Supplementary Materials: Synthesis of Tertiary and Quaternary Amine Derivatives from Wood Resin as Chiral NMR Solvating Agents

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1. NMR Measurement and Processing Parameters

1.1. Compound Characterisation

All NMR experiments were performed using Varian UNITY INOVA 500 and Varian Mercury Plus 300 instruments at 27 °C. 1H-NMR spectra were recorded with 4–16 transients, 8000–3565 Hz spectral width, and 1.9 s acquisition time at 500 MHz. 13C-NMR spectra were recorded with 1828–816 transients, 31,446–20,000 Hz spectral width and 1–1.9 s acquisition time at 125 or 75 MHz. All 2D HSQC spectra were recorded using Varian UNITY INOVA 500 with 4 transients, 250–128 increments, 8000–4278 Hz spectral width in 1H-dimension, 25133–241546 Hz spectral width in 13C-dimension, 1.0–2.0 s relaxation delay, and 1.3 s acquisition time.

1.2. Resolution Experiments

All NMR measurements were recorded using Varian UNITY INOVA 500 at 27 °C. 1H-NMR spectra were recorded with 16 transients, 8000 Hz spectral width, 5.0 s relaxation delay and 1.9 s acquisition time at 500 MHz. 19F-NMR spectra were recorded with 16–32 transients, 19047 Hz spectral width, 5.0 s relaxation delay and 1.0 s acquisition time at 470 MHz. HSQC spectra were recorded using Varian UNITY INOVA 500 with 32 transients, 300 increments, 2.0 s relaxation delay and 0.128 s acquisition time. The spectral widths were 4157 Hz and 212653 Hz in 1H- and 13C-dimensions, respectively. NOESY experiments with 0.4 ms mixing time were recorded with 16 transients, 300 increments, 2.0 relaxation delay and 0.24 s acquisition time at 500 MHz. Spectral width in both dimensions was 4157 Hz.

2. Chiral Recognition Studies

Solutions of 3 and 4 (22.0 mM in CDCl3) were prepared. Compound 2–9c (1.0 eq or 2.0 eq) was dissolved in 0.5 mL (1.0 eq) of prepared solution and both 1H- and 19F-NMR spectra were recorded.

Figure S1. Host:guest ratio 1:1 both (a) 1H- (−OCH3) and (b) 19F-NMR (−CF3) spectra of 3.
Figure S2. Host:guest ratio 2:1 both (a) $^1$H- (–OCH$_3$) and (b) $^{19}$F-NMR (–CF$_3$) spectra of 3.

Figure S3. Host:guest ratio 1:1 both (a) $^1$H- (–OCH$_3$) and (b) $^{19}$F-NMR (–CF$_3$) spectra of 4.

Figure S4. Host:guest ratio 2:1 both (a) $^1$H- (–OCH$_3$) and (b) $^{19}$F-NMR (–CF$_3$) spectra of 4.
3. Titration

For titration, solutions containing the guest (2.0 mM) and host (46.6 mM) were prepared and 0.5 mL of guest solution was measured into an NMR tube. Guest was titrated by 2.5 or 5.0 μ doses of host solution. Both 1H- and 19F-NMR spectra were recorded.

3.1. Titration of 3 with 5

Concentration of guest (3) is presumed to remain constant during titration.

![Figure S5. (a) Δδ on 1H-NMR (b) Δδ on 19F-NMR.](image)

| c of 1 (μM) | V of 1 (mL) | δ of S (ppm) | δ of R (ppm) | Δδ of S (ppm) | Δδ of R (ppm) | δ of S (ppm) | δ of R (ppm) | Δδ of S (ppm) | Δδ of R (ppm) |
|------------|-------------|-------------|-------------|--------------|--------------|-------------|-------------|--------------|--------------|
| 0          | 0           | 3.535       | 3.535       | 0            | 0            | -71.082     | -71.082     | 0            | 0            |
| 0.461386139 | 0.005       | 3.516       | 3.51        | 0.019        | 0.025        | -71.172     | -71.201     | 0.09         | 0.119        |
| 0.91372549  | 0.01        | 3.505       | 3.489       | 0.03         | 0.046        | -71.24      | -71.296     | 0.158        | 0.214        |
| 1.357281553 | 0.015       | 3.501       | 3.475       | 0.034        | 0.06         | -71.271     | -71.362     | 0.189        | 0.28         |
| 1.575845411 | 0.0175      | 3.501       | 3.47        | 0.034        | 0.065        | -71.274     | -71.38      | 0.192        | 0.298        |
| 1.792307692 | 0.02        | 3.501       | 3.467       | 0.034        | 0.068        | -71.271     | -71.392     | 0.189        | 0.31         |
| 2.006698565 | 0.0225      | 3.502       | 3.465       | 0.033        | 0.07         | -71.266     | -71.396     | 0.184        | 0.314        |
| 2.219047619 | 0.025       | 3.503       | 3.465       | 0.032        | 0.07         | -71.26      | -71.399     | 0.178        | 0.317        |
| 2.637735849 | 0.03        | 3.505       | 3.464       | 0.03         | 0.071        | -71.254     | -71.399     | 0.172        | 0.317        |
| 3.048598131 | 0.035       | 3.503       | 3.464       | 0.032        | 0.071        | -71.25      | -71.397     | 0.168        | 0.315        |
| 3.451851852 | 0.04        | 3.507       | 3.465       | 0.028        | 0.07         | -71.248     | -71.397     | 0.166        | 0.315        |
| 3.847706422 | 0.045       | 3.507       | 3.465       | 0.028        | 0.07         | -71.247     | -71.396     | 0.165        | 0.314        |
| 4.236363636 | 0.05        | 3.507       | 3.465       | 0.028        | 0.07         | -71.247     | -71.396     | 0.165        | 0.314        |
| 4.618018018 | 0.055       | 3.508       | 3.466       | 0.027        | 0.069        | -71.244     | -71.394     | 0.162        | 0.312        |
| 4.992857143 | 0.06        | 3.508       | 3.466       | 0.027        | 0.069        | -71.245     | -71.394     | 0.163        | 0.312        |
Figure S6. (a) The change of chemical shifts of S and R enantiomers of 3 and (b) the magnitude of non-equivalence (Δδ) of 3, as a function of the concentration of 5 (☐ R enantiomer and + S enantiomer) at 1H-NMR.

Figure S7. (a) The change of chemical shifts of S and R enantiomers of 3 and (b) the magnitude of non-equivalence (Δδ) of 3, as a function of the concentration of 5 (☐ R enantiomer and + S enantiomer) at 19F-NMR.

Figure S8. Job’s plot.

3.2. Titration of 4 with 6

Concentration of guest (4) is presumed to remain constant during titration.

| c of 1 (µM) | V of 1 (mL) | δ of S (ppm) | δ of R (ppm) | Δδ of S (ppm) | Δδ of R (ppm) | δ of S (ppm) | δ of R (ppm) | Δδ of S (ppm) | Δδ of R (ppm) |
|------------|------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|
| 0          | 0          | 3.63         | 3.63         | 0            | 0            | -70.611      | -70.611      | 0            | 0            |
| 0.230693069| 0.0025     | 3.612        | 3.612        | 0.018        | 0.018        | -70.814      | -70.814      | 0.203        | 0.203        |
| 0.461386139| 0.005      | 3.601        | 3.601        | 0.029        | 0.029        | -70.907      | -70.926      | 0.296        | 0.315        |
| 0.91372549 | 0.01       | 3.565        | 3.547        | 0.065        | 0.083        | -71.158      | -71.22       | 0.547        | 0.609        |
| 1.357281553| 0.015      | 3.535        | 3.51         | 0.095        | 0.12         | -71.255      | -71.344      | 0.644        | 0.733        |
| 1.792307692| 0.02       | 3.499        | 3.464        | 0.131        | 0.166        | -71.261      | -71.383      | 0.65         | 0.772        |
| 2.219047619| 0.025      | 3.495        | 3.462        | 0.135        | 0.168        | -71.236      | -71.354      | 0.625        | 0.743        |
| 2.637735849| 0.03       | 3.491        | 3.459        | 0.139        | 0.171        | -71.205      | -71.322      | 0.594        | 0.711        |
| 3.048598131| 0.035      | 3.49        | 3.458        | 0.14         | 0.172        | -71.181      | -71.297      | 0.57         | 0.686        |
| 3.451851852| 0.04       | 3.487        | 3.456        | 0.143        | 0.174        | -71.155      | -71.271      | 0.544        | 0.66         |
| 3.847706422| 0.045      | 3.483        | 3.454        | 0.147        | 0.176        | -71.127      | -71.238      | 0.516        | 0.627        |
| 4.236363636| 0.05       | 3.48        | 3.452        | 0.15         | 0.178        | -71.101      | -71.21       | 0.49         | 0.599        |
| 4.618018018| 0.055      | 3.477        | 3.451        | 0.153        | 0.179        | -71.075      | -71.182      | 0.464        | 0.571        |
| 4.992857143| 0.06       | 3.475        | 3.45         | 0.155        | 0.18         | -71.062      | -71.17       | 0.451        | 0.559        |
Figure S9. (a) $\Delta\delta$ on $^1$H-NMR (b) $\Delta\delta$ on $^{19}$F-NMR.

Figure S10. (a) The change of chemical shifts of S and R enantiomers of 4 and (b) the magnitude of non-equivalence ($\Delta\delta$) of 4, as a function of the concentration of 6 (☐ R enantiomer and + S enantiomer) at $^1$H-NMR.

Figure S11. (a) The change of chemical shifts of S and R enantiomers of 4 and (b) the magnitude of non-equivalence ($\Delta\delta$) of 4, as a function of the concentration of 6 (☐ R enantiomer and + S enantiomer) at $^{19}$F-NMR.

Figure S12. Job’s plot.
4. Enantiomeric Excess Measurements

For ee determination studies, solutions of racemic 3 and S-3 (as well as 4 and S-4) were made (2.0 mM). Mixtures of enantiomerically enriched samples were prepared in an NMR tube (0.5 mL, 1.0 eq), CSA added (22.5 μ, 46.6 mM, 1.0 eq) and spectra recorded.

4.1. Enantiomeric Excess Measurements of 3 with 5

Table S3. ee% determined from 1H-NMR spectra.

| S (mL) | R/S (mL) | Expected S/R | Measured S/R | Area S | Area R | Expected ee% (S) | Measured ee% (S) |
|-------|----------|--------------|--------------|--------|--------|-----------------|-----------------|
| 0     | 0.5      | 1            | 1.009820258  | 5758.292 | 5702.294 | 50              | 50.24430688     |
| 0.1   | 0.4      | 1.5          | 1.718569863  | 6547.05  | 3809.592 | 60              | 63.21595359     |
| 0.2   | 0.3      | 2.333        | 2.148910936  | 7841.881 | 3649.235 | 70              | 68.24298876     |
| 0.25  | 0.25     | 3            | 2.872851376  | 8265.406 | 2877.074 | 75              | 74.17923119     |
| 0.3   | 0.2      | 4            | 3.758461241  | 9028.023 | 2402.053 | 80              | 78.98480308     |

Figure S13. Results from ee% determination (1H-NMR).

Table S4. ee% determined from 19F-NMR spectra.

| S (mL) | R/S (mL) | Expected S/R | Measured S/R | Area S | Area R | Expected ee% (S) | Measured ee% (S) |
|-------|----------|--------------|--------------|--------|--------|-----------------|-----------------|
| 0     | 0.5      | 1            | 0.888463708  | 1115.388 | 1255.412 | 50              | 47.046904       |
| 0.1   | 0.4      | 1.5          | 1.299177815  | 1089.041 | 838.254  | 60              | 56.50619132     |
| 0.2   | 0.3      | 2.333        | 1.767438588  | 1105.22  | 625.323  | 70              | 63.86550349     |
| 0.25  | 0.25     | 3            | 3.516458349  | 1842.48  | 523.959  | 75              | 77.8587574      |
| 0.3   | 0.2      | 4            | 4.737135083  | 1444.992 | 305.035  | 80              | 82.5696975      |

Figure S14. Results from ee% determination (19F-NMR).
4.2. Enantiomeric Excess Measurements of 4 with 6

Table S5. ee% determined from 1H-NMR spectra.

| S (mL) | R/S (mL) | Expected S/R | Measured S/R | Area S | Area R | Expected ee% (S) | Measured ee% (S) |
|--------|----------|--------------|--------------|--------|--------|-----------------|-----------------|
| 0      | 0.5      | 1            | 1.160136853  | 6054.441 | 5218.73 | 50              | 53.70663676     |
| 0.1    | 0.4      | 1.5          | 1.466312442  | 7015.893 | 4784.719 | 60              | 59.45363681     |
| 0.2    | 0.3      | 2.333        | 2.430381361  | 9471.551 | 3897.146 | 70              | 70.84872221     |
| 0.25   | 0.25     | 3            | 3.289686745  | 8685.477 | 2640.214 | 75              | 76.68827447     |
| 0.3    | 0.2      | 4            | 4.025612356  | 8939.778 | 2220.725 | 80              | 80.10192731     |

Figure S15. Results from ee% determination (1H-NMR).

Table S6. ee% determined from 19F-NMR spectra.

| S (mL) | R/S (mL) | Expected S/R | Measured S/R | Area S | Area R | Expected ee% (S) | Measured ee% (S) |
|--------|----------|--------------|--------------|--------|--------|-----------------|-----------------|
| 0      | 0.5      | 1            | 0.980533751  | 5213.697 | 5317.203 | 50              | 49.50856052     |
| 0.1    | 0.4      | 1.5          | 1.438918884  | 5676.158 | 3944.738 | 60              | 58.99822636     |
| 0.2    | 0.3      | 2.333        | 2.122697901  | 6909.076 | 3254.856 | 70              | 67.97640913     |
| 0.25   | 0.25     | 3            | 3.414083583  | 7432.518 | 2177.017 | 75              | 77.34524095     |
| 0.3    | 0.2      | 4            | 3.549660407  | 6804.699 | 1917.00  | 80              | 78.02033755     |

Figure S16. Results from ee% determination (19F-NMR).

5. Resolution of racemic carboxylic acids

For chiral recognition ability determination study of racemic carboxylic acids, solutions of different racemic carboxylic acids (n-Bu4N salts of carboxylic acids in the case of 6) were prepared (2.0 mM). Experiment was performed by adding 22.5 μ of solution containing host (46.6 mM, 1.0 eq) to NMR tube containing 0.5 mL of guest (2.0 mM, 1.0 eq) and recording the spectra.
2.2. Separation of Carboxylic Acids with 5

Table S7. Determination of magnitude of non-equivalences (Δδ) of five racemic carboxylic acids in the presence of 5, using ¹H-NMR (500 MHz) in CDCl₃ at 27 °C.

| No. | Racemic Carboxylic Acid | Actual Multiplet | Spectra (If Split Is Detected) | Δδ   |
|-----|-------------------------|------------------|--------------------------------|------|
| 10a |ellarbutol| Me d | ![Spectra](image1.png) | 0.0023 |
| 11a | Phenylbutylic Acid| H q | ![Spectra](image2.png) | 0.0059 |
| 12a | Benzyl Alcohol| H q | ![Spectra](image3.png) | 0.0047 |
| 13a | Lactic Acid| Me d | ![Spectra](image4.png) | 0.013 |
| No. | Racemic Carboxylic Acid | Actual Multiplet | Spectra (If Split Is Detected) | \( \Delta \delta \) |
|-----|------------------------|------------------|-----------------------------|------------------|
|     |                        |                  | ![Spectra Image](image1) | 0.012            |
|     |                        |                  | ![Spectra Image](image2) | 0.013            |
| 14a | ![Molecule Image](image3) |                  | ![Spectra Image](image4) | 0.0028           |
|     |                        |                  | ![Spectra Image](image5) | 0.072            |
|     |                        |                  | ![Spectra Image](image6) | 0.027            |
|     |                        |                  | ![Spectra Image](image7) |                  |
| 15a | ![Molecule Image](image8) |                  | ![Spectra Image](image9) | 0.023            |
|     |                        |                  | ![Spectra Image](image10) | 0.016            |
| 16a | ![Molecule Image](image11) |                  | ![Spectra Image](image12) | 0.020            |
5.2. Separation of Carboxylic Acid n-Bu4N Salts with 6

Table S8. Determination of magnitude of non-equivalences (Δδ) of five racemic carboxylic acid n-Bu4N salts in the presence of 6, using 1H-NMR (500 MHz) in CDCl3 at 27 °C.

| No. | n-Bu4N Salt of Racemic Carboxylic Acid | Actual Multiplet | Spectra | Δδ    |
|-----|--------------------------------------|------------------|---------|-------|
| 10b | ![Structure 10b](image1.png)          | Me d             | -       | -     |
| 11b | ![Structure 11b](image2.png)          | Me d             | 0.0041  | 1.56 ppm 1.52 |
| No. | n-BuN Salt of Racemic Carboxylic Acid | Actual Multiplet | Spectra | $\Delta \delta$ |
|-----|--------------------------------------|-----------------|---------|--------------|
| 11b | ![Image](image1.png) H q             | ![Spectrum](spectrum1.png) | 0.0021  |
| 12b | ![Image](image2.png) H q             | ![Spectrum](spectrum2.png) | -       |
| 13b | ![Image](image3.png) Me d            | ![Spectrum](spectrum3.png) | 0.017   |
| 14b | ![Image](image4.png) NH d            | ![Spectrum](spectrum4.png) | 0.014   |
6. Modified RES-TOCSY, A Phase Sensitive Version

Recently, Lokesh et al., reported new homonuclear 2D technique, RES-TOCSY [1], for obtaining improved separation of enantiomer spectra when chiral resolving agents are utilized. RES-TOCSY is based on homonuclear decoupling in f₁-dimension for selectively excited protons and for the whole coupled homonuclear spin system. Homonuclear decoupling is achieved by applying selective refocusing pulse followed by non-selective 180° pulse in between t₁-period. The net effect is thus 0° pulse for selected protons and 180° pulse for other protons leading to homonuclear decoupling for the selected protons (and thus collapse of the multiplets into a single lines in f₁-dimension) while retaining chemical shift evolution of the selected protons. Subsequent TOCSY-period transfers the magnetization through entire coupled homonuclear spin system. The original RES-TOCSY is a
magnitude mode experiment with two selective pulses (90° and 180°) and the coherence selection is performed by phase cycling. The modified RES-TOCSY pulse sequence utilized in this work is presented in Figure S19 and pulse sequence code in Varian syntax is shown in the end of this section. The presented pulse sequence is actually a simplified BASHD-TOCSY [2,3] where a single selective 180° pulse flanked by pulsed field gradient of opposite amplitudes is applied, followed by a non-selective 180° pulse in the middle of t1-period. Gradients with opposite polarities \( g_1 \) label the desired magnetization and, as with original RES-TOCSY, the net effect of the two pulses allows selective homonuclear decoupling in f1-dimension. After t1-period TOCSY transfers the magnetization throughout the spin system and finally magnetization with gradient encoding is refocused during spin-echo period prior to the acquisition (AQ). Phase sensitive data is obtained with echo-anti echo method, where N- and P-type coherences are recorded separately by inverting the polarity of the refocusing gradient \( g_2 \). Since all signals in the f1-dimension of the resulting spectrum are originating from the excitation bandwidth of the selective pulse, it is possible to utilize small spectral width in the indirectly detected dimension.

![Figure S19. Pulse sequence for phase sensitive BASHD-TOCSY-based [2,3] RES-TOCSY [1] utilizing single selective 180° pulse and gradient selection. Narrow and wide black bars represent hard 90° and 180° rectangular pulses, respectively, while black half ellipse indicates multiplet selective 180° pulse. Low-power TOCSY spinlock sequence is indicated by grey rectangle denoted MLEV-17[4] flanked by two trim pulses (tr1 and tr2). Pulsed field gradients are represented by rectangles marked with \( g_1 \) and \( g_2 \). Delay t1 represents incremented delay while delays t1 and t2 include gradient pulse duration and following eddy current recovery delay. Phase cycle: \( \phi_1 = y, -y; \phi_2 = x, x, y, y; \phi_3 = x, x, x, y, y, y, y; \phi_4 = x, -x; \phi_5 = x, x, x, -x, -x, x, x, -x \). The N-and P-type coherences are separately recorded by inverting the sign of the gradient \( g_2 \). Axial peak displacement is obtained using States-TPPI method [5] by inverting the phases \( \phi_1 \) and \( \phi_R \) on every second increment.]

Figure S18 show expansion of 2D spectrum recorded with pulse sequence presented in Figure S19 from 2.0 mM racemic N-acetyl-phenylalanine sample doped with CSA 5 with 1:1 host:guest ratio in CDCl3. The selective 180° pulse was applied at enantiomeric resonances at 4.67 ppm. The separation between the enantiomers \( \Delta \delta = 6.1 \) Hz for the selectively inverted proton is present in each expansion (TOCSY transfer). Due to homonuclear decoupling, multiplets collapse into single lines in f1-dimension and thus allow good separation of the enantiomeric signals. Obviously, if the CSA induced \( \Delta \delta \) between the enantiomer signals is of same magnitude as natural line width, baseline separation is naturally not possible even with homonuclear decoupling. Figure S21 shows expansion of the modified RES-TOCSY spectrum recorded from 2.0 mM ketoprofen sample doped with the same CSA as well as f2-traces extracted from locations marked by arrows. Since \( \Delta \delta \) and linewidth in f1-dimension are of similar magnitude (~2.0 Hz), some cross talk between the traces is unavoidable. The data in Figure S19 was acquired by selectively inverting multiplet region at 1.55 ppm. Other acquisition and processing parameters were identical to data presented in Figure S20.

The results by Lokesh et al. [1], suggested the possibility to utilize 2D RES-TOCSY to actually estimate ee% values with good accuracy. Obviously, in order to obtain reliable results, there should not be significant differences in host-guest association constants between the enantiomers. Such big differences could easily result in a significant difference also in transverse relaxation times, \( T_2 \) (i.e., one enantiomer has significantly shorter \( T_2 \) than the other due to stronger interaction with the host), and thus the corresponding magnetization experiences more attenuation during the pulse sequence.
(relatively long selective pulses as well as TOCSY mixing emphasize this). This would lead to an underestimation of the corresponding enantiomer signal and thus erroneous ee%. The aforementioned result could be the most pronounced when the chiral auxiliary is a very large molecule or polymer. Then, depending on the differences in association constant, the molecular mobilities can be very different, leading to differences in T<sub>2</sub>. For small auxiliaries and relatively weak association, this is likely not a major problem. One could speculate that, if a significant difference appears in line the widths of relevant signals, RES-TOCSY-based method cannot be reliably utilized for ee% determination. In general, one may assume only small differences in quantitation affecting NMR properties (relaxation times, coupling constants) of enantiomer signals when chiral auxiliaries are used. Provided coupling constants (heteronuclear, homonuclear), relaxation times (T<sub>1</sub>, T<sub>2</sub>) or internuclear distances remain essentially the same in both resolved enantiomers, rather many classic 2D NMR methods can be used for ee% determination, at least at a semi quantitative level.

**Figure S20.** Expansion of modified RES-TOCSY spectrum of 2.0 mM racemic N-acetylated phenylalanine sample with equimolar amount of CSA 5 in CDCl<sub>3</sub>. The 2D experiment was performed at 27 °C using a Varian Unity INOVA 500 spectrometer equipped with PFG inverse-detection probehead incorporating z-gradient coil capable of delivering gradient amplitudes up to up to 20 G/cm. Spectral widths were 4550 Hz (f<sub>2</sub>) and 25 Hz in the 1H-decoupled dimension (f<sub>1</sub>). The 2D data was acquired using 16 steady state scans, 8 transients and 25 increments. The number of acquired complex point was 4550 corresponding acquisition time of 1.0 s. The relaxation delay was 0.5 s. The duration for hard rectangular 'H 90° pulse was 7.1 μs. The pulses in MLEV-17 TOCSY-period were applied at RF-power of 7.7 kHz. Durations for trim pulses were 1.0 ms (tr1) and 1.6 ms (tr2). TOCSY mixing time was 60 ms. RE-BURP shape<sup>6</sup> was used for multiplet selective refocusing pulse of duration 97.5 ms, corresponding excitation bandwidth of 50 Hz. Selective pulse was applied at protons resonating at 4.67 ppm. Gradient strengths (durations) were: g<sub>1</sub> = 5.0 G/cm (1.0 ms), and g<sub>2</sub> = -5.0 G/cm (2.0 ms). All the gradients were block shaped. The data was apodized using gaussian functions in both dimensions (1.5 Hz gaussian broadening) and zero-filled up to 8192 × 256 complex points prior to Fourier transformation (MestReNova 10.0.1, Mestrelab Research S.L.)

**Figure S21.** Expansion of the selectively inverted region of the modified RES-TOCSY spectrum from a 2.0 mM racemic ketoprofen sample with an equimolar amount of CSA 5 in CDCl<sub>3</sub>. The traces (a) and (b) represent doublets of each enantiomeric signal.
References

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6.1. Pulse Sequence

/* Modified RES-TOCSY –with MLEV17 spinlock and gradient coherence selection

Selective 180 pulse applied at selfrq-frequency. During t1, transmitter is at selfrq, while during detection transmitter is at tof.

Use normal sw and small sw1

Features included:
Axial peak displacement in F1
Randomization of Magnetization prior to relaxation delay G-90-G - with PFG
Solvent suppression during relaxation delay

For phase sensitive data use f1coef = '1 0 1 0 0 1 0 -1'

Parameters

sspul : y - selects magnetization randomization option
hsgvlv1 : Homospoil gradient level (DAC units)
hsgr : Homospoil gradient time
satmode : y - selects presaturation during relaxation delay
satfrq: presaturation frequency
satdly : presaturation delay
satpwr : presaturation power
selfrq : Selective frequency (for selective 90 and 180)
selwpwr180 : Power for selective 180 deg pulse
selw180 : Selective 180 deg pulse width
selshape180: Selective 180 deg pulse shape
gzvlv1 : Coherence selection gradient level
gv1 : Coherence selection gradient duration
gzvlv2 : Coherence selection gradient level
gv2 : Coherence selection gradient duration
gstab : Eddy current recovery delay
mix : TOCSY (MLEV17) spinlock mixing time
trim1 : trim pulse preceding spinlock
trim2 : trim pulse after spinlock
slpwr : spin-lock power level
slpw : 90 deg pulse width for spinlock
d1 : Relaxation delay
d2 : Evolution delay

S.H. 17.4.2015

*/

#include <standard.h>

static double d2_init = 0.0;

static int ph11[2] = [1,3],
    ph12[4] = [0,0,1,1],
    ph13[8] = [0,0,0,0,1,1,1,1],
    ph2[2] = [0,2],
    ph3[2] = [3,1],
    ph4[2] = [0,2],
    ph5[2] = [1,3],
    ph6[2] = [2,0],
    ph7[2] = [0,2],
    ph8[2] = [0,2],
    ph31[8] = [0,2,2,0,2,0,0,2];

pulsesequence()
{
    char sspul[MAXSTR],
    satmode[MAXSTR],
    selshape180[MAXSTR];

    int t1_counter,
    icosel;

    double selfrq = getval("selfrq"),
    selpwr180 = getval("selpwr180"),
    selpw180 = getval("selpw180"),
    slpwr = getval("slpwr"),
slpw = getval("slpw"),
trim1 = getval("trim1"),
trim2 = getval("trim2"),
mix = getval("mix"),
hsgvl1 = getval("hsgvl1"),
hsgt = getval("hsgt"),
gzlvl1 = getval("gzlvl1"),
gt1 = getval("gt1"),
gzlvl2 = getval("gzlvl2"),
gt2 = getval("gt2"),
gstab = getval("gstab"),
satfrq = getval("satfrq"),
satpwr = getval("satpwr"),
satdly = getval("satdly"),
phase = getval("phase"),
cycles;

/* LOAD VARIABLES */
getstr("satmode",satmode);
getstr("sspul", sspul);
getstr("selshape180",selshape180);

cycles = (mix - (trim1+trim2) ) / ( (64.66*slpw)+ 98.0e-6 );
cycles = 2.0*(double) (int) (cycles/2.0);
initval(cycles, v9); /* V9 is the MIX loop count */

settable(t11,2,ph11);
settable(t12,4,ph12);
settable(t13,8,ph13);
settable(t2,2,ph2);
settable(t3,2,ph3);
settable(t4,2,ph4);
settable(t5,2,ph5);
settable(t6,2,ph6);
settable(t7,2,ph7);
settable(t8,2,ph8);
settable(t31,8,ph31);

if (phase == 1)
  icosel = +1;
if (phase == 2)
  icosel = -1;

/* Calculate modifications to phases based on current t1/t2 values
 for axial displacement */

if(ix==1)
  d2_init = d2;

t1_counter = (int) ( (d2-d2_init)*sw1 + 0.5);
if(t1_counter % 2)
{
  tsadd(t11,2,4);
  tsadd(t31,2,4);
}

if(ix == 1)
{
  printf("The precise mixing time is %f\n",(cycles*64.66*slpw + 98.0e-6 + trim1 + trim2));
}

/* CHECK VALIDITY OF PARAMETERS */

if( satpwr > 8 )
{
  printf("Presaturation power satpwr too large !!! ");
  abort(1);
}

if(mix > 0.250)
{
  printf("The time mix is too long");
  abort(1);
}

if(slpwr > 44)
{
  printf("Toesy spinlock power slpwr is too high; must be < 45\n");
  abort(1);
}
/^ BEGIN ACTUAL PULSE SEQUENCE CODE */

status(A);

obspower(tpwr);

obsoffset(tof);

if (sspul[0] == 'y')
{
  zgradpulse(hsglvl,hsgt);
  rgpulse(pw,zero,rof1,rof1);
  zgradpulse(hsglvl,hsgt);
}

delay(d1);

if (satmode[0] == 'y')
{
  if (satfrq != tof)
    obsoffset(satfrq);
  obspower(satpwr);
  rgpulse(satdly,zero,rof1,rof1);
  obspower(tpwr);
  if (satfrq != tof)
    obsoffset(tof);
}

obsoffset(selfrq);

status(B);

rgpulse(pw,t11,2.0e-6,0.0);

delay(0.5*d2);

txphase(t12);

obspower(selpwr180);

zgradpulse(1.0*gzlvl1,gt1);

delay(gstab);
shaped_pulse(selshape180,selpw180,t12,20.0e-6,20.0e-6);

txphase(t13);
obspower(tpwr);

zgradpulse(-1.0*gzlv11,gt1);
delay(gstab);

rgpulse(2.0*pw,t13,2.0e-6,2.0e-6);

delay(0.5*d2);

obspower(slpwr);

txphase(t2);

obsoffset(tof);

if (cycles > 1.0)
{
    rcvroff();
    txphase(t2);
    rgpulse(trim1, t2, 1.0e-6, 1.0e-6);

    starthardloop(v9);
    /* A */
    txphase(t3);
    rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
    txphase(t4);
    rgpulse(2.0*slpw, t4, 1.0e-6, 1.0e-6);
    txphase(t3);
    rgpulse(slpw, t3, 1.0e-6, 1.0e-6);

    /* A */
    txphase(t3);
    rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
    txphase(t4);
    rgpulse(2.0*slpw, t4, 1.0e-6, 1.0e-6);
    txphase(t3);
    rgpulse(slpw, t3, 1.0e-6, 1.0e-6);

    /* B */
    txphase(t5);
    rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
txphase(t6);
rgpulse(2.0*slpw, t6, 1.0e-6, 1.0e-6);
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
/* B */
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
txphase(t6);
rgpulse(2.0*slpw, t6, 1.0e-6, 1.0e-6);
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
/* B */
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
txphase(t6);
rgpulse(2.0*slpw, t6, 1.0e-6, 1.0e-6);
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
/* A */
txphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
txphase(t4);
rgpulse(2.0*slpw, t4, 1.0e-6, 1.0e-6);
txphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
/* A */
txphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
txphase(t4);
rgpulse(2.0*slpw, t4, 1.0e-6, 1.0e-6);
txphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
/* B */
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
txphase(t6);
rgpulse(2.0*slpw, t6, 1.0e-6, 1.0e-6);
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
/* B */
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
taxphase(t6);
rgpulse(2.0*slpw, t6, 1.0e-6, 1.0e-6);
taxphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
/* B */
taxphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
taxphase(t6);
rgpulse(2.0*slpw, t6, 1.0e-6, 1.0e-6);
taxphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
/* A */
taxphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
taxphase(t4);
rgpulse(2.0*slpw, t4, 1.0e-6, 1.0e-6);
taxphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
/* A */
taxphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
taxphase(t4);
rgpulse(2.0*slpw, t4, 1.0e-6, 1.0e-6);
taxphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
/* A */
taxphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
taxphase(t4);
rgpulse(2.0*slpw, t4, 1.0e-6, 1.0e-6);
taxphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
/* B */
taxphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
taxphase(t6);
rgpulse(2.0*slpw, t6, 1.0e-6, 1.0e-6);
taxphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
/* B */

txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);
txphase(t6);
rgpulse(2.0*slpw, t6, 1.0e-6, 1.0e-6);
txphase(t5);
rgpulse(slpw, t5, 1.0e-6, 1.0e-6);

/* A */

txphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);
txphase(t4);
rgpulse(2.0*slpw, t4, 1.0e-6, 1.0e-6);
txphase(t3);
rgpulse(slpw, t3, 1.0e-6, 1.0e-6);

txphase(t7);
rgpulse(0.66*slpw, t7, 1.0e-6, 1.0e-6);
endhardloop();


txphase(t8);
rgpulse(trim2, t8, 1.0e-6, 1.0e-6);
rcvron();
}
delay(gt2 + gstab + 2.0*GRADIENT_DELAY);
obspower(tpwr);
rgpulse(2.0*pw,zero,2.0e-6,2.0e-6);
zgradpulse(icosel*-1.0*gzlv2,gt2);
delay(gstab + POWER_DELAY);
status(C);
setreceiver(t31);
}
7. NMR Spectra of Synthesised CSAs

7.1. $^1$H, $^{13}$C and HSQC Spectra of Compound 5

Figure S22. $^1$H Spectra of Compound 5.
Figure S23. $^{13}$C Spectra of Compound 5.

| Parameter      | Value                      |
|----------------|----------------------------|
| Origin         | Varian                     |
| Spectrometer   | Inova                      |
| Solvent        | CDCl$_3$                   |
| Temperature    | 27.0                       |
| Pulse Sequence | gHSQC                      |
| Setup          | HSQC-EDITED                |
| Phase          | unboby                     |
| Number of Scan | 4                          |
| Receiver Gain  | 36                         |
| Relaxation Delay | 1.00000                  |
| Pulse Width    | 0.30000                    |
| Acquisition Time | 0.10000                  |
| Spectrometer Frequency | 600.000 - 125.46          |
| Spectral Width | 2213.6 - 25133.0           |
| Lowest Frequency | -7713.5 - 15553.0         |
| nucleus        | 1H                 13C       |
| Acquired Size  | 8000 - 10000              |
| Spectral Size  | 6000 - 6000               |

Figure S24. HSQC Spectra of Compound 5.

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7.2. $^1$H, $^{13}$C and HSQC Spectra of Compound 6

**Figure S25.** $^1$H Spectra of Compound 6.

**Figure S26.** $^{13}$C Spectra of Compound 6.
Figure S27. HSQC Spectra of Compound 6.

7.3. $^1$H, $^{13}$C and HSQC Spectra of Compound 7a

Figure S28. $^1$H Spectra of Compound 7a.
Figure S29. $^{13}$C Spectra of Compound 7a.

Figure S30. HSQC Spectra of Compound 7a.
7.4. $^1$H, $^{13}$C and HSQC Spectra of Compound 7b

Figure S31. $^1$H Spectra of Compound 7b.

Figure S32. $^{13}$C Spectra of Compound 7a.
7.5. $^1$H, $^{13}$C and HSQC Spectra of Compound 7c

Figure S33. HSQC Spectra of Compound 7a.

Figure S34. $^1$H Spectra of Compound 7c.
Figure S35. $^{13}$C Spectra of Compound 7c.

Figure S36. HSQC Spectra of Compound 7c.
7.6. $^1$H, $^{13}$C and HSQC Spectra of Compound 8a

Figure S37. $^1$H Spectra of Compound 8a.
Figure S38. $^{13}$C Spectra of Compound 8a.

Figure S39. HSQC Spectra of Compound 8a.
7.7. \(^1\)H, \(^{13}\)C and HSQC Spectra of Compound 8b

Figure S40. \(^1\)H Spectra of Compound 8b.

Figure S41. \(^{13}\)C Spectra of Compound 8b.
Figure S42. HSQC Spectra of Compound 8b.

7.8. $^1$H, $^{13}$C and HSQC Spectra of Compound 8c

Figure S43. $^1$H Spectra of Compound 8c.
Figure S44. $^{13}$C Spectra of Compound 8c.

Figure S45. HSQC Spectra of Compound 8c.
7.9. $^1$H, $^{13}$C and HSQC Spectra of Compound 9a
Figure S48. HSQC Spectra of Compound 9a.

7.10. $^1$H, $^1$C and HSQC Spectra of Compound 9b

Figure S49. $^1$H Spectra of Compound 9b.
Figure S50. $^{13}$C Spectra of Compound 9b.

Figure S51. HSQC Spectra of Compound 9b.
7.11. $^1$H, $^{13}$C and HSQC Spectra of Compound 9c

Figure S52. $^1$H Spectra of Compound 9c.

Figure S53. $^{13}$C Spectra of Compound 9c.
**Figure S54.** HSQC Spectra of Compound 9c.

| Parameter        | Value                                      |
|------------------|--------------------------------------------|
| Origin           | Varian                                     |
| Spectrometer     | DRX500                                    |
| Solvent          | CDCl3                                      |
| Temperature      | 27.0                                    |
| Pulse Sequence   | gHMQC                                     |
| Experiment       | HSQC, EDDYED                               |
| Probe            | uniformly                                 |
| Number of Scans  | 4                                          |
| Receiver Gain    | 40                                         |
| Relaxation Delay | 1.0000                                    |
| Pulse Width      | 0.0000                                    |
| Acquisition Time | 0.5000                                    |
| Spectrometer Frequency | 94,62, 155, 60            |
| Spectrum Width   | (600.0, 25130.0)                          |
| Lowest Frequency | (-1534, -1235)                             |
| Number           | (1H, 13C)                                  |
| Acquired Size    | (1024, 128)                                |
| Spectra Size     | (1024, 128)                                |

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