Direct Organocatalytic Aldol Reactions in Buffered Aqueous Media

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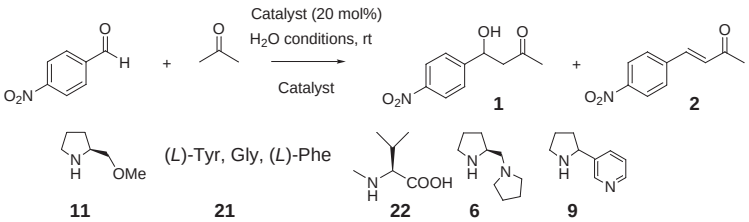
Supporting Information

General. Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/ or by treatment with a solution of phosphomolybdic acid (25g), $Ce(SO_4)_2 \bullet H_2O$) (10g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *P*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 300, AMX 250, AMX 500 and AMX 400 instruments. The chemical shifts are given in δ relative to TMS (δ = 0 ppm). The spectra were in $CDCl_3$ and CD_3OD at room temperature. High-resolution mass spectra were recorded on an Ion Spec Fourier Transform Mass Spectrometer using dihydrobenzoic acid (DHB) as the matrix. HPLC was carried out using a Hitachi organizer consisting of a D-2500 Chromato-Integrator, a L-4000 UV-Detector, and a L-6200A Intelligent Pump.

General procedure for direct aldol reactions with acetone and 4-nitrobenzaldehyde:
In a typical experiment, 4-nitrobenzaldehyde (1.0 mmol) was added to the aqueous solution (8 mL), acetone (2 mL) was added to obtain a total volume of 10 mL, followed by catalyst (20 mol %) and the mixture was stirred for 24-48h at room temperature. Following aqueous work-up with half-saturated ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried ($MgSO_4$), filtered and concentrated. ^{1}H NMR analyses determined the conversion and the ratio between aldol product **1** and dehydration product **2**. Furthermore, HPLC analysis was also performed by injecting an aliquot (5 μL) of the reaction mixture to a RP-C18 Vydac HPLC column (HPLC conditions: acetonitrile:water-25:75 with 0.1% TFA, λ = 254 nm and flow rate = 1.0 mL/min). The ee of **1** derived from the L-proline-, **6**- and **11**-catalyzed reactions was determined by Chiral-phase HPLC (Daicel Chiralpak AD, hexane:i-Pr-80:20, *v* = 1.0 mL/min, λ = 254 nm); t_R (major) = 19.87 min; t_R (minor) = 21.54.

Table 1S. Study of the direct catalytic aldol reactions of acetone with p-nitrobenzaldehyde with primary and secondary amines.



Entry	Conditions	Catalyst	Time (h)	**1**[a]	**2**[a]
1	PBS[b]	L-Proline	24	99%	trace
2	PBS[b]	**11**	24	75%	15%
3	PBS[b]	none	24	trace	0%
4	PBS[b]	**21**	48	<10%	0%
5	PBS[b]	**22**	48	<10%	0%
6	PBS[b]	**6**	24	64%	36%
7	water	**6**	24	81%	19%
8	PBS[b]	**9**	24	94%	6%
9	PBS	pyrrolidine	24	57%	43%

[a] Conversion as determined by 1H NMR and reverse phase HPLC after extractive workup. [b] 0.1 equiv SDS used.

NaCN inhibition of the proline-catalyzed aldol reaction with acetone and 4-nitrobenzaldehyde:
4-Nitrobenzaldehyde (1.0 mmol) and SDS (0.1 mmol) was added to the PBS solution (8 mL), acetone (2 mL) was added to obtain a total volume of 10 mL, followed by L-proline (20 mol %) and NaCN (40 mol%) and the mixture was stirred for 24h at room temperature. HPLC analysis was performed and confirmed that only trace amounts of **1** and no elimination product **2** was formed.

Procedure for the synthesis of 1, 3, 4-Trihydroxy-4-(4-nitrophenyl)-2-butanone (10):

In a typical experiment, 4-nitrobenzaldehyde (1.0 mmol) was added to the aqueous solution (8 mL), dihydroxyacetone (0.1 mol) was added, followed by catalyst (25 mol %) and the mixture was stirred for 2-48h at room temperature. Following aqueous work-up with half-saturated ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried ($MgSO_4$), filtered and concentrated and the residue purified by column chromatography (silica, hexanes:ethyl acetate-1:10) to afford the corresponding aldol product **10**.

1, 3, 4-Trihydroxy-4-(4-nitrophenyl)-2-butanone 10:

^{1}H NMR (500 MHz, CD_3OD): (1:1 mixture of diastereomers) δ = 4.12 (d, 1H, J = 19.4 Hz), 4.25 (d, 1H, *J* = 5.8 Hz), 4.30 (d, 1H, *J* = 2.6 Hz), 4.44 (d, 1H, *J* = 19.4 Hz), 4.48 (d, 2H, *J* = 4.0 Hz), 4.86 (d, 1H, *J* =

5.9 Hz), 5.15 (d, 1H, *J* = 2.20 Hz), 7.53 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.60 (d, 2H, *J* = 8.4 Hz, Ar*H*), 8.12 (m, 4H, Ar*H*); ^{13}C NMR (125 MHz): δ = 212.6, 212.1, 150.9, 150.2, 148.9, 148.7, 129.3, 128.7, 124.1, 124.0, 80.7, 79.7, 75.4, 74.7, 68.3, 68.2. HRMS calcld for $C_{10}H_{11}NO_6$ ($M+Na^+$) calcld 264.0479, found 264.0485 Da.

Procedure for the cross-aldol reactions with dihydroxy acetone:
In a typical experiment, aldehyde (1.0 mmol) was added to a 1:1 mixture of PBS buffer and DMSO (10 mL), dihydroxyacetone (0.1 mol) was added, followed by catalyst **6** (25 mol %) and the mixture was stirred for 24-48h at room temperature. Following aqueous work-up with half-saturated ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried ($MgSO_4$), filtered and concentrated and the residue purified by column chromatography (silica, hexanes:ethyl acetate-1:10) to afford the corresponding aldol products.

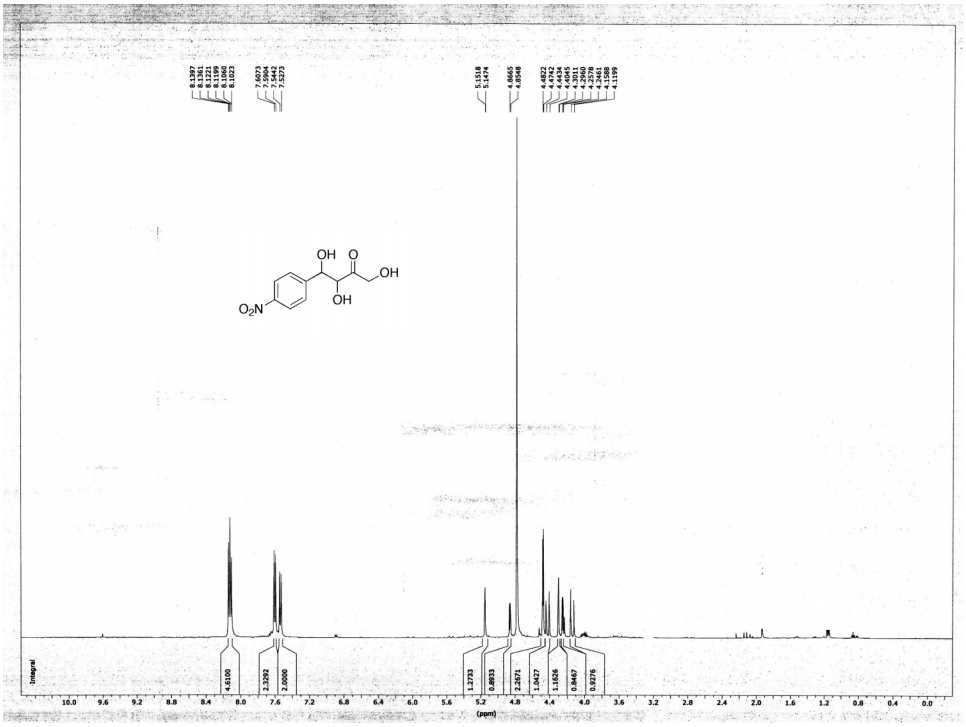
1, 3, 4-Trihydroxy-4-*O*-benzyl-2-pentanone 17:
^{1}H NMR (500 MHz, CD_3OD): δ = 3.59 (m, 1H), 3.71 (m, 1H,), 4.18 (m, 1H), 4.38 (bs, 1H), 4.39-4.60 (m, 2H, 4.95 (s, 2H, OC*H*$_2$Ph), 7.41 (5H, Ar*H*); ^{13}C NMR (125 MHz): δ = 212.6, 138.6, 128.4, 127.9, 127.7, 76.2, 73.3, 71.1, 70.6, 66.9 HRMS calcld for $C_{12}H_{16}O_5$ ($M+Na^+$) calcld 263.089, found 263.0889 Da.

1, 3, 4-Trihydroxy-4-phenyl-2-butanone 18:
^{1}H NMR (500 MHz, CD_3OD): (1:1 mixture of diastereomers) δ = 4.00 (d, 1H, *J* = 19.1 Hz), 4.22 (s, 1H), 4.25 (d, 1H, *J* = 5.9 Hz), 4.37 (d, 1H, *J* = 1.8 Hz), 4.39 (d, 2H, *J* = 19.4 Hz) 4.87 (d, 1H, *J* = 5.9 Hz), 4.95(d, 1H, *J* = 2.9 Hz), 7.53 (m, 10H, Ar*H*); ^{13}C NMR (125 MHz): δ = 213.1, 212.4, 142.8, 142.2, 129.2, 129.1, 128.8, 128.5, 128.3, 127.6, 81.0, 80.0, 76.3, 75.6, 68.2, 68.1. HRMS calcld for $C_{10}H_{12}O_4$ ($M+Na^+$) calcld 219.0628, found 219.0629 Da.

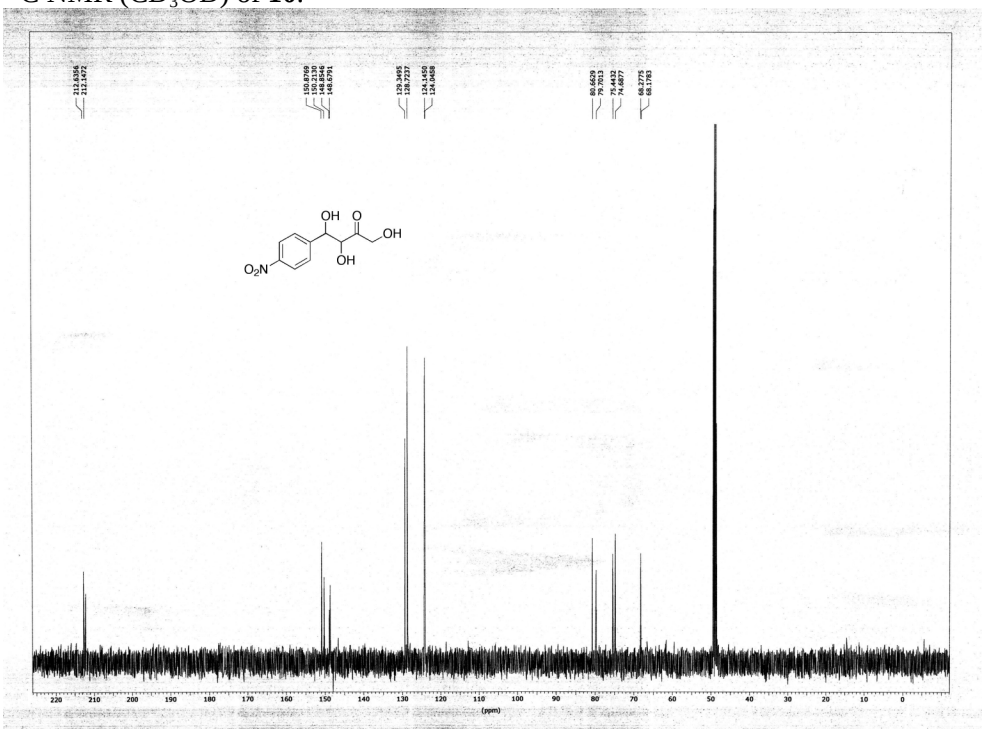
1, 3, 4-Trihydroxy-4-cyclohexyl-2-butanone 19:
^{1}H NMR (500 MHz, CD_3OD): δ = 1.05-1.39 (m, 4H), 1.6-1.84 (m, 6H), 2.15 (m, 1H), 3.59 (d, 1H, *J* = 9.2 Hz), 4.39 (d, 1H, *J* = 5.9 Hz), 4.57 (q, 2H, *J* = 33.0 Hz, *J* = 19.07 Hz); ^{13}C NMR (125 MHz): δ = 213.7, 77.1, 76.2, 66.9, 65.8, 40.0, 29.6, 29.3, 26.5, 26.1, 26.08 HRMS calcld for $C_{10}H_{18}O_4$ ($M+Na^+$) calcld 225.1097, found 225.1100 Da.

1, 3, 4-Trihydroxy-5, 6-O-isopropylidene-2-hexanone 20:
^{1}H NMR (500 MHz, CD_3OD): (1:1 mixture of diastereomers) δ = 1.25 (bs, 6H), 1.31 (bs, 6H), 3.29 (bs, 1H), 3.77 (m, 2H), 3.86 (m, 2H), 3.94 (m, 2H), 3,99 (m, 2H), 4.08 (m, 1H), 4.22 (bs, 2H), 4,32 (s, 1H), 4.39 (q, 2H); ^{13}C NMR (125 MHz): δ = 211.56, 108.0, 97.1, 76.6, 76.3, 74.6, 73.7, 71.9, 65.5, 64.5, 64.3, 24.6, 24.3, 24.2, 23.02. HRMS calcld for $C_9H_{16}O_6$ ($M+Na^+$) calcld 243.0839, found 243.0844 Da.

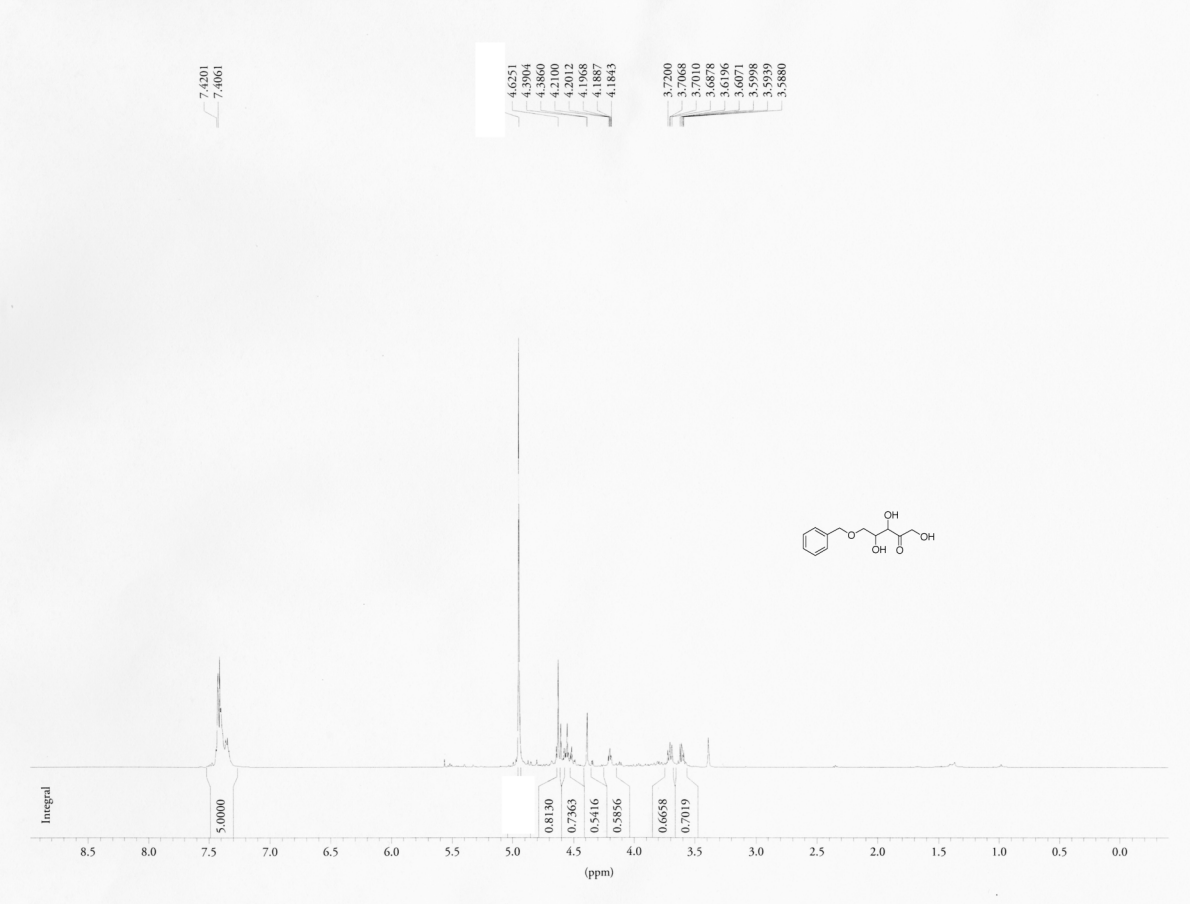
^{1}H NMR (500 MHz, CD_3OD) of **10**.



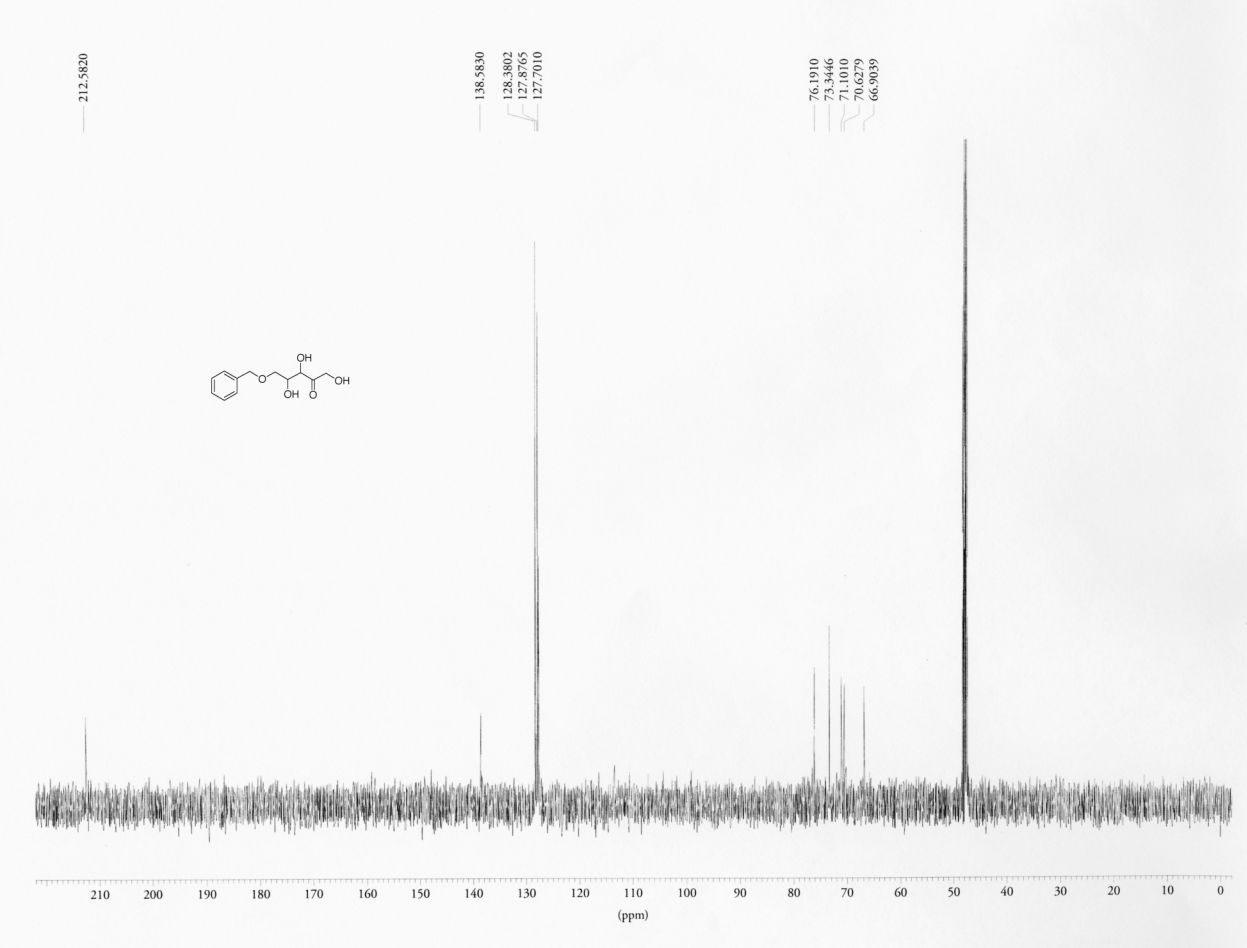
^{13}C NMR (CD_3OD) of **10**.



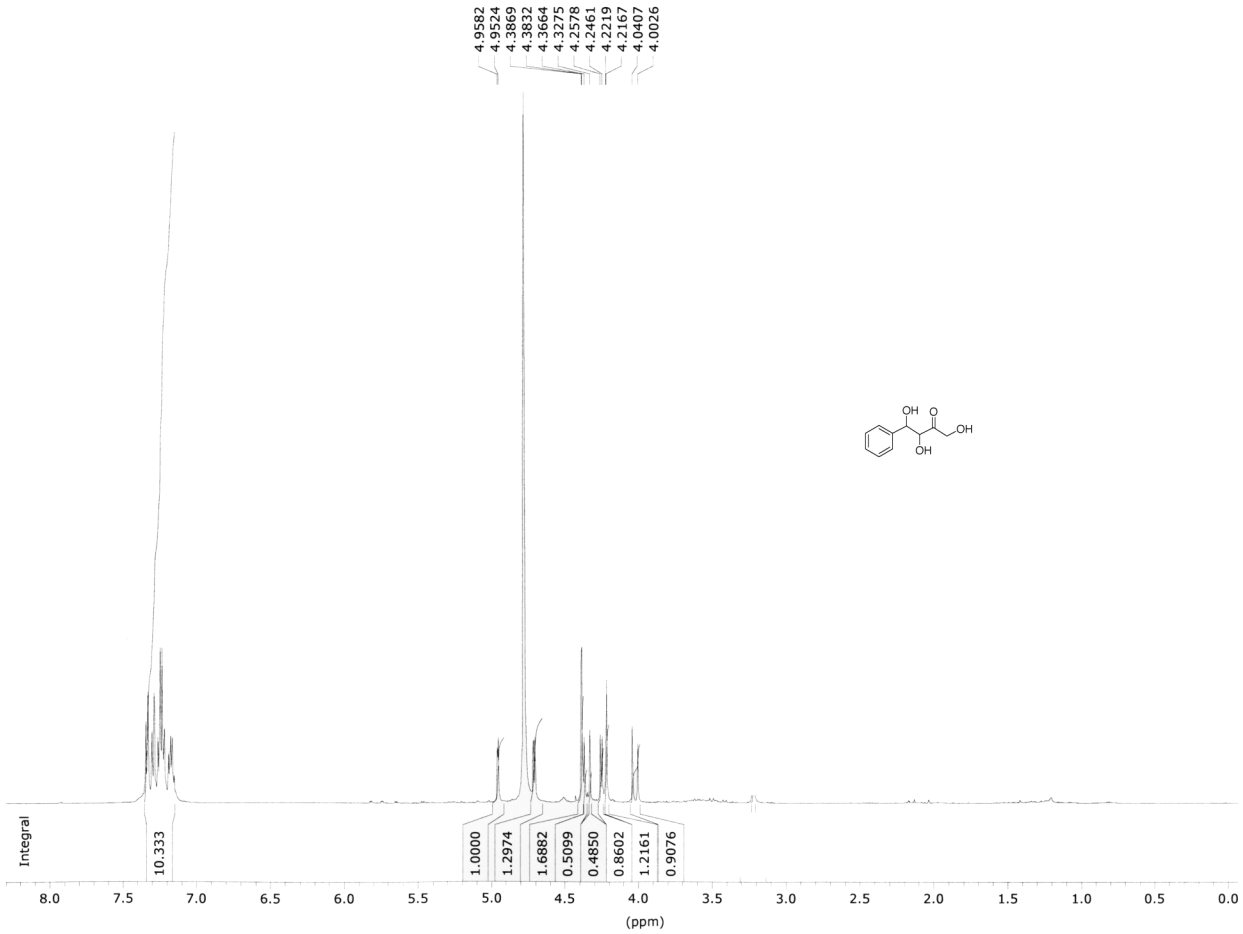
^{1}H NMR (500 MHz, CD_3OD) of **17**.



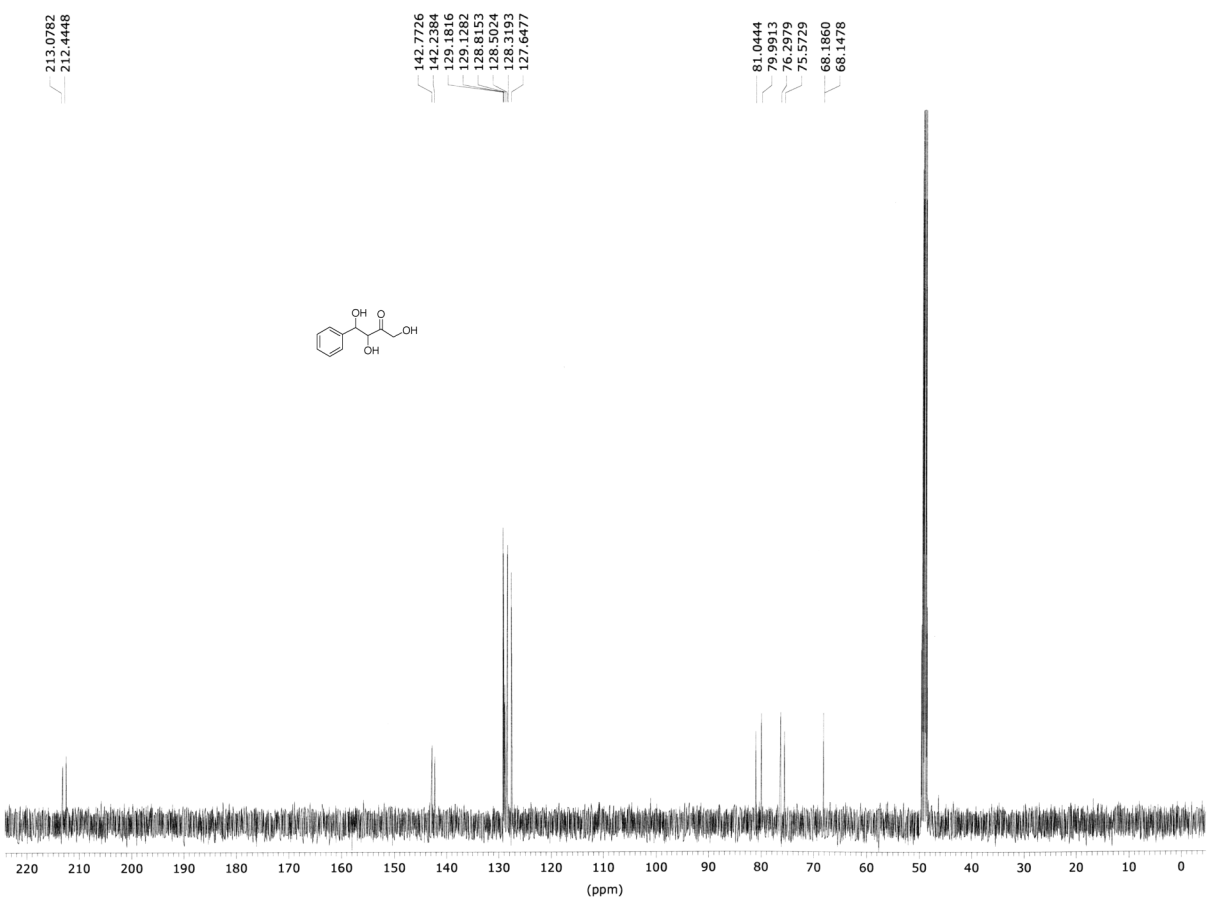
^{13}C NMR (500 MHz, CD_3OD) of **17**.



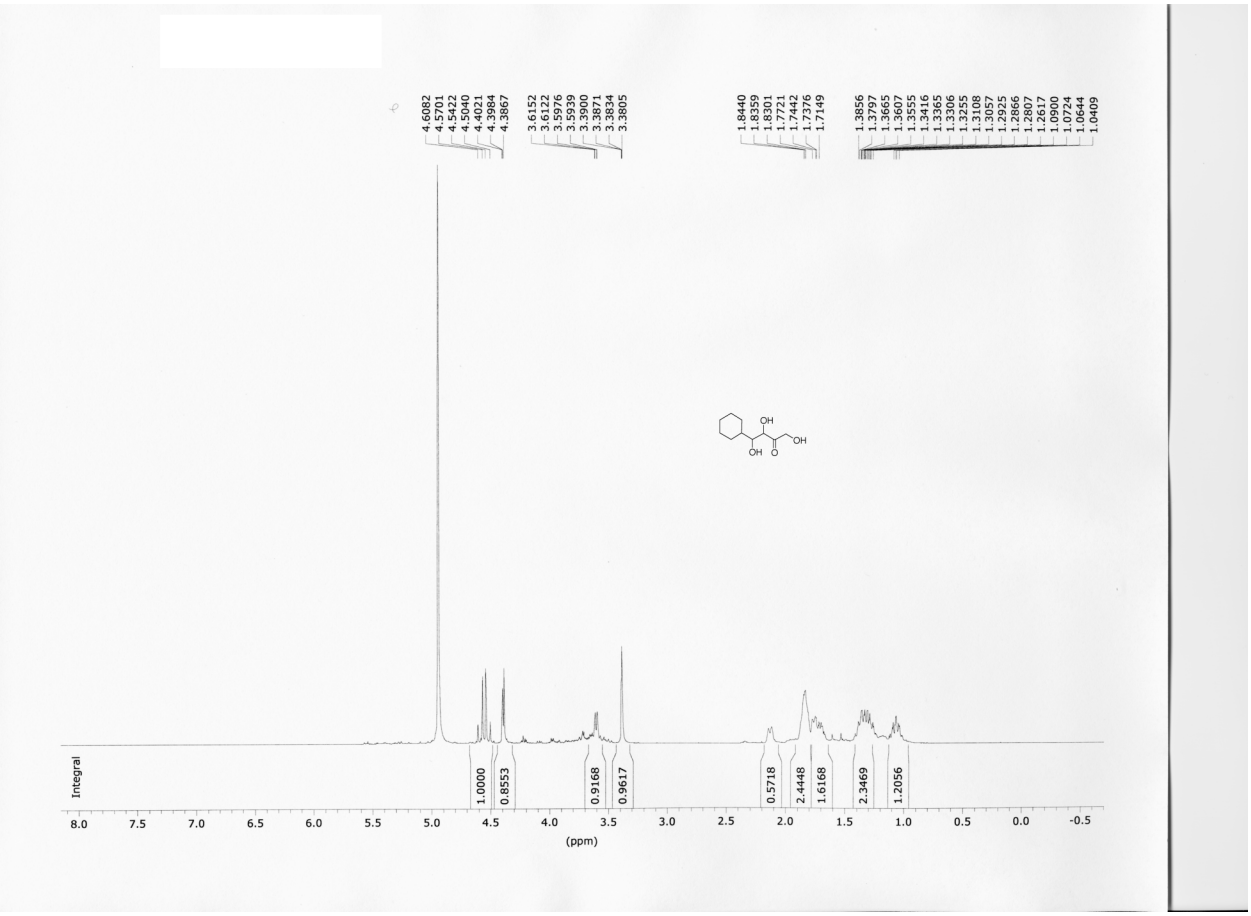
^{1}H NMR (500 MHz, CD_3OD) of **18**.



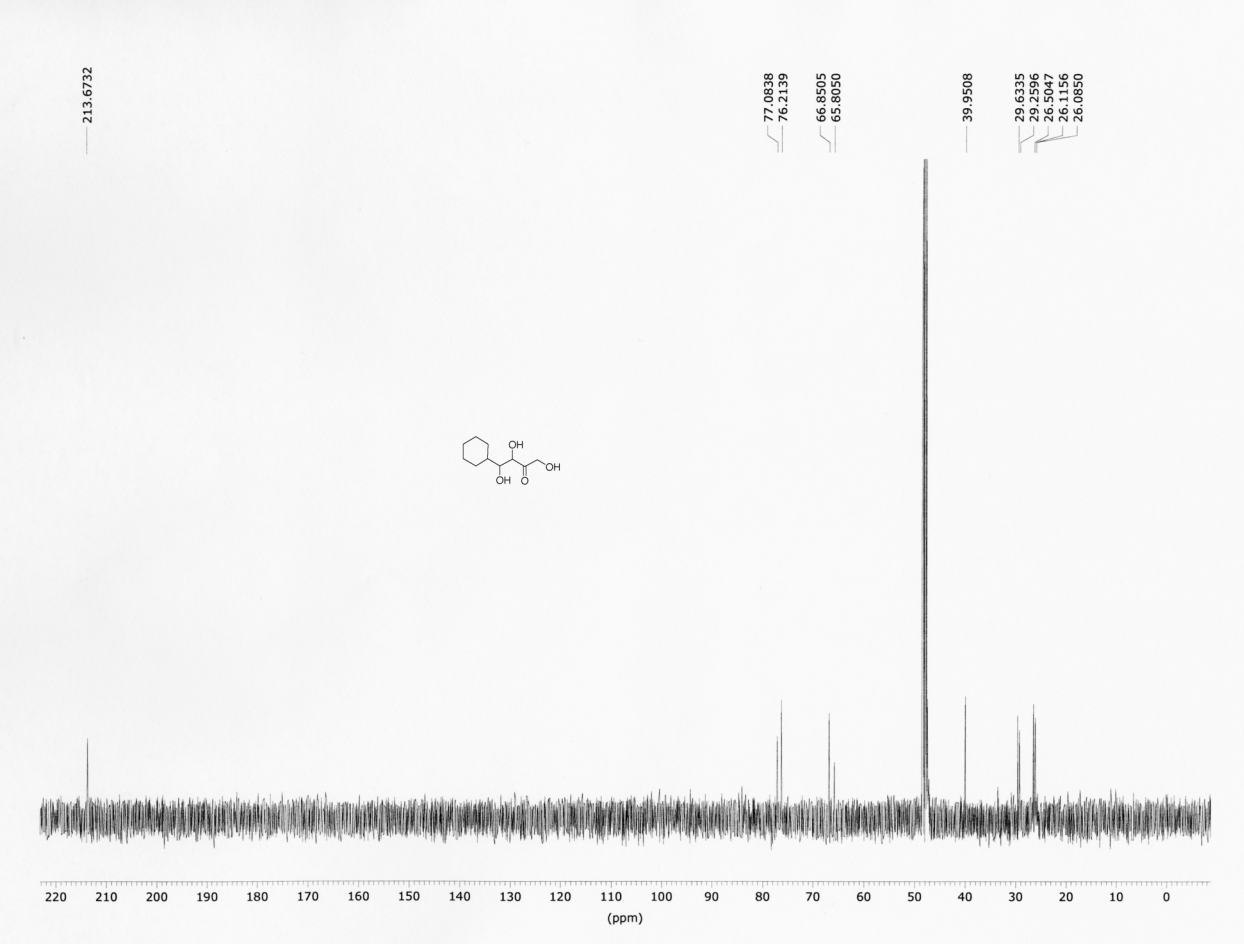
^{13}C NMR (500 MHz, CD_3OD) of **18**.



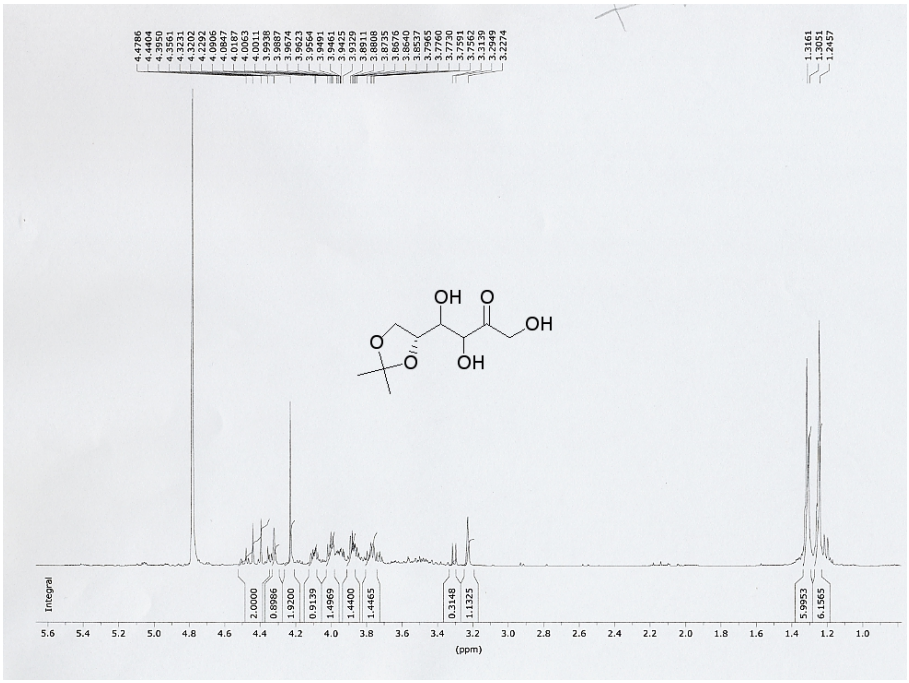
^{1}H NMR (500 MHz, CD_3OD) of **19**.



^{13}C NMR (500 MHz, CD_3OD) of **19**.



^{1}H NMR (500 MHz, CD_3OD) of **20**.



^{13}C NMR (125 MHz, CD_3OD) of **20**.