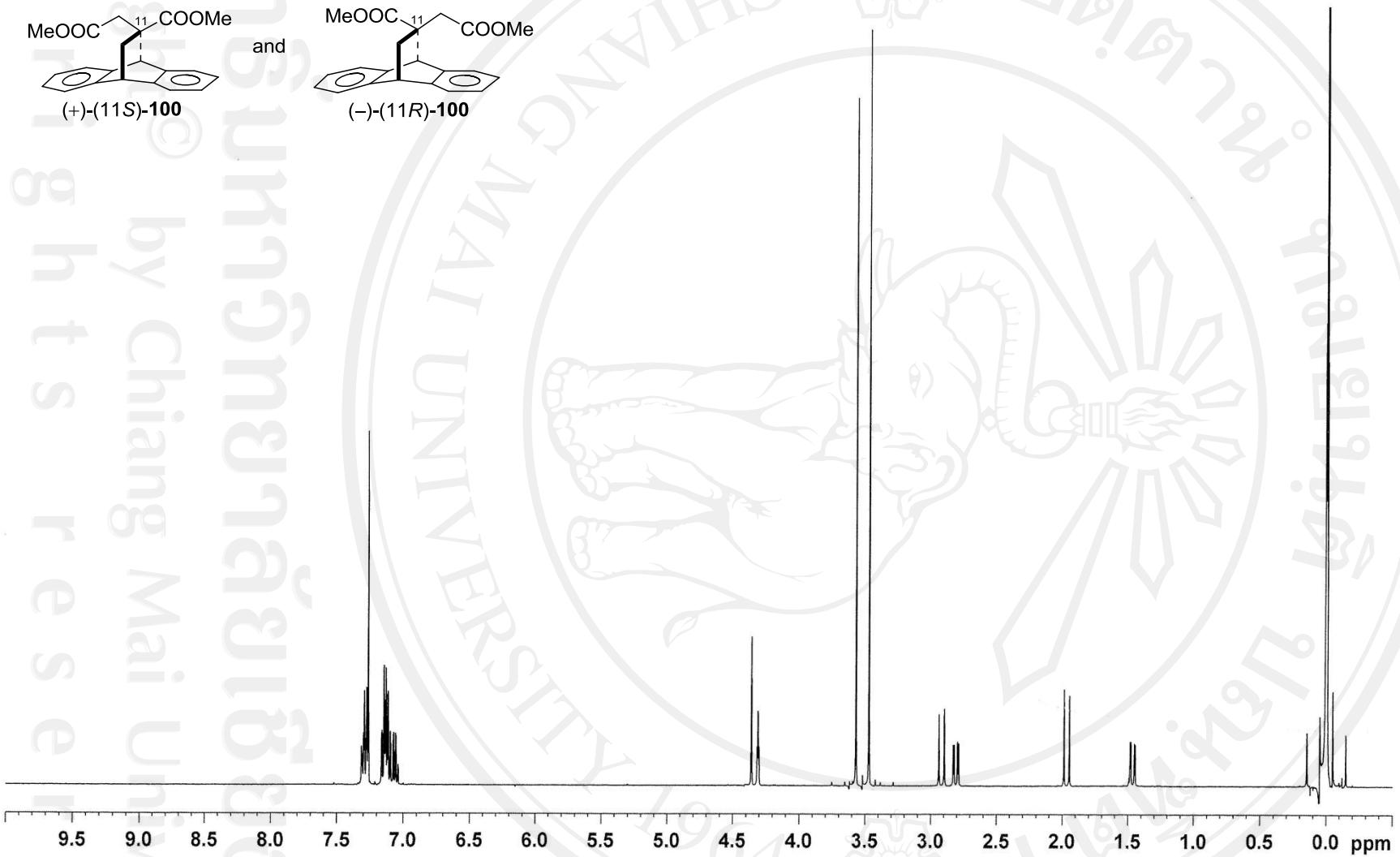
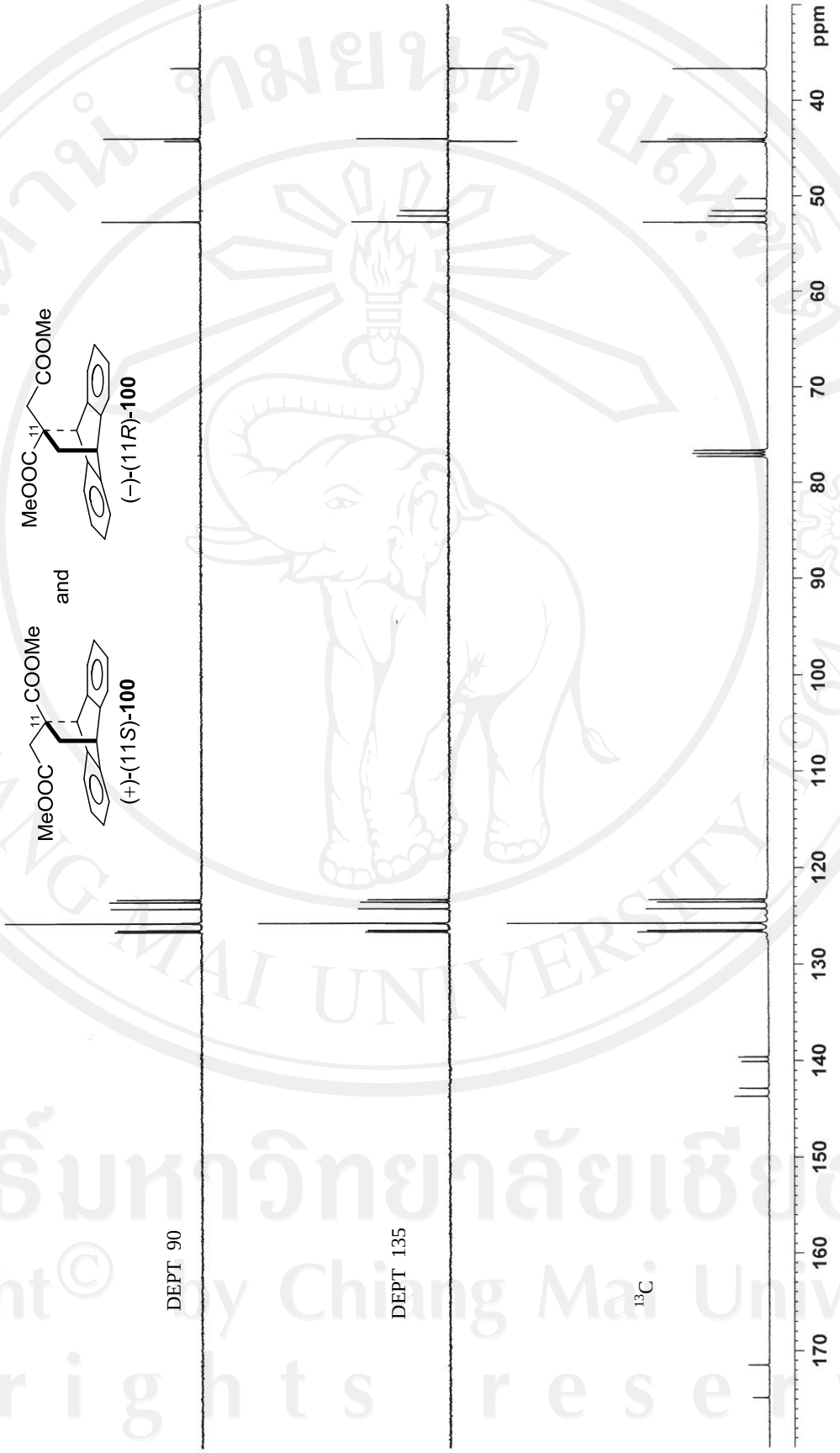
APPENDIX

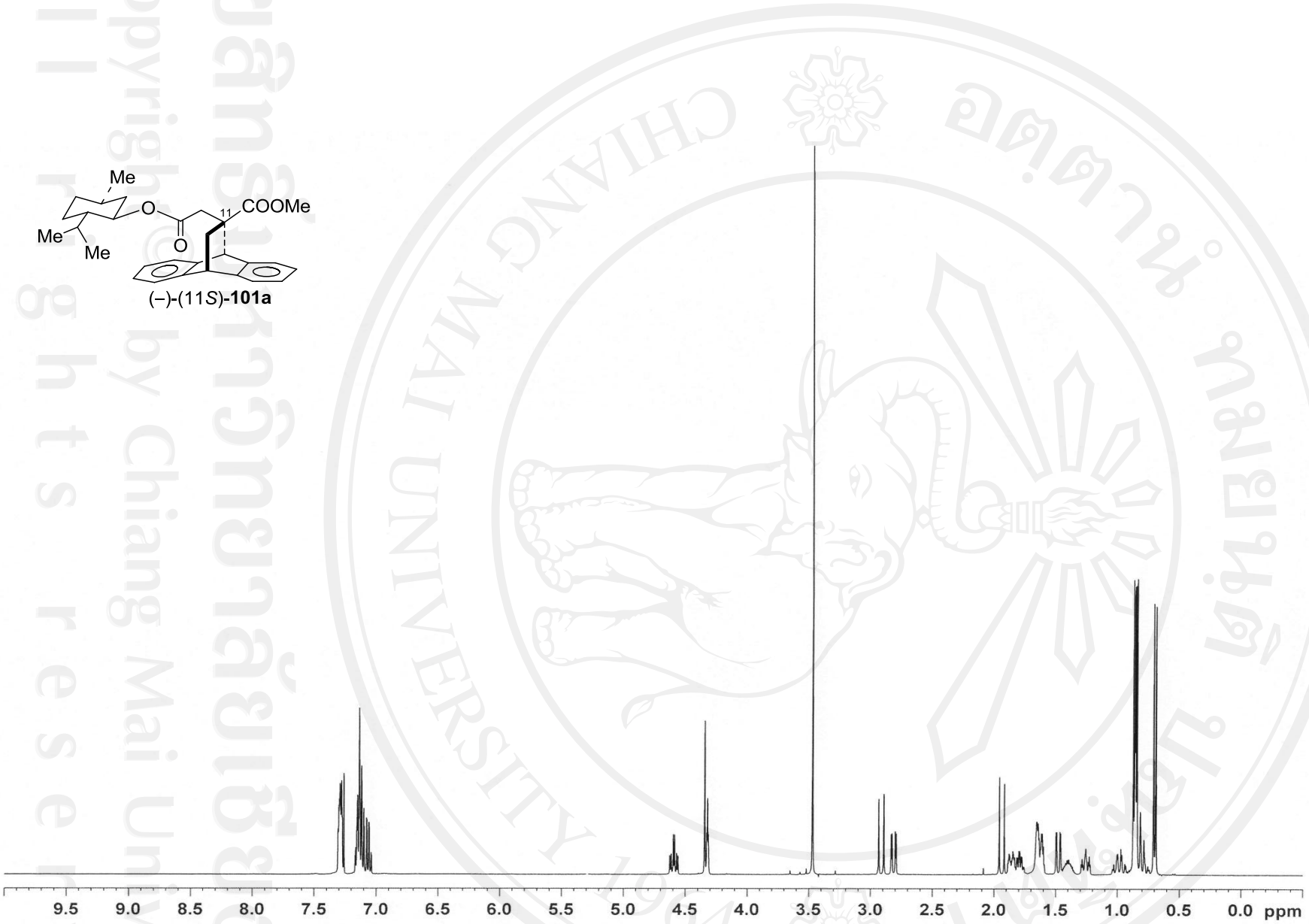
(^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz))



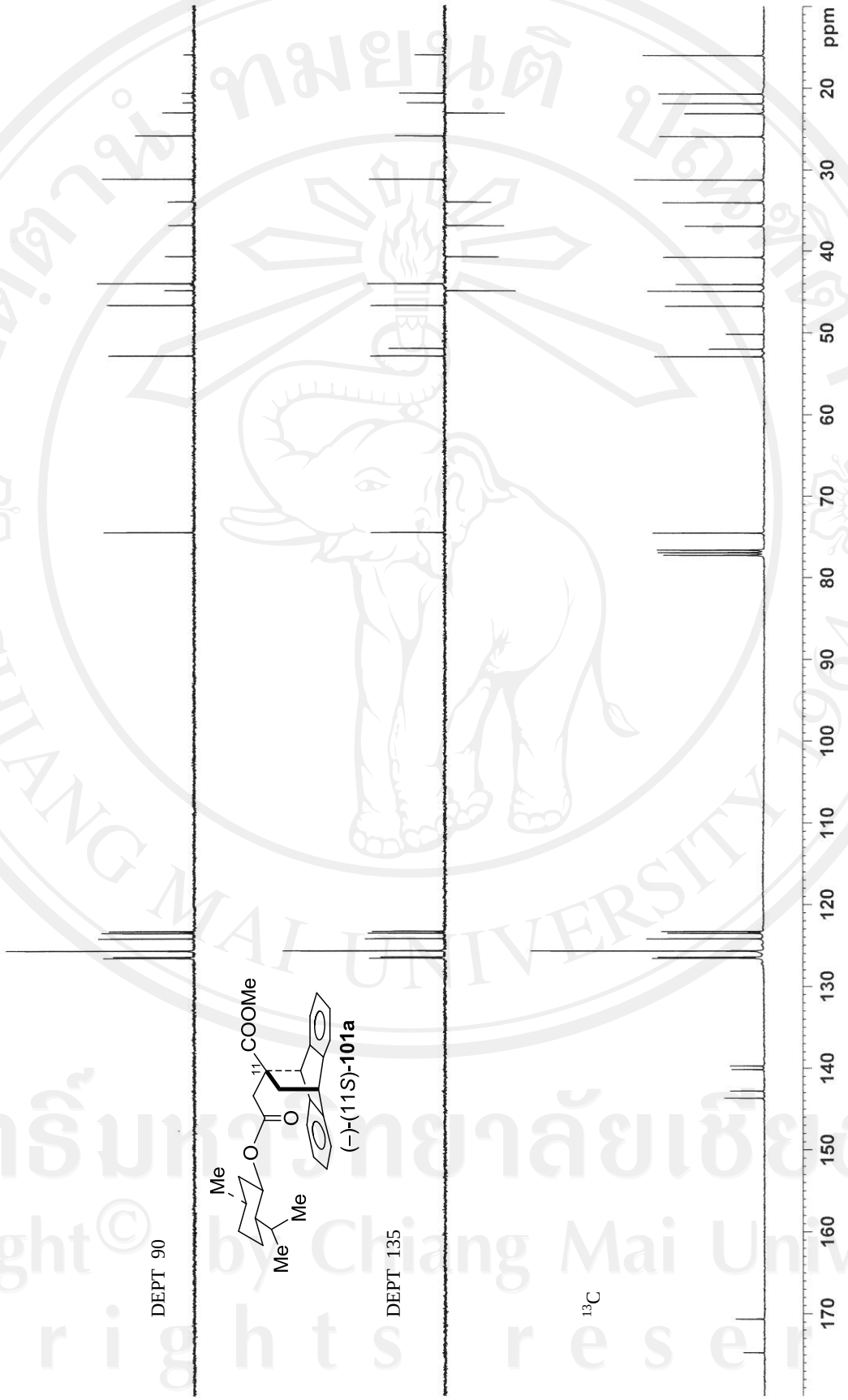
Appendix 1 ^{1}H-NMR spectrum of compounds (+)-(11*S*)-**100** and (–)-(11*R*)-**100**



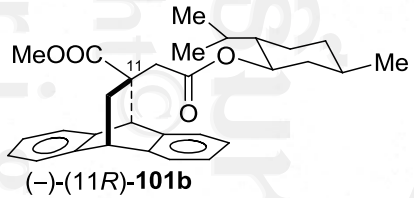
Appendix 2 ^{13}C-NMR spectrum of compounds (+)-(11*S*)-**100** and (–)-(11*R*)-**100**



Appendix 3 ^{1}H-NMR spectrum of compound (−)-(11*S*)-**101a**

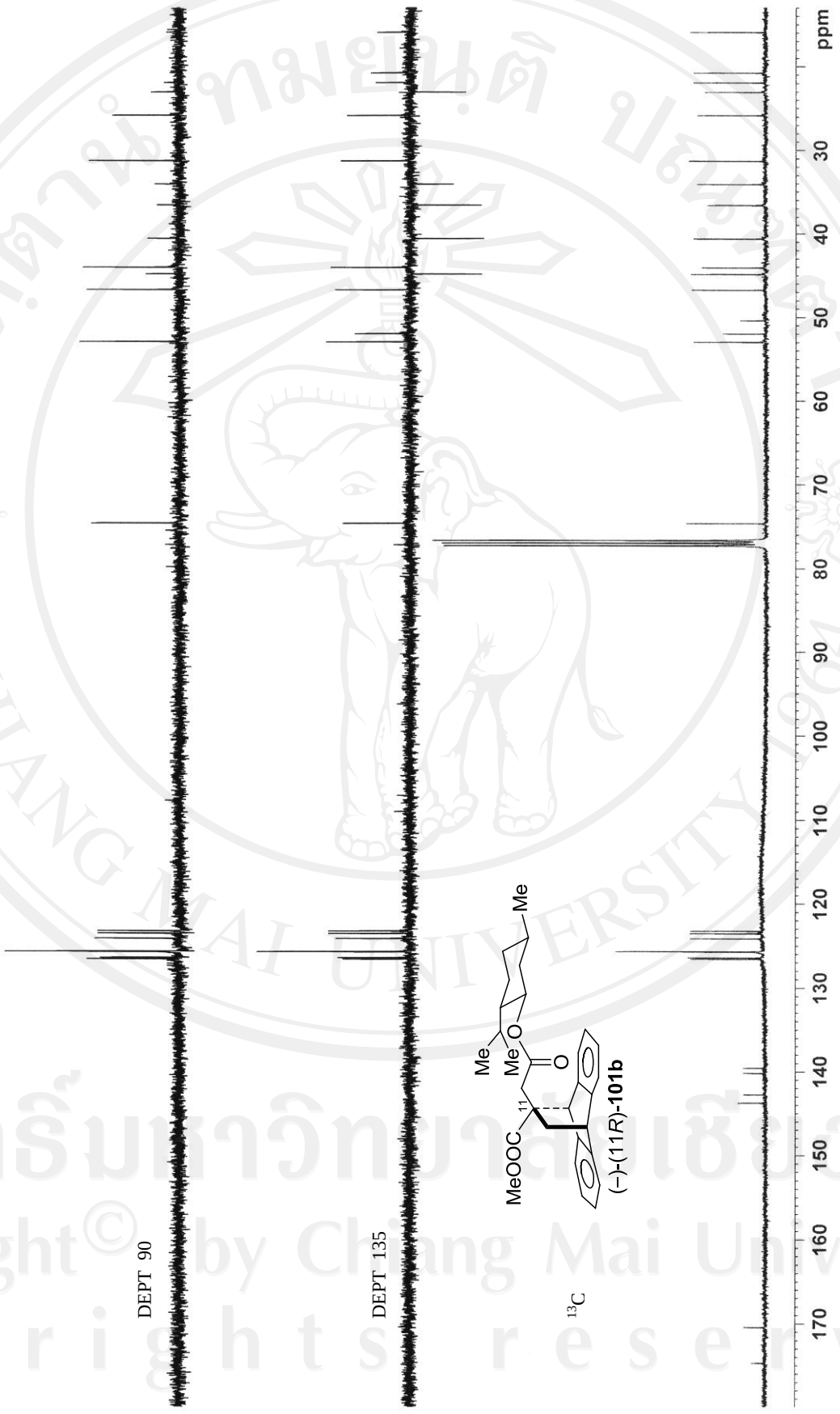


Appendix 4 ^{13}C-NMR spectrum of compound (–)-(11*S*)-**101a**

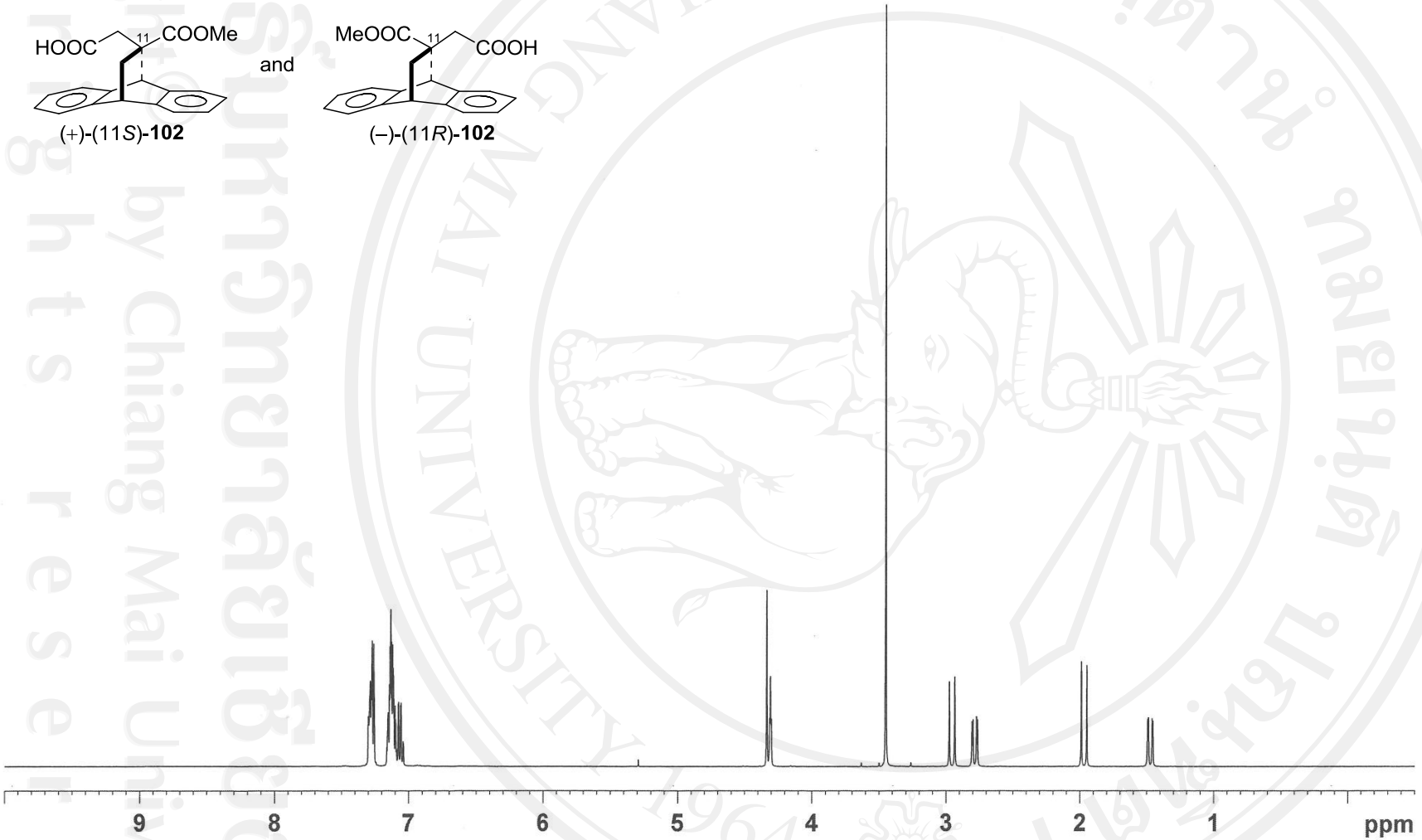


(–)-(11*R*)-**101b**

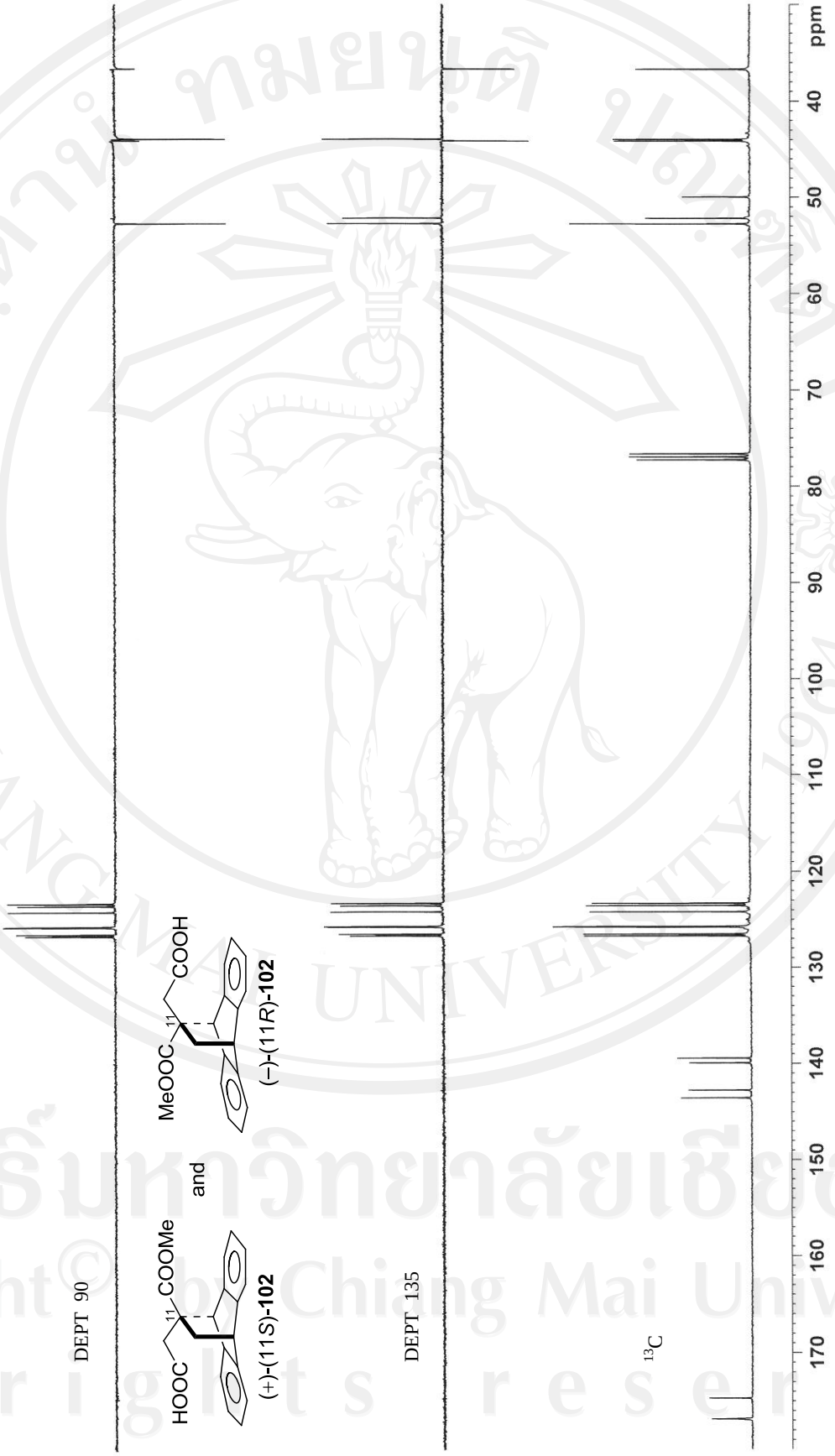
Appendix 5 ^{1}H-NMR spectrum of compound (–)-(11*R*)-**101b**



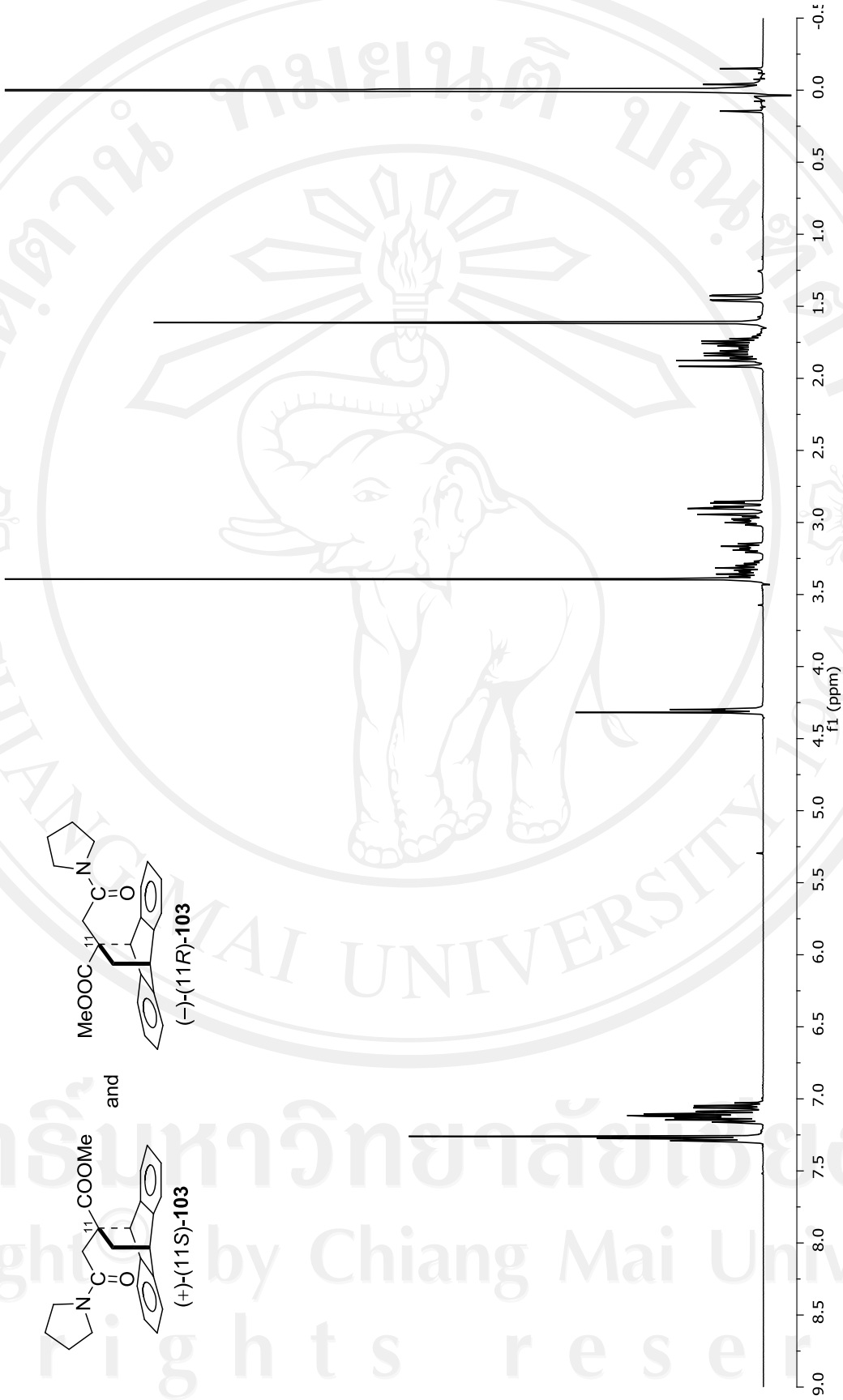
Appendix 6 ^{13}C-NMR spectrum of compound (–)-(11*R*)-**101b**



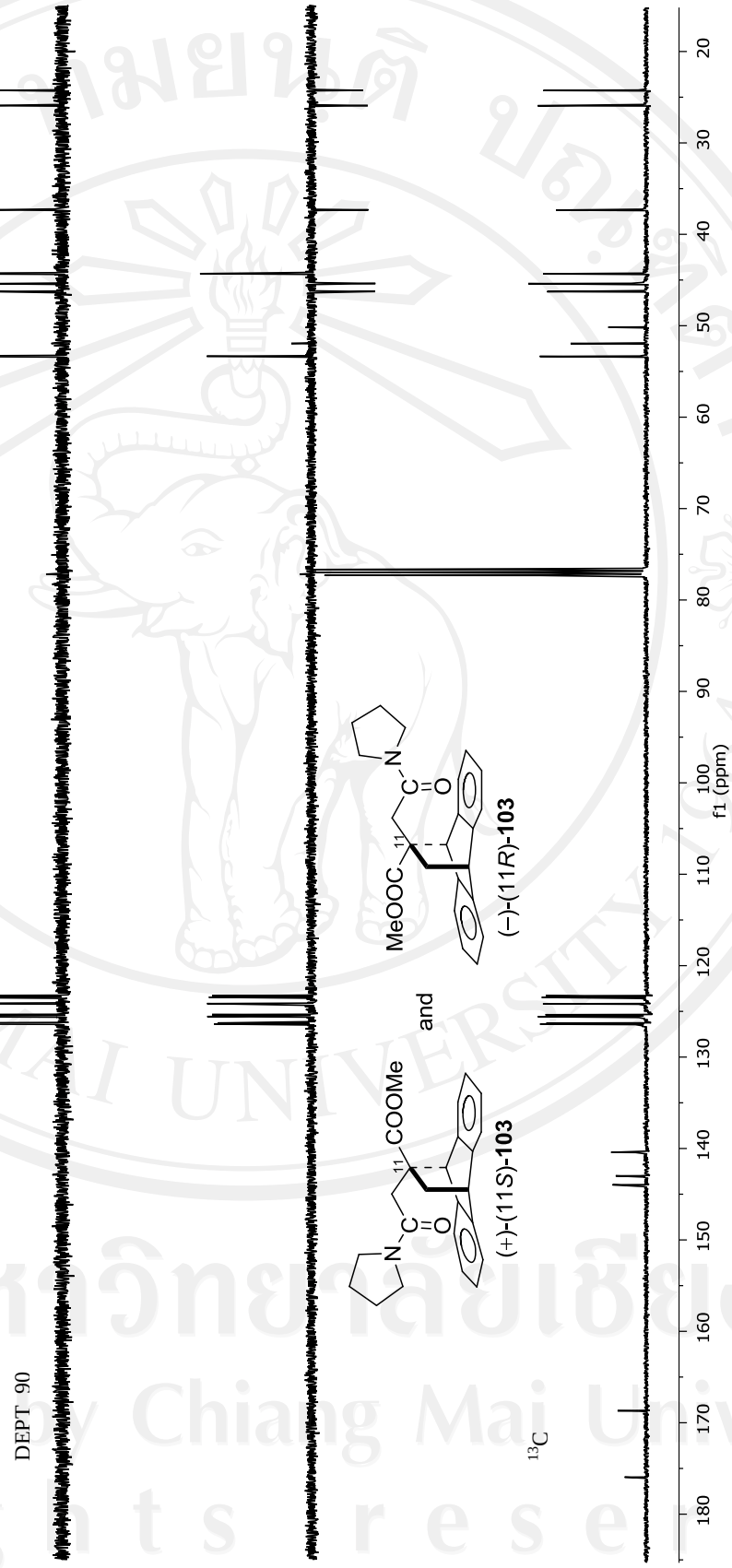
Appendix 7 ^{1}H-NMR spectrum of compounds (+)-(11*S*)-**102** and (–)-(11*R*)-**102**



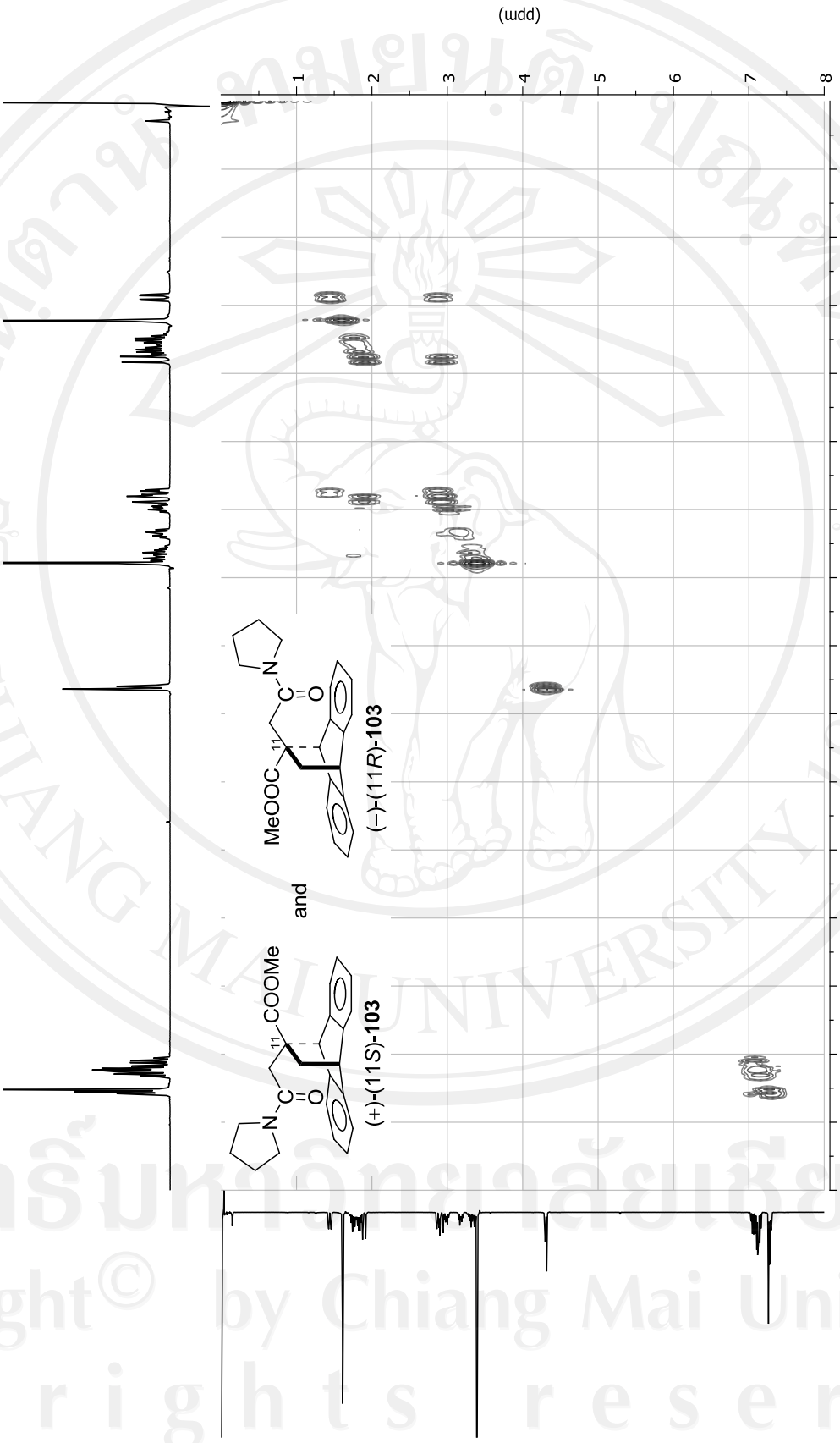
Appendix 8 ^{13}C-NMR spectrum of compounds (+)-(11*S*)-**102** and (–)-(11*R*)-**102**



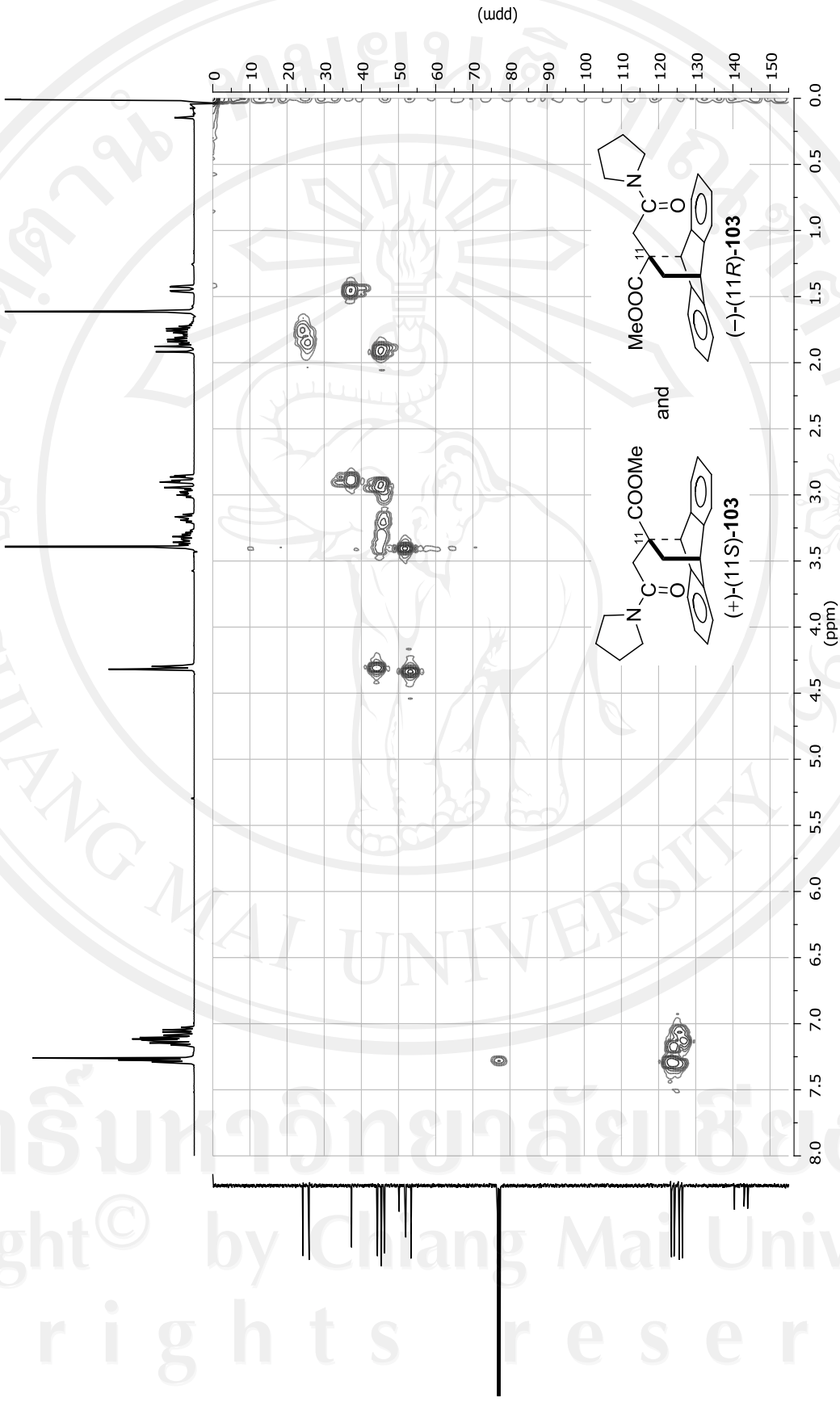
Appendix 9 ^{1}H-NMR spectrum of compounds (+)-(11*S*)-**103** and (–)-(11*R*)-**103**



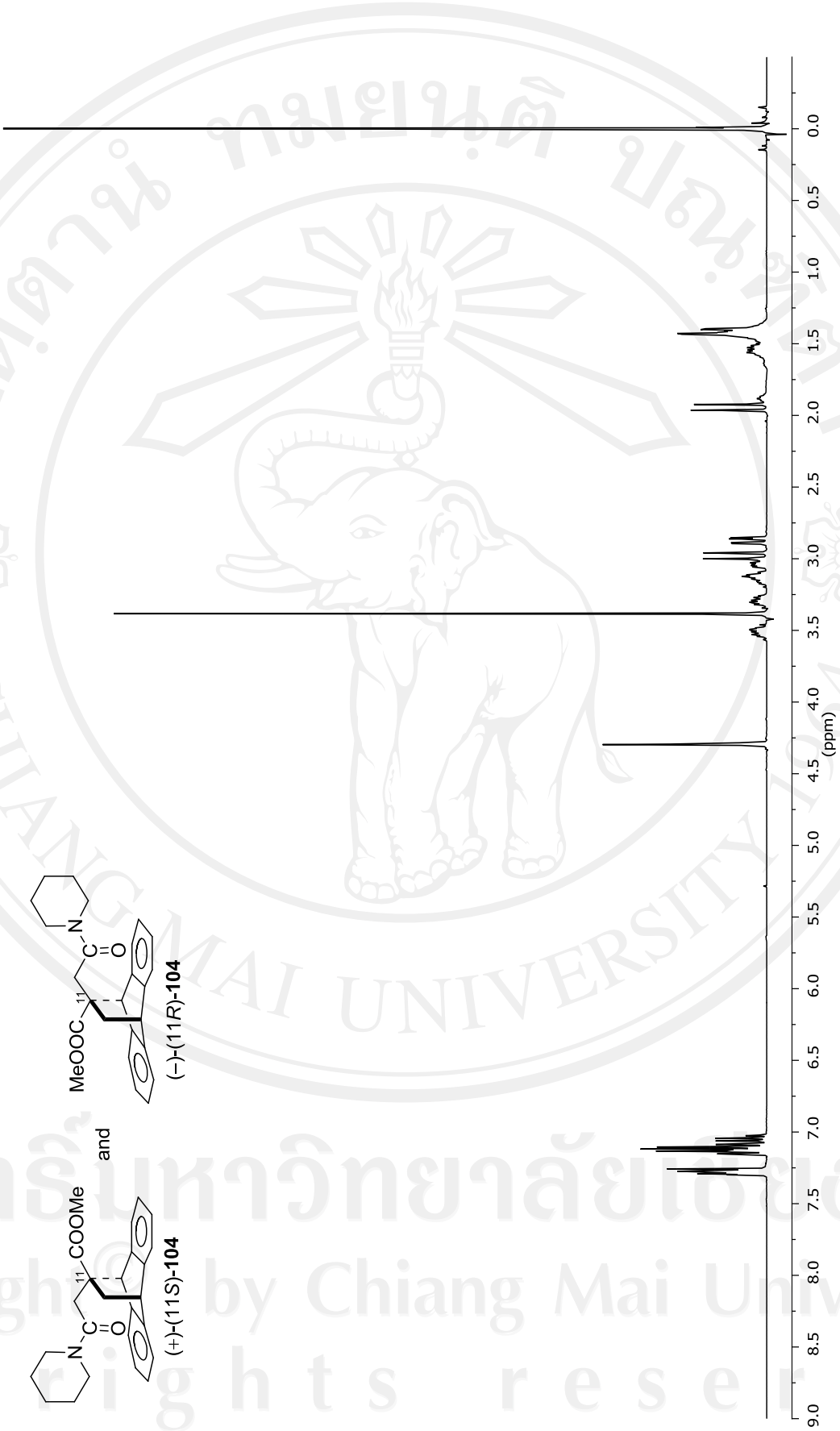
Appendix 10 ^{13}C-NMR spectrum of compounds (+)-(11*S*)-**10**3 and (–)-(11*R*)-**10**3



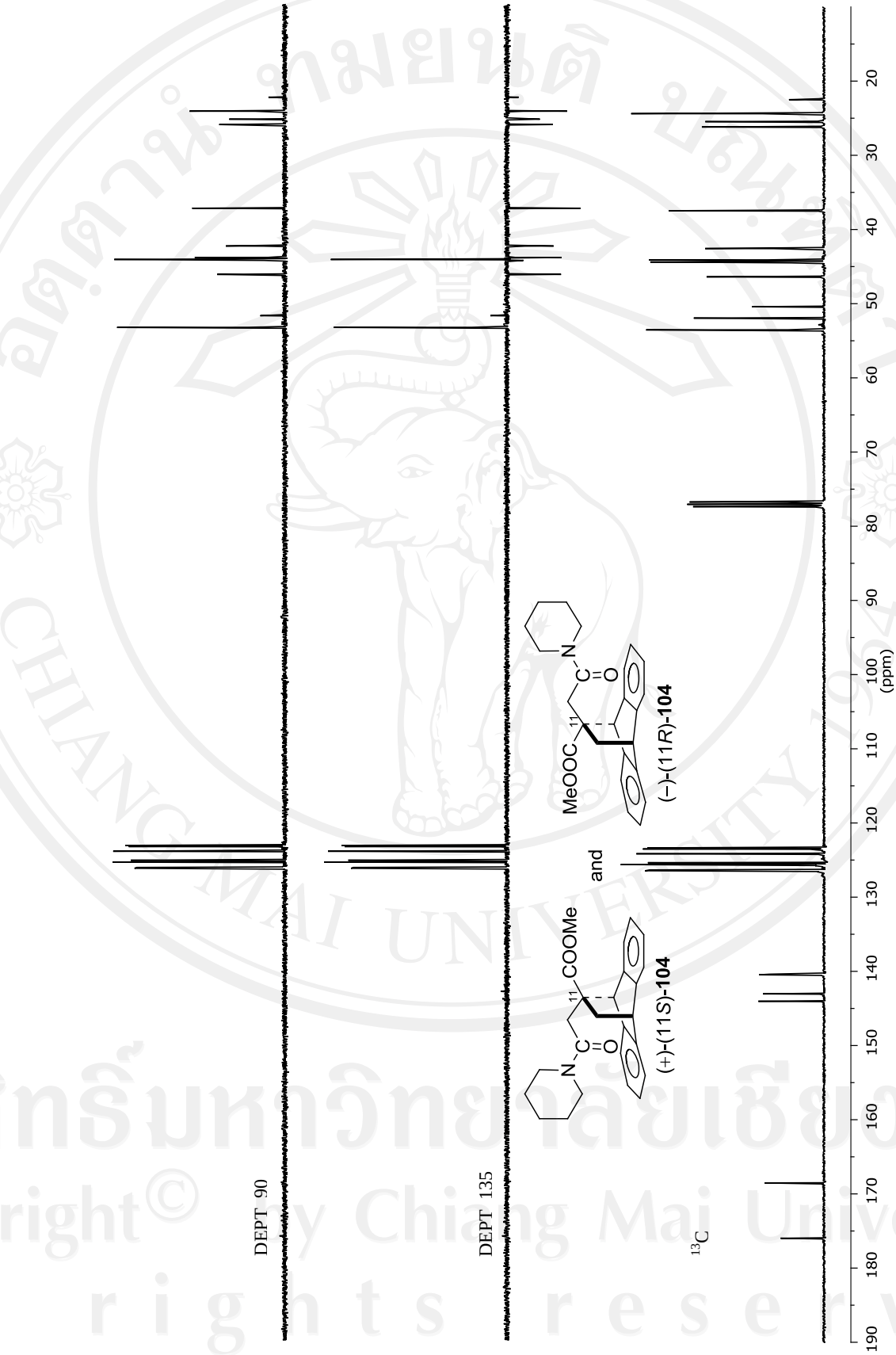
Appendix 11 COSY spectrum of compounds (+)-(11*S*)-**10**3 and (−)-(11*R*)-**10**3



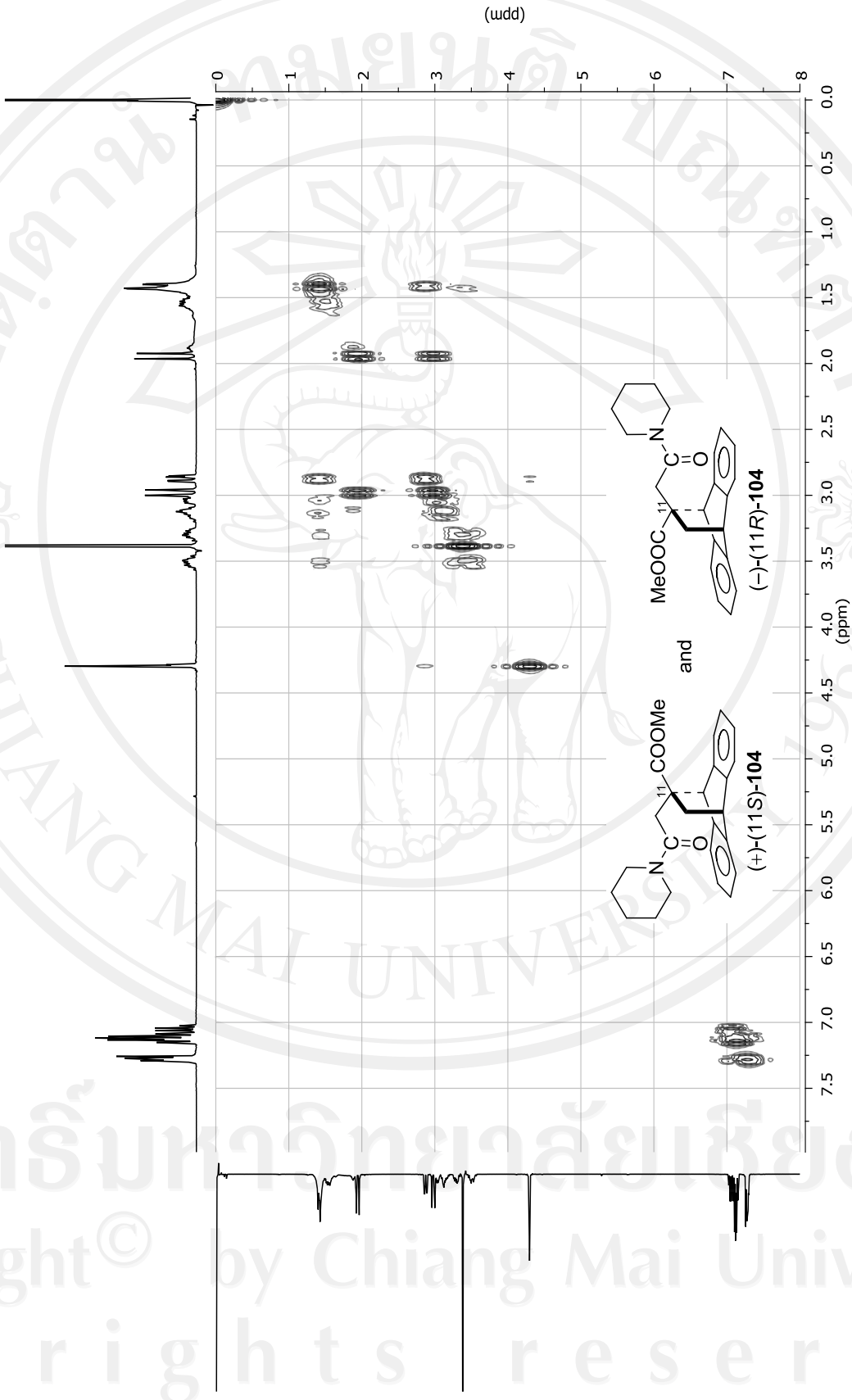
Appendix 12 HMQC spectrum of compounds (+)-(11*S*)-**103** and (−)-(11*R*)-**10**3



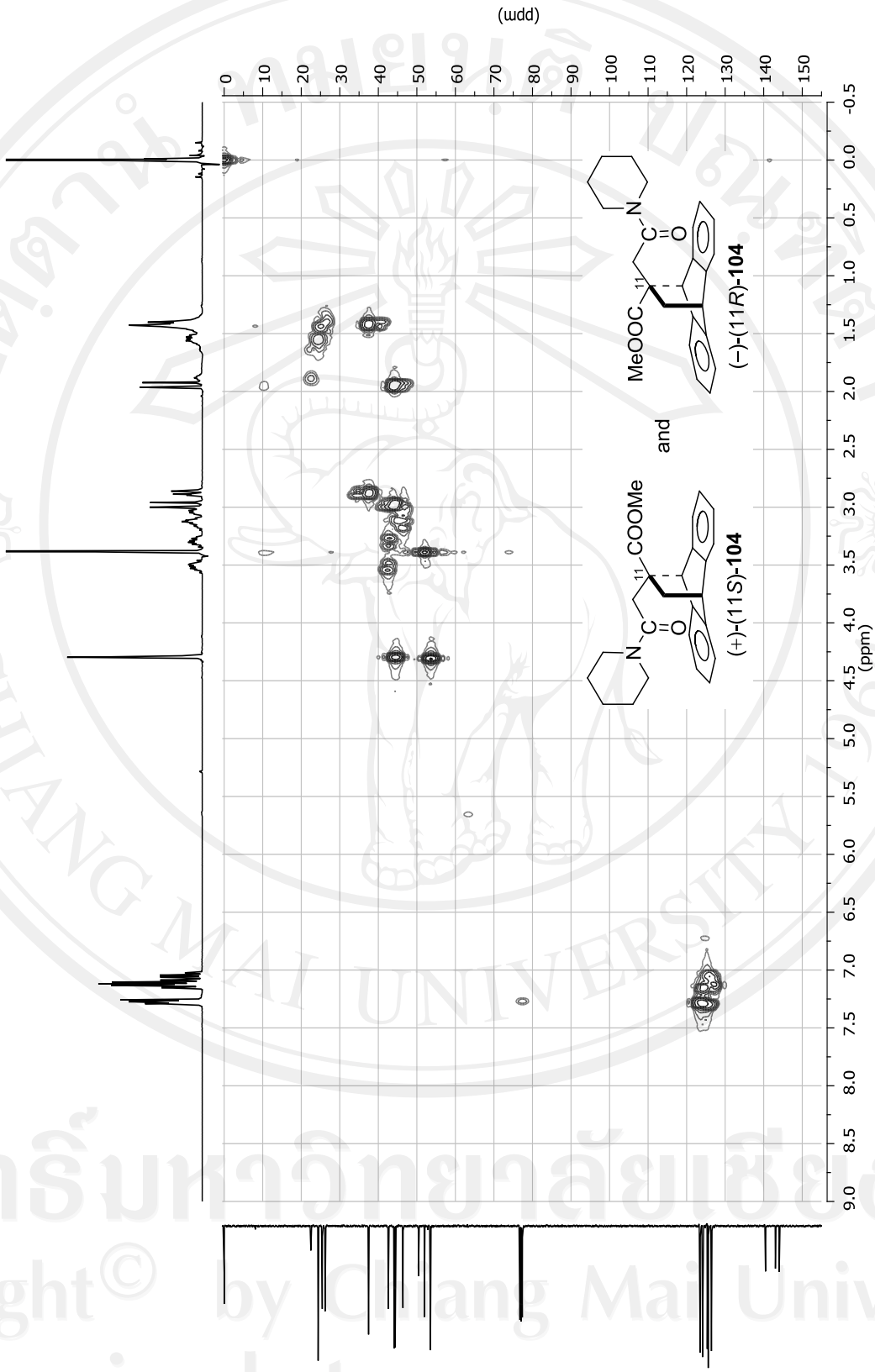
Appendix 13 ^{1}H-NMR spectrum of compounds (+)-(11*S*)-**104** and (−)-(11*R*)-**104**



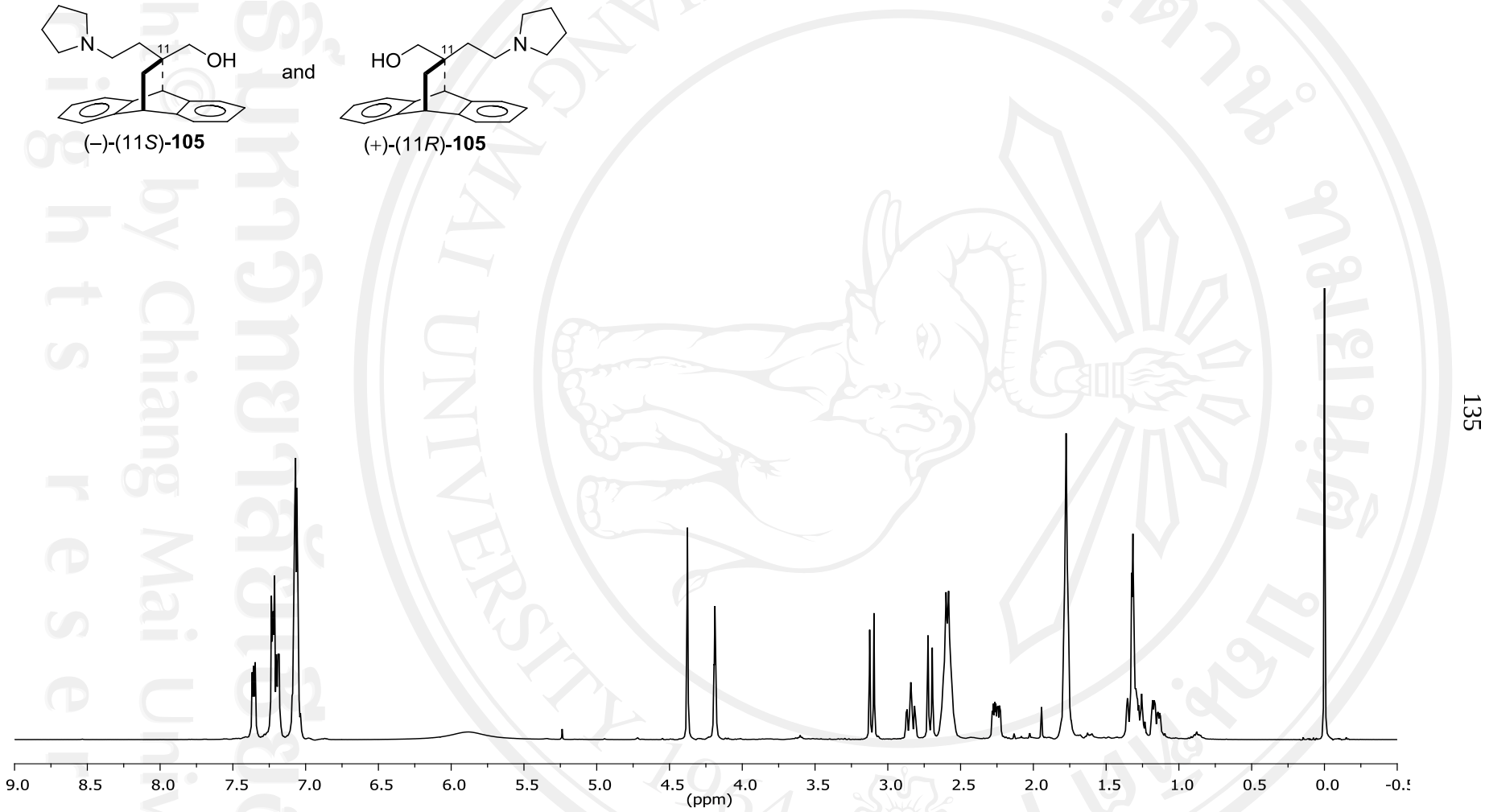
Appendix 14 ^{13}C-NMR spectrum of compounds (+)-(11*S*)-**104** and (–)-(11*R*)-**104**



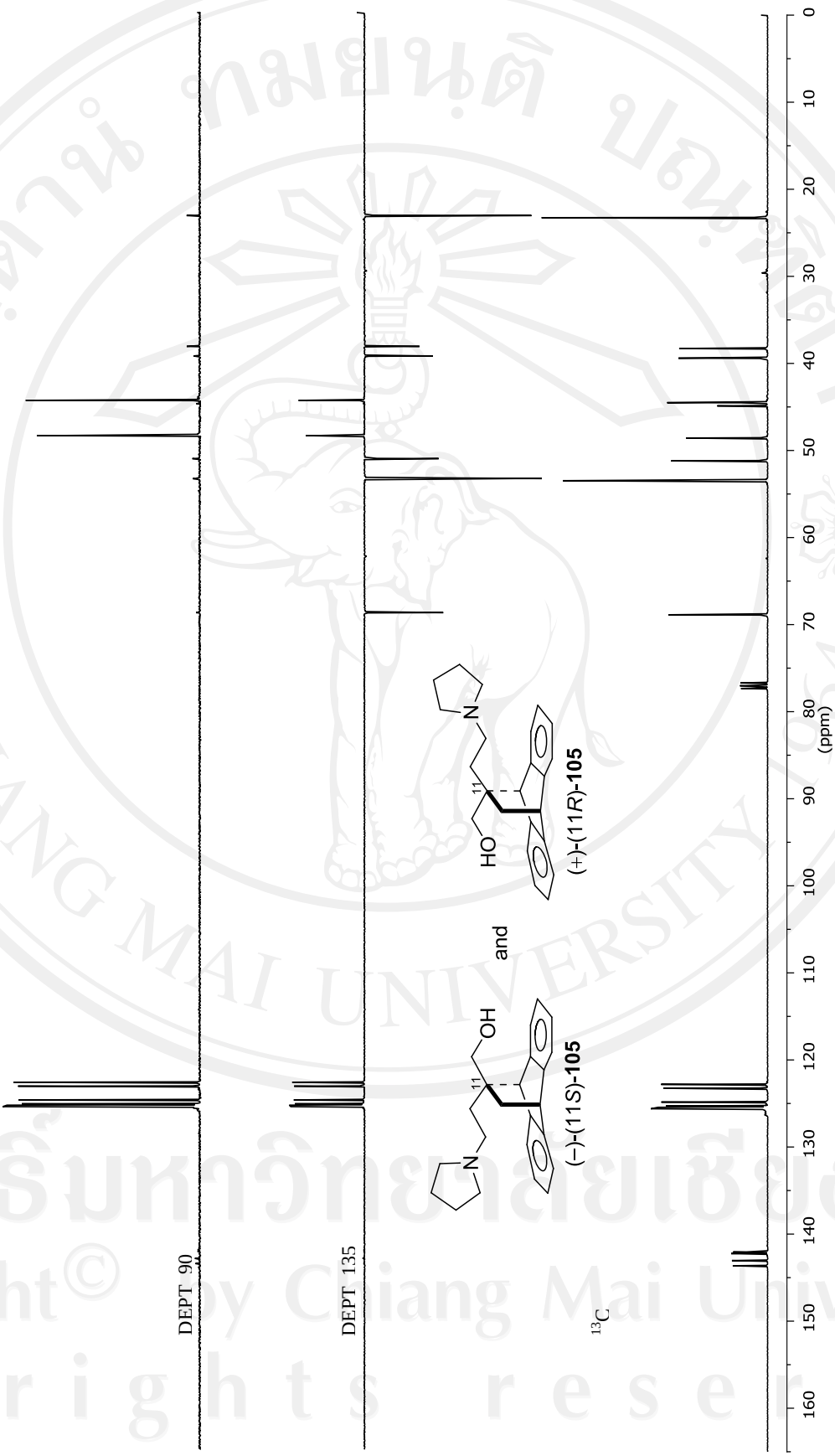
Appendix 15 HMQC spectrum of compounds (+)-(11*S*)-**104** and (−)-(11*R*)-**104**



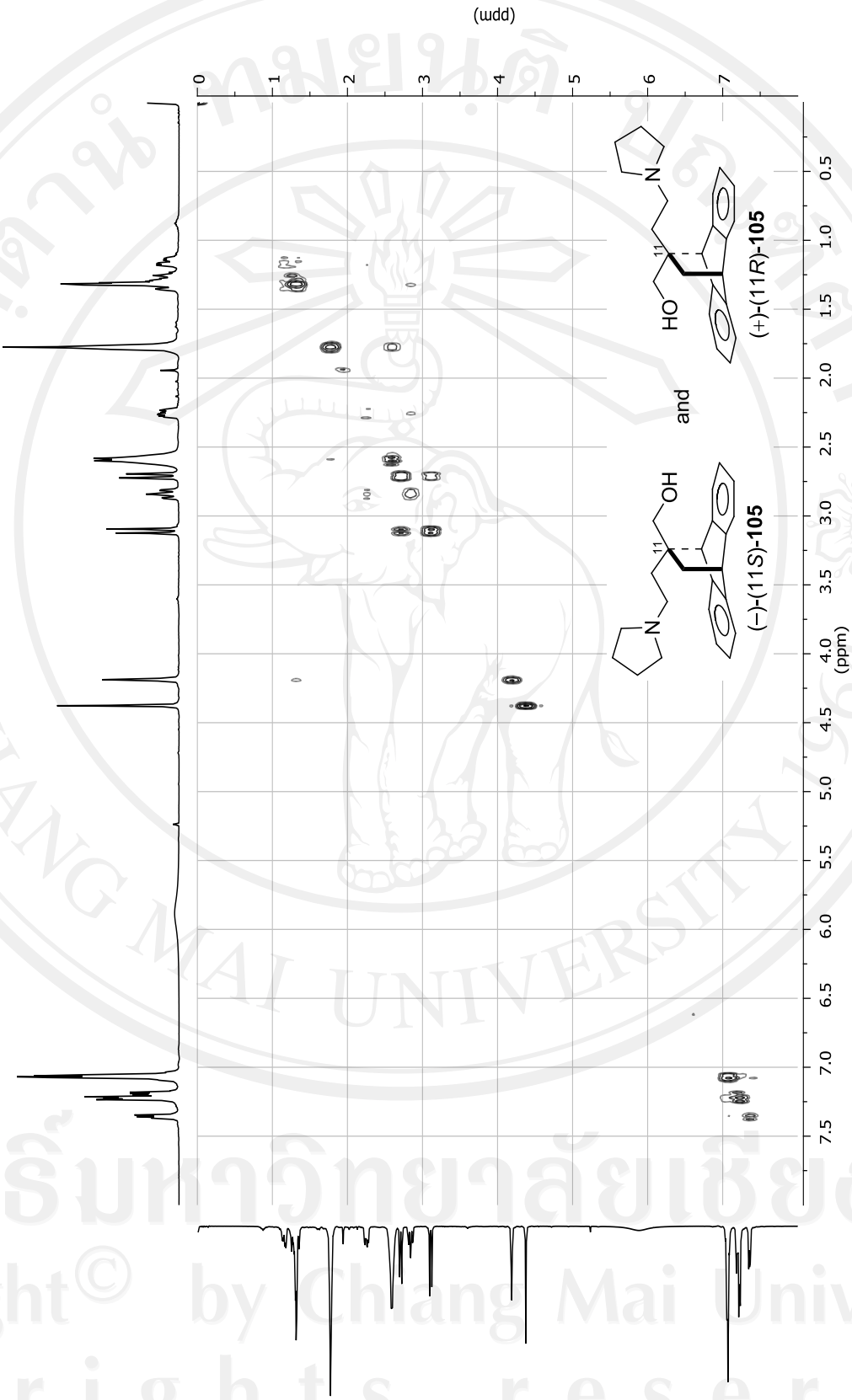
Appendix 16 HMQC spectrum of compounds (+)-(11*S*)-**104** and (−)-(11*R*)-**104**



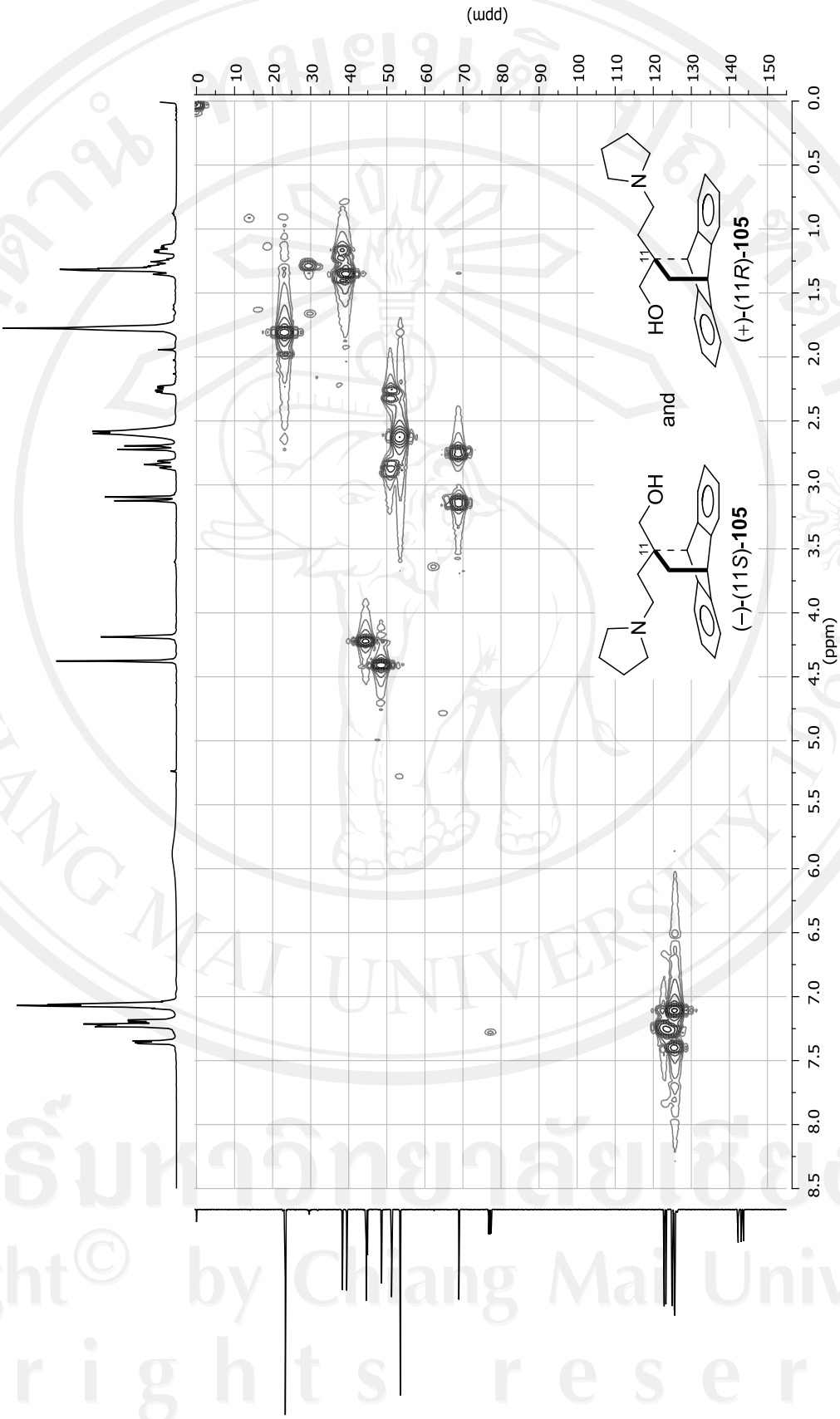
Appendix 17 ^{1}H-NMR spectrum of compounds (–)-(11*S*)-**105** and (+)-(11*R*)-**105**



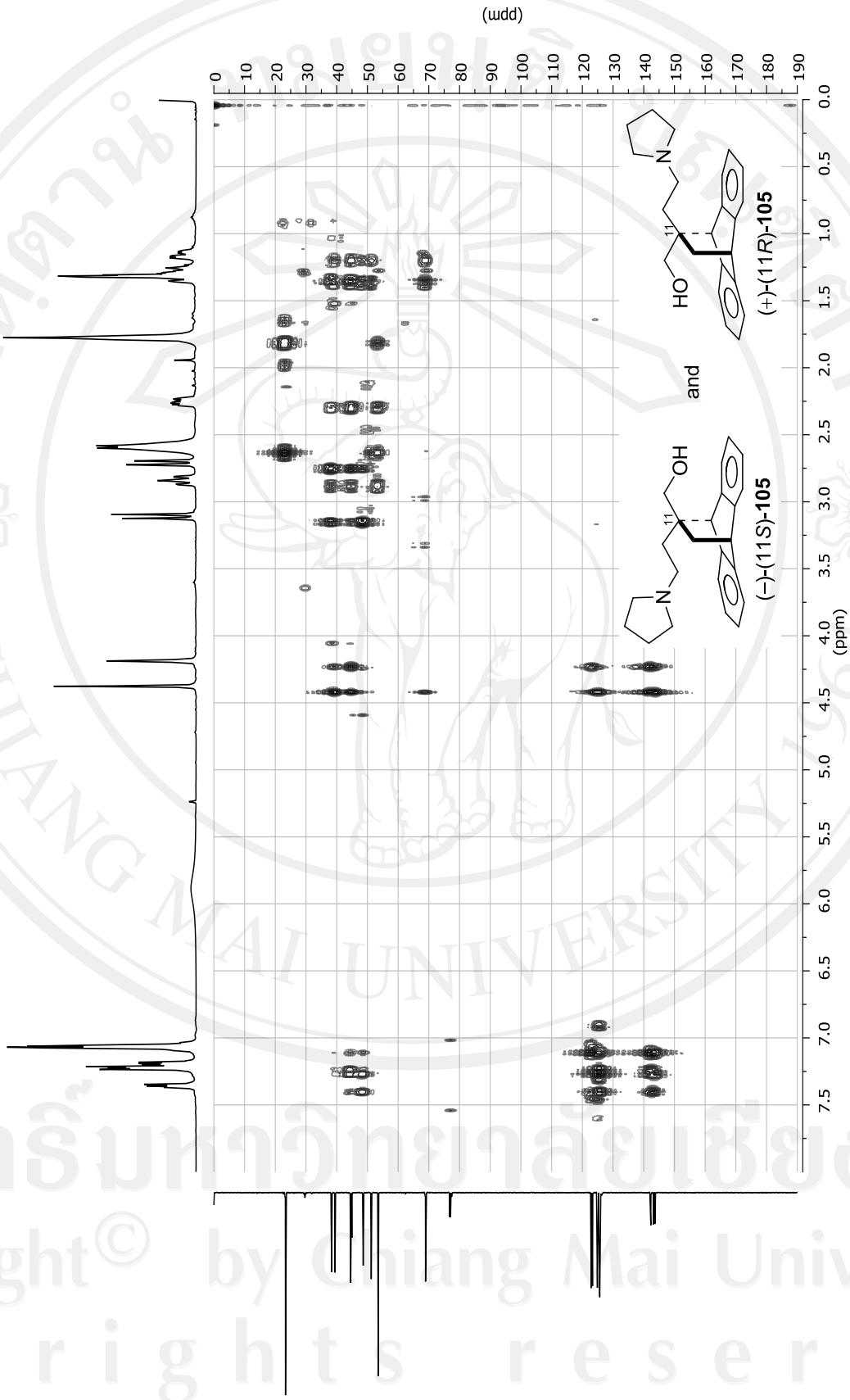
Appendix 18 ^{13}C-NMR spectrum of compounds (–)-(11*S*)-**105** and (+)-(11*R*)-**105**



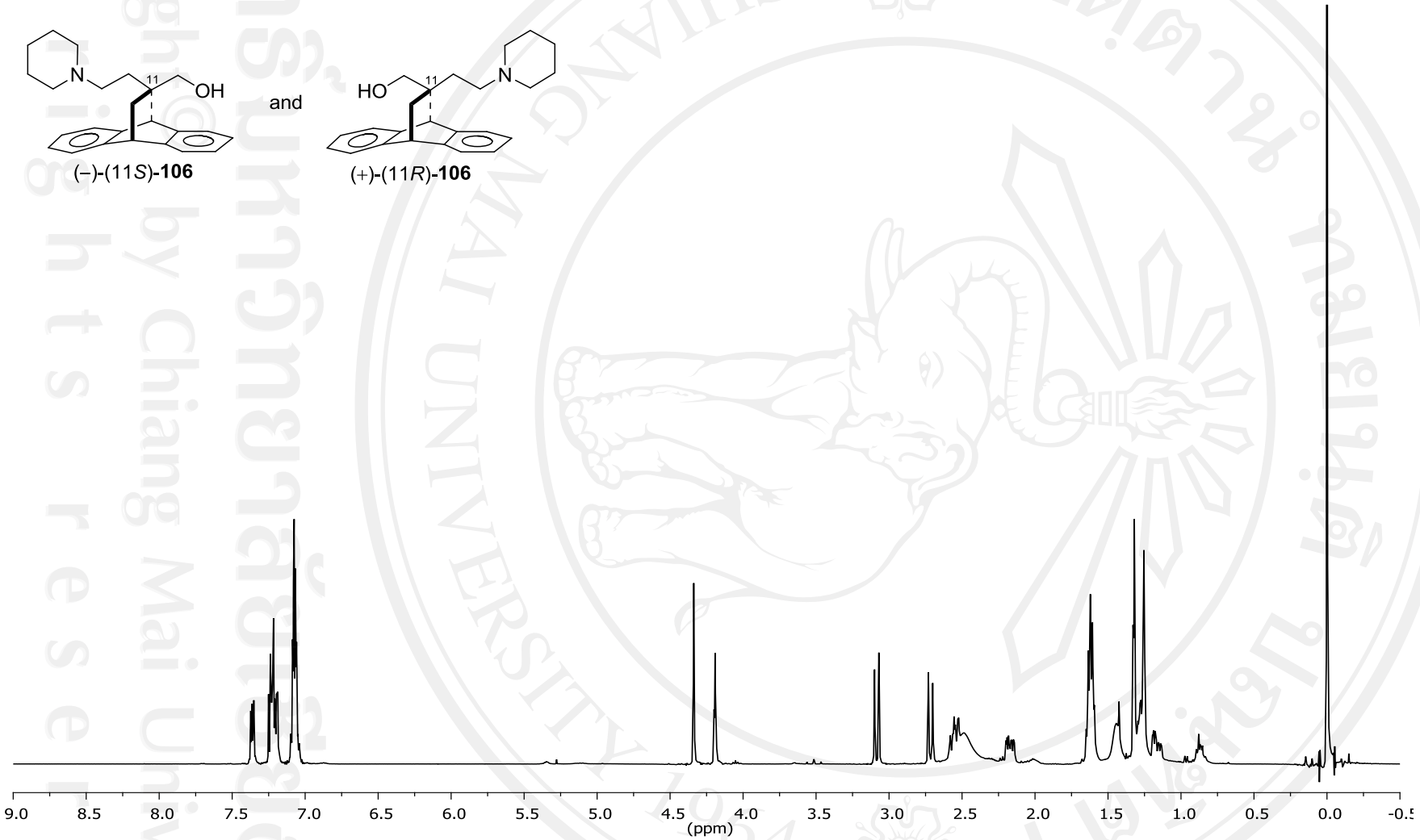
Appendix 19 COSY spectrum of compounds (−)-(11*S*)-**105** and (+)-(11*R*)-**105**



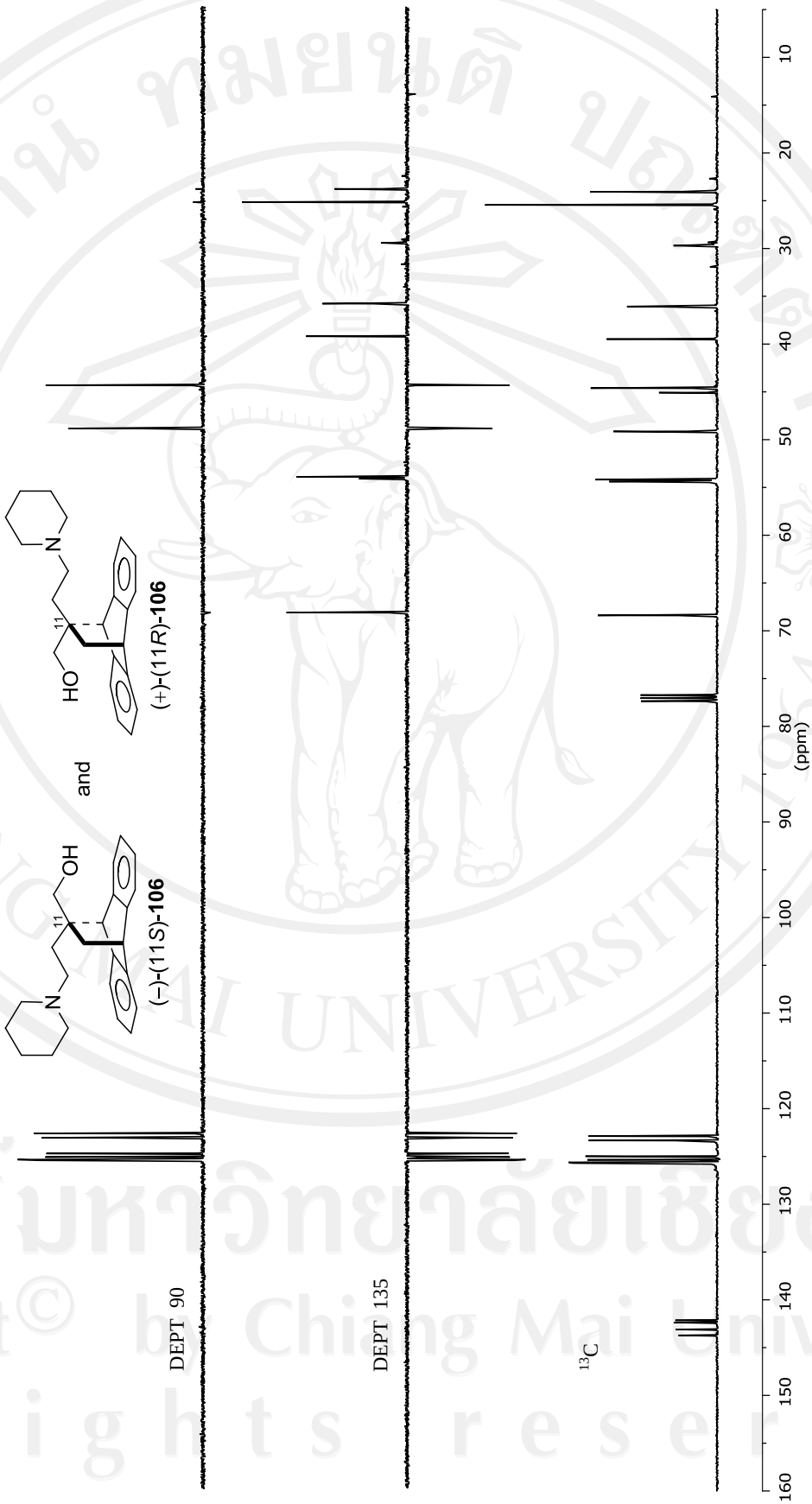
Appendix 20 HMQC spectrum of compounds (−)-(11*S*)-**105** and (+)-(11*R*)-**105**



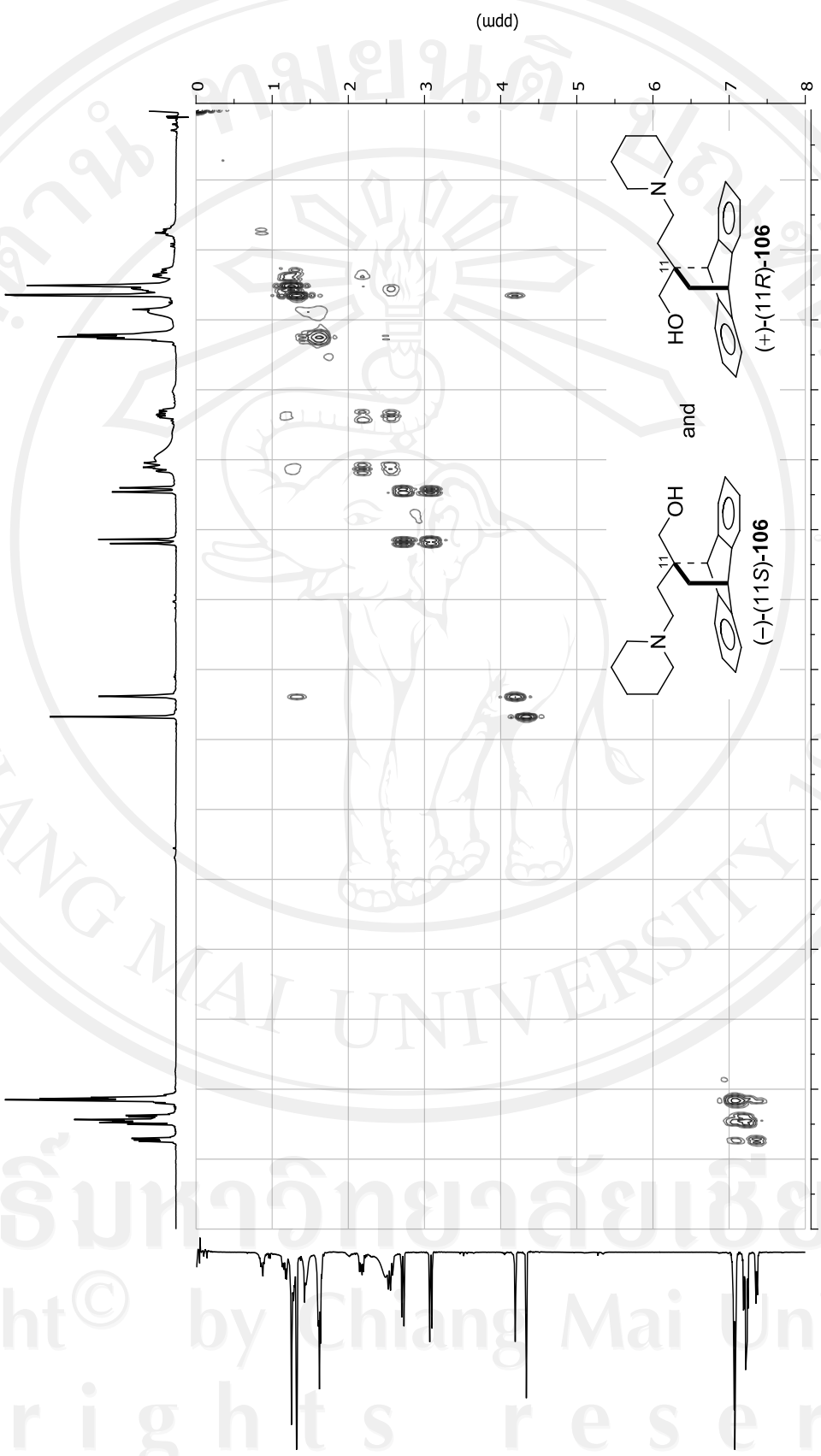
Appendix 21 HMBC spectrum of compounds (−)-(11*S*)-**105** and (+)-(11*R*)-**105**



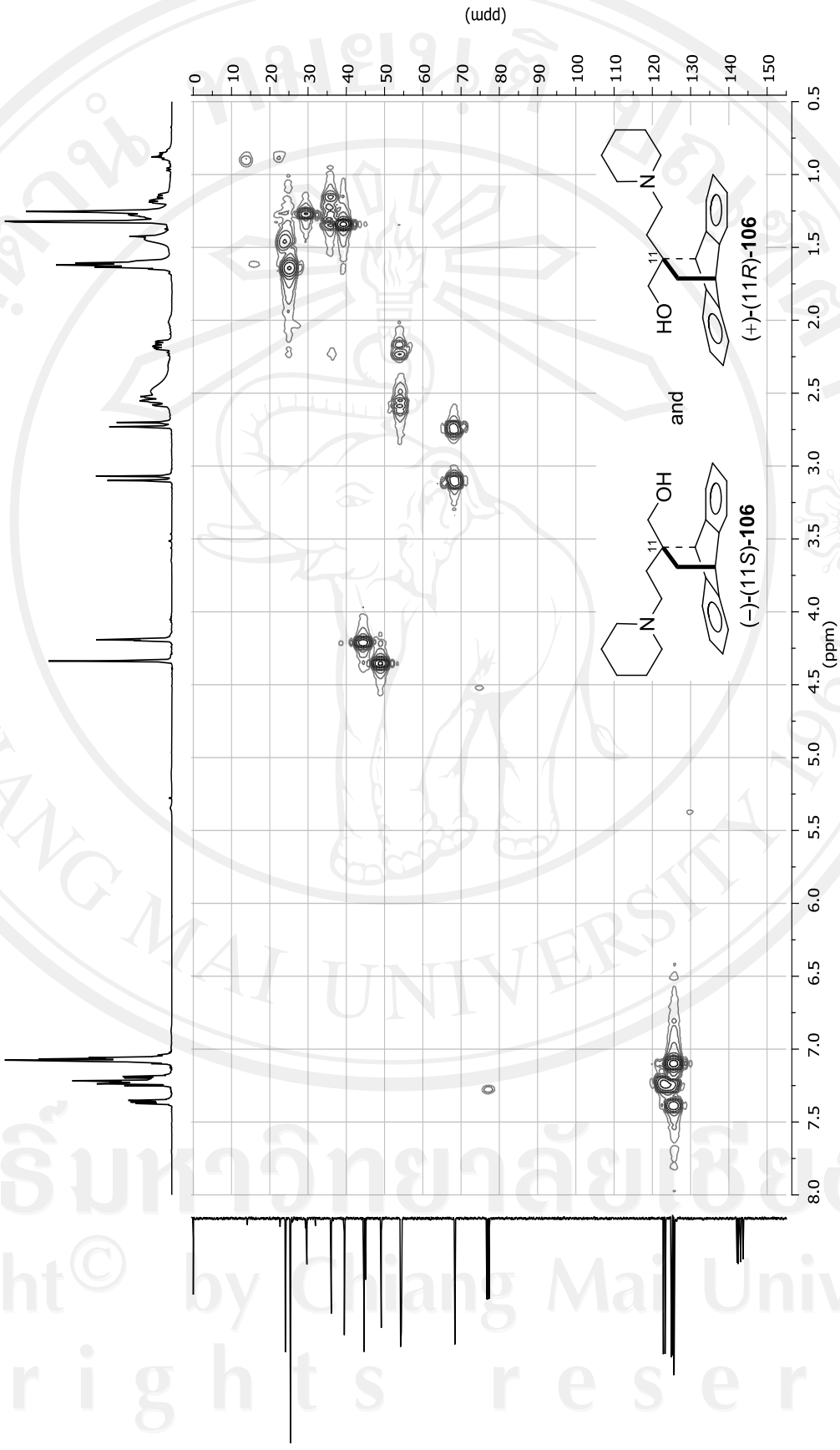
Appendix 22 ^{1}H-NMR spectrum of compounds (–)-(11*S*)-**106** and (+)-(11*R*)-**106**



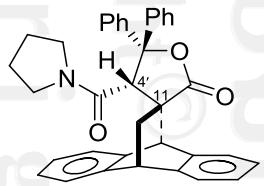
Appendix 23 ^{13}C-NMR spectrum of compounds (–)-(11S)-**106** and (+)-(11*R*)-**106**



Appendix 24 COSY spectrum of compounds (−)-(11*S*)-**106** and (+)-(11*R*)-**106**

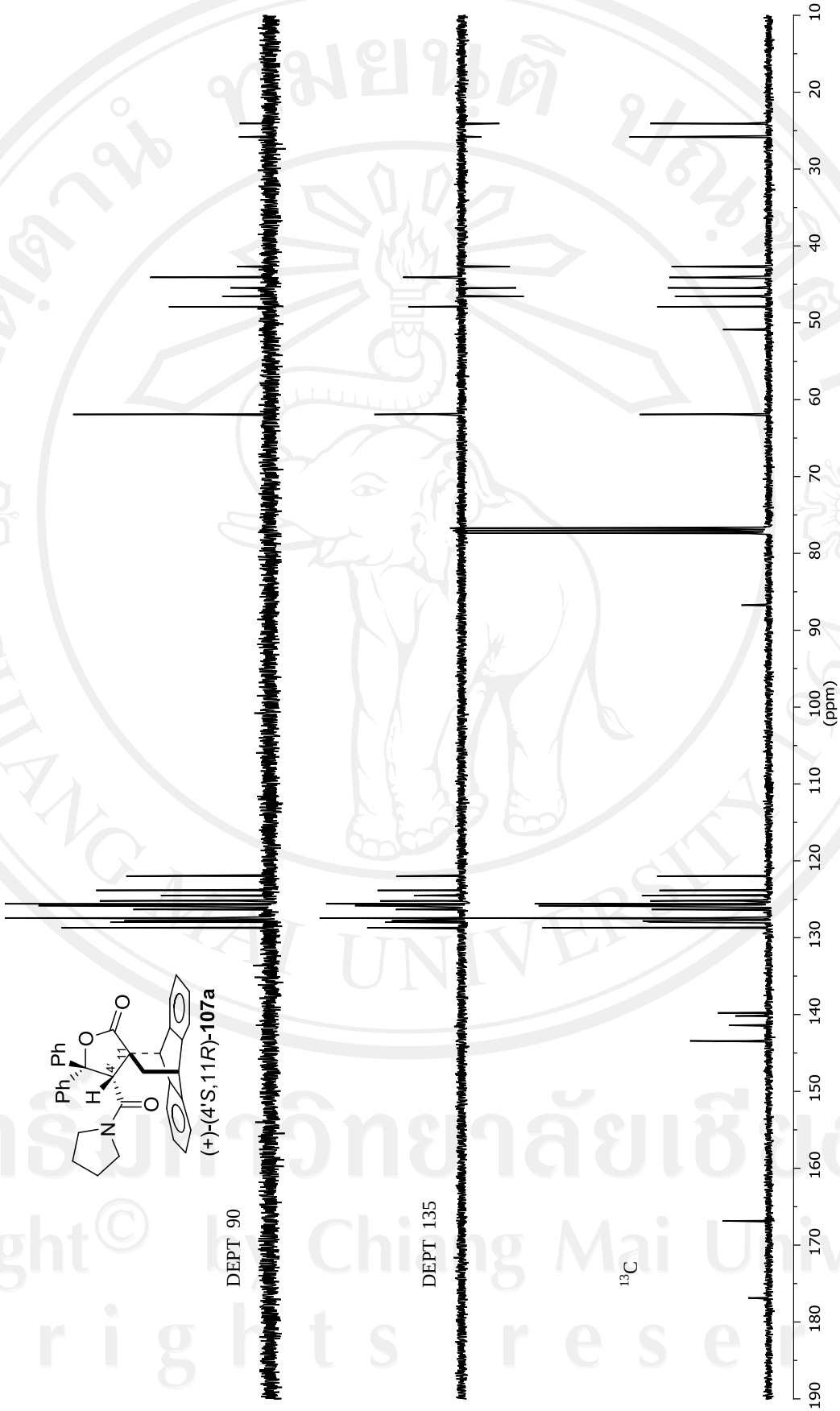


Appendix 25 HMQC spectrum of compounds (–)-(11*S*)-**106** and (+)-(11*R*)-**106**

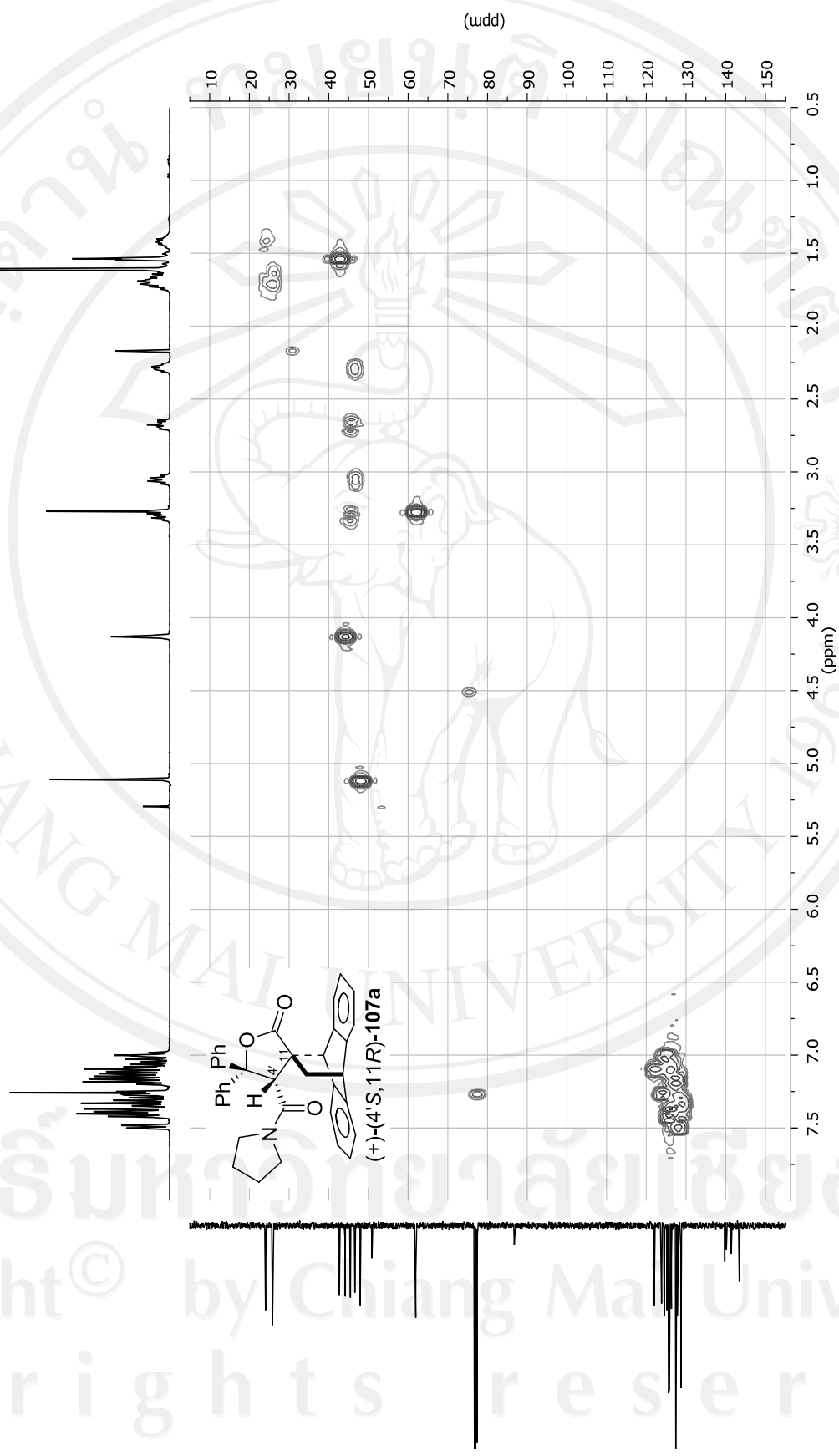


(+)-(4′*S*,11*R*)-**107a**

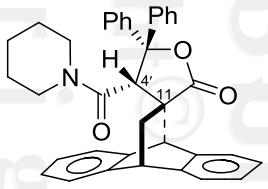
Appendix 26 ^{1}H-NMR spectrum of compound (+)-(4′*S*,11*R*)-**107a**



Appendix 27 ^{13}C-NMR spectrum of compound (+)-(4′*S*,11 *R*)-**107a**

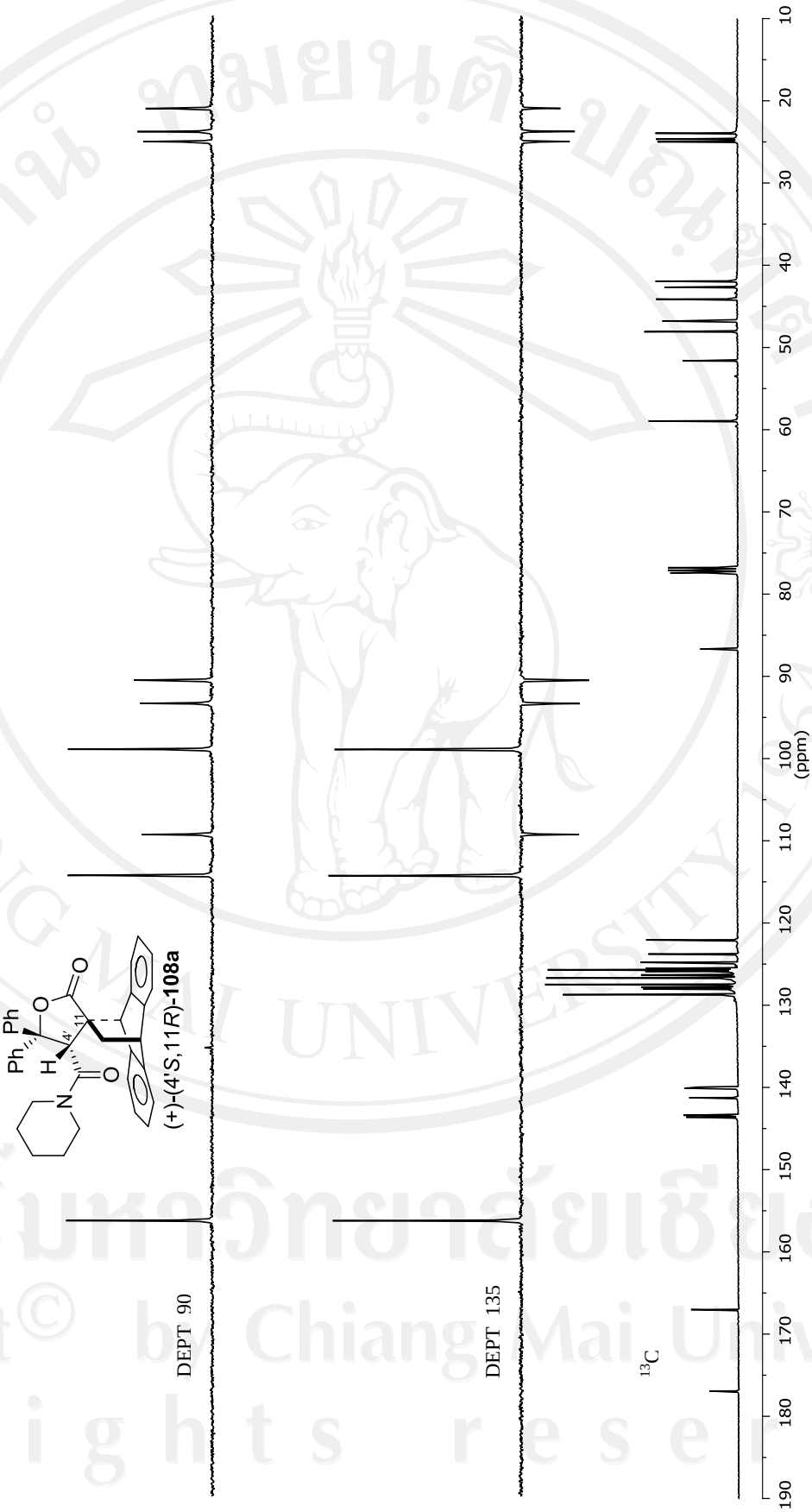


Appendix 28 HMQC spectrum of compound (+)-(4′*S*,11*R*)-**107a**

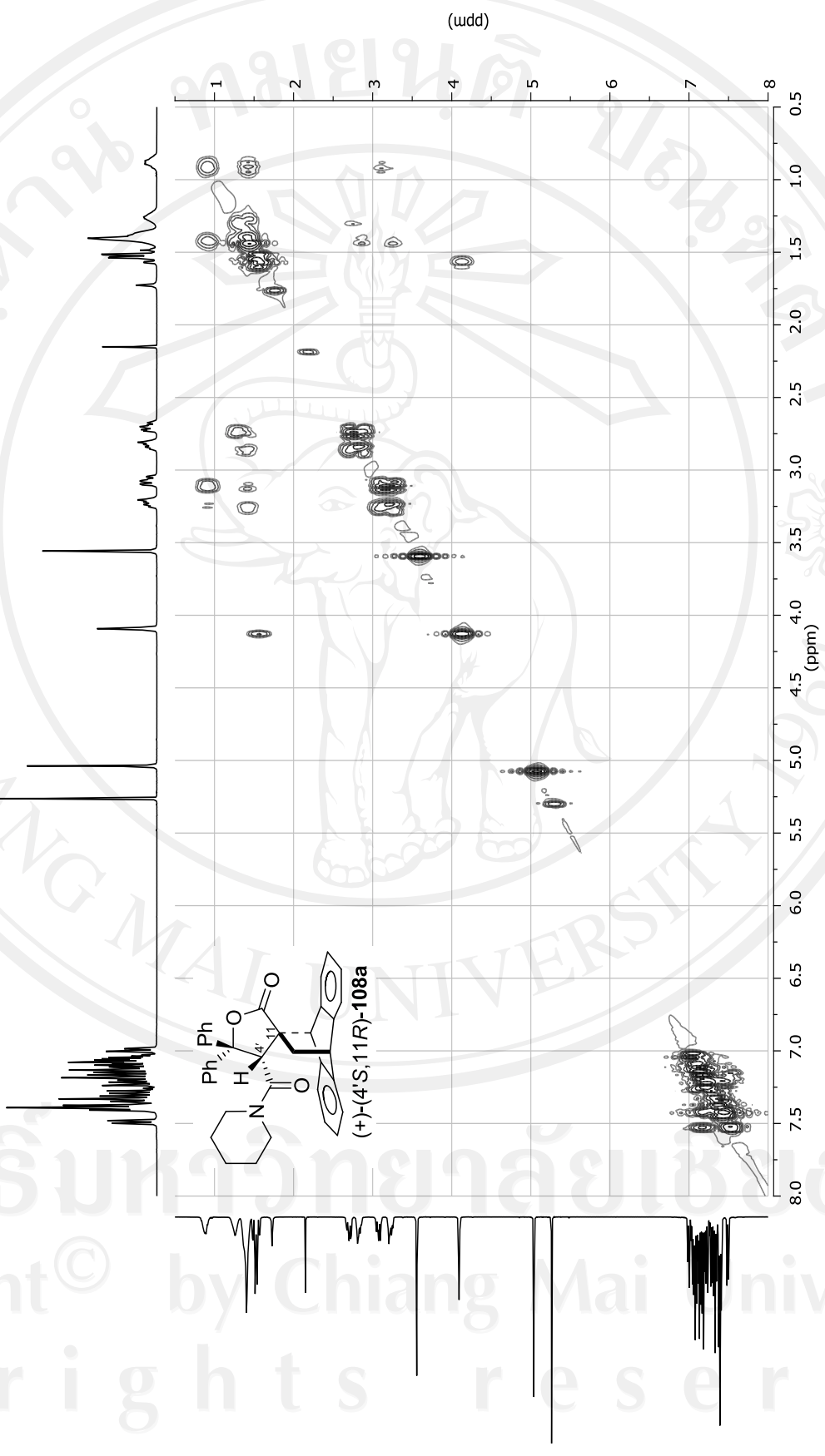


(+)-(4′*S*,11*R*)-**108a**

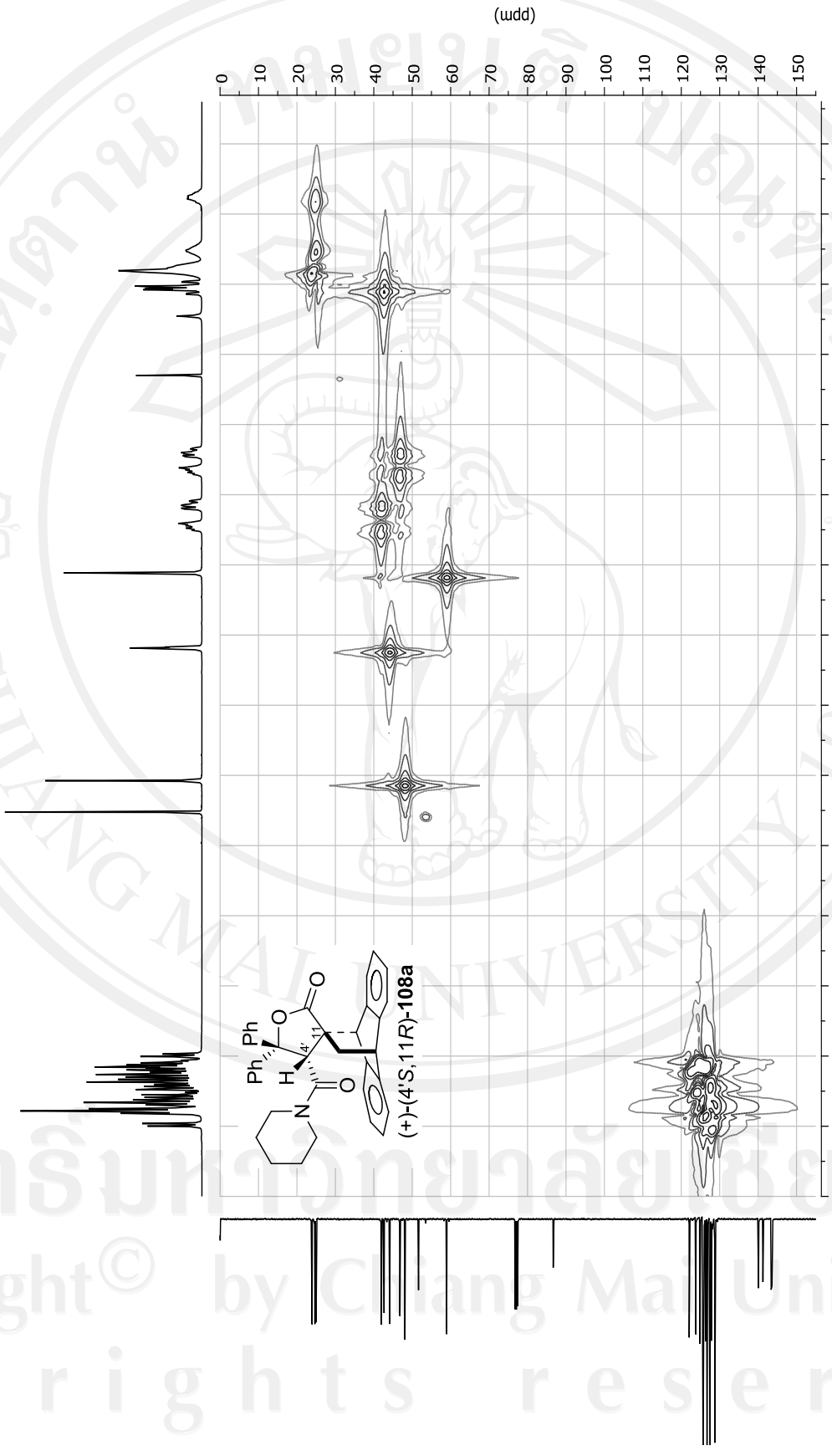
Appendix 29 ^{1}H-NMR spectrum of compound (+)-(4′*S*,11*R*)-**108a**



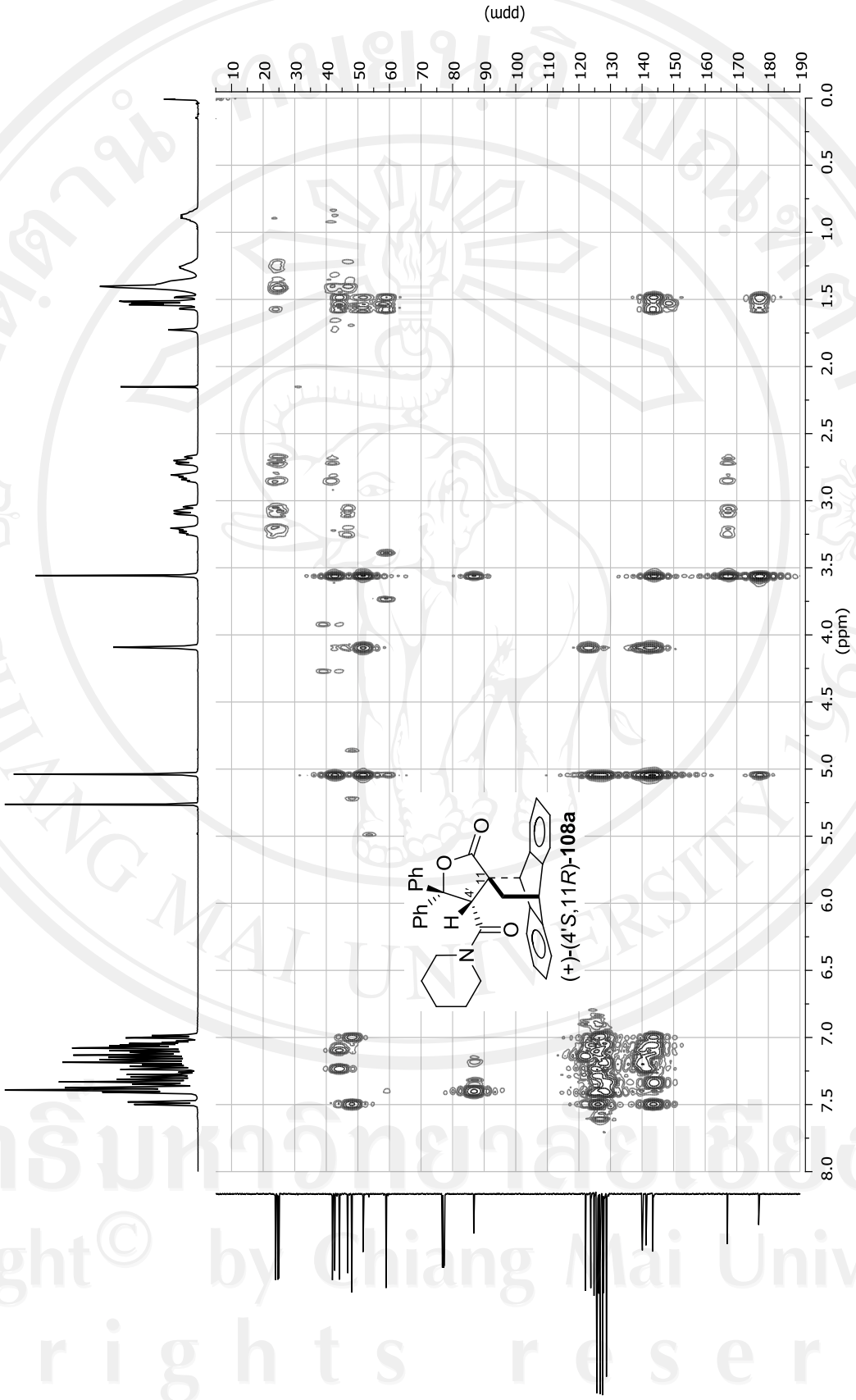
Appendix 30 ^{13}C-NMR spectrum of compound (+)-(4′*S*,11*R*)-**108a**



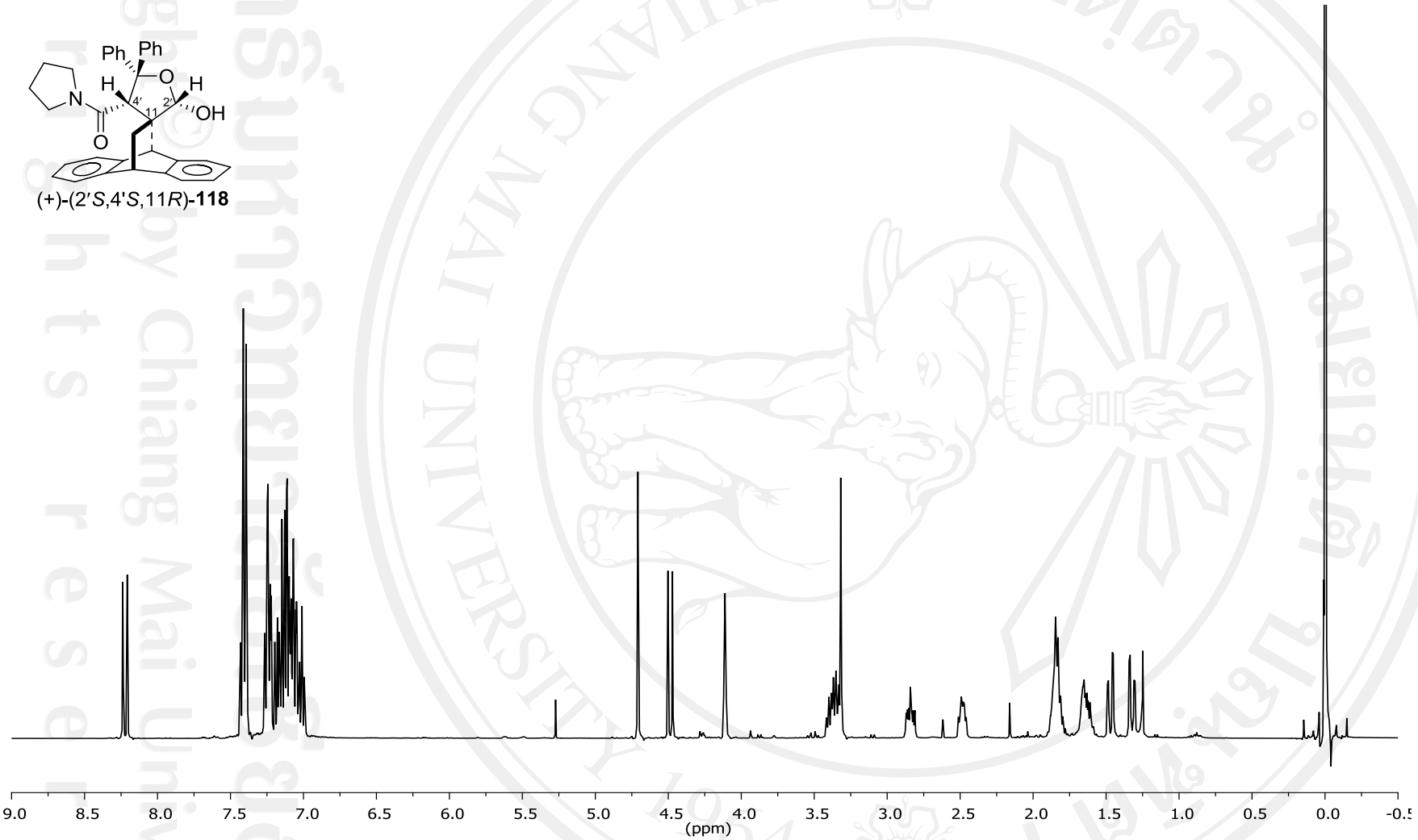
Appendix 31 COSY spectrum of compound (+)-(4′*S*,11*R*)-**108a**



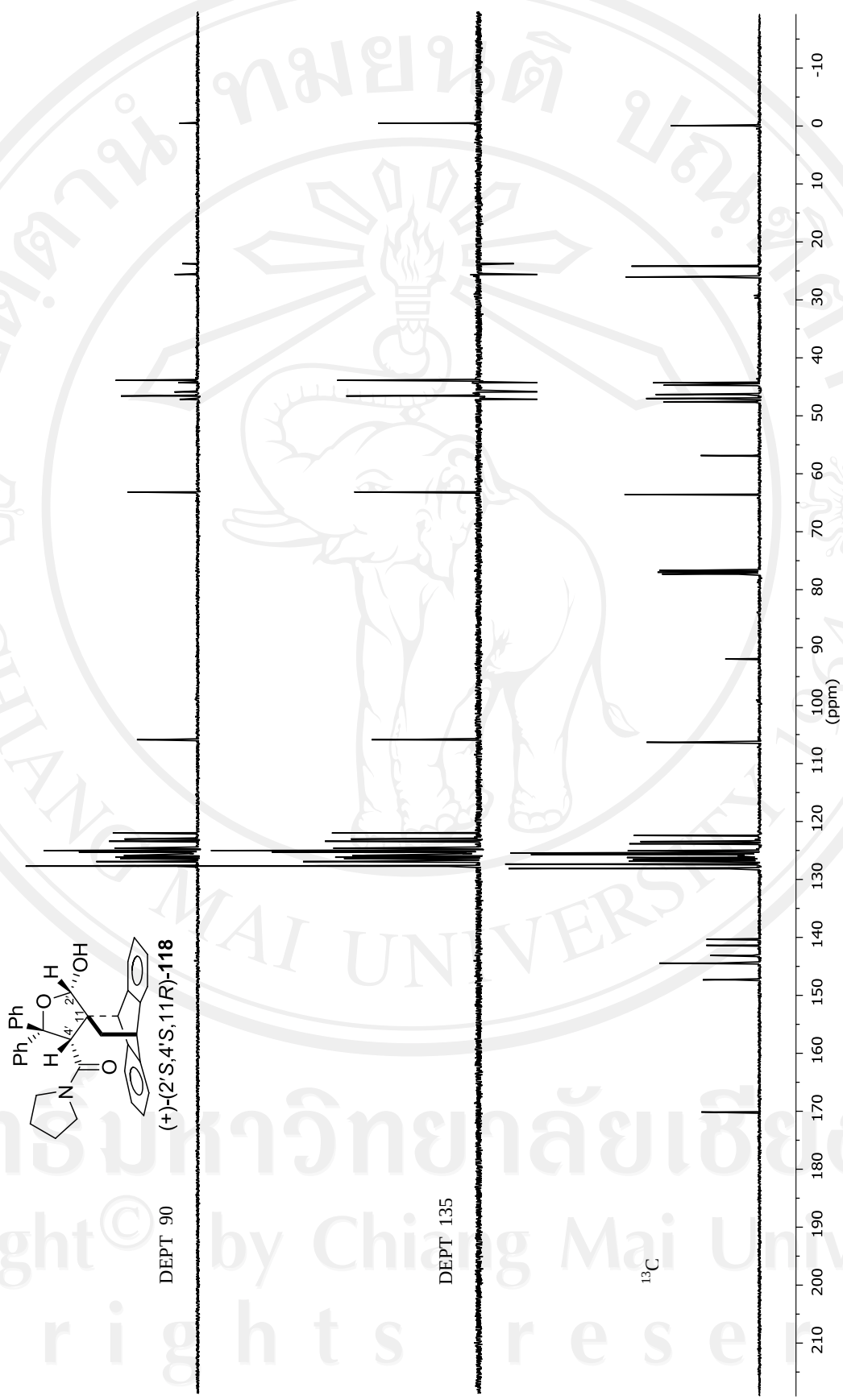
Appendix 32 HMQC spectrum of compound (+)-(4′*S*,11*R*)-**108a**



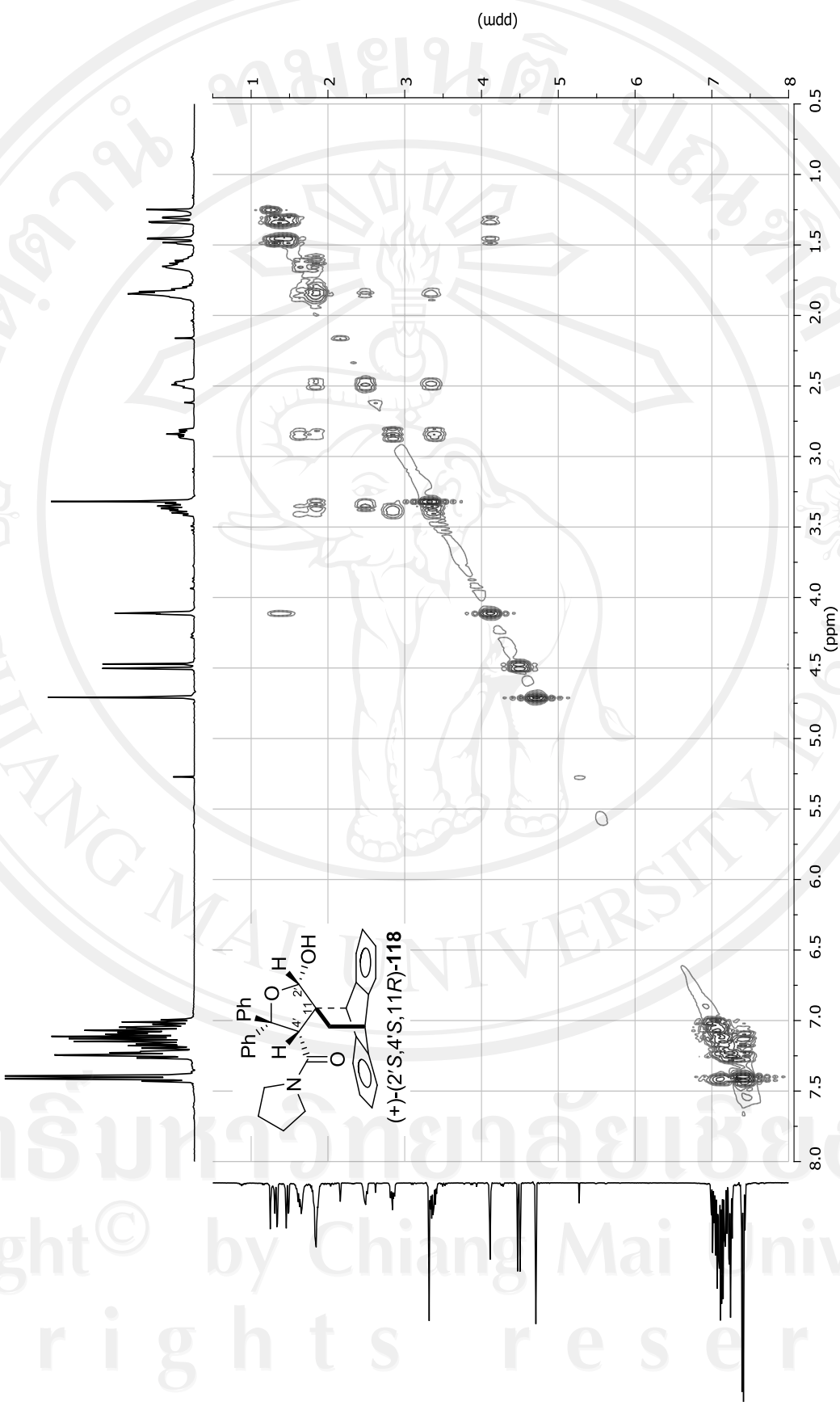
Appendix 33 HMBC spectrum of compound (+)-(4′*S*,11*R*)-**108a**



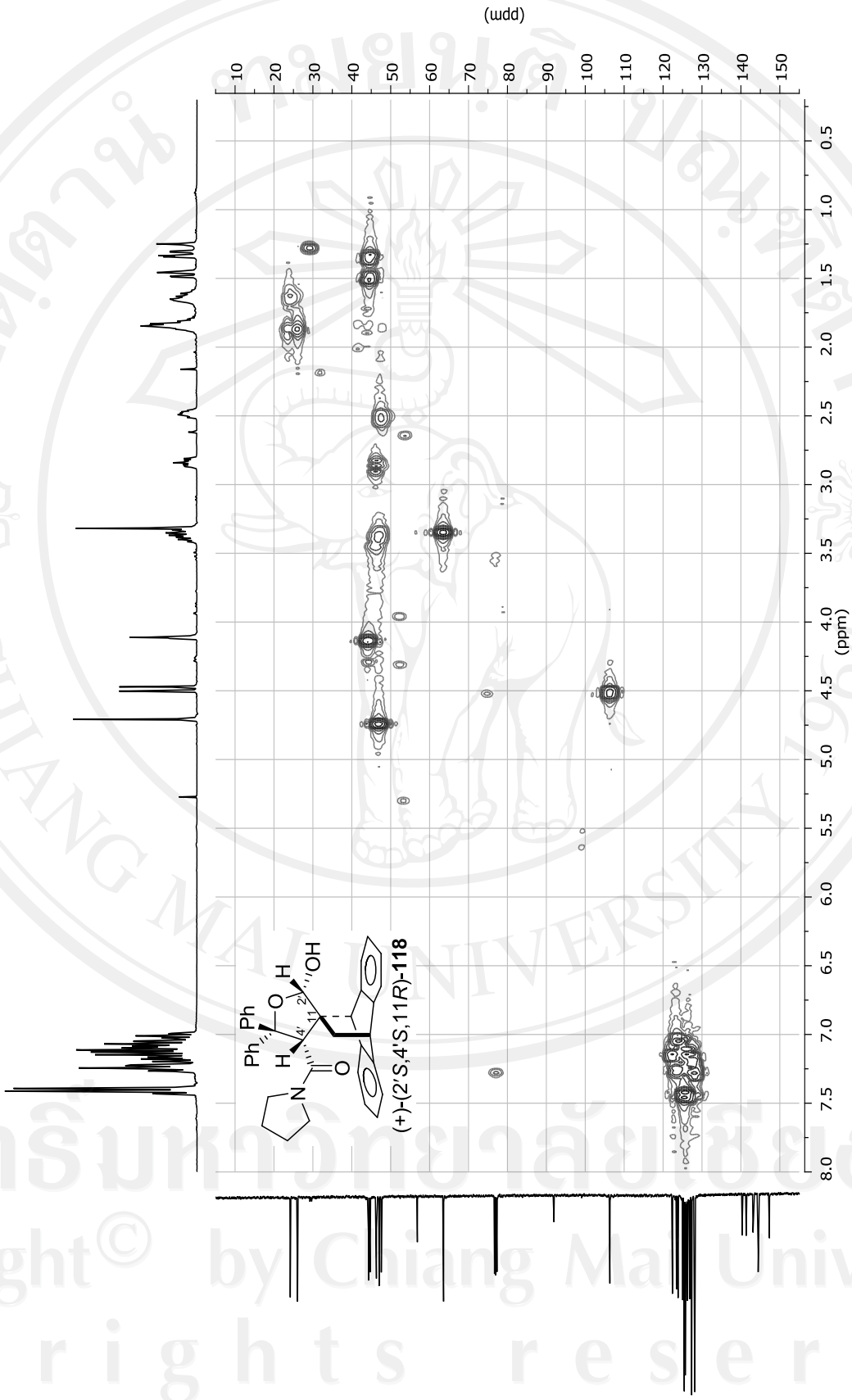
Appendix 34 ^{1}H-NMR spectrum of compound (+)-(2′*S*,4′*S*,11*R*)-**118**



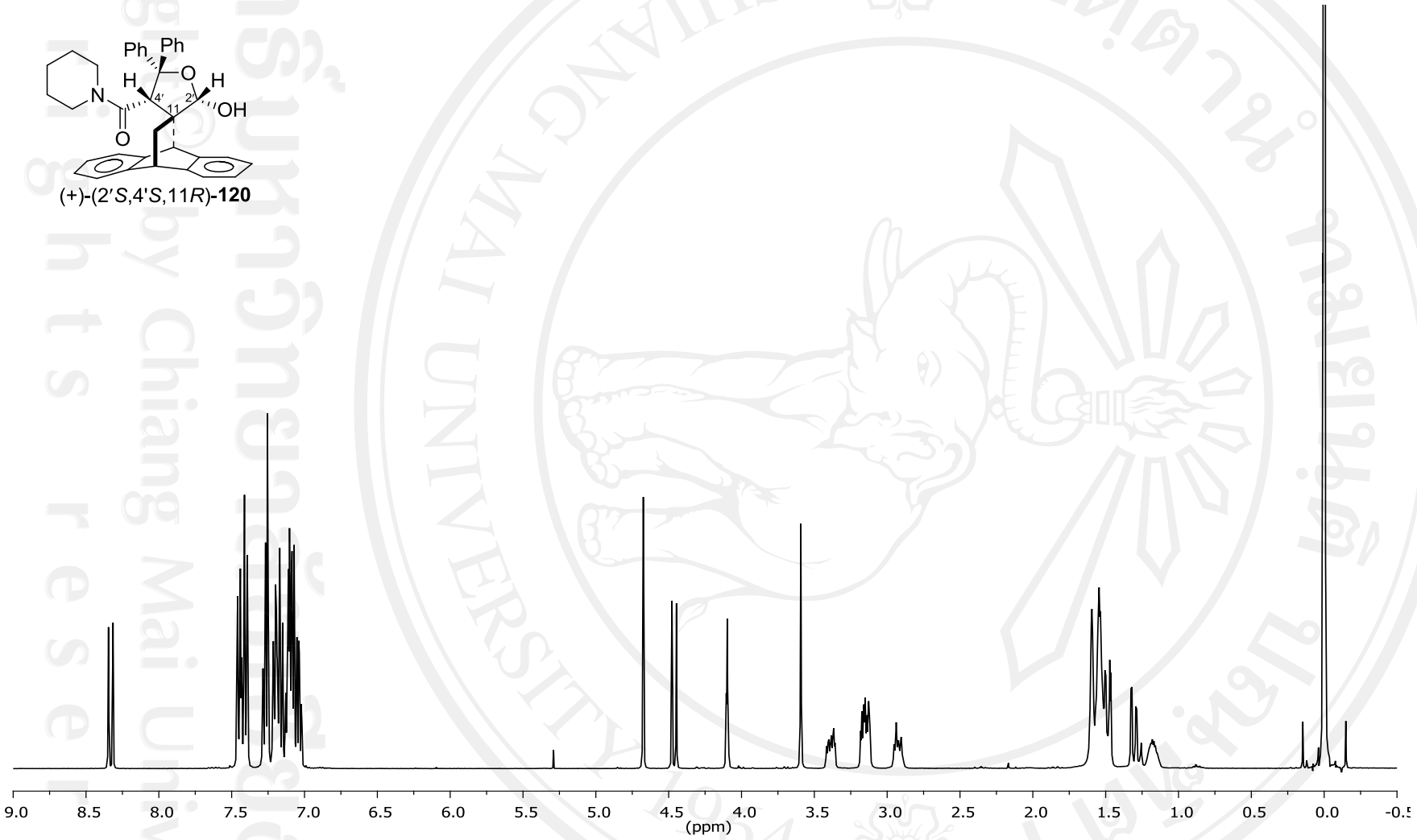
Appendix 35 ^{13}C-NMR spectrum of compound (+)-(2′*S*,4′*S*,11*R*)-**118**



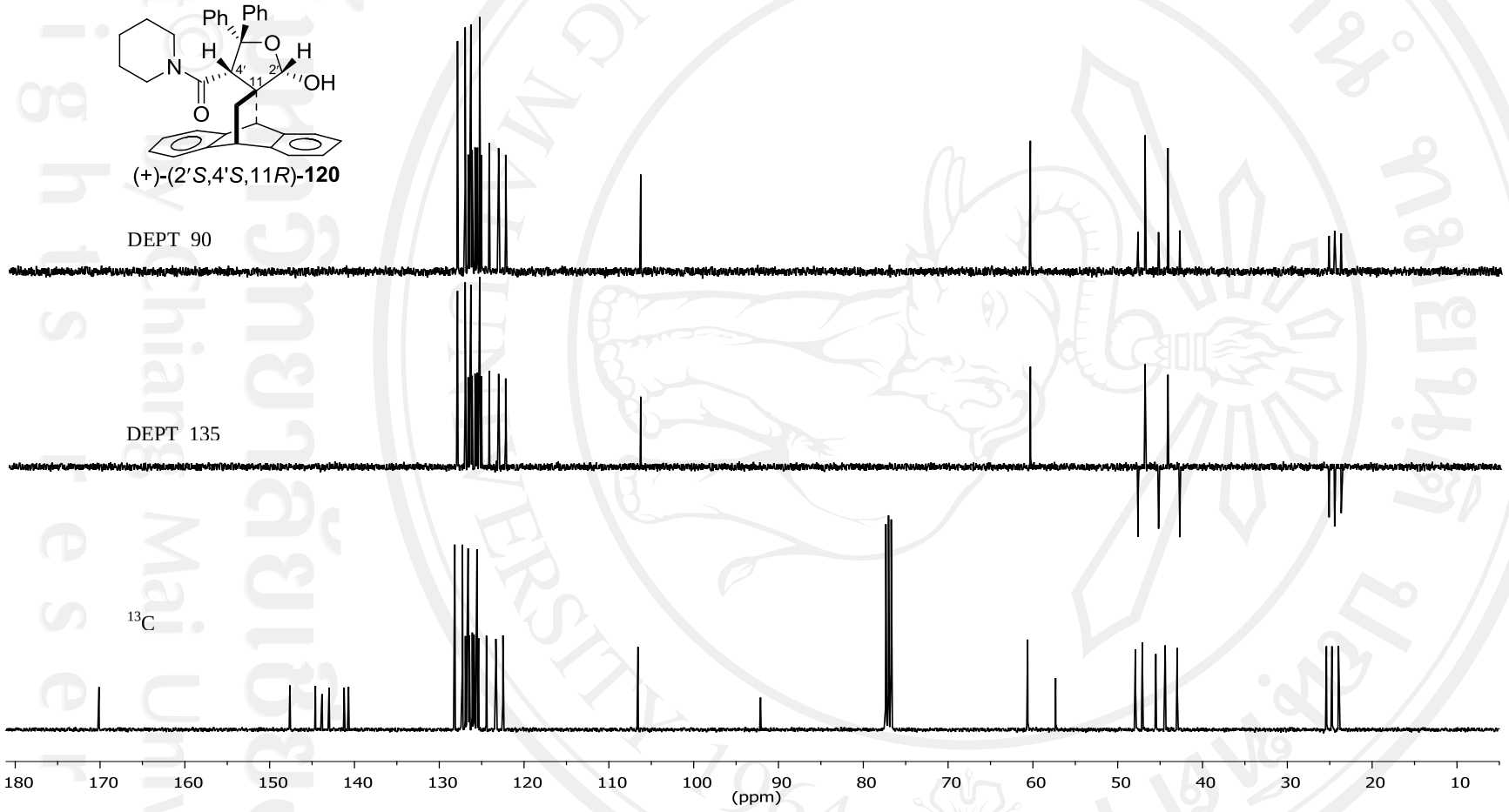
Appendix 36 COSY spectrum of compound (+)-(2′S,4′S,11*R*)-**118**



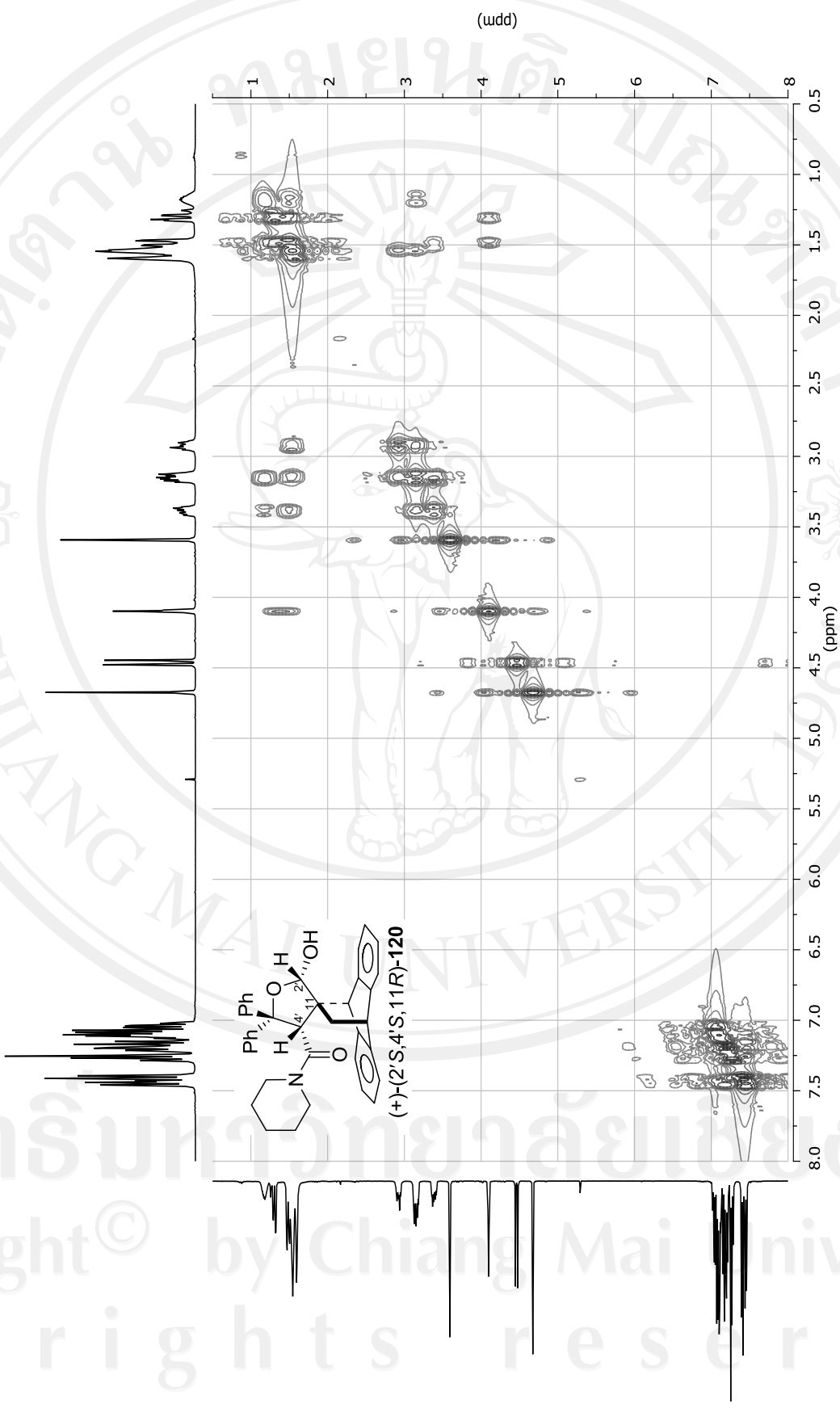
Appendix 37 HMQC spectrum of compound (+)-(2′*S*,4′S,11*R*)-**118**



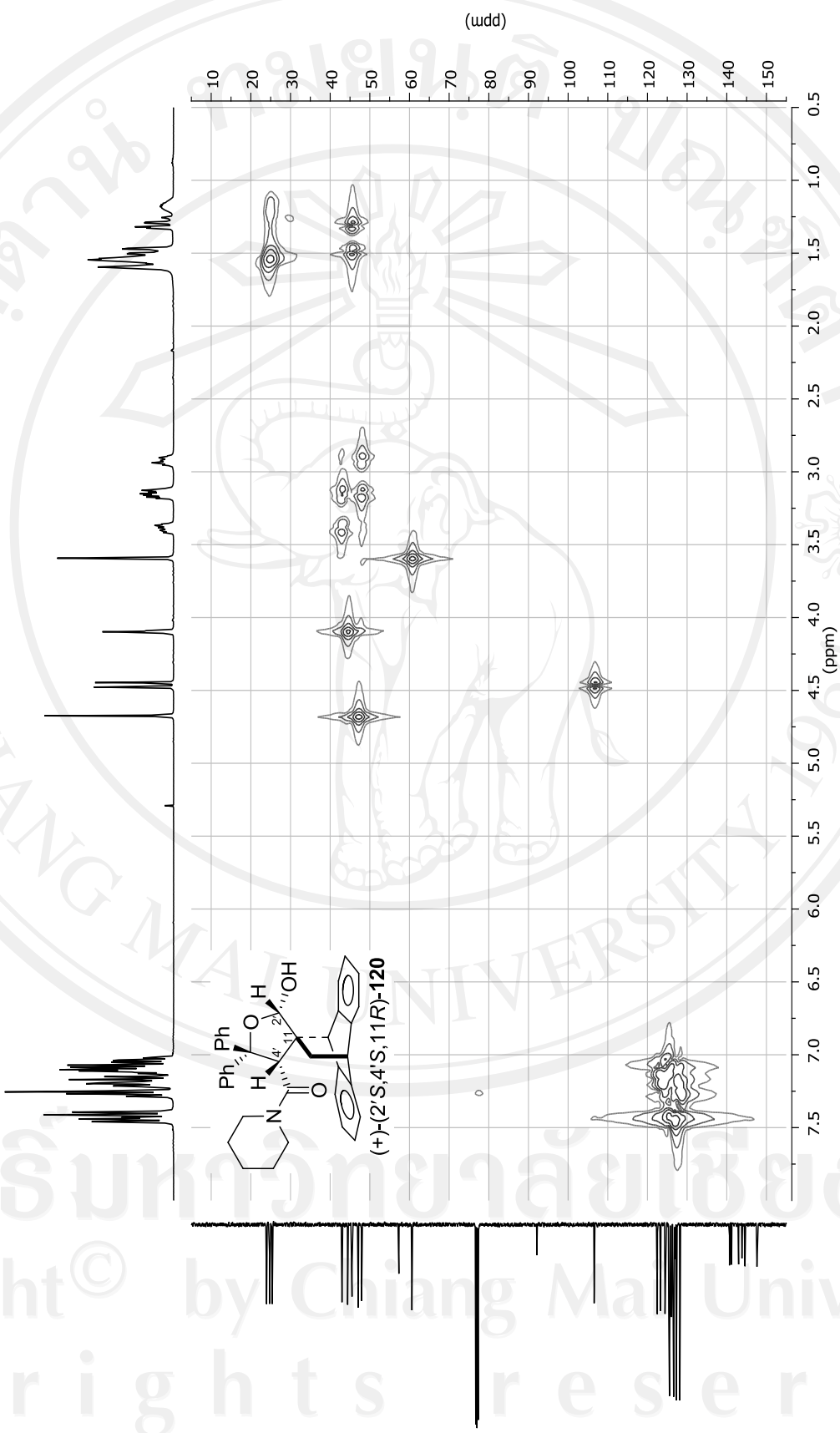
Appendix 38 ^{1}H-NMR spectrum of compound (+)-(2′*S*,4′*S*,11*R*)-**120**



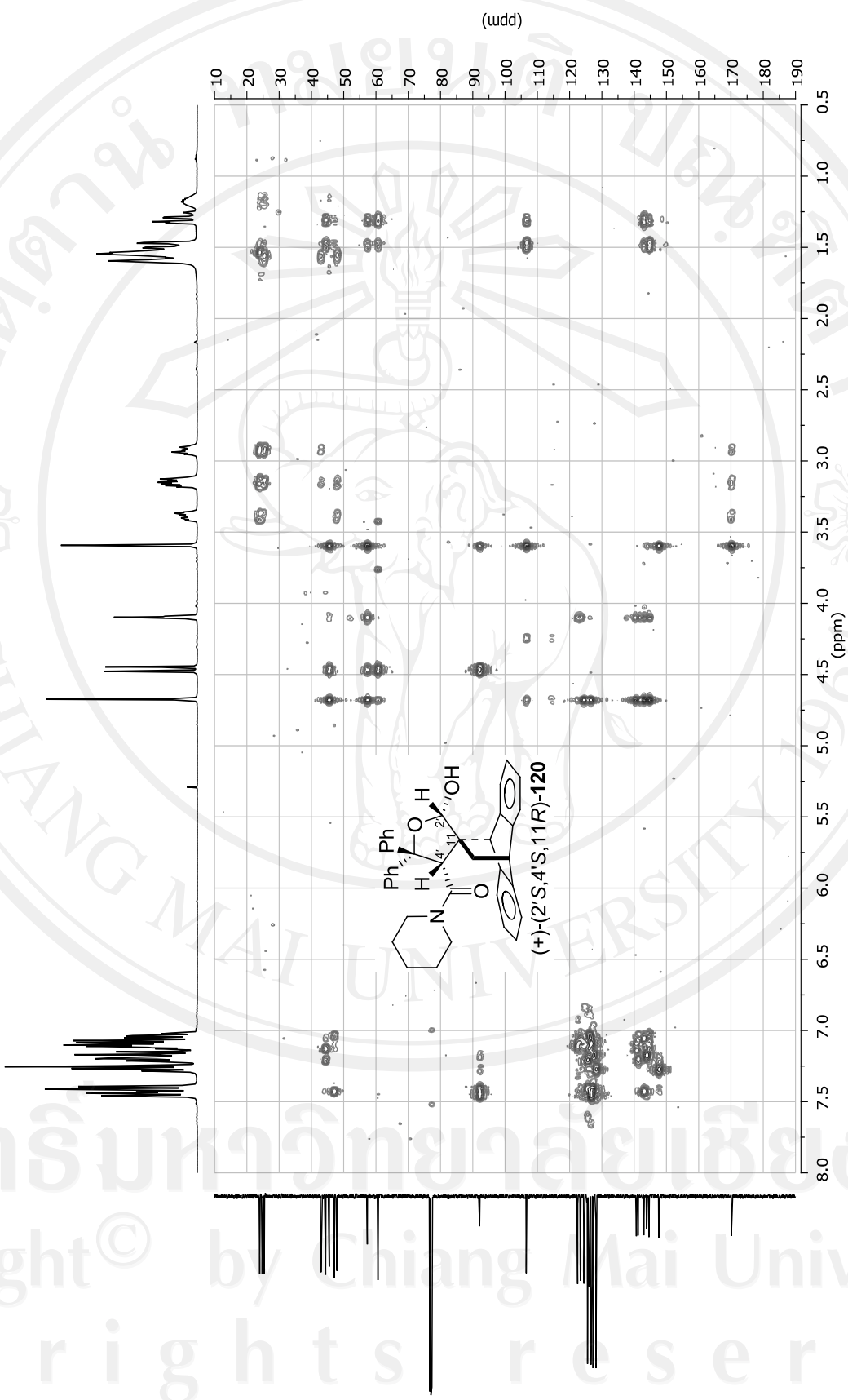
Appendix 39 ^{13}C-NMR spectrum of compound (+)-(2′*S*,4′*S*,11*R*)-**120**



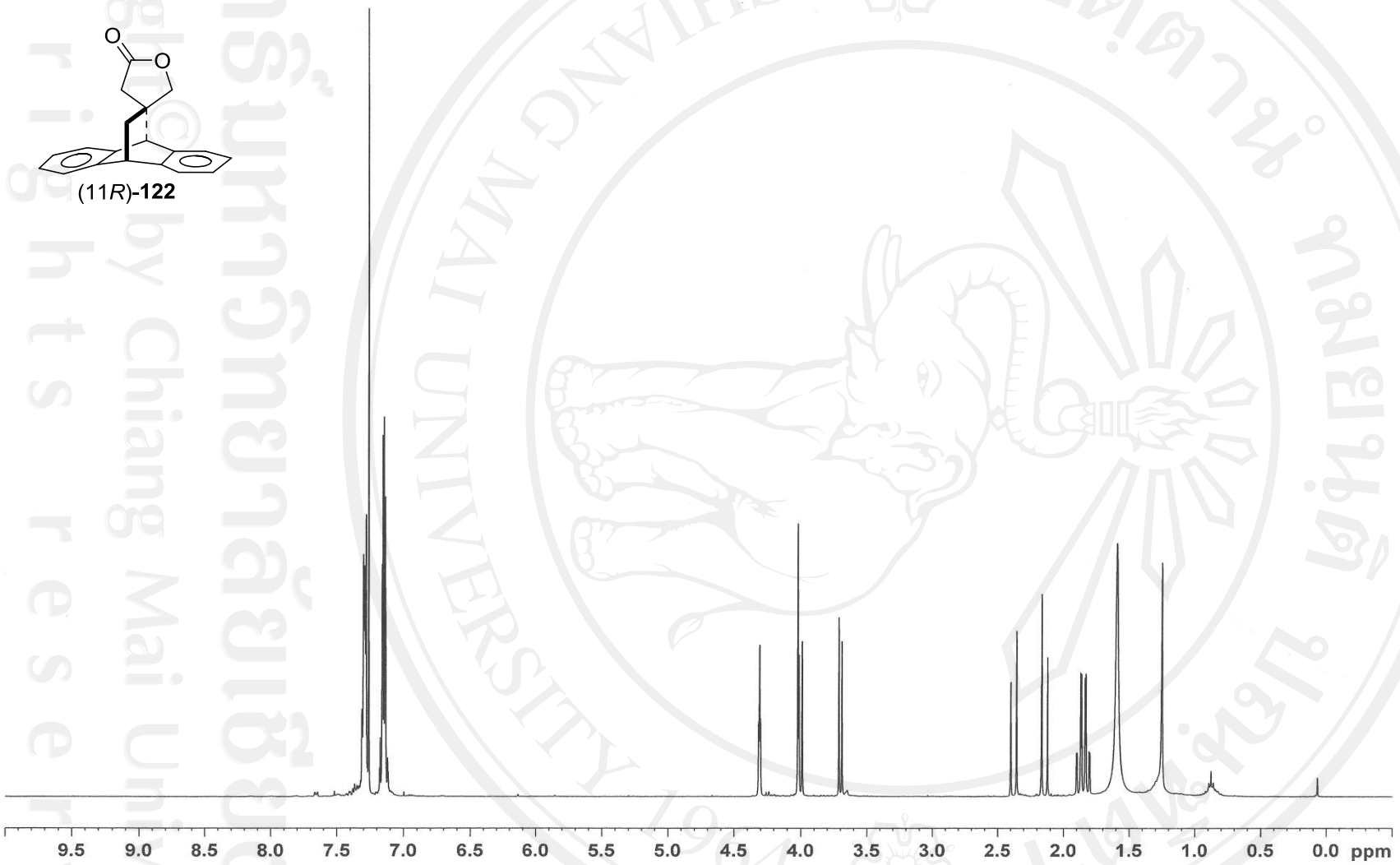
Appendix 40 COSY spectrum of compound (+)-(2′*S*,4′*S*,11*R*)-**120**



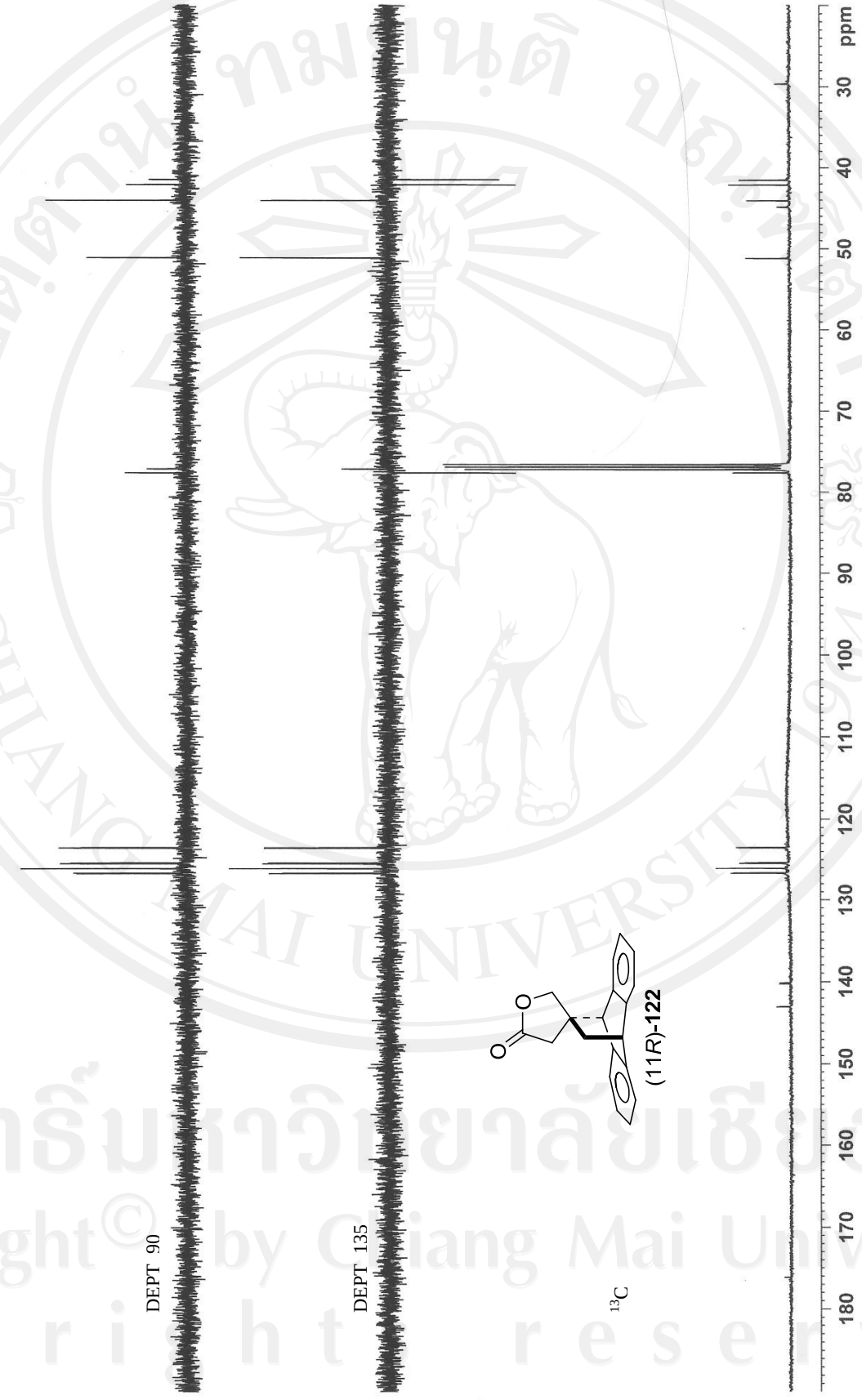
Appendix 41 HMQC spectrum of compound (+)-(2′*S*,4′S,11*R*)-**120**



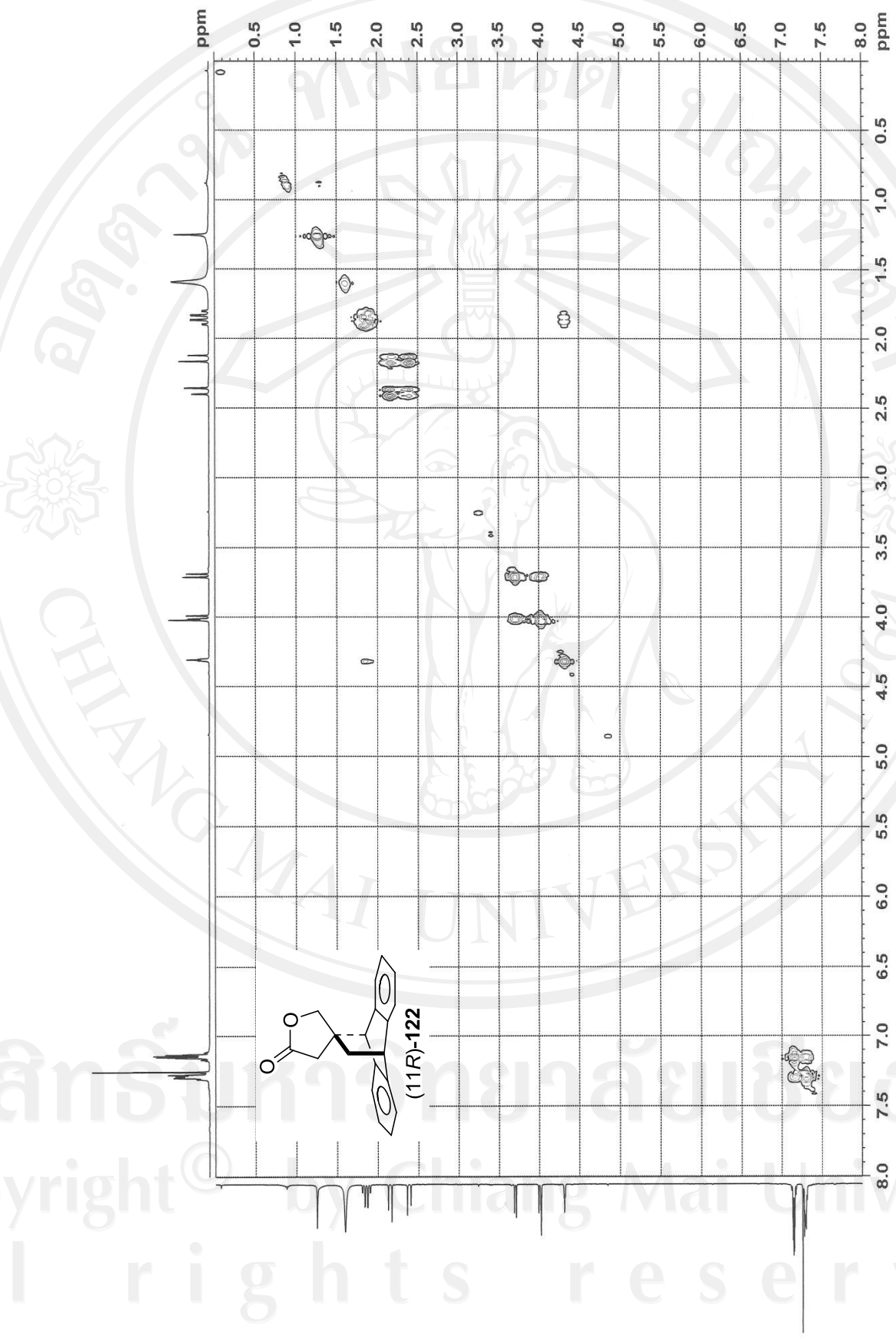
Appendix 42 HMBC spectrum of compound (+)-(2′*S*,4′*S*,11*R*)-**120**



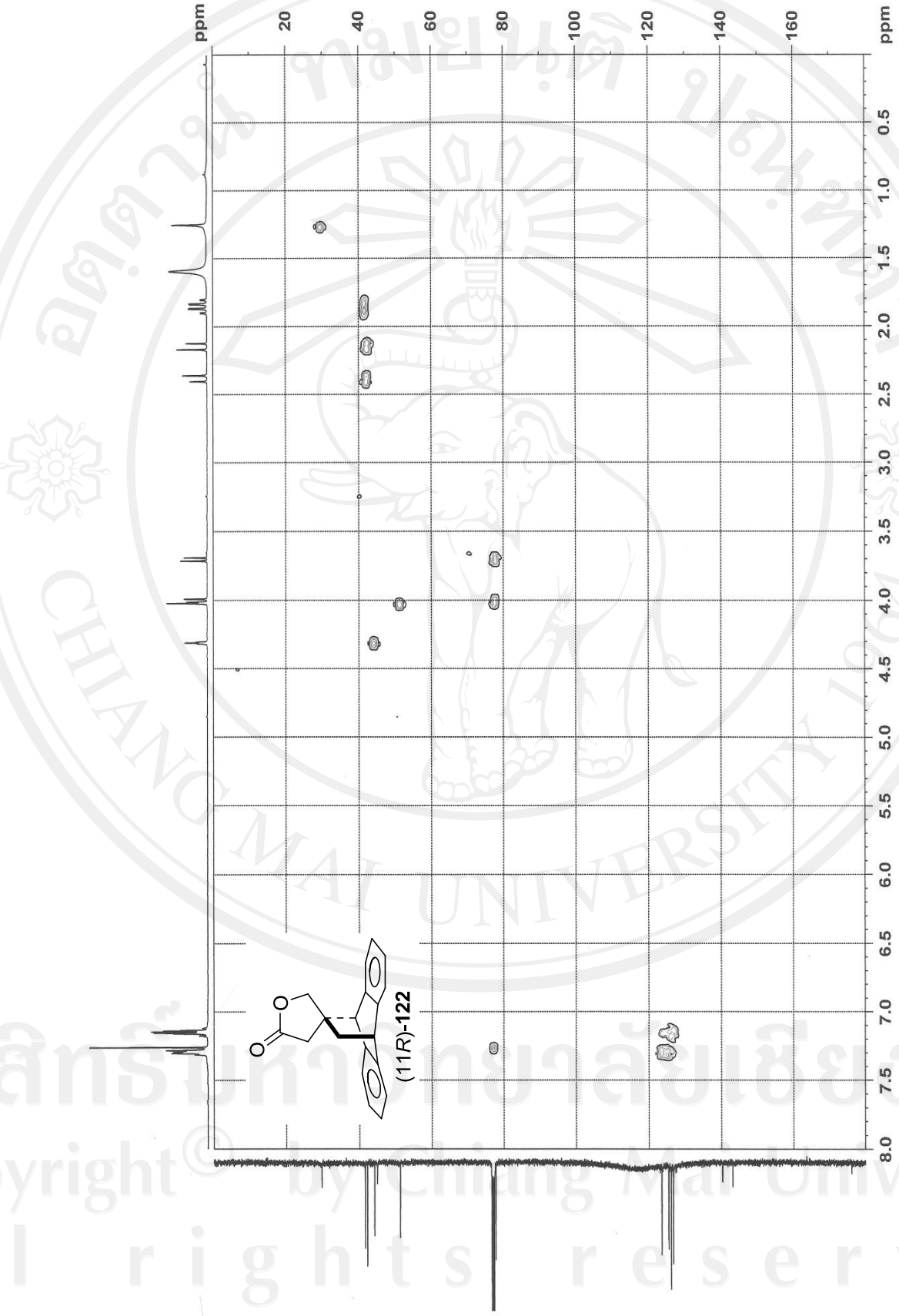
Appendix 43 ^{1}H-NMR spectrum of compound (11*R*)-**122**



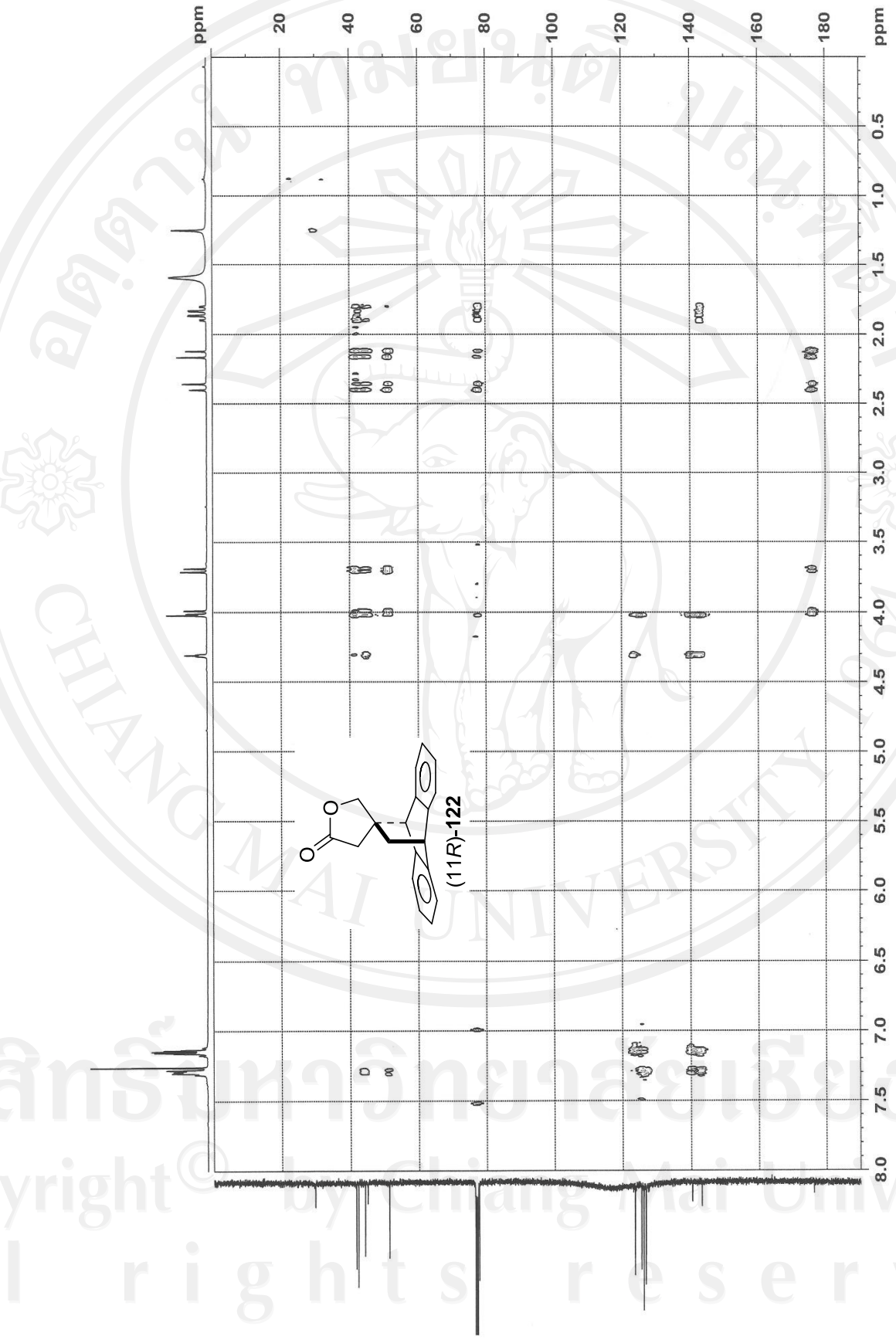
Appendix 44 ^{13}C-NMR spectrum of compound (11*R*)-**122**



Appendix 45 COSY spectrum of compound (11*R*)-**122**



Appendix 46 HMQC spectrum of compound (11*R*)-**122**



Appendix 47 HMBC spectrum of compound (11*R*)-**122**

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2012 M.S. in Chemistry, Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand.

Scholarship

2006–2009 Pechthongkwao (chemistry) Scholarship from faculty of Science, Chiang Mai University, Chiang Mai, Thailand

2010–present Human Resource Development in Science Project (Science Achievement Scholarship of Thailand, SAST)

National Conference

2008 Supaporn Kradtap Hartwell, Supada Khongyoung, Warisra Kochasit, Worathip Sripaoraya, **Sutthichat Kerdphon**, Jaroon Jakmunee, Somchai Lapanantnoppakhun, Torpong Sanguansermsri and Kate Grudpan, "Flow Injection with Spectrophotometric Detection for Automatic Screening of Thalassemia" (Poster Presentation), Symposium for Younger Generation Researchers on 29 August 2008, Chiang Mai University, Chiang Mai, Thailand.

International Conferences

2012 **Sutthichat Kerdphon** and Puttinan Meepowpan, "Syntheses of *N,O* Heteroatoms TADDOLs–like Anthracene Adducts as Asymmetric Ligands" (Proceeding), The 6th Pure and Applied Chemistry International Conference 2012 (PACCON 2012) on 11–13 January 2012, The Empress Convention Center, Chiang Mai, Thailand, 1783-1786.

2011 **Sutthichat Kerdphon** and Puttinan Meepowpan, "Syntheses of Novel TADDOLs–Anthracene Adducts as Chiral Catalysts Using in Asymmetric Reaction" (Poster presentation), The International Congress for Innovation in Chemistry (PERCH-CIC CONGRESS VII) on 4–7 May 2011**,** Jomtien Palm Beach Resort, Chonburi, Thailand.

2010 **Sutthichat Kerdphon**, Jaroon Jakmunee, Kate Grudpan, Supaporn Kradtap Hartwell, "Development of Hydrodynamic Injection System for Online Single Concentration Standard Addition" (Poster presentation), The 16th International Conference on Flow Injection Analysis (ICFIA2010) on 25–30 April 2010, Pattaya, Thailand.

2008 Warisra Kochasit, **Sutthichat Kerdphon**, Torpong Sanguansermsri, Jaroon Jakmunee, Somchai Lapanantnoppakhun, Supaporn Kradtap Hartwell and Kate Grudpan, "Development of a Flow-Based Dichlorophenolindophenol Precipitation System for Screening of Hemoglobin E" (Poster Presentation), The 15th International Conference on Flow Injection Analysis (ICFIA2008) on 28 September – 3 October 2008, Nagoya, Japan.

Publication

2009 Supaporn Kradtap Hartwell, Warisra Kochasit, **Sutthichat Kerdphon**, Jaroon Jakmunee, Somchai Lapanantnoppakhun, Torpong Sanguansermsri and Kate Grudpan, "Hydrodynamic Sequential Injection System for a Rapid Dichlorophenol Indophenol Precipitation Test for Hemoglobin E", Microchimica Acta **2009**, *167*, 201–209. (Impact factor = 1.91)

Syntheses of Novel TADDOLs–Anthracene Adducts as Chiral Catalysts Using in Asymmetric Reaction

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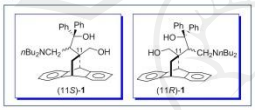
Introduction

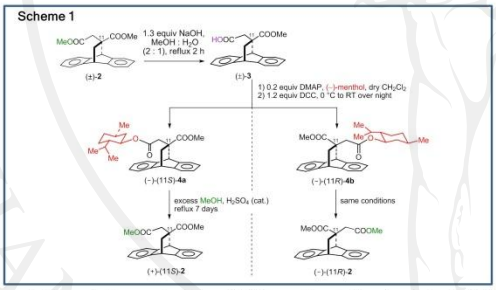
TADDOLs (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols) were prepared by Seebach *et al.* in 1987. In the previous study, preparation of TADDOLs and its analogues systems were included TADDOLs with N-, P-, O- and S- heteroatom ligands appropriate for metals. In this work, we are interested in synthesizing TADDOLs-anthracene adducts (11*S*)-**1** and (11*R*)-**1** included TADDOLs with N- and O- heteroatom ligands for titanium metal, which will be used as catalysts in asymmetric reactions.



Methodology

The optically active adducts, (+)-(11*S*)-**2** and (–)-(11*R*)-**2**, could be prepared by separation of the mixture of diastereoisomers (–)-(11*S*)-**4a** and (–)-(11*R*)-**4b** which were obtained according to the process as shown in Scheme 1.

Scheme 1



In Scheme 1, the racemic mixture of (±)-**2** was refluxed with sodium hydroxide (1.3 equiv) in the solution of MeOH:H_2O (2:1) for 2 h to give mono acid adduct (±)-**3**, after crystallization from CH_2Cl_2/Hexane. The mono acid adduct (±)-**3** was reacted with DCC (1.2 equiv) and catalytic amount of DMAP followed by treating with (–)-(1*R*,3*R*,4*S*)-menthol in dry CH_2Cl_2. The crude product was purified by crystallization from CH_2Cl_2/Hexane to afford (–)-(11*S*)-**4a**. Compound (–)-(11*R*)-**4b** was crystallized from CH_2Cl_2/MeOH. Thus, pure diastereoisomers (–)-(11*S*)-**4a** and (–)-(11*R*)-**4b** were characterized using ^{1}H NMR, ^{13}C NMR, DEPT, 2D NMR and specific rotation, and comparison of spectroscopic data with those reported by Kongsaeree *et al. Tetrahedron: Asymmetry* **2001**, *12*, 1913-1922.

Hence the enantiomerically pure dimethyl itaconate–antracene adducts, (+)-(11*S*)-**2** and (–)-(11*R*)-**2**, were obtained in high yield by transmethylation of (–)-(11*S*)-**4a** and (–)-(11*R*)-**4b**, respectively, by refluxing in excess anhydrous MeOH and catalytic amount of conc. H_2SO_4.

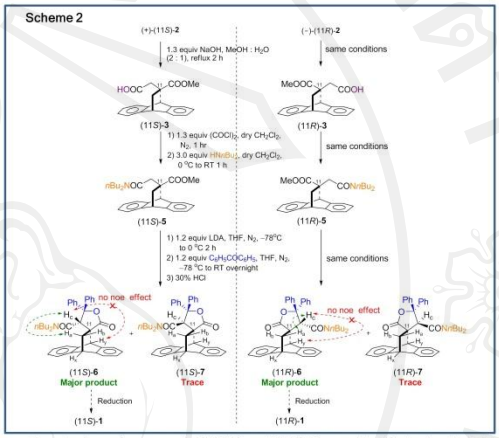
In Scheme 2, syntheses of compounds (11*S*)-**1** and (11*R*)-**1** were started from dimethyl itaconate–antracene adducts (–)-(11*S*)-**2** and (–)-(11*R*)-**2** which were hydrolyzed to give mono acid adducts (11*S*)-**3** and (11*R*)-**3** respectively, after crystallization from CH_2Cl_2/Hexane. Then the mono acids (11*S*)-**3** and (11*S*)-**3** were converted to the corresponding acid chloride by oxalyl chloride (1.3 equiv) in dry CH_2Cl_2 for 1 h followed by 3.0 equiv of nBu$_2$NH. The crude products were separated by column chromatography (silica gel, EtOAc:Hexane = 1 : 9 as eluent) to afford (11*S*)-**5** and (11*S*)-**5**, respectively. The next step, compound (11*S*)-**5** and (11*S*)-**5** were reacted with 1.2 equiv LDA at –78 °C to 0 °C for 2 h and then trapped with benzophenone to provide (11*S*)-**6** and (11*R*)-**6**, respectively after purification by flash column chromatography (silica gel, EtOAc:CH_2Cl_2:Hexane = 1 : 1 : 9 as eluent). Finally, the TADDOLs–anthracene adducts (11*S*)-**1** and (11*R*)-**1** obtained from reduction with LAH of the compounds (11*S*)-**6** and (11*R*)-**6**, respectively.

Results and Discussions

Compounds (11*S*)-**3** and (11*R*)-**3** were reacted with nBu$_2$NH to give the adducts (11*S*)-**5** and (11*R*)-**5**, respectively, in high yields. Then, both the adducts (11*S*)-**6** and (11*R*)-**6**, as major product, were obtained in moderate yields, which were synthesized through tandem aldol–lactonization reactions.

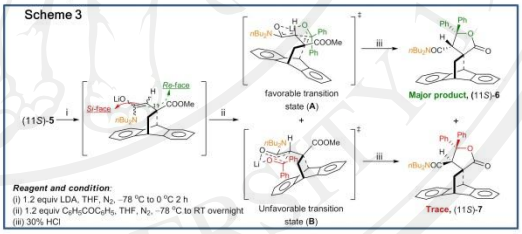
Keywords: TADDOLs-anthracene adduct, asymmetric reaction

Scheme 2



The structure of compounds (11*S*)-**6** and (11*R*)-**6** were identified using their ^{1}H NMR and ^{13}C NMR. In the ^{1}H NMR spectrum of these compounds, the proton H_a, H_c and H_d appeared at δ 1.62, 3.5 and 5.2 ppm, respectively. By observation from NOE experiments of compound (11*S*)-**6** and (11*R*)-**6**, the stereochemistries of these compounds were finally confirmed in Scheme 3. Irradiation of the proton H_c gave a NOE effect on the proton H_a but no NOE effect on the proton H_y; thus the orientation of the proton H_c is on the upper face and *syn*- with the proton H_a but anti- with the proton H_y.

Scheme 3



The stereochemistry outcome of the aldol condensation reaction can be explained by the chair–like transition states (**A** and **B**) in Scheme 3. The transition states A would lead to the major product (11*S*)-**6**. In contrast, the transition states **B** would lead to the formation of the trace (11*S*)-**7**. The latter is less favorable due to the large steric repulsion between the phenyl group and the anthracene ring. The stereochemistry of (11*R*)-**6** and (11*R*)-**7** were explained in the similar reasons.

Conclusion

The adducts (11*S*)-**6** and (11*R*)-**6** can be synthesized through tandem aldol–lactonization, as the key step, using both enantiomerically active forms (11*S*)-**3** and (11*R*)-**3** as starting materials. The TADDOLs–anthracene adducts (11*S*)-**1** and (11*R*)-**1** will be prepared by reduction and used as chiral catalyst for asymmetric reaction in the future.

Acknowledgements

We acknowledge the Human Resource Development in Science Project (Science Achievement Scholarship of Thailand, SAST), Materials Science Research Center and Department of Chemistry, Faculty of Science, Chiang Mai University.

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1) Kongsaeree, P.; Meepowpan, P.; Thebtaranonth, Y. *Tetrahedron: Asymmetry*, **2001**, *12*, 1913-1922.
2) Pellissier, H. *Tetrahedron*, **2008**, *64*, 10279-10317.
3) Seebach, D.; Beck, A.K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92-138.

SYNTHESIS OF *N,O* HETEROATOMS TADDOLS-ANTHRACENE ADDUCTS AS ASYMMETRIC LIGANDS

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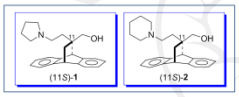
Introduction

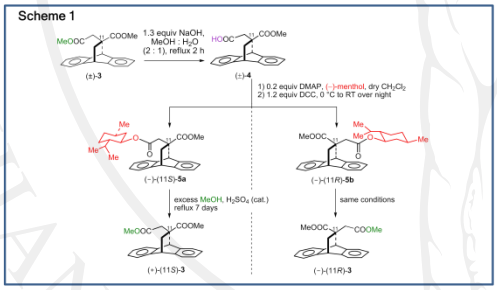
TADDOLs (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols) were prepared by Seebach *et al.* in 1987. In the previous study, preparation of TADDOLs and its analogues systems were included TADDOLs with N-, P-, O- and S- heteroatom ligands appropriate for metals. In this work, we are interested in synthesizing *N,O* TADDOLs-anthracene adducts (11*S*)-1 and (11*S*)-2 included TADDOLs with N- and O- heteroatom ligands for titanium metal, which will be used as catalysts in asymmetric reactions.



Methodology

The optically active adducts, (+)-(11*S*)-3 and (−)-(11*R*)-3, could be prepared by separation of the mixture of diastereoisomers (−)-(11*S*)-**5a** and (−)-(11*R*)-**5b** which were obtained according to the process as shown in Scheme 1.

Scheme 1



In Scheme 1, the racemic mixture of (±)-3 was refluxed with sodium hydroxide (1.3 equiv) in the solution of MeOH:H_2O (2:1) for 2 h to give monoacid-anthracene adduct (±)-4, after crystallization from CH_2Cl_2/Hexane. The monoacid-anthracene adduct (±)-4 was reacted with DCC (1.2 equiv) and catalytic amount of DMAP followed by treating with (−)-(1*R*,3*R*,4*S*)-menthol in dry CH_2Cl_2. The crude product was purified by crystallization from CH_2Cl_2/Hexane to afford (−)-(11*S*)-**5a**. Compound (−)-(11*R*)-**5b** was crystallized from MeOH. Thus, pure diastereisomers (−)-(11*S*)-**5a** and (−)-(11*R*)-**5b** were characterized using ^{1}H NMR, ^{13}C NMR, DEPT, 2D NMR and specific rotation, and comparison of spectroscopic data with those reported by Kongsaeree *et al. Tetrahedron: Asymmetry* 2001, *12*, 1913-1922.

Hence the enantiomerically pure dimethyl itaconate–anthracene adducts, (+)-(11*S*)-3 and (−)-(11*R*)-3, were obtained in high yield by transmethylation of (−)-(11*S*)-**5a** and (−)-(11*R*)-**5b**, respectively, by refluxing in excess anhydrous MeOH and catalytic amount of conc. H_2SO_4.

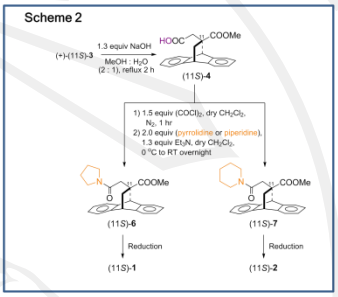
In Scheme 2, syntheses of compounds (11*S*)-1 and (11*S*)-2 were started from dimethyl itaconate–antracene adducts (+)-(11*S*)-3 which was hydrolyzed to give monoacid-anthracene adducts (11*S*)-4, after crystallization from CH_2Cl_2/Hexane. Then the adducts (11*S*)-4 was converted to the corresponding acid chloride-anthracene adducts by oxalyl chloride (1.5 equiv) in dry CH_2Cl_2 for 1 h followed by 2.0 equiv of (pyrrolidine or piperidine) and 1.3 equiv of Et_3N. The crude products were separated by flash column chromatography (silica gel, EtOAc:Hexane = 4 : 6 as eluent) to afford adducts (11*S*)-6 or (11*S*)-7. Finally, the *N,O* heteroatoms TADDOLs–anthracene adducts (11*S*)-1 and (11*S*)-2 obtained from reduction with $LiAlH_4$ of the adducts (11*S*)-6 and (11*S*)-7, respectively.

Results and Discussions

Hydrolysis of addduct (+)-(11*S*)-3 with NaOH in Methanol/H_2O to give the adducts (11*S*)-4 in high yields. Then, the adduct (11*S*)-4 was reacted with (pyrrolidine or piperidine) to give adducts (11*S*)-6 and (11*S*)-7 in 93.33% and 89.68% yield of isolated compound, respectively.

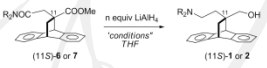
Keywords: TADDOLs-anthracene adduct, asymmetric reaction, chiral ligand, chiral catalyst

Scheme 2



From the study of the reduction reaction of The amide-anthracene adduct (11*S*)-6 and (11*S*)-7 by using $LiAlH_4$ as the reducing agent gave the results which are summarized in Table 1. The adduct (11*S*)-6 was reduced by 5.0 equiv of $LiAlH_4$ in the conditions (−78 °C to room temperature, 2 days) to give the highest percentage yield (64%) and the adduct (11*S*)-7 was reduced by 5.0 equiv of $LiAlH_4$ in the conditions (Reflux, overnight) to give the highest percentage yield (83%). The reduction of adduct (11*S*)-6 was increased the equiv of $LiAlH_4$ in the same conditions (entry1) led to decrease in percentage yield but the reduction of adduct (11*S*)-7 was increased the equiv of $LiAlH_4$ in the same conditions (entry2) led to increase in percentage yield.

Table 1



Entry	R	Equiv of $LiAlH_4$	conditon	Yield[a] (%)
1		5.0	Reflux, overnight	56
		5.0	-78 °C to RT, 2 days	64
		10.0	-78 °C to RT, 2 days	53
		15.0	-78 °C to RT, 2 days	42
2		5.0	Reflux, overnight	83
		5.0	-78 °C to RT, 2 days	54
		10.0	-78 °C to RT, 2 days	70
		15.0	-78 °C to RT, 2 days	78

[a] Isolated yield.

Conclusion

The adducts (11*S*)-6 and (11*S*)-7 can be synthesized through hydrolysis and amide formation as the key step, using the enantiomerically active forms (+)-(11*S*)-3 as starting materials. The *N,O* heteroatoms TADDOLs–anthracene adducts (11*S*)-1 and (11*S*)-2 will be prepared by reduction with $LiAlH_4$. In the future, we expect that these adducts will be used as chiral catalyst for asymmetric diethylzinc 1,2 addition to benzaldehyde.

Acknowledgements

We acknowledge the Human Resource Development in Science Project (Science Achievement Scholarship of Thailand, SAST), Department of Chemistry, Center for innovation in chemistry (PERCH-CIC) and Materials Science Research Center, Faculty of Science, Chiang Mai University.

References

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THE 6th PURE AND APPLIED CHEMISTRY INTERNATIONAL CONFERENCE 2012

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SYNTHESIS OF *N,O* HETEROATOMS TADDOLS–LIKE ANTHRACENE ADDUCTS AS ASYMMETRIC LIGANDS

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Abstract: The developments of chiral ligands for chiral catalysts are important in asymmetric syntheses. As an alternative chiral ligands, the compound (11*S*)-5, *N,O* heteroatoms TADDOLs-anthracene adducts, can be successfully synthesized from the enantiomerically pure dimethyl itaconate-anthracene adducts (+)-(11*S*)-4, which was prepared form Diels-Alder reaction between anthracene with dimethyl itaconate, and then resolved into the enantiomerically pure form using (–)-(1*R*,3*R*,4*S*)-menthol as a chiral auxiliary, in moderate yields. These TADDOLs-anthracene adducts were synthesized *via* hydrolysis, amide formation and reduction with $LiAlH_4$ respectively, as the key steps. These adducts will be evaluated as chiral ligand or chiral catalyst for asymmetric reactions such as 1,2 addition reaction of diethylzinc with benzaldehyde in the future.

1. Introduction

TADDOLs (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols) are the chiral diols which were firstly prepared by Seebach *et al.* in 1987. They contain two adjacent diaryhydroxymethyl groups in a *trans* relationship on a 1,3-dioxolane ring, as shown in Figure 1. They were generally prepared from acetals or ketals of tartrate esters by reaction of the latter with aromatic Grignard reagents [1]. In addition, TADDOLs analogues can be synthesized by derivatization or replacement of one or both TADDOLs OH- groups. The OH of the TADDOLs may be functionalized with alkyl, aryl or silyl ethers, phosphonite, sulfites or phosphoric acid esters. These heteroatoms may be replaced by other heteroatom, such as N, P, OOH, S, F, Cl, Br and *etc* [2].

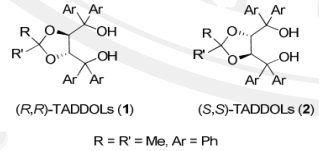


Figure 1. Structure of TADDOLs.

The chiral diols can be used as chiral reagent, chiral organocatalysts and catalytically asymmetric reaction for nucleophilic addition to C=O bonds, nucleophilic conjugate addition to electron-deficient C=C bonds, nucleophilic substitution reaction, cycloaddition reaction, oxidation reaction and reduction reaction [3]. Moreover, the chiral diols were used as chiral ligands for some metal ions such as Ti(IV) which were effective catalysts in Diels-Alder reaction [4-5], Aldol reaction [6] and pinacol coupling reaction [7]. Furthermore, Qian and coworkers have reported the use of amino-TADDOL derivatives (Figure 2) as catalysts of the enantioselective addition of diethylzinc to aromatic aldehydes to give moderate to good yields and enantioselcetivities were obtained (up to 88% *ee*) [8].

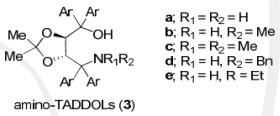
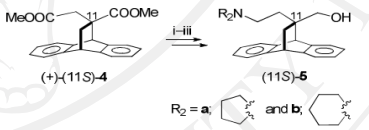


Figure 2. Structure of amino–TADDOLs.

In this research, we are interested to synthesize the new chiral ligands, *N,O* heteroatom TADDOLs–like anthracene adducts (11*S*)-**5** which prepared from dimethyl itaconate–anthracene adducts (+)-(11*S*)-**4** as shown in Scheme 1.



Scheme 1. Syntheses of *N,O* heteroatom TADDOLs–like anthracene adducts. *Methods:* (i) hydrolysis; (ii) amide formation; (iii) reduction with $LiAlH_4$.

2. Materials and Methods

2.1 General methods

All reaction were carried out under nitrogen atmosphere. Unless otherwise noted, meterials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Gallenkamp Electrothermal apparatus and were uncorrected. Optical rotations were measured in $CHCl_3$ on an Atago AP-300 polarimeter. The ^1H and ^{13}C NMR spectra were recorded on Bruker DRX 400 MHz spectrometers and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). All NMR spectra were measured in $CDCl_3$ and chemical shift were reported as δ-values in parts per million (ppm) relative to residue $CHCl_3$ as internal reference (^1H: δ7.26, ^{13}C: δ77) and coupling constants (*J*

values) were reported in hertz (Hz). Peak multiplicities are indicated as follows: *s* (singlet), *d* (doublet), *dt* (doublet of triplets), *ddd* (doublet of doublet of doublets) and *m* (multiplet). Flash column chromatography was performed employing Merck silica gel 60 and Merck silica gel 60H. Preparative thin layer chromatography (PLC) plates were carried out using Merck silica gel 60 PF_{254}. Analytical thin layer chromatography was performed with Merck silica gel 60 F_{254} aluminum plates. Solvents were dried over CaH_2 and distilled before used. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone ketyl under nitrogen. Pyrrolidine, piperidine and triethylamine were died over CaH_2 and freshly distilled before used. Enantiomeric excesses were determined by ^{1}H NMR spectroscopy using the chiral lanthanide shift reagent, tris[3-(haptafluoro propylhydroxymethylene)-*d*-camphorato]praseody-mium(III), Pr(hfc)$_3$.

2.2 Chemistry

Synthesis of (11S)-11-carbomethoxy-11-carbox ylmethyl-9,10-dihydro-9,10-ethanoanthracene: A solution of NaOH (1.3 equiv, 1.5930 g, 39.83 mmol) in H_2O (250 mL) was added to a solution of (+)-dimethyl itaconate–anthracene adduct (+)-(11*S*)-**3** [9] (10.3051 g, 30.64 mmol) in MeOH (500 mL) and heated to reflux for 2 h. The mixture was adjusted to pH 2-3 by 30% HCl. After that the resulting solution was extracted with CH_2Cl_2 (3 times) and the combined organic portions were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was crystallized from CH_2Cl_2/hexane to give the enantiomerically pure monoacid–anthracene adduct (11*S*)-**6** as major product.

*(11S)-11-carbomethoxy-11-carbox ylmethyl-9,10-dihydro-9,10-ethanoanthracene [(11S)-**6**] (Monoacid –anthracene adduct):* white solid; mp 148.2–149.8 °C (CH_2Cl_2/hexane); $[\alpha]_D^{27.5}$ = +74.5; δ_H (400 MHz, $CDCl_3$) 1.47, 2.78, 4.30 (3H, *ABX* system, *J* = 13.1, 3.0, 2.4 Hz, C*H*$_2$, ArC*H*), 1.96 (1H, *d*, *J* = 16.5 Hz, C*H*CO), 2.94 (1H, *d*, *J* = 16.5 Hz, C*H*CO), 3.44 (3H, *s*, COO*Me*), 4.33 (1H, *s*, ArC*H*), 6.99–7.33 (8H, *m*, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 36.8, 44.1, 44.2, 50.1, 52.2, 52.9, 123.4, 123.6, 124.3, 125.7(6), 125.7(9), 125.8, 126.6, 126.8, 139.5, 140.0, 142.8, 143.6, 174.7, 176.3.

General procedure for the synthesis of (11S)-11-carbomethoxy-11-(pyrrolidinyl or piperidinyl)acetyl-9,10-dihydro-9,10-ethanoanthracene: Oxalyl chloride (1.5 equiv, 0.65 mL, 7.76 mmol) was added slowly under nitrogen gas to a solution of mono acid–anthracene adduct (11*S*)-**6** (1.6473 g, 5.11 mmole) in dry of CH_2Cl_2 (15 mL) at room temperature and stirred for 1 h. Then, the excess oxalyl chloride and CH_2Cl_2 were evaporated to dryness by rotary evaporator to give the acid chloride–anthracene adduct (11*S*)-**7**. CH_2Cl_2 (15 mL) was added to this acid chloride adducts (11*S*)-**7** under nitrogen gas at room temperature. The solution mixture was cooled down by ice, then the 2°-amine (pyrrolidine or piperidine) (2.0 equiv, 10 mmol) and Et_3N (1.3 equiv, 0.93 mL, 6.64 mmol) were added. The reaction mixture was stirred at room temperature for overnight. After that, the resulting solution was washed with H_2O (3 times) and the combined organic portions were dried ($MgSO_4$), filtered and concentrated in *vacuo*. Purification of residue by flash column chromatography (EtOAc/hexane = 4:6 as eluent) gave the amide–anthracene adducts (11*S*)-**8**.

*(11S)-11-Carbomethoxy-11-pyrrolidinylacetyl-9,10-dihydro-9,10-ethanoanthracene [(11S)-**8a**]:* white solid; mp 162.3–163.5 °C (CH_2Cl_2/hexane); $[\alpha]_D^{27.2}$ = +127.2; δ_H (400 MHz, $CDCl_3$) 1.44, 2.88, 4.30 (3H, *ABX* system, *J* = 13.2, 3.12, 2.4 Hz, C*H*$_2$, ArC*H*), 1.68–1.89 (4H, *m*, C*H*$_2$), 1.90 (1H, *d*, *J* = 16.3 Hz, C*H*CO), 2.92 (1H, *d*, *J* = 16.3 Hz, C*H*CO), 2.99 (1H, *dt*, *J* = 10.2, 6.7 Hz, CH$_2$NC*H*), 3.18 (1H, *dt*, *J* = 10.2, 6.5 Hz, CH$_2$NC*H*), 3.41–3.26 (2H, *m*, C*H*$_2$NCH$_2$), 3.39 (3H, *s*, COO*Me*), 4.32 (1H, *s*, ArC*H*), 7.00–7.33 (8H, *m*, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 24.3, 25.9, 37.4, 44.3, 45.4(0), 45.4(1), 46.3, 50.2, 52.0, 53.4, 123.3, 123.5, 124.2, 125.4, 125.5, 125.6, 126.3, 126.4, 140.3, 140.4, 143.0, 144.0, 168.7, 176.0.

*(11S)-11-Carbomethoxy-11-piperidinylacetyl-9,10-dihydro-9,10-ethanoanthracene [(11S)-**8b**]:* white solid; mp 188.8–190.5 °C (CH_2Cl_2/hexane); $[\alpha]_D^{27.4}$ = +149.7; δ_H (400 MHz, $CDCl_3$) 1.41, 2.87, 4.29 (3H, *ABX* system, *J* = 13.3, 3.0, 2.5 Hz, C*H*$_2$, ArC*H*), 1.32–1.70 (6H, *m*, C*H*$_2$), 1.94 (1H, *d*, *J* = 16.2 Hz, C*H*CO), 2.98 (1H, *d*, *J* = 16.2 Hz, C*H*CO), 3.01–3.07, 3.08–3.21 (2H, *m*, *H*$_2$CNCH$_2$), 3.23–3.36, 3.38 (3H, *s*, COO*Me*), 3.45–3.58 (2H, *m*, H$_2$CNC*H*$_2$), 4.29 (1H, *s*, ArC*H*), 6.96–7.36 (8H, *m*, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 24.4, 25.5, 26.2, 37.5, 42.6, 44.1, 44.4, 46.4, 50.4, 51.9, 53.5, 123.4, 123.5, 124.2, 125.4, 125.6(0), 125.6(1), 126.3, 136.4, 140.4, 140.5, 143.0, 144.0, 168.5, 176.0.

General procedure for the reduction of (11S)-11-carbomethoxy-11-(pyrrolidinyl or piperidinyl)acetyl-9,10-dihydro-9,10-ethanoanthracene by using $LiAlH_4$: The amide–anthracene adducts (11*S*)-**8** (0.28 mmol) was added to a cooled solution (-78 °C) of $LiAlH_4$ (5 equiv, 1.44 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 2 days (or refluxed for overnight) and then quenched by dropwise addition of acetone (1 mL). After that, the resulting solution was extraction with CH_2Cl_2 (3 times) and combined organic portions were dried ($MgSO_4$), filtered and concentrated in *vacuo*. Purification of the crude product by preparative thin layer chromatography (PLC) (MeOH:EtOAc:hexane = 1:4:5 as eluent) gave the *N,O* heteroatoms TADDOLs–like anthracene adducts (11*S*)-**5** as a major products.

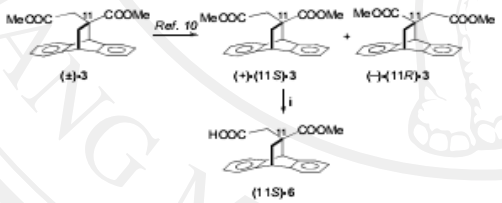
*(11S)-11-hydroxylmethyl-11-((2-pyrrolidinyl)ethyl) -9,10-dihydro-9,10-ethanoanthracene [(11S)-**5a**]:* white solid; mp 162.8–164.6 °C (EtOAc/hexane); $[\alpha]_D^{26.2}$ = +111.1; δ_H (400 MHz, $CDCl_3$) 1.09–1.40

(4H, *m*, CH_2), 1.68–1.86 (4H, *m*, CH_2), 2.25 (1H, *ddd*, *J* = 12.8, 6.4, 2.9 Hz, NC*H*), 2.48–2.66 (4H, *m*, CH_2NCH_2), 2.71 (1H, *d*, *J* = 11.7, C*H*OH), 2.84 (1H, *ddd*, *J* = 12.8, 10.2 , 2.6 Hz, NC*H*), 3.11 (1H, *d*, *J* = 11.7 Hz, C*H*OH), 4.19 (1H, *m*, ArC*H*), 4.38 (1H, *s*, ArC*H*), 5.88 (1H, *s*, O*H*), 6.93–7.45 (8H, *m*, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 23.3, 38.4, 39.5, 44.6, 44.9, 48.6, 51.2, 53.5, 68.9, 122.9, 123.3, 124.9, 125.3, 125.5, 125.6(0), 125.6(4), 125.7, 142.1, 142.3, 143.1, 143.7.

*(11S)-11-hydroxylmethyl-11-((2-piperidinyl)ethyl) -9,10-dihydro-9,10-ethanoanthracene [(11S)-**5b**]:* white solid; mp 188.1–190.0 °C (EtOAc/hexane); $[\alpha]_D^{27.3}$ = +71.1; δ_H (400 MHz, $CDCl_3$) 1.09–1.34 (6H, *m*, CH_2), 1.53–1.72 (4H, *m*, CH_2), 2.09–2.22 (1H, *m*, NC*H*), 2.22–2.67 (5H, *m*, NC*H*, H_2CNCH_2), 2.72 (1H, *d*, *J* = 11.8 Hz, C*H*OH), 3.08 (1H, *d*, *J* = 11.8 Hz, C*H*OH), 4.19 (1H, *m*, ArC*H*), 4.34 (1H, *s*, ArC*H*), 6.94–7.43 (8H, *m*, Ar*H*); δ_C (100.6 MHz, $CDCl_3$) 24.1, 25.4, 29.7, 36.1. 39.5, 44.6, 45.1, 49.1, 54.2, 54.4, 68.4, 122.87, 123.3, 125.0, 125.4, 125.6(0), 125.6(1), 125.6(5), 125.7, 142.2, 142.4, 143.1, 143.7.

3. Results and Discussion

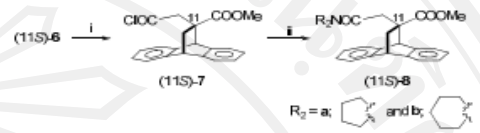
The enantiomerically pure monoacid–anthracene adducts (11*s*)-**6** was prepared from the hydrolysis of the enantiomerically pure dimethyl itaconate–anthracene adduct (+)-(11*S*)-**3** [10] using NaOH (1.3 equiv) in MeOH:H_2O (2:1) gave a white solid in 95% yield and >99% *ee*, as shown in Scheme 2.



Scheme 2. Synthesis of (11*S*)-monoacid–anthracene adducts (**6**). *Reagents and conditions:* (i) a. 1.3 equiv NaOH, MeOH:H_2O (2:1), reflux, 2h, b. 30% HCl.

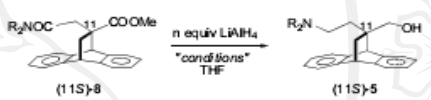
The monoacid adducts (11*S*)-**6** was converted to acid chloride by oxalyl chloride (1.5 equiv) in dry of CH_2Cl_2 for 1 h followed by treatment with the 2°-amine (pyrrolidine or piperidine) (2.0 equiv) and Et_3N (1.3 equiv) to provide the (11*S*)-amide **8a** (93%) and (11*S*)-amide **8b** (90%) (Scheme 3).

Reduction reaction of the amide adducts (11*S*)-**8** using $LiAlH_4$ as the reducing agent gave the results which are summarized in Table 1. The amide adduct (11*S*)-**8a** was reduced by 5.0 equiv of $LiAlH_4$ at −78 °C to room temperature, for 2 days to give the highest percentage yield. The amide adduct (11*S*)-**8b** was reduced by 5.0 equiv of $LiAlH_4$ under reflux, overnight to give the highest percentage yield. Increasing the amount of the reducing reagent led to decrease the percentage yield for the reduction of the amide adduct (11*S*)-**8a** (entry 1). On the other hand the reduction of amide adduct (11*S*)-**8b** (entry 2) led to increase in percentage yield.



Scheme 3. Synthesis of amide adducts (11*S*)-**8**. *Reagents and conditions:* (i) 1.5 equiv $(COCl)_2$, dry of CH_2Cl_2, N_2, RT, 1h; (ii) 2.0 equiv pyrrolidine or piperidine, 1.3 equiv Et_3N, dry of CH_2Cl_2, N_2, 0 °C to RT, overnight.

Table 1. Reduction of (11*S*)-amide–anthracene adducts (**8**) with $LiAlH_4$



Entry	R_2	Equiv of $LiAlH_4$	Conditons	Yield[a] (%)
1	a;	5.0	Reflux, overnight	56
		5.0	-78 °C to RT, 2 days	64
		10.0	-78 °C to RT, 2 days	53
		15.0	-78 °C to RT, 2 days	42
2	b;	5.0	Reflux, overnight	83
		5.0	-78 °C to RT, 2 days	54
		10.0	-78 °C to RT, 2 days	70
		15.0	-78 °C to RT, 2 days	78

[a] Isolated yield.

4. Conclusions

An alternative chiral ligand, *N,O* heteroatoms TADDOLs–anthracene adducts (11*S*)-**5a** and (11*S*)-**5b** were successfully synthesized form enantiomerically pure dimethyl itaconate–anthracene adducts (+)-(11*S*)-**3** *via* hydrolysis, amide formation and reduction with $LiAlH_4$, respectively. In the future, these adducts will be evaluated as chiral ligands for asymmetric 1,2 addition of diethylzinc to benzaldehyde.

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