Diastereomeric Ratio Determination by High Sensitivity Band-Selective Pure Shift NMR Spectroscopy – Electronic Supplementary Information

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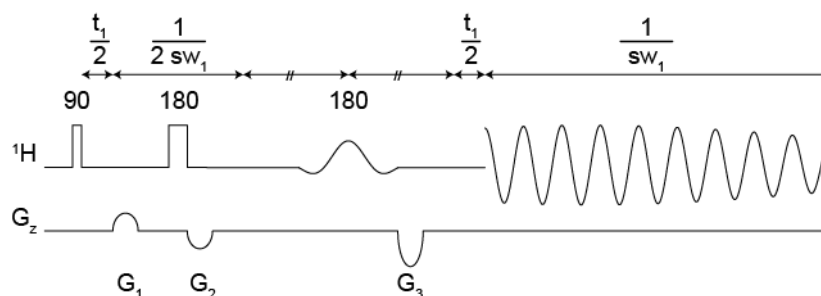
Figure S1: Pulse sequence diagram for the interferogram-based band-selective pure shift experiment. The pulse sequence is based on those in references 2 and 8 of the main manuscript but with the gradient during the band-selective refocusing pulse switched off. Gradients G_1, G_2 and G_3 in the ratio 1:-1:-2 are used to enforce the desired coherence transfer pathway. t_1 is incremented in steps of $1/sw_1$.

NMR experiments with Hesperidin

NMR experiments were acquired using a 5 kHz spectral window for 68.9 mg of commercial hesperidin sample in d_6-DMSO (1 mL) with $c.$ 3 µL tetramethylsilane. 4096 complex data points were used, with zero-filling to 16384 complex points, without weighting. The recycle time in each experiment was 5 s. 4 steady state scans were used and 16 transients. 50 chunks of data, each 16.38 ms long with 82 complex points, were collected in each of the pure shift experiments. The total acquisition times for the standard acquisition real time pure shift and experiments were 111 s, for the interferogram pure shift experiment the experiment took 73 min. The total data collected for the pure shift experiments comprised 4100 complex points so 4 complex points were discarded from the end of each of the pure shift FIDs to make them consistent with the standard acquisition FID. Experiments were performed on a Bruker Avance II+ 500 MHz spectrometer equipped with 5 mm BBO probe capable of delivering z-gradients up to 53 G cm^{-1}. For the real time pure shift experiment initial excitation was performed using a 60 ms eBURP pulse. Refocusing was performed using a 10 ms Gaussian pulse. 5.8 G cm^{-1} 500 µs half-sine gradient pulses were applied either side of the broadband pulse and 2.6 G cm^{-1} 500 µs half-sine gradient pulses were applied either side of the refocusing pulse to enforce CTP. There was a stabilisation delay of 200 µs after each gradient pulse. For the interferogram-based pure shift experiment a prefocusing element was used that contained the same Gaussian pulse as used in the real time experiment. CTP was enforced around the broadband and selective refocusing pulses using 42.4 G cm^{-1} 1500 µs half-sine gradient pulses of intensity ratio 0.5:-0.5:-1. Pseudo-2D interferogram-based pure shift experiments were reconstructed using a bespoke AU programme coded by the authors for use in Bruker Topspin versions 2 and 3, and downloadable from http://nmr.chemistry.manchester.ac.uk.

Integrals and linewidths

Integrals for both overlapping multiplets, in the range 2.87 – 2.71 ppm, normalised to the integral in the interferogram pure shift experiment: interferogram: 1.00, real time: 1.07, standard proton acquisition: 1.14. The dr values for hesperidin $2S{:}2R$, determined from the integrals are given in table S1. The linewidth (full width at half height) was measured in the NMR experiments for the signal at 2.80 ppm in the standard experiment, 2.78 ppm in the pure shift experiments. The linewidth was 2.1 Hz for the standard experiment, 2.2 Hz for the interferogram pure shift, and 3.3 Hz for the real-time pure shift.
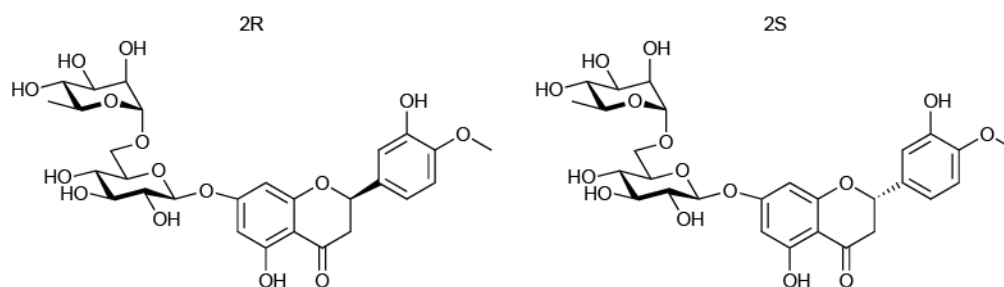
Figure S2: The chemical structures of 2R and 2S epimers of the flavanone glycoside hesperidin.

Band-selective pure shift NMR for determining dr for the amide oligomer product of 1,61-asymmetric induction.

Band-selective pure shift NMR spectra were recorded for the crude reaction mixture of an asymmetrically induced enamide reaction. A modified[8] interferogram-based Zangger-Sterk[2] pure shift sequence was used to achieve resolution of the signals diagnostic of diastereomeric ratio (dr). A frequency-selective 14575 μs (160 Hz bandwidth) rSNOB pulse, centred on the diagnostic signals, was used to refocus the effects of couplings between the diagnostic and other signals. Very high resolution was achieved by acquiring 80 chunks of data of 19.968 ms duration. The resulting 20480 complex points were Fourier transformed, zero filling to 32768 complex points, without weighting to produce a spectrum. The relevant region of the spectrum is given in Figure 3 of the main manuscript. For each chunk 4 transients were acquired. A total recycle time of 9.3 s was used to ensure full relaxation. 8 dummy scans were used. The total experiment time was 55 min. Experiments were performed on a Bruker Avance III 800 MHz spectrometer with a TCI (H-C/N-D-05-Z) CryoProbe, with maximum z-gradient of 53 G cm^{-1}.

Table S1: Signal ratios measured in the three NMR experiments using standard integration and Lorentzian lineshape fitting with the ldcon tool in Bruker Topspin 3.1 software (parameters "detection sensitivity = 1" and "peak overlapping factor = 1"). The signal ratio is directly proportional to the diastereomeric ratio (dr) 2S : 2R for the epimers of hesperidin.[23]

	Integral	Lorentzian lineshape fitting
Standard acquisition	70.9 : 29.1	74.6 : 25.4
Real time pure shift	74.6 : 25.4	75.1 : 24.9
Interferogram pure shift	75.2 : 24.8	75.1 : 24.9

Determining dr for the amide oligomer product of 1,61-asymmetric induction

The main diastereomer has *R* configuration at the benzylic chiral centre, the other two chiral centres have *S* configuration. The minor diastereomer contains only *S* configuration chiral centres. For the standard ^{1}H experiment integrating the signals in the region of interest gives a ratio of 7.2:92.8. Integrating the signals in the pure shift experiment, which allows one impurity resonance to be excluded, gives a ratio of 7.6:92.4. The signal on the shoulder of the main diastereomer signal can be removed from the integration using Lorentizan lineshape fitting. Fitting was performed using the ldcon tool in Bruker Topspin 3.1 software using the parameters Detection sensitivity = 1, Peak overlapping factor = 1. Fitting the signals in the standard coupled spectrum gives a signal area ratio of 10.7:89.3 with some impurities, visible in the pure shift experiment, distorting the ratio. Lorentzian lineshape fitting of the pure shift NMR data gives a ratio of 11.6:88.4. The ratio measured in the pure shift experiment removes contributions from impurity signals and is consistent with the value predicted for this length of achiral helix using extrapolation of results for other members of the homologous series.
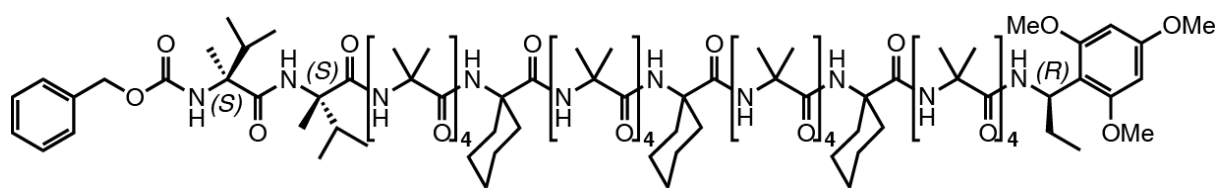
Figure S3: The amide oligomer product of 1,61-asymmetric induction through nineteen achiral residues. The rightmost chiral centre is formed in the final reaction step. Full details of the synthesis can be found in reference 12 of the main manuscript.

References

See main manuscript.