Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Simultaneous ^{1}H and ^{13}C NMR enantiodifferentiation from highly resolved pure shift HSQC spectra

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Experimental Section

NMR experiments were performed on a Bruker Avance 600 spectrometer (Bruker AG, Rheinstetten, Germany) equipped with TXI HCN z-grad probes. The temperature for all measurements was set to 298 K and data were acquired and processed with TOPSPIN 3.1 (Bruker AG, Rheinstetten, Germany).

All spectra were recorded on a 600 μL fresh solution stock of racemic 3-ethyl-3-(3-hydroxyphenyl)-1-methylazepan-2-one (compound **1**, 29 mM) in $CDCl_3$, containing 9.6 equiv. (46.2 mg) of *R*-Pirkle alcohol (PA). Ii is referred to as compound **1** throughout the manuscript and this SI.

Slice selection in the 1D Zangger-Sterk (ZS) experiment (Fig. 1B) was performed using a selective 180 ^{1}H R-Snob pulse of 60 ms applied simultaneously to a weak rectangular gradient of 2%. Data was acquired in a pseudo 2D mode using 4 scans for each one of the 16 t_1 increments and a recycle delay of 1s. The FID reconstruction was performed with the AU program pshift (available at http://nmr.chemistry-manchester.ac.uk), followed by conventional Fourier transformation. The total experimental time was of 9 minutes.

The 2D ^{1}H-^{13}C pure shift HSQC spectrum (pulse scheme of Fig. 2A) was recorded as described in ref. 6. Pulse phases are x unless indicated otherwise and a basic two-step phase cycling scheme is applied: Φ_1=x,-x, Φ_r=x,-x. ^{13}C 180º pulses are applied as CHIRP inversion and refocusing pulses of 500 μs and 2000 μs of duration, respectively. The recycle delay was 3 s and the interpulse delays in the INEPT and BIRD modules were optimized for 140 Hz (Δ=3.57 ms). 2 scans were accumulated for each one of the 256 t_1 increments (512 experiments defined applying 50% non-uniform sparse sampling), the spectral windows in F1 and F2 dimensions were 377 Hz (2.5 ppm) and 4200 Hz, respectively, the number of data points in t_2 was set to 2048 and the acquisition time (AQ) was 0.24 s giving a FID resolution of 1.47 and 4.10 Hz, respectively. The total experimental time was of 30 min. Homodecoupling during acquisition was achieved applying 130 loops (n) with τ=7.7 ms. Broadband heteronuclear decoupling was applied during the τ periods using 1.5 ms chirped pulses combined in a p5m4 supercycle scheme. The ratio between the G1:G2 gradients were 40:20.1, measured as percentage of the absolute gradient strength of 53.5 G/cm. Data were acquired and processed using the echo/anti-echo protocol. Sine bell shaped gradients of 1 ms duration were used, followed by a recovery delay of 20 μs

(δ=1.02ms). Prior to Fourier-transformation of each data, zero filling to 1024 in F1, 8192 points in F2, linear prediction in F1 and a π/2-shifted sine squared window function in both dimensions were applied. The final digital resolution was of 0.51 and 0.36 Hz in F2 and F1 dimensions, respectively.

To determine ΔΔδ on quaternary carbons, a conventional non-refocused gradient-enhanced HSQMBC experiment optimized to 8 Hz was collected with the same acquisition and processing parameters described for the HSQC experiments. 16 scans were acquired per t_1 increment giving a total experimental time of 4 hours. Conventional 2D HSQC experiments were recorded under the same conditions as described previously for the pure shift analogues. HSQC and HSQMBC experiments were also recorded with ^{13}C spectral windows of 5 ppm (Fig. S6 and S9-10).

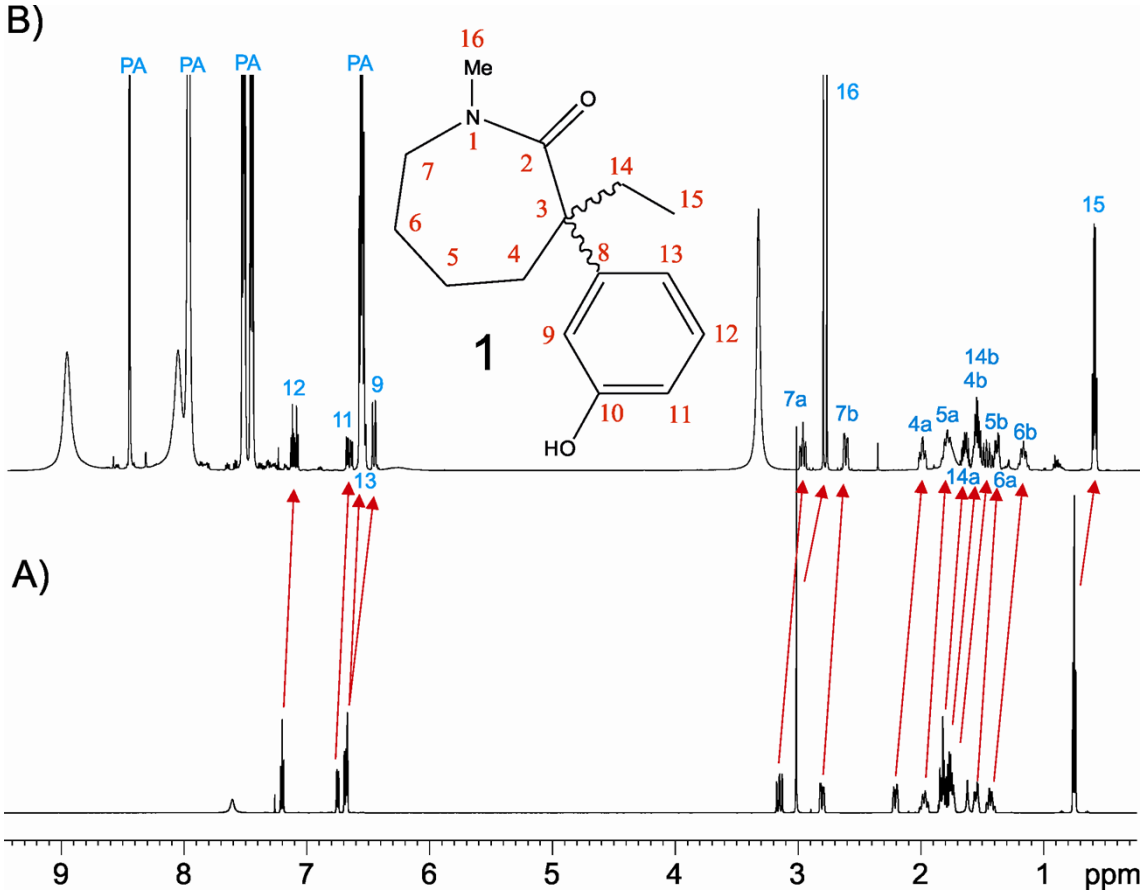


Figure S1: A) ^{1}H NMR spectrum of racemic compound (**1**) in $CDCl_3$; B) Resulting ^{1}H NMR spectrum after adding 9.6 equivalents of Pirkle Alcohol (*R*-PA).

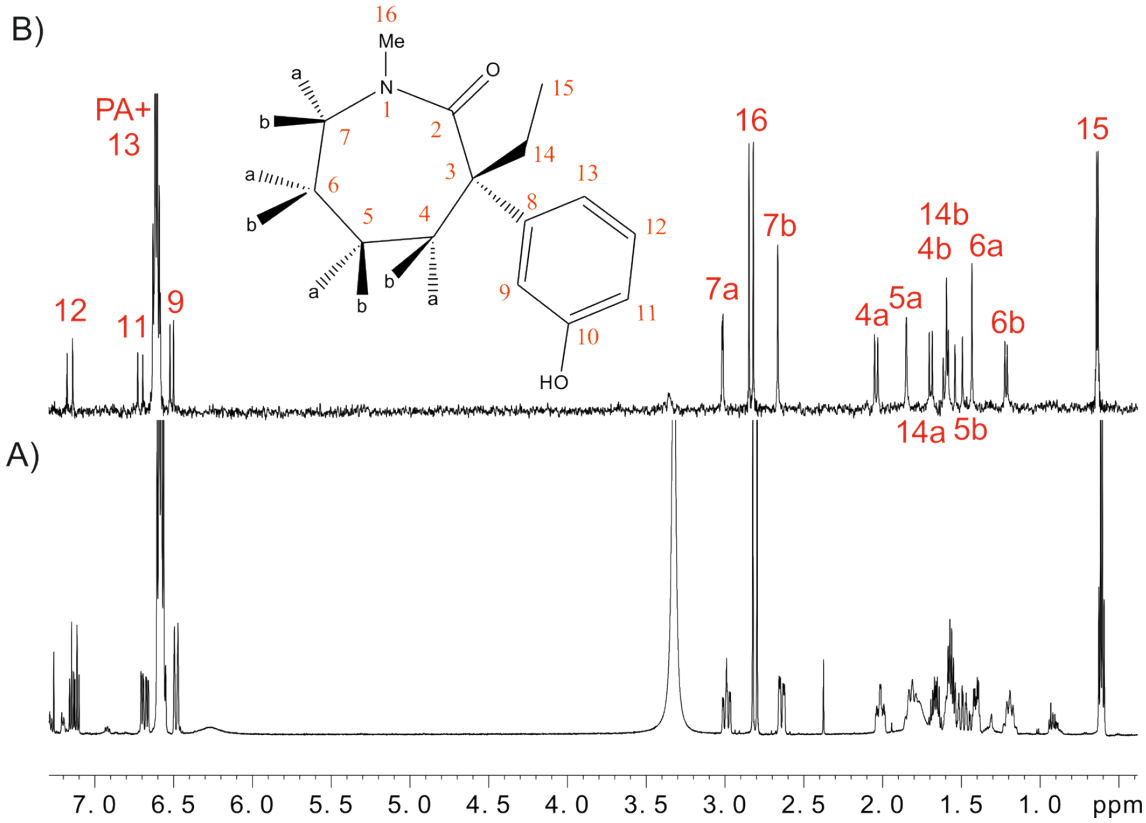


Figure S2: A) 1D conventional and B) pure shift ^{1}H spectrum of racemic compound **1** and *R*-PA. The structure of the *R*-**1** enantiomer is shown for stereoassignment purposes. See Fig. 1C and 1D for selected expansions and experimental $\Delta\Delta\delta(^{1}H)$ values.

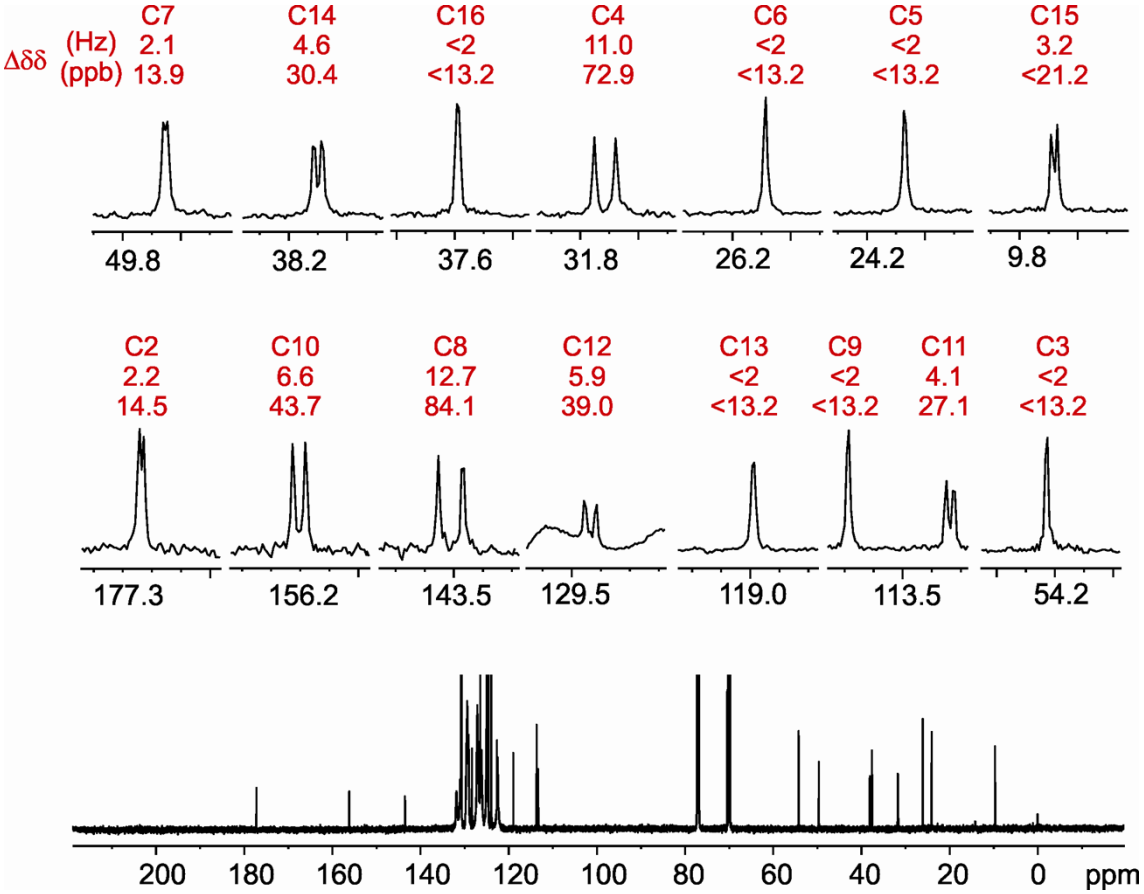


Figure S3: (Bottom) 150.9 MHz Broadband heterodecoupled ^{13}C NMR spectrum of racemic compound **1** and *R*-PA; (top) expanded multiplets to show individual signal splitting (in Hz and ppb) due to the enantiodifferenation.

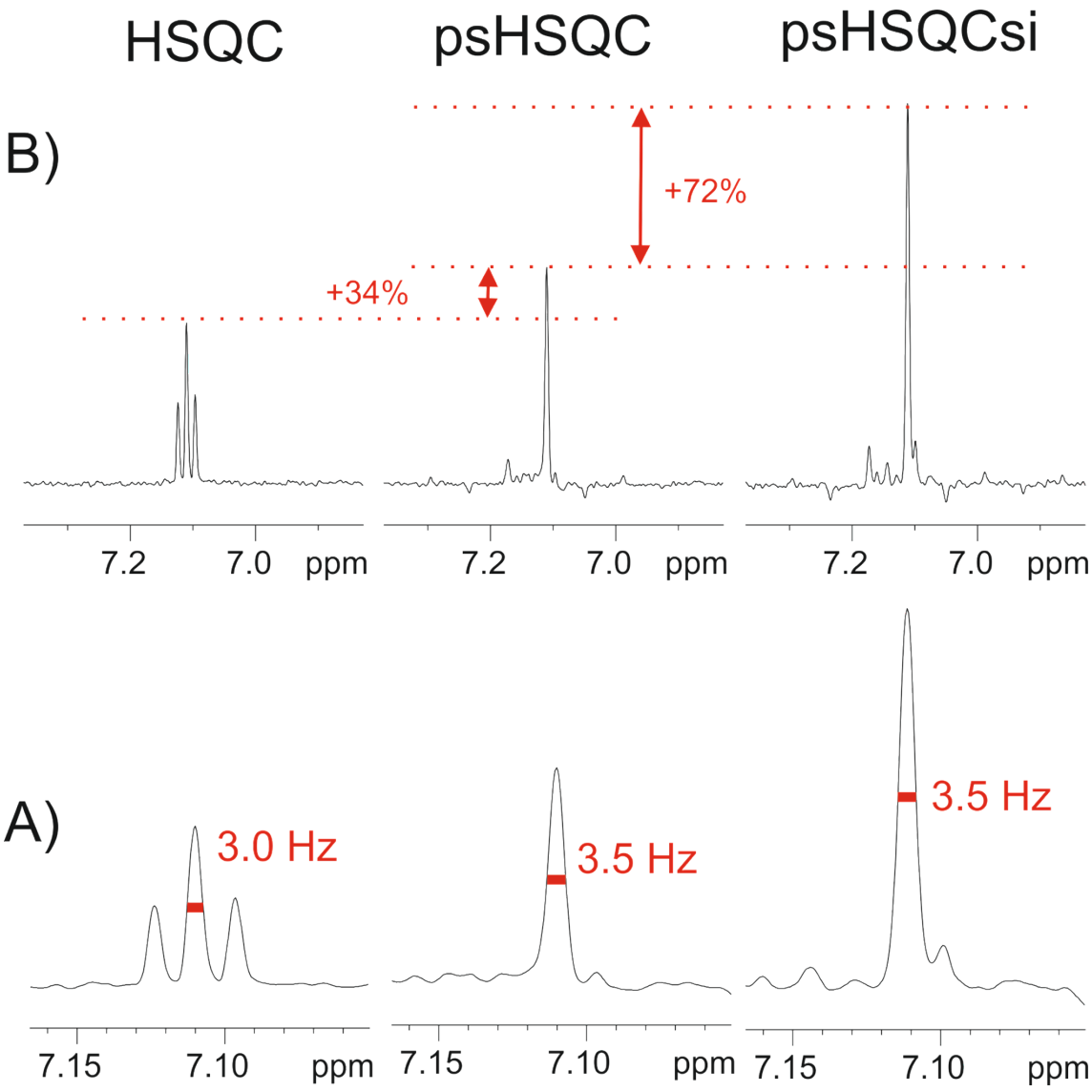


Figure S4: (A) Experimental line widths and B) relative sensitivities obtained in conventional HSQC, pure shift HSQC (psHSQC) and pure shift sensitivity-improved HSQC (psHSQCsi) experiments. 1D traces correspond to the upfield H12/C12 carbon frequency.

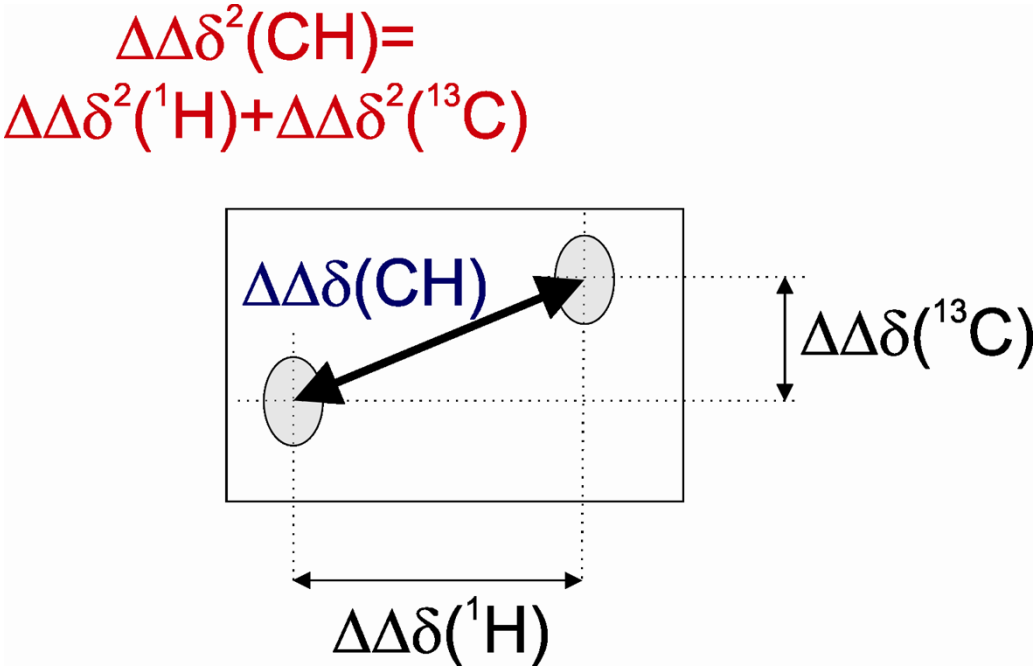
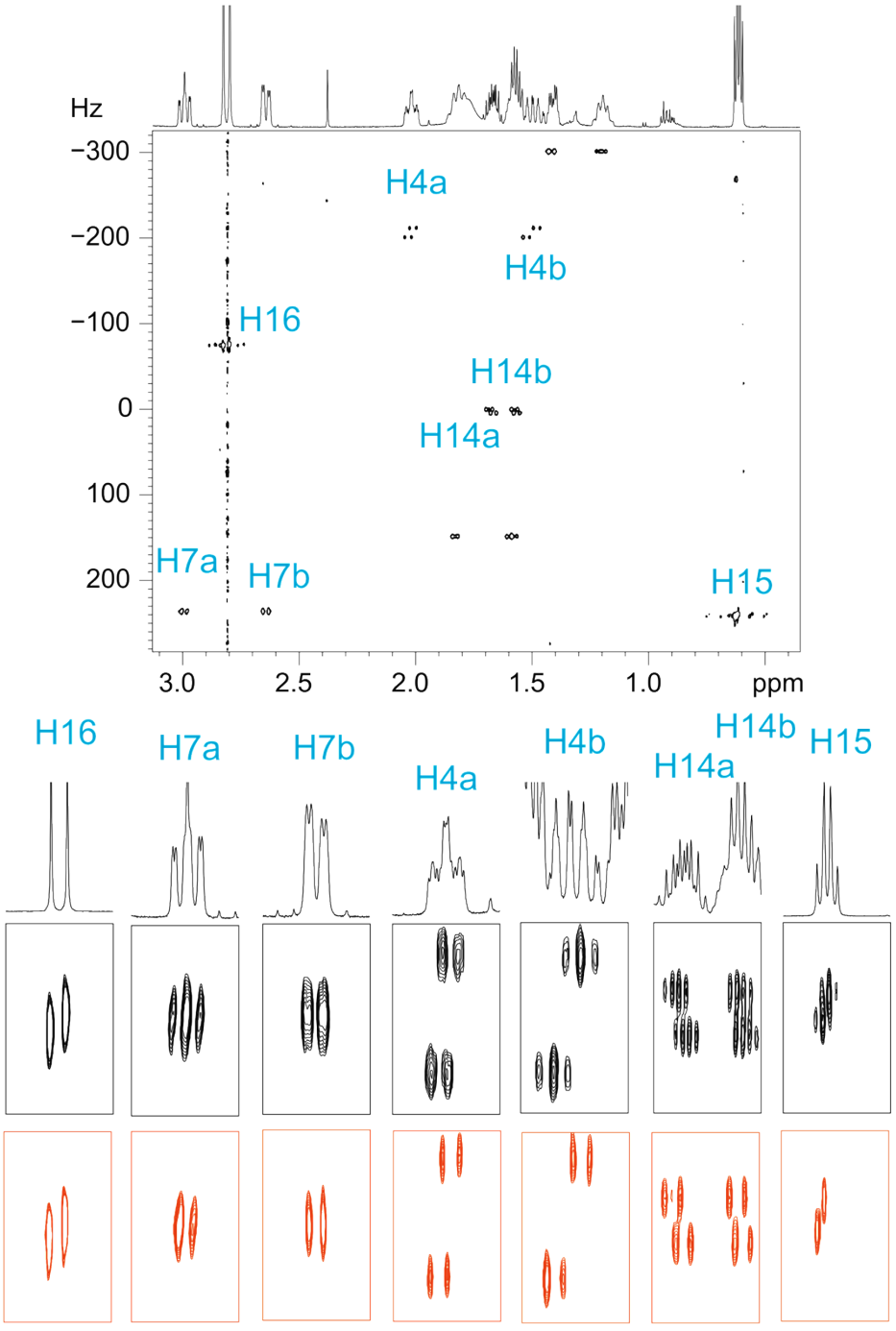


Figure S5: Schematic representation of the new parameter ΔΔδ(CH) that defines the separation between two cross-peaks from the individual ΔΔδ(^{1}H) and ΔΔδ(^{13}C) separations along each dimension of a 2D map.



$\Delta\Delta\delta(^{1}H)$=	27.1	-	-	-	-	-/-	11.5
$\Delta\Delta\delta(^{13}C)$=	<13.2	13.9	13.9	72.9	73.5	29.8	18.5
$\Delta\Delta\delta$(CH)=	28.4	14.0	13.2	76.4	86.7	35.2/31.1	22.0

Figure S6: (Top) Expanded area corresponding to the 0.4-3.2 ppm region of the 2D psHSQCsi spectrum of **1** acquired with SW(^{13}C)=5 ppm; (medium) Expanded cross-peaks show the distinction between enantiomeric signals in 1D ^{1}H, conventional HSQC and psHSQCsi spectra; (bottom) experimental values extracted from the conventional ^{1}H spectrum ($\Delta\Delta\delta(^{1}H)$), 1D ^{13}C spectrum ($\Delta\Delta\delta(^{13}C)$) and calculated ($\Delta\Delta\delta$(CH)) values calculated from the splitting measured in the 2D spectrum.

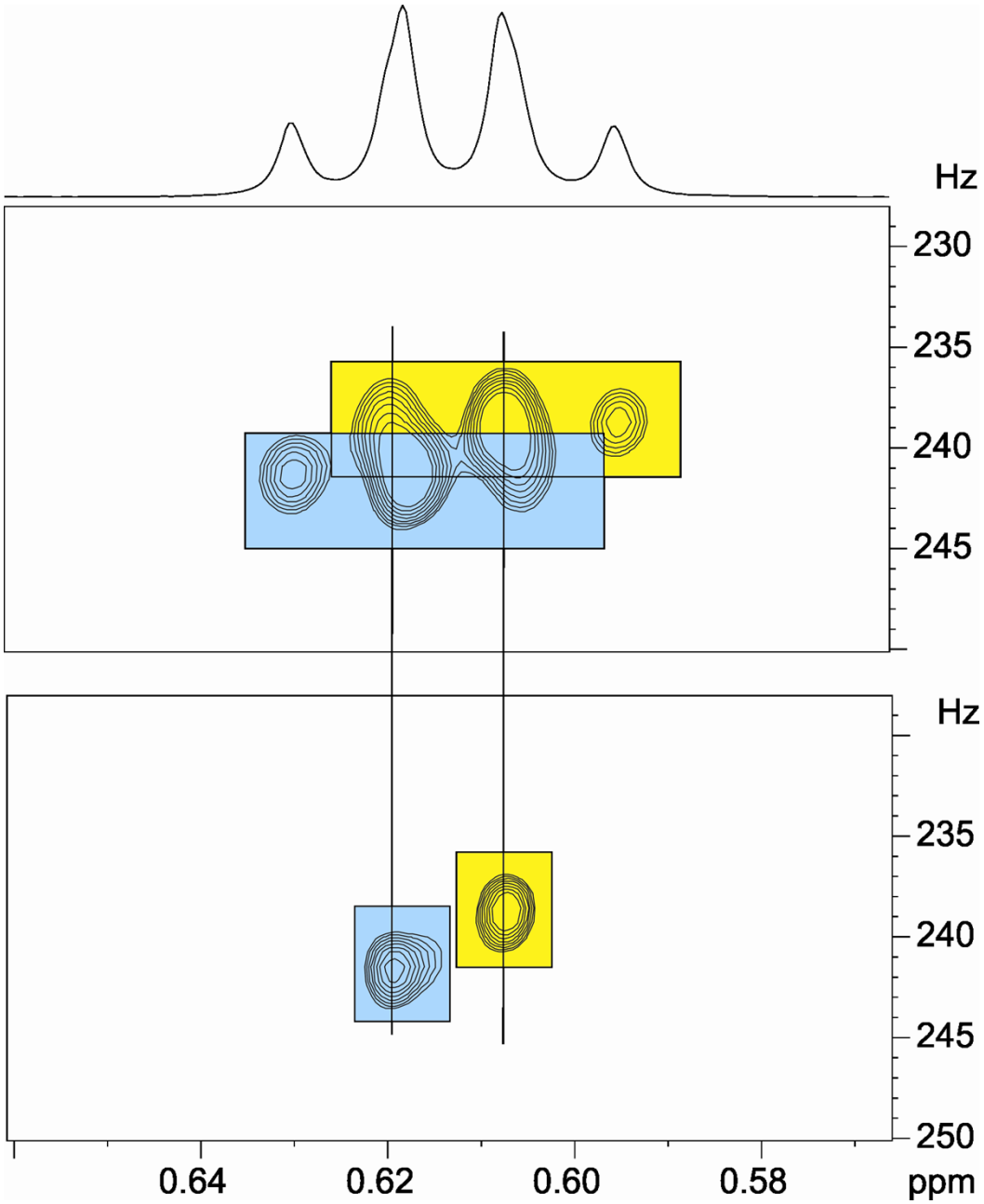


Figure S7: Expanded area corresponding to the C15/H15 cross-peak in (top) SA-HSQC and B) SAPS-HSQC spectra. The H15 signal consists of two overlapped triplets where is difficult to extract the exact ^{1}H chemical shift in both 1H and conventional HSQC spectra. Note the superior features of the SAPS approach to perform: i) automatic peak picking, ii) accurate and simultaneous determination of ^{1}H and ^{13}C chemical shift differences, and iii) an improved quantification by peak volume integration of each individual singlet signal.

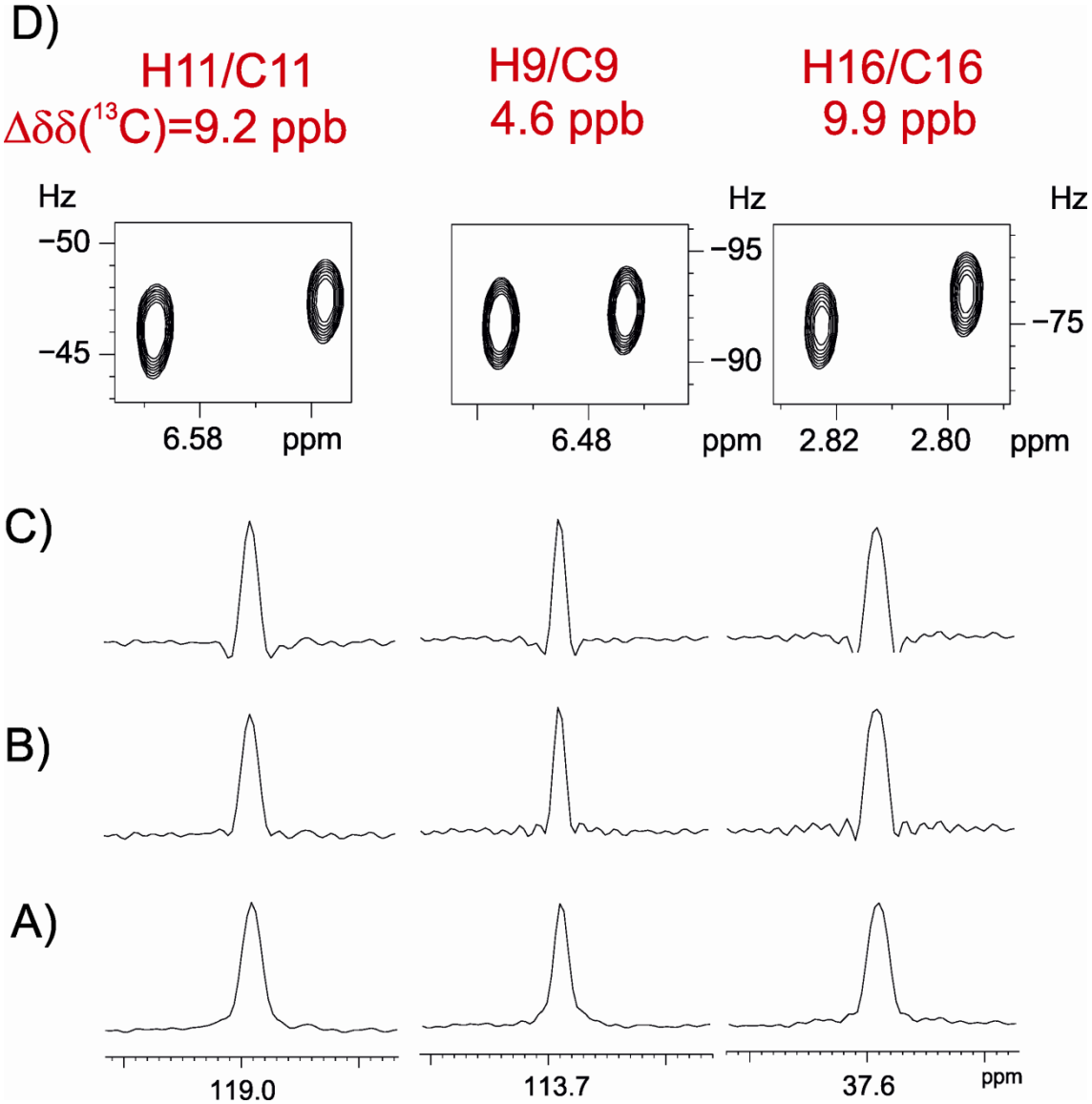


Figure S8: Example showing how the good dispersion along the detected ^{1}H dimensions allows the differentiation of small chemical shift differences along the indirect ^{13}C dimension, even smaller than the line width observed in the conventional ^{13}C spectrum. A-C) show some not resolved ^{13}C signals obtained in the conventional ^{13}C spectrum of 2mM racemic compound 1 complexed with R-PA. Data were acquired with 32K data points and an spectral width of 36057 Hz and further processed with a zero filling up to 64K giving a digital resolution of 0.6 Hz: A) processed with an exponential multiplication with a line broadening of 1 Hz; B) processed without any window function; C) processed with a Gaussian function with LB=-2 Hz and GB=0.5. The line widths at the half of well resolved signals in spectra B was about 1.7 Hz. D) Expansions of the corresponding cross-peaks obtained from the SAPS-HSQC spectra.

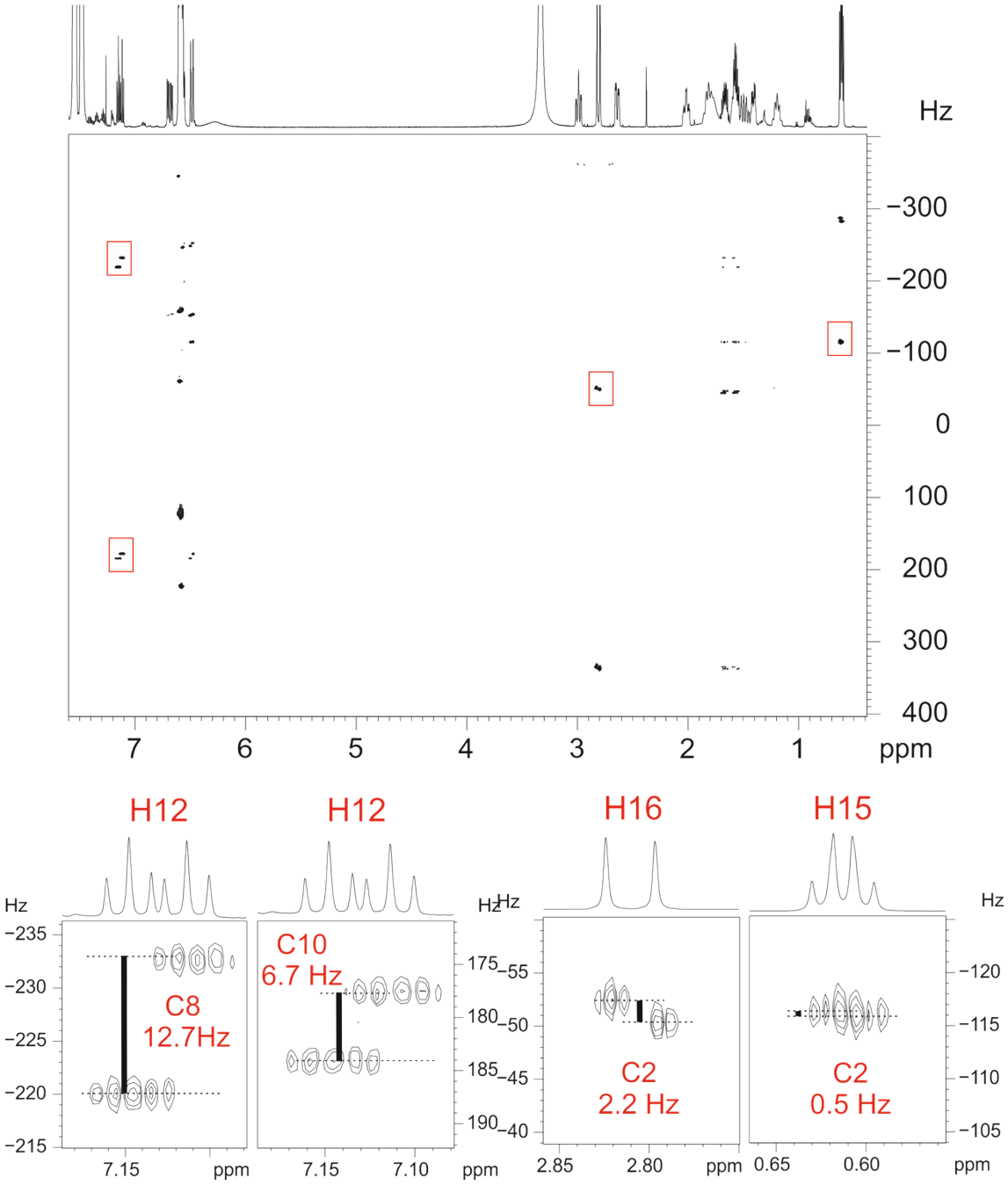
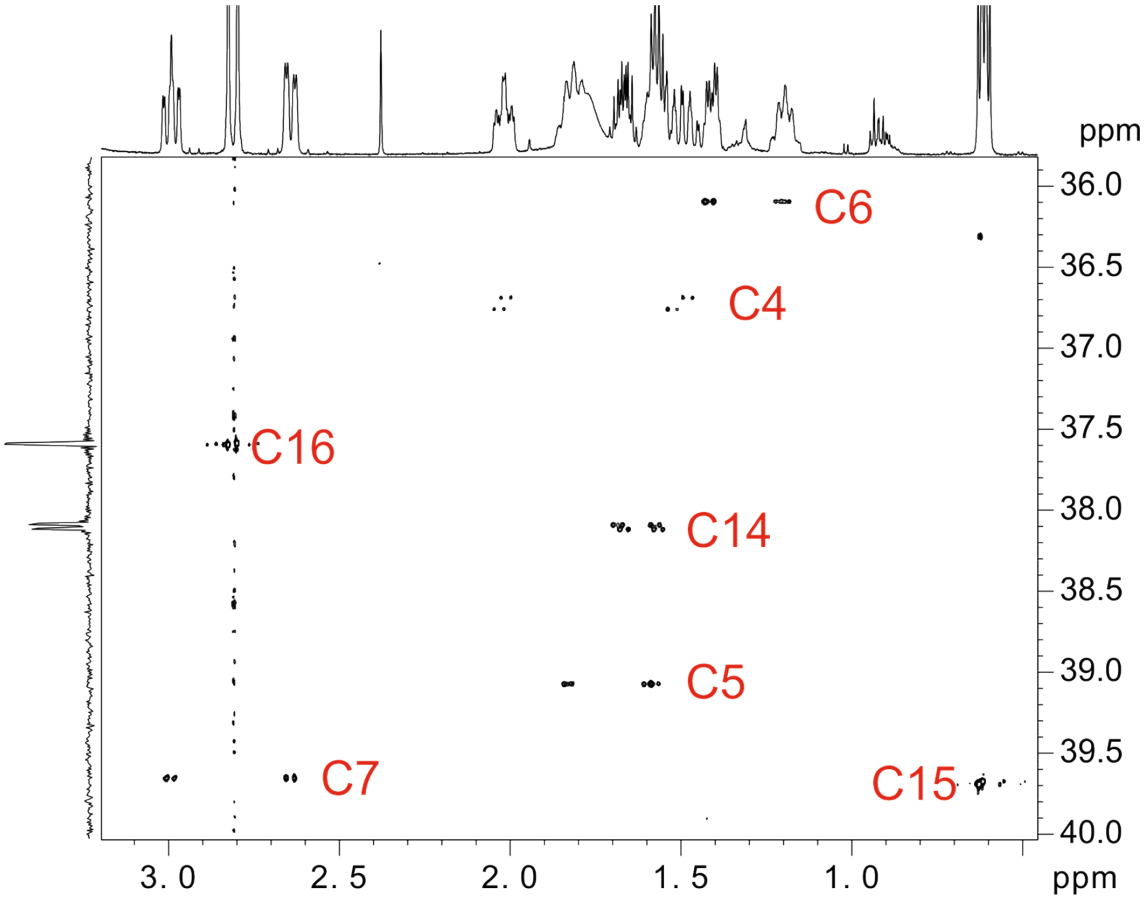


Figure S9: (top) Aliased 2D HSQMBC spectrum of **1**, acquired with a ^{13}C spectral width of 5.0 ppm. (bottom) Some selected 2D cross-peaks corresponding to quaternary carbons where $\Delta\Delta\delta(^{13}C)$ values ranging from 12.7 to 0.5 Hz (84.1 to 3.3 ppb, respectively) can be extracted from the F1 dimension.



Position	δ(^{13}C) Aliased HSQC	δ(^{13}C) HSQC	K factor
C6	36.08	26.08	-2
C4	36.67/36.75	31.67/31.75	-1
C16	37.60	37.60	0
C14	38.08/38.11	38.08/38.11	0
C15	39.06	24.06	-3
C7	39.64/39.65	49.64/49.65	2
C15	39.67/39.69	9.67/9.69	-6

Figure S10: Chemical shifts in aliased and conventional 2D psHSQCsi spectra. Experimental parameters in the indirect dimension: carrier frequency= 38.0 ppm and ^{13}C spectral width= 5 ppm.

Table S1: ^{1}H and ^{13}C NMR chemical shift differences (($\Delta\Delta\delta(^{1}H)$ and $\Delta\Delta\delta(^{13}C)$ in Hz) of racemic compound **1** (2 mM) enantiodifferentiated with *R*-PA (9.6 equiv.) measured from different NMR experiments at 600MHz.

Position	**$\Delta\Delta\delta(^{1}H)$ [in Hz]**			**$\Delta\Delta\delta(^{13}C)$ [in Hz]**			**$\Delta\Delta\delta$ (CH) [in Hz]**
	1D ^{1}H	1D ZS-^{1}H	Pure shift HSQC[c]	1D ^{13}C	Pure shift HSQC[c]	HSQMBC[b]	
2	-	-	-	2.2	-	2.2	16.1
3	-	-	-	<2	-	0.5	7.2
4a/4b	x[a]/x[a]	12.0/28.2	12.5/27.7	11.0	11.1	-	16.7/29.8
5a/5b	x[a]/x[a]	<2/ x[a]	1.5/12.6	<2	0.8	-	1.7/12.6
6a/6b	x[a]/x[a]	<2/9.4	<2/10.0	<2	<0.5	-	<1/10.0
7a/7b	x[a]/x[a]	3.5/<2	2.8/0.7	2.1	2.0	-	3.4/2.1
8	-	-	-	12.7	-	12.7	24.3
9	13.5	13.7	14.0	<2	0.7		14.0
10	-	-	-	6.6	-	6.7	21.7
11	18.5	19.1	18.4	4.1	3.9	-	18.8
12	20.7	20.9	20.7	5.9	5.8	-	21.4
13	x[a]	x[a]	19.2	<2	1.4	-	19.2
14a/14b	x[a]/x[a]	11.5/ x[a]	11.3/5.9	4.6	4.5	-	12.1/7.4
15	6.9	6.7	7.2	3.2	2.8	-	7.7
16	16.2	16.3	16.0	<2	1.5	-	16.1

[a] Not determined

[b] Only relevant data on quaternary carbons is shown

[c] Digital resolution of ±0.3 and ±0.4 Hz for ^{1}H and ^{13}C respectively.