

## Selective C-acylation of 3-methyl-1-phenyl-pyrazol-5-one

### Supplementary Material

#### Table of Contents

<b>Experimental remarks</b>	<b>1</b>
<b><i>Synthesis of 4-aryoyl-3-methyl-1-phenyl-pyrazol-5-ons</i></b>	<b>1</b>
<b><i>Assignment of NMR spectra</i></b>	<b>3</b>
<b>Figures</b>	<b>5</b>
<b><i>C-acylation of 3-methyl-1-phenyl-1H-pyrazol-5-one</i></b>	<b>5</b>
<b><i>TLC of crude 4-(4-methylbenzoyl)-3-methyl-1-phenyl-1H-pyrazol-5-one</i></b>	<b>6</b>
<b><i>Crystals of C-acylated pyrazolones</i></b>	<b>7</b>
<b><i>NMR spectra</i></b>	<b>8</b>

#### Experimental remarks

##### ***Synthesis of 4-aryoyl-3-methyl-1-phenyl-pyrazol-5-ons***

This particular laboratory experiment meets the goals of providing students with practical experience in regioselective acylation of heterocyclic compounds and acquiring skills in interpreting 1D and 2D NMR spectra. 3-Methyl-1-phenyl-pyrazol-5-on is chosen as starting material due to a combination of its low prize and the broad applicability of C-acylated compounds as extractants in separation science. Several 4-substituted aroyl chlorides are selected as acylating agents as the corresponding acylpyrazolones are displayed great complexation and extraction ability towards metal ions.

The protocol is appropriate for student's exercises due to several practical features:

- ✓ Fast conversion – all synthetic work can be performed in less than 5 h.
- ✓ Simple manipulation – do not need special precautions.
- ✓ No tedious work-up – simple recrystallization and filtration.
- ✓ Applicable to other heterocyclic systems possessing tautomeric C-OH/C=O group; for instance isoxazolones.

The experiment is suitable for second/third year undergraduate students and can be achieved individually or in couples. If necessary to shorten the students' class room, the experiment can be performed in 3-3.5 h and to filter the crude product on next day.

To achieve the C-acylation selectively and effectively, several experimental issues have to be taken into account:

**Note 1.** It is important to protect the reaction mixture from moisture to avoid acyl chloride hydrolysis. Use anhydrous dioxane; water content below 0.05 %.

**Note 2.** Grind pyrazolone with pestle in a mortar before addition of 1,4-dioxane to accelerate the dissolution.

**Note 3.** It is important to dissolve fully the starting pyrazolone before addition of calcium hydroxide; Figure SM 2.2.1.1.

**Note 4.** Use calcium hydroxide in 2 equivalents to trap the liberated hydrogen chloride and keep the reaction media basic.

**Note 5.** It is necessary to use high turbulence magnetic stir bar to afford the efficient complex formation because calcium hydroxide forms very heavy residue, which cannot be stirred with common bars.

**Note 6.** It is crucial to form calcium complex before the addition of acylating agent! If the latter is added to free pyrazolone, the corresponding O-acylated compound is the only or main reaction product.

**Note 7.** Follow the complex formation by TLC on basic alumina; the complex is not stable enough to be monitored by TLC on silica gel.

**Note 8.** The addition of acyl chloride to the mixture can generate heat. Be very careful and add the reagent drop-wise under cooling.

**Note 9.** Observe the colour of the reaction mixture. It changes from yellow to orange; Figure SM 2.2.1.2.

**Note 10.** Stir vigorously during the addition of the reaction mixture to hydrochloric acid in order to avoid lumps formation. The latter hindered the decomposition of the complex and can result in a decrease of the product yield. If the lumps are formed, they have to be grinded.

**Note 11.** Keep the acidic mixture at room temperature at least 1.5 h before filtration to achieve complete complex decomposition.

**Note 12.** Wash carefully the residue to dissolve fully  $\text{CaCl}_2$  and eventually traces of  $\text{Ca}(\text{OH})_2$ .

**Note 13.** Wash further with small portions of ethanol to eliminate the dark brown coloured impurities.

Several acyl derivatives are obtained, namely 4-(4-methylbenzoyl)-, 4-(4-fluorobenzoyl)-, 4-(4-phenylbenzoyl)-, and 4-(4-trifluoromethylbenzoyl)-3-methyl-1-phenyl-1H-pyrazol-5-one. All experiments are performed at least 6 times by the teachers. The synthesis of 4-(4-methylbenzoyl)-3-methyl-1-phenyl-1H-pyrazol-5-one, the cheapest example, is reproduced 4 times by eight second-year undergraduate students working in couples. All reaction parameters are the same except the duration

of the acylation step, which is dependent on the substituent in aroyl chloride, and solvents used for recrystallization. The reaction details are summarised on Table SM 2.2.1.1.

**Table SM 2.2.1.1.** Data for the acylation step.

R	Reaction time, h	Yield, <sup>1</sup> %	ArCOCl price, approximately
Me	1.5	74-76 (MeOH-acetone)	30 €/100 g
F	2	75-78 (EtOH)	35 €/25 g
Ph	2	84-87 (EtOH)	50 €/10 g
CF <sub>3</sub>	9	81-83 (MeOH)	120 €/5 g

<sup>1</sup> After recrystallization; the solvent is given in parenthesis.

As seen, the last reagent is not appropriate for students' laboratories due to its high price and the relatively long reaction time necessary to achieve full conversion. Nevertheless, the prolongation of the reaction does not influence the reaction yield and so, the acylation can be carried out overnight if necessary to obtain 4-(4-trifluoromethylbenzoyl)-3-methyl-1-phenyl-1H-pyrazol-5-one.

The pure products, shown on Figure SM 2.2.1.5, are analysed by TLC on silica gel and melting points. The mobile phase was varied and was found that 5 % methanol in dichloromethane (5 % MeOH/DCM) lead to best separation. The data are given on Table SM 2.2.1.2.

**Table SM 2.2.1.2.** R<sub>f</sub>-values (5 % MeOH/DCM) and melting points of C-acylated and O-acylated compounds..

R	C-acylated compounds		O-acylated compounds	
	R <sub>f</sub> -value	m. p., °C	R <sub>f</sub> -value	m. p., °C
Me	0.55	126-127	0.67	94.5-95
F	0.41	132.5-133	0.72	73.5-74
Ph	0.51	151-151.5		
CF <sub>3</sub>	0.42	147.5-148		

### Assignment of NMR spectra

It is very important for second year undergraduate students to acquire basic knowledge in the interpretation of NMR spectra and in the application of the method for structure determination. At the end of these exercises they are able to analyse the spectra of the crude products, which is much more complicated than the analyses of pure compounds.

The assignment of the signals in NMR spectra of all compounds is achieved by following a common step-wise sequence. As the original spectra are already published, *J. Chem. Educ.*<sup>1</sup> except CF<sub>3</sub> derivative,<sup>2</sup> herein we are presenting this sequence only on the example of 3-methyl-4-(4-

fluorobenzoyl)-1-phenyl-pyrazol-5-one (Figures SM 2.2.1.6-SM 2.2.1.12), where significant carbon-fluorine constants are observed.

The key elements are the following:

- ✓  $^1\text{H}$  spectrum (Figure SM 2.2.1.6) – singlet in strong field for  $\text{CH}_3$  group, broad singlet for  $\text{OH}$ ; aromatic area: two AA'BB' signals (chemically but not magnetically equivalent protons) with integrals of 2 for CH-2+6 and CH-3+5 of aromatic group, doublet for 2 protons for CH-2+6, triplet for 2 protons for CH-3+5 and triplet for 1 proton for CH-4 of phenyl.
- ✓  $^1\text{H}$ - $^1\text{H}$  NOESY (Figure SM 2.2.1.7) - interaction of methyl with CH-2+6 Ar; explicitly distinguishing the aromatic protons of the acyl group.
- ✓  $^1\text{H}$ - $^1\text{H}$  COSY experiment (Figure SM 2.2.1.8) – recognition of the neighbouring protons.
- ✓  $^{13}\text{C}$  spectrum (Figure SM 2.2.1.9) –  $\text{CH}_3$  group in strong field;  $\text{C}=\text{O}$  at 190 ppm for conjugated ketone; aromatic area: two doublets for aryl CH ( $J_{\text{CF}}$ ), two double intensive signals for CH-2+6 and CH-3+5 phenyl carbons, and a signal for CH-4 phenyl; quaternary carbons: total 7 signals, two of them doublets ( $J_{\text{CF}}$ ).
- ✓ DEPT experiment (Figure SM 2.2.1.9) – recognition of CH from quaternary carbons.
- ✓  $^1\text{H}$ - $^{13}\text{C}$  HSQC interaction (Figure SM 2.2.1.10) – direct connection between protons and carbons; recognition of the doublets for CH-2+6 and CH-3+5 of aryl group and determination of  $J_{\text{CF}}$ -constants.
- ✓  $^1\text{H}$ - $^{13}\text{C}$  HMBC experiment – recognition of quaternary carbons:  $\text{CH}_3/\text{C}_q\text{-3}$  (weaker) and  $\text{CH}_3/\text{C}_q\text{-4}$  (Figure SM 2.2.1.11); Figure SM 2.2.1.12:  $\text{C}_q\text{-5}$  of pyrazolone – no interactions; Ar:  $\text{C}_q\text{-1}/\text{CH-3+5}$ ,  $\text{C}_q\text{-1}/\text{CH-2+6}$  (weaker),  $\text{C}_q\text{-4}/\text{CH-2+6}$ ,  $\text{C}_q\text{-4}/\text{CH-3+5}$  (weaker); Ph:  $\text{C}_q\text{-1}/\text{CH-3+5}$ ,  $\text{C}_q\text{-1}/\text{CH-2+6}$  (weaker); recognition of the doublets for  $\text{C}_q\text{-1}$  and  $\text{C}_q\text{-4}$  of aryl group and determination of  $J_{\text{CF}}$ -constants.

At the end, the spectra of two esters, the corresponding O-acylated compounds, are analysed and the signals are compared with those of the corresponding C-acyl derivatives. As illustrated on Figures SM 2.2.1.9 and SM 2.2.1.10, all proton and carbon resonances are shifted in esters in respect to C-acylated compounds. The most informative signals, which even permit to avoid detailed assignment, are the broad singlet at 11.5-12 ppm for  $\text{OH}$  proton and  $\text{C}_q\text{-4}$  at 105 ppm and  $\text{C}=\text{O}$  at 190 ppm, which cannot belong to ester group, in C-acylated product compared to CH-4 proton and carbon in O-acylated, which appear in relatively strong field, 6.3 ppm and 95 ppm, respectively. This pattern allows to distinguish explicitly both type of products and to analyse crude reaction mixtures.

## Figures

### **C-acylation of 3-methyl-1-phenyl-1H-pyrazol-5-one**



**Figure SM 2.2.1.1.** Mixture of 3-methyl-1-phenyl-1H-pyrazol-5-one and  $\text{Ca}(\text{OH})_2$  before (left) and after (right) heating.

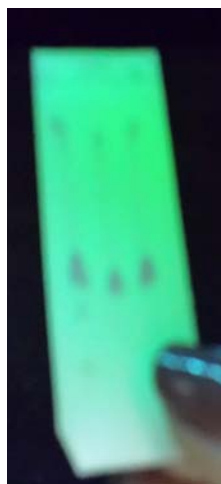


**Figure SM 2.2.1.2.** Reaction mixture before (left) and after (right) addition of p-toluoyl chloride.



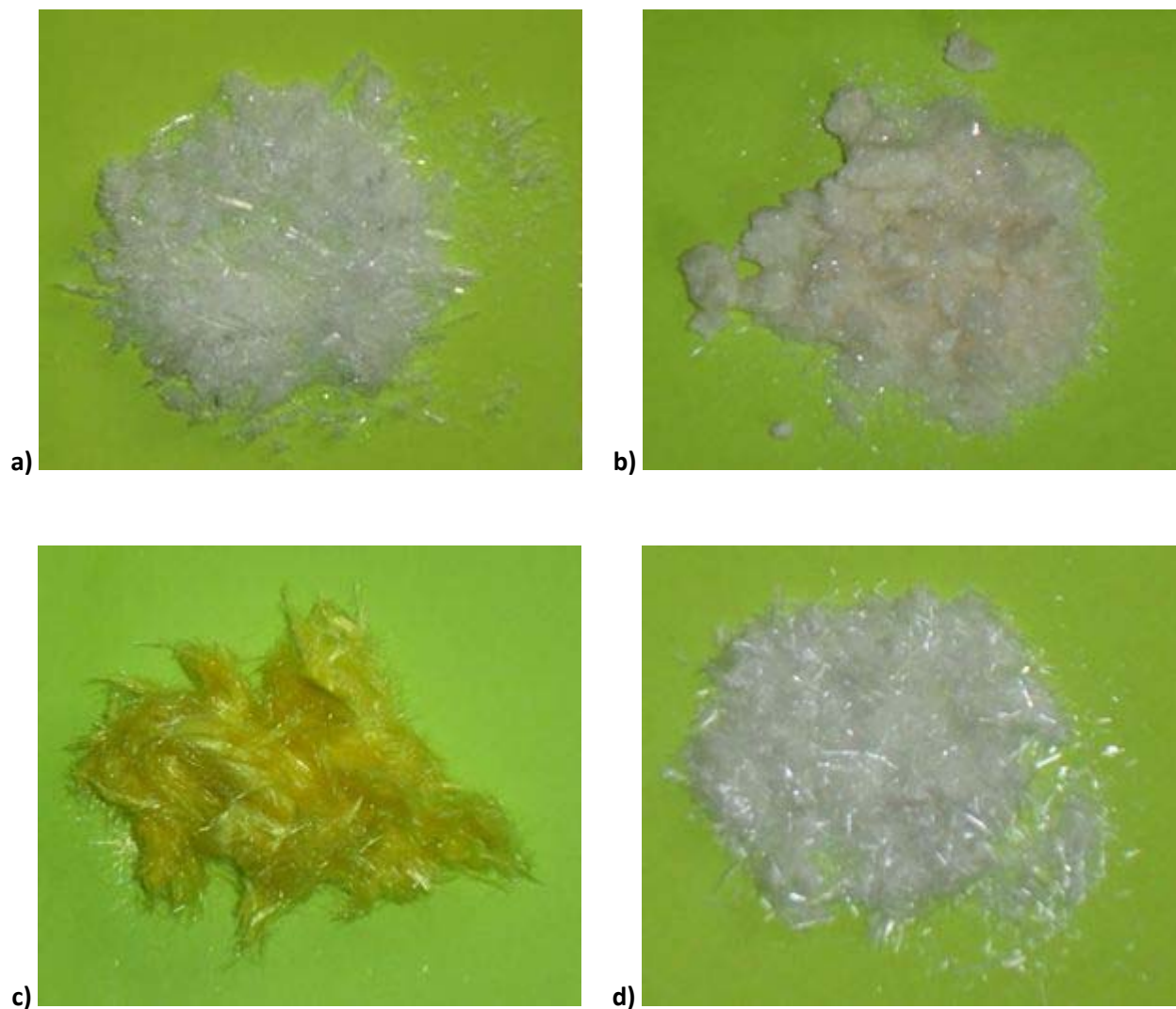
**Figure SM 2.2.1.3.** Crude 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

***TLC of crude 4-(4-methylbenzoyl)-3-methyl-1-phenyl-1H-pyrazol-5-one***



**Figure SM 2.2.1.4.** TLC of the crude 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one in different concentrations.

**Crystals of C-acylated pyrazolones**



**Figure SM 2.2.1.5.** Crystals of: a) 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one from methanol-acetone; b) 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one from ethanol; c) 3-methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one from ethanol; d) 3-methyl-4-(4-trifluoromethylbenzoyl)-1-phenyl-pyrazol-5-one from methanol.

### NMR spectra

The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (Rheinstetten, Germany) at 25°C as chloroform-d solutions; the chemical shifts were quoted in ppm in  $\delta$ -values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The spectra were processed with Topspin 2.1 program.

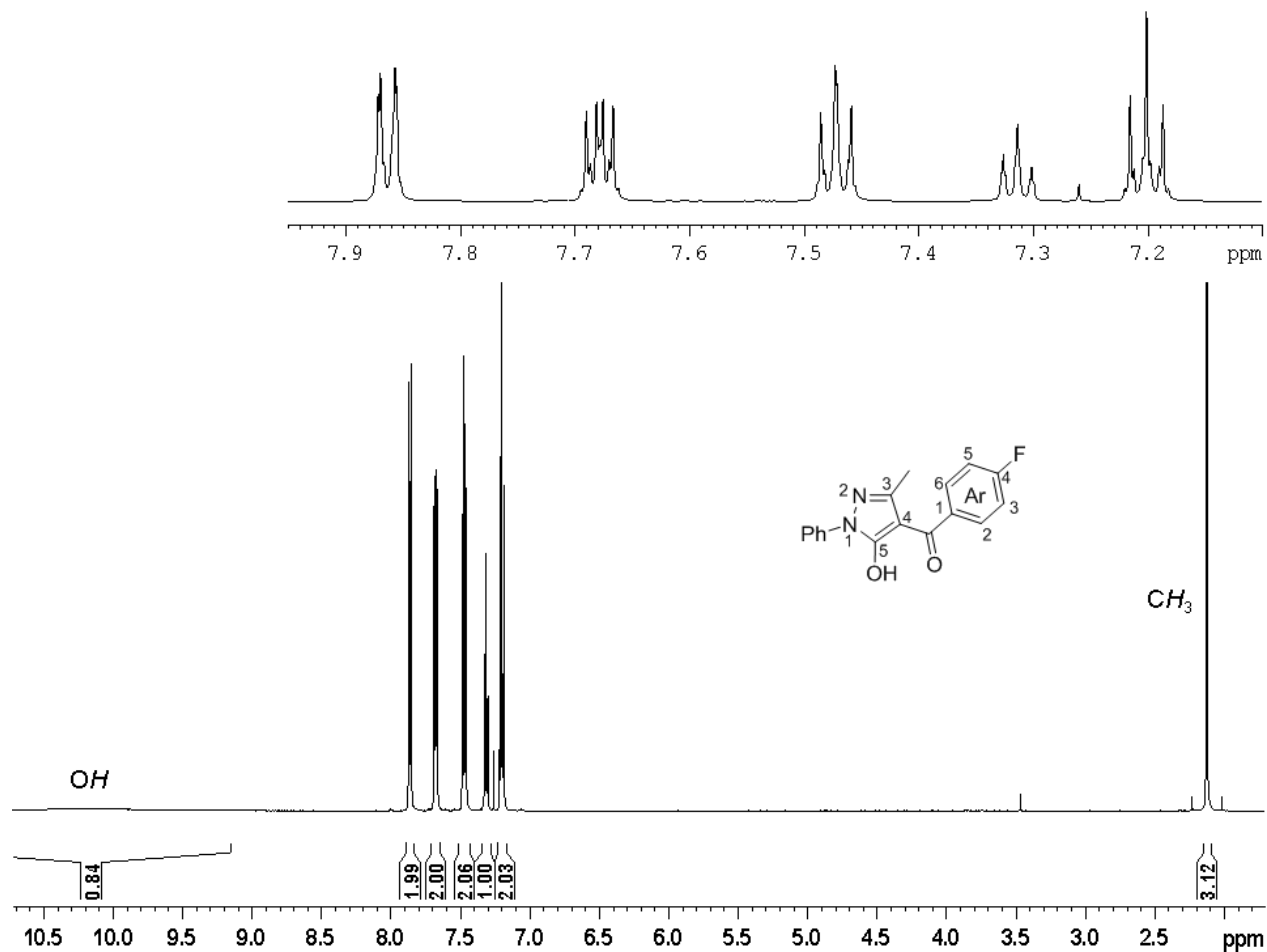


Figure SM 2.2.1.6.  $^1\text{H}$  spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.



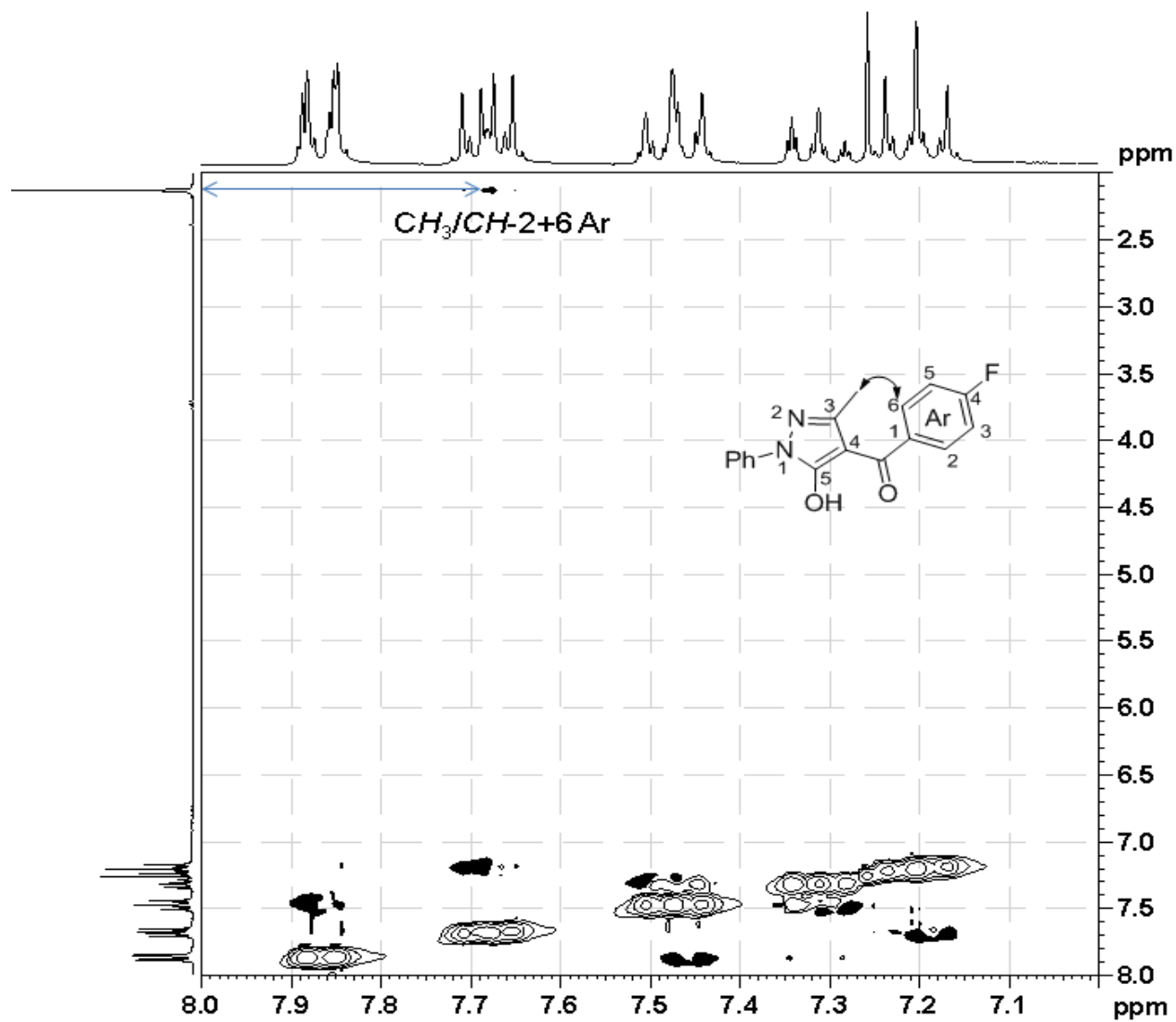


Figure SM 2.2.1.7.  $^1\text{H}$ - $^1\text{H}$  NOESY spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

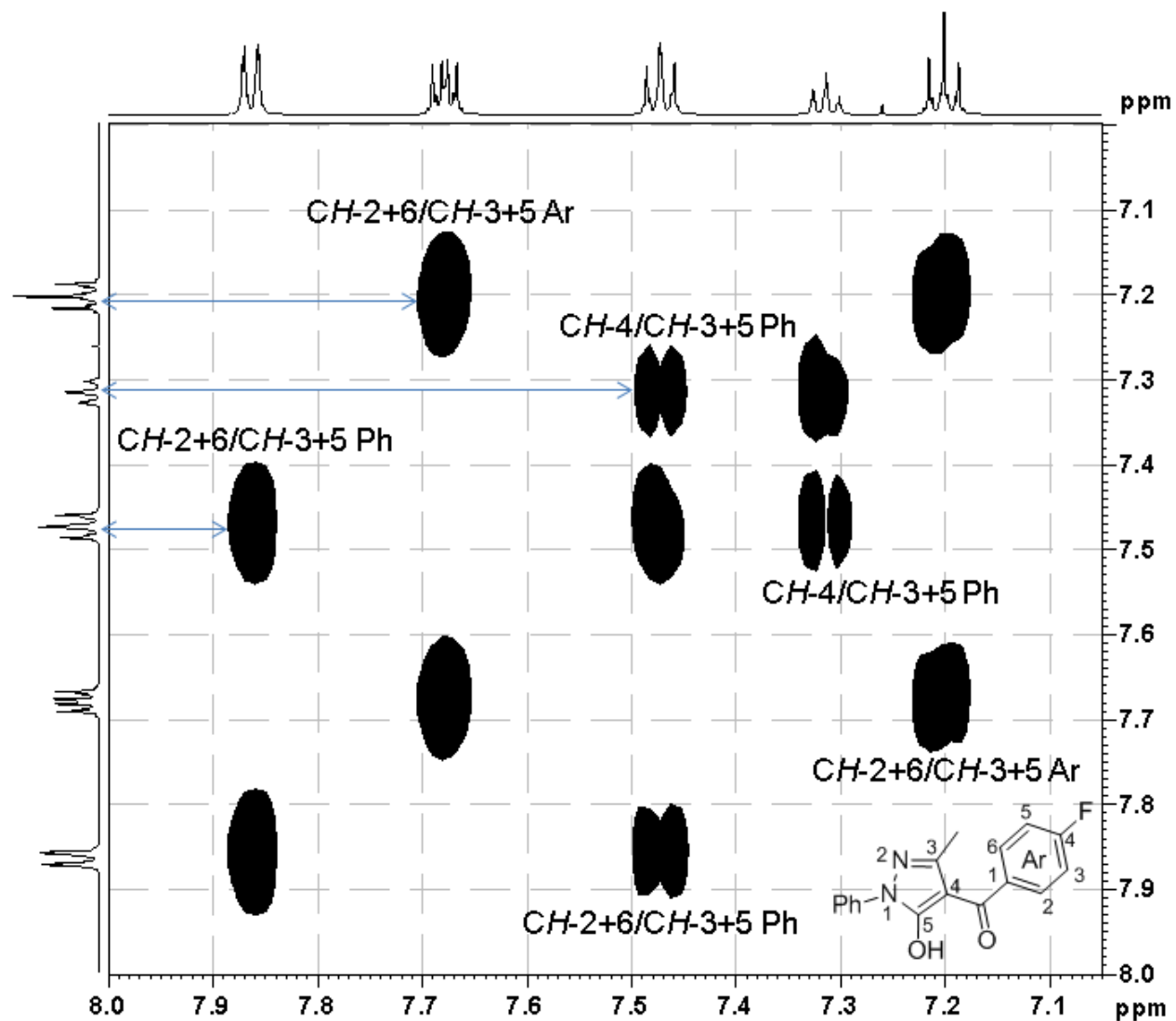
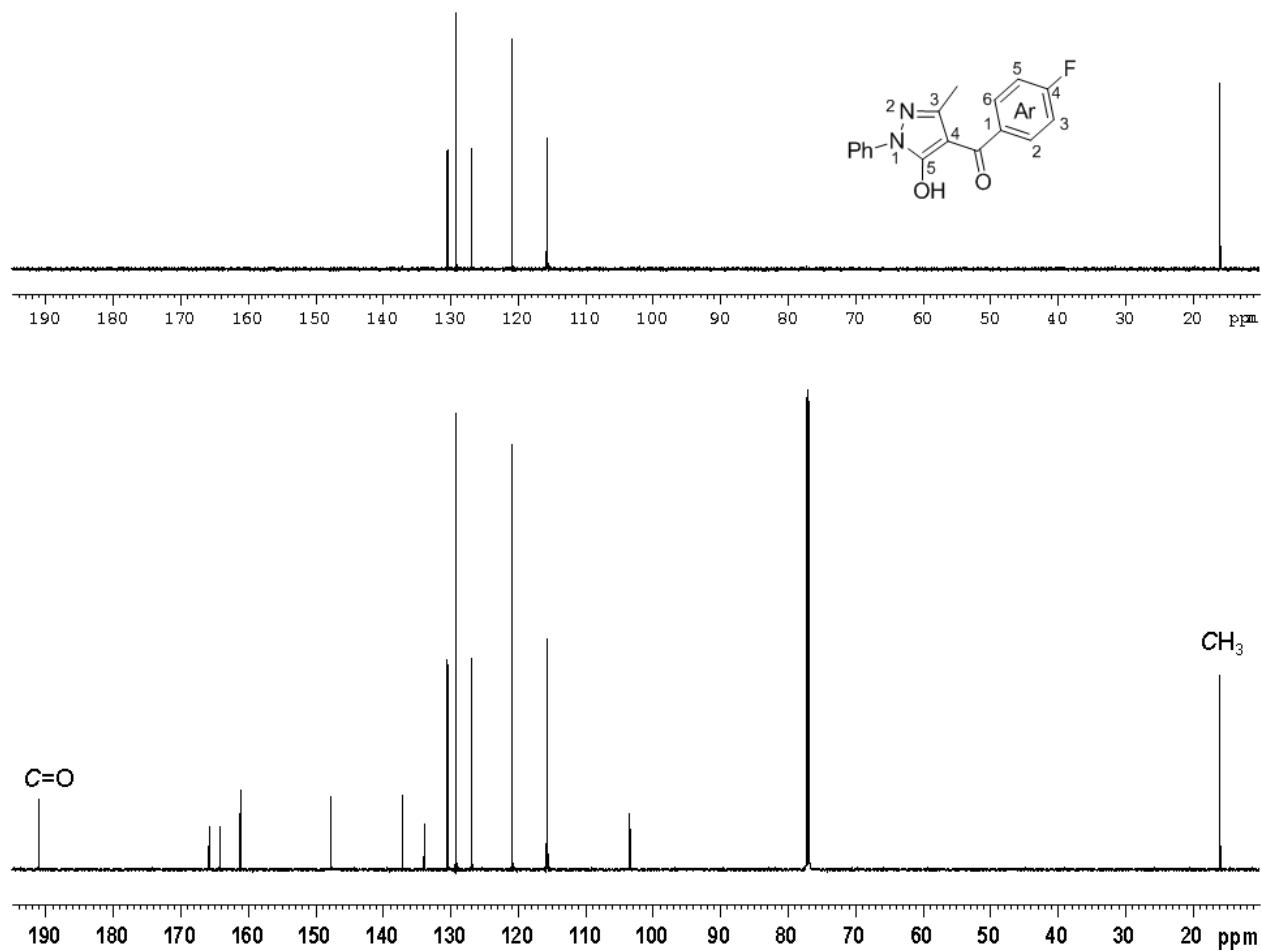


Figure SM 2.2.1.8.  $^1\text{H}$ - $^1\text{H}$  COSY spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.



**Figure SM 2.2.1.9.**  $^{13}\text{C}$  (down) and DEPT (up) spectra of 3-methyl-4-(4-fluorobenzoyl)-1-phenylpyrazol-5-one.

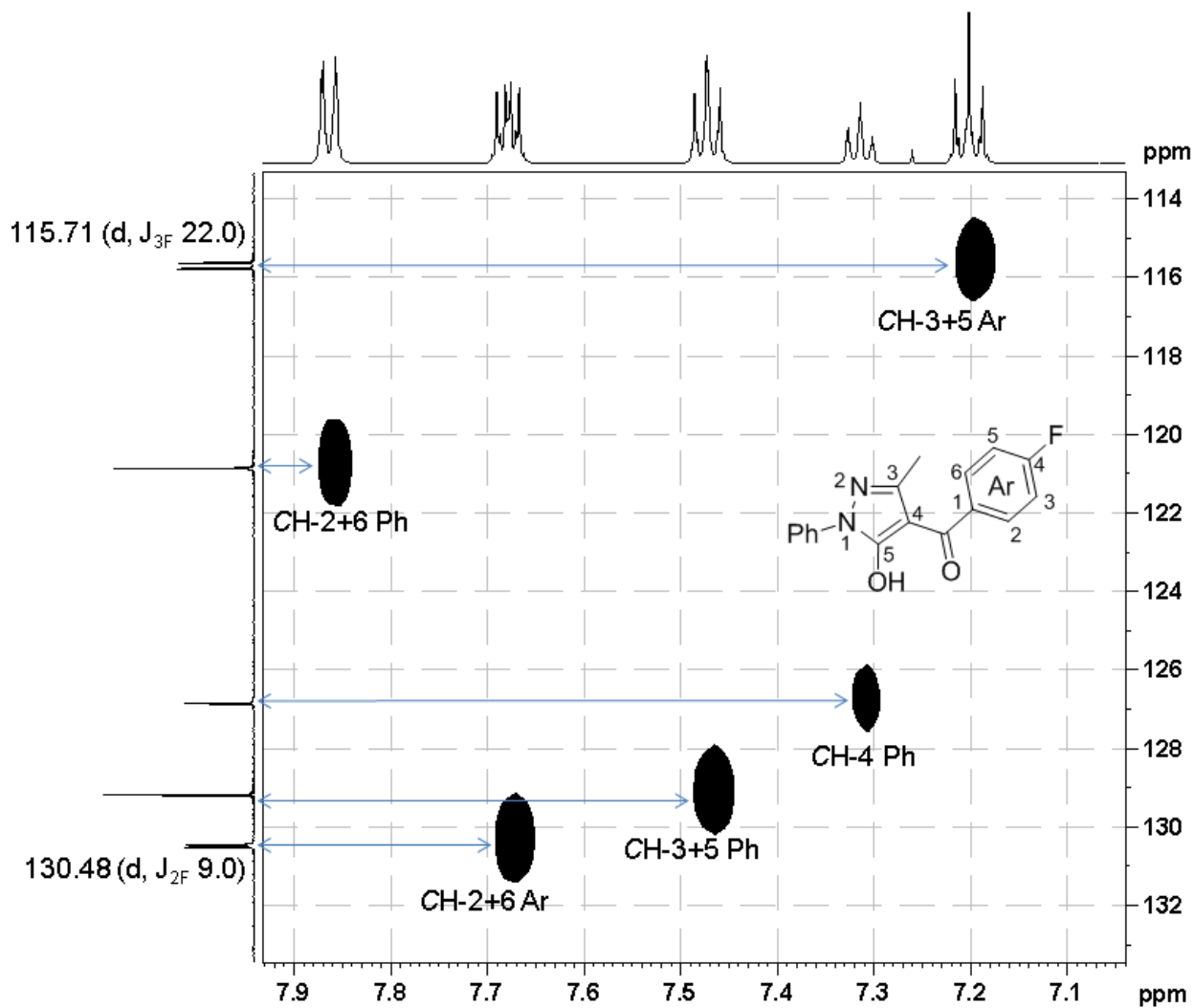


Figure SM 2.2.1.10.  $^1\text{H}$ - $^{13}\text{C}$  HSQC spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

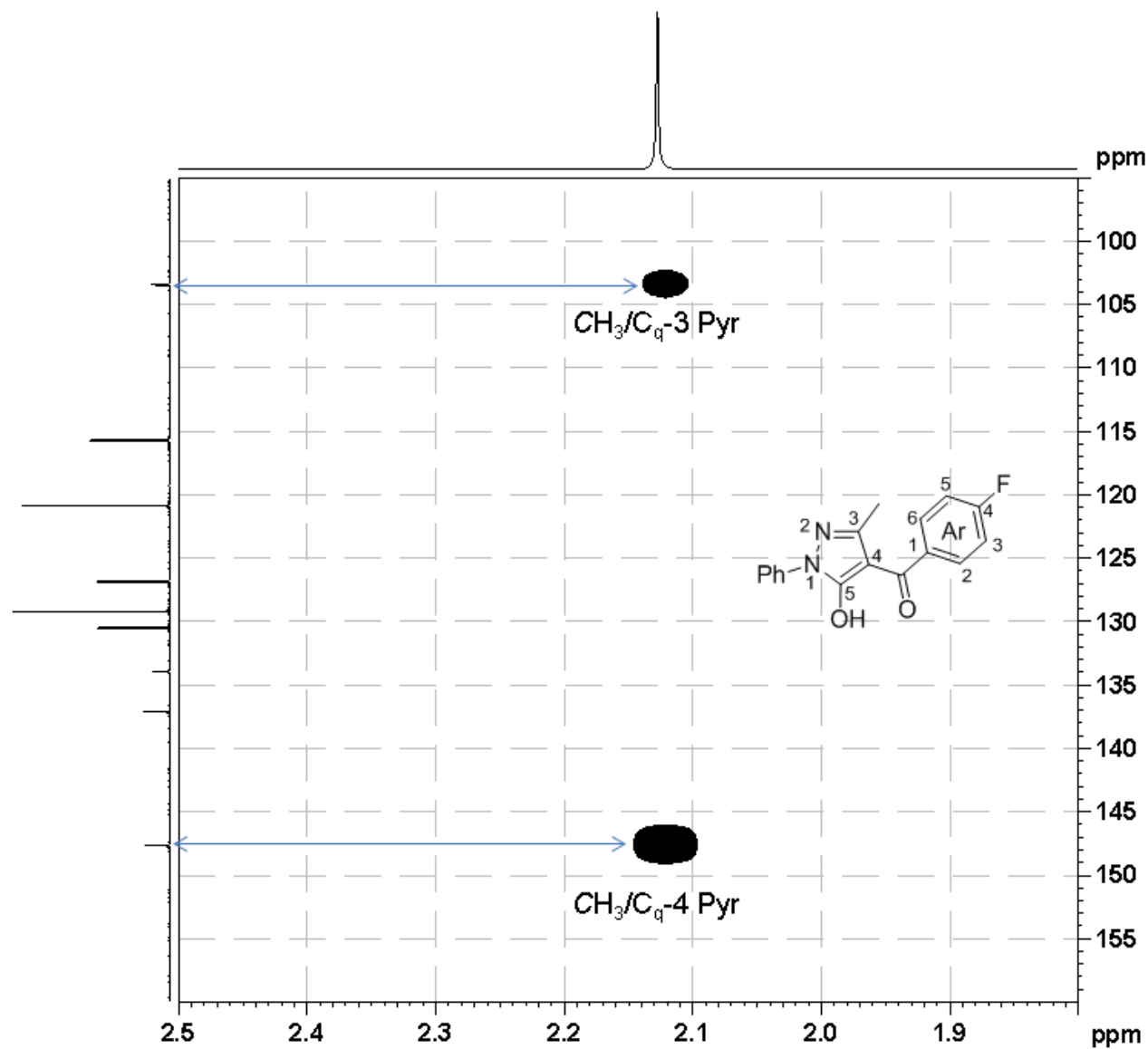


Figure SM 2.2.1.11.  $^1\text{H}$ - $^{13}\text{C}$  HMBC spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

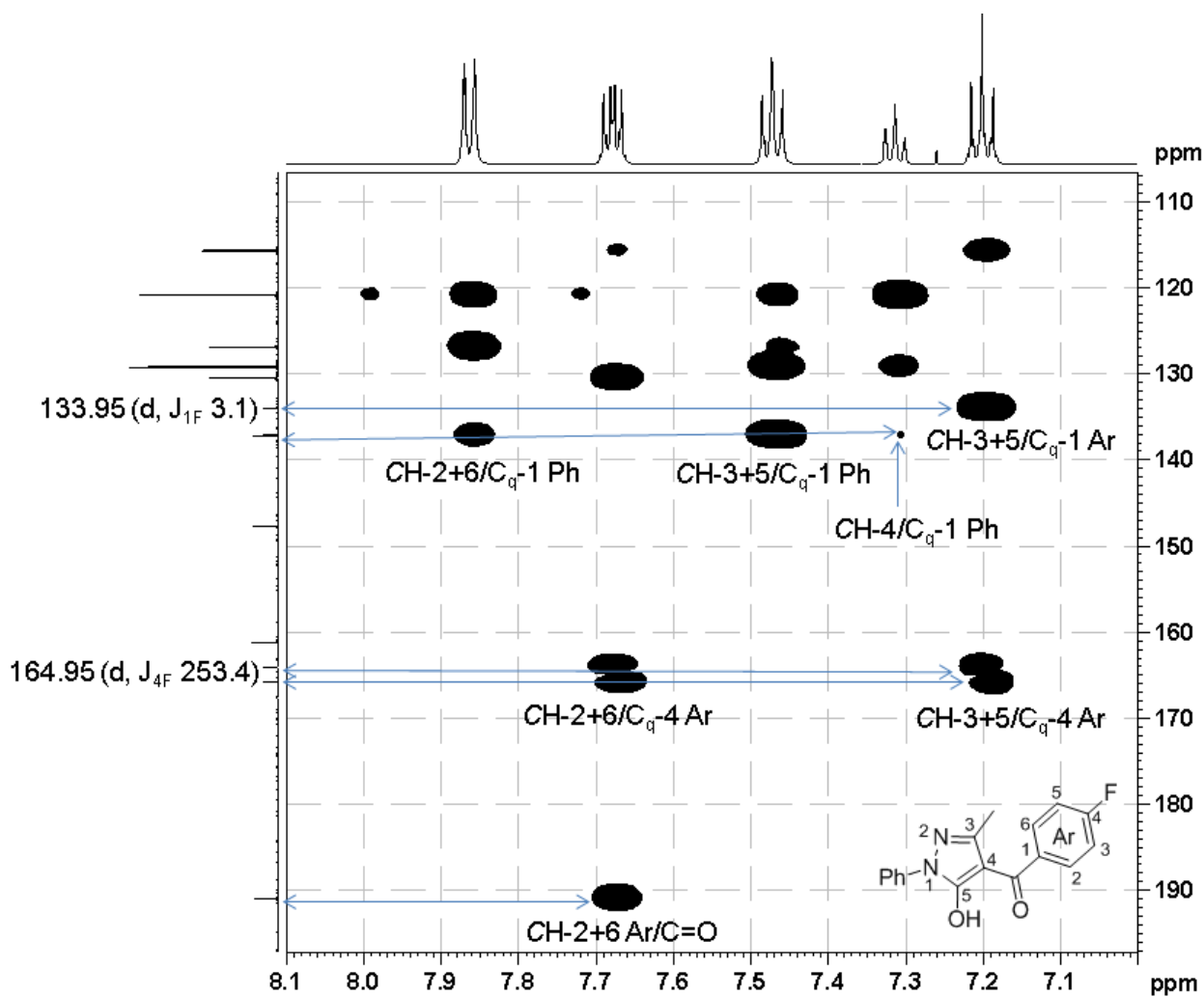
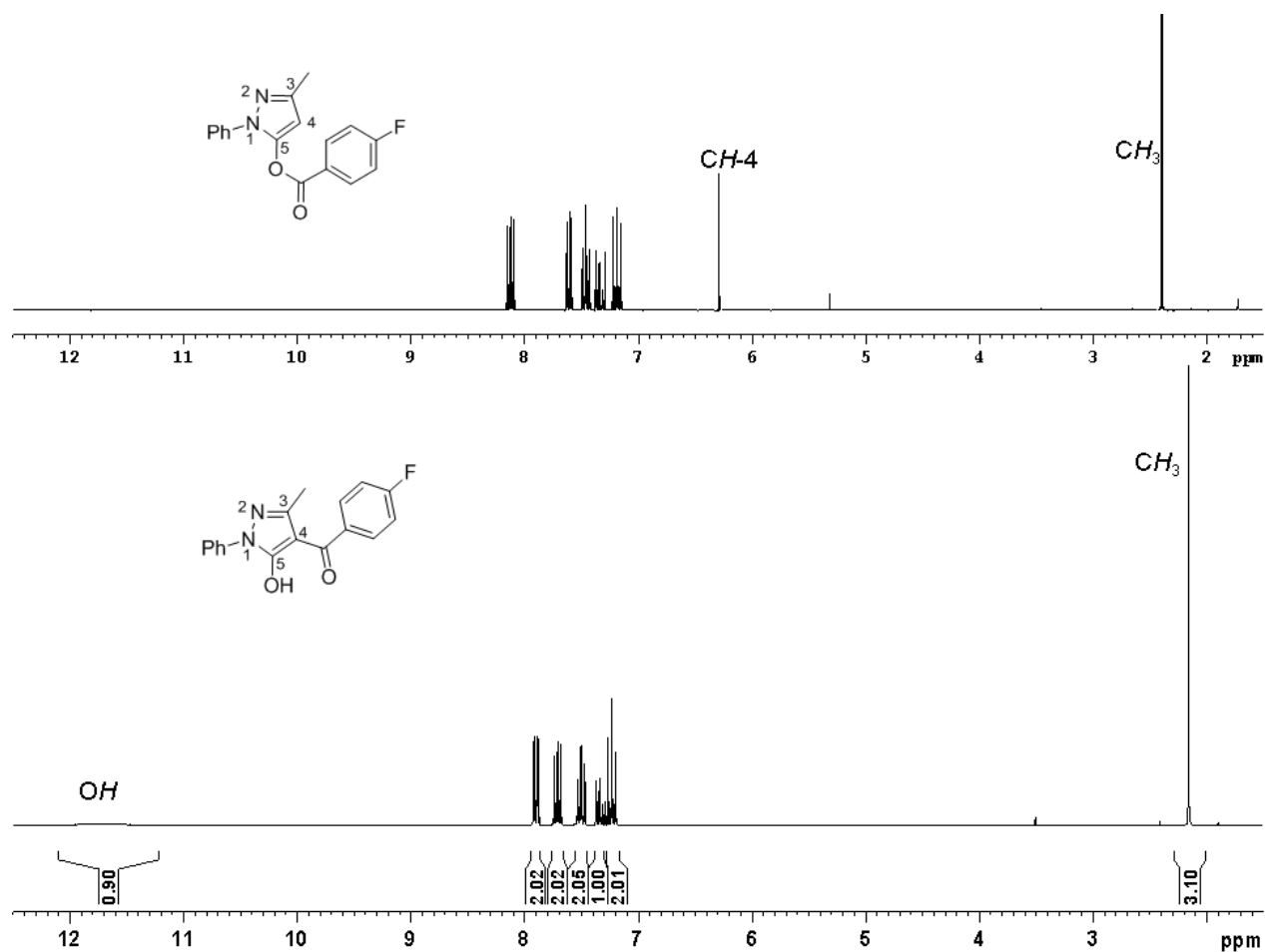
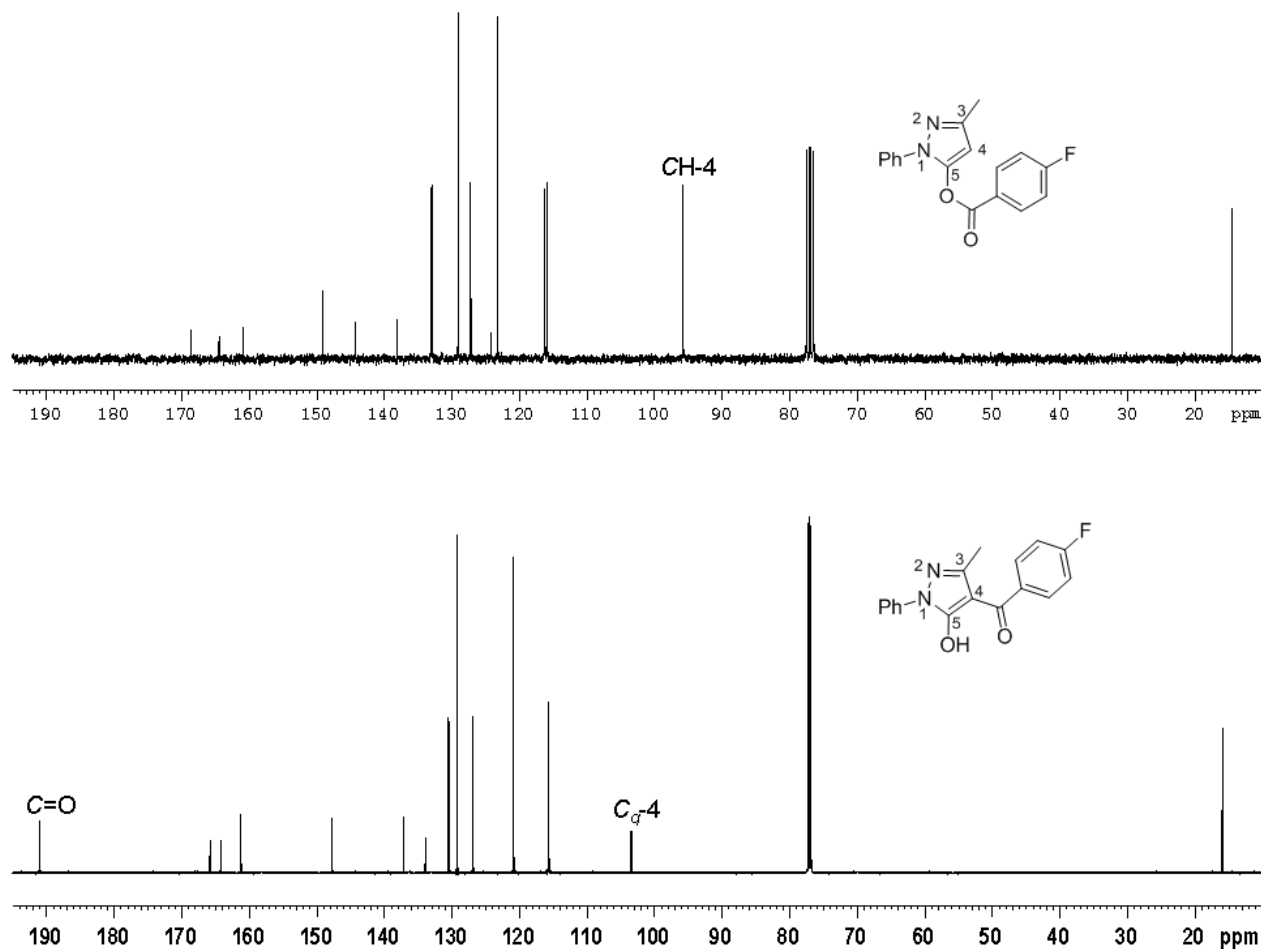


Figure SM 2.2.1.12.  $^1\text{H}$ - $^{13}\text{C}$  HMBC spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.



**Figure SM 2.2.1.13.**  $^1\text{H}$  spectra of C-acylated (down) and O-acylated (up) compounds.



**Figure SM 2.2.1.14.**  $^{13}\text{C}$  spectra of C-allylated (down) and O-acylated (up) compounds.

### Acknowledgement

Reprinted (adapted) with permission from *J. Chem. Educ.* 2015, **92**, 382-384. Copyright (2014) American Chemical Society.

The financial support by the EU Social Fund and Ministry of Education and Science, EU operational program "Development of human resources", project BG051PO001-3.3.07-0002 Student Practices, and by the Bulgarian Science Fund, projects UNA-17/2005 and DRNF-02-13/2009, is gratefully acknowledged.



## References

- <sup>1</sup> V. Kurteva, M. Petrova, *J. Chem. Educ.* 2015, **92**, 382-384.
- <sup>2</sup> M. Atanassova, V. Kurteva, L. Lubenov, I. Billard, *RSC Adv.* 2014, **4**, 38820-38829.

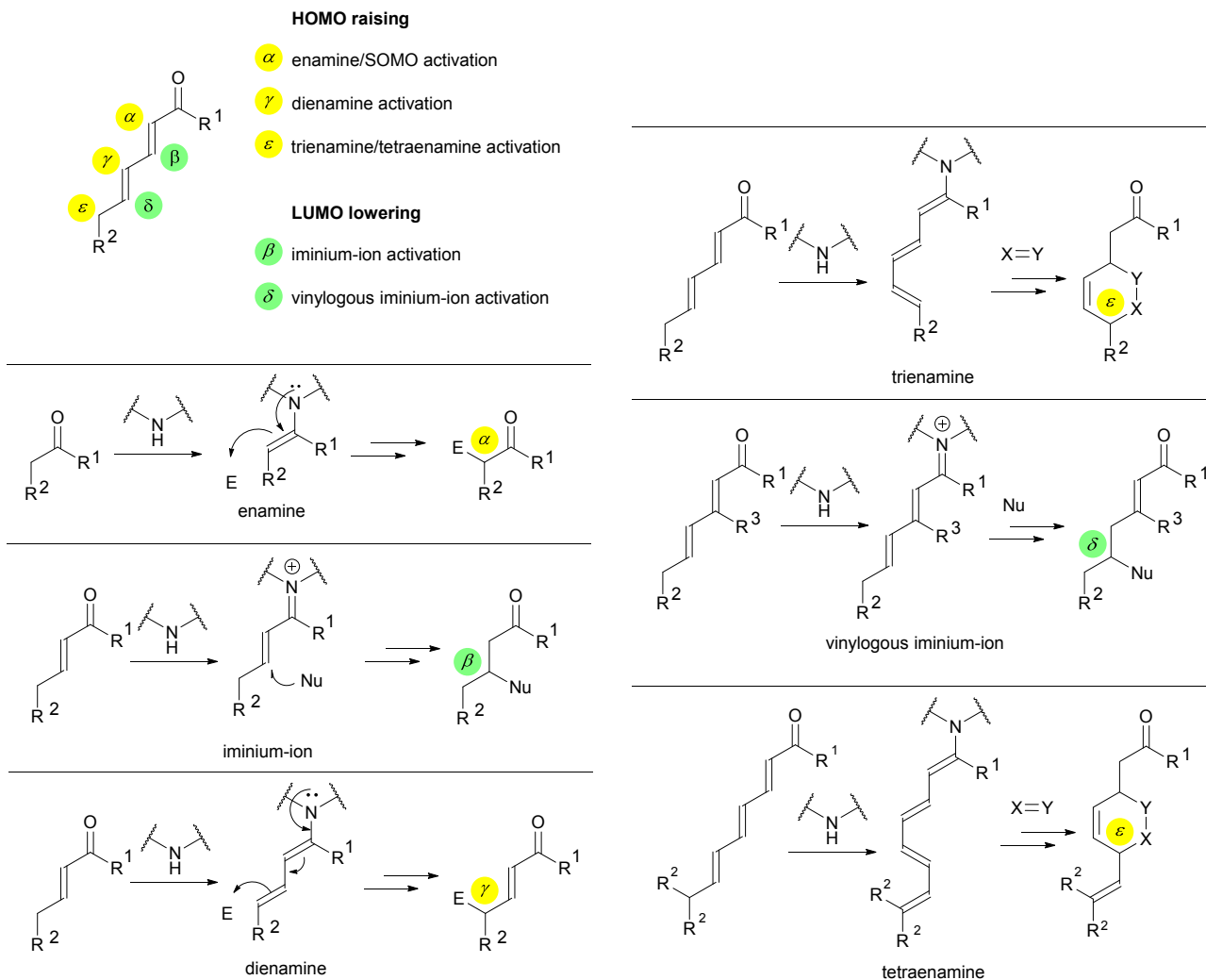
## Organocatalytic Asymmetric $\alpha$ -Arylation of Aldehydes

### Supplementary Material

#### Experimental Background

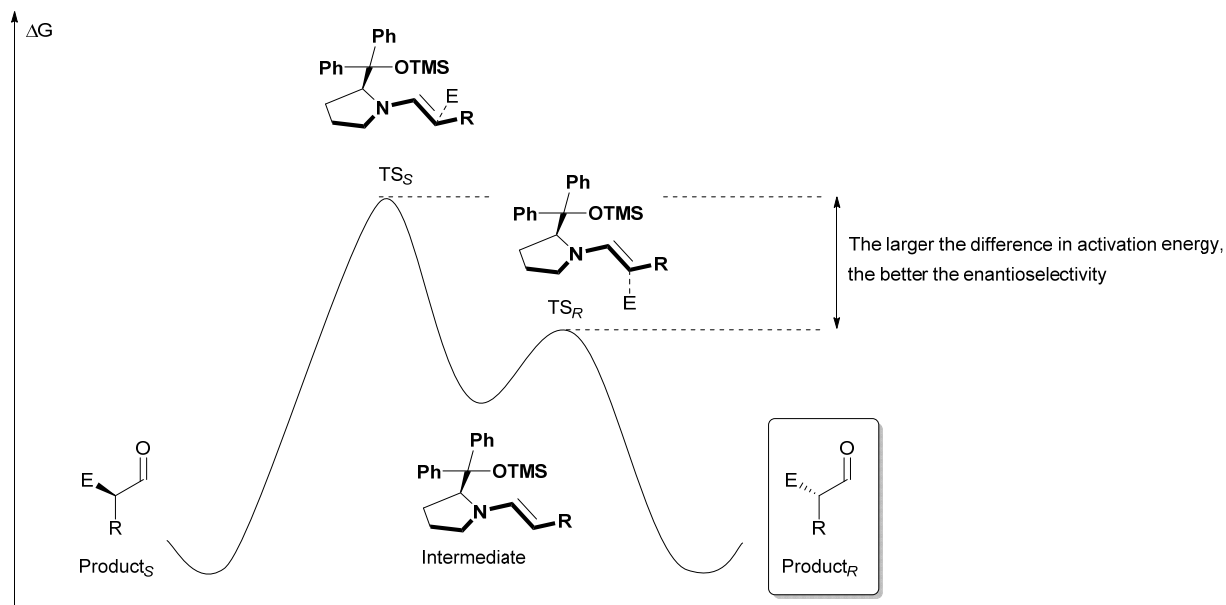
The evolution of asymmetric aminocatalysis can greatly be attributed the recognition that chiral amines can be used to activate carbonyl compounds, thus enabling a large number of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -functionalizations involving enamine,<sup>1</sup> iminium-ion<sup>2</sup> and dienamine<sup>3</sup> intermediates, respectively. Even tetraenamine activation and more remote functionalization strategies involving trienamine intermediates have been described.<sup>4</sup>

The carbonyl compounds are activated through fundamental and general activity concepts. For iminium-ion catalysis the LUMO (Lowest Unoccupied Molecular Orbital) of the iminium-ion is lower in energy than that of the carbonyl, thus the iminium-ion is more electrophile and more susceptible for nucleophilic attack. In contrast, the HOMO (Highest Occupied Molecular Orbital) of the enamine intermediates is higher in energy than that of the carbonyl compounds thus enhancing their reactivity towards electrophiles. In both cases the energy gap between the LUMO of the electrophile and the HOMO of the nucleophile is decreased, thus enhancing the reactivity. Scheme SM 2.2.2.1 outlines the aminocatalytic strategies described.



**Scheme SM 2.2.2.1** Aminocatalytic activation strategies. Nu: Nucleophile. E: Electrophile

When an enantiopure catalyst is used, e.g. a secondary amine diarylprolinol silyl ether catalyst, two diastereomeric transition states can be formed from the common enamine intermediate, a pro-*S* ( $TS_S$ ) and a pro-*R* transition state ( $TS_R$ ), with possibly two different energies. If a difference in activation energy exists between the two transition states, one of the product enantiomers is formed in excess (see Figure SM 2.2.2.1). This is a simplified explanation as the enamine intermediate can have several different configurations that can result in different stereoselectivities.<sup>5</sup>



**Figure SM 2.2.2.1** Asymmetric enamine catalysis. TS: Transition state

For a very simple case of asymmetric catalysis, the enantiomeric excess (ee) of the reaction only depends on the difference in activation energy between the two diastereomeric transition states, but in reality the reactions are often complicated by several factors such as competing achiral pathways and equilibrating intermediates. To achieve high enantioselectivity, background reactions and epimerization of the products has to be minimized.

## Experiment Notes

The experiment has been executed by a first year master student, and a bachelor student with good knowledge of the basics of synthetic organic chemistry should also be able to conduct the experiment. It is helpful if the student is familiar with flash column chromatography.

In order to determine the ee of the reaction, the retention times on the HPLC of both of the product enantiomers should be known. Hence, a racemic mixture of the enantiomers should be prepared. This can be done by performing the reaction as described using a 1:1 mixture of (*S*)-(-)- $\alpha,\alpha$ -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether and (*R*)-(+)- $\alpha,\alpha$ -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether to catalyse the reaction. Alternatively one of the students can perform the reaction with the (*R*)-(+)- $\alpha,\alpha$ -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether catalyst and a mixture of the products can then be used as the reference sample.

The experiment has also been performed at a 15 mmol scale and at a 0.2 mmol scale.

### **Laboratory session 1 (2 hours): Organocatalytic asymmetric $\alpha$ -arylation of 3-methylbutanal**

(S)-(-)- $\alpha,\alpha$ -Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether is a sticky oil and the weighing of the catalyst can be time consuming for the students. Time can be saved if the instructor prepares a stock solution of the catalyst in EtOH.

The ratio of naphthoquinone to aldehyde, and the composition of the solvent (H<sub>2</sub>O to EtOH ratio), are both significant due to the oxidation-reduction chemistry of the naphthoquinone. Through the reaction screening it has been found that 5 equivalents of aldehyde and 5 equivalents of H<sub>2</sub>O are necessary in order to minimize reduction of the quinone to the hydroquinone.

Benzoic acid is used as an additive as it facilitates the condensation and hydrolysis of the catalyst.

Some heating of the reaction mixture can be observed when the benzoic acid is added. If this is observed, the reaction should be left stirring until it has returned to room temperature (5-15 min.), prior to adding the 1,4-naphthoquinone.

The conversion of the reaction can be monitored by <sup>1</sup>H NMR spectroscopy: 1,4-Naphthoquinone shows a multiplet at 7.82-7.71 ppm, corresponding to 2 hydrogen atoms. When this signal is no longer observable, the reaction can be judged complete.

The hemiacetal product of this step is unstable on silica. However, it can be isolated by flash column chromatography using Iatrobeds (spherical silica gel).

The reaction time can be varied to some degree; 17–26 h has previously resulted in good yields and selectivities. The temperature should not exceed 25 °C.

### **Laboratory session 2 (4 hours): Removal of excess aldehyde, acetylation and work-up**

Aldehydes are known to form water soluble bisulfite adducts with NaHSO<sub>3</sub>, and the excess aldehyde in the crude mixture is therefore removed with the water layer of the NaHSO<sub>3</sub> wash.

When the reaction is washed with NaHSO<sub>3</sub> a web of brown solid might be formed, this can make the separation of the two layers difficult. However, adding a small amount of water can solve the problem.

The flushing with argon can be done simply by using a balloon filled with argon. If access to dry CH<sub>2</sub>Cl<sub>2</sub> is limited, then the reaction can be done with CH<sub>2</sub>Cl<sub>2</sub> taken from a newly opened bottle.

Some students might need to be asked why Et<sub>3</sub>N and acid anhydride are used in excess (two hydroxyl groups are acetylated).

During the work-up of the acetylation step acid and base solution are combined resulting in formation of CO<sub>2</sub> gas. The instructor should make sure, that the students do not shake the separatory funnel directly after mixing the acid and base. Frequent venting is necessary.

### Laboratory session 3 (5 hours): Flash column purification, NMR and chiral HPLC

The amount of time needed for this session is highly dependent on the students' prior experience with flash column chromatography. An experienced student might be much faster than the indicated time.

The amount of Celite does not need to be weighed. The use of Celite is not critical, but it does ease the loading on the column.

When the chromatography is followed with TLC it is advantageous to use 25% EtOAc in pentane for the eluting TLC solvent.

Around 800 mL of eluent is used for the column, and fractions 22-40 contain product when using 38 g silica and collecting in 15 mL fractions. Depending on the laboratory practice it might be beneficial to collect in larger fractions.

An IR-spectrum and a MS-spectrum can be recorded.

### Results

(2*S*,3*R*)-3-Isopropyl-2,3-dihydronaphtho[1,2-*b*]furan-2,5-diyl diacetate is obtained as a clear orange oil (70-77% yield) and has the following physical and spectroscopic data:  $R_f = 0.34$  (25% EtOAc in pentane).  $[\alpha]_{20}^D = -192.4$  ( $c = 2.0$ ,  $\text{CH}_2\text{Cl}_2$ ); FT-IR (ATR): 2961, 1751, 1599, 1459, 1435, 1365, 1199, 1159, 1061  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05-7.98 (m, 1H), 7.81 (m, 1H), 7.55-7.46 (m, 2H), 7.17 (s, 1H), 6.75 (s, 1H), 3.34 (d,  $J = 5.1$  Hz, 1H), 2.46 (s, 3H), 2.13-2.06 (m, 4H), 0.98 (d,  $J = 6.7$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.1, 169.9, 151.5, 141.0, 127.0, 126.6, 126.3, 122.1, 121.6, 120.7, 119.8, 115.4, 102.0, 55.4, 30.7, 21.3, 21.1, 19.3, 19.3; HRMS calculated for:  $[\text{C}_{19}\text{H}_{20}\text{O}_5 + \text{Na}]^+$  351.1203; found 351.1207. The ee is determined to be 97-98% ee by HPLC using a Chiralpak IB column 95% hexane/5% isopropanol, 1.0 mL/min. Retention times are: 5.8 min (minor), 6.5 min (major).

### Question Answers

1. As there are two stereocenters in the product compound, two possible diastereoisomers can be formed. However, if the experiment has been conducted properly, only one diastereoisomer should be observed in the  $^1\text{H}$  NMR spectrum, hence the dr is >20:1. It might be possible to see trace amounts of the small diastereoisomer. When looking at the HPLC data, 4 peaks is observed, consistent with two pairs of diastereoisomers and two pairs of enantiomers.
2. The ee is calculated by:

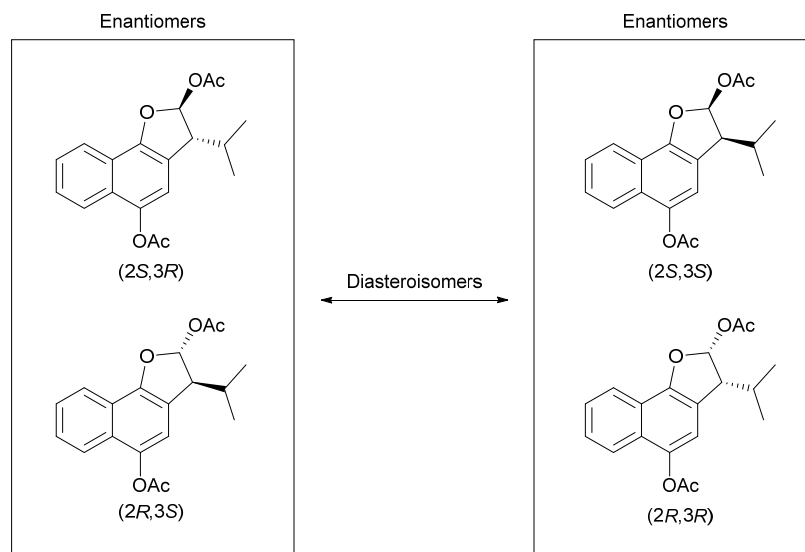
$$ee = \% \text{ major enantiomer} - \% \text{ minor enantiomer}$$

From the HPLC data in Figure SM X.8 the ee is calculated by:

$$ee = \frac{\% \text{ Area}(\text{major}) - \% \text{ Area}(\text{minor})}{\% \text{ Area}(\text{major}) + \% \text{ Area}(\text{minor})} \times 100\% = \frac{96.4 - 1.4}{96.4 + 1.4} \times 100\% = 97\%$$

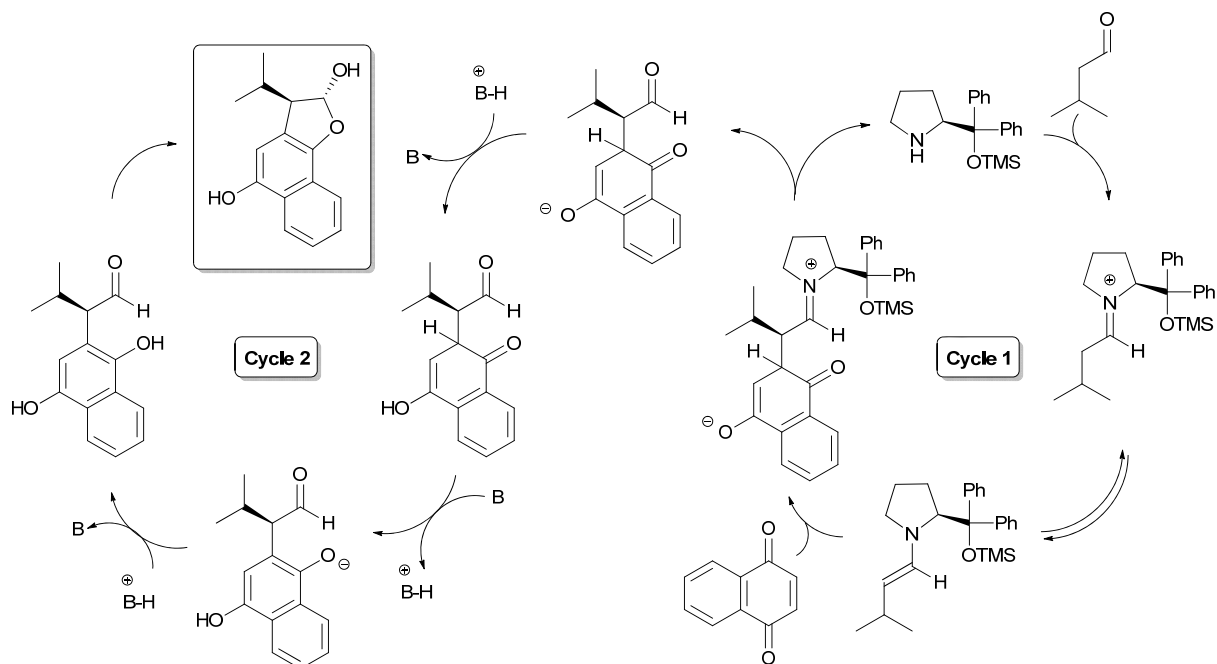
The high diastereomeric ratio means, that of the two possible diastereoisomers that can be formed, only one of them is selectively formed in this reaction. The high ee shows that of the two possible enantiomers, of the selectively formed diastereoisomer, one is formed in 97% excess.

The high dr and ee shows that the reaction is very selective.



**Scheme SM 2.2.2.2** The two pairs of enantiomers and diastereoisomers

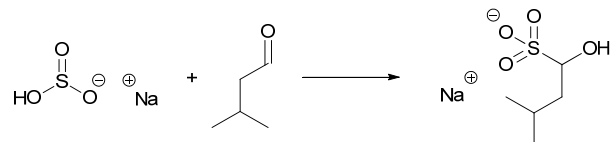
3. A suggested mechanism consists of two catalytic cycles as illustrated in Scheme SM 2.2.2.3.



**Scheme SM 2.2.2.3** The two catalytic cycles of the proposed mechanism for the organocatalytic  $\alpha$ -arylation of 3-methylbutanal. B: Base

The first cycle involves the reaction of the enamine intermediate with the naphthoquinone; the first stereogenic center is formed here by the naphthoquinone approaching the *Si*-face of the enamine intermediate resulting in attack from below the system. The second cycle consists of a series of proton-transfer reactions, essentially an aromatization sequence, followed by naphthol cyclization with the aldehyde, resulting in the most stable hemiacetal.  $\text{H}_2\text{O}$  is thought to have a crucial role in the reaction mechanism as no reaction occurs in its absence.

4. Aldehydes are known to form water soluble bisulfite adducts with  $\text{NaHSO}_3$  (Scheme SM 2.2.2.4),<sup>6</sup> hence when the crude is washed with sat. aq.  $\text{NaHSO}_3$  the aldehyde precipitates out as a solid bisulfite adduct and is dissolved in the water layer.

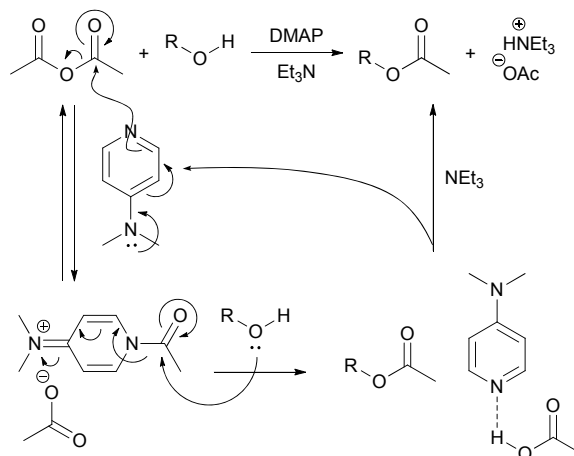


**Scheme SM 2.2.2.4** Reaction of sodium bisulfite with 3-methylbutanal

5. 4-Dimethylaminopyridine (DMAP) acts as a nucleophilic catalyst; as DMAP is more nucleophilic than the alcohols, it attacks the  $\text{Ac}_2\text{O}$  faster and forms a very electrophilic intermediate (the acylpyridinium cation in Scheme SM 2.2.2.5). The alcohols react with the

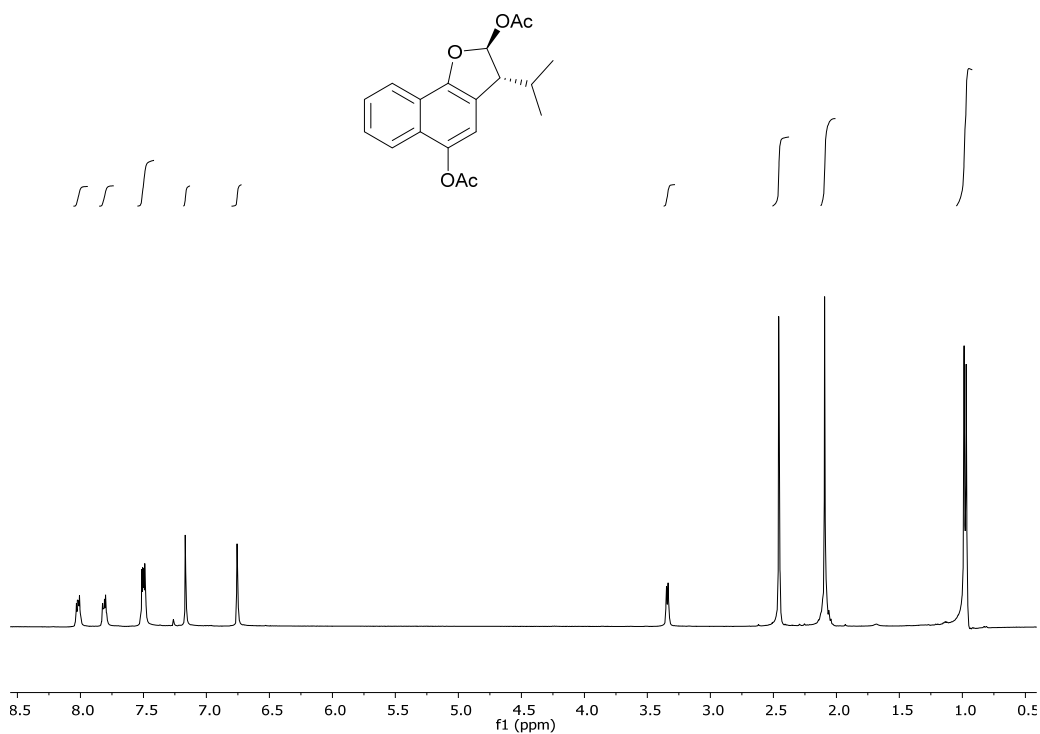


acetylated DMAP to form the product and deactivated catalyst. Lastly active DMAP is regenerated by the  $\text{Et}_3\text{N}$ .<sup>7</sup>

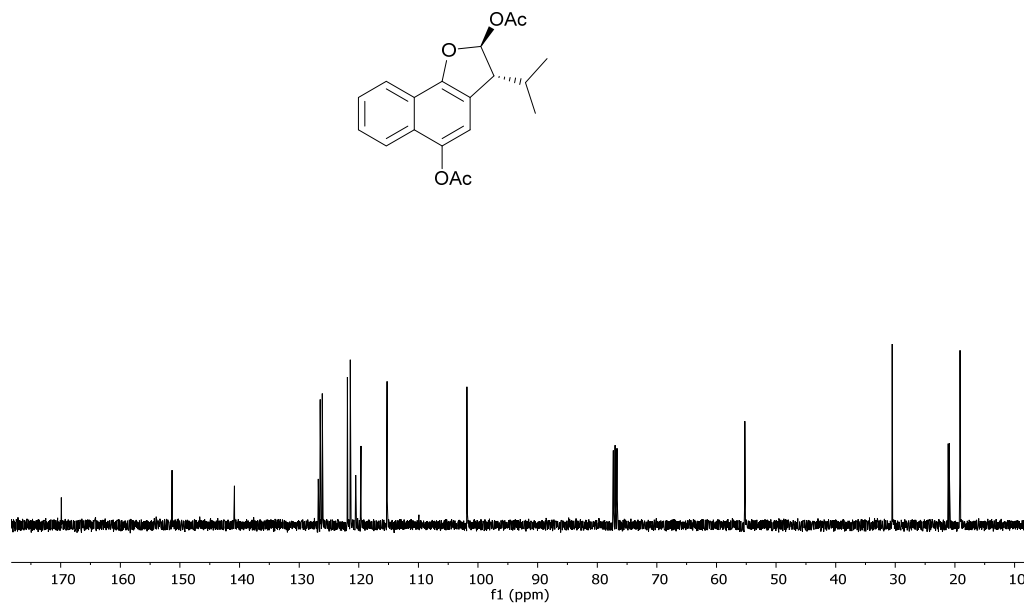


**Scheme SM 2.2.2.5** Acetylation of an alcohol

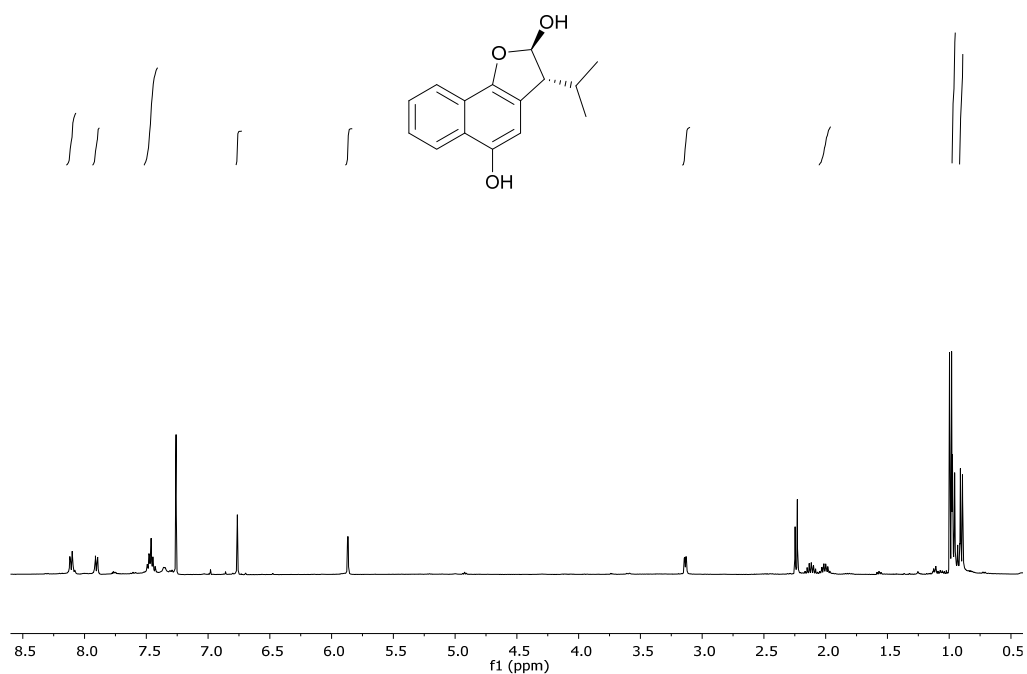
## Spectra



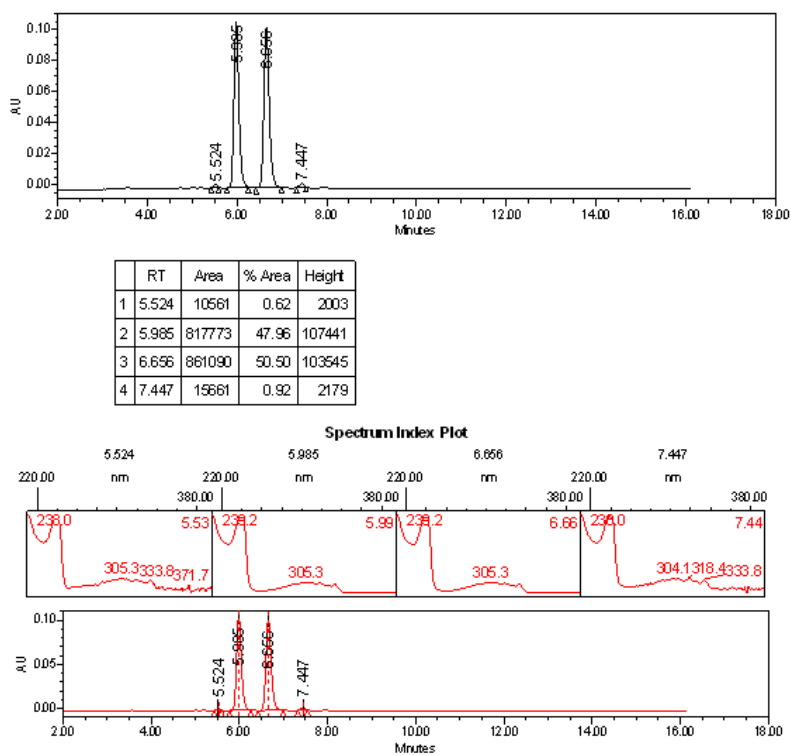
**Figure SM 2.2.2.2** <sup>1</sup>H NMR spectrum of (2S,3R)-3-isopropyl-2,3-dihydro-2,5-diacetylnaphtho[1,2-b]furan (CDCl<sub>3</sub>)



**Figure SM 2.2.2.3** <sup>13</sup>C NMR spectrum of (2S,3R)-3-isopropyl-2,3-dihydro-2,5-diacetylnaphtho[1,2-b]furan (CDCl<sub>3</sub>)



**Figure SM 2.2.2.4** Crude <sup>1</sup>H NMR spectrum of (2*R*,3*R*)-3-isopropyl-2,3-dihydro[1,2-*b*]furan-2,5-diol from the first step (CDCl<sub>3</sub>)



**Figure SM 2.2.2.5** HPLC data for racemic 3-isopropyl-2,3-dihydro[1,2-*b*]furan-2,5-diol diacetate

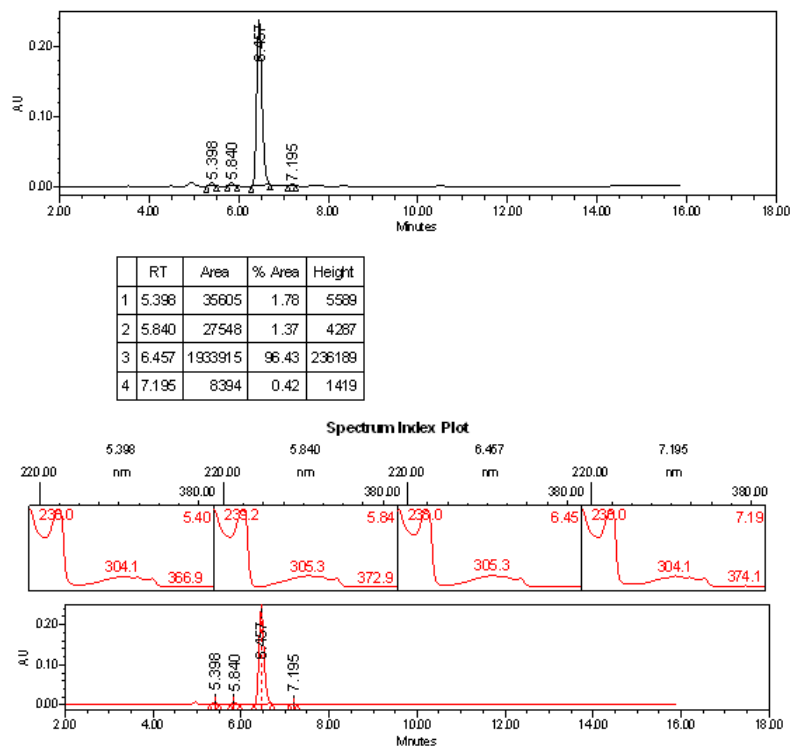


Figure SM 2.2.2.6 HPLC data for (2*S*,3*R*)-3-isopropyl-2,3-dihydronaphtho[1,2-*b*]furan-2,5-diyl diacetate

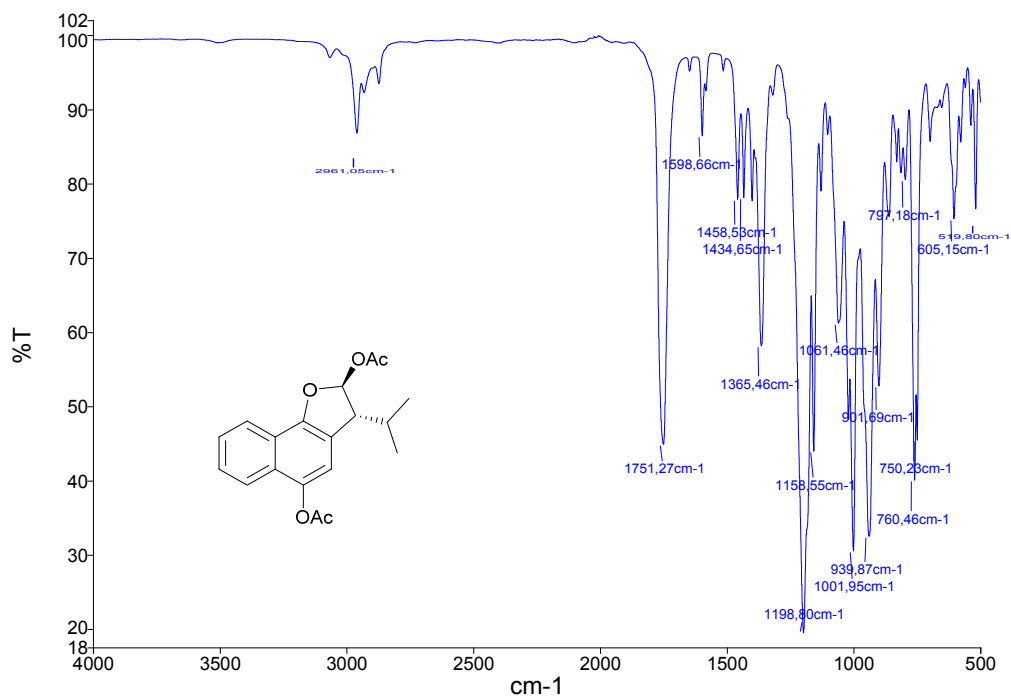


Figure SM 2.2.2.7 FT-IR of (2*S*,3*R*)-3-isopropyl-2,3-dihydronaphtho[1,2-*b*]furan-2,5-diyl diacetate

- <sup>1</sup> For a review, see e.g.: S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* 2007, **107**, 5471.
- <sup>2</sup> For review, see e.g.: A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* 2007, **107**, 5416.
- <sup>3</sup> For a review, see e.g.: D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* 2012, 865.
- <sup>4</sup> For a review on remote functionalizations, see: a) H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Chem. Sci.* 2013, **4**, 2287; for examples of tetraenamine activation, see: b) J. Stiller, P. H. Poulsen, D. C. Cruz, J. Dourado, R. L. Davis, K. A. Jørgensen, *Chem. Sci.* 2014, **5**, 2052; c) Q.-Q. Zhou, Y.-C. Xiao, X. Yuan, Y.-C. Chen, *Asian J. Org. Chem.* 2014, **3**, 545.
- <sup>5</sup> M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* 2011, **47**, 632.
- <sup>6</sup> J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, New York, 1<sup>st</sup> edn, 2001, chapter 6, 148-149.
- <sup>7</sup> S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich, H. Zipse, *Chem. Eur. J.* 2005, **11**, 4751.

## Matteson homologation of pinacol boronic ester: an efficient method using the boron-ate complexes

### Supplementary Material

#### Figures

SM X.1 –Methanol bath cooling at -98°C.....	1
SM X.2 - Bohlender PTFE tubing needle.....	2
SM X.3 – Reaction apparatus .....	3
SM X.4 – <sup>1</sup> H NMR spectrum (300 MHz, CDCl <sub>3</sub> ) of the crude product.....	4
SM X.5 – GC-MS trace of the crude product.....	5

#### Information for Instructors

The following experiment is devoted for the practical teaching of advanced organic chemistry (typically Master students). The aim of the experiment deal with the acquisition of good practices by

- working at low temperature and under inert atmosphere,
- handling corrosive organic compounds,
- controlling reaction temperature,
- purifying organic compounds by filtration on silica gel,
- analyzing and interpreting <sup>1</sup>H NMR and GC-MS spectra.

#### Reproducibility by the students

This experiment is suitable for students with previous laboratory experience in organic chemistry. Master and PhD students from the Department of Chemistry, Faculty of Sciences, Rouen University, assessed the reproducibility of the experiment reported herein. No significant changes were observed in the yield of the reaction (less than 10%) nor in the conversion rate (at least 93 %) during twice repetitions.

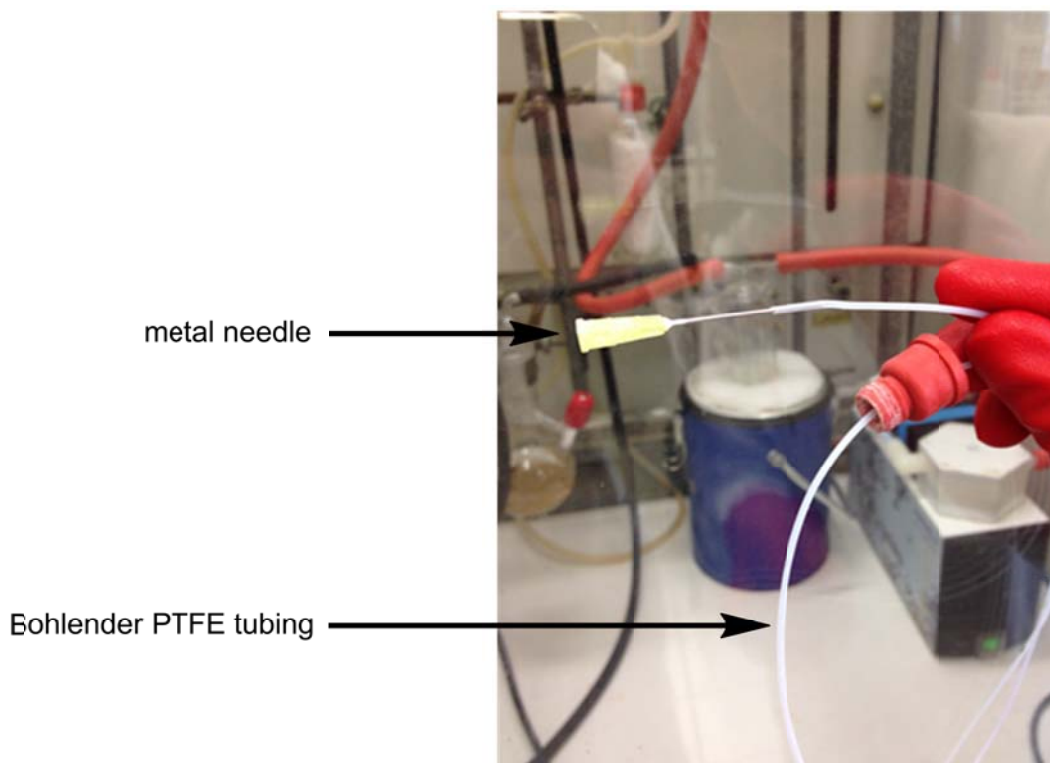
#### Experimental details

The reaction aims to use the carbenoids chemistry and the ate-complexes through the boronic ester in the Matteson homologation. The solution of starting boronic ester (200 mg, 0.92 mmol, 1 equiv) and bromochloromethane (107 μL, 1.65 mmol, 1.8 equiv) in Et<sub>2</sub>O (7 mL) was cooled at -98°C with a methanol bath and liquid nitrogen. In order to control the temperature, a mixture of solid and liquid methanol should be present in the bath during all the experiment. (Figure Figure Error! *Not a valid bookmark self-reference.*1).



**Figure** Error! Not a valid bookmark self-reference.1 –Methanol bath cooling at -98°C

Then *n*-BuLi (1.03 mL, 1.6 M in hexane, 1.8 equiv) is added with a syringe pump at 50  $\mu\text{L}\cdot\text{min}^{-1}$  through a Bohlender PTFE tubing needle dipping in the reaction mixture. The needle can be made with a classic needle where the Bohlender tubing is passed through (Figure Figure SM 2.2.3.1).



**Figure SM 2.2.3.1** - Bohlender PTFE tubing needle

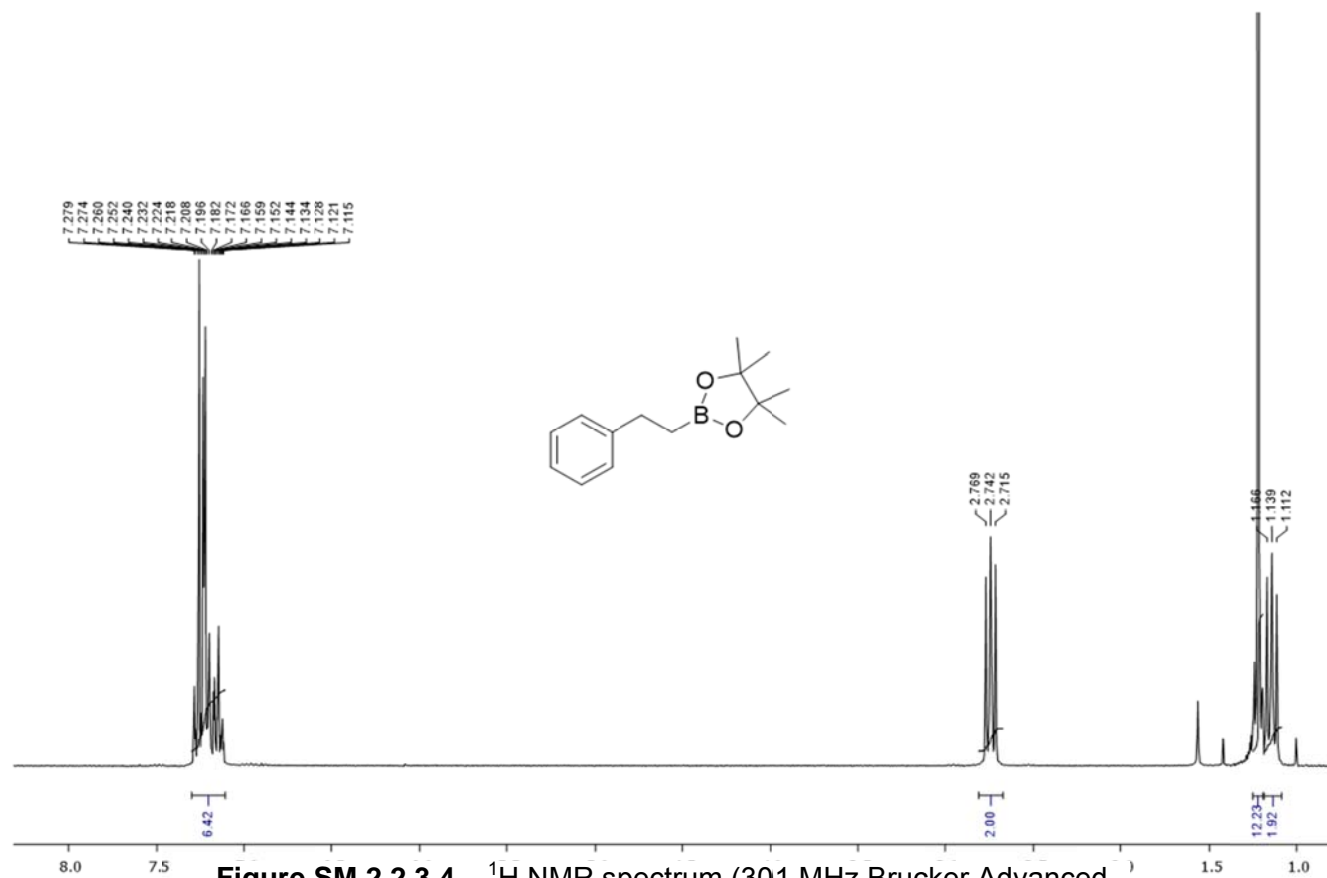
The dead volume of the needle should be taken in account for the amount of *n*-BuLi withdraw. The needle is passed through a septum to assure an inert atmosphere during the reaction and introduced into the flask with the three way valve (Figure Figure SM 2.2.3.). Then, the syringe is fitted to the syringe pump and the addition is started. **This point is important**, the needle must stay outside the reaction mixture until the first drop is observed then the needle can be dipped into the reaction mixture. If this point is not respected, there is a risk of clogging the needle (overpressure and explosion of the syringe).





**Figure SM 2.2.3.3** – Reaction apparatus (except the syringe pump)

Once the addition of *n*-BuLi is finished, the flask is removed from the cold bath and let warm up until room temperature and a white precipitate appears. The mixture was filtered through a plug of silica gel. Then, the solvent was removed under vacuum to afford 196 mg of the homologated product in 92% yield. The structure of the resulting compound was assigned by  $^1\text{H}$  NMR (Figure SM 2.2.3.4) and its purity was checked by GC-MS (Figure SM 2.2.3.5).



**Figure SM 2.2.3.4** –  $^1\text{H}$  NMR spectrum (301 MHz Bruker Advanced spectrometer,  $\text{CDCl}_3$ ) of the product.

$^1\text{H}$  NMR (301 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.32 – 7.09 (m, 5H, CH aromatic), 2.74 (t,  $J$  = 8.2 Hz, 2H,  $\text{CH}_2$ -Ph), 1.21 (s, 12H,  $\text{CH}_3$  pinacol), 1.14 (t,  $J$  = 8.2 Hz, 2H, B- $\text{CH}_2$ ).

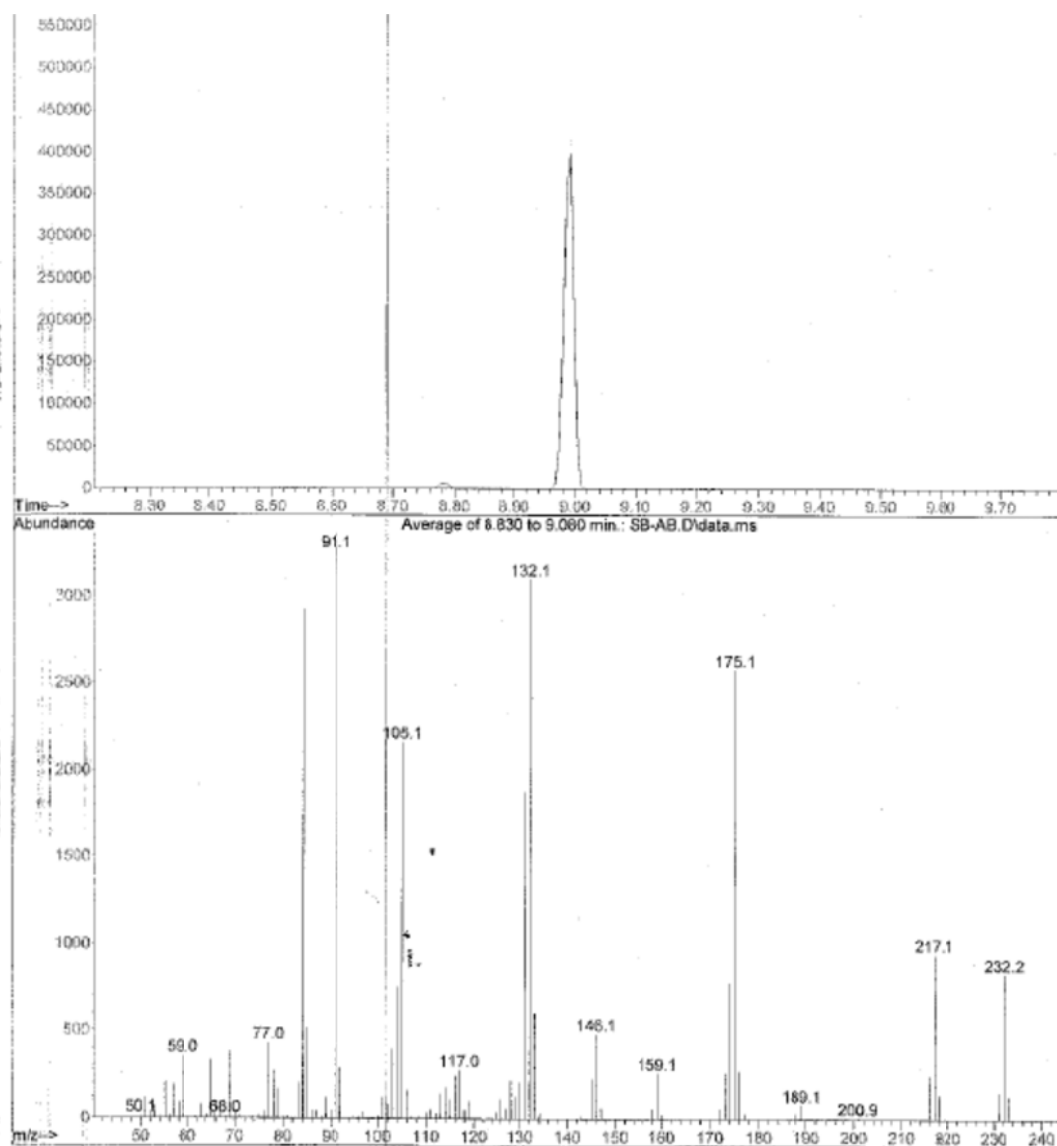
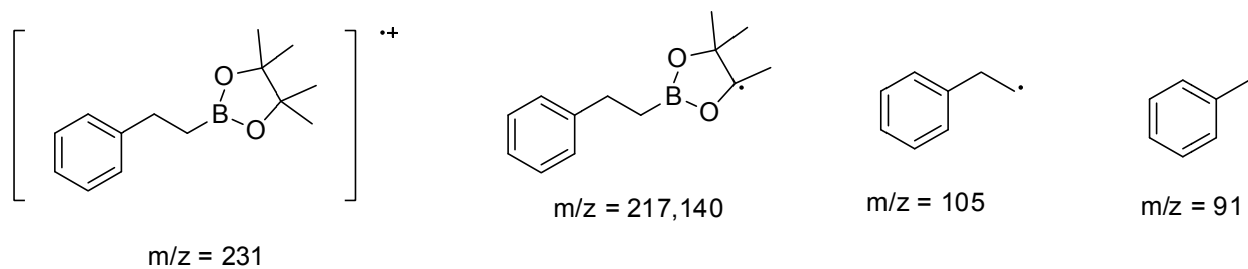


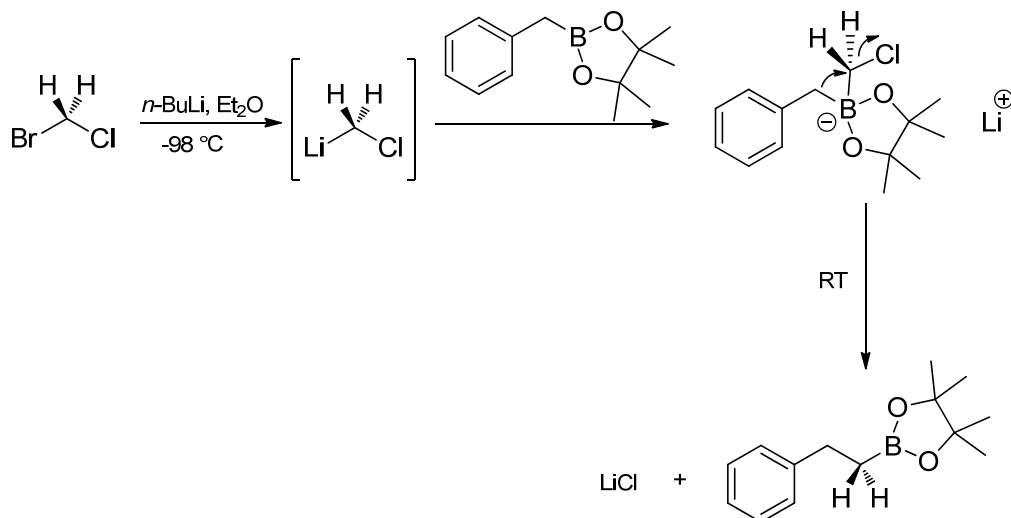
Figure SM 2.2.3.5 - GC-MS trace of the product.

GC-MS: rt = 8.99 min;  $m/z$  = 231 [ $M^+$ ], 216 [ $M - CH_3$ ] $^+$ , 174, 131, 105 [ $M - Bpin$ ] $^+$ , 91 [benzyl] $^+$ .



### Answers to the additional questions:

1. Propose a mechanism leading to the final compound.

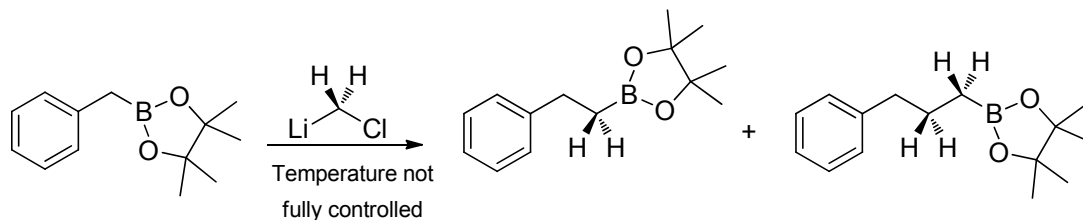


2. Explain why the excess of  $n\text{-BuLi}$  and bromochloromethane do not afford over-homologated products.

The excess of chloromethyl lithium generated *in situ* at 175 K decomposes before reaching the temperature of the boron-ate-complex rearrangement.

3. Discuss the importance of the control of the reaction temperature.

If the temperature is not fully controlled, there is a risk to start the rearrangement during the generation of the chloromethyl lithium and to get mixture of over- and homologated compounds:



## A practical Organocatalytic Alkylation Reaction with Benzodithiolylum Tetrafluoroborate Supplementary Material

### Experiments note:

Note for instructor.....	1
Characterization for compounds <b>4</b> and <b>5</b> .....	2

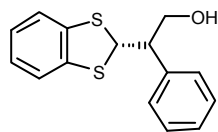
### Figures:

HPLC traces for compound <b>4</b> .....	3
<sup>1</sup> H and <sup>13</sup> C NMR spectra of compounds <b>4</b> and <b>5</b> .....	4
Photos of the experiment.....	6

### Notes for the instructor:

- To prevent loss of enantiopurity of the aldehydic alkylated intermediate, it is recommended to not use high temperatures to evaporate the solvent before reduction with sodium borohydride (session 2, point 2).
- Racemic **4** could be prepared using the same procedure for the enantioselective organocatalytic alkylation but using racemic MacMillan catalyst.
- The success of the reductive removal of benzodithiol group, depends on the quality of Raney<sup>®</sup>-nickel used. If this is not fresh or poorly preserved, it is recommended to use a double or triple of the amount of Raney<sup>®</sup>-nickel.
- To add an adequate amount of Raney<sup>®</sup>-nickel, it is suggested to leave settle the powder inside the Pasteur pipette (see figure SM 2.2.4.8). The Raney<sup>®</sup>-nickel will be added dropwise to the solution, leaving the water of the slurry inside the Pasteur pipette (see figure SM 2.2.4.8).
- To avoid unpleasant incidents caused from Raney<sup>®</sup>-nickel, it is recommended to not dry out the slurry, and to handle Raney<sup>®</sup>-nickel as slurry.
- In order to obtain well resolved NMR spectra of the compound **5**, an accurate filtration over silica gel pad should be performed to remove metal residues from the crude.
- Session 3 could be started in the same day of the session 2, and the reaction of the benzodithiol removal could be stirred for 24 h without any problem.

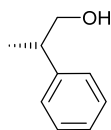
X. Spectral properties of compound **4**.



**(4)**: 96% yield; 96% ee. The desired product was isolated by flash column chromatography (cyclohexane/AcOEt = 90/10 to 80/20) as yellow oil; The ee was determined by HPLC analysis Daicel Chiralcel IC column: *n*-hexane/*i*-PrOH 96:4,

flow rate 0.50 mL/min, 30°C,  $\lambda = 232, 254 \text{ nm}$ ;  $t_{\text{major}} = 41.5 \text{ min.}$ ,  $t_{\text{minor}} = 35.5 \text{ min.}$ ;  $[\alpha]_{\text{D}}^{20} = +22.6$  ( $c=0.2$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta$  7.31-7.18 (5H, m), 7.16-7.11 (1H, m), 7.07-7.03 (1H, m), 6.96-6.90 (2H, m), 5.28 (1H, d,  $J = 9.5 \text{ Hz}$ ), 4.02-3.94 (2H, m), 3.27 (1H, ddd,  $J = 4.9, 6.8, 9.5 \text{ Hz}$ );  $^{13}\text{CNMR}$  (100 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta$  139.1, 137.2, 137.2, 128.7 (2C), 128.6 (2C), 127.7, 125.5, 125.4, 122.3, 122.2, 64.4, 56.2, 54.9.

X. Spectral properties of compound **5**.



**(5)**: 91% yield. The desired product was isolated by flash column chromatography (cyclohexane/AcOEt = 90/10 to 80/20) as yellow oil;  $[\alpha]_{\text{D}}^{20} = -15.4$  ( $c=0.5$  in  $\text{CHCl}_3$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta$  7.33-7.30 (2H, m), 7.24-7.20 (3H, m), 3.69 (2H, d,  $J = 7.0 \text{ Hz}$ ),

3.69 (1H, ses,  $J = 7.0 \text{ Hz}$ ), 1.43 (1H, bs), 1.26 (3H, d,  $J = 7.0 \text{ Hz}$ );  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta$  143.7, 128.5 (2C), 127.4 (2C), 126.5, 68.5, 42.3, 17.5.

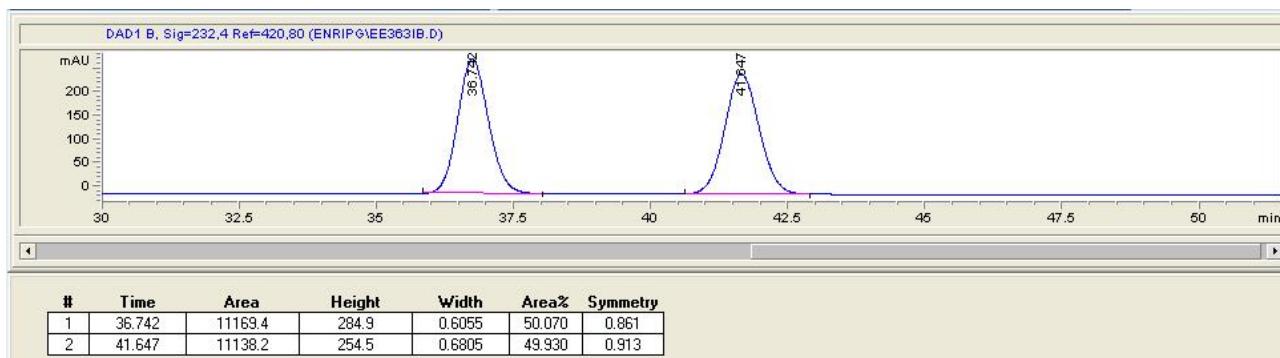


Figure SM 2.2.4.1 –Copy of HPLC trace of racemic **4**.

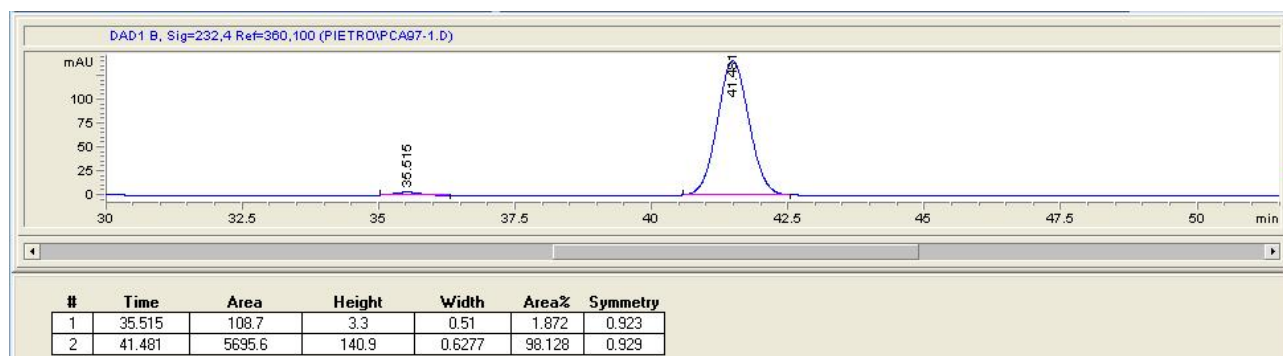


Figure SM 2.2.4.2 –Copy of HPLC trace of **4** obtained from enantioselective organocatalytic alkylation.

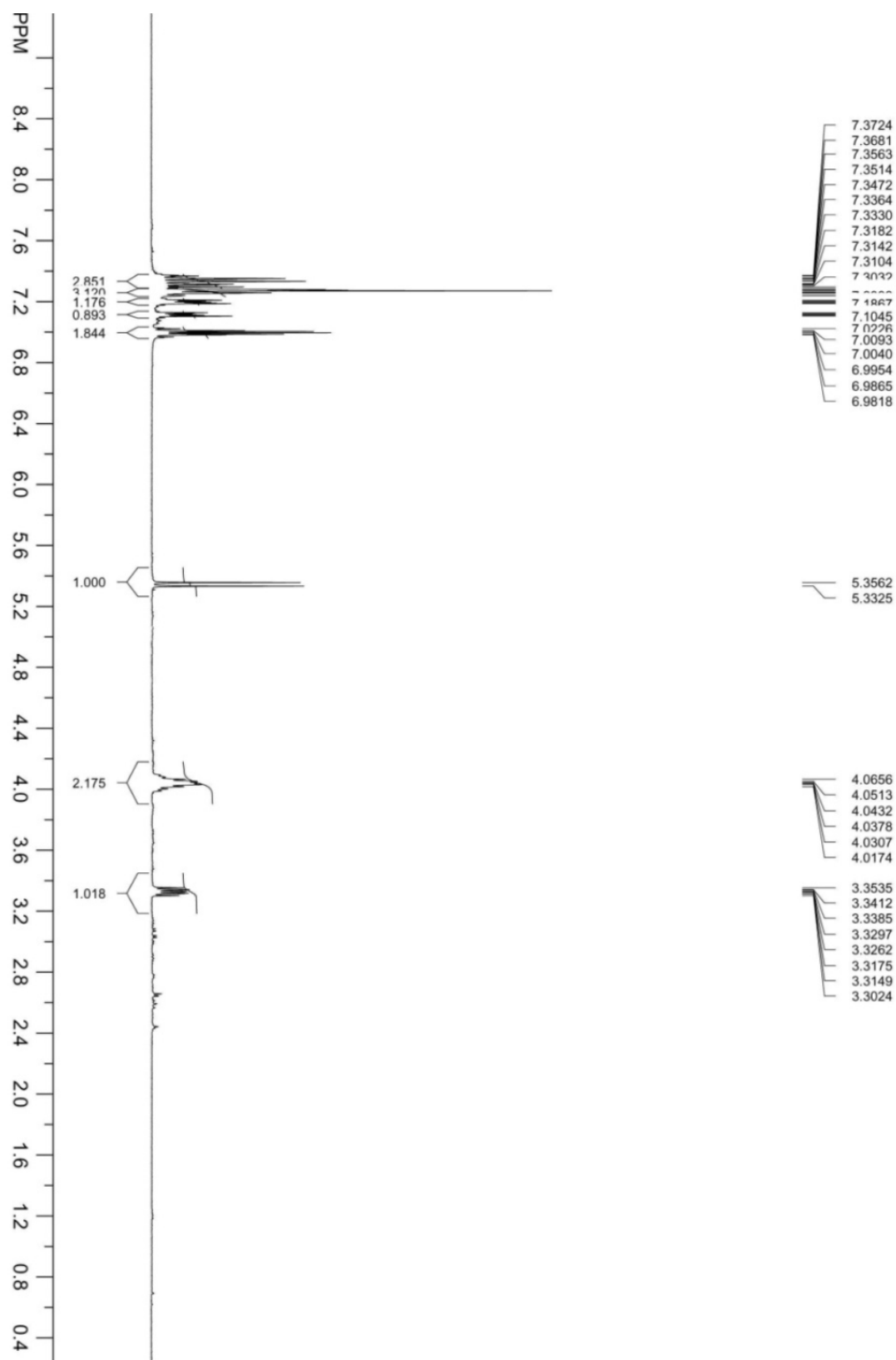


Figure SM 2.2.4.3 –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ) of compound 4.



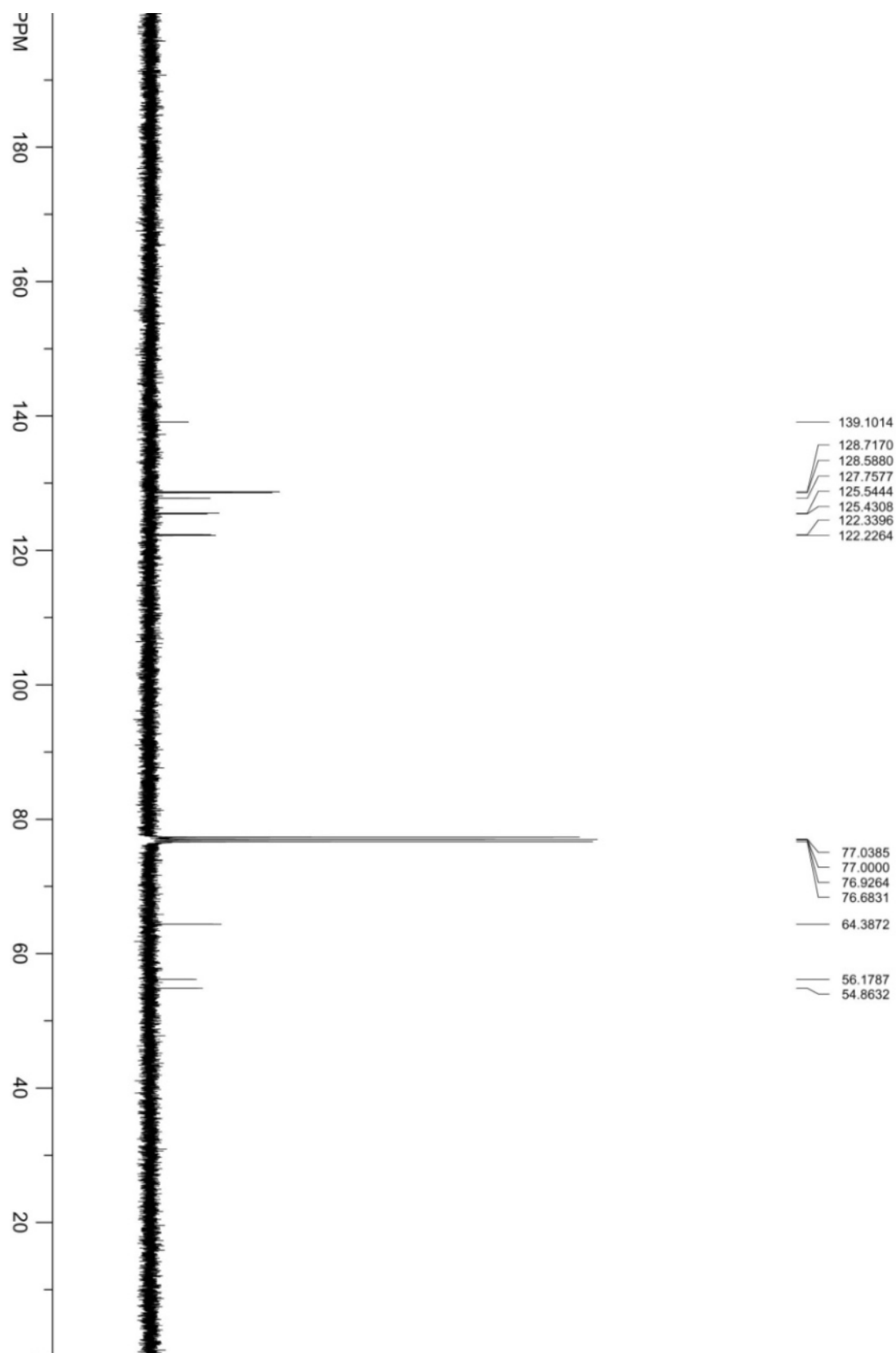


Figure SM 2.2.4.4- <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C) of compound 4.

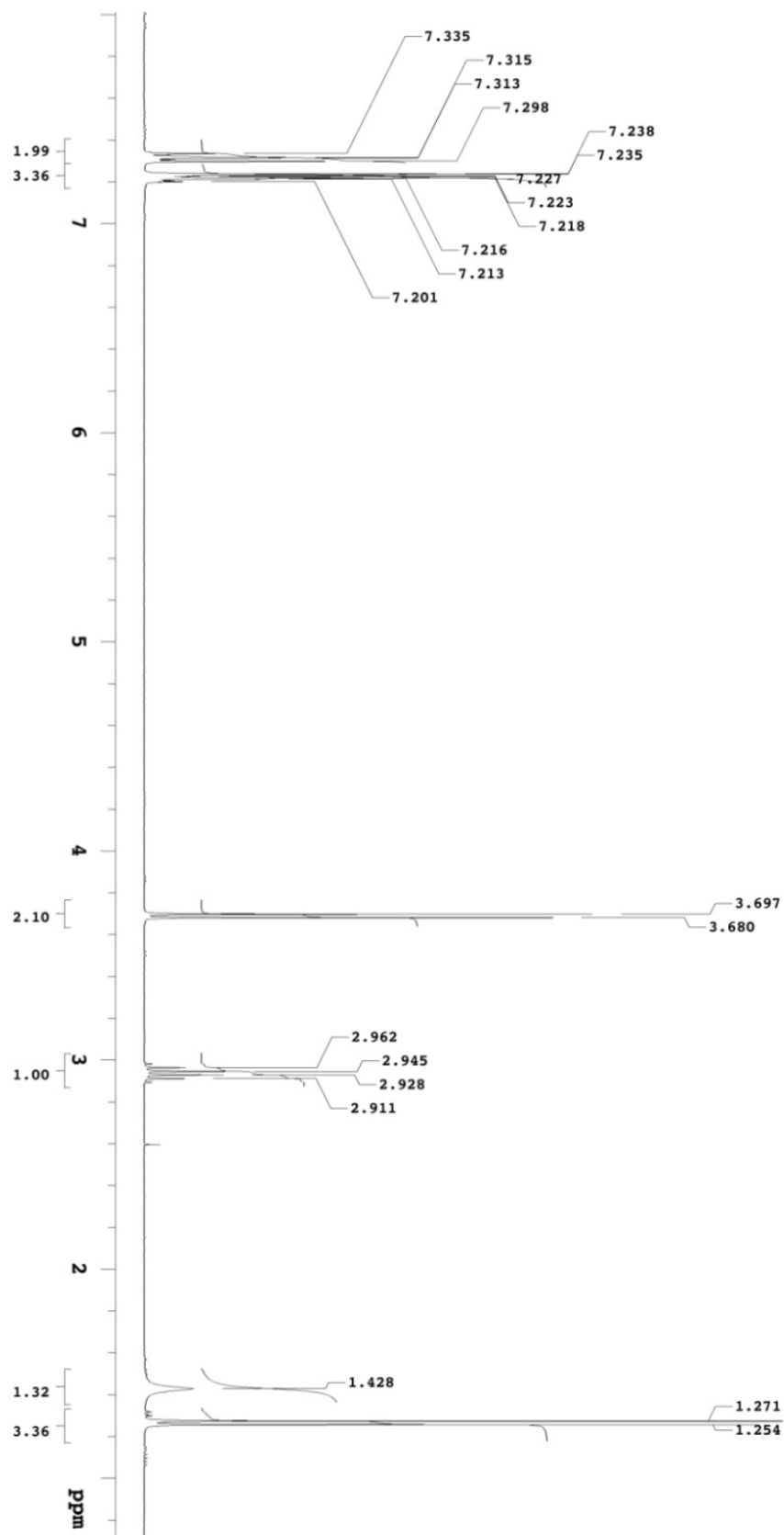


Figure SM 2.2.4.5 –  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ) of compound **5**.

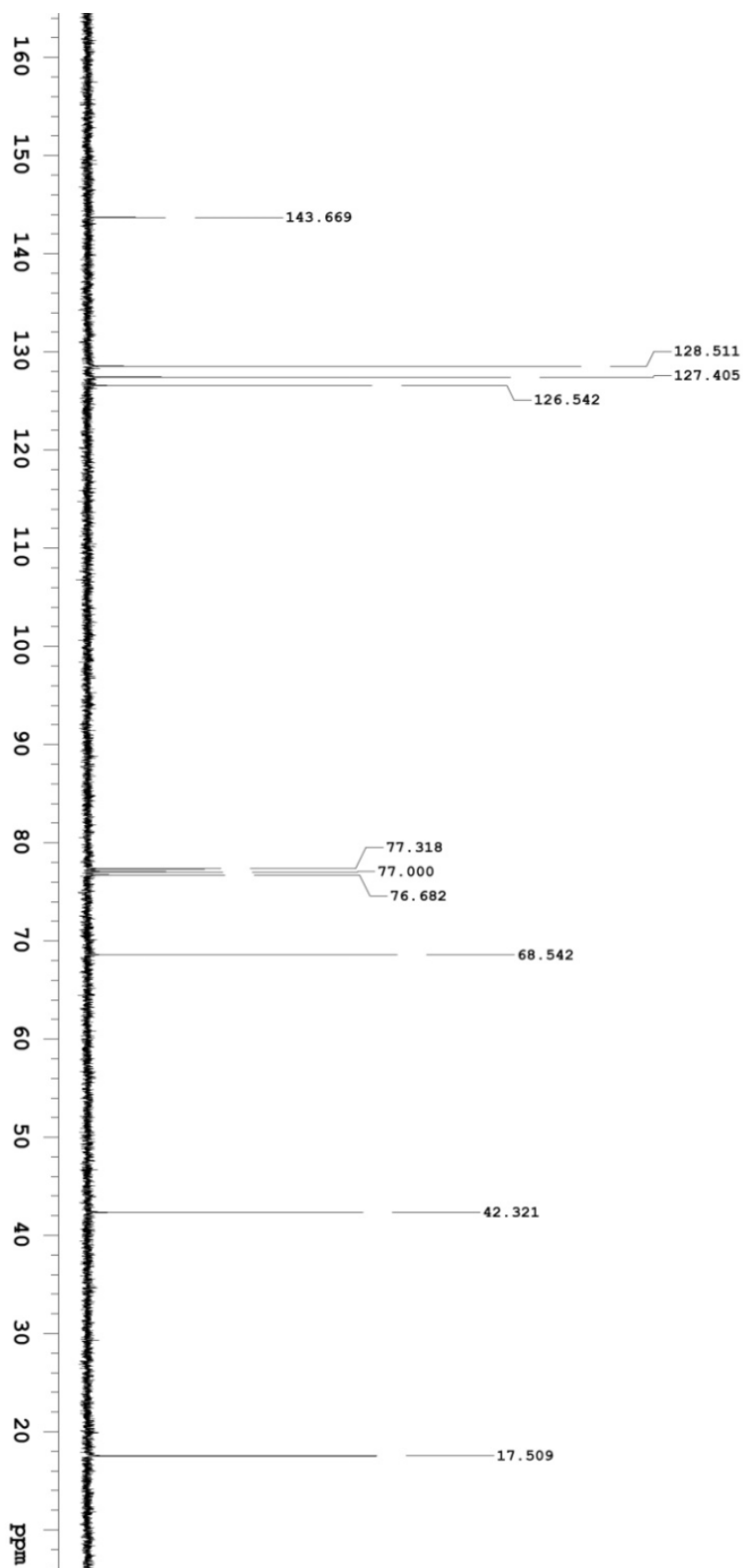


Figure SM 2.2.4.6 -  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , 25°C) of compound 5.



Figure SM 2.2.4.7 – Setup of the experimental apparatus for organocatalytic alkylation of aldehyde.

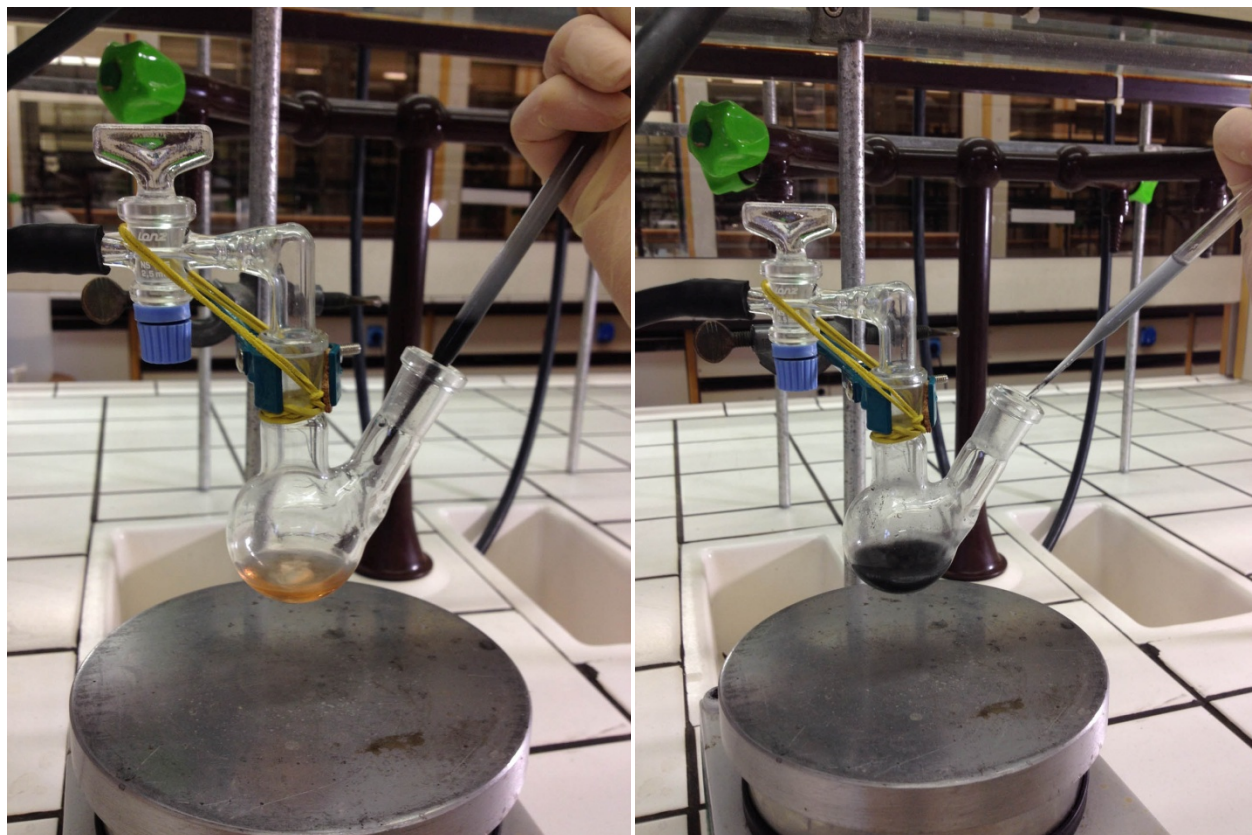


Figure SM 2.2.4.8 – Reductive removal of the benzodithiol group: Raney<sup>®</sup>-nickel addition.

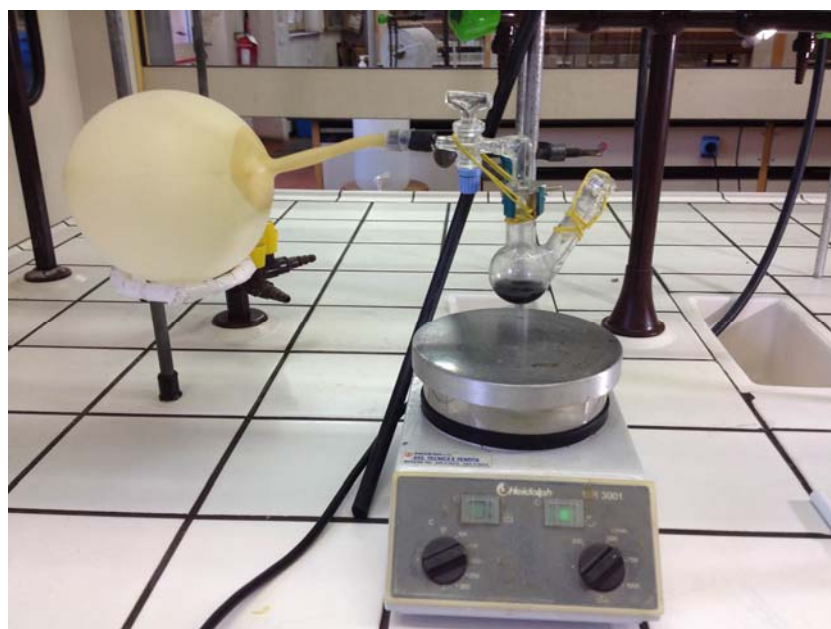


Figure SM 2.2.4.9 – Reductive removal of the benzodithiol group: hydrogenation.



Figure SM 2.2.4.10 – Reductive removal of the benzodithiol group: work-up procedure.

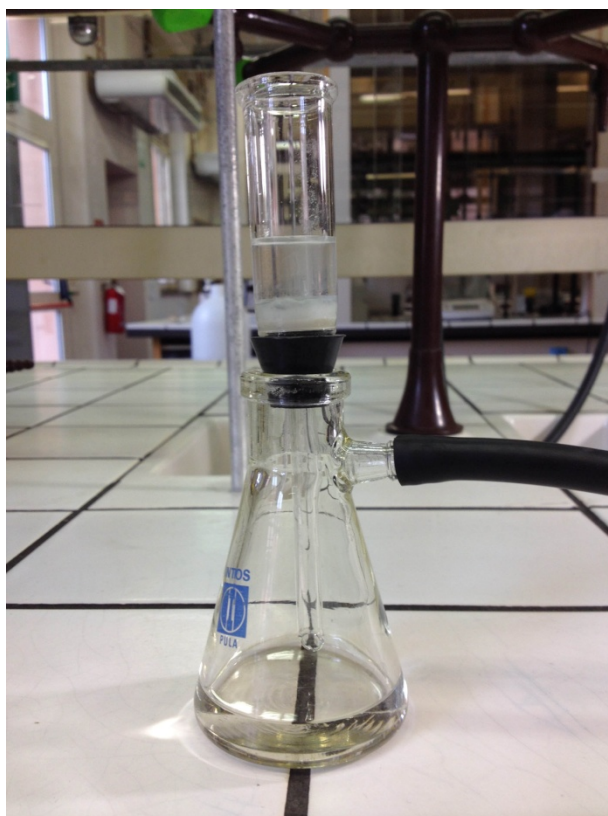


Figure SM 2.2.4.11 – Reductive removal of the benzodithiol group: work-up procedure.

## Oxazolidinone mediated enantioselective allylation

### Supporting Information

This experiment is designed as a series of 4 sequential steps to introduce third year undergraduate students to multi-step organic synthesis (adapted from Smith et al.<sup>1</sup>). In addition, the experiment exposes the student cohort to a plethora of practical (handling pyrophoric reagents, vacuum distillation, recrystallisation, utilising dry solvents, column chromatography) and theoretical (planning experimental quantities, time management) skills, which they will utilise going forward to their 4th year studies or take away into industry. Below are highlighted additional comments for each synthetic step along with the associated spectrum of the product.

**Solvent swaps:** Diethyl ether may be substituted for ethyl acetate, but not for Step 3 as this would compromise the atmospheric distillation. Likewise, *n*-hexane may be substituted for *n*-heptane.

#### Typical student timeline and levels of supervision

Our class sizes are 80 students and for this experiment require 1 senior member of staff and 4 postgraduate students (1 staff to 16 students)

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Begin synthesis of step 1	Purify step 1 and begin step 2	Purify step 2 and begin synthesis of step 3	Purify step 3 and begin step 4	Purify step 4	

Whilst this maybe over simplistic, it demonstrates a very ideological progression through the experiment. Students have free time throughout the sessions to address experimental calculations and further reading. Furthermore, mistakes or mishaps can be accommodated easily as there is a free week (2 sessions) to repeat the steps.

#### Additional information for Step 1 (can be stored in solution or left as a solid indefinitely)

Cyclisation of the commercially available optically pure valinol (available from Activate Scientific UK Ltd) is achieved easily by the students and as such provides the oxazolidinone product in excellent yield 75 – 95 %.

Problems arise during this step, as the students do not reflux the solution for long enough or hot enough to afford cyclisation. This leaves them with an oil at the end of the experiment which cannot be triturated.

#### Additional information for Step 2 (can be stored in solution or as an oil for several weeks)

The students again achieved acylation of the oxazolidinone, producing the product in 80 – 95 % yield. The column was conducted using a gradient of 9:1 *n*-hexane/EtOAc with an  $R_f = 0.4$ .

Problems arose for the students undertaking chromatography, as the product has no chromophore and is hard to visualize with TLC staining. Nevertheless, the use of phosphomolybdic acid (PMA)/cerium sulphate dip or an iodine tank enabled this product to be visualized sufficiently to allow purification by column chromatography.

**Additional information for Step 3 (once distilled is stable for ~1 week)**

Whilst synthesis of allyl iodide is easily achieved using this procedure, purification by atmospheric distillation can be problematic. The product has to be distilled three/four times (once to remove the ether, then the acetone, and then the product) and the fourth time to distill the product. The scale of the reaction provides a large volume of solvent (acetone and diethylether), which needs to be removed first, before distillation of the product. The trick is to remove the solvent by distillation first, and then transfer the remaining liquors to a smaller distillation apparatus for the final distillation of the product. Yields of between 20 – 50 % of an orange oil can be achieved. This product is only stable for 1 week so should be used within this time.

**Additional information for Step 4 (can be stored in solution or as an oil for several weeks)**

This step was achieved by the students expediently and provided the major diastereoisomer in >99:1 dr with a yield between 40 – 60 %. TLC of the crude material (n-hexane/EtOAc 9:1) reveals two spots, one  $R_f = 0.8$  and the other  $R_f = 0.2$ . The spot with  $R_f = 0.8$  is an impurity which accounts for the loss in mass from the reaction, the spot with  $R_f = 0.2$  is the desired product as a pale yellow oil (~50 %)

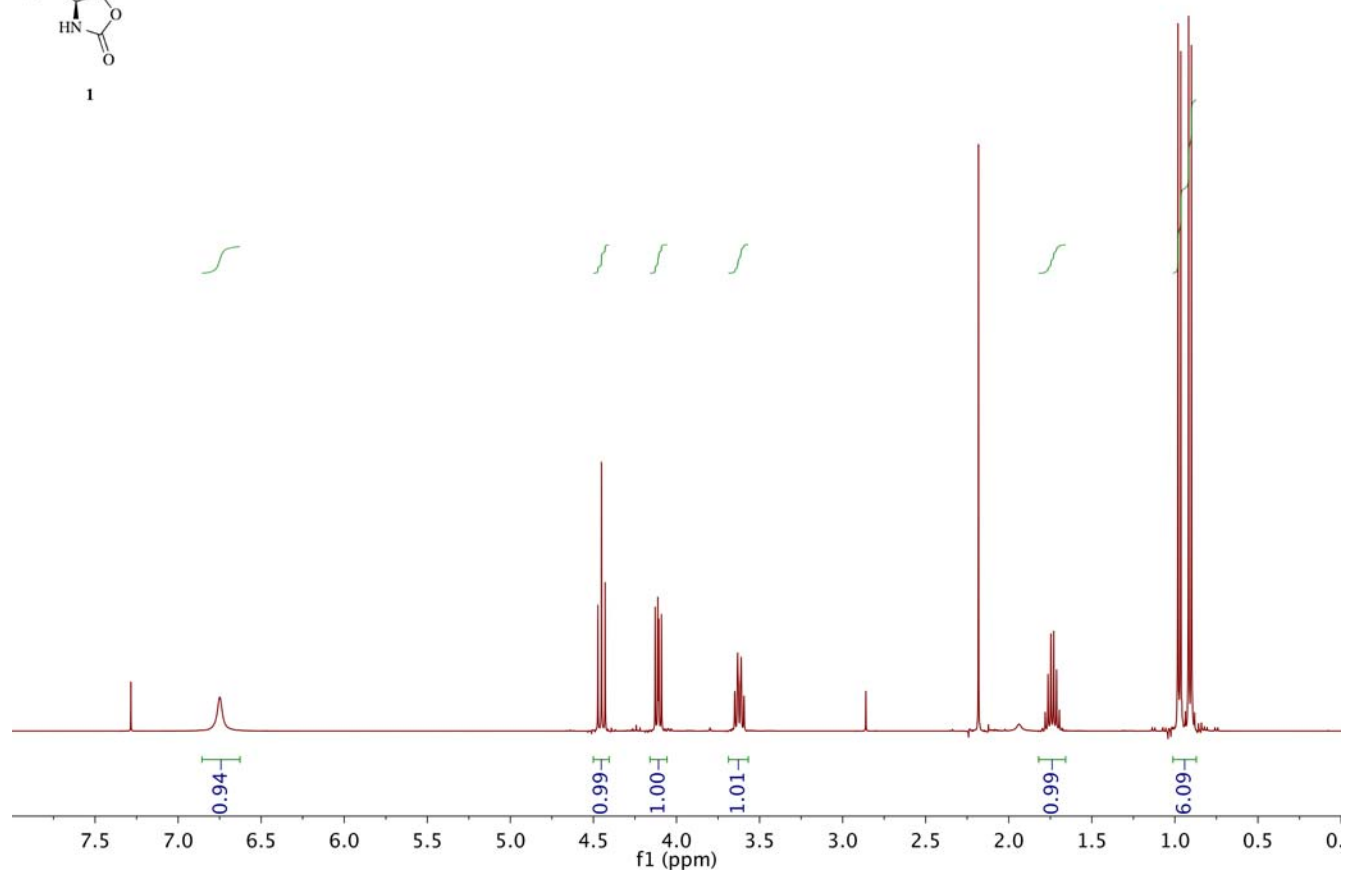
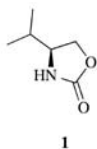


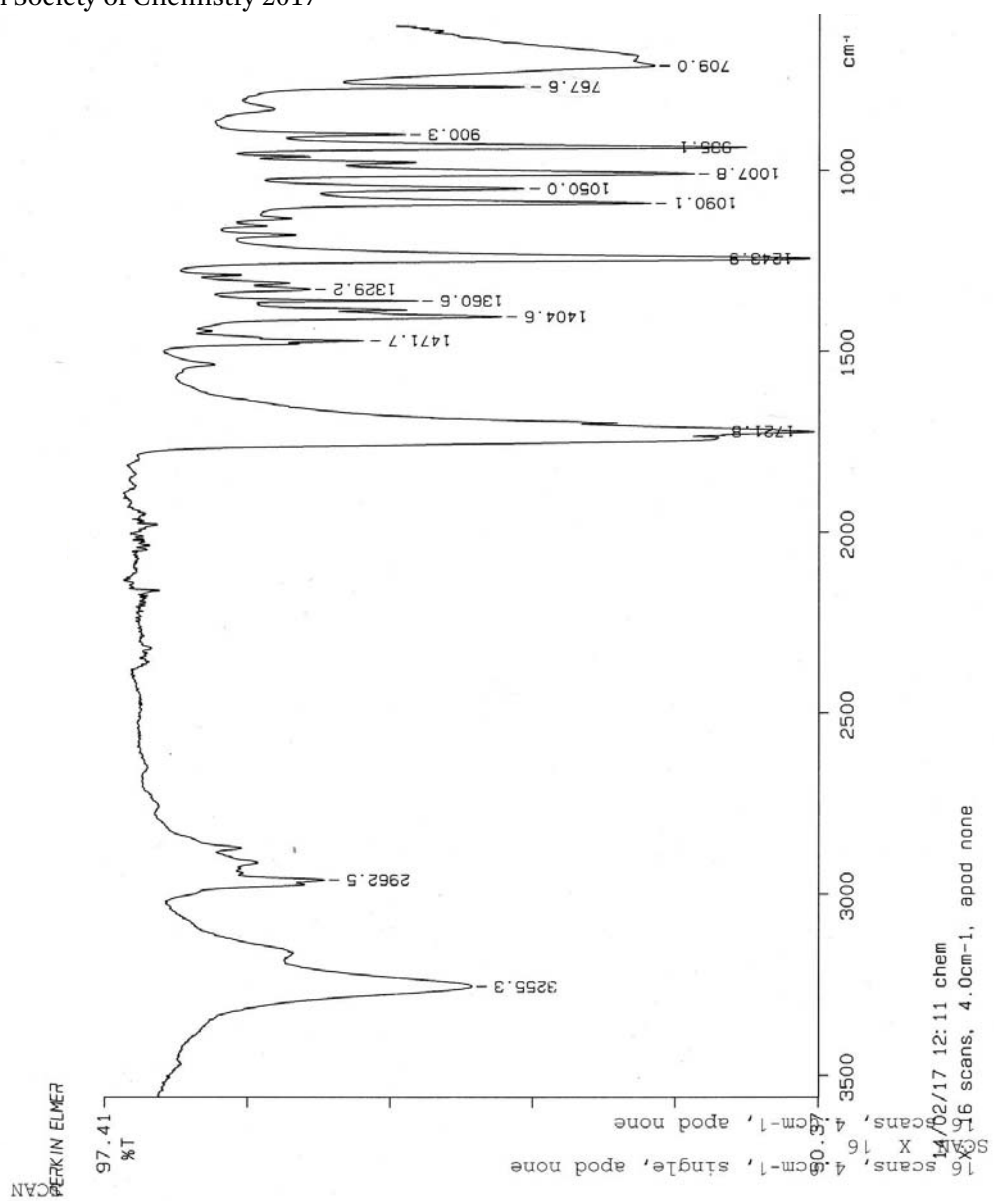
## Spectra

### Step 1

#### (4S)-4-(Propan-2-yl)-1,3-oxazolidin-2-one (1)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

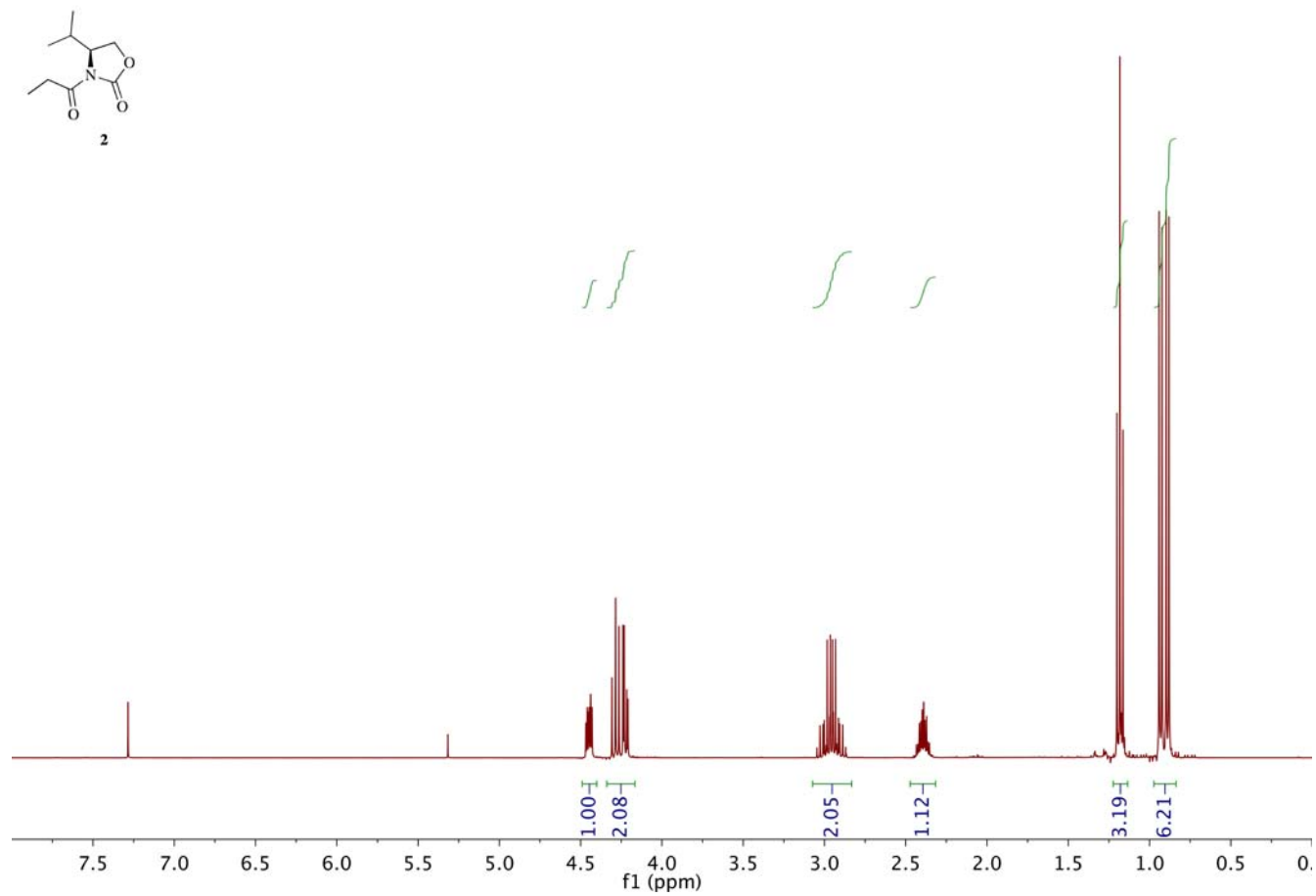


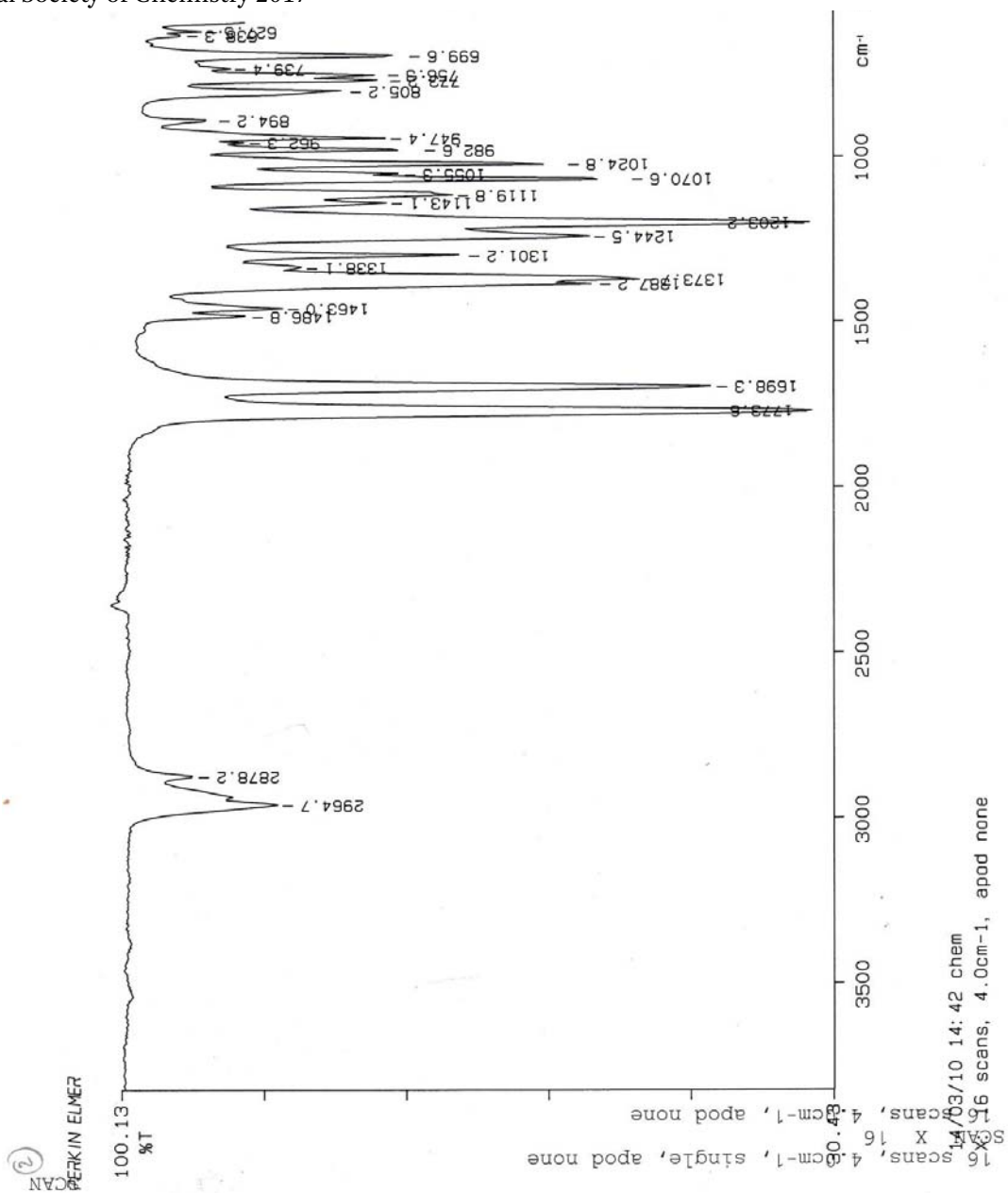


## Step 2

### (4S)-4-(Propan-2-yl-3-propanoyl-1,3-oxazolidin-2-one (2)

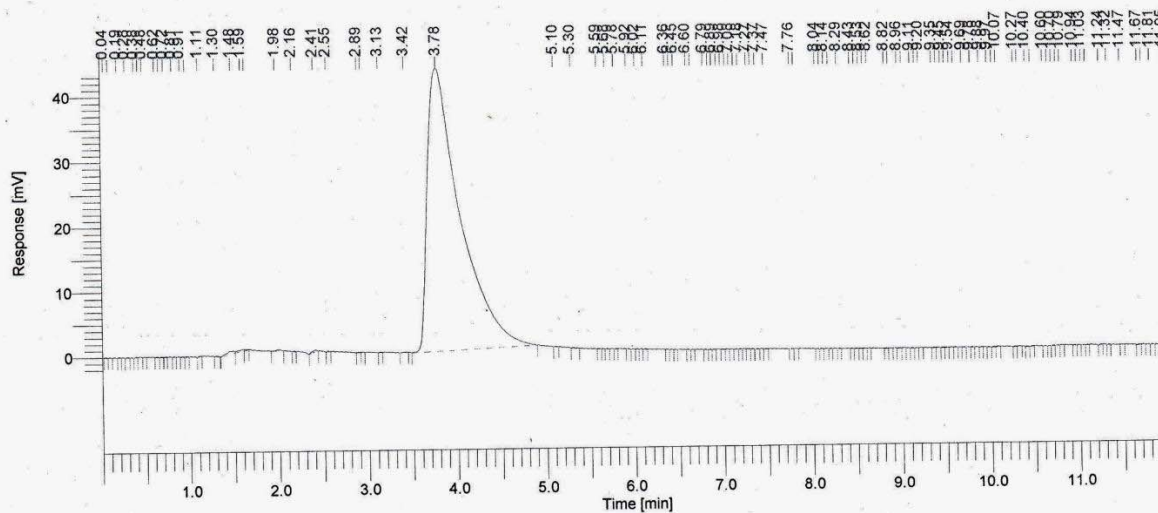
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)





Software Version	: 6.3.1.0504	Date	: 10/03/2014 16:55:02
Reprocess Number	: bioactivehplc2: 8682		
Sample Name	: RS S2	Data Acquisition Time	: 10/03/2014 16:42:54
Instrument Name	: HPLC2	Channel	: A
Rack/Vial	: 0/12	Operator	: dch5lwl
Sample Amount	: 1.000000	Dilution Factor	: 1.000000
Cycle	: 12		

Result File : E:\data\Teaching L3 Org Chiral HPLC\10\_03\_2014\_RS S2\_012.rst  
 Sequence File : E:\data\Teaching L3 Org Chiral HPLC\10th March 2014 a.seq



## HPLC 2

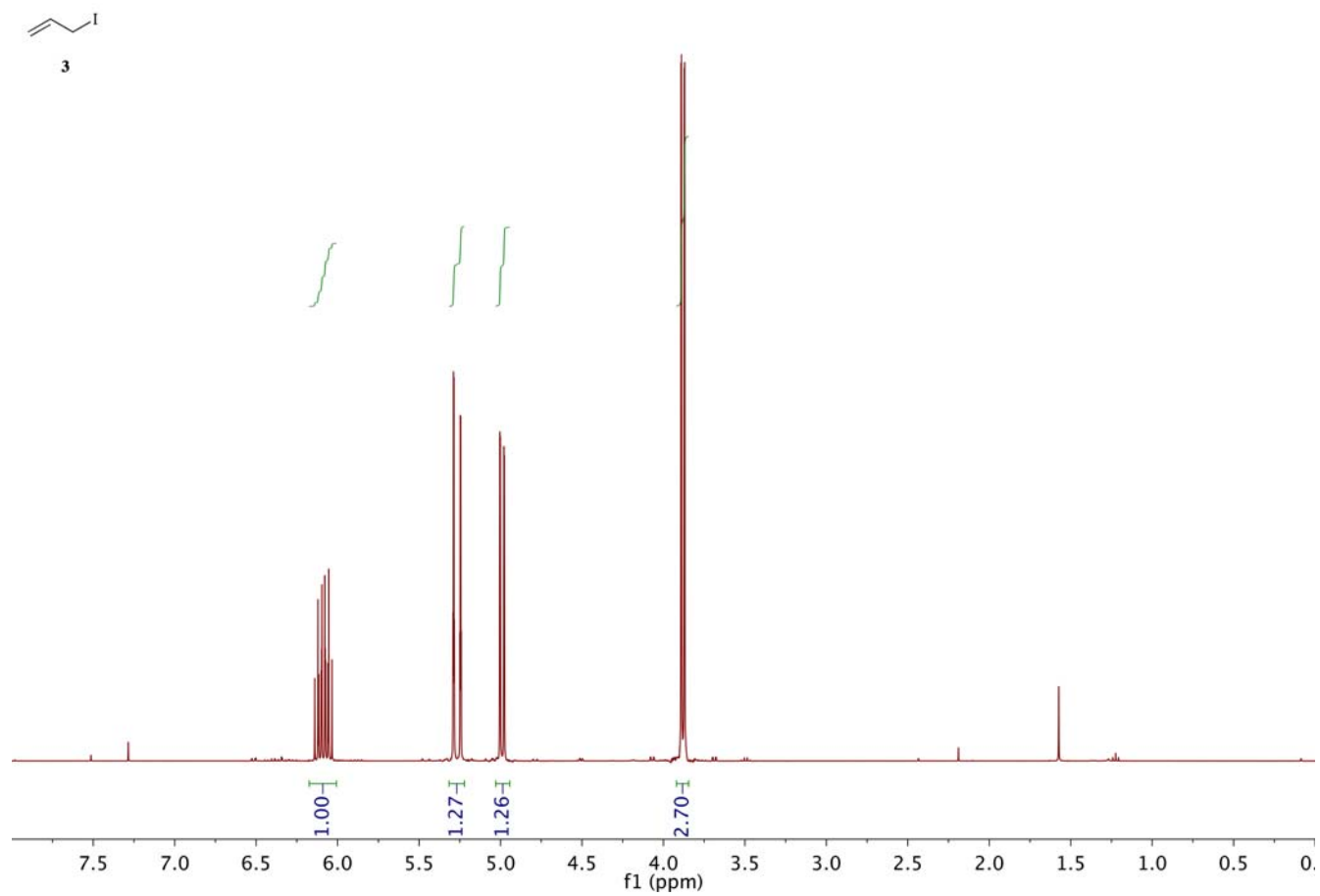
Peak #	Time [min]	Area [μV·s]	Height [μV]	Area [%]	Norm. Area [%]	BL	Area/Height [s]
27	3.779	1109119.88	43599.98	100.00	100.00	BB	25.4385
		1109119.88	43599.98	100.00	100.00		

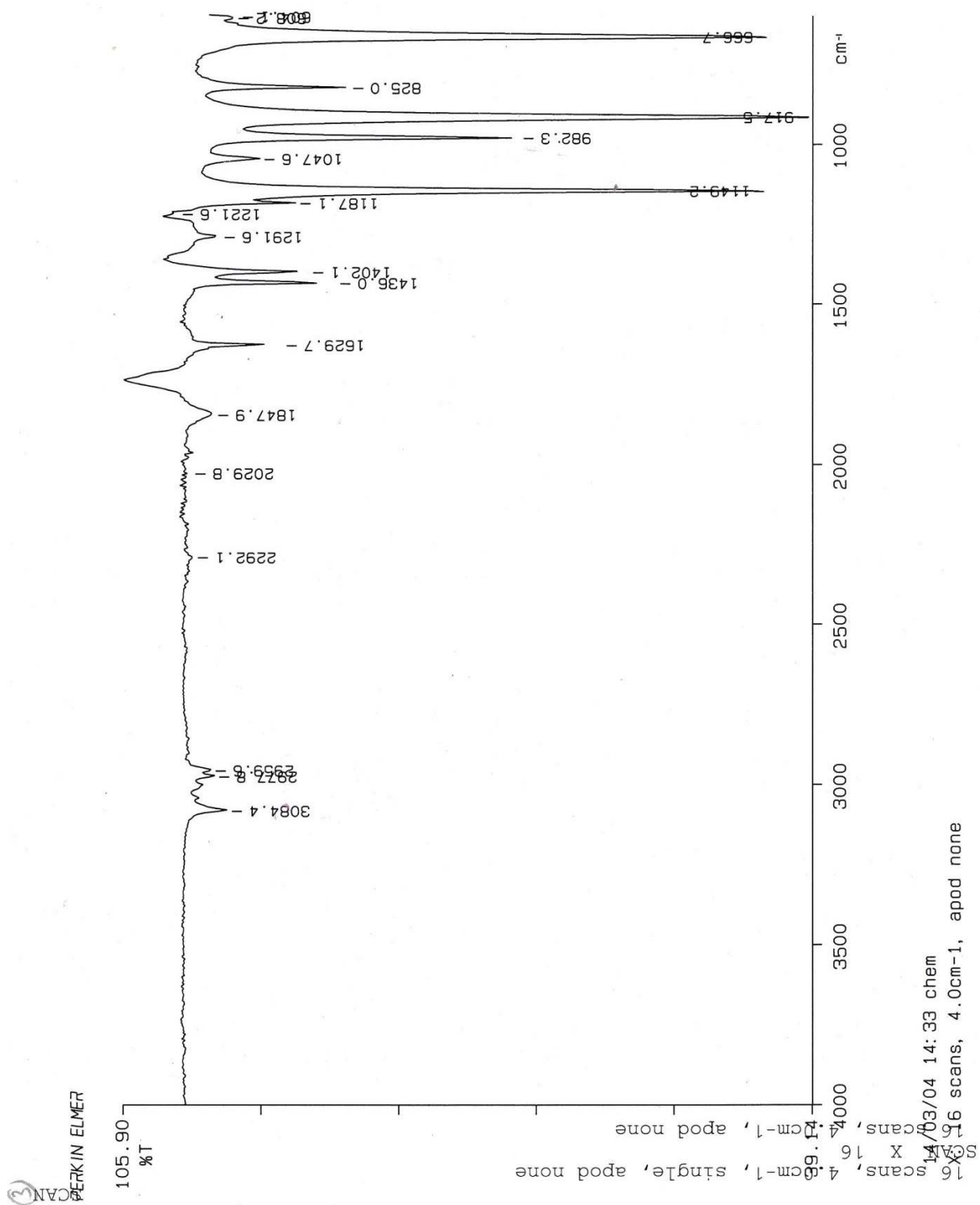
Conditions: Chiralcell OD column 4.6 mm x 150 mm x 3 μm particle size ran with an isocratic gradient of 5 % EtOH/*n*-hexane.

### Step 3

#### 3-Iodoprop-1-ene (3)

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )

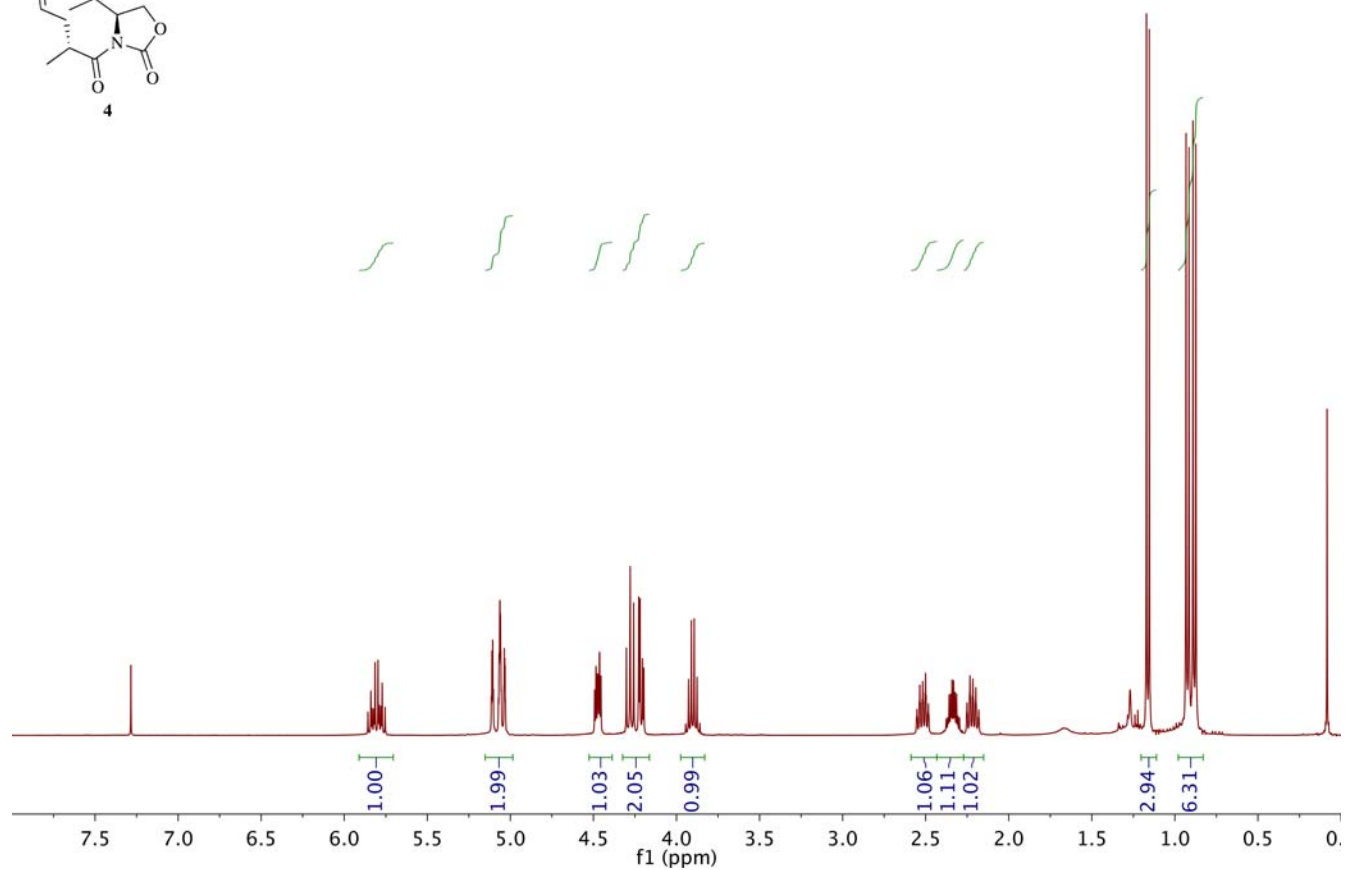
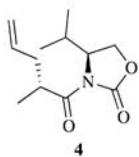




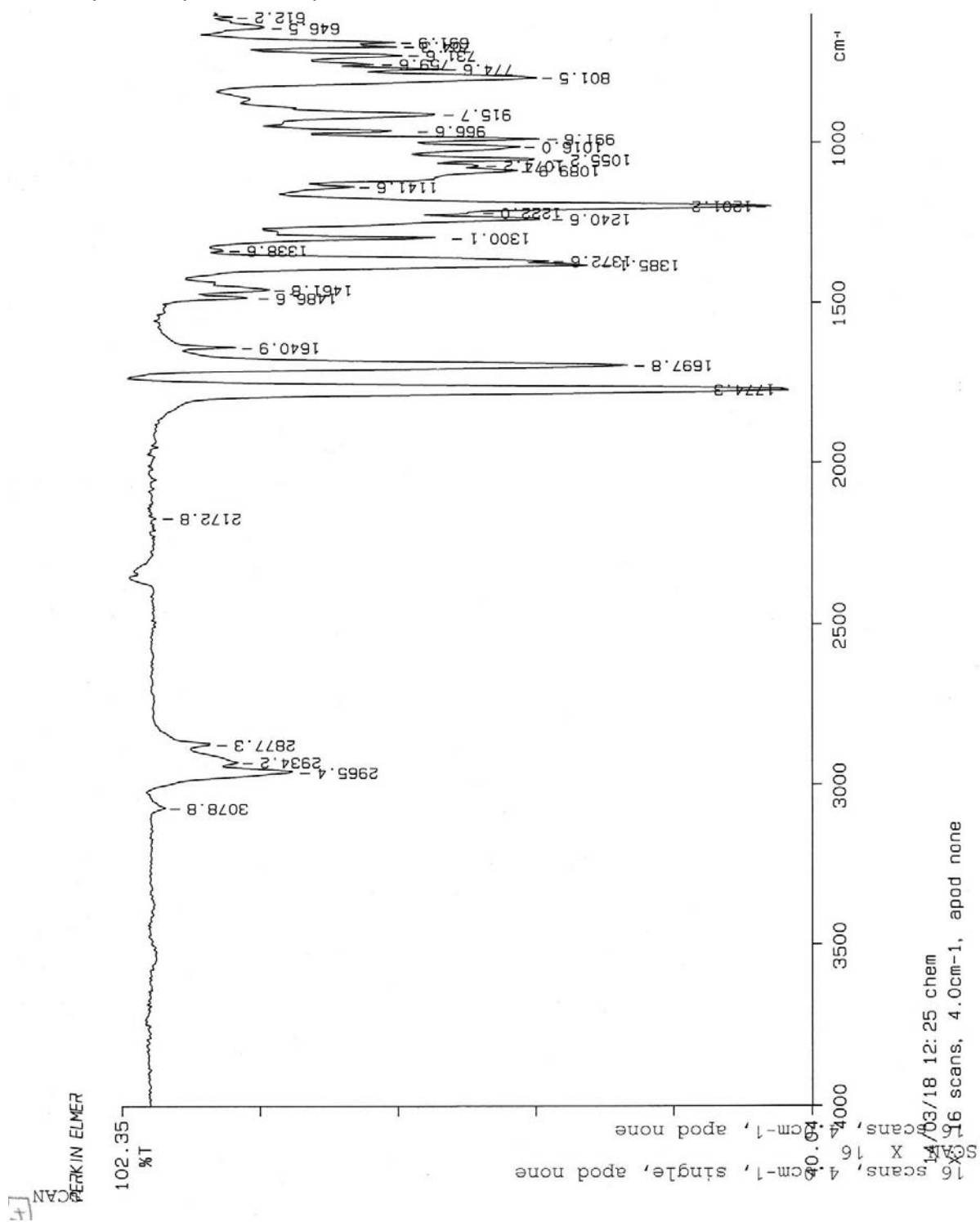
**Step 4**

**(4S)-3-[(2R)-2-Methylpent-4-enoyl]-4-(propan-2-yl)-1,3-oxazolidin-2-one (4)**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)







1. T. E. Smith, D. P. Richardson and G. A. Truran, *J. Chem. Educ.*, **2008**, 85, 695.