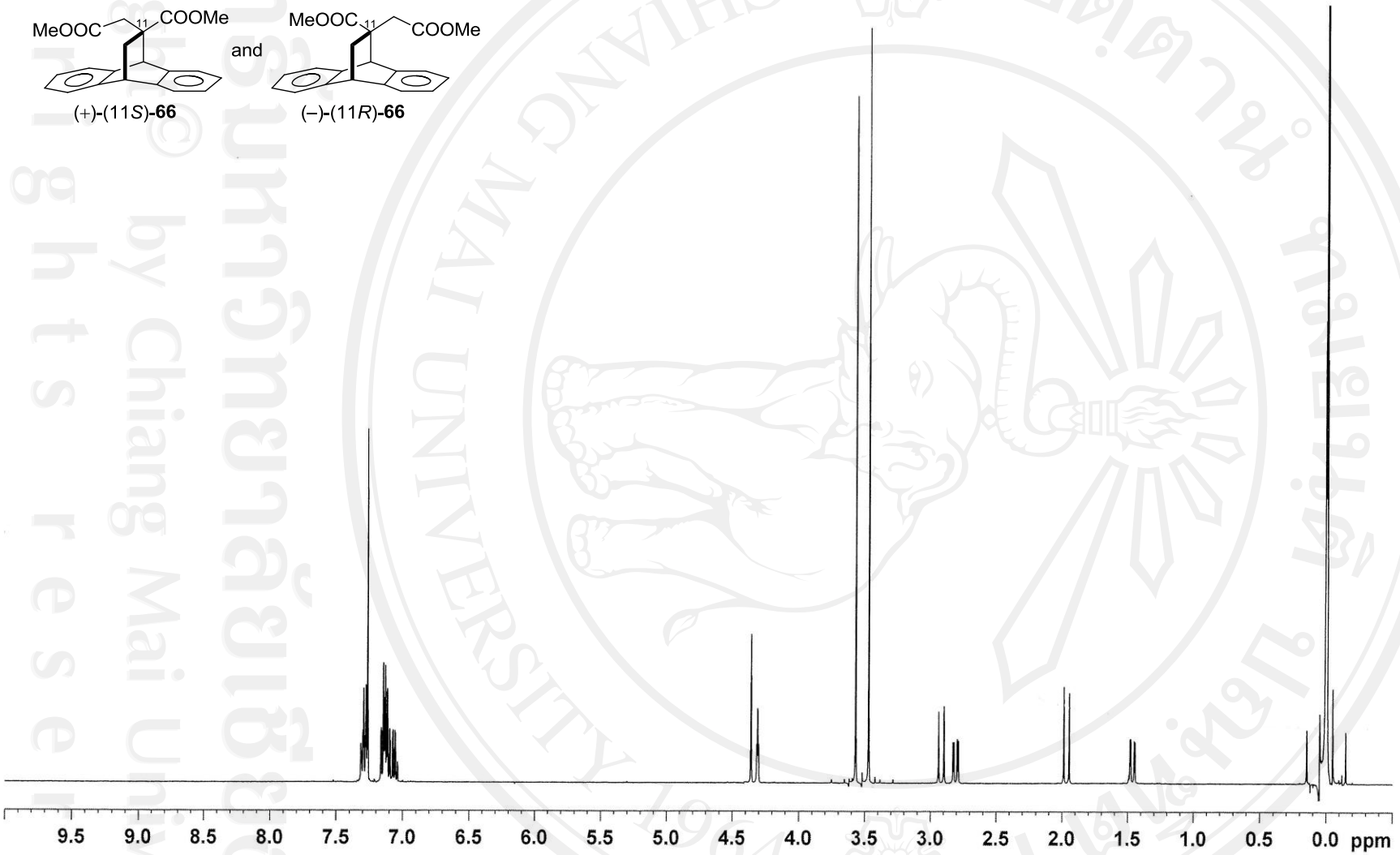
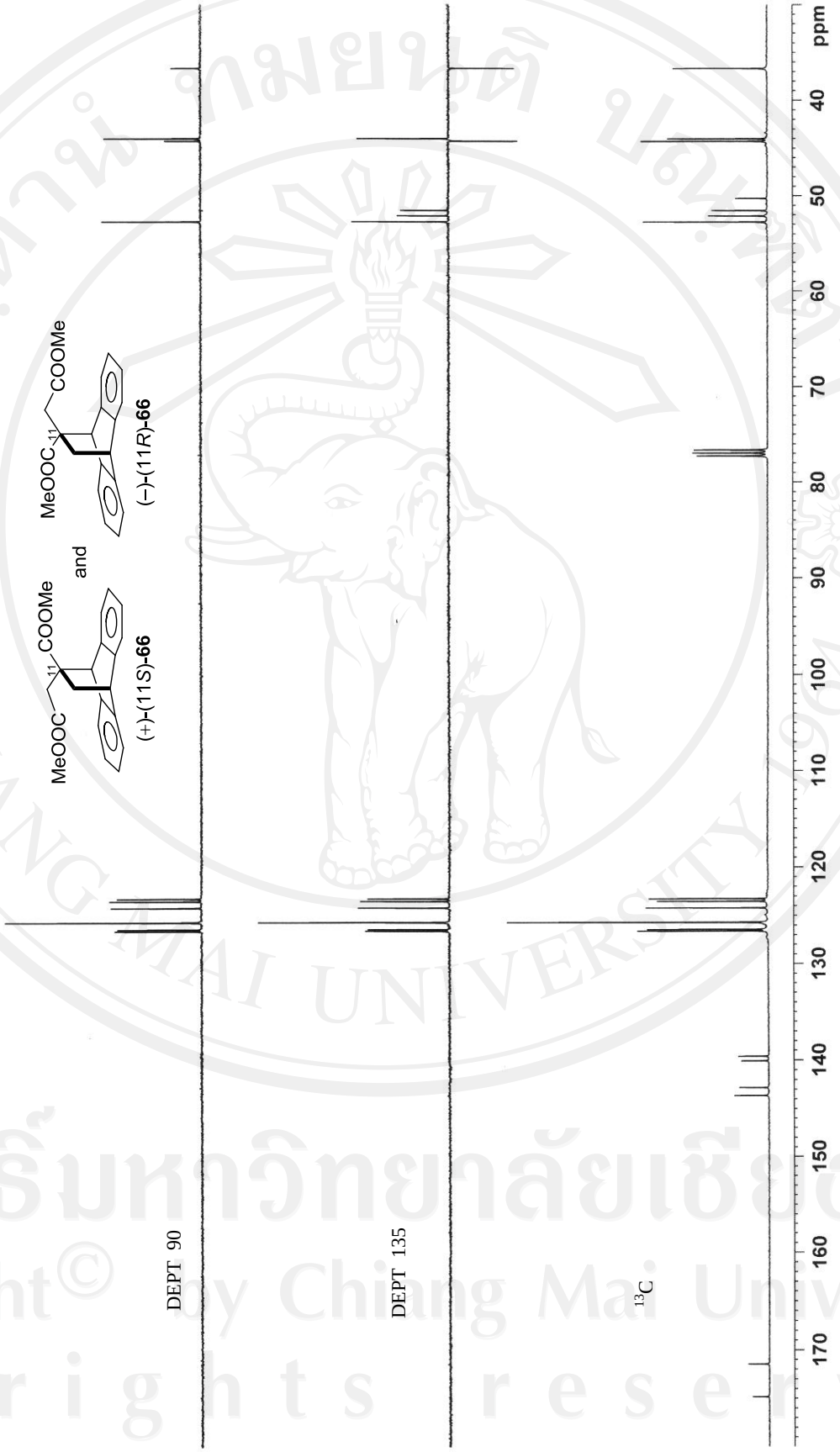
APPENDIX

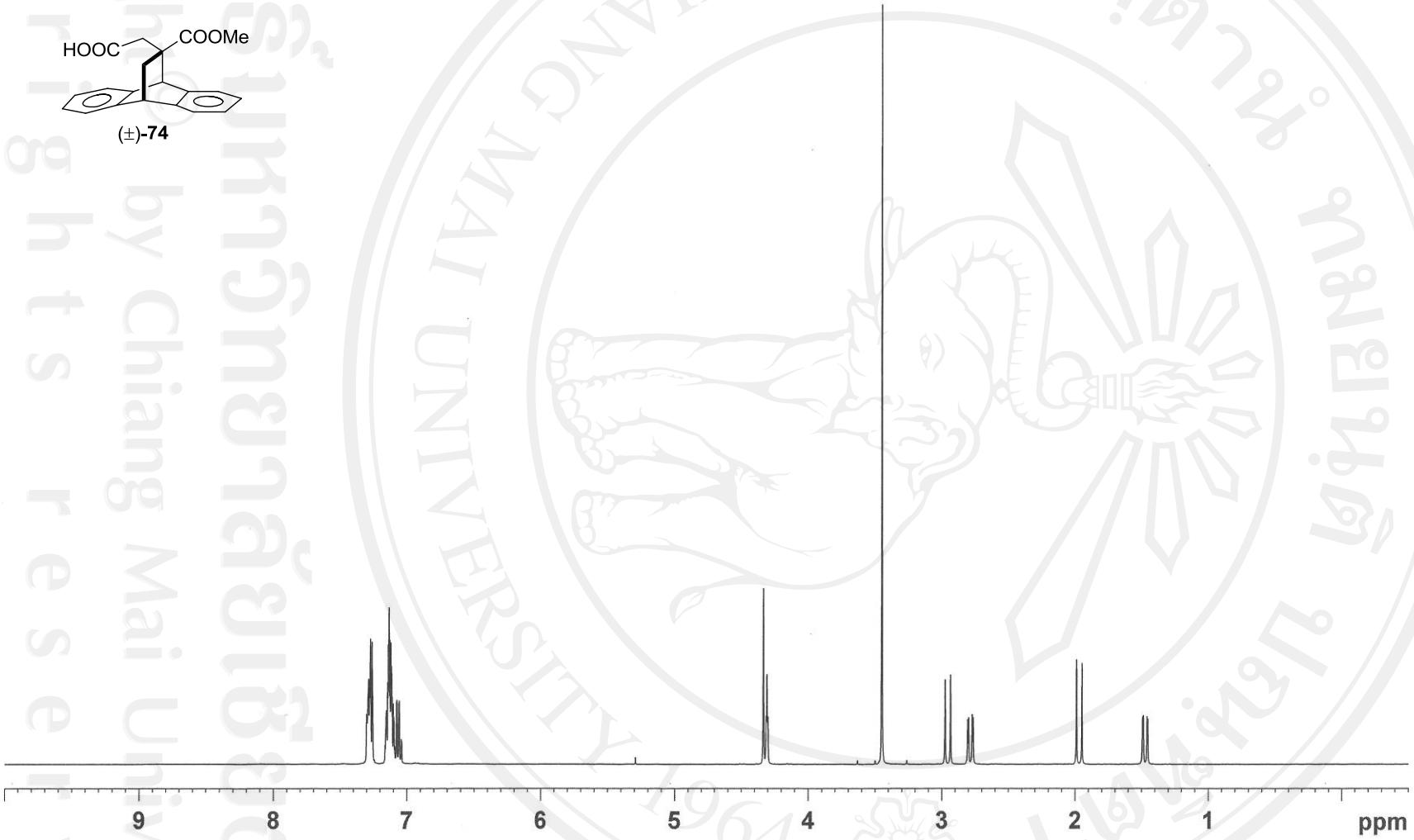
(^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz))



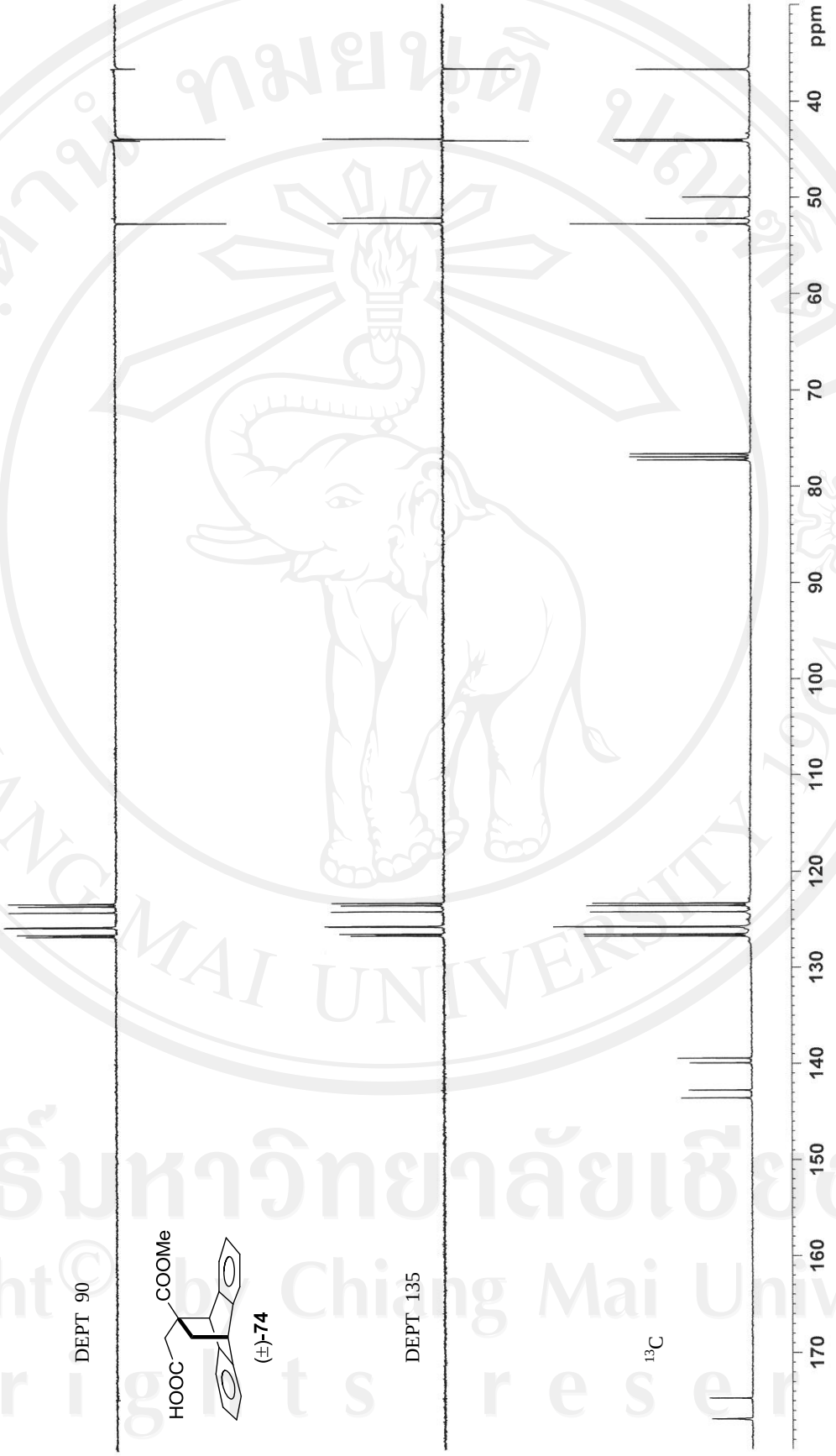
Appendix 1 ^{1}H-NMR spectrum of compounds (+)-(11*S*)-**66** and (–)-(11*R*)-**66**



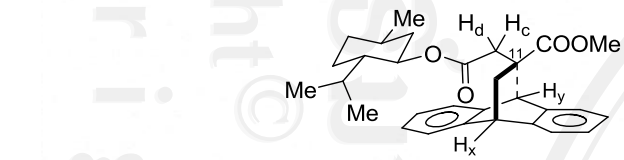
Appendix 2 ^{13}C-NMR spectrum of compounds (+)-(11*S*)-**66** and (–)-(11*R*)-**66**



Appendix 3 ^{1}H-NMR spectrum of compound **(±)-74**

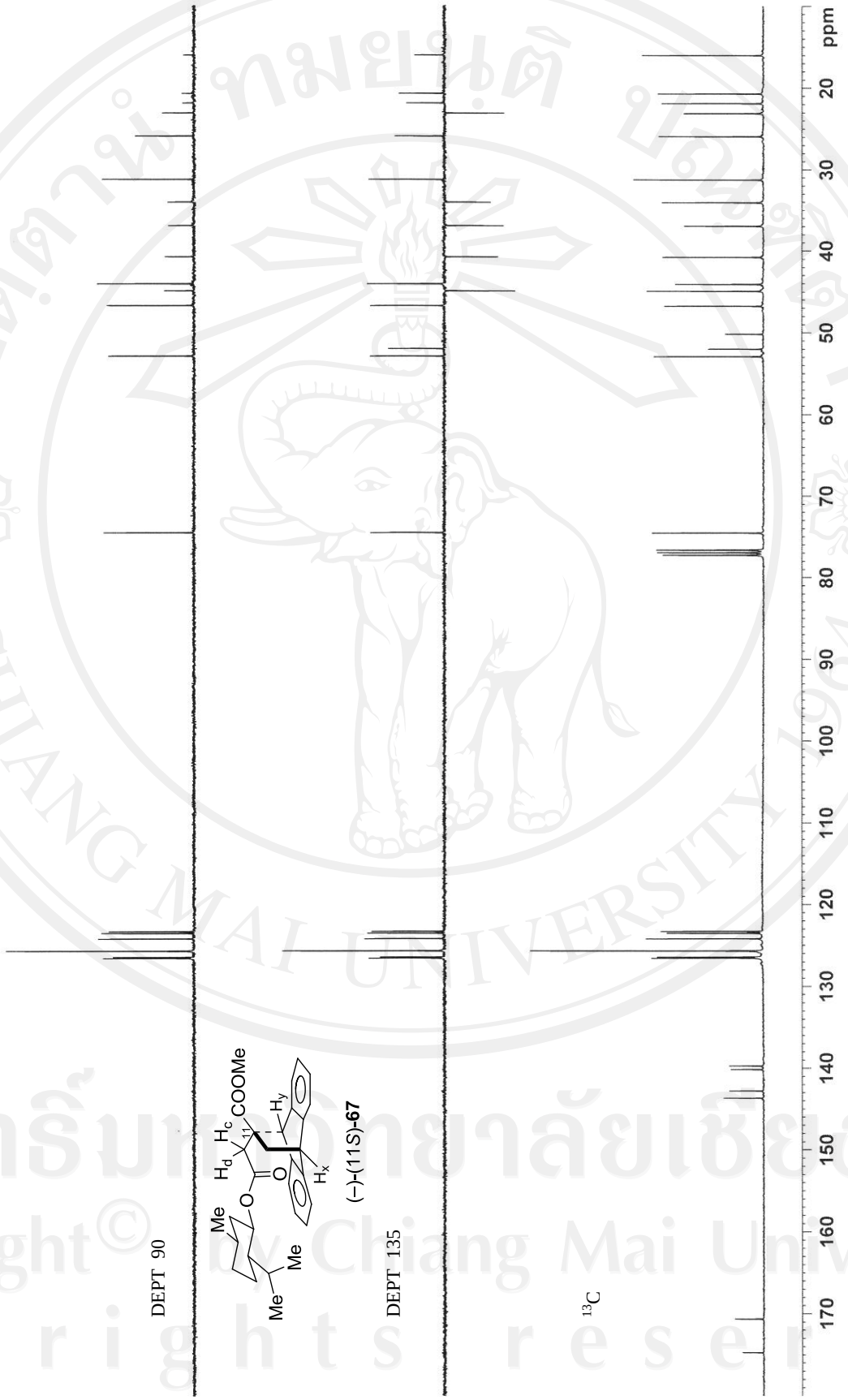


Appendix 4 ^{13}C-NMR spectrum of compound **(±)-74**

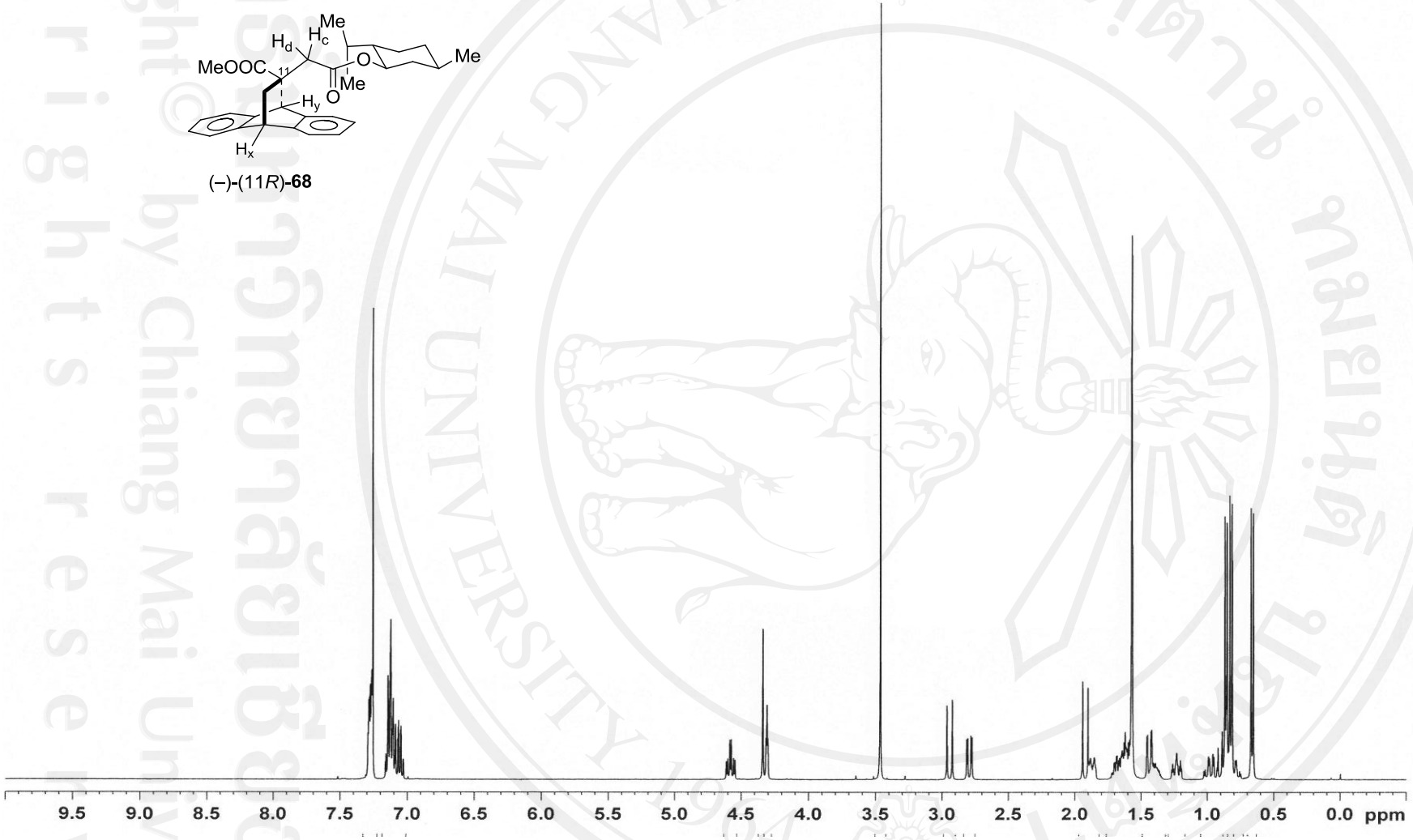


(–)-(11*S*)-**67**

Appendix 5 ^{1}H-NMR spectrum of compound (–)-(11*S*)-**67**

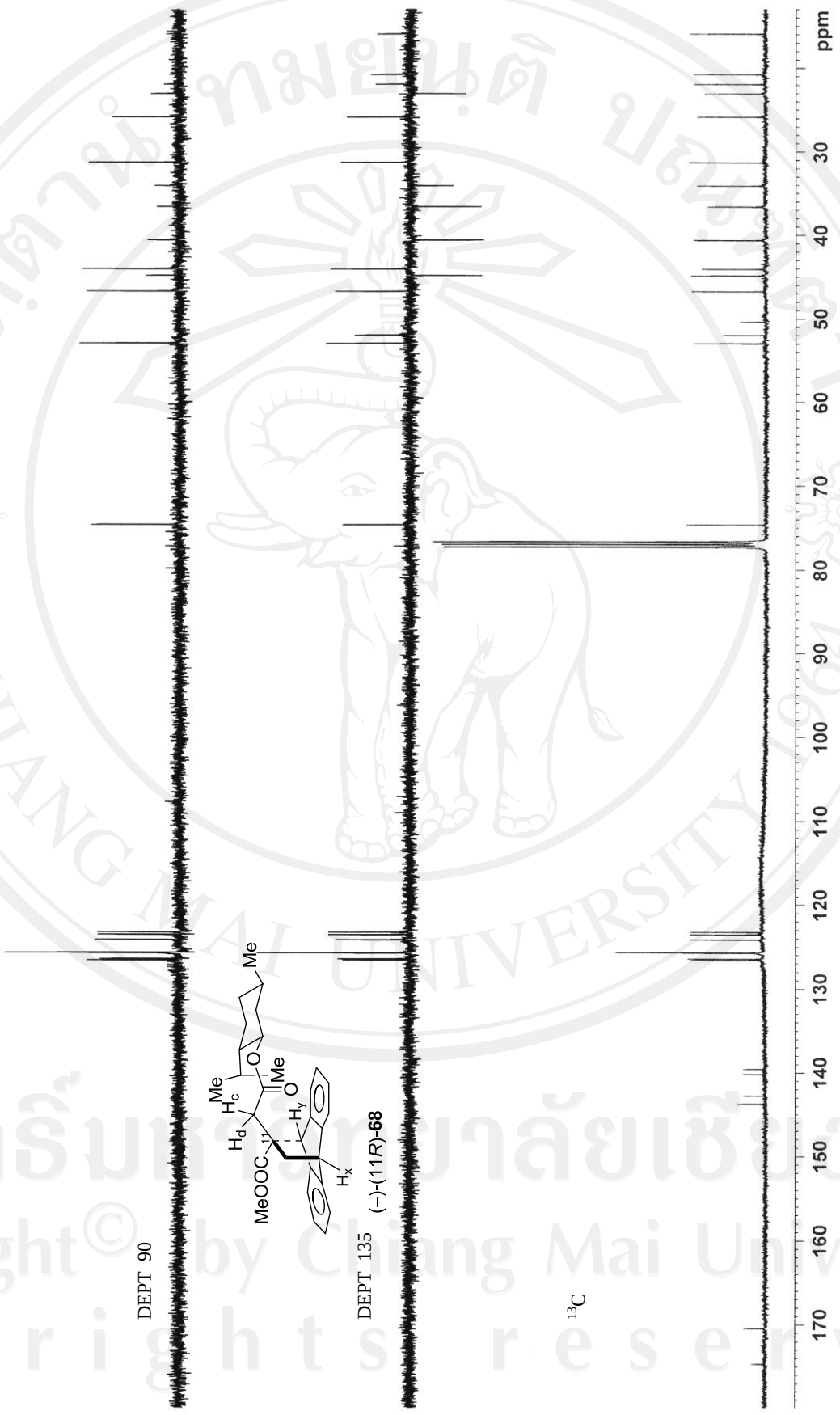


Appendix 6 ^{13}C-NMR spectrum of compound (–)-(11*S*)-**67**

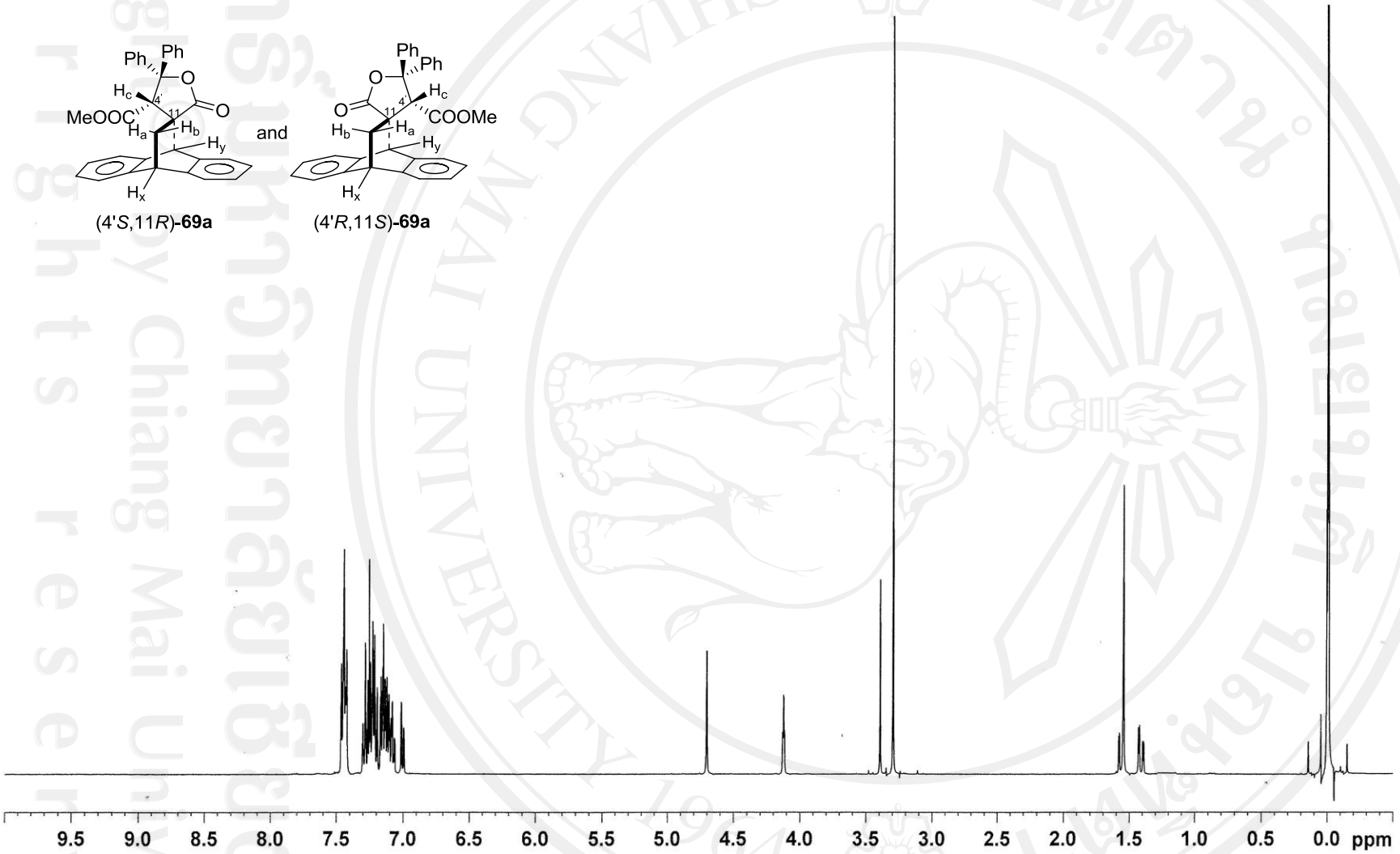


(–)-(11*R*)-**68**

Appendix 7 ^{1}H-NMR spectrum of compound (–)-(11*R*)-**68**

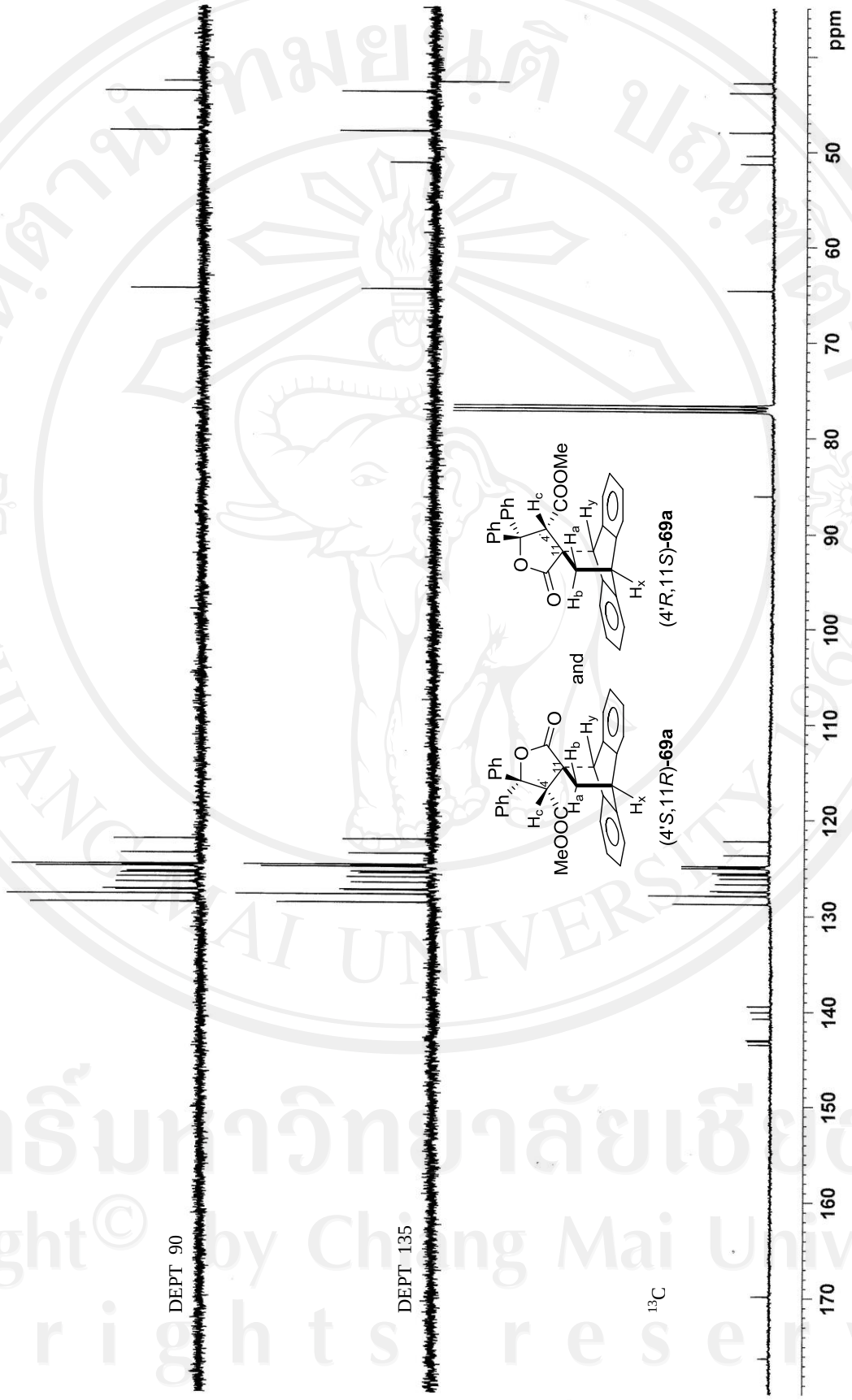


Appendix 8 ^{13}C-NMR spectrum of compound (–)-(11*R*)-**68**

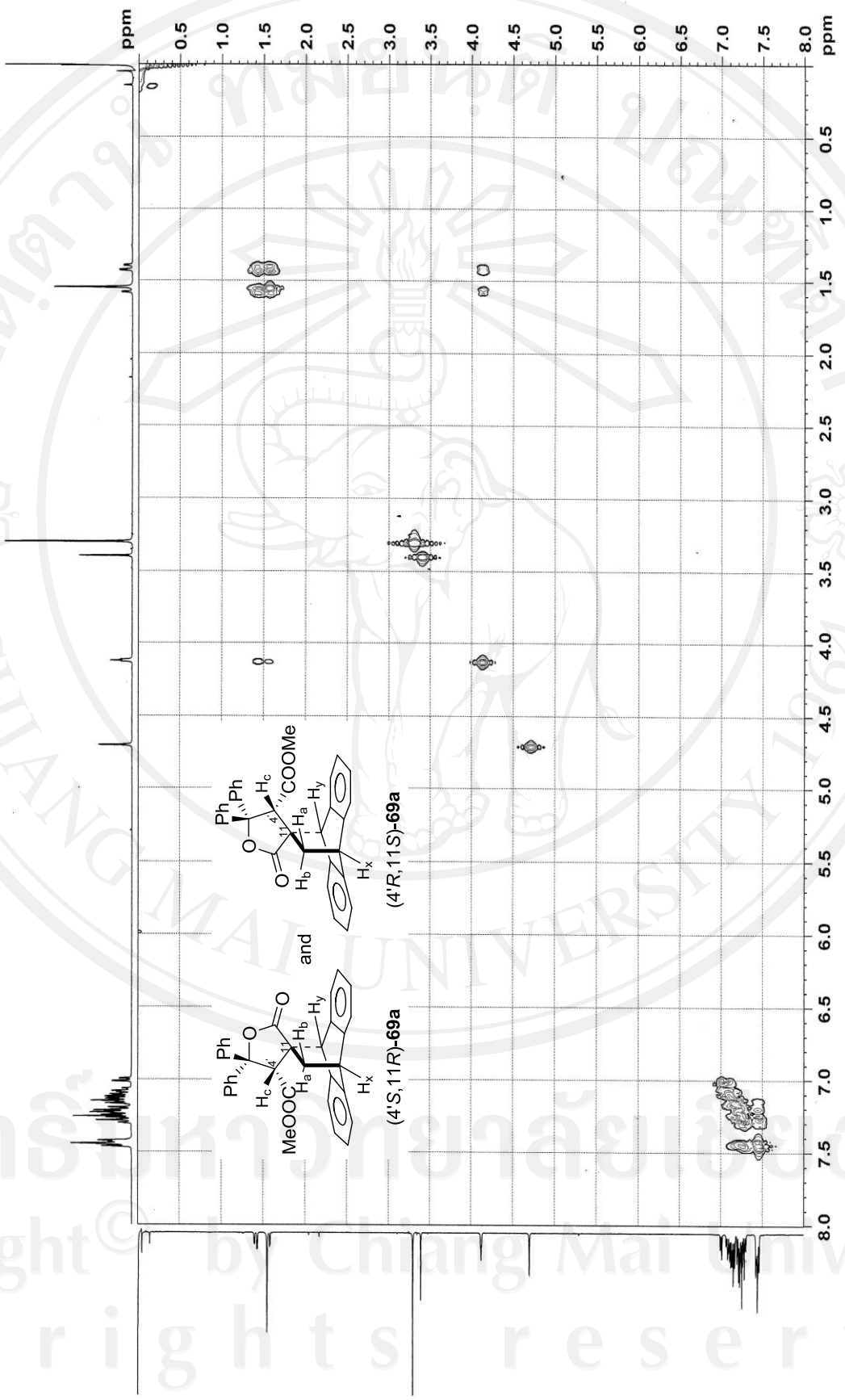


(4'*S*,11*R*)-**69a** (4'*R*,11*S*)-**69a**

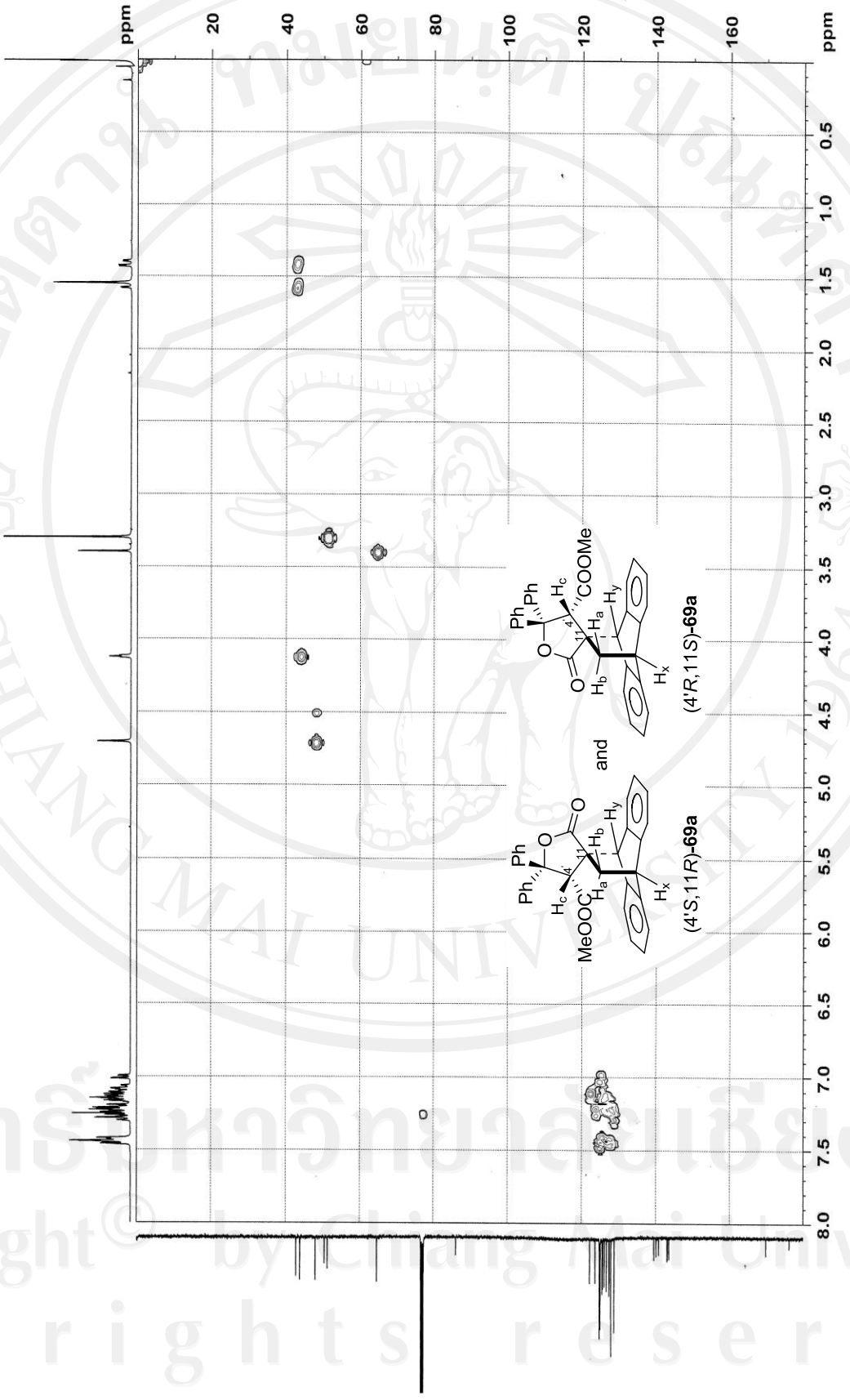
Appendix 9 ^{13}H-NMR spectrum of compound (4′*S*,11*R*)-**69a** and (4′*R*,11*S*)-**69a**



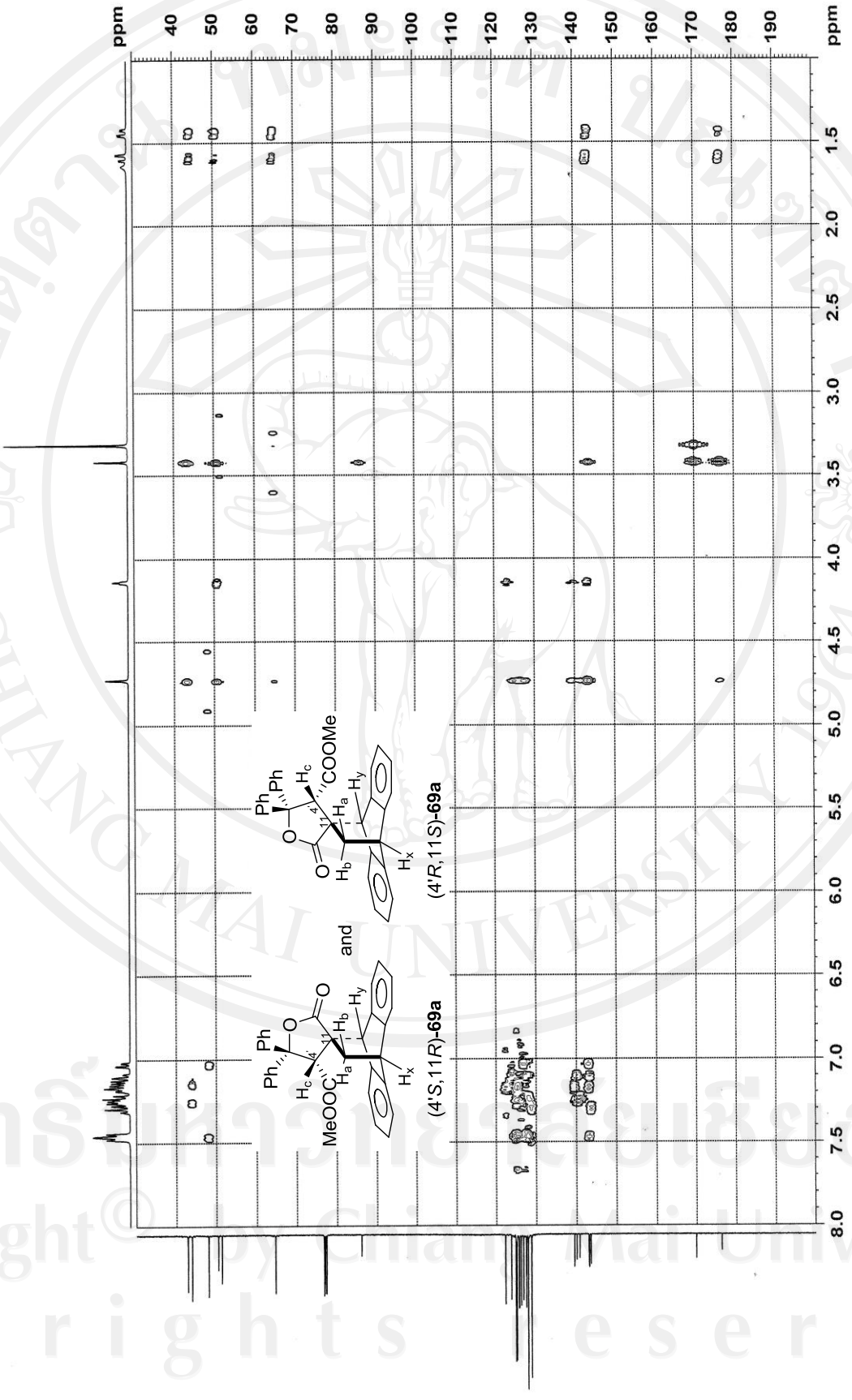
Appendix 10 ^{13}C-NMR spectrum of compound (4′*S*,11*R*)-**69a** and (4′*R*,11*S*)-**69a**



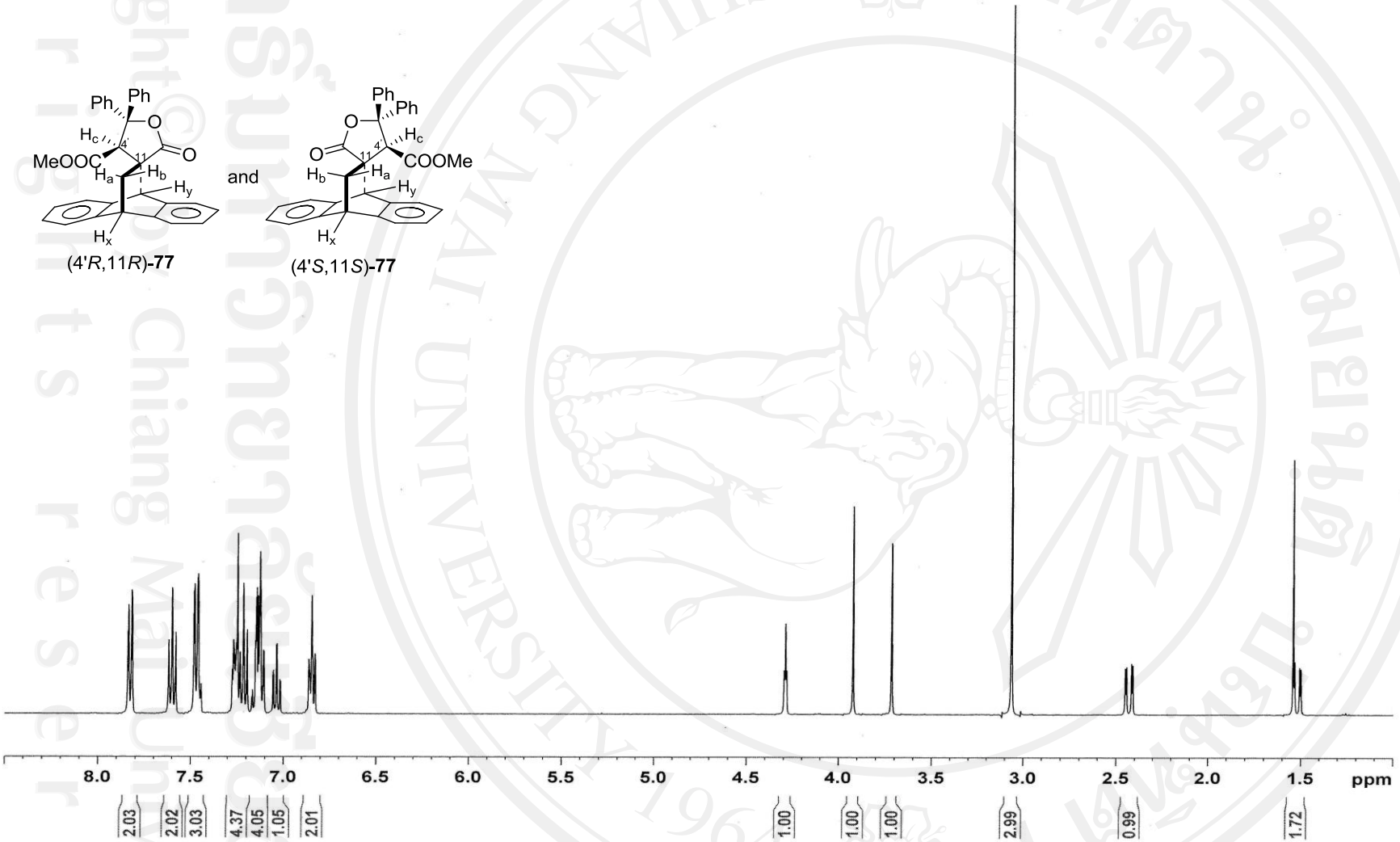
Appendix 11 COSY spectrum of compound (4′*S*,11*R*)-**69a** and (4′*R*,11*S*)-**69a**



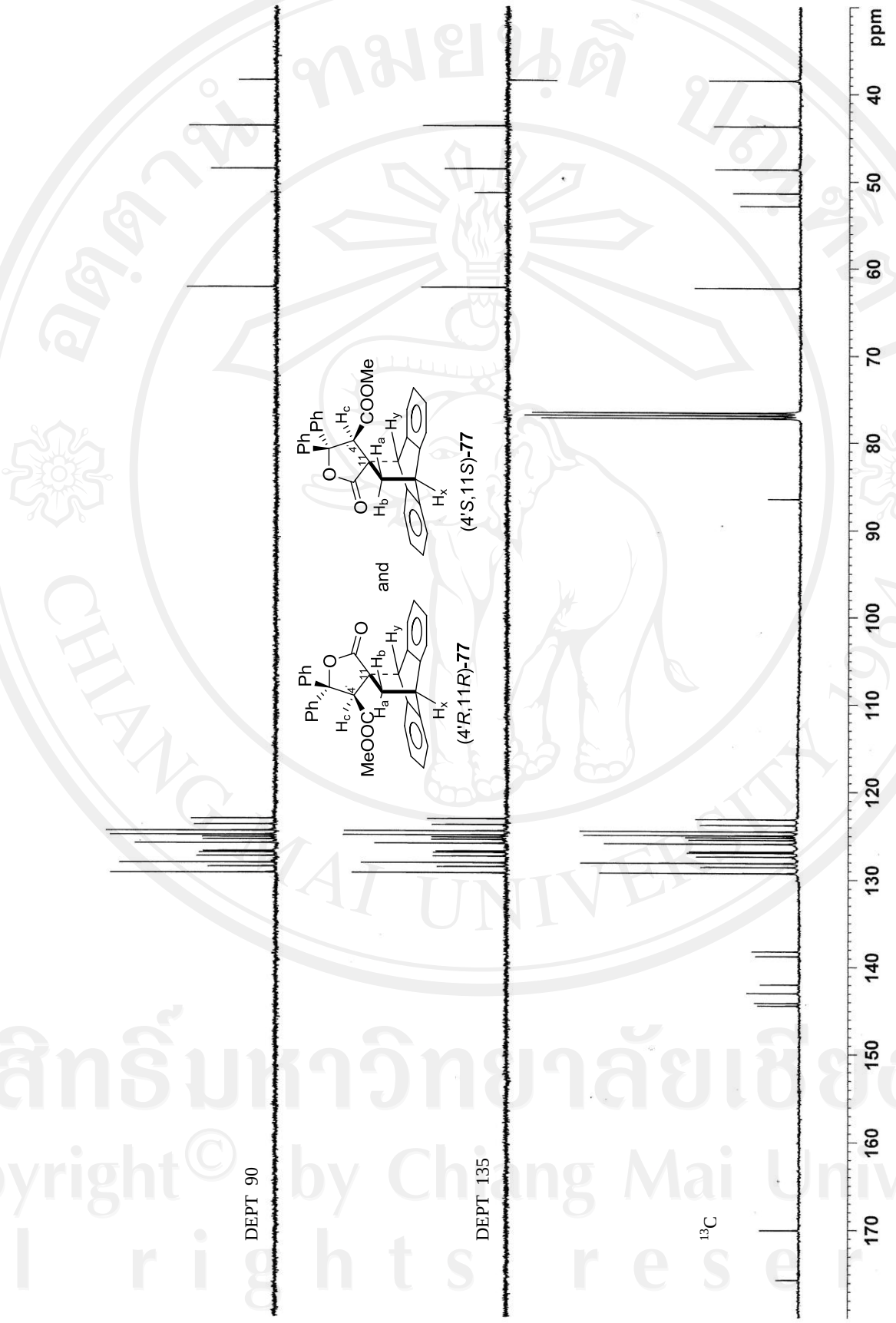
Appendix 12 HMQC spectrum of compound (4′*S*,11*R*)-**69a** and (4′*R*,11*S*)-**69a**



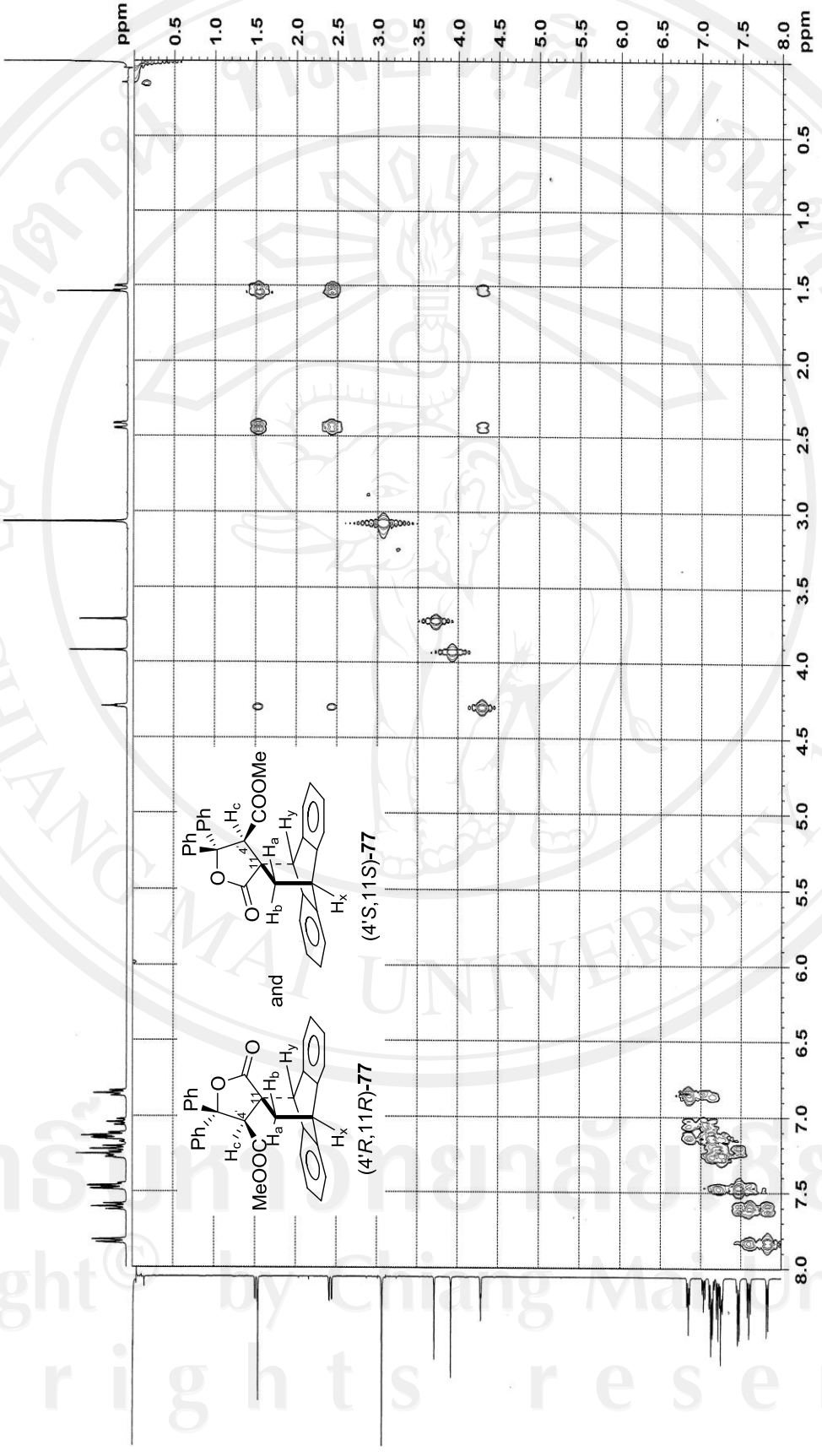
Appendix 13 HMBC spectrum of compound (4′*S*, 11*R*)-**69a** and (4′*R*,11*S*)-**69a**



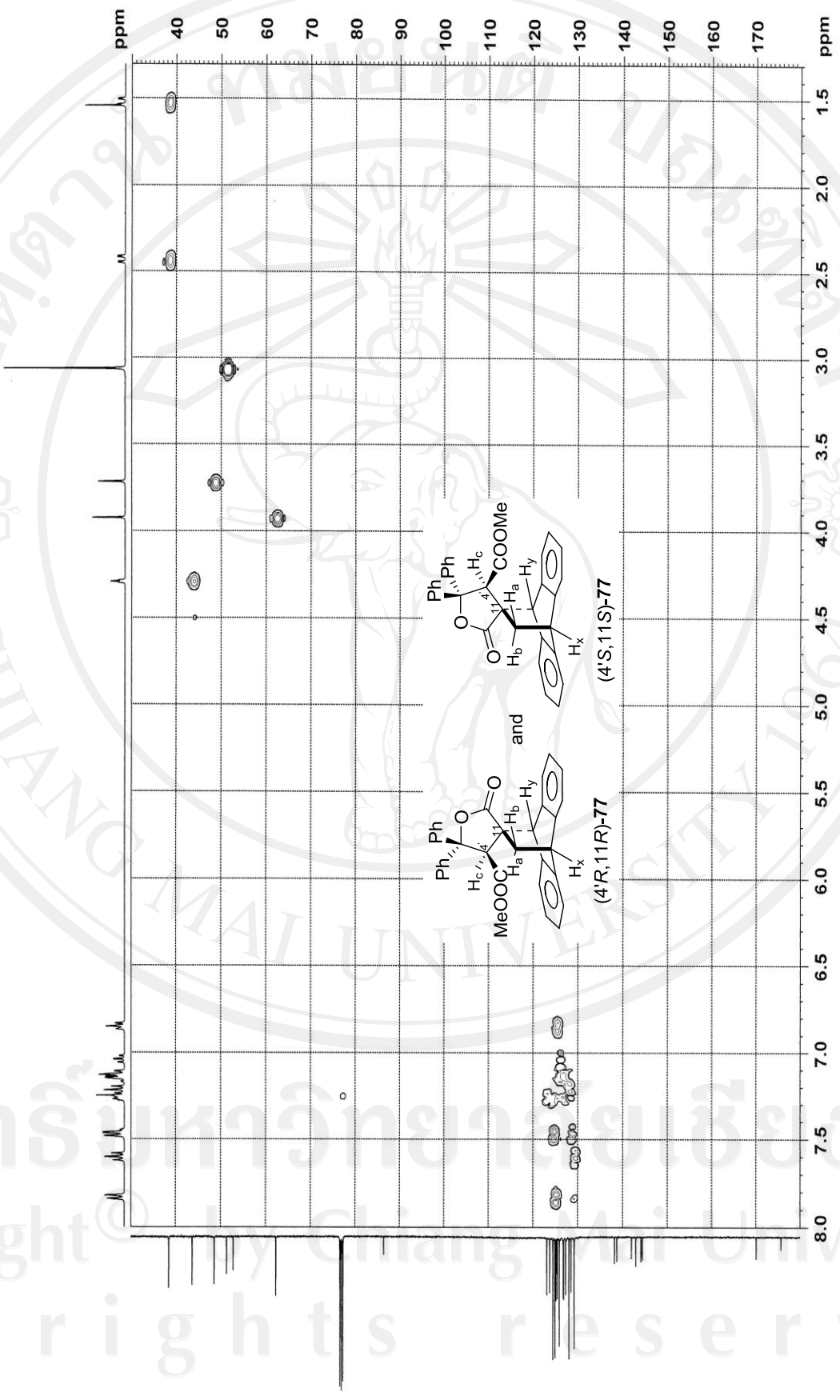
Appendix 14 ^{1}H-NMR spectrum of compound (4′*R*,11*R*)-**77** and (4′*S*,11*S*)-**77**



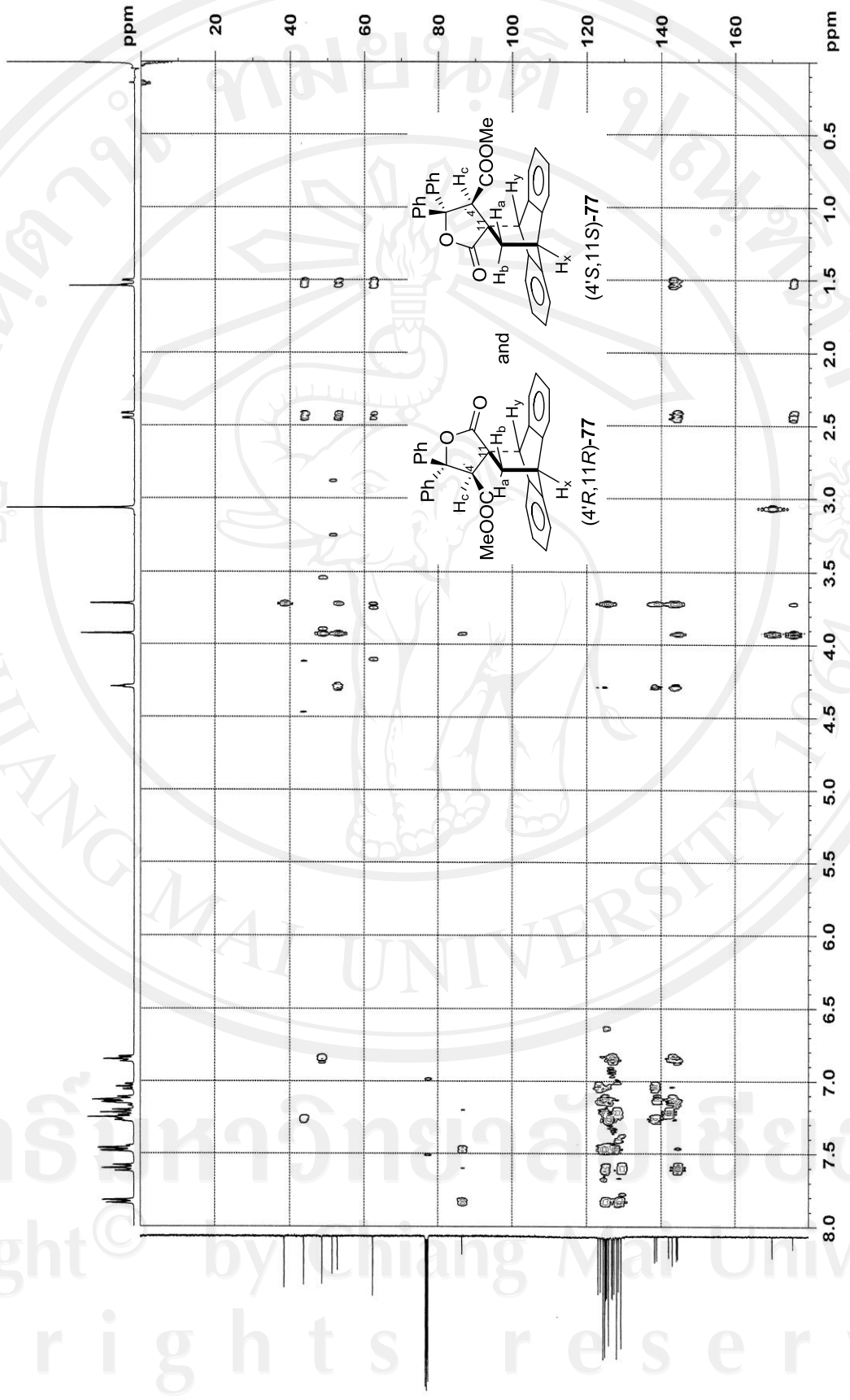
Appendix 15 ^{13}C-NMR spectrum of compound (4′*R*,11*R*)-**77** and (4′*S*,11*S*)-**77**



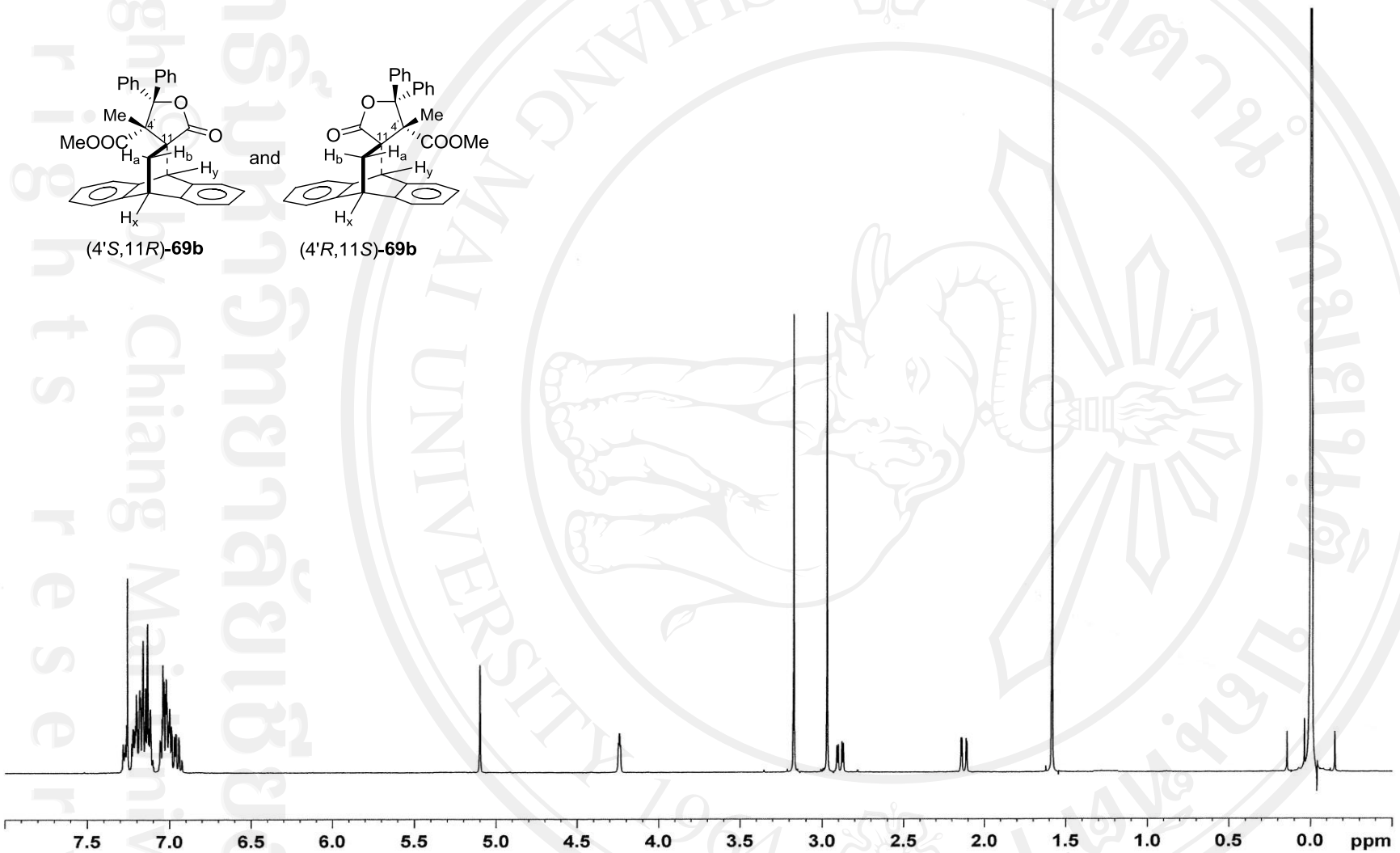
Appendix 16 COSY spectrum of compound (4′*R*,11*R*)-**77** and (4′*S*,11*S*)-**77**



Appendix 17 HMQC spectrum of compound (4′*R*,11*R*)-**77** and (4′S,11*S*)-**77**

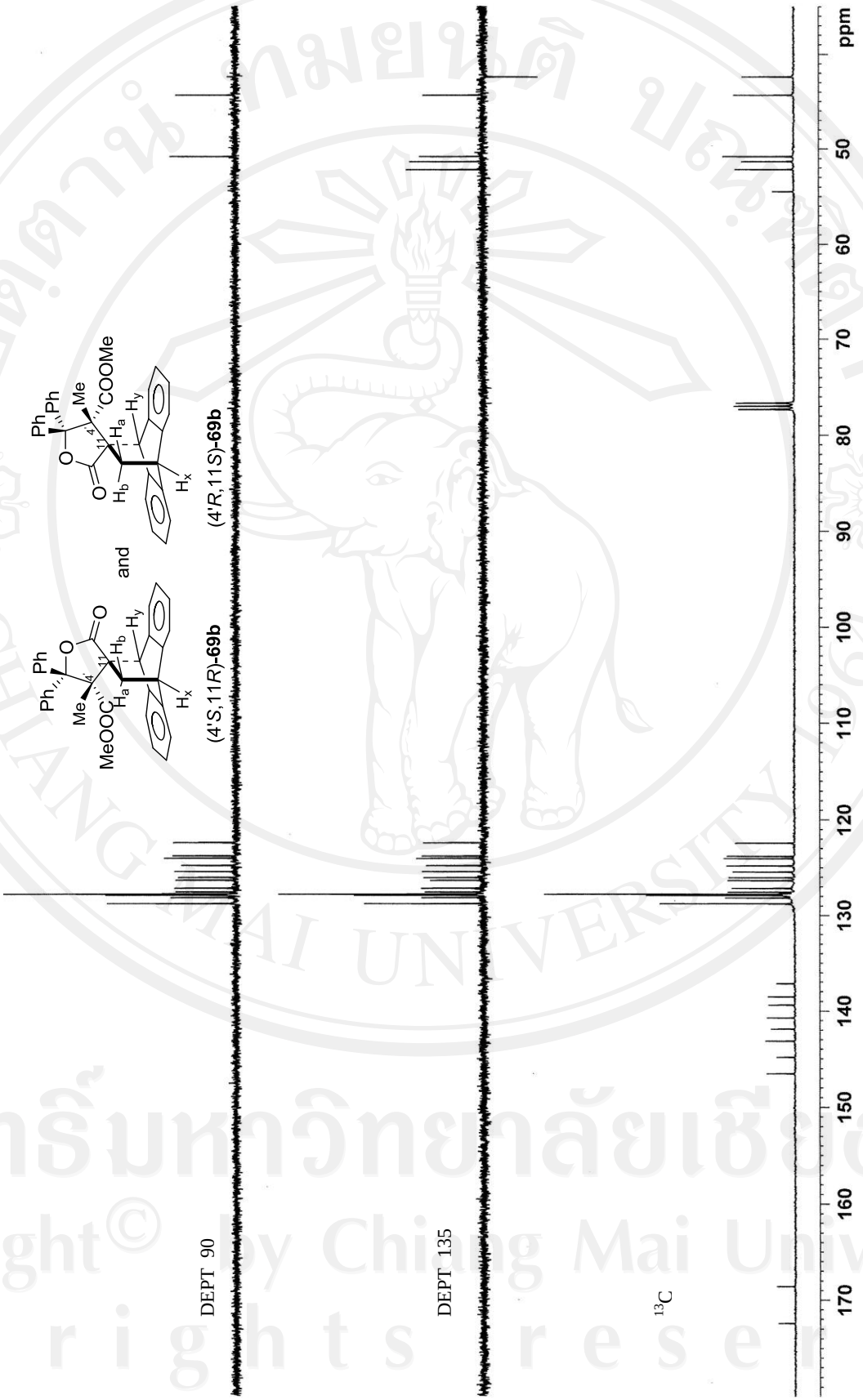


Appendix 18 HMBC spectrum of compound (4′*R*,11*R*)-**77** and (4′*S*,11*S*)-**77**

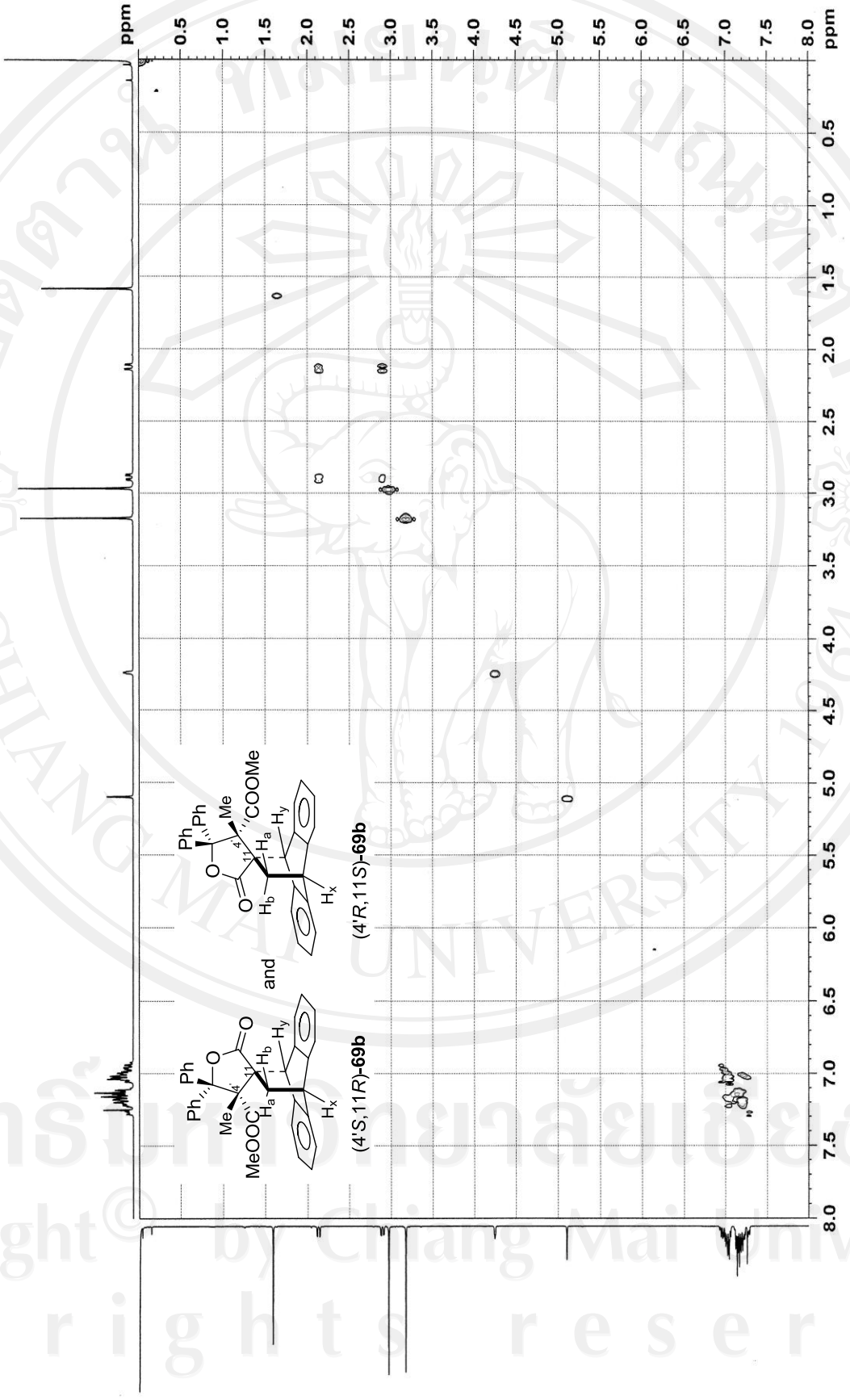


(4'*S*,11*R*)-**69b** (4'*R*,11*S*)-**69b**

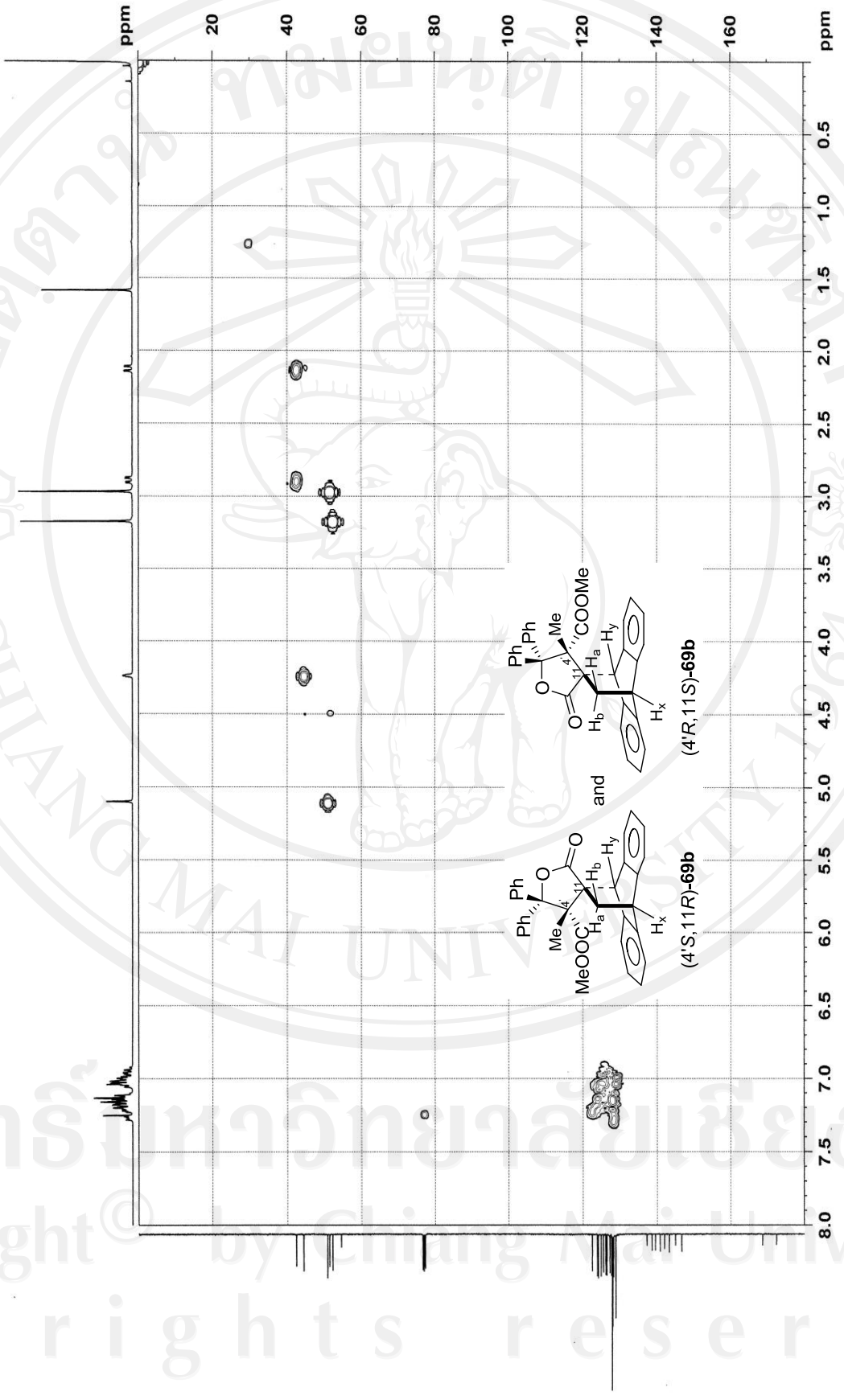
Appendix 19 ^{1}H-NMR spectrum of compound (4′*R*,11*R*)-**69b** and (4′*S*,11*S*)-**69b**



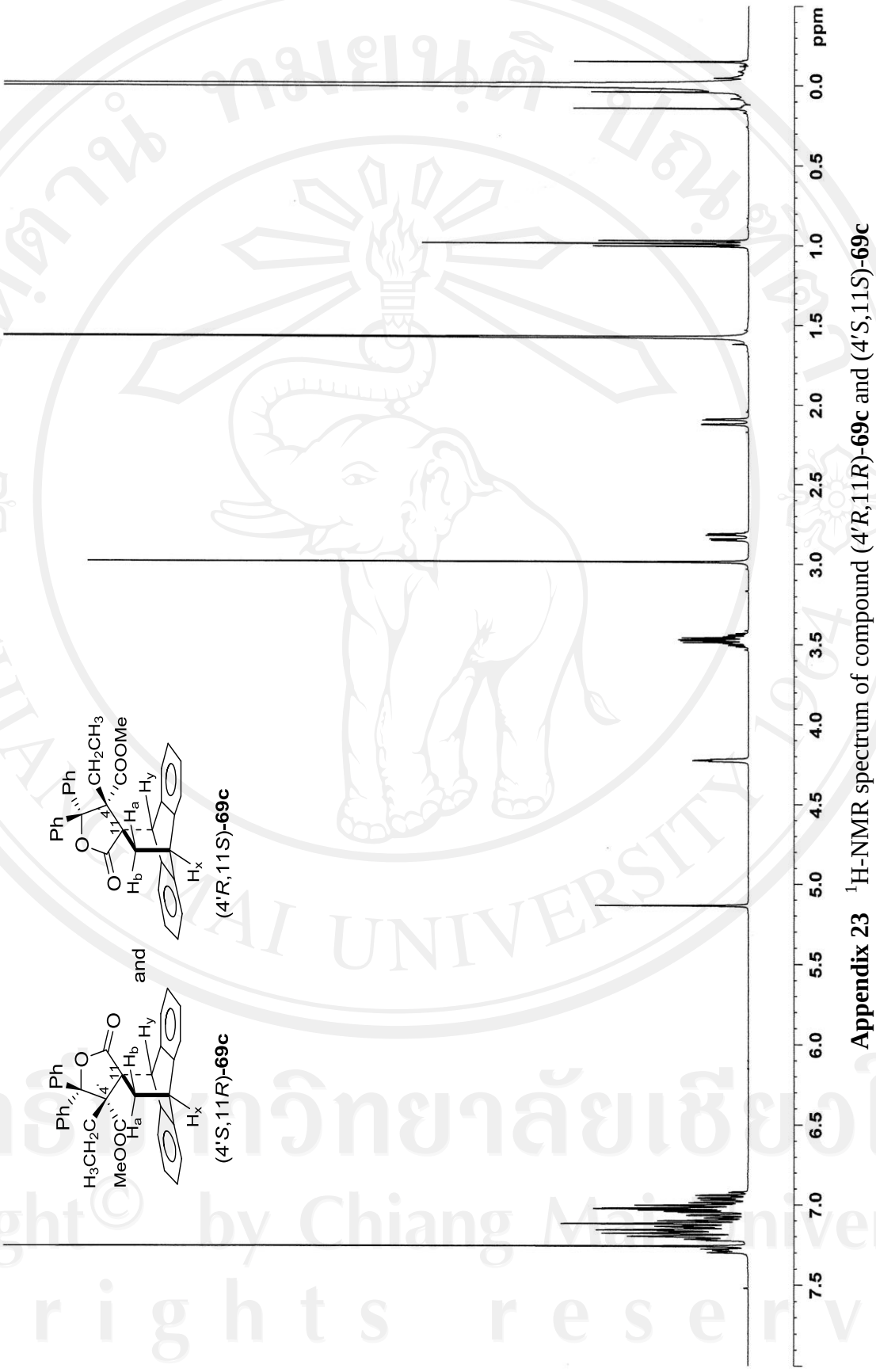
Appendix 20 ^{13}C-NMR spectrum of compound (4′*R*,11*R*)-**69b** and (4′*S*,11*S*)-**69b**



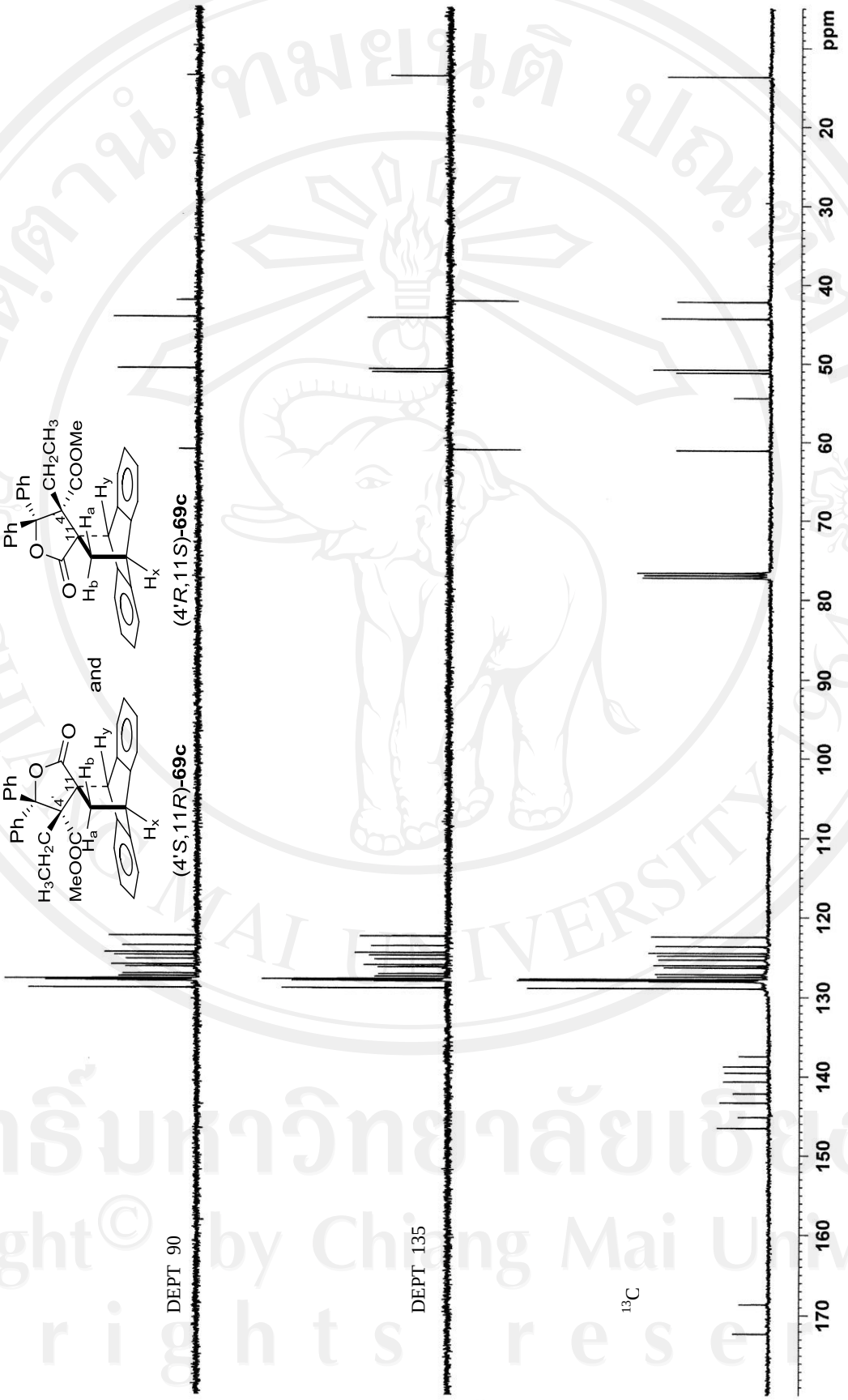
Appendix 21 COSY spectrum of compound (4′*R*,11*R*)-**69b** and (4′S,11*S*)-**69b**



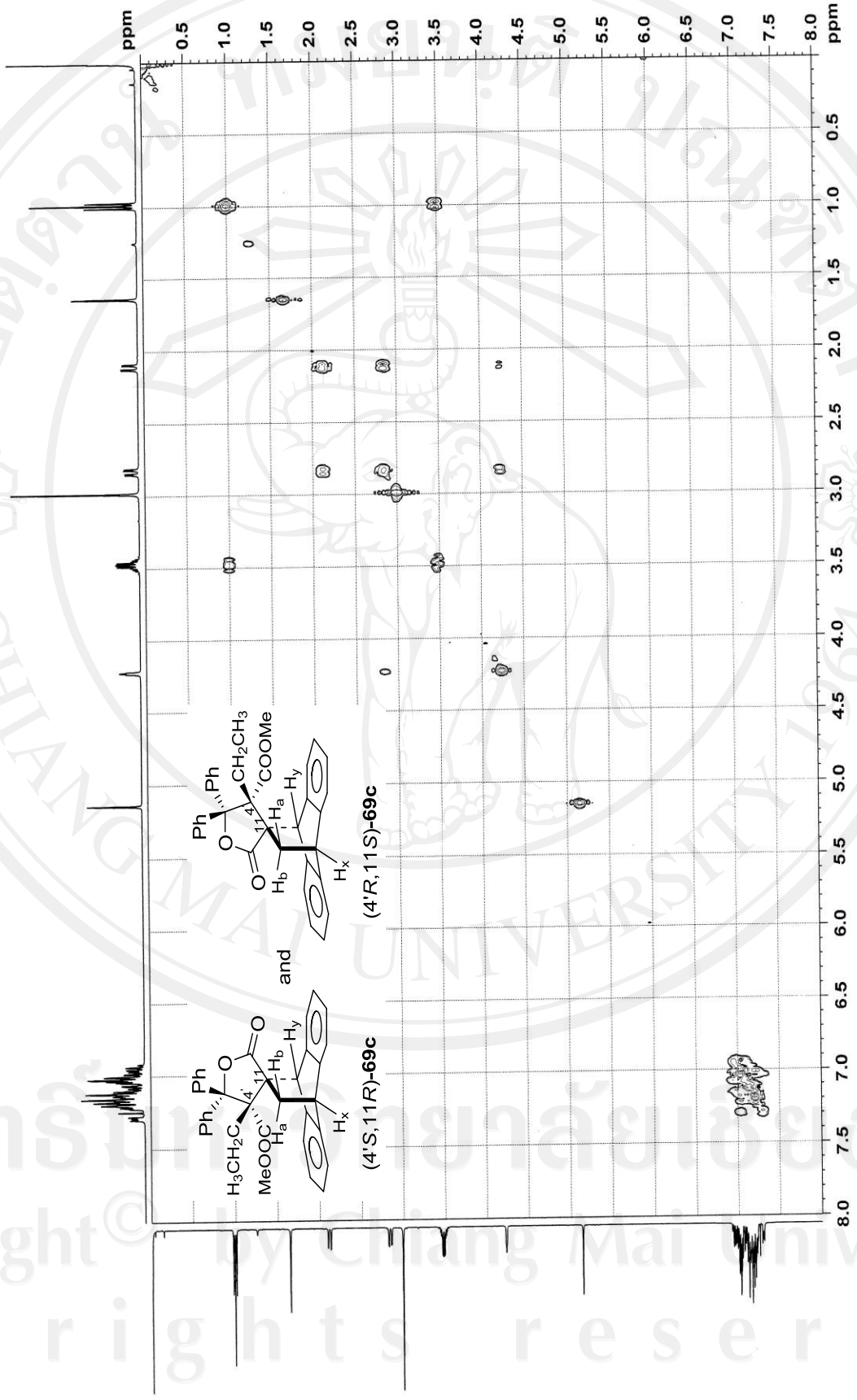
Appendix 22 HMQC spectrum of compound (4′*R*,11*R*)-**69b** and (4′*S*,11*S*)-**69b**



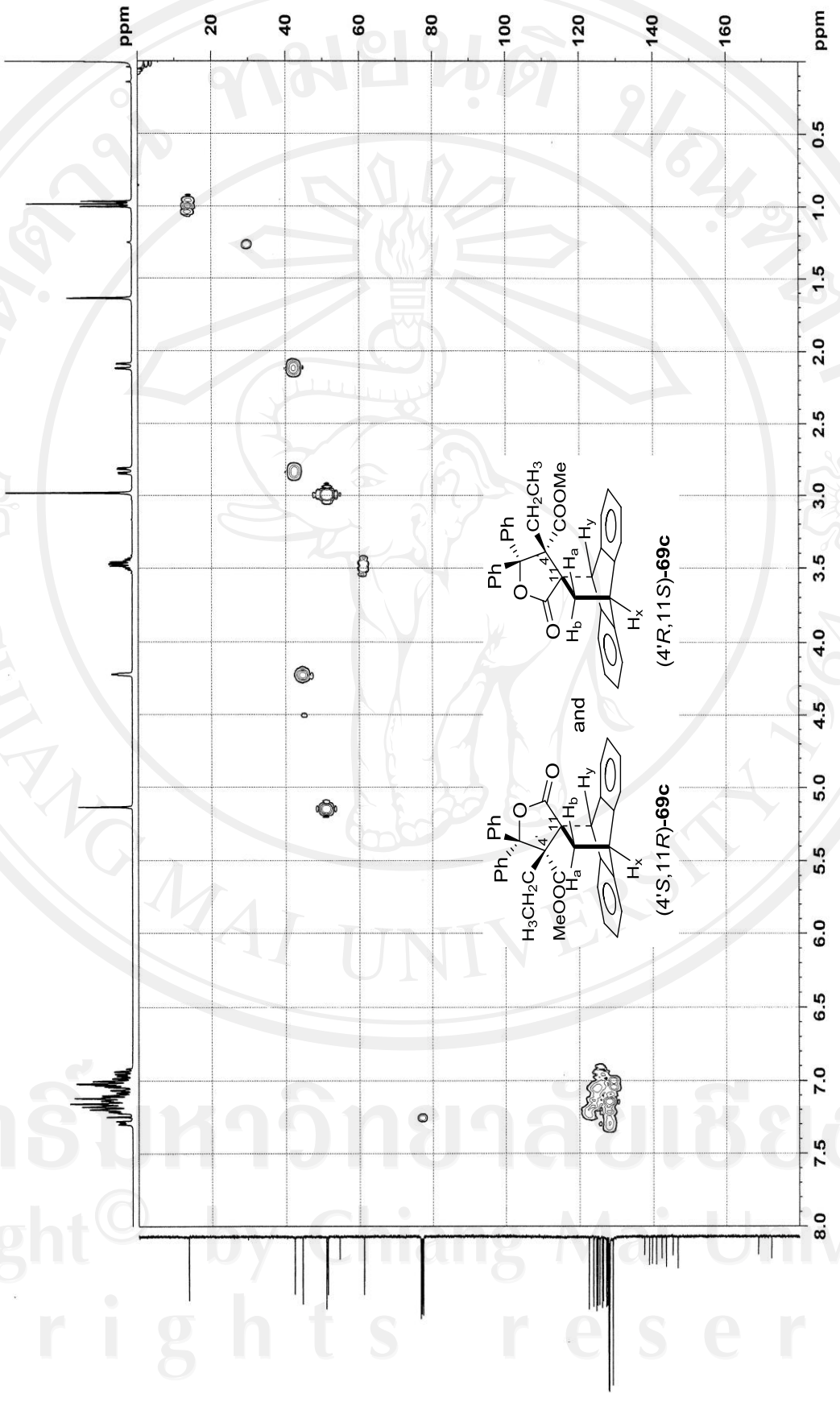
Appendix 23 ^{1}H-NMR spectrum of compound (4′*R*,11*R*)-**69c** and (4′S,11S)-**69c**



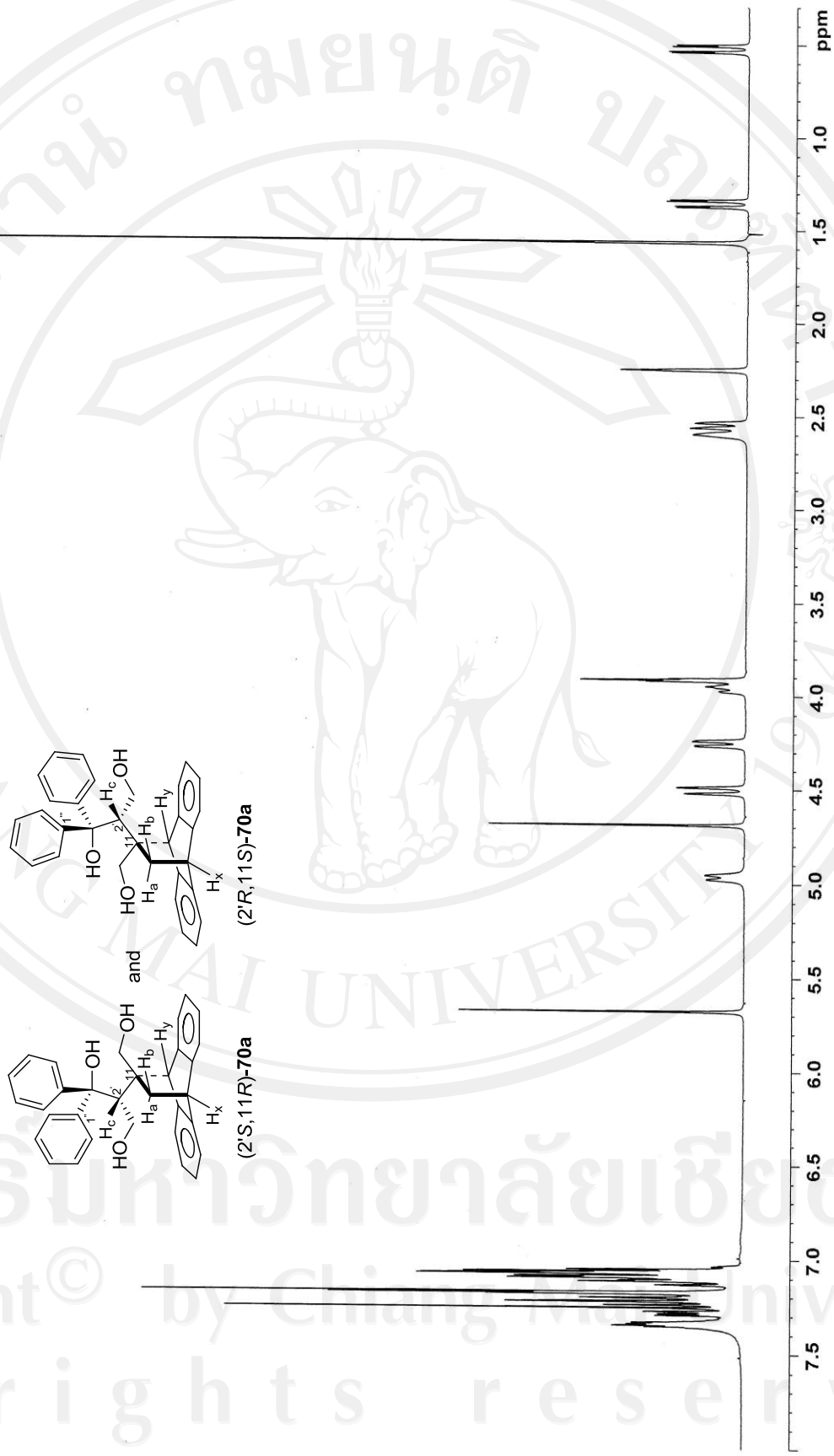
Appendix 24 ^{13}C-NMR spectrum of compound (4′*R*,11*R*)-**69c** and (4′*S*,11*S*)-**69c**



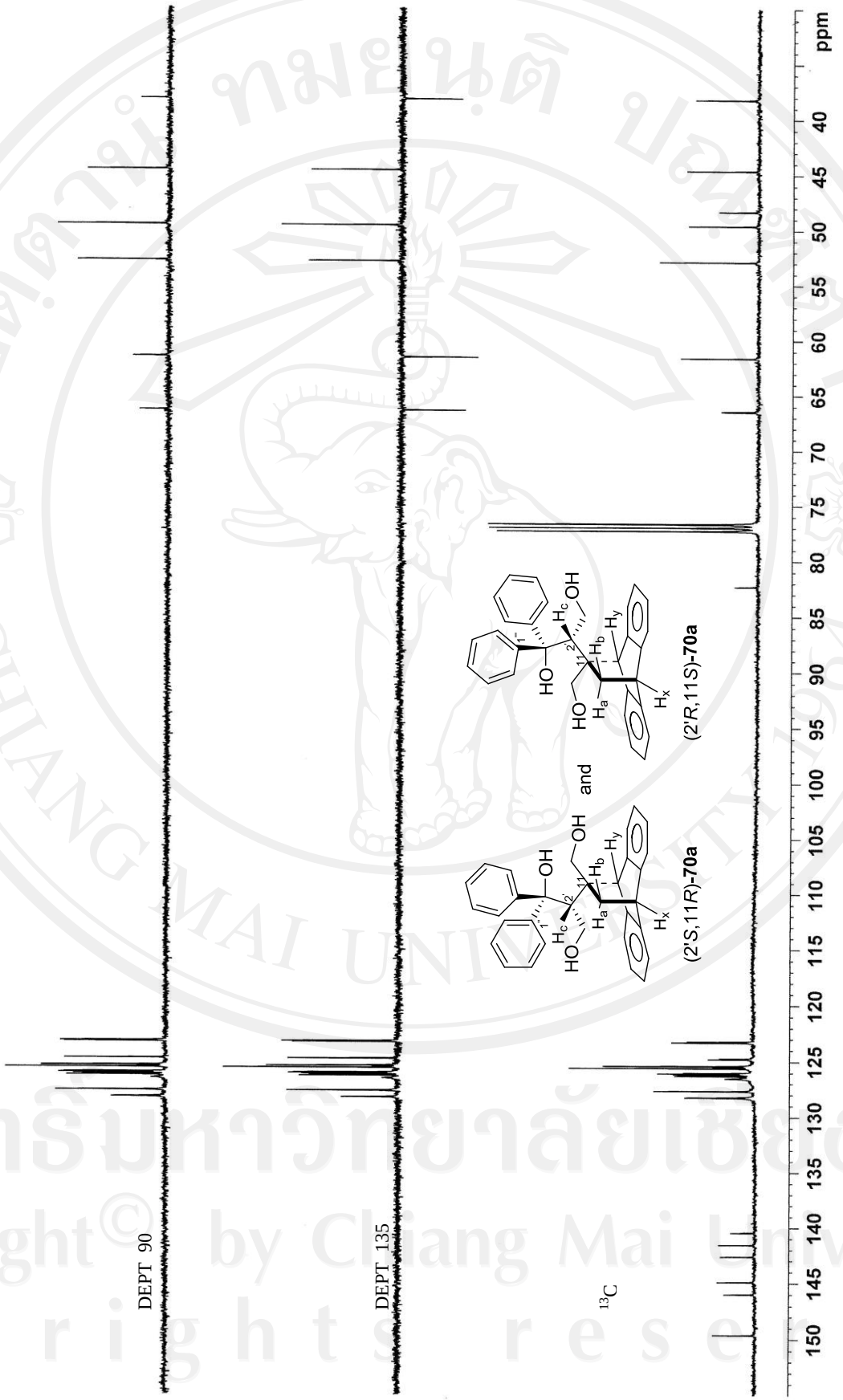
Appendix 25 COSY spectrum of compound (4′*R*,11*R*)-**69c** and (4′S,11*S*)-**69c**



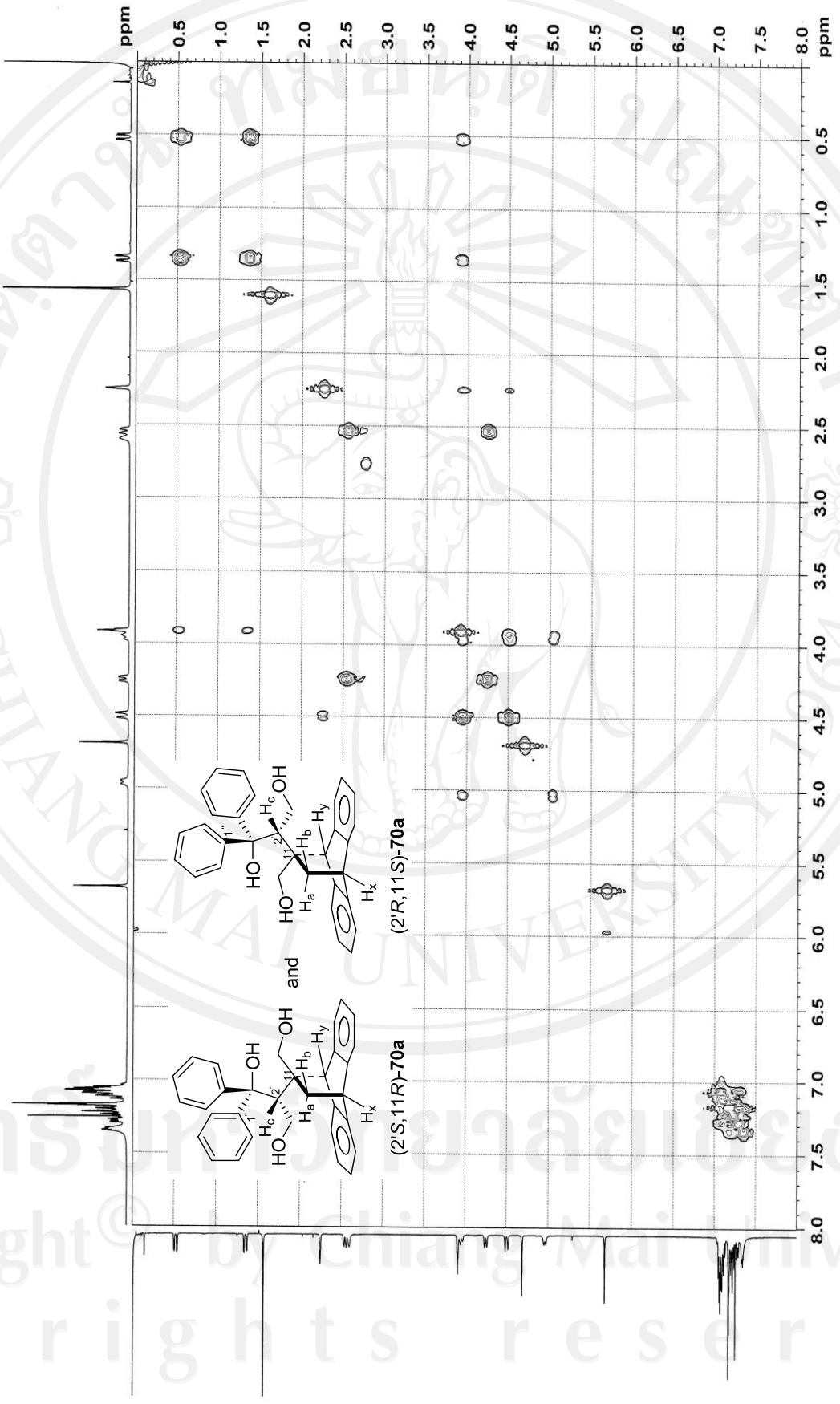
Appendix 26 HMQC spectrum of compound (4′*R*,11*R*)-**69c** and (4′S,11*S*)-**69c**



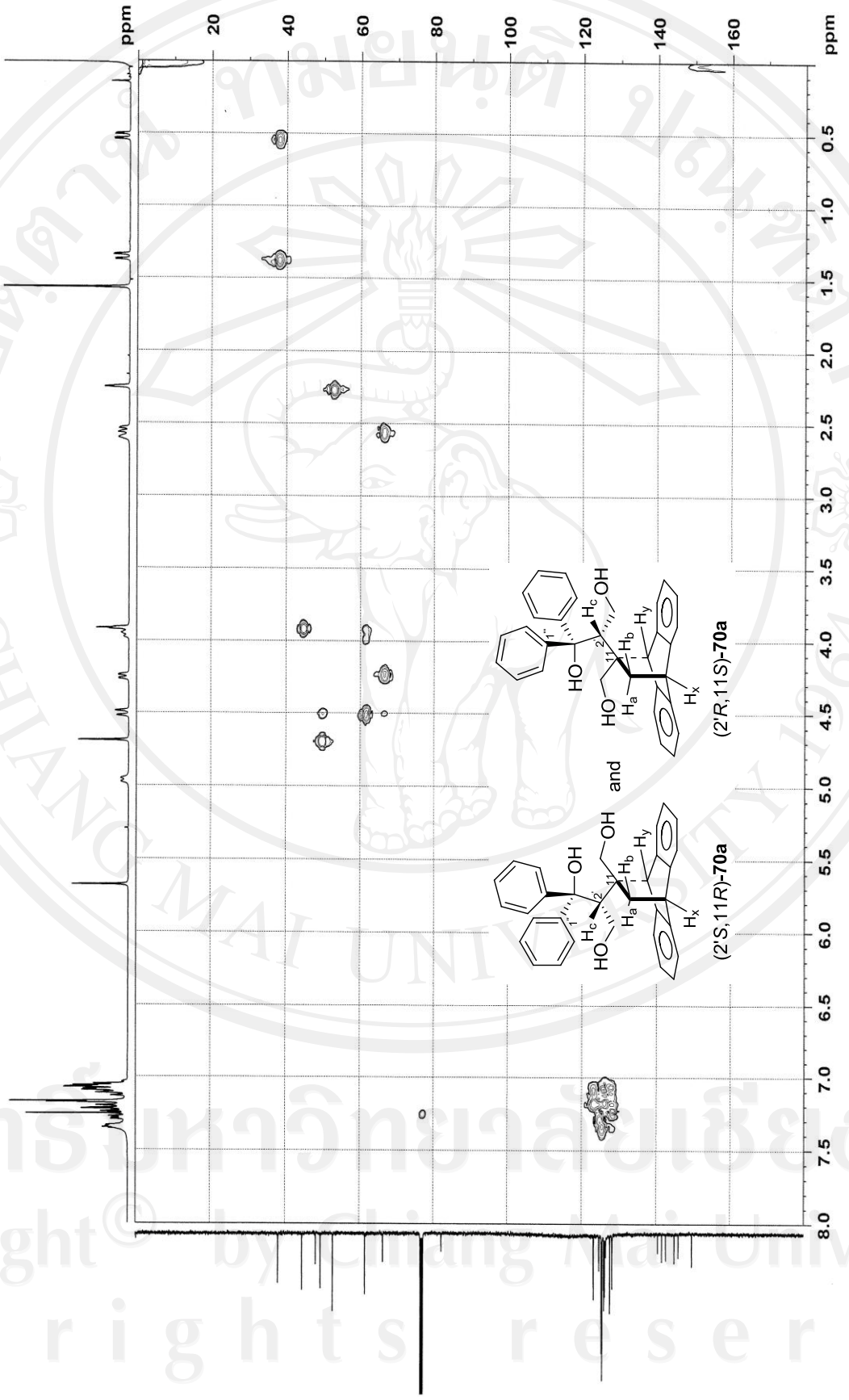
Appendix 27 ^{1}H-NMR spectrum of compound (2′*S*,11*R*)-**70a** and (2′*S*,11*R*)-**70a**



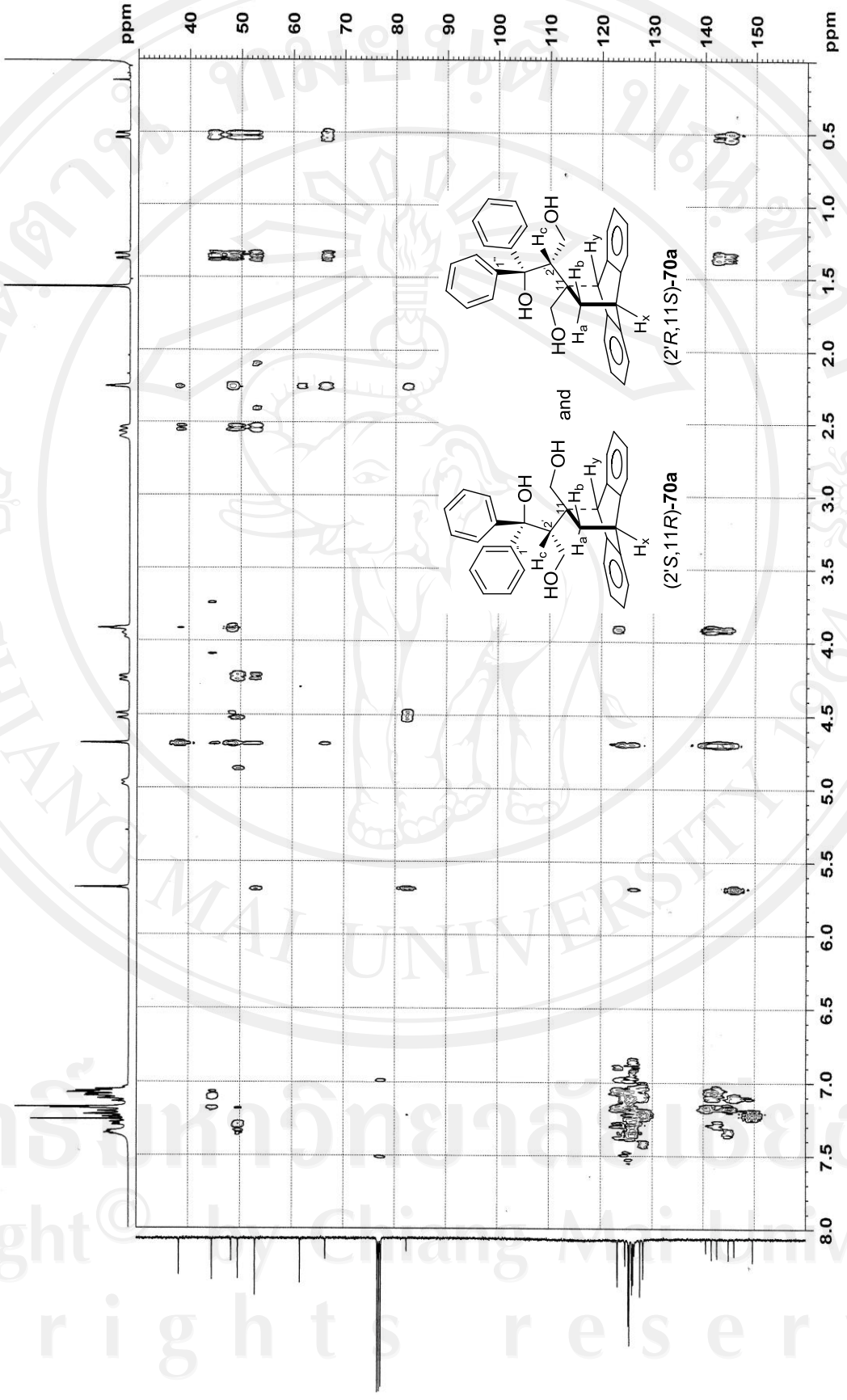
Appendix 28 ^{13}C-NMR spectrum of compound (2′*S*,11*R*)-**70a** and (2′*S*,11*R*)-**70a**



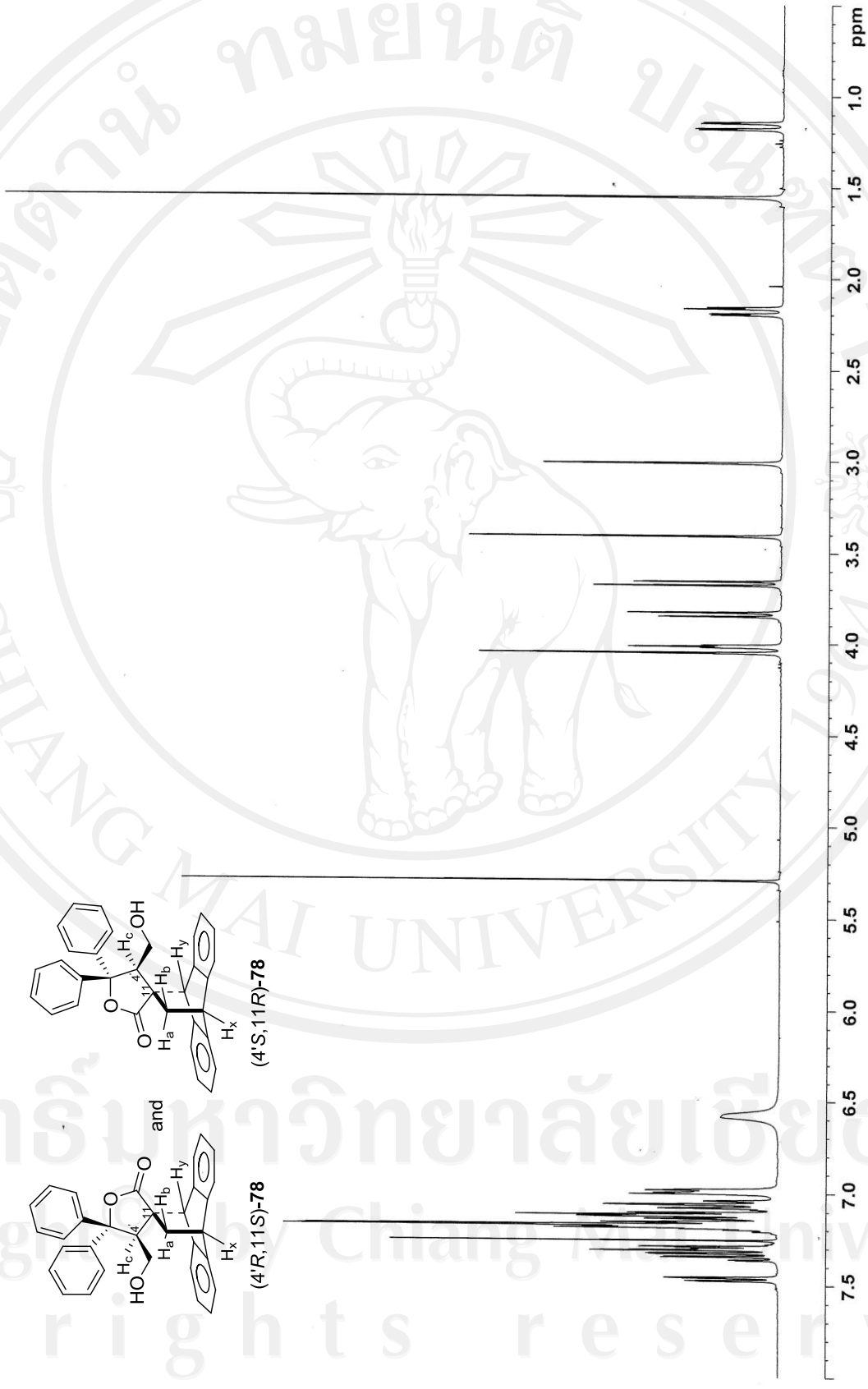
Appendix 29 COSY spectrum of compound (2′*S*,11*R*)-**70a** and (2′*S*,11*R*)-**70a**



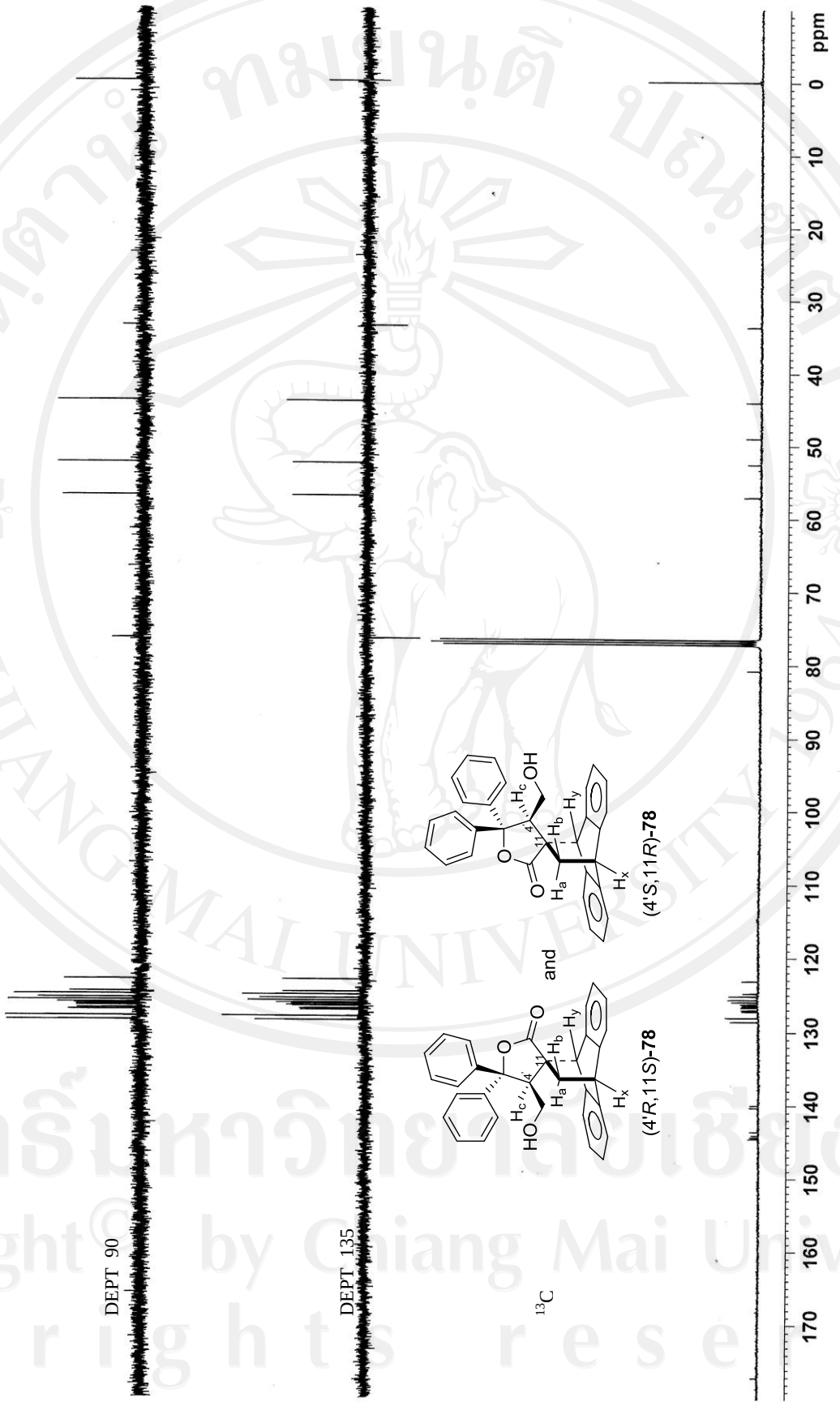
Appendix 30 HMQC spectrum of compound (2'*S*,11*R*)-**70a** and (2'*S*,11*R*)-**70a**



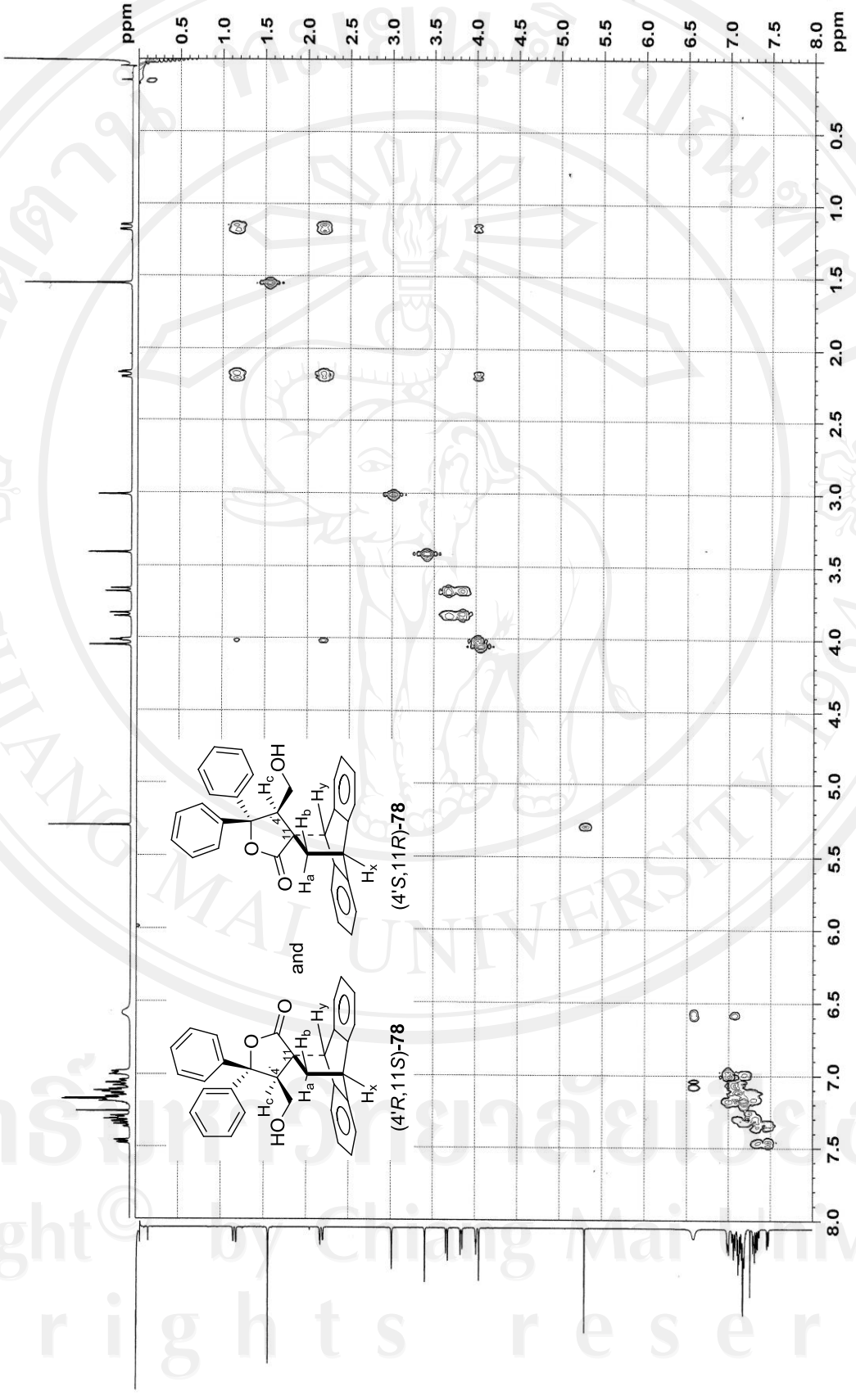
Appendix 31 HMBC spectrum of compound (2′*S*,11*R*)-**70a** and (2′*S*,11*R*)-**70a**



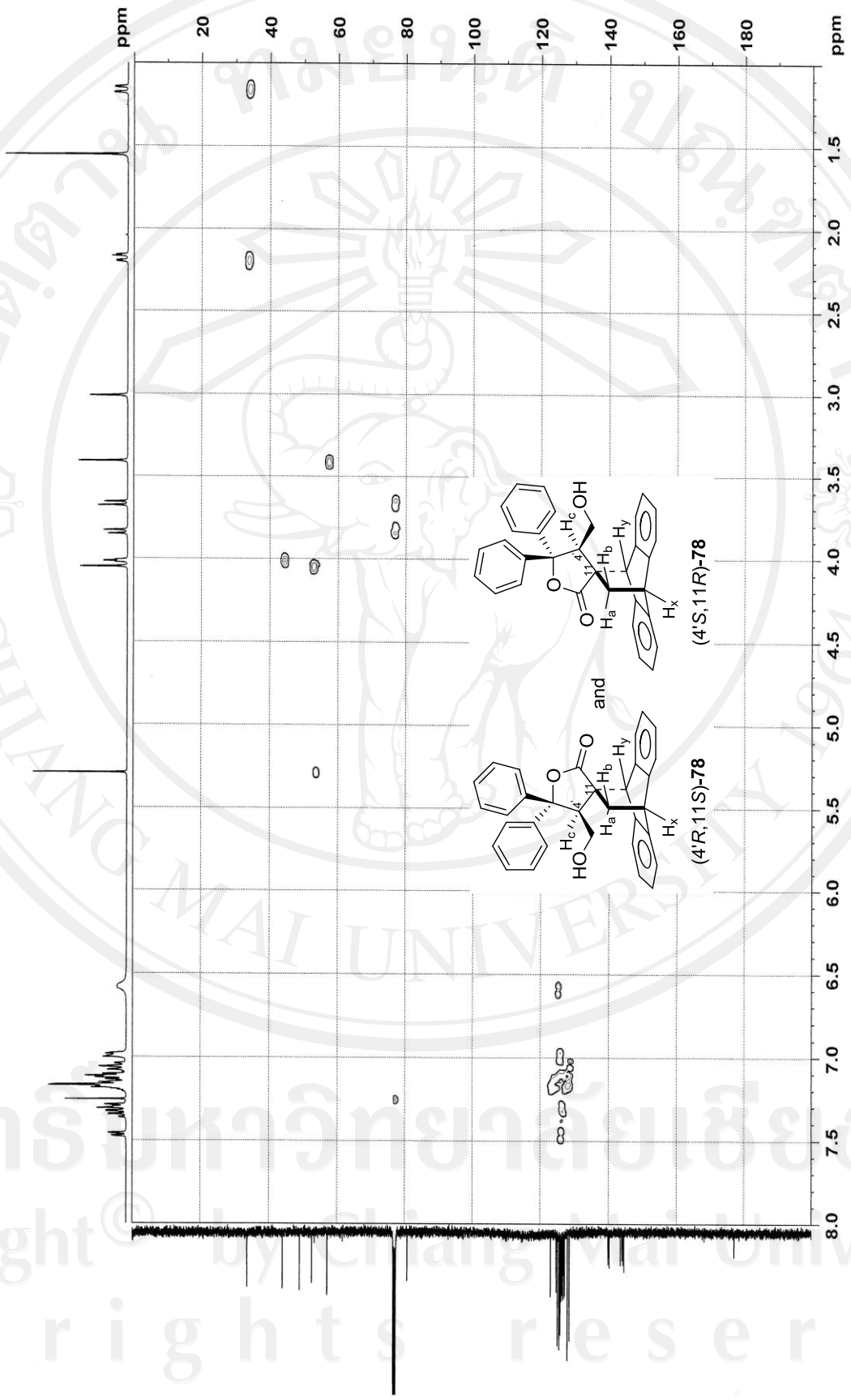
Appendix 32 ^{1}H-NMR spectrum of compound (4′*R*,11*S*)-**78** and (4′S,11*R*)-**78**



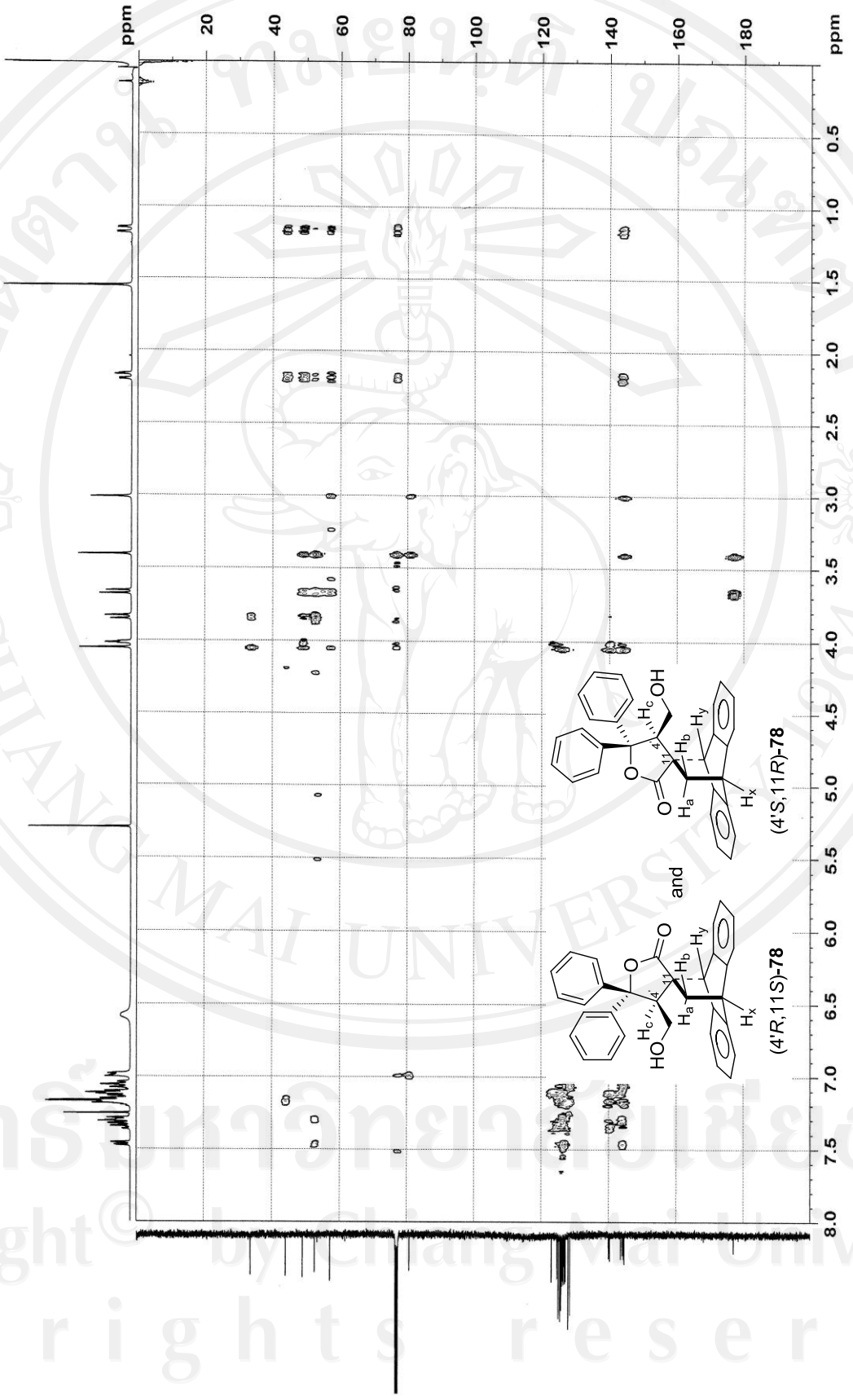
Appendix 33 ^{13}C-NMR spectrum of compound (4′*R*,11*S*)-**78** and (4′*S*,11*R*)-**78**



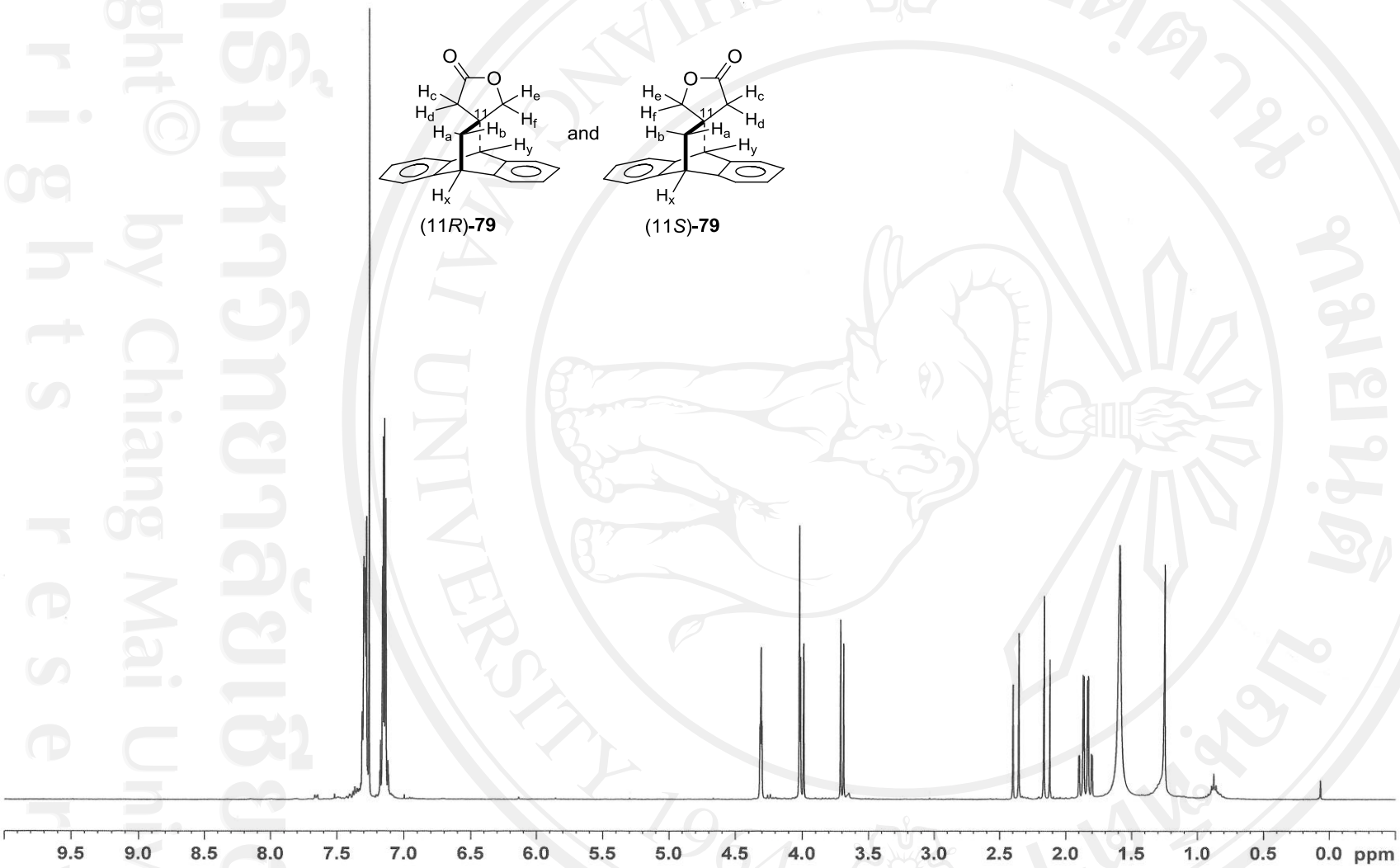
Appendix 34 COSY spectrum of compound (4′*R*,11*S*)-**78** and (4′*S*,11*R*)-**78**



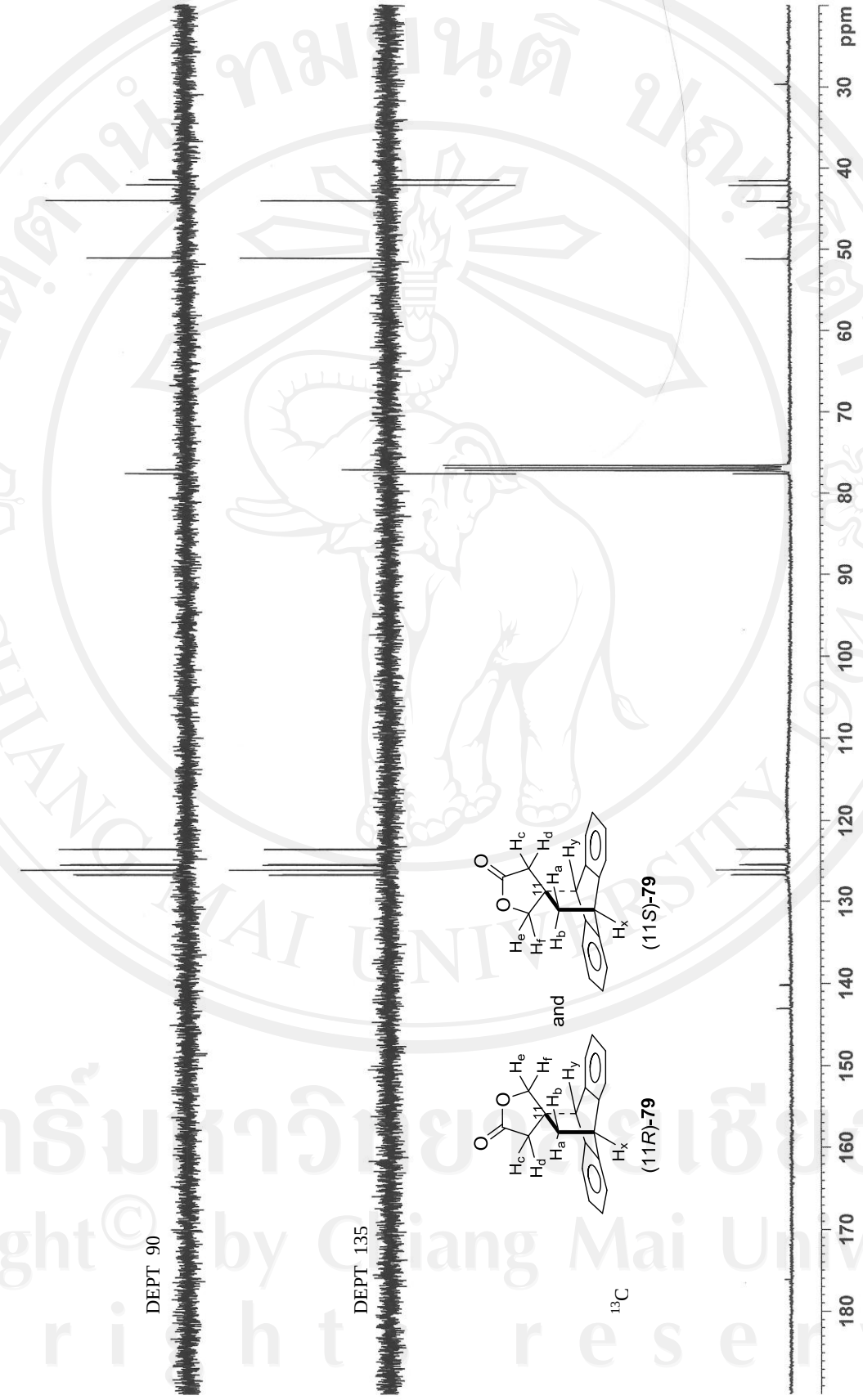
Appendix 35 HMQC spectrum of compound (4′*R*,11*S*)-**78** and (4′*S*,11*R*)-**78**



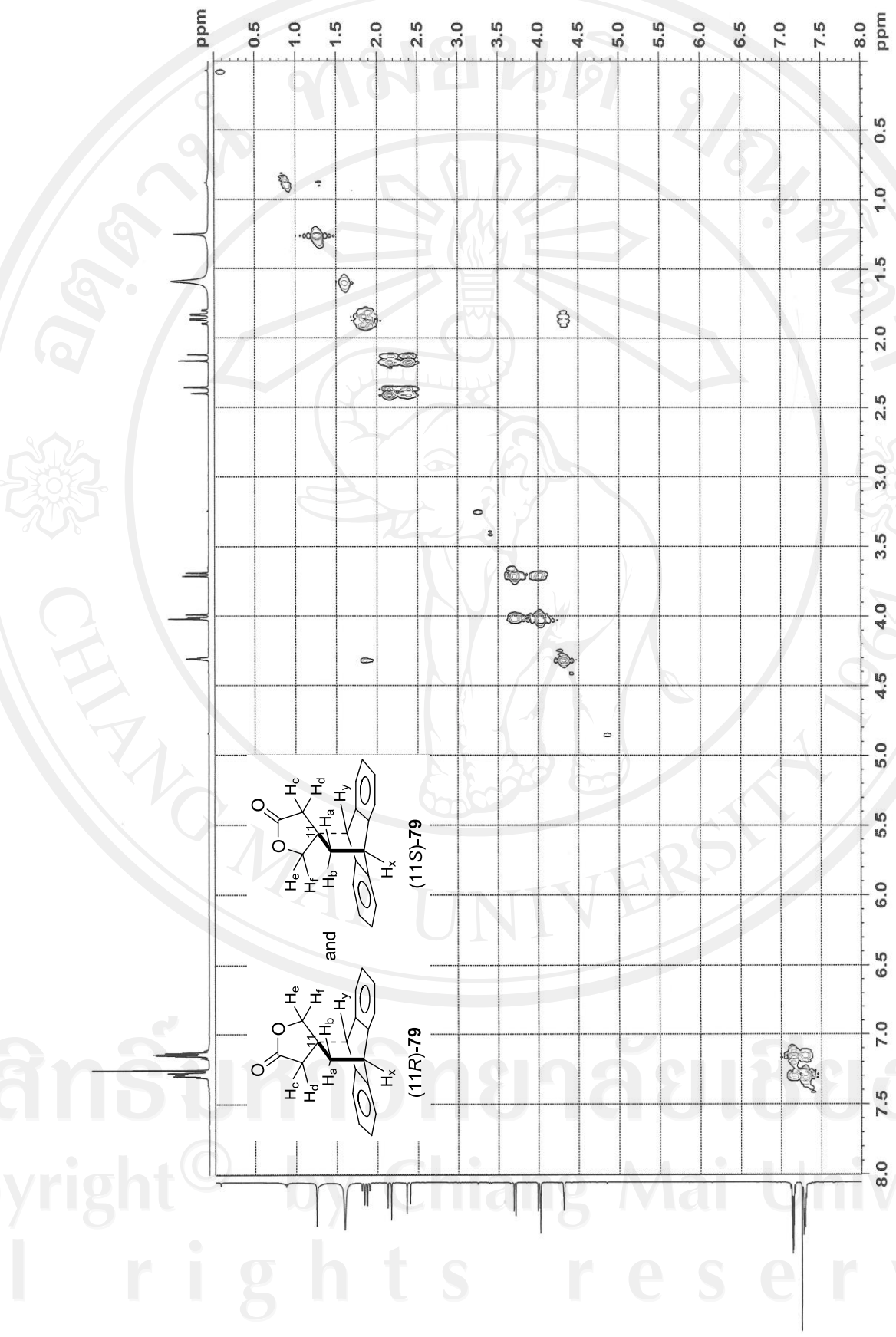
Appendix 36 HMBC spectrum of compound (4′*R*,11*S*)-**78** and (4′*S*,11*R*)-**78**



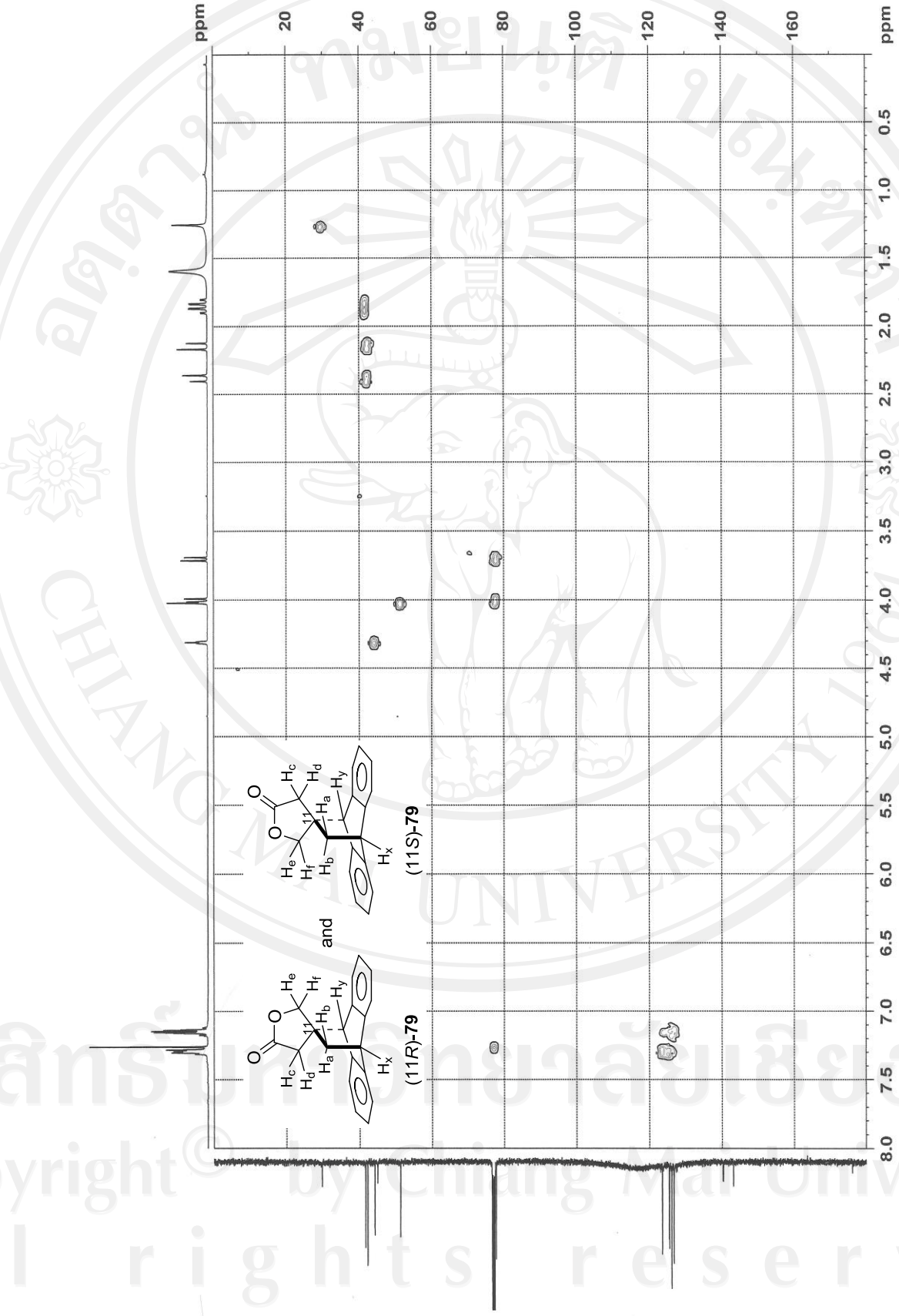
Appendix 37 ^{1}H-NMR spectrum of compound (11*R*)-**79** and (11*S*)-**79**



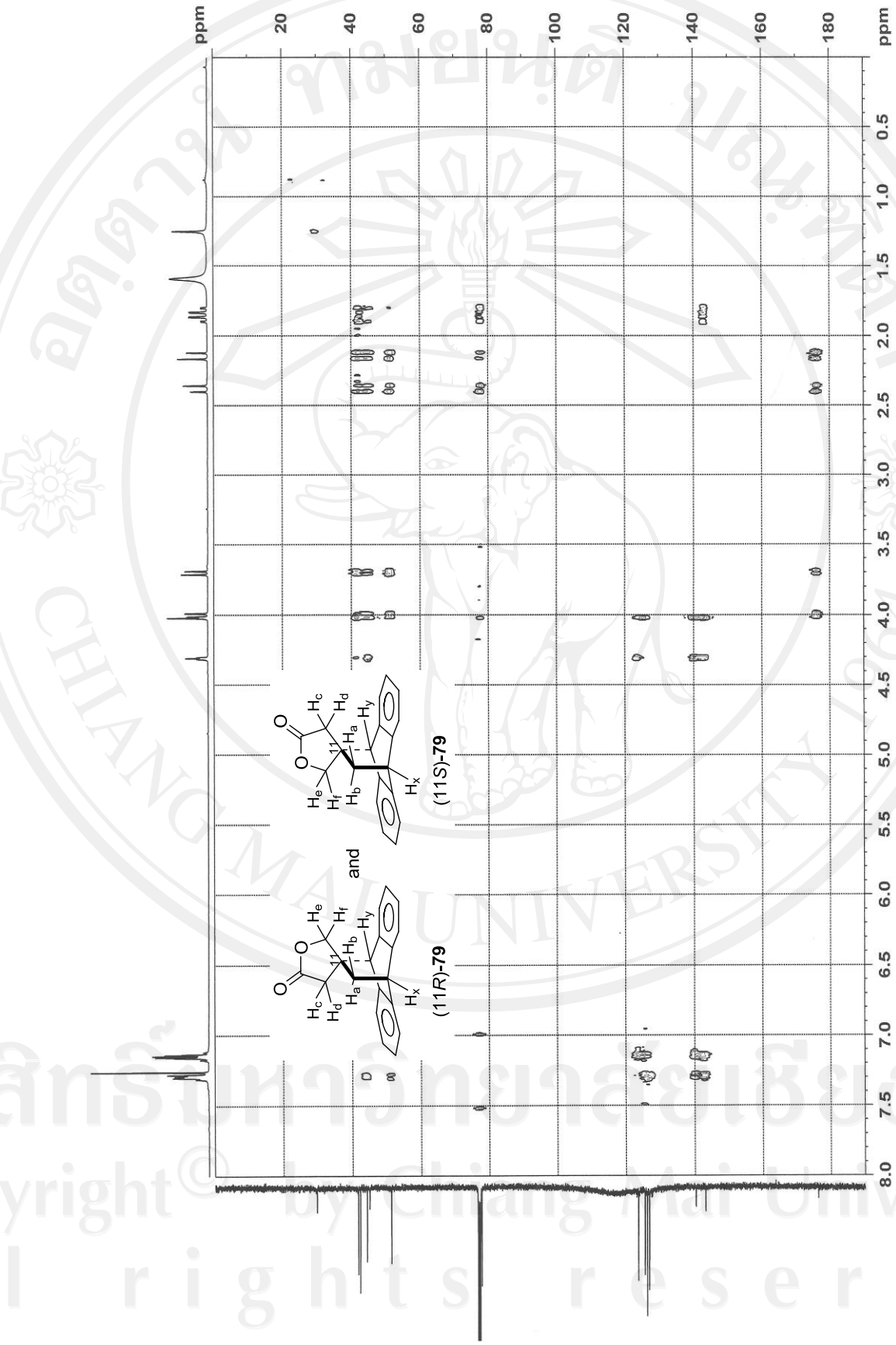
Appendix 38 ^{13}C-NMR spectrum of compound (11*R*)-**79** and (11*S*)-**79**



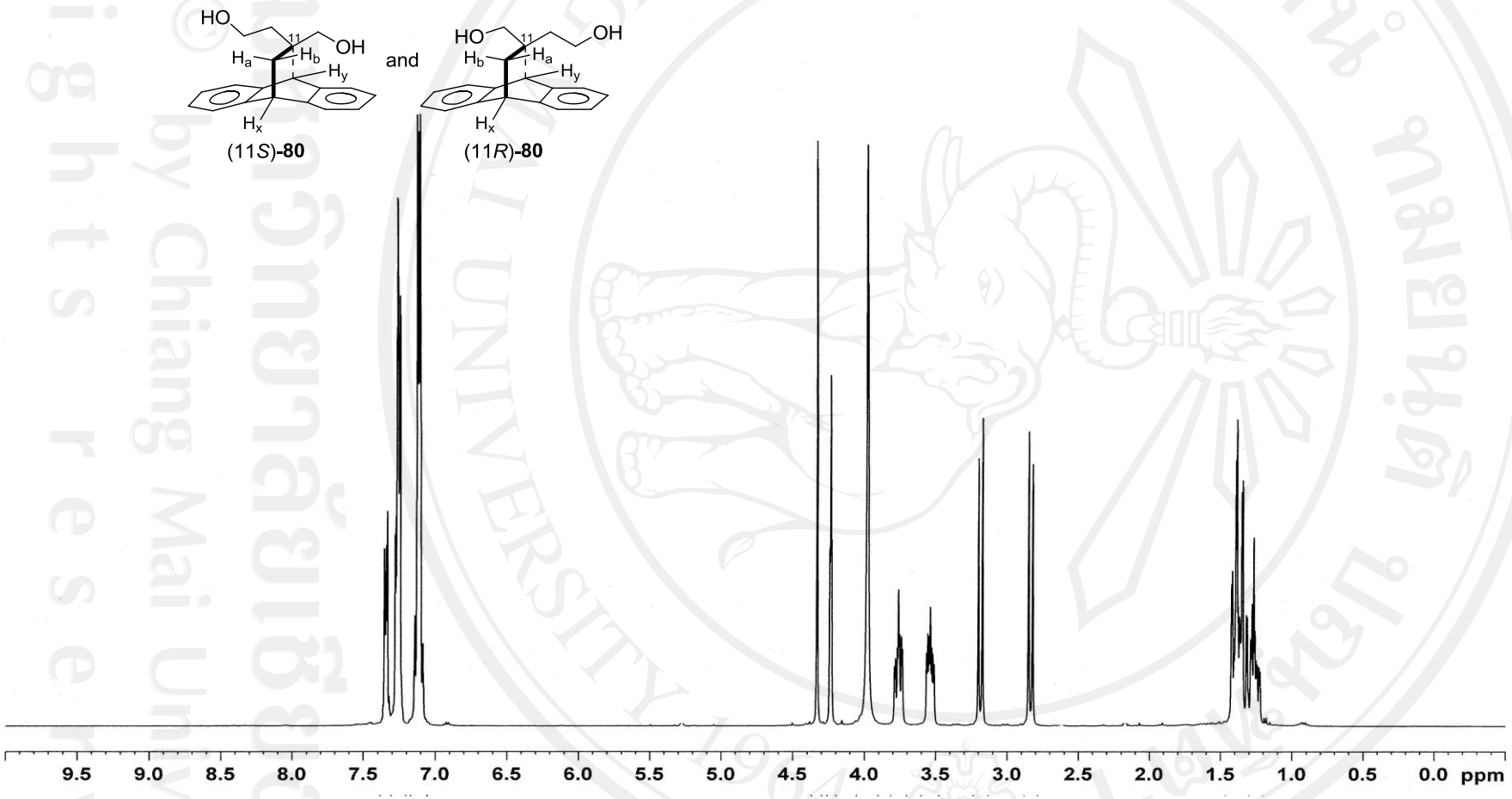
Appendix 39 COSY spectrum of compound (11*R*)-**79** and (11*S*)-**79**



Appendix 40 HMQC spectrum of compound (11*R*)-**79** and (11*S*)-**79**



Appendix 41 HMBC spectrum of compound (11*R*)-**79** and (11*S*)-**79**



Appendix 42 ^{1}H-NMR spectrum of compound (11*S*)-**80** and (11*R*)-**80**

CURRICULUM VITAE

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2009 B.S., Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, Thailand.

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National conferences

1. Duangrat Nim-anssornkul, Phatcharin Wiriyasukhsawat and Puttinan Meepowpan, "Syntheses of TADDOL–Anthracene Adducts as Chiral Catalysts for Use in Asymmetric 1,2-Addition Reactions", Pure and Applied Chemistry International Conference 2011 (PACCON 2011) on 5-7 January 2011, Miracle Grand Hotel, Bangkok, Thailand (**2011**), pp. 724-727.
2. Duangrat Nim-anssornkul and Puttinan Meepowpan, "Syntheses of TADDOL–Anthracene Adducts as Chiral Catalysts for Use in Reduction of β-Keto Ester"

The 6th Congress on Science and Technology for Youth on 18-19 March 2011, BITECH Bangna Convention Hall, Bangkok, Thailand (**2011**), pp. 234.

3. Duangrat Nim-anssornkul and Puttinan Meepowpan, "Syntheses of TADDOL–Anthracene Adducts as Chiral Catalysts for Use in Reduction of β-Keto Ester" The International Congress for Innovation in Chemistry (PERCH-CIC CONGRESS VII) on 4-7 May 2011**,** Jomtien Palm Beach Resort, Chonburi, Thailand (**2011**), pp. 344.

Syntheses of TADDOL-Anthracene Adducts as Chiral Catalyst for Use in Asymmetric Addition Reactions

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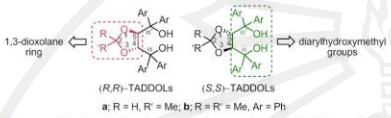
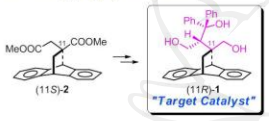
Introduction

TADDOLs ($\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanols)[1] which were introduced by Seebach *et. al.*[1a], containing two adjacent diarylhydroxymethyl groups in a *trans*- relationship on a 1,3-dioxolane ring.

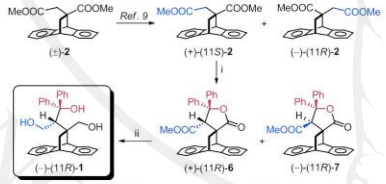


TADDOLs and their derivatives can be used as chiral ligands for both stoichiometric and catalytic asymmetric reactions and even chiral organocatalysts. As a result, TADDOLs would be applied and designed for many asymmetric syntheses. Therefore, we are interested to design the new chiral catalyst, TADDOL-anthracene adduct (11*R*)-**1** which were created by modification of dimethyl-itaconate anthracene addcuts [(+)-(11*R*)-**2**] in enantiomerically pure form. This new chiral catalyst will be studied in reduction of *β*-ketodiester [(±)-**3**] by using $NaBH_4$.



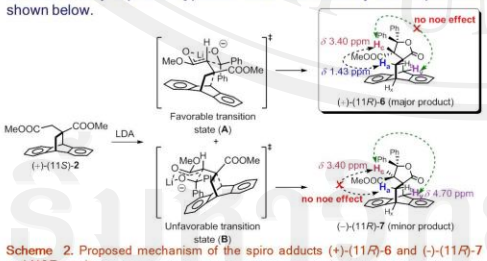
Methodology, Results and Discussion

The TADDOL-anthracene adduct catalyst (-)-(11*R*)-**1** was synthesized by using dimethyl itaconate-anthracene addcuts [(+)-(11*S*)-**2**] as starting materials. The dimethyl itaconate-anthracene addcuts [(+)-(11*S*)-**2**] was treated with 1.2 eq LDA. at -78 °C to 0 °C for 1 h. and then trapped with benzophenone obtained two diastereomers adducts of spiro-lactones; (+)-(11*R*)-**6** and (-)-(11*R*)-**7** as major and minor products, respectively. Then, the spiro-lactone, major product (+)-(11*R*)-**6** was reduced by using LAH to provide the TADDOL-anthracene catalyst (-)-(11*R*)-**1**.



Scheme 1.. Synthesis of TADDOL-anthracene adduct. *Reagents and conditions:* (i) a. 1.2 eq. LDA, THF, -78 °C to 0 °C, 2 h, b. 1.2 eq. benzophenone, 0 °C to rt, 2 h, (i) c. 10% HCl; (ii) a. 20 eq. $LiAlH_4$, THF -78 °C to rt, 3 days, b. 10% HCl.

The stereochemistry of the major products **6** and minor products **7** can be explained through the chair-like transition states **A** and **B**. In case of minor product **7**, the steric repulsion between phenyl group and the anthracene ring of transition state **B** affected to the stereochemistry at H_c position, so transition state **A** which stable more than **B** led to the major product **6**. The relative stereochemistry at proton H_c position were determined by NOE experiment as shown below.



Scheme 2. Proposed mechanism of the spiro adducts (+)-(11*R*)-**6** and (-)-(11*R*)-**7** and NOE results..

The structure of TADDOL-anthracene catalyst (-)-(11*R*)-**1** could be confirmed by MM2 force field calculations for energy minimization from modeling program ChemBio3D Ultra 11.0 program. Besides, the orientation of the proton H_c and H_a were affirmed by the NOE experiment (Figure 1).

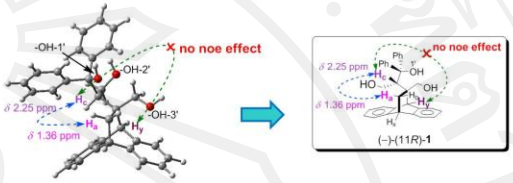
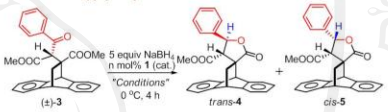


Figure 1. 3D structural conformation of TADDOL-anthracene adduct (-)-(11*R*)-**1** generated by MM2 force field calculations for energy minimization from modeling program ChemBio3D Ultra 11.0 and GaussView 3.09 program

To study the effect of TADDOL-anthracene (-)-(11*R*)-**1**, as catalyst, in reduction reaction of the *β*-keto diester [(±)-**3**] by using $NaBH_4$ as the reducing agent gave the results as shown in Table 1.

Table 1. Reduction of the *β*-keto diester adduct 3 with various mol% of TADDOL-anthracene (-)-(11*R*)-**1**



Entry	conditions	n mol% of **1** (cat.)	Yield (%)[a] *trans*-**4**	Yield (%)[a] *cis*-**5**	Ratio *trans*:*cis*	%conversion
1	THF:MeOH (1:3)	-	61	17	3.5:1.0[b]	87
2	THF	1	18	9	2.0:1.0	87
3	THF	5	10	12	0.8:1.0	91
4	THF	10	14	10	1.4:1.0	98

[a] Isolated yield.
[b] Jongkol , R.; Choommongkol, R.; Tarnchompoo, B.; Nimmanpipug, P.; Meepowpan, P. *Tetrahedron* **2009**, *65*, 6382–6389.

In 2009, Jongkol and co-workers has been reported the reduction of the *β*-keto diester adduct by $NaBH_4$ in THF:MeOH systems that obtained *tran*-**4** and *cis*-**5** in the highest diastereoselectivity (entry 1)[2]. The low concentration of catalyst (entry 2) afforded the ratio of *trans*:*cis* isomers in 2:1. On the other hand, when concentration of catalysts were increased (entry 2 and 3), the ratio of *trans*:*cis isomers* decreased to 1:1 of *trans*:*cis* isomers. On the contrary, percent conversion increased when the concentration of catalysts increased too. Surprisingly, the high concentration of catalyst will be obtained the percent yield of *cis*- more than *trans*- isomer.

Conclusion

The new chiral catalyst, TADDOL-anthracene adduct (-)-(11*R*)-**1**, would be applied as catalyst in low concentration (1 mol% of catalyst) for reduction of the *β*-keto diester. This catalytic system was successfully which increased the ratio of *cis*-isomer when decreasing of mol% of catalyst was used. On the other hand, we can expect that the use of other optically active form of TADDOL-antrhracene adduct (+)-(11*S*)-**1** will be increase the ratio of *trans*-isomer. In the future work, these two catalysts will be applied for asymmetric1,2-addition reaction of EtMgBr to benzaldehyde.

Acknowledgements

We are grateful to the Human Resource Development in Science Project (Science Achievement Scholarship of Thailand, SAST) and Department of Chemistry, Faculty of Science, Chiang Mai University.

References

[1] For the reviews of the applications of TADDOLs and their derivatives: (a) D. Seebach, A. K. Beck, And A. Heckel, *Angew. Chem. Int. Ed.* **2001**, *40*, 92-138; (b) H. Pellissier *Tetrahedron* **2008**, *64*, 10279-10317.

[2] R. Jongkol, R. Choommongkol, B. Tarnchompoo, P. Nimmanpipug, P. Meepowpan, *Tetrahedron* **2009**, *65*, 6382-6389.

[3] P. Kongsaeree, P. Meepowpan, Y. Thebtaranonth, Tetrahedron: *Asymmetry* **2001**, *12*, 1913-1922.

Keywords: TADDOLs, enantioselective, asymmtric addition.

Syntheses of TADDOL-Anthracene Adduct as Chiral Catalyst for Use in Reduction of β-Keto Ester

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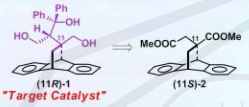
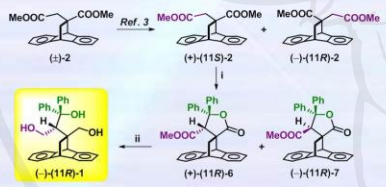
Introduction

TADDOLs (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols)[1] have been firstly reported by Seebach *et. al.*[1a]. Herein, designed and applied of the new chiral catalyst, TADDOL–anthracene adduct (11*R*)-1 in enantiomerically pure form had been described. The new chiral catalyst had been tested for reduction of the β-keto ester adduct (±)-3 using $NaBH_4$ as reducing agents.



Methodology, Results and Discussion

The TADDOL–anthracene catalyst (–)-(11*R*)-1 was synthesized using dimethyl itaconate–anthracene adduct [(+)-(11*S*)-2] as starting material. The adduct [(+)-(11*S*)-2] was treated with 1.2 equiv LDA at –78 °C to 0 °C for 1 h and then trapped with benzophenone to obtain two diastereomers of spiro–lactone adducts, (+)-(11*R*)-6 and (–)-(11*R*)-7, as major and minor products, respectively. Then, the spiro–lactone adduct (+)-(11*R*)-6 was reduced by LAH to provide the TADDOL–anthracene catalyst (–)-(11*R*)-1.



Scheme 1. Synthesis of TADDOL-anthracene adduct (–)-(11*R*)-1.
Reagents and conditions: (i) a. 1.2 equiv LDA, THF, –78 °C to 0 °C, 2 h, b. 1.2 equiv benzophenone, 0 °C to rt, 2 h (ii) 20 equiv $LiAlH_4$, THF –78 °C to rt, 3 days

The relative stereochemistries of TADDOL–anthracene catalyst (–)-(11*R*)-1 could be confirmed by the NOE experiments and compared with MM2 force field calculations for energy minimization from modeling program ChemBio3D Ultra 11.0 program (Figure 1). Therefore, the orientation of the proton H_c has not been changed by these reduction conditions.

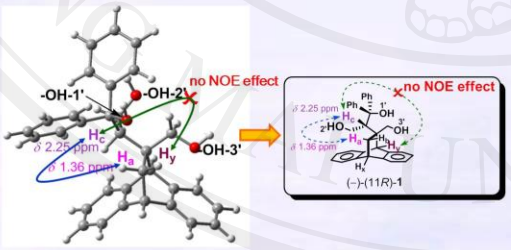


Figure 1. 3D structural conformation of TADDOL–anthracene adduct (–)-(11*R*)-1 generated by MM2 force field calculations for energy minimization from modeling program ChemBio3D Ultra 11.0 and GaussView 3.09 program

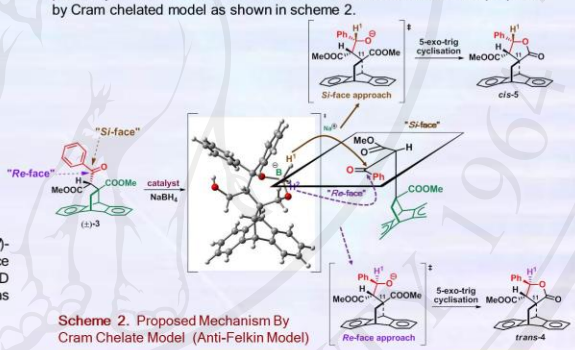
To study the effect of TADDOL–anthracene (–)-(11*R*)-1, as catalyst, in reduction of the β-keto ester adduct (±)-3 by $NaBH_4$, as the reducing agent, gave the results as shown in Table 1.

Table 1. Reduction of the β-keto ester adduct (±)-3 with various mol% of TADDOL–anthracene (–)-(11*R*)-1

Entry	conditions	n mol% of 1 (cat.)	Yield (%)[a] trans-4	cis-5	Ratio trans:cis
1	THF:MeOH (1:3)	-	61	17	3.5:1.0[b]
2	THF	1	18	9	2.0:1.0
3	THF	5	10	12	0.8:1.0
4	THF	10	14	10	1.4:1.0

[a] Isolated yield
[b] Jongkol, R.; Choommongkol, R.; Tarnchompoo, B.; Nimmanpipug, P.; Meepowpan, P. *Tetrahedron* **2009**, *65*, 6382-6389.

The reduction of the β-keto ester adduct (±)-3 by $NaBH_4$ in THF : MeOH systems had been reported by Jongkol and co-workers that obtained *trans*-4 and *cis*-5 in the highest diastereoselectivity (entry 1)[2]. The low concentration of catalyst (entry 2) afforded the ratio of *trans*:*cis* isomers in 2:1. On the other hand, when concentration of catalysts were increased (entries 3 and 4), the ratio of *trans*:*cis* isomers decreased to 1:1 of *trans*:*cis* isomers. On the contrary, percent conversion increased when the concentration of catalysts increased. Surprisingly, the high concentration of catalyst will be obtained percent yield of *cis*- more than *trans*- isomer. The mechanism was proposed by Cram chelated model as shown in scheme 2.



Scheme 2. Proposed Mechanism By Cram Chelate Model (Anti-Felkin Model)

Conclusion

The new chiral catalyst, TADDOL–anthracene adduct (–)-(11*R*)-1, would be applied as catalyst in low concentration (1 mol% of catalyst) for reduction of the β-keto ester adduct (±)-3. This catalytic system was successfully which increased the ratio of *cis*-isomer when decreasing of mol% of catalyst was used. On the other hand, we can expect that the use of other optically active form of TADDOL–antrhracene adduct (+)-(11*S*)-1 will be increase the ratio of *trans*-isomer.

Acknowledgement

We acknowledge the Human Resource Development in Science Project (Science Achievement Scholarship of Thailand, SAST), the National Research University Project under Thailand's office of the Higher Education Commission for financial support and Department of Chemistry, Faculty of Science, Chiang Mai University.

References

[1] (a) D. Seebach, A. K. Beck, And A. Heckel, *Angew. Chem. Int. Ed.* **2001**, *40*, 92-138; (b) H. Pellissier *Tetrahedron* **2008**, *64*, 10279-10317.
[2] R. Jongkol, R. Choommongkol, B. Tarnchompoo, P. Nimmanpipug, P. Meepowpan, *Tetrahedron* **2009**, *65*, 6382-6389.
[3] P. Kongsaeree, P. Meepowpan, Y. Thebtaranonth, Tetrahedron: *Asymmetry* **2001**, *12*, 1913-1922.

Keywords: TADDOLs, enantioselective, asymmetric addition.