Stereoselective Synthesis of Highly Substituted Tetrahydropyrans through an Evans Aldol-Prins Strategy

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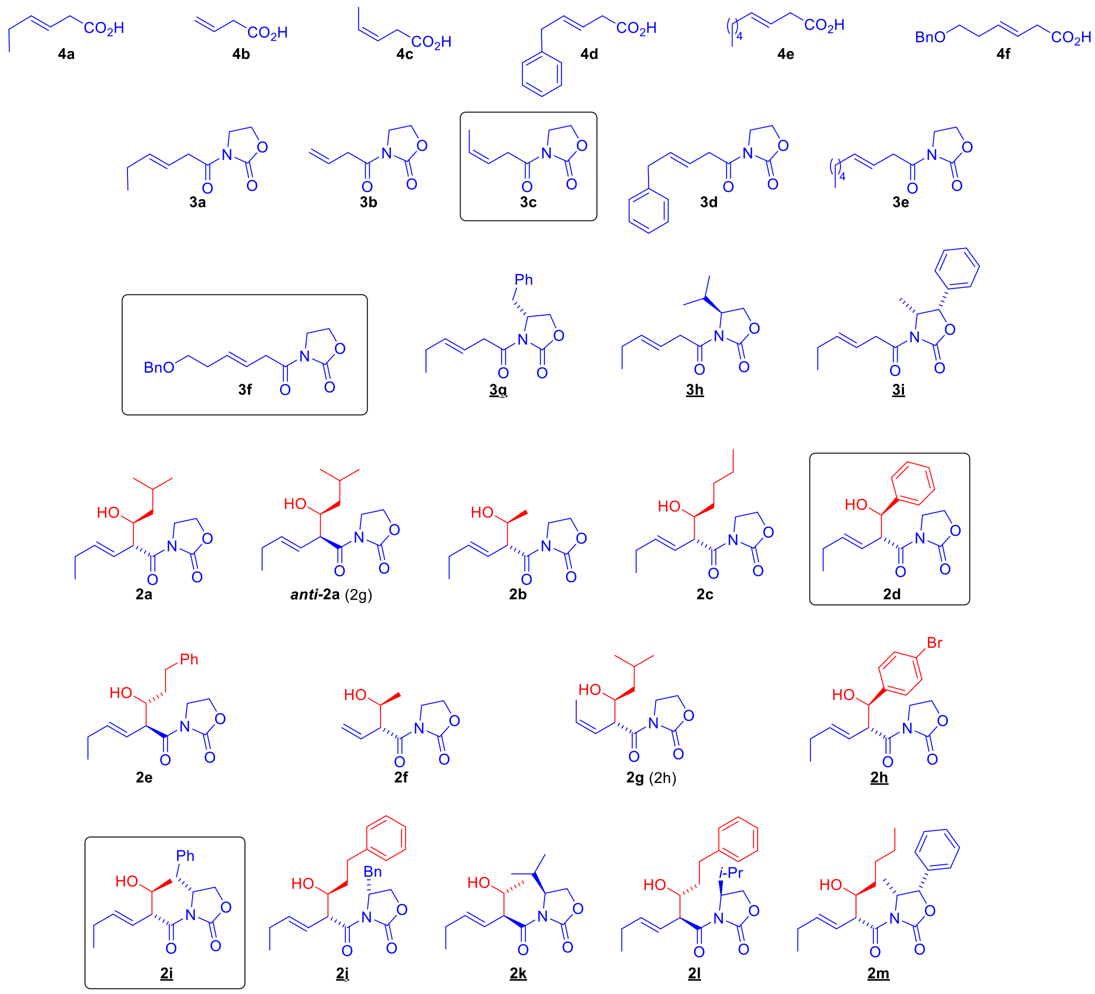
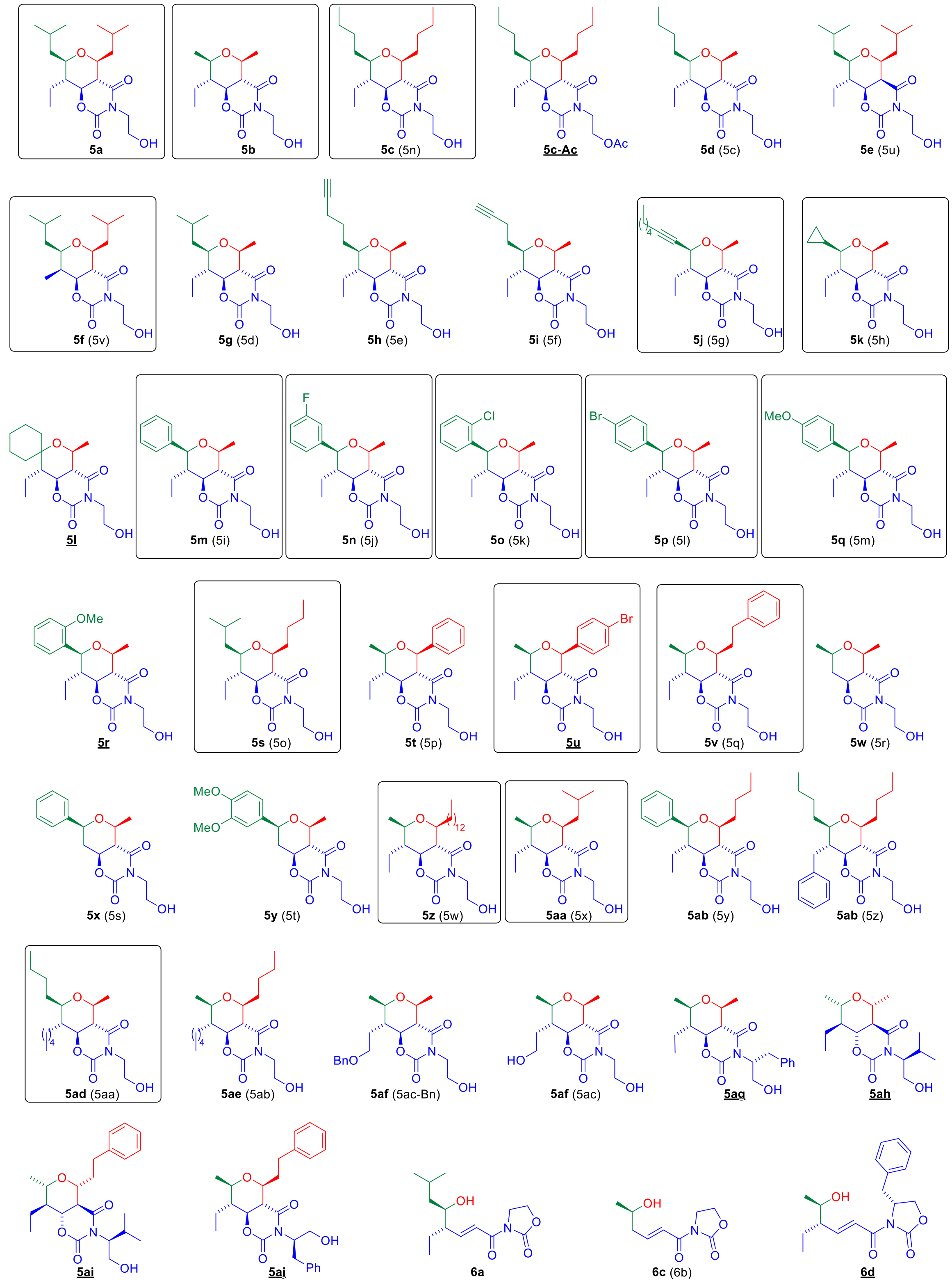
Supporting information index

Molecules index

The bold numbers below each molecule correspond to the numeration used in this work. For those molecules that were firstly described in our previous report[1] with a different numeration, that numeration is given in parentheses. New molecules are underlined. The 33 compounds that were biologically evaluated are highlighted in boxes.

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5b
5c (5n)
5c-Ac
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5e (5u)
5f (5v)
5g (5d)
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5j (5g)
5k (5h)
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5o (5k)
5p (5l)
5q (5m)
5r
5s (5o)
5t (5p)
5u
5v (5q)
5w (5r)
5x (5s)
5y (5t)
5z (5w)
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5ab (5y)
5ab (5z)
5ad (5aa)
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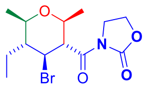
5ag
5ah
5ai
5aj
6a
6c (6b)
6d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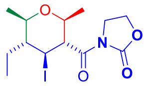
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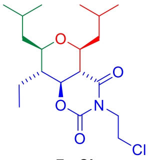
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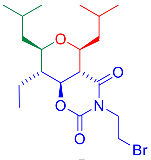
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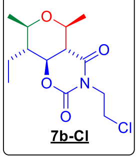
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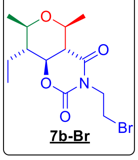
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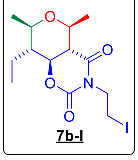
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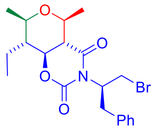
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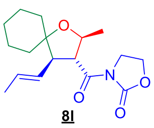
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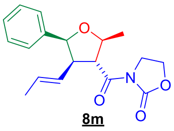
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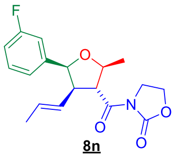
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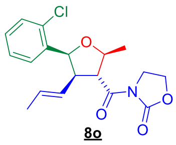
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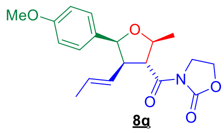
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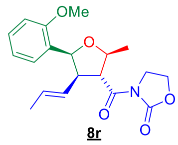
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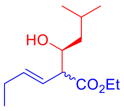
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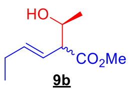
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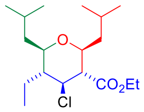
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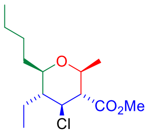
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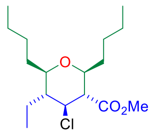
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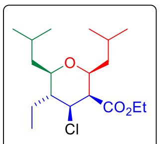
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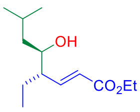
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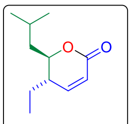
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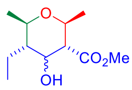
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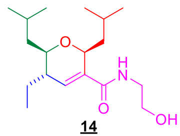
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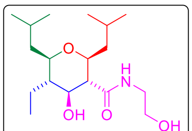
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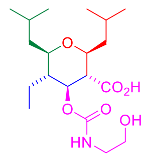
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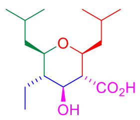
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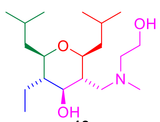
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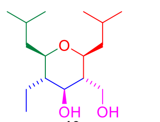
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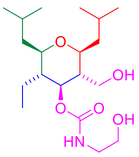
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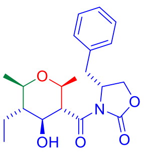
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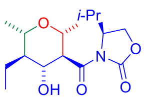
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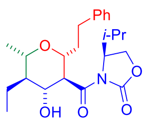
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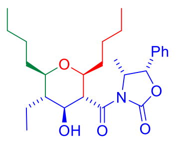
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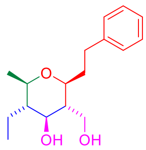
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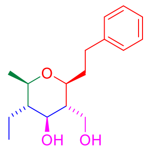
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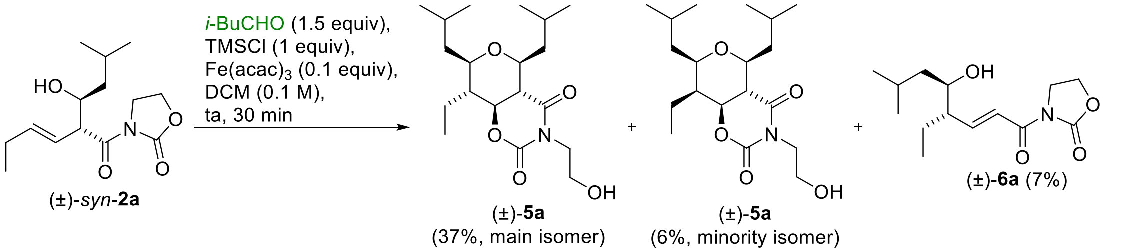
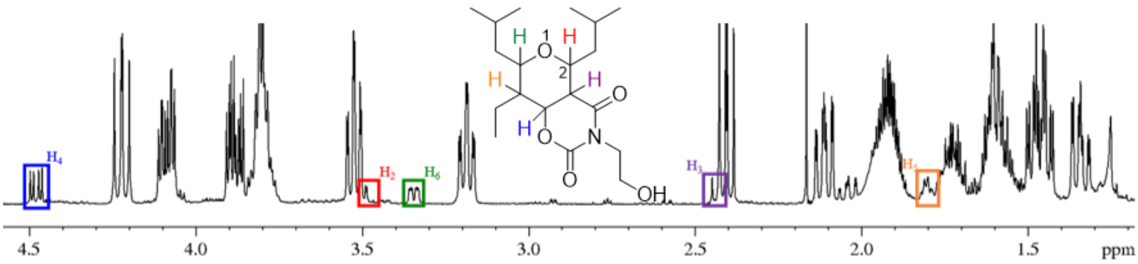
Peripheral discussions

Determination of the stereochemistry of the minor diastereoisomer obtained during the synthesis of bicycle 5a

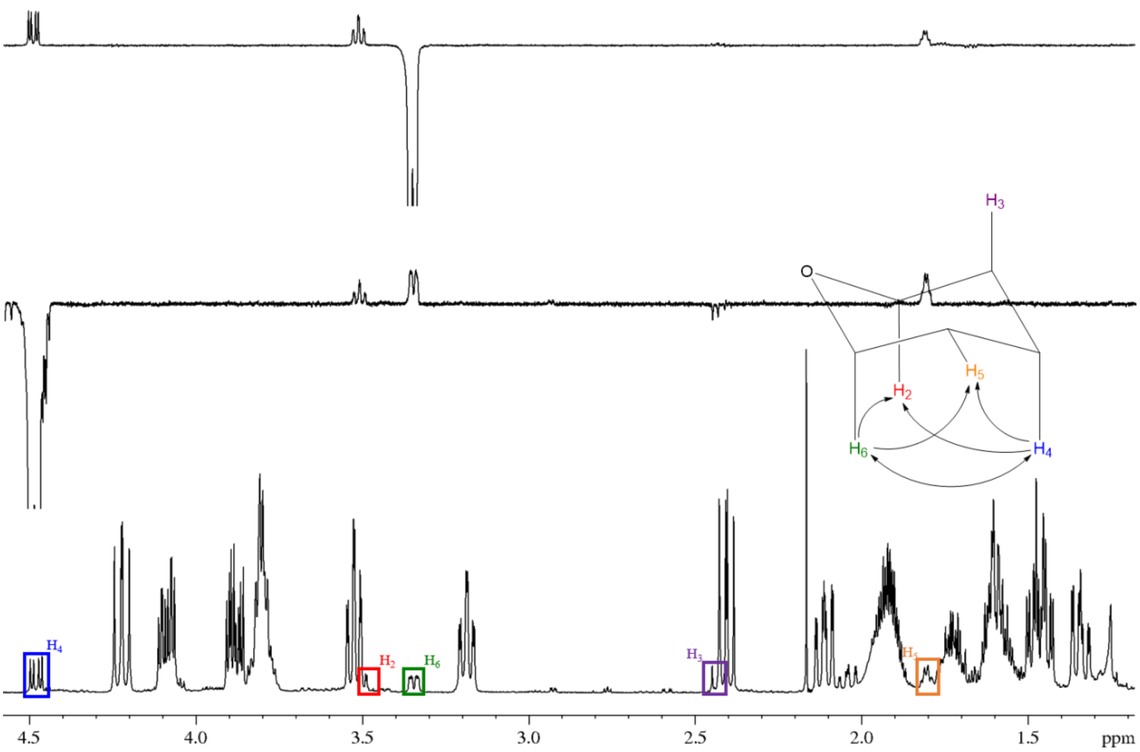
Bicycle **5a** was obtained for the first time, under not optimized conditions (see Scheme 2 in the manuscript), as a 85:15 mixture of diastereoisomers.



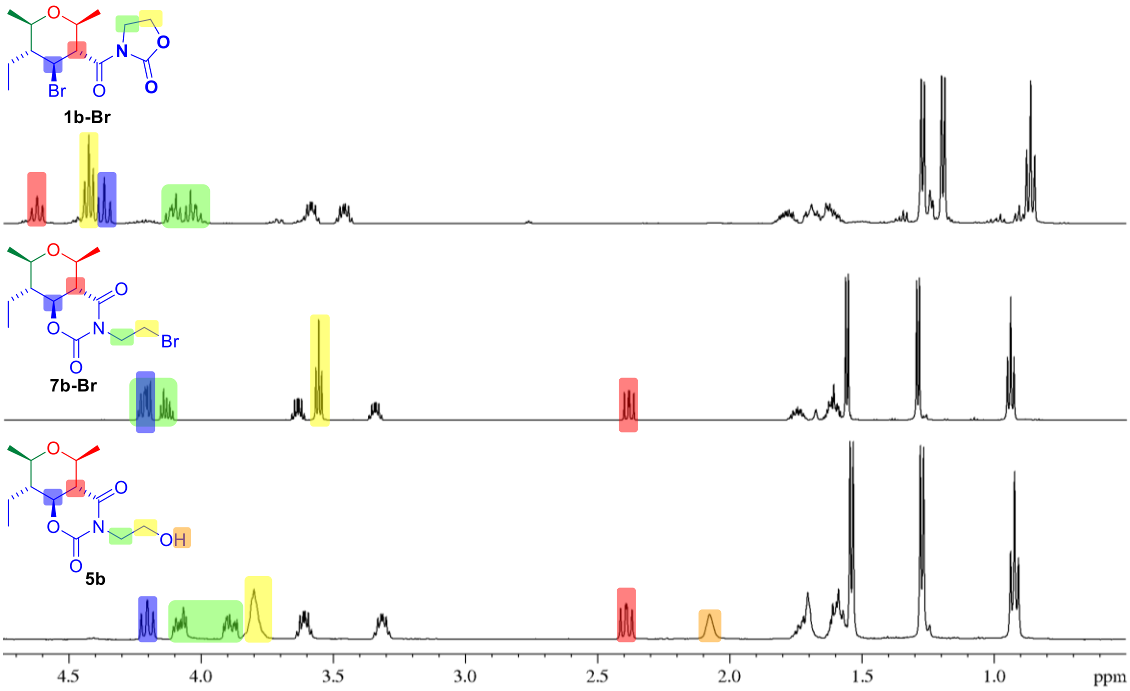
Signals of the H from the minor THP core are highlighted below.

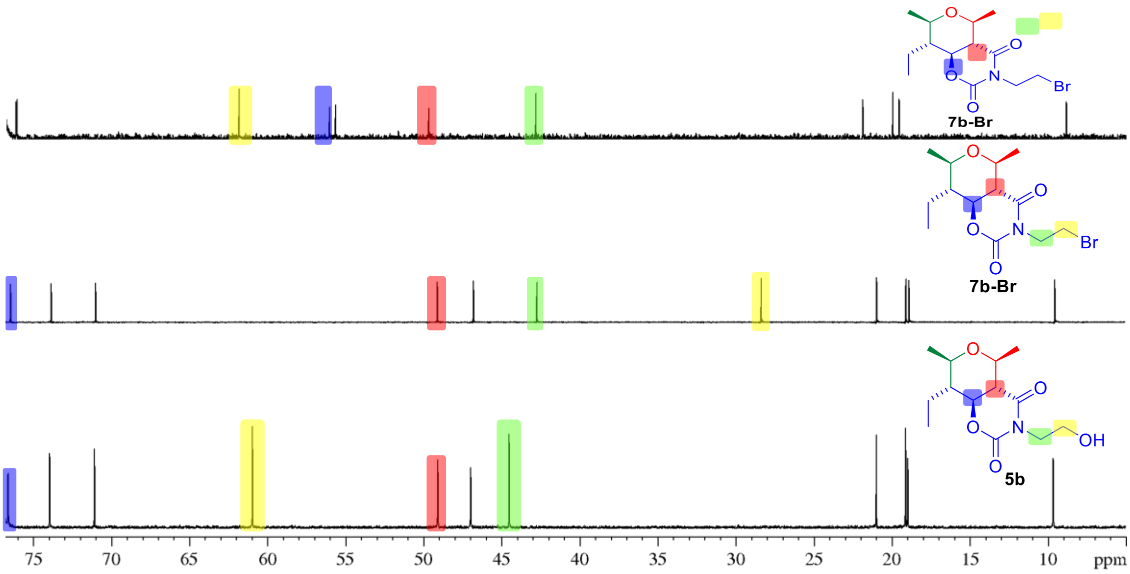


GOESY analyses revealed that the by-product was the C$_5$-epimer of the major **5a**.



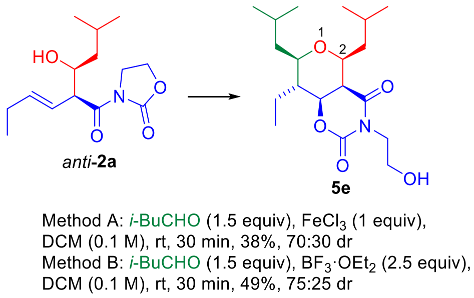
Comparison of representative signals of 1b-Br, 5b and 7b-Br in NMR spectra





NMR analysis of bicycle 5e and its minor diastereoisomers

The equation 2 of the Scheme 3 of the manuscript shows the synthesis of bicycle **5e** through two different conditions (Scheme S1).



Scheme S1

According to the [1]H NMR spectra, in both cases together with bicycle **5e** it was obtained at least another THP with similar signals to **5e**. The intensity relation found in signals with δ = 3.49 and δ = 4.23 ppm was 3/1, which indicates that two by-products were obtained (Figure S1).

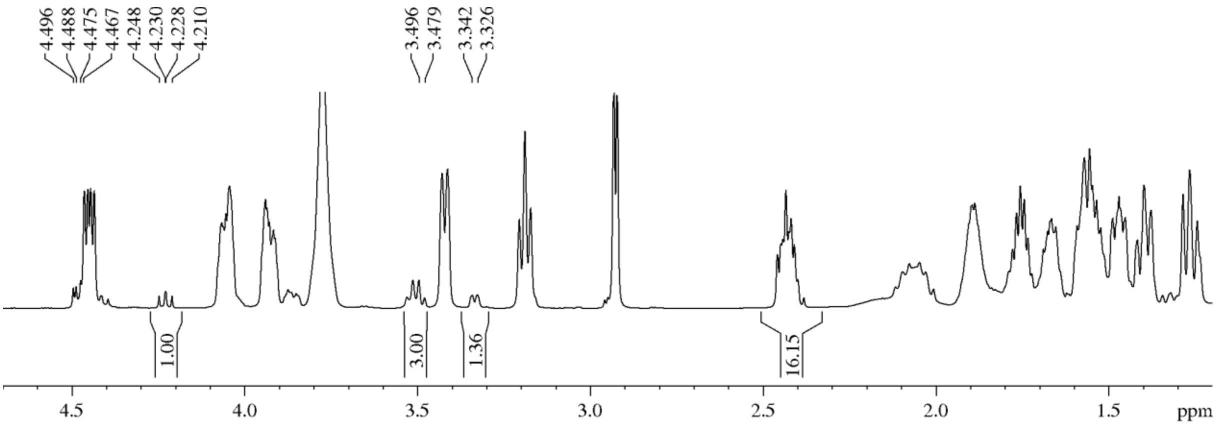


Figure S1

GOESY analysis of the main product allowed us to confirm the predicted stereochemistry of the bicycle **5e** (**Figure S2**).

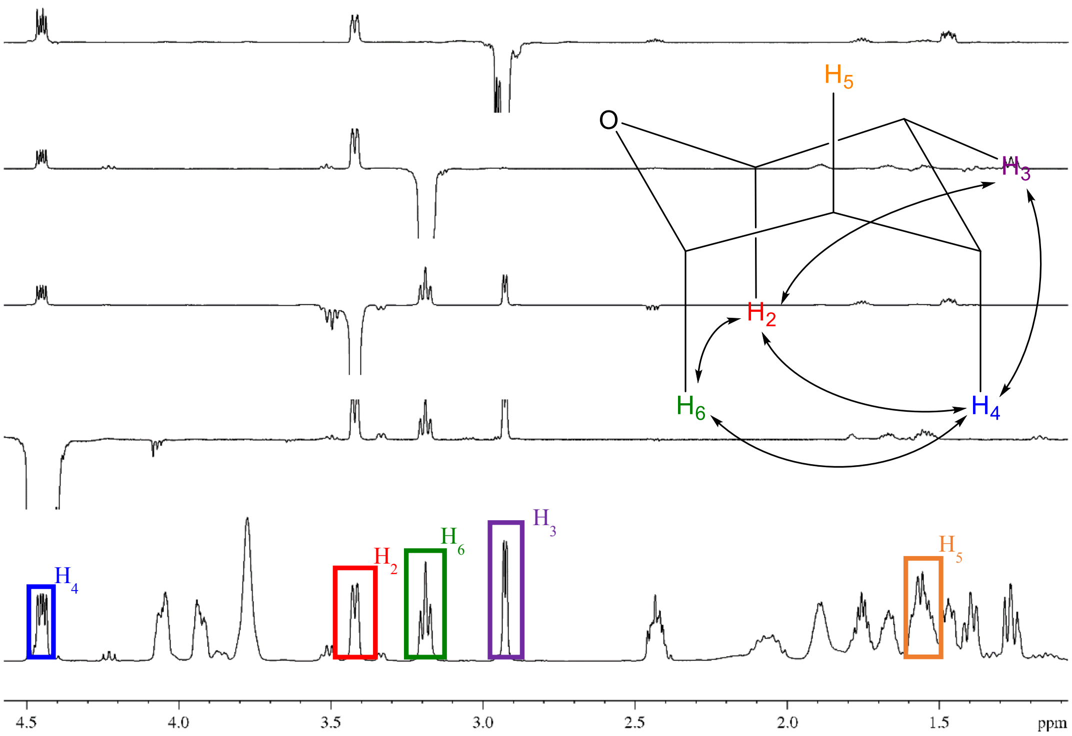


Figure S2

GOESY analysis of the non-overlapped signals of the minor diastereomers ($\delta = 4.23$ ppm for the major and $\delta = 3.33$ ppm for the minor) allowed their elucidation (**Figure S3**). The upper spectrum is from the 5.7/1 mixture of the isomers **5a**/**5a'** obtained as described in Scheme 2 of the manuscript.

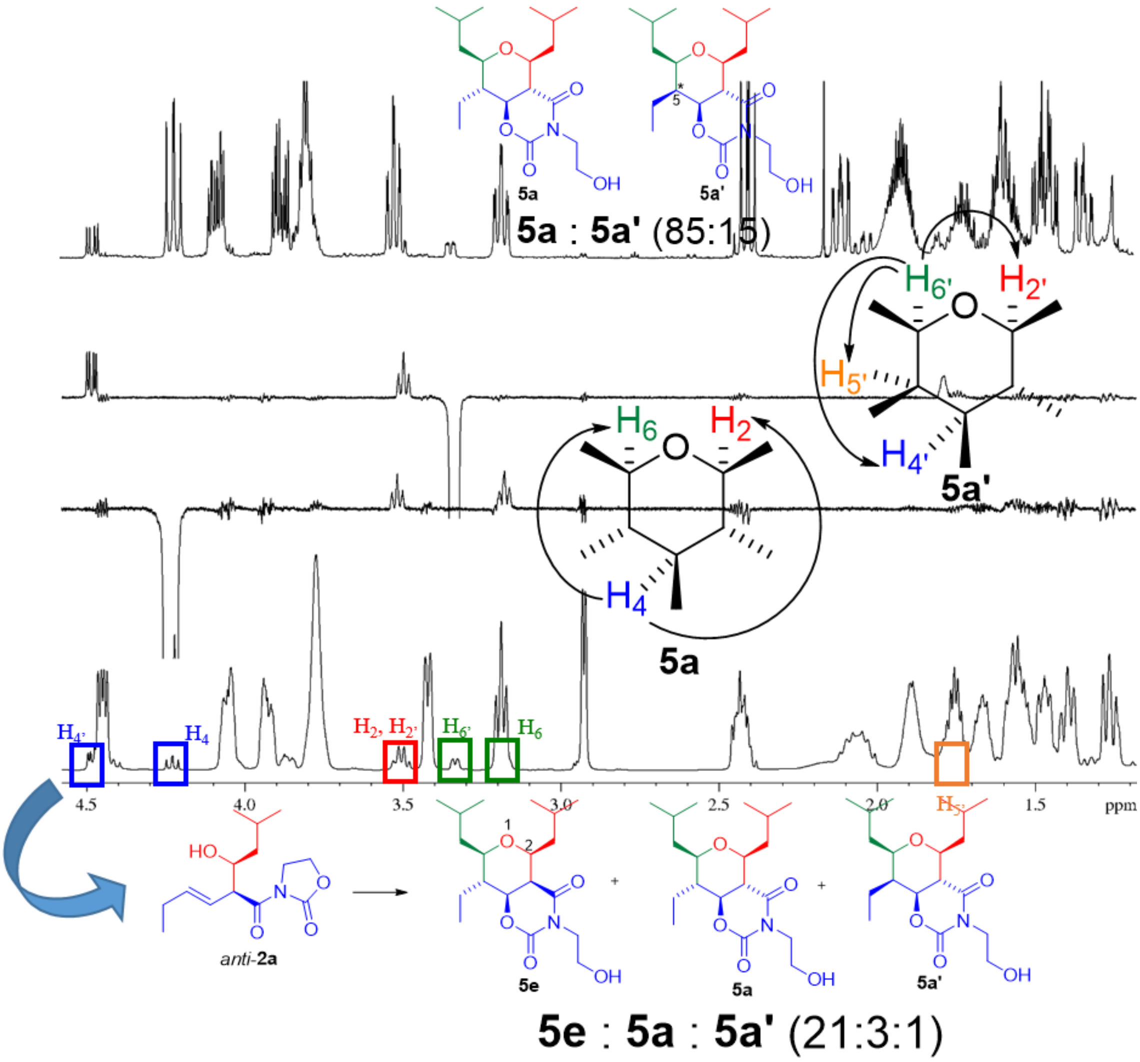
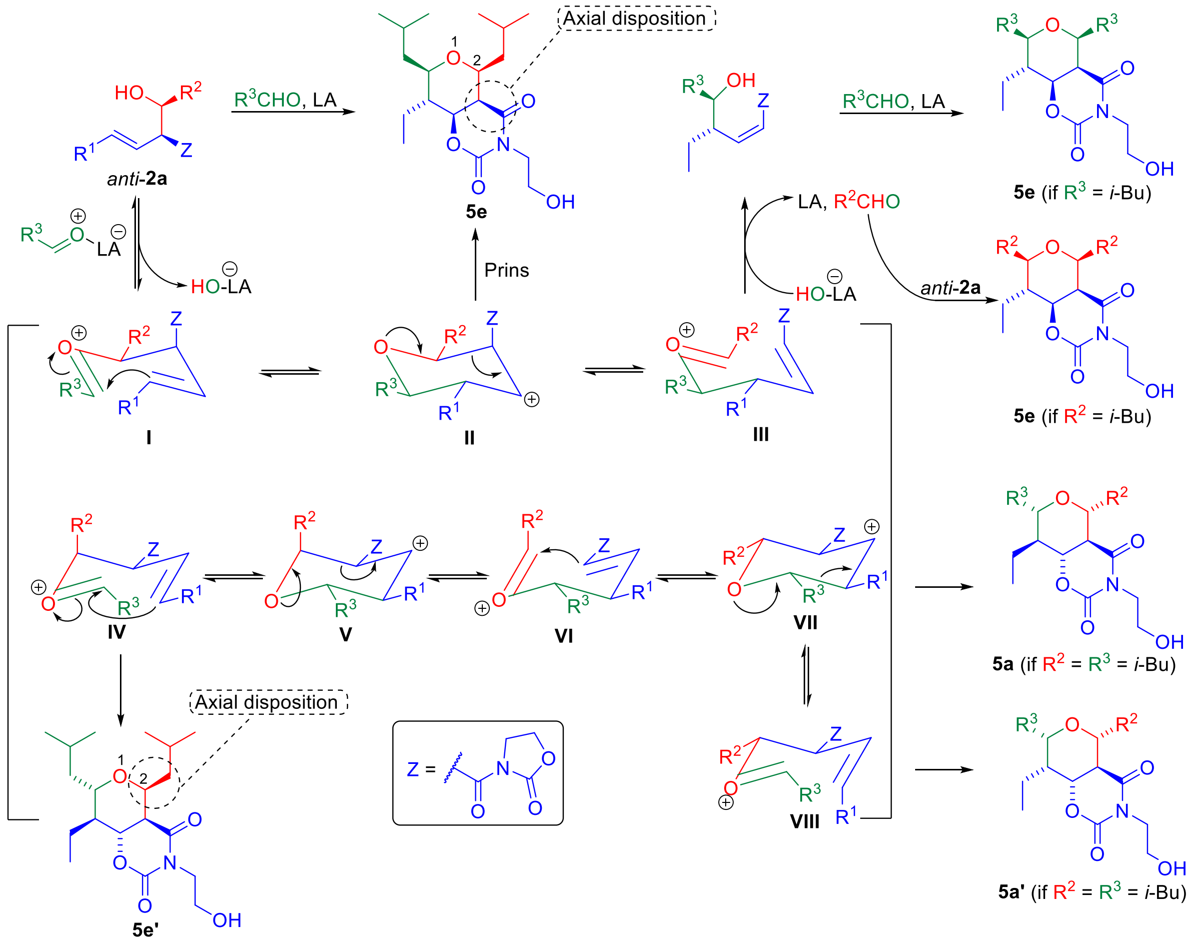


Figure S3

Surprisingly, both by-products show substituents at positions 2 and 3 with a *trans* orientation, in spite of the starting aldol *anti*-**2a** bears both substituents with a *cis* orientation. Thus, the obtaining of theses diastereomers seems to be a consequence of a isomerization of an intermediate originating from the starting *anti*-**2a** during the Prins cyclization (Scheme S2). Firstly, it occurs the nucleophilic addition of the aldol over the LA-activated aldehyde. The *trans* orientation of the substituents of the aldol forces one of them to adopt an axial position in the chair-like transition state: in **I**, the *N*-acyl oxazolidin-2-one group adopts the axial position, whereas in the inverted chair conformation **IV** that position is adopted by $R^2 = i$-Bu. On the one hand, all the intermediates **I-III**, obtained as a consequence of the 2-oxonia-Cope, lead to the proposed bicycle **5e**, whose substituent at C_3 adopts an axial disposition. On the other hand, all the intermediates **IV-VI**, should conduct to the bicycle **5e'**, a diastereomer of **5e** in which substituent at C_2 adopts the axial disposition. As product **5e'** was not detected, it seems that the most stable intermediates are those which show the group *N*-acyl oxazolidin-2-one group in an axial position. However, oxocarbenium ion **VI** could be related with the obtaining of the detected by-products **5a** and **5a'**, due to its rearrangement to generate carbocation **VII**, in which all the substituents adopt equatorial dispositions. As **VII** is the precursor of bicycle **5a**, its postulation would explain the isolation of that bicycle, as well as the isolation of **5a'** as minor diastereomer via the oxocarbenium ion **VIII**.

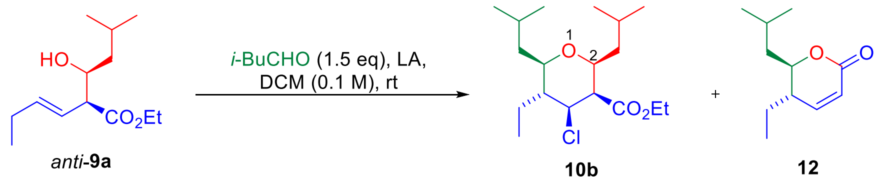


Scheme S2

Conversion of *anti*-aldol 9a into products 10b and 12

As discussed in the manuscript (Scheme 5, equation 2), *anti*-aldol **9a** was also submitted to the Fe-based Prins cyclization pursuing the synthesis of THP **10b**. Table S1 gathers those results, remarking the differences in the proportion of undesired lactone **12** and unreacted ***anti*-9a** through the reaction time.

Table S1. Fe-Based Prins Cyclization of *anti*-9a



Entry	LA (equiv)	t	**10b** (%)[a]	**12** (%)[a]	**Recovered *anti*-9a** (%)[b]
1	$FeCl_3$ (1)	20 min	17	26[b]	44
2	$FeCl_3$ (1)	4 h	20	42[b]	10
3	Fe(acac)$_3$/TMSCl (0.1/1)	21 h	20	62	-

[a] Isolated yield. [b] Calculated by ^{1}H NMR spectroscopy.

Once finished the three reactions indicated in Table S1, the crudes were purified by flash chromatography, allowing us to separate product **10b** from the inseparable mixture of **12** and unreacted starting ***anti*-9a**. Figure S4 show a comparison of the ^{1}H NMR spectra of the mixtures of products **12**/***anti*-9a**, in different proportion according to the time in which the reaction was quenched.

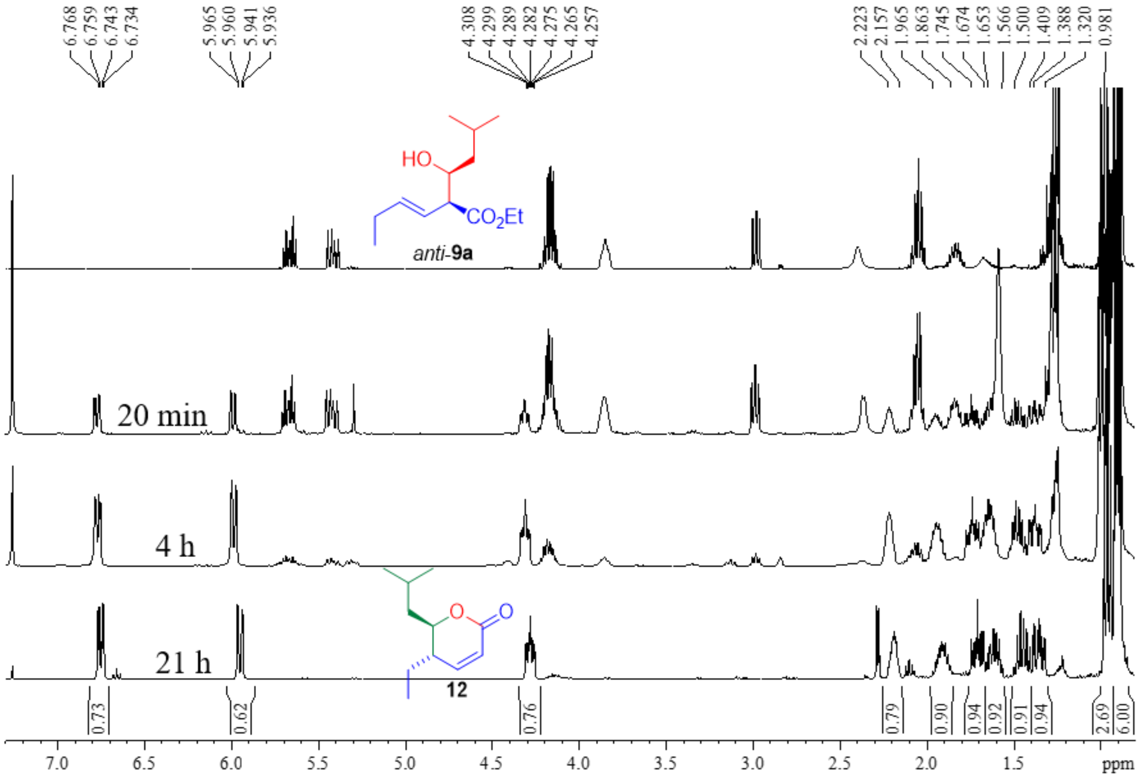
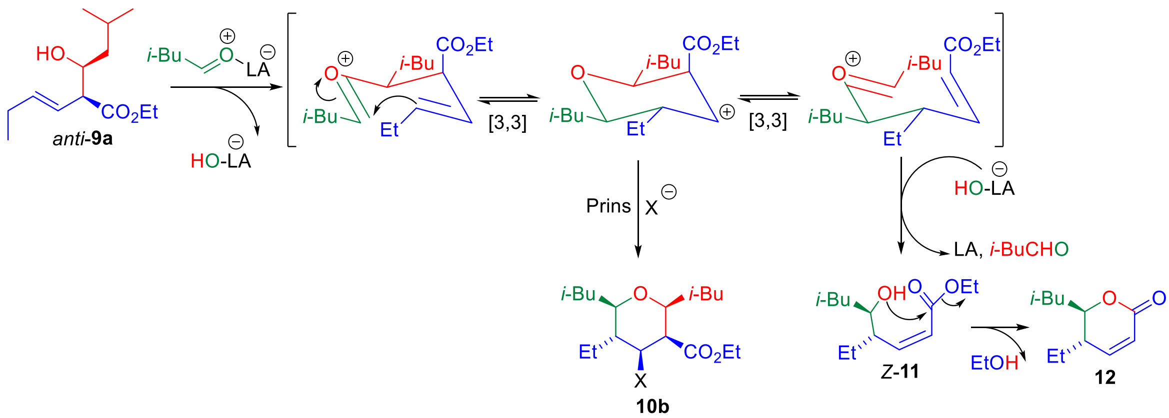


Figure S4

The obtaining of lactone **12** may be explained keeping in mind that the CO_2Et group adopts an axial disposition in the 6-membered transition state. As consequence, on the one hand, Prins product **10b** shows the ester group in axial position and, on the other hand, the homoallylic alcohol ***Z*-11** is generated in the medium due to the 2-oxonia-Cope rearrangement and suffers an *in situ* lactonization (Scheme S3).



Scheme S3

Helpful information for the identification of bicycles 5 and THPs-Xc 21

Scheme 8 of the manuscript tackles the $BF_3 \cdot OEt_2$-mediated cyclization of chiral aldols, whose oxazolidin-2-ones bear different substituents into the adjacent position to the nitrogen (and also into the adjoining position to the oxygen, in the case of aldol **2m**). With these substrates, bicycles **5** were mainly obtained, as it occurred in the non-chiral approach, but also THPs-Xc **21** were isolated as minor products (due to the steric hindrance difficults the nucleophilic attack over the oxazolidin-2-one). Both kinds of structures are substantially different, but their NMR spectra are similar and it is needed a careful analysis to discern between them. In this section, we show a comparison between representative regions of the NMR spectra of compound **5b** and its chiral analogues shown in equations 1 and 2 of the Scheme 8 (**5ag**, **5ah**, **21a** and **21b**). The patterns found in these molecules were also observed in the other bicycles and THPs-Xc, so a general tendency can be envisaged.

Figure S5shows ^{1}H NMR spectra in the region between δ = 1.8-5.0 ppm. H from the OH group appears as a doublet in THPs-Xc **21**, whereas in bicycles **5** is a multiplet. H_3 exhibits a higher value of its shift in THPs-Xc **21** than in bicycles **5**.

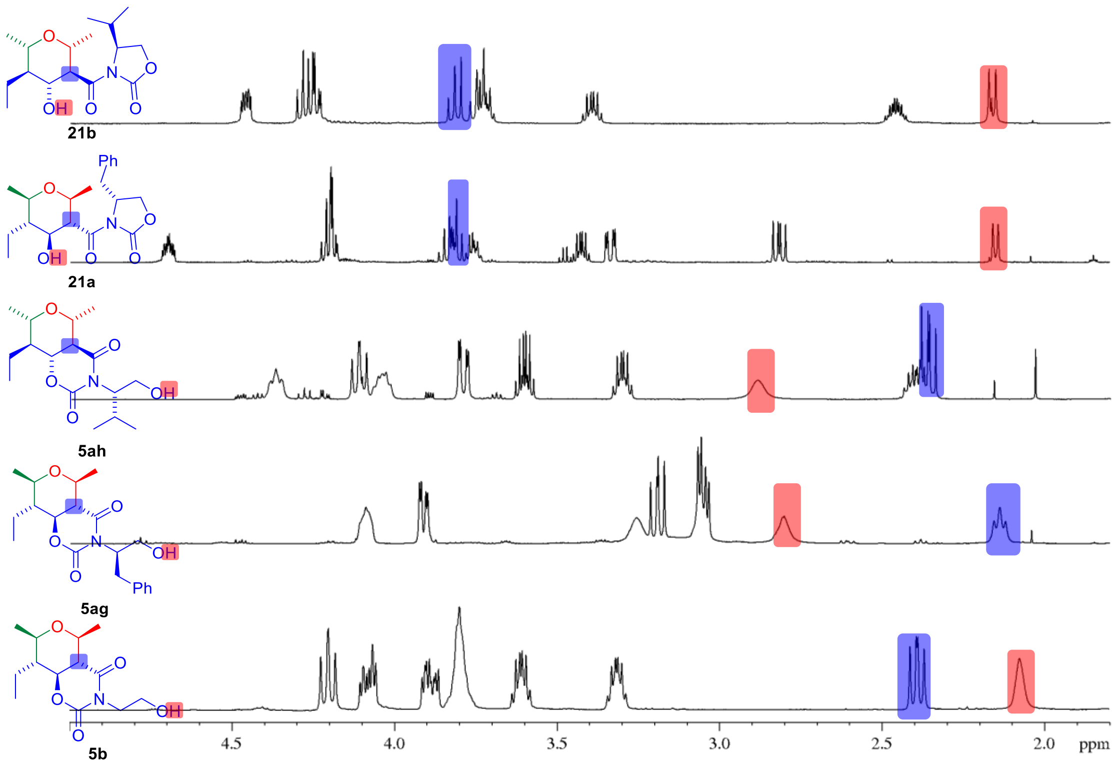


Figure S5

Figure S6 illustrates ^{13}C NMR spectra in the region between δ = 45-77 ppm. It is really noteworthy that the <u>C</u>H directly attached to the nitrogen does not appear in bicycles **5**, although its aspect is the conventional in THPs-Xc **21**.

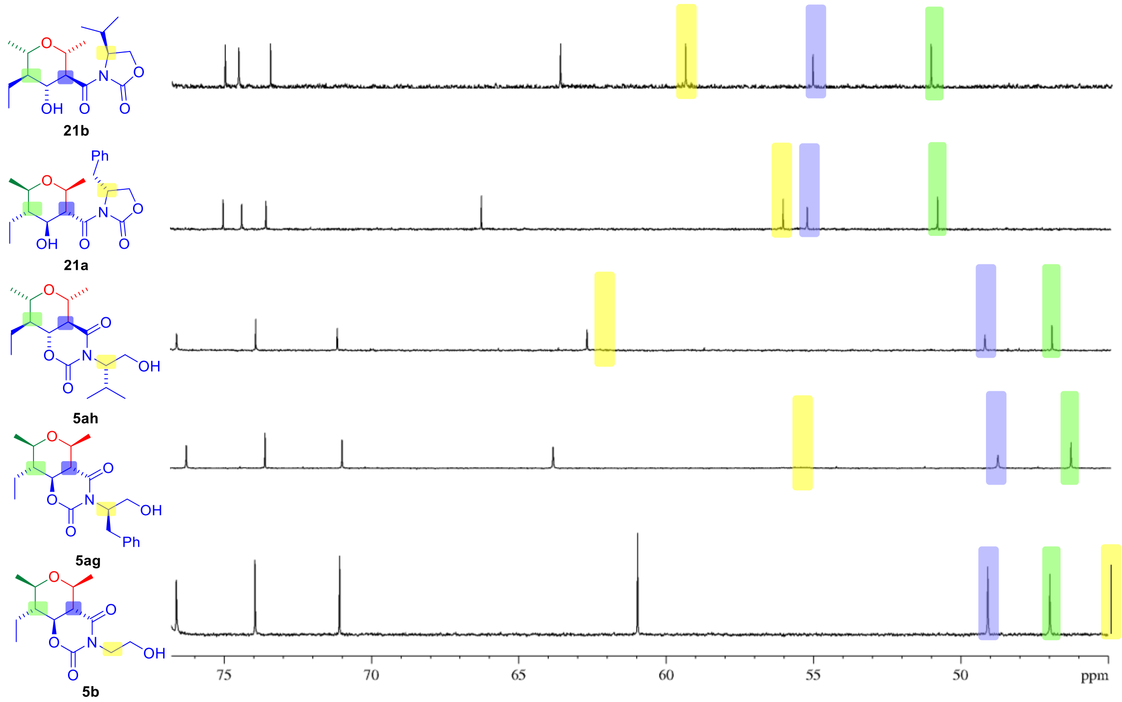


Figure S6

In Figure S7 is highlighted the region between δ = 140-180 ppm of the ^{13}C NMR spectra. The shift of the carbonyl group directly attached to C_3 is always higher in THPs-Xc than in bicycles.

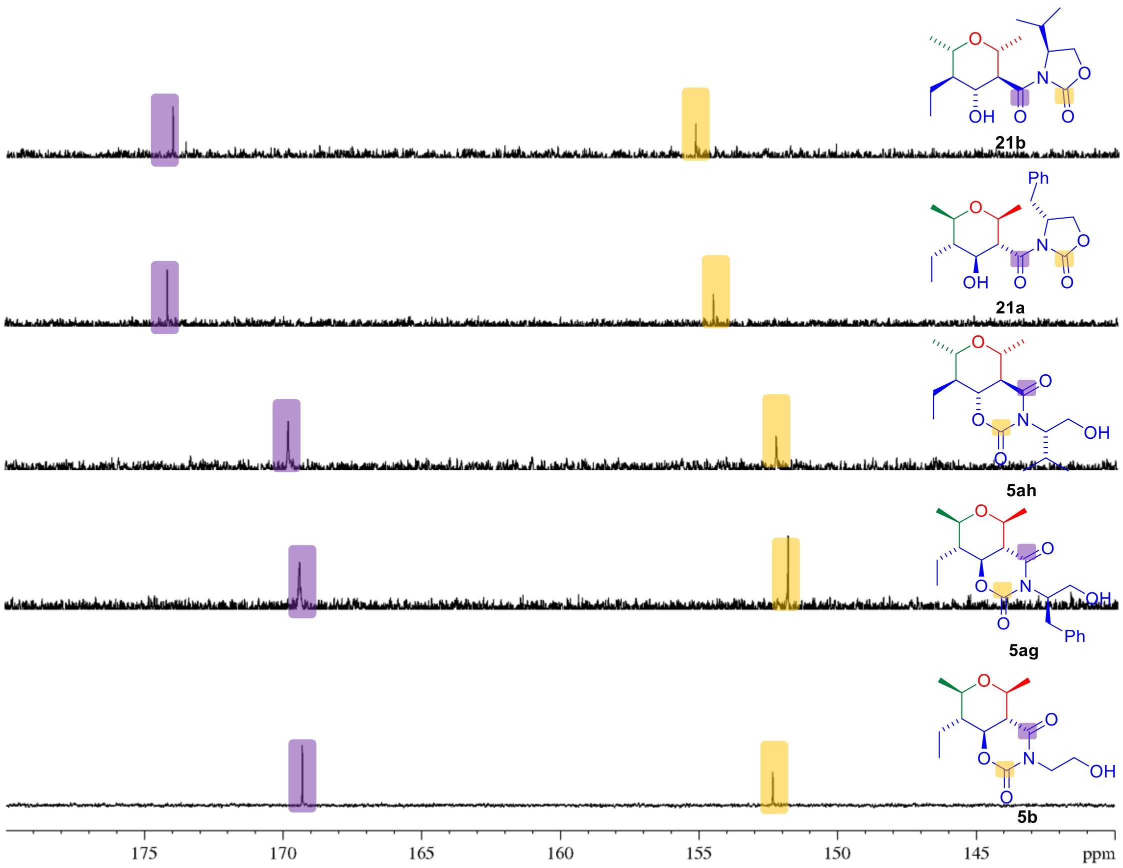


Figure S7

All this information have been collected in Figure S8, together with typical fragmentations observed in the mass spectra.

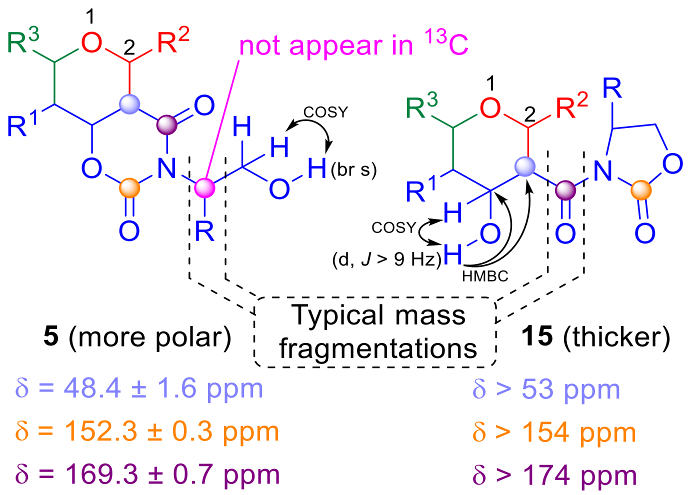
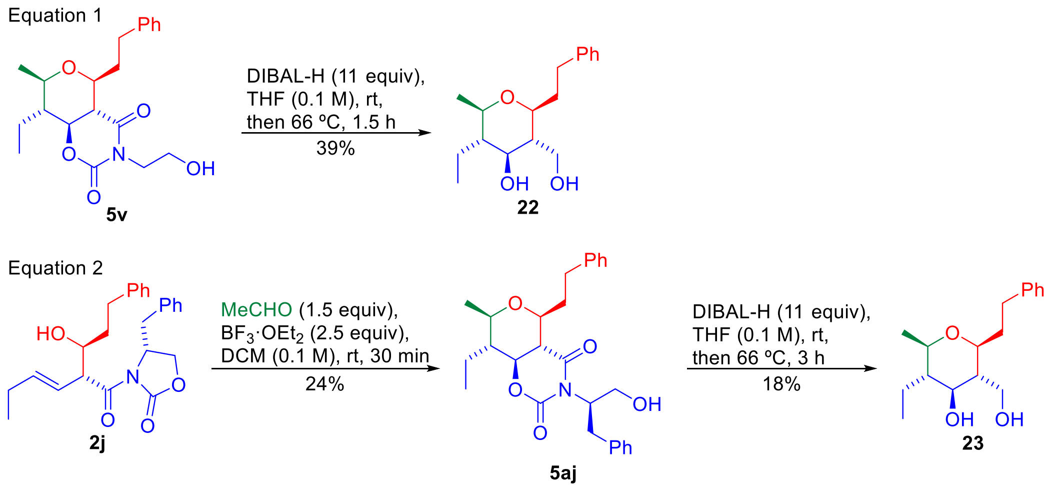


Figure S8

Chiral HPLC information

Reactions shown in Scheme S4 were carried out for checking the preservation of the chirality during the enantiomeric approach to the EAP protocol. Firstly, bicycle **5v** (synthesized as indicated in the manuscript, see Table 5, entry 6) was reduced to racemic diol **22** by treatment with DIBAL-H (equation 1). Secondly, chiral aldol **2j** (Table 1, entry 19) was submitted to the optimized $BF_3\cdot OEt_2$-mediated Prins cyclization to yield **5aj**, a equivalent of bicycle **5v**, which also was treated with DIBAL-H to yield chiral diol **23** (equation 2). Both diols **22** and **23** were injected in a HPLC performed with CHIRAL CEL OD-H WITH AN UV-DETETION (λ = 254 nm), flow: 1mL/min in a 9/1 mixture of *n*-hexane/*i*-propanol using 1 mg/mL of sample. For the racemic diol **22** it was observed t_{R1} = 8.015 min and t_{R2} = 9.204 min (Figure S9); for the chiral diol **23** it was just observed t_{R1} = 8.735 min (Figure S10).

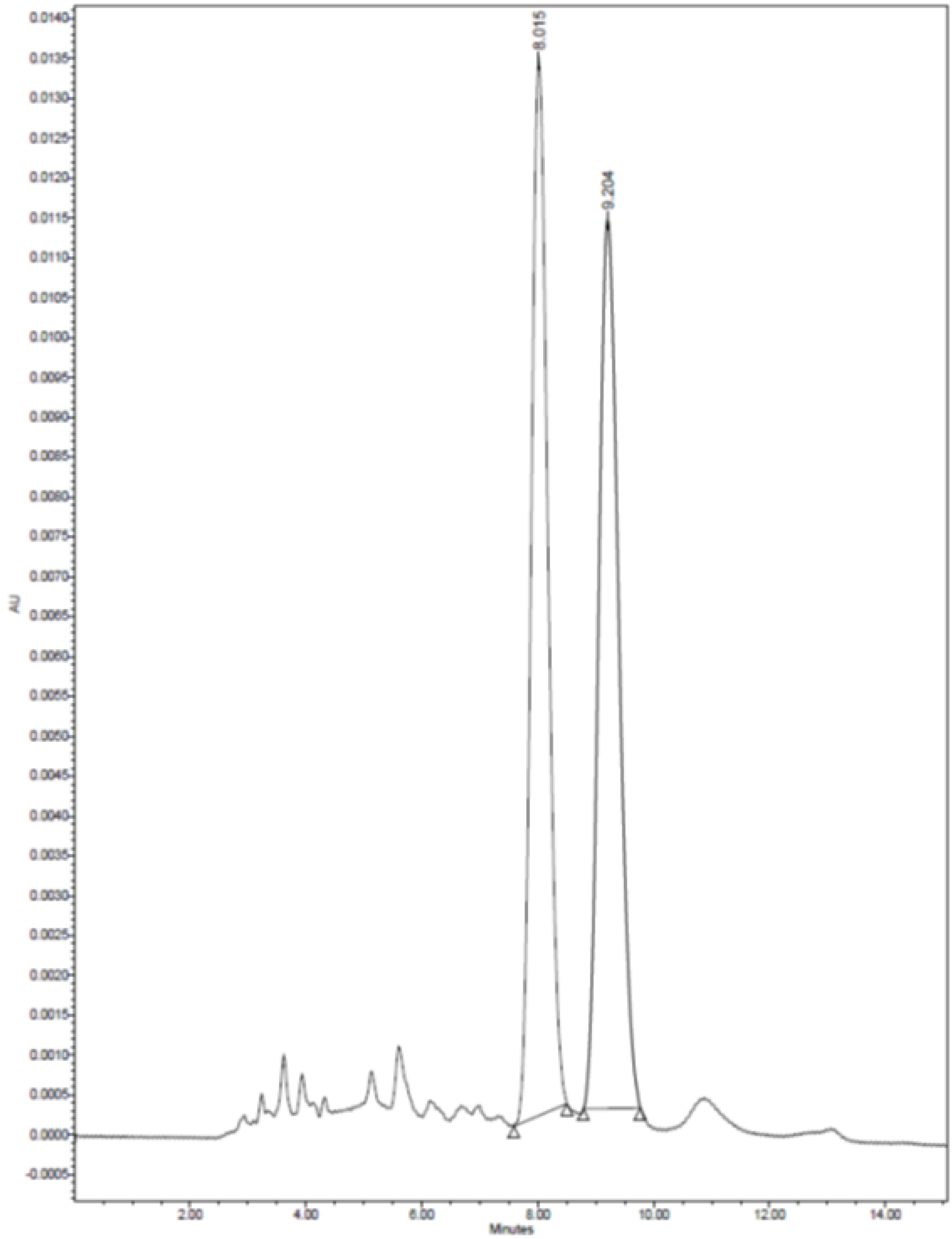


Scheme S4

(4a*S*,5*S*,7*R*,8*R*,8a*S*)-8-Ethyl-3-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-7-methyl-5-phenethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5aj). Aldol **2j** (326 mg, 0.83 mmol) and acetaldehyde (0.38 mL of a 3.3 M solution in DCM, 1.25 mmol, 1.5 equiv) were submitted to the general procedure for the synthesis of the bicycles **5** (two-steps EAP) and yielded, after purification by flash chromatography (29 cm of height of silica gel, *n*-hexane/ EtOAc 70/30) to yield title bicycle **5aj** (91.2 mg, 24%, >95:5 dr) as a yellow solid. R_F : 0.74 (*n*-hexane/EtOAc 60/40); $[\alpha]^{25}_D$ –12.9 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.80 (t, *J* = 7.4 Hz, 3H, $H_{2'''}$), 1.23 (d, *J* = 6.3 Hz, 3H, $H_{1''}$), 1.40-1.47 (m, 2H, H_8, 1x$H_{1'''}$), 1.57-1.64 (m, 1H, $H_{1'''}$), 1.73-1.80 (m, 1H, $H_{1'}$), 2.02 (br s, 1H, OH), 2.21 (dd, *J* = 10.8, 10.8 Hz, 1H, H_{4a}), 2.51-2.58 (m, 1H, $H_{1'}$), 2.63-2.70 (m, 1H, $H_{2'}$), 2.83 (ddd, *J* = 14.1, 10.1, 4.7 Hz, 1H, $H_{2'}$), 2.99-3.18 (br m, 3H, H_5, H_7, H_{8a}), 3.04 (dd, *J* = 14.1, 6.1 Hz, 1H, NCH(C$\underline{H}_2$Ph)CH$_2$OH), 3.18 (dd, *J* = 13.9, 11.2 Hz, 1H, NCH(C$\underline{H}_2$Ph)CH$_2$OH), 3.88 (dd, *J* = 11.9, 3.7 Hz, 1H, C$\underline{H}_2$OH), 4.06 (dd, *J* = 11.8, 7.3 Hz, 1H, C$\underline{H}_2$OH), 5.10-5.17 (br m, 1H, NC$\underline{H}$(CH$_2$Ph)CH$_2$OH), 7.14-7.29 (m, 10H, Ph); ^{13}C-NMR (150MHz , δ, $CDCl_3$): 9.2 (q, $C_{2'''}$), 18.7 (t, $C_{1'''}$), 18.8 (q, $C_{1''}$), 31.6 (t, $C_{2'}$), 33.3 (t, $\underline{C}$H$_2$Ph), 35.4 (t, $C_{1'}$), 46.4 (d, C_8), 47.1 (d, C_{4a}), 55.5 (d, NC$\underline{H}$(CH$_2$Ph)CH$_2$OH), 63.7 (t, CH$_2$OH), 73.5 (d, C_5 or C_7), 73.6 (d, C_5 or C_7), 76.3 (d, C_{8a}), 125.7 (d, Ph), 126.8 (d, Ph), 128.4 (d, 2C, Ph), 128.55 (d, 2C, Ph), 128.58 (d, 2C, Ph), 129.1 (d, 2C, Ph), 137.4 (s, Ph), 141.8 (s, Ph), 151.7 (s, C_2), 169.3 (s, C_4); HRMS: calcd for $C_{27}H_{33}NO_5Na$ $[(M + Na)^+]$ 474.5443, found: 474.2260.

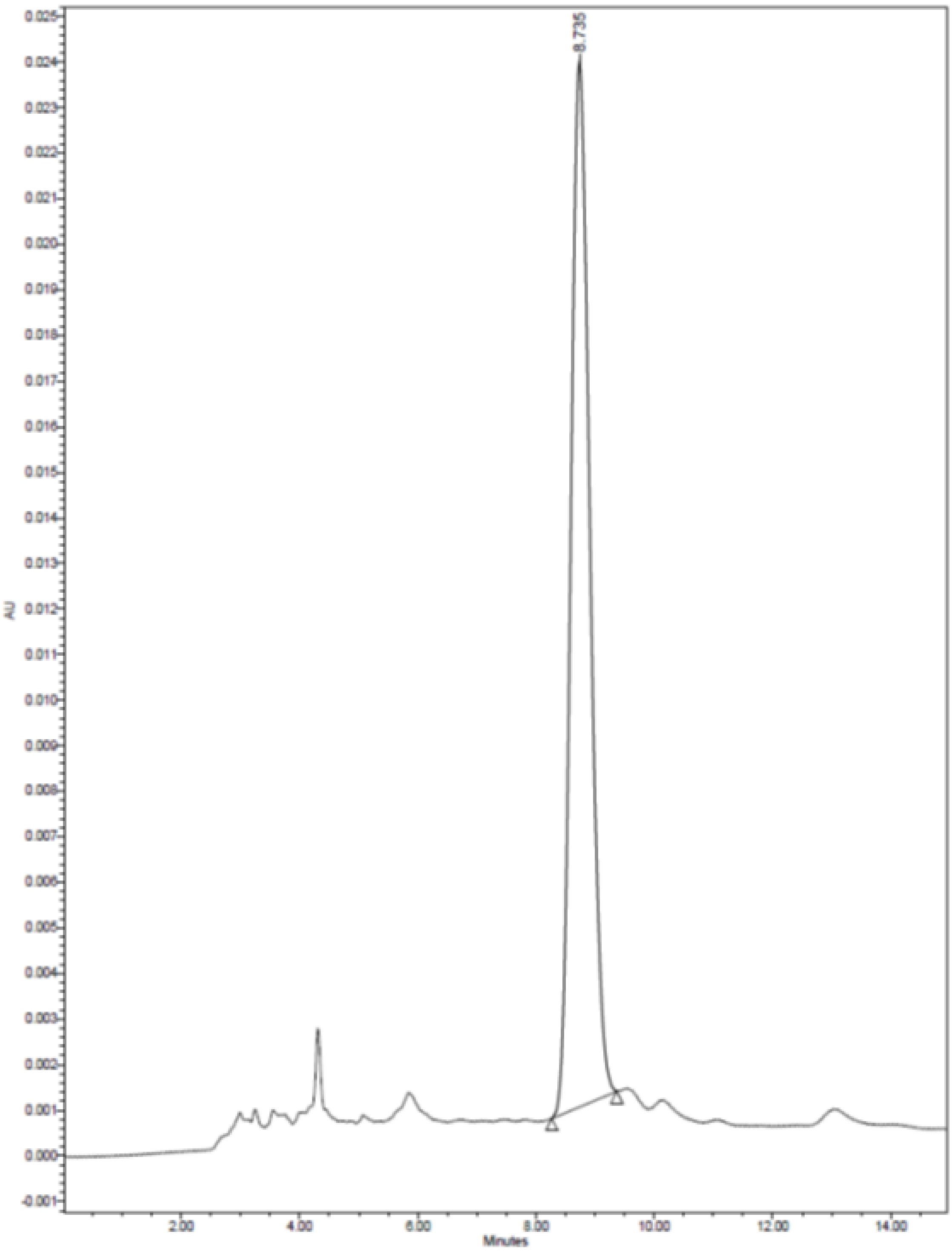
(2*R,3*S**,4*S**,5*R**,6*S**)-3-Ethyl-5-(hydroxymethyl)-2-methyl-6-phenethyltetrahydro-2*H*-pyran-4-ol (22)**. To a solution of non-chiral bicycle **5v** (119 mg, 0.33 mmol) in THF (3.3 mL, 0.1 M) was dropwise added, at rt and under Ar atmosphere, a 1 M of DIBAL-H in *n*-hexanes (3.63 mL, 3.63 mmol, 11 equiv). Then, the reaction mixture was heated at 66 °C for 1.5 h. Once TLC analysis revealed that the reaction was completed, it was cooled to rt, dilute with ET_2O (26 mL) and quenched with a saturated Rochelle salt aqueous solution (6 mL). The mixture was vigorously stirred for 1 h, and then was poured into separatory funnel together with H_2O (18 mL).The layers were separated, the aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered, concentrate and purified by flash chromatography (26 cm of height of silica gel, *n*-hexane/EtOAc 70/30) to yield racemic diol **22** (36 mg, 39%) a white solid. R_F: 0.54 (*n*-hexane/EtOAc50/50); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.90 (t, J = 7.6 Hz, 3H, $H_{2''}$), 1.28 (d, J = 6.1 Hz, 3H, $H_{1'}$), 1.28-1.34 (m, 1H, H_3), 1.50-1.56 (m, 1H, $H_{1''}$), 1.57-1.62 (m, 1H, H_5), 1.63-1.69 (m, 1H, $H_{1''}$), 1.72-1.78 (m, 1H, $H_{1'''}$), 1.84-1.89 (m, 1H, $H_{1'''}$), 2.66 (ddd, J = 16.6, 9.2, 7.4 Hz, 1H, $H_{2'''}$), 2.86 (ddd, J = 13.8, 9.5, 4.9 Hz, 1H, $H_{2'''}$), 3.06 (td, J = 19.4, 2.70 Hz, 1H, H_6), 3.26 (dq, J = 10.2, 6.1 Hz, 1H, H_2), 3.61 (dd, J = 10.7, 7.9 Hz, 1H, $C\underline{H}_2OH$), 3.64 (dd, J = 9.9, 9.9 Hz, 1H, H_4), 3.93 (dd, J = 10.6, 3.40 Hz, 1H, $C\underline{H}_2OH$), 7.16-7.19 (m, 2H, Ph), 7.26-7.29 (m, 3H, Ph); ^{13}C-NMR (150MHz , δ, $CDCl_3$): 9.7 (q, $C_{2''}$), 19.3 (t, $C_{1''}$), 19.6 (q, $C_{1'}$), 31.6 (t, $C_{2'''}$), 35.1 (t, $C_{1'''}$), 49.9 (d, C_3), 50.5 (d, C_5), 63.7 (CH_2OH), 74.3 (d, C_6), 74.5 (d, C_4), 75.0 (d, C_2), 125.9 (d, Ph), 128.5 (d, 2C, Ph), 128.7 (d, 2C, Ph), 142.4 (s, Ph); HRMS: calcd for $C_{17}H_{26}O_3Na$ $[(M + Na)^+]$ 301.3762, found 301.1780.

(2*R*,3*S*,4*S*,5*R*,6*S*)-3-Ethyl-5-(hydroxymethyl)-2-methyl-6-phenethyltetrahydro-2*H*-pyran-4-ol (23). To a solution of chiral bicycle **5aj** (84.2 mg, 0.19 mmol) in THF (1.87 mL, 0.1 M) was dropwise added, at rt and under Ar atmosphere, a 1 M of DIBAL-H in hexanes (2.05 mL, 2.04 mmol, 11 equiv). Then, the reaction mixture was heated at 66 °C for 3 h. Once TLC analysis revealed that the reaction was completed, it was cooled to rt, dilute with Et_2O (15 mL) and quenched with a saturated Rochelle salt aqueous solution (3.4 mL). The mixture was vigorously stirred for 1 h, and then was poured into separatory funnel together with H_2O (15 mL).The layers were separate, the aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, concentrate and purified by flash chromatography (20 cm of height of silica gel, *n*-hexane/EtOAc 70/30) to yield chiral diol **23** (9.4 mg, 18 %) a white solid. R_F: 0.54 (*n*-hexane/EtOAc50/50); $[\alpha]^{25}_D$ –43.7 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.90 (t, J = 7.6 Hz, 3H, $H_{2''}$), 1.28 (d, J = 6.1 Hz, 3H, $H_{1'}$), 1.29-1.33 (m, 1H, H_3), 1.49-1.57 (m, 1H, $H_{1''}$), 1.57-1.70 (m, 2H, H_5, $H_{1''}$), 1.72-1.79 (m, 1H, $H_{1'''}$), 1.83-1.87 (m, 1H, $H_{1'''}$), 2.66 (ddd, J = 16.6, 9.2, 7.4 Hz, 1H, $H_{2'''}$), 2.86 (ddd, J = 13.8, 9.5, 4.9 Hz, 1H, $H_{2'''}$), 3.06 (td, J = 19.4, 2.70 Hz, 1H, H_6), 3.26 (dq, J = 10.2, 6.1 Hz, 1H, H_2), 3.61 (dd, J = 10.7, 7.9 Hz, 1H, H_6), 3.64 (dd, J = 9.9, 9.9 Hz, 1H, H_4), 3.93 (dd, J = 10.6, 3.40 Hz, 1H, $C\underline{H}_2OH$), 7.09-7.12 (m, 2H, Ph), 7.19-7.21 (m, 3H, Ph); ^{13}C-NMR (150MHz , δ, $CDCl_3$): 9.7 (q, $C_{2''}$), 19.3 (t, $C_{1''}$), 19.6 (q, $C_{1'}$), 31.6 (t, $C_{2'''}$), 35.1 (t, $C_{1'''}$), 49.9 (d, C_3), 50.5 (d, C_5), 63.7 (CH_2OH), 74.3 (d, C_6), 74.5 (d, C_4), 75.0 (d, C_2), 125.9 (d, Ph), 128.5 (d, 2C, Ph), 128.7 (d, 2C, Ph), 142.4 (s, Ph); HRMS: calcd for $C_{17}H_{26}O_3Na$ $[(M + Na)^+]$ 301.3762, found 301.1780.



	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type
1		8.015	264052	49.54	13230	bb			Unknown
2		9.204	268955	50.46	11154	bb			Unknown

Figure S9. Chromatogram and table for the racemic **22**.



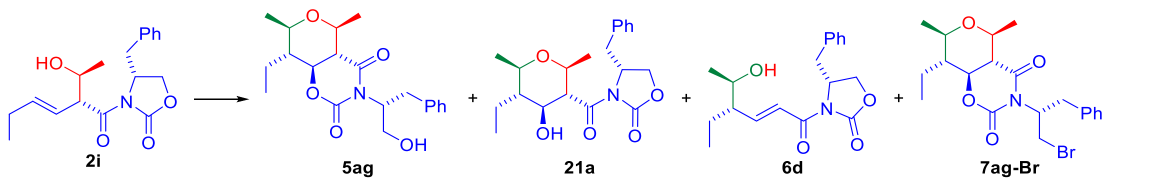
	Name	Retention Time (min)	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type
1		8.735	513185	100.00	22924	BB			Unknown

Figure S10. Chromatogram and table for the chiral 23.

Screening of Lewis acids for the enantiomeric version of Prins cyclization

After the result shown in the equation 1 of Scheme 8, we decided to tune the reaction conditions in order to control the relative amount of isomers **5ag** and **21a**. To this aim, a new screening of the Lewis acids was performed, choosing acetaldehyde and aldol **2i** as model substrate (Table S2). Entry 1 reflects the result shown in the equation 1 of the Scheme 8, corresponding to the use of 2.5 equiv of $BF_3 \cdot OEt_2$. Entry 2 shows that when the amount of the promoter was reduced to 0.05 equiv the total consumption of the starting aldol was achieved, though a greater reaction time (16 h) was required, as it happened in the non-chiral variant (Table 2, entry 10). Under these conditions, the percentage of **21a** was doubled (18%), although the bicycle **5ag** remained as the major product (55%). Additionally, alcohol **6d** was obtained (12%), and this skeletal isomer of starting aldol **2i** is a consequence of the 2-oxonia-Cope rearrangement. When the $Fe(acac)_3$/TMSCl tandem was selected as promoter, only the bicycle **5ag** (25%) and the rearranged isomer **6d** (19%) were isolated (entry 3). A practically identical result was obtained in the presence of 1.5 equiv of $InCl_3$ (entry 4). Entry 5 illustrates that similar yields of these products were achieved when 3 equiv of $FeBr_3$ was selected as promoter, although it was also obtained compound **7ag-Br** (21%), whose structure is similar to that of compound **7b-Br**, obtained via the Prins cyclization mediated by TMSBr (Table 2, entry 15).

Table S2. Screening of Lewis Acids for the Enantiomeric Version of Prins Cyclization[a]



Entry	LA	Equiv	t (h)	**5ag** (%)[b]	**21a** (%)[b]	**6d** (%)[b]	**7ag-Br** (%)[b]
1	$BF_3 \cdot OEt_2$	2.5	0.5	62	9	-	-
2	$BF_3 \cdot OEt_2$	0.05	16	55	18	12	-
3	$Fe(acac)_3$/TMSCl	0.6/1.7	3	25	-	19	-
4	$InCl_3$	1.5	17	25	-	20	-
5	$FeBr_3$	3	5	14	-	21	21

[a] Reaction conditions: MeCHO (1.5 equiv), Lewis acid, DCM (0.1 M), rt. [b] Yield of isolated product; in all the cases THPs were obtained with >95:5 dr.

(*R*)-4-Benzyl-3-((4*S*,5*R*,*E*)-4-ethyl-5-hydroxyhex-2-enoyl)oxazolidin-2-one (6d). Obtained as a by-product during the synthesis of **7ag-Br**, see procedure there. Appearance: thick colourless oil. R_F: 0.43 (*n*-hexane/EtOAc 60/40 three times); $[\alpha]^{25}_D$ –30.7 (*c* 0.5, $CHCl_3$); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.93 (t, *J* = 7.5 Hz, $C\underline{H}_3CH_2C_{4'}$), 1.21 (d, *J* = 6.3 Hz, 3H, $H_{6'}$), 1.44-1.52 (m, 1H, $1xCH_3C\underline{H}_2C_{4'}$), 1.62-1.70 (m, 1H, $1xCH_3C\underline{H}_2C_{4'}$), 2.17-2.22 (m, 1H, $H_{4'}$), 2.81 (dd, *J* = 13.4, 9.7 Hz, 1H, $C\underline{H}_2Ph$), 3.36

(dd, J = 13.4, 3.3 Hz, 1H, $C\underline{H}_2Ph$), 3.86 (dq, J = 7.4, 6.2 Hz, 1H, $H_{5'}$), 4.18 (dd, J = 8.9, 2.9 Hz, 1H, H_5), 4.22 (dd, J = 9.1, 8.5 Hz, 1H, H_5), 4.73 (ddt, J = 9.5, 7.6, 3.1 Hz, 1H, H_4), 7.07 (dd, J = 15.4, 9.7 Hz, 1H, $H_{3'}$), 7.21-7.24 (m, 2H, Ph), 7.27-7.29 (m, 2H, Ph), 7.32 (d, J = 9.7 Hz, 1H, $H_{2'}$), 7.33-7.35 (m, 1H, Ph); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 12.1 (q, $\underline{C}H_3CH_2C_{4'}$), 21.5 (q, $C_{6'}$), 23.7 (t, $CH_3\underline{C}H_2C_{4'}$), 38.1 (t, $\underline{C}H_2Ph$), 52.5 (d, $C_{4'}$), 55.5 (d, C_4), 66.3 (t, C_5), 69.8 (d, $C_{5'}$), 123.0 (d, $C_{2'}$), 127.5 (d, Ph), 129.1 (d, 2C, Ph), 129.6 (d, 2C, Ph), 135.5 (s, Ph), 151.5 (d, $C_{3'}$), 153.6 (s, C_2), 164.8 (s, $C_{1'}C(O)N$); MS (EI) m/z (relative intensity): 300 $(M - OH)^+$ (2), 273 $(M + 1 - CH_3CHOH)^+$ (36), 141 (M – oxazolidin-2-one)$^+$ (11), 96 (100); HRMS: calcd for $C_{18}H_{22}NO_3$ $[(M - OH)^+]$ 300.1600, found 300.1591.

(4a*S*,5*S*,7*R*,8*R*,8a*S*)-3-((*R*)-1-Bromo-3-phenylpropan-2-yl)-8-ethyl-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (7ag-Br). To a solution of aldol **2i** (18 mg, 57 μmol) in dry DCM (0.6 mL, 0.1 M) was sequentially added, at rt and under Ar atmosphere, acetaldehyde (26 μL of a 3.3 M solution in DCM, 86 μmol, 1.5 equiv) and $FeBr_3$ (52 mg, 3 equiv). At 5 h, TLC analysis showed that the starting material had been fully consumed and the reaction was stopped with H_2O (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. After purification by flash chromatography (18 cm of height of silica gel, *n*-hexane/EtOAc 75/25), title compound **7ag-Br** (5 mg, 21%, >95:5 dr), previously described bicycle **5ag** (3 mg, 14%, >95:5 dr) and rearranged isomer **6d** (4 mg, 21%) were obtained. **7ag-Br** was isolated as a yellow oil and its description is given below. R_F: 0.55 (*n*-hexane/EtOAc 60/40); $[\alpha]^{25}_D$ –34.1 (*c* 0.5, $CHCl_3$); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.82 (t, J = 7.5 Hz, 3H, $H_{2'''}$), 1.20 (d, J = 6.2 Hz, 3H, $H_{1''}$), 1.41-1.50 (m, 1H, $H_{1'''}$), 1.46 (d, J = 6.0 Hz, 3H, $H_{1'}$), 1.60-1.67 (m, $H_{1'''}$), 2.15 (dd, J = 11.8, 9.6 Hz, 1H, H_{4a}), 3.07-3.12 (m, 1H, H_7), 3.15 (dd, J = 13.8, 10.6 Hz, 1H, $NCH(CH_2Ph)C\underline{H}_2Br$), 3.22 (dd, J = 13.6, 6.5 Hz, 1H, $NCH(CH_2Ph)C\underline{H}_2Br$), 3.30 (br s, 2H, H_5, H_{8a}), 3.68 (dd, J = 10.3, 5.8 Hz, 1H, $NCH(C\underline{H}_2Ph)CH_2Br$), 4.10 (dd, J = 10.1, 9.5 Hz, 1H, $NCH(C\underline{H}_2Ph)CH_2Br$), 5.21-5.28 (m, 1H, $NC\underline{H}(CH_2Br)CH_2Ph$), 7.15-7.18 (m, 2H, Ph), 7.20-7.24 (m, 1H, Ph), 7.26-7.30 (m, 2H, Ph); ^{1}H-NMR (500 MHz, δ, C_6D_6): 0.62 (t, J = 7.6 Hz, 3H, $H_{2'''}$), 0.93 (d, J = 6.2 Hz, 3H, $H_{1''}$), 1.04-1.18 (m, 2H, H_8, $H_{1'''}$), 1.34-1.42 (m, 1H, $H_{1'''}$), 1.52 (d, J = 6.0 Hz, 3H, $H_{1'}$), 1.71 (dd, J = 12.0, 9.6 Hz, 1H, H_{4a}), 2.59 (dq, J = 9.8, 6.2 Hz, 1H, H_7), 2.70 (dd, J = 13.9, 6.1 Hz, 1H, $1xC\underline{H}_2Ph$), 3.00 (dd, J = 14.0, 11.2 Hz, 1H, $1xC\underline{H}_2Ph$), 3.04-3.16 (m, 2H, H_5, H_{8a}), 3.26 (dd, J = 11.4, 4.4 Hz, 1H, $C\underline{H}_2Br$), 4.10 (dd, J = 11.4, 7.4 Hz, 1H, $C\underline{H}_2Br$), 5.24-5.30 (br m, 1H, $NC\underline{H}(CH_2Ph)CH_2Br$), 6.95-7.08 (m, 5H, Ph); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.2 (q, $C_{2'''}$), 18.7 (t, $C_{1'''}$), 19.0 (q, $C_{1''}$), 20.9 (q, $C_{1'}$), 32.8 ($NCH(\underline{C}H_2Ph)CH_2Br$), 36.0 ($NCH(CH_2Ph)\underline{C}H_2Br$), 46.4 (d, C_8), 48.9 (d, C_{4a}), 55.4 (d, $N\underline{C}H(CH_2Br)CH_2Ph$), 70.9 (d, C_5), 73.6 (d, C_7), 76.0 (d, C_{8a}), 127.2 (d, Ph), 128.8 (d, 2C, Ph), 129.2 (d, 2C, Ph), 137.1 (s, Ph), 151.0 (s, C_2), 168.9 (s, C_4); MS (EI) m/z (relative intensity): 425 $(^{79}M)^+$ (1), 346 $(^{79}M - Ph)^+$ (1), 344 $(M - Br)^+$ (5), 117 (100), 249 (M – oxazolidin-2-one)$^+$ (1),[2] 228 $(M + 2 - CH(Bn)CH_2OH)^+$ (26);[3] HRMS: calcd for $C_{20}H_{26}{}^{81}BrNO_4$ $[(^{81}M)^+]$ 425.1025, found 425.1037.

DFT Calculation results (B3LYP/6-31G(d))

Cartesian coordinates corresponding to stationary points shown in Scheme 7:

***E*-INT1:**

C	-1.13618300	-1.99522200	0.06698200
C	-3.24304200	-0.90084800	0.13341100
C	-1.55628300	1.50293900	-0.01618000
C	-1.00393600	0.45970500	0.64076200
C	-0.30029300	-0.68768800	-0.03940300
H	-1.32231500	-2.24713200	1.11417900
H	-1.46889500	1.53207500	-1.10322400
H	-1.02009200	0.43901600	1.73214800
H	-0.14227000	-0.44958400	-1.09221800
H	-3.12138000	-0.85156000	1.21552700
O	-2.44396000	-1.62654900	-0.53940200
C	-4.45417100	-0.35913100	-0.51114300
H	-5.30992500	-0.97617800	-0.19382800
H	-4.65595700	0.65435000	-0.14852200
H	-4.37952900	-0.37886900	-1.59969100
C	-0.60941100	-3.17903600	-0.71532600
H	0.33756100	-3.49800600	-0.27272700
H	-1.30540100	-4.02067600	-0.66170200
H	-0.44474400	-2.91947000	-1.76543600
C	-2.20416700	2.68930500	0.63040200
H	-3.22767600	2.79906900	0.24053600
H	-2.28432000	2.53749700	1.71348300
C	-1.43188400	3.99171700	0.33200900
H	-1.35940800	4.17356300	-0.74521400
H	-1.94613200	4.84336800	0.78682500
H	-0.41651000	3.94658100	0.73704400
C	1.04177600	-0.93635900	0.67077400
O	1.10558700	-1.66673300	1.64673100
N	2.16873300	-0.29664400	0.19316700
C	3.45780000	-0.45704000	0.87804000

C	2.25641900	0.67973600	-0.83008600
C	4.40093400	0.25589200	-0.10494700
H	3.42253400	0.02116400	1.86193300
H	5.11584600	0.92013100	0.38057700
O	1.35410400	1.11560300	-1.50097400
O	3.53609400	1.06790500	-0.93399600
H	3.69462900	-1.51333800	1.01547700
H	4.93290500	-0.44112600	-0.75797300

***Z*-INT1:**

C	1.22817100	-1.78116800	0.37036500
C	3.27028100	-0.85322900	-0.37796200
C	1.66215800	1.43525500	-0.96090800
C	1.00550900	0.25683700	-1.09653500
C	0.35582600	-0.54075900	0.00607500
H	1.30753000	-2.44624700	-0.49337500
H	0.91094600	-0.17019600	-2.09533200
H	0.21047100	0.07145900	0.89430700
H	3.03469200	-1.26974400	-1.35719200
O	2.57648400	-1.22284900	0.62643900
C	4.53710200	-0.13060800	-0.15175000
H	5.34472400	-0.88013600	-0.12053800
H	4.75792300	0.53562700	-0.99007300
H	4.53046100	0.41337700	0.79481500
C	0.80786500	-2.52387700	1.62055000
H	-0.17562900	-2.97134100	1.45219900
H	1.50814000	-3.33271400	1.84644000
H	0.74952800	-1.85155400	2.48166400
C	-0.98927100	-1.08164400	-0.51492900
O	-1.02530700	-2.08353700	-1.21126300
N	-2.15109800	-0.40724100	-0.19505700
C	-3.44173700	-0.86740300	-0.72442000
C	-2.29161800	0.83554900	0.46911200
C	-4.41300400	0.05406500	0.03132400
H	-3.47364100	-0.72724700	-1.80936800

H	-5.19196500	0.47958500	-0.60123300
O	-1.40914100	1.52626200	0.91616600
O	-3.59460900	1.14483200	0.51774100
H	-3.59363000	-1.92609700	-0.50814000
H	-4.86898400	-0.43349900	0.89705200
H	2.06309500	1.86889700	-1.87937600
C	1.84461200	2.28121800	0.26216800
H	2.92110200	2.46372700	0.40003500
H	1.48027000	1.77744000	1.16140800
C	1.13654000	3.64499400	0.10977200
H	0.05431500	3.50835300	0.05049200
H	1.35634200	4.27311100	0.97794500
H	1.47797000	4.17482900	-0.78616800

***E*-TS1:**

C	1.16844000	-2.00640200	0.07811500
C	2.93660400	-0.56436400	-0.46767500
C	1.85477800	1.11774900	0.13553800
C	0.77767700	0.42905700	-0.38222400
C	0.18104300	-0.77804500	0.25628700
H	1.12144100	-2.34177900	-0.96211500
H	2.08885900	0.96151400	1.18852600
H	0.46252600	0.67592800	-1.39664600
H	0.07200900	-0.59882700	1.33107200
H	2.66981600	-0.67529200	-1.52085000
O	2.48766800	-1.50592400	0.35274700
C	4.34545400	-0.12684800	-0.19383400
H	4.99507500	-0.96635700	-0.47748500
H	4.62726200	0.73019300	-0.80633400
H	4.50897000	0.08931400	0.86409900
C	0.89880500	-3.14947000	1.03885800
H	-0.09320500	-3.56348600	0.84962100
H	1.63542900	-3.94304100	0.88623200
H	0.96140000	-2.81011500	2.07756600
C	2.34599700	2.41135100	-0.46996300

H	3.42652600	2.50880100	-0.32211000
H	2.16245700	2.41366400	-1.55168900
C	1.64492700	3.61884800	0.18700200
H	1.85570700	3.66167000	1.26078800
H	2.01221200	4.54530200	-0.26425800
H	0.56062200	3.56947800	0.05787800
C	-1.18601100	-1.16816200	-0.34375800
O	-1.35090800	-2.21165700	-0.94838000
N	-2.25345300	-0.31054500	-0.13318100
C	-3.60910800	-0.65310000	-0.58473400
C	-2.20412500	1.01563200	0.32878800
C	-4.41988300	0.47081200	0.08143400
H	-3.66170800	-0.63061100	-1.67761200
H	-5.17669700	0.91055800	-0.56742700
O	-1.20445300	1.63979700	0.61487700
O	-3.44448400	1.50575500	0.38044400
H	-3.88911100	-1.65069300	-0.24286100
H	-4.87560200	0.16147700	1.02537100

***Z*-TS1:**

C	-1.43163600	1.91012100	0.01819500
C	-2.98867700	0.24524000	-0.75387100
C	-2.04523600	-0.95844700	-0.46080000
C	-0.64628700	-0.38718000	-0.66969400
C	-0.33721300	0.81495600	0.21629400
H	-1.32845900	2.31340400	-1.00332100
H	-0.50049000	-0.13100800	-1.72637300
H	-0.36724700	0.49613300	1.26882300
H	-2.77877600	0.60393100	-1.77686100
O	-2.70356700	1.30236300	0.16707700
C	-4.47462900	-0.06014800	-0.64277800
H	-5.04849800	0.83362700	-0.90202100
H	-4.75713100	-0.86497300	-1.32864400
H	-4.74490300	-0.35142700	0.37571700
C	-1.35815500	3.03967500	1.03613300

H	-0.42536100	3.59835500	0.94160400
H	-2.19697200	3.72021200	0.86803100
H	-1.44296200	2.64305000	2.05357100
C	1.07037700	1.27702400	-0.08447400
O	1.47890800	2.40778500	-0.11542000
N	2.01036700	0.19090000	-0.35059200
C	3.41638000	0.56328700	-0.67318600
C	1.61013100	-1.10542500	-0.33676200
C	4.41795700	0.31549300	0.44415600
H	3.71669600	0.02165000	-1.57521000
H	5.36094500	0.80965600	0.18760200
O	0.36429800	-1.44305900	-0.39764800
O	2.43539800	-2.08734000	-0.28071600
H	3.38270100	1.62889900	-0.90033200
H	4.05320300	0.71220800	1.39843700
H	-2.20414500	-1.71681300	-1.23843800
C	-2.25589500	-1.59435100	0.93628300
C	-3.12736600	-2.85687500	0.90553100
H	-2.69123900	-0.84602000	1.60799700
H	-1.28469100	-1.86603500	1.36813800
H	-3.25208100	-3.26045000	1.91535500
H	-4.12511200	-2.65832000	0.50300700
H	-2.66698200	-3.63753600	0.28896200

***E*-INT2:**

C	1.19619600	1.99207900	0.17884300
C	2.78060000	0.17654300	0.33237700
C	1.74442100	-0.92040700	-0.06127900
C	0.37542400	-0.37109400	0.31162600
C	0.06115700	1.01509000	-0.25402500
H	1.18304400	2.07543700	1.27886700
H	1.78945200	-1.01494600	-1.15465300
H	0.25083800	-0.37851400	1.40136400
H	0.08425300	0.96532800	-1.35344200
H	2.78755800	0.28073700	1.43126100

O	2.41899500	1.42894700	-0.25362100
C	4.19085100	-0.11435000	-0.16779100
H	4.83921200	0.72766500	0.08816500
H	4.61071500	-1.01587200	0.28431000
H	4.19360400	-0.22997000	-1.25644200
C	1.09582100	3.37424500	-0.45223600
H	0.19939200	3.90056100	-0.12079600
H	1.97646400	3.95347100	-0.16248900
H	1.08674300	3.29574900	-1.54451300
C	2.02145600	-2.29483200	0.60274500
H	3.08279900	-2.35299200	0.86130400
H	1.48398300	-2.35364600	1.55922300
C	1.66954200	-3.50708800	-0.26998500
H	2.23536600	-3.49095300	-1.20841900
H	1.92229300	-4.43556600	0.25153900
H	0.60502300	-3.54401000	-0.51989200
C	-1.34587900	1.43647200	0.13814500
O	-1.77432200	2.52870800	0.39445200
N	-2.25963700	0.32311600	0.12436000
C	-3.72966100	0.40964200	0.23603000
C	-1.88752500	-0.94210500	-0.10624300
C	-4.13911500	-1.00558500	-0.23507100
H	-4.01175700	0.62098000	1.27002600
H	-4.80004700	-1.53262400	0.45074700
O	-0.67989100	-1.35809500	-0.16130100
O	-2.87171000	-1.77402200	-0.26558300
H	-4.10690900	1.20576600	-0.40778100
H	-4.53887400	-1.03437100	-1.24929900

***Z*-INT2:**

C	-0.49251400	-1.86222500	0.37337800
C	-2.36217000	-0.40729700	0.77329700
C	-2.01649800	0.54686100	-0.39224700
C	-0.53077200	0.44927600	-0.72845200
C	0.01131100	-0.98252800	-0.82661800

H	-0.02798900	-1.48701600	1.30333600
H	-2.51978400	0.14802400	-1.28624000
H	-0.39068000	-1.42681900	-1.74312600
H	-1.85136300	-0.06201000	1.68789800
O	-1.89154500	-1.72549000	0.45511700
C	-3.85404300	-0.54234600	1.04401400
H	-4.01458700	-1.32171900	1.79368900
H	-4.27677100	0.39047600	1.42601500
H	-4.39113500	-0.82779900	0.13320900
C	-0.18278800	-3.34201300	0.19851800
H	0.89261700	-3.52884900	0.13450100
H	-0.58442300	-3.89336700	1.05261500
H	-0.65739700	-3.72491700	-0.71021700
C	-2.49242400	2.00034900	-0.17652800
H	-3.57818400	1.97028700	-0.04458600
H	-2.07956300	2.38643100	0.76355900
C	-2.16653000	2.96454000	-1.32429200
H	-2.53405700	2.58670900	-2.28590500
H	-2.64528600	3.93239900	-1.14859500
H	-1.09141400	3.15715400	-1.42197300
C	1.51933500	-1.00691600	-0.95155100
O	2.20502500	-1.82004700	-1.51097100
N	2.15444000	0.05893500	-0.22386100
C	3.60441000	0.20731000	0.00699400
C	1.47960100	1.01020700	0.43102200
C	3.61260300	1.28974900	1.11271900
H	4.03044200	-0.74423200	0.32904200
H	3.83881800	0.90303700	2.10691400
O	0.21657300	1.19351600	0.37400500
O	2.21714100	1.78582100	1.16726100
H	4.09657300	0.52559500	-0.91488900
H	4.23622500	2.15358200	0.88902300
H	-0.28781100	1.03027600	-1.62206600

***E*-INT3:**

C	1.59399100	2.01433200	0.17597600
C	3.23138000	0.24732800	0.34065200
C	2.23100300	-0.87866300	-0.05968400
C	0.84354000	-0.37246100	0.30873700
C	0.49130500	1.00400000	-0.25802100
H	1.57332900	2.10077900	1.27574800
H	2.28330800	-0.96897300	-1.15310900
H	0.51699500	0.95236900	-1.35727200
H	3.22733000	0.35186700	1.43969700
O	2.83753400	1.48871200	-0.24780000
C	4.65378400	-0.00092700	-0.14833300
H	5.27310000	0.86271200	0.10766800
H	5.09899100	-0.88623000	0.31148500
H	4.66831300	-0.12187700	-1.23639100
C	1.45595800	3.39161500	-0.45862900
H	0.53972600	3.88825300	-0.13592200
H	2.31506800	3.99959100	-0.16308500
H	1.45820400	3.31051500	-1.55080900
C	2.54703400	-2.24673000	0.59960500
H	3.60896000	-2.27535500	0.86101100
H	2.00890400	-2.32693700	1.55424300
C	2.23332400	-3.46458100	-0.28001500
H	2.80448300	-3.42909900	-1.21469900
H	2.50751200	-4.38838300	0.23916500
H	1.17177400	-3.52810000	-0.53679100
C	-0.92927500	1.38205300	0.13306000
O	-1.38469200	2.46502500	0.38770100
N	-1.80783400	0.24665400	0.12231900
C	-3.28447100	0.29202600	0.22263200
C	-1.39908900	-1.00704300	-0.10971500
C	-3.65474400	-1.13812200	-0.22548600
H	-3.58013900	0.51233000	1.24930200
H	-4.28672600	-1.67930700	0.47182800
O	-0.17576300	-1.38607200	-0.16555600
O	-2.35294400	-1.86733500	-0.26979500

H	-3.68615000	1.06353800	-0.43178900
H	-4.06717000	-1.19496300	-1.23104200
H	0.71993300	-0.37975300	1.39874200
O	-6.18105500	0.12044700	0.01344500
H	-6.77928700	0.27342900	-0.73431800
H	-6.74869400	0.23383200	0.79147000

***Z*-INT3:**

C	-1.54966200	1.91681800	-0.08673600
C	-3.08476000	0.21395100	-0.81471700
C	-2.14467100	-0.96947800	-0.43370800
C	-0.74522900	-0.40167800	-0.62758200
C	-0.46347100	0.83765700	0.22496400
H	-1.40771300	2.25254000	-1.12803500
H	-0.57024800	-0.18161300	-1.68722600
H	-0.56170000	0.56979000	1.28747300
H	-2.84936200	0.51646000	-1.85018000
O	-2.82789500	1.31974800	0.05362200
C	-4.57168900	-0.09420100	-0.72554700
H	-5.14208200	0.78139100	-1.04699900
H	-4.83295400	-0.93594500	-1.37446600
H	-4.86696100	-0.33184300	0.29988300
C	-1.51188100	3.11048000	0.85738600
H	-0.57497900	3.66166500	0.76219200
H	-2.34361500	3.77665400	0.61344700
H	-1.63447300	2.78094800	1.89463500
C	0.97068400	1.29857200	0.02236700
O	1.41782800	2.41453000	0.03541400
N	1.87182400	0.19396800	-0.14886000
C	3.35029300	0.27690900	-0.14616500
C	1.48127500	-1.08519500	-0.22335000
C	3.72967600	-1.21278800	-0.00498800
H	3.69848100	0.72409000	-1.07824800
H	4.41139700	-1.57819200	-0.76676100
O	0.26682400	-1.48214000	-0.32755700

O	2.44557100	-1.94820400	-0.19886600
H	3.69494800	0.88757400	0.68641500
H	4.08835100	-1.48712400	0.98523400
H	-2.27751600	-1.76401900	-1.17949300
C	-2.39282300	-1.53990600	0.98522100
C	-3.25873500	-2.80651600	0.99020000
H	-2.84897400	-0.76288100	1.60884800
H	-1.43291100	-1.78607700	1.45657600
H	-3.40852200	-3.16320600	2.01411500
H	-4.24617200	-2.63137300	0.55300000
H	-2.77967900	-3.61290100	0.42289700
O	6.23496800	0.09490400	0.18678400
H	6.84107000	0.38222800	-0.51356300
H	6.78843700	0.08560000	0.98304400

***E*-TS2:**

C	1.44052900	2.03305300	0.14579100
C	3.18103500	0.36427900	0.28530800
C	2.24488900	-0.81762100	-0.09315700
C	0.82623100	-0.40643200	0.29626700
C	0.39373600	0.95712900	-0.24620800
H	1.44283700	2.13450200	1.24476900
H	2.28259300	-0.91210900	-1.18718600
H	0.37369600	0.90319200	-1.34537700
H	3.18779500	0.47540100	1.38421900
O	2.70625800	1.57981100	-0.30040500
C	4.61016900	0.20548500	-0.22198700
H	5.17423000	1.11240500	0.01175000
H	5.12053800	-0.64141300	0.24257900
H	4.61723600	0.06910000	-1.30848700
C	1.21050400	3.39266400	-0.50060800
H	0.27269200	3.83675600	-0.16371100
H	2.03819400	4.05498700	-0.23280200
H	1.19393100	3.29668200	-1.59172700
C	2.66059500	-2.15981600	0.56164100

H	3.74000300	-2.14526900	0.74090400
H	2.19868200	-2.23745300	1.55584900
C	2.32920600	-3.40963300	-0.26539900
H	2.82136200	-3.37101000	-1.24422300
H	2.68601700	-4.30895500	0.24737400
H	1.25471000	-3.52059000	-0.43298600
C	-1.02336800	1.23943600	0.21961000
O	-1.50829400	2.31091600	0.50746500
N	-1.82707900	0.06950800	0.27846500
C	-3.23978200	0.16995000	0.63997900
C	-1.40230300	-1.21370000	-0.05907800
C	-4.07007900	-0.73557800	-0.24982300
H	-3.38091400	-0.09844500	1.69268200
H	-4.49305700	-1.64777100	0.14932800
O	-0.11317000	-1.43650600	-0.18965300
O	-2.25100300	-2.08532500	-0.23482000
H	-3.51751300	1.21861200	0.50335600
H	-3.85965100	-0.73534800	-1.31258200
H	0.73532500	-0.41550800	1.39109000
O	-5.56348300	0.21113600	-0.38043700
H	-6.17081100	-0.16893400	-1.04718000
H	-6.05899300	0.25903700	0.46190300

***Z*-TS2:**

C	-1.41939700	1.91796900	-0.04656100
C	-3.04745300	0.29574800	-0.76266400
C	-2.15662000	-0.93022300	-0.41840200
C	-0.72689300	-0.43751500	-0.63799200
C	-0.37785600	0.78860900	0.20835800
H	-1.29091700	2.27406800	-1.08314200
H	-0.58275400	-0.20385600	-1.70095300
H	-0.43714200	0.51067600	1.27111300
H	-2.81968000	0.60193200	-1.79916600
O	-2.72312000	1.37975000	0.11269500
C	-4.54605200	0.06075800	-0.64612000

H	-5.08079400	0.96704200	-0.94357200
H	-4.86172800	-0.75906200	-1.29919300
H	-4.83106400	-0.17699400	0.38234100
C	-1.30799300	3.08733600	0.92219300
H	-0.34836800	3.59582700	0.81660100
H	-2.11396700	3.79663800	0.71539900
H	-1.42112600	2.73807500	1.95431600
C	1.05950900	1.18496600	-0.07167100
O	1.53049500	2.30069200	-0.07490800
N	1.90114400	0.06962700	-0.32832400
C	3.33039500	0.27374700	-0.55748400
C	1.49735100	-1.26521300	-0.32871600
C	4.13173200	-0.79644300	0.15913500
H	3.54770000	0.25549200	-1.63111500
H	4.60881600	-1.58509300	-0.40730500
O	0.21099400	-1.53560300	-0.34680000
O	2.36192300	-2.13810100	-0.30081400
H	3.56415100	1.26820300	-0.16774000
H	3.84942200	-1.04681800	1.17474000
H	-2.34400800	-1.71182000	-1.16649400
C	-2.40048000	-1.50572700	0.99880400
C	-3.32737800	-2.72833900	1.01168800
H	-2.80324400	-0.71547300	1.64268000
H	-1.44229000	-1.80495200	1.44035300
H	-3.47087700	-3.09121500	2.03472300
H	-4.31539000	-2.50109200	0.59978700
H	-2.90099800	-3.54947100	0.42373700
O	5.57681600	0.11819500	0.61081100
H	6.12222900	0.37431400	-0.16017600
H	6.15396700	-0.39731800	1.21006500

***E*-INT4:**

C	1.37217100	2.04526800	0.14571200
C	3.16255700	0.42979000	0.28385300
C	2.26437400	-0.77918600	-0.09775200

C	0.83173900	-0.41547600	0.29144500
C	0.35901400	0.93792900	-0.24344100
H	1.37262600	2.14856900	1.24457700
H	2.30553000	-0.87058200	-1.19199000
H	0.33444000	0.88500900	-1.34259000
H	3.16398200	0.53992300	1.38296400
O	2.65142200	1.63143000	-0.30080800
C	4.59722000	0.31765800	-0.22050900
H	5.13090800	1.24274300	0.01352800
H	5.13410800	-0.51179600	0.24564500
H	4.61097700	0.18067000	-1.30690800
C	1.10113200	3.39683100	-0.50194900
H	0.15080600	3.81290800	-0.16439000
H	1.90898200	4.08410200	-0.23628300
H	1.08622700	3.29885600	-1.59298200
C	2.72266800	-2.10884100	0.55366700
H	3.80375600	-2.06630200	0.71813200
H	2.27612000	-2.19533100	1.55421900
C	2.41285500	-3.36944300	-0.26544700
H	2.88926800	-3.31995200	-1.25161400
H	2.80200800	-4.25724200	0.24402400
H	1.33955700	-3.50961800	-0.41678300
C	-1.06226300	1.17345800	0.23282600
O	-1.57116900	2.23384000	0.52803300
N	-1.83109500	-0.01809600	0.29942700
C	-3.23229700	0.05727300	0.69851300
C	-1.37478400	-1.29582800	-0.06427900
C	-4.12891400	-0.65578500	-0.30411600
H	-3.36395400	-0.37806500	1.69460900
H	-4.51532200	-1.63033200	-0.02496500
O	-0.07192000	-1.46392200	-0.20422100
O	-2.18596600	-2.18832900	-0.25103100
H	-3.46434400	1.12650600	0.74118400
H	-3.80802300	-0.59849400	-1.34001300
H	0.74255000	-0.43077500	1.38668500

O	-5.47051900	0.27274600	-0.38657900
H	-6.10764800	-0.05316500	-1.05782800
H	-5.94251800	0.34102700	0.47049200

***Z*-INT4**:

C	-1.36470900	1.92322300	-0.04898700
C	-3.03506900	0.34028700	-0.75676700
C	-2.17427000	-0.90610600	-0.41313700
C	-0.73178500	-0.45211300	-0.63882700
C	-0.35020200	0.76925600	0.20038600
H	-1.23223800	2.27704400	-1.08590100
H	-0.58776700	-0.22412200	-1.70335000
H	-0.40722500	0.49488700	1.26424200
H	-2.80293800	0.63906500	-1.79452700
O	-2.68110200	1.41794000	0.11546400
C	-4.53887800	0.14408600	-0.63523700
H	-5.05152300	1.06334400	-0.93193400
H	-4.87744100	-0.66822800	-1.28626400
H	-4.82653200	-0.08544000	0.39437800
C	-1.22184800	3.08942700	0.91961800
H	-0.25079000	3.57486600	0.81030700
H	-2.01166900	3.81781300	0.71669500
H	-1.33913200	2.74227200	1.95204900
C	1.09299800	1.12928700	-0.09448500
O	1.58397200	2.23825100	-0.10271400
N	1.90705100	-0.00219400	-0.36399000
C	3.32907800	0.19071400	-0.62821900
C	1.47614700	-1.33989200	-0.33978400
C	4.18016800	-0.71992800	0.24545200
H	3.54419000	0.00302300	-1.68541600
H	4.62269500	-1.59267700	-0.22279900
O	0.17528900	-1.56683200	-0.34232700
O	2.30846200	-2.23199800	-0.30383500
H	3.52523400	1.24441800	-0.40459200
H	3.78889400	-0.91334400	1.23976300

H	-2.38389300	-1.68495100	-1.15824200
C	-2.42756800	-1.47221000	1.00612400
C	-3.38443000	-2.67144300	1.02530400
H	-2.80836700	-0.67083700	1.64972000
H	-1.47535300	-1.79428300	1.44418400
H	-3.53347900	-3.02846000	2.04967800
H	-4.36798200	-2.42101300	0.61602600
H	-2.98028800	-3.50415800	0.43794000
O	5.47873200	0.19235900	0.64232600
H	6.00428300	0.47039200	-0.13769400
H	6.08134700	-0.26956300	1.26370000

***E*-FIN**:

C	0.85176900	2.06464900	0.23166300
C	2.93579100	0.83748000	0.38233900
C	2.32990600	-0.50698100	-0.10137400
C	0.83882400	-0.46154800	0.22668700
C	0.11619900	0.78187100	-0.29260800
H	0.78126500	2.07598500	1.33294300
H	2.43900000	-0.53337700	-1.19430600
H	0.71051700	-0.52891200	1.31588200
H	0.18738400	0.81387000	-1.39118800
H	2.86932800	0.88665500	1.48305600
O	2.19668200	1.93718800	-0.17144500
C	4.37731700	1.06312100	-0.05719500
H	4.69454100	2.06260200	0.25202200
H	5.05908600	0.33707100	0.39126600
H	4.46059200	0.99863200	-1.14698600
C	0.35781000	3.38697000	-0.34295500
H	-0.64287600	3.64088900	0.00783700
H	1.05039000	4.17138300	-0.02670200
H	0.36019800	3.35734000	-1.43751100
C	3.02174700	-1.74615100	0.52232700
H	4.06488700	-1.49295900	0.73479400
H	2.56659500	-1.96255900	1.49902700

C	3.00356700	-3.00590300	-0.35458300
H	3.49200600	-2.81738800	-1.31756400
H	3.55042000	-3.81558800	0.13910200
H	1.98861400	-3.35865700	-0.55454300
C	-1.34029600	0.64057600	0.03755400
O	-2.06775900	1.69845400	0.10360700
N	-1.85173700	-0.57887200	0.24516400
C	-3.22099900	-0.81514300	0.79152900
C	-1.11907400	-1.79006100	-0.16913000
C	-4.36769200	-0.46302700	-0.14235300
H	-3.26024000	-1.87772500	1.02577800
H	-5.29145700	-0.89350100	0.25729100
O	0.18077200	-1.63891000	-0.34197000
O	-1.72902600	-2.80415400	-0.34961300
H	-3.30897900	-0.24273700	1.72064000
H	-4.19433700	-0.85493100	-1.15049500
O	-4.47557400	0.97669200	-0.14784400
H	-5.07791200	1.28800900	-0.84404800
H	-3.08682800	1.52873400	0.05428200

***Z*-FIN**:

C	-1.43163600	1.91012100	0.01819500
C	-2.98867700	0.24524000	-0.75387100
C	-2.04523600	-0.95844700	-0.46080000
C	-0.64628700	-0.38718000	-0.66969400
C	-0.33721300	0.81495600	0.21629400
H	-1.32845900	2.31340400	-1.00332100
H	-0.50049000	-0.13100800	-1.72637300
H	-0.36724700	0.49613300	1.26882300
H	-2.77877600	0.60393100	-1.77686100
O	-2.70356700	1.30236300	0.16707700
C	-4.47462900	-0.06014800	-0.64277800
H	-5.04849800	0.83362700	-0.90202100
H	-4.75713100	-0.86497300	-1.32864400
H	-4.74490300	-0.35142700	0.37571700

C	-1.35815500	3.03967500	1.03613300
H	-0.42536100	3.59835500	0.94160400
H	-2.19697200	3.72021200	0.86803100
H	-1.44296200	2.64305000	2.05357100
C	1.07037700	1.27702400	-0.08447400
O	1.47890800	2.40778500	-0.11542000
N	2.01036700	0.19090000	-0.35059200
C	3.41638000	0.56328700	-0.67318600
C	1.61013100	-1.10542500	-0.33676200
C	4.41795700	0.31549300	0.44415600
H	3.71669600	0.02165000	-1.57521000
H	5.36094500	0.80965600	0.18760200
O	0.36429800	-1.44305900	-0.39764800
O	2.43539800	-2.08734000	-0.28071600
H	3.38270100	1.62889900	-0.90033200
H	4.05320300	0.71220800	1.39843700
H	-2.20414500	-1.71681300	-1.23843800
C	-2.25589500	-1.59435100	0.93628300
C	-3.12736600	-2.85687500	0.90553100
H	-2.69123900	-0.84602000	1.60799700
H	-1.28469100	-1.86603500	1.36813800
H	-3.25208100	-3.26045000	1.91535500
H	-4.12511200	-2.65832000	0.50300700
H	-2.66698200	-3.63753600	0.28896200

Negative frequencies corresponding to Transition State Structures in Scheme 7 (only one negative frequency each):

E-TS1: -150.18 cm^{-1}

Z-TS1: -184.39 cm^{-1}

E-TS2: -370.12 cm^{-1}

Z-TS2: -399.04 cm^{-1}

Cartesian coordinates corresponding to stationary points to study the 2-oxonia-Cope rearrangement (Scheme 7 starting from aldol **2** with a terminal olefin):

Starting material (equivalent to *E*-INT1 with R^1 = H)

C	1.61417100	1.21598200	-0.16423300
C	3.59759900	-0.08142800	0.23207900
C	1.35516400	-2.15341300	0.85251900
C	1.01530800	-0.88125900	1.10640900
C	0.56176200	0.09880700	0.04971500
H	1.86769400	1.70251700	0.78087800
H	1.27794500	-2.57625700	-0.14582200
H	1.04174000	-0.50081200	2.12866500
H	0.39187200	-0.42552100	-0.89155700
H	3.46451700	0.15283400	1.28995300
O	2.84507800	0.47783200	-0.61390200
C	4.72290000	-0.91576800	-0.21892100
H	5.65726500	-0.37895700	0.01006800
H	4.75531000	-1.84187800	0.36698100
H	4.67103200	-1.12939200	-1.28754600
C	1.30708500	2.21787100	-1.25650400
H	0.45000600	2.81940100	-0.94393400
H	2.15208300	2.89385200	-1.41372500
H	1.06960000	1.71717000	-2.19979900
C	-0.73212500	0.77178200	0.54370100
O	-0.68198500	1.74605400	1.27798200
N	-1.94281300	0.22869800	0.16713100
C	-3.19784400	0.78397100	0.68959100
C	-2.18279600	-0.94315300	-0.59581400
C	-4.23267600	0.00654400	-0.14155900
H	-3.27565300	0.58829500	1.76350600

H	-5.05849800	-0.38794400	0.45048700
O	-1.35890300	-1.67850500	-1.07954500
O	-3.50806000	-1.11833200	-0.69270400
H	-3.23930200	1.86288300	0.53107700
H	-4.62728400	0.59137300	-0.97659500
H	1.66103700	-2.82447600	1.65090900

Transition state (imaginary frequency -214.04 cm^{-1})

C	-1.33097600	-0.45678700	1.00485300
C	-3.43175900	0.15428100	0.14688800
C	-2.53691200	0.95886800	-1.50738900
C	-1.43879700	1.27262600	-0.74028600
C	-0.53620800	0.23554400	-0.21540300
H	-1.46701100	0.30104700	1.78401400
H	-2.56116700	0.03395600	-2.07788900
H	-1.33256800	2.27486000	-0.32524100
H	-0.31813600	-0.55410600	-0.93427300
H	-3.43938900	1.02066800	0.81069000
O	-2.60724500	-0.82854600	0.47601000
C	-4.75642500	-0.28538700	-0.40154500
H	-5.35310200	-0.64728800	0.44738200
H	-5.29578900	0.54880100	-0.85508300
H	-4.64598600	-1.10114600	-1.11881200
C	-0.64564100	-1.70251300	1.53377000
H	0.31307100	-1.43469200	1.98639000
H	-1.26609400	-2.15929600	2.30992000
H	-0.46684800	-2.42728400	0.73642300
C	0.72737300	0.88136700	0.38157700
O	0.61778700	1.85101200	1.11334600

N	1.96078400	0.35981500	0.06259200
C	3.18628600	0.96419400	0.60383500
C	2.26064200	-0.82116300	-0.67053300
C	4.26051900	0.22662500	-0.21222800
H	3.18650900	2.04362100	0.44429300
H	4.62766200	0.81585400	-1.05643700
O	1.47261700	-1.60620800	-1.13672300
O	3.59023800	-0.94127100	-0.74643900
H	3.25747000	0.77127500	1.67872500
H	5.10221000	-0.12023000	0.38682700
H	-3.20210600	1.74943300	-1.84586400

Final product (2-oxonia-Cope)

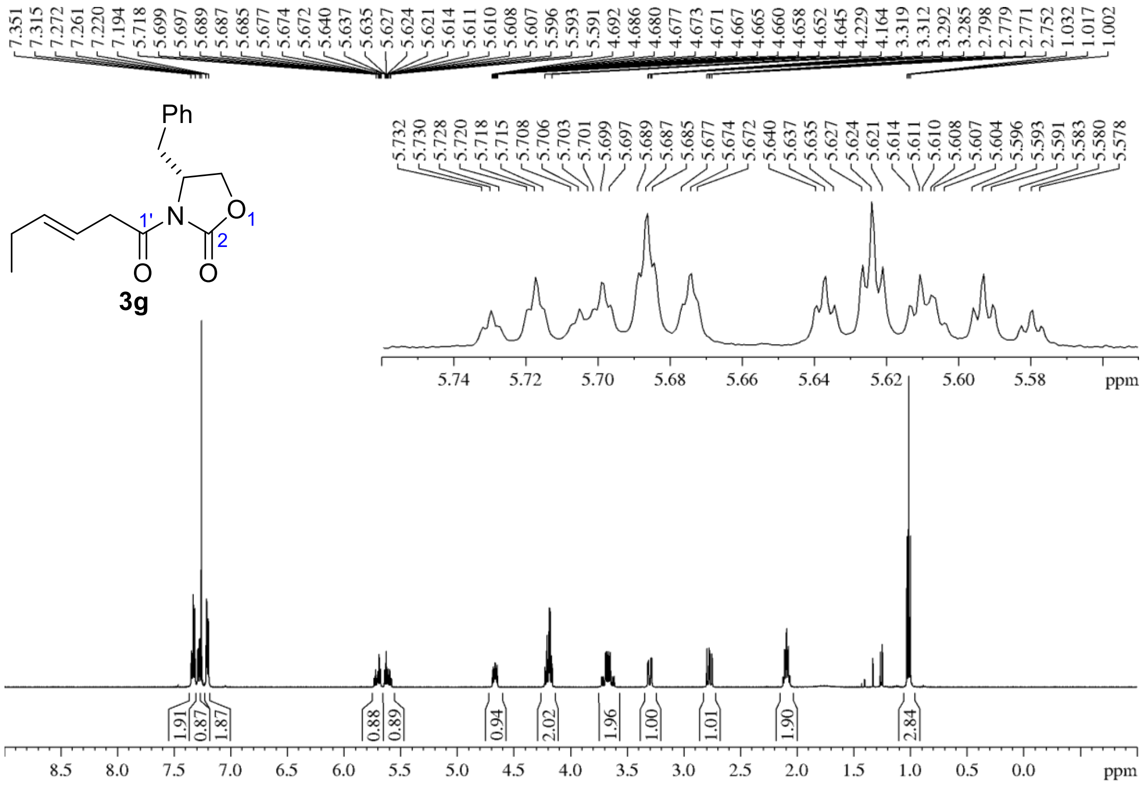
C	-2.02205300	-1.44451300	0.75378900
C	-3.46996900	0.43009200	0.19028800
C	-2.59021600	1.36516900	-0.65257600
C	-1.22970700	1.59694700	-0.05910000
C	-0.10143300	1.02208400	-0.49920700
H	-1.69089600	-0.84791900	1.60898900
H	-2.52750900	0.96239600	-1.66975900
H	-1.16267700	2.28088400	0.78662700
H	-0.09753100	0.33187900	-1.33578400
H	-3.37315300	0.63914900	1.26078500
O	-2.91120000	-0.96548600	-0.00057400
C	-4.91880400	0.34397200	-0.24264000
H	-5.46448900	-0.40466000	0.33812000
H	-5.39188900	1.31625000	-0.07263200
H	-4.99902000	0.10127000	-1.30623500
C	-1.45831300	-2.76602800	0.49423900

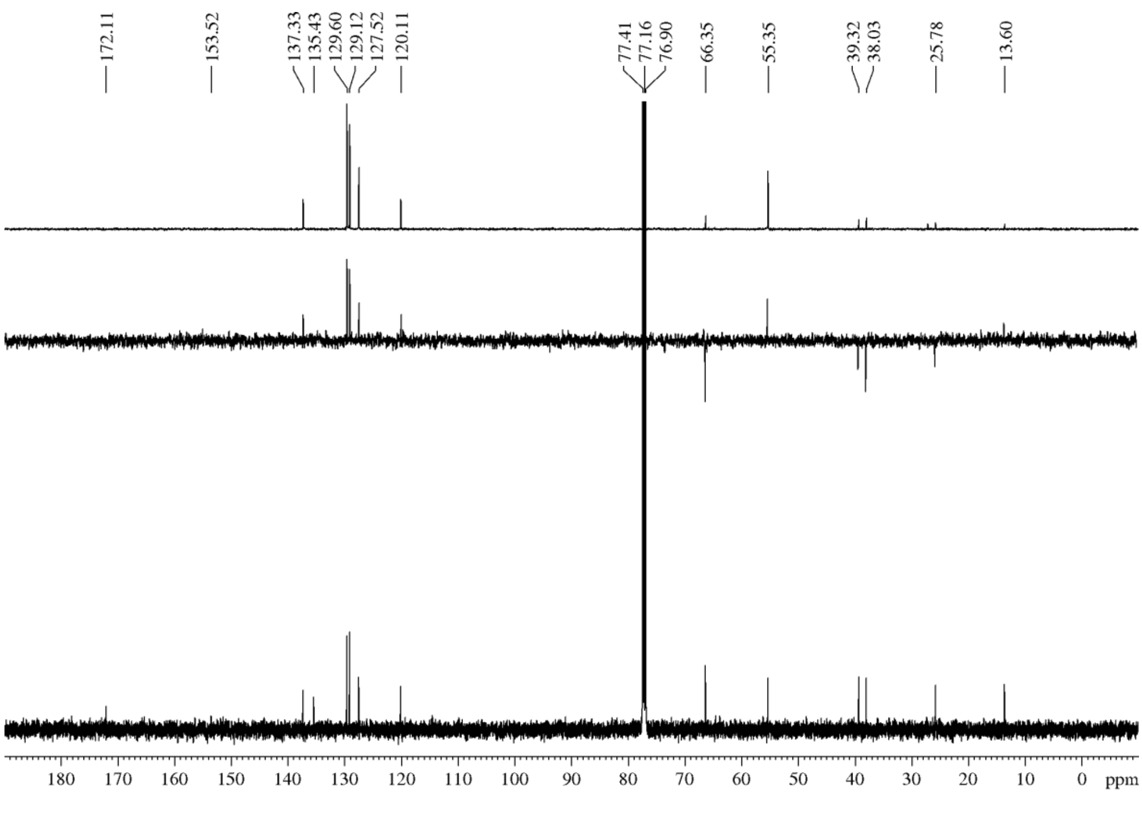
H	-0.41262800	-2.60460000	0.16687000
H	-1.40260400	-3.33631500	1.43016900
H	-2.00924300	-3.30518900	-0.27799200
C	1.20305200	1.37520800	0.13706700
O	1.37482100	2.39691100	0.77760900
N	2.27540700	0.49879200	-0.07421300
C	3.62912600	0.84188700	0.37646400
C	2.18188200	-0.87048500	-0.33823900
C	4.41075900	-0.37095300	-0.15019600
H	3.95447200	1.78886800	-0.05726700
H	4.86230400	-0.18890800	-1.12905600
O	1.16544600	-1.50548400	-0.53782800
O	3.40735100	-1.40935800	-0.31095800
H	3.65734500	0.93039300	1.46733900
H	5.16552100	-0.74499200	0.54103300
H	-3.13314400	2.31699300	-0.71703700

NMR spectra

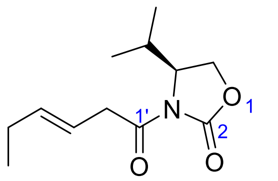
N-acyl oxazolidin-2-ones 3

(*R*,*E*)-4-Benzyl-3-(hex-3-enoyl)oxazolidin-2-one (3g)

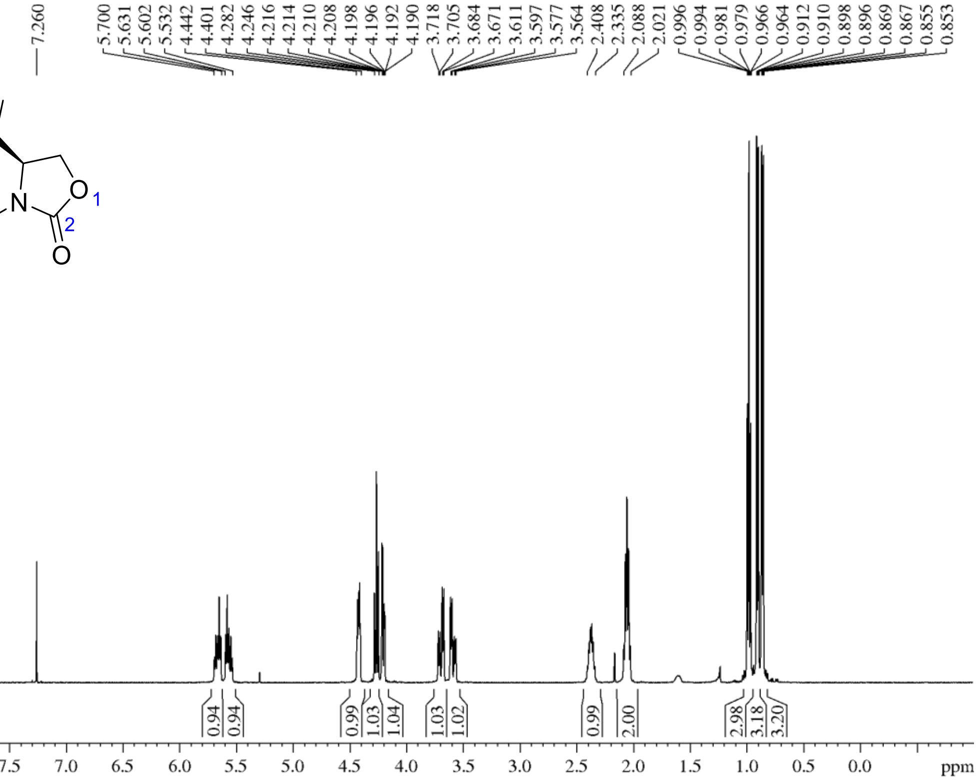


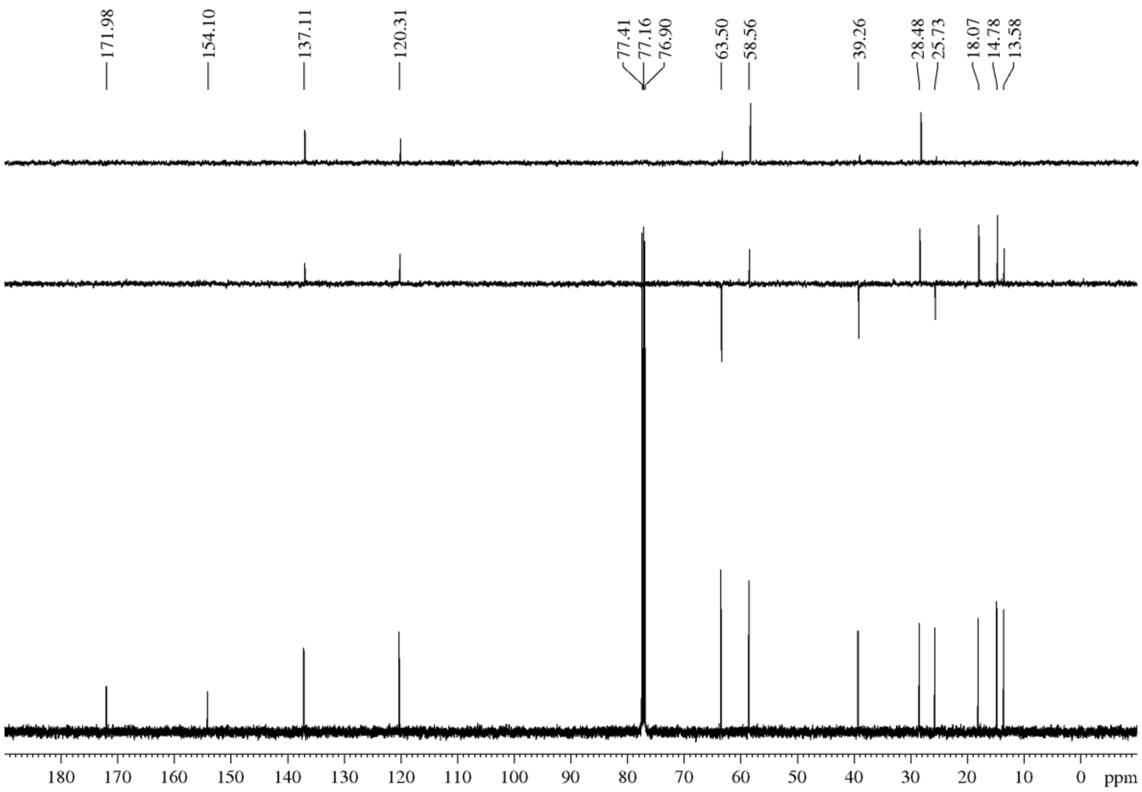


(*S*,*E*)-3-(Hex-3-enoyl)-4-isopropyloxazolidin-2-one (3h)

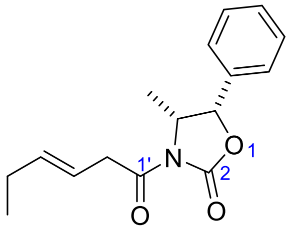


3h

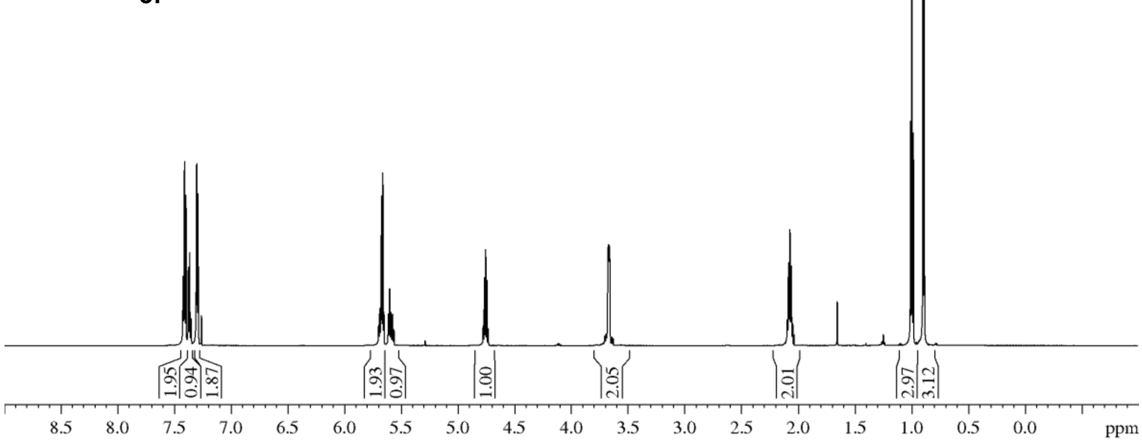


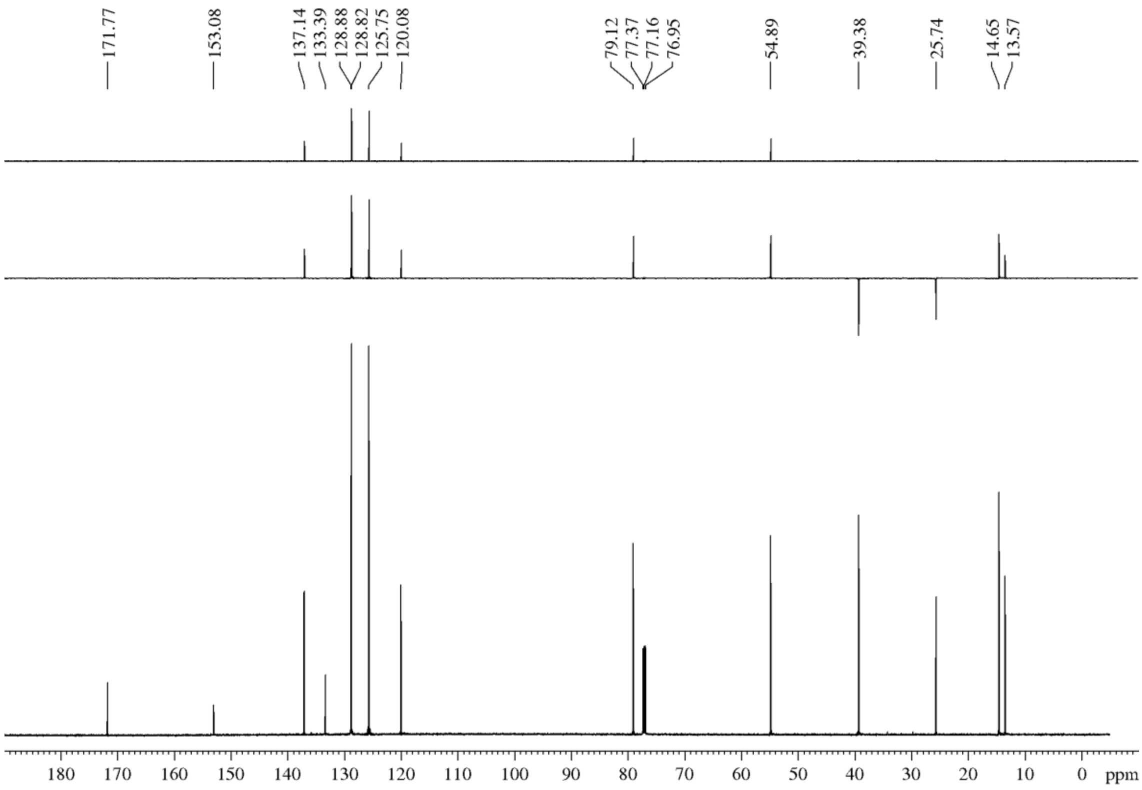


(4*R*,5*S*)-3-((*E*)-Hex-3-enoyl)-4-methyl-5-phenyloxazolidin-2-one (3i)



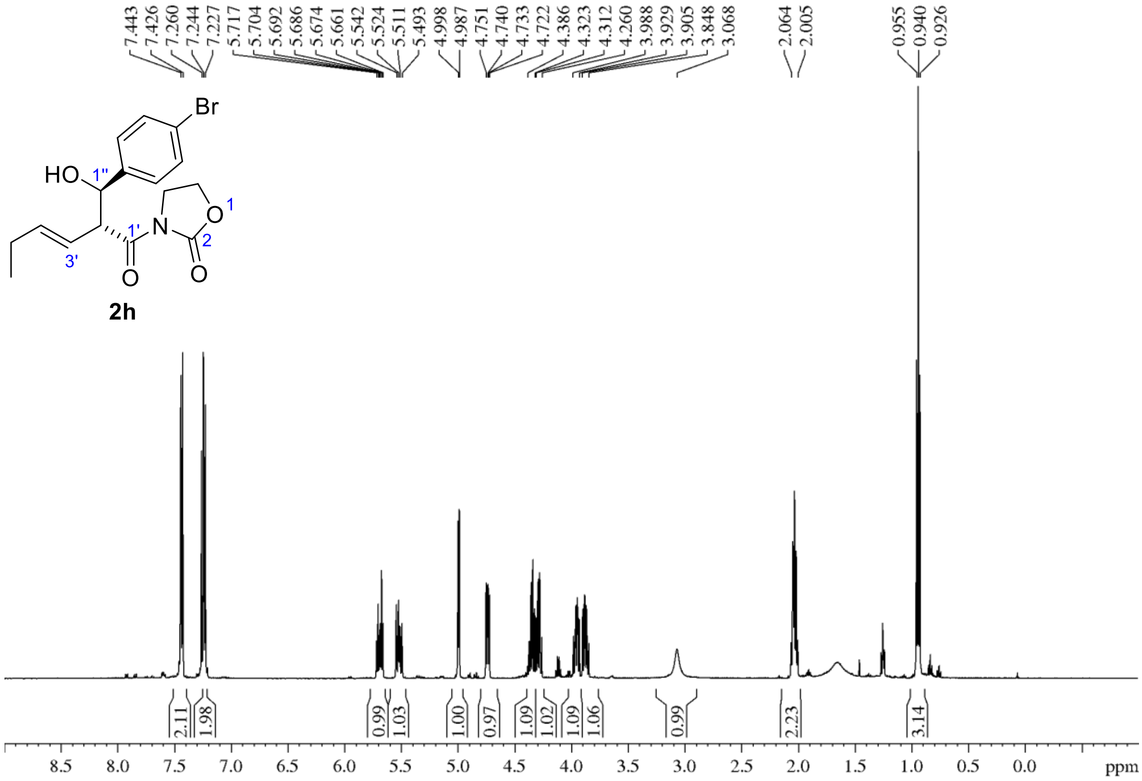
3i

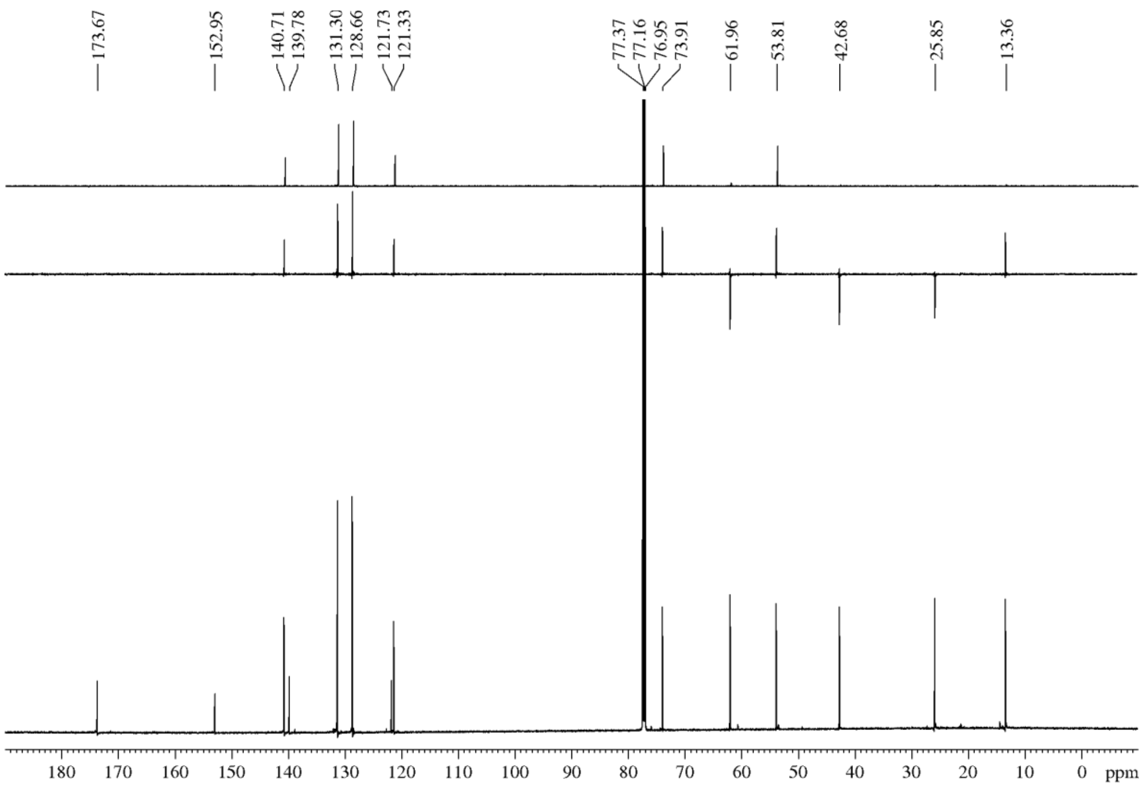




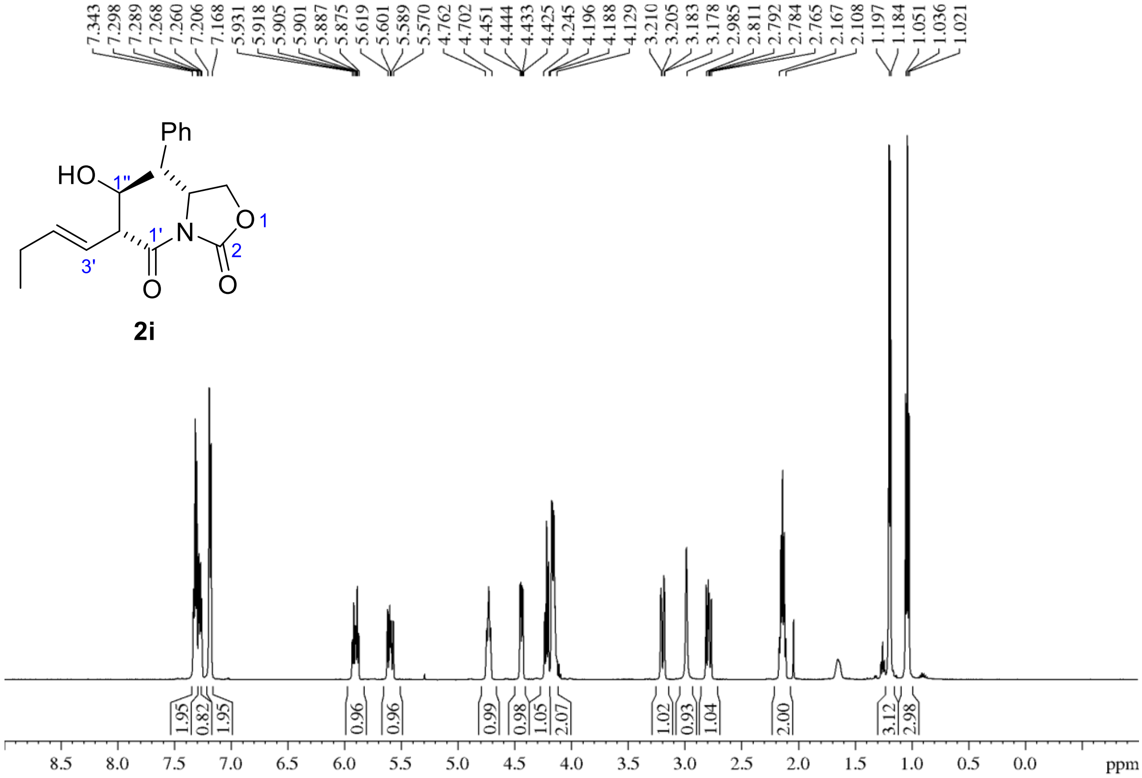
Aldols 2

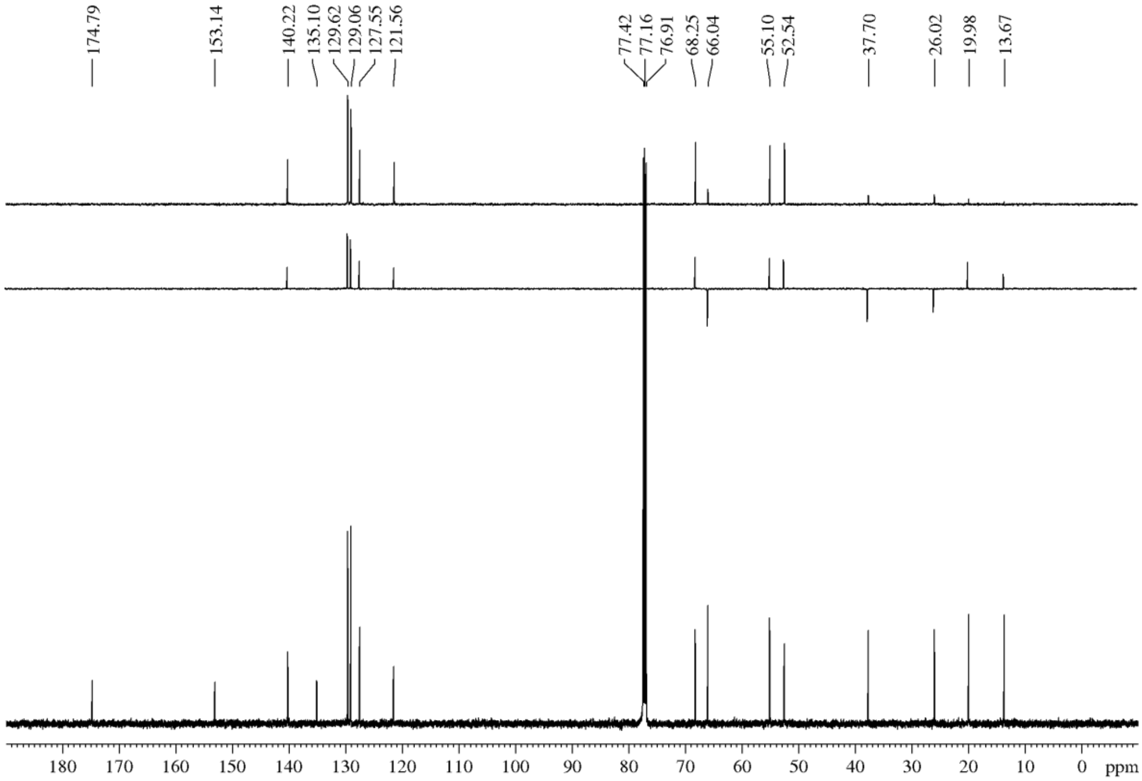
3-((*R**,*E*)-2-((*R**)-(4-Bromophenyl)(hydroxy)methyl)hex-3-enoyl)oxazolidin-2-one (2h)



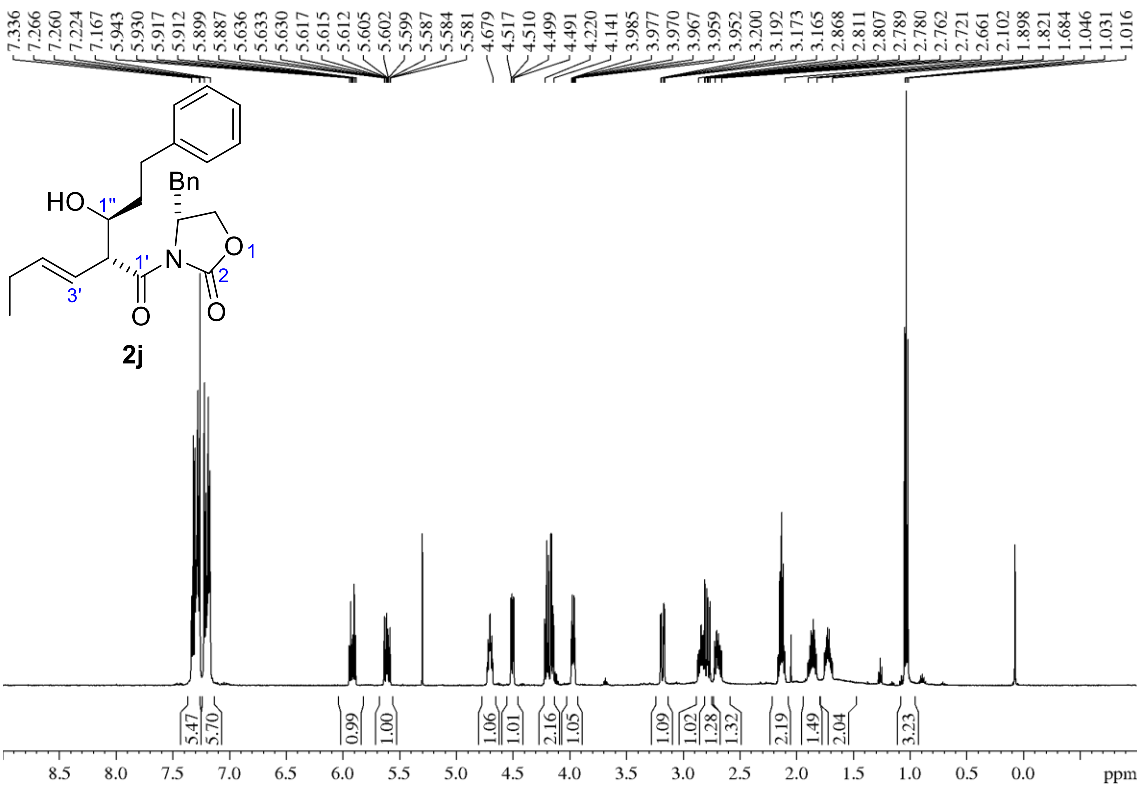


(*R*)-4-Benzyl-3-((*R*,*E*)-2-((*S*)-1-hydroxyethyl)hex-3-enoyl)oxazolidin-2-one (2i)

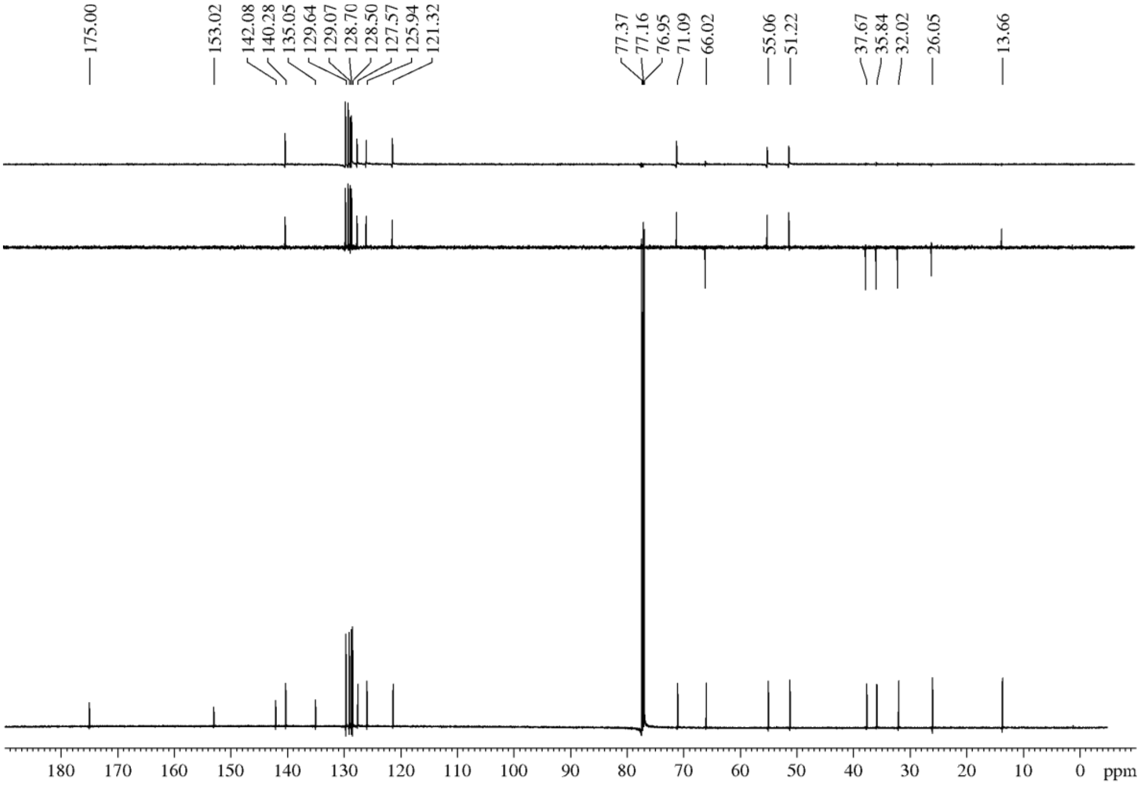




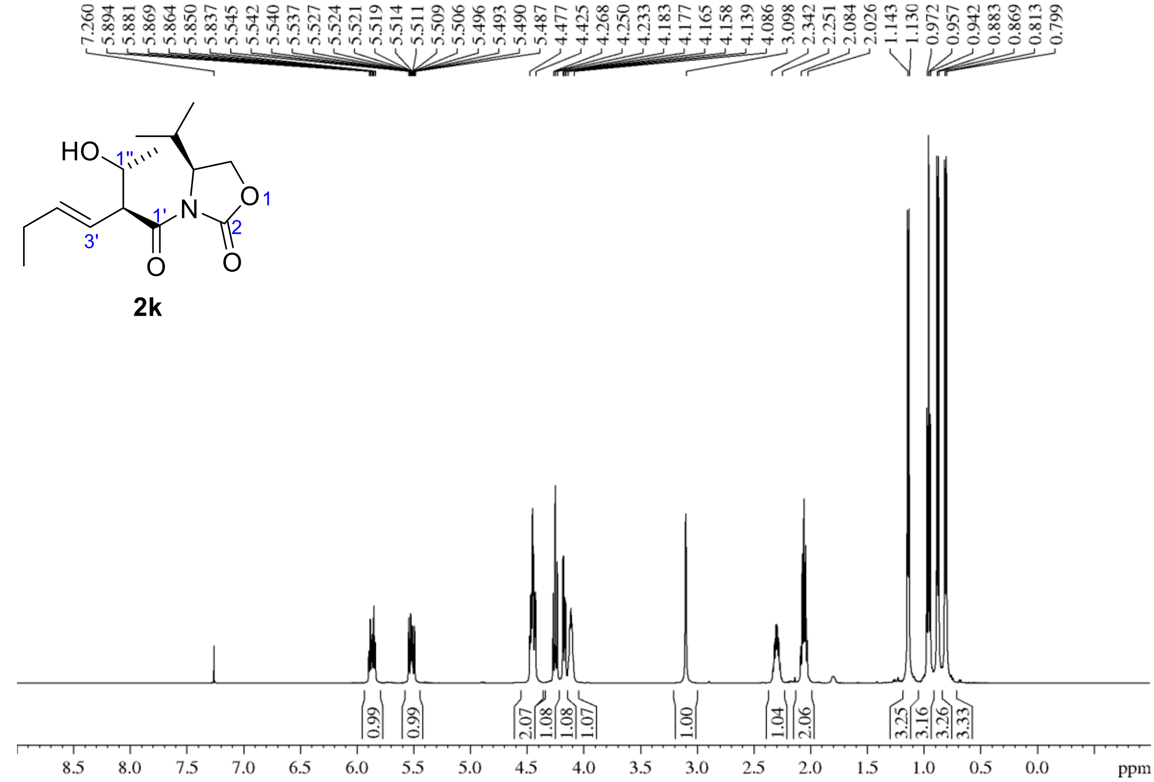
(*R*)-4-Benzyl-3-((*R*,*E*)-2-((*S*)-1-hydroxy-3-phenylpropyl)hex-3-enoyl)oxazolidin-2-one (2j)

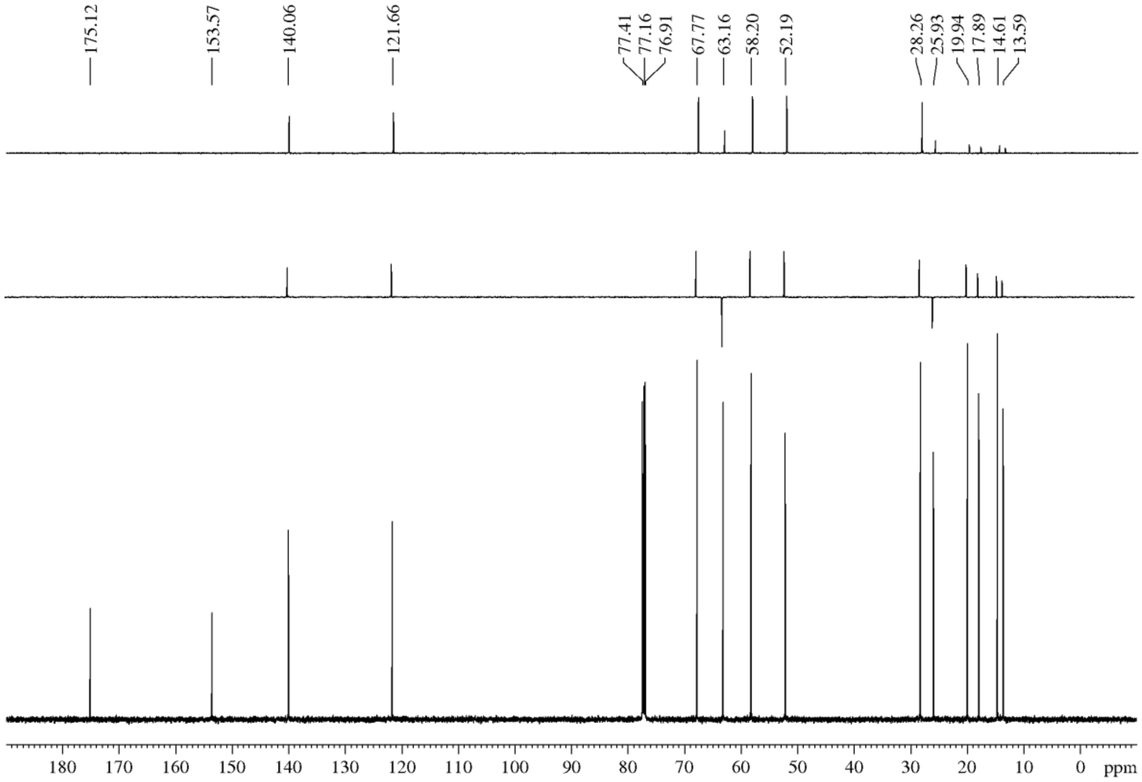


2j

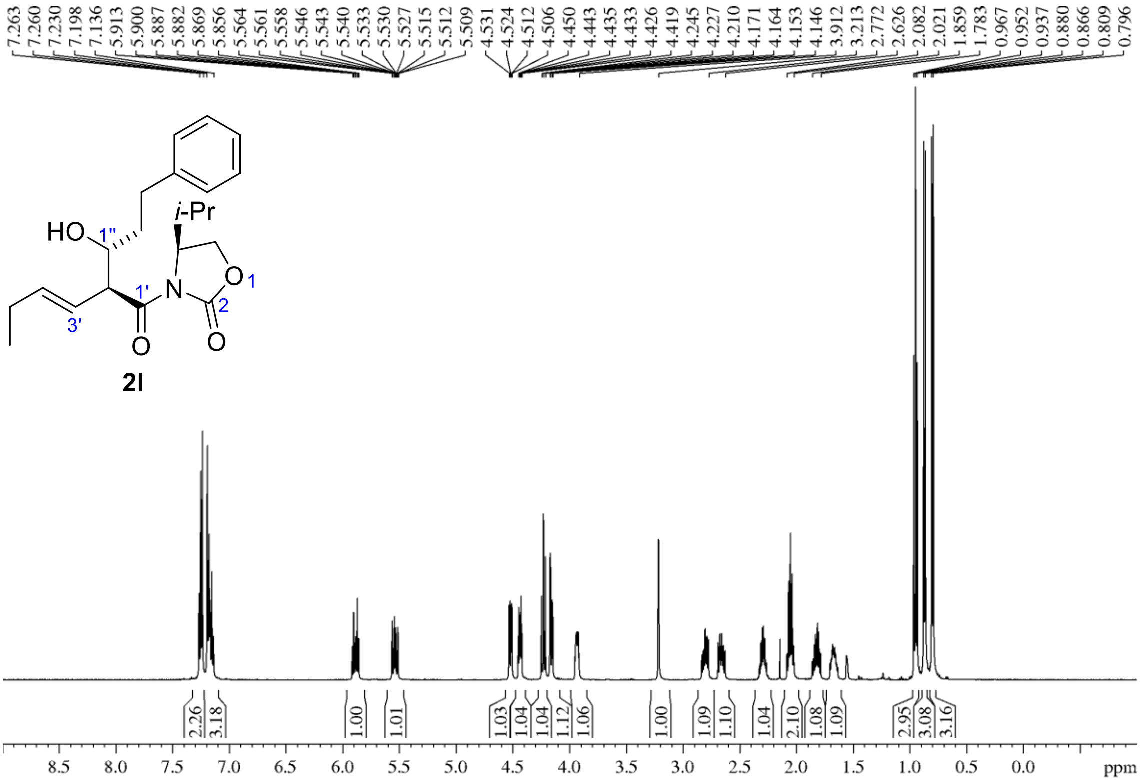


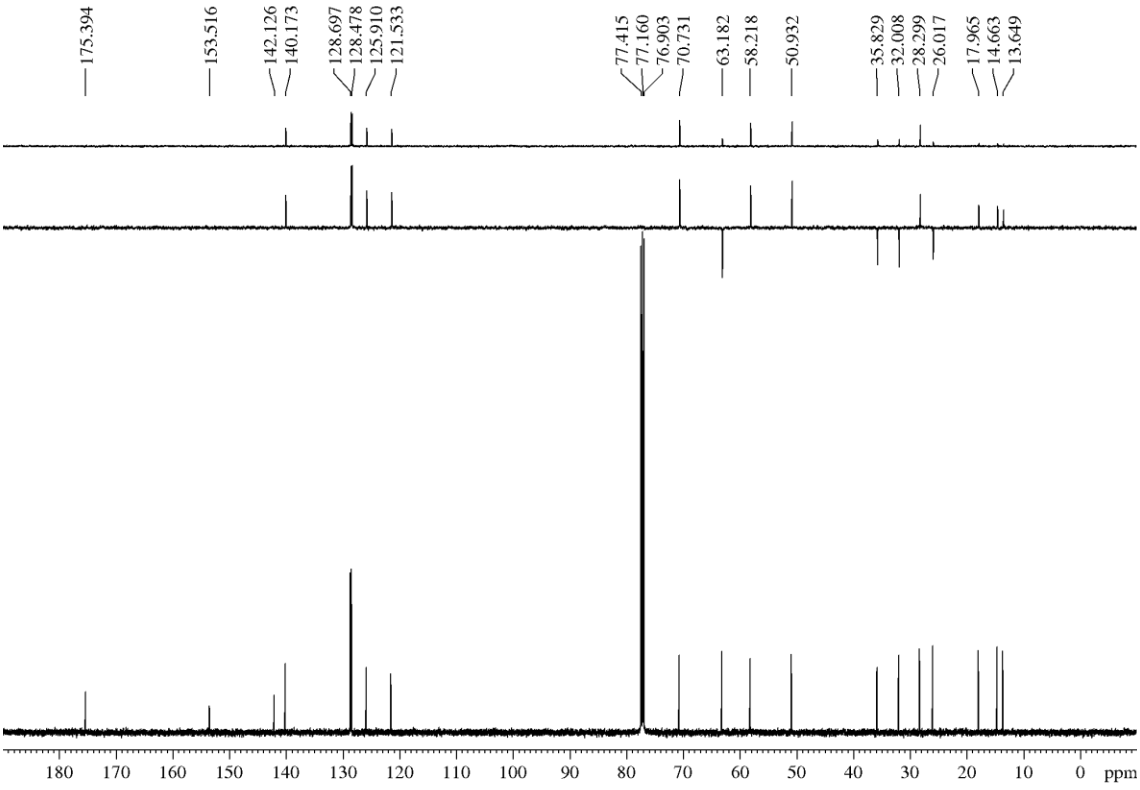
(*S*)-3-((*S*,*E*)-2-((*R*)-1-Hydroxyethyl)hex-3-enoyl)-4-isopropyloxazolidin-2-one (2k)



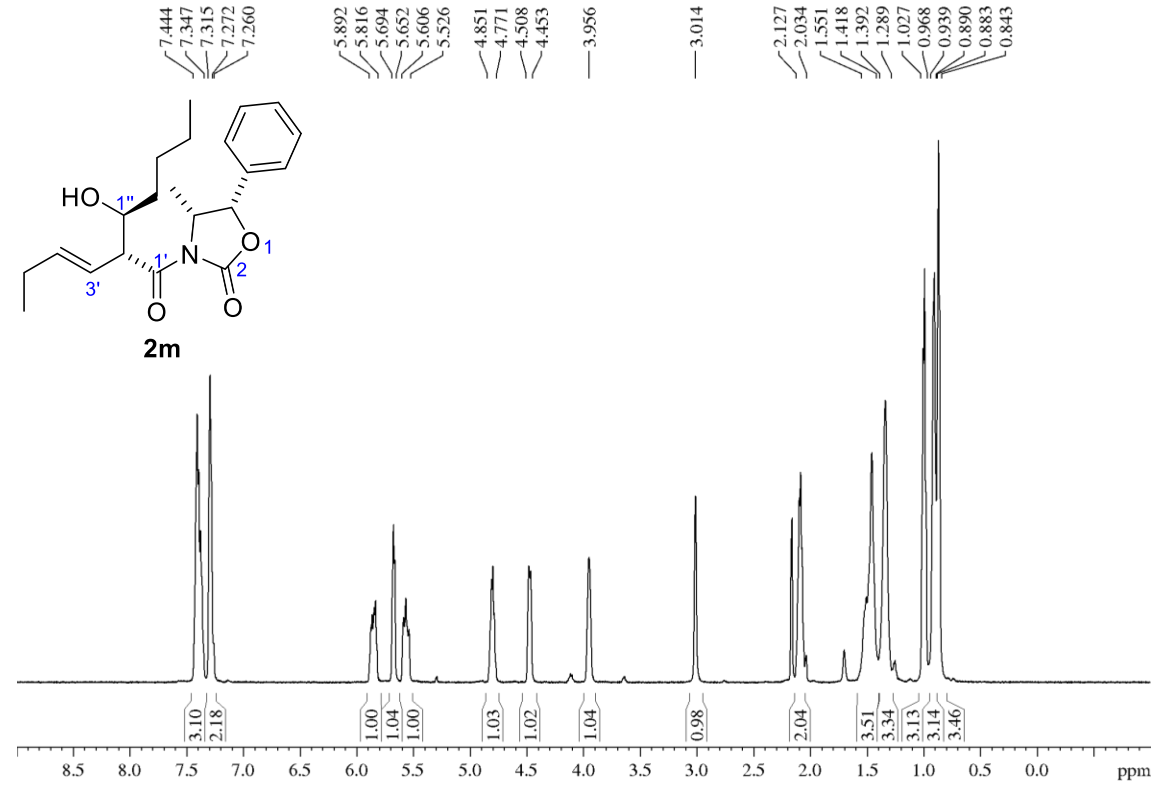


(*S*)-3-((*S*,*E*)-2-((*R*)-1-Hydroxy-3-phenylpropyl)hex-3-enoyl)-4-isopropyloxazolidin-2-one (2l)

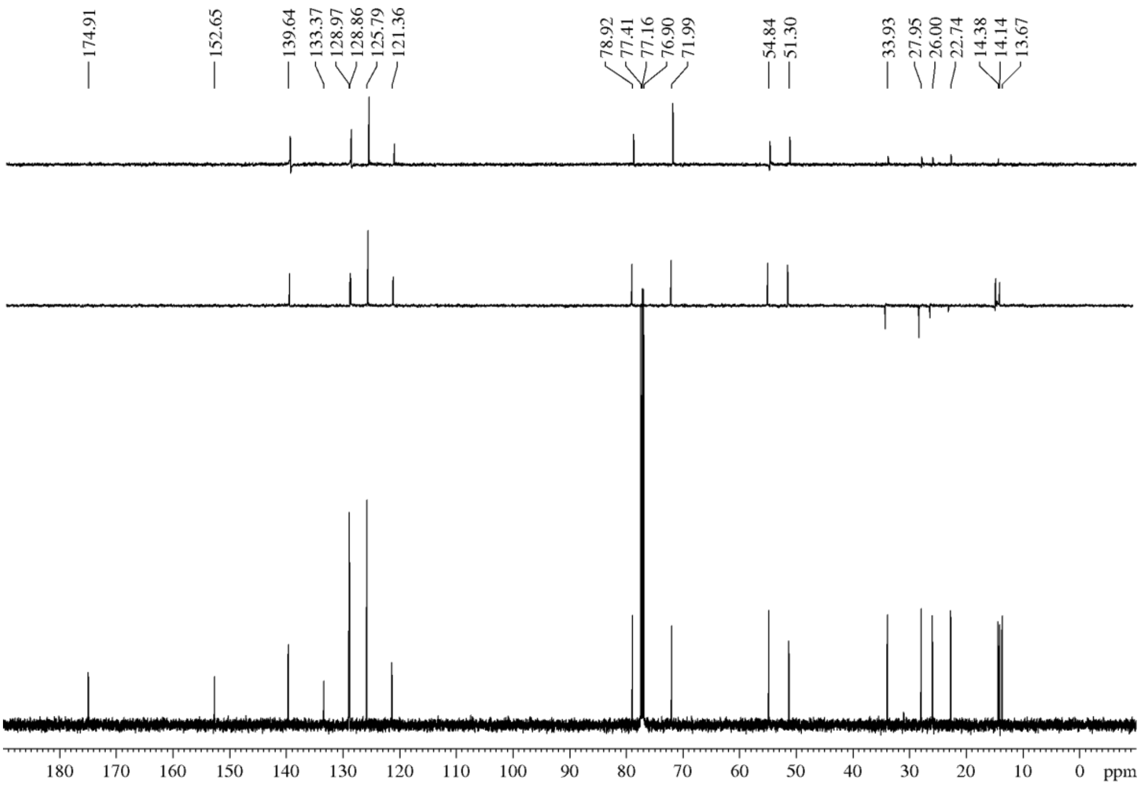




(4*R*,5*S*)-3-((2*R*,3*S*)-2-((*E*)-But-1-en-1-yl)-3-hydroxyheptanoyl)-4-methyl-5-phenyloxazolidin-2-one (2m)[4]

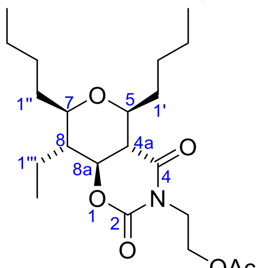


2m

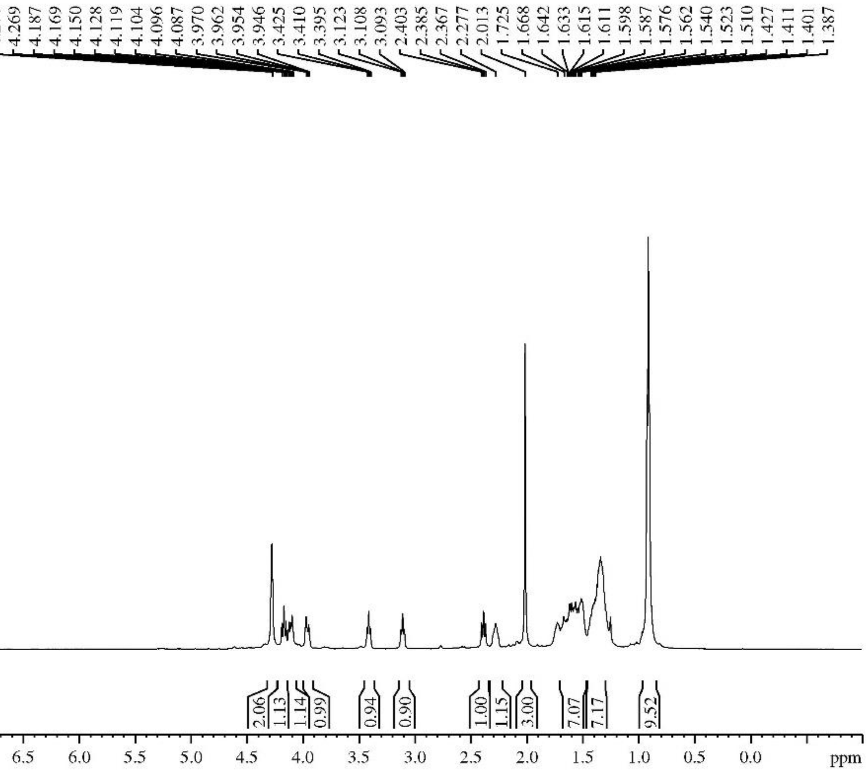


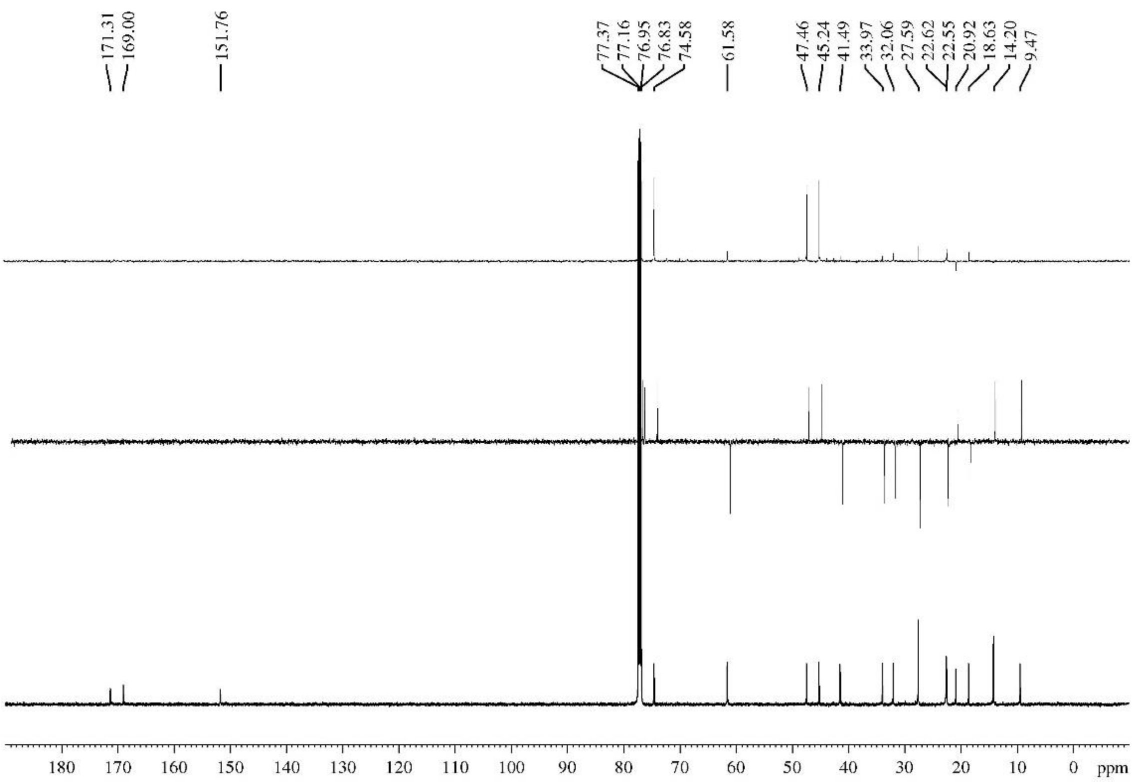
Bicycles 5

2-((4a*S*,5*S*,7*R*,8*R*,8a*S*)-5,7-Dibutyl-8-ethyl-2,4-dioxotetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazin-3(4*H*)-yl)ethyl acetate (5c-Ac)

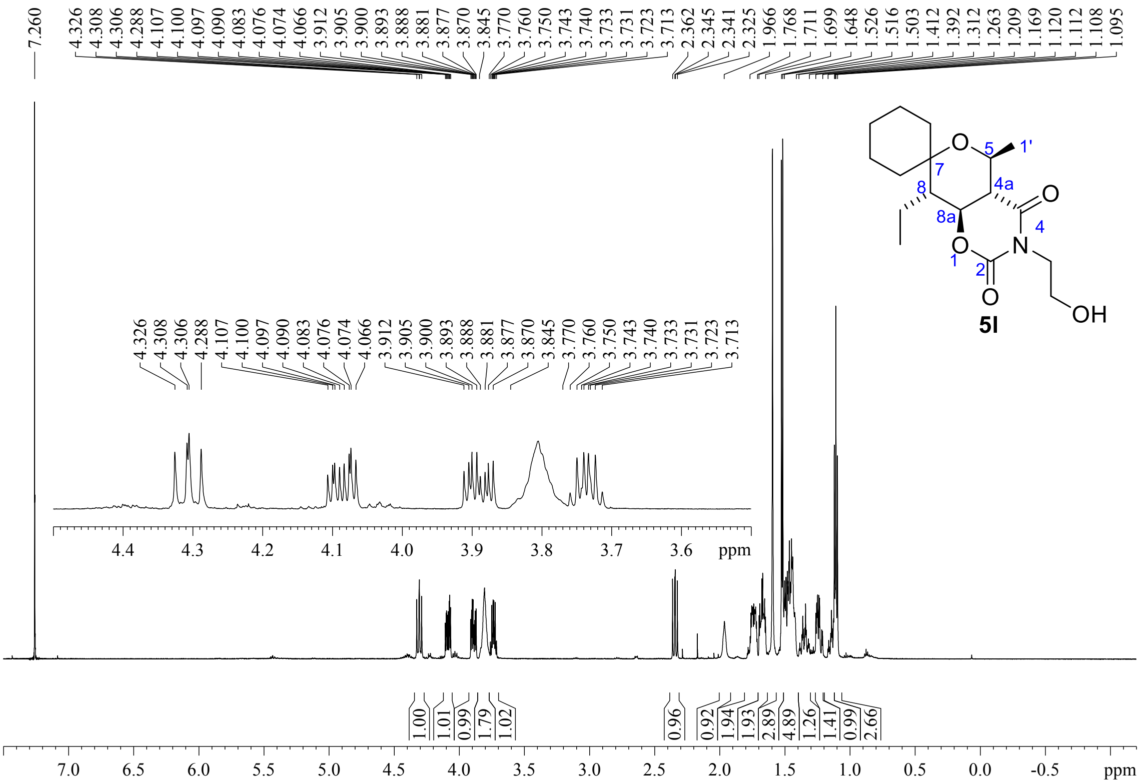


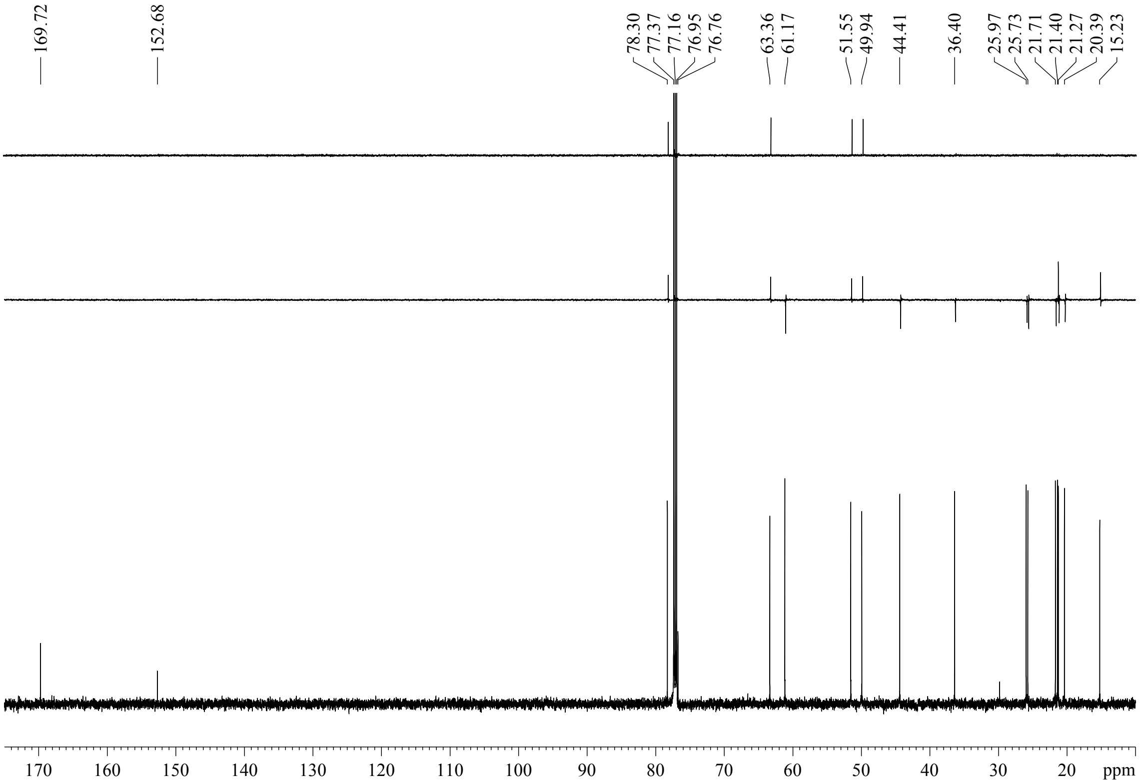
5c-Ac



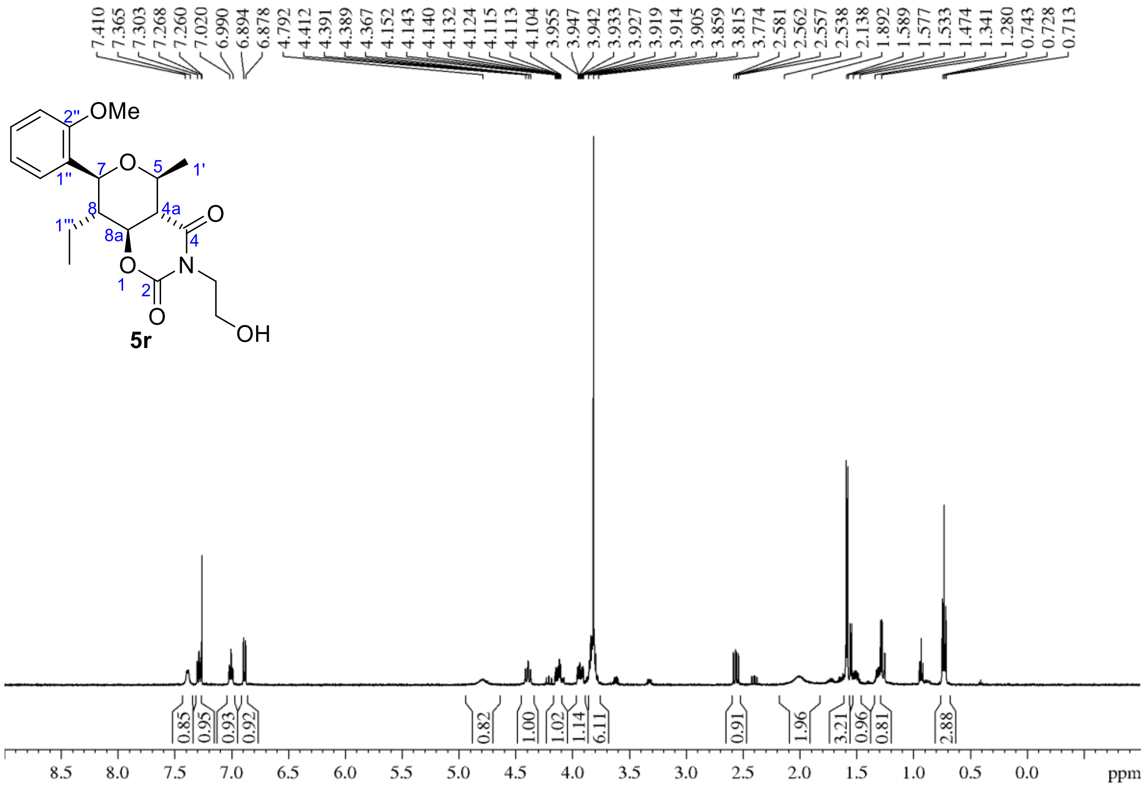


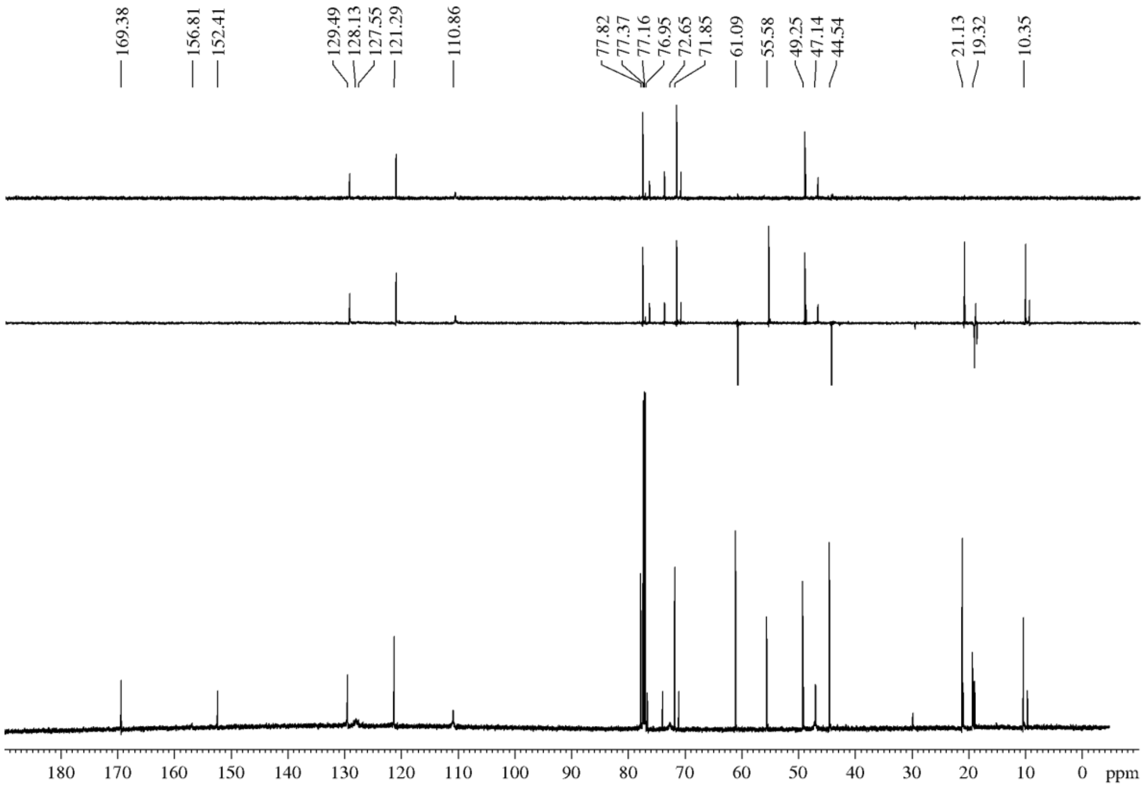
(4a'*S,5'*S**,8'*,8a'*S**)-8'-Ethyl-3'-(2-hydroxyethyl)-5'-methyltetrahydro-2'*H*-spiro[cyclohexane-1,7'-pyrano[3,4-*e*][1,3]oxazine]-2',4'(3'*H*)-dione (5l)**



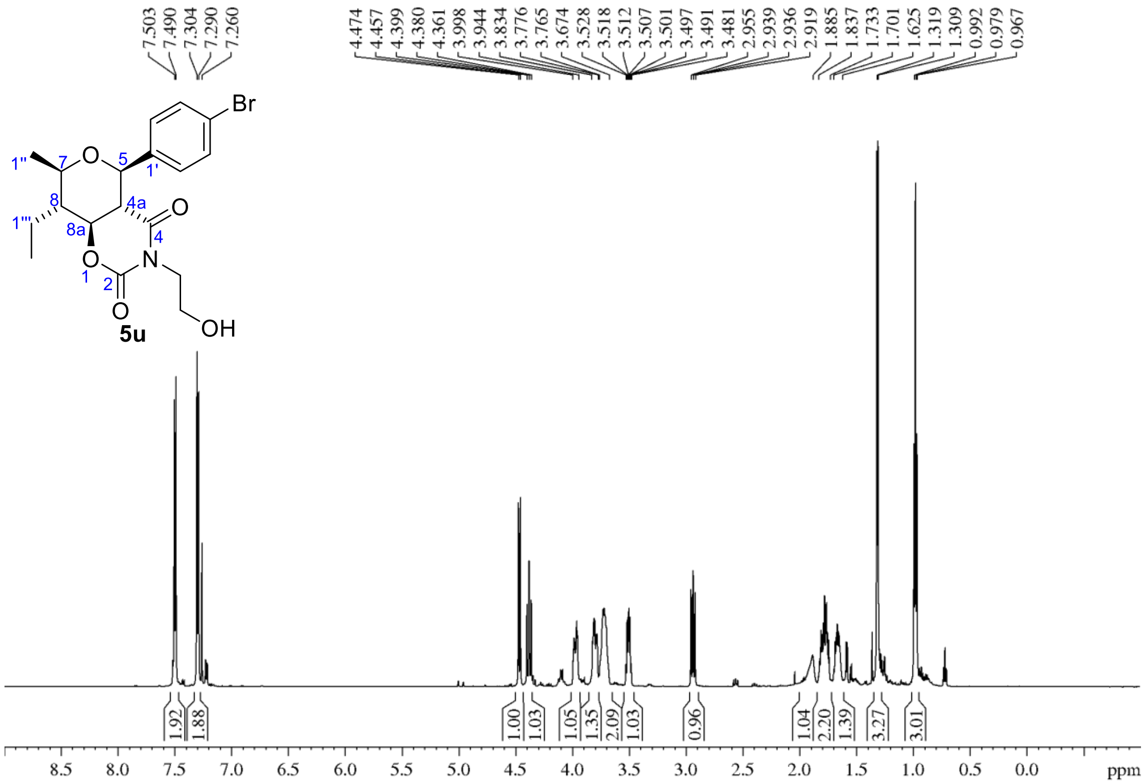


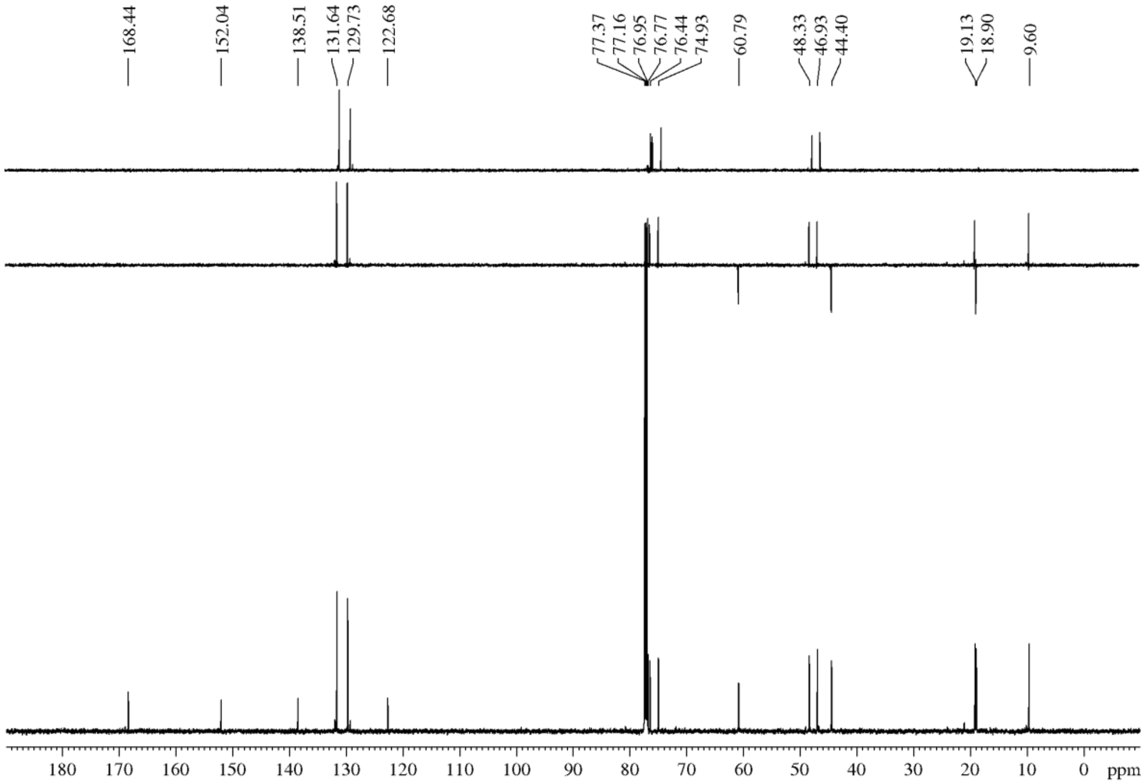
(4a*S,5*S**,7*S**,8*S**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-(2-methoxyphenyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5r)**



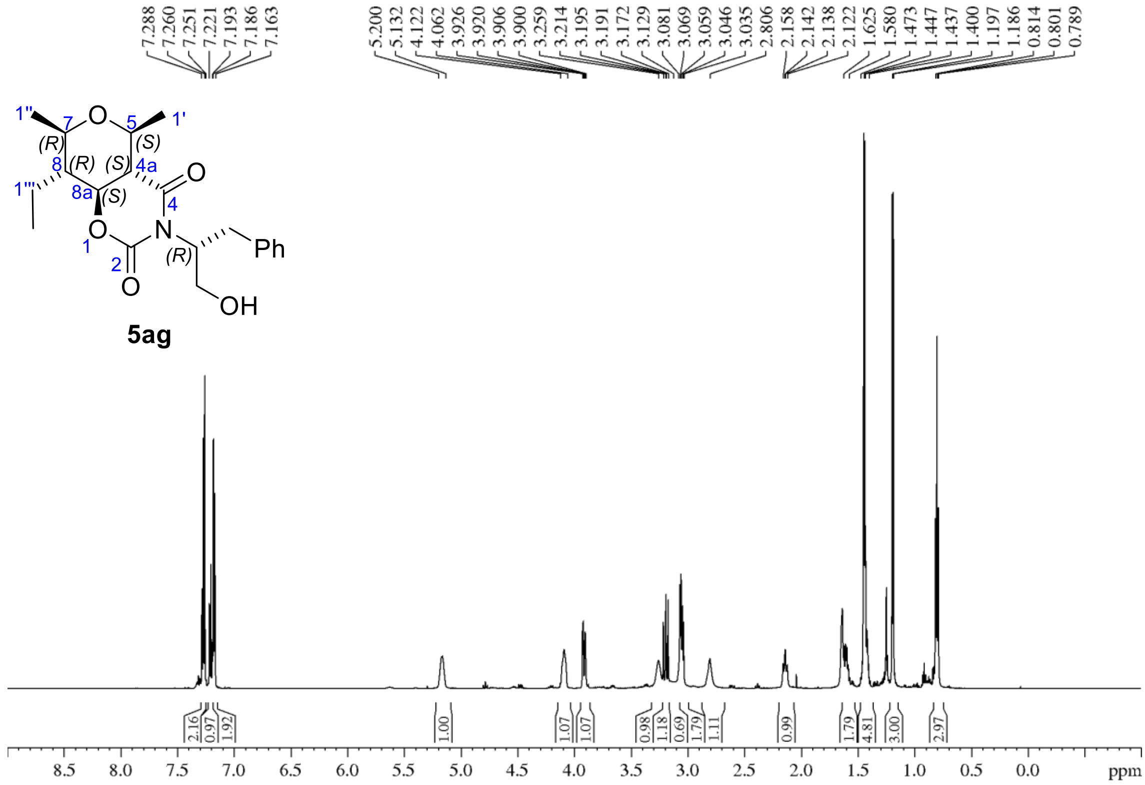


(4a*R,5*R**,7*R**,8*R**,8a*S**)-5-(4-Bromophenyl)-8-ethyl-3-(2-hydroxyethyl)-7-methyltetrahydro-2*H*,5*H*-pyrano[3,4-e][1,3]oxazine-2,4(3*H*)-dione (5u)**

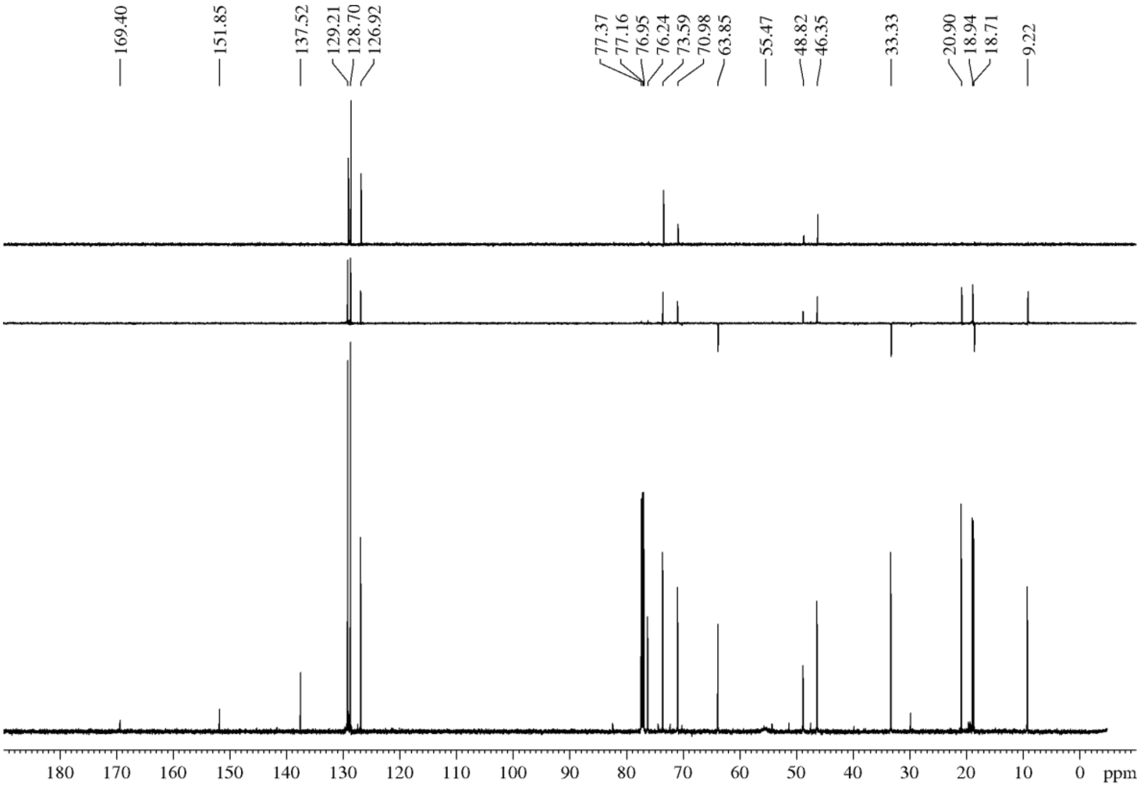




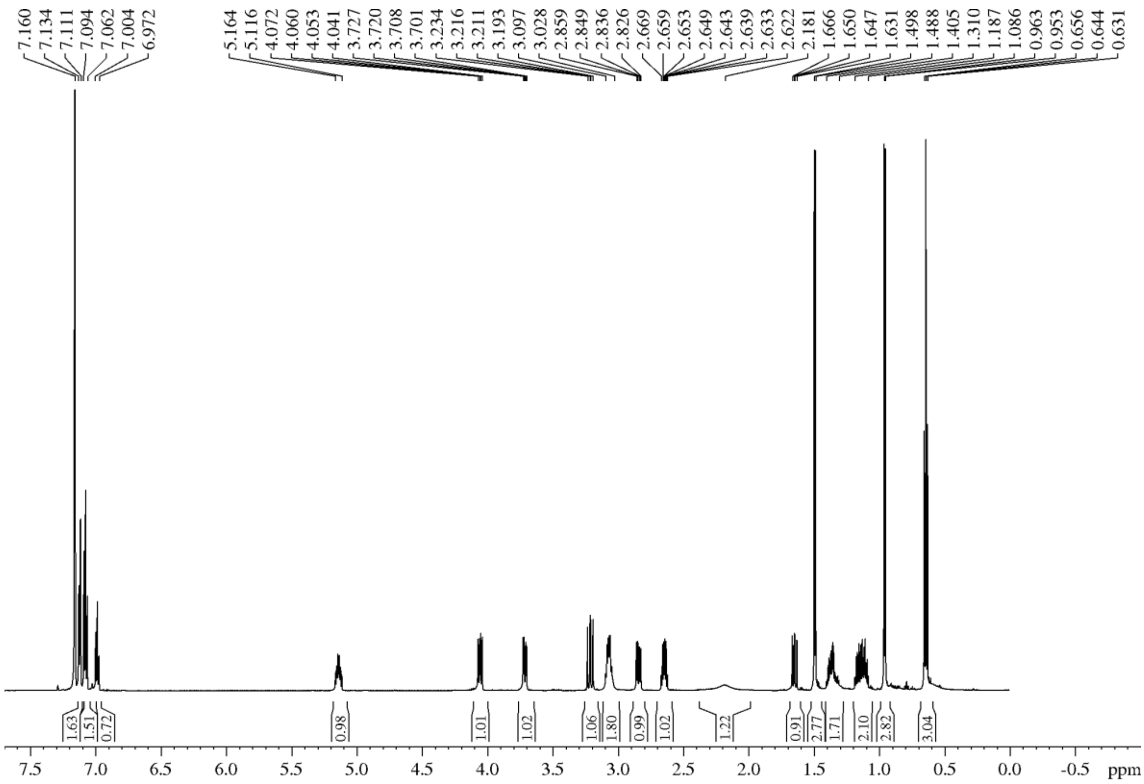
(4a*S*,5*S*,7*R*,8*R*,8a*S*)-8-Ethyl-3-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-5,7-dimethyltetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5ag)



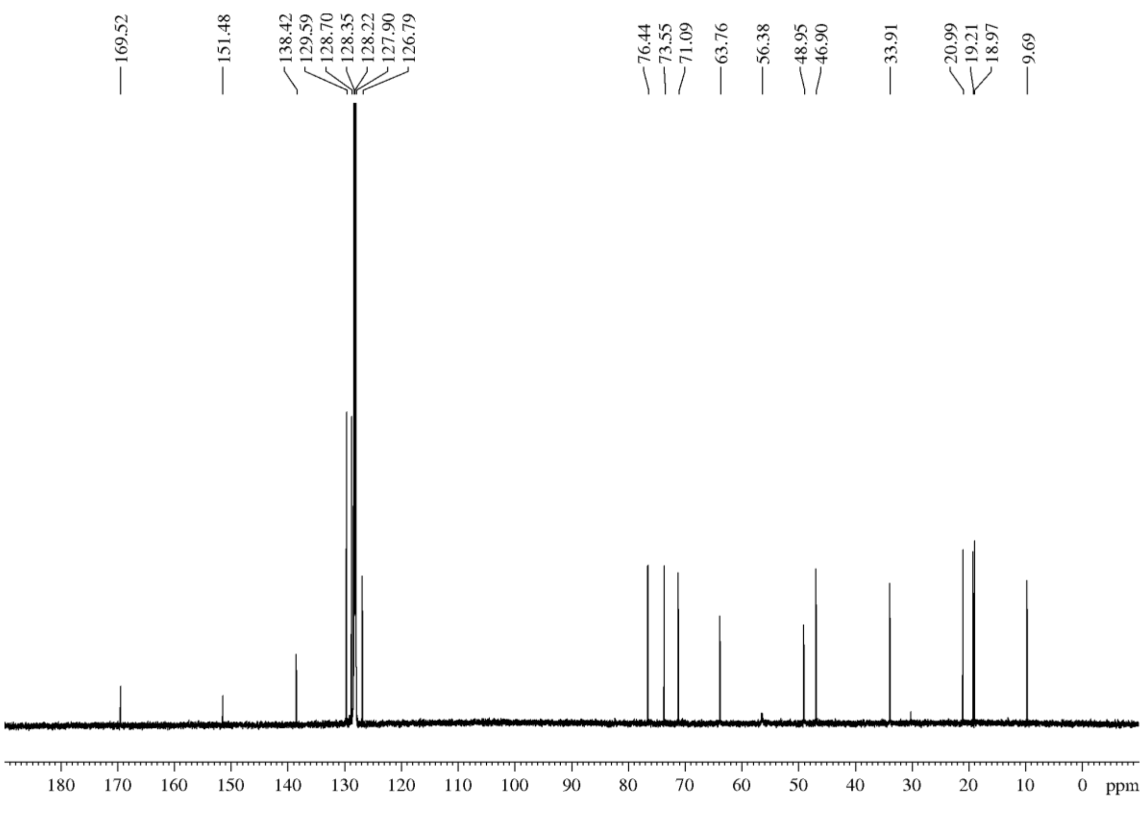
5ag

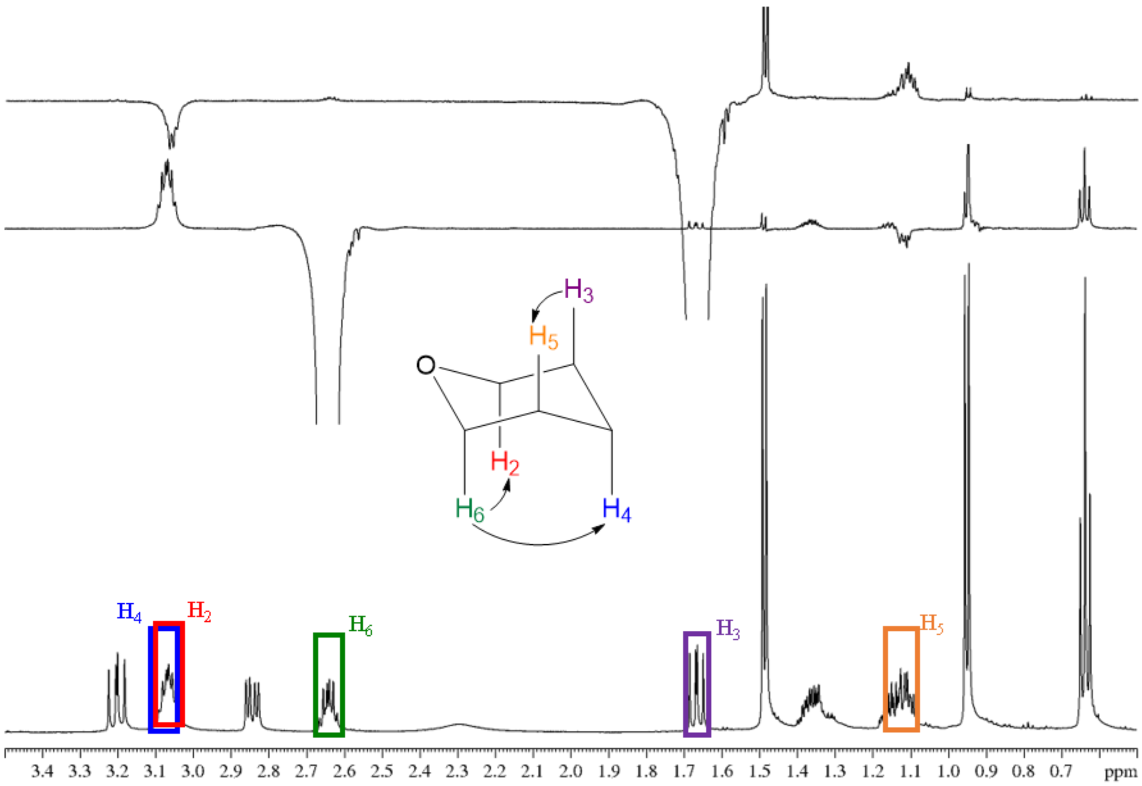


^{1}H-NMR C_6D_6, T = 320 K

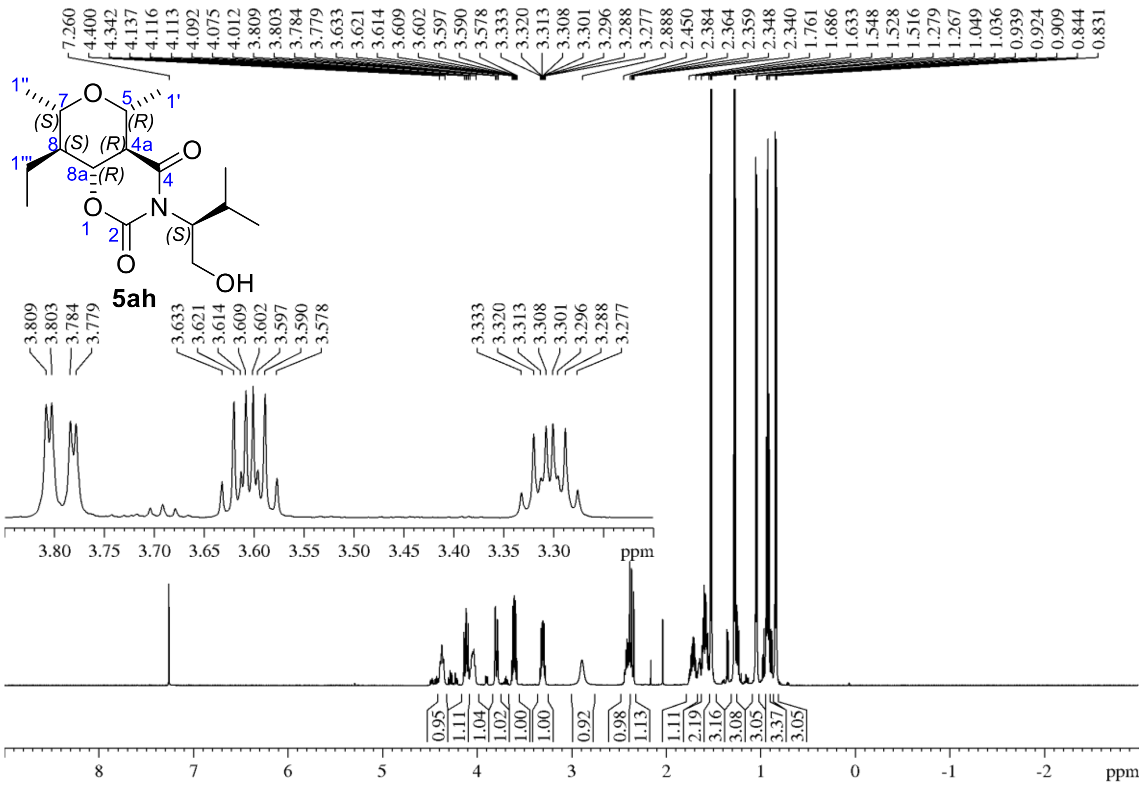


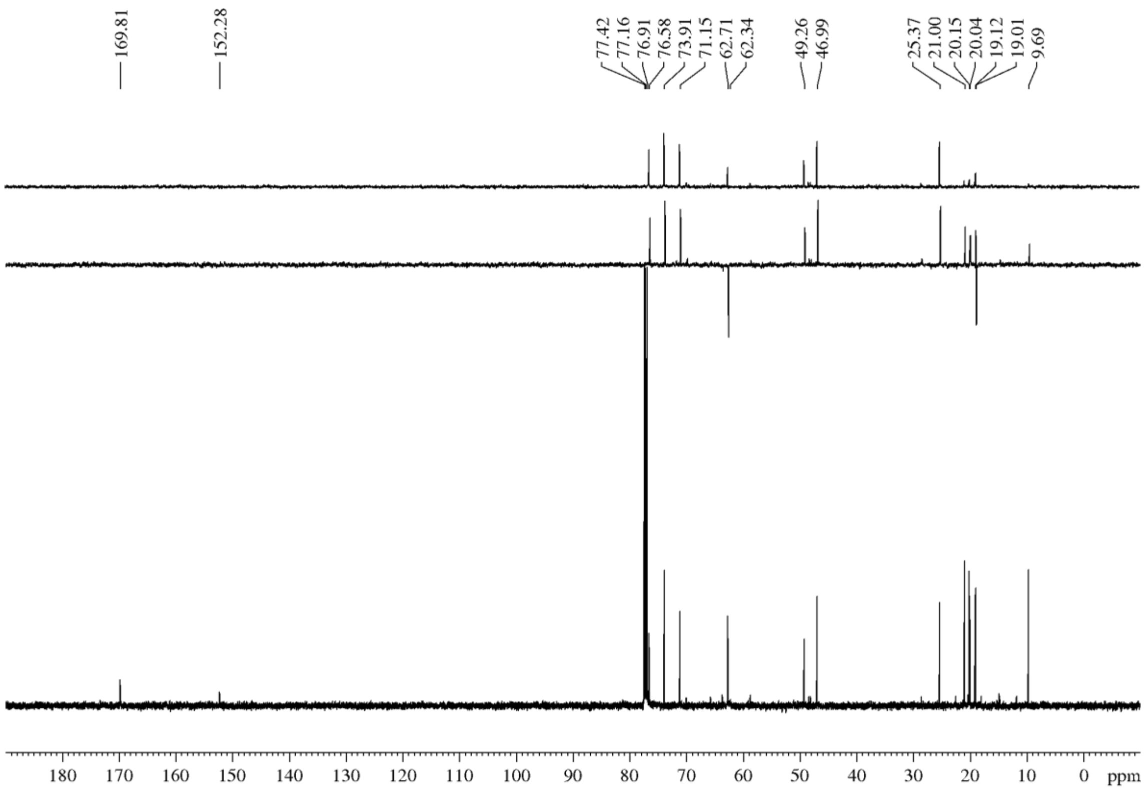
^{13}C-NMR C_6D_6, T = 320 K



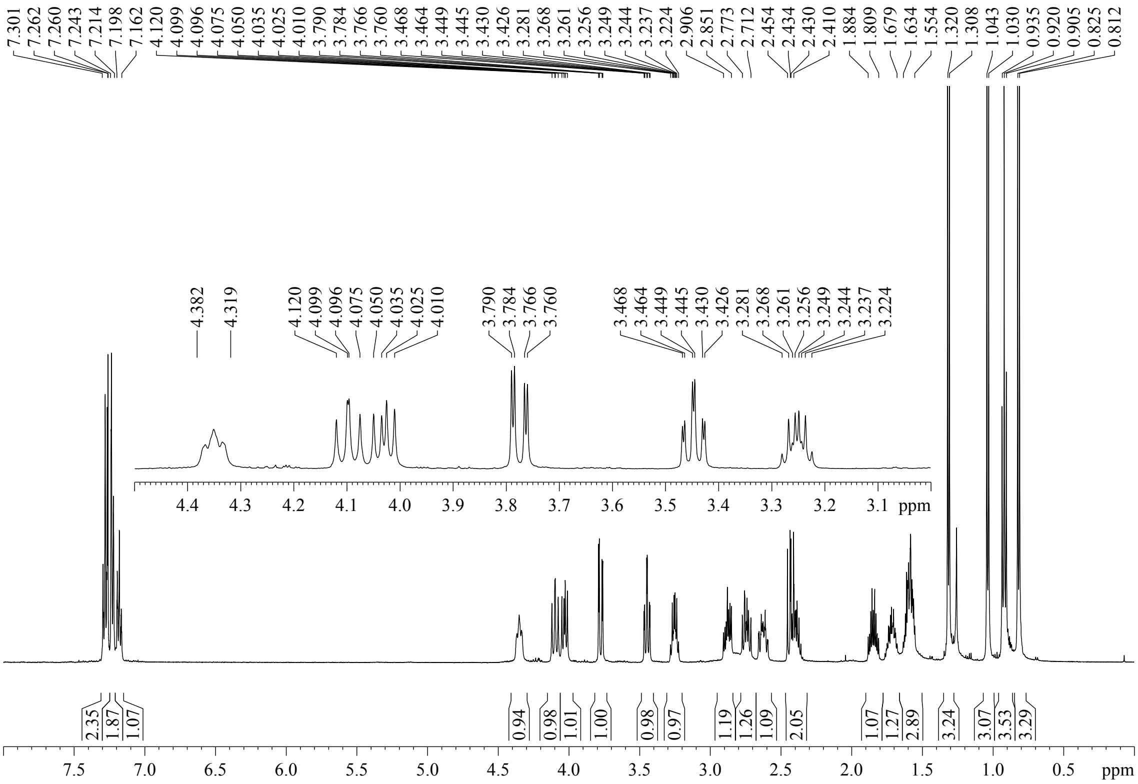

H3
H5
O
H2
H6
H4
H4
H2
H6
H3
H5
3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8 0.7 ppm

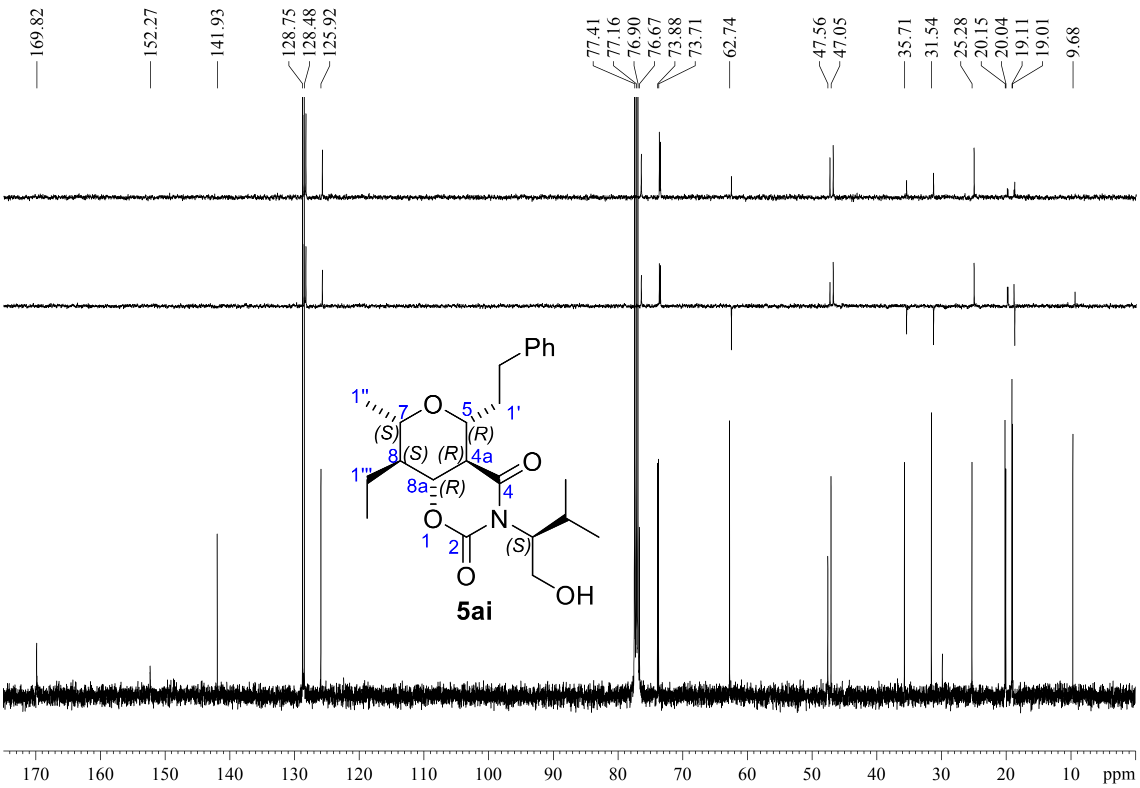
(4a*R*,5*R*,7*S*,8*S*,8a*R*)-8-Ethyl-3-((*S*)-1-hydroxy-3-methylbutan-2-yl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5ah)



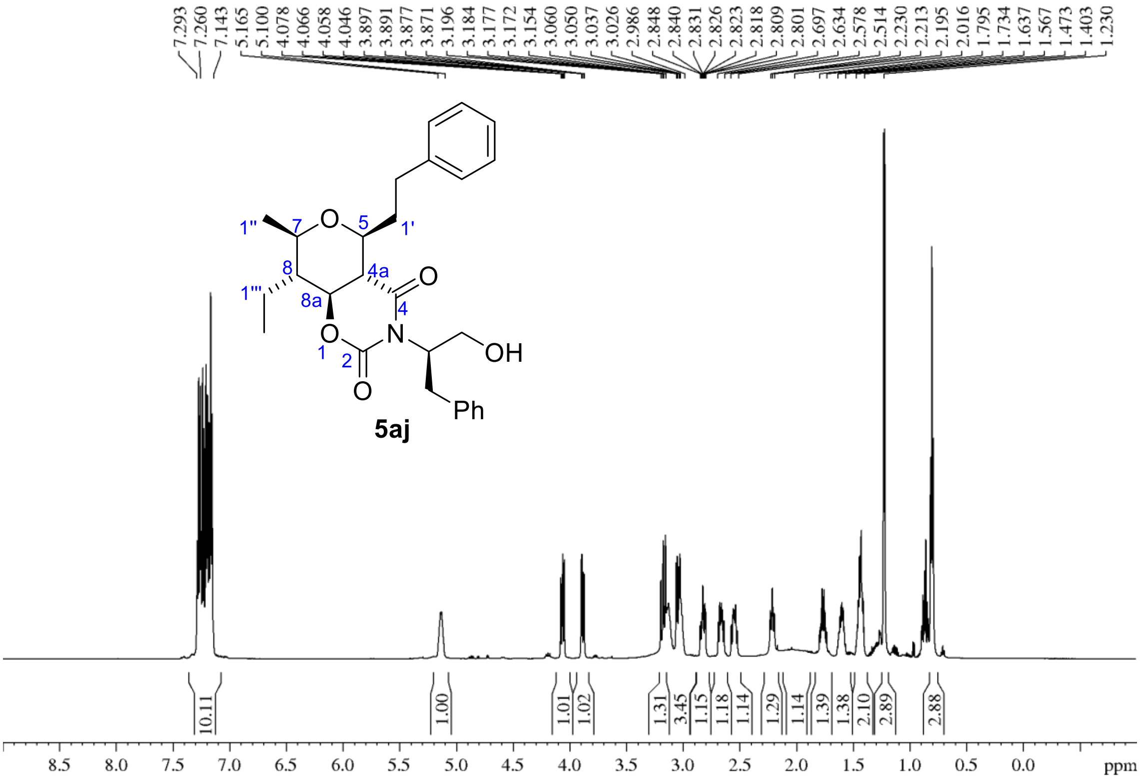


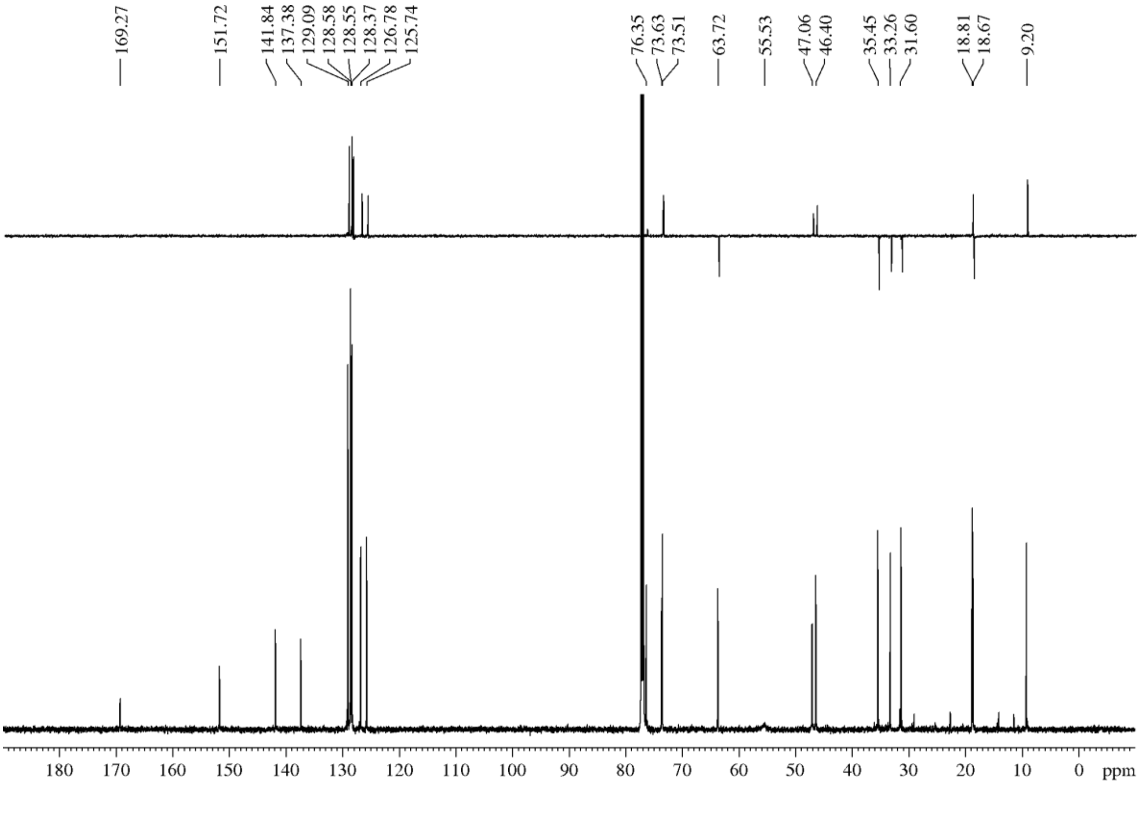
(4a*R*,5*R*,7*S*,8*S*,8a*R*)-8-Ethyl-3-((*S*)-1-hydroxy-3-methylbutan-2-yl)-7-methyl-5-phenethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5ai)





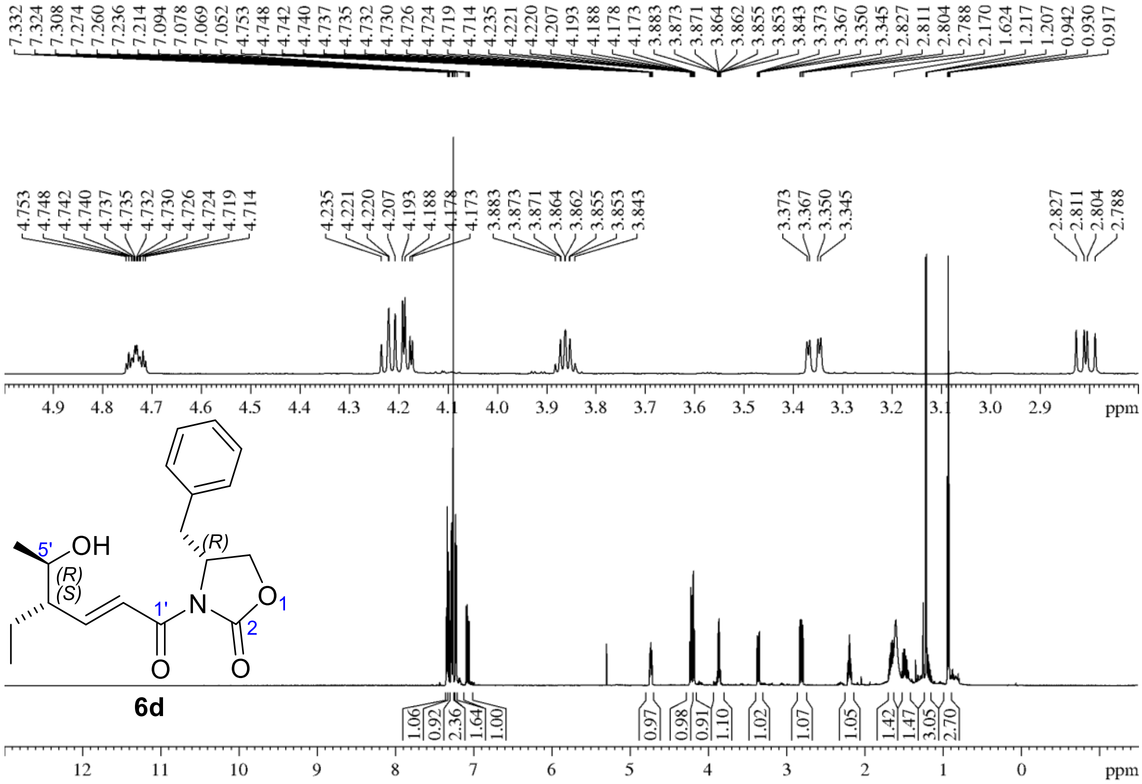
(4a*S*,5*S*,7*R*,8*R*,8a*S*)-8-Ethyl-3-((*R*)-1-hydroxy-3-phenylpropan-2-yl)-7-methyl-5-phenethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5aj)

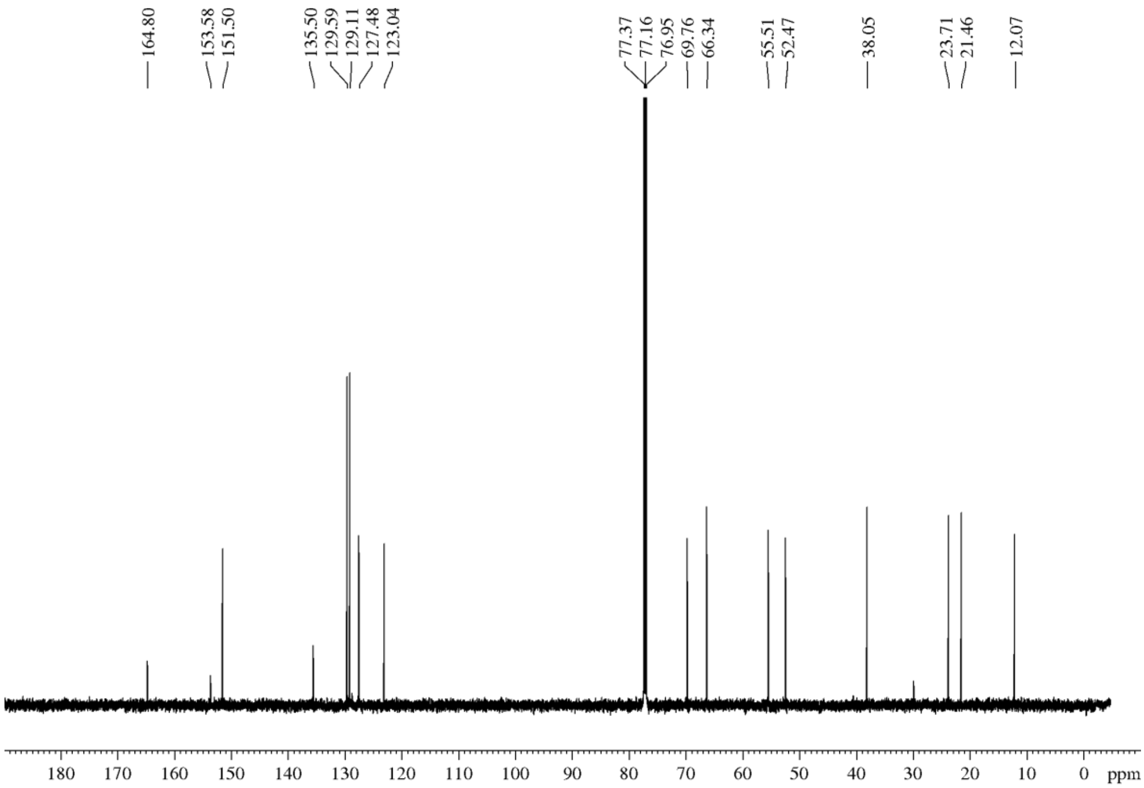




2-oxonia-Cope rearranged isomers 6

(*R*)-4-Benzyl-3-((4*S*,5*R*,*E*)-4-ethyl-5-hydroxyhex-2-enoyl)oxazolidin-2-one (6d)

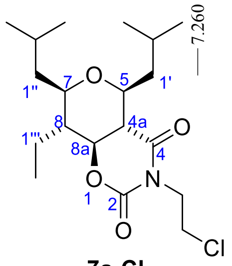




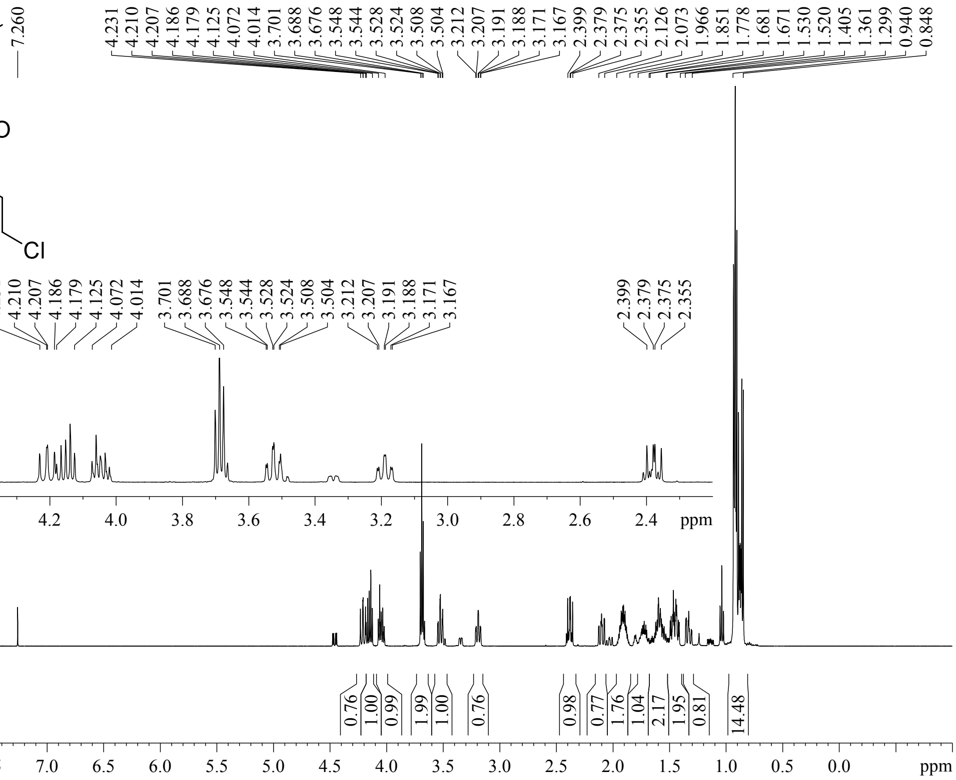
Halogenated 2,3,4,5,6-pentasubstituted THPs 1 and 7

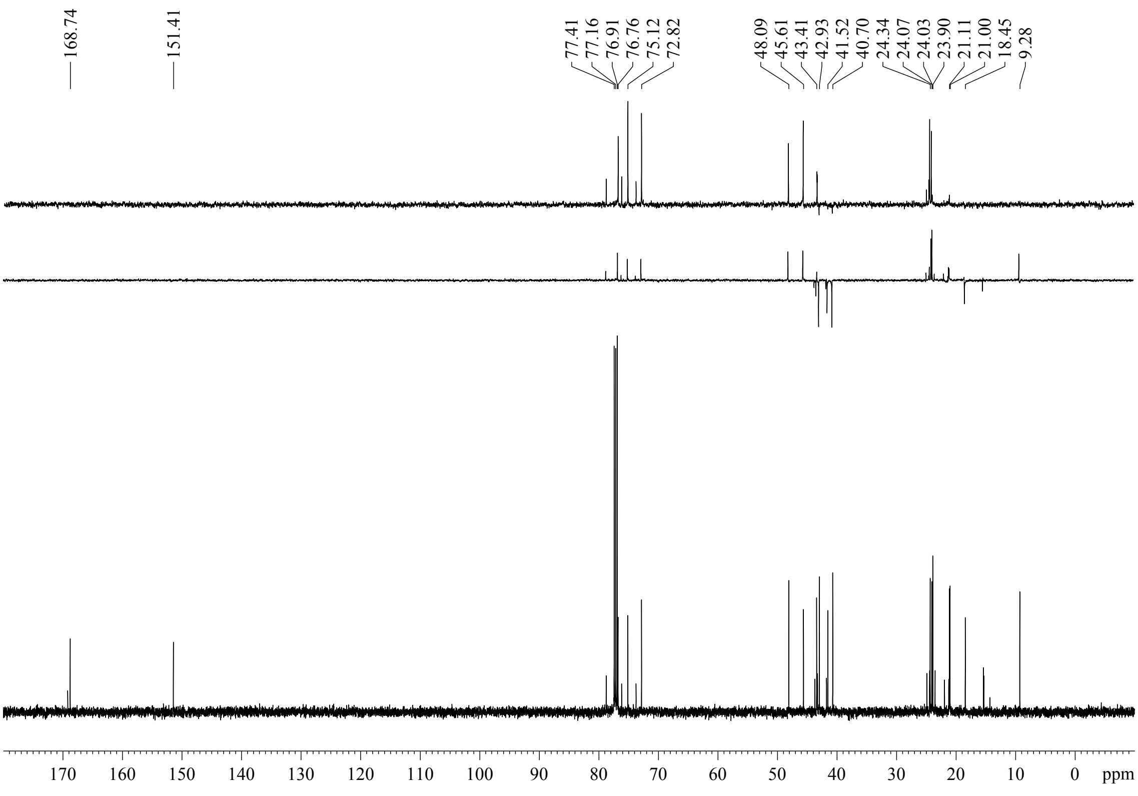
(4a*S**,5*S**,7*R**,8*R**,8a*S**)-3-(2-Chloroethyl)-8-ethyl-5,7-diisobutyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (7a-Cl)

$CDCl_3$

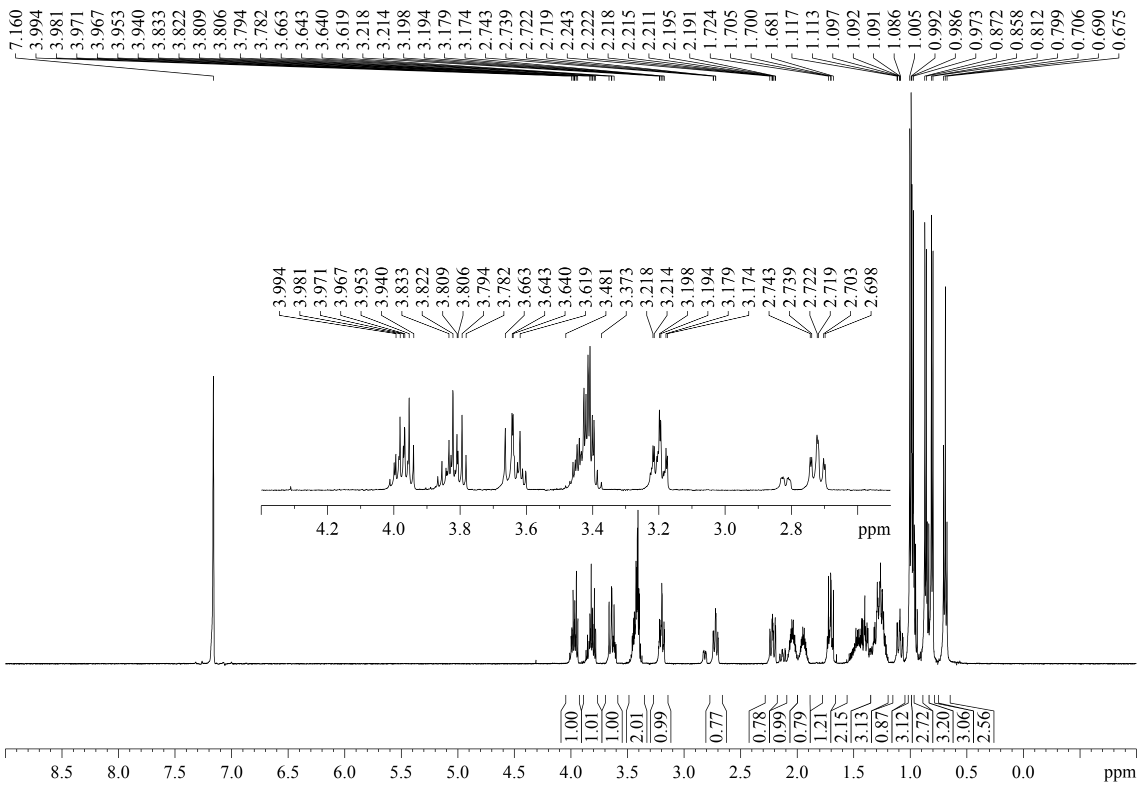


7a-Cl

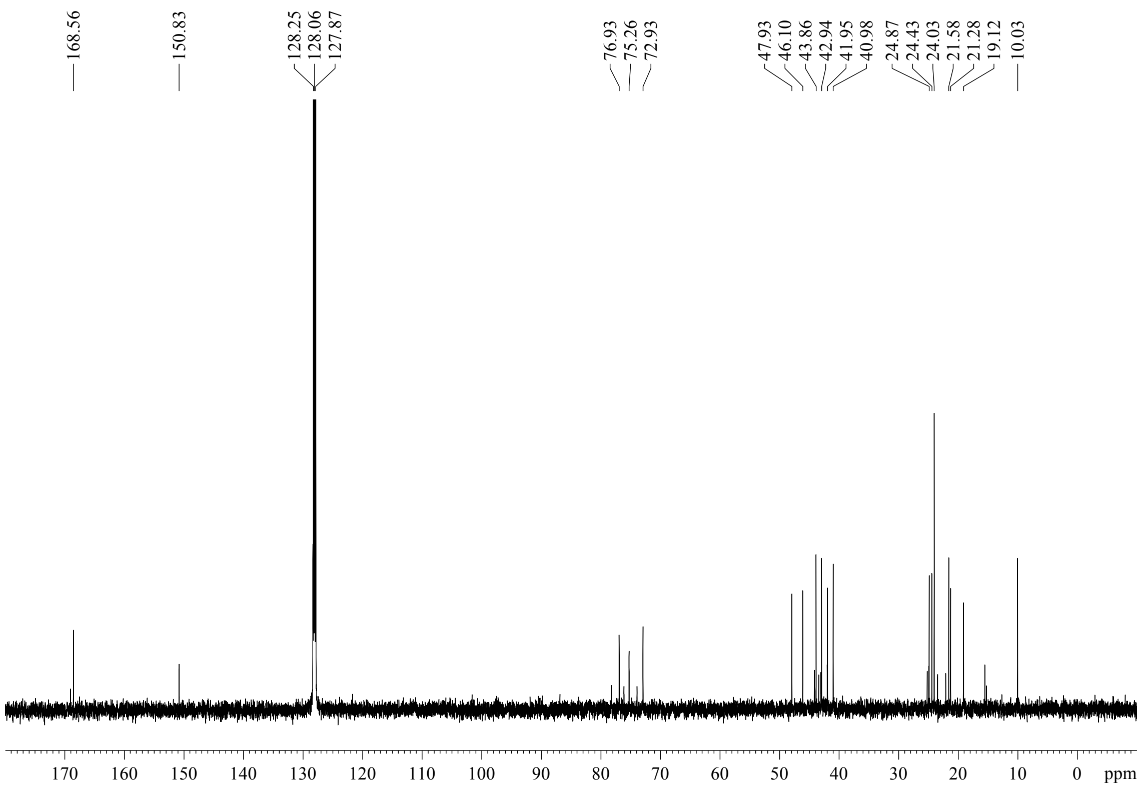




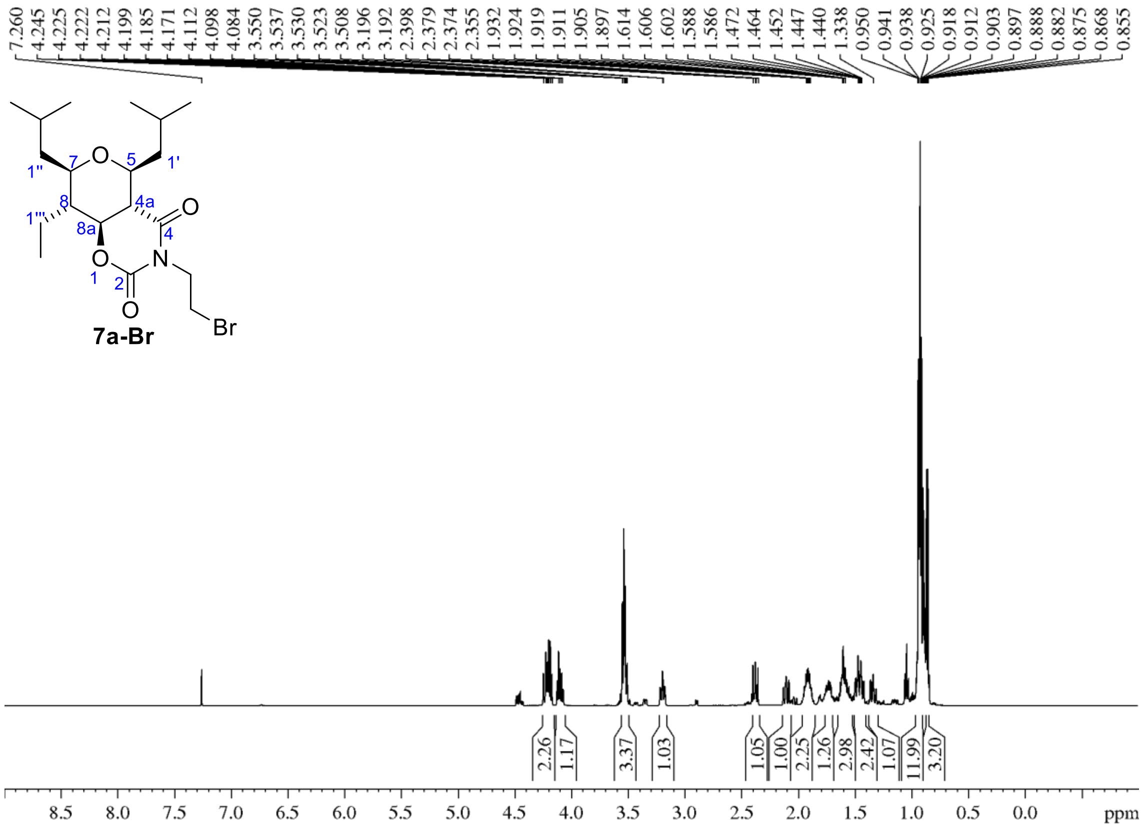
^{1}H-NMR C_6D_6

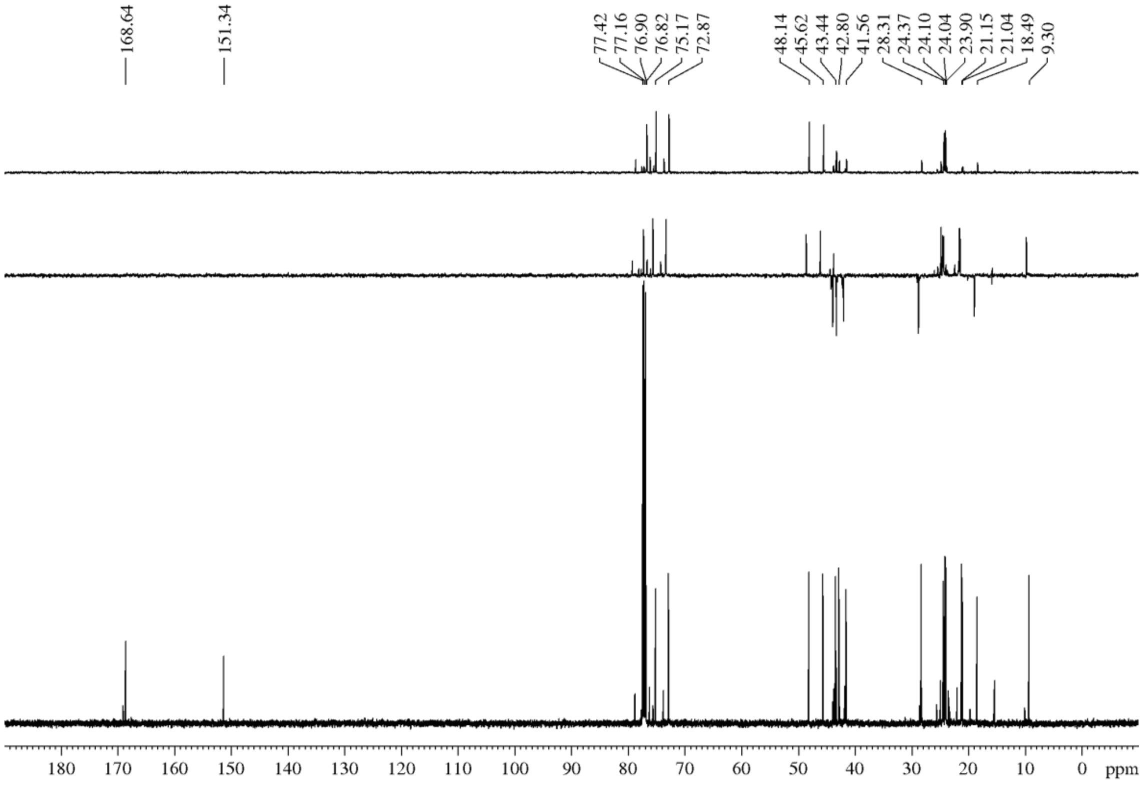


^{13}C-NMR C_6D_6

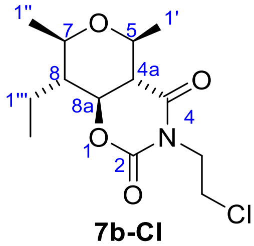


(4*aS*,5*S*,7*R*,8*R*,8*aS*)-3-(2-Bromoethyl)-8-ethyl-5,7-diisobutyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (7a-Br)

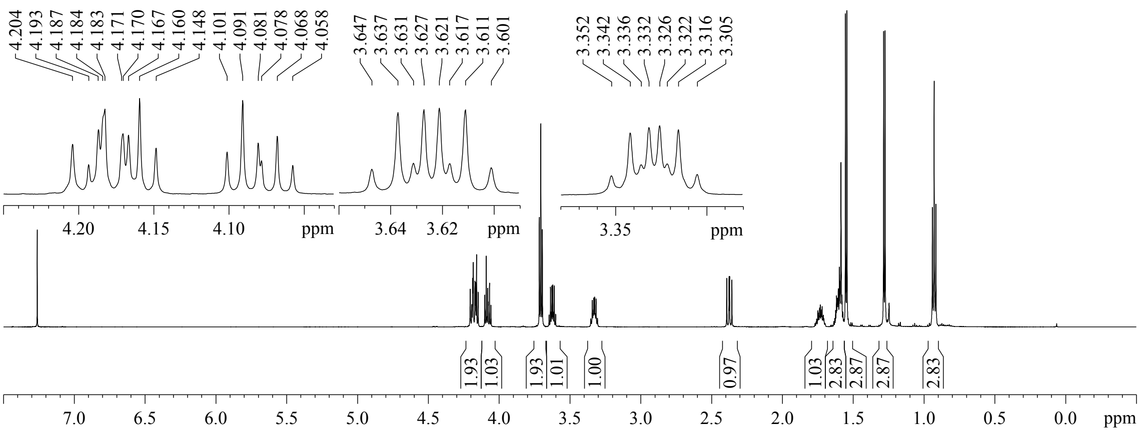


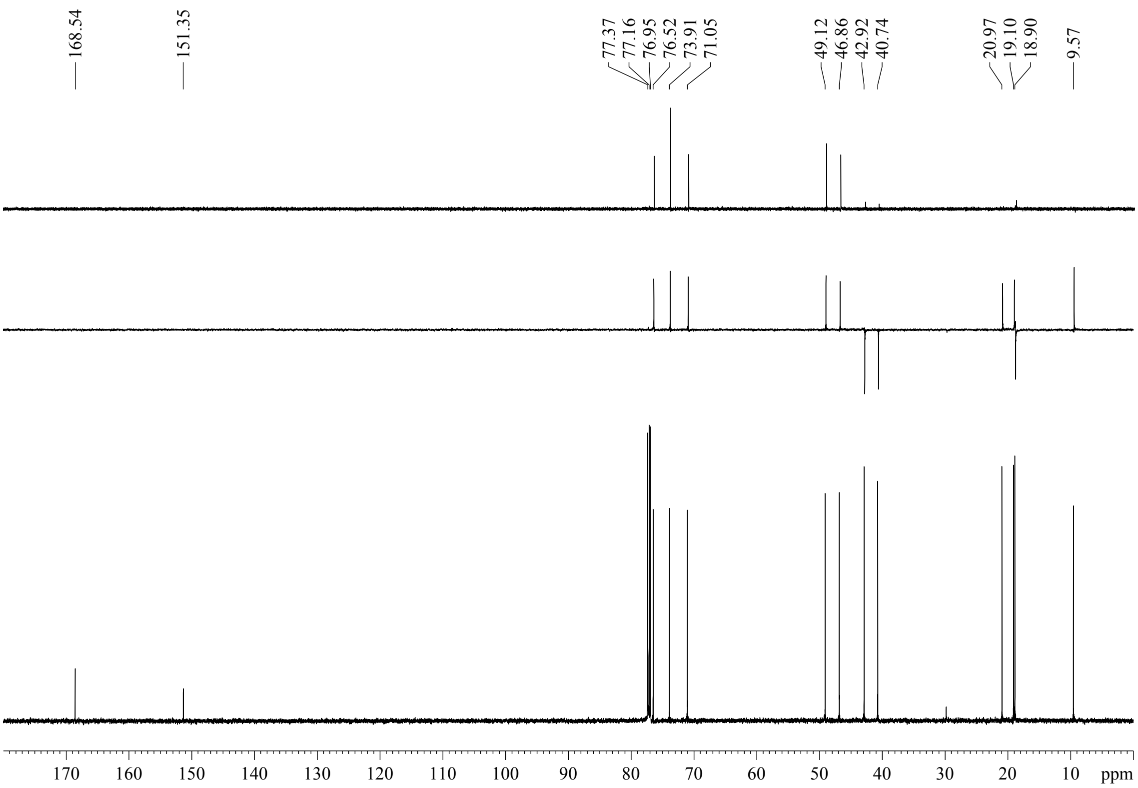


(4a*S,5*S**,7*R**,8*R**,8a*S**)-3-(2-Chloroethyl)-8-ethyl-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (7b-Cl)**

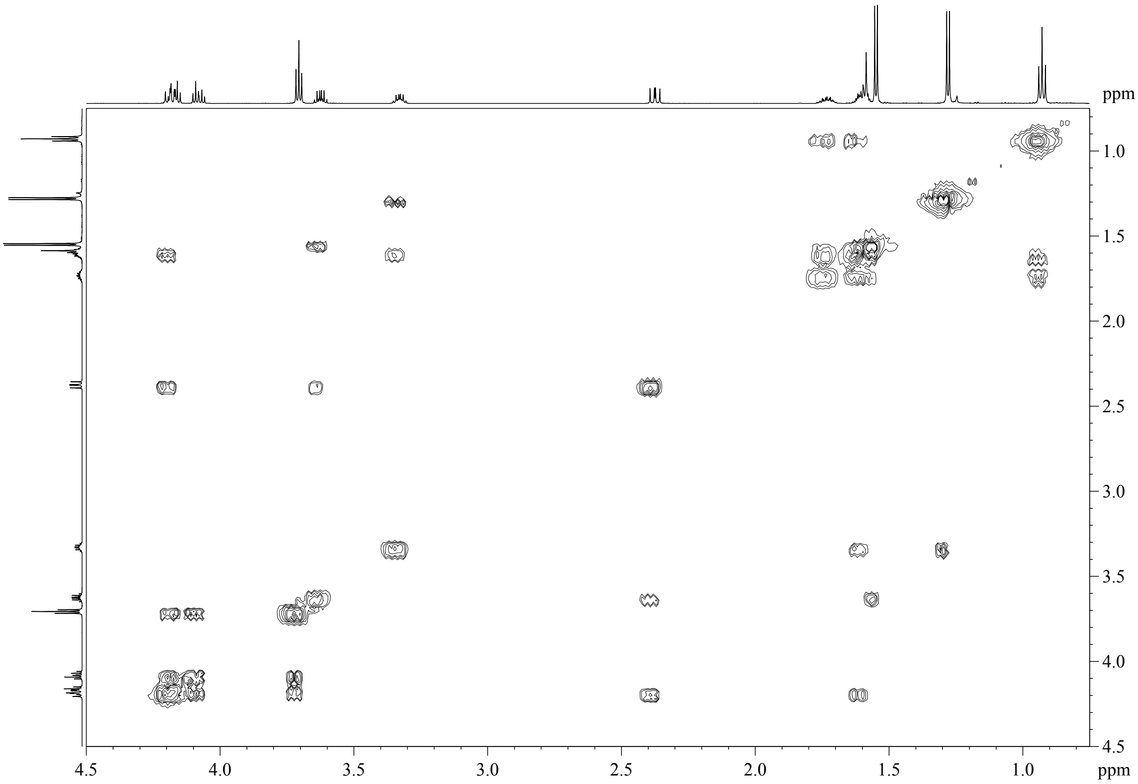


7b-Cl





COSY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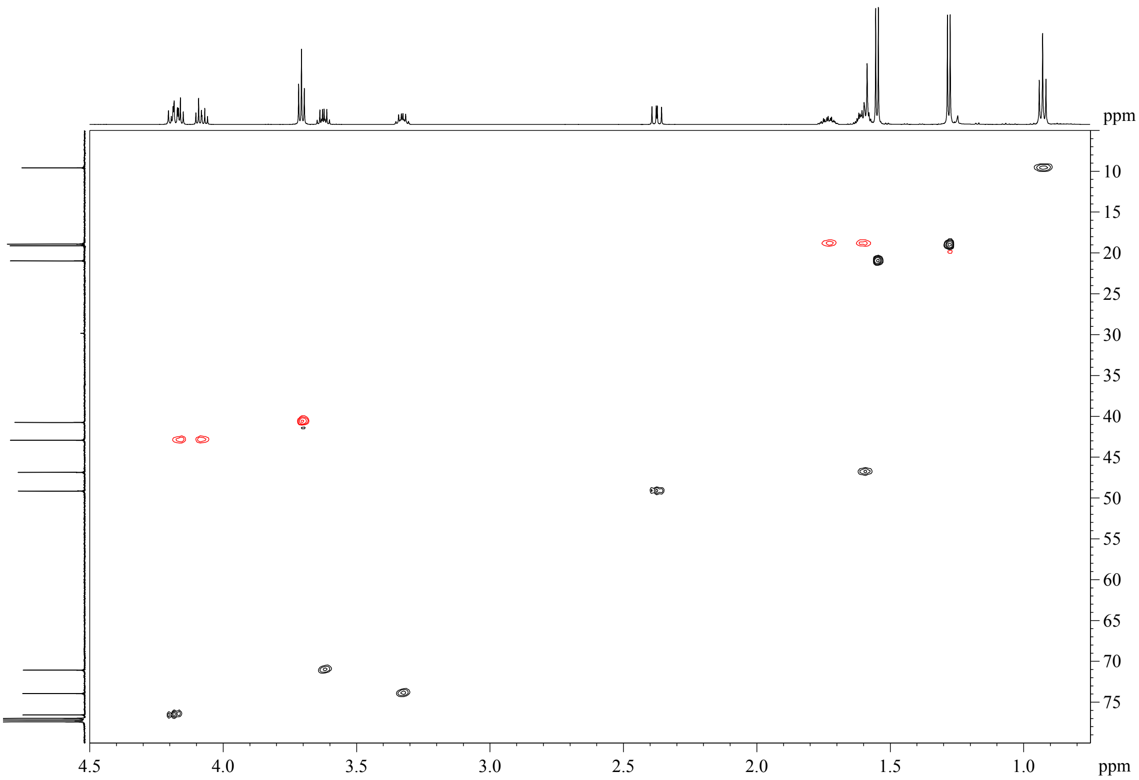
2.0
2.5
3.0
3.5
4.0
4.5
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

HSQCed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15
20
25
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35
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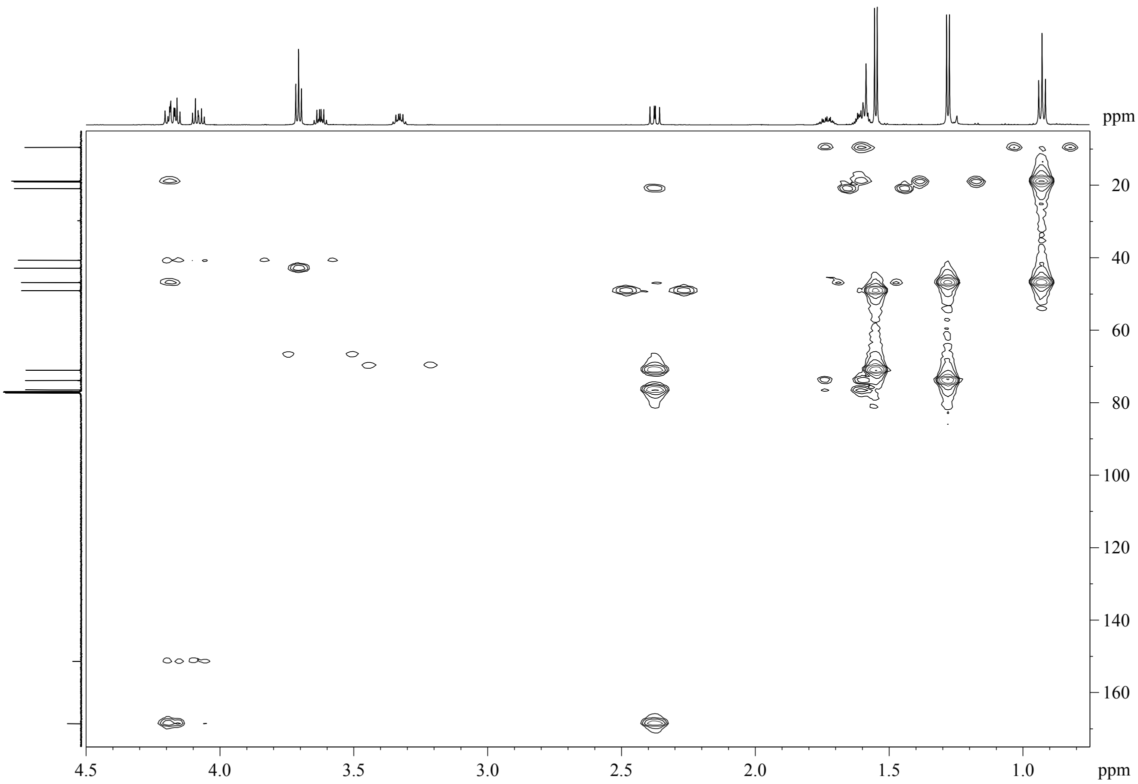
45
50
55
60
65
70
75
4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

HMBC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40
60
80
100
120
140
160
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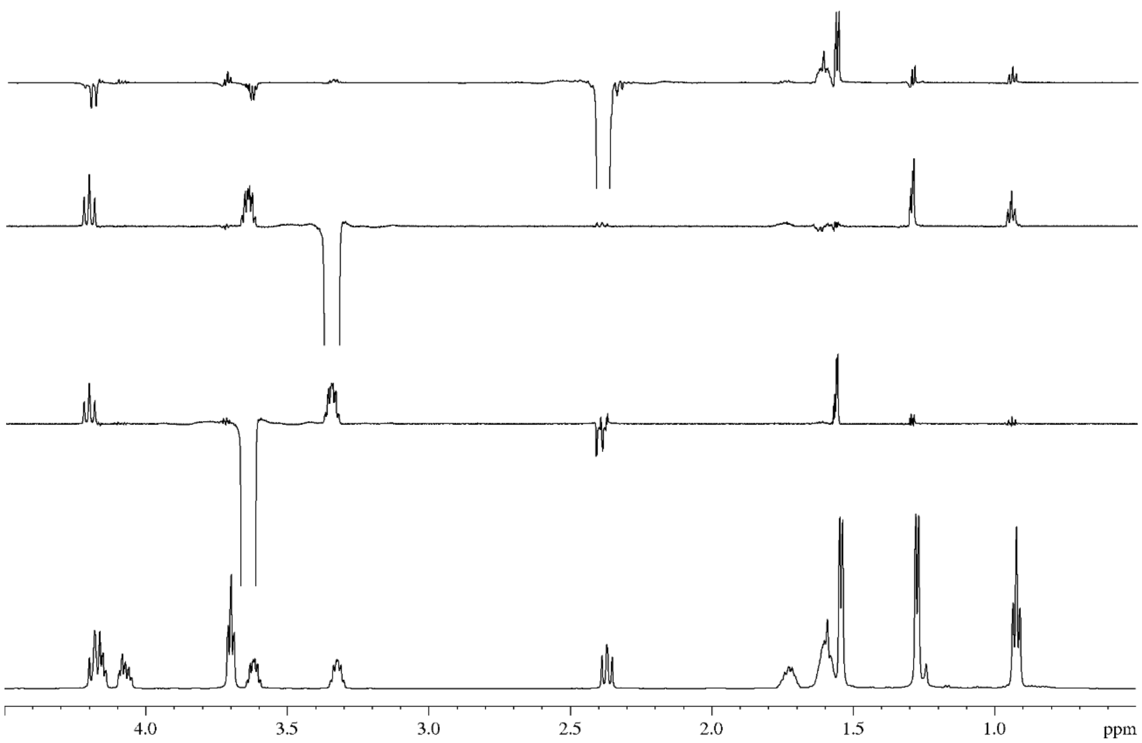
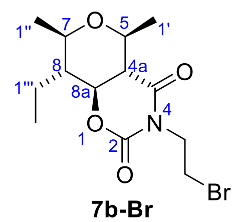
3.5
3.0
2.5
2.0
1.5
1.0
ppm

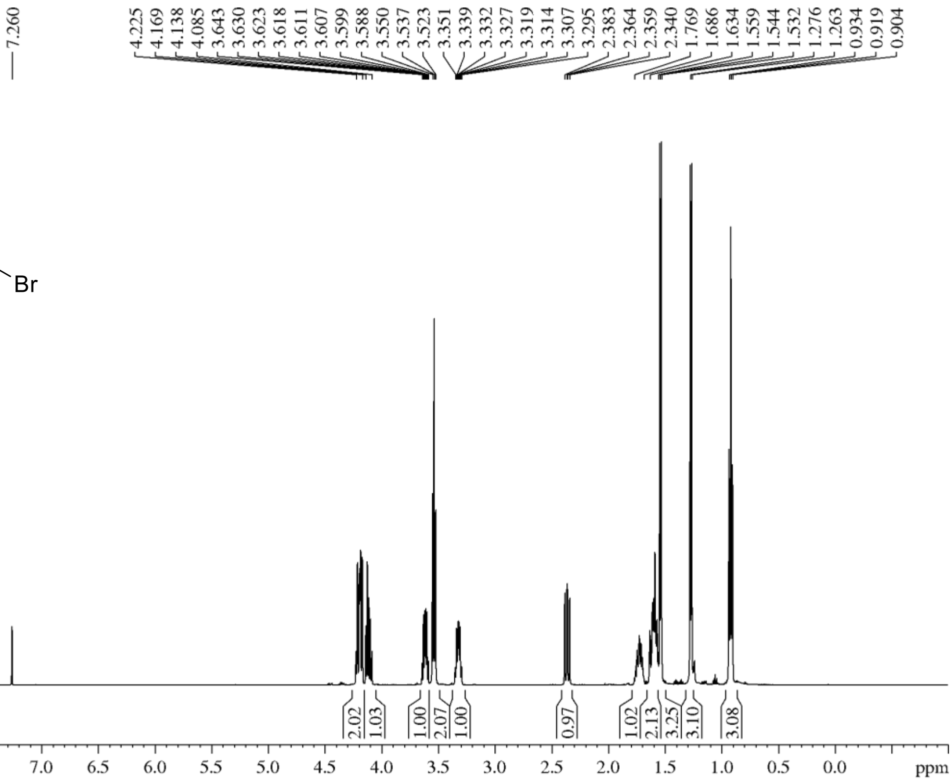
GOESY

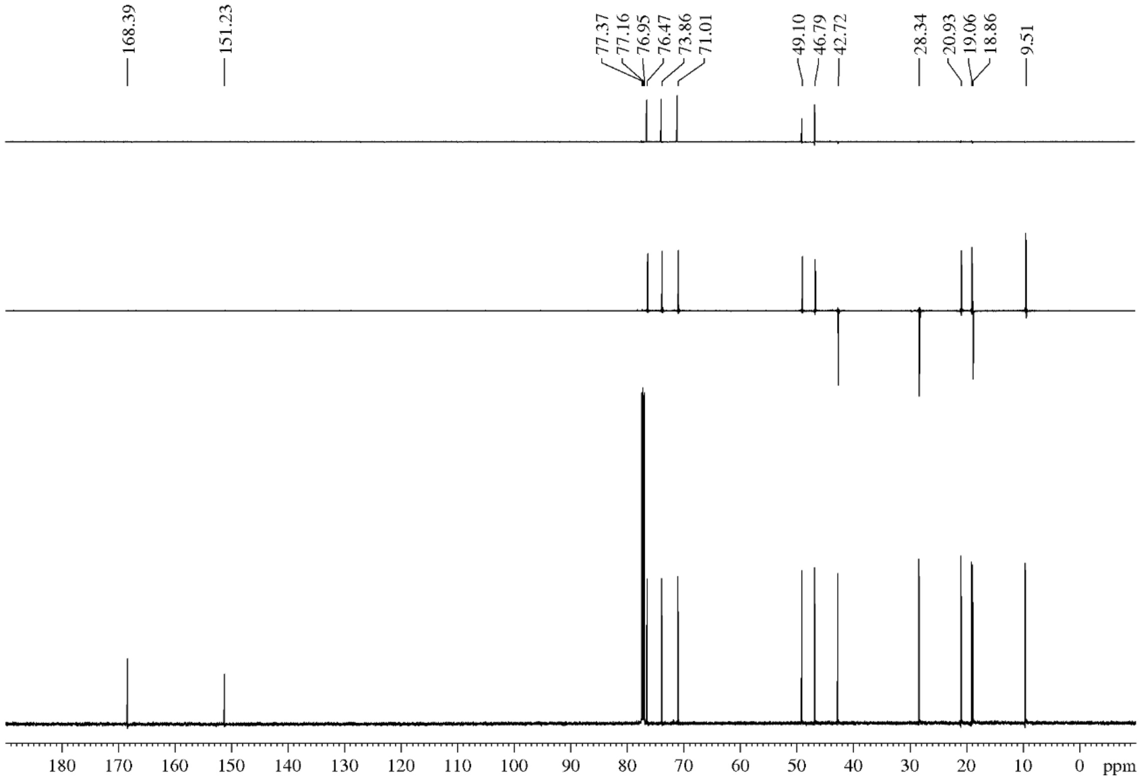

4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

(4a*S,5*S**,7*R**,8*R**,8a*S**)-3-(2-Bromoethyl)-8-ethyl-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (7b-Br)**

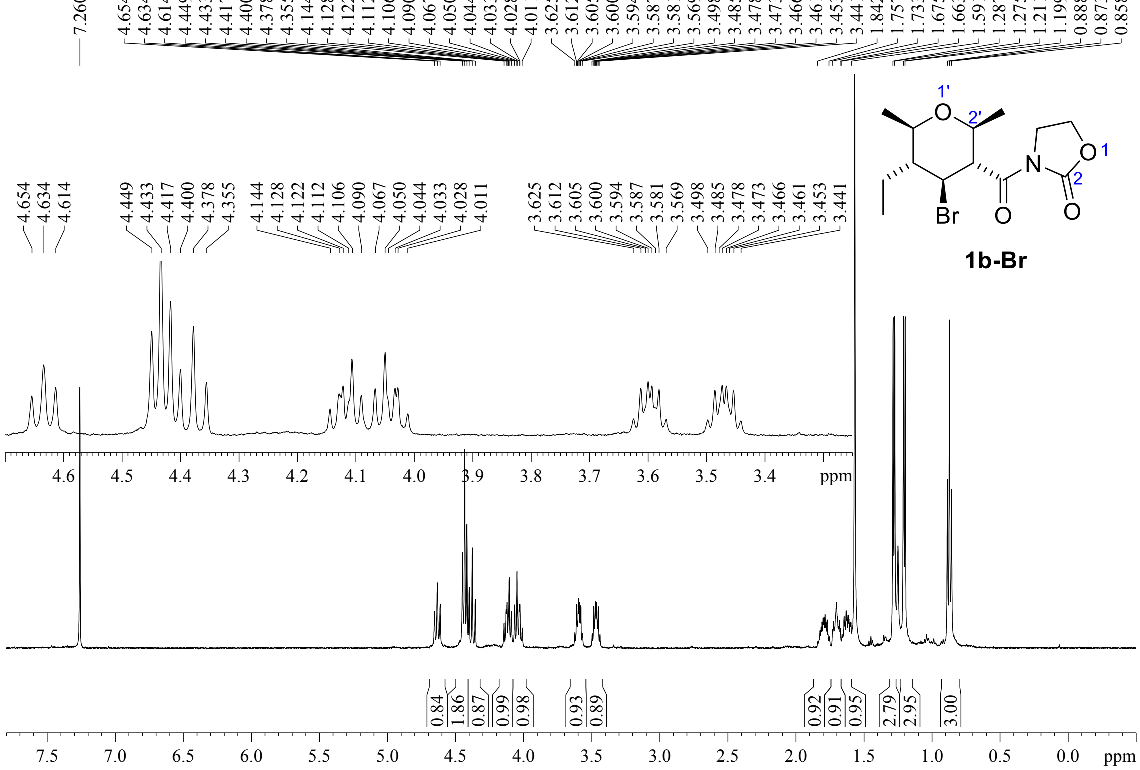


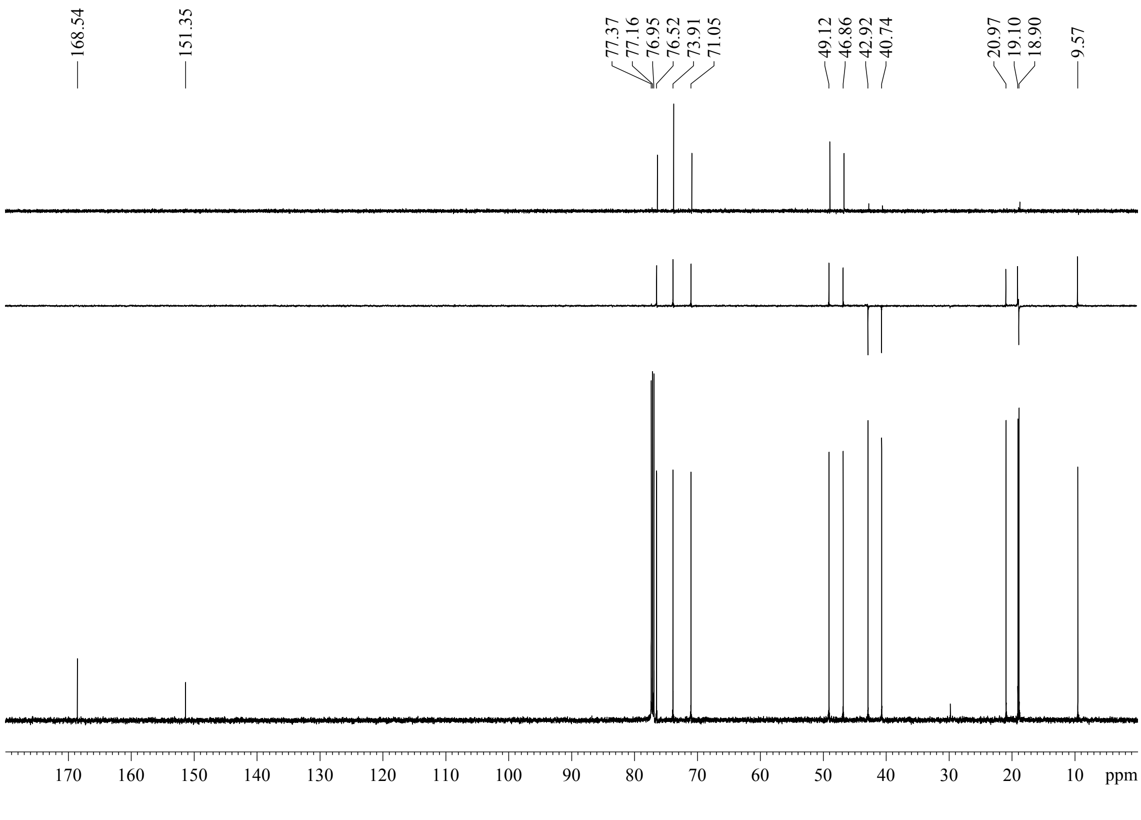
7b-Br



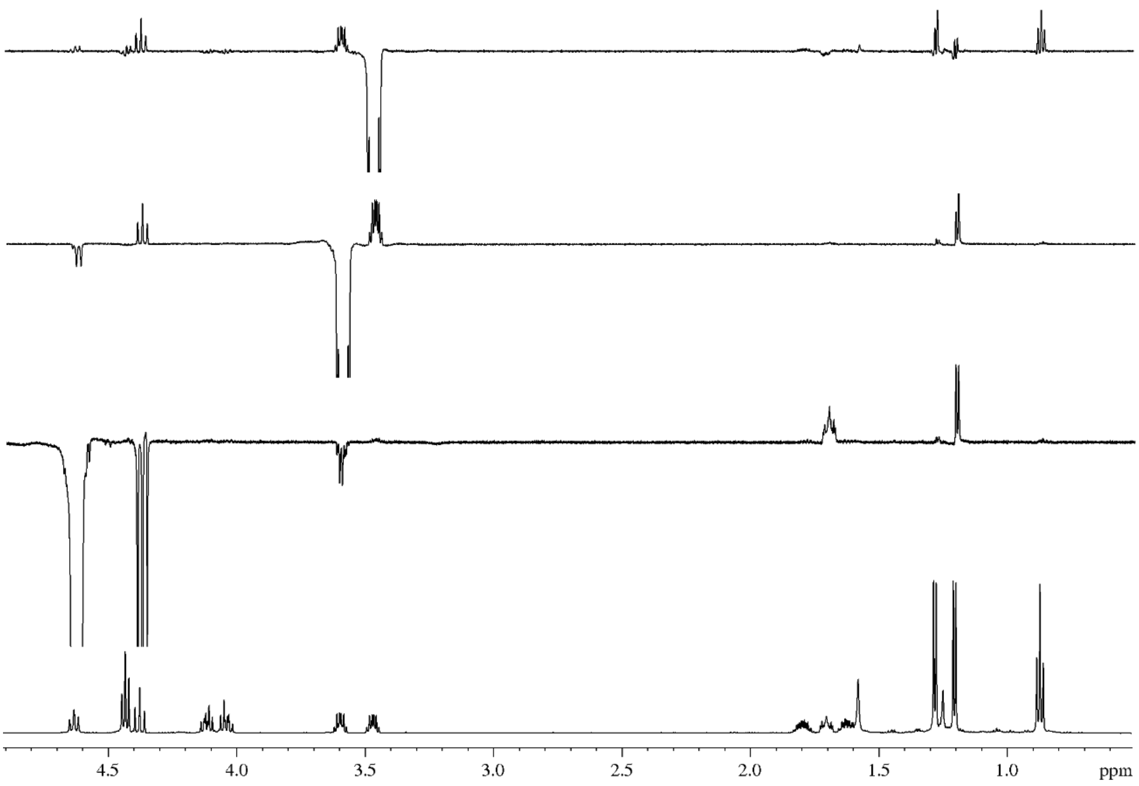


3-((2*S,3*R**,4*S**,5*R**,6*R**)-4-Bromo-5-ethyl-2,6-dimethyltetrahydro-2*H*-pyran-3-carbonyl)oxazolidin-2-one (1b-Br)**

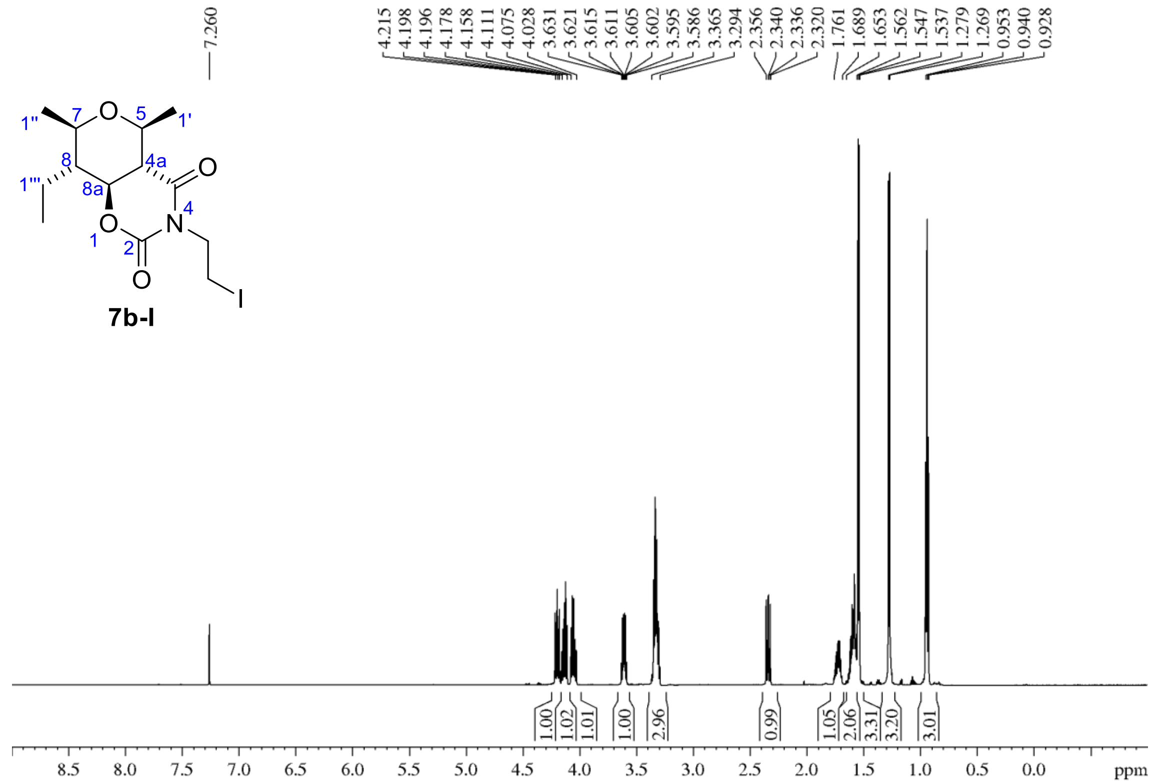


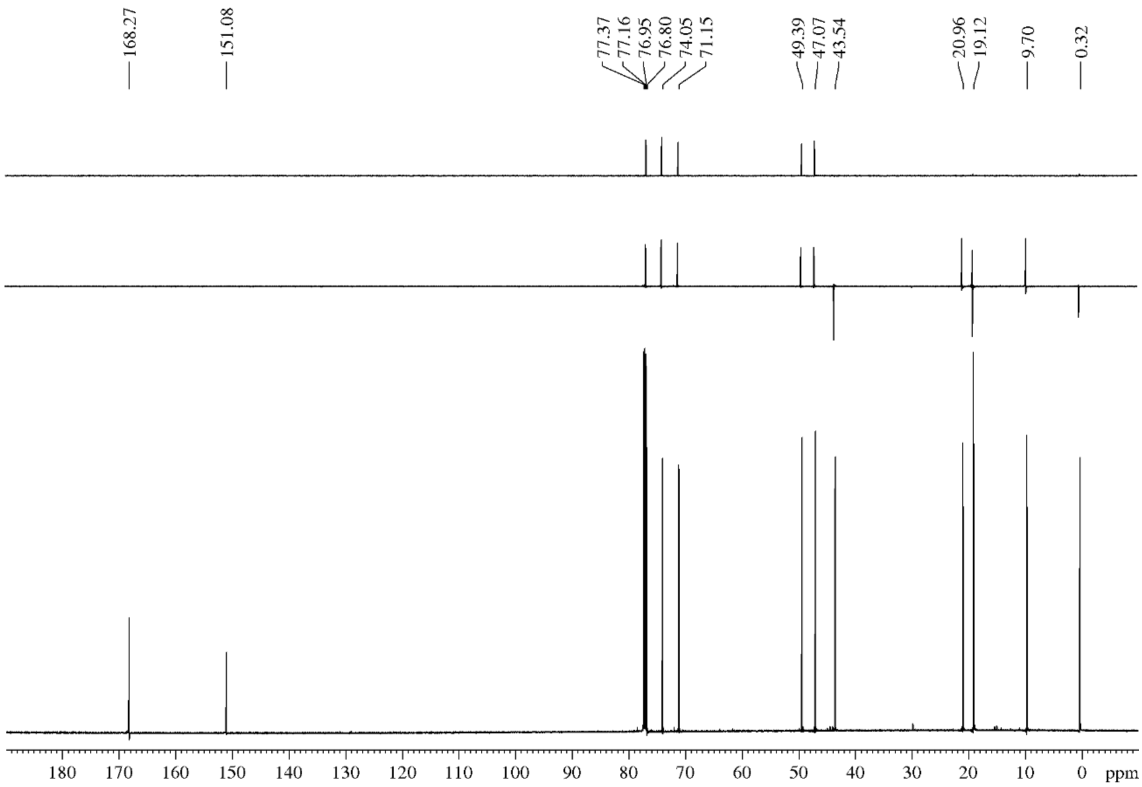


GOESY

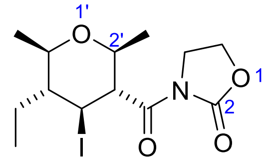


(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-iodoethyl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (7b-I)**

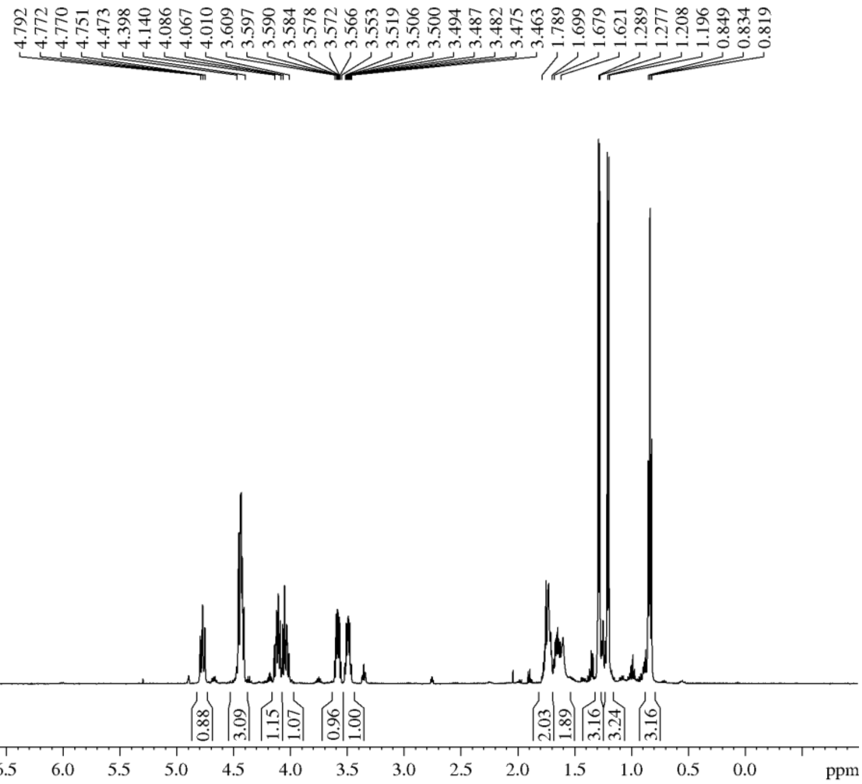


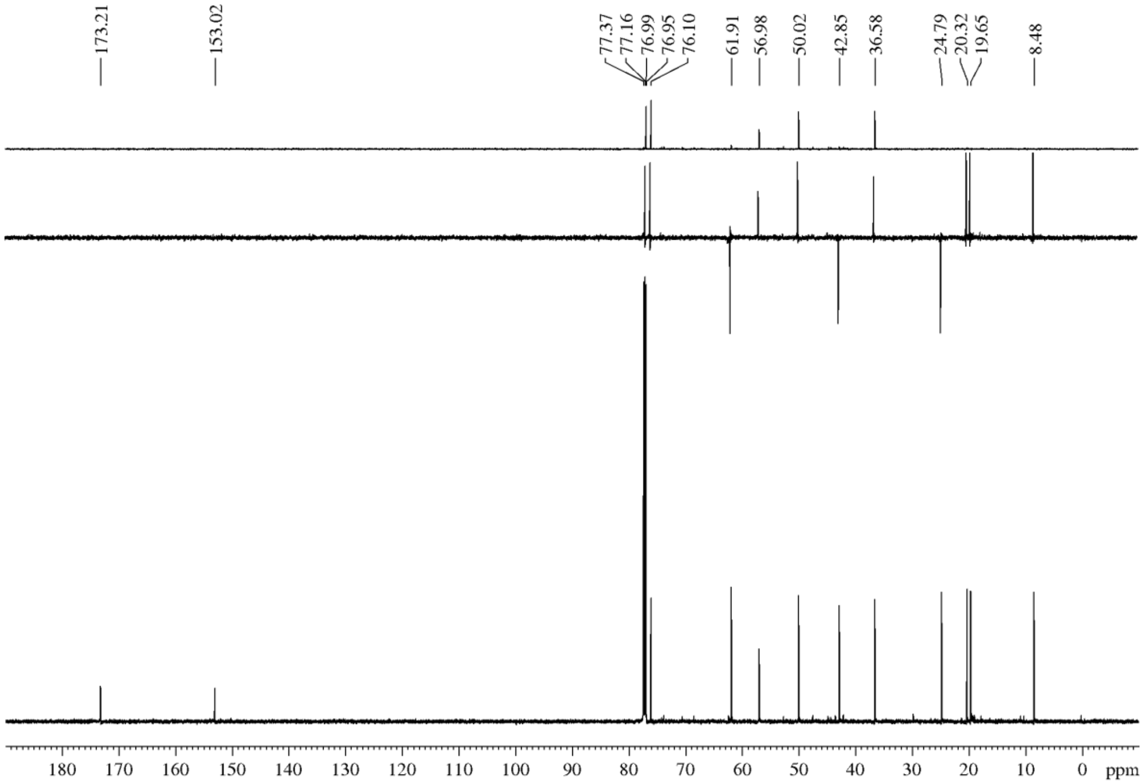


3-((2*S,3*R**,4*S**,5*R**,6*R**)-5-ethyl-4-iodo-2,6-dimethyltetrahydro-2*H*-pyran-3-carbonyl)oxazolidin-2-one (1b-I)**

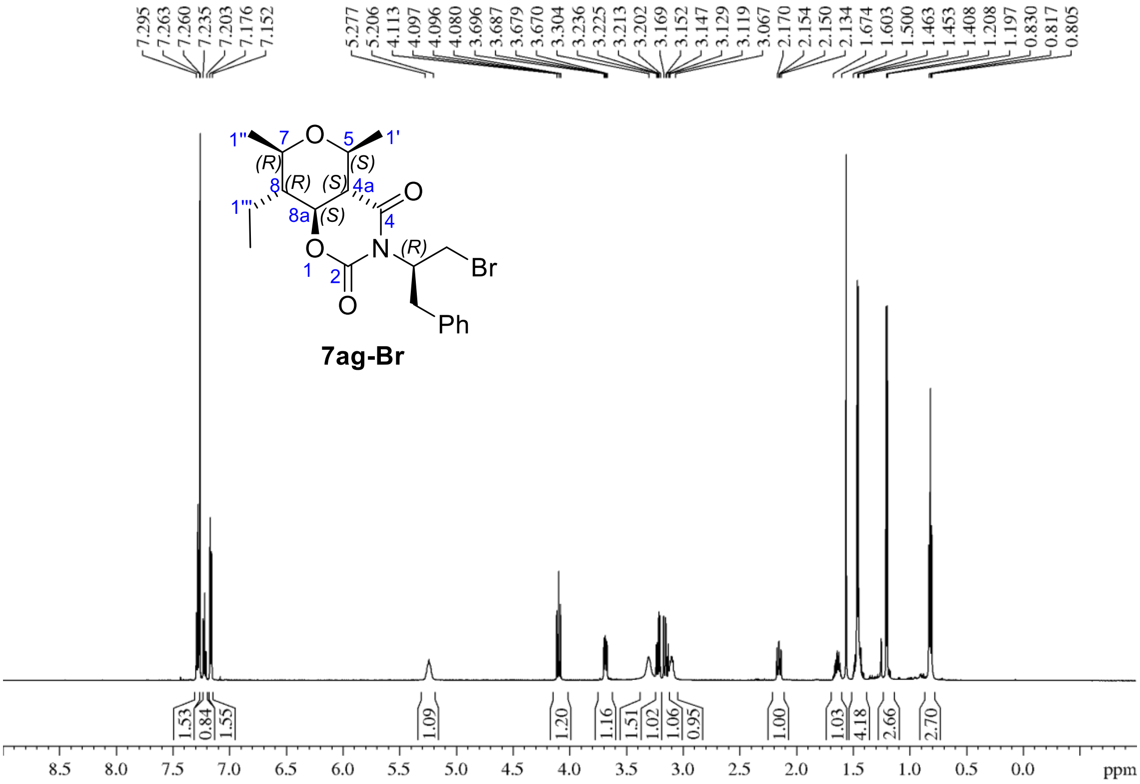


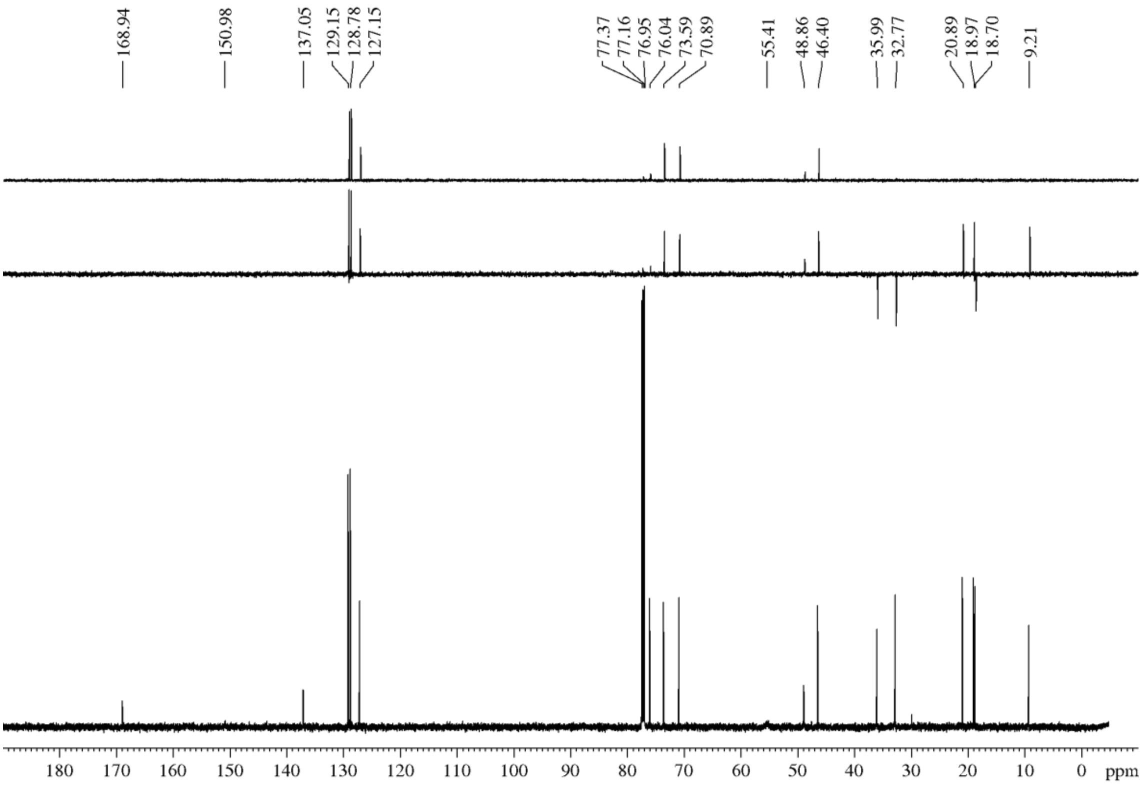
1b-I



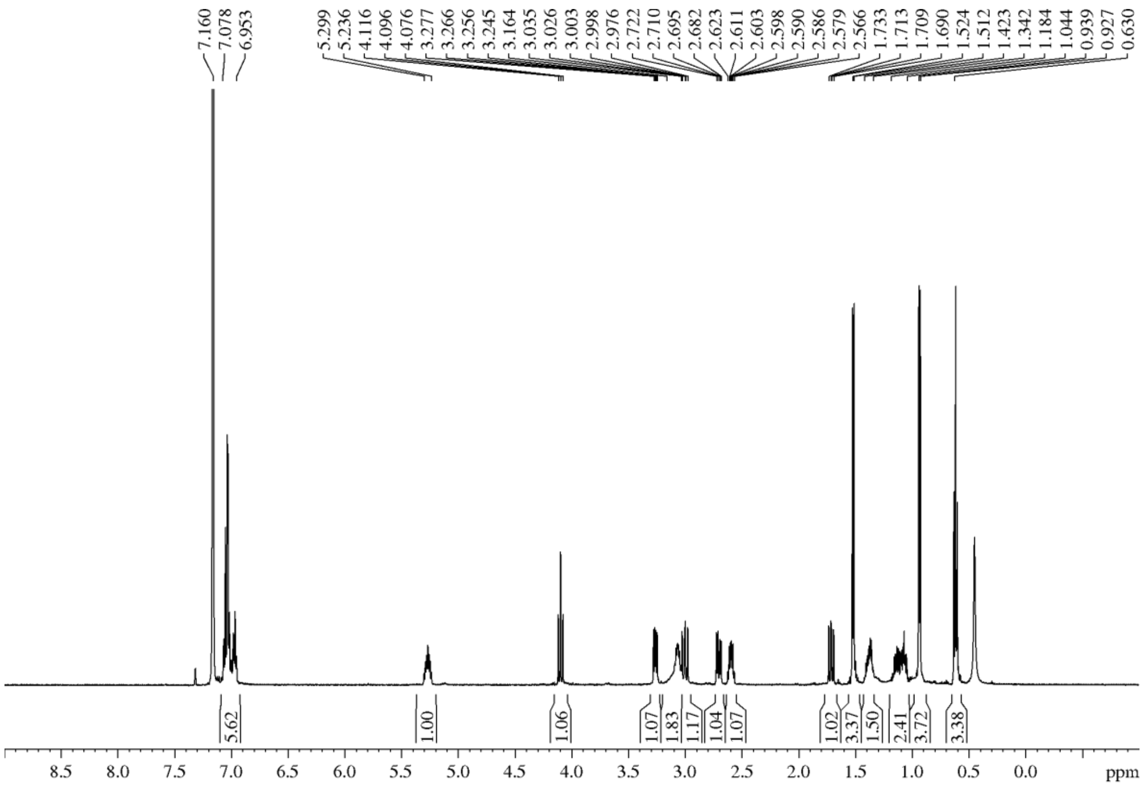


(4a*S*,5*S*,7*R*,8*R*,8a*S*)-3-((*R*)-1-Bromo-3-phenylpropan-2-yl)-8-ethyl-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (7ag-Br)

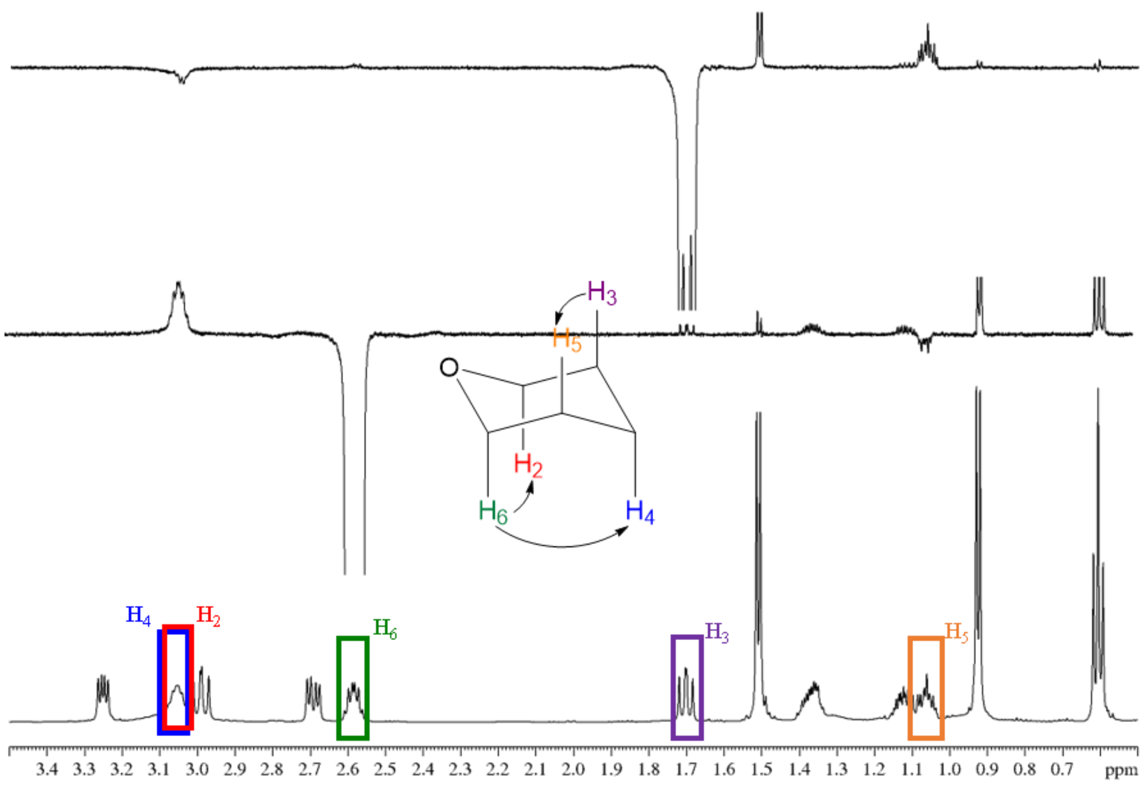




[1]H-NMR C_6D_6

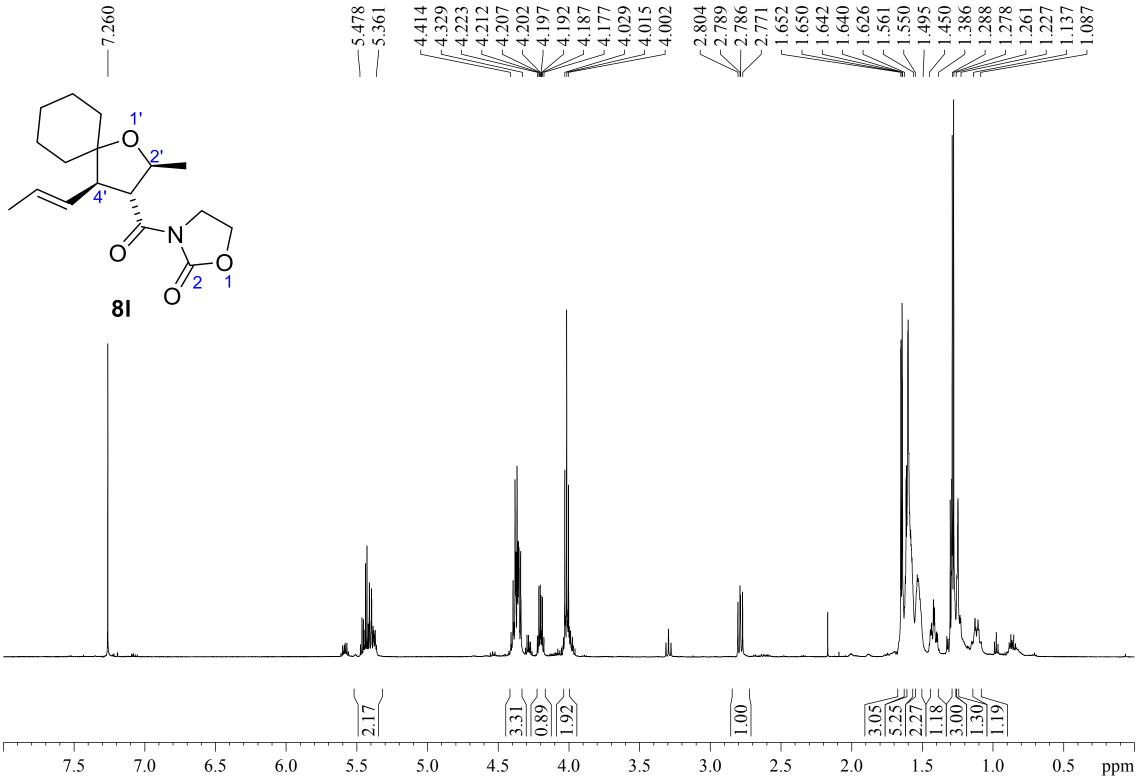


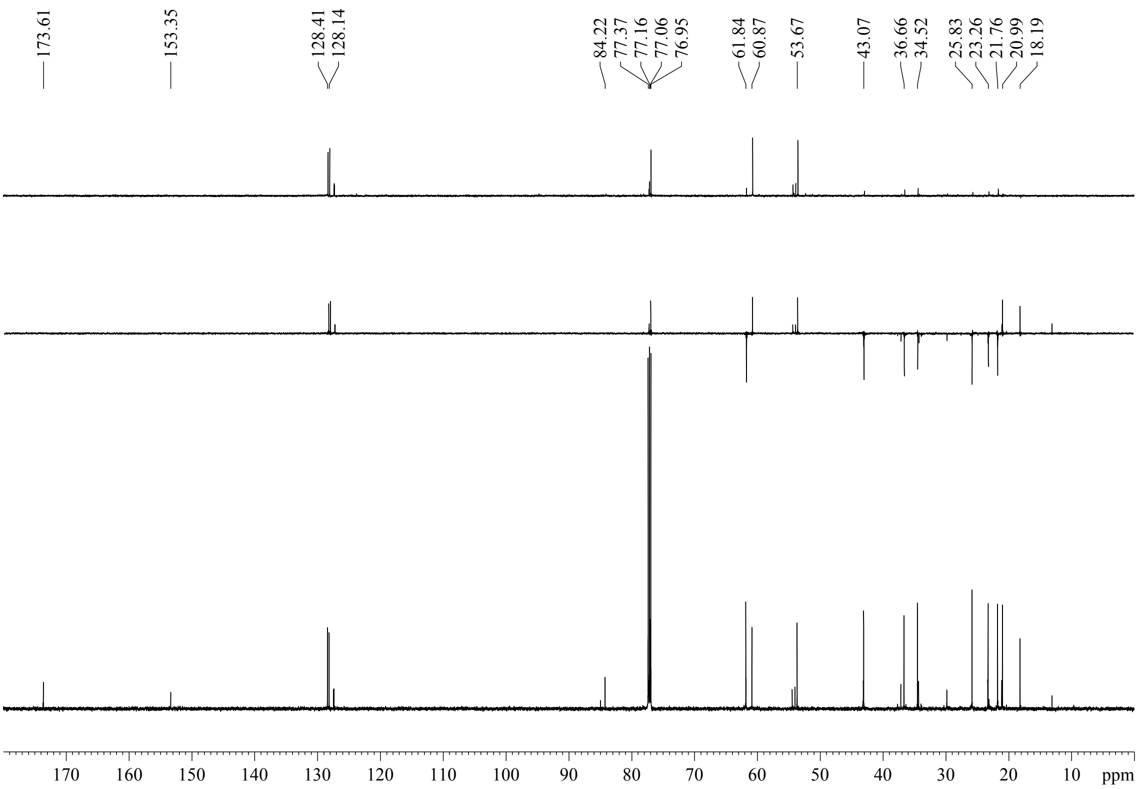
GOESY



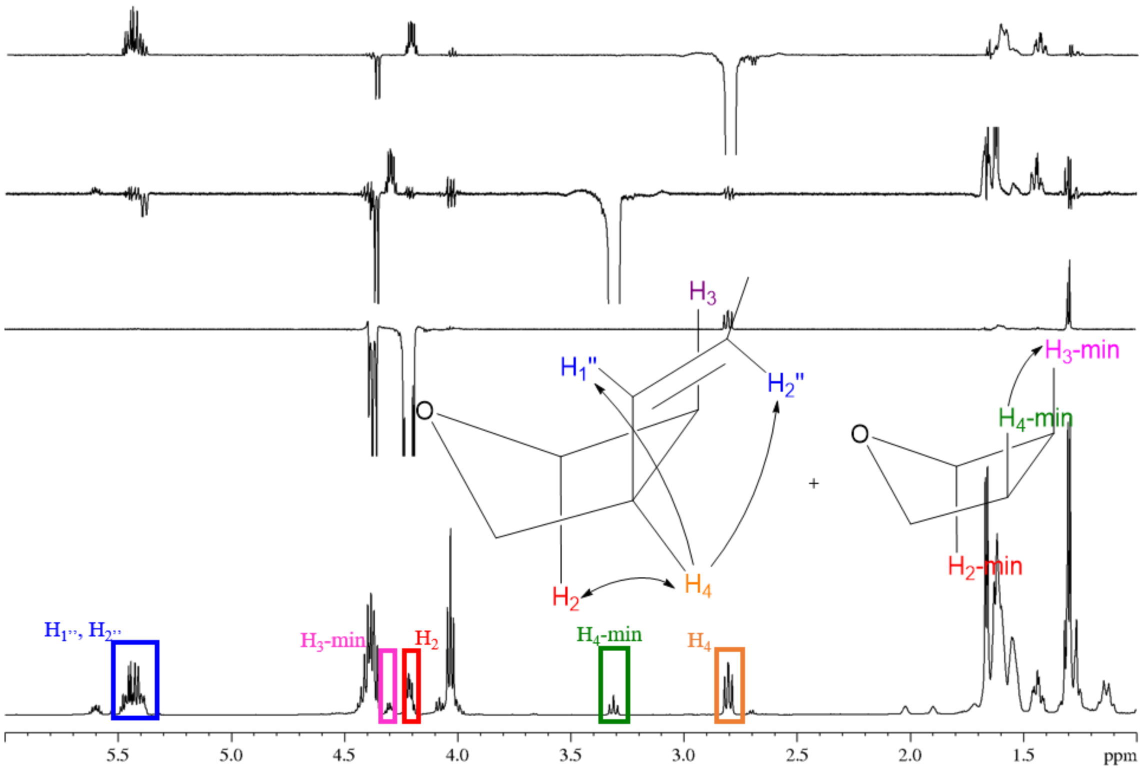
2,3,4,5-tetrasubstituted THFs 8

3-((2*S**,3*R**,4*R**)-2-Methyl-4-((*E*)-prop-1-en-1-yl)-1-oxaspiro[4.5]decane-3-carbonyl)oxazolidin-2-one (8l)



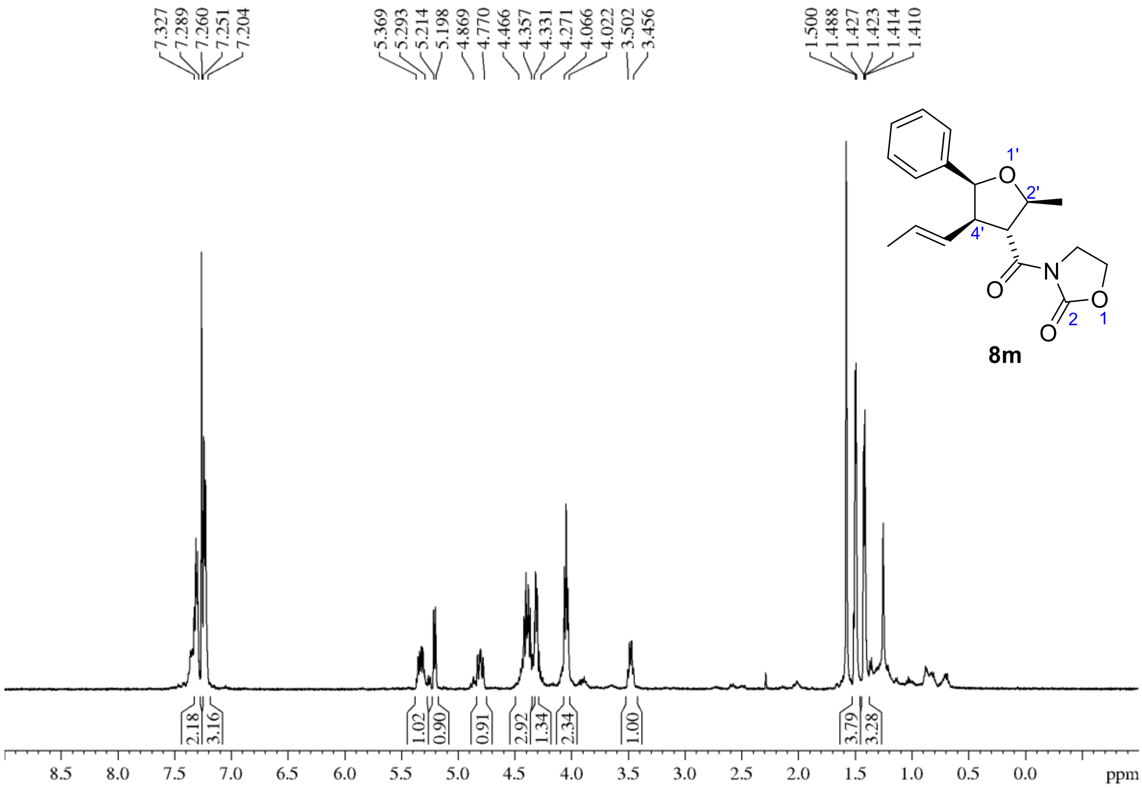


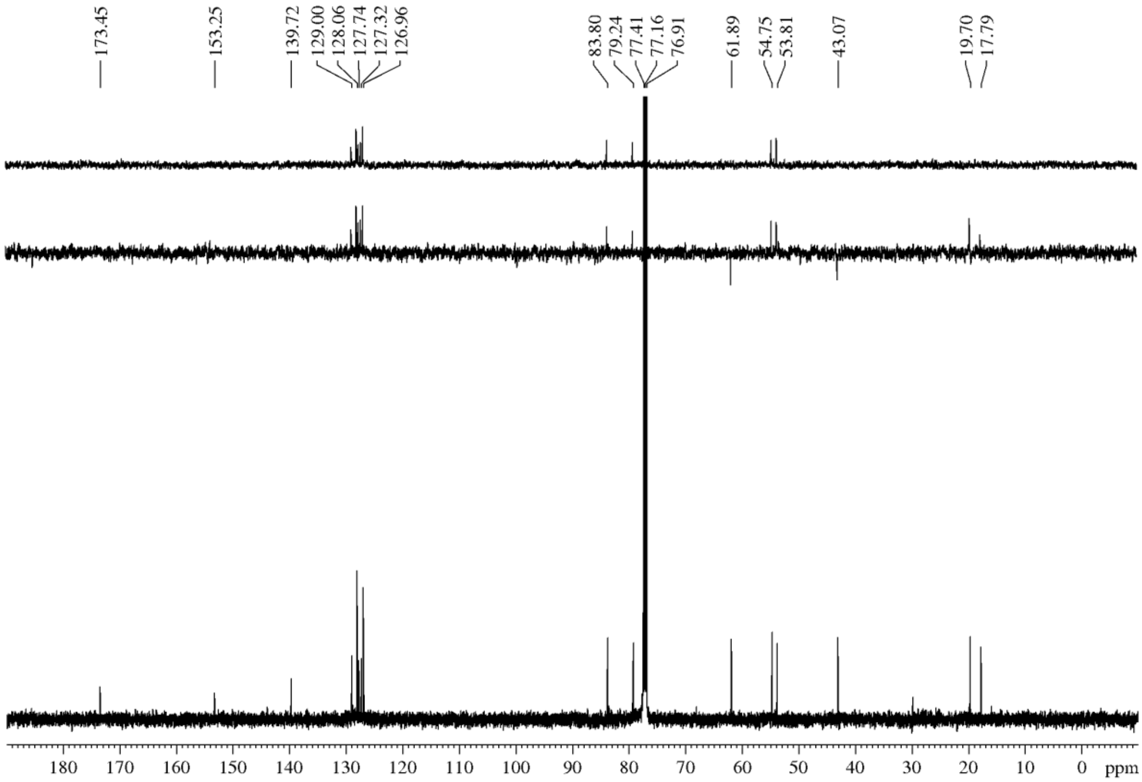
GOESY



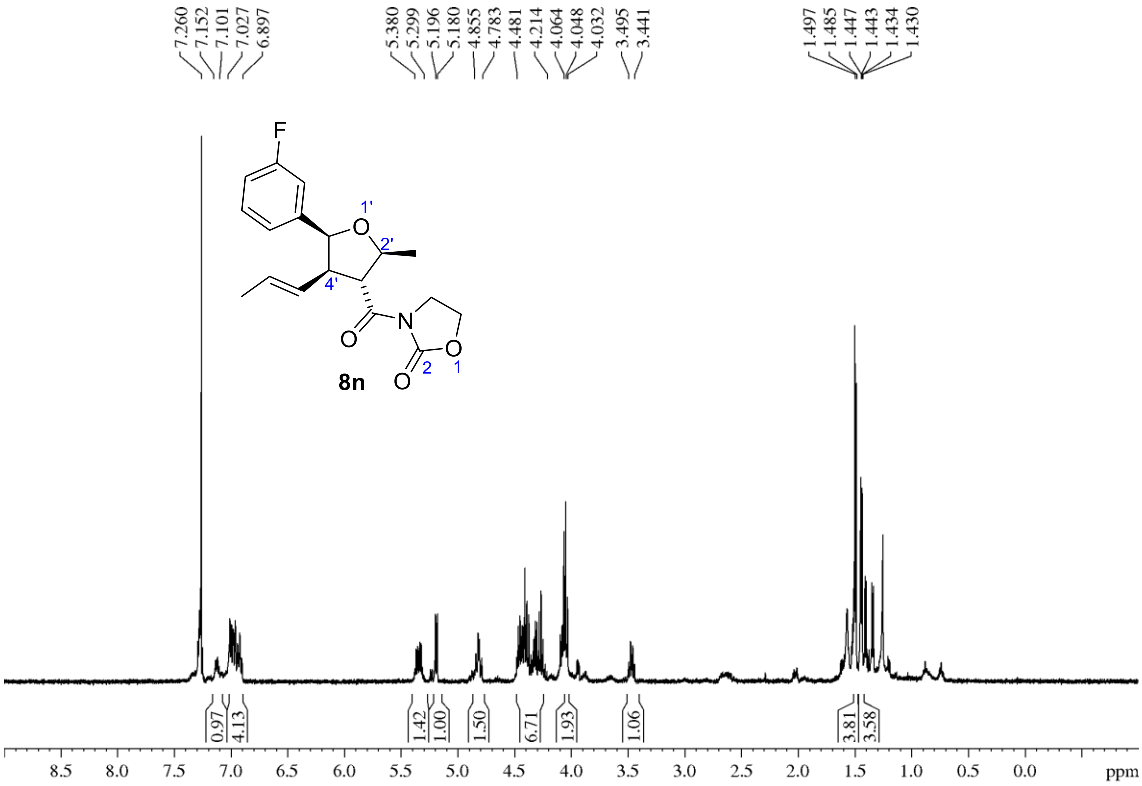
H3
H1''
H2''
O
H2
H4
+
O
H3-min
H4-min
H2-min
H1'', H2''
H3-min
H2
H4-min
H4
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

3-((2*S,3*R**,4*R**,5*R**)-2-Methyl-5-phenyl-4-((*E*)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (8m)**



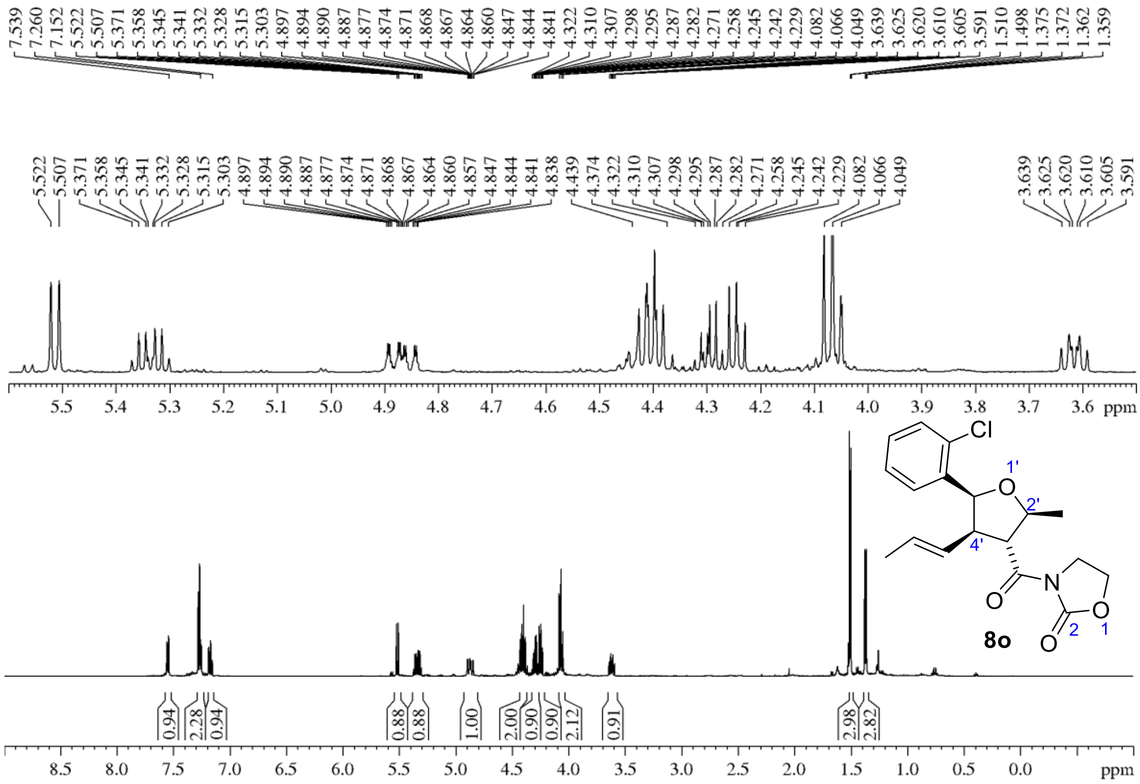


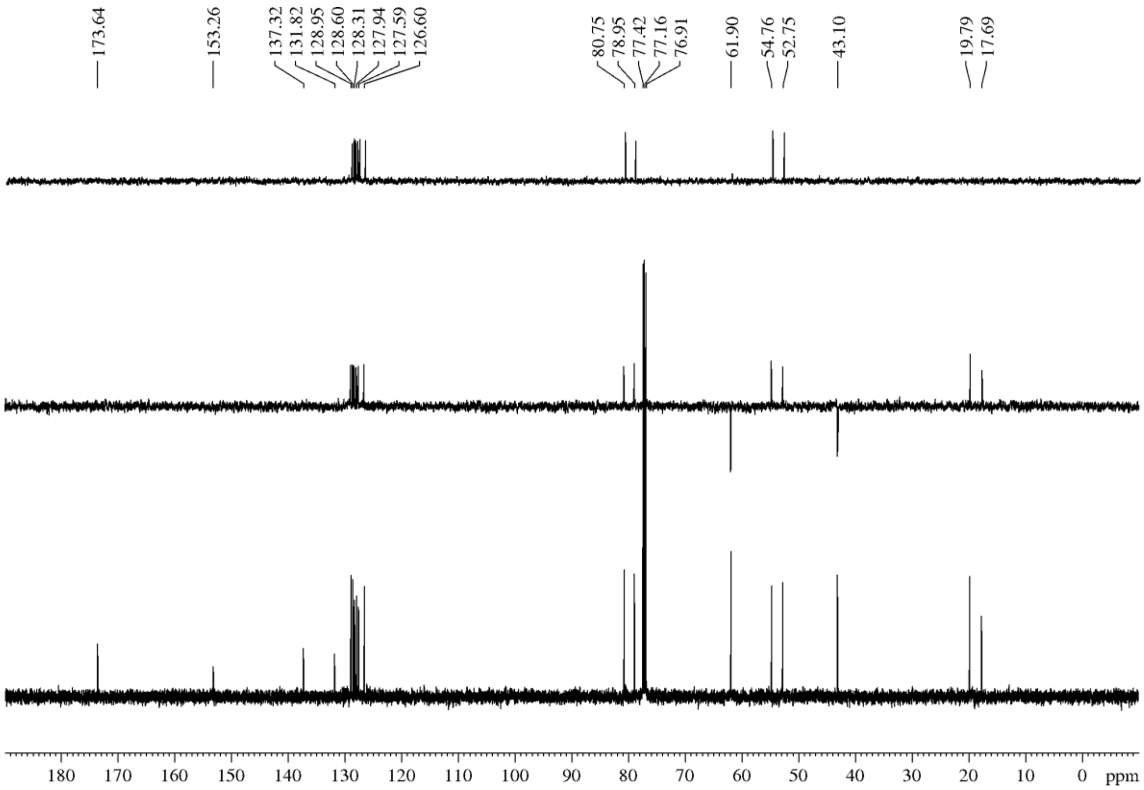
3-((2*S*,3*R*,4*R*,5*S*)-5-(3-fluorophenyl)-2-methyl-4-((*E*)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (8n)



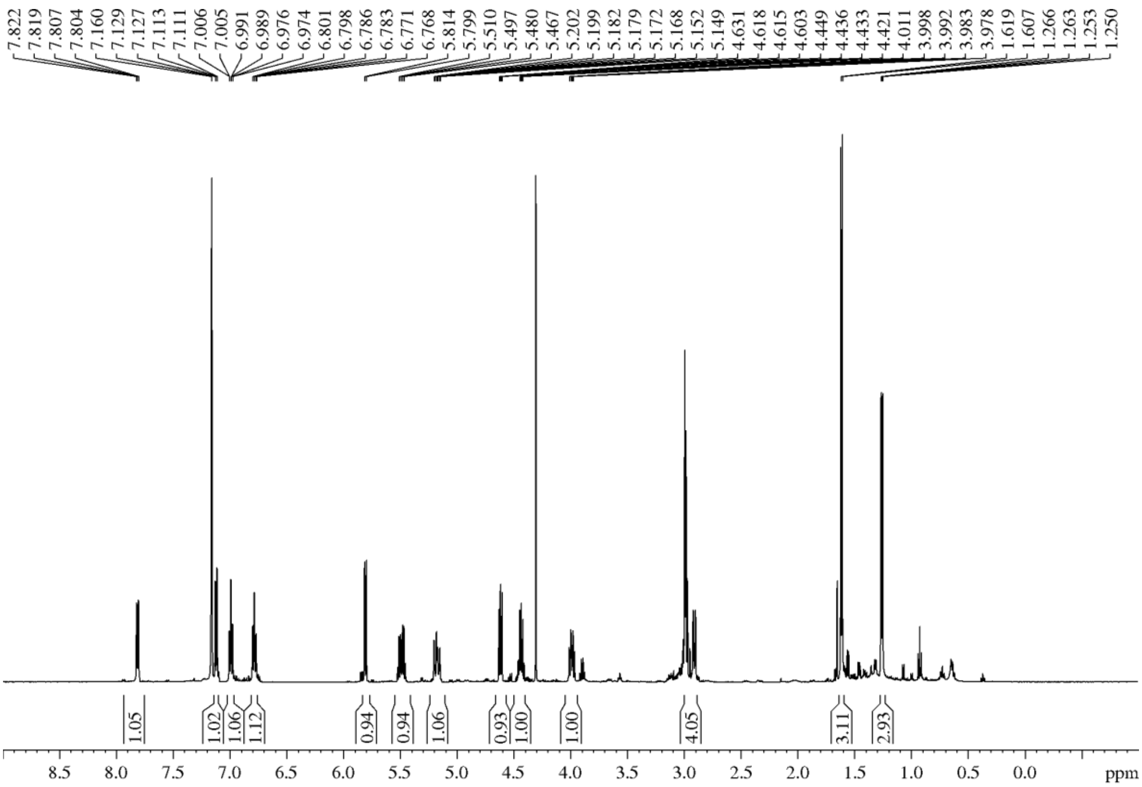
3-((2*S,3*R**,4*R**,5*S**)-5-(2-Chlorophenyl)-2-methyl-4-((*E*)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (8o)**

$CDCl_3$

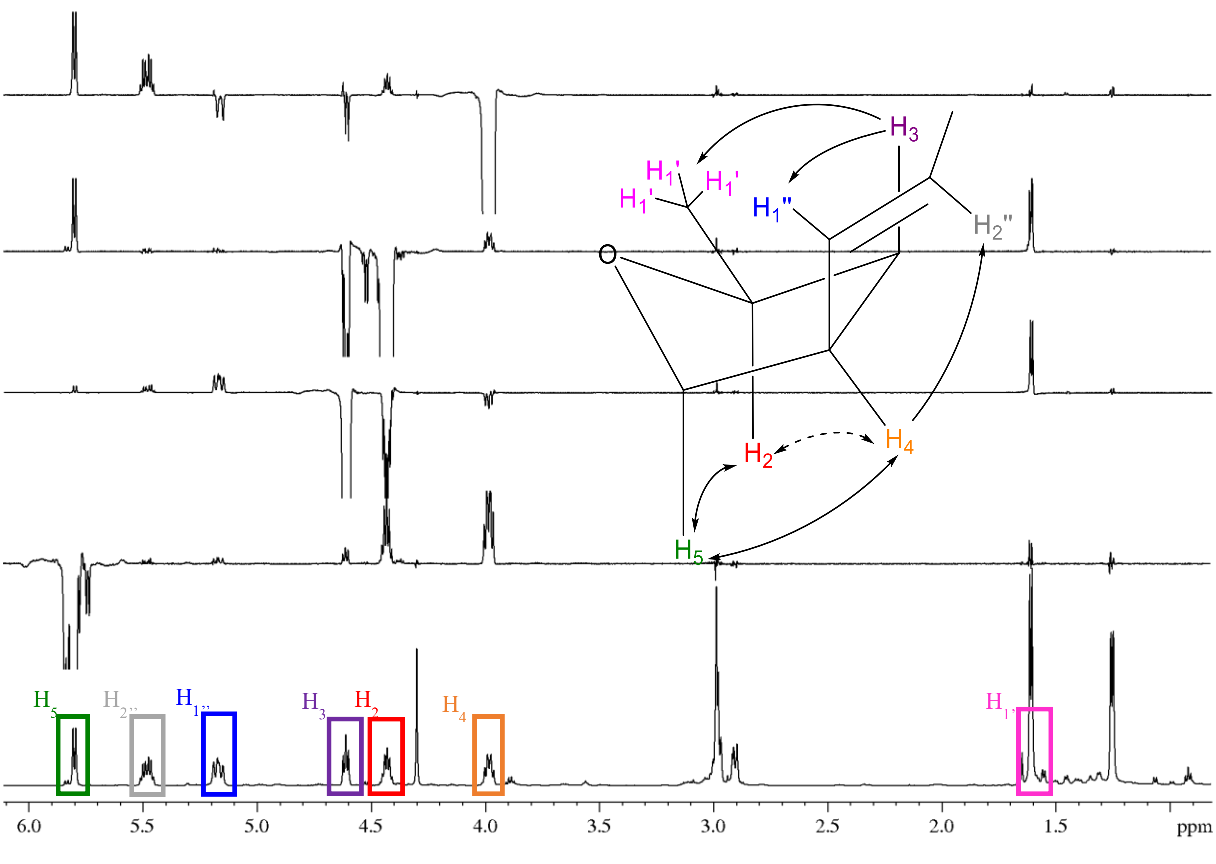




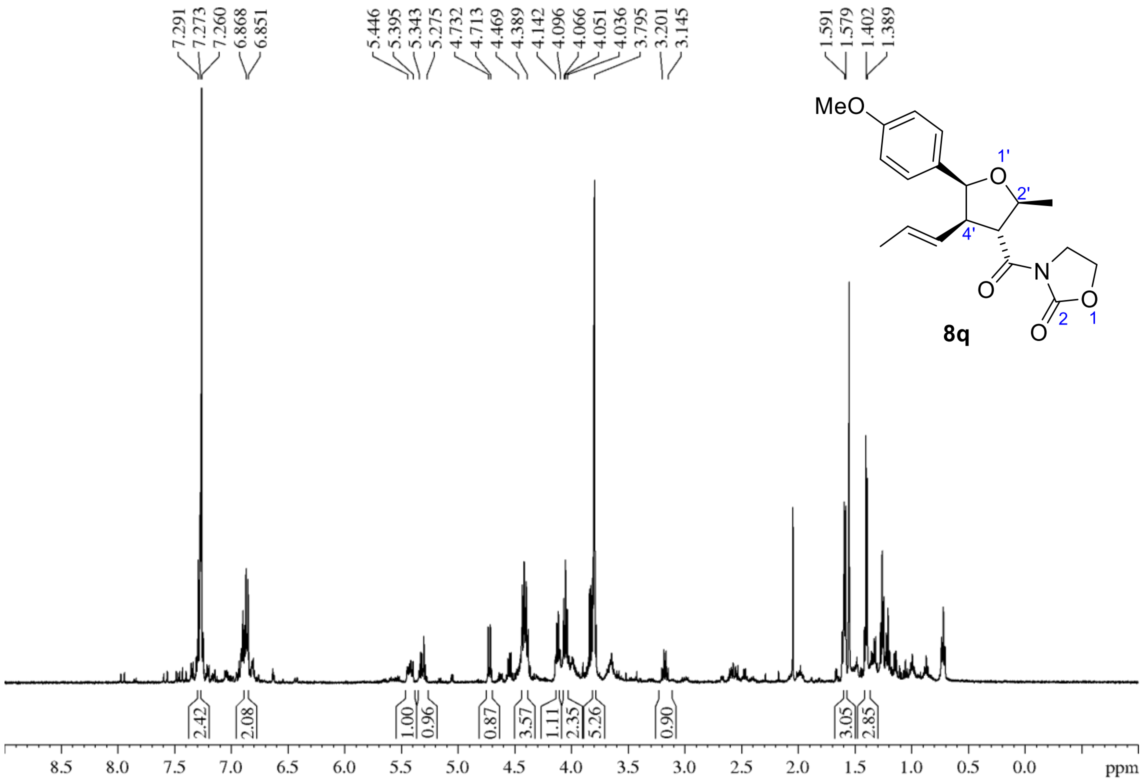
^{1}H-NMR C_6D_6

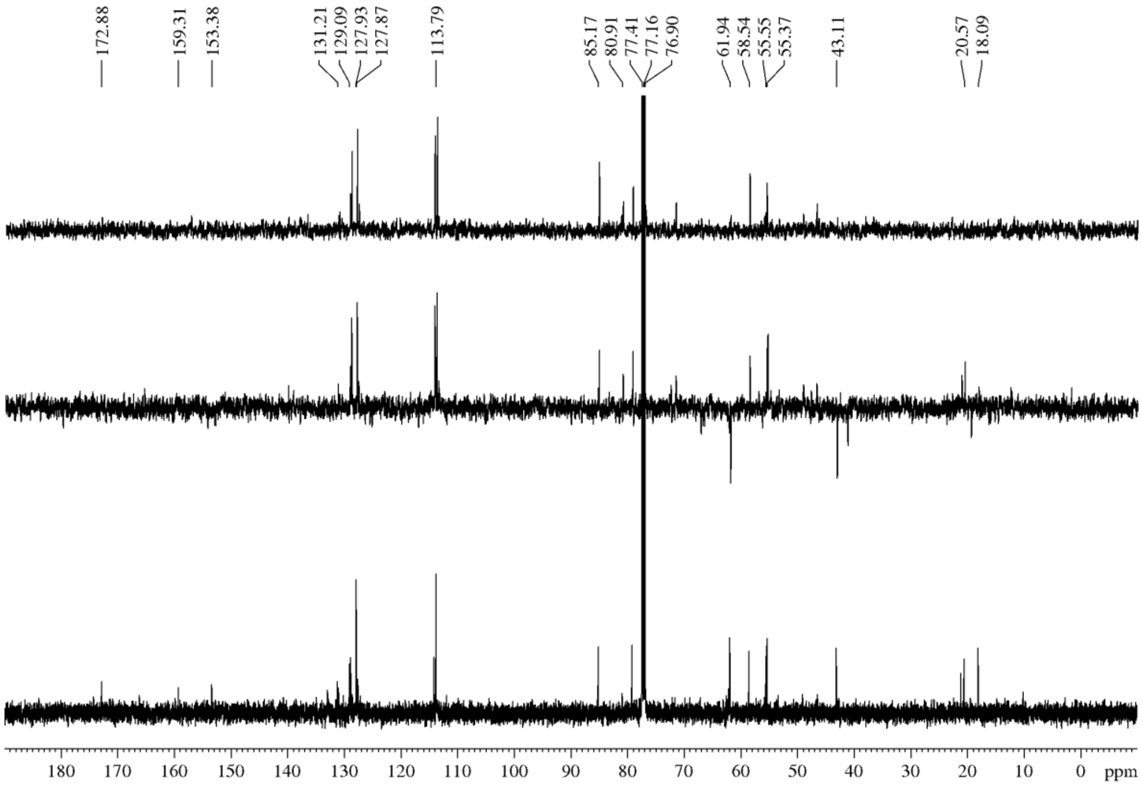


GOESY

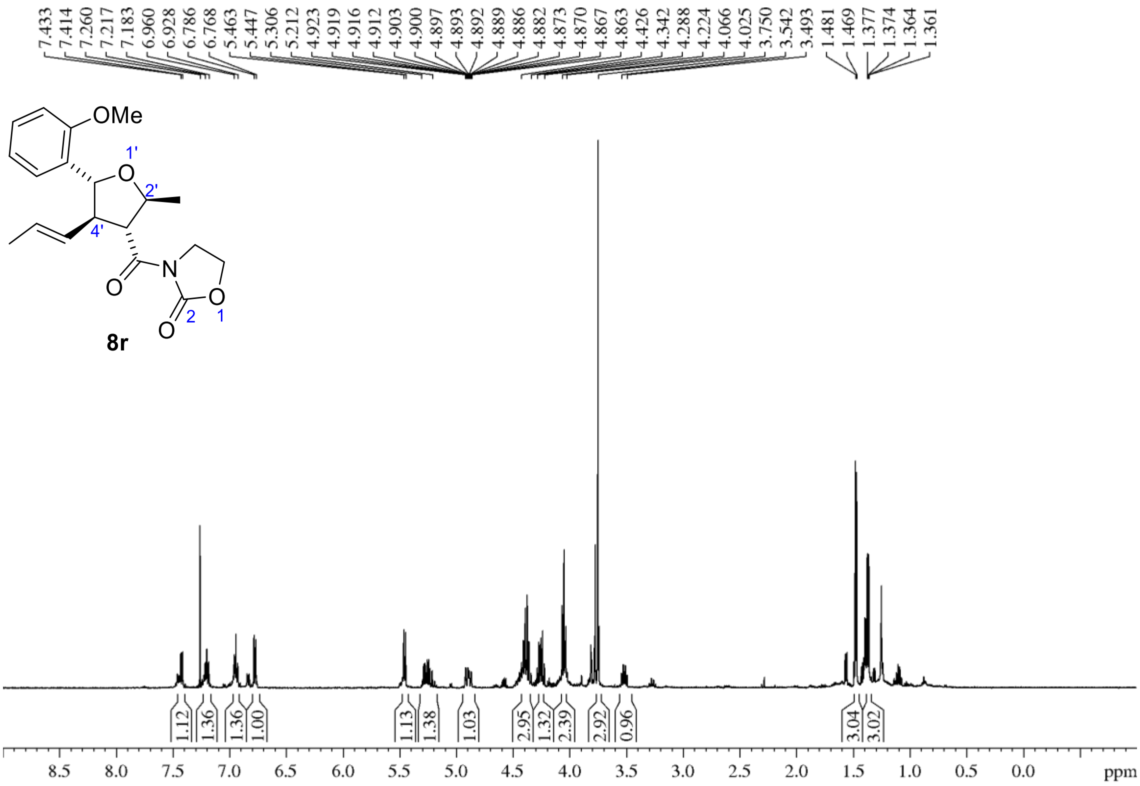


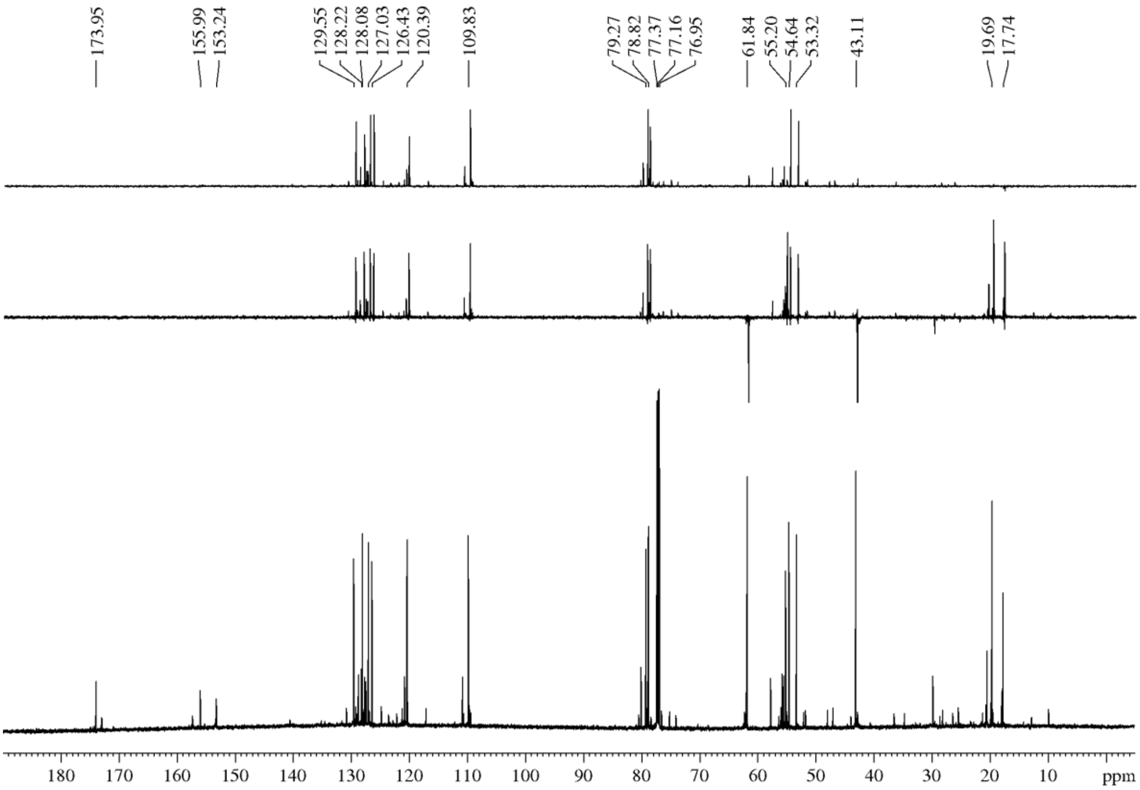
3-((2*S*,3*R*,4*R*,5*S*)-5-(4-methoxyphenyl)-2-methyl-4-((*E*)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (8q)





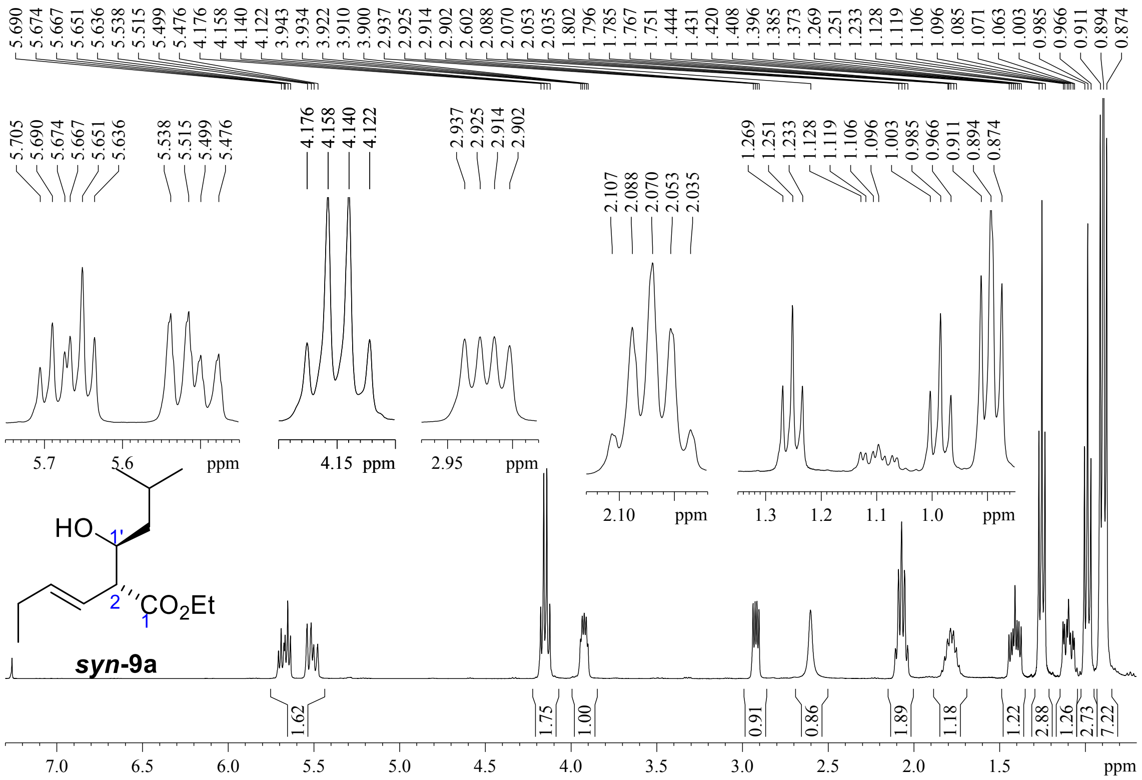
3-((2*S,3*R**,4*R**,5*R**)-5-(2-Methoxyphenyl)-2-methyl-4-((*E*)-prop-1-en-1-yl)tetrahydrofuran-3-carbonyl)oxazolidin-2-one (8r)**

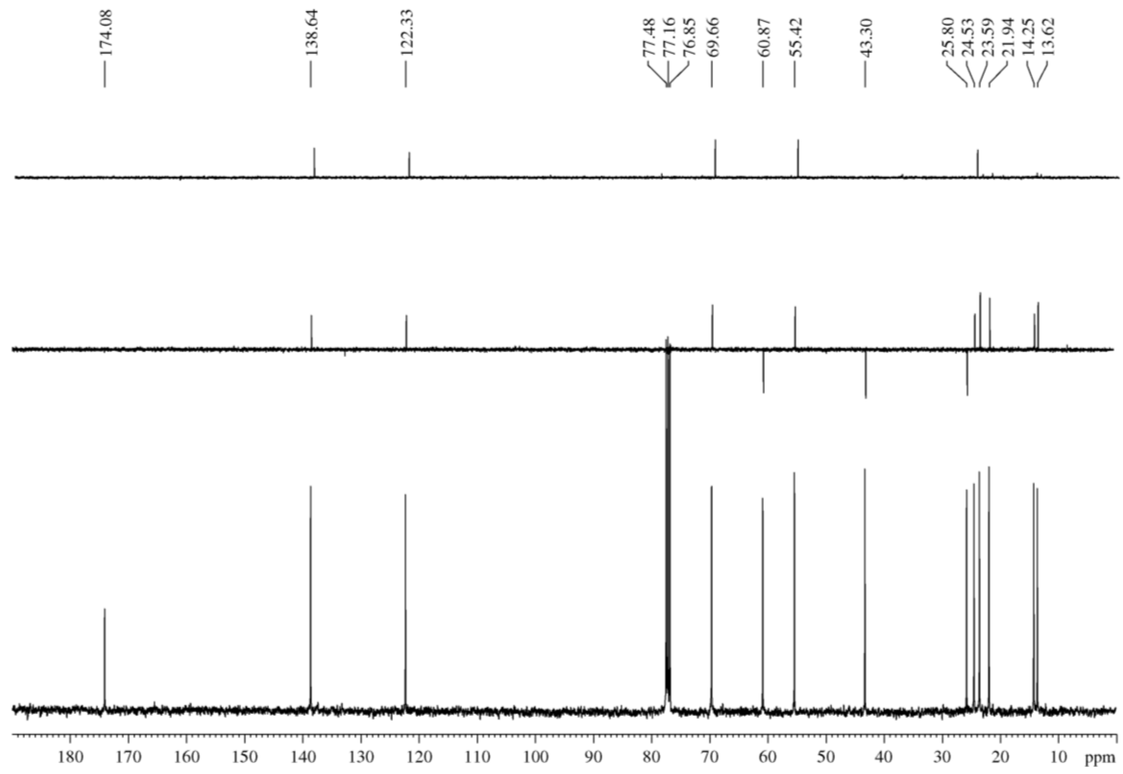




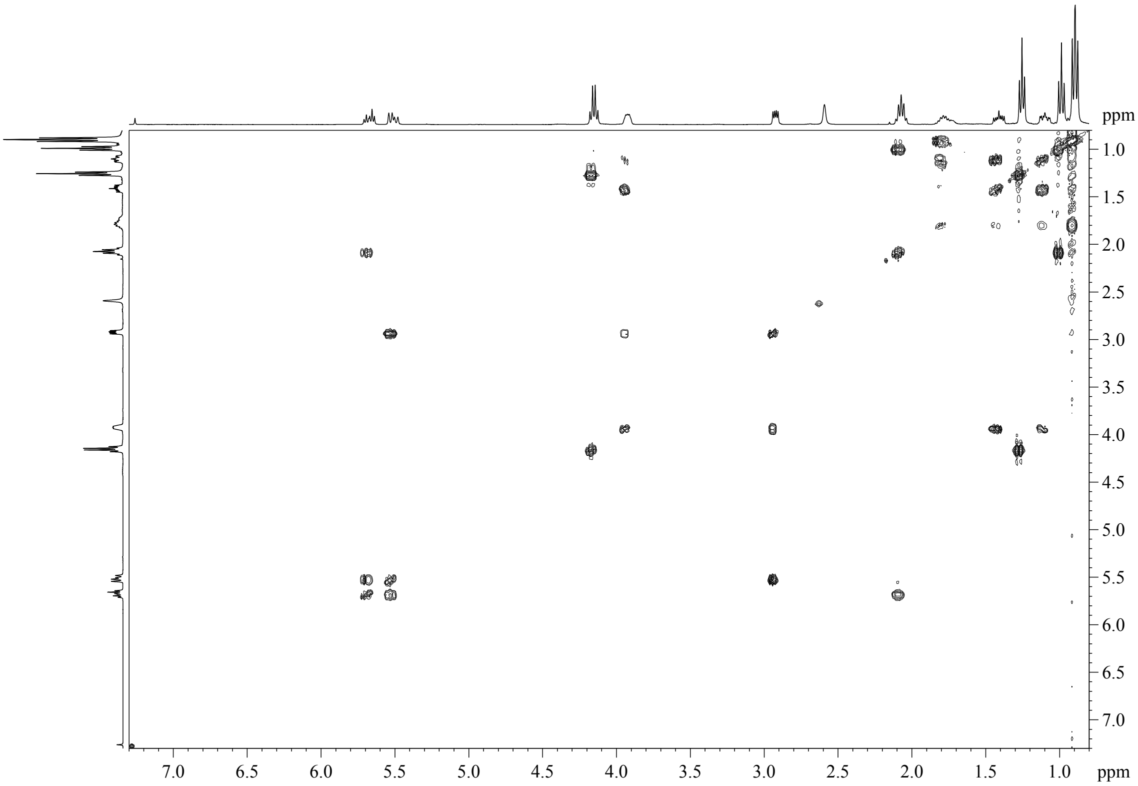
Aldols 9

Ethyl (*R**,*E*)-2-((*S**)-1-hydroxy-3-methylbutyl)hex-3-enoate (*syn*-9a)

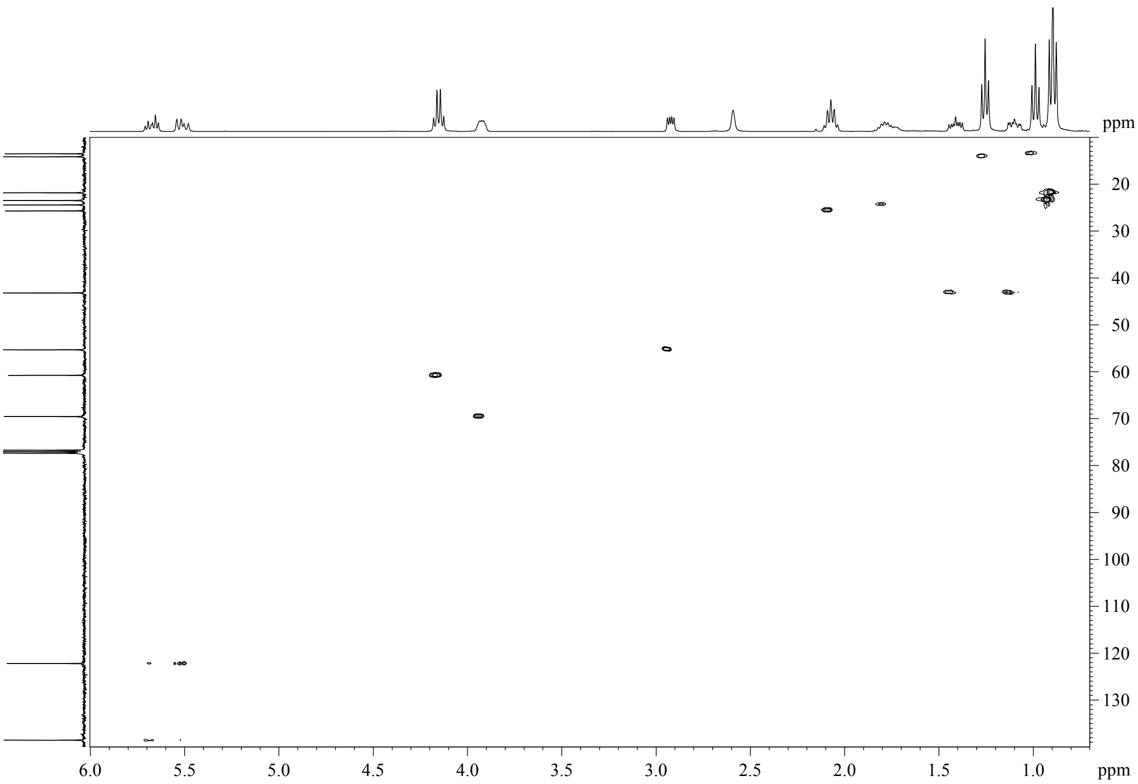




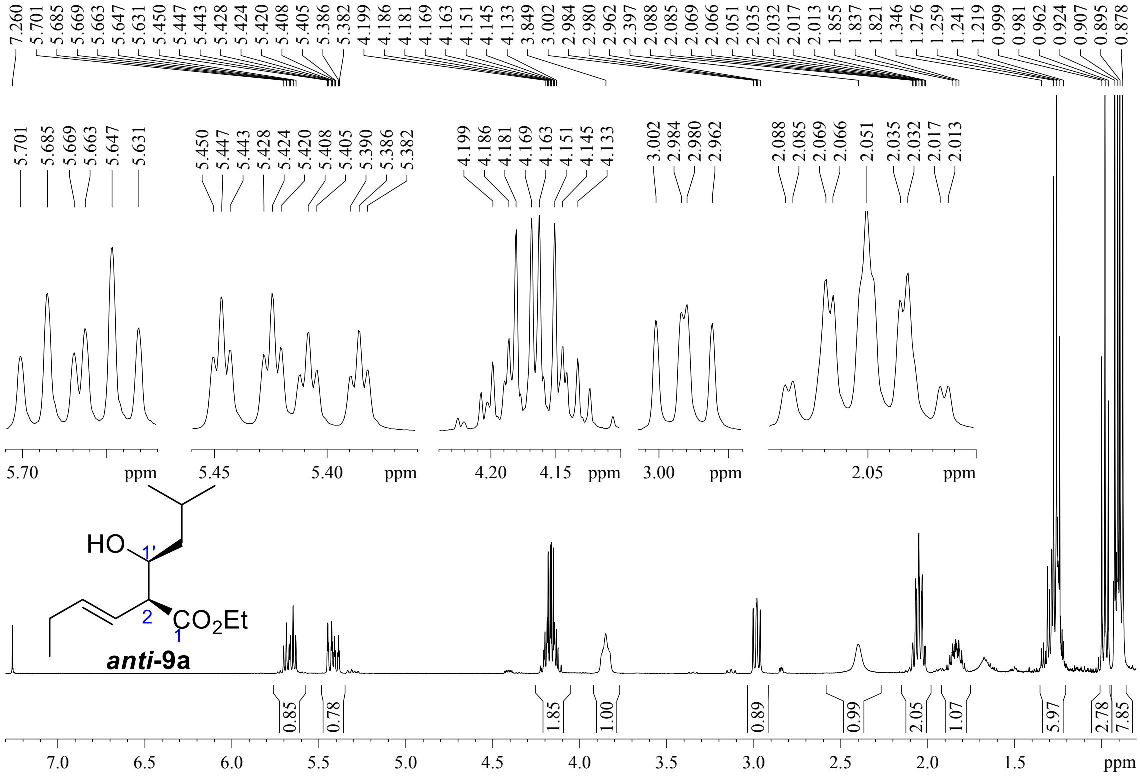
COSY

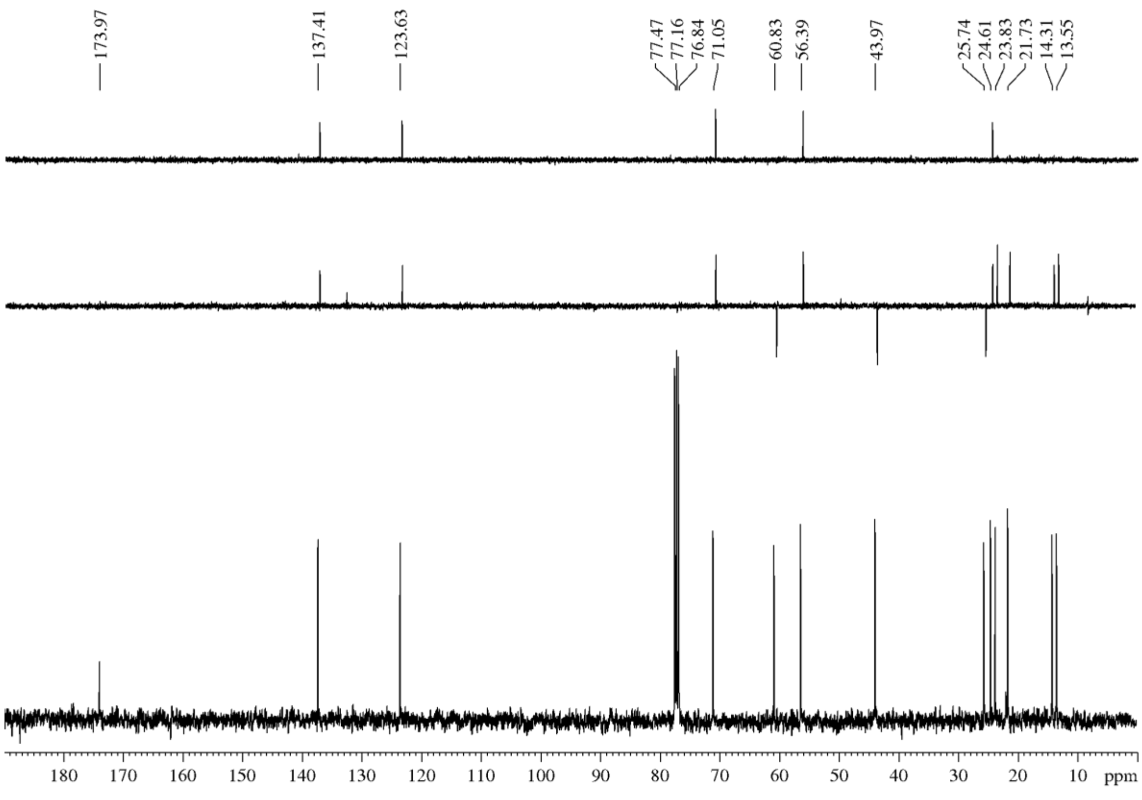

ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

HSQC

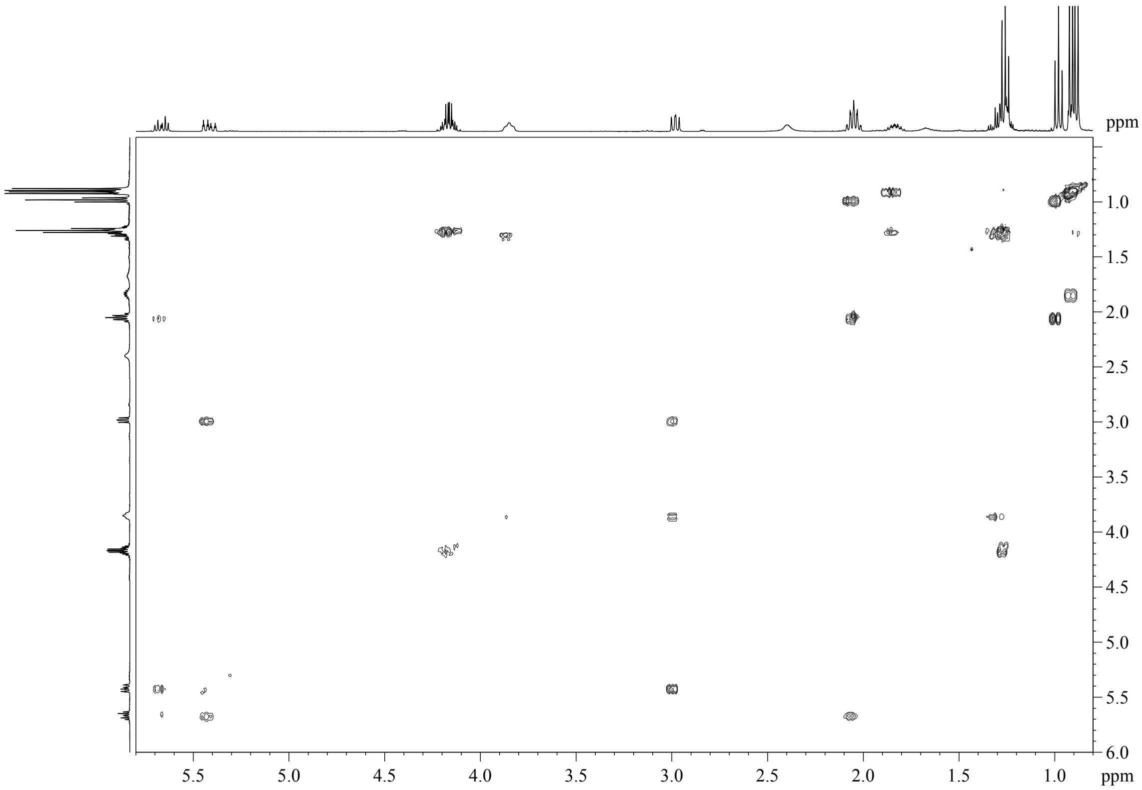

ppm
20
30
40
50
60
70
80
90
100
110
120
130
6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

Ethyl (S*,E)-2-((S*)-1-hydroxy-3-methylbutyl)hex-3-enoate (*anti*-9a)

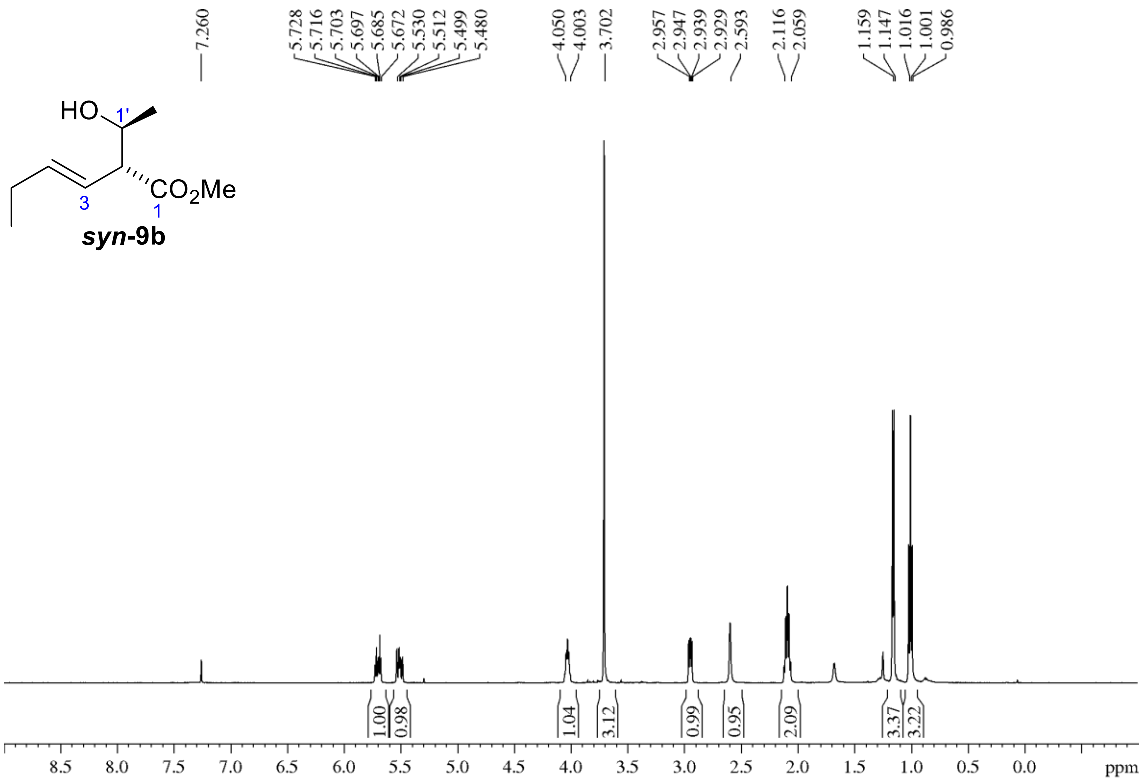


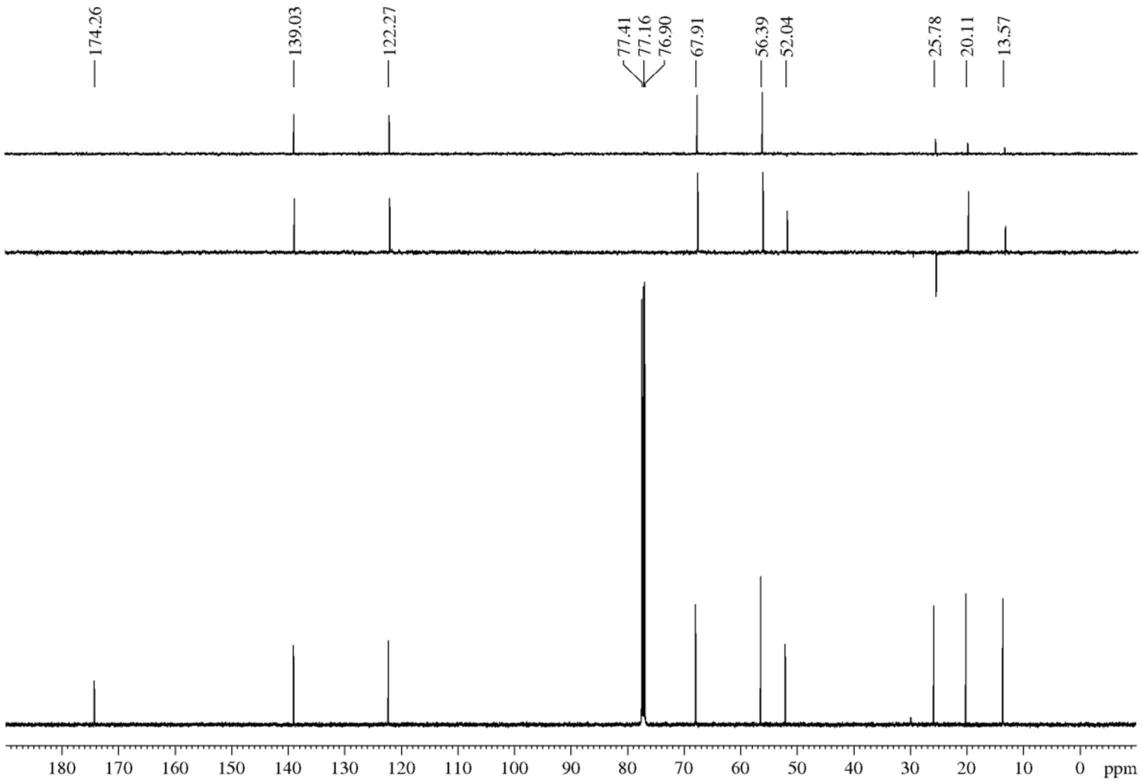


COSY



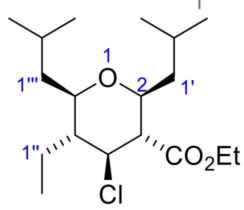
Methyl (*R,*E*)-2-((*S**)-1-hydroxyethyl)hex-3-enoate (*syn*-9b)**



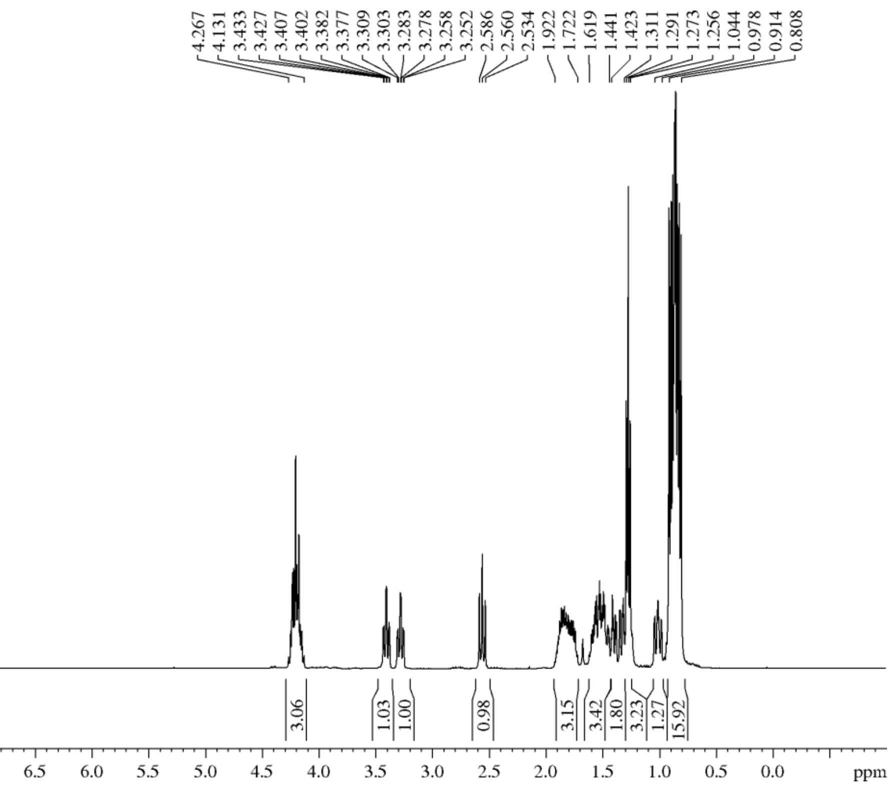


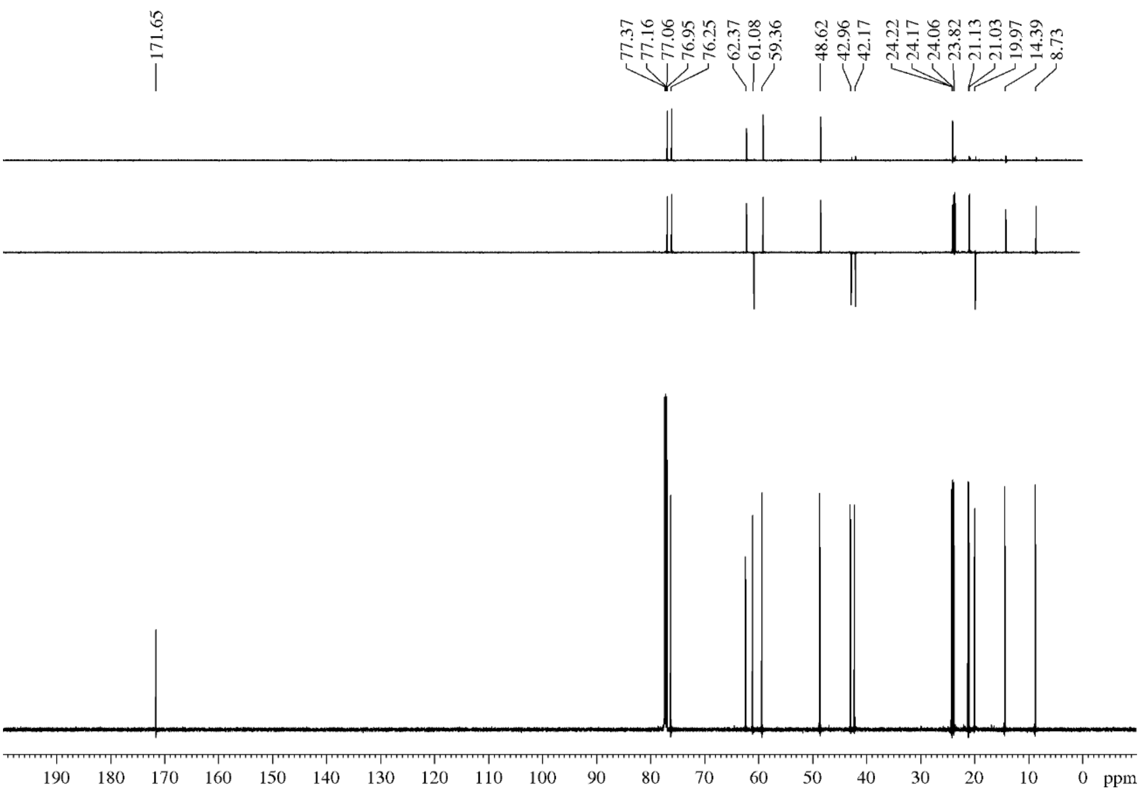
4-halo-2,3,4,5,6-pentasubstituted THPs 10

Ethyl (2*S,3*R**,4*S**,5*R**,6*R**)-4-chloro-5-ethyl-2,6-diisobutyltetrahydro-2*H*-pyran-3-carboxylate (10a)**

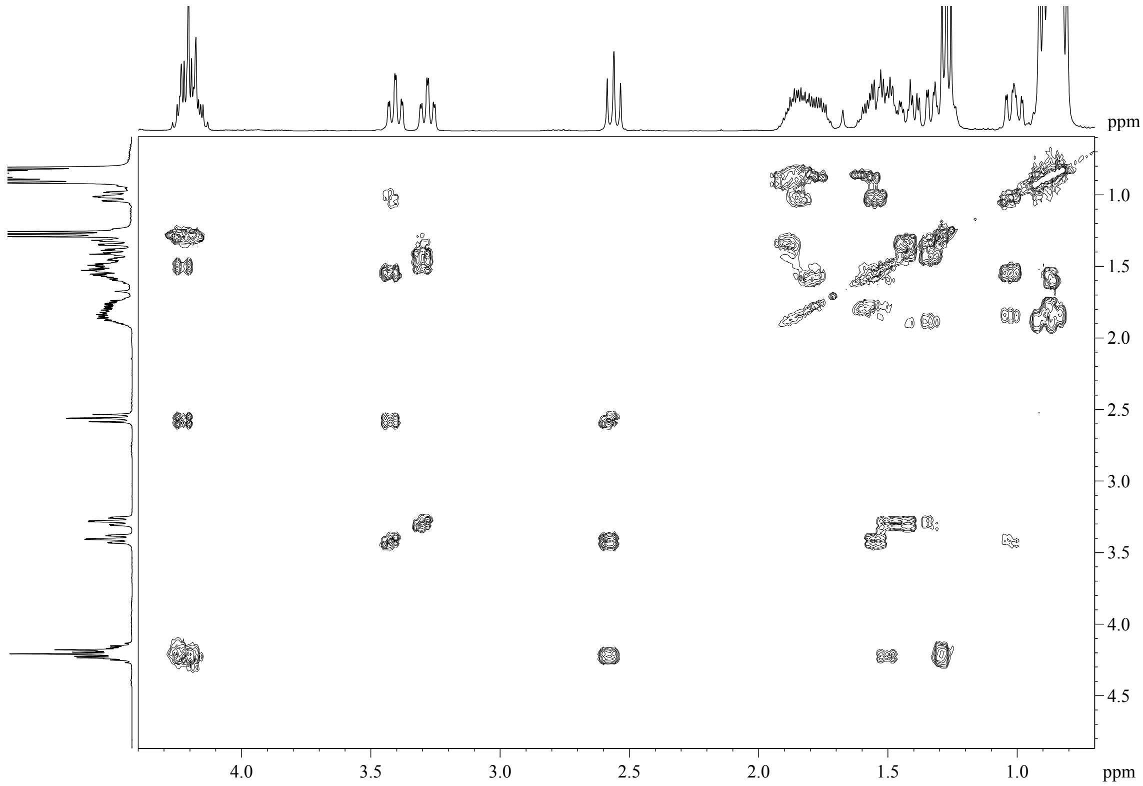


10a



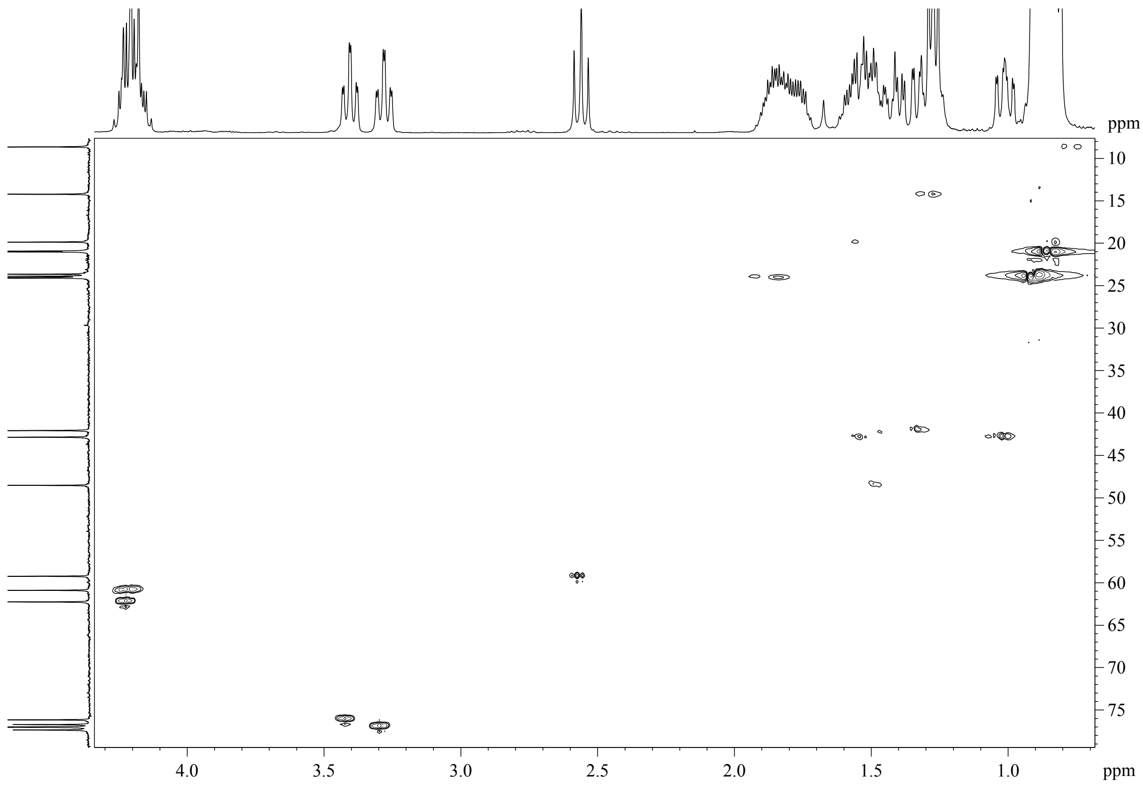


COSY



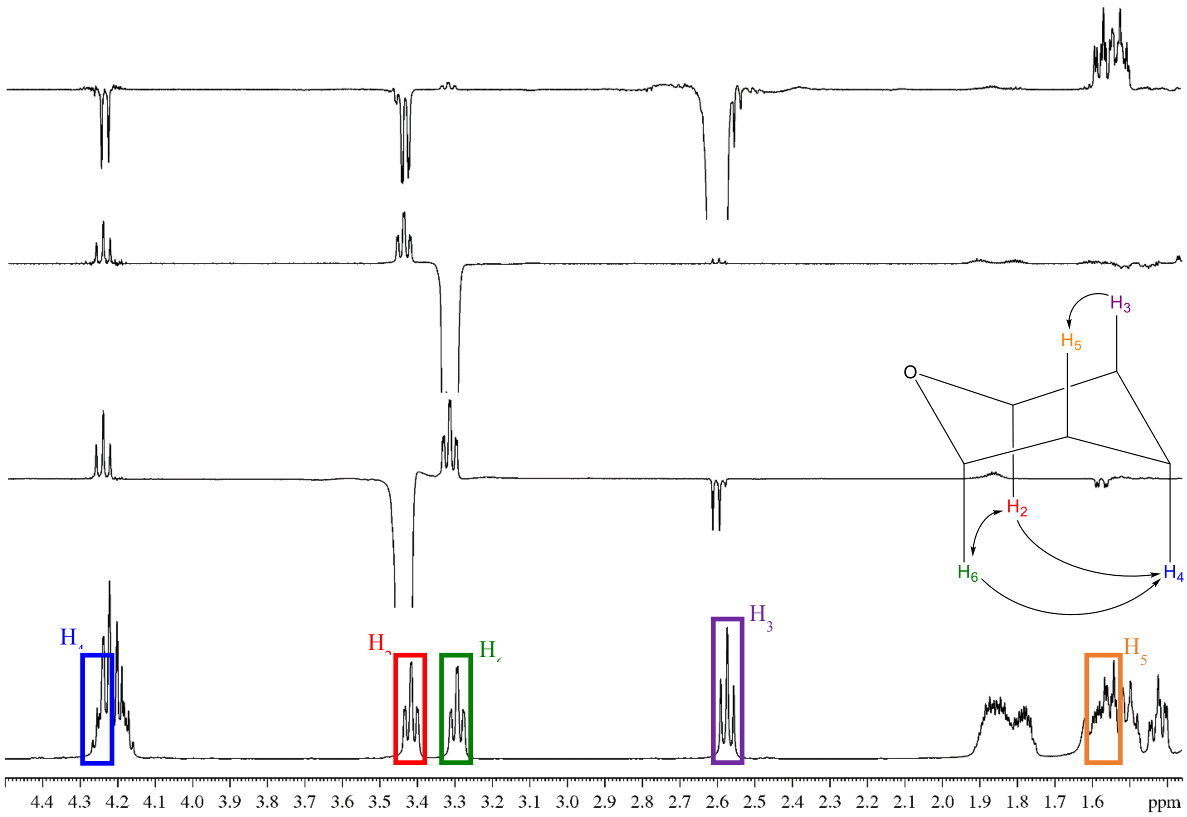
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

HSQC

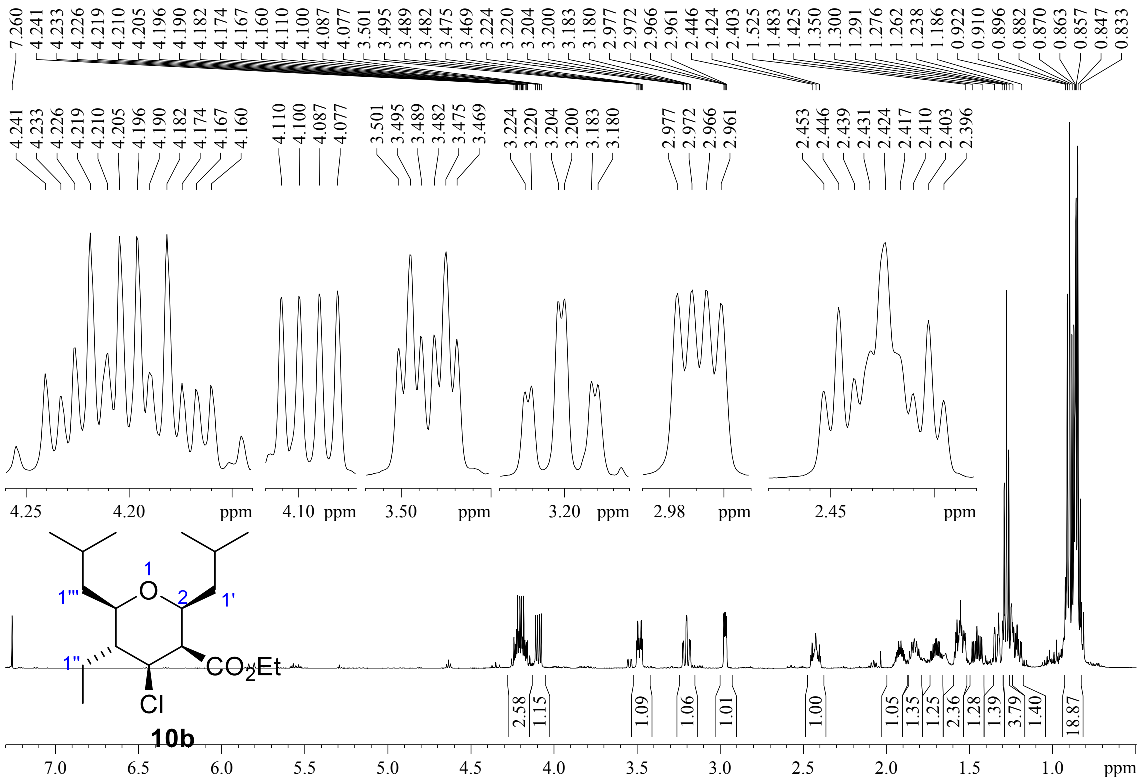


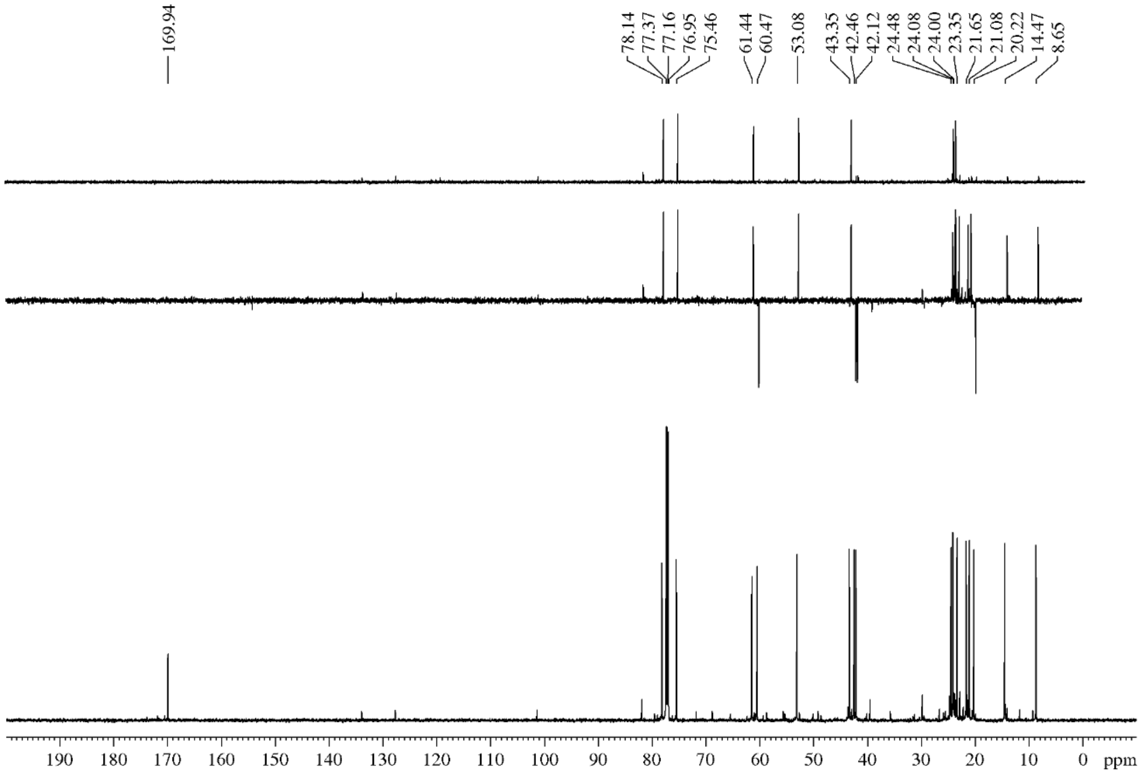
ppm
10
15
20
25
30
35
40
45
50
55
60
65
70
75
4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

GOESY

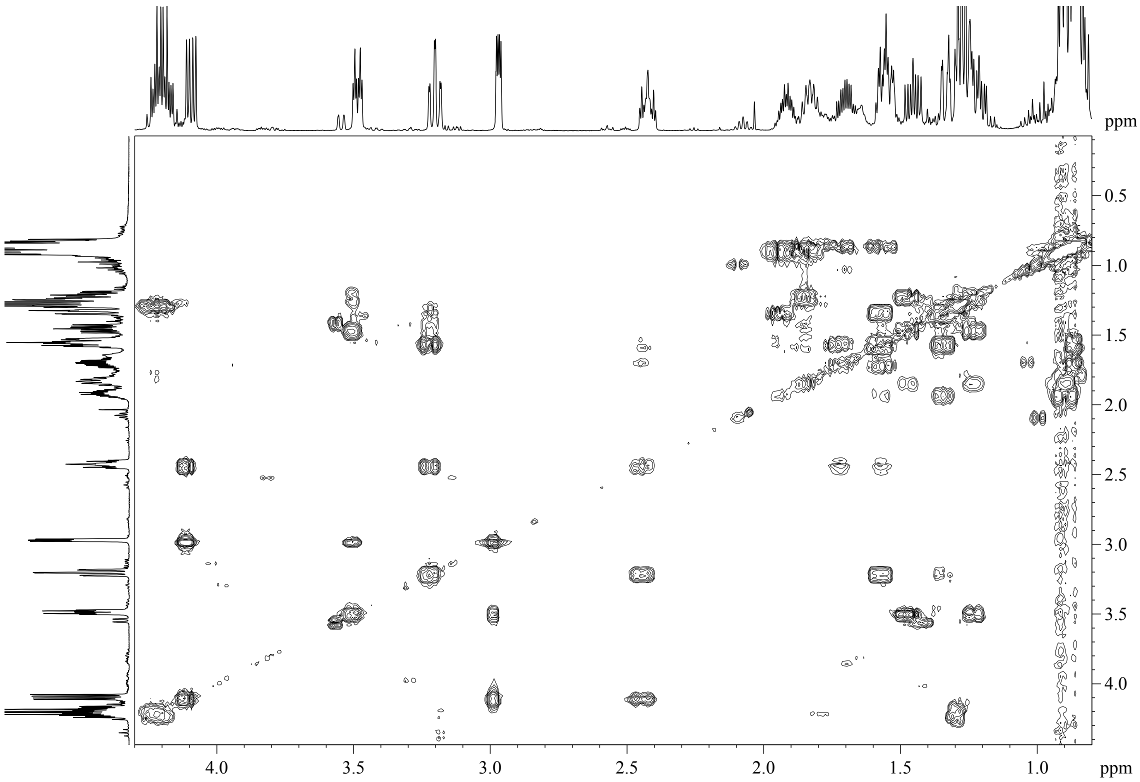

H3
H5
O
H2
H6
H4
H4
H2
H6
H3
H5
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 ppm

Ethyl (2*S,3*S**,4*S**,5*R**,6*R**)-4-chloro-5-ethyl-2,6-diisobutyltetrahydro-2*H*-pyran-3-carboxylate (10b)**

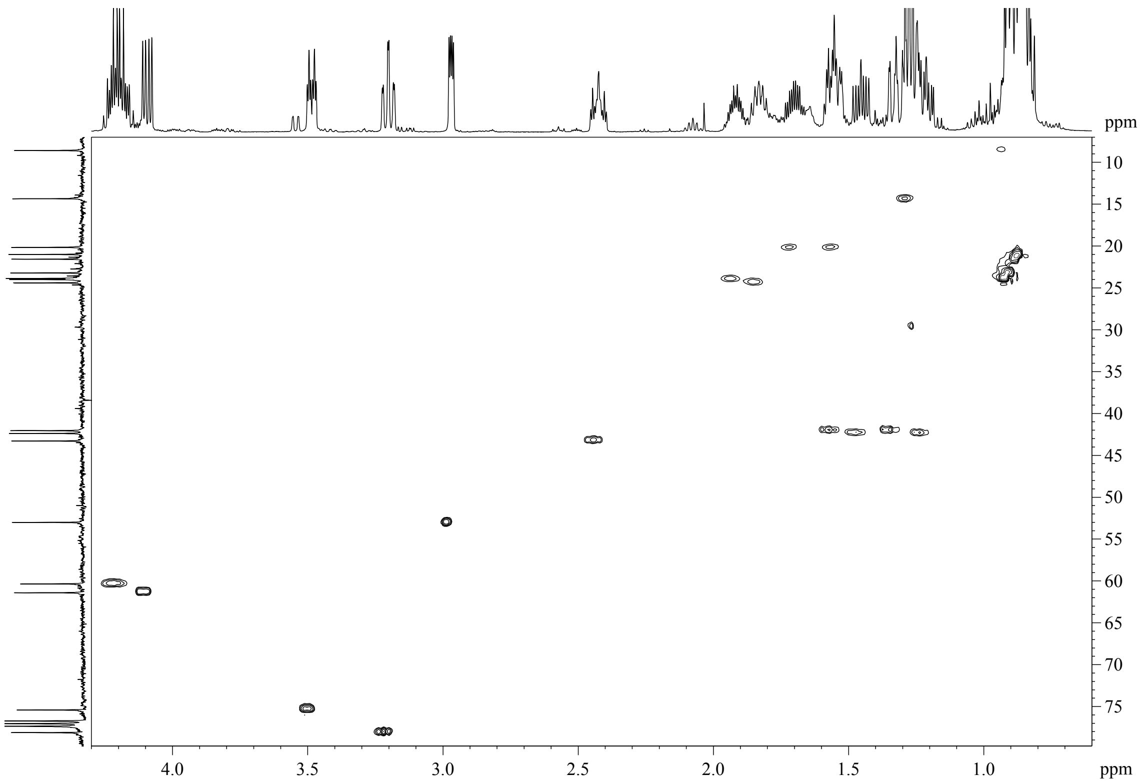




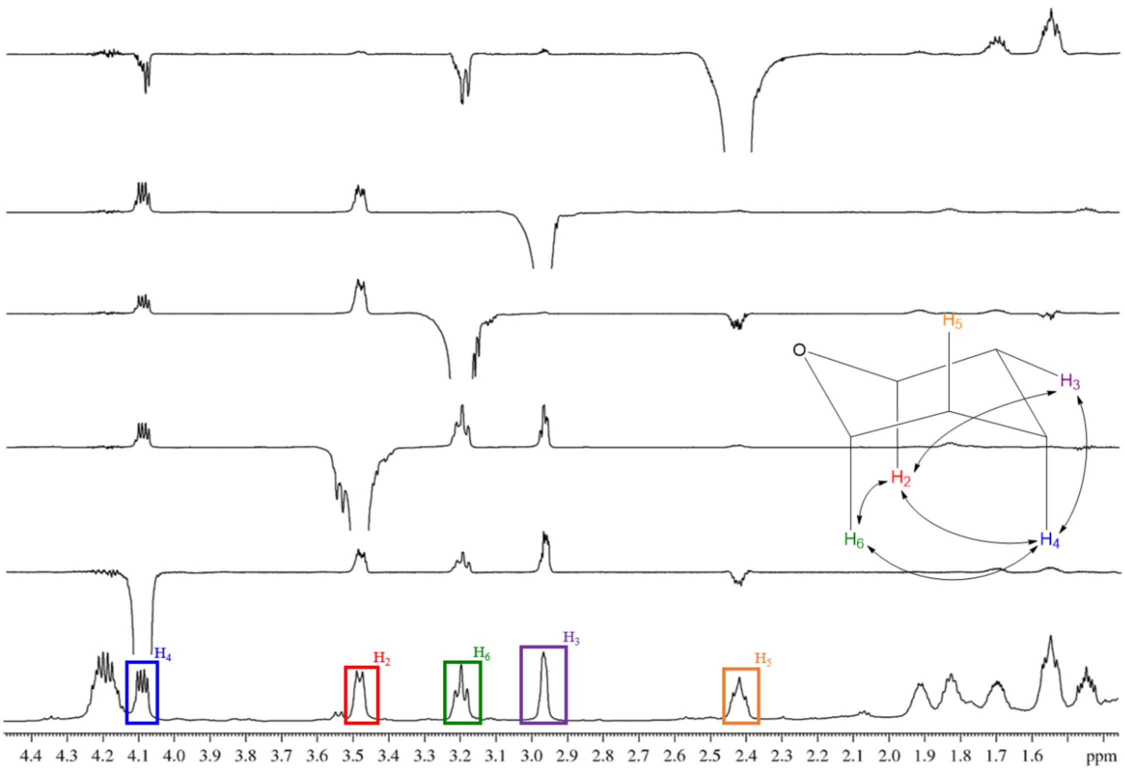
COSY


ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

HSQC

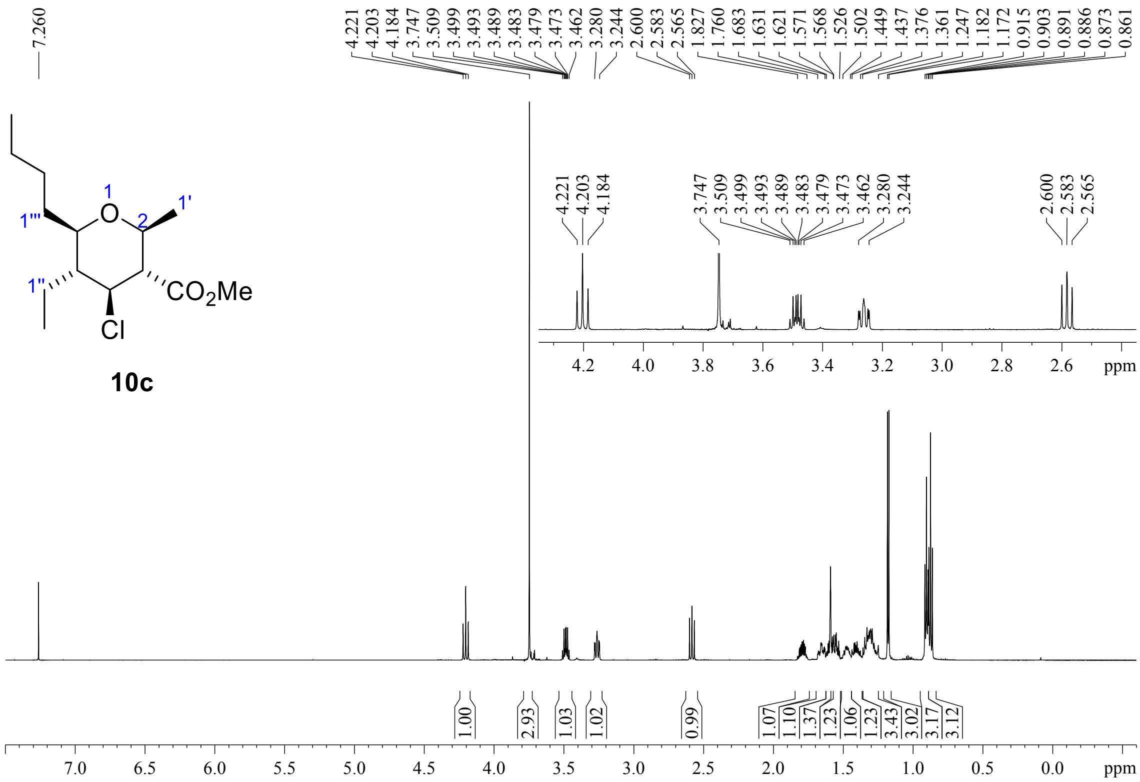

ppm
10
15
20
25
30
35
40
45
50
55
60
65
70
75
4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

GOESY

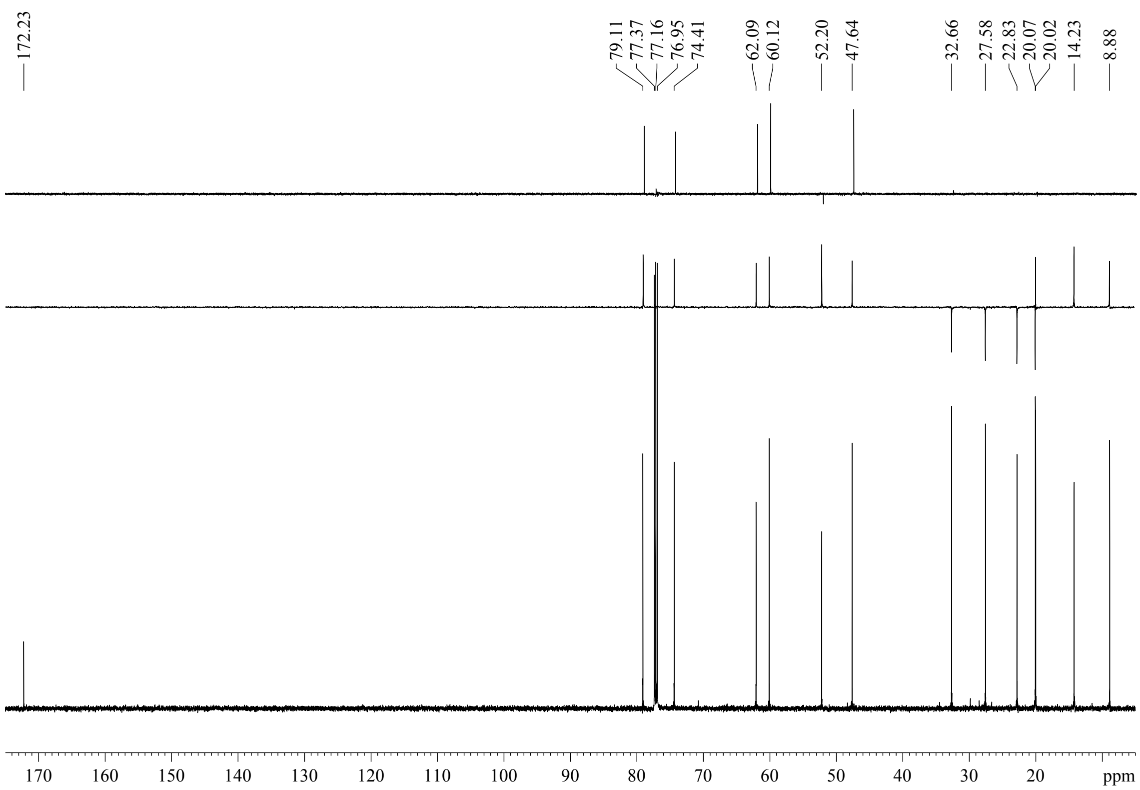


H5
O
H3
H2
H6
H4
H4
H2
H6
H3
H5
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 ppm

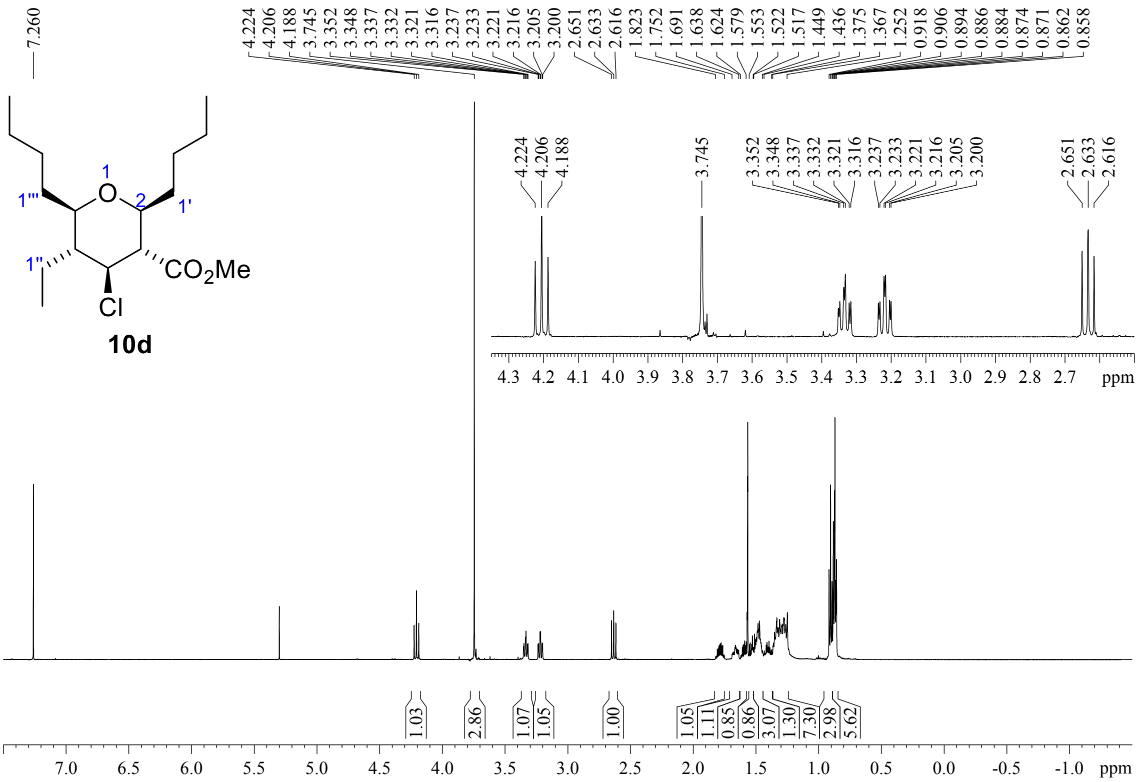
Methyl (2*S,3*R**,4*S**,5*R**,6*R**)-6-butyl-4-chloro-5-ethyl-2-methyltetrahydro-2*H*-pyran-3-carboxylate (10c)**

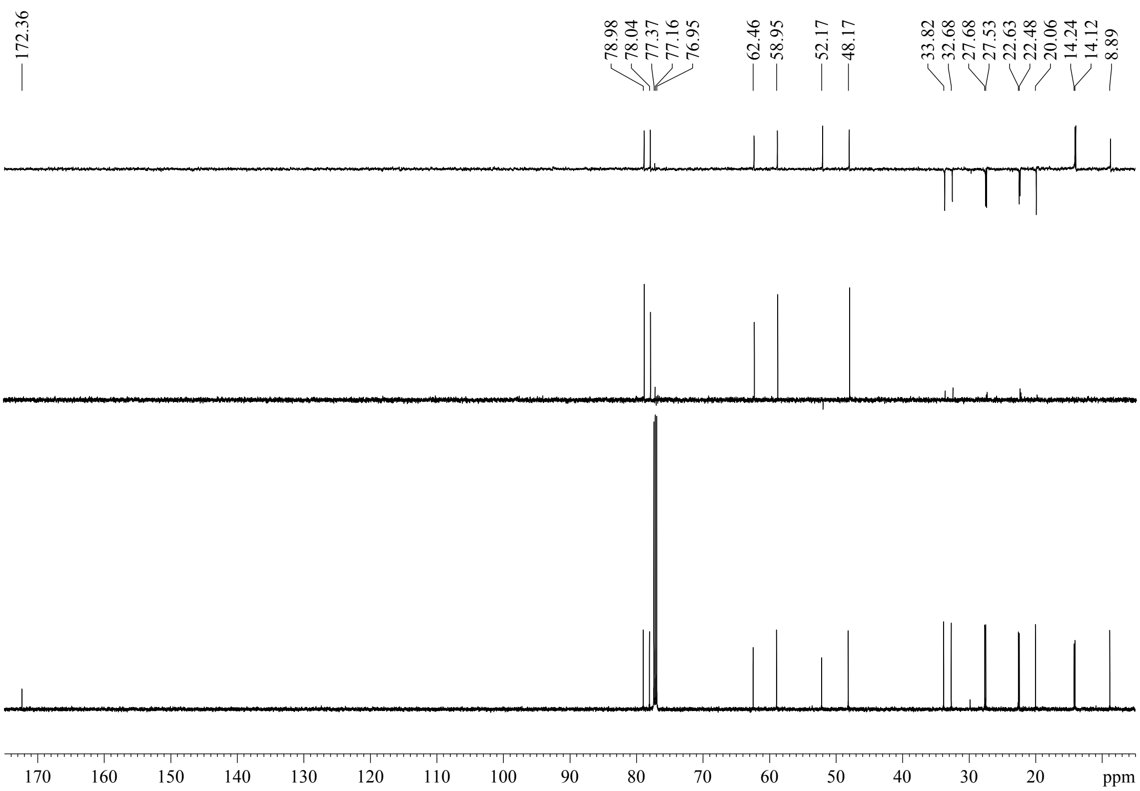


10c

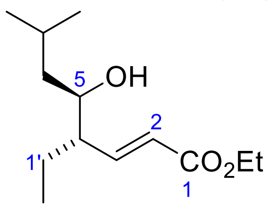


Methyl (2*S,3*R**,4*S**,5*R**,6*R**)-2,6-dibutyl-4-chloro-5-ethyltetrahydro-2*H*-pyran-3-carboxylate (10d)**

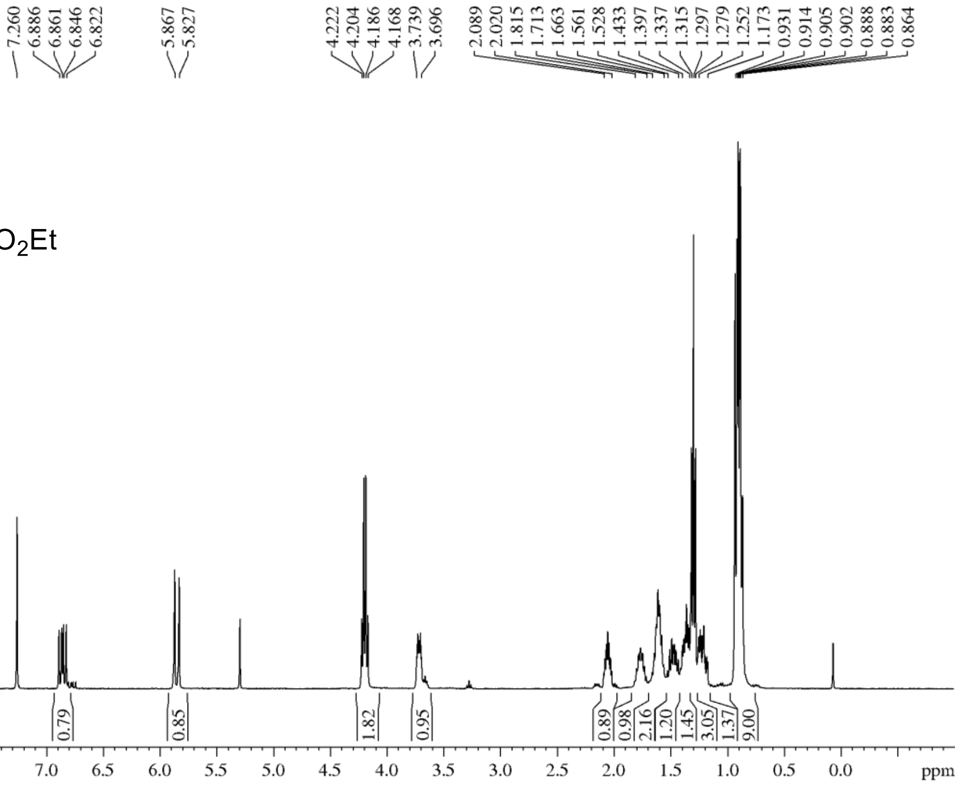


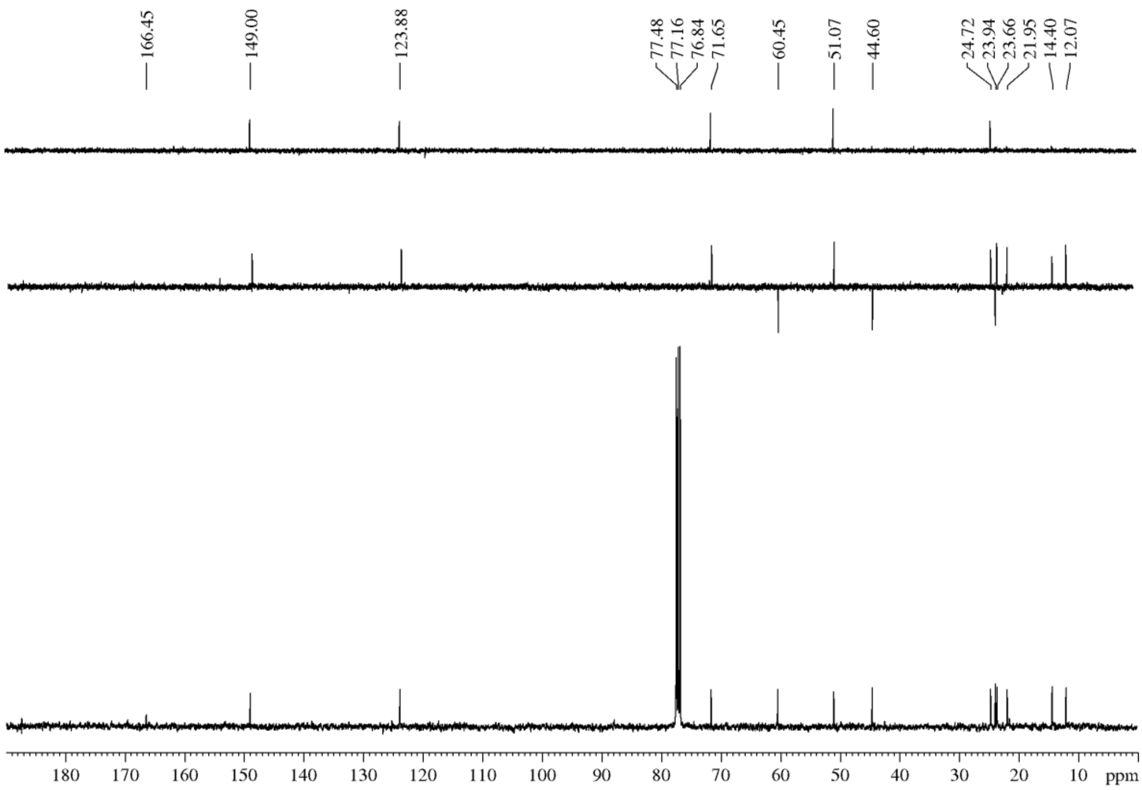


Ethyl (4*S**,5*R**,*E*)-4-ethyl-5-hydroxy-7-methyloct-2-enoate (11)

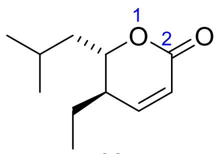


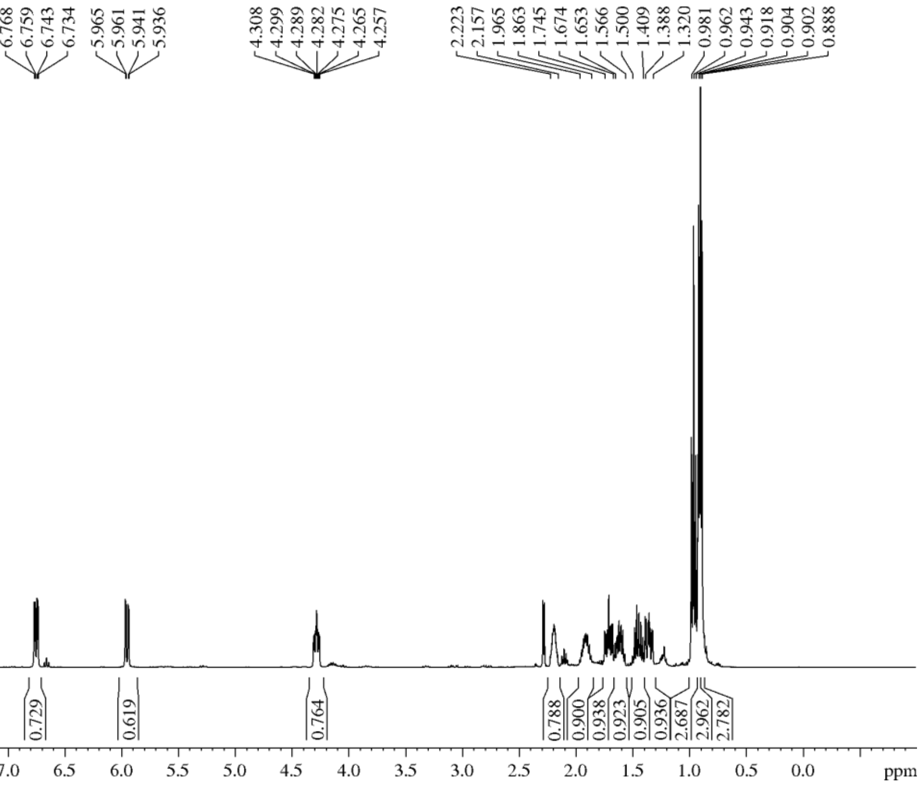
11

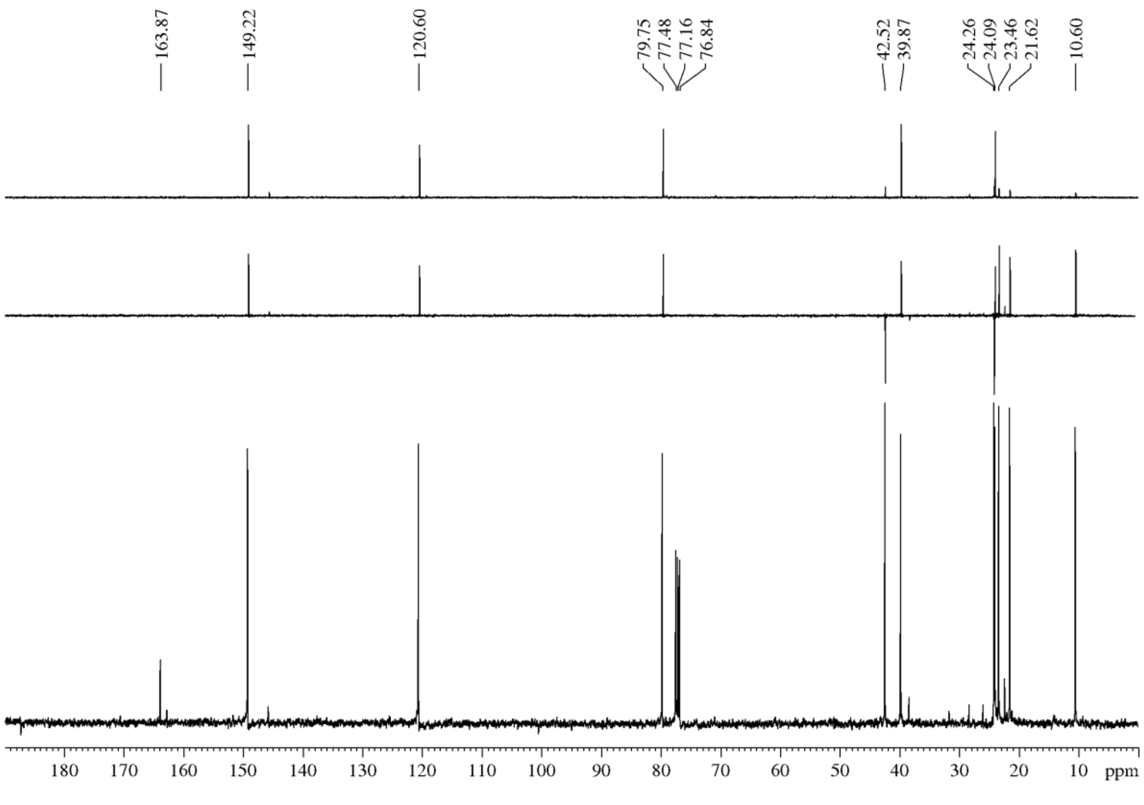




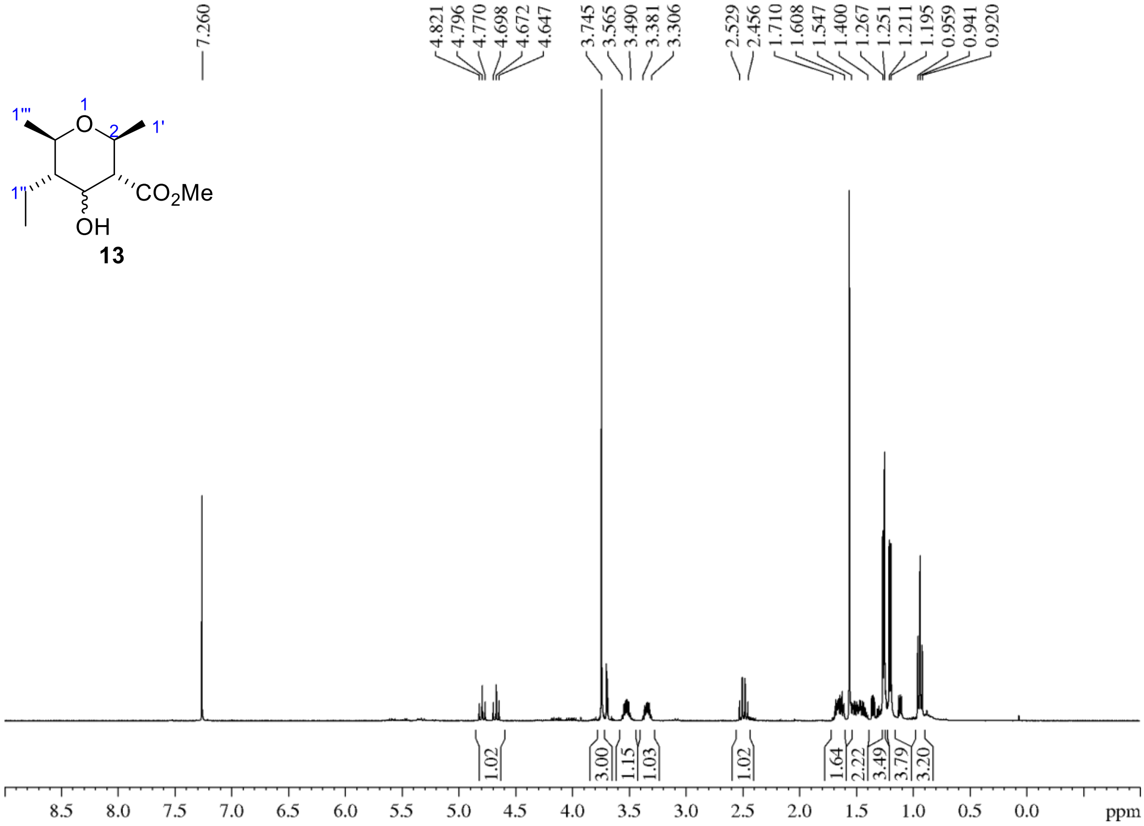
(5*R**,6*S**)-5-Ethyl-6-isobutyl-5,6-dihydro-2*H*-pyran-2-one (12)

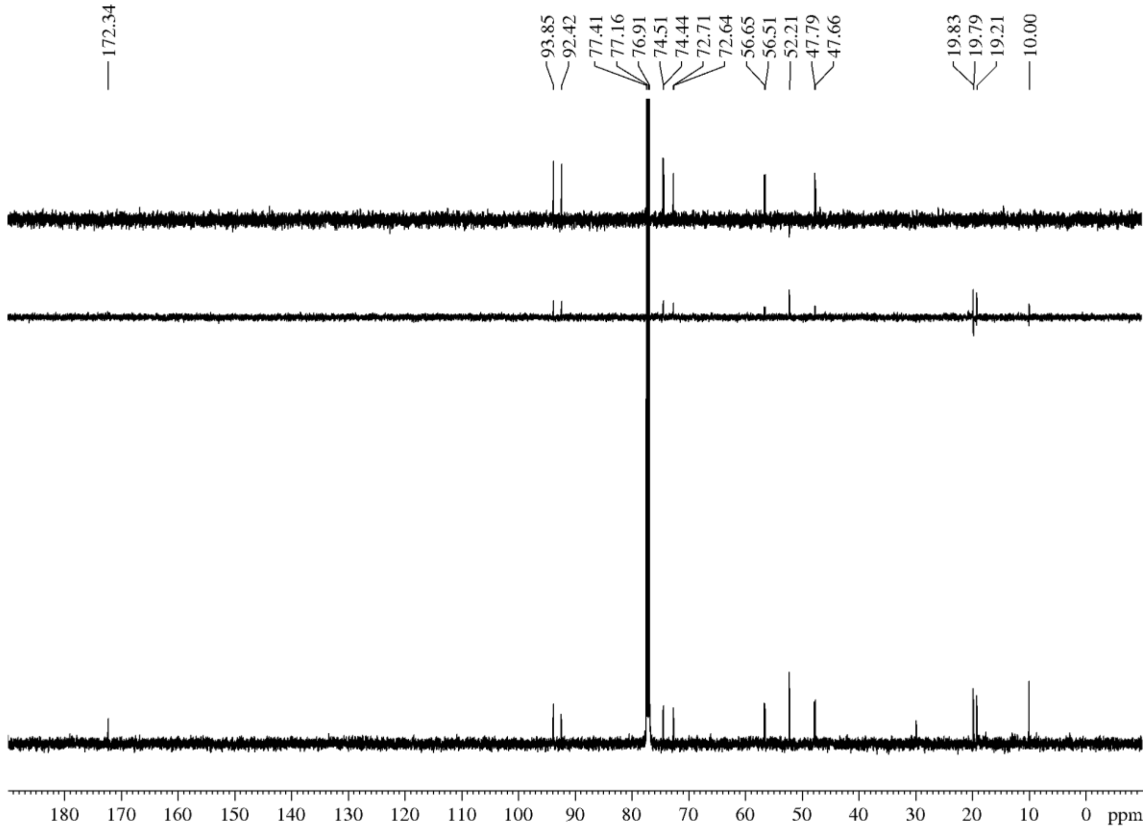






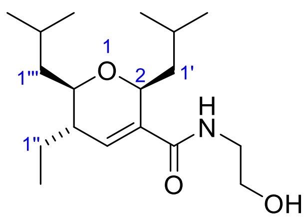
Methyl (2*S,3*R**,5*S**,6*R**)-5-ethyl-4-hydroxy-2,6-dimethyltetrahydro-2*H*-pyran-3-carboxylate (13)**



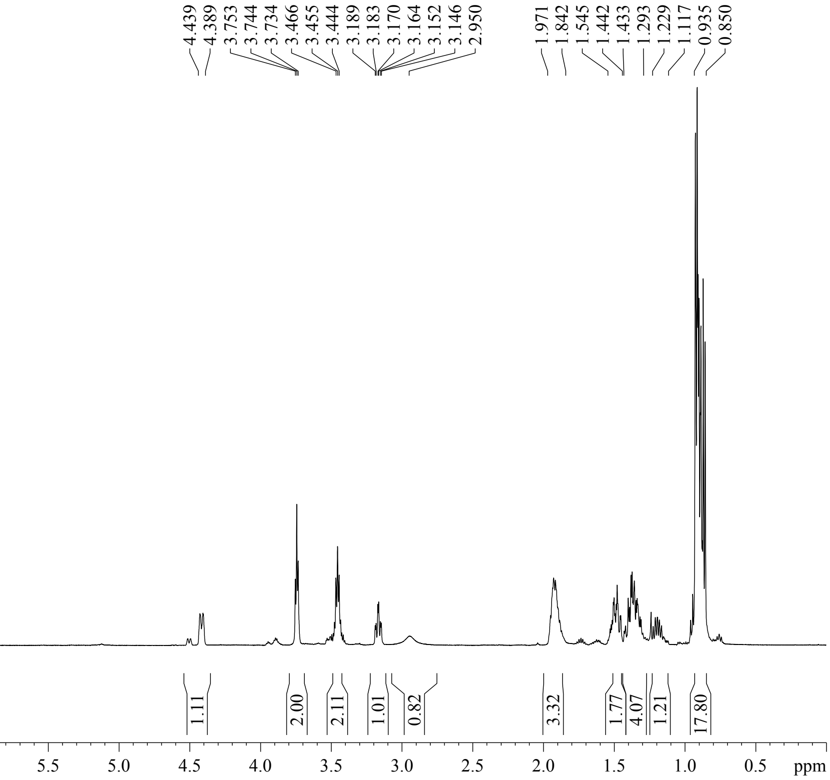


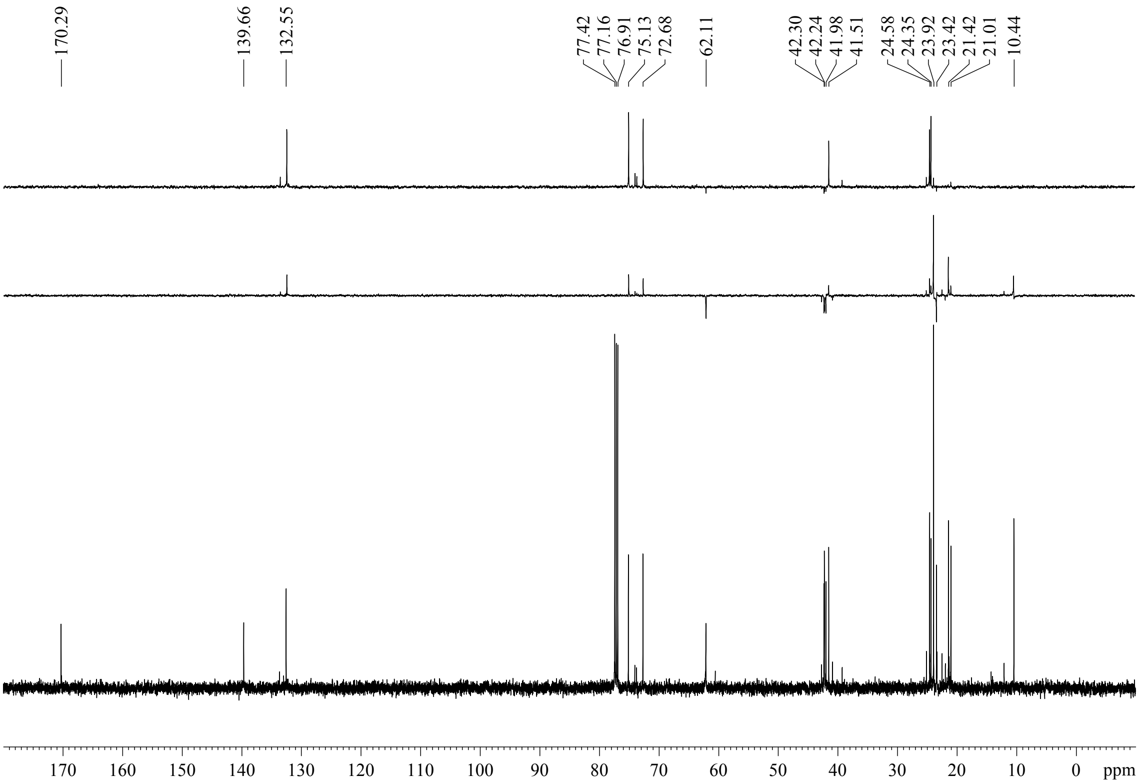
172.34
93.85
92.42
77.41
77.16
76.91
74.51
74.44
72.71
72.64
56.65
56.51
52.21
47.79
47.66
19.83
19.79
19.21
10.00
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

(2*S,5*S**,6*R**)-5-Ethyl-*N*-(2-hydroxyethyl)-2,6-diisobutyl-5,6-dihydro-2*H*-pyran-3-carboxamide (14)**[5]

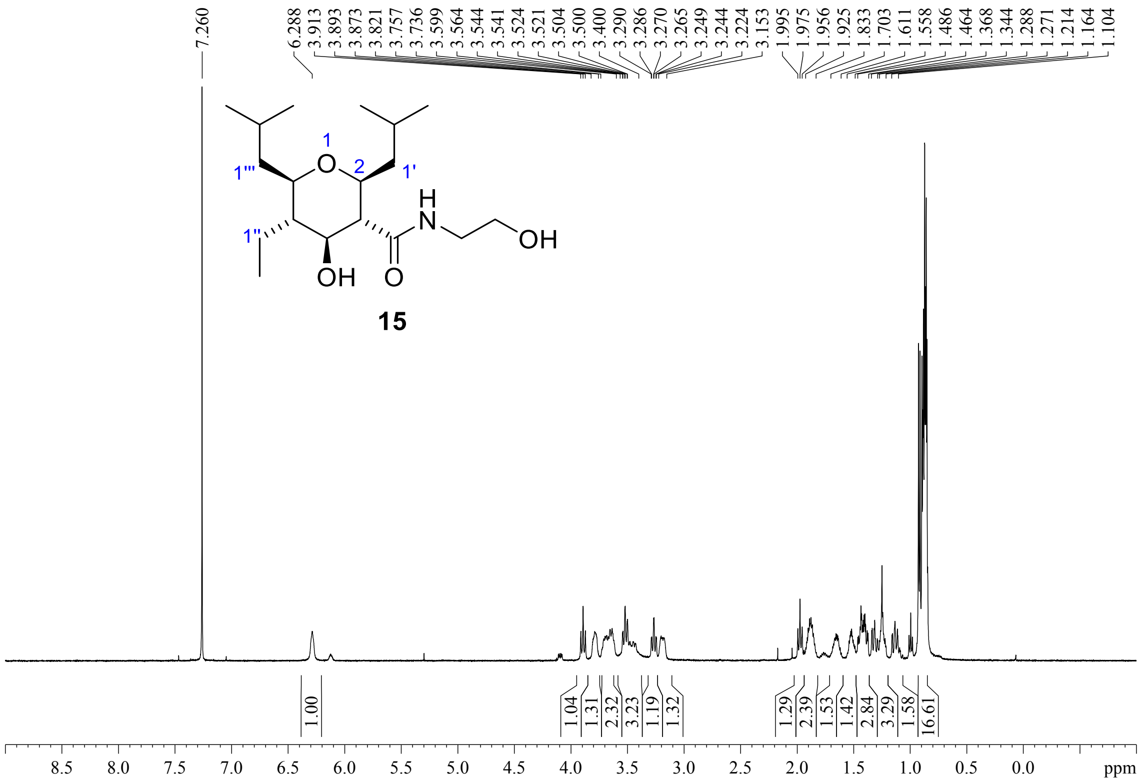


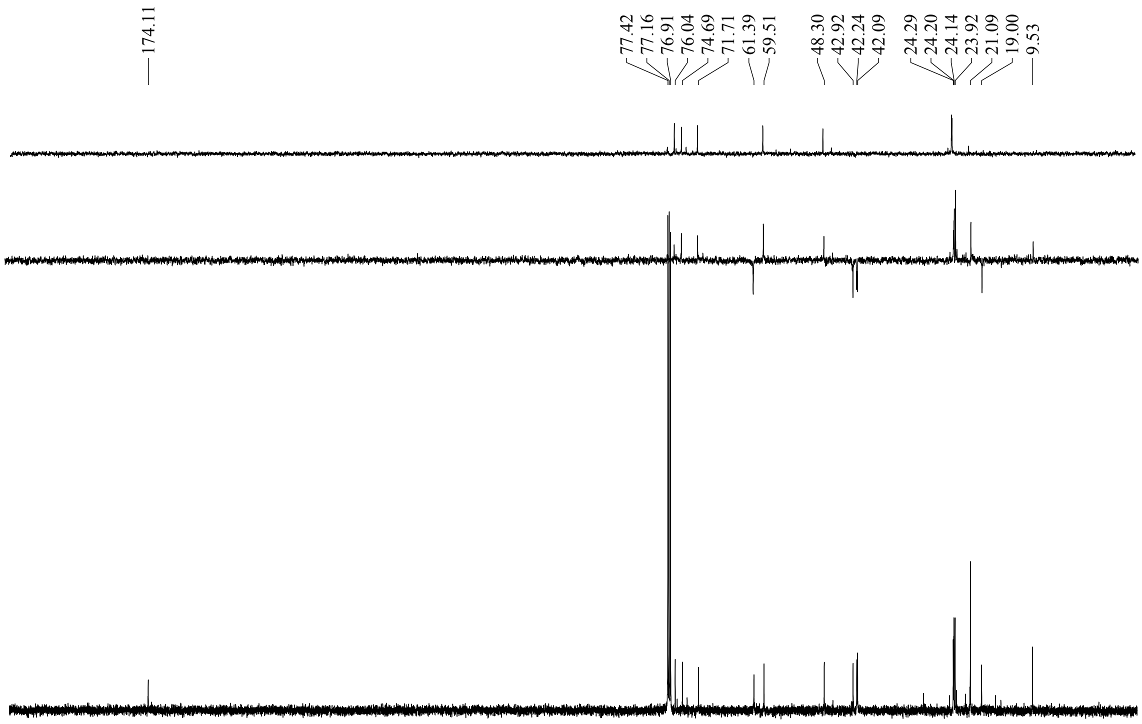
14





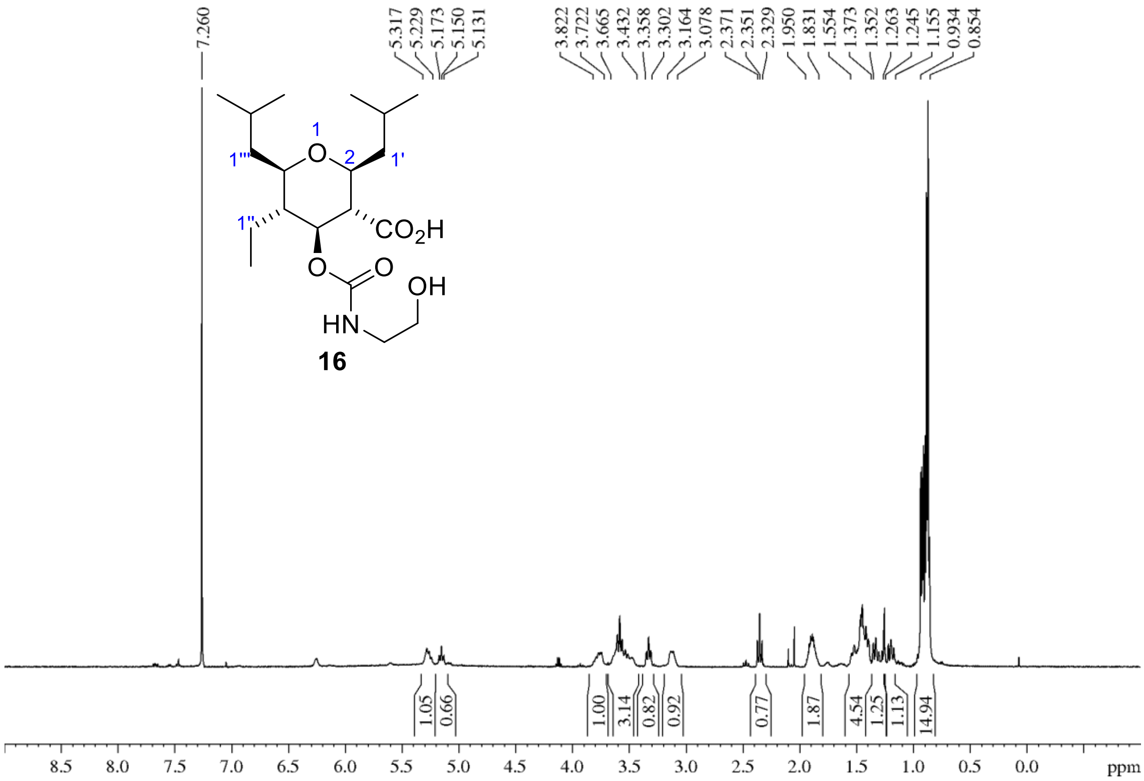
(2*S,3*R**,4*S**,5*S**,6*R**)-5-Ethyl-4-hydroxy-*N*-(2-hydroxyethyl)-2,6-diisobutyltetrahydro-2*H*-pyran-3-carboxamide (15)**

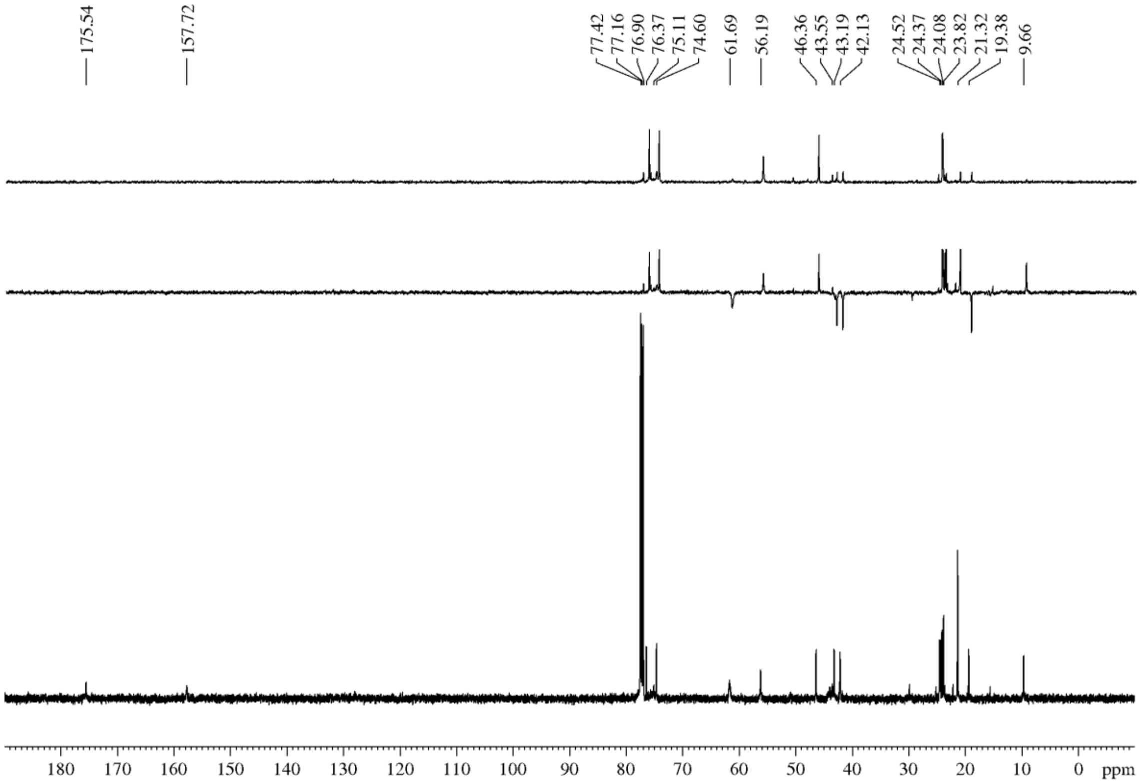




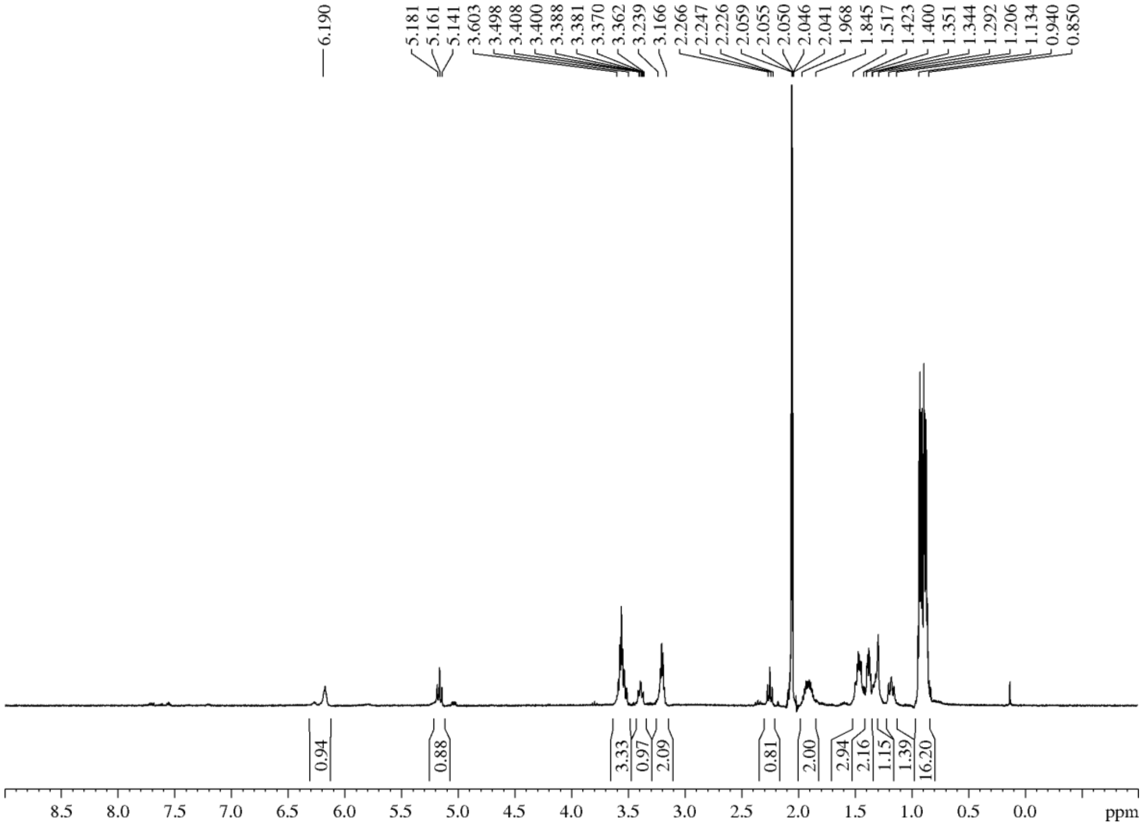
(2*S,3*S**,4*S**,5*R**,6*R**)-5-Ethyl-4-(((2-hydroxyethyl)carbamoyl)oxy)-2,6-diisobutyltetrahydro-2*H*-pyran-3-carboxylic acid (16)**

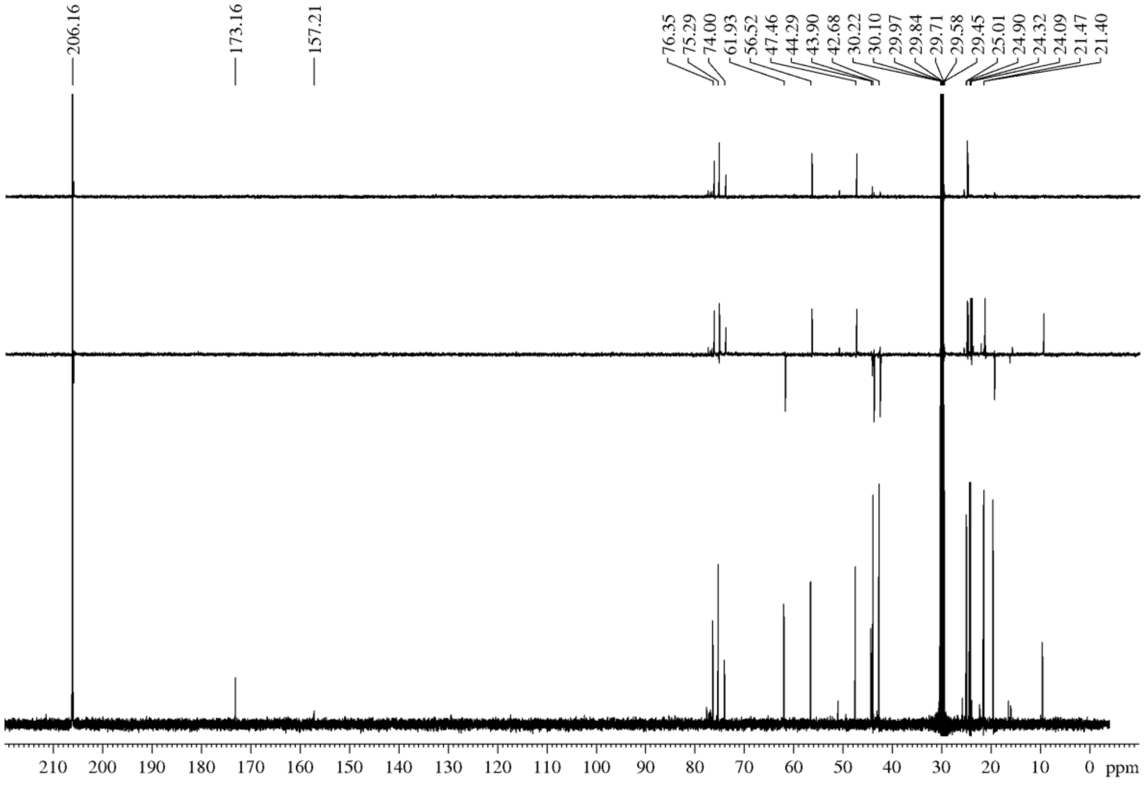
$CDCl_3$



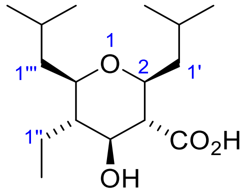


$(D_3C)_2CO$

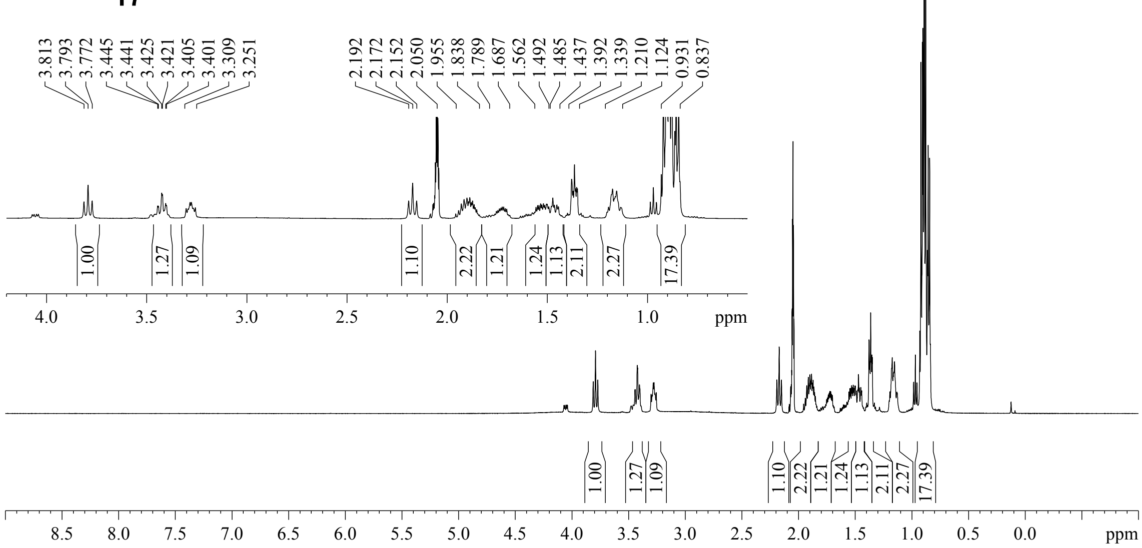

6.190
5.181
5.161
5.141
3.603
3.498
3.408
3.400
3.388
3.381
3.370
3.362
3.239
3.166
2.266
2.247
2.226
2.059
2.055
2.050
2.046
2.041
1.968
1.845
1.517
1.423
1.400
1.351
1.344
1.292
1.206
1.134
0.940
0.850
0.94
0.88
3.33
0.97
2.09
0.81
2.00
2.94
2.16
1.15
1.39
16.20
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm

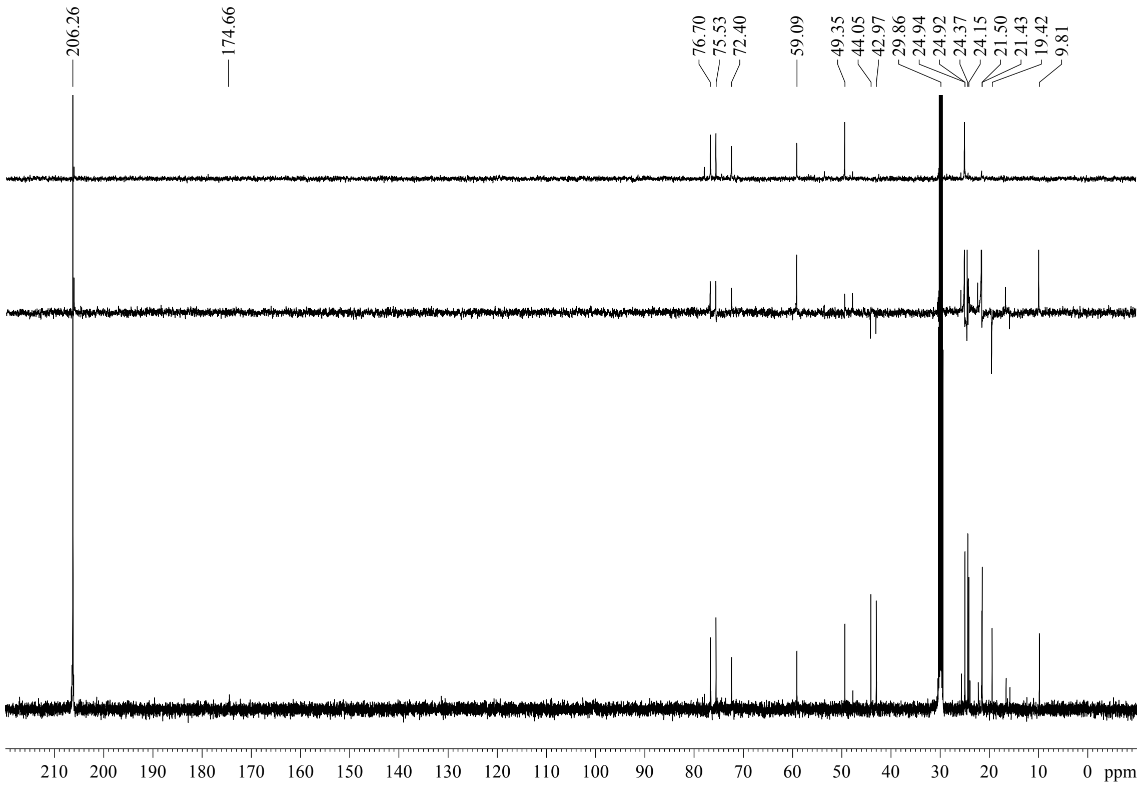

206.16
173.16
157.21
76.35
75.29
74.00
61.93
56.52
47.46
44.29
43.90
42.68
30.22
30.10
29.97
29.84
29.71
29.58
29.45
25.01
24.90
24.32
24.09
21.47
21.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

(2*S**,3*R**,4*S**,5*S**,6*R**)-5-Ethyl-4-hydroxy-2,6-diisobutyltetrahydro-2*H*-pyran-3-carboxylic acid (17)

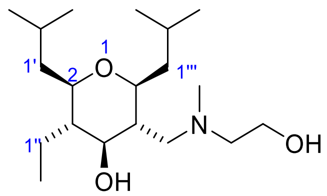


17

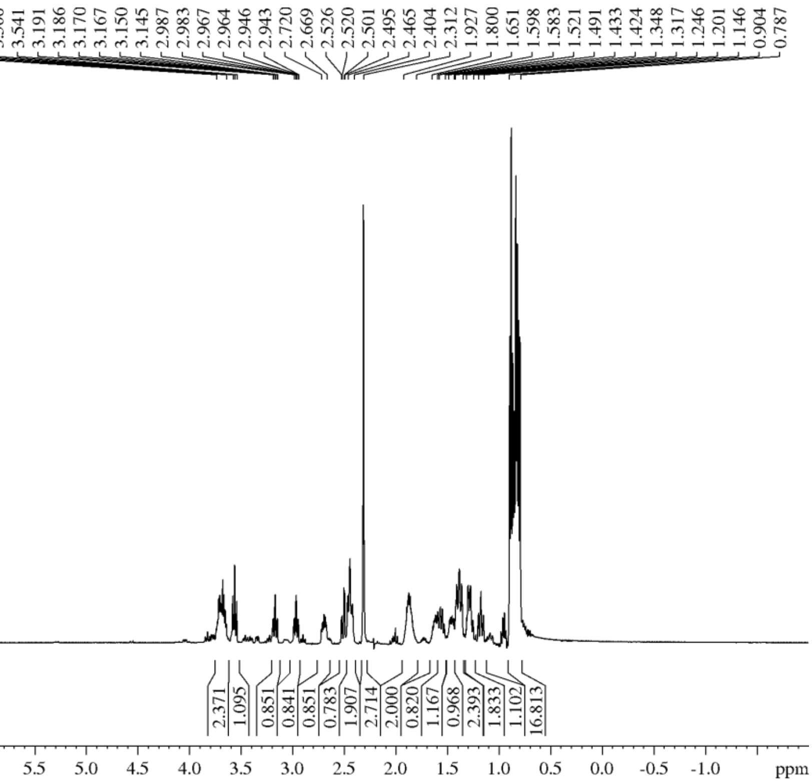


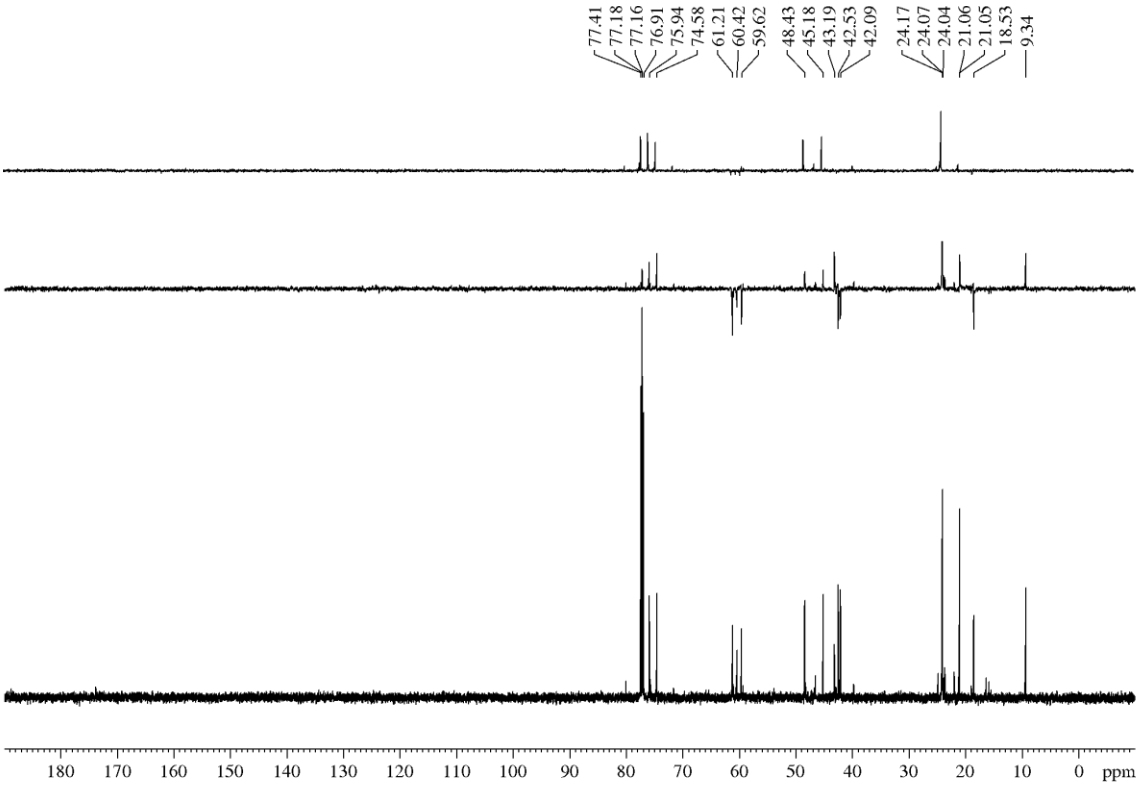


(2*R,3*S**,4*S**,5*R**,6*S**)-3-Ethyl-5-(((2-hydroxyethyl)(methyl)amino)methyl)-2,6-diisobutyltetrahydro-2*H*-pyran-4-ol (18)**



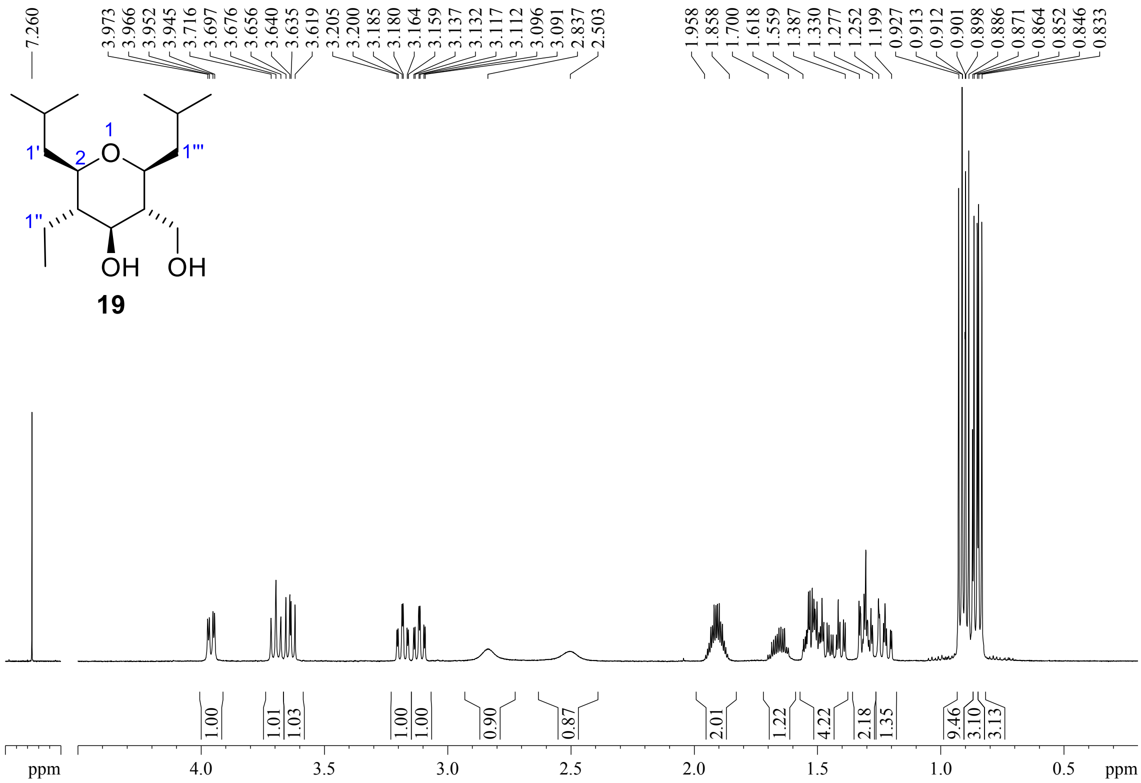
18

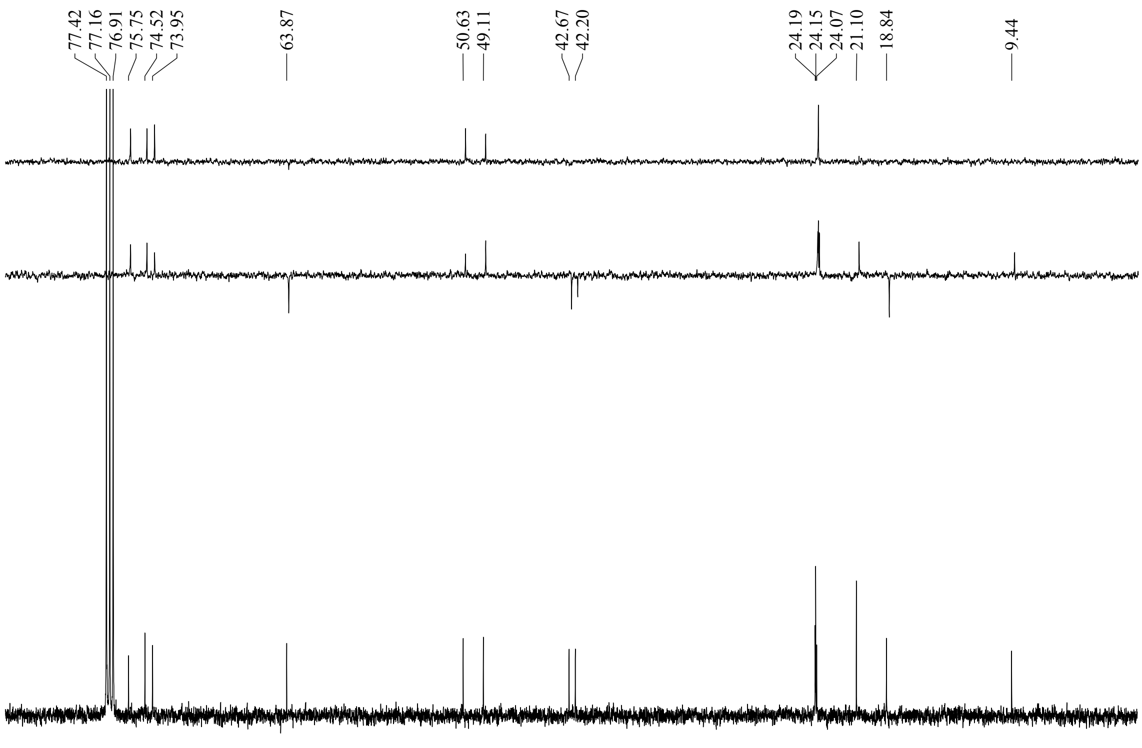




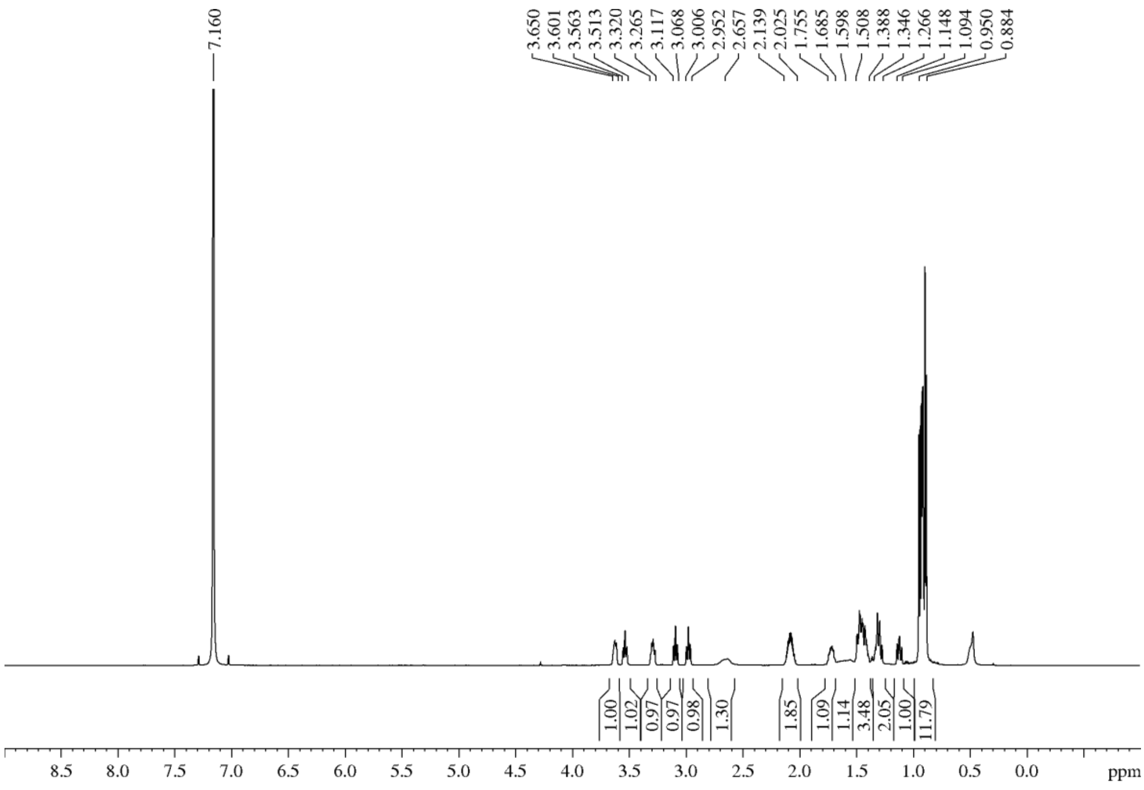
(2*R,3*S**,4*S**,5*R**,6*S**)-3-Ethyl-5-(hydroxymethyl)-2,6-diisobutyltetrahydro-2*H*-pyran-4-ol (19)**

$CDCl_3$

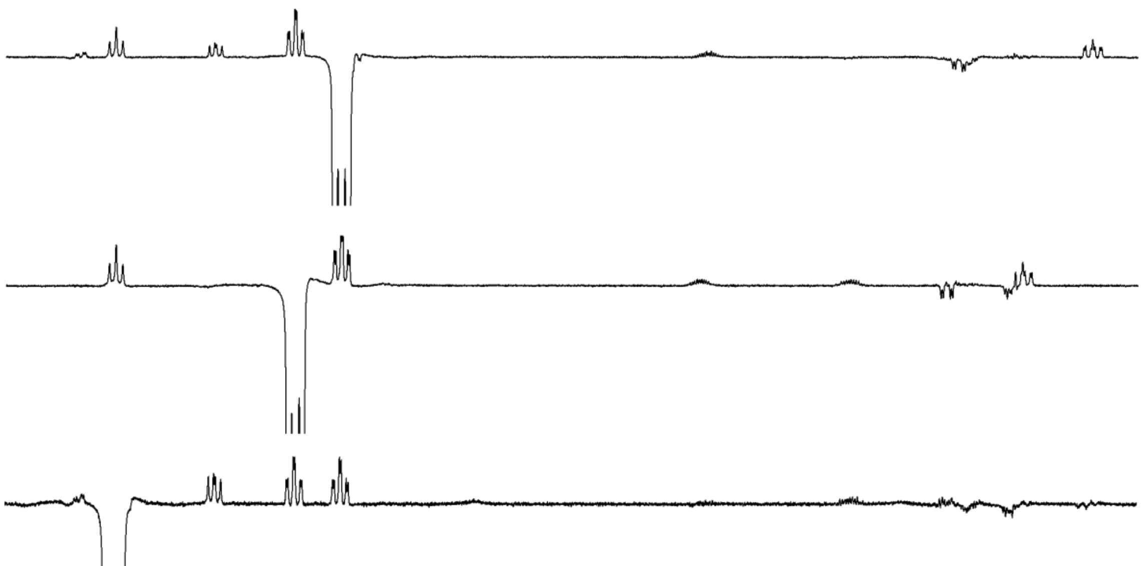




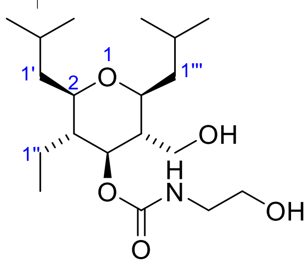
^1H-NMR C_6D_6



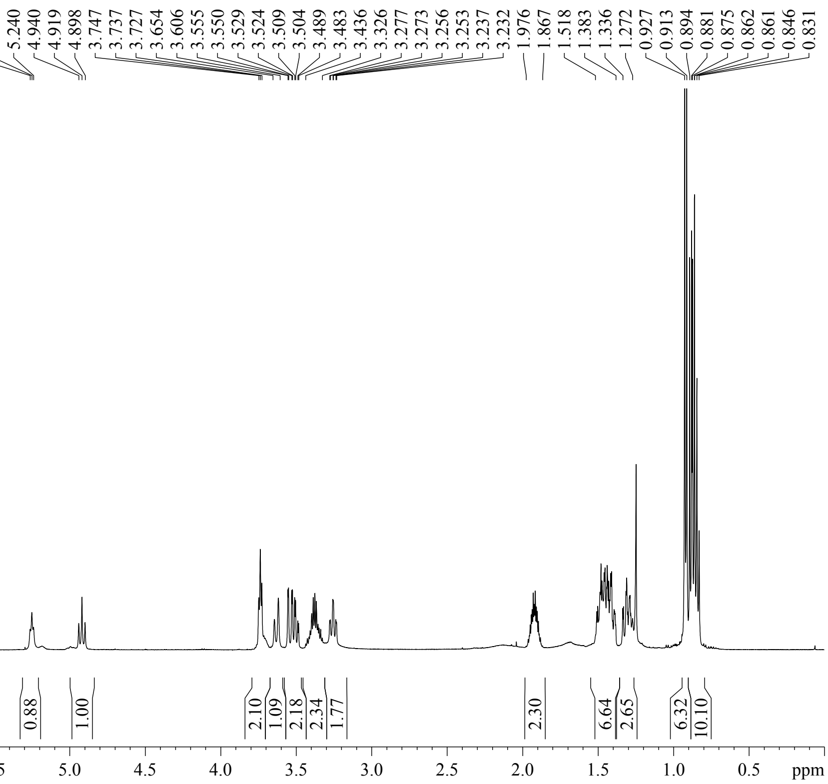
GOESY

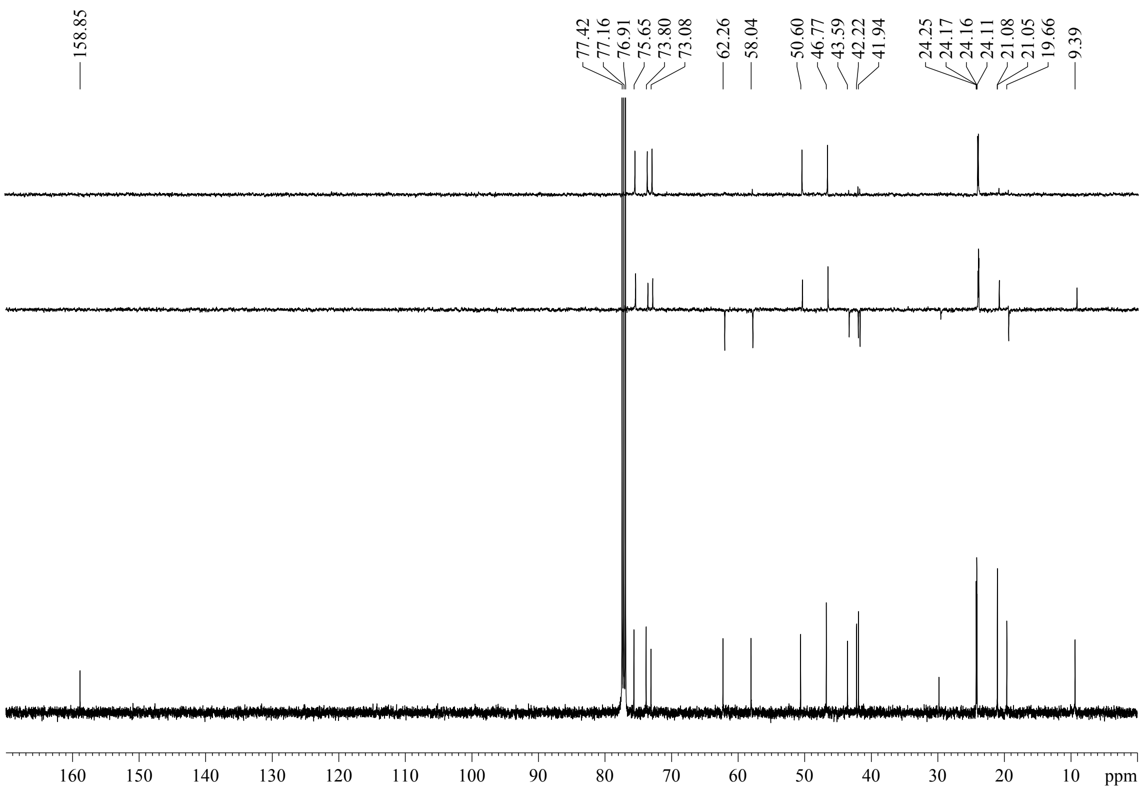


(2*R,3*R**,4*S**,5*S**,6*S**)-3-Ethyl-5-(hydroxymethyl)-2,6-diisobutyltetrahydro-2*H*-pyran-4-yl (2-hydroxyethyl)carbamate (20)**



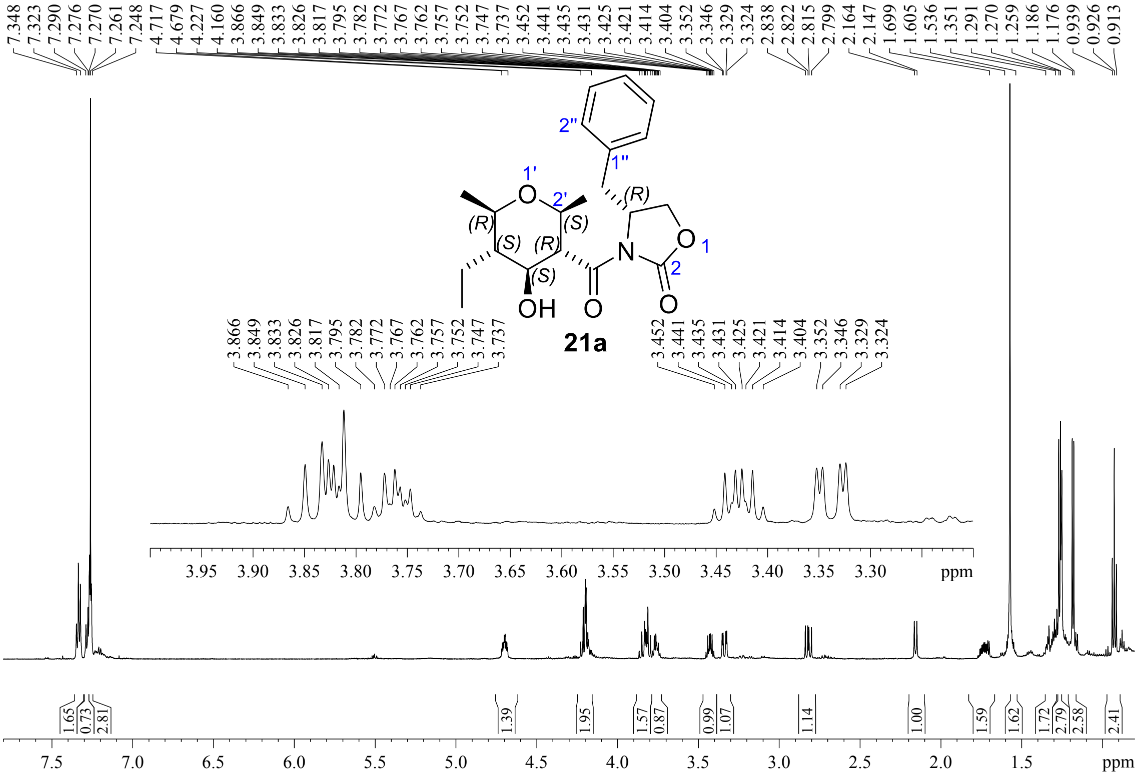
20

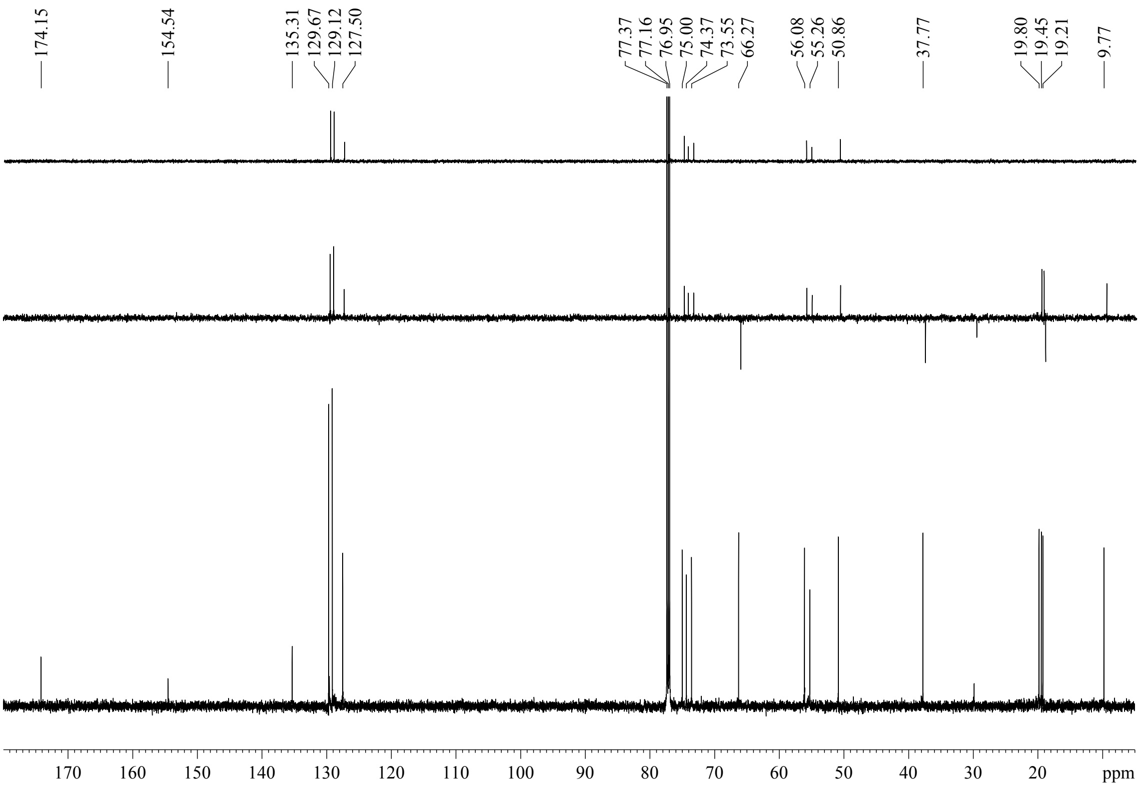




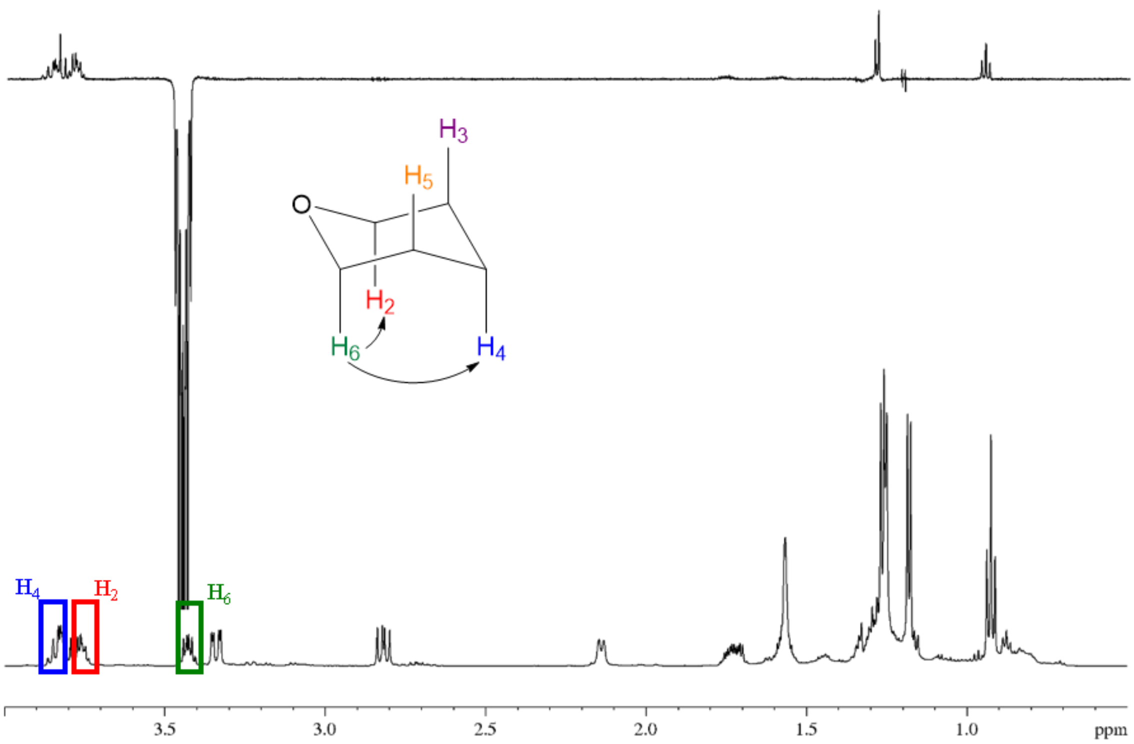
3-(*N*-acyl oxazolidin-2-one)-THPs 21

(*R*)-4-Benzyl-3-((2*S*,3*R*,4*S*,5*S*,6*R*)-5-ethyl-4-hydroxy-2,6-dimethyltetrahydro-2*H*-pyran-3-carbonyl)oxazolidin-2-one (21a)

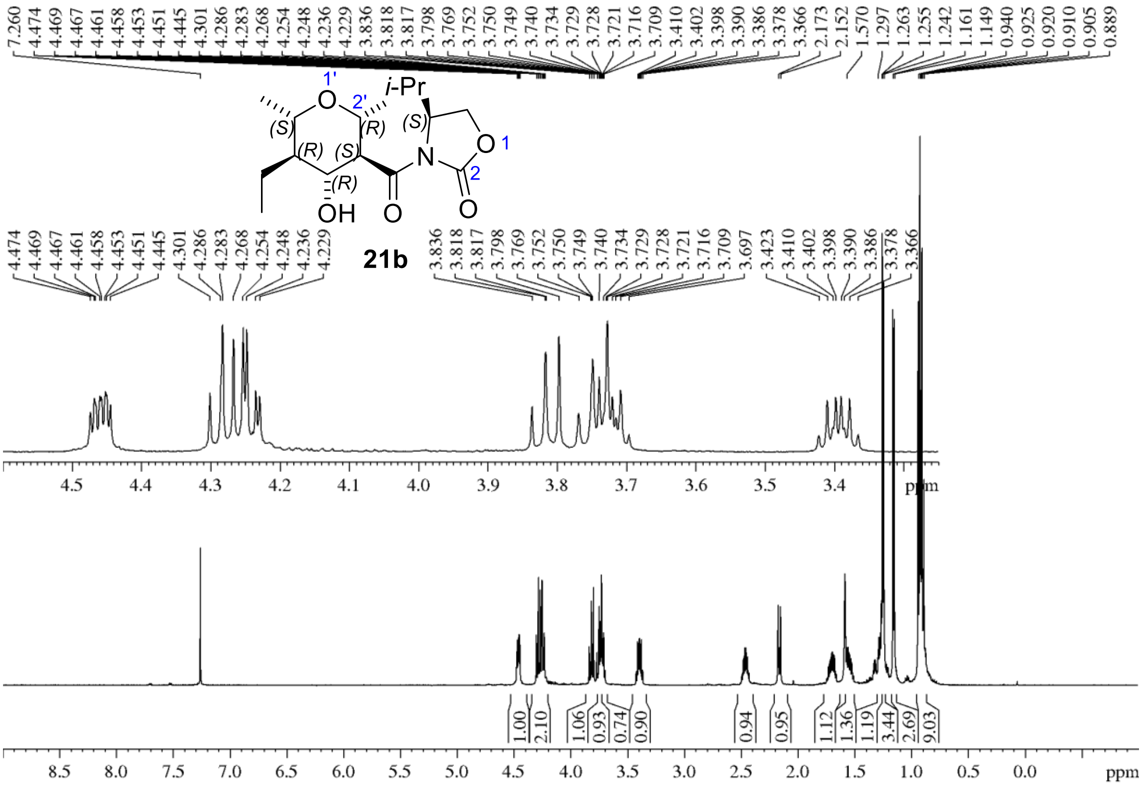




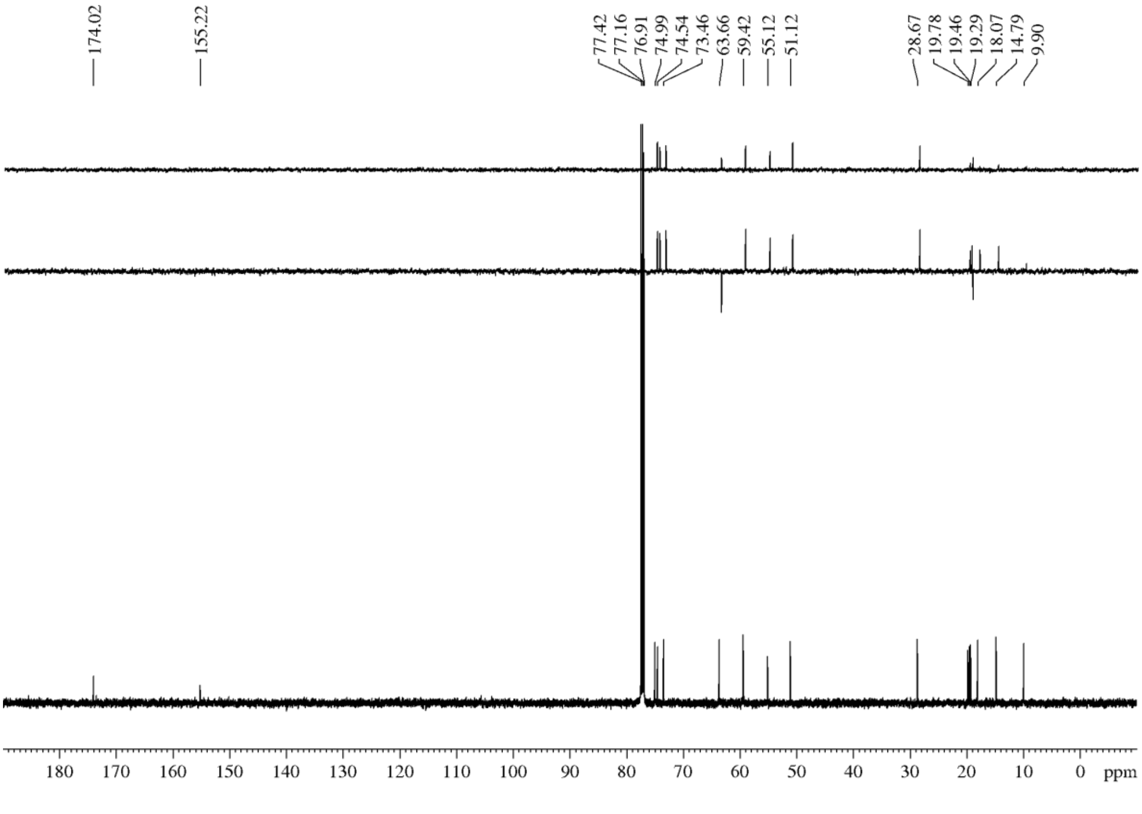
GOESY



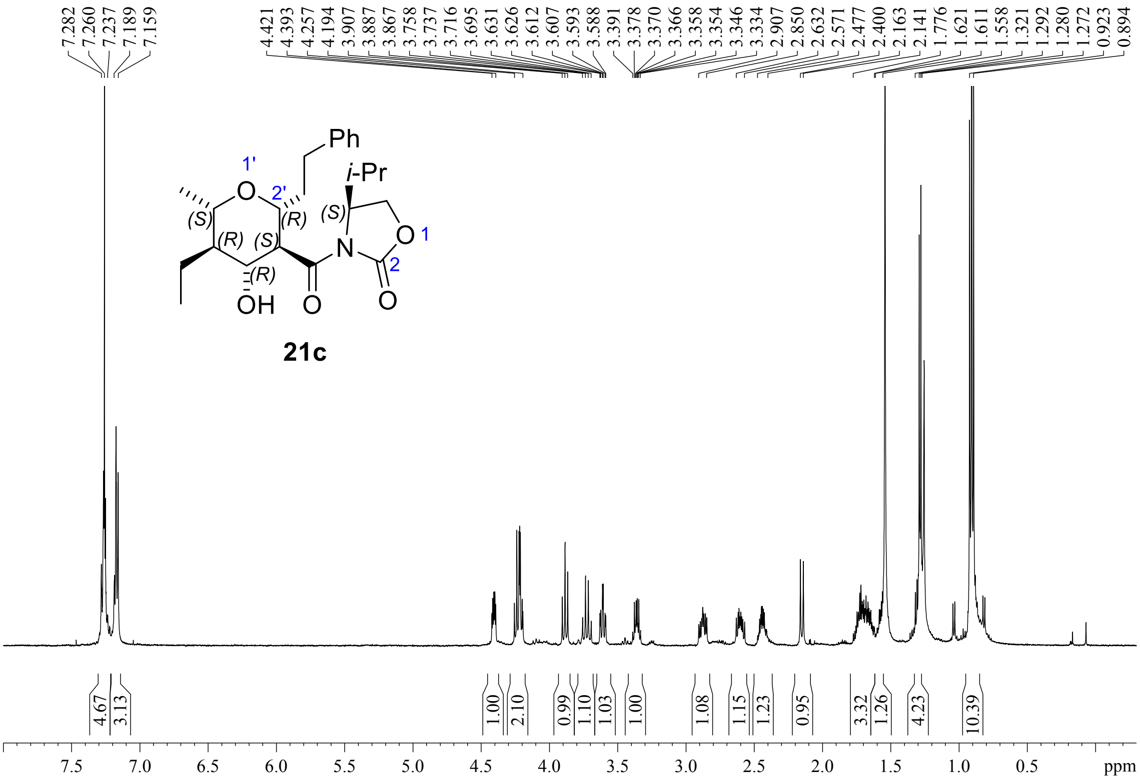
(*S*)-3-((2*R*,3*S*,4*R*,5*R*,6*S*)-5-Ethyl-4-hydroxy-2,6-dimethyltetrahydro-2*H*-pyran-3-carbonyl)-4-isopropyloxazolidin-2-one (21b)

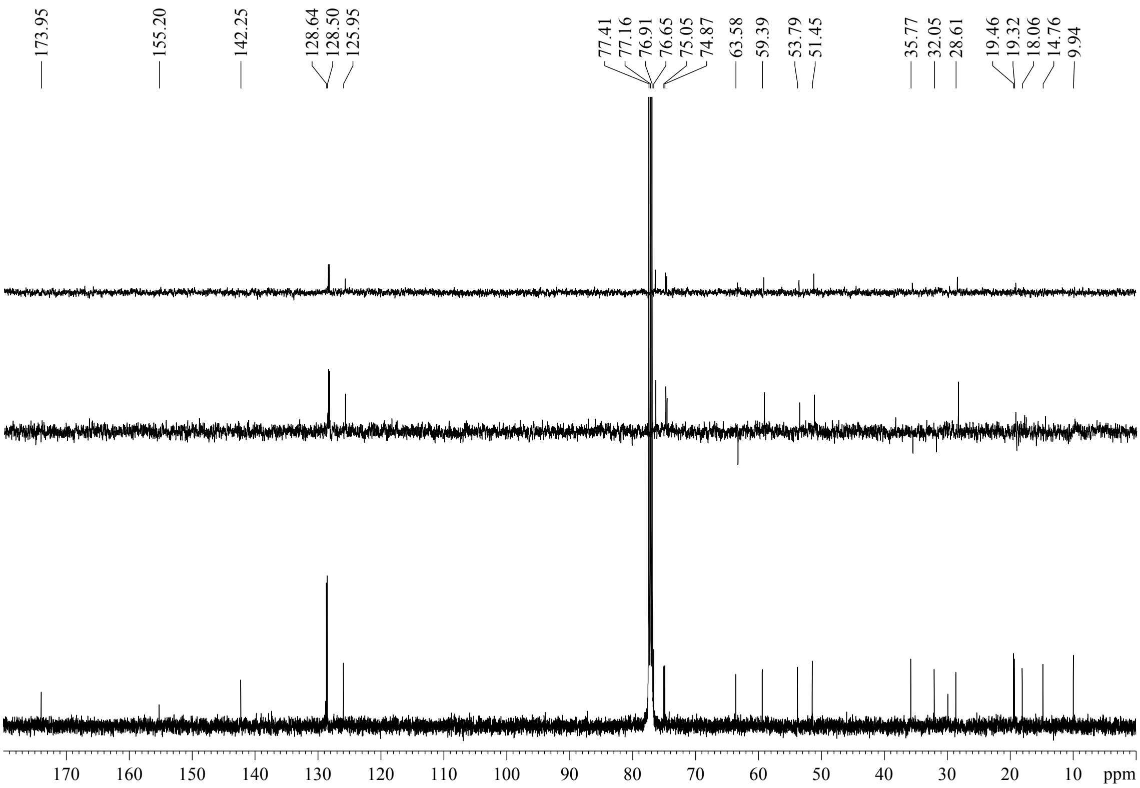


21b

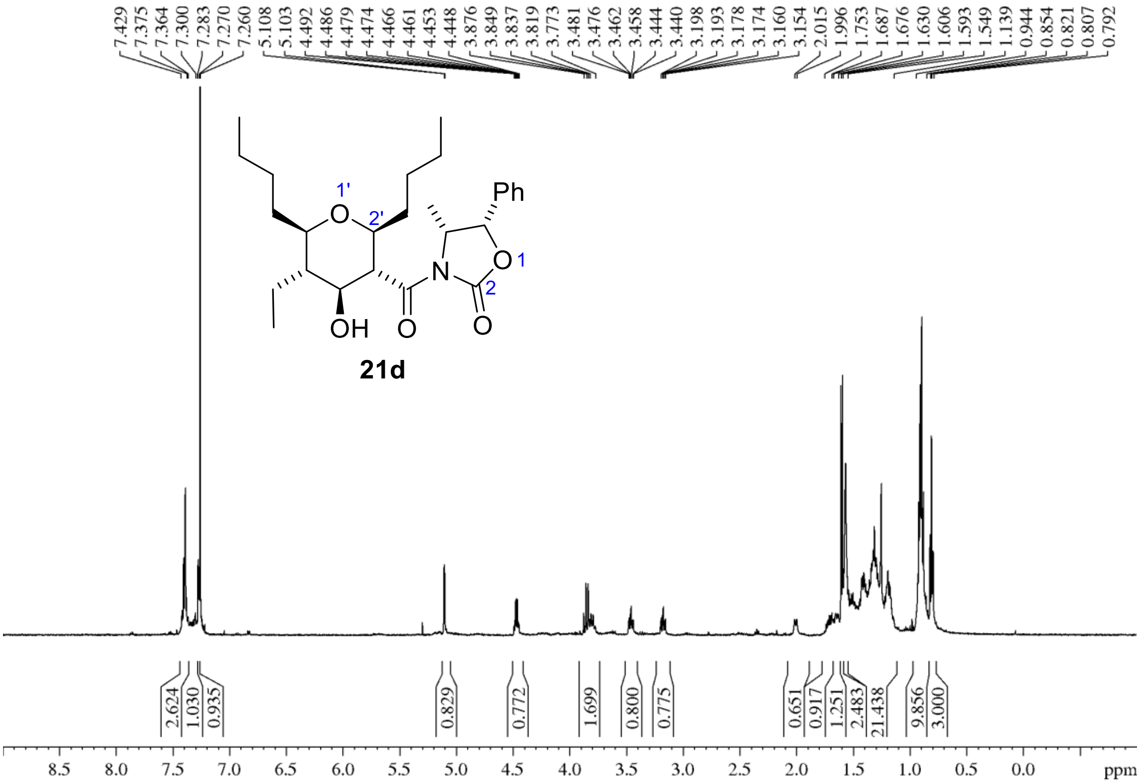


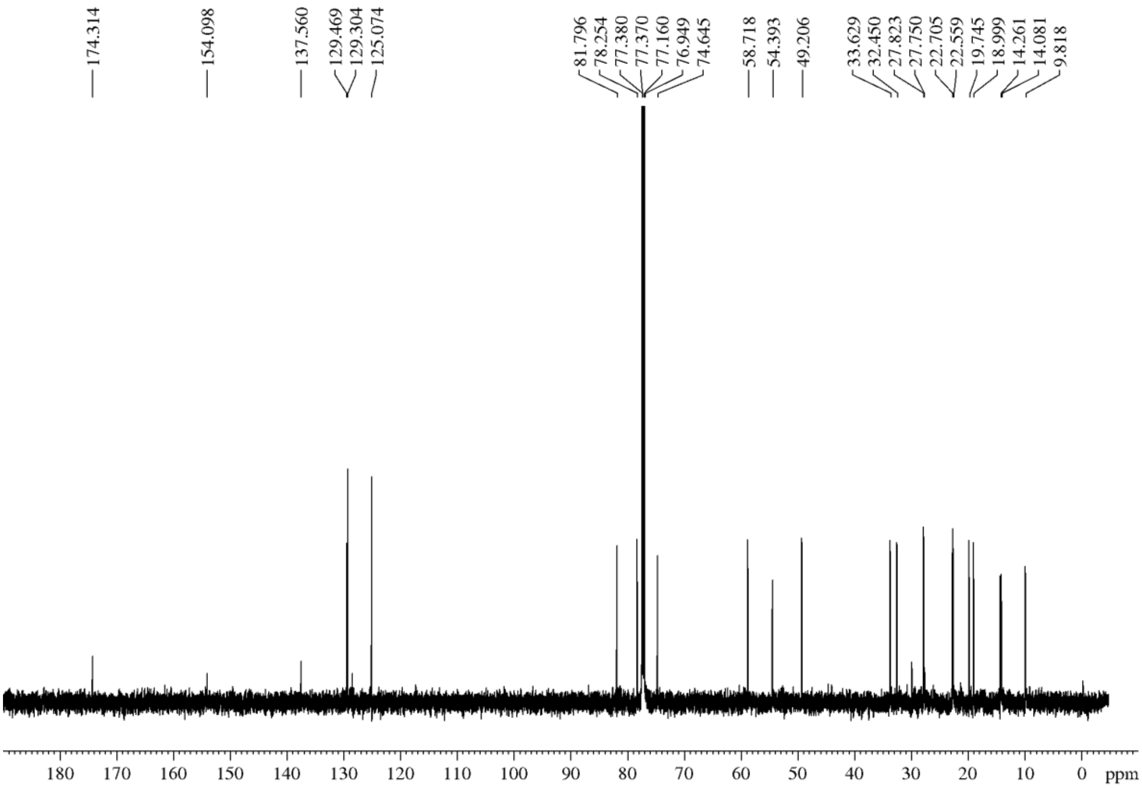
(*S*)-3-((2*R*,3*S*,4*R*,5*R*,6*S*)-5-Ethyl-4-hydroxy-6-methyl-2-phenethyltetrahydro-2*H*-pyran-3-carbonyl)-4-isopropyloxazolidin-2-one (21c)



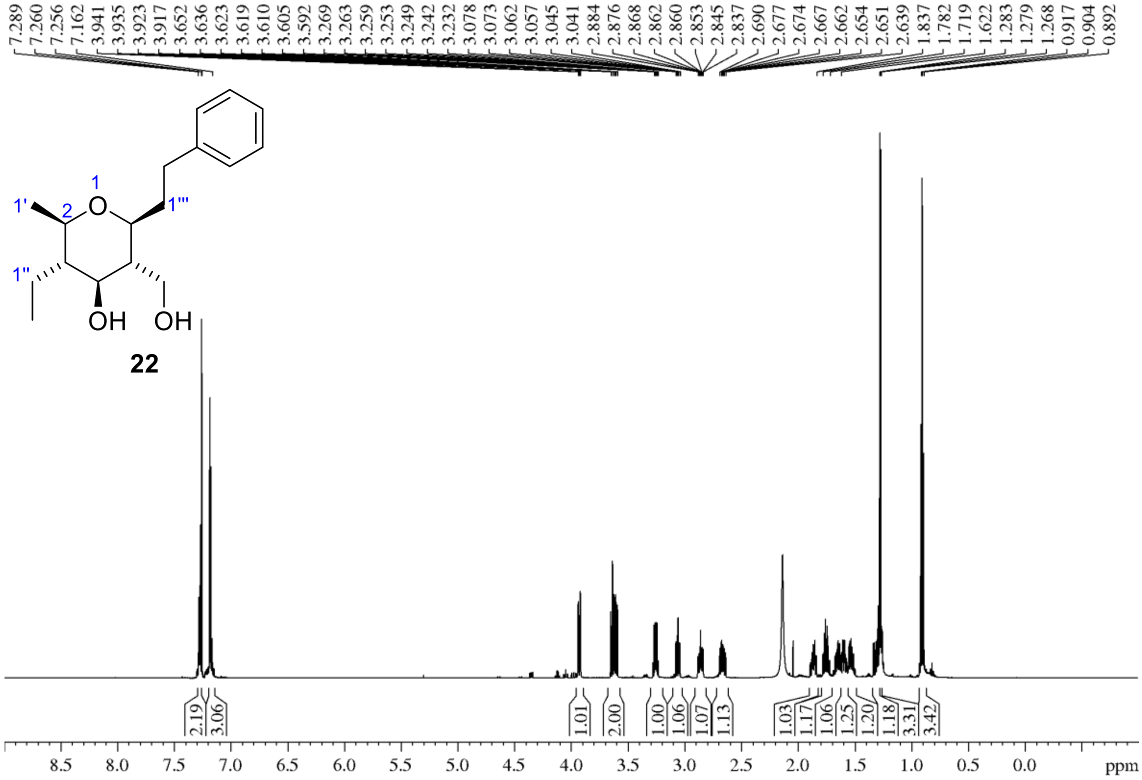


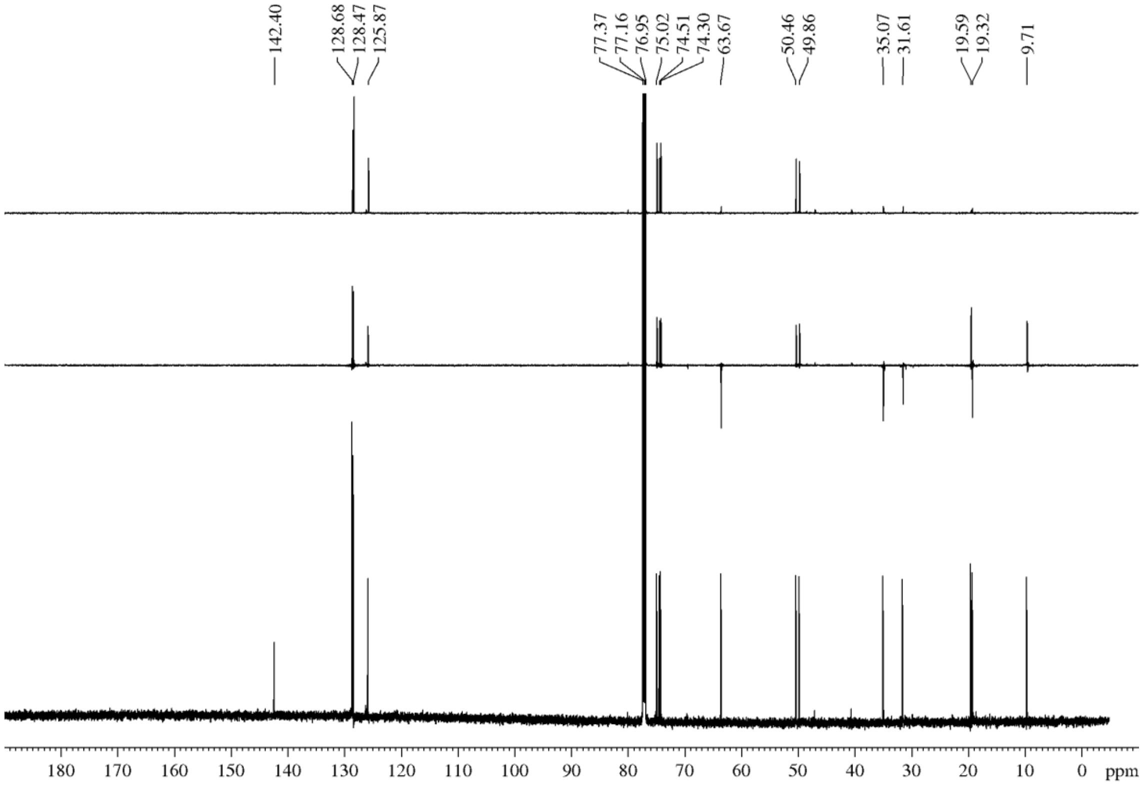
(4*R*,5*S*)-3-((2*S*,3*R*,4*S*,5*S*,6*R*)-2,6-Dibutyl-5-ethyl-4-hydroxytetrahydro-2*H*-pyran-3-carbonyl)-4-methyl-5-phenyloxazolidin-2-one (21d)



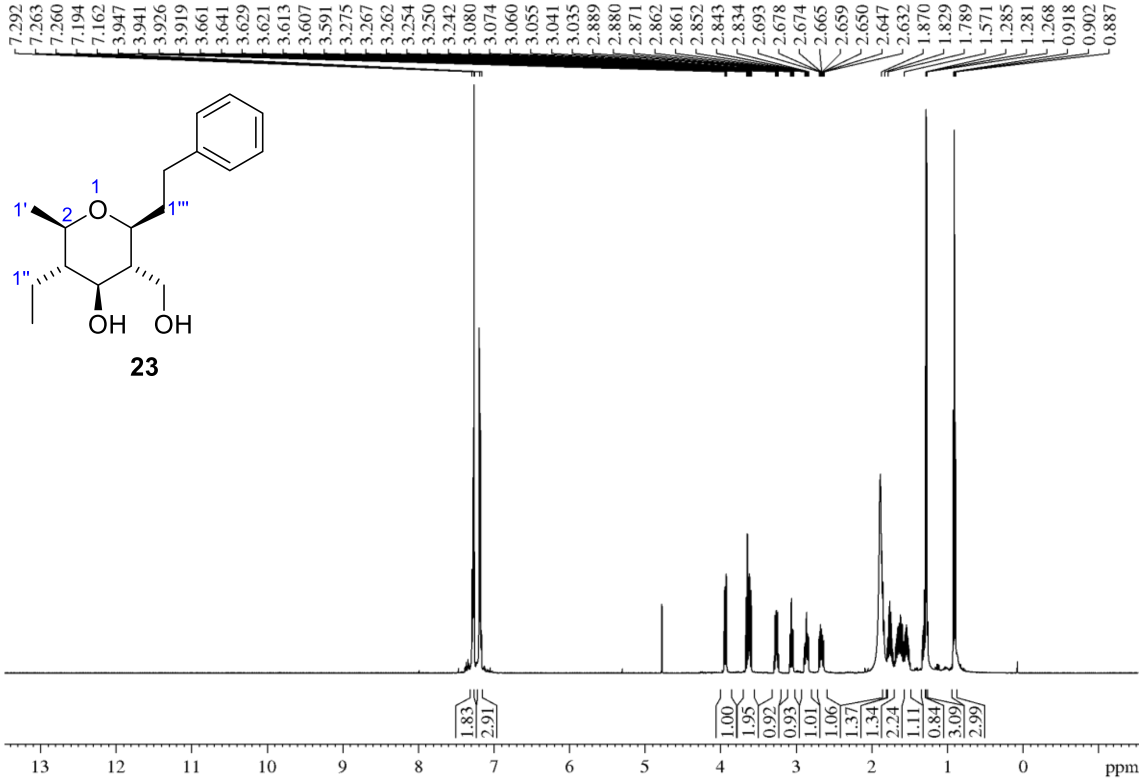


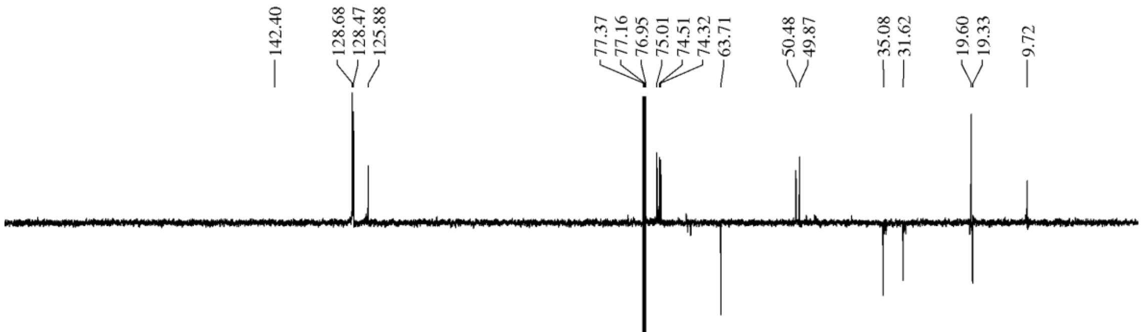
(2*R,3*S**,4*S**,5*R**,6*S**)-3-Ethyl-5-(hydroxymethyl)-2-methyl-6-phenethyltetrahydro-2*H*-pyran-4-ol (22)**

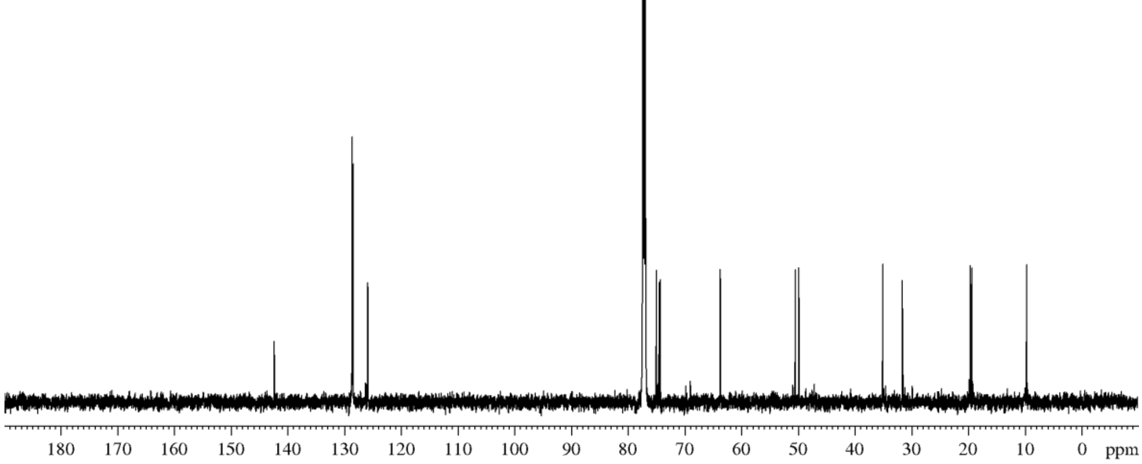




(2*R*,3*S*,4*S*,5*R*,6*S*)-3-Ethyl-5-(hydroxymethyl)-2-methyl-6-phenethyltetrahydro-2*H*-pyran-4-ol (23)







[1] Álvarez-Méndez, S. J.; García, C.; Martín, V. S. The Evans Aldol–Prins Cyclization: a General and Stereoselective Method for the Synthesis of 2,3,4,5,6-Pentasubstituted Tetrahydropyrans. *Chem. Commun.* **2016**, *52*, 3380-3383.

[2] This fragmentation appears in bicyclic compounds with lower intensity than in their isomeric compound, the THP-Xc.

[3] Typical fragmentation of a bicyclic compound.

[4] According to the IUPAC name, the main chain attached to $C_{2'}$ is the chain which contains the OH group, instead of the chain which contains the olefin. However, to maintain the coherence with the major of the aldol products synthesized, we preferred to number the chain which contains the olefin as the main chain.

[5] According to the proportion found in signals with δ = 4.39-4.44 ppm and δ = 4.49-4.52 ppm, compound **17** was obtained with a 87:13 dr due to the starting material **5a** was a diastereomeric mixture.