Operationally Simple, Efficient and Diastereoselective Synthesis of *Cis*-2,6-disubstituted-4-methylene Tetrahydropyrans by Triflic Acid

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Supporting Information

General. All reactions were carried out in oven-dried (135 °C) glassware under an inert atmosphere of dry N_2 unless otherwise stated. Infrared (IR) spectra were recorded on a Nicolet 210 spectrophometer, υ_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) or weak (w). ^{1}H-NMR spectra were recorded on a Varian Gemini 2000 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuteration as the internal reference ($CDCl_3$: δ 7.26, C_6D_6: δ 7.16). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration and assignment. ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$:δ 77.16, C_6D_6:δ 128.06). High-resolution mass spectrometry was performed at the University of Illinois Mass Spectrometry Laboratory. Silica gel chromatography was carried out on $AgNO_3$ 5% w/w on silica gel.[1]

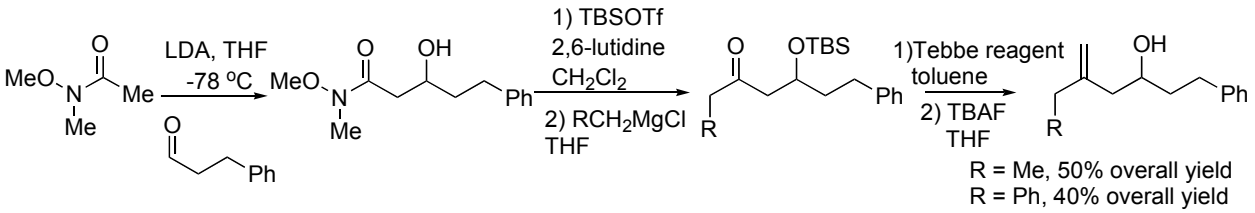
The enol ether substrates were prepared from the corresponding alcohols using known literature methods. Substrates **1**, **5**, **7**, **9**, and **11** were synthesized through Pd-catalyzed transfer vinylation method reported by Bosch and Schlaf.[2] Enol ether **13** was prepared by Tebbe

(1) Williams, C.M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425–447.

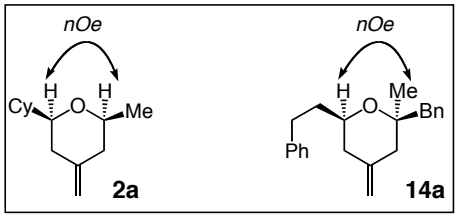
(2) Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225–5227.

olefination of the corresponding phenylacetate.[3] Substrate **15** was accessed through a conjugate addition method recently described by Hart.[4]

The homoallylic alcohol precursors were also synthesized based on known literature methods. Homoallylic alcohol precursors to enol ethers **1**, **5**, **13**, and **15** were obtained by addition of methallyl Grignard reagents to the corresponding aldehydes.[5] The alcohol precursor to **11** was obtained by reaction of excess methallyl Grignard reagent with ethyl formate.[6] Alcohol precursors to enol ethers **7** and **9** were prepared by the sequence of reactions reported below, partially described by Evans.[7]



Proof of relative stereochemistry. In general, NOE experiments indicate that the major compound formed is the *cis*-2,6-disubstituted diastereomer (e.g., enhancement of the carbinol methine protons in **2a**; see below). Comparison of ^{1}H NMR spectrum of pyran product **6a** with values reported in the literature further supports these assignments.[8] For compound **14a**, bearing a tertiary ether site, as illustrated below, the appropriate NOE between the Me group and the carbinol proton was observed (NOESY).



(3) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270–3272.

(4) Hart, D. J.; Bennett, C. E.; *Org. Lett.* **2003**, *5*, 1499–1502.

(5) Uchiai, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *Chem. Pharm. Bull.* **1985**, *33*, 989–997.

(6) Breit, B.; Breuninger, D.; *J. Am. Chem. Soc.*, **2004**, *126*, 10244–10245.

(7) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343.

(8) Kopecky, D. J.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **2001**, *123*, 8420–8421.

Representative procedure for the triflic acid catalysed synthesis of *cis*-2,6-disubstituted-4-methylene tetrahydropyrans. *Cis*-2-cyclohexyl-6-methyl-4-methylenetetrahydro-2*H*-pyran (2a). To a benzene solution of enol ether **1** (20 mg, 0.10 mmol) was added a solution of triflic acid in benzene (10 μL, 10^{-4} mmol). After stirring for 10 minutes at 22 °C the reaction was quenched by addition of a saturated solution of $NaHCO_3$ (aq.). The aqueous phase was extracted with pentane and the organic phase was dried over $MgSO_4$. Isomer ratio was determined by ^{1}H-NMR of the crude mixture. Purification through $AgNO_3$ on silica gel chromatography using pentane as the eluent afforded the desired product as a colorless oil (11 mg, 0.055 mmol, 55% yield). IR (neat): 3075(w), 2930 (s), 2855 (s), 1659 (m), 1451 (m), 1376 (w), 1350 (w), 1325 (w), 1193 (w), 1117 (m), 1067 (m), 891 (s), 847 (w), 664 (w) cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.67 (s, 2H, C=CH_2), 3.36-3.28 (m, 1H, OC*H*), 2.98-2.93 (m, 1H, OC*H*), 2.20-2.15 (m, 2H, CH_2C=C), 1.97-1.84 (m, 3H, CH_2C=C and Cy-*H*), 1.74-1.60 (m, 4H, Cy-*H*), 1.43-1.34 (m, 1H, Cy-*H*), 1.28-1.08 (m, 3H, Cy-*H*), 1.19 (d, *J* = 5.9 Hz, 3H, CH_3), 1.02-0.88 (m, 2H, Cy-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 108.1, 83.0, 74.7, 43.3, 43.0, 37.7, 29.6, 28.7, 26.8, 26.4, 26.3, 22.1. HRMS calcd for $C_{13}H_{22}O$: 194.1671. Found: 194.1667.

***Cis*-2-methyl-4-methylene-6-phenethyltetrahydro-2*H*-pyran (6a).** IR (neat): 3069 (w), 3024 (w), 2974 (w), 2930 (s), 2886 (w), 2862 (w), 1652 (w), 1602 (w), 1495 (w), 1462 (w), 1375 (w), 1325 (m), 1096 (m), 746 (w), 702 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H, Ar-*H*), 7.20-7.16 (m, 3H, Ar-*H*), 4.68 (s, 2H, C=CH_2), 3.42-34 (m, 1H, OC*H*), 3.28-3.20 (m, 1H, OC*H*), 2.80 (ddd, *J* = 13.5, 9.8, 5.6 Hz, 1H, PhC*H*HCH$_2$), 2.71 (ddd, *J* = 13.5, 9.3, 7.2 Hz, 1H, PhCH*H*CH$_2$), 2.23-2.15 (m, 2H, CH_2), 1.99-1.86 (m, 3H, CH$_2$), 1.78-1.71 (m, 1H, CH$_2$), 1.27 (d, *J* = 6.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 142.4, 128.7, 128.5, 125.9, 108.3, 77.4, 74.7, 42.7, 40.8, 38.1, 32.0, 22.1. HRMS calcd for $C_{15}H_{22}O$: 216.1514. Found: 216.1512.

***Cis*-4-ethylidene-2-methyl-6-phenethyltetrahydro-2*H*-pyran (8a).** This cyclization product was isolated as a 1.6:1 inseparable mixture of *E* and *Z* olefin isomers. ^{1}H NMR (400 MHz, C_6D_6): δ 7.13-6.99 (m, 5H x 2, Ar-*H*), 5.16-5.08 (m, 1H x 2, C=C*H*CH$_3$), 3.30-3.08 (m, 2H x 2, OC*H*), 2.84-2.74 (m, 2H x 2, PhC*H*HCH$_2$), 2.69-2.61 (m, 2H x 2, PhCH*H*CH$_2$), 2.33-2.82 (m, 1H x 2, CH_2), 1.90-1.78 (m, 3H x 2, CH_2), 1.66-1.51 (m, 2H x 2, CH_2), 1.47-1.44 (m, 3H x 2, C=CHCH_3), 1.16 (d, 3H, *J* = 6.2 Hz, OCHCH_3), 1.14 (d, 3H, *J* = 6.2 Hz, OCHCH_3). To facilitate

characterization, this olefin mixture was hydrogenated in the presence of H_2 and Pd(C) (20% w/w) in MeOH at 22 °C for 6 h to afford the corresponding hydrogenation product as a single diastereomer. IR (neat): 2961 (m), 2924 (s), 2855 (w), 1464 (w), 1376 (w), 1325 (w), 1168 (w), 1086 (w), 753 (w), 696 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22-7.04 (m, 5H, Ar-*H*), 3.32-3.21 (m, 1H, OC*H*), 3.19-3.10 (m, 1H, OC*H*), 2.93-2.82 (m, 1H, B segment of an AB system, C*H*H), 2.81-2.72 (m, 1H, A part of an AB system, CH*H*), 1.97-1.85 (m, 1H, C*H*H), 1.70-1.60 (m, 1H, C*H*H), 1.35 (t, *J* = 7.0 Hz, 2H, CH_2CH_3), 1.21 (d, J = 5.0 Hz, 3H, CH_3), 1.18-1.05 (m, 3H, CH_2 and C*H*H), 0.86-0.77 (m, 2H, CH_2), 0.70 (q, *J* = 7.0 Hz, 3H, CH_2CH_3). ^{13}C NMR (100 MHz, C_6D_6): δ 143.1, 128.9, 128.7, 126.0, 76.1, 73.3, 40.3, 38.8, 38.3, 37.3, 32.3, 30.0, 22.5, 11.2. HRMS calcd for $C_{16}H_{24}O$: 232.1827. Found: 232.1834.

***Cis*-4-benzylidene-2-methyl-6-phenethyltetrahydro-2*H*-pyran (10a)**. This cyclization product was isolated as a 1:1 inseparable mixture of *E* and *Z* olefin isomers. ^1H NMR (400 MHz, $CDCl_3$) 7.33-7.13 (m, 20H, Ar-*H*), 6.28 (s, 2H, C=C*H*Ph), 3.54-3.46 (m, 1H, OC*H*), 3.40-3.32 (m, 2H, OC*H*), 3.25-3.18 (m, 1H, OC*H*), 2.87-2.62 (m, 6H, CH_2), 2.28-2.18 (m, 4H, CH_2), 1.98-1.67 (m, 6H, CH_2), 1.29 (d, *J* = 6.2 Hz, 3H, CH_3), 1.24 (d, *J* = 6.2 Hz, 3H, CH_3). To facilitate characterization, this unpurified olefin mixture was hydrogenated in the presence of H_2 and Pd (C) (20% w/w) in MeOH at 22 °C for 6 h to afford the corresponding hydrogenation product as a mixture of two diastereomers at C_4 (1.6:1 ratio; identity of isomers not determined). IR (neat): 3062 (w), 3031 (m), 2924 (s), 2848 (s), 1602 (w), 1495 (s), 1451 (s), 1382 (m), 1325 (w), 1269 (w), 1149 (w), 1080 (m), 1036 (m), 815 (w), 765 (m), 708 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): major isomer δ 7.33-1.08 (m, Ar-*H*), 3.83-3.73 (minor isomer, m, 1H, OC*H*), 3.68-3.57 (Minor isomer, m, 1H, OC*H*), 3.44-3.33 (major isomer, m, 1H, OC*H*), 3.27-3.18 (major isomer, m, 1H, OC*H*), 2.84-2.62 (major isomer, m, 4H, PhCH_2 and PhCH_2), 2.58-2.47 (minor isomer, m, 1H, PhC*H*H), 2.50 (minor isomer, d, *J* = 5 Hz, 2H, PhCH_2), 2.26-2.18 (minor isomer, m, 1H, PhCH*H*), 1.91-1.40 (bs, CH_2, CH_2 and C*H* of the two isomers), 1.18 (major isomer, d, *J* = 7.0 Hz, 3H, CH_3), 1.15 (minor isomer, d, *J* = 7.0 Hz, 3H, CH_3), 1.00-0.80 (broad s, CH_2 of the two diastereomers). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.61, 142.60, 141.4, 140.5, 129.3, 129.2, 128.73, 128.70, 128.56, 128.50, 128.49, 128.45, 128.42, 126.1, 125.9, 125.8, 76.3, 73.5, 71.6, 68.6, 43.8, 40.2, 38.4, 38.3, 38.3, 38.1, 37.8, 37.0, 34.8, 33.7, 32.03, 32.02, 22.5, 22.3. HRMS calcd for $C_{21}H_{26}O$: 294.1984. Found: 294.1990.

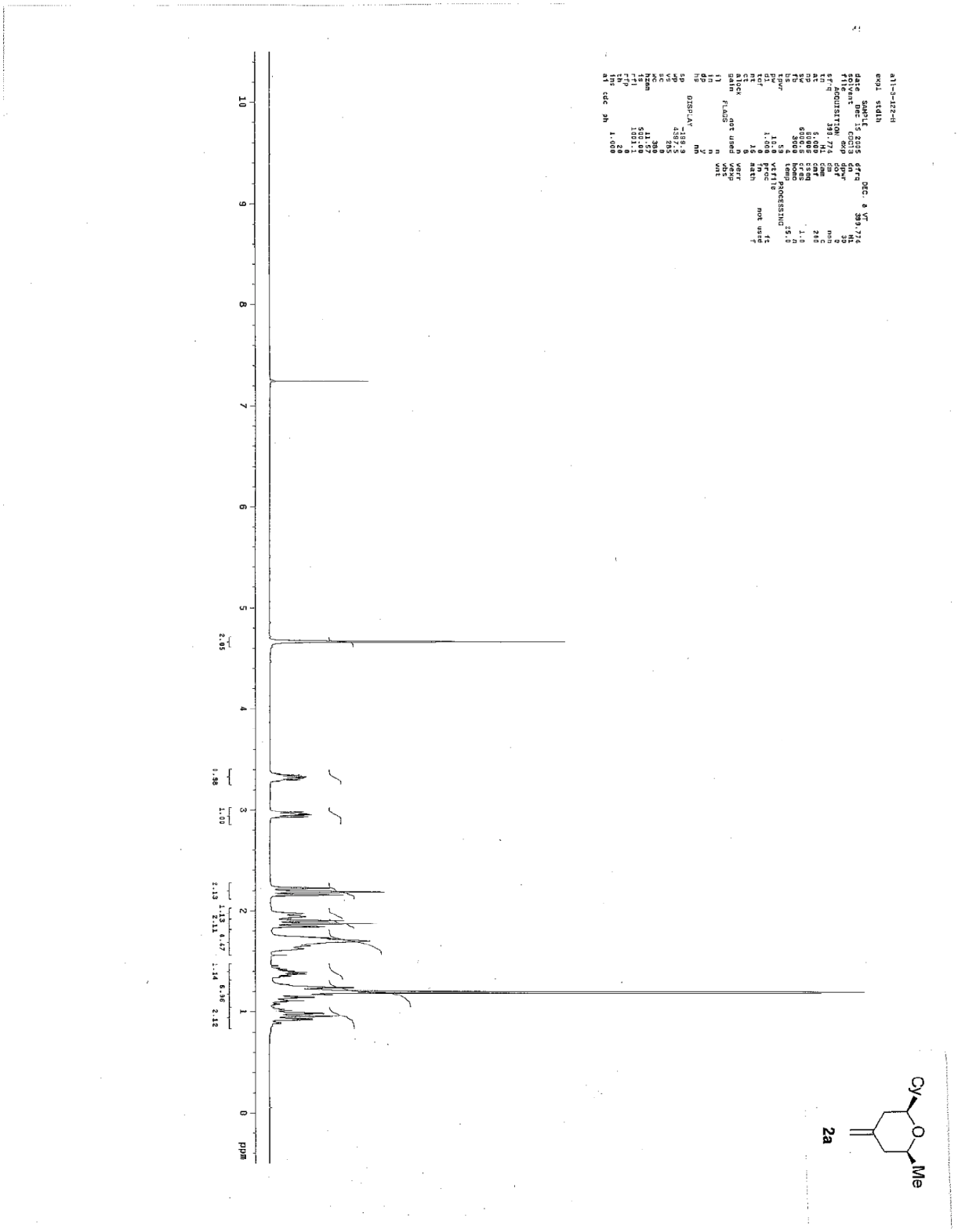
***Cis*-2-methyl-6-(2-methylallyl)-4-methylenetetrahydro-2*H*-pyran (12a).** IR (neat): 2961 (w), 2917 (s), 2855 (m), 1457 (w), 1369 (w), 1256 (w), 1099 (w), 1023 (w), 803 (m) cm^{-1}. ^{1}H-NMR (400 MHz, C_6D_6): δ 4.77 (d, *J* = 9 Hz, 2H, C=C*H*$_2$), 4.64 (d, *J* = 2 Hz, 2H, C=C*H*$_2$), 3.39-31 (m, 1H, OC*H*), 3.26-3.17 (m, 1H, OC*H*), 2.32 (dd, *J* = 13.8, 6.9 Hz, 1H, C*H*H), 2.10-2.02 (m, 2H, C*H*H and C*H*H), 1.90 (d, *J* = 13.0 Hz, 1H, C*H*H), 1.85-1.72 (m, 2H, C*H*H and C*H*H), 1.64 (s, 3H, C*H*$_3$), 1.07 (d, *J* = 6.0 Hz, 3H, C*H*$_3$). ^{13}C NMR (100 MHz, C_6D_6): δ 145.3, 142.7, 112.6, 108.1, 77.0, 74.5, 44.9, 42.6, 40.5, 23.0, 22.0. HRMS calcd for $C_{11}H_{18}O$: 166.1358. Found: 166.1353.

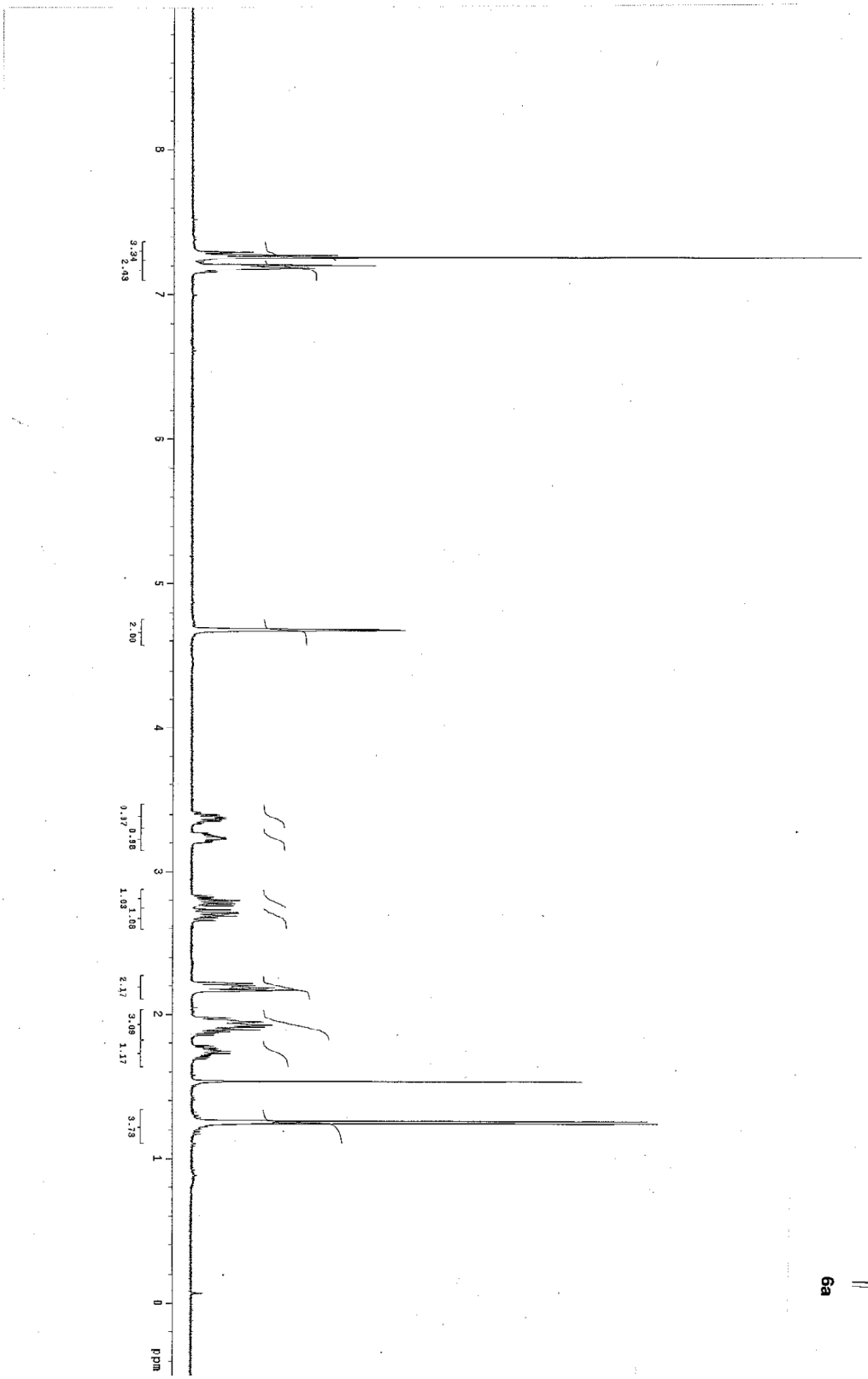
***Cis*-2-benzyl-2-methyl-4-methylene-6-phenethyltetrahydro-2*H*-pyran (14a).** IR (neat): 3055 (w), 3024 (m), 2392 (m), 1652 (w), 1602 (w), 1495 (m), 1454 (m), 1375 (w), 1313 (w), 1092 (w), 1060 (w), 1029 (w), 973 (w), 897 (w), 751 (s), 699 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.11 (m, 10H, Ar-*H*), 4.74 (d, *J* = 2.0 Hz, 1H, C=C*H*H), 4.63 (d, *J* = 2.0 Hz, 1H, C=CH*H*), 3.43 (m, 1H, OC*H*), 2.89 (d, *J* = 13.2 Hz, 1H, PhC*H*HCO), 2.80-2.73 (m, 2H, PhCH*H*CO and PhC*H*HCH$_2$), 2.64 (dt, *J* = 13.6, 8.0 Hz, 1H, PhCH*H*CH$_2$), 2.15 (d, *J* = 14.0 Hz, 1H, CH$_2$), 2.13 (d, *J* = 14.0 Hz, 1H, CH$_2$), 1.99 (d, *J* = 12.8 Hz, 1H, CH$_2$), 1.89-1.78 (m, 2H, CH$_2$), 1.76-1.67 (m, 1H, CH$_2$), 0.98 (s, 3H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 142.7, 138.2, 131.2, 128.8, 128.4, 127.9, 126.3, 125.8, 109.9, 75.3, 69.9, 50.2, 45.1, 41.1, 38.6, 31.9, 20.4. HRMS calcd for $C_{22}H_{26}O$: 306.1984. Found: 306.1978.

Methyl 2-(*cis*-4-methylene-6-phenethyltetrahydro-2*H*-pyran-2-yl)acetate (16a). IR (neat): 3081 (w), 3024 (w), 2949 (m), 2861 (w), 1741 (s), 1652 (w), 1495 (w), 1457 (w), 1438 (w), 1369 (w), 1338 (w), 1250 (w), 1180 (w), 1149 (w), 1092 (m), 1073 (w), 1023 (w), 897 (w) cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ 7.34-7.23 (m, 3H, Ar-*H*), 7.24-7.16 (m, 2H, Ar-*H*), 4.67 (d, *J* = 2.0 Hz, 2H, C=C*H*$_2$), 3.74 (s, 3H, OC*H*$_3$), 3.66-3.78 (m, 1H, OC*H*), 3.30-3.20 (m, 1H, OC*H*), 2.80-2.71 (m, 1H, B part of an AB system, C*H*H), 2.70-2.60 (m, 2H, A part of an AB system CH*H* and B part of an AB system C*H*H), 2.45 (dd, *J* = 9.0, 3.0 Hz, 1H, A part of an AB system, CH*H*), 2.28 (d, *J* = 8.0 Hz, 1H, B part of an AB system, C*H*H), 2.18 (d, *J* = 9.0 Hz, 1H, B part of an AB system, C*H*H), 2.05-1.90 (m, 2H, A part of an AB system, CH*H* and A part of an AB system, CH*H*), 1.90-1.80 (m, 1H, B part of an AB system, C*H*H), 1.75-1.65 (m, 1H, A part of an AB system CH*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 144.0, 142.4, 128.8, 128.5, 125.9,

109.4, 77.4, 75.0, 51.9, 41.5, 40.7, 40.6, 38.0, 34.9. HRMS calcd for $C_{17}H_{22}O_3$: 274.1569. Found: 274.1566.

■ **Representative 1H NMR (400 MHz) spectra of cyclization products:**

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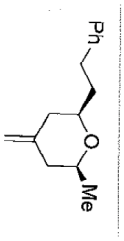
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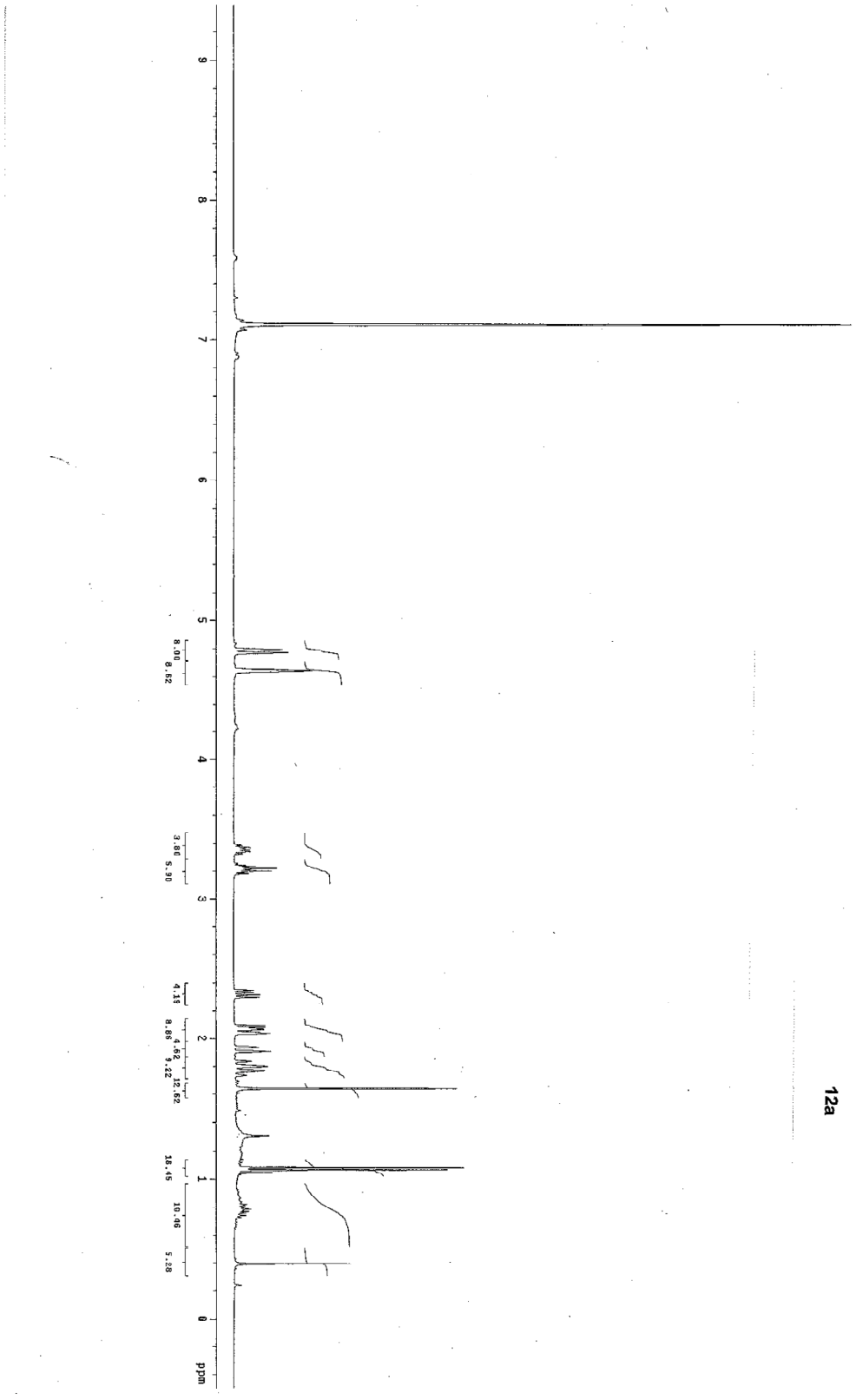
6a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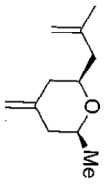
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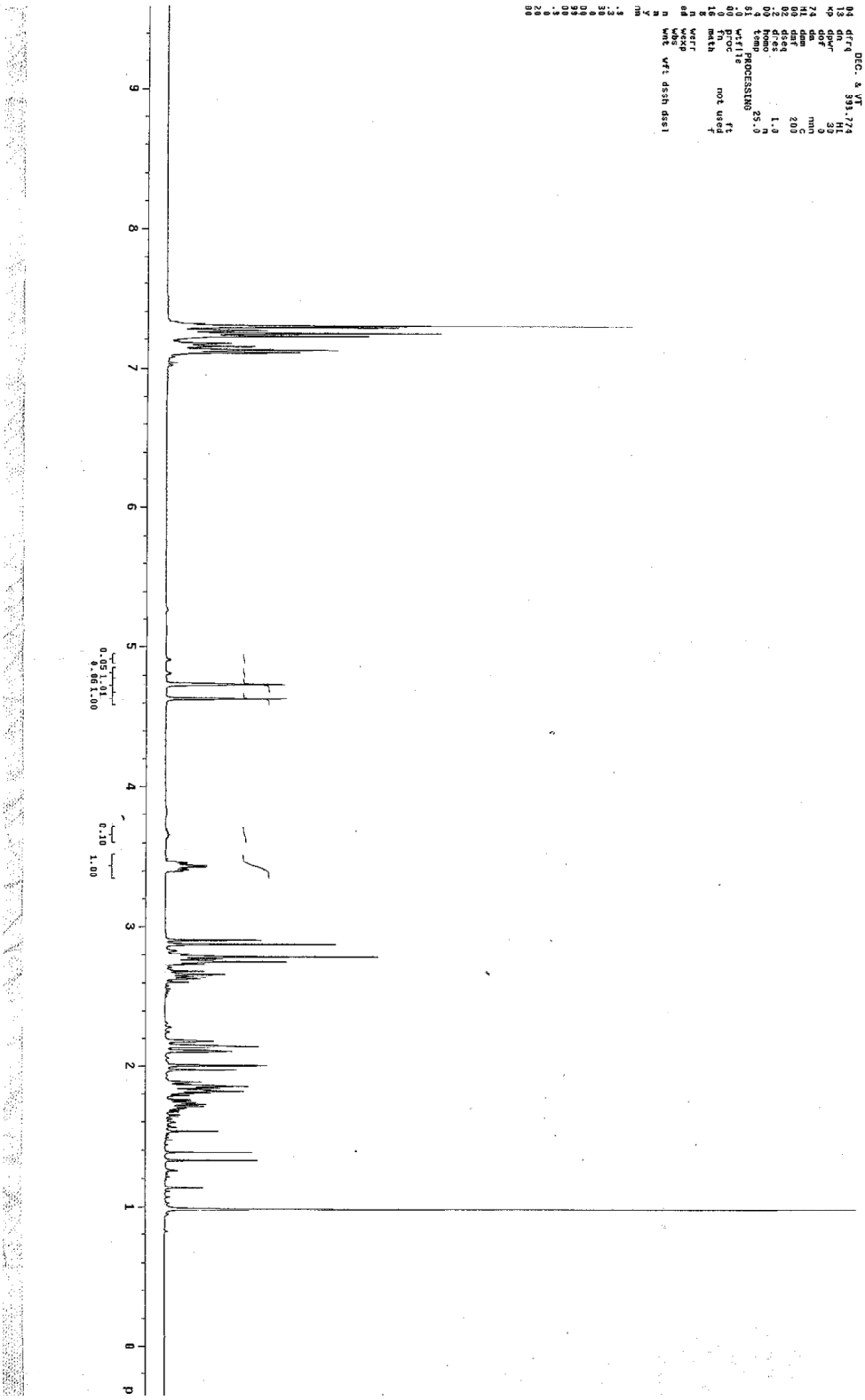
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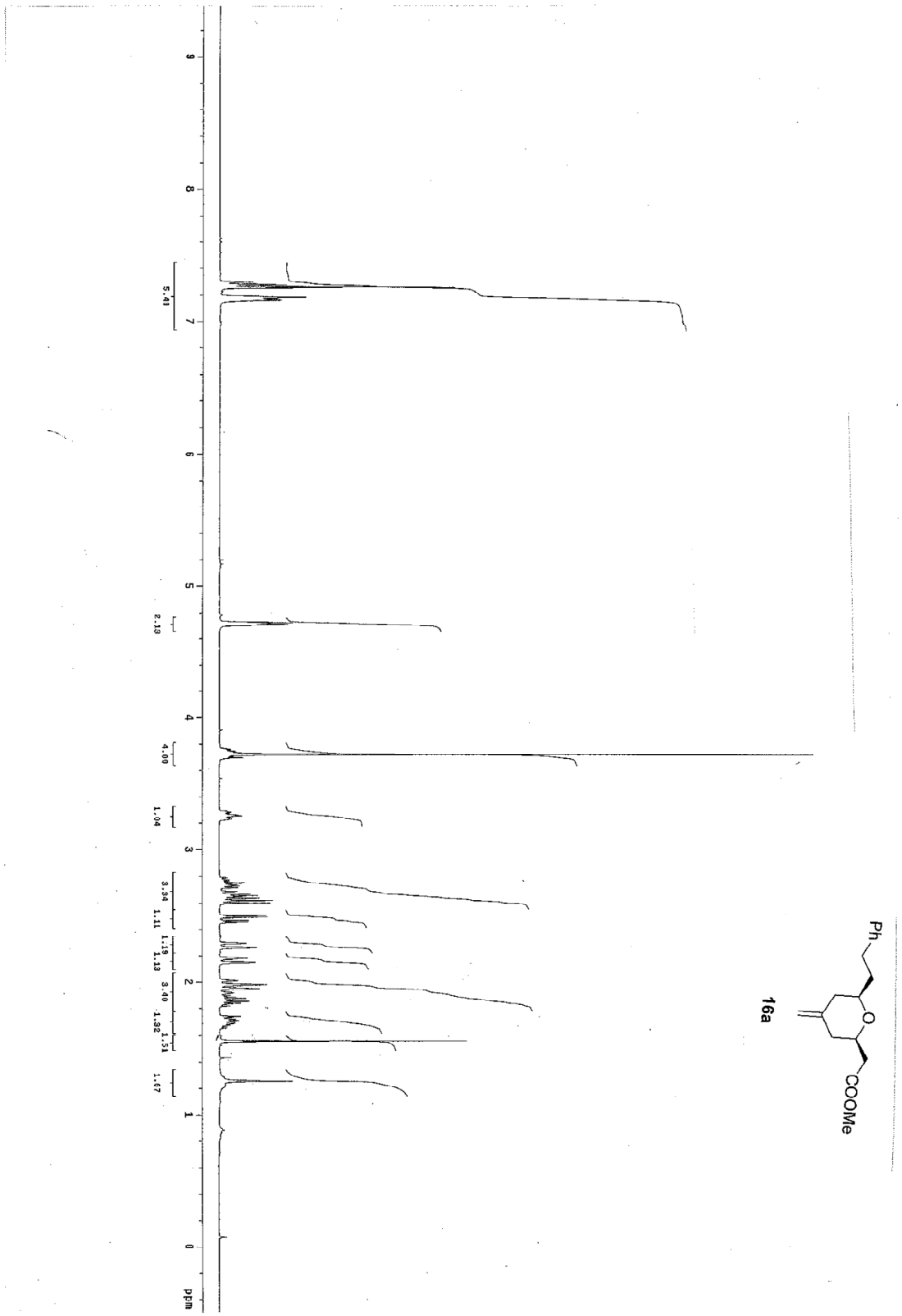
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