

**An Oxazaphospholidine Approach for the Stereocontrolled Synthesis of
Oligonucleoside Phosphorothioates**

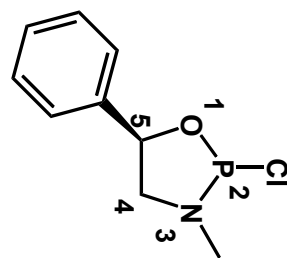
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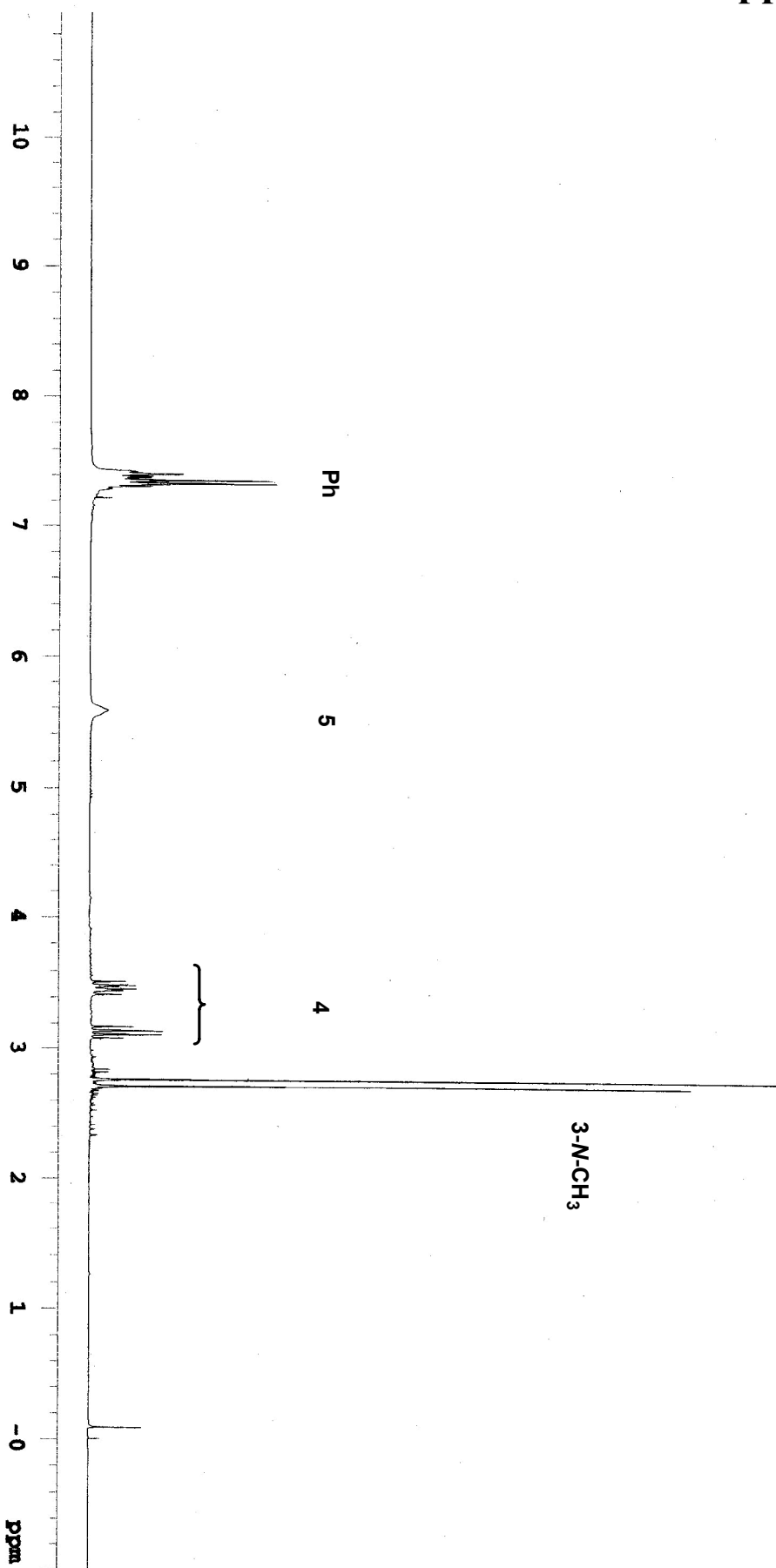
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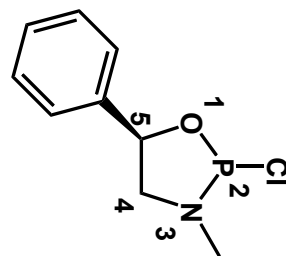
Bioscience Building 702, Kashiwanoha, Kashiwa 277-8562, Japan

Supporting Information

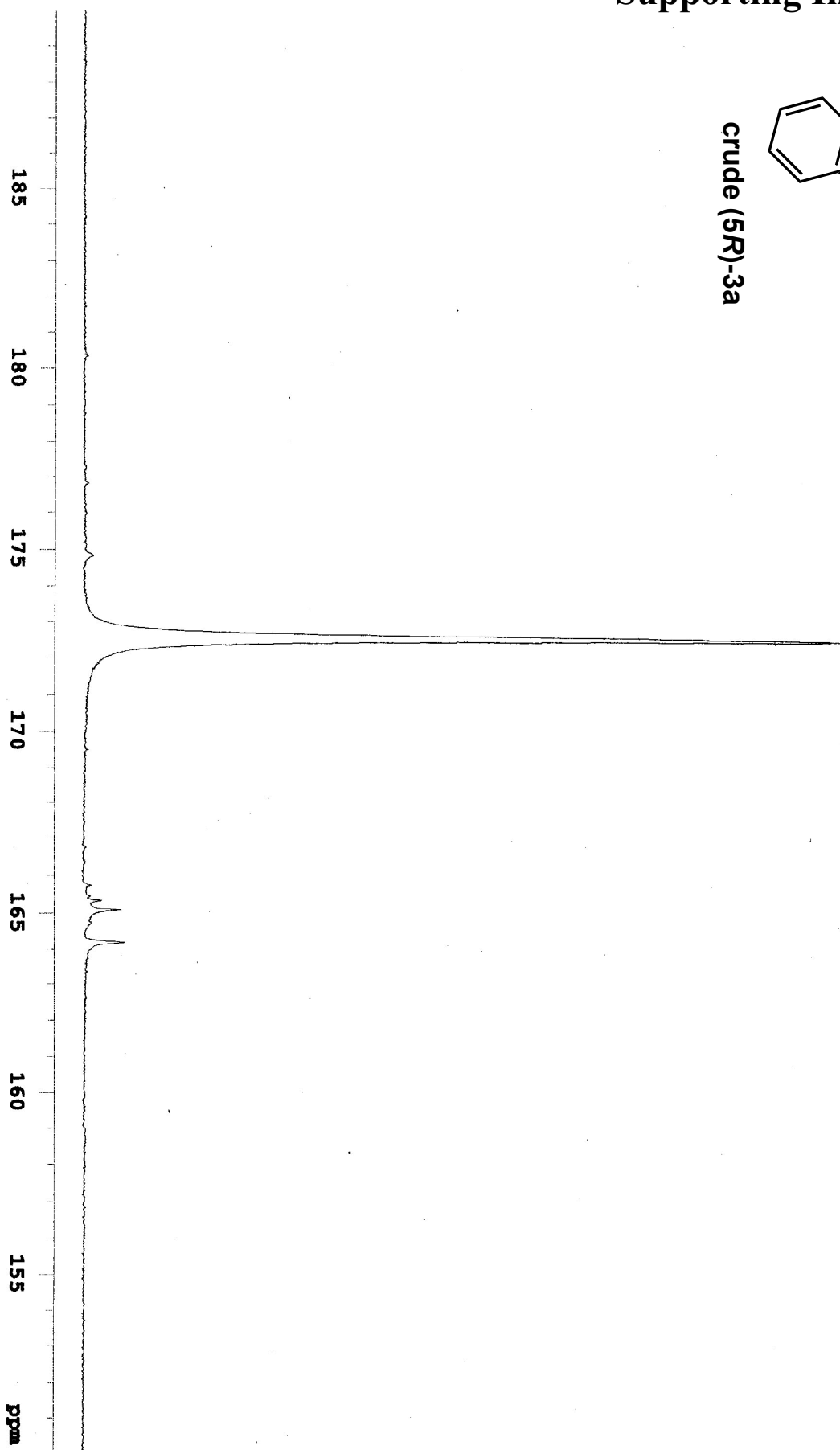


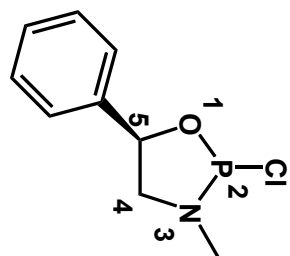
crude (5R)-3a



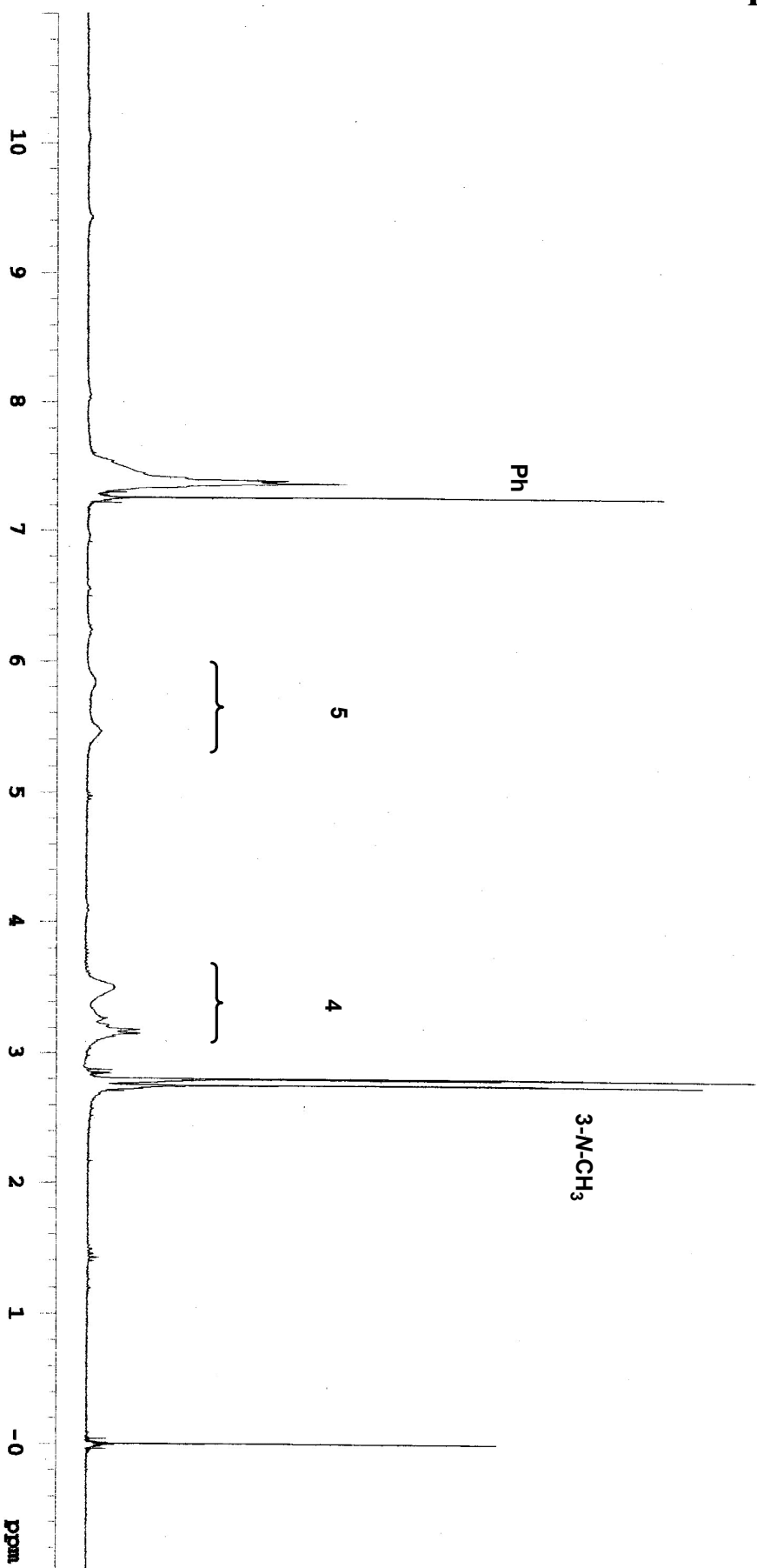


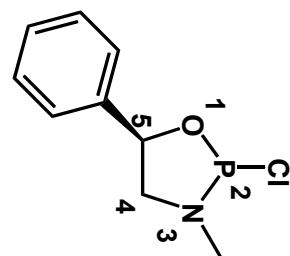
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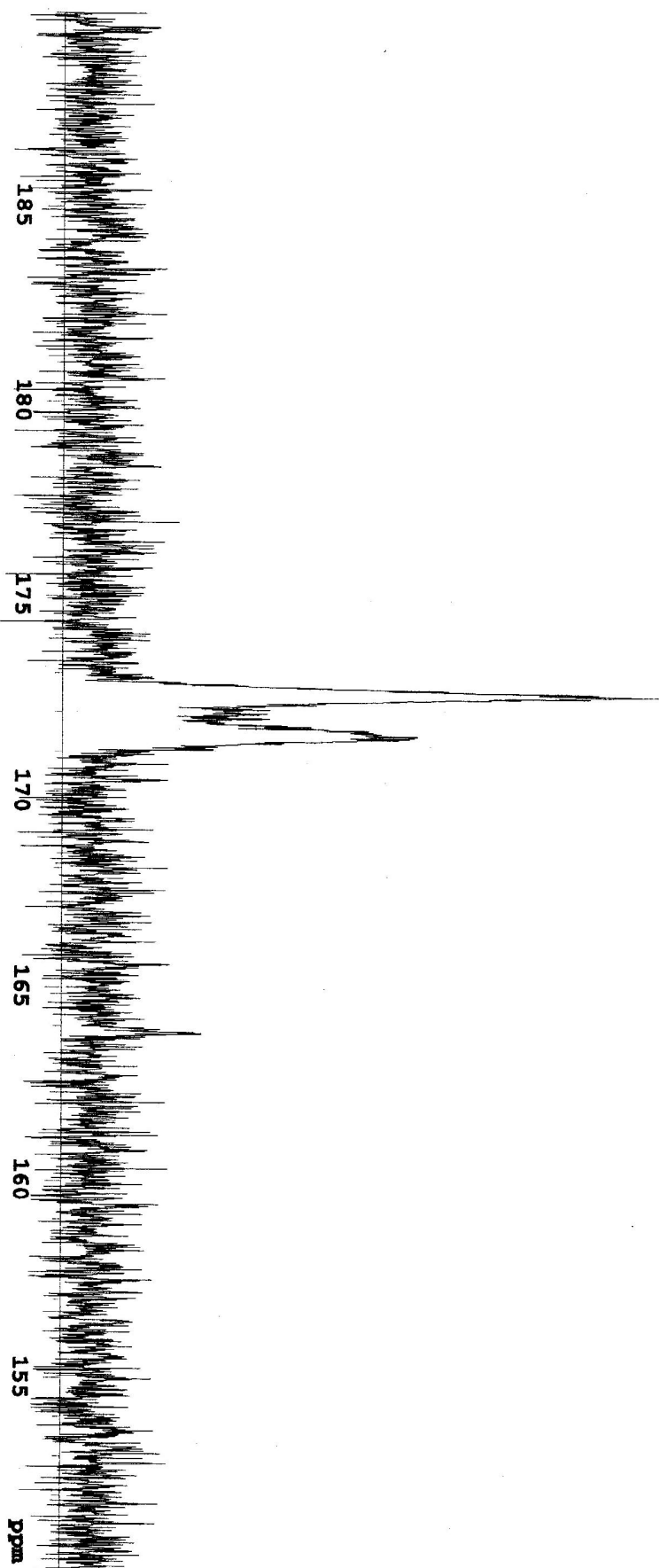


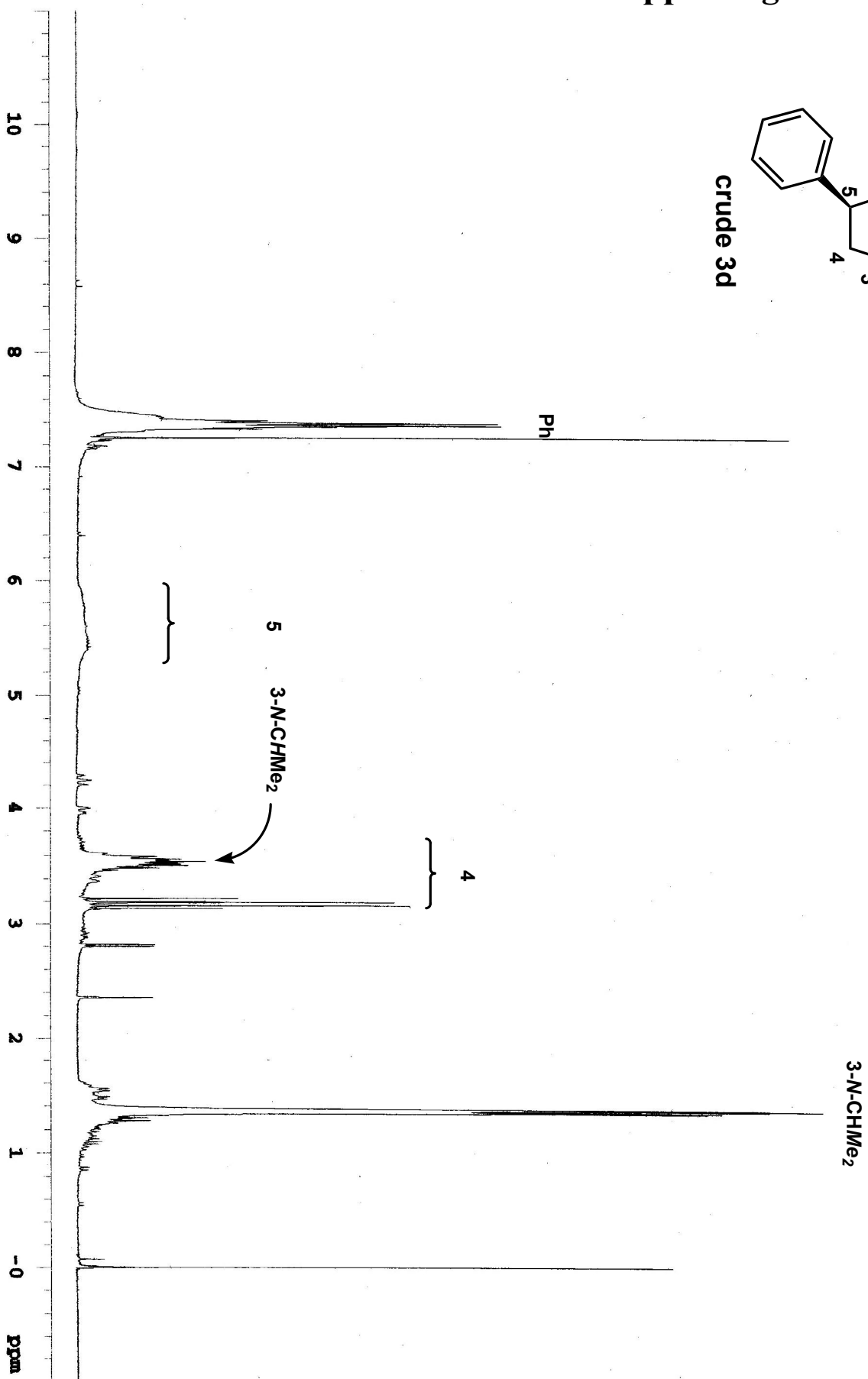
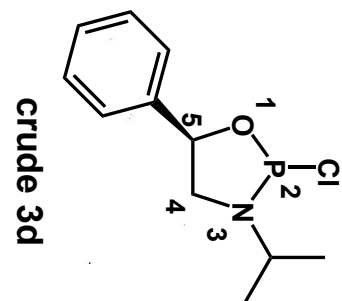
distilled (5R)-3a





distilled (5R)-3a

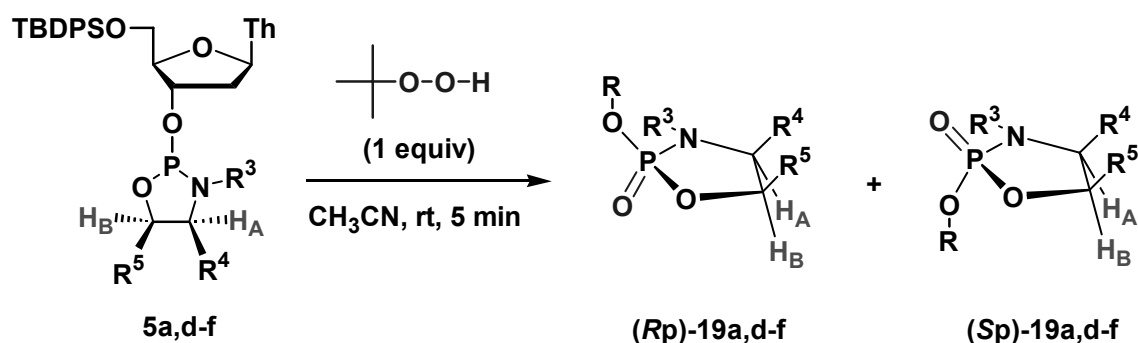




Experimental details for the configurational assignment of 5.

Configurational assignment of 5a-f. The *P*-configurations of **5a-f** were determined as follows: **5a,d-f** were oxidized stereoretentively by *tert*-butylhydroperoxide²⁸ to give **19a,d-f**, and the chemical shifts of the protons at the 5-position (4-position in the case of **19f**) in the oxazaphospholidine rings of (*Rp*)-**19** (obtained from *cis*-**5**) and (*Sp*)-**19** (obtained from *trans*-**5**) were compared with each other. It has been reported that a ¹H in a 1,3-*cis* relation to a P=O group are deshielded.²⁹ Therefore, the signal of the 5- or 4-H of (*Rp*)-**19**, which is in a 1,3-*cis* relation to a P=O group, is downfield of that of (*Sp*)-**19**. The *P*-configuration of **5b** was assigned by comparison of the ³¹P chemical shifts of *trans*- and *cis*-**5b** with those of *trans*- and *cis*-2-methoxy-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidine, which have been reported in the literature.³⁰ The *P*-configuration of another 4,5-disubstituted oxazaphospholidine derivative **5c** was assigned in analogy with **5b**; the signal around 150 ppm in the ³¹P NMR spectrum was assigned to the *cis*-isomer, and the signal around 142 ppm was assigned to the *trans*-isomer.

Table 7. Stereoretentive oxidation of **5a,d-f**.^a



| 5 | R ³ | R ⁴ | R ⁵ | <i>trans</i> - 5 : <i>cis</i> - 5 | yield ^b | (<i>Rp</i>)- 19 :(<i>Sp</i>)- 19 | chemical shifts of H _A , H _B |
|----------|----------------|----------------|----------------|---|--------------------|--|---|
| a | Me | H | Ph | >99:1 59:41 | quant 94% | 1:99 39:61 | 5.41 (H _B) 5.52, 5.41 (38:62) (H _B) |
| d | iPr | H | Ph | >99:1 67:33 | quant 90 | 2:98 32:68 | 5.46, 5.37 (2:98) (H _B) 5.46, 5.37 (32:68) (H _B) |
| e | Me | H | iPr | 85:15 | 94% | 13:87 | 4.19, 4.10 (ca.13:87) (H _B) |
| f | Me | iPr | H | 20:80 | 90% | 82:18 | 3.37, 3.28 (ca.80:20) (H _A) |

^aR = 5'-*O*-(TBDPS)thymidin-3'-yl.

^b**19a,d-f** were isolated by PTLC [hexane-ethyl acetate (1:4, v/v)] as a mixture of (*Sp*)-**19** and (*Rp*)-**19**.

5'-*O*-*tert*-Butyldiphenylsilyl-3'-*O*-(2-oxo-3-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl)thymidine (19a**).** 80% *tert*-butylhydroperoxide solution in di-*tert*-butylperoxide (6.3 μl, 50 μmol) was added to a stirred solution of (*Rp*)-**5a** (33.0 mg, 50 μmol) in CH₃CN (500 μl). After stirring for 5 min, the solution was concentrated to dryness under reduced pressure. The residue was purified by PTLC

Experimental details and characterization data for 1a-e,g-n, 2a-f, 5a-f, 6b,d, and 13a-d.

***N*-(Cyanomethyl)dimethylammonium tetrafluoroborate (1a).** 54% HBF₄ solution in Et₂O (689 μ l, 5.0 mmol) was added dropwise to a stirred solution of *N*-(cyanomethyl)dimethylamine (483 μ l, 5.0 mmol) in dry CH₂Cl₂ (5.0 ml) at -78 °C under argon and the mixture was allowed to warm up to room temperature. Stirring was stopped and the supernatant liquid was removed via a syringe. Dry CH₂Cl₂ (5 ml) was added to the residual solid and the mixture was vigorously stirred, and then the supernatant liquid was removed via a syringe. This washing step was repeated twice and the residual solid was dried under vacuum to afford **1a** (849 mg, 4.9 mmol) as a crystalline solid. mp 169.0-169.5 °C. IR (KBr) ν_{\max} 3010, 2990, 2951, 2554, 2463, 1472, 1421, 1274, 1036, 991 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 7.23 (bs, 1H), 4.17 (s, 2H), 2.95 (s, 6H). ¹³C NMR (75 MHz, CD₃CN) δ 111.7, 45.5, 44.4. Anal. Calcd for C₄H₉BF₄N₂: C, 27.94; H, 5.28; N, 16.29. Found: C, 27.64; H, 5.39; N, 16.19.

***N*-(Cyanomethyl)dimethylammonium hexafluorophosphate (1b).** *N*-(Cyanomethyl)dimethylamine (483 μ l, 5.0 mmol) was added dropwise to a stirred mixture of 61% HPF₆ aqueous solution (1.20 g, 5.0 mmol) and H₂O (5.0 ml) at room temperature. H₂O was then removed by a vacuum freeze dryer. Dry CH₂Cl₂ (5 ml) and dry Et₂O (10 ml) were added to the residue, and the mixture was vigorously stirred. The resultant precipitate was collected by filtration, washed with dry Et₂O (3 \times 1 ml), and dried under vacuum to afford **1b** (1.15 g, 5.0 mmol) as a crystalline solid. mp 112.0-112.5 °C. IR (KBr) ν_{\max} 3010, 2989, 2951, 2550, 2460, 1472, 1421, 1274, 1180, 1150, 1016, 991, 956, 837 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 6.47 (br, 1H), 4.18 (s, 2H), 2.96 (s, 6H). ¹³C NMR (75 MHz, CD₃CN) δ 111.8, 45.8, 44.5. ³¹P NMR (121 MHz, CD₃CN) δ -146.0 (septet, ¹J_{PF} = 706 Hz). Anal. Calcd for C₄H₉F₆N₂P: C, 20.88; H, 3.94; N, 12.17. Found: C, 20.63; H, 4.03; N, 11.90.

***N*-(Cyanomethyl)dimethylammonium trifluoromethanesulfonate (1c).** Trifluoromethanesulfonic acid (442 μ l, 5.0 mmol) was added dropwise to a stirred solution of *N*-(cyanomethyl)dimethylamine (483 μ l, 5.0 mmol) in dry CH₂Cl₂ (5.0 ml) at 0 °C. The mixture was diluted with dry Et₂O (10 ml), cooled down to -78 °C, and then allowed to warm up to room temperature again. The resultant precipitate was collected by filtration, washed with dry Et₂O (3 \times 1 ml), and dried under vacuum to afford **1c** (1.17 g, 5.0 mmol) as a crystalline solid. mp 64.0-65.0 °C. IR (KBr) ν_{\max} 2998, 2667, 1637, 1475, 1259, 1172, 1032, 993, 852, 762, 641 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 8.40 (m, 1H), 4.22 (d, ³J_{HH} = 4.8 Hz, 2H), 2.98 (d, ³J_{HH} = 5.1 Hz 6H). ¹³C NMR (75 MHz, CD₃CN) δ 121.7 (q, ¹J_{CF} = 320 Hz), 111.9, 45.8, 44.5. Anal. Calcd for C₅H₉F₃N₂O₃S: C, 25.64; H, 3.87; N, 11.96. Found: C, 25.38; H, 3.93; N, 11.86.

***N*-(Cyanomethyl)pyrrolidinium tetrafluoroborate (1d).** 54% HBF₄ solution in Et₂O (689 ml, 5.0 mmol) was added dropwise to a stirred solution of *N*-(cyanomethyl)pyrrolidine (551 mg, 5.0 mmol) in dry Et₂O (5.0 ml) at -78 °C under argon, and the mixture was concentrated to dryness under reduced

(hexane-ethyl acetate, 1:4, v/v) to afford **19a** (33.8 mg, 50 μ mol) as a colorless foam. ^{31}P NMR (121 MHz, CDCl_3) δ 20.8 (99%), 20.0 (1%). FAB^+ m/z 698, $[\text{M} + \text{Na}]^+$.

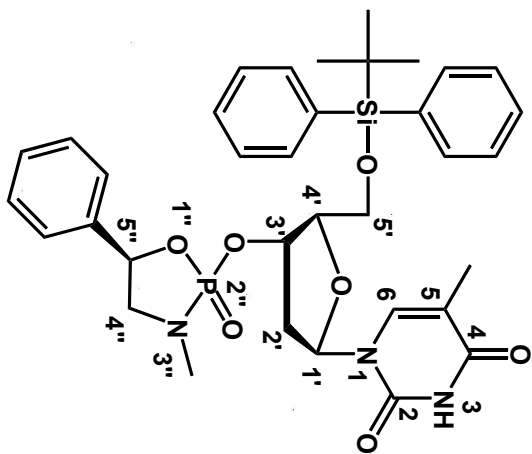
5'-O-tert-Butyldiphenylsilyl-3'-O-(3-methyl-2-oxo-5-phenyl-1,3,2-oxazaphospholidin-2-yl)thymidine (19a). (*Rp*)-**5a** (33.0 mg, 50 μ mol) was dried by repeated coevaporations with dry pyridine and dry toluene, and then dissolved in THF (500 μ l). The solution was heated in a tightly sealed 5 ml round bottom flask for 1 h, and then concentrated to dryness under reduced pressure to afford a diastereomeric mixture of *trans*-**5a** and *cis*-**5a** (59:41). The mixture was oxidized by *tert*-butylhydroperoxide and purified same as above to afford **19a** (31.8 mg, 47 μ mol) as a colorless foam. ^{31}P NMR (121 MHz, CDCl_3) δ 20.8 (61%), 20.0 (39%).

5'-O-tert-Butyldiphenylsilyl-3'-O-(2-oxo-3-isopropyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl)thymidine (19d). 80% *tert*-butylhydroperoxide solution in di-*tert*-butylperoxide (12.6 μ l, 100 μ mol) was added to a stirred solution of (*Rp*)-**5d** (68.8 mg, 100 μ mol) in CH_3CN (1.0 ml). After stirring for 5 min, the solution was concentrated to dryness under reduced pressure. The residue was purified by PTLC (hexane-ethyl acetate, 1:4, v/v) to afford **19d** (70.4 mg, 100 μ mol) as a colorless foam. ^{31}P NMR (121 MHz, CDCl_3) δ 18.9 (98%), 18.5 (2%). FAB^+ m/z 726, $[\text{M} + \text{Na}]^+$.

5'-O-tert-Butyldiphenylsilyl-3'-O-(2-oxo-3-isopropyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl)thymidine (19d). (*Rp*)-**5d** (68.8 mg, 100 μ mol) was dried by repeated coevaporations with dry pyridine and dry toluene, and then dissolved in THF (1.0 ml). The solution was heated in a tightly sealed 5 ml round bottom flask for 1 h, and then concentrated to dryness under reduced pressure to afford a diastereomeric mixture of *trans*-**5d** and *cis*-**5d** (67:33). The mixture was oxidized by *tert*-butylhydroperoxide and purified same as above to afford **19d** (63.3 mg, 90 μ mol) as a colorless foam. ^{31}P NMR (121 MHz, CDCl_3) δ 18.9 (68%), 18.5 (32%).

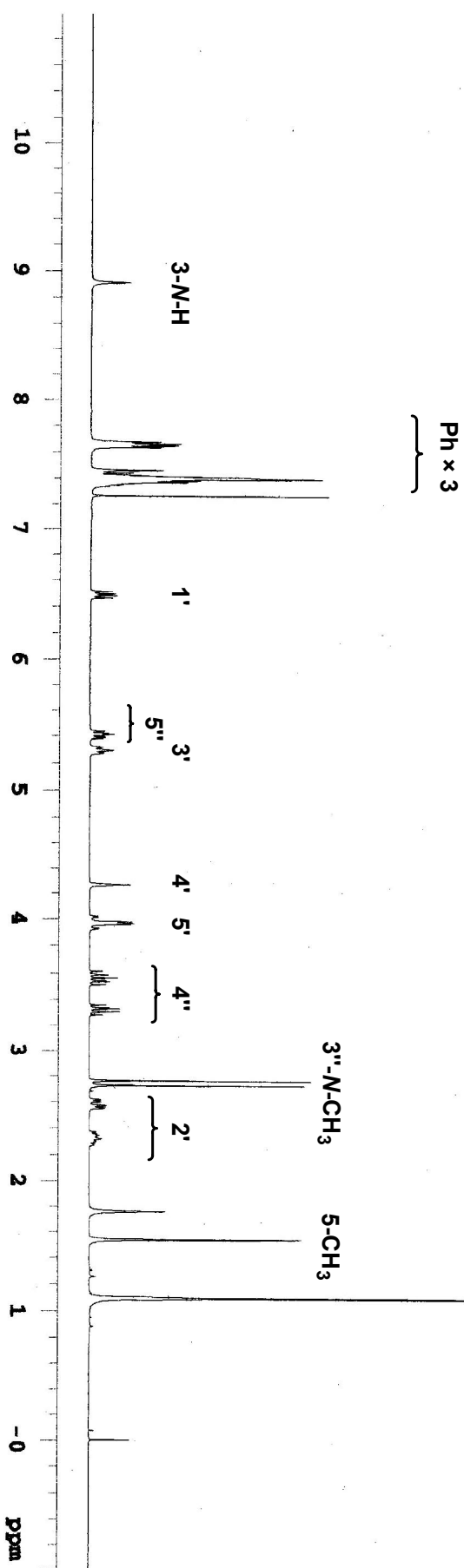
5'-O-tert-Butyldiphenylsilyl-3'-O-(5-isopropyl-3-methyl-2-oxo-1,3,2-oxazaphospholidin-2-yl)thymidine (19e). 80% *tert*-butylhydroperoxide solution in di-*tert*-butylperoxide (6.3 μ l, 50 μ mol) was added to a stirred solution of crude **5e** (*trans*:*cis* = 85:15, 31.3 mg, 50 μ mol) in CH_3CN (500 μ l). After stirring for 5 min, the solution was concentrated to dryness under reduced pressure. The residue was purified by PTLC (hexane-ethyl acetate, 1:4, v/v) to afford **19e** (30.2 mg, 47 μ mol) as a colorless foam. ^{31}P NMR (121 MHz, CDCl_3) δ 21.0 (87%), 20.3 (13%). FAB^+ m/z 642, $[\text{M} + \text{H}]^+$.

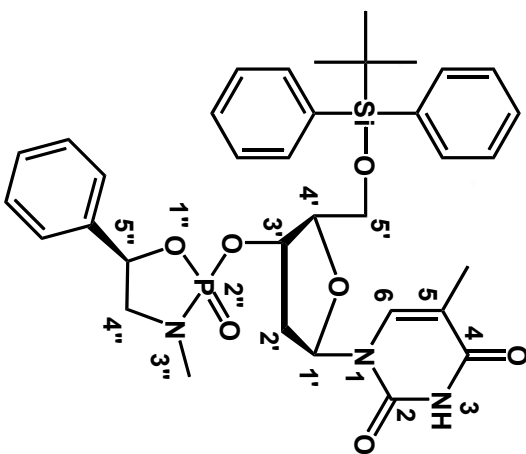
5'-O-tert-Butyldiphenylsilyl-3'-O-(4-isopropyl-3-methyl-2-oxo-1,3,2-oxazaphospholidin-2-yl)thymidine (19f). 80% *tert*-butylhydroperoxide solution in di-*tert*-butylperoxide (6.3 μ l, 50 μ mol) was added to a stirred solution of crude **5f** (*trans*:*cis* = 20:80, 31.3 mg, 50 μ mol) in CH_3CN (500 μ l). After stirring for 5 min, the solution was concentrated to dryness under reduced pressure. The residue was purified by PTLC (hexane-ethyl acetate, 1:4, v/v) to afford **19f** (28.9 mg, 45 μ mol) as a colorless foam. ^{31}P NMR (121 MHz, CDCl_3) δ 24.1 (82%), 22.5 (18%). FAB^+ m/z 642, $[\text{M} + \text{H}]^+$.



19a

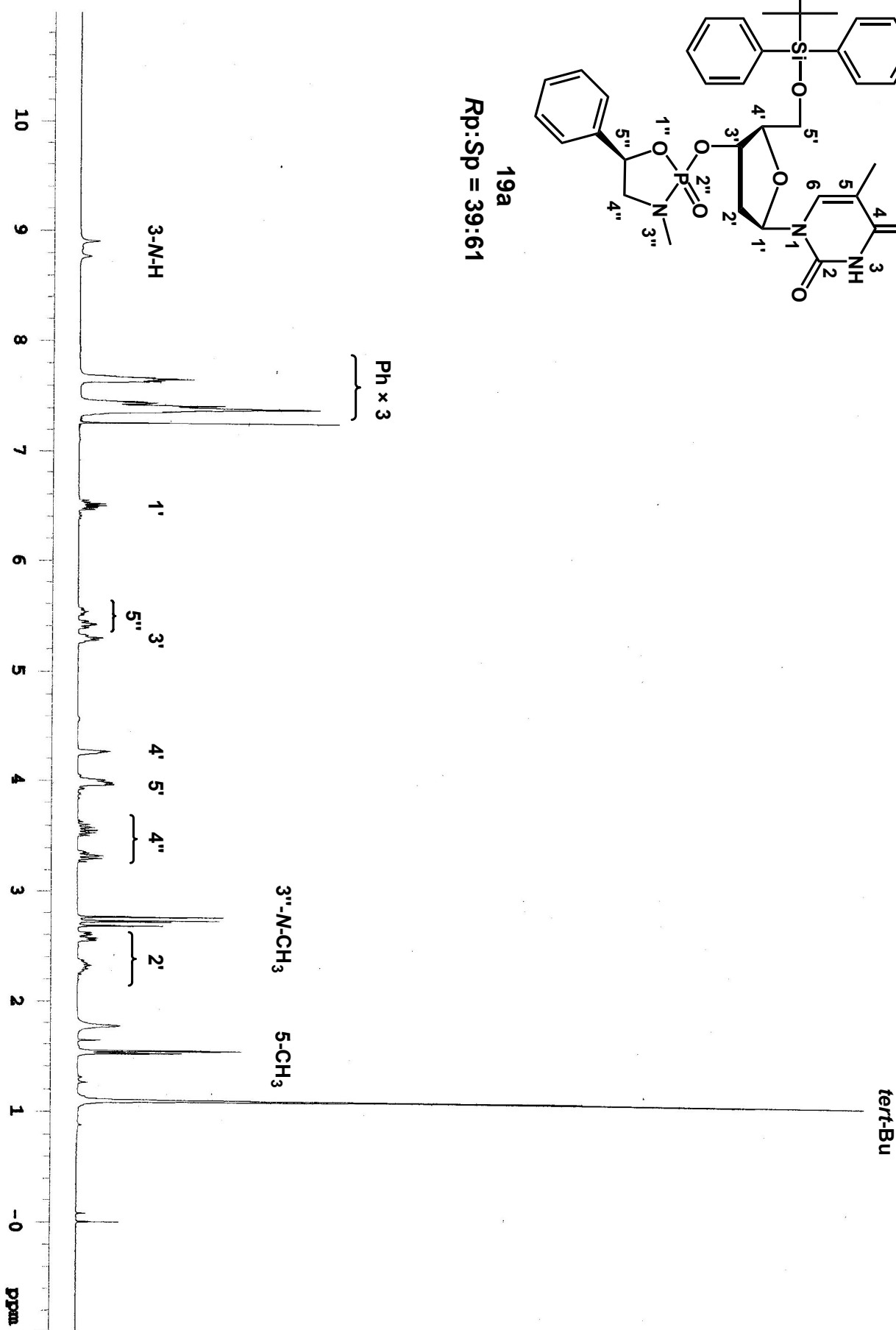
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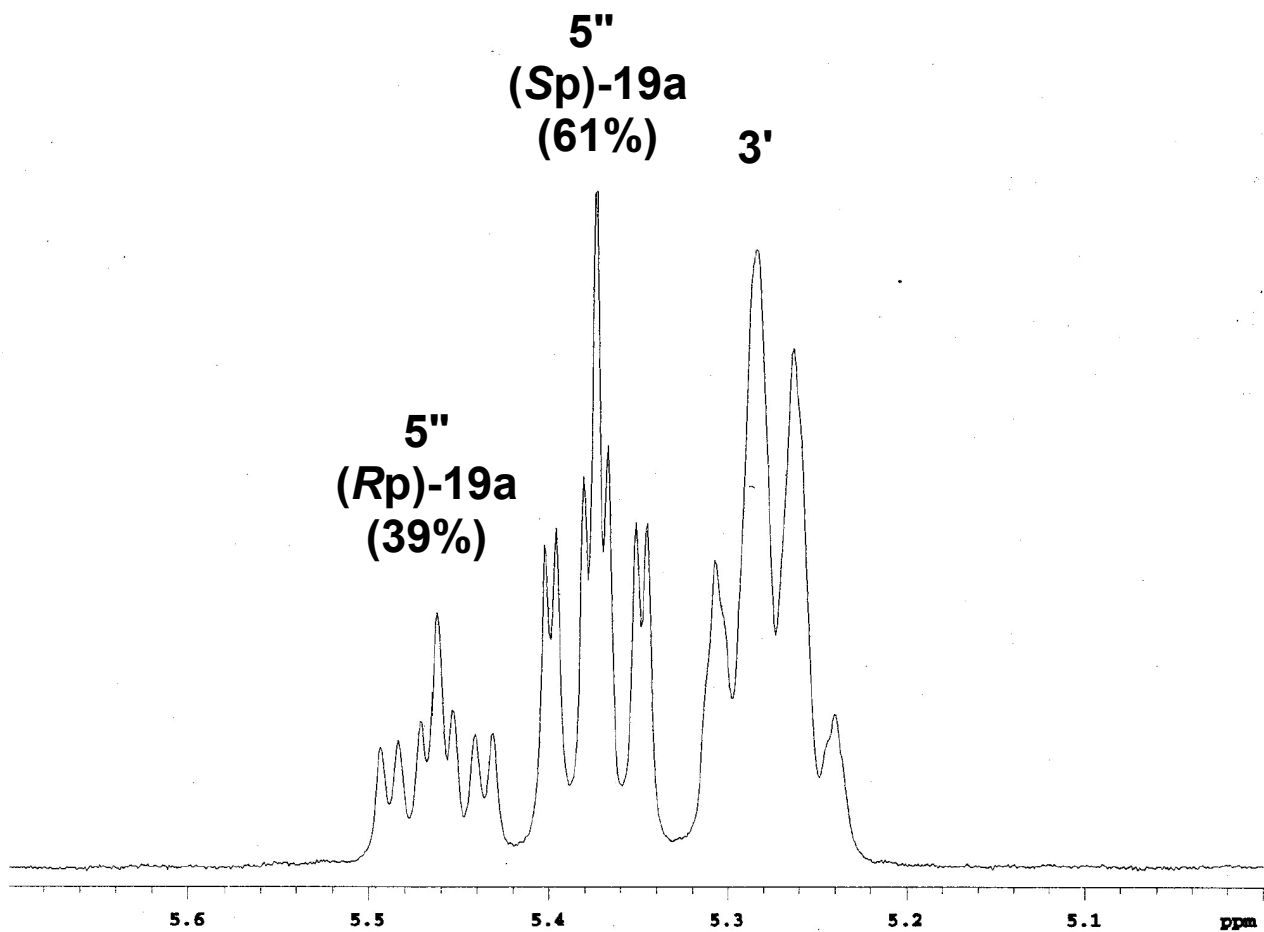
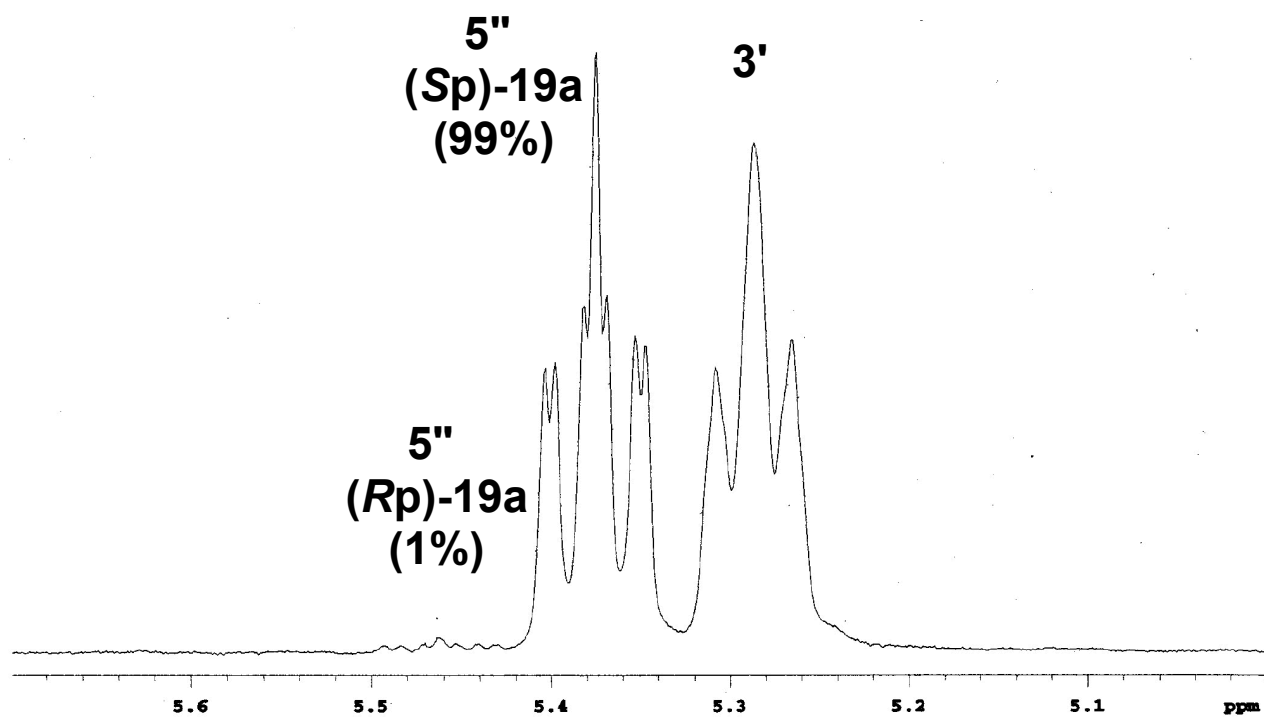


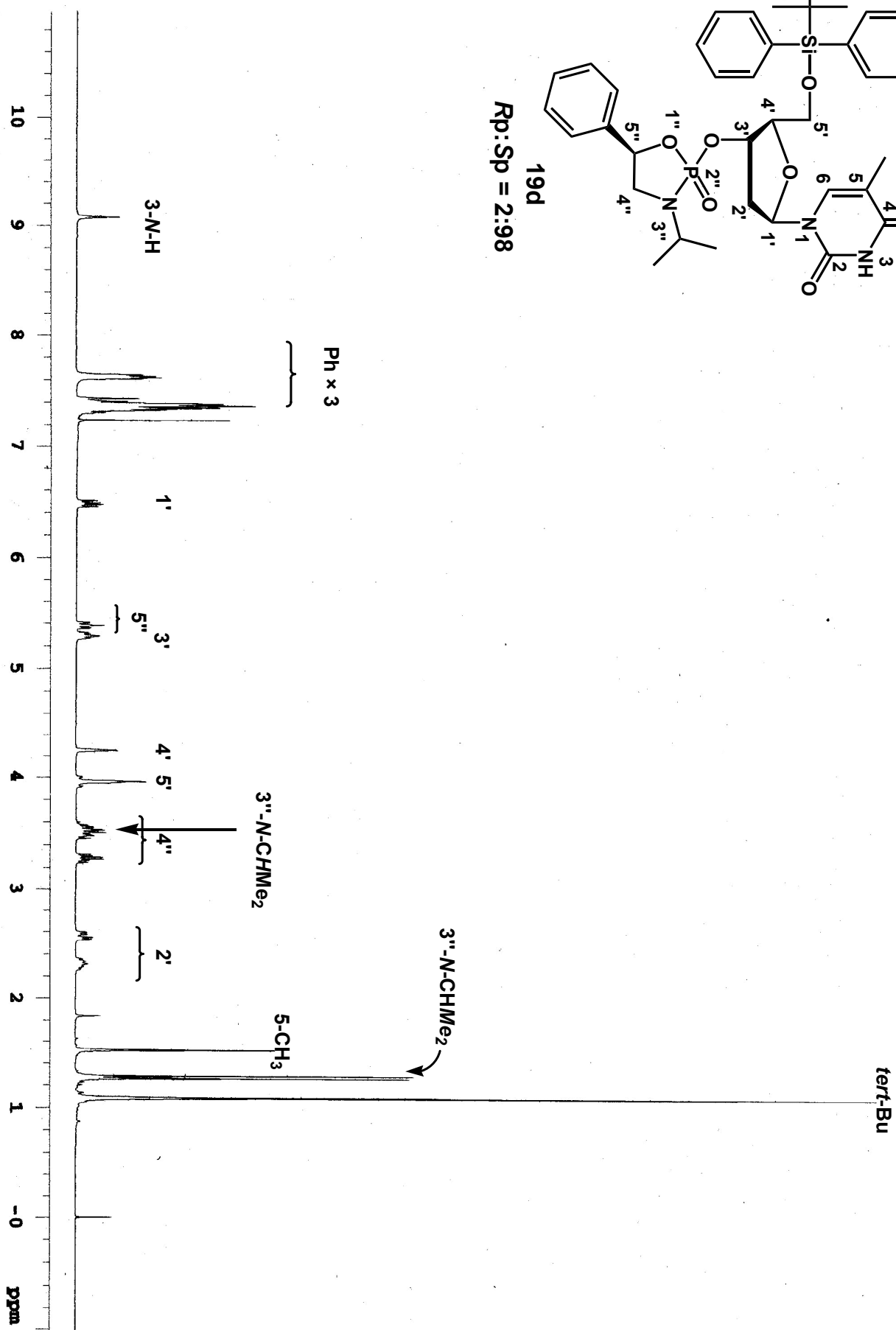
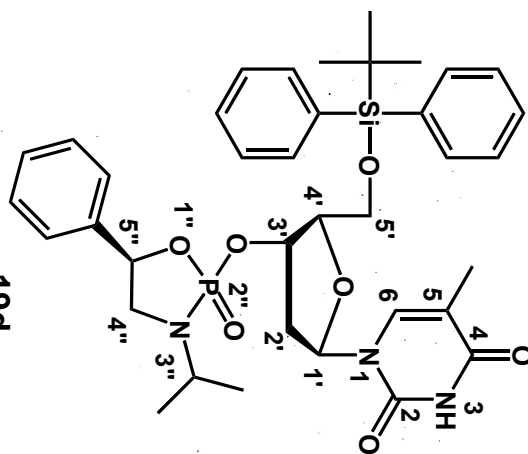


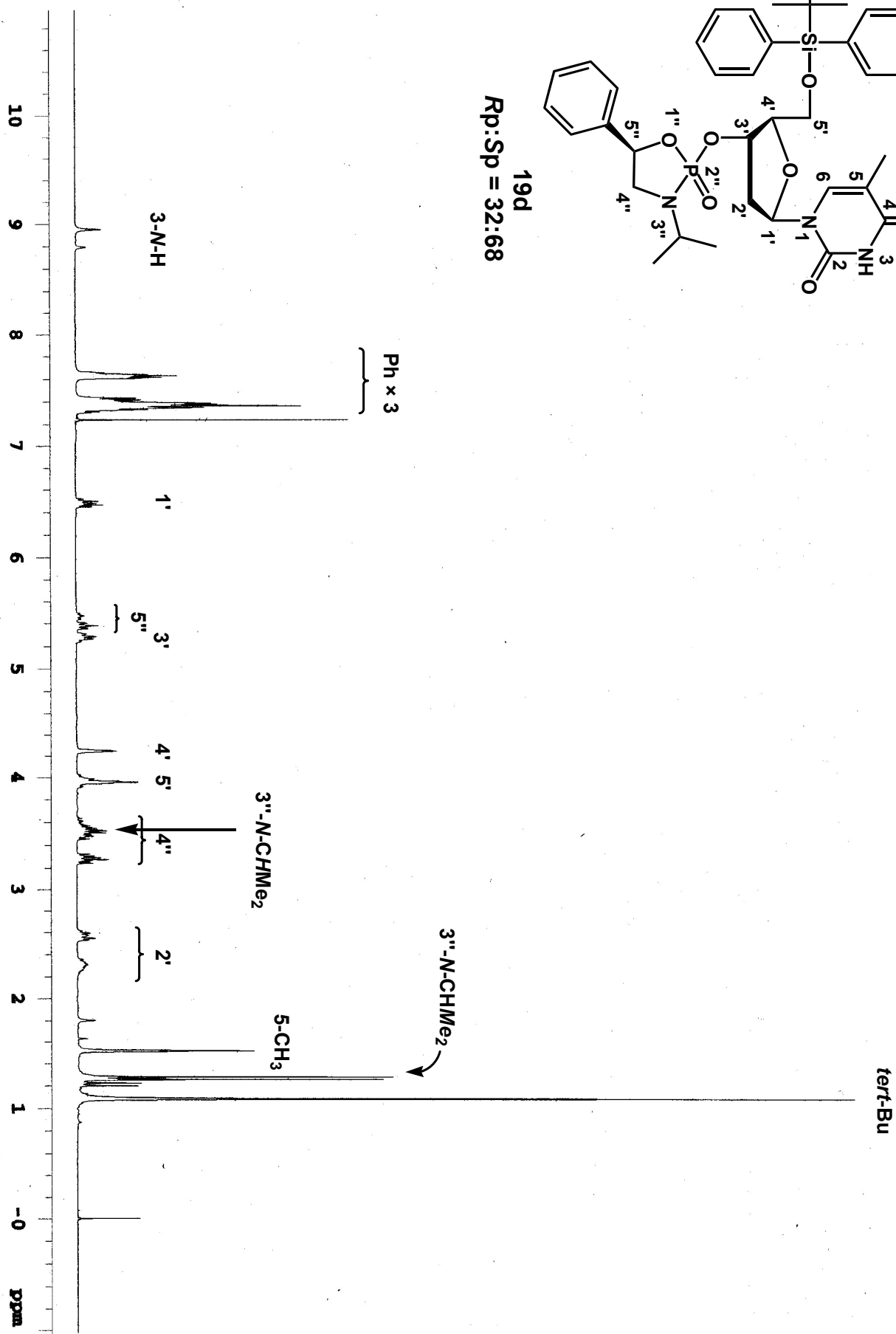
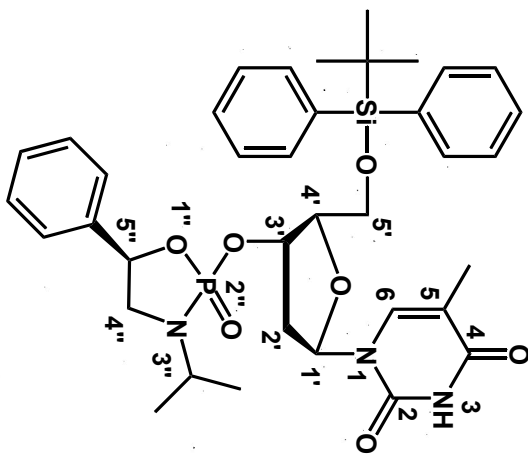
19a

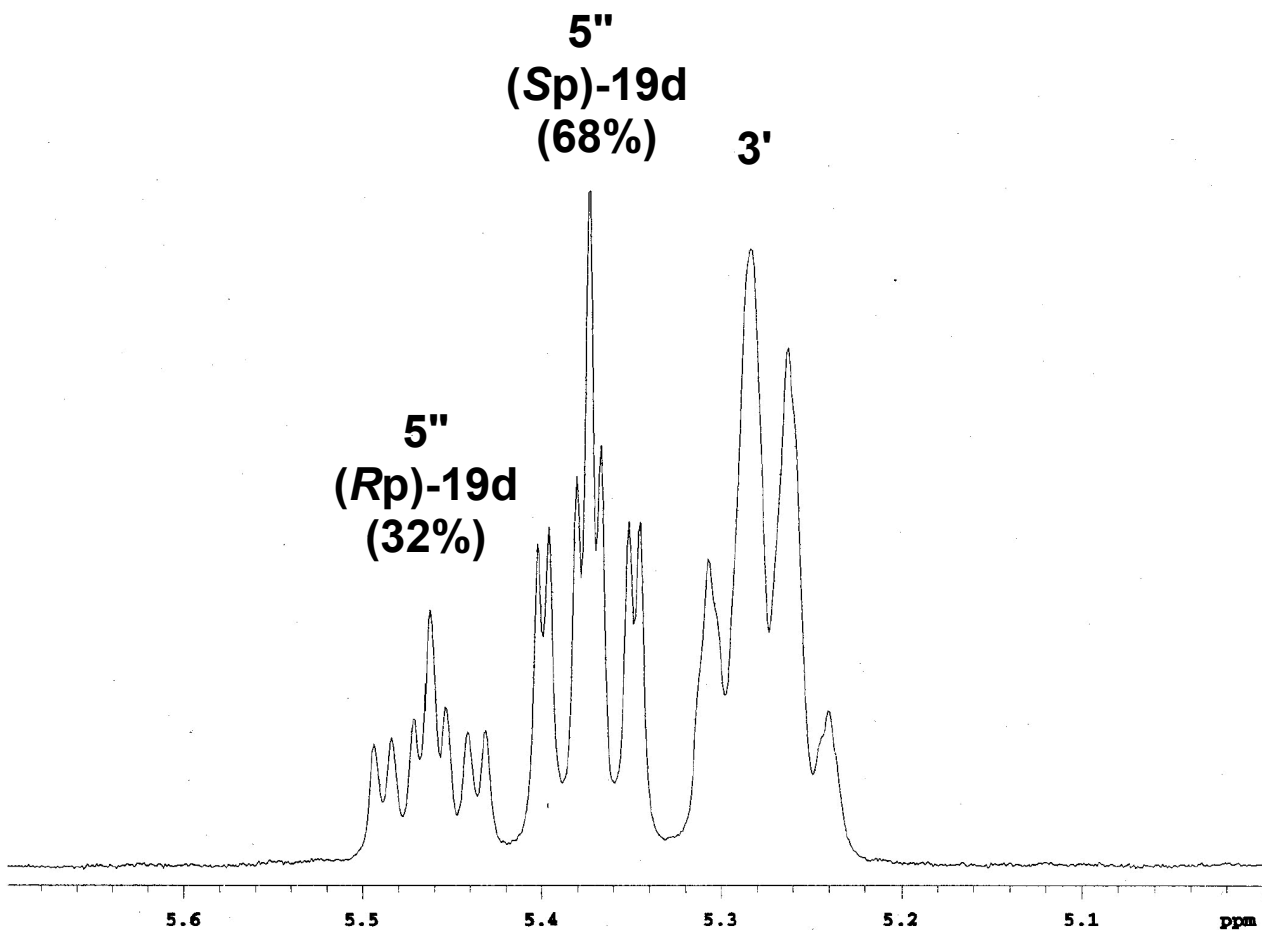
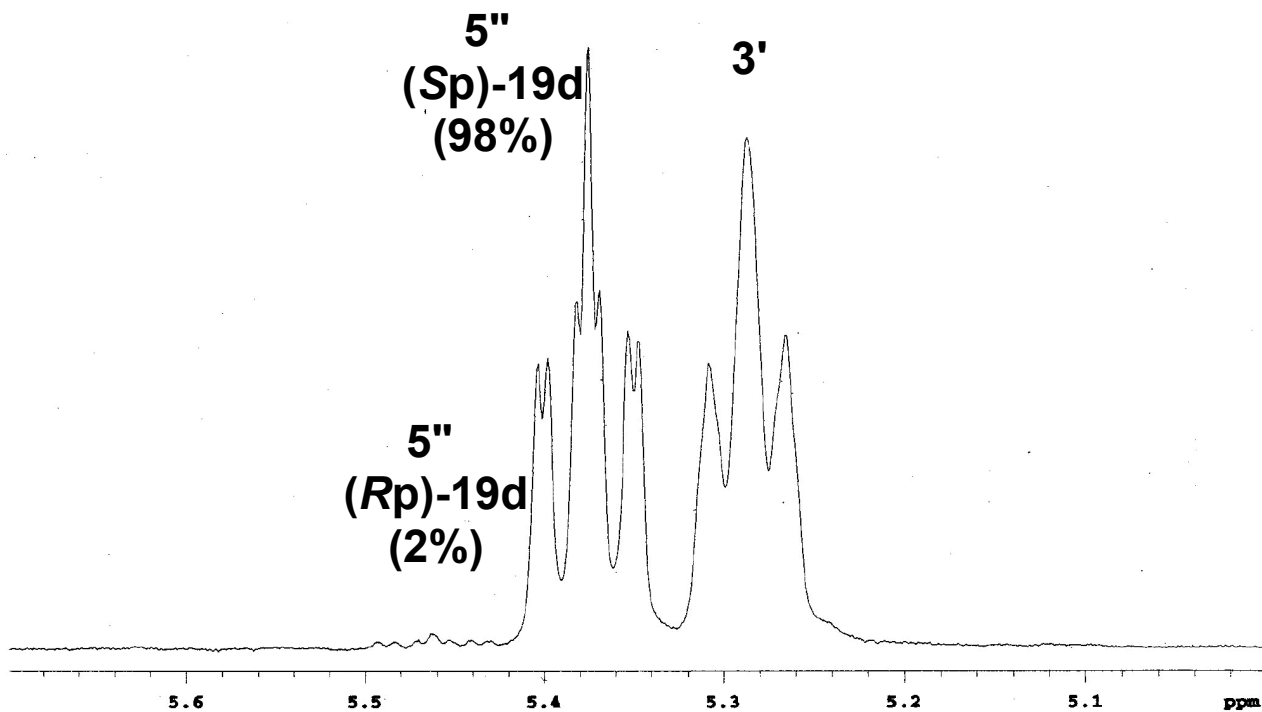
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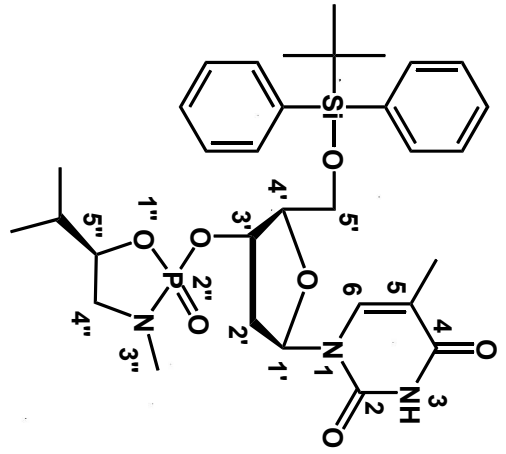




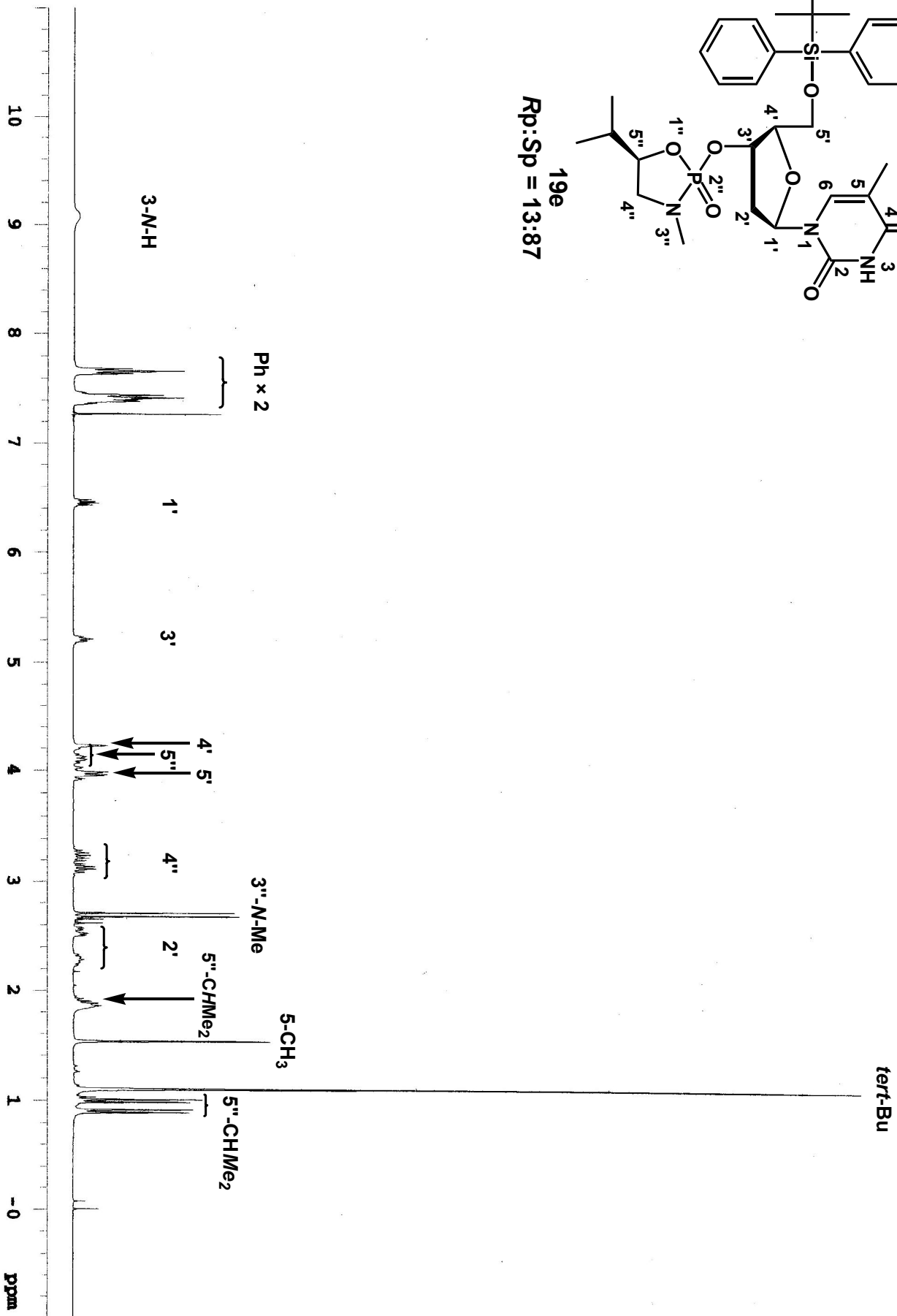


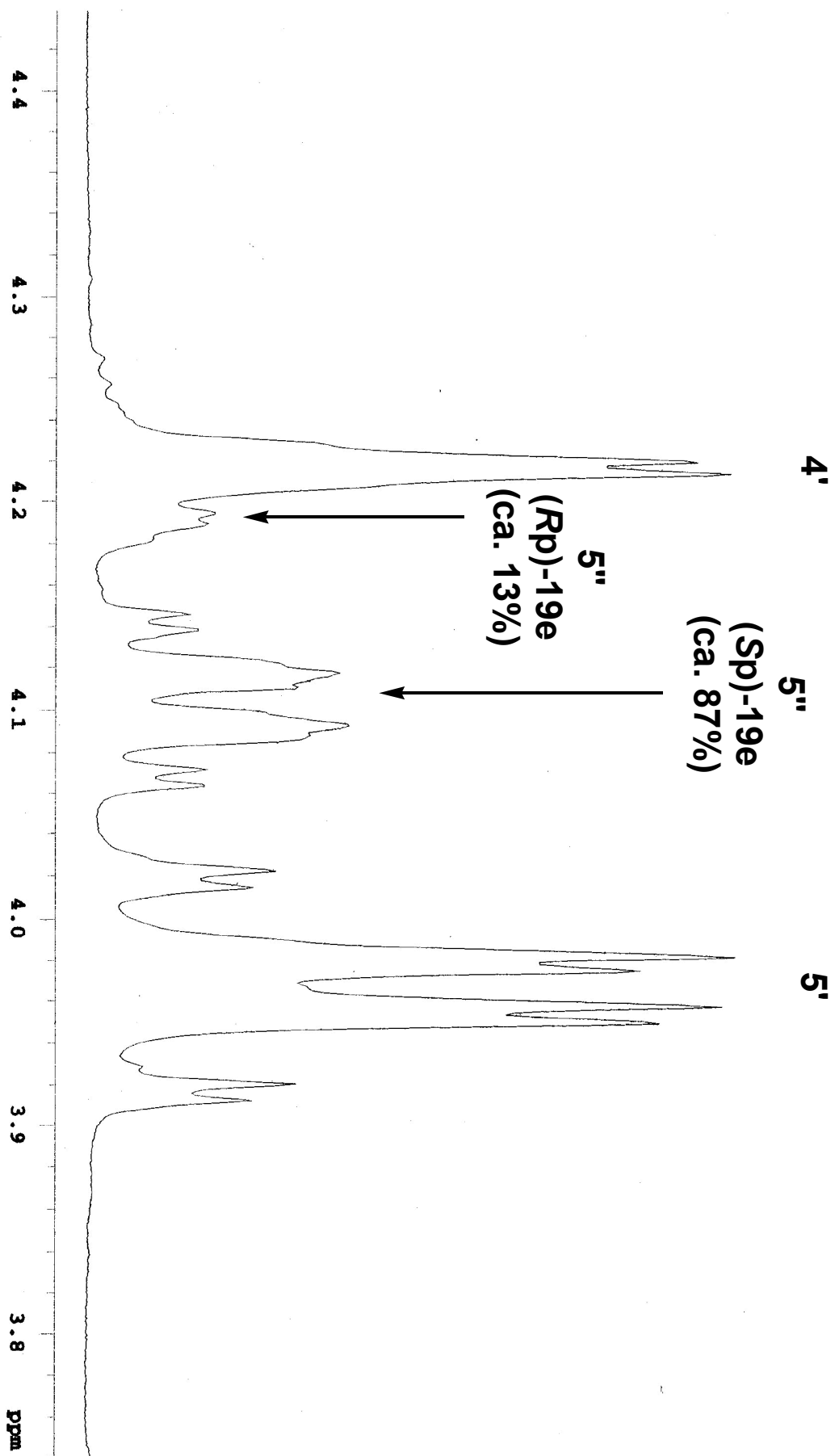


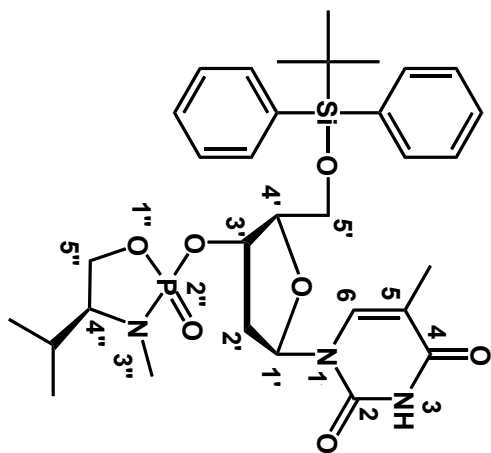




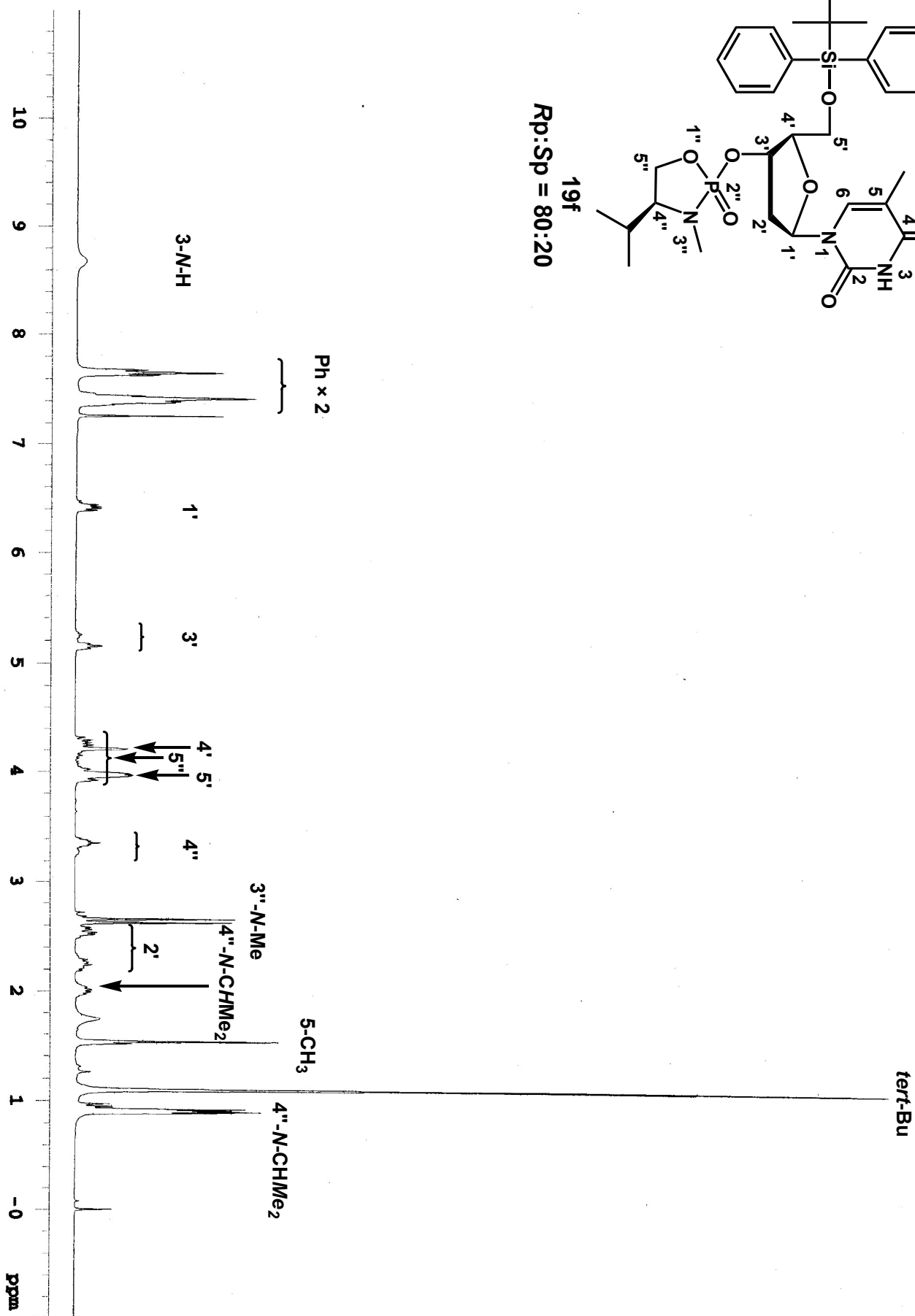
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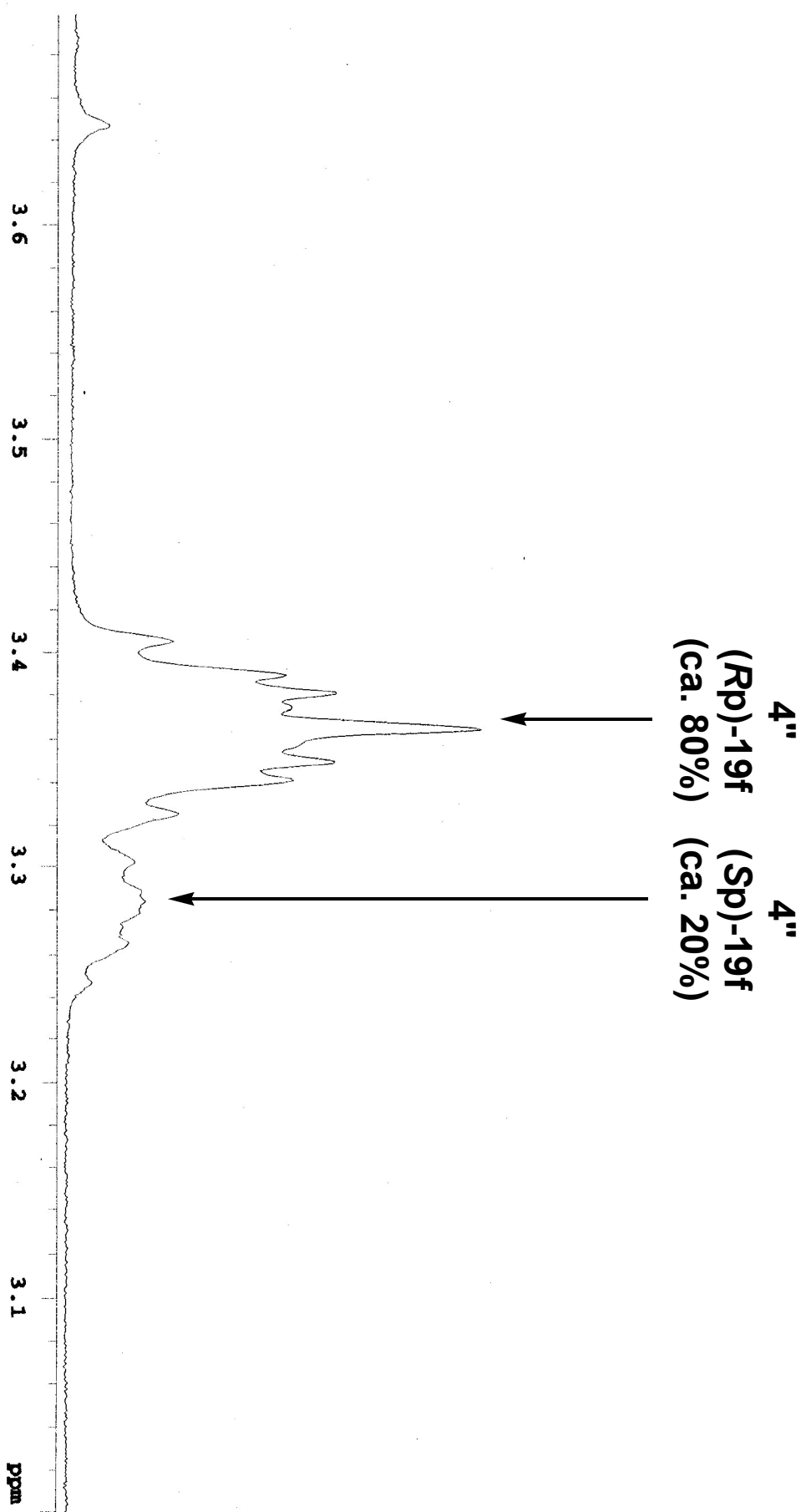






Rp:Sp = 80:20





pressure. Dry Et₂O (2 ml) was added to the residue under argon. The mixture was vigorously stirred, and the supernatant liquid was then removed via a syringe. This washing step was repeated 5 times, and the residue was dried under vacuum to afford **1d** (990 mg, 5.0 mmol) as a crystalline solid. mp 113.0-114.0 °C. IR (KBr) ν_{max} 2988, 2950, 2825, 2527, 2445, 1451, 1407, 1374, 1298, 1119, 929 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 7.18 (br, 1H), 4.28 (s, 2H), 3.49 (br, 4H), 2.08 (m, 4H). ¹³C NMR (75 MHz, CD₃CN) δ 112.4, 56.3, 42.2, 23.6. Anal. Calcd for C₆H₁₁BF₄N₂·1/3H₂O: C, 35.33; H, 5.77; N, 13.73. Found: C, 35.39; H, 5.92; N, 13.79.

***N*-(Cyanomethyl)pyrrolidinium hexafluorophosphate (1e).** *N*-(Cyanomethyl)pyrrolidine (551 mg, 5.0 mmol) was added dropwise to a stirred mixture of 61% HPF₆ aqueous solution (1.20 g, 5.0 mmol) and H₂O (5.0 ml) at room temperature. H₂O was then removed by a vacuum freeze dryer. Dry CH₂Cl₂ (5 ml) and dry Et₂O (10 ml) were added to the residue. The mixture was vigorously stirred and the supernatant liquid was removed via a syringe. Dry Et₂O (10 ml) was added to the residue, the mixture was then vigorously stirred, and the supernatant liquid was removed via a syringe. This washing with dry Et₂O was repeated once more, and the residue was dried under vacuum to afford **1e** (1.28 g, 5.0 mmol) as a crystalline solid. mp 56.0-57.0 °C. IR (KBr) ν_{max} 2988, 2828, 2532, 2448, 1626, 1457, 1296, 1082, 987, 834 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 8.25 (br, 1H), 4.22 (s, 2H), 3.46 (br, 4H), 2.09 (m, 4H). ¹³C NMR (75 MHz, CD₃CN) δ 112.5, 56.4, 42.5, 23.9. ³¹P NMR (121 MHz, CD₃CN) δ -146.0 (septet, ¹J_{PF} = 707 Hz). Anal. Calcd for C₆H₁₁F₆N₂P: C, 28.14; H, 4.33; N, 10.94. Found: C, 27.93; H, 4.66; N, 10.77.

***N*-(Cyanomethyl)pyrrolidinium bistrifluoromethanesulfonimide (1g).** Bistrifluoromethanesulfonimide (1.41 g, 5.0 mmol) was added in portions to a stirred solution of *N*-(cyanomethyl)pyrrolidine (551 mg, 5.0 mmol) in dry CH₂Cl₂ (5.0 ml) at 0 °C under argon. The mixture was allowed to warm up to room temperature, diluted with dry Et₂O (10 ml), and then cooled down to -78 °C to precipitate a white solid. The mixture was allowed to warm up to room temperature again, and the supernatant liquid was removed via a syringe. Dry Et₂O (10 ml) was added to the residue and the mixture was vigorously stirred, and then the supernatant liquid was removed via a syringe. This washing with dry Et₂O was repeated once more, and the residue was dried under vacuum to afford **1g** (1.96g, 5.0 mmol) as a crystalline solid. mp 43.0-44.0 °C. IR (KBr) ν_{max} 3125, 3001, 2603, 1628, 1464, 1351, 1199, 1137, 1059, 915, 793, 765, 742, 655, 617 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 8.13 (br, 1H), 4.22 (s, 2H), 3.46 (m, 4H), 2.08 (m, 4H). ¹³C NMR (75 MHz, CD₃CN) δ 120.8 (q, ¹J_{CF} = 321 Hz), 112.5, 56.5, 42.7, 24.0. Anal. Calcd for C₈H₁₁F₆N₃O₄S₂·H₂O: C, 23.47; H, 3.20; N, 10.27. Found: C, 23.93; H, 3.20; N, 10.27.

***N*-(Cyanomethyl)piperidinium tetrafluoroborate (1h).** 54% HBF₄ solution in Et₂O (1.38 ml, 10 mmol) was added dropwise to a stirred solution of *N*-(cyanomethyl)piperidine (1.24 g, 10 mmol) in dry CH₂Cl₂ (10 ml) at room temperature. Dry Et₂O (20 ml) was added to the solution, and the resultant precipitate was collected by filtration, washed with dry Et₂O (2 × 10 ml), and dried under vacuum to

afford **1h** (2.03 g, 9.6 mmol) as a crystalline solid. mp 103.0-103.5 °C. IR (KBr) ν_{\max} 3149, 2997, 2952, 2876, 2591, 2570, 2491, 2372, 1457, 1422, 1296, 1074, 980, 935, 850, 641 cm^{-1} . ^1H NMR (300 MHz, CD_3CN) δ 6.72 (br, 1H), 4.20 (s, 2H), 3.56 (br, 2H), 3.13 (br, 2H), 1.95-1.49 (m, 6H). ^{13}C NMR (75 MHz, CD_3CN) δ 111.6, 55.0, 44.4, 23.3, 20.9. Anal. Calcd for $\text{C}_7\text{H}_{13}\text{BF}_4\text{N}_2$: C, 39.66; H, 6.18; N, 13.21. Found: C, 39.84; H, 6.08; N, 13.09.

***N*-(Cyanomethyl)piperidinium hexafluorophosphate (1i)**. *N*-(Cyanomethyl)piperidine (621 mg, 5.0 mmol) was added dropwise to a stirred mixture of 61% HPF₆ aqueous solution (1.20 g, 5.0 mmol) and H₂O (5.0 ml) at room temperature. H₂O was then removed by a vacuum freeze dryer, and dry CH₂Cl₂ (5 ml), dry Et₂O (10 ml) were added to the residue. The mixture was vigorously stirred at -78 °C to precipitate a white solid, then allowed to warm up to room temperature again, and the supernatant liquid was removed via a syringe. Dry Et₂O (10 ml) was added to the residue, the mixture was then vigorously stirred, and the supernatant liquid was removed via a syringe. This washing with dry Et₂O was repeated once more, and the residue was dried under vacuum to afford **1i** (1.31 g, 4.9 mmol) as a crystalline solid. mp 54.0-55.0 °C. IR (KBr) ν_{\max} 2997, 2953, 2876, 2589, 2570, 2490, 2372, 1655, 1455, 1422, 1297, 1192, 1142, 1084, 1037, 981, 953, 837, 746 cm^{-1} . ^1H NMR (300 MHz, CD_3CN) δ 7.92 (br, 1H), 4.13 (s, 2H), 3.29 (br, 4H), 1.86 (m, 4H), 1.61 (br, 2H). ^{13}C NMR (75 MHz, CD_3CN) δ 111.9, 54.9, 44.6, 23.5, 21.1. ^{31}P NMR (121 MHz, CD_3CN) δ -145.9 (septet, $^1J_{\text{PF}} = 707$ Hz). Anal. Calcd for $\text{C}_7\text{H}_{13}\text{F}_6\text{N}_2\text{P}$: C, 31.12; H, 4.85; N, 10.37. Found: C, 30.99; H, 5.04; N, 10.27.

***N*-(Cyanomethyl)piperidinium trifluoromethanesulfonate (1j)**. Trifluoromethanesulfonic acid (442 μl , 5.0 mmol) was added dropwise to a stirred solution of *N*-(cyanomethyl)piperidine (621 mg, 5.0 mmol) in dry CH₂Cl₂ (5.0 ml) at 0 °C. The solution was allowed to warm up to room temperature, and then diluted with dry Et₂O (10 ml). The resultant precipitate was collected by filtration, washed with dry Et₂O (3 \times 1 ml), and dried under vacuum to afford **1j** (1.37 g, 5.0 mmol) as a crystalline solid. mp 110.0-110.5 °C. IR (KBr) ν_{\max} 2999, 2723, 1460, 1289, 1226, 1168, 1083, 1027, 978, 936, 762, 641 cm^{-1} . ^1H NMR (300 MHz, CD_3CN) δ 8.10 (br, 1H), 4.17 (s, 2H), 3.56 (br, 2H), 3.08 (br, 2H), 1.80 (br, 5H), 1.50 (br, 1H). ^{13}C NMR (75 MHz, CD_3CN) δ 121.3 (q, $^1J_{\text{CF}} = 319$ Hz), 111.7, 54.9, 44.6, 23.4, 21.0. Anal. Calcd for $\text{C}_8\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3\text{S}$: C, 35.03; H, 4.78; N, 10.21. Found: C, 34.79; H, 4.66; N, 10.20.

***N*-(Cyanomethyl)diisopropylammonium tetrafluoroborate (1k)**. 54% HBF₄ solution in Et₂O (689 μl , 5.0 mmol) was added dropwise to a stirred solution of *N*-(cyanomethyl)diisopropylamine (702 mg, 5.0 mmol) in dry CH₂Cl₂ (5.0 ml) at room temperature. Dry Et₂O (10 ml) was added to the solution, and the resultant precipitate was collected by filtration, washed with dry Et₂O (3 \times 1 ml), and dried under vacuum to afford **1k** (1.12 g, 4.9 mmol) as a crystalline solid. mp 132.5-133.0 °C. IR (KBr) ν_{\max} 2998, 2941, 2856, 2738, 2629, 2593, 2500, 1477, 1407, 1272, 1085, 985 cm^{-1} . ^1H NMR (300 MHz, CD_3CN) δ 7.24 (bs, 1H), 4.17 (s, 2H), 3.88 (septet, $^3J_{\text{HH}} = 6.6$ Hz, 2H), 1.39 (d, $^3J_{\text{HH}} = 6.6$ Hz, 12H). ^{13}C NMR (75 MHz, CD_3CN) δ 113.2, 58.3, 34.9, 18.4 (br), 17.4 (br). Anal. Calcd for $\text{C}_8\text{H}_{17}\text{BF}_4\text{N}_2$: C, 42.14; H, 7.51; N, 12.28. Found: C, 42.35; H, 7.77; N, 12.05.

***N*-(Cyanomethyl)diisopropylammonium hexafluorophosphate (1l).**

N-(Cyanomethyl)diisopropylamine (701 mg, 5.0 mmol) was added dropwise to a stirred mixture of 61% HPF₆ aqueous solution (1.20 g, 5.0 mmol) and H₂O (5.0 ml) at room temperature. H₂O was then removed by a vacuum freeze dryer, and then dry CH₂Cl₂ (5 ml) and dry Et₂O (10 ml) were added to the residue. The mixture was vigorously stirred, and the precipitate was collected by filtration, washed with dry Et₂O (3 × 1 ml), and dried under vacuum to afford **1l** (1.34 g, 4.7 mmol) as a crystalline solid. mp 117.0-118.0 °C. IR (KBr) ν_{\max} 2940, 2604, 2501, 1442, 1403, 1314, 1175, 1121, 1089, 843 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 7.53 (bs, 1H), 4.18 (s, 2H), 3.90 (septet, ³J_{HH} = 6.6 Hz, 2H), 1.39 (d, ³J_{HH} = 6.6 Hz, 12H). ¹³C NMR (75 MHz, CD₃CN) δ 113.0, 58.3, 34.8, 18.6 (br), 17.0 (br). ³¹P NMR (121 MHz, CD₃CN) δ -146.0 (septet, ¹J_{PF} = 707 Hz). Anal. Calcd for C₈H₁₇F₆N₂P: C, 33.57; H, 5.99; N, 9.79. Found: C, 33.68; H, 5.92; N, 9.61.

***N*-(Cyanomethyl)diisopropylammonium trifluoromethanesulfonate (1m).**

Trifluoromethanesulfonic acid (442 μ l, 5.0 mmol) was added dropwise to a stirred solution of *N*-(cyanomethyl)diisopropylamine (701 mg, 5.0 mmol) in dry CH₂Cl₂ (5.0 ml) at 0 °C. The solution was allowed to warm up to room temperature, diluted with dry Et₂O (10 ml), cooled down to -78 °C to precipitate a white solid, and then allowed to warm up to room temperature again. The resultant precipitate was collected by filtration, washed with dry Et₂O (3 × 1 ml), and dried under vacuum to afford **1m** (1.31 g, 4.5 mmol) as a crystalline solid. mp 62.0-63.0 °C. IR (KBr) ν_{\max} 3035, 2967, 2817, 2712, 1486, 1402, 1389, 1286, 1240, 1166, 1089, 1033, 938, 815, 762, 640 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 8.30 (bs, 1H), 4.22 (s, 2H), 3.91 (septet, ³J_{HH} = 6.6 Hz, 2H), 1.41 (d, ³J_{HH} = 6.6 Hz, 12H). ¹³C NMR (75 MHz, CD₃CN) δ 121.4 (q, ¹J_{CF} = 320 Hz), 113.2, 57.8, 34.8, 18.6 (br), 17.0 (br). Anal. Calcd for C₉H₁₇F₃N₂O₃S: C, 37.24; H, 5.90; N, 9.65. Found: C, 37.06; H, 5.89; N, 9.66.

***N*-(Cyanomethyl)diisopropylammonium bistrifluoromethanesulfonimide (1n).**

N-(Cyanomethyl)diisopropylamine (701 mg, 5.0 mmol) was added to a stirred solution of bistrifluoromethanesulfonimide (1.41 g, 5.0 mmol) in dry CH₂Cl₂ (5.0 ml) at 0 °C. The solution was allowed to warm up to room temperature, diluted with dry Et₂O (10 ml), cooled down to -78 °C to precipitate a white solid, and then allowed to warm up to room temperature again. The resultant precipitate was collected by filtration, washed with dry Et₂O (3 × 1 ml), and dried under vacuum to afford **1n** (1.77 g, 4.2 mmol) as a crystalline solid. mp 53.0-54.0 °C. IR (KBr) ν_{\max} 3006, 2662, 1629, 1473, 1404, 1351, 1197, 1138, 1058, 904, 794, 765, 742, 655, 618 cm⁻¹. ¹H NMR (300 MHz, CD₃CN) δ 7.45 (br, 1H), 4.18 (s, 2H), 3.90 (septet, ³J_{HH} = 6.6 Hz, 2H), 1.39 (d, ³J_{HH} = 6.6 Hz, 12H). ¹³C NMR (75 MHz, CD₃CN) δ 120.7 (q, ¹J_{CF} = 321 Hz), 113.0, 58.4, 34.8, 18.6, 17.0. Anal. Calcd for C₁₀H₁₇F₆N₃O₄S₂: C, 28.50; H, 4.07; N, 9.97. Found: C, 28.63; H, 4.14; N, 9.84.

(*R*)-2-Methylamino-1-phenylethanol [(*R*)-2a]. Enantiomer ratio of (*R*)-**2a** prepared according to the procedure described in the literature²⁷ was ca. 97:3. Enantiopure (*R*)-**2a** was obtained as follows: (*R*)-**2a**

(*R:S* = 97:3, 5.82 g, 39 mmol) was dissolved in CH₂Cl₂ (50 ml) and *trans*-cinnamic acid (5.70 g, 39 mmol) was added. The mixture was concentrated to dryness and the residual solid was recrystallized from dry EtOH twice (25 ml, 20 ml, respectively) to afford *trans*-cinnamic acid salt of (*R*)-**2a** (8.24 g, 28 mmol) as colorless crystals. The crystals were suspended in CH₂Cl₂ (100 ml) and washed with 2 M KOH aqueous solution (100 ml). The aqueous layer was back-extracted with CH₂Cl₂ (2 × 100 ml), and the combined organic layers were washed with saturated NaCl aqueous solution (2 × 100 ml), dried over Na₂SO₄, filtered and concentrated to dryness to afford (*R*)-**2a** (4.16 g, 28 mmol) as a colorless oil. ¹H NMR spectrum was identical to the reported one.³¹ The enantiomer ratio of (*R*)-**2a** was determined as follows: 4 M imidazole solution in THF (250 μl, 1.0 mmol) and 2 M *tert*-butyldimethylsilylchloride (TBDMSCl) solution in THF (250 μl, 500 μmol) were added to (*R*)-**2a** (15 mg, 100 μmol) and stirred for 12 h at room temperature. Saturated NaHCO₃ aqueous solution (3 ml) was added to the mixture and extracted with Et₂O (3 × 3 ml). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to dryness. The residue was analyzed by chiral HPLC³² [CHIRALCEL OD-H, hexane-*i*PrOH (99.2:0.8, v/v), at a flow rate of 0.5 ml]. The enantiomer ratio was determined to be >99.5:0.5.

(*S*)-2-Methylamino-1-phenylethanol [(*S*)-2a]. Enantiopure (*S*)-**2a** was prepared according to the same procedure as (*R*)-**2a** in a similar yield.

(1*R,2S*)-2-Methylamino-1,2-diphenylethanol (2c). **2c** was synthesized from (1*R,2S*)-2-amino-1,2-diphenylethanol³³ according to the procedure described in the literature³⁴ with minor modifications.

(*R*)-2-Isopropylamino-1-phenylethanol (2d). Enantiomer ratio of **2d** synthesized by *N*-isopropylation³⁵ of 2-amino-1-phenylethanol³⁶ was ca. 98:2. Enantiopure **2d** was obtained by a single recrystallization from hexane (recrystallization of 2.0 g of **2d** from 10 ml of hexane afforded 1.25 g of enantiopure **2d**). ¹H NMR spectrum was identical to the reported one.³² Enantiomer ratio of **2d** was determined as follows: 4 M imidazole solution in THF (250 μl, 1.0 mmol) and 2 M TBDMSCl solution in THF (250 μl, 500 μmol) were added to **2d** (15 mg, 100 μmol) and stirred for 12 h at room temperature. Saturated NaHCO₃ aqueous solution (3 ml) was added to the mixture and extracted with Et₂O (3 × 3 ml). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated to dryness. The residue was analyzed by chiral HPLC³² [CHIRALCEL OD-H, hexane-*i*PrOH (99.7:0.3, v/v), at a flow rate of 0.5 ml]. The enantiomer ratio was determined to be >99.5:0.5.

(*R*)-2-Methylamino-3-methyl-2-butanol (2e).³⁷ **2e** was synthesized from (*S*)-2-hydroxy-3-methylbutanoic acid (**19**)³⁸ by the same procedure used for the preparation of **2a**.³¹ The procedure was as follows: **19** (11.8 g, 100 mmol) was dissolved in acetone (44 ml, 600 mmol) and the mixture was cooled down to -15 °C. Concentrated H₂SO₄ (5.34 ml, 100 mmol) was added dropwise to the stirred mixture at a rate sufficient to maintain the reaction temperature of below -5 °C, resulting in

the formation of a white precipitate. The mixture was poured into ice-cold Na₂CO₃ aqueous solution (20 g in 180 ml) and extracted with CH₂Cl₂ (2 × 200 ml). The combined organic layers were dried over Na₂SO₄, filtered, evaporated, and dried under vacuum to afford (*R*)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-one **20** (11.2 g, 71 mmol) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃) δ 4.26 (d, ³J_{HH} = 3.6 Hz, 1H), 2.16 (m, 1H), 1.61 (s, 3H), 1.54 (s, 3H), 1.08 (d, ³J_{HH} = 6.6 Hz, 3H), 0.99 (d, ³J_{HH} = 6.9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 172.7, 110.1, 78.5, 30.0, 26.7, 26.0, 18.4, 16.4. **20** was used without further purification for the next step.

36-40% methylamine solution in methanol (16.0 ml) was added to a stirred solution of **20** (11.1 g, 70 mmol) in toluene (70 ml). The flask was tightly sealed, and the reaction mixture was stirred for 15 h, and then concentrated to dryness to afford (*R*)-*N*-methyl-2-hydroxy-3-methylbutanamide **21** (8.08 g, 62 mmol) as colorless needles. ¹H NMR spectrum was identical to the reported one.³⁹ **21** was used without further purification for the next step.

21 (6.56 g, 50 mmol) was dried by repeated coevaporations with dry pyridine and toluene, and then dissolved in dry THF (125 ml). The solution was added dropwise to a stirred mixture of lithium aluminium hydride (9.49 g, 250 mmol) in dry THF (125 ml) at 0 °C. The mixture was refluxed for 40 h, and then cooled with ice bath. The mixture was diluted with Et₂O (350 ml), and saturated Na₂SO₄ aqueous solution (100 ml) was carefully added to the mixture. The resultant white precipitate was removed by filtration through Celite, and the filtrate was concentrated. The residue was purified by bulb-to-bulb distillation (120 °C, 10 mmHg) to afford **2e** (2.97 g, 25 mmol) as a colorless liquid. ¹H NMR (300 MHz, CDCl₃) δ 3.34 (m, 1H), 2.69 (dd, ²J_{HH} = 11.8 Hz, ³J_{HH} = 3.3 Hz, 1H), 2.46 (dd, ²J_{HH} = 11.8 Hz, ³J_{HH} = 9.9 Hz, 1H), 2.44 (s, 3H), 1.64 (m, 1H), 0.97 (d, ³J_{HH} = 6.6 Hz, 3H), 0.91 (d, ³J_{HH} = 6.9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 73.9, 54.9, 36.2, 32.2, 18.5, 18.3. The enantiomer ratio of **2e** was determined as follows: Benzoyl chloride (578 μl, 5.0 mmol) was added dropwise to a stirred solution of **2e** (118 mg, 1.0 mmol) in dry pyridine (2.0 ml) at 0 °C and the mixture was stirred for 8 h at room temperature. Pyridine was removed by repeated coevaporations with toluene, and the residue was diluted with Et₂O (5 ml), washed with saturated NaHCO₃ aqueous solution (5 ml), and the aqueous layer was back-extracted with Et₂O (2 × 5 ml). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by PTLC (hexane-ethyl acetate, 1:2, v/v) to afford *N,O*-dibenzoyl-**2e** (309 mg, 0.95 mmol) as a pale yellow oil. The product was analyzed by chiral HPLC [CHIRALPAK AD-H, hexane-*i*PrOH (9:1, v/v), at a flow rate of 1.0 ml]. The enantiomer ratio was determined to be 98:2.

(S)-*N*-Methylvalinol (2f). **2f** was synthesized according to the procedure described in the literature⁴⁰ with minor modifications.

5'-*O*-(*tert*-Butyldiphenylsilyl)-3'-*O*-[(2*R*,5*R*)-3-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]thymidine [(*Rp*)-5a**]**. ¹H NMR (300 MHz, CDCl₃) δ 9.00 (br, 1H), 7.69-7.65 (m, 4H), 7.49-7.32 (m, 12H), 6.43 (dd, ³J_{HH} = 8.1, 5.8 Hz, 1H), 5.58 (dd, ³J_{HH} = 7.4, 7.4 Hz, 1H), 4.95-4.90 (m, 1H), 4.05-4.04 (m, 1H), 3.98 (dd, ²J_{HH} = 11.7 Hz, ³J_{HH} = 2.3 Hz, 1H), 3.88 (dd, ²J_{HH} = 11.7 Hz, ³J_{HH} = 2.3 Hz, 1H), 3.51

(ddd, $^2J_{\text{HH}} = 8.6$ Hz, $^3J_{\text{HH}} = 7.4$ Hz, $^3J_{\text{PH}} = 3.5$ Hz, 1H), 2.90 (dd, $^2J_{\text{HH}} = 8.6$ Hz, $^3J_{\text{HH}} = 7.4$ Hz, 1H), 2.74 (d, $^3J_{\text{PH}} = 12.0$ Hz, 1H), 2.44 (ddd, $^2J_{\text{HH}} = 13.5$ Hz, $^3J_{\text{HH}} = 5.8$, 2.1 Hz, 1H), 2.24 (ddd, $^2J_{\text{HH}} = 13.5$ Hz, $^3J_{\text{HH}} = 8.1$, 6.6 Hz, 1H), 1.59 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.8, 150.4, 140.3 (d, $^2J_{\text{PC}} = 3.2$ Hz), 135.5, 135.2, 135.2, 132.9, 132.2, 130.1, 130.0, 128.5, 128.1, 128.0, 127.9, 125.8, 111.3, 86.4 (d, $^3J_{\text{PC}} = 2.0$ Hz), 84.4, 81.8 (d, $^2J_{\text{PC}} = 9.8$ Hz), 72.5 (d, $^2J_{\text{PC}} = 15.8$ Hz), 63.5, 57.1 (d, $^2J_{\text{PC}} = 4.8$ Hz), 40.4 (d, $^3J_{\text{PC}} = 4.9$ Hz), 31.8 (d, $^2J_{\text{PC}} = 23.0$ Hz), 27.0, 19.4, 12.0. ^{31}P NMR (121 MHz, CDCl_3) δ 144.6. FAB-HRMS: calcd for $\text{C}_{35}\text{H}_{43}\text{N}_3\text{O}_6\text{PSi}^+$ ($\text{M} + \text{H}^+$) 660.2659, found 660.2658.

5'-O-(tert-Butyldiphenylsilyl)-3'-O-[(2*S*,5*S*)-3-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]thymidine [(*Sp*)-5a**].** Purification by silica gel column chromatography (2.5 × 14 cm, 40 g of silica gel, hexane-ethyl acetate-triethylamine, 50:50:2, v/v/v) afforded (*Sp*)-**5a** (772 mg, 1.2 mmol) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ 8.96 (br, 1H), 7.71-7.65 (m, 4H), 7.46-7.33 (m, 12H), 6.42 (dd, $^3J_{\text{HH}} = 8.2$, 5.6 Hz, 1H), 5.60 (dd, $^3J_{\text{HH}} = 7.2$, 7.2 Hz, 1H), 4.91-4.85 (m, 1H), 4.06-4.05 (m, 1H), 4.01 (dd, $^2J_{\text{HH}} = 11.4$ Hz, $^3J_{\text{HH}} = 2.7$ Hz, 1H), 3.86 (dd, $^2J_{\text{HH}} = 11.4$ Hz, $^3J_{\text{HH}} = 2.7$ Hz, 1H), 3.53 (ddd, $^2J_{\text{HH}} = 9.0$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, $^3J_{\text{PH}} = 3.3$ Hz, 1H), 2.91 (dd, $^2J_{\text{HH}} = 9.0$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, 1H), 2.71 (d, $^3J_{\text{PH}} = 12.0$ Hz, 3H), 2.42 (ddd, $^2J_{\text{HH}} = 13.5$ Hz, $^3J_{\text{HH}} = 5.6$, 2.3 Hz, 1H), 2.20 (ddd, $^2J_{\text{HH}} = 13.5$ Hz, $^3J_{\text{HH}} = 8.2$, 6.3 Hz, 1H), 1.61 (s, 3H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.7, 150.4, 140.3 (d, $^3J_{\text{PC}} = 3.4$ Hz), 135.5, 135.3, 135.1, 132.8, 132.3, 130.2, 130.0, 128.5, 128.1, 128.0, 128.0, 125.9, 111.3, 86.5 (d, $^3J_{\text{PC}} = 5.5$ Hz), 84.3, 81.9 (d, $^2J_{\text{PC}} = 9.8$ Hz), 72.3 (d, $^2J_{\text{PC}} = 14.9$ Hz), 63.6, 57.0 (d, $^2J_{\text{PC}} = 4.9$ Hz), 40.2 (d, $^3J_{\text{PC}} = 1.4$ Hz), 31.8 (d, $^2J_{\text{PC}} = 22.7$ Hz), 27.0, 19.4, 12.0. ^{31}P NMR (121 MHz, CDCl_3) δ 143.9. FAB-HRMS: calcd for $\text{C}_{35}\text{H}_{43}\text{N}_3\text{O}_6\text{PSi}^+$ ($\text{M} + \text{H}^+$) 660.2659, found 660.2655.

5'-O-(tert-Butyldiphenylsilyl)-3'-O-[(2*R*,4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]thymidine (5b**).** The reaction under kinetic conditions gave the crude product. ^{31}P NMR (121 MHz, CDCl_3) δ 148.2 (18%, *cis*-**5b**), 142.2 (82%, *trans*-**5b**). Purification of the crude product by silica gel column chromatography (2 × 9 cm, 20 g of silica gel, hexane-ethyl acetate-triethylamine, 70:30:2, v/v/v) afforded **5b** (608 mg, 0.90 mmol) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ 8.63 (br, 1H), 7.68-7.64 (m, 4H), 7.48-7.24 (m, 12H), 6.41 (dd, $^3J_{\text{HH}} = 8.2$, 5.7 Hz, 1H), 5.61 (d, $^3J_{\text{HH}} = 6.9$ Hz, 1H), 4.96-4.91 (m, 1H), 4.04-4.02 (m, 1H), 3.97 (dd, $^2J_{\text{HH}} = 11.7$ Hz, $^3J_{\text{HH}} = 2.4$ Hz, 1H), 3.88 (dd, $^2J_{\text{HH}} = 11.7$ Hz, $^3J_{\text{HH}} = 2.4$ Hz, 1H), 3.56 (m, 1H), 2.67 (d, $^3J_{\text{PH}} = 12.3$ Hz, 3H), 2.42 (ddd, $^2J_{\text{HH}} = 13.2$ Hz, $^3J_{\text{HH}} = 5.7$, 2.3 Hz, 1H), 2.24 (ddd, $^2J_{\text{HH}} = 13.2$ Hz, $^3J_{\text{HH}} = 8.2$, 6.5 Hz, 1H), 1.57 (s, 3H), 1.10 (s, 9H), 0.63 (d, $^3J_{\text{HH}} = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.8, 150.5, 147.8 (d, $^3J_{\text{PC}} = 3.2$ Hz), 135.5, 135.2, 135.2, 132.8, 132.9, 130.2, 130.1, 130.0, 128.1, 128.0, 127.9, 127.7, 126.7, 111.3, 86.4, 84.5 (d, $^2J_{\text{PC}} = 9.2$ Hz), 84.4, 72.6 (d, $^2J_{\text{PC}} = 17.8$ Hz), 63.5, 57.6 (d, $^2J_{\text{PC}} = 5.2$ Hz), 40.5 (d, $^3J_{\text{PC}} = 1.4$ Hz), 28.8 (d, $^2J_{\text{PC}} = 18.1$ Hz), 27.0, 19.4, 14.6 (d, $^3J_{\text{PC}} = 3.8$ Hz), 12.0. ^{31}P NMR (121 MHz, CDCl_3) δ 142.3. FAB-HRMS: calcd for $\text{C}_{36}\text{H}_{45}\text{N}_3\text{O}_6\text{PSi}^+$ ($\text{M} + \text{H}^+$) 674.2815, found 674.2806.

5'-O-(tert-Butyldiphenylsilyl)-3'-O-[(2*R*,4*S*,5*R*)-3-methyl-4,5-diphenyl-1,3,2-oxazaphospholidin-2-yl]thymidine (5c**).** Purification of the crude product by silica gel column chromatography (2 × 40 cm,

50 g of silica gel, hexane-ethyl acetate-triethylamine, 67:33:2 then 0:100:2, v/v/v) afforded **5c** (1.41 g, 1.9 mmol) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ 7.99 (br, 1H), 7.69-7.65 (m, 4H), 7.50 (d, $^4J_{\text{HH}} = 1.1$ Hz, 1H), 7.44-7.32 (m, 6H), 7.08-7.03 (m, 6H), 6.91-6.88 (m, 2H), 6.82-6.79 (m, 2H), 6.45 (dd, $^3J_{\text{HH}} = 8.5, 5.7$ Hz, 1H), 5.88 (d, $^3J_{\text{HH}} = 7.0$ Hz, 1H), 5.06-5.01 (m, 1H), 4.52 (dd, $^3J_{\text{HH}} = 7.0, 2.3$ Hz, 1H), 4.10-4.07 (m, 1H), 3.98 (dd, $^2J_{\text{HH}} = 11.8$ Hz, $^3J_{\text{HH}} = 2.3$ Hz, 1H), 3.91 (dd, $^2J_{\text{HH}} = 11.8$ Hz, $^3J_{\text{HH}} = 2.3$ Hz, 1H), 2.60 (d, $^3J_{\text{PH}} = 11.1$ Hz, 3H), 2.49 (ddd, $^2J_{\text{HH}} = 13.4$ Hz, $^3J_{\text{HH}} = 5.7, 2.1$ Hz, 1H), 2.30 (ddd, $^2J_{\text{HH}} = 13.4$ Hz, $^3J_{\text{HH}} = 8.5, 6.3$ Hz, 1H), 1.59 (d, $^4J_{\text{HH}} = 1.1$ Hz, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.7, 150.5, 137.0 (d, $^3J_{\text{PC}} = 3.7$ Hz), 136.0 (d, $^3J_{\text{PC}} = 3.8$ Hz), 135.5, 135.2, 135.2, 132.9, 132.2, 130.1, 130.0, 128.2, 128.0, 127.9, 127.7, 127.5, 127.3, 126.6, 111.3, 86.5 (d, $^3J_{\text{PC}} = 1.7$ Hz), 85.2 (d, $^2J_{\text{PC}} = 8.9$ Hz), 84.4, 72.7 (d, $^2J_{\text{PC}} = 18.2$ Hz), 68.8 (d, $^2J_{\text{PC}} = 4.9$ Hz), 63.5, 40.5 (d, $^3J_{\text{PC}} = 4.8$ Hz), 29.5 (d, $^2J_{\text{PC}} = 19.3$ Hz), 27.0, 19.4, 12.0. ^{31}P NMR (121 MHz, CDCl_3) δ 142.3. FAB-HRMS: calcd for $\text{C}_{41}\text{H}_{47}\text{N}_3\text{O}_6\text{PSi}^+$ ($\text{M} + \text{H}^+$) 736.2972, found 736.2975.

5'-O-(tert-Butyldiphenylsilyl)-3'-O-[(2R,5R)-3-isopropyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]thymidine (5d). The reaction under kinetic conditions gave the crude product. ^{31}P NMR (121 MHz, CDCl_3) δ 143.0 (93%, *trans*-**5d**), 142.8 (7%, *cis*-**5d**). Purification of the crude product by silica gel column chromatography (2.5 \times 15 cm, 45 g of silica gel, hexane-ethyl acetate-triethylamine, 50:50:2, v/v/v) afforded **5d** (874 mg, 1.3 mmol) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ 7.96 (br, 1H), 7.66 (d, $^3J_{\text{HH}} = 8.1$ Hz, 4H), 7.48 (d, $^4J_{\text{HH}} = 1.2$ Hz, 1H), 7.49-7.27 (m, 11H), 6.41 (dd, $^3J_{\text{HH}} = 8.1, 5.7$ Hz, 1H), 5.53 (dd, $^3J_{\text{HH}} = 7.5, 7.5$ Hz, 1H), 4.97-4.90 (m, 1H), 4.05 (m, 1H), 3.98 (dd, $^2J_{\text{HH}} = 11.7$ Hz, $^3J_{\text{HH}} = 2.4$ Hz, 1H), 3.88 (dd, $^2J_{\text{HH}} = 11.7$ Hz, $^3J_{\text{HH}} = 2.4$ Hz, 1H), 3.55-3.44 (m, 2H), 2.89 (m, 1H), 2.45 (ddd, $^2J_{\text{HH}} = 13.4$ Hz, $^3J_{\text{HH}} = 5.9, 2.3$ Hz, 1H), 2.29-2.22 (m, 1H), 1.57 (d, $^4J_{\text{HH}} = 1.2$ Hz, 3H), 1.25 (d, $^3J_{\text{HH}} = 5.1$ Hz, 3H), 1.23 (d, $^3J_{\text{HH}} = 4.8$ Hz, 3H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.9, 150.5, 140.2 (d, $^3J_{\text{PC}} = 3.5$ Hz), 135.5, 135.2, 132.9, 132.2, 130.0, 129.9, 128.4, 128.0, 127.9, 127.9, 125.8, 111.2, 86.4, 84.4, 80.7 (d, $^2J_{\text{PC}} = 9.5$ Hz), 72.2 (d, $^2J_{\text{PC}} = 16.4$ Hz), 63.4, 51.3 (d, $^2J_{\text{PC}} = 4.6$ Hz), 46.5 (d, $^2J_{\text{PC}} = 19.2$ Hz), 40.4 (d, $^3J_{\text{PC}} = 4.6$ Hz), 26.9, 22.8 (d, $^3J_{\text{PC}} = 8.7$ Hz), 22.6 (d, $^3J_{\text{PC}} = 7.8$ Hz), 19.3, 11.9. ^{31}P NMR (121 MHz, CDCl_3) δ 142.8. FAB-HRMS: calcd for $\text{C}_{37}\text{H}_{47}\text{N}_3\text{O}_6\text{PSi}^+$ ($\text{M} + \text{H}^+$) 688.2972, found 688.2975.

5'-O-(tert-Butyldiphenylsilyl)-3'-O-[(2R,5R)-3-methyl-5-isopropyl-1,3,2-oxazaphospholidin-2-yl]thymidine (5e). Crude **5e** (958 mg) was obtained, using 5'-O-(tert-butyldiphenylsilyl)thymidine **4** (721 mg, 1.5 mmol) and **3e** (300 mg, 1.7 mmol) as starting materials. ^{31}P NMR spectrum of the crude product was measured to determine the diastereoselectivity of the phosphorylation. ^{31}P NMR (121 MHz, CDCl_3) δ 142.8 (15%), 142.7 (85%).

5'-O-(tert-Butyldiphenylsilyl)-3'-O-[(2R,4S)-3-methyl-4-isopropyl-1,3,2-oxazaphospholidin-2-yl]thymidine (5f). Crude **5f** (345 mg) was obtained, using 5'-O-(tert-butyldiphenylsilyl)thymidine **4** (240 mg, 0.5 mmol) and **3f** (100 mg, 0.55 mmol) as starting materials. ^{31}P NMR spectrum of the crude

product was measured to determine the diastereoselectivity of the phosphitylation. ^{31}P NMR (121 MHz, CDCl_3) δ 154.0 (80%), 142.6 (20%).

5'-O-[bis(4-methoxyphenyl)phenylmethyl]-3'-O-[(2*R*,5*R*)-3-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]thymidine [(*Rp*)-13a**].** Purification of the crude product (*trans:cis* = 95:5) by silica gel column chromatography (2.5 × 17 cm, 50 g of silica gel, hexane-ethyl acetate-triethylamine, 30:70:2, v/v/v) afforded (*Rp*)-**13a** (818 mg, 1.1 mmol) as a colorless foam, which contained 1% of *cis*-isomer. ^1H NMR (300 MHz, CDCl_3) δ 9.64 (br, 1H), 7.63 (s, 1H), 7.43-7.24 (m, 14H), 6.82 (d, $^3J_{\text{HH}} = 7.8$ Hz, 4H), 6.44 (dd, $^3J_{\text{HH}} = 6.9, 6.0$ Hz, 1H), 5.53 (dd, $^3J_{\text{HH}} = 7.6, 7.6$ Hz, 1H), 4.91 (m, 1H), 4.10 (m, 1H), 3.75 (s, 6H), 3.51-3.36 (m, 3H), 3.35 (dd, $^2J_{\text{HH}} = 10.4$ Hz, $^3J_{\text{HH}} = 2.6$ Hz, 1H), 2.87 (dd, $^2J_{\text{HH}} = 15.8$ Hz, $^3J_{\text{HH}} = 7.6$ Hz, 1H), 2.69 (d, $^3J_{\text{PH}} = 12.0$ Hz, 3H), 2.48 (ddd, $^2J_{\text{HH}} = 13.6$ Hz, $^3J_{\text{HH}} = 6.0, 2.9$ Hz, 1H), 2.38 (ddd, $^2J_{\text{HH}} = 13.6$ Hz, $^3J_{\text{HH}} = 6.9, 6.9$ Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.8, 158.7, 150.4, 144.3, 140.4 (d, $^3J_{\text{PC}} = 3.5$ Hz), 135.6, 135.3, 130.1, 128.4, 128.1, 128.0, 127.9, 127.1, 125.8, 113.2, 111.2, 86.9, 85.6 (d, $^3J_{\text{PC}} = 1.7$ Hz), 84.6, 81.8 (d, $^2J_{\text{PC}} = 9.7$ Hz), 72.9 (d, $^2J_{\text{PC}} = 15.3$ Hz), 62.9, 57.0 (d, $^2J_{\text{PC}} = 4.6$ Hz), 55.2, 40.4, 31.7 (d, $^2J_{\text{PC}} = 23.0$ Hz), 11.7. ^{31}P NMR (121 MHz, CDCl_3) δ 143.8 (99%), 143.3 (1%). FAB-HRMS: calcd for $\text{C}_{40}\text{H}_{43}\text{N}_3\text{O}_8\text{P}^+$ ($\text{M} + \text{H}^+$) 724.2788, found 724.2784.

5'-O-[bis(4-methoxyphenyl)phenylmethyl]-3'-O-[(2*S*,5*S*)-3-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]thymidine [(*Sp*)-13a**].** Purification of the crude product (*trans:cis* = 95:5) by silica gel column chromatography (2.5 × 17 cm, 50 g of silica gel, hexane-ethyl acetate-triethylamine, 30:70:2, v/v/v) afforded (*Sp*)-**13a** (782 mg, 1.1 mmol) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ 9.21 (br, 1H), 7.63 (s, 1H), 7.43-7.21 (m, 14H), 6.84 (d, $^3J_{\text{HH}} = 8.7$ Hz, 4H), 6.42 (dd, $^3J_{\text{HH}} = 6.8, 6.8$ Hz, 1H), 5.54 (dd, $^3J_{\text{HH}} = 7.6, 7.6$ Hz, 1H), 4.88 (m, 1H), 4.10 (m, 1H), 3.78 (s, 6H), 3.56-3.47 (m, 2H), 3.35 (dd, $^2J_{\text{HH}} = 10.4$ Hz, $^3J_{\text{HH}} = 2.6$ Hz, 1H), 2.88 (dd, $^2J_{\text{HH}} = 15.5$ Hz, $^3J_{\text{HH}} = 7.6$ Hz, 1H), 2.65 (d, $^3J_{\text{PH}} = 11.7$ Hz, 3H), 2.45 (ddd, $^2J_{\text{HH}} = 13.6$ Hz, $^3J_{\text{HH}} = 6.8, 3.2$ Hz, 1H), 2.34 (ddd, $^2J_{\text{HH}} = 13.6$ Hz, $^3J_{\text{HH}} = 6.8, 6.8$ Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 163.9, 158.7, 150.4, 144.2, 140.3 (d, $^3J_{\text{PC}} = 3.1$ Hz), 135.5, 135.3, 130.1, 128.4, 128.1, 128.0, 127.9, 127.1, 125.8, 113.2, 111.2, 86.9, 85.5 (d, $^3J_{\text{PC}} = 4.9$ Hz), 84.5, 81.8 (d, $^2J_{\text{PC}} = 9.8$ Hz), 72.4 (d, $^2J_{\text{PC}} = 14.1$ Hz), 62.9, 57.1 (d, $^2J_{\text{PC}} = 4.9$ Hz), 55.2, 40.2, 31.7 (d, $^2J_{\text{PC}} = 23.1$ Hz), 11.7. ^{31}P NMR (121 MHz, CDCl_3) δ 142.9. FAB-HRMS: calcd for $\text{C}_{40}\text{H}_{43}\text{N}_3\text{O}_8\text{P}^+$ ($\text{M} + \text{H}^+$) 724.2788, found 724.2775.

***N*⁶-Benzoyl-5'-O-[bis(4-methoxyphenyl)phenylmethyl]-3'-O-[(2*S*,5*S*)-3-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]-2'-deoxyadenosine [(*Sp*)-**13b**].** Purification of the crude product (*trans:cis* = 93:7) by silica gel column chromatography (2.5 × 14 cm, 40 g of silica gel, hexane-ethyl acetate-triethylamine, 20:80:2, v/v/v) afforded (*Sp*)-**13b** (819 mg, 0.98 mmol) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ 8.94 (br, 1H), 8.76 (s, 1H), 8.21 (s, 1H), 8.02 (d, $^3J_{\text{HH}} = 7.2$ Hz, 2H), 7.62 (t, $^3J_{\text{HH}} = 7.2$ Hz, 1H), 7.53 (t, $^3J_{\text{HH}} = 7.2$ Hz, 2H), 7.42-7.18 (m, 14H), 6.79 (d, $^3J_{\text{HH}} = 8.7$ Hz, 4H), 6.51 (dd, $^3J_{\text{HH}} = 6.3, 6.3$ Hz, 1H), 5.60 (dd, $^3J_{\text{HH}} = 7.5, 7.5$ Hz, 1H), 5.03 (m, 1H), 4.26 (m, 1H), 3.76 (s, 6H), 3.54 (ddd, $^2J_{\text{HH}} = 8.8$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, $^3J_{\text{PH}} = 3.3$ Hz, 1H), 3.47 (dd, $^2J_{\text{HH}} = 10.5$ Hz, $^3J_{\text{HH}} = 4.2$ Hz, 1H),

3.37 (dd, $^2J_{\text{HH}} = 10.5$ Hz, $^3J_{\text{HH}} = 4.2$ Hz, 1H), 3.00-2.87 (m, 2H), 2.71 (d, $^3J_{\text{PH}} = 12.6$ Hz, 3H), 2.62 (ddd, $^2J_{\text{HH}} = 13.6$ Hz, $^3J_{\text{HH}} = 6.3$, 3.7 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 164.6, 158.4, 152.4, 151.3, 149.4, 144.3, 141.4, 140.2 (d, $^3J_{\text{PC}} = 3.5$ Hz), 135.5, 135.4, 133.5, 132.5, 129.9, 128.6, 128.3, 128.0, 127.9, 127.7, 126.8, 125.6, 123.5, 113.0, 86.4, 85.8 (d, $^3J_{\text{PC}} = 4.3$ Hz), 84.5, 81.8 (d, $^2J_{\text{PC}} = 10.1$ Hz), 72.5 (d, $^2J_{\text{PC}} = 12.7$ Hz), 62.9, 57.1 (d, $^2J_{\text{PC}} = 4.2$ Hz), 55.0, 39.6, 31.7 (d, $^2J_{\text{PC}} = 23.6$ Hz). ^{31}P NMR (121 MHz, CDCl_3) δ 142.5. FAB-HRMS: calcd for $\text{C}_{47}\text{H}_{46}\text{N}_6\text{O}_7\text{P}^+$ ($\text{M} + \text{H}^+$) 837.3166, found 837.3156.

***N*⁴-Benzoyl-5'-*O*-[bis(4-methoxyphenyl)phenylmethyl]-3'-*O*-[(2*S*,5*S*)-3-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]-2'-deoxycytidine [(*Sp*)-13c].** Purification of the crude product (*trans:cis* = 96:4) by silica gel column chromatography (2.5 × 16 cm, 45 g of silica gel, hexane-ethyl acetate-triethylamine, 20:80:2, v/v/v) afforded (*Sp*)-13c (756 mg, 0.93 mmol) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ 8.60 (br, 1H), 8.41 (d, $^3J_{\text{HH}} = 7.5$ Hz, 1H), 7.88 (d, $^3J_{\text{HH}} = 7.5$ Hz, 2H), 7.62 (t, $^3J_{\text{HH}} = 7.5$ Hz, 1H), 7.52 (t, $^3J_{\text{HH}} = 7.5$ Hz, 2H), 7.44-7.29 (m, 15H), 6.87 (d, $^3J_{\text{HH}} = 9.0$ Hz, 4H), 6.29 (dd, $^3J_{\text{HH}} = 6.2$, 5.0 Hz, 1H), 5.57 (dd, $^3J_{\text{HH}} = 7.5$, 7.5 Hz, 1H), 4.88 (m, 1H), 4.14 (m, 1H), 3.77 (s, 6H), 3.56-3.48 (m, 2H), 3.44 (dd, $^2J_{\text{HH}} = 10.8$ Hz, $^3J_{\text{HH}} = 3.0$ Hz, 1H), 2.89 (dd, $^2J_{\text{HH}} = 16.2$ Hz, $^3J_{\text{HH}} = 7.5$ Hz, 1H), 2.75-2.66 (m, 1H), 2.66 (d, $^3J_{\text{PH}} = 12.6$ Hz, 3H), 2.41-2.33 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 162.1, 158.6, 158.6, 154.6, 144.6, 144.0, 140.1 (d, $^3J_{\text{PC}} = 3.2$ Hz), 135.3, 135.1, 133.1, 132.9, 130.0, 129.9, 128.8, 128.4, 128.1, 127.9, 127.4, 127.0, 125.8, 113.2, 96.3, 86.9, 86.6, 85.4 (d, $^3J_{\text{PC}} = 4.9$ Hz), 81.8 (d, $^2J_{\text{PC}} = 10.0$ Hz), 70.2 (d, $^2J_{\text{PC}} = 13.3$ Hz), 61.5, 57.0 (d, $^2J_{\text{PC}} = 4.6$ Hz), 55.1, 41.1, 31.7 (d, $^2J_{\text{PC}} = 23.3$ Hz). ^{31}P NMR (121 MHz, CDCl_3) δ 143.8. FAB-HRMS: calcd for $\text{C}_{46}\text{H}_{46}\text{N}_4\text{O}_8\text{P}^+$ ($\text{M} + \text{H}^+$) 813.3053, found 813.3057.

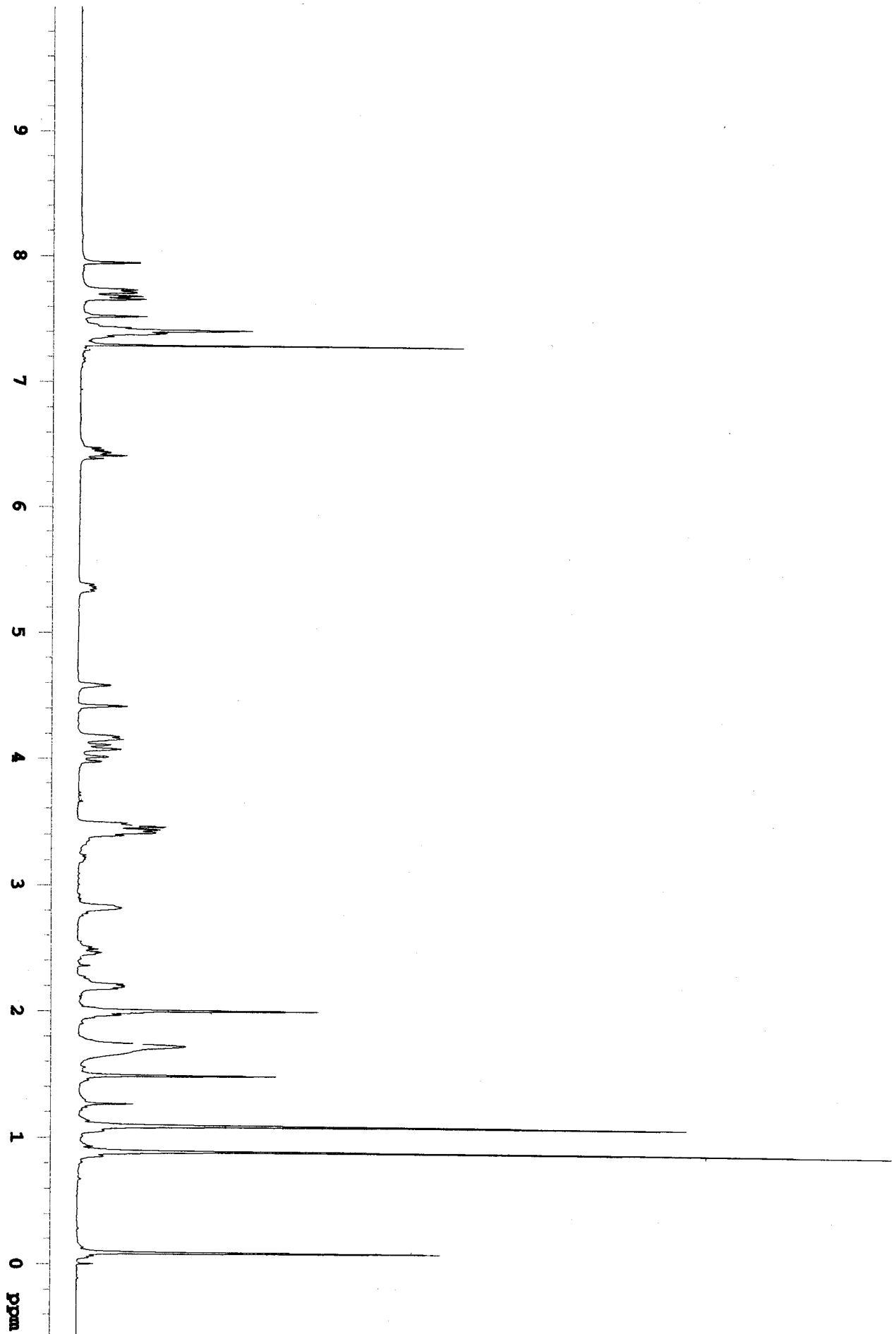
***O*⁶-Cyanoethyl-*N*²-isobutyryl-5'-*O*-[bis(4-methoxyphenyl)phenylmethyl]-3'-*O*-[(2*S*,5*S*)-3-methyl-5-phenyl-1,3,2-oxazaphospholidin-2-yl]-2'-deoxyguanosine [(*Sp*)-13d].** Purification of the crude product (*trans:cis* = 95:5) by silica gel column chromatography (3.5 × 10 cm, 50 g of silica gel, hexane-ethyl acetate-triethylamine, 20:80:2, v/v) afforded (*Sp*)-13d (912 mg, 1.1 mmol) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ 8.02 (s, 1H), 7.67 (s, 1H), 7.44-7.20 (m, 14H), 6.79 (d, $^3J_{\text{HH}} = 9.0$ Hz, 4H), 6.39 (dd, $^3J_{\text{HH}} = 7.2$, 6.0 Hz, 1H), 5.56 (dd, $^3J_{\text{HH}} = 7.2$, 7.2 Hz, 1H), 4.98 (m, 1H), 4.80 (t, $^3J_{\text{HH}} = 6.6$ Hz, 2H), 4.21 (m, 1H), 3.77 (s, 6H), 3.53 (ddd, $^2J_{\text{HH}} = 8.0$ Hz, $^3J_{\text{HH}} = 7.2$ Hz, $^3J_{\text{PH}} = 3.5$ Hz, 1H), 3.42 (dd, $^2J_{\text{HH}} = 10.4$ Hz, $^3J_{\text{HH}} = 3.9$ Hz, 1H), 3.35 (dd, $^2J_{\text{HH}} = 10.4$ Hz, $^3J_{\text{HH}} = 3.9$ Hz, 1H), 3.03 (t, $^3J_{\text{HH}} = 6.6$ Hz, 2H), 2.91 (dd, $^2J_{\text{HH}} = 8.0$ Hz, $^3J_{\text{HH}} = 8.0$ Hz, 1H), 2.81 (m, 1H), 2.70 (d, $^3J_{\text{PH}} = 11.7$ Hz, 3H), 2.69 (m, 1H), 2.56 (ddd, $^2J_{\text{HH}} = 13.1$ Hz, $^3J_{\text{HH}} = 6.0$, 3.2 Hz, 1H), 1.20 (d, $^3J_{\text{HH}} = 6.9$ Hz, 3H), 1.16 (d, $^3J_{\text{HH}} = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 175.3, 159.5, 158.5, 152.8, 151.6, 144.4, 140.4, 140.3 (d, $^3J_{\text{PC}} = 3.2$ Hz), 135.6, 135.5, 129.9, 128.4, 128.0, 128.0, 127.8, 126.9, 125.7, 118.2, 116.8, 113.1, 86.4, 85.9 (d, $^3J_{\text{PC}} = 4.6$ Hz), 84.3, 81.8 (d, $^2J_{\text{PC}} = 10.1$ Hz), 72.6 (d, $^2J_{\text{PC}} = 13.5$ Hz), 63.2, 61.5, 57.1 (d, $^2J_{\text{PC}} = 4.6$ Hz), 55.1, 39.9, 35.7, 31.7 (d, $^2J_{\text{PC}} = 23.3$ Hz), 19.1, 18.0. ^{31}P NMR (121 MHz, CDCl_3) δ 143.0. FAB-HRMS: calcd for $\text{C}_{47}\text{H}_{51}\text{N}_7\text{O}_8\text{P}^+$ ($\text{M} + \text{H}^+$) 872.3537, found 872.3535.

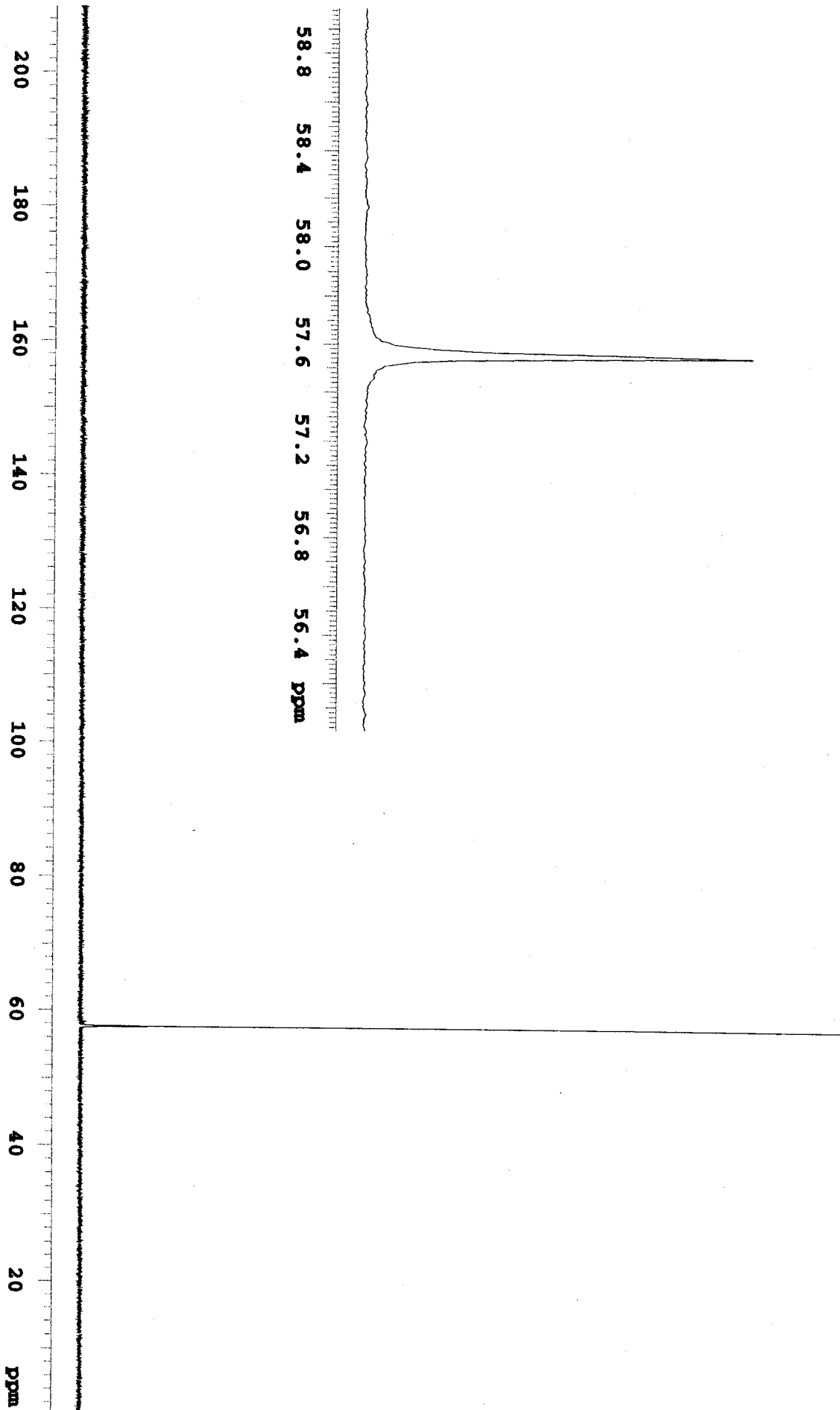
***N*-(Cyanomethyl)pyrrolidine (6b).** Pyrrolidine (16.5 ml, 200 mmol) was added dropwise to a stirred solution of bromoacetonitrile (6.97 ml, 100 mmol) in dry Et₂O (100 ml) at 0 °C under argon. The mixture was allowed to warm up to room temperature and stirred for 20 min. The resultant pyrrolidinium hydrobromide was then removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (110 °C /20 mmHg) from Na to afford **6b** (9.08 g, 82 mmol) as a colorless liquid. ¹H, ¹³C NMR spectra of the product were identical to those of **6b** purchased from Lancaster Synthesis Ltd. ¹H NMR (300 MHz, CDCl₃) δ 3.68 (s, 2H), 2.67 (m, 4H), 1.85 (m, 4H). ¹³C NMR (75 MHz, CDCl₃) δ 115.0, 52.0, 41.7, 23.6.

***N*-(Cyanomethyl)diisopropylamine (6d).** Diisopropylamine (14.1 ml, 100 mmol) was added dropwise to a stirred solution of bromoacetonitrile (3.48 ml, 50 mmol) in dry *N,N*-dimethylformamide (25 ml) at room temperature. The mixture was stirred for 5 h, and then diluted with ethyl acetate (200 ml), washed with water (7 × 100 ml), and back-extracted with ethyl acetate (200 ml). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was distilled under reduced pressure (68-69 °C/6 mmHg) to afford **6d** (4.32g, 31 mmol) as a pale yellow liquid. ¹H NMR (300 MHz, CDCl₃) δ 3.56 (s, 2H), 3.18 (septet, ³J_{HH} = 6.6 Hz, 2H), 1.12 (d, ³J_{HH} = 6.6 Hz, 12H). ¹³C NMR (75 MHz, CDCl₃) δ 119.0, 49.0, 33.3, 20.3.

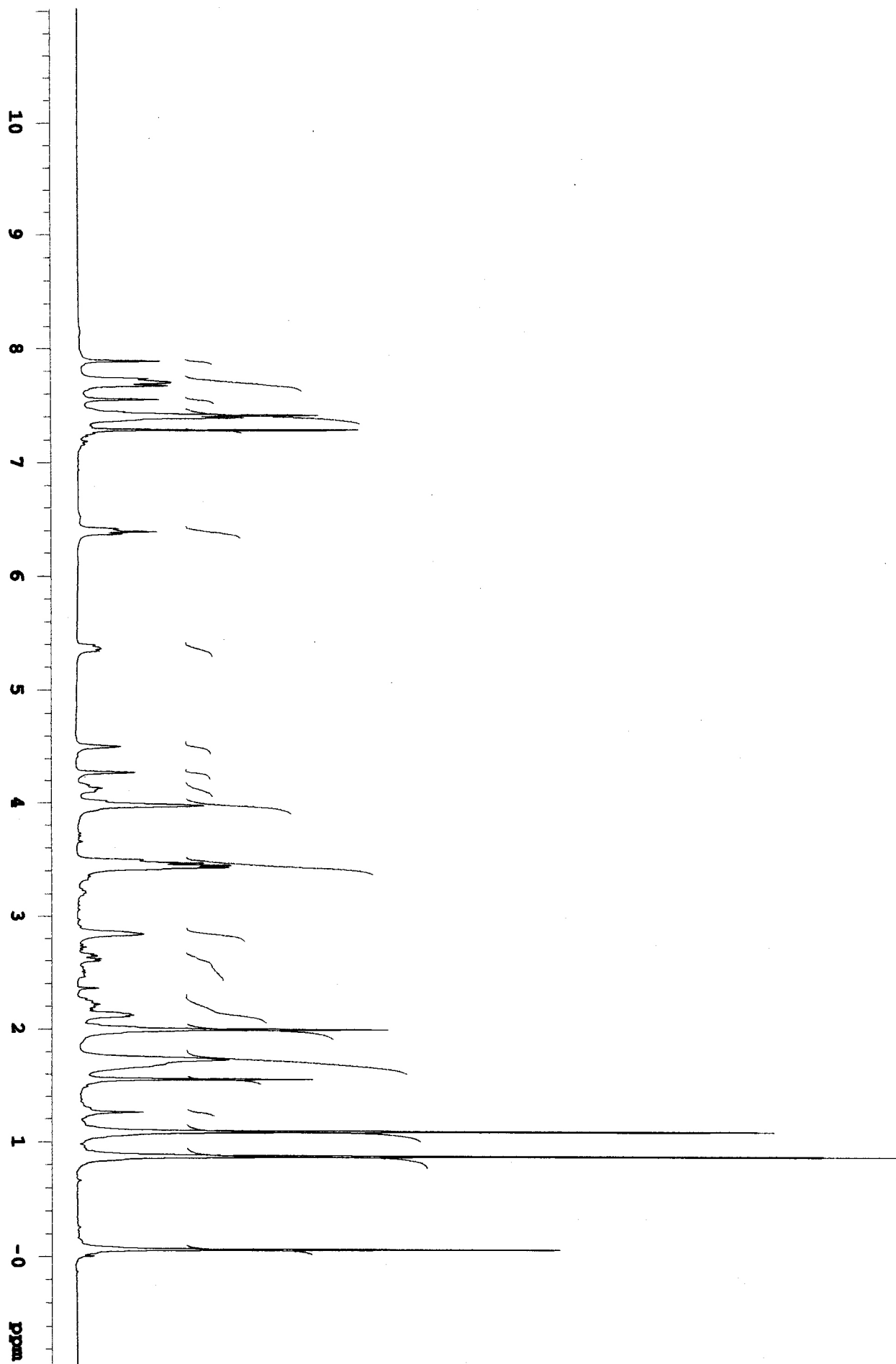
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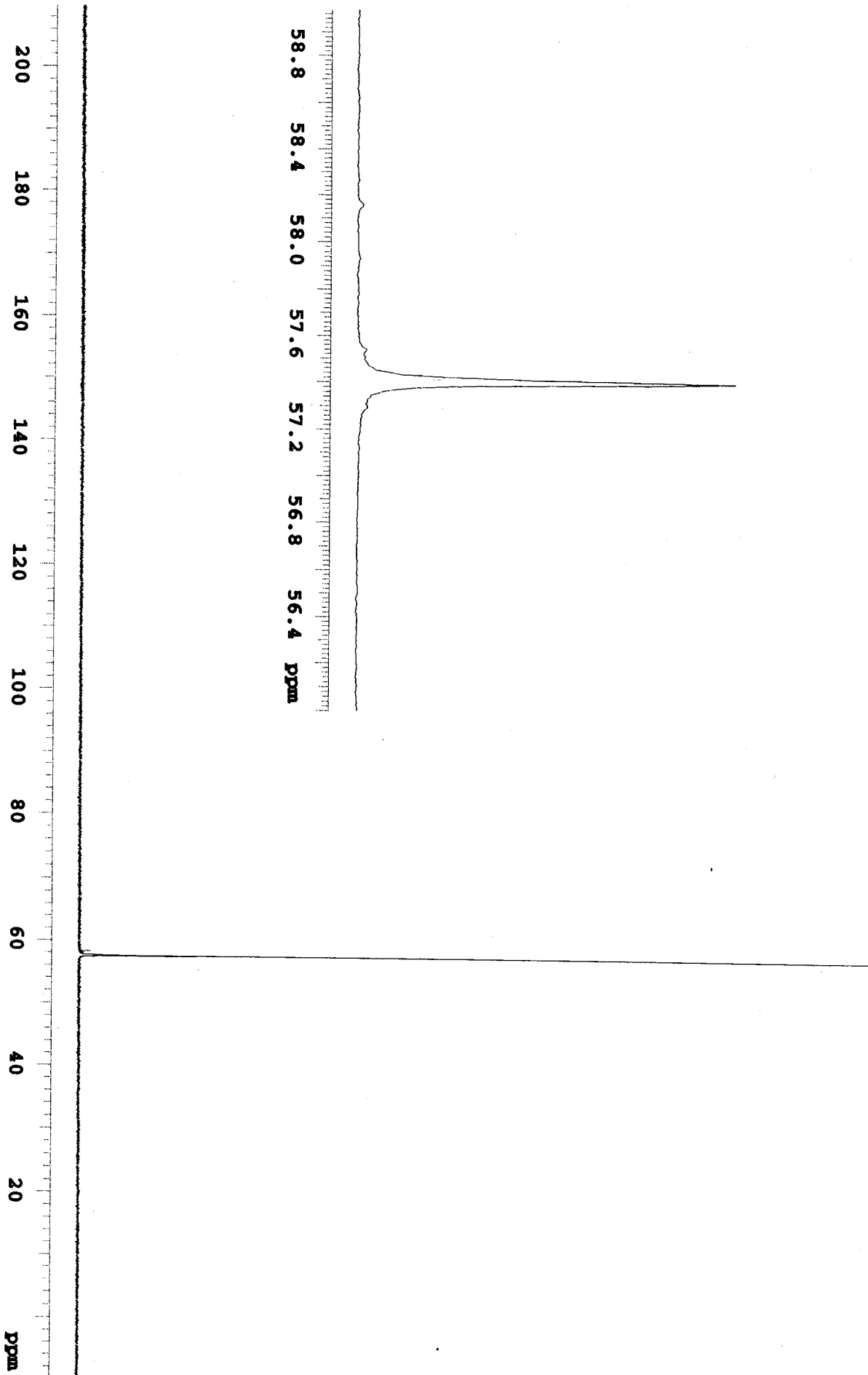
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 ^1H NMR spectrum of (Rp)-11

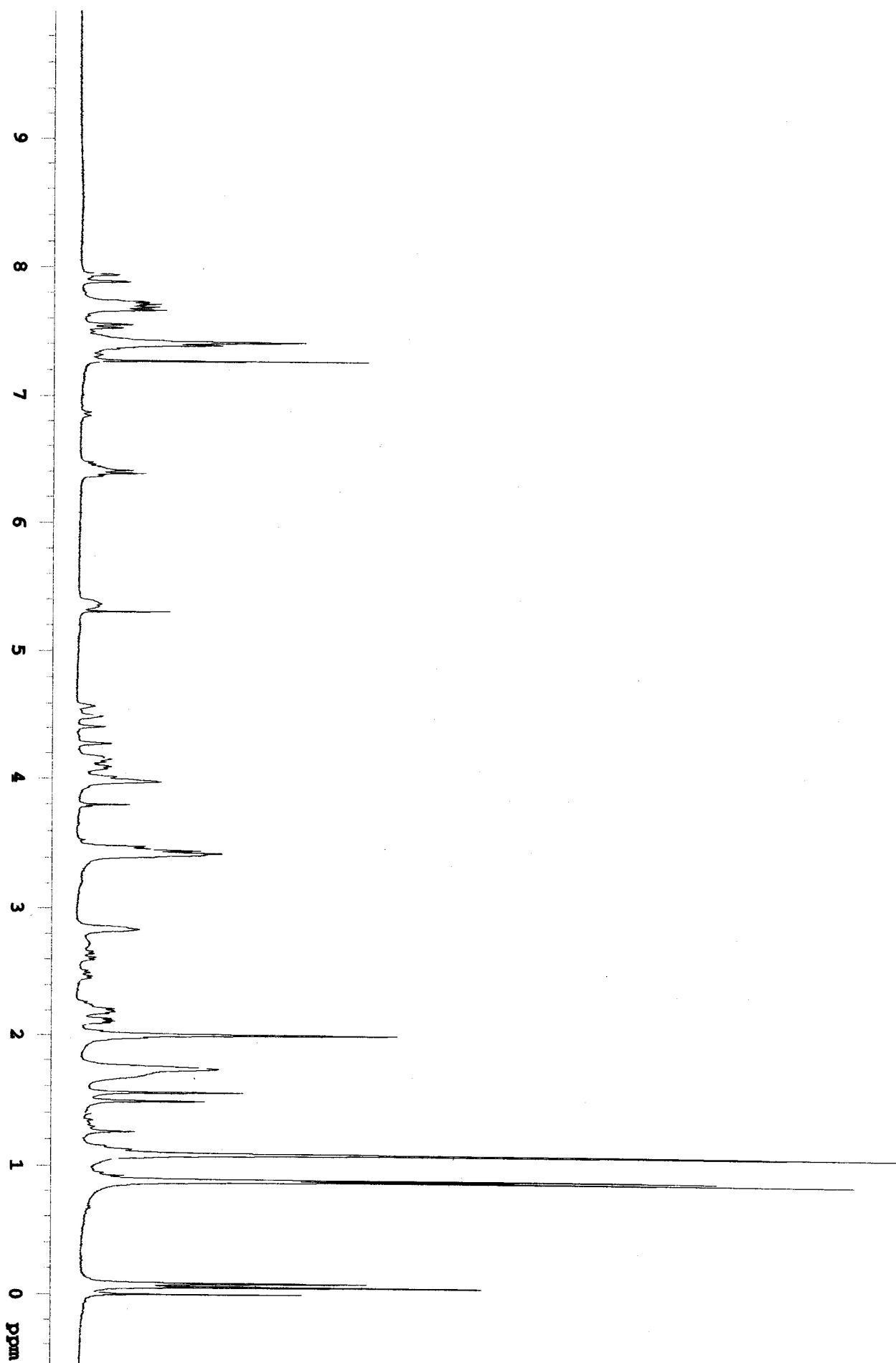


31P NMR spectrum of (Rp)-11

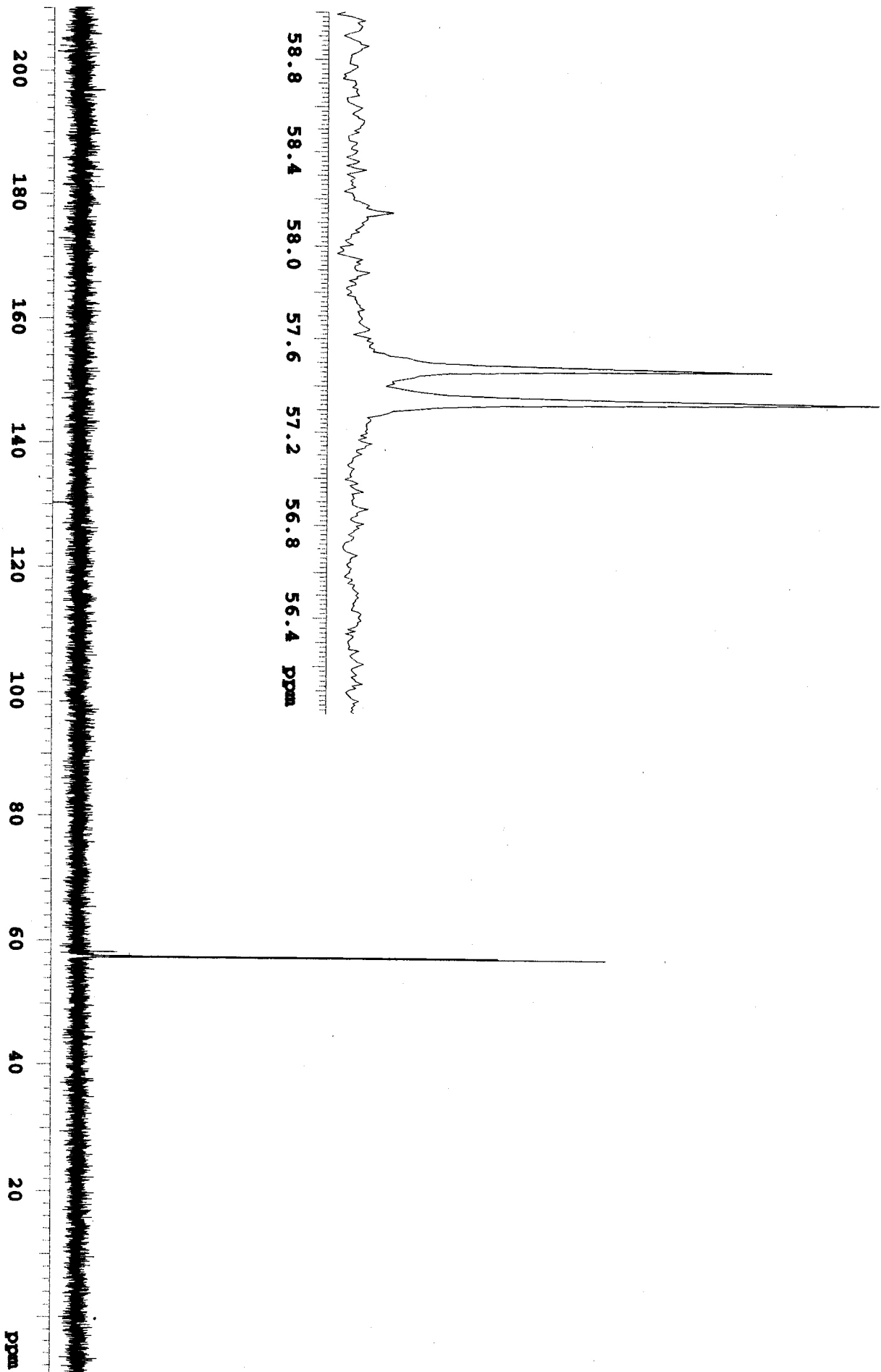
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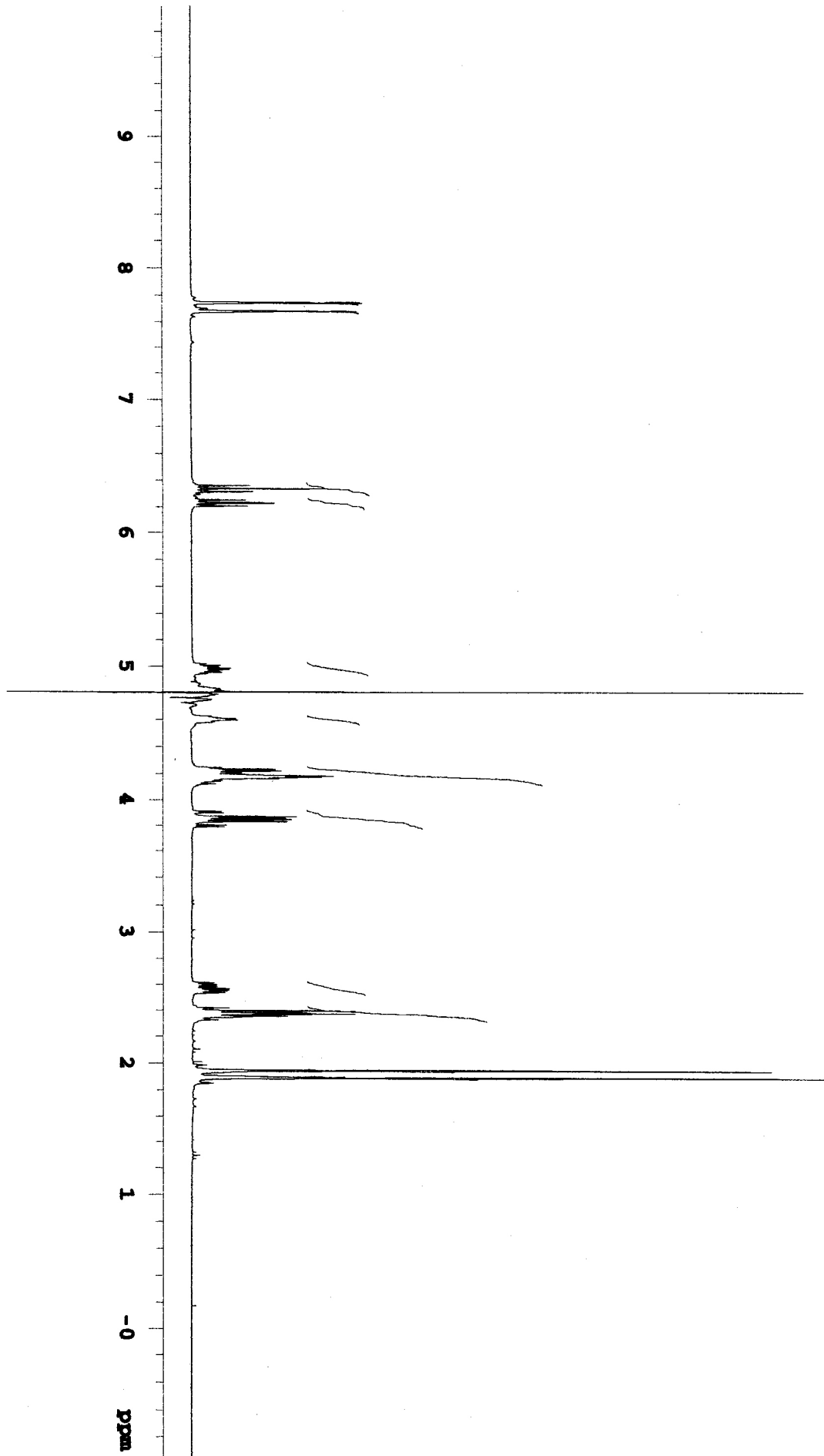
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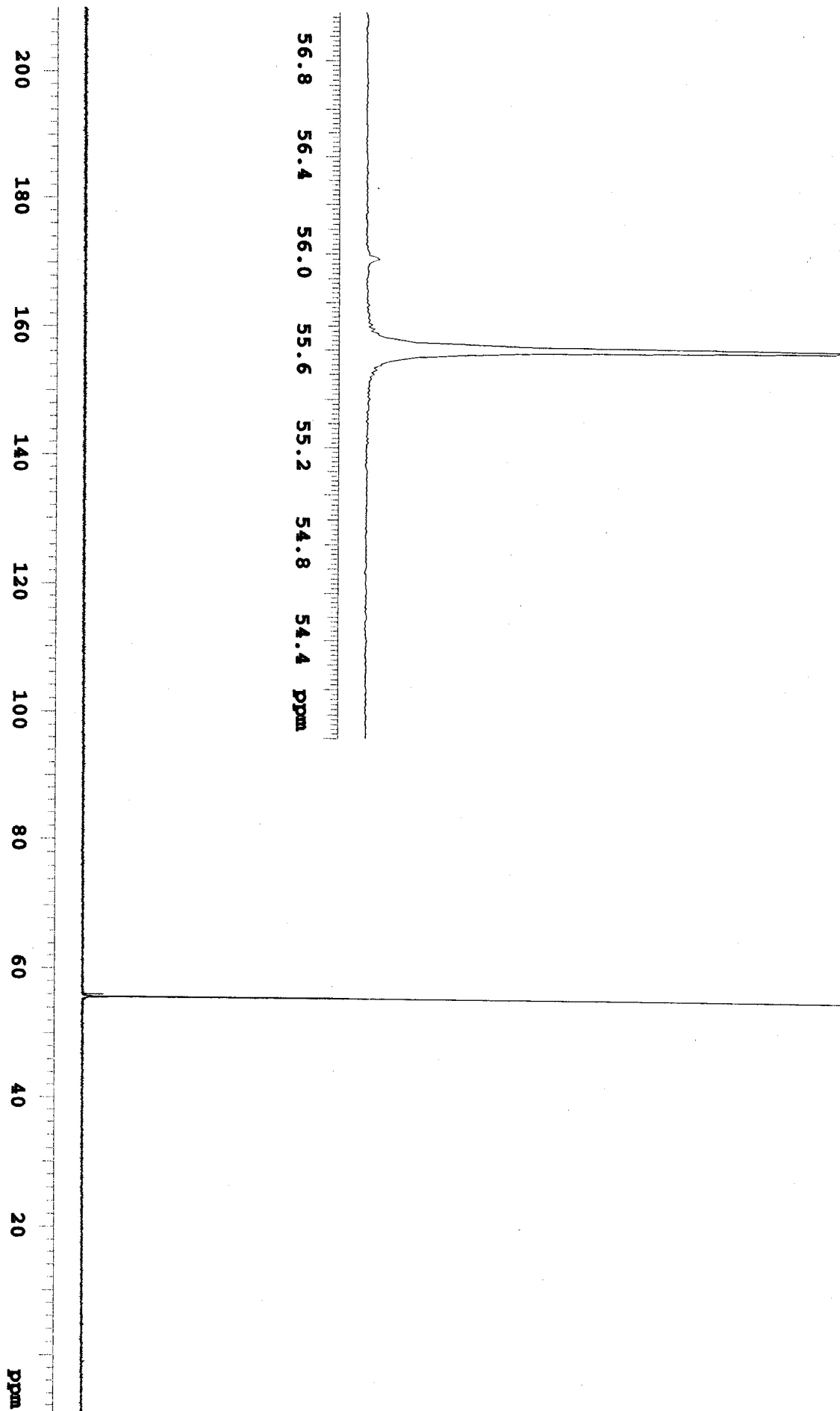


**¹H NMR spectrum of 11
(mixture of diastereomers)**

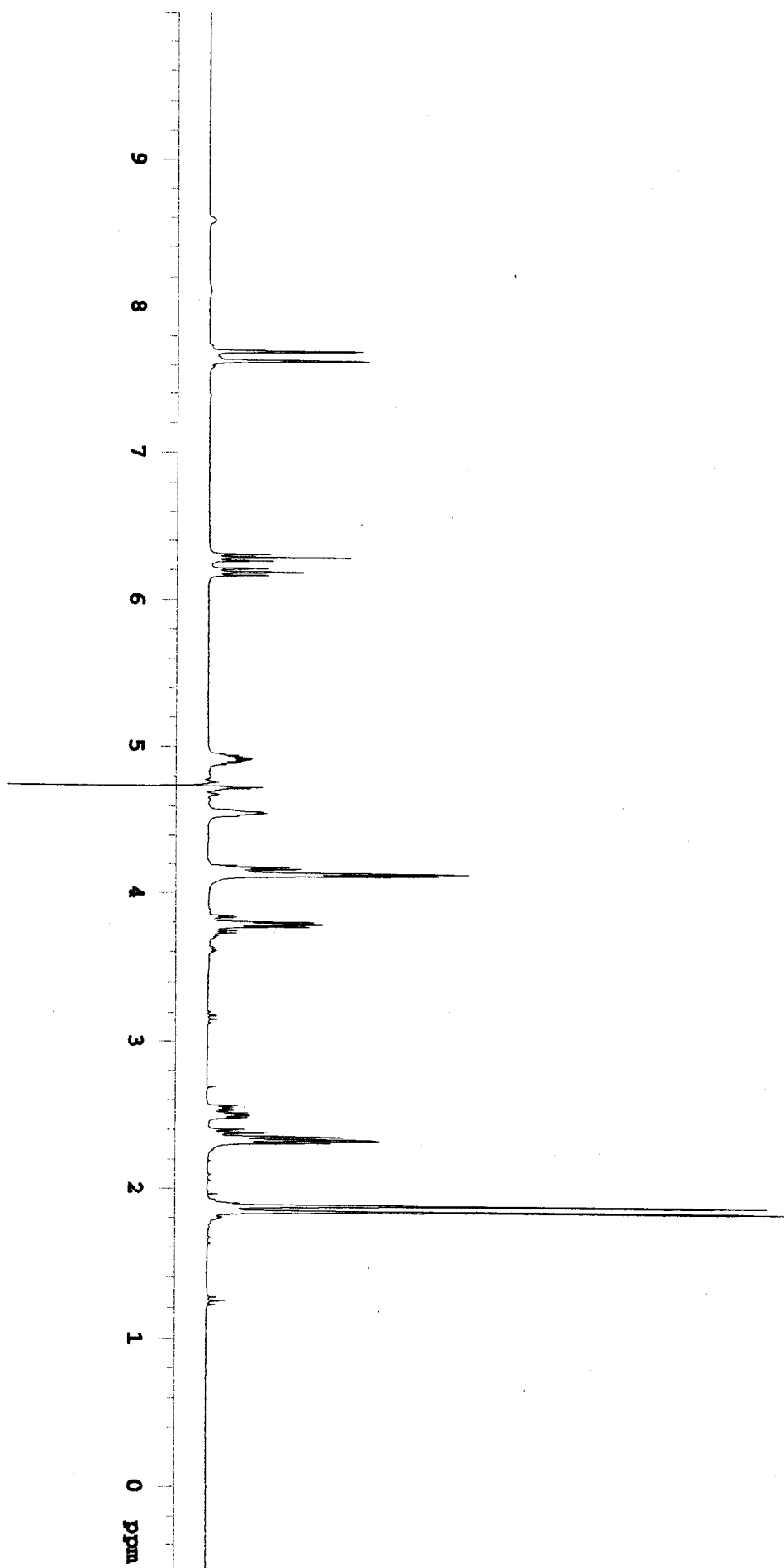


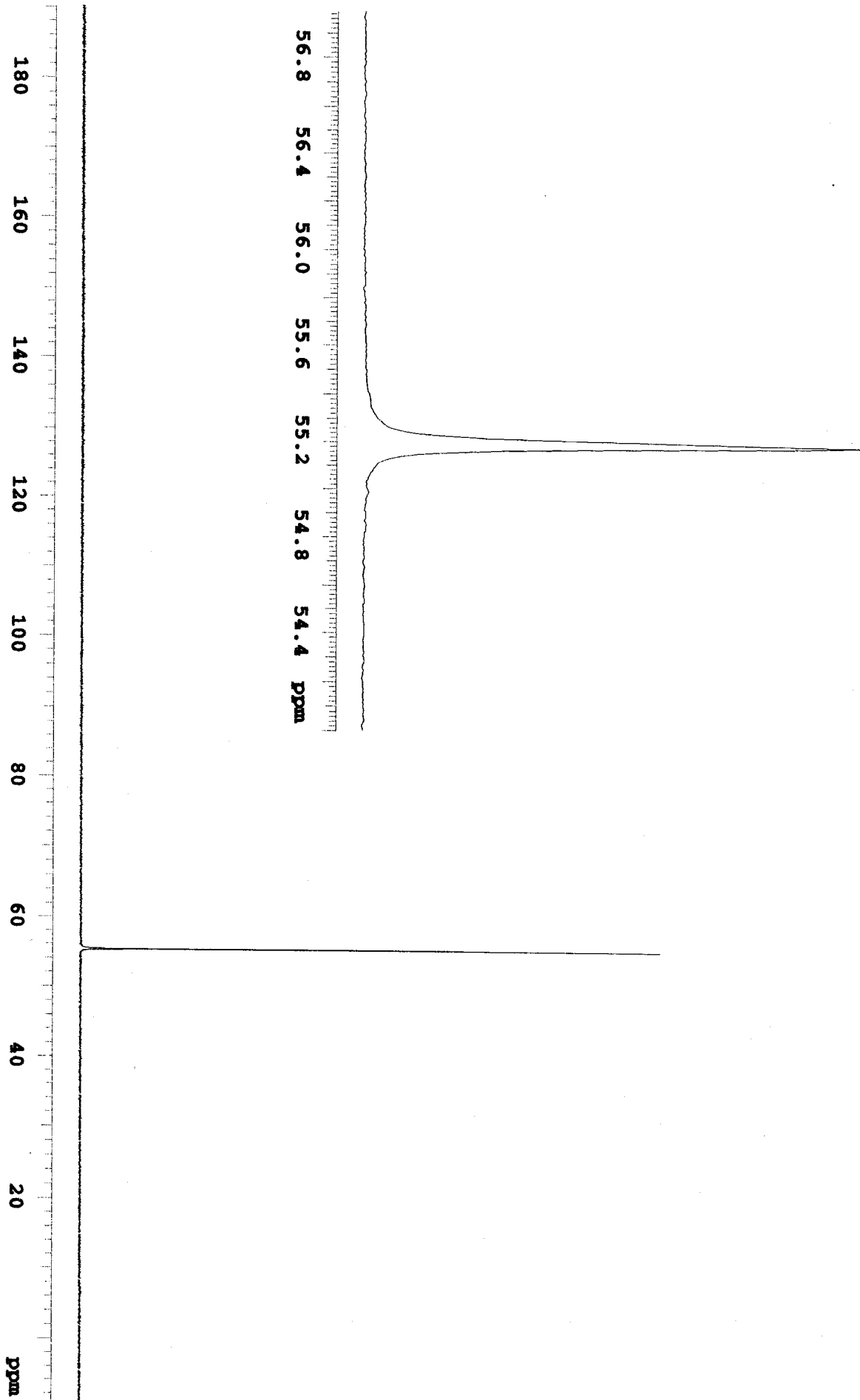
31P NMR spectrum of 11
(mixture of diastereomers)

 ^1H NMR spectrum of (Rp)-12a

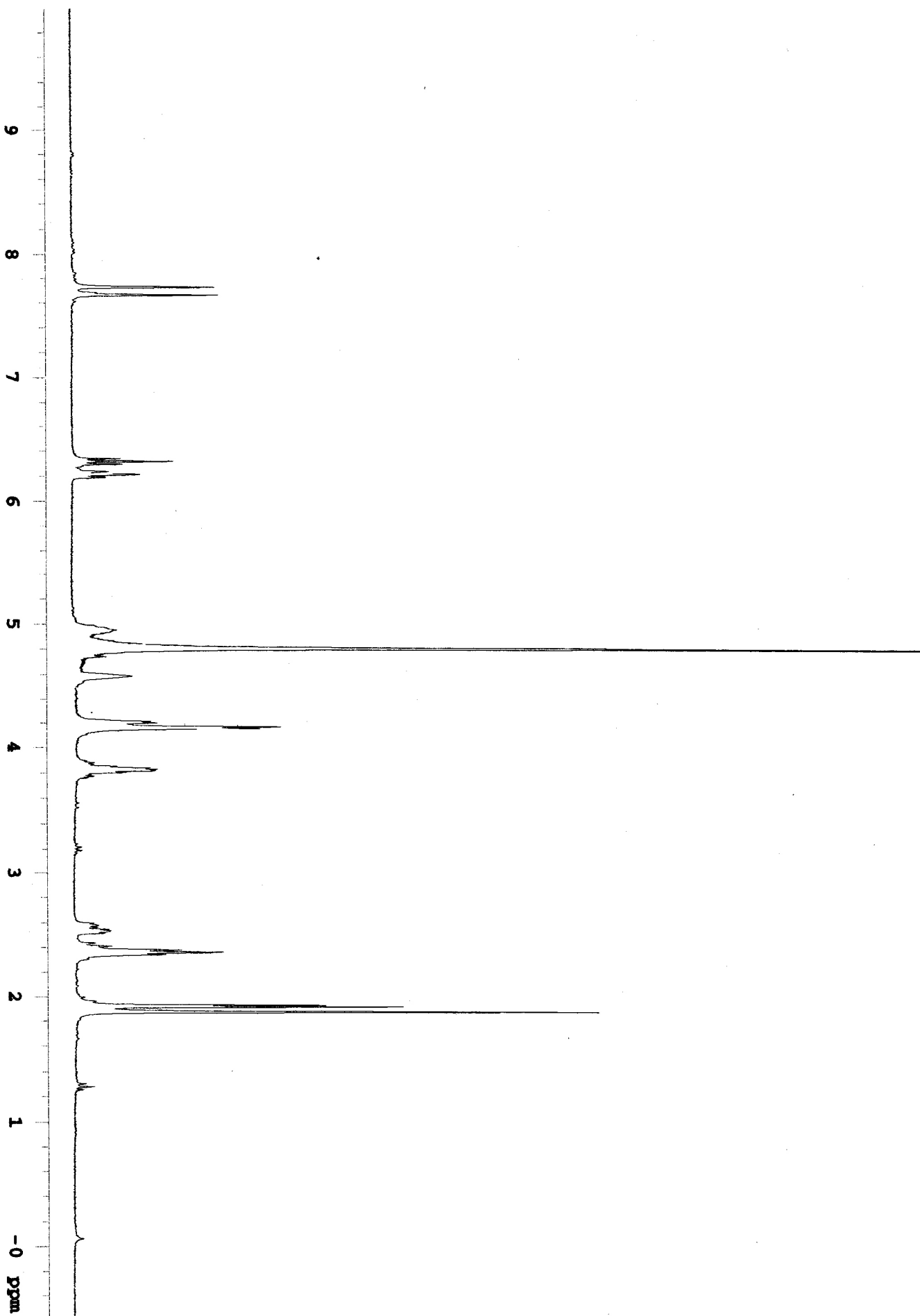


31P NMR spectrum of (Rp)-12a

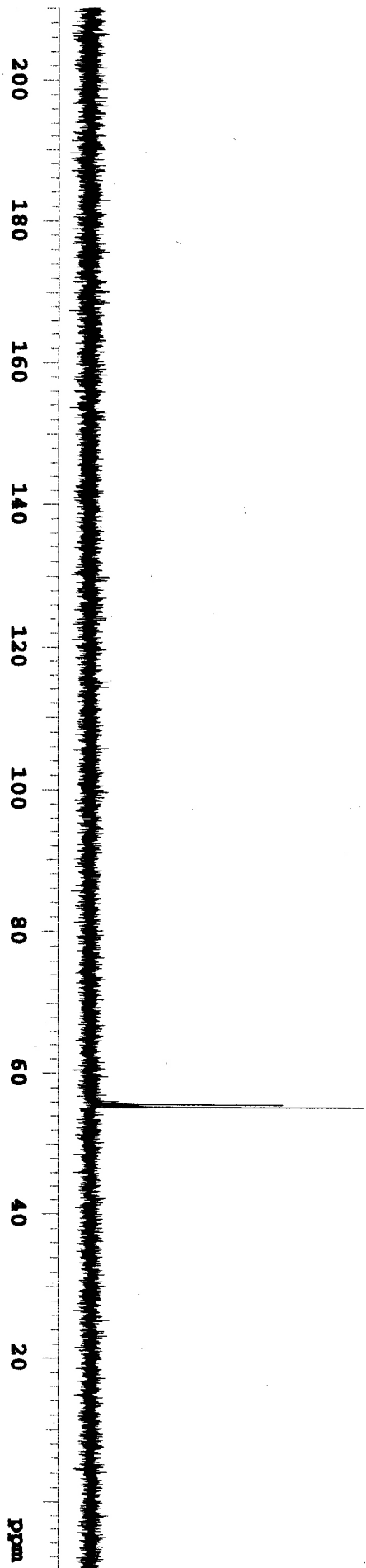
 ^1H NMR spectrum of (Sp)-12a



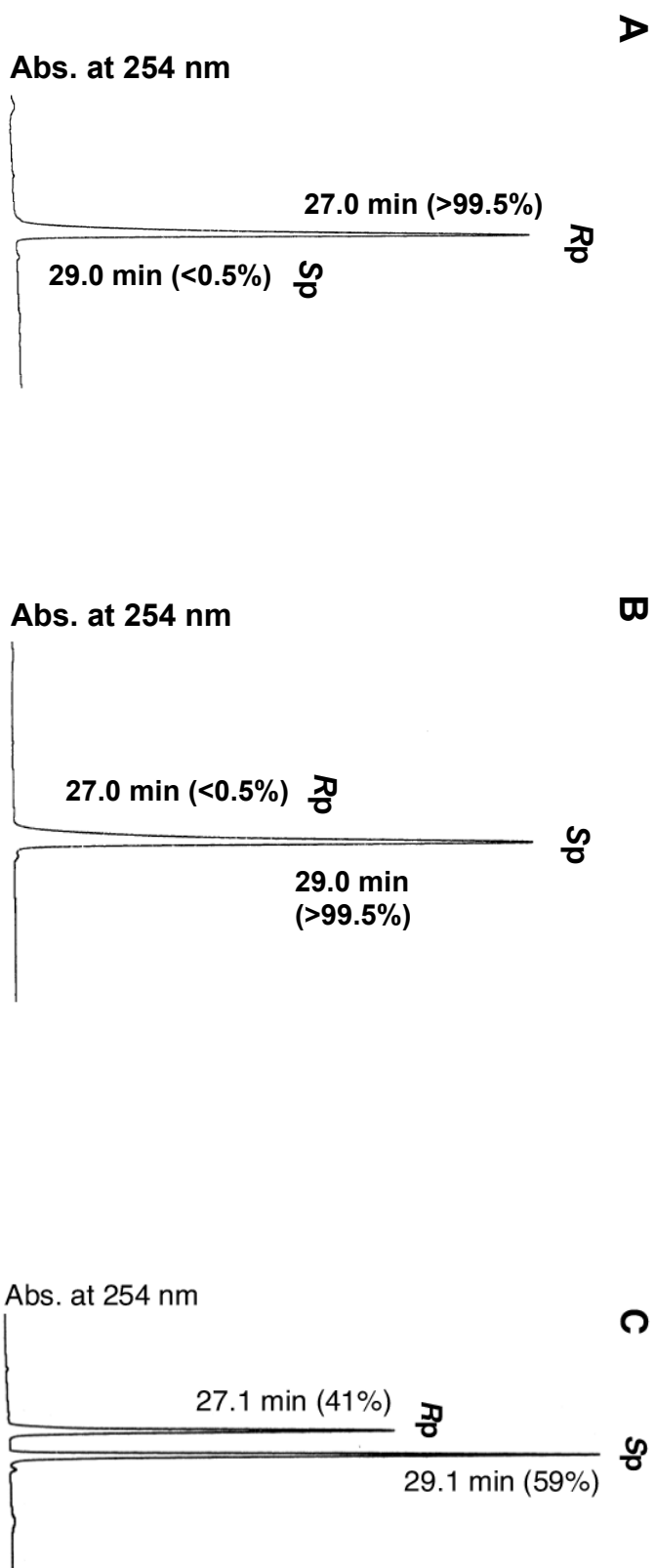
31P NMR spectrum of (Sp)-12a



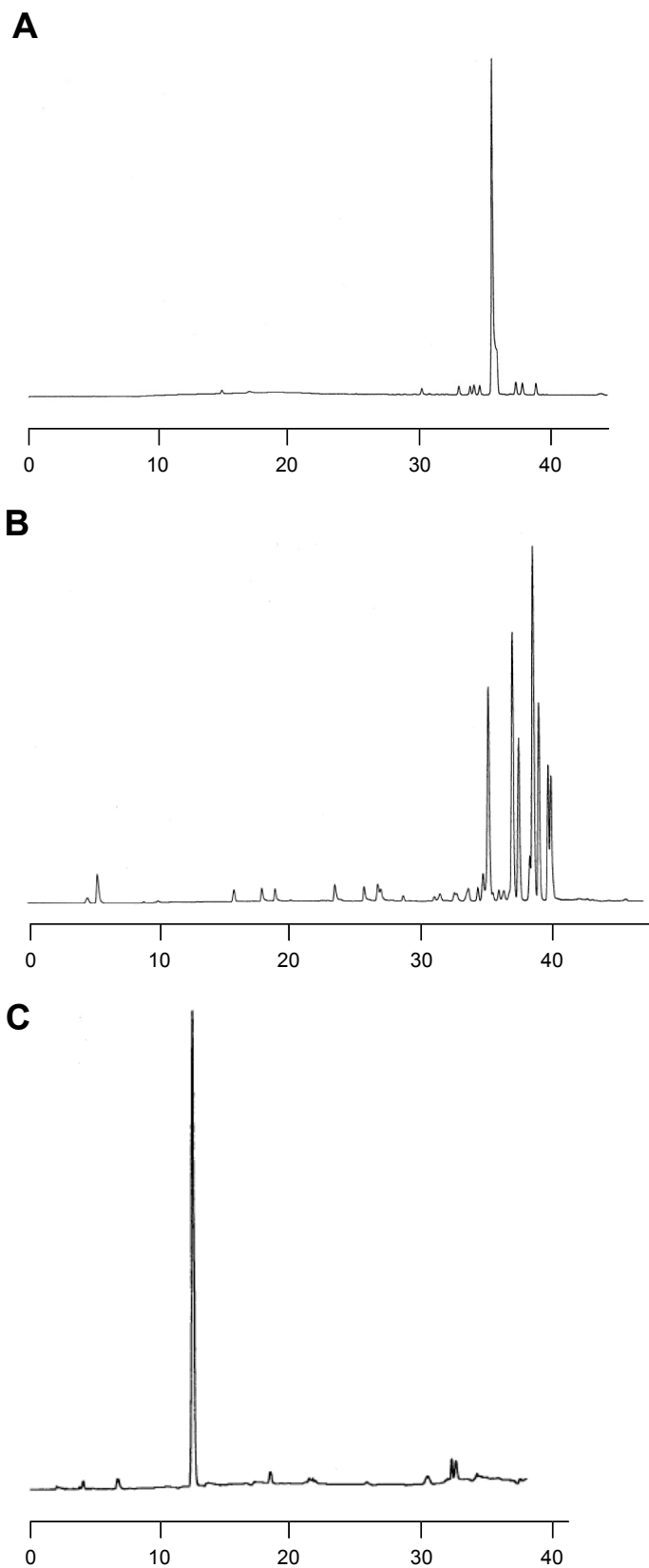
^1H NMR spectrum of 12a
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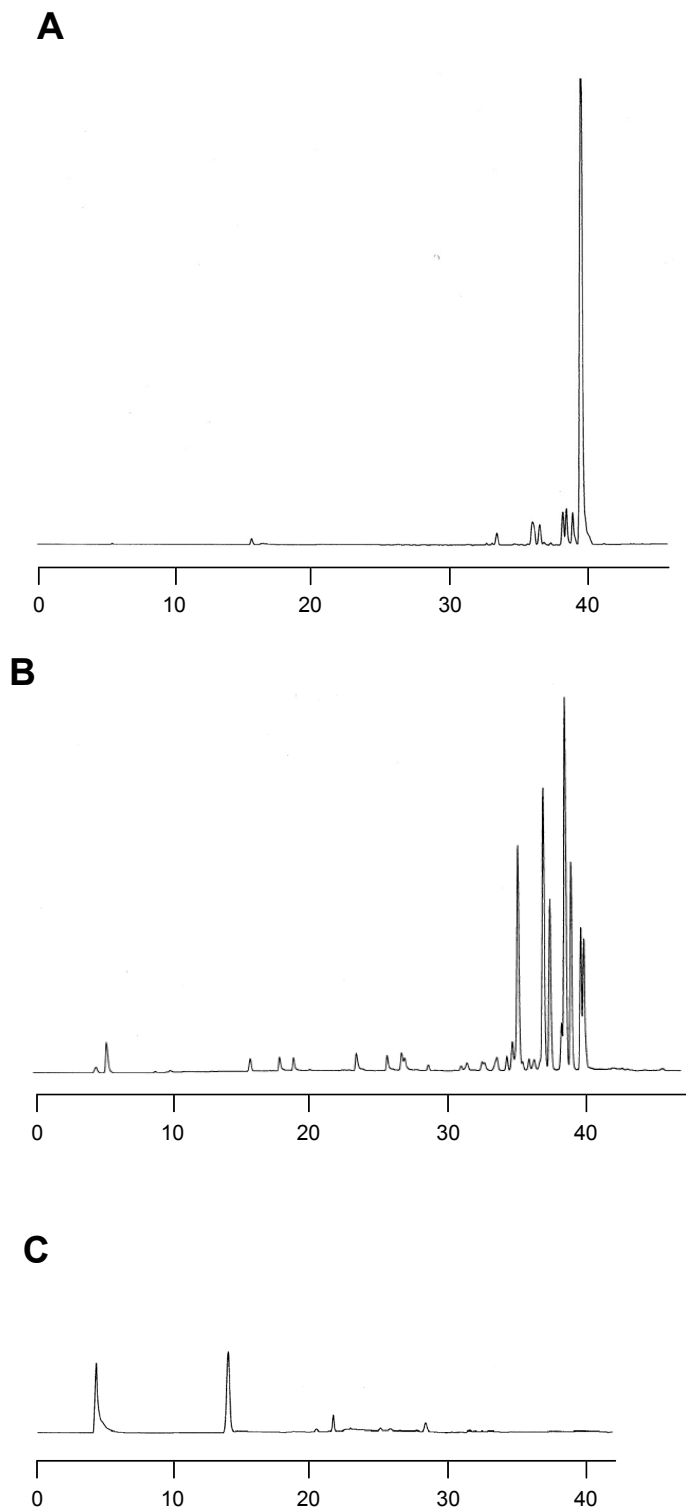
^{31}P NMR spectrum of 12a
(mixture of diastereomers)



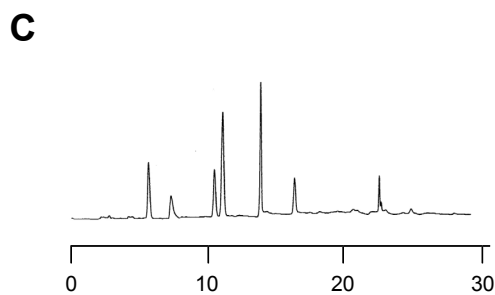
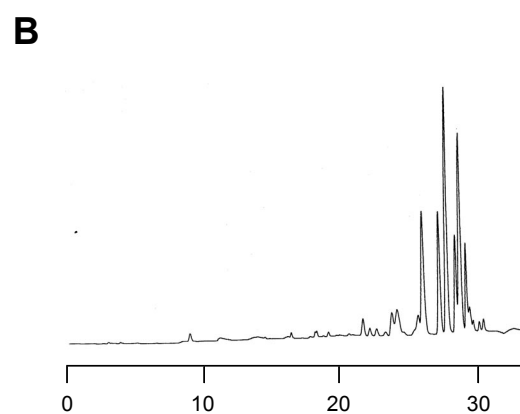
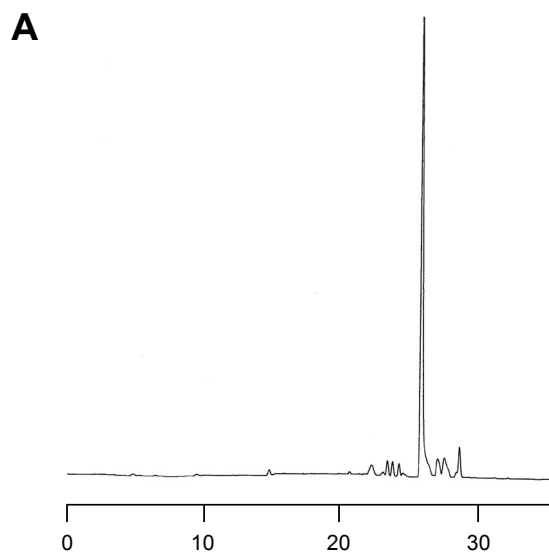
Reverse-phase HPLC profiles of: (A) (Rp)-**12a**; (B) (Sp)-**12a**; (C) diastereomeric mixture of (Rp)-**12a** and (Sp)-**12a** synthesized by a conventional *H*-phosphonate method. RP-HPLC was performed with a linear gradient of 0-10% (30 min) then 10% (10 min) acetonitrile in 0.1 M ammonium acetate buffer (pH 7.0) at 50 °C at a rate of 1.0 ml/min.



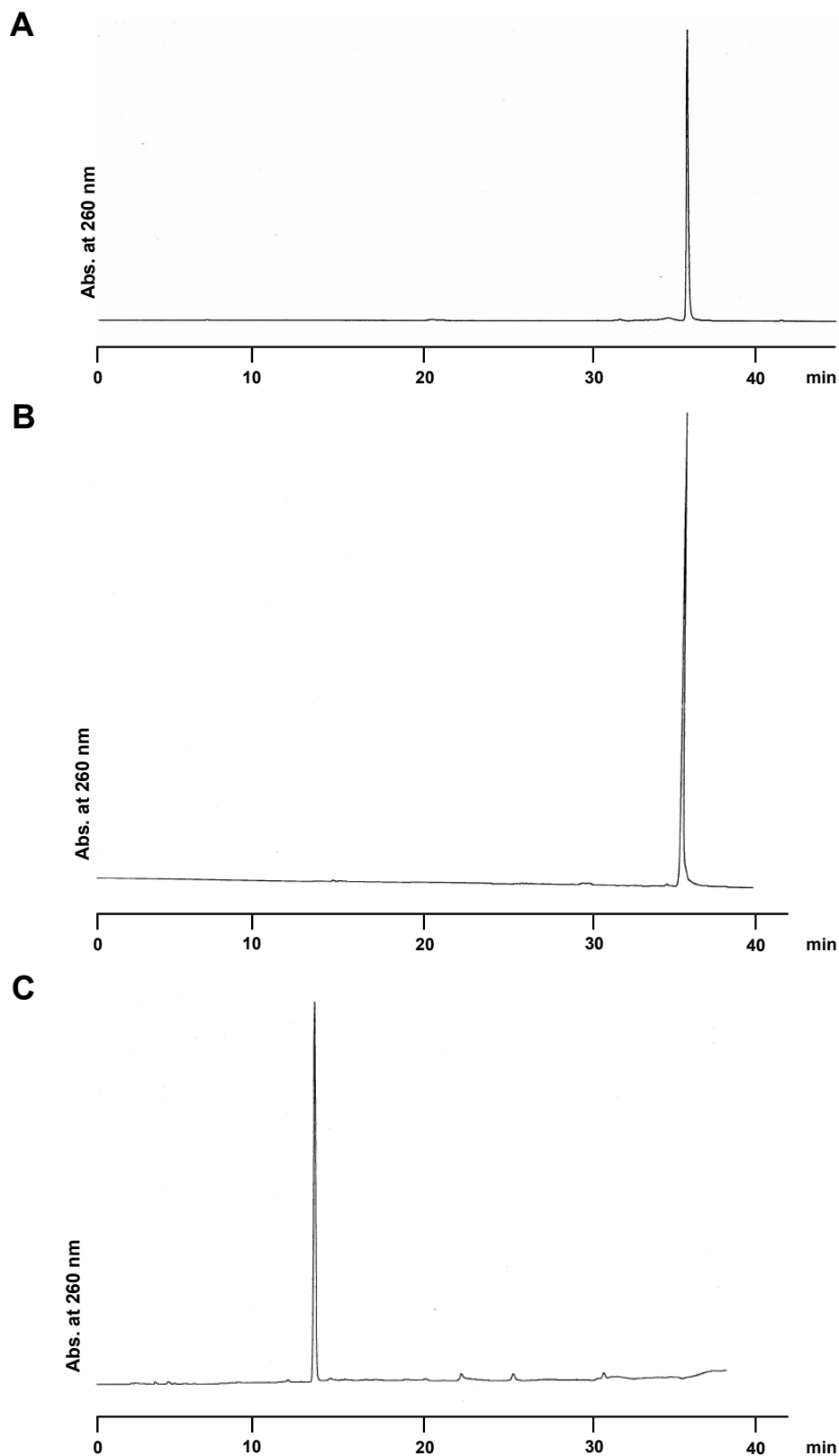
Reverse-phase HPLC chromatograms of: (A) crude all-(*R*_p)-d[T_{PS}]T (**15**), (B) random-d[T_{PS}]T, (C) the mixture obtained by the digestion of **15** with svPDE. RP-HPLC was performed with a linear gradient of 0-20% acetonitrile in 0.1 M ammonium acetate buffer (pH 7.0) for 60 min at 50 °C at a rate of 0.5 ml/min.



Reverse-phase HPLC chromatograms of: (A) crude all-(*S*p)-d[T_{PS}]T (**16**), (B) random-d[T_{PS}]T, (C) the mixture obtained by the digestion of **16** with Nuclease P1. RP-HPLC was performed with a linear gradient of 0-20% acetonitrile in 0.1 M ammonium acetate buffer (pH 7.0) for 60 min at 50 °C at a rate of 0.5 ml/min.



Reverse-phase HPLC chromatograms of: (A) crude all-(*Rp*)-d[C_{PS}A_{PS}G_{PS}]C (**17**), (B) random-d[C_{PS}A_{PS}G_{PS}]C, (C) the mixture obtained by the digestion of **17** with svPDE. RP-HPLC was performed with a linear gradient of 0-20% acetonitrile in 0.1 M ammonium acetate buffer (pH 7.0) for 60 min at 50 °C at a rate of 0.5 ml/min.



Reverse-phase HPLC chromatograms of: (A) purified **18** (B) the mixture obtained by the digestion of purified **18** with Nuclease P1, (C) the mixture obtained by the digestion of purified **18** with svPDE. RP-HPLC was performed with a linear gradient of 0-20% acetonitrile in 0.1 M ammonium acetate buffer (pH 7.0) for 60 min at 50 °C at a rate of 0.5 ml/min.