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Regioselective reduction of keto groups in Michael adducts of levoglucosenone and cyclohexanone

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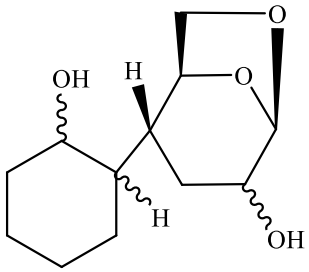
The spectral and analytical data were obtained using the equipment of the *Khimiya* Joint Center at the Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance III, (500.13 MHz for ^{1}H and 125.47 MHz for ^{13}C). IR spectra were recorded on spectrophotometers Shimadzu IRPrestige-21 or Bruker Tensor 27 (from films or mulls in mineral oil). Mass spectra were measured on a GC-MS instrument Hewlett Packard, chromatograph HP 6890 with a mass-selective detector HP 5973. Optical rotation was determined on a polarimeter Perkin Elmer-341. Analytic TLC was carried out on Sorbfil plates of the grade PTSKh-AF-A (”Sorbpolymer” Co., Krasnodar). The melting points were measured on a Boëtius 05 heating block.

(1*S*,2*R*,5*R*)-2-(2-Hydroxycyclohexyl)-6,8-dioxabicyclo[3.2.1]octan-4-ol (diastereomers 2a-h).



Method i). To a solution of diketones **1a,b** (0.30 g, 1.34 mol) of in EtOH (7.0 ml) $NaBH_4$ (0.05 g, 1.34 mol) was added in portions, and this was stirred until the starting material disappeared (TLC monitoring). Then acetone (3.0 ml) was added, the solvent was distilled off, the residue was chromatographed on a silica gel column. Yield 0.28 g (94%).

Method ii) To a solution of diketones **1a,b** (0.30 g, 1.34 mmol) of in THF (4.0 ml) at 0 °C under argon RedAl (toluene solution, 0.78 ml, 4.02 mmol) was added. The mixture was stirred at 0 °C for 2 h. Then it was treated with a 6% HCl solution until the precipitate completely disappeared, the reaction products were extracted with EtOAc (3 × 7.0 ml), the organic layers were combined and dried over $MgSO_4$. The solvent was distilled off on a rotary evaporator, the residue was chromatographed on SiO_2. Yield 0.27 g (88%). Oily substance. R_f 0.10 (light petroleum–EtOAc, 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89-2.12 (m, 12H, C$^{3'}$H$_2$, C$^{4'}$H$_2$, C$^{5'}$H$_2$, C$^{6'}$H$_2$, C$^{2'}$H, C^{2}H, C^{3}H$_2$), 3.06 (br s, 1H, OH), 3.26 [3.32, 3.41, 3.57] (dt, 1H, J = 9.8, 9.8, 4.3 Hz, C$^{1'}$H) {4.02, (4.12, 4.22, 4.24) (brs, 1H, C$^{1'}$H)}, 3.43-3.63 (m, 1H, C^{4}H), 4.54 [4.42, 4.44, 4.46, 4.47, 4.62, 4.65, 4.70] (d, 1H, C^{1}H, J = 4.5 Hz), 5.18-5.24 (s,1H, H^{5}).

^{13}C NMR (500 MHz, $CDCl_3$): δ 24.66 [19.47, 19.67, 19.76, 19.68, 24.43, 24.60, 24.63] ($C^{5'}$), 25.58 [25.57, 25.67, 25.77, 25.83, 25.93, 26.04, 26.81] ($C^{4'}$), 26.41 [26.67, 27.73, 28.21, 23.01, 23.65, 23.81, 24.11] (C^{3}), 28.49 [29.82, 30.80, 31.09, 24.86, 29.90, 24.97, 25.34] ($C^{6'}$), 36.20 [36.08, 35.69, 35.37, 33.86, 33.78, 33.63, 33.62] ($C^{3'}$), 38.74 [38.75, 40.30, 40.36, 41.26, 41.64, 41.77, 42.46] ($C^{2'}$), 47.53 [48.22, 48.35, 46.12, 38.21, 38.58, 39.72, 41.36] (C^{2}), 67.42 [66.46, 66.75, 66.91, 66.98, 67.02, 67.25, 67.40] (C^{4}), 69.24 [67.95, 68.03, 68.17, 68.66, 68.76, 69.04, 69.42] (C^{7}), 72.42 [71.57, 71.69, 72.86, 66.01, 66.12, 66.16, 66.89] ($C^{1'}$), 78.11 [73.26, 73.42, 73.79, 74.10, 74.89, 75.19, 75.47] (C^{1}), 102.37-103.04 (C^{5}).

Mass spectrum, *m/z*: 229 $[M\text{H}]^+$. Calcd for $C_{12}H_{20}O_4$. 228.28.

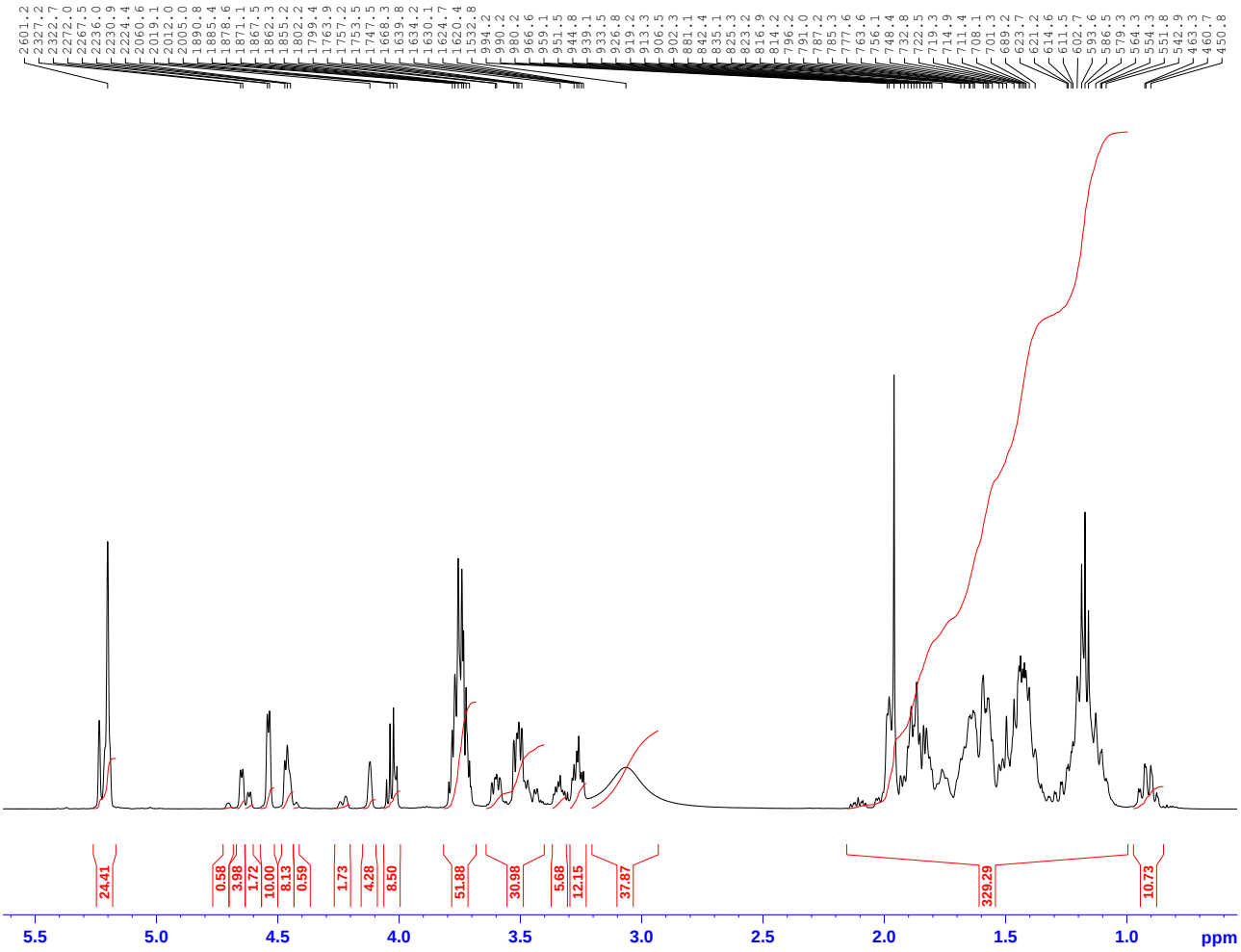


Figure S1.1. Complete ^1H NMR (500 MHz) spectrum in $CDCl_3$.

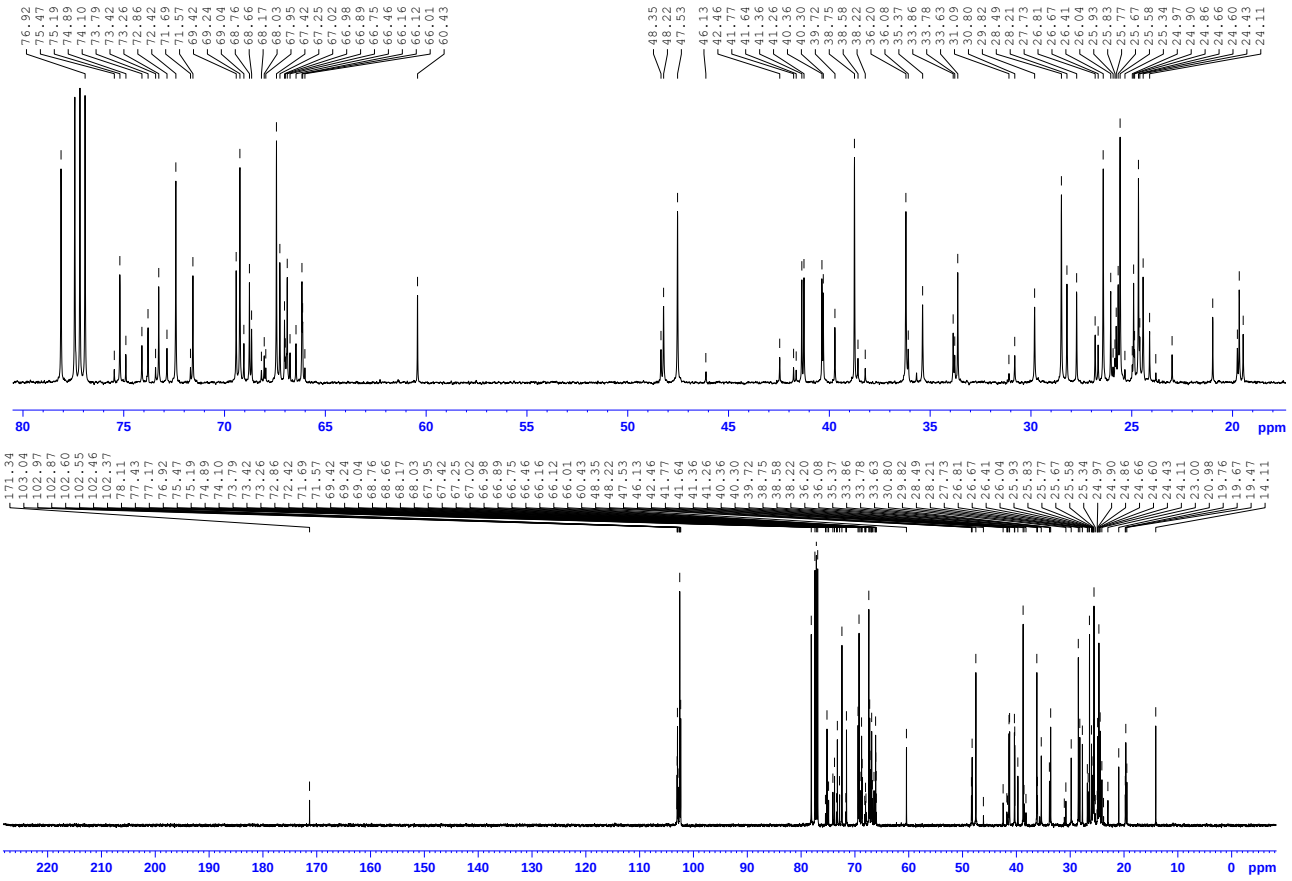


Figure S1.2. Complete $^{13}C\{^{1}H\}$ NMR spectrum in $CDCl_3$.

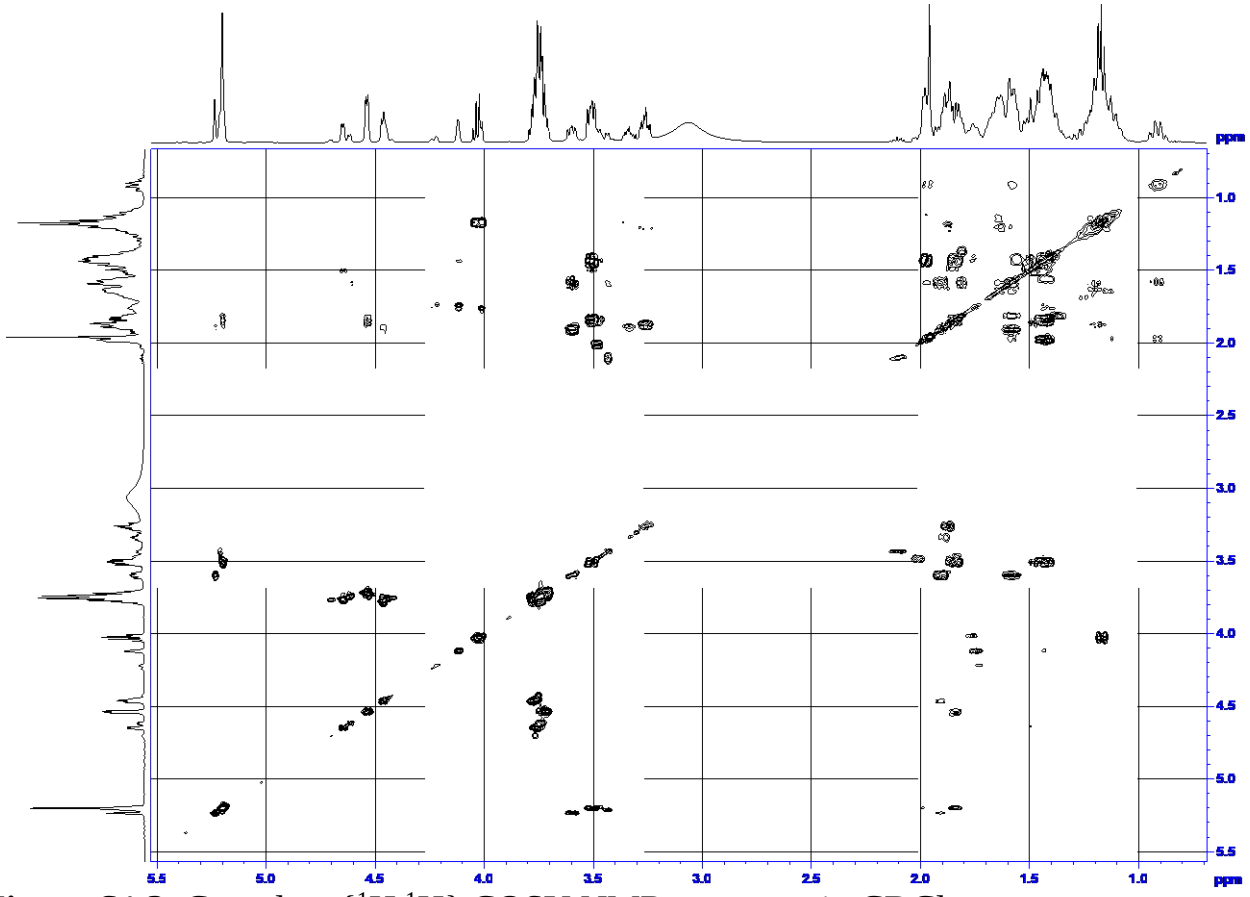


Figure S1.3. Complete $\{^{1}H,^{1}H\}$ COSY NMR spectrum in $CDCl_3$

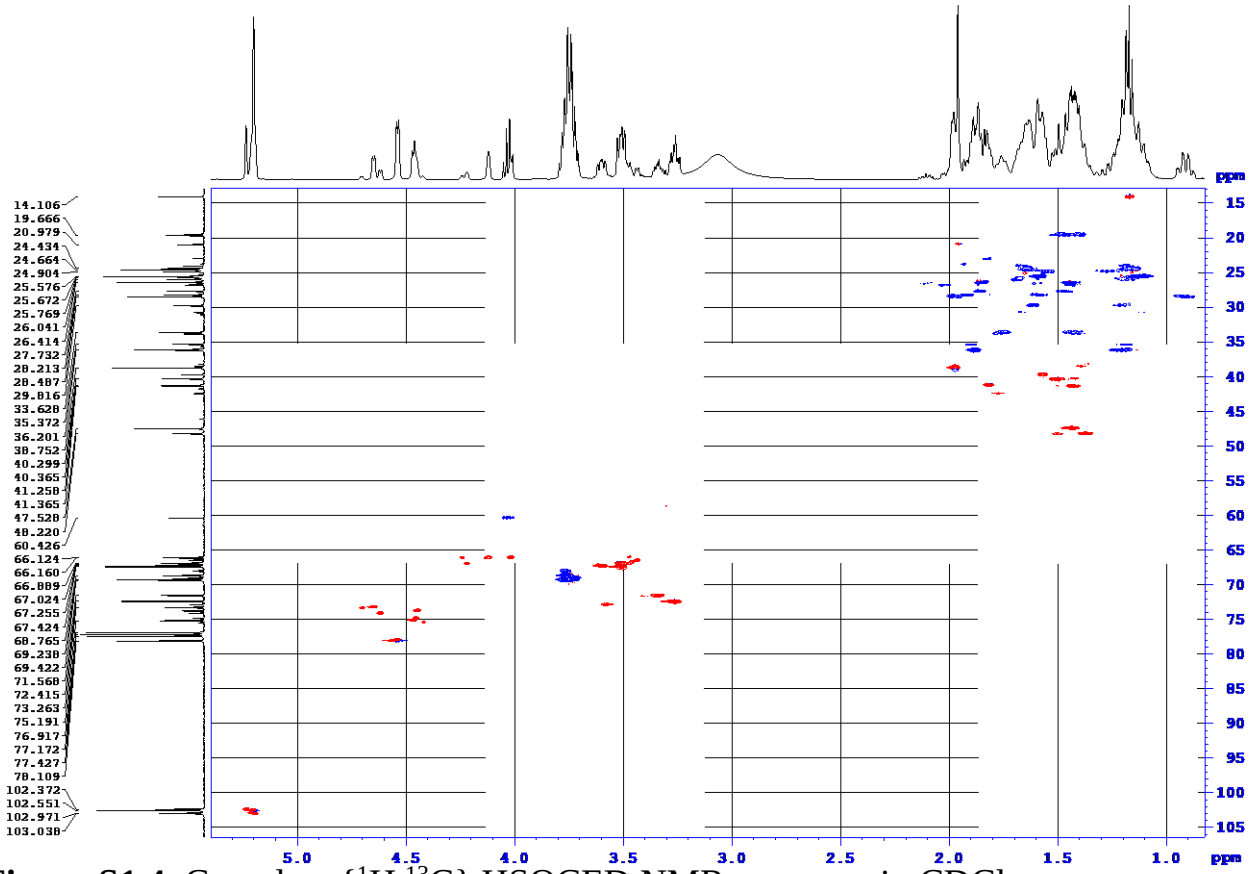


Figure S1.4. Complete {^{1}H,^{13}C} HSQCED NMR spectrum in $CDCl_3$.

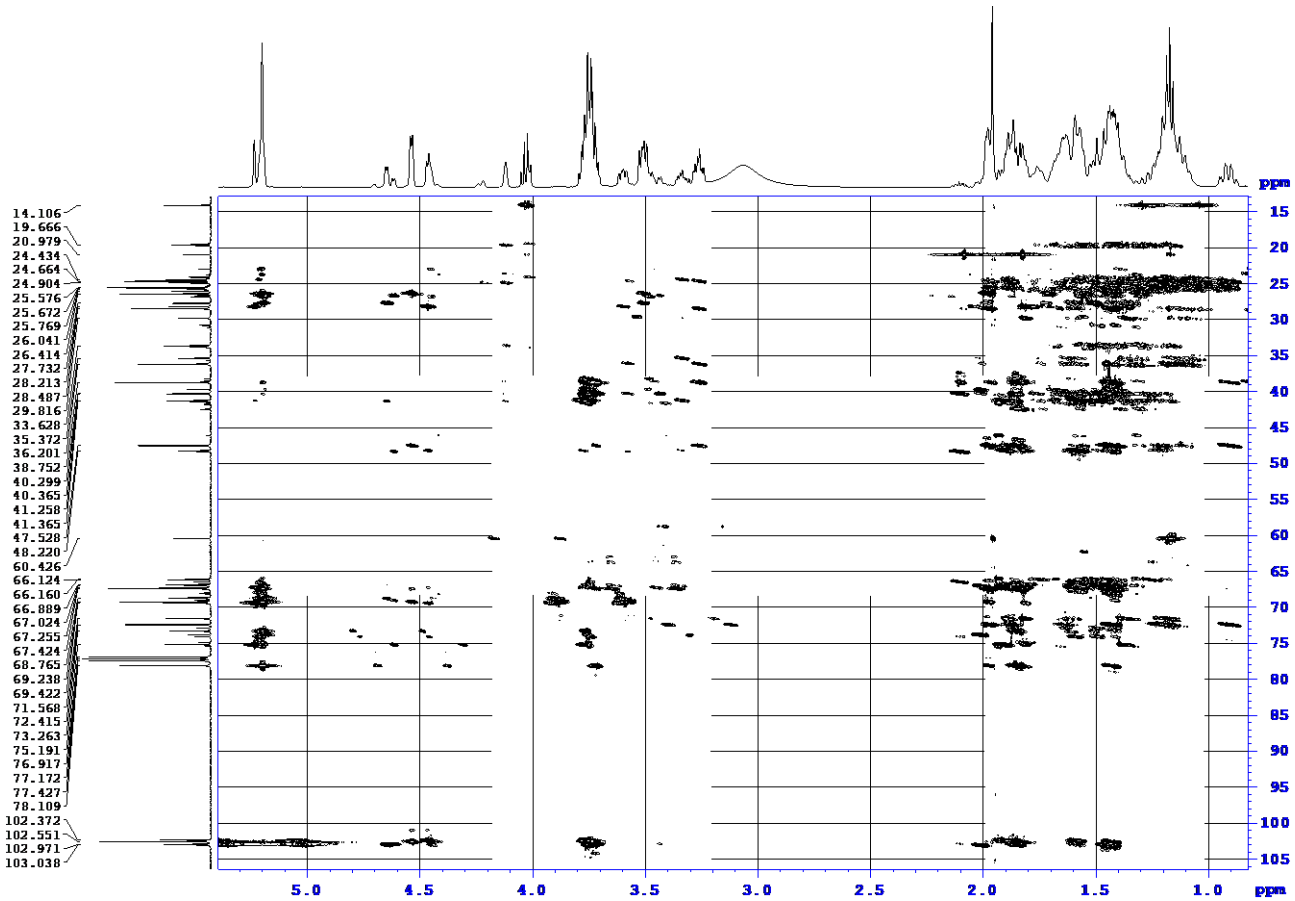


Figure S1.5. Complete {^{1}H,^{13}C} HMBC NMR spectrum in $CDCl_3$.

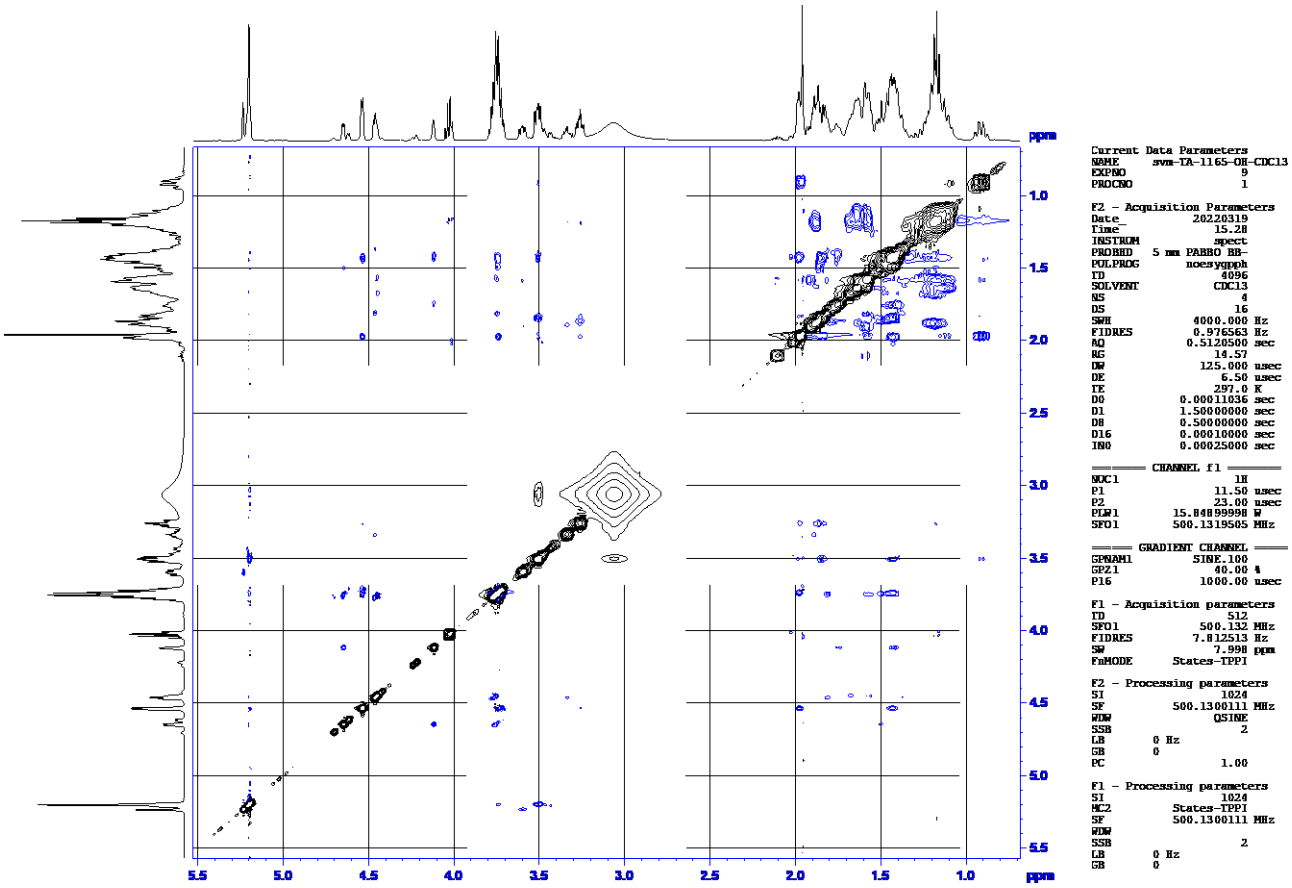
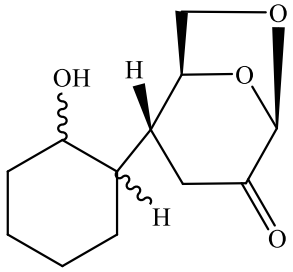


Figure S1.6. Complete {^{1}H,^{1}H} NOESY NMR spectrum in $CDCl_3$

(1*S*,2*R*,5*R*)-2-(2-Hydroxycyclohexyl)-6,8-dioxabicyclo[3.2.1]octan-4-one (diastereomers 3a-d).



A solution of diketones **1a,b** (1.0 g, 0.0045 mol) of in anhydrous THF (5.0 ml) was added to a solution of lithium metal (0.2 g, 0.027 mol) in liquid ammonia (15.0 ml, pre-distilled over Na), the mixture was stirred at –33°C for 0.5 min, then ammonia was distilled off in flow of argon. The reaction products were extracted with EtOAc (3 × 20.0 ml), the organic layers were combined, and dried over $MgSO_4$. The solvent was distilled off on a rotary evaporator, the residue was chromatographed on SiO_2. Yield 0.99 g (92%). Oily substance. R_f 0.32 (petroleum ether – EtOAc, 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01-1.47 (m, 4H, $C^{3'B}H_2C^{4'B}H_2C^{5'B}H_2C^{6'B}H_2$), 1.57 [1.40, 1.81, 1.55] (m, 1H, $C^{1'}H$), 1.66-2.03 (m, 4H, $C^{3'A}H_2C^{4'A}H_2C^{5'A}H_2C^{6'A}H_2$), 2.32 [2.21, 1.46, 1.27] (d, 1H, $C^{3B}H_2$, J = 16.8 Hz), 2.60 [2.63, 1.67, 1.83] (m, 1H, $C^{2}H$), 2.65 [2.83, 2.20, 1.96] (dd,

1H, $C^{3A}H_2$, J = 16.8, 9.4 Hz), 3.54 [3.38, 3.57, 4.64] (m, 1H, $C^{2'}H$), 3.96 [3.95, 3.74, 3.73] (dd, 1H, $C^{7A}H_2$, J = 7.1, 4.6 Hz), 4.00 [3.98, 3.85, 3.90] (d, 1H, $C^{7B}H_2$, J = 7.1 Hz), 4.68 [4.72, 4.21, 4.57] (d, 1H, $C^{1}H$, J = 4.6 Hz), 5.05 [5.04, 4.93, 5.14] (s, 1H, H^5).

^{13}C NMR (500 MHz, $CDCl_3$): δ 24.80 [24.67, 24.90, 25.02] ($C^{6'}$), 26.07 [25.46,24.92, 26.40] ($C^{5'}$), 27.09 [27.31, 26.18, 28.90] ($C^{4'}$), 33.08 [35.95, 34.97, 35.54] (C^{3}), 36.46 [36.56, 34.97, 35.54] ($C^{3'}$), 40.26 [40.21, 38.18, 38.87] (C^{2}), 49.53 [50.18, 43.88, 47.50] ($C^{1'}$), 69.11 [69.04, 66.21, 67.37] (C^{7}), 71.53 [71.35, 75.57, 80.03] ($C^{2'}$), 78.14 [74.03, 75.70, 74.28] (C^{1}), 101.08 [101.17, 102.86, 104.80] (C^{5}), 201.47 [201.51, 201.44, 201.25] (C^{4}).

Mass spectrum, *m/z*: 227 $[MH]^+$. Calcd for $C_{12}H_{18}O_4$. 226.26.

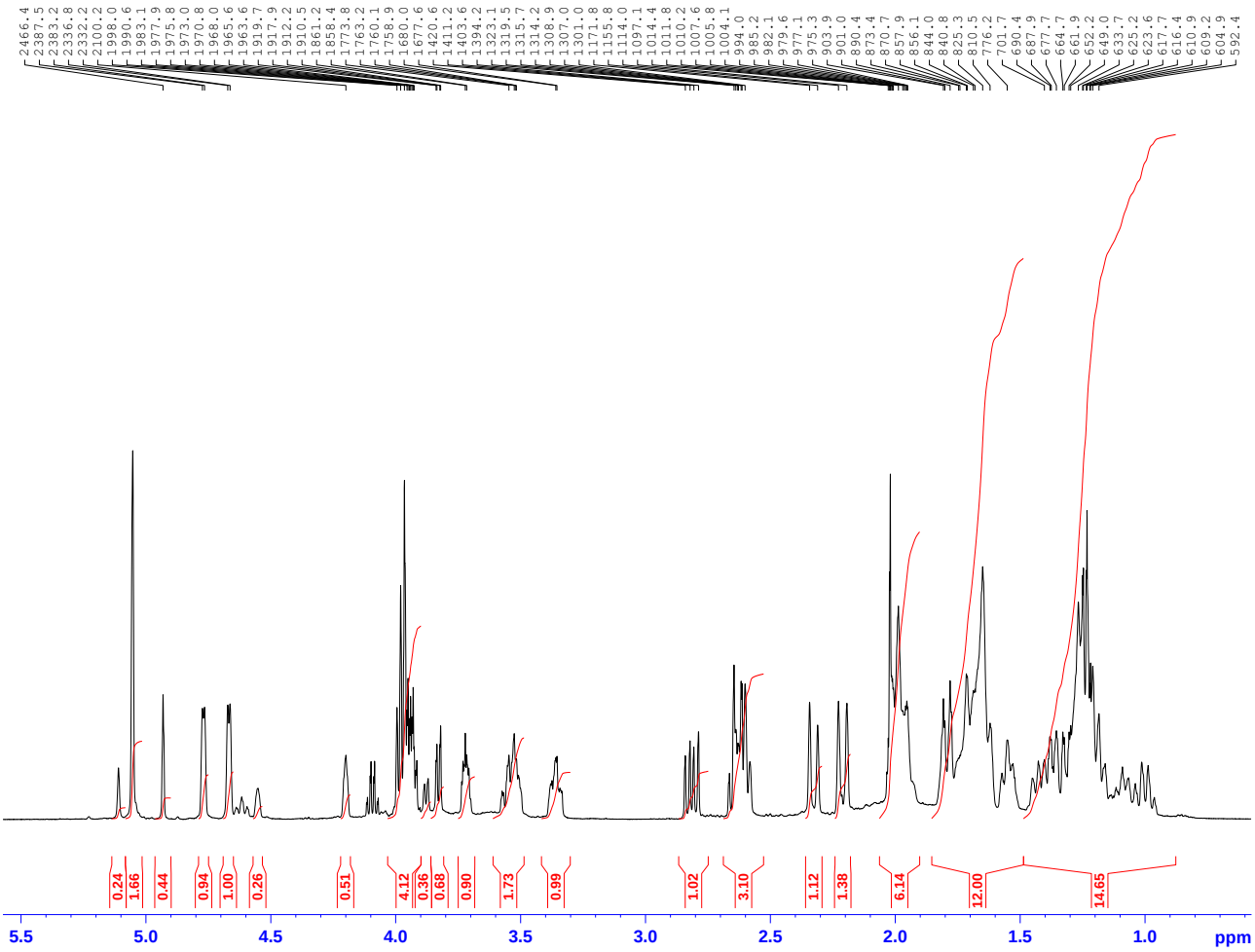


Figure S2.1. Complete ^1H NMR (500 MHz) spectrum in $CDCl_3$.

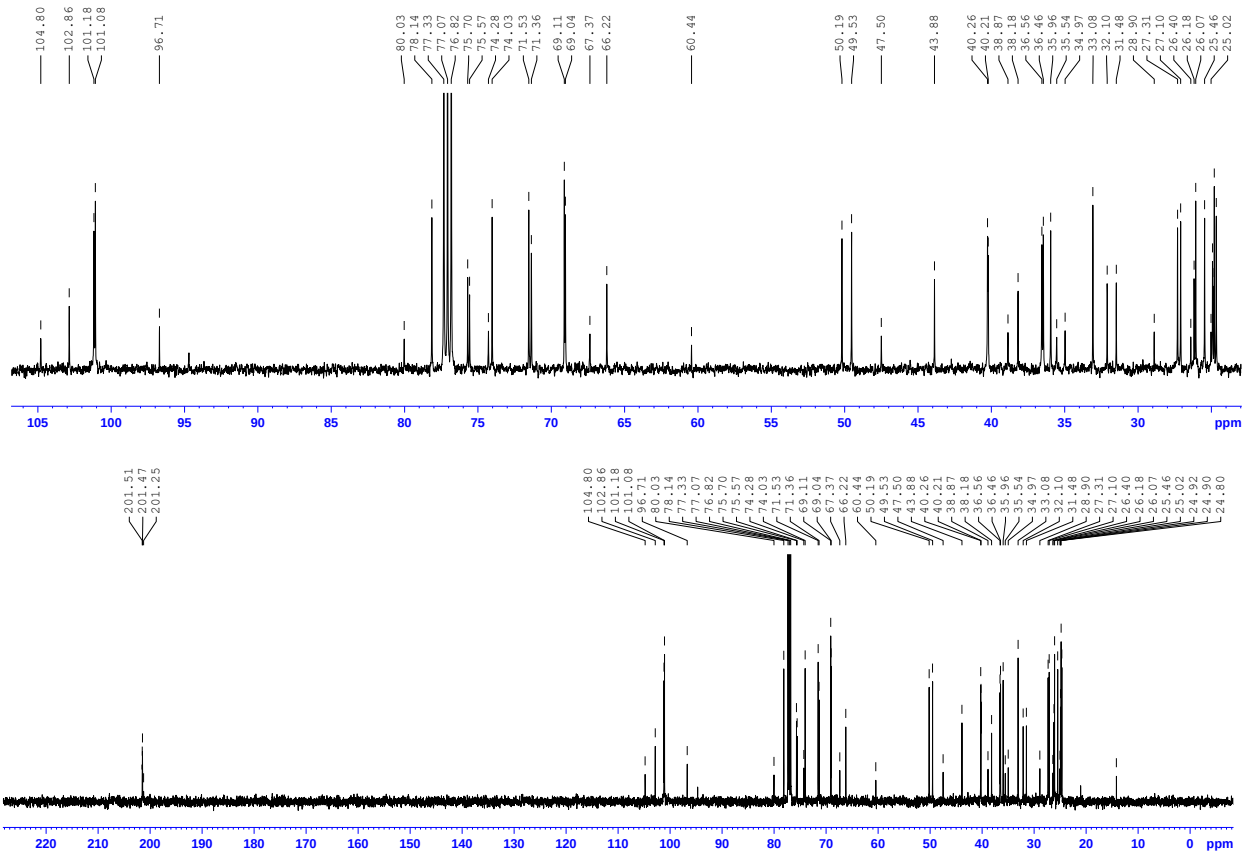


Figure S2.2. Complete $^{13}C\{^{1}H\}$ NMR spectrum in $CDCl_3$.

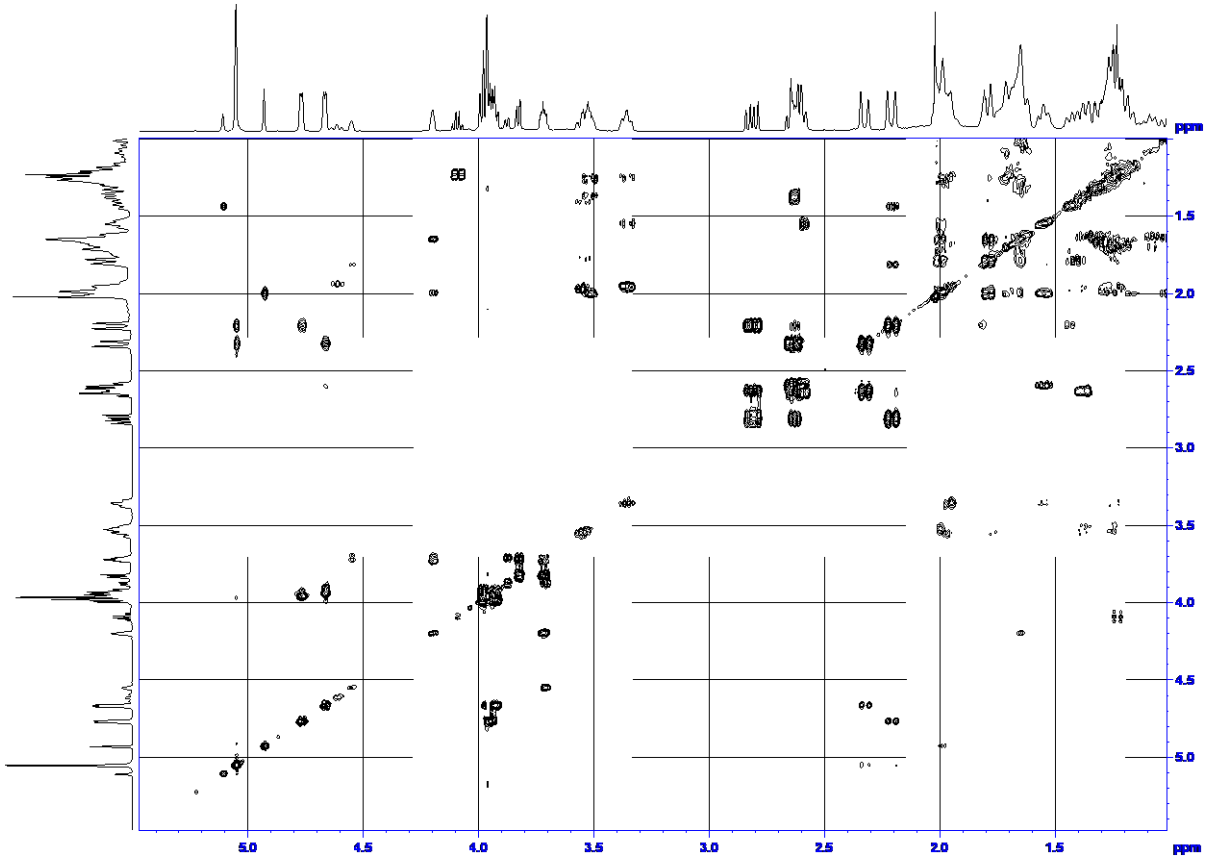


Figure S2.3. Complete $\{^{1}H,^{1}H\}$ COSY NMR spectrum in $CDCl_3$

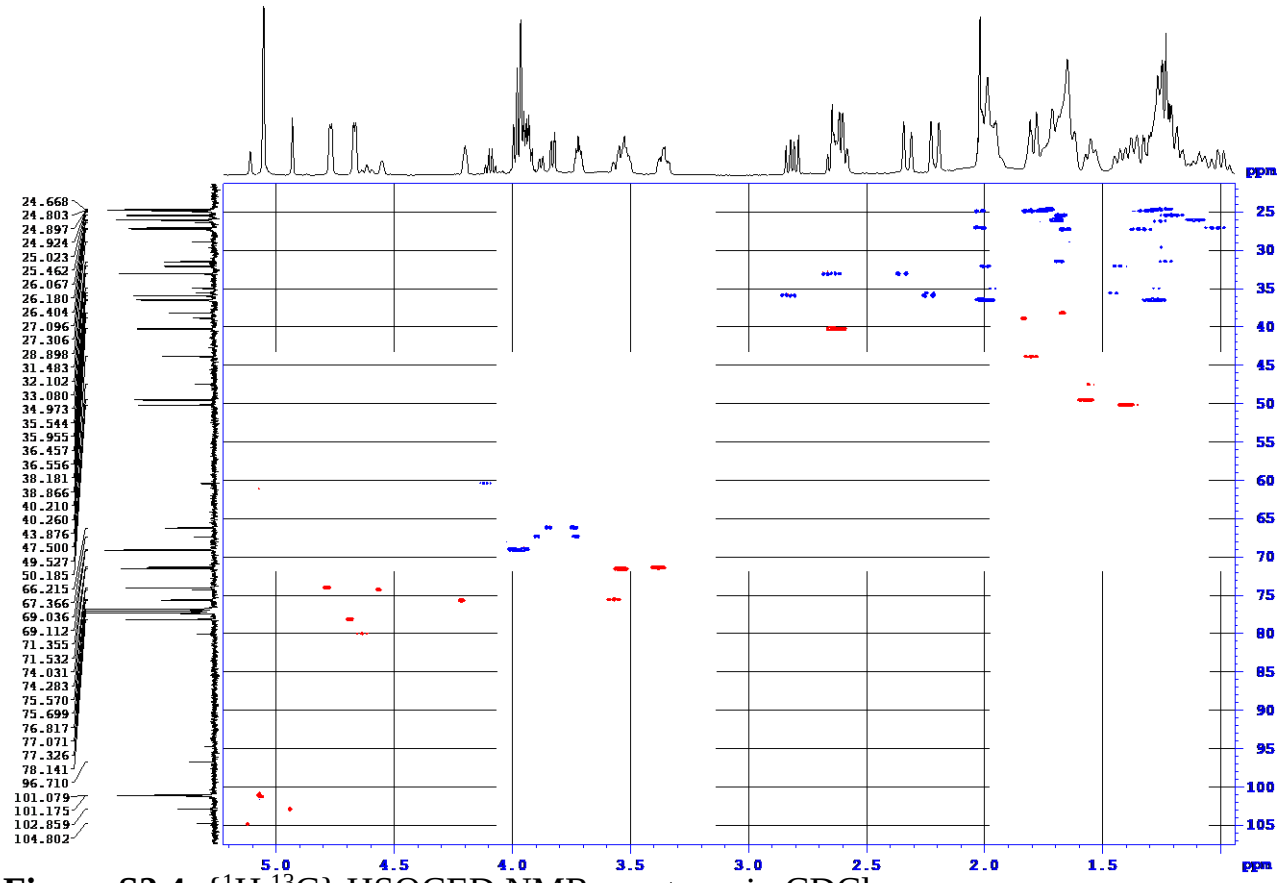


Figure S2.4. {^{1}H,^{13}C} HSQCED NMR spectrum in $CDCl_3$.

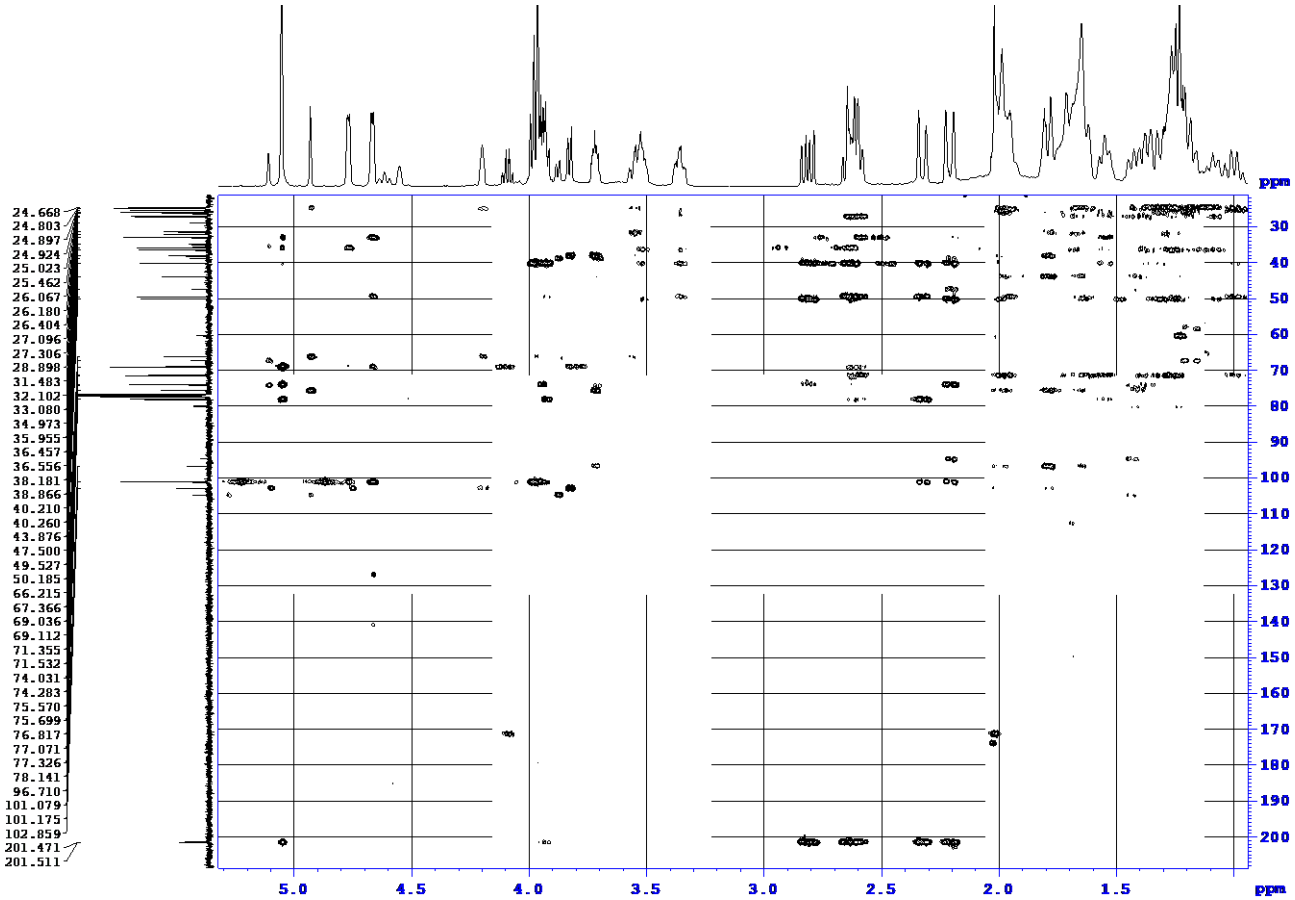


Figure S2.5. {^{1}H,^{13}C} HMBC NMR spectrum in $CDCl_3$.

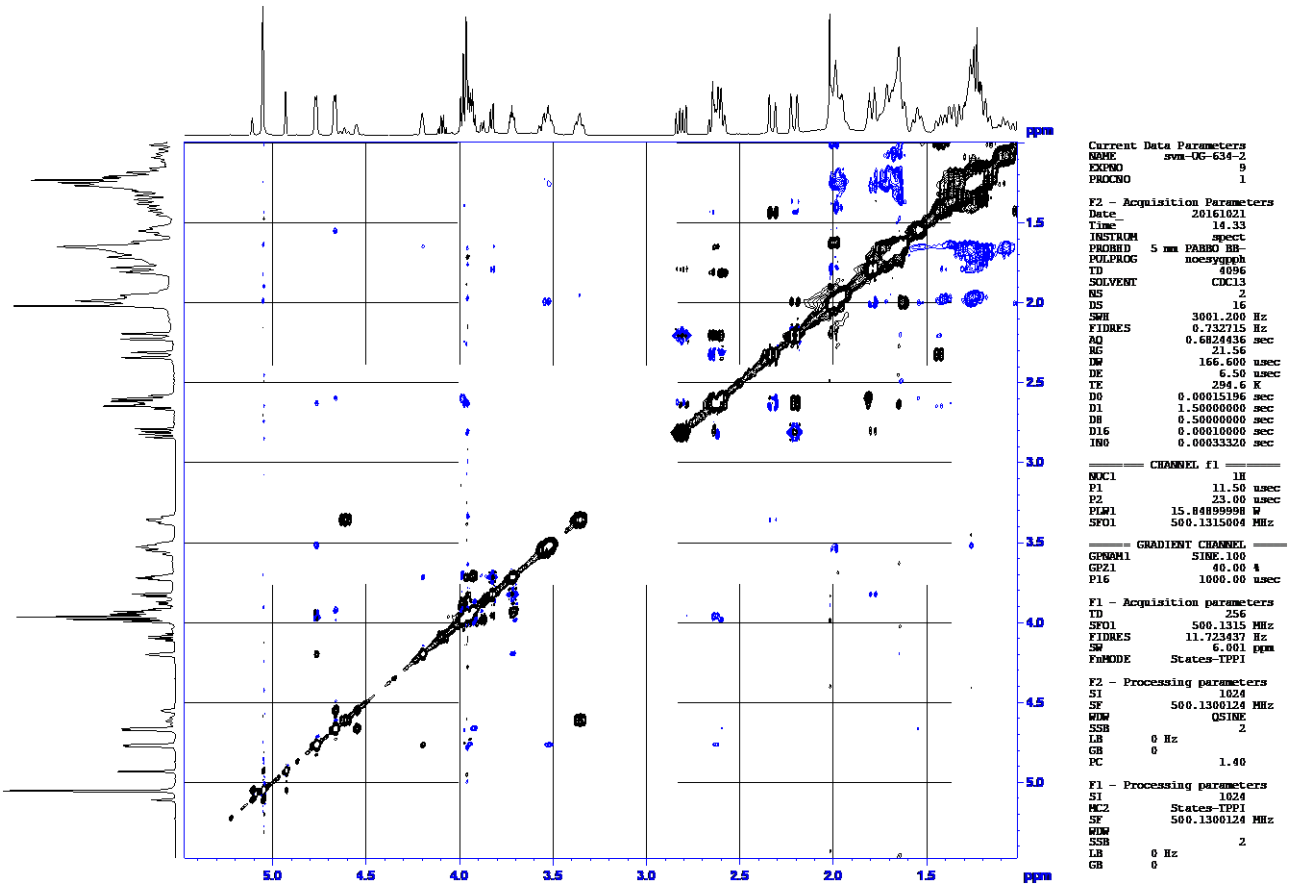
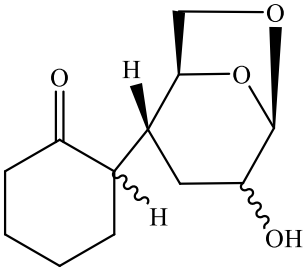


Figure S2.6. Complete {^{1}H,^{1}H} NOESY NMR spectrum in $CDCl_3$

2-((1*S*,2*R*,5*R*)-4-Hydroxy-6,8-dioxabicyclo[3.2.1]octan-2-yl)cyclohexanone (diastereomers 4a-d).



Method i) Reagent $NaBH(OAc)_3$ was obtained by refluxing a solution of $NaBH_4$ (0.033 g, 0.88 mol) in C_6H_6 (3.0 ml) and glacial acetic acid (0.04 ml, 0.71 mmol) for 15 minutes. To this reagent, a solution of diketones **1a,b** (0.05 g, 0.22 mmol) in C_6H_6 (1.0 ml) was added, and this was boiled for 30 minutes, then cooled to room temperature. One more portion of $NaBH(OAc)_3$ was added, and boiling was continued until the starting compound disappeared (TLC control). The reaction mixture was cooled to room temperature, treated with a 6% aqueous solution of HCl until the precipitate completely disappeared, the reaction products were extracted with EtOAc (3×7.0 ml), the organic layers were combined and dried over $MgSO_4$. The solvent was distilled off on a rotary evaporator, the residue was chromatographed on SiO_2. Yield 0.028 g (70%).

Method ii) D-Glucose (0.75 g) was dissolved in water (40 ml) in a round bottom flask equipped with a magnetic stirrer, thermometer and bubble counter. Baker yeast (*Saccharomyces cerevisiae*, 0.5 g) was added, and this was stirred for 1 hour at 30 °C. After 1 hour, diketones **1a,b** (0.05 g) were added, and stirring was continued at the same temperature for another 24 hours (TLC control). Then, a syrup of D-glucose (0.5 g) in water (5 ml) and the next portion (0.05 g) of substrate **1a,b** were added, and the mixture was stirred for 11 days at 30 °C. At the end of the reaction (TLC control), the reaction mixture was filtered through a Schott filter (pore 4), the filtrate was evaporated, and the residue was chromatographed on SiO_2. Yield 0.06 g (70%).

Yellow oily substance. R_f 0.18 (petroleum ether – EtOAc, 2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22-1.41 (m, 2H, $C^{5'B}H_2$[$C^{5'B}H_2$]), 1.48-1.57 (m, 2H, $C^{3B}H_2$[$C^{3B}H_2$]), 1.62-1.75 (m, 4H, $C^{3'B}H_2$, $C^{4'B}H_2$ [$C^{4'B}H_2$, $C^{3'B}H_2$]), 1.82-1.91 (m, 5H, $C^{3'A}H_2$, $C^{3}H_2$ [$C^{3'A}H_2$, $C^{2'}H$]), 2.01-2.09 (m, 4H, $C^{2'}H$, $C^{4'A}H_2$ [$C^{3A}H_2$, $C^{4'A}H_2$]), 2.19 (brs, 1H, OH), 2.23-2.29 (m, 1H, $C^{5'A}H_2$), 2.31-2.39 (m, 4H, $C^{6'}H_2$ [$C^{6'}H_2$]), [2.42-2.44 (m, 1H, $C^{5'A}H_2$)], [2.51 (brs, 1H, OH)], 2.56 (dddd, 1H, $C^{2}H$, J = 5.4, 9.6, 11.8 Hz), [2.75 (ddt, 1H, $C^{2}H$, J = 5.5, 5.6, 9.9, 9.5 Hz)], 3.52 (dddd, 1H, $C^{4}H$, J = 1.2, 5.7, 6.5 Hz), [3.58 (dddd, 1H, $C^{4}H$, J = 1.5, 5.9, 6.1 Hz)], 3.82-3.90 (m, 4H, $C^{7}H_2$[$C^{7}H_2$]), 4.41 (d, 1H, $C^{1}H$, J = 5.0 Hz), [4.49 (d, 1H, $C^{1}H$, J = 4.9 Hz)], 5.23 [5.26] (s, 2H, H^5).

^{13}C NMR (500 MHz, $CDCl_3$): δ 25.5 [24.7] ($C^{3'}$), 26.4 [26.8] (C^{3}), 28.4 [28.5] ($C^{4'}$), 32.1 [31.9] ($C^{5'}$), 36.8 [34.9] ($C^{2'}$), 42.9 [42.8] ($C^{6'}$), 49.6 [52.4] (C^{2}), 66.9 [67.0] (C^{4}), 68.9 [67.5] (C^{7}), 75.5 [73.3] (C^{1}), 102.8 [102.4] (C^{5}), 212.9 [213.8] ($C^{1'}$).

Mass spectrum, *m/z*: 227 [*M*H]$^+$. Calcd for $C_{12}H_{18}O_4$. 226.26.

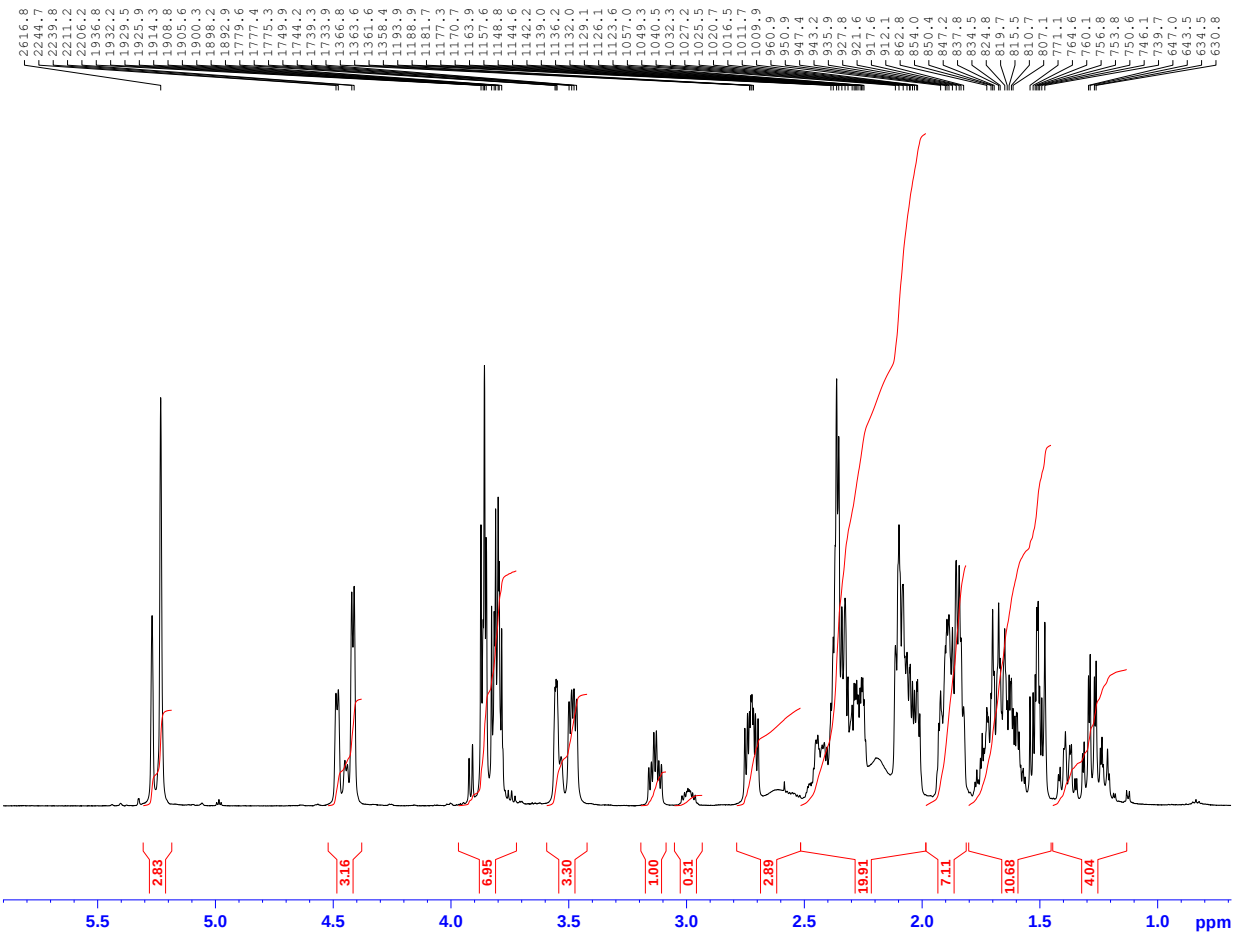


Figure S3.1. Complete ^{1}H NMR (500 MHz) spectrum in $CDCl_3$.

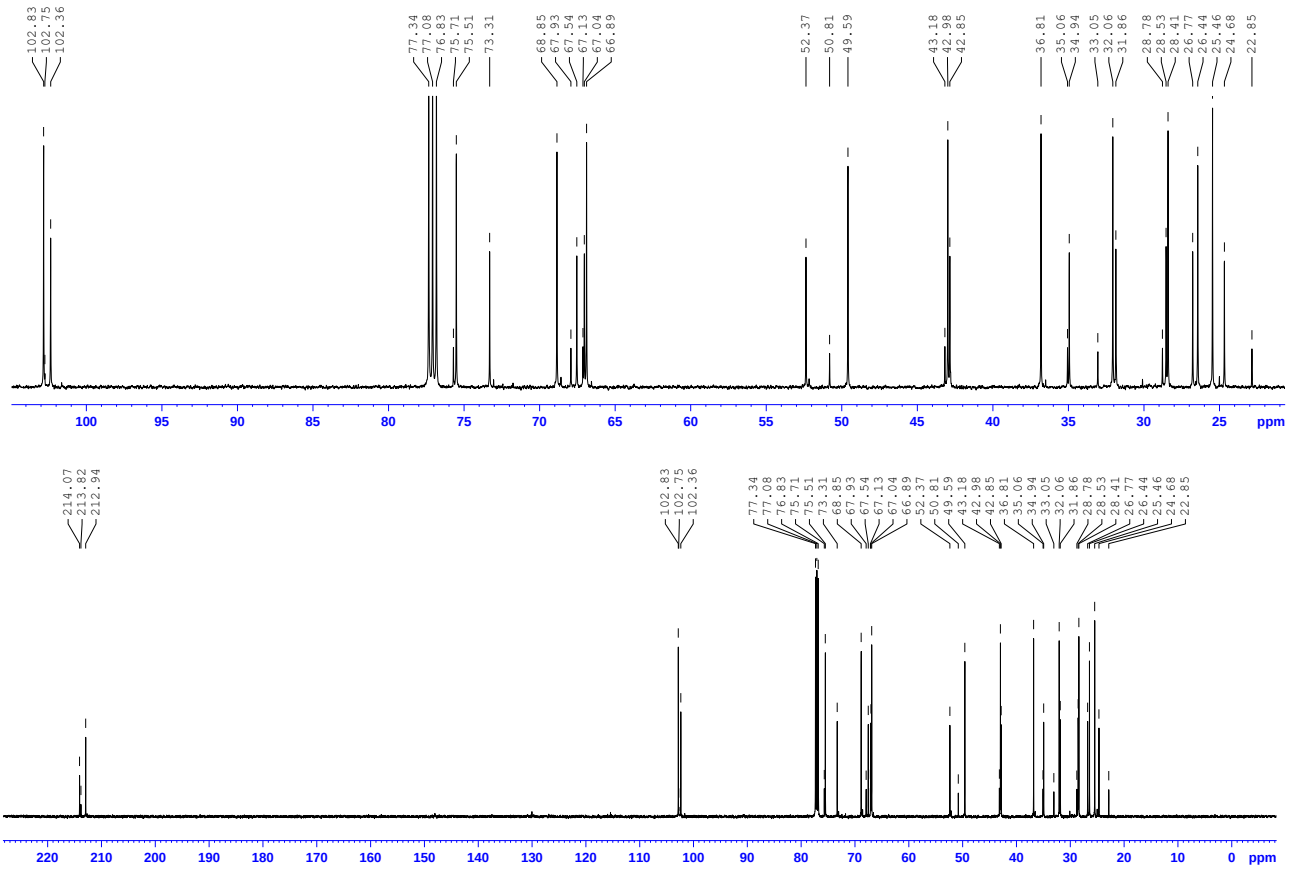


Figure S3.2. Complete $^{13}C\{^{1}H\}$ NMR spectrum in $CDCl_3$.

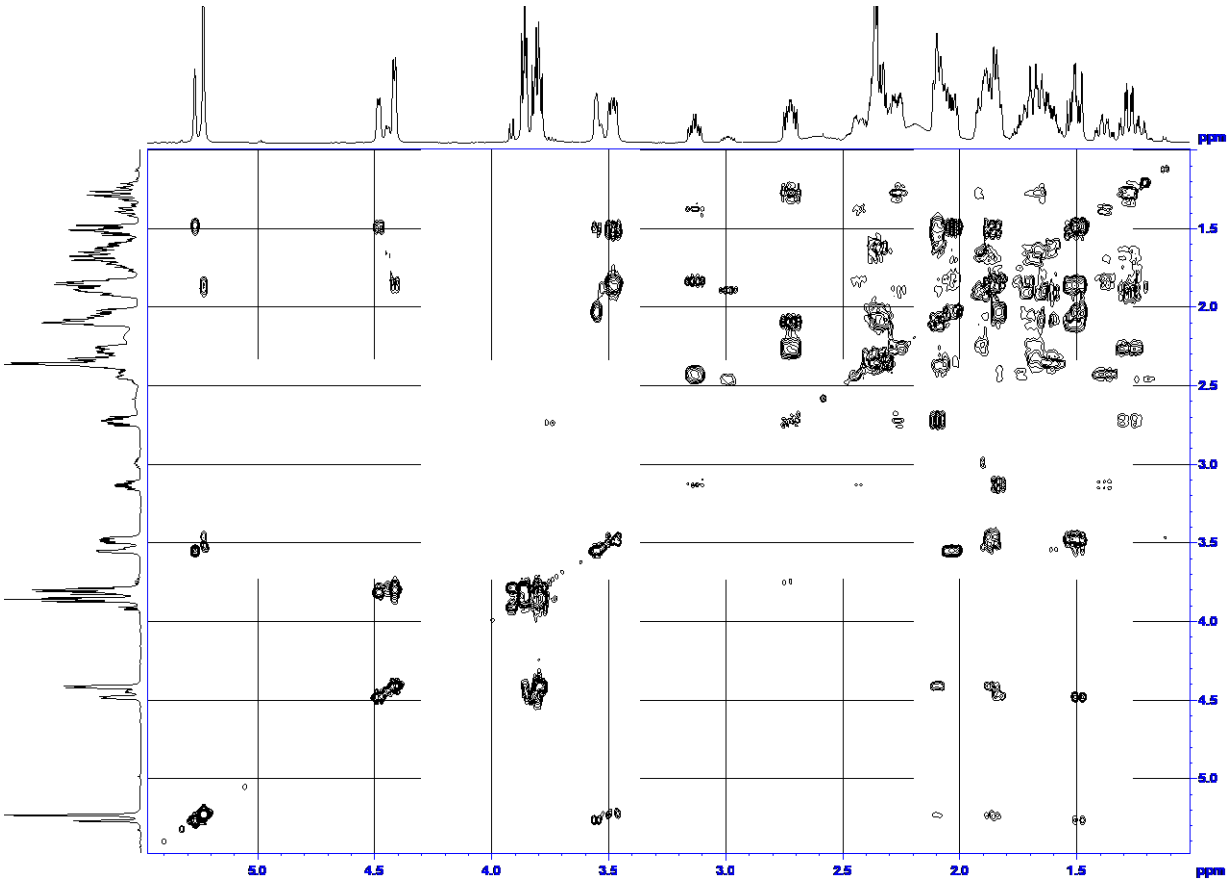


Figure S3.3. Complete $\{^{1}H,^{1}H\}$ COSY NMR spectrum in $CDCl_3$

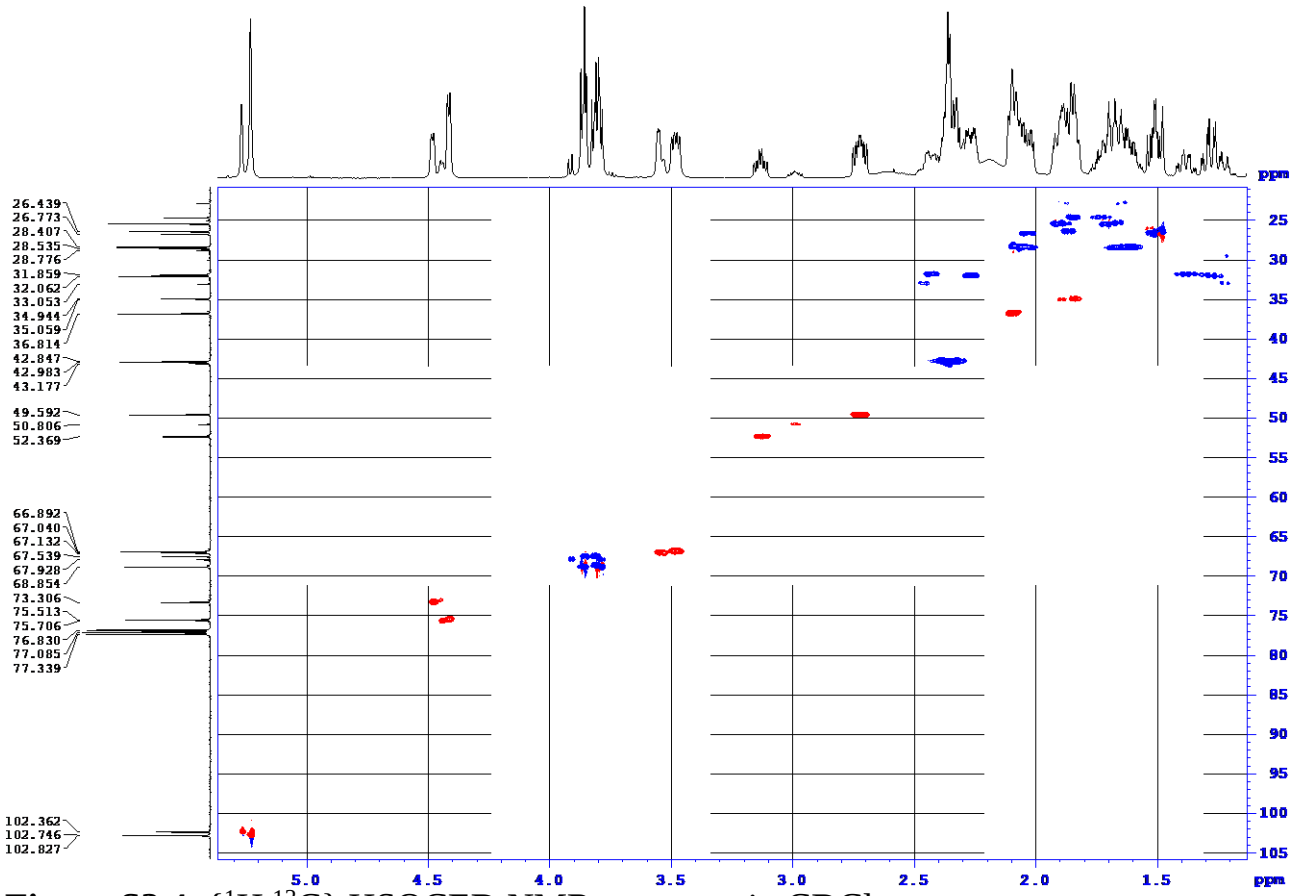


Figure S3.4. {^{1}H,^{13}C} HSQCED NMR spectrum in $CDCl_3$.

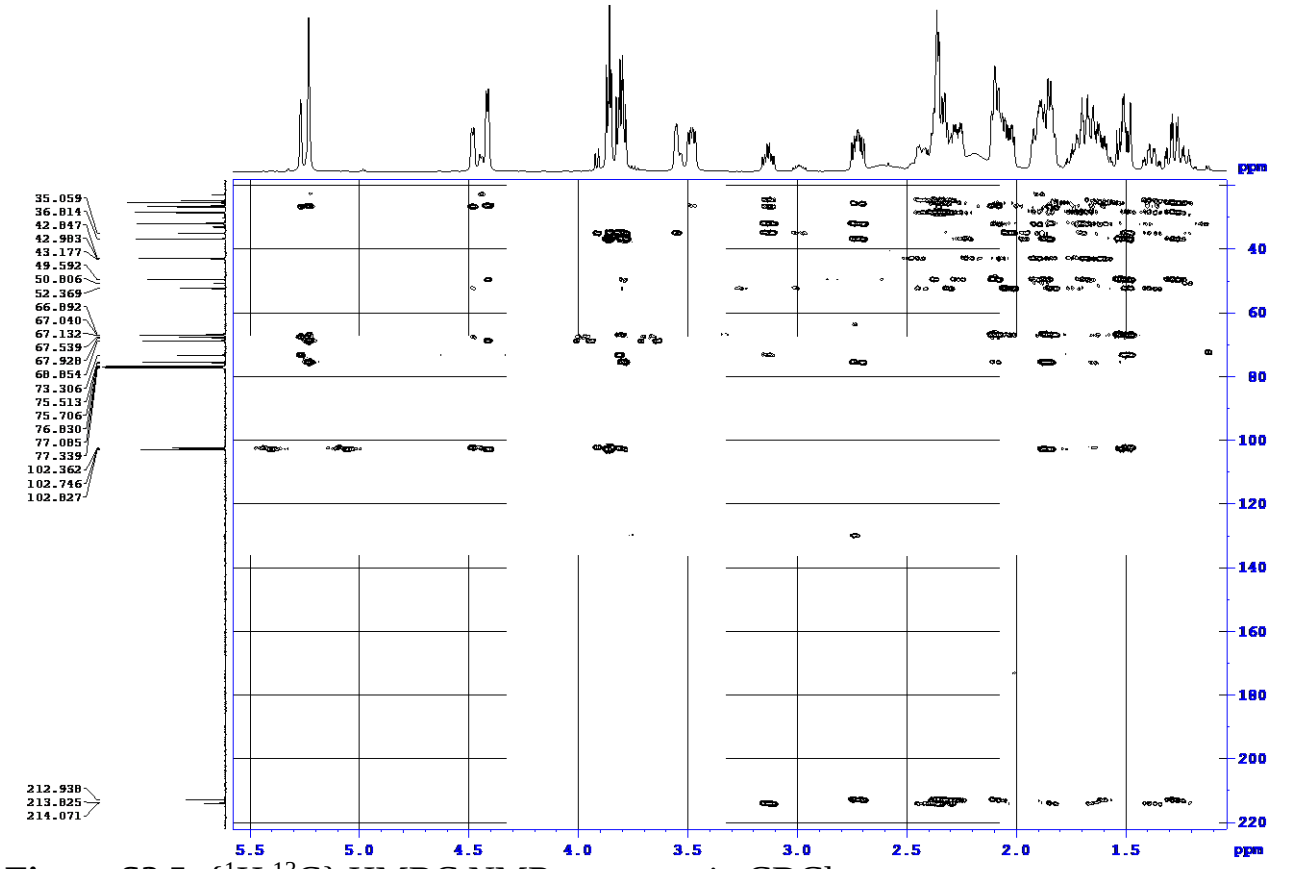


Figure S3.5. {^{1}H,^{13}C} HMBC NMR spectrum in $CDCl_3$.

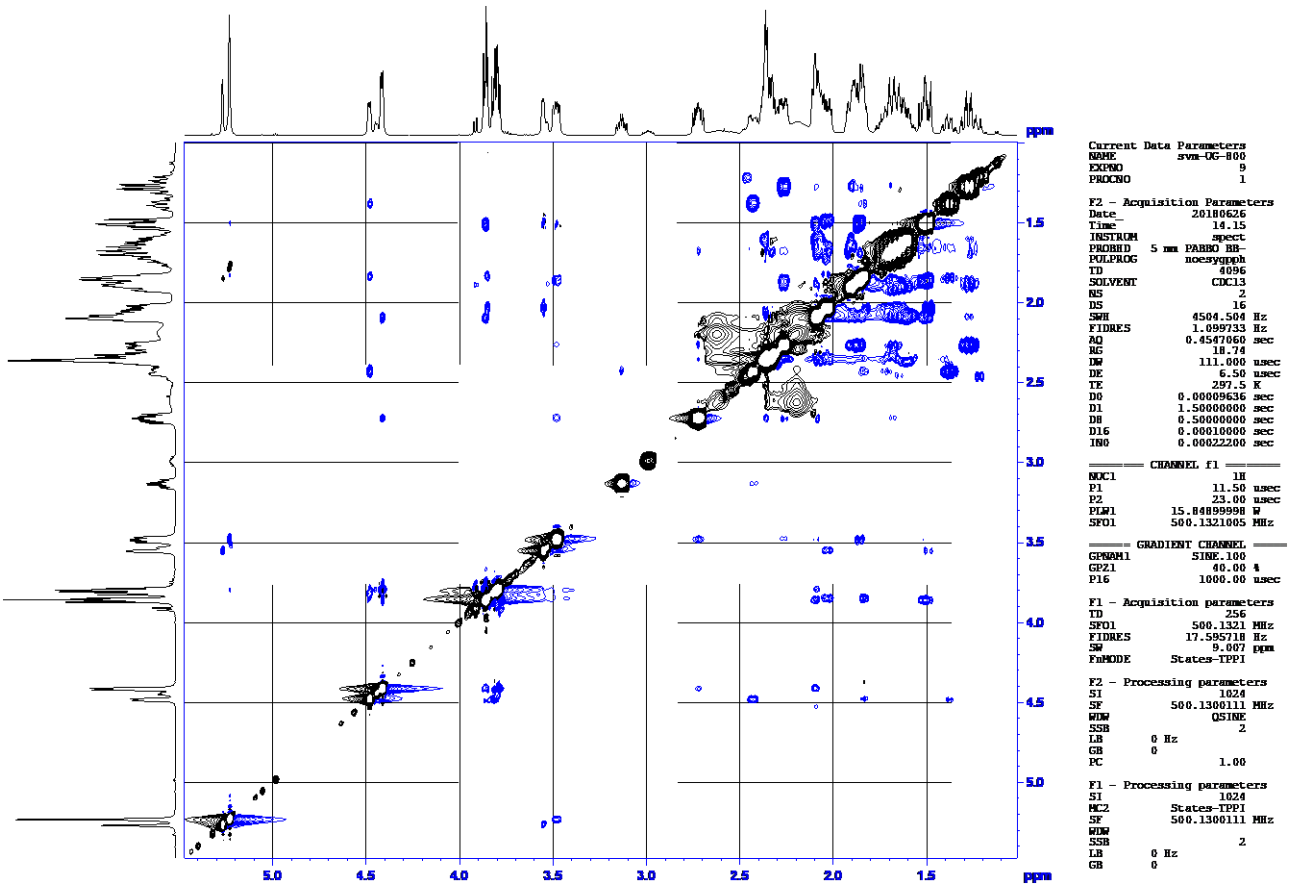


Figure S3.6. Complete {^{1}H,^{1}H} NOESY NMR spectrum in $CDCl_3$

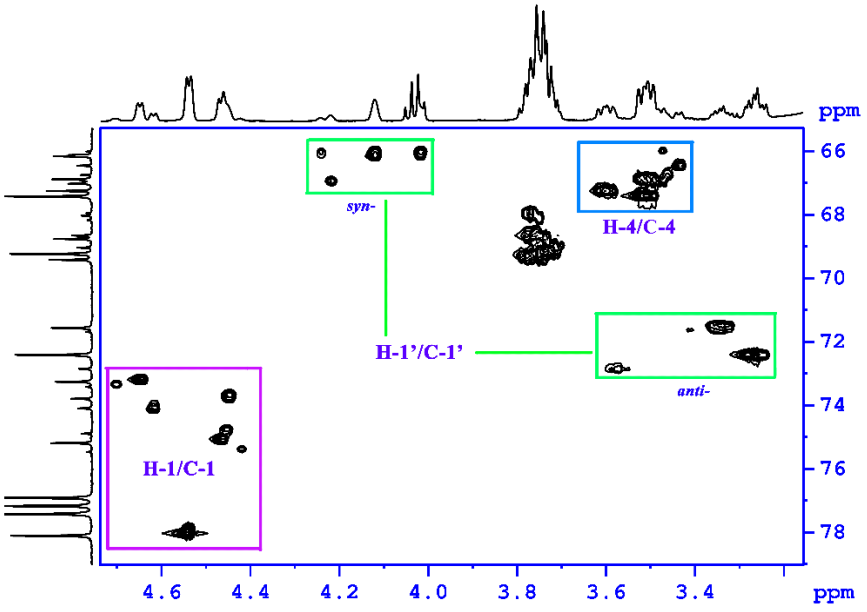
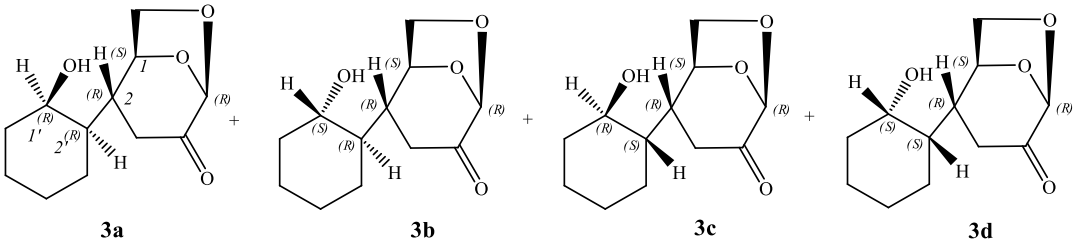


Figure S4 A fragment of the 2D^{1}H-^{13}C–HSQC spectrum of diastereomer mixture **2a-h**.

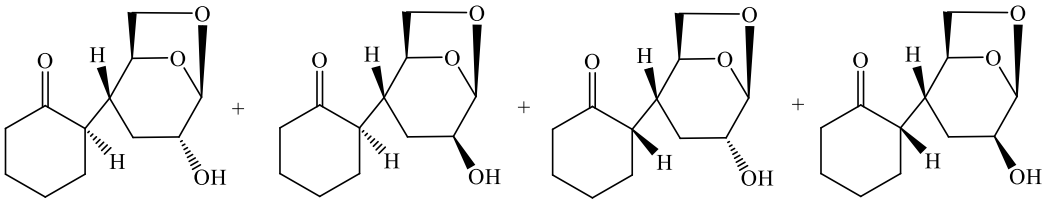
In fact, the 2D^{1}H-^{13}C–HSQC spectra of compounds **2a-h** obtained by reduction with RedAl showed that the region of δ 4.41-4.70 (δ_C 73-78) contains well pronounced correlation peaks H-1/C-1 of all the eight diastereomers. The signals of protons corresponding to the C-1′ center are separated into two groups, 4 signals in each. One of the groups of signals is observed at higher fields, δ 3.23-3.58 (δ_C 71-73), as a doublet of triplets with coupling constants of 9.8, 9.8 and 4.3 Hz and indicates the *anti*-arrangement of the H-1′ and H-2′ protons (**2a**, **2c**, **2f**, **2h**). The second group of signals is observed at weaker fields, δ 4.02-4.25 (δ_C 66-67), as broadened singlets (apparently due to small values of the coupling constants) and indicates the *syn*-arrangement of the H-1′ and H-2′ protons (**2b**, **2d**, **2e**, **2g**). In addition, correlation peaks H-1/H-1′ are observed in the NOESY spectrum of the four isomers whose H-1′ signals appear at δ 3.25, 3.34, 4.13 and 4.23, which is evidence of the *R*-configuration of the C-1′ center in these diastereomers (**2a**, **2b**, **2c**, **2d**). It should be noted that a similar NOE between H-1 and H-1′ in the 1′S isomers is absent. In the NOESY spectrum of two isomers with chemical shifts of δ 3.35 and 4.12 corresponding to the H-1′ proton, NOE with the H-4 proton is observed, which is only possible in the case of the S-configuration of the C-4 center (**2a**, **2b**). Analysis of the integral curves in the ^{1}H NMR spectrum of the H-1 protons showed the **2a:2b:2c:2d:2e:2f:2g:2h** ratio to be 5.0:4.0:10.0:0.6:0.5:1.7:1.0:2.0. Reduction of diketones **1a,b** by treatment with $NaBH_4$ gives the same eight diastereomers **2a-h** in the 8.0:6.6:10.0:3.1:4.0:2.2:3.0:4.0 ratio.



3a **3b** **3c** **3d**

3a:3b:3c:3d, 10:9:5:3

In the ^{1}H NMR spectra of alcohols **3a,b,c,d**, the H-2 proton signal of the major 1'*R*,2'*R*- and 1'*S*,2'*R*-diastereomers **3a** and **3b** is recorded at δ 2.60 (δ_C 40.26) and 2.63 (δ_C 40.21), respectively, while this proton signal of the minor 1'*R*,2'*S*- and 1'*S*,2'*S*-diastereomers **3c** and **3d** is recorded at stronger field, namely, at δ 1.67 (δ_C 38.18) and 1.83 (δ_C 38.87), respectively, as a multiplet. The carbon signals corresponding to these protons were assigned by heteronuclear two-dimensional ^{1}H-^{13}C-HSQCED spectroscopy. The H-2' proton signal of diastereomer **3a** with the 2'*R*,1'*R*-configuration is recorded at δ 3.54 (δ_C 71.53), while a similar proton of diastereomer **3b** with the 2'*R*,1'*S*-configuration is recorded at stronger field, δ 3.38 (δ_C 71.35). The signal of the same proton in diastereomer **3c** with the 2'*S*,1'*R* configuration is recorded at δ 3.57 (δ_C 75.57), while that of diastereomer **3d** with the 2'*S*,1'*S*-configuration, in weaker field at δ 4.64 (δ_C 80.03).



4a **4b** **4c** **4d**

In the ^{1}H NMR spectra of the major 2'*R*,4*R*- and 2'*R*,4*S*-diastereomers of alcohols **4a** and **4b**, the H-4 proton signal is recorded at δ 3.52 (δ_C 66.9) and 3.58 (δC 67.0), respectively. The carbon signals corresponding to these protons were assigned using heteronuclear two-dimensional ^{1}H-^{13}C-HSQCED spectroscopy. The reduction of the keto group in the carbohydrate moiety of diastereomeric compounds **4a,b** is confirmed by the presence of $C^{1'}$ (δ_C) signals in the ^{13}C NMR spectrum at weaker field, δ 212.9 [213.8], respectively, whereas the carbonyl at C4 in alcohols **3a,b** is detected at stronger field, δ 201.47 [201.51]. This agrees with the signals of the keto groups in the original diketones **1a,b**: the cyclohexanone moiety is detected at δ 211.79 [212.06], while the cyrenone moiety, at δ 200.91 [201.00].

Additional evidence is given by the presence of cross-peaks between $C^{1'}$-$H^{2'}$, $C^{1'}$-H^{2}, C^{4}-H^{3}, C^{4}-H^{5}, C^{2}-H^{1} in the ^{1}H-^{13}C-HMBC spectra. The stereochemistry of C-2' was identified from the NOE interactions H^{1}-$H^{2'}$, $H^{2'}$-H^{4} in both diastereomers **4a,b**. The existence of cross-peaks between H^{5}-H^{3B} and H^{1}-H^{3B} and H^{2}-H^{3A} and H^{4}-H^{3B}, H^{5}-H^{4} in the NOESY spectrum of major alcohol **4a**, H^{4}-H^{2} in the COSY spectra and the absence of a NOE effect H^{4}-H^{2} in the minor diastereomer **4b** is evidence of the configuration at C-4 *R* and *S*, respectively.