



# Recycling the undesired enantiomer of naproxen

A context/problem-based learning (C/PBL) resource

## Teacher's guide

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## General notes

Instead of using face to face lectures, the lecture notes could be provided to students to read in their own time. The time spent in the lecture could then be used to engage students in peer and self-assessment. A guide to using self and peer assessment can be found by clicking the following link <http://spark.uts.edu.au/>

Students could be asked to include additional information in their report that is related to the aims of the project – eg an environmental impact assessment; Hazard and Operability analysis; planning for pilot plant equipment needed and preparing process instructions / batch sheets.

The final report could be jointly submitted by the students with just an individual reflection instead.

(S)-Naproxen can be purchased from many commercial suppliers. The spectral assignments for (S)-Naproxen are given below.

(R)-naproxen is significantly more expensive so a procedure to produce the (R)-enantiomer is provided in this document.

Some of the procedures require stirring for 2 days for optimal results. However, it should be possible to stir these reactions for longer or shorter depending on the laboratory provision.

The results of the experimental trials are listed later in the document. Readily available additives and enzymes were chosen to minimise cost.

## Experimental details

### (S)-naproxen

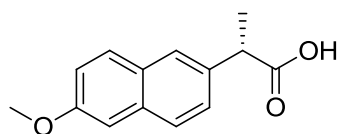


Figure 1: Structure of (S)-naproxen

$$[\alpha]_{\text{D}}^{25} + 68.9^{\circ} \text{ (c 1.00, CHCl}_3\text{)} \text{ {lit.} }^1 [\alpha]_{\text{D}}^{25} + 66.0 \text{ (c 1.00, CHCl}_3\text{)}$$

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<sup>1</sup> J. Med. Chem., 1970, 13, 203

$^1\text{H}$  NMR (500 MHz, DMSO- $d^6$ )  $\delta$  12.30 (s, 1H), 7.78 (d,  $J$  = 0.8 Hz, 1H), 7.76 (d,  $J$  = 8.6 Hz, 1H), 7.70 (d,  $J$  = 1.8 Hz, 1H), 7.40 (dd,  $J$  = 8.5, 1.8 Hz, 1H), 7.27 (d,  $J$  = 2.5 Hz, 1H), 7.14 (dd,  $J$  = 8.9, 2.6 Hz, 1H), 3.85 (s, 3H), 3.79 (q,  $J$  = 7.1 Hz, 1H), 1.44 (d,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (125 MHz, DMSO)  $\delta$  175.43, 157.09, 136.31, 133.21, 129.07, 128.39, 126.80, 126.37, 125.53, 118.64, 105.69, 55.12, 44.58, 18.42; MS (ES)  $m/z$  231.0  $[\text{M}+\text{H}]^+$

## Initial preparation of (*R*)-naproxen

### Racemisation using LDA

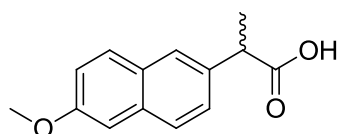


Figure 2: Structure of racemic naproxen

Di-isopropylamine (freshly distilled over sodium hydride) (1.27 mL, 9.1 mmol) was dissolved in anhydrous THF (30 mL) and cooled to  $-78\text{ }^\circ\text{C}$  (dry ice/acetone) under  $\text{N}_2$ .  $n\text{-BuLi}$  (2.5 M in hexane, 3.6 mL, 9.1 mmol) was added dropwise and the reaction stirred for 30 minutes at  $-78\text{ }^\circ\text{C}$ , warmed to  $0\text{ }^\circ\text{C}$  and stirred for 30 minutes then cooled again to  $-78\text{ }^\circ\text{C}$ . A solution of (*S*)-naproxen (1 g, 4.35 mmol) in anhydrous THF was added dropwise to the solution of LDA at which point an orange colour developed. The reaction was stirred at  $-78\text{ }^\circ\text{C}$  for 30 minutes then  $0\text{ }^\circ\text{C}$  for 30 minutes after which the reaction was quenched via dropwise addition of water (2 mL) upon which the orange colour dissipated. The reaction mixture was then allowed to warm to r.t. and poured into 2 M aqueous HCl (50 ml) which was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with 2 M aqueous HCl and brine, dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to a colourless solid (891 mg, 90%). Shown to be racemic by optical rotation and chiral HPLC, NMR data as above for (*S*)-Naproxen.

### Chiral HPLC of acid

The racemate was dissolved in 10% IPA 90% hexane and the enantiomers were separated on a Chiralcel® AD-H column eluting with 10% IPA 90% hexane at a flow rate of 1 ml/min and detected at 254 nm. An authentic sample of (*S*)-naproxen identified the peak at 14.7 minutes as the S enantiomer.

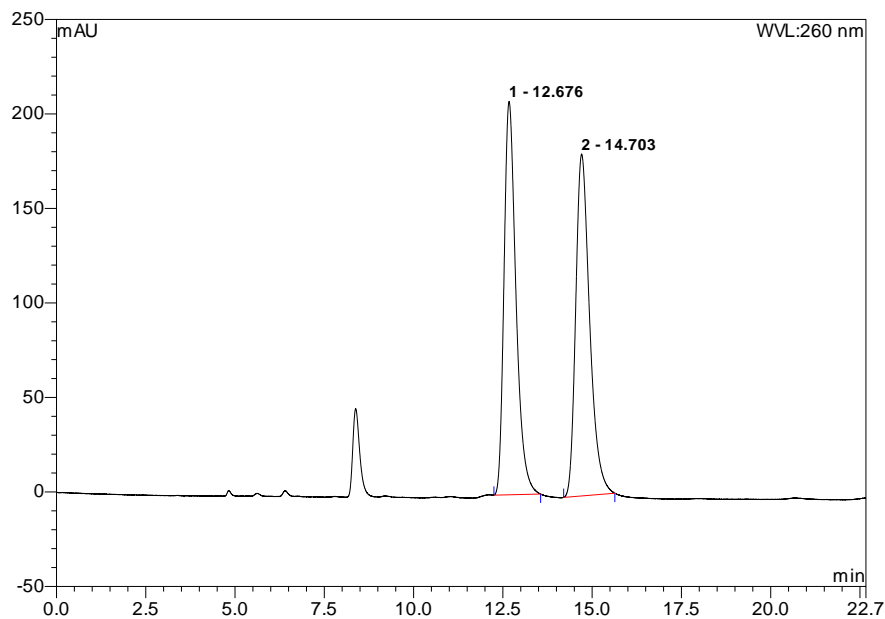


Figure 3: Chromatogram of racemic naproxen

### Resolution

Hot solution of the racemate (890 mg) in a mixture 20 mL of methanol and 5 mL of acetone and cinchonidine (1.16 g) in a mixture of 15 mL of methanol and 10 ml of acetone were mixed and allowed to cool to r.t. The resulting salt was removed by filtration and recrystallised from methanol/acetone (7:3) twice then partitioned between ethyl acetate (30 mL) and 1 M HCl (aq.). The organic layer was washed with 1 M HCl (aq.) (3 x 20 mL), dried over  $\text{MgSO}_4$  and concentrated *in vacuo* to a colourless solid (170 mg, 20% recovery)

Analytically pure - NMR data as above for (S)-Naproxen.

er – 95:5 by chiral HPLC

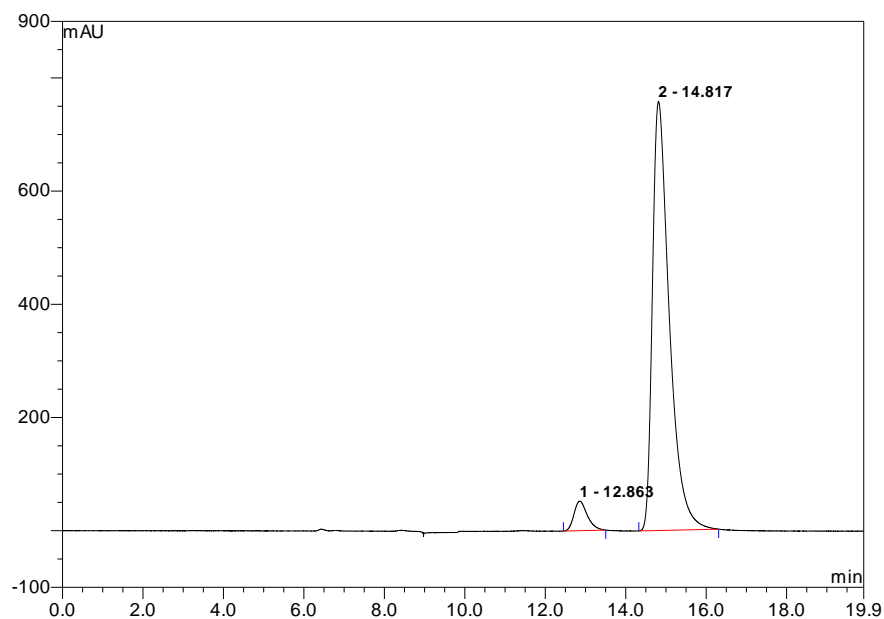


Figure 4: Chromatogram of purified (S)-naproxen

The mother liquors were diluted with 1 M HCl (aq.) and extracted with ethyl acetate (2 x 30 ml). The organic layers were combined and washed with 1 M HCl (aq.) (3 x 20 ml), dried over MgSO<sub>4</sub> and concentrated *in vacuo* to a colourless solid (320 mg, 35% recovery).

Analytically pure - NMR data as above for (S)-Naproxen.

er – 70:30 by chiral HPLC

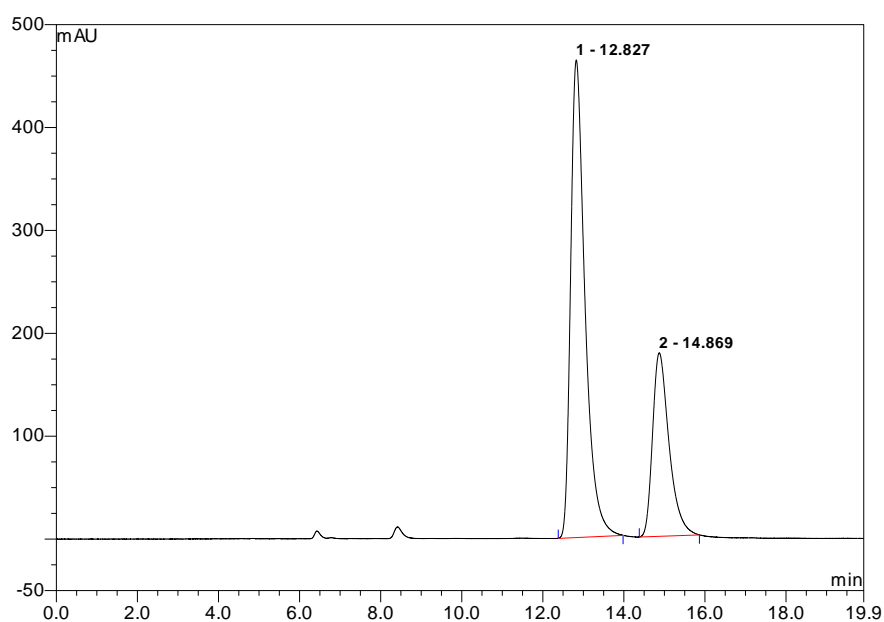


Figure 5: Chromatogram of mother liquors

## Esterification of (*R*)-naproxen

Procedures for sulfuric acid catalysed and resin catalysed esterification of (*R*)-naproxen are given below.

### Sulfuric acid method

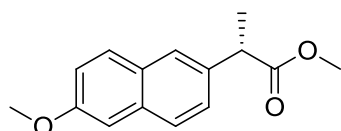


Figure 6: Structure of (*S*)-naproxen

Concentrated sulfuric acid (0.23 mL, 0.43 mmol) was added dropwise to a solution of (*R*)-naproxen (1 g, 4.35 mmol) in methanol (30 mL). The resulting solution was heated to reflux for 1 hour, allowed to cool to rt and poured into a saturated aqueous solution of sodium bicarbonate (50 mL). This suspension was extracted with ethyl acetate (3 x 30 mL) and the combined organics washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated *in vacuo* to a colourless solid (0.96 g, 91%).  $[\alpha]_D^{25} +73.3^\circ$  (c 1.00, CHCl<sub>3</sub>) {lit.<sup>2</sup>  $[\alpha]_D^{25}$  74.0 (c 1.00, CHCl<sub>3</sub>)}; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sup>6</sup>)  $\delta$  7.82 – 7.74 (m, 2H), 7.70 (d, J = 1.8 Hz, 2H), 7.37 (dd, J = 8.5, 1.9 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 7.14 (dd, J = 8.9, 2.6 Hz, 1H), 3.91 (q, J = 7.1 Hz, 1H), 3.85 (s, 3H), 3.58 (s, 3H), 1.46 (d, J = 7.1 Hz, 3H); <sup>13</sup>C NMR (125 MHz, DMSO)  $\delta$  174.36, 157.18, 135.66, 133.30, 129.10, 128.38, 126.99, 126.17, 125.58, 118.73, 105.70, 55.15, 51.74, 44.29, 18.41. MS (ES) *m/z* 267.0 [M+Na]<sup>+</sup>

### Resin method

(*R*)-Naproxen (2 g) was dissolved in methanol (50 mL) containing Dowex-H<sup>+</sup> resin (500 mg) and stirred at 40 °C for 2 days. Reaction mixture filtered to remove resin and concentrated *in vacuo*. Residue dissolved in ethyl acetate (50 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 20 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo* to a colourless solid (1.91 g, 90%).

Analytically pure – NMR data as above.

No racemisation observed by chiral HPLC

### Soft-enolisation screen

A general esterification method, along with the results of a screen of the different variables is given to show the scope for optimisation in this step:

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<sup>2</sup> Tetrahedron: Asymmetry, 1998, 9, 3203

(S)-naproxen methyl ester (20 mg, 0.08 mmol), amine base (0.16 mmol, see Table 1) and additive (0.08 mmol, see Table 1) were dissolved/suspended in solvent (3 ml, see Table 1) and stirred at the indicated temperature for 16 hours. The reaction mixture was then diluted with 1 M HCl aq. (5 mL) and extracted with ethyl acetate. The organic layer was concentrated *in vacuo* and analysed by chiral HPLC.



**Table 1: Soft enolisation screen**

Reaction	Base	Solvent	Additive	Temperature	Enantiomeric ratio (S:R)
(a)	DIPEA	THF	None	rt	>99:1
(b)	DIPEA	DCM	MgBr <sub>2</sub> .Et <sub>2</sub> O	rt	98.5:1.5
(c)	DIPEA	MeOH	LiCl	rt	98.5:1.5
(d)	Triethylamine	DCM	None	rt	>99:1
(e)	Triethylamine	MeOH	LiCl	rt	>99:1
(f)	Triethylamine	THF	MgBr <sub>2</sub> .Et <sub>2</sub> O	rt	>99:1
(g)	DBU	MeOH	None	rt	54:46
(h)	DBU	DCM	LiCl	rt	51:49
(i)	DBU	THF	MgBr <sub>2</sub> .Et <sub>2</sub> O	rt	84:16
(j)	DBU	MeOH	MgBr <sub>2</sub> .Et <sub>2</sub> O	rt	65:35
(k)	DIPEA	THF	None	Reflux	>99:1
(l)	DIPEA	DCM	MgBr <sub>2</sub> .Et <sub>2</sub> O	Reflux	>99:1
(m)	DIPEA	MeOH	LiCl	Reflux	82:18
(n)	Triethylamine	DCM	None	Reflux	>99:1
(o)	Triethylamine	MeOH	LiCl	Reflux	90:10
(p)	Triethylamine	THF	MgBr <sub>2</sub> .Et <sub>2</sub> O	Reflux	>99:1
(q)	DBU	THF	MgBr <sub>2</sub> .Et <sub>2</sub> O	Reflux	70:30
(r)	DBU	MeOH	MgBr <sub>2</sub> .Et <sub>2</sub> O	Reflux	50:50

An example procedure for the best conditions found is given below.

### Preparation of racemate methyl ester

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was added to a solution of (S)-Naproxen methyl ester (1 g, 4.1 mmol) in DCM (50 mL) containing lithium chloride (172 mg, 4.1 mmol) and the reaction stirred at rt overnight. The reaction mixture was then concentrated *in vacuo* and the residue partitioned between ethyl acetate (30 ml) and 1 M HCl (aq.) (30 ml). The organic layer was washed with 1 M HCl (aq.) (30 ml), dried over MgSO<sub>4</sub> and concentrated *in vacuo* to a colourless solid (888 mg, 89%).

Analytically pure – NMR data as above for (S)-Naproxen methyl ester.

Shown to be racemic by chiral HPLC.

### Enzymatic resolution screen

A general resolution method, along with the results of a screen of the different variables is given to show the scope for optimisation in this step.

#### Enzymatic resolution screen

Racemic naproxen methyl ester (100 mg) was suspended in phosphate buffer (0.1 mM, pH 7.4, 4 mL) along with the enzyme (see tables 2 and 3 below, 100 mg) and the reaction stirred at rt for 2 days. Samples were taken after 24 hours and 48 hours, diluted with methanol, centrifuged and the supernatant analysed by LC-MS.

Reactions showing progress were diluted with 1 M HCl (10 ml) and extracted with ethyl acetate (3 x 10 mL). The organic layer was then washed with saturated sodium bicarbonate solution (3 x 10 mL), concentrated *in vacuo* and analysed by chiral HPLC (see method for naproxen methyl ester). The basic washes were acidified with conc. HCl and extracted with ethyl acetate (3 x 10 mL), concentrated *in vacuo* and analysed by chiral HPLC (see method for naproxen).

**Table 2: Enzymatic resolution screen (varying lipase)**

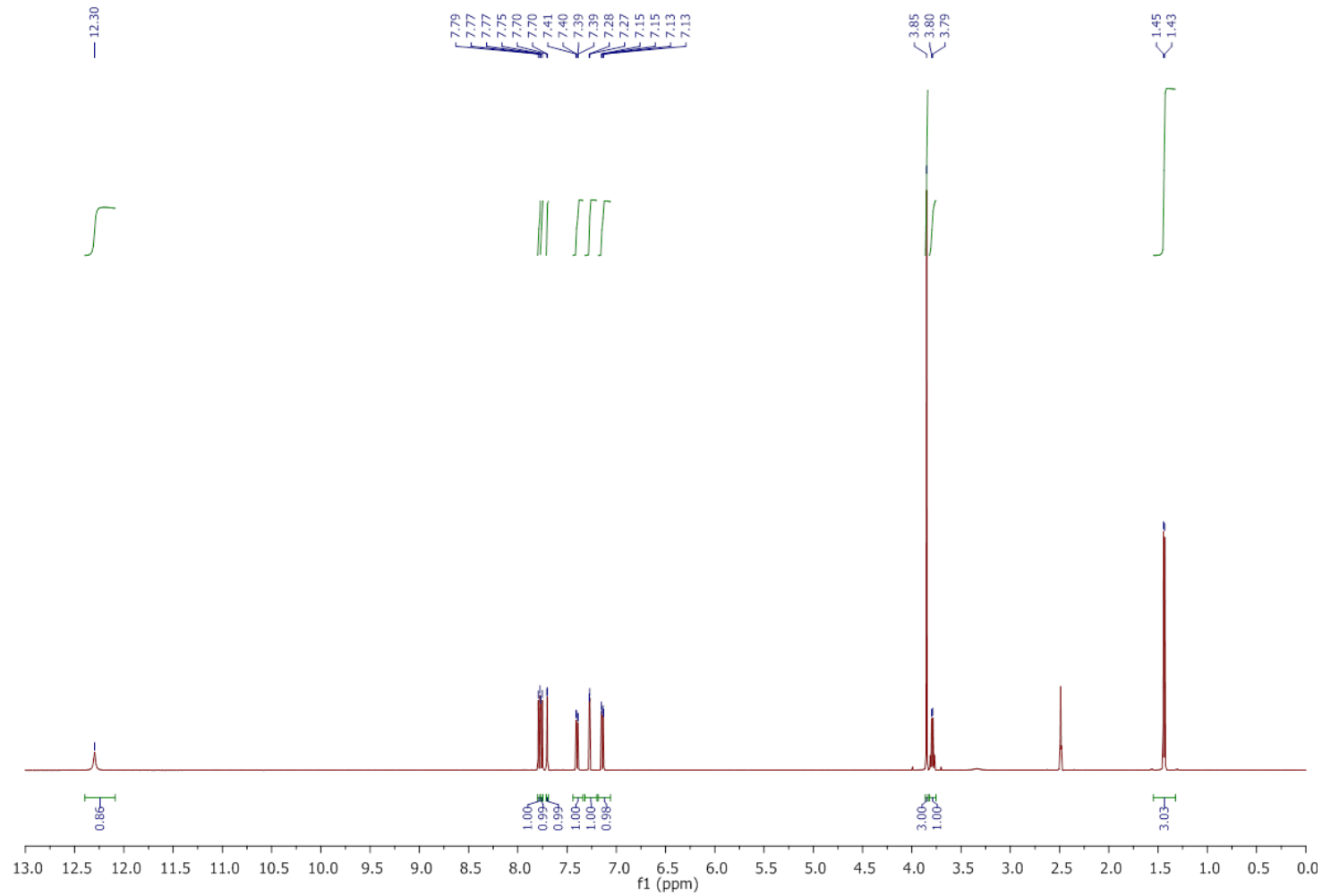
Lipase	Progression after 48 hours	Enantiomeric ratio of remaining ester (S:R)	Enantiomeric ratio of naproxen (S:R)
Burkholderia Cepacia	None	n.d.	n.d.
Candida Rugosa	~30%	42:58	95:5
Candida Cylindracea	~30%	40:60	95:5
Pseudomonas Fluorescens	None	n.d.	n.d.
Porcine Pancreas	None	n.d.	n.d.

**Table 3: Enzymatic resolution screen (varying solvent)**

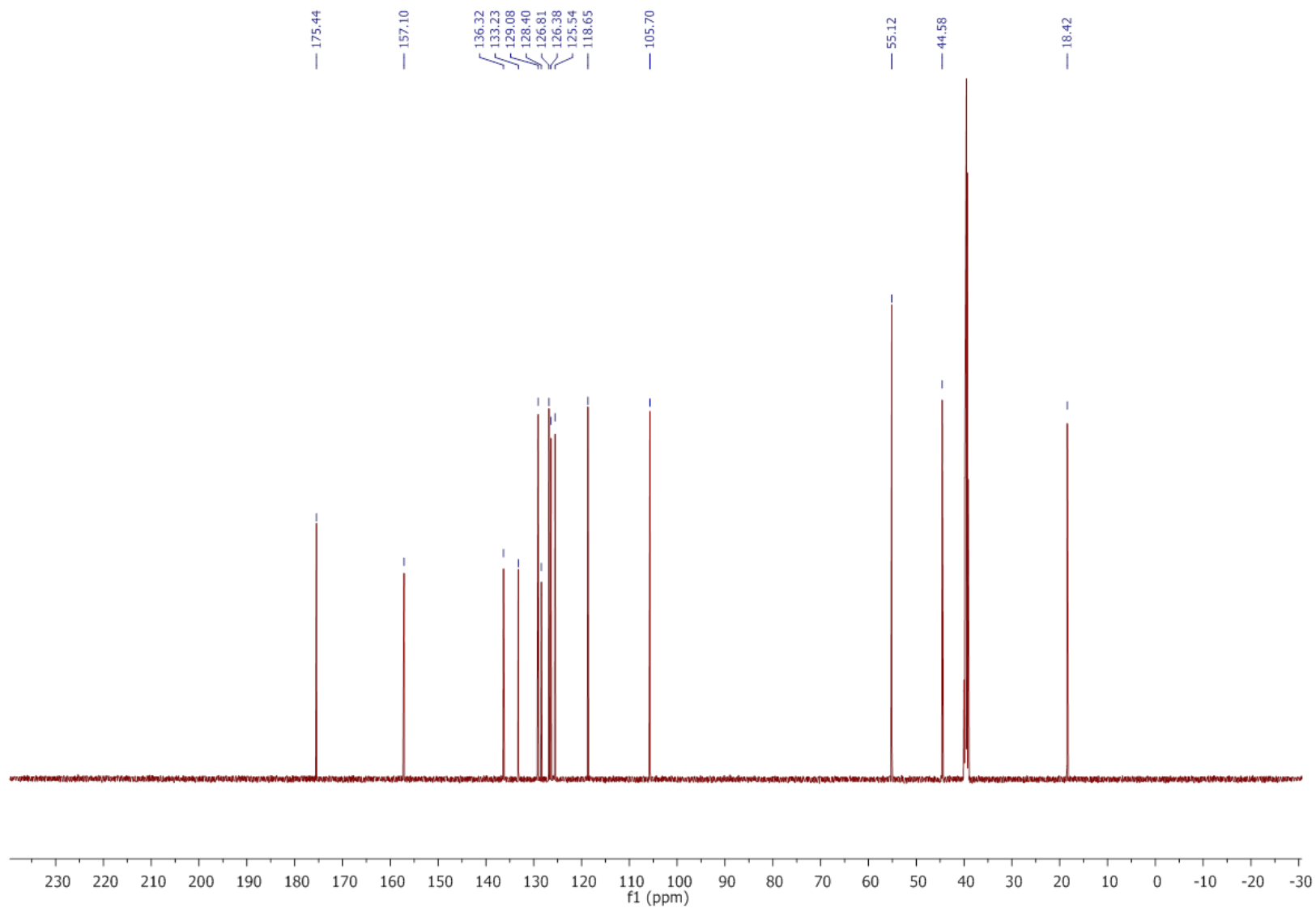
<b>Solvent</b>	<b>Additive</b>	<b>Temp.</b>	<b>Progression after 48 hours</b>	<b>Enantiomeric ratio of remaining ester (S:R)</b>	<b>Enantiomeric ratio of naproxen (S:R)</b>
Phosphate buffer	None	40 °C	45%	12:88	98:2
Phosphate buffer	THF (10% v/v THF)	rt	None	n.d	n.d
Water	None	rt	30%	30:70	95:5

# Spectra

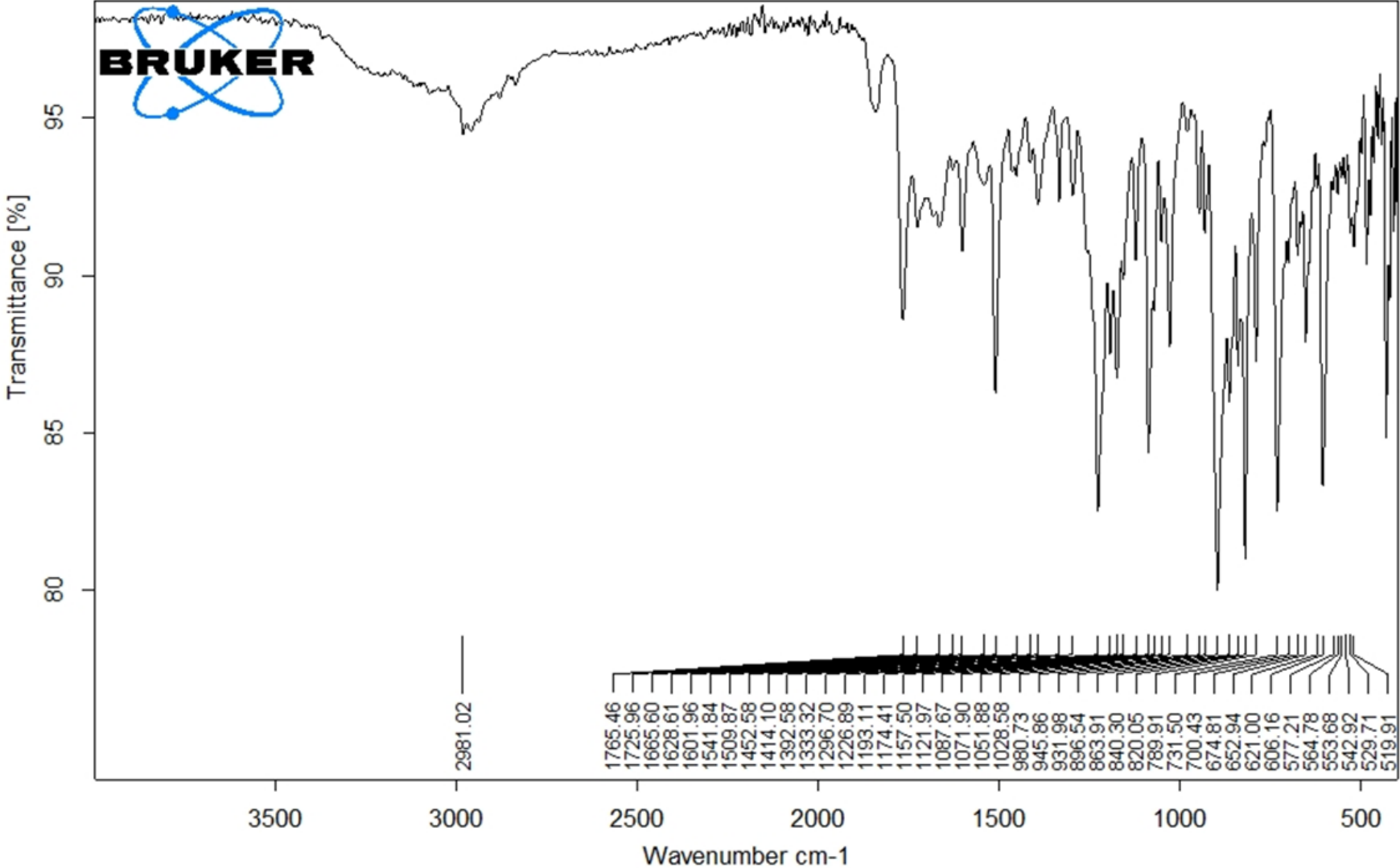
## <sup>1</sup>H NMR – Naproxen



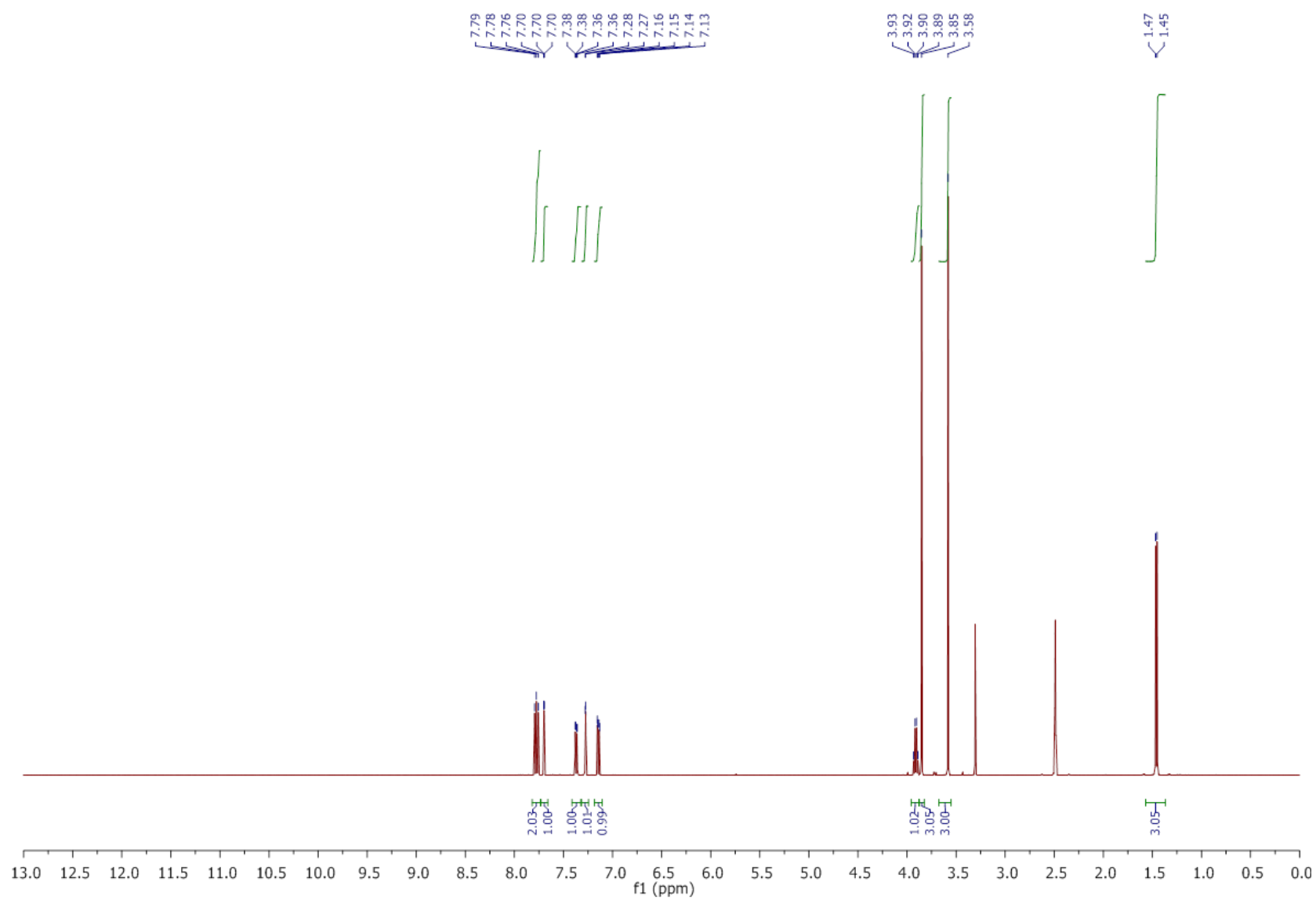
# <sup>13</sup>C NMR – Naproxen



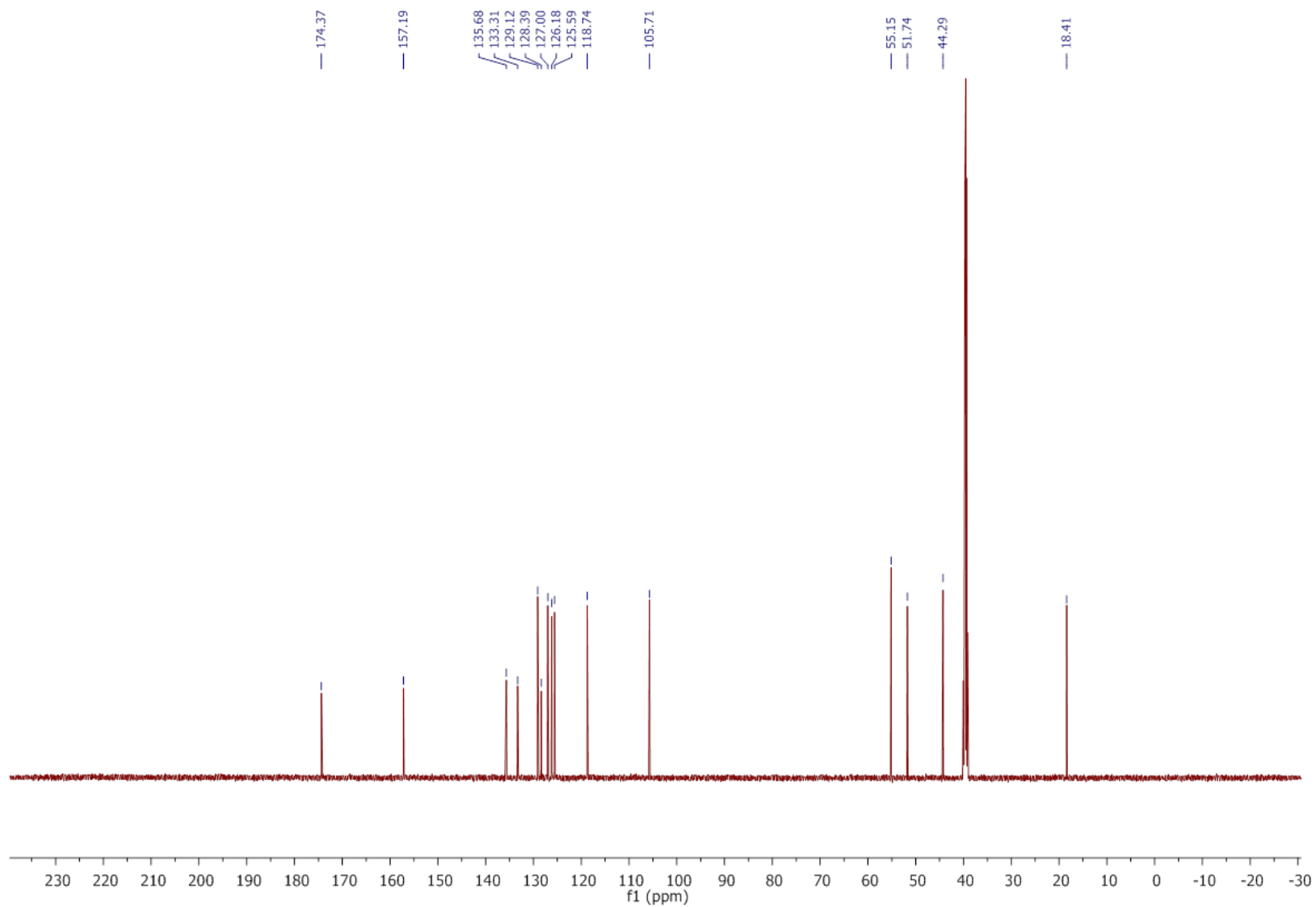
FTIR – Naproxen



# <sup>1</sup>H NMR – Naproxen methyl ester



# <sup>13</sup>C NMR – Naproxen methyl ester





FTIR – Naproxen methyl ester

