The Evans Aldol–Prins cyclization: a general and stereoselective method for the synthesis of 2,3,4,5,6-pentasubstituted tetrahydropyrans

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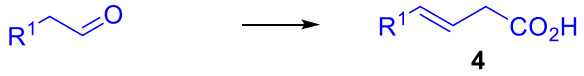
General experimental methods

Chemical nomenclature was generated using ChemBioDraw Ultra 13.0, and atoms of all the compounds were numbered according to the IUPAC name. All reagents were commercially available and used as received without further purification, unless noted otherwise. A 3.3 M solution of acetaldehyde in DCM was prepared by diluting 23 mL of commercial and volatile acetaldehyde in 100 mL of dry DCM; the molarity of the solution was checked by ^{1}H-NMR spectroscopy; the solution was stored at 2-8 ºC under Ar, being stable for at least 12 months. $BF_3{\cdot}OEt_2$ (bp = 129 ºC) was distilled and stored at –18 ºC under Ar. All solvents were dried and distilled under Ar immediately prior to use, or stored appropriately; THF was refluxed over sodium and benzophenone; DCM was distilled from CaH_2. Reactions were monitored by thin-layer chromatography (TLC) analysis employing UV light (365 nm), a phosphomolybdic acid solution 10 wt.% in methanol or a vanillin solution (6 g of vanillin, 450 mL of ethanol, 40 mL of AcOH and 30 mL of H_2SO_4); TLC was run on silica gel 60 F_{254} aluminium sheets. Flash chromatography was performed with silica gel (230–400 mesh) as the stationary phase and mixtures of *n*-hexane and EtOAc, in different proportions given in each case, as the mobile phase. ^{1}H-NMR (400, 500 or 600 MHz) and ^{13}C-NMR (100, 125 or 150 MHz) spectra were recorded on Bruker Avance instruments at room temperature, and data were processed using Topspin software (versions 2.1 and 3.2); chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are quoted in Hertz (Hz); ^{1}H-NMR spectra are referenced to the resonance from residual $CHCl_3$ at 7.26 ppm; multiplicity is expressed by the abbreviations m (multiplet), br (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), and combinations thereof for more highly coupled system; ^{13}C-NMR spectra are referenced to the central peak of the signal from $CDCl_3$ at 77.16 ppm; multiplicity was assigned from DEPT135 and DEPT90 experiments and is expressed by the abbreviations s (C), d (CH), t (CH_2) and q (CH_3); structure elucidation was made according to literature precedents or using 2D NMR techniques such as COSY, HSQC, edited HSQC and/or HMBC; spatial elucidation was performed via NMR according to the GOESY technique.[1] IR spectra were recorded neat on a Bruker IFS 66 spectrometer, and the data are given in reciprocal centimeters (cm^{-1}). Mass spectra were recorded with an AutoSpec Micromass spectrometer by using electronic impact (EI-TOF 70 eV) or with a Waters LCT Premier XE Micromass spectrometer by using electrospray ionization (ESI^{+}-TOF), as specified in each case.

[1] (a) K. Stott, J. Stonehouse, J. Keeler, T.-L. Hwang and A. J. Shaka, *J. Am. Chem. Soc.*, 1995, **117**, 4199-4200; (b) J. Stonehouse, P. Adell, J. Keeler and A. J. Shaka, *J. Am. Chem. Soc.*, 1994, **116**, 6037-6038.

Experimental procedures and compound characterization

General procedure for the synthesis of the β,γ-unsaturated carboxylic acids (4)[2]



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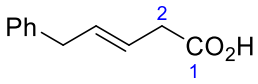
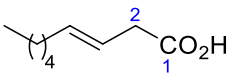
A mixture of the aldehyde,[3] malonic acid (1.1 eq) and NMM (1.1 eq), prepared under Ar, was heated at 95 ºC[4] until the reaction was complete (2-8 h approx).[5] After that, the mixture was cooled to 0 ºC, treated with a 2 M aqueous solution of H_2SO_4 (1.1 eq) and extracted three times with DCM. The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography to yield acids **4**. Acids **4a** (R^1 = Et) and **4b** (R^1 = H) are commercially available and they were used as received without further purification. Carboxylic acid **4c** (*Z*, R^1 = Me) is also commercial, or it may be prepared according to the literature procedure.[6] Acids **4d-f** (R^1 = $PhCH_2$, *n*-pentyl and $BnOCH_2CH_2$, respectively) were prepared as described above, and they were stored under Ar at –18 ºC, being stable for at least 12 months.

(*E*)-5-Phenylpent-3-enoic acid (4d)



Hydrocinnamaldehyde (1 mL, 6.84 mmol) was submitted to the general procedure for the synthesis of the β,γ-unsaturated carboxylic acids and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 75/25), **4d** as a yellowish oil (662 mg, 55%). R_F: 0.33 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 3.13 (d, *J* = 6.8 Hz, 2H, H_2), 3.40 (d, *J* = 6.8 Hz, 2H, H_5), 5.63 (dt, *J* = 15.2, 7.0 Hz, 1H, H_3), 5.77 (dt, *J* = 15.2, 7.0 Hz, 1H, H_4), 7.18-7.22 (m, 3H, Ph), 7.28-7.31 (m, 2H, Ph); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 37.8 (t, C_2), 39.0 (t, C_5), 122.5 (d, C_3), 126.3 (d, Ph), 128.6 (d, 2C, Ph), 128.7 (d, 2C, Ph), 134.0 (d, C_4), 140.1 (s, Ph), 178.5 (s, C_1); HRMS: calcd for $C_{11}H_{12}O_2Na$ [(M + $Na)^+$] 199.0735, found 199.0739.

(*E*)-Non-3-enoic acid (4e)



Freshly distilled heptaldehyde (1 mL, 7.19 mmol; bp = 153 ºC) was submitted to the general procedure for the synthesis of the β,γ-unsaturated carboxylic acids. The crude was

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[2] Adapted from S.-J. Zhang and W.-X. Hu, *Synth. Commun.*, 2010, **40**, 3093-3100.

[3] It can be even used an aldehyde freshly obtained through a Parikh-Doering oxidation, or a PCC-mediated oxidation, without further purification.

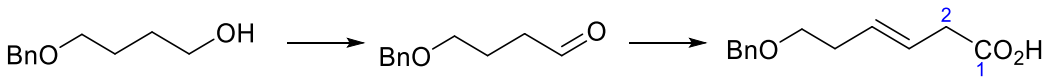
[4] It was checked that the inner temperature was about 80 ºC.

[5] Longer reaction time could lead to a bigger amount of the undesired α,β-isomer. These reactions were monitored by TLC analysis, or by ^{1}H-NMR analysis of aliquots taken of the reaction medium and then treated with a few drops of a 2 M aqueous solution of H_2SO_4 and a few drops of AcOEt.

[6] T. Šmejkal and B. Breit, *Angew. Chem. Int. Ed.*, 2008, **47**, 311-315.

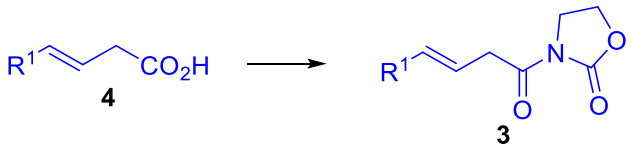
purified by flash chromatography (*n*-hexane/EtOAc 85/15), affording **4e** (863 mg, 77%) as a colourless oil. R_F: 0.34 (*n*-hexane/EtOAc 70/30); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.88 (t, *J* = 6.9 Hz, 3H, H_9), 1.24-1.34 (m, 4H, 2xH_7, 2xH_8), 1.35-1.40 (m, 2H, H_6), 2.03 (dt, *J* = 7.2, 7.2 Hz, 2H, H_5), 3.07 (d, *J* = 6.9 Hz, 2H, H_2), 5.51 (dt, *J* = 15.5, 6.6 Hz, 1H, H_3 or H_4), 5.60 (dt, *J* = 15.3, 6.7 Hz, 1H, H_3 or H_4); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 14.2 (C_9), 22.6 (C_8), 28.9 (C_6), 31.5 (C_7), 32.6 (C_5), 38.0 (C_2), 120.8 (C_3), 135.7 (C_4), 179.0 (C_1); this compound has been previously reported, and all data were consistent with those published in the literature.[7]

(*E*)-6-(Benzyloxy)hex-3-enoic acid (4f)



Commercial, or easily obtainable according to the literature,[8] 4-(benzyloxy)butan-1-ol (1.52 g, 8.43 mmol) was submitted to a Parikh-Doering oxidation: firstly the alcohol was dissolved in DCM (21 mL, 0.4 M), and then to the solution were added, sequentially and under an Ar atmosphere, DMSO (6.7 mL, 11.4 eq), TEA (7 mL, 6 eq) and SO_3·Py (5.48 g, 4 eq). After 2 h, TLC analysis revealed that the reaction was complete. The reaction mixture was diluted with DCM (100 mL) and poured into a separatory funnel. After that, a 5% HCl aqueous solution (100 mL) was added and the biphasic system was slowly shaken. The layers were separated and the organic layer was sequentially washed with a saturated $NaHCO_3$ aqueous solution (100 mL) and brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude was submitted, without further purification, to the general procedure for the synthesis of the β,γ-unsaturated carboxylic acids. After purification by flash chromatography (*n*-hexane/EtOAc 60/40), acid **4f** (925 mg, 50% after two steps) was obtained as an amorphous white solid. R_F: 0.22 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 2.35-2.44 (m, 2H, H_5), 3.08-3.13 (m, 2H, H_2), 3.54 (t, *J* = 6.7 Hz, 2H, H_6), 4.54 (s, 2H, Ph$\underline{CH_2}$O), 5.61-5.69 (m, 2H, H_3, H_4), 7.28-7.40 (m, 5H, Ph), 10.8 (br s, 1H, $CO_2\underline{H}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 32.9 (t, C_5), 37.9 (t, C_2), 69.6 (t, C_6), 72.9 (t, Ph$\underline{CH_2}$O), 123.1 (d, C_3), 127.7 (d, Ph), 127.8 (d, 2C, Ph), 128.4 (d, 2C, Ph), 131.5 (d, C_4), 138.3 (s, Ph), 178.0 (s, $\underline{C}O_2H$); MS (EI) m/z (relative intensity): 220 $(M)^+$ (1), 175 $(M - CO_2H)^+$ (1), 160 (22), 91 (100); HRMS: calcd for $C_{13}H_{16}O_3$ $[(M)^+]$ 220.1099, found 220.1108.

General procedure for the synthesis of the *N*-acyl oxazolidin-2-ones (3)[9]

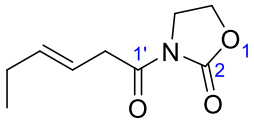


All the subsequent operations were carried out under an Ar atmosphere. To a solution of the carboxylic acid in dry THF (0.16 M) was added, at 0 ºC, TEA (1.1 eq). After 5

[7] D. M. Browne, O. Niyomura and T. Wirth, *Org. Lett.*, 2007, **9**, 3169-3171.
[8] C. García, T. Martín and V. S. Martín, *J. Org. Chem.*, 2001, **66**, 1420-1428.
[9] Adapted from A. Morita and S. Kuwahara, *Org. Lett.*, 2006, **8**, 1613-1616.

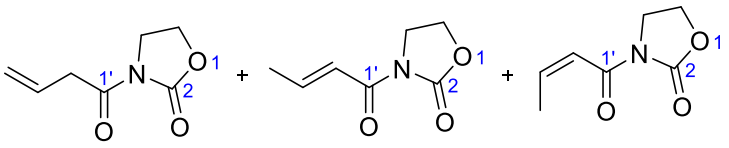
minutes, pivaloyl chloride (1.3 eq) was added at 0 ºC too, obtaining a suspension of the mixed acid anhydride that was stirred 1 h at rt. Meanwhile, in another flask, a solution of the oxazolidin-2-one (1.3 eq) in dry THF (0.3 M) was cooled to –78 ºC, treated dropwise with a 2.5 M solution of *n*-butyllithium in hexanes (1.2 eq) and kept at that temperature until it was poured[10] into the –78 ºC cooled suspension of the anhydride. After that, the mixture was allowed to warm to rt, and after 15 h it was stopped with a saturated NH_4Cl aqueous solution. Then, it was extracted three times with AcOEt, and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, concentrated and purified by flash chromatography to yield the desired compound **3**. The *N*-acyl oxazolidin-2-one is usually slightly more apolar than the starting carboxylic acid; other more apolar unidentified by-products are usually obtained in this reaction. Compounds with the structure of **3** are stable for six months if they are properly stored under Ar at –18 ºC, although they begin to decompose after that time. The following compounds were prepared as described above.

(*E*)-3-(Hex-3-enoyl)oxazolidin-2-one (3a)



trans-3-Hexenoic acid (7.5 mL, 61.4 mmol) was submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **3a** (7.68 g, 68%) as a yellow oil. R_F: 0.48 (*n*-hexane/EtOAc 70/30); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 0.99 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 2.03-2.10 (m, 2H, $H_{5'}$), 3.65 (d, *J* = 6.5 Hz, 2H, $H_{2'}$), 4.02 (t, *J* = 8.1 Hz, 2H, H_4), 4.41 (t, *J* = 8.1 Hz, 2H, H_5), 5.57 (dt, *J* = 15.4, 6.5 Hz, 1H, $H_{3'}$), 5.67 (dt, *J* = 15.4, 6.0 Hz, 1H, $H_{4'}$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 13.6 (q, $C_{6'}$), 25.7 (t, $C_{5'}$), 38.9 (t, $C_{2'}$), 42.7 (t, C_4), 62.2 (t, C_5), 120.1 (d, $C_{3'}$), 137.2 (d, $C_{4'}$), 153.6 (s, C_2), 172.2 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 183 $(M)^+$ (26), 96 (100), 88 (31), 81 (80); HRMS: calcd for $C_9H_{13}NO_3$ [$(M)^+$] 183.0895, found 183.0890.

3-(But-3-enoyl)oxazolidin-2-one (3b)



3b-β,γ **3b**-*E*-α,β **3b**-*Z*-α,β

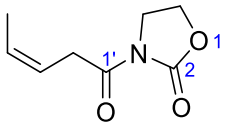
3-Butenoic acid[11] (2 mL, 23.5 mmol) was submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones. Partial isomerization of the starting material occurred during the process, because ^{1}H-NMR analysis of the crude revealed a mixture of the desired product 3-(but-3-enoyl)oxazolidin-2-one (**3b**-β,γ) and its isomers (*E*)-3-(but-2-enoyl)oxazolidin-2-one (**3b**-*E*-α,β) and (*Z*)-3-(but-2-enoyl)oxazolidin-2-one (**3b**-

[10] A slow addition is not required.

[11] ^{1}H-NMR analysis of the starting acid showed that it was mixed with a 10% of (*E*)-but-2-enoic acid (its α,β-isomer).

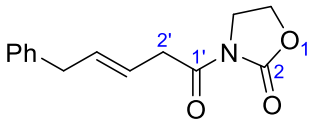
Z-α,β) in a 3.3/1.3/1 proportion.[12] Purification by flash chromatography (*n*-hexane/EtOAc 70/30) allowed as to separate **3b**-*Z*-α,β (253 mg, 7%, yellow oil)[13] from the mixture, but desired **3b**-β,γ and minority **3b**-*E*-α,β eluted together (1.98 g, 54% of a 2.5/1 mixture, thick colourless oil).[14] The NMR spectra showed in the corresponding section at the end of this Electronic Supplementary Information were recorded from a fraction which showed a 2/1 mixture of the desired product **3b**-β,γ with **3b**-*E*-α,β. The desired major product is described below. R_F: 0.27 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 3.69 (d, *J* = 6.8 Hz, 2H, $H_{2'}$), 4.01 (t, *J* = 8.0 Hz, 2H, H_4), 4.41 (t, *J* = 8.0 Hz, 2H, H_5), 5.18-5.19 (m, 1H, $H_{4'}$), 5.20-5.22 (m, 1H, $H_{4'}$), 5.93-6.00 (m, 1H, $H_{3'}$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 39.9 (t, $C_{2'}$), 42.6 (t, C_4), 62.2 (t, C_5), 119.3 (t, $C_{4'}$), 129.8 (d, $C_{3'}$), 153.6 (s, C_2), 171.4 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 155 $(M)^+$ (7), 127 (5), 88 (15), 68 (100); HRMS: calcd for $C_7H_9NO_3$ [$(M)^+$] 155.0582, found 155.0579.

(*Z*)-3-(Pent-3-enoyl)oxazolidin-2-one (3c)



Acid **4c** (212 mg, 2.12 mmol) was submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **3c** (268 mg, 75%) as a yellow oil. R_F: 0.59 (*n*-hexane/EtOAc 20/80); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 1.67 (dm, *J* = 6.6 Hz, 3H, $H_{5'}$), 3.72 (d, *J* = 6.9 Hz, 2H, $H_{2'}$), 4.03 (t, *J* = 8.3 Hz, 2H, H_4), 4.42 (t, *J* = 8.3 Hz, 2H, H_5), 5.60-5.66 (m, 1H, $H_{3'}$), 5.69-5.75 (m, 1H, $H_{4'}$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 13.3 (q, $C_{5'}$), 33.5 (t, $C_{2'}$), 42.7 (t, C_4), 62.2 (t, C_5), 121.1 (d, $C_{3'}$), 128.3 (d, $C_{4'}$), 153.6 (s, C_2), 171.7 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 169 $(M)^+$ (4), 88 (15), 82 (100), 55 (27); HRMS: calcd for $C_8H_{11}NO_3$ [$(M)^+$] 169.0739, found 169.0745.

(*E*)-3-(5-Phenylpent-3-enoyl)oxazolidin-2-one (3d)



Acid **4d** (138 mg, 0.79 mmol) was submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **3d** (116 mg, 60%) as a yellowish oil. R_F: 0.33 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 3.40 (d, *J* = 6.6 Hz, 2H, $H_{2'}$), 3.70 (dd, *J* = 6.6, 0.9 Hz, 2H, $H_{5'}$), 4.01 (t, *J* = 8.1 Hz, 2H, H_4), 4.40 (t, *J* = 8.0 Hz, 2H, H_5), 5.67-5.81 (m, 2H, $H_{3'}$, $H_{4'}$), 7.17-7.22 (m, 3H, Ph), 7.26-7.30 (m, 2H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 38.8 (t, $C_{2'}$), 39.1 (t, $C_{5'}$), 42.6 (t, C_4), 62.2 (t, C_5), 122.7 (d, $C_{3'}$), 126.2

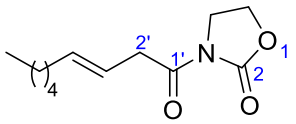
[12] By-products **3b**-*E*-α,β and **3b**-*Z*-α,β have been previously described in the following reference: S. J. Heffernan, J. M. Beddoes, M. F. Mahon, A. J. Hennessy and D. R. Carbery, *Chem. Comm.*, 2013, **49**, 2314-2316 (supporting information, page 11).

[13] R_F 0.32 (*n*-hexane/EtOAc 60/40).

[14] It is described that compound **3b**-*E*-α,β reacts in an aldol addition providing the same β,γ-unsaturated alcohol **2** expected to be obtained from **3b**-β,γ. Thus, this mixture is not a problem since a synthetic point of view. For previously reported examples, see: (a) T. Nakamura, M. Oshida, T. Nomura, A. Nakazaki and S. Kobayashi, *Org. Lett.*, 2007, **9**, 5533-5536, Supporting Information page S4; (b) W. R. Roush and A. D. Palkowitz, *J. Org. Chem.*, 1989, **54**, 3009-3011.

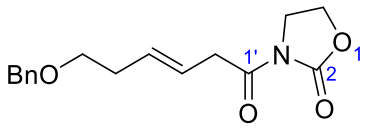
(d, Ph), 128.5 (d, 2C, Ph), 128.6 (d, 2C, Ph), 133.9 (d, $C_{4'}$), 140.2 (s, Ph), 153.6 (s, C_2), 171.8 (s, $C_{1'}$); HRMS: calcd for $C_{14}H_{15}NO_3Na$ [(M + Na)$^+$] 268.0950, found 268.0944.

(*E*)-3-(Non-3-enoyl)oxazolidin-2-one (3e)



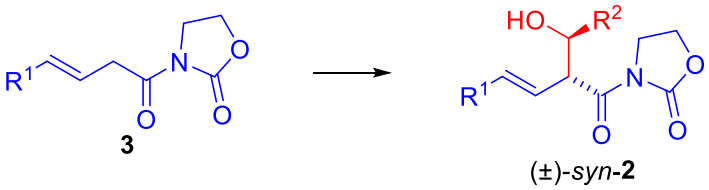
Acid **4e** (200 mg, 1.29 mmol) was submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 50/50), compound **3e** (267 mg, 90%) as a yellowish oil. R_F: 0.38 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.89 (t, *J* = 7.1 Hz, 3H, $H_{9'}$), 1.25-1.33 (m, 4H, CH_2 from alkyl chain), 1.36-1.41 (m, 2H, CH_2 from alkyl chain), 2.04 (dt, *J* = 7.0, 7.0 Hz, 2H, $H_{5'}$), 3.65 (d, *J* = 6.3 Hz, 2H, $H_{2'}$), 4.01 (t, *J* = 8.1 Hz, 2H, H_4), 4.40 (t, *J* = 8.1 Hz, 2H, H_5), 5.55-5.67 (m, 2H, $H_{3'}$, $H_{4'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 14.1 (q, $C_{9'}$), 22.6 (t, CH_2 from alkyl chain), 28.9 (t, CH_2 from alkyl chain), 31.5 (t, CH_2 from alkyl chain), 32.6 (t, CH_2 from alkyl chain), 38.8 (t, $C_{2'}$), 42.7 (t, C_4), 62.2 (t, C_5), 121.1 (d, $C_{3'}$), 135.7 (d, $C_{4'}$), 153.6 (s, C_2), 172.0 (s, $C_{1'}$); HRMS: calcd for $C_{12}H_{19}NO_3Na$ [(M + Na)$^+$] 248.1263, found 248.1268.

(*E*)-3-(6-(Benzyloxy)hex-3-enoyl)oxazolidin-2-one (3f)



Acid **4f** (190 mg, 0.87 mmol) was submitted to the general procedure for the synthesis of the *N*-acyl oxazolidin-2-ones and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **3f** (150 mg, 60%) as an amorphous white solid. R_F: 0.22 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 2.38 (dt, *J* = 6.1, 6.1 Hz, 2H, $H_{5'}$), 3.51 (t, *J* = 6.7 Hz, 2H, $H_{6'}$), 3.66 (d, *J* = 5.8 Hz, 2H, $H_{2'}$), 3.98 (t, *J* = 8.1 Hz, 2H, H_4), 4.37 (t, *J* = 8.0 Hz, 2H, H_5), 4.50 (s, 2H, PhC$\underline{H}_2$O), 5.62-5.72 (m, 2H, $H_{3'}$, $H_{4'}$), 7.25-7.36 (m, 5H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 33.2 (t, $C_{5'}$), 38.9 (t, $C_{2'}$), 42.6 (t, C_4), 62.2 (t, C_5), 69.8 (t, $C_{6'}$), 73.0 (t, Ph$\underline{C}H_2$O), 123.2 (d, $C_{3'}$), 127.6 (d, Ph), 127.7 (d, 2C, Ph), 128.5 (d, 2C, Ph), 131.7 (d, $C_{4'}$), 138.6 (s, Ph), 153.5 (s, C_2), 171.8 (s, $C_{1'}$); HRMS: calcd for $C_{16}H_{19}NO_4Na$ [(M + Na)$^+$] 312.1212, found 312.1220.

General procedure for the synthesis of the aldols (2)[15]

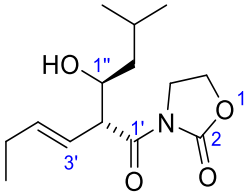


All the subsequent operations were carried out under an Ar atmosphere. A solution of the *N*-acyl oxazolidin-2-one in dry DCM (1 M) was cooled to –78 ºC. TEA (1.3 eq) and a 1

[15] Adapted from D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127-2129.

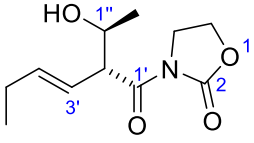
M solution of *n*-Bu_2BOTf[16] in DCM (1.2 eq) were dropped sequentially, and then the mixture was stirred at that temperature for 30 min. After that, it was warmed to 0 ºC, and after 20 min it was re-cooled to –78 ºC, the aldehyde R^2CHO (1.5 eq) was added and the mixture was allowed to warm to rt. After 15 h,[17] the mixture was cooled to 0 ºC and it was applied an oxidative work-up: it was sequentially added a pH 7 buffer solution (1.1 mL/mmol *N*-acyl oxazolidin-2-one), MeOH (2.6 mL/mmol *N*-acyl oxazolidin-2-one) and a 35 wt. % solution of H_2O_2 in water (1.1 mL/mmol *N*-acyl oxazolidin-2-one). The layers were then separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated.[18] The crude was purified by flash chromatography (the homoallylic alcohol is usually slightly more polar than the starting *N*-acyl oxazolidin-2-one) to yield the desired compound. Stored under Ar at –18 ºC, aldols were stable for at least 12 months. Except *anti*-aldol **2g**, the following compounds were prepared as described above.

3-((*R,*E*)-2-((*S**)-1-Hydroxy-3-methylbutyl)hex-3-enoyl)oxazolidin-2-one (2a)**



N-acyl oxazolidin-2-one **3a** (1.02 g, 5.57 mmol) was submitted to the general procedure for the aldol addition and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **2a** (1.21 g, 81%) as a thick colourless oil. R_F: 0.22 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.89 (d, *J* = 6.6 Hz, 3H, $C_{3''}(CH_3)_2$), 0.91 (d, *J* = 6.6 Hz, 3H, $CH(CH_3)_2$), 0.98 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 1.15 (ddd, *J* = 13.8, 8.6, 3.8 Hz, 1H, $H_{2''}$), 1.45 (ddd, *J* = 13.8, 9.2, 5.2 Hz, 1H, $H_{2''}$), 1.75-1.84 (m, 1H, $H_{3''}$), 2.04-2.09 (m, 2H, $H_{5'}$), 2.89 (br s, 1H, OH), 3.98-4.07 (m, 3H, 2xH_4, $H_{2'}$), 4.36-4.45 (m, 3H, 2xH_5, $H_{1''}$), 5.53 (ddt, *J* = 15.6, 9.2, 1.6 Hz, 1H, $H_{3'}$), 5.79 (dt, *J* = 15.5, 6.5 Hz, 1H, $H_{4'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.5 (q, $C_{6'}$), 21.9 (q, $CH(CH_3)_2$), 23.5 (q, $CH(CH_3)_2$), 24.4 (d, $C_{3''}$), 25.9 (t, $C_{5'}$), 42.8 (t, $C_{2''}$), 43.1 (t, C_4), 51.4 (d, $C_{2'}$), 61.9 (t, C_5), 70.0 (d, $C_{1''}$), 121.5 (d, $C_{3'}$), 139.6 (d, $C_{4'}$), 153.2 (s, C_2), 175.1 (s, $C_{1'}$); HRMS: calcd for $C_{14}H_{23}NO_4Na$ [$(M + Na)^+$] 292.1525, found 292.1519.

3-((*R,*E*)-2-((*S**)-1-Hydroxyethyl)hex-3-enoyl)oxazolidin-2-one (2b)**

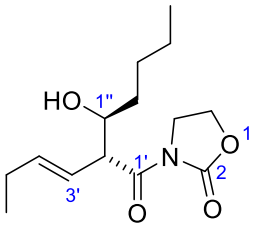


N-acyl oxazolidin-2-one **3a** (2.14 g, 11.69 mmol) and acetaldehyde (5.3 mL of a 3.3 M solution in DCM, 1.5 eq) were submitted to the general procedure for the aldol addition

[16] This solution is normally stable for at least 12 months if it is properly stored under Ar at rt. However, septum can suffer damage by reiterative drilling of the needles, allowing then the entrance of moisture to the solution; this process can liberate TfOH, whom can direct to the obtaining of undesired by-products.
[17] TLC analysis usually shows that the reaction is complete after 1 h, although longer reaction times does not worsen the yield.
[18] A non-aqueous simplified work-up is also valid: a small amount of silica gel 60 (35–70 mesh) was added, the solvent was removed in the rotavap and the silica-supported crude was purified.

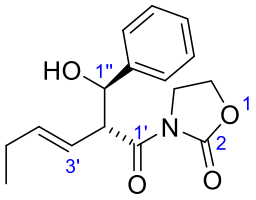
and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **2b** (1.98 g, 75%) as a colourless oil. R_F: 0.44 (*n*-hexane/EtOAc 20/80); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.00 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 1.18 (d, *J* = 6.4 Hz, 3H, $H_{2''}$), 2.05-2.11 (m, 2H, $H_{5'}$), 2.92 (br s, 1H, OH), 3.99-4.08 (m, 2H, H_4), 4.10-4.15 (m, 1H, $H_{2'}$), 4.39-4.46 (m, 3H, 2xH_5, $H_{1''}$), 5.53 (ddt, *J* = 15.4, 9.3, 1.4 Hz, 1H, $H_{3'}$), 5.82 (dt, *J* = 15.4, 6.4 Hz, 1H, $H_{4'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.5 (q, $C_{6'}$), 19.8 (q, $C_{2''}$), 25.9 (t, $C_{5'}$), 42.8 (t, C_4), 52.4 (d, $C_{2'}$), 62.0 (t, C_5), 68.4 (d, $C_{1''}$), 121.6 (d, $C_{3'}$), 139.9 (d, $C_{4'}$), 153.3 (s, C_2), 174.8 (s, $C_{1'}$); HRMS: calcd for $C_{11}H_{17}NO_4Na$ [(M + Na)$^+$] 250.1055, found 250.1053.

3-((2*R,3*S**)-2-((*E*)-But-1-en-1-yl)-3-hydroxyheptanoyl)oxazolidin-2-one (2c)**



N-acyl oxazolidin-2-one **3a** (1.38 g, 7.51 mmol) was submitted to the general procedure for the aldol addition and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **2c** (1.70 g, 84%) as a colourless oil. R_F: 0.27 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.89 (t, *J* = 7.0 Hz, 3H, $H_{5''}$), 0.99 (t, *J* = 7.3 Hz, 3H, $H_{6'}$), 1.29-1.36 (m, 3H, $C_{1''}(C\underline{H}_2)_3$), 1.40-1.52 (m, 3H, $C_{1''}(C\underline{H}_2)_3$), 2.06-2.11 (m, 2H, $H_{5'}$), 2.86 (br s, 1H, OH), 3.91-3.95 (m, 1H, $H_{2'}$), 3.99-4.08 (m, 2H, H_4), 4.38-4.45 (m, 2H, H_5), 4.49 (dd, *J* = 9.4, 3.7 Hz, 1H, $H_{1''}$), 5.54 (ddt, *J* = 15.6, 9.3, 1.5 Hz, 1H, $H_{3'}$), 5.81 (dt, *J* = 15.5, 6.5 Hz, 1H, $H_{4'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.5 (q, $C_{6'}$ or $C_{5''}$), 14.1 (q, $C_{5''}$ or $C_{6'}$), 22.6 (t, $C_{4''}$), 25.9 (t, $C_{3''}$), 27.8 (t, $C_{5'}$), 33.7 (t, $C_{2''}$), 42.8 (t, C_4), 51.1 (d, $C_{2'}$), 62.0 (t, C_5), 72.1 (d, $C_{1''}$), 121.4 (d, $C_{3'}$), 139.6 (d, $C_{4'}$), 153.2 (s, C_2), 175.1 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 251 (M – H_2O)$^+$ (1), 183 (84), 114 (20), 96 (100); HRMS: calcd for $C_{14}H_{21}NO_3$ [(M – H_2O)$^+$] 251.1521, found 251.1530.

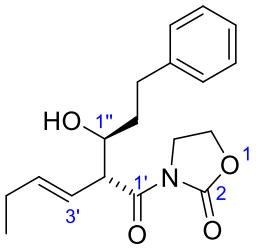
3-((*R,*E*)-2-((*R**)-Hydroxy(phenyl)methyl)hex-3-enoyl)oxazolidin-2-one (2d)**



N-acyl oxazolidin-2-one **3a** (2.34 g, 12.79 mmol) was submitted to the general procedure for the aldol addition and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **2d** (2.98 g, 81%) as a colourless oil. R_F: 0.29 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.95 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 2.02-2.08 (m, 2H, $H_{5'}$), 2.95 (br s, 1H, OH), 3.79 (ddd, *J* = 11.0, 9.5, 6.7 Hz, 1H, H_4), 3.91 (ddd, *J* = 11.0, 9.5, 7.3 Hz, 1H, H_4), 4.17 (td, *J* = 8.8, 7.2 Hz, 1H, H_5), 4.29 (td, *J* = 8.9, 7.0 Hz, 1H, H_5), 4.81 (dd, *J* = 9.0, 6.0 Hz, 1H, $H_{2'}$), 5.00 (d, *J* = 6.0 Hz, 1H, $H_{1''}$), 5.58 (ddt, *J* = 15.4, 9.1, 1.5 Hz, 1H, $H_{3'}$), 5.72 (dt, *J* = 15.4, 6.2 Hz, 1H, $H_{4'}$), 7.24-7.28 (m, 1H, Ph), 7.29-7.33 (m, 2H, Ph), 7.34-7.37 (m, 2H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.4 (q, $C_{6'}$), 25.8 (t, $C_{5'}$), 42.7 (t, C_4), 54.1 (d, $C_{2'}$), 61.9 (t, C_5), 72.1 (d, $C_{1''}$), 122.1 (d,

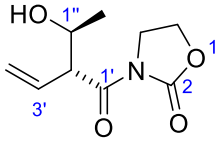
$C_{3'}$), 126.9 (d, 2C, Ph), 127.9 (d, Ph), 128.2 (d, 2C, Ph), 140.1 (d, $C_{2''}$), 140.8 (s, Ph), 152.9 (s, C_2), 173.7 (s, $C_{1'}$); HRMS: calcd for $C_{16}H_{19}NO_4Na$ [$(M + Na)^+$] 312.1212, found 312.1215.

3-((*R,*E*)-2-((*S**)-1-Hydroxy-3-phenylpropyl)hex-3-enoyl)oxazolidin-2-one (2e)**



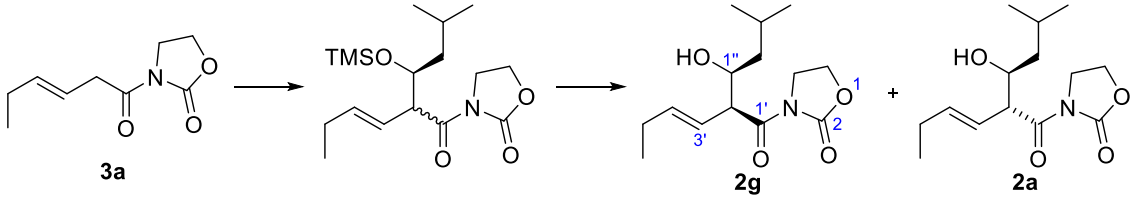
N-acyl oxazolidin-2-one **3a** (1.56 g, 8.53 mmol) was submitted to the general procedure for the aldol addition and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **2e** (2.2 g, 81%) as a thick colourless oil. R_F: 0.29 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.99 (t, *J* = 7.5 Hz, 3H, $H_{6'}$), 1.68-1.74 (m, 1H, $H_{2''}$), 1.81-1.87 (m, 1H, $H_{2''}$), 2.05-2.10 (m, 2H, $H_{5'}$), 2.68 (ddd, *J* = 16.2, 9.6, 7.1 Hz, 1H, $H_{3''}$), 2.83 (ddd, *J* = 13.7, 9.8, 5.3 Hz, 1H, $H_{3''}$), 3.10 (br s, 1H, OH), 3.93-3.97 (m, 1H, $H_{1''}$), 3.98-4.04 (m, 2H, H_4), 4.37-4.40 (m, 2H, H_5), 4.50 (dd, *J* = 9.3, 3.6 Hz, 1H, $H_{2'}$), 5.55 (ddt, *J* = 15.5, 9.3, 1.3 Hz, 1H, $H_{3'}$), 5.83 (dt, *J* = 15.5, 6.3 Hz, 1H, $H_{4'}$), 7.17-7.22 (m, 3H, Ph), 7.26-7.30 (m, 2H, Ph); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 13.5 (q, $C_{6'}$), 25.9 (t, $C_{5'}$), 32.0 (t, $C_{3''}$), 35.7 (t, $C_{2''}$), 42.8 (t, C_4), 51.1 (d, $C_{2'}$), 61.9 (t, C_5), 71.2 (d, $C_{1''}$), 121.3 (d, $C_{3'}$), 125.9 (s, Ph), 128.5 (d, 2C, Ph), 128.7 (d, 2C, Ph), 140.0 (d, $C_{4'}$), 142.0 (s, Ph), 153.1 (s, C_2), 175.1 (s, $C_{1'}$). HRMS: calcd for $C_{18}H_{23}NO_4Na$ [$(M + Na)^+$] 340.1525, found 340.1529.

3-((*R)-2-((S*)-1-Hydroxyethyl)but-3-enoyl)oxazolidin-2-one (2f)**



A 2.5/1 mixture of *N*-acyl oxazolidin-2-ones **3b**-β,γ and **3b**-*E*-α,β (830 mg, 5.36 mmol) and acetaldehyde (2.4 mL of a 3.3 M solution in DCM, 1.5 eq) were submitted to the general procedure for the aldol addition. As expected, ^{1}H-NMR analysis of the crude revealed that both isomers evolved to the desired aldol **2f**.[14] The crude was purified by flash chromatography (*n*-hexane/EtOAc 60/40), and compound **2f** (808 mg, 76%) was isolated as a colourless oil. R_F: 0.17 (*n*-hexane/EtOAc 50/50); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.12-1.16 (m, 3H, $H_{2''}$), 3.04 (br s, 1H, OH), 3.94-4.04 (m, 2H, H_4), 4.08-4.16 (m, 1H, $H_{1''}$), 4.32-4.40 (m, 2H, H_5), 4.41-4.46 (m, 1H, $H_{2'}$), 5.23-5.32 (m, 2H, $H_{4'}$), 5.86-5.95 (m, 1H, $H_{3'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 19.9 (q, $C_{2''}$), 42.7 (t, C_4), 53.3 (d, $C_{2'}$), 62.0 (t, C_5), 68.1 (d, $C_{1''}$), 121.3 (t, $C_{4'}$), 131.3 (d, $C_{3'}$), 153.3 (s, C_2), 174.0 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 198 $(M - H)^+$ (1), 181 $(M - H_2O)^+$ (1), 155 (35), 68 (100); HRMS: calcd for $C_9H_{12}NO_4$ [$(M - H)^+$] 198.0766, found 198.0770.

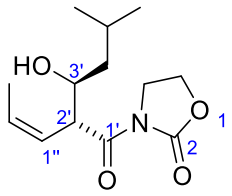
3-((*S,*E*)-2-((*S**)-1-Hydroxy-3-methylbutyl)hex-3-enoyl)oxazolidin-2-one (2g)**[19]



N-acyl oxazolidin-2-one **3a** (884 mg, 4.83 mmol) was dissolved in dry EtOAc (12 mL, 0.4 M) and treated, sequentially and under Ar atmosphere, with $MgCl_2$ (47 mg, 0.48 mmol, 0.1 eq), $NaSbF_6$ (375 mg, 1.45 mmol, 0.3 eq), TEA (1.4 mL, 9.67 mmol, 2 eq), isovaleraldehyde (0.64 mL, 5.80 mmol, 1.2 eq) and TMSCl (0.93 mL, 7.25 mmol, 1.5 eq). After 4 days, the TLC analysis revealed the presence of starting material together with two new apolar products (R_F 0.64 and 0.58, *n*-hexane/EtOAc 80/20). The resulting slurry was filtered through a pad of celite, eluting with Et_2O (300 mL), and the solvent was removed under reduced pressure to yield a yellowish oil. Silylated precursor of the product was detected via HRMS (calcd for $C_{17}H_{31}NO_4SiNa$ [$(M + Na)^+$] 364.1920, found 364.1923.). The residue was immediately dissolved in dry methanol (100 mL, 0.05 M), cooled to 0 ºC and treated with TFA (0.77 mL, 10.1 mmol, 2.1 eq). Once TLC analysis revealed full conversion (30 min approx.), the solvent was evaporated, the crude was purified by flash chromatography (*n*-hexane/EtOAc 75/25) and desired *anti*-aldol **2g** (37 mg, 3% after two steps) was obtained together with undesired and previously described *syn*-aldol **2a** (28 mg, 2% after two steps).

2g: thick colourless oil. R_F: 0.22 (*n*-hexane/EtOAc 60/40); mp 55 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.90 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.93 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.97 (t, *J* = 7.6 Hz, 3H, $H_{6'}$), 1.34-1.37 (m, 2H, $H_{2''}$), 1.81-1.89 (m, 1H, $H_{3''}$), 2.01-2.07 (m, 2H, $H_{5'}$), 2.26 (br s, 1H, OH), 3.90-3.95 (m, 1H, $H_{2'}$), 3.98-4.14 (m, 2H, H_4), 4.36-4.47 (m, 3H, 2xH_5, $H_{1''}$), 5.45 (ddt, *J* = 15.6, 9.1, 1.5 Hz, 1H, $H_{3'}$), 5.76 (dt, *J* = 15.5, 6.4 Hz, 1H, $H_{4'}$); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 13.3 (q, $C_{6'}$), 21.5 (q, $CH(\underline{C}H_3)_2$), 23.8 (q, $CH(\underline{C}H_3)_2$), 24.4 (d, $C_{3''}$), 25.6 (t, $C_{5'}$), 42.7 (t, $C_{2''}$), 43.8 (t, C_4), 53.4 (d, $C_{2'}$), 61.9 (t, C_5), 71.8 (d, $C_{1''}$), 123.8 (d, $C_{3'}$), 137.8 (d, $C_{4'}$), 153.5 (s, C_2), 174.5 (s, $C_{1'}$); HRMS: calcd for $C_{14}H_{23}NO_4Na$ [$(M + Na)^+$] 292.1525, found 292.1527.

3-((2*R,3*S**)-3-Hydroxy-5-methyl-2-((*Z*)-prop-1-en-1-yl)hexanoyl)oxazolidin-2-one (2h)**

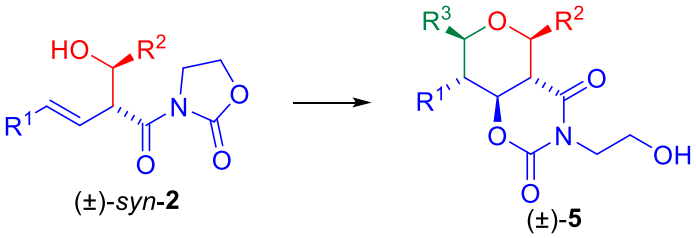


[19] The described *anti*-aldol protocol was developed by Evans and checked with several aromatic aldehydes; the authors declared that aliphatic aldehydes suffer low conversion, although no values were given (see D. A. Evans, J. S. Tedrow, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2002, **124**, 392-393). Indeed, this protocol has been later applied to aliphatic aldehydes affording low yields and diastereoselectivities (see J. M. Botubol, A. J. Macías-Sánchez, I. G. Collado and R. Hernández-Galán, *Eur. J. Org. Chem.*, 2013, **12**, 2420-2427). Alternative attempts to obtain **2g** in a better yield, such as the modification of the *anti*-aldol protocol for enolizable aldehydes (see A. E. May, N. T. Connell, H. A. Dahlmann and T. R. Hoye, *Synlett*, 2010, **13**, 1984-1986) or the treatment of **3a** with LDA at –78 ºC and subsequent addition of isovaleraldehyde, were both unsuccessful.

N-acyl oxazolidin-2-one **3c** (126 mg, 0.75 mmol) was submitted to the general procedure for the aldol addition. ^{1}H-NMR analysis of the crude revealed that isomerization occurred under the employed reaction conditions, because desired aldol **2h** was detected as a 2/1 mixture of the *Z*- and *E*-isomers. Desired **2h**-*Z*-isomer (91 mg, 48%) was obtained as a thick colourless oil after purification by flash chromatography (*n*-hexane/EtOAc 80/20). R_F: 0.21 (*n*-hexane/EtOAc 60/40);[20] ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.89 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.91 (dd, *J* = 6.7, 0.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.12-1.17 (m, 1H, $H_{4'}$), 1.44-1.49 (m, 1H, $H_{4'}$), 1.72 (d, *J* = 6.9 Hz, 3H, $H_{3''}$), 1.76-1.83 (m, 1H, $H_{5'}$), 2.73 (br s, 1H, OH), 3.99-4.07 (m, 3H, 2xH_4, $H_{3'}$), 4.37-4.44 (m, 2H, H_5), 4.88 (dd, *J* = 10.1, 3.9 Hz, 1H, $H_{2'}$), 5.52 (dd, *J* = 10.6, 10.6 Hz, 1H, $H_{1''}$), 5.80-5.85 (m, 1H, $H_{2''}$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 14.1 (q, $C_{3''}$), 21.9 (q, $CH(\underline{C}H_3)_2$), 23.7 (q, $CH(\underline{C}H_3)_2$), 24.5 (d, $C_{5'}$), 42.9 (t, C_4 or $C_{4'}$), 43.1 (t, C_4 or $C_{4'}$), 46.8 (d, $C_{2'}$), 62.0 (t, C_5), 70.7 (d, $C_{3'}$), 123.3 (d, $C_{1''}$), 131.1 (d, $C_{2''}$), 153.3 (s, C_2), 174.9 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 238 $(M - OH)^+$ (1), 169 (52), 142 (6), 82 (100); HRMS: calcd for $C_{13}H_{21}NO_4$ $[(M)^+]$ 255.1471, found 255.1460.

General procedures for the synthesis of the bicycles (5). Description of undesired rearranged by-products (6)

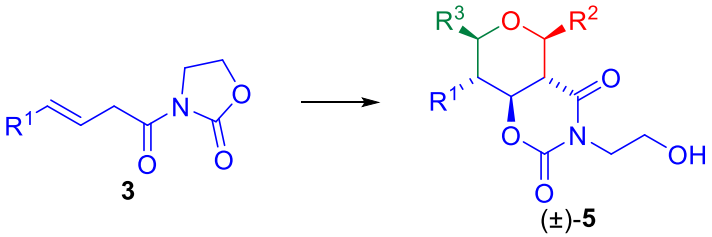
General procedure for the Prins cyclization



To a solution of the homoallylic alcohol and the aldehyde R^3CHO (1.5 eq) in dry DCM (0.1 M) was added, under Ar atmosphere, $BF_3{\cdot}OEt_2$ (2.5 eq). Once TLC analysis showed full conversion (less than 30 min), the mixture was quenched with H_2O. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated.[18] The crude was purified by flash chromatography (the bicycle is usually slightly more apolar than the starting homoallylic alcohol) to yield the desired product; traces of an UV-visible polar by-product, the 2-oxonia-Cope rearranged isomer **6**, could be punctually detected. Bicycles **5** are highly stable, and they can be stored without an Ar atmosphere at rt without decomposition.

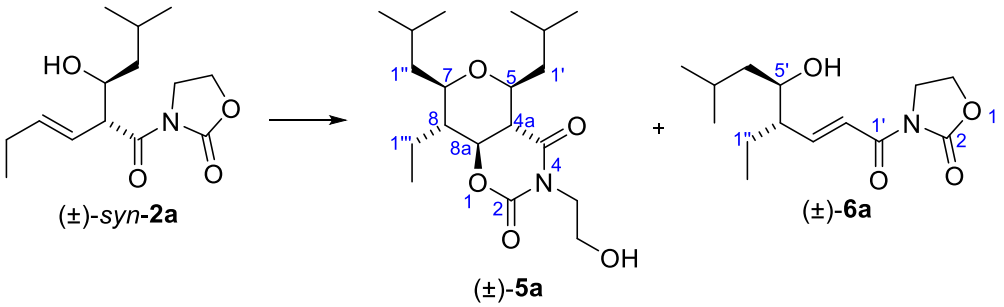
General procedure for the one-pot Evans–Aldol–Prins (one-pot EAP) cyclization

[20] Desired *Z*-isomer is slightly more polar than minority *E*-isomer: R_F 0.36 facing 0.39 (*n*-hexane/EtOAc 60/40 two times).



A solution of the *N*-acyl oxazolidin-2-one in dry DCM (1 M) was cooled to –78 ºC. TEA (1.3 eq) and a 1 M solution of *n*-Bu_2BOTf in DCM (1.2 eq) were dropped under an Ar atmosphere sequentially and the mixture was stirred at that temperature for 30 min. Then, it was warmed to 0 ºC, and after 20 min it was re-cooled to –78 ºC, the aldehyde R^2CHO (1 eq) was added and the mixture was allowed to warm to rt. After 15 h, the aldehyde R^3CHO (1.5 eq) and $BF_3{\cdot}OEt_2$ (2.5 eq) were sequentially added under an Ar atmosphere. Once TLC analysis revealed full conversion (less than 30 min), the mixture was quenched and purified as described above in the general procedure for the Prins cyclization.

(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5,7-diisobutyltetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5a)**



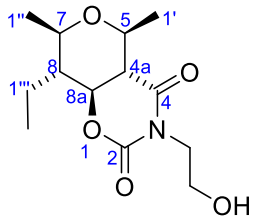
Aldol **2a** (76 mg, 0.28 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 75/25), compound **5a** (78 mg, 78%, >95:5 dr). Alternatively, *N*-acyl oxazolidin-2-one **3a** (4.52 g, 24.70 mmol) was submitted to the general procedure for the one-pot EAP cyclization. Once completed, 60 g of silica gel 60 (35–70 mesh) were added to the mixture and the solvent was removed in a rotavap. The crude was purified by flash chromatography (*n*-hexane/EtOAc 80/20) to yield compound **5a** (5.26 g, 60%, 85:15 dr). When the system $Fe(acac)_3$/TMSCl (0.1/1 eq) was employed as promotor instead of $BF_3{\cdot}OEt_2$ (see Scheme 2 in the manuscript), bicycle **5a** (43%, 85:15 dr) was obtained together with undesired rearranged by-product **6a** (7%).

5a: white solid. R_F: 0.45 (*n*-hexane/EtOAc 50/50); mp 96 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.86 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.90 (t, *J* = 7.5 Hz, 3H, $H_{2'''}$), 0.92 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.94 (d, *J* = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.31-1.37 (m, 1H, $H_{1''}$), 1.43-1.51 (m, 2H, $H_{1'}$, $H_{1''}$), 1.54-1.64 (m, 2H, H_8, $H_{1'''}$), 1.69-1.78 (m, 1H, $H_{1'''}$), 1.86-1.98 (m, 2H, $C\underline{H}(CH_3)_2$), 2.09-2.14 (m, 1H, $H_{1'}$), 2.41 (dd, *J* = 12.0, 9.7, 1H, H_{4a}), 3.19 (td, *J* = 10.5, 1.7 Hz, 1H, H_7), 3.53 (td, *J* = 10.1, 1.9 Hz, 1H, H_5), 3.76-3.85 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.89 (ddd, *J* = 13.9, 6.9, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.10 (ddd, *J* = 14.1, 5.8, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.23 (dd, *J* = 12.0, 10.4 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.3 (q, $C_{2'''}$), 18.5 (t, $C_{1'''}$), 21.0 (q, $CH(\underline{C}H_3)_2$), 21.1 (q, $CH(\underline{C}H_3)_2$), 23.9 (q, $CH(\underline{C}H_3)_2$), 24.06 (q, $CH(\underline{C}H_3)_2$), 24.09 (d, $\underline{C}H(CH_3)_2$), 24.4 (d, $\underline{C}H(CH_3)_2$), 41.5 (t, $C_{1''}$), 43.4 (t, $C_{1'}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 45.7 (d, C_8), 48.0 (d, C_{4a}),

61.1 (t, $NCH_2\underline{C}H_2OH$), 72.9 (d, C_5), 75.2 (d, C_7), 76.9 (d, C_{8a}), 152.5 (s, C_2), 169.6 (s, C_4); MS (EI) m/z (relative intensity): 356 (2), 355 $(M)^+$ (3), 338 (1), 312 (6), 298 (M – *i*-Bu)$^+$ (100), 254 (27), 242 (33), 226 (53); HRMS: calcd for $C_{19}H_{33}NO_5$ [$(M)^+$] 355.2359, found 355.2345.

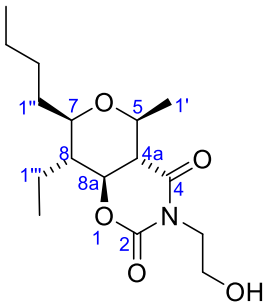
3-((4*S,5*R**,*E*)-4-Ethyl-5-hydroxy-7-methyloct-2-enoyl)oxazolidin-2-one (6a)**: thick colourless oil. R_F: 0.17 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.90 (t, *J* = 7.4 Hz, 3H, $H_{2''}$), 0.90 (d, *J* = 6.6 Hz, 3H, $C_{7'}(C\underline{H}_3)_2$), 0.92 (d, *J* = 6.6 Hz, 3H, $C_{7'}(C\underline{H}_3)_2$), 1.21-1.24 (m, 1H, $H_{6'}$), 1.33-1.39 (m, 1H, $H_{6'}$), 1.48-1.53 (m, 1H, $H_{1''}$), 1.62-1.68 (m, 1H, $H_{1''}$), 1.75-1.81 (m, 1H, $H_{7'}$), 2.16-2.21 (m, 1H, $H_{4'}$), 3.73-3.77 (m, 1H, $H_{5'}$), 4.08 (t, *J* = 8.0 Hz, 2H, H_4), 4.43 (t, *J* = 8.0 Hz, 2H, H_5), 7.07 (dd, *J* = 15.5, 9.7 Hz, 1H, $H_{3'}$), 7.26 (d, *J* = 15.5, 1H, $H_{2'}$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 12.1 (q, $C_{2''}$), 22.0 (q, $C_{7'}(\underline{C}H_3)_2$), 23.7 (q, $C_{7'}(\underline{C}H_3)_2$), 24.0 (t, $C_{1''}$), 24.7 (d, $C_{7'}$), 42.9 (t, C_4), 44.7 (t, $C_{6'}$), 51.2 (d, $C_{4'}$), 62.2 (t, C_5), 71.7 (d, $C_{5'}$), 122.4 (d, $C_{2'}$), 151.3 (d, $C_{3'}$), 153.7 (s, C_2), 165.0 (s, $C_{1'}$); HRMS: calcd for $C_{14}H_{23}NO_4Na$ [$(M + Na)^+$] 292.1525, found 292.1529.

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



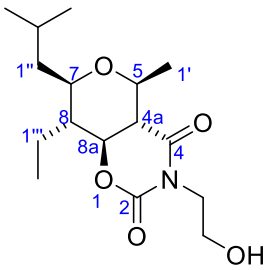
Aldol **2b** (15 mg, 65 μmol) and acetaldehyde (29 μL of a 3.3 M solution in DCM, 1.5 eq) were submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **5b** (14 mg, 78%, >95:5 dr). Alternatively, *N*-acyl oxazolidin-2-one **3a** (88 mg, 0.48 mmol) was submitted to the general procedure for the one-pot EAP cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30) to yield compound **5b** (71 mg, 54%, >95:5 dr) as a thick colourless oil. R_F: 0.29 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.92 (t, *J* = 7.5 Hz, 3H, $H_{2'''}$), 1.27 (d, *J* = 6.1 Hz, 3H, $H_{1''}$), 1.54 (d, *J* = 6.1 Hz, 3H, $H_{1'}$), 1.56-1.63 (m, 2H, H_8, 1x$H_{1'''}$), 1.67-1.77 (m, 1H, $H_{1'''}$), 2.08 (br s, 1H, OH), 2.39 (dd, *J* = 12.1, 9.7 Hz, 1H, H_{4a}), 3.32 (dq, *J* = 9.8, 6.1 Hz, 1H, H_7), 3.61 (dq, *J* = 9.5, 6.1 Hz, 1H, H_5), 3.76-3.85 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.89 (ddd, *J* = 13.8, 6.7, 4.3 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.08 (ddd, *J* = 13.8, 5.5, 4.3 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.20 (dd, *J* = 11.7, 10.4 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.6 (q, $C_{2'''}$), 19.0 (t, $C_{1'''}$), 19.1 (q, $C_{1''}$), 21.0 (q, $C_{1'}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 47.0 (d, C_8), 49.1 (d, C_{4a}), 61.0 (t, $NCH_2\underline{C}H_2OH$), 71.1 (d, C_5), 74.0 (d, C_7), 76.6 (d, C_{8a}), 152.3 (s, C_2), 169.3 (s, C_4); HRMS: calcd for $C_{13}H_{21}NO_5Na$ [$(M + Na)^+$] 294.1317, found 294.1324.

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



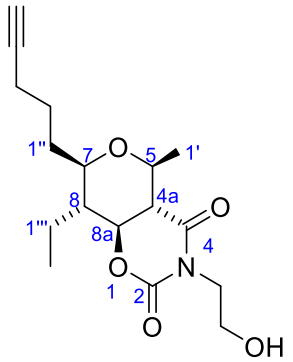
Aldol **2b** (49 mg, 0.22 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **5c** (48 mg, 69%, >95:5 dr) as a colourless oil. R_F: 0.39 (*n*-hexane/EtOAc 30/70); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.91 (t, *J* = 7.2 Hz, 6H, 3x$H_{4''}$, 3x$H_{2'''}$), 1.26-1.37 (m, 3H, 1x$H_{2''}$, 2x$H_{3''}$), 1.38-1.45 (m, 1H, $H_{1''}$), 1.47-1.53 (m, 1H, $H_{2''}$), 1.53 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 1.56-1.61 (m, 1H, $H_{1'''}$), 1.62-1.69 (m, 2H, H_8, 1x$H_{1''}$), 1.70-1.77 (m, 1H, $H_{1'''}$), 2.10 (br s, 1H, OH), 2.37 (dd, *J* = 11.8, 9.8 Hz, 1H, H_{4a}), 3.15 (td, *J* = 8.9, 2.1 Hz, 1H, H_7), 3.56 (dq, *J* = 9.5, 5.8 Hz, 1H, H_5), 3.75-3.84 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.89 (ddd, *J* = 13.7, 6.8, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.08 (ddd, *J* = 13.7, 5.8, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.20 (dd, *J* = 11.8, 10.8 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.6 (q, $C_{2'''}$), 14.2 (q, $C_{4''}$), 18.7 (t, $C_{1'''}$), 20.9 (q, $C_{1'}$), 22.8 (t, $C_{3''}$), 27.5 (t, $C_{2''}$), 32.0 (t, $C_{1''}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 45.1 (d, C_8), 49.2 (d, C_{4a}), 61.0 (t, $NCH_2\underline{C}H_2OH$), 71.2 (d, C_5), 76.8 (d, C_{8a}), 77.4 (d, C_7), 152.4 (s, C_2), 169.4 (s, C_4); HRMS: calcd for $C_{16}H_{27}NO_5Na$ [$(M + Na)^+$] 336.1787, found 336.1776.

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



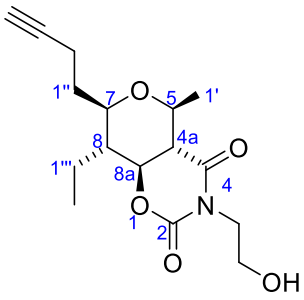
Aldol **2b** (36 mg, 0.16 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **5d** (35 mg, 70%, >95:5 dr) as a thick colourless oil. R_F: 0.37 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.87 (d, *J* = 6.5 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.91 (t, *J* = 7.6 Hz, 3H, $H_{2'''}$), 0.94 (d, *J* = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.31-1.38 (m, 1H, $H_{1''}$), 1.40-1.45 (m, 1H, $H_{1''}$), 1.54 (d, *J* = 6.1 Hz, 3H, $H_{1'}$), 1.56-1.67 (m, 2H, H_8, 1x$H_{1'''}$), 1.69-1.77 (m, 1H, $H_{1'''}$), 1.87-1.94 (m, 1H, $H_{2''}$), 1.97 (br s, 1H, OH), 2.38 (dd, *J* = 10.0, 2.0 Hz, 1H, H_{4a}), 3.21 (td, *J* = 10.0, 2.0 Hz, 1H, H_7), 3.56 (dq, *J* = 9.6, 6.0 Hz, 1H, H_5), 3.74-3.86 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.90 (ddd, *J* = 14.0, 6.8, 4.3 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.09 (ddd, *J* = 14.0, 5.7, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.21 (dd, *J* = 11.8, 10.7 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.4 (q, $C_{2'''}$), 18.5 (t, $C_{1'''}$), 21.0 (q, $C_{1'}$), 21.4 (q, $CH(\underline{C}H_3)_2$), 24.0 (q, $CH(\underline{C}H_3)_2$), 24.2 (d, $C_{2''}$), 41.4 (t, $C_{1''}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 45.6 (d, C_8), 49.2 (d, C_{4a}), 61.1 (t, $NCH_2\underline{C}H_2OH$), 71.2 (d, C_5), 75.5 (d, C_7), 76.8 (d, C_{8a}), 152.4 (s, C_2), 169.4 (s, C_4); HRMS: calcd for $C_{16}H_{27}NO_5Na$ [$(M + Na)^+$] 336.1787, found 336.1788.

(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5-methyl-7-(pent-4-yn-1-yl)tetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5e)**



Aldol **2b** (19 mg, 84 μmol) and hex-5-ynal (12 mg, 0.13 mmol, 1.5 eq)[21] were submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **5e** (18 mg, 65%, >95:5 dr) as a thick colourless oil. R_F: 0.20 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.93 (t, *J* = 7.6 Hz, 3H, $H_{2'''}$), 1.49-1.52 (m, 1H, $H_{1''}$), 1.53 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 1.57-1.64 (m, 2H, 1x$H_{2''}$, 1x$H_{1'''}$), 1.64-1.69 (m, 1H, H_8), 1.71-1.81 (m, 2H, 1x$H_{2''}$, 1x$H_{1'''}$), 1.82-1.87 (m, 1H, $H_{1''}$), 1.95 (br s, 1H, OH), 1.96 (t, *J* = 2.6 Hz, 1H, $H_{5''}$), 2.23 (td, *J* = 7.0, 2.6 Hz, 2H, $H_{3''}$), 2.38 (dd, *J* = 12.1, 9.6 Hz, 1H, H_{4a}), 3.20 (td, *J* = 9.5, 2.4 Hz, 1H, H_7), 3.57 (dq, *J* = 9.7, 6.0 Hz, 1H, H_5), 3.78-3.85 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.90 (ddd, *J* = 14.0, 6.9, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.10 (ddd, *J* = 14.0, 5.9, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.21 (dd, *J* = 12.0, 10.5 Hz, 1H, H_{8a}); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.5 (q, $C_{2'''}$), 18.3 (t, $C_{3''}$), 18.6 (t, $C_{1'''}$), 20.9 (q, $C_{1'}$), 24.2 (t, $C_{2''}$), 31.1 (t, $C_{1''}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 45.1 (d, C_8), 49.1 (d, C_{4a}), 61.1 (t, $NCH_2\underline{C}H_2OH$), 68.8 (d, $C_{5''}$), 71.2 (d, C_5), 76.65 (d, C_{8a}), 76.73 (d, C_7), 84.3 (s, $C_{4''}$), 152.4 (s, C_2), 169.3 (s, C_4); MS (EI) m/z (relative intensity): 308 $(M - Me)^+$ (1), 256 (25), 81 (48), 69 (100); HRMS: calcd for $C_{17}H_{25}NO_5$ $[(M)^+]$ 323.1733, found 323.1725.

(4a*S,5*S**,7*R**,8*R**,8a*S**)-7-(But-3-yn-1-yl)-8-ethyl-3-(2-hydroxyethyl)-5-methyltetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5f)**

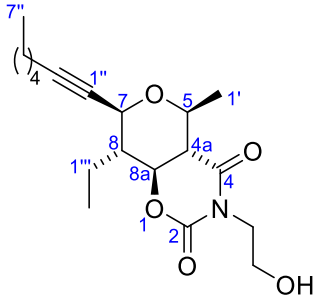


Aldol **2b** (19 mg, 84 μmol) and pent-4-ynal (10 mg, 0.12 mmol, 1.5 eq)[21] were submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **5f** (16 mg, 60%, >95:5 dr) as a thick colourless oil. R_F: 0.20 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.93 (t, *J* = 7.6 Hz, 3H, $H_{2'''}$), 1.53 (d, *J* = 6.1 Hz, 3H, $H_{1'}$), 1.57-1.62 (m, 2H, 1x$H_{1''}$,

[21] It was synthesized through a PCC-mediated oxidation of the corresponding commercial alcohol (see L. S. Kocsis, E. Benedetti and K. M. Brummond, *Org. Lett.*, 2012, **14**, 4430-4433), and then was employed in the Prins cyclization without further purification.

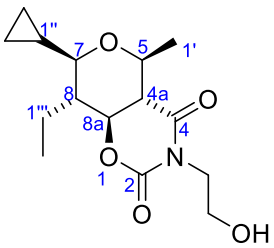
1x$H_{1'''}$), 1.63-1.69 (m, 1H, H_8), 1.73-1.79 (m, 1H, $H_{1'''}$), 1.89-1.93 (m, 1H, $H_{1''}$), 1.94 (t, *J* = 2.6 Hz, 1H, $H_{4''}$), 2.02 (br s, 1H, OH), 2.35-2.40 (m, 2H, $H_{2''}$), 2.38 (dd, *J* = 12.2, 9.6 Hz, 1H, H_{4a}), 3.33 (td, *J* = 9.9, 2.2 Hz, 1H, H_7), 3.60 (dq, *J* = 9.7, 6.1 Hz, 1H, H_5), 3.77-3.84 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.89 (ddd, *J* = 14.1, 6.9, 4.3 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.08 (ddd, *J* = 14.2, 6.0, 4.5 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.24 (dd, *J* = 12.1, 10.6 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.4 (q, $C_{2'''}$), 14.7 (t, $C_{2''}$), 18.4 (t, $C_{1'''}$), 20.9 (q, $C_{1'}$), 31.2 (t, $C_{1''}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 45.0 (d, C_8), 49.1 (d, C_{4a}), 61.0 (t, $NCH_2\underline{C}H_2OH$), 68.8 (d, $C_{4''}$), 71.2 (d, C_5), 75.5 (d, C_7), 76.4 (d, C_{8a}), 83.9 (s, $C_{3''}$), 152.3 (s, C_2), 169.2 (s, C_4); MS (EI) m/z (relative intensity): 310 $(M + H)^+$ (1), (25), 81 (31), 69 (100); HRMS: calcd for $C_{16}H_{23}NO_5$ [$(M)^+$] 309.1576, found 309.1575.

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



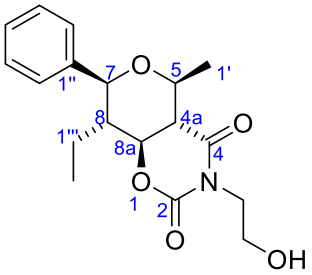
Aldol **2b** (26 mg, 0.12 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **5g** (19 mg, 46%, 90:10 dr) as a yellowish solid. R_F: 0.22 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.89 (t, *J* = 7.1 Hz, 3H, $H_{7''}$), 1.00 (t, *J* = 7.7 Hz, 3H, $H_{2'''}$), 1.27-1.40 (m, 4H, $H_{5''}$, $H_{6''}$), 1.49-1.56 (m, 2H, $H_{4''}$), 1.60 (d, *J* = 5.8 Hz, 3H, $H_{1'}$), 1.72-1.80 (m, 1H, $H_{1'''}$), 1.80-1.86 (m, 1H, $H_{1'''}$), 1.89-1.95 (m, 1H, H_8), 1.97 (br s, 1H, OH), 2.24 (td, *J* = 7.3, 1.9 Hz, 2H, $H_{3''}$), 2.44 (dd, *J* = 11.9, 9.7 Hz, 1H, H_{4a}), 3.64 (dq, *J* = 9.5, 5.9 Hz, 1H, H_5), 3.75-3.85 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.89 (ddd, *J* = 14.0, 6.9, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 3.94 (dt, *J* = 10.5, 2.0 Hz, 1H, H_7), 4.04-4.12 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.19 (dd, *J* = 11.9, 10.8 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.9 (q, $C_{2'''}$), 14.1 (q, $C_{7''}$), 18.9 (t, $C_{3''}$), 20.0 (t, $C_{1'''}$), 20.9 (q, $C_{1'}$), 22.3 (t, $C_{6''}$), 28.2 (t, $C_{4''}$), 31.2 (t, $C_{5''}$), 44.6 (t, $N\underline{C}H_2CH_2OH$), 46.3 (d, C_8), 48.7 (d, C_{4a}), 60.9 (t, $NCH_2\underline{C}H_2OH$), 69.6 (d, C_7), 71.7 (d, C_5), 76.1 (s, $C_{1''}$), 76.3 (d, C_{8a}), 88.1 (s, $C_{2''}$), 152.0 (s, C_2), 168.9 (s, C_4); HRMS: calcd for $C_{19}H_{29}NO_5Na$ [$(M)^+$] 374.1943, found 374.1951.

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



Aldol **2b** (39 mg, 0.17 mmol) and cyclopropanecarbaldehyde (18 mg, 0.26 mmol, 1.5 eq)[22] was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **5h** (33 mg, 63%, >95:5 dr) as a white solid. R_F: 0.19 (*n*-hexane/EtOAc 60/40); mp 74 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.34-0.44 (m, 2H, $C_{1''}C\underline{H}_2$), 0.54-0.59 (m, 1H, $C_{1''}C\underline{H}_2$), 0.61-0.66 (m, 1H, $C_{1''}C\underline{H}_2$), 0.88-0.95 (m, 1H, $H_{1''}$), 0.99 (t, *J* = 7.3 Hz, 3H, $H_{2'''}$), 1.54 (d, *J* = 6.1 Hz, 3H, $H_{1'}$), 1.77-1.84 (m, 3H, H_8, $H_{1'''}$), 2.07 (br s, 1H, OH), 2.38 (dd, *J* = 12.1, 9.6 Hz, 1H, H_{4a}), 2.55 (dd, *J* = 9.3, 8.1 Hz, 1H, H_7), 3.51 (dq, *J* = 9.6, 6.1 Hz, 1H, H_5), 3.75-3.82 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.88 (ddd, *J* = 14.0, 6.7, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.07 (ddd, *J* = 14.0, 5.8, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.17 (dd, *J* = 12.1, 10.2 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 2.0 (t, $C_{2''}$), 4.3 (t, $C_{2''}$), 10.4 (q, $C_{2'''}$), 14.6 (d, $C_{1''}$), 19.1 (t, $C_{1'''}$), 20.9 (q, $C_{1'}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 47.1 (d, C_8), 49.0 (d, C_{4a}), 61.0 (t, $NCH_2\underline{C}H_2OH$), 71.1 (d, C_5), 77.0 (d, C_{8a}), 81.4 (d, C_7), 152.3 (s, C_2), 169.3 (s, C_4); MS (EI) m/z (relative intensity): 297 $(M)^+$ (6), 282 $(M - Me)^+$ (2), 268 (1), 256 (2), 253 (7), 241 (13), 211 (2), 184 (10); HRMS: calcd for $C_{15}H_{23}NO_5$ $[(M)^+]$ 297.1576, found 297.1574.

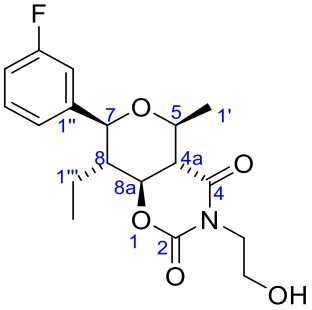
(4a*S,5*S**,7*S**,8*S**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5-methyl-7-phenyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5i)**



Aldol **2b** (110 mg, 0.48 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **5i** (117 mg, 72%, >95:5 dr) as a white solid. R_F: 0.29 (*n*-hexane/EtOAc 60/40); mp 130 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.71 (t, *J* = 7.4 Hz, 3H, $H_{2'''}$), 1.27-1.36 (m, 1H, $H_{1'''}$), 1.47-1.56 (m, 1H, $H_{1'''}$), 1.60 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 2.00-2.06 (m, 1H, H_8), 2.16 (br s, 1H, OH), 2.58 (dd, *J* = 12.2, 9.8 Hz, 1H, H_{4a}), 3.77-3.87 (m, 3H, H_5, $NCH_2C\underline{H}_2OH$), 3.90-3.95 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.09-4.13 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.13 (d, *J* = 10.4 Hz, 1H, H_7), 4.37 (dd, *J* = 12.1, 10.5 Hz, 1H, H_{8a}), 7.31-7.40 (m, 5H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 10.0 (q, $C_{2'''}$), 19.3 (t, $C_{1'''}$), 21.1 (q, $C_{1'}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 46.7 (d, C_8), 49.0 (d, C_{4a}), 60.9 (t, $NCH_2\underline{C}H_2OH$), 71.8 (d, C_5), 77.2 (d, C_{8a}), 81.5 (d, C_7), 127.6 (d, 2C, Ph), 128.76 (d, Ph), 128.81 (d, 2C, Ph), 138.8 (s, Ph), 152.2 (s, C_2), 169.1 (s, C_4); MS (EI) m/z (relative intensity): 334 (1), 333 $(M)^+$ (6), 289 (17), 212 (1), 197 (3), 183 (3), 168 (2); HRMS: calcd for $C_{18}H_{23}NO_5$ $[(M)^+]$ 333.1576, found 333.1561.

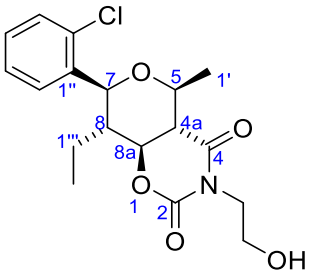
(4a*S,5*S**,7*S**,8*S**,8a*S**)-8-Ethyl-7-(3-fluorophenyl)-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5j)**

[22] Cyclopropanecarbaldehyde is an apparently problematic aldehyde for the Prins cyclization due to the presence of an acid-sensitive motif, see (a) A. B., III Smith and V. Simov, *Org. Lett.*, 2006, **8**, 3315-3318; (b) D. C. Poulter and S. J. Winstein, *J. Am. Chem. Soc.*, 1969, **91**, 3650-3652.



Aldol **2b** (56 mg, 0.25 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **5j** (56 mg, 64%, >95:5 dr) as a thick colourless oil. R_F: 0.18 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.72 (t, *J* = 7.7 Hz, 3H, $H_{2'''}$), 1.27-1.37 (m, 1H, $H_{1'''}$), 1.47-1.56 (m, 1H, $H_{1'''}$), 1.59 (d, *J* = 5.9 Hz, 3H, $H_{1'}$), 1.93-2.00 (m, 1H, H_8), 2.32 (br s, 1H, OH), 2.58 (dd, *J* = 12.2, 9.7 Hz, 1H, H_{4a}), 3.76-3.87 (m, 3H, H_5, NCH_2CH_2OH), 3.93 (ddd, *J* = 14.0, 6.4, 4.7 Hz, 1H, NCH_2CH_2OH), 4.08-4.13 (m, 1H, NCH_2CH_2OH), 4.13 (d, *J* = 10.1 Hz, 1H, H_7), 4.36 (dd, *J* = 11.9, 10.5 Hz, 1H, H_{8a}), 7.01-7.09 (m, 2H, Ar), 7.10-7.14 (m, 1H, Ar), 7.31-7.36 (m, 1H, Ar); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 10.1 (q, $C_{2'''}$), 19.2 (t, $C_{1'''}$), 21.0 (q, $C_{1'}$), 44.5 (t, NCH_2CH_2OH), 46.8 (d, C_8), 49.0 (d, C_{4a}), 60.8 (t, NCH_2CH_2OH), 71.9 (d, C_5), 77.0 (d, C_{8a}), 80.8 (d, C_7), 114.6 (s, $J_{C\text{-}F}$ = 21.8 Hz, Ar), 115.7 (d, $J_{C\text{-}F}$ = 21.3 Hz, Ar), 123.4 (d, $J_{C\text{-}F}$ = 2.7 Hz, Ar), 130.3 (d, $J_{C\text{-}F}$ = 8.3 Hz, Ar), 141.3 (s, $J_{C\text{-}F}$ = 7.0 Hz, Ar), 152.1 (s, C_2), 163.1 (s, $J_{C\text{-}F}$ = 246.8 Hz, Ar), 169.0 (s, C_4); HRMS: calcd for $C_{18}H_{22}NO_5FNa$ [(M + Na)$^+$] 374.1380, found 374.1383.

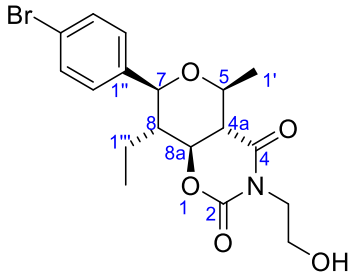
(4a*S,5*S**,7*S**,8*S**,8a*S**)-7-(2-Chlorophenyl)-8-ethyl-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5k)**



Aldol **2b** (102 mg, 0.45 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **5k** (100 mg, 60%, >95:5 dr) as a white solid. R_F: 0.24 (*n*-hexane/EtOAc 60/40); mp 153 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.74 (t, *J* = 7.7 Hz, 3H, $H_{2'''}$), 1.36-1.44 (m, 1H, $H_{1'''}$), 1.49-1.56 (m, 1H, $H_{1'''}$), 1.59 (d, *J* = 5.8 Hz, 3H, $H_{1'}$), 1.93-1.99 (m, 1H, H_8), 2.04 (br s, 1H, OH), 2.58 (dd, *J* = 12.1, 9.9 Hz, 1H, H_{4a}), 3.79-3.89 (m, 3H, H_5, NCH_2CH_2OH), 3.94 (ddd, *J* = 14.1, 7.0, 4.3 Hz, 1H, NCH_2CH_2OH), 4.13 (ddd, *J* = 14.0, 6.0, 4.7 Hz, 1H, NCH_2CH_2OH), 4.41 (dd, *J* = 11.0, 11.0 Hz, 1H, H_{8a}), 4.79 (d, *J* = 10.2 Hz, 1H, H_7), 7.25-7.29 (m, 1H, Ar), 7.31-7.36 (m, 1H, Ar), 7.37-7.40 (m, 1H, Ar), 7.48-7.49 (m, 1H, Ar); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 10.9 (q, $C_{2'''}$), 19.4 (t, $C_{1'''}$), 21.0 (q, $C_{1'}$), 44.4 (t, NCH_2CH_2OH), 47.1 (d, C_8), 49.0 (d, C_{4a}), 60.6 (t, NCH_2CH_2OH), 71.9 (d, C_5), 76.2 (d, C_7), 77.6 (d, C_{8a}), 127.6 (d, Ar), 128.8 (d, Ar), 129.6 (d, Ar), 129.7 (d, Ar), 133.7 (s, Ar), 136.7 (s, Ar), 152.1 (s, C_2),

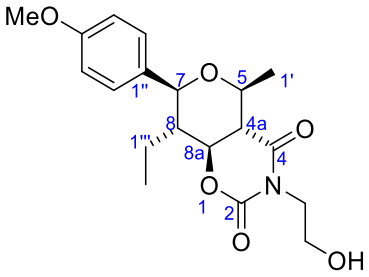
168.9 (s, C_4); MS (EI) m/z (relative intensity): 368 (1), 367 $(M)^+$ (2), 323 (6), 288 (1), 279 (2), 168 (8); HRMS: calcd for $C_{18}H_{22}NO_5Cl$ [$(M)^+$] 367.1187, found 367.1199.

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



Aldol **2b** (39 mg, 0.17 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **5l** (48 mg, 68%, >95:5 dr) as a white solid. R_F: 0.14 (*n*-hexane/EtOAc 60/40); mp 165 ºC (from DCM/*n*-hexane); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.72 (t, *J* = 7.3 Hz, 3H, $H_{2'''}$), 1.24-1.35 (m, 1H, $H_{1'''}$), 1.47-1.55 (m, 1H, $H_{1'''}$), 1.58 (d, *J* = 5.5 Hz, 3H, $H_{1'}$), 1.92-1.99 (m, 1H, H_8), 2.03 (br s, 1H, OH), 2.56 (dd, *J* = 10.7, 10.7 Hz, 1H, H_{4a}), 3.75-3.80 (m, 1H, H_5), 3.80-3.86 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.90-3.95 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.06-4.14 (m, 2H, H_7, 1x$NC\underline{H}_2CH_2OH$), 4.35 (dd, *J* = 11.2, 11.2 Hz, 1H, H_{8a}), 7.22 (d, *J* = 7.8 Hz, 2H, Ar), 7.50 (d, *J* = 7.8 Hz, 2H, Ar); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 10.1 (q, $C_{2'''}$), 19.2 (t, $C_{1'''}$), 21.0 (q, $C_{1'}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 46.7 (d, C_8), 49.0 (d, C_{4a}), 60.7 (t, $NCH_2\underline{C}H_2OH$), 71.8 (d, C_5), 77.0 (d, C_{8a}), 80.7 (d, C_7), 122.6 (s, Ar), 129.3 (d, 2C, Ar), 132.0 (d, 2C, Ar), 137.9 (s, $C_{1''}$), 152.1 (s, C_2), 169.0 (s, C_4); HRMS: calcd for $C_{18}H_{22}{}^{79}BrNO_5Na$ [$(M + Na)^+$] 434.0579, found 434.0569.

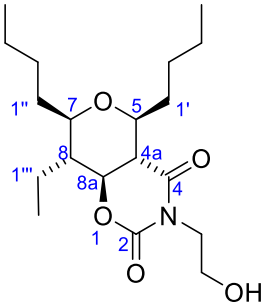
(4a*S,5*S**,7*S**,8*S**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-(4-methoxyphenyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5m)**



Aldol **2b** (119 mg, 0.53 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **5m** (119 mg, 63%, >95:5 dr) as a thick yellowish oil. R_F: 0.18 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.71 (t, *J* = 7.6 Hz, 3H, $H_{2'''}$), 1.28-1.35 (m, 1H, $H_{1'''}$), 1.45-1.55 (m, 1H, $H_{1'''}$), 1.58 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 1.98-2.06 (m, 2H, H_8, OH), 2.58 (dd, *J* = 12.1, 9.6 Hz, 1H, H_{4a}), 3.75-3.87 (m, 3H, H_5, 2x$NCH_2C\underline{H}_2OH$), 3.81 (s, 3H, MeO), 3.93 (ddd, *J* = 13.9, 6.7, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.08 (d, *J* = 10.2 Hz, 1H, H_7), 4.12 (ddd, *J* = 14.0, 5.9, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.35 (dd, *J* = 12.1, 10.7 Hz, 1H, H_{8a}), 6.89-6.91 (m, 2H, Ar), 7.25-7.27 (m, 2H, Ar); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 10.0 (q, $C_{2'''}$), 19.4 (t, $C_{1'''}$), 21.1 (q, $C_{1'}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 46.6 (d, C_8), 49.1 (d, C_{4a}), 55.4 (q, MeO), 61.0 (t, $NCH_2\underline{C}H_2OH$), 71.7 (d, C_5), 77.4 (d,

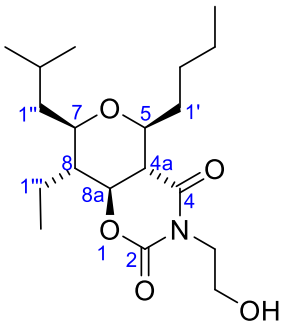
C_{8a}), 81.0 (d, C_7), 114.2 (d, 2C, Ar), 128.9 (d, 2C, Ar), 131.0 (s, $C_{1''}$), 152.3 (s, Ar), 159.9 (s, C_2), 169.2 (s, C_4); MS (EI) m/z (relative intensity): 364 $(M + 1)^+$ (17), 363 $(M)^+$ (77), 345 (1), 333 (1), 348 (1), 318 (1), 258 (2), 183 (5), 121 (100); HRMS: calcd for $C_{19}H_{25}NO_6$ [$(M)^+$] 363.1682, found 363.1683.

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



Aldol **2c** (105 mg, 0.39 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **5n** (91 mg, 66%, >95:5 dr) as a white solid. R_F: 0.39 (*n*-hexane/EtOAc 60/40); mp 58 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.88-0.92 (m, 9H, 3xCH_3), 1.26-1.75 (m, 14H, H_8, 1x$H_{1'}$, 6xCH_2), 2.06 (br s, 1H, OH), 2.26-2.32 (m, 1H, $H_{1'}$), 2.42 (dd, *J* = 12.0, 9.6 Hz, 1H, H_{4a}), 3.10 (td, *J* = 9.5, 2.5 Hz, 1H, H_7), 3.42 (td, *J* = 9.1, 2.1 Hz, 1H, H_5), 3.76-3.84 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.86-3.91 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.06-4.11 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.20 (dd, *J* = 12.0, 10.4 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.5 (q, $C_{2'''}$), 14.17 (q, $C_{4'}$ or $C_{4''}$), 14.19 (q, $C_{4'}$ or $C_{4''}$), 18.6 (t, $C_{1'''}$), 22.5 (t, $C_{3'}$ or $C_{3''}$), 22.6 (t, $C_{3'}$ or $C_{3''}$), 27.57 (t, $C_{2'}$ or $C_{2''}$), 27.62 (t, $C_{2'}$ or $C_{2''}$), 32.0 (t, $C_{1''}$), 34.0 (t, $C_{1'}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 45.3 (d, C_8), 47.5 (d, C_{4a}), 61.0 (t, $NCH_2\underline{C}H_2OH$), 74.6 (d, C_5), 77.0 (d, C_{8a}), 77.1 (d, C_7), 152.5 (s, C_2), 169.5 (s, C_4); HRMS: calcd for $C_{19}H_{33}NO_5Na$ [$(M + Na)^+$] 378.2256, found 378.2248.

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

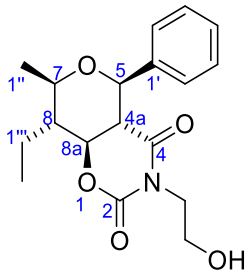


Aldol **2c** (56 mg, 0.21 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 80/20), compound **5o** (37 mg, 50%, >95:5 dr) as a white solid.[23] R_F: 0.39 (*n*-hexane/EtOAc 60/40); mp 83 ºC (from DCM/*n*-hexane); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.86-0.95 (m, 12H, 4xCH_3), 1.28-1.41 (m, 4H, 1x$H_{2'}$, 2x$H_{3'}$, 1x$H_{1''}$), 1.43-1.65 (m, 5H,

[23] Traces of bicycle **5a** (with *i*-Bu chains at positions 5 and 7) were also detected due to the 2-oxonia-Cope rearrangement.

H_8, 1x$H_{1'}$, 1x$H_{2'}$, 1x$H_{1''}$, 1x$H_{1'''}$), 1.69-1.76 (m, 1H, $H_{1'''}$), 1.88-1.95 (m, 1H, $H_{2''}$), 1.99 (br s, 1H, OH), 2.29-2.35 (m, 1H, 1x$H_{1'}$), 2.42 (dd, *J* = 12.0, 9.7 Hz, 1H, H_{4a}), 3.18 (td, *J* = 10.5, 2.3 Hz, 1H, H_7), 3.42 (td, *J* = 9.6, 1.9 Hz, 1H, H_5), 3.77-3.84 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.89 (ddd, *J* = 13.9, 6.9, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.09 (ddd, *J* = 14.0, 5.6, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.22 (dd, *J* = 11.7, 10.6 Hz, 1H, H_{8a}); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.4 (q, $C_{2'''}$), 14.2 (q, $C_{4'}$), 18.5 (t, $C_{1'''}$), 21.1 (q, $CH(\underline{C}H_3)_2$), 22.5 (t, $C_{3'}$), 24.0 (q, $CH(\underline{C}H_3)_2$), 24.2 (d, $C_{2''}$), 27.7 (t, $C_{2'}$), 34.0 (t, $C_{1'}$), 41.5 (t, $C_{1''}$), 44.5 (t, $N\underline{C}H_2CH_2OH$), 45.7 (d, C_8), 47.6 (d, C_{4a}), 61.1 (t, $NCH_2\underline{C}H_2OH$), 74.7 (d, C_5), 75.2 (d, C_7), 76.9 (d, C_{8a}), 152.5 (s, C_2), 169.6 (s, C_4); HRMS: calcd for $C_{19}H_{33}NO_5Na$ [$(M + Na)^+$] 378.2256, found 378.2263.

(4a*R,5*R**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-methyl-5-phenyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5p)**

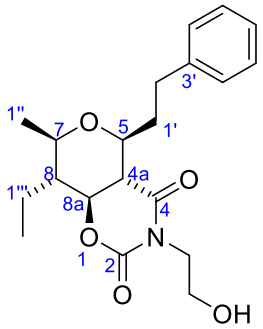


Aldol **2d** (56 mg, 0.19 mmol) and acetaldehyde (0.09 mL of a 3.3 M solution in DCM, 1.5 eq) were submitted to the general procedure for the Prins cyclization. After purification by flash chromatography (*n*-hexane/EtOAc 80/20), bicycle **5b** (21 mg, 55%, >95:5 dr)[24] and desired title compound **5p** (22 mg, 35%, 90:10 dr) were isolated.

5p: thick colourless oil. R_F: 0.25 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.99 (t, *J* = 7.3 Hz, 3H, $H_{2'''}$), 1.33 (d, *J* = 6.1 Hz, 3H, $H_{1''}$), 1.64-1.71 (m, 1H, $H_{1'''}$), 1.76-1.84 (m, 2H, H_8, 1x$H_{1'''}$), 1.87 (br s, 1H, OH), 3.02 (dd, *J* = 11.8, 9.9 Hz, 1H, H_{4a}), 3.52 (dq, *J* = 9.7, 6.2 Hz, 1H, H_7) 3.68-3.76 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.81 (ddd, *J* = 14.0, 7.1, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 3.98 (ddd, *J* = 14.1, 5.7, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.39 (dd, *J* = 11.8, 10.6 Hz, 1H, H_{8a}), 4.50 (d, *J* = 9.9 Hz, 1H, H_5), 7.31-7.35 (m, 1H, Ph), 7.36-7.39 (m, 2H, Ph), 7.40-7.43 (m, 2H, Ph); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.7 (q, $C_{2'''}$), 19.0 (t, $C_{1'''}$), 19.2 (q, $C_{1''}$), 44.4 (t, $N\underline{C}H_2CH_2OH$), 47.0 (d, C_8), 48.3 (d, C_{4a}), 60.9 (t, $NCH_2\underline{C}H_2OH$), 74.9 (d, C_7), 76.7 (d, C_{8a}), 77.5 (d, C_5), 128.0 (d, 2C, Ph), 128.5 (d, 2C, Ph), 128.7 (d, Ph), 139.5 (s, Ph), 152.2 (s, C_2), 168.5 (s, C_4); HRMS: calcd for $C_{18}H_{23}NO_5Na$ [$(M + Na)^+$] 356.1474, found 356.1484.

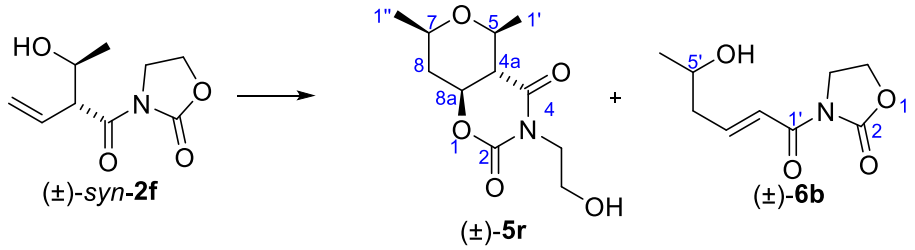
(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-methyl-5-phenethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5q)**

[24] Obtained as fruit of side chain exchange via 2-oxonia-Cope rearrangement.



Aldol **2e** (77 mg, 0.24 mmol) and acetaldehyde (0.1 mL of a 3.3 M solution in DCM, 1.5 eq) were submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), compound **5q** (47 mg, 54%, 90:10 dr) as a white solid. R_F: 0.29 (*n*-hexane/EtOAc 60/40); mp 117 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.92 (t, *J* = 7.5 Hz, 3H, $H_{2'''}$), 1.31 (d, *J* = 6.1 Hz, 3H, $H_{1''}$), 1.54-1.63 (m, 2H, H_8, 1x$H_{1'''}$), 1.67-1.75 (m, 1H, $H_{1'''}$), 1.83-1.90 (m, 1H, $H_{1'}$), 2.24 (br s, 1H, OH), 2.46 (dd, *J* = 12.1, 9.7 Hz, 1H, H_{4a}), 2.63-2.70 (m, 1H, $H_{1'}$), 2.72-2.78 (m, 1H, $H_{2'}$), 2.84-2.90 (m, 1H, $H_{2'}$), 3.22-3.28 (m, 1H, H_7), 3.43 (td, *J* = 9.5, 2.1 Hz, 1H, H_5), 3.72-3.80 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.85 (ddd, *J* = 14.0, 6.4, 4.6 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.04 (dt, *J* = 14.0, 5.3 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.17 (dd, *J* = 12.1, 10.3 Hz, 1H, H_{8a}), 7.16-7.19 (m, 1H, Ar), 7.22-7.24 (m, 2H, Ar), 7.25-7.30 (m, 2H, Ar); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.6 (q, $C_{2'''}$), 18.9 (t, $C_{1'''}$), 19.1 (q, $C_{1''}$), 31.4 (t, $C_{2'}$), 35.5 (t, $C_{1'}$), 44.4 (t, $N\underline{C}H_2CH_2OH$), 47.0 (d, C_8), 47.3 (d, C_{4a}), 60.7 (t, $NCH_2\underline{C}H_2OH$), 73.5 (d, C_5), 73.9 (d, C_7), 76.7 (d, C_{8a}), 125.9 (d, Ph), 128.4 (d, 2C, Ph), 128.7 (d, 2C, Ph), 141.9 (s, $C_{3'}$), 152.3 (s, C_2), 169.2 (s, C_4); HRMS: calcd for $C_{20}H_{27}NO_5Na$ [$(M + Na)^+$] 384.1787, found 384.1798.

(4a*S,5*S**,7*R**,8a*S**)-3-(2-Hydroxyethyl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5r)**



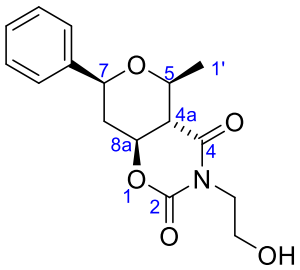
Aldol **2f** (154 mg, 0.77 mmol) and acetaldehyde (0.35 mL of a 3.3 M solution in DCM, 1.5 eq) were submitted to the general procedure for the Prins cyclization. After purification by flash chromatography (*n*-hexane/EtOAc 50/50), desired title compound **5r** (71 mg, 38%, >95:5 dr) and undesired rearranged by-product **6b** (62 mg, 40%) were isolated.

5r: thick colourless oil. R_F: 0.44 (*n*-hexane/EtOAc 20/80); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 1.29 (d, *J* = 6.1 Hz, 3H, $H_{1''}$), 1.57 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 1.57-1.62 (m, 1H, $H_{8,ec}$), 1.83-1.94 (m, 1H, OH), 2.17 (dd, *J* = 12.3, 4.9 Hz, 1H, $H_{8,ax}$), 2.30 (dd, *J* = 12.1, 9.6 Hz, 1H, H_{4a}), 3.50-3.55 (m, 1H, H_7), 3.63 (dq, *J* = 9.6, 6.0 Hz, 1H, H_5), 3.77-3.85 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.89-3.93 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.06-4.14 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.41 (td, *J* = 11.8, 4.9 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 20.9 (q, $C_{1'}$), 21.5 (q, $C_{1''}$), 37.7 (t, C_8), 44.4 (t, $N\underline{C}H_2CH_2OH$), 48.5 (d, C_{4a}), 60.6 (t, $NCH_2\underline{C}H_2OH$), 70.5

(d, C_7), 71.3 (d, C_5), 74.5 (d, C_{8a}), 152.1 (s, C_2), 169.0 (s, C_4); MS (EI) m/z (relative intensity): 244 $(M + H)^+$ (1), 228 $(M - Me)^+$ (8), 213 (24), 200 (100), 184 (5); HRMS: calcd for $C_{11}H_{18}NO_5$ [$(M + H)^+$] 244.1185, found 244.1184.

(*E*)-3-(5-Hydroxyhex-2-enoyl)oxazolidin-2-one (6b): colourless oil. R_F: 0.29 (*n*-hexane/EtOAc 80/20); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 1.26 (d, J = 6.2 Hz, 3H, $H_{6'}$), 1.55 (br s, 1H, OH), 2.45 (dd, J = 7.2, 6.3 Hz, 2H, $H_{4'}$), 4.01 (dt, J = 6.2, 6.2 Hz, 1H, $H_{5'}$), 4.07 (t, J = 8.1 Hz, 2H, H_4), 4.43 (t, J = 8.1 Hz, 2H, H_5), 7.16 (dt, J = 15.4, 7.3 Hz, 1H, $H_{3'}$), 7.31 (d, J = 15.4 Hz, 1H, $H_{2'}$); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 23.4 (q, $C_{6'}$), 42.3 (t, $C_{4'}$), 42.8 (t, C_4), 62.2 (t, C_5), 67.0 (d, $C_{5'}$), 122.6 (d, $C_{2'}$), 147.3 (d, $C_{3'}$), 153.7 (s, C_2), 165.1 (s, $C_{1'}$); MS (EI) m/z (relative intensity): 200 (2), 184 (1), 182 $(M - OH)^+$ (1), 113 (10), 85 (34), 68 (100); HRMS: calcd for $C_9H_{12}NO_3$ [$(M - OH)^+$] 182.0817, found 182.0821.

(4a*S,5*S**,7*S**,8a*S**)-3-(2-Hydroxyethyl)-5-methyl-7-phenyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5s)**

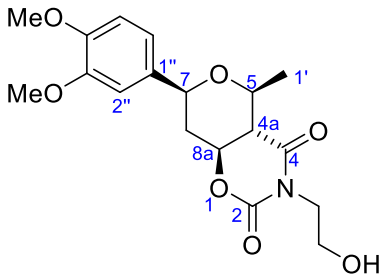


Aldol **2f** (31 mg, 0.16 mmol) was submitted to the general procedure for the Prins cyclization. Once completed, ^{1}H-NMR analysis of the crude revealed a 2.8/1 mixture of the desired product **5s** and the above described bicycle **5r**,[25] together with traces of the corresponding rearranged by-product **6**. After purification by flash chromatography (*n*-hexane/EtOAc 60/40), desired title compound **5s** (19 mg, 39%, 90:10 dr) and undesired bicycle **5r** (2.6 mg, 14%) were isolated.

5s: thick colourless oil. R_F: 0.36 (*n*-hexane/EtOAc 40/60); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 1.66 (d, J = 6.1 Hz, 3H, $H_{1'}$), 1.94 (dt, J = 12.5, 11.5 Hz, 1H, H_8), 1.94 (br s, 1H, OH), 2.41-2.48 (m, 2H, H_8, H_{4a}), 3.78-3.87 (m, 3H, 2x$NCH_2C\underline{H}_2OH$, H_5), 3.94 (ddd, J = 14.0, 6.5, 4.5 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.12 (ddd, J = 14.0, 6.2, 4.7 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.44 (dd, J = 11.5, 1.9 Hz, 1H, H_7), 4.60 (td, J = 11.6, 4.9 Hz, 1H, H_{8a}), 7.29-7.40 (m, 5H, Ar); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 21.0 (q, $C_{1'}$), 37.9 (t, C_8), 44.5 (t, $N\underline{C}H_2CH_2OH$), 48.8 (d, C_{4a}), 60.9 (t, $NCH_2\underline{C}H_2OH$), 72.0 (d, C_5), 74.8 (d, C_{8a}), 76.4 (d, C_7), 126.0 (d, 2C, Ar), 128.3 (d, Ar), 128.8 (d, 2C, Ar), 140.3 (s, Ar), 152.1 (s, C_2), 168.9 (s, C_4); HRMS: calcd for $C_{16}H_{19}NO_5Na$ [$(M + Na)^+$] 328.1161, found 328.1171.

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

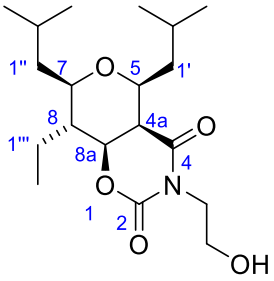
[25] The side chain exchanged compound **5r** was obtained as result of the releasing of ethanal to the medium after the 2-oxonia-Cope rearrangement.



Aldol **2f** (31 mg, 0.16 mmol) was submitted to the general procedure for the Prins cyclization. Once completed, ^{1}H-NMR analysis of the crude revealed the presence of the desired product **5t** together with the previously described side chain exchanged bicycle **5r** (in a 2.9/1 proportion)[25] and traces of the corresponding rearranged by-product **6**. After purification by flash chromatography (*n*-hexane/EtOAc 60/40), desired title compound **5t** (24 mg, 41%, >95:5 dr) and undesired bicycle **5r** (2.8 mg, 14%) were isolated.

5t: thick colourless oil. R_F: 0.27 (*n*-hexane/EtOAc 40/60); ^{1}H-NMR (400 MHz, δ, $CDCl_3$): 1.65 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 1.88 (br s, 1H, OH), 1.96 (ddd, *J* = 11.9, 11.9, 11.9 Hz, 1H, H_8), 2.42 (ddd, *J* = 12.6, 4.9, 2.0 Hz, 1H, H_8), 2.45 (dd, *J* = 12.2, 9.5 Hz, 1H, H_{4a}), 3.79-3.86 (m, 3H, H_5, 2x$NCH_2C\underline{H}_2OH$), 3.88 (s, 3H, MeO), 3.91 (s, 3H, MeO), 3.95 (ddd, *J* = 14.0, 6.6, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.13 (ddd, *J* = 14.0, 5.9, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.38 (dd, *J* = 11.4, 1.8 Hz, 1H, H_7), 4.57 (td, *J* = 11.5, 4.8 Hz, 1H, H_{8a}), 6.84-6.91 (m, 3H, Ar); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 21.0 (q, $C_{1'}$), 37.8 (t, C_8), 44.6 (t, $N\underline{C}H_2CH_2OH$), 48.8 (d, C_{4a}), 56.1 (q, MeO), 56.2 (q, MeO), 61.0 (t, $NCH_2\underline{C}H_2OH$), 72.1 (d, C_5), 74.8 (d, C_{8a}), 76.4 (d, C_7), 109.6 (d, $C_{2''}$), 111.4 (d, $C_{5''}$), 118.5 (d, $C_{6''}$), 132.9 (s, $C_{1''}$), 149.2 (s, $C_{3''}$), 149.3 (s, $C_{4''}$), 152.1 (C_2), 169.0 (C_4); HRMS: calcd for $C_{18}H_{23}NO_7Na$ [$(M + Na)^+$] 388.1372, found 388.1385.

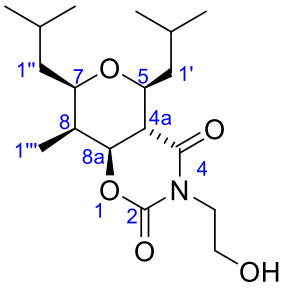
(4a*R,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5,7-diisobutyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5u)**



Aldol **2g** (31 mg, 0.12 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 60/40), compound **5u** (20 mg, 49%, 75:25 dr) as a thick yellowish oil. R_F: 0.44 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.83-0.94 (m, 15H, 5xCH_3), 1.23-1.29 (m, 1H, $H_{1''}$), 1.38-1.42 (m, 1H, $H_{1''}$), 1.45-1.49 (m, 1H, $H_{1'}$), 1.51-1.60 (m, 2H, H_8, $H_{1'''}$), 1.63-1.70 (m, 1H, $H_{1'''}$), 1.72-1.79 (m, 1H, $H_{2'}$), 1.86-1.93 (m, 1H, $H_{2''}$), 2.07 (br m, 1H, OH), 2.40-2.46 (m, 1H, $H_{1'}$), 2.93 (dd, *J* = 6.0, 1.3 Hz, 1H, H_{4a}), 3.19 (t, *J* = 9.9 Hz, 1H, H_7), 3.42 (d, *J* = 9.6 Hz, 1H, H_5), 3.74-3.81 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.90-3.96 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.03-4.08 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.45 (dd, *J* = 11.3, 6.4 Hz, 1H, H_{8a}); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 9.7 (q, $C_{2'''}$), 19.5 (t, $C_{1'''}$), 21.1 (q, $C_{2''}(\underline{C}H_3)_2$), 21.9 (q, $C_{2'}(\underline{C}H_3)_2$), 23.3 (q, $C_{2'}(\underline{C}H_3)_2$), 23.9 (q, $C_{2''}(\underline{C}H_3)_2$), 24.0 (d, $C_{2''}$), 25.5 (d, $C_{2'}$), 41.7 (t, $C_{1''}$), 41.8 (t, $C_{1'}$), 43.7 (d, C_{4a}), 43.8 (d, C_8), 44.0 (t, $N\underline{C}H_2CH_2OH$), 60.9 (t,

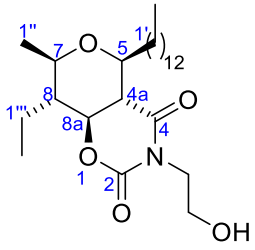
$NCH_2\underline{C}H_2OH$), 75.6 (d, C_5), 77.1 (d, C_{8a}), 77.5 (d, C_7), 151.3 (s, C_2), 168.4 (s, C_4); HRMS: calcd for $C_{19}H_{33}NO_5Na$ [$(M + Na)^+$] 378.2256, found 378.2249.

(4a*S,5*S**,7*R**,8*S**,8a*S**)-3-(2-Hydroxyethyl)-5,7-diisobutyl-8-methyltetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5v)**



Aldol **2h** (48 mg, 0.19 mmol) was submitted to the general procedure for the Prins cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 75/25), compound **5v** (49 mg, 76%, >95:5 dr) as a white solid. R_F: 0.4 (*n*-hexane/EtOAc 60/40); mp 101 ºC (from DCM/*n*-hexane); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.88 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.91-0.94 (m, 9H, $CH(C\underline{H}_3)_2$), 1.00 (d, *J* = 6.9 Hz, 3H, $H_{1'''}$), 1.06-1.12 (m, 1H, $H_{1''}$), 1.47-1.53 (m, 1H, $H_{1'}$), 1.58-1.63 (m, 1H, $H_{1''}$), 1.71-1.77 (m, 1H, $H_{2'}$), 1.89-1.96 (m, 1H, $H_{2''}$), 1.98 (br s, 1H, OH), 2.02-2.06 (m, 1H, $H_{1'}$), 2.07-2.12 (m, 1H, H_8), 2.49 (dd, *J* = 12.7, 9.7, 1H, H_{4a}), 3.37 (ddd, *J* = 9.5, 3.6, 1.8 Hz, 1H, H_7), 3.52 (td, *J* = 9.9, 1.8 Hz, 1H, H_5), 3.75-3.83 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.87 (ddd, *J* = 14.1, 6.8, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.07 (ddd, *J* = 14.0, 6.1, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.49 (dd, *J* = 12.7, 5.1 Hz, 1H, H_{8a}); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 5.9 (q, $C_{1'''}$), 21.2 (q, $CH(\underline{C}H_3)_2$), 22.1 (q, $CH(\underline{C}H_3)_2$), 23.4 (q, $CH(\underline{C}H_3)_2$), 23.9 (q, $CH(\underline{C}H_3)_2$), 24.4 (d, $C_{2'}$), 24.8 (d, $C_{2''}$), 35.6 (d, C_8), 41.3 (t, $C_{1''}$), 42.4 (d, C_{4a}), 43.6 (t, $C_{1'}$), 44.4 (t, $N\underline{C}H_2CH_2OH$), 60.9 (t, $NCH_2\underline{C}H_2OH$), 73.7 (d, C_5), 75.3 (d, C_7), 78.0 (d, C_{8a}), 152.5 (s, C_2), 170.0 (s, C_4); MS (EI) m/z (relative intensity): 342 $(M + 1)^+$ (12), 324 (4), 284 $(M - i\text{-Bu})^+$ (91), 81 (100); HRMS: calcd for $C_{18}H_{32}NO_5$ [$(M + 1)^+$] 342.2280, found 342.2293.

(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-methyl-5-tridecyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5w)**

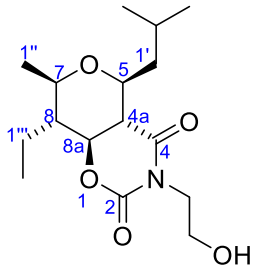


N-acyl oxazolidin-2-one **3a** (36 mg, 0.20 mmol) was submitted to the general procedure for the one-pot EAP cyclization[26] and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 85/15), compound **5w** (35 mg, 41%, >95:5 dr) as a white solid. R_F: 0.54 (*n*-hexane/EtOAc 60/40); mp 48 ºC (from DCM/*n*-hexane); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.89 (t, *J* = 6.9 Hz, 3H, $H_{13'}$), 0.95 (t, *J* = 7.5 Hz, 3H, $H_{2'''}$), 1.22-1.35 (m, 23H, $20x(C\underline{H}_2)_{12}CH_3$, $3xH_{1''}$,), 1.38-1.45 (m, 1H, $H_{2'}$), 1.54-1.64 (m, 4H, H_8, $1xH_{1'}$, $1xH_{2'}$,

[26] Tetradecanal is commercially available, or it can be easily prepared from non-expensive tetradecan-1-ol through a PCC-oxidation protocol (see ref. 21). Tetradecanal thus synthesized must be distilled (166 ºC, 24 mmHg) before being employed in the Evans aldol addition.

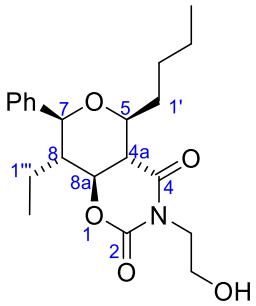
1x$H_{1'''}$), 1.67-1.76 (m, 1H, $H_{1'''}$), 1.88 (br s, 1H, OH), 2.21-2.28 (m, 1H, $H_{1'}$), 2.44 (dd, *J* = 12.0, 9.5 Hz, 1H, H_{4a}), 3.27 (dq, *J* = 9.7, 6.1 Hz, 1H, H_7), 3.47 (td, *J* = 8.5, 2.0 Hz, 1H, H_5), 3.76-3.85 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.90 (ddd, *J* = 14.1, 6.8, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.09 (ddd, *J* = 14.0, 6.0, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.17 (dd, *J* = 11.9, 10.5 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.9 (q, $C_{2'''}$), 14.2 (q, $C_{13'}$), 19.1 (t, $C_{1'''}$), 19.2 (q, $C_{1''}$), 22.8 (t, 1x$(\underline{C}H_2)_{12}CH_3$), 25.4 (t, 1x$(\underline{C}H_2)_{12}CH_3$), 29.5 (t, 1x$(\underline{C}H_2)_{12}CH_3$), 29.7 (t, 1x$(\underline{C}H_2)_{12}CH_3$), 29.77 (t, 1x$(\underline{C}H_2)_{12}CH_3$), 29.80 (t, 1x$(\underline{C}H_2)_{12}CH_3$), 29.81 (t, 2C, 2x$(\underline{C}H_2)_{12}CH_3$), 29.9 (t, 2C, 2x$(\underline{C}H_2)_{12}CH_3$), 32.1 (t, 1x$(\underline{C}H_2)_{12}CH_3$), 34.3 (t, 1x$(\underline{C}H_2)_{12}CH_3$), 44.6 (t, NCH_2CH_2OH), 47.3 (d, C_8), 47.4 (d, C_{4a}), 61.2 (t, $NCH_2\underline{C}H_2OH$), 74.1 (d, C_7), 74.9 (d, C_5), 77.3 (d, C_{8a}), 152.4 (s, C_2), 169.6 (s, C_4); HRMS: calcd for $C_{25}H_{45}NO_5Na$ [(M + Na)$^+$] 462.3195, found 462.3179.

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



N-acyl oxazolidin-2-one **3a** (88 mg, 0.48 mmol) was submitted to the general procedure for the one-pot EAP cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 80/20), compound **5x** (63 mg, 42%, >95:5 dr) as a colourless oil. R_F: 0.37 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 0.89-0.95 (m, 9H, 6xCH($C\underline{H}_3$)$_2$, 3x$H_{2'''}$), 1.23-1.27 (m, 3H, $H_{1''}$), 1.41-1.48 (m, 1H, $H_{1'}$), 1.53-1.62 (m, 2H, H_8, 1x$H_{1'''}$), 1.67-1.76 (m, 1H, $H_{1'''}$), 1.87-1.95 (m, 1H, $H_{2'}$), 2.00-2.17 (m, 2H, 1x$H_{1'}$, OH), 2.35-2.43 (m, 1H, H_{4a}), 3.23-3.29 (m, 1H, H_7), 3.55 (dd, *J* = 9.7, 9.7 Hz, 1H, H_5), 3.74-3.83 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.85-3.92 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.01-4.11 (m, 1H, $NC\underline{H}_2CH_2OH$), 4.21 (dd, *J* = 11.6, 10.6 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 9.6 (q, $C_{2'''}$), 18.9 (t, $C_{1'''}$), 19.1 (q, $C_{1''}$), 21.5 (q, CH($\underline{C}H_3$)$_2$), 23.9 (q, CH($\underline{C}H_3$)$_2$), 24.5 (d, $C_{2'}$), 43.3 (t, $C_{1'}$), 44.5 (t, NCH_2CH_2OH), 46.9 (d, C_8), 47.8 (d, C_{4a}), 61.0 (t, $NCH_2\underline{C}H_2OH$), 73.0 (d, C_5), 73.9 (d, C_7), 76.8 (d, C_{8a}), 152.4 (s, C_2), 169.5 (s, C_4); HRMS: calcd for $C_{16}H_{27}NO_5Na$ [(M + Na)$^+$] 336.1787, found 336.1787.

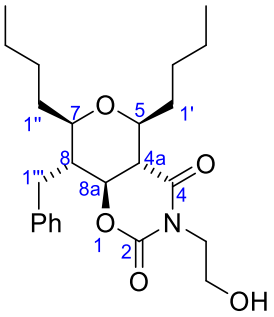
(4a*S,5*S**,7*S**,8*S**,8a*S**)-5-Butyl-8-ethyl-3-(2-hydroxyethyl)-7-phenyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5y)**



N-acyl oxazolidin-2-one **3a** (44 mg, 0.24 mmol) was submitted to the general procedure for the one-pot EAP cyclization and yielded, after purification by flash chromatography

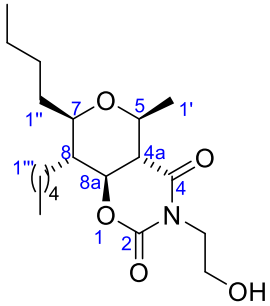
(*n*-hexane/EtOAc 75/25), compound **5y** (28 mg, 31%, 90:10 dr) as a thick colourless oil. R_F: 0.34 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.70 (t, *J* = 7.6 Hz, 3H, $H_{2'''}$), 0.87 (t, *J* = 7.3 Hz, 3H, $H_{4'}$), 1.27-1.46 (m, 5H, 2x$H_{2'}$, 2x$H_{3'}$, 1x$H_{1'''}$), 1.47-1.55 (m, 1H, $H_{1'''}$), 1.72-1.80 (m, 1H, $H_{1'}$), 1.94-2.00 (m, 2H, H_8, OH), 2.18-2.25 (m, 1H, $H_{1'}$), 2.66 (dd, *J* = 12.0, 9.7 Hz, 1H, H_{4a}), 3.68 (td, *J* = 7.6, 2.3 Hz, 1H, H_5), 3.79-3.89 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.93 (ddd, *J* = 13.9, 6.9, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.09 (d, *J* = 10.3 Hz, 1H, H_7), 4.13 (ddd, *J* = 14.0, 6.0, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.36 (dd, *J* = 12.1, 10.6 Hz, 1H, H_{8a}), 7.31-7.39 (m, 5H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 10.1 (q, $C_{2'''}$), 14.2 (q, $C_{4'}$), 19.3 (t, $C_{1'''}$), 22.8 (t, $C_{3'}$), 27.2 (t, $C_{2'}$), 33.8 (t, $C_{1'}$), 44.6 (t, $NC\underline{H}_2CH_2OH$), 46.8 (d, C_{4a}), 46.9 (d, C_8), 61.1 (t, $NCH_2C\underline{H}_2OH$), 75.2 (d, C_5), 77.6 (d, C_{8a}), 81.4 (d, C_7), 127.6 (d, 2C, Ph), 128.6 (d, Ph), 128.7 (d, 2C, Ph), 139.1 (s, Ph), 152.3 (s, C_2), 169.4 (s, C_4); MS (EI) m/z (relative intensity): 376 $(M + 1)^+$ (4), 375 (13), 357 (1), 332 (4), 318 (5), 298 (1), 274 (6), 242 (48); HRMS: calcd for $C_{21}H_{29}NO_5$ [$(M)^+$] 375.2046, found 375.2043.

(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Benzyl-5,7-dibutyl-3-(2-hydroxyethyl)tetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5z)**



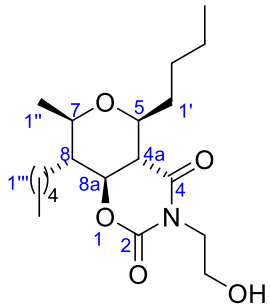
N-acyl oxazolidin-2-one **3d** (58 mg, 0.24 mmol) was submitted to the general procedure for the one-pot EAP cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 75/25), compound **5z** (29 mg, 32%, >95:5 dr) as a colourless oil. R_F: 0.39 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.89 (t, *J* = 7.2 Hz, 3H, $H_{4'}$ or $H_{4''}$), 0.90 (t, *J* = 7.2 Hz, 3H, $H_{4''}$ or $H_{4'}$), 1.24-1.38 (m, 6H, 6x$(C\underline{H}_2)_3CH_3$), 1.41-1.56 (m, 4H, 4x$(C\underline{H}_2)_3CH_3$), 1.86-2.01 (m, 2H, H_8, 1x$H_{1''}$), 1.93 (br s, 1H, OH), 2.22-2.30 (m, 1H, $H_{1'}$), 2.47 (dd, *J* = 12.3, 9.8 Hz, 1H, H_{4a}), 2.91 (dd, *J* = 14.5, 5.8 Hz, 1H, $H_{1'''}$), 3.01 (dd, *J* = 14.5, 2.8 Hz, 1H, $H_{1'''}$), 3.05 (td, *J* = 9.3, 2.6 Hz, 1H, H_7), 3.28 (td, *J* = 9.3, 2.2 Hz, 1H, H_5), 3.75-3.83 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.87 (ddd, *J* = 13.8, 6.7, 4.2 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.06 (dd, *J* = 12.0, 10.8 Hz, 1H, H_{8a}), 4.09 (ddd, *J* = 14.0, 6.1, 4.6 Hz, 1H, $NC\underline{H}_2CH_2OH$), 7.15-7.19 (m, 2H, Ph), 7.21-7.24 (m, 1H, Ph), 7.28-7.31 (m, 2H, Ph); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 14.17 (q, $C_{4'}$ or $C_{4''}$), 14.21 (q, $C_{4''}$ or $C_{4'}$), 22.5 (t, $C_{3'}$ or $C_{3''}$), 22.6 (t, $C_{3''}$ or $C_{3'}$), 27.5 (t, $C_{2'}$ or $C_{2''}$), 27.6 (t, $C_{2''}$ or $C_{2'}$), 31.9 (t, $C_{1'''}$), 32.6 (t, $C_{1''}$), 33.9 (t, $C_{1'}$), 44.5 (t, $NC\underline{H}_2CH_2OH$), 45.5 (d, C_8), 47.3 (d, C_{4a}), 61.0 (t, $NCH_2C\underline{H}_2OH$), 74.3 (d, C_5), 76.6 (d, C_{8a}), 77.1 (d, C_7), 126.7 (d, Ph), 128.7 (d, 2C, Ph), 129.9 (d, 2C, Ph), 137.5 (s, Ph), 152.3 (C_2), 169.3 (s, C_4); MS (EI) m/z (relative intensity): 418 $(M + 1)^+$ (2), 417 (8), 399 (1), 374 (1), 360 $(M - Bu)^+$ (22), 326 (4), 316 (8), 282 (27), 196 (100), 91 (73); HRMS: calcd for $C_{24}H_{35}NO_5$ [$(M)^+$] 417.2515, found 417.2528.

(4a*S,5*S**,7*R**,8*R**,8a*S**)-7-Butyl-3-(2-hydroxyethyl)-5-methyl-8-pentyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5aa)**



N-acyl oxazolidin-2-one **3e** (109 mg, 0.48 mmol) was submitted to the general procedure for the one-pot EAP cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 80/20), compound **5aa** (53 mg, 31%, >95:5 dr) as a colourless oil. R_F: 0.37 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.89 (t, *J* = 7.0 Hz, 3H, $H_{4''}$ or $H_{5'''}$), 0.92 (t, *J* = 7.1 Hz, 3H, $H_{5'''}$ or $H_{4''}$), 1.23-1.52 (m, 12H, 12x$C\underline{H}_2$ from alkyl chain), 1.54 (d, *J* = 6.2 Hz, 3H, $H_{1'}$), 1.56-1.61 (m, 1H, 1x$C\underline{H}_2$ from alkyl chain), 1.63-1.69 (m, 2H, H_8, 1x$C\underline{H}_2$ from alkyl chain), 1.88-1.95 (m, 1H, OH), 2.36 (dd, *J* = 12.1, 9.6 Hz, 1H, H_{4a}), 3.13 (ddd, *J* = 10.8, 8.7, 2.5 Hz, 1H, H_7), 3.56 (dq, *J* = 9.6, 6.0 Hz, 1H, H_5), 3.77-3.86 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.90 (ddd, *J* = 14.0, 7.0, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.14 (ddd, *J* = 14.1, 5.8, 4.1 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.17 (dd, *J* = 12.1, 10.6 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 14.16 (q, $C_{4''}$ or $C_{5'''}$), 14.18 (q, $C_{5'''}$ or $C_{4''}$), 20.9 (q, $C_{1'}$), 22.6 (t, alkyl chain), 22.8 (t, alkyl chain), 25.3 (t, alkyl chain), 26.3 (t, alkyl chain), 27.5 (t, alkyl chain), 32.1 (t, alkyl chain), 32.4 (t, alkyl chain), 44.47 (t, $N\underline{C}H_2CH_2OH$), 44.51 (d, C_8), 49.2 (d, C_{4a}), 61.0 (t, $NCH_2\underline{C}H_2OH$), 71.1 (d, C_5), 77.6 (d, C_{8a}), 77.9 (d, C_7), 152.4 (s, C_2), 169.4 (s, C_4); HRMS: calcd for $C_{19}H_{33}NO_5Na$ [$(M + Na)^+$] 378.2256, found 378.2245.

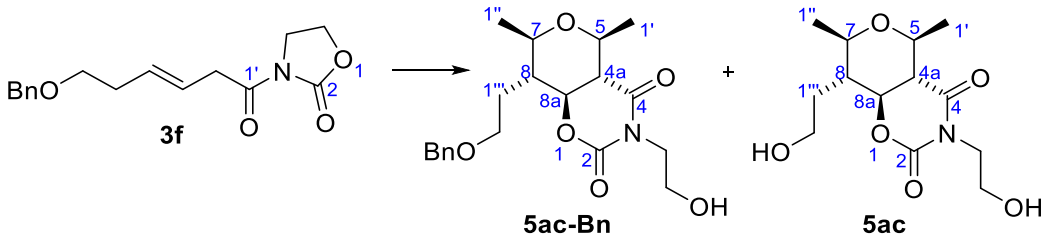
(4a*S,5*S**,7*R**,8*R**,8a*S**)-5-Butyl-3-(2-hydroxyethyl)-7-methyl-8-pentyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5ab)**



N-acyl oxazolidin-2-one **3e** (145 mg, 0.64 mmol) was submitted to the general procedure for the one-pot EAP cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 90/10), compound **5ab** (68 mg, 30%, >95:5 dr) as a colourless oil. R_F: 0.24 (*n*-hexane/EtOAc 70/30); ^{1}H-NMR (500 MHz, δ, $CDCl_3$): 0.90 (t, *J* = 6.9 Hz, 3H, $H_{4'}$ or $H_{5'''}$), 0.92 (t, *J* = 7.1 Hz, 3H, $H_{5'''}$ or $H_{4'}$), 1.27 (d, *J* = 6.4 Hz, 3H, $H_{1''}$), 1.29-1.43 (m, 9H, 9x$C\underline{H}_2$ from alkyl chain), 1.47-1.64 (m, 5H, H_8, 1x$H_{1'}$, 3x$C\underline{H}_2$ from alkyl chain), 1.90 (br s, 1H, OH), 2.21-2.28 (m, 1H, $H_{1'}$), 2.43 (dd, *J* = 12.0, 9.7 Hz, 1H, H_{4a}), 3.24 (dq, *J* = 9.4, 6.2 Hz, 1H, H_7), 3.47 (td, *J* = 8.9, 2.2 Hz, 1H, H_5), 3.76-3.84 (m, 2H, $NCH_2C\underline{H}_2OH$), 3.89 (ddd, *J* = 14.0, 6.8, 4.4 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.09 (ddd, *J* = 14.0, 6.0, 4.5 Hz, 1H, $NC\underline{H}_2CH_2OH$), 4.14 (dd, *J* = 11.9, 10.3 Hz, 1H, H_{8a}); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 14.18 (q, $C_{4'}$ or $C_{5'''}$), 14.21 (q, $C_{5'''}$ or $C_{4'}$), 19.2 (q, $C_{1''}$), 22.6 (t, alkyl chain), 22.7 (t, alkyl chain), 25.4 (t, alkyl chain), 26.6 (t, alkyl chain), 27.6 (t, alkyl chain),

32.5 (t, alkyl chain), 34.0 (t, $C_{1'}$), 44.5 (t, N<u>C</u>H$_2$CH$_2$OH), 46.4 (d, C_8), 47.2 (d, C_{4a}), 61.1 (t, NCH$_2$<u>C</u>H$_2$OH), 74.4 (d, C_7), 74.7 (d, C_5), 77.7 (d, C_{8a}), 152.5 (s, C_2), 169.5 (s, C_4); HRMS: calcd for $C_{19}H_{33}NO_5Na$ [(M + Na)$^+$] 378.2256, found 378.2249.

(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-(2-(Benzyloxy)ethyl)-3-(2-hydroxyethyl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5ac-Bn)**



N-acyl oxazolidin-2-one **3f** (105 mg, 0.36 mmol) was submitted to the general procedure for the one-pot EAP cyclization and yielded, after purification by flash chromatography (*n*-hexane/EtOAc 70/30), a separable 1.3/1 mixture of the compounds **5ac-Bn** (41 mg, 30%, >95:5 dr) and **5a** (25 mg, 24%, >95:5 dr).

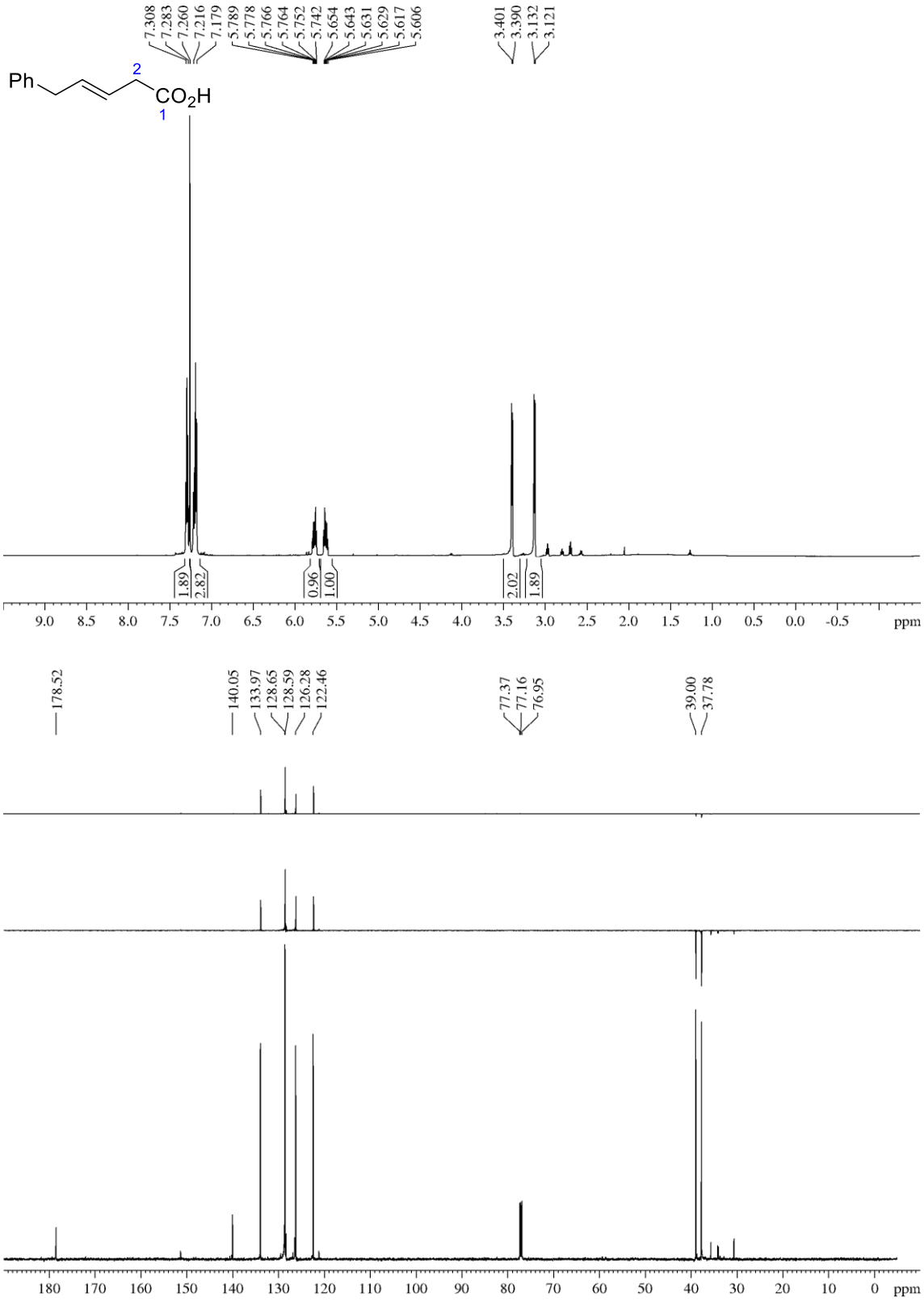
5ac-Bn: thick colourless oil. R_F: 0.15 (*n*-hexane/EtOAc 60/40); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 1.29 (d, *J* = 6.2 Hz, 3H, $H_{1''}$), 1.54 (d, *J* = 5.9 Hz, 3H, $H_{1'}$), 1.68-1.74 (m, 1H, H_8), 1.76-1.83 (m, 1H, $H_{1'''}$), 1.94-2.02 (m, 2H, 1x$H_{1'''}$, OH), 2.36 (dd, *J* = 11.9, 10.0 Hz, 1H, H_{4a}), 3.35-3.41 (m, 1H, H_7), 3.55-3.66 (m, 3H, H_5, 2x$H_{2'''}$), 3.73-3.82 (m, 2H, NCH$_2$C<u>H</u>$_2$OH), 3.84-3.90 (m, 1H, NC<u>H</u>$_2$CH$_2$OH), 4.03-4.09 (m, 1H, NC<u>H</u>$_2$CH$_2$OH), 4.26 (dd, *J* = 11.3, 11.3 Hz, 1H, H_{8a}), 4.50 (s, 2H, PhC<u>H</u>$_2$O), 7.28-7.36 (m, 5H, Ph); ^{13}C-NMR (150 MHz, δ, $CDCl_3$): 19.4 (q, $C_{1''}$), 20.9 (q, $C_{1'}$), 27.0 (t, $C_{1'''}$), 44.41 (t, N<u>C</u>H$_2$CH$_2$OH), 44.44 (d, C_8), 49.1 (d, C_{4a}), 60.8 (t, NCH$_2$<u>C</u>H$_2$OH), 67.6 (t, $C_{2'''}$), 71.1 (d, C_5), 73.1 (t, Ph<u>C</u>H$_2$O), 74.4 (d, C_7), 77.0 (d, C_{8a}), 127.8 (d, 2C, Ph), 128.5 (d, 2C, Ph), 129.7 (d, Ph), 138.3 (s, Ph), 152.2 (s, C_2), 169.1 (s, C_4); MS (EI) m/z (relative intensity): 378 (M + 1)$^+$ (7), 377 (M)$^+$ (18), 361 (1), 333 (1), 286 (1), 271 (2), 256 (1), 242 (2), 227 (5), 198 (11), 183 (8), 168 (8), 91 (100); HRMS: calcd for $C_{20}H_{27}NO_6$ [(M)$^+$] 377.1838, found 377.1832.

(4a*S,5*S**,7*R**,8*R**,8a*S**)-3,8-Bis(2-hydroxyethyl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5ac)**: white solid. R_F: 0.10 (*n*-hexane/EtOAc 60/40); mp 139 ºC (from DCM/*n*-hexane); ^{1}H-NMR (600 MHz, δ, $CDCl_3$): 1.25 (d, *J* = 6.0 Hz, 3H, $H_{1'}$), 1.27 (d, *J* = 6.0 Hz, 3H, $H_{1''}$), 1.46-1.53 (m, 1H, H_8), 1.55-1.60 (m, 1H, $H_{1'''}$), 1.94-2.00 (m, 1H, $H_{1'''}$), 3.45-3.51 (m, 1H, H_7), 3.58 (t, *J* = 10.1 Hz, 1H, H_{8a}), 3.61-3.66 (m, 1H, H_5), 3.89-3.93 (m, 2H, $H_{2'''}$), 3.98-4.03 (m, 1H, NC<u>H</u>$_2$CH$_2$OH), 4.05-4.10 (m, 1H, NC<u>H</u>$_2$CH$_2$OH), 4.11-4.17 (m, 1H, H_{4a}), 4.35-4.42 (m, 2H, NCH$_2$C<u>H</u>$_2$OH); ^{13}C-NMR (125 MHz, δ, $CDCl_3$): 19.1 (q, $C_{1'}$), 20.2 (q, $C_{1''}$), 26.6 (t, $C_{1'''}$), 42.9 (t, N<u>C</u>H$_2$CH$_2$OH), 49.0 (d, C_8), 51.9 (d, C_{4a}), 61.8 (t, NCH$_2$<u>C</u>H$_2$OH), 67.3 (t, $C_{2'''}$), 74.6 (d, C_5), 76.2 (d, C_7), 83.5 (d, C_{8a}), 153.2 (s, C_2), 173.0 (s, C_4); MS (EI) m/z (relative intensity): 269 (M – H_2O)$^+$ (2), 226 (4), 197 (7), 183 (10), 182 (70), 168 (2); HRMS: calcd for $C_{13}H_{19}NO_5$ [(M – H_2O)$^+$] 269.1263, found 269.1262.

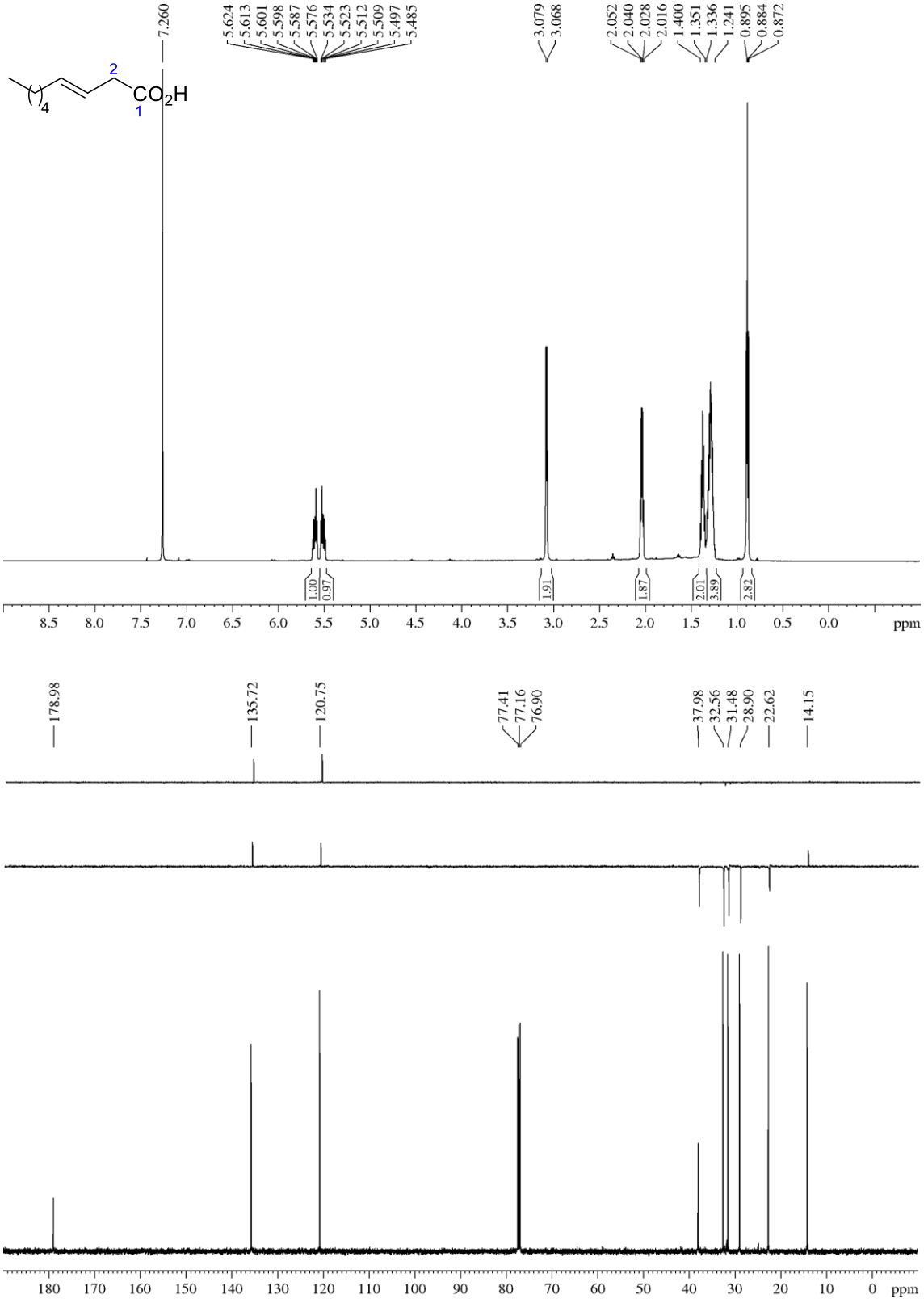
NMR spectra

β,γ-Unsaturated carboxylic acids (4)

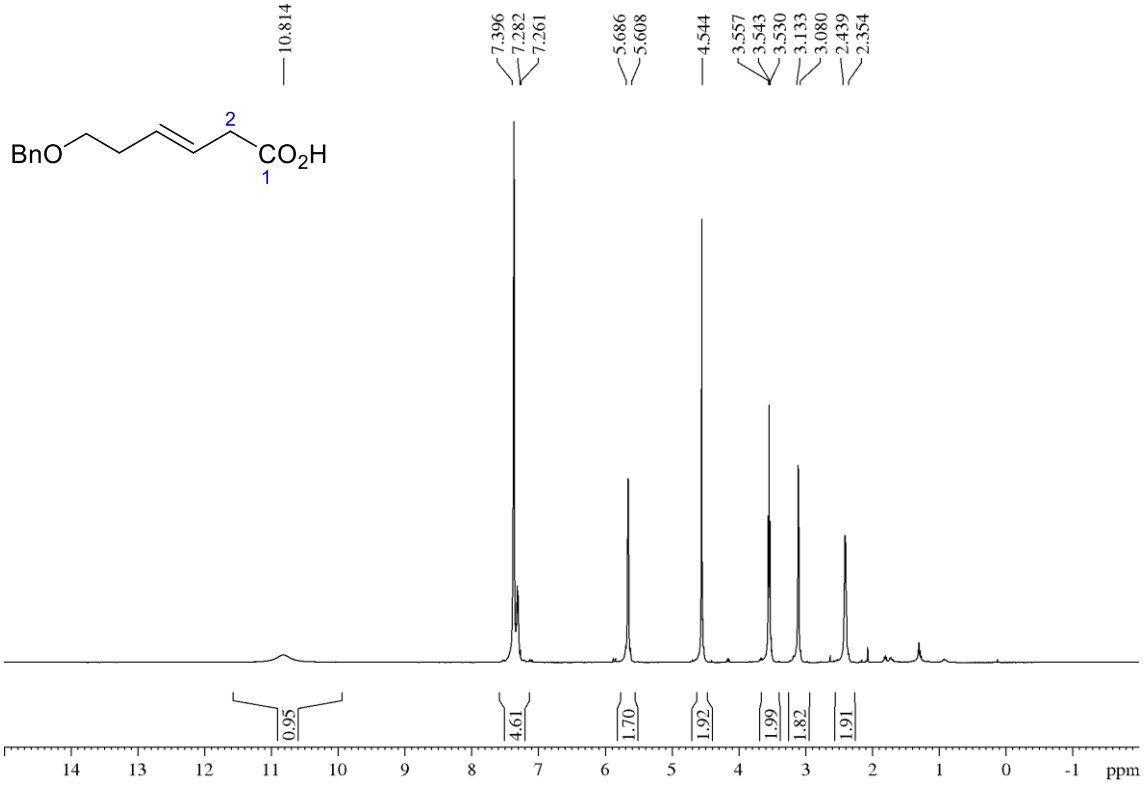
(*E*)-5-Phenylpent-3-enoic acid (4d)

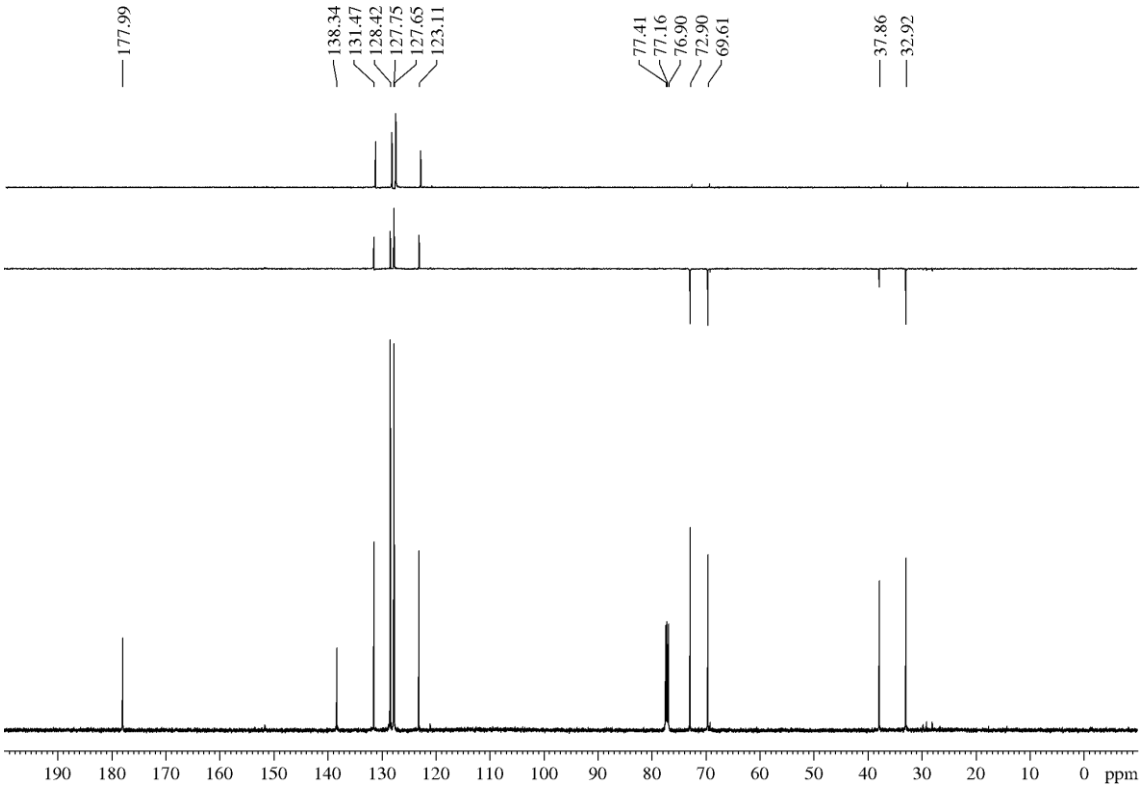


(*E*)-Non-3-enoic acid (4e)



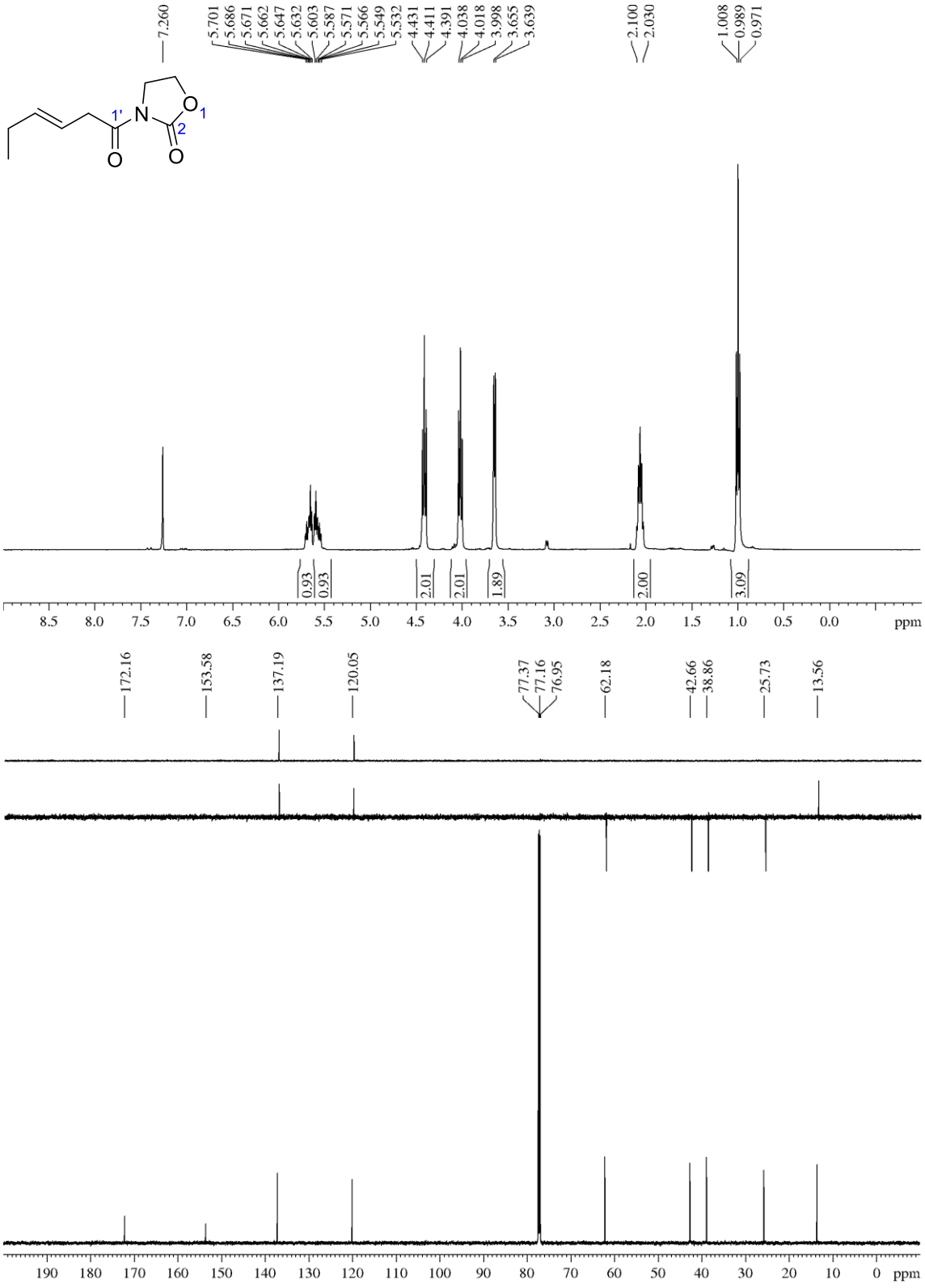
(*E*)-6-(Benzyloxy)hex-3-enoic acid (4f)



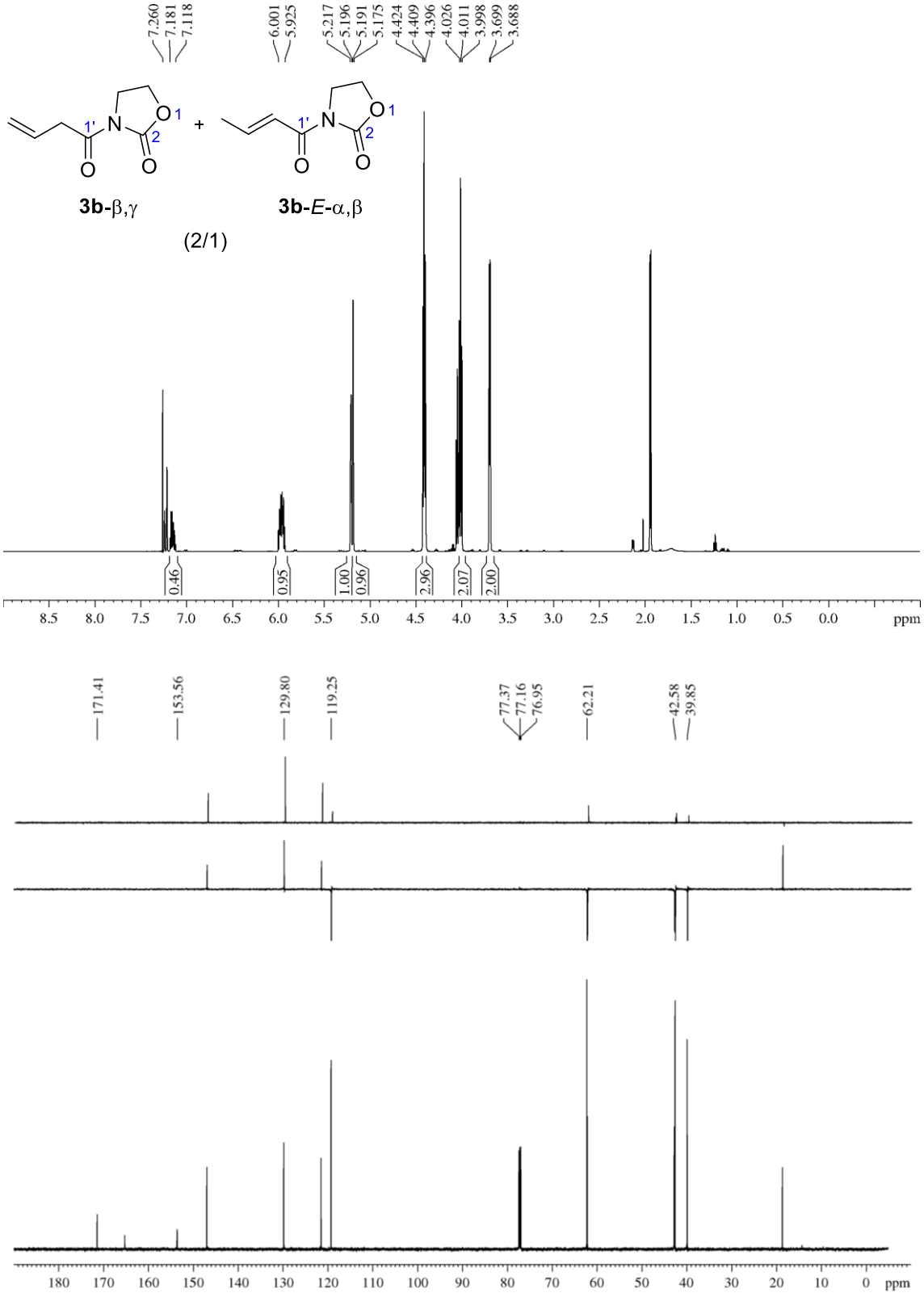


N-acyl oxazolidin-2-ones (3)

(*E*)-3-(Hex-3-enoyl)oxazolidin-2-one (3a)

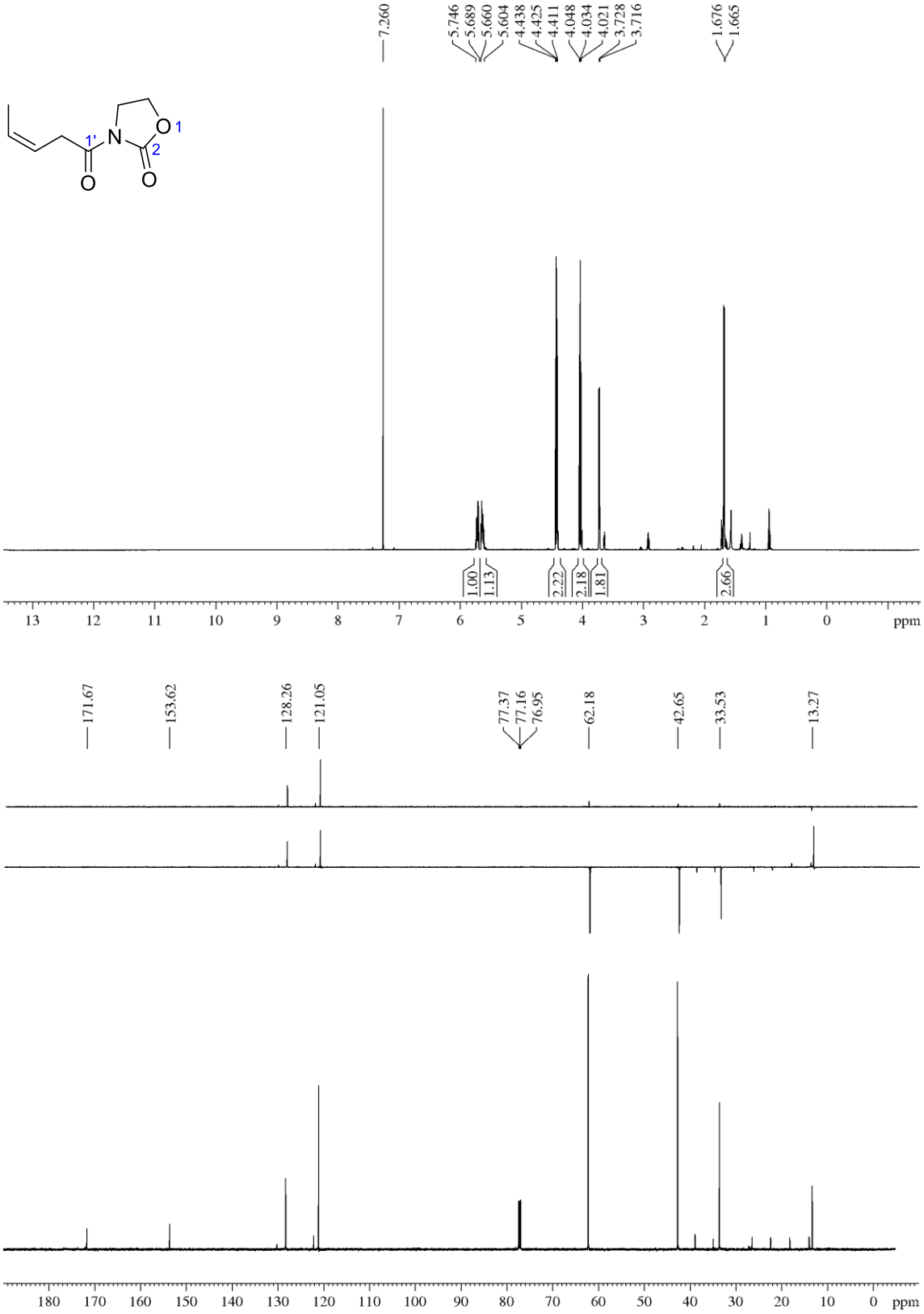


3-(But-3-enoyl)oxazolidin-2-one (3b)[27]

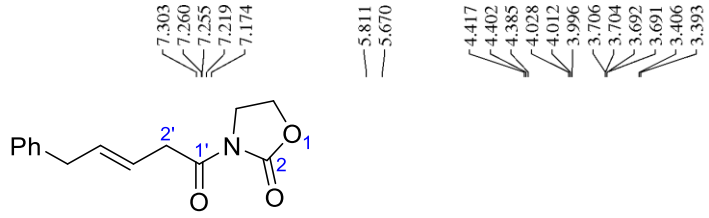


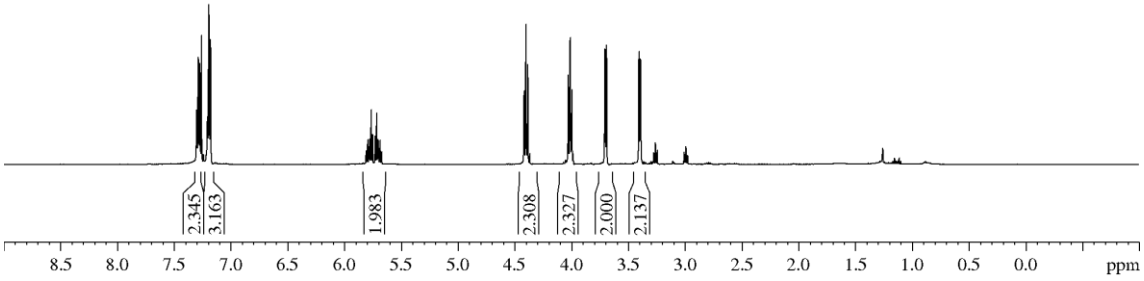
[27] As described previously, the spectra show a 2/1 mixture of the desired product **3b**-β,γ with **3b**-*E*-α,β. Integration and peak peaking was performed ignoring the undesired minority product.

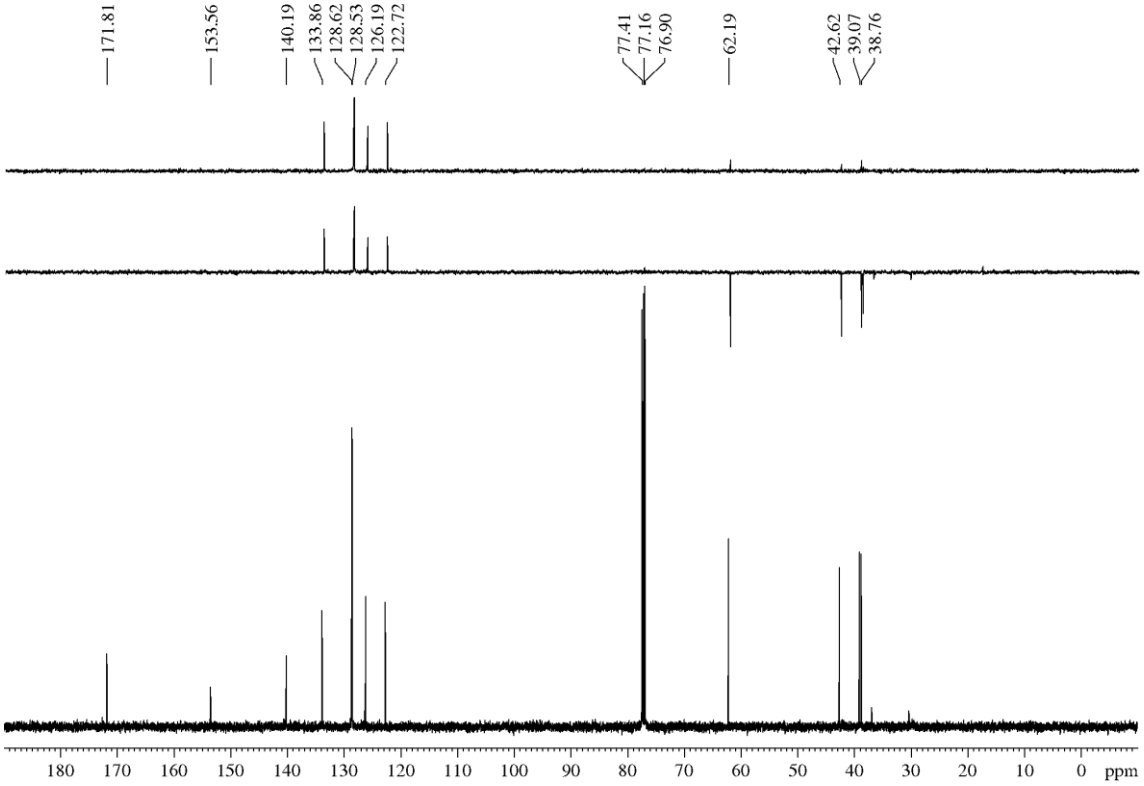
(Z)-3-(Pent-3-enoyl)oxazolidin-2-one (3c)



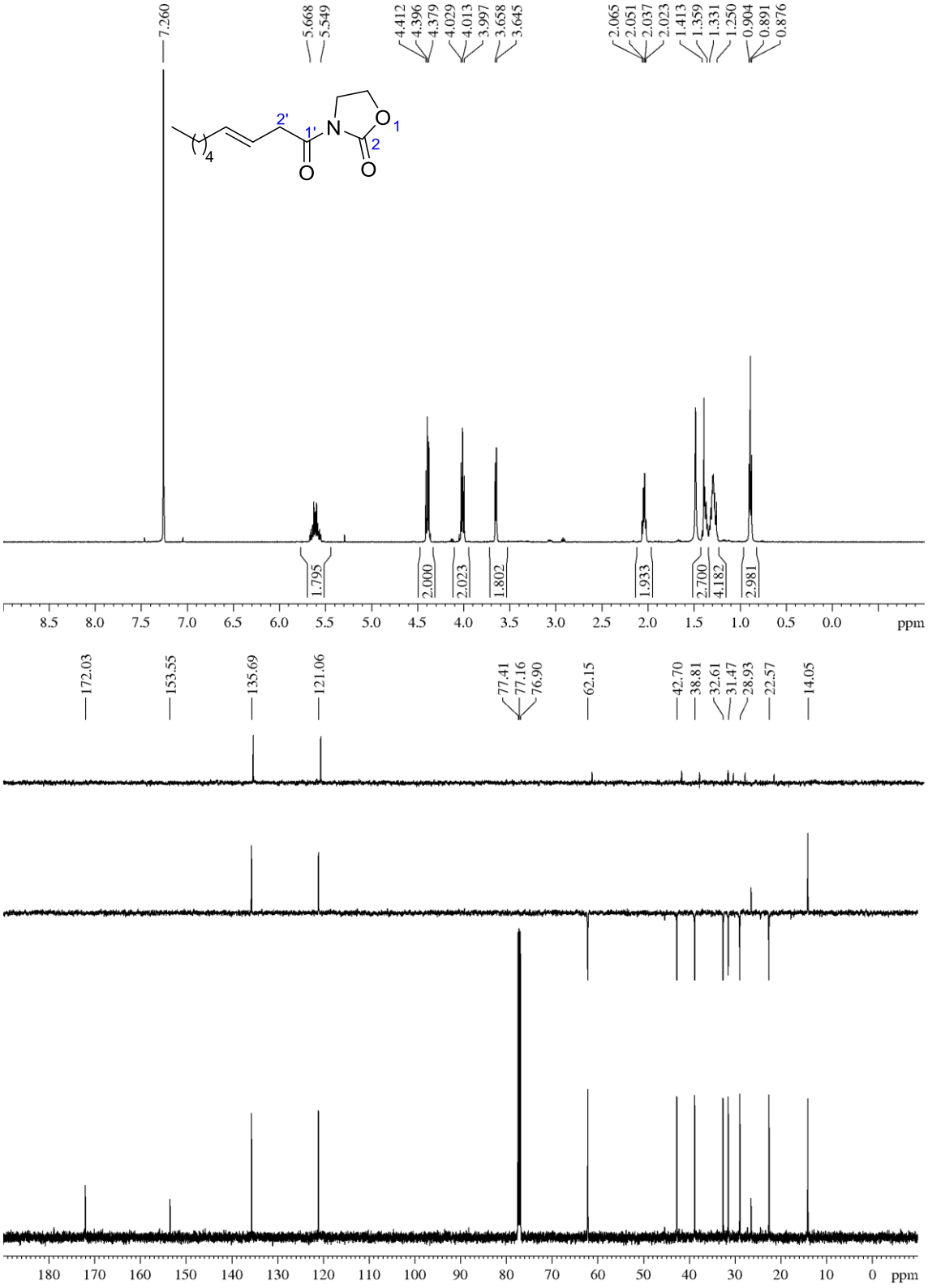
(*E*)-3-(5-Phenylpent-3-enoyl)oxazolidin-2-one (3d)



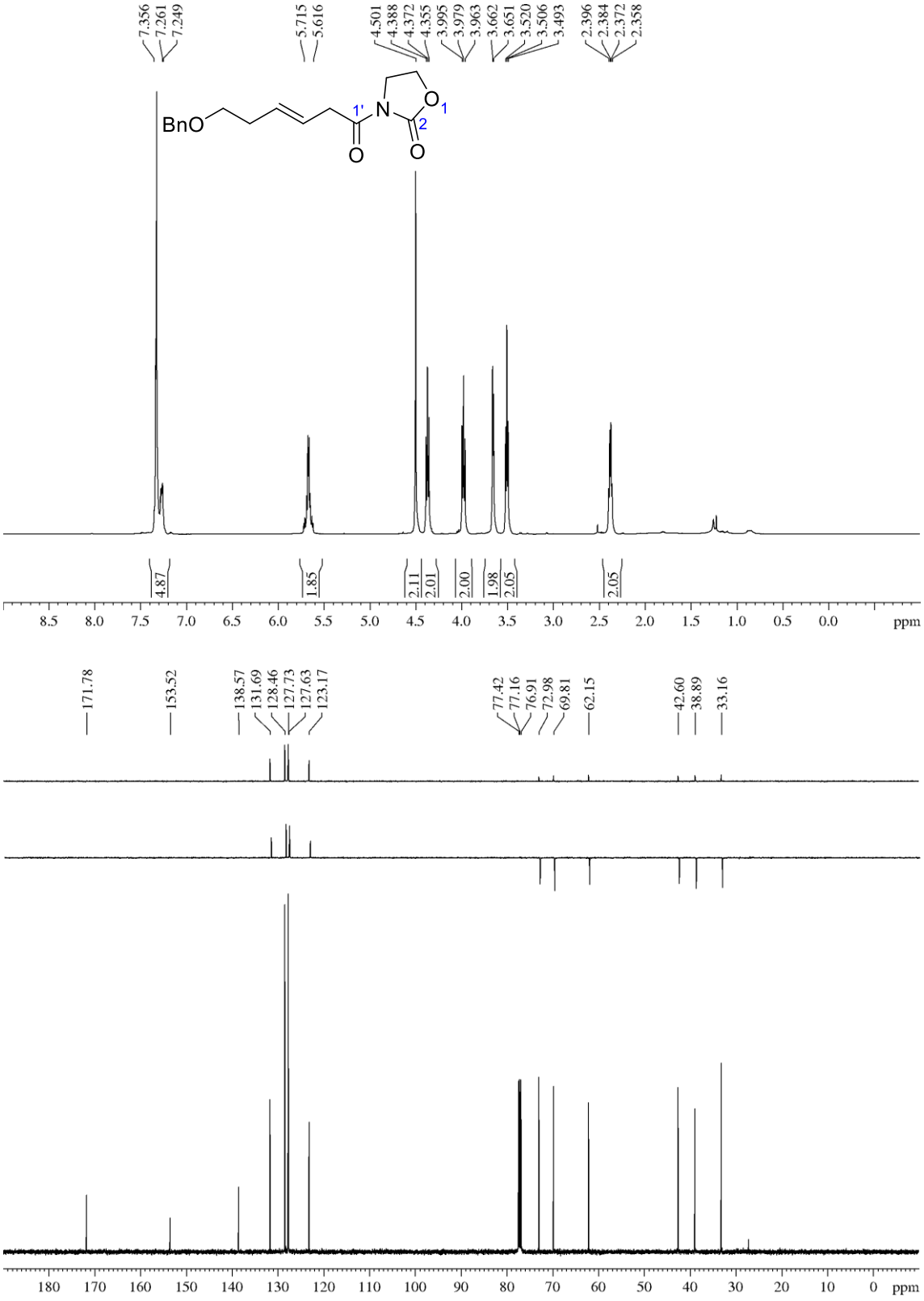




(*E*)-3-(Non-3-enoyl)oxazolidin-2-one (3e)

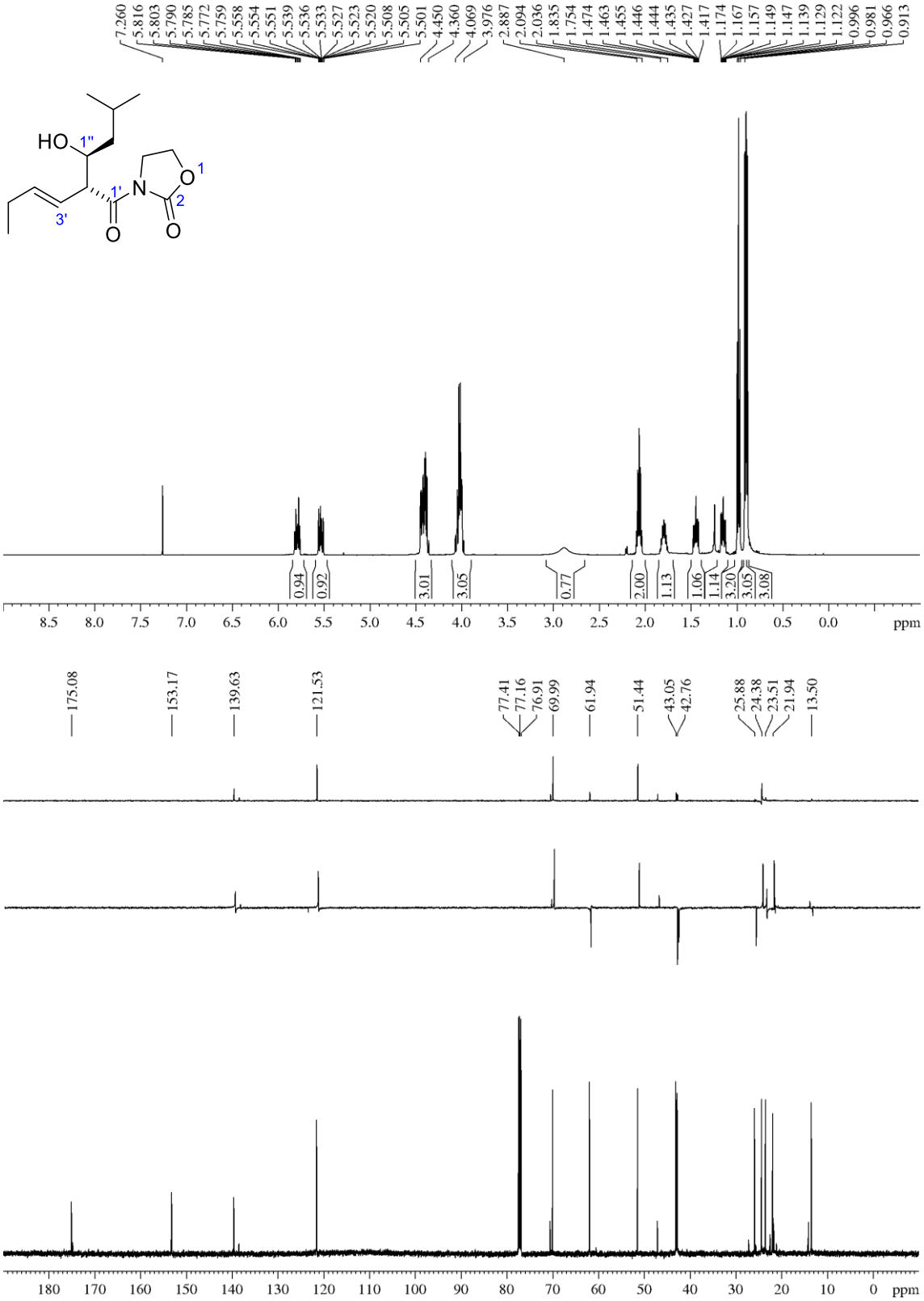


(*E*)-3-(6-(Benzyloxy)hex-3-enoyl)oxazolidin-2-one (3f)

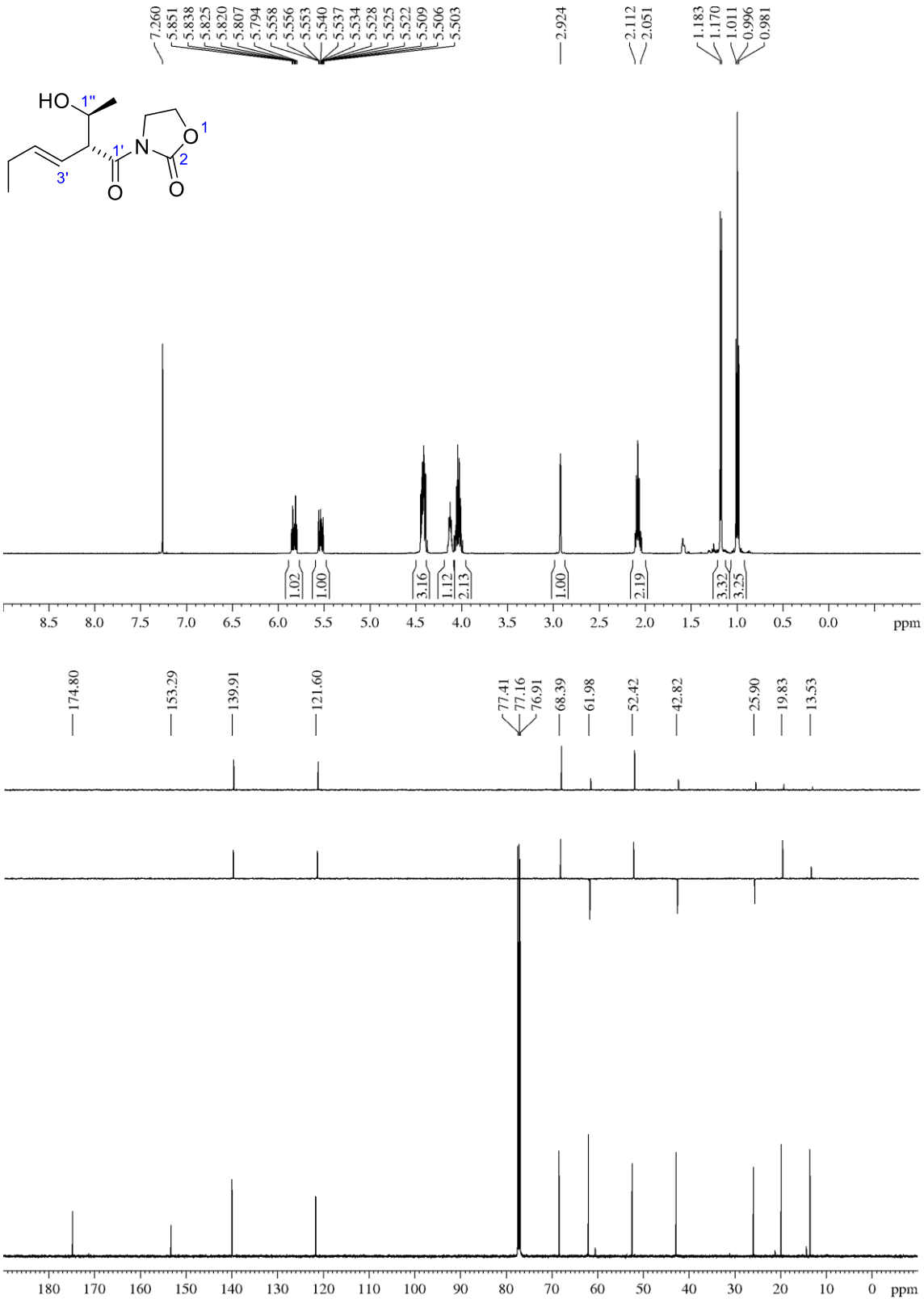


Aldols (2)

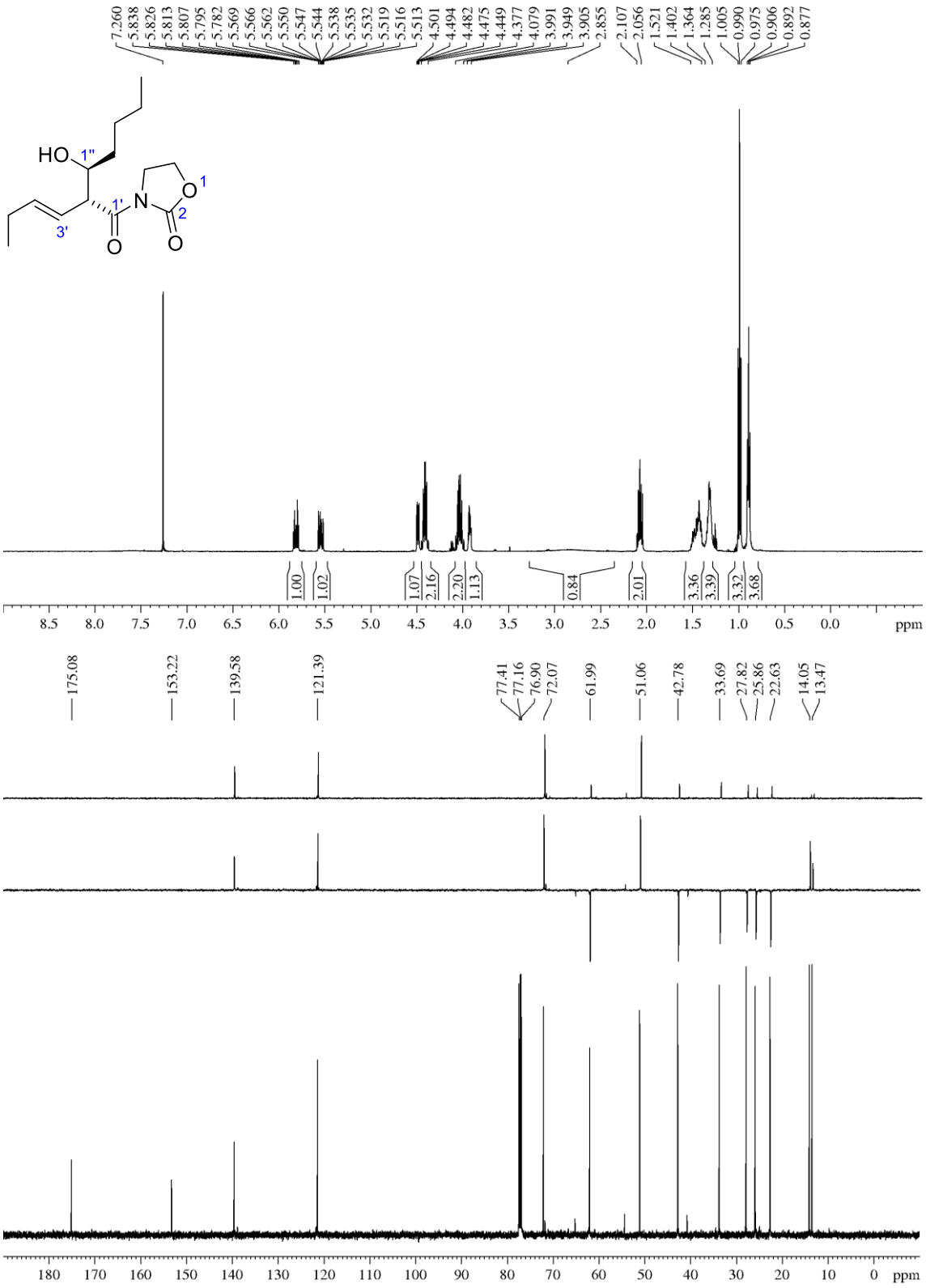
3-((*R**,*E*)-2-((*S**)-1-Hydroxy-3-methylbutyl)hex-3-enoyl)oxazolidin-2-one (2a)



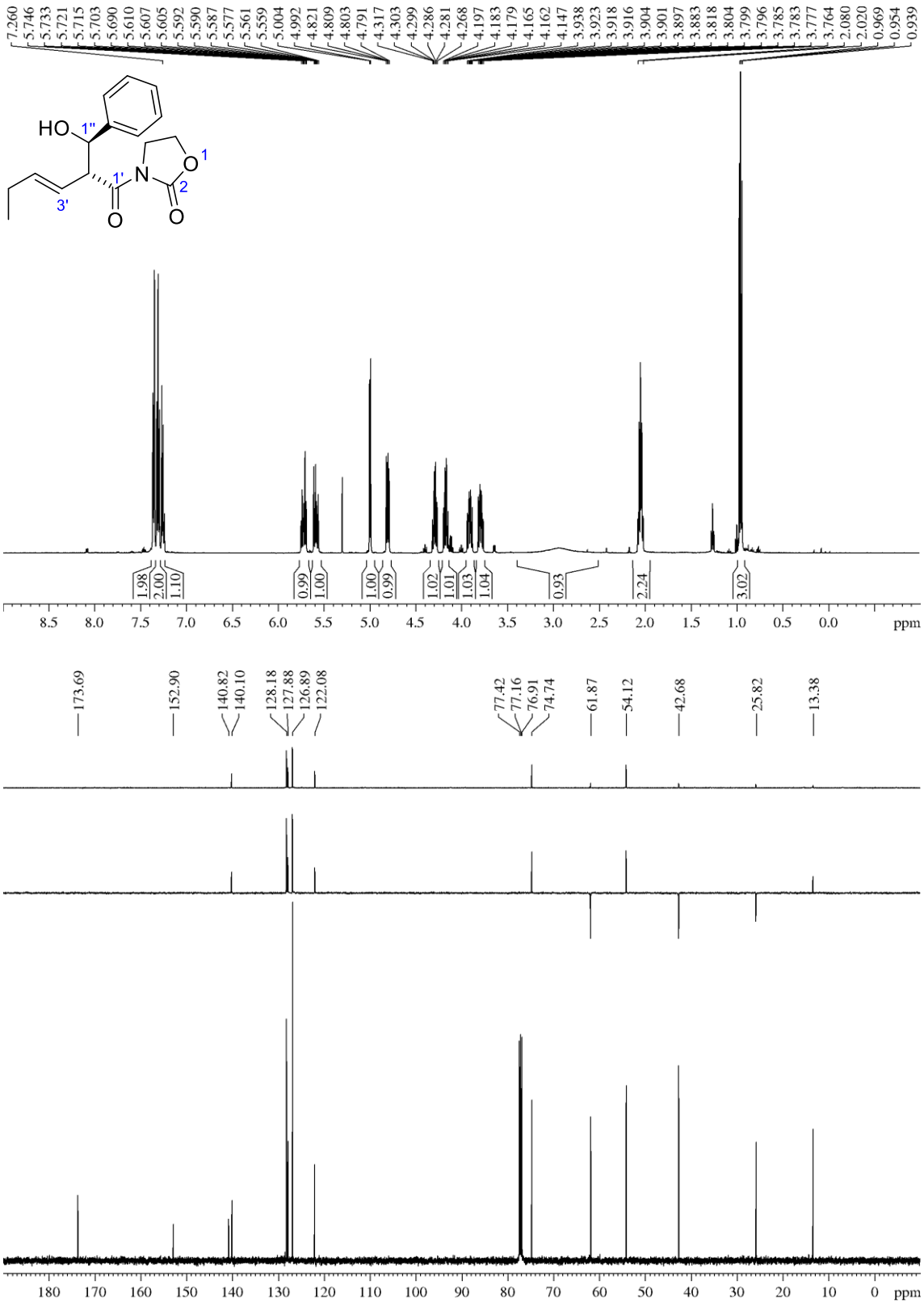
3-((*R,*E*)-2-((*S**)-1-Hydroxyethyl)hex-3-enoyl)oxazolidin-2-one (2b)**



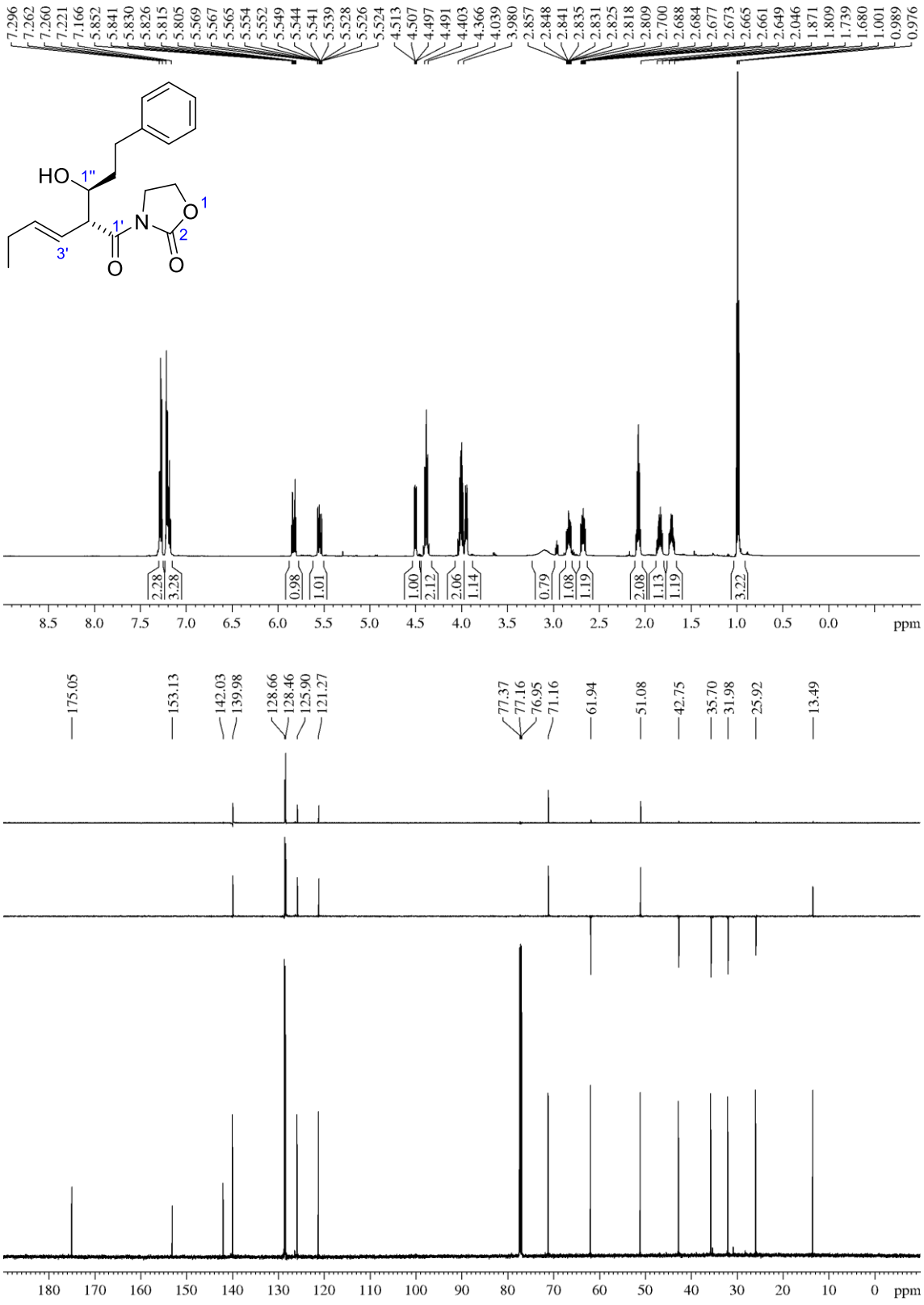
3-((2*R,3*S**)-2-((*E*)-But-1-en-1-yl)-3-hydroxyheptanoyl)oxazolidin-2-one (2c)**



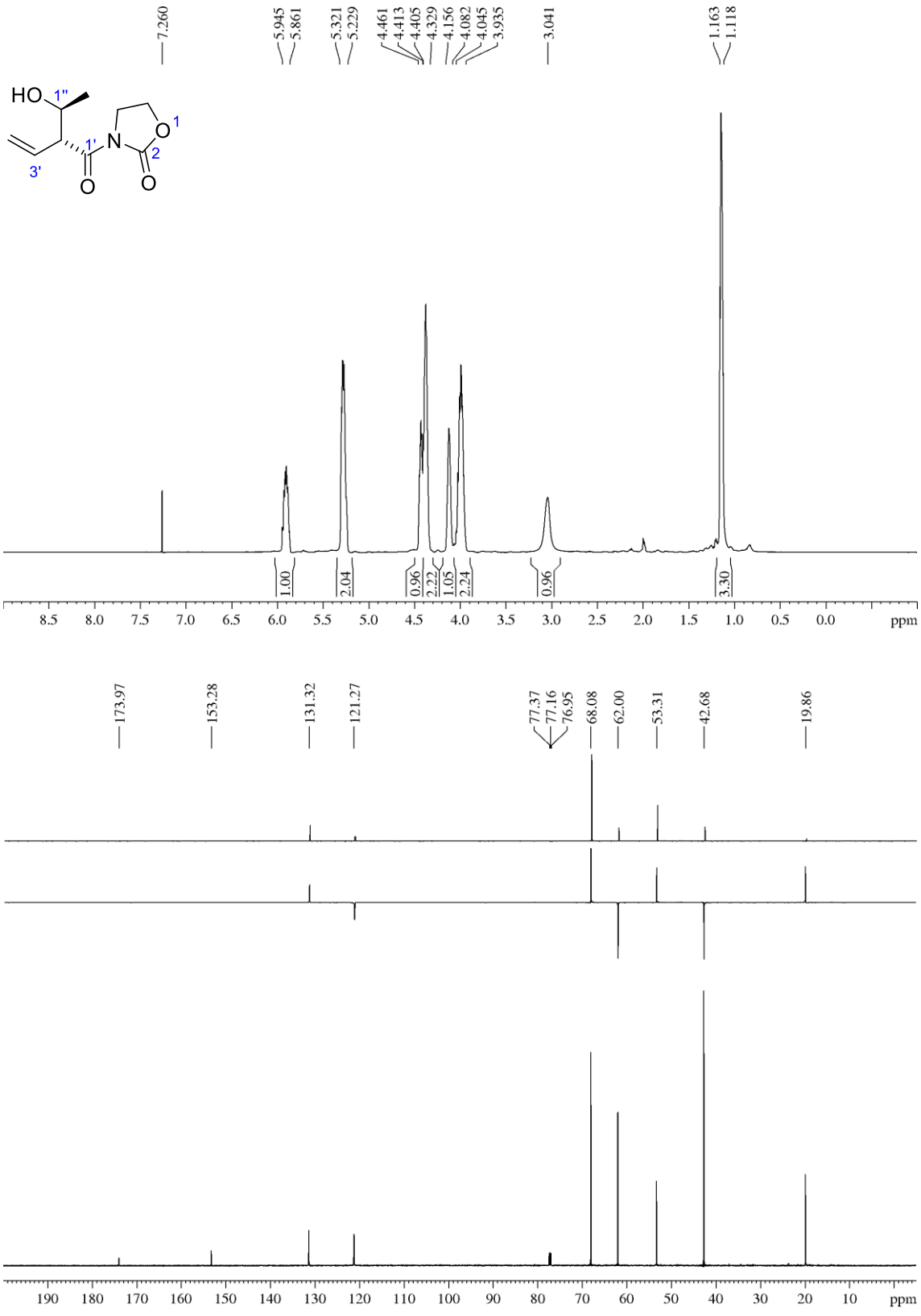
3-((*R,*E*)-2-((*R**)-Hydroxy(phenyl)methyl)hex-3-enoyl)oxazolidin-2-one (2d)**



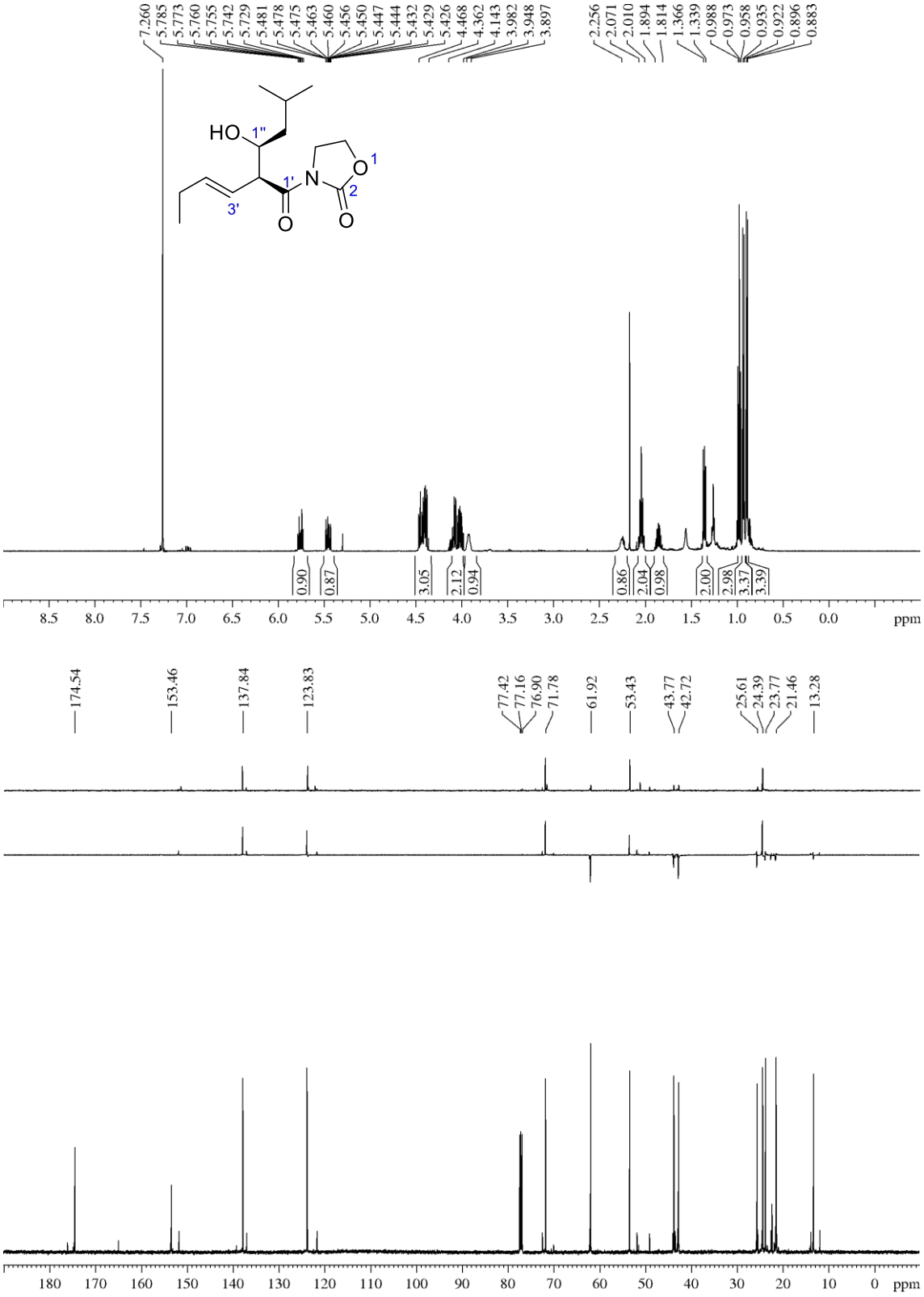
3-((*R,*E*)-2-((*S**)-1-hydroxy-3-phenylpropyl)hex-3-enoyl)oxazolidin-2-one (2e)**



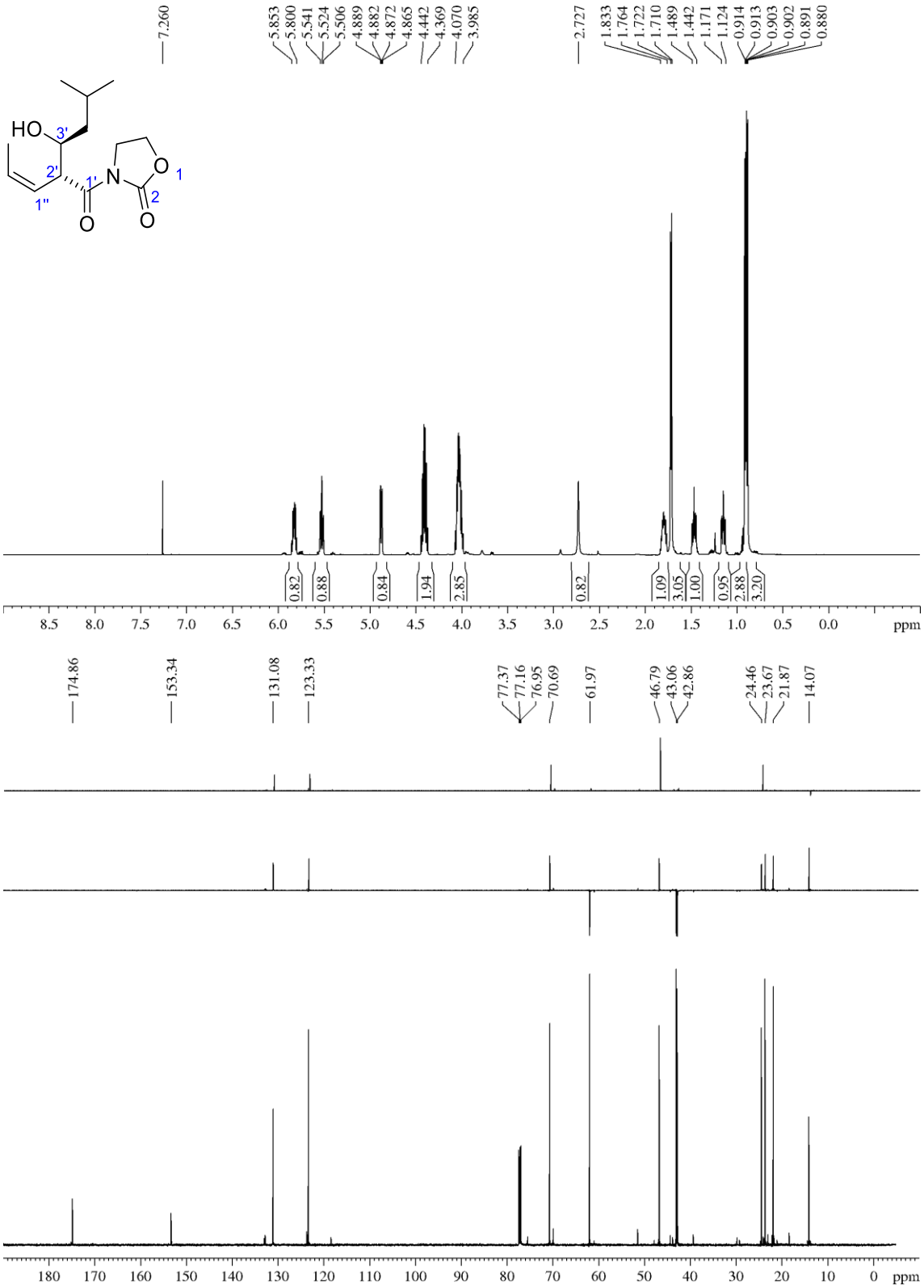
3-((*R)-2-((*S**)-1-Hydroxyethyl)but-3-enoyl)oxazolidin-2-one (2f)**



3-((*S,*E*)-2-((*S**)-1-Hydroxy-3-methylbutyl)hex-3-enoyl)oxazolidin-2-one (2g)**

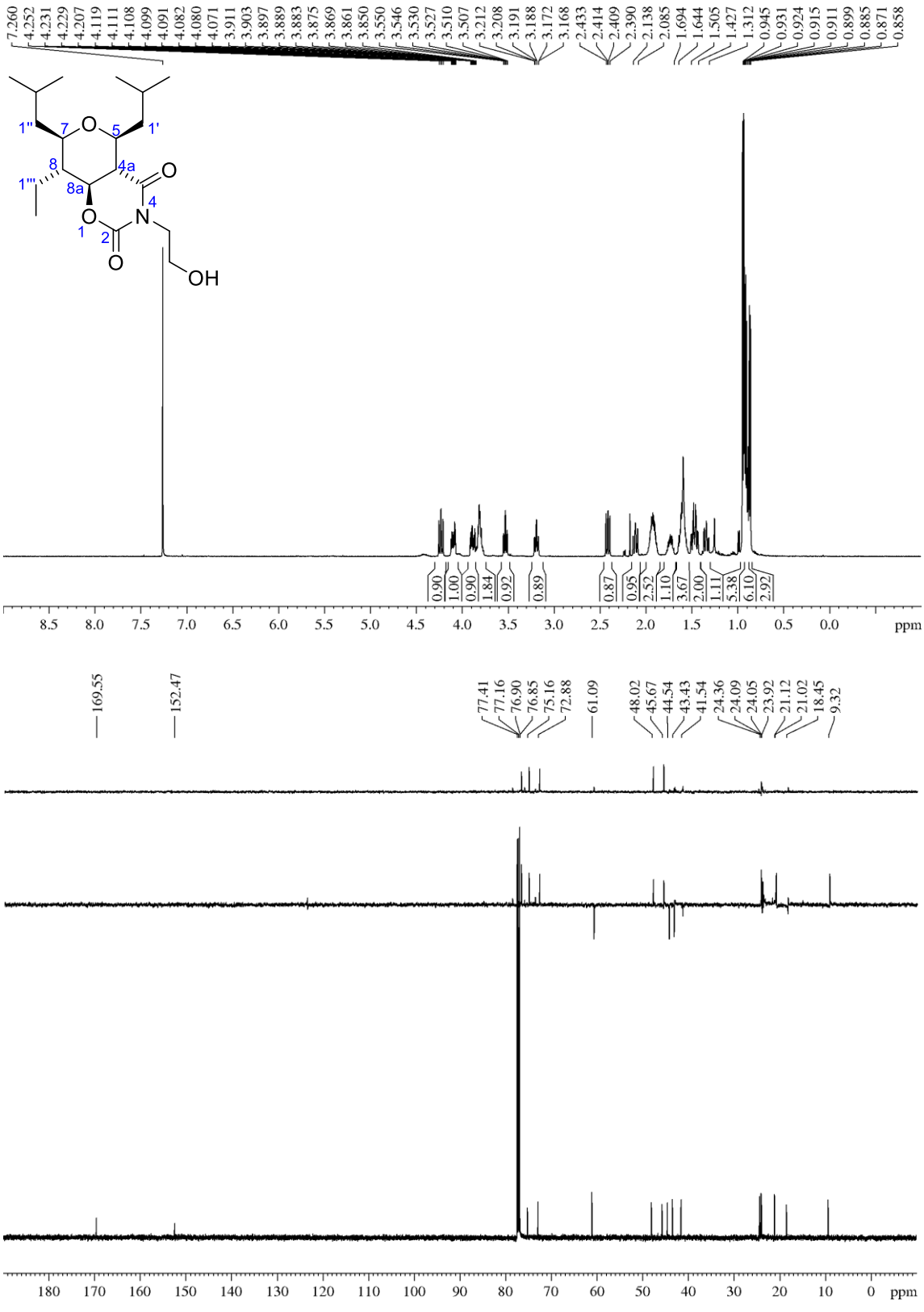


3-((2*R,3*S**)-3-Hydroxy-5-methyl-2-((*Z*)-prop-1-en-1-yl)hexanoyl)oxazolidin-2-one (2h)**

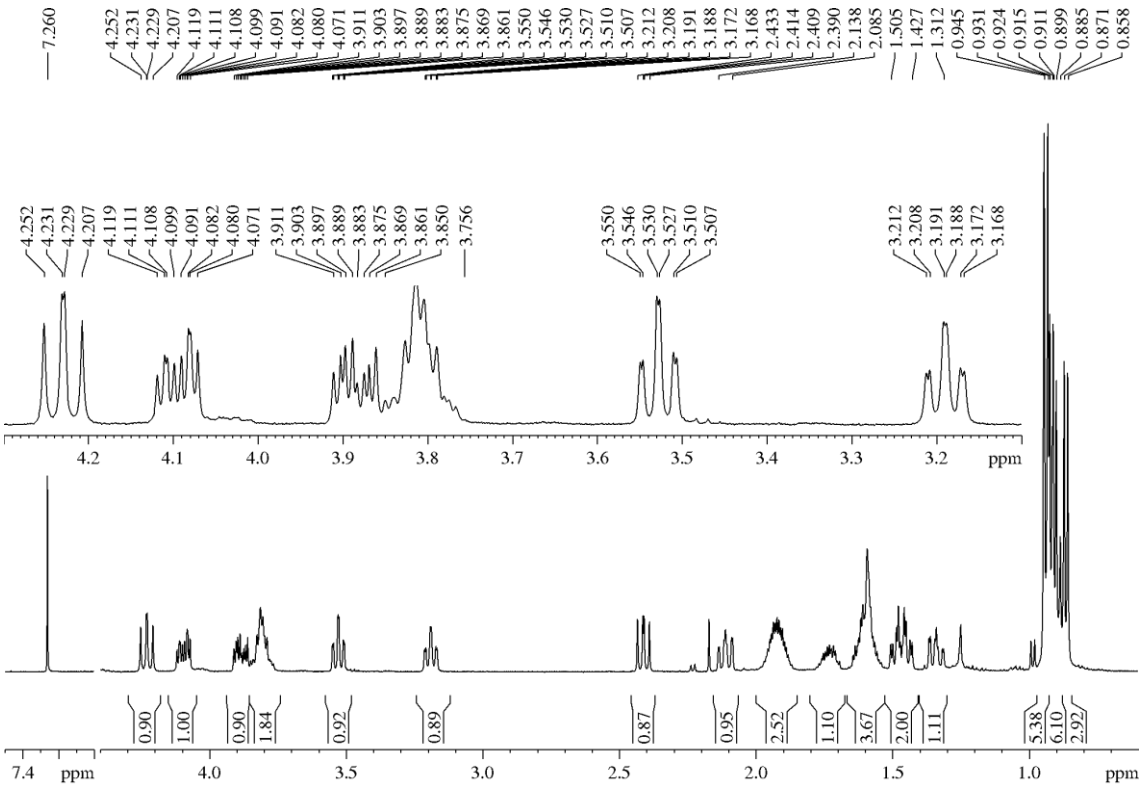


Bicycles (5)

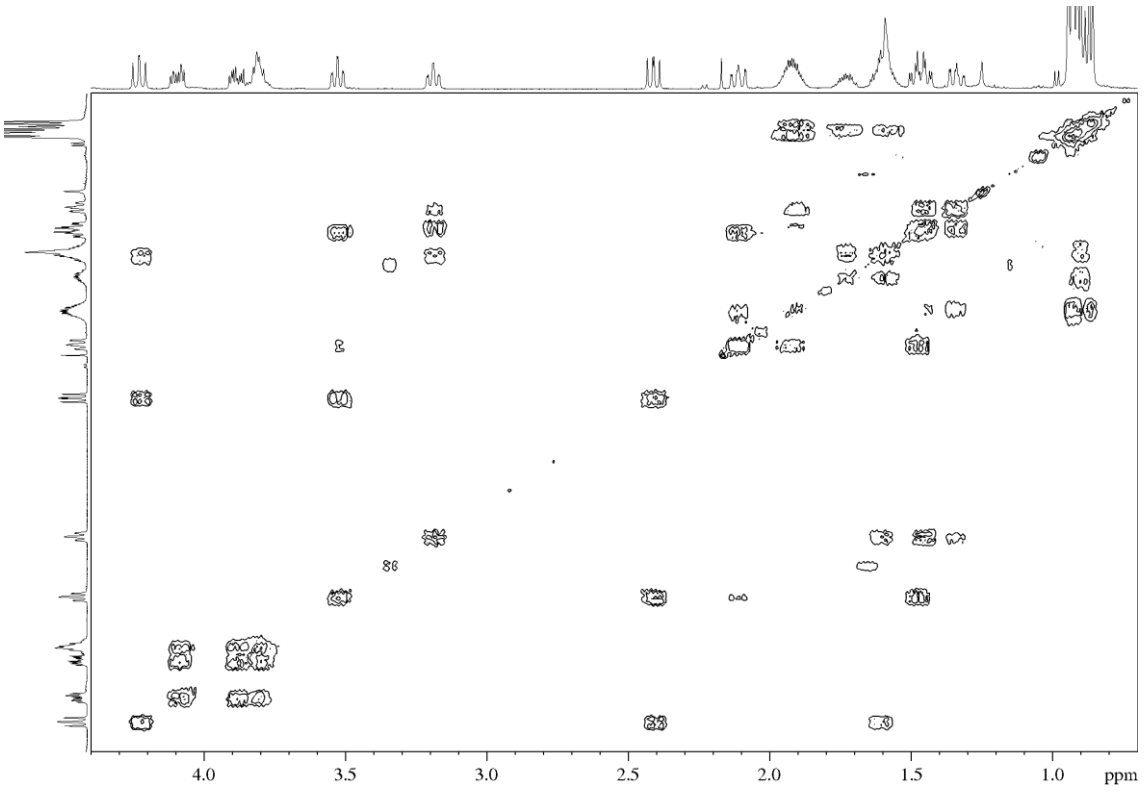
(4a*S**,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5,7-diisobutyltetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5a)



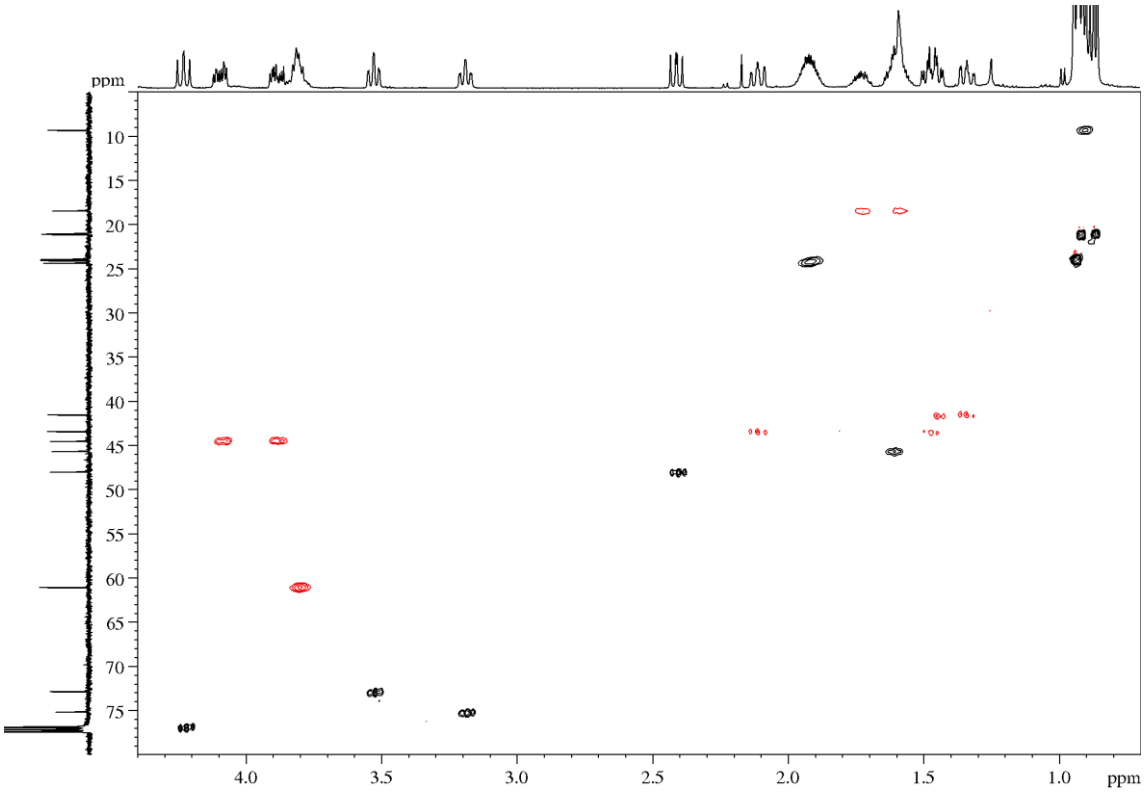
Detailed ^{1}H



COSY



HSQCed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25
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35
40
45
50
55
60
65
70
75
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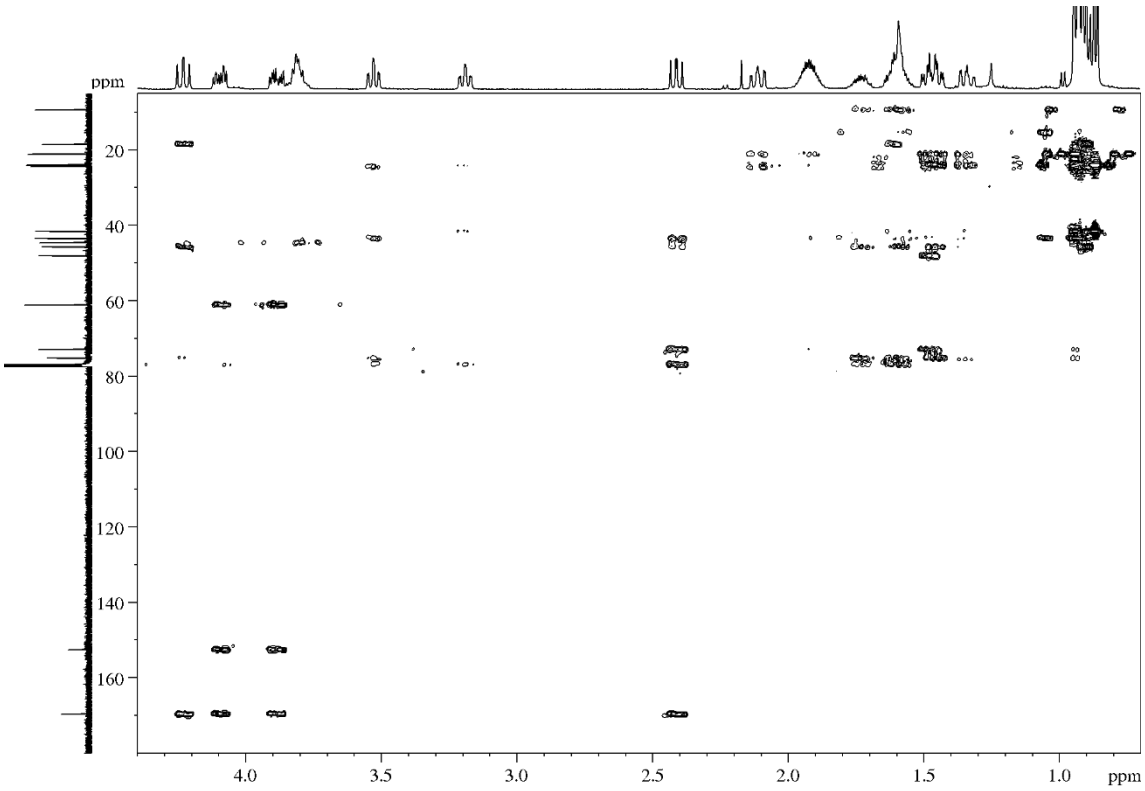
3.5
3.0
2.5
2.0
1.5
1.0
ppm

HMBC


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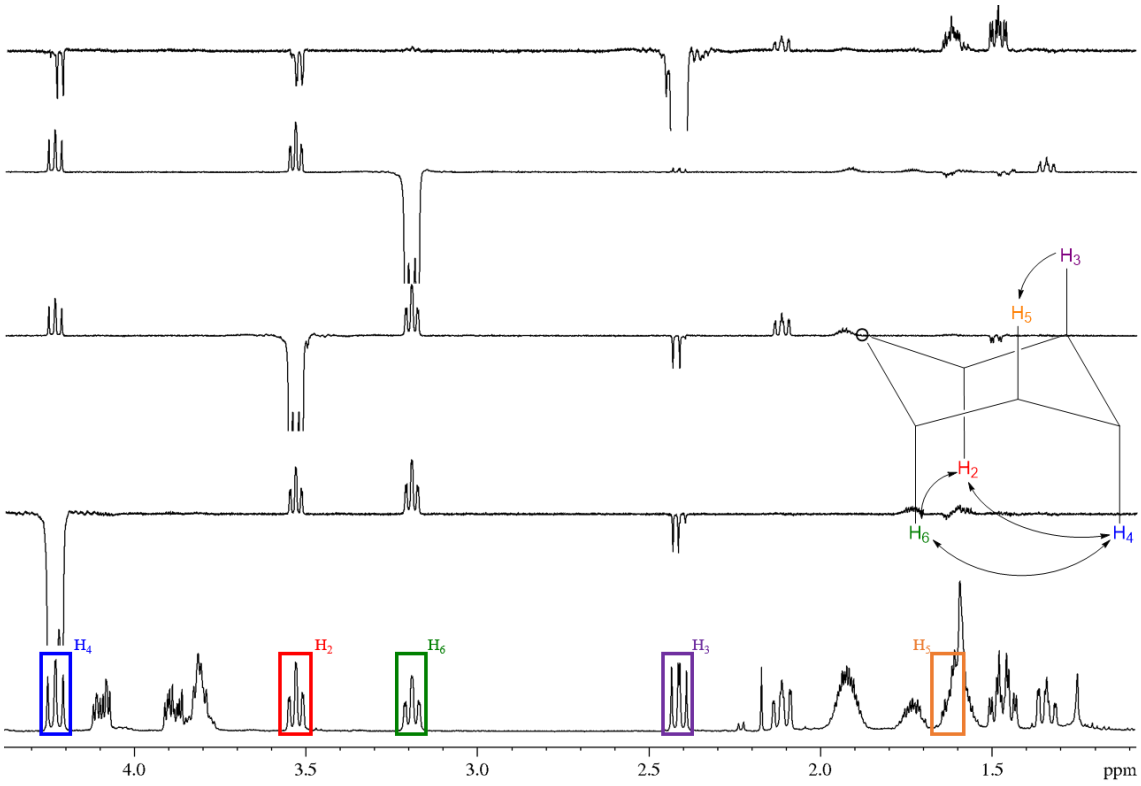
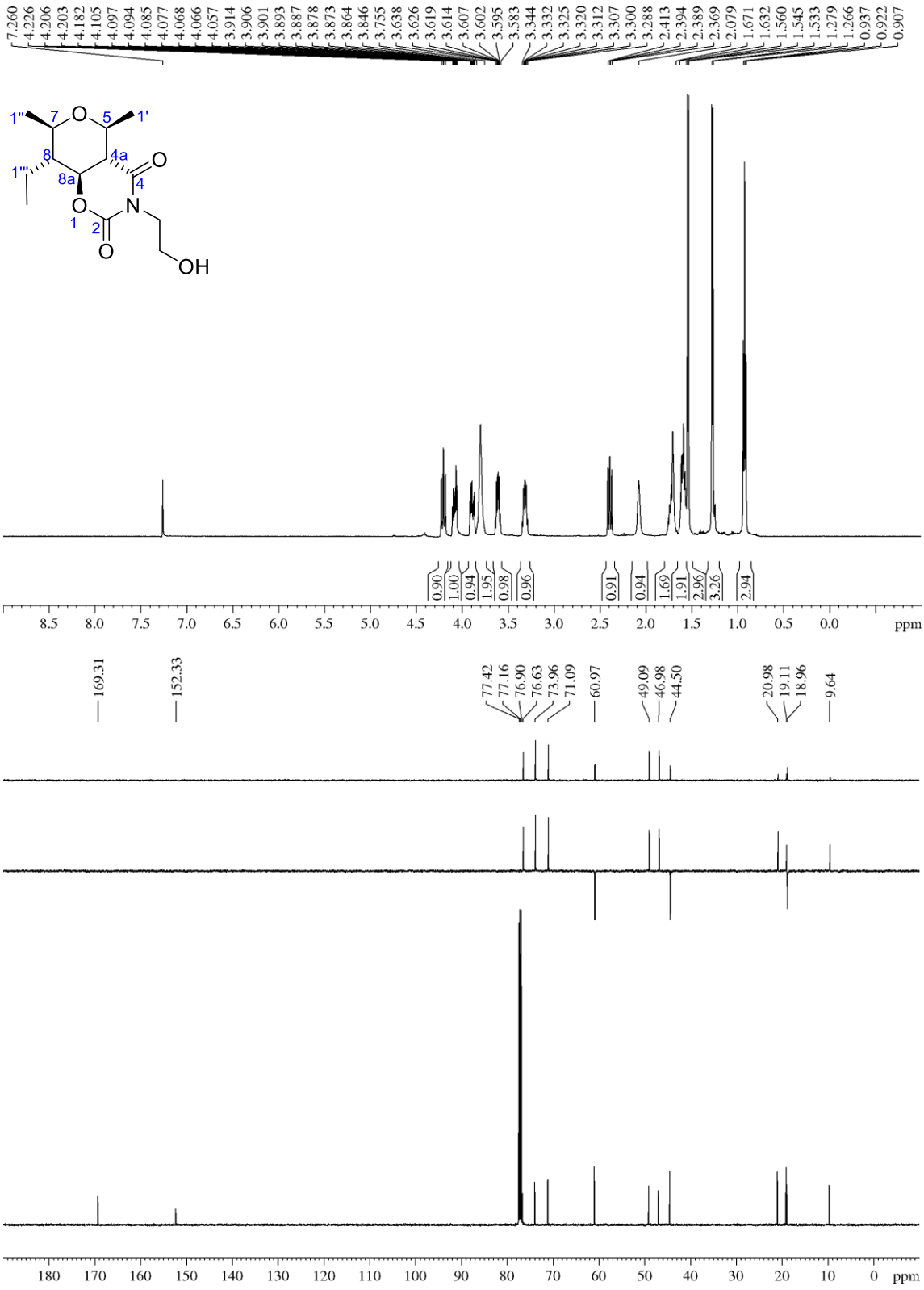
3.5
3.0
2.5
2.0
1.5
1.0
ppm

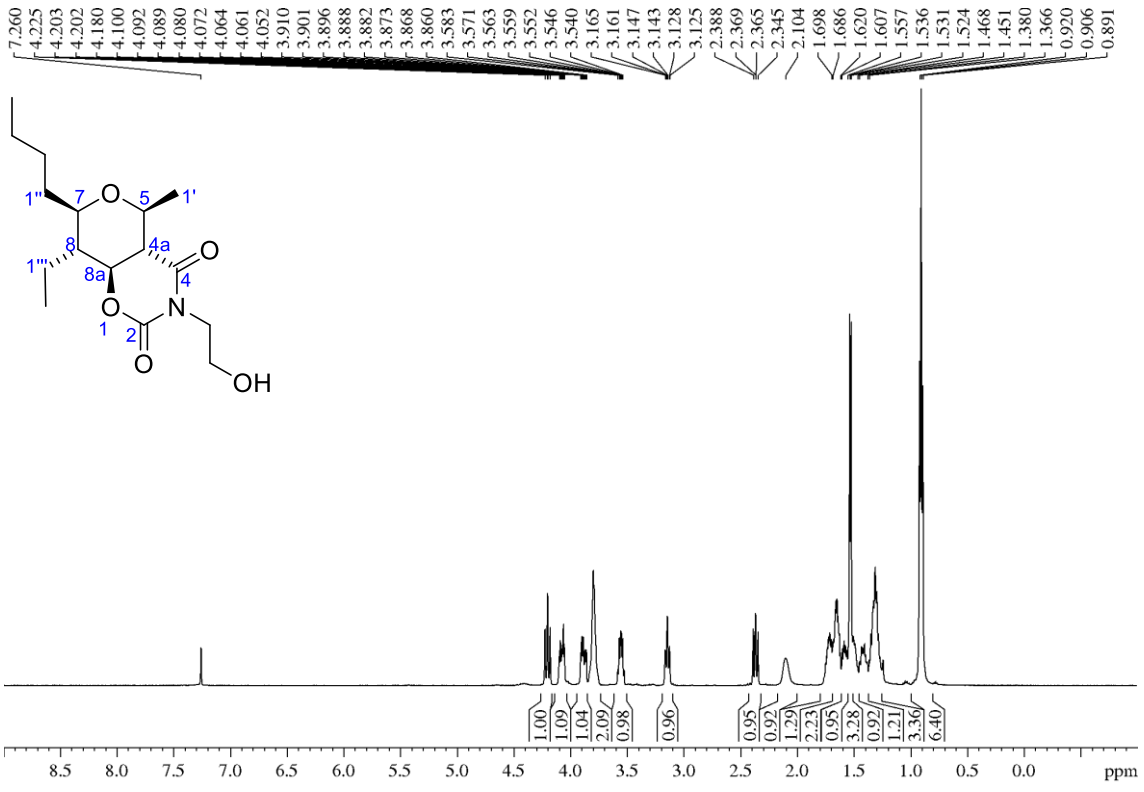
GOESY

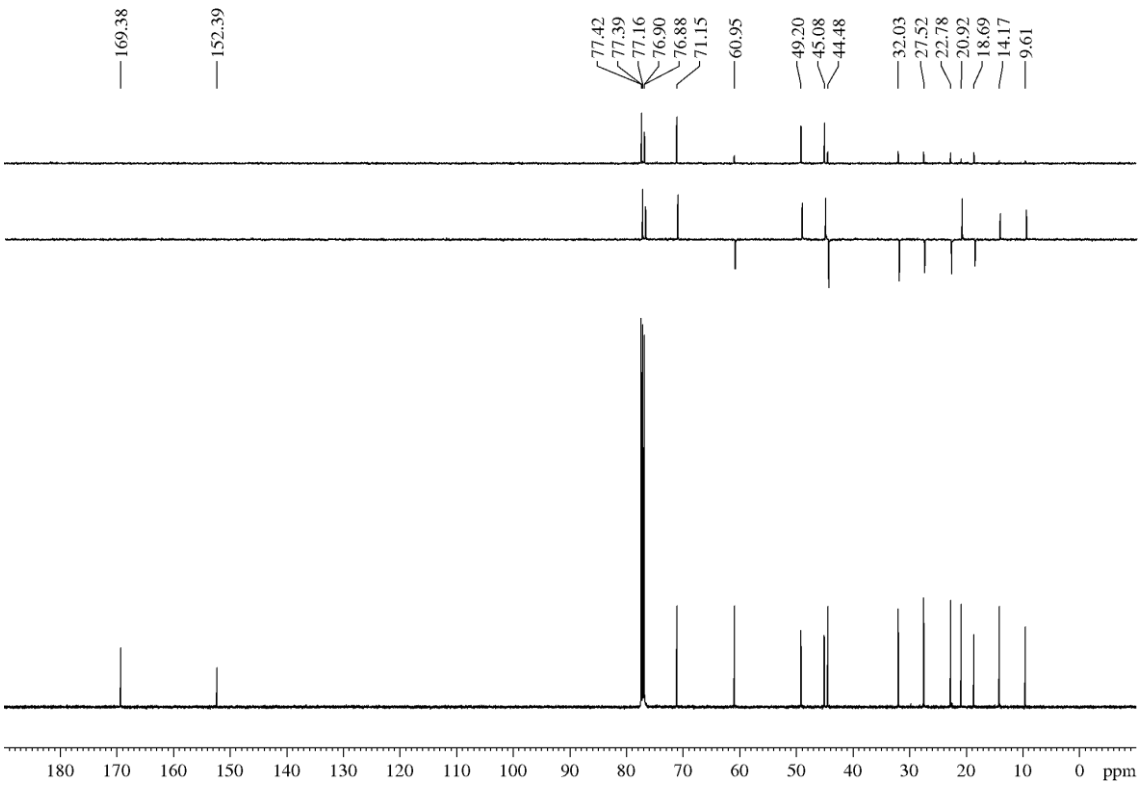


(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5b)**

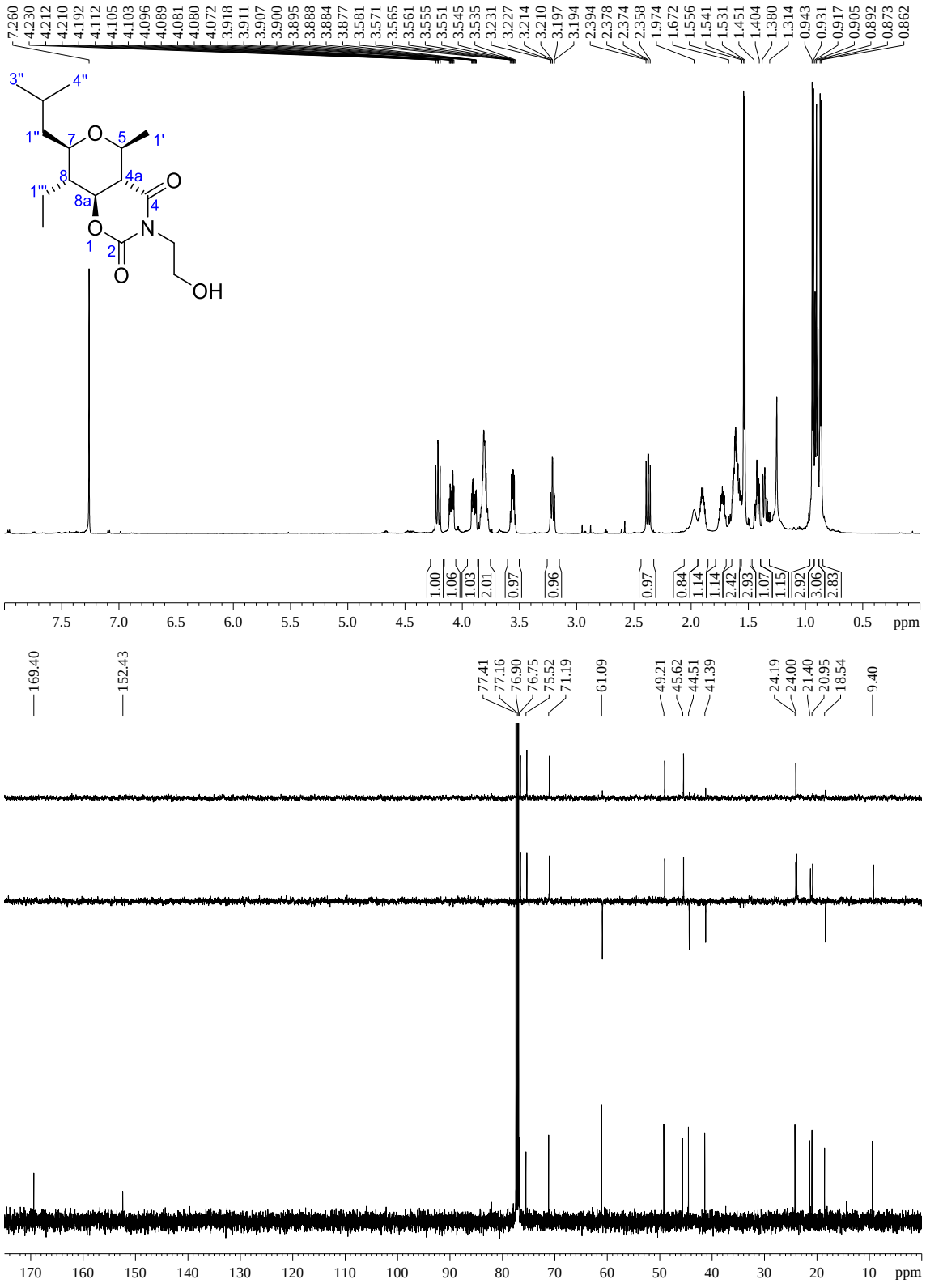


(4a*S,5*S**,7*R**,8*R**,8a*S**)-7-Butyl-8-ethyl-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5c)**

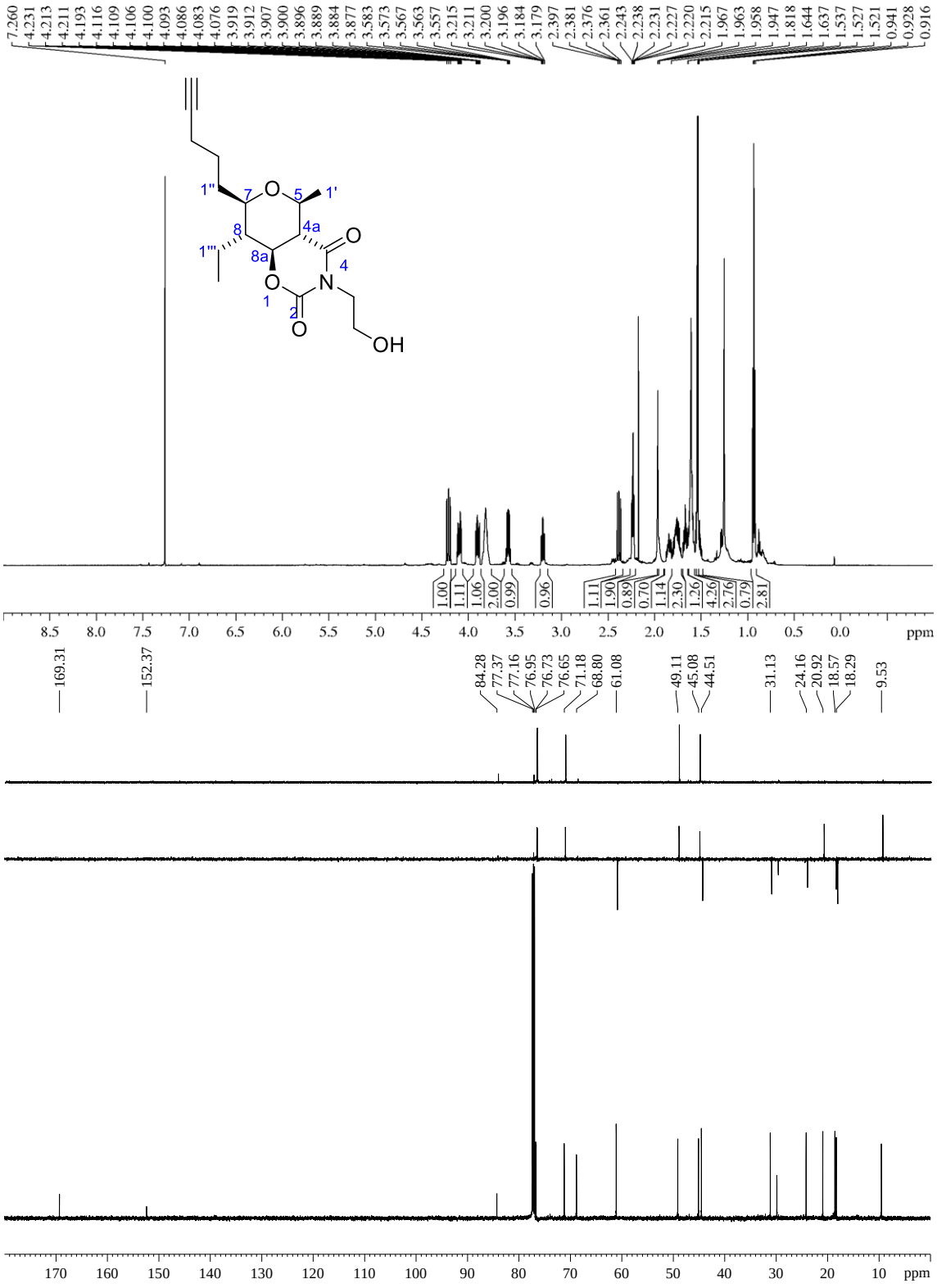




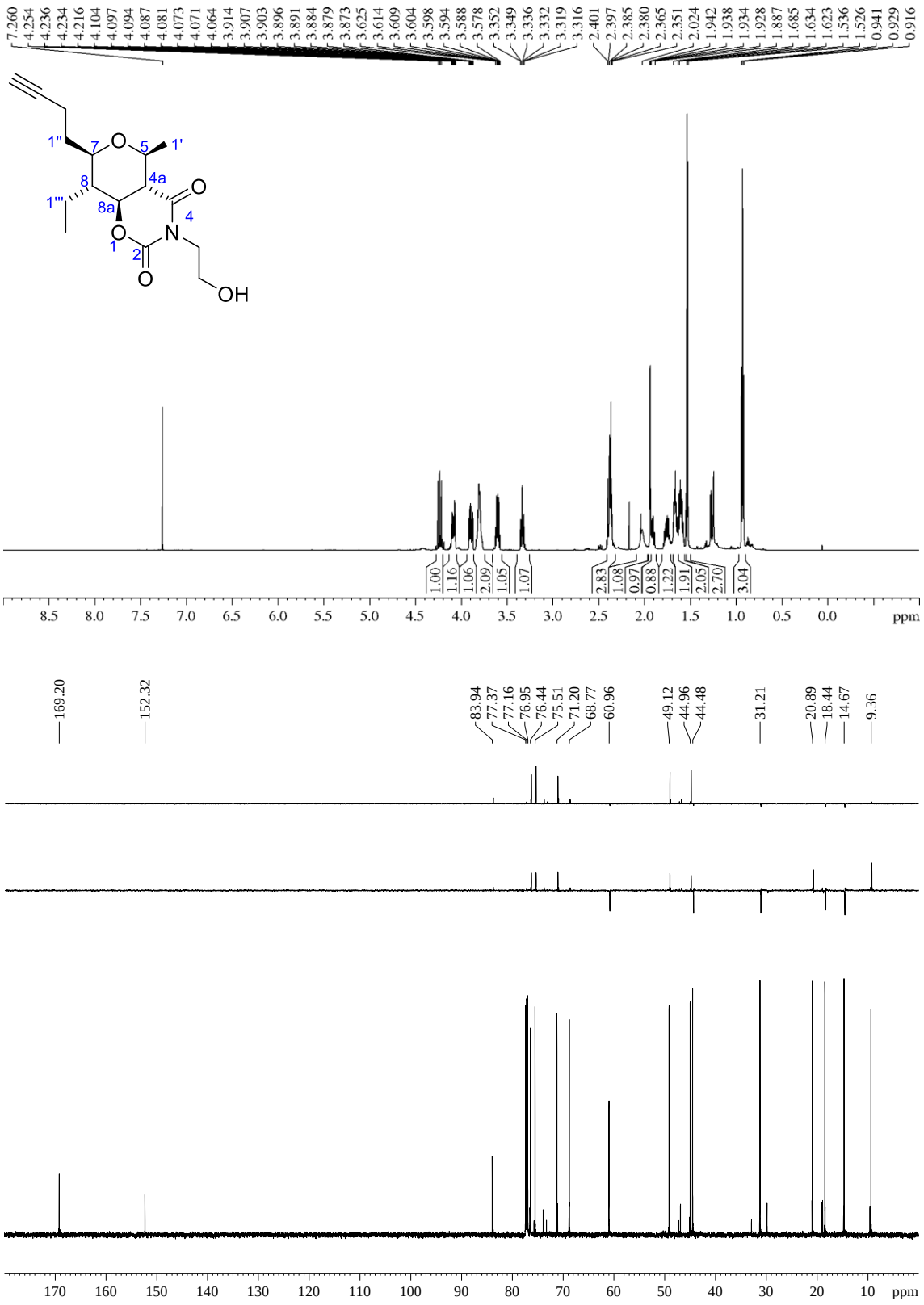
(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-isobutyl-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5d)**



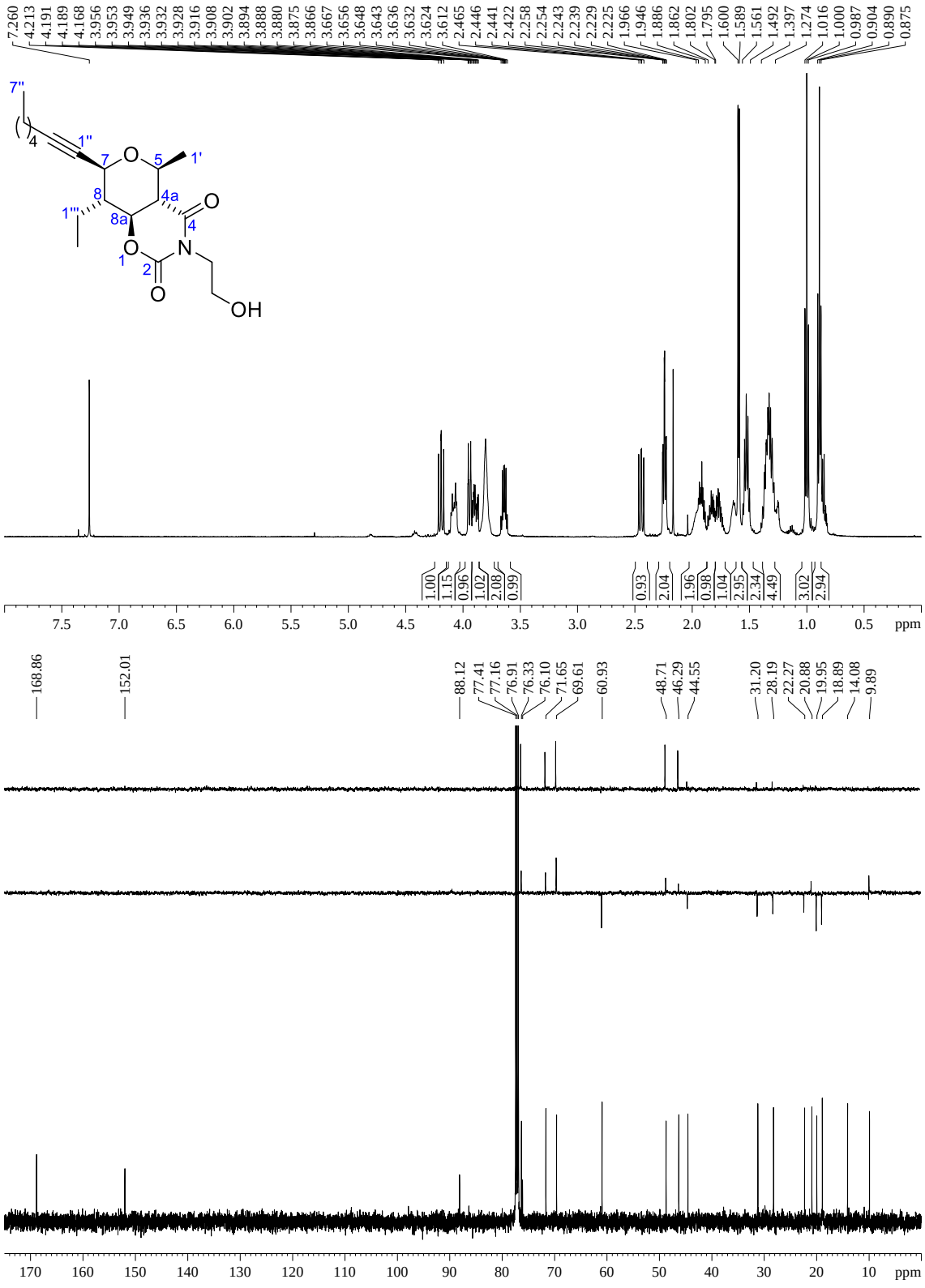
(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5-methyl-7-(pent-4-yn-1-yl)tetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5e)**



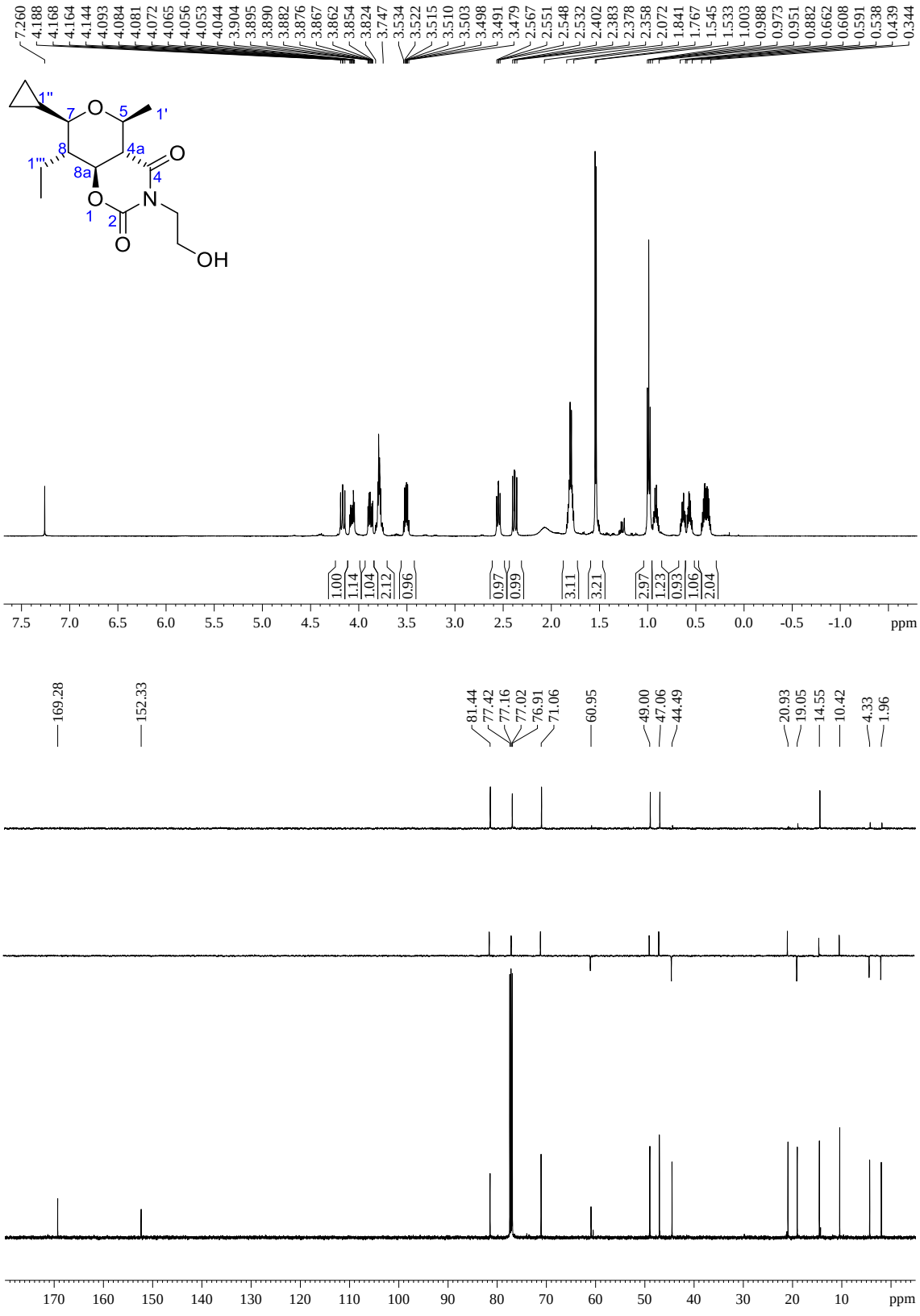
(4a*S,5*S**,7*R**,8*R**,8a*S**)-7-(But-3-yn-1-yl)-8-ethyl-3-(2-hydroxyethyl)-5-methyltetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5f)**



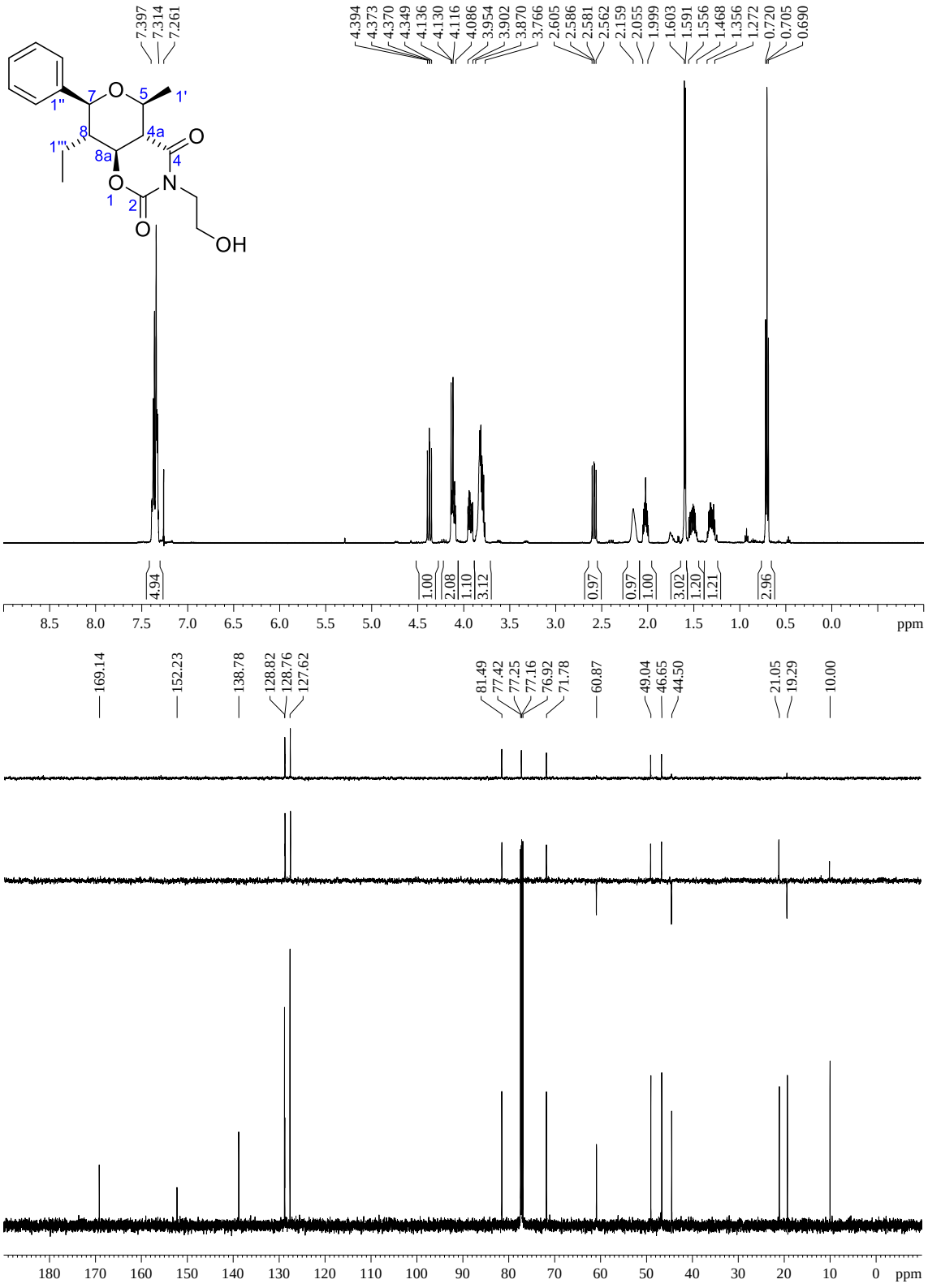
(4a*S,5*S**,7*S**,8*S**,8a*S**)-8-Ethyl-7-(hept-1-yn-1-yl)-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5g)**



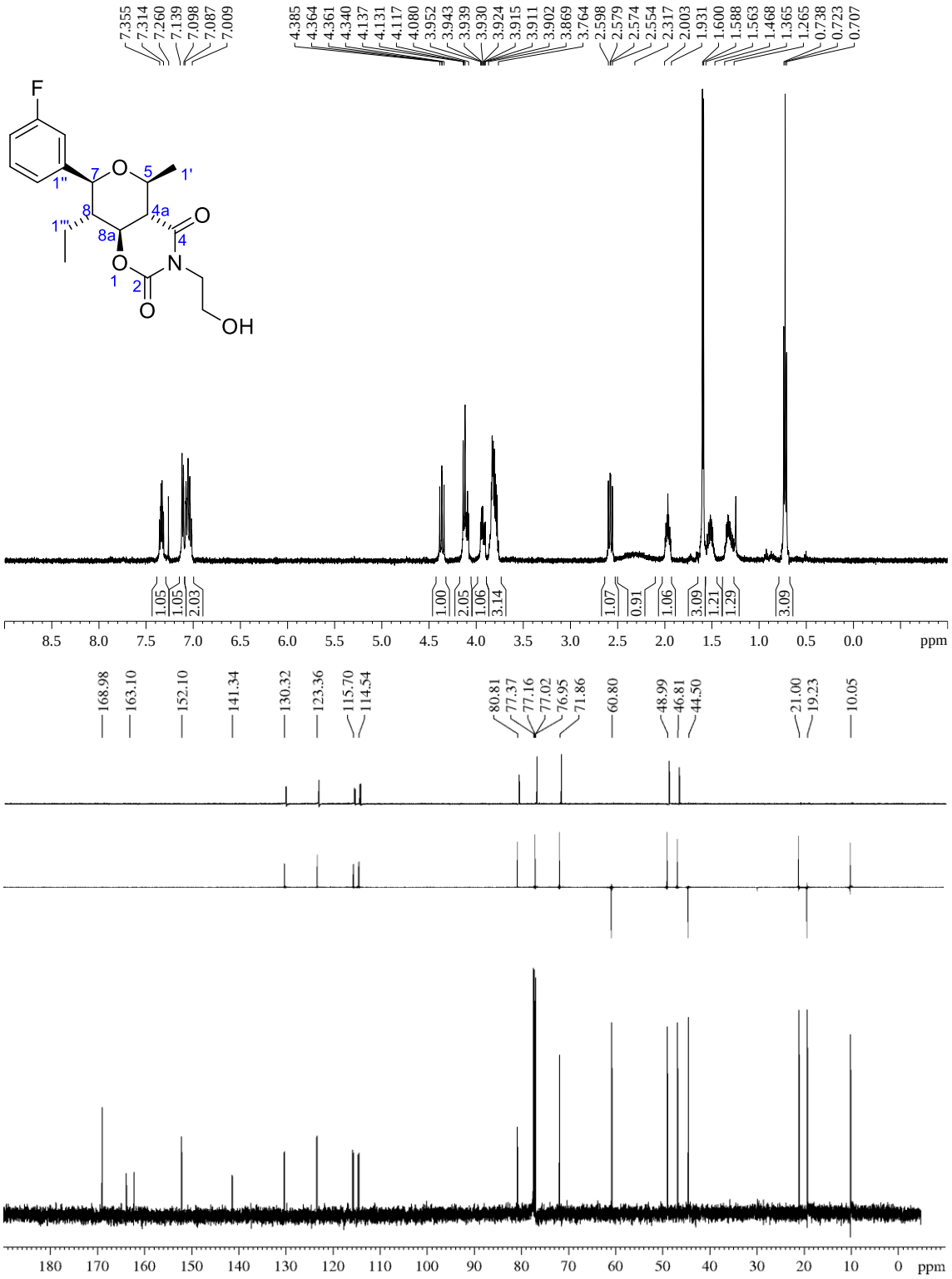
(4a*S,5*S**,7*R**,8*R**,8a*S**)-7-Cyclopropyl-8-ethyl-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5h)**



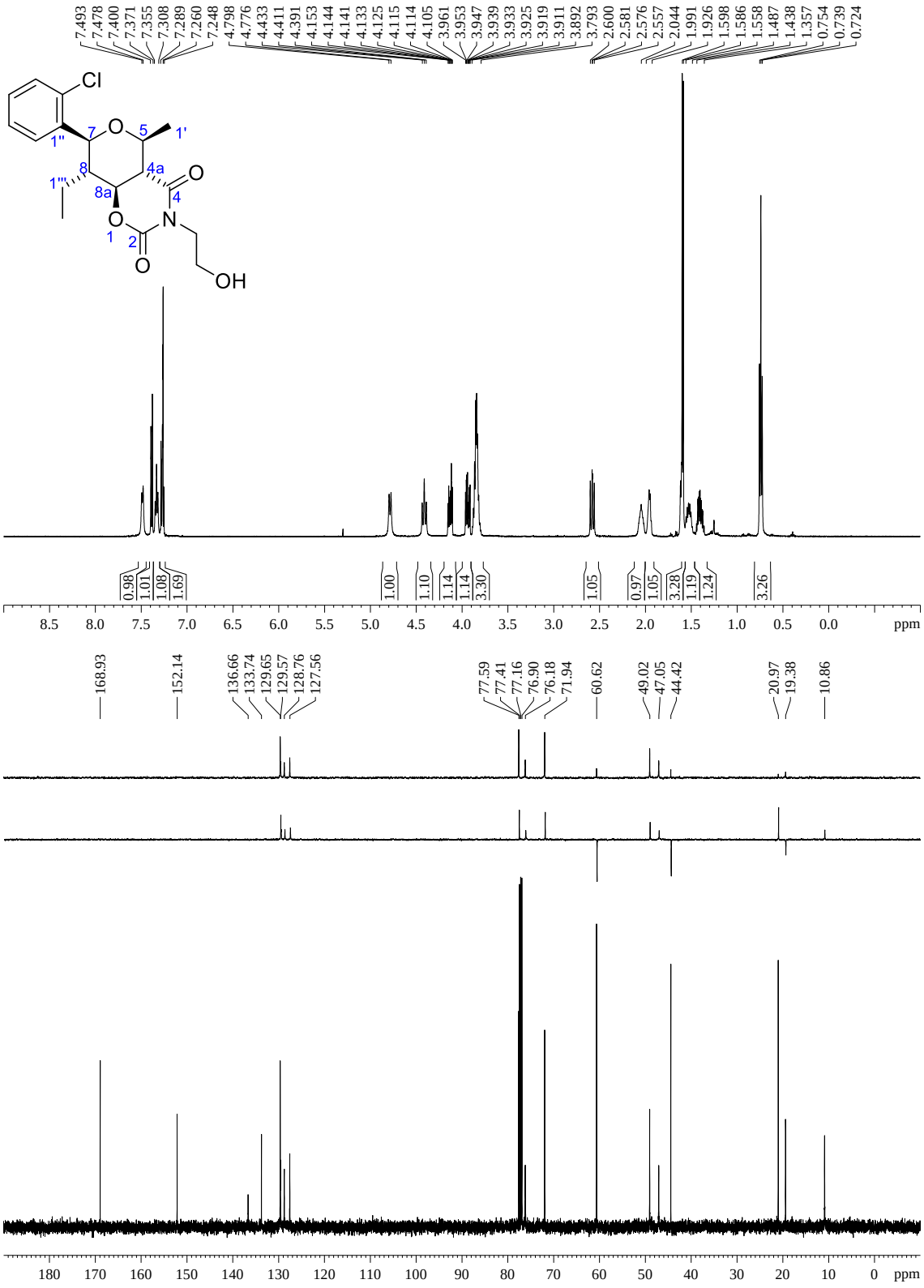
(4a*S,5*S**,7*S**,8*S**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5-methyl-7-phenyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5i)**



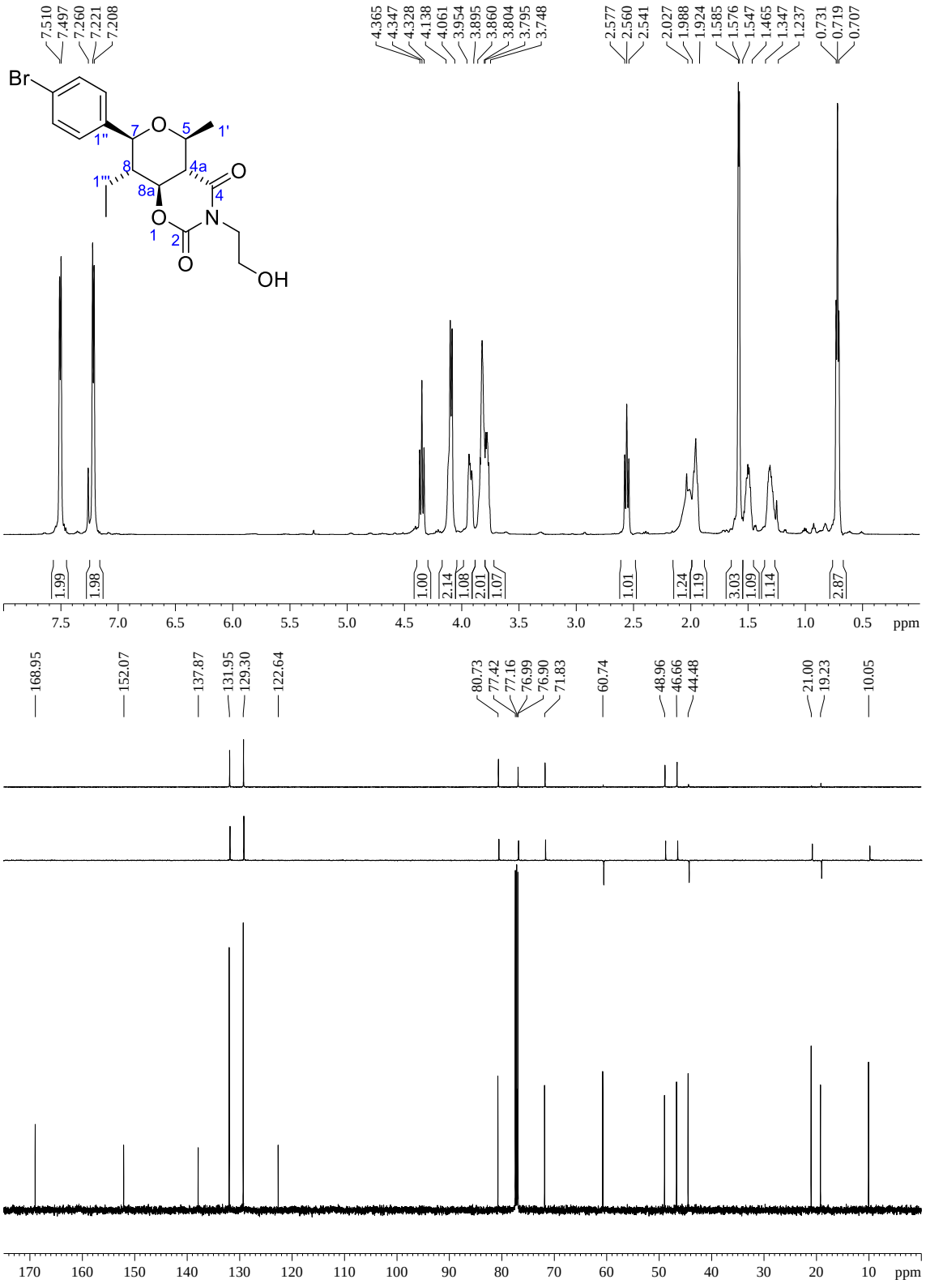
(4a*S,5*S**,7*S**,8*S**,8a*S**)-8-Ethyl-7-(3-fluorophenyl)-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5j)**



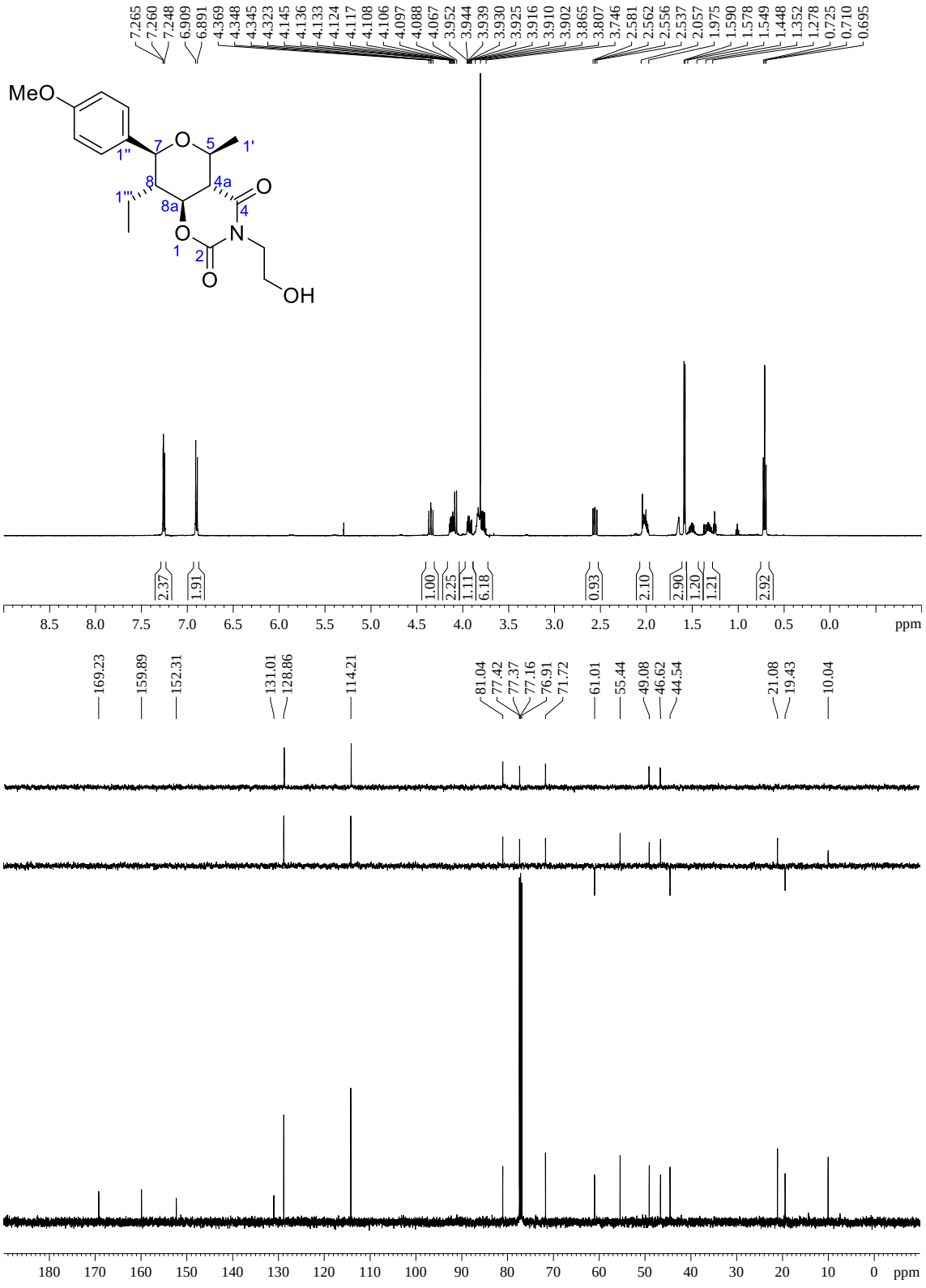
(4a*S,5*S**,7*S**,8*S**,8a*S**)-7-(2-Chlorophenyl)-8-ethyl-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5k)**



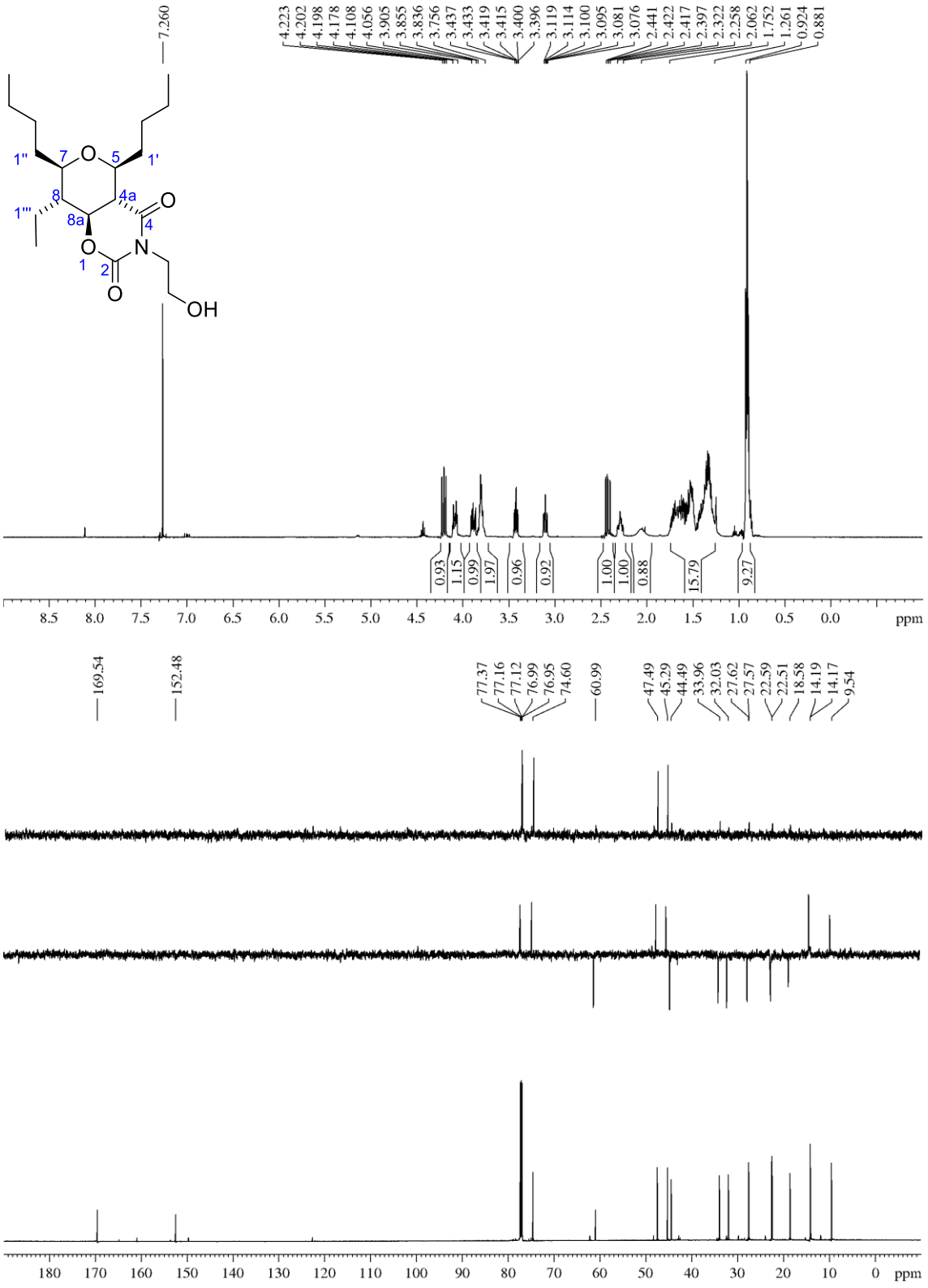
(4a*S,5*S**,7*S**,8*S**,8a*S**)-7-(4-Bromophenyl)-8-ethyl-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5l)**



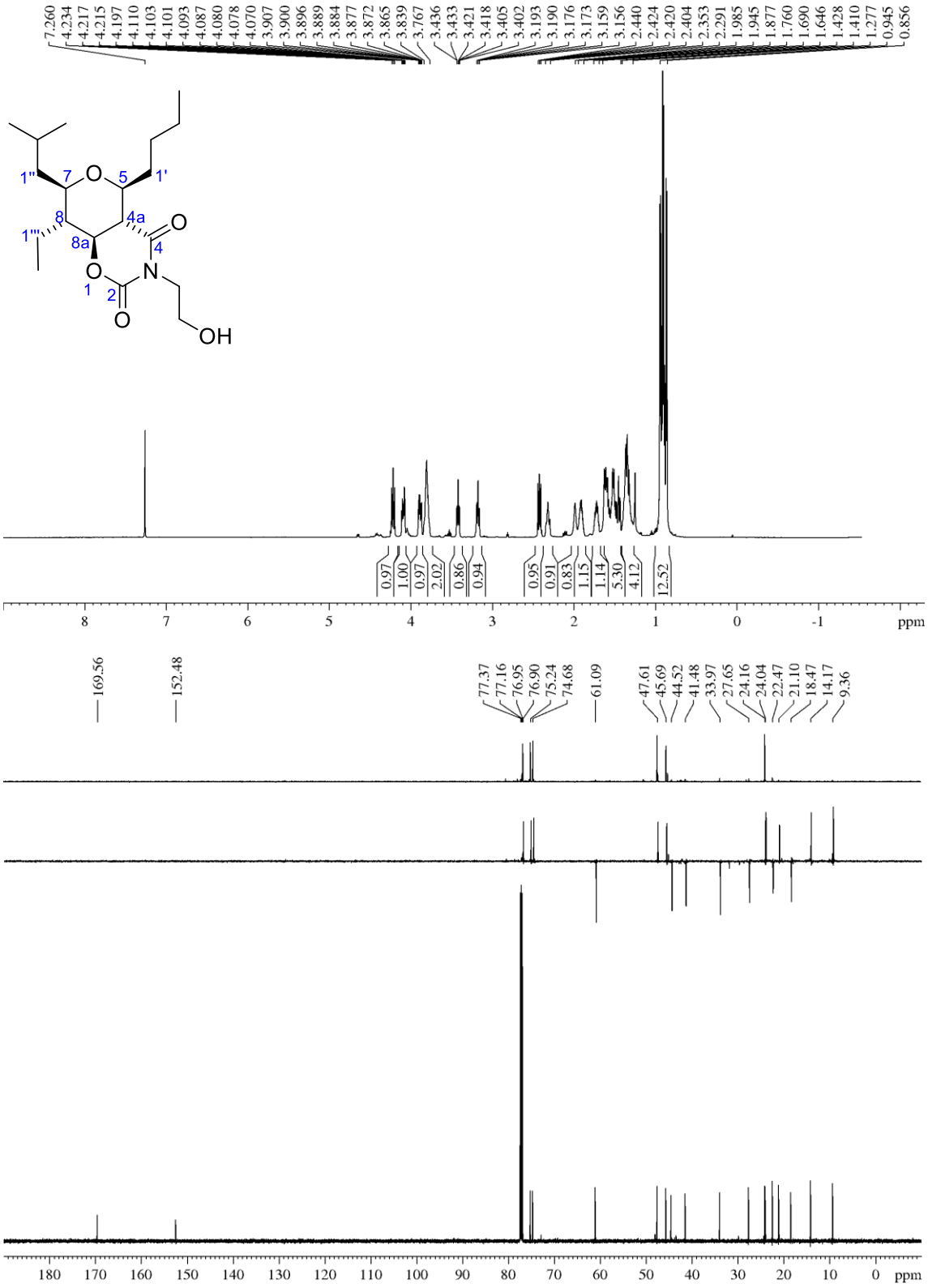
(4a*S,5*S**,7*S**,8*S**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-(4-methoxyphenyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5m)**



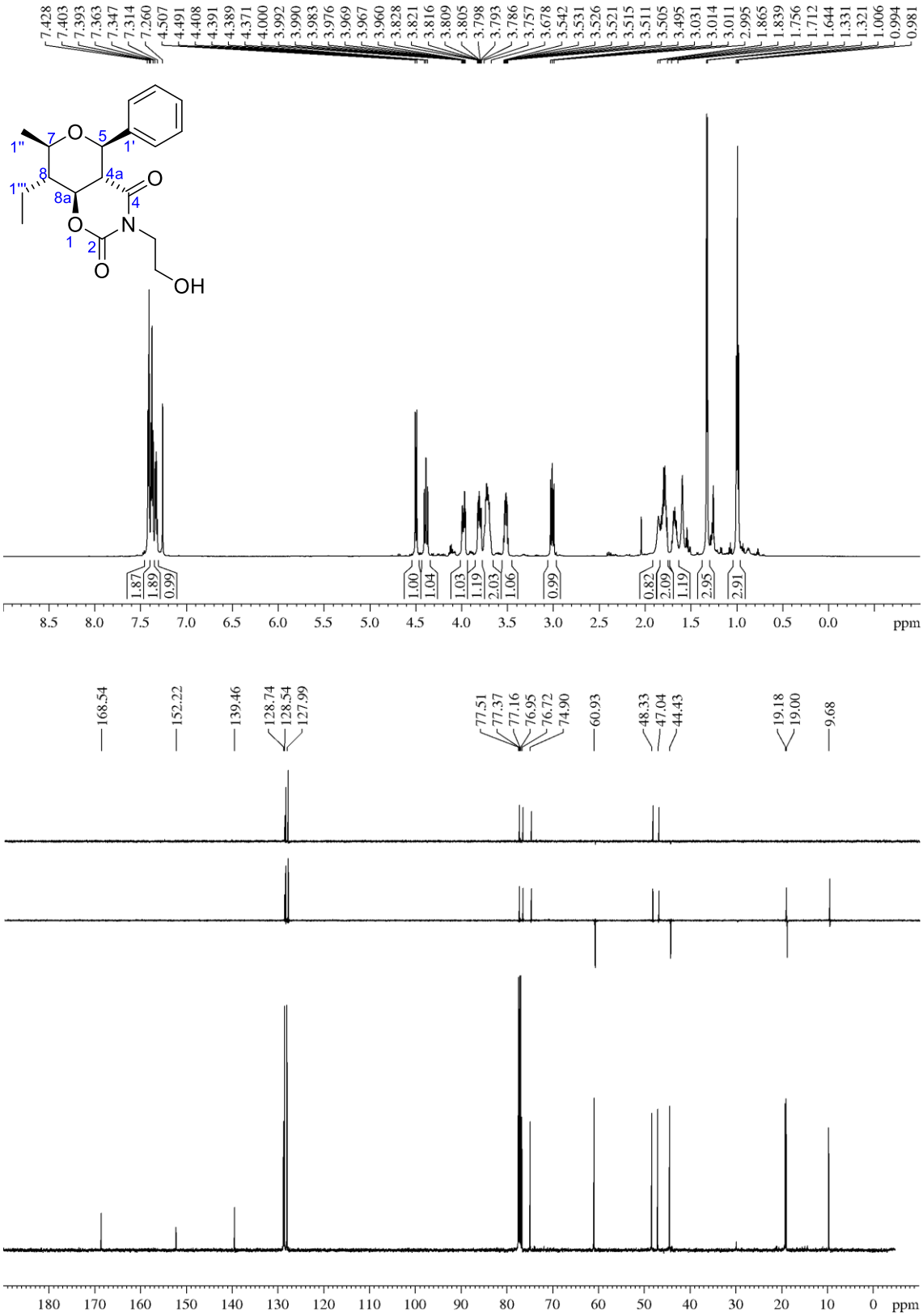
(4a*S,5*S**,7*R**,8*R**,8a*S**)-5,7-Dibutyl-8-ethyl-3-(2-hydroxyethyl)tetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5n)**



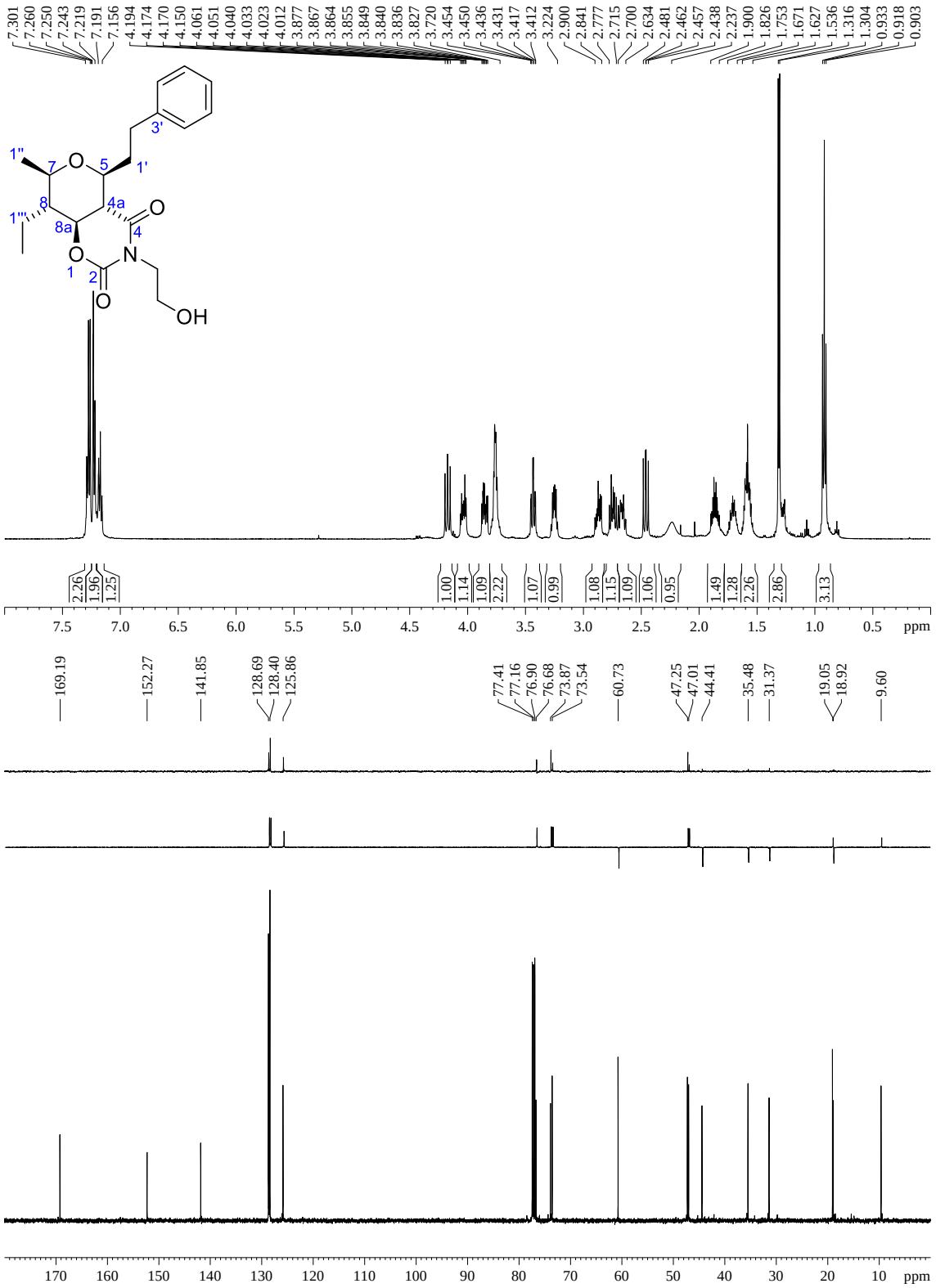
(4a*S,5*S**,7*R**,8*R**,8a*S**)-5-Butyl-8-ethyl-3-(2-hydroxyethyl)-7-isobutyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5o)**



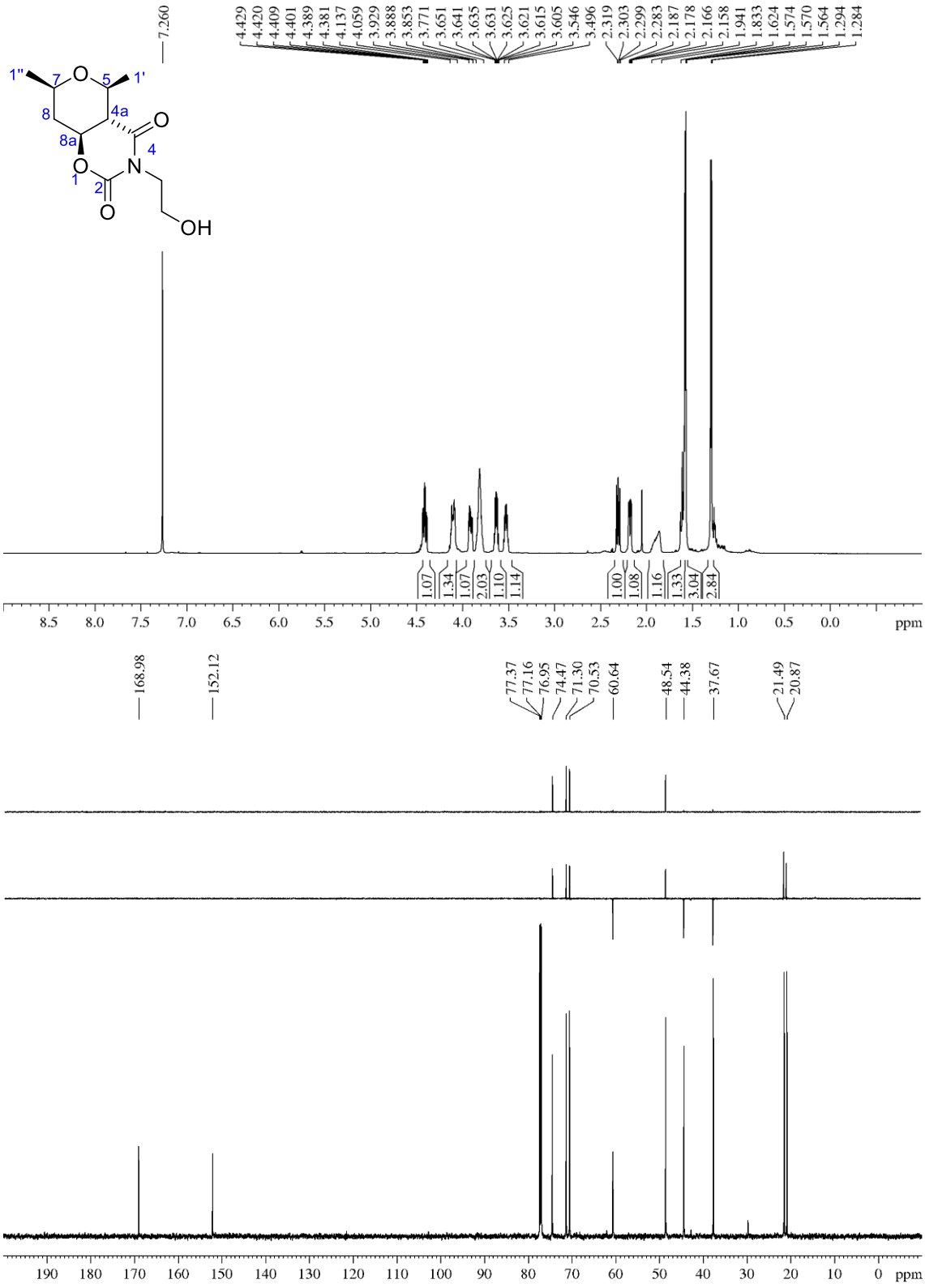
(4a*R*,5*R***,7*R***,8*R***,8a*S***)-8-Ethyl-3-(2-hydroxyethyl)-7-methyl-5-phenyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5p)**



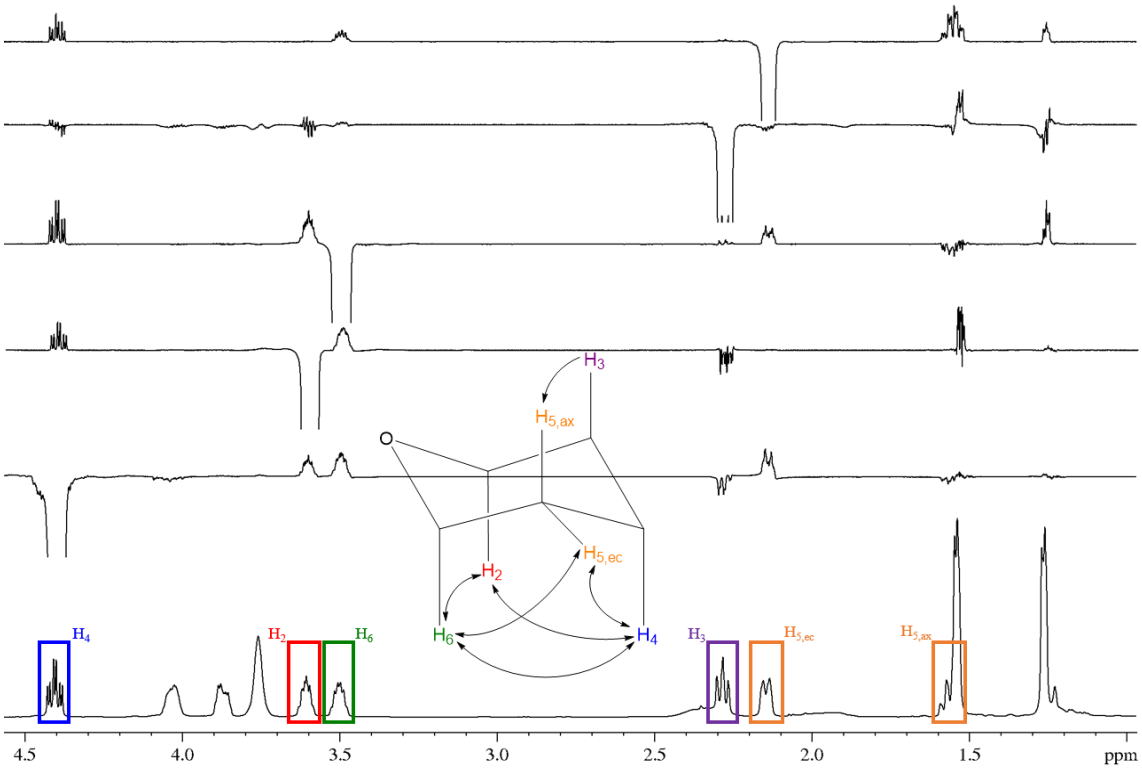
(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-methyl-5-phenethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5q)**



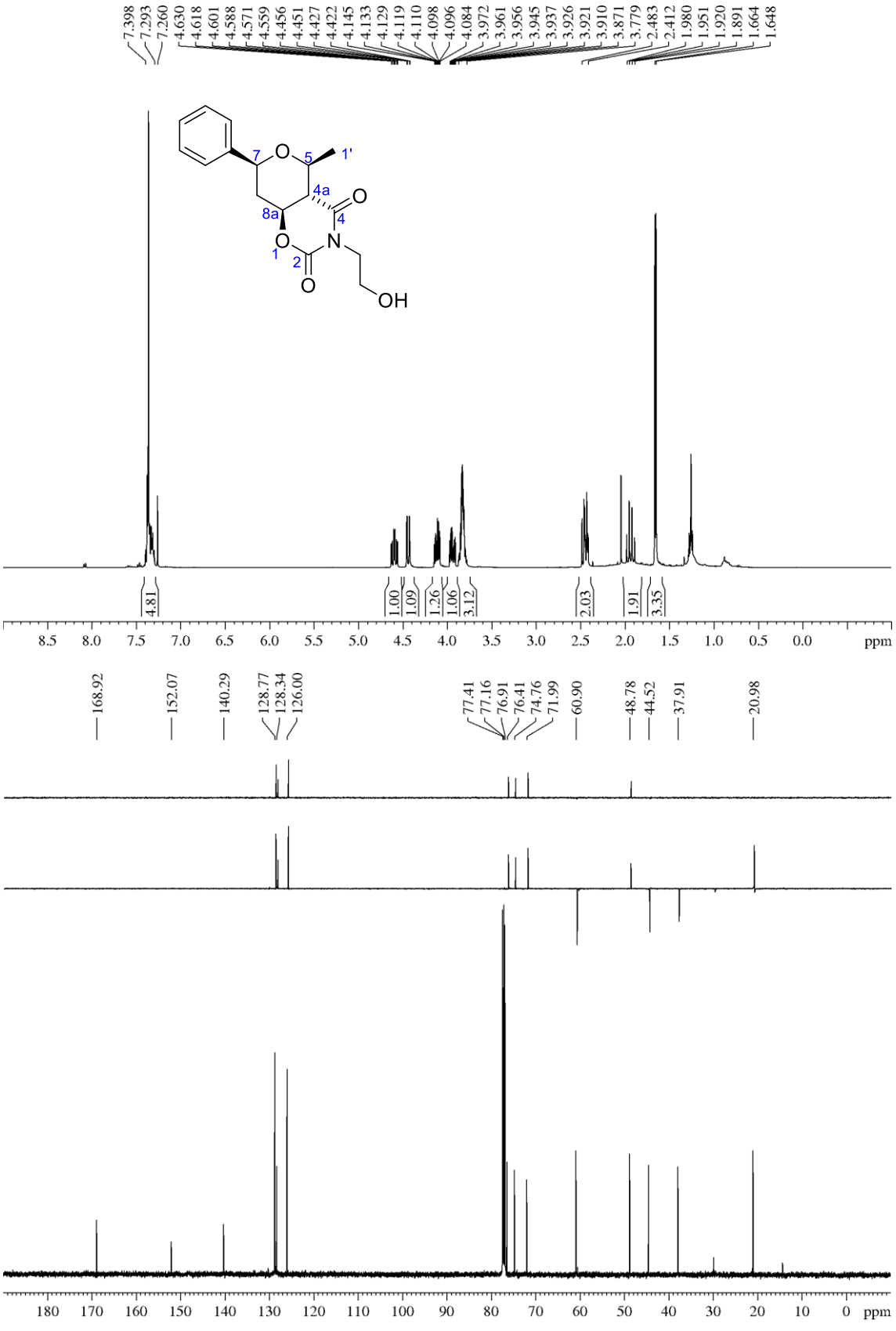
(4a*S,5*S**,7*R**,8a*S**)-3-(2-Hydroxyethyl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5r)**



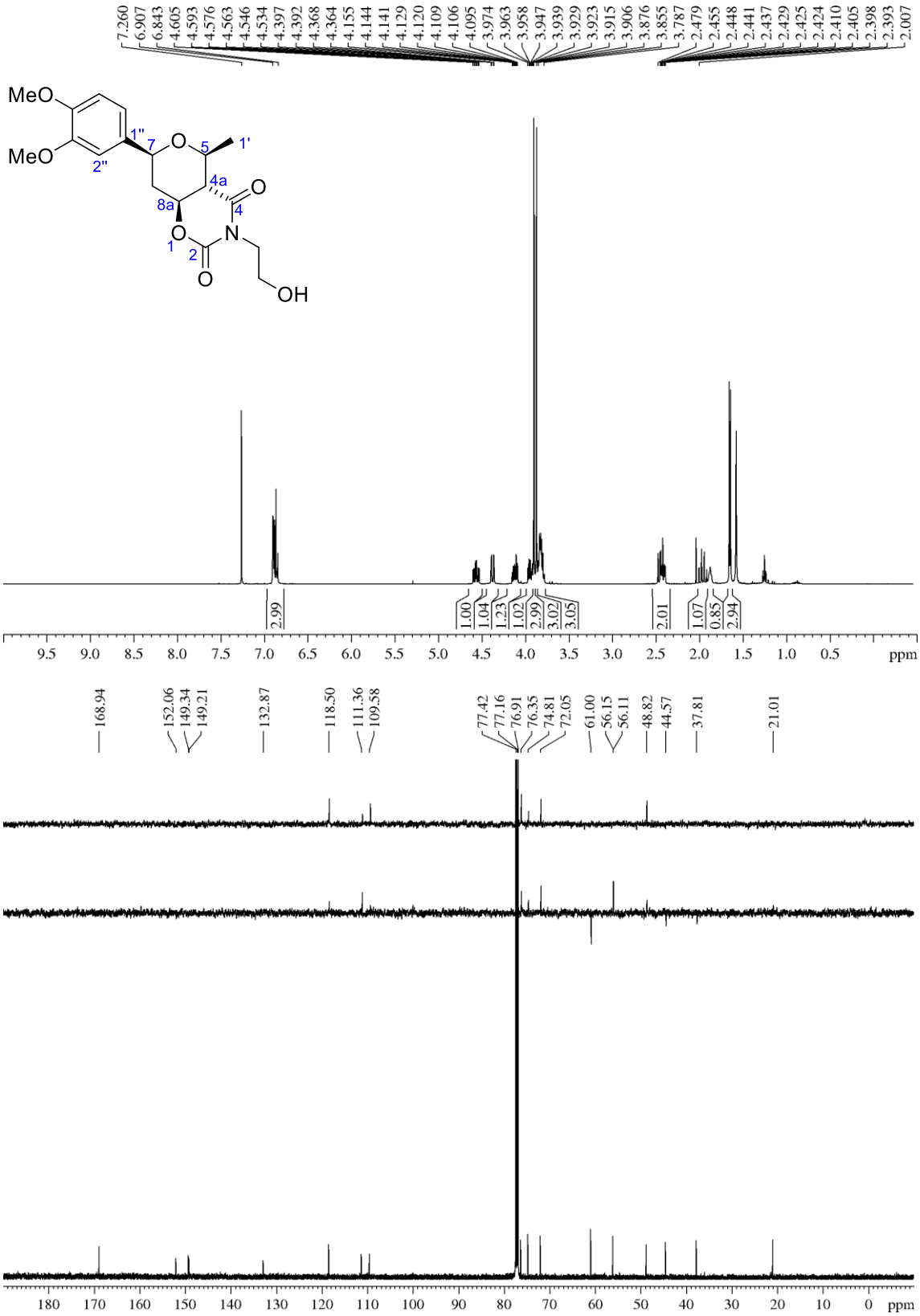
GOESY


H3
H5,ax
O
H2
H5,ec
H6
H4
H4
H2
H6
H3
H5,ec
H5,ax
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

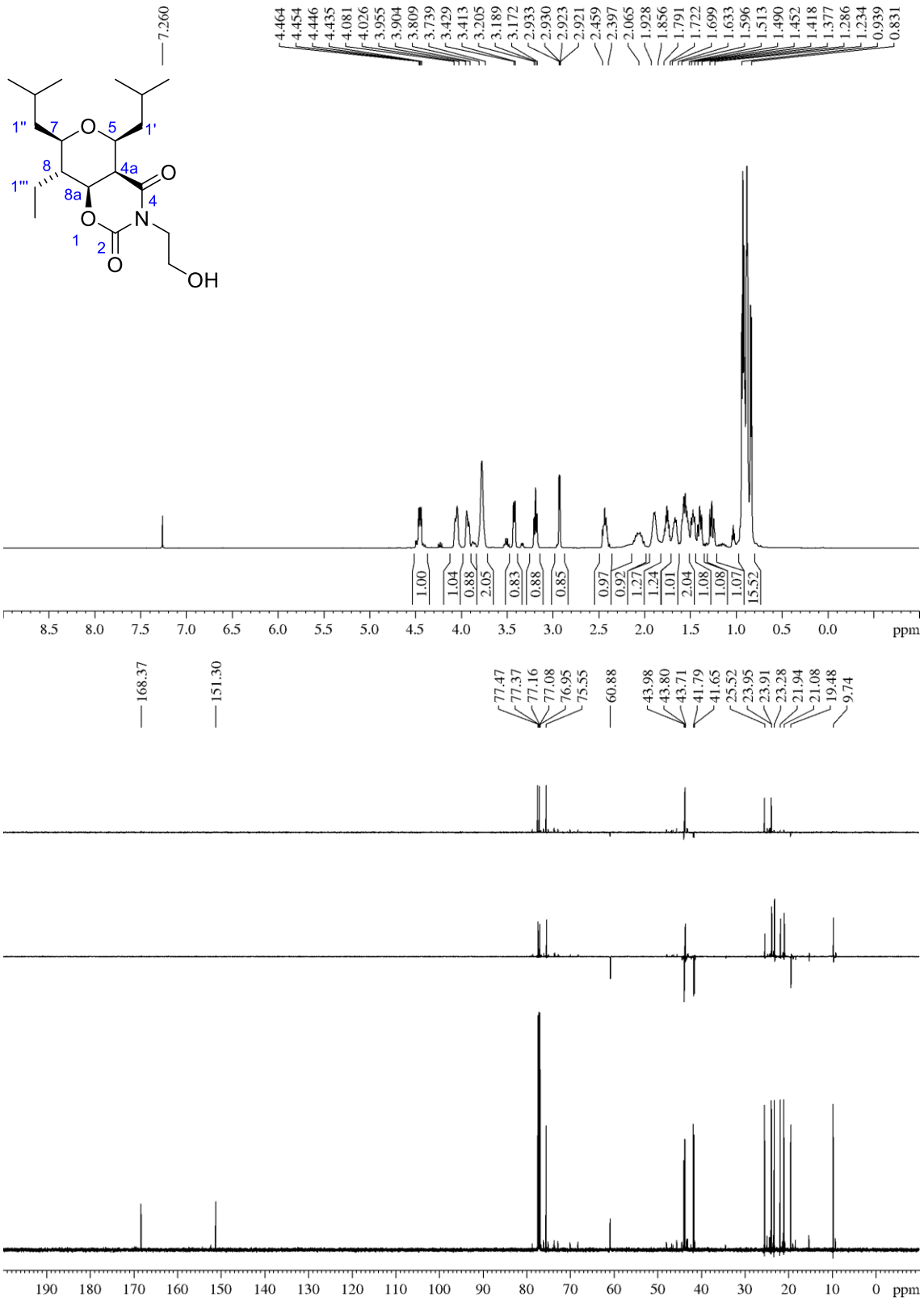
(4a*S,5*S**,7*S**,8a*S**)-3-(2-Hydroxyethyl)-5-methyl-7-phenyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5s)**



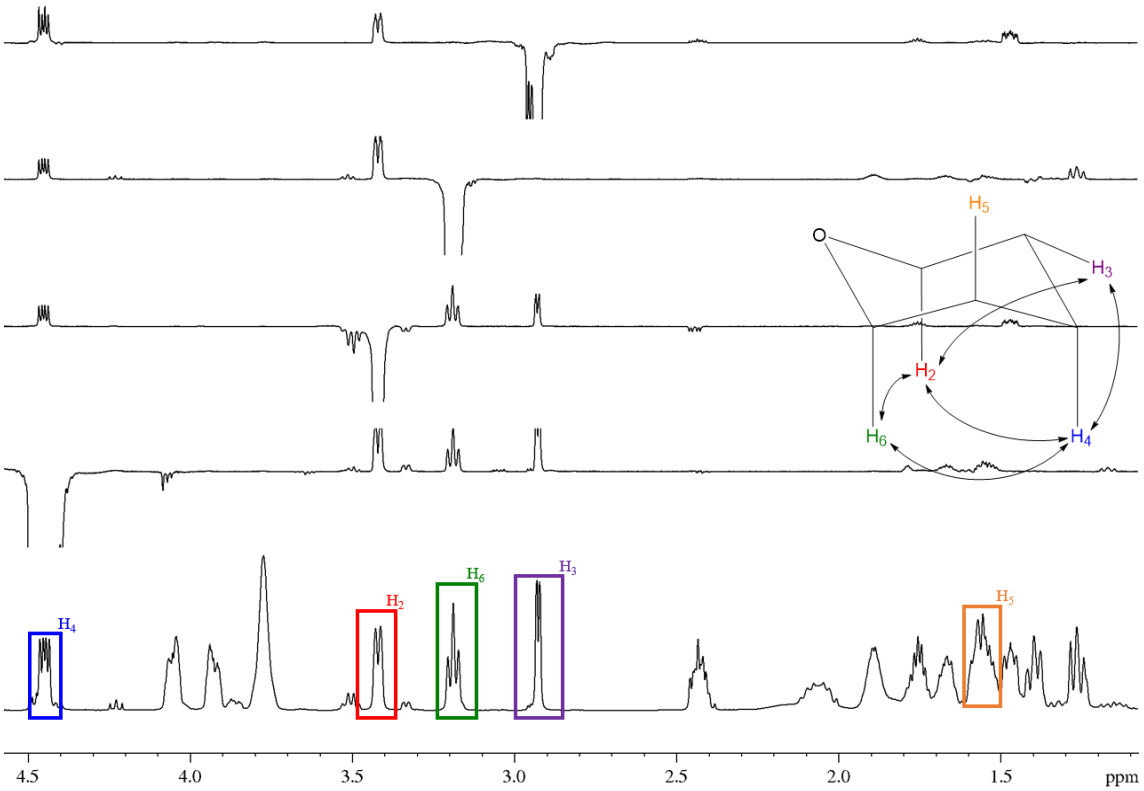
(4a*S,5*S**,7*S**,8a*S**)-7-(3,4-Dimethoxyphenyl)-3-(2-hydroxyethyl)-5-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5t)**



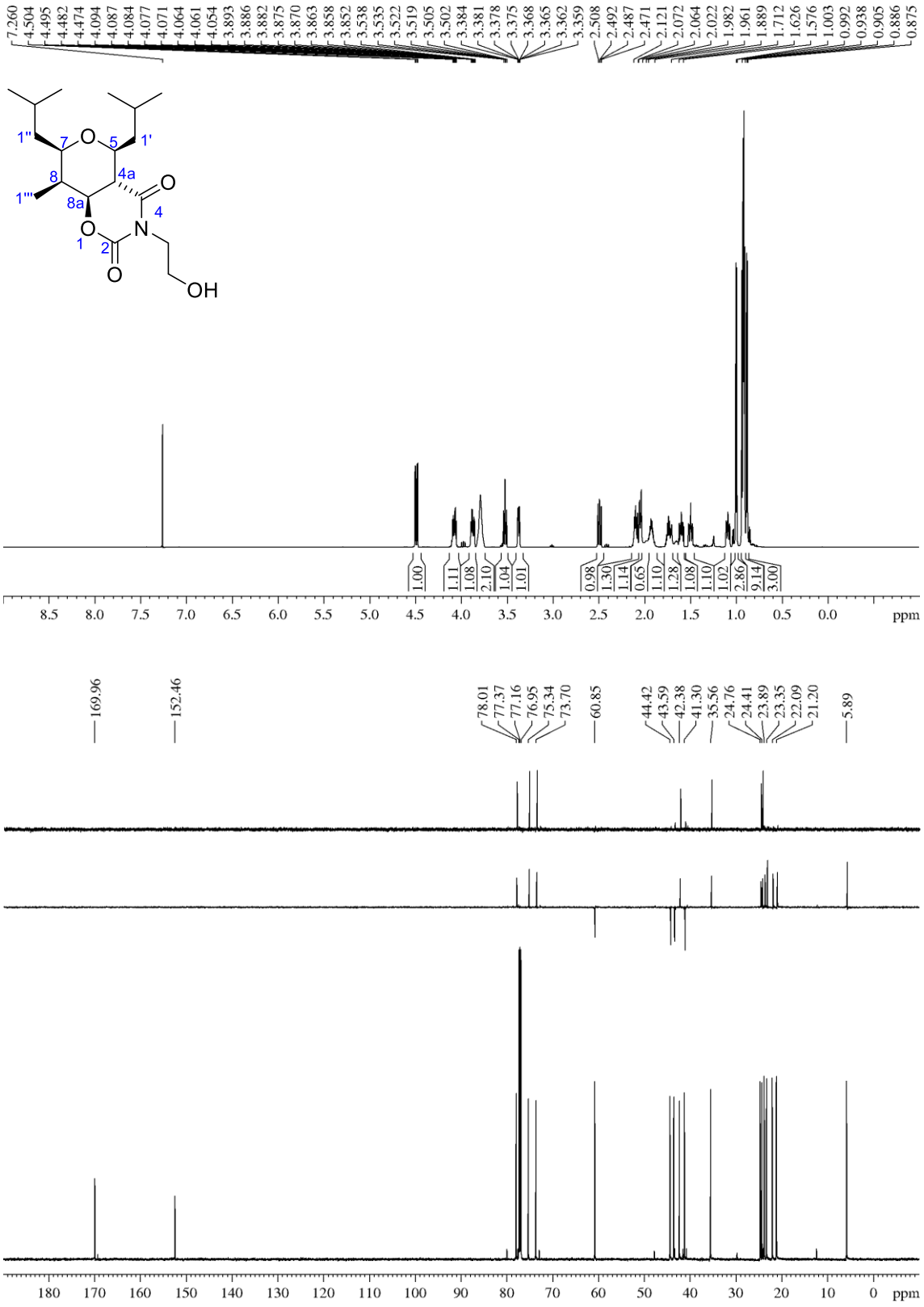
(4a*R,5*S**,7*R*,*8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5,7-diisobutyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5u)**

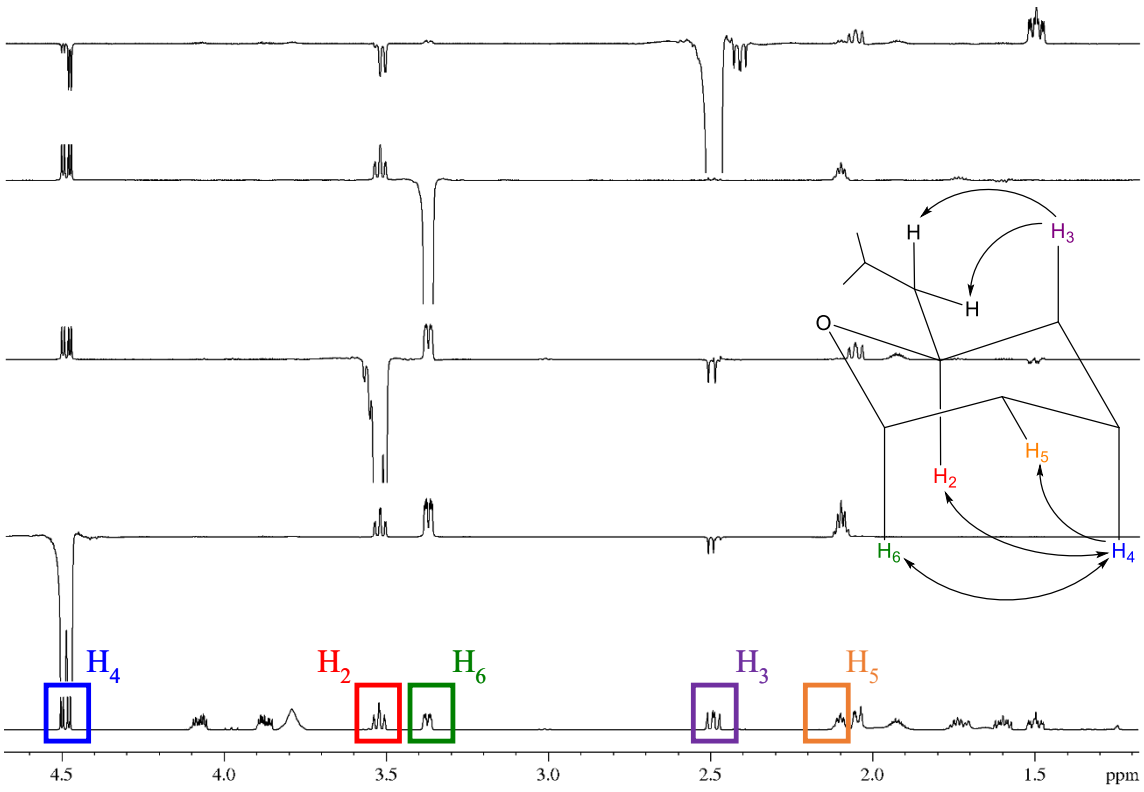


GOESY



(4a*S,5*S**,7*R**,8*S**,8a*S**)-3-(2-Hydroxyethyl)-5,7-diisobutyl-8-methyltetrahydropyrano[3,4-*e*][1,3]oxazine-2,4(3*H*,7*H*)-dione (5v)**




H
H3
H
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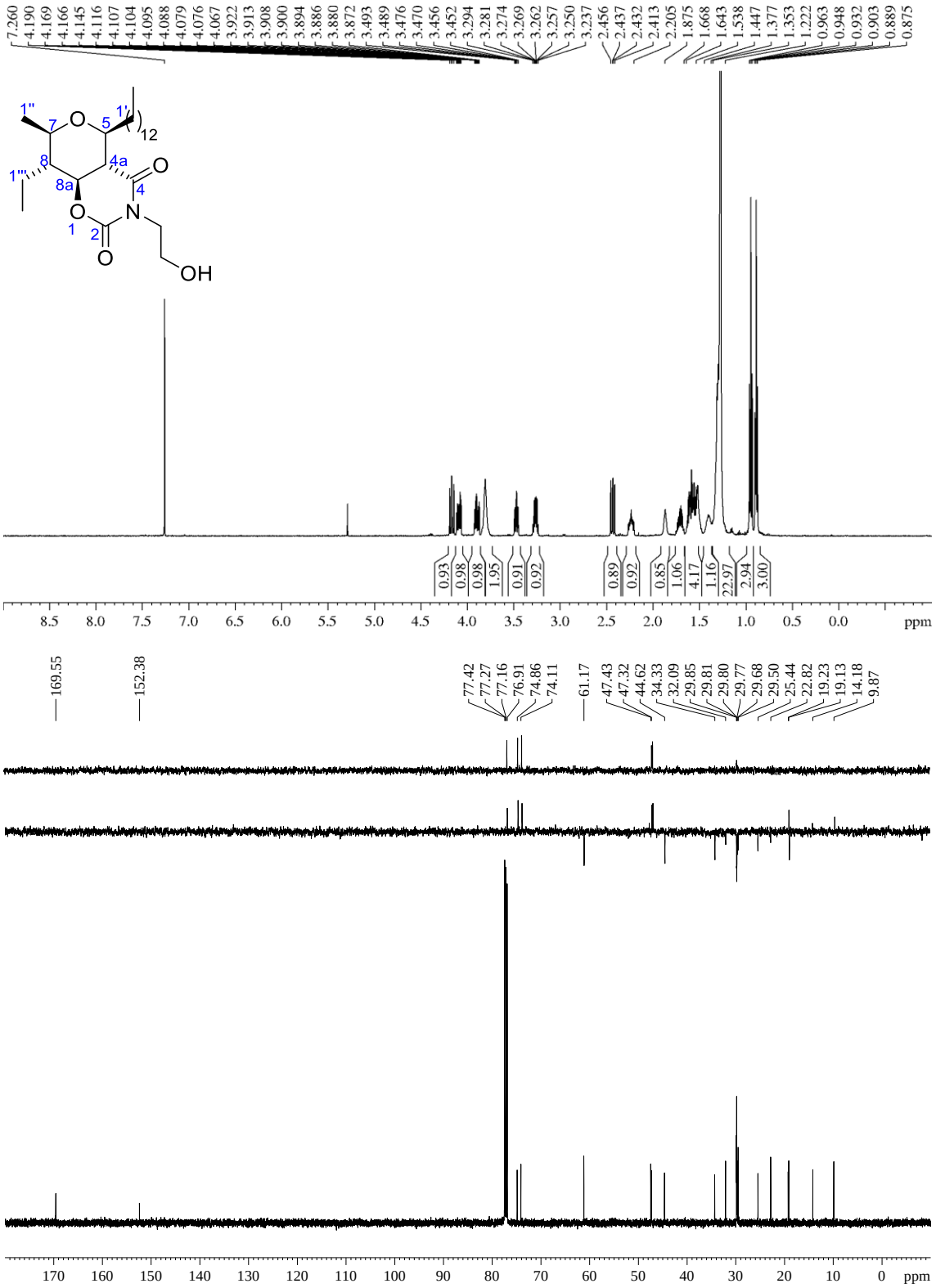
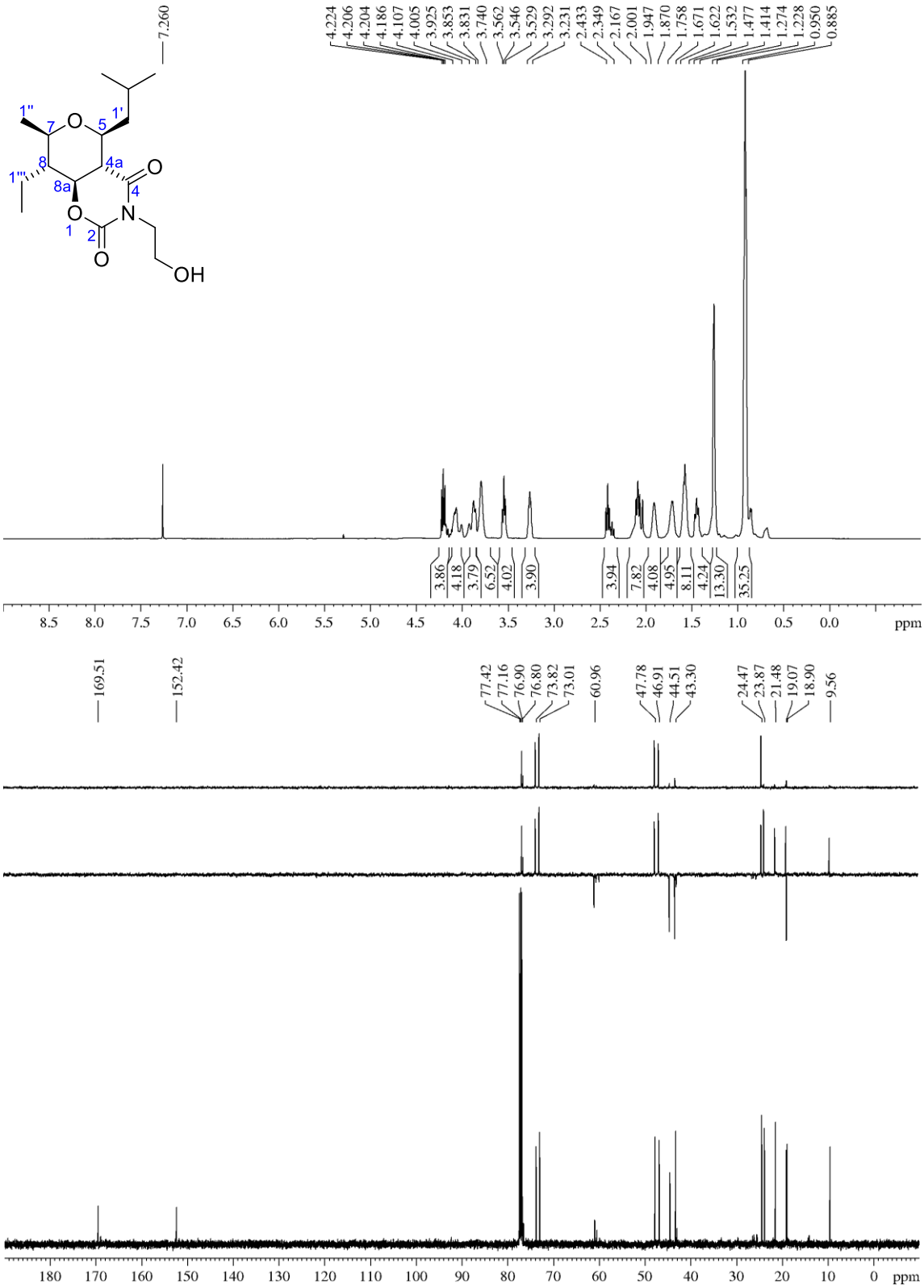
H5
H2
H6
H4
H4
H2
H6
H3
H5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

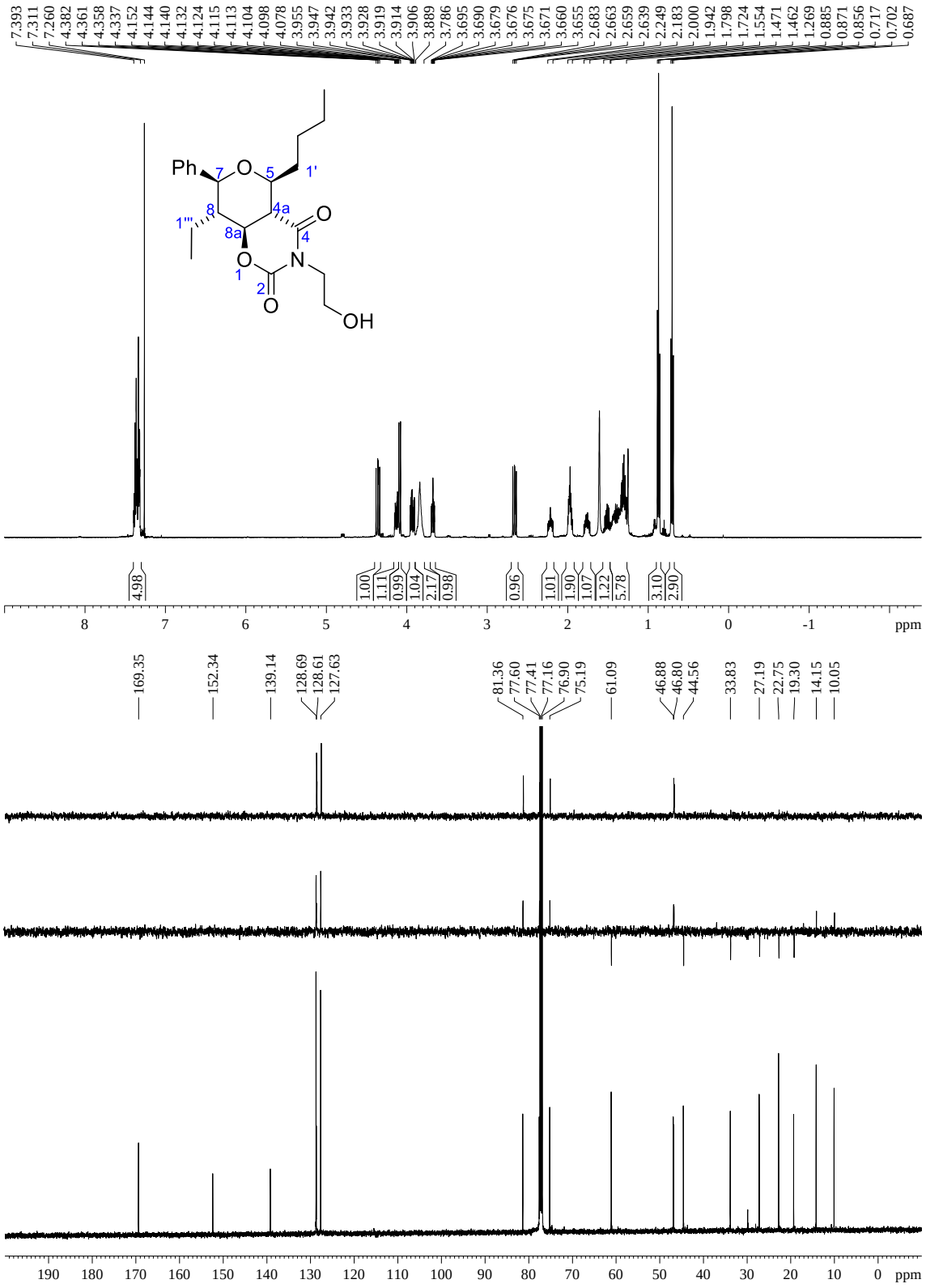
(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-7-methyl-5-tridecyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5w)**



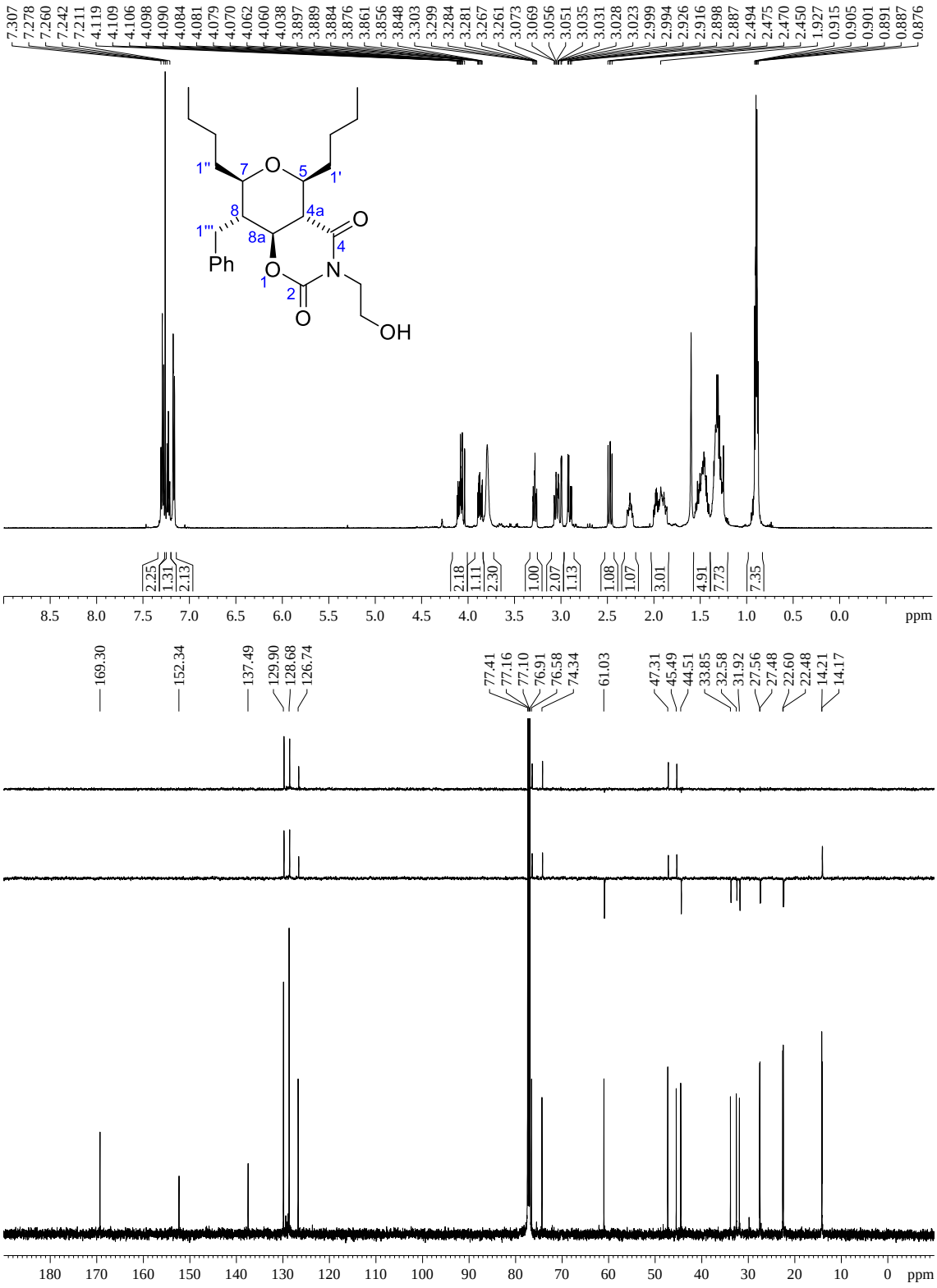
(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Ethyl-3-(2-hydroxyethyl)-5-isobutyl-7-methyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5x)**



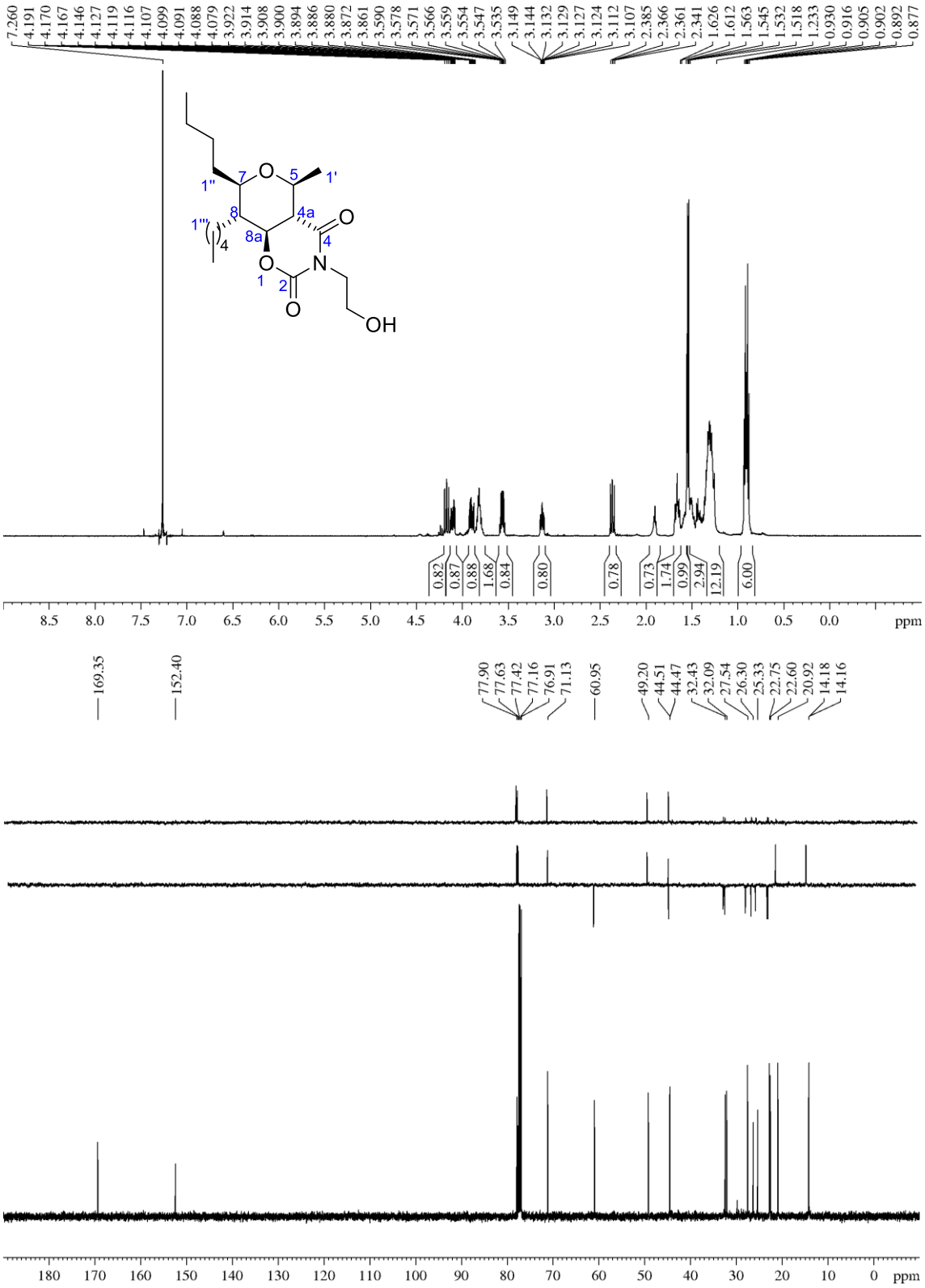
(4a*S,5*S**,7*S**,8*S**,8a*S**)-5-Butyl-8-ethyl-3-(2-hydroxyethyl)-7-phenyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5y)**



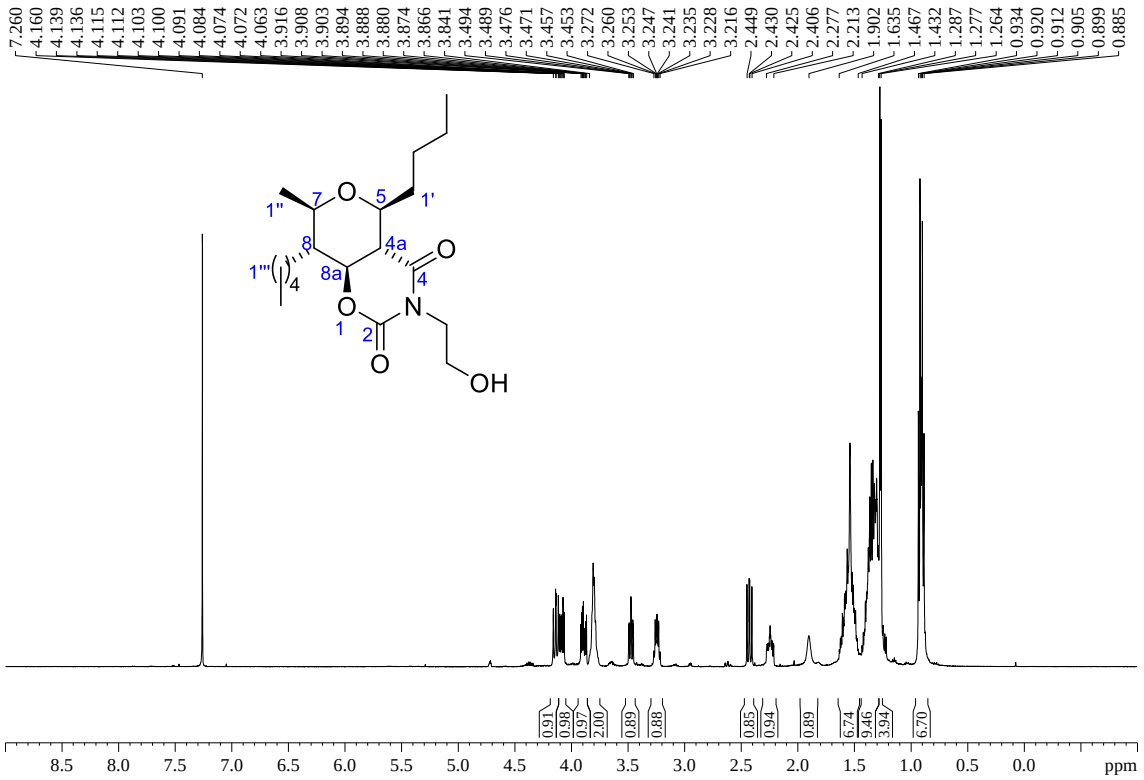
(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-Benzyl-5,7-dibutyl-3-(2-hydroxyethyl)tetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5z)**

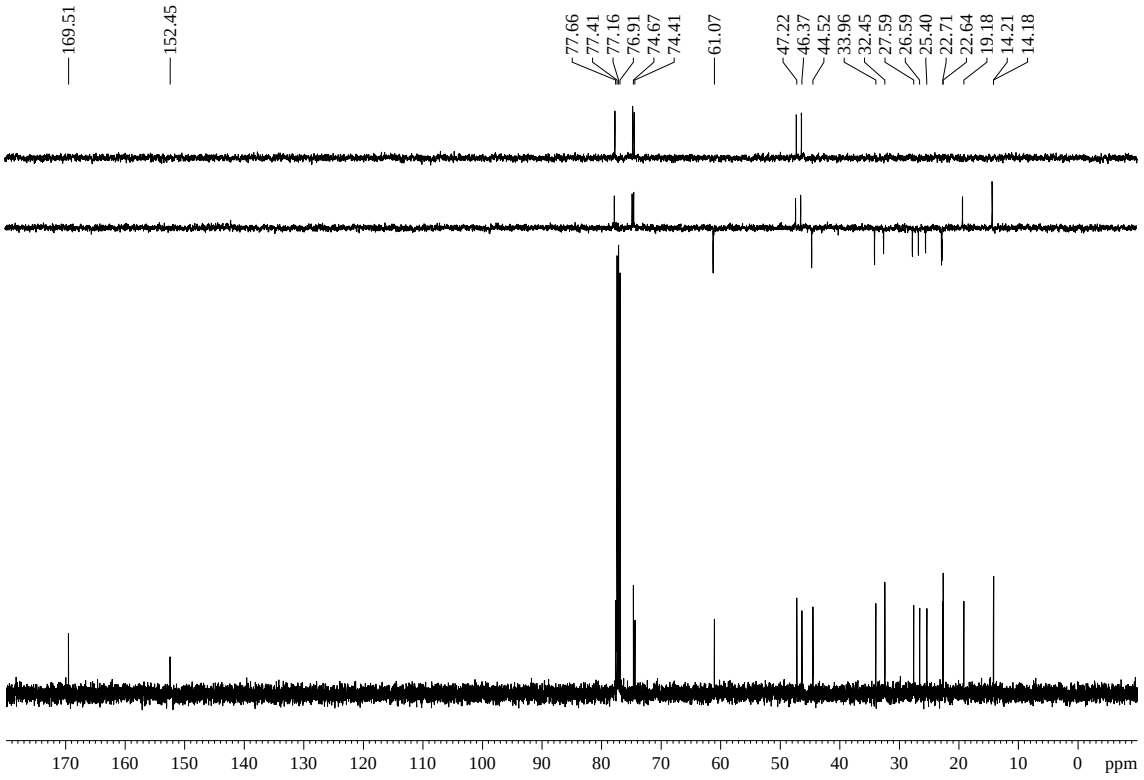


(4a*S,5*S**,7*R**,8*R**,8a*S**)-7-Butyl-3-(2-hydroxyethyl)-5-methyl-8-pentyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5aa)**

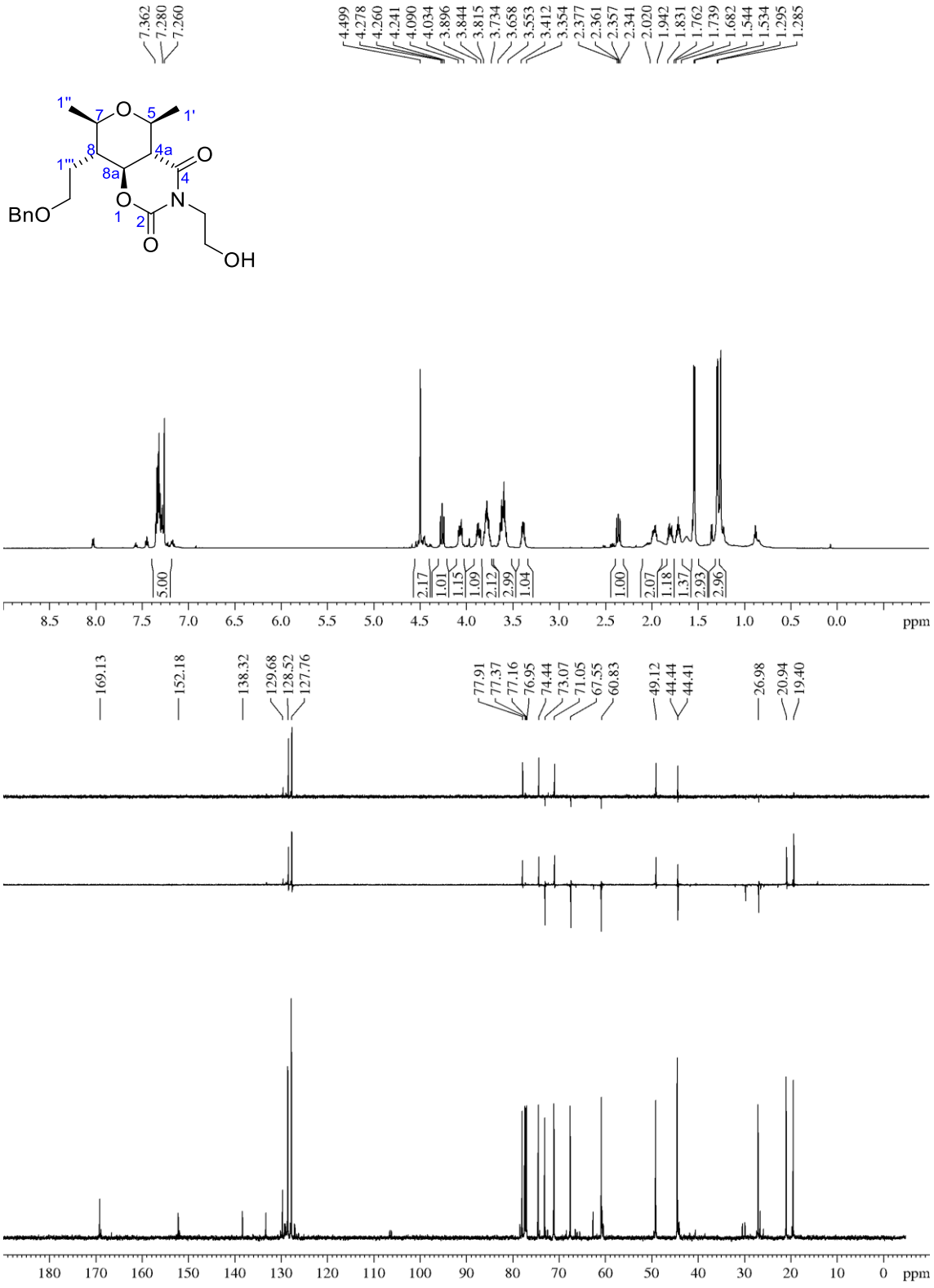


(4a*S,5*S**,7*R**,8*R**,8a*S**)-5-Butyl-3-(2-hydroxyethyl)-7-methyl-8-pentyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5ab)**

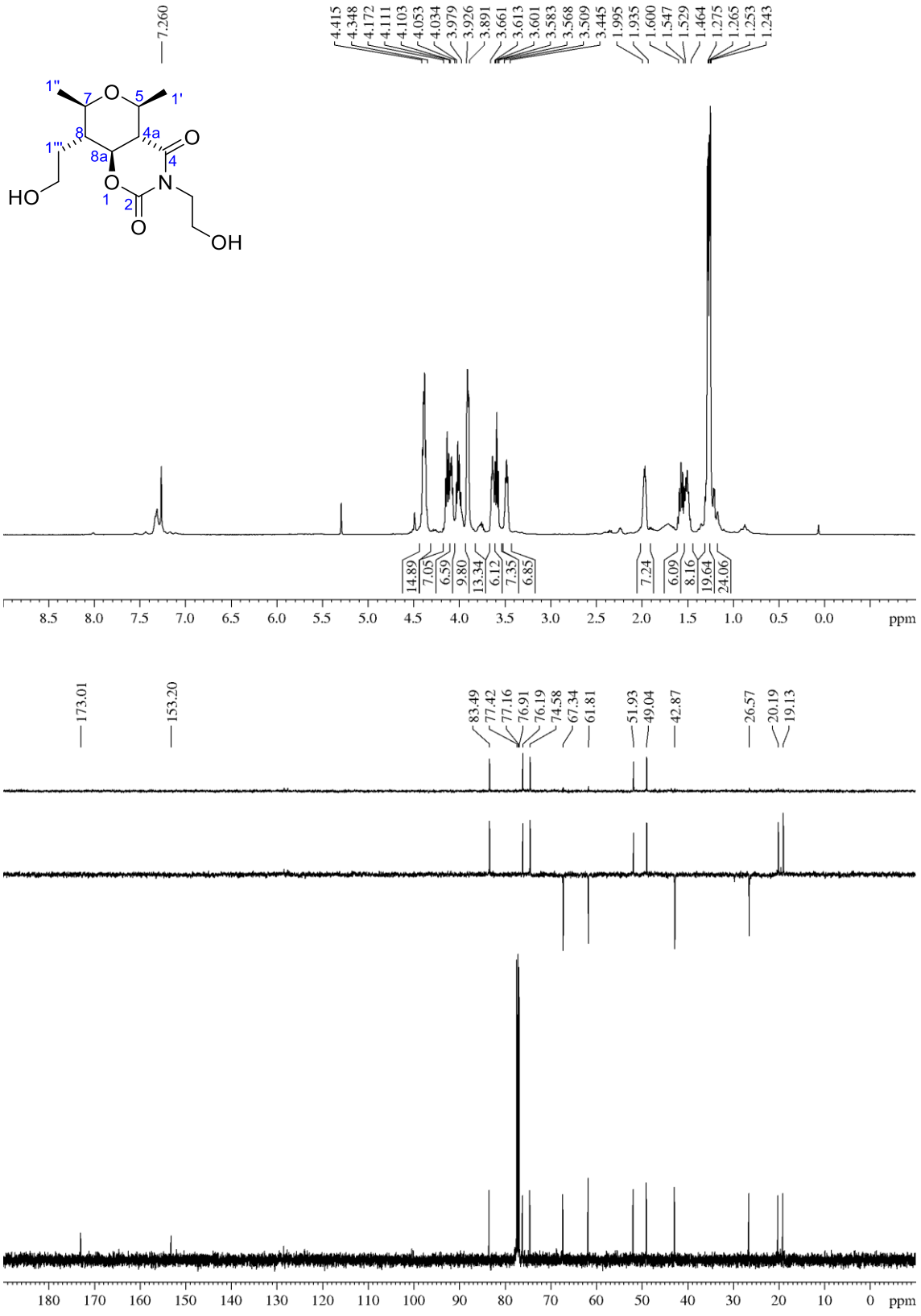




(4a*S,5*S**,7*R**,8*R**,8a*S**)-8-(2-(Benzyloxy)ethyl)-3-(2-hydroxyethyl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5ac-Bn)**

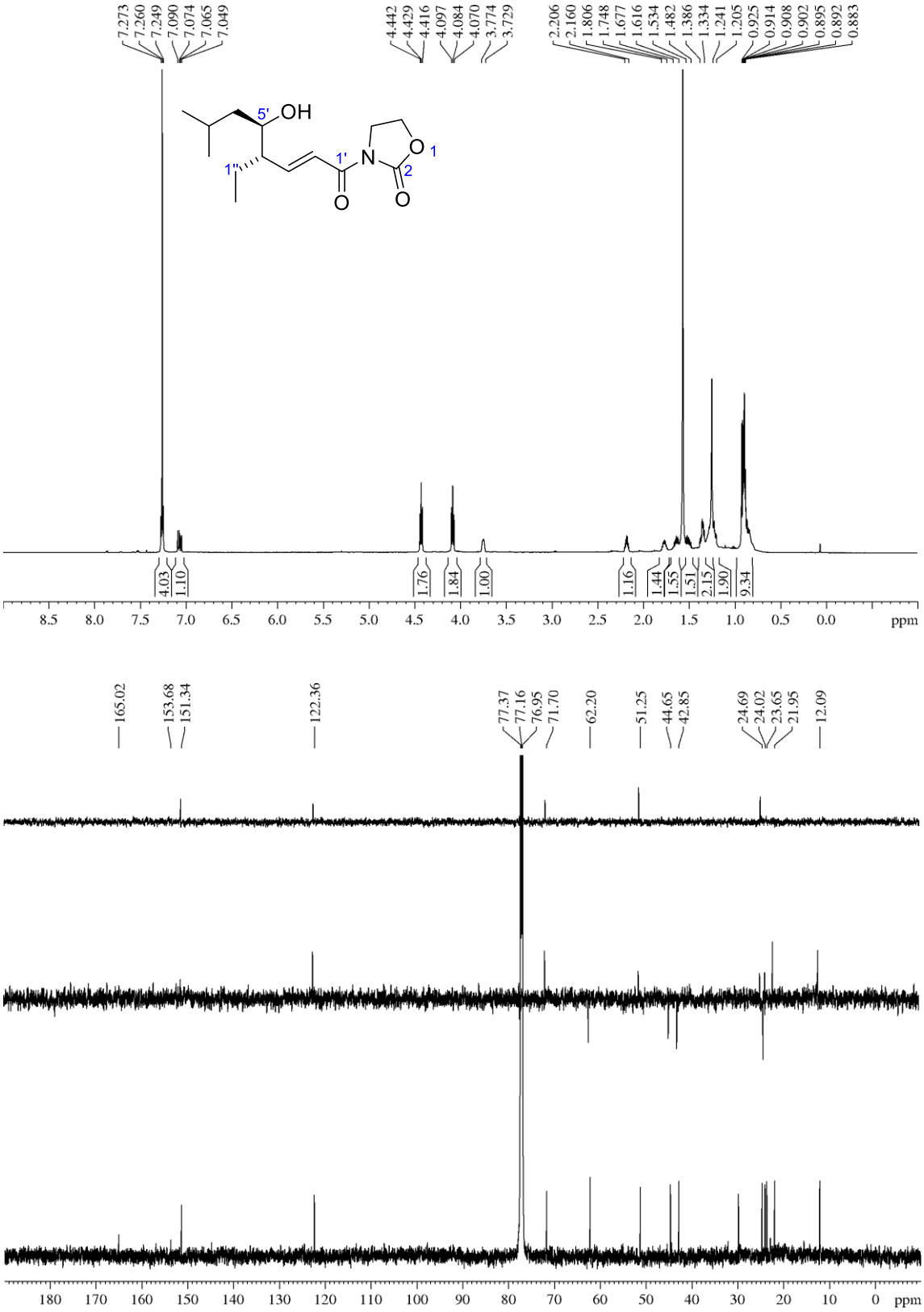


(4a*S,5*S**,7*R**,8*R**,8a*S**)-3,8-Bis(2-hydroxyethyl)-5,7-dimethyltetrahydro-2*H*,5*H*-pyrano[3,4-*e*][1,3]oxazine-2,4(3*H*)-dione (5ac)**

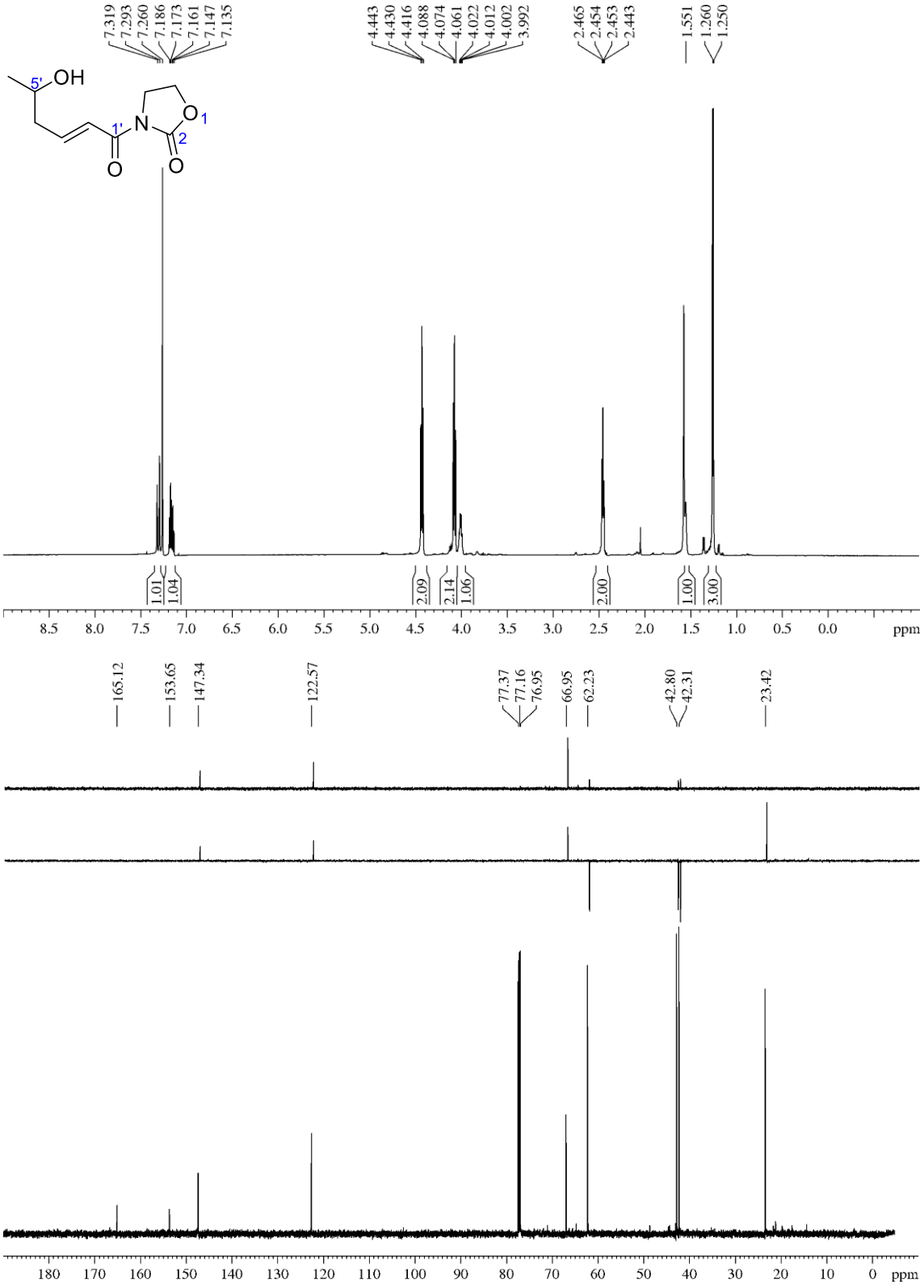


α,β-Unsaturated *N*-acyl oxazolidin-2-ones (6)

3-((4*S**,5*R**,*E*)-4-Ethyl-5-hydroxy-7-methyloct-2-enoyl)oxazolidin-2-one (6a)

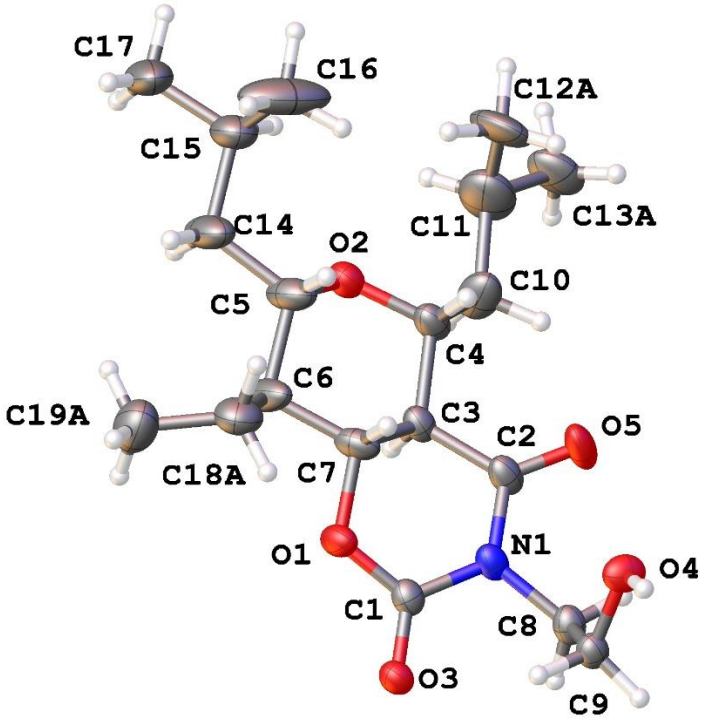


(*E*)-3-(5-Hydroxyhex-2-enoyl)oxazolidin-2-one (6b)



Crystallographic data for compound 5a

X-ray diffraction data on a single crystal was collected with an Agilent SuperNOVA diffractometer with microfocus X-ray using Cu Kα radiation (λ = 1.54184 Å). CrysAlisPro software[28] was used to collect, index, scale and apply numerical absorption correction based on gaussian integration over a multifaceted crystal model and empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm into CrysAlisPro. The structure was solved applying the novel dual-space algorithm implemented in SHELXT program.[29] Fourier recycling and least-squares refinement were used for the model completion with SHELXL-2014.[30] All non-hydrogen atoms have been refined anisotropically, and all hydrogen atoms have been placed in geometrically suitable positions and refined riding with isotropic thermal parameter related to the equivalent isotropic thermal parameter of the parent atom. The geometrical analysis of interactions in the structure was performed with Olex2 program.[31] The hydrogen atoms were geometrically positioned with C-H = 0.93Å and Uiso(H) = 1.2 Ueq(C).



Crystal data for **5a**. $C_{19}H_{33}NO_5$, M_r = 355.46, monoclinic, space group $P2_1/c$, final R indices [$I > 2\s(I)$], R_1 = 0.0788, wR_2 = 0.2167, R indices (all data) R_1 = 0.0895, wR_2 = 0.2303, a = 19.4474(11), b = 10.8872(5), c = 9.4942(5) Å, b = 99.138(5)º, V = 1984.67(18) Å^3, T = 100 K, Z = 4, reflections collected/unique: 7912/3866 (R_{int} = 0.0341), number of observations [$I > 2\s(I)$], parameters: 272. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 1442874).

[28] Rigaku Oxford Diffraction, (2015), CrysAlisPro Software system, version 1.171.38.41, Rigaku Corporation, Oxford, UK.
[29] G. M. Sheldrick, *Acta Cryst.*, 2015, **A71**, 3-8.
[30] G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112-122.
[31] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339-341.