1,4-Cycloaddition of Anthracenes and Practical Method for The Synthesis of Chiral Diamino Alcohols

Dissertation

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Herrn Prof. Oliver Reiser möchte ich herzlich für die Überlassung des äußerst interessanten Themas, die anregenden Diskussionen und seine stete Unterstützung während der Durchführung dieser Arbeit danken.

Meinen Eltern

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Acknowledgement

Curriculum vitae

Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane	EWG	Electron-Withdrawing Group
atm	atmosphere	Fc	ferrocenyl
BA	Brønsted Acids	h	hour
Bn	benzyl	Hal	halogen
Boc	*tert*-butyloxycarbonyl	HOMO	High Occupied Molecular Orbital
Cat.	catalyst	HPLC	High-Performance Liquid Chromatography
Cbz	carboxybenzyl	HRMS	High-resolution mass spectroscopy
DABCO	1,4-diazabicyclo[2.2.2]octane	IR	infra-red
DCM	dichloromethane	LA	Lewis Acid
DMAD	dimethylacetylenedicarboxylate	LUMO	Low Unoccupied Molecular Orbital
DMAP	dimethylaminopyridine	*m-*	*meta-*
DMF	dimethyl formamide	M	metal
EDG	Electron-Donating Group	Me	methyl
ee	enantiomeric excess	min	minute
equiv.	equivalent	Mp.	melting point
ESI-MS	Electrospray Ionization Mass Spectroscopy	MS	Molecular Sieves

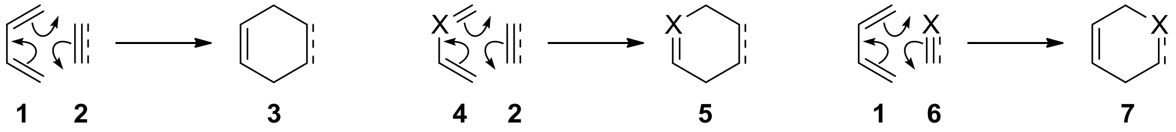
Et	ethyl	MS/MS	Tandem Mass Spectroscopy
NMR	Nuclear Magnetic Resonance	rf.	reflux
p-	*para*-	OAc	acetate
PE	Petroleum Ether	OTf	trifluoromethanesulfonate or triflate
PG	Protecting Group	OTs	*p*-toluenesulfonate
Ph	phenyl	temp.	temperature
Phe	phenylalanine	THF	tetrahydrofuran
^{i}Pr	*iso*-propyl	UV	ultraviolet
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride	X	arbitrary anion

Part I:
1,4-Cycloaddition of Anthracenes

1. Introduction

1.1. Diels-Alder reaction

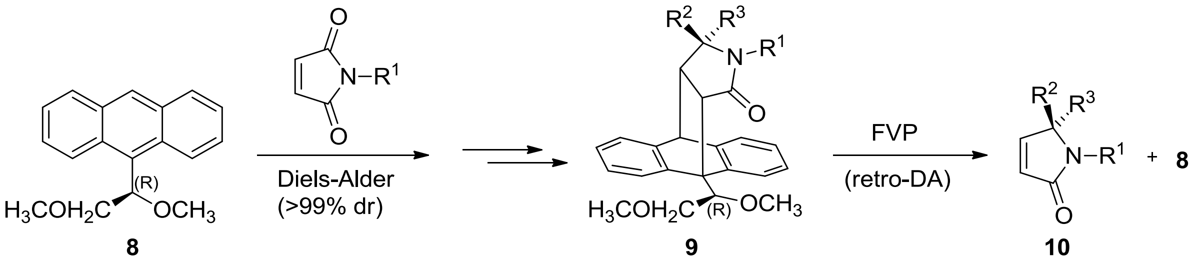
The Diels-Alder reaction[1] is a cycloaddition reaction. In this reaction, four π electrons from a conjugated diene **1** and two π electrons from a dienophile **2** (double or triple bond), combine to form two new σ bonds between the diene and the dienophile and one new π bond on the carbon skeleton of the diene (Scheme 1). The reaction is not limited to all carbon substrates. When one or more heteroatoms are involved, this reaction is called *hetero*-Diels-Alder reaction,[2] which is useful for synthesizing six-membered heterocycles. The heteroatom can be in the diene, for example as shown in **4**, or can be in the dienophile, as shown in **6**.



Scheme 1. The Diels-Alder reactions

The Diels-Alder reaction is usually reversible.[3] The reverse reaction which is called retro-Diels-Alder reaction occurs at a higher temperature than the forward reaction. An example that makes use of the retro-Diels-Alder reaction is the synthesis of chiral α,β-unsaturated γ-lactams **10** by using the chiral-substituted anthracene **8** as a chiral auxiliary (Scheme 2).[4]

Dienes can be cyclic or acyclic but the two double bonds of dienes must be conjugated and must be able to obtain a *cisoid* conformation as in **11**, **12** or **13** (Figure 1).[1c,5] If the two double bonds of dienes are fixed in a *transoid* conformation as depicted in **14** (Figure 1), the Diels-Alder reaction cannot happen.



Scheme 2. The asymmetric synthesis of chiral α,β-unsaturated γ-lactams

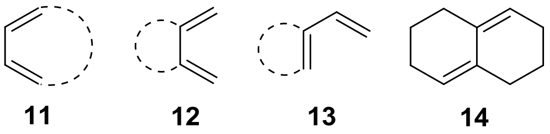
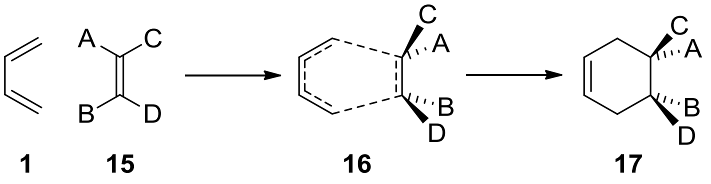


Figure 1. Possible conformations of conjugated dienes

There is much evidence that the Diels-Alder reaction proceeds in a concerted fashion.[6] This reaction takes place in one step in which two new σ bonds are formed simultaneously, so no rotation about single bonds can happen. Consequently, the Diels-Alder reaction is a stereospecific reaction with *syn*-addition. Substituents on the dienophile which are *cis* to each other will be *cis* (*syn*) on the newly formed ring (A-B and C-D). Similarly, substituents on the dienophile which are *trans* to each other will be *trans* (*anti*) on the newly formed ring (A-D and B-C) (Scheme 3).

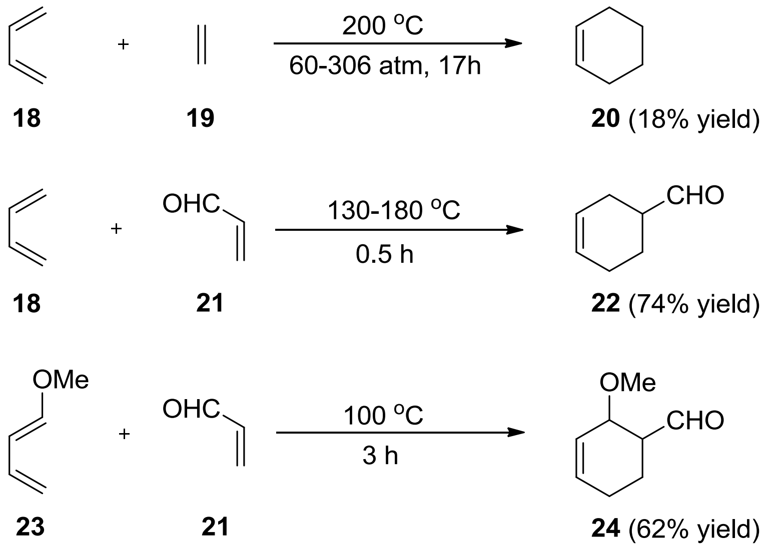


Scheme 3. *Syn*-addition in Diels-Alder reactions

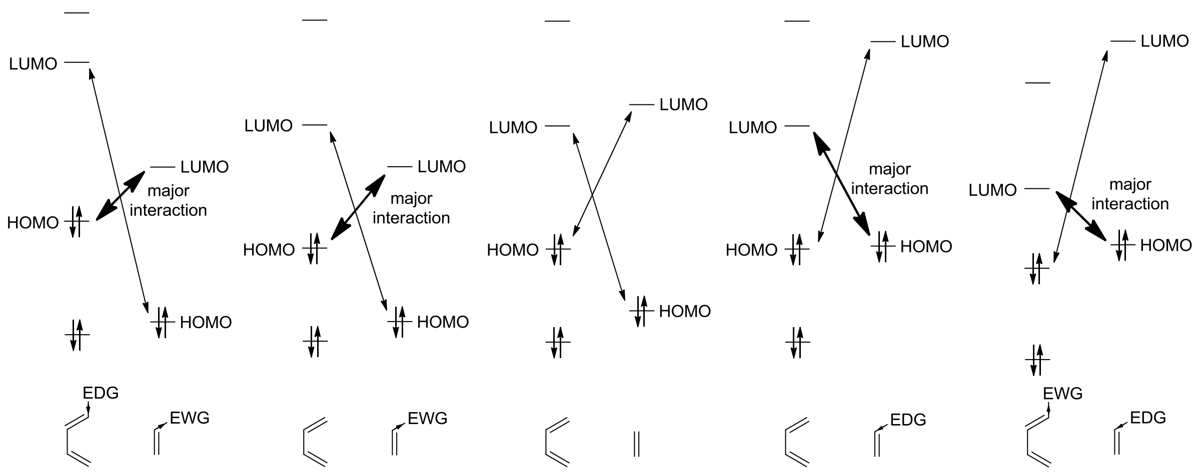
Most dienophiles in the Diels-Alder reaction carry an activating group, or they cannot react smoothly and readily. The Diels-Alder reaction between butadiene (18) and ethylene (19) takes place at high temperature (200 °C), high pressure, and requires a long reaction time

(17h).[7] When there is an electron-withdrawing group (EWG), for example, with acrolein (21) the reaction occurs at a lower temperature (130 °C), and less time (Scheme 4).[8] The reaction is even faster when there is an electron-donating group (EDG) on the diene, for example, 1-methoxybutadiene (23), as well as an electron-withdrawing group on the dienophile such as acrolein (21) (Scheme 4).[9] This phenomenon can be explained by considering frontier molecular orbitals. The electron-withdrawing group on the dienophile lowers its LUMO energy, while the electron-donating group on the diene increases its HOMO energy. Thus, the energy gap between the HOMO of diene and the LUMO of dienophile decreases, resulting in an acceleration of the reaction (Figure 2a). In this case, we have a normal-electron-demand Diels-Alder reaction. Schubert *et al.*[10] showed a good correlation between the $\mathrm{HOMO_{diene}/LUMO_{dienophile}}$ separations and the reactivity. The smaller the energy gap between the HOMO and the LUMO, the faster the reaction. The energy separation between the HOMO and the LUMO can also be lowered by putting an electron-withdrawing group on the diene and putting an electron-donating group on the dienophile. The electron-withdrawing group lowers the LUMO energy of the diene, whereas the electron-donating group moves the HOMO energy of the dienophile to a higher level. In this case, we have an inverse-electron-demand Diels-Alder reaction[1d,11] (Figure 2b).

Substituents affect not only the rate but also the regioselectivity in Diels-Alder reactions. Diels-Alder reactions of unsymmetrically substituted dienes and unsymmetrically substituted dienophiles can produce different regioisomeric products. For example, the Diels-Alder reaction of 1-phenylbutadiene (25) and methyl acrylate (26) gives the *ortho*-adduct **27a** rather than the *meta*-adduct **27b**, while the reaction of 2-phenylbutadiene (28) and methyl acrylate (26) preferably leads to the *para*-adduct **29a** to the *meta*-adduct **29b** (Scheme 5). The regioselectivity in the Diels-Alder reaction can be explained by analyzing the coefficients of the atomic orbitals in the decisive pair of frontier orbitals, i.e. the HOMO/LUMO pair with the smaller energy gap, being involved in the reaction.[1d,12] The major product is formed from the interaction of the decisive pair of frontier orbitals in the way that the atomic orbitals which have the larger coefficient on each component interact together and the atomic orbitals which have the smaller coefficient on each component interact together (as described in **30**, Scheme 5). Although the *ortho*- or the *para*-adduct is usually the major product (the o*rtho*-*para* rule), in some cases the *meta*-adduct is mainly formed because of steric effects as in the reaction of piperylene (31) with vinyl-9-BBN **32** (Scheme 6).[13]

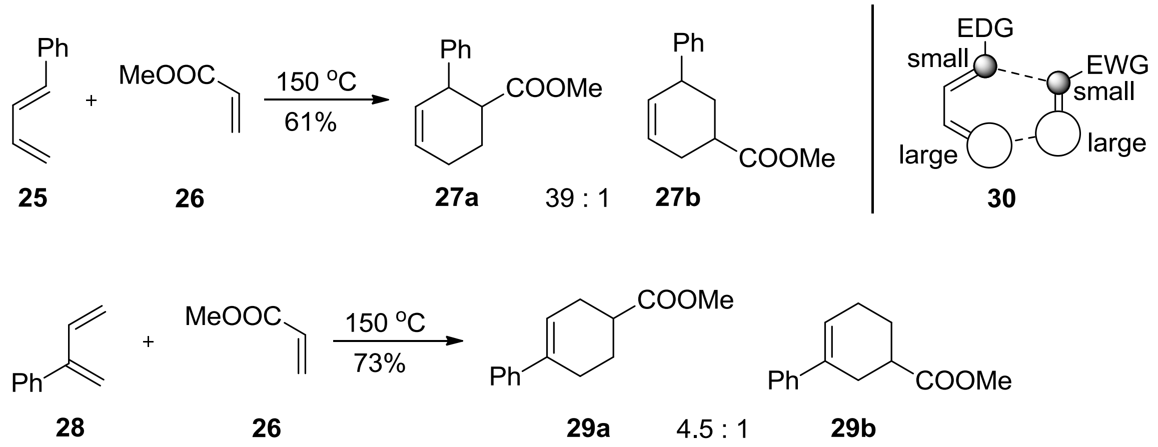


Scheme 4. Effects of substituents on Diels-Alder reactions

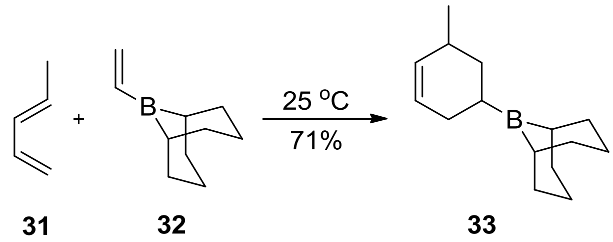


a) normal-electron-demand Diels-Alder reaction neutral b) inverse-electron-demand Diels-Alder reaction

Figure 2. Normal-electron-demand and inverse-electron-demand Diels-Alder reactions



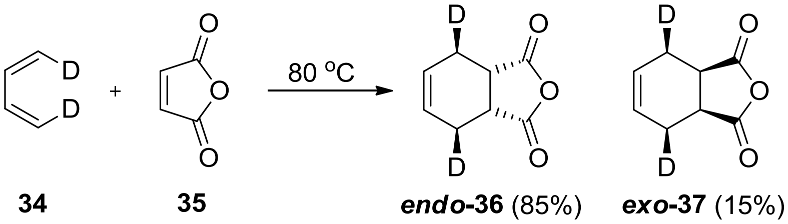
Scheme 5. The regioselectivity in Diels-Alder reactions



Scheme 6. The exception *meta*-adduct in the Diels-Alder reaction

Besides the *ortho*-*para* rule as described above, the Diels-Alder reaction has another rule, i.e. *endo* or Alder rule.[1d,14] With substituted dienophiles, the Diels-Alder reaction can go through two geometrically different transition states to afford two isomeric adducts: the *endo*- (usually the major adduct under kinetic conditions) and the *exo*-adduct (usually the major adduct under thermodynamic conditions). For example, the addition to *cis*,*cis*-1,4-dideuterio-1,3-butadiene (34) of maleic anhydride (35) leads to an 85:15 mixture of the *endo*-adduct **36** and the *exo*-adduct **37** (Scheme 7).[15]

The *endo*-adduct is kinetically more favorable due to secondary orbital interactions in the *endo*-transition state being, however, sterically more crowded.[16] Thus, given the reversibility of the Diels-Alder reaction, the *exo*-adduct typically forms under thermodynamic conditions, i.e. extended heating. Later the concept of secondary orbital interactions was challenged by Salvatella *et al.*[17]



Scheme 7. The *endo*-selectivity in the Diels-Alder reaction

Solvents have a little effect on the rate of the Diels-Alder reaction, being a signature of concerted reactions. However, both experimental and theoretical studies showed that an increase of polarity of solvents increases the *endo*/*exo* ratio of this reaction.[18]

Diels-Alder reactions exhibited a largely negative activation volume which is a signature of concerted reactions and a largely negative reaction volume which is a signature of addition reactions.[6c] Both characteristics can be utilized to accelerate the reaction and to improve the *endo*-selectivity by applying high pressure.[9,19]

Diels-Alder reactions do not often need catalysts. Nevertheless, this reaction can be catalyzed by Lewis acids (LA) or Brønsted acids (BA). These catalysts coordinate to basic sites in dienophiles to lower the LUMO energy of dienophiles (Figure 3), generally allowing running the reaction at lower temperatures. In this way, the regioselectivity and diastereoselectivity can be improved (enhance the *endo*/*exo* ratio) and in the case of chiral catalysts, also the enantioselectivity.[2c,2d,20] Lewis acids are effective catalysts especially when the activating group on dienophile is a C=O or C=N.[21]

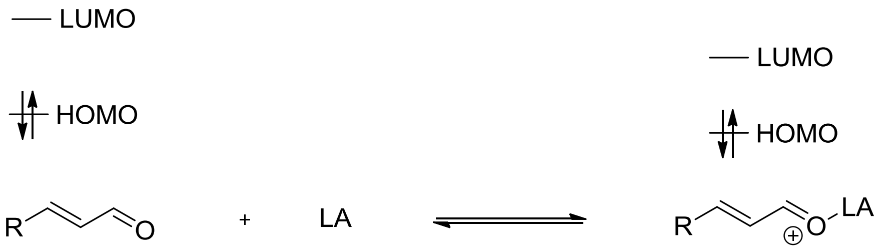
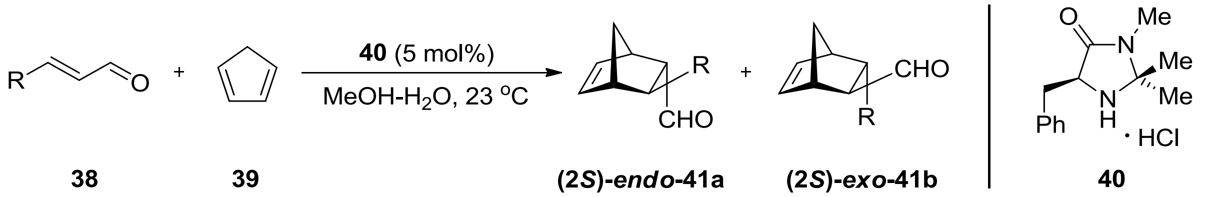


Figure 3. Lewis acid activation dienophile

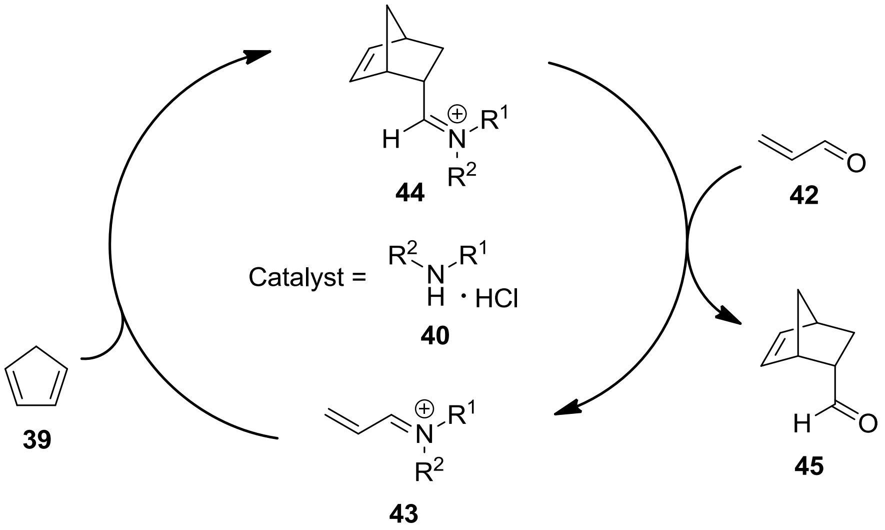
In addition to Lewis acids and Brønsted acids, small organic molecules known as organocatalysts are good alternatives to produce Diels-Alder adducts with high enantioselectivities. The MacMillan group[22] designed the chiral imidazolidinone **40** which catalyzes Diels-Alder reactions and affording cycloadducts in good yields and high stereoselectivities (Table 1).

In contrast to Lewis acid, the catalyst **40** forms covalent bonds with the dienophile **42** and resulting in an iminium ion **43**, having a lower LUMO energy level compared to the corresponding carbonyl compound (Scheme 8).

Table 1. The organocatalyzed Diels-Alder reaction between dienophiles **38** and cyclopentadiene (39)



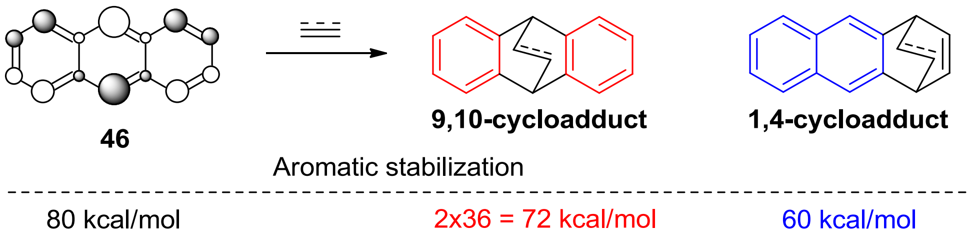
R	time (h)	yield (%)	*exo* : *endo*	*exo* ee (%)	*endo* ee (%)
Me	16	75	1 : 1	86	90
Pr	14	92	1 : 1	86	90
i-Pr	14	81	1 : 1	84	93
Ph	21	99	1.3 : 1	93	93
Furyl	24	89	1 : 1	91	93



Scheme 8. The proposed mechanism for organocatalyzed Diels-Alder reactions

1.2. 1,4-cycloaddition of anthracenes

Anthracene (46), a compound in coal tar, was discovered by Dumas and Laurent in 1832.[23] Because of the largest coefficients in the HOMO of (46) (Scheme 9)[24] and the smaller aromaticity loss during the reaction at the center ring (8 kcal/mol compared to 20 kcal/mol in the outer rings),[25] Diels-Alder reactions of anthracenes furnish 9,10-cycloadducts rather than 1,4-cycloadducts (Scheme 9). Only a few exceptions for Diels-Alder reactions that take place at 1,4-positions have been reported. In principle, there are two ways to favor the 1,4-cycloadduct in Diels-Alder reactions of anthracenes, i.e. disfavoring the 9,10-positions for the cycloaddition by steric or electronic factors.



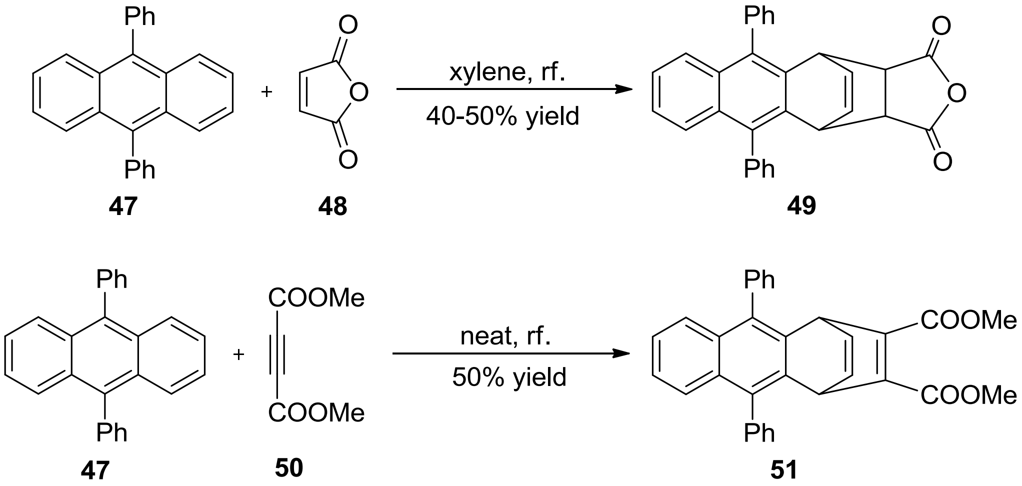
Scheme 9. Orbital coefficients in the HOMO and possible [4+2]-cycloadditions of anthracene (46)

1.2.1. Using steric and electronic factors in substituted anthracenes to favor the formation of the 1,4-cycloadduct

Cook *et al.*[26] found that anthracenes which have bulky groups at the 9,10-positions like 9,10-diphenylanthracene (47) undergo the unusual 1,4-cycloaddition with maleic anhydride (48) to furnish the 1,4-cycloadduct **49** exclusively instead of the normal 9,10-cycloadduct (Scheme 10). Likewise, when the dienophile is dimethyl acetylenedicarboxylate (DMAD) (50), only the 1,4-cycloadduct **51** is found in the reaction of 9,10-diphenylanthracene as well (Scheme 10).[27] Bulky groups both at 9- and at 10-positions are crucial to obtain exclusively the 1,4-cycloadduct **49**. For example, when 9-bromo, 9-chloro or 9-nitro-10-phenylanthracene is employed, both 9,10- and 1,4-cycloadducts are formed.

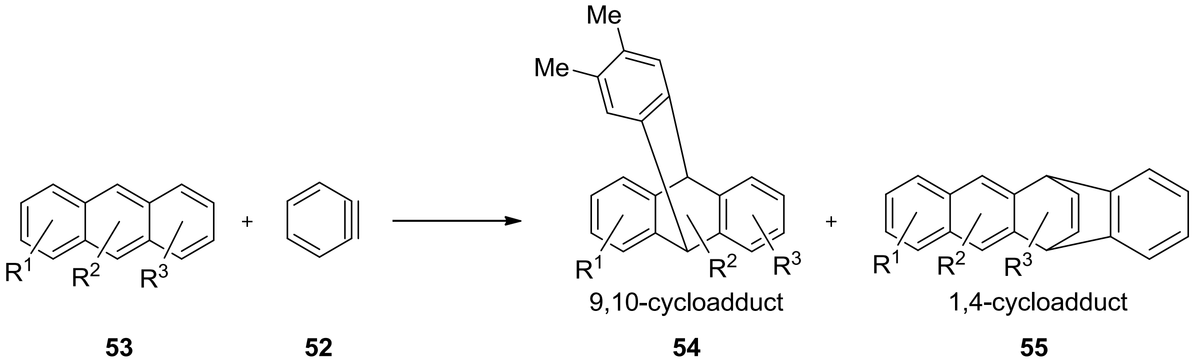
Benzyne (52) is a particular reactive dienophile. Klanderman *et al.*[28] reported that it reacts with anthracenes both at 1,4- and 9,10-positions. The results (Table 2) show that when electron-donating groups are introduced into the terminal rings (entry 4-6, Table 2) or the center ring carries electron-withdrawing groups (entry 8 and 9, Table 2) or bulky groups (entry 9 and 10, Table 2), the ratio of 1,4-cycloadduct/9,10-cycloadduct is increased. However, no anthracene substrate gives the 1,4-cycloadduct exclusively. The highest 1,4-cycloadduct/9,10-cycloadduct ratio is found in the reaction employing 9,10-diphenylanthracene (entry 10, Table 2).

Instead of using two phenyl groups, Nikitin *et al.*[29] used ferrocenyl groups to control the regioselectivity in the Diels-Alder reaction of anthracenes. The reactions of 9-ferrocenylanthracene (56) with benzoquinone, *N*-methyl maleimide, *N*-phenyl maleimide, DMAD, 4,5-dimethylbenzyne (57), benzyne (52) give exclusively 9,10-cycloadducts, for example, the compound **58**. In contrast, with tetrafluorobenzyne (59) as dienophile 9-ferrocenylanthracene gives **60** and **61** as an equimolar mixture of 9,10- and 1,4-cycloadducts (Scheme 11). The exclusive 1,4-cycloaddition can be achieved when the second ferrocenyl group is introduced to the 10-position such as **62**, but the reactivity of **62** is significantly diminished. DMAD and 3-trifluoromethylbenzyne (64) react exclusively at the 1,4-positions of 9,10-diferrocenylanthracene, while benzyne (52) and 3-fluorobenzyne (67) undergo 9,10-cycloaddition (Scheme 12). *N*-methyl maleimide gives a mixture of 1,4- and 9,10-cycloadducts.



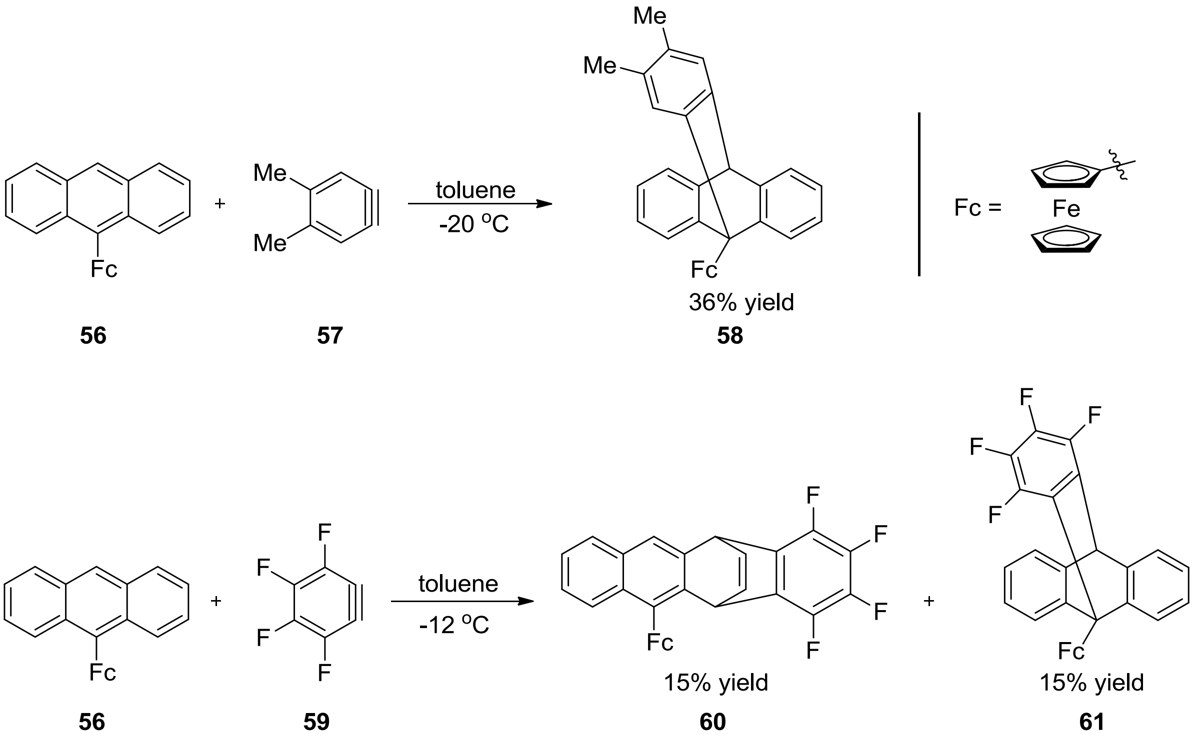
Scheme 10. 1,4-cycloadducts in the Diels-Alder reaction of 9,10-diphenylanthracene (47)

Table 2. The reactivity of benzyne toward anthracenes

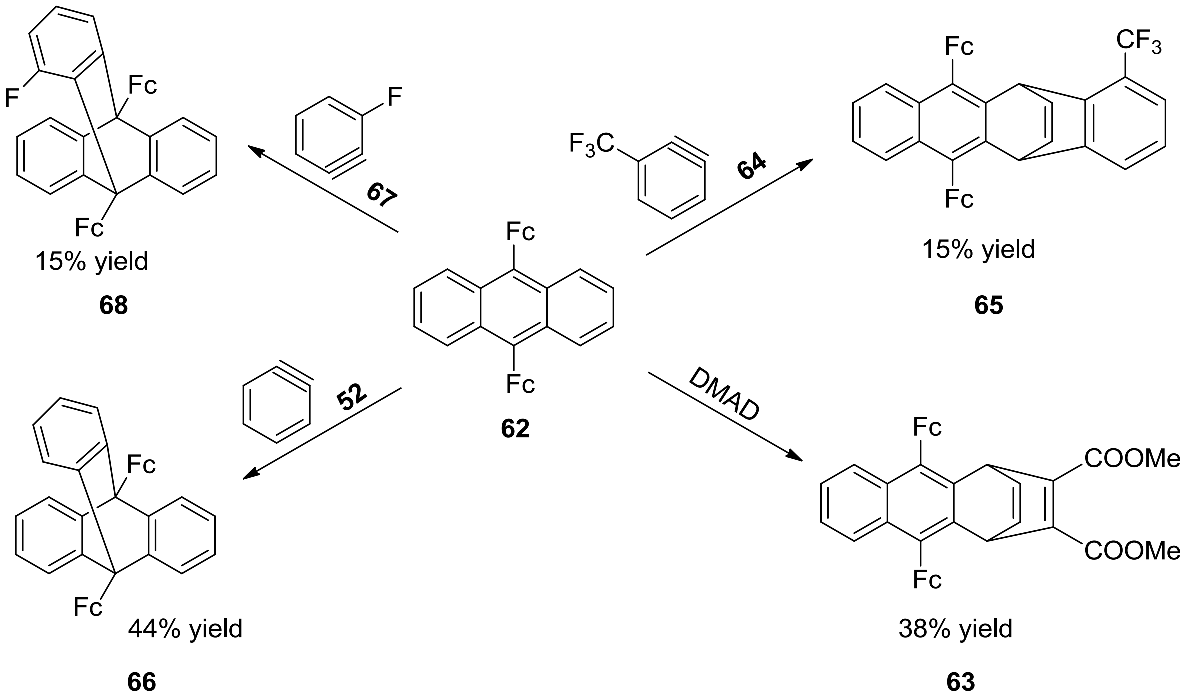


entry	anthracene substrate	9,10-cycloadduct/1,4-cycloadduct
1	9,10-Dimethylanthracene	~200
2	9-Methylanthracene	~70
3	9,10-Dimethoxyanthracene	28
4	1,4-Dimethylanthracene	13.0

entry	anthracene substrate	9,10-cycloadduct/1,4-cycloadduct
5	2,6-Dimethylanthrancene	14.0
6	1,4-Dimethoxyanthracene	2.5
7	Anthracene	30
8	9-Cyanoanthracene	3.7
9	9-Nitroanthracene	4.3
10	9,10-Diphenylanthracene	0.08
11	9,10-dicyanoanthracene	1.0



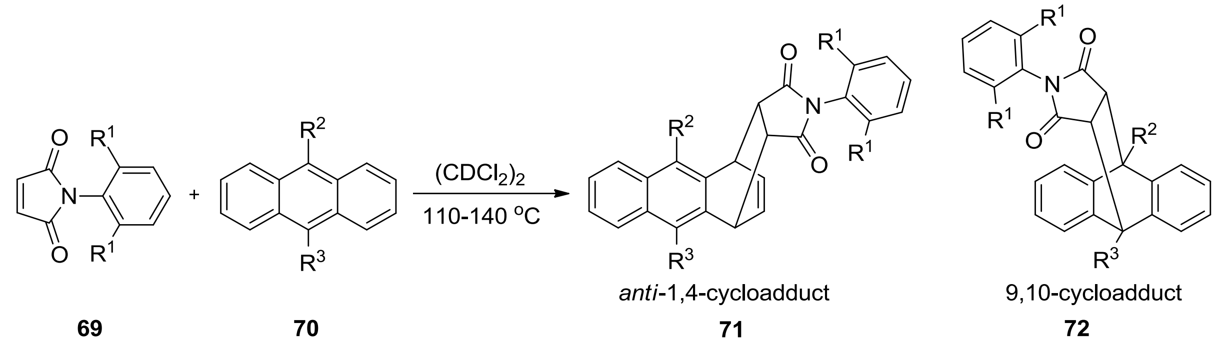
Scheme 11. The cycloaddition of 9-ferrocenylanthracene

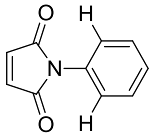
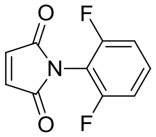
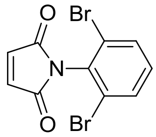
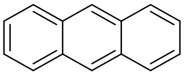
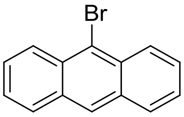
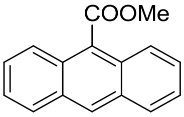
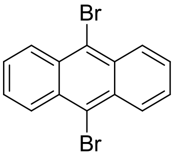
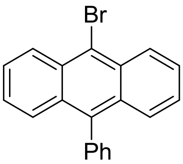
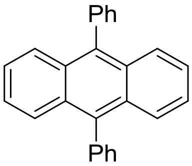


Scheme 12. The cycloaddition of 9,10-diferrocenylanthracene

Recently, Ma *et al.*[30] used maleimide with a bulky group on the nitrogen atom to obtain 1,4-cycloadducts. The strong steric interactions between bulky dienophiles **69** and bulky dienes **70** suppress the 9,10-cycloaddition in favor for the *anti*-1,4-cycloaddition. The results in Table 3 show that *N*-phenylmaleimides bearing bulky substituents at the *ortho*-position and again anthracenes carrying two bulky substituents at 9,10-positions would give the highest 1,4-cycloadduct/9,10-cycloadduct ratio. Because of the steric effect, only *anti*-1,4-cycloadducts are found. The authors also mentioned that electron-withdrawing groups on the center ring motivate the reaction to give 1,4-cycloadducts, but steric effects are always the dominating factor in giving the highest 1,4-cycloadduct/9,10-cycloadduct ratio.

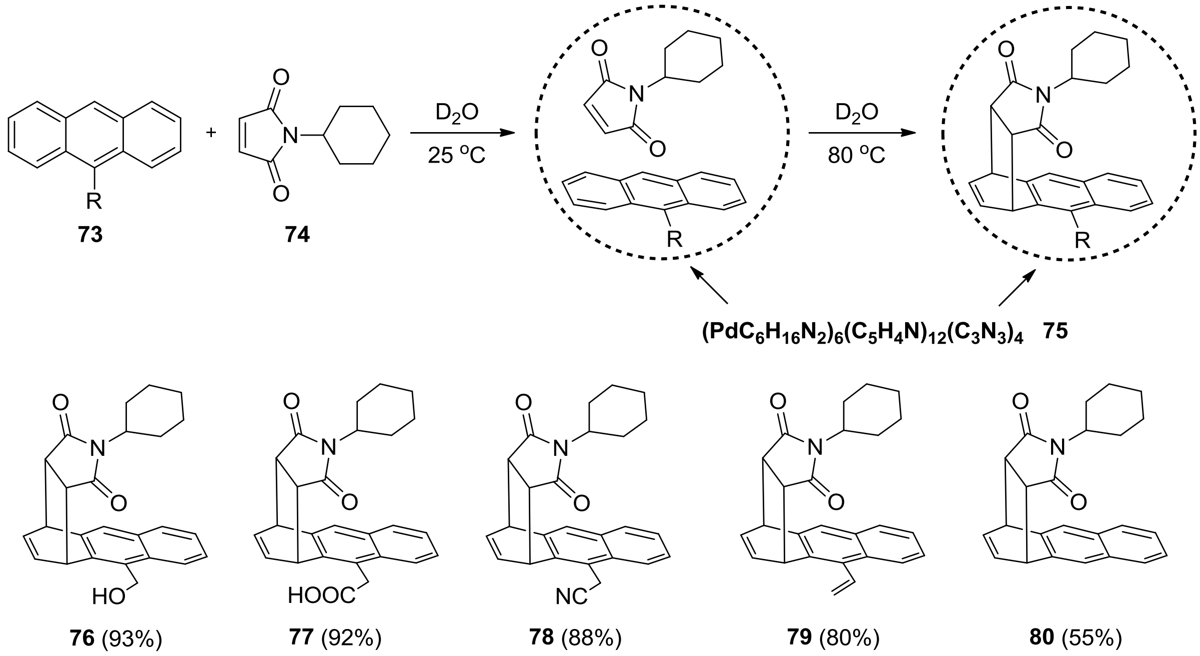
Table 3. Diels-Alder reactions between different steric *N*-phenylmaleimides **69** and anthracenes **70**



entry	anthracene substrate	*anti*-1,4-cycloadduct / 9,10-cycloadduct		
				
1		0 : 100	2 : 98	13 : 87
2		0 : 100	6 : 94	26 : 74
3		1 : 99	23 : 77	59 : 41
4		2 : 98	28 : 72	67 : 23
5		43 : 57	88 : 12	100 : 0
6		93 : 7	100 : 0	100 : 0

1.2.2. Using molecular host to obtain 1,4-cycloadducts of anthracenes

In 2006, the Fujita group[31] designed the molecular host **75** which could catalyze Diels-Alder reactions of anthracenes **73** with *N*-cyclohexylmaleimide (74) in water to afford 1,4-cycloadducts. Because of the limited space of the cavity in the molecular host **75**, *N*-cyclohexylmaleimide (74) has to locate near the terminal ring (1,4-positions), explaining that only *syn*-1,4-cycloadducts are formed (Scheme 13) regardless of the higher π-electron density at the center ring. As we have seen before, the introduction of substituents at 9- and/or 10-position of the anthracene framework would lead to the 1,4-cycloadduct at high yields, thereby producing of **76**, **77**, **78**, and **79** at high yields. Although the 1,4-cycloadduct **80** is formed in moderate yield (55%), up to now, it is the highest yield for the 1,4-cycloaddition of 9,10-unsubstitued-anthracenes. The bulkiness of the substituent on the nitrogen atom of maleimide is the key factor for the 1,4-cycloaddition. When the cyclohexyl group in *N*-cyclohexylmaleimide is replaced by a phenyl group, only 9,10-cycloadducts are formed.



73 **74**

76 (93%) **77** (92%) **78** (88%) **79** (80%) **80** (55%)

Scheme 13. Diels-Alder reactions of anthracenes within the molecular host leading to *syn*-1,4-cycloadducts

Conclusion: The Diels-Alder reaction proceeds with the high stereoselectivity via a *syn*-cycloaddition (*cis*-principle) as a result of the concerted reaction mechanism, and this reaction preferentially produces the *endo*-cycloadduct (*endo*-rule) as a result of secondary orbital interactions. The rate and the regioselectivity are controlled by frontier molecular orbitals of reactants. In anthracenes, the π-electrons concentrate at the center ring (the highest coefficients of frontier molecular orbital are at the 9- and 10-positions), which induces the 9,10-cycloaddition instead of the 1,4-cycloaddition. There are, however, two ways to obtain 1,4-cycloadducts: a) introducing bulky groups at the 9- and/or 10-position of the anthracene ring; b) using a molecular host to make dienophiles locate near the terminal ring so that the 1,4-cycloaddition can happen.

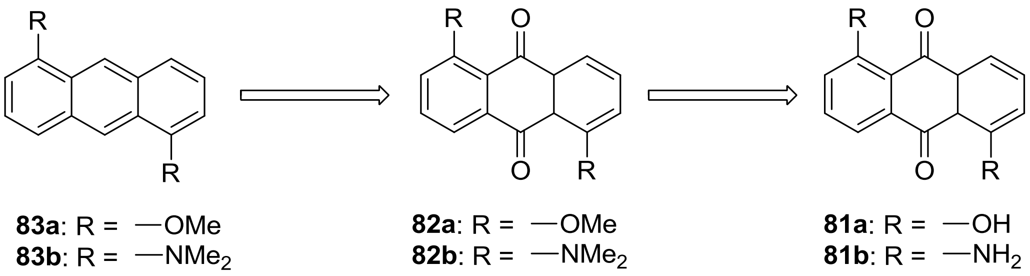
2. Aim of the work

As we have seen so far, the 1,4-cycloadduct/9,10-cycloadduct ratio can be adjusted by introducing either electron-withdrawing groups or bulky groups to the 9- and/or 10-position of anthracenes and the latter always leads to the highest 1,4-cycloadduct/9,10-cycloadduct ratio. Entry 4, 5, and 6 in Table 2 show that when electron-donating groups are introduced to the terminal rings, the amount of 1,4-cycloadduct is increased but not so high. The formation of both 1,4- and 9,10-cycloadducts leads to difficulties in separating of cycloadducts[32]. Until now, we have seen that introducing bulky substituents on the center ring besides using a molecular host is the key factor to get the exclusive 1,4-cycloadduct. We wonder how much the amount of the 1,4-cycloadduct is formed when the terminal rings are introduced stronger electron-donating groups, i.e. *N*,*N*-dialkylamino groups. Can these strongly electron-donating groups on the terminal rings of anthracenes promote the creation of the 1,4-cycloadduct exclusively?

The aim of this work is to investigate the Diels-Alder reaction of 1,5-bis(*N*,*N*-dimethylamino)anthracene and 1,5-bis(pyrrolidin-1-yl)anthracene which are synthesized from the available compound, i.e. 1,5-diamino-9,10-anthraquinone.

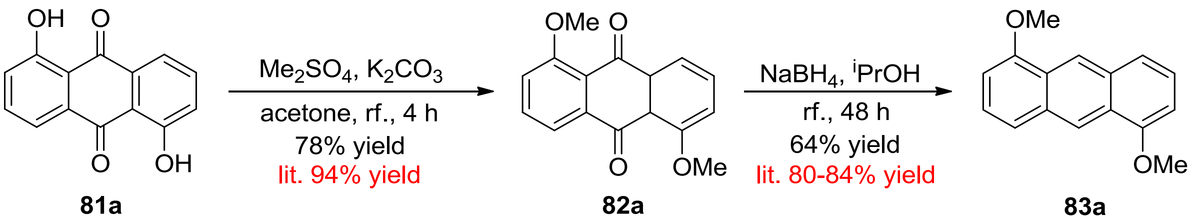
3. Synthesis of starting materials

The retrosynthesis of starting materials 1,5-dimethoxyanthracene (83a) and 1,5-bis(dimethylamino)anthracene (83b) is shown in Scheme 14.



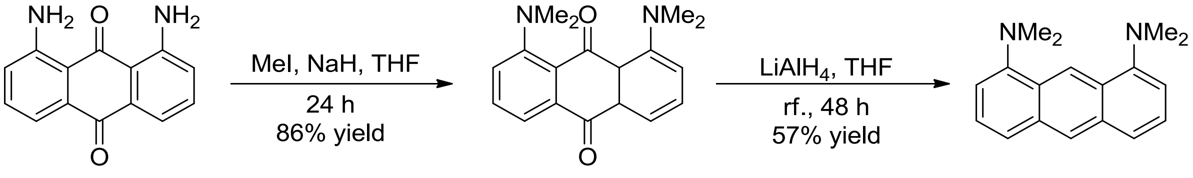
Scheme 14. The retrosynthesis of starting materials (83a) and (83b)

1,5-dihydroxy-9,10-anthraquinone (81a) was converted into 1,5-dimethoxy-9,10-anthraquinone (82a) in 78% yield by using dimethyl sulfate in acetone in the present of K_2CO_3 (Scheme 15).[33] The reductive aromatization of (82a) was accomplished by treatment with an excess amount of sodium borohydride in refluxing isopropanol for two days to afford (83a) in 64% yield (Scheme 15).[34]



Scheme 15. The preparation of 1,5-dimethoxyanthracene

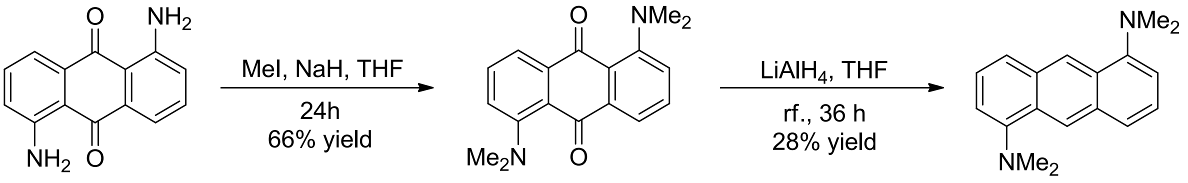
1,8-bis(dimethylamino)anthracene (86) was synthesized in 49% yield over two steps (Scheme 16)[35], so the same procedure was applied to synthesize 1,5-bis(dimethylamino)anthracene (83b).



84 **85** **86**

Scheme 16. The synthesis of 1,8-bis(dimethylamino)anthracene

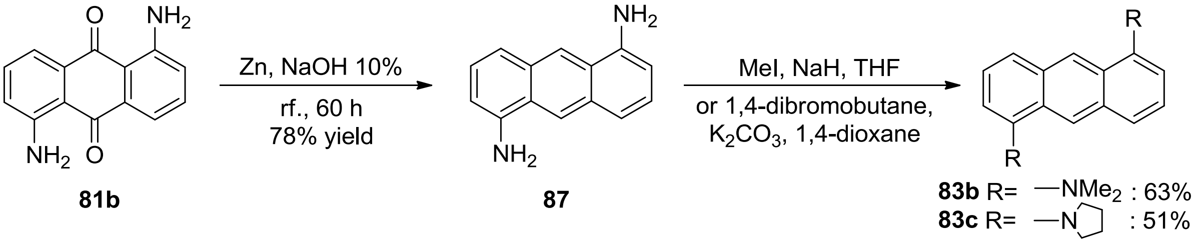
The methylation of 1,5-diamino-9,10-anthraquinone (81b) with methyl iodide and sodium hydride in THF afforded 1,5-bis(dimethylamino)-9,10-anthraquinone (82b) in 66% yield. However, the reduction of (82b) gave 1,5-bis(dimethylamino)anthracene (83b) in 28% yield (Scheme 17) due to the steric hindrance of dimethylamino groups.



81b **82b** **83b**

Scheme 17. The synthesis of 1,5-bis(dimethylamino)anthracene

A modified procedure was suggested to obtain (83b) in a higher yield. To avoid the steric hindrance of dimethylamino group in the reduction step, (81b) was reduced to 1,5-diaminoanthracene (87) in 78% yield[36] and then the 1,5-diaminoanthracene was methylated to give (83b) in 63% yield (Scheme 18). The analogous compound 1,5-bis(pyrrolidin-1-yl)anthracene (83c) was similarly synthesized in 51% yield (Scheme 18).



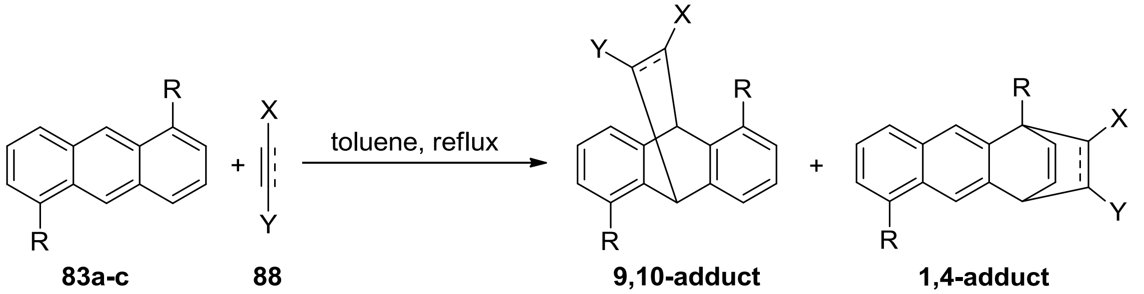
81b **87**

Scheme 18. The synthesis of 1,5-bis(dialkylamino)anthracenes

4. The Diels-Alder reaction of anthracenes (83a-c)

These three anthracene compounds (83a-c) were employed in Diels-Alder reactions with such dienophiles as dimethyl acetylenedicarboxylate (DMAD, 88a), methyl phenylpropiolate (88b), dimethyl fumarate (88c), and maleic anhydride (88d) (Table 4), however, in all cases, 9,10-cycloadducts were formed exclusively except DMAD. A mixture of 1,4- and 9,10-cycloadducts (**91a** / **92a** = 10 : 1, Scheme 19) was observed in the reaction of DMAD and 1,5-dimethoxyanthrancene (81a). With the dimethylamino substituted anthracene (83b), the 1,4-cycloadduct **94a** became the major product (**93a** / **94a** = 1 : 2.4, Scheme 19). Steglich *et al.*[37] demonstrated that 4-pyrrolidinopyridine is more nucleophilic than dimethylaminopyridine (DMAP) due to the reduced steric demand of the pyrrolidine group resulting in a more efficient orbital interaction of the lone pair on nitrogen with the pyridine moiety. Following the lead of Steglich *et al.*, the anthracene (83c), which was assumed that the electron density in the terminal rings would be further increased, was next investigated. We were pleased to find that the reaction between (83c) and DMAD indeed yielded the 1,4-cycloadduct **96a** exclusively (Scheme 19).

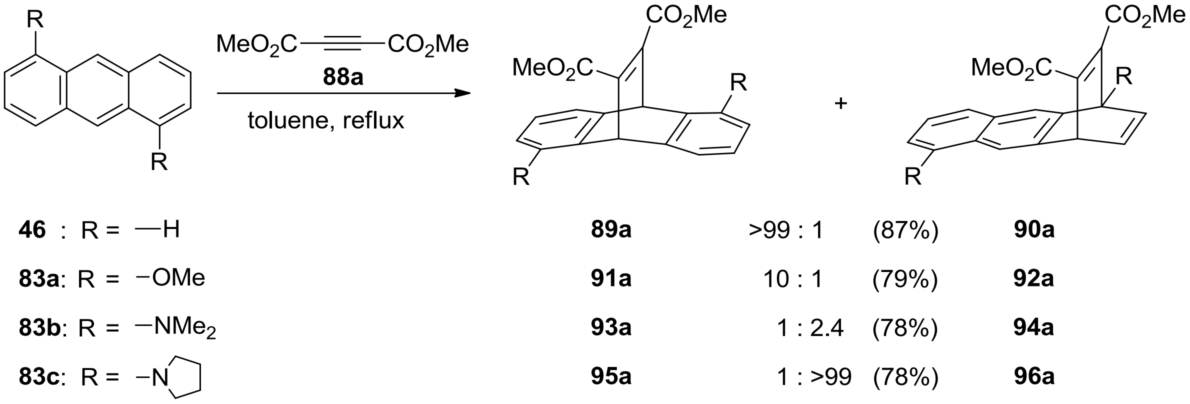
Table 4. The Diels-Alder reactions of 9,10-unsubstituted anthracenes



entry	diene	dienophile	time	temp. (°C)	yield[a] (%)	ratio of 9,10-adduct / 1,4-adduct[b]
1	Anthracene	(88a)	24h	reflux	87	100 : 0, **89a** / **90a**
2	**83a**	(88a)	48h	reflux	79	10 : 1.0; **91a** / **92a**

entry	diene	dienophile	time	temp. (°C)	yield[a] (%)	ratio of 9,10-adduct / 1,4-adduct[b]
3	**83b**	(88a)	24h	reflux	78	1.0 : 2.38; **93a** / **94a**
			24h	80	19[b]	1.0 : 2.54; **93a** / **94a**
4	**83b**	(88b)	72h	reflux	19	100 : 0; **93b** / **94b**
5	**83b**	(88c)	24h	reflux	78	100 : 0; **93c** / **94c**
6	**83b**	(88d)	0.5h	reflux	88	100 : 0; **93d** / **94d**
7	**83c**	(88a)	24h	reflux	78	1 : >99; **95a** / **96a**
8	**83c**	(88b)	72h	reflux	23	100 : 0; **95b** / **96b**
9	**83c**	(88c)	24h	reflux	86	100 : 0; **95c** / **96c**
10	**83c**	(88d)	0.5h	reflux	75	100 : 0; **95d** / **96d**

Reactions were carried out with 200 mg of diene and 1.1 equiv. of dienophile in toluene (0.5M) in seal tubes at 150 °C. [a] Isolated yield. [b] determined by ^{1}H NMR integration



46 : R = —H	**89a**	>99 : 1	(87%)	**90a**
83a: R = −OMe	**91a**	10 : 1	(79%)	**92a**
83b: R = $-NMe_2$	**93a**	1 : 2.4	(78%)	**94a**
83c: R = −N	**95a**	1 : >99	(78%)	**96a**

Scheme 19. The effect of electron-donating groups on the regioselectivity

The structures of **92a, 94a, 96a** were assigned by NMR spectroscopic experiments and were confirmed by the single crystal X-ray diffraction analysis (Figure 4).

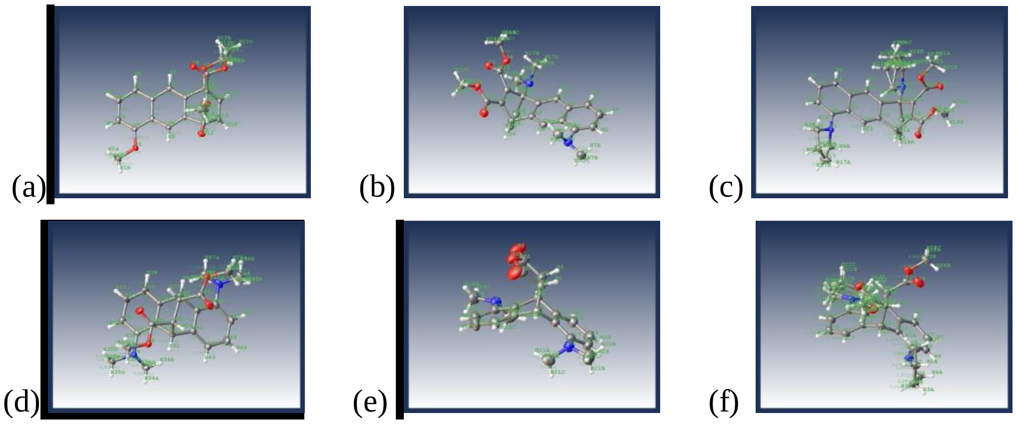
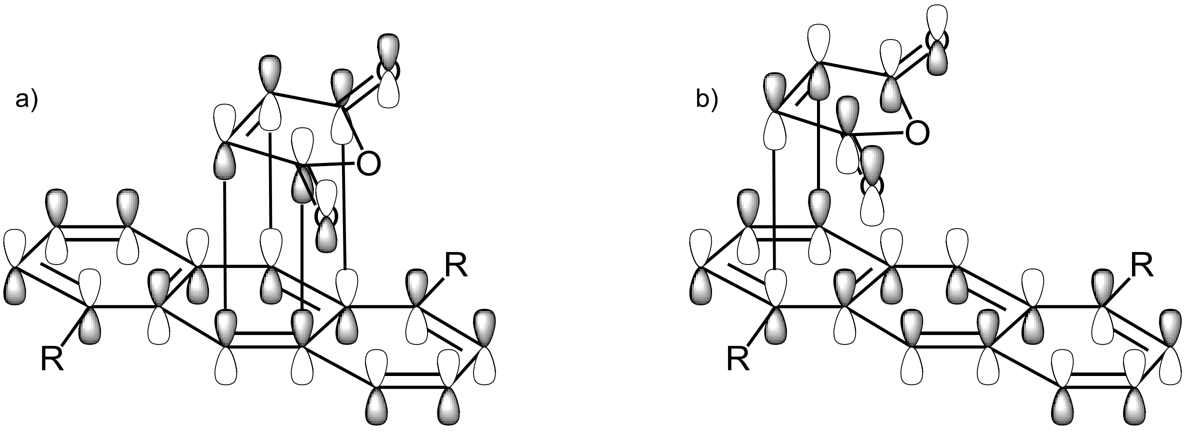


Figure 4. Crystal structure of (a) **92a**, (b) **94a**, (c) **96a**, (d) ***cis*-93c**, (e) **93d**, (f) ***trans*-95c**

Under reflux condition with toluene for 24 hours or in a microwave oven at 163 ^{o}C for 1h, the 9,10-cycloadduct **93a** did not cross over to the 1,4-cycloadduct **94a** and vice versa. Entry 3 in Table 4 showed that the reaction temperature gave no significant change in the ratio of 1,4- and 9,10-cycloadducts. So 1,4- and 9,10-cycloadducts are both kinetically and thermodynamically preferred in the current reaction condition.

Explanation the 1,4-cycloaddition of anthracenes (83a-c) and DMAD

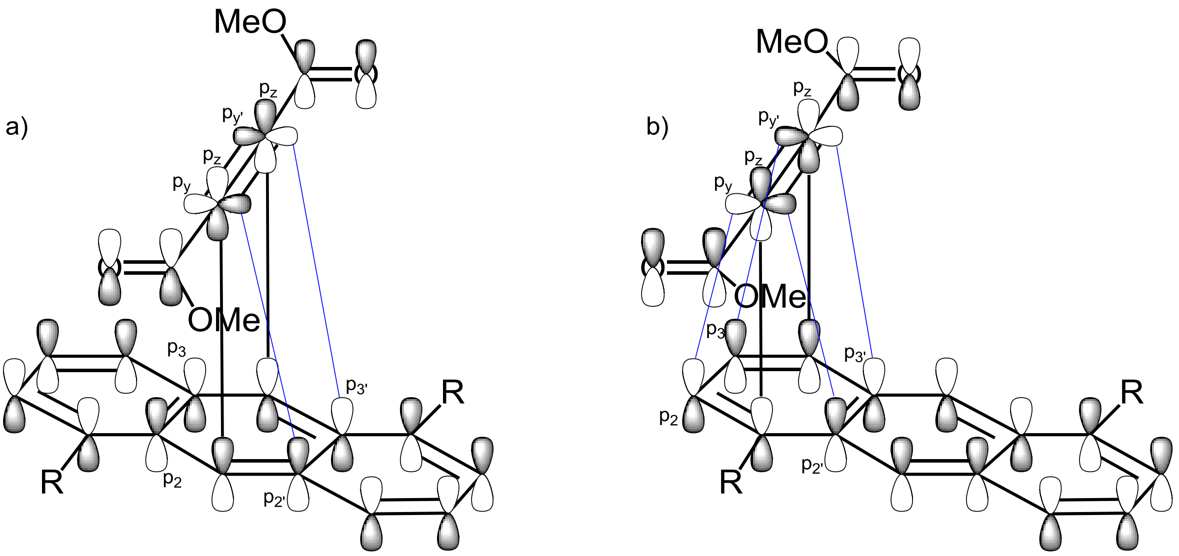
The orbital coefficients of the HOMO of (83b) predicted that the 9,10-attack is still preferred. Dienophiles have double bond such as (88c) and (88d) have to approach the anthracene rings in the way that the double bond plane of dienophiles is parallel to the anthracene plane. When these dienophiles react with the anthracenes at 9,10-positions, the secondary orbital interaction will assist the construction of the second phenyl ring and to form the 9,10-cycloadduct (Figure 5a). This interaction does not exist when these dienophiles react at 1,4-positions (Figure 5b). Therefore, the 9,10-cycloaddition is still preferred with dienophiles (88c) and (88d). Dienophiles have triple bond such as benzynes should approach the anthracene ring perpendicularly to reduce the steric interaction between the substituents on dienophiles and the anthracene ring. However, DMAD can approach the anthracene ring parallel or perpendicularly to the plane of anthracene ring so that the steric interaction between its substitutions and the anthracene ring is minimized. In Figure 6b, when DMAD reacts with anthracenes at 1,4-positions, the secondary orbital interactions between p_y and p_2, $p_{2'}$ and between $p_{y'}$ and p_3, $p_{3'}$ are developed on both sides. In contrast, when DMAD reacts with anthracenes at 9,10-positions, the secondary orbital interactions between p_y and p_2, $p_{2'}$ and between $p_{y'}$ and p_3, $p_{3'}$ are developed on one side and are canceled on the other side (Figure 6a). Therefore, when there is an electron-donating group on the terminal ring of anthracenes, the 1,4-cycloadduct can be formed and the stronger the electron-donating group (pyrrolidin-1-yl>dimethylamino>methoxy≫hydrogen) on the terminal ring, the more amount of the 1,4-adduct is formed as shown in Scheme 19. However, when the volume of dienophiles increases from DMAD to methyl 3-phenylpropiolate (88b), the 9,10-cycloadduct will be preferred (entry 3 vs. entry 4 and entry 7 vs. entry 8 in Table 4) and the yield is dropped because this dienophile is less electrophilic and more steric than DMAD.



a) secondary orbital interactions when (88d) reacts with anthracenes at 9,10-positions

b) there is no net secondary orbital interactions when (88d) reacts with anthracenes at 1,4-positions

Figure 5. Orbital interactions between anhydride maleic acid and anthracenes



a) there is no net secondary orbital interactions when DMAD reacts with anthracenes at 9,10-positions

b) secondary orbital interactions when DMAD reacts with anthracene at 1,4-positions

Figure 6. Orbital interactions in the Diels-Alder reaction between DMAD and anthracenes

Conclusion:

Although the high localization of the π-electron density at the center ring, the formation of an adduct bridging the terminal ring (1,4-cycloadduct) of anthracenes occurs with a) anthracenes have strong electron-donating groups on terminal rings. The stronger the electron-donating group on the terminal ring, the higher the 1,4-cycloadduct/9,10-cycloadduct ratio; b) small highly reactive dienophiles have a triple bond, for example, benzynes or DMAD.

DMAD reacted with anthracene (83c) gave exclusively 1,4-cycloadduct in 78% yield. It is the highest yield, up to now, for the 1,4-cycloadditon of 9,10-unsubstituted anthracenes.

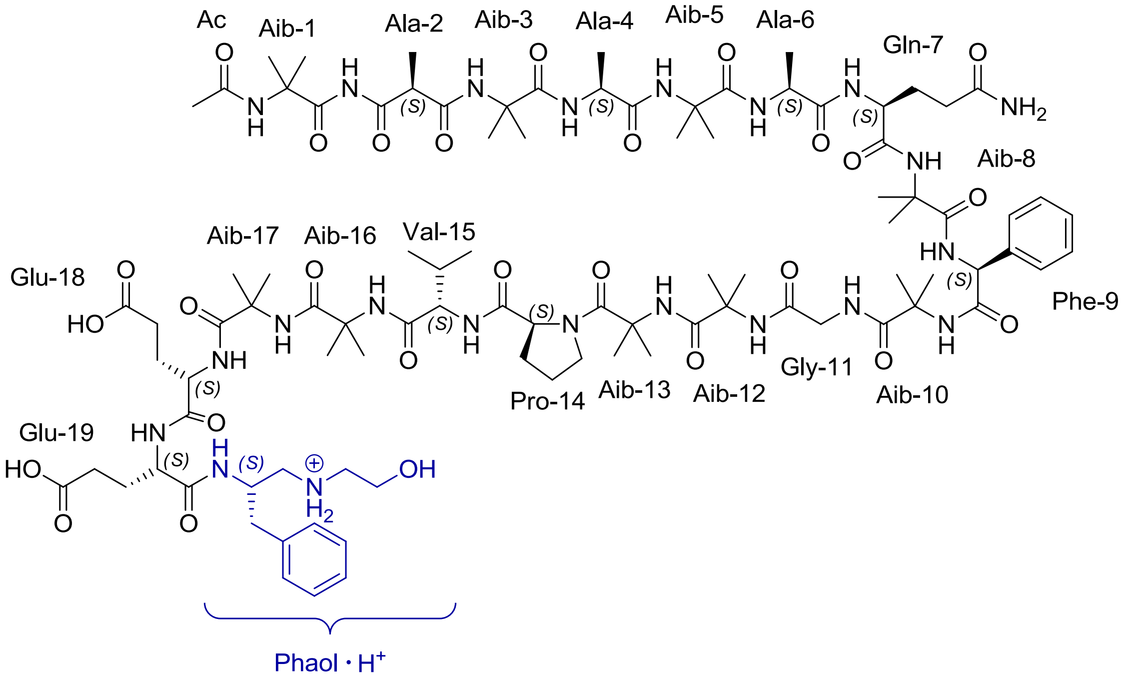
Part II:

A Practical Method for the Synthesis of Chiral Diamino Alcohols

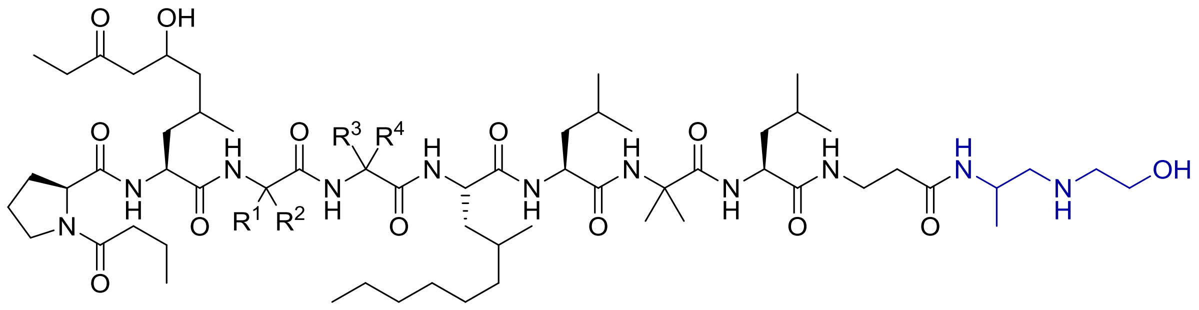
5. A practical method for the synthesis of chiral diamino alcohols

5.1. Introduction

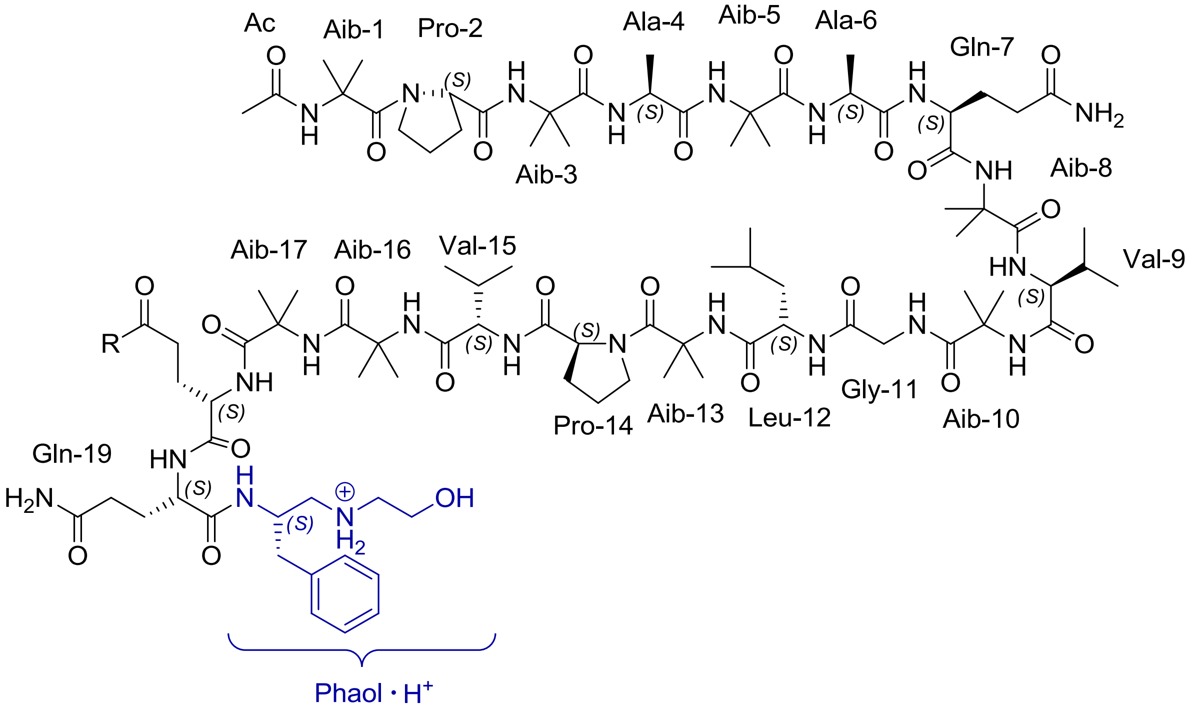
Diamino alcohols are present at the *C*-terminus of some peptaibols which are short polypeptides containing a large amount of the marker *α*-aminoisobutyric acid (Aib), for example, Aibellin, Culicinin A-D, Septocylindrin A and Septocylindrin B (Figure 7).[38] Peptaibols possess interesting biological activities such as antibacterial, antifungal, antiviral, and antitumor activities, but the synthesis of peptaibols has not been so efficient. One of the reasons which have impeded the progress in the synthesis of peptaibols is the inefficient (low yields and using an excess amount of reagents) and the irreproducible synthesis of diamino alcohols **100** (Figure 8) present in peptaibols. There are a few reports on the synthesis of the diamino alcohols **100**. The diamino alcohols **100** are synthesized by the reduction of dipeptides or the coupling of two amino alcohols.



Aibellin (97)

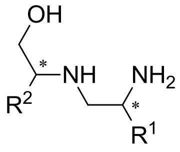


$R^1 = R^3 = H$, $R^2 = R^4 = Me$: **Culicinin A (98a)**
$R^1 = R^2 = R^3 = Me$, $R^4 = H$: **Culicinin B (98b)**
R =H, $R^2 = R^3 = R^4 = Me$: **Culicinin C (98c)**
$R^1 = R^2 = R^3 = R^4 = Me$: **Culicinin D (98d)**



R = OH : **Septocylindrin A (99a)**
R = NH_2 : **Septocylindrin B (99b)**

Figure 7. Some peptaibols having a diamino alcohol at *C*-terminus

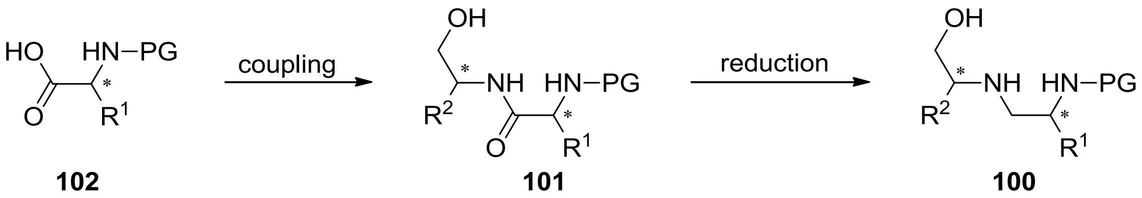


100

Figure 8. General structure of diamino alcohols in peptaibols

5.1.1. Synthesis of diamino alcohols by the reduction of dipeptides

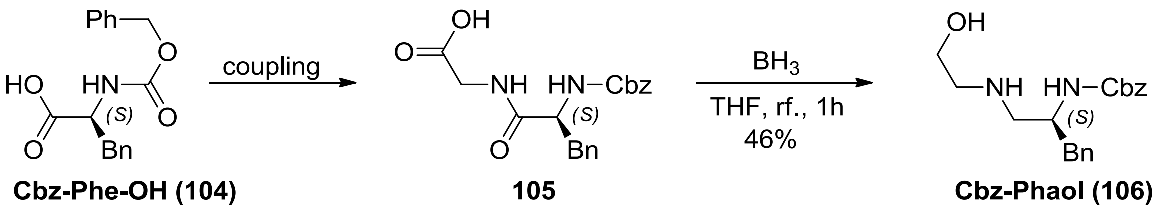
In this route, the dipeptides **101** which are formed by the coupling of two amino acids are reduced to yield the diamino alcohols **100** (Scheme 20).



Scheme 20. The synthesis of the diamino alcohols **100** by the reduction of dipeptides

Phaol (103), 2-(2-amino-3-phenylpropylamino)ethanol, is the *C*-terminal amino alcohol residue found in such peptaibols as Aibellin, Septocylindrin A and Septocylindrin B (Figure 7). This diamino alcohol is considered as a reduced form of dipeptide Phe-Gly-OH.

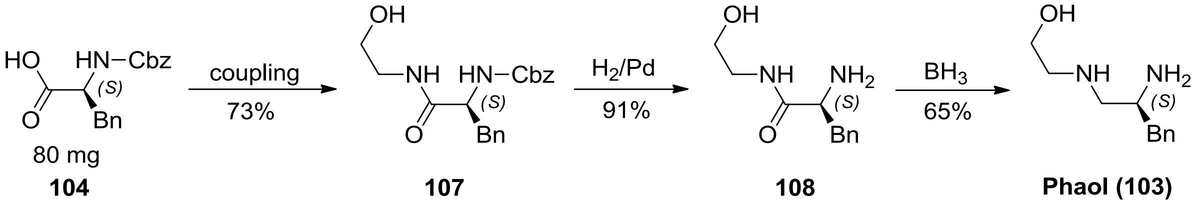
On the synthesizing a tripeptide for the inhibition of the angiotensin-converting enzyme, Almquist *et al.*[39] used BH_3 to reduce the amide group of the dipeptide **105** prepared by the coupling of glycine and Cbz-Phe-OH (104). They obtained Cbz-Phaol (106) in 46% yield (Scheme 21).



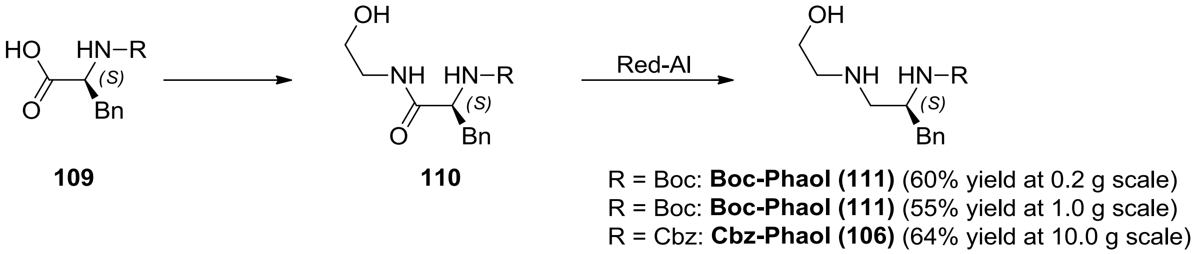
Scheme 21. The synthesis of Cbz-Phaol using borane BH_3

Kumazawa *et al.*[40] reported the synthesis of Phaol which is similar to Almquist's. They coupled (104) with ethanolamine to form Cbz-Phe-ethanolamine **107**. After removing the Cbz protecting group of **107**, they also used BH_3 to reduced amide group to give (103) in

43% yield over three steps (Scheme 22). However, later Borggraeve *et al.*[41] could not achieve the yield (65%) as reported by Kumazawa in the reduction step although they carried out the reaction at the same scale (80 mg). Therefore, instead of using BH_3, they used sodium bis(2-methoxyethoxy)aluminum hydride solution (Red-Al) which was introduced by Voight *et al.*[42] in the reduction step (Scheme 23). They also found that the preparation of Cbz-Phaol (106) is easier than that of Boc-Phaol (111) on a large scale (1.0 g) because (106) can be purified by the recrystallization. Nonetheless, the reaction time in the reduction step must be optimized.

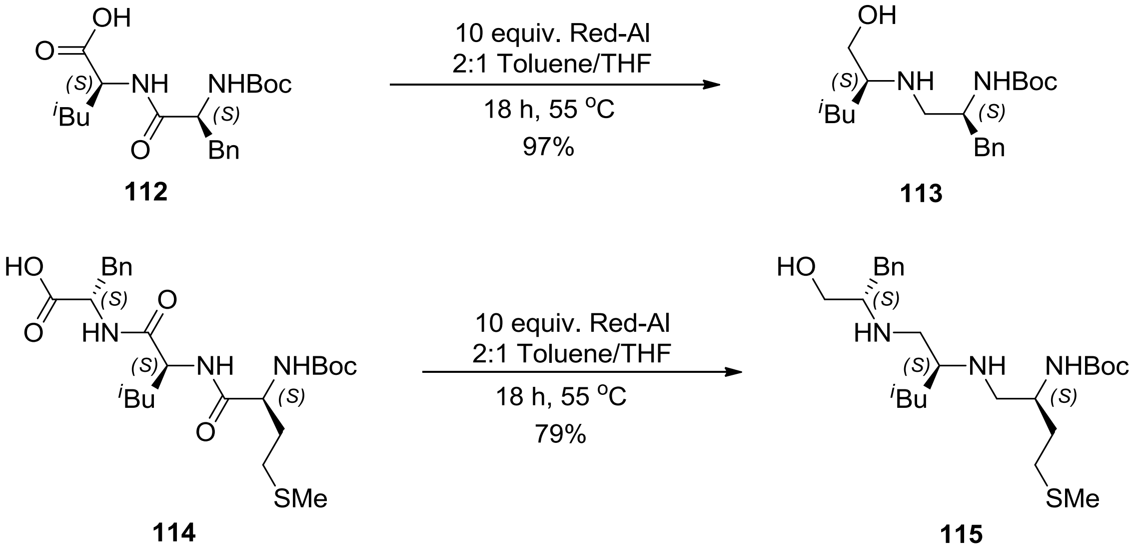


Scheme 22. The synthesis of Phaol according to Kumazawa *et al.*

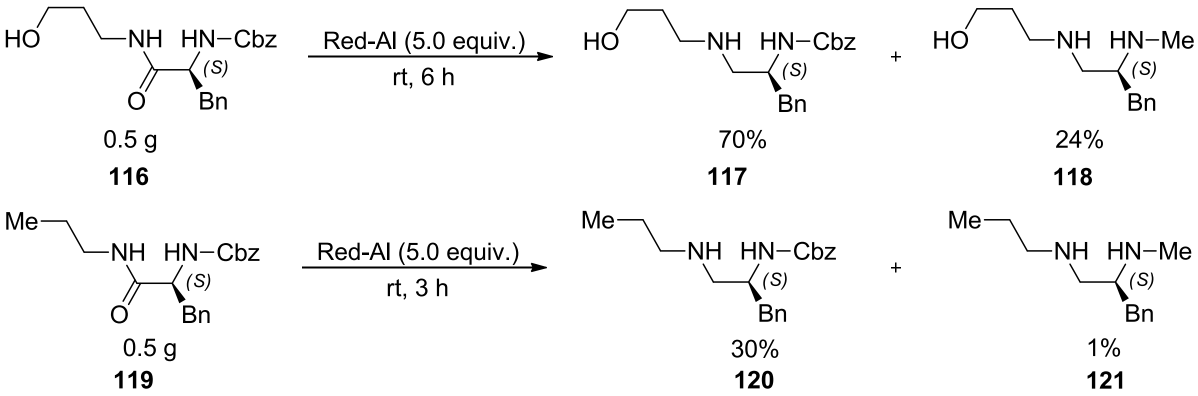


Scheme 23. The synthesis of *N*-protected Phaol via Red-Al

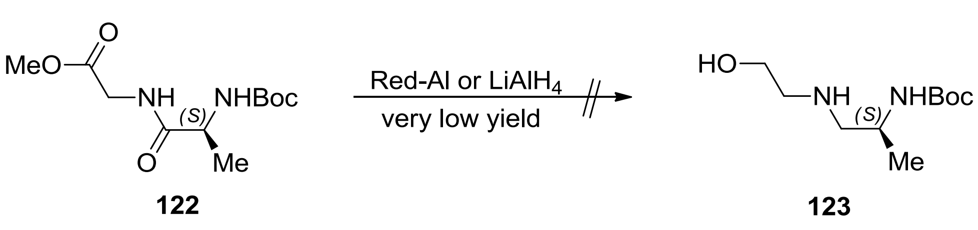
Red-Al can also reduce the dipeptide **112** and the tripeptide **114** into amino alcohols **113** and **115**, respectively (Scheme 24).[42] According to Voight *et al.*, in contrast to $LiAlH_4$ which usually reduces the carbamate in Boc or Cbz group, Red-Al reduces only the amide and carboxylic acid with no evidence of carbamate reduction. Nevertheless, Borggraeve *et al.* found that amide groups and carbamate groups were reduced simultaneously on preparing Phaol analog **117** and **120** (Scheme 25).[41] They showed that the by-products are depressed when reactions are carried out at room temperature and short reaction time, but the yields are still so low. Furthermore, Red-Al fails to prepare 2-(2’-aminopropyl)aminoethanol (123) in good yield (Scheme 26).[43]



Scheme 24. The synthesis of di- and triamino alcohols using Red-Al

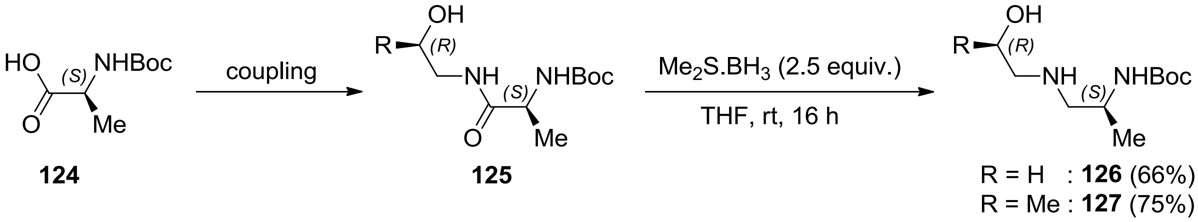


Scheme 25. The unwanted reduction of carbamates with Red-Al



Scheme 26. The unsuccessful preparation of the diamino alcohol **123** from **122**

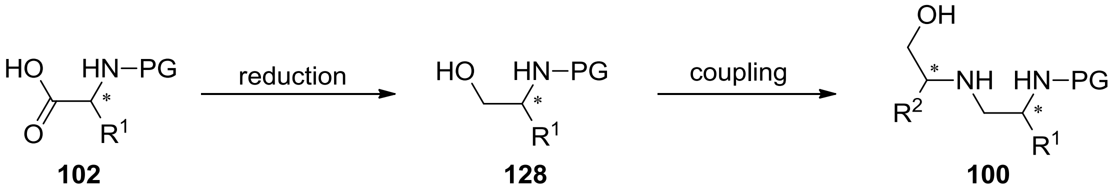
Besides Red-Al, borane-dimethyl sulfide (BH_3.DMS) can also reduce amides to give diamino alcohols.[44] This reagent does not reduce the Boc group in **125** as described in Scheme 27.



Scheme 27. The synthesis of diamino alcohols using borane-dimethyl sulfide

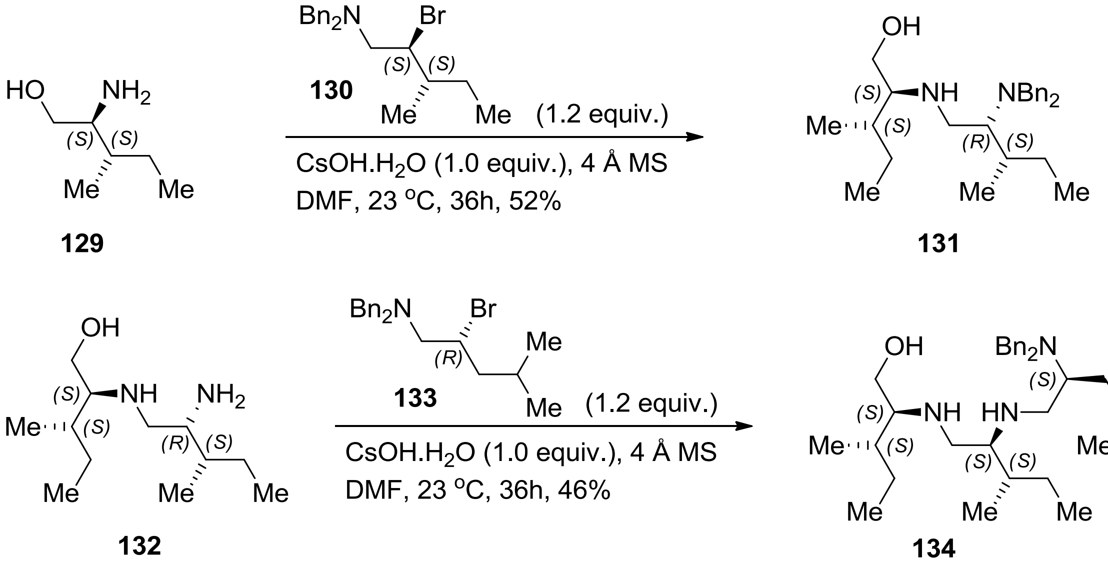
5.1.2. Synthesis of diamino alcohol by the coupling of two amino alcohols

In this approach, the amino alcohol **128** reduced from an amino acid is coupled with another amino alcohol (Scheme 28). In the coupling step, the alcohol group of the first amino alcohol is transformed into such good leaving groups as –OTs and –Hal and then is coupled with other amino alcohols to yield the diamino alcohols **100**.



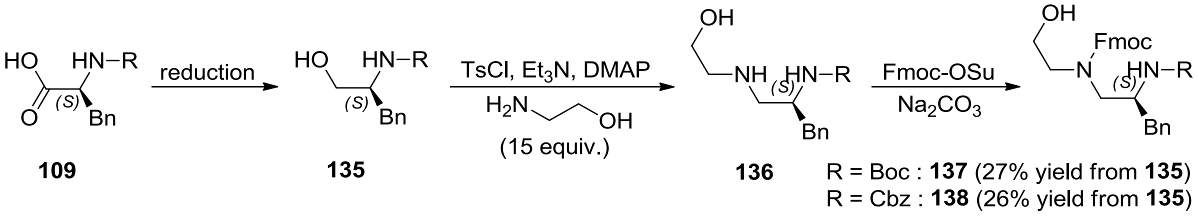
Scheme 28. The synthesis of diamino alcohols by the coupling of two amino alcohols

Cesium hydroxide is an effective base for the mono-*N*-alkylation of primary amine. Cesium ion coordinates with secondary amines so strongly that it is capable of suppressing further alkylations of these secondary amines and consequently they are produced in good yield. For example, cesium hydroxide is used to couple the amino alcohol **129** with the bromide compound **130** to give the diamino alcohol **131** in 52% yield. Cesium hydroxide can also be applied to synthesize the triamino alcohol **134** by coupling the free amino form of **131** with the bromide compound **133** (Scheme 29),[45] which confirms that cesium hydroxide prevents secondary amines from the further alkylation.

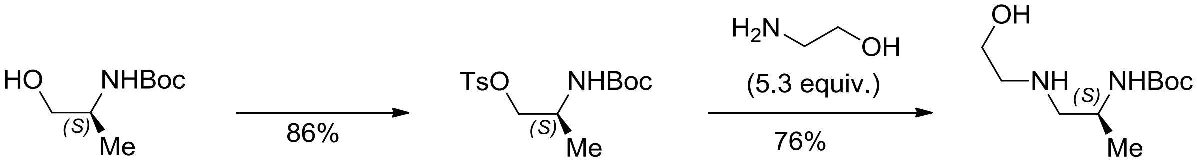


Scheme 29. The synthesis of diamino and triamino alcohols using cesium hydroxide.

Without using cesium hydroxide, Phaol can be synthesized from the *N*-protected amino alcohol **135** but the yield is low (27% yield) and an excess amount of the second amino alcohol (15 equiv.) is required (Scheme 30).[41] However, the synthesis of (123), the *C*-terminal residue of peptaibols Culicinin **A**-**D**, does not need so much amount of the second amino alcohol and is in high yield (Scheme 31).[43] Surprisingly, (123) cannot be prepared in good yield by the reduction of the corresponding dipeptide (Scheme 26).



Scheme 30. The synthesis of Phaol via amino alcohols



139 **140** **123**

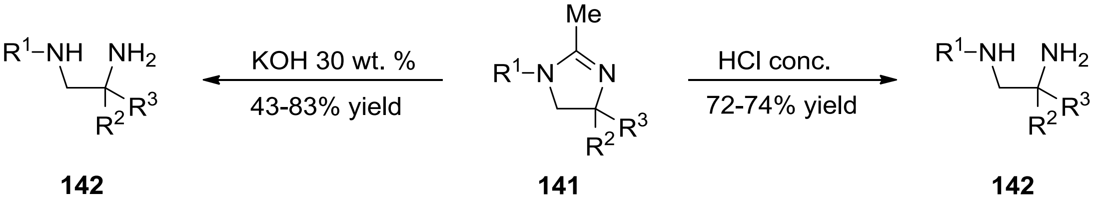
Scheme 31. The synthesis of 2-(2’-aminopropyl)aminoethanol (123) via amino alcohols

Conclusion: There are two ways to get diamino alcohol: a) the reduction of dipeptides and b) the coupling of two amino alcohols. In the reduction of dipeptides, to suppress by-products the reaction condition in the reduction step needs to be optimized such as the reaction time, the reaction temperature and the amount of reductants (an excess amount is usually required). For example, the carbamate group in protecting groups is reduced if more amounts of reductants are used, or the reaction lasts longer than the optimized time, while less amount of reductants or shorter reaction time will make the reduction incomplete. In the coupling of two amino alcohols, the yields of the coupling step are low (the highest yield is achieved with cesium hydroxide, 52% yield in the coupling step) and usually, the excess amount of the second amino alcohol is required (5 to 15 equiv.).

5.2. Aim of the work

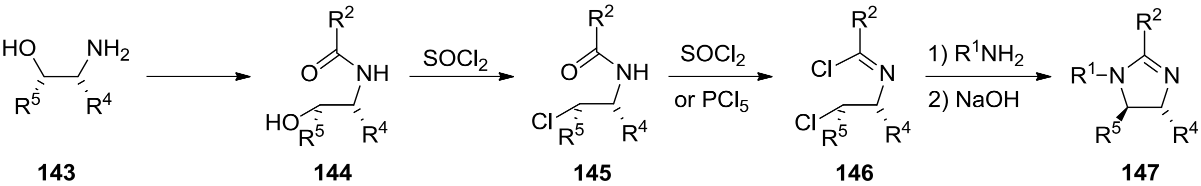
Although there are two ways to synthesize diamino alcohols, there are still some drawbacks, for example, low yields as well as requirements of a large amount of the second amino alcohol and particularly the irreproducibility.

In 1949, Hawkin *et al.*[46] reported the synthesis of diamines **142** via the hydrolysis of 2-imidazolines **141** in acidic or in basic conditions (Scheme 32).



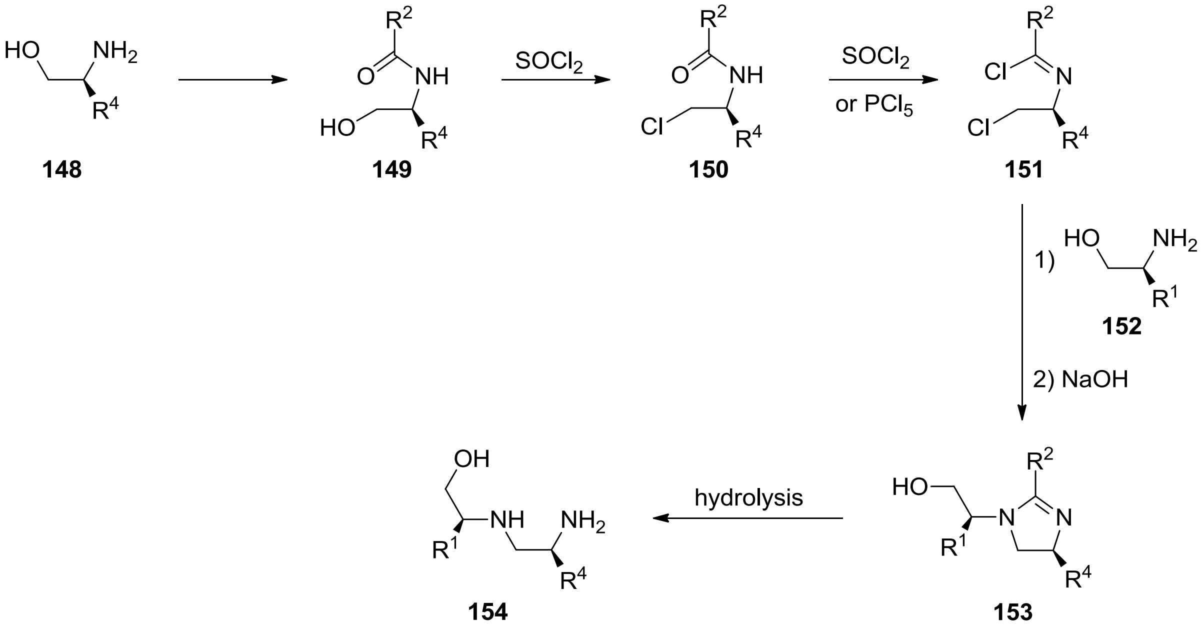
Scheme 32. The hydrolysis of the 2-imidazolines **141** under acidic and basic conditions

In addition to the Hawkin's work, Boland *et al.*[47] described a general method for the preparation of enantiopure 2-imidazolines **147** from amino alcohols **143** (Scheme 33).



Scheme 33. The preparation of enantiopure 2-imidazolines **147** via amino alcohols

We wonder that whether we can obtain 2-imidazolines **153** from the two corresponding diamino alcohols **148** and **152**, and then these 2-imidazolines can be hydrolyzed to give diamino alcohols **154** which can have up to two chiral centers (Scheme 34).



Scheme 34. The preparation of **154** via the hydrolysis of 2-imidazolines **153**

The aim of this work is to find a method for synthesizing diamino alcohols **154** via the hydrolysis of 2-imidazolines **153** and to apply this method for the preparation of Phaol.

5.3. The synthesis of diamino alcohols 154

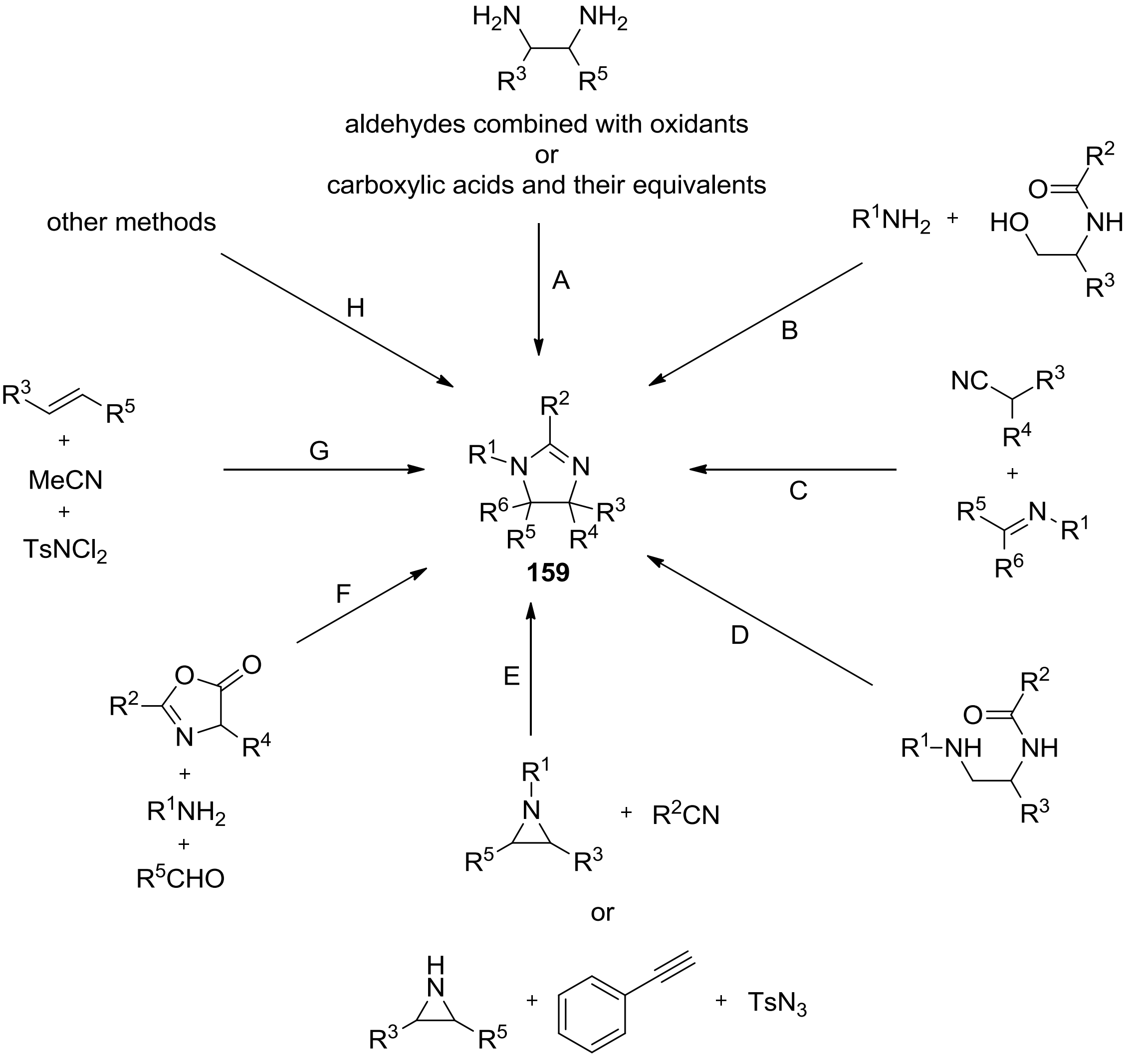
5.3.1. The synthesis of 2-imidazolines

Imidazolines (dihydroimidazoles) which are five-membered heterocycles are classified as 2-imidazolines **155**, 3-imidazolines **156**, or 4-imidazolines **157** depending on the position of the double bond in the ring (Figure 9). 2-Imidazolines are more important than 3- and 4-imidazolines because of many applications in pharmacology[48] and organic syntheses such as ligands[49] and catalysts.[50] Despite many ways to synthesize 2-imidazolines (Scheme 35),[51] only route B (the Boland's method) can afford 2-imidazolines **159** via two diamino alcohols.

2-Imidazoline (155) **3-Imidazoline (156)** **4-Imidazoline (157)** **Imidazolidine (158)**

Figure 9. Classification of imidazolines

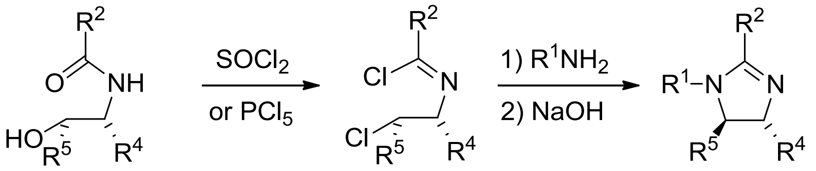
According to the Boland's method, enantiopure hydroxyethyl amides **160** obtained from enantiopure amino alcohols are smoothly converted into chloroethyl imidoyl chlorides **161** by heating to reflux in neat thionyl chloride in one step and then the compounds **161** are reacted with amines to afford 2-imidazolines **155**. The results in Table 5[47] show that the highest yield is obtained when R^2 is the phenyl group (entry 3 and 9, Table 5), so we converted all the amino alcohols **148** to benzamides **162a-c** (Table 6). Because the benzamides **162a-c** were clean enough, they were reacted directly with other amino alcohols to yield 2-imidazolines **163a-j** in good yield (Table 7).



Scheme 35. Different routes to obtain 2-imidazolines **159**

All of the imidazolines **163a-j** were purified by column chromatography on silica gel or by the recrystallization, but the compound **163k** was so easy to undergo the hydrolysis during column chromatography or exposure to air. So, the crude product of the compound **163k** was used for the next step without purification. All of the imidazolines **163a-k** were prepared with the retention of the configuration of chiral carbons in the original amino alcohols and the Boland's method can be applied not only to amines as shown in Table 5 but also to a lot of amino alcohols as presented in Table 7.

Table 5. The preparation of imidazolines **155** from hydroxyethyl amides **160**[47]



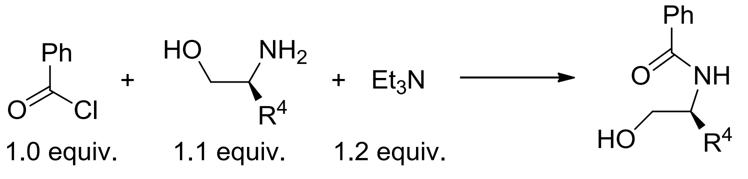
160 **161** **155**

entry	R^1	R^2	R^4	R^5	method[a]	product	yield[b] (%)
1	Tol	Ph	*i*-Pr	H	A	**155a**	63
2	Me	Ph	*i*-Pr	H	A[c]	**155b**	72
3	H	Ph	*i*-Pr	H	A[d]	**155c**	79
4	Tol	$2\text{-FC}_6\text{H}_4$	*i*-Pr	H	A	**155d**	66
5	$4\text{-ClC}_6\text{H}_4$	$2\text{-FC}_6\text{H}_4$	*i*-Pr	H	A	**155e**	71
6	$4\text{-CF}_3\text{C}_6\text{H}_4$	$2\text{-FC}_6\text{H}_4$	*i*-Pr	H	A	**155f**	64
7	Me	$2\text{-FC}_6\text{H}_4$	*i*-Pr	H	A[c]	**155g**	63
8	Tol	Ph	Me	Ph	A	**155h**	60
9	Me	Ph	Ph	H	A	**155i**	76[e]
10	Tol	2-pyridyl	*i*-Pr	H	B	**155j**	74
11	Tol	2-pyridyl	*i*-Bu	H	B	**155k**	43[f]
12	Tol	PhCH_2CH_2	*i*-Pr	H	C	**155l**	47
13	*i*-Pr	Me	Bn	H	C	**155m**	46
14	Tol	H	*i*-Pr	H	C	**155n**	68

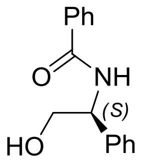
[a] Method A: SOCl_2, reflux; 1.1 equiv. of R^1NH_2, 3 equiv. of Et_3N, CH_2Cl_2, rt; NaOH(aq) wash. Method B: 1.1 equiv. of SOCl_2, CHCl_3, 60 °C; 1.1 equiv. of PCl_5, CHCl_3, 60 °C; 1.1 equiv. of R^1NH_2, 3 equiv. of Et_3N, MeCN, 60 °C; NaOH(aq) wash. Method C: 1.1 equiv. of SOCl_2, CHCl_3, 60 °C; 1.1 equiv. of PCl_5, 1.1 equiv. of R^1NH_2, toluene or CHCl_3, reflux; NaOH(aq) wash. [b] Yield, based on hydroxyamide, after chromatography or

recrystallization. [c] Using excess aqueous $MeNH_2$. [d] By the addition of the imidoyl chloride to a solution of dry NH_3 in $CHCl_3$. [e] The (*R*)-amino acid was used. [f] Crude yield.

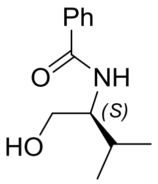
Table 6. The synthesis of the benzamides **162a-c** from amino alcohols **148**[a]



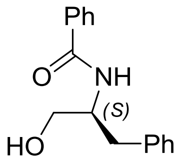
148 **162**



162a (99%)



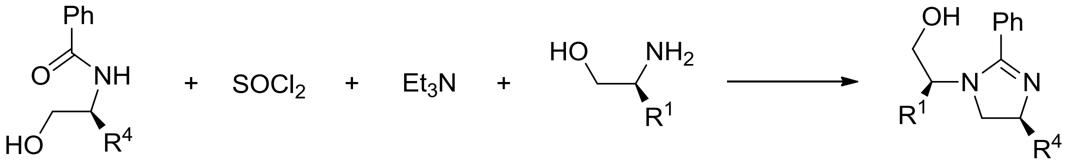
162b (99%)



162c (99%)

[a] The reaction was carried out with benzoyl chloride (35.57 mmol, 1 equiv.), **148** (39.13 mmol, 1.1 equiv) and Et_3N (42.68 mmol, 1.2 equiv.) in dry CH_2Cl_2 under nitrogen at 0 °C overnight

Table 7. The synthesis of the 2-imidazolines **163a-k** using thionyl chloride ($SOCl_2$)[a]



162 **152** **163**

entry	R^1	R^4	product	yield[b] (%)
1	Ph	*i*-Pr	**163a**	68
2	Ph	Ph	**163b**	76
3	Ph	Bn	**163c**	83
4	*i*-Pr	*i*-Pr	**163d**	72
5	*i*-Pr	Ph	**163e**	88

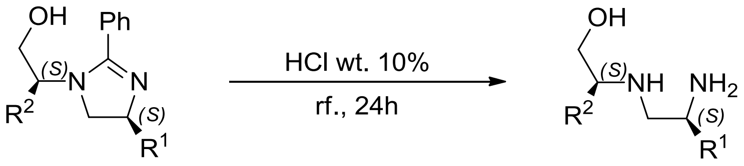
entry	**R^1**	**R^4**	**product**	**yield[b] (%)**
6	*i*-Pr	Bn	**163f**	75
7	Bn	*i*-Pr	**163g**	77
8	Bn	Ph	**163h**	76
9	Bn	Bn	**163i**	89
10	Bn	2-hydroxyphenyl	**163j**	91
11	Bn	2-hydroxyethyl	**163k**	nd[c]

[a] The reaction was carried out with **162** (5.0 mmol, 1.0 equiv.), thionyl chloride (30 mmol, 6.0 equiv.) reflux for 4 h, producing crude chloroethyl imidoyl chlorides which were added to the mixture of Et_3N (15 mmol, 3.0 equiv.) and **152** (5.25 mmol, 1.05 equiv) in dry CH_2Cl_2 under nitrogen atmosphere at 0 °C. The reaction mixture was stirred overnight at room temperature. [b] isolated yield. [c] crude product was used for the next step without purification.

5.3.2. The hydrolysis of 2-imidazolines 163

The Hawkins' procedure (Scheme 32) presented the yields obtained in the hydrolysis of 2-imidazolines under acidic conditions are more consistent than those obtained under basic conditions. That can be explained that under basic conditions, the reaction mixture is incompletely homogeneous. Indeed, the imidazolines **163a** and **163b** were checked for the hydrolysis under both acidic conditions (with concentrated hydrochloric acid) and basic conditions (with 20 wt. % solution of potassium hydroxide). After 24 hours refluxing, the reaction with the potassium solution would give incomplete conversions due to the heterogeneity of the reaction mixture whereas the complete conversion was obtained in the acidic condition. Then we found that the full conversion can also be achieved with 10 wt. % hydrochloric acid solution. So, we decided all of the 2-imidazolines **163a-i** were hydrolyzed with 10 wt. % hydrochloric acid solution (Table 8).

Table 8. The synthesis of the diamino alcohols **154a-k**[a]



163 **154**

entry	R^1	R^2	product	yield[b] (%)
1	Ph	*i*-Pr	**154a**	92
2	Ph	Ph	**154b**	95
3	Ph	Bn	**154c**	92
4	*i*-Pr	*i*-Pr	**154d**	90
5	*i*-Pr	Ph	**154e**	91
6	*i*-Pr	Bn	**154f**	92
7	Bn	*i*-Pr	**154g**	91
8	Bn	Ph	**154h**	91
9	Bn	Bn	**154i**	92
10	Bn	Bn	**154i**	95[c]
11	Bn	2-hydroxyphenyl	**154j**	76[d]
12	Bn	2-hydroxyethyl	**154k** (Phaol)	72[c, d, e]

[a] The reaction was carried out with **163** (2.0 mmol) and HCl 10 wt. % (30ml), reflux, 24 h. [b] isolated yield. [c] the reaction was run at 18 mmol of starting material. [d] The reaction was carried out with potassium hydroxide 20 wt. % (30ml), reflux, 72 h. [e] The reaction was carried out with the crude product of a 2-imidazoline.

The 2-imidazolines **163j** and **163k** could not be hydrolyzed completely under acidic conditions, so they were hydrolyzed with 20 wt. % potassium hydroxide solution under reflux condition for 72 h. The diamino alcohol **154k** was prepared by hydrolyzing the crude product of the 2-imidazoline **163k** because of the compound **163k** could not be isolated in pure form (the experimental part). The configuration at the chiral centers of 2-imidazolines **163** is maintained during the hydrolysis, which can be confirmed indirectly by the crystal structure of the compound **154b** (Figure 10).

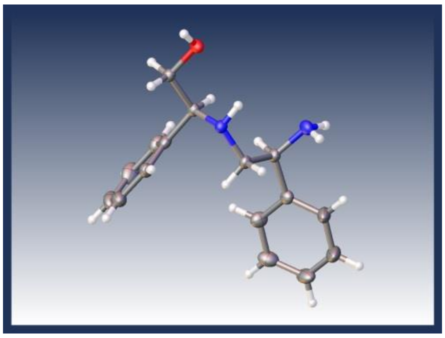


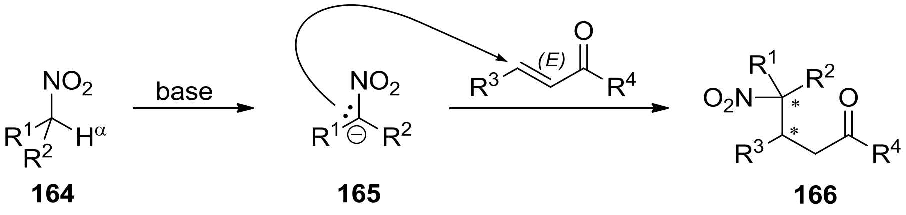
Figure 10. The crystal structure of the diamino alcohol **154b**

Conclusion: We could prepare diamino alcohols with up to two chiral centers in the simple protocol. The preparation of diamino alcohols by this method, i.e. hydrolyses of 2-imidazolines, has a wide scope, is in high yields and can be performed in large scale. The configuration of the chiral centers in starting materials, i.e. 2-imidazolines, is maintained during the hydrolysis. By applying this method, Phaol can be prepared in large scale, and the yield is not dropped when the reaction lasts longer than the optimized time.

6. The diamino alcohol 154i catalyze the Michael reactions of 2-nitropropane

6.1. The Michael reaction of nitroalkanes to α,β-unsaturated enones: an introduction

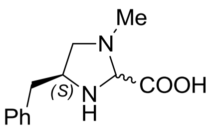
The Michael reaction is an important method to construct a carbon skeleton. In this reaction nucleophiles which are from compounds having acidic hydrogens or from compounds being able to stabilize carbanions (nitroalkane or ester malonate) add to electron-poor alkenes, for example α,β-unsaturated enones, to create a new C-C bond with up to two new chiral centers (Scheme 36).



Scheme 36. The Michael reaction of nitroalkanes and α,β-unsaturated enones

The proton H^{α} in nitroalkanes **164** is so acidic (pKa $MeNO_2$ = 10) that it can be eliminated by a wide range of bases such as K_2CO_3 and tertiary amines to generate nitronate anions **165** which then add to α,β-unsaturated enones and afford 1,4-adducts **166**. The asymmetric Michael reaction of nitroalkanes to α,β-unsaturated enones furnishes very useful products which can be converted into many important compounds. For example, the 1,4-adducts **166** can be transformed into aminocarbonyls or multi-substituted pyrrolidines by the reduction of the nitro group. There are many efforts to achieve the asymmetric Michael reaction of nitroalkanes to α,β-unsaturated enones. All of these efforts can be classified into three primary methods: a) using chiral metal complexes; b) using chiral organocatalysts; c) using chiral phase-transfer catalysts. In this part, we will focus on chiral organocatalysts for the asymmetric Michael reaction of nitroalkanes.

At the beginning chiral organocatalysts for the asymmetric Michael reaction of nitroalkanes were designed based on proline, for example, organocatalysts **167**[52], **168**[53], a mixture of **169** and *trans*-2,5-dimethylpiperazine (170)[54], and a mixture of **171**[55] and (170) (Figure 11). These organocatalysts require long reaction time (72-300 h), high catalyst loading (up to 20 mol%) to afford 1,4-Michael adducts in good to excellent yield and enantioselectivity. Later such chiral organocatalysts as **172**[56], **173**[57], and **174a-b**[58] (Figure 11) prepared from cinchona alkaloids were employed to reduce the reaction time (22-192 h), to lower the catalyst loading (2-20 mol%), and to improve the yield as well as the enantioselectivity. Recently, the reaction rate, the yield, and the enantioselectivity were enhanced by using chiral organocatalysts such as **175**[59], a mixture of **176** and 4-nitrophenol [60], and a combination of **177** and Boc-*L*-phenylalanine[61] prepared from simple amines (Figure 11). Up to now the highest yield (61-96% yield) and enantioselectivity (90-96% ee) for this reaction are achieved by using the mixture of organocatalysts **177** and Boc-*L*-phenylalanine.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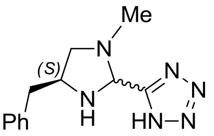
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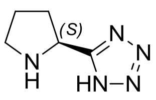
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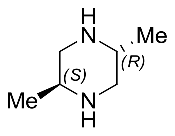
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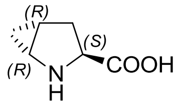
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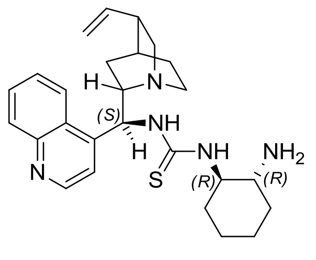
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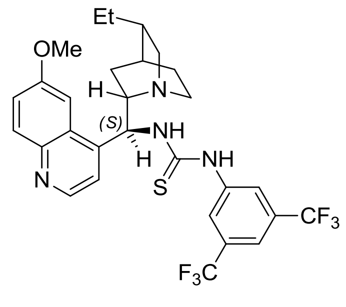
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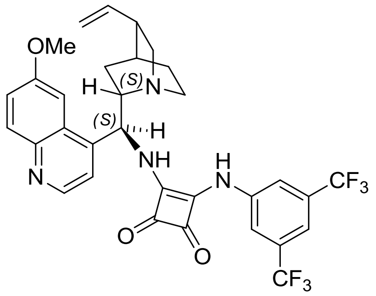
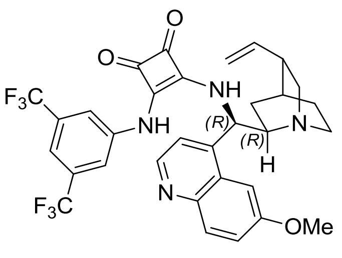
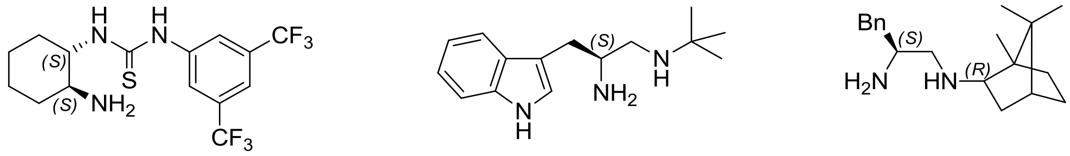

174a


174b



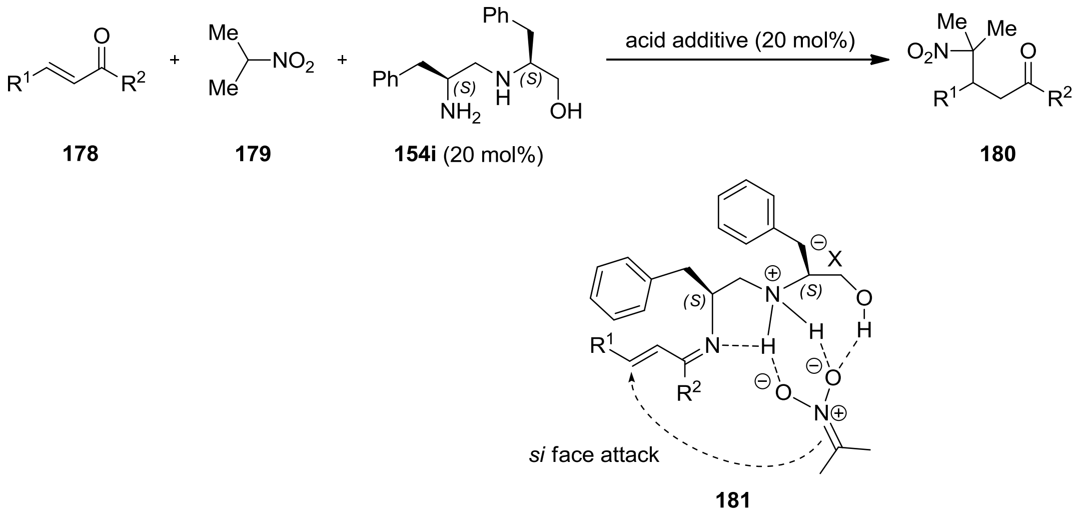
175 **176** **177**

Figure 11. Chiral organocatalysts used in the asymmetric Michael reaction of nitroalkanes

In spite the fact that a variety of organocatalysts have been developed for this reaction to improve the yield up to 99% and the enantioselectivity up to 99% ee, this reaction still requires long reaction time, high catalyst loading, and low diastereoselectivity. Furthermore, there is no versatile catalyst for a wide range of Michael donors or Michael acceptors. Therefore, the development of more efficient chiral organocatalysts for broad substrates in the Michael addition of nitroalkanes is still a challenge.

6.2. Aim of the work

As we have seen, the best chiral organocatalyst for the asymmetric Michael addition of nitroalkanes to α,β-unsaturated enones is the organocatalyst **177**, but this organocatalyst requires a chiral acid additive, and the preparation of this catalyst required many steps. After analyzing the structure of organocatalysts **167**, **168**, **176** and **177**, we have realized that the chiral carbon bearing the primary amine must carry a bulky group such as benzyl or indolyl group to get high enantioselectivities. Moreover, the substituents on the secondary amine must be bulky groups to get better chiral induction (the *tert*-butyl group on the organocatalyst **176** vs. the camphor moiety on the organocatalyst **177**). We have synthesized a series of chiral diamino alcohols **154a-k** in a practical method (Part II, Section 5). The compound **154i** has an alcohol group besides primary and secondary diamines (compared to the organocatalyst **176** and the organocatalyst **177**), so will the diamino alcohol **154i** bearing a free hydroxyl group be better in the catalytic activity than the organocatalyst **177** in the asymmetric Michael reaction of 2-nitropropane to α,β-unsaturated enones? Can the benzyl group next to the secondary amine make the benzyl group next to the primary amine shield the *re*-face of activated enones more efficiently? The possible transition state for the Michael reaction catalyzed by the compound **154i** is shown in Scheme 37.

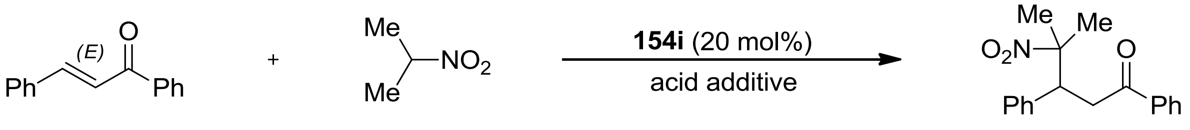


Scheme 37. A possible transition state for the Michael reaction catalyzed by the compound **154i**

6.3. The catalytic activity of the compound 154i in the asymmetric Michael reaction

The asymmetric Michael reactions under the presence of the organocatalysts **167**, **168**, **176**, or **177** were carried out in solvents: $CHCl_3$, THF or in neat condition. So, the catalytic activity of the compound **154i** in the asymmetric Michael reaction of 2-nitropropane to benzylideneacetophenone was screened in solvents: $CHCl_3$, THF, and 2-nitropropane (Table 9). In these solvents, the reaction in 2-nitropropane gives the best enantioselectivity (entry 6, Table 9). The amount of 2-nitropropane, acid additive, and the reaction temperature affect the yield and the enantioselectivity. The addition of an appropriate acid additive improves not only the yield but also the enantioselectivity. Entry 1-4 in Table 9 shows that the more acidic, the higher enantioselectivity. When the reaction temperature rises, the reaction rate increases but the lower ee is obtained (entry 8, Table 9). The less amount of 2-nitropropane was used to save the nitroalkane, but the yield was dropped (entry 4 vs. entry 6). If the solution is slightly concentrated, the yield is higher, but the enantioselectivity is a little bit lower (entry 6 vs. entry 7). So, the reaction condition as in entry 6 is the optimized reaction condition, and it was applied to other Michael acceptors to know how good the catalyst **154i** is (Table 10).

Table 9. The optimization of reaction conditions[a]



182a **179** **183a**

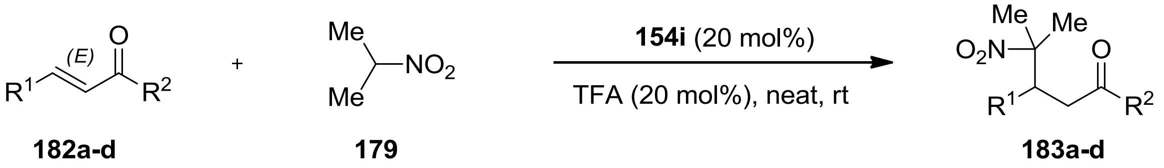
entry	solvent	2-nitropropane (equiv.)	acid additive (mol%)	T (°C)	reaction time (h)	yield[b] (%)	ee[c] (%)
1	THF	5.5	–	rt	288	36	47
2	THF	5.5	(*L*)-tartaric acid (10)	rt	96	6	–
3	THF	5.5	4-nitrobenzoic acid	rt	96	45	90

entry	solvent	2-nitropropane (equiv.)	acid additive (mol%)	T (°C)	reaction time (h)	yield[b] (%)	ee[c] (%)
			(20)				
4	THF	5.5	TFA (20)	rt	288	54	94
5	$CHCl_3$	5.5	TFA (20)	rt	96	22	87
6	neat	16.7	TFA (20)	rt	96	67	94
7	neat	11.1	TFA (20)	rt	96	93	91
8	neat	16.7	TFA (20)	40	48	96	89

[a] The reaction was carried out with **182a** (0.5 mmol, 1.0 equiv.) and **179** in 0.5 ml of solvent in the presence of catalyst **154i** (0.1 mmol, 0.2 equiv.) and acid additive at room temperature for the specific time. [b] isolated yield. [c] determined by chiral HPLC analysis using Chiralpak AS-H as a column.

The results in Table 10 showed that the compound **154i** could catalyze the asymmetric conjugate addition of 2-nitropropane to chalcone and benzylidene ketones to afford the adducts in very good yield and good to excellent ee. However, the reaction catalyzed by the compound **154i** needed long reaction time to finish. It should be noted that there are no by-products observed in these reactions. The results in Table 10 show that the catalytic activity of the compound **154i** is not so good as that of the organocatalyst **177**.

Table 10. The enantioselective Michael reactions catalyzed by the mixture of **154i** and TFA[a]



entry	R¹	R²	Product	reaction time (h)		yield[c] (%)		ee[d] (%)	
				177[b]	154i	177[b]	154i	177[b]	154i

entry	R[1]	R[2]	Product	reaction time (h)		yield[c] (%)		ee[d] (%)	
1	C_6H_5	C_6H_5	**183a**	96	192	76	97	95	94
2	C_6H_5	Me	**183b**	48	168	96	91	94	89
3	4-$MeOC_6H_4$	Me	**183c**	48	168	90	89	92	94
4	4-ClC_6H_4	Me	**183d**	48	168	96	94	96	78

[a] The reaction was carried out with **182a** (0.2 mmol, 1.0 equiv.) and **179** (3.34 mmol, 16.7 equiv.) in the presence of catalyst **154i** (0.04 mmol, 0.2 equiv.) and TFA (0.04 mmol, 0.2 equiv.) at room temperature for the specific time. [b] results from Gong *et al.*.[61] [c] isolated yield. [d] determined by chiral HPLC analysis using Chiralpak AS-H as a column.

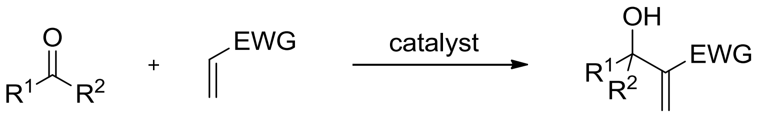
Conclusion: The catalytic activity of the compound **154i** is better than the organocatalysts **167** and **168** but is not so good as the organocatalyst **177** regarding yields and enantioselectivities in the asymmetric Michael reaction. However, the compound **154i** could be prepared in gram scale in fewer reaction steps than the organocatalyst **177**.

7. 2-Imidazolidines catalyze the Morita-Baylis-Hillman reaction

7.1. The Morita-Baylis-Hillman reaction: introduction and mechanism

Organic reactions are divided into two aspects, i.e. bond-forming and bond-breaking reactions. The former are more fundamental and more important in organic chemistry because of their unique in building carbon frameworks for a large number of organic compounds used in pharmaceutical, agriculture, materials, and many others. There are many reactions for constructing carbon skeletons, but only a few ones such as the aldol reaction, the Diels-Alder reaction, the Michael reaction and the Morita-Baylis-Hillman (MBH) reaction meet the requirement in modern organic synthesis, i.e. atom economy.

The MBH reaction[62] is a coupling of an electron-deficient alkene and an aldehyde or an activated ketone (MBH) catalyzed by a tertiary amine or a tertiary phosphine (Scheme 38). Recently, this reaction has been taken much attention due to its atom-economical nature and its ability to yield densely functionalized products widely applied in the synthesis of medicinal compounds as well as complex natural products.[63]



R^1 = aryl, alkyl, heteroaryl
R^2 = H, CO_2R, alkyl
EWG = electron-withdrawing group

Scheme 38. The Morita-Baylis-Hillman reaction

Although possessing fascinating characteristics and large synthetic utility, this reaction had been abandoned by the chemists for nearly a decade since it was discovered by Morita in 1968. The author reported the reaction of acrylonitrile or methyl acrylate with various aldehydes in the presence of tricyclohexylphosphine as a catalyst produces vinyl compounds in low yield. The scope of this reaction was expanded in 1972 by Baylis and Hillman. They described that activated alkenes, for example, α,β-unsaturated esters, amides, nitriles, and ketones can take part in this reaction, but instead of using phosphine catalysts they used such tertiary amines as 1,4-diazabicyclo[2.2.2]octane (DABCO), pyrrocoline (indolizine) or quinuclidine as catalysts. Maybe the low yield, slow reaction rate and limited substrate scope of this reaction were the reason for the missing attention of organic chemists, but these drawbacks have been solved recently by applying physical[64] (pressure, temperature, ultrasound, or microwave irradiation) or chemical[65] (catalysts, or solvents) methods. Only after the work of Drewes *et al.* and Hoffmann *et al.* at the beginning of the 1980s describing the application of the MBH reaction in the synthesis of integerrinecic acid[66] and of racemic mikanecic acid[67] respectively, this reaction has been attracting considerable interest from the chemists. That is evidenced by a significant number of research papers including some major reviews[68] and mini reviews.[65f,69] The reasons for the exponential growth and receiving remarkable interest are some advantages of this reaction.[68g] 1) feasible large-scale production due to the commercial availability of starting materials. 2) the atom-economical nature. 3) the multifunctional MBH adducts can be easily transformed into other synthetically interesting products. 4) the avoidable heavy-metal contamination due to the involvement of a Lewis base organocatalyst. 5) this reaction can be performed under simple and mild conditions.

In recent years, all of the three essential components of this reaction have been investigated. 1) A variety of acyclic and cyclic alkenes, alkynes, and allenes activated by aldehyde, ketone, ester, amide, nitrile, nitro, sulfonate, or phosphate functional groups (Figure 12);[70] 2) electrophiles which are generally aldehydes, activated ketones (MBH reaction), activated aldimines (aza-MBH reaction), activated alkenes (Rauhut-Courrier reaction), and many others (Figure 13);[70s,71] 3) catalysts which are involved amine catalysts (Figure 14)[65a,70a,70j,72] and non-amine catalysts (Figure 15)[68c,70d,70e,70k,70n,71x,73] have been successfully employed in this fascinating reaction. In case electrophiles are prochiral aldehydes, prochiral ketones or prochiral activated imines, the MBH/aza-MBH reaction will produce adducts with a newly chiral center, which gives a chance to develop the asymmetric version of the MBH reaction.

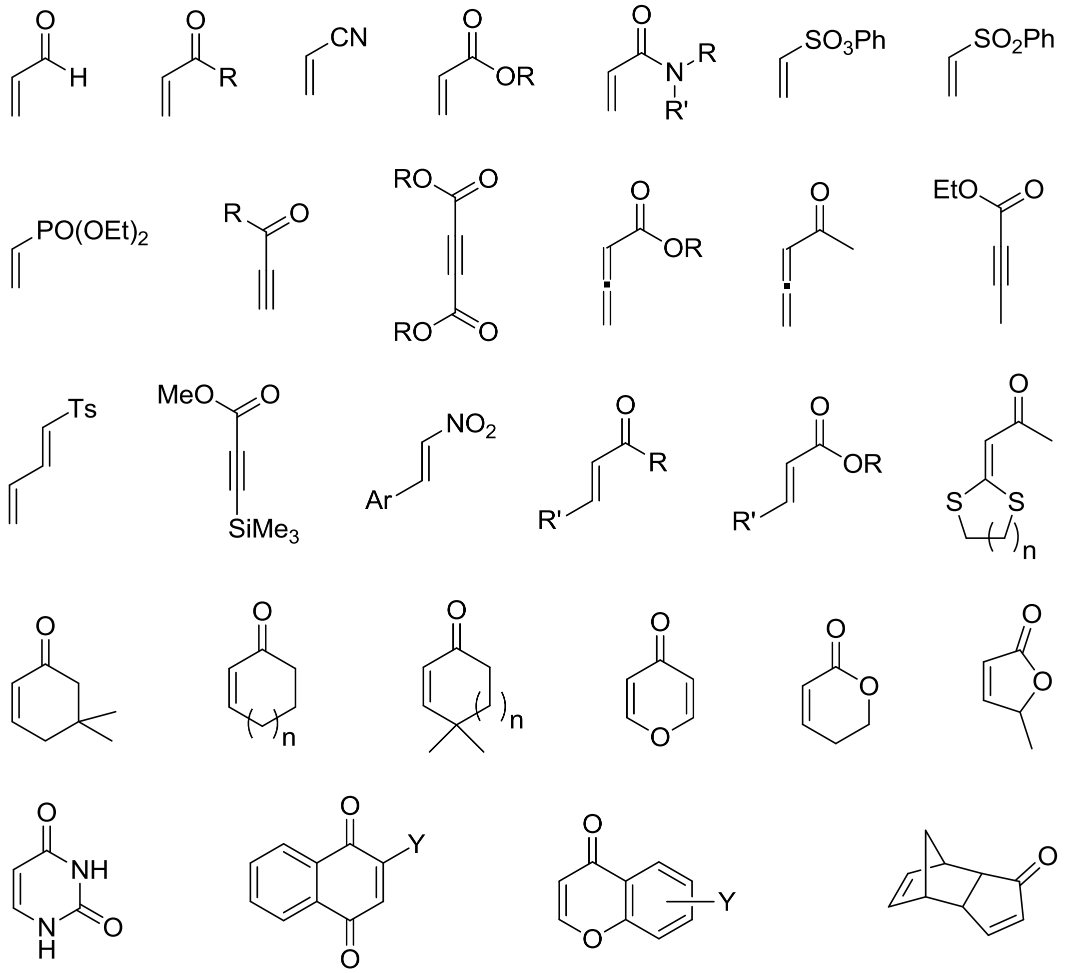
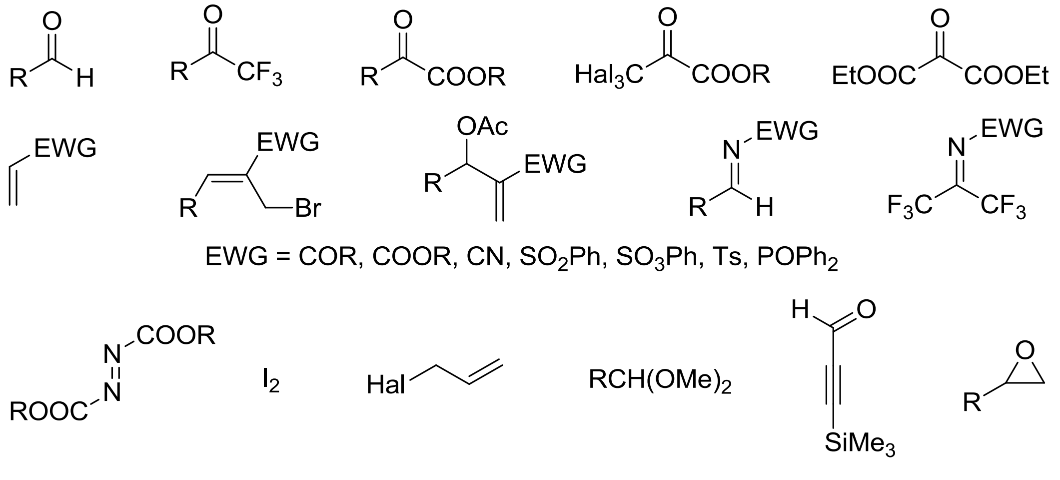


Figure 12. Acyclic and cyclic activated alkenes, alkynes and allenes in the MBH reaction



EWG = COR, COOR, CN, SO_2Ph, SO_3Ph, Ts, $POPh_2$

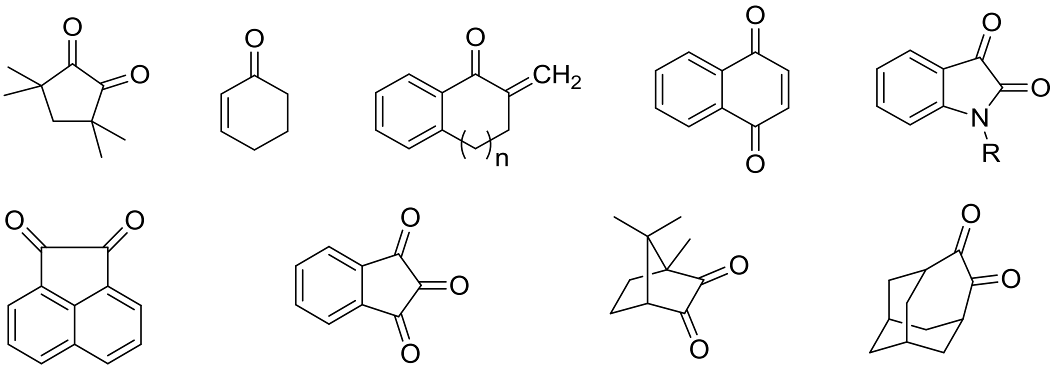


Figure 13. Some electrophiles in the MBH reaction

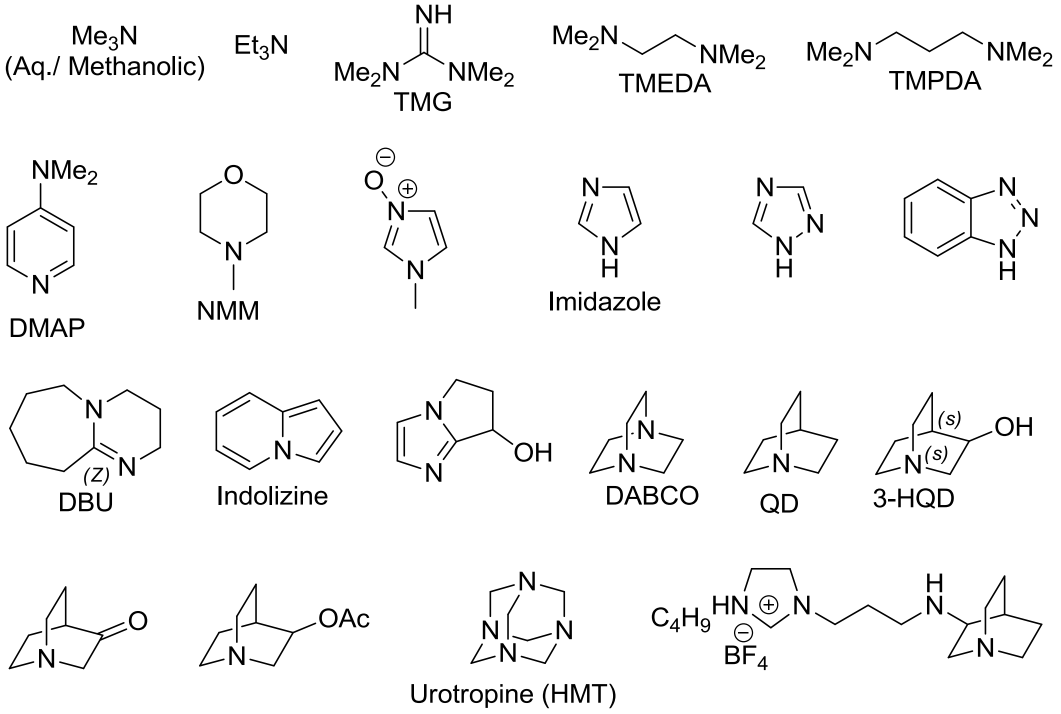


Figure 14. Amine catalysts in the MBH reaction

PR_3
R = alkyl, aryl

$TiCl_4$/Chalcogenides; $TiCl_4$
$BF_3.OEt_2$/Tetrahydrothiophene derivatives;
BBr_3/Me_2S; Et_3Al/PBu_3; TiI_4; $ZrCl_4$; BCl_3
R_2AlI/NaOMe; K_2CO_3/MeOH; MgI_2; $MgBr_2$

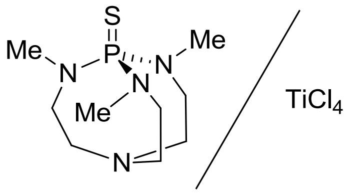
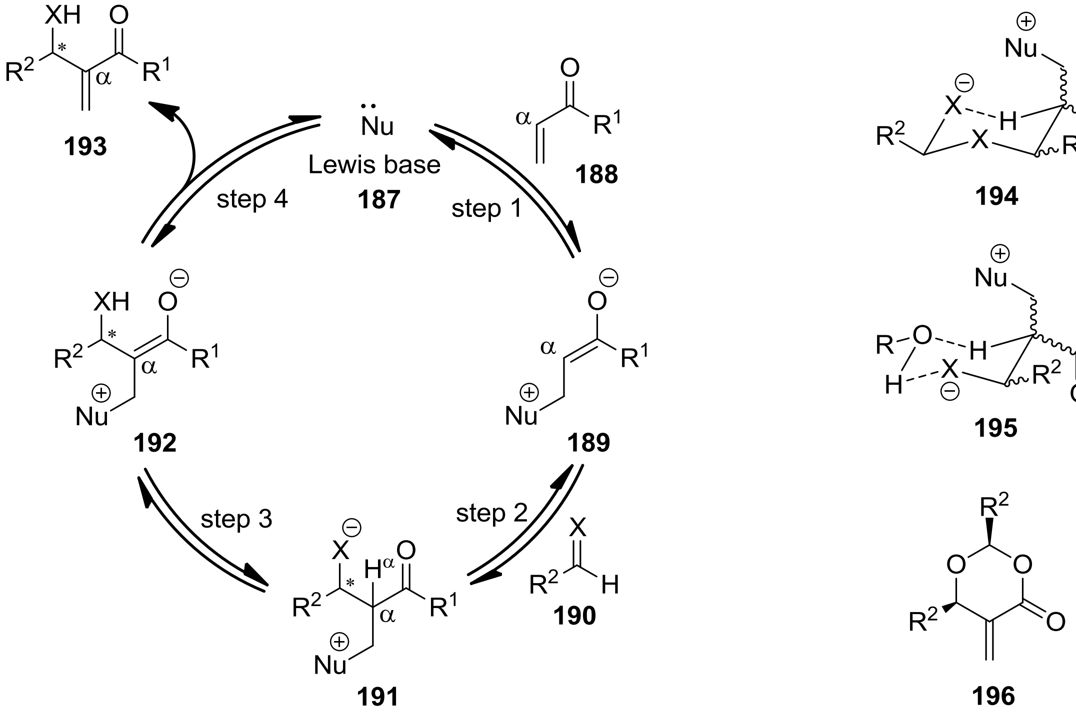


Figure 15. Non-amine catalysts in the MBH reaction

Mechanism:

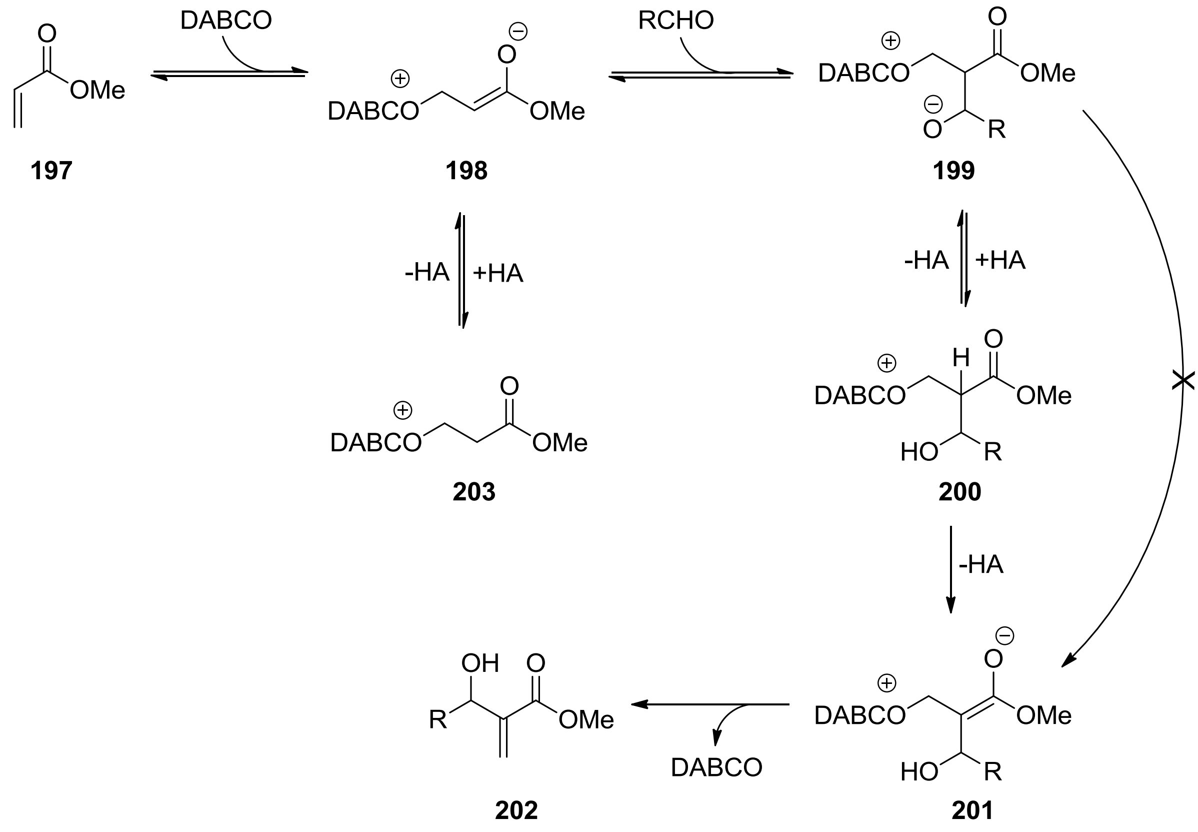
The mechanism of the MBH reaction was firstly suggested by Hill and Isaacs[74] and then refined by others.[65e,75] The MBH reaction proceeds through four steps as shown in Scheme 39.



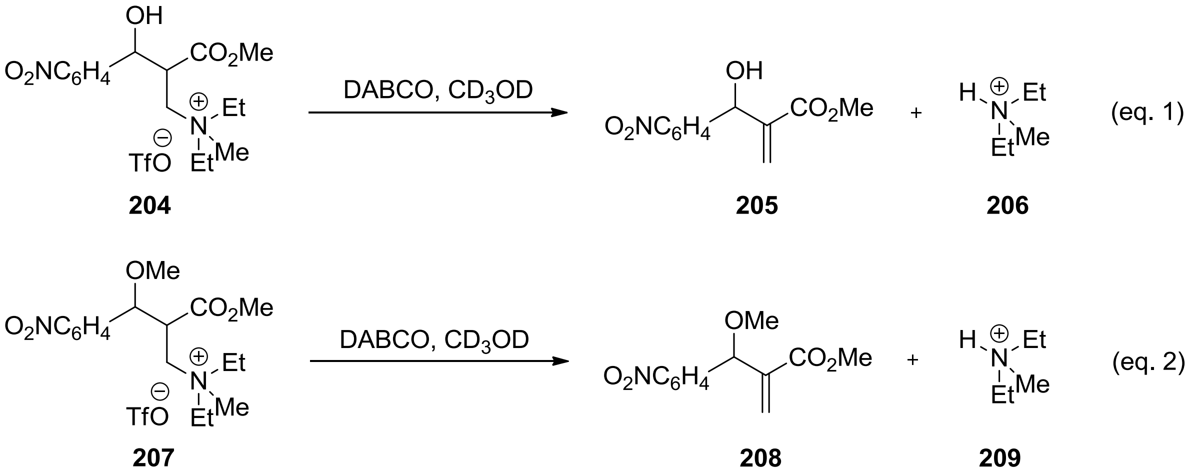
Scheme 39. The general mechanism of the MBH reaction

This reaction is initiated by the Michael addition of the Lewis base **187** to the activated alkene **188** to form the zwitterionic enolate **189** with the enhancement of the nucleophilicity at C^{α} (step 1). The zwitterionic enolate **189** attacks the electrophile **190** (aldehyde) to generate the zwitterionic **191** (step 2). The deprotonation at C^{α} and the protonation of the anion atom X^{-} of **191** (step 3) affords **192** collapsed to yield the MBH adduct **193** and to release the Lewis base **187** concurrently (step 4). The stability of **189** and **191** and that the whole reaction is equilibrium[75b] explain the low rate of MBH reactions. In case there is no additional interaction (with Brønsted acid or Lewis acid) to stabilize the zwitterionic **189**, this species will be formed, however, in low concentration, resulting in a low reaction rate in the carbon-carbon bond-forming step. As a result of that, the zwitterionic **191** is also in low concentration and so on. The proposed **189** and **192** were structurally characterized by ESI-MS and MS/MS (through [**189**+H]$^+$ and [**192**+H]$^+$).[69c,76]

The carbon-carbon bond-forming step (step 2) had been thought to be the rate-determining step (RDS) until the reinvestigations on the mechanism of Aggarwal *et al.*[77] and McQuade *et al.*[78] (on the MBH reaction) and of Leitner *et al.*[79] and Jacobsen *et al.*[76b] (on the aza-MBH reaction) were carried out recently. McQuade *et al.* reported that the RDS is not the carbon-carbon bond-forming step but the proton shift occurring in **191**. The authors proposed the transition state **194** for the proton shift in **191** due to the two key observations in the reaction between methyl acrylate and *p*-nitrobenzaldehyde catalyzed by DABCO in the absence of added protic species. 1) that the reaction is second-order in *p*-nitrobenzaldehyde provides a clue as to that two benzaldehyde molecules must be present in the RDS. 2) the reaction has a primary kinetic isotope effect when α-deuterioacrylate is used (K_H/K_D=2.2-5.2 is a clue for the RDS involving the α-proton cleavage) and a large inverse kinetic isotope effect when α-deuterio-*p*-nitrobenzaldehyde is used (K_H/K_D=0.72-0.80 is another clue for the presence of two benzaldehyde molecules in the RDS). Furthermore, the existence of the intermediate **194** is supported by the fact that the dioxane **196**, a by-product of MBH reactions, has been frequently isolated.[78a,80] On the other hand, Aggarwal *et al.* with kinetic studies realized that in the early phase (<20% conversion), the proton-transfer step (step 3) is the RDS. When the conversion of the reaction exceeds 20%, the MBH adduct will accelerate the reaction (autocatalytic reaction) by moving the proton from the hydroxyl group present in the MBH adduct to the anion atom X^- with the concomitant deprotonation at C^α in **189** (described by **195**) to give the enolate **192**. Consequently, the carbon-carbon bond-forming step will become the RDS. The transition state **195** involving six-membered cyclic transition state was supported by many reports on the computationally investigating mechanism of MBH reactions.[81] Regardless of these computationally mechanistic studies, based on experimental observations and computational studies, the Singleton group[82] suggested that the proton-transfer step occurs by simple acid-base reactions (Scheme 40) and not by the proton shuttle process **195**. This suggestion is supported by K_H/K_D=0.96±0.1 for the reaction of methyl acrylate and *p*-nitrobenzaldehyde with DABCO as a catalyst in unlabeled methanol and d_4-methanol. It is also supported by the fact that the elimination takes place at nearly the same rate for the hydroxy compound **204** (eq. 1, Scheme 41) and the methoxy analog **207** (eq. 2, Scheme 41). The proton-transfer step (step 3, Scheme 39) is the primary RDS at 25 ^{o}C while the aldol step (step 2, Scheme 39) is the partially RDS. The aldol step becomes the primary RDS at low temperature.



Scheme 40. The mechanism for the MBH reaction via mediating acid-base steps

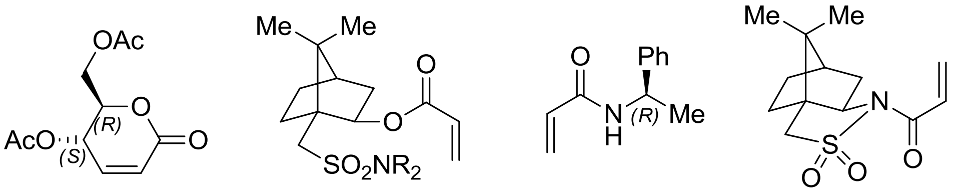


Scheme 41. The elimination of the hydroxy compound **204** and the methoxy analog **207**

Conclusion: The MBH reaction can afford multi-functional adducts from simple starting materials through one-pot reaction. This reaction, however, has a complicated reaction mechanism due to its multistep-reaction nature involving some transition states and some intermediates which are difficult to investigate. Fortunately, recently with substantial efforts at understanding this reaction to improve the reaction rate and the yield, its mechanism was refined as in Scheme 40 or as in Scheme 39 with the revision in step 3. The proton-transfer step (step 3, Scheme 39) and the aldol step (step 2, Scheme 39) are competitive rate-determining steps depending on reaction conditions. At 25 ^{o}C the proton-transfer step is the primary RDS, whereas at low temperature the aldol step becomes the primary RDS.

7.2. The asymmetric Morita-Baylis-Hillman reaction with chiral catalysts

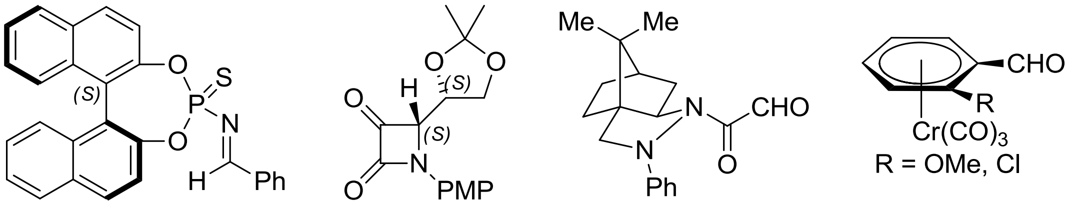
The asymmetric version of the MBH reaction can be achieved when one of the three components (the Michael acceptor or the electrophile or the catalyst) or chiral additives (chiral Brønsted acid or chiral Lewis acid) have a chiral center at appropriate positions. In the asymmetric MBH reaction using chiral activated alkenes, chiral acrylates are mostly used because of the accessibility of chiral acrylates as well as the easy removal of auxiliaries from products. Some chiral acrylates (Figure 16)[80a,83] were synthesized and employed in the MBH reaction with aldehydes in the present of DABCO. The highest enantiomeric excess (>99% ee) is achieved in the case of using the chiral acrylate **213** derived from the Oppolzer's chiral auxiliary.[83g] So this strategy limits the scope of the reaction because only some chiral acrylates can be used and it has another weak point is that two more steps are added to the procedure.



210 **211** **212** **213**

Figure 16. Activated Michael acceptors bearing chiral auxiliaries

The second route to get the asymmetric induction in the MBH reaction is the use of chiral electrophiles. Similar to the first route using chiral activated alkenes, there are only a few examples (Figure 17) for the use of chiral aldehydes to achieve chiral MBH adducts, but the diastereoselectivities in these reactions are very low.[83d,84] Fortunately, chiral α-methylene-β-hydroxy esters or α-methylene-β-hydroxy nitriles in high enantiomeric excess (>98% ee) can be prepared from the decomplexation of the MBH products formed in the reaction of the chiral aryl-aldehyde tricarbonylchromium complexes **217** with methyl acrylate or acrylonitrile in the presence of a catalytic amount of DABCO.[85] Despite this, the limitation of the substrate scope and the addition of two more steps in the procedure are still the drawbacks of this route.



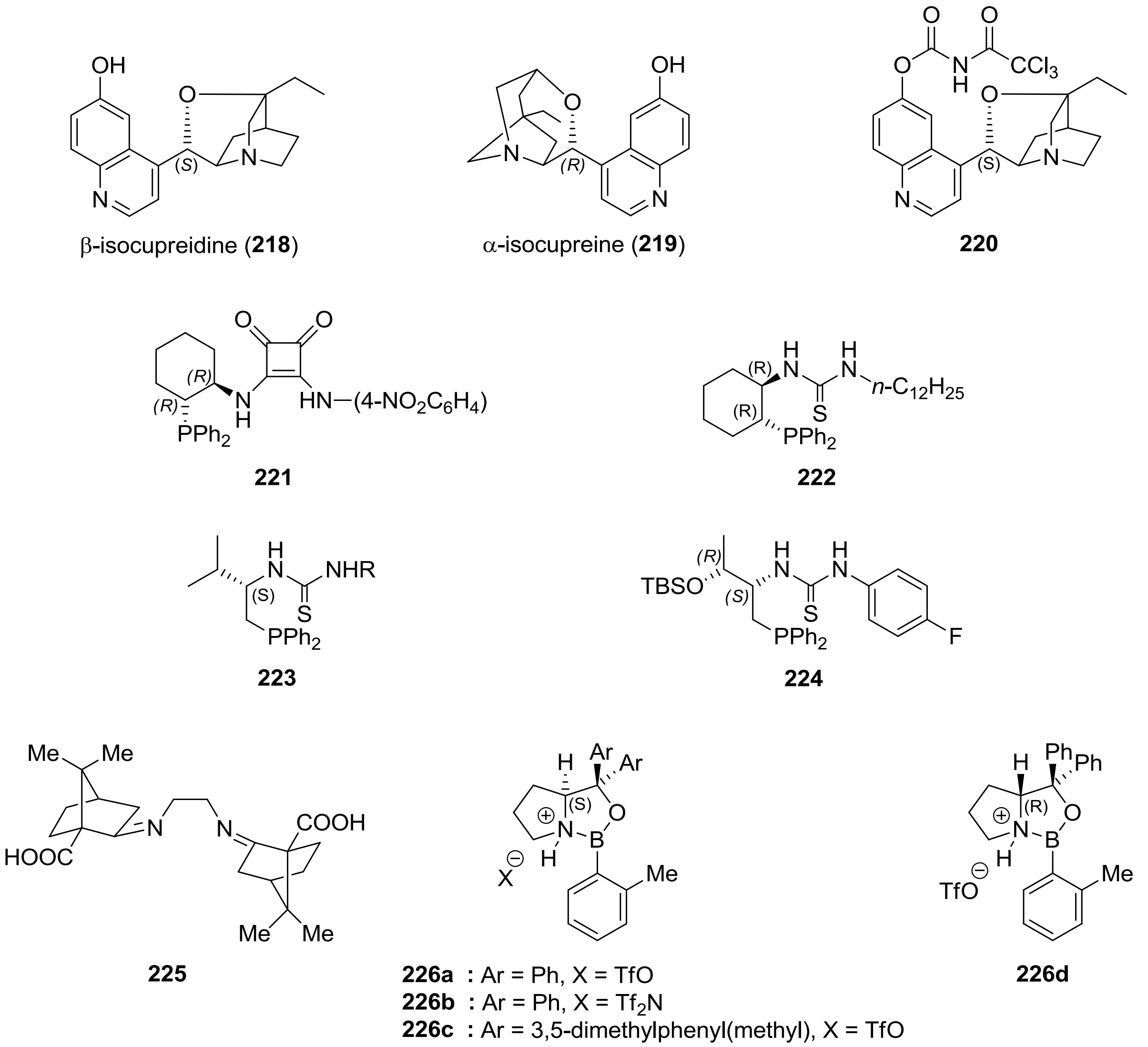
214 **215** **216** **217**

Figure 17. Electrophiles bearing chiral auxiliaries

The third route is the use of chiral catalysts or a mixture of a Lewis base and a chiral additive to perform the asymmetric catalytic MBH reaction. This way is more interesting and more challenging because only a catalytic amount of chiral catalysts or chiral additives can produce chiral MBH adducts from achiral substrates. Additionally, it does not require two additional steps for assembling chiral auxiliaries to substrates and for disassembling these auxiliaries from the MBH adducts.

7.2.1. The asymmetric catalytic MBH reaction of acrylates

The asymmetric catalytic MBH reaction of acrylates is too difficult due to the low reactivity of acrylates, so there are two ways to carry out this reaction. The first way is the use of highly reactive acrylates, e.g. HFIPA, and such chiral organocatalysts derived from quinidine or quinine as β-isocupreidine (218)[80d], α-isocupreine (219)[86], and the organocatalyst **220**[81i] (Figure 18). The second way is the use of chiral bifunctional organocatalysts having a strongly nucleophilic center, e.g. phosphine-squaramide catalyst **221**[87] or phosphine-thiourea catalysts **222**[88], **223**[89], and **224**[90] (Figure 18). Especially, the chiral oxazaborolidinium catalysts **226a-d**[91] (Figure 18) can solve the most challenge of the synthesis of chiral β-substituent MBH ester (Scheme 42). Although there are many efforts to design organocatalysts after the pioneered work of the Hatakeyama group,[80d] in fact, the most efficient approach to highly enantioenriched MBH adducts is still represented by the β-isocupreidine (218)/HFIPA method (Scheme 43). Moreover, the asymmetric catalytic MBH reaction of aromatic aldehydes carrying an electron-donating group and simple acrylates is still an issue.



β-isocupreidine (**218**)

α-isocupreine (**219**)

220

221

222

223

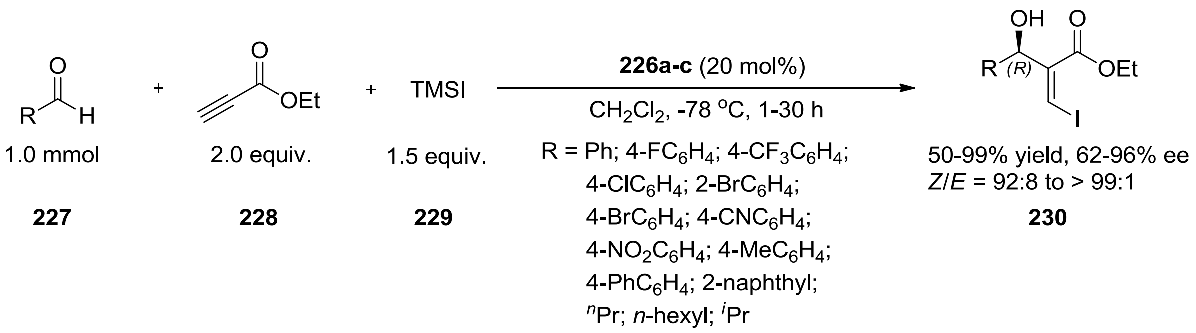
224

225

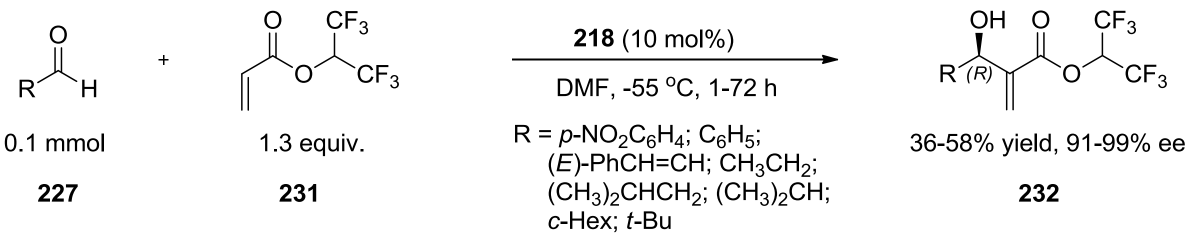
226a : Ar = Ph, X = TfO
226b : Ar = Ph, X = Tf_2N
226c : Ar = 3,5-dimethylphenyl(methyl), X = TfO

226d

Figure 18. Successful catalysts for the asymmetric MBH reaction of acrylates



Scheme 42. The synthesis of chiral (*Z*)-β-iodo MBH esters



Scheme 43. The asymmetric MBH reaction of aldehydes catalyzed by β-isocupreidine (218)

7.2.2. The asymmetric catalytic MBH reaction of methyl vinyl ketone or acrolein

Although β-isocupreidine (218) is a powerful catalyst for the enantioselective MBH reaction of acrylates, it is not a good catalyst for the asymmetric MBH reaction of methyl vinyl ketone (MVK).[80e] There are many efforts to perform the catalytic enantioselective MVK-based MBH reaction (Figure 19),[92,93,94,95,96, 97,98,99,100] and the most successful catalyst is the catalyst **240** (Scheme 44).[99] Most of the catalysts mentioned above are successful in the reaction of aromatic aldehydes bearing a strong electron-withdrawing group. Hence, designing an efficient catalyst for the asymmetric MVK-based MBH reaction of aromatic aldehydes bearing an electron-donating group as well as acyclic aldehydes is still a high demand.

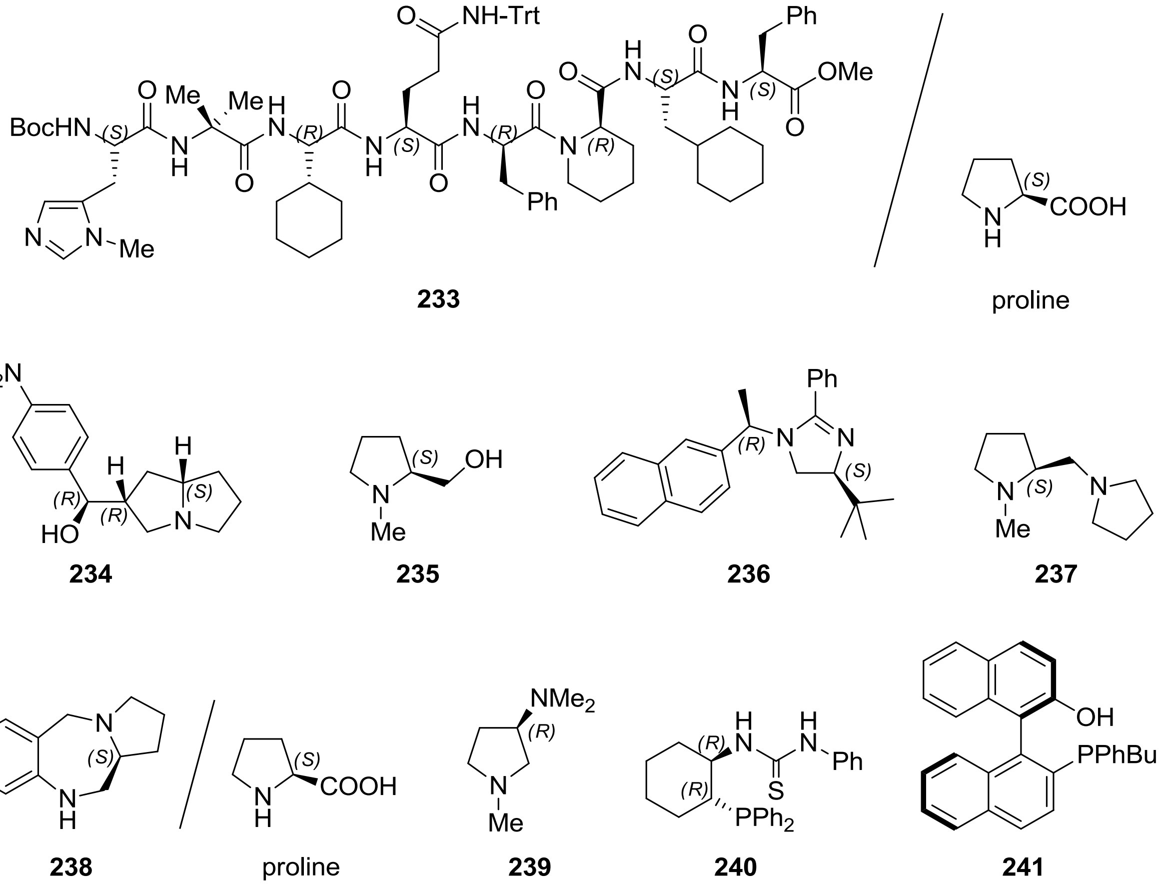
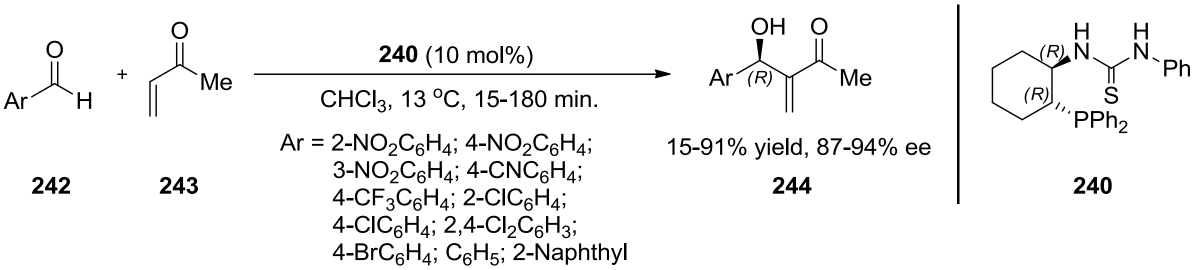


Figure 19. Some catalysts for the asymmetric MBH reaction of MVK

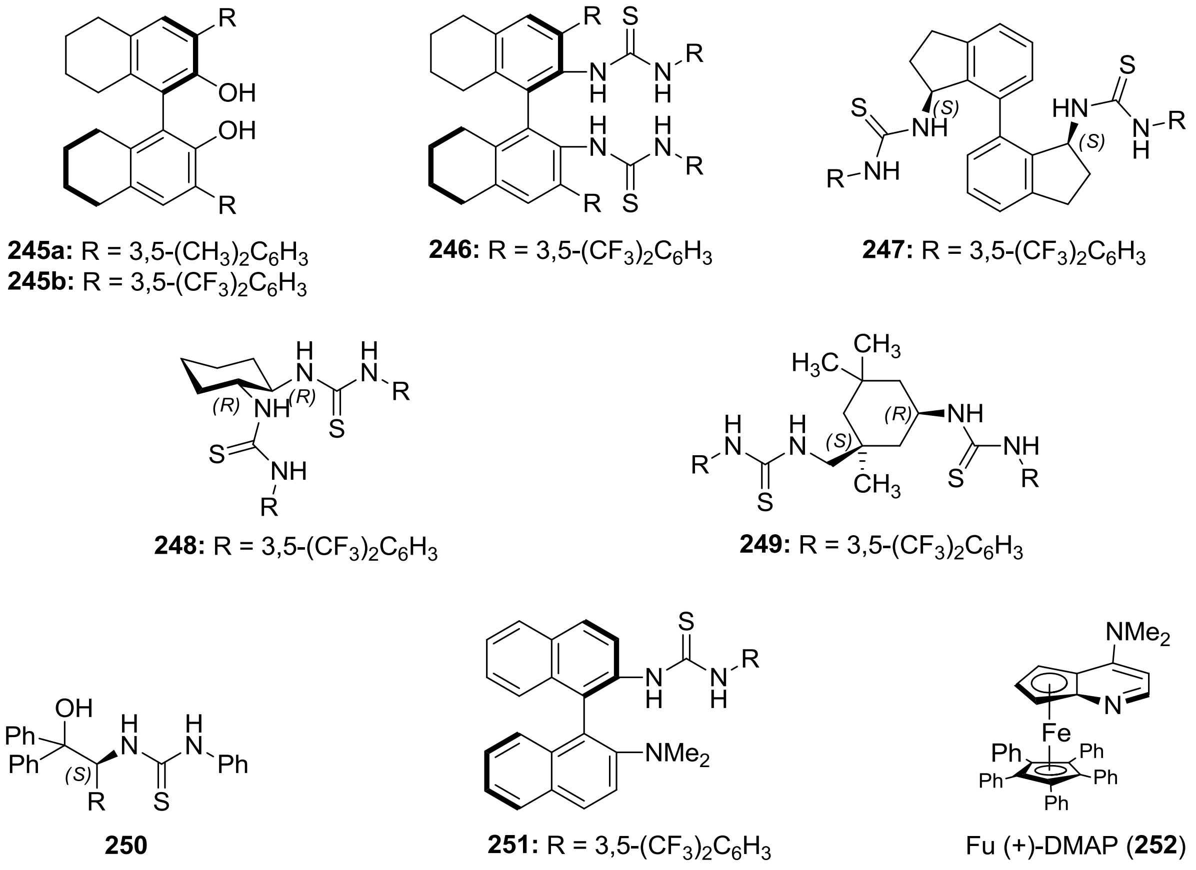


Scheme 44. The MBH reaction of MVK catalyzed by chiral phosphinothiourea **240**

7.2.3. The asymmetric catalytic MBH reaction of cyclopentenone and cyclohexenone

2-cycloalkenones are the most challenge in the asymmetric catalytic MBH due to the low reactivity of 2-cycloalkenones compare to HFIPA and MVK. There are some successful organocatalysts for the asymmetric catalytic MBH reaction of 2-cycloalkenone (Figure 20).

[101,102,103,104,105,106,107,108] Most of them are chiral acid co-catalyst containing two Brønsted acids like compounds **245a-b**, **246-250**. However, there is no versatile catalyst for the asymmetric catalytic MBH of 2-cycloalkenones. For example, the organocatalysts **245a-b**, **246-251** succeed in the reaction of 2-cyclohexenone, while the organocatalyst **252** succeeds in the reaction of 2-cyclopentenone.



245a: R = 3,5-$(CH_3)_2C_6H_3$
245b: R = 3,5-$(CF_3)_2C_6H_3$

246: R = 3,5-$(CF_3)_2C_6H_3$

247: R = 3,5-$(CF_3)_2C_6H_3$

248: R = 3,5-$(CF_3)_2C_6H_3$

249: R = 3,5-$(CF_3)_2C_6H_3$

250

251: R = 3,5-$(CF_3)_2C_6H_3$

Fu (+)-DMAP (**252**)

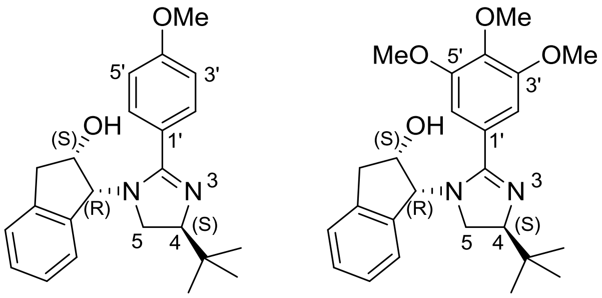
Figure 20. Some successful organocatalysts for the asymmetric catalytic MBH of 2-cycloalkenones

Conclusion: There are so many efforts to design chiral catalysts for the asymmetric MBH reaction and some great success is achieved, for example, the chiral catalyst (218), **226a-d**, **240**, **245a-b**, and **252**. However, there is no versatile catalyst and the asymmetric MBH of acyclic aldehydes, electron rich aromatic aldehydes, and unactivated ketones is still issues.

7.3. Aim of the work

The catalyst (218) is the best catalyst for the enantioselective MBH reaction, but it can work well only with the highly reactive acrylate, i.e. HFIPA, or the highly reactive ketone, i.e. isatins. For the MBH reaction of simple acrylates or MVK, phosphine-derived catalysts are used, but the reaction time must be optimized to suppress the second Baylis-Hillman reaction.[100] Moreover, there are no privilege catalysts for the MBH reaction. We are interested in catalysts which are facilely prepared, for example, the catalysts **235**, **236**, **238**, **239**, **248**, or **249**. In the synthesis of the diamino alcohols **154a-k**, some imidazolines **163a-k** similar to the catalysts **236** are synthesized. Since the *tert*-butyl group in the catalysts **236** played a major role for the enantioselectivities in the MBH reaction, it is kept in the proposed compounds **253a-b**. As we have seen, a hydroxy group at an appropriate position is well-known about enhancing the rate and the asymmetric induction in the MBH reaction, for example, the catalysts (218), **234**, **235**, **241**, **245a-b**, and **250**. We wonder that whether the 2-imidazolines **253a-b** possessing electron-donating groups on the phenyl ring and bearing a hydroxy group will show better catalytic activities in the MBH reaction than the catalyst **236**.

In this work, we synthesized the following compounds (Figure 21) and screened their catalytic activities in the MBH reaction.



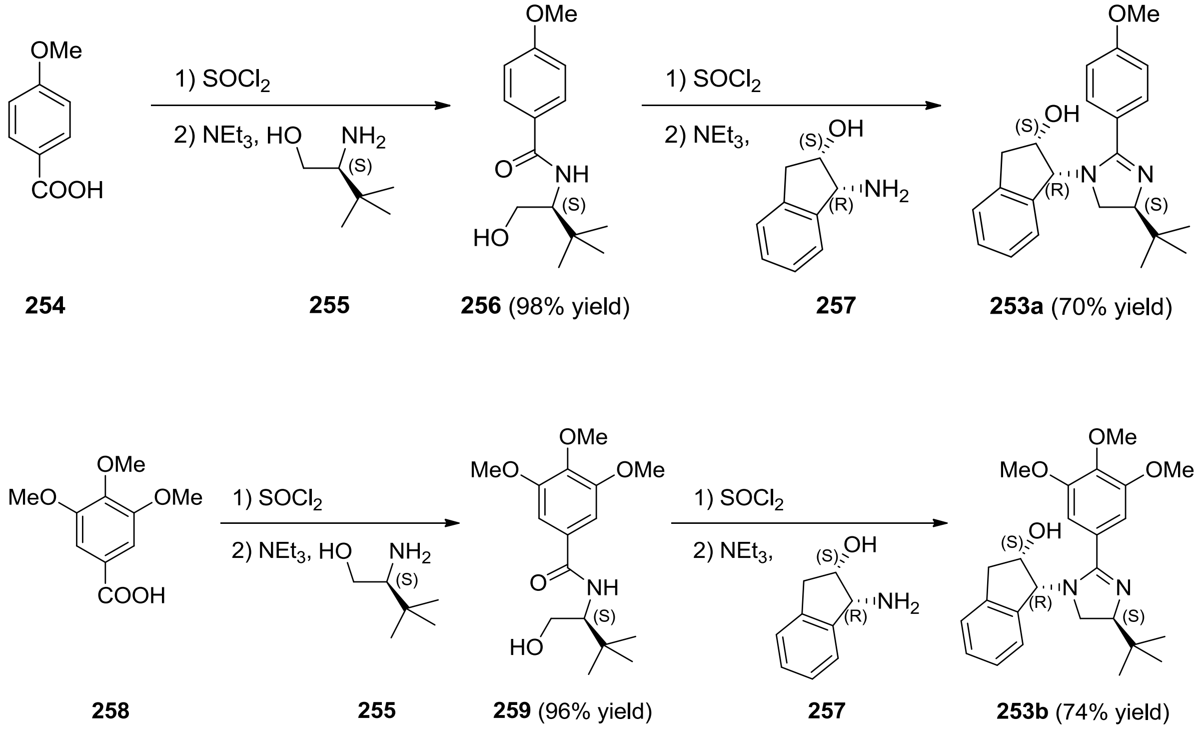
253a **253b**

Figure 21. Proposed catalysts for the MBH reaction

7.4. Catalytic activities of imidazolines 253a-b

7.4.1. Synthesis of imidazolines 253a-b

The synthesis of the 2-imidazolines **163** was used for preparing the 2-imidazolines **253a** and **253b**. The enantiopure benzamides **256** and **259** were prepared from (*S*)-*tert*-leucinol (255). Without purification, the compounds **256** and **259** were used in the synthesis of the 2-imidazolines **253a** and **253b** (Scheme 45). Both of the compounds **253a** and **253b** were purified by recrystallization from PE-DCM.

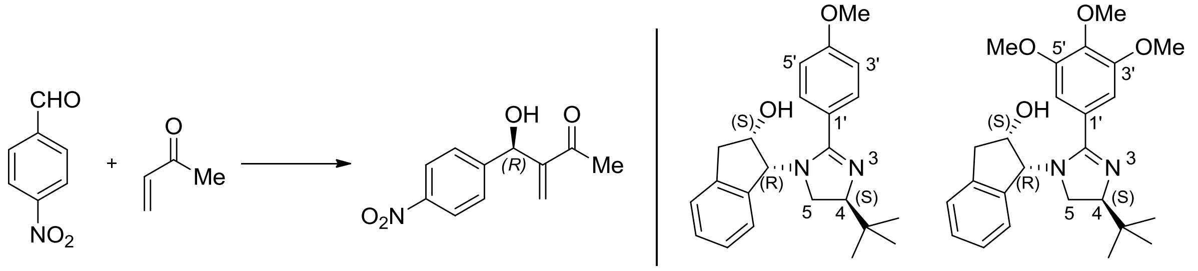


Scheme 45. The synthesis of the 2-imidazolines **253a** and **253b**

7.4.2. Catalytic activities of the 2-imidazolines 253a-b in the MBH reaction

The asymmetric MBH reactions catalyzed by the catalyst **236** were carried out in such solvents as THF, toluene, or in neat condition. So, the catalytic activity of the compounds **253a** and **253b** in the MBH reaction of *p*-$NO_2C_6H_4CHO$ and MVK was screened in such solvents as toluene, DCM, THF, dioxane, and in neat condition (Table 11). These results show that the compound **253b** gives the better yield and enantioselectivity than the compound **253a** (entry 4 vs. entry 5, Table 11). While the reaction is slow in DCM, toluene, or in neat condition and afforded the product in low yields, the reaction faster in THF and dioxane (entry 2, 8, and 9 vs. entry 4 and 6, Table 11). The compound **253b** which has three methoxy groups on the phenyl ring shows better reactivity in the MBH reaction than the compound **253a** which has one methoxy group on the phenyl ring. Measurement of the optical rotation and comparison to the literature[108] shows that the compound **262** to be of the (*R*)-configuration. The absolute configuration of the MBH adducts can be understood by using the transition-state model **264a** (Figure 22). The nucleophilic nitrogen atom of the compound **253b** attacks the MVK to form the zwitterionic species **263** which has the enolate moiety locating below the five member ring to avoid the interaction with the *tert*-butyl group. The zwitterionic **263** then attacks the *si*-face of the carbonyl carbon of the aldehyde rather than the *re*-face since the Ar group must avoid the interaction with the carbon C-1'' and with the *tert*-butyl group. From the intermediate **264a**, the MBH adducts with *R* configuration at the newly created chiral center are formed. The enantioselectivity in the MBH reaction catalyzed by compound **253b** is lower than the one in the MBH reaction catalyzed by the catalyst **236**. The low enantioselectivity in the MBH reaction catalyzed by **253b** can be explained by the interference of the methoxy groups at carbon C-3' or carbon C-5' of the compound **253b** in the approaching of the aldehyde to the enolate moiety. Therefore, we speculated that the replacement of the methoxy groups by the dimethylamino or pyrrolidin-1-yl group as in the compounds **265a** and **265b** (Figure 23) might improve the yield and the enantioselectivity further due to the stronger electron-donating group and less steric demand of these amino groups. The synthesis of the compound **265a** was carried out similarly to those of the compounds **253a** and **253b**, but unsuccessful (Scheme 46). The amino acid **266** was transformed into the amino amide **267** in high yield, but the conversion of this amide to the imidazoline **265a** is failed. That was confirmed by the unsuccessful synthesis of the compound **265c** analogous to the compound **265b**. A closer look showed that only the undesired product **271** was produced (Scheme 47). We think the pyrrolidin-1-yl group is protonated, which makes the imidoyl chloride **273** not be able to be formed, and the undesired product **271** is produced from the compound **272** exclusively (Scheme 48).

Table 11. The optimization of reaction conditions[a]

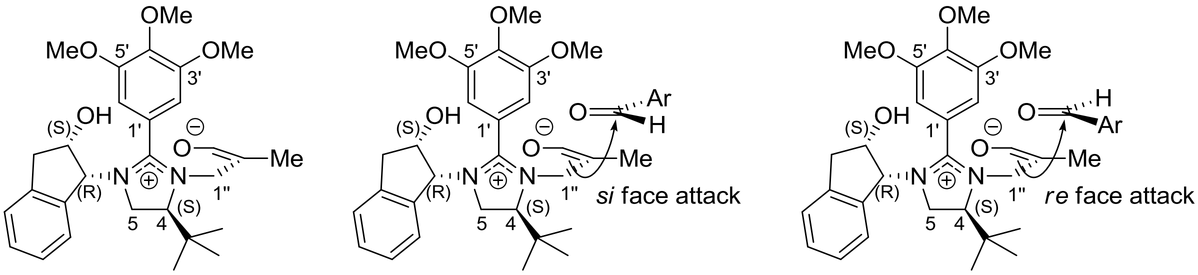


260 **261** **262** **253a** **253b**

entry	solvent	MVK (equiv.)	catalysts (mol %)	reaction time (h)	yield (%)[b]	ee (%)[c]
1	DCM	1.1	**253a** (10)	48	32	29 (*R*)
2	DCM	1.1	**253b** (10)	48	34	32 (*R*)[d]
3	THF	1.1	**253b** (10)	48	39	
4	THF	3.0	**253b** (10)	47	58	45 (*R*)
5	THF	3.0	**253a** (10)	48	35	19 (*R*)
6	Dioxane	3.0	**253b** (10)	47	60	46 (*R*)
7	Dioxane	3.0	**253b** (10)	72	58	45 (*R*)
8	neat	10.4	**253b** (10)	39	34	15 (*R*)

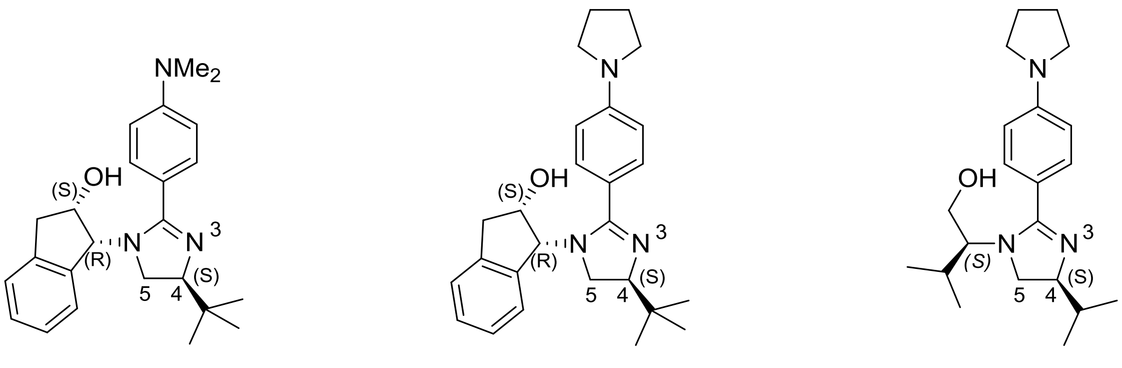
entry	solvent	MVK (equiv.)	catalysts (mol %)	reaction time (h)	yield (%)[b]	ee (%)[c]
9	Toluene	3.0	**253b** (10)	168	18	10 (*S*)

[a] The reaction was carried out with **260** (0.66 mmol, 1.0 equiv.) and **261** (0.17 ml, ≈ 3.0 equiv.) in 0.6 ml of solvent in the presence of catalyst **253a** or **253b** (0.066 mmol, 0.1 equiv.) at room temperature for the specific time. [b] isolated yield. [c] determined by chiral HPLC analysis using Chiralpak AS-H as a column. [d] determined by measurement of the optical rotation and comparison to the literature showed the sample to be of the (*R*)-configuration



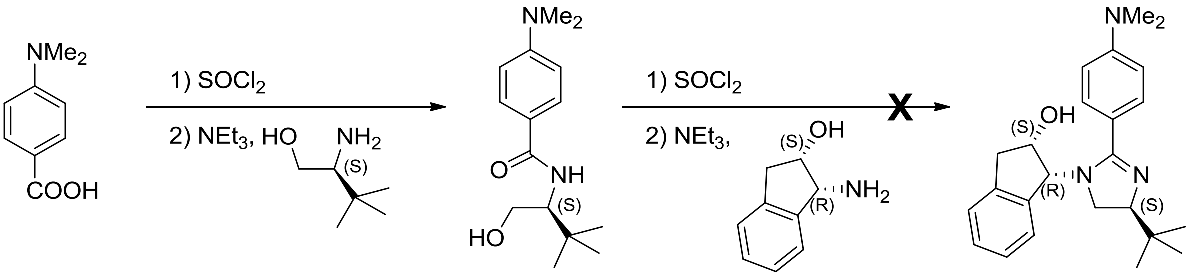
263 **264a** **264b**

Figure 22. Postulated transition-state models in the enantioselective MBH reaction catalyzed by **253b**



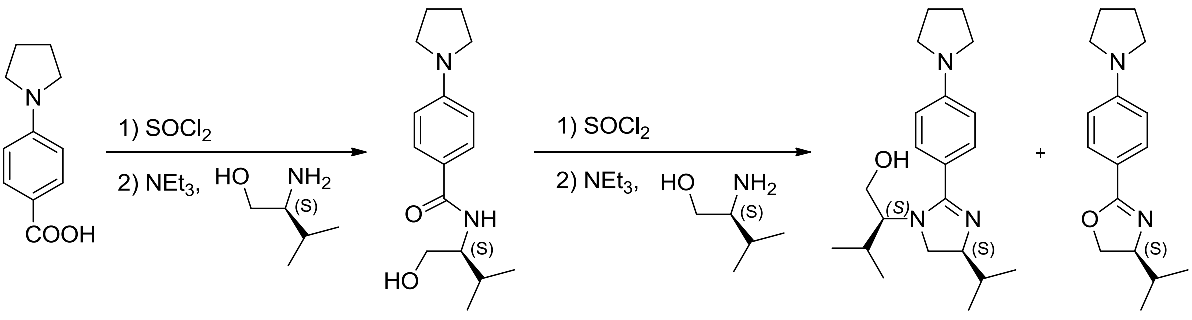
265a **265b** **265c**

Figure 23. Unsuccessfully synthesized 2-imidazolines



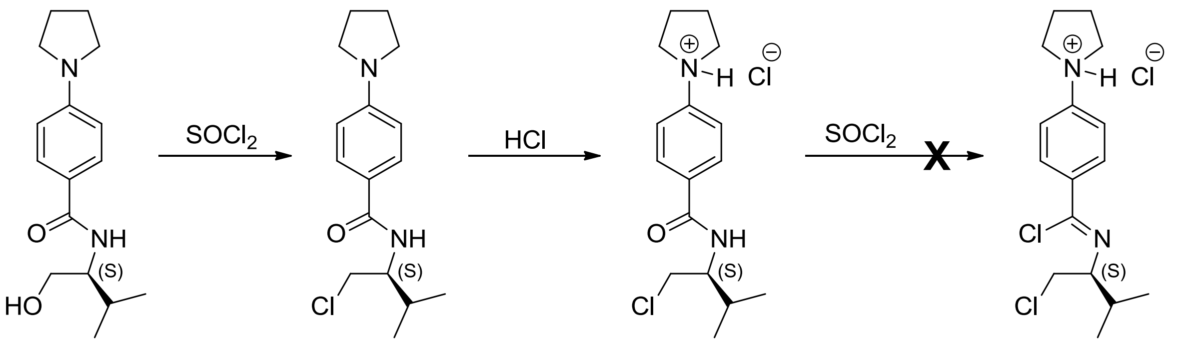
266 **255** **267** (85% yield) **257** **265a**

Scheme 46. The unsuccessful preparation of the compound **265a**



268 **269** **270** (91% yield) **269** **265c** (not formed) **271** (94%)

Scheme 47. The undesired product formed in the synthesis of compound **265c**

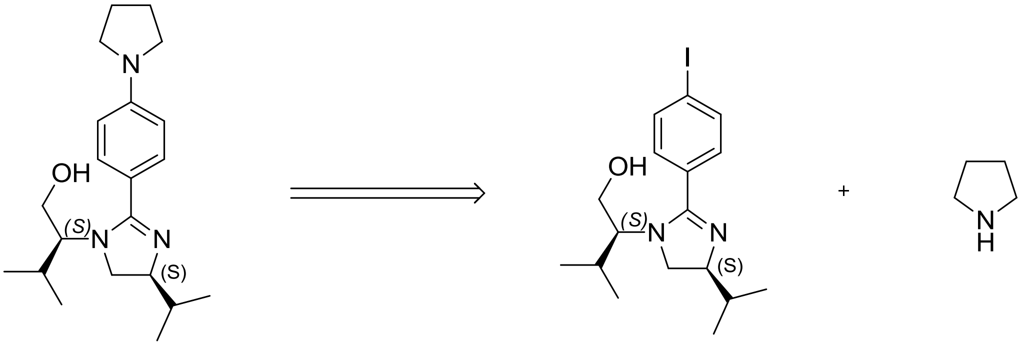


270 **271** **272** **273** (not formed)

Scheme 48. The pyrrolidin-1-yl group interference in the formation of imidoyl chloride **273**

Another possible route to synthesize the compound **265c** is the coupling reaction of the iodoarene **274** and pyrrolidine (Scheme 49). In principle, there are some reactions (palladium- and nickel-catalyzed Buchwald-Hartwig reactions and copper-catalyzed Ullmann type couplings as well as copper-catalyzed Lam-Chan reactions) for the construction of C_{sp2}-

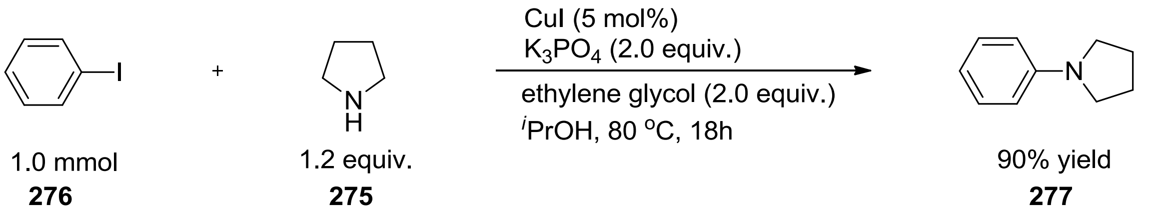
N bonds. That the Buchwald-Hartwig amination reactions rely on palladium complexes bearing specific ligands and the Lam-Chan reactions require boronic acids to achieve good results makes these methods unsuitable for the coupling of the iodoarene **274** and pyrrolidine due to the presence of the imidazoline group and the free hydroxy group in the arene **274**. On the other hand, the copper-catalyzed Ullmann type couplings may be suitable for the synthesis of **265c** because the role of ancillary ligands in the copper-catalyzed Ullmann couplings is not so critical as that of ancillary ligands in the palladium-catalyzed Buchwald-Hartwig reactions.



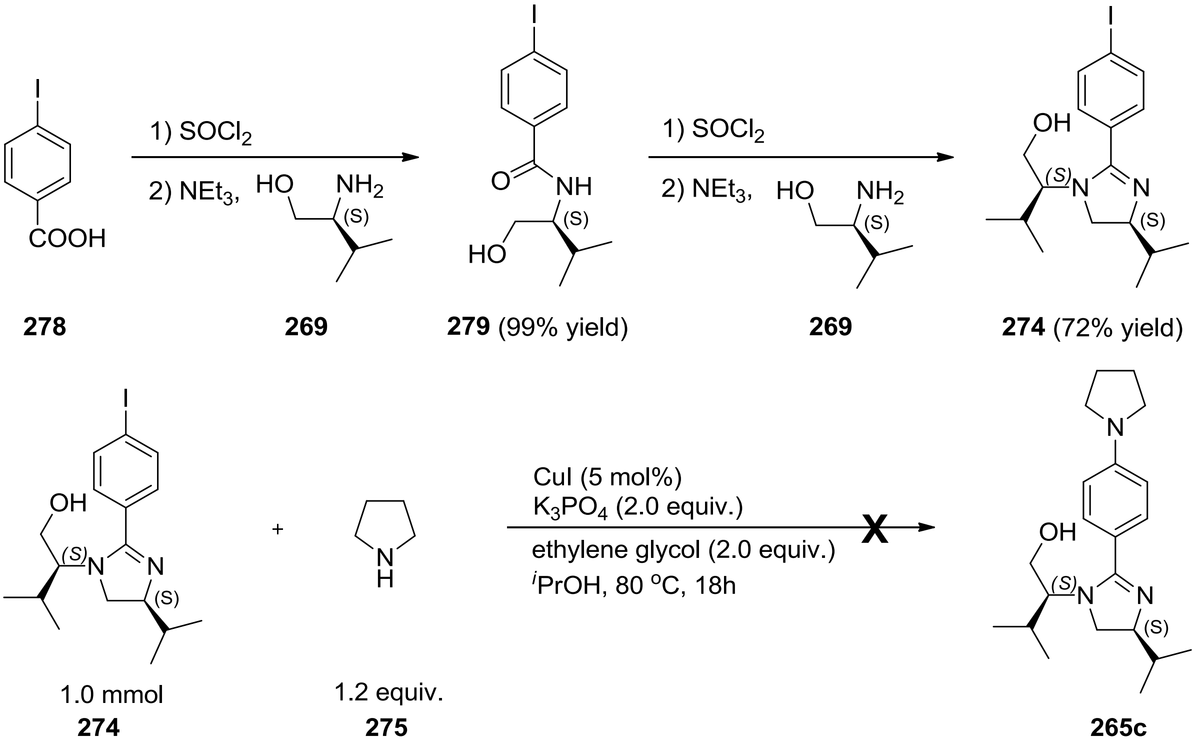
265c **274** **275**

Scheme 49. The retrosynthesis of compound **265c**

In 2002, Buchwald *et al.*[109] reported a mild method for the copper-catalyzed amination of iodobenzene (276) to afford 1-phenylpyrrolidine (277) in 90% yield (Scheme 50). This protocol was applied to the synthesis of the compound **265c** from pyrrolidine and the aryl iodide **274** which was synthesized from 4-iodobenzoic acid (278) and (*S*)-valinol (269). After refluxing for 18 h, the reaction mixture was poured into distilled water and was extracted with DCM. The thin layer chromatography with DCM-MeOH (90:10) showed that there was no the desired product (Scheme 51).



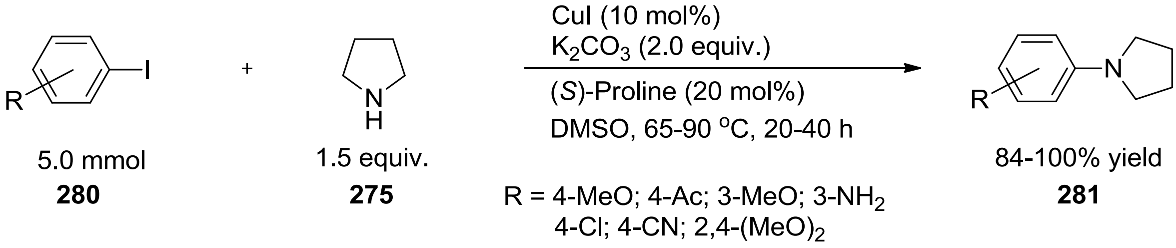
Scheme 50.The copper-catalyzed amination of iodobenzene



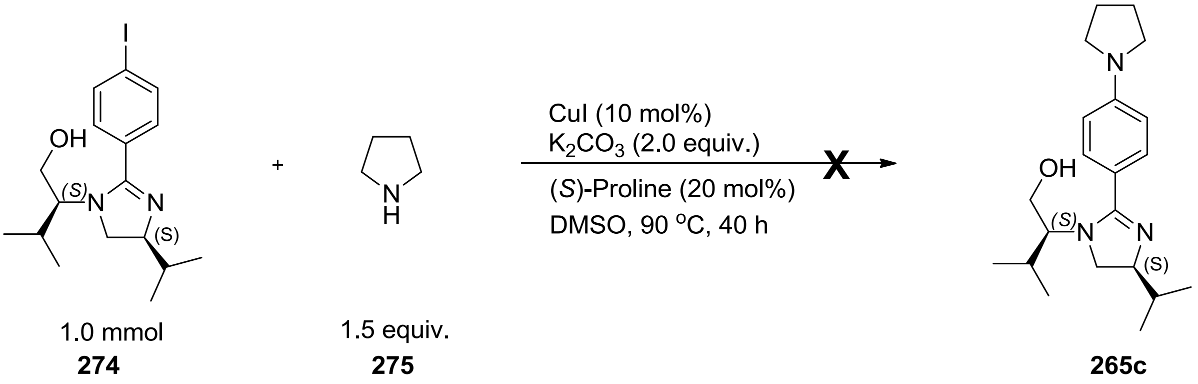
Scheme 51. The unsuccessful synthesis of **265c** by Buchwald's method

In 2005, Ma *et al.*[110] introduced a CuI-catalyzed coupling reaction of electron-deficient aryl iodides with aliphatic secondary amines at 65-90 °C in the presence of (*S*)-proline (Scheme 52), but this method fails in the synthesis of the compound **265c** from **274** and (275) (Scheme 53).

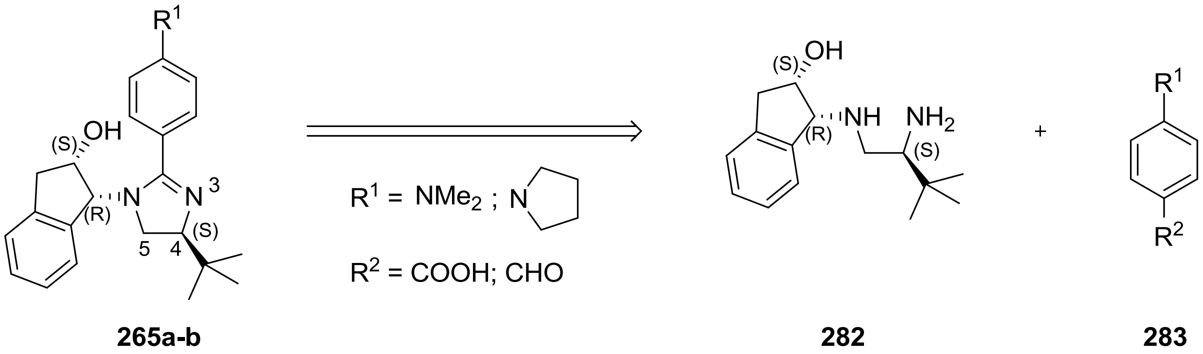
Another possible route to achieve the compound **265a** and **265b** is the condensation of carbonyl compound **283** and diamino alcohol **282** respectively (Scheme 54). For example, Fujioka *et al.*[111] presented the synthesis of imidazoline **286** via the condensation of benzaldehyde (284) and diamine **285** and Shu *et al.*[112] described a one-step synthesis of imidazoline **289** in multi-kilogram scale by using boric acid as a catalyst (Scheme 55). These methods were applied in the synthesis of imidazolines **292** and **294** analogous with the imidazolines **265a** and **265b**, but these methods failed in the synthesis of **292** or **294** (Scheme 56).



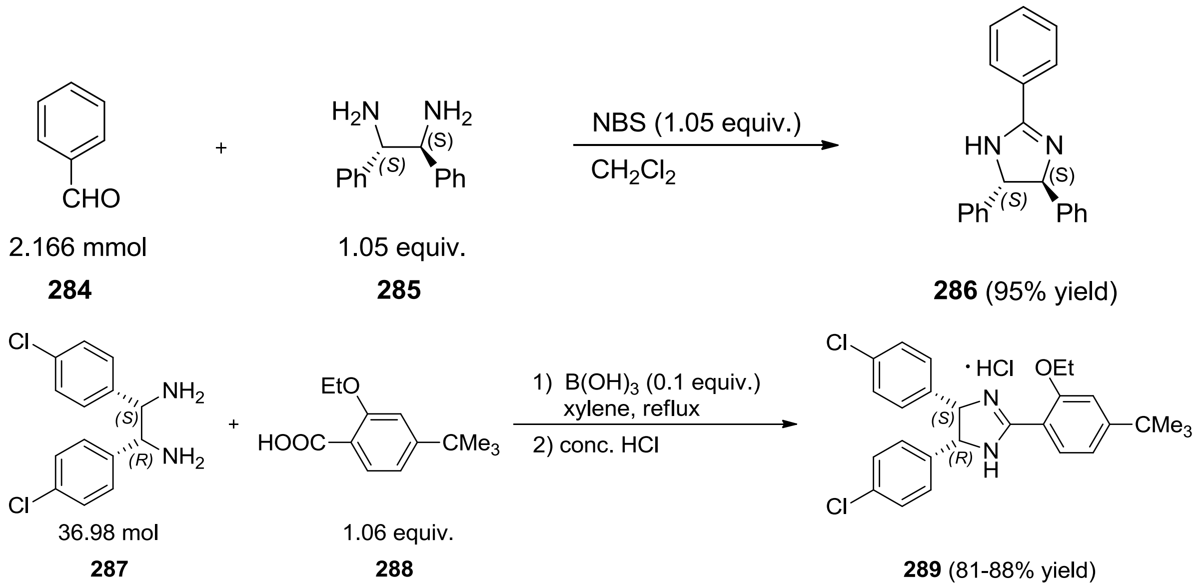
Scheme 52. The CuI-catalyzed coupling reaction of aryl iodides



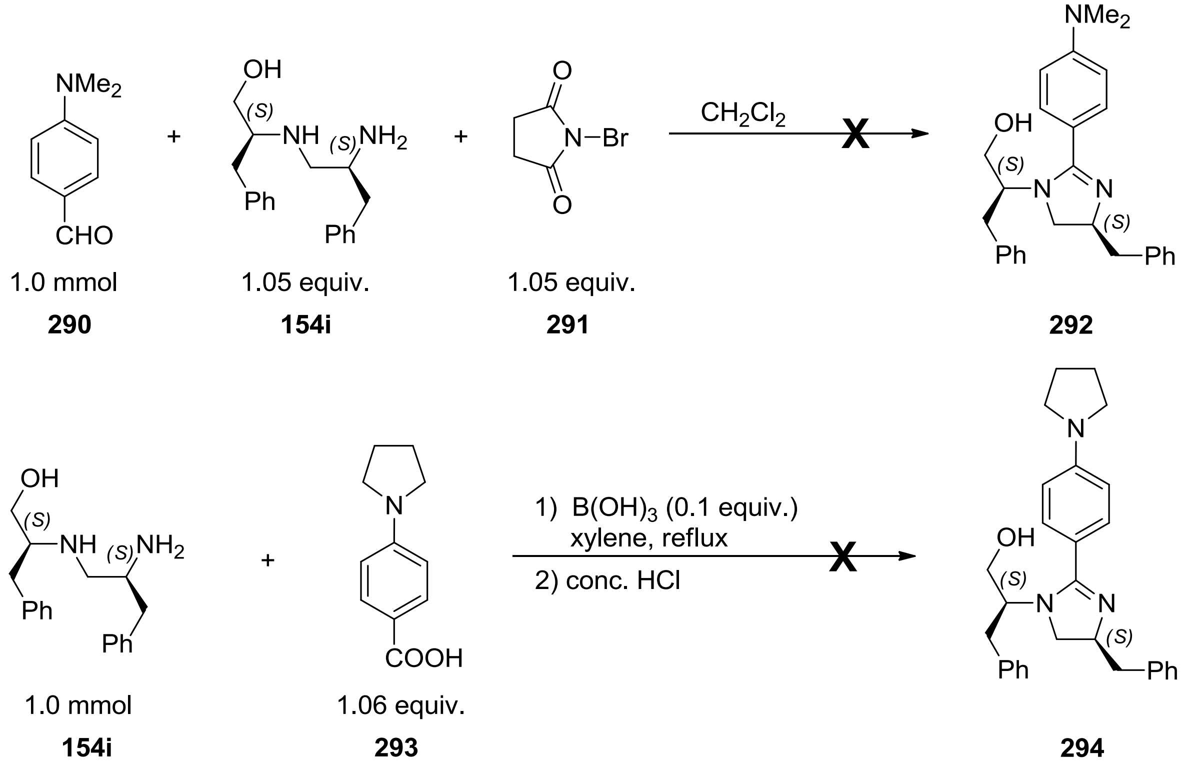
Scheme 53. The unsuccessful synthesis of **265c** using the CuI/(*S*)-proline catalyst



Scheme 54. The retrosynthesis of the imidazolines **265a-b** from the diamine **282**



Scheme 55. The synthesis of imidazolines via the condensation of carbonyl compounds with diamines.



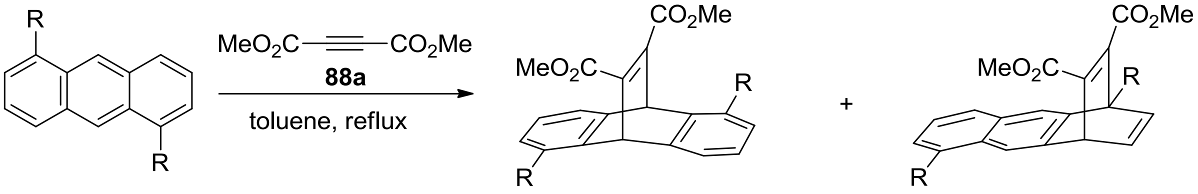
Scheme 56. The unsuccessful synthesis of analogous imidazolines **292** and **294**

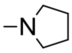
Conclusion: We synthesized the imidazoline **253a-b** from the commercially available amino alcohol **255** and used them as catalysts in the MBH reaction. However, the results are far from ideal because of low chemical yield (60% yield) and low optical purity (46% ee) of the products. Despite many efforts, we are unsuccessful in the synthesis of analogous imidazolines **265a-c** due to the interference of the dimethylamino group or the pyrrolidin-1-yl present in these compounds.

8. Summary

8.1. 1,4-Cycloaddition of anthracenes

The Diels-Alder reactions of anthracenes preferably lead to 9,10-cycloadducts because of the high π-electron concentration at the center ring and the smaller aromaticity loss during reaction at the center ring of anthracenes. The 1,4-cycloadducts can be formed when 1) the terminal rings carry electron-donating groups, or the center ring carries bulky groups; or 2) using molecular host to force electrophiles to locate near the terminal rings so that the 1,4-cycloaddition can happen. We have synthesized three 9,10-unsubstituted-anthracenes (83a), (83b), and (83c) reacting with DMAD to give 1,4-cycloadducts. The results (Scheme 57) shows that the stronger the electron-donating group on the terminal ring, the higher the 1,4-cycloadduct/9,10-cycloadduct ratio and together with benzyne, DMAD is also a special electrophile in the Diels-Alder reactions of anthracenes. The isolated yield of the compound **96a** (78% yield) is the highest yield up to now for the formation of 1,4-cycloadducts of 9,10-unsubstituted-anthracenes.

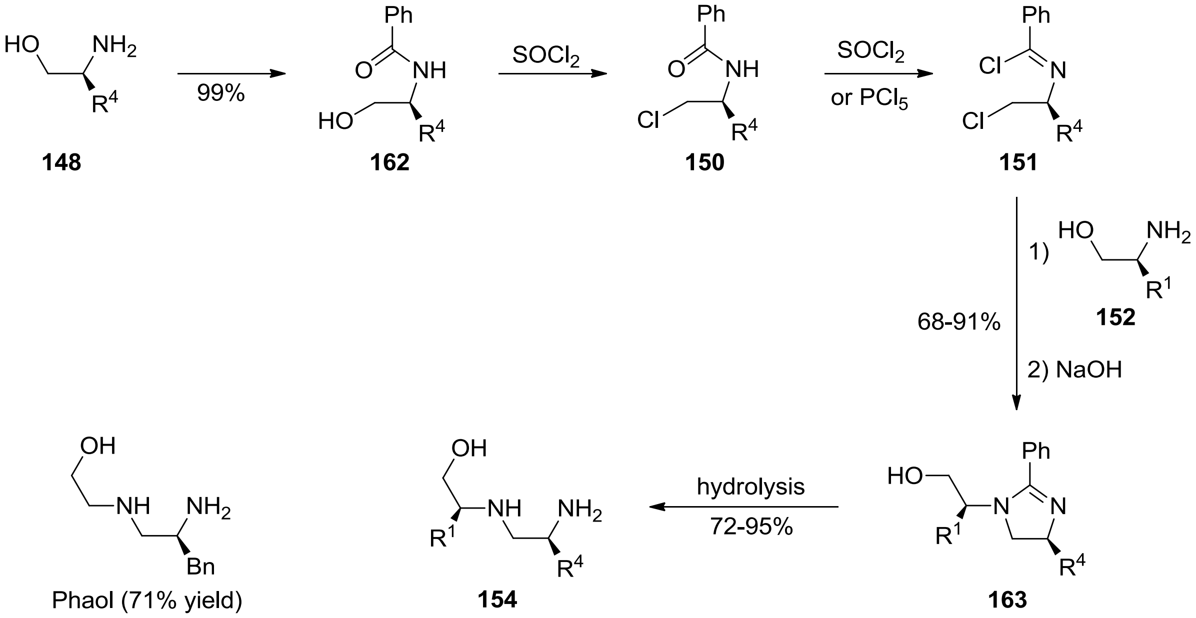


46 : R = —H		**89a**	>99 : 1	(87%)	**90a**
83a: R = −OMe		**91a**	10 : 1	(75%)	**92a**
83b: R = −NMe_2		**93a**	1 : 2.4	(68%)	**94a**
83c: R = −N		**95a**	1 : >99	(78%)	**96a**

Scheme 57. The effect of electron-donating groups on the regioselectivity

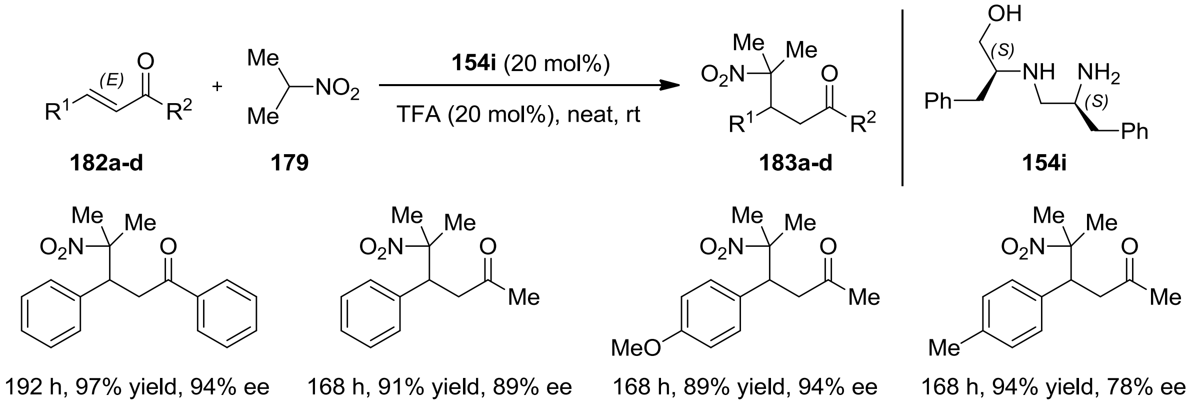
8.2. A practical method for the synthesis of diamino alcohols

Diamino alcohols found in peptaibols have been prepared by the reduction of dipeptides or the coupling of two amino alcohols, however inefficiently, due to the low yield, the requirement of an excess amount of reagents, and the irreproducible syntheses. This thesis describes a practical method to synthesize chiral diamino alcohols in high yields (up to 95% yield) with the retention of the configuration of chiral starting materials by the hydrolysis of 2-imidazolines formed from two chiral amino alcohols (Scheme 58). With this protocol, Phaol was synthesized in large scale and in high yield (71% total yield from (*S*)-phenylalaninol)



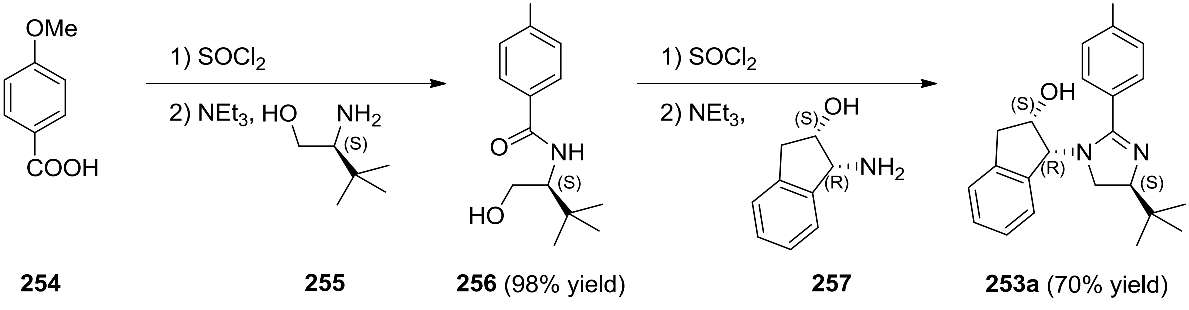
Scheme 58. The preparation of **154** from amino alcohols

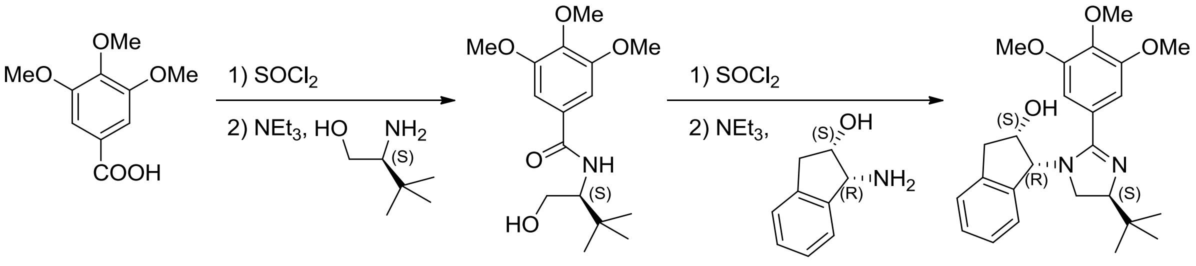
The product **154i** which has a mild Brønsted acid, i.e. alcohol group, in its structure was used as a catalyst in the Michael additions of 2-nitropropane to α,β-unsaturated enones to give Michael adducts in high yield and enantioselectivity (Scheme 59). The catalytic activity in the asymmetric Michael reaction of the compound **154i** prepared in gram scale is better than the catalysts **167** and **168** but is not so good as the catalyst **177** in term of yield and enantioselectivity.



Scheme 59. The enantioselective Michael reaction catalyzed by **154i**

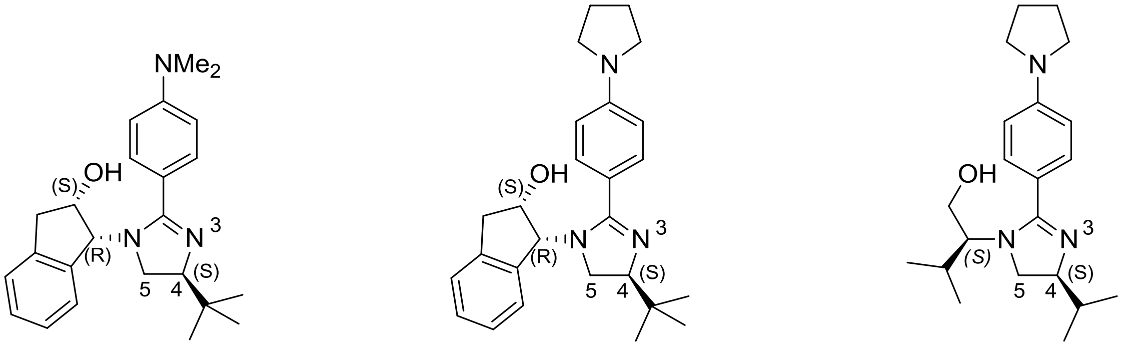
The 2-imidazolines **253a** and **253b** analogous to the compounds **163a-k** were synthesized from such commercial amino alcohols as (*S*)-*tert*-leucinol and (1*R*,2*S*)-*cis*-1-amino-2-indanol (Scheme 60). The catalytic activity of **253a** and **253b** was screened in the MVK-based MBH reaction, and the results showed that the compound **253b** has better catalytic activity than the compound **253a,** but the results are far from ideal because of the low chemical yield (60% yield) and low enantioselectivity (46% ee). We fail in the synthesis of the compounds **265a** and **265b** (Scheme 61) which are speculated to have better catalytic activity than the compound **253b**.





258 **255** **259** (96% yield) **257** **253b** (74% yield)

Scheme 60. The synthesis of the 2-imidazoline catalysts **253a-b** for the MVK-based MBH reaction



265a **265b** **265c**

Scheme 61. The unsuccessful synthesis of the 2-imidazoline catalysts **265a-c**

9. Experimental part

9.1. General comments

Commercial chemicals were used as received without any further purification. Reactions with moisture-sensitive chemicals were performed in a flame-dried flask under nitrogen atmosphere. Solvents were dried by standard methods or taken from the MB-SPS solvent purification system. Hexane (40-60 ^{o}C), dichloromethane, ethyl acetate were distilled before using. Triethylamine was dried with KOH and then was distilled under a nitrogen atmosphere. Analytical thin layer chromatography was performed on Merck TLC aluminium sheets silica gel 60 F254. Visualization was accomplished with UV light (254 nm). For staining vanillin, ninhydrin or permanganate solutions followed by heating were used. Liquid chromatography was performed using Merck flash silica gel 60 (0.040-0.063 mm).

^{1}H NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400. The chemical shifts, δ, are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26 ppm; DMSO-d_6, δ = 2.50 ppm; MeOD-d_4, δ = 3.31 and 4.87 ppm). The following abbreviations for the spin multiplicity were used: s = singlet, d = doublet, t = triplet, q = quartet, qt = quintet, m = multiplet, br = broad, dt = doublet of a triplet, dd = double doublet, ddd = doublet of a double doublet, sept = septet. Data are reported as follows: chemical shift, multiplicity, coupling constants (Hz) and integration.

^{13}C NMR-Spectra were recorded on Bruker Avance 300, Bruker Avance 400. The chemical shifts, δ, are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 77.16 ppm; DMSO-d_6, δ = 39.50 ppm; MeOD-d_4, δ = 49.00 ppm). The multiplicity of the signals was detected by DEPT 135 and 90 (DEPT = distortionless enhancement by polarization transfer)

Mass spectrometry was performed on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000 or Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS at the Central Analytical Laboratory (University of Regensburg). The percentage set in brackets gives the peak intensity related to the basic peak (I = 100%). High-resolution mass spectrometry (HRMS): The molecular formulas were calculated from the precise mass measurements.

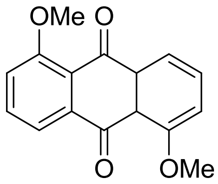
X-ray analysis: All X-ray measurements were performed by the crystallographic department of the University of Regensburg.

Melting points: The melting points were measured on a Büchi SMP-20 apparatus in a silicon oil bath or on a SRS MPA 100 OptiMelt. Values thus were not corrected.

Optical rotation: The optical rotation was determined in a Perkin Elmer 241 polarimeter at 589 nm wavelength (sodium-d-line) in a 1.0 dm measuring cell of ca. 2 mL volume.

HPLC: High-performance liquid chromatography was carried out using Varian 920-LC with DAD. Phenomenex Lux Cellulose-2 or Chiralcel OD-H served as a chiral stationary phase.

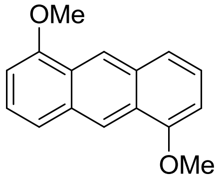
9.2. Diels-Alder reaction of anthracene compounds (83a-c)



1,5-dimethoxy-9,10-anthraquinone (**82a)**

To a stirred solution of 1,5-dihydroxy-9,10-anthraquinone (9.61 g, 40 mmol) and K_2CO_3 (15.81 g, 114.40 mmol) in 50 ml of acetone, dimethyl sulfate (8.27 ml, 87.20 mmol) was added. The reaction mixture was refluxed for 48 h. After being cooled to room temperature, the solvent of the reaction mixture was removed to dry. The crude product was purified by flash chromatography (DCM) and the product (82a) was obtained as yellow needles (8.43 g, 78% yield).

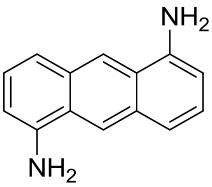
This is a known compound. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.01 – 7.78 (m, 2H), 7.77 – 7.51 (m, 2H), 7.38 – 7.09 (m, 2H), 4.13-3.82 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 182.8, 159.8, 137.5, 135.1, 120.9, 119.8, 116.8, 56.6



1,5-bis(dimethoxy)anthracene (83a)

To a stirred solution of 1,5-dimethoxy-9,10-anthraquinone (82a) (2.62 g, 9.75 mmol) in 50 ml ^{i}PrOH, sodium borohydride (737 mg, 19.50 mmol) was added. The mixture was refluxed for 48 h, and cooling down to room temperature and then with an ice bath to 0-5 ^{o}C. HCl 10 wt. % was added to the mixture until the pH of the solution was 3-4. The crude product was extracted with DCM (3 x 25 ml) and was purified by flash column chromatography using PE-DCM (60:40) as eluent to give the product (83a) as white needles (1.48 g, 64% yield).

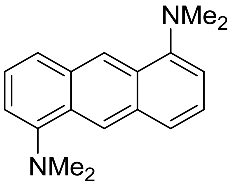
This is a known compound. **Mp** 232.5 °C (lit.[113] **mp** 227-228 °C); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.79 (s, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.36 (dd, J = 8.5, 7.4 Hz, 2H), 6.75 (d, J = 7.3 Hz, 1H), 4.08 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.5, 132.3, 125.3, 121.3, 120.6, 102.1, 55.7; **HRMS** *m/z*: [M^+] calcd. for $C_{16}H_{14}O_2$ 238.0094; Found 238.0096



1,5-diaminoanthracene (87)

This compound was prepared by the method of Kendall and Shechter.[36] A suspension of 1,5-diamino-9,10-anthraquinone (81b) (6.6 g, 27.7 mmol), zinc (10 g, 153.9 mmol), and sodium hydroxide (200 ml, 10 wt. %) was stirred. The mixture was then warmed to 90 °C, and addition zinc (10 g) was added in portions (be careful: the solution will be spilled out if the addition of zinc is fast). After heating the mixture at 90 °C for 30 min, more zinc (10 g) was added. The mixture was heated for 60 h. The solids were filtered under vacuum from the hot solution, washed with water, dried in an oven, and placed on a continuous column extractor of silica gel. With chloroform as refluxing eluent, the solid was extracted until the extract was almost colorless or light color. Chilling of chloroform, followed by vacuum-filtration, yielded (87) as dark brown needles (4.5 g, 78% yield).

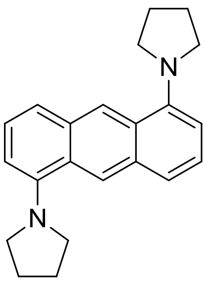
The compound (87) is a known compound. **^{1}H NMR** (300 MHz, DMSO-d_6): δ 8.57 (s, 2H), 7.40 – 6.97 (m, 4H), 6.61 (d, J = 6.9 Hz, 2H), 5.83 (s, 4H); **^{13}C NMR** (75 MHz, DMSO-d_6): δ 144.2, 131.3, 125.8, 123.0, 120.5, 116.0, 104.7



1,5-bis(*N*,*N*-dimethylamino)anthracene (83b)

To a solution of 1,5-diaminoanthracene (87) (4.0 g, 19.2 mmol) and methyl iodide (12.0 ml, 192 mmol) in THF dry (200 ml) at 0-5 °C under the nitrogen atmosphere was added sodium hydride 60% dispersion in mineral oil (7.68 g, 192 mmol) in portions. The resulting mixture was stirred at room temperature for 12 h and then reflux for another 12 h. When the reaction was finished (monitored by TLC with PE-EA = 80:20), the mixture was cooled by an ice bath, and water was added slowly. After evaporation of THF under reduced pressure, the mixture was extracted with DCM (3 x 40 ml). The combined extracts were washed with brine, dried over $MgSO_4$ and removed the solvent to give a black residue which was purified by flash column chromatography to afford bright yellow solids (83b) (3.2 g, 63% yield).

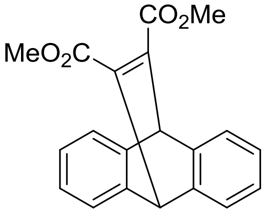
Mp 145.2 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.78 (d, J = 3.5 Hz, 1H), 7.75 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 10.4, 5.2 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 3.01 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.6, 132.8, 127.5, 125.2, 123.6, 112.6, 45.3; **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{21}N_2$ 265.1699; Found 265.1702



1,5-bis(pyrrolidin-1-yl)anthracene (83c)

To a suspension of 1,5-diaminoanthracene (87) (2.0 g, 9.60 mmol) and K_2CO_3 (5.31 g, 38.41 mmol) in 40 ml dioxane-water (1:1 v/v), 1,4-dibromobutane (3.49 ml, 28.81 mmol) was added at room temperature. After heating the mixture at reflux condition for 24h, another amount of 1,4-dibromobutane (3.49 ml, 28.81mmol) was added. The stirred mixture was refluxed for other 24 h. Cool water was added to the reaction mixture, and the crude product was extracted with DCM (3 x 25 ml). The combined extracts were dried over $MgSO_4$ and removed the solvent to give a black residue which was purified by flash column chromatography to afford bright yellow solids (83c) (1.55g, 51% yield).

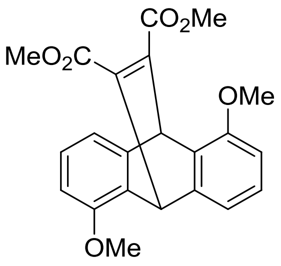
Mp 195.7 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.74 (s, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.45-7.28 (m, 2H), 6.91 (d, J = 7.3 Hz, 2H), 3.50 (t, J = 6.4 Hz, 8H), 2.27 – 1.91 (m, 8H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 147.3, 132.4, 127.1, 125.1, 123.9, 122.1, 109.7, 52.8, 25.0; **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{25}N_2$ 317.2012; Found 317.2013



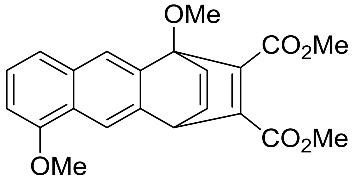
Dimethyl 9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate[114] (89a)

A sealed tube containing anthracene (46) (200 mg, 1.12 mmol) and (88a) (175 mg, 1.23 mmol) in 2.2 ml of toluene was heated to reflux for 24 h. The volatile substances were removed under reduced pressure to give a crude product which was purified by flash column chromatography (PE-DCM = 50:50) to yield the pure product as white solids (314 mg, 87% yield).

The compound **89a** is a known compound. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 – 7.32 (m, 4H), 7.10 – 6.94 (m, 4H), 5.48 (s, 2H), 3.79 (s, 6H). Analytical data match published values.



(±)-91a



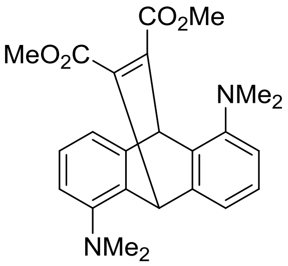
(±)-92a

Dimethyl 1,5-dimethoxy-9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate (91a) and dimethyl 1,5-dimethoxy-1,4-dihydro-1,4-ethenoanthracene-2,3-dicarboxylate (92a)

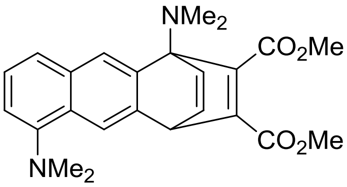
A sealed tube containing (83a) (300 mg, 1.26 mmol) and (88a) (197 mg, 1.38 mmol) in 2.5 ml of toluene was heated to reflux for 48 h. The volatile substances were removed under reduced pressure to give a crude product which was purified by flash column chromatography (PE-DCM = 50:50) to afford **91a** (351 mg, 73% yield) as white solids and **92a** (29 mg, 6% yield) as white solids.

91a: **mp** 239.7 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.07 (d, *J* = 7.2 Hz, 1H), 7.02 – 6.91 (m, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.93 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.1, 154.6, 147.8, 146.3, 131.9, 126.3, 116.8, 108.7, 55.8, 52.4, 45.9; **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{21}O_6$ 381.1333; Found 381.1337

92a: **mp** 144.2 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.81 (s, 1H), 7.45 – 7.29 (m, 2H), 7.16 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.02 (dd, *J* = 7.4, 6.1 Hz, 1H), 6.81 (dd, *J* = 5.9, 2.8 Hz, 1H), 5.93 (s, 1H), 5.44 (dd, *J* = 6.1, 1.4 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.83 (s, 3H), 3.73 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.5, 163.3, 155.2, 141.7, 139.0, 138.2, 135.6, 132.0, 126.1, 122.8, 120.5, 119.1, 115.6, 104.7, 89.3, 55.6, 52.5, 46.9; **HRMS** *m/z*: $[M+H]^+$ cacld. for $C_{22}H_{21}O_6$ 381.1333; Found 381.1338



(±)-93a



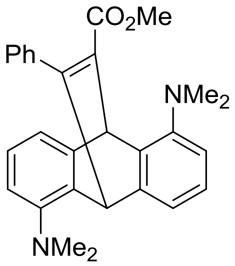
(±)-94a

Dimethyl 1,5-bis(dimethylamino)-9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate (93a) and dimethyl 1,5-bis(dimethylamino)-1,4-dihydro-1,4-ethenoanthracene-2,3-dicarboxylate (94a)

A sealed tube containing (83b) (200 mg, 756 µmol) and (88a) (118 mg, 832 µmol) in 1.5 ml of toluene was heated to reflux for 24 h. The volatile substances were removed under reduced pressure to give a crude product which was purified by flash column chromatography (DCM-EA = 96:4) to yield **93a** (61 mg, 20% yield) as white solids and **94a** (178 mg, 58% yield) as white solids.

93a: **mp** 183.6 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.14 (d, *J* = 7.1 Hz, 2H), 6.95 (t, *J* = 7.7 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 5.95 (s, 2H), 3.79 (s, 6H), 2.77 (s, 12H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 166.4, 150.0, 147.8, 145.3, 137.8, 125.8, 118.8, 115.8, 52.4, 48.5, 45.1; **HRMS** *m/z*: $[M+H]^+$ cacld for $C_{24}H_{27}N_2O_4$ 407.1965; Found 407.1974

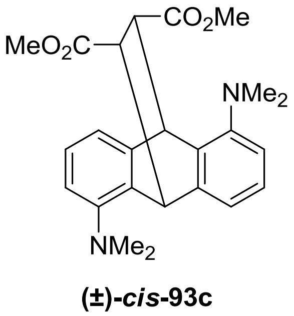
94a: **mp** 156.7 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 8.03 (s, 1H), 7.86 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.08-7.04 (m, 3H), 5.40 (t, *J* = 3.9 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.90 (s, 6H), 2.87 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 168.5, 163.7, 154.2, 150.5, 142.7, 142.1, 141.7, 139.0, 136.5, 132.2, 126.0, 123.5, 122.74, 117.6, 114.8, 78.6, 52.5, 47.7, 45.3, 42.4; **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{27}N_2O_4$ 407.1965; Found 407.1966



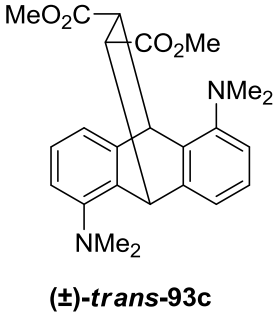
Methyl 1,5-bis(dimethylamino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene-11-carboxylate (93b)

A sealed tube containing (83b) (200 mg, 756 µmol) and (88b) (182 mg, 1.13 mmol) in 1.5 ml of toluene was heated to reflux for 72 h. The volatile substances were removed under reduced pressure to give a crude product which was purified by flash column chromatography with PE-EA= 90:10 as eluent to yield **93b** (62 mg, 19% yield) as white solids.

Mp 174.5 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 – 7.29 (m, 5H), 7.29 – 7.20 (m, 1H), 7.16 (d, J = 7.1 Hz, 1H), 7.01 (dd, J = 14.2, 7.2 Hz, 2H), 6.85-6.79 (m, 2H), 6.27 (s, 1H), 5.85 (s, 1H), 3.61 (d, J = 0.7 Hz, 3H), 2.88 (s, 6H), 2.72 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.5, 162.0, 149.5 (2C), 146.7, 145.5, 138.8, 138.5, 138.4, 136.8, 128.1, 127.8, 127.7, 125.6, 125.4, 118.6, 118.3, 115.5, 115.2, 55.9, 51.5, 48.4, 45.1 (4C); **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{29}N_2O_2$ 425.2224; Found 425.2230



(±)-*cis*-93c



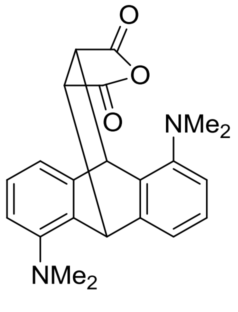
(±)-*trans*-93c

***Cis*- and *trans*-dimethyl 1,5-bis(dimethylamino)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (*cis*-93c and *trans*-93c)**

A sealed tube containing (83b) (200 mg, 756 µmol) and (88c) (118 mg, 832 µmol) in 1.5 ml of toluene was heated to reflux for 24 h. The volatile substances were removed under reduced pressure to give a crude product which was purified by flash column chromatography (PE-EA= 80:20) to give ***cis*-93c** (125 mg, 40% yield) as white solids and ***trans*-93c** (87 mg, 28% yield) as white solids.

***cis*-93c**: **mp** 160.5 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.19 – 6.96 (m, 4H), 6.96 – 6.68 (m, 2H), 5.21 (s, 2H), 3.60 (s, 6H), 3.38 (s, 2H), 2.73 (s, 12H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 173.1, 150.4, 143.0, 134.7, 126.8, 118.5, 116.5, 52.0, 47.5, 45.1, 42.6; **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{29}N_2O_4$ 409.2122; Found 409.2125

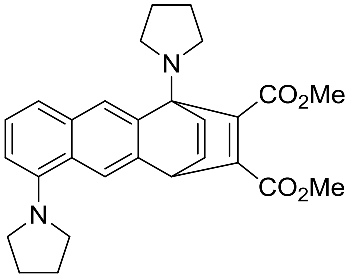
***trans*-93c**: **mp** 140.0 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.15 – 6.96 (m, 4H), 6.87 (d, *J* = 7.6 Hz, 2H), 5.18 (s, 2H), 3.67 (s, 6H), 3.39 (s, 2H), 2.79 (s, 12H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 173.2, 149.2, 141.5, 135.9, 126.5, 119.4, 116.1, 52.3, 47.5, 45.0, 42.1; **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{29}N_2O_4$ 409.2122; Found 409.2127



1,5-bis(dimethylamino)-9,10,11,15-tetrahydro-9,10-[3',4']furanoanthracene-12,14-dione (93d)

A sealed tube containing (83b) (100 mg, 378 µmol) and (88d) (41 mg, 416 µmol) in 0.8 ml of toluene was heated to reflux for 0.5 h. The volatile substances were removed under reduced pressure to give a crude product which was recrystallized from DCM to afford **93d** (120 mg, 88% yield) as white solids.

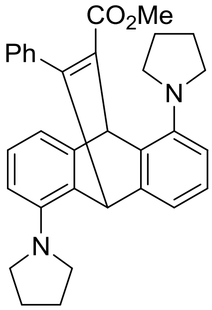
Mp 266.4 °C; **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.21 – 7.00 (m, 4H), 7.00 – 6.84 (m, 2H), 5.37 (d, *J* = 3.0 Hz, 1H), 5.25 (d, *J* = 2.8 Hz, 1H), 3.57 – 3.30 (m, 2H), 2.77 (s, 6H), 2.74 (s, 6H); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 171.0, 170.5, 150.7, 150.3, 142.0, 139.0, 134.7, 133.1, 128.1, 127.4, 119.9, 118.7, 118.0, 117.0, 48.0, 47.9, 45.1, 45.0, 41.3, 40.9; **HRMS** *m/z*: [M$^+$] calcd. for $C_{22}H_{22}N_2O_3$ 362.1630; Found 362.1627



Dimethyl 1,5-bis(pyrrolidin-1-yl)-1,4-dihydro-1,4-ethenoanthracene-2,3-dicarboxylate (96a)

A sealed tube containing (83c) (200 mg, 632 µmol) and (88a) (99 mg, 695 µmol) in 1.3 ml of toluene was heated to reflux for 24 h. The volatile substances were removed under reduced pressure to give a crude product which was purified by flash column chromatography (DCM-EA = 95:5) to yield **96a** (226 mg, 78% yield) as white solids.

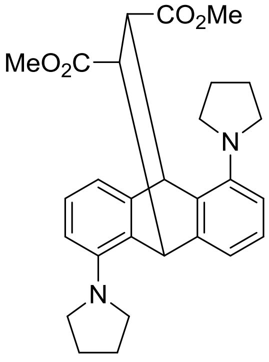
Mp 200.1 °C; **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.98 (s, 1H), 7.87 (s, 1H), 7.39 – 7.28 (m, 2H), 7.08 – 7.04 (m, 1H), 7.01 – 6.93 (m, 2H), 5.40 (dd, *J* = 6.0, 1.6 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.53 – 3.29 (m, 6H), 3.29 – 3.16 (m, 2H), 2.03 (br, 8H); **^{13}C NMR** (75 MHz, CDCl$_3$): δ 168.1, 163.8, 154.9, 147.4, 142.3, 142.0, 140.6, 139.3 (2C), 132.4, 125.9, 125.5, 122.6, 122.1, 118.1, 112.7, 79.0, 52.8 (2C), 52.7, 52.4, 51.4 (2C), 47.8, 26.3 (2C), 24.7 (2C); **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{31}N_2O_4$ 459.2278; Found 459.2280

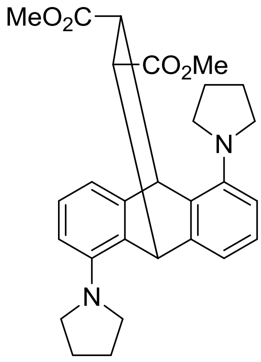


Methyl 12-phenyl-1,5-bis(pyrrolidin-1-yl)-9,10-dihydro-9,10-ethenoanthracene-11-carboxylate (95b)

A sealed tube containing (83c) (200 mg, 632 µmol) and (88b) (506 mg, 3.16 mmol) in 1.3 ml of toluene was heated to reflux for 24 h. The volatile substances were removed under reduced pressure to give a crude product which was purified by flash column chromatography (PE-DCM = 40:60) to yield **95b** (69 mg, 23% yield) as white solids.

Mp 189.7 °C; ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.32 (d, J = 5.3 Hz, 5H), 7.04 (d, J = 6.5 Hz, 1H), 7.00 – 6.76 (m, 3H), 6.58 (d, J = 8.0 Hz, 2H), 6.34 (s, 1H), 5.81 (s, 1H), 3.70 – 3.42 (br, 7H), 3.42 – 3.03 (m, 4H), 2.59 – 1.53 (m, 8H); ^{13}**C NMR** (75 MHz, $CDCl_3$): δ 166.5, 162.1, 147.6, 146.6, 146.2, 145.8, 138.8, 136.9, 133.0, 132.3, 127.9, 127.7 (2C), 125.6, 125.5, 115.4, 114.5, 112.6, 112.5, 57.6, 52.1 (2C), 51.8 (2C), 51.4, 49.6, 25.9 (2C), 25.6 (2C); **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{32}H_{33}N_2O_2$ 477.2537; Found 477.2538


(±)-*cis*-95c

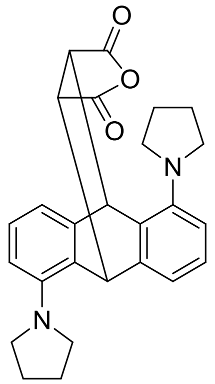

(±)-*trans*-95c

***Cis*- and *trans*-dimethyl 1,5-bis(pyrrolidin-1-yl)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (*cis*-95c and *trans*-95c)**

A sealed tube containing (83c) (200 mg, 632 μmol) and (88c) (99 mg, 695 μmol) in 1.3 ml of toluene was heated to reflux for 24 h. The volatile substances were removed under reduced pressure to give a crude product which was purified by flash column chromatography (DCM-EA = 90:10) to yield ***cis*-95c** (160 mg, 55% yield) as white solids and ***trans*-95c** (89 mg, 31% yield) as white solids.

***cis*-95c**: **mp** 189.7 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.03 (t, J = 7.7 Hz, 2H), 6.91 (d, J = 7.0 Hz, 2H), 6.63 (d, J = 8.2 Hz, 2H), 5.29 (s, 2H), 3.71 – 3.47 (m, 10H), 3.42 (s, 2H), 3.23 – 3.21 (br, 4H), 2.06 – 2.05 (br, 4H), 1.93 – 1.89 (br, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.3, 146.3, 144.2, 128.6, 126.8, 114.9, 113.4, 51.8, 51.8, 47.5, 44.2, 25.7; **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{33}N_2O_4$ 461.2435; Found 461.2441

***trans*-95c**: **mp** 209.6 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.98 (t, J = 7.7 Hz, 2H), 6.83 (d, J = 7.0 Hz, 2H), 6.68 (d, J = 8.0 Hz, 2H), 5.18 (s, 2H), 3.66 (s, 6H), 3.53 – 3.17 (m, 10H), 2.00 (br, 8H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.3, 145.9, 142.3, 131.3, 126.3, 116.6, 113.6, 52.2, 52.0, 47.7, 43.6, 25.5; **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{33}N_2O_4$ 461.2435; Found 461.2437



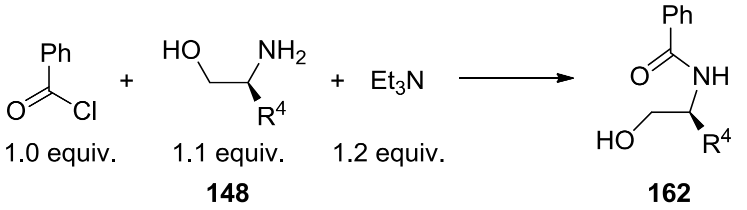
1,5-bis(pyrrolidin-1-yl)-9,10,11,15-tetrahydro-9,10-[3',4']furanoanthracene-12,14-dione (95d)

A sealed tube containing (83c) (100 mg, 316 µmol) and (88d) (34 mg, 348 µmol) in 0.6 ml of toluene was heated to reflux for 24 h. The volatile substances were removed under reduced pressure to give a crude product which was recrystallized from DCM to afford **95d** (98mg, 75% yield) as white solids.

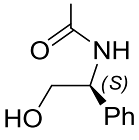
Mp 221.3 °C; **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.03 – 6.97 (m, 3H), 6.75 (d, *J* = 7.0 Hz, 1H), 6.69 (dd, *J* = 6.4, 3.0 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 5.31 (d, *J* = 3.1 Hz, 1H), 5.01 (d, *J* = 2.7 Hz, 1H), 3.64 – 3.53 (m, 2H), 3.51 – 3.39 (m, 2H), 3.36 – 3.28 (m, 2H), 3.28 – 3.12 (m, 4H), 2.03 – 1.78 (m, 8H); **^{13}C NMR** (101 MHz, DMSO-d_6): δ 171.8, 171.7, 146.1, 145.8, 143.3, 140.6, 129.2, 127.2, 126.8, 126.1, 115.8, 115.4, 114.0, 113.8, 51.6, 51.3, 48.0, 47.7, 42.2, 41.4, 25.2, 25.0.; **HRMS** *m/z*: [M$^+$] calcd. for $C_{26}H_{26}N_2O_3$ 414.1943; Found 414.1939

9.3. Preparation of diamino alcohols 154a-k

9.3.1. General procedure for the preparation of hydroxy amides 162



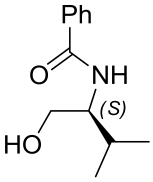
To a mixture of amino alcohol **148** (39.13 mmol, 1.1 equiv.) and dry triethylamine (5.76 mL, 42.68 mmol, 1.2 equiv.) in dry DCM (80 ml), a solution of benzoyl chloride (35.57 mmol, 1.0 equiv.) in dry DCM (70 ml) was added dropwise with magnetic stirring at 0 ºC. After the stirring for 10 h (overnight) at room temperature, the reaction mixture was washed with 10 wt. % solution of sodium hydroxide (2 x 150 ml) and then with 10 wt. % solution of hydrochloric acid (3 x 150 ml). The organic phase was removed solvent under reduced pressure to afford **162** which was used for the next step without further purification.



(*S*)-*N*-(Benzoyl)phenylglycinol (162a)

According to the general procedure, (*S*)-phenylglycinol (5.37 g, 39.13 mmol), dry triethylamine (5.76 ml, 42.68 mmol), and benzoyl chloride (5.00 g, 35.57 mmol), afforded **162a** (8.50 g, 99% yield) as white solids.

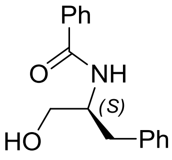
Mp 179.9 °C; **^{1}H NMR** (300 MHz, MeOD): *δ* 7.89 – 7.85 (m, 2H), 7.58 – 7.20 (m, 8H), 5.21 (t, *J* = 6.6 Hz, 1H), 3.86 (d, 6.6 Hz, 2H); **^{13}C NMR** (75 MHz, MeOD): *δ* 170.3, 141.1, 135.8, 132.7, 129.5, 128.4 (2C), 128.0, 66.0, 57.8.



(*S*)-*N*-(Benzoyl)valinol (162b)

According to the general procedure, (*S*)-valinol (4.04 g, 39.13 mmol), dry triethylamine (5.76 ml, 42.68 mmol), and benzoyl chloride (5.00 g, 35.57 mmol) afforded **162b** (7.32 g, 99% yield) as white solids.

Mp 102.5 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.78 – 7.68 (m, 1H), 7.49 – 7.40 (m, 1H), 7.40 – 7.29 (m, 1H), 6.69 (d, *J* = 8.7 Hz, 1H), 3.88 (qd, *J* = 8.8, 4.4 Hz, 1H), 3.72 (d, *J* = 4.5 Hz, 1H), 3.51 (s, 1H), 1.99 (dq, *J* = 13.8, 6.8 Hz, 1H), 0.97 (dd, *J* = 6.7, 5.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 168.5, 134.6, 131.6, 128.6, 127.1, 63.4, 57.4, 29.2, 19.7, 19.1.

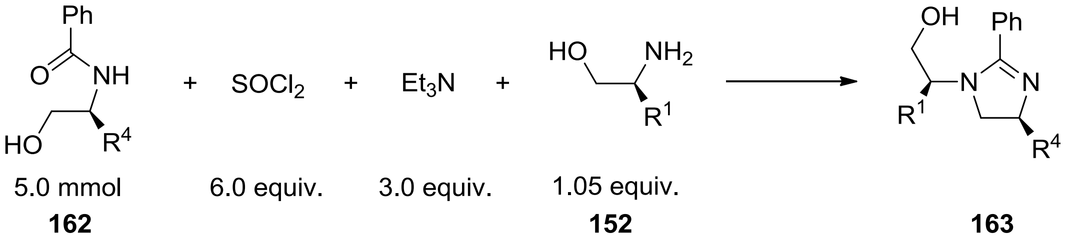


(*S*)-*N*-(Benzoyl)phenylalaninol (162c)

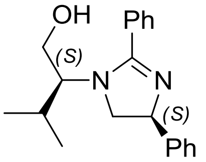
According to the general procedure, (*S*)-phenylalaninol (5.92 g, 39.13 mmol), dry triethylamine (5.76 ml, 42.68 mmol), and benzoyl chloride (5.00 g, 35.57 mmol) afforded **162c** (9.01 g, 99% yield) as white solids.

Mp 170.1 °C; **^{1}H NMR** (300 MHz, DMSO): δ 8.19 (d, J = 8.4 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.55 – 7.37 (m, 3H), 7.32 – 7.21 (m, 4H), 7.21 – 7.09 (m, 1H), 4.87 (s, 1H), 4.26 – 4.09 (m, 1H), 3.59 – 3.36 (m, 2H), 2.97 (dd, J = 13.7, 5.2 Hz, 1H), 2.80 (dd, J = 13.7, 9.1 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO): δ 166.0, 139.5, 134.8, 131.0, 129.1, 128.2, 128.1, 127.2, 125.9, 62.9, 53.3, 36.5.

9.3.2. General procedure for the preparation of 2-imidazolines 163[47]



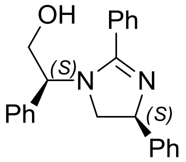
A solution of hydroxyamide **162** (5.0 mmol, 1.0 equiv.) in thionyl chloride (30.0 mmol, 6.0 equiv.) was stirred for 4 h at reflux to form the chloroalkyl imidoyl chloride. Excess thionyl chloride was removed under reduced pressure, and the crude dichloride was dissolved in dry DCM (10 ml). This solution was added dropwise to a magnetically stirred solution of the second amino alcohol **152** (5.25 mmol, 1.05 equiv.) and dry triethylamine (≈ 2.0 ml, 15 mmol, 3.0 equiv.) in dry DCM (10 ml) at 0 °C. After being stirred at room temperature for 10 h (overnight), the reaction mixture was washed with 10 wt. % NaOH (20 ml) and the aqueous was extracted with DCM (3 x 20 ml). The combined organics were washed with brine and dried over MgSO4, and the solvent was removed in vacuo. The resulting crude product was then purified by flash column chromatography or recrystallization to yield the 2-imidazoline **163**.



(4*S*)-1-((2*S*)-1-hydroxy-3-methyl-but-2-yl)-2,4-diphenyl-4,5-dihydroimidazole (163a)

According to the general procedure, hydroxyamide **162a** (1.21 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-valinol (542 mg, 5.25 mmol) afforded **163a** (1.051 g, 68% yield) as white solids after crystallization from PE-EA.

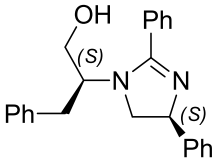
$[\alpha]_D^{20}$ = -93.56 (*c* 1.002, $CHCl_3$). **Mp** 150.4 °C; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58 – 7.46 (m, 1H), 7.43 – 7.27 (m, 3H), 7.27 – 7.18 (m, 1H), 5.22 – 5.06 (m, 1H), 3.86 – 3.68 (m, 1H), 3.63 – 3.44 (m, 1H), 3.43 – 3.28 (m, 1H), 3.28 – 3.12 (m, 1H), 2.67 (br, 1H), 1.79 – 1.57 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 1H), 0.80 – 0.68 (m, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.2, 145.1, 132.0, 129.6, 129.0, 128.7, 128.4, 127.1, 126.9, 67.4, 62.9, 60.7, 51.9, 28.4, 20.4, 19.8. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{25}N_2O_1$ 309.1961; Found 309.1967



(4*S*)-1-((1*S*)-2-hydroxy-1-phenyl-eth-1-yl)-2,4-diphenyl-4,5-dihydroimidazole (163b)

According to the general procedure, hydroxyamide **162a** (1.21 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-phenylglycinol (720 mg, 5.25 mmol) afforded **163b** (1.301 g, 76% yield) as white solids after crystallization from PE-DCM.

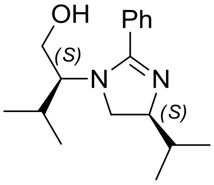
$[\alpha]_D^{20}$ = -128.91 (*c* 0.510, $CHCl_3$). **Mp** 168.2 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.58 (br, 2H), 7.46 – 7.13 (m, 11H), 7.01 (d, *J* = 1.8 Hz, 2H), 5.00 – 4.82 (m, 1H), 4.80 – 4.65 (m, 1H), 4.21 – 3.50 (m, 4H), 3.44 – 3.27 (m, 1H); **^{13}C NMR** (75 MHz, CDCl$_3$): *δ* 167.4, 144.8, 137.9, 131.4, 130.0, 128.8, 128.7, 128.6, 128.6, 127.8, 127.2, 127.1, 126.9, 67.3, 60.8, 60.0, 52.4. **HRMS** *m/z*: [M+H]$^+$ calcd. for $C_{23}H_{23}N_2O_1$ 343.1805; Found 343.1811



(4*S*)-1-((2*S*)-1-hydroxy-3-phenyl-prop-2-yl)-2,4-diphenyl-4,5-dihydroimidazole (163c)

According to the general procedure, hydroxyamide **162a** (1.21 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-phenylalaninol (794 mg, 5.25 mmol) afforded **163c** (1.47 g, 83% yield) as light yellow liquid after flash column chromatography on silica gel (DCM-MeOH = 90:10).

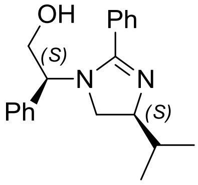
$[\alpha]_D^{20}$ = -179.82 (*c* 0.502, CHCl$_3$). **^{1}H NMR** (300 MHz, CDCl$_3$): *δ* 7.37 – 7.13 (m, 1H), 7.07 – 6.88 (m, 1H), 5.06 – 4.86 (m, 1H), 4.31 – 3.78 (m, 1H), 3.70 (br, 1H), 3.45 – 3.12 (m, 1H), 2.62 – 2.37 (m, 1H); **^{13}C NMR** (75 MHz, CDCl$_3$): *δ* 167.4, 144.6, 138.2, 130.9, 129.6, 129.1, 128.6, 128.6, 128.6, 128.2, 127.2, 126.9, 126.6, 66.9, 61.9, 59.0, 51.7, 35.5. **HRMS** *m/z*: [M+H]$^+$ calcd. for $C_{24}H_{25}N_2O_1$ 357.1961; Found 357.1968



(4*S*)-1-((2*S*)-1-hydroxy-3-methyl-but-2-yl)-2-phenyl-4-isopropyl-4,5-dihydroimidazole (163d)

According to the general procedure, hydroxyamide **162b** (1.04 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-valinol (542 mg, 5.25 mmol) afforded **163d** (985 mg, 72% yield) as white solids after crystallization from PE-DCM.

$[\alpha]_D^{20}$ = -107.05 (*c* 0.514, $CHCl_3$). **Mp** 127.4 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 – 7.39 (m, 2H), 7.34 (br d, *J* = 5.1 Hz, 3H), 4.00 – 3.83 (m, 1H), 3.62 – 3.48 (m, 1H), 3.48 – 3.29 (m, 2H), 3.28 – 3.16 (m, 1H), 3.15 – 3.00 (m, 1H), 1.96 – 1.79 (m, 1H), 1.79 – 1.60 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.9, 131.9, 129.4, 128.9, 128.4, 69.7, 62.9, 61.0, 45.8, 33.4, 27.9, 20.2, 19.8, 19.0, 17.9. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{27}N_2O_1$ 275.2118; Found 275.2120

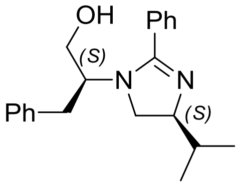


(4*S*)-1-((1*S*)-2-hydroxy-1-phenyl-eth-1-yl)-2-phenyl-4-isopropyl-4,5-dihydroimidazole (163e)

According to the general procedure, hydroxyamide **162b** (1.04 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-phenylglycinol (720 mg, 5.25 mmol) afforded **163e** (1.35 g, 88% yield) as white solids after crystallization from PE-DCM.

$[\alpha]_D^{20}$ = -56.05 (*c* 0.504, $CHCl_3$). **Mp** 147.0 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 5.1, 1.8 Hz, 2H), 7.43 – 7.20 (m, 6H), 7.05 (d, *J* = 6.8 Hz, 2H), 4.68 (d, *J* = 3.6 Hz, 1H), 3.80 (br d, *J* = 2.9 Hz, 4H), 3.31 – 3.13 (m, 2H), 1.95 – 1.72 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.2, 137.8, 131.6, 129.8, 128.7

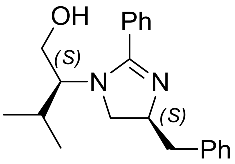
(2C), 128.6, 127.7, 127.2, 69.8, 61.2, 59.9, 46.4, 33.4, 19.0, 17.8. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{20}H_{25}N_2O_1$ 309.1961; Found 309.1962



(4*S*)-1-((2*S*)-1-hydroxy-3-phenyl-prop-2-yl)-2-phenyl-4-isopropyl-4,5-dihydroimidazole (163f)

According to the general procedure, hydroxyamide **162b** (1.04 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-phenylalaninol (794 mg, 5.25 mmol) afforded **163f** (1.21 g, 75% yield) as white solids after crystallization from PE-DCM.

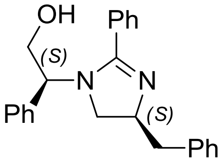
$[\alpha]_D^{20}$ = -188.57 (*c* 0.504, $CHCl_3$). **Mp** 160.3 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 – 7.25 (m, 1H), 7.25 – 7.13 (m, 5H), 7.03 – 6.86 (m, 4H), 3.95 – 3.77 (m, 1H), 3.77 – 3.24 (m, 5H), 3.17 (t, *J* = 8.9 Hz, 1H), 2.68 – 2.44 (m, 2H), 1.81 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.1, 138.4, 131.7, 129.3, 129.1, 128.5, 128.5, 128.1, 126.5, 69.9, 62.4, 58.9, 45.7, 35.3, 33.4, 19.0, 17.9. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{27}N_2O_1$ 323.2118; Found 323.2123



(4*S*)-1-((2*S*)-1-hydroxy-3-methyl-but-2-yl)-2-phenyl-4-benzyl-4,5-dihydroimidazole (163g)

According to the general procedure, hydroxyamide **162c** (1.28 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-valinol (542 mg, 5.25 mmol) afforded **163g** (1.24 g, 77% yield) as white solids after flash column chromatography (DCM-EA = 80:20).

$[\alpha]_D^{20}$ = -64.79 (*c* 0.502, $CHCl_3$). **Mp** 146.0 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39 – 7.23 (m, 10H), 4.59 – 4.44 (m, 1H), 3.48 – 3.29 (m, 2H), 3.22 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.18 (d, *J* = 11.2 Hz, 1H), 3.05 – 2.88 (m, 3H), 1.70 – 1.51 (m, 1H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.68 (d, *J* = 6.6 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.5, 138.1, 131.9, 130.1, 129.4, 128.8, 128.4, 128.3, 126.6, 64.1, 63.0, 61.0, 46.4, 41.8, 27.5, 20.0, 19.7. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{21}H_{27}N_2O_1$ 323.2118; Found 323.2121

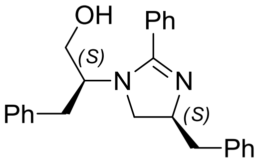


(4*S*)-1-((1*S*)-2-hydroxy-1-phenyl-eth-1-yl)-2-phenyl-4-benzyl-4,5-dihydroimidazole (163h)

According to the general procedure, hydroxyamide **162c** (1.28 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-phenylglycinol (720 mg, 5.25 mmol) afforded **163h** (1.35 g, 76% yield) as white solids after flash column chromatography (first, PE-EA = 60:40 and then DCM-MeOH = 90:10).

$[\alpha]_D^{20}$ = -76.53 (*c* 0.506, $CHCl_3$). **Mp** 58.4 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51 – 7.44 (m, 2H), 7.42 – 7.36 (m, 2H), 7.34 – 7.21 (m, 8H), 6.95 – 6.87 (m, 2H), 4.61 (dd, *J* = 9.6, 5.2 Hz, 1H), 4.34 (dq, *J* = 10.8, 5.5 Hz, 1H), 3.81 – 3.58 (m, 2H), 3.25 (dd, *J* = 9.4, 5.6 Hz, 1H), 3.19 – 3.07 (m, 1H), 2.93 (d, *J* = 5.3 Hz, 2H), 2.20 (br, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ

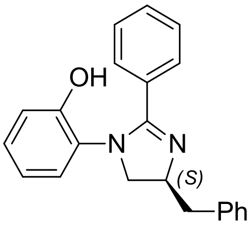
166.7, 138.2, 136.9, 131.4, 130.0, 129.9, 128.7, 128.6 (2C), 128.3, 127.9, 127.2, 126.6, 64.1, 61.0, 59.8, 47.2, 41.8. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{25}N_2O_1$ 357.1961; Found 357.1961



(4*S*)-1-((2*S*)-1-hydroxy-3-phenyl-prop-2-yl)-2-phenyl-4-benzyl-4,5-dihydroimidazole (163i)

According to the general procedure, hydroxyamide **162c** (1.28 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and (*S*)-phenylalaninol (794 mg, 5.25 mmol) afforded **163i** (1.64 g, 89% yield) as white solids after flash column chromatography (DCM-MeOH = 90:10).

$[\alpha]_D^{20}$ = -144.08 (*c* 0.510, $CHCl_3$). **Mp** 150.5 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.39 – 7.12 (m, 11H), 7.02 – 6.91 (m, 2H), 6.89 – 6.76 (m, 2H), 4.52 – 4.31 (m, 1H), 3.61 (dt, *J* = 13.2, 7.5 Hz, 1H), 3.51 (t, *J* = 10.1 Hz, 1H), 3.39 – 3.14 (m, 3H), 3.00 (dd, *J* = 13.5, 4.4 Hz, 1H), 2.88 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.47 (d, *J* = 7.1 Hz, 2H), 2.35 (br, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.7, 138.3, 137.9, 131.3, 130.0 (2C), 129.4, 129.0, 128.6, 128.4, 128.4, 128.1, 126.6, 64.3, 62.3, 58.9, 46.8, 41.9, 35.0. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{25}H_{27}N_2O_1$ 371.2118; Found 371.2119

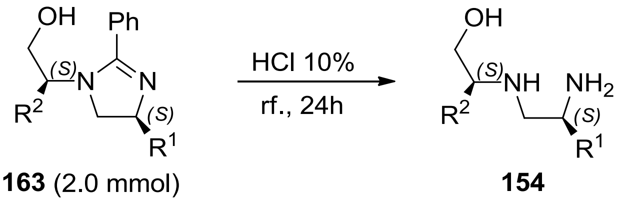


(4*S*)-1-(2-hydroxy-phenyl)-2-phenyl-4-benzyl-4,5-dihydroimidazole (163j)

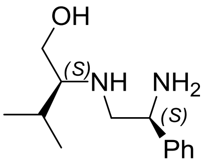
According to the general procedure, hydroxyamide **162c** (1.28 g, 5.0 mmol), thionyl chloride (1.8 ml, 30 mmol), dry triethylamine (2.0 ml, 15 mmol), and 2-aminophenol (573 mg, 5.25 mmol) afforded **163j** (1.49 g, 91% yield) as white solids after flash column chromatography (100% EA).

$[\alpha]_D^{20}$ = -72.84 (*c* 0.506, DMSO). **Mp** 187.2 °C; **^{1}H NMR** (300 MHz, DMSO-d_6): δ 9.67 (br, 1H), 7.46 – 7.37 (m, 2H), 7.24 (m, 8H), 6.92 (td, *J* = 8.1, 1.7 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.51 (td, *J* = 7.6, 1.2 Hz, 1H), 6.41 (d, *J* = 7.5 Hz, 1H), 4.53 – 4.35 (m, 1H), 3.87 (t, *J* = 9.8 Hz, 1H), 3.38 – 3.19 (m, 1H), 3.02 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.83 (dd, *J* = 13.4, 7.2 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO-d_6): δ 162.7, 153.0, 138.7, 131.3, 131.0, 129.6, 129.6, 128.2, 128.1, 128.0, 127.8, 127.1, 126.1, 119.0, 116.3, 65.6, 57.8, 42.0. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{21}N_2O_1$ 329.1648; Found 329.1653

9.3.3. General procedure for the preparation of diamino alcohol 154



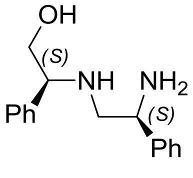
The mixture of 10 wt. % solution of hydrochloric acid (30 ml) and 2-imidazoline **163** (2.0 mmol) was refluxed for 24 h. Then, the reaction mixture was cooled down to room temperature and was added 30 wt. % solution of sodium hydroxide until pH > 12. The product was extracted with DCM (3 x 20 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography on silica gel with DCM-MeOH (90:10) as eluent to give the desired product.



(2*S*)-2-(((2*S*)-2-amino-2-phenylethyl)amino)-3-methylbutan-1-ol (154a)

According to the general procedure, 2-imidazoline **163a** (617 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154a** (409 mg, 92% yield) as light yellow liquid after flash column chromatography (DCM-MeOH = 90:10).

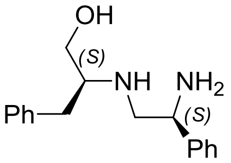
$[\alpha]_D^{20}$ = +50.19 (*c* 0.514, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 – 7.16 (m, 5H), 4.01 (t, *J* = 6.5 Hz, 1H), 3.59 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.32 (dd, *J* = 10.7, 8.0 Hz, 1H), 2.82 (d, *J* = 6.7 Hz, 2H), 2.63 (s, 4H), 2.45 – 2.29 (m, 1H), 1.72 (dt, *J* = 13.5, 6.7 Hz, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.9, 128.7, 127.5, 126.4, 64.7, 61.5, 56.0, 54.8, 29.5, 19.5, 18.7. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{23}N_2O_1$ 223.1805; Found 223.1805



(2*S*)-2-(((2*S*)-2-amino-2-phenylethyl)amino)-2-phenylethanol (154b)

According to the general procedure, 2-imidazoline **163b** (685 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154b** (487 mg, 95% yield) as white solids after crystallization from PE-DCM.

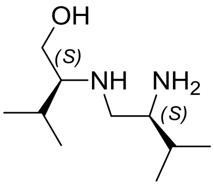
$[\alpha]_D^{20}$ = +121.87 (*c* 0.506, $CHCl_3$). **Mp** 110.9 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.42 – 7.14 (m, 10H), 4.02 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.79 (dd, *J* = 8.8, 4.2 Hz, 1H), 3.68 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.53 (dd, *J* = 10.7, 8.8 Hz, 1H), 2.72 (dd, *J* = 12.0, 4.5 Hz, 1H), 2.63 (dd, *J* = 11.9, 8.7 Hz, 1H), 1.83 (br, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 144.5, 140.8, 128.7, 128.6, 127.6, 127.3 (2C), 126.4, 67.0, 64.4, 55.7, 55.0. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{21}N_2O_1$ 257.1648; Found 257.1651



(2*S*)-2-(((2*S*)-2-amino-2-phenylethyl)amino)-3-phenylpropan-1-ol (154c)

According to the general procedure, 2-imidazoline **163c** (713 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154c** (497 mg, 92% yield) as light yellow liquid after flash column chromatography on silica gel (DCM-MeOH = 90:10 to 70:30).

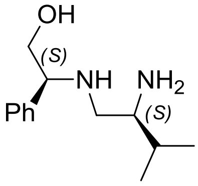
$[\alpha]_D^{20}$ = +19.76 (*c* 0.514, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.37 – 7.17 (m, 8H), 7.17 – 7.09 (m, 2H), 3.96 (dd, *J* = 7.7, 5.1 Hz, 1H), 3.58 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.32 (dd, *J* = 10.8, 6.2 Hz, 1H), 2.90 (qd, *J* = 6.7, 3.9 Hz, 1H), 2.85 – 2.63 (m, 4H), 2.06 (br, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 144.5, 138.7, 129.3, 128.7, 128.6, 127.4, 126.4, 126.3, 63.1, 60.4, 56.0, 54.6, 38.3. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{23}N_2O_1$ 271.1805; Found 271.1806



(2*S*)-2-(((2*S*)-2-amino-3-methylbutyl)amino)-3-methylbutan-1-ol (154d)

According to the general procedure, 2-imidazoline **163d** (549 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154d** (339 mg, 90% yield) as light yellow liquid after flash column chromatography on silica gel (DCM-MeOH = 90:10 to 70:30).

$[\alpha]_D^{20}$ = +43.61 (*c* 0.504, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 3.57 (dd, *J* = 10.7, 4.1 Hz, 1H), 3.30 (dd, *J* = 10.7, 7.7 Hz, 1H), 2.63 (dd, *J* = 11.3, 3.3 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.41 (dd, *J* = 11.3, 9.2 Hz, 1H), 2.32 (ddd, *J* = 7.6, 6.5, 4.1 Hz, 1H), 1.95 (br, 3H), 1.74 (m, 1H), 1.55 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.90 – 0.82 (m, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 64.6, 61.4, 57.0, 51.4, 32.6, 29.5, 19.6, 19.5, 18.7, 17.8. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{10}H_{25}N_2O_1$ 189.1961; Found 189.1963

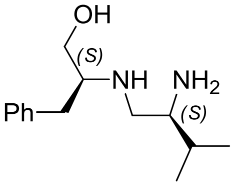


(2*S*)-2-(((2*S*)-2-amino-3-methylbutyl)amino)-2-phenylethanol (154e)

According to the general procedure, 2-imidazoline **163e** (617 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154e** (406 mg, 91% yield) as light yellow liquid after flash column chromatography on silica gel (DCM-MeOH = 90:10 to 70:30).

$[\alpha]_D^{20}$ = +95.47 (*c* 0.516, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.42 – 7.14 (m, 5H), 3.76 (dd, *J* = 8.9, 4.2 Hz, 1H), 3.67 (dd, *J* = 10.7, 4.2 Hz, 1H), 3.52 (dd, *J* = 10.7, 8.9 Hz, 1H), 2.58 (m, 2H), 2.41 – 2.03 (m, 4H), 1.52 (dq, *J* = 13.3, 6.7 Hz, 1H), 0.84 (d, *J* = 2.3 Hz, 3H), 0.82

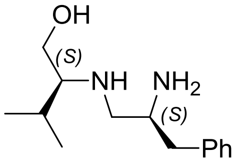
(d, *J* = 2.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 141.1, 128.6, 127.5, 127.3, 67.0, 64.6, 56.8, 51.2, 32.5, 19.4, 18.1. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{23}N_2O_1$ 223.1805; Found 223.1809



(2*S*)-2-(((2*S*)-2-amino-3-methylbutyl)amino)-3-phenylpropan-1-ol (154f)

According to the general procedure, 2-imidazoline **163f** (645 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154f** (435 mg, 92% yield) as light yellow liquid after flash column chromatography on silica gel (DCM-MeOH = 90:10 to 70:30).

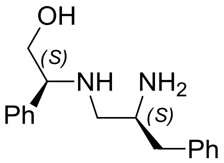
$[\alpha]_D^{20}$ = +9.15 (*c* 0.504, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.36 – 7.11 (m, 5H), 3.57 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.32 (dd, *J* = 10.8, 6.1 Hz, 1H), 2.86 (ddd, *J* = 13.0, 6.6, 3.9 Hz, 1H), 2.80 – 2.58 (m, 3H), 2.51 (ddd, *J* = 8.9, 5.4, 3.5 Hz, 1H), 2.38 (dd, *J* = 11.4, 9.0 Hz, 1H), 1.89 (br, 4H), 1.60 – 1.41 (m, 1H), 0.86 (d, *J* = 1.5 Hz, 3H), 0.84 (d, *J* = 1.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 138.9, 129.3, 128.6, 126.4, 63.0, 60.6, 57.0, 50.9, 38.4, 32.5, 19.5, 17.8. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{25}N_2O_1$ 237.1961; Found 237.1967



(2*S*)-2-(((2*S*)-2-amino-3-phenylpropyl)amino)-3-methylbutan-1-ol (154g)

According to the general procedure, 2-imidazoline **163g** (645 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154g** (430 mg, 91% yield) as light yellow liquid after flash column chromatography on silica gel (DCM-MeOH = 90:10).

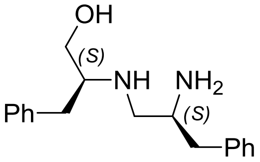
$[\alpha]_D^{20}$ = +20.91 (*c* 0.502, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34 – 7.11 (m, 5H), 3.59 (dd, *J* = 10.7, 4.1 Hz, 1H), 3.32 (dd, *J* = 10.7, 7.8 Hz, 1H), 3.06 (dq, *J* = 12.9, 4.4 Hz, 1H), 2.80 (dd, *J* = 13.4, 4.8 Hz, 1H), 2.69 (dd, *J* = 12.1, 4.0 Hz, 1H), 2.55 (dd, *J* = 12.1, 8.4 Hz, 1H), 2.47 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.36 (ddd, *J* = 7.8, 6.3, 4.1 Hz, 1H), 1.92 (br, 4H), 1.75 (dq, *J* = 13.5, 6.8 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 139.0, 129.3, 128.6, 126.5, 64.8, 61.5, 53.6, 53.2, 43.2, 29.6, 19.6, 18.7. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{25}N_2O_1$ 237.1961; Found 237.1966



(2*S*)-2-(((2*S*)-2-amino-3-phenylpropyl)amino)-2-phenylethanol (154h)

According to the general procedure, 2-imidazoline **163h** (713 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154h** (491 mg, 91% yield) as white solids after flash column chromatography on silica gel (DCM-MeOH = 90:10 to 70:30).

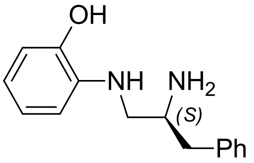
$[\alpha]_D^{20}$ = + 82.26 (*c* 0.506, $CHCl_3$). **Mp** 148.8 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40 – 7.06 (m, 10H), 3.76 (dd, *J* = 8.9, 4.0 Hz, 1H), 3.68 (dd, *J* = 10.8, 4.1 Hz, 1H), 3.55 (dd, *J* = 10.7, 9.0 Hz, 1H), 3.11 (qd, *J* = 8.6, 5.0 Hz, 1H), 2.79 – 2.56 (m, 6H), 2.56 – 2.34 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.9, 138.8, 129.3, 128.6, 128.6, 127.6, 127.4, 126.4, 67.0, 64.6, 52.8, 52.7, 42.4. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{23}N_2O_1$ 271.1805; Found 271.1807



(2*S*)-2-(((2*S*)-2-amino-3-phenylpropyl)amino)-3-phenylpropan-1-ol (154i)

According to the general procedure, 2-imidazoline **163i** (741 mg, 2.0 mmol) and 30 ml HCl 10 wt. % under reflux condition for 24 h afforded **154i** (524 mg, 92% yield) as white solids after flash column chromatography on silica gel (DCM-MeOH = 90:10 to 70:30). This reaction was scaled up. **163i** (6.67 g, 18 mmol) furnished **154i** (4.86 g, 95% yield).

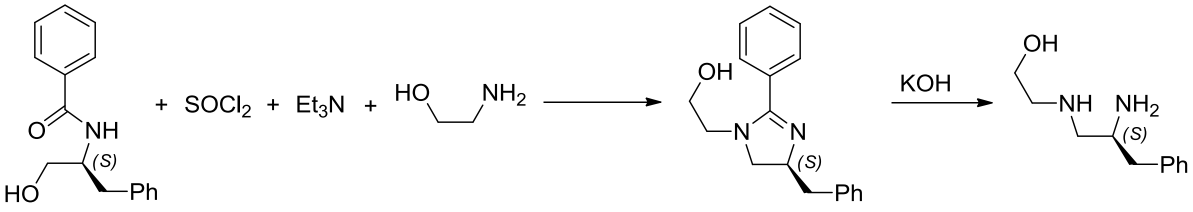
$[\alpha]_D^{20}$ = +3.10 (*c* 0.506, $CHCl_3$). **Mp** 62.7 °C; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 – 7.07 (m, 10H), 3.58 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.34 (dd, *J* = 10.8, 6.1 Hz, 1H), 3.02 (ddd, *J* = 12.8, 8.6, 4.6 Hz, 1H), 2.88 (qd, *J* = 6.6, 3.9 Hz, 1H), 2.81 – 2.60 (m, 4H), 2.47 (ddd, *J* = 15.8, 12.8, 8.3 Hz, 2H), 1.89 (s, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.7, 138.5, 129.3 (2C), 128.7, 128.7, 126.6, 126.5, 63.2, 60.7, 53.0, 51.8, 42.0, 38.3. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{18}H_{25}N_2O_1$ 285.1961; Found 285.1965



(2*S*)-2-((2-amino-3-phenylpropyl)amino)phenol (154j)

This compound was prepared by the hydrolysis of 2-imidazoline **163j** (657 mg, 2.0 mmol) with KOH 20 wt. % (30 ml) under reflux condition for 72 h. Then the mixture was cooled to room temperature and was neutralized with HCl 10 wt. % until pH ≈ 4 and then added $NaHCO_3$ saturated until pH ≈ 7. The product was extract with DCM (3 x 40 ml). The combined organic extracts were dried over anhydrous MgSO4, filtered, and concentrated under vacuum. The crude residue was recrystallized from PE-EA to furnish **154j** (369 mg, 76% yield) as white solids.

$[\alpha]_D^{20}$ = +33.317 (*c* 0.512, DMSO). **Mp** 158.3 °C; **^{1}H NMR** (300 MHz, DMSO): *δ* 7.39 – 7.03 (m, 5H), 6.77 – 6.49 (m, 2H), 6.40 (t, *J* = 7.7 Hz, 2H), 4.84 (s, 1H), 3.56 (br, 3H), 3.16 – 2.94 (m, 2H), 2.88 – 2.68 (m, 2H), 2.58 (dd, *J* = 13.1, 7.4 Hz, 1H); **^{13}C NMR** (75 MHz, DMSO): *δ* 144.2, 139.7, 137.8, 129.2, 128.3, 126.0, 119.7, 115.8, 113.4, 109.9, 52.0, 49.0, 42.4. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{19}N_2O_1$ 243.1492; Found 243.1495



162c **163k** **154k**

(2*S*)-2-((2-amino-3-phenylpropyl)amino)ethanol (154k)

A solution of hydroxyamide **162c** (5.0 g, 19.58 mmol, 1.0 equiv.) in thionyl chloride (7.2 ml, 117.50 mmol, 6.0 equiv.) was stirred for 4 h at reflux to form the chloroalkyl imidoyl chloride. Excess thionyl chloride was removed under reduced pressure, and the crude dichloride was dissolved in dry DCM (40 ml). This solution was added dropwise to a magnetically stirred solution of ethanolamine (1.26 g, 20.56 mmol, 1.05 equiv.) and dry triethylamine (≈ 8.0 ml, 58.75 mmol, 3.0 equiv.) in dry DCM (40 ml) at 0 °C. After being stirred at room temperature for 10 h (overnight), the reaction mixture was washed with 10 wt. % NaOH (100 ml) and the aqueous was extracted with DCM (3 x 100 ml). The combined organics were washed with brine and dried over $MgSO_4$, and the solvent was removed in vacuo to give crude oil **163k** which was then hydrolyzed with 300 ml of KOH 20 wt. % under reflux condition for 72 h, and after that the mixture was cooled to room temperature. The crude product was extracted with DCM (3 x 50 ml), then was purified by flash column chromatography on silica gel with DCM-MeOH (90:10 to 60:40) as eluent to afford the desired product **154k** as a light yellow liquid (2.71 g, 72% yield).

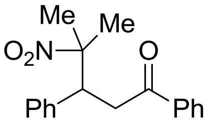
$[\alpha]_D^{20}$ = +3.39 (*c* 0.508, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.34 – 7.11 (m, 5H), 3.72 – 3.52 (m, 2H), 3.20 – 3.07 (m, 1H), 2.88 (s, 4H), 2.82 – 2.68 (m, 4H), 2.54 (ddd, *J* = 11.4, 8.7, 3.0 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 138.6, 129.4, 128.7, 126.6, 60.6, 54.8, 52.5, 51.4, 42.5. **HRMS** *m/z*: $[M+H]^+$ calcd. for $C_{11}H_{19}N_2O_1$ 195.1492; Found 195.1494

9.4. Application of compound 154i in the asymmetric Michael reaction

General procedure for the catalytic Michael addition

Preparing the catalyst solution (stock solution **A**): In 1-ml volumetric flask contained 114 mg of catalyst **154i** dissolved in about 0.8 ml of 2-nitropropane was added 31 µl of TFA. This solution was added 2-nitropropane to the volumetric flask's calibration mark.

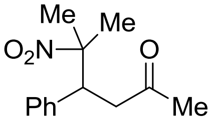
To a mixture of α,β-unsaturated enones (0.2 mmol) and 2-nitropropane (0.2 ml) was added 0.1 ml of the stock solution **A** under an aerobic atmosphere, taking no precaution to exclude moisture and the reaction mixture was stirred at ambient temperature for the time indicated in Table 10. After evaporation of 2-nitropropane, the crude reaction mixture was purified by flash column chromatography on silica gel, eluting with DCM to afford the Michael adduct.



4-methyl-4-nitro-1,3-diphenylpentan-1-one (183a)

According to the general procedure, the reaction of benzylideneacetophenone (42 mg, 0.2 mmol) and 2-nitropropane (0.2 ml) in the presence of 0.1 ml of the stock solution **A** afforded Michael adduct **183a** as white solids (57 mg, 97% yield, 94% ee) after flash column chromatography on silica gel eluting with DCM.

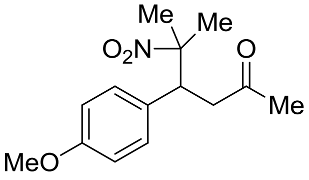
This is a known compound. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.92 – 7.80 (m, 2H), 7.59 – 7.48 (m, 1H), 7.42 (dd, *J* = 10.4, 4.7 Hz, 2H), 7.34 – 7.15 (m, 5H), 4.17 (dd, *J* = 10.4, 3.3 Hz, 1H), 3.69 (dd, *J* = 17.3, 10.4 Hz, 1H), 3.27 (dd, *J* = 17.3, 3.4 Hz, 1H), 1.63 (s, 3H), 1.55 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.8, 138.0, 136.7, 133.4, 129.3, 128.7, 128.5, 128.0, 127.8, 91.3, 49.0, 39.2, 26.2, 22.7. Enantiomers were separated by HPLC using a Chiralpak AS-H chiral stationary phase in *n*-heptane/2-isopropanol 80/20, 0.5 ml/min: $t_{(minor)}$ = 15.19, $t_{(major)}$ = 16.56.



5-Methyl-5-Nitro-4-phenylhexane-2-one (183b)

According to the general procedure, benzylideneacetone (29 mg, 0.2 mmol) and 2-nitropropane (0.2 ml) in the presence of 0.1 ml of the stock solution **A** afforded Michael adduct **183b** as light yellow oil (43 mg, 91% yield, 89% ee) after flash column chromatography on silica gel eluting with DCM.

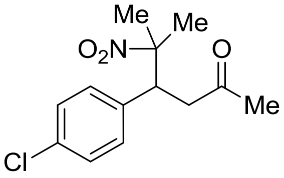
This is a known compound. **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.35 – 7.14 (m, 5H), 3.93 (dd, *J* = 10.6, 3.5 Hz, 1H), 3.09 (dd, *J* = 17.0, 10.6 Hz, 1H), 2.70 (dd, *J* = 17.0, 3.5 Hz, 1H), 2.02 (s, 3H), 1.54 (s, 3H), 1.47 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 205.3, 137.7, 129.3, 128.6, 128.0, 91.2, 48.9, 44.1, 30.4, 25.9, 22.5. Enantiomers were separated by HPLC using a Chiralpak AS-H chiral stationary phase in *n*-heptane/2-isopropanol 80/20, 0.5 ml/min: $t_{(minor)}$ = 16.07, $t_{(major)}$ = 22.01



4-(4-methoxyphenyl)-5-methyl-5-nitrohexan-2-one (183c)

According to the general procedure, 4-methoxybenzylideneacetone (35 mg, 0.2 mmol) and 2-nitropropane (0.2 ml) in the presence of 0.1 ml of the stock solution **A** afforded Michael adduct **183c** as colorless oil (47 mg, 89% yield, 94% ee) after flash column chromatography on silica gel eluting with DCM.

This is a known compound. **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.14 – 7.05 (m, 2H), 6.86 – 6.77 (m, 2H), 3.86 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.77 (s, 3H), 3.03 (dd, *J* = 16.7, 10.9 Hz, 1H), 2.66 (dd, *J* = 16.8, 3.5 Hz, 1H), 2.01 (s, 3H), 1.53 (s, 3H), 1.46 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 205.5, 159.2, 130.3, 129.5, 114.0, 91.3, 55.3, 48.3, 44.2, 30.4, 25.8, 22.5. Enantiomers were separated by HPLC using a Chiralpak AS-H chiral stationary phase in *n*-heptane/2-isopropanol 80/20, 0.5 ml/min: $t_{(major)}$ = 20.99, $t_{(minor)}$ = 24.11



4-(4-Chlorophenyl)-5-methyl-5-nitrohexan-2-one (183d)

According to the general procedure, 4-chlorobenzylideneacetone (36 mg, 0.2 mmol) and 2-nitropropane (0.2 ml) in the presence of 0.1 ml of the stock solution **A** afforded Michael adduct **183d** as light yellow oil (51 mg, 94% yield, 78% ee) after flash column chromatography on silica gel eluting with DCM.

This is a known compound. **^{1}H NMR** (300 MHz, $CDCl_3$): *δ* 7.31 – 7.23 (m, 2H), 7.16 – 7.08 (m, 2H), 3.90 (dd, *J* = 10.7, 3.4 Hz, 1H), 3.04 (dd, *J* = 17.2, 10.7 Hz, 1H), 2.73 (dd, *J* = 17.3, 3.4 Hz, 1H), 2.04 (s, 3H), 1.53 (s, 3H), 1.47 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 204.9, 136.3, 133.9, 130.5, 128.9, 90.8, 48.2, 44.0, 30.5, 25.7, 22.8. Enantiomers were separated by

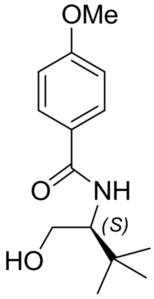
HPLC using a Chiralpak AS-H chiral stationary phase in *n*-heptane/2-isopropanol 80/20, 0.5 ml/min: $t_{(minor)}$ = 20.28, $t_{(major)}$ = 22.01

9.5. Application of 253a and 253b in the Morita-Baylis-Hillman reaction

9.5.1. Synthesis of imidazolines 253a, 253b, and 274

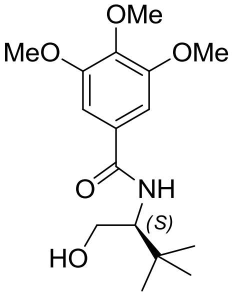
General procedure for the preparation of hydroxy amides 256, 259, and 279

A solution of a benzoic acid derivative (5.0 mmol, 1.0 equiv.) and thionyl chloride (≈ 1.2 ml, 19.77 mmol, 4.0 equiv.) in 10 ml of dry DCM was stirred for 4.5 h at reflux to form the benzoyl chloride. DCM and excess thionyl chloride were removed under reduced pressure, and the crude benzoyl chloride was dissolved in dry DCM (10.0 ml). This solution was added dropwise to a magnetically stirred solution of amino alcohol (5.5 mmol, 1.1 equiv.) and dry triethylamine (≈ 0.8 ml, 6.0 mmol, 1.2 equiv.) in dry DCM (11.0 ml) at 0 °C. After being stirred for 4 h at room temperature, the reaction mixture was washed with 10 wt. % solution of sodium hydroxide (2 x 20 ml) and then with 10 wt. % solution of hydrochloric acid (2 x 20 ml). The organic phase was removed solvent under reduced pressure to afford hydroxy amides which were used for the next step without further purification.



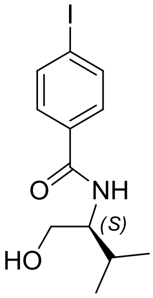
(*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-methoxybenzamide (256)

According to the general procedure, 4-methoxybenzoic acid (761 mg, 5.0 mmol), thionyl chloride (≈ 1.20 ml, 19.77 mmol), (*S*)-*tert*-leucinol (644 mg, 5.50 mmol), and dry triethylamine (≈ 0.8 ml, 6.0 mmol) afforded **256** (1.24 g, 98% yield) as white solids.



(*S*)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)-3,4,5-trimethoxybenzamide (259)

According to the general procedure, 3,4,5-methoxybenzoic acid (1.06 g, 5.0 mmol), thionyl chloride (≈ 1.20 ml, 19.77 mmol), (*S*)-*tert*-leucinol (644 mg, 5.50 mmol), and dry triethylamine (≈ 0.8 ml, 6.0 mmol) afforded **259** (1.5 g, 96% yield) as white solids.

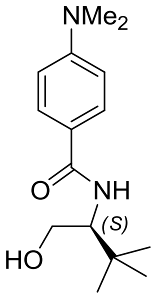


(*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-iodobenzamide (279)

According to the general procedure, 4-iodobenzoic acid (1.24 g, 5.0 mmol), thionyl chloride (≈ 1.20 ml, 19.77 mmol), (*S*)-valinol (567 mg, 5.50 mmol), and dry triethylamine (≈ 0.8 ml, 6.0 mmol) afforded **279** (1.65 g, 99% yield) as white solids.

General procedure for the preparation of hydroxy amides 267 and 270

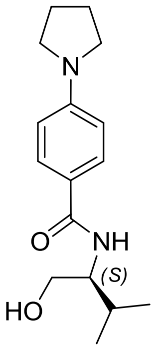
A solution of a benzoic acid derivative (5.0 mmol, 1.0 equiv.) and thionyl chloride (≈ 1.2 ml, 19.77 mmol, 4.0 equiv.) in 10 ml of dry DCM was stirred for 1 h at 0 °C to form the benzoyl chloride. DCM and excess thionyl chloride were removed under reduced pressure, and the crude benzoyl chloride was dissolved in dry DCM (10.0 ml). This solution was added dropwise to a magnetically stirred solution of amino alcohol (5.5 mmol, 1.1 equiv.) and dry triethylamine (≈ 0.8 ml, 6.0 mmol, 1.2 equiv.) in dry DCM (11.0 ml) at 0 °C. After being stirred for 4 h at room temperature, the reaction mixture was washed with distilled water (3 x 20 ml) and then with brine (1 x 20 ml). The organic phase was removed solvent under reduced pressure to afford hydroxy amides which were purified by flash column chromatography on silica gel.



(*S*)-4-(Dimethylamino)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzamide (267)

According to the general procedure, 4-dimethylaminobenzoic acid (826 mg, 5.0 mmol), thionyl chloride (≈ 1.20 ml, 19.77 mmol), (*S*)-*tert*-leucinol (644 mg, 5.50 mmol), and dry triethylamine (≈ 0.8 ml, 6.0 mmol) afforded **267** (1.12 g, 85% yield) as white solids after purified by flash column chromatography eluting with DCM-EA (70:30).

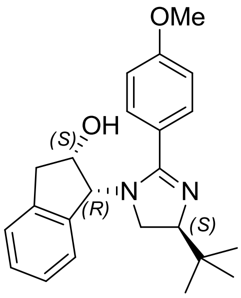
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 – 7.64 (m, 2H), 6.64 (d, J = 8.9 Hz, 2H), 6.27 (d, J = 8.7 Hz, 1H), 4.04 – 3.95 (m, 1H), 3.89 (dd, J = 11.1, 3.3 Hz, 1H), 3.64 (dd, J = 11.1, 7.7 Hz, 1H), 2.99 (s, 6H), 1.01 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.9, 152.5, 128.6, 121.3, 111.3, 63.6, 60.0, 40.3, 33.9, 27.2.



(*S*)-*N*-(1-Hydroxy-3-methylbutan-2-yl)-4-(pyrrolidin-1-yl)benzamide (270)

According to the general procedure, 4-(pyrrolidine-1-yl)benzoic acid (956 mg, 5.0 mmol), thionyl chloride (≈ 1.20 ml, 19.77 mmol), (*S*)-valinol (567 mg, 5.50 mmol), and dry triethylamine (≈ 0.8 ml, 6.0 mmol) afforded **270** (1.26 g, 91% yield) as white solids after purified by flash column chromatography eluting with DCM-EA (70:30).

^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.68 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 7.2 Hz, 2H), 6.41 (d, *J* = 7.3 Hz, 1H), 3.95 – 3.81 (m, 1H), 3.81 – 3.62 (m, 3H), 3.31 (t, *J* = 6.2 Hz, 4H), 2.12 – 1.90 (m, 5H), 1.05 – 0.93 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$): *δ* 168.7, 149.8, 128.8, 121.0, 111.4, 64.4, 57.7, 48.1, 29.4, 25.5, 19.8, 19.2.

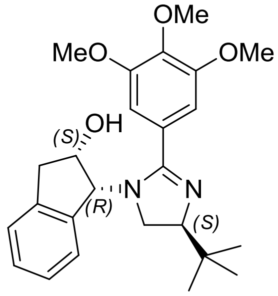


(1*R*, 2*S*)-1-((*S*)-4-(*tert*-butyl)-2-(4-methoxyphenyl)-4,5-dihydro-1H-imidazol-1-yl)-2,3-dihydro-1H-inden-2-ol (253a)

According to the procedure for the synthesis of 2-imidazolines **163a-k**, hydroxyamide **256** (1.01 g, 4.0 mmol), thionyl chloride (≈ 1.5 ml, 24.0 mmol), dry triethylamine (≈ 1.6 ml, 12.0

mmol), and (1*R*, 2*S*)-*cis*-1-amino-2-indanol (626 mg, 4.20 mmol) afforded **253a** (1.03 g, 70% yield) as white solids after crystallization from PE-EA.

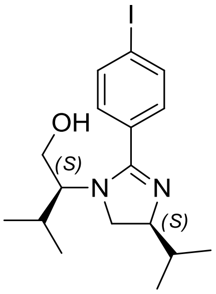
$[\alpha]_D^{20}$ = -57.308 (*c* 0.510, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.68 – 7.56 (m, 2H), 7.20 (m, 3H), 7.01 – 6.89 (m, 3H), 5.07 (d, *J* = 7.3 Hz, 1H), 4.52 (q, *J* = 7.5 Hz, 1H), 3.90 – 3.56 (m, 5H), 3.38 (t, *J* = 10.2 Hz, 1H), 3.21 (dd, *J* = 16.3, 7.6 Hz, 1H), 2.84 (dd, *J* = 16.2, 7.4 Hz, 1H), 2.62 (t, *J* = 10.0 Hz, 1H), 0.77 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.2, 161.0, 141.1, 137.5, 130.4, 129.1, 127.2, 125.9, 125.4, 123.4, 114.2, 73.8, 71.6, 62.9, 55.5, 47.3, 40.5, 34.1, 26.2.



(1*R*, 2*S*)-1-((*S*)-4-(*tert*-butyl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-imidazol-1-yl)-2,3-dihydro-1H-inden-2-ol (253b)

According to the procdure for the synthesis of 2-imidazolines **163a-k**, hydroxyamide **259** (1.25 g, 4.0 mmol), thionyl chloride (≈ 1.5 ml, 24.0 mmol), dry triethylamine (≈ 1.6 ml, 12.0 mmol), and (1*R*, 2*S*)-*cis*-1-amino-2-indanol (626 mg, 4.20 mmol) afforded **253b** (1.26 g, 74% yield) as white solids after crystallization from PE-EA.

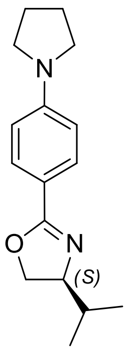
$[\alpha]_D^{20}$ = -54.018 (*c* 0.512, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 – 7.14 (m, 3H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.93 (s, 2H), 5.12 (d, *J* = 7.2 Hz, 1H), 4.54 (q, *J* = 7.3 Hz, 1H), 4.01 – 3.80 (m, 9H), 3.80 – 3.63 (m, 1H), 3.51 – 3.13 (m, 3H), 2.86 (dd, *J* = 16.2, 7.3 Hz, 1H), 2.66 (t, *J* = 10.0 Hz, 1H), 0.79 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.3, 153.6 (2C), 141.0, 139.6, 137.2, 129.2, 127.2, 125.9, 125.6, 106.1, 71.9, 63.0, 61.0, 56.5 (2C), 47.6, 40.6, 34.1, 26.2.



(4*S*)-1-((2*S*)-1-Hydroxy-3-methyl-but-2-yl)-2-(4-iodophenyl)-4-isopropyl-4,5-dihydroimidazole (274)

According to the procdure for the synthesis of 2-imidazolines **163a-k**, hydroxyamide **279** (1.33 g, 4.0 mmol), thionyl chloride (≈ 1.5 ml, 24.0 mmol), dry triethylamine (≈ 1.6 ml, 12.0 mmol), and (*S*)-valinol (434 mg, 4.2 mmol) afforded **274** (1.16 g, 72% yield) as white solids after crystallization from PE-EA.

$[\alpha]_D^{20}$ = -60.425 (*c* 0.510, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 8.3, 1.8 Hz, 2H), 7.21 (dd, *J* = 8.2, 2.7 Hz, 2H), 4.00 – 3.84 (m, 1H), 3.58 (d, *J* = 1.9 Hz, 1H), 3.53 – 3.33 (m, 2H), 3.33 – 3.17 (m, 1H), 3.07 (br, 1H), 1.96 – 1.62 (m, 2H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.3, 137.7, 130.8 (2C), 96.1, 69.2, 63.2, 60.7, 46.0, 33.3, 28.0, 20.2, 19.8, 19.0, 17.9.

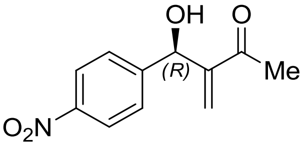


(*S*)-4-Isopropyl-2-(4-(pyrrolidin-1-yl)phenyl)-4,5-dihydrooxazole (271)

According to the procedure for the synthesis of 2-imidazolines **163a-k**, hydroxyamide **270** (500 mg, 1.81 mmol), thionyl chloride (≈ 0.7 ml, 10.85 mmol), dry triethylamine (≈ 0.7 ml, 5.43 mmol), and (*S*)-valinol (196 mg, 1.90 mmol) afforded **271** (439 mg, 94% yield) as white solid after crystallization from PE-EA.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, J = 8.9 Hz, 2H), 6.49 (d, J = 8.9 Hz, 2H), 4.41 – 4.26 (m, 1H), 4.13 – 3.98 (m, 2H), 3.30 (t, J = 6.6 Hz, 4H), 2.08 – 1.91 (m, 4H), 1.91 – 1.68 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.2, 149.9, 129.8, 113.9, 110.9, 72.0, 69.7, 47.5, 32.9, 25.5, 19.1, 18.0.

9.5.2. The MVK-based Morita-Baylis-Hillman reaction catalyzed by 253b



(*R*)-3-(Hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (262)

The experimental procedure for the MBH reaction between MVK and *p*-nitrobenzaldehyde: the compound **253b** (28 mg, 0.066 mmol, 0.1 equiv.) was added to an oven-dried vial. It was followed by *p*-nitrobenzaldehyde (100 mg, 0.66 mmol, 1.0 equiv.), 0.6 ml of 1,4-dioxane, and MVK (0.17 ml, 1.99 mmol, 3.0 equiv.). After 47 h, the reaction was quenched by adding HCl solution (2M, 2 ml), and the product was extracted with DCM (2 x 10.0 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified by flash column chromatography on silica gel eluting with PE-EA (30%) to give the desired product **262** (87 mg, 60% yield, 46% ee). The enantiomeric excess was determined by chiral HPLC analysis using Phenomenex Lux Cellulose-1 column, *n*-heptane/2-isopropanol 80/20, 1.0 ml/min: $t_{(major)}$ = 51.57, $t_{(minor)}$ = 57.64.

This is a known compound. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.54 (dd, *J* = 8.9, 0.6 Hz, 2H), 6.27 (s, 1H), 6.04 (d, *J* = 1.0 Hz, 1H), 5.67 (s, 1H), 2.35 (s, 3H).

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11. Appendix

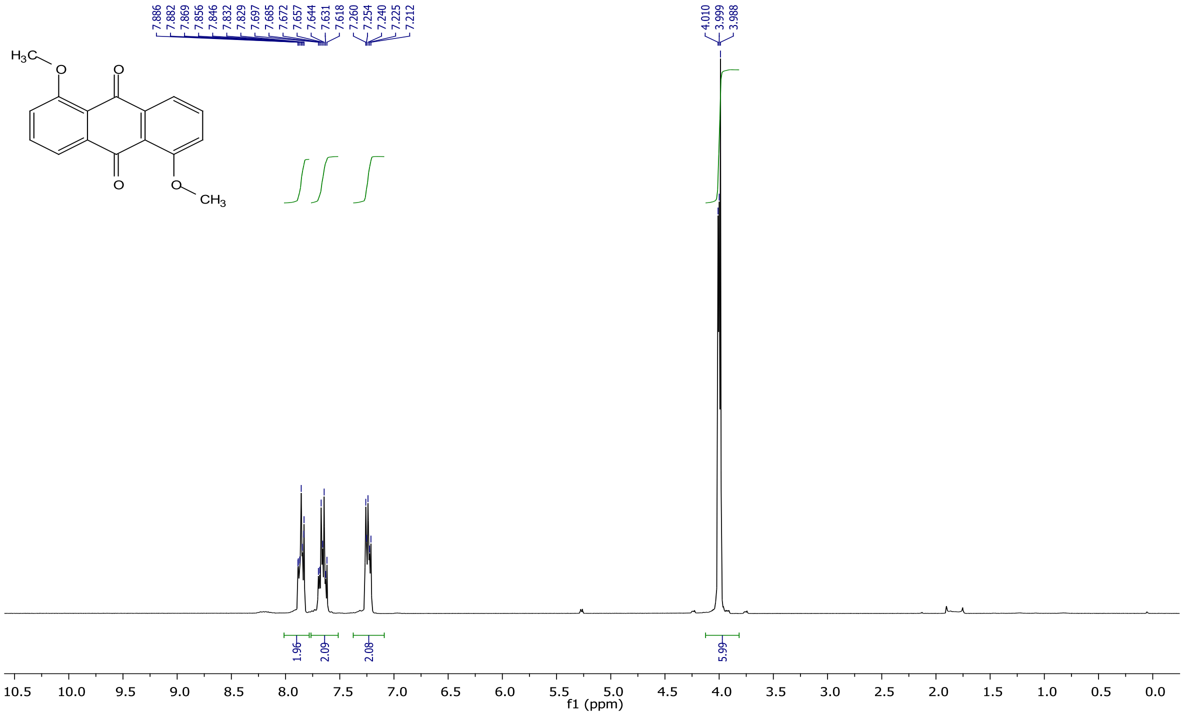
11.1. NMR-spectra

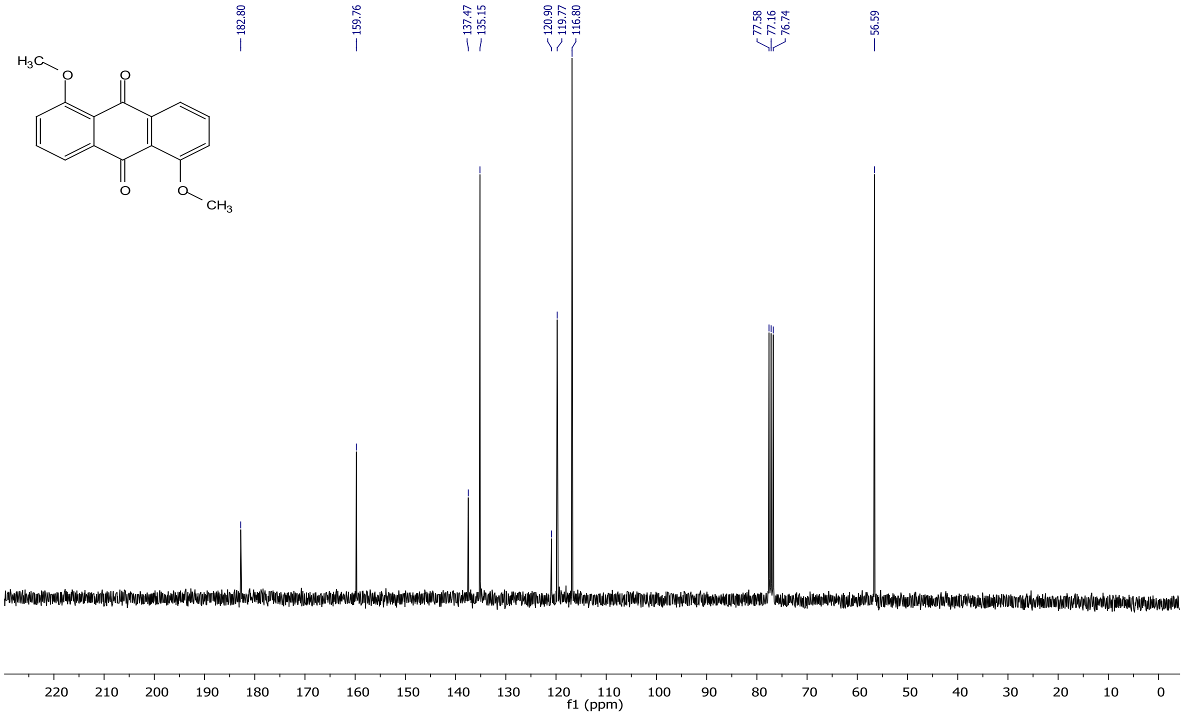
^{1}H-NMR (300 MHz, $CDCl_3$): -upper image

^{13}C-NMR (75 MHz, $CDCl_3$): -lower image

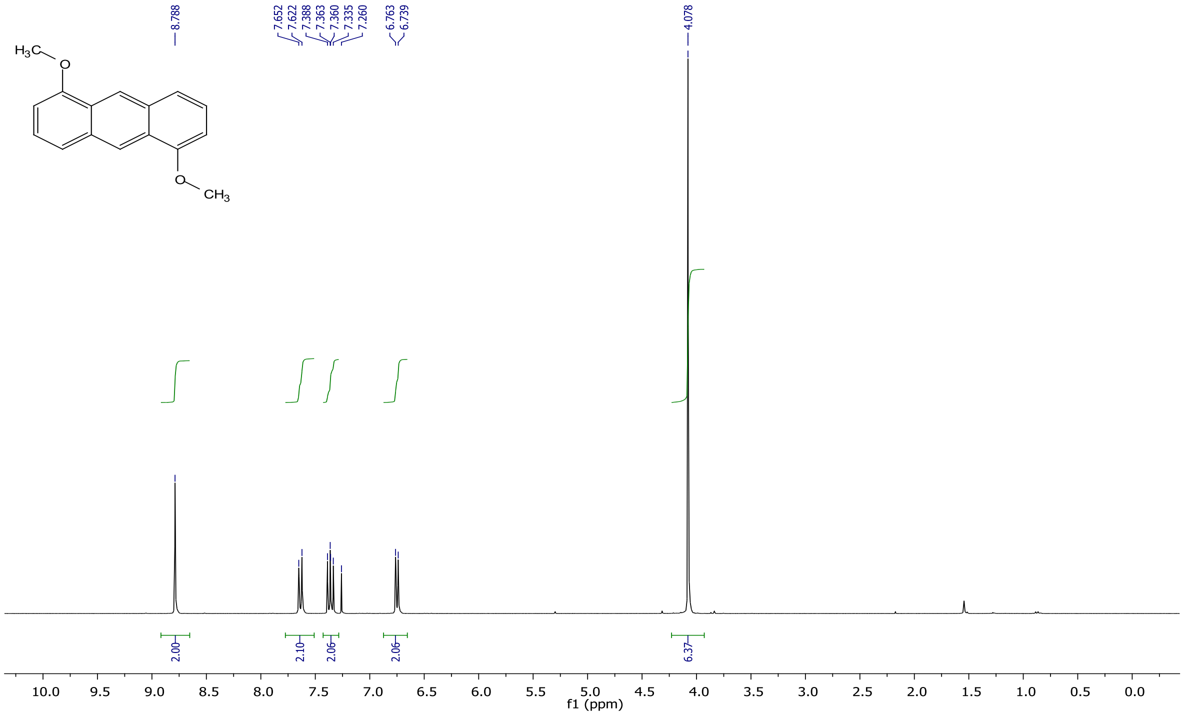
Solvent (if not stated otherwise): $CDCl_3$

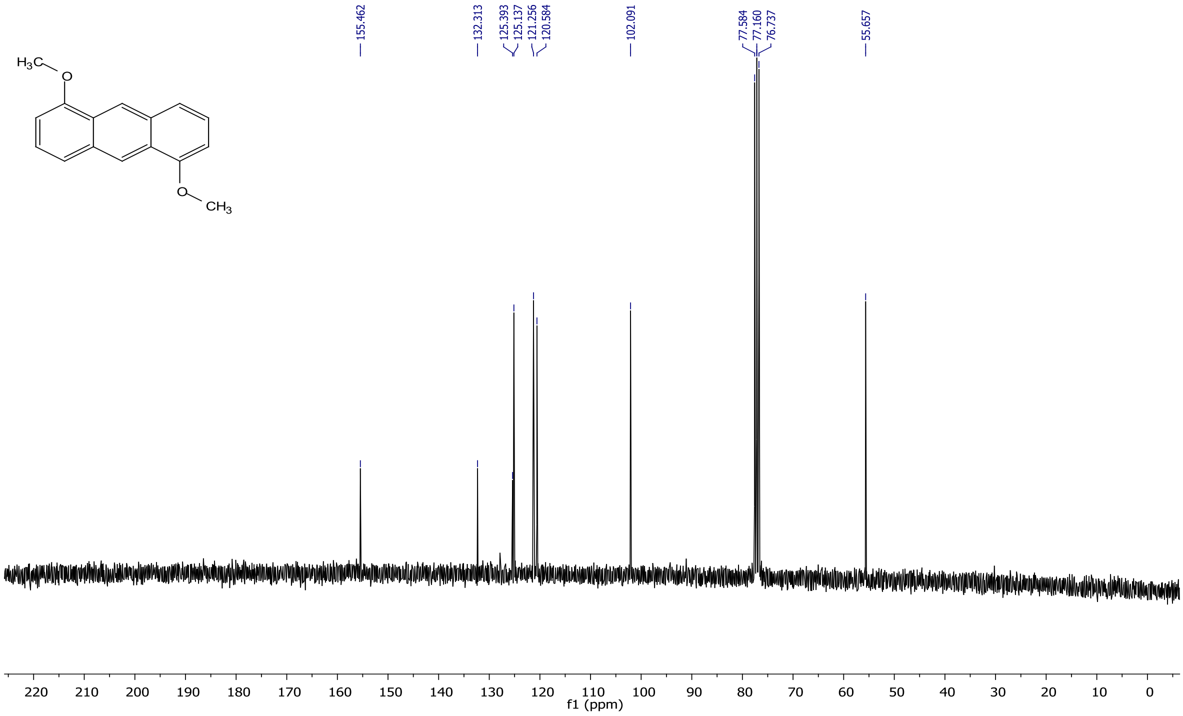
1,5-dimethoxy-9,10-anthraquinone (82a)



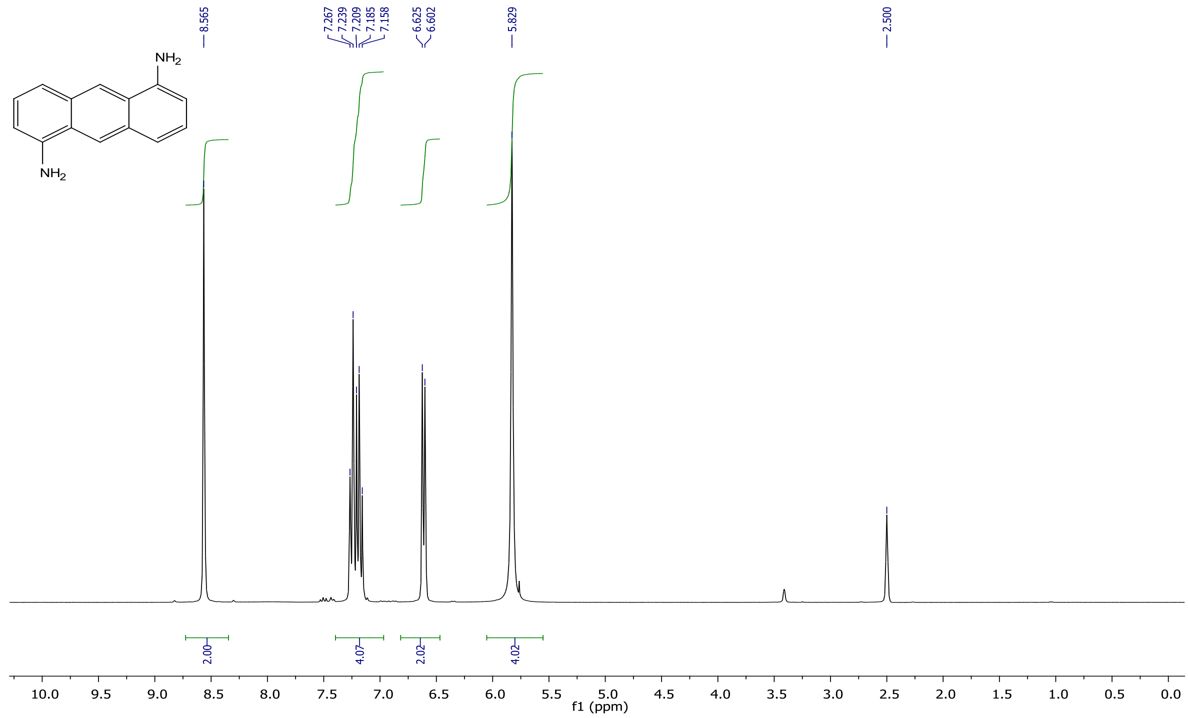


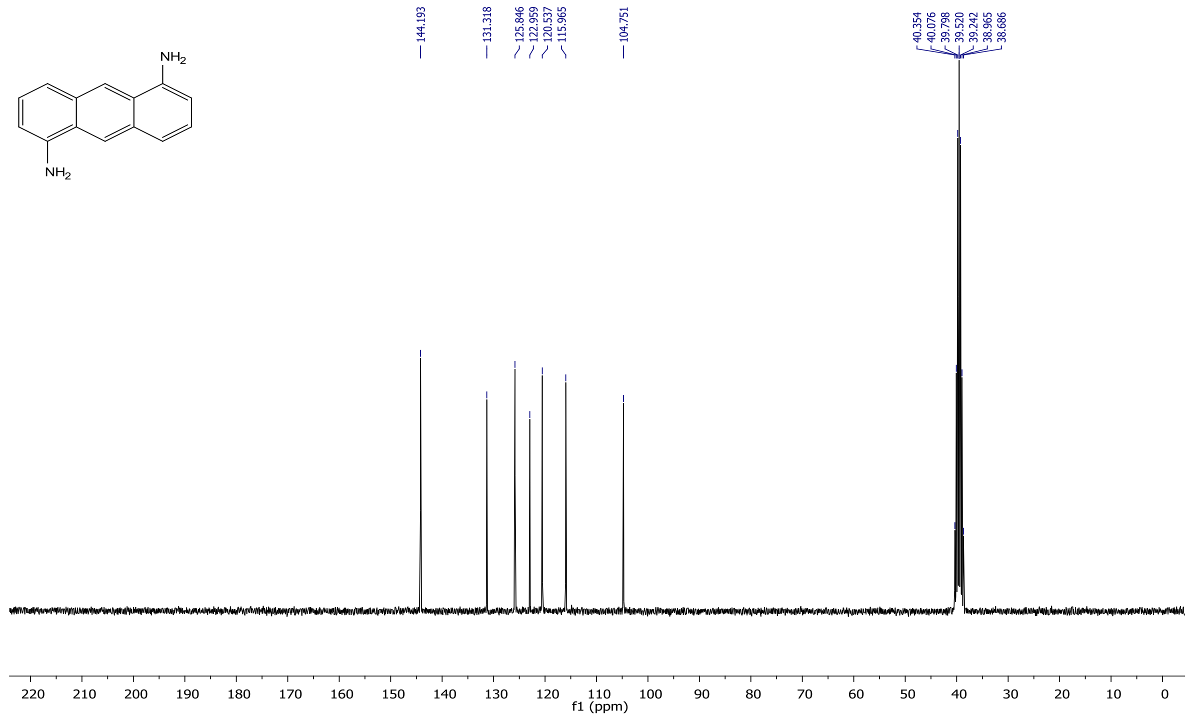
1,5-bis(dimethoxy)anthracene (83a)



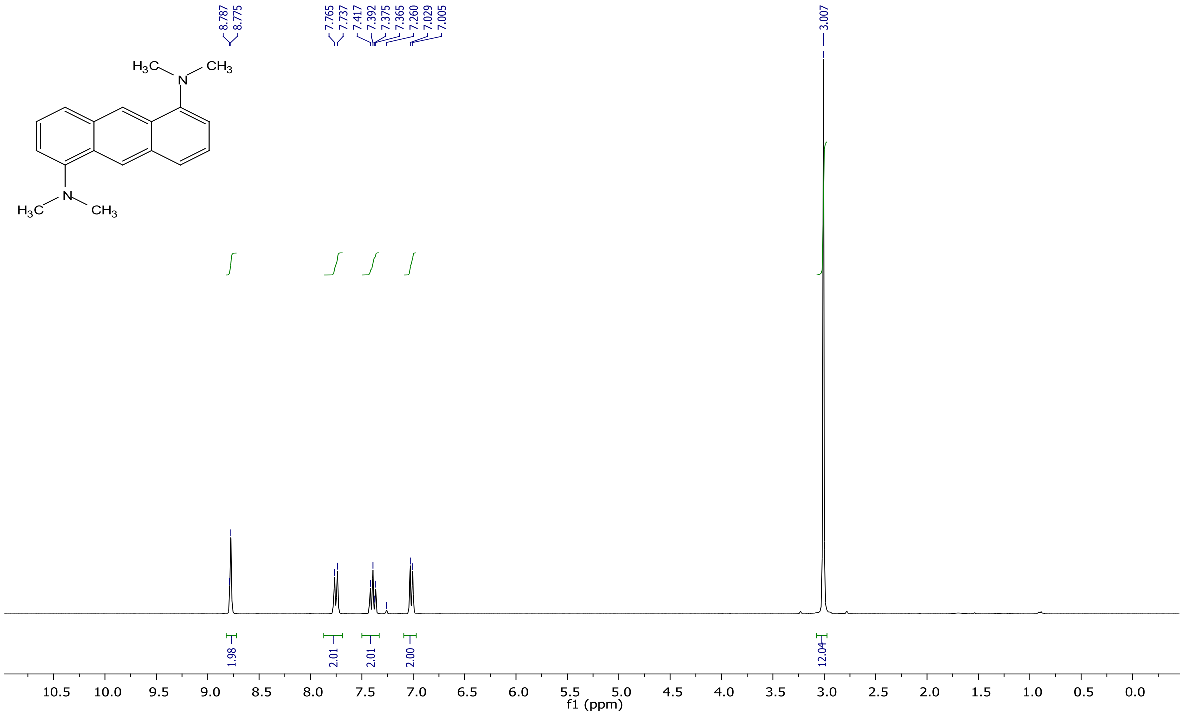


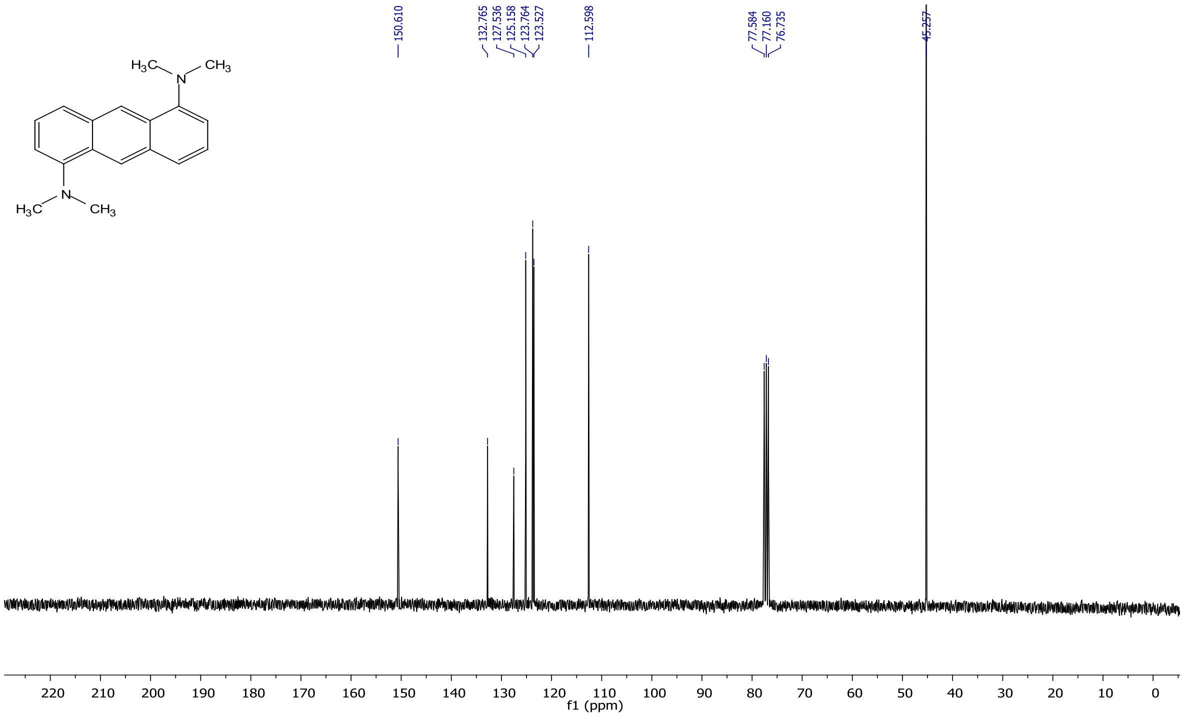
1,5-diaminoanthracene (87) (DMSO)



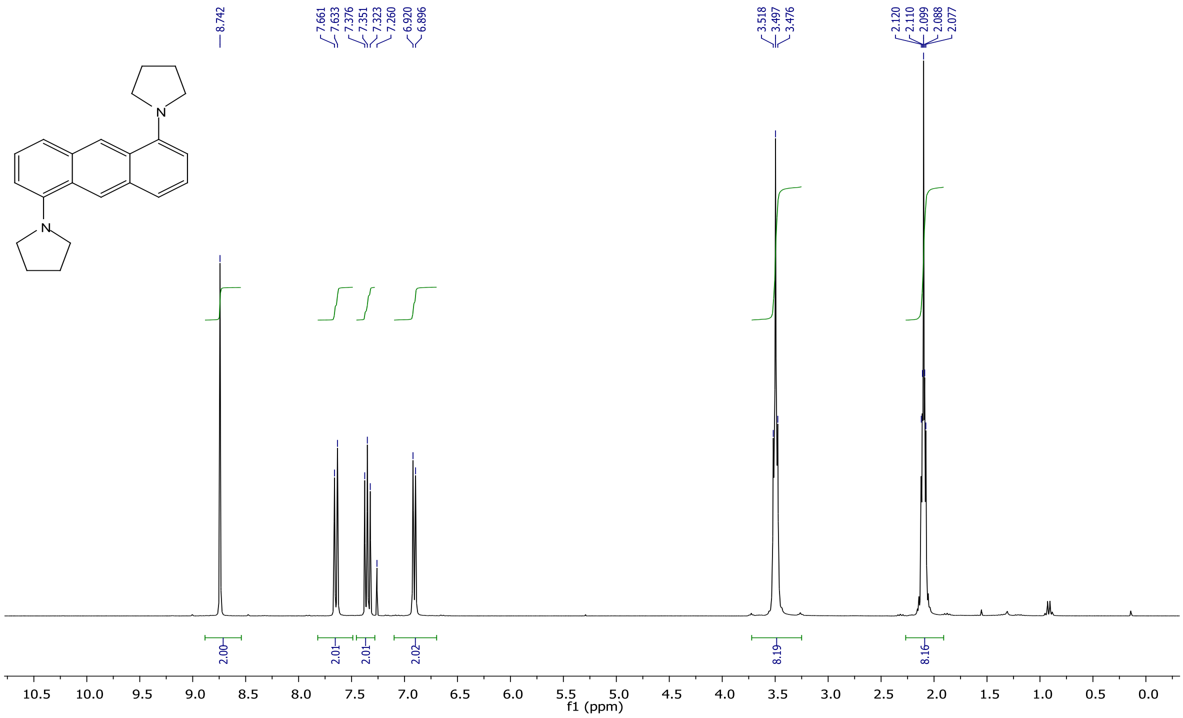


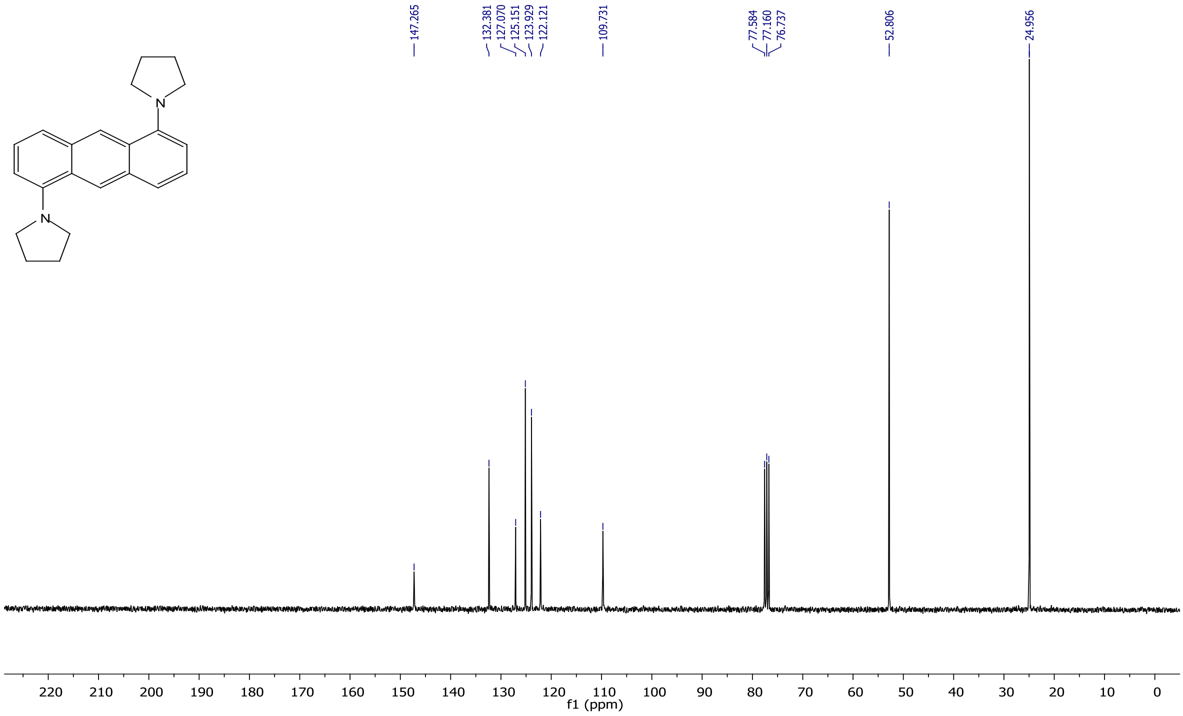
1,5-bis(*N*,*N*-dimethylamino)anthracene (83b)



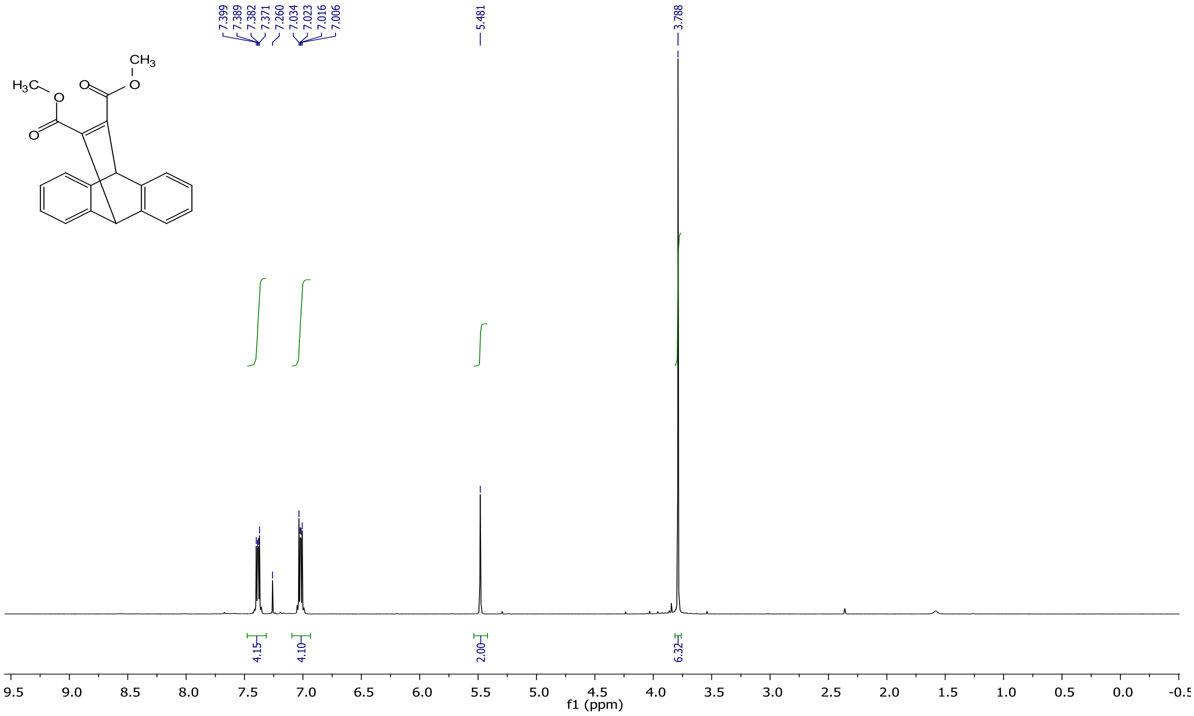


1,5-bis(pyrrolidin-1-yl)anthracene (83c)





Dimethyl 9,10-dihydro-9,10-ethenoanthracene-11,12-dicarboxylate (89a)



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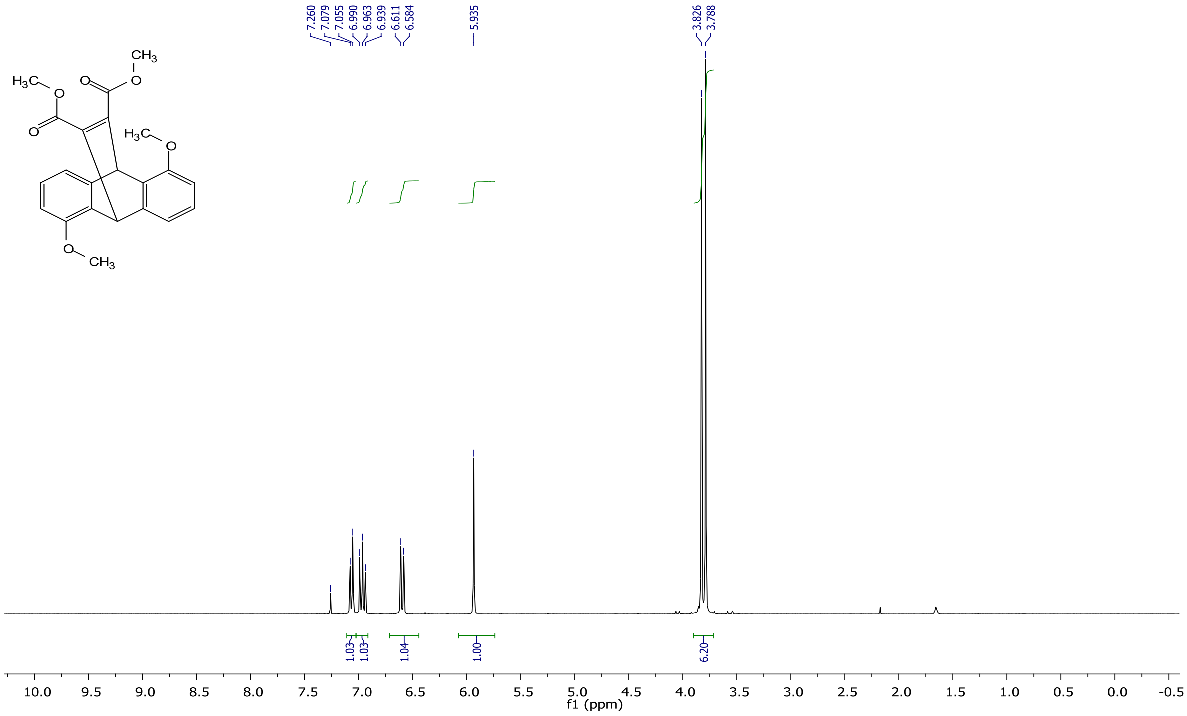

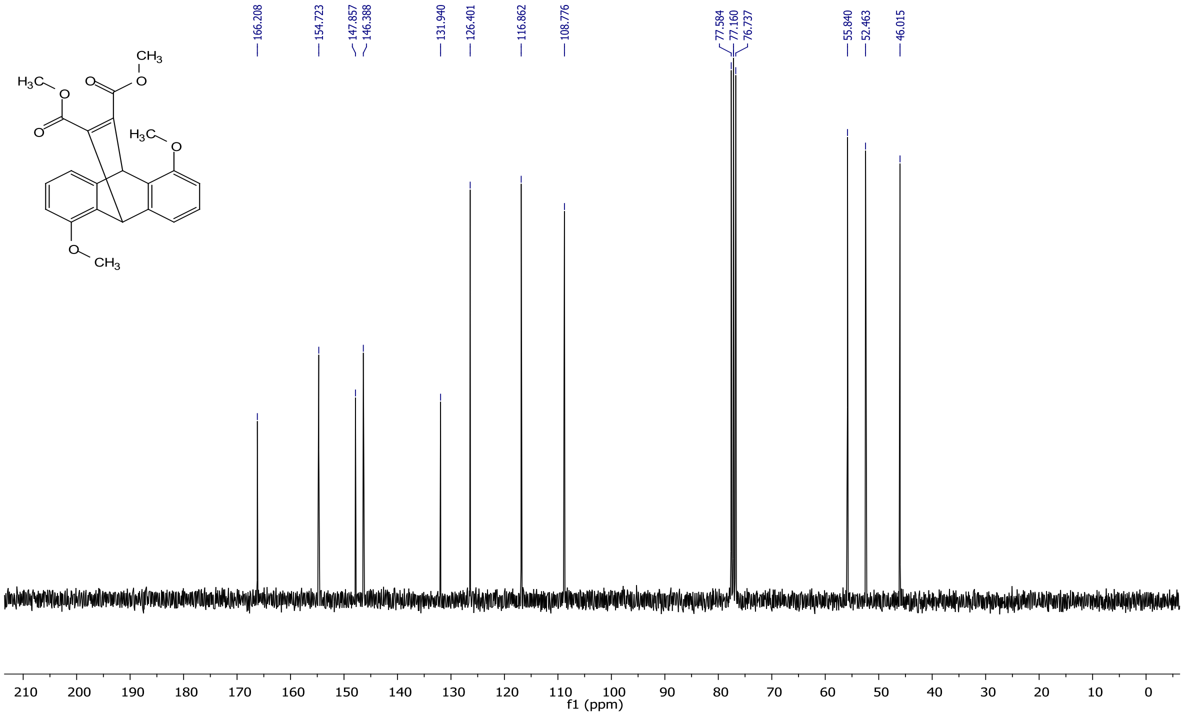

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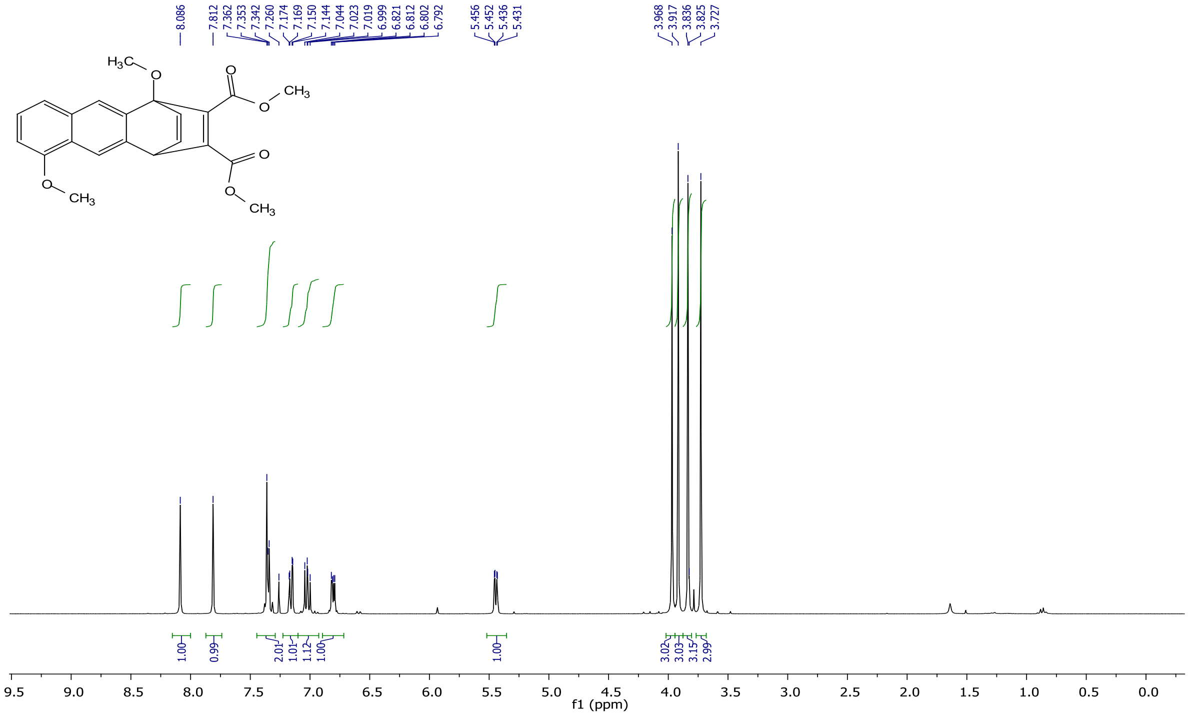

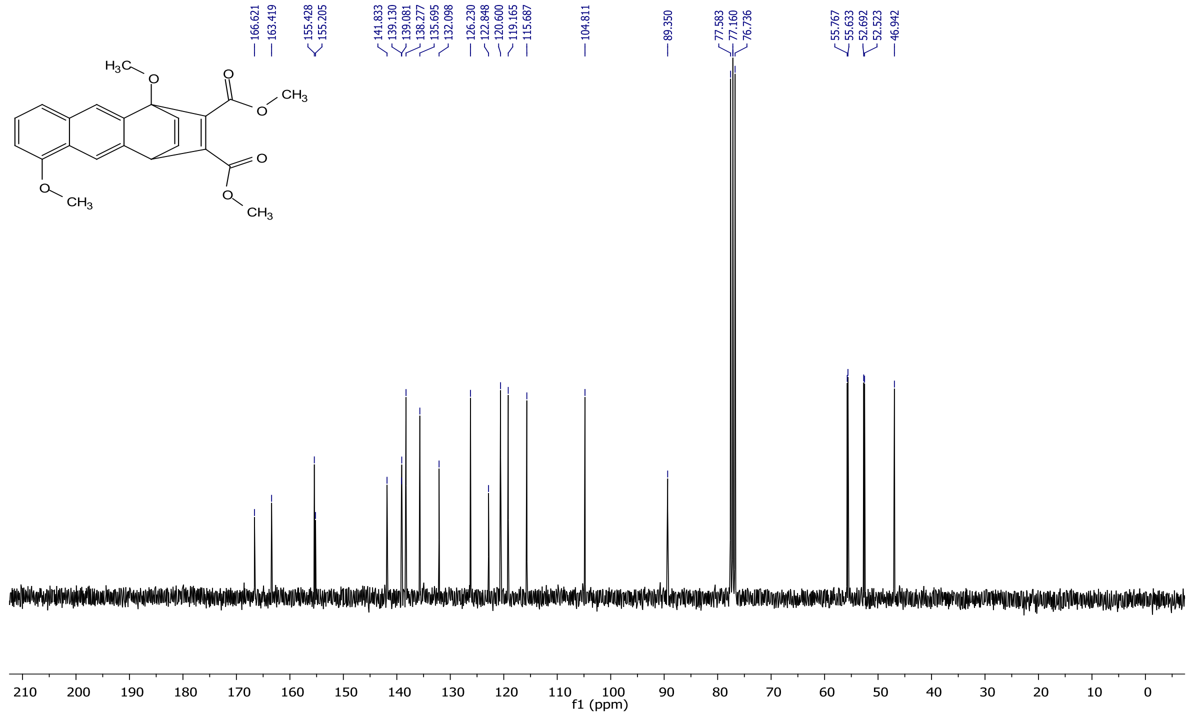

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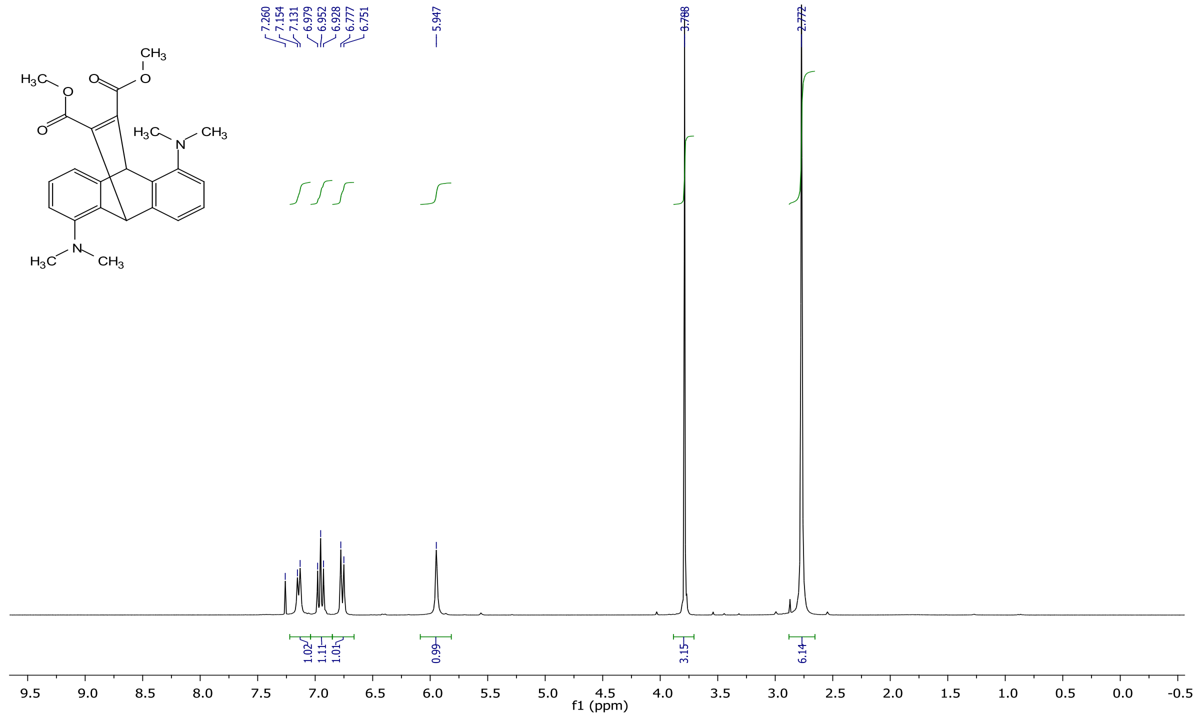

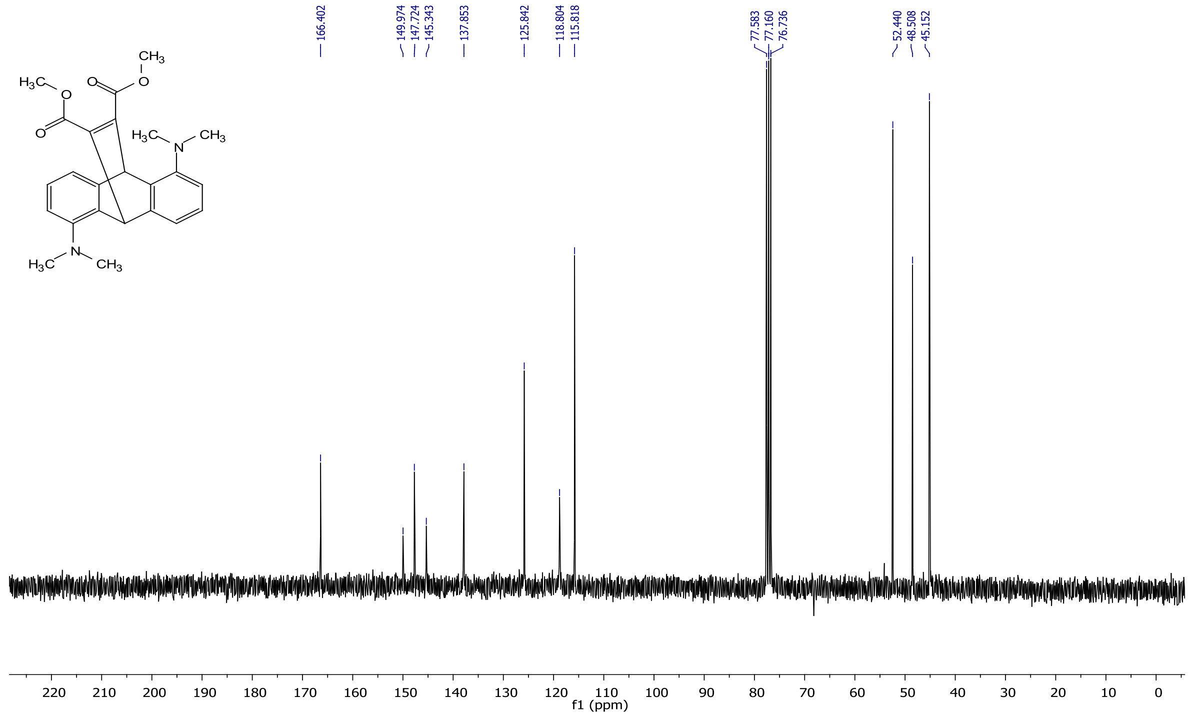

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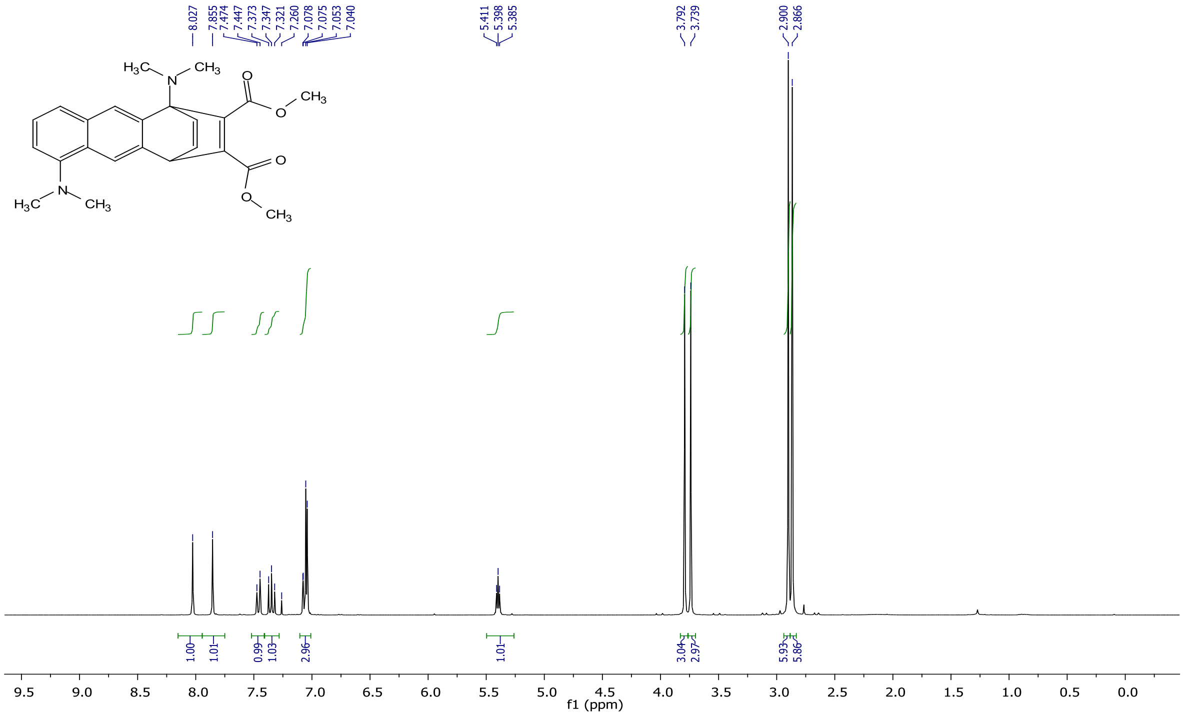
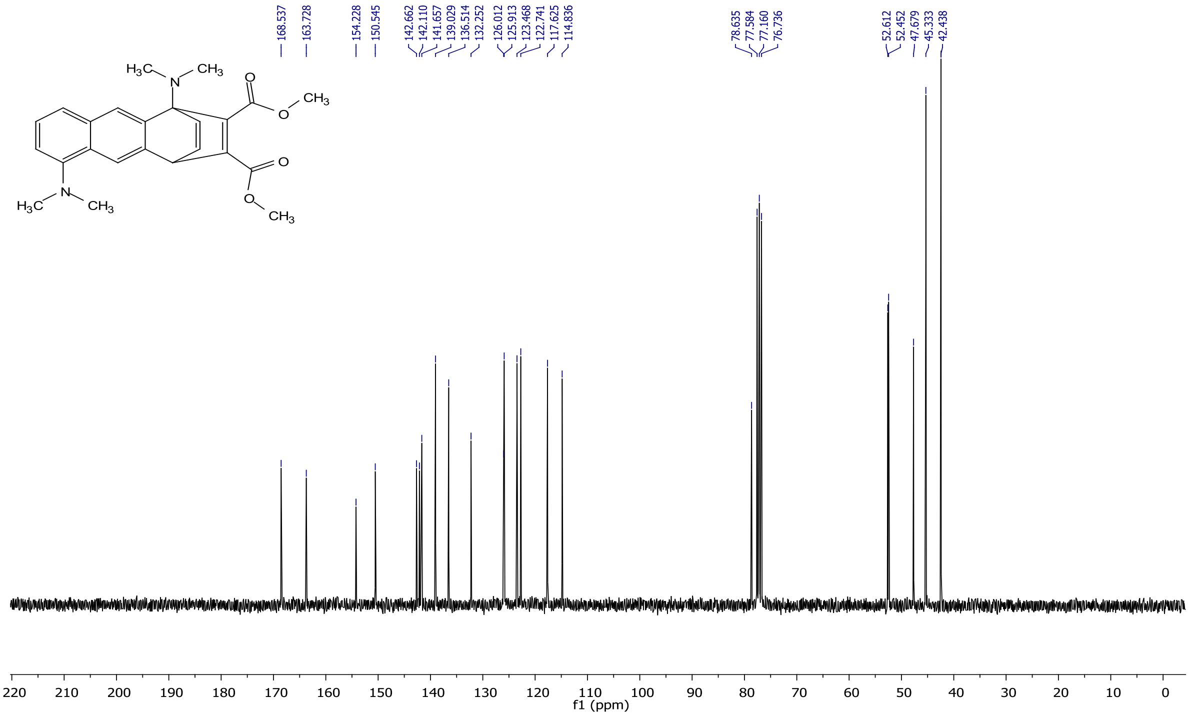
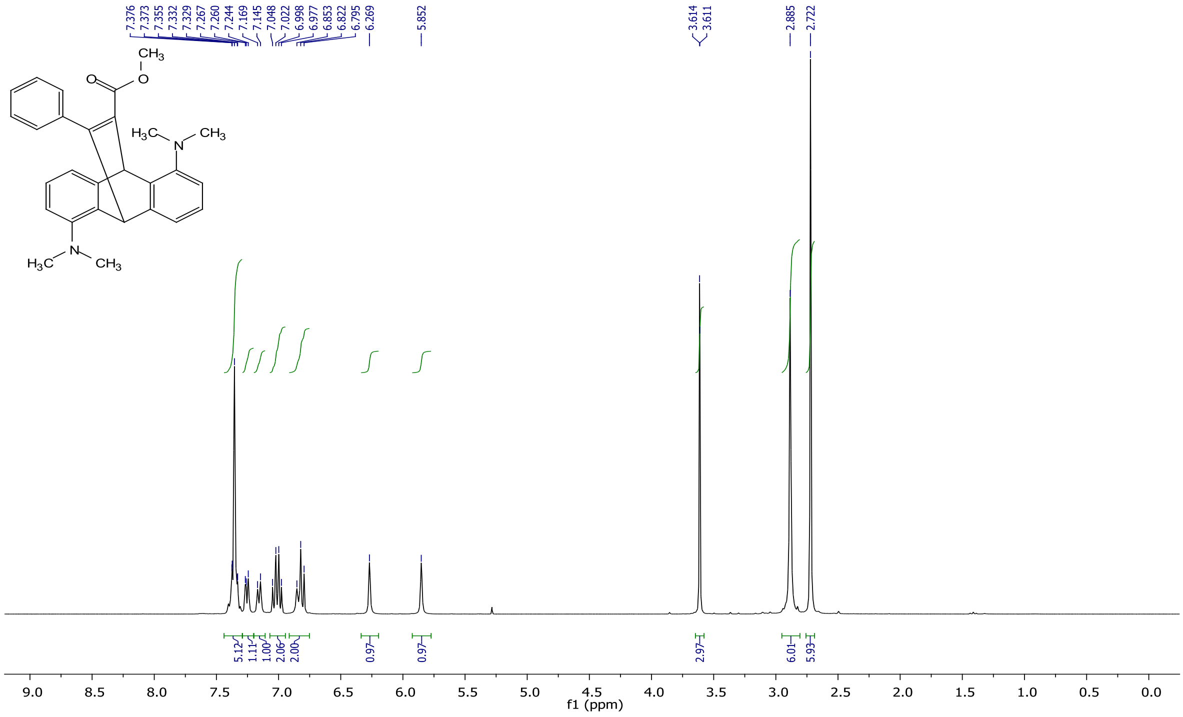
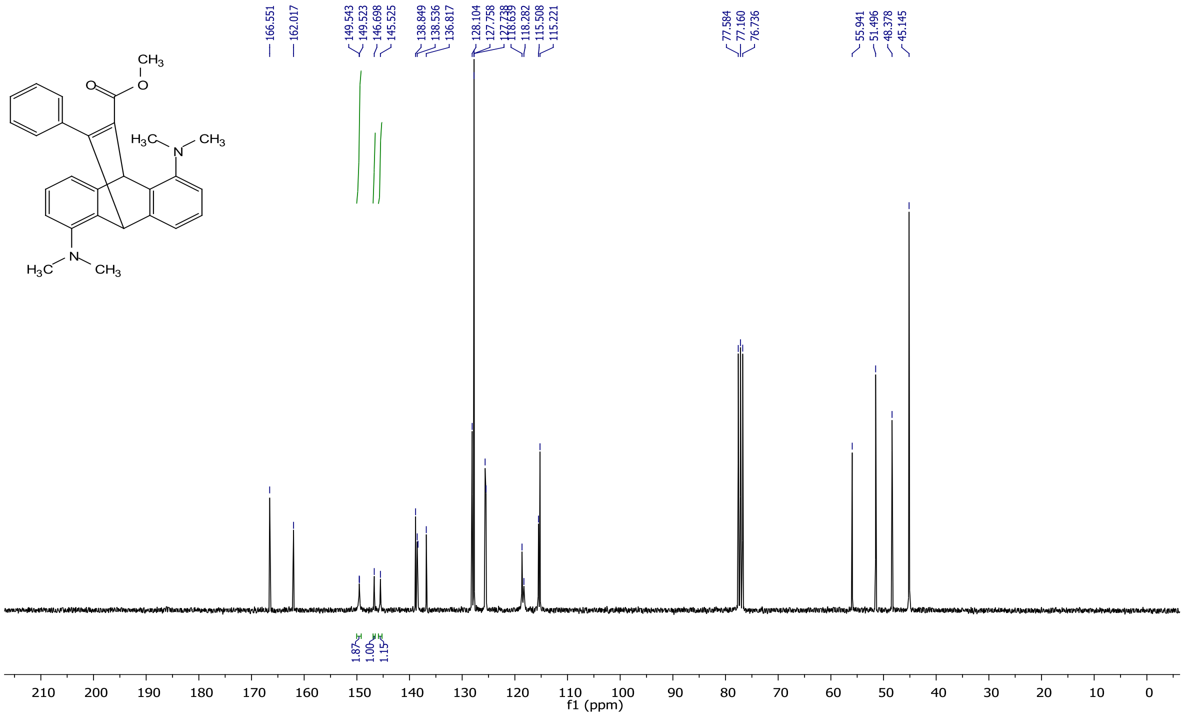


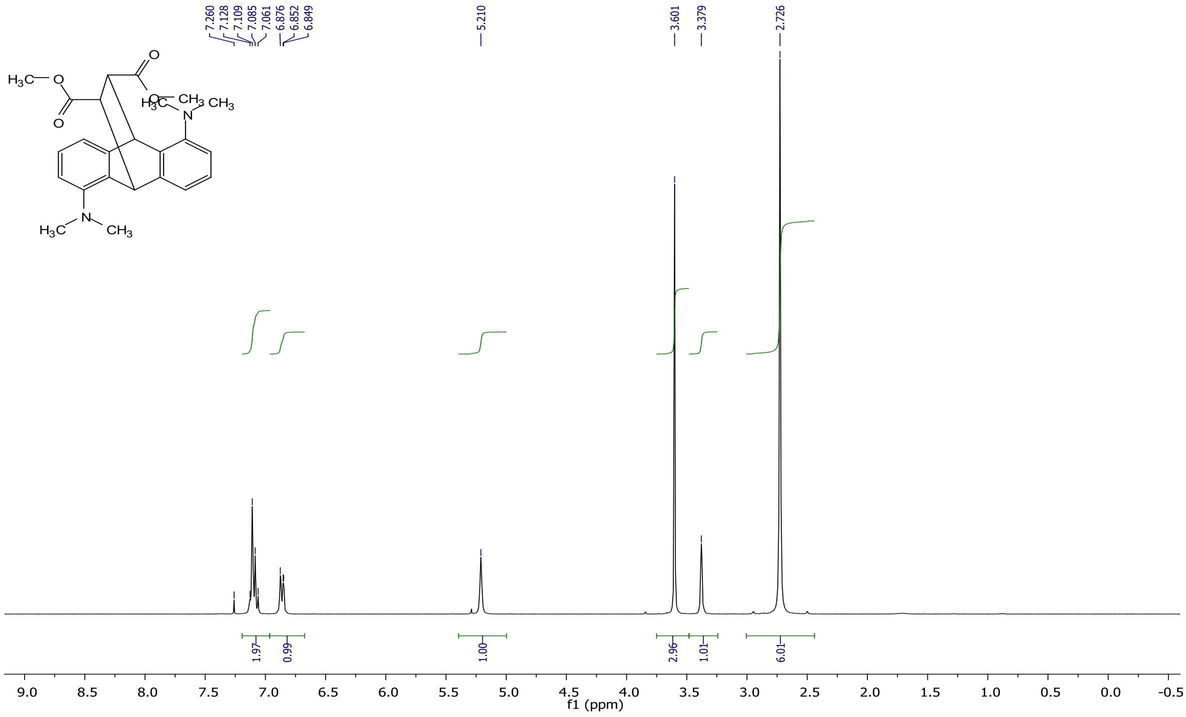


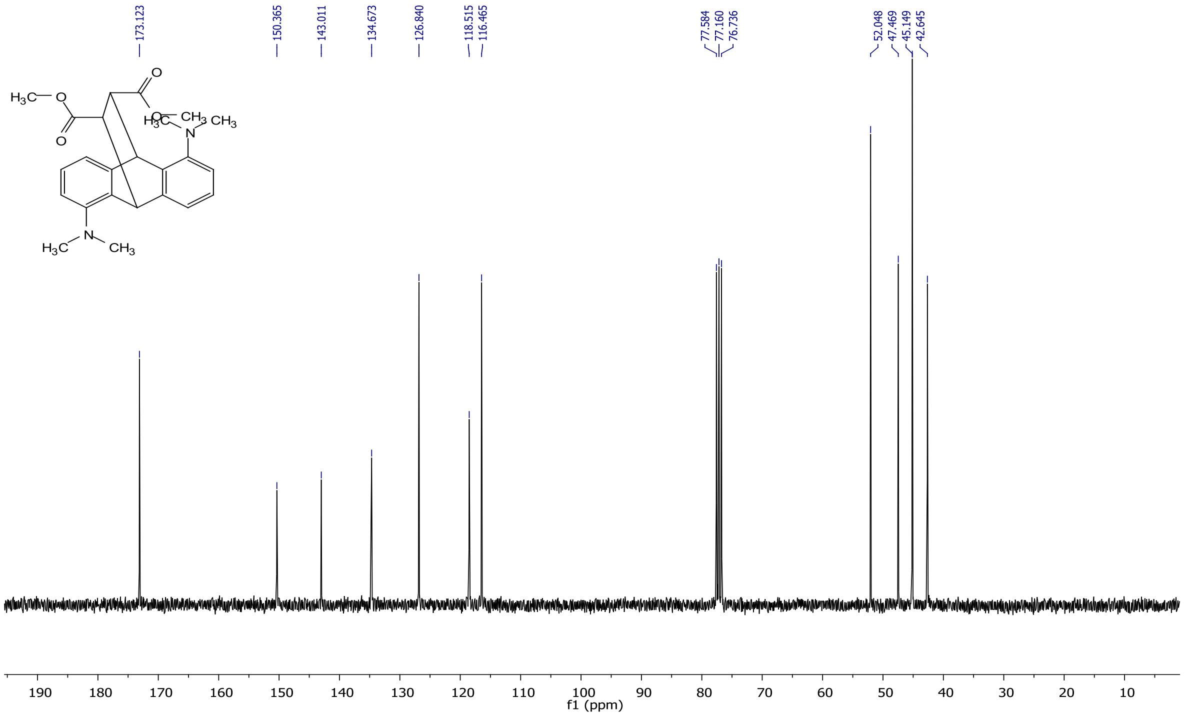
Methyl 1,5-bis(dimethylamino)-12-phenyl-9,10-dihydro-9,10-ethenoanthracene-11-carboxylate (93b)



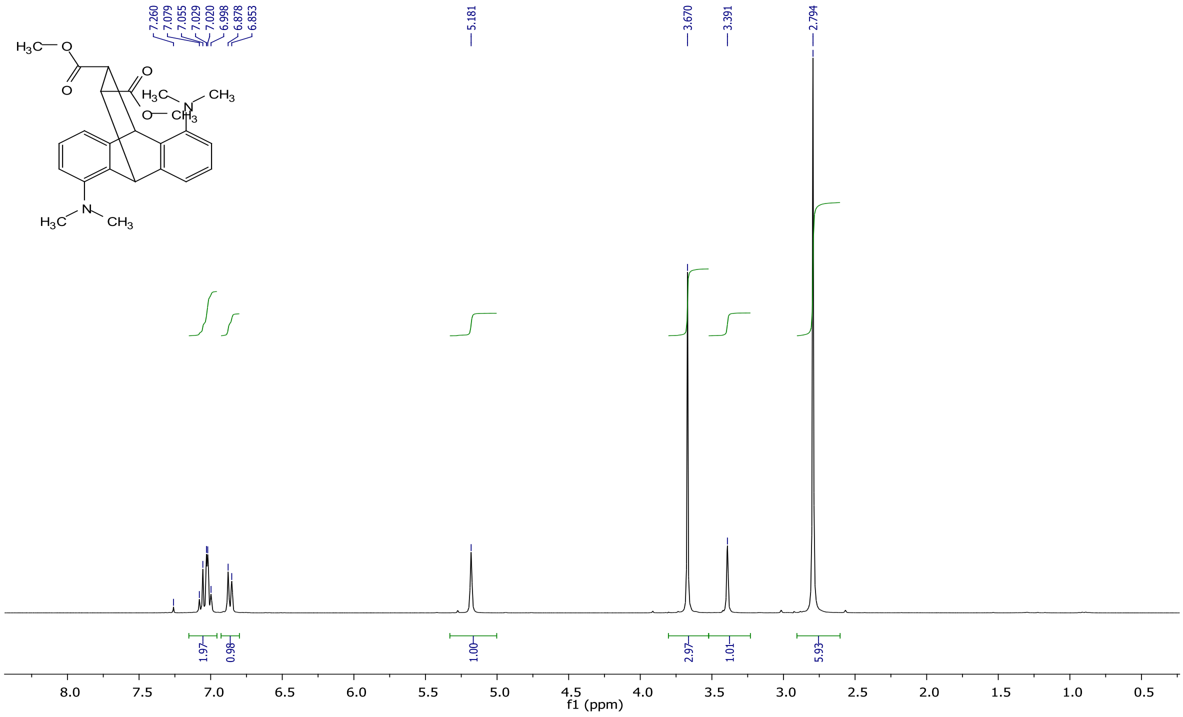


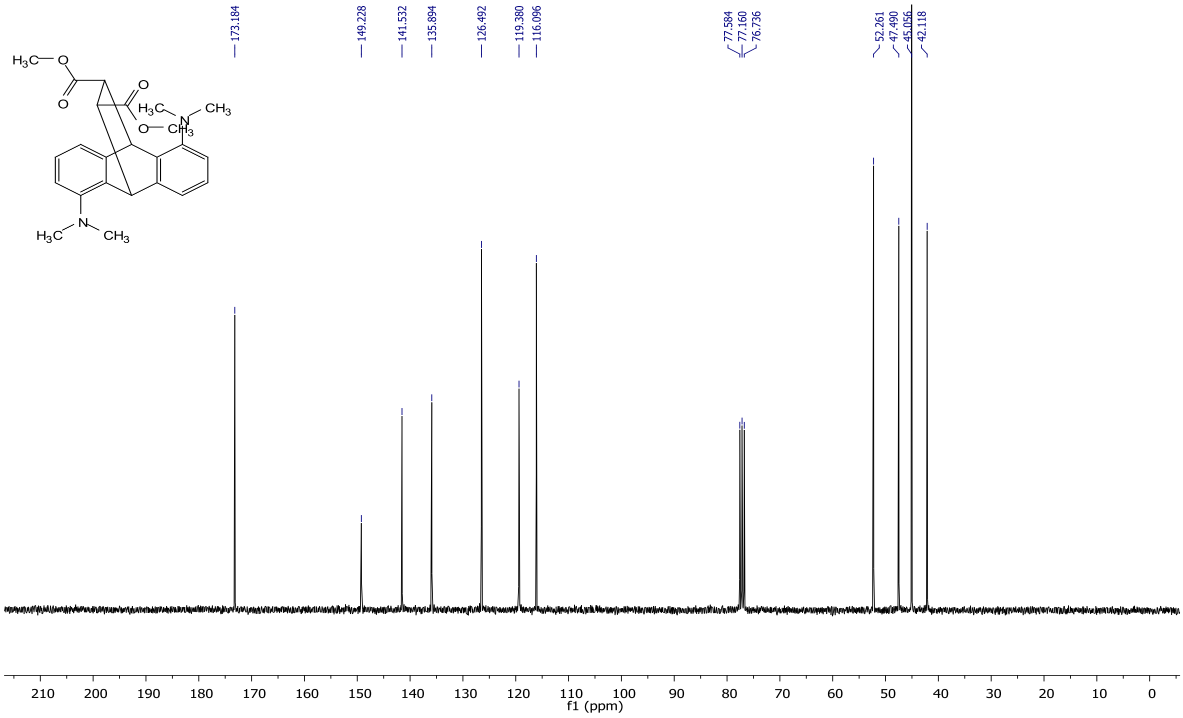
Cis-dimethyl 1,5-bis(dimethylamino)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (*cis*-93c)



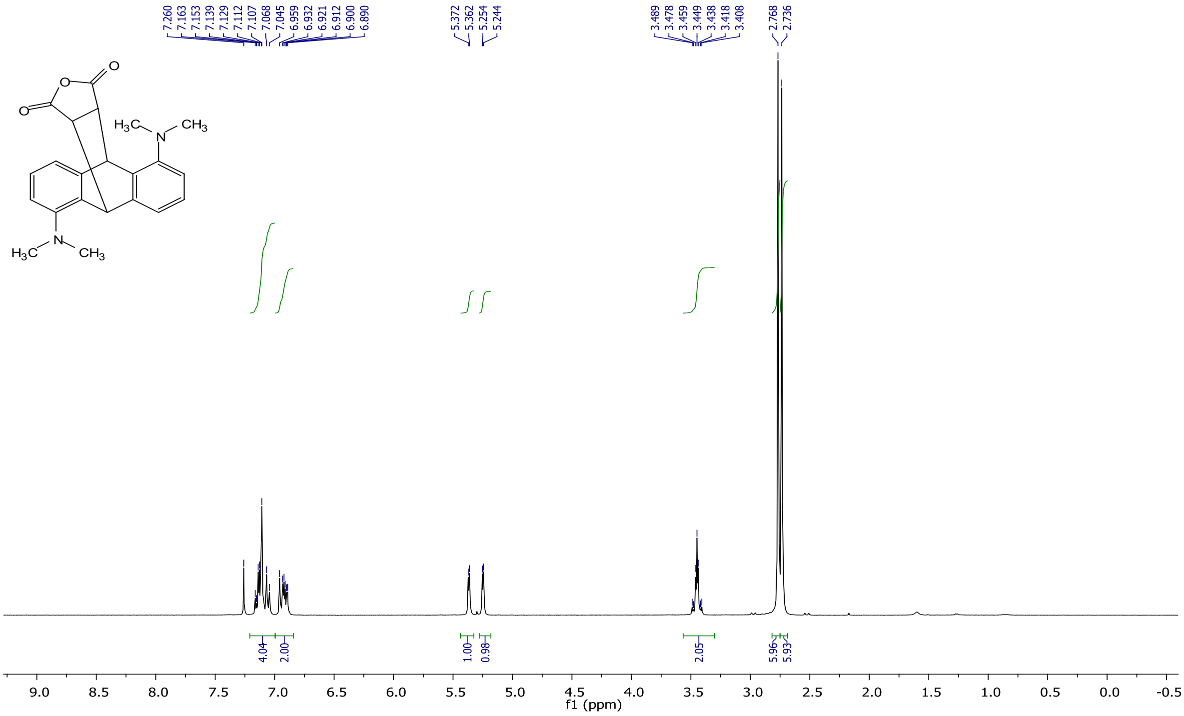


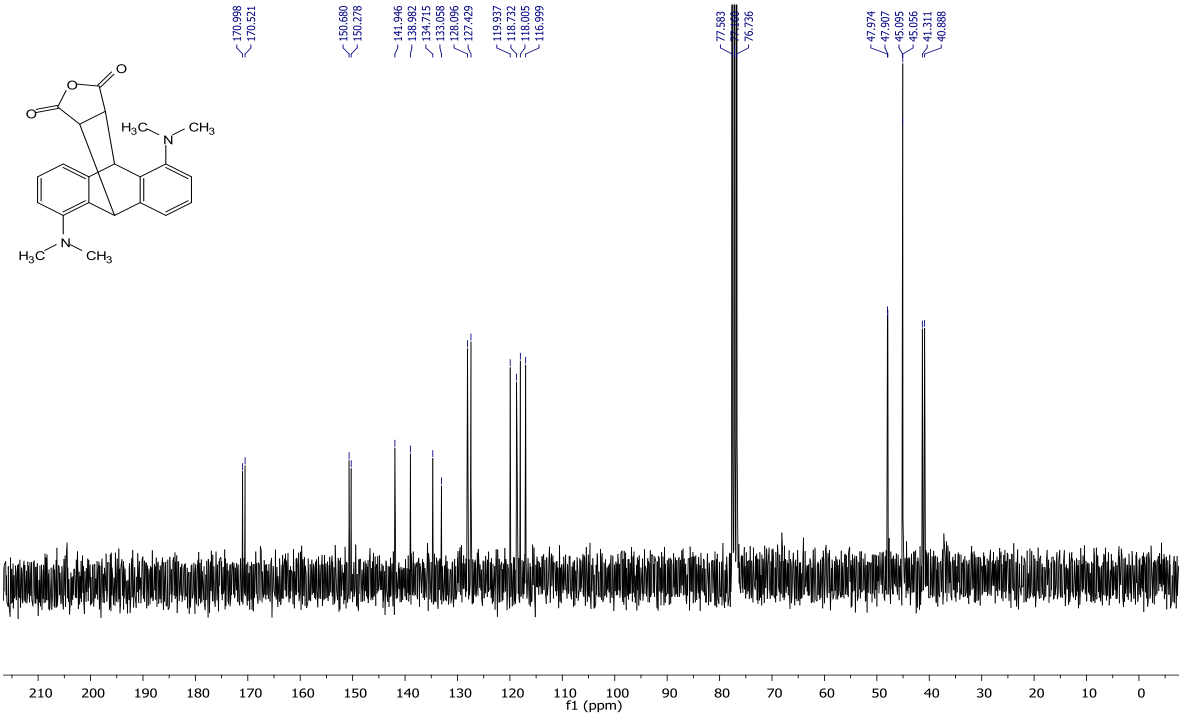
***Trans*-dimethyl 1,5-bis(dimethylamino)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (*trans*-93c)**



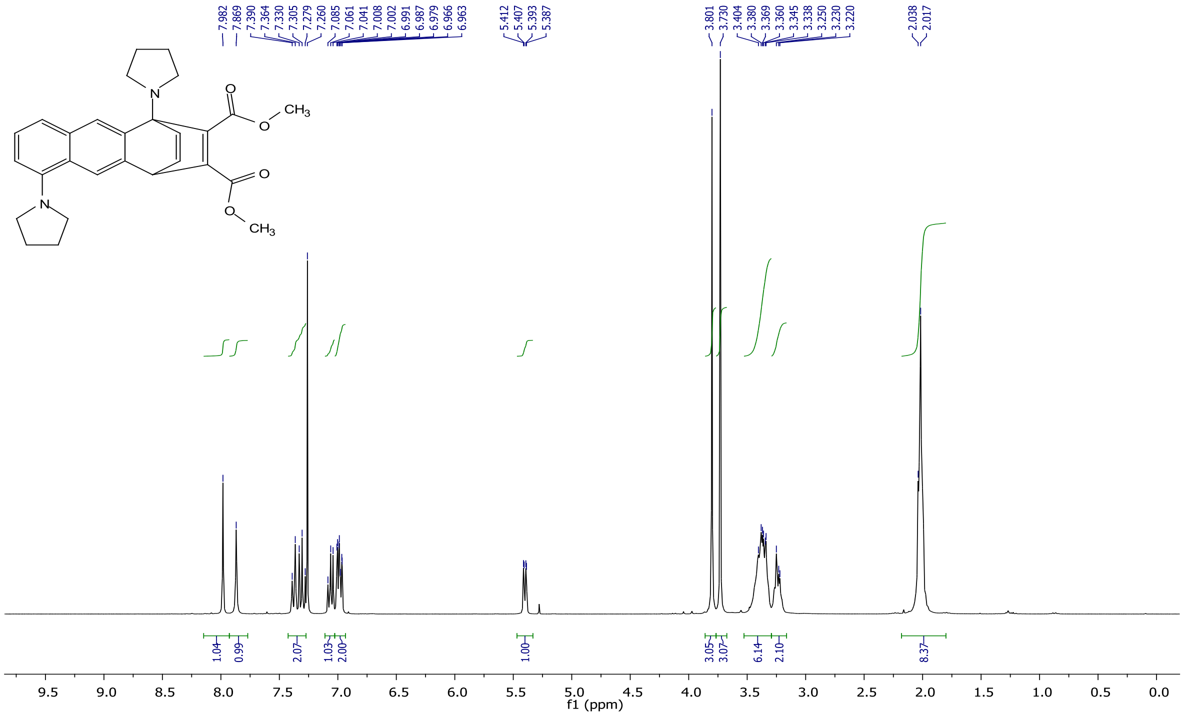


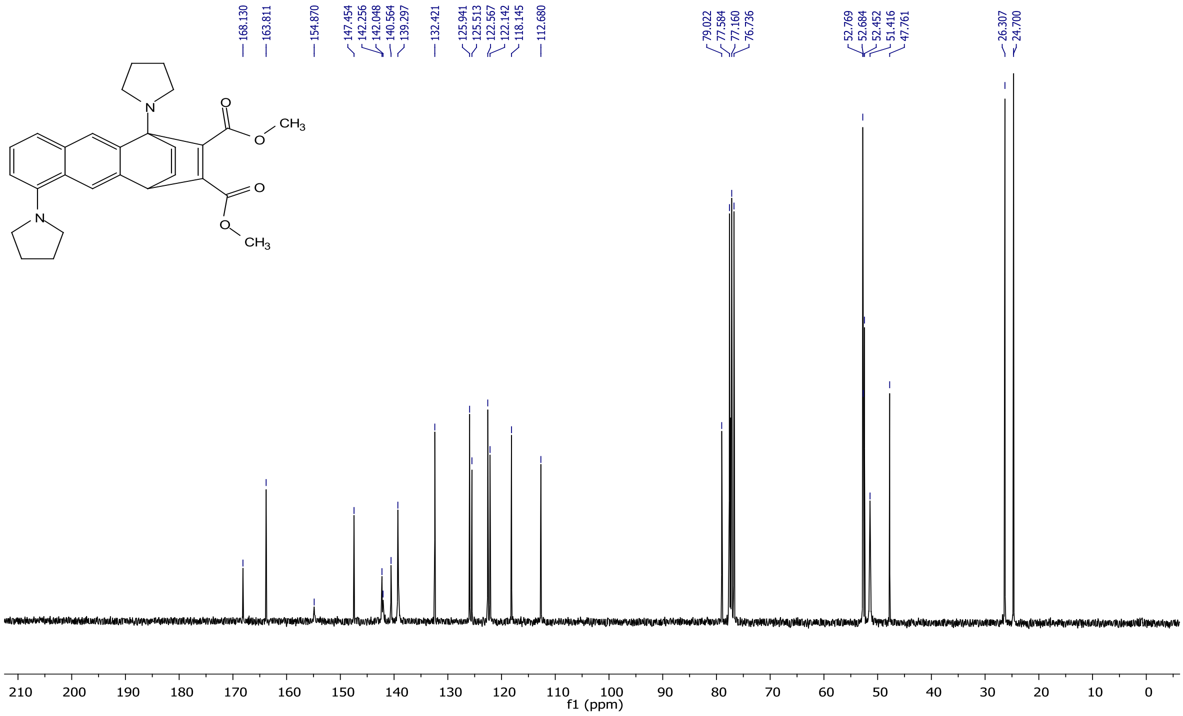
1,5-bis(dimethylamino)-9,10,11,15-tetrahydro-9,10-[3’,4’]furanoanthracene-12,14-dione (93d)



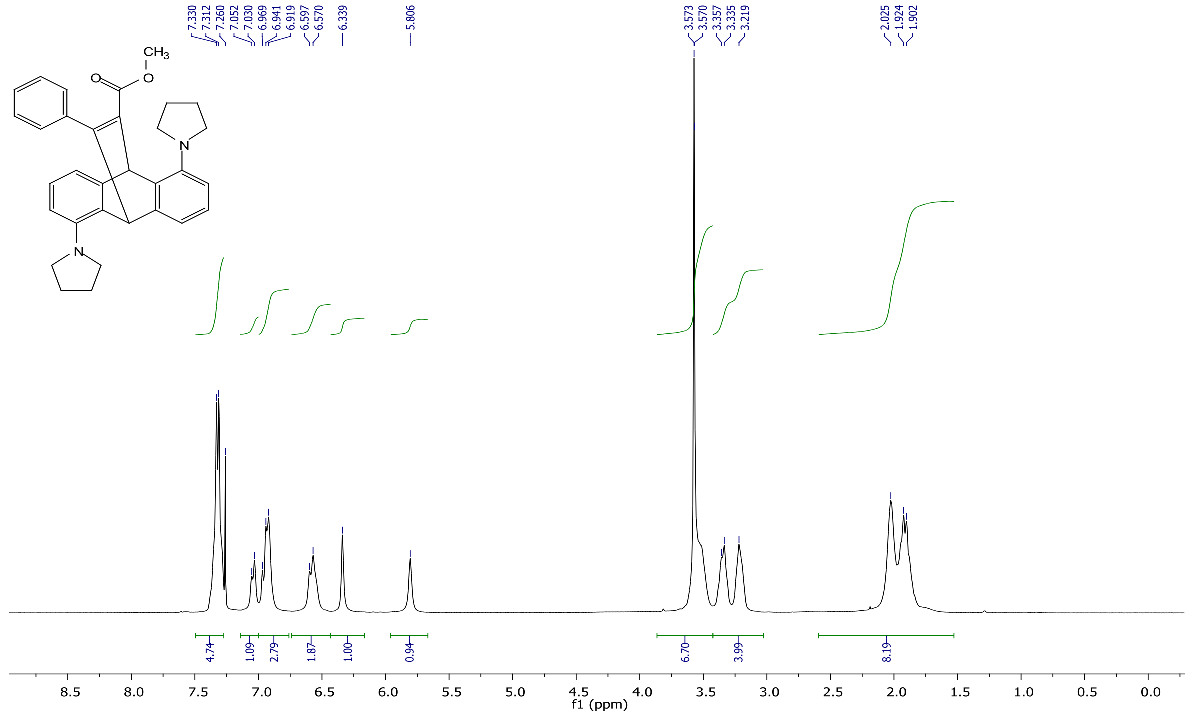


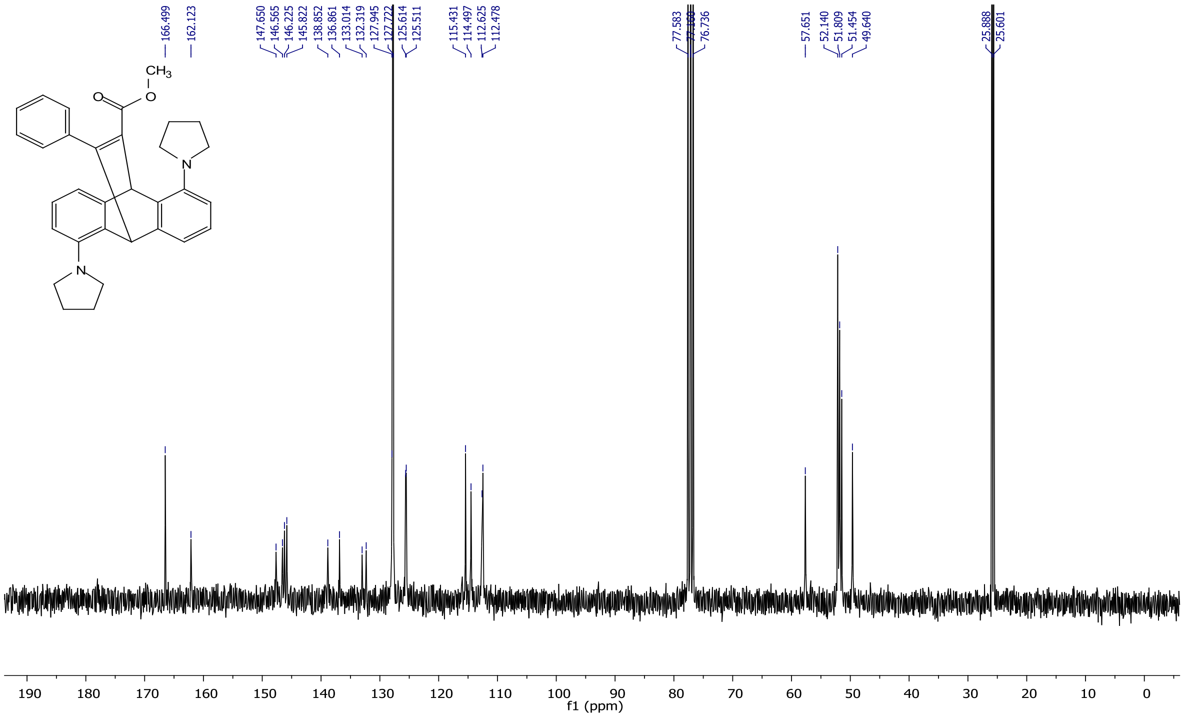
Dimethyl 1,5-bis(pyrrolidin-1-yl)-1,4-dihydro-1,4-ethenoanthracene-2,3-dicarboxylate (96a)



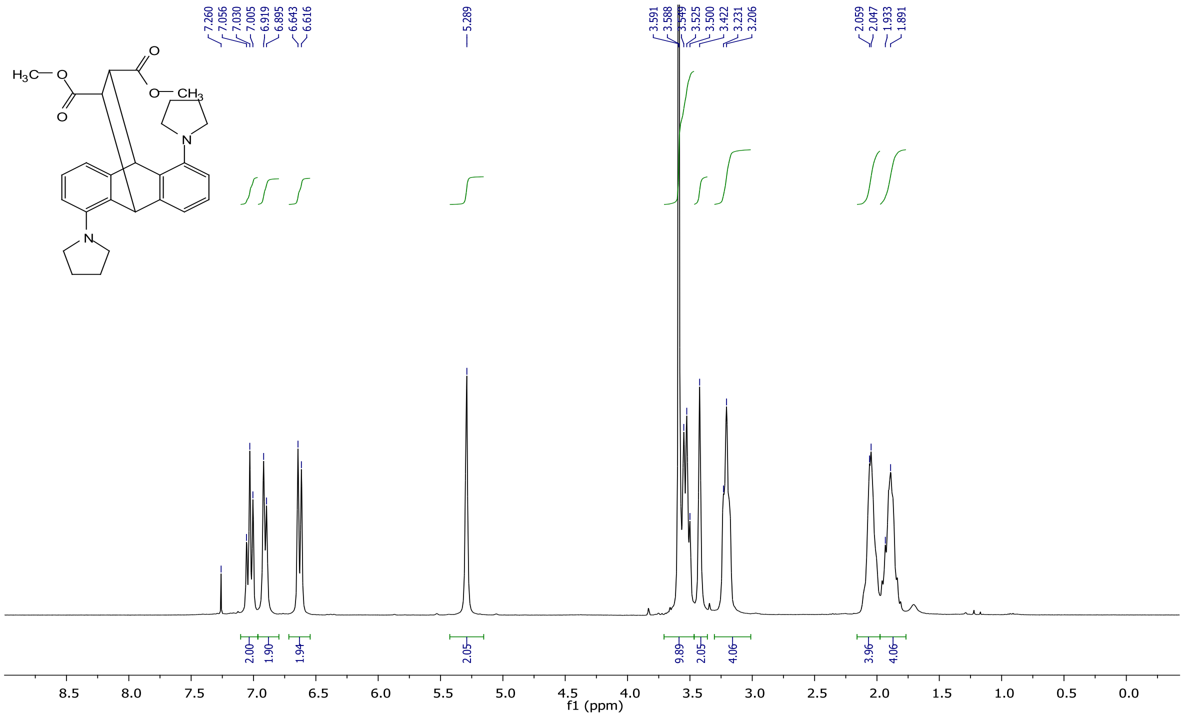


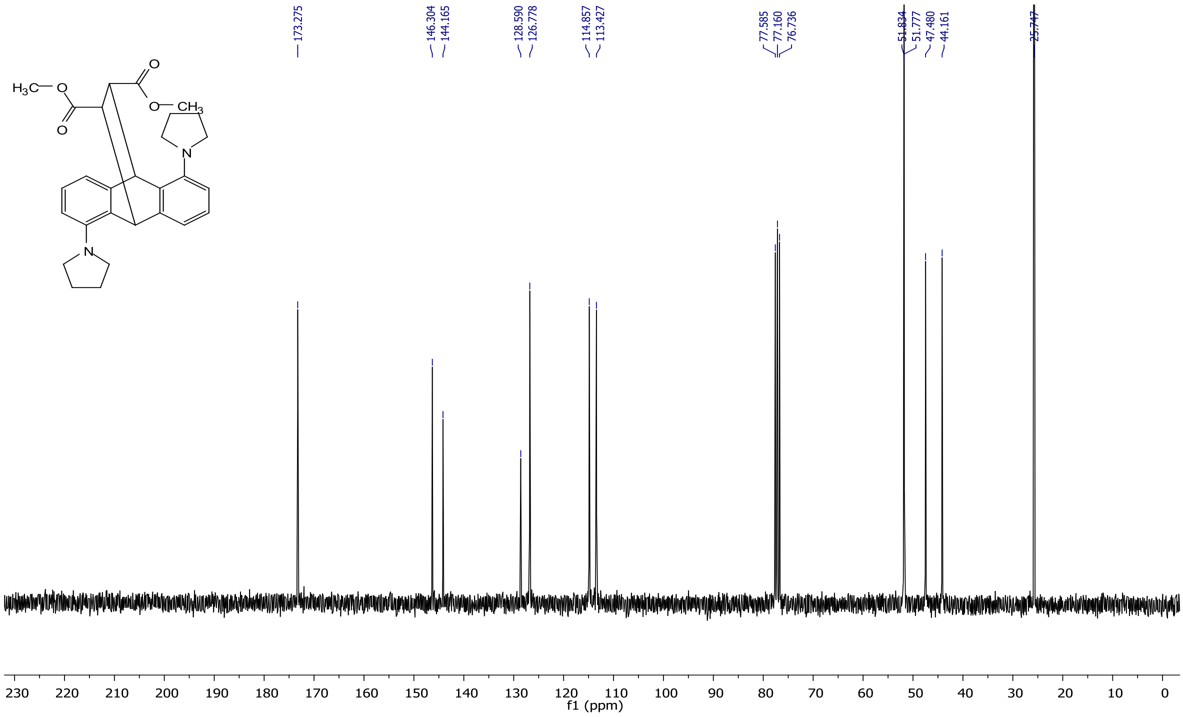
Methyl 12-phenyl-1,5-bis(pyrrolidin-1-yl)-9,10-dihydro-9,10-ethenoanthracene-11-carboxylate (95b)



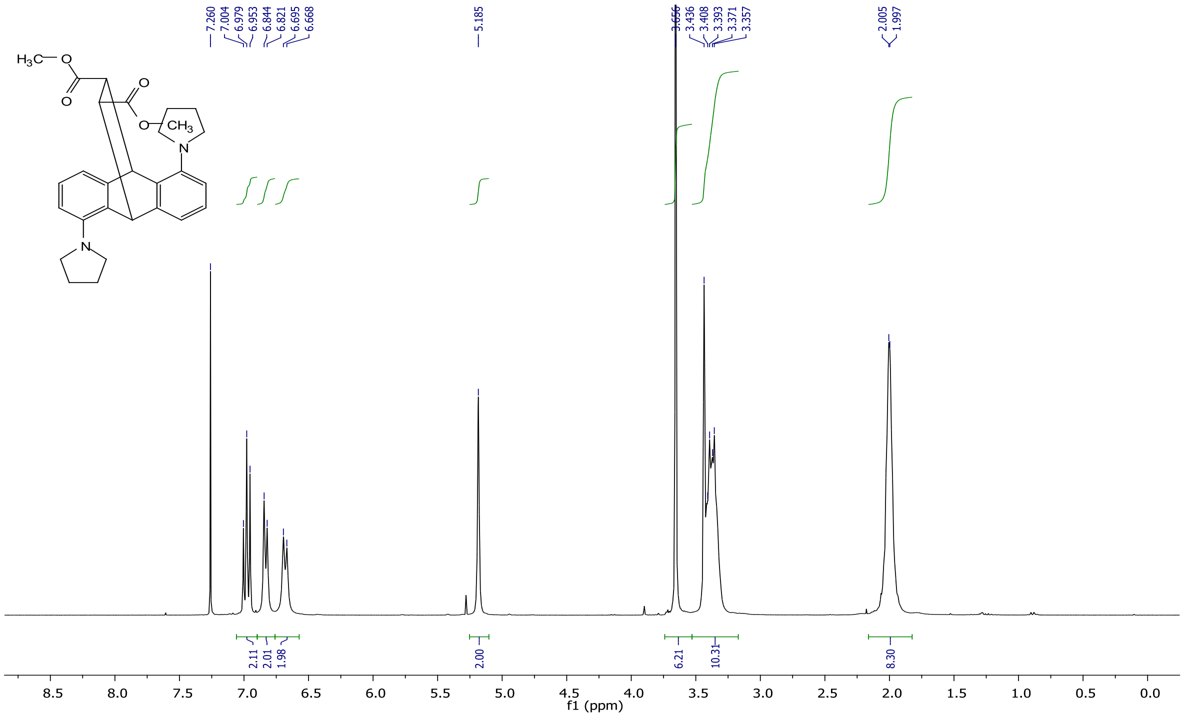


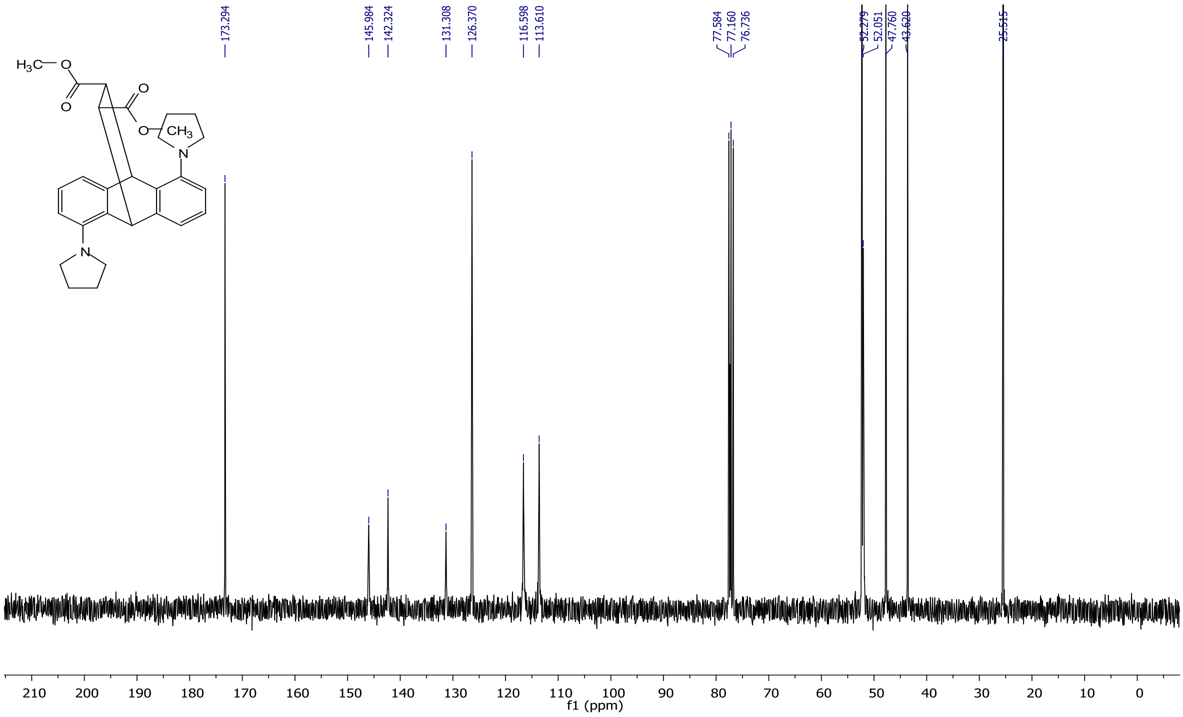
Cis-dimethyl 1,5-bis(pyrrolidin-1-yl)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (*cis*-95c)



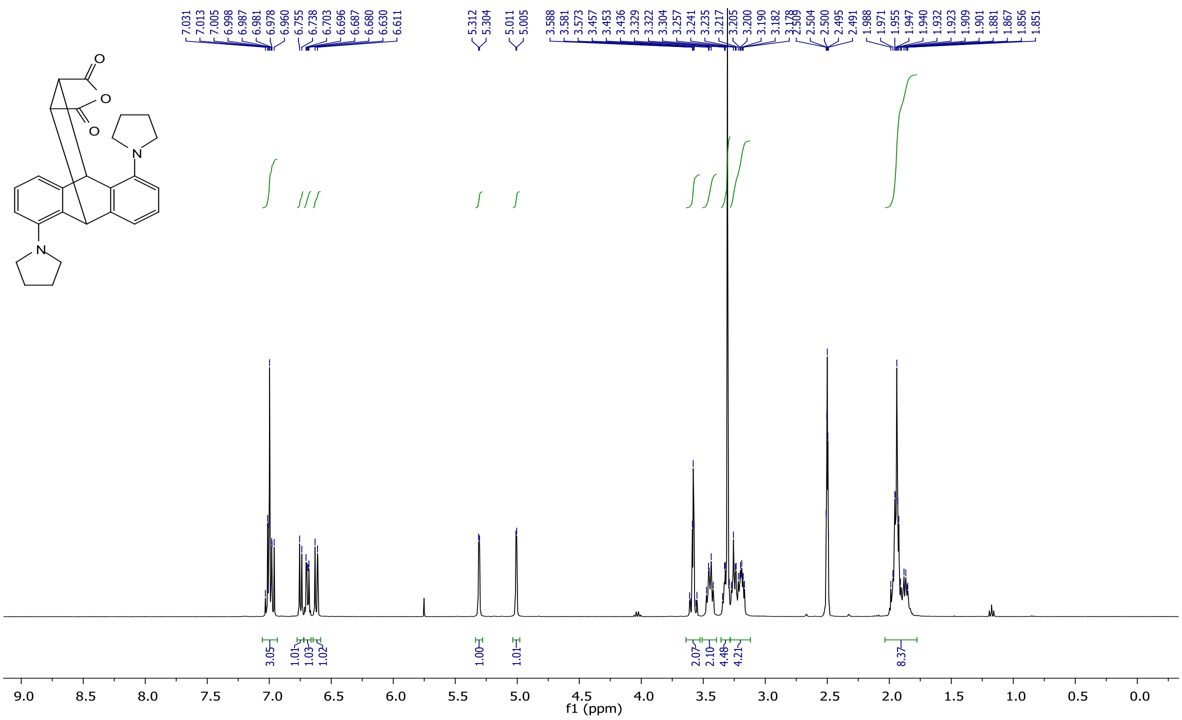


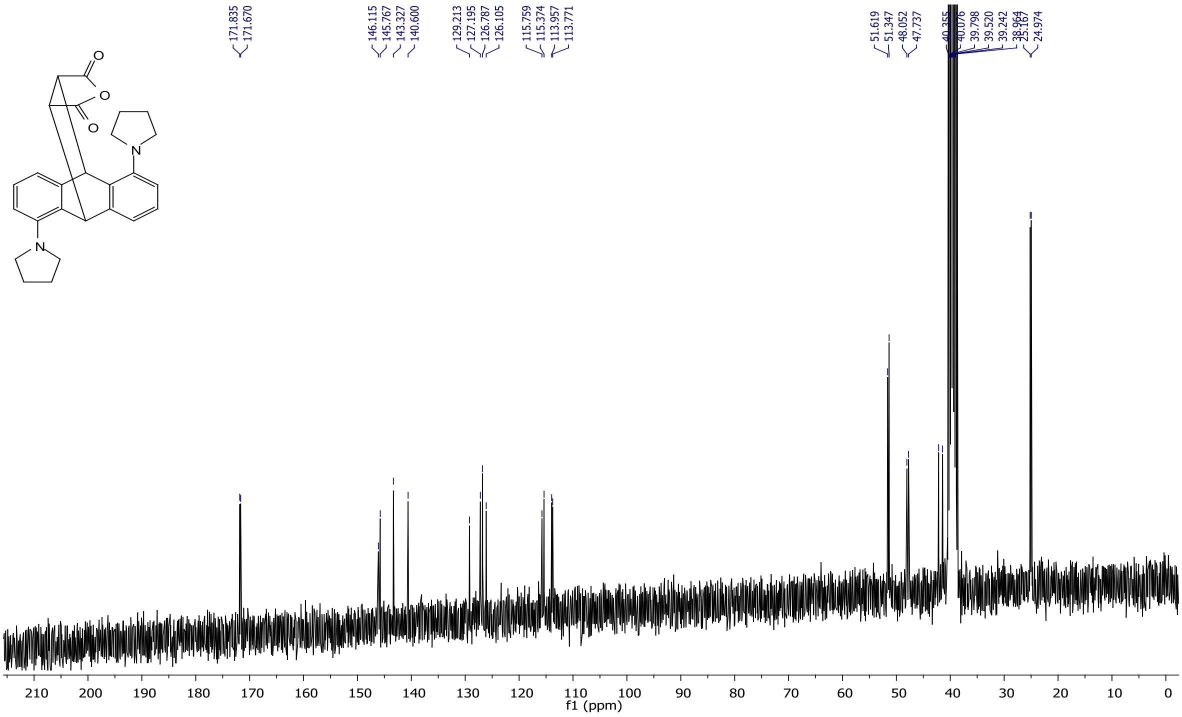
Trans-dimethyl 1,5-bis(pyrrolidin-1-yl)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (*trans*-95c)



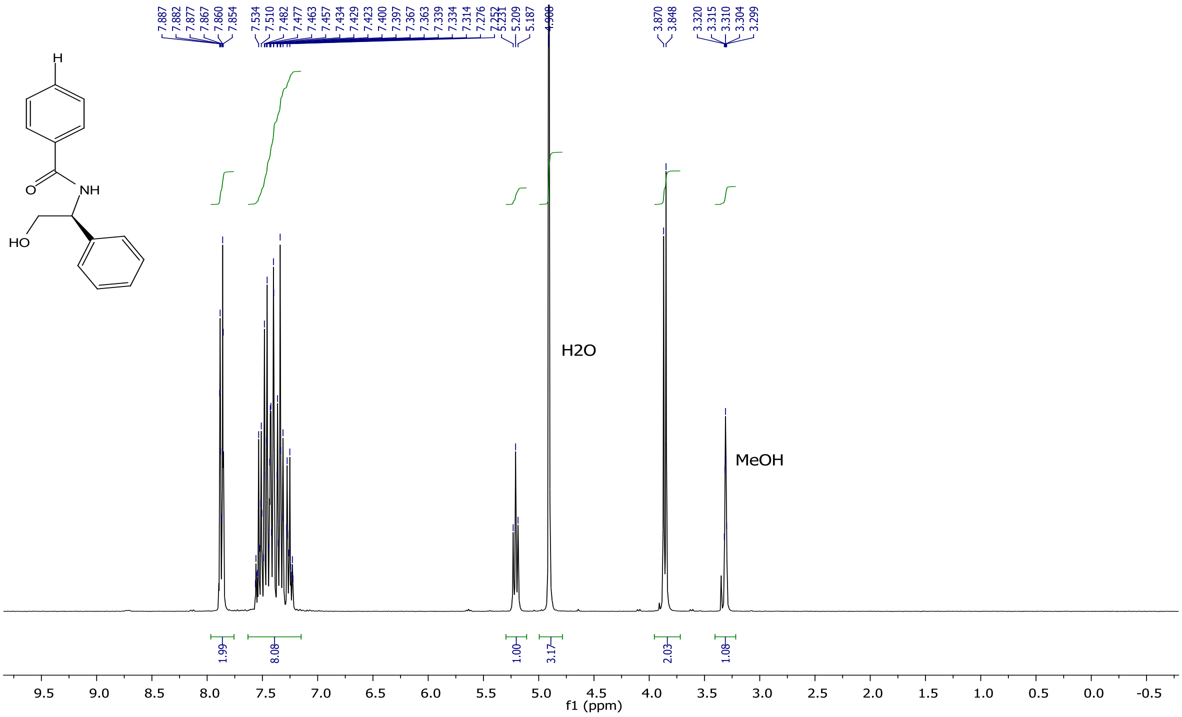


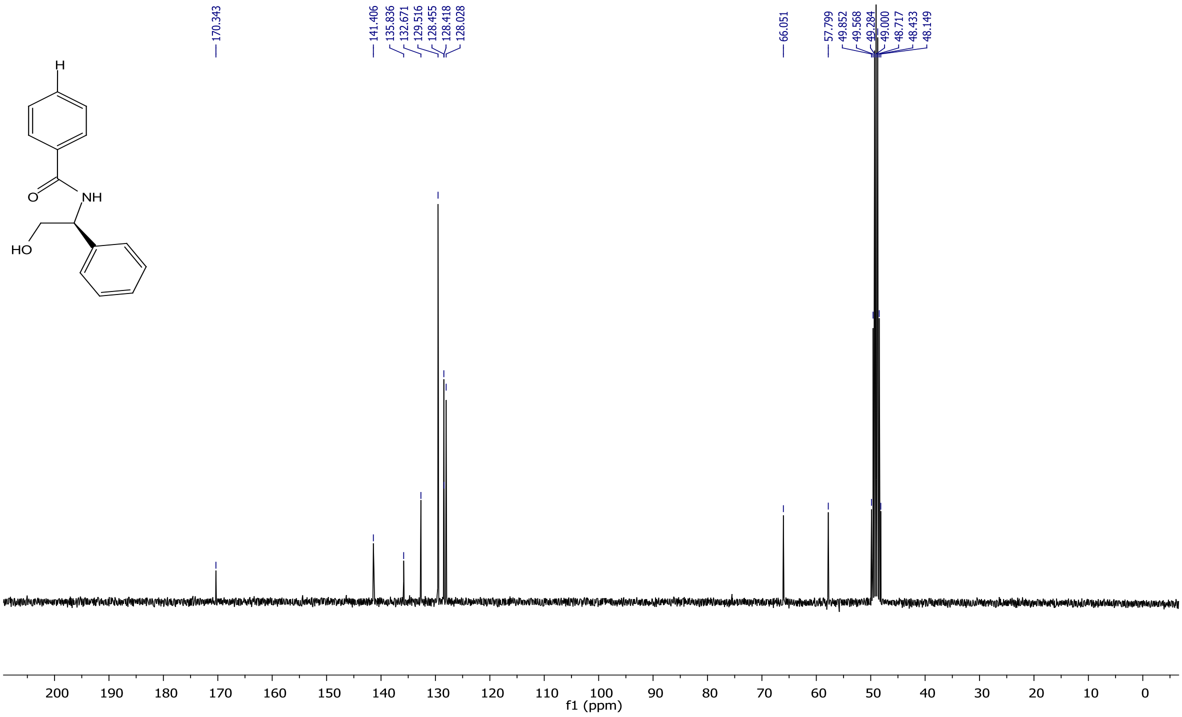
1,5-bis(pyrrolidin-1-yl)-9,10,11,15-tetrahydro-9,10-[3’,4’]furanoanthracene-12,14-dione (95d) (DMSO)



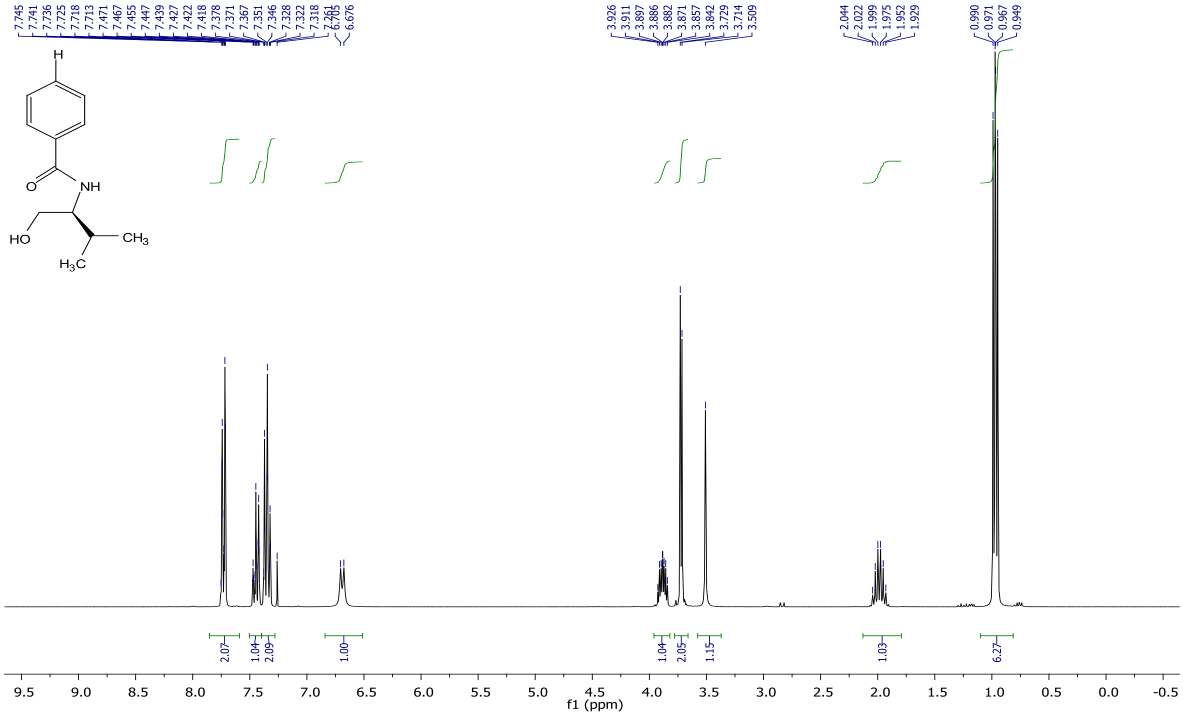


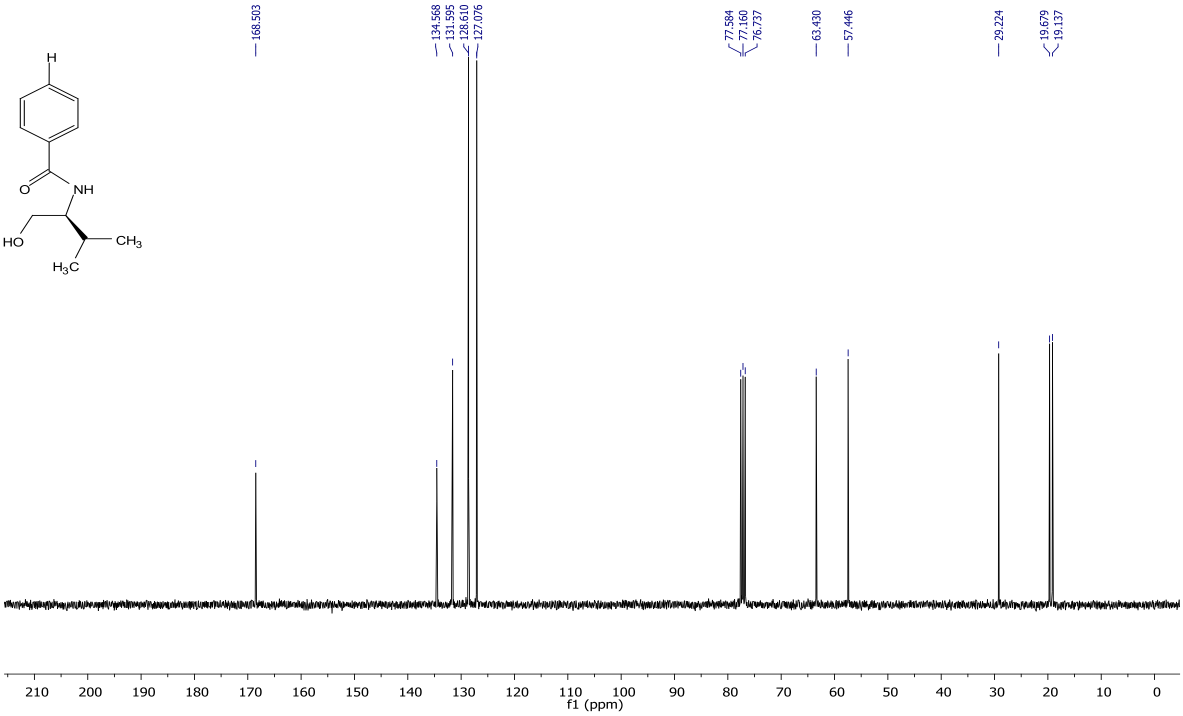
(*S*)-*N*-(Benzoyl)phenylglycinol (162a) (MeOD)



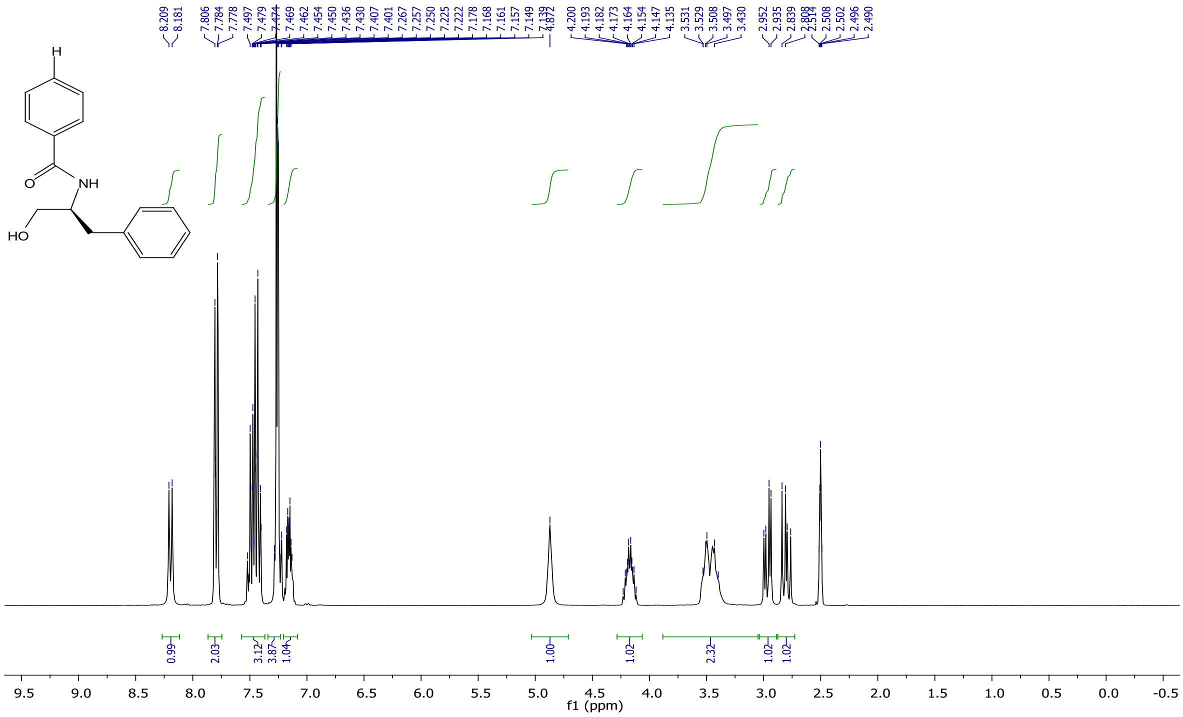


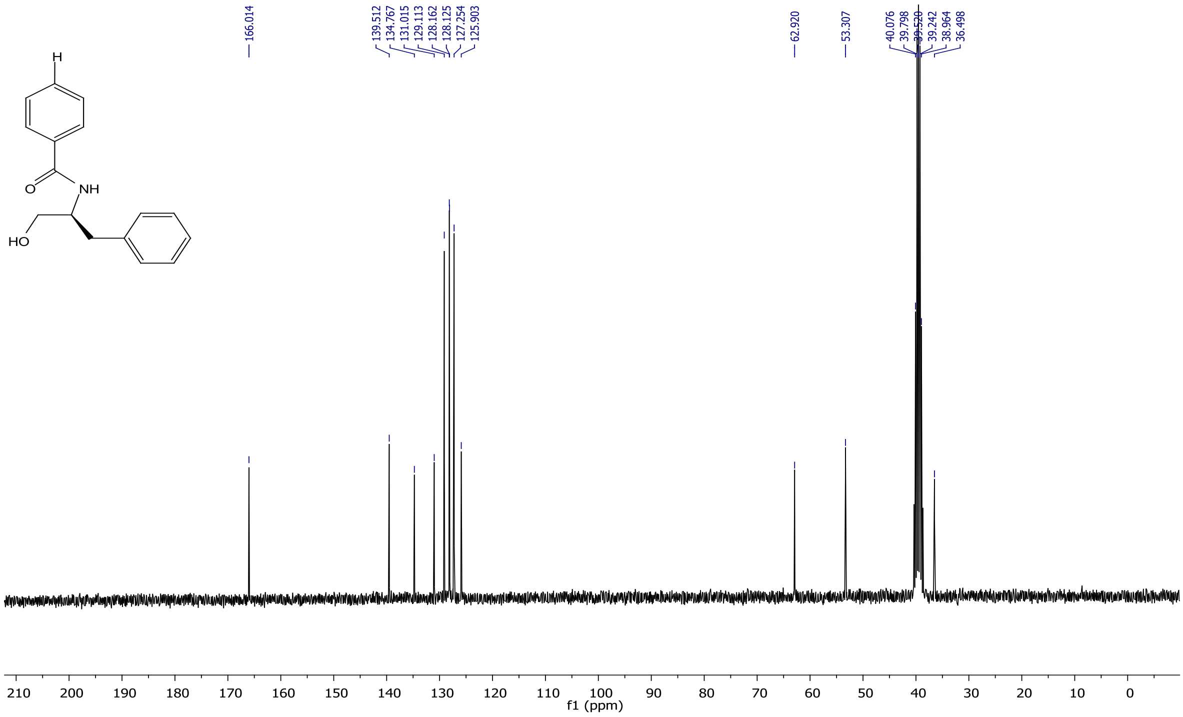
(*S*)-*N*-(Benzoyl)valinol (162b)



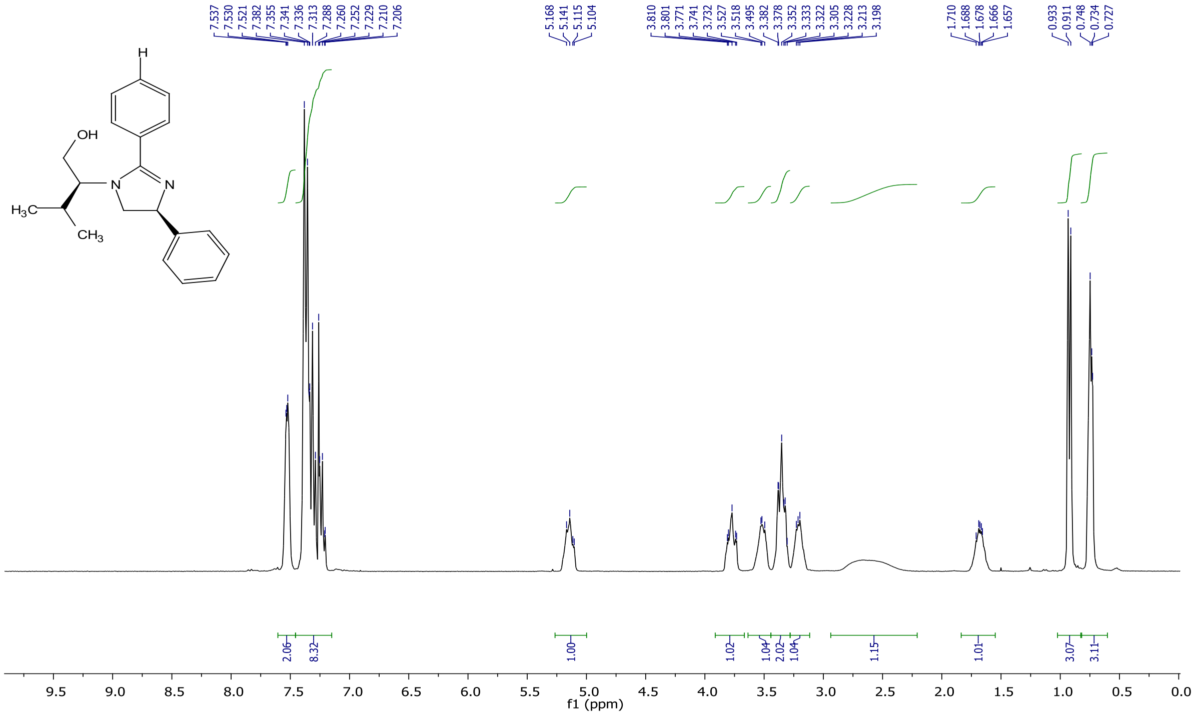


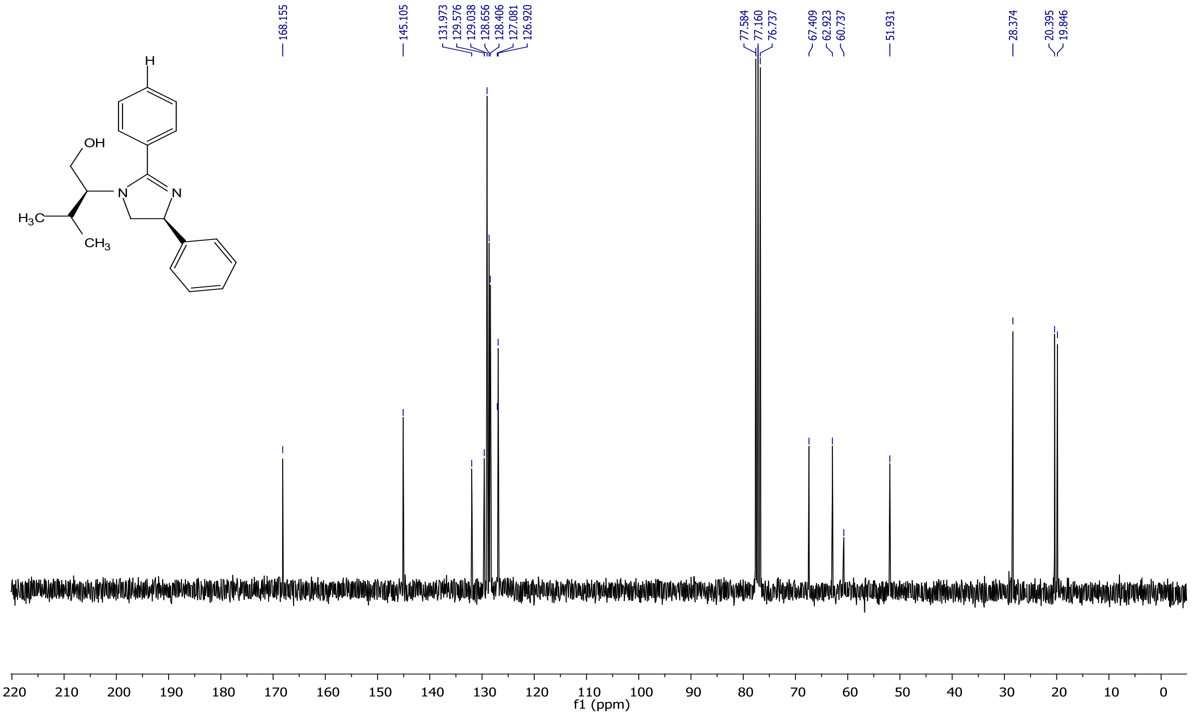
(*S*)-*N*-(Benzoyl)phenylalaninol (162c) (DMSO)



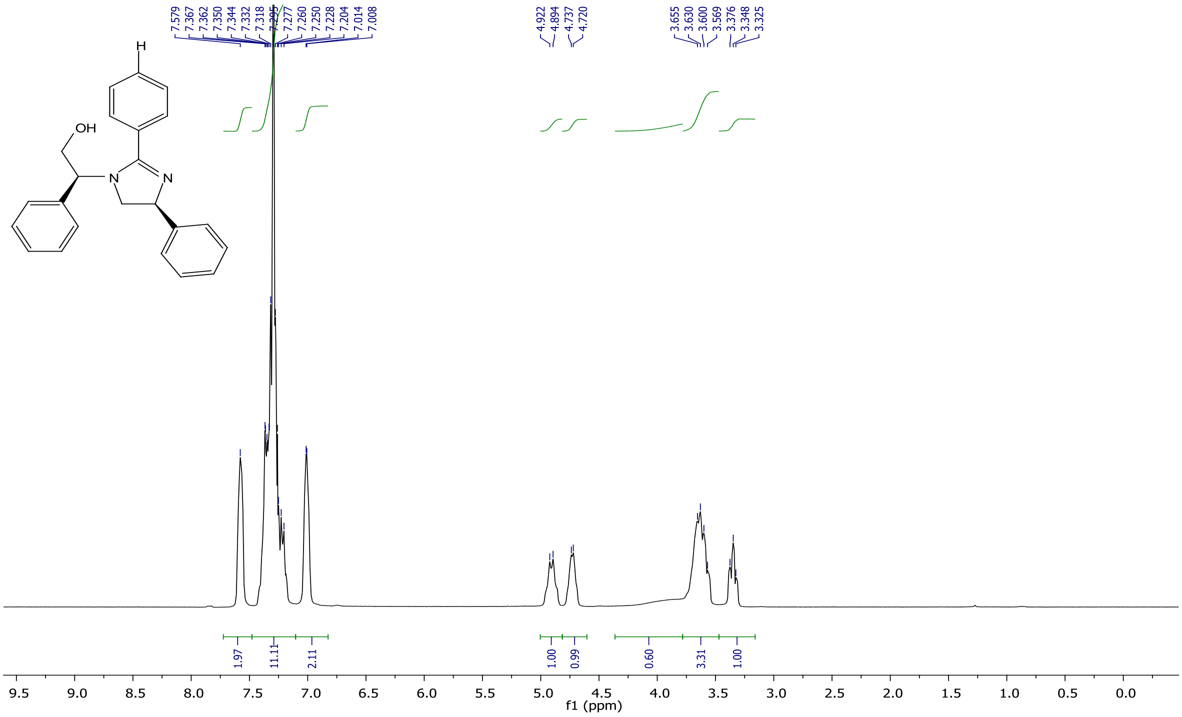


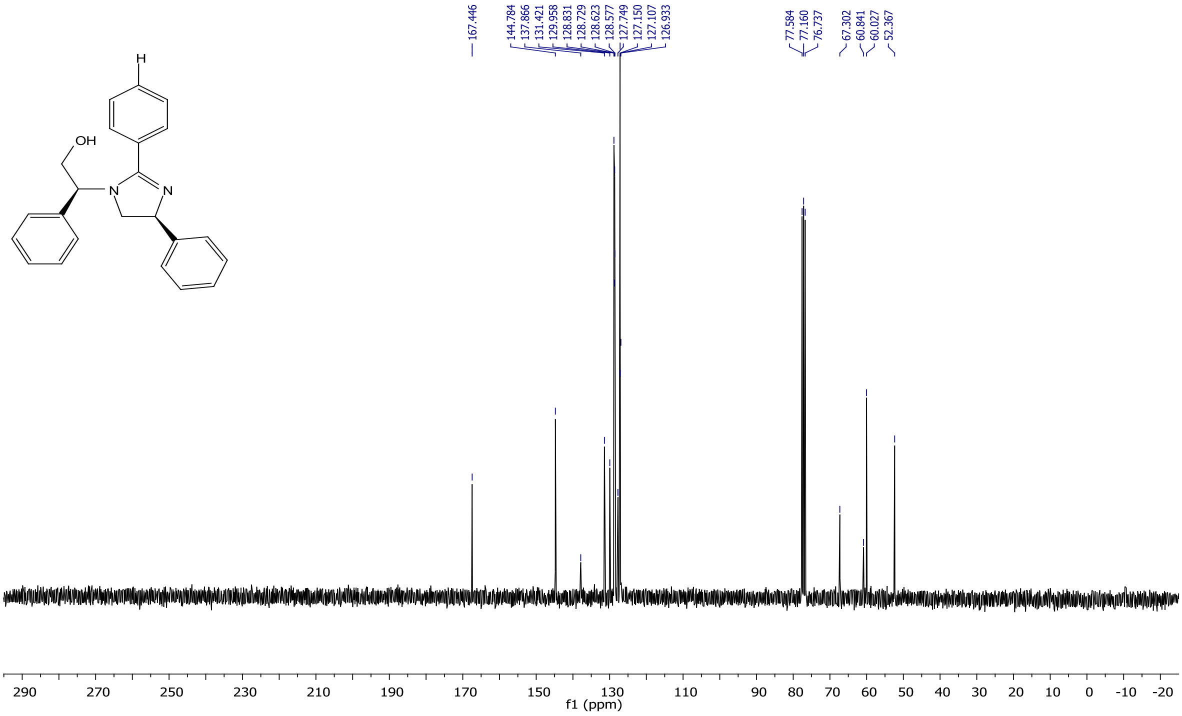
(4*S*)-1-((2*S*)-1-hydroxy-3-methyl-but-2-yl)-2,4-diphenyl-4,5-dihydroimidazole (163a)



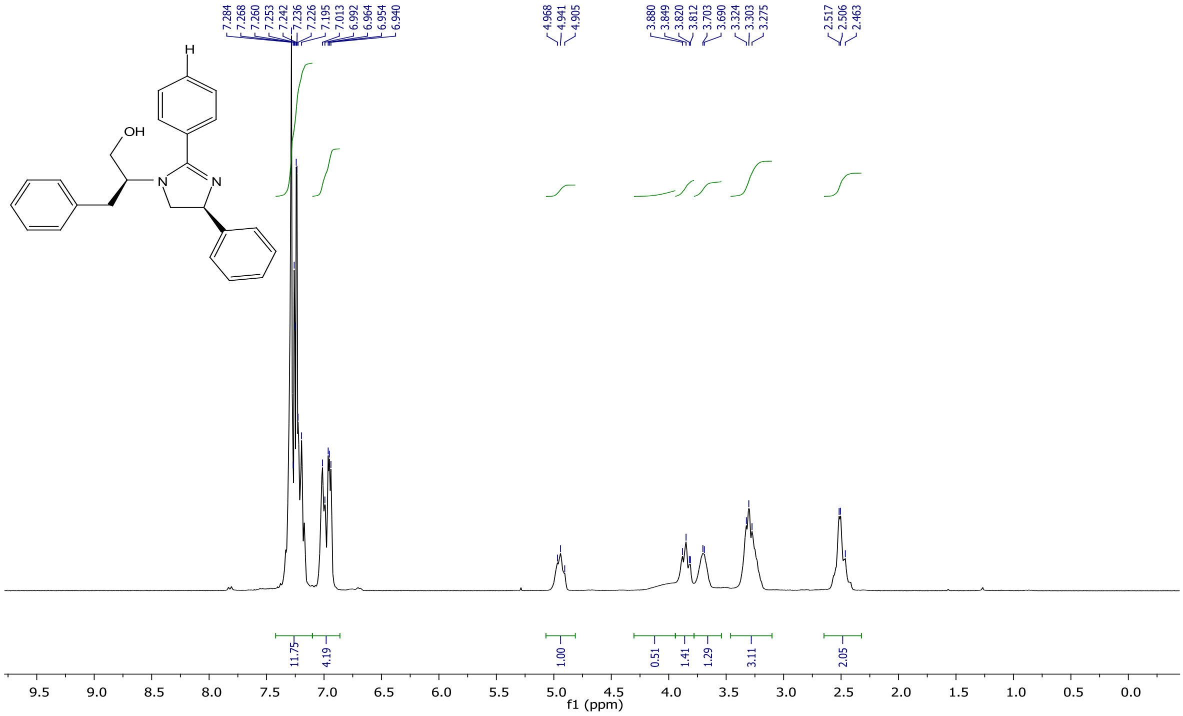


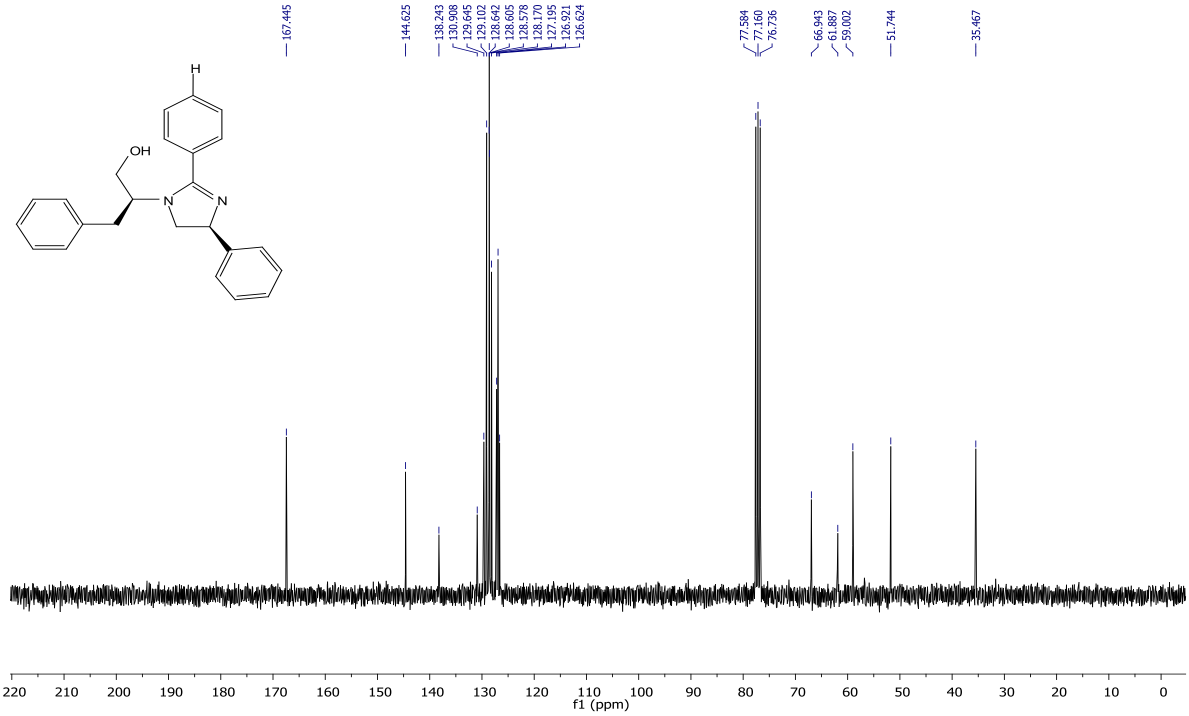
(4*S*)-1-((1*S*)-2-hydroxy-1-phenyl-eth-1-yl)-2,4-diphenyl-4,5-dihydroimidazole (163b)





(4*S*)-1-((2*S*)-1-hydroxy-3-phenyl-prop-2-yl)-2,4-diphenyl-4,5-dihydroimidazole (163c)





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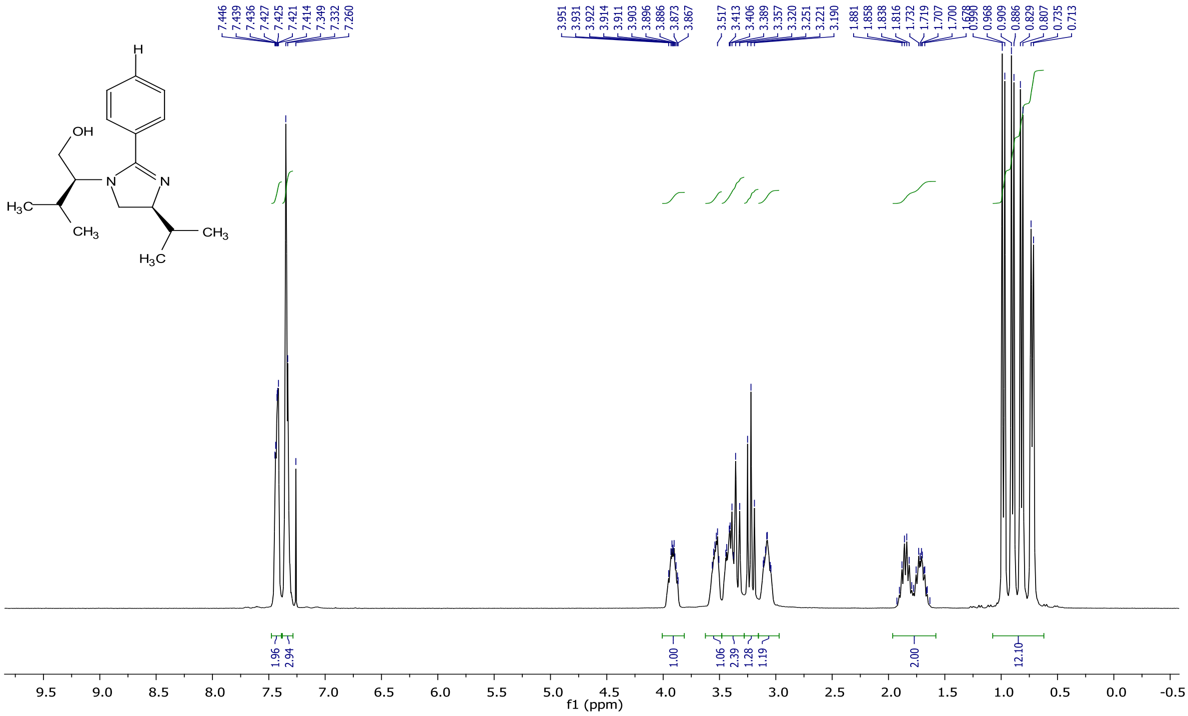
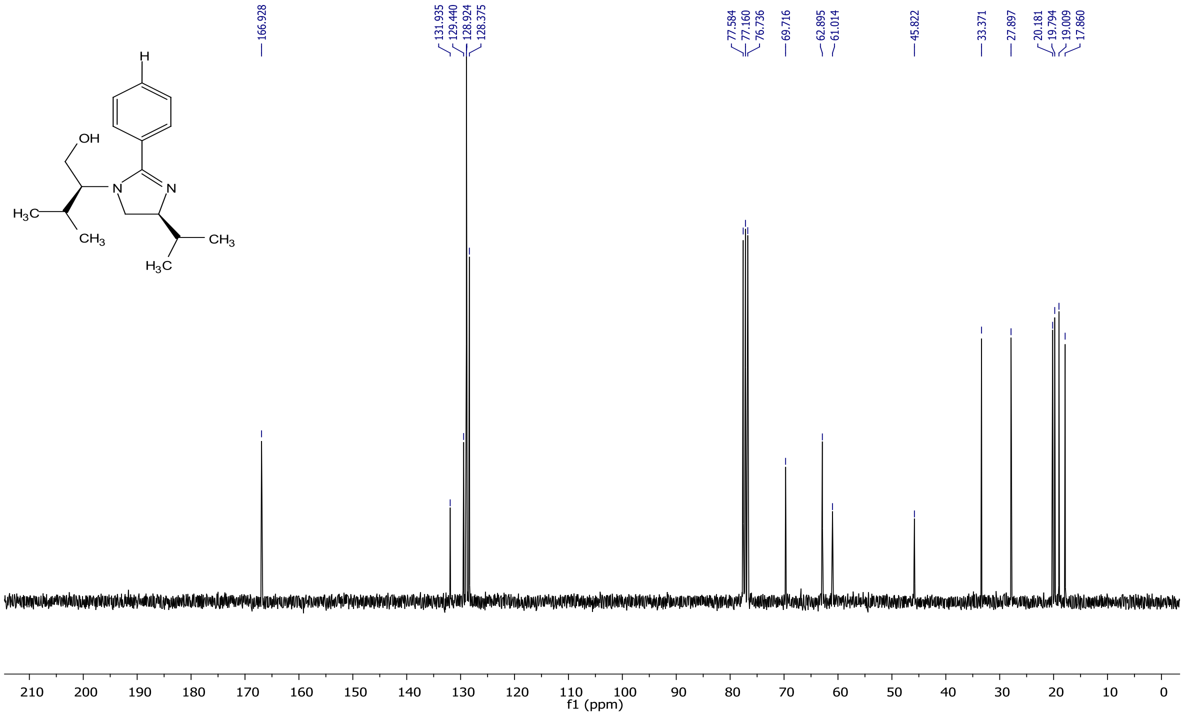
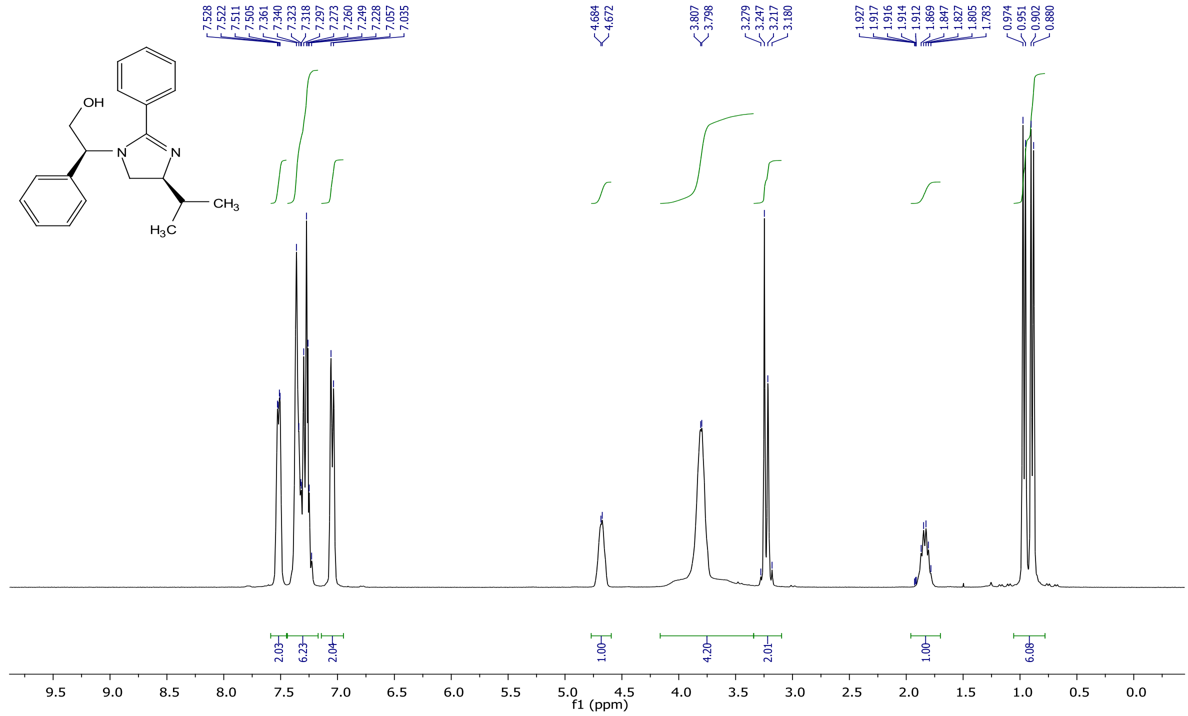
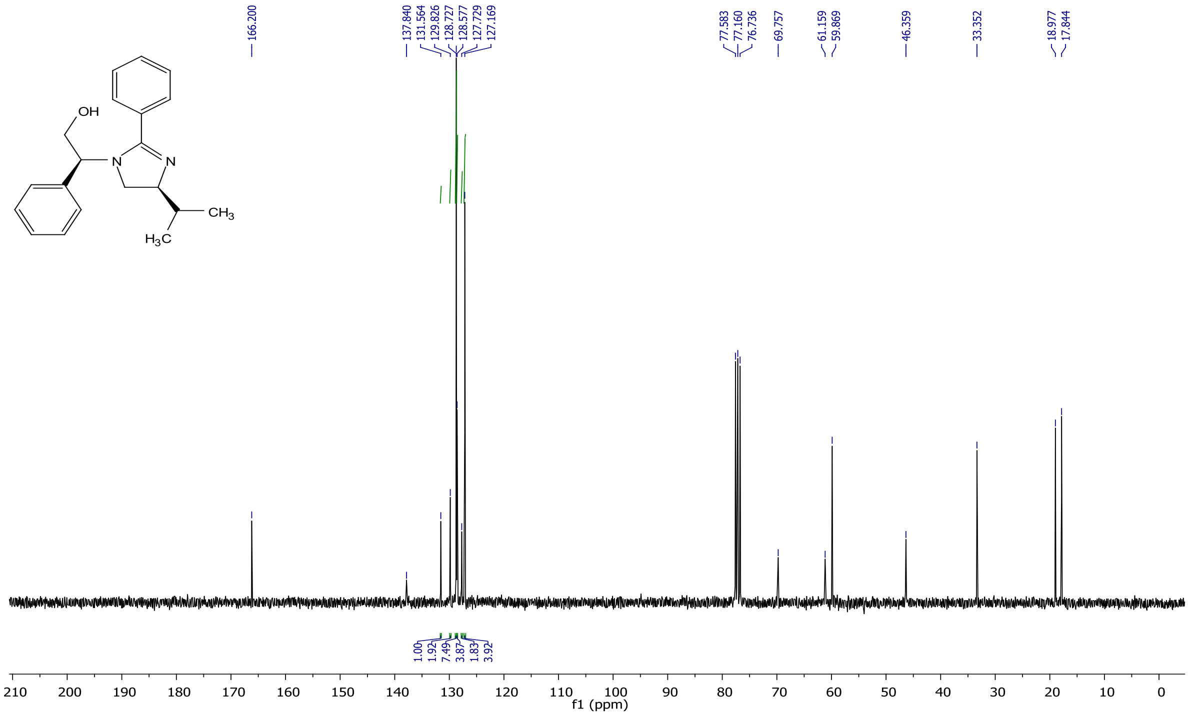


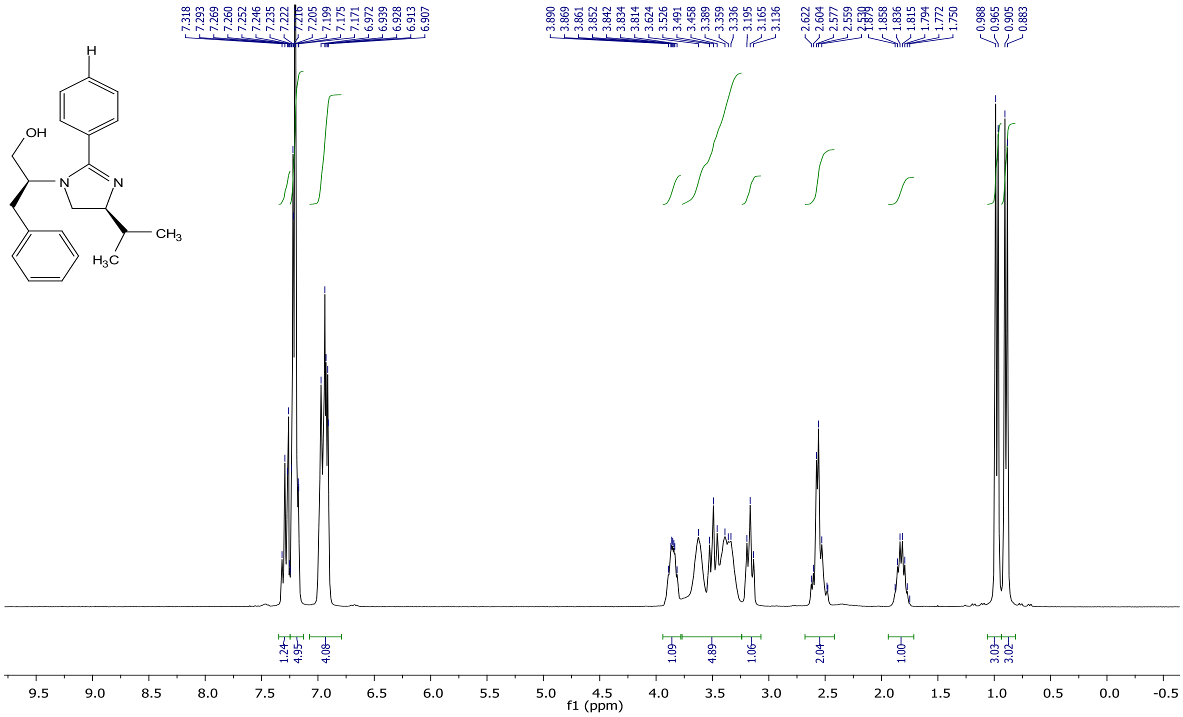


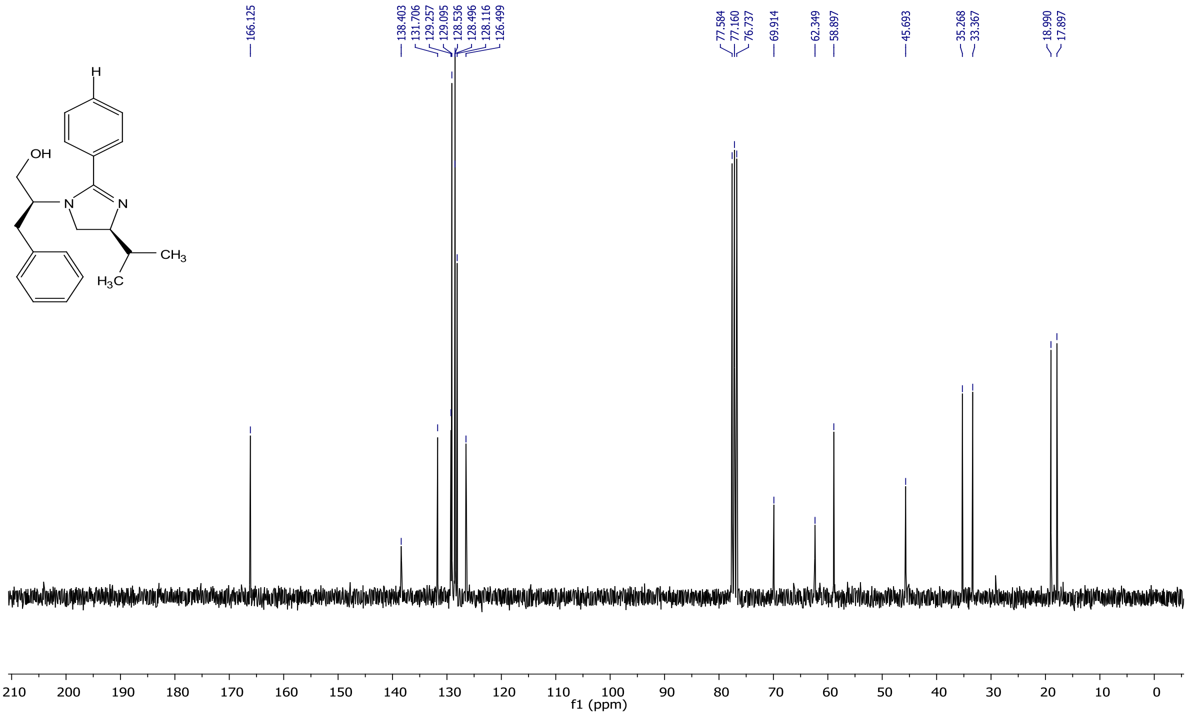
(4*S*)-1-((1*S*)-2-hydroxy-1-phenyl-eth-1-yl)-2-phenyl-4-isopropyl-4,5-dihydroimidazole (163e)



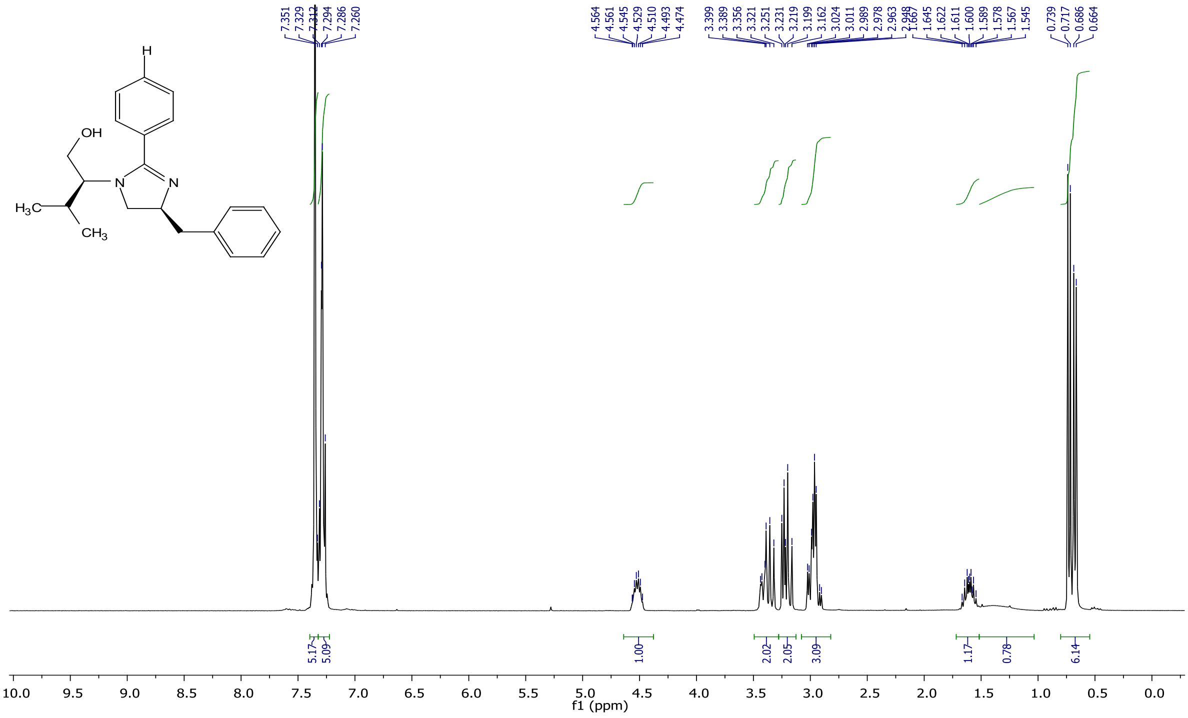


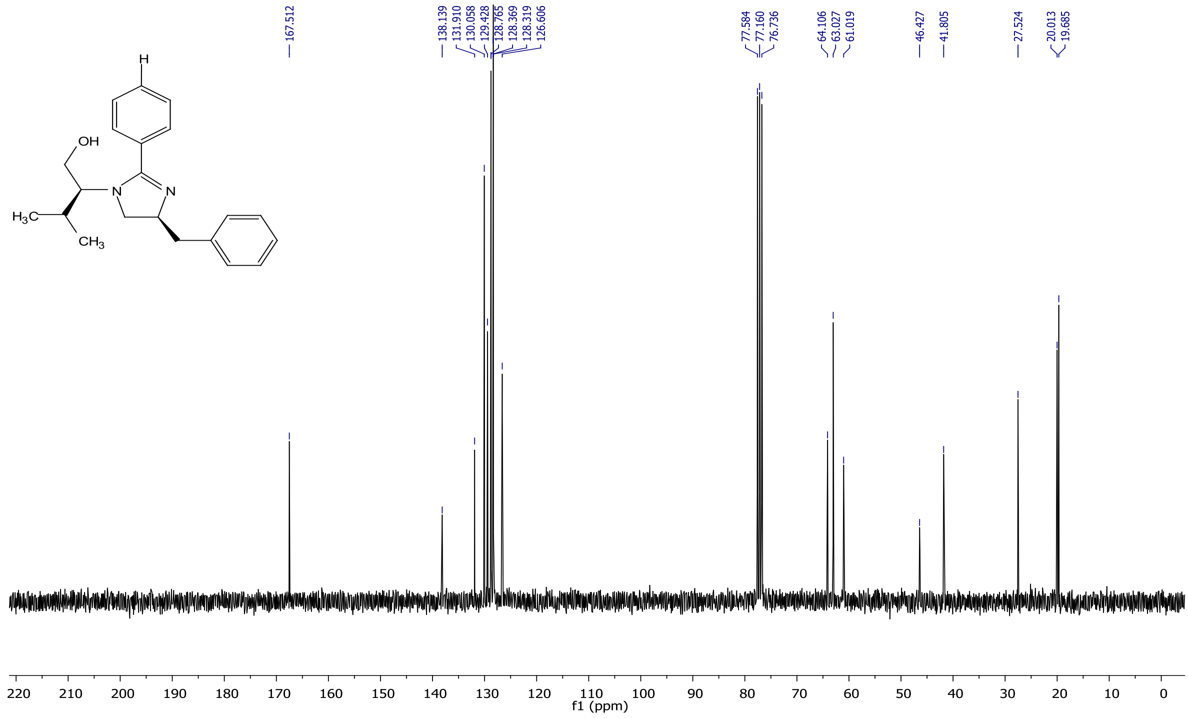
(4*S*)-1-((2*S*)-1-hydroxy-3-phenyl-prop-2-yl)-2-phenyl-4-isopropyl-4,5-dihydroimidazole (163f)



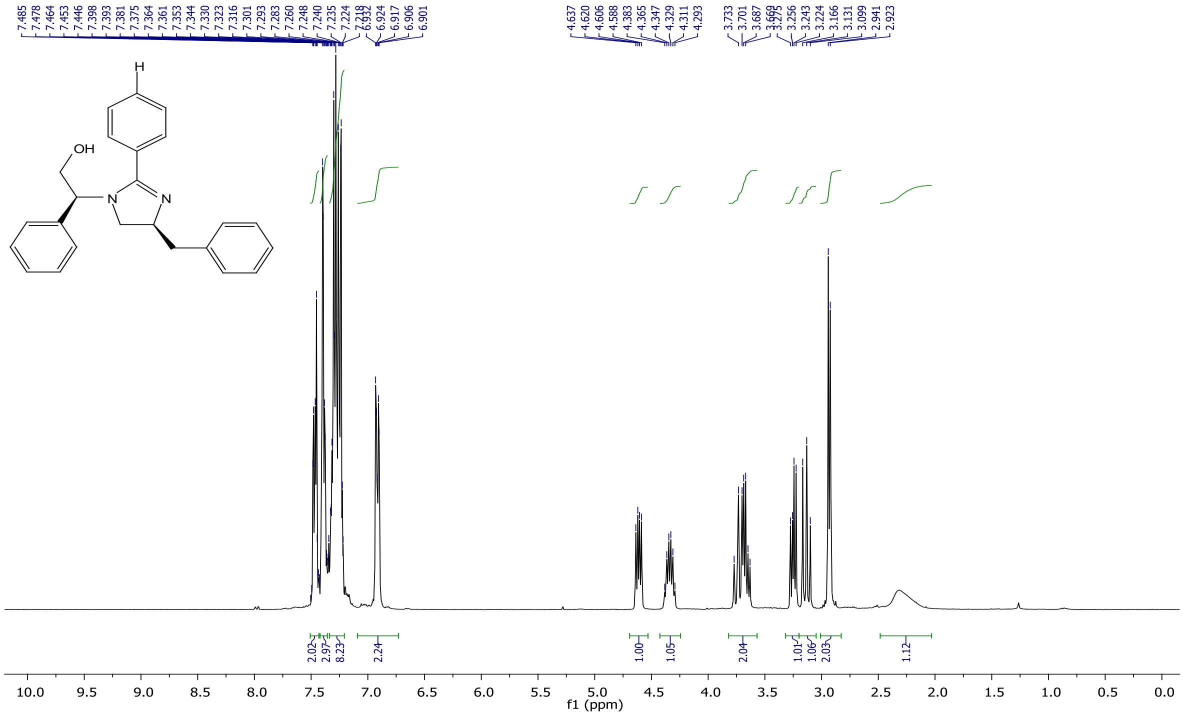


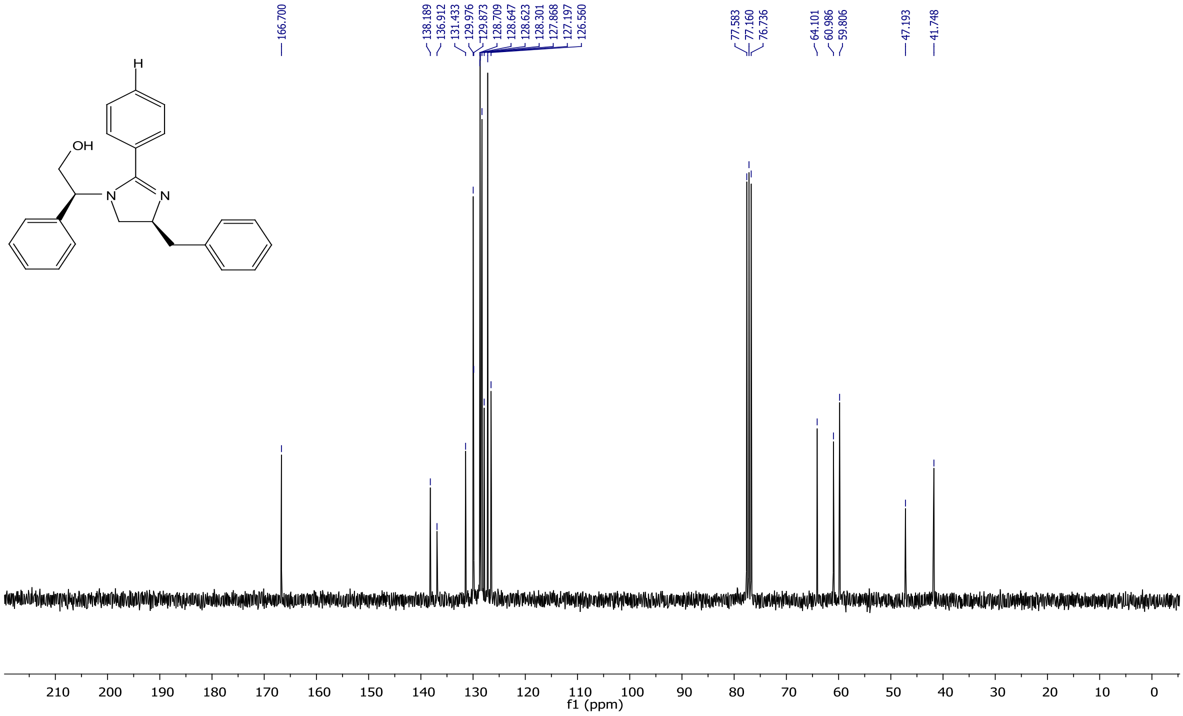
(4*S*)-1-((2*S*)-1-hydroxy-3-methyl-but-2-yl)-2-phenyl-4-benzyl-4,5-dihydroimidazole (163g)



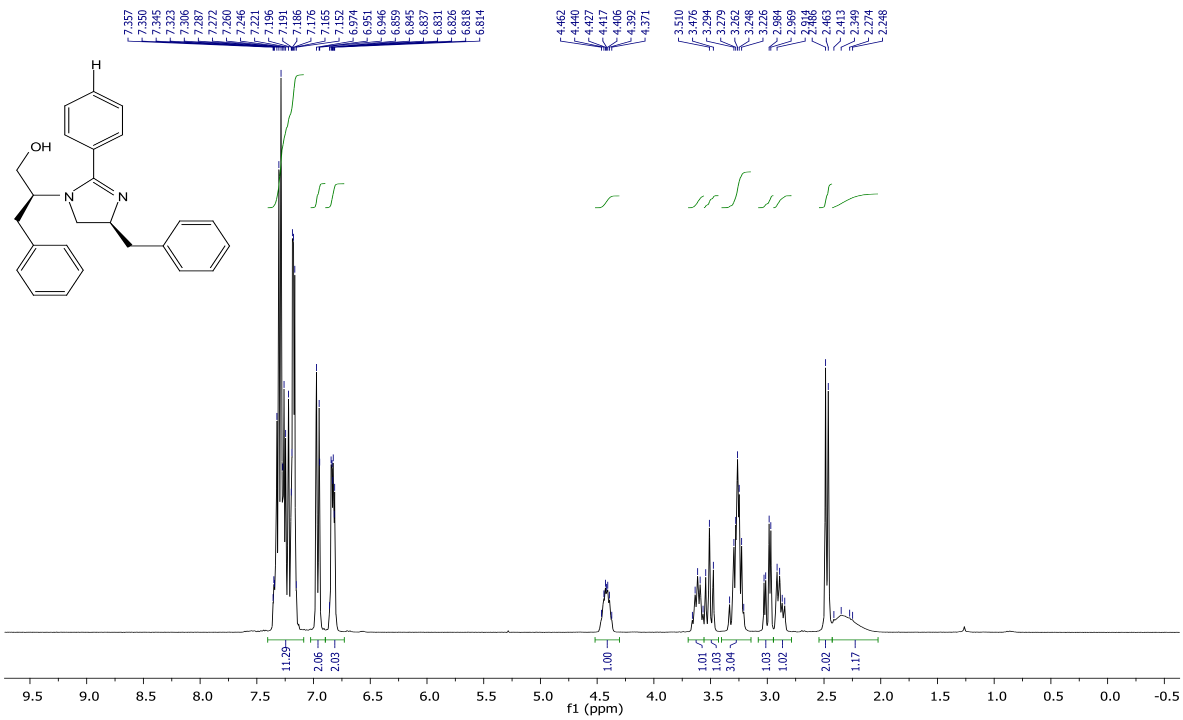


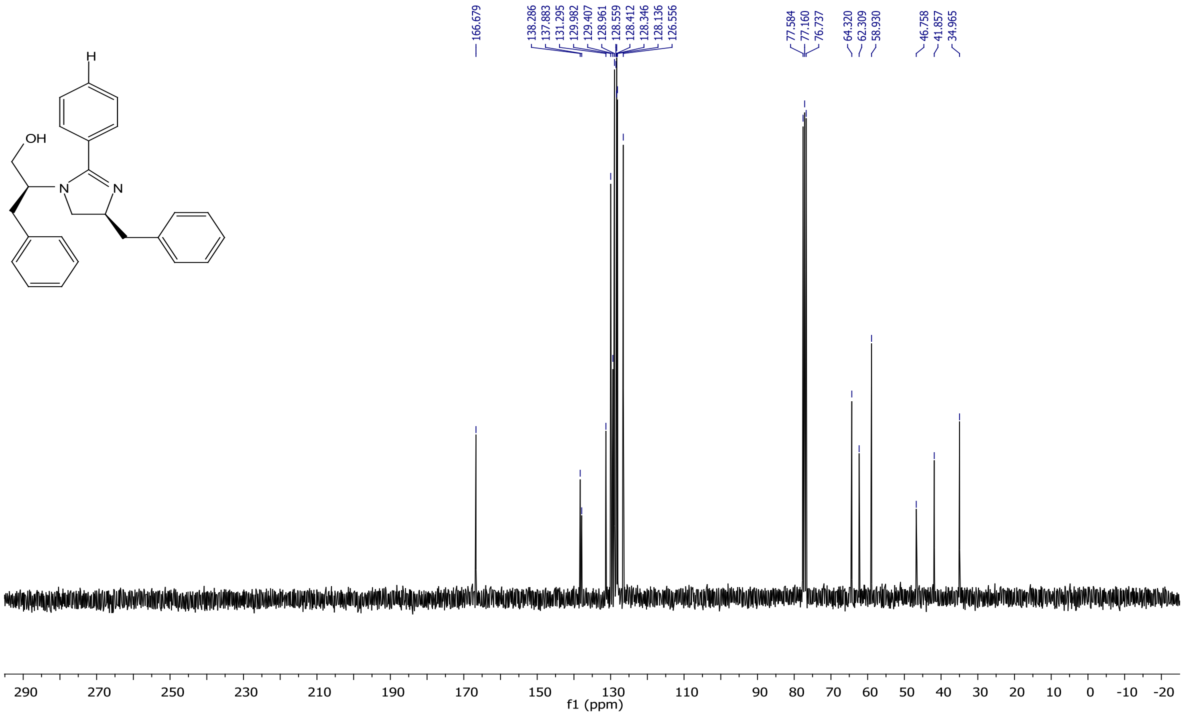
(4*S*)-1-((1*S*)-2-hydroxy-1-phenyl-eth-1-yl)-2-phenyl-4-benzyl-4,5-dihydroimidazole (163h)



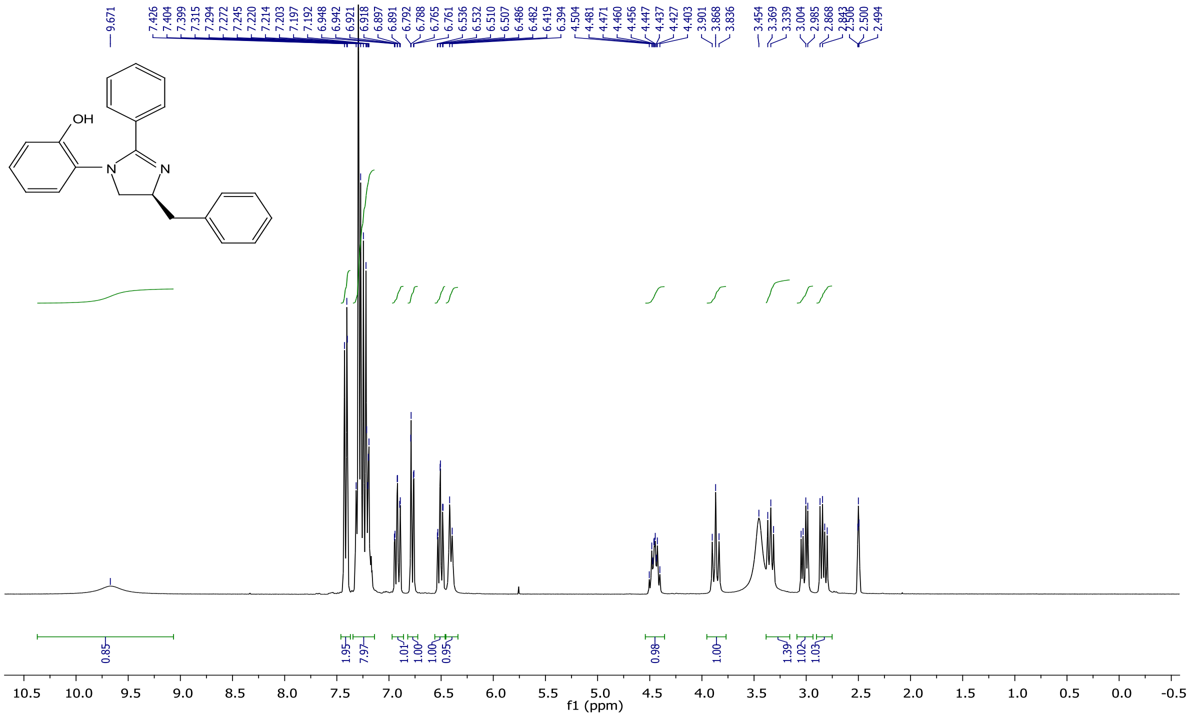


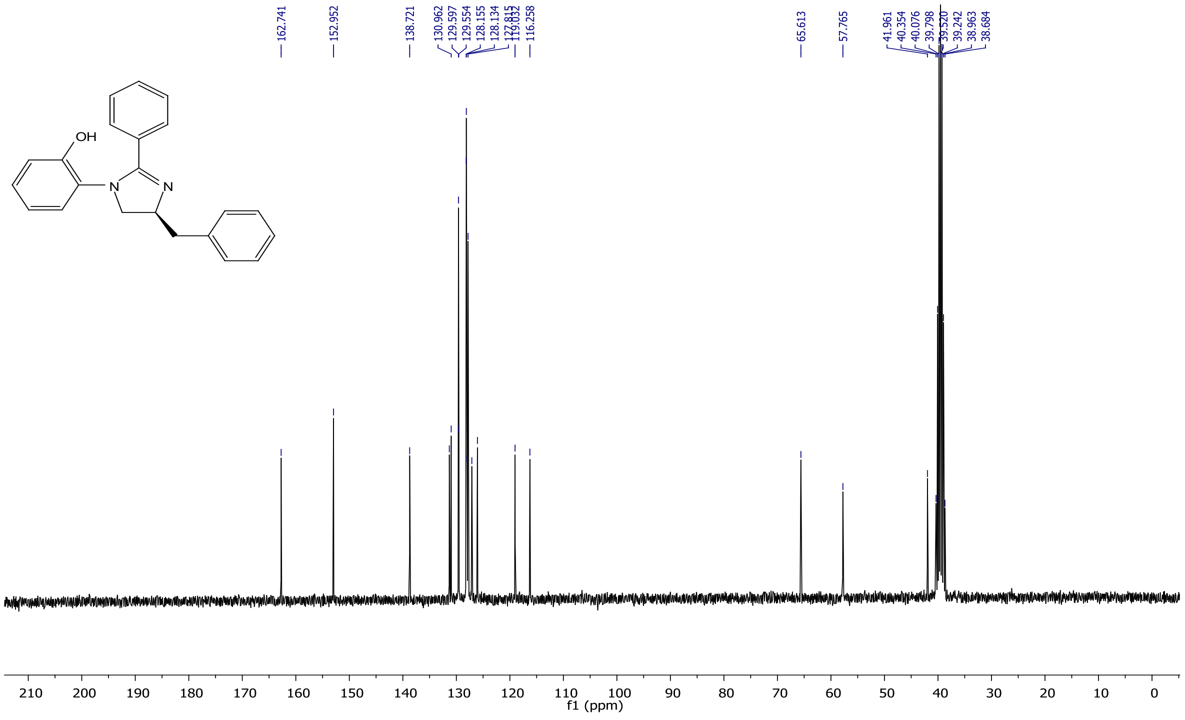
(4*S*)-1-((2*S*)-1-hydroxy-3-phenyl-prop-2-yl)-2-phenyl-4-benzyl-4,5-dihydroimidazole (163i)



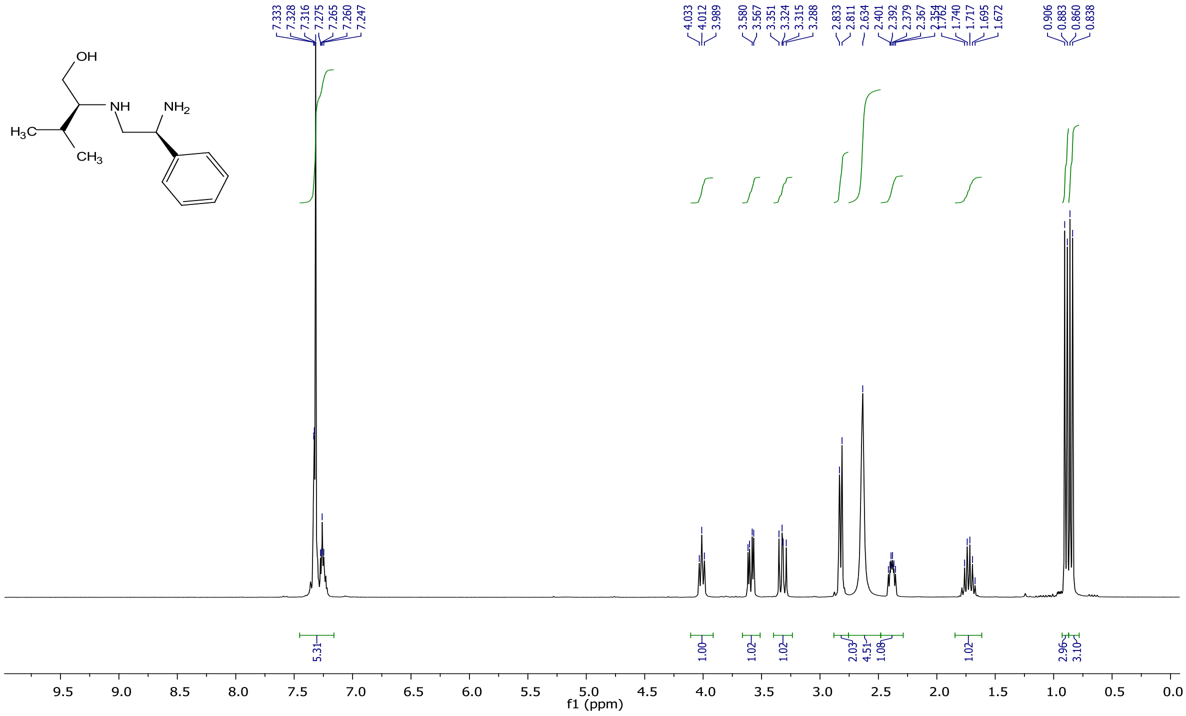


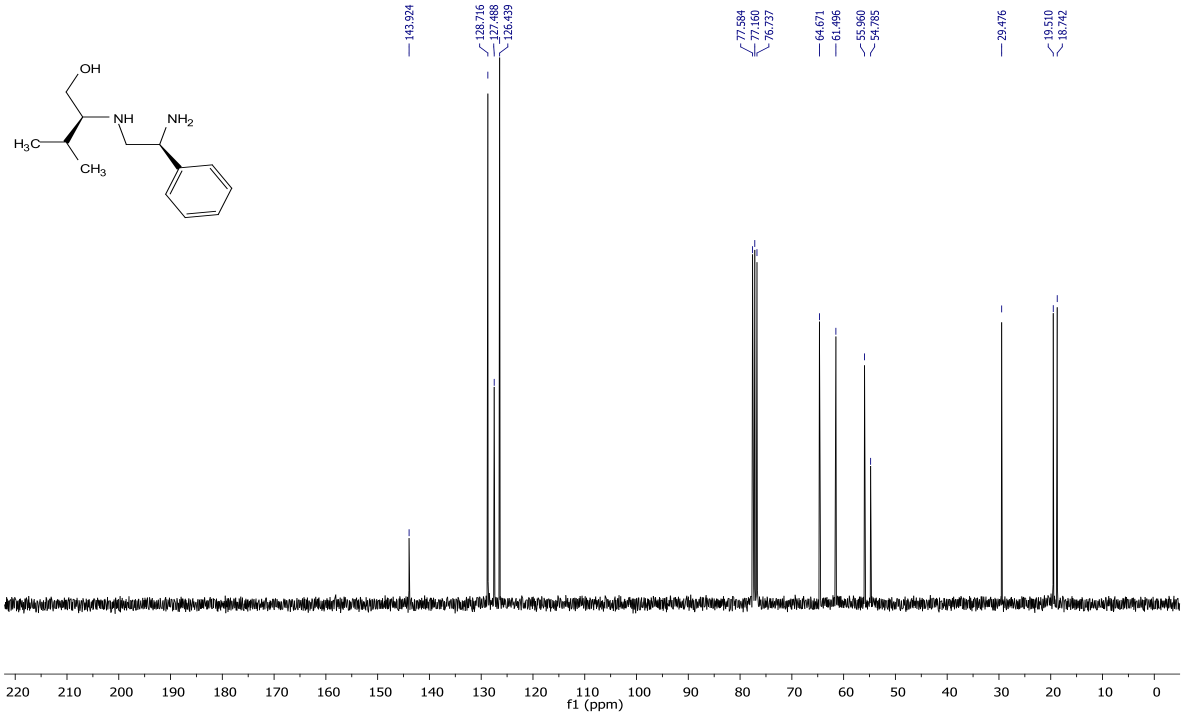
(4*S*)-1-(2-hydroxy-phenyl)-2-phenyl-4-benzyl-4,5-dihydroimidazole (163j) (DMSO)



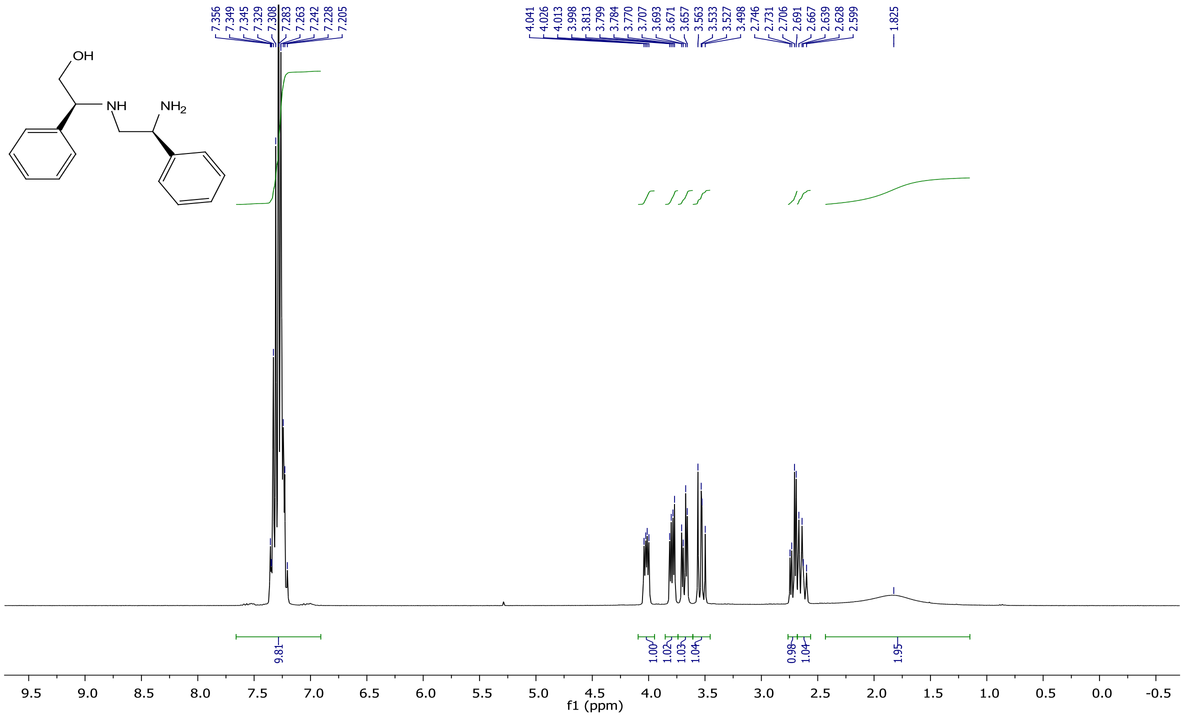


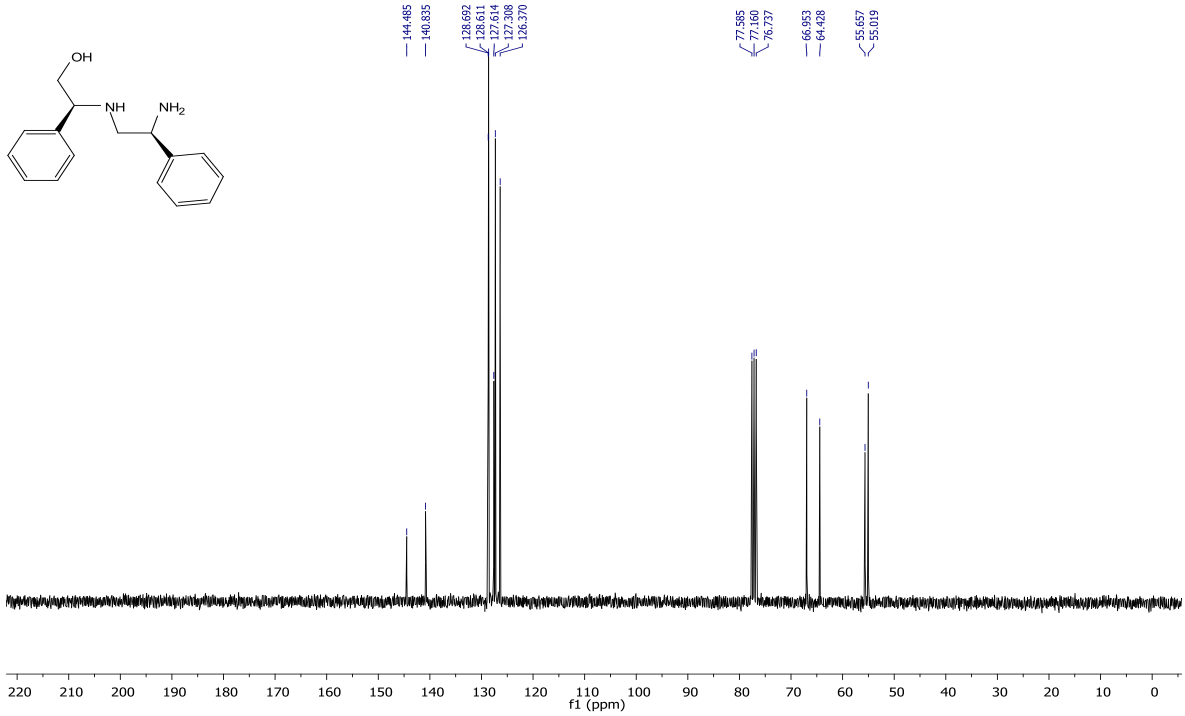
(2*S*)-2-(((2*S*)-2-amino-2-phenylethyl)amino)-3-methylbutan-1-ol (154a)



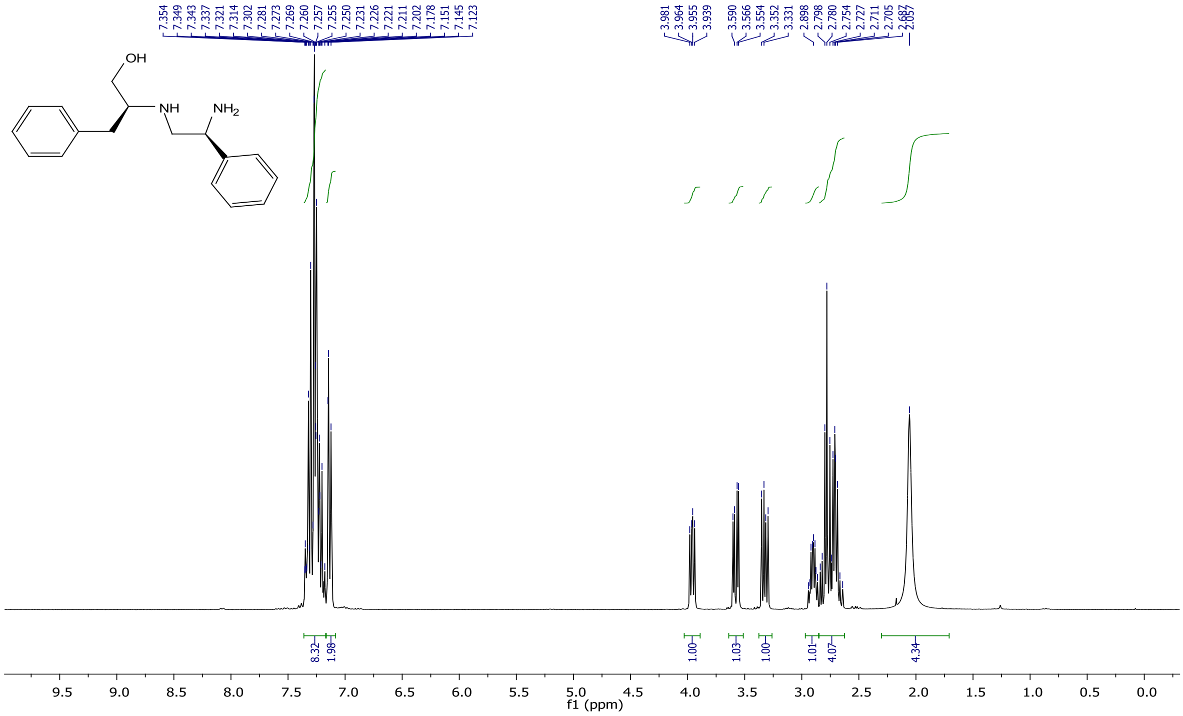


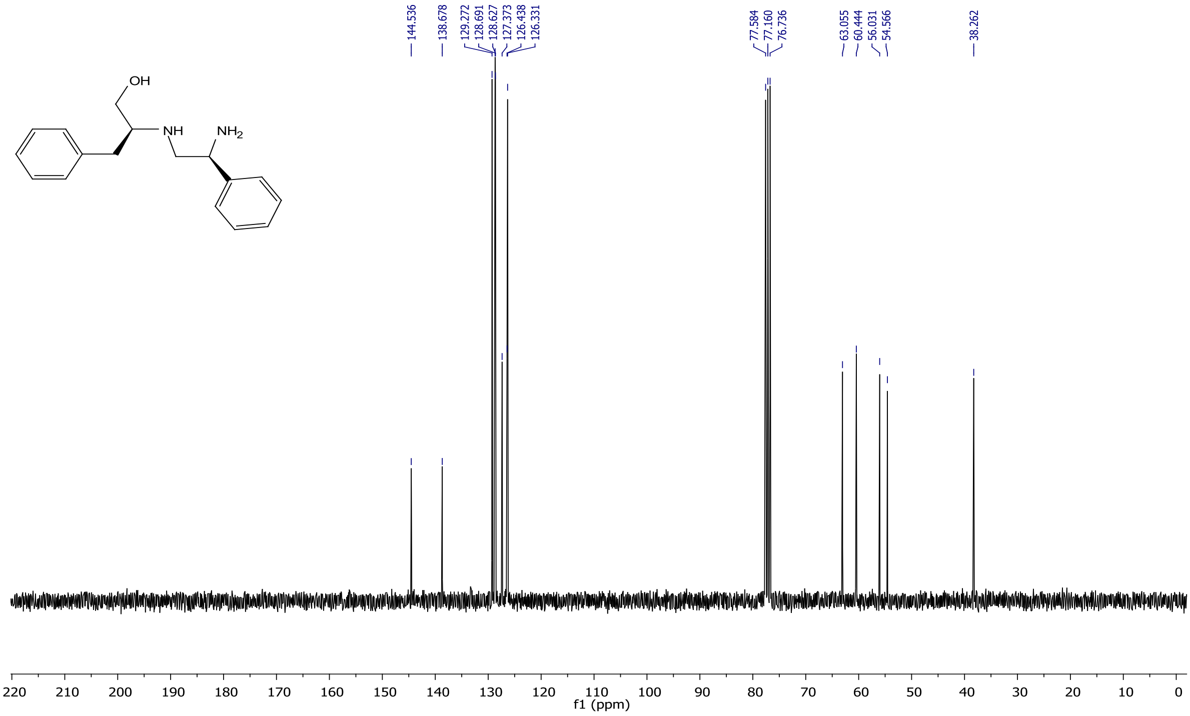
(2*S*)-2-(((2*S*)-2-amino-2-phenylethyl)amino)-2-phenylethanol (154b)



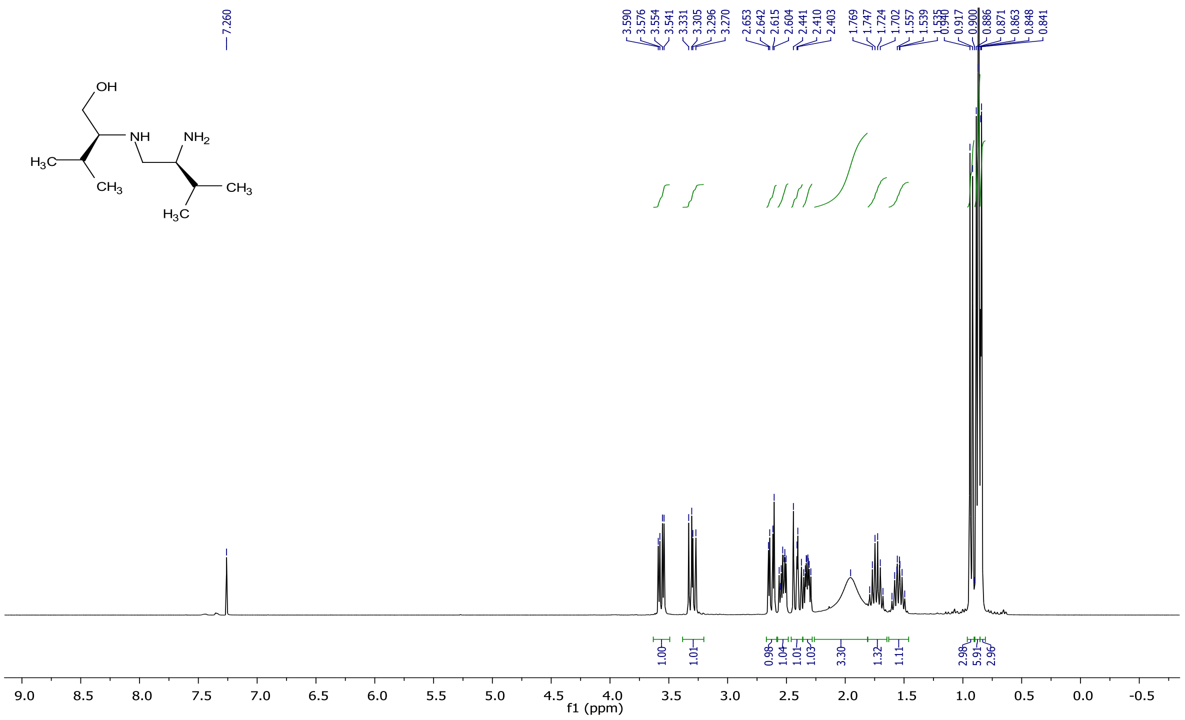


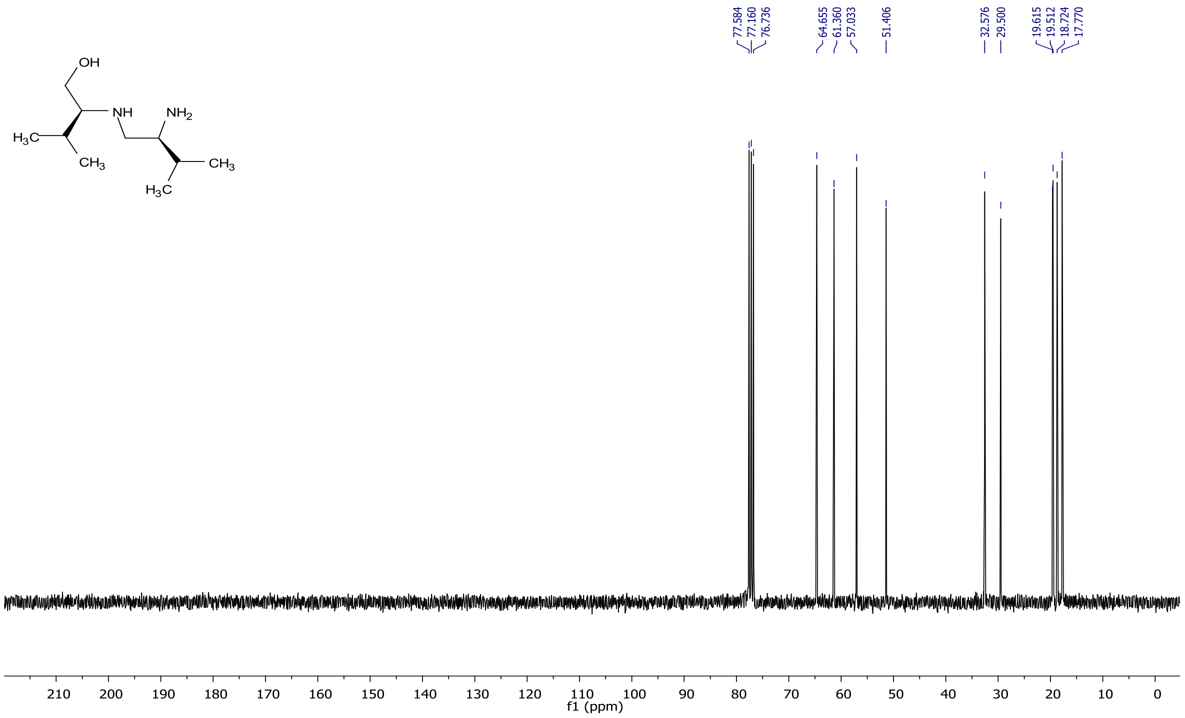
(2*S*)-2-(((2*S*)-2-amino-2-phenylethyl)amino)-3-phenylpropan-1-ol (154c)



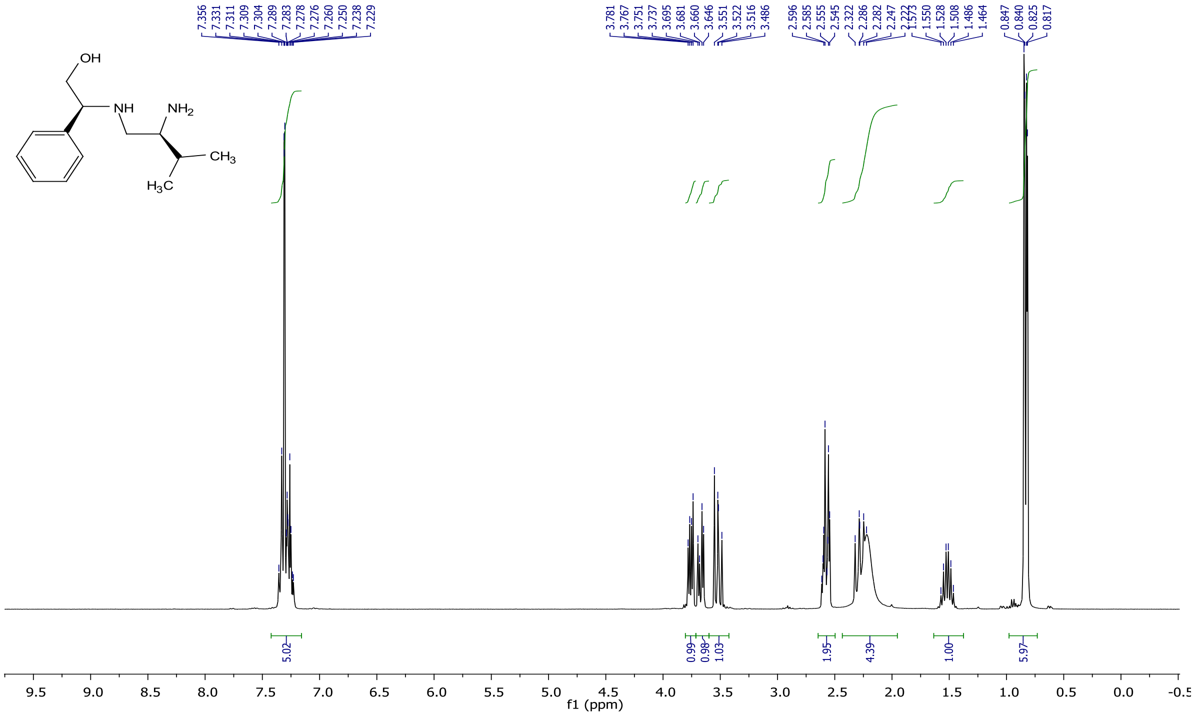


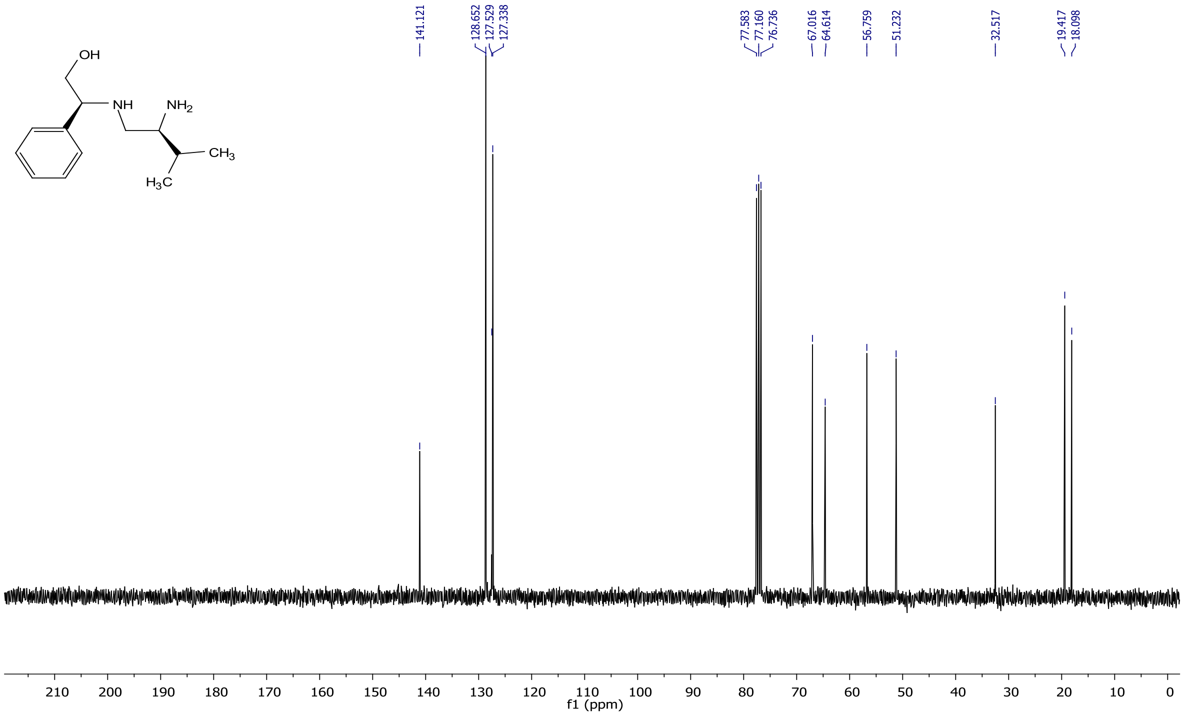
(2*S*)-2-(((2*S*)-2-amino-3-methylbutyl)amino)-3-methylbutan-1-ol (154d)



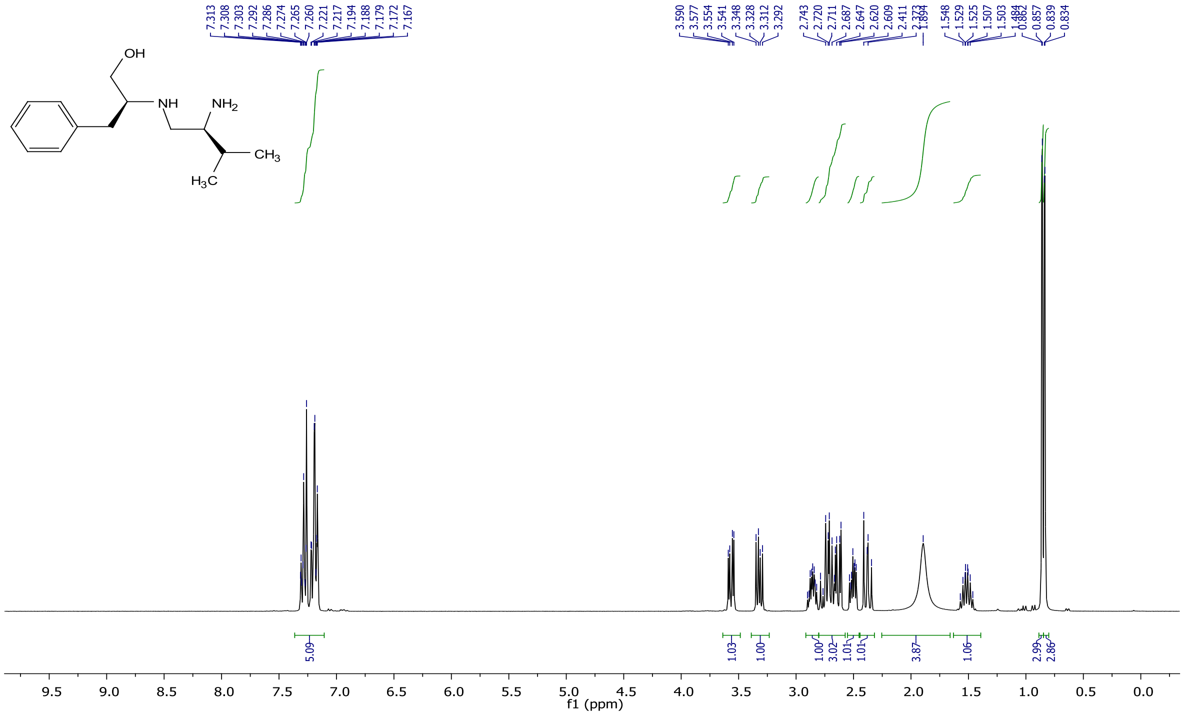


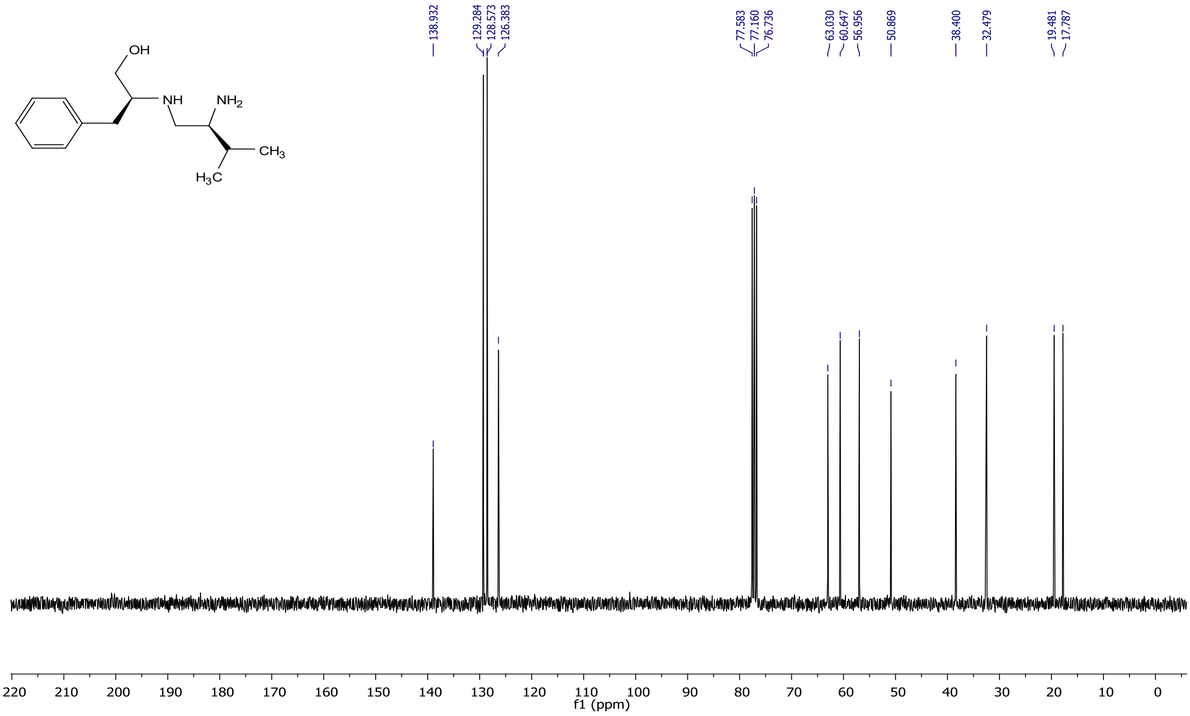
(2*S*)-2-(((2*S*)-2-amino-3-methylbutyl)amino)-2-phenylethanol (154e)



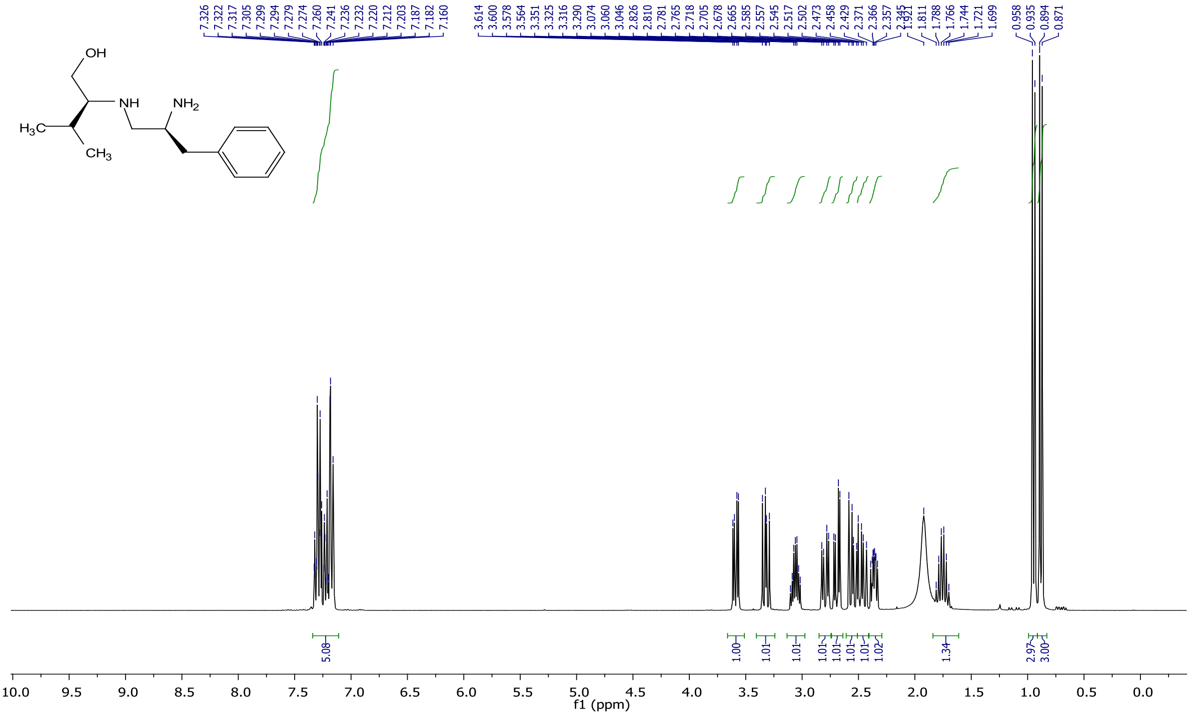


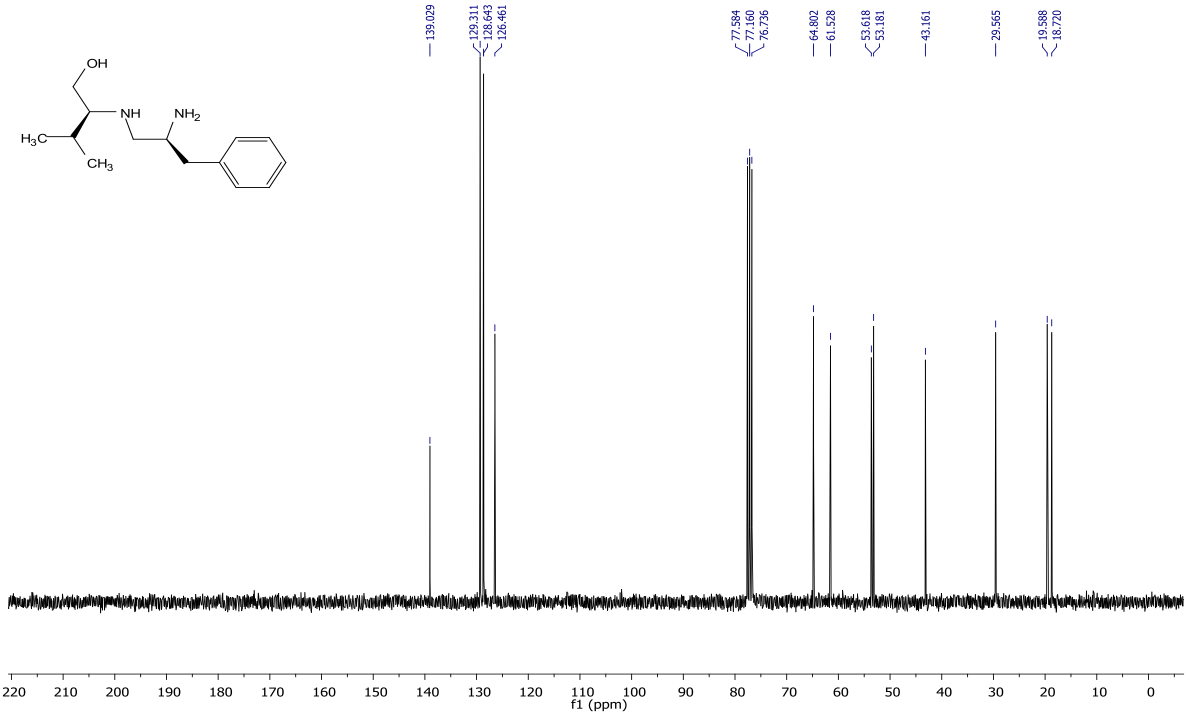
(2*S*)-2-(((2*S*)-2-amino-3-methylbutyl)amino)-3-phenylpropan-1-ol (154f)



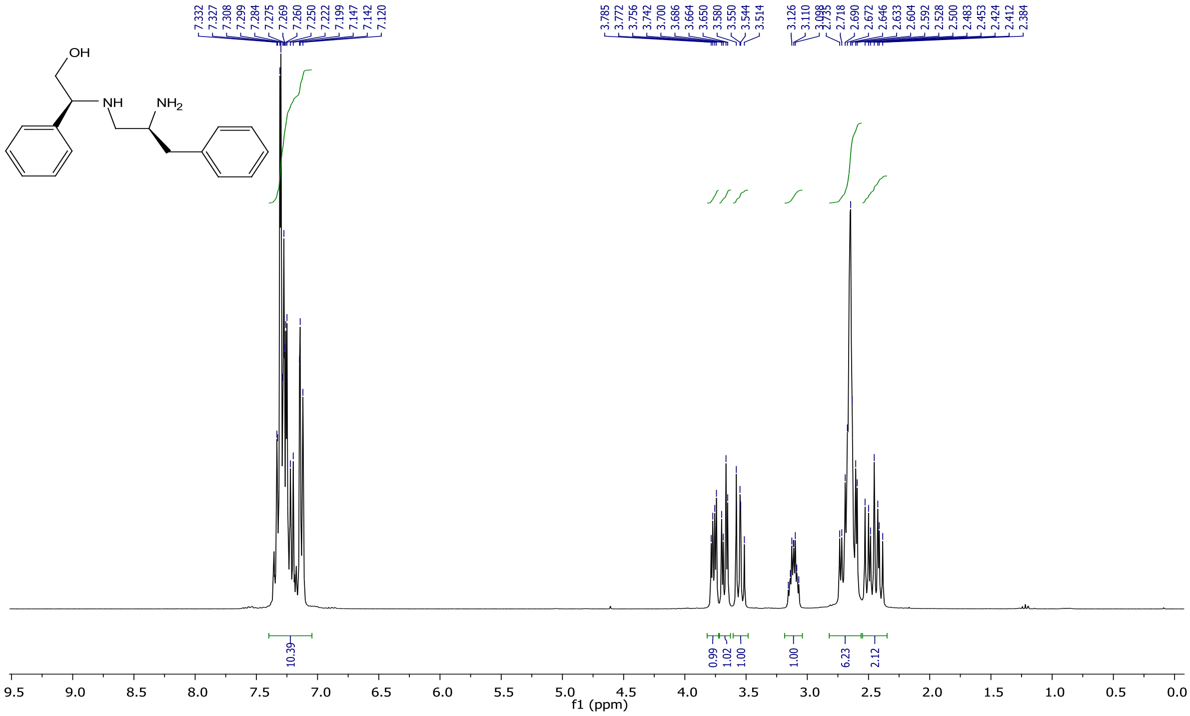


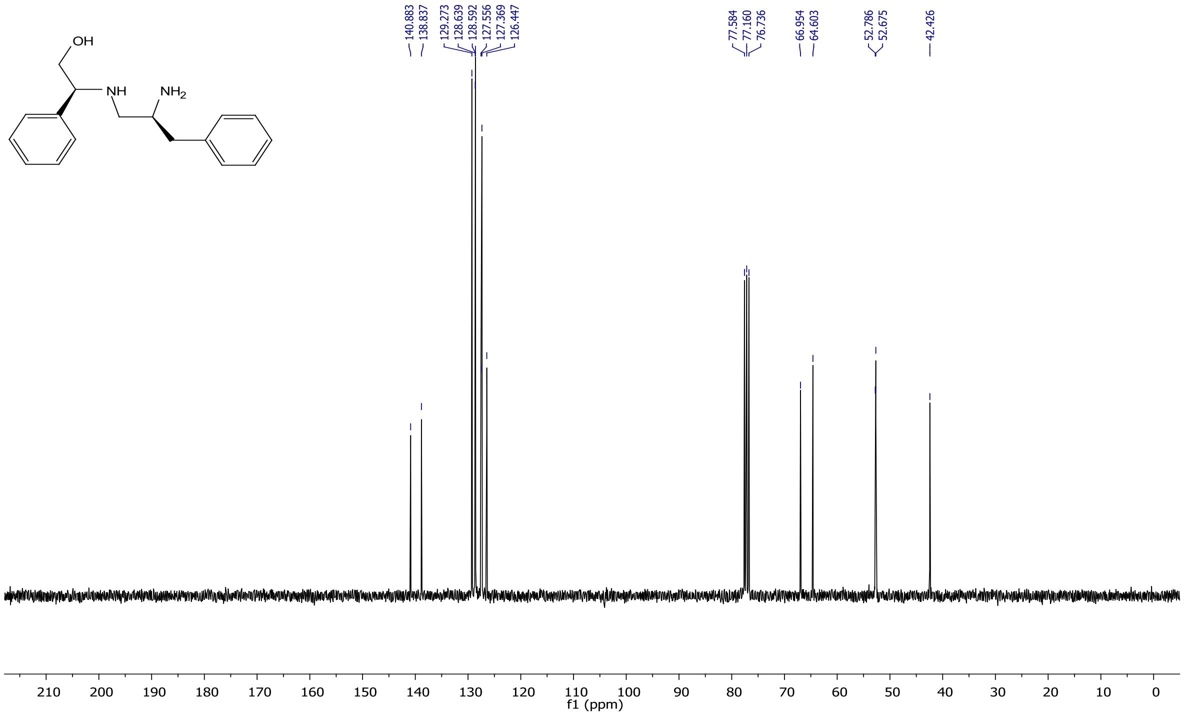
(2*S*)-2-(((2*S*)-2-amino-3-phenylpropyl)amino)-3-methylbutan-1-ol (154g)



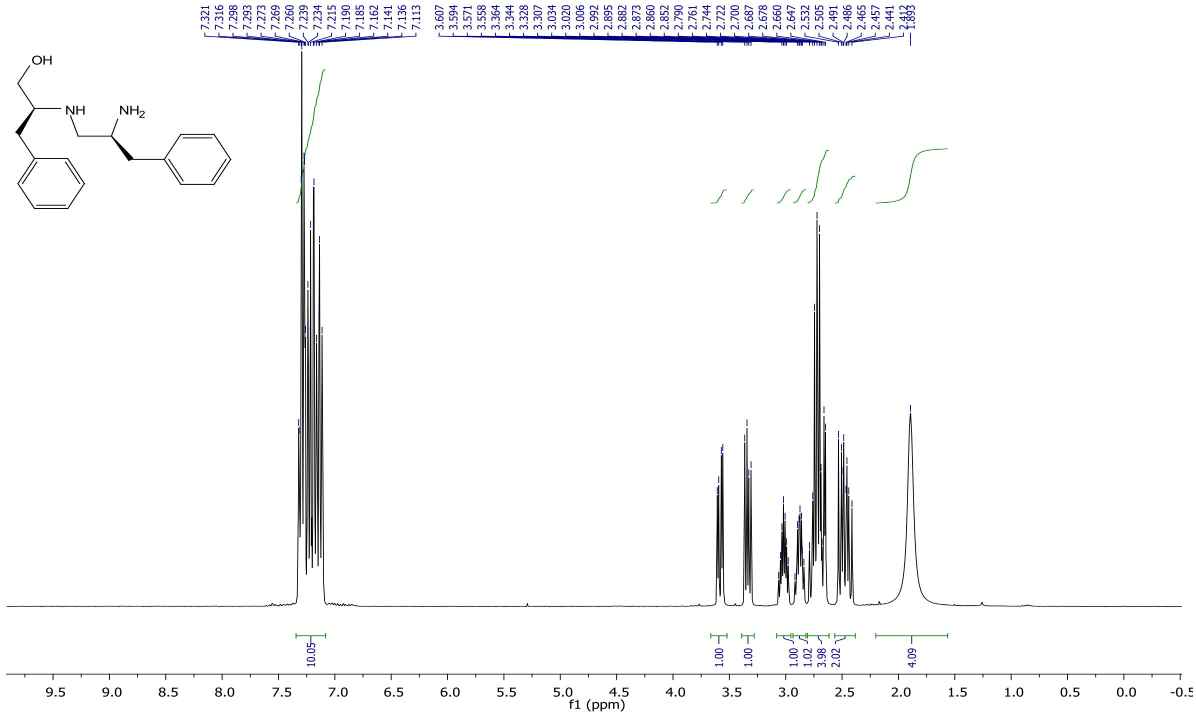


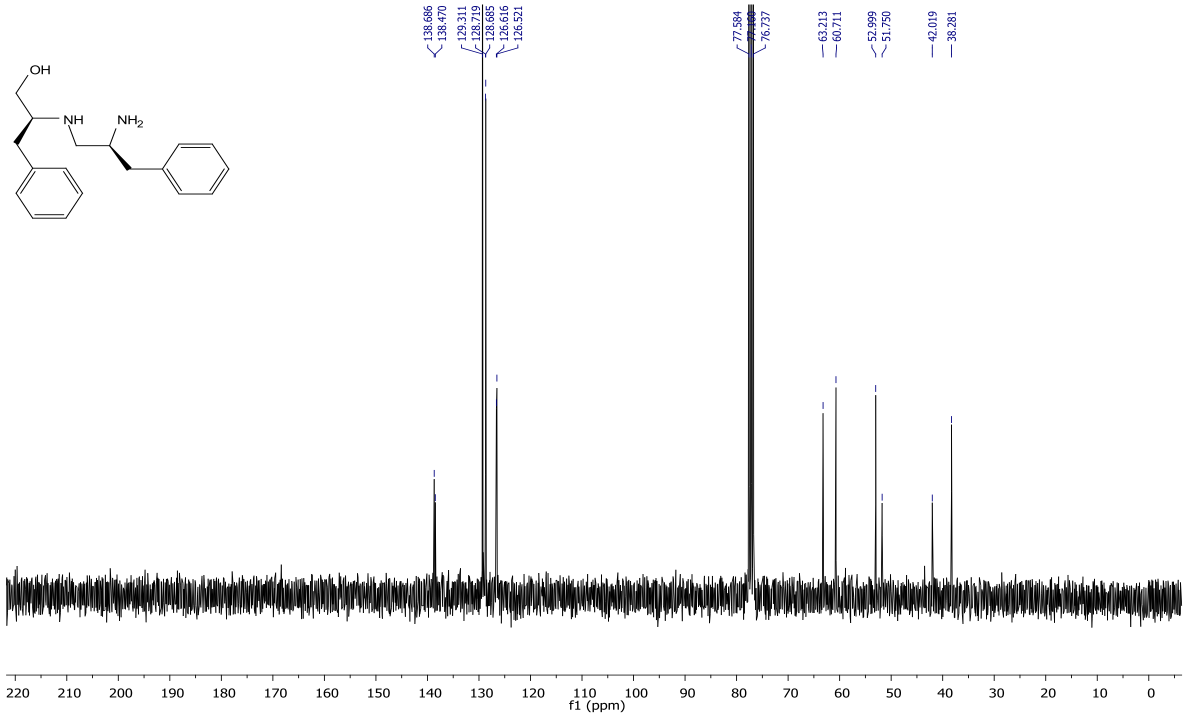
(2*S*)-2-(((2*S*)-2-amino-3-phenylpropyl)amino)-2-phenylethanol (154h)



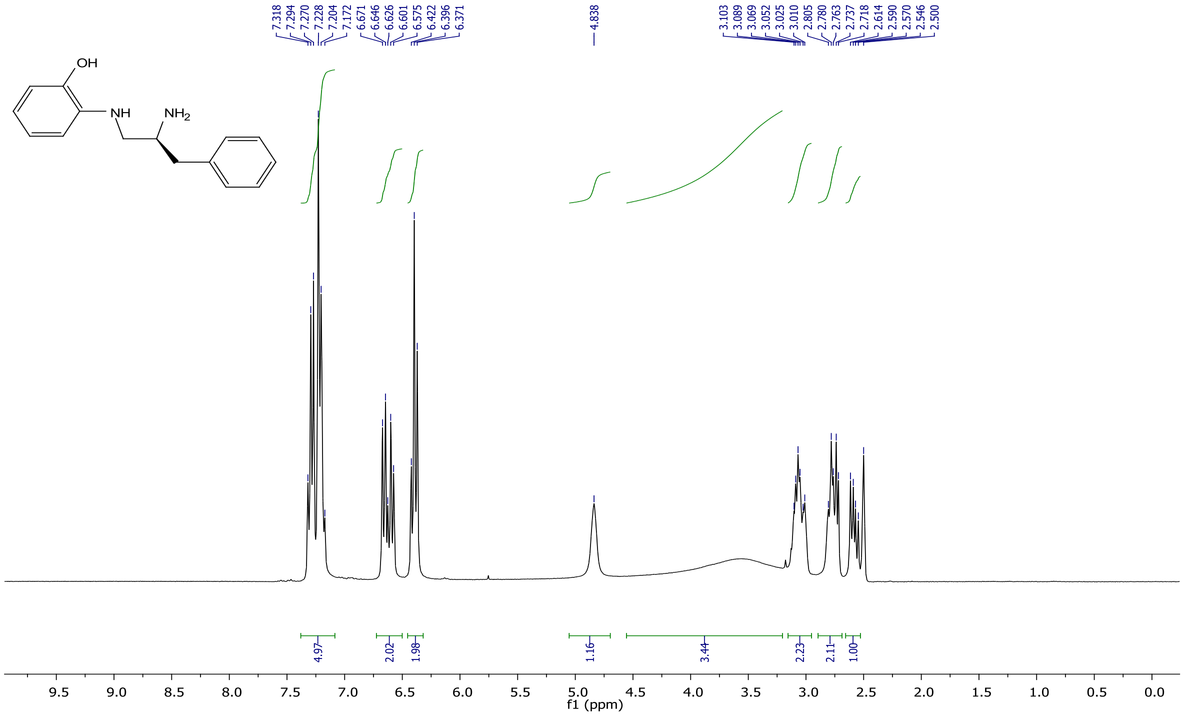


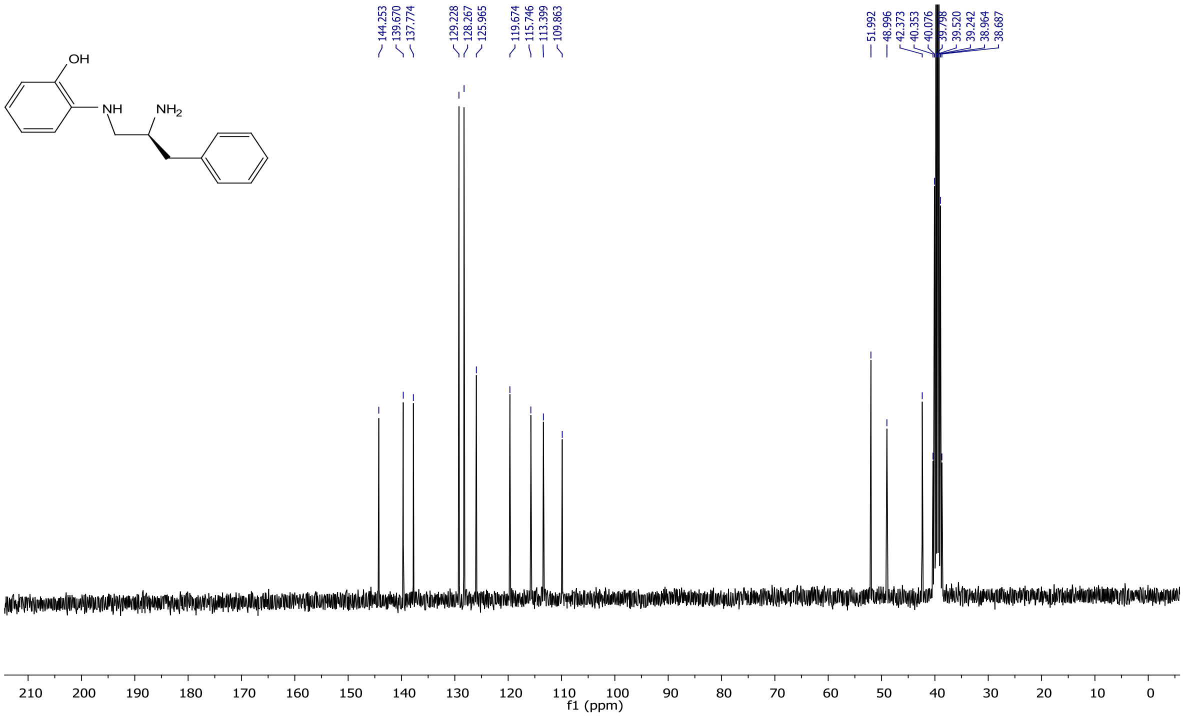
(2*S*)-2-(((2*S*)-2-amino-3-phenylpropyl)amino)-3-phenylpropan-1-ol (154i)



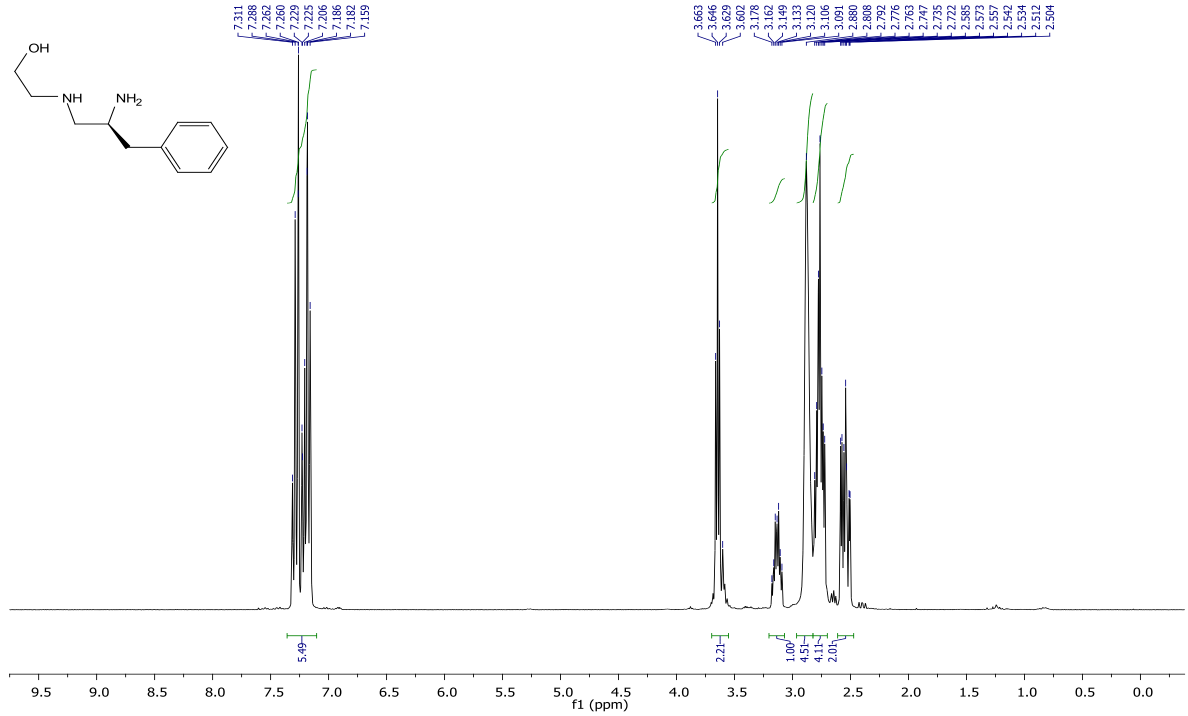


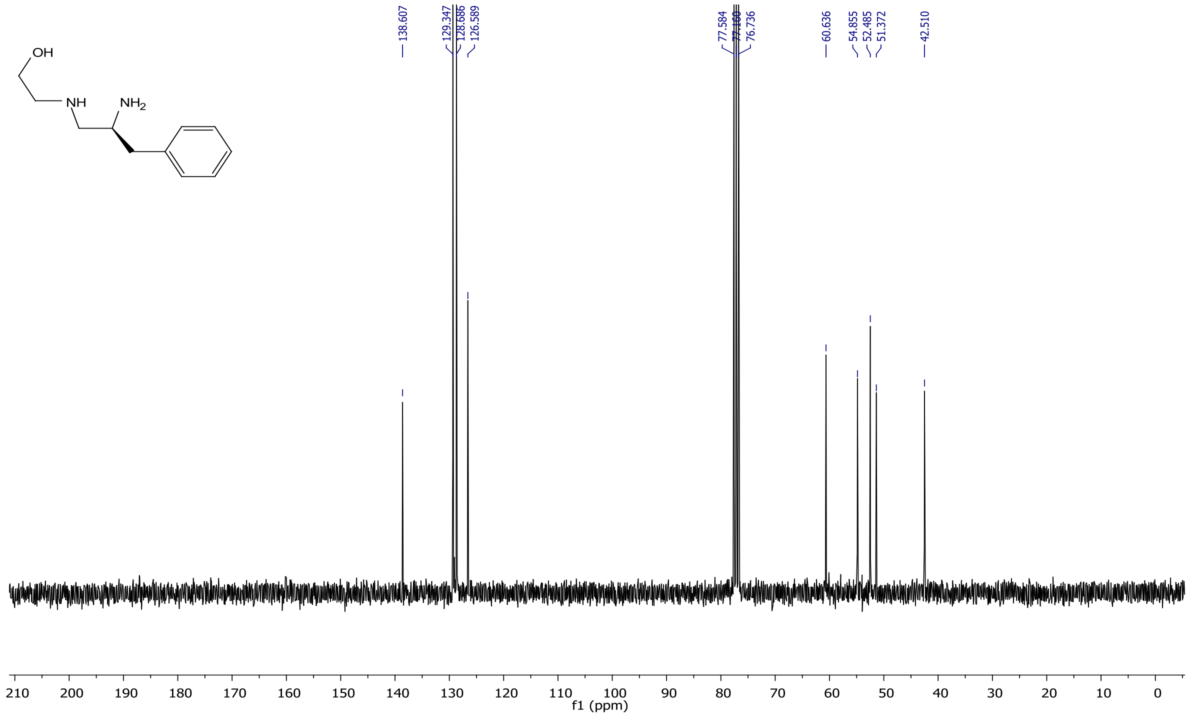
(2*S*)-2-((2-amino-3-phenylpropyl)amino)phenol (154j) (DMSO)



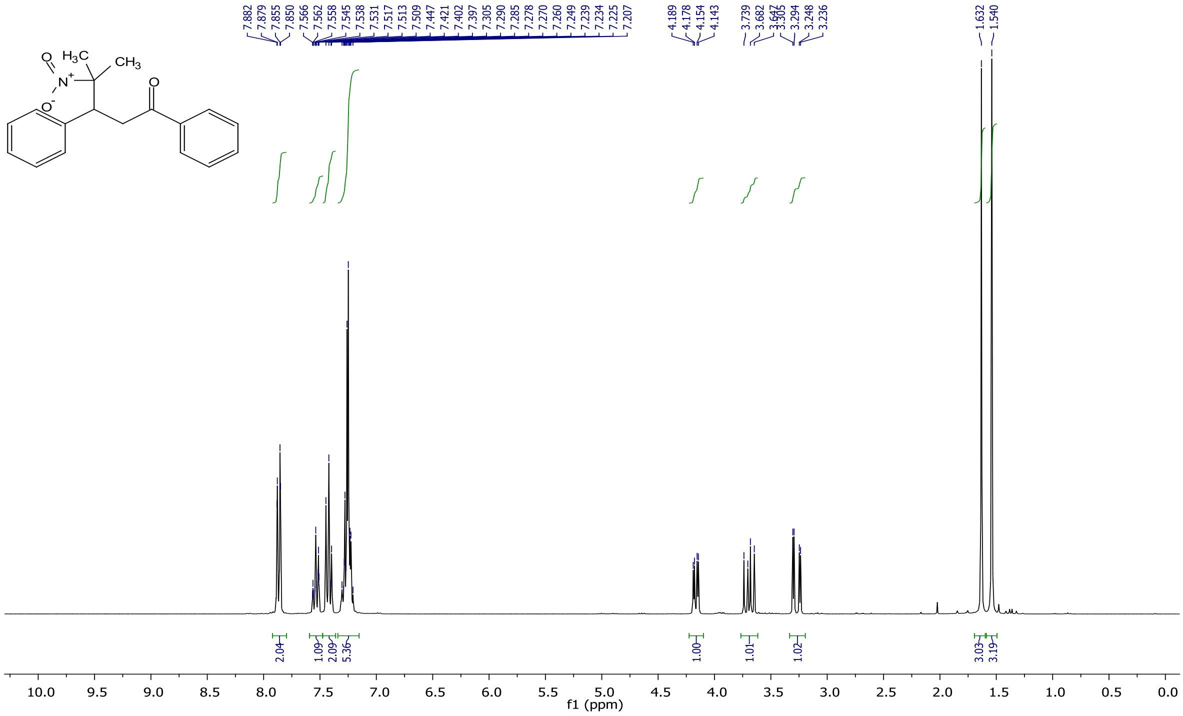


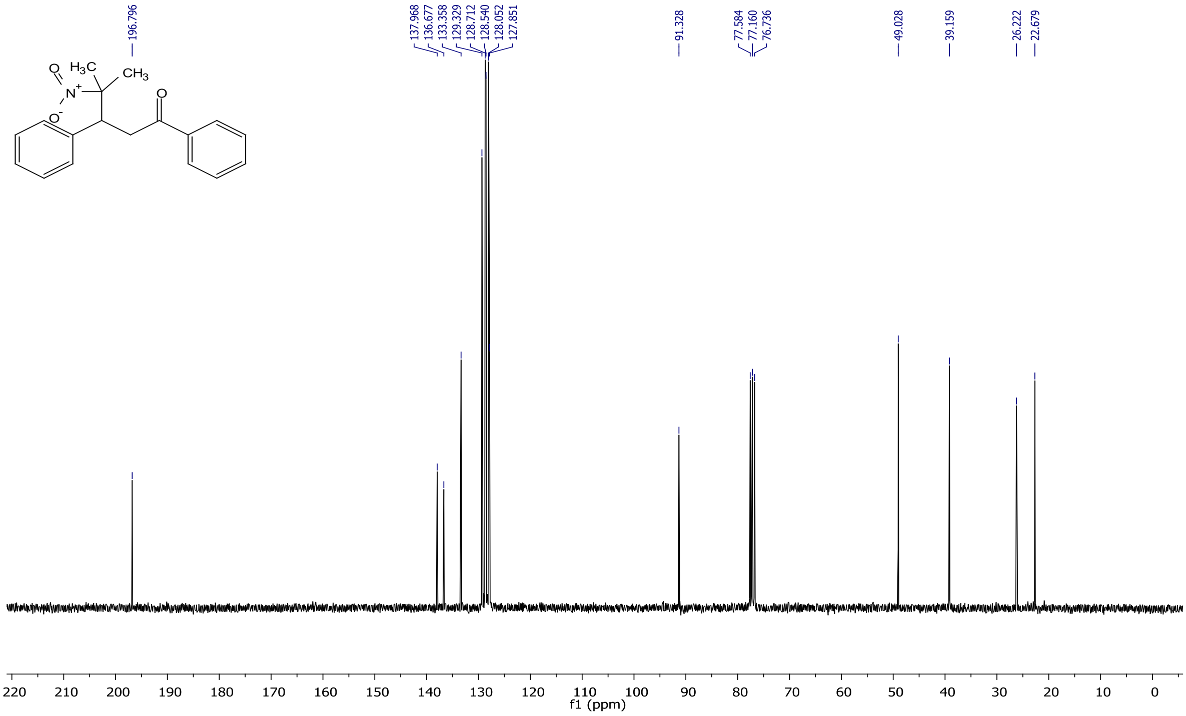
(2*S*)-2-((2-amino-3-phenylpropyl)amino)ethanol (154k)



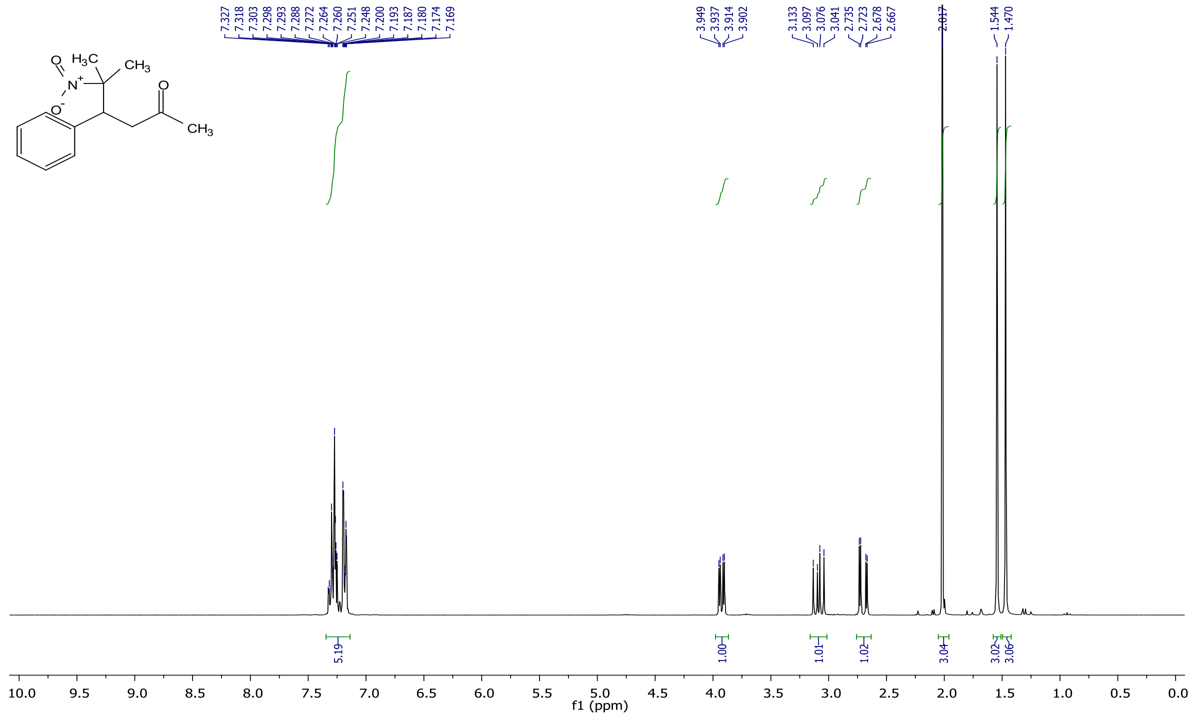


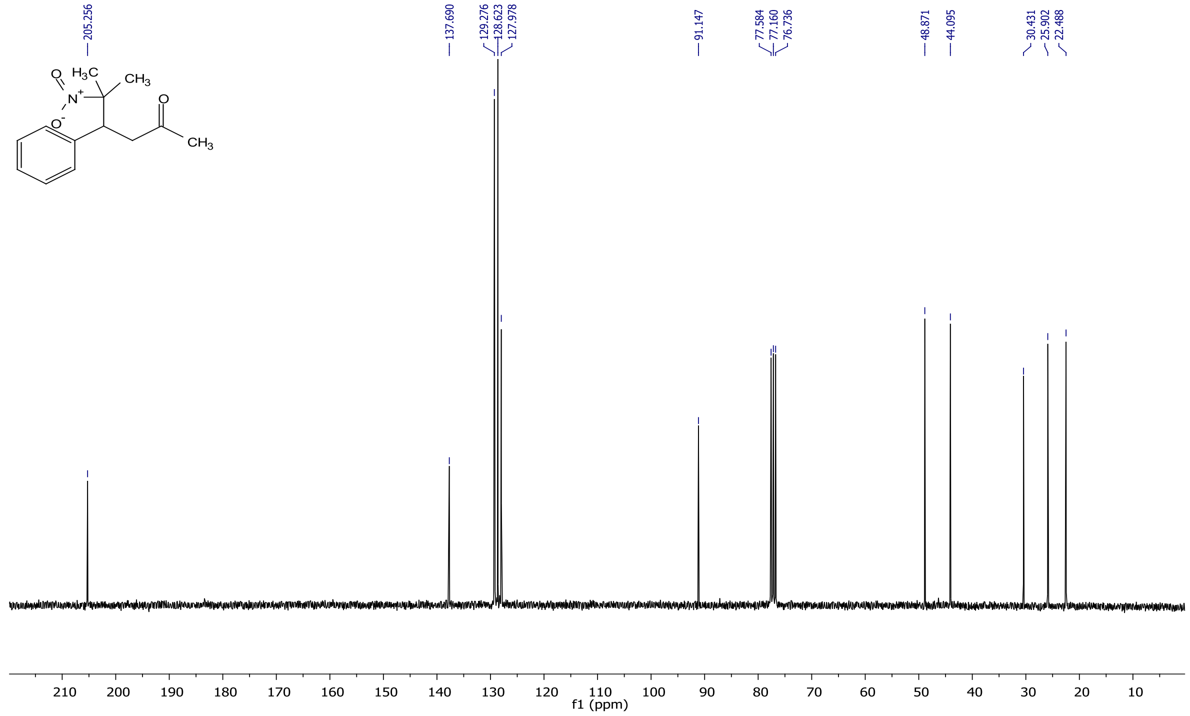
4-methyl-4-nitro-1,3-diphenylpentan-1-one (183a)



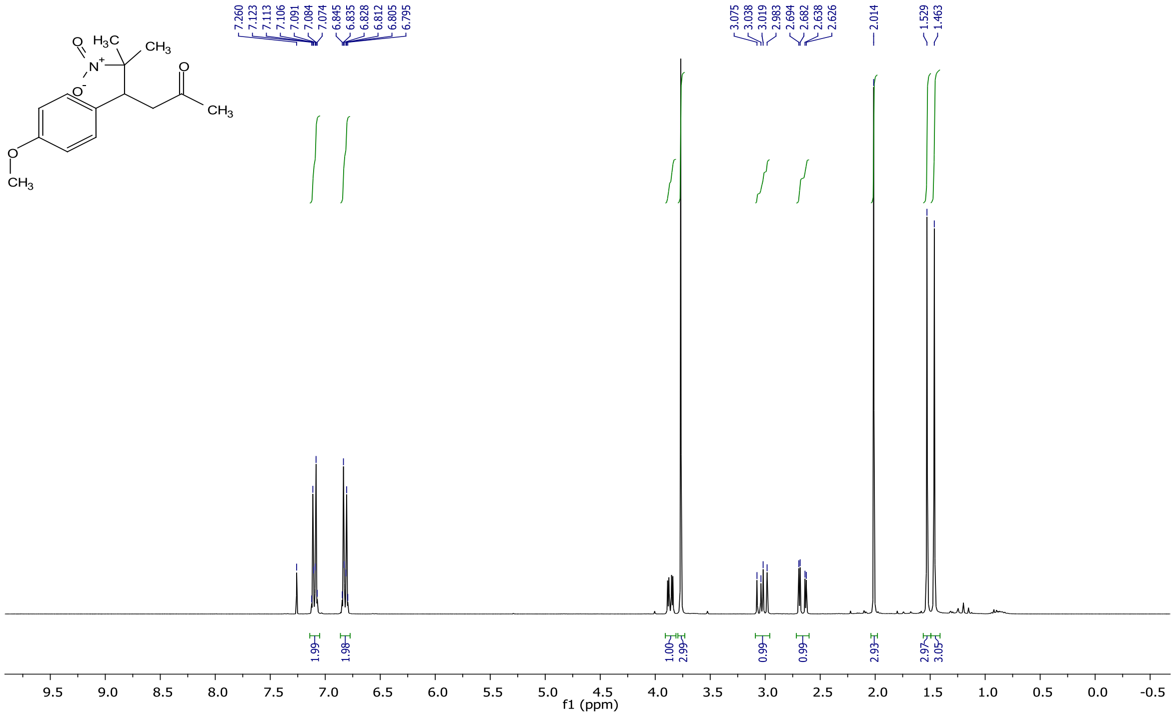


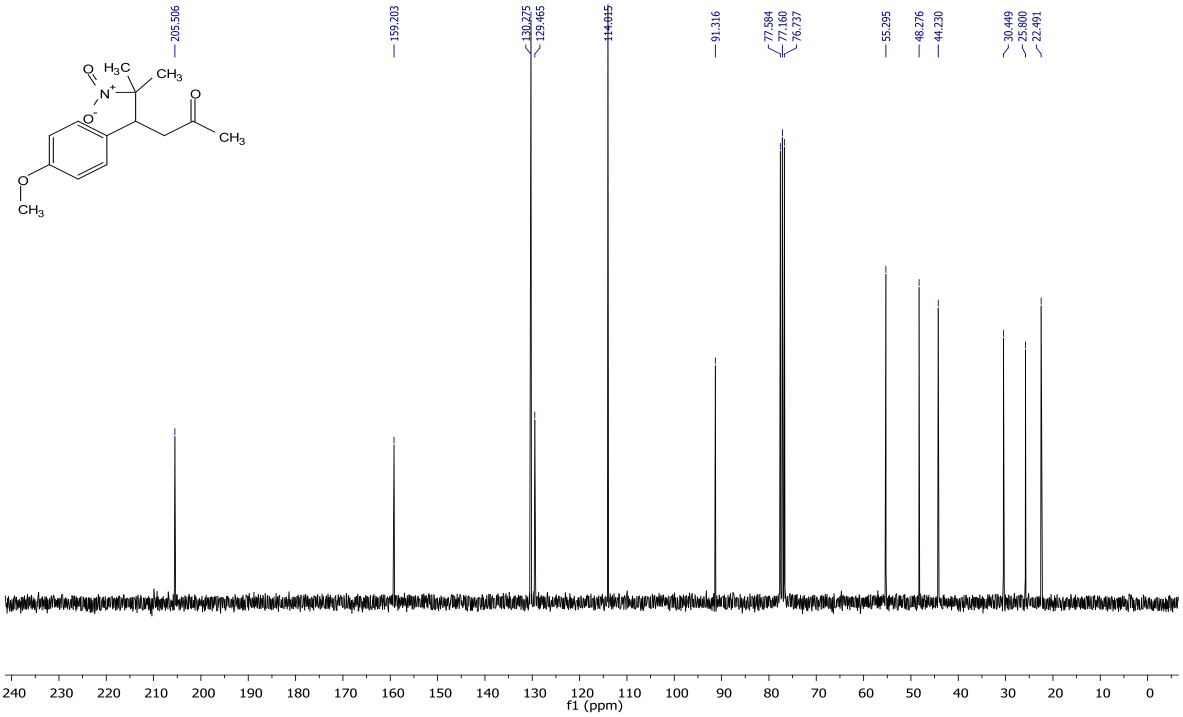
5-Methyl-5-Nitro-4-phenylhexane-2-one (183b)



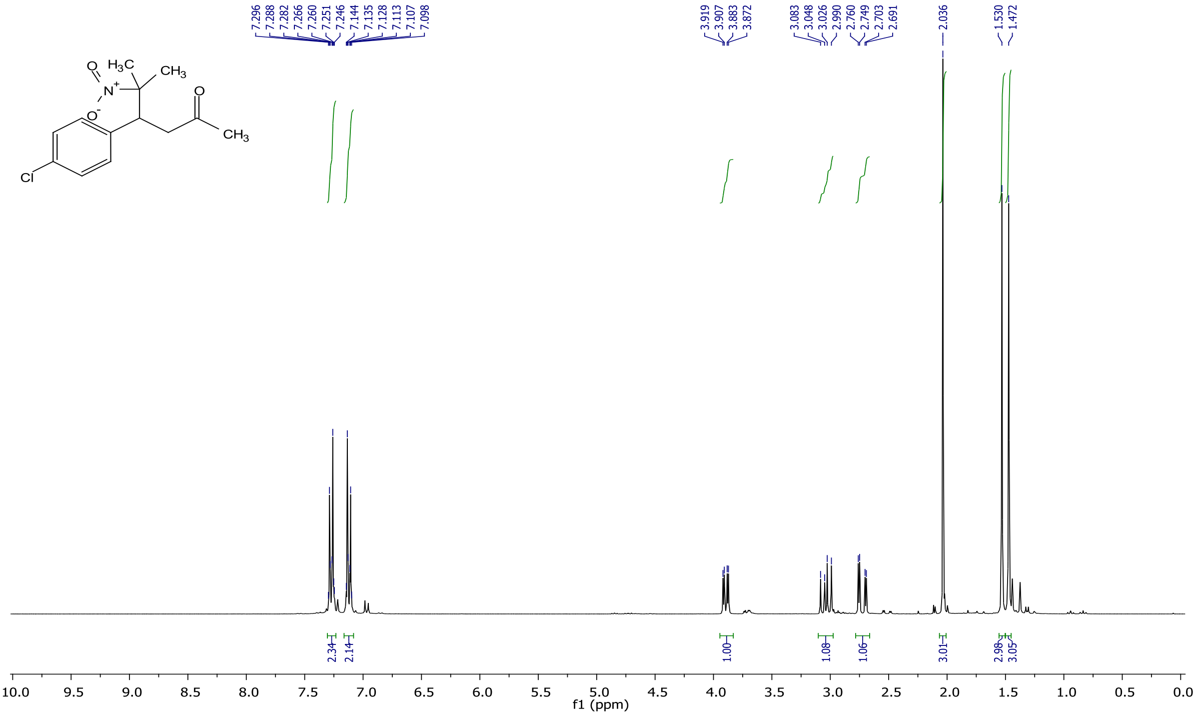


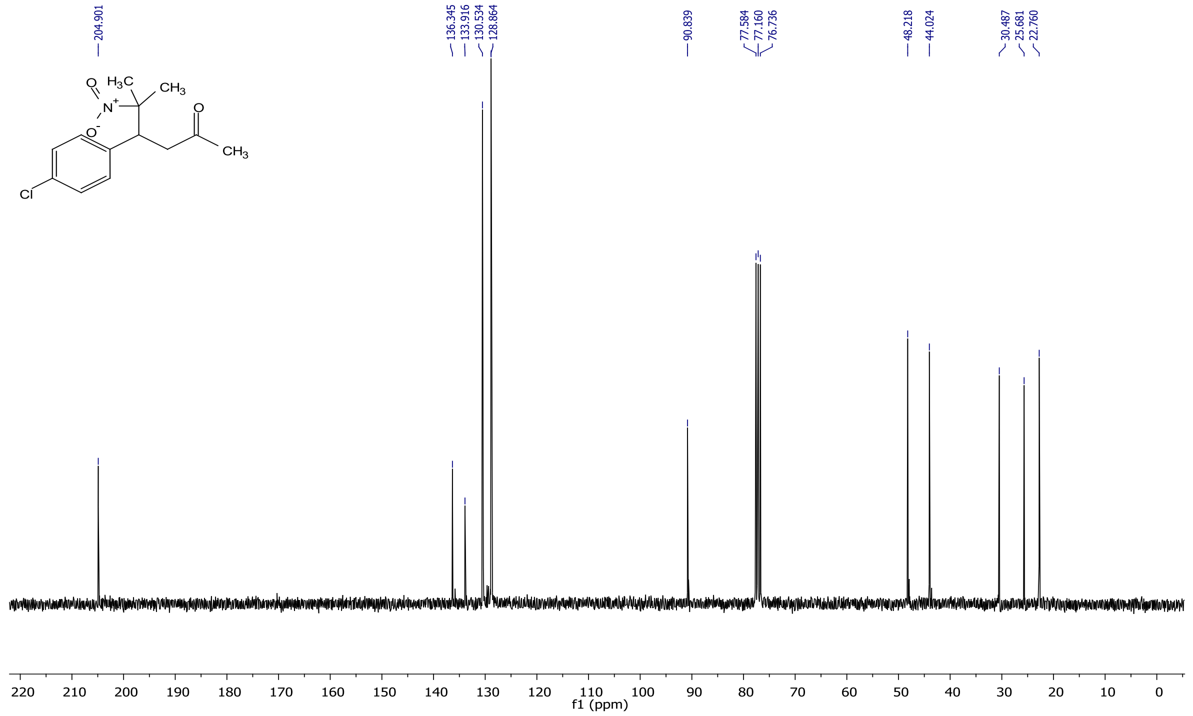
4-(4-methoxyphenyl)-5-methyl-5-nitrohexan-2-one (183c)



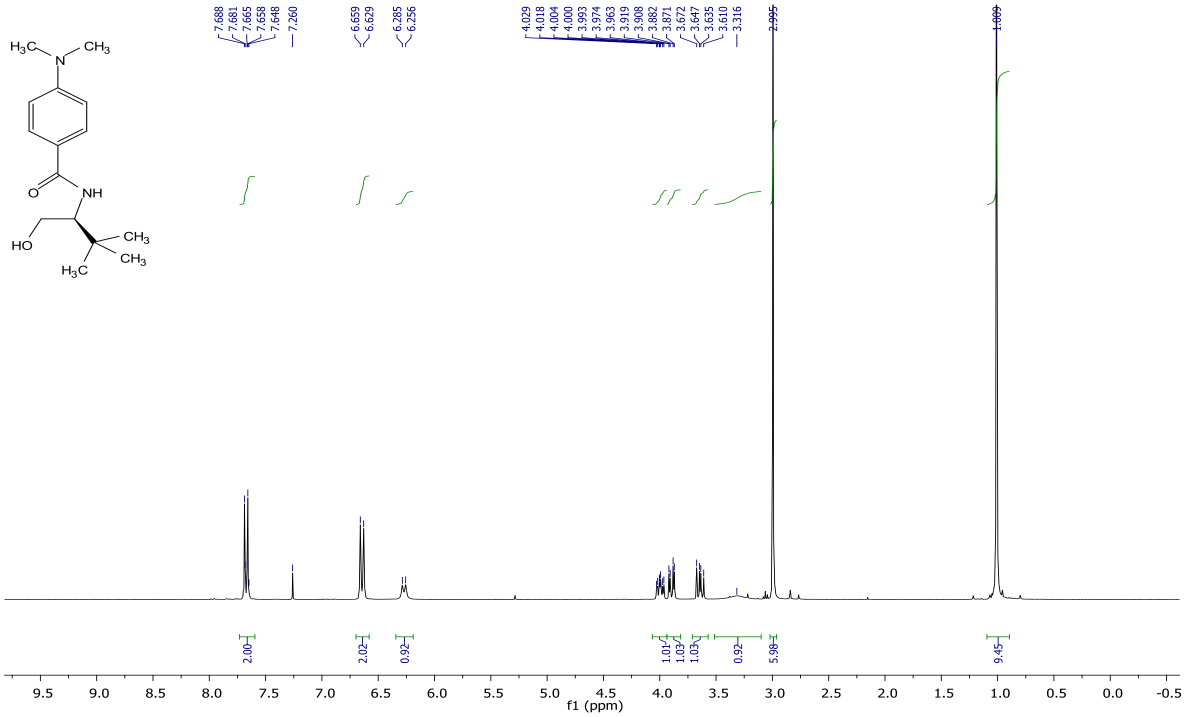


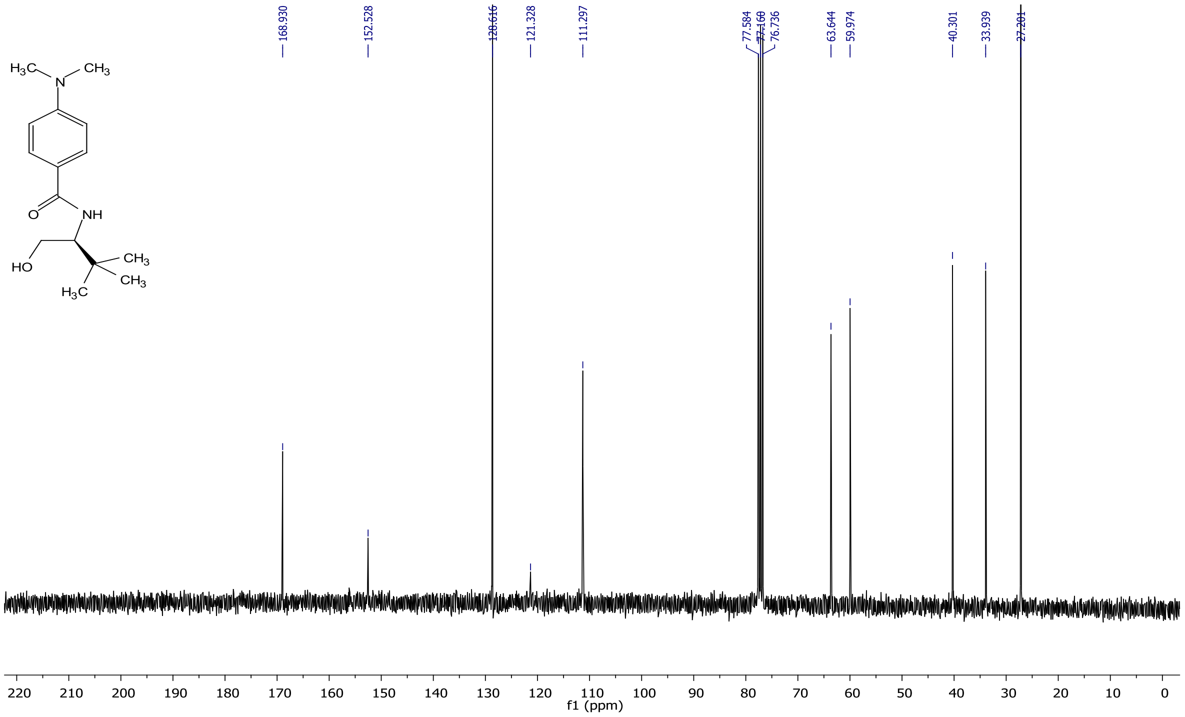
4-(4-Chlorophenyl)-5-methyl-5-nitrohexan-2-one (183d)



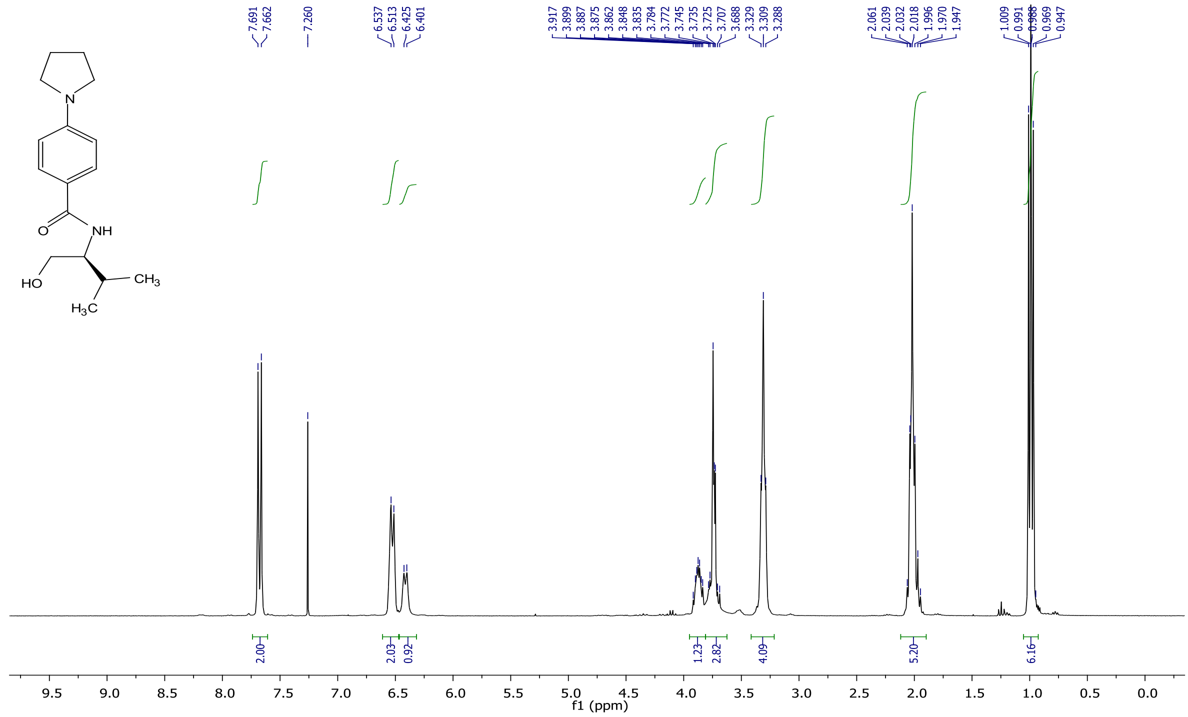


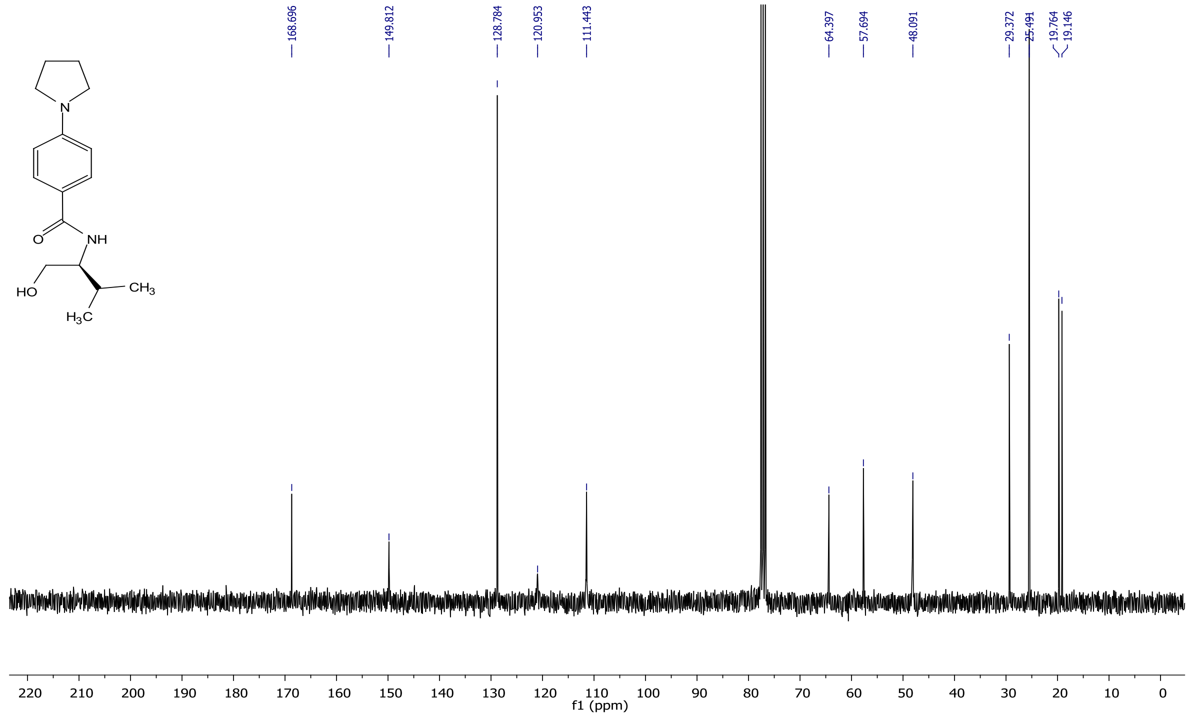
(*S*)-4-(dimethylamino)-*N*-(1-hydroxy-3,3-dimethylbutan-2-yl)benzamide (267)



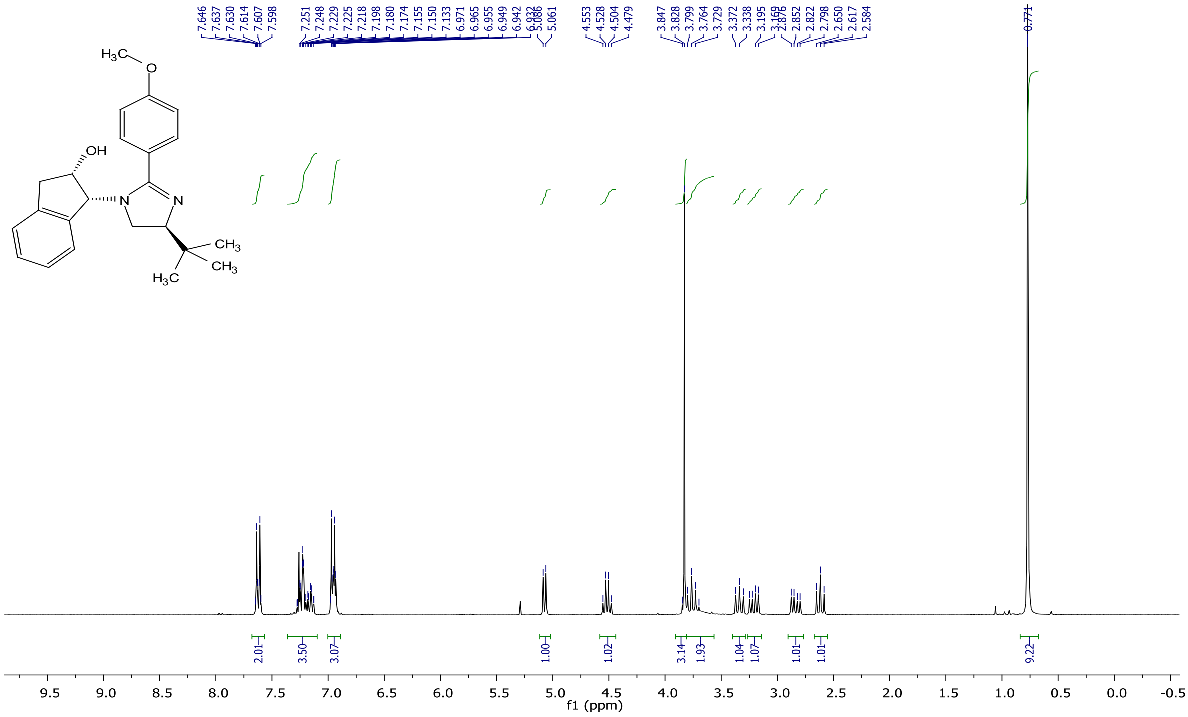


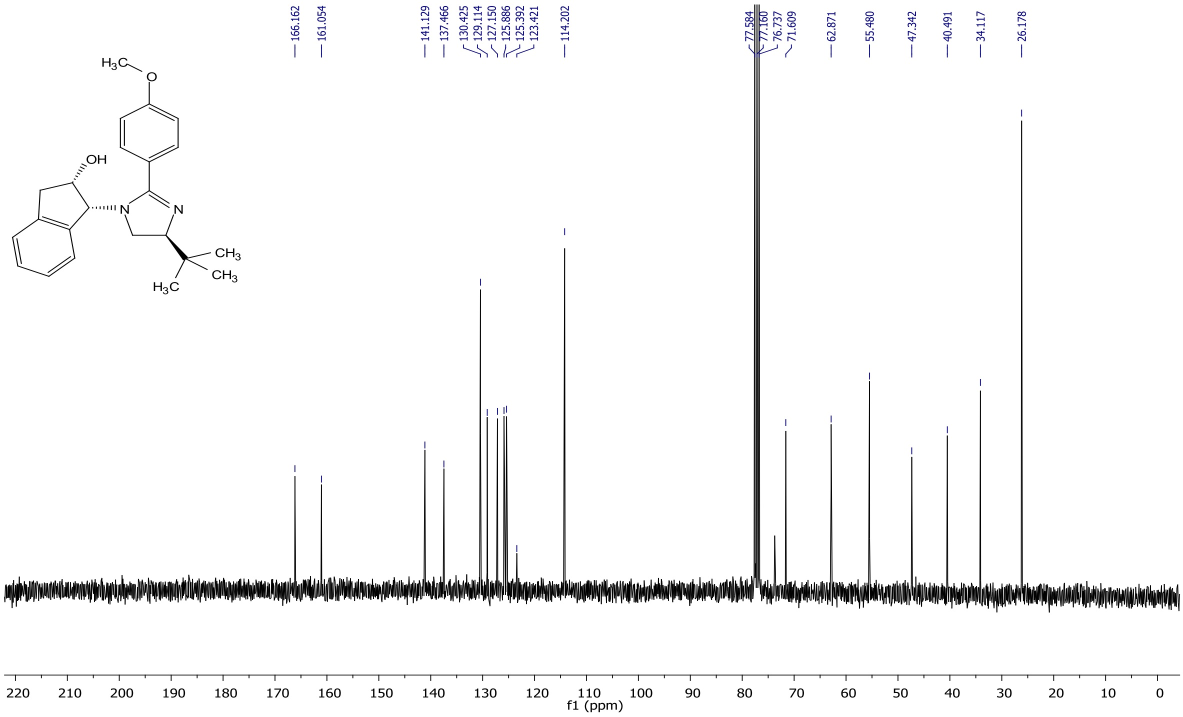
(*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-4-(pyrrolidin-1-yl)benzamide (270)



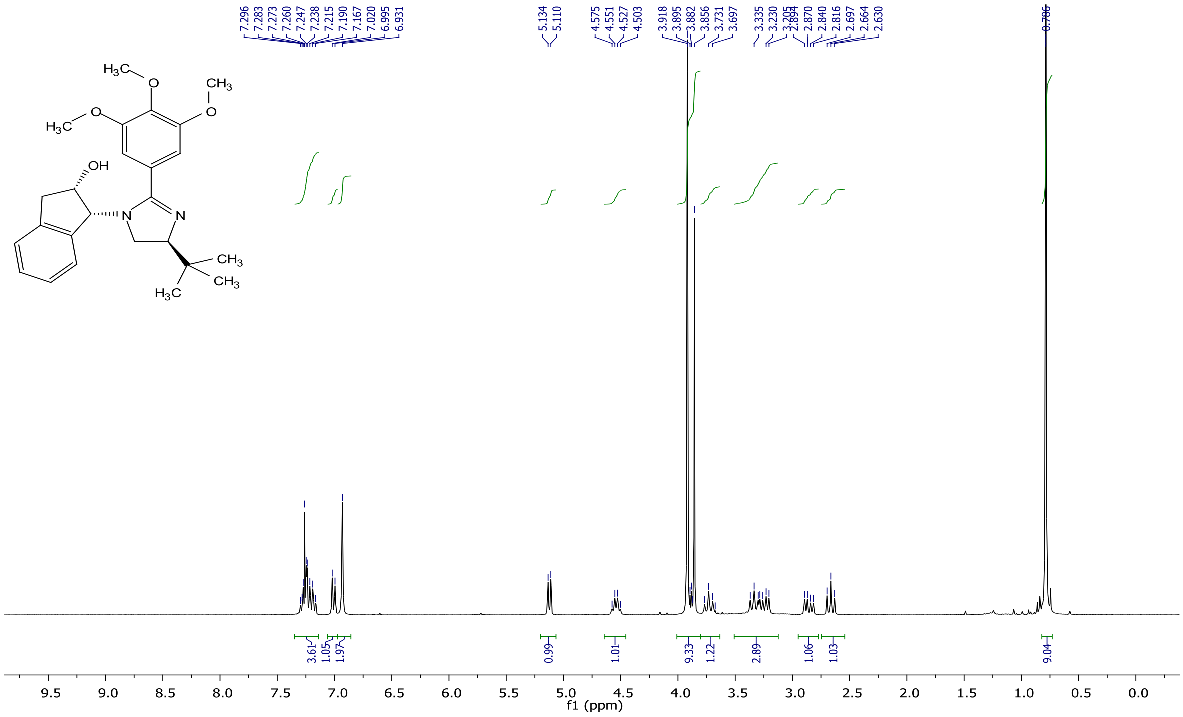


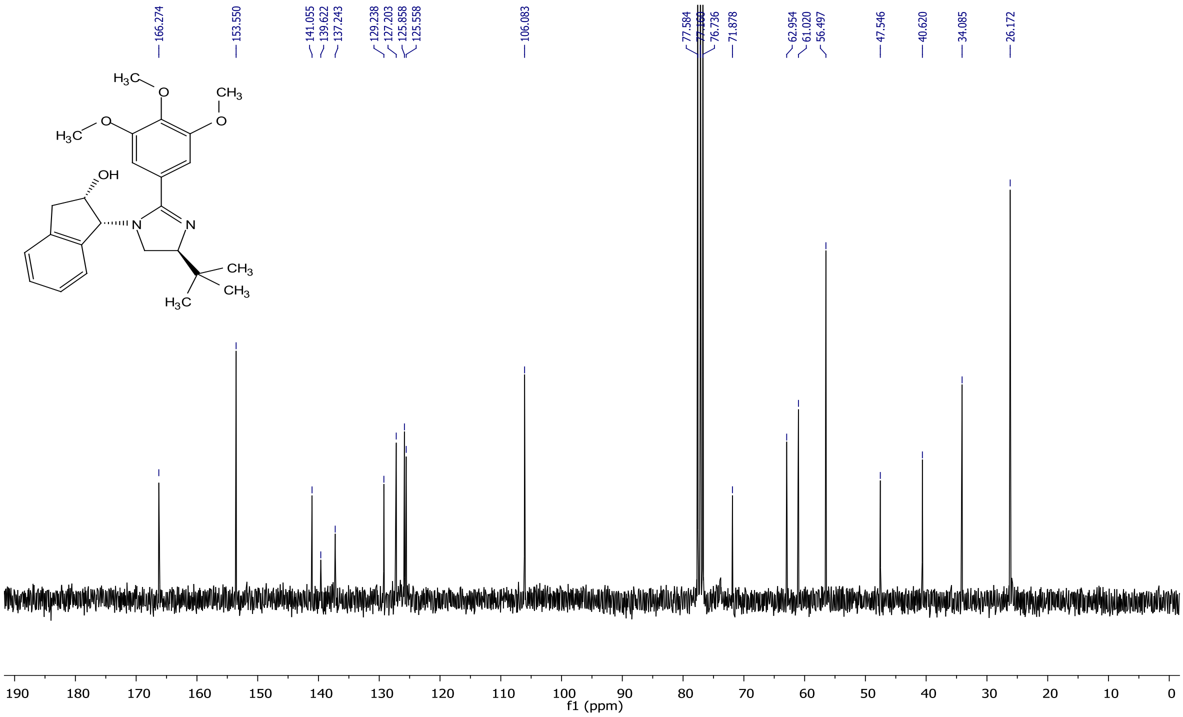
(1*R*, 2*S*)-1-((*S*)-4-(tert-butyl)-2-(4-methoxyphenyl)-4,5-dihydro-1H-imidazol-1-yl)-2,3-dihydro-1H-inden-2-ol (253a)



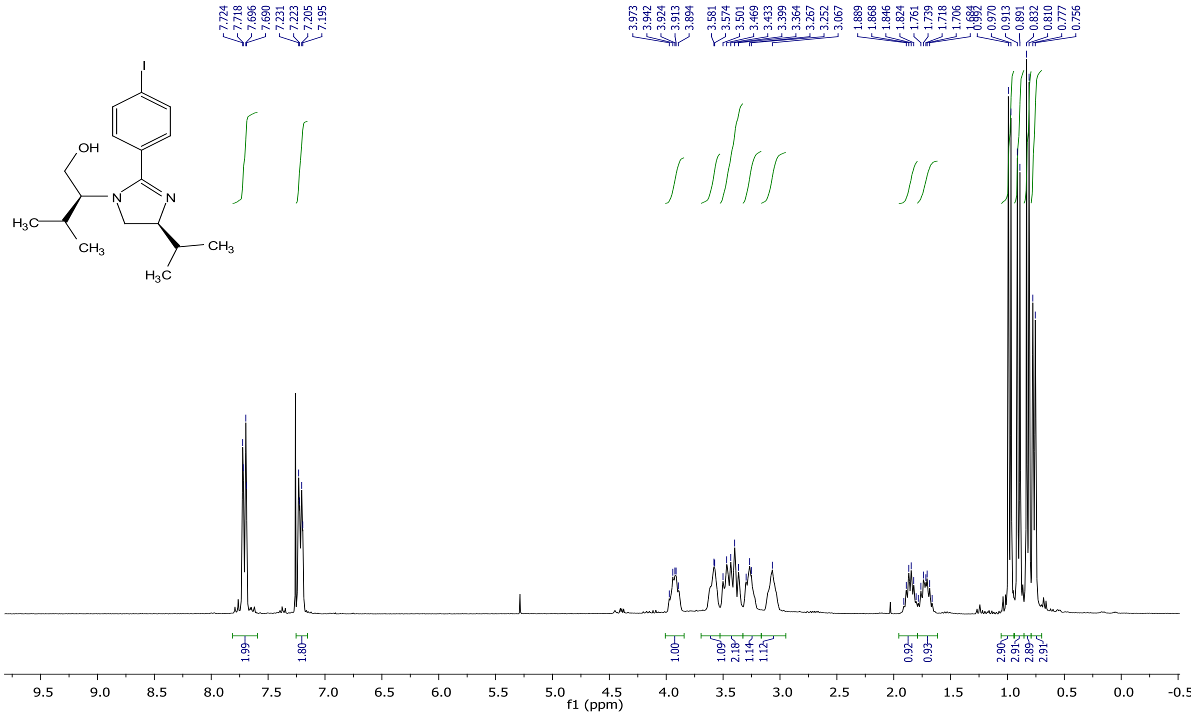


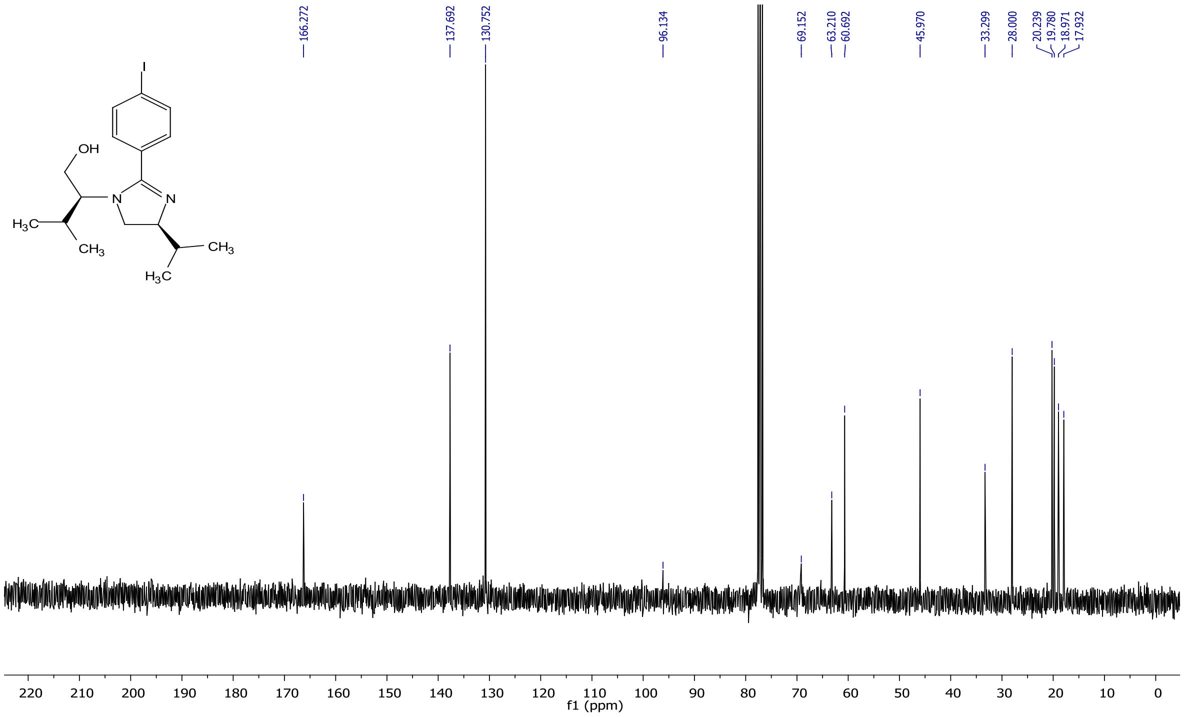
(1*R*, 2*S*)-1-((*S*)-4-(tert-butyl)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-imidazol-1-yl)-2,3-dihydro-1H-inden-2-ol (253b)



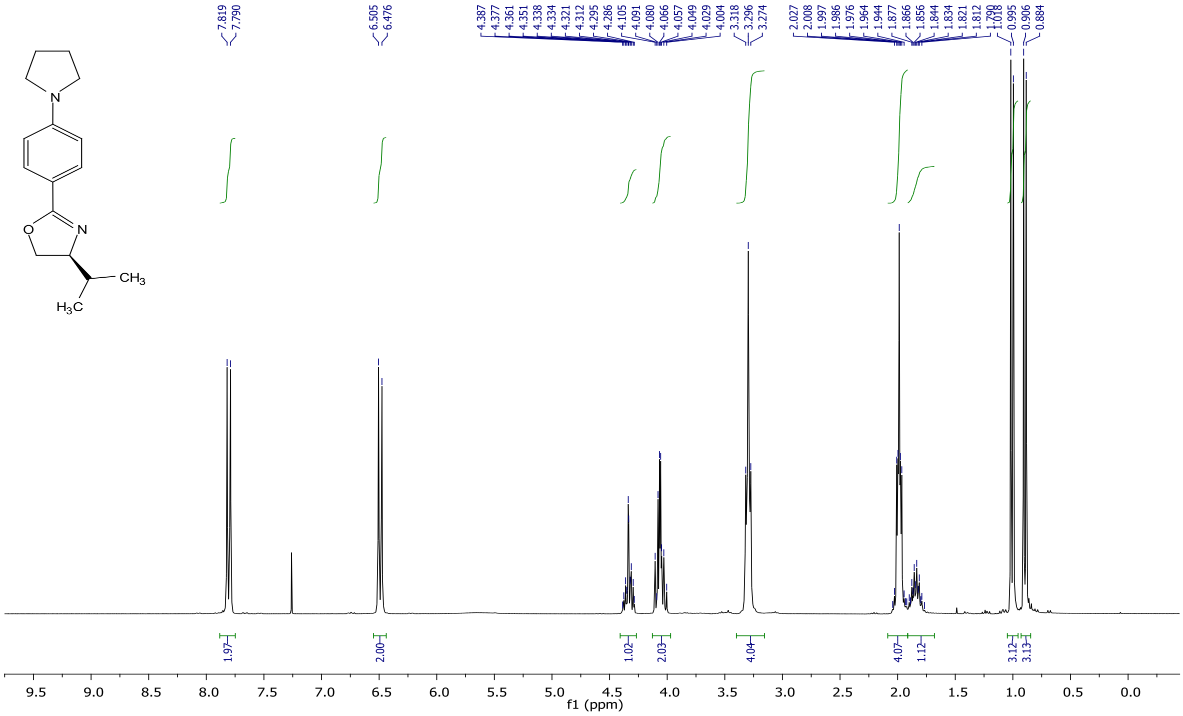


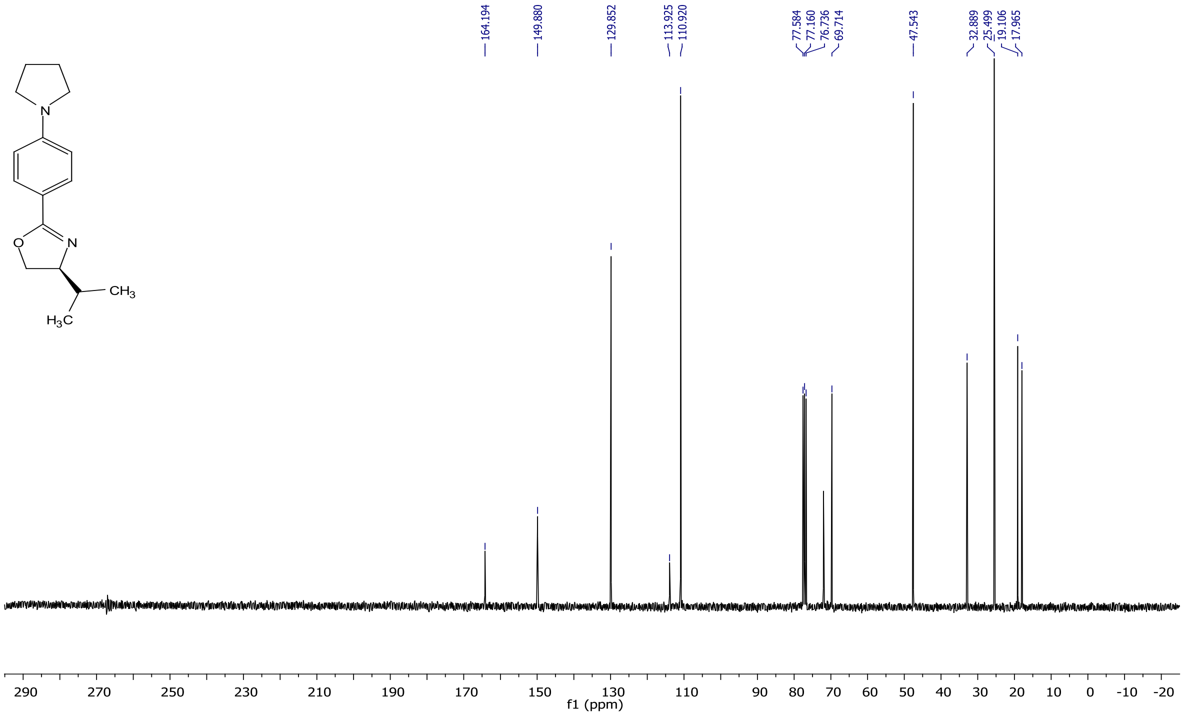
(4*S*)-1-((2*S*)-1-hydroxy-3-methyl-but-2-yl)-2-(4-iodophenyl)-4-isopropyl-4,5-dihydroimidazole (274)



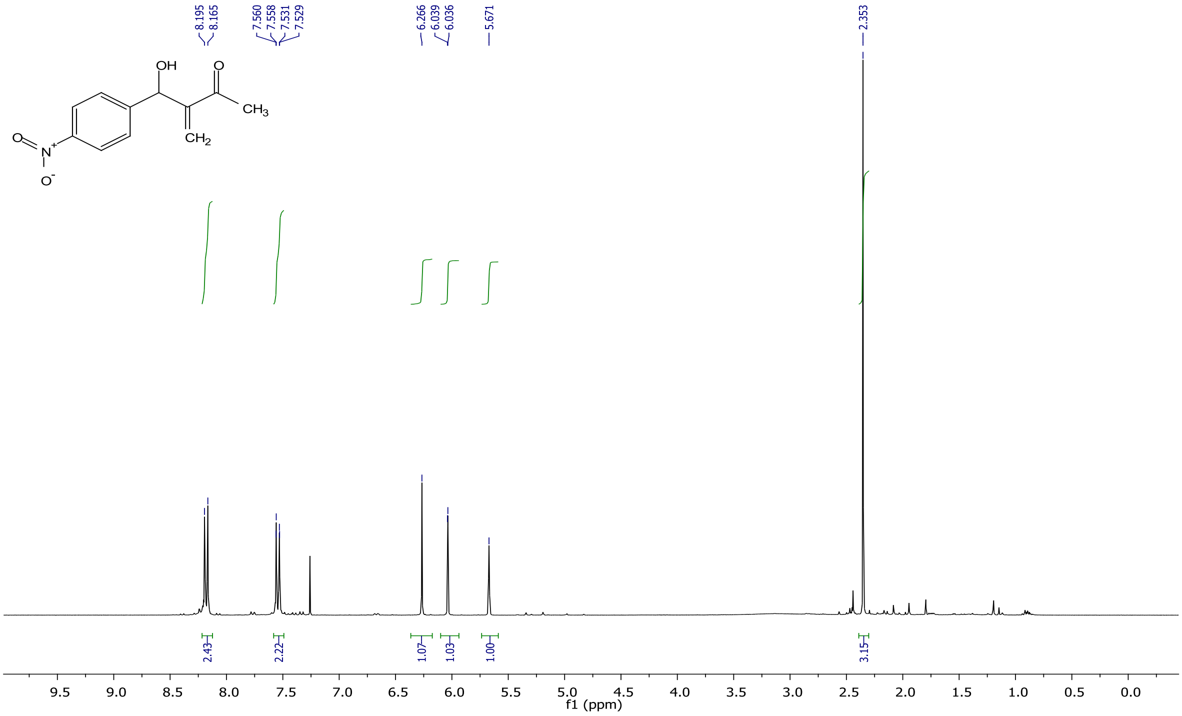


(*S*)-4-isopropyl-2-(4-(pyrrolidin-1-yl)phenyl)-4,5-dihydrooxazole (271)



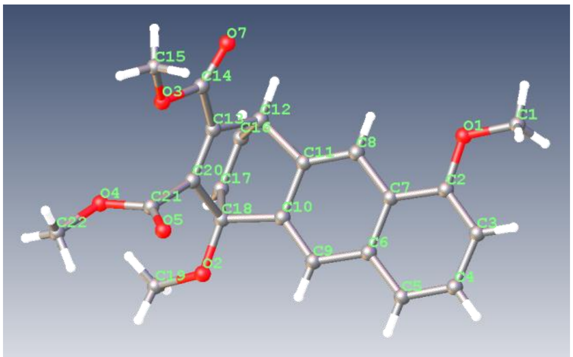


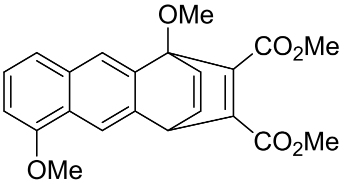
(*R*)-3-(hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (262)



11.2. X-ray structure and data

Dimethyl 1,5-dimethoxy-1,4-dihydro-1,4-ethenoanthracene-2,3-dicarboxylate (92a)



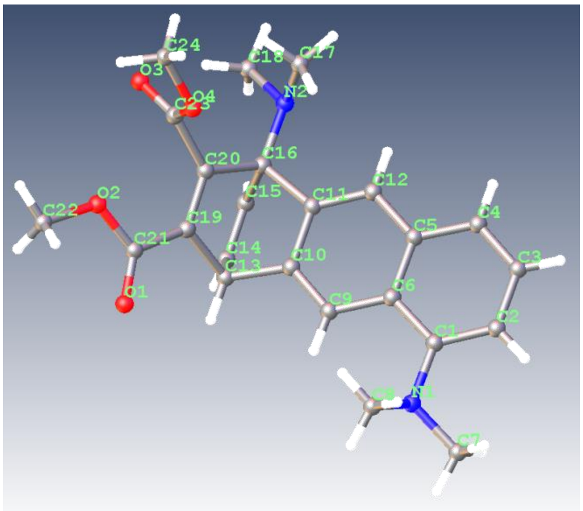


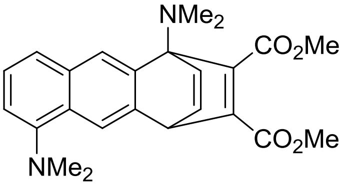
Crystal data and structure refinement for **92a**

Empirical formula	$C_{22}H_{20}O_6$
Formula weight	380.38
Temperature/K	124(1)
Crystal system	triclinic
Space group	P-1
a/Å	9.0753(2)
b/Å	9.76091(19)
c/Å	10.8610(2)
α/°	91.7335(16)
β/°	108.5566(19)
γ/°	92.3162(17)

Volume/Å^3	910.40(3)
Z	2
ρ_{calc}g/cm^3	1.388
μ/mm^{-1}	0.838
F(000)	400.0
Crystal size/mm^3	0.2624 × 0.1117 × 0.074
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	8.596 to 132.06
Index ranges	$-10 \leq h \leq 9$, $-11 \leq k \leq 11$, $-12 \leq l \leq 12$
Reflections collected	10461
Independent reflections	3154 [R_{int} = 0.0202, R_{sigma} = 0.0164]
Data/restraints/parameters	3154/0/257
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0372, wR_2 = 0.1004
Final R indexes [all data]	R_1 = 0.0399, wR_2 = 0.1032
Largest diff. peak/hole / e Å^{-3}	0.28/-0.25

Dimethyl 1,5-bis(dimethylamino)-1,4-dihydro-1,4-ethenoanthracene-2,3-dicarboxylate (94a)



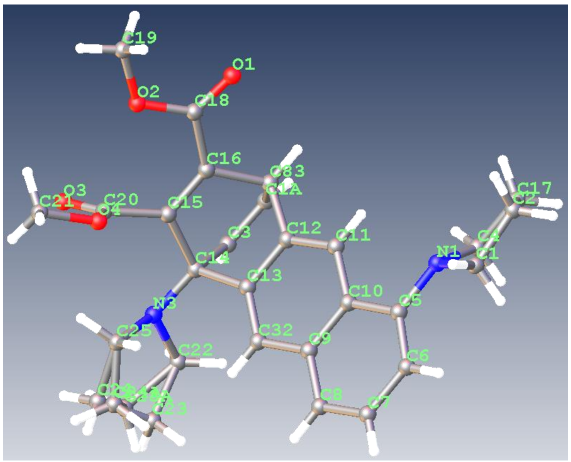


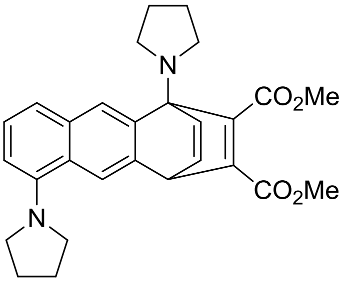
Crystal data and structure refinement for **94a**

Empirical formula	$C_{24}H_{26}N_2O_4$
Formula weight	406.47
Temperature/K	123.0
Crystal system	monoclinic
Space group	C2/c
a/Å	19.2416(13)
b/Å	19.8451(8)
c/Å	12.2391(8)
α/°	90
β/°	117.999(9)

γ/°	90
Volume/Å^3	4126.5(5)
Z	8
ρ_{calc}g/cm^3	1.309
μ/mm^{-1}	0.724
F(000)	1728.0
Crystal size/mm^3	0.0754 × 0.0492 × 0.0427
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.84 to 126.14
Index ranges	$-16 \leq h \leq 21$, $-22 \leq k \leq 22$, $-14 \leq l \leq 14$
Reflections collected	9176
Independent reflections	3208 [R_{int} = 0.0235, R_{sigma} = 0.0232]
Data/restraints/parameters	3208/0/275
Goodness-of-fit on F^2	1.048
Final R indexes [I>=2σ (I)]	R_1 = 0.0413, wR_2 = 0.1135
Final R indexes [all data]	R_1 = 0.0483, wR_2 = 0.1191
Largest diff. peak/hole / e Å^{-3}	0.27/-0.20
Flack parameter	.

Dimethyl 1,5-bis(pyrrolidin-1-yl)-1,4-dihydro-1,4-ethenoanthracene-2,3-dicarboxylate (96a)



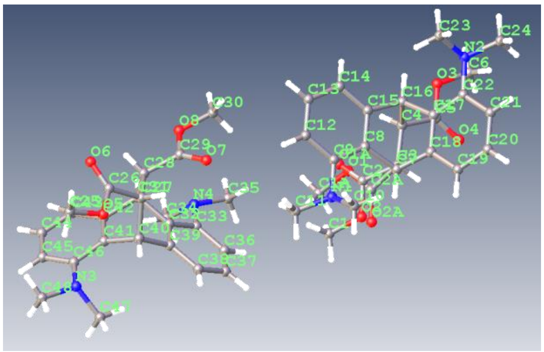


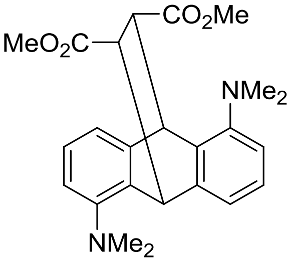
Crystal data and structure refinement for **96a**

Empirical formula	$C_{28}H_{30}N_2O_4$
Formula weight	458.54
Temperature/K	123.01(10)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.08860(17)
b/Å	9.11769(15)
c/Å	27.3374(4)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	2265.37(7)

Z	4
ρ_{calc}g/cm^3	1.344
μ/mm^{-1}	0.724
F(000)	976.0
Crystal size/mm^3	0.236 × 0.11 × 0.081
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.228 to 148.126
Index ranges	$-11 \leq h \leq 10$, $-11 \leq k \leq 11$, $-33 \leq l \leq 34$
Reflections collected	35025
Independent reflections	4539 [R_{int} = 0.0436, R_{sigma} = 0.0198]
Data/restraints/parameters	4539/36/343
Goodness-of-fit on F^2	1.057
Final R indexes [I>=2σ (I)]	R_1 = 0.0329, wR_2 = 0.0871
Final R indexes [all data]	R_1 = 0.0335, wR_2 = 0.0878
Largest diff. peak/hole / e Å^{-3}	0.28/-0.16
Flack parameter	0.22(5)

Cis-dimethyl 1,5-bis(dimethylamino)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (*cis*-93c)



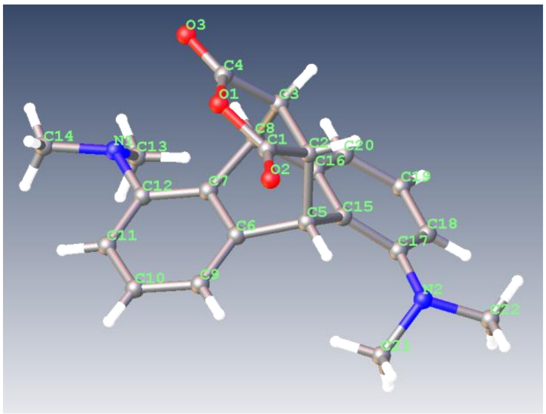


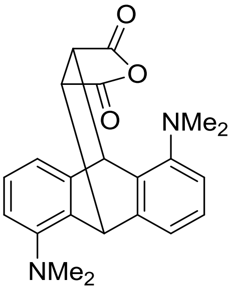
Crystal data and structure refinement for ***cis*-93c**

Empirical formula	$C_{24}H_{28}N_2O_4$
Formula weight	408.48
Temperature/K	123.01(10)
Crystal system	triclinic
Space group	P-1
a/Å	8.3692(2)
b/Å	15.0458(4)
c/Å	18.6920(5)
α/°	69.973(2)
β/°	84.132(2)
γ/°	75.663(2)
Volume/Å^3	2142.12(10)

Z	4
ρ_{calc}g/cm^3	1.267
μ/mm^{-1}	0.698
F(000)	872.0
Crystal size/mm^3	0.2023 × 0.14 × 0.1379
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.73 to 147.048
Index ranges	$-10 \leq h \leq 10$, $-18 \leq k \leq 17$, $-23 \leq l \leq 21$
Reflections collected	21460
Independent reflections	8330 [R_{int} = 0.0313, R_{sigma} = 0.0317]
Data/restraints/parameters	8330/0/653
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0383, wR_2 = 0.1028
Final R indexes [all data]	R_1 = 0.0435, wR_2 = 0.1092
Largest diff. peak/hole / e Å^{-3}	0.32/-0.33

1,5-bis(dimethylamino)-9,10,11,15-tetrahydro-9,10-[3’,4’]furanoanthracene-12,14-dione (93d)



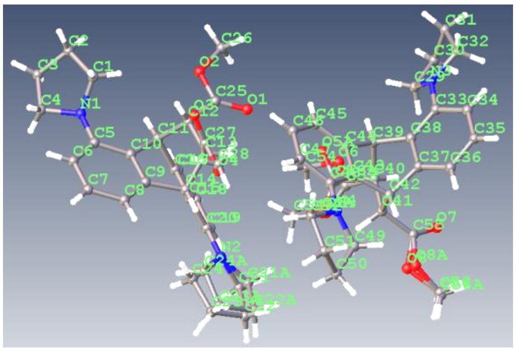


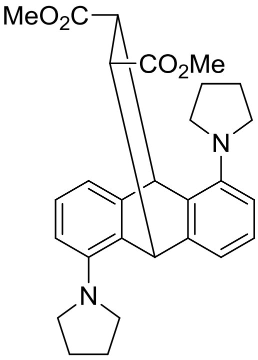
Crystal data and structure refinement for **93d**

Empirical formula	$C_{22}H_{22}N_2O_3$
Formula weight	362.42
Temperature/K	123.0
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	9.75488(19)
b/Å	11.9945(3)
c/Å	15.7122(3)
α/°	90
β/°	90
γ/°	90

Volume/Å^3	1838.40(7)
Z	4
ρ_{calc}g/cm^3	1.309
μ/mm^{-1}	0.707
F(000)	768.0
Crystal size/mm^3	0.3549 × 0.0664 × 0.0664
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.28 to 127.06
Index ranges	$-11 \leq h \leq 8$, $-13 \leq k \leq 10$, $-17 \leq l \leq 16$
Reflections collected	4865
Independent reflections	2829 [R_{int} = 0.0345, R_{sigma} = 0.0423]
Data/restraints/parameters	2829/0/249
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0338, wR_2 = 0.0807
Final R indexes [all data]	R_1 = 0.0394, wR_2 = 0.0873
Largest diff. peak/hole / e Å^{-3}	0.15/-0.13
Flack parameter	0.1(3)

***Trans*-dimethyl 1,5-bis(pyrrolidin-1-yl)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (*trans*-95c)**



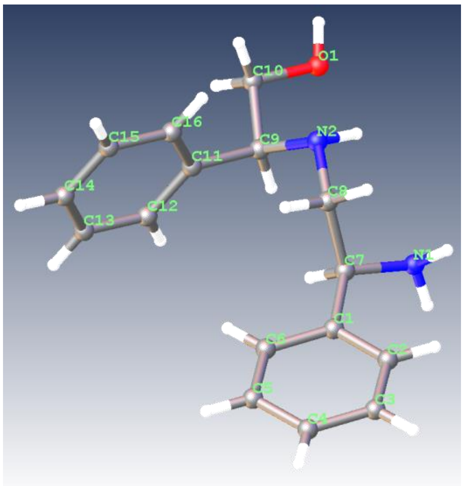


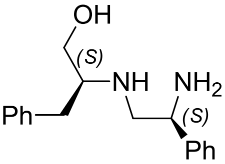
Crystal data and structure refinement for ***trans*-95c**

Empirical formula	$C_{28}H_{32}N_2O_4$
Formula weight	460.56
Temperature/K	123.01(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.0465(5)
b/Å	13.2439(7)
c/Å	20.1475(7)
α/°	101.285(4)
β/°	90.099(4)
γ/°	90.132(5)
Volume/Å^3	2367.22(19)

Z	4
ρ_{calc}g/cm^3	1.292
μ/mm^{-1}	0.693
F(000)	984.0
Crystal size/mm^3	0.2241 × 0.1339 × 0.1031
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.38 to 141.6
Index ranges	$-11 \leq h \leq 10$, $-16 \leq k \leq 16$, $-24 \leq l \leq 24$
Reflections collected	42375
Independent reflections	8920 [R_{int} = 0.0642, R_{sigma} = 0.0389]
Data/restraints/parameters	8920/174/706
Goodness-of-fit on F^2	1.108
Final R indexes [I>=2σ (I)]	R_1 = 0.0687, wR_2 = 0.1947
Final R indexes [all data]	R_1 = 0.0767, wR_2 = 0.2099
Largest diff. peak/hole / e Å^{-3}	0.45/-0.43

(2*S*)-2-(((2*S*)-2-amino-2-phenylethyl)amino)-3-phenylpropan-1-ol (154c)





Crystal data and structure refinement for **154c**

Empirical formula	$C_{16}H_{20}N_2O$
Formula weight	256.34
Temperature/K	123.01(10)
Crystal system	N/A
Space group	$P2_12_12_1$
a/Å	6.03835(11)
b/Å	8.48732(14)
c/Å	27.9013(5)
α/°	90
β/°	90
γ/°	90

Volume/Å^3	1429.93(4)
Z	4
ρ_{calc}g/cm^3	1.191
μ/mm^{-1}	0.588
F(000)	552.0
Crystal size/mm^3	0.4558 × 0.2840 × 0.0728
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	10.9 to 147.3
Index ranges	$-7 \leq h \leq 7$, $-10 \leq k \leq 10$, $-34 \leq l \leq 33$
Reflections collected	10718
Independent reflections	2822 [R_{int} = 0.0319, R_{sigma} = N/A]
Data/restraints/parameters	2822/0/184
Goodness-of-fit on F^2	1.075
Final R indexes [I>=2σ (I)]	R_1 = 0.0313, wR_2 = 0.0755
Final R indexes [all data]	R_1 = 0.0352, wR_2 = 0.0782
Largest diff. peak/hole / e Å^{-3}	0.12/-0.17
Flack parameter	-0.1(2)

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Curriculum vitae

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Since 10/2009-9/2014	Ph.D. thesis at the University of Regensburg under supervision of Prof. Dr. Oliver Reiser
2003 – 2006	University of Natural Sciences – Vietnam National University Ho Chi Minh City. Graduation: Master of Science in Organic Chemistry.
1998 – 2002	University of Natural Sciences – Vietnam National University Ho Chi Minh City. Graduation: Bachelor of Science in Chemistry

Professional activities and honors

The author of the University grade research project: “Contribution to study on the chemical constituents of leaves of *Tithonia tagetiflora* Desf. (Asteraceae)”, University of Natural Sciences, 2004-2006.

The 4th Scientific Conference, Vietnam National University Ho Chi Minh City – University of Natural Sciences, Ho Chi Minh City, Vietnam. October 21st, 2004.

The 5th Scientific Conference, Vietnam National University Hochiminh City – University of Natural Sciences, Hochiminh City, Vietnam. November 16th, 2006.

A fellowship in Denmark for study at the Department of Life Sciences and Chemistry, Roskilde University during the period August 1st, 2005 – January 31st, 2006.

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Publications

1. Ngoc Vinh Huynh, Thi Hoai Thu Nguyen, Kim Phi Phung Nguyen and Poul Erik Hansen. Structural studies of the chemical constituents of Tithonia tagetiflora Desv. (Asteraceae). *Magn. Reson. Chem*. **2013**, 51, 439.

2. Nguyen Thanh Hoang, Huynh Ngoc Vinh, Ton That Quang, Nguyen Kim Phi Phung. “Contribution to the study on *Wedelia trilobata* (L.) Hitch (Asteraceae)”. *Journal of Chemistry* **2006**, 44(1), 91.

3. Huynh Ngoc Vinh, Nguyen Huynh Mai Hanh, Ton That Quang, Nguyen Kim Phi Phung. “Contribution to the study on chemical constituents of *Cosmos sulphureus* Cav. (Asteraceae)”. *Journal of Chemistry* **2005**, 43(4), 517.

Herewith I declare that this thesis is a presentation of my original work single-handed. I have only used the stated utilities.

Regensburg,

HUYNH NGOC VINH