Green and Practical Direct Asymmetric Aldol Reaction of Hydroxyacetone and Aromatic Aldehydes Catalyzed by 9-Amino Cinchona Alkaloids Tartrates.

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Supplementary information

General information:

Acetol (technical grade, Aldrich, containing 1.79% of water by Karl-Fischer titration), aromatic aldehydes, quinine, quinidine, cinchonine and cinchonidine, (*R*,*R*)-, (*S*,*S*)- and *meso*-tartaric acids, benzoic, trifluoroacetic, succinic acids, 2,4-dinitrophenol and all other reagents and solvents were purchased from commercial suppliers and were used without further purification. Dihydrocinchonine was obtained form Aldrich and 10,11-didehydroquinine was synthesized according to previously published work [1]. Dichloromethane was distilled from calcium hydride, tetrahydrofuran over potassium/benzophenone other solvents were used as received. Flash chromatography was performed on silica gel 60 (Fluka, 70-230 mesh). HPLC analyses were performed on Hitachi-Merck Elite LaChrom chromatograph equipped with CHIRALPAK IA column (250 x 4 mm ID). Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL300 (300 MHz) spectrometer, chemical shifts are reported in parts per million relative to tetramethylsilane. IR spectra (KBr pellets) were recorded on a Brucker ITS 113v spectrometer.

Preparation of 9-amino-9-epi-*Cinchona* alkaloids [2].

9-amino-9-(deoxy)epiquinine (**1a**), 9-amino-9-(deoxy)-10,11-didehydroepiquinine (**1b**), 9-amino-9-(deoxy)epicinchonidine (**2**), 9-amino-9-(deoxy)epiquinidinine (**3**), 9-amino-9-(deoxy)epicinchonine (**4a**) and 9-amino-9-(deoxy)-10,11-dihydroepicinchonine (**4b**) and were synthesized as trihydrochlorides salts from corresponding alkaloids by Mitsunobu/Staudinger one-pot protocol according to Brunner et al. [2]. Free amines were liberated from their salts by treatment aqueous solution with excess of saturated Na_2CO_3 aq (pH 12) and extraction with dichloromethane (3 x 15 mL). After drying, filtration and evaporation of the combined organic phases the desired amines were obtained as opalescent white-off oils, with average yields 60-70%.

9-Amino-9-epi-Cinchona ditartrates

To the stirred solution of 9-amino-9-(deoxy)epicinchonine (193 mg, 1 eq.) or 9-amino-9-(deoxy)epiquinine (213 mg, 1 eq.) in 5 mL of methanol (*R*,*R*)-tartaric acid monohydrate (200 mg, 2 eq.) dissolved in 10 mL of methanol was added. The mixture was magnetically stirred for 5 minutes followed by evaporation of solvent. The respective ditartrates have been obtained as white solids with quantitative yield and dried on air before use.

9-amino-9-(deoxy)epiquinine ditartrate (1a): ^{1}H NMR (400 MHz, MeOD) δ 8.74 (d, *J* = 5.8 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.70 (m, 2H), 7.55 (dd, J = 8.7, 5.8 Hz, 1H), 5.93 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.24 (dd, *J* = 17.2, 10.4 Hz, 2H), 5.24 (d, *J* = 10.9 Hz, 1H), 4.47 (s, 4H), 4.10 – 3.85 (m, 6H), 3.69 (dd, *J* = 13.2, 10.6 Hz, 1H), 2.79 (m, 1H), 2.08 – 1.93 (m, 3H), 1.80 (t, *J* = 12.0 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 0.5 H from remaining 10,11-dihydroquinine), 1.10 (dd, *J* = 13.7, 6.6 Hz, 1H); IR (KBr) ν cm^{-1} 3406, 2980, 1730, 1623, 1597, 1513, 1480, 1360, 1268, 1240, 1123, 1077, 1028, 992, 859, 833, 780, 751, 714;

9-amino-9-(deoxy)epicinchonine ditartrate (4a):

^{1}H NMR (400 MHz, MeOD) δ 8.94 (d, *J* = 4.1 Hz, 1H), 8.42 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.88 – 7.75 (m, 3H), 5.92 (ddd, *J* = 17.0, 10.6, 6.1 Hz, 1H), 5.31 – 5.22 (m, 3H), 4.50 (s, 4H), 4.11 (m, 1H), 3.59 – 3.37 (m, 4H), 2.74 (d, *J* = 6.4 Hz, 1H), 2.08 – 1.88 (m, 4H), 1.41 – 1.21 (m, 3H), 0.94 (t, *J* = 7.3 Hz, 0.3H from remaining 10,11-dihydrocinchonine), IR (KBr) ν cm^{-1} 3409, 2983, 1730, 1598, 1517, 1468, 1374, 1259, 1126, 1078, 766;

Crystallization of *syn*-(3*S*,4*R*)-3,4-dihydroxy-4-(4-nitrophenyl)butan-2-one (*syn*-6a)

1.60 g of crude aldol product *syn*-**6a** (**4a** as catalysts) was dissolved on heating in 20 mL mixture of He/AcOEt (2:1) to give almost homogeneous solution. This was cooling to rt and then placing in fridge for 3-7 days. After this time large white-off crystals of product were separated by filtration and washed with cold mixture of He/AcOEt (3:1) and small portion of hexane. Yield 550 mg, e.e. (*syn*) 99%, (*anti*) traces 74% ee, dr 1:42.

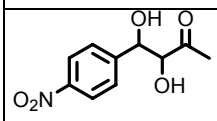
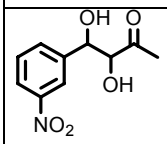
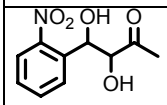
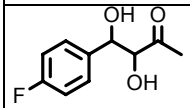
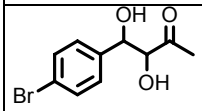
^{1}H NMR ($CDCl_3$) 8.26 (d, J = Hz, 2H), 7.62 (d, J = Hz, 2H), 5.23 (dd, q J = Hz, 1H), 4.42 (dd, J = Hz, 1H), 3.74 (dd, J = Hz, 1H), 2.75 (d, J = Hz, 1H), 2.37 (s, 3H); IR (KBr) ν cm^{-1} 3385, 1705, 1607, 1599, 1347, 1099, 1057, 872, 856, 812,731;

Crystallization of *syn*-(3*R*,4*S*)-3,4-dihydroxy-4-(4-nitrophenyl)butan-2-one (*syn*-6a, opposite enantiomer)

730 mg of crude aldol product obtained with the use of catalyst **1a** was dissolved in 5 mL AcOEt (heating) and diluted with 20 mL of mixture He/AcOEt (2:1) to give almost homogeneous solution. This was cooling to rt and then placing in fridge for 24-48 hours. After this time large white-off crystals of product were separated by filtration and washed with cold mixture of He/AcOEt (3:1) and small portion of hexane. Yield 460 mg, e.e. (*syn*) 99%, (*anti,* traces) 10% ee, dr 1:50.

Enantioseparation of aldol products 6a-e.

All retention times has been compared with reference racemates which has been obtained using literature procedure [3]. Column: CHIRALPAK IA (250 x 4 mm ID)

product	Method[a]	Retention times (min)	
		syn-aldol	*anti*-aldol
	80:20 He/IPA, 0.75 mL/min	t_1 =17.4 t_2 =24.8	t_1 =13.2 t_2 =14.2
	80:20 He/EtOH, 0.75 mL/min	t_1 =25.7 t_2 =29.3	t_1 =16.3 t_2 =22.0
	80:20 He/EtOH, 0.75 mL/min	t_1 =23.0 t_2 =24.2	t_1 =15.9 t_2 =18.8
	90:10 He/IPA, 0.75 mL/min	t_1 =19.8 t_2 =23.5	t_1 =15.8 t_2 =17.4
	80:20 He/IPA, 0.75 mL/min	t_1 =9.5 t_2 =10.3	t_1 =11.9 t_2 =14.9

[a] IPA = isopropanol

Crystal data of (*syn*-6a): crystallized from mixture (1:1) of ethyl acetate and *n*-hexane with the formula $C_{10}H_{11}NO_5$, M_r=225.20, T=130.0(1)K. Crystal system: orthorhombic. Space

group: $P2_12_12_1$ (no.19). Unit cell dimensions: a=4.6835(4), b=9.2616(8), c=23.4038(16) Å, V=1015.19(15) Å^3, Z=4, ρ_{cal}=1.473 Mg/cm^3, ω-scan, F(000)=472, μ=1.024 mm^{-1}.

Data was collected with SuperNova diffractometer, equipped with a Cu Kα source (λ=1.5418 Å) and 135mm Atlas CCD detector. Theta range for data collection was 3.78 to 76.63° and the *hkl* ranges were -5/5, -11/11, -29/29, respectively. Of the 7733 reflection collected, 2060 were unique (R_{int}=0.013) and 2053 were considered as observed with $I>2\sigma(I)$. The intensity data were corrected for absorption and Lp effects. Final *R1*=0.026 for 2053 observed reflection [$I>2\sigma(I)$], 178 parameters, *wR2*=0.069 for all data, *GoF*= 1.083, $\Delta\rho_{min/max}$= –0.13/0.21 eÅ^{-3}.

Data reduction and analysis for this structure was carried out with CrysAlisPro program *v*.171.33.34d. [4] The structure was solved by direct methods using SHELXS97 [5] and refined by the full matrix least-squares techniques with SHELXL97. All non-hydrogen atoms were refined with anisotropic displacement parameters. The position of H atoms were located from the difference-Fourier maps and their positions and isotropic displacement parameters were refined, except methyl H atoms which were idealized but free to rotate (*AFIX* 137). U_{iso} values for methyl H atoms were $1.2U_{eq}$ for the methyl C atom. The correct absolute configuration for the molecules in the crystal was determined as 3*S* and 4*R* by means of the Hooft *y* parameter of 0.059 (23)[6]. The thermal ellipsoid diagram was generated with ORTEP3 [7].

Atomic coordinates, bond lengths, bond angles and displacement parameters have been deposited at the Cambridge Crystallographic data Center (CCDC) and allocated the deposition number CCDC 783759.

References:

[1] K.M. Kacprzak, W. Linder, N.M. Maier, *Chirality*, **2008**, *20*, 441-445.

[2] H. Brunner, J. Bügler, B. Nuber, *Tetrahedron:Asymmetry*, **1995**, *6*, 1699.

[3] M. Markert, M. Mulzer, B. Schetter, R. Mahrwald, *J. Am. Chem. Soc.*, 2007, 129, 7258–7259.

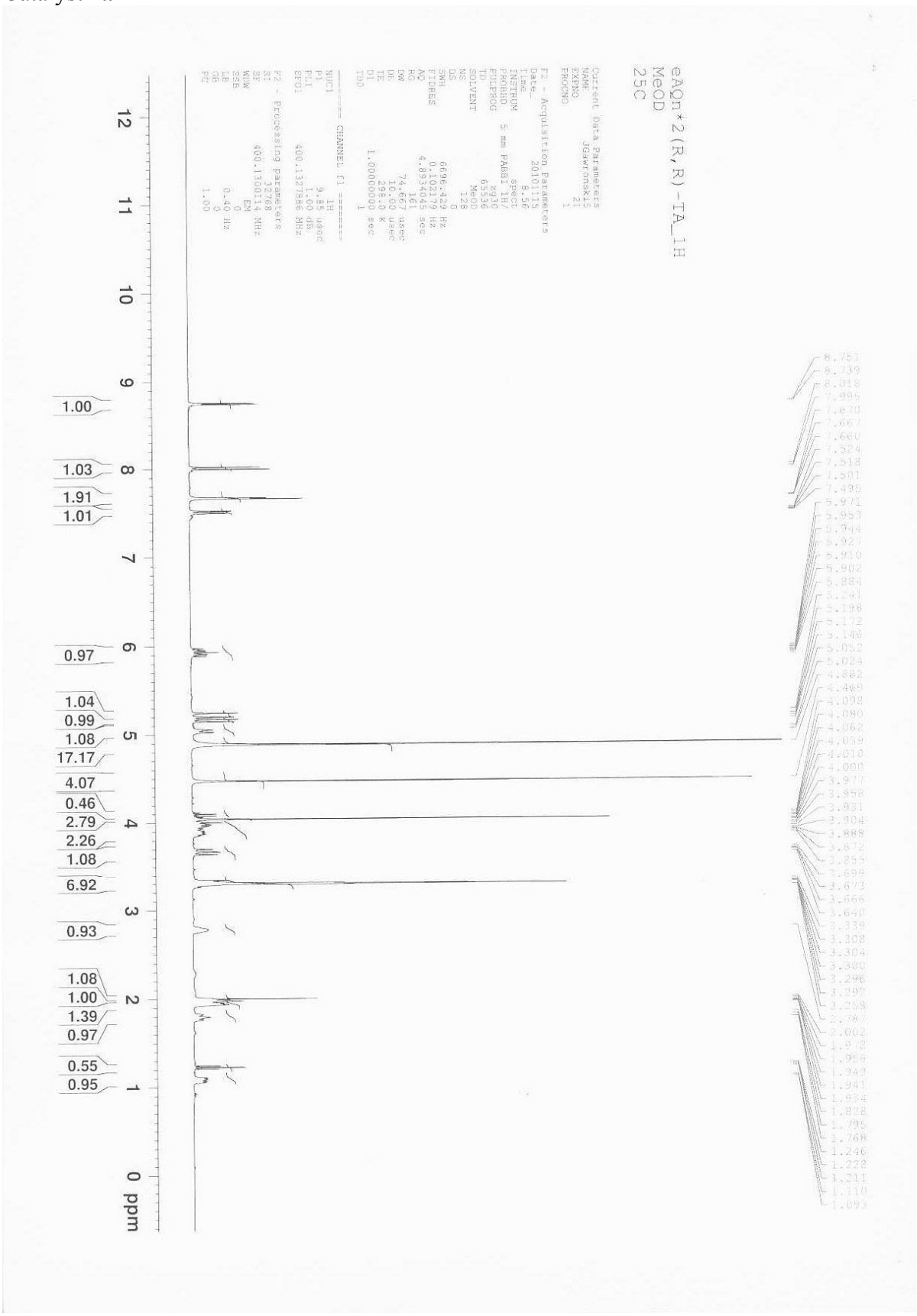
[4] Oxford Diffraction. **2009** CrysAlisPro. Version 1.171.33.34d. Oxford Diffraction Ltd, Yarnton, England.

[5] G. M. Sheldrick, *Acta Cryst A*. **2008**, *64*, 112-122.

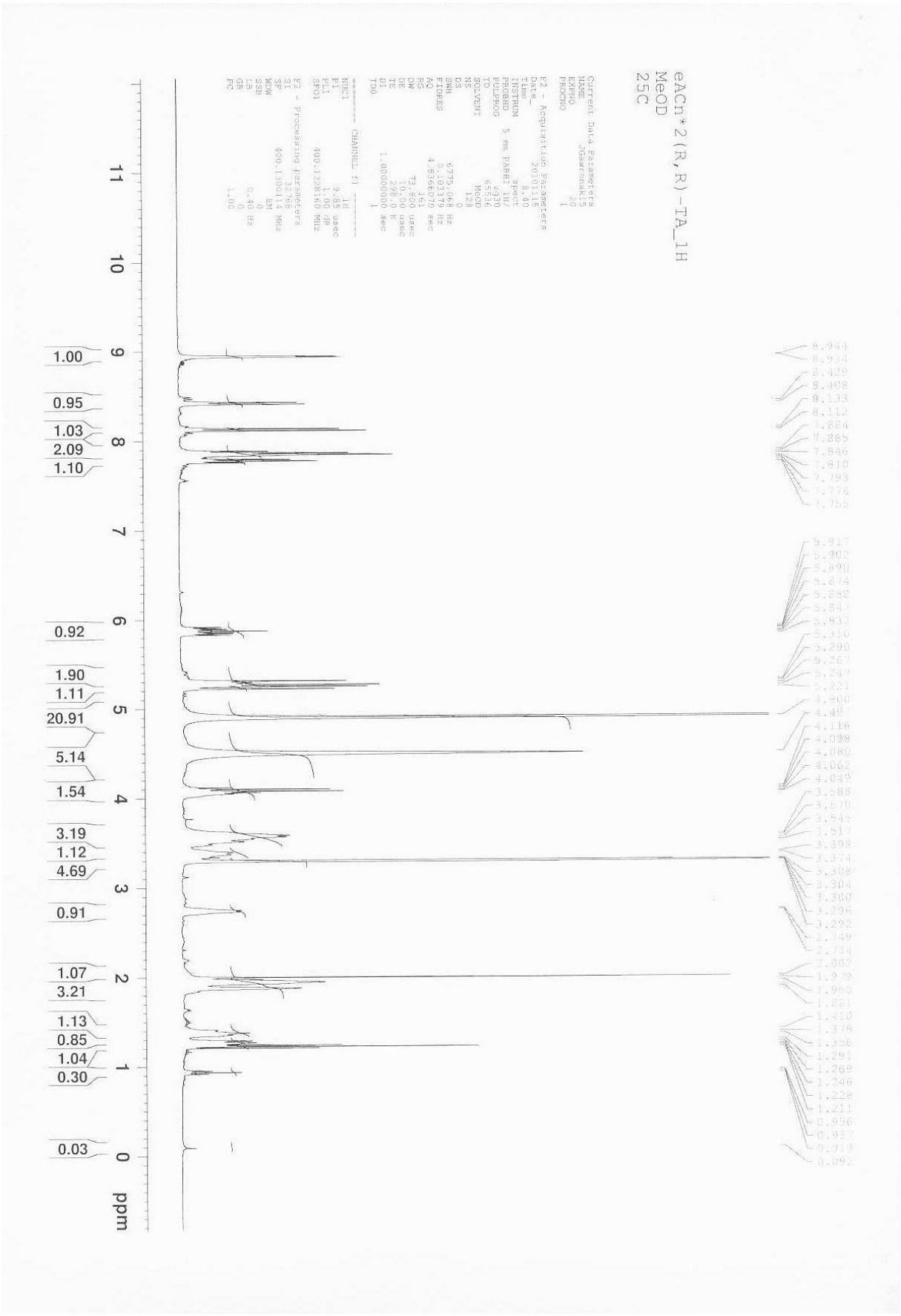
[6] R. W. W. Hooft; L. H. Straver, A. L. Spek, *J. Appl. Cryst.* **2008**, *41*, 96–103.

[7] ORTEP3 for Windows. Farrugia, L. J. *J. Appl. Cryst*. **1997**, *30*, 565.

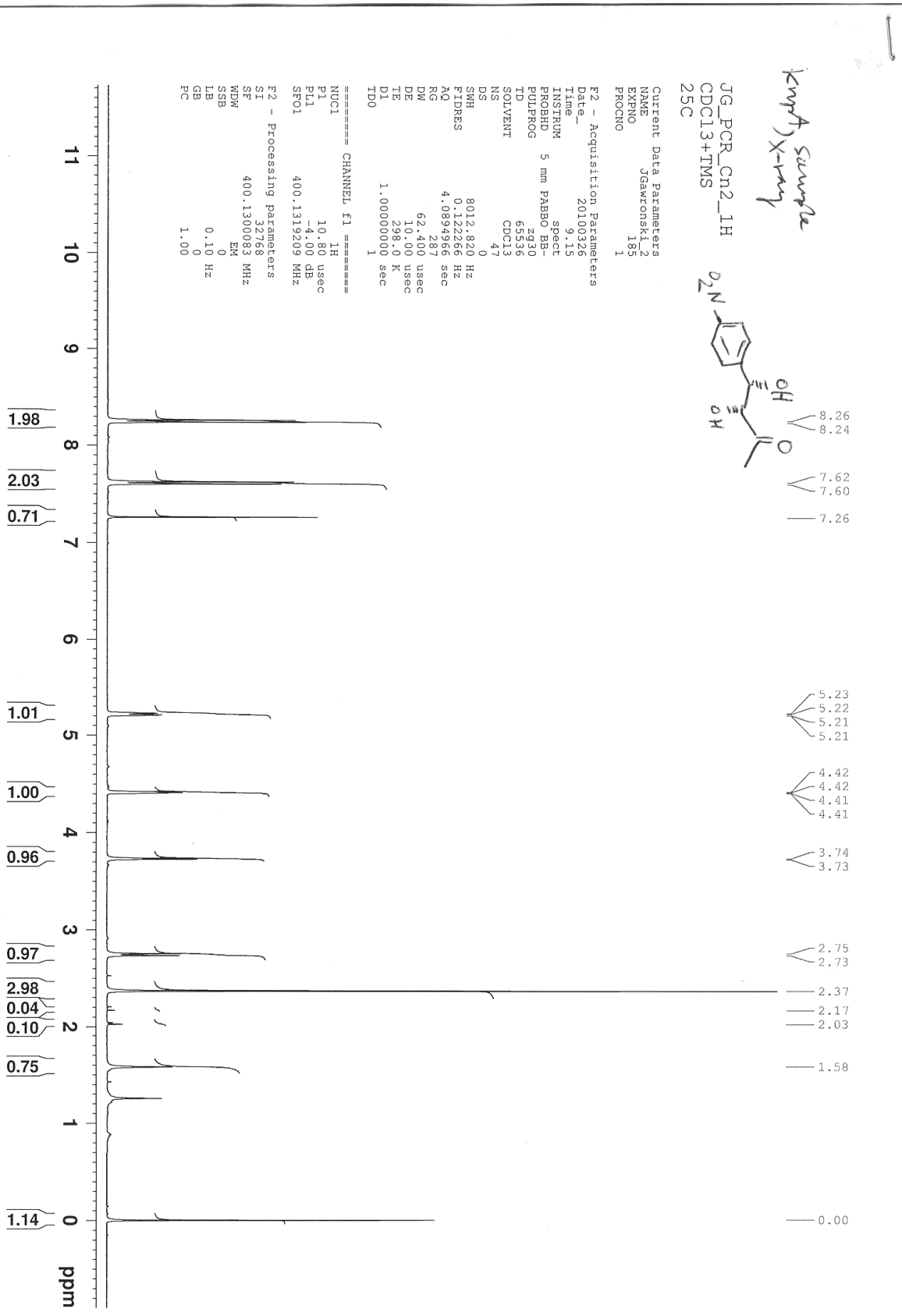
Catalyst **1a**



Catalyst **4a**


eACn*2(R,R)-TA_1H
MeOD
25C
1.00
0.95
1.03
2.09
1.10
0.92
1.90
1.11
20.91
5.14
1.54
3.19
1.12
4.69
0.91
1.07
3.21
1.13
0.85
1.04
0.30
0.03
ppm

Aldol *syn*-6a (cat. 4a) after crystallization



Chromatogram of crystallized ***syn*-6b**

Area % Report

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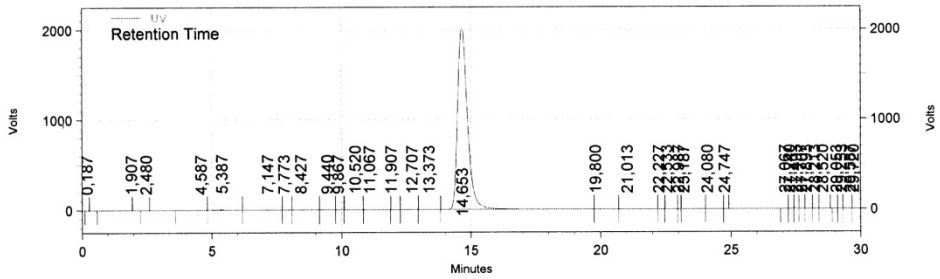

UV Results

Retention Time	Area	Area %	Height	Height %
0,187	169	0,00	33	0,00
1,907	2194	0,00	34	0,00
2,480	1344	0,00	89	0,00
4,587	82418	0,04	2161	0,03
5,387	632709	0,29	24924	0,31
7,147	287435	0,13	10004	0,12
7,773	18964	0,01	912	0,01
8,427	152397	0,07	5744	0,07
9,440	38533	0,02	1315	0,02
9,867	14392	0,01	826	0,01
10,520	125822	0,06	4993	0,06
11,067	57251	0,03	1847	0,02
11,907	4924	0,00	252	0,00
12,707	15305	0,01	482	0,01
13,373	53106	0,02	1878	0,02
14,653	214503073	99,22	7999433	99,24
19,800	71860	0,03	1499	0,02
21,013	81079	0,04	1231	0,02
22,227	8400	0,00	551	0,01
22,533	12832	0,01	500	0,01
22,987	2918	0,00	381	0,00
23,187	13460	0,01	357	0,00
24,080	3509	0,00	150	0,00
24,747	226	0,00	45	0,00
27,067	1509	0,00	108	0,00
27,240	1035	0,00	99	0,00
27,493	768	0,00	87	0,00
27,707	587	0,00	67	0,00
27,893	508	0,00	45	0,00
28,213	263	0,00	30	0,00
28,520	553	0,00	48	0,00
29,053	353	0,00	56	0,00
29,253	483	0,00	59	0,00

Chromatogram of crystallized ***syn*-6c**

Area % Report

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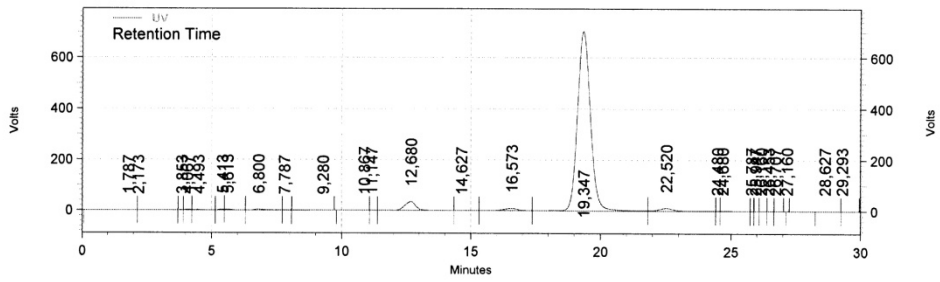

UV Results

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3,853	58863	0,06	6255	0,20
4,067	133828	0,13	7289	0,24
4,493	187147	0,18	7223	0,23
5,413	180561	0,17	13109	0,42
5,613	252974	0,24	13793	0,44
6,800	404340	0,38	16828	0,54
7,787	16588	0,02	903	0,03
9,280	44893	0,04	925	0,03
10,867	22240	0,02	440	0,01
11,147	7582	0,01	453	0,01
12,680	4059141	3,83	134786	4,35
14,627	56688	0,05	1314	0,04
16,573	1338867	1,26	35620	1,15
19,347	97178823	91,71	2812919	90,74
22,520	1653817	1,56	42595	1,37
24,480	6545	0,01	644	0,02
24,680	24586	0,02	627	0,02
25,787	852	0,00	126	0,00
25,947	1034	0,00	100	0,00
26,160	1061	0,00	84	0,00
26,453	376	0,00	38	0,00
26,707	466	0,00	32	0,00
27,160	64	0,00	16	0,00
28,627	4832	0,00	112	0,00
29,293	2924	0,00	131	0,00
Totals	105961719	100,00	3099935	100,00