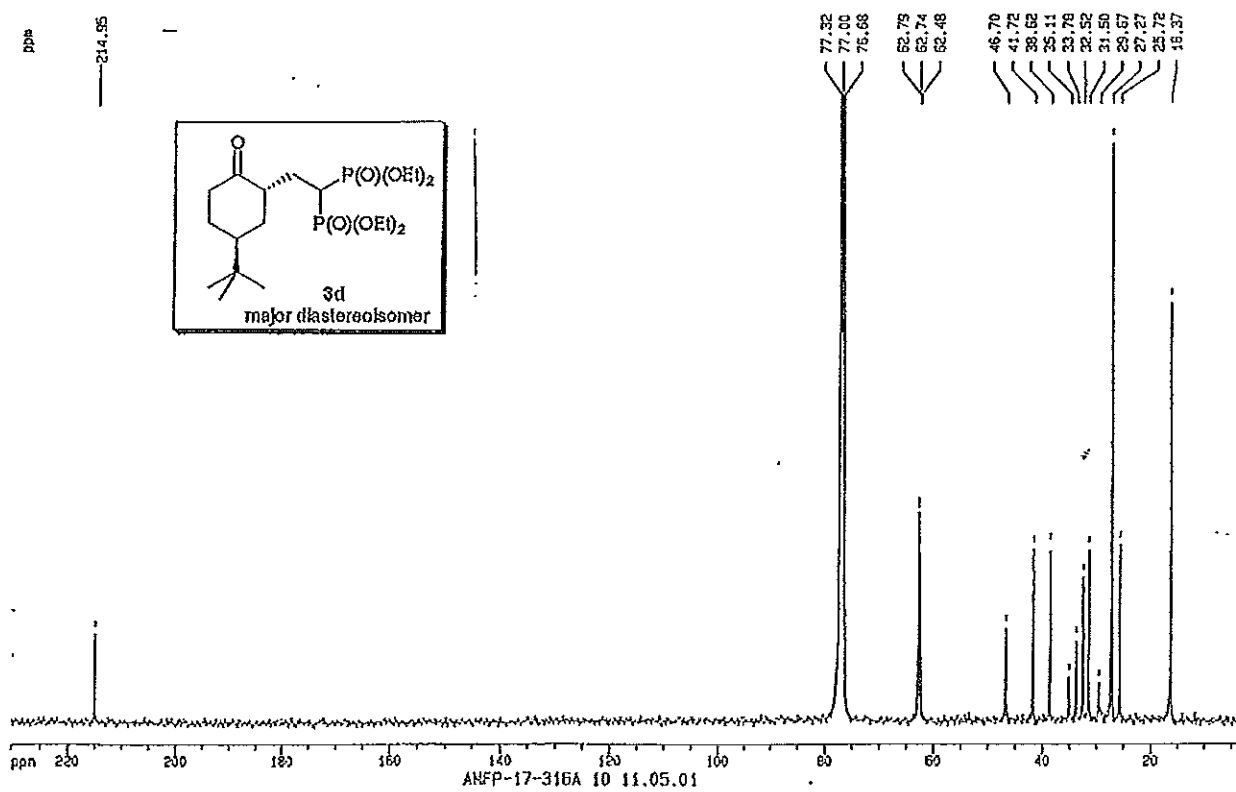
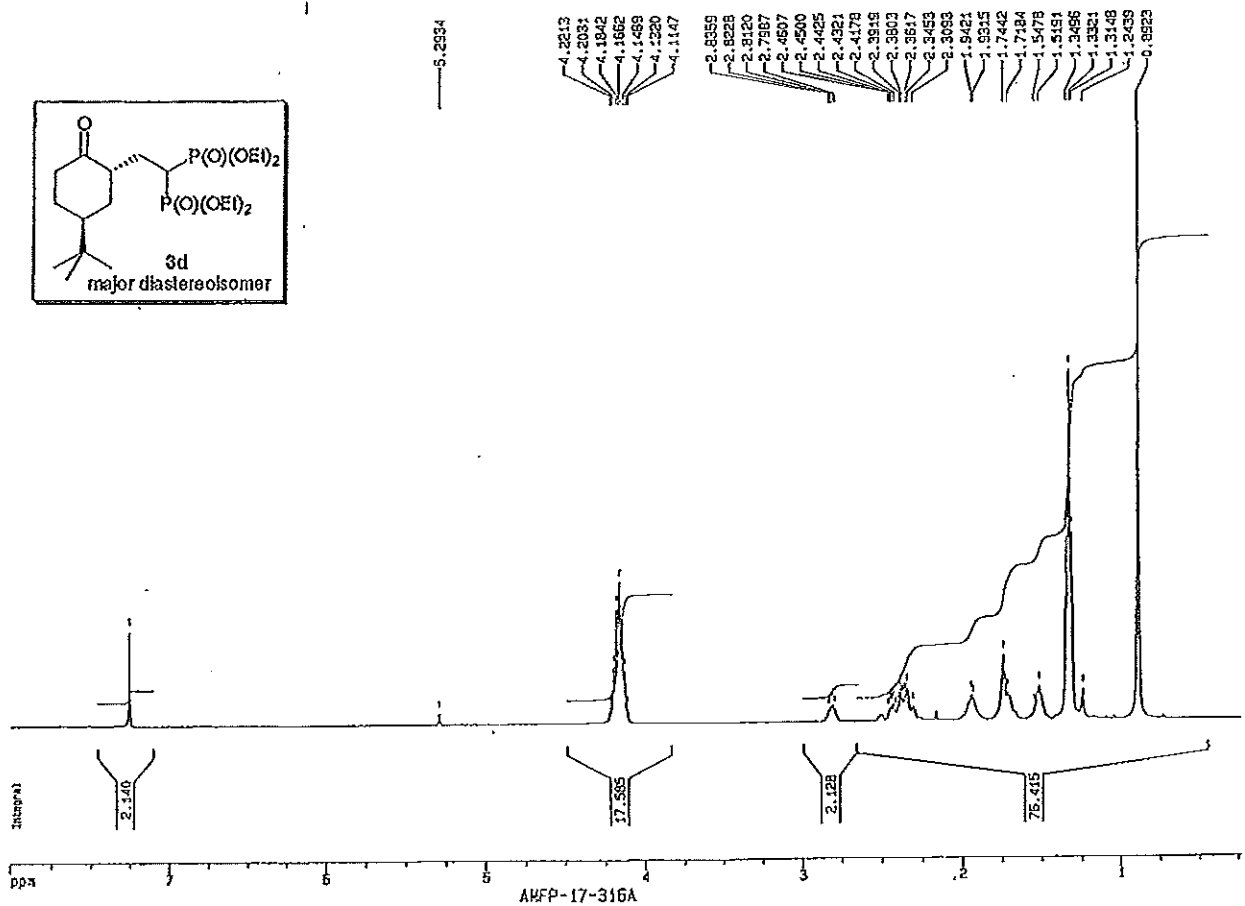
Dinitrophenylhydrazine adduct of tetraethyl [2-(8'-oxo-1',4'-dioxo-spiro[4.5]dec-7'-yl)-ethane-1,1-diyl]bisphosphonate (7b): Prepared from 3f and dinitrophenylhydrazine according to the general procedure. The crude product was purified by preparative TLC on silica gel with EtOAc/acetone 1:1 as eluent to give 7b as a yellow hygroscopic solid (18 mg, 67%). δ_H (400 MHz; CDCl₃) 1.35 (t, 12 H, *J* 6.0 Hz, 4 × POCCH₃), 1.64 (t, *J* 12.3 Hz, 1 H, H-6'), 1.81 (td, *J* 4.9, 12.9 Hz, 1 H, H-10'), 1.88–2.17 (m, 3 H, PCCH, H-10', H-6'), 2.41 (ddd, *J* 5.2, 11.6, 14.7 Hz, 1 H, H-9'), 2.60–2.96 (superimp. dt + m, *J* 4.7, 14.6 Hz, H-9', PCHP, PCCH), 3.21–3.38 (m, 1 H, PCCCH), 4.00–4.01 (m, 4 H, 4 × acetal-H), 4.12–4.33 (m, 8 H, 4 × POCH₂), 8.18 (d, 1 H, *J* = 9.6 Hz, H-6'', Ar), 8.31 (d, 1 H, *J* = 9.62 Hz, H-5'', Ar), 9.13 (d, 1 H, *J* = 2 Hz, H-3'', Ar), 11.27 (s, 1 H, N-NH); δ_C (100 MHz; CDCl₃) 16.45 (CH₃, 4 × POCCH₃), 23.72 (CH₂, C-9'), 27.21 (CH₂, PCCH₂), 33.82 (CH₂, C-10'), 34.51 (d, CH, *J*_{CP} 133.9 Hz, PCH), 39.76 (CH, PCCCH), 42.01 (CH₂, C-6'), 62.43–62.75 (CH₂, 4 × POCH₂),

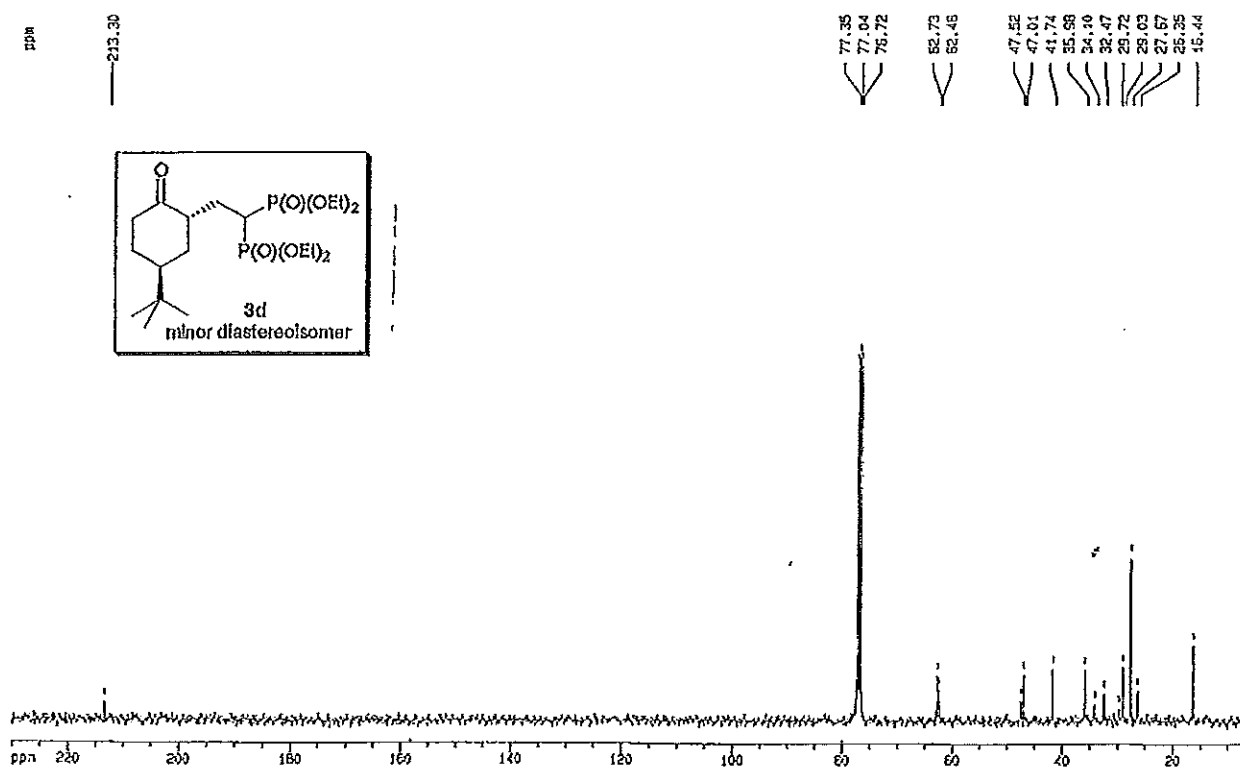
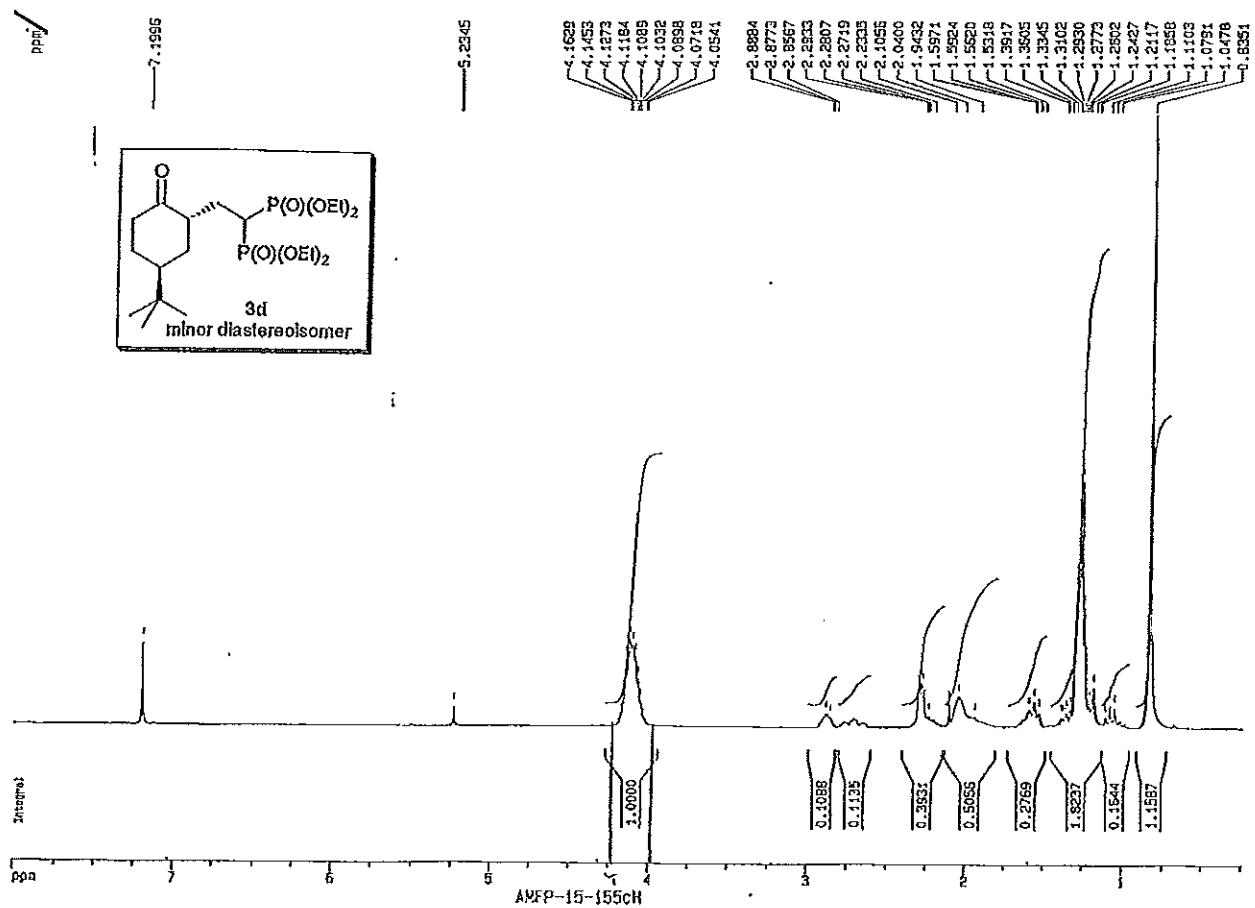
64.58 (CH₂, acetal CH₂), 64.78 (CH₂, acetal CH₂), 107.4 (Cq, O-C-O), 116.8 (CH, C-6'', Ar), 123.5 (CH, C-3'', Ar), 129.1 (Cq, C-2'', Ar), 130.1 (CH, C-5'', Ar), 137.9 (Cq, C-4'', Ar), 145.5 (Cq, C-1'', Ar), 159.8 (C=N); δ_p (162 MHz; CDCl₃) 24.26, 24.40; m/z 636 (M⁺, 20), 601 (66), 454 (33), 437 (53), 409 (35), 408 (38), 363 (35), 301 (67), 299 (79), 288 (59), 273 (34), 261 (57), 245 (35), 233 (44), 217 (36), 205 (39), 202 (50), 189 (37), 177 (34), 170 (66), 166 (34), 165 (82), 164 (40), 163 (52), 159 (31), 153 (44), 152 (66), 137 (54), 136 (32), 135 (53), 134 (37), 125 (31), 123 (44), 122 (46), 119 (37), 110 (30), 109 (79), 108 (41), 107 (50), 106 (32), 105 (49), 100 (41), 99 (87), 98 (30), 97 (54), 96 (41), 95 (63), 94 (41), 93 (35), 92 (31), 91 (65), 86 (53), 83 (69), 82 (66), 81 (61), 80 (45), 79 (65), 78 (30), 77 (50), 76 (34), 72 (37), 71 (31), 70 (30), 69 (75), 68 (30), 67 (63), 65 (32), 59 (54), 57 (69), 56 (40), 55 (100), 54 (46), 53 (37), 45 (60).

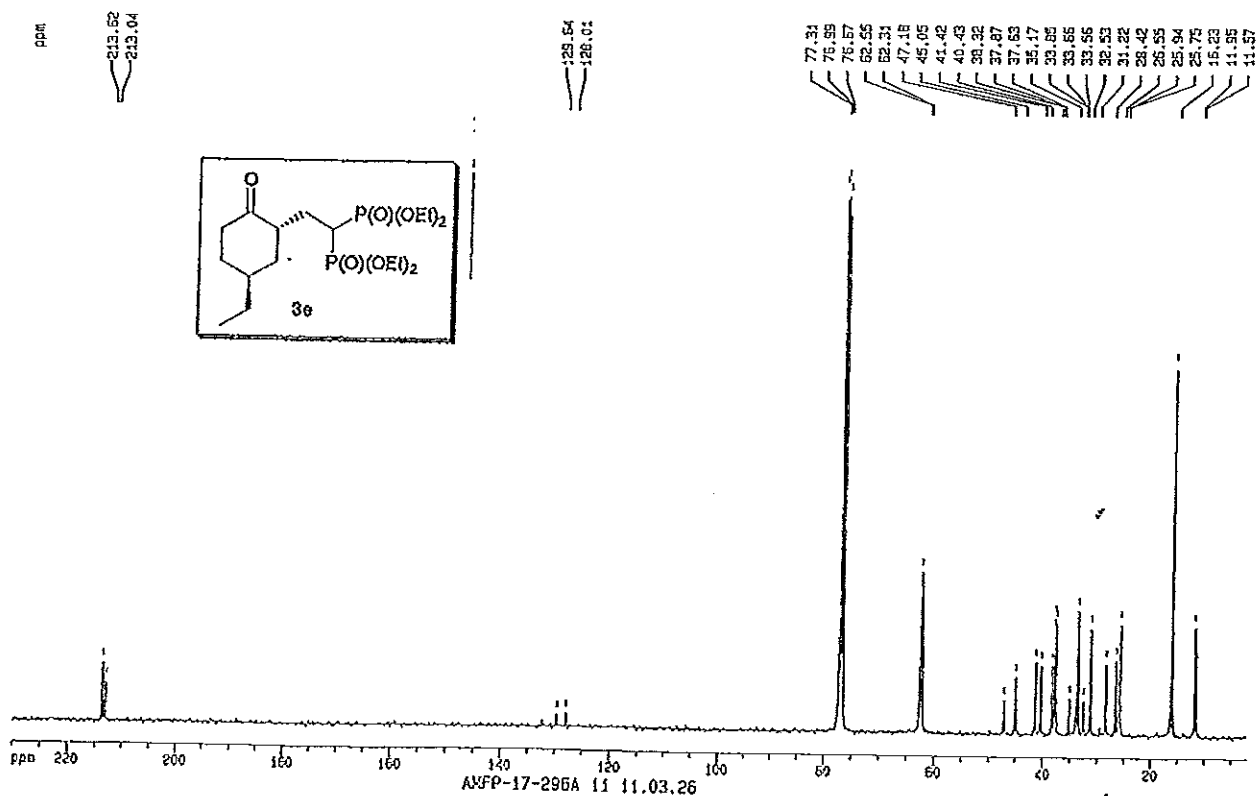
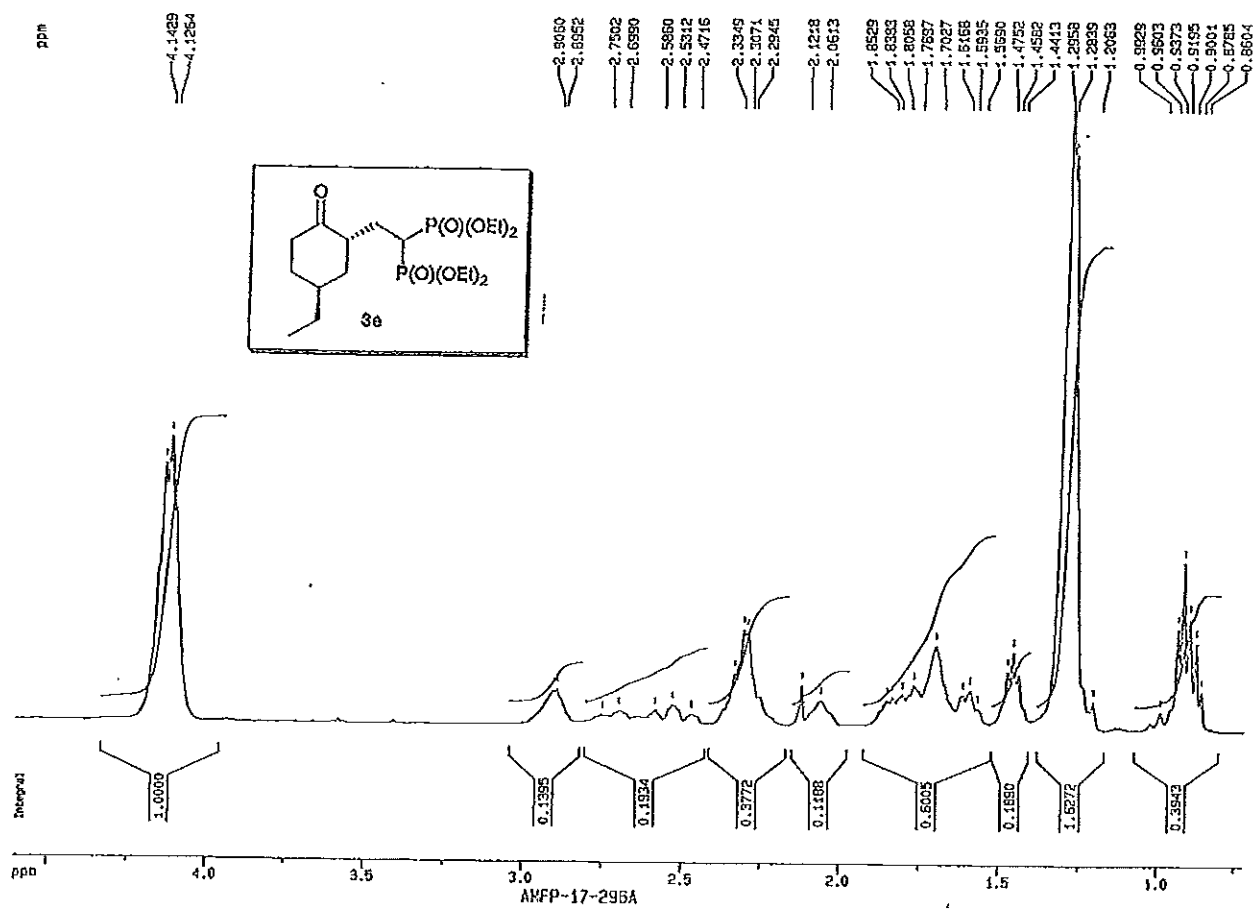
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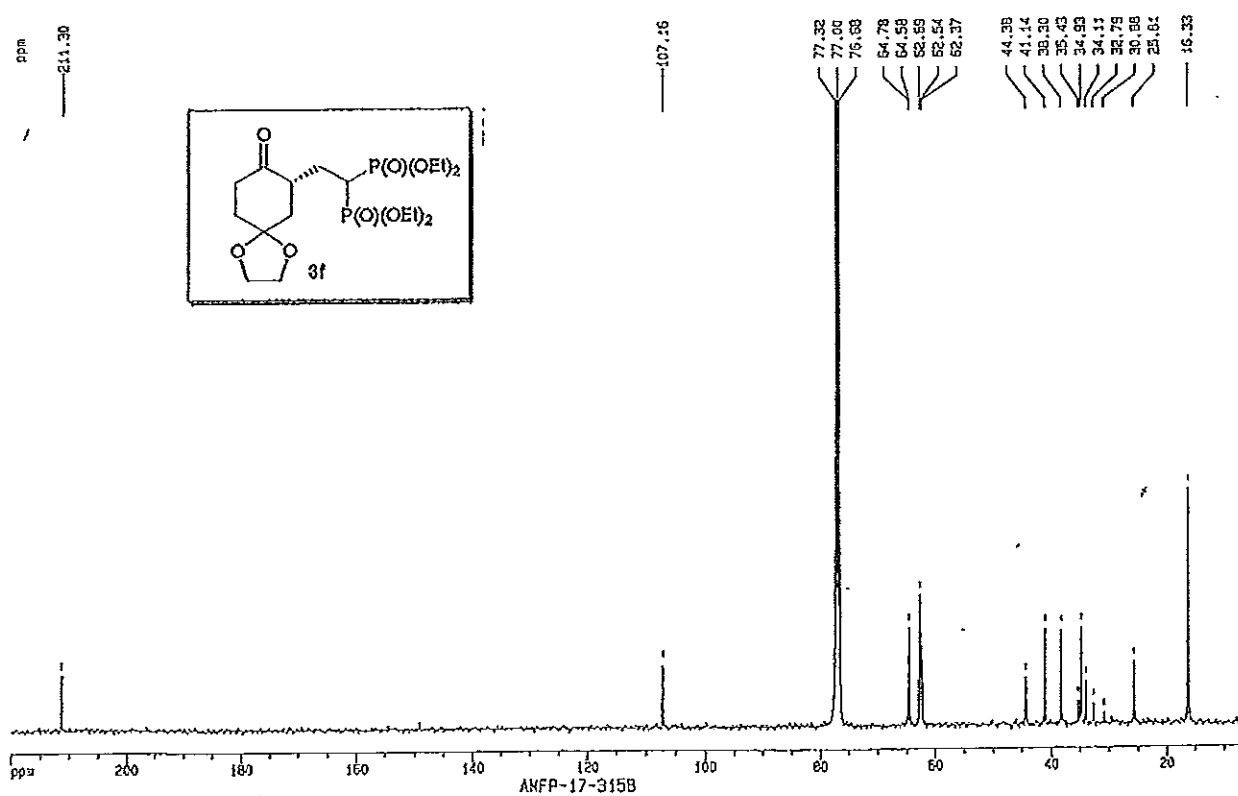
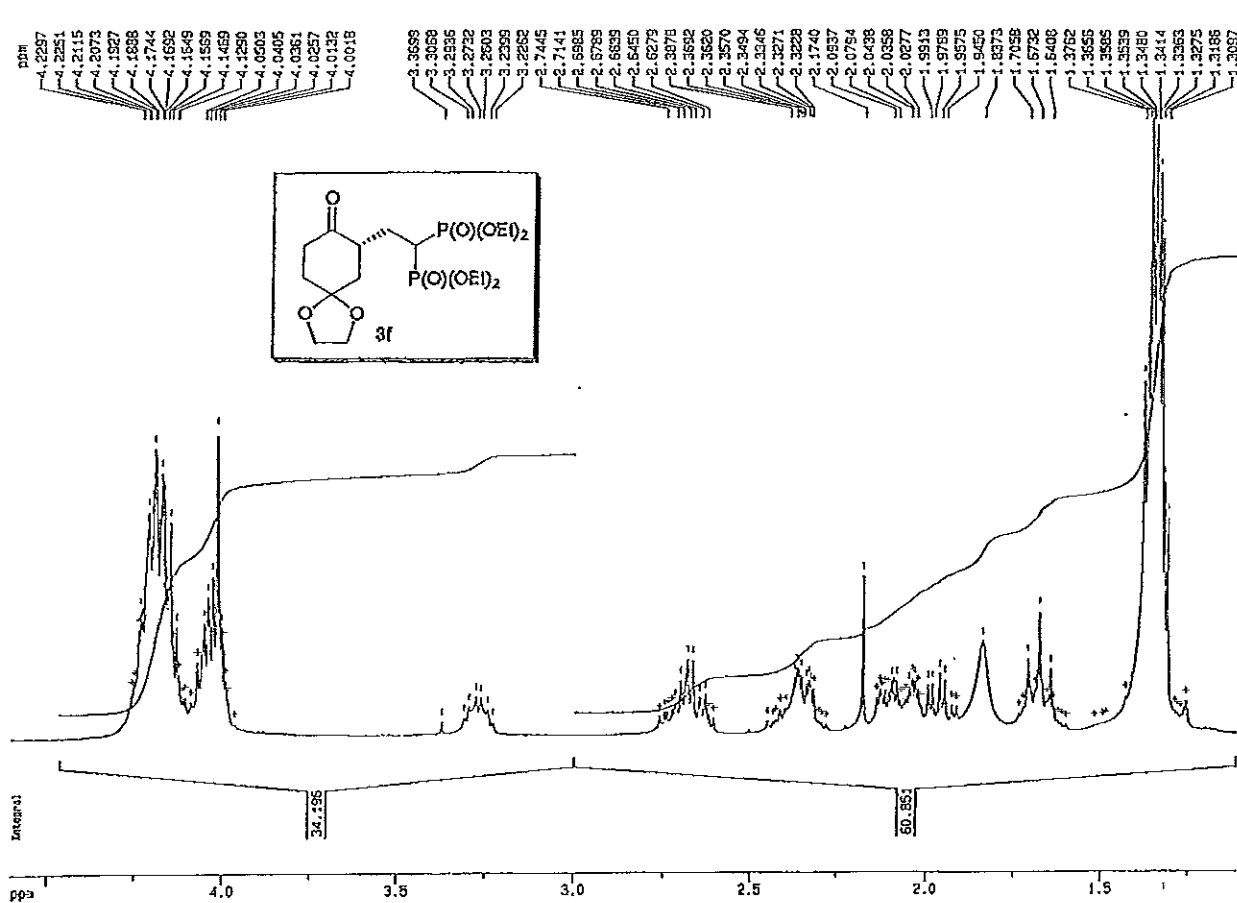
1. M. T. Barros and A. M. Faisca Phillips, *Eur. J. Org. Chem.*, 2008, **15**, 2525–2529.
2. R. A. Nugent, S. T. Schlachter, M. Murphy, C. J. Dunn, N. D. Staite, N. A. Galinet, S. K. Shields, H. Wu, D. G. Aspar and K. A. Richard, *J. Med. Chem.*, 1994, **37**, 4449–4454.
3. For a method on the determination of the enantiomeric purity of chiral ketones using their butane-2,3-diol acetals see H. Hiemstra and H. Wynberg, *Tetrahedron Lett.*, 1977, 2183–2186.
4. For previous descriptions on the use of aromatic hydrazines to derivatize ketones for configuration studies see, for example: a) Y. Kawai, M. Hayashi, N. Tokitoh, *Tetrahedron*, 2005, **61**, 5049–5055; b) Y. Kawai, M. Hayashi and N. Tokitoh, *Tetrahedron Lett.*, 2002, **43**, 465–467.

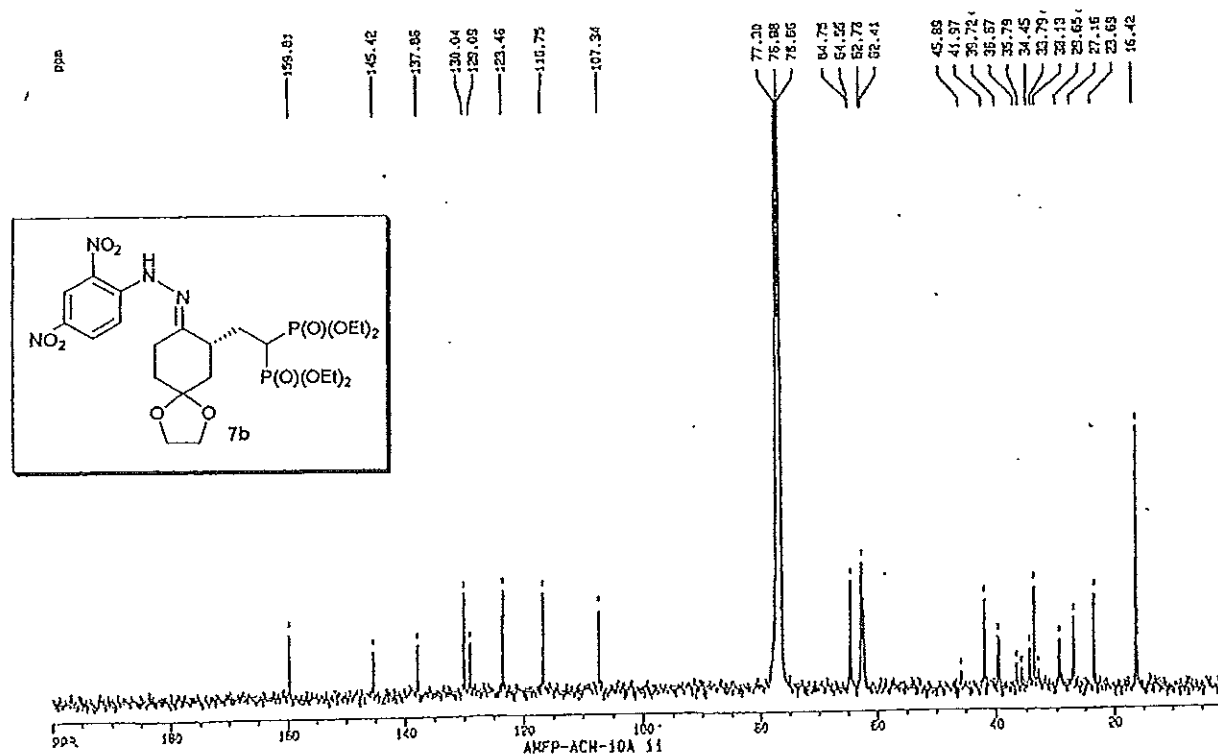
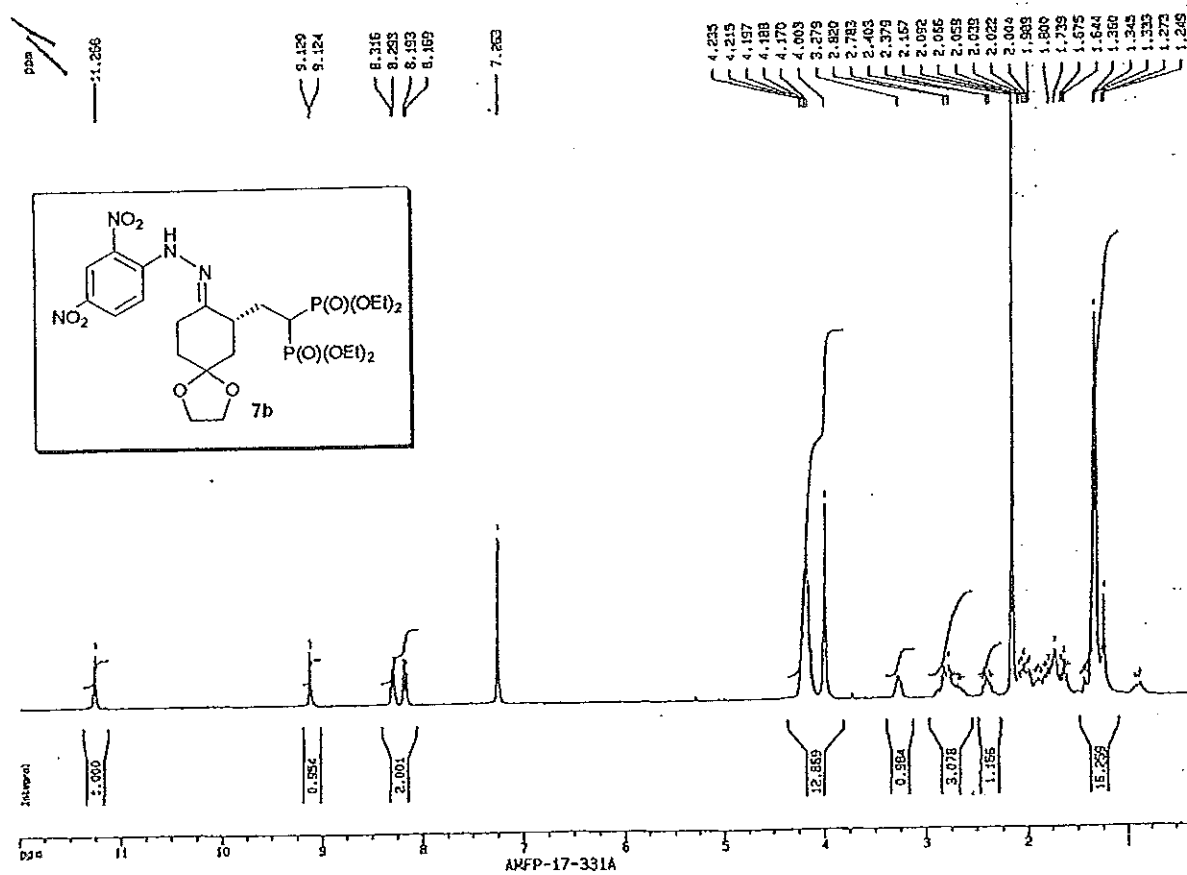
NMR Spectra

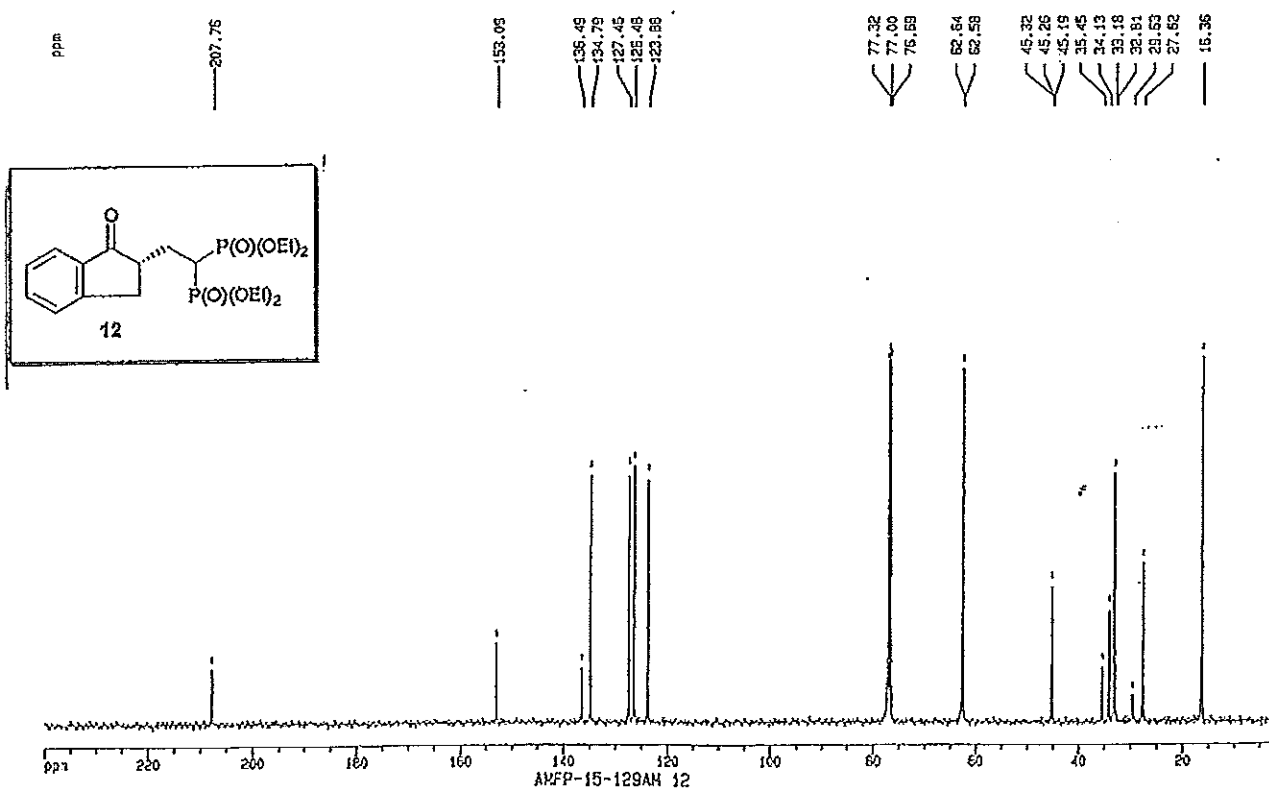
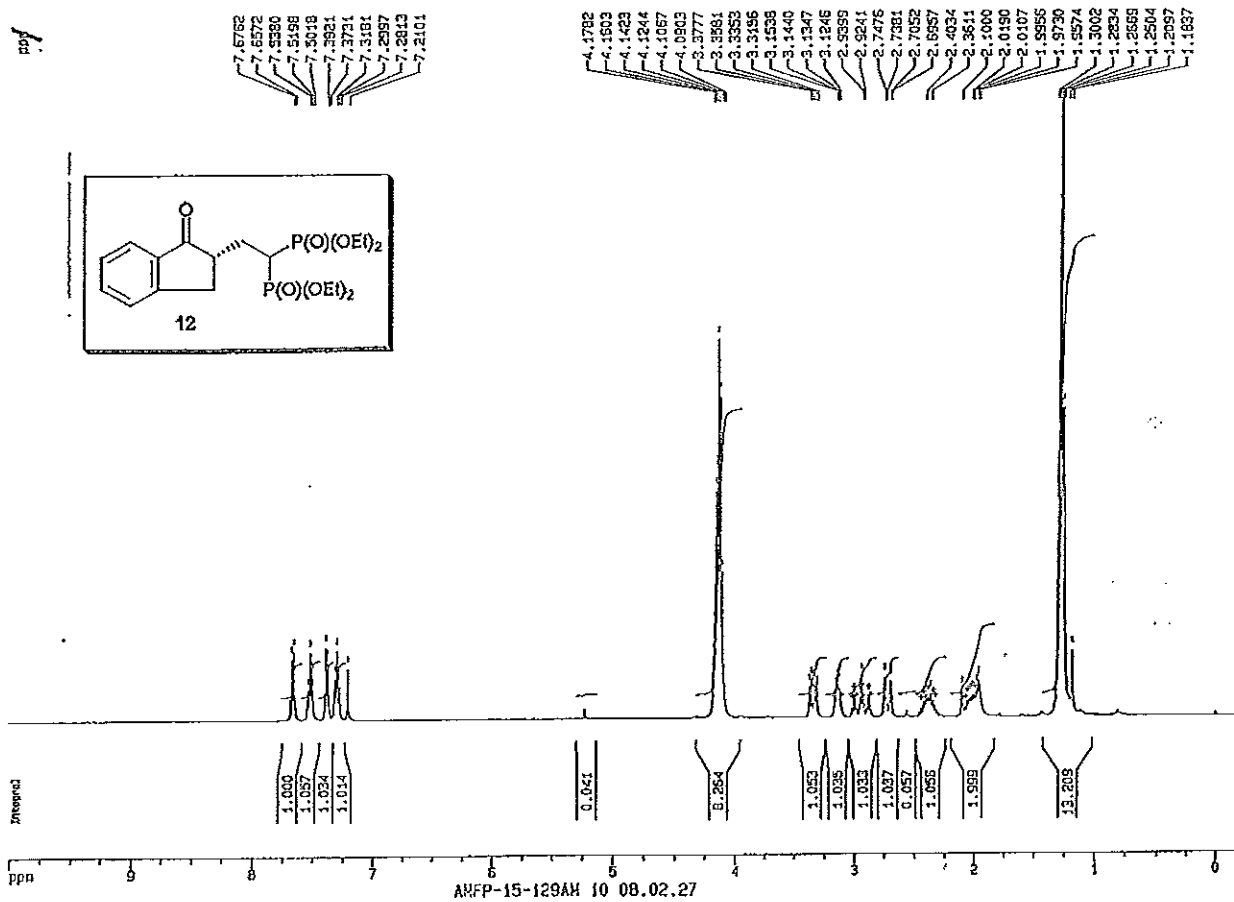


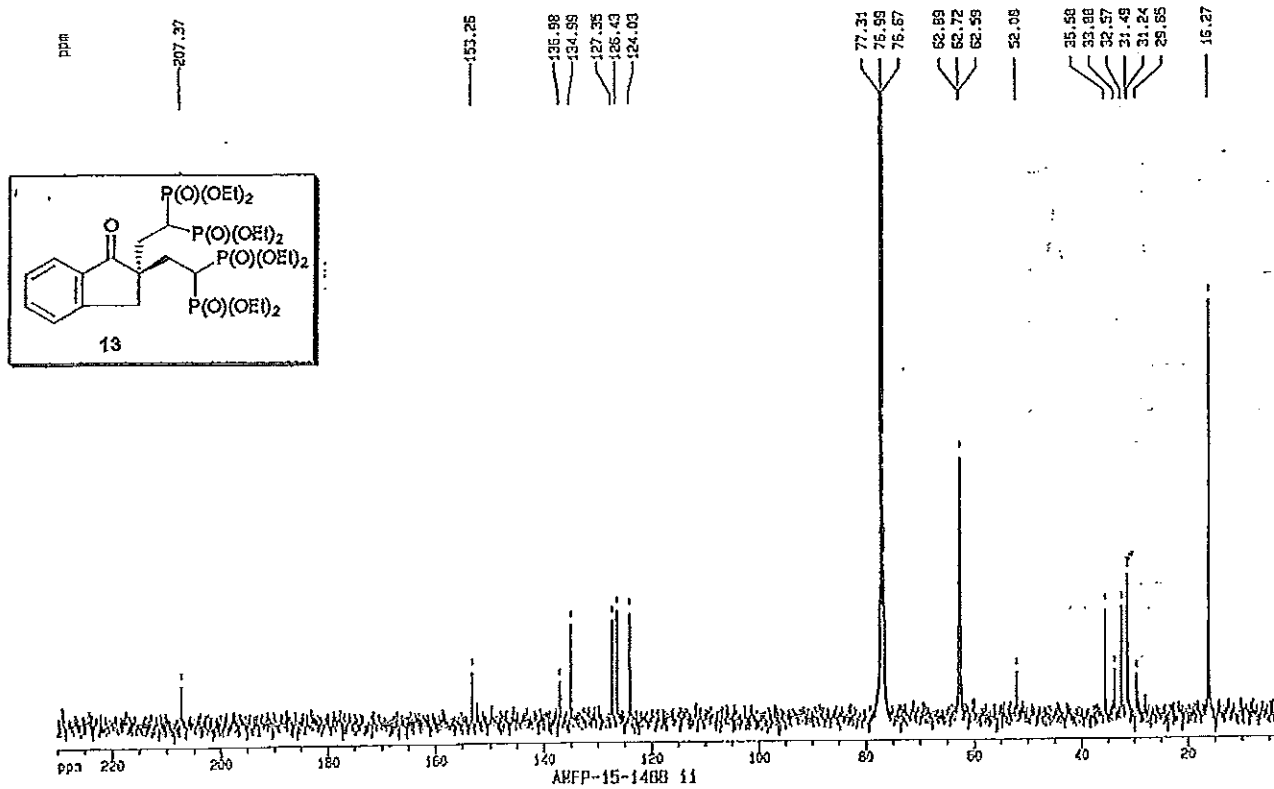
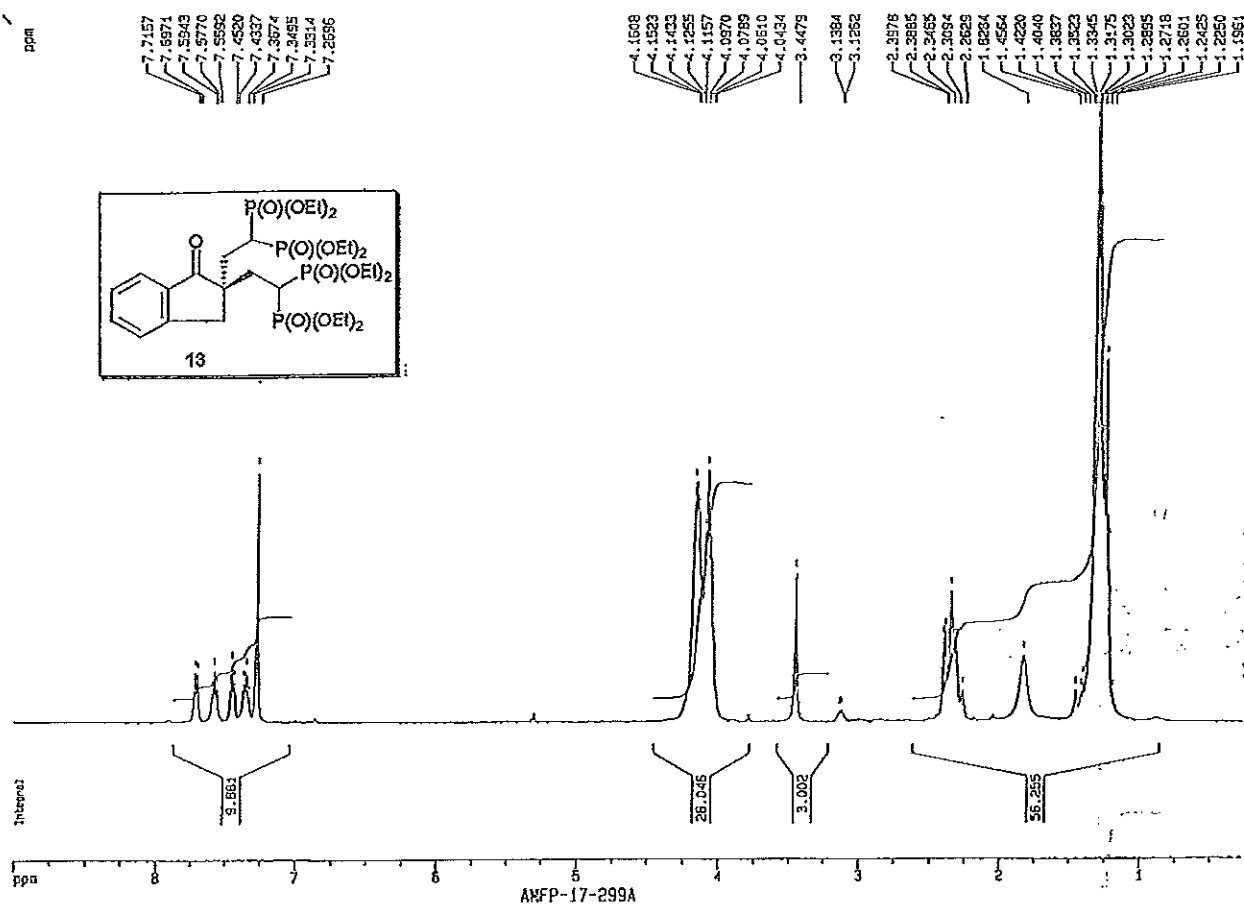


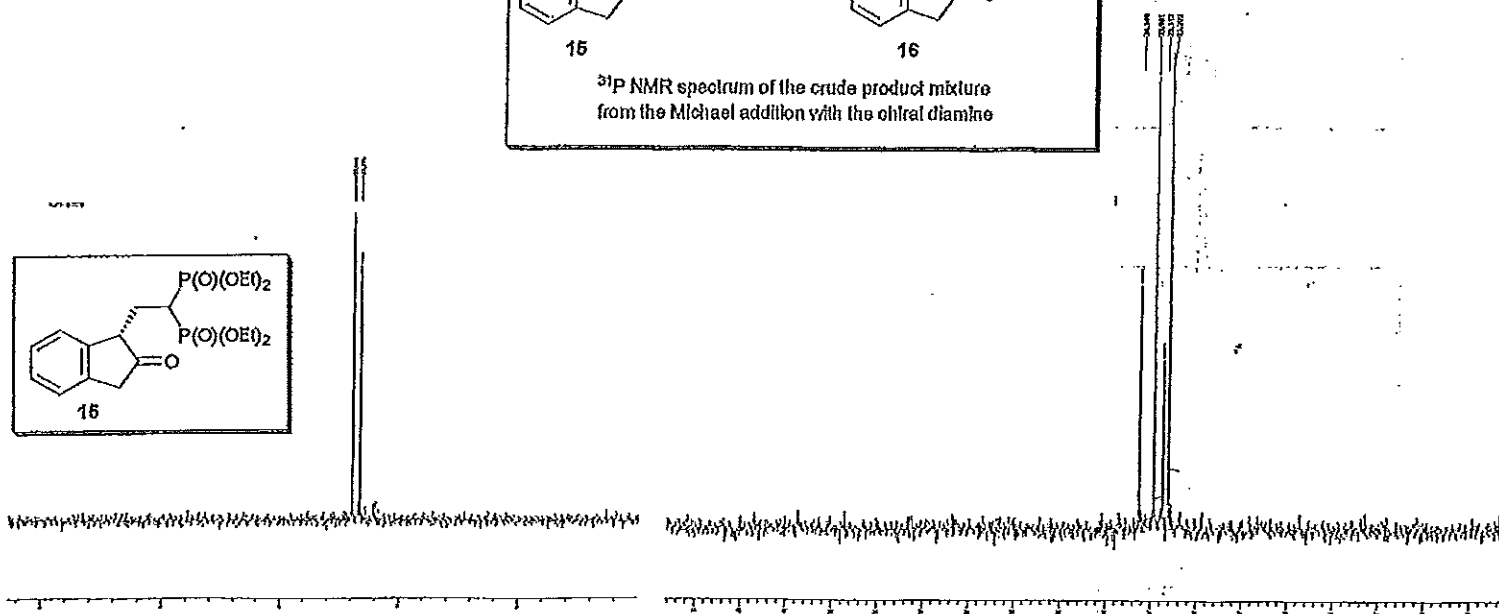
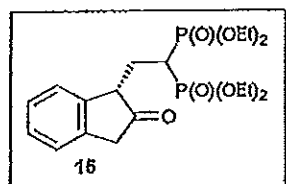
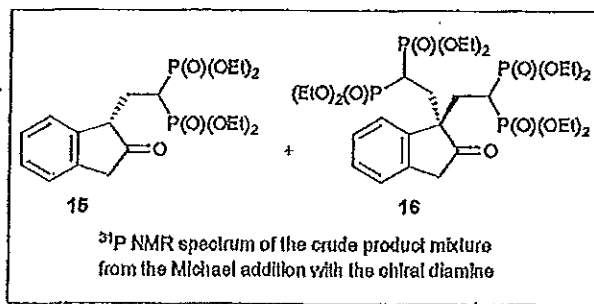
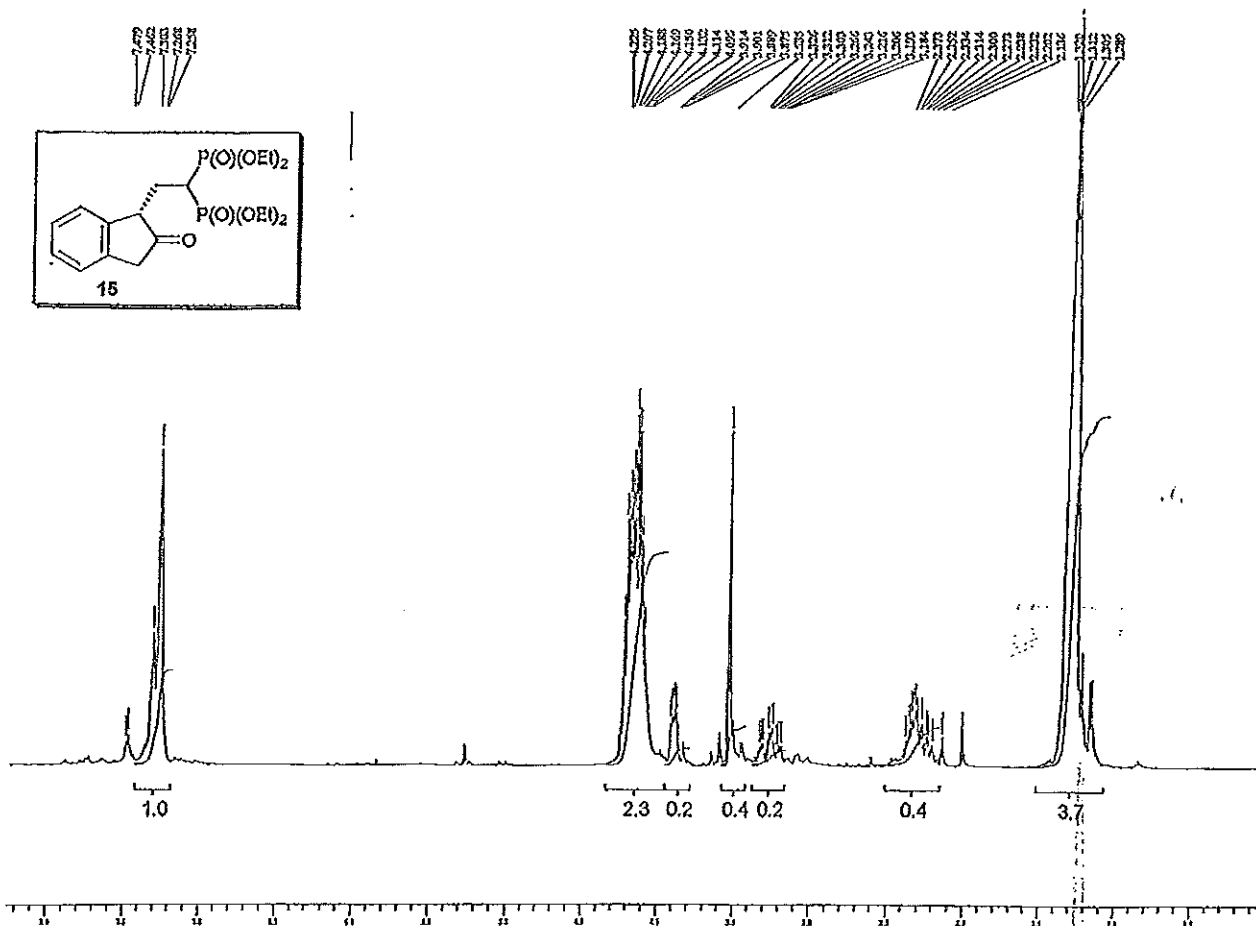


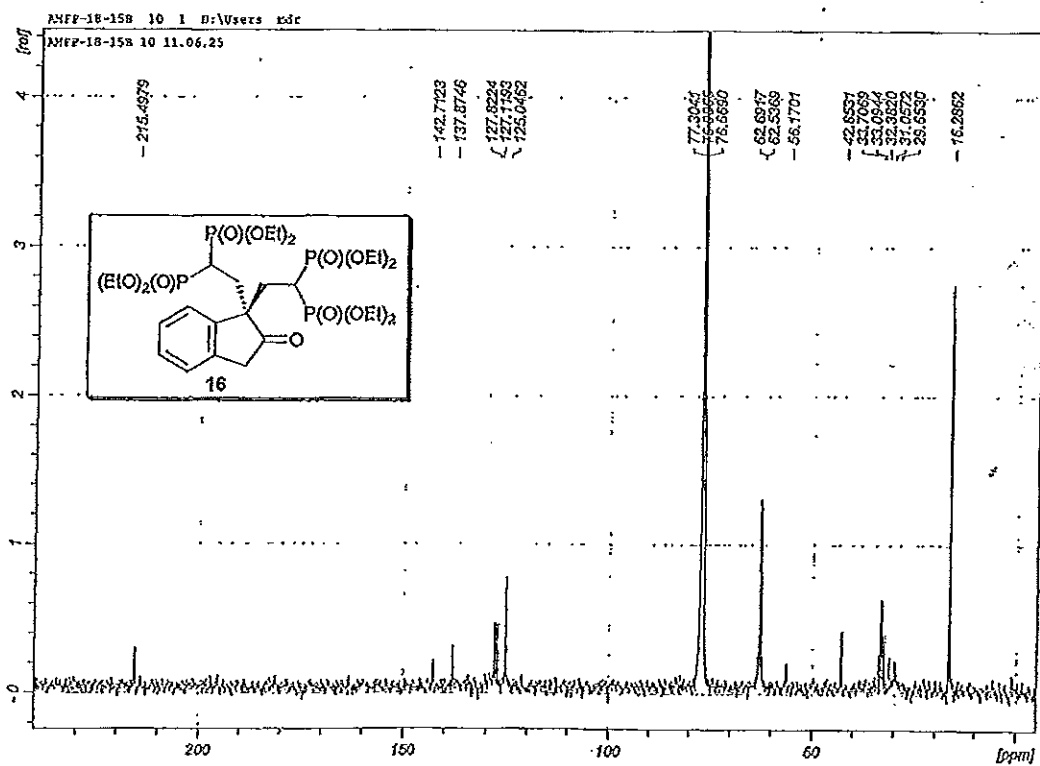
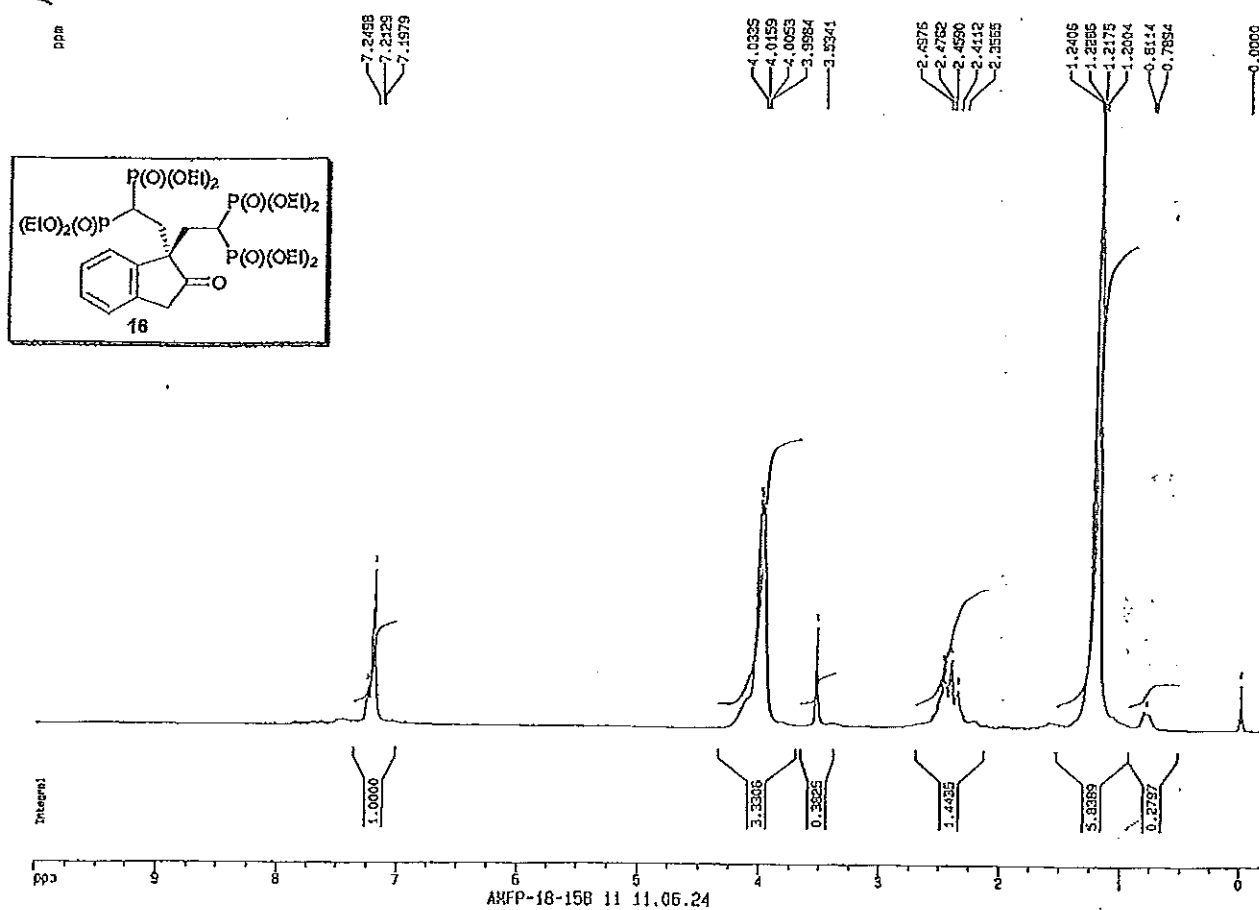


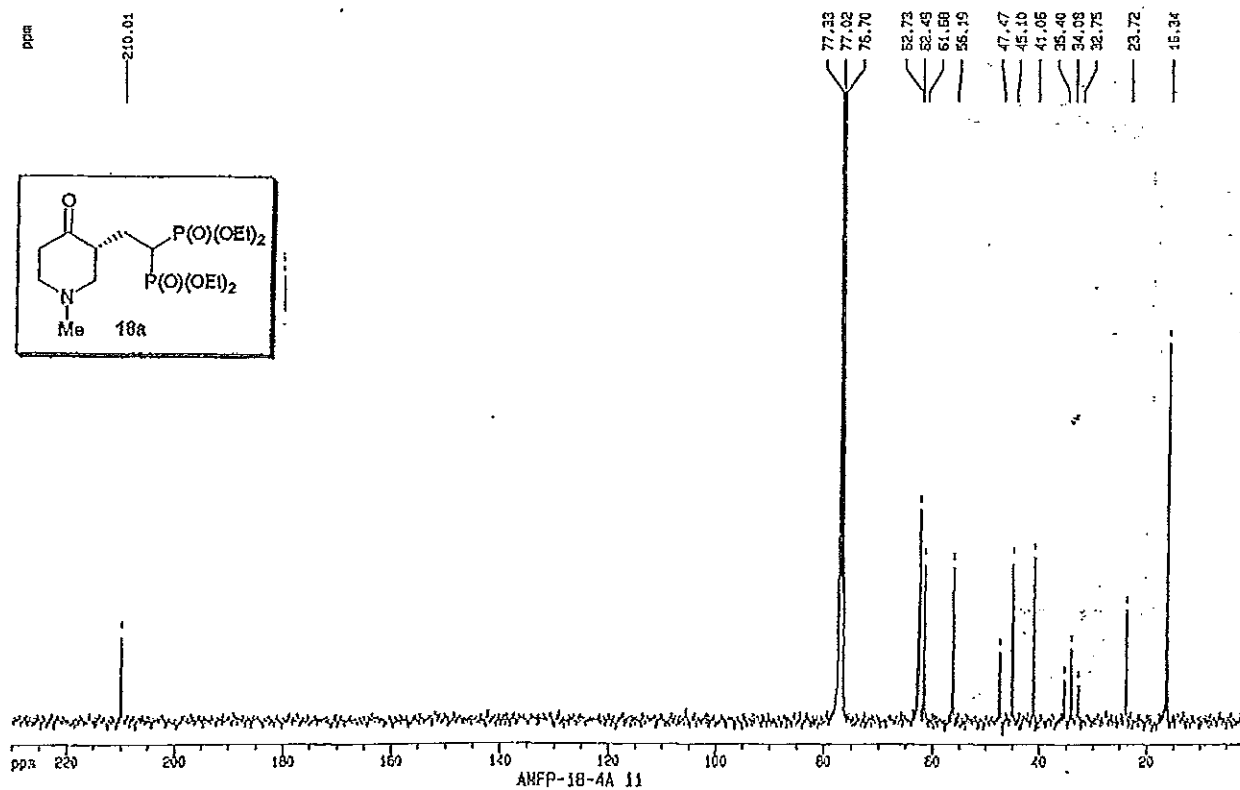
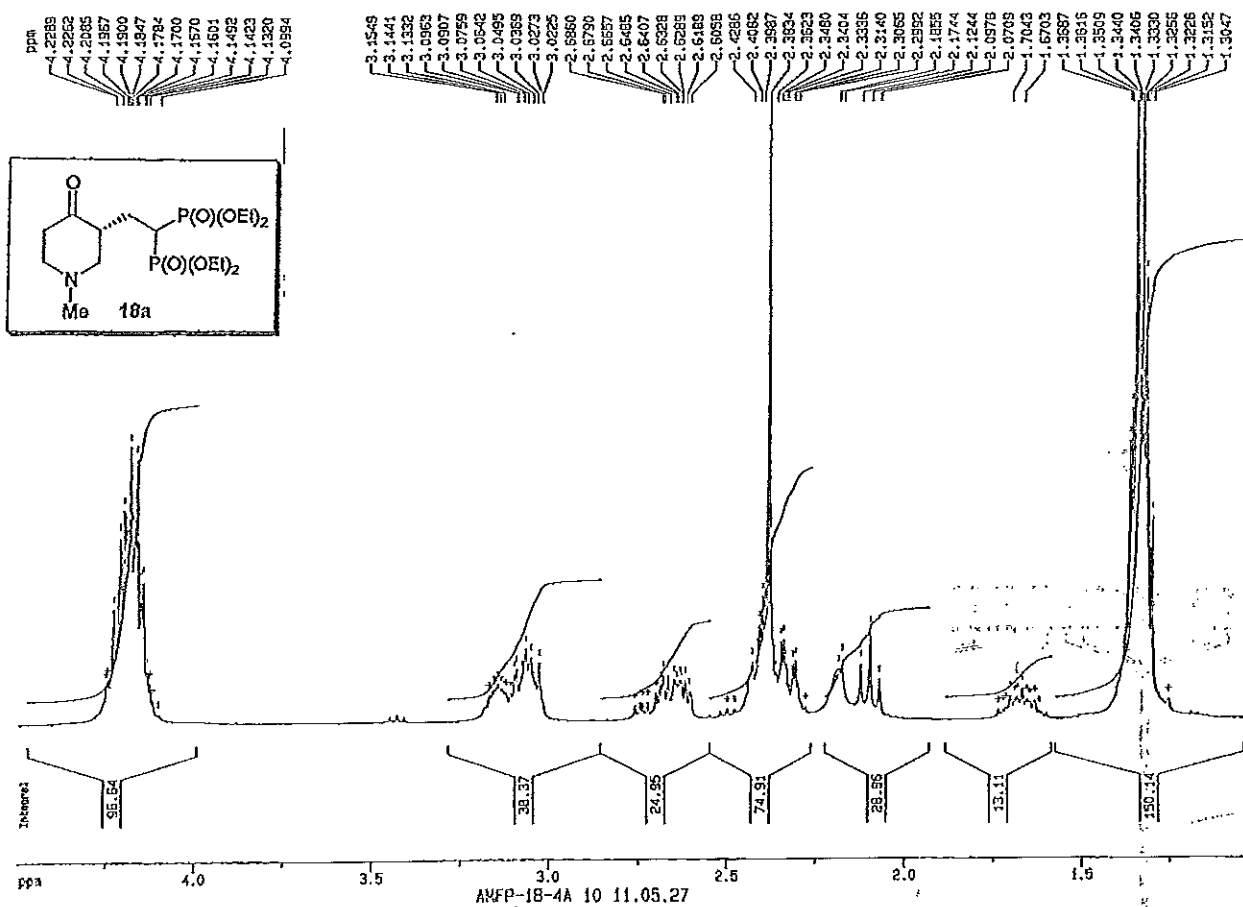


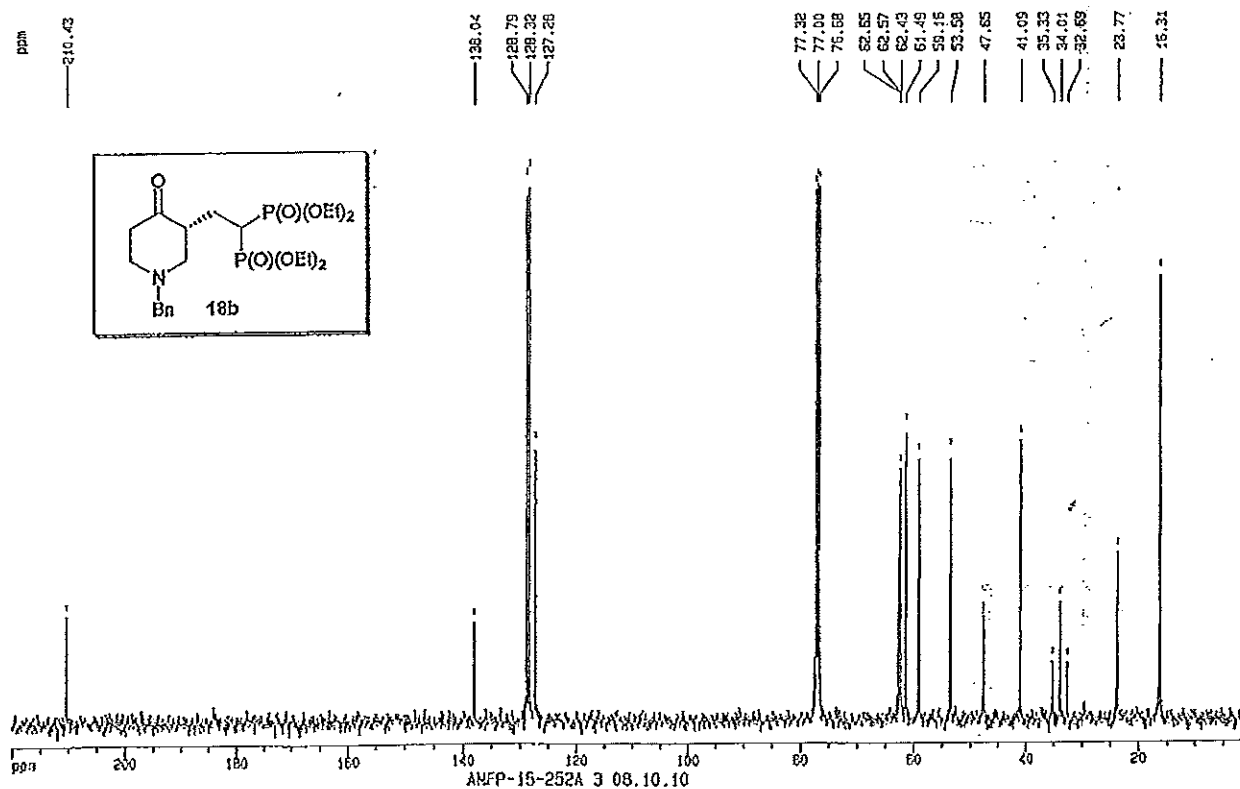
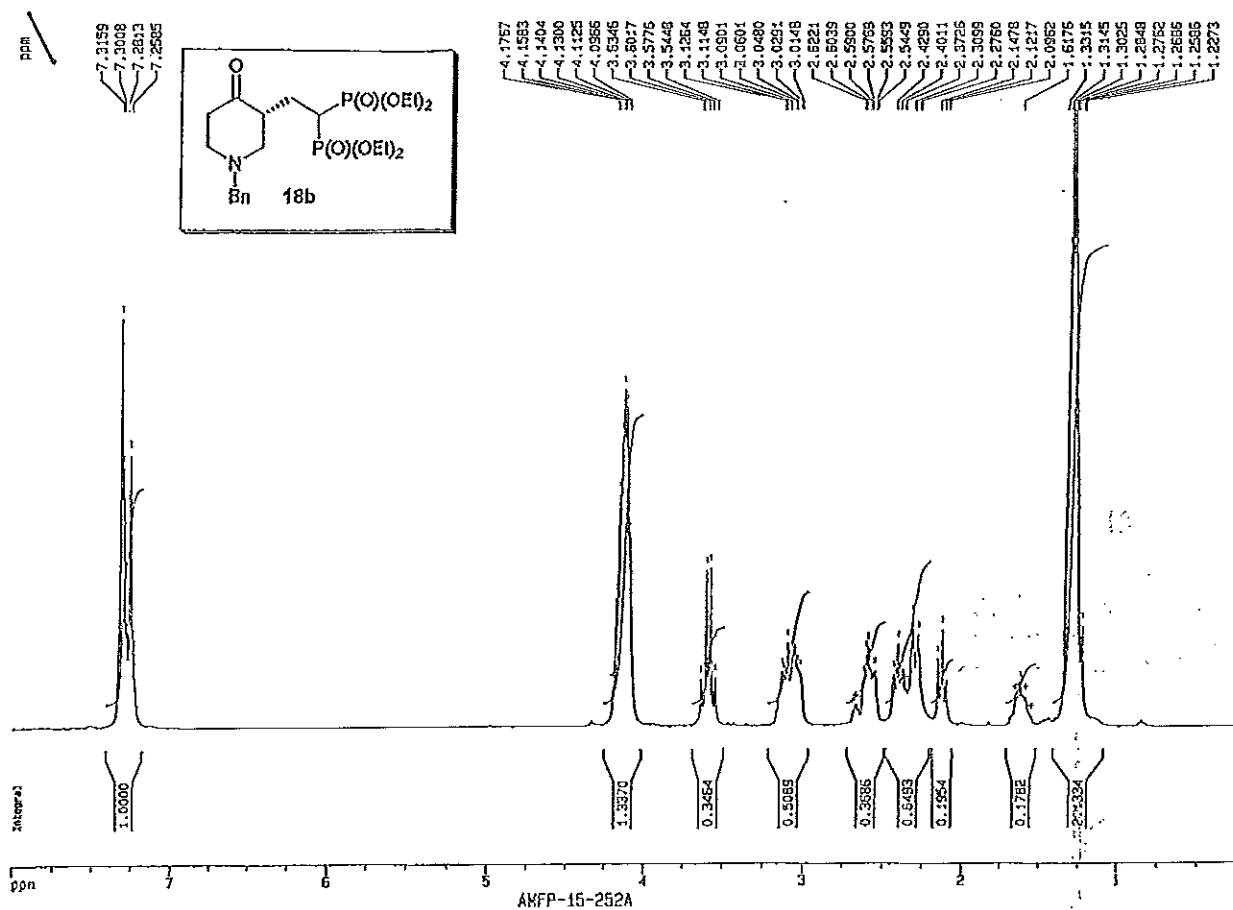


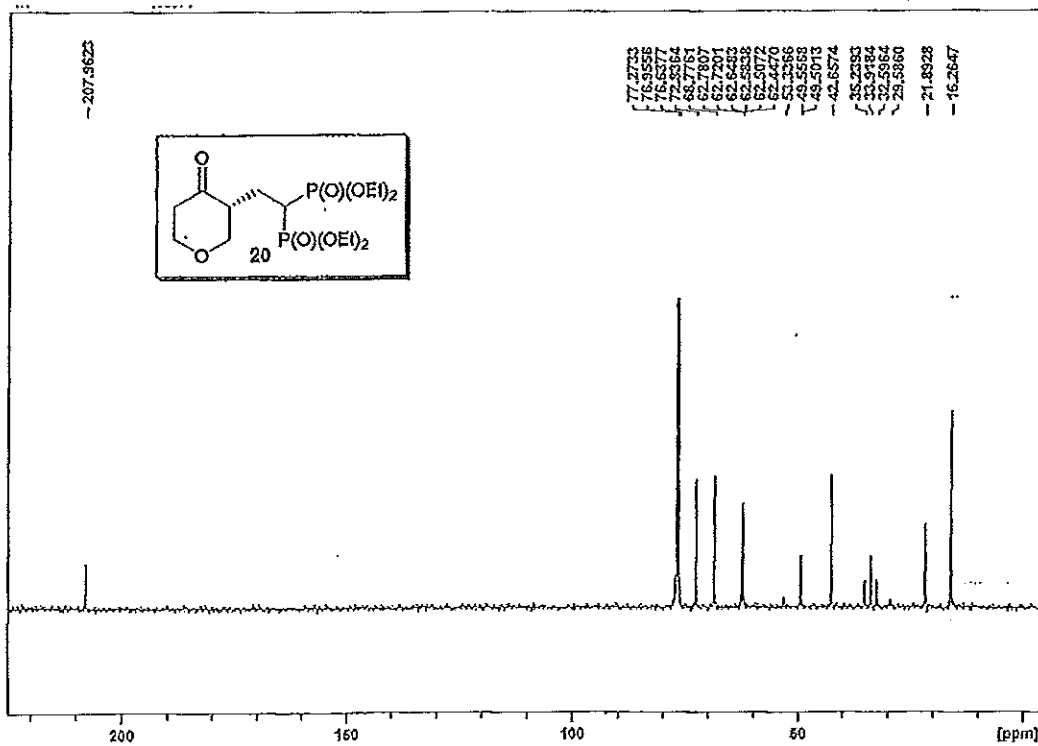
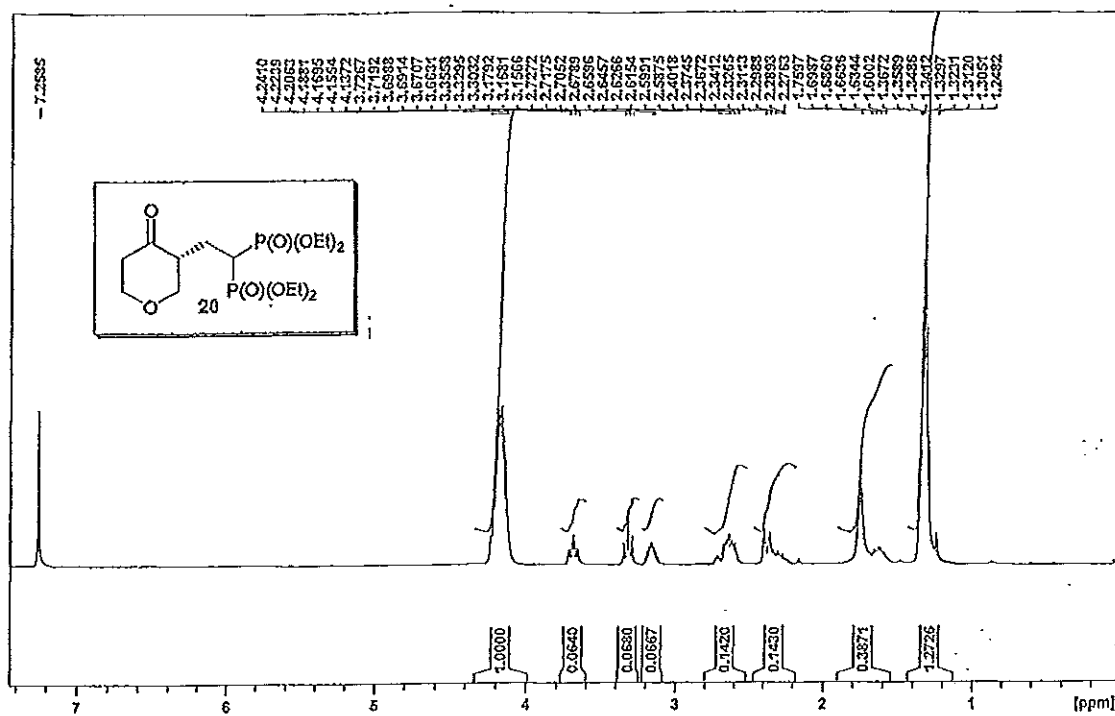






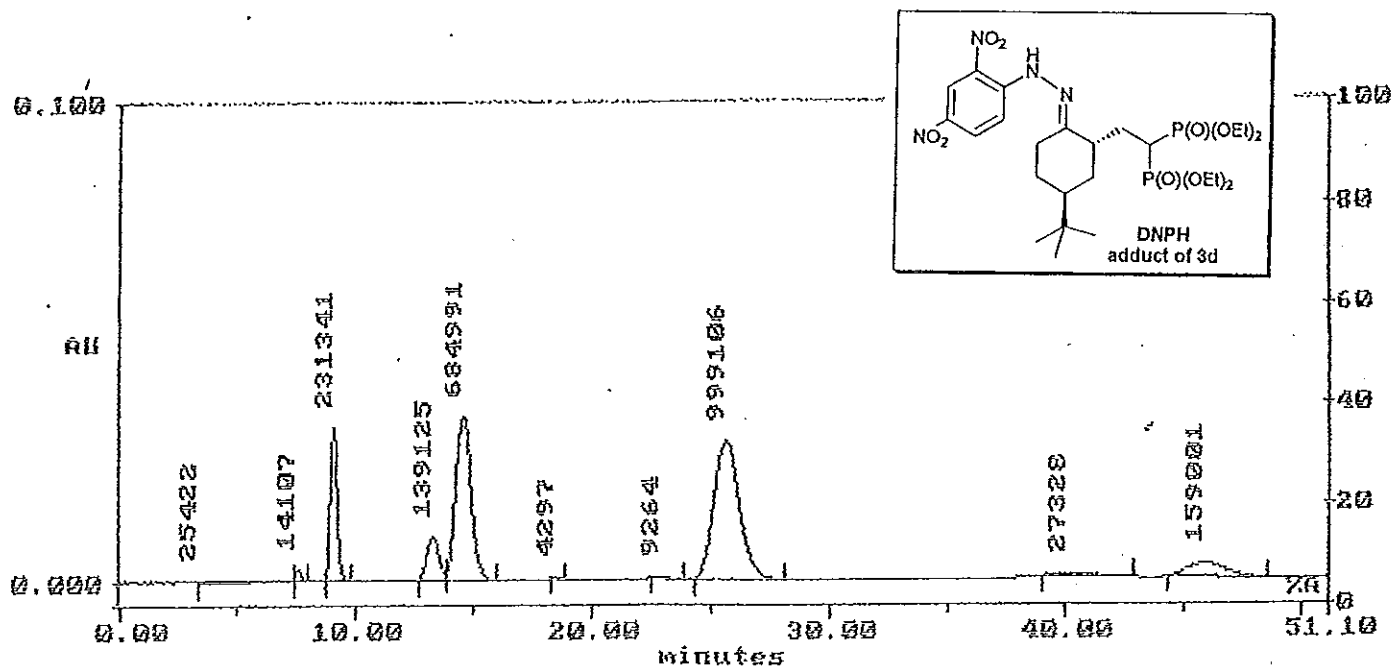
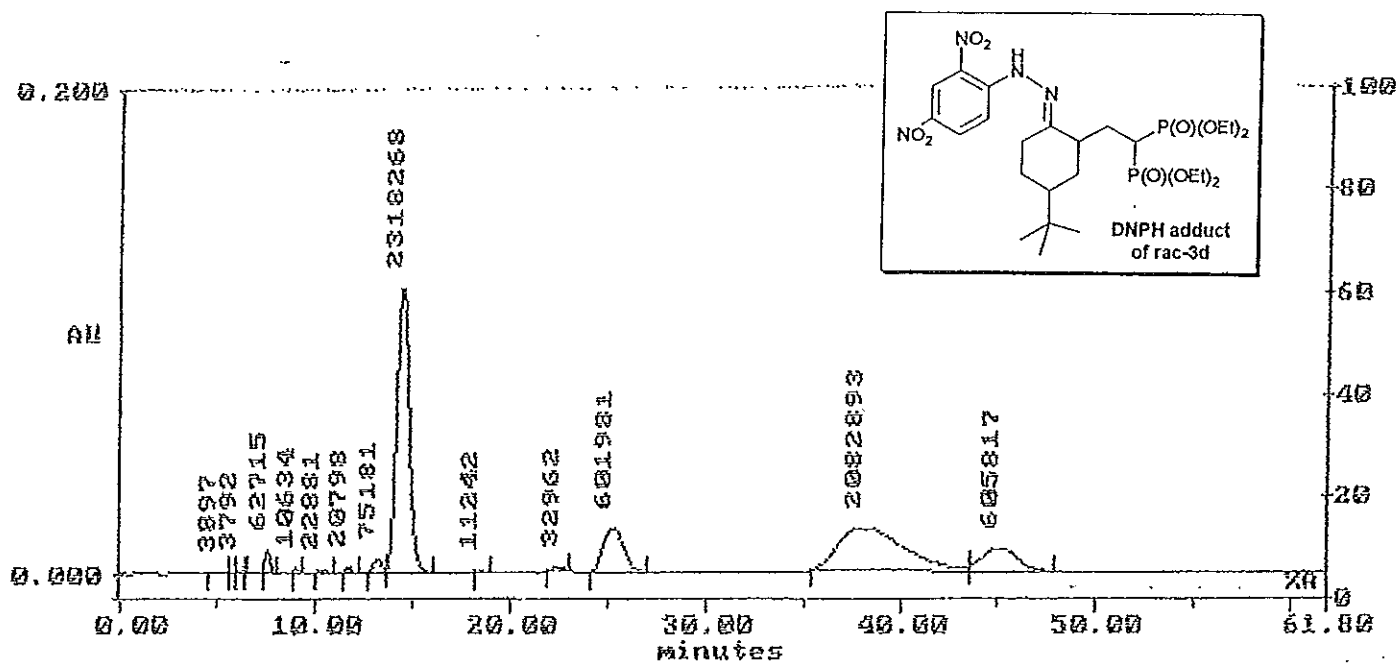




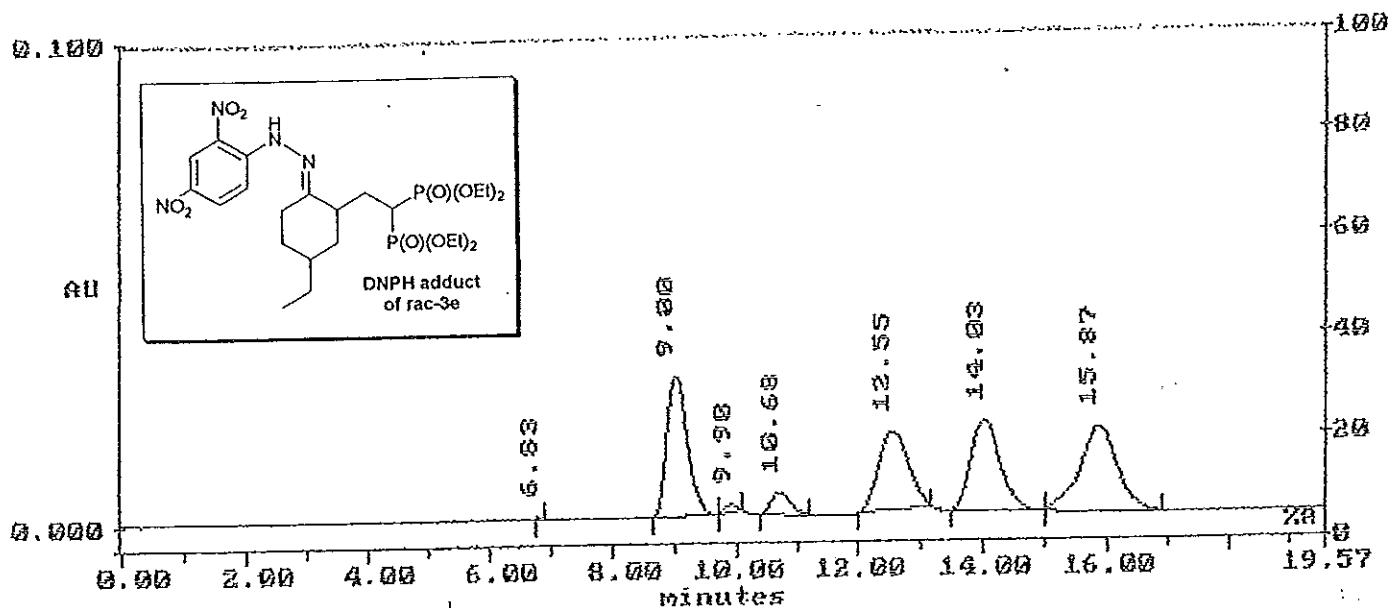


HPLC chromatograms

Determination of the % ee of **3d**
HPLC traces of the DNPH adducts

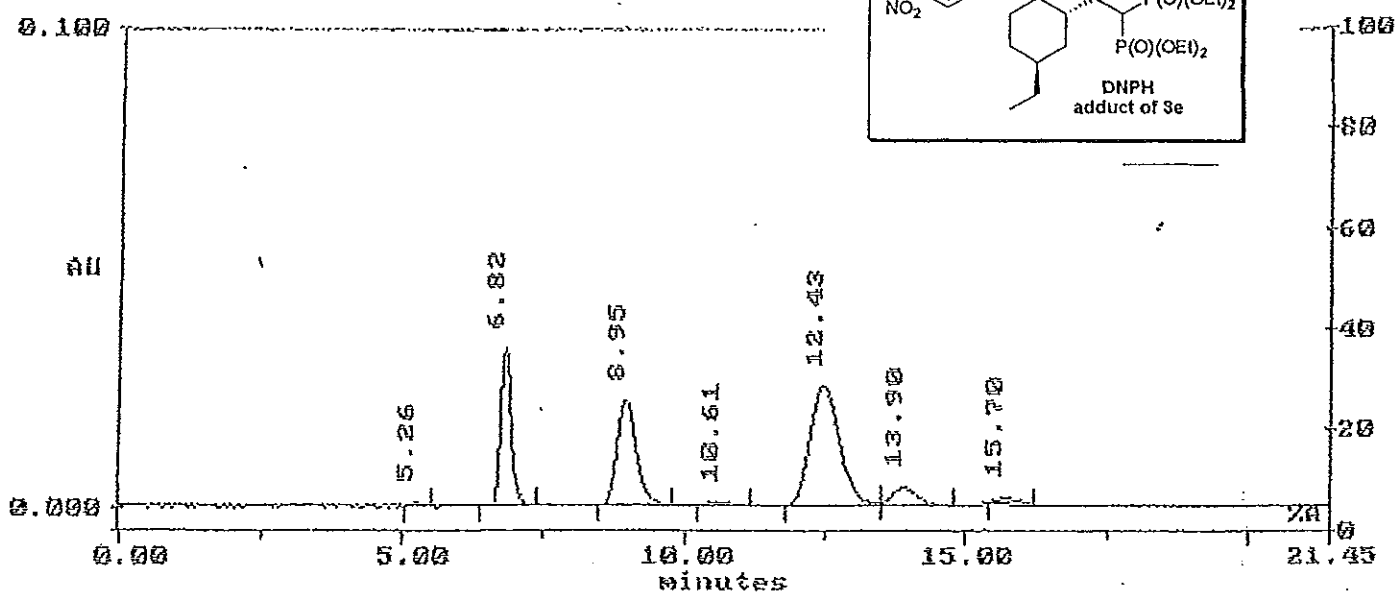


Determination of the % ee of **3e**
 HPLC traces of the DNPH adducts

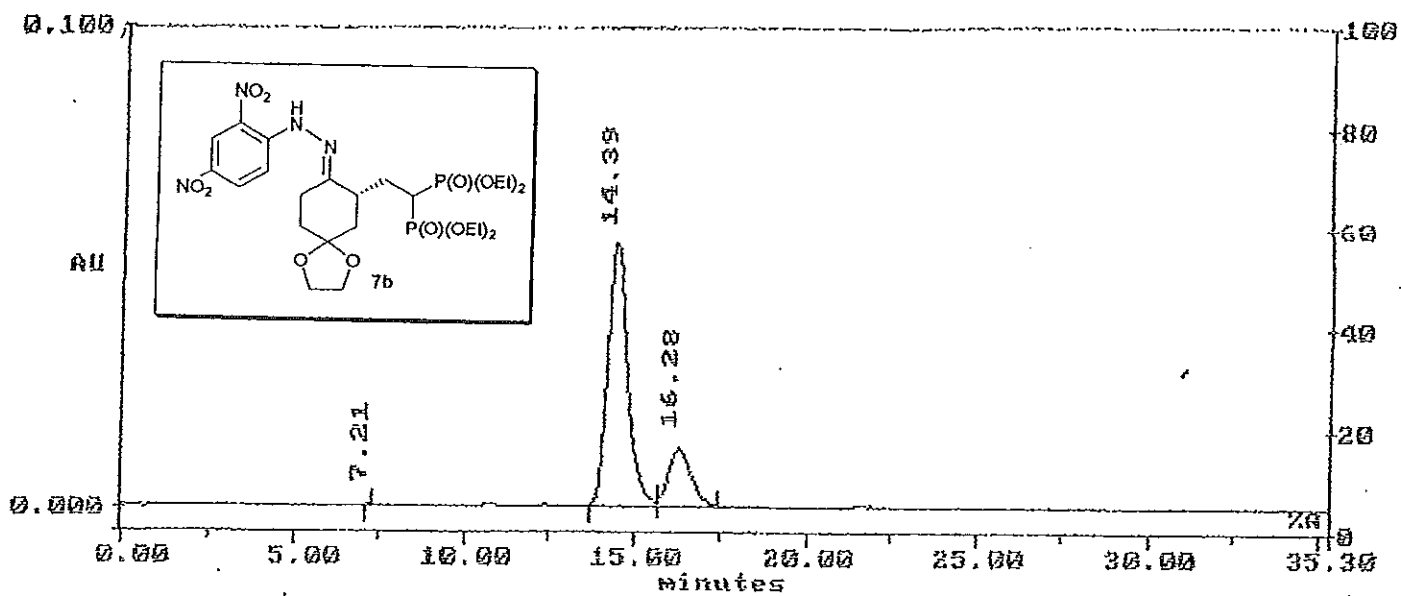
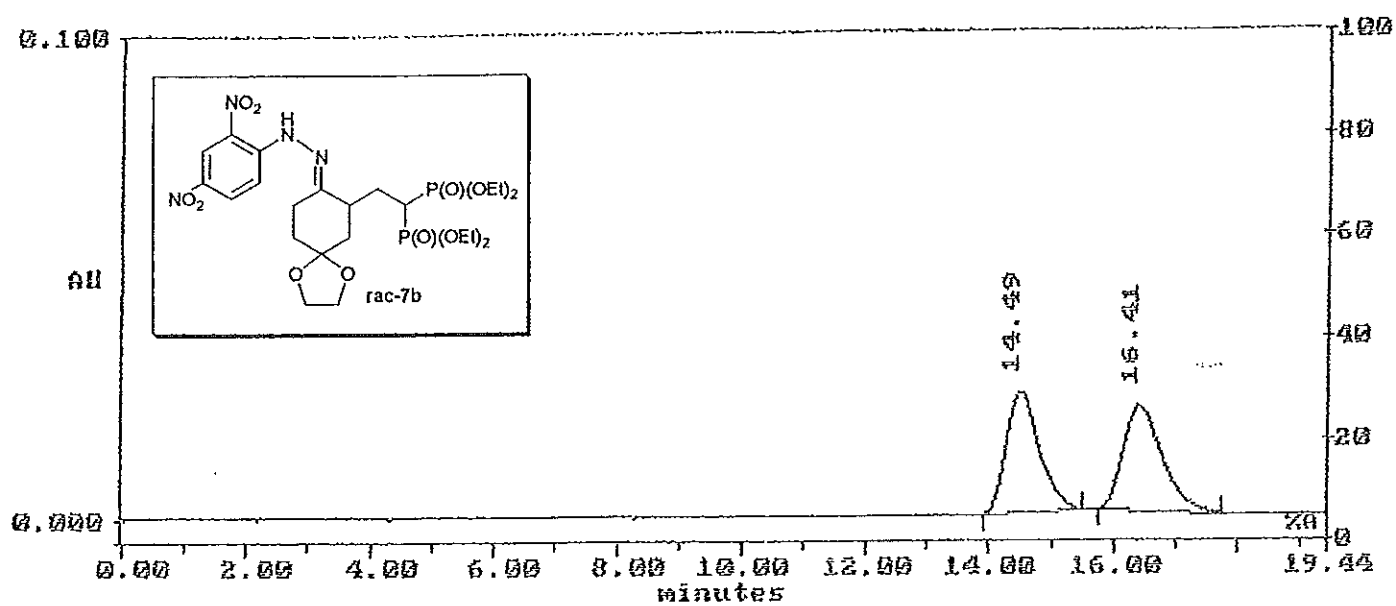


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1	4.77	437	0.031	BB
2	5.16	167	0.012	BB
3	5.94	1651	0.116	BB
4	6.58	964	0.068	BB
5	6.83	6153	0.433	BB
6	9.00	312569	21.991	BV
7	9.90	28653	2.016	VV
8	10.68	65307	4.595	VV
9	12.55	312513	21.987	VV
10	14.03	316703	22.282	VV
11	15.87	376220	26.469	VB

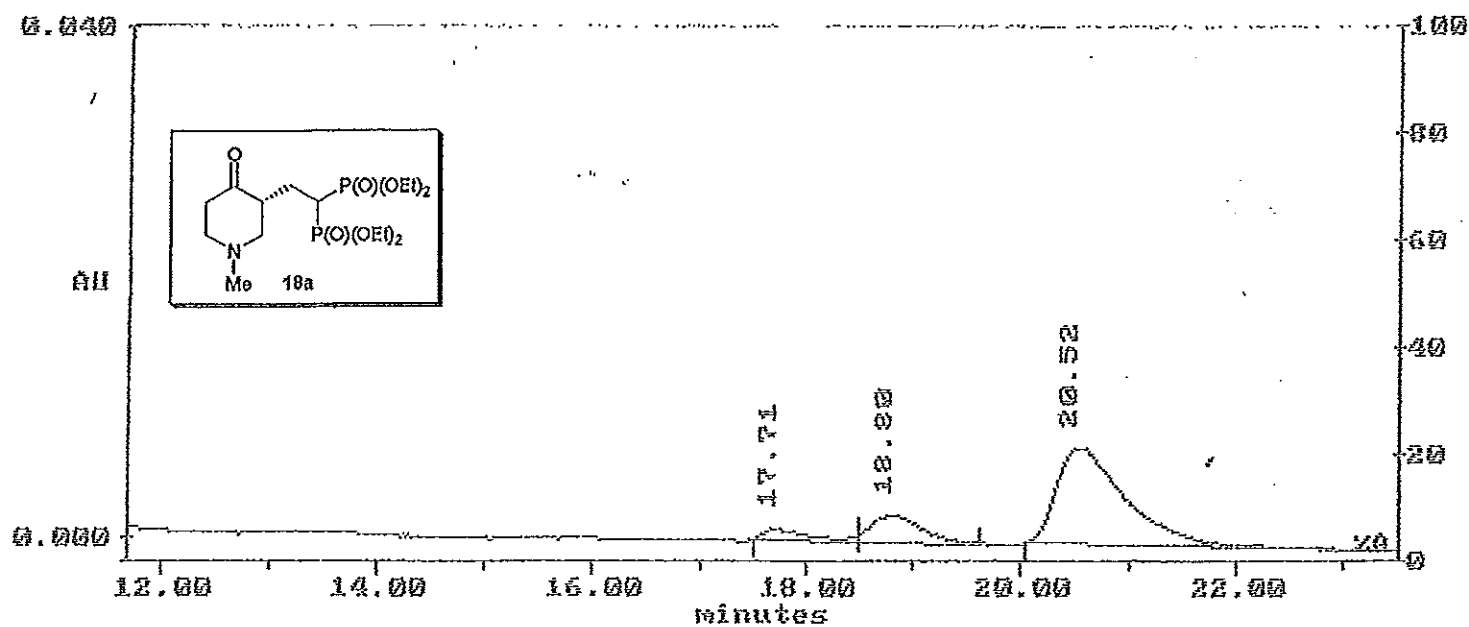
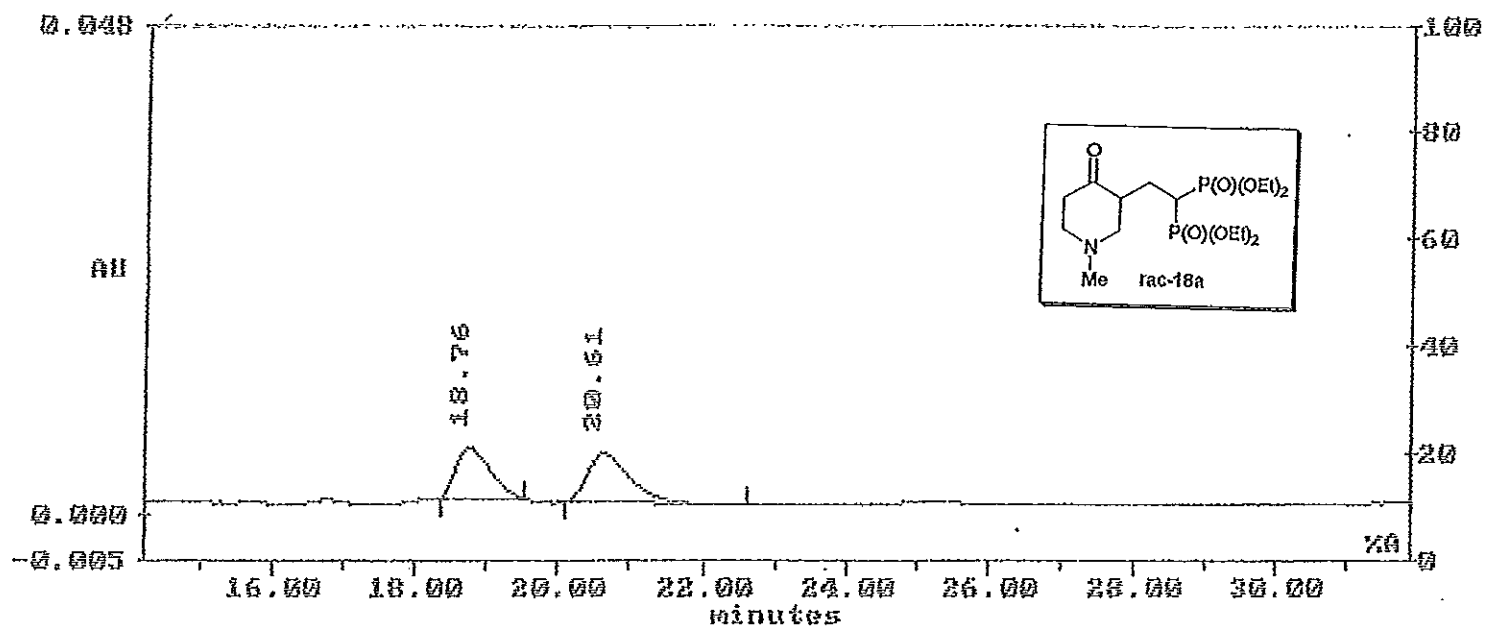
TOTAL 1421337 100.000



Determination of the % ee of 3f HPLC traces of the DNPH adducts



Determination of the % ee of 18a HPLC traces



Determination of the % ee of 18b HPLC traces

