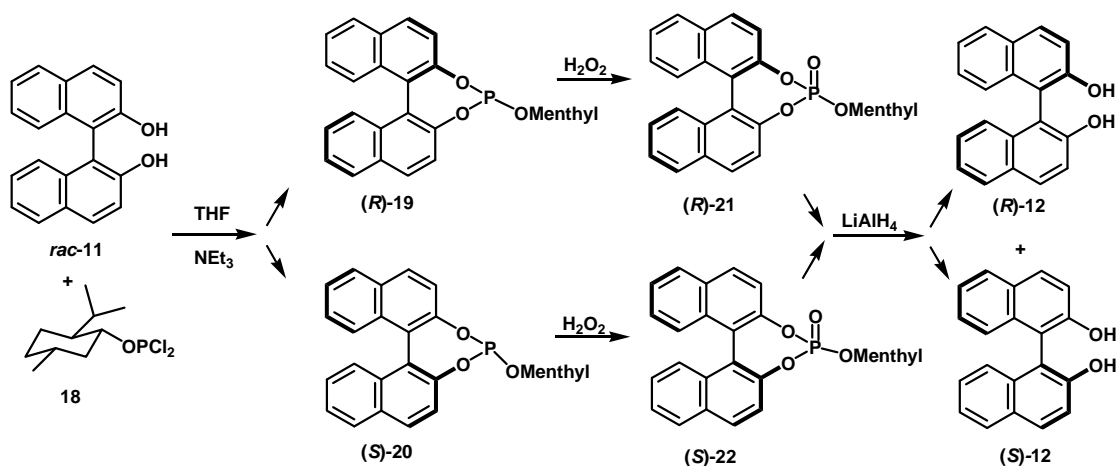


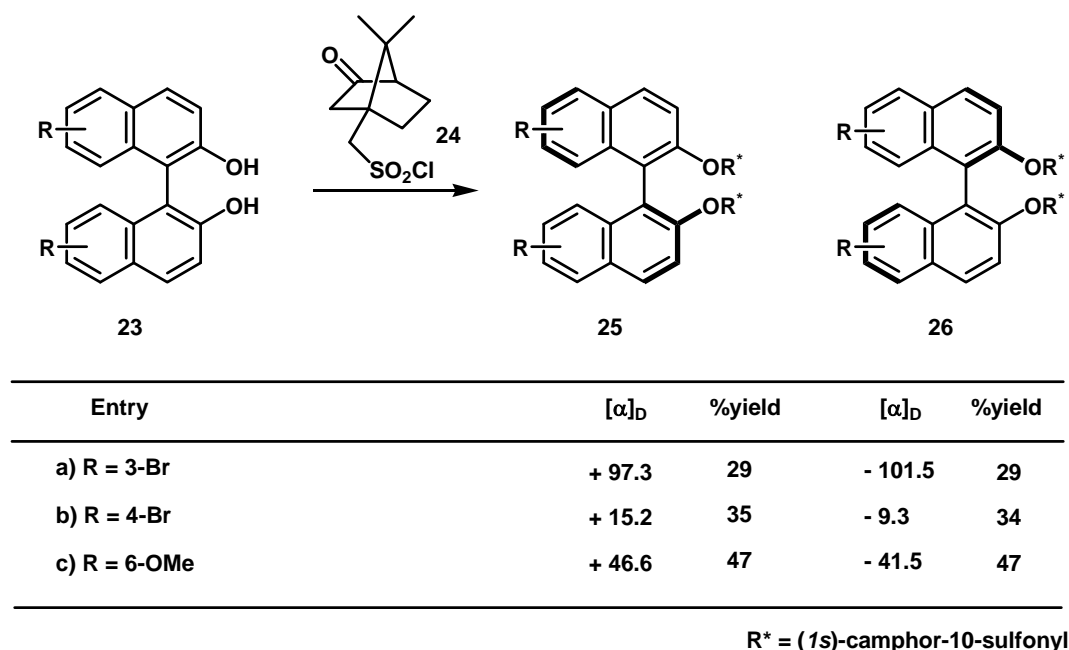
Scheme 6. The preparation of chiral phosphorus tricoordinated compound.

Compound **18** then reacted with *rac*-binaphthol **11** leading to a 1:1 mixture of diastereomers (*R*)-**19** and (*S*)-**20** in quantitative yield. Complete separation of the two diastereomers was achieved in a single recrystallization from diethyl ether. Oxidation with 30% hydrogen peroxide led to the phosphites **21** and **22**, which were reduced with LiAlH_4 to afford enantiomerically pure (*R*)-binaphthol **12** and (*S*)-binaphthol **12** in 81% and 85% overall yields, respectively (Scheme 7).



Scheme 7. Reaction of *rac*-binaphthol with chiral phosphorus compound.

Interestingly, Chow *et al.* discovered a versatile method for the resolution of disubstituted-1,1'-binaphthyl-2,2'-diols **23** by using (*1S*)-camphor-10-sulfonyl chloride **24** as a chiral auxiliary (Scheme 8).¹³

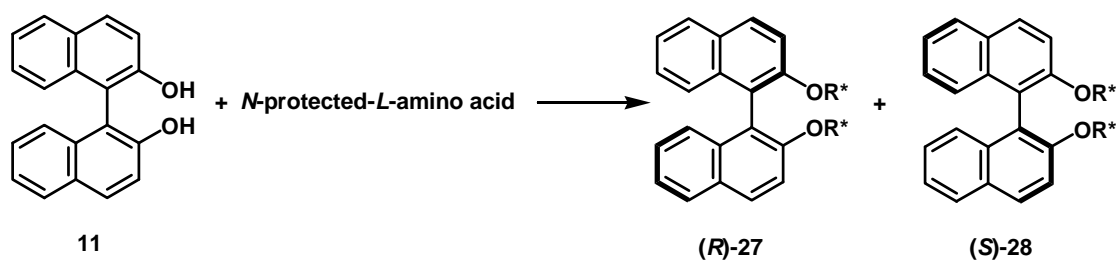


Scheme 8. The resolution of disubstituted-1,1'-binaphthyl-2,2'-diols.

Not only could the *rac*-**23** be resolved *via* its diastereomeric bis-(*S*)-camphor-10-sulfonates **25** and **26**, but the absolute configurations of the diastereomeric pairs **25** and **26** could also be inferred from their relative chromatographic mobility. In all of the less polar bis-(camphor-10-sulfonate)-**25a–c**, the diastereomeric methylene groups adjacent to the sulfonyl moiety appeared as an AX system ($J = 15$ Hz) with a chemical shift difference of less than 0.5 ppm, while those of the more polar diastereomeric **26 a–c** compounds had a significantly larger chemical shift difference of 1 ppm.

Furthermore, circular dichroism (CD) spectra of the hydrolyzed products derived from the less polar diastereoisomers **25a–c** all gave a negative first Cotton effect at around 236–240 nm and a positive second Cotton effect at 224–228 nm. The observed Cotton effect pattern is closely parallel to those previously reported by Mason¹⁴ and Harada.¹⁵ In both ¹H NMR and CD spectra, the less polar diastereomers **25a–c** could be assigned as having an (*S*)-configuration.

Extensive studies of the convenient and highly efficient chromatographic resolution of the *rac*-binaphthol **11** *via* esterification with *N*-protected-*L*-amino acid were reported by Einhorn *et al.* (Scheme 9).¹⁶



Entry	Amino acid derivative	R _f 27	R _f 28	α_a
1	<i>N</i> -Boc-phenylglycine	0.76	0.74	1.03
2	<i>N</i> -Boc-phenylalanine	0.78	0.70	1.11
3	<i>N</i> -Cbz-phenylalanine	0.80	0.74	1.08
4	<i>N</i> -(α)-Boc-tryptophan	0.54	0.26	2.15
5	<i>N</i> -(α)-Cbz-tryptophan	0.68	0.36	1.89

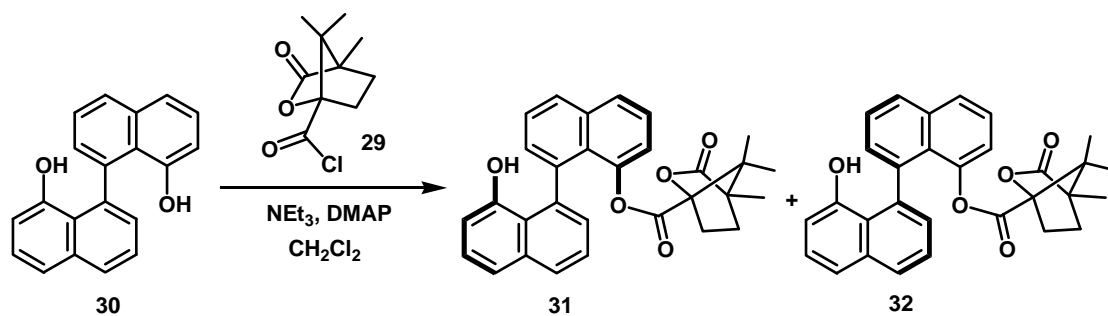
a) α defined as separation factor, $\alpha = R_{f27} / R_{f28}$

Scheme 9. TLC data for diester of *rac*-binaphthol and *N*-protected-*L*-amino acid.

R_f values and separation factors (α) were determined by TLC analysis, in order to select the most promising candidates for efficient separation. *N*-(α)-Boc-tryptophan was shown to be an excellent resolving agent for the resolution of binaphthol **11**. After hydrolysis, the less polar isomer, (*R*)-(+)-**11**, was obtained in 91% yield (100% ee) and the more polar isomer, (*S*)-(–)-**11**, was obtained in 93% yield (100% ee). However, the effect of the resolving agents on the different polarities of the diastereomeric pairs was not explained.

The resolution of binaphthol derivatives, using (1*S*)-camphanoyl chloride **29** as a resolving agent was first investigated by Fuji *et al.*¹⁸ in 1998 and it was found the applications in the field of asymmetric synthesis as well as chiral molecular recognition. Chiral recognition of amino acid derivatives by optically active 8,8'-dihydroxy-1,1'-binaphthyl **30** was used as a chiral derivatizing agent for the ¹H NMR determination of the absolute configuration of carboxylic acids.¹⁹

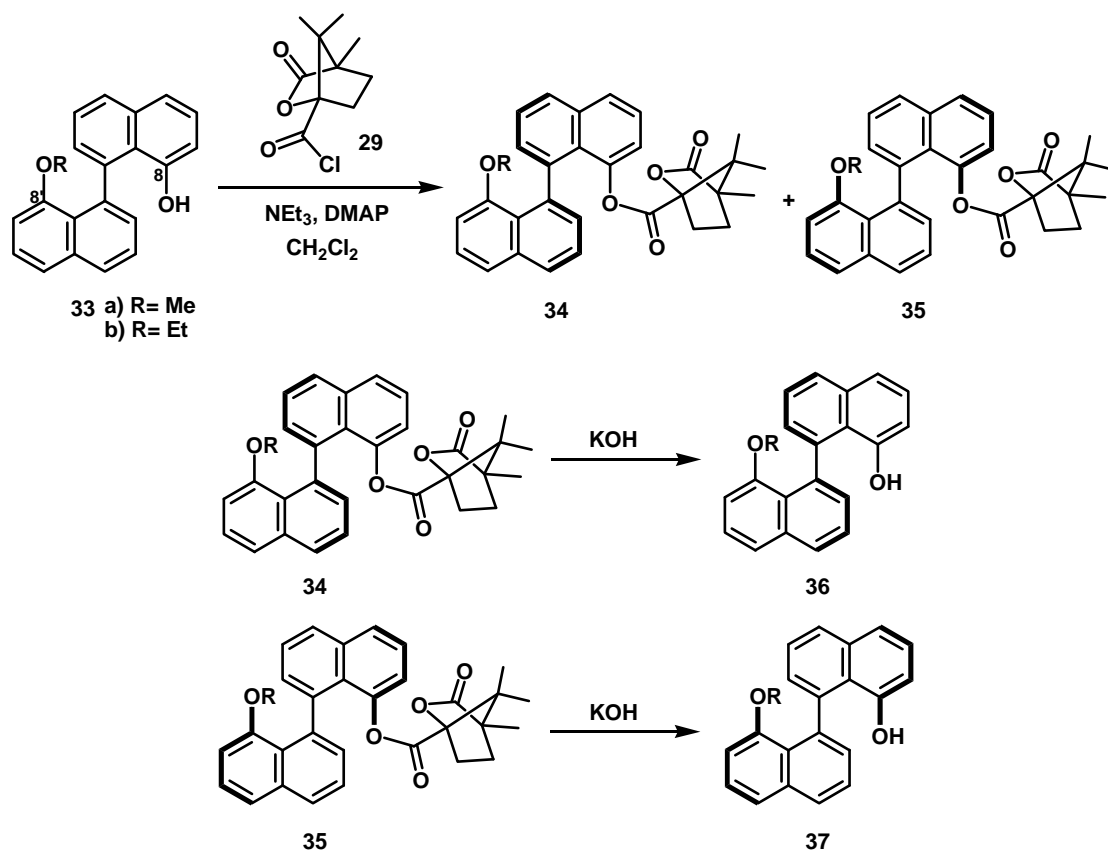
For the resolution of compound **30**, mono-acylation of racemic **30** with (1*S*)-camphanoyl chloride **29** gave a mixture of diastereoisomers **31** and **32** in 32% and 21% yields, respectively (Scheme 10).²⁰



Scheme 10. Resolution of 8,8'-dihydroxy-1,1'-binaphthyl.

Diastereoisomer **31** was reported to have a larger R_f value than its corresponding isomer **32**. After chromatographic separation, the camphanate moieties in **31** and **32** are readily removed in aqueous KOH to give the optically pure (*S*)-**30** and (*R*)-**30**, respectively.

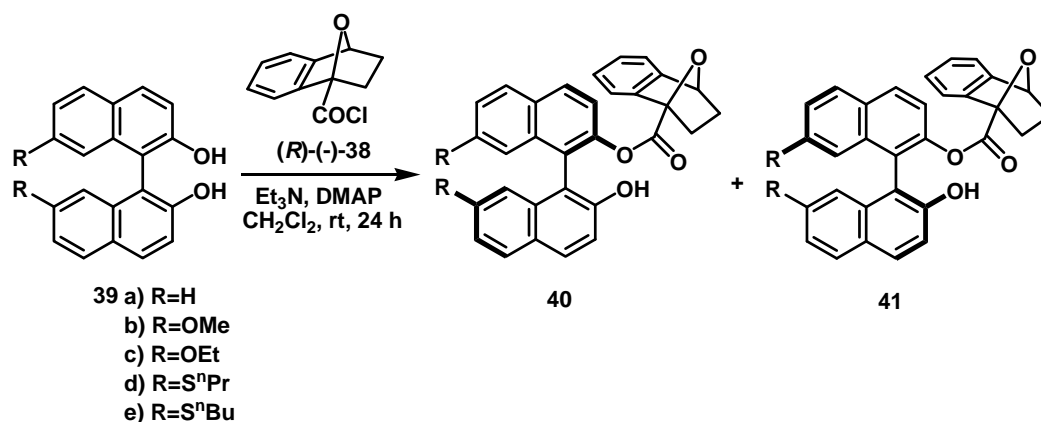
Moreover, a series of 8'-alkoxyl-1,1'-binaphthalen-8-ols was investigated by Hua. Enantiopure 8'-alkoxy-8-hydroxy-1,1'-binaphthyl (*R*)-**36** or (*S*)-**37** were obtained from *rac*-**33** as described in Scheme 11.²¹



Scheme 11. Resolution of 8'-alkoxyl-1,1'-binaphthalen-8-ols with (*1S*)-camphanate.

Interestingly, all of the faster running isomers **34** had an (*R*)-configuration. These results controverted to those from the resolution of 8,8'-dihydroxy-1,1'-binaphthyl **30** which indicated that the fast running on TLC, less polar isomer had an (*S*)-configuration. Apparently, types of substituted groups at position 8 might affect the different polarity of the diastereomeric pairs of compounds **30** and **33**.

Our interest then focused on the resolution of the binaphthol derivatives which would be derived from the reactions of chiral α -alkoxa bicyclic acid chloride **38** and binaphthols **39**. The resolution of 7,7'-disubstituted binaphthols at the 2,2'-position of binaphthyls **39** (entry 1–5) by using (*R*)-(-)-2,3-dihydro-1,4-epoxynaphthalene-1(2*H*)-carboxylic acid **4** (refer to compound **4** in Scheme 1, PART I) as a new resolving agent was carried out. Treatment of binaphthols **39** with (*R*)-(-)-acid chloride **38** in dichloromethane in the presence of triethylamine and a catalytic amount of DMAP afforded a diastereomeric mixture of (*R,R*)-**40** and (*R,S*)-**41** in good yields. It was found that the isomers **40** had larger R_f value than their corresponding diastereoisomers **41** (Scheme 12). %Yields, R_f values and separation factors of diastereomers **40** and **41** are summarized in Table 1.



Scheme 12. Resolution of binaphthols with (*R*)-(-)-acid chloride **38**.

Table 1. Separation factors (α), %yields and R_f values of diastereomers **40** and **41**.

Entry	%Yield of (<i>R,R</i>)- 39	R_f of (<i>R,R</i>)- 39	%Yield of (<i>R,S</i>)- 40	R_f of (<i>R,S</i>)- 40	α (R_{f39}/R_{f40})
1. a) R=H	48	0.46	43	0.34	1.35
2. b) R=OMe	45	0.45	42	0.35	1.29
3. c) R=OEt	47	0.60	45	0.49	1.22
4. d) R=S ⁿ Pr	24	0.46	25	0.37	1.24
5. e) R=S ⁿ Bu	22	0.45	20	0.37	1.21

Careful examination of the ^1H NMR spectra of all diastereoisomers revealed an interesting feature. For example, ^1H NMR spectra of compound **40b** and **41b**, displayed in Figure 4, showed a significant difference of chemical shifts of their methylene groups on the α -alkoxa bicyclic acid. It could be observed that methylene protons (a) and (b) of compound **41b** were upfield shifted by diamagnetic anisotropic effect of naphthalene moiety when compared to its diastereomer **40b**.

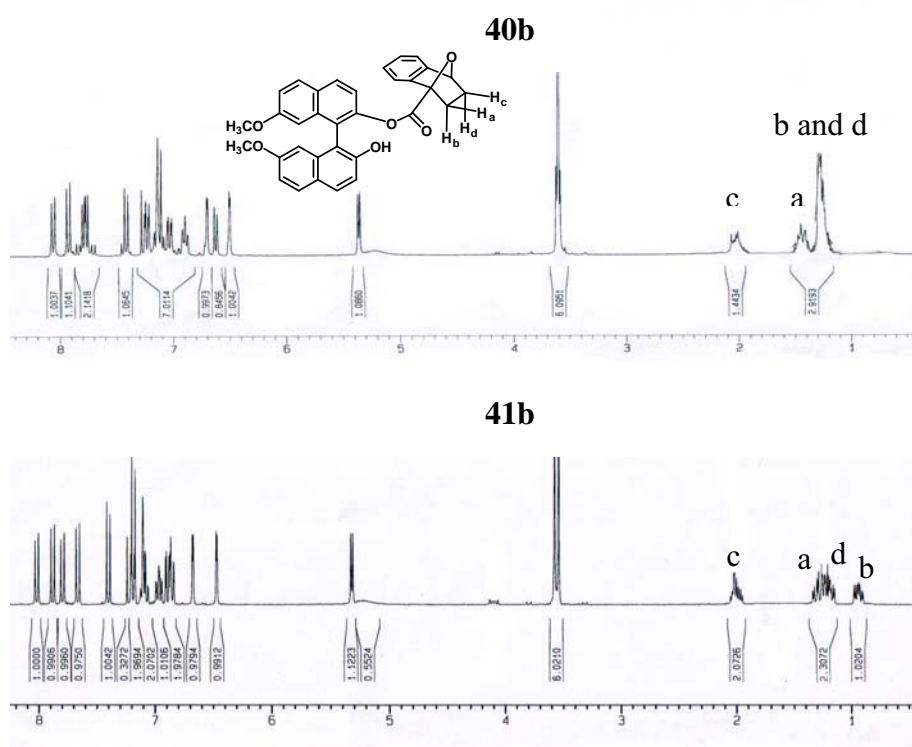


Figure 4. The difference on the ^1H NMR spectra of compounds **40b** and **41b**.

Chemical shifts of the methylene protons of the other derivative compounds are summarized in Table 2. In all case, chemical shifts of H_a and H_b of **40** were all shifted lower field than those of **41**.

Table 2. Chemical shifts of methylene protons of compounds **40a–e** and **41a–e**.

Entry	Chemical shift (ppm)							
	Compound 40				Compound 41			
	H _a	H _b	H _c	H _d	H _a	H _b	H _c	H _d
1. a) R=H	1.49	1.29	2.01	1.29	1.33	0.95	2.05	1.22
2. b) R=OMe	1.45	1.30	2.05	1.30	1.35	0.99	2.05	1.25
3. c) R=OEt	1.46	1.25	2.02	1.25	1.31	0.95	2.01	1.20
4. d) R=S ⁿ Pr	1.52	1.23	1.97	1.23	1.23	0.70	1.93	1.15
5. e) R=S ⁿ Bu	1.64	1.28	2.16	1.28	1.30	0.90	2.02	1.20

*Chiroptical properties of all diastereomers **40a–e** and **41a–e***

Circular dichroism of each diastereomer was then determined. The faster moving isomer **40a** displayed first positive Cotton effect at 278 nm and second negative Cotton effect at 242 nm as demonstrated in Figure 23. On the other hand, ester **40b** showed first negative Cotton effect at 326, 277 nm and strong negative Cotton effect at 249 nm, which was similar in shape to the CD spectra of compound **40c**, which showed negative Cotton effect at 329, 278 nm and strong negative Cotton effect at 251 nm (Figures 5–7). Esters **40d–e** showed first negative Cotton effect at 307 nm and a negative second Cotton effect at 264 nm (Figures 8–9).

CD spectra of compounds **41a–e** appeared rather like mirror image of those of their corresponding diastereomers **40a–e**. For isomer **41a**, it displayed a negative first Cotton effect at 282 nm and a positive second Cotton effect at 239 nm. In contrast, **41b–c** showed positive Cotton effect at 326, 278 nm and strong positive Cotton effect at 247 nm. The esters **41d–e** similarly exhibited a first positive Cotton effect at 307 nm and a negative second

Cotton effect at 265 nm. The observed bathochromic shift in CD spectra could be from the effect of substituents on binaphthols.

Circular dichroism (CD) spectra of diastereomeric compounds 40 and 41.

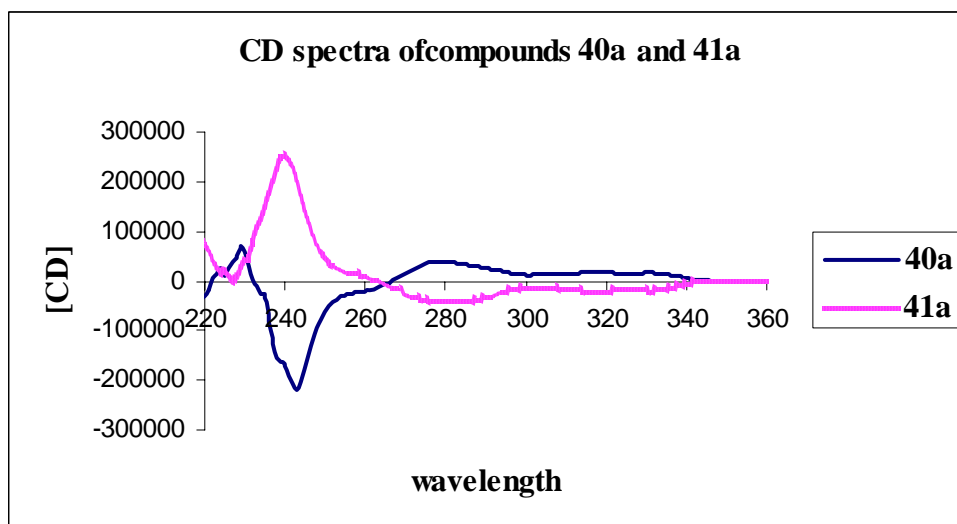


Figure 5. CD spectra of compounds **40a** and **41a**.

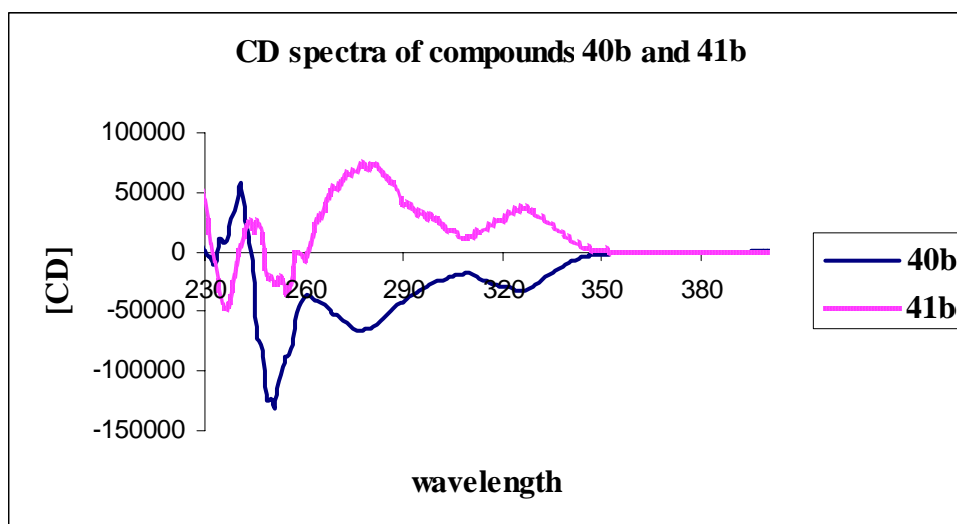


Figure 6. CD spectra of compounds **40b** and **41b**.

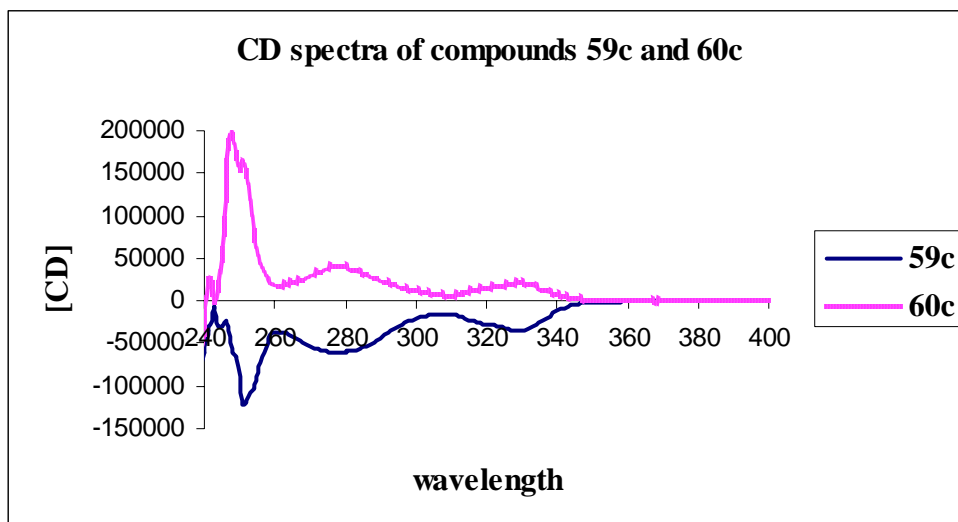


Figure 7. CD spectra of compounds **40c** and **41c**.

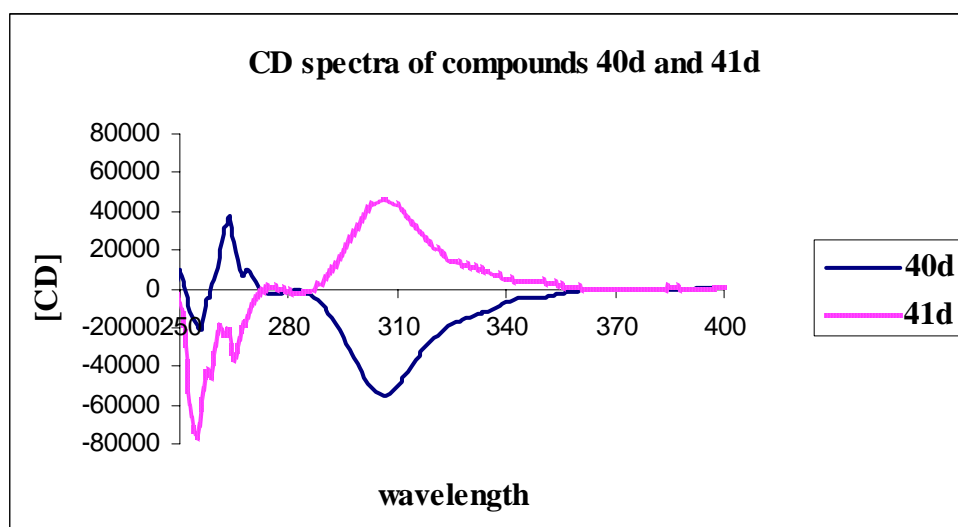


Figure 8. CD spectra of compounds **40d** and **41d**.

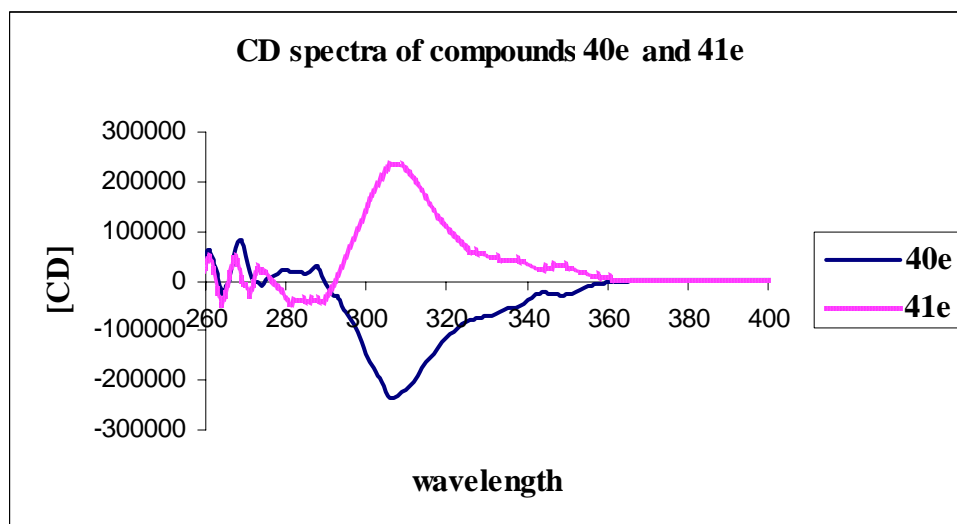


Figure 9. CD spectra of compounds **40e** and **41e**.

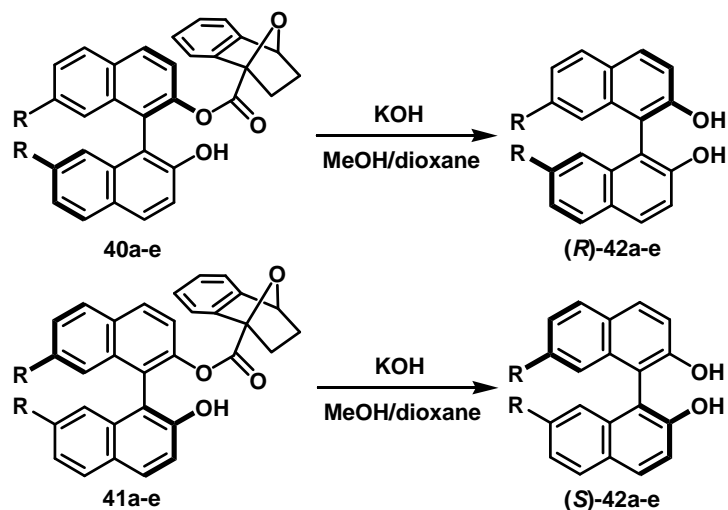
Moreover, the specific rotations $[\alpha]_D$ of compounds **40** and **41** were recorded as shown in Table 3.

Table 3. Specific Rotation of diastereomers **40a–e** and **41a–e** in CH_3CN .

Entry	$[\alpha]_D$ of compound 40	$[\alpha]_D$ of compound 41
1. a) R=H	−48.66	−95.12
2. b) R=OMe	−62.63	−16.98
3. c) R=OEt	−279.76	+10.62
4. d) R=S ⁿ Pr	−496.80	−377.57
5. e) R=S ⁿ Bu	−497.14	−399.92

Absolute Configuration Assignment

The absolute configurations of each diastereoisomer were determined by converting them to the corresponding binaphthols **42**. To recover the enantiopure (*R*)- and (*S*)-**42**, esters **40a–e** and **41a–e** were hydrolyzed with KOH in methanol and dioxane to yield binaphthol derivatives (*R*)-**42a–e** and (*S*)-**42a–e** (Scheme 13).



Scheme 13. Formation of the optically active binaphthols **42**.

%Yield and the optical rotation of all hydrolyzed binaphthols (*R*)-**42** and (*S*)-**42** were summarized in Table 4 and 5, respectively.

Table 4. % Yields of compounds (*R*)-**42** and (*S*)-**42**.

Entry	%Yield of (<i>R</i>)- 42	%Yield of (<i>S</i>)- 42
1. a) R=H	84	85
2. b) R=OMe	91	87
3. c) R=OEt	87	92
4. d) R=S ⁿ Pr	89	79
5. e) R=S ⁿ Bu	82	86

Table 5. Specific optical rotations of compounds (*R*)-**42** and (*S*)-**42** in CH₃CN.

Entry	$[\alpha]_D$ of compound (<i>R</i>)- 42	$[\alpha]_D$ of compound (<i>S</i>)- 42
1. a) R=H	+45.32 ^a at 25.2 °C, c = 1.00	−43.82 at 25.9 °C, c = 1.00
2. b) R=OMe	−119.97 ^b at 25.9 °C, c = 1.00	+117.95 at 25.7 °C, c = 1.15
3. c) R=OEt	−218.50 ^c at 25.5 °C, c = 1.02	+217.12 at 25.8 °C, c = 1.03
4. d) R=S ^{''} Pr	−334.52 ^c at 25.8 °C, c = 0.80	+375.68 at 26.0 °C, c = 0.60
5. e) R=S ^{''} Bu	−132.98 at 26.2 °C, c = 1.00	+190.63 at 26.1 °C, c = 0.80

a Ref. 26: (*R*)-**42a**; $[\alpha]_D$ = +43.0 (c=0.19, THF) and (*S*)-**42a**; $[\alpha]_D$ = −95.5 (c=1.1, benzene)

b Ref. 13: (*R*)-**42b**; $[\alpha]_D$ = −125.5 (c=0.17, CHCl₃) and (*S*)-**42b**; $[\alpha]_D$ = +127.4 (c=0.17, CHCl₃)

c Ref. 25: (*R*)-**42c**; $[\alpha]_D$ = −196.0 (c=0.27, CH₃CN) and (*S*)-**42c**; $[\alpha]_D$ = +193.6 (c=0.27, CH₃CN)

(*R*)-**42d**; $[\alpha]_D$ = −300.5 (c=0.20, CH₃CN) and (*S*)-**42d**; $[\alpha]_D$ = +300.4 (c=0.20, CH₃CN)

By direct comparison between $[\alpha]_D$ of the samples and values in the literature,^{13,24,25} the absolute configurations of both enantiomers of (*R*)-**42a–d** and (*S*)-**42a–d** could then be assigned. However, more evidences were still required for the stereochemical assignments of (*R*)-**42a–e** and (*S*)-**42a–e**. Circular dichroism spectra of all (*R*)-**42** and (*S*)-**42** were therefore determined (Figures 10–14). In fact, all compounds assigned as (*S*)-configuration displayed similar CD curves with first negative Cotton effect around 300–350 nm, while compounds assigned as (*R*)-configuration showed the mirror image curves in comparison to the (*S*)-isomer, giving CD curves with the first positive Cotton effect. These results were in good agreement with the results reported by Areephong.²⁵ Accordingly, the conclusion of the absolute configuration of binaphthol derivatives could be assured and related to the chiral sense of both binaphthols **40** and **41**.

Consequently, the faster moving, less polar, isomers **40a–e** consist of (*R*)-binaphthol whereas binaphthols of the slow moving, more polar isomers **41a–e**, have an (*S*)-configuration.

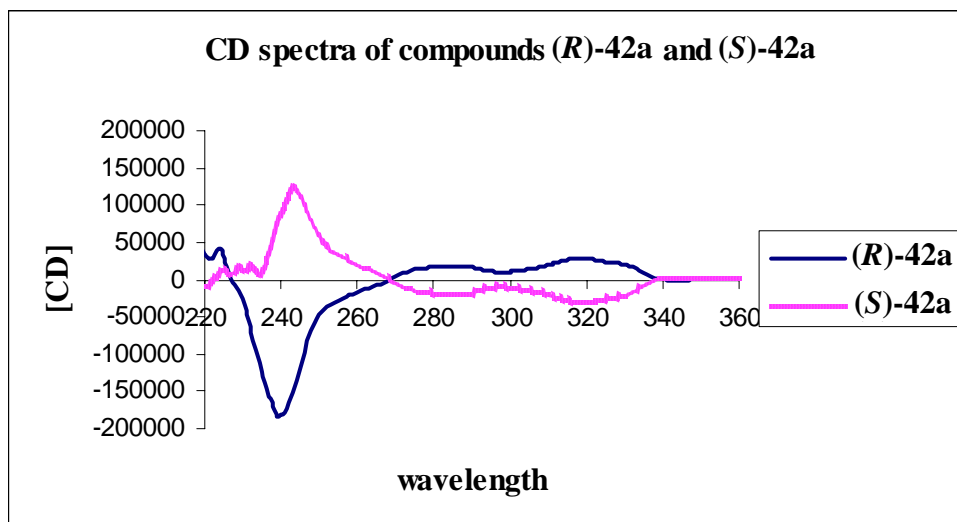


Figure 10. CD spectra of compound (*R*)-42a and (*S*)-42a.

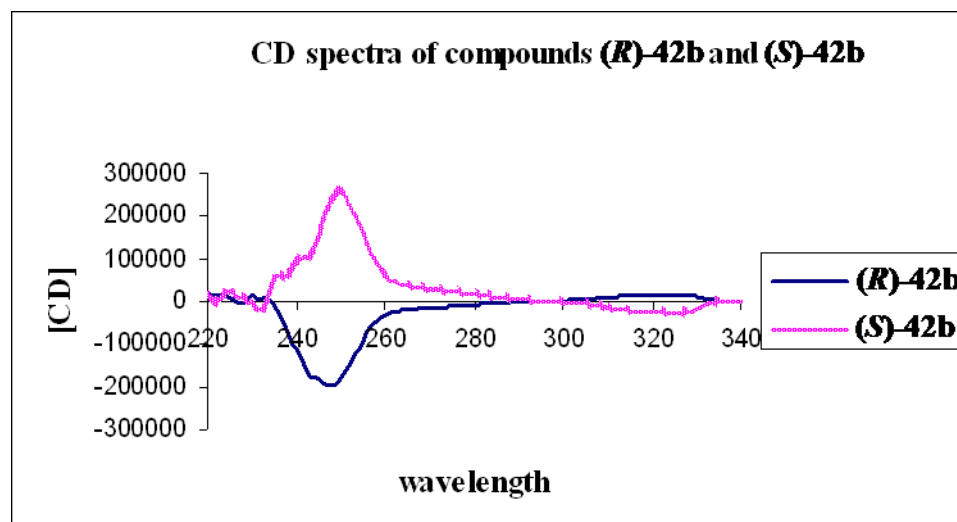


Figure 11. CD spectra of compound (*R*)-42b and (*S*)-42b.

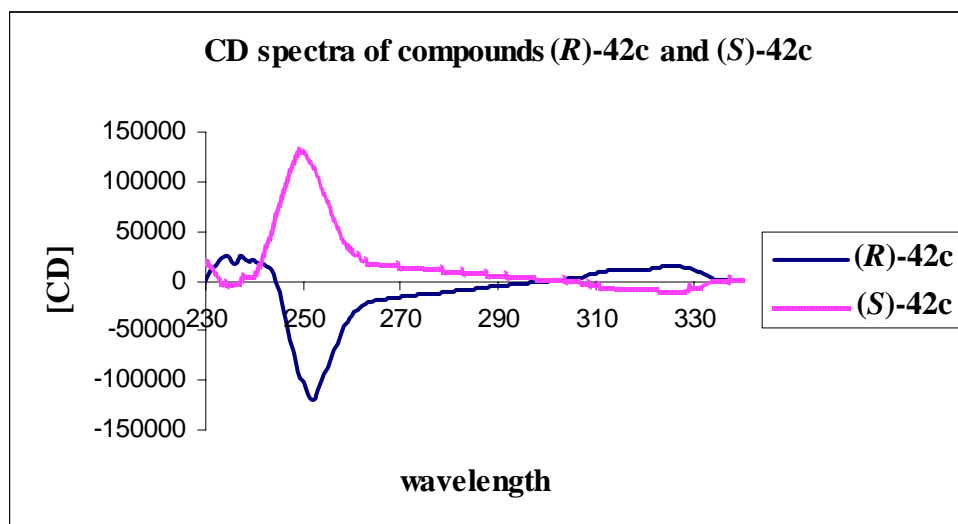


Figure 12. CD spectra of compound (R)-42c and (S)-42c.

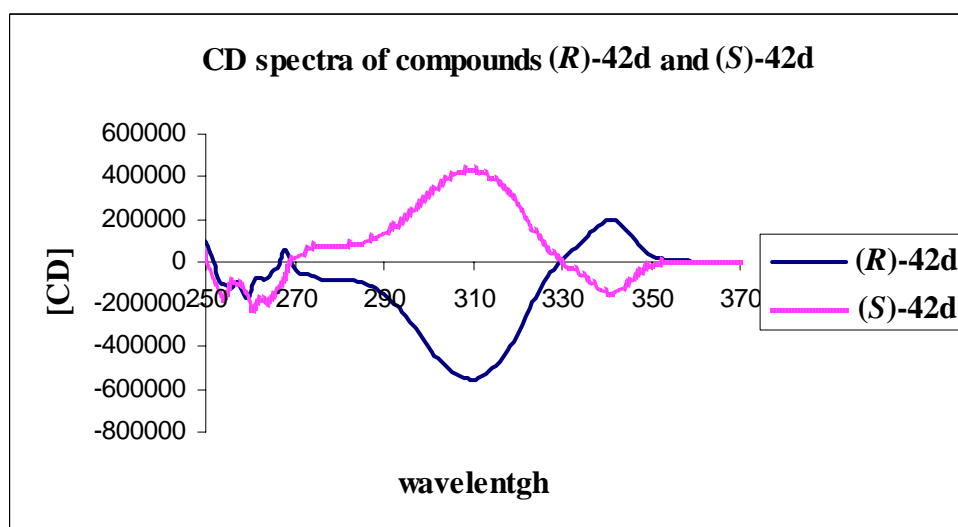


Figure 13. CD spectra of compound (R)-42d and (S)-42d.

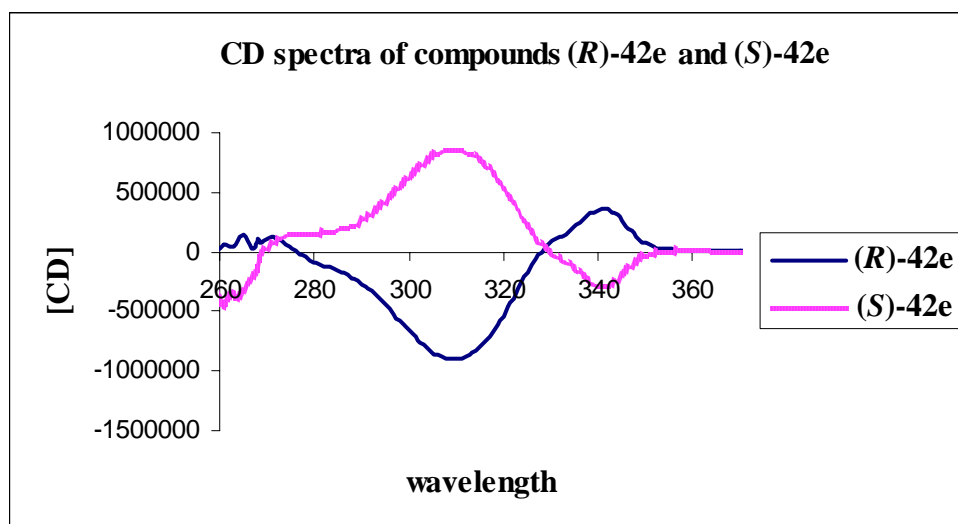
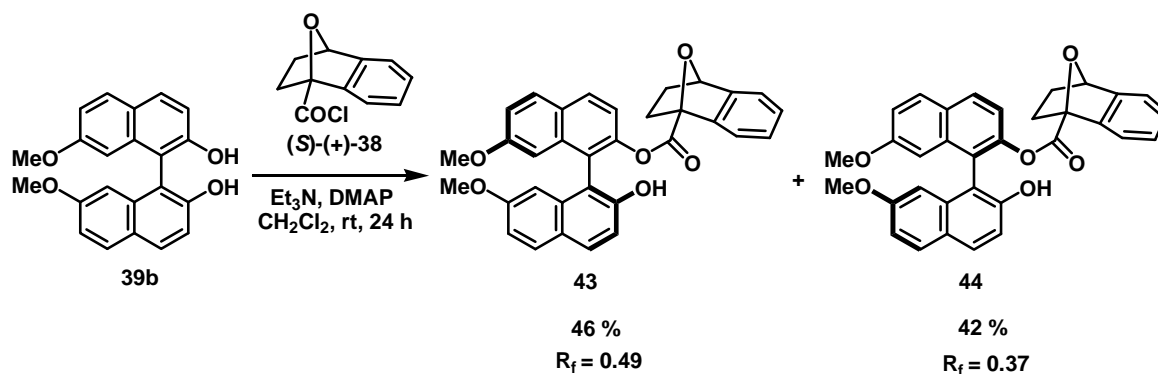


Figure 14. CD spectra of compound (*R*)-42e and (*S*)-42e.

The extended study of the resolution by using (*S*)-(+)-2,3-dihydro-1,4-epoxynaphthalene-1(2*H*)-carboxylic acid **4** with 7,7'-Dimethoxy-[1,1']-binaphthalenyl-2,2'-diol was also performed to compare the results with those of (*R*)-(-)-acid **4**. A mixture of chiral acid chloride (*S*)-(+)-**38**, *rac*-binaphthol **39b**, NEt_3 and DMAP in CH_2Cl_2 was stirred for 24 h, yielding a diastereomeric mixture of esters. The mixture was separated by PLC on silica gel (hexane: EtOAc 85:15; separation factor $\alpha = 1.32$) (Scheme 14). The first-eluted ester **43** (46%, $[\alpha]_{\text{D}} -3.74$ ($c = 1.50$ w/v, CH_3CN)) and the second one **44** (42%, $[\alpha]_{\text{D}} -17.23$ ($c = 1.50$ w/v, CH_3CN)) were obtained.



Scheme 14. Resolution of binaphthols **39b** with (*S*)-(+)-acid chloride **38**.

^1H NMR signals of esters **43** and **44** similarly showed a significant difference of chemical shifts of their methylene group on the α -oxa acid (Table 3). Chemical shift of methylene protons ($H_a = 1.23$ and $H_b = 0.89$) of compound **44** were upfield shifted by diamagnetic anisotropic effect of naphthalene moiety when compared to its diastereomer **43** ($H_a = 1.40$ and $H_b = 1.25$).

In addition, CD spectra of the first-eluted ester **43**, was directly opposite to **40b**, *i.e.* it displayed first positive Cotton effect at 326, 277 nm and strong positive Cotton effect at 248 nm. Moreover, CD of ester **44** was opposite to the CD spectra of compound **41b**, displayed first negative Cotton effect at 327, 277 nm and strong positive Cotton effect at 250 nm (Figure 15).

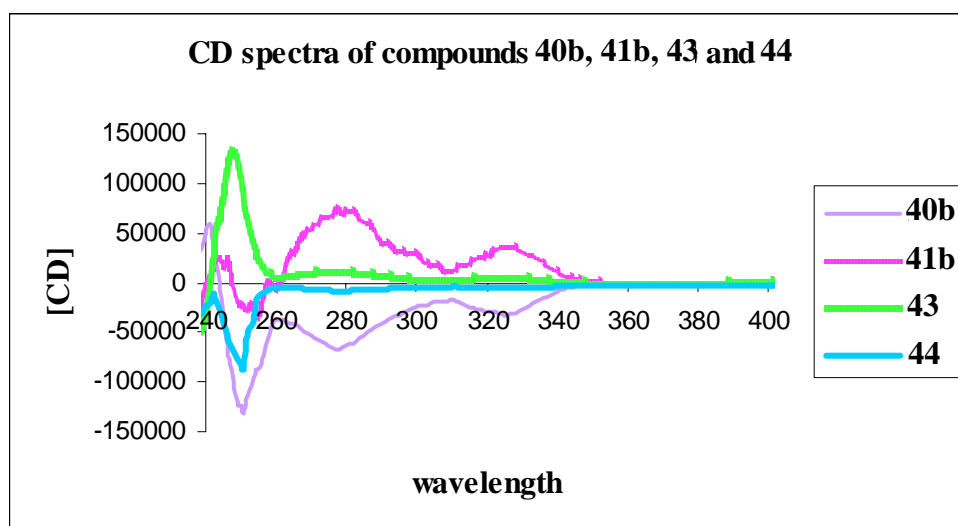
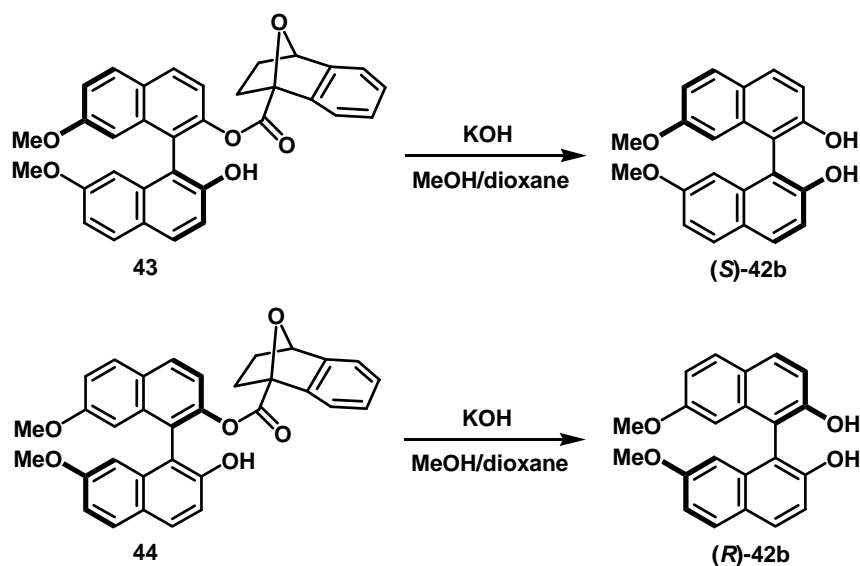


Figure 15. CD spectra of compound **43** and **44** from (*S*)-(+)-acid **4** compared with compound **40b** and **41b** from (*R*)-(-)-acid **4**.

The absolute configuration of each diastereoisomer was determined by converting them to the corresponding binaphthol. Esters **43** and **44** were hydrolyzed with KOH in MeOH and dioxane to give binaphthol derivatives (*S*)-**42b** (79% yield) and (*R*)-**42b** (82% yield), respectively (Scheme 15).



Scheme 15. Formation of optically active binaphthols **42b** from (*S*)-(+)-acid **4**.

The optical rotations of binaphthols (*R*)-**42b** and (*S*)-**42b** from (*R*)-(–)-acid and (*S*)-(+)-acid **4** were also exhibited in Table 6.

Table 6. Specific optical rotations of 7,7'-Dimethoxy-[1,1']-binaphthalenyl-2,2'-diols (*R*)-**42b** and (*S*)-**42b**, hydrolyzed from (*R*)-(–)-acid and (*S*)-(+)-acid **4**.

Entry	$[\alpha]_D$ of binaphthol (<i>R</i>)- 42b	$[\alpha]_D$ of binaphthol (<i>S</i>)- 42b
1.From (<i>R</i>)-(–)-acid	–119.97 at 25.9 °C, c = 1.00	+117.95 at 25.7 °C, c = 1.15
2.From (<i>S</i>)-(+)-acid	–132.44 at 25.6 °C, c = 1.20	+103.57 at 25.7 °C, c = 1.10

Based on the CD analysis, the faster moving, less polar isomer **43**, suggested (*S*)-binaphthol **42b**, while binaphthol of the slow moving, more polar isomer **44**, has an (*R*)-configuration (Figure 16).

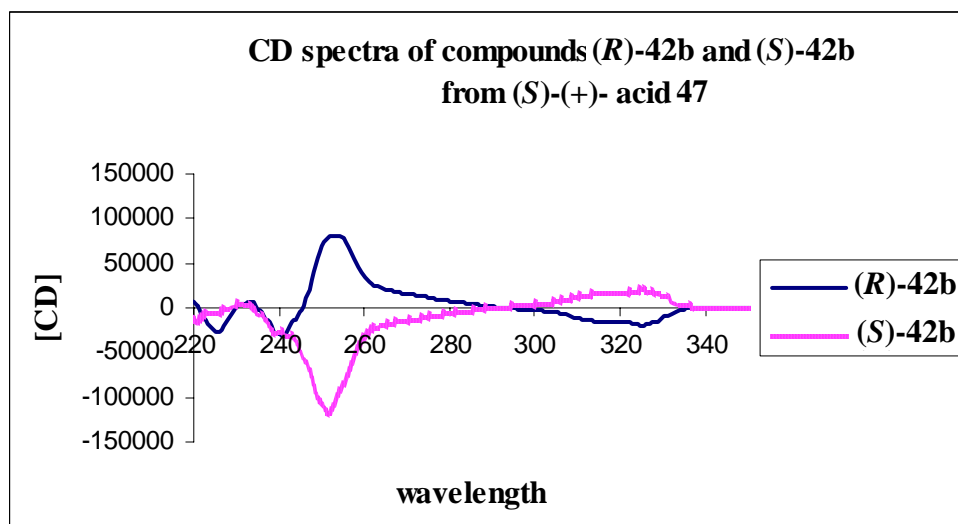


Figure 16. CD spectra of compound (*S*)-**42b** and (*R*)-**42b** from (*S*)-(+)-acid **47**.

It is clear that (*S*)-(+)-acid **47** can be used as a chiral derivatizing agent in the same manner as its corresponding isomer, (*R*)-(–)-acid, does.

In addition to the CD analysis, compounds with good quality crystals, *i.e.* **40a**, **40b**, **40c**, **41b** and **41c**, were then subjected to X-ray diffraction analyses. Molecular structures were as shown in Figures 17–21. X-ray data clearly confirmed the assignment of absolute stereochemistry of binaphthols.

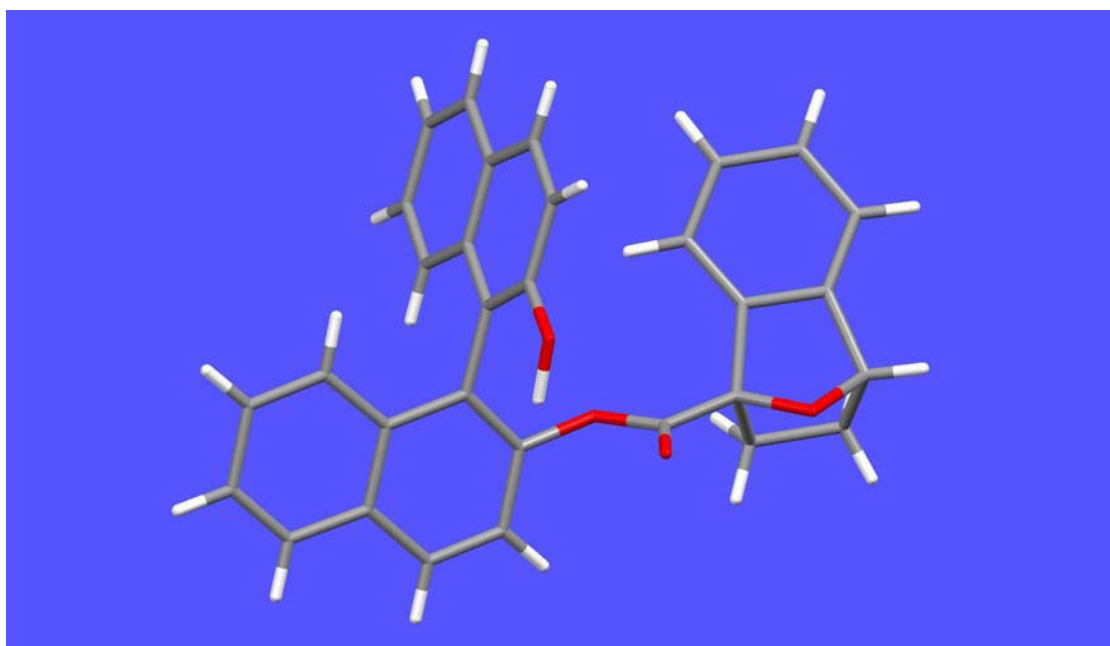


Figure 17. X-ray structure of compound (*R,R*)-**40a**.

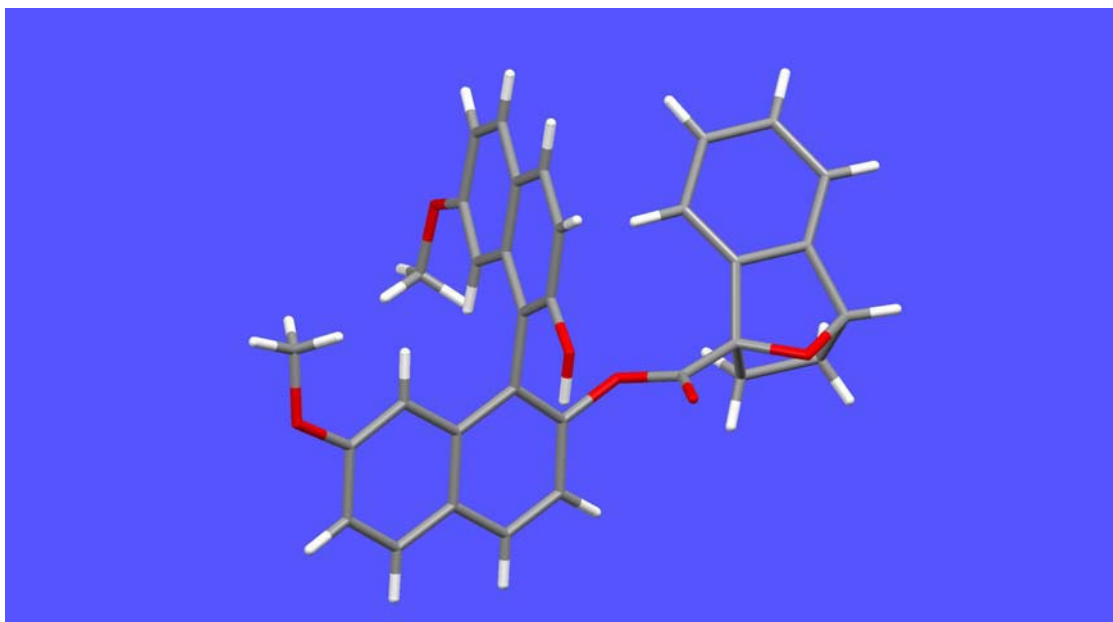


Figure 18. X-ray structure of compound (*R,R*)-**40b**.

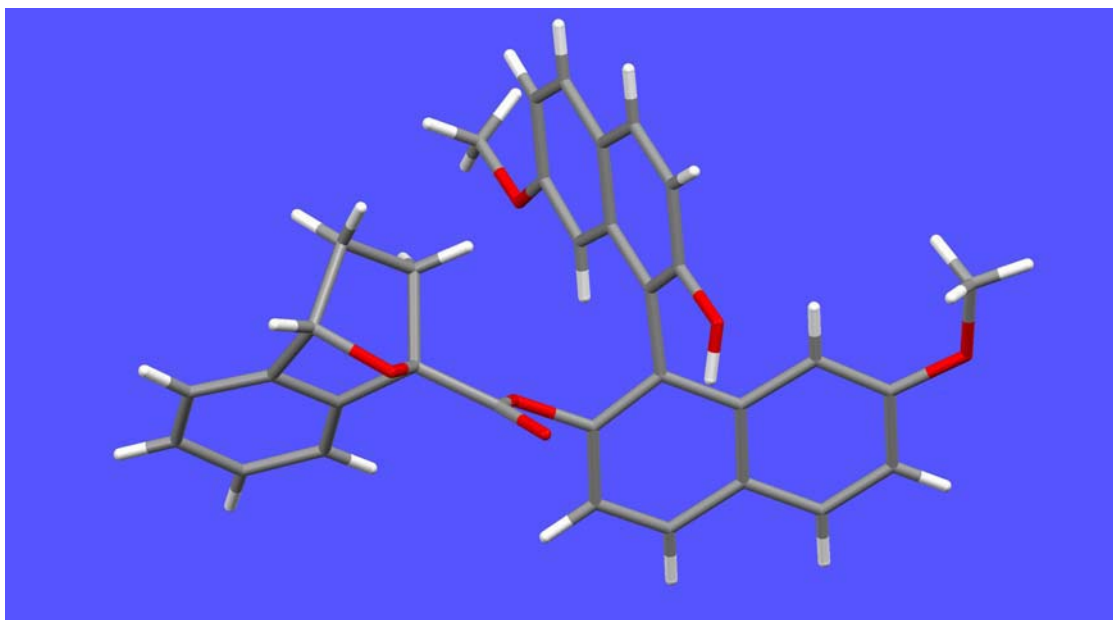


Figure 19. X-ray structure of compound (*R,S*)-**41b**.

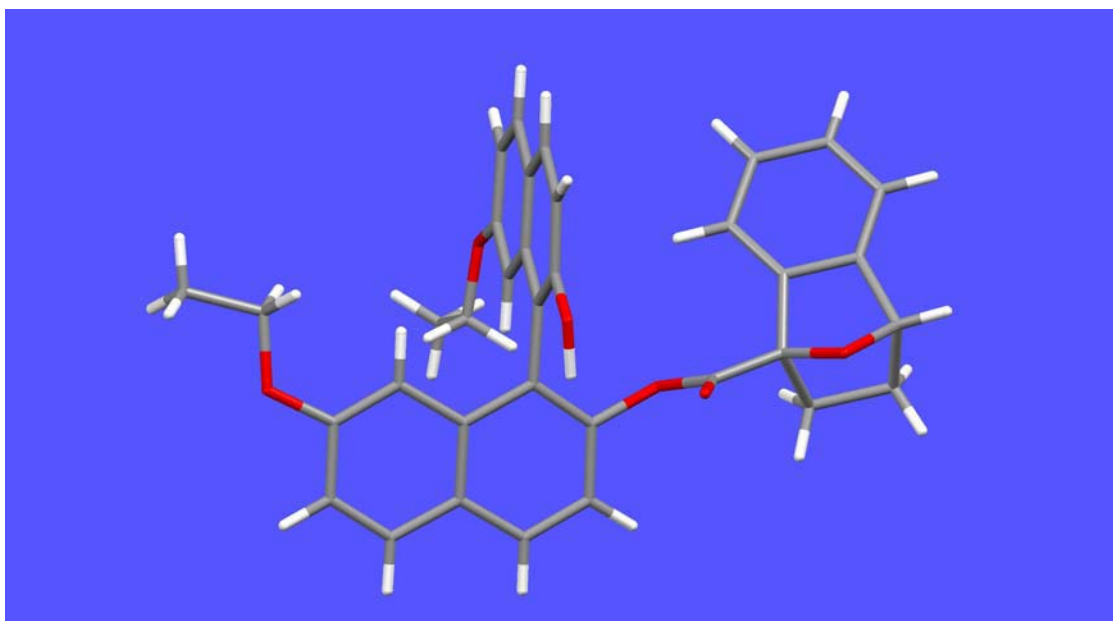


Figure 20. X-ray structure of compound (*R,R*)-**40c**.

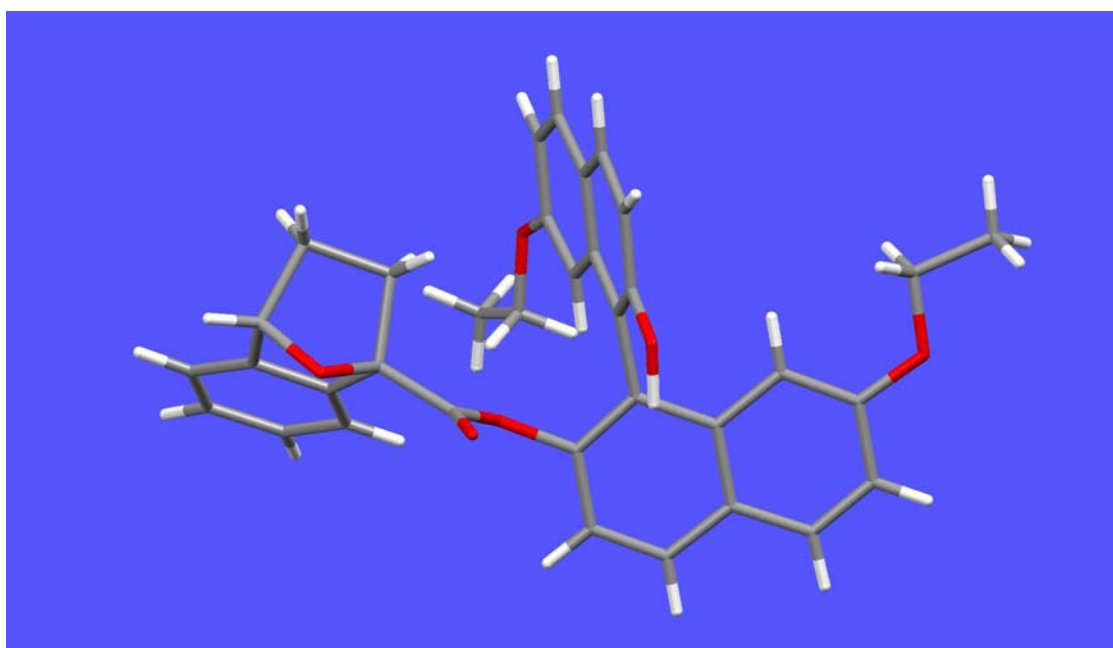


Figure 21. X-ray structure of compound (*R,S*)-**41c**.

It is remarkable that all diastereomers with similar chirality display the same chromatographic behavior. Thus, not only that the X-ray data provided the absolute configuration of binaphthol derivatives, but it also displayed the orientation of α -oxa bicyclic acid group over binaphthol moiety. Models to provide rationalization of this observation were then constructed, as analogy to the camphanate-binaphthol system.²⁵ Considering the structure of α -oxa acid-binaphthol derivatives (Figure 22), the orientation of α -oxa acid with respect to the binaphthol system was determined by the dihedral angles about four single bonds **a**, **b**, **c**, and **d**. The angles could be defined as follows: **a** ($\text{O}=\text{C}-\text{C}\alpha-\text{O}$), **b** ($\text{C}2-\text{O}-\text{C}=\text{O}$), **c** ($\text{C}1-\text{C}2-\text{O}-\text{C}$), and **d** ($\text{C}2-\text{C}3-\text{C}4-\text{C}5$) and the dihedral angle parameters **a**, **b**, **c**, and **d** were then studied from the X-ray analyses and the results were listed in Table 7.

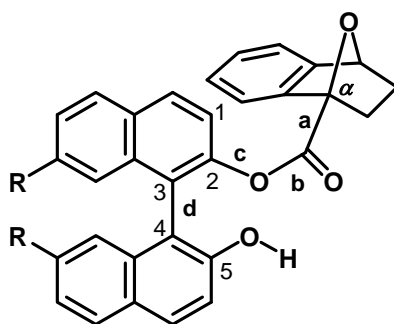


Figure 22. Defined parameters for conformational analysis.

Table 7. Structural parameters for binaphthol-(*R*)- α -oxa bicyclic acid according to X-ray Diffraction Analyses.

Entry	X-ray			
	a	b	c	d
40a	5.29	-6.16	-83.85	-87.19
40b	11.57	-10.35	-88.29	-102.11
40c	6.10	-11.18	-92.57	-96.55
41b	-5.39	-2.59	106.16	109.95
41c	-17.21	-7.86	102.59	110.27

The preferred conformation of bond **a** was proposed by Mosher²² that the ester carbonyl and methoxy groups of the mandelic acid moiety lie in the same plane (Figure 23). The calculations on this mandelate derivative reveal that the mandelic acid moiety is in the conformation that dihedral angle **a** ($\text{O}=\text{C}-\text{C}_\alpha-\text{OCH}_3$) is 0° . Because of the high EN of oxygen, the stereoelectronic effect would present the orientation in the way that the electron poor (C–O) σ bond will align in perpendicular to C–O π^* bond. Thus C–OMe bond should either be syn- or antiperiplanar to C=O group.

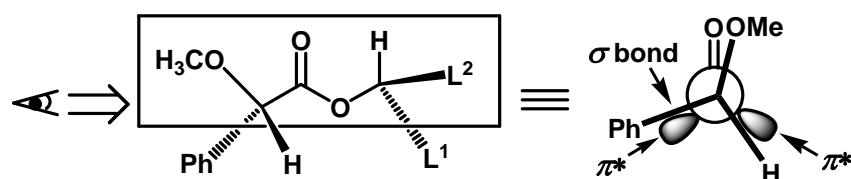


Figure 23. The stable conformation of mandelate model.

As expected, bond **a** in X-ray data shows its angle = $0 \pm 17^\circ$ which greatly resembles the mandelic ester model.

The preferred conformation of bond **c** was clearly reported. The carbonyl group of ester would not lie in the plane of the benzene ring due to the steric repulsion between the carbonyl oxygen and the phenyl's C-1 hydrogen. Thus the C=O of the ester bond, in Figure 40, must point either up, away from the binaphthol moiety (*exo*), or point down, toward the aromatic ring (*endo*). From the X-ray data, the preferred angles of bond **c** would most likely be perpendicular to the aromatic plane, being $90 \pm 16^\circ$ or $-90 \pm 2^\circ$ (*exo*).

The ester bond **b**, in general, is planar and resumes *s-trans* configuration rather than *s-cis*. This can be attributed to the stereoelectronic effect from the lone pair electron of oxygen ether which is oriented antiperiplanar to the C–O σ bond of the carbonyl group. This orbital can therefore overlap with the antibonding orbital (σ^*) of the carbonyl, or in other words, the hyperconjugation between an ether oxygen lone pair and a σ^* orbital of the carbonyl group as shown in Figure 24.²⁷ Thus the dihedral angle **b** in the binaphthol structure should be $0 \pm 5^\circ$. From the X-ray structures, the C=O bond of diastereomers **40** and **41** would most likely be planar, being $0 \pm 11^\circ$.

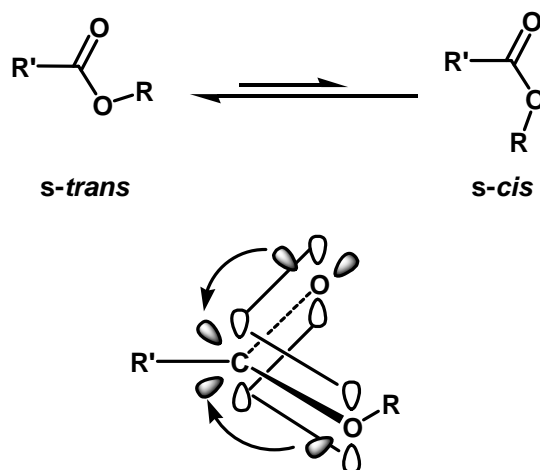


Figure 24. Favored configuration of ester bond.

For binaphthol derivatives, their structures, especially bond **d** are not conformationally rigid. They can therefore exist in both cisoid and transoid conformations.²⁸ The X-ray crystallographic studies for binaphthol derivatives showed the dihedral angle **d** in the range of 96–110° (transoid) except ester **40a** displayed the dihedral angle **d** = 87° (cisoid).

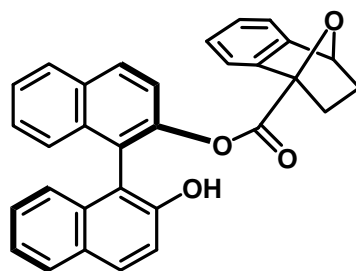
Apparently X-ray analysis gave information on key dihedral angles on each binaphthol derivatives. Unlike helicene-camphanate system,¹⁷ this analysis did not provide sufficient evidence to explain the difference in polarity of each diastereomeric pair. Detailed molecular structures, derived from the NMR data, implemented with computational chemistry calculations, are still required.

References

1. Eliel, E. L. Stereochemistry of organic compounds. New York: John Wiley and Sons 1994.
2. Moss, G. P. *Pure Appl. Chem* **1996**, 68, 2193-2222.
3. Cooke, A. S.; Harris, M. M. *J. Chem. Soc.* **1963**, 2365-2373.
4. Hall, D. M.; Turner, E. E. *J. Chem. Soc.* **1995**, 1242-1251.
5. Akimoto, H.; Yamada, S. *Tetrahedron* **1971**, 27, 5999-6009.
6. Noyori, R. *Acc. Chem. Res.* **1990**, 23, 345-350.
7. Noyori, R.; Ohta, T.; Takay, H. Catalytic Asymmetric Synthesis. New York: John Wiley and Sons 1993.
8. Ding, K.; Wang, Y.; Zang, L.; Wu, Y.; Matsuura, T. *Tetrahedron* **1996**, 52, 1005-1010.
9. Kamikawa, K.; Watanabe, T.; Daimon, A.; Uemura, M. *Tetrahedron* **2000**, 56, 2325-2337.
10. Meyers, A. I.; McKennon, M. J. *Tetrahedron Lett.* **1995**, 36, 5869-5872.
11. Meyers, A. I.; Nelson, T. D. *J. Org. Chem.* **1994**, 59, 2655-2658.
12. Brunel, J. M.; Buono, G. *J. Org. Chem.* **1993**, 58, 7313-7314.
13. Chow, H. F.; Wan, C. W.; Ng, M. K. *J. Org. Chem.* **1996**, 61, 8712-8714.
14. Mason, S. F.; Seal, R. H.; Roberts, D. R. *Tetrahedron* **1974**, 30, 1671-1682.
15. Harada, N.; Nakashi, K. Circular dichroic spectroscopy, exciton coupling in organic stereochemistry. Mill Valley, CA; University Science Books 1983, 193-201.
16. Panchal, B. M.; Einhorn, C.; Einhorn, J. *Tetrahedron Lett.* **2002**, 43, 9245-9248.
17. Thongpanchang, T.; Paruch, K.; Katz, T. J.; Rheingold, A. L.; Lam, K. C.; Liable-Sands L. *J. Org. Chem.* **2000**, 65, 1850-1856.
18. Fuji, K.; Sakurai, M.; Kinoshita, T.; Kawabata, T.; *Tetrahedron Lett.* **1998**, 39, 6323-6326.
19. Fukushi, Y.; Shigematsu, K.; Mizutani, J.; Tahara, S. *Tetrahedron Lett.* **1996**, 37, 4737-4740.
20. Fuji, K.; Yang, X. S.; Ohnishi, H.; Hao, X. J.; Obata, Y.; Tanaka, K. *Tetrahedron: Asym.* **1999**, 10, 3243-3248.
21. Hua, D. H.; Nguyen, T. X. C.; McGill, J. W.; Chen, Y.; Robinson, P. D. *Tetrahedron: Asym.* **2001**, 12, 1999-2004.

22. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.
23. Kakisawa, H.; Ohtani, I.; Kusumi, T.; Kashman, Y. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.
24. Best, W. M.; Collins, P. A.; McCulloch, R. K.; Wege, D. *Aust. J. Chem.* **1982**, *35*, 843-848.
25. Areephong, J. [M.Sc. Thesis in Organic Chemistry]. Bangkok: Faculty of Graduate Studies, Mahidol University; 2005.
26. Akimoto, H.; Shioiri, T.; Iitaka, Y. *Tetrahedron Lett.* **1968**, *1*, 97-102.
27. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*. Pergamon Press: Oxford 1983, *1*.
28. a) Mason S F. *Molecular optical activity and the chiral discriminations*. New York: Cambridge University Press; **1982**: 73.
- b) Gottarelli, G., Spada, G. P. *J. Org. Chem.* **1986**, *51*, 589-592.

APPENDIX



40a

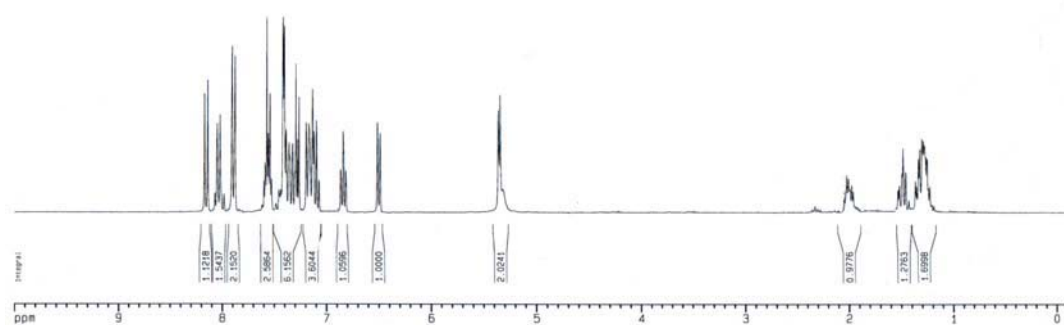


Figure A1. ^1H NMR spectrum of compound **40a**.

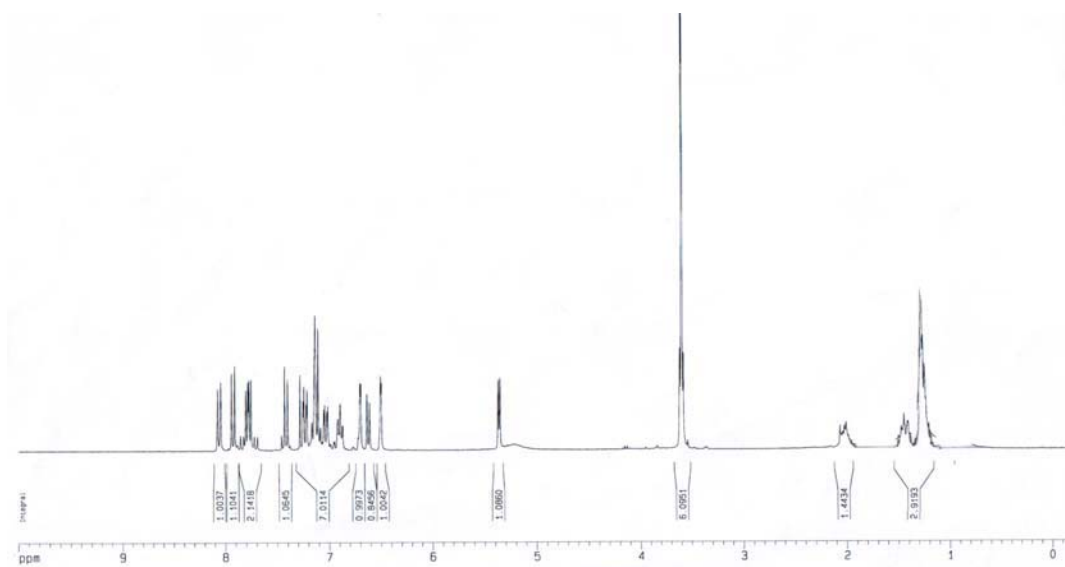
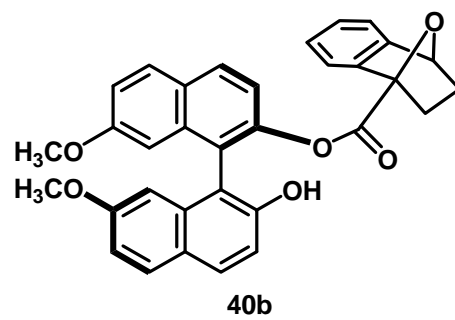


Figure A2. ^1H NMR spectrum of compound **40b**.

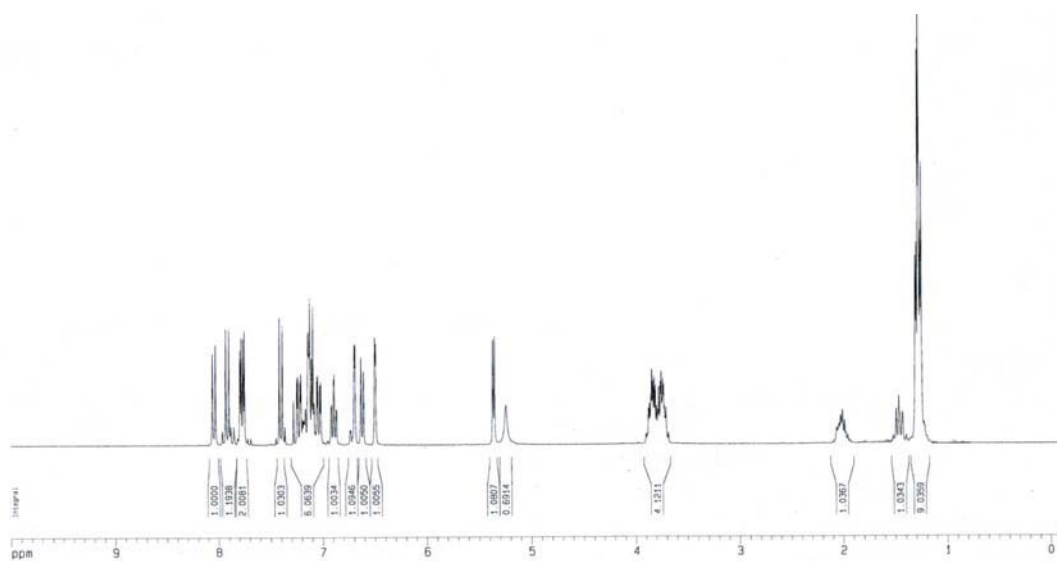
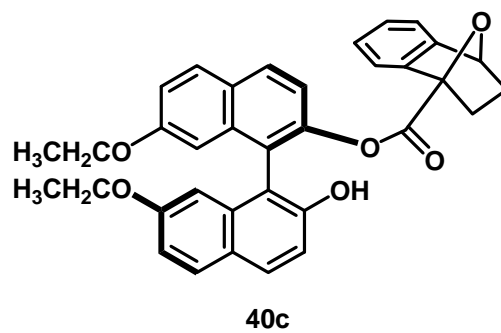


Figure A3. ^1H NMR spectrum of compound **40c**.

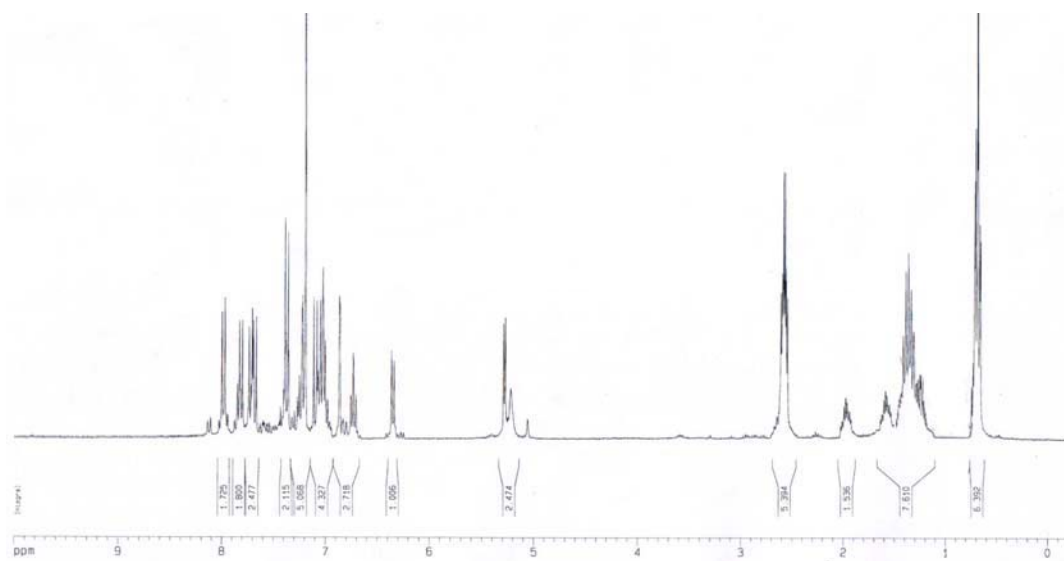
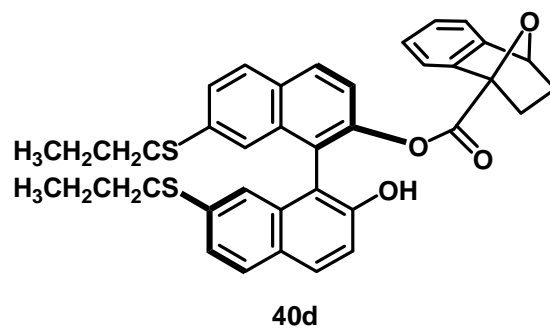


Figure A4. ^1H NMR spectrum of compound **40d**.

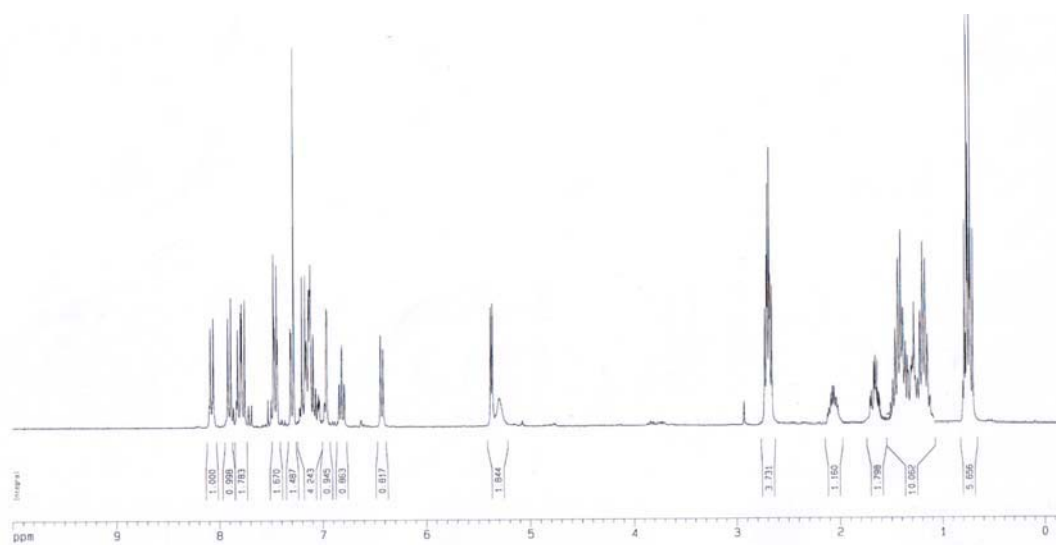
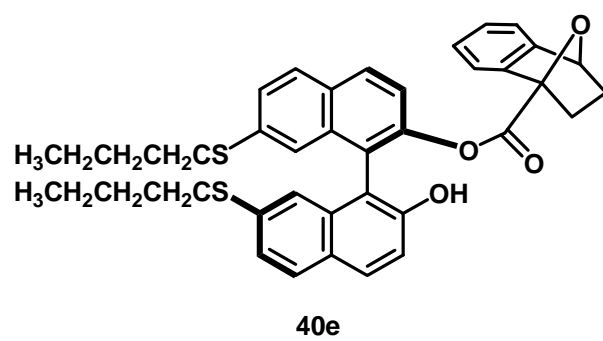
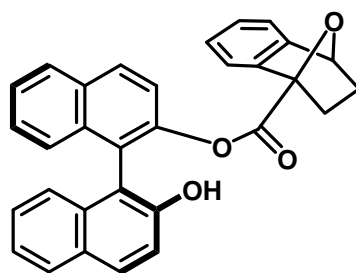


Figure A5. ^1H NMR spectrum of compound **40e**.



41a

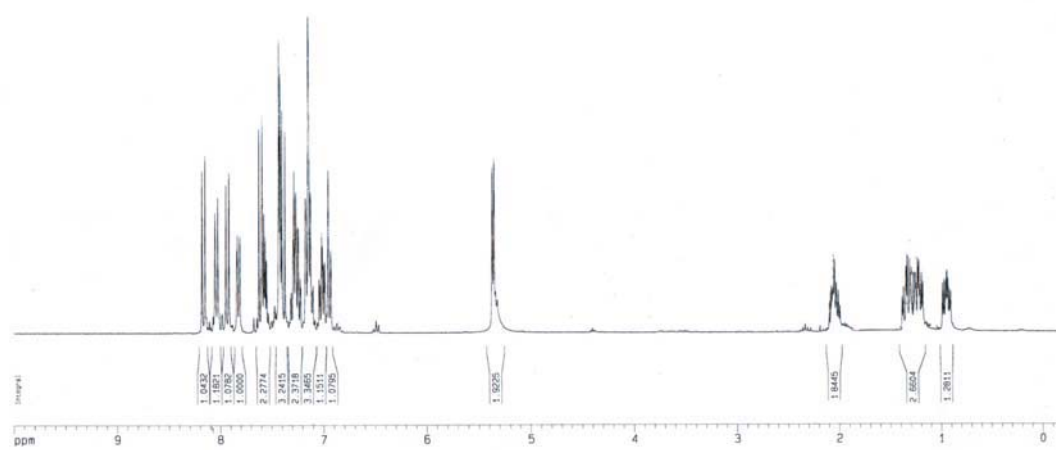


Figure A6. ^1H NMR spectrum of compound **41a**.

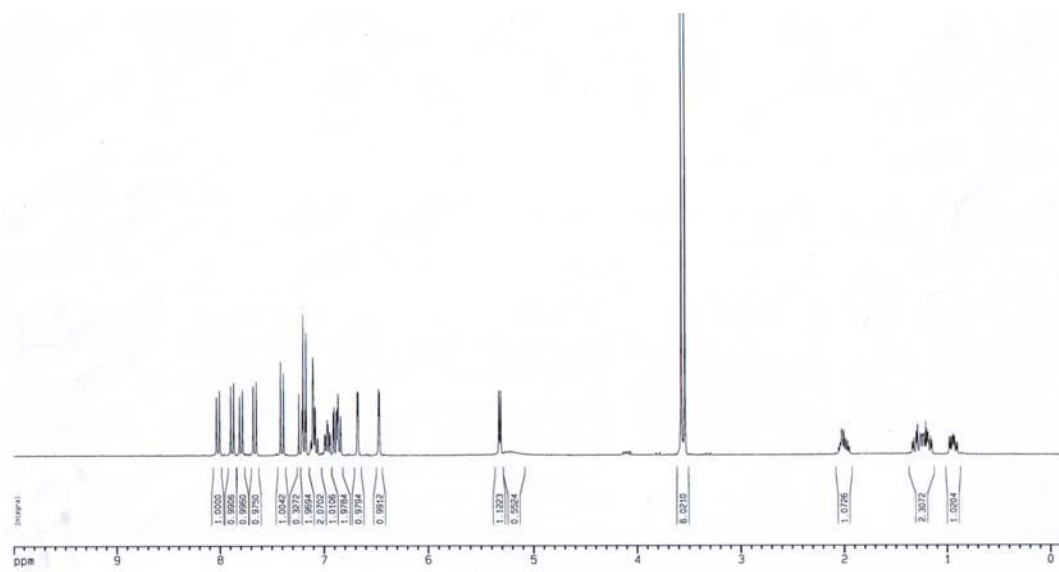
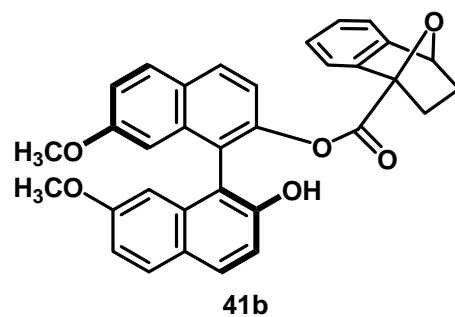


Figure A7. ^1H NMR spectrum of compound **41b**.

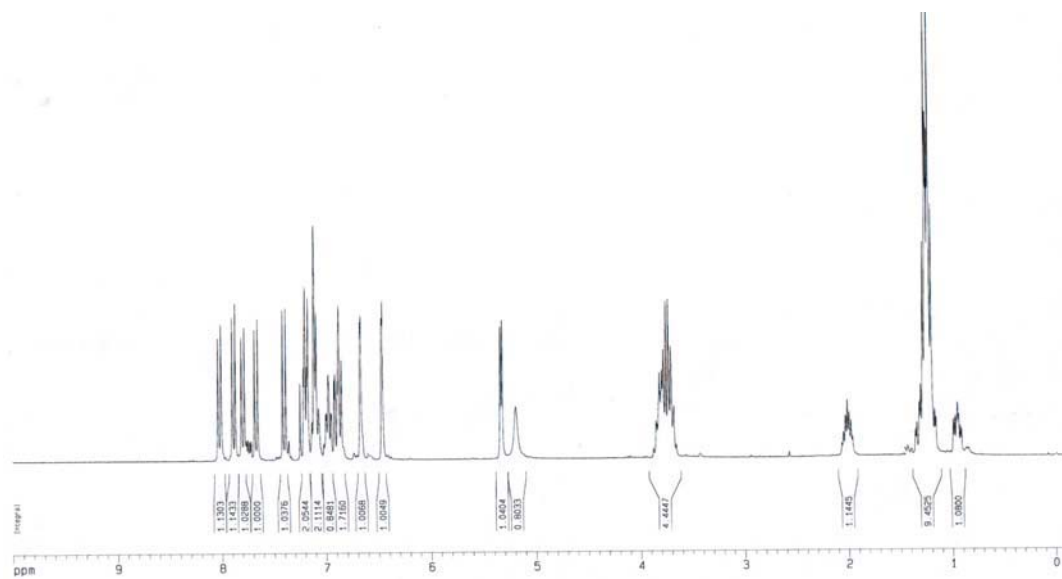
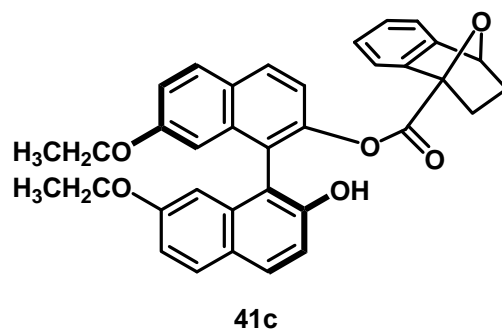


Figure A8. ¹H NMR spectrum of compound **41c**.

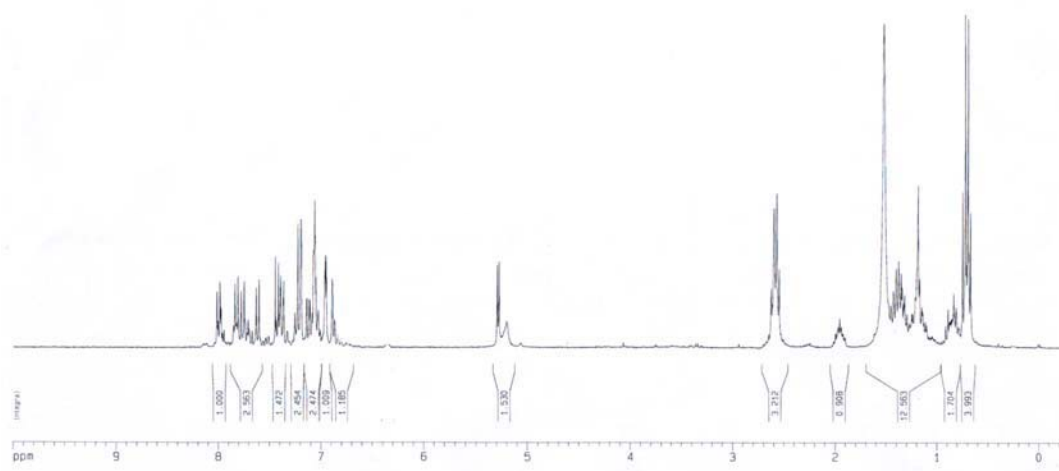
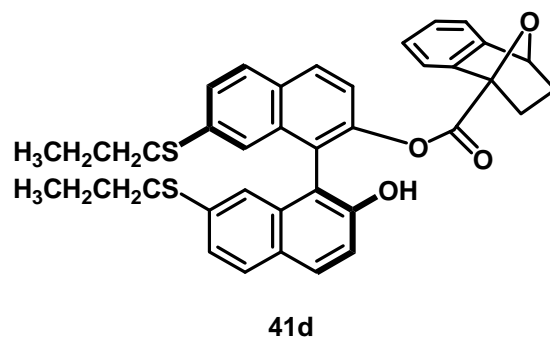


Figure A9. ^1H NMR spectrum of compound **41d**.

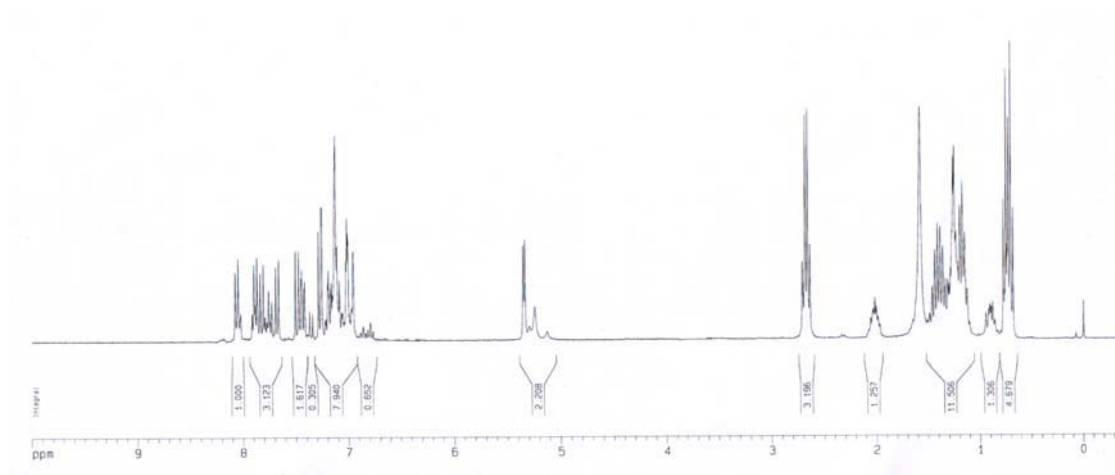
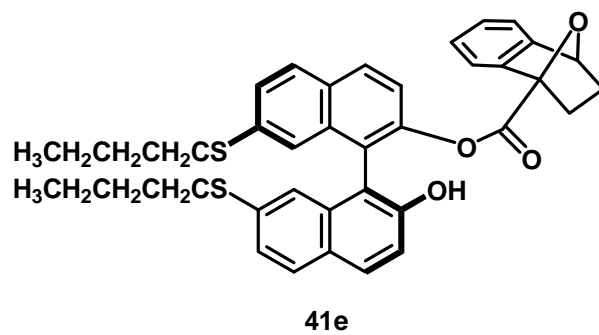
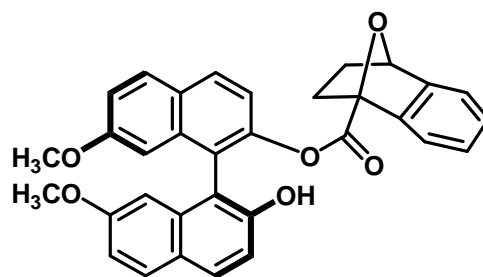


Figure A10. ^1H NMR spectrum of compound **41e**.



42

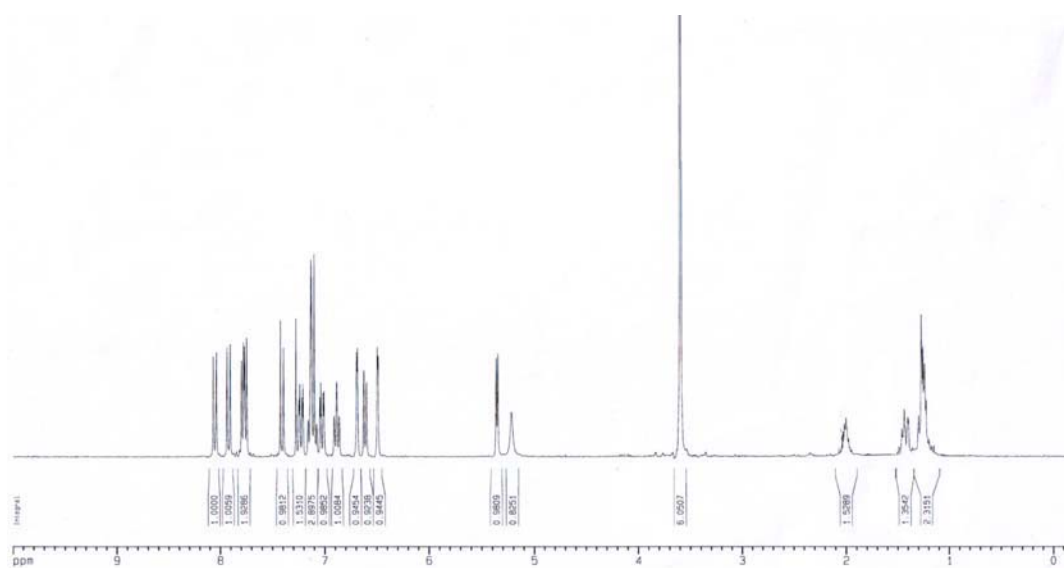
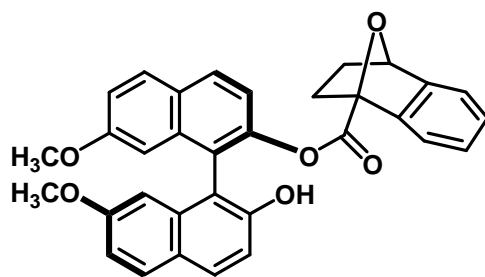


Figure A11. ^1H NMR spectrum of compound **42**.



43

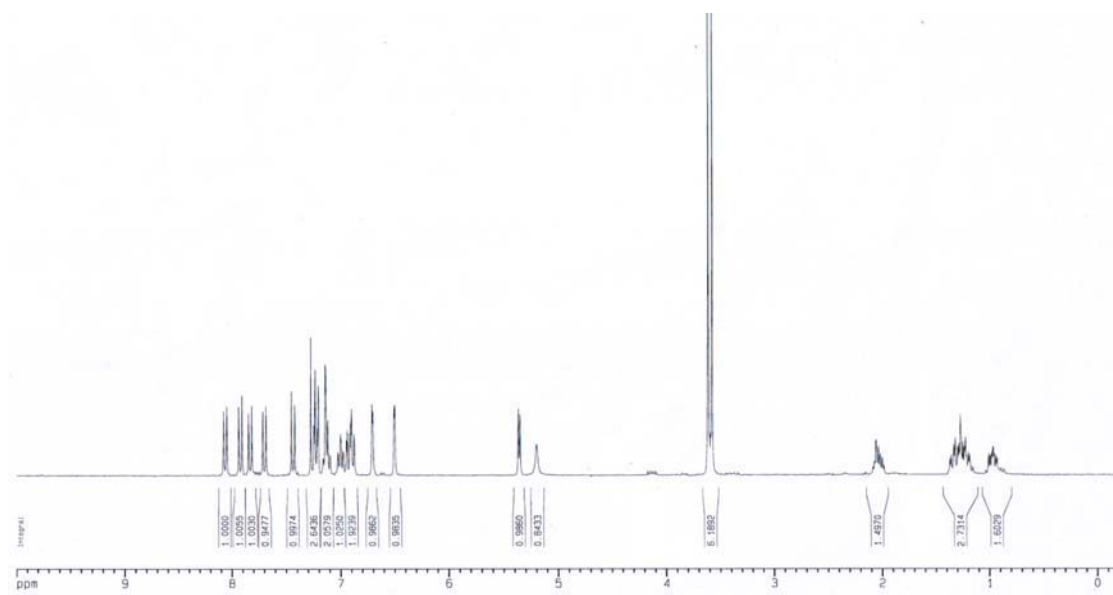


Figure A12. ^1H NMR spectrum of compound **43**.

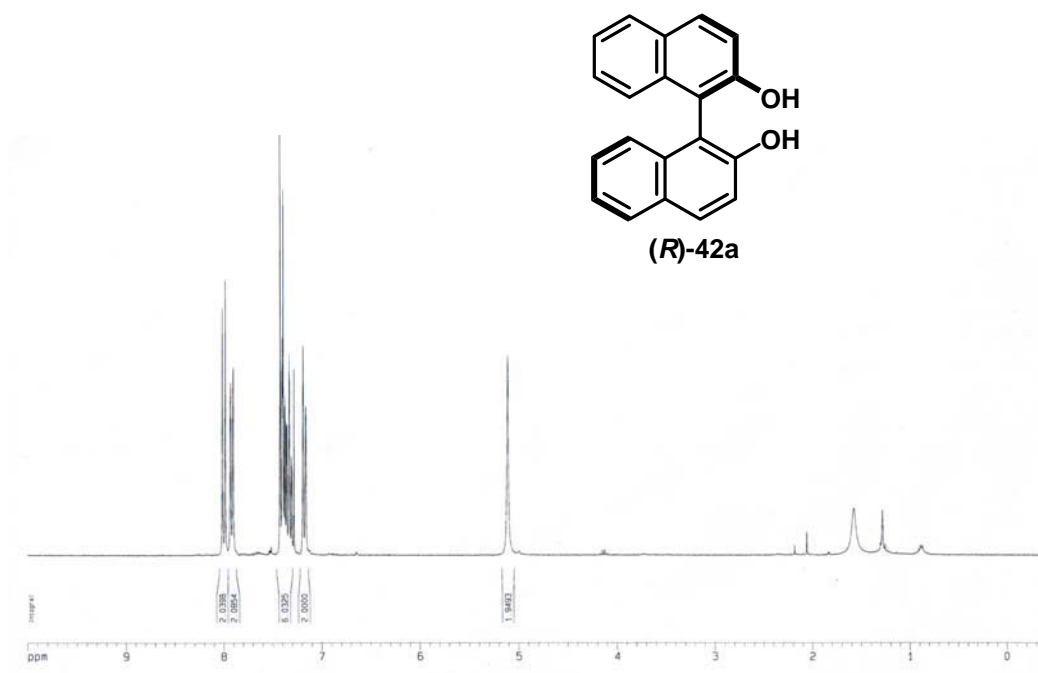


Figure A13. ¹H NMR spectrum of compound (R)-42a.

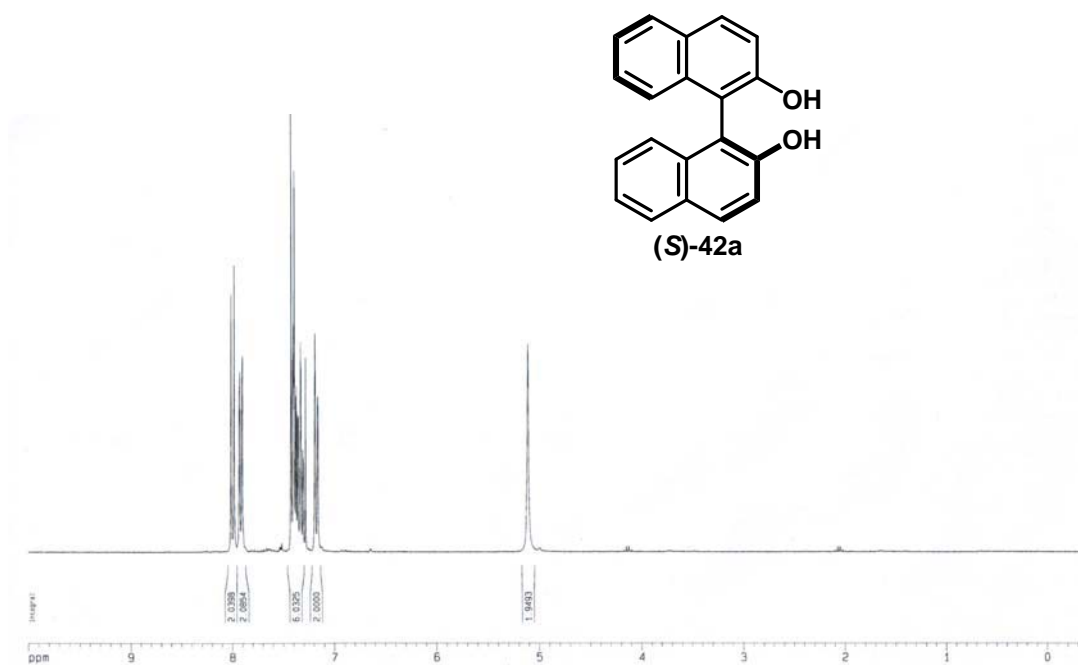


Figure A14. ¹H NMR spectrum of compound (S)-42a.

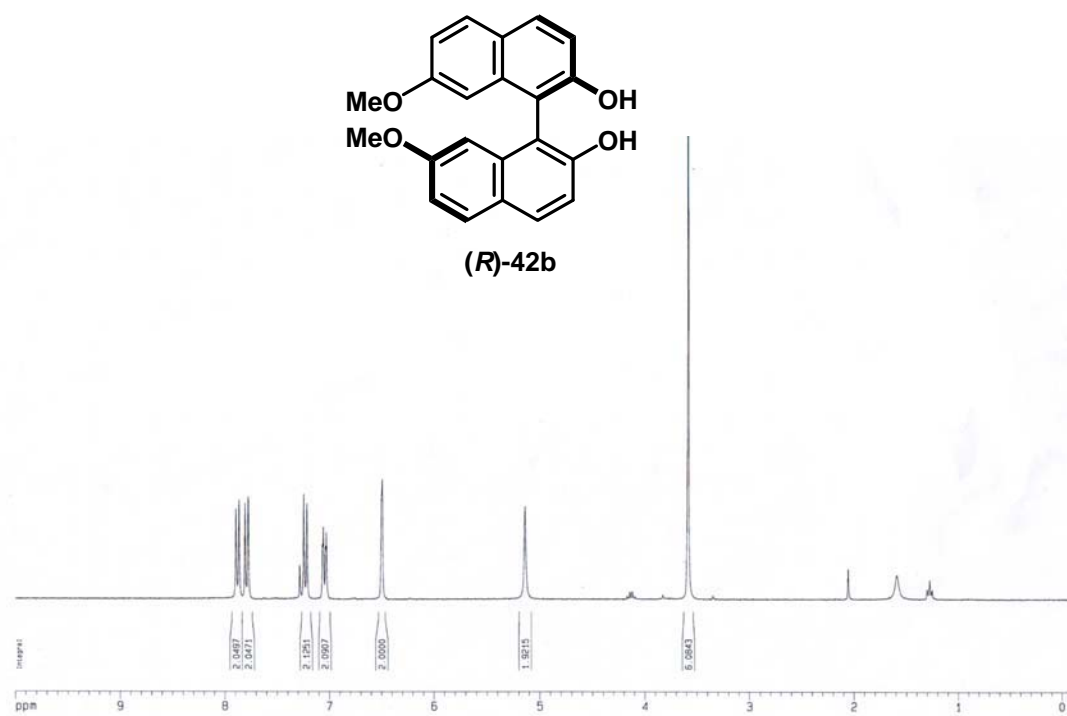


Figure A15. ¹H NMR spectrum of compound (R)-42b.

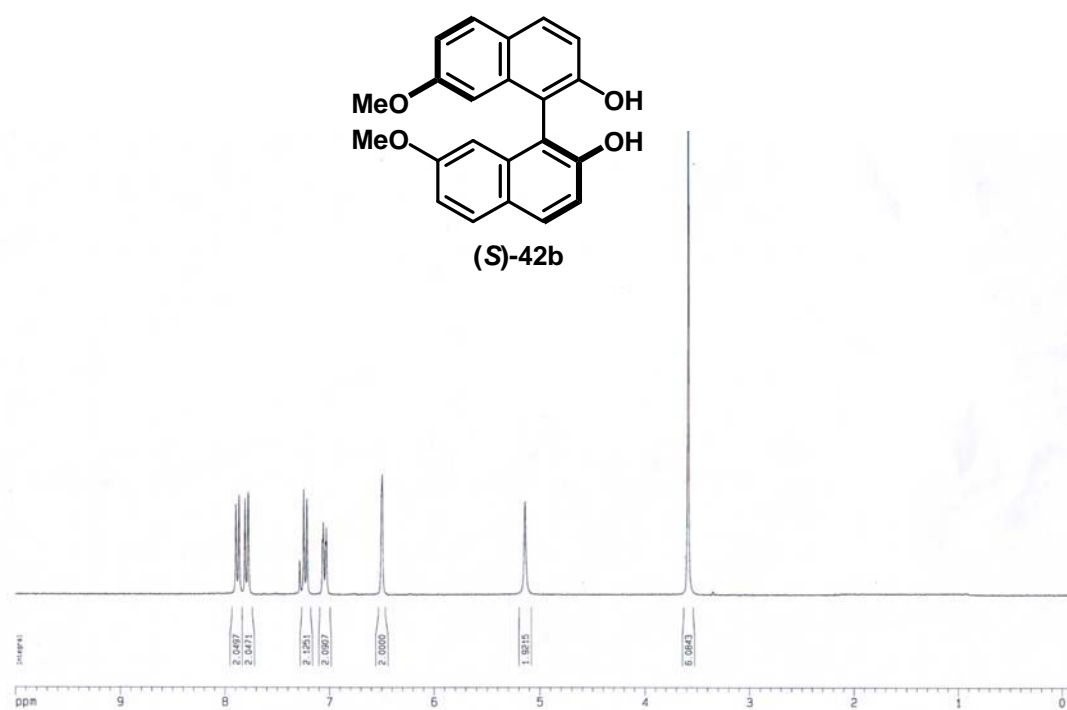


Figure A16. ¹H NMR spectrum of compound (S)-42b.

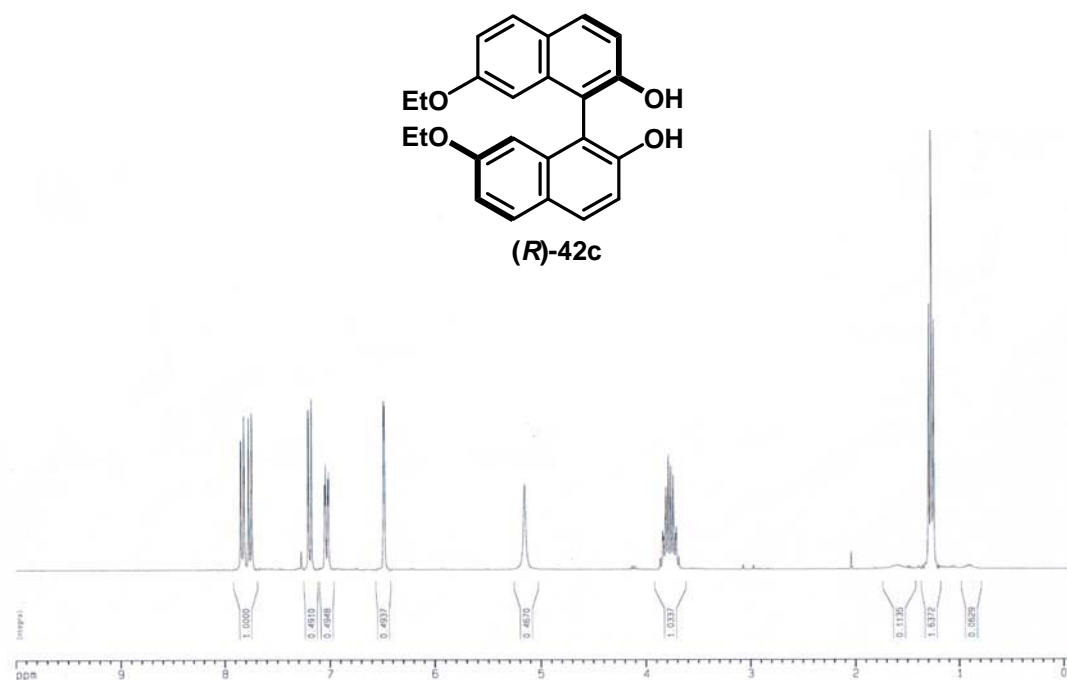


Figure A17. ^1H NMR spectrum of compound (*R*)-42c.

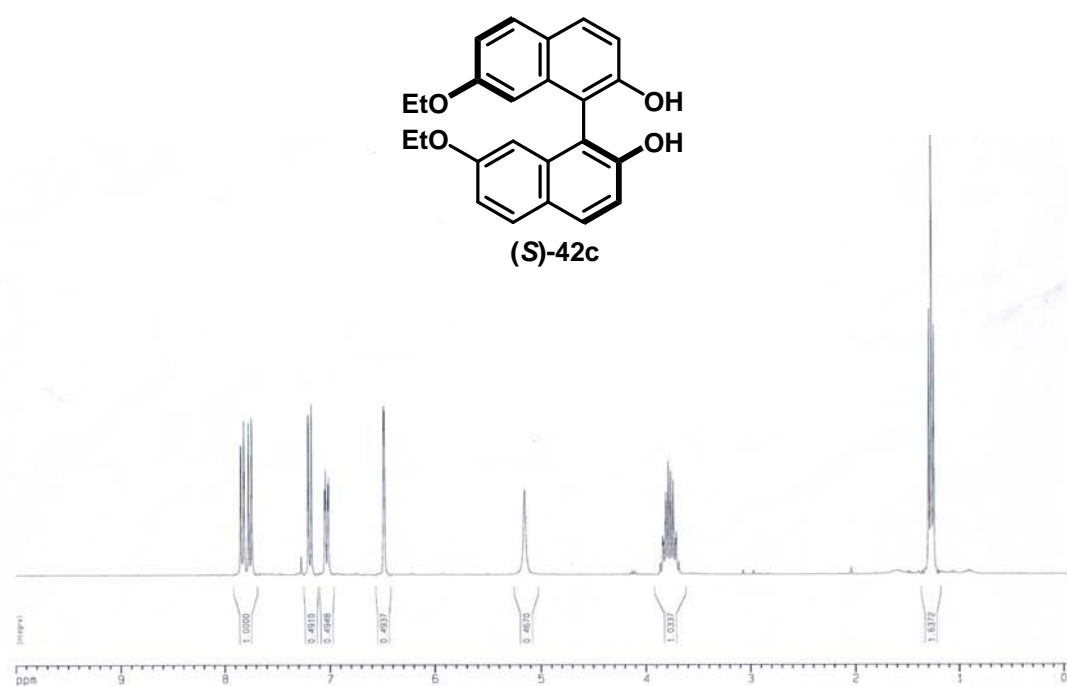


Figure A18. ^1H NMR spectrum of compound (*S*)-42c.

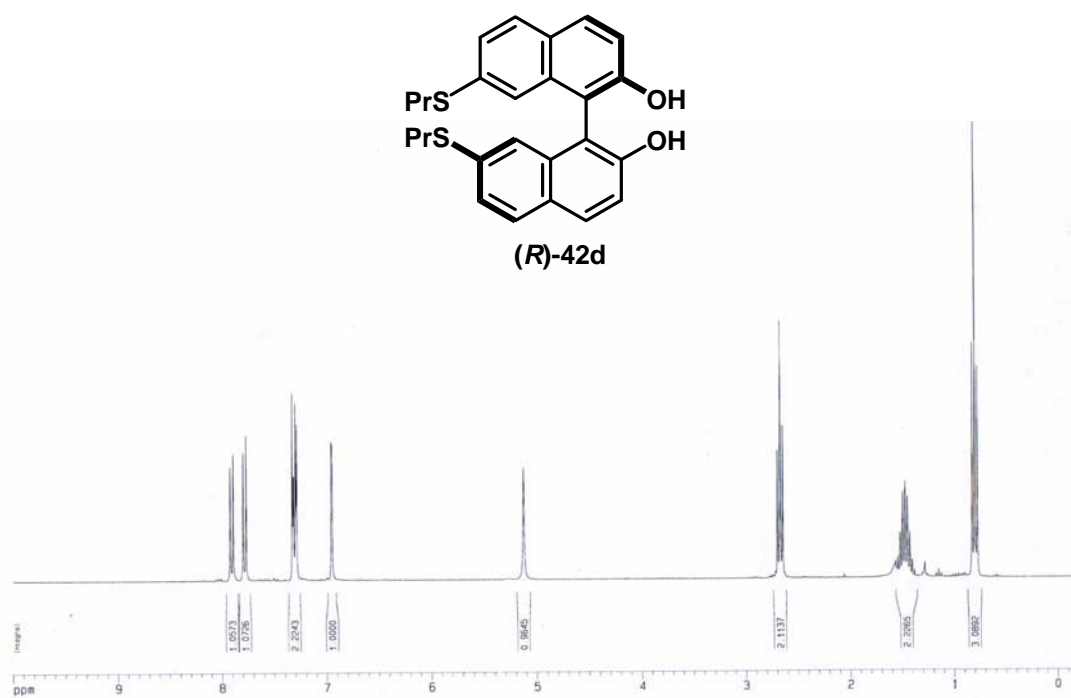


Figure A19. ^1H NMR spectrum of compound (R)-42d.

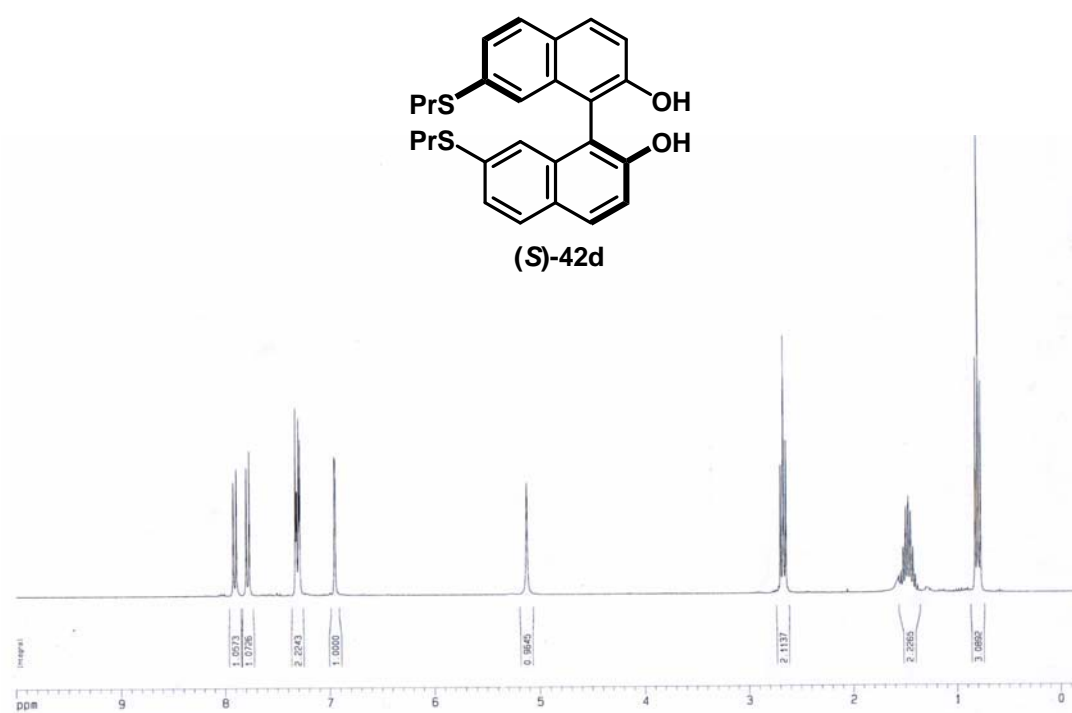


Figure A20. ^1H NMR spectrum of compound (S)-42d.

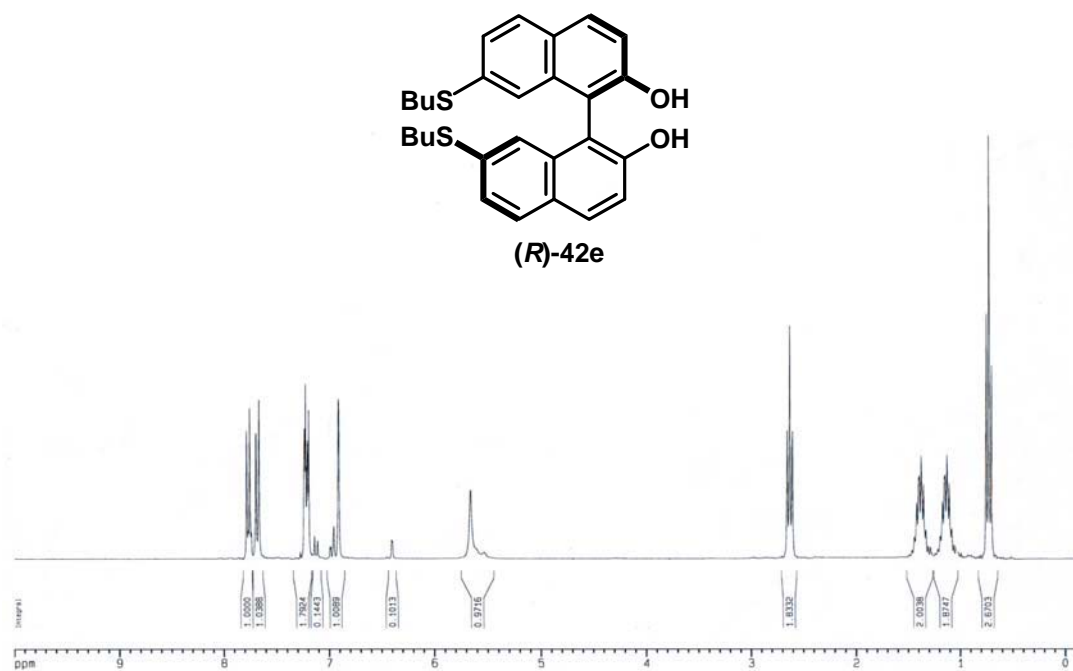


Figure A21. ^1H NMR spectrum of compound **(R)-42e**.

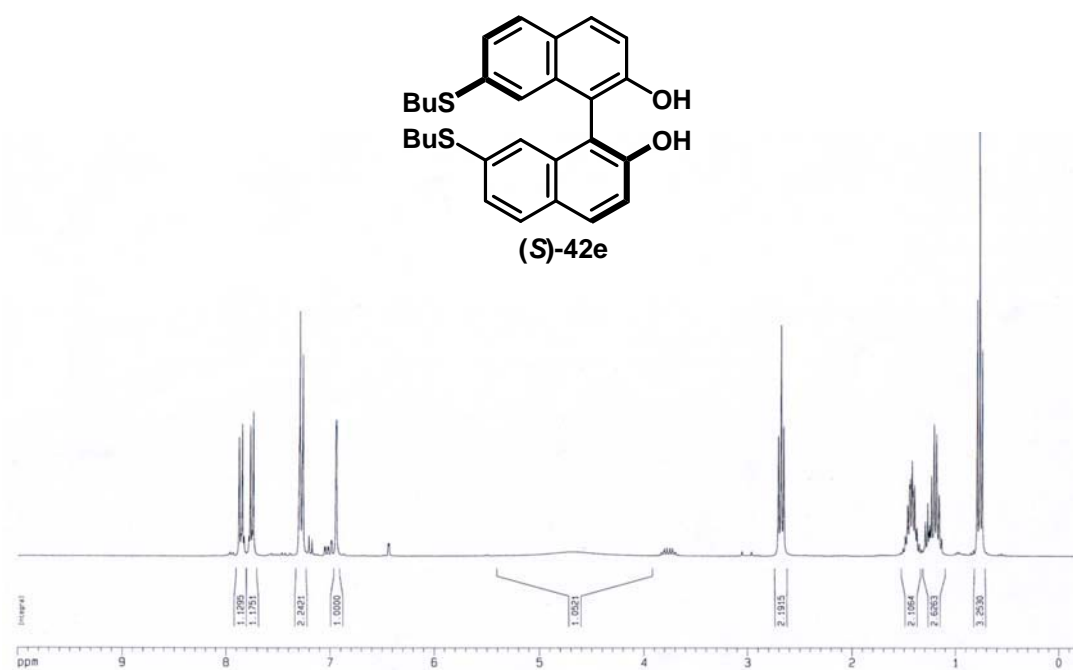


Figure A22. ^1H NMR spectrum of compound **(S)-42e**.

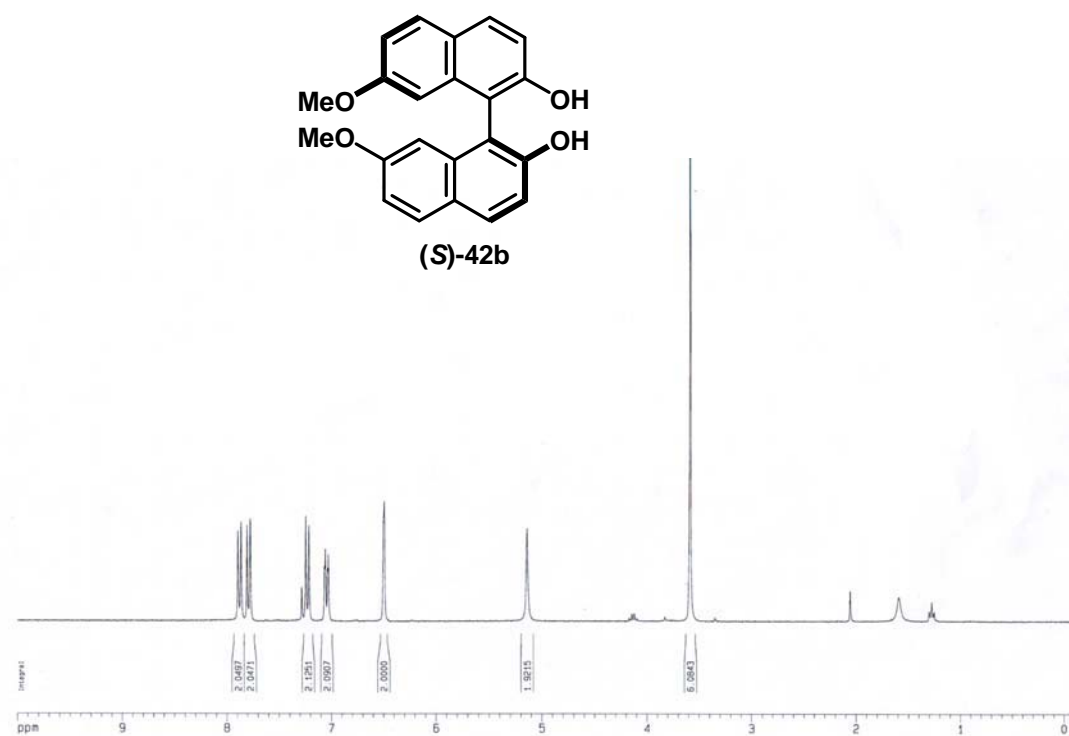


Figure A23. ¹H NMR spectrum of compound (*R*)-42b from (*S*)-acid.

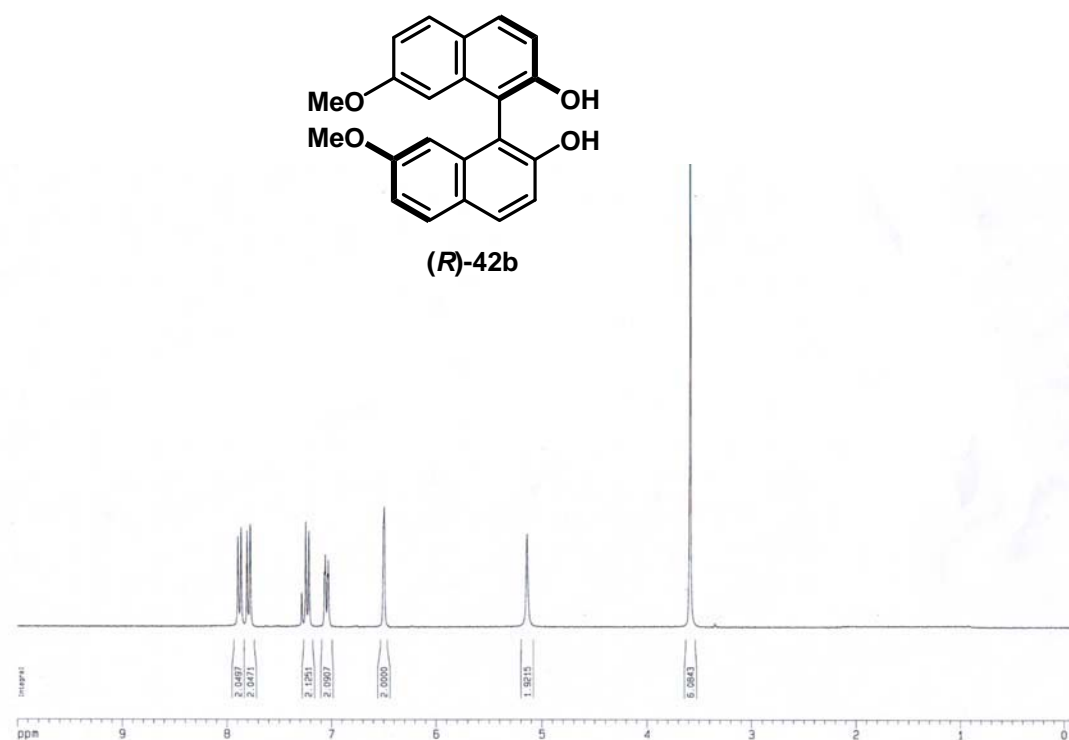


Figure A24. ¹H NMR spectrum of compound (*S*)-42b from (*S*)-acid.

Part III. Oxidative photocyclization of diaryl sulfides:

A new approach towards new thiophene-based organic materials

During the study of the preparation of binaphthol derivatives and the synthesis of oxa-[5]-helicenes, it was found that our chemistry on the acid catalyzed nucleophilic substitution of phenols could lead to the synthesis of dinaphthothiophene derivatives. Thus this part of this report then described briefly the investigation of this chemistry.

Introduction

Due to the high polarizability of sulfur electron in the thiophene ring which resulting in the great intermolecular interactions such as Van der Waals interactions, π - π or sulfur-sulfur interaction, sulfur containing heteroaromatic molecules are of great interest due to their potential application for organic light emitting diodes (OLEDs)¹ or organic field-effect transistors (OFETs).^{2,3} For example, thieno[3,2-*f*:4,5-*f'*]bis[1] benzothiophene (*syn*-**1**) and thieno[2,3-*f*:5,4-*f'*]bis[1]benzothiophene (*anti*-**1**) have recently been characterized as new P-type organic semiconducting materials for OFETs (Figure 1).³

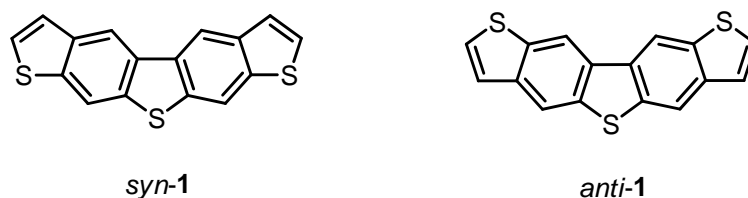
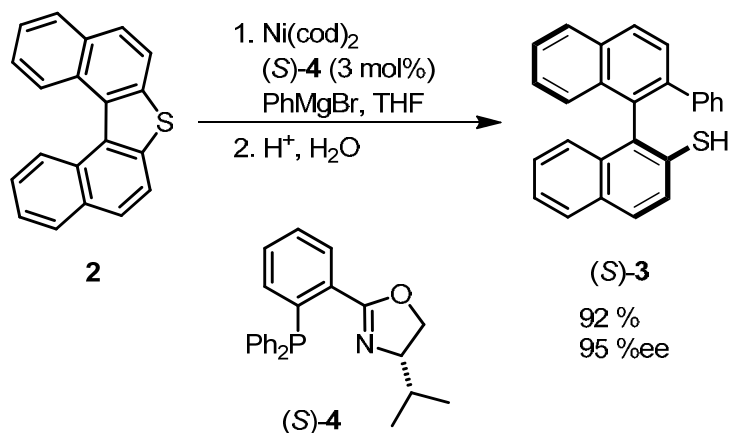


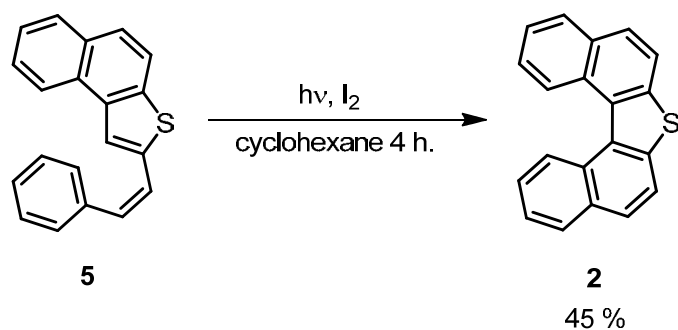
Figure 1. Thieno[3,2-*f*:4,5-*f'*]bis[1]benzothiophene (*syn*-**1**) and Thieno[2,3-*f*:5,4-*f'*]bis[1]benzothiophene (*anti*-**1**).

Furthermore, the applications of the fused ring thiophene derivatives have been found in the asymmetric catalysis. Dinaphtho[2,1-*b*:1',2'-*d*]thiophene **2**, for example, was used as a precursor for the synthesis of axially chiral binaphthyl derivative **3**, a chiral building block for the catalytic asymmetric reactions (Scheme 1).⁴⁻⁶



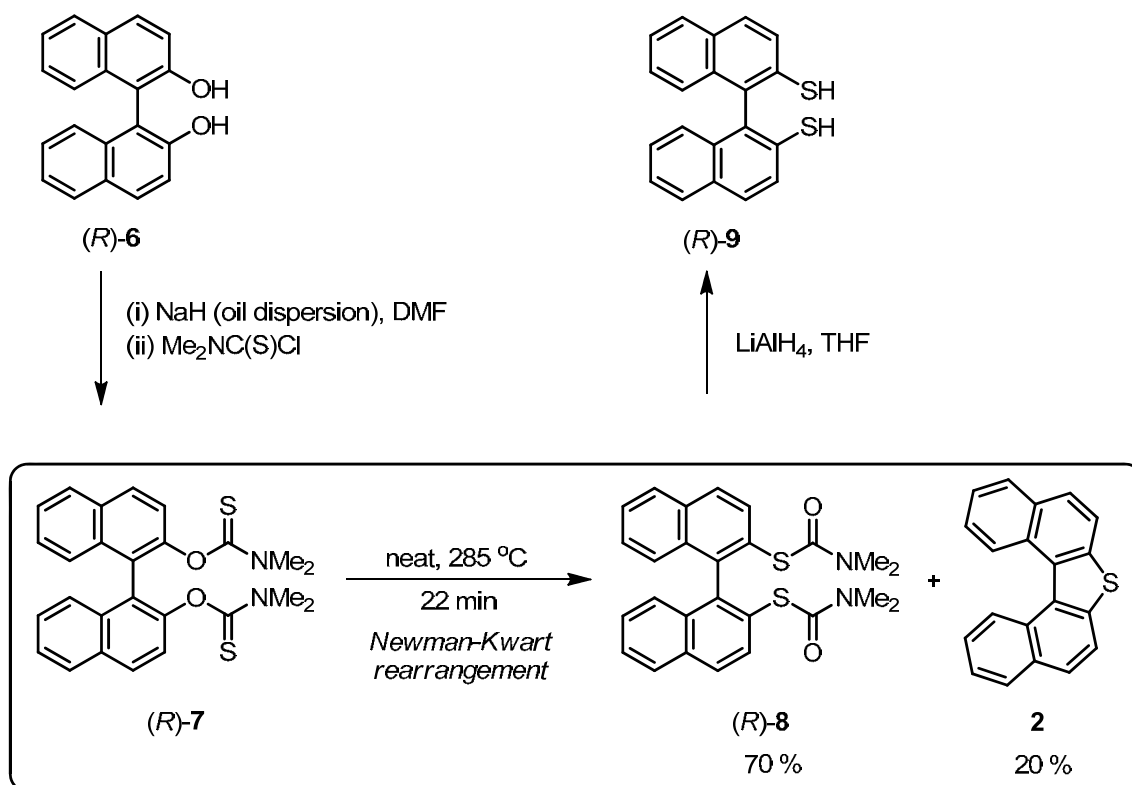
Scheme 1. Dinaphthothiophene **2** and its Nickel-catalyzed asymmetric Grignard cross-coupling to form axially chiral binaphthyl ligand **3**.

Accordingly, it is of great interest to study the synthesis of fused ring thiophene derivatives, such as dinaphthothiophene **2**. Previous reports described many procedures for the synthesis of dinaphthothiophene **2**. For example, Tedjamulia and co-workers reported that iodine-catalyzed oxidative photocyclization of 2-styrylnaphtho[2,1-*b*]thiophene **5** in the presence of iodine in cyclohexane for 4 hours provided dinaphtho[2,1-*b*:1',2'-*d'*]-thiophene **2** in 45% yield (Scheme 2).⁷



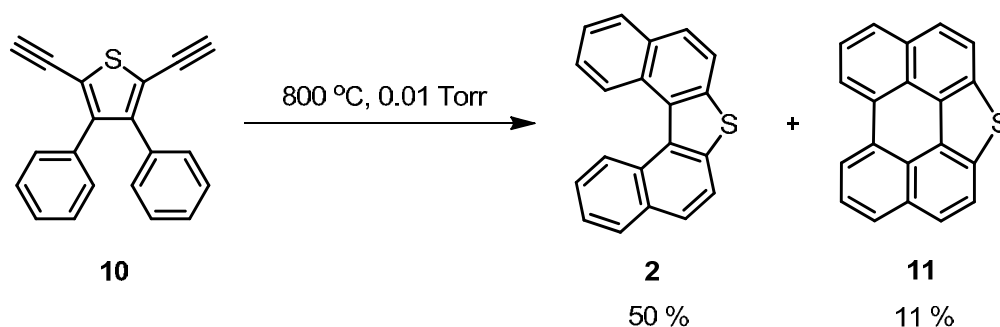
Scheme 2. Iodine-catalyzed oxidative photocyclization of stilbene analogue compound **5**.

Later, Fabbri and co-workers reported the preparation of enantiomerically pure (*R*)-1,1'-binaphthyl-2,2'-dithiol **9** from (*R*)-1,1'-binaphthalene-2,2'-diol **6** via Newman-Kwart rearrangement (Scheme 3).⁸ Thermal rearrangement of (*R*)-thiocarbamate **7** provided the product (*R*)-**8** in 70% yield and also dinaphthothiophene **2** in 20% yield.^{8,9}



Scheme 3. Newman-Kwart rearrangement of $(R)\text{-}7$.

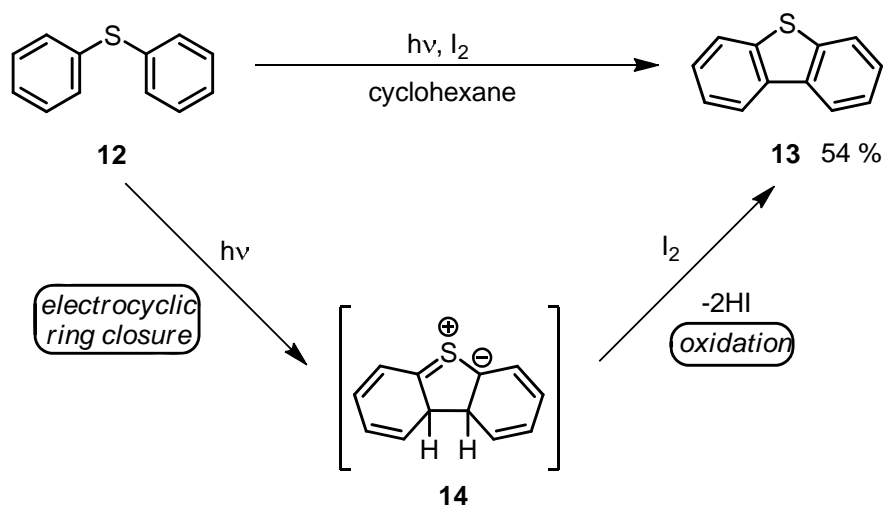
In 1999, Imamura and co-workers reported an application of the flash vacuum pyrolysis to synthesize sulfur containing heteroaromatic system.¹⁰ Pyrolysis of bis-ethynyl thiophene **10** could afford not only the desired compound **2** but also the fused compound **11** (Scheme 4).



Scheme 4. Flash Vacuum Pyrolysis (FVP) of compound **10**.

The methodology was inspired by the work of Zeller, *et al.* which reported that diphenyl sulfide **12** could undergo oxidative photocyclization in the presence of iodine to

yield dibenzothiophene **13**.¹¹ The mechanism of this photocyclization was proposed to occur *via* the electrocyclic ring closure of diphenyl sulfide **12** followed by oxidation of cyclic intermediate **14** by iodine to provide dibenzothiophene **13** and hydrogen iodide (HI) as a by-product (Scheme 5).¹¹

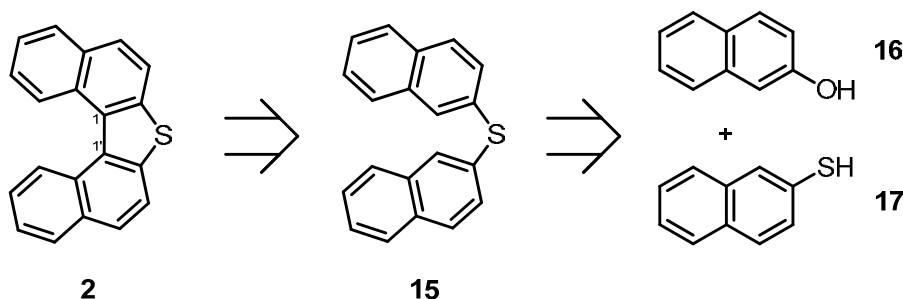


Scheme 5. Iodine-catalyzed oxidative photocyclization of diphenyl sulfide **12**.

Accordingly, this oxidative photocyclization of diphenyl sulfide **12**¹¹ could be an alternative approach for the synthesis of dinaphthothiophene **2** and its derivatives.

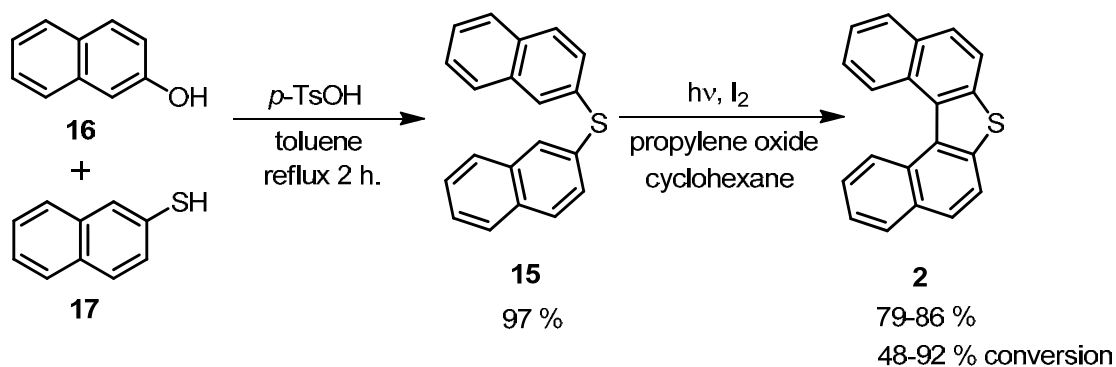
Results

The structure and our retrosynthetic strategy of dinaphtho[2,1-*b*:1',2'-*d*]thiophene **2** is as shown below (Scheme 6).



Scheme 6. The structure and retrosynthetic analysis of dinaphthothiophene **2**.

Disconnection at the C1–C1' bond of dinaphthothiophene **2** indicated that the possible precursor for the oxidative photocyclization could be dinaphthyl sulfide **15** which could be synthesized from 2-naphthol **16** and 2-naphthalenethiol **17** through the acid-mediated nucleophilic aromatic substitution.



Scheme 7. The novel synthetic route of dinaphthothiophene **2**.

Thus, as shown in Scheme 7, treatment of 2-naphthol **16** with 2-naphthalenethiol **17** in the presence of *p*-TsOH under refluxing toluene for 2 hours gave the desired dinaphthyl sulfide **15** in 97% yield.¹² The next step of this synthetic route is the iodine-catalyzed

oxidative photocyclization reaction.^{11,13} The solution of disulfide **15**, iodine and propylene oxide in cyclohexane was purged with argon gas and irradiated in a photochemical reactor with Hanovia 450 watt medium pressure mercury lamp to provide dinaphthothiophene **2** in 79–86% yield (48–92% conversion). Conditions for the oxidative photocyclization process, %conversions and %yields were as summarized in Table 1.

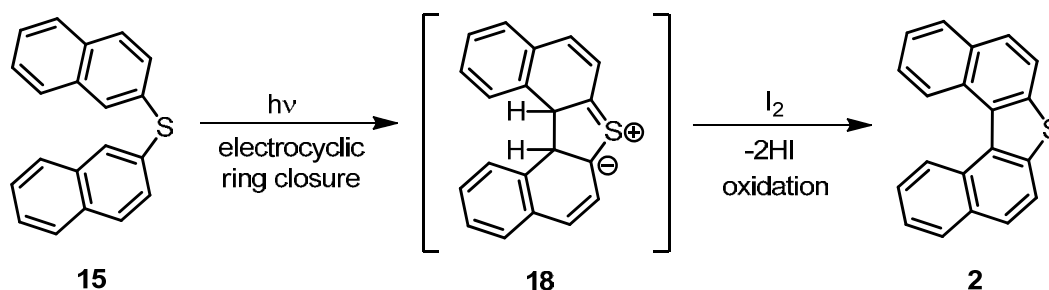
Table 1. Iodine-catalyzed oxidative photocyclization of dinaphthothiophene **2** in various conditions.

Entry	Time (minutes)	Iodine (equivalent)	Propylene oxide (equivalent to iodine)	%conversion	%yield
1	10	1.0	10.0	48	79
2	20	1.0	10.0	80	83
3	30	1.0	10.0	87	85
4	40	1.0	10.0	89	84
5	60	1.0	10.0	88	86
6	30	0.8	10.0	86	82
7	30	1.2	10.0	91	85
8	30	1.5	10.0	92	84
9	30	1.2	0.0	80	81
10	30	1.2	5.0	90	85

Accordingly, the optimal condition for the iodine-catalyzed oxidative photocyclization of dinaphthyl sulfide **15** could be deduced. The reaction could be carried out in the presence of 1.2 equivalent of iodine and excess propylene oxide in cyclohexane under a stream of argon gas for 30 minutes (Entry 7).

The mechanism of the reaction was assumed to be similar to that reported by Zeller (Scheme 8).¹¹ Sulfide **15** underwent electrocyclic ring closure to provide the cyclic intermediate **18** which was then oxidized by iodine to give dinaphthothiophene **2** along with

HI as a by-product. Propylene oxide was used to consume hydrogen iodide (HI) that was formed in the reaction.¹³



Scheme 8. The mechanism of oxidative photocyclizaion of dinaphthothiophene **2**.

Later, the oxidative photocyclization procedure was applied for the synthesis of other dinaphthothiophene derivatives **19**, **20** and **21** in 84%, 83% and 80% yields, respectively (Figure 2).

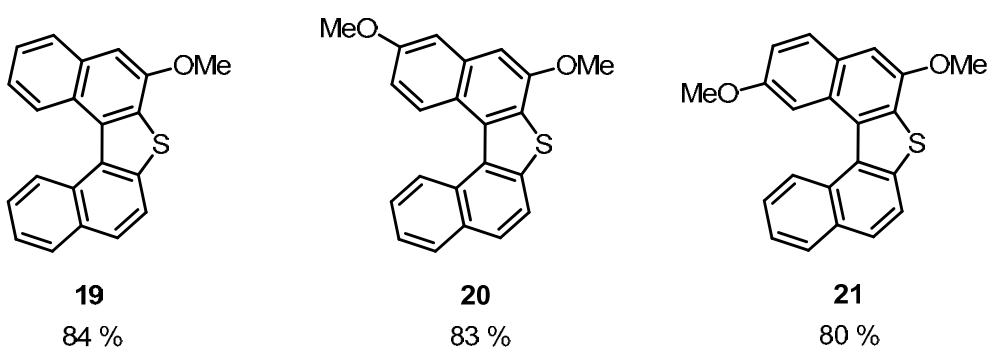
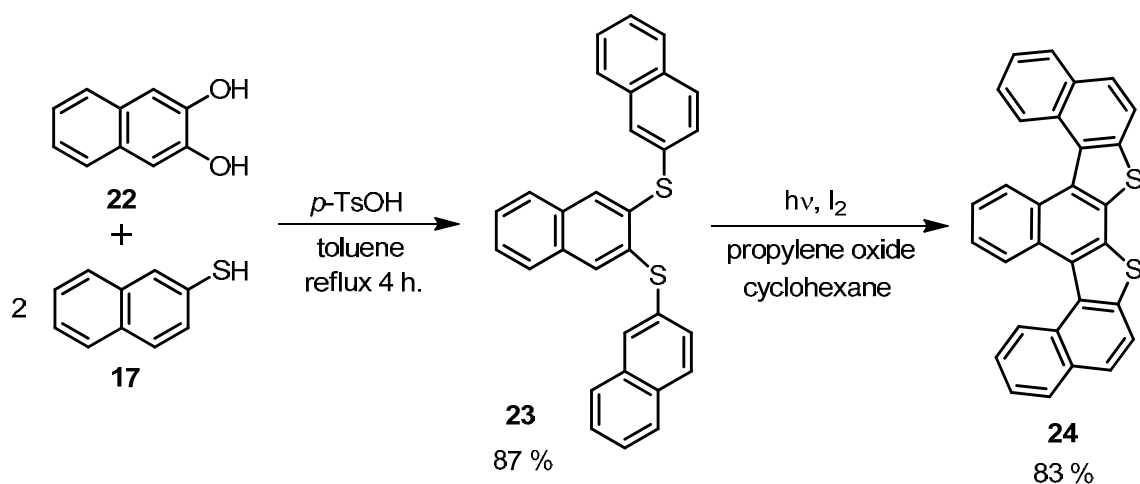


Figure 2. Oxidative photocyclizaion products **19**, **20** and **21**.

Furthermore, the oxidative photocyclization would also be used in the synthesis of a more complex skeleton such as compound **24**. Indeed, the acid-mediated nucleophilic aromatic substitution of 2,3-dihydroxynaphthalene **22** with 2-naphthalenethiol **17** in refluxing toluene provided disulfide compound **23** in 87% yield. The oxidative photocyclization of **23** then yielded compound **24** in 83% yield (Scheme 9).



Scheme 9. The synthetic route of M-like molecule **24**.

Structure of **24** could be recrystallized from CH_2Cl_2 : MeOH providing a yellow needle crystal and its X-ray analysis was shown below (Figure 3). Detailed investigation of this molecule as a new type of organic materials is currently in progress.

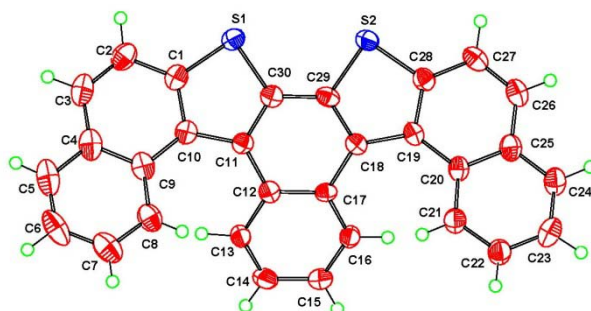


Figure 3. X-ray structure of M-like molecule **24**.

In conclusion, an alternative, highly efficient synthesis of dinaphthothiophene **2** and its analogues was achieved by using the oxidative photocyclization reaction as the key step.¹⁴

References

1. (a) Burroughes, J. H.; Bradley, D. D.; Brown, A. R.; Mards, R. N.; Mackay, K.; Friend, R.H.; Burns, P. L.; Holmes, A. B. *Nature*, **1990**, *347*, 539-541. (b) Kovac, J.; Peternai, L.; Lengyel, O. *Thin Solid Films*. **2003**, *433*, 22-26.
2. (a) Torrent, M. M.; Hadley, P.; Bromley, S. T.; Ribas, X.; Tarrés, J.; Mas, M.; Molins, E.; Veciana, J.; Rovira, C. *J. Am. Chem. Soc.* **2004**, *126*, 8546-8553. (b) Xia, K.; Liu, Y.; Qi, T.; Zhang, W.; Wang, F.; Gao, J.; Qui, W.; Ma, Y. ; Cui, G.; Chen, S.; Zhan, X.; Yu, G.; Qin, J.; Hu, W.; Zhu, D. *J. Chem. Soc.* **2005**, *127*, 13281-13286. (c) Yamada, H.; Kawamura, E.; Sakamoto, S.; Yamashita, Y.; Okujima, T.; Uno, H.; Ono, N. *Tetrahedron Letters*. **2006**, *47*, 7501-7504. (d) Murphy, A. R.; Frécher, J. M. *Chem. Rev.* **2007**, *107*, 1066-1096.
3. Wex, B.; Kaafarani, B.; Kirschbaum, K.; Neckors, D. C. *J. Org. Chem.* **2005**, *70*, 4502-4505.
4. Shimada, T.; Cho, Y. H.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 13396-13397.
5. Cho, Y. H.; Kina, A.; Shimada, T.; Hayashi, T. *J. Org. Chem.* **2004**, *69*, 3811-3823.
6. (a) Kitayama, K.; Uozumi, Y.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1995**, 1533-1534. (b) Hayashi, T. *Acc.Chem. Rev.* **2000**, *33*, 354-362. (c) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. *J. Org. Chem.* **2001**, *66*, 1441-1449.
7. Tedjamulia, M. L.; Tominaga, Y.; Castle, R. N. *J. Heterocyclic. Chem.* **1983**, *20*, 1143-1148.
8. Fabbri, D.; Delogu, G.; Lucchi, O. D. *J. Org. Chem.* **1993**, *58*, 1748-1750.
9. Bandarage, U. K.; Simpson, J.; Smith, A. J.; Weavers, R. T. *Tetrahedron*. **1994**, *50*, 3463-3472.
10. Imamura, K.; Hirayama, D.; Yoshimura, H.; Takimiya, K.; Aso, Y.; Otsubo, T. *Tetrahedron Letters*. **1999**, *40*, 2789-2792.
11. Zeller, K. P.; Petersen, H. *Synthesis*. **1975**, *8*, 532-533.
12. Charoonniyomporn, P.; Karoonnirun, O.; Thongpanchang, T.; Witayakran, S.; Thebtaranonth, Y.; Phillip, K. E. S.; Katz, T. J. *Tetrahedron Letters*. **2004**, *45*, 1343-1346.

13. Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769-3775.
14. Sadorn, K.; Sinananwanich, W.; Areephong, J.; Nerungsi, C.; Wongma, C.; Pakawatchai, C.; Thongpanchang *Tetrahedron Lett.* **2008**, *49*, 4519-4521.

Output

งานวิจัยที่เกี่ยวข้องกับโครงการวิจัยนี้ ได้ทำการตีพิมพ์เพื่อเผยแพร่ผลงานในวารสารวิชาการดังนี้

1. Sadorn, K.; Sinananwanich, W.; Areephong, J.; Nerungsi, C.; Wongma, C.; Pakawatchai, C.; Thongpanchang *Tetrahedron Lett.* **2008**, *49*, 4519-4521.
2. Saisaha, P.; Nerungsi, C.; Iamsaard, S.; Thongpanchang, T. *Tetrahedron Lett.* **2009**, *50*, 4217-4220.
3. Sungsuwan, S.; Ruangsapapichart, N.; Prabpai, S.; Kongsaree, P.; Thongpanchang, T. *Angewandte Chemie International Edition*, submitted for publication.

และได้มีการนำเสนอผลงานในการประชุมวิชาการระดับชาติและนานาชาติได้แก่

Sungsuwan, S.; Ruangsapapichart, N.; Thongpanchang, T. The 4th International Conference on Cutting-Edge Organic Chemistry in Asia. November 29-December 3, 2009 Thailand.

สารเตรียมอนุพันธ์ไครัลที่พัฒนาขึ้นจากโครงการวิจัยนี้ มีศักยภาพที่จะนำไปต่อยอดเพื่อช่วยในการวิจัยทางด้านเคมีผลิตภัณฑ์ธรรมชาติในวงกว้าง และมีแนวโน้มที่จะนำไปใช้ประโยชน์ในเชิงพาณิชย์ต่อไป

ภาคผนวก



An efficient synthesis of dinaphthothiophene derivatives

Karoon Sadorn^a, Warapon Sinananwanich^a, Jetsuda Areephong^a, Chakkrapan Nerungsi^a, Chalayut Wongma^a, Chaveng Pakawatchai^b, Tienthong Thongpanchang^{a,*}

^a Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand

^b Department of Chemistry, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand

ARTICLE INFO

Article history:

Received 10 April 2008

Revised 7 May 2008

Accepted 8 May 2008

Available online 13 May 2008

ABSTRACT

A short and efficient synthesis of dinaphthothiophene and its derivatives was achieved by employing oxidative photocyclization of the corresponding dinaphthyl sulfides as a key step.

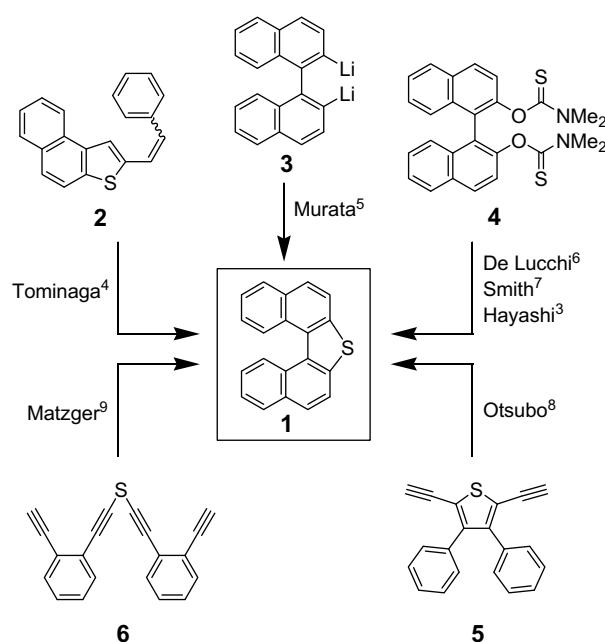
© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Dinaphthothiophene **1** can be classified as a sulfur-containing heteroaromatic system with a unique structure. Despite its helical structure, the molecule does not exhibit optical activity due to rapid racemization at ambient temperature.^{1,2} The molecule has received much attention recently due to its potential as a precursor for the synthesis of axially chiral binaphthyl derivatives, which are effective chiral building blocks in asymmetric reactions.^{2,3}

A number of dinaphthothiophene syntheses have been reported in the literature as outlined in Scheme 1. For example, in chronological order, Tominaga and co-workers reported the synthesis of dinaphthothiophene derivatives via the photocyclization of **2**.⁴ Later Murata et al. reported that the reaction between the lithiated binaphthyl **3** and sulfur provided dinaphthothiophene **1** in 19% yield.⁵ De Lucchi et al.⁶ and Smith et al.⁷ reported the application of the Newman–Kwart thermal rearrangement of the dimethylthiocarbamate of binaphthol **4** to provide the desired product **1**. This approach was later improved by Hayashi and co-workers⁸ and the yield was increased to 68%.³ In 1999, Otsubo and co-workers⁸ reported an approach via the flash vacuum pyrolysis of diethynyl thiophene **5**. Finally, Matzger and co-workers⁹ employed a cascade Bergman cyclization of **6** to furnish dinaphthothiophene **1** in trace amount.

Our research focuses on the development of new methodology towards helical conjugated structures.¹⁰ Interestingly, it was reported, by Zeller and Petersen,¹¹ that the oxidative photocyclization of diphenyl sulfide could lead to dibenzothiophene. It was envisioned that such an approach could be applied for the direct synthesis of dinaphthothiophene **1**. Retrosynthetic disconnection at the C1–C1' bond of dinaphthothiophene suggested that the precursor for photochemical reaction could be dinaphthyl sulfide **7** which could be derived straightforwardly from the acid-mediated



Scheme 1. Reported syntheses of dinaphthothiophene **1**.

nucleophilic aromatic substitution between 2-naphthol **8** and 2-naphthalenethiol **9** (Scheme 2).¹²

2. Result and discussion

The reaction of 2-naphthol **8** and 2-naphthalenethiol **9** was thus carried out in the presence of *p*-TsOH in refluxing toluene for 2 h to provide the desired dinaphthyl sulfide **7** in 97% yield. The sulfide **7** was then subjected to oxidative photocyclization in the presence of I₂ and propylene oxide (PO), Scheme 3.^{11,13} Conditions for the oxidative photo-cyclization process and yields are summarized in Table 1.

* Corresponding author. Tel./fax: +66 2 201 5139.

E-mail address: tett@mahidol.ac.th (T. Thongpanchang).

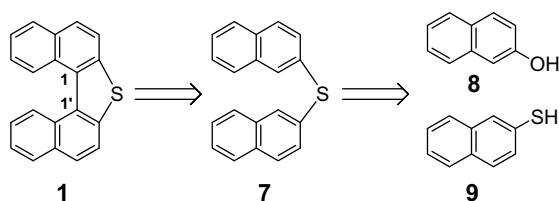
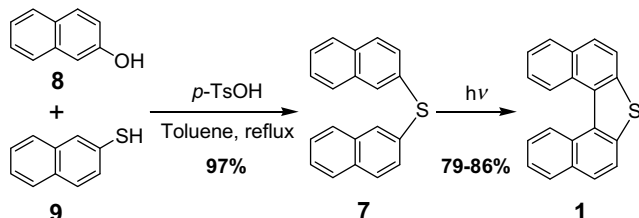
Scheme 2. Retrosynthetic analysis of dinaphthothiophene **1**.Scheme 3. Synthesis of dinaphthothiophene **1**.

Table 1

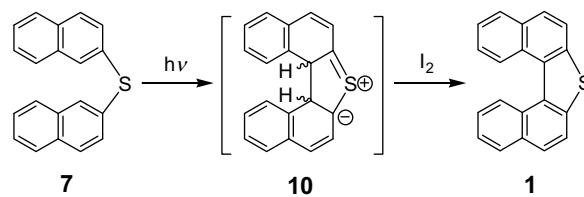
Conditions and yields of the oxidative photocyclization reaction of dinaphthyl sulfide **7**^a

Entry	Time (min)	I ₂ (equiv)	PO (equiv to I ₂)	Yield % (conversion %) ^b
1	10	1.0	10.0	79 (48)
2	20	1.0	10.0	83 (78)
3	30	1.0	10.0	85 (87)
4	40	1.0	10.0	84 (89)
5	60	1.0	10.0	86 (88)
6	30	0.8	10.0	82 (86)
7	30	1.2	10.0	85 (91)
8	30	1.5	10.0	84 (92)
9	30	1.2	0.0	81 (80)
10	30	1.2	5.0	85 (90)

^a The reaction was conducted in a 1 L Hanovia 450 W medium pressure Hg lamp photochemical reactor. All experiments were performed on 1 mmol scale at a concentration of 1 mM.

^b The % conversion refers to the percentage of reacted starting material; the % yield refers to the percentage of the product from the reacted starting material.

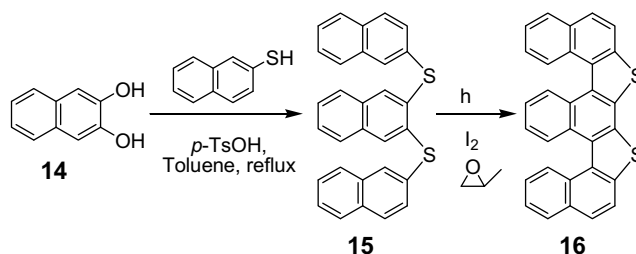
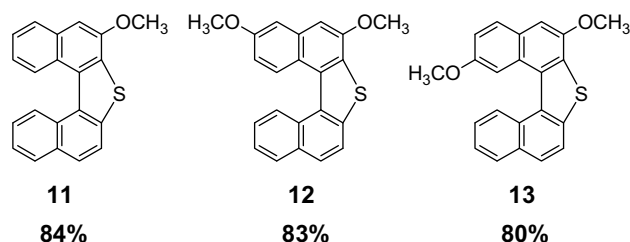
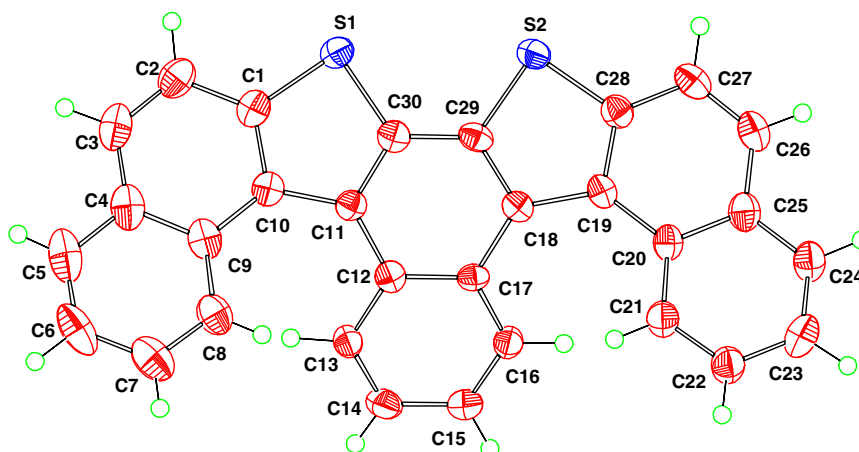
It was found that a stoichiometric amount of I₂ was required for the reaction. On 1 mmol scale, the appropriate reaction time was 30 min. A shorter reaction time led to a decreased percent conversion whilst prolonged irradiation did not increase the yield and % conversion, but did result in the formation of a brownish stain on the surface of the quartz tube and reactor. Addition of propylene oxide did not significantly improve the percent yield and conversion, but it did influence the purity of the crude product.



Scheme 4. Mechanism of the oxidative photocyclization.

The mechanism of the reaction is proposed to be similar to that reported by Zeller and Petersen¹¹ (Scheme 4). Electrocyclic ring closure of dinaphthyl sulfide **7** provided the cyclic intermediate **10** which, upon reaction with I₂, yielded the dinaphthothiophene **1**. Propylene oxide served as a HI-quencher.¹³ The decreased extent of aromatic energy in naphthalene is believed to facilitate the photo-electrocyclic process and this provides a rationalization for the better yield and higher conversion when compared to the reaction of diphenyl sulfide.

This oxidative photocyclization was a very efficient and convenient procedure for the construction of other dinaphthothiophene derivatives. For example, compounds **11**, **12** and **13** could be prepared by photocyclization of their corresponding dinaphthyl sulfides in 84%, 83% and 80% yields, respectively.

Scheme 5. Two-step synthesis of **16**.Figure 1. ORTEP diagram of compound **16**.

Compounds with complicated skeletons, such as **16**, could also be accessed via this oxidative photocyclization method. Indeed, treatment of 2,3-naphthalenediol **14** with 2-naphthalenethiol **9** in refluxing toluene in the presence of *p*-TsOH yielded **15** (87%), which upon oxidative photocyclization by the aforementioned procedure provided **16** in 83% yield (Scheme 5).

X-ray analysis of compound **16**¹⁴ (Fig. 1) revealed an interesting structural feature where the product adopted a conformation that possessed a plane of symmetry, rather than a C₂-axis. A detailed investigation of this molecule as a new type of organic material is currently in progress.

In conclusion, an alternative synthesis of dinaphthothiophene has been described. The method is highly efficient and can be applied to the synthesis of a variety of dinaphthothiophene derivatives.

3. General procedures¹⁵

3.1. Synthesis of dinaphthyl sulfide 7

A solution of 2-naphthol **8** (1.24 g, 8.60 mmol) and 2-naphthalenethiol **9** (2.07 g, 12.90 mmol) in the presence of *p*-TsOH (1.64 g, 8.60 mmol) was refluxed in toluene for 2 h. The reaction was cooled down and then quenched with saturated NaHCO₃ solution. The mixture was then extracted with CH₂Cl₂ (3 times), and the combined organic extracts were washed with H₂O, dried over Na₂SO₄ and then evaporated to dryness. The crude product was purified by column chromatography (SiO₂, hexane as eluent) to yield dinaphthyl sulfide **7** (2.39 g, 97% yield).

3.2. Oxidative photocyclization of diaryl sulfide: synthesis of dinaphthothiophene 1

A solution of dinaphthyl sulfide **7** (300 mg, 1.05 mmol) and I₂ (320 mg, 1.26 mmol) in cyclohexane (1000 mL) was charged into a 1 L Hanovia photochemical reactor equipped with a 450 W medium pressure Hg lamp. The solution was purged with argon for 20 min. Then, propylene oxide (366 mg, 0.44 mL, 6.30 mmol) was added and the solution was irradiated for 30 min. Upon completion, the solution was evaporated to dryness and the crude product was subjected to column chromatography (SiO₂, hexane as eluent) to yield dinaphthothiophene **1** (228 mg, 85% yield, 90% conversion).

Acknowledgements

Financial support from the Thailand Research Fund (TRF-RMU4980021) and National Synchrotron Research Center (Grant 2-2549/PS01) for T.T. is gratefully acknowledged. K.S., C.N. and C.W. thank the Center for Innovation in Chemistry: Postgraduate Education and Research Program in Chemistry (PERCH-CIC), the Development and Promotion of Science and Technology Talents (DPST) program and the Royal Golden Jubilee (RGJ) program for their scholarships.

Supplementary data

Supplementary data (¹H and ¹³C NMR spectra of compounds **1**, **7**, **11**, **12**, **13**, **15** and **16**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.045.

References and notes

- Fabbri, D.; Dore, A.; Gladiali, S.; De Lucchi, O.; Valle, G. *Gazz. Chim. Ital.* **1996**, 126, 11.
- Shimada, T.; Cho, Y.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, 124, 13396.
- Cho, Y.-H.; Kina, A.; Shimada, T.; Hayashi, T. *J. Org. Chem.* **2004**, 69, 3811.
- Tedjamulia, M. L.; Tominaga, Y.; Castle, R. N.; Lee, M. L. *J. Heterocycl. Chem.* **1983**, 20, 1143.
- Murata, S.; Suzuki, T.; Yanagisawa, A.; Suga, S. *J. Heterocycl. Chem.* **1991**, 28, 433.
- Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.* **1993**, 58, 1748.
- Bandarage, U. K.; Simpson, J.; Smith, R. A. J.; Weavers, R. T. *Tetrahedron* **1994**, 50, 3463.
- Imamura, K.; Hirayama, D.; Yoshimura, H.; Takimiya, K.; Aso, Y.; Otsubo, T. *Tetrahedron Lett.* **1999**, 40, 2789.
- Lewis, K. D.; Rowe, M. P.; Matzger, A. J. *Tetrahedron* **2004**, 60, 7191.
- Areephong, J.; Ruangsapichart, N.; Thongpanchang, T. *Tetrahedron Lett.* **2004**, 45, 3067.
- Zeller, K.-P.; Petersen, H. *Synthesis* **1975**, 532.
- Charoonniyomporn, P.; Thongpanchang, T.; Witayakran, S.; Thebtaranonth, Y.; Phillips, K. E. S.; Katz, T. J. *Tetrahedron Lett.* **2004**, 45, 457.
- Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, 56, 3769.
- Crystallographic data for compound **16** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 680516. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/data_request/cif).
- Compound characterization: Dinaphthyl sulfide 7:** ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.48–7.55 (m, 6H, Ar-H); 7.76–7.78 (m, 6H, Ar-H); 7.94 (br s, 2H, Ar-H). ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 133.8, 133.1, 132.3, 129.8, 128.9, 128.7, 127.7, 127.4, 126.6, 126.2. MS (EI [70 eV], *m/z* (%)): 286 (100) [M⁺]; 252 (34) [(M–H₂S)⁺]. CHN: Required for C₂₀H₁₄S: C, 83.88; H, 4.93. Found: C, 83.72; H, 4.53. Melting point 157–160 °C. **Dinaphthothiophene 1:** ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.60 (m, 4H, Ar-H); 7.95 (d, *J* = 8.6 Hz, 2H, Ar-H); 7.99 (d, *J* = 8.6 Hz, 2H, Ar-H); 8.06 (m, 2H, Ar-H); 8.90 (m, 2H, Ar-H). ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 138.5, 132.1, 131.4, 129.9, 128.6, 127.4, 126.1, 125.2, 124.8, 120.8. MS (EI [70 eV], *m/z* (%)): 284 (72) [M⁺]. CHN: Required for C₂₀H₁₂S: C, 84.47; H, 4.25. Found: C, 84.92; H, 4.18. Melting point 213–216 °C. **6-Methoxy-dinaphthothiophene 11:** ¹H NMR (300 MHz, CDCl₃, δ/ppm): 4.20 (s, 3H, OCH₃); 7.26 (s, 1H, Ar-H); 7.47 (m, 1H, Ar-H); 7.54–7.62 (m, 3H, Ar-H); 7.93–8.07 (m, 4H, Ar-H); 8.85–8.94 (m, 2H, Ar-H). ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 152.5, 139.0, 134.1, 133.4, 132.2, 131.7, 131.6, 130.0, 128.6, 127.6, 127.4, 126.2, 126.0, 125.9, 125.5, 125.2, 124.8, 122.5, 121.1, 103.5, 55.9. MS (EI [70 eV], *m/z* (%)): 314 (100) [M⁺]; 282 (60) [(M–CH₃OH)⁺]. CHN: Required for C₂₁H₁₄OS: C, 80.22; H, 4.49. Found: C, 80.57; H, 4.41. Melting point 190–192 °C. **3,6-Dimethoxy-dinaphthothiophene 12:** ¹H NMR (300 MHz, CDCl₃, δ/ppm): 4.02 (s, 3H, OCH₃); 4.17 (s, 3H, OCH₃); 7.12 (dd, *J* = 2.69, 9.21 Hz, 1H, Ar-H); 7.18 (s, 1H, Ar-H); 7.33 (d, *J* = 2.65, 1H, Ar-H); 7.56–7.62 (m, 2H, Ar-H); 7.93 (d, *J* = 8.65 Hz, 1H, Ar-H); 7.98 (d, *J* = 8.64 Hz, 1H, Ar-H); 8.04 (m, 1H, Ar-H); 8.77 (d, *J* = 9.21 Hz, 1H, Ar-H); 8.89 (m, 1H, Ar-H). ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 157.4, 153.1, 139.0, 135.7, 133.5, 132.1, 131.5, 130.3, 129.2, 128.6, 127.5, 127.3, 126.0, 125.1, 124.8, 121.1, 120.9, 113.4, 107.2, 103.1, 55.9, 55.4. MS (EI [70 eV], *m/z* (%)): 344 (100) [M⁺]; 312 (20) [(M–H₃OH)⁺]. CHN: Required for C₂₂H₁₆O₂S: C, 76.72; H, 4.68. Found: C, 76.97; H, 4.65. Melting point 213–216 °C. **2,6-Dimethoxy-dinaphthothiophene 13:** ¹H NMR (300 MHz, CDCl₃, δ/ppm): 3.89 (s, 3H, OCH₃); 4.17 (s, 3H, OCH₃); 7.23–7.26 (m, 2H, Ar-H); 7.58–7.62 (m, 2H, Ar-H); 7.87 (d, *J* = 8.88 Hz, 1H, Ar-H); 7.94–8.08 (m, 3H, Ar-H); 8.18 (d, *J* = 2.27 Hz, 1H, Ar-H); 8.92 (m, 1H, Ar-H). ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 155.4, 151.0, 138.9, 132.5, 132.2, 132.0, 131.6, 129.7, 129.0, 128.7 (2C), 127.2, 126.7, 126.6, 125.2, 124.3, 121.1, 117.3, 106.6, 103.6, 55.9, 55.4. MS (EI [70 eV], *m/z* (%)): 344 (100) [M⁺]. CHN: Required for C₂₂H₁₆O₂S: C, 76.72; H, 4.68. Found: C, 76.38; H, 4.57. Melting point 184–186 °C. **2,3-Dinaphthyl disulfide 15:** ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.43 (m, 2H, Ar-H); 7.48–7.55 (m, 6H, Ar-H); 7.64 (m, 2H, Ar-H); 7.74–7.80 (m, 4H, Ar-H); 7.83–7.88 (m, 4H, Ar-H); 7.93 (br s, 2H, Ar-H). ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 135.3, 134.0, 132.8, 132.5, 132.2, 130.9, 130.6, 129.0, 128.9, 127.8, 127.5, 127.1, 126.5, 126.3. MS (EI [70 eV], *m/z* (%)): 444 (75) [M⁺]; 284 (100) [(M–C₁₀H₈S)⁺]. CHN: Required for C₃₀H₂₀S₂: C, 81.04; H, 4.53. Found: C, 80.46; H, 4.52. Melting point 122–125 °C. **Compound 16:** ¹H NMR (300 MHz, CDCl₃, δ/ppm): 7.57 (m, 2H, Ar-H); 7.65 (m, 4H, Ar-H); 7.98 (d, *J* = 8.68 Hz, 2H, Ar-H); 8.03 (d, *J* = 8.63 Hz, 2H, Ar-H); 8.09 (m, 2H, Ar-H); 8.98 (m, 2H, Ar-H); 9.05 (m, 2H, Ar-H). ¹³C NMR (75 MHz, CDCl₃, δ/ppm): 137.9, 133.3, 132.3, 131.7, 131.6, 129.7, 129.3, 128.8, 127.5, 126.4, 126.1, 125.5, 125.3, 124.7, 120.9. MS (EI [70 eV], *m/z* (%)): 440 (100) [M⁺]. CHN: Required for C₃₀H₁₆S₂: C, 81.78; H, 3.66. Found: C, 81.91; H, 3.55. Melting point 316–318 °C.



Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Pyridine stabilized oxiranyl remote anions

Pattama Saisaha^a, Chakkrapan Nerungsi^a, Supitchaya Iamsaard^a, Tienthong Thongpanchang^{a,b,*}^a Department of Chemistry and Center for Innovation in Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand^b National Center for Genetic Engineering and Biotechnology, Thailand Science Park, Klong Luang, Patumthani 12130, Thailand

ARTICLE INFO

Article history:

Received 18 February 2009

Revised 10 April 2009

Accepted 28 April 2009

Available online 3 May 2009

ABSTRACT

The chemistry of oxiranyl remote anions derived from α,β -epoxypyridines is investigated. Deprotonation of α,β -epoxy pyridines at the β -position and reactions of the corresponding anions with a variety of electrophiles are found to be highly regioselective, possibly as a consequence of stabilization from the chelation between lithium and the pyridine moiety in the form of a five-membered cyclic intermediate.

© 2009 Elsevier Ltd. All rights reserved.

The chemistry of oxiranyl remote anions, although in its early stage, has received significant attention due to unique and fascinating chemical characteristics and its high potential as a new approach towards substituted epoxides, which are key precursors in natural products synthesis.^{1,2} As revealed in the literature, the generation of oxiranyl remote anions and their reactions can be exemplified as shown in Scheme 1. It was suggested that the stability of the anions could be promoted by chelation between lithium and the carbonyl oxygen of ketone **2**,³ ester **4**,¹ lactone or imide **6**,⁴ or the nitrogen of oxazoline **8**.² These groups apparently used lone pair electrons to promote anion stabilization via chelation.

Pyridine is a fundamentally important heterocyclic aromatic compound which has been used as a directing group in coordination chemistry.⁵ In principle, the pyridyl group attached to an epoxide would also serve as a lithium-chelator and thus stabilize the oxiranyl remote anion **10** (Scheme 1). To further extend the chemistry and synthetic utility of the oxiranyl remote anion intermediates, we report here our investigations on the pyridine stabilized oxiranyl remote anion and its reactions with electrophiles.

In analogy to compound **1**, epoxypyridine **9** in which the stabilizing group is pyridine instead of a ketone was prepared following the reaction summarized in Scheme 2. Treatment of 2-picoline **11** with *n*-BuLi then with PhCHO gave, after dehydration, alkene **13**. Two-step epoxidation of **13** with NBS in dioxane-H₂O (2:1), followed by base-induced epoxide ring closure gave the desired product **9**.

Treatment of epoxypyridine **9** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in the presence of a variety of electrophiles, including TMSCl, EtI, MeCOMe, MeCONMe₂ and cyclohexanone, gave the substituted products **14a–e** in moderate⁶ to good yields as shown in Table 1. The regiochemistry of the substituted products **14**, wherein H_x was abstracted and replaced by an elec-

trophile, could be deduced by HMBC in which the key correlations were those between H_y and pyridine carbons C3, C4 and C5 (Fig. 1).

In principle, two major factors that govern the regioselectivity of the deprotonation could be envisioned; (i) α -stabilization from the phenyl group⁷ and/or (ii) β -stabilization through coordination between the pyridine nitrogen and lithium in the form of a five-membered cyclic chelate (intermediate **10**, Scheme 1). To substantiate the significance of each factor, the chemistry of the oxiranyl remote anion derived from epoxypyridine **15** of which the phenyl group was relocated to the α -position of the epoxypyridine was investigated.

Epoxypyridine **15** could be prepared straightforwardly via the Corey-Chaykovsky reaction between 2-benzoylpyridine and trimethylsulfoxonium iodide.⁸ Treatment of epoxy-pyridine **15** with LTMP in the presence of a variety of electrophiles including TMSCl, PhCOPh, MeCOMe and ClCO₂Et yielded substituted products **16a–d** as summarized in Table 2.

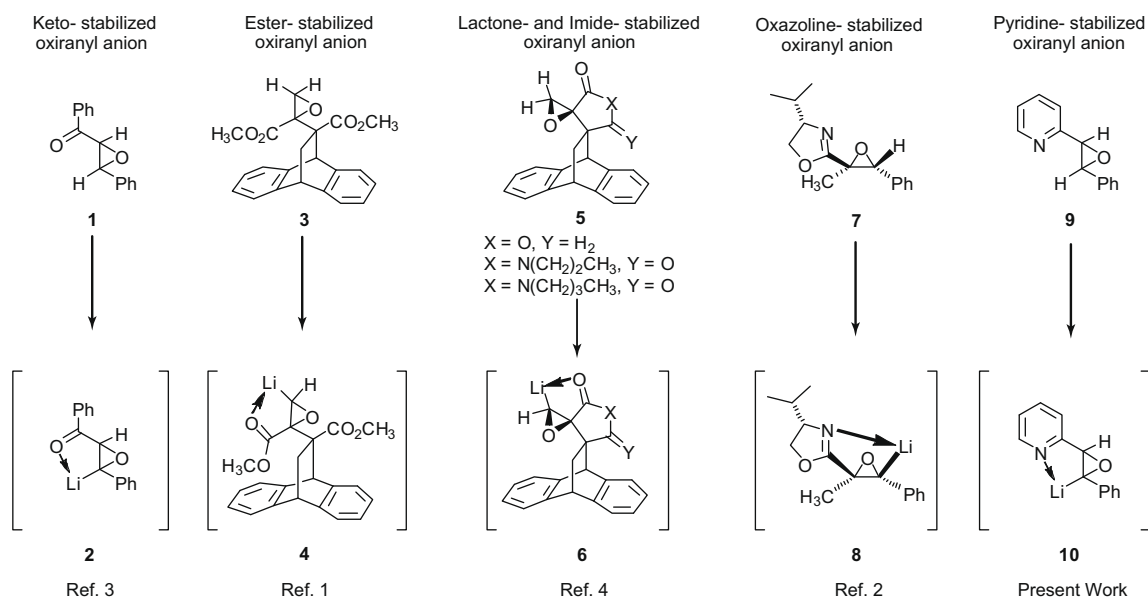
Interestingly, the reaction provided the products in which the substituents were oriented regioselectively *syn* to the pyridine group as confirmed by NOESY experiments (Fig. 2). For example, in the case of **16a**, correlations between a methyl of the TMS group and H_a and H_b of the pyridine ring as well as between H_y and H_A of the phenyl ring were observed. Moreover, the observation of the disubstituted product **16d**, entry 4, could be rationalized considering that the first deprotonation–substitution occurred at H_x (via the β -anion, governed by the pyridine moiety), followed by deprotonation–substitution at H_y (via the α -anion of the ester group).

The regiochemical outcomes of the aforementioned reactions unambiguously demonstrate the significance of the chelation effect from pyridine in the induction of the regioselectivity of β -deprotonation. However, the decrease in yield compared between the reaction of compounds **9** (Table 1) and **15** (Table 2) also alludes to participation in anion stabilization of the phenyl group.

To establish that the regioselectivity of deprotonation in **9** was indeed a consequence of the stabilization effect from pyridine through chelation, *cis*-epoxide **20** was prepared. As shown in

* Corresponding author. Tel./fax: +66 2 201 5139.

E-mail address: tett@mahidol.ac.th (T. Thongpanchang).



Scheme 1. Formation of remote stabilized oxiranyl anions.

Scheme 3, Wittig reaction of **18** with 2-pyridinecarboxaldehyde yielded *cis*-adduct **19** in 64% yield. Alkene **19** was then subjected to epoxidation with NBS, dioxane-H₂O (2:1) and finally, base-catalyzed epoxide ring closure, to afford the desired product **20** in 33% yield.

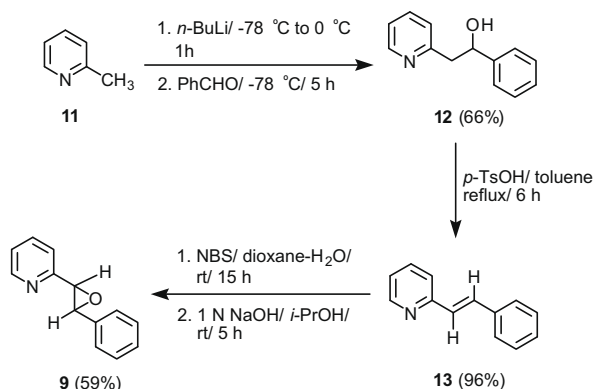
Treatment of epoxide **20** with LTMP and then quenching with CD₃OD yielded ketone **21** exclusively, without any deuterium incorporation (**Scheme 4**). The regiochemistry of the product was assigned by HMBC experiments of which correlations between the α -methylene proton and the phenyl carbons were observed exclusively (**Fig. 3**).

Formation of **21** could take place via a mechanism similar to that reported by Hodgson et al.,⁹ as shown in **Scheme 5**. In this case, due to the diminishing chelation by the pyridine moiety, the regioselectivity of the deprotonation was thus influenced by the acidity of protons H_x and H_y. Because of its greater acidity,¹⁰ proton abstraction from epoxide **20** occurred at the α -position to the pyridine group (H_y-abstraction). The lithiated species then directed the addition of LTMP to the epoxide regioselectively at the carbon adjacent to the pyridine group, leading to the epoxide ring opening to afford dianion **22**. Elimination of Li₂O from dianion **22** gave enamine **23**. Upon normal work-up, ketone **21**, in which the carbonyl group is adjacent to the pyridine group was thus obtained. This finding confirmed that the highly regioselective

deprotonation at H_x of epoxypyridine **9** was the result of the chelation effect from the pyridine and lithium in the form of five-membered cyclic intermediate, instead of the acidity of protons H_x or H_y.

Table 1
Lithiation and substitution reactions of α,β -epoxypyridine **9**

Entry	Electrophile	Product (%yield)
1	TMSCl	14a (94)
2	EtI	14b (44)
3	MeCOMe	14c (55)
4	MeCONMe ₂	14d (56)
5	Cyclohexanone	14e (67)

Scheme 2. Preparation of epoxypyridine **9**.

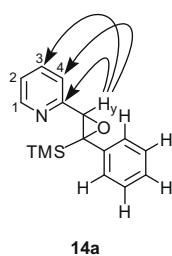
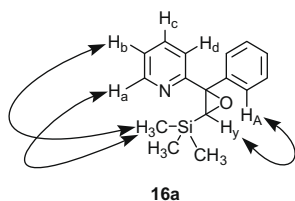
Figure 1. Key HMBC correlations in compound **14a**.

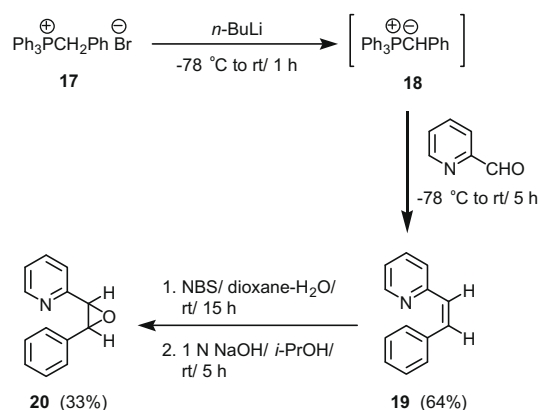
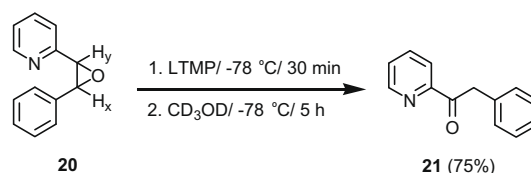
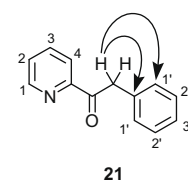
Table 2
Lithiation and substitution reactions of α,β -epoxy pyridine **15**

Entry	Electrophile	Product (%yield)
1	TMSCl	16a (73)
2	PhCOPh	16b (77)
3	MeCOMe	16c (29)
4	ClCO ₂ Et	16d (16)

Figure 2. Key NOE correlations in compound **16a**.

In conclusion, this investigation has described the highly regioselective formation of oxiranyl remote anions derived from α,β -epoxy pyridines. It was also found that the stabilization from the chelation between the lithium and the pyridine moiety in the form of a five-membered cyclic intermediate played a key role in the regioselectivity. In addition, the phenyl group at the β -position of the α,β -epoxy pyridine could also facilitate the formation of the oxiranyl anion, thus enhancing the yields of the substituted products.

General procedure for lithiation and substitution reactions of α,β -epoxy pyridine **9.** To a solution of LTMP (1.52 mmol, generated in situ from *n*-BuLi (1.33 N in hexanes, 1.14 mL, 1.52 mmol) and

Scheme 3. Preparation of epoxy pyridine **20**.Scheme 4. Deprotonation of epoxy pyridine **20** with LTMP.

evaporated to dryness. Purification by preparative thin layer chromatography (SiO₂; 5% EtOAc/hexane) gave 2-(3-phenyl-3-(trimethylsilyl)oxiran-2-yl)pyridine **14a** (129.5 mg, 0.48 mmol, 94% yield) as a white solid. mp 48–51 °C. ¹H NMR (300 MHz, CDCl₃): δ –0.10 (s, 9H, Si(CH₃)₃), 4.24 (s, 1H, H_x), 7.32–7.39 (m, 2H, 1ArH, H_b), 7.42–7.47 (m, 2H, 2ArH), 7.53–7.59 (m, 3H, 2ArH, H_d), 7.80 (td, *J* = 7.68, 1.46 Hz, 1H, H_c), 8.74 (d, *J* = 4.87 Hz, 1H, H_a); ¹³C NMR (75 MHz, CDCl₃): δ –2.0, 63.2, 65.5, 121.6, 122.6, 126.0, 126.5, 128.0, 136.1, 142.7, 148.9, 156.9; IR (cm^{–1}): 3057, 3023, 2900, 1590, 1568, 1494, 1471, 1446, 1432, 1247, 839, 776, 755, 703; exact mass: *m/z* [M+H⁺] found 270.1141.

Acknowledgements

Fellowships from the Development and Promotion of Science and Technology Talents program (DPST), the Royal Golden Jubilee (RGJ) Scholarship and Post-Graduate Education and Research in Chemistry (PERCH-CIC) for P.S., C.N. and S.I. and research support from the Thailand Research Fund (RMU4980021) and from the Commission on Higher Education, Ministry of Education are gratefully acknowledged.

Supplementary data

Supplementary data (¹H and ¹³C NMR spectra of compounds **9**, **14a–e**, **15**, **16a–d**, **20** and **21** are available) associated with this

article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.04.106](https://doi.org/10.1016/j.tetlet.2009.04.106).

References and notes

1. Lertvorachon, J.; Thebtaranonth, Y.; Thongpanchang, T.; Thongyoo, P. *J. Org. Chem.* **2001**, *66*, 4692–4694.
2. (a) Capriati, V.; Degennaro, L.; Flavia, R.; Florio, S.; Luisi, R. *Org. Lett.* **2002**, *4*, 1551–1554; (b) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Punzi, P. *Org. Lett.* **2006**, *8*, 4803–4806; (c) Florio, S.; Perna, F. M.; Luisi, R.; Barluenga, J.; Fananas, F. J.; Rodriguez, F. J. *Org. Chem.* **2004**, *69*, 9204–9207.
3. Baramee, A.; Clardy, J.; Kongsaree, P.; Rajviroongit, S.; Suteerachanon, C.; Thebtaranonth, Y. *Chem. Commun.* **1996**, 1511–1512.
4. Chaiyanurakkul, A.; Jitchati, R.; Kaewpet, M.; Rajviroongit, S.; Thebtaranonth, Y.; Thongyoo, P.; Watcharin, W. *Tetrahedron* **2003**, *59*, 9825–9837.
5. (a) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577–11585; (b) Fort, Y.; Rodriguez, A. L. *J. Org. Chem.* **2003**, *68*, 4918–4922.
6. Aside from TMSCl, the decrease in yield could also reflect the low-compatibility nature of electrophiles with LTMP.
7. For selected references on phenyl stabilized oxiranyl anions, see: (a) Capriati, V.; Florio, S.; Luisi, R. *Chem. Rev.* **2008**, *108*, 1918–1942. and references cited therein; (b) Capriati, V.; Florio, S.; Luisi, R. *Synlett* **2005**, 1359–1369; (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, 1625–1642; (d) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445–2448.
8. (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867–868; (b). *Synth. Commun.* **2003**, *33*, 2135–2143.
9. (a) Hodgson, D. M.; Bray, C. D.; Kindon, N. D.; Reynolds, N. J.; Coote, S. J.; Um, J. M.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 1019–1028; (b) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870–6871.
10. Although the p*K*_a of both H_x and H_y in this particular system has not been reported, it could be postulated, based on the p*K*_a of 2-methylpyridine and toluene, that H_y is more acidic than H_x Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232–3234.