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Total Synthesis of Coibacin D via Enantioselective Allylation and Metathesis Reactions.

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Abstract: The first total asymmetric synthesis of coibacin D, a metabolite isolated from the marine cyanobacterium cf. *Oscillatoria* sp. was achieved in 6 steps starting from simple hept-6-en-1-ol. The synthetic strategy was based on a chiral Brønsted acid catalyzed enantioselective allylboration and a Ru-carbene complex catalyzed sequential ring closing- and cross-metathesis methodology. The recorded spectroscopic data and the sign of its optical rotation of the synthesized coibacin D were in agreement with the published data for the isolated compound confirming its proposed structure and absolute configuration.

Introduction

Marine organisms are a rich source of structurally diverse compounds exhibiting a broad range of various biological activities. Many of these compounds provide a unique inspiration for the synthesis of new classes of pharmaceutically relevant substances.[1] One of such marine microorganisms are cyanobacteria that produce a range of compounds with various structural features.[2] Coibacins A-D (Figure 1), isolated from Panamanian marine cyanobacterium *Oscillatoria* sp. and exhibiting selective anti-leishmanial and anti-inflammatory activity occupy an important position among recently isolated compounds. Their structural features are characterized by the presence of the 6-membered unsaturated lactone moiety, and a long lipophilic chain bearing either substituted cyclopropane ring (coibacins A and B) or vinyl chloride moiety (coibacins C and D).[4] Notably, the δ-lactone substructure is often found in compounds with anti-leishmannial activity.[3] Recently, syntheses of coibacins A and B have been accomplished by using Witting and Julia olefinations as the crucial synthetic steps.[5]

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Supporting information containing all experimental procedures, characterization data, and spectra copies for this article is given via a link at the end of the document.

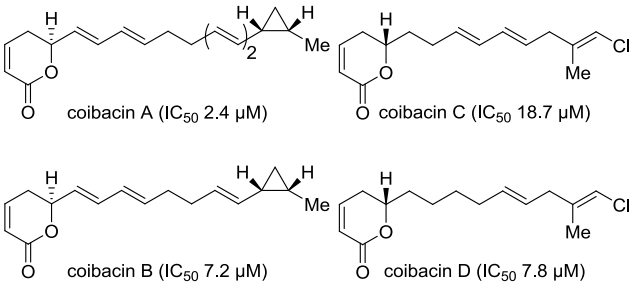
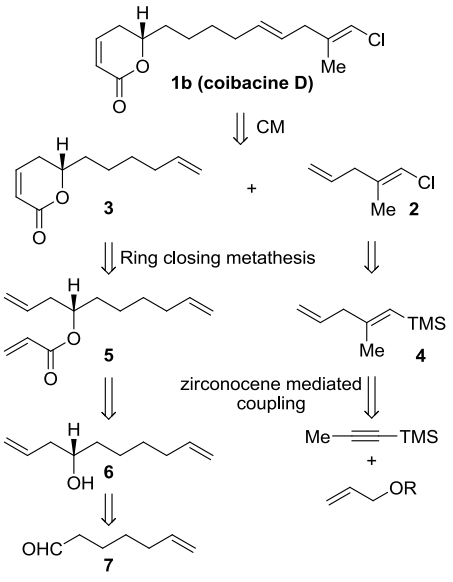


Figure 1. Coibacins A-D and their anti-leishmanial activity (in parentheses).

The presence of several olefinic bonds within their structure inspired us envisioning that the compounds could be synthesized via alkene metathesis as the principal synthetic tool, and enantioselective allylation installing the chiral homoallylic alcohol moiety.[6] The retrosynthetic analysis of coibacin D is outlined in Scheme 1.



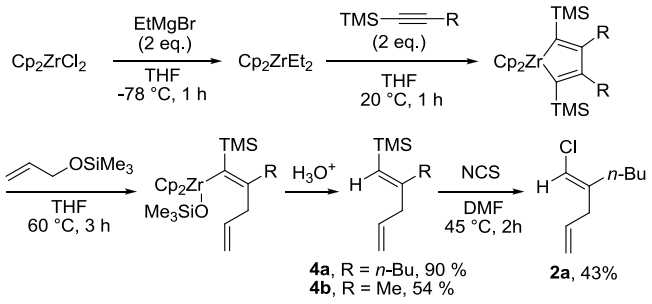
Scheme 1. Retrosynthetic analysis of coibacin D.

In principle, coibacin D **1b** could be assembled from the terminal alkene **3** and chlorodiene **2** by a cross-metathesis reaction. The former could be prepared by ring-closing metathesis of acrylic acid ester **5** that in turn could be obtained by esterification of alcohol **6** (arising from enantioselective

allylation of the unsaturated aldehyde **7**) with acryloyl chloride. The synthesis of chlorodiene **2** could commence with oxidative coupling of an allyl ether with trimethylsilylpropyne using zirconocene methodology giving rise to the silylated diene **4**, which would be subjected to electrophilic chlorination. Of course, other variants of this route, such as cross metathesis between **3** and **4** followed by exchange of the trimethylsilyl group for Cl, were also considered.

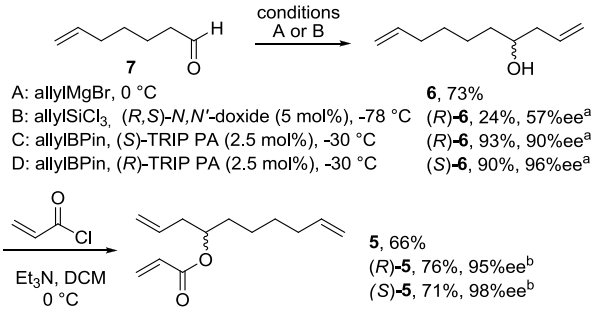
Results and Discussion

Synthesis of fragment 2. One of the optimal methods for synthesis of selectively substituted 1,4-pentadienes could rely on oxidative coupling of suitably substituted allylic compounds with alkynes by using zirconocene methodology.[7] In this regard a step-wise oxidative coupling of 1-trimethylsilylhexyne and 1-trimethylsilylpropyne with 3-trimethylsilyloxypropene by using diethylzirconocene (Cp_2ZrEt_2) provided the corresponding silylated (*E*)-1,4-pentadienes **4a** and **4b** in 90 and 54% isolated yields. The lower isolated yield in the latter case is associated with a low boiling point of **4b** and difficulties encountered during its separation from solvents and other substances, such as the starting material and compounds formed by side-reactions. It should be noted that small amounts of the corresponding *Z*-isomers were detected as well (**4a**/***Z*-4a** = 97/3, **4b**/***Z*-4b** = 95/5). It is assumed that their formation could be caused by acid catalyzed isomerization of the double bond during work-up. Halogenolysis of **4a** was tackled next. Exchange of the trimethylsilyl (TMS) group for both Cl and Br with NCS and NBS under various conditions[8] was studied (see SI-Table-1 in the SI section). Out of numerous experiments, we found that the best yield of **2a** (43%) was obtained by treating **4a** with NCS in DMF at 45 °C for 2 days (**2a**/***Z*-2a** = 88/12). An increased amount of the ***Z*** isomer in comparison with the starting material (**4a**) could be probably attributed to partial isomerization during the course of the halogen exchange. NOESY experiment confirmed the expected configuration of the vinyl halide moiety in both **2a** and **Br-2a**. Since it was later found that chloro-1,4-dienes were not suitable substrates for cross-metathesis, attempts to convert diene **4b** to the respective chlorodiene **2b** were not undertaken.



Scheme 2. Synthesis of substituted 1,4-dienes.

Asymmetric allylation. Synthesis of fragment **3** started from the commercially available 1-hept-6-en-ol, which was oxidized under Swern conditions to aldehyde **7** in 82% isolated yield. Its allylation by allylmagnesium bromide provided the racemic alcohol **6** in 73% isolated yield and subsequent esterification with acryloyl chloride furnished the unsaturated ester **5** in 66% isolated yield. As for the synthesis of the chiral alcohol **6**, out of several available methods for enantioselective allylation,[9] we opted to test enantioselective allylation with allyltrichlorosilane catalyzed by chiral Lewis base (*N,N'*-dioxide catalyst)[10] and allylboration with allylboronic acid pinacol ester catalyzed by a chiral phosphoric acid.[11] The allylation with allyltrichlorosilane catalyzed by (*R,S*)-*N,N'*-dioxide provided the corresponding enantioenriched alcohol (*R*)-**6** in a low yield (24%) and with a mediocre asymmetric induction of 57 % ee. On the other hand, allylboration catalyzed by (*S*)-TRIP PA or (*R*)-TRIP PA gave rise to the corresponding alcohols (*R*)-**6** and (*S*)-**6**, respectively, with a very good enantioselectivity of 90% and 96% ee. The absolute configuration of these compounds was in agreement with the previously obtained results. Conversion of (*S*)-**6** to ester (*S*)-**5** in 71% isolated yield was carried out analogously to the synthesis of **5**.



[a] Determined from the corresponding Mosher esters.
[b] Determined on HPLC equipped with a column with a chiral stationary phase

Scheme 3. Allylation of **7** to **6** and their conversion to esters **5**.

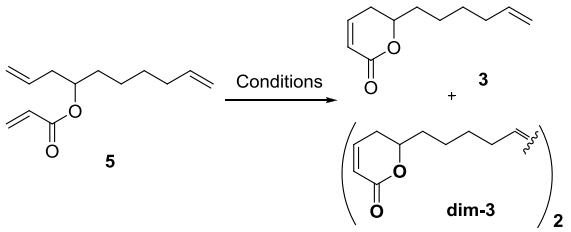
Metathesis reactions. With the crucial intermediates on hand we proceeded with an exploratory study of metathesis reactions by using racemic substances. Ring closing metathesis reactions were carried out in the presence of G II catalyst[12] under various conditions. An acceptable yield of **3** (52%) was obtained when the ring closing metathesis was done in the combination of G II (7 mol%)/CuI (20 mol%)[13] in dichloromethane at 20 °C (for other results see SI-Table 2 in the SI section). Cross metathesis with trimethylsilylated 1,5-pentadiene **4** followed. Somewhat unexpectedly, this goal proved to be a rather difficult step: despite a number of various condition tested (for representative examples see SI-Table 3) the highest yield of **8a** was only 26%. In order to elucidate the reason(s) for such low yields, we decided to have a closer look at metathesis steps. Firstly, homometathesis of both reactants, i.e. **3** as well as **4**, was studied. Whereas homometathesis of **4** surprisingly did not take place at all in the presence of H-G II catalyst[14] (5 mol%) at 20 or 45 °C, lactone **3** was in the presence of the same catalyst

readily converted almost quantitatively into the dimer **dim-3** (90%) within 24 h at 40 °C (at 20 °C the reaction did not take place). Owing to low reactivity of 1,4-pentadiene **4a** in the reaction with **3**, we attempted to carry out cross metathesis with 1-chloropenta-1,4-diene **2a** in the presence of H-G II (5 mol%) in dichloromethane. However, not even traces of the expected product were detected. On the other hand, when **dim-3** was reacted with **2a**, coibacin D analog **1a** was formed in 22% yield (according to ^{1}H NMR analysis). Unfortunately, it was not possible to separate **1a** from **3** due to their similar polarity. Although this approach could not be employed for the synthesis of coibacin D due to problems with separation, the obtained results provided important information for further endeavors in that **dim-3** could be a better substrate for cross-metathesis reactions in comparison with **3**.

In the next step, we explored the possibility of making **dim-3** directly from ester **5**. Once again, homometatheses of **5** were tested under various conditions (Table 1). By using G II catalyst at 45 °C, a small amount of **dim-3** (14%) was formed within 6 h reaction time (Entry 1). Upon prolonging to 20 h, almost quantitative consumption of the starting material was observed and **3** and **dim-3** were isolated in 47 and 45% yields, respectively (Entry 2). Adding the catalyst in two portions provided **dim-3** in almost the same yield (Entry 3). Change of the solvent to toluene did not have a positive effect on the formation of **dim-3,** and **3** was formed as the major product (Entry 4). By using H-G II in dichloromethane or toluene, selectivity for the formation of **dim-3** increased (Entries 5 and 6). Since it is known that G II is a good catalyst for ring metathesis and H-G II for cross metathesis, both catalysts were used in a sequence. However, their use provided almost the same results as the exclusive use of H-G II (Entry 7).

Thus the best conversion of the starting material was obtained with G II in dichloromethane and the best (highest) **dim-3/3** ratio was obtained with H-G II in dichloromethane. It should be noted that in many cases (Entries 3-7) formation of unidentified side-products was noticed.

Table 1. Conversions of **5** to **dim-3** under various conditions.

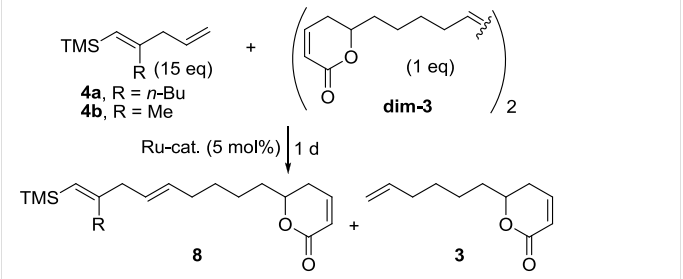


				Yield (%)[a]	
Entry	Catalyst (mol%)	Solvent	T (°C)	**3**	**dim-3**
1[b]	G II	DCM	45	0	14
2	G II	DCM	45	47	45
3	G II	DCM	45	23	42
4	G II	toluene	80	52	28
5	HG II	DCM	45	9	48
6	HG II	toluene	80	16	64
7	G II + HG II	DCM	45	14	46

[a] Isolated yields (based on the conversion **5**). [b] Reaction time was 6h. In other cases 20 h.

In the next step, cross-metathesis of 1-trimethylsilyl-1,4-pentadienes **4a** and **4b** with **dim-3** was screened (Table 2). In theory, a reaction of one molecule of **dim-3** with **4** should result in formation of one molecule of **8** and **3**. Then **3** could react with **4** giving rise to **8**. Thus two molecules of **8** could be formed from one molecule of **dim-3**. Hence the overall yield of **8** could be up to 200%. Cross metathesis of **dim-3** with **4a** catalyzed by H-G II in dichloromethane at 20 °C provided only a low yield (37%) of product **8a** (Entry 1), Interestingly, the product was not formed at all at 45 °C (Entry 2). The use of G II in dichloromethane gave **8a** in 76% isolated yield (Entry 3). Switching the solvent to toluene resulted in somewhat improved yields when G II and H-G II were used: **8a** was obtained in 84% and 115% isolated yields (Entries 4 and 5). The latter result indicates that all **dim-3** was consumed and even a small portion (15%) of the formed **3** participated in the cross-metathesis reaction. Since the best result of the cross metathesis reaction was obtained with G II in toluene, the reaction of **4b** with **dim-3** was run under the same conditions furnishing **8b** in a very encouraging isolated yield of 60% (Entry 6). The lower yield of **8b** in comparison with **8a** might be attributed to a lower observed reactivity of **4b**, the origin of which is unclear. In respect to the obtained results **4a** and **4b** could be considered as type III and **3** as type I alkene according to Grubbs' classification of olefins.[15]

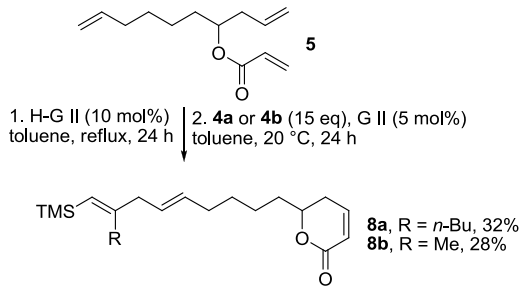
Table 2. Cross metathesis of trimethylsilyl-1,4-pentadienes **4** with **dim-3**.



Entry	4	Catalyst (mol%)	Solvent	T (°C)	Yield (%)[a]
1[b]	**4a**	HG II	DCM	20	37[b]
2	**4a**	HG II	DCM	45	0[b,c]
3	**4a**	G II	DCM	20	76[b]
4	**4a**	HG II	toluene	20	84[b]
5	**4a**	G II	toluene	20	115[c]
6	**4b**	G II	toluene	20	60[b]

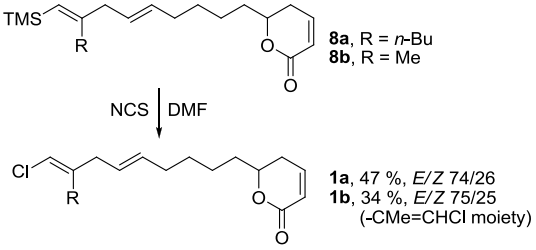
[a] Isolated yields (based on the conversion **dim-3**). Amount of the formed 3 was not determined. [b] Unreacted starting material was detected.. [c] Formation of unidentified side-products was detected.

Although sequential one-pot metathesis reactions are challenging by their nature, we attempted to carry out all metathesis steps starting from **5** in one setup as well (Scheme 4). Thus, **5** was initially heated under reflux in toluene in the presence of H-G II (10 mol%) until almost full conversion to **dim-3** was observed (~ 24 h). Excess of **4a** or **4b** (15 eq) along with G II (5 mol%) was then added to the reaction mixture, which was stirred at 20 °C for additional 24 h. Work-up followed by isolation furnished **8a** and **8b** in 32 and 28% yields, respectively. These values are similar to combined yields of these compounds prepared in a step-wise fashion (52% for **8a**, and 28% **8b**).



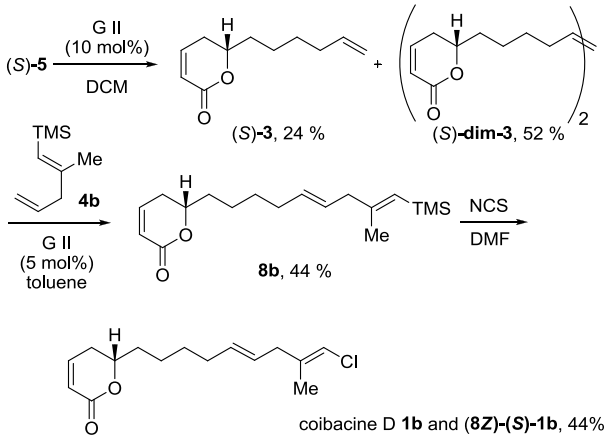
Scheme 4. One-pot metathesis of **5** to **8a** or **8b**.

Racemic and enantioselective synthesis of 1a and 1b (coibacin D). Importantly, compounds **8a** and **8b** were not stable, and their slow degradation (within 24 h at 20 °C) was observed (on the other hand, degradation during metathesis reaction was not noted). It seems that relatively fast double bond migration takes place, as judged from ^{1}H NMR analysis (for the corresponding NMR charts, see the SI section). Hence both compounds, **8a** and **8b**, had to be exposed to NCS immediately after isolation to ensure their smooth transformation to the corresponding chloro derivatives **1a** and **1b**. By using the same reaction conditions as for the synthesis of **2a**, **1a** and **1b** were obtained in 47 and 34% isolated yields as a mixture of *E* and *Z* isomers (74/26 ration for **1a** and 75/25 ratio for **1b**) on the vinyl chloride moiety (Scheme 5). The ^{1}H NMR spectrum of the isolated coibacin D and the spectrum of **1b** were identical. NOESY experiment confirmed the expected configuration of the vinyl chloride moiety.



Scheme 5. Halogenolysis of **8** with NCS.

Having resolved suitable metathesis reaction conditions, we embarked on enantioselective synthesis of coibacin **1b** with enantioenriched ester (*S*)-**5** (98% ee) (Scheme 6). Exposure of ester (*S*)-**5** to G II (10 mol%) in dichloromethane provided (*S*)-**3** and (*S*)-**dim-3** in 24 and 52% isolated yields. Cross-metathesis of (*S*)-**dim-3** with (1*E*)-1-trimethylsilyl-2-methyl-1,4-pentadiene **4b** in the presence of a catalytic amount of G II (5 mol%) in toluene furnished (*S*)-**8b** in 44% yield after isolation (which is the same range as the reaction with racemic **dim-3**). Its exposure to NCS in DMF gave rise to a mixture coibacin D **1b** and **(8*Z*)-(*S*)-1b** in 44% yield in 73/27 ratio. The ^{1}H NMR spectrum of the prepared coibacin D **1b** and its published spectrum were otherwise almost identical (apart from impurities in the aliphatic region, apparent in the published spectrum). The sense of optical rotation of the prepared sample was the same as that of the natural product; the difference in the optical rotation values 56.6° (this work) and +6° (the isolated sample) could be attributed to the presence of impurities.[16]



Scheme 6. Enantioselective synthesis of coibacin D **1b**.

Conclusions

In summary, we showed that sequential ring closing and cross-metathesis reactions executed either step-wise or in one pot delivered the target compounds with approximately the same efficiency, and that such reaction pathway could be used for the synthesis of natural compounds possessing several double bonds. This methodology was exploited in the enantioselective synthesis of coibacin D stereoisomers possessing a *trans*-configured vinyl chloride moiety in the side-chain. The synthesis also confirmed that the natural substance possesses the 5*S* absolute configuration. The total enantioselective synthesis of coibacin D was carried out in 6 steps and 5% overall yield. In addition, we synthesized coibacin D derivative bearing *n*-butyl group instead of Me in the side-chain.

Experimental Section

Hept-6-enal (7). To the solution of oxalyl chloride (7.4 mL, 0.09 mol) in DCM (70 mL) under argon atmosphere cooled to -78 °C DMSO (12.5 mL, 0.18 mol) was added. After 15 min the solution of hept-6-enol (5 g, 0.04 mol) in DCM (5 mL) was added. After another 15 min Et_3N (30.6 mL, 0.22mmol) was added and the reaction mixture was stirred for 10 min at -78 °C and then at 20 °C until the completion of the reaction (monitored by TLC). The reaction mixture was quenched by water (25 mL), extracted by DCM (3×20 ml) and washed with brine. The combined organic fractions were dried over $MgSO_4$ and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (hexane) gave 4.05 g (82 %) of the title compound as a colorless viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 1.34-1.49 (m, 2H), 1.54-1.74 (m, 2H), 1.99-2.20 (m, 2H), 2.43 (td, *J* = 7.3, 1.8 Hz, 2H), 4.88-5.08 (m, 2H), 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 9.76 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC) δ 21.47, 28.30, 33.39, 43.69, 114.81, 138.20, 202.56; IR (KBr) ν 3078, 2926, 2860, 1727, 1712, 1643, 1458, 1437, 1356, 1260, 1132, 1081, 994, 908 cm^{-1}; MS-ESI m/z (% relative intensity) 113.1 (M+, 10), 96.1 (7), 95.1 (100), 69.1 (13), 68.1 (4); HR-ESI calculated for $C_7H_{13}O$ 113.0966, found 113.0963. R_f (hexane) = 0.5.

(*S*)-Deca-1,9-dien-4-ol ((*S*))-6). *Reaction with allylboronic acid pinacol ester* (Method D). To a solution of hepten-6-enal **7** (1.6 g, 14.29 mmol) and (*R*)-TRIP-PA (269 mg, 0.36 mmol, 2.5 mol %) in toluene (100 mL) cooled to -30°C was added dropwise allylboronic acid pinacol ester (17.15 mmol, 3.2 mL) over 30 seconds under argon atmosphere. The reaction mixture was stirred at -30°C for 2 days, then volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexan/EtOAc) gave 1.98 g (90 %, 96 % ee) of the title compound as a colorless viscous liquid[α]$_D$-5.6° (c 0.006, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 1.19-1.56 (m, 6H), 1.72 (s, 1H), 1.96-2.18 (m, 3H), 2.18-2.38 (m, 1H), 3.51-3.74 (m, 1H), 4.83-5.05 (m, 2H), 5.05-5.25 (m, 2H), 5.66-5.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC) δ 25.13, 28.89, 33.70, 36.62, 41.93, 70.59, 114.37, 118.06, 134.85, 138.86; IR (KBr) ν 3342, 3075, 2977, 2932, 2860, 1640, 1437, 1078, 991, 914, 635 cm^{-1}; MS-ESI m/z (% relative intensity) 155.1 (M+, 6), 137.1 (65), 135.1 (17), 131.1 (87), 109.1 (9), 96.1 (57), 95.7 (100), 95.1 (93), 93.1 (41), 83.1 (70), 81.1 (85), 79.1 (21), 71.0 (59), 69.1 (62), 67.0 (89), 57.0 (28), 55.0 (36); HR-ESI calculated for $C_{10}H_{19}O$ 155.1436, found 155.1437. R_f (10/1 hexane/EtOAc) = 0.43.

(*S*)-Deca-1,9-dien-4-yl acrylate ((*S*)-5). To a solution of (*S*)-**6** (1 g, 6.48 mmol) v DCM (5 mL) Et_3N (3.2 ml, 22.90 mmol) was added under argon atmosphere. Then a solution of acryloyl chloride (1.04 g, 11.45 mmol) in DCM (1 mL) was added at 0 °C. After 5 h of stirring the reaction mixture was quenched by brine (5 mL) and extracted with DCM (3×5 mL). The combined organic fractions were dried over Na_2SO_4 and volatiles were removed moved under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc) gave 0.95 g (71 %, 98 % ee) of the title compound as a colorless viscous liquid. [α]$_D$ -18.2° (c 0.0142, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 1.11-1.48 (m, 4H), 1.47-1.70 (m, 2H), 1.93-2.14 (m, 2H), 2.19-2.49 (m, 2H), 4.84-5.19 (m, 5H), 5.61-5.93 (m, 3H), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.39 (dd, *J* = 17.3, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC) δ 24.69, 28.66, 33.37, 33.55, 38.57, 73.48, 114.44, 117.68, 128.84, 130.33, 133.61, 138.68, 165.88; IR (KBr) ν 3075, 2932, 2857, 1724, 1637, 1404, 1293, 1269, 1195, 1048, 985, 961, 914, 812 cm^{-1}; MS-ESI m/z (% relative intensity) 209.2 (M+,19), 167.1 (32), 138.1 (10), 137.1 (76), 135.1 (27), 127.0 (26), 101.1 (70), 95.7 (89), 95.1(58), 94.1 (36), 82.1 (24), 81.6 (64), 81.1 (80), 80.1 (21), 73.0 (54), 67.0 (81), 55.5 (11), 55.1 (19); HR-ESI calculated for $C_{13}H_{21}O_2$ 209.1542, found 209.1539. R_f (20:1 hexane/EtOAc) = 0.61.

(*S*)-6-(Hex-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((*S*)-3) and (6*S*,6'*S*)-6,6'-((*E*)-dec-5-ene-1,10-diyl)bis(5,6-dihydro-2*H*-pyran-2-one) ((*S*)-dim-3). To a solution of the Grubbs 2nd generation catalyst (82 mg, 0.10 mmol) in DCM (100 mL) (*S*)-**5** (200 mg, 0.96 mmol) was added at 20 °C under argon atmosphere. After 24 h of stirring under reflux volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 hexane/EtOAc) gave 41 mg of (*S*)-**3** (24 %, 96% ee) and 83 mg of (*S*)-**dim-3** (52 %) as brownish viscous liquids.

(*S*)-3: [α]$_D$+96.9° (c 0.0075,$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 1.30-1.73 (m, 5H), 1.72-1.92 (m, 1H), 1.92-2.16 (m, 2H), 2.16-2.55 (m, 2H), 4.34-4.49 (m, 1H), 4.82-5.14 (m, 2H), 5.64-5.90 (m, 1H), 6.02 (dt, *J* = 9.4, 1.8 Hz, 1H), 6.88 (ddd, *J* = 9.7, 5.1, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25ºC) δ 24.29, 28.60, 29.39, 33.55, 34.72, 77.91, 114.65, 121.47 138.55, 144.96, 164.54; IR (KBr) ν 3069, 2932, 2860, 1721, 1643, 1389, 1245, 1039, 958, 914, 818 cm^{-1}; MS-ESI m/z (% relative intensity) 182.1 (M+H$^+$,13), 181.1 (M+, 100), 164.1 (11), 163.1 (82), 145.1 (9), 135.1 (63), 95.1 (23), 81.1 (8); HR-ESI calculated for $C_{11}H_{17}O_2$ 181.1229, found 181.1226. R_f (5/1 hexane/EtOAc) = 0.26.

(*S*)-Dim-3: [α]$_D$ +96.65° (c 0.0054, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 1.32-1.73 (m, 5H), 1.75-1.94 (m, 1H), 1.94-2.12 (m, 2H), 2.21-2.50 (m, 2H), 4.343 (ddt, *J* = 10.3, 7.4, 5.2, 1H), 5.27-5.53 (m, 1H), 6.03 (ddd, *J* = 9.7, 2.3, 1.4, 1H), 6.84-6.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 24.30, 29.25, 29.41, 32.34, 34.74, 77.97, 121.42, 130.25, 145.05,

164.59; IR (KBr) ν 2926, 2857, 1718, 1392, 1251, 1141, 1066, 1039, 970, 818, 665 cm^{-1}; MS-ESI m/z (% relative intensity) 334.2 (18), 333.2 (M+, 100), 316.2 (9), 315.2 (43), 297.2(8); HR-ESI calculated for $C_{20}H_{29}O_4$ 332.2066, found 332.2063. R_f (1/1 hexane/EtOAc) = 0.24.

(*S*)-6-((5*E*,8*E*)-8-Methyl-9-(trimethylsilyl)nona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one (8b). To a solution of **dim-3** (59 mg, 0.18 mmol) and **4b** in toluene (20 mL) the Grubbs 2nd generation catalyst (23 mg, 0.03 mmol) was added at 20 °C under argon atmosphere. After 2 days of stirring volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (5/1 hexane/EtOAc) gave **(*S*)-8b** (24 mg, 44 %) of the title compound as a brownish viscous liquid. $[\alpha]_D$ +48.6° (c 0.0058,$CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 0.06-0.27 (m, 9H),1.29-1.52 (m, 3H), 1.52-1.74 (m, 2H), 1.74-1.93 (m, 4H), 1.93-2.25 (m, 2H), 2.25-2.5 2 (m, 2H), 2.61-2.90 (m, 2H), 4.36-4.56 (m, 1H), 5.23 (dq, *J* = 7.5, 1.2 Hz, 1H), 5.33-5.54 (m, 2H), 6.04 (ddd, *J* = 9.8, 2.3, 1.4 Hz, 1H), 6.80-7.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 0.10 (3C), 21.59, 24.31, 29.19, 29.39, 32.34, 34.72, 45.76, 77.95, 121.46, 123.53, 128.22, 131.78, 144.96, 154.13, 164.55; IR (KBr) ν 2944, 2857, 1718, 1613, 1440, 1386, 1245, 1144, 1039, 970, 869, 836, 815, 773, 682 cm^{-1}; HR-ESI calculated for $C_{18}H_{31}O_2Si$ 307.2093, found 307.2085. R_f (5/1 hexane/EtOAc) = 0.31.

(*S*)-6-((5*E*,8*E*)-9-Chloro-8-methylnona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one (1b, coibacin B) and (*S*)-6-((5*E*,8*Z*)-9-Chloro-8-methylnona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one (8*Z*)-(*S*)-1b. To a solution of **8b** (24 mg, 0.08 mmol) in DMF (2 mL) under argon atmosphere NCS (14 mg, 0.10 mmol) was added at 20 °C. The reaction mixture was stirred overnight at 45 °C and then quenched with the saturated solution of $NaHCO_3$ (1 mL), extracted by hexane (3×2 mL). The combined organic fractions were dried over Na_2SO_4 and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (3/1 hexane/EtOAc) provided 9 mg (44%) of the title compound as a colorless viscous liquid. $[\alpha]_D$ +56.6° (c 0.0032, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 1.34-1.95 (m, 9H), 1.98-2.15 (m, 2H), 2.23-2.50 (m, 2H), 2.83 (ddt, *J* = 6.6, 1.2 Hz, 2H), 4.36-4.52 (m, 1H), 5.26-5.44 (m, 1H), 5.49 (ddt, *J* = 14.3, 6.5, 1.2 Hz, 1H), 5.75-5.91 (m, 1H), 6.04 (ddt, *J* = 9.7, 2.4, 1.2 Hz, 1H), 6.90 (ddd, *J* = 9.6, 5.6, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 16.59, 24.33, 29.08, 29.40, 32.25, 34.71, 40.19, 77.90, 112.57, 121.47, 126.59, 132.82, 137.91, 144.96, 164.53. R_f (3/1 hexane/EtOAc) = 0.34. The spectral characteristics were in agreement with previously reported data.[4]

Acknowledgements

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Keywords: allylation • Lewis base • Brønsted acid • asymmetric synthesis • metathesis

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[16] A series of coibacin D chiral analogs was synthesized and the optical rotation values of the prepared compounds were in the range of 45-60° (unpublished work).

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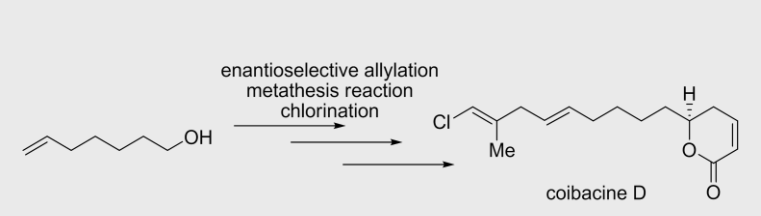

Coibacin D was synthesized from 6-hepten-1-ol in 6 step using enantioselective allylation catalyzed by a chiral Brønsted acid, ring closing and cross metathesis reactions, and electrophilic chlorination as crucial synthetic steps. The synthesis confirmed the proposed structure and absolute configuration.

*Kristýna Kolská, Mukund Ghavre, Milan Pour, Simona Hybelbauerová and Martin Kotora**

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Total Synthesis of Coibacin D by Using Enantioselective Allylation and Metathesis Reactions.

SUPPORTING INFORMATION

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I General remarks

The following general procedures were used in all reactions unless otherwise noted. Reaction vessels were dried by heat gun under dry argon pressure. Oxygen and moisture sensitive reactions were carried out under slight argon overpressure and in dry solvents. All commercially available reagents were purchased in the best quality and used without further purification unless otherwise noted. Solvents were purified and dried by distillation as follows: THF, Et_2O, and toluene from sodium/benzophenone and CH_2Cl_2 from CaH_2. All reactions were monitored by using TLC on E. Merck silica gel 60 F_{254} coated aluminium plates. Compounds were detected at long wave UV (254 nm) or visualized using anisaldehyde stain (15 g anisaldehyde, 2.5 mL conc. H_2SO_4 / 250 mL EtOH) and subsequent heating. Column chromatography was performed on Merck Silica gel 60 (0.040-0.063 µm, 240-400 mesh) or Merck PLC Silica gel 60 F_{254}, 0.5 mm. ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on Varian UNITY 300 MHz and Bruker AVANCE III 600 MHz spectrometer. Chemical shifts are given in δ scale (ppm units). All NMR spectra were referenced to residual solvent signal of $CDCl_3$ (^{1}H δ 7. 26, ^{13}C δ 77. 0). NMR experiments with internal standard were performed by using mesitylene. Infrared spectra were recorded with Thermo Nicolet AVATAR 370 FT-IR spectrometer on KBr tablets of the compounds via DRIFT method and reported in wave numbers (cm^{-1}). High resolution mass spectra were recorded on VG-Analytical ZAB-SEQ or AT 6530 Accurate-Mass Q-TOF LC/MS. Optical rotations were recorded on AUTOMATIC POLARIMETR, Autopol III are measured with accuracy of ±2 given in (deg·mL)/(g·dm)cm^2 g^{-1} with accuracy ±2 and the mass concentrations (marked as *c* are given in g/100 mL. In this respect it is necessary to note that given the low concentration of some measured samples, the final error in the measurement was rather large.

II Preparation of 1,5-pentadienes 2 and 4

(*E*)-(2-Allylhex-1-enyl)trimethylsilane (4a). The synthesis was based on the previously reported methodology.[1] To a solution of Cp_2ZrCl_2 (5 g, 17.10 mmol) in THF (70 mL) ethylmagnesium bromide (34.2 mL, 34.20 mmol) was added at -78 °C under argon atmosphere and stirred for 30 min at -78 °C and then for 1 h at room temperature. Then 1-trimethylsilylhex-1-yne (5.8 mL, 28.50 mmol) was added. After 1 h of stirring allyloxytrimethysilane (3.0 mL, 17.80mmol) was added and reaction was heated to 60 °C for 3 hs under reflux. The reaction was quenched with 3M HCl (8 mL) and extracted by CH_2Cl_2 (3×15 mL). The organic layer was separated and dried over Na_2SO_4 and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (hexane) gave 2.53 g (90%) of a mixture of **4a** and ***Z*-4a** (97/3) as a colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 0.04-0.15 (s, 9H), 0.84-1.05 (m, 3H), 1.19-1.51 (m,4H), 2.02-2.23 (m, 2H), 2.82 (dd, *J* = 7.1, 1.5 Hz, 2H), 4.95-5.13 (m, 2H), 5.20 (s, 1H), 5.69-5.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 0.37 (3C), 14.09, 23.00, 31.25, 35.96, 43.45, 115.95, 124.26, 136.88, 157.95; IR (KBr) ν 3081, 2956, 2926, 2860, 1607, 1467, 1458, 1245, 911, 887, 839, 689 cm^{-1}; MS-EI m/z (% relative intensity) 196.2 (M+, 14), 182.1 (12), 181.1. (62), 155.1 (18), 154.1 (76), 153.1 (14), 140.1 (6), 139.1 (44), 137.1 (6), 125.1 (17), 123.1 (12), 121.1 (8), 111.1 (17), 109.0 (10), 99.1 (60), 97.0 (21), 95.0 (8), 85.0 (16), 80.1 (16), 75.0 (8), 74.0 (18), 73.6 (24), 73.0 (100), 71.0 (7), 59.0 (54); HR-EI calculated for $C_{12}H_{24}Si$ 196.1647, found 196.1649. R_f (hexane) = 0.89.

Characteristic signals of ***Z*-4a** isomer: 2.88 (td, *J* = 7.9, 1.5 Hz, 2H), 5.27 (s, 1H), other peaks were overlapped by the major product.

(*E*)-Trimethyl(2-methylpenta-1,4-dien-1-yl)silane (4b). To a solution of Cp_2ZrCl_2 (7 g, 23.95mmol) in THF (70 mL) ethylmagnesium bromide (48.0 mL, 48.00 mmol) was added at -78 °C under argon atmosphere and stirred for 30 min at -78 °C and then for 1 h at room temperature. Then 1-trimethylsilylprop-1-yne (6 mL, 22.0 mmol) was added. After 1 h of stirring allyloxytrimethysilane (4.2 mL, 24.92mmol) was added and reaction was heated to 60 °C for 3 h under reflux. The reaction was quenched with 3M HCl (5 mL) and extracted by ether (3×10 mL). The organic layer was separated and dried over Na_2SO_4 and decaline was added. Fractional distillation of the mixture containing the product furnished several fractions containg various amounts of **4b**. The collected fractions provided 1.5 g (54 %) of a colorless viscous liquid containing mostly the desired product **4b** (~85%), **(*Z*)-4b** (**4b**/**(*Z*)-4b** 95/5), small amounts of decaline, and other unidentified compounds. The total amount of **4b** in each fraction was determined by ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 0.02-0.23 (m, 9H), 1.77-1.83 (m, 3H), 2.80 (dd, *J* = 6.8, 1.2 Hz, 2H), 4.93-5.19 (m, 2H), 5.23 (s, 1H), 5.74-5.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 0.11, 21.66, 46.88, 115.89, 124.17, 136.60, 153.20. The spectral characteristics were in agreement with the previously reported data.[2]

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Characteristic signals of ***Z*-4b** isomer: 2.86 (td, *J* = 7.6, 2.7, 1.4 Hz, 2H), 5.29 (s, 1H), other peaks were overlapped by the major product.

(*E*)-4-(Halogenomethylene)oct-1-ene (2). To a solution of **4** (200 mg, 1.00 mmol) in DMF/MeCN (3 mL) NBS/NCS (362/272 mg, 2.00 mmol) was added at 0 °C under argon atmosphere. The reaction mixture was stirred for 1-3 days at 20 or 45 °C (see Table 1). The reaction was quenched with the saturated solution of $NaHCO_3$ (1 mL) and extracted by hexane (3×2 mL). The combined organic fractions were dried over Na_2SO_4 and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (hexane) provided products as viscous liquids.

(*E*)-4-(Chloromethylene)oct-1-ene (2a) and (*Z*)-4-(chloromethylene)oct-1-ene ((*Z*)-2a). Column chromatography provided 70 mg (43 %) of a mixture of **2a** and **(*Z*)-2a** (88/12) as a yellowish viscous liquid.
^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 0.79-1.05 (m, 3H), 1.18-1.48 (m, 4H), 2.13-2.41 (m, 2H), 2.78 (dq, *J* = 6.7, 4.1, 1.5 Hz, 2H), 4.96-5.19 (m, 2H), 5.65-5.91 (m, 1H); 5.80 (s, 1H), ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 13.93, 22.56, 29.07, 29.98, 39.20, 113.12, 117.03, 135.09, 141.26; IR (KBr) ν 3081, 2956, 2875, 2860, 1640, 1467, 1455, 1251, 991, 919, 893, 842, 797, 764 cm^{-1}; MS-EI m/z (% relative intensity) 160.1 (M+2, 33), 158.1(99), 123.1 (81), 121.1 (23), 116.0 (34), 115.0 (13), 109.1 (15), 107.1 (15), 95.1 (20), 93.1 (17), 82.1 (11), 81.1 (100), 79.1 (25), 67.1 (49); HR-EI calculated for $C_9H_{15}Cl$ 158.0862, found 158.0861. R_f (hexane) = 0.86.
Characteristic signals of **(*Z*)-2a** isomer: 2.92 (td, *J* = 6.3, 2.8, 1.7 Hz, 2H), 5.83 (s, 1H), other peaks were overlapped by the major product.

(*E*)-4-(Bromomethylene)oct-1-ene (Br-2a) and (*Z*)-4-(bromomethylene)oct-1-ene ((*Z*)-Br-2a). Column chromatography provided 107 mg (52 %) of a mixture of **Br-2a** and **(*Z*)-Br-2a** (92/8) as a yellowish viscous liquid.
^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 0.78-1.02 (m, 3H), 1.19-1.50 (m, 4H), 2.16-2.29 (m, 2H), 2.83 (dq,*J* = 7.0, 3.9, 1.2 Hz, 2H), 4.99-5.17 (m, 2H), 5.66-5.85 (m, 1H), 5.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC) δ 13.95, 22.56, 29.06, 32.45, 40.34, 102.37, 117.12, 134.94, 144.11; IR (KBr) ν 3081, 2950, 2932, 2869, 2860, 1637, 1464, 1455, 1251, 994, 914, 845, 779 cm^{-1}; MS-EI m/z (% relative intensity) 204.0 (M+2, 24), 202.0 (24), 161.0 (13), 124.1 (9), 123.1 (69), 121.1 (14), 82.1 (9), 81.1 (100), 79.1 (8), 67.1 (47); HR-EI calculated for $C_9H_{15}Br$202.0357, found 202.0363. R_f (hexane) = 0.83.
Characteristic signals of **(*Z*)-Br-2a** isomer: 2.98 (td, *J* = 6.9, 3.0, 1.4 Hz, 2H), 5.95 (s, 1H), other peaks were overlapped by the major product.

SI-Table 1. Halogenolysis of trimethylsilylpenta-1,4-dienes **4** with NBS and NCS

Entry	NXS	Solvent	T (°C)	t (d)	Yield (%)[a]
1	NBS	DMF	r.t.	1	24
2	NBS	DMF	r.t./45	1/1.5h	35
3	NCS	DMF	r.t.	3	0
4	NCS	DMF	45	3	33
5	NCS	DMF	45	2	43
6	NBS	MeCN	r.t.	1	52
7	NCS	MeCN	r.t.	1	0
8	NCS	MeCN	r.t.	3	0
9	NCS	MeCN	r.t./45	3	11
10	NCS	MeCN	45	1	27

[a] Isolated yields.

III Preparation of racemic and enantioenriched ester 5

Hept-6-enal (7). To the solution of oxalylchloride (7.4 mL, 0.09 mol) in DCM (70 mL) under argon atmosphere cooled to -78 °C DMSO (12.5 mL, 0.18 mol) was added. After 15 min the solution of hept-6-enol (5 g, 0.04 mol) in DCM (5 mL) was added. After another 15 min Et_3N (30.6 mL, 0.22mmol) was added and the reaction mixture was stirred for 10 min at -78 °C and then at 20 °C until the completion of the reaction (monitored by TLC). The reaction mixture was quenched by water (25 mL), extracted by DCM (3×20 ml) and washed with brine. The combined organic fractions were dried over $MgSO_4$ and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (hexane) gave 4.05 g (82 %) of the title compound as a colorless viscous liquid.
^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 1.34-1.49 (m, 2H), 1.54-1.74 (m, 2H), 1.99-2.20 (m, 2H), 2.43 (td, *J* = 7.3, 1.8 Hz, 2H), 4.88-5.08 (m, 2H), 5.79 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 9.76 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC) δ 21.47, 28.30, 33.39, 43.69, 114.81, 138.20, 202.56; IR (KBr) ν 3078, 2926, 2860, 1727, 1712, 1643, 1458, 1437, 1356, 1260, 1132, 1081, 994, 908 cm^{-1}; MS-ESI m/z (% relative intensity) 113.1 (M+, 10), 96.1 (7), 95.1 (100), 69.1 (13), 68.1 (4); HR-ESI calculated for $C_7H_{13}O$ 113.0966, found 113.0963. R_f (hexane) = 0.5.

Deca-1,9-dien-4-ol (6) (Method A). To the solution of **7** (400 mg, 3.57 mmol) in Et_2O (13 mL) allylmagnesium bromide (3.9 ml, 3.92 mmol) was added at 0 °C under argon atmosphere. After 2 h of stirring the saturated solution of NH_4Cl (5 mL) was added and the reaction mixture was extracted by Et_2O (3×3 mL). The combined organic fractions were dried over $MgSO_4$ and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexane/EtOAc) gave 401 mg (73 %) of the title compound as a colorless viscous liquid.
^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 1.19-1.56 (m, 6H), 1.72 (s, 1H), 1.96-2.18 (m, 3H), 2.18-2.38 (m, 1H), 3.51-3.74 (m, 1H), 4.83-5.05 (m, 2H), 5.05-5.25 (m, 2H), 5.66-5.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC) δ 25.13, 28.89, 33.70, 36.62, 41.93, 70.59, 114.37, 118.06, 134.85, 138.86; IR (KBr) ν 3342, 3075, 2977, 2932, 2860, 1640, 1437, 1078, 991, 914, 635 cm^{-1}; MS-ESI m/z (% relative intensity) 155.1 (M+, 6), 137.1 (65), 135.1 (17), 131.1 (87), 109.1 (9), 96.1 (57), 95.7 (100), 95.1 (93), 93.1 (41), 83.1 (70), 81.1 (85), 79.1 (21), 71.0 (59), 69.1 (62), 67.0 (89), 57.0 (28), 55.0 (36); HR-ESI calculated for $C_{10}H_{19}O$ 155.1436, found 155.1437. R_f (10/1 hexane/EtOAc) = 0.43.

(*R*)-Deca-1,9-dien-4-ol ((*R*))-6). *Reaction with allyltrichlorosilane* (Method B). To a solution of (*R*,*S*)-*N*,*N*'-dioxide (16 mg, 0.036 mmol) in THF (2 mL) hepten-6-enal **7** (80 mg, 0.71 mmol), diisopropylethylamine (149 μL, 0.86 mmol) and allyltrichlorsilane (123 μL, 0.86 mmol) were added at -78 °C under argon atmosphere. After 1 day of stirring at -78 °C the saturated solution of $NaHCO_3$ (2 mL) was added and the reaction mixture was extracted by Et_2O (3×2 mL). The combined organic fractions were dried over $MgSO_4$ and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexane/EtOAc) gave 28 mg (24 %, 57 % ee) of the title compound as a colorless viscous liquid.

(*R*)-Deca-1,9-dien-4-ol ((*R*))-6). *Reaction with allylboronic acid pinacol ester* (Method C). To a solution of hepten-6-enal **7** (400 mg, 3.57 mmol) and (*S*)-TRIP-PA (67 mg, 0.09 mmol, 2.5 mol %) in toluene (30 mL) cooled to -30°C was added dropwise allylboronic acid pinacol ester (4.28 mmol, 803 µL) over 30 seconds under argon atmosphere. The reaction mixture was stirred at -30°C for 2 days, then volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexane/EtOAc) gave 517 mg (93%, 90 % ee) of the title compound as a colorless viscous liquid.
$[\alpha]_D$ +10.8° (c 0.0093, $CHCl_3$).

(*S*)-Deca-1,9-dien-4-ol ((*S*)-6). *Reaction with allylboronic acid pinacol ester* (Method D). To a solution of hepten-6-enal **7** (1.6 g, 14.29 mmol) and (*R*)-TRIP-PA (269 mg, 0.36 mmol, 2.5 mol %) in toluene (100 mL) cooled to -30°C was added dropwise allylboronic acid pinacol ester (17.15 mmol, 3.2 mL) over 30 seconds under argon atmosphere. The reaction mixture was stirred at -30°C for 2 days, then volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (10/1 hexane/EtOAc) gave 1.98 g (90 %, 96 % ee) of the title compound as a colorless viscous liquid.
$[\alpha]_D$-5.6° (c 0.006, $CHCl_3$).

Deca-1,9-dien-4-yl acrylate (5). To a solution of **6** (0.98 g, 6.40 mmol) v DCM (5 mL) Et_3N (3.1 mL, 22.60 mmol) was added under argon atmosphere. Then a solution of acryloyl chloride (1.02 g, 11.3 mmol) in DCM (1 mL) was addend at 0 °C. After 5 h of stirring the reaction mixture was quenched by brine (5 mL) and extracted by DCM (3×5 mL). The combined organic fractions were dried over $MgSO_4$ and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (15/1 hexane/EtOAc) gave 886 mg (66 %) of the title compound as a colorless viscous liquid.
^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 1.11-1.48 (m, 4H), 1.47-1.70 (m, 2H), 1.93-2.14 (m, 2H), 2.19-2.49 (m, 2H), 4.84-5.19 (m, 5H), 5.61-5.93 (m, 3H), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.39 (dd, *J* = 17.3, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 ºC) δ 24.69, 28.66, 33.37, 33.55, 38.57, 73.48, 114.44, 117.68, 128.84, 130.33, 133.61, 138.68, 165.88; IR (KBr) ν 3075, 2932, 2857, 1724, 1637, 1404, 1293, 1269, 1195, 1048, 985, 961, 914, 812 cm^{-1}; MS-ESI m/z (% relative intensity) 209.2 (M+,19), 167.1 (32), 138.1 (10), 137.1 (76), 135.1 (27), 127.0 (26), 101.1 (70), 95.7 (89), 95.1(58), 94.1 (36), 82.1 (24), 81.6 (64), 81.1 (80), 80.1 (21), 73.0 (54), 67.0 (81), 55.5 (11), 55.1 (19); HR-ESI calculated for $C_{13}H_{21}O_2$ 209.1542, found 209.1539. R_f (20/1 hexane/EtOAc) = 0.61.

(*R*)-Deca-1,9-dien-4-yl acrylate ((*R*)-5). To a solution of (*R*)-**6** (400 mg, 2.59 mmol) v DCM (3 mL) Et_3N (1.3 mL, 9.15 mmol) was added under argon atmosphere. Then a solution of acryloyl chloride (413 mg, 4.56 mmol) in DCM (2 mL) was addend at 0 °C. After 5 h of stirring the reaction mixture was quenched by brine (5 mL) and extracted with DCM (3×5 mL). The combined organic fractions were dried over $MgSO_4$ and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (15/1 hexane/EtOAc) gave 410 mg (76 %, 95 % ee) of the title compound as a colorless viscous liquid.
$[\alpha]_D$ +19.2° (c 0.0068, $CHCl_3$).

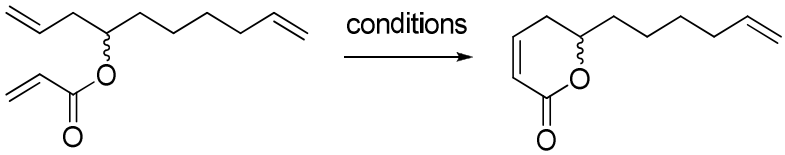
(*S*)-Deca-1,9-dien-4-yl acrylate ((*S*)-5). To a solution of (*S*)-**6** (1 g, 6.48 mmol) v DCM (5 mL) Et_3N (3.2 ml, 22.90 mmol) was added under argon atmosphere. Then a solution of acryloyl chloride (1.04 g, 11.45 mmol) in DCM (1 mL) was added at 0 °C. After 5 h of stirring the reaction mixture was quenched by brine (5 mL) and extracted with DCM (3×5 mL). The combined organic fractions were dried over Na_2SO_4 and volatiles were removed moved under reduced pressure. Column chromatography of the residue on silica gel (20/1 hexane/EtOAc) gave 0.95 g (71 %, 98 % ee) of the title compound as a colorless viscous liquid.
$[\alpha]_D$ -18.2° (c 0.0142, $CHCl_3$).

IV Metathesis reactions

6-(Hex-5-enyl)-5,6-dihydro-2H-pyran-2-one (3). To a solution of the Grubbs 2nd generation catalyst (143 mg, 0.17 mmol) in DCM (200 mL) **5** (350 mg, 1.68 mmol) and CuI (see Table 2) were added at 20 °C under argon atmosphere. After 20 h volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (5/1 hexane/EtOAc) gave the title compound as a brownish viscous liquid.

^{1}H NMR (300 MHz, $CDCl_3$, 25 ºC) δ 1.30-1.73 (m, 5H), 1.72-1.92 (m, 1H), 1.92-2.16 (m, 2H), 2.16-2.55 (m, 2H), 4.34-4.49 (m, 1H), 4.82-5.14 (m, 2H), 5.64-5.90 (m, 1H), 6.02 (dt, *J* = 9.4, 1.8 Hz, 1H), 6.88 (ddd, *J* = 9.7, 5.1, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25ºC) δ 24.29, 28.60, 29.39, 33.55, 34.72, 77.91, 114.65, 121.47, 138.55, 144.96, 164.54; IR (KBr) ν 3069, 2932, 2860, 1721, 1643, 1389, 1245, 1039, 958, 914, 818 cm^{-1}; MS-ESI m/z (% relative intensity) 182.1 ($M+H^+$,13), 181.1 (M+, 100), 164.1 (11), 163.1 (82), 145.1 (9), 135.1 (63), 95.1 (23), 81.1 (8); HR-ESI calculated for $C_{11}H_{17}O_2$ 181.1229, found 181.1226. R_f (5/1 hexane/EtOAc) = 0.26.

SI-Table 2. Ring closing metathesis of **5** to **3** under various conditions.



Entry	Cat. (mol%)	Solvent	Aditives	T (°C)	t (d)	Yield (%)[a]
1	5	DCM	-	20	1	34
2	10	DCM	-	20	1	37
3	5	DCM	CuI (6 mol%)	20	1	38
4	10	DCM	CuI (6 mol%)	20	1	40
5	10	DCM	CuI (10 mol%)	20	1	44
6	10	DCM	CuI (20 mol%)	20	1	48
7	7	DCM	CuI (20 mol%)	20	1	52
8	10	Et_2O	CuI (6 mol%)	20	2	0

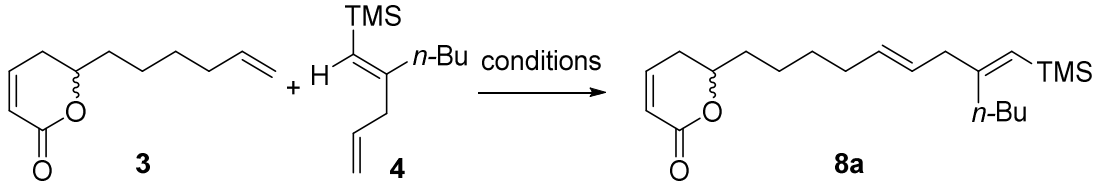
[a] Isolated yields.

General procedure for formation of 6-((5*E*,8*E*)-8-((trimethylsilyl)methylene)dodec-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (8a) and 6-((5*E*,8*Z*)-8-((trimethylsilyl)methylene)dodec-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((8*Z*)-8a). Cross metathesis of 3 with 4 (see SI-Table 3). To a solution of **3** (50 mg, 0.28mmol) and **4** in DCM (50 mL) the Hoveyda-Grubbs 2nd generation catalyst and additives were added at 20 °C under argon atmosphere. After 20 h volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (5/1 hexane/EtOAc) gave a mixture of **8a** and **(8*Z*)-8a** (78/22) as a brownish viscous liquid.

^{1}H NMR (600 MHz, $CDCl_3$, 25 ºC) δ 0.06-0.15 (m, 9H), 0.83-0.98 (m, 4H), 1.22-1.92 (m, 9H), 1.92-2.20 (m, 4H), 2.20-2.42 (m, 2H), 2.77 (d, *J* = 4.4 Hz, 2H), 4.32-4.48 (m, 1H), 5.19 (s, 1H), 5.31-5.52 (m, 2H), 5.97-6.09 (m, 1H), 6.82-6.92 (m, 1H); ^{13}CNMR (150 MHz, $CDCl_3$, 25 ºC)

δ 0.42 (3C), 14.11, 23.01, 24.32, 29.22, 29.39, 31.25, 32.35, 34.73, 35.90, 42.26, 77.95, 121.48, 123.61, 128.53, 131.68, 144.94, 158.87, 164.54; IR (KBr) ν 2953, 2929, 2860, 1736, 1721, 1610, 1458, 1392, 1248, 1141, 1069, 1039, 970, 839, 815, 689 cm^{-1}; MS-EI m/z (% relative intensity) 349.3 ($M+H^+$, 4), 348.2 (M+, 10), 334.2 (22), 333.2 (87), 291.2 (8),235.1 (9), 231.2 (9), 216.2 (18), 201.1 (15), 191.2 (95), 187.1 (14), 173.1 (32), 169.1 (100),158.1 (42), 147.1 (33), 142.0 (78), 133.1 (36), 129.0 (34), 121.1 (27), 119.1 (23), 105.1(19), 97.0 (26), 93.1 (32), 91.1 (11), 81.1 (19), 79.1 (22), 75.0 (31), 68.0 (32), 59.0 (31); HR-EI calculated for $C_{21}H_{36}O_2Si$ 348.2485, found 348.2495. R_f (5/1 hexane/EtOAc) = 0.33.
Characteristic signals of **(8*Z*)-8a** isomer: 2.82 (d, *J* = 6.6 Hz, 2H), 5.21 (s, 1H), other peaks were overlapped by the major product.

SI-Table 3. Cross metathesis of **3** with **4** in DCM under various conditions.



Entry	**4** (eq)	H-G II (mol%)	Additives (mol%)	T (°C)	t (d)	Yield (%)[a]	Comment[a]
1	1	2 × 5	-	20	2	0	SP + SM
2	2	5	-	20	1	0	SP + SM
3	5	5	-	20	1	0	SP + SM
4	15	5	-	20	1	18	SP + SM
5	9	5	CuI (10)	20	4	17	P + SM
6	9	5	CuI(20)	20	7	6	
7	15	5	-	45	1	26	P + SP

[a] Isolated yields. [b] SM = starting material, P = product, SP = unidentified side-products.

General procedure for formation of 6-((5*E*,8*E*)-8-((trimethylsilyl)methylene)dodec-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (8a) and 6-((5*E*,8*Z*)-8-((trimethylsilyl)methylene)dodec-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((8*Z*)-8a). One-pot metathesis of 5 with 4a. To a solution of **5** (100 mg, 0.48 mmol) in toluene (48 mL) the Hoveyda-Grubbs 2nd generation catalyst (30 mg, 0.048 mmol) was added at 20 °C under argon atmosphere. The reaction mixture was stirred for 24 hours under reflux and then was cooled to the room temperature. Then **4a** (654 mg,, 3.33 mmol) and Grubbs 2nd generation catalyst (20 mg, 0.024 mmol) was added After 24 h of stirring volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (5/1 hexane/EtOAc) gave 27 mg (32%) of a mixture of **8a** and **(8*Z*)-8a** (82/18) as a brownish viscous liquid.

6-((5*E*,8*E*)-8-Methyl-9-(trimethylsilyl)nona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one (8b) 6-((5*E*,8*Z*)-8-methyl-9-(trimethylsilyl)nona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-

one ((8*Z*)-8b). To a solution of **dim-3** (60 mg, 0.18 mmol) and **4b** (417 mg, 2.70 mmol) in toluene (20 mL) the Grubbs 2nd generation catalyst (23 mg, 0.03 mmol) was added at 20 °C under argon atmosphere. After 2 days of stirring volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (5/1 hexane/EtOAc) gave 33 mg (60%) of a mixture of **8b** and **(8*Z*)-8b** (82/18) as a brownish viscous liquid. The spectral and other characteristic are listed in section VII.

General procedure for formation of 6-((5*E*,8*E*)-8-Methyl-9-(trimethylsilyl)nona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one (8b) and 6-((5*E*,8*Z*)-8-methyl-9-(trimethylsilyl)nona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((8*Z*)-8b). One-pot metathesis of 5 with 4b. To a solution of **5** (100 mg, 0.48 mmol) in toluene (48 mL) the Hoveyda-Grubbs 2nd generation catalyst (30 mg, 0.048 mmol) was added at 20 °C under argon atmosphere. The reaction mixture was stirred for 24 hours under reflux and then was cooled to the room temperature. Then **4b** (695 mg, 4.50 mmol) and Grubbs 2nd generation catalyst (20 mg, 0.024 mmol) was added After 24 h of stirring volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (5/1 hexane/EtOAc) gave 21 mg (28 %) of a mixture of **8b** and **(8*Z*)-8b** (73/27) as a brownish viscous liquid. The spectral and other characteristic are listed in section VII.

V Synthesis of racemic 1

6-((5*E*,8*E*)-8-(Chloromethylene)dodec-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one (1a) and 6-((5*E*,8*E*)-8-(chloromethylene)dodec-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((8*Z*)-1a). To a solution of **8a** (50 mg, 0.14 mmol) in DMF (3 ml) NCS (25 mg, 0.19 mmol) was added at room temperature under argon atmosphere. Reaction mixture was stirred overnight at 45 °C. The reaction was quenched with the saturated solution of $NaHCO_3$ (1 ml) and extracted by hexane (3 × 2 ml). The organic layer was separated and dried over Na_2SO_4 and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (5/1 hexane/EtOAc) provided 34 mg (75%) of a mixture of **1a** and **(8*Z*)-1a** (74/26) as a colorless viscous liquid.

^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 0.78-1.06 (m, 3H), 1.24-1.97 (m, 10H), 1.97-2.15 (m, 2H), 2.15-2.28 (m, 2H), 2.30-2.47 (m, 2H), 2.75 (d, *J* = 6.7 Hz, 2H), 4.33-4.57 (m, 1H), 5.26-5.65 (m, 2H), 5.80 (s, 1H), 5.98-6.11 (m, 1H), 6.82-6.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) 13.95, 22.56, 24.35, 29.09 (2C), 29.40, 29.98, 32.26, 34.71, 38.03, 77.89, 112.68, 121.47, 126.77, 132.76, 142.22, 144.95, 164.58; IR (KBr) ν 2954, 2932, 2861, 1720, 1459, 1386, 1248, 1147, 1039, 971, 816 cm^{-1}, compound did not have the molecular peak. R_f (3/1 hexane/EtOAc) = 0.23.

Characteristic signals of **(8*Z*)-1a** isomer: 2.81 (d, *J* = 7.2 Hz, 2H), 5.82 (s, 1H), other peaks were overlapped by the major product.

6-((5*E*,8*E*)-9-Chloro-8-methylnona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one (1b) and 6-((5*E*,8*Z*)-9-chloro-8-methylnona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((8*Z*)-1b). To a solution of **8b** (30 mg, 0.10 mmol) in DMF (2 mL) under argon atmosphere NCS (17 mg, 0.13 mmol) was added at 20 °C. The reaction mixture was stirred overnight at 45 °C and then quenched with the saturated solution of $NaHCO_3$ (1 mL), extracted by hexane (3×2 mL). The combined organic fractions were dried over Na_2SO_4 and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (3/1 hexane/EtOAc) provided 9 mg (34%) of a mixture of **1b** and **(8*Z*)-1b** (75/25) as a colorless viscous liquid.

The spectral and other characteristic are listed in chiral section.

VI Decomposition of 8a

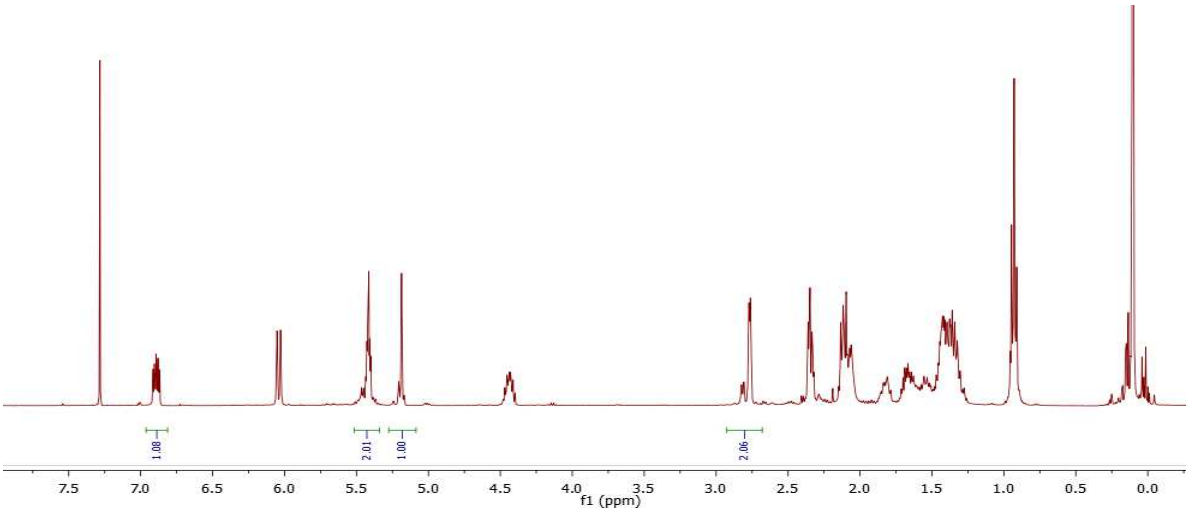


Figure SI-1. Sample of **8a** in $CDCl_3$ (immediately after isolation ~ 10 min).

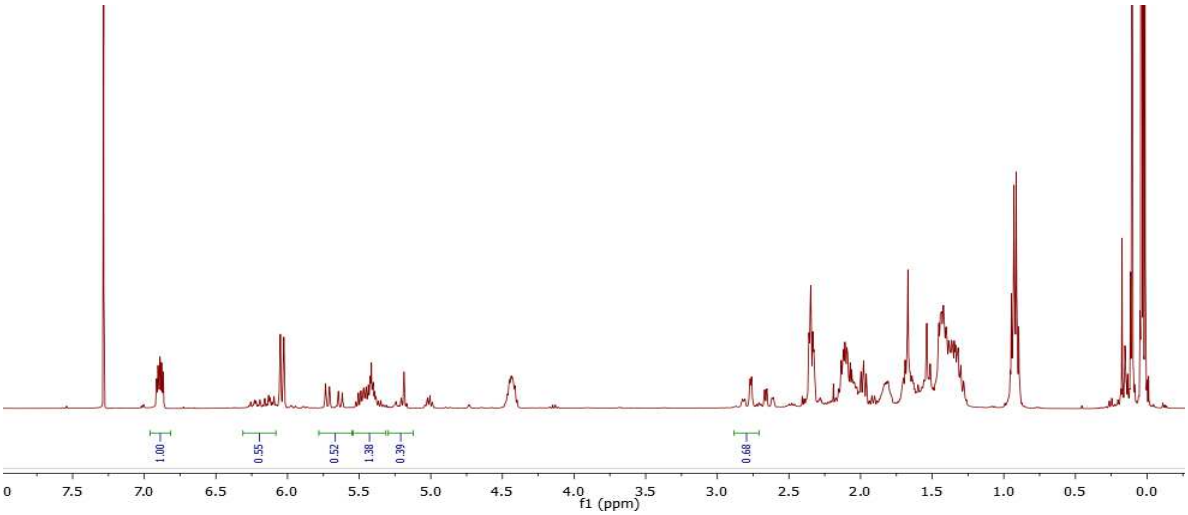


Figure SI-2. Sample of **8a** in $CDCl_3$ (after 5 h).

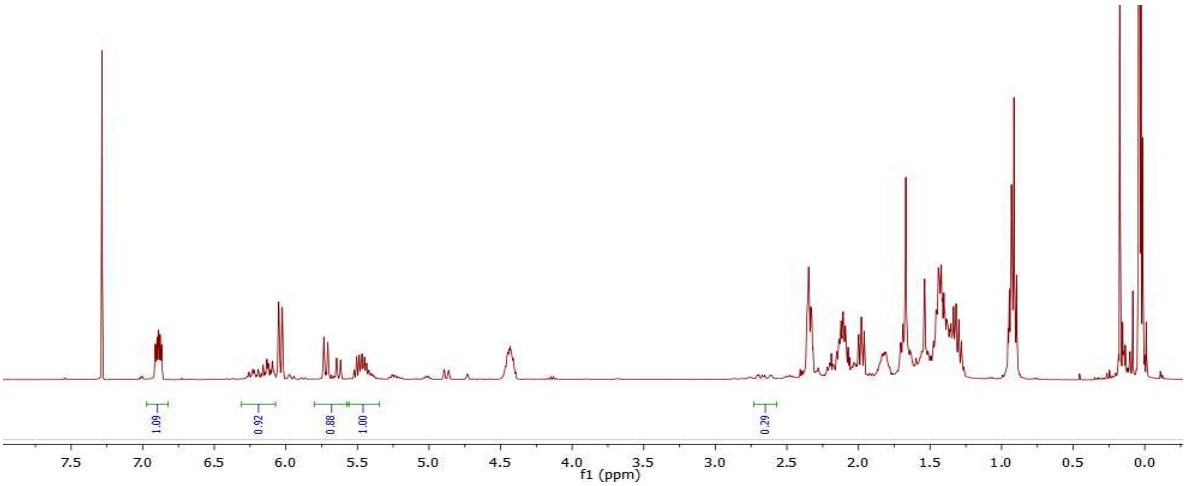


Figure SI-3. Sample of **8a** in $CDCl_3$ (after 22 h).

VII Synthesis of coibacin D

(*S*)-6-(Hex-5-en-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((*S*)-3) and (6*S*,6'*S*)-6,6'-((*E*)-dec-5-ene-1,10-diyl)bis(5,6-dihydro-2*H*-pyran-2-one) ((*S*)-dim-3).
To a solution of the Grubbs 2nd generation catalyst (82 mg, 0.10 mmol) in DCM (100 mL) (*S*)-**5** (200 mg, 0.96 mmol) was added at 20 °C under argon atmosphere. After 24 h of stirring under reflux volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (1/1 hexane/EtOAc) gave (*S*)-**3** (41 mg, 24%, 96% ee) and (*S*)-**dim-3** (83 mg, 52 %) as brownish viscous liquids.
(*S*)-3
$[\alpha]_D$+96.9° (c 0.0075,$CHCl_3$);
(*S*)-Dim-3
$[\alpha]_D$ +96.65° (c 0.0054, $CHCl_3$);
^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 1.32-1.73 (m, 5H), 1.75-1.94 (m, 1H), 1.94-2.12 (m, 2H), 2.21-2.50 (m, 2H), 4.343 (ddt, *J* = 10.3, 7.4, 5.2, 1H), 5.27-5.53 (m, 1H), 6.03 (ddd, *J* = 9.7, 2.3, 1.4, 1H), 6.84-6.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 24.30, 29.25, 29.41, 32.34, 34.74, 77.97, 121.42, 130.25, 145.05, 164.59; IR (KBr) ν 2926, 2857, 1718, 1392, 1251, 1141, 1066, 1039, 970, 818, 665 cm^{-1}; MS-ESI m/z (% relative intensity) 334.2 (18), 333.2 (M+, 100), 316.2 (9), 315.2 (43), 297.2(8); HR-ESI calculated for $C_{20}H_{29}O_4$ 332.2066, found 332.2063. R_f (1/1 hexane/EtOAc) = 0.24.

(*S*)-6-((5*E*,8*E*)-8-Methyl-9-(trimethylsilyl)nona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((*S*)-8b) and (*S*)-6-((5*E*,8*E*)-8-methyl-9-(trimethylsilyl)nona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((8*Z*)-(*S*)-8b).
To a solution of **dim-3** (59 mg, 0.18 mmol) and **4b** in toluene (20 mL) the Grubbs 2nd generation catalyst (23 mg, 0.03 mmol) was added at 20 °C under argon atmosphere. After 2 days of stirring volatiles were removed under reduced pressure and column chromatography of the residue on silica gel (5/1 hexane/EtOAc) gave 24 mg (44 %) of a mixture of **(*S*)-8b** and **(8*Z*)-(*S*)-8b** (82/18) as a brownish viscous liquid.
$[\alpha]_D$ +48.6° (c 0.0058,$CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 0.06-0.27 (m, 9H),1.29-1.52 (m, 3H), 1.52-1.74 (m, 2H), 1.74-1.93 (m, 4H), 1.93-2.25 (m, 2H), 2.25-2.52 (m, 2H), 2.75 (d, *J* = 4.2 Hz, 2H), 4.36-4.56 (m, 1H), 5.22 (d, *J* = 1.0 Hz, 1H 5.33-5.54 (m, 2H), 6.04 (ddd, *J* = 9.8, 2.3, 1.4 Hz, 1H), 6.80-7.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 0.10 (3C), 21.59, 24.31, 29.19, 29.39, 32.34, 34.72, 45.76, 77.95, 121.46, 123.53, 128.22, 131.78, 144.96, 154.13, 164.55; IR (KBr) ν 2944, 2857, 1718, 1613, 1440, 1386, 1245, 1144, 1039, 970, 869, 836, 815, 773, 682 cm^{-1}; HR-ESI calculated for $C_{18}H_{31}O_2Si$ 307.2093, found 307.2085. R_f (5/1 hexane/EtOAc) = 0.31.
Characteristic signals of **(8*Z*)-(*S*)-8b** isomer: 2.81 (d, *J* = 6.7 Hz, 2H), 5.24 (d, *J* = 1.0 Hz, 1H) other peaks were overlapped by the major product.

(*S*)-6-((5*E*,8*E*)-9-Chloro-8-methylnona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one (1b) and (*S*)-6-((5*E*,8*Z*)-9-chloro-8-methylnona-5,8-dien-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((8*Z*)-(*S*)-1b). To a solution of **8b** (24 mg, 0.08 mmol) in DMF (2 mL) under argon atmosphere

NCS (14 mg, 0.10 mmol) was added at 20 °C. The reaction mixture was stirred overnight at 45 °C and then quenched with the saturated solution of $NaHCO_3$ (1 mL), extracted by hexane (3×2 mL). The combined organic fractions were dried over Na_2SO_4 and volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (3/1 hexane/EtOAc) provided 9 mg (44%) of a mixture of **1b** and **8*Z*-(*S*)-1b** (73/27) as a colorless viscous liquid.

$[[\alpha]_D$ +56.6° (c 0.0032, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ºC) δ 1.34-1.95 (m, 9H), 1.98-2.15 (m, 2H), 2.23-2.50 (m, 2H), 2.74 (d, *J* = 6.7 Hz, 2H), 4.36-4.52 (m, 1H), 5.26-5.44 (m, 1H), 5.49 (ddt, *J* = 14.3, 6.5, 1.2 Hz, 1H), 5.83 (q, *J* =1.5, 2.8 Hz, 1H), 6.04 (ddt, *J* = 9.7, 2.4, 1.2 Hz, 1H), 6.90 (ddd, *J* = 9.6, 5.6, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ºC) δ 16.59, 24.33, 29.08, 29.40, 32.25, 34.71, 40.19, 77.89, 112.57, 121.47, 126.59, 132.82, 137.91, 144.96, 164.53. R_f (3/1 hexane/EtOAc) = 0.34. The spectral characteristics were in agreement with previously reported data.[3]

Characteristic signals of **8*Z*-(*S*)-1b** isomer: 2.81 (d, *J* = 7.5 Hz, 2H), 5.81 (t, *J* = 0.7, 1H), other peaks were overlapped by the major product.

[3] Balunas, M.J.; Grosso, M.F.; Villa, F.A.; Engene, N.; McPhail, K.L.; Tidgewell, K.; Pineda, L.M.; Gerwick, L.; Spadafora, C.; Kyle, D.E.; Gerwick, W.H. *Org.Lett.* **2012,***14*, 3878-3881.

VIII Determination of *ee* and absolute configuration of products

General procedure for the preparation of Mosher´s esters. To a solution of an alcohol (0.04 mmol) and DMAP (0.2 mmol, 24 mg) in CH_2Cl_2 (2 mL) (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic chloride (0.04 mmol, 10.1 mg) was added under argon atmosphere at 20 °C and the reaction mixture was stirred overnight. The reaction mixture was quenched with the saturated aqueous solution of NH_4Cl (5 mL), washed with the saturated aqueous solution of $NaHCO_3$ (4 mL), and extracted by ether (3×5 mL). The combined organic fractions were dried over $MgSO_4$ and volatiles were removed under reduced pressure. The crude product was used for determination of the diastereoisomeric ratio without further purification to avoid possible amplification of the ee.

Preparation from 6 (Method A). The final mixture of diastereoisomeric Mosher's esters (*R*)-(-)-MTPA-(*S*)-**11** a (*R*)-(-)-MTPA-(*R*)-**11** was obtained in 13 mg (86 %) as a colorless viscous liquid.

^{19}F NMR (300 MHz, C_6D_6, 25 ºC) δ -71.20 (50 %), -71.29 (50 %).

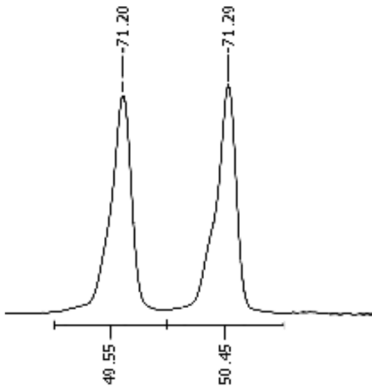


Figure SI-4. ^{19}F NMR (*R*)-(-)-MTPA-(*S*)-**11** a (*R*)-(-)-MTPA-(*R*)-**11** (from racemic **6**).

Preparation from (*R*)-6 (Method B). The final mixture of diastereoisomeric Mosher's esters (*R*)-(-)-MTPA-(*S*)-**11** a (*R*)-(-)-MTPA-(*R*)-**11** was obtained in 12 mg (81 %) as a colorless viscous liquid.

ee 57%, ^{19}F NMR (300 MHz, C_6D_6, 25 ºC) δ -71.19 (21.5 %), -71.28 (78.5 %).

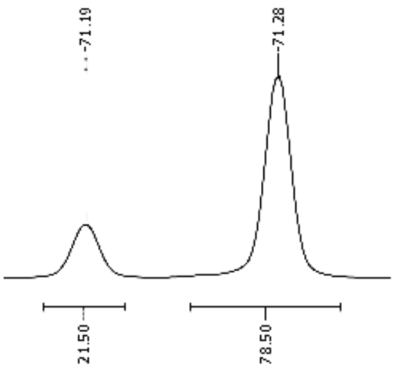


Figure SI-5. ^{19}F NMR of (*R*)-(-)-MTPA-(*S*)-**11** a (*R*)-(-)-MTPA-(*R*)-**11** (from (*R*)-**6**).

Preparation from (*R*)-6 (Method C). The final mixture of diastereoisomeric Mosher's esters (*R*)-(-)-MTPA-(*S*)-**11** a (*R*)-(-)-MTPA-(*R*)-**11** was obtained in 12 mg (81 %) as a colorless viscous liquid.
ee 90 %, ^{19}F NMR (300 MHz, C_6D_6, 25 ºC) δ -71.19 (5 %), -71.27 (95 %).

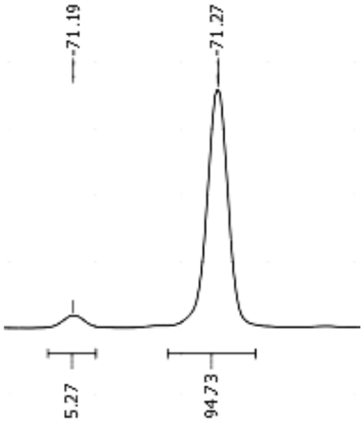


Figure SI-6. ^{19}F NMR of (*R*)-(-)-MTPA-(*S*)-**11** a (*R*)-(-)-MTPA-(*R*)-**11** (from (*R*)-**6**).

Preparation from (*S*)-6 (Method D). The final mixture of diastereoisomeric Mosher's esters (*R*)-(-)-MTPA-(*S*)-**11** a (*R*)-(-)-MTPA-(*R*)-**11** was obtained in 12 mg (81 %) as a colorless viscous liquid.
ee 96 %, ^{19}F NMR (300 MHz, C_6D_6, 25 ºC) δ -71.19 (98 %), -71.27 (2 %).

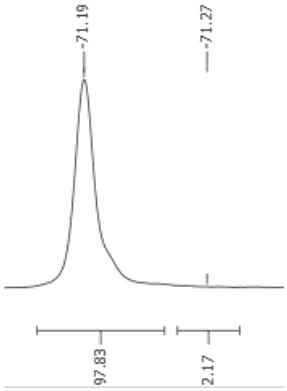
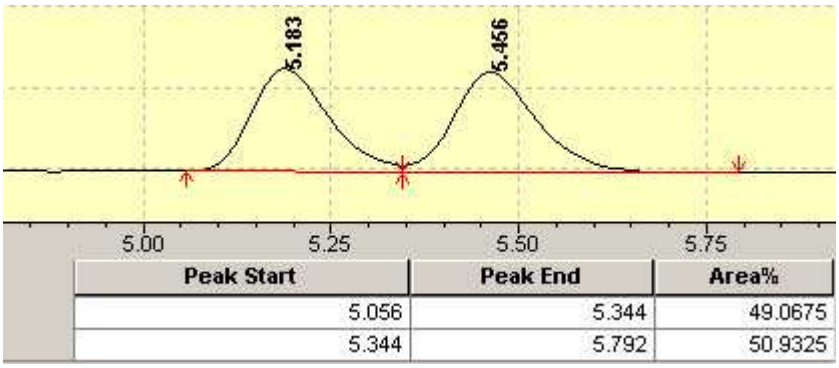


Figure SI-7. ^{19}F NMR of (*R*)-(-)-MTPA-(*S*)-**11** a (*R*)-(-)-MTPA-(*R*)-**11** (from (*S*)-**6**).

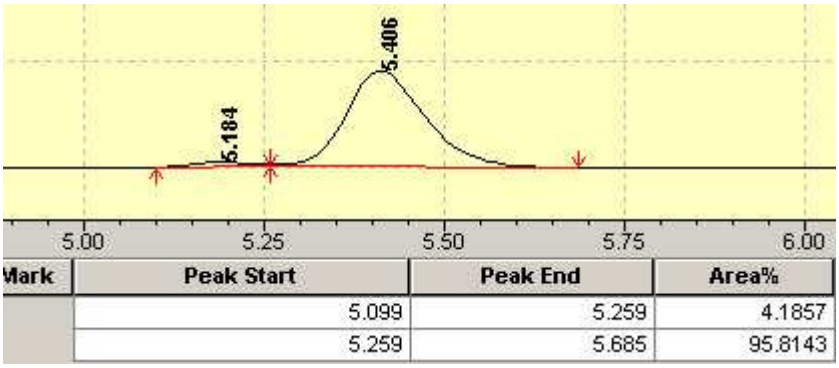
For compound (*R*)-**5** (ee 92 %*) enantiomeric excess was determined by HPLC equipped with Chiralpak IC column (t_S = 5.18 min, t_R = 5.41 min, *i*-PrOH/heptane 0.1/99.9, flow rate 1 mL/min, 35°C).
* (Taking into the account non-optimal resolution of enantiomers, the real ee could be higher.)

For compound (*S*)-**5** (ee 98 %) enantiomeric excess was determined by HPLC equipped with Chiralpak IC column (t_S = 5.11 min, t_R= 5.32 min, *i*-PrOH/heptane 0.1/99.9, flow rate 1 mL/min, 35°C).



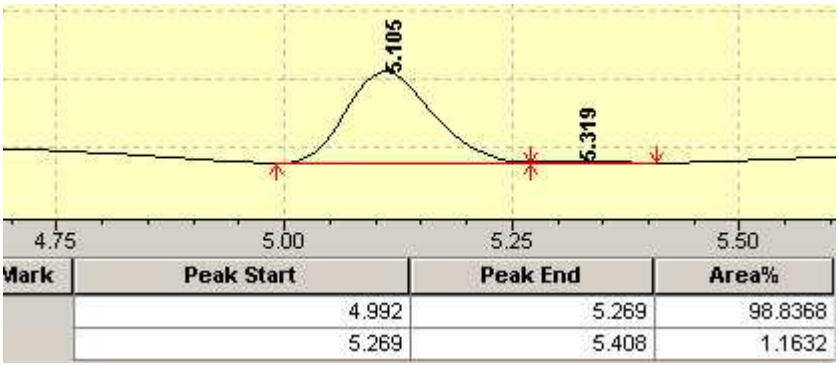
Peak Start	Peak End	Area%
5.056	5.344	49.0675
5.344	5.792	50.9325

Figure SI-8. HPLC of racemic **5**.



Mark	Peak Start	Peak End	Area%
	5.099	5.259	4.1857
	5.259	5.685	95.8143

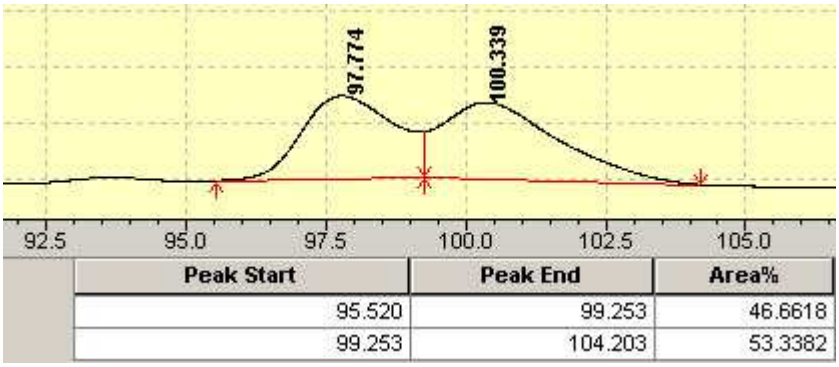
Figure SI-9. HPLC of (*R*)-**5**.



Mark	Peak Start	Peak End	Area%
	4.992	5.269	98.8368
	5.269	5.408	1.1632

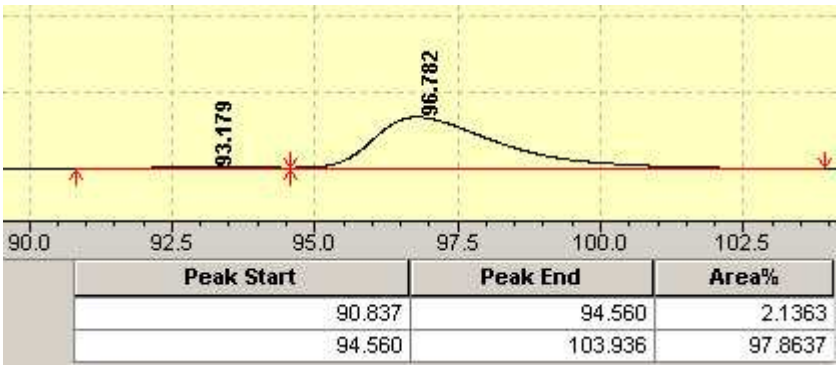
Figure SI-10. HPLC of (*S*)-**5**.

For compound (*S*)-**3** (ee 96 %) enantiomeric excesses were determined by HPLC equipped with Chiralpak IC column (t_R = 93.18 min, t_S = 96.78 min, *i*-PrOH/heptane 1.0/99.0, flow rate 1 mL/min, 35°C).



Peak Start	Peak End	Area%
95.520	99.253	46.6618
99.253	104.203	53.3382

Figure SI-11. HPLC of racemic **3**.



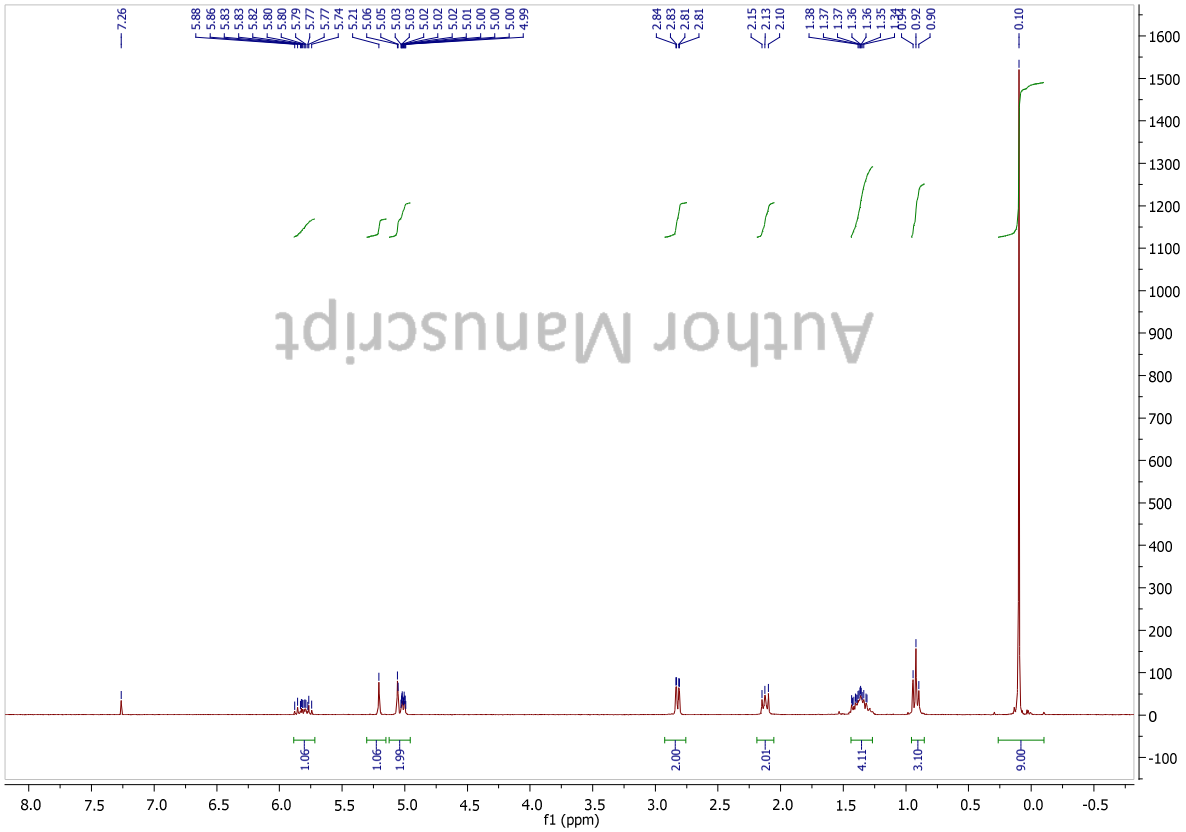
Peak Start	Peak End	Area%
90.837	94.560	2.1363
94.560	103.936	97.8637

Figure SI-12. HPLC of racemic (*S*)-**3**.

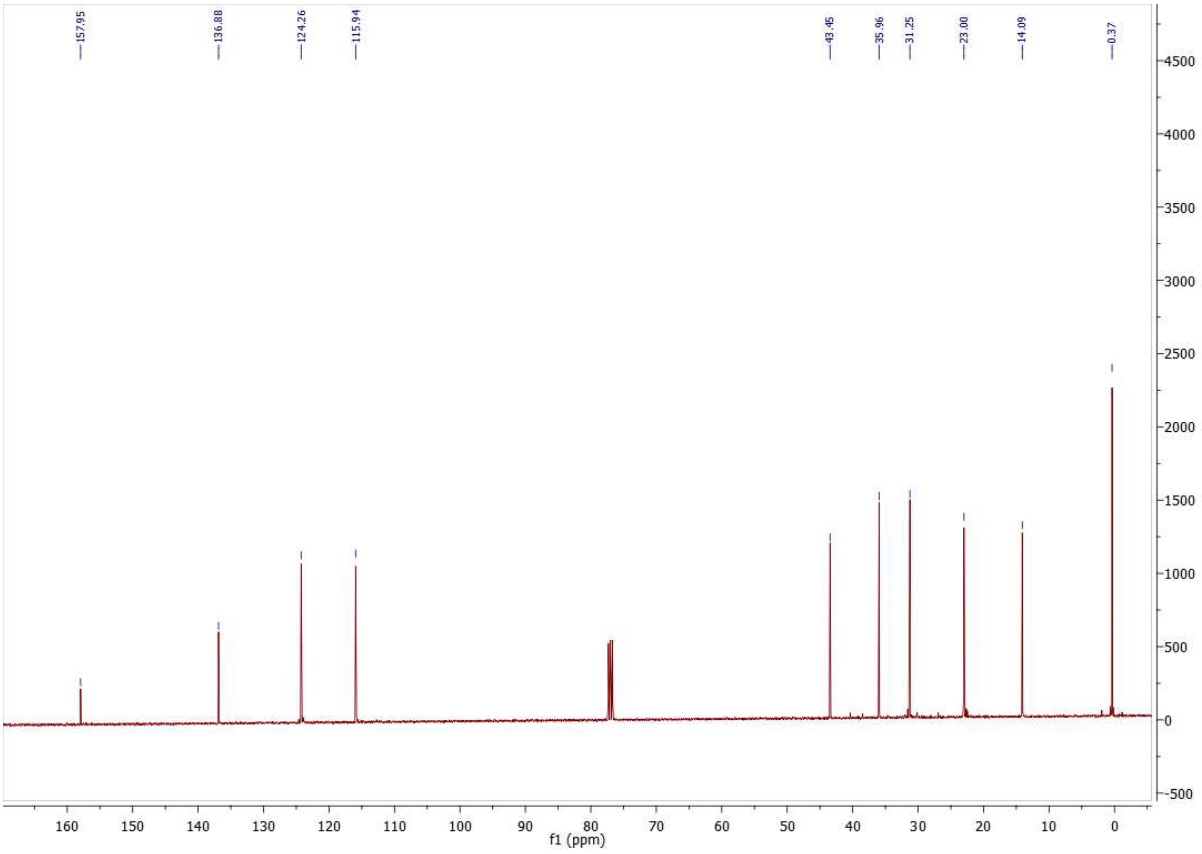
For compound (*S*)-**dim-3** could not be found suitable conditions.

IX Copies of ^{1}H and ^{13}C NMR spectra

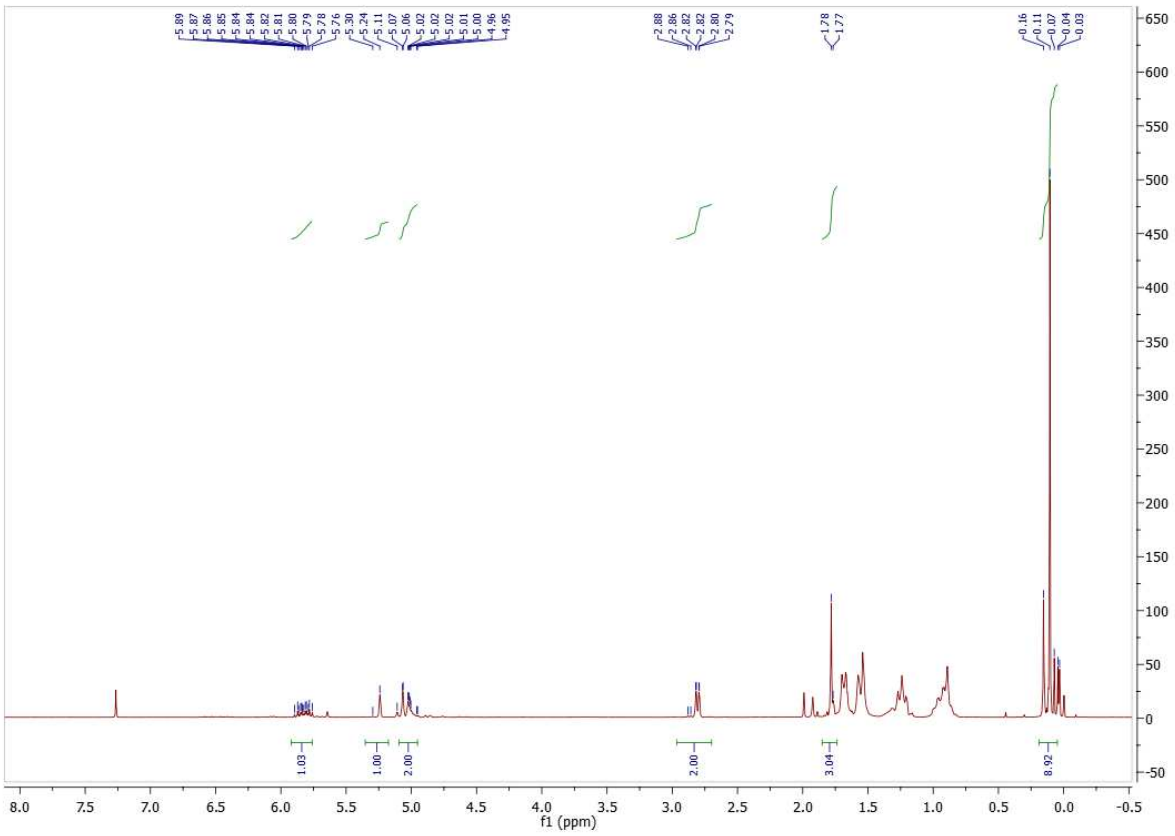
4a – ^{1}H NMR spectrum



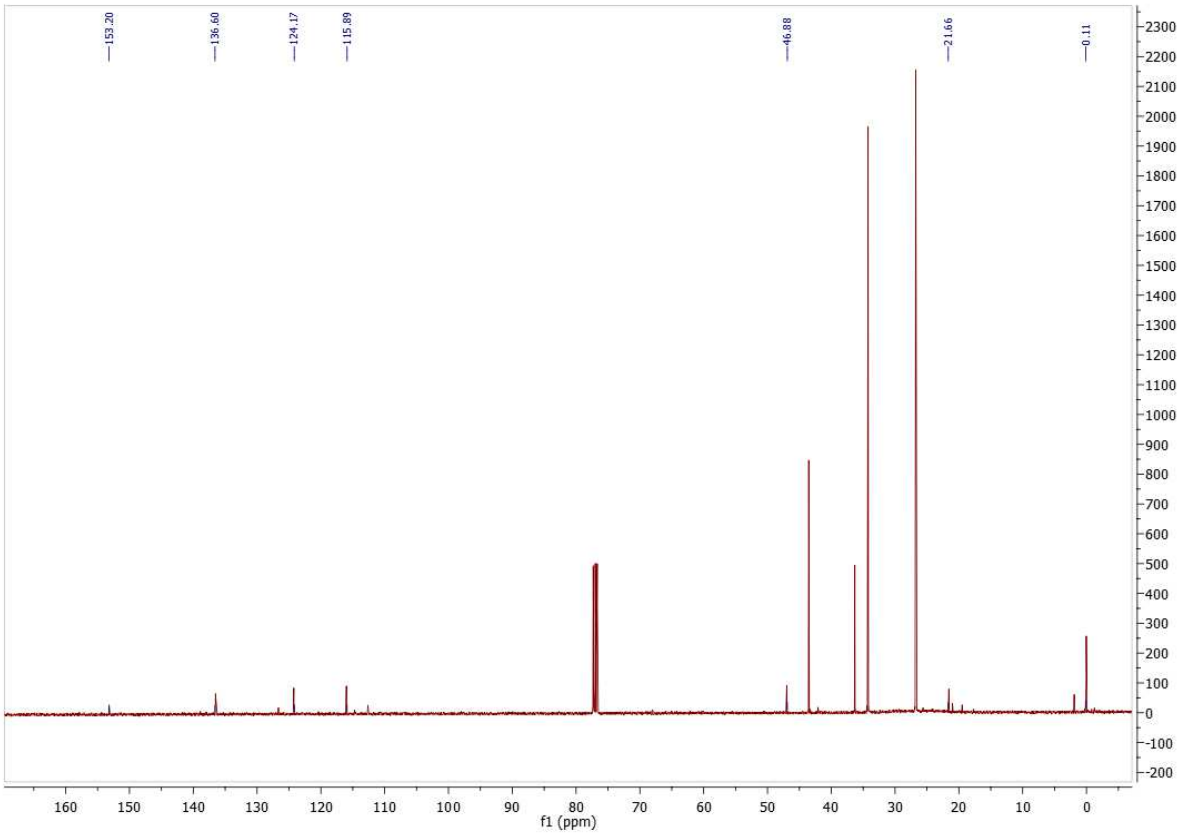
4a – ^{13}C NMR spectrum



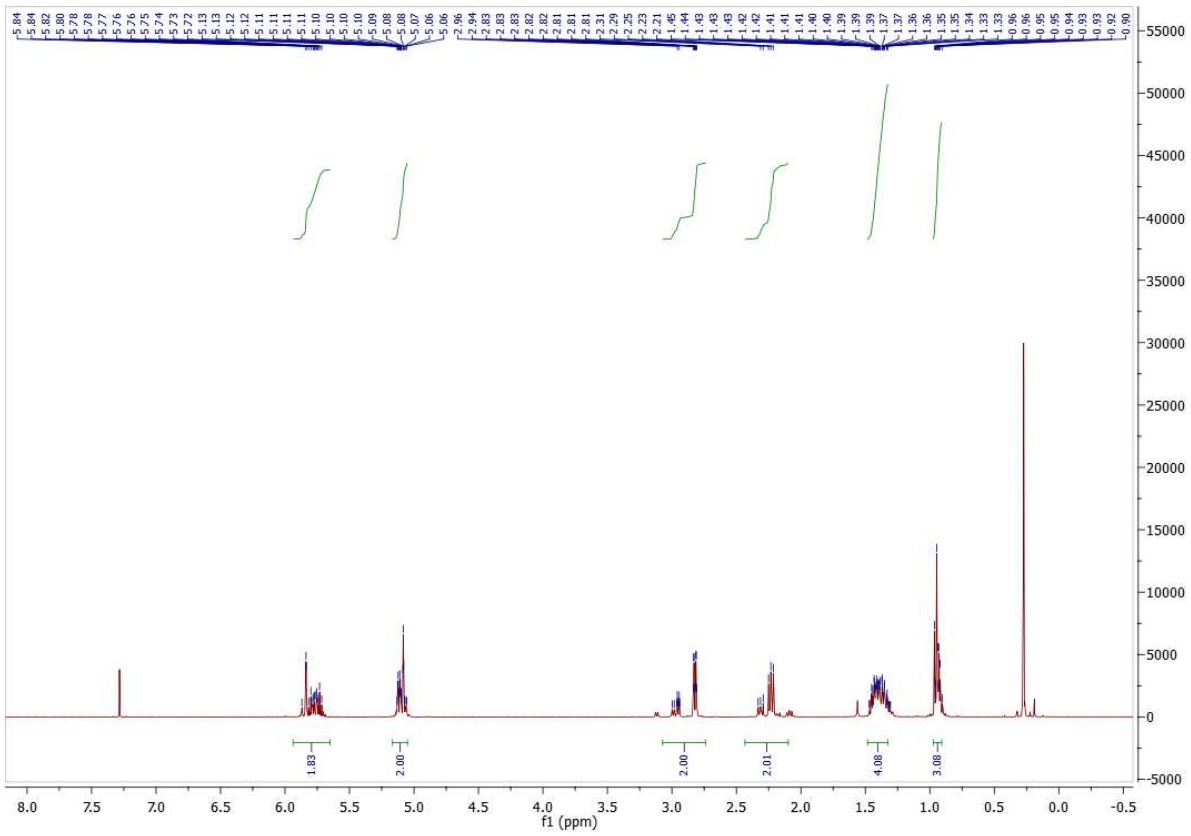
4b – ^{1}H NMR spectrum



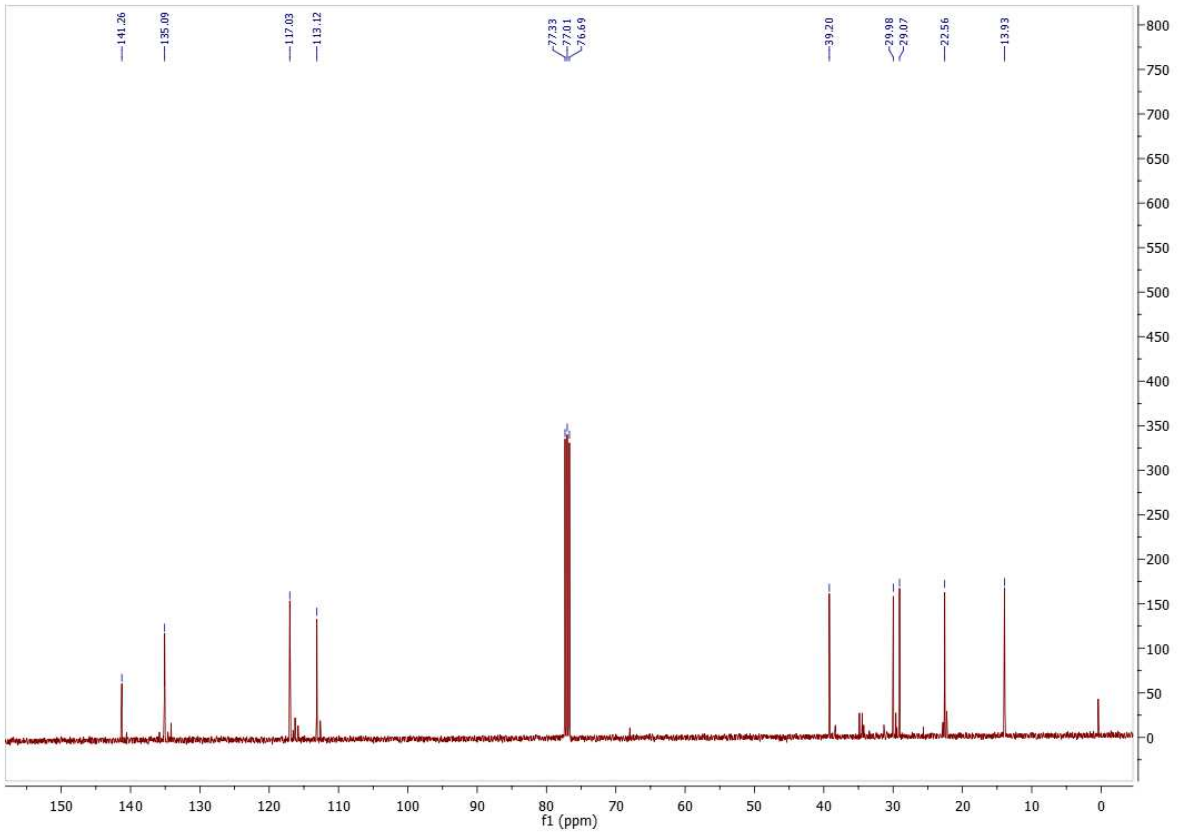
4b – ^{13}C NMR spectrum



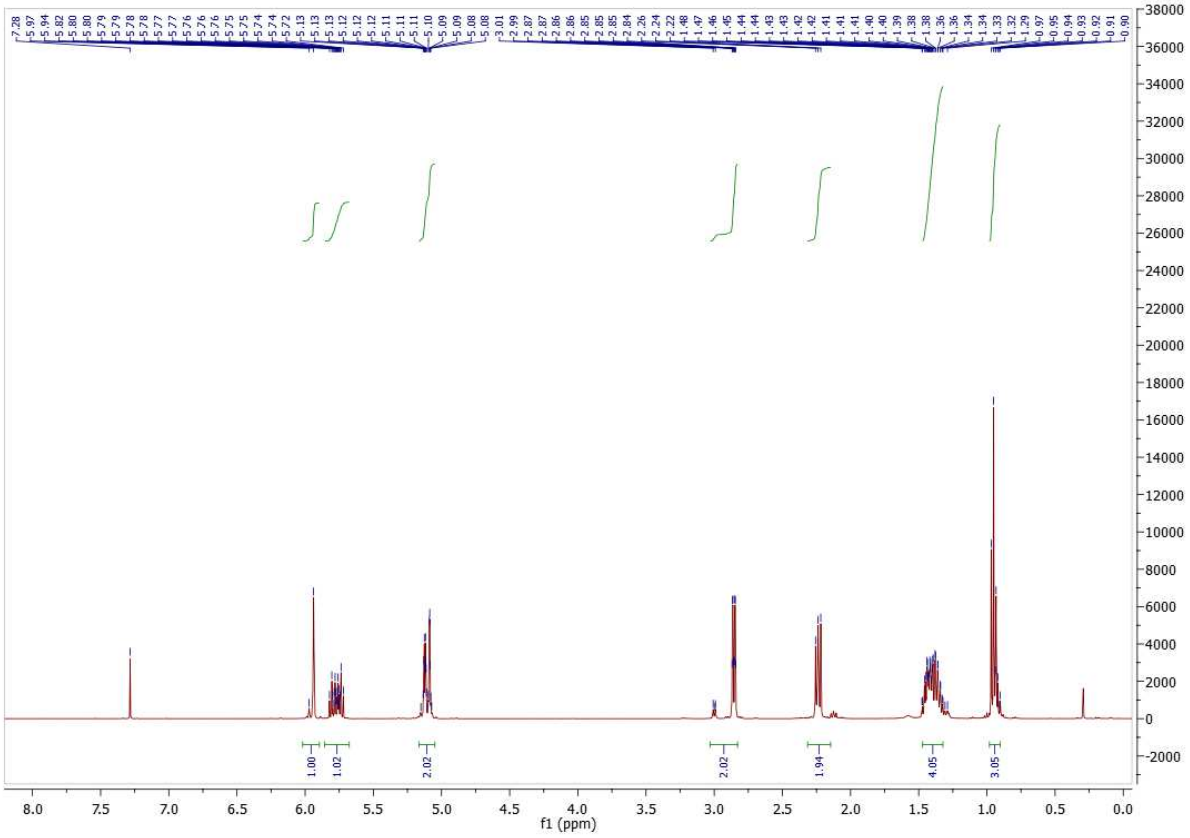
2-Cl – ^{1}H NMR spectrum



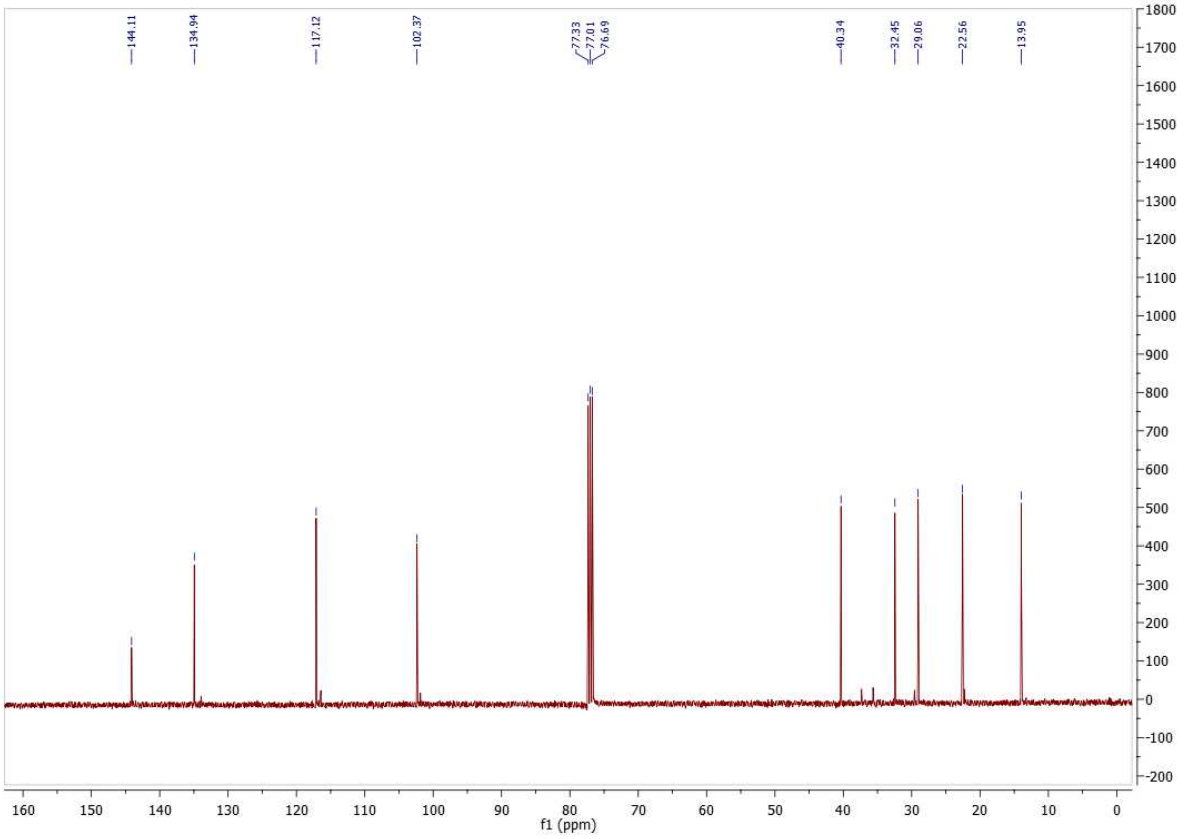
2-Cl – ^{13}C NMR spectrum



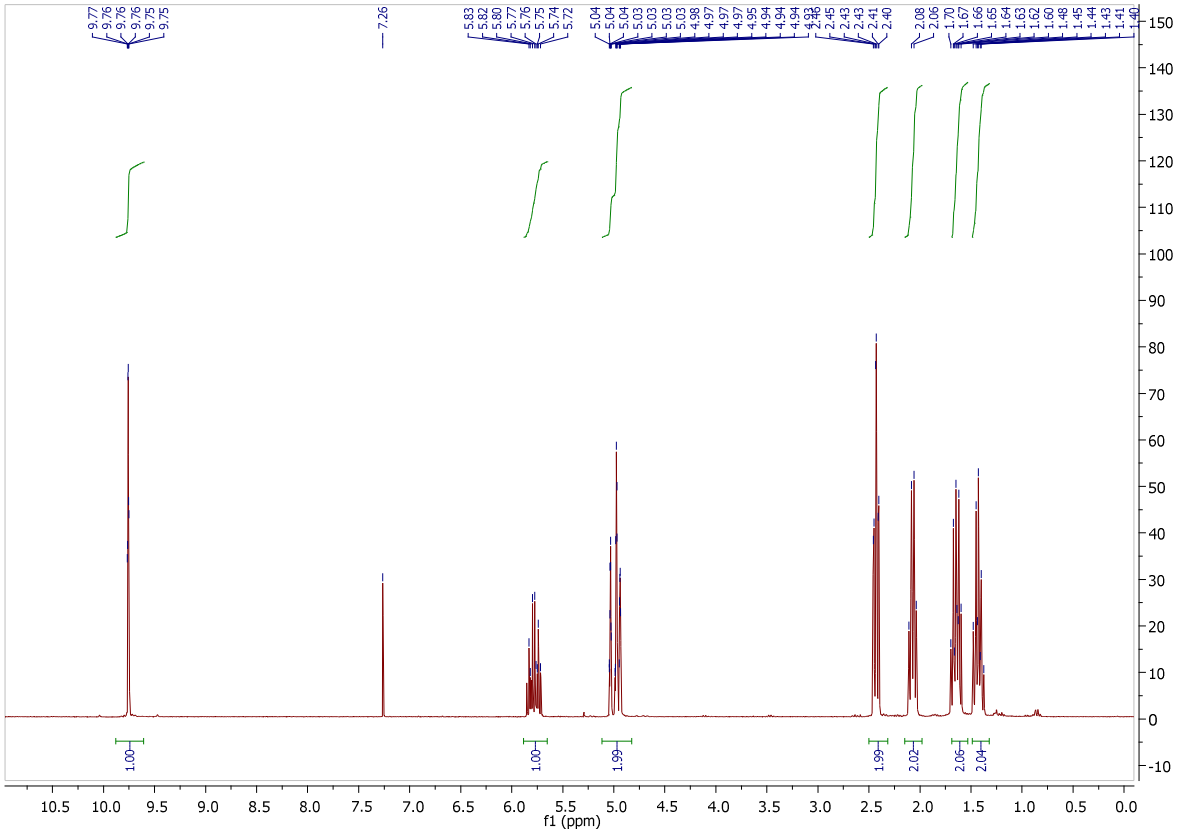
2-Br – ^{1}H NMR spectrum



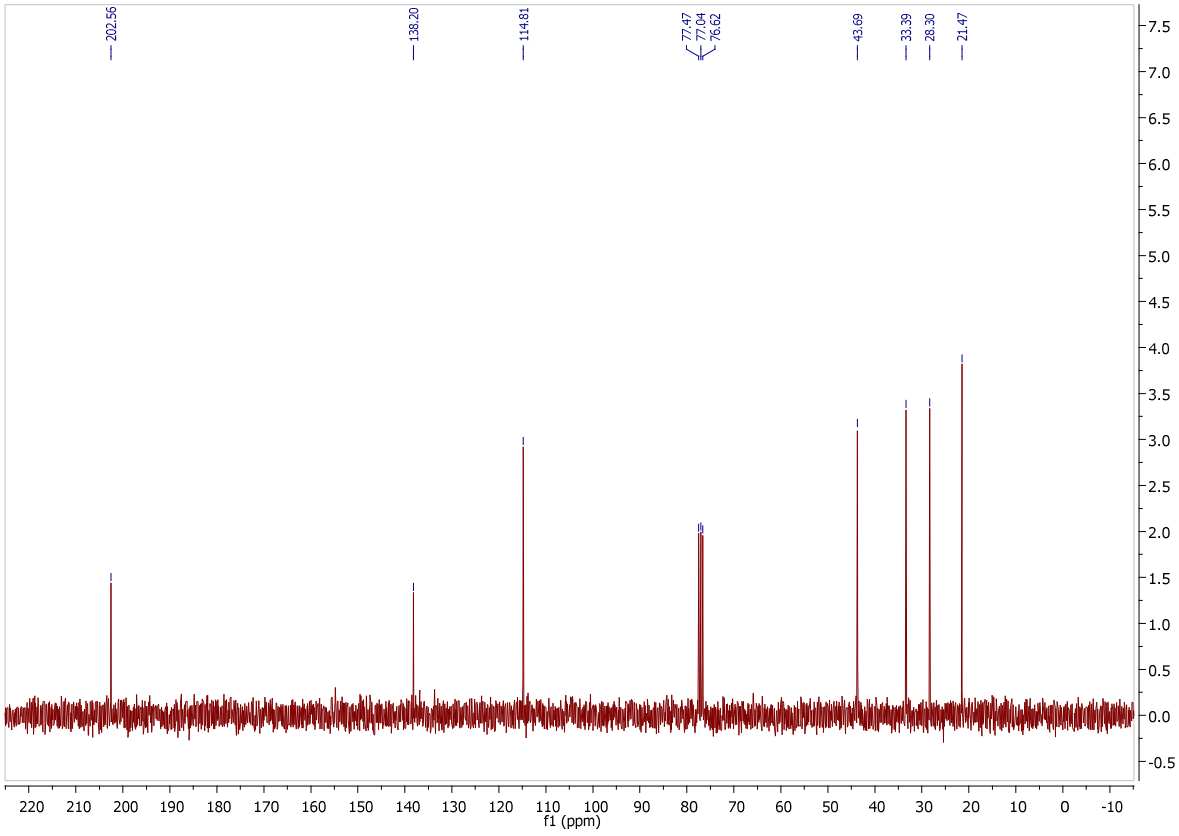
2-Br – ^{13}C NMR spectrum



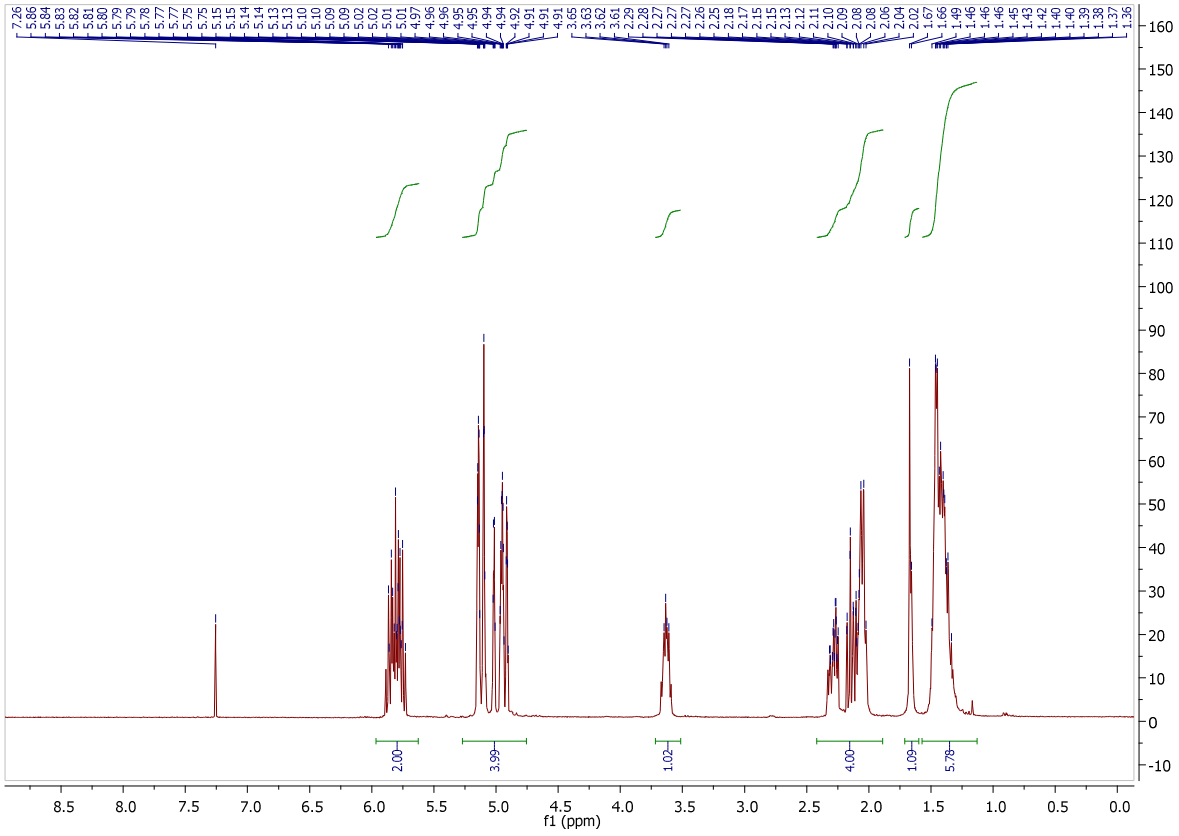
7 – ^{1}H NMR spectrum



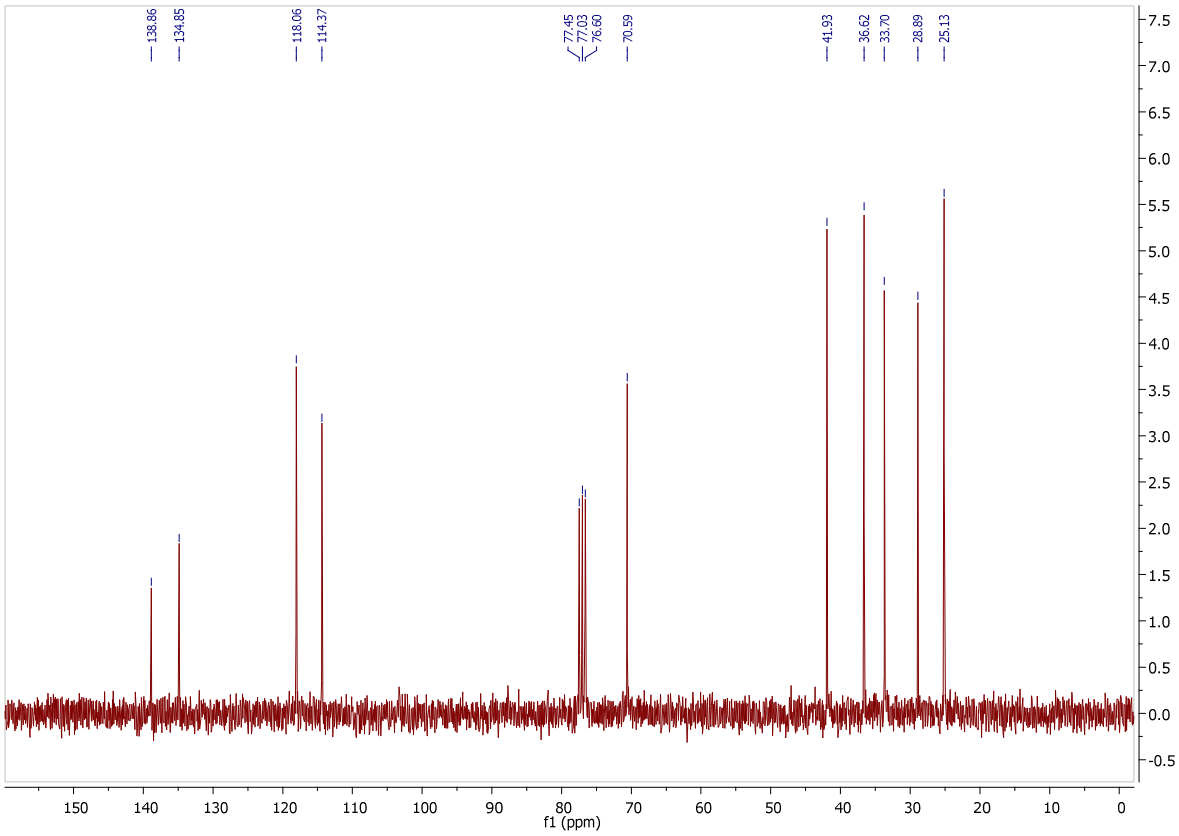
7 – ^{13}C NMR spectrum



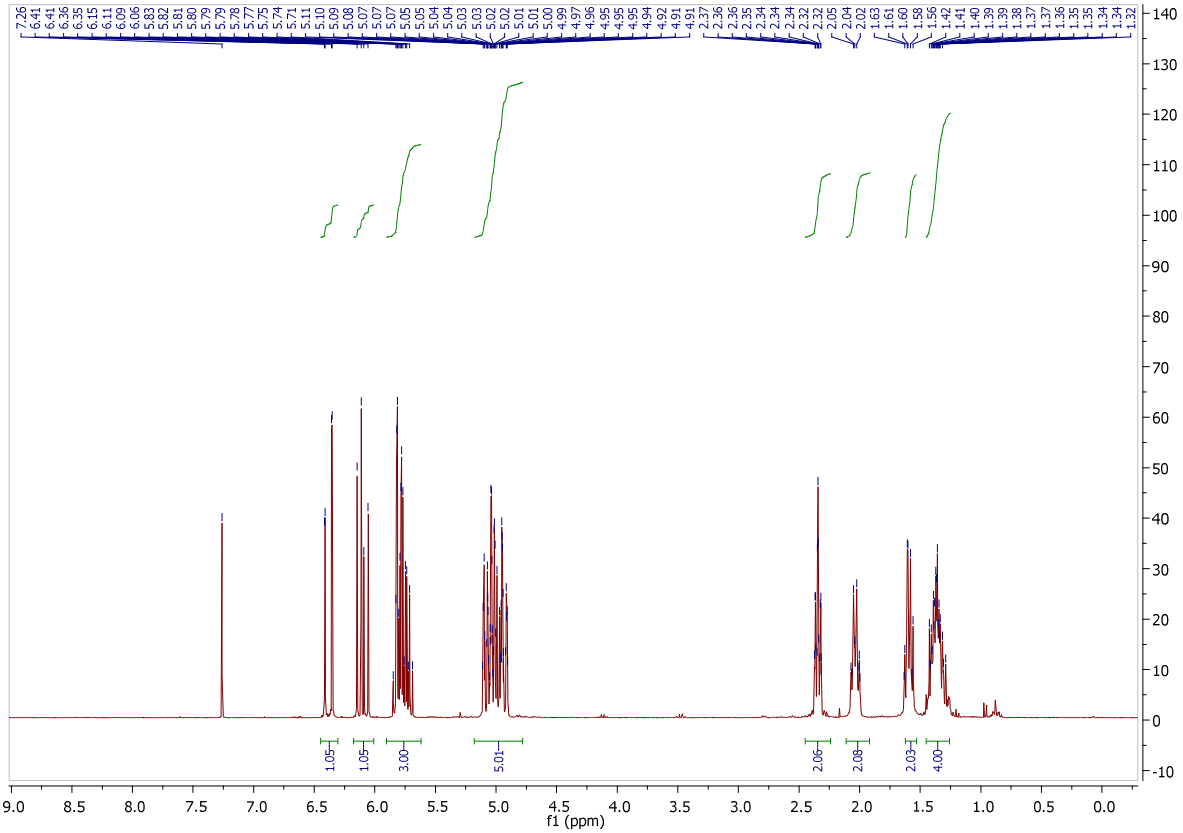
6 – ^{1}H NMR spectrum



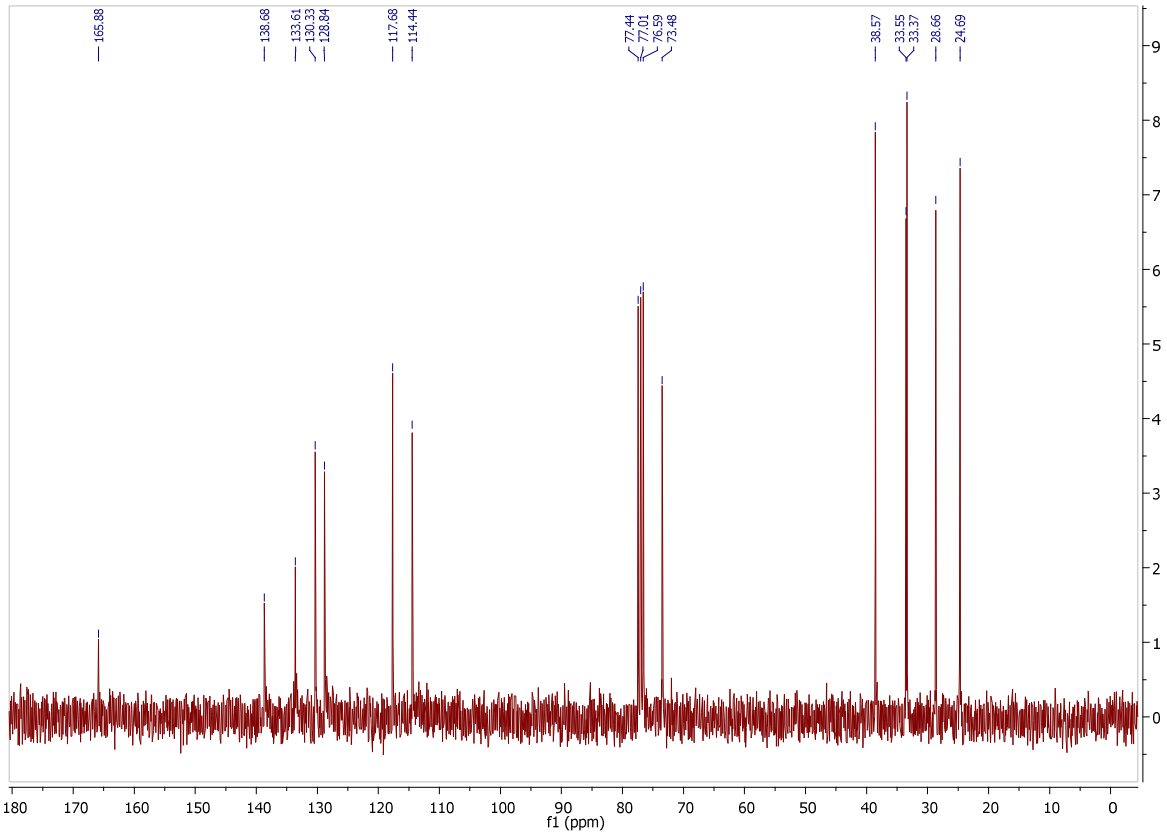
6 – ^{13}C NMR spectrum



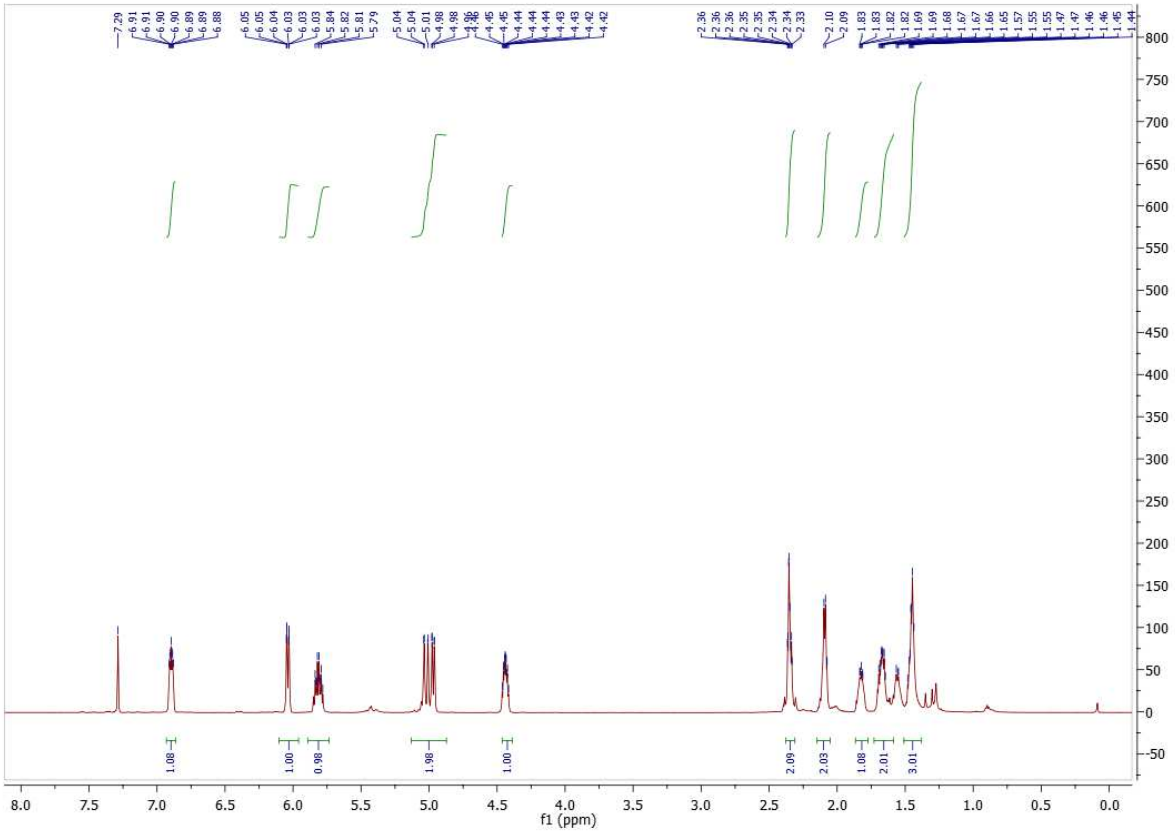
5 – ^{1}H NMR spectrum



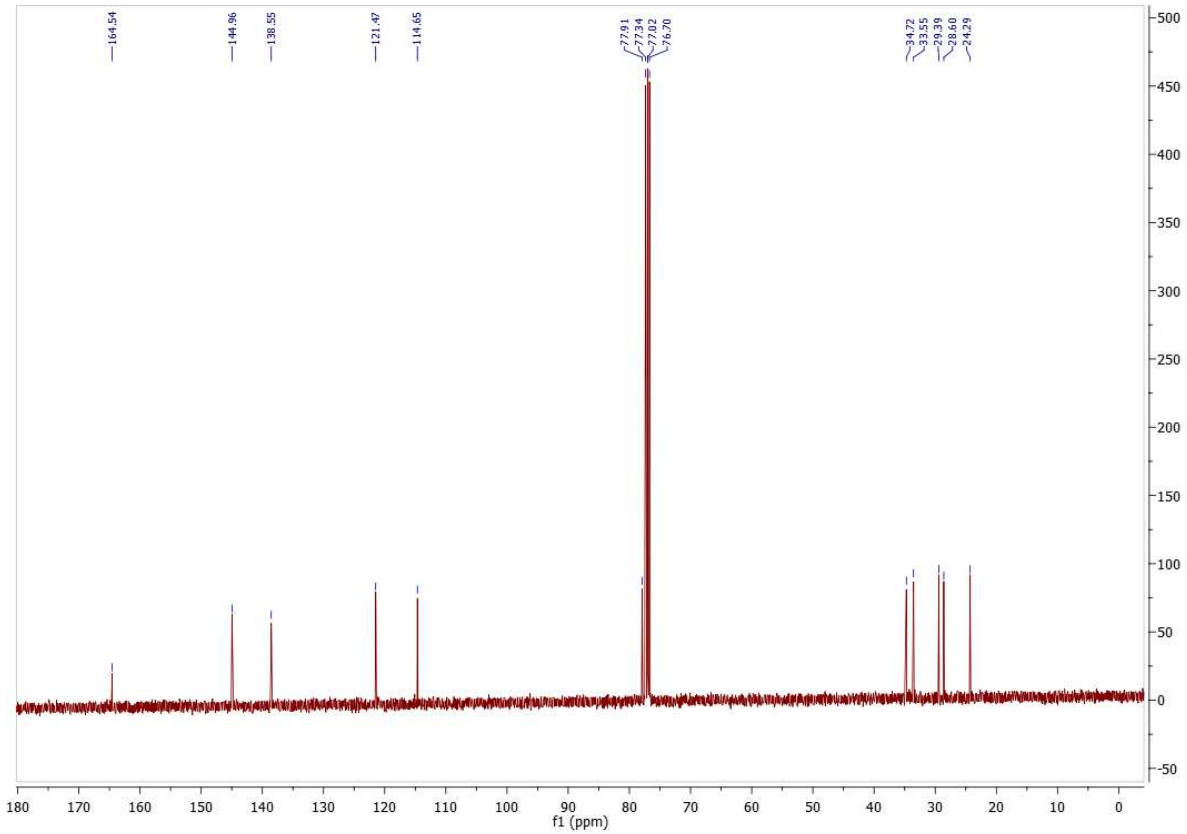
5 – ^{13}C NMR spectrum



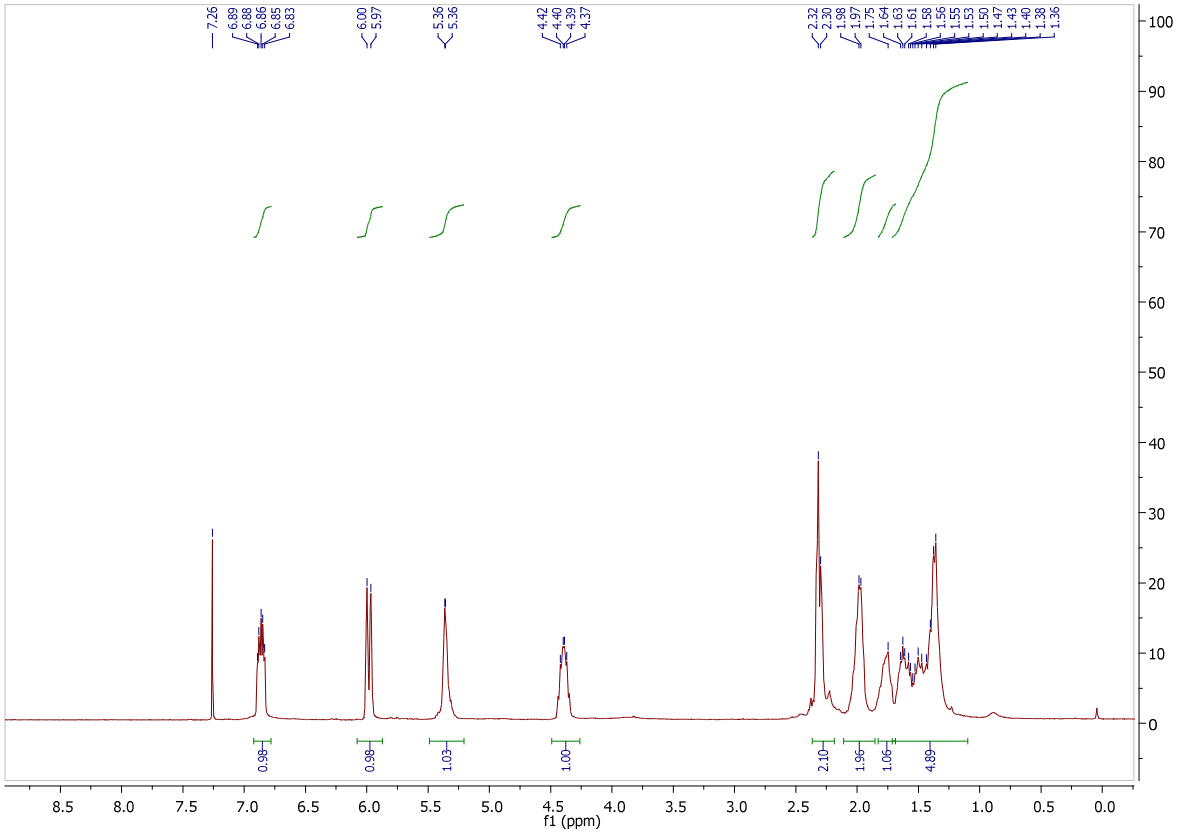
mon-3 – ^{1}H NMR spectrum



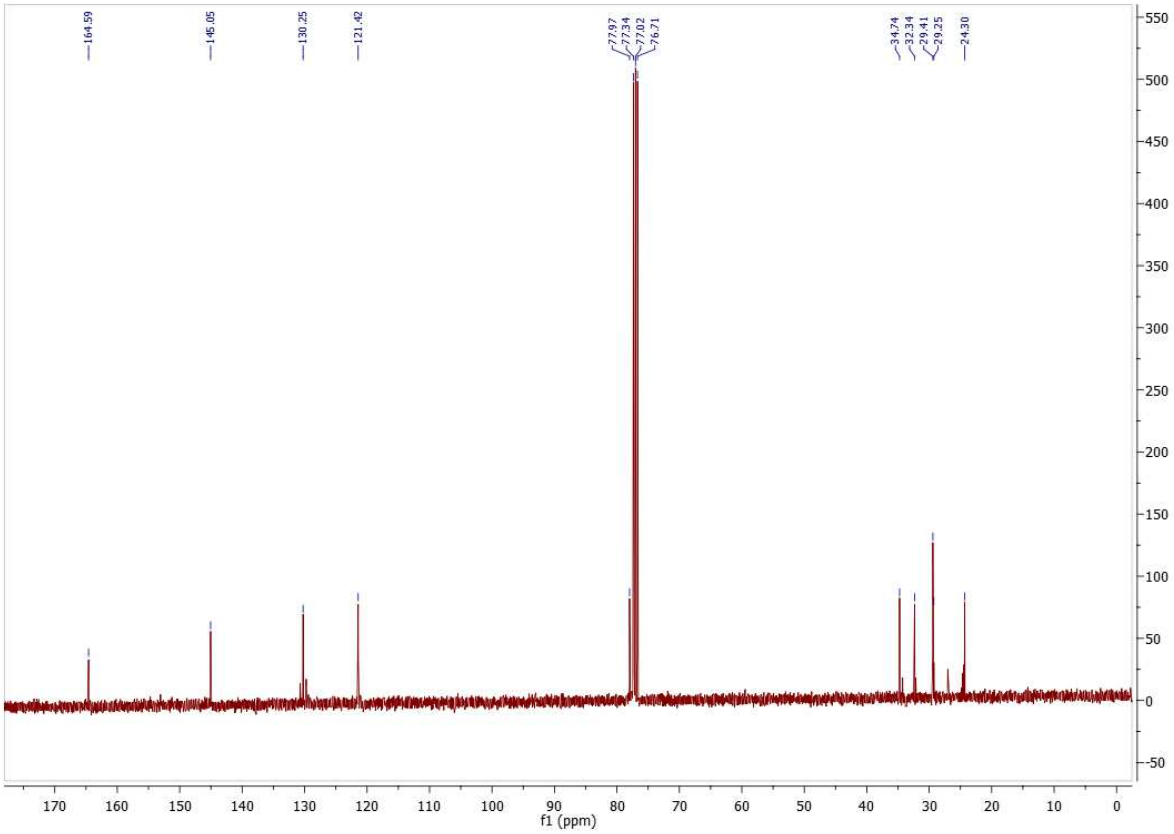
mon-3 – ^{13}C NMR spectrum



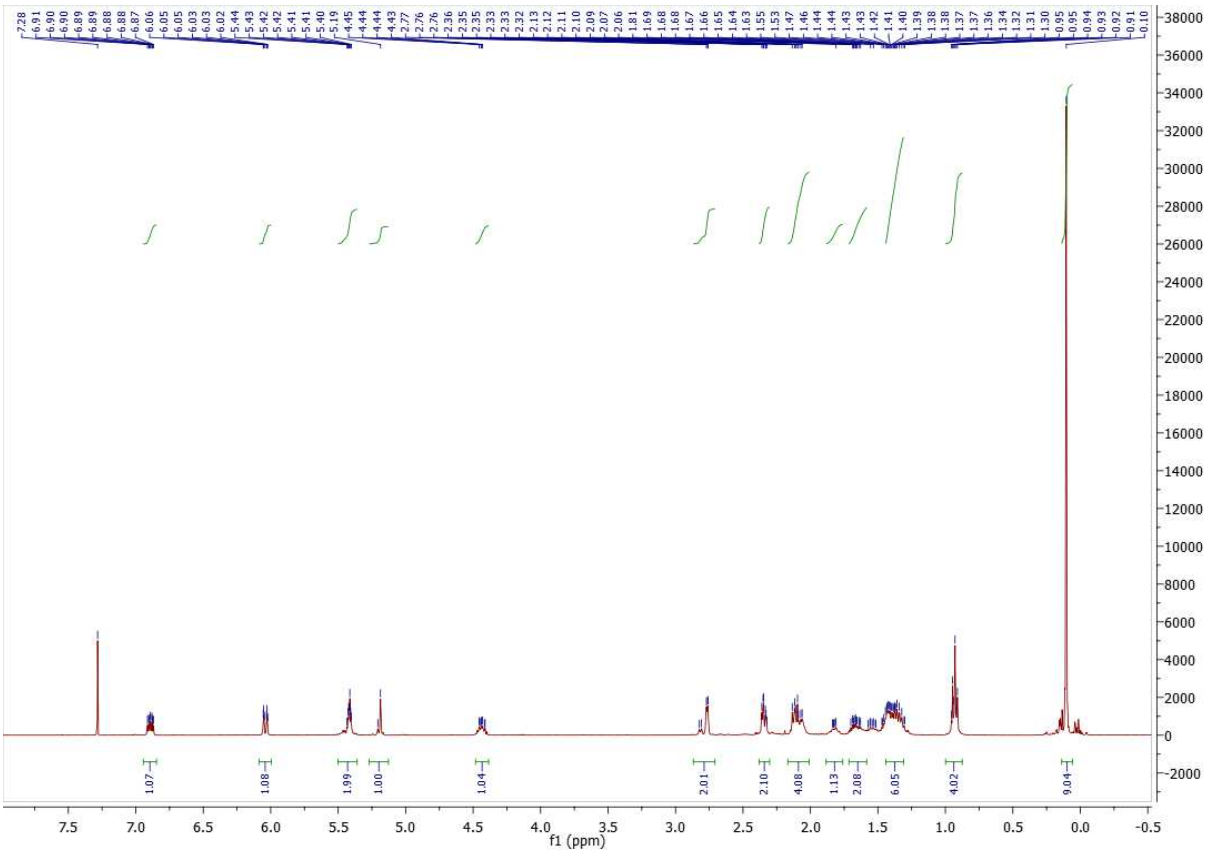
Dim-3 – ^{1}H NMR spectrum



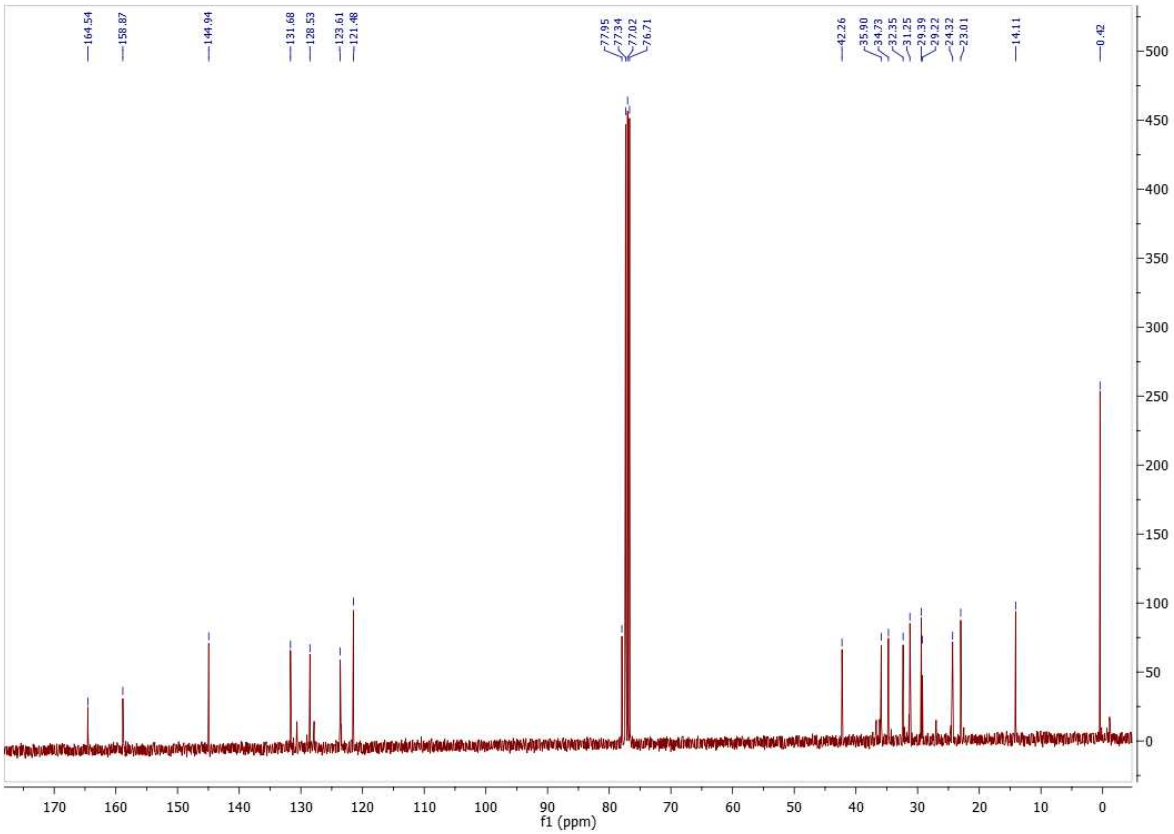
Dim-3 – ^{13}C NMR spectrum



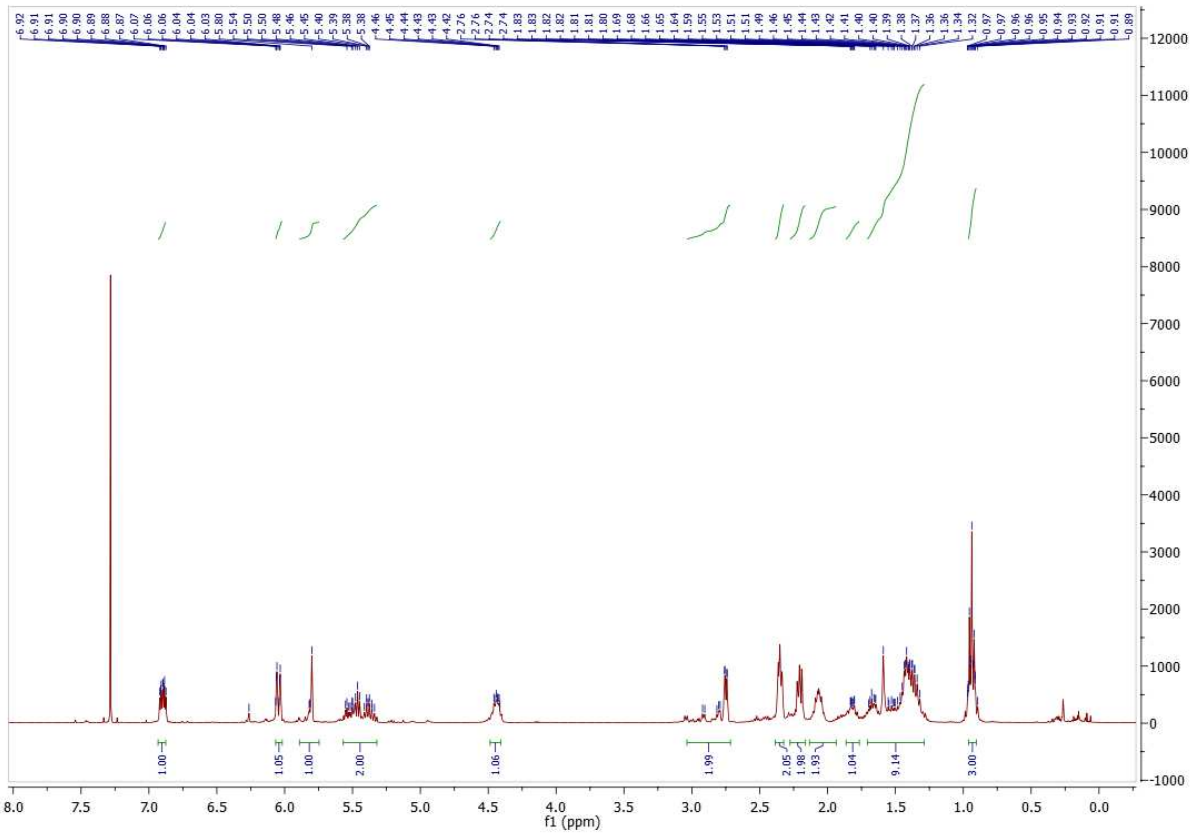
8a – ^{1}H NMR spectrum



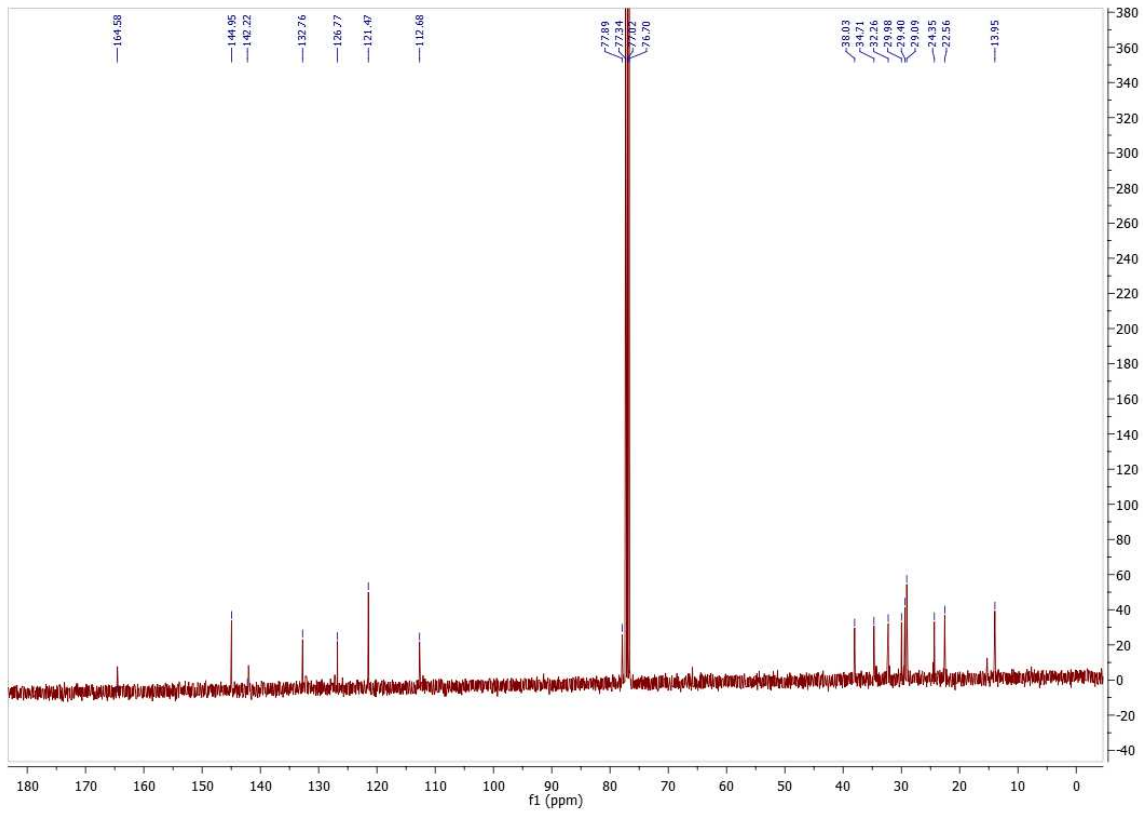
8a – ^{13}C NMR spectrum



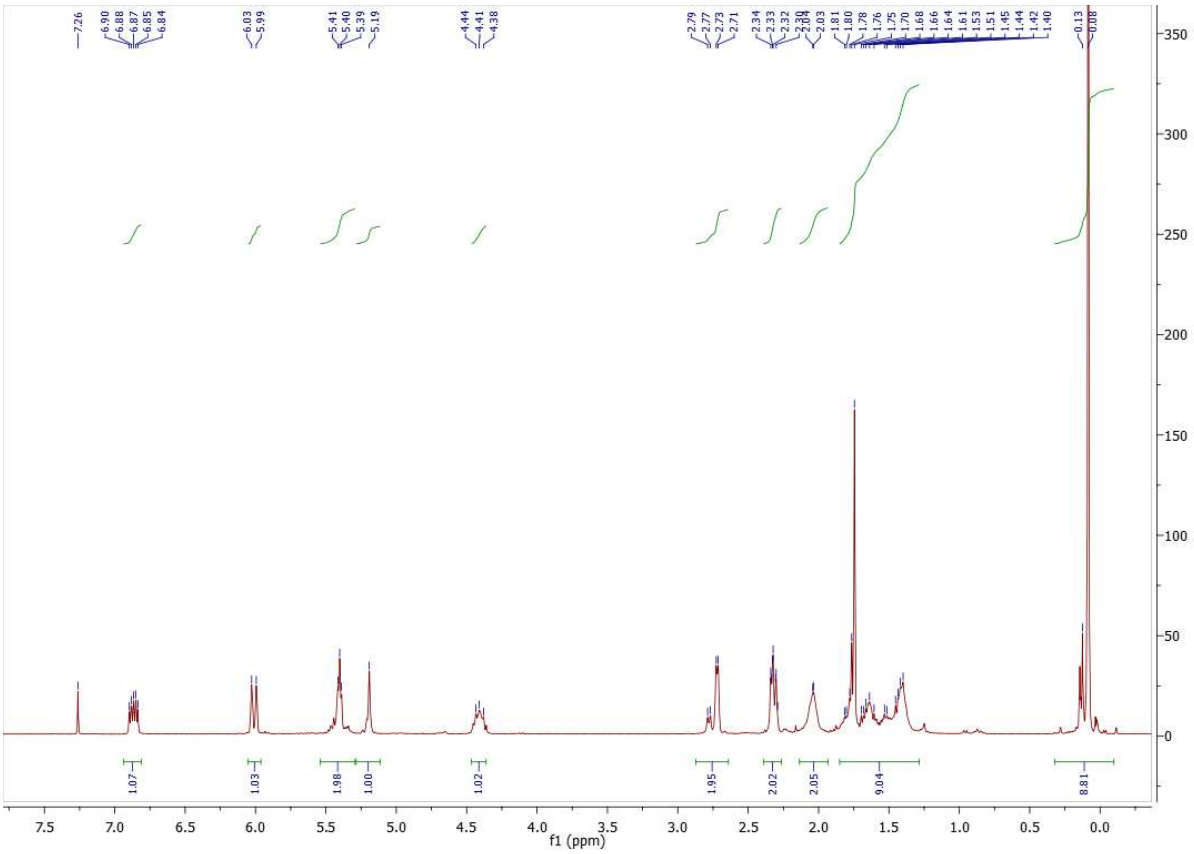
1a – ^{1}H NMR spectrum



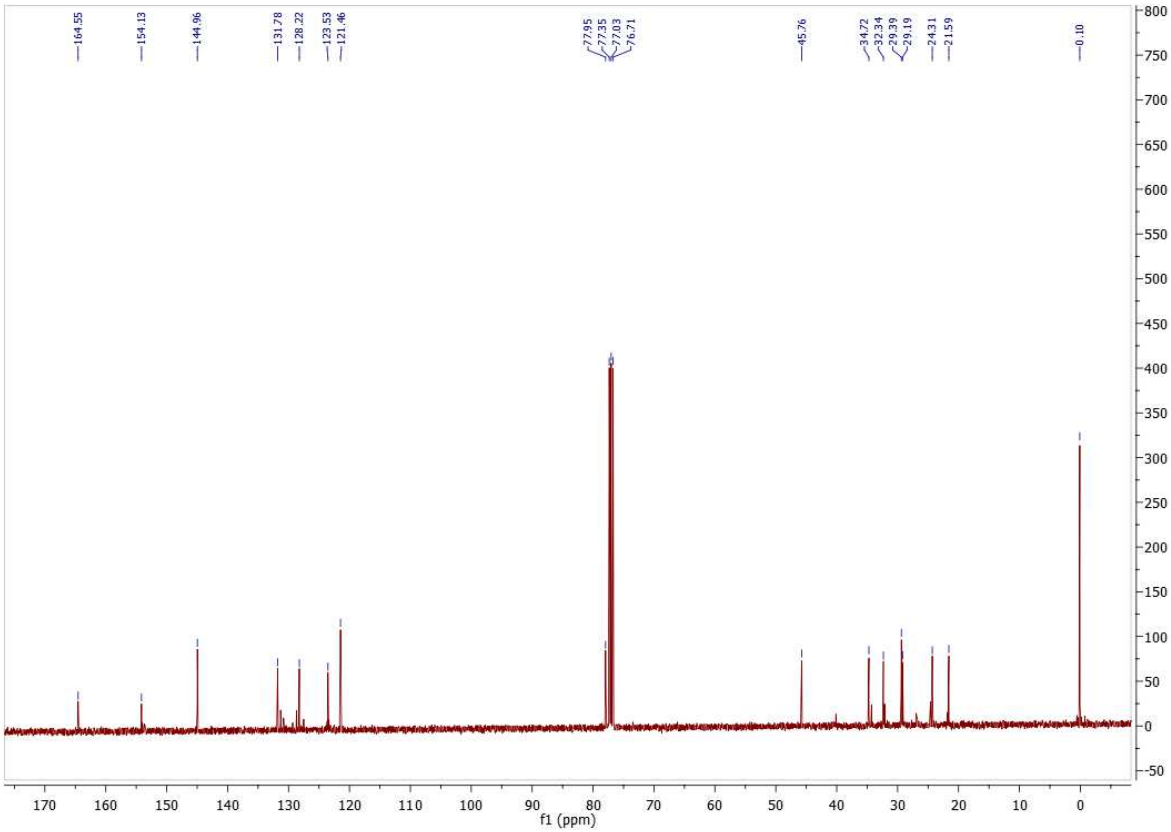
1a – ^{13}C NMR spectrum



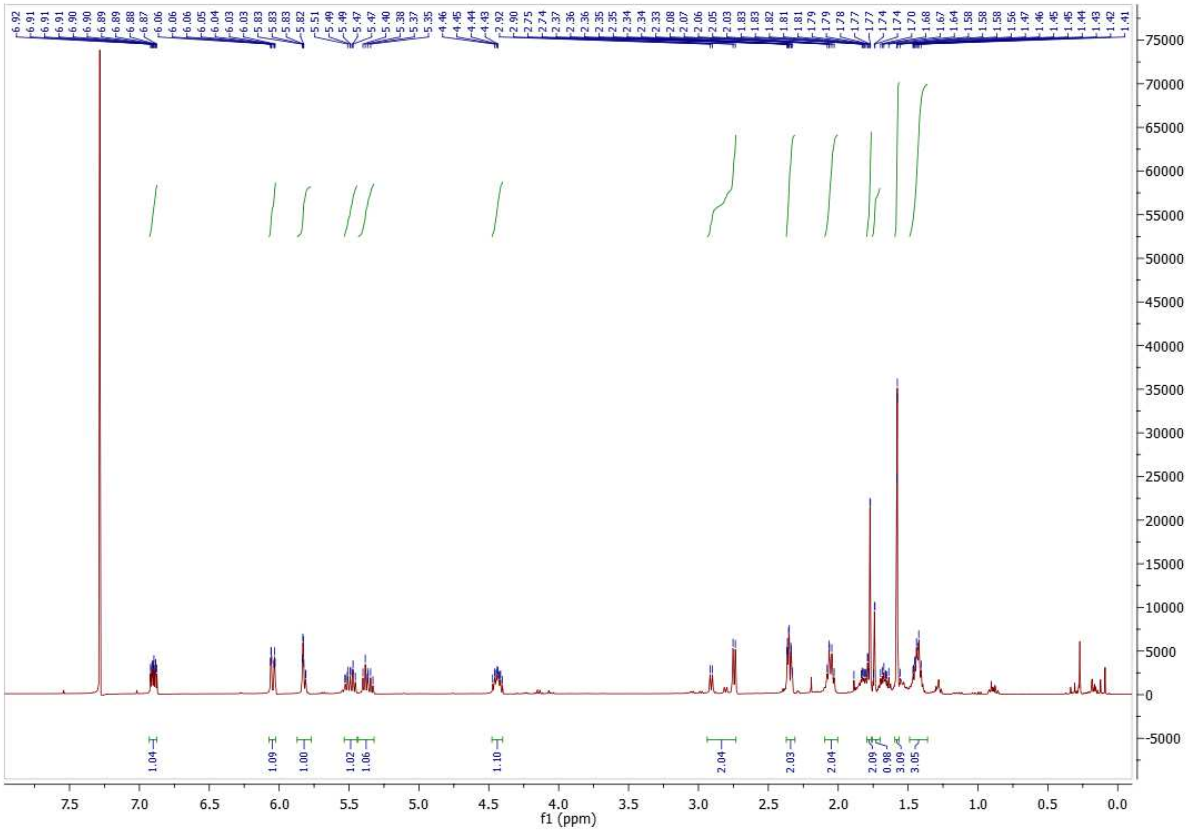
8b – ^{1}H NMR spectrum



8b – ^{13}HCNMR spectrum



1b – ^{1}H NMR spectrum



1b – ^{13}CNMR spectrum