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Catalytic Enantiospecific [3+2] Annulation of Aminocyclopropanes with Ketones

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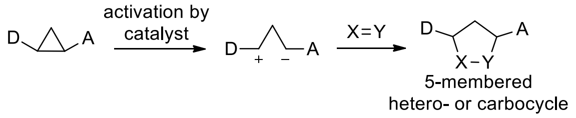
Dedication ((optional))

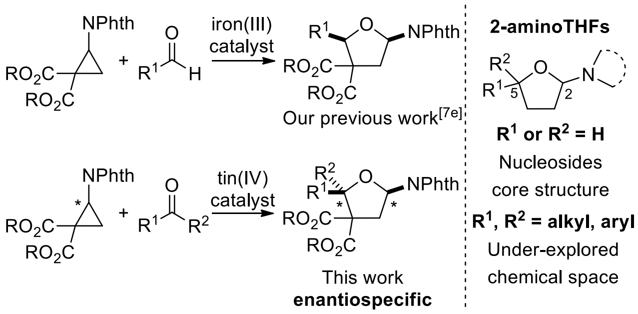
The exploitation of strain release in small rings as a driving force to trigger synthetic transformations has received increased attention over the last decade. In this context, cyclopropanes have been predominantly investigated, due to the abundance of efficient methods for their preparation, combined with their exceptional reactivity. A strategy to further enhance the inherent strain energy of cyclopropanes consists in the introduction of vicinal Donor and Acceptor groups (D and A, Scheme 1), able to stabilize the incipient positive and negative charges derived from the cleavage of the activated σ bond. The so-called D-A cyclopropanes can therefore be considered synthetic equivalent to 1,3 zwitterionic synthons.[1] As such, they have been extensively used in [3+2] annulations.[2] These reactions allow the efficient assembly of a variety of 5-membered hetero- and carbocycles. In particular, the [3+2] reaction with carbonyl compounds[3,4] represents a valuable tool for the synthesis of tetrahydrofurans (THFs).[5]



Scheme 1. Donor-Acceptor cyclopropanes as 1,3 zwitterionic synthons. D = donor. A = acceptor. X=Y = generic double bond.

The annulation of D-A cyclopropanes with aldehydes is well established, and efficient catalytic as well as enantioselective protocols have been reported.[3f,h-n] On the contrary, only a few catalytic methods have been described for the annulation involving the less reactive ketones as reaction partners.[4] Furthermore, the scarcity of highly diastereoselective protocols indicates an intrinsic difficulty to achieve face discrimination in the addition of D-A cyclopropanes onto non-symmetrical ketones.[6]

In this context, and with our recent advancements involving cyclization and annulation reactions of D-A cyclopropanes in hand,[7] we sought out to develop a catalytic and stereoselective protocol for the [3+2] annulation between D-A aminocyclopropanes and ketones. There are only few reports of annulation and cyclization reactions of D-A aminocyclopropanes,[8] despite their high synthetic potential for the preparation of N-containing hetero- and carbocycles. Implementing the [3+2] annulation of D-A cyclopropanes with ketones would indeed allow an expedient access to a variety of 2-aminotetrahydrofurans bearing a rare quaternary carbon in position 5 (Scheme 2). Furthermore, the 2-aminotetrahydrofuran scaffold can be rightly considered as a "privileged structure", due to its occurrence in nucleosides and in nucleosides-derived synthetic drugs.[9] It is noteworthy that current methods mainly yield analogues bearing a tertiary centre at C5 (Scheme 2), with little deviation from the natural molecules.[10] The methodology described herein, however, allows to access the less explored chemical space populated by structures bearing a quaternary C5. Herein, we report the first catalytic [3+2] annulation of D-A aminocyclopropanes with ketones, allowing the preparation of rare C5-disubstituted aminotetrahydrofurans. In contrast with our previous work with aldehydes using an iron catalyst which proceeded with racemization,[7f] the tin-catalyzed annulation of ketones is enantiospecific, giving access to enantioenriched aminotetrahydrofurans.



Scheme 2. [3+2] annulation of D-A aminocyclopropanes with carbonyl compounds. Phth = phthaloyl.

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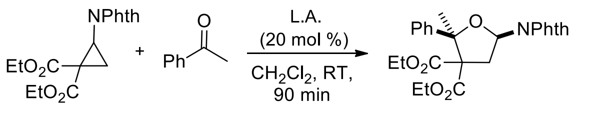
We commenced our investigation by screening Lewis acids for the model reaction of phthaloyl cyclopropane **1a** with acetophenone (**2a**). At first, we tested iron (III) chloride on alumina, which successfully promoted the [3+2] annulation with aldehydes (Table 1, entry 1).[7f] Unfortunately, a poor yield was obtained, due to extensive degradation of the cyclopropane partner in the presence of the catalyst. We then examined tin(IV) chloride, which we had employed to promote the [3+2] annulation of phthaloyl cyclopropane with silyl enol ethers (Table 1, entry 2).[7e] At -78 °C, complete conversion was observed after 90 minutes, and the desired aminotetrahydrofuran **3aa** was formed quantitatively, as a single diastereoisomer. The relative configuration of **3aa** was unambiguously assigned to be 2,5-*cis* on the basis of x-ray diffraction analysis.[11] Other metal chloride salts failed to catalyse the process, with the surprising exception of gold(III) chloride, which gave **3aa** in modest yield (entry 3). Due to decomposition of **1a**, the screening of metal triflates (entries 4-8) did not lead to improved results.[12]

Table 1. Screening of Lewis acids in the reaction with acetophenone.[a]

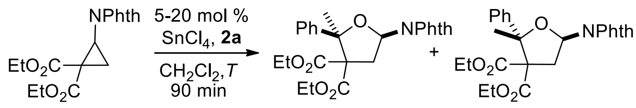


entry	Lewis acid[b]	yield (%)[c]	entry	Lewis acid[b]	yield (%)[c]
1	$FeCl_3$-Al_2O_3	20	5	$In(OTf)_3$	33
2	$SnCl_4$[d]	100	6	$Sc(OTf)_3$	25
3	$AuCl_3$	50	7	$Sn(OTf)_2$	13
4	$Cu(OTf)_2$	10	8	$Hf(OTf)_4$	decomp.

[a] Reaction conditions: 1.0 equiv. **1a**, 1.5 equiv. **2a**, 20 mol % of Lewis acid, 0.1 M in dichloromethane. [b] No reaction with: $Zn(OTf)_2$, $TiCl_4$, AuCl, $EtAlCl_2$, Me_2AlCl, $CeCl_3$. [c] Yield was determined via ^1H NMR spectroscopy using hexamethyldisiloxane as internal standard. [d] Performed at -78 °C; at RT, only traces of **3aa** were detected. Phth = phthaloyl. d.r. = diastereomeric ratio. OTf = trifluoromethanesulfonate.

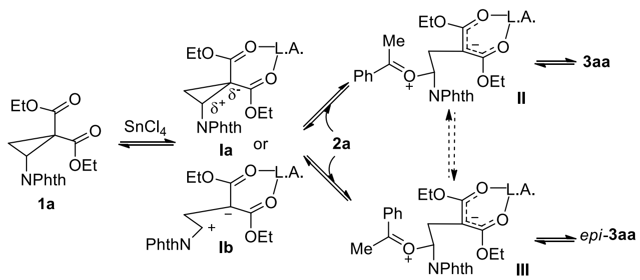
Therefore, we selected $SnCl_4$ as catalyst to further screen for the effects of temperature (*T*) and catalyst loading on the diastereoselectivity of the [3+2] annulation between **1a** and acetophenone (**2a**) (Table 2). Using 5 mol % of catalyst, the reaction showed a classic inverse d.r. dependence with respect to temperature, as the diastereoselectivity decreased with an increase in *T*. The 2,5-*trans* isomer *epi*-**3aa** became detectable in the crude when running the reaction at -10 °C (entry 4).[13] In the presence of 20 mol % of $SnCl_4$, *epi*-**3aa** was already formed at -20 °C, although the increased amount of catalyst induced significant decomposition (entry 3). At -10 °C, it was the only diastereoisomer observed in the crude reaction mixture (entry 4). Unfortunately, the isolated yield under these conditions was poor (19%), hampering the development of a temperature-dependent synthesis of both diastereoisomers of aminoTHFs. To verify if *epi*-**3aa** could derive from **3aa** *via* a tin(IV)-catalyzed isomerization, aminotetrahydrofuran **3aa** was treated with 20 mol % $SnCl_4$ at -10 °C. In this case, mainly its partial conversion in starting material **1a**, likely *via* a retro-[3+2] annulation, was observed. To explain this result, we assume that **3aa** might isomerize to *epi*-**3aa** *via* a sequence of retro-[3+2] annulation/[3+2] annulation (Scheme 3).[14] As intermediates, both an intimate ion pair **Ia** or a completely dissociated zwitterion **Ib** could be considered. In the presence of 1 equiv of **2a**, full conversion of **3aa** was achieved and *epi*-**3aa** was obtained in 45% yield. Although this result would be in good agreement with a process having **Ia** or **Ib** as intermediate, as a higher concentration of **2a** would be particularly important to allow efficient isomerization in this case, the interconversion of the open zwitterions **II** and **III** or the reaction of **Ia** or **Ib** with acetophenone (**2a**) to give **3aa** directly are also possible reaction pathways.

Table 2. Diastereomeric ratios observed in the reaction of **1a** with **2a** with 5-20 mol % of $SnCl_4$ depending on the temperature.[a]



entry	*T* (°C)	d.r.[b] (5 mol % $SnCl_4$)	d.r.[b] (20 mol % $SnCl_4$)
1	-78	> 20:1	> 20:1
2	-40	> 20:1	> 20:1
3	-20	> 20:1	9:1
4	-10	5:1[c]	< 1:20[d]
5	0	3:1	< 1:20

[a] Reaction conditions: 1.0 equiv. **1a**, 1.5 equiv. **2a**, 5-20 mol % of $SnCl_4$, 0.1 M in dichloromethane at the indicated *T*. [b] Determined by ^1H NMR spectroscopy on the crude reaction mixture and expressed as *cis*:*trans* (**3aa**:*epi*-**3aa**). [c] 80% combined isolated yield. [d] 19% isolated yield. Phth = phthaloyl. d.r. = diastereomeric ratio.

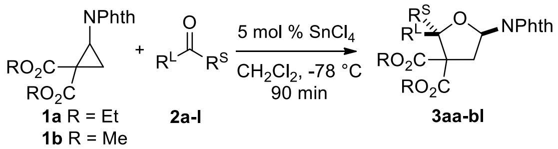


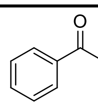
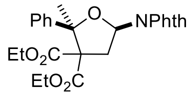
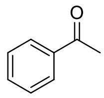
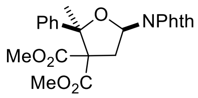
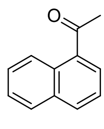
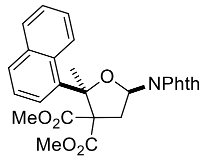
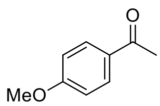
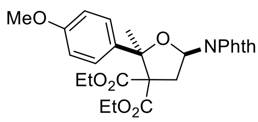
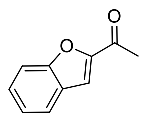
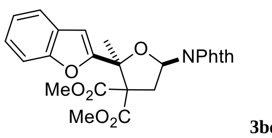
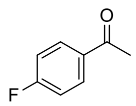
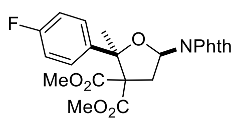
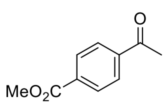
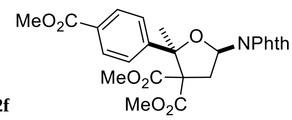
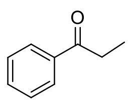
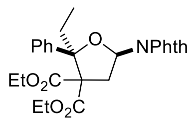
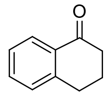
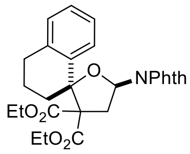
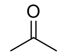
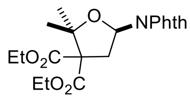
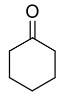
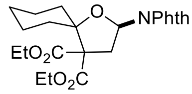
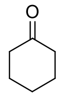
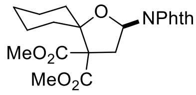
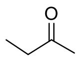
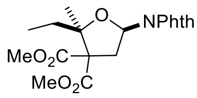
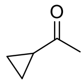
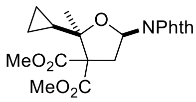
Scheme 3. Formation of tetrahydrofurans **3aa** and *epi*-**3aa** *via* [3+2] annulation. Phth = phthaloyl. L.A. = Lewis acid.

Next, the scope of the reaction was evaluated by applying the optimized conditions to a variety of aromatic, heteroaromatic and aliphatic ketones (Table 3). D-A cyclopropanes **1a** and **1b** displayed a similar reactivity toward acetophenone (**2a**), affording aminoTHFs **3aa** and **3ba** in excellent yields and diastereoselectivity (entries 1-2).[15] A lower yield (79%, entry 3) was obtained in the case of 1'-acetonaphthone (**2b**), most likely due to the unfavourable *ortho* substitution. Electron-rich aromatic ketone **2c** and heteroaromatic **2d** showed lower diastereoselectivities for the [3+2] annulation (entries 4-5). Nevertheless, the d.r. could be improved through a single recrystallization.

Electron-poor aromatic ketones **2e-f** were also tested, and they gave the corresponding aminoTHFs **3be** and **3bf** in high yields, as single diastereoisomers (entries 6-7). Excellent stereochemical discrimination between the phenyl and the ethyl substituent was observed also with propiophenone (**2g**), demonstrating the versatility of our methodology (entry 8). 1-Tetralone (**2h**) displayed excellent reactivity and selectivity, delivering **3ah** in high yield and diastereoselectivity, but favouring the 2,5-*trans* isomer for this cyclic system (entry 9).[16] Aliphatic symmetric ketones (**2i-j**) are more established substrates in [3+2] annulation with D-A cyclopropanes. Under our conditions, they cleanly afforded the corresponding aminoTHFs in nearly quantitative yields (entries 10-12). In general, obtaining a high degree of diastereocontrol when employing non-symmetric aliphatic ketones remains a challenge. Gratifyingly, utilizing our optimized conditions on ketones **2k-l** gave yields and diastereoselectivities comparable to those obtained with aromatic substrates (entries 13-14). Ketone substrate **2k** highlights the efficacy of the developed methodology as a good d.r. (10:1, entry 13) was obtained with two carbonyl substituents, methyl and ethyl, possessing only a small difference in size.

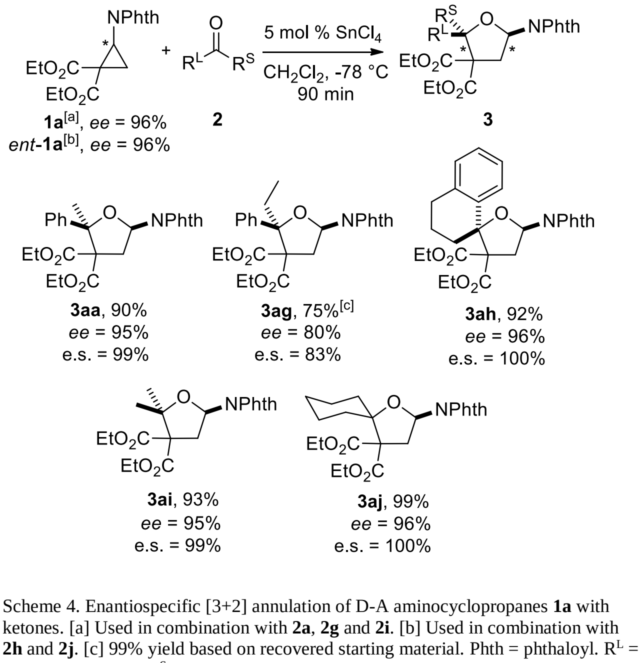
Table 3. Scope of the [3+2] annulation with ketones.[a]



entry (substrate)	ketone		product		Yield d.r.[b,c]
1(**1a**)		**2a**		**3aa**	99% >20:1
2(**1b**)		**2a**		**3ba**	96% >20:1
3(**1b**)		**2b**		**3bb**	79% >20:1
4(**1a**)		**2c**		**3ac**	90% 16:1 *>20:1*[d]
5(**1b**)		**2d**		**3bd**	95% 4:1 14:1[d]
6(**1b**)		**2e**		**3be**	93% >20:1
7(**1b**)		**2f**		**3bf**	99% >20:1
8(**1a**)		**2g**		**3ag**	95% >20:1
9(**1a**)		**2h**		**3ah**	94% >20:1
10(**1a**)		**2i**		**3ai**	94% -
11(**1a**)		**2j**		**3aj**	99% -
12(**1b**)		**2j**		**3bj**	99% -
13(**1b**)		**2k**		**3bk**	89% 10:1 16:1[d]
14(**1b**)		**2l**		**3bl**	96% >20:1

[a] Standard reaction conditions: 0.2 mmol **1a-b**, 1.5 equiv. **2a-l**, 5 mol % of $SnCl_4$, 0.1 M in dichloromethane at -78 °C. [b] Determined by ^1H NMR spectroscopy on the crude reaction mixture. [c] Expressed as *cis*:*trans*. [d] Obtained after one single recrystallization (see supporting information). Phth = phthaloyl. d.r. = diastereomeric ratio. R^L = Larger substituent. R^S = Smaller substituent.

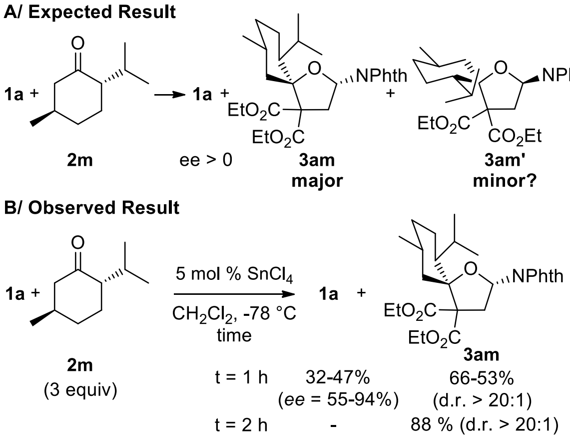
To assess the stereospecificity of the tin(IV)-catalysed [3+2] annulation, a selection of ketones was reacted with enantioenriched phthaloyl cyclopropane **1a** at -78 °C (Scheme 4).[17] Under these conditions, no loss of stereochemical purity was observed with acetophenone (**2a**) and ketones **2h-j**, while aminotetrahydrofuran **3ag** was isolated with a slightly decreased enantiomeric excess (enantiospecificity e.s. = 83%).



Scheme 4. Enantiospecific [3+2] annulation of D-A aminocyclopropanes **1a** with ketones. [a] Used in combination with **2a**, **2g** and **2i**. [b] Used in combination with **2h** and **2j**. [c] 99% yield based on recovered starting material. Phth = phthaloyl. R^L = Larger substituent. R^S = Smaller substituent. *ee* = enantiomeric excess. e.s. = enantiospecificity ([*ee* of product/ *ee* of starting material] * 100 %).

The preservation of optical purity in [3+2] annulations of D-A- cyclopropanes was already reported by Johnson[3h-i,l] and by our group;[7e] nevertheless, this is the first enantiospecific reaction between aminocyclopropanes and carbonyl compounds.[18] This result is not only important for the application of the reaction in the synthesis of enantioenriched products, it also demonstrated that an open zwitterion (**Ib** in Scheme 3) is not formed during the annulation.

Based on the high enantiospecificity and diastereoselectivity of the reaction, we wondered if the reaction of racemic **1a** with a chiral ketone would allow for a kinetic resolution to take place. For example, the reaction of cyclopropane **1a** with (-)-menthone (**2m**) should in principle favour the formation of the two diastereoisomers **3am** and **3am'**, as both have the phthalimide group in *cis* relationship to the more bulky group (Scheme 5, **A**). Both products would be obtained as single enantiomers, as enantiopure (-)-menthone (**2m**) is used as starting material. The opposite absolute stereochemistry at the nitrogen center would result from the enantiospecific reaction of both enantiomers of **1a**.[19] However, a severe steric interaction between the ester and the isopropyl group of (-)-menthone (**2m**) is present only in **3am'**: the formation of this diastereoisomer is consequently expected to be slower (mismatched case), allowing a kinetic resolution with re-isolation of enantioenriched **1a**. Unfortunately, the kinetic resolution of **1a** using sub-stoichiometric amount of (-)-menthone (**2m**) could not be accomplished, mainly due to the sluggish reactivity observed in this case. When increasing to 3 equivalents the amount of **2m**, the reaction was accelerated, allowing the isolation of enantioenriched **1a** after 1 h, although yield and enantiomeric excess showed a strong batch dependency (Scheme 5, **B**). Unexpectedly, after the conversion was complete (2 h), the annulation product **3am** was isolated as a single diastereoisomer in 88% yield. Consequently, the reaction was not enantiospecific, but stereoconvergent. [20]



Scheme 5. Reaction of racemic **1a** with (-)-menthone (**2m**). Phth = phthaloyl. *ee* = enantiomeric excess. d.r. = diastereomeric ratio.

Different rationales could account for this result: tin(IV) chloride is either active in the racemization of the D-A aminocyclopropane **1a** or in the isomerization of the product **3am**. To obtain additional clues, the loss of enantiomeric purity of enantioenriched **1a** (*ee* = 94%) in the presence of 5 mol % $SnCl_4$ was monitored at -78 °C. After one hour, **1a** was recovered with an *ee* = 75%, while after 2.5 hours almost all its stereochemical information was lost (*ee* = 20%).[3i,21] This result supports the hypothesis that the observed dynamic kinetic resolution could take place *via* racemization of the aminocyclopropane **1a**, probably via an open zwitterionic intermediate **Ib** (Scheme 3) The apparently contradicting results obtained with (-)-menthone (**2m**) could be explained by a limited lifetime for a tight ion-pair **Ia**: If the following annulation reaction is fast, an enantiospecific reaction takes place, but if the desired reaction is slow, as for the mismatched case with (-)-menthone (**2m**), dissociation would have time to occur, which would lead to racemization even at -78 °C and to the stereoconvergent reaction observed. In contrast, the *cis-trans* isomerization described in table 2 would require higher temperature to proceed. We note that further experiments would be required to confirm this interpretation.

In conclusion, we have reported the first enantiospecific [3+2] annulation of D-A cyclopropanes with ketones. Catalytic amounts of tin(IV) chloride were used to catalyze the reaction with a broad range of ketones, including non-symmetric ones. Yields and diastereomeric ratios were generally excellent, demonstrating the potential of this method for the stereoselective synthesis of aminoTHFs bearing a rare C5-quaternary center. Furthermore, the developed transformation is enantiospecific, allowing access to enantioenriched aminoTHFs when starting from an enantioenriched aminocyclopropane.
Attempts to expand the scope of N-containing cyclopropanes, as well as further functionalization of the obtained products are currently under evaluation in our laboratory.

Experimental Section

In a two-neck flask equipped with a nitrogen inlet, aminocyclopropanes **1a-b** (0.20 mmol, 60-66 mg, 1 equiv.) and ketones **2a-l** (1.5 equiv.) were dissolved in anhydrous dichloromethane (2 mL) at -78 °C. After 5 min, $SnCl_4$ (5 mol %, 0.01 mmol, 23 μL of 0.43 M solution in dichloromethane) was added. The mixture was stirred under nitrogen at -78 °C for 90 min, then it was quenched by the addition of triethylamine (0.2 mL) and subsequently flushed through a short plug of silica gel, eluting with EtOAc (5 mL). The solvent was removed *in vacuo*, affording the crude reaction mixture, which was submitted to ^1H NMR analysis to determine the d.r. before purification via flash chromatography (SiO_2, 8/2 to 1/1 (*n*-hexane: AcOEt)).

Acknowledgements

We thank the European Commission (Marie Curie IEF fellowship to F.B., grant number 253274) and the Swiss National Science Foundation (SFN, grant number 200021_129874) for financial support. Dr. Rosario Scopelliti (EPFL) is acknowledged for the X-ray studies. We thank Dr. Reto Frei for proofreading the manuscript.

Keywords: D-A aminocyclopropane • ketone • catalysis • enantiospecificity • aminotetrahydrofuran • [3+2]annulation

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that "cycloaddition" is completely correct in this case (see reference 2b). According to a seminal publication of Huisgen, "Cycloaddition reactions do not involve the cleavage of sigma bonds" (rule 3): (f) R. Huisgen, *Angew. Chem., Int. Ed.* **1968**, *7*, 321-406. In view of this controversy, we still kept the term annulation throughout our publication, as it is accepted as correct by all scientists in the field. We let the reader make his own choice if he prefers to use the word cycloaddition.

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[5] For a review on the stereoselective synthesis of tetrahydrofurans, see: J. P. Wolfe, M. B. Hay, *Tetrahedron* **2007**, *63*, 261-290.

[6] The highest d.r. obtained in catalytic reactions with prochiral ketones is 3.7:1 for intermolecular reactions (ref. 4d) and >95:5 for intramolecular ones (ref. 4e).

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[9] *Modified Nucleosides: in Biochemistry, Biotechnology and Medicine*, (Ed: P. Herdewijn), WILEY-VCH, Weinheim, **2008**.

[10] A 2-aminoTHF substructure search on PubChem Compound database gave >164,000 entries for the compounds with tertiary C5 (3299 active in bioassays), and 3 entries for those with quaternary C5. For PubChem Compound database see: E. Bolton, Y. Wang, P. A.Thiessen, S. H. Bryant, in *Annual Reports in Computational Chemistry*, Vol. 4, AMERICAN CHEMICAL SOCIETY, Washington, DC, **2008**.

[11] The crystal structure of **3aa** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 858768.

[12] All the Lewis acid that gave some conversion afforded **3aa** as a single diastereoisomer, except $FeCl_3$-Al_2O_3 and $Sc(OTf)_3$ (see supporting information for details).

[13] The crystal structure of *epi*-**3aa** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 858769.

[14] According to Johnson and coworkers (ref. 3i), intermediates **II** and **III** would afford respectively the 2,5-cis tetrahydrofuran **3aa** and the 2,5-trans tetrahydrofuran *epi*-**3aa.** Nevertheless, pathways leading from **II** to *epi*-**3aa** and from **III** to **3aa** could also be conceived.

[15] 2,5-relative stereochemistry was assigned on the basis of x-ray diffraction analysis performed on compound **3aa** and extended to the other compounds of the series (**3bb-3am**) on the basis of the regularity in their NMR spectra.

[16] See supporting information for details.

[17] Enantioenriched **1a** was obtained by preparative HPLC separation on chiral stationary phase (see supporting information for details).

[18] The [3+2] annulation of aminocyclopropanes with aldehydes was not enantiospecific (see ref. 7f).

[19] The most probable stereochemical course for the enantiospecific reaction is inversion of the stereochemistry next to nitrogen, as observed by Johnson (see reference 2b). However, this still needs to be established experimentally and will be the topic of further investigation in our laboratory.

[20] The crystal structure of **3am** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: CCDC 861951.

[21] K. Sapeta, M. A. Kerr, *J. Org. Chem* **2007**, *72*, 8597-8599.

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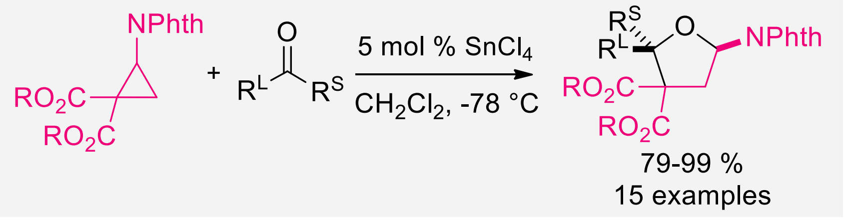
Enantiospecific Annulation

*Fides Benfatti, Florian de Nanteuil and Jérôme Waser** Page – Page

Catalytic Enantiospecific [3+2] Annulation of Aminocyclopropanes with Ketones



The first enantiospecific [3+2] annulation of D-A aminocyclopropanes with ketones is reported herein (see scheme; Phth = phthaloyl). The reaction is catalyzed by 5 mol % of tin(IV) chloride at -78 °C and gives aminotetrahydrofurans bearing a C5-quaternary stereocenter in high yield, diastereoselectivity and enantiospecificity.

Table of contents

List of Abbreviations

Ac	acetyl
DCM	dichloromethane
d.r.	diastereomeric ratio
eq	equivalent
ESI	Electrospray Ionization
Et	ethyl
h	hours
hept	heptet
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectra
iPr	isopropyl
M	molar mol/L
Me	methyl
Mp	melting point
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
OTf	Trifluoromethanesulfonate
Ph	phenyl
Phth	phthaloyl
R_f	Retention Factor
rt	room temperature
TMS	trimethylsilyl

1 Experimental procedures

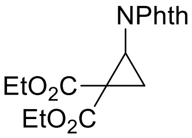
1.1 General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. CH_2Cl_2 was dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 30 ppm, Karl-Fischer titration). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC plastic plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a calibrated Büchi B-540 melting point apparatus using open glass capillaries. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration; interpretation). ^{13}C-NMR spectra were recorded with 1H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, sh = shoulder). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAK IC, IB or IA column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used. The ketones used in this study are all commercially available and were used as received.

1.2 Preparation of aminocyclopropanes 1a-b

Diethyl 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (1a)

Following a reported procedure[1], a two-neck flask equipped with a nitrogen inlet was loaded with 14 mg (0.018 mmol, 0.1 mol %) of bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] inside the glove box, then the flask was sealed with a rubber septum and evacuated from the glove box. A solution of *N*-vinyl-phthalimide (3.0 g, 18 mmol, 1 eq) in 30 mL of dry dichloromethane was added to the flask and the resulting green suspension was cooled down to 0 °C with an ice/water bath. A solution of diethyl-2-diazomalonate[2] (4.0 g, 21 mmol, 1.2 eq) in 20 mL of dichloromethane was added over five minutes. When the addition was complete, the reaction was allowed to warm to room temperature. After 5 h at room temperature, the solvent was removed under reduced pressure and the crude was directly purified by column chromatography (SiO_2, 9/1 to 7/3 (*n*-hexane: AcOEt). 5.4 g (16 mmol, 90 % yield) of **1a** as a colorless solid were obtained.



1a

R_f 0.36 (*n*-hex/EtOAc 6/4);

Mp 93 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (m, 2 H, *Phth*), 7.74 (m, 2 H, *Phth*), 4.30 (m, 2 H, *OCH_2*), 4.07 (m, 2 H, *OCH_2*), 3.71 (dd, 1 H, *J* = 8.5, 6.6 Hz, *N-C-H*), 2.74 (t, 1 H, *J* = 6.5 Hz, *CH_2*), 2.02 (dd, 1 H, *J* = 8.5, 6.4 Hz, *CH_2*), 1.34 (t, 3 H, *J* = 7.1 Hz, *CH_3*), 1.12 (t, 3 H, *J* = 7.1 Hz, *CH_3*);

^{13}C NMR (101 MHz, CDCl3) δ 168.2, 167.8, 166.4, 134.3, 131.6, 123.4, 62.0, 61.8, 34.7, 33.5, 19.2, 14.1, 13.8;

IR 2985 (w), 2938 (w), 2907 (w), 1783 (m), 1719 (s), 1614 (w), 1393 (s), 1321 (m), 1218 (s), 1133 (m), 719 (s);

HRMS (ESI) calcd for $C_{17}H_{18}NO_6^+$ $[M+H]^+$ 332.1129; found 332.1135.

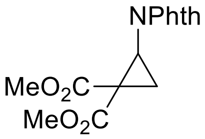
HPLC analysis: Chiracel IA (0.46 x 25 cm): 85:15 (hexane: *i*-PrOH), flow 1.0mL/min. t_1: 9.0 min, t_2: 11.2 min.

Preparative HPLC: Chiracel IA (20 x 250 mm), 85:13.5:1.5 (hexane: AcOEt: *i*-PrOH), flow 10 mL/min. t_1 = 18 min, $[\alpha]_D^{25}$ 115 (er: 98:2, *c* 1.0, $CHCl_3$), t_2 = 24 min, $[\alpha]_D^{25}$ -115 (er: 98:2, *c* 1.0, $CHCl_3$).

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1,1-dicarboxylate (1b)

[1] De Nanteuil, F.; Waser, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 12075-12079.
[2] P. Wyatt, A. Hudson, J. Charmant, A. G. Orpen, H. Phetmung, *Org. Biomol. Chem.* **2006**, *4*, 2218

Following the same procedure described above, using 2.5 g (14 mmol, 1 eq) of *N*-vinyl-phthalimide, 2.5 g (15 mmol, 1.1 eq) of dimethyl-2-diazomalonate and 11 mg (0.014 mmol, 0.1 mol %) of bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)], 3.40 g (11.2 mmol, 78 % yield) of **1b** were isolated as a colorless solid.



1b

$\mathbf{R_f}$ 0.27 (*n*-hex/EtOAc 6/4);

Mp 124-125 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2 H, *Phth*), 7.75 (m, 2 H, *Phth*), 3.85 (s, 3 H, *OMe*), 3.72 (dd, 1 H, *J* = 8.5, 6.6 Hz, *N-CH*), 3.64 (s, 3 H, *OMe*), 2.73 (dd, 1 H, *J* = 6.5, 6.5 Hz, *CH_2*), 2.06 (dd, 1H, *J* = 8.5, 6.4 Hz, *CH_2*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 167.8, 166.9, 134.3, 131.4, 123.5, 53.1, 53.0, 34.9, 33.1, 19.6;

IR 2956 (w), 1783 (w), 1727 (s), 1468 (w), 1439 (w), 1399 (m), 1329 (m), 1294 (m), 1222 (m), 1134 (w), 909 (w), 876 (w), 720 (m);

HRMS (ESI) calcd for $C_{15}H_{14}NO_6^+$ $[M+H]^+$ 304.0816; found 304.0804.

1.3 Standard procedure for the screening of Lewis acids

1.3.1 Reactions with acetophenone

All the reactions were carried out under nitrogen in glass vials equipped with rubber septa and Teflon-coated stir bars. The Lewis acid (4 μmol, 20 mol %) was added to the vial in the glove box, followed by a solution of aminocyclopropane **1a** (20 μmol, 6.6 mg, 1 equiv.) and acetophenone **2a** (30 μmol, 3.5 μL, 1.5 equiv.) in anhydrous dichloromethane (0.1 M, 0.2 mL) was added under nitrogen. The mixture was stirred for 90 min at the indicated temperature, and then it was diluted with dichloromethane (0.5 mL) and flushed through a short plug of silica gel. The solvent was removed *in vacuo*, then a ^{1}H-NMR sample was prepared by dissolving the crude mixture in $CDCl_3$ (0.7 mL) and a standard hexamethyldisiloxane solution (0.01 M, 0.111 mL) was added. The ^{1}H-NMR yield was calculated according to the following calibration curve.

<u>^{1}H-NMR calibration curve</u>

Hexamethyldisiloxane (4.3 μL, 0.02 mmol) was dissolved in $CDCl_3$ (2.0 mL), to give a 0.01 M standard solution. Compound **3aa** (4.5 mg, 0.01 mmol) was dissolved in $CDCl_3$ (0.7 mL), then the following volumes of standard 0.01 M solution were added: 55.0 μL for sample A (0.55 μmol); 13.2 μL for sample B (0.13 μmol); 23.1 μL for sample C (0.23 μmol); 46 μL for sample D (0.46 μmol); 139 μL for sample E (1.39 μmol) .

[1]H NMR spectra were acquired for solution A-E, and the ratios between the integrals of the signal at δ 6.31 (dd, 1 H, *J* = 8.2, 7.0 Hz, *CH*NPhth) of **3aa** and the signal at δ 0.06 (s, 1 H, TMS) of hexamethyldisiloxane were determined. These experimental ratios were plotted vs. the ratios mmol **3aa** / mmol hexamethyldisiloxane to give the calibration graph.

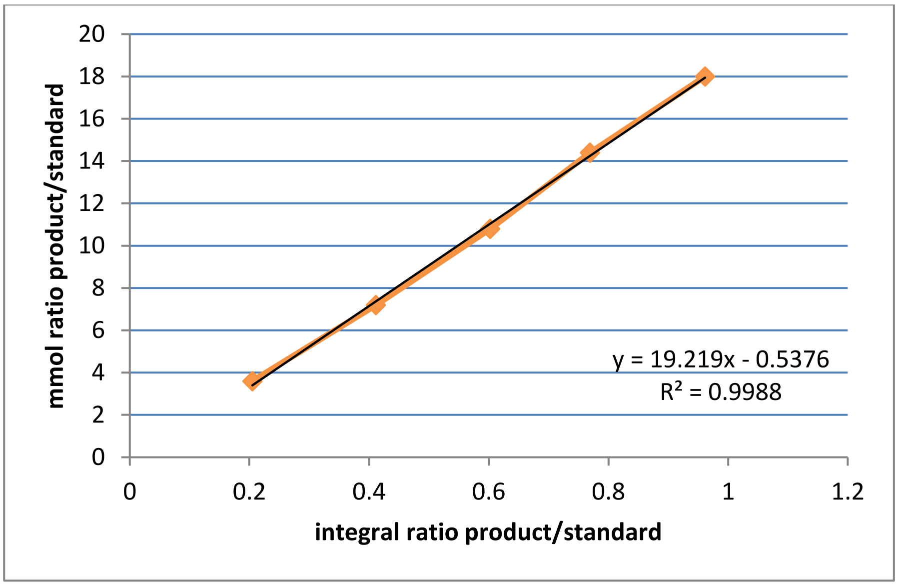


Table S1. Screening of Lewis Acids in the reaction with acetophenone.[a]

entry	Lewis acid	yield (%)	d.r. (*cis*:*trans*)
1	$FeCl_3$-Al_2O_3	20	> 1:20
2	$SnCl_4$[b]	100	> 20:1
3	$AuCl_3$	50	> 20:1
4	$Cu(OTf)_2$	10	n.d.
5	$In(OTf)_3$	33	> 20:1
6	$Sc(OTf)_3$	25	5:1
7	$Sn(OTf)_2$	13	> 20:1
8	$Hf(OTf)_4$	decomp.	-

[a] No reaction with: $Zn(OTf)_2$, $TiCl_4$, AuCl, $EtAlCl_2$, Me_2AlCl, $CeCl_3$. [b] Performed at -78 °C.

1.3.2 Reactions with cyclohexanone

All the reactions were carried out under nitrogen in glass vials equipped with rubber septa and Teflon-coated stir bars. The Lewis acid (4 µmol, 20 mol %) was added to the vial in the glove box, followed by a solution of aminocyclopropane **1a** (20 µmol, 6.6 mg, 1 equiv.) and cyclohexanone **2i** (30 µmol, 3.1 µL, 1.5 equiv.) in anhydrous dichloromethane (0.1 M, 0.2 mL) was added under nitrogen. The mixture was stirred for 90 min at the indicated temperature, and then it was diluted with dichloromethane (0.5 mL) and flushed through a short plug of silica gel. The solvent was removed *in vacuo*, then a ^{1}H-NMR sample was prepared by dissolving the crude mixture in $CDCl_3$ (0.7 mL) and a standard hexamethyldisiloxane solution (0.01 M, 0.111 mL) was added. The ^{1}H-NMR yield was calculated according to the following calibration curve.

^{1}H-NMR calibration curve

Hexamethyldisiloxane (4.3 µL, 0.02 mmol) was dissolved in $CDCl_3$ (2.0 mL), to give a 0.01 M standard solution. Compound **3aj** (6.6 mg, 15 µmol) was dissolved in $CDCl_3$ (0.7 mL), then the following volumes of standard 0.01 M solution were added: 88 µL for sample A (0.88 µmol); 22 µL for sample B (0.22 µmol); 37 µL for sample C (0.37 µmol); 74 µL for sample D (0.74 µmol); 222 µL for sample E (2.22 µmol).

^{1}H NMR spectra were acquired for solution A-E, and the ratios between the integrals of the signal at δ 6.39 (dd, 1 H, J = 9.4, 6.6 Hz, *CH*NPhth) of **3aj** and the signal at δ 0.06 (s, 1 H, TMS) of hexamethyldisiloxane were determined. These experimental ratios were plotted vs. the ratios mmol 3ai / mmol hexamethyldisiloxane to give the calibration graph.

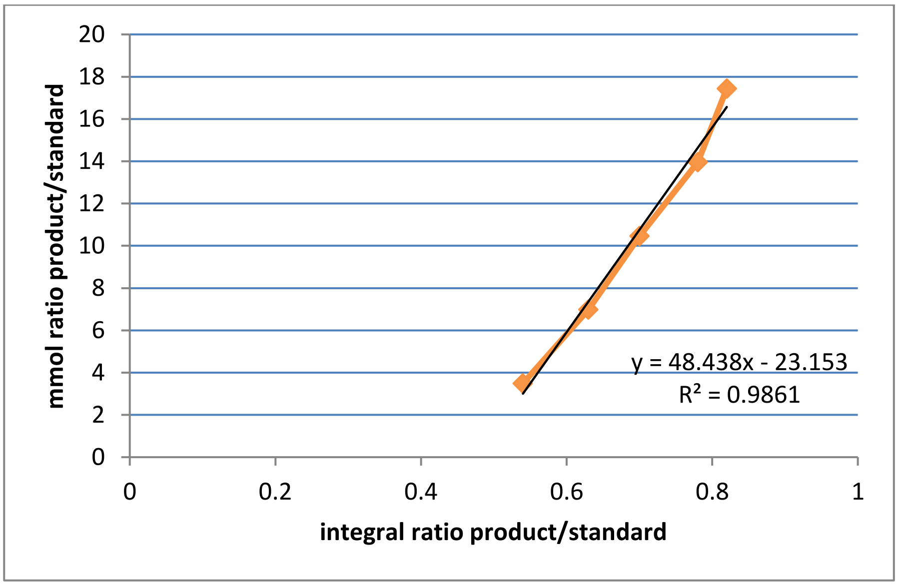


Table S2. Screening of Lewis Acids in the reaction with cyclohexanone.[a]

entry	Lewis acid	yield (%)
1	$FeCl_3$-Al_2O_3	100
2	$SnCl_4$[b]	100
3	$InCl_3$	80
4	AuCl	60

5	$Cu(OTf)_2$	40
6	$In(OTf)_3$	80
7	$Sc(OTf)_3$	100
8	$Sn(OTf)_2$	70
9	$Hf(OTf)_4$	90

[a] No reaction with: $Zn(OTf)_2$, AgOTf, MgI_2. [b] Performed at -78 °C.

1.4 Standard procedure for testing the dependence of d.r. on temperature and $SnCl_4$ loading (Table 2)

In a two-neck flask equipped with a nitrogen inlet, aminocyclopropane **1a** (0.20 mmol, 66 mg, 1 equiv) and acetophenone **2a** (0.30 mmol, 35 μL, 1.5 equiv) were dissolved in anhydrous dichloromethane (2 mL) at -78 °C. After 5 min, $SnCl_4$ (5-20 mol %, 0.01-0.04 mmol, 23- 92 μL of 0.43 M solution in dichloromethane)[3] was added. The mixture was stirred under nitrogen at -78 °C for 90 min, then it was quenched by the addition of triethylamine (0.2 mL) and subsequently flushed through a short plug of silica gel, eluting with EtOAc (5 mL). The solvent was removed *in vacuo*, affording the crude reaction mixture, which was submitted to ^{1}H NMR analysis for d.r. determination.

1.5 Standard procedure for the $SnCl_4$-catalysed [3+2] annulation of aminocyclopropanes with ketones

In a two-neck flask equipped with a nitrogen inlet, aminocyclopropane **1a-b** (0.20 mmol, 60-66 mg, 1 equiv.) and ketone **2a-m** (1.5 equiv for **2a-l**, 3 equiv for **2m**) were dissolved in anhydrous dichloromethane (2 mL) at -78 °C. After 5 min, $SnCl_4$ (5 mol %, 0.01 mmol, 23 μL of 0.43 M solution in dichloromethane) was added. The mixture was stirred under nitrogen at -78 °C for 90 min, then it was quenched by the addition of triethylamine (0.2 mL) and subsequently flushed through a short plug of silica gel, eluting with EtOAc (5 mL). The solvent was removed *in vacuo*, affording the crude reaction mixture, which was submitted to ^{1}H NMR analysis to determine the d.r. before purification *via* flash chromatography (SiO_2, 8/2 to 1/1 (*n*-hexane: AcOEt)).

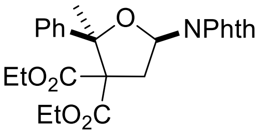
[3] Prepared by diluting 100 μL of $SnCl_4$ (0.86 mmol) in 2 mL of anhydrous dichloromethane.

2 Scope of the reaction

Diethyl 5-(1,3-dioxoisoindolin-2-yl)-2-methyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (3aa)

Flash chromatography afforded the title compound (90 mg, 0.20 mmol, 99% yield) as a colorless solid, as a single diastereoisomer (d.r. > 20:1).

R_f 0.58 (*n*-hex/EtOAc 6/4);



3aa

Mp 88-90 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, 2 H, *J* = 5.5, 3.0 Hz, Phth), 7.78 (dd, 2 H, *J* = 5.5, 3.0 Hz, Phth), 7.69 (d, 2 H, *J* = 7.2 Hz, Ph), 7.35-7.20 (m, 3 H, Ph), 6.31 (dd, 1 H, *J* = 8.2, 7.0 Hz, *CH*NPhth), 4.36 (q, 2 H, *J* = 7.1 Hz, O$CH_2$$CH_3$), 3.92-3.69 (m, 3 H, O$CH_2$$CH_3$ + CH_2CHNPhth), 3.13 (dd, 1 H, *J* = 13.9, 7.0 Hz, CH_2CHNPhth), 1.80 (s, 3H, CH_3), 1.39 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3), 0.97 (t, 3 H, *J* = 7.1 Hz, OCH_2CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 164.5, 163.4, 140.3, 131.8, 129.3, 125.2, 124.8, 124.1, 121.5, 85.9, 77.8, 67.9, 62.7, 61.9, 37.3, 28.2, 16.6, 16.2;

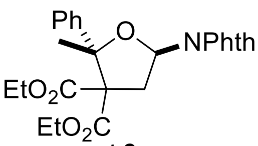
IR 3060 (w), 2984 (w), 2940 (w), 2905 (w), 1782 (m), 1721 (s), 1612 (w), 1469 (w), 1447 (w), 1368 (s), 1301 (m), 1256 (m), 1219 (m), 1193 (w), 1138 (m), 1112 (m), 1095 (m), 1065 (m), 1031 (m), 1022 (m), 981 (w), 908 (m), 870 (w), 767 (m), 719 (s), 702 (m), 657 (w);

HRMS (ESI) calcd for $C_{25}H_{25}NNaO_7^+$ $[M+Na]^+$ 474.1523; found 474.1528.

HPLC analysis: Chiracel IA: 85:15 (hexane: *i*-PrOH), flow 1.0 mL/min. t_1 = 8.9 min, $[\alpha]_D^{25}$ -55 (er: 97.5:2.5, *c* 0.5, $CHCl_3$), t_2 = 13.0 min.

Diethyl 5-(1,3-dioxoisoindolin-2-yl)-2-methyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (*epi*-3aa)

Flash chromatography afforded the title compound (19 mg, 0.04 mmol, 21% yield) as a colorless solid, as a single diastereoisomer (d.r. > 20:1).



epi-**3aa**

R_f 0.67 (*n*-hex/EtOAc 6/4);

Mp 118-119 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.71-7.75 (m, 3 H, Phth + Ar), 7.34-7.19 (m, 4 H, Ph), 6.72 (dd, 1 H, *J* = 9.8, 6.2 Hz, *CH*NPhth), 4.40-4.26 (m, 2 H, O$CH_2$$CH_3$), 4.02 (dd, 1 H, *J* = 13.3, 9.8 Hz, CH_2CHNPhth), 3.71 (dq, 1 H, *J* = 10.7, 7.2 Hz, O$CH_2$$CH_3$), 3.58 (dq, 1 H, *J* = 10.7, 7.2 Hz, O$CH_2$$CH_3$), 2.70 (dd, 1 H, *J* = 13.3, 6.2 Hz, CH_2CHNPhth), 2.00 (s, 3H, CH_3), 1.36 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3), 0.83 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3);

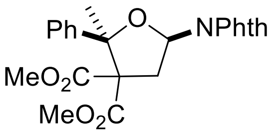
^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.5, 168.2, 167.9, 143.3, 134.4, 131.9, 127.6, 127.2, 126.2, 123.6, 87.8, 79.6, 68.8, 61.7, 34.3, 28.6, 14.0, 13.3;[4]

IR 2983 (w), 2940 (w), 1781 (w), 1720 (s), 1609 (w), 1495 (w), 1469 (w), 1447 (w), 1369 (m), 1332 (w), 1300 (w), 1275 (m), 1250 (m), 1217 (w), 1131 (m), 1115 (w), 1090 (m), 1066 (m), 1033 (w), 1018 (w), 990 (w), 909 (w), 868 (w), 767 (m), 730 (m), 704 (m), 659 (w);

HRMS (ESI) calcd for $C_{25}H_{25}NNaO_7^+$ $[M+Na]^+$ 474.1523; found 474.1527.

Dimethyl 5-(1,3-dioxoisoindolin-2-yl)-2-methyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (3ba)

Flash chromatography afforded the title compound (81 mg, 0.19 mmol, 96% yield) as a colorless solid, as a single diastereoisomer (d.r. > 20:1).



3ba

$\mathbf{R_f}$ 0.48 (*n*-hex/EtOAc 6/4);

Mp 148-150 °C;

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.93 (dd, 2 H, *J* = 5.4, 3.0 Hz, Phth), 7.79 (dd, 2 H, *J* = 5.4, 3.0 Hz, Phth), 7.65 (d, 2 H, *J* = 7.3 Hz, Ph), 7.33 (t, 1 H, *J* = 7.3 Hz, Ph), 7.29-7.22 (m, 2 H, Ph), 6.31 (pseudo t, 1 H, *J* = 7.2 Hz, *CH*NPhth), 3.90 (s, 3 H, OCH_3), 3.93-3.83 (m, 1 H, CH_2CHNPhth), 3.38 (s, 3 H, OCH_3), 3.15 (dd, 1 H, *J* = 13.9, 7.2 Hz, CH_2CHNPhth), 1.79 (s, 3H, CH_3);

^{13}**C NMR** (101 MHz, $CDCl_3$) δ 169.7, 168.9, 167.5, 143.0, 134.4, 131.8, 127.5, 127.2, 126.3, 123.7, 86.6, 77.9, 67.5, 53.1, 52.3, 35.6, 25.9;

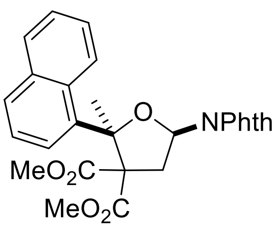
IR 2955 (w), 1783 (w), 1724 (m), 1436 (w), 1375 (m), 1259 (w), 1140 (w), 1068 (w), 907 (s), 730 (s), 703 (m), 651 (m), 639 (w);

HRMS (ESI) calcd for $C_{23}H_{21}NNaO_7^+$ $[M+Na]^+$ 446.1210; found 446.1232.

Dimethyl 5-(1,3-dioxoisoindolin-2-yl)-2-methyl-2-(naphthalen-1-yl)dihydrofuran-3,3(2H)-dicarboxylate (3bb)

Flash chromatography afforded the title compound (75 mg, 0.16 mmol, 79% yield) as a colorless solid, as a single diastereoisomer (d.r. > 20:1).

$\mathbf{R_f}$ 0.52 (*n*-hex/EtOAc 6/4);



3bb

Mp 211-213 °C;

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.67 (d, 1 H, *J* = 8.5 Hz, Naphth), 7.97 (d, 1 H, *J* = 7.2 Hz, Naphth), 7.91 (dd, 2 H, *J* = 5.4, 3.0 Hz, Phth), 7.83-7.70 (m, 4 H, Naphth + Phth), 7.50-7.35 (m, 3 H, Naphth) 6.33

[4] Two carbons (O**C**H_2CH_3) are overlapping.

(dd, 1 H, J = 8.4, 6.8 Hz, *CH*NPhth), 3.98 (s, 3 H, OCH_3), 4.05-3.93 (m, 1 H, *CH2*CHNPhth), 3.24 (dd, 1 H, J = 13.6, 6.8 Hz, *CH2*CHNPhth), 3.18 (s, 3 H, OCH_3), 2.00 (s, 3H, CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 170.0, 167.5, 139.0, 134.4, 131.7, 130.6, 128.9, 128.5, 126.7, 125.3, 124.8, 124.7, 123.7, 89.1, 77.6, 68.1, 53.2, 52.3, 36.1, 27.3;[5]

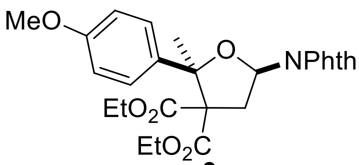
IR 3050 (w), 2952 (w), 1783 (w), 1721 (s), 1468 (w), 1435 (w), 1371 (m), 1301 (w), 1259 (m), 1222 (m), 1138 (m), 1108 (w), 1088 (m), 1059 (m), 1032 (m), 1031 (m), 1005 (w), 994 (w), 971 (w), 910 (m), 871 (w), 807 (m), 780 (m), 724 (s), 684 (w), 672 (m), 649 (m), 627 (w), 613 (w);

HRMS (ESI) calcd for $C_{27}H_{23}NNaO_7^+$ $[M+Na]^+$ 496.1367; found 496.1380.

Dimethyl 5-(1,3-dioxoisoindolin-2-yl)-2-(4-methoxyphenyl)-2-methyldihydrofuran-3,3(2H)-dicarboxylate (3ac)

Flash chromatography afforded the title compound (82 mg, 0.18 mmol, 90% yield) as a colorless solid, as an inseparable mixture of diastereoisomers; d.r. = 16:1 determined by integration of ^{1}H NMR signals: *δminor* 6.02 (dd), *δmajor* 6.31 ppm (dd).

Recrystallization from *i*PrOH afforded analytically pure *cis* isomer (d.r. > 20:1).



3ac

R_f 0.39 (*n*-hex/EtOAc 6/4);

Mp 132-134 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, 2 H, J = 5.5, 3.0 Hz, Phth), 7.78 (dd, 2 H, J = 5.5, 3.0 Hz, Phth), 7.59 (d, 2 H, J = 9.0 Hz, Ar), 6.86 (d, 2 H, J = 9.0 Hz, Ar), 6.31 (dd, 1 H, J = 8.0, 6.9 Hz, *CH*NPhth), 3.91 (dd, 1 H, J = 13.8, 8.0 Hz, *CH2*CHNPhth), 3.88 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.41 (s, 3 H, OCH_3), 3.06 (dd, 1 H, J = 13.8, 6.9 Hz, *CH2*CHNPhth), 1.79 (s, 3H, CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 168.8, 167.5, 158.7, 135.1, 134.4, 131.8, 127.7, 123.7, 112.8, 86.5, 78.0, 67.5, 55.2, 53.0, 52.3, 35.4, 25.8;

IR 2998 (w), 2954 (w), 2839 (w), 1782 (m), 1721 (s), 1612 (w), 1515 (m), 1467 (w), 1435 (m), 1373 (s), 1251 (s), 1183 (m), 1139 (m), 1078 (m), 1033 (m), 914 (m), 832 (m), 724 (s), 637 (m);

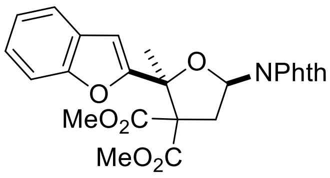
HRMS (ESI) calcd for $C_{24}H_{24}NO_8^+$ $[M+H]^+$ 454.1496; found 454.1493.

Dimethyl 2-(benzofuran-2-yl)-5-(1,3-dioxoisoindolin-2-yl)-2-methyldihydrofuran-3,3(2H)-dicarboxylate (3bd)

[5] Two C of the naphthyl group are not resolved.

Flash chromatography afforded the title compound (87 mg, 0.19 mmol, 95% yield) as a colorless solid, as an inseparable mixture of diastereoisomers; d.r. = 4:1 determined by integration of ^{1}H NMR signals: *δminor* 6.68 (dd), *δmajor* 6.53 ppm (dd).

Recrystallization from *i*PrOH gave increased d.r. in favour of the *cis* isomer (14:1).



3bd

R$_f$ 0.46 (*n*-hex/EtOAc 6/4);

Mp 90-92 °C;

^{1}H NMR (*cis* isomer, 400 MHz, $CDCl_3$) δ 7.87 (dd, 2 H, *J* = 5.4, 3.0 Hz, Phth), 7.73 (dd, 2 H, *J* = 5.4, 3.0 Hz, Phth), 7.55 (d, 1 H, *J* = 7.8 Hz, Ar), 7.49 (d, 1 H, *J* = 7.8 Hz, Ar), 7.27 (t, 1 H, *J* = 7.8 Hz, Ar), 7.18 (t, 1 H, *J* = 7.8 Hz, Ar), 6.90 (s, 1 H, Ar), 6.53 (dd, 1 H, *J* = 9.8, 5.8 Hz, *CH*NPhth), 4.59 (dd, 1 H, *J* = 13.4, 9.8 Hz, *CH$_2$*CHNPhth), 3.90 (s, 3 H, OCH_3), 3.54 (s, 3 H, OCH_3), 2.79 (dd, 1 H, *J* = 13.4, 5.8 Hz, *CH$_2$*CHNPhth), 1.94 (s, 3H, CH_3);

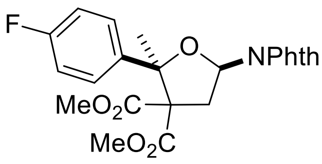
^{13}C NMR (*cis* isomer, 101 MHz, $CDCl_3$) δ 169.7, 168.0, 167.7, 158.2, 154.4, 134.3, 131.7, 128.1, 124.3, 123.6, 122.7, 121.3, 111.2, 104.3, 83.0, 80.3, 67.0, 53.2, 52.7, 34.0, 22.9;

IR 2954 (w), 1782 (w), 1720 (s), 1454 (w), 1435 (w), 1367 (m), 1327 (w), 1256 (s), 1217 (m), 1175 (w), 1140 (m), 1120 (m), 1072 (m), 1012 (w), 992 (m), 972 (m), 944 (w), 921 (w), 887 (w), 872 (m), 813 (w);

HRMS (ESI) calcd for $C_{25}H_{21}NNaO_8^+$ $[M+Na]^+$ 486.1159; found 486.1153.

Dimethyl 5-(1,3-dioxoisoindolin-2-yl)-2-(4-fluorophenyl)-2-methyldihydrofuran-3,3(2H)-dicarboxylate (3be)

Flash chromatography afforded the title compound (82 mg, 0.18 mmol, 93% yield) as a colorless solid, as a single diastereoisomer (d.r. > 20:1).



3be

R$_f$ 0.48 (*n*-hex/EtOAc 6/4);

Mp 152-153 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, 2 H, *J* = 5.5, 3.0 Hz, Phth), 7.79 (dd, 2 H, *J* = 5.5, 3.0 Hz, Phth), 7.64 (dd, 2 H, *J* = 8.8, 5.4 Hz, Ar), 7.01 (pseudo t, 2 H, *J* = 8.8 Hz, Ar), 6.30 (pseudo t, 1 H, *J* = 7.5 Hz, *CH*NPhth), 3.90 (s, 3 H, OCH_3), 3.85 (dd, 1 H, *J* = 14.0, 7.7 Hz, *CH$_2$*CHNPhth), 3.44 (s, 3 H, OCH_3), 3.16 (dd, 1 H, *J* = 14.0, 7.3 Hz, *CH$_2$*CHNPhth), 1.76 (s, 3H, CH_3);

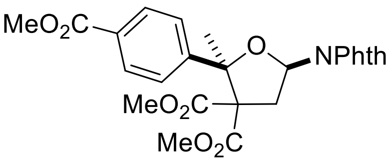
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 168.8, 167.5, 162.0 (d, $J_{C\text{-}F}$ = 246 Hz), 138.7 (d, $J_{C\text{-}F\ para}$ = 3 Hz), 134.5, 131.7, 128.1 (d, $J_{C\text{-}F\ meta}$ = 8 Hz), 123.8, 114.2 (d, $J_{C\text{-}F\ ortho}$ = 21 Hz), 86.2, 77.8, 67.3, 53.1, 52.4, 35.6, 26.0;

IR 2954 (w), 1723 (s), 1605 (w), 1511 (m), 1458 (w), 1436 (w), 1374 (s), 1275 (m), 1139 (m), 1078 (m), 1019 (w), 972 (w), 913 (m), 870 (w), 839 (w), 731 (m), 722 (s);

HRMS (ESI) calcd for $C_{23}H_{20}FNNaO_7^+$ $[M+Na]^+$ 464.1116; found 464.1139.

Dimethyl 5-(1,3-dioxoisoindolin-2-yl)-2-(4-(methoxycarbonyl)phenyl)-2-methyldihydrofuran-3,3(2H)-dicarboxylate (3bf)

Flash chromatography afforded the title compound (96 mg, 0.20 mmol, 99% yield) as a colorless solid, as as a single diastereoisomer (d.r. > 20:1).



3bf

R_f 0.25 (*n*-hex/EtOAc 6/4);

Mp 151-152 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, 2 H, *J* = 8.6 Hz, Ar), 7.93 (dd, 2 H, *J* = 5.5, 3.0 Hz, Phth), 7.79 (dd, 2 H, *J* = 5.5, 3.0 Hz, Phth), 7.71 (d, 2 H, *J* = 8.6 Hz, Ar), 6.29 (pseudo t, 1 H, *J* = 7.5 Hz, *CH*NPhth), 3.92 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.79 (dd, 1 H, *J* = 14.1, 7.3 Hz, CH_2CHNPhth), 3.44 (s, 3 H, OCH_3), 3.28 (dd, 1 H, *J* = 14.1, 7.7 Hz, CH_2CHNPhth), 1.73 (s, 3H, CH_3);

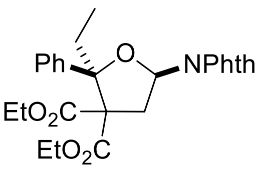
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 168.7, 167.4, 167.0, 148.2, 134.6, 131.7, 128.8, 128.0, 126.1, 123.8, 86.3, 77.4, 67.2, 53.2, 52.4, 52.0, 35.8, 25.9;

IR 2954 (w), 1717 (s), 1613 (w), 1436 (w), 1371 (m), 1277 (s), 1255 (s), 1193 (m), 1135 (m), 1114 (m), 1074 (m), 969 (w), 929 (w), 899 (w), 871 (w), 842 (w);

HRMS (ESI) calcd for $C_{25}H_{23}NNaO_9^+$ $[M+Na]^+$ 504.1265; found 504.1260.

Diethyl 5-(1,3-dioxoisoindolin-2-yl)-2-ethyl-2-phenyldihydrofuran-3,3(2H)-dicarboxylate (3ag)

Flash chromatography afforded the title compound (88 mg, 0.19 mmol, 95% yield) as a colorless solid, as a single diastereoisomer (d.r. > 20:1).



3ag

R_f 0.63 (*n*-hex/EtOAc 6/4);

Mp 104-105 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, 2 H, *J* = 5.4, 3.1 Hz, Phth), 7.77 (dd, 2 H, *J* = 5.4, 3.1 Hz, Phth), 7.64 (d, 2 H, *J* = 7.7 Hz, Ph), 7.37-7.17 (m, 3 H, Ph), 6.10 (pseudo t, 1 H, *J* = 7.6 Hz, *CH*NPhth), 4.37 (q, 2 H, *J* = 7.1 Hz, O$CH_2$$CH_3$), 3.90-3.81 (m, 2 H, O$CH_2$$CH_3$), 3.77 (dd, 1 H, *J* = 14.0, 7.4 Hz, CH_2CHNPhth), 3.30 (dd, 1 H, *J* = 14.0, 7.8 Hz, CH_2CHNPhth), 2.19-1.99 (m, 2 H, $CH_2$$CH_3$), 1.39 (t, 3 H, *J* = 7.1 Hz, $OCH_2$$CH_3$), 0.96 (t, 3 H, *J* = 7.1 Hz, $OCH_2$$CH_3$), 0.71 (t, 3 H, *J* = 7.2 Hz, $CH_2$$CH_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 168.9, 167.4, 140.2, 134.4, 131.8, 127.2, 126.8, 126.7, 123.7, 88.8, 76.7, 67.9, 62.1, 61.3, 35.8, 29.2, 14.0, 13.5, 7.2;

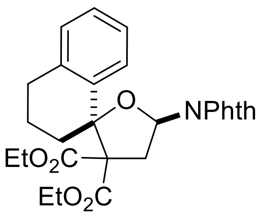
IR 2980 (w), 2940 (w), 1782 (w), 1720 (s), 1613 (w), 1468 (w), 1451 (w), 1368 (m), 1253 (m), 1218 (m), 1137 (m), 1071 (m), 1014 (m), 974 (m), 914 (m), 872 (m), 718 (s), 673 (m), 652 (m);

HRMS (ESI) calcd for $C_{26}H_{28}NO_7^+$ $[M+H]^+$ 466.1860; found 466.1856.

HPLC analysis: Chiracel IA: 85:15 (hexane: *i*-PrOH), flow 1.0 mL/min t_1 = 7.9 min, $[\alpha]_D^{25}$ -7 (er: 90:10, *c* 0.4, $CHCl_3$), t_2 = 10.9 min.

Diethyl 5-(1,3-dioxoisoindolin-2-yl)-3',4,4',5-tetrahydro-2'H,3H-spiro[furan-2,1'-naphthalene]-3,3-dicarboxylate (3ah)

Flash chromatography afforded the title compound (90 mg, 0.19 mmol, 94% yield) as a colorless solid, as a single diastereoisomer (d.r. > 20:1). The assignment of the 2,5-relative configuration was made on the basis of the similarity in ^{1}H NMR spectra between **3ah** and epi-**3aa**. The 2,5-*cis* compounds derived from aromatic ketones have the *CH*NPhth signal between δ = 6.10-6.33 ppm, while *epi*-**3aa** and **3ah** have this signal at δ = 6.72 and 6.65 ppm respectively.



3ah

$\mathbf{R_f}$ 0.59 (*n*-hex/EtOAc 6/4);

Mp 172-174 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, 1 H, *J* = 7.6, 1.2 Hz, Ar), 7.90 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.75 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.27 (td, 1 H, *J* = 7.6, 1.2 Hz, Ar), 7.15 (td, 1 H, *J* = 7.6, 1.2 Hz, Ar), 7.04 (dd, 1 H, *J* = 7.6, 1.2 Hz, Ar), 6.65 (dd, 1 H, *J* = 11.0, 4.6 Hz, *CH*NPhth), 4.42 (dd, 1 H, *J* = 13.2, 11.0 Hz, CH_2CHNPhth), 4.38-4.22 (m, 2 H, OCH_2CH_3), 3.81 (dq, 1H, *J* = 10.7, 7.0 Hz, OCH_2CH_3), 3.47 (dq, 1H, *J* = 10.7, 7.0 Hz, OCH_2CH_3), 2.86-2.69 (m, 2 H, CH_2Ar), 2.50 (dd, 1 H, *J* = 13.2, 4.6 Hz, CH_2CHNPhth), 2.46-2.37 (m, 1 H, CH_2CH_2Ar), 2.32-2.21 (m, 1 H, CH_2CH_2Ar), 2.08-1.95 (m, 1 H, $CH_2CH_2CH_2$Ar), 1.87-1.74 (m, 1 H, $CH_2CH_2CH_2$Ar), 1.36 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3), 0.87 (t, 3 H, *J* = 7.0 Hz, OCH_2CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 168.7, 167.8, 139.4, 138.0, 134.4, 131.8, 128.4, 127.9, 127.5, 126.2, 123.6, 85.4, 79.9, 69.3, 62.2, 61.3, 36.0, 35.2, 30.0, 19.8, 14.0, 13.3;

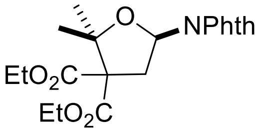
IR 2982 (w), 2939 (w), 2938 (w), 1781 (w), 1720 (s), 1468 (w), 1452 (w), 1367 (m), 1305 (m), 1258 (m), 1207 (w), 1195 (w), 1140 (m), 1112 (m), 1092 (m), 1061 (m), 1050 (m), 1014 (m), 1006 (m), 976 (w), 914 (m), 874 (m), 764 (m), 718 (s), 653 (m);

HRMS (ESI) calcd for $C_{27}H_{27}NNaO_7^+$ $[M+Na]^+$ 500.1680; found 500.1672.

HPLC analysis: Chiracel IA: 85:15 (hexane: *i*-PrOH), flow 1.0 mL/min. t_1 = 11.3 min, $[\alpha]_D^{25}$ 115 (er: 98:2, *c* 0.3, $CHCl_3$), t_2 = 15.4 min.

Diethyl 5-(1,3-dioxoisoindolin-2-yl)-2,2-dimethyldihydrofuran-3,3(2H)-dicarboxylate (3ai)

Flash chromatography afforded the title compound (74 mg, 0.19 mmol, 94% yield) as a colorless solid.



3ai

R_f 0.54 (*n*-hex/EtOAc 6/4);

Mp 126-127 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.74 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 6.37 (dd, 1 H, *J* = 9.3, 6.7 Hz, *CH*NPhth), 4.28 (q, 4 H, *J* = 7.0 Hz, O$CH_2$$CH_3$), 3.92 (dd, 1 H, *J* = 13.6, 9.3 Hz, CH_2CHNPhth), 2.56 (dd, 1 H, *J* = 13.6, 6.7 Hz, CH_2CHNPhth), 1.60 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.33 (t, 3 H, *J* = 7.0 Hz, $OCH_2$$CH_3$), 1.32 (t, 3 H, *J* = 7.0 Hz, $OCH_2$$CH_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 165.1, 164.7, 132.6, 130.2, 122.3, 84.7, 79.6, 67.9, 63.3, 63.0, 35.9, 30.0, 28.4, 17.6, 17.5;

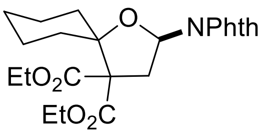
IR 2983 (w), 2941 (w), 1779 (w), 1717 (s), 1468 (w), 1366 (m), 1330 (m), 1266 (m), 1206 (m), 1158 (w), 1126 (m), 1086 (m), 1017 (m), 995 (m), 959 (w), 912 (w), 876 (m), 832 (w), 795 (w), 720 (s), 653 (m);

HRMS (ESI) calcd for $C_{20}H_{23}NNaO_7^+$ $[M+Na]^+$ 412.1367; found 412.1362.

HPLC analysis: Chiracel IA: 95:5 (hexane: *i*-PrOH), flow 1.0 mL/min. t_1 = 13.8 min, $[\alpha]_D^{25}$ +12 (er: 97.5:2.5, *c* 0.3, $CHCl_3$), t_2 = 14.7 min.

Diethyl 2-(1,3-dioxoisoindolin-2-yl)-1-oxaspiro[4.5]decane-4,4-dicarboxylate (3aj)

Flash chromatography afforded the title compound (86 mg, 0.20 mmol, 99% yield) as a colorless solid.



3aj

R_f 0.66 (*n*-hex/EtOAc 6/4);

Mp 97-98 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.76 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 6.39 (dd, 1 H, *J* = 9.4, 6.6 Hz, *CH*NPhth), 4.34-4.20 (m, 4 H, O$CH_2$$CH_3$), 3.83 (dd, 1 H, *J* = 13.5, 9.4 Hz, CH_2CHNPhth), 2.52 (dd, 1 H, *J* = 13.5, 6.6 Hz, CH_2CHNPhth), 2.48-2.41 (m, 1 H, *cyclohexyl*), 1.81-1.69 (m, 2 H, *cyclohexyl*), 1.66-1.44 (m, 6 H, *cyclohexyl*), 1.34 (t, 6 H, *J* = 7.1 Hz, $OCH_2$$CH_3$), 1.24-1.09 (m, 1 H, *cyclohexyl*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 168.3, 167.9, 134.2, 131.9, 123.5, 85.8, 78.9, 67.2, 61.8, 61.4, 33.3, 33.0, 32.8, 25.3, 22.8, 21.7, 14.1, 14.0;

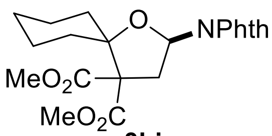
IR 2982 (w), 2937 (w), 2863 (w), 1779 (w), 1720 (s), 1468 (w), 1453 (w), 1367 (m), 1331 (w), 1302 (m), 1284 (m), 1265 (m), 1219 (w), 1207 (w), 1139 (m), 1118 (m), 1101 (m), 1073 (m), 1053 (w), 1018 (m), 989 (w), 874 (w), 796 (w), 730 (m), 656 (w), 656 (w);

HRMS (ESI) calcd for $C_{23}H_{28}NO_7^+$ $[M+H]^+$ 430.1860; found 430.1859.

HPLC analysis: Chiracel IA: 85:15 (hexane: *i*-PrOH), flow 1.0 mL/min. t_1 = 8.3 min, $[\alpha]_D^{25}$ -22 (er: 98:2, *c* 0.2, $CHCl_3$), t_2 = 9.4 min.

Dimethyl 2-(1,3-dioxoisoindolin-2-yl)-1-oxaspiro[4.5]decane-4,4-dicarboxylate (3bj)

Flash chromatography afforded the title compound (80 mg, 0.20 mmol, 99% yield) as a colorless solid.



3bj

R_f 0.57 (*n*-hex/EtOAc 6/4);

Mp 163-165 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, 2 H, *J* = 5.4, 3.0 Hz, Phth), 7.76 (dd, 2 H, *J* = 5.4, 3.0 Hz, Phth), 6.38 (dd, 1 H, *J* = 9.3, 6.7 Hz, *CH*NPhth), 3.96 (dd, 1 H, *J* = 13.6, 9.3 Hz, *CH_2*CHNPhth), 3.83 (s, 6 H, OCH_3), 2.55 (dd, 1 H, *J* = 13.6, 6.7 Hz, *CH_2*CHNPhth), 2.50-2.37 (m, 1 H, *cyclohexyl*), 1.82-1.65 (m, 2 H, *cyclohexyl*), 1.64-1.40 (m, 6 H, *cyclohexyl*), 1.30-1.07 (m, 1 H, *cyclohexyl*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 168.7, 167.9, 134.4, 131.8, 123.6, 86.0, 78.9, 67.3, 52.8, 52.6, 33.1, 33.1, 32.7, 25.2, 22.8, 21.7;

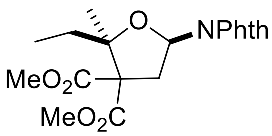
IR 2951 (w), 2936 (w), 2860 (w), 1776 (w), 1735 (s), 1717 (s), 1613 (w), 1455 (w), 1369 (m), 1355 (m), 1288 (m), 1267 (m), 1214 (m), 1138 (m), 1118 (m), 1090 (m), 1072 (m), 1053 (m), 993 (m), 946 (w), 912 (s), 874 (w), 729 (s), 651 (m);

HRMS (ESI) calcd for $C_{21}H_{24}NO_7^+$ $[M+H]^+$ 402.1547; found 402.1563.

Dimethyl 5-(1,3-dioxoisoindolin-2-yl)-2-ethyl-2-methyldihydrofuran-3,3(2H)-dicarboxylate (3bk)

Flash chromatography afforded the title compound (67 mg, 0.18 mmol, 89% yield) as a colorless solid, as an inseparable mixture of diastereoisomers; d.r. = 10:1 determined by integration of ^{1}H NMR signals: *δminor* 2.60 (dd), *δmajor* 2.50 ppm (dd).

Recrystallization from *i*PrOH gave increased d.r. in favour of the *cis* isomer (16:1).



3bk

R_f 0.50 (*n*-hex/EtOAc 6/4);

Mp 135-136 °C;

^{1}H NMR (*cis* isomer, 400 MHz, $CDCl_3$) δ 7.89 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.76 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 6.40 (dd, 1 H, *J* = 9.4, 6.7 Hz, *CH*NPhth), 3.96 (dd, 1 H, *J* = 13.7, 9.4 Hz, *CH_2*CHNPhth), 3.84 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 2.52 (dd, 1 H, *J* = 13.7, 6.7 Hz, *CH_2*CHNPhth), 2.23-2.09 (m, 1 H, *CH_2*CH_3), 1.73-1.59 (m, 1 H, *CH_2*CH_3), 1.39 (s, 3 H, CH_3), 0.87 (t, 3 H, CH_2*CH_3*);

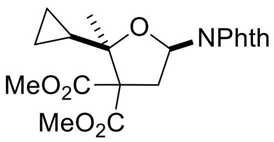
^{13}C NMR (*cis* isomer, 101 MHz, $CDCl_3$) δ 170.4, 168.7, 167.9, 134.4, 131.7, 123.6, 86.5, 79.2, 67.8, 52.9, 52.6, 32.9, 30.0, 20.7, 7.7;

IR 2985 (w), 2954 (w), 1782 (w), 1716 (s), 1467 (w), 1456 (w), 1435 (w), 1366 (m), 1358 (m), 1310 (m), 1267 (m), 1219 (m), 1205 (m), 1122 (m), 1087 (m), 1036 (m), 1017 (m), 990 (m), 972 (m), 914 (m), 887 (m), 779 (w), 722 (s), 651 (m);

HRMS (ESI) calcd for $C_{19}H_{22}NO_7^+$ $[M+H]^+$ 376.1391; found 376.1395.

Dimethyl 2-cyclopropyl-5-(1,3-dioxoisoindolin-2-yl)-2-methyldihydrofuran-3,3(2H)-dicarboxylate (3bl)

Flash chromatography afforded the title compound (74 mg, 0.19 mmol, 96% yield) as a colorless solid, as as a single diastereoisomer (d.r. > 20:1).



3bl

R_f 0.43 (*n*-hex/EtOAc 6/4);

Mp 178-180 °C;

^{1}H NMR (*cis* isomer, 400 MHz, THF-d8)[6] δ 7.85 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.79 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 6.26 (dd, 1 H, *J* = 9.9, 6.0 Hz, *CH*NPhth), 4.12 (dd, 1 H, *J* = 13.5, 9.9 Hz, *CH_2*CHNPhth), 3.75 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 2.39 (dd, 1 H, *J* = 13.5, 6.0 Hz, *CH_2*CHNPhth), 1.64-1.55 (m, 1 H, *cyclopropyl*), 1.18 (s, 3 H, CH_3), 0.64-0.57 (m, 1 H, *cyclopropyl*), 0.43-0.24 (m, 3 H, *cyclopropyl*);

^{13}C NMR (101 MHz, THF-d8) δ 170.8, 168.7, 168.0, 134.9, 132.8, 123.7, 85.9, 79.7, 68.0, 52.5, 52.0, 34.3, 19.6, 19.1, 3.8, 1.5;

IR 3011 (w), 2954 (w), 1781 (w), 1717 (s), 1436 (w), 1395 (w), 1369 (m), 1330 (m), 1270 (m), 1219 (m), 1205 (m), 1151 (w), 1118 (m), 1081 (m), 1050 (m), 1025 (w), 1013 (w), 993 (m), 974 (w), 923 (w), 887 (m);

HRMS (ESI) calcd for $C_{20}H_{22}NO_7^+$ $[M+H]^+$ 388.1391; found 388.1394.

Diethyl 2-(1,3-dioxoisoindolin-2-yl)-6-isopropyl-9-methyl-1-oxaspiro[4.5]decane-4,4-dicarboxylate (3am)

Flash chromatography afforded the title compound (85 mg, 0.175 mmol, 88% yield) as a colorless solid, as a single diastereoisomer (d.r. > 20:1).

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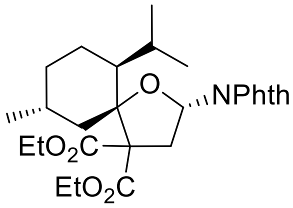
[6] The compound proved to be sensitive to traces of acid present in $CDCl_3$.



3am

$[\alpha]_D^{25}$ -23 (*c* 0.4, $CHCl_3$);

R$_f$ 0.75 (*n*-hex/EtOAc 6/4);

Mp 136-138 °C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 7.76 (dd, 2 H, *J* = 5.5, 3.1 Hz, Phth), 6.19 (dd, 1 H, *J* = 11.0, 4.0 Hz, *CH*NPhth), 4.32-4.19 (m, 4 H, O*CH$_2$*CH_3), 3.97 (dd, 1 H, *J* = 12.7, 11.0 Hz, *CH$_2$*CHNPhth), 2.58 (dd, 1 H, *J* = 12.7, 4.0 Hz, *CH$_2$*CHNPhth), 2.03 (dd, 1 H, *J* = 12.2, 4.2 Hz, *menthyl*), 1.81-1.55 (m, 6 H, *menthyl*), 1.52-1.24 (m, 2 H, *menthyl*), 1.33 (m, 6 H, OCH_2*CH$_3$*), 1.00-0.67 (m, 9H, *i*Pr + CH_3);

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 168.5, 168.0, 134.3, 131.8, 123.5, 89.9, 78.9, 66.7, 62.1, 61.6, 46.1, 44.5, 35.1, 34.2, 29.4, 27.8, 22.8, 22.6, 22.3, 19.1, 14.0, 13.9;

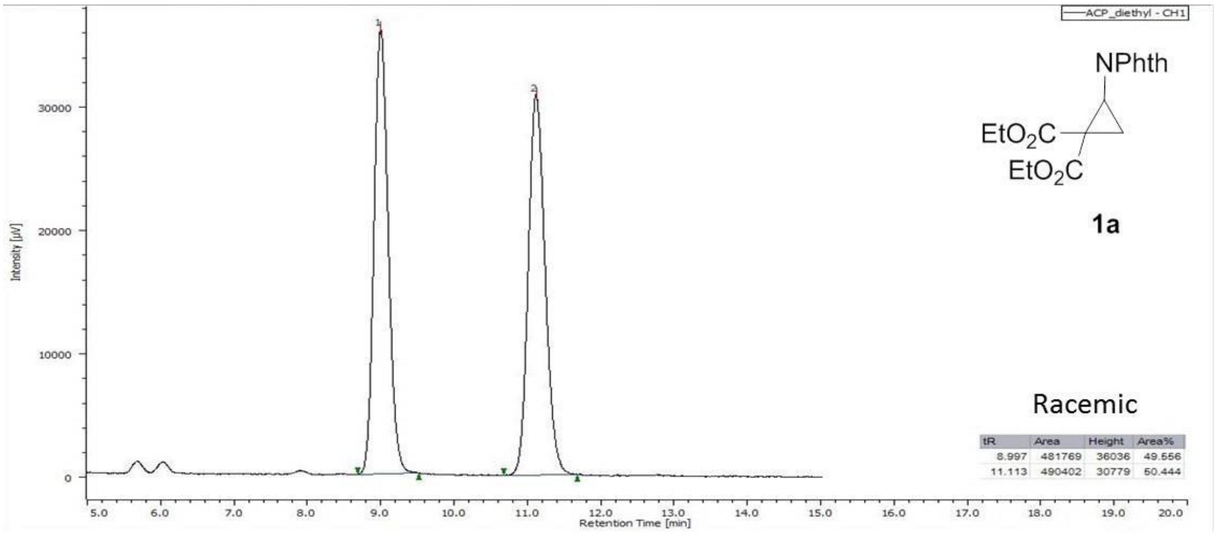
IR 2951 (w), 2931 (w), 2870 (w), 1782 (w), 1722 (s), 1467 (w), 1457 (w), 1368 (m), 1328 (w), 1299 (w), 1270 (w), 1250 (m), 1231 (m), 1208 (m), 1155 (w), 1130 (m), 1106 (m), 1087 (m), 1063 (m), 1030 (w), 1013 (m), 1002 (m), 985 (w), 943 (w), 912 (w), 873 (w), 849 (w);

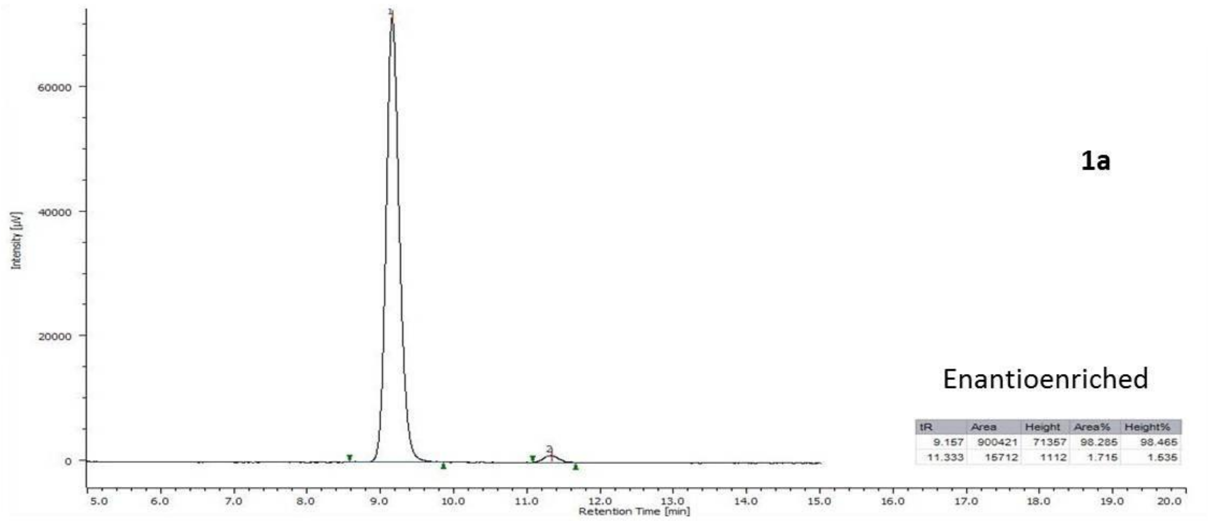
HRMS (ESI) calcd for $C_{27}H_{36}NO_7^+$ $[M+H]^+$ 486.2486; found 486.2493.

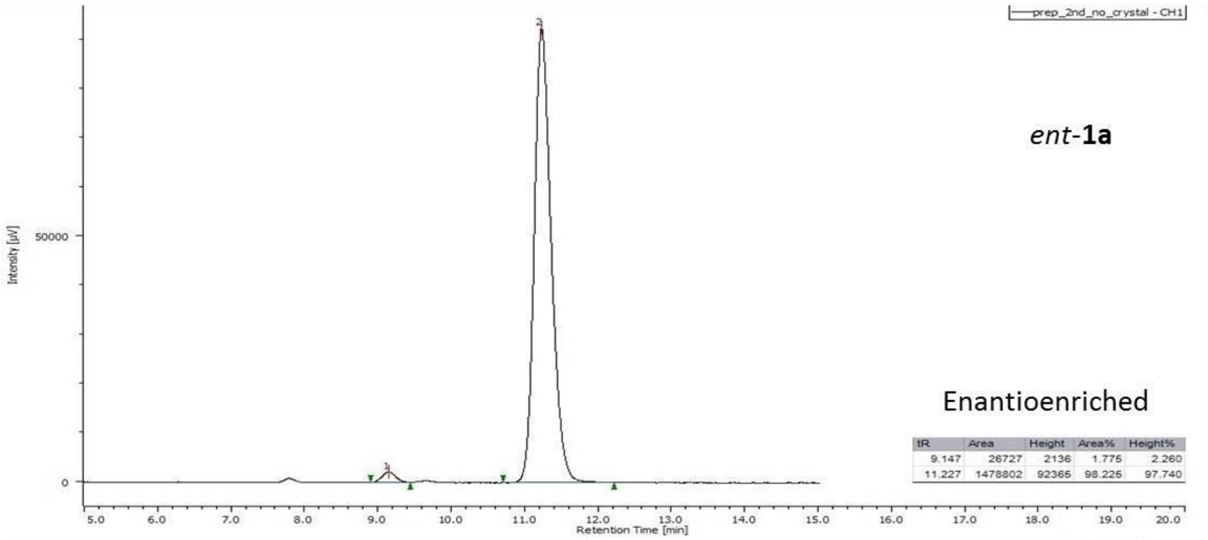
3 Enantiospecific reactions

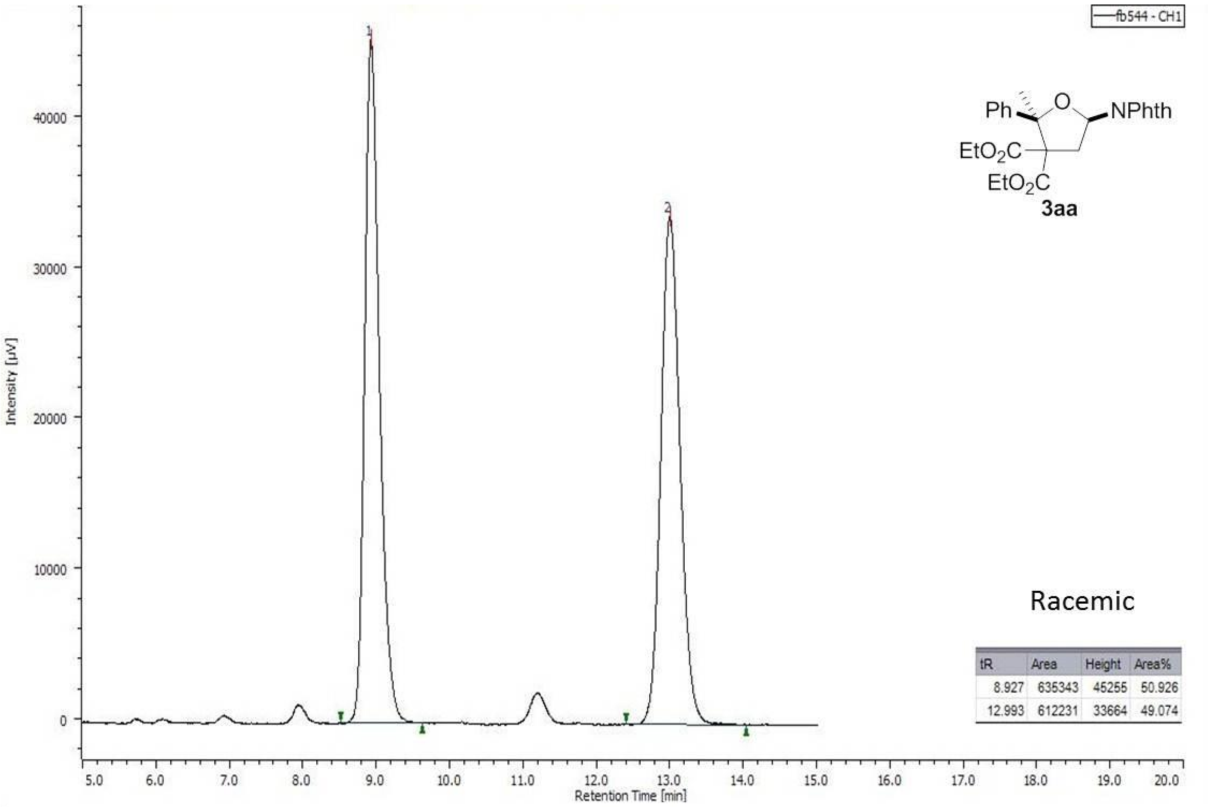
All reactions were performed on 16 mg (0.05 mmol, 1 eq) of enantioenriched aminocyclopropane **1a** (ee = 96%) or *ent*-**1a** (ee = 96%), following the standard procedure for the tin-catalysed [3+2] annulation (S8).

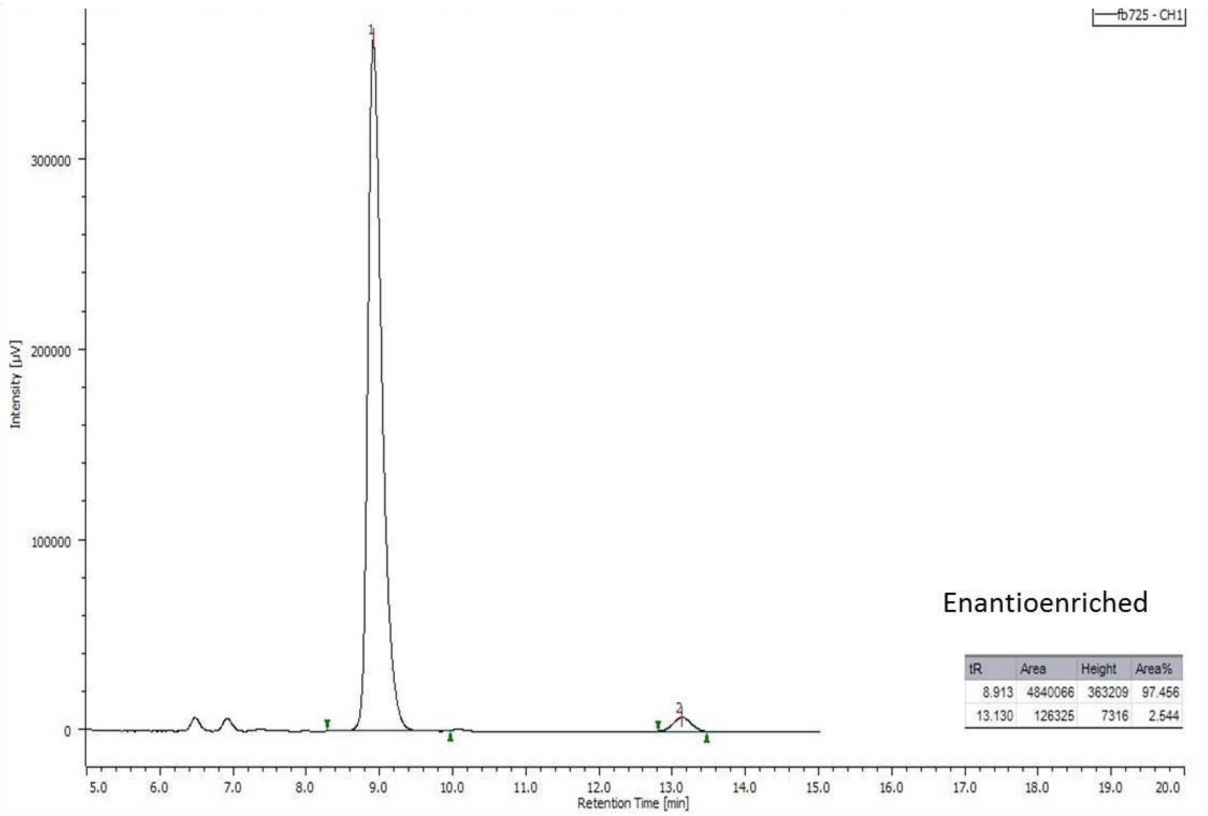
4 HPLC traces








fb544 - CH1
Ph
O
NPhth
EtO2C
EtO2C
3aa
Racemic
Intensity [µV]
Retention Time [min]
tR Area Height Area%
8.927 635343 46255 50.926
12.993 612231 33664 49.074


fb725 - CH1
Enantioenriched
Intensity [µV]
Retention Time [min]
tR Area Height Area%
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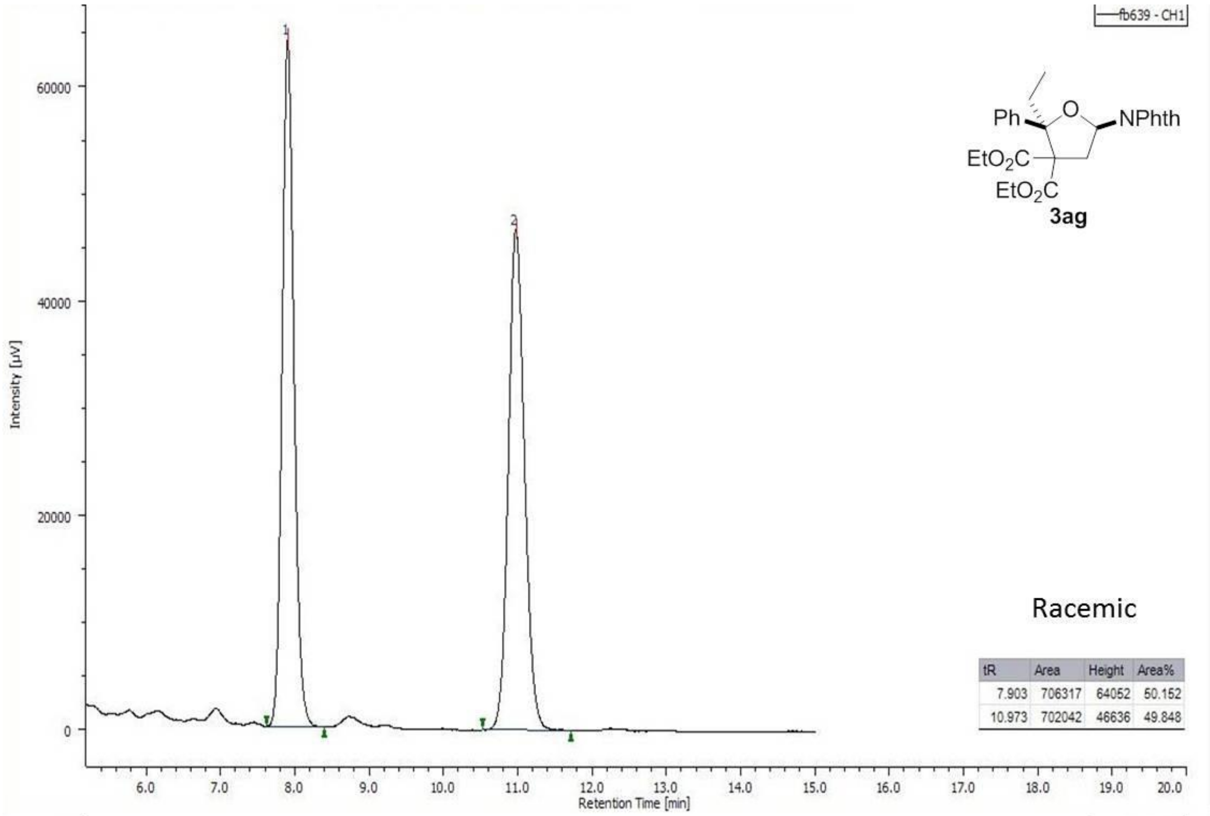
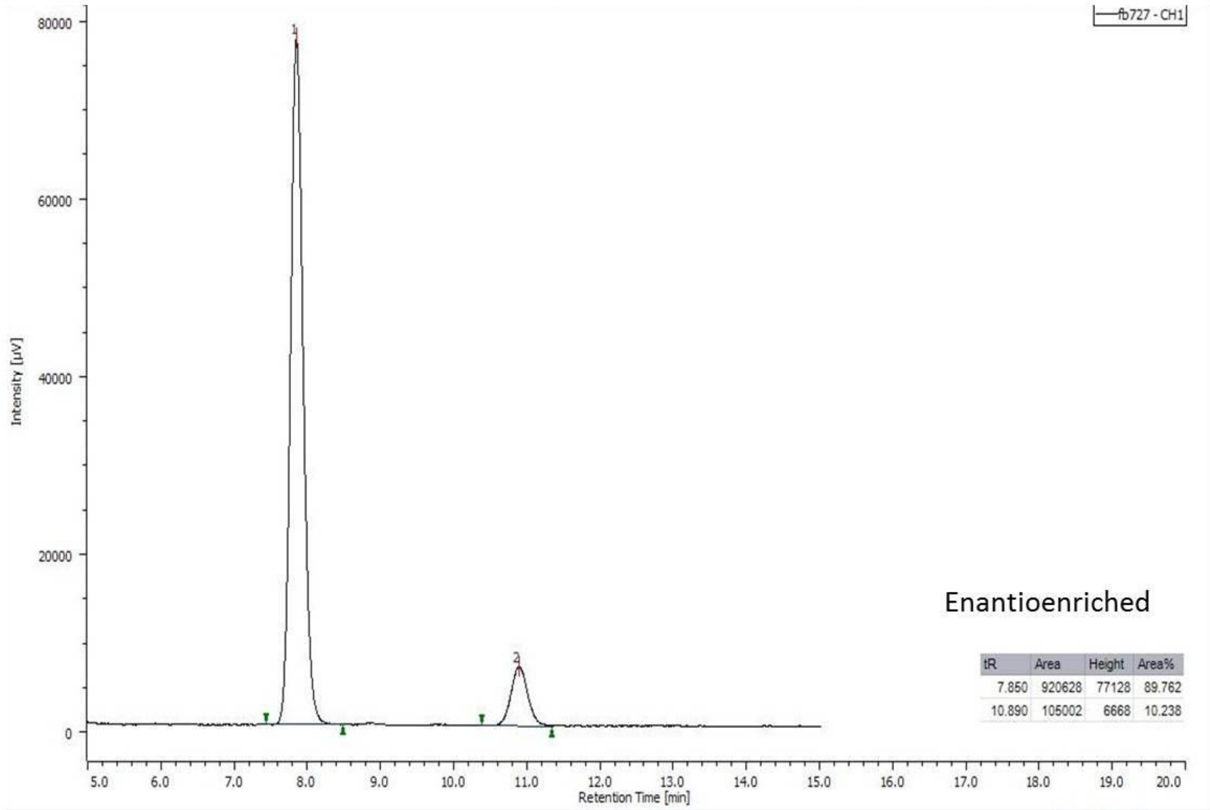
13.130 126325 7316 2.544


fb639 - CH1
Ph
O
NPhth
EtO2C
EtO2C
3ag
Racemic
tR Area Height Area%
7.903 706317 64052 50.152
10.973 702042 46636 49.848
Intensity [µV]
Retention Time [min]


fb727 - CH1
Enantioenriched
tR Area Height Area%
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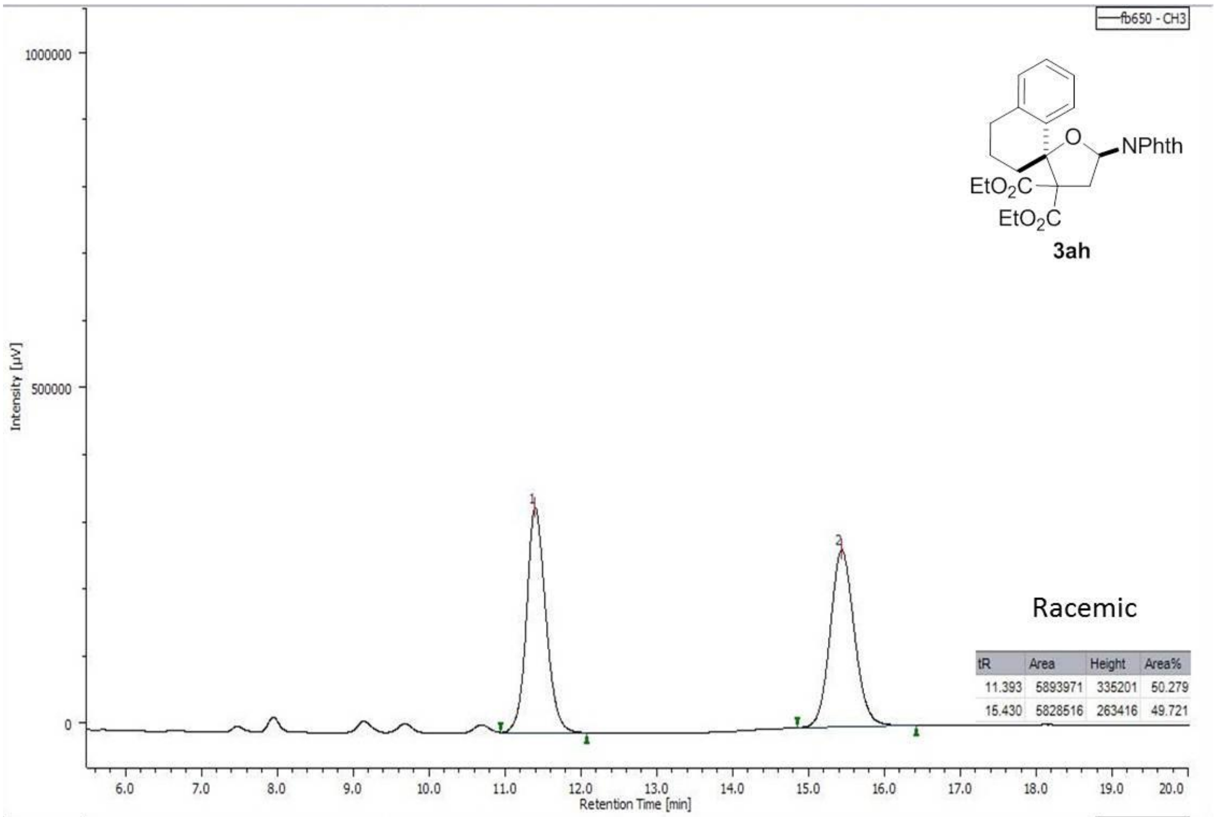
10.890 105002 6668 10.238
Intensity [µV]
Retention Time [min]



tR	Area	Height	Area%
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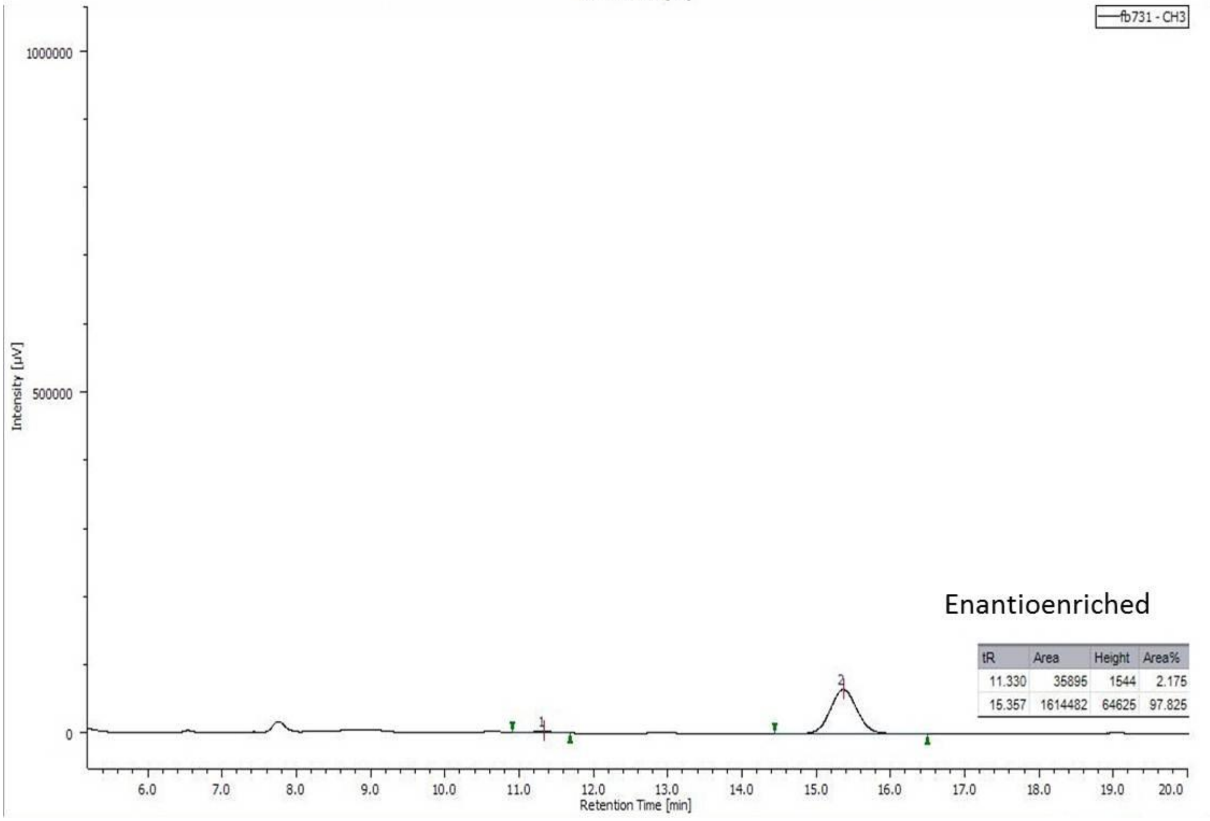
15.430	5828516	263416	49.721



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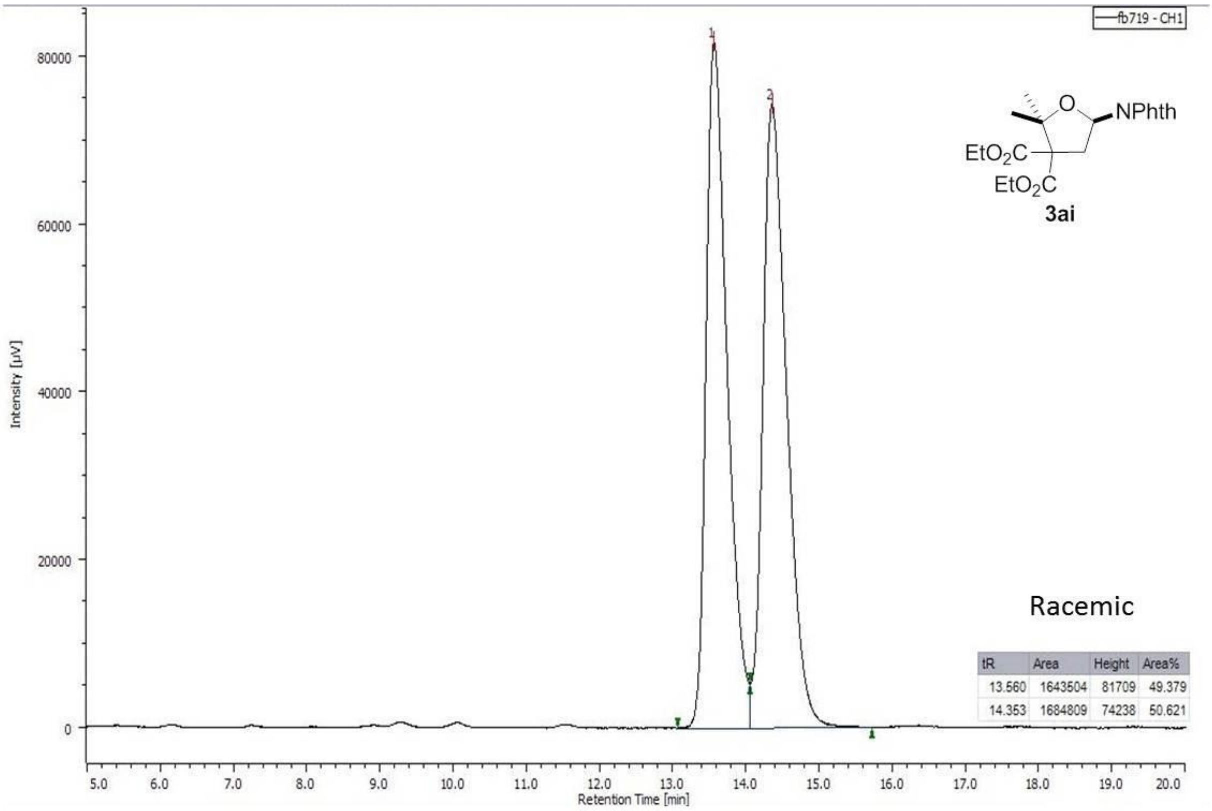
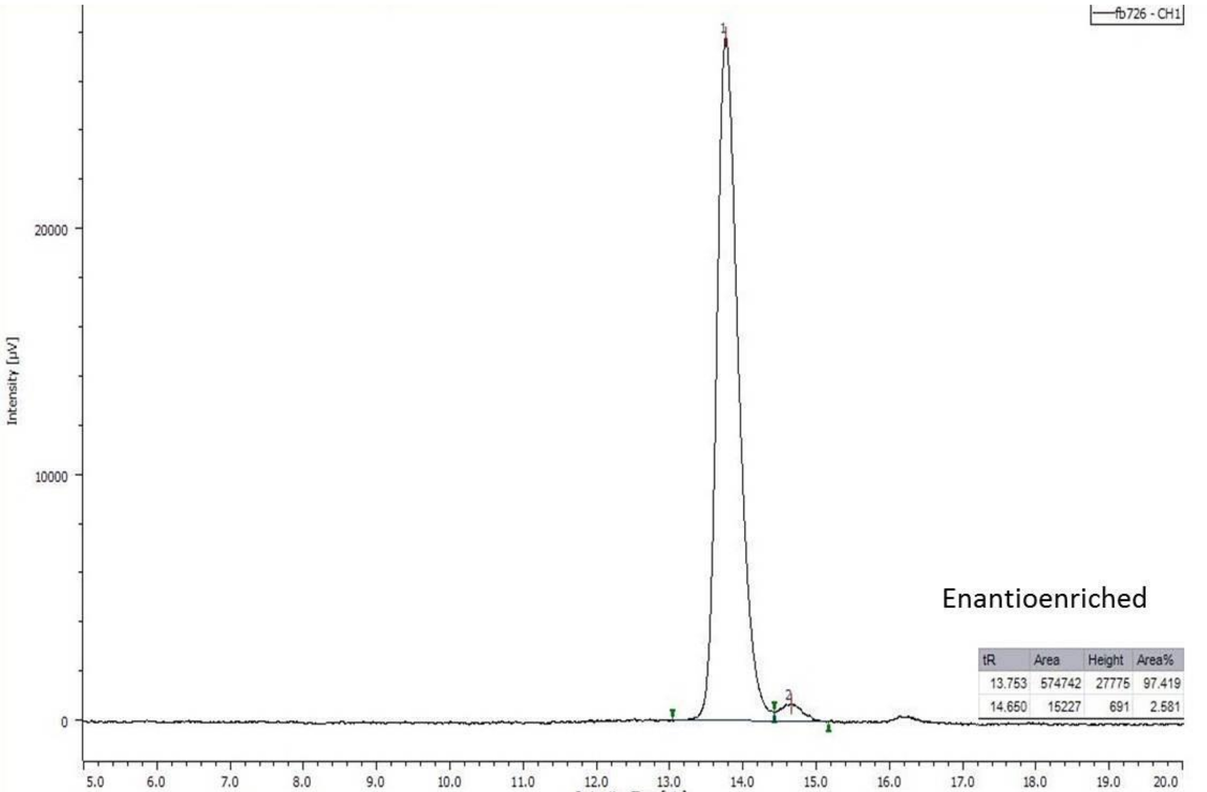


tR	Area	Height	Area%
13.560	1643504	81709	49.379
14.353	1684809	74238	50.621



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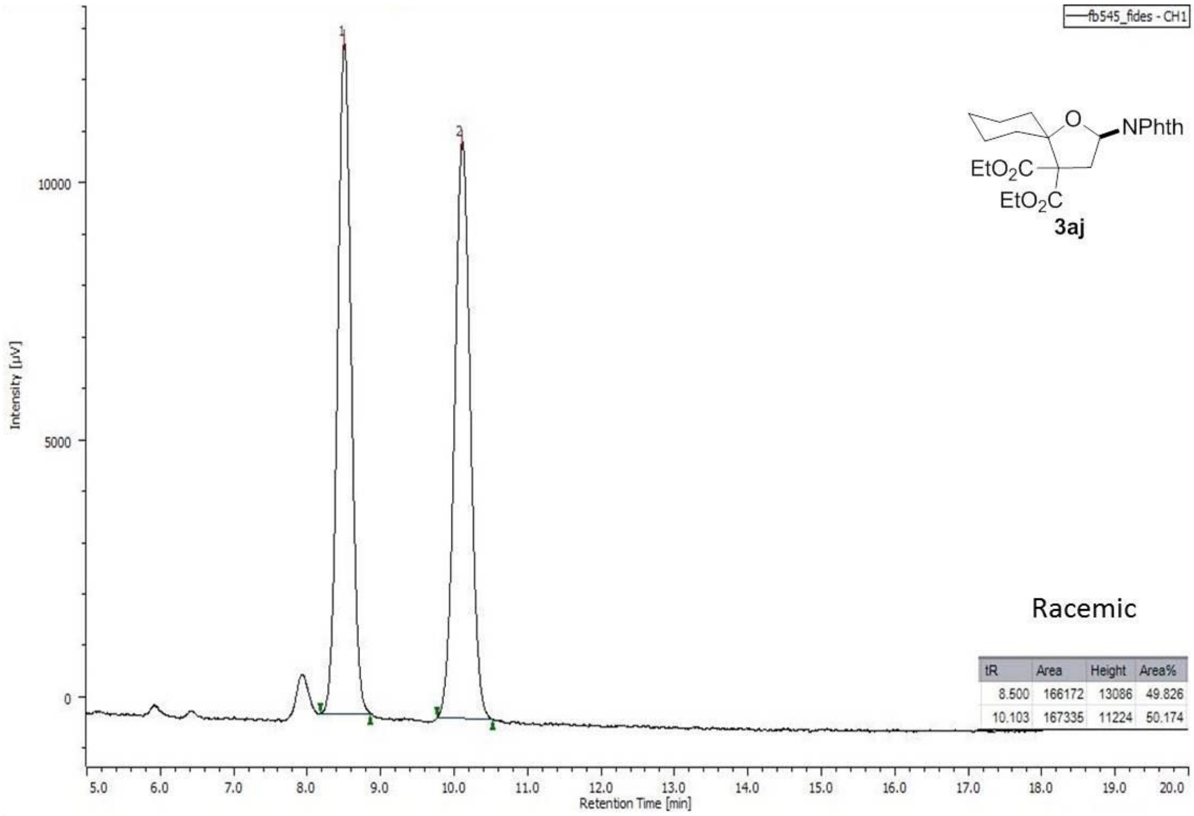

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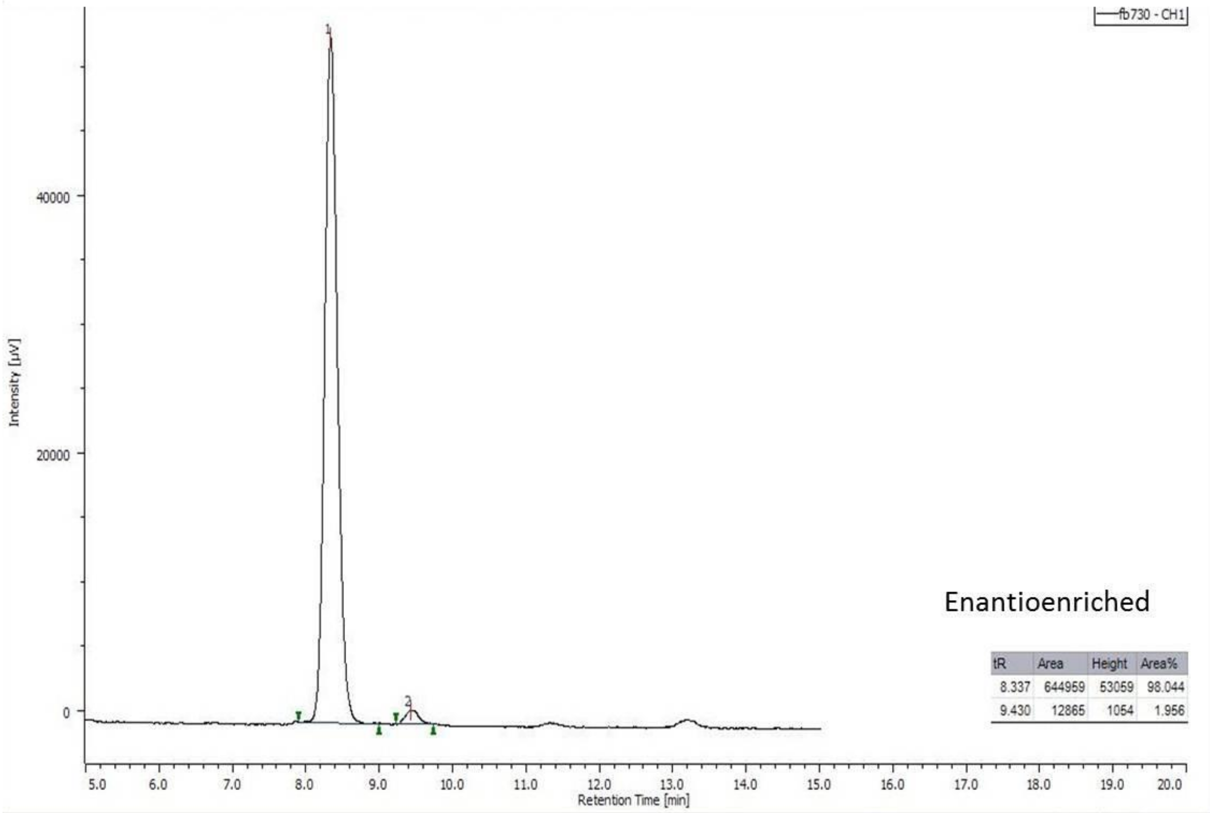
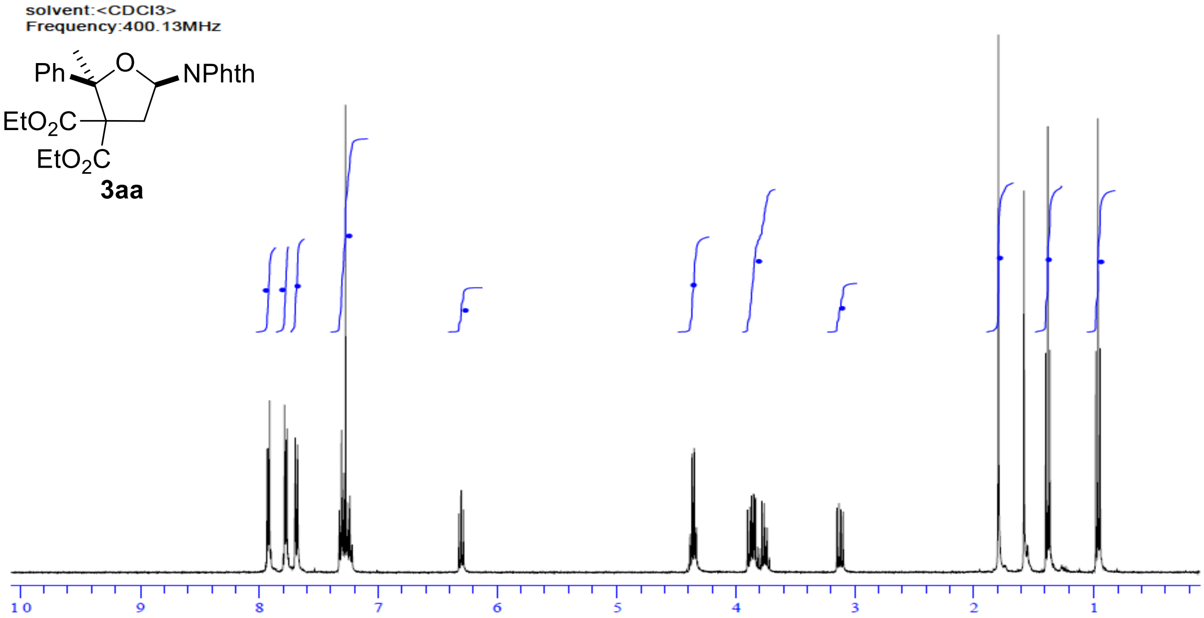
10.103	167335	11224	50.174



tR	Area	Height	Area%
8.337	644959	53059	98.044
9.430	12865	1054	1.956

5 Spectra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NPhth
EtO_2C
EtO_2C
3aa
10
9
8
7
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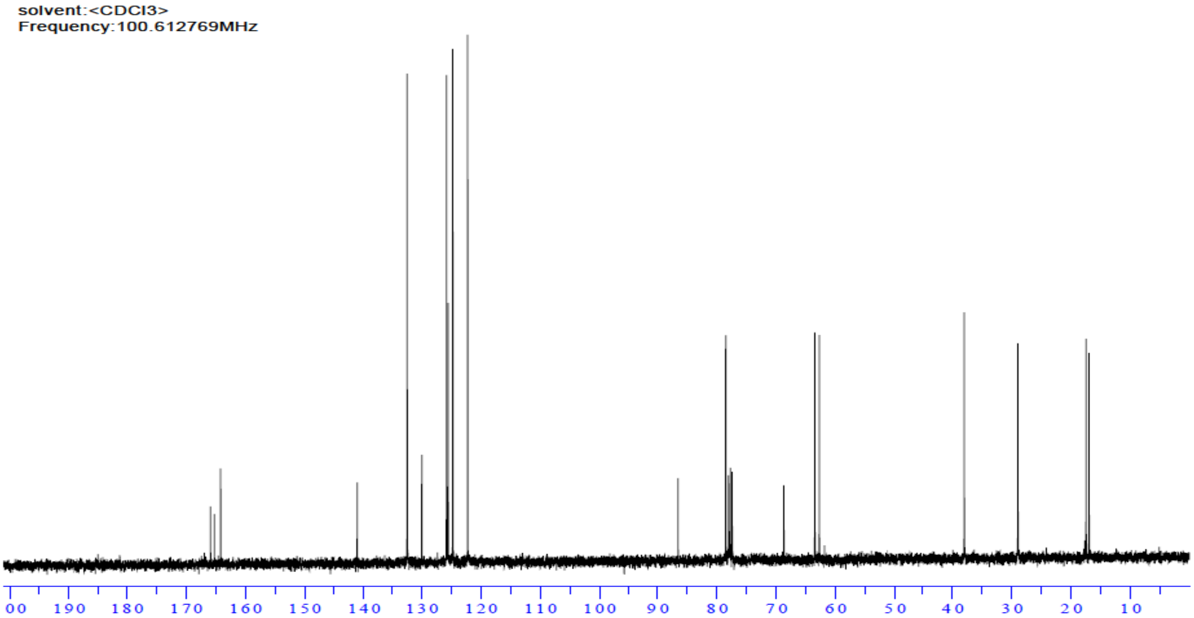
5
4
3
2
1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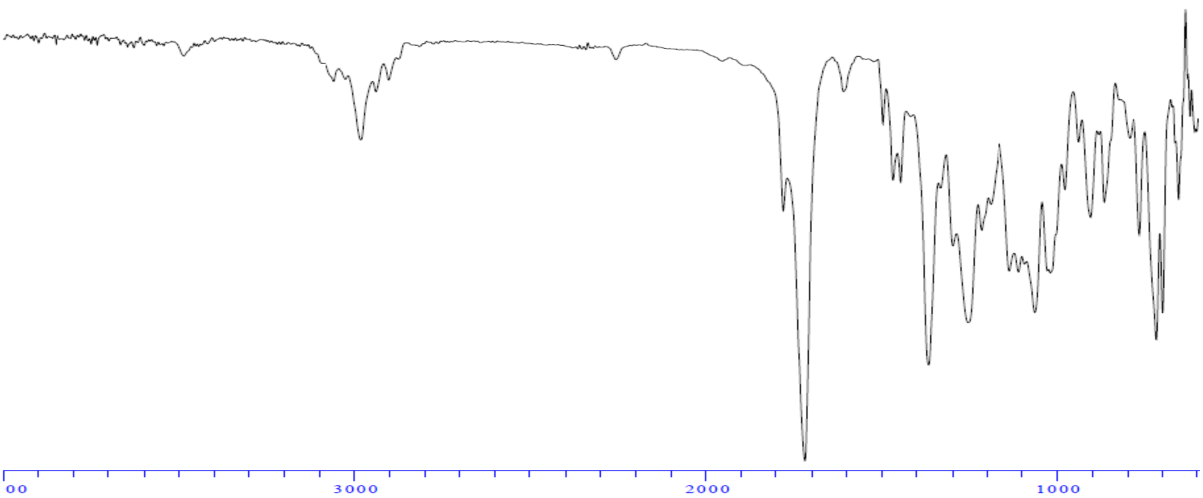
40
30
20
10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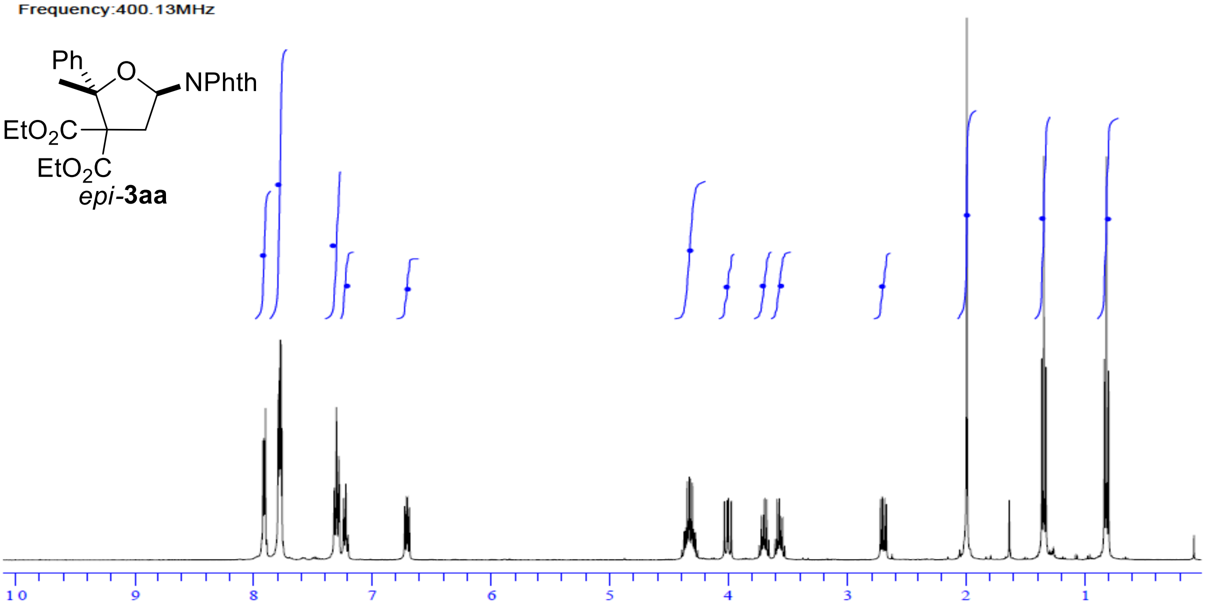

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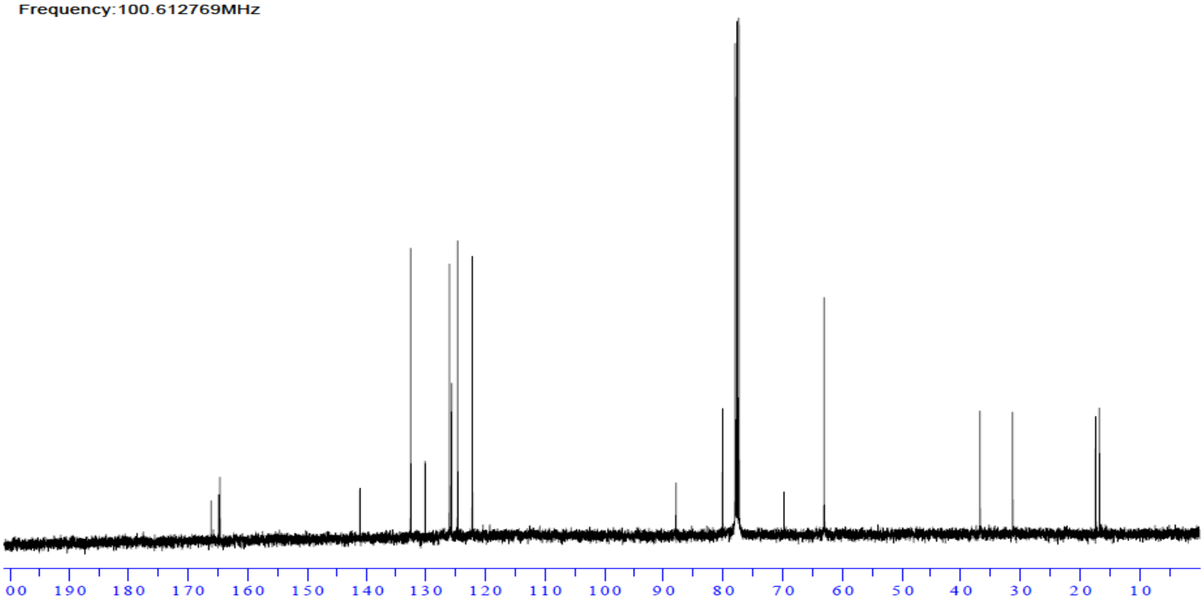

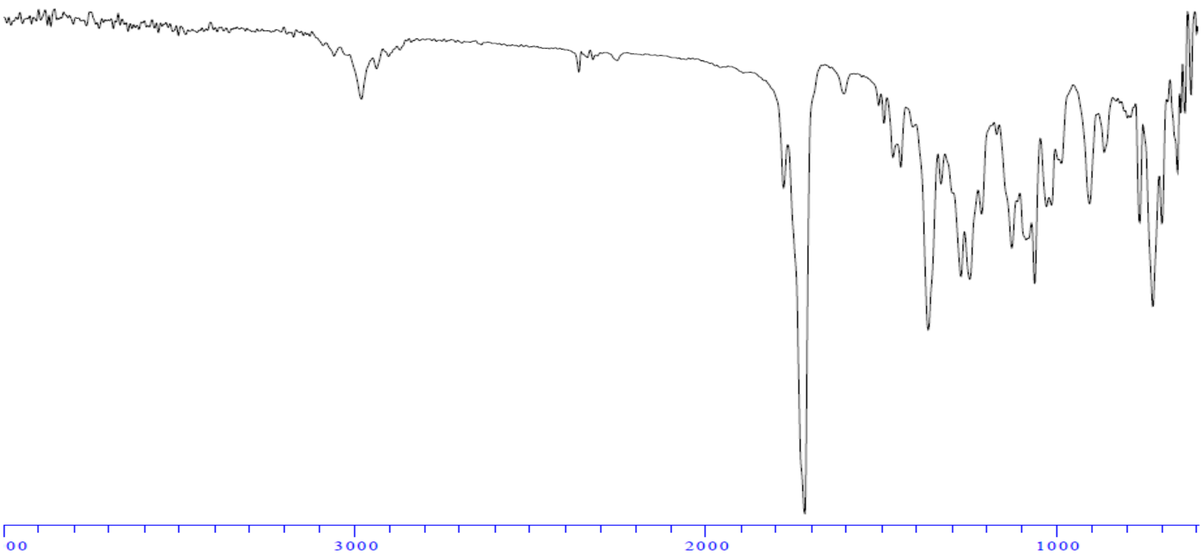

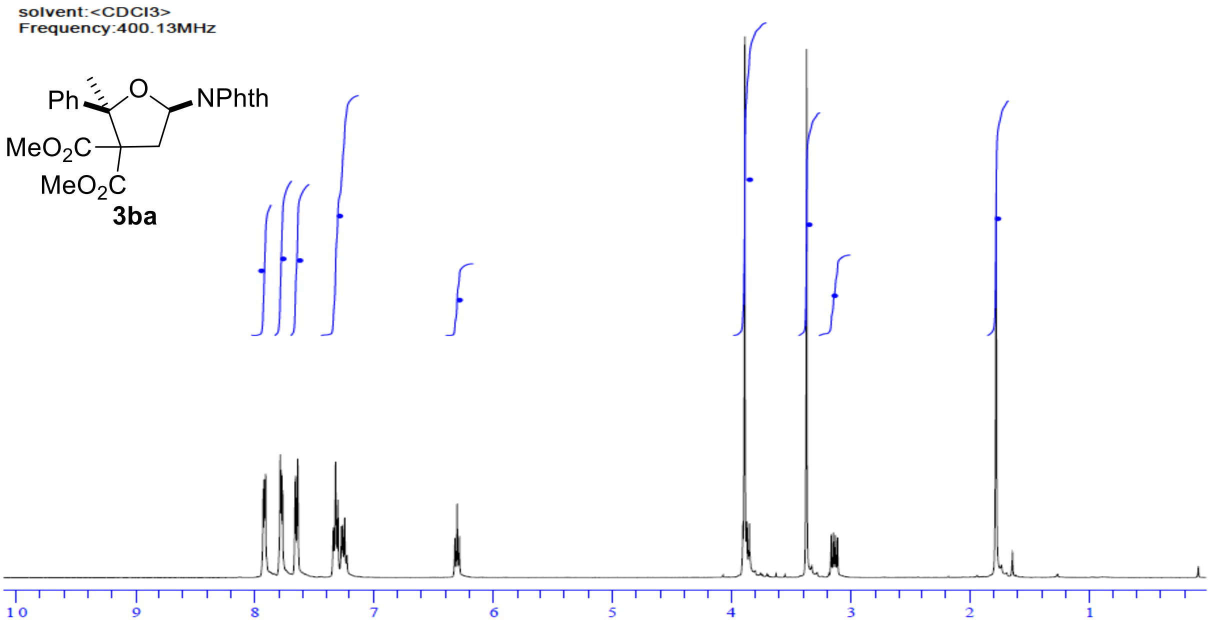
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NPhth
MeO2C
MeO2C
3ba
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9
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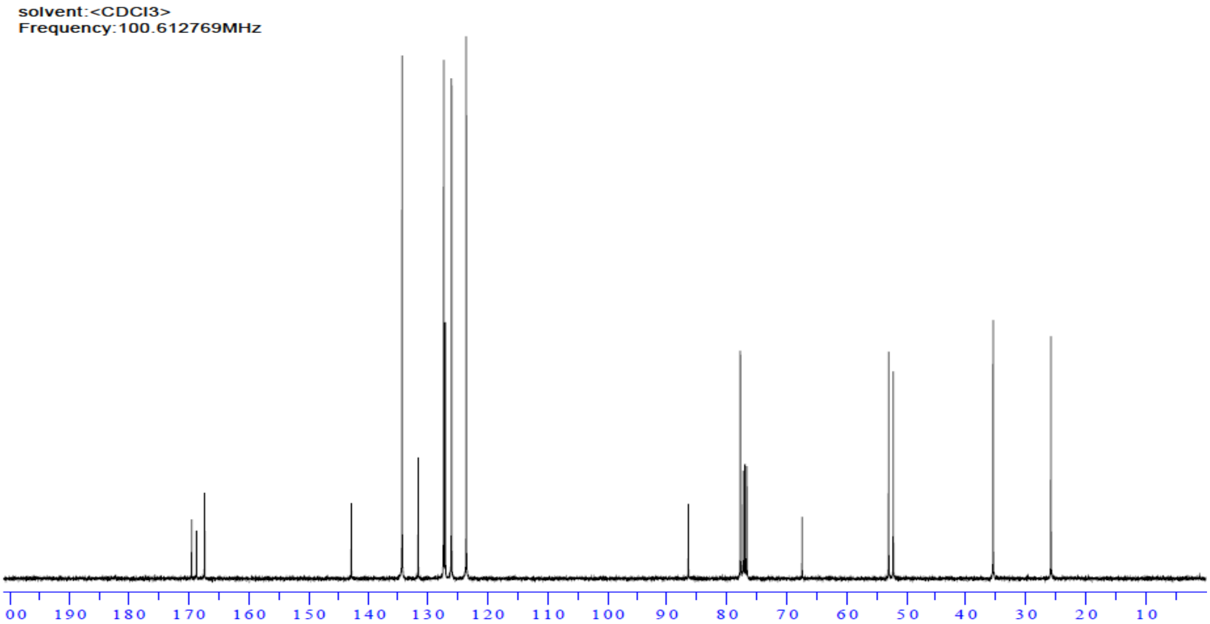
5
4
3
2
1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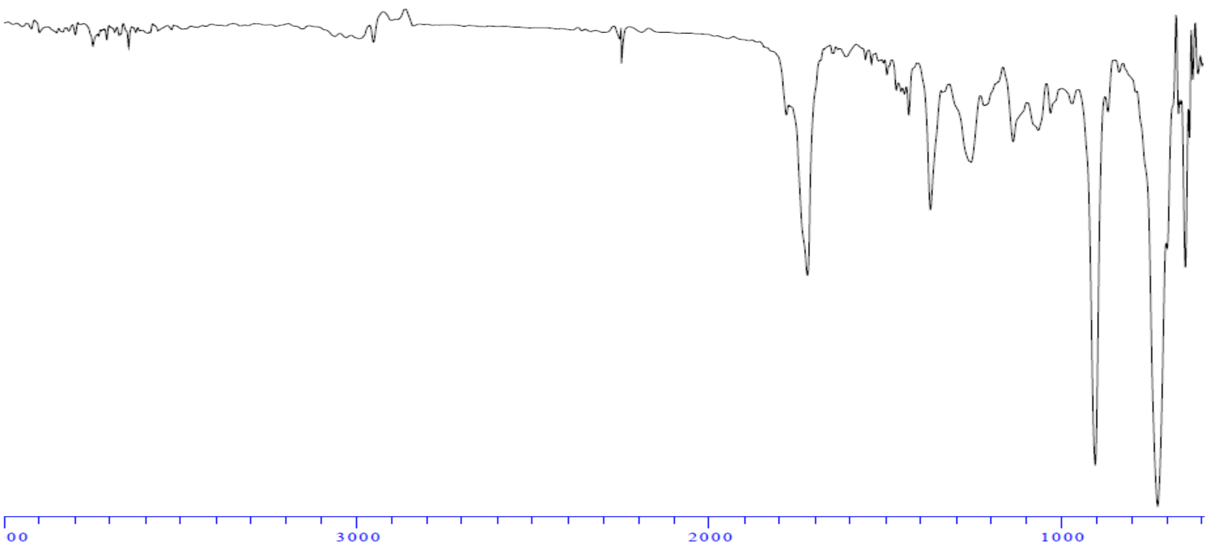
40
30
20
10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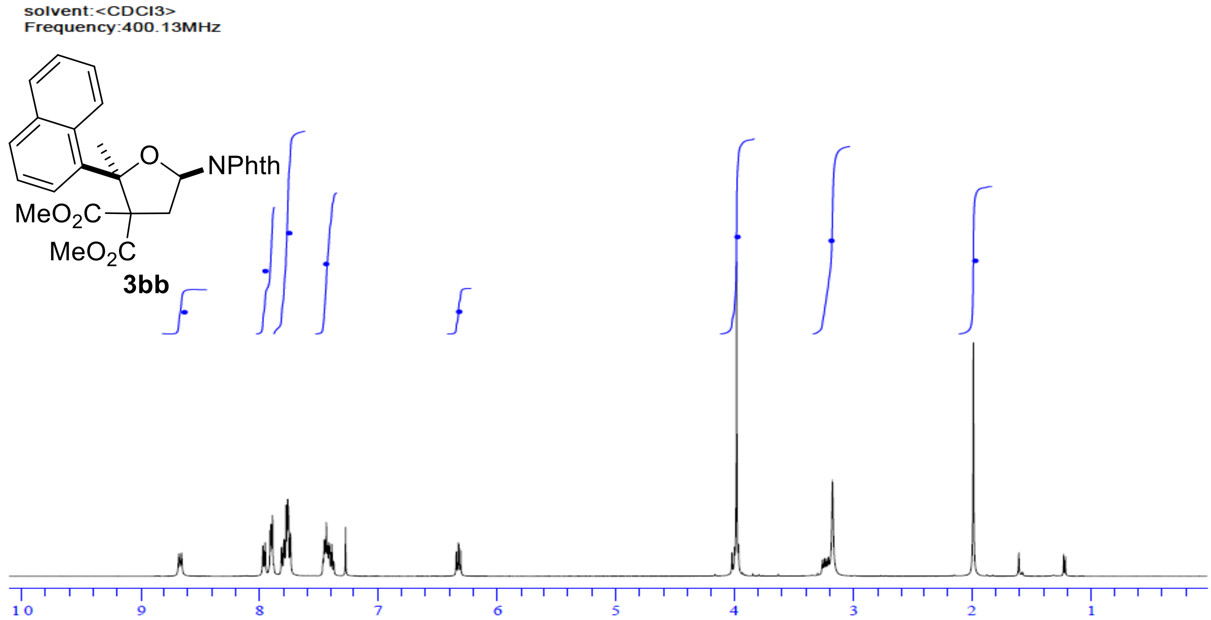
3000
2000
1000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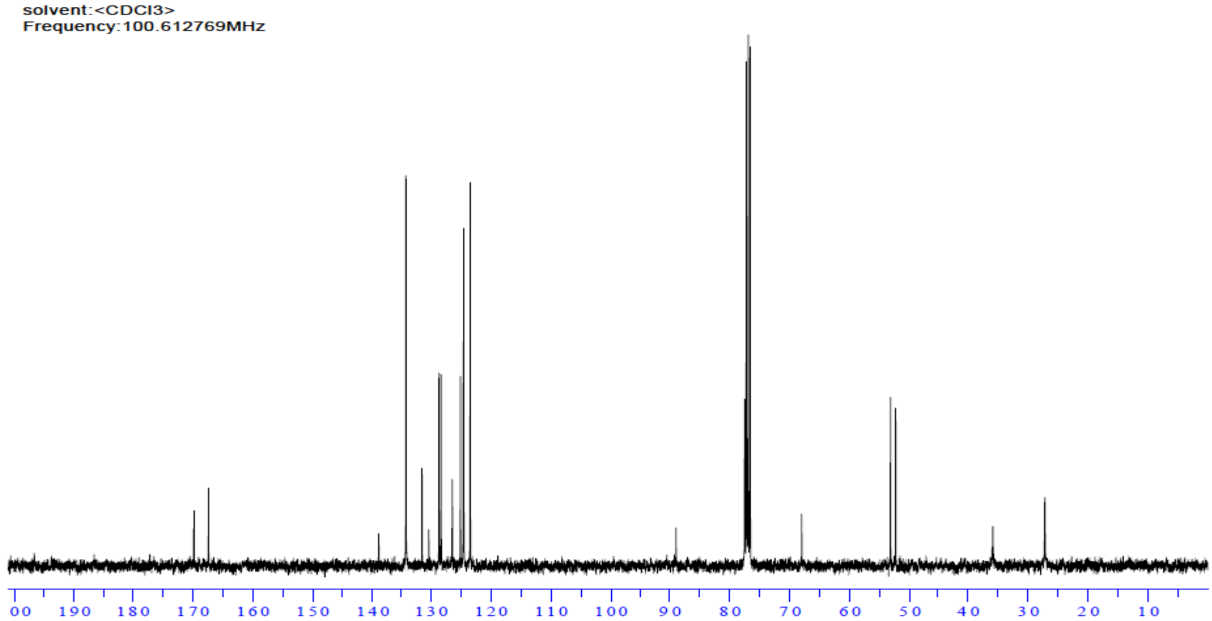
NPhth
MeO_2C
MeO_2C
3bb
10
9
8
7
6
5
4
3
2
1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190
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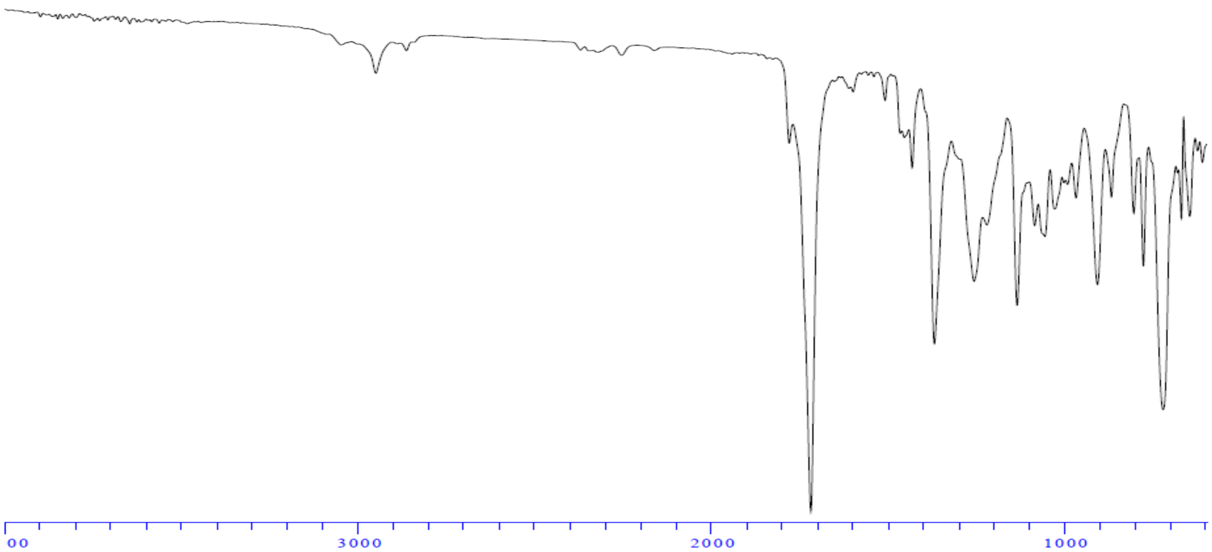
20
10


00
3000
2000
1000

solvent:<CDCl3>
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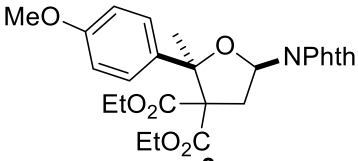
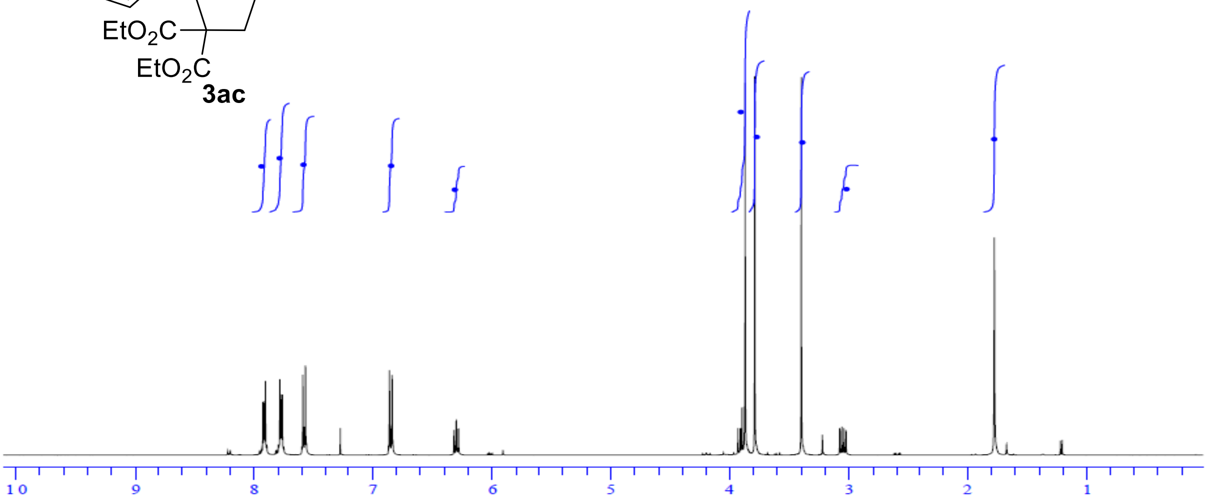


3ac



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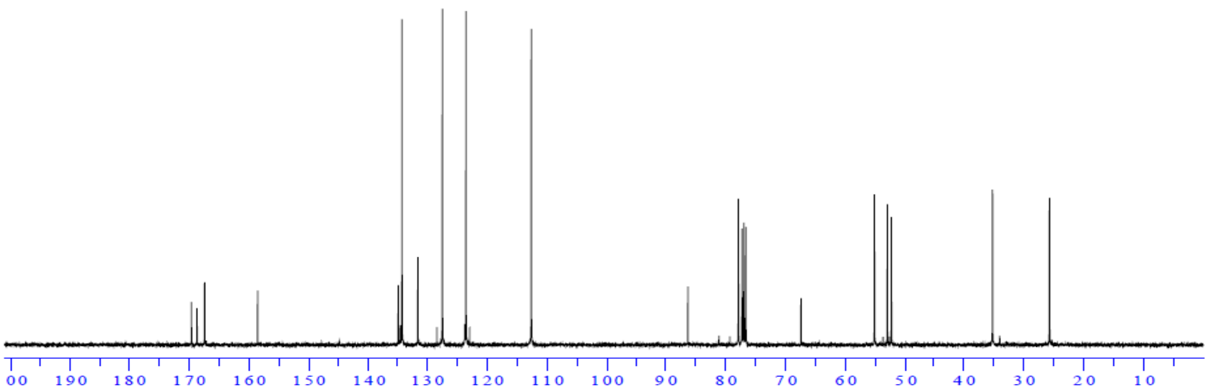

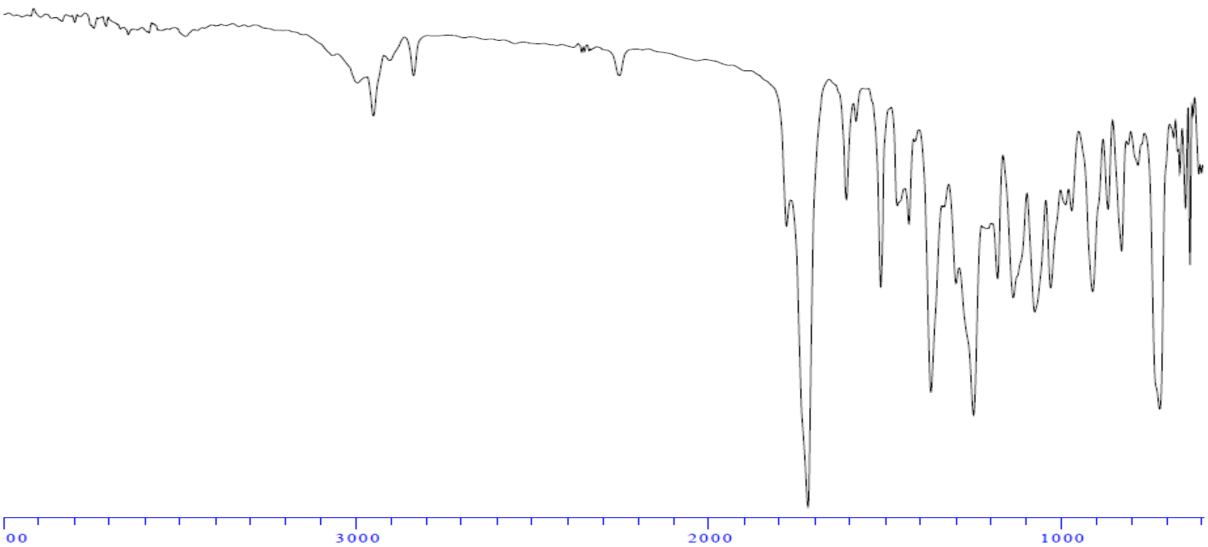

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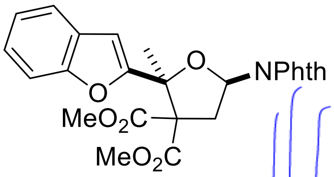

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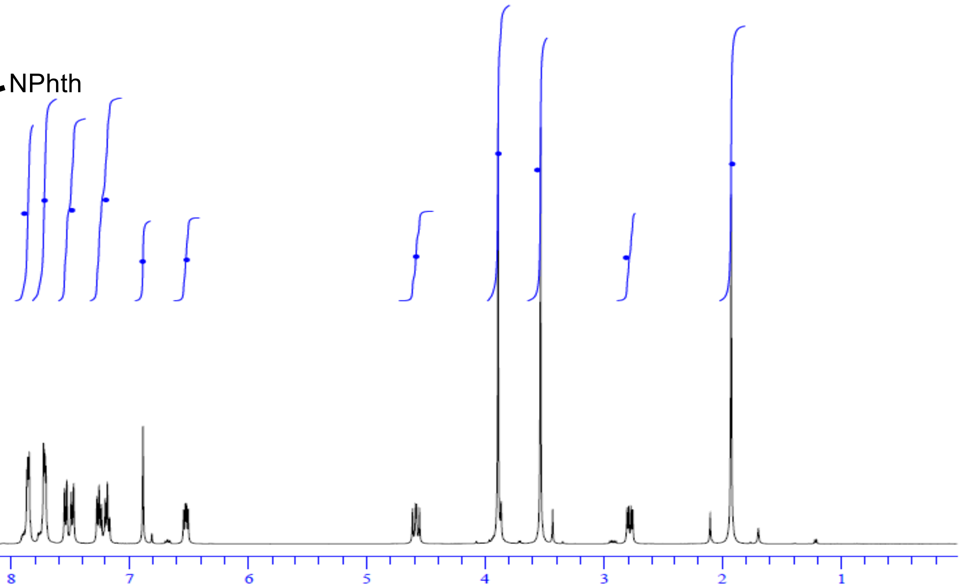

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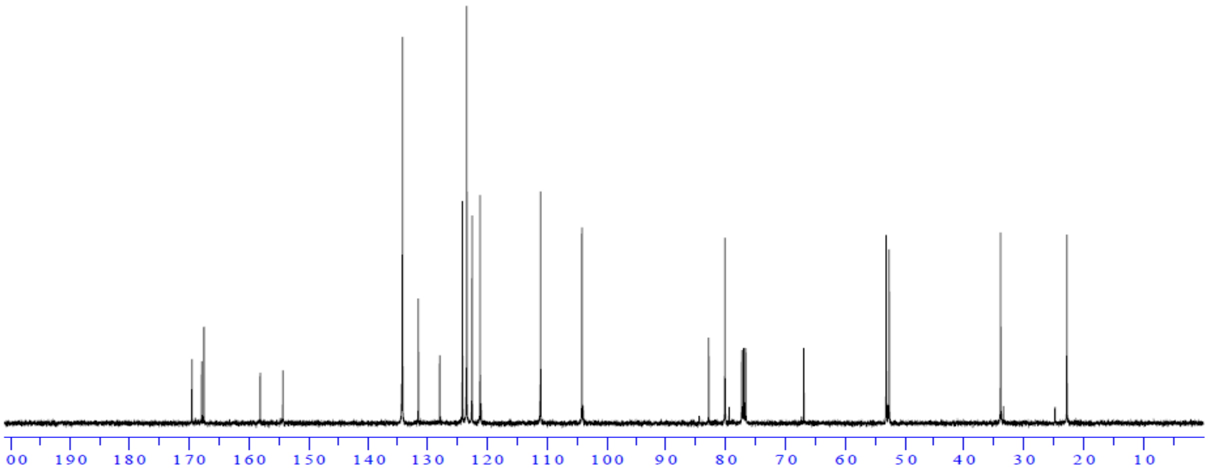

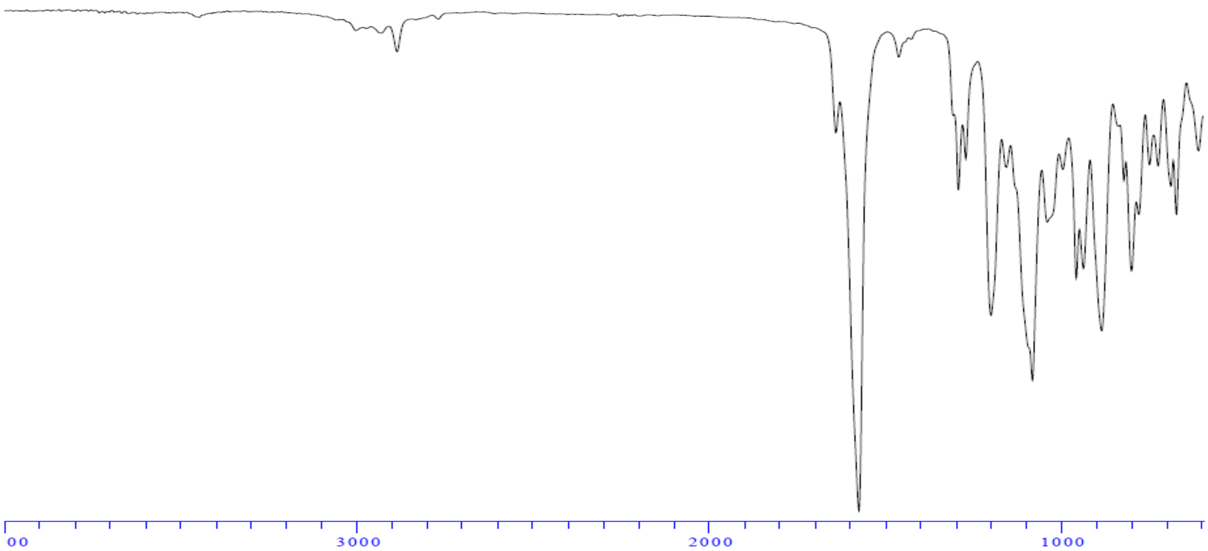

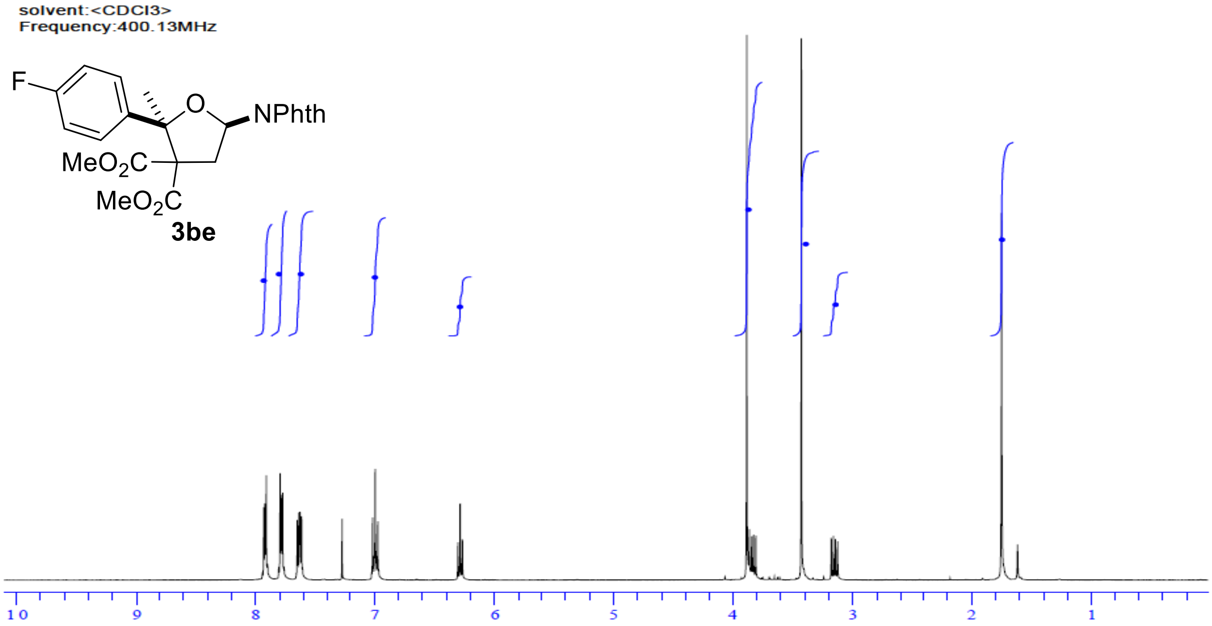
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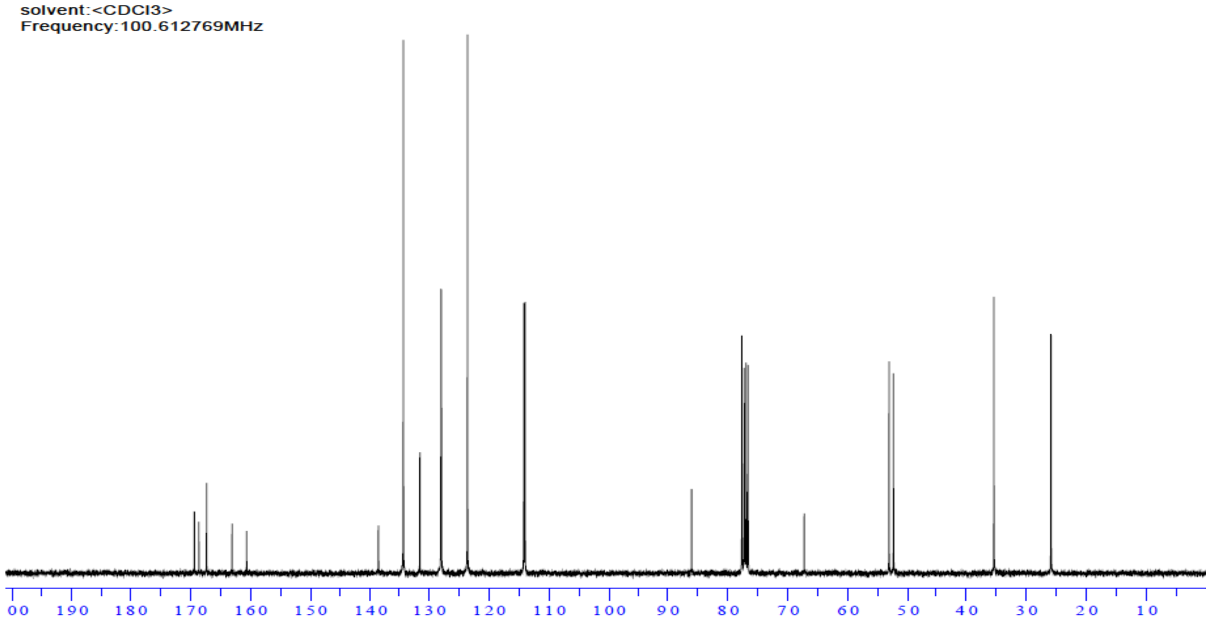
F
O
NPhth
MeO2C
MeO2C
3be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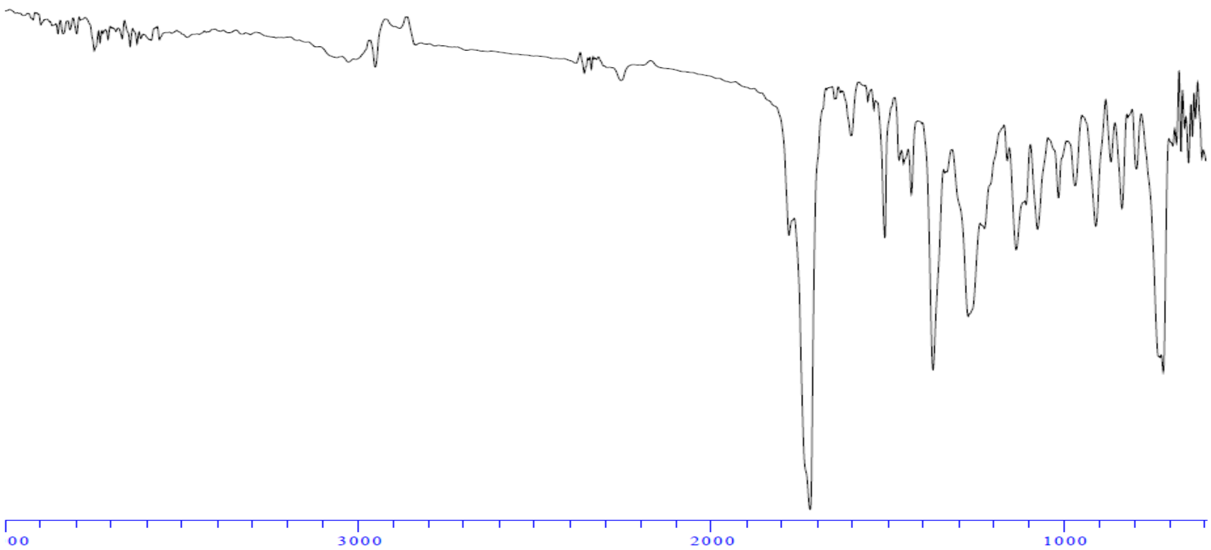

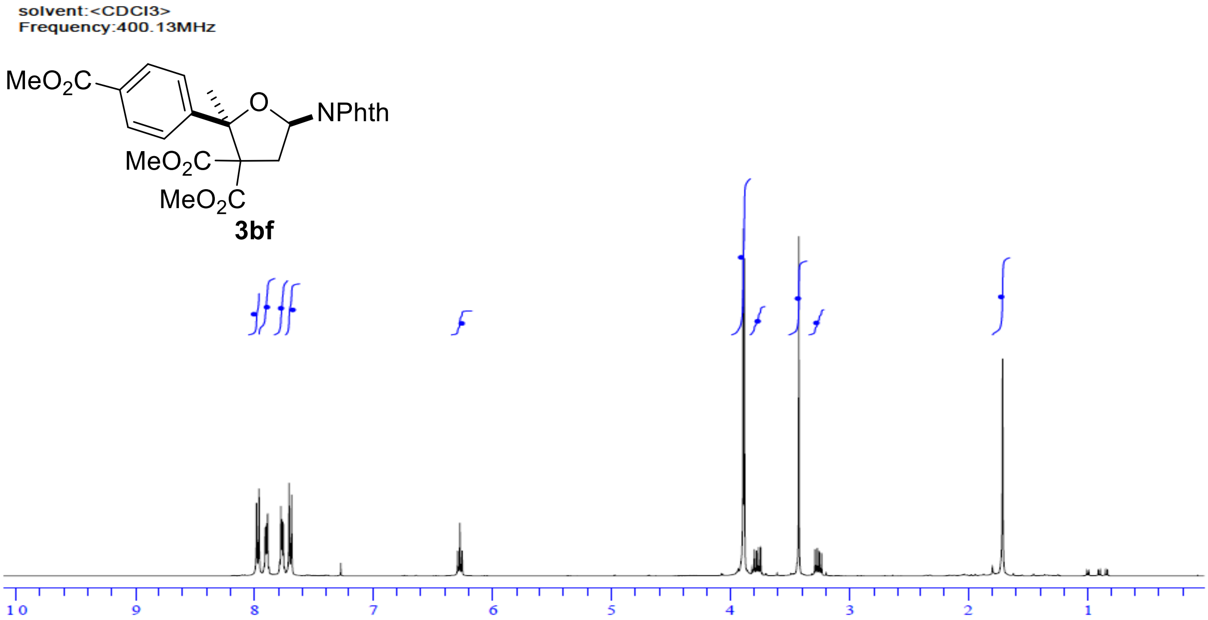
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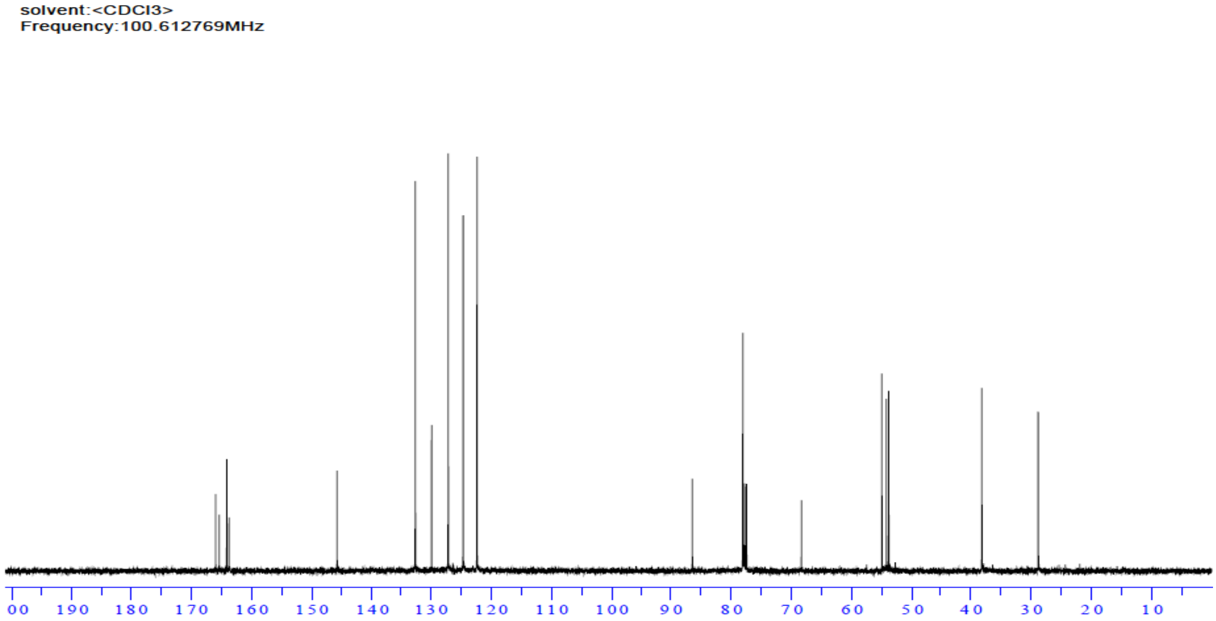
MeO2C
O
NPhth
MeO2C
MeO2C
3bf
10 9 8 7 6 5 4 3 2 1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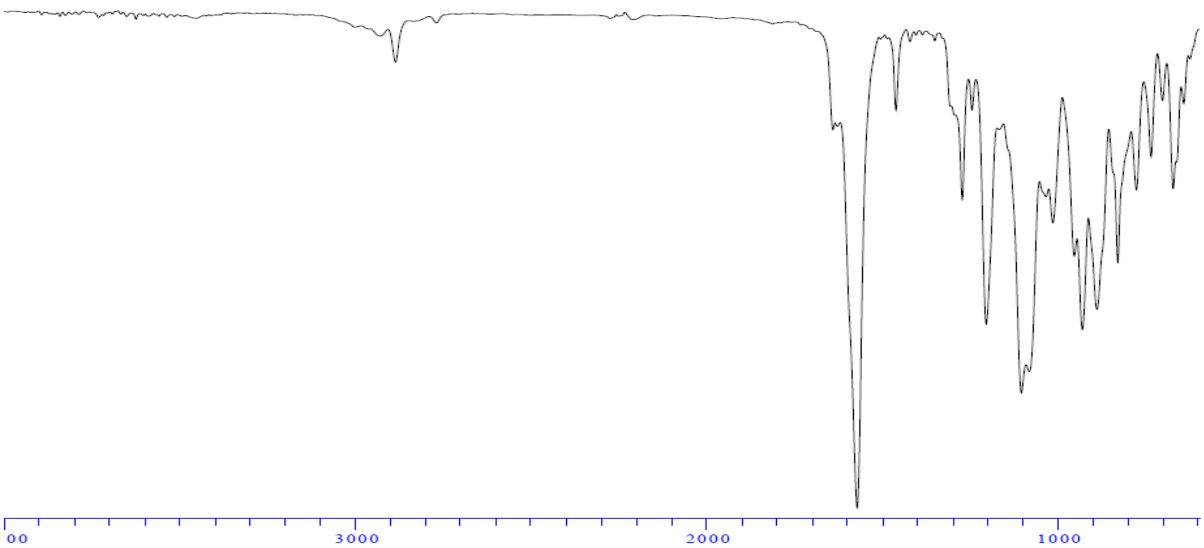
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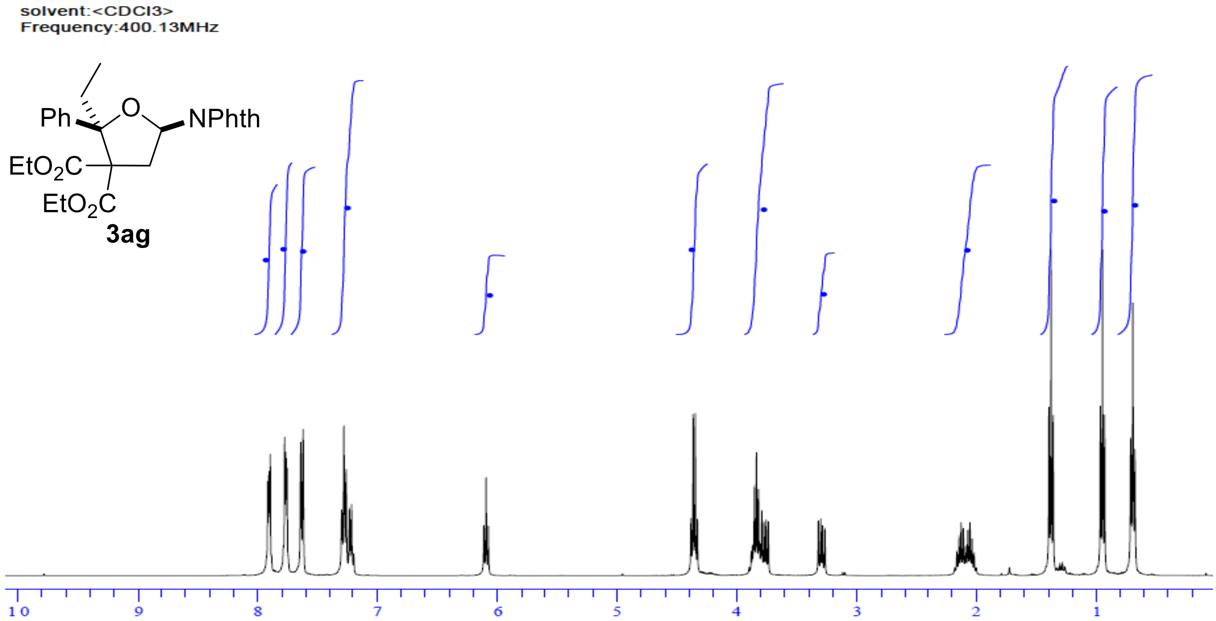
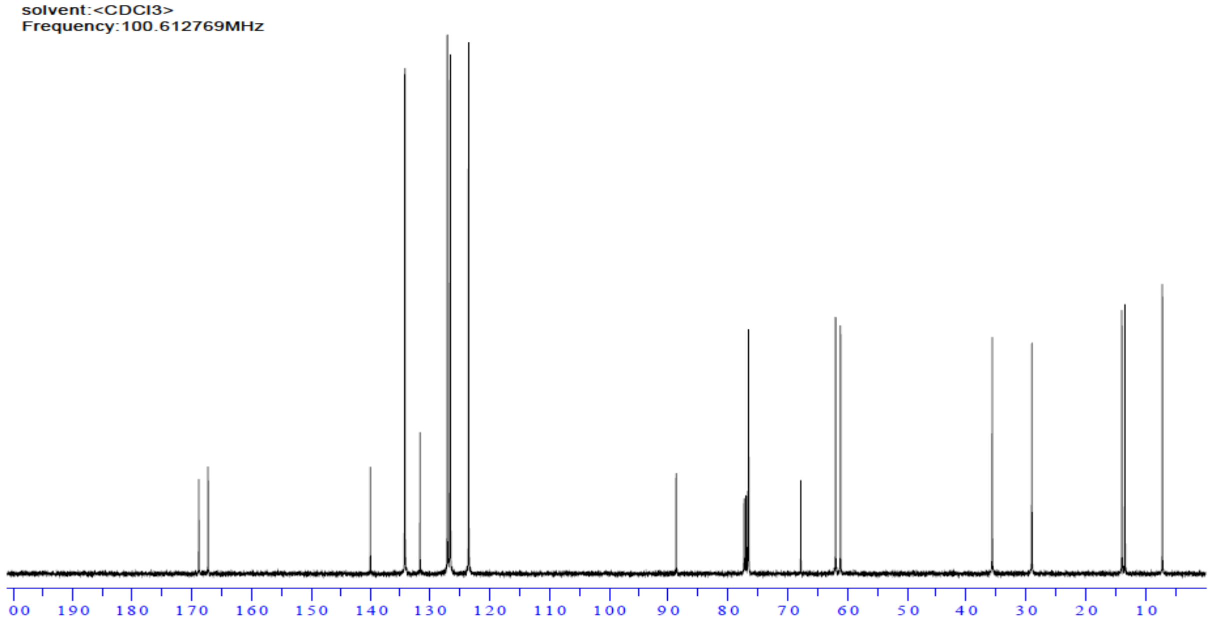

solvent:<CDCl3>
Frequency:400.13MHz
Ph
O
NPhth
EtO_2C
EtO_2C
3ag
10 9 8 7 6 5 4 3 2 1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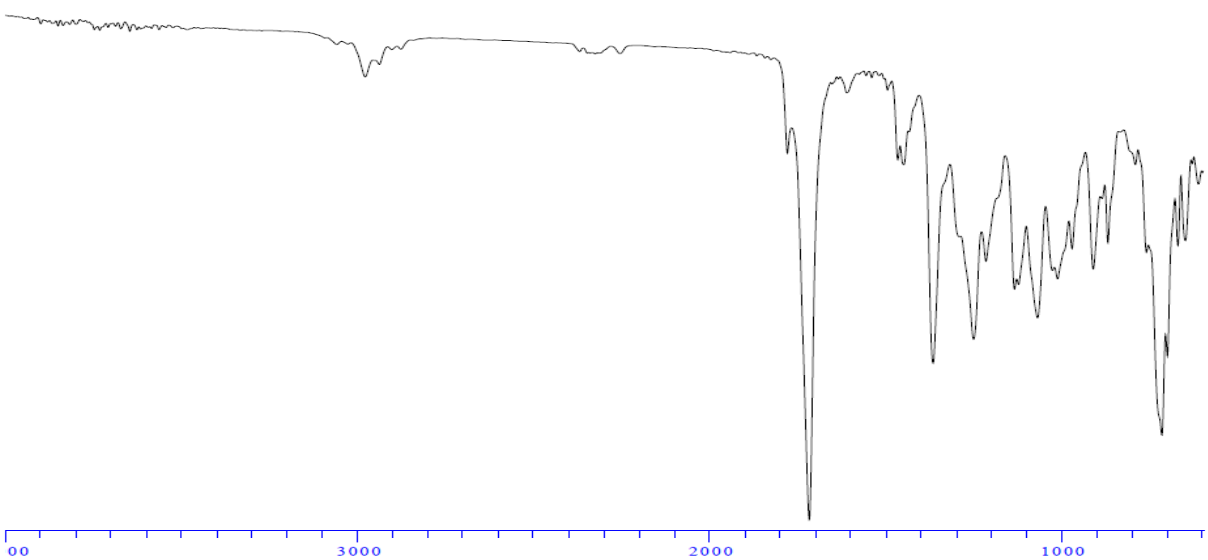
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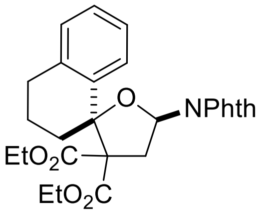

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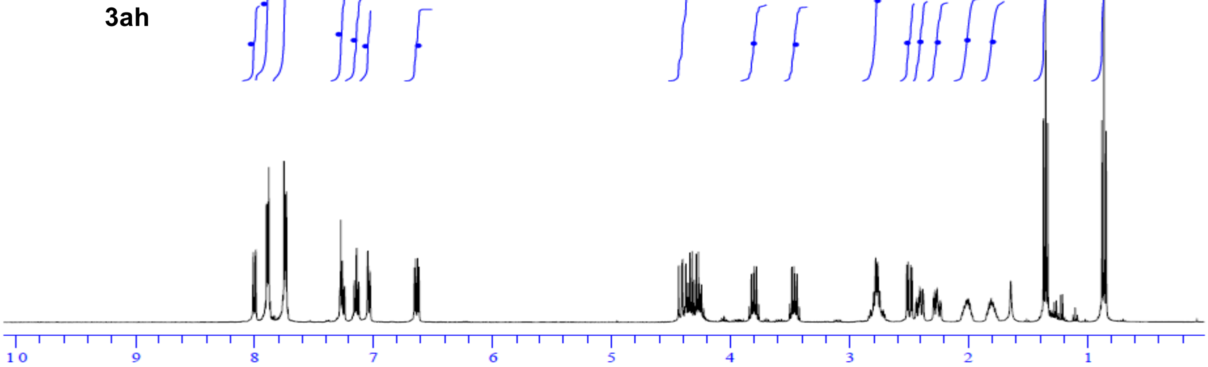

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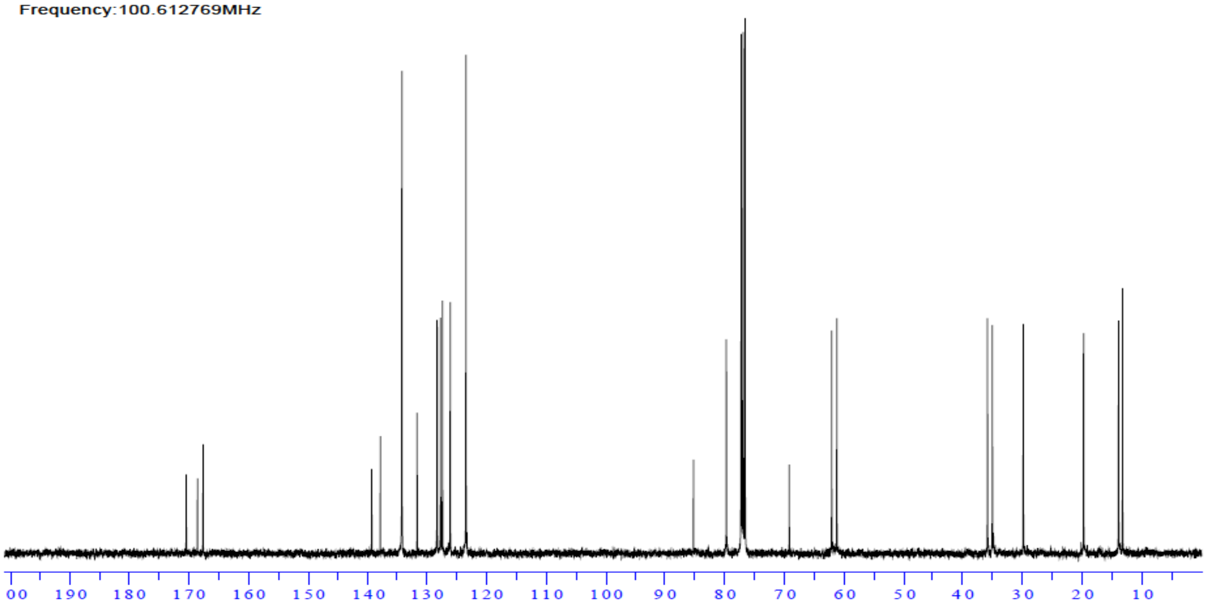

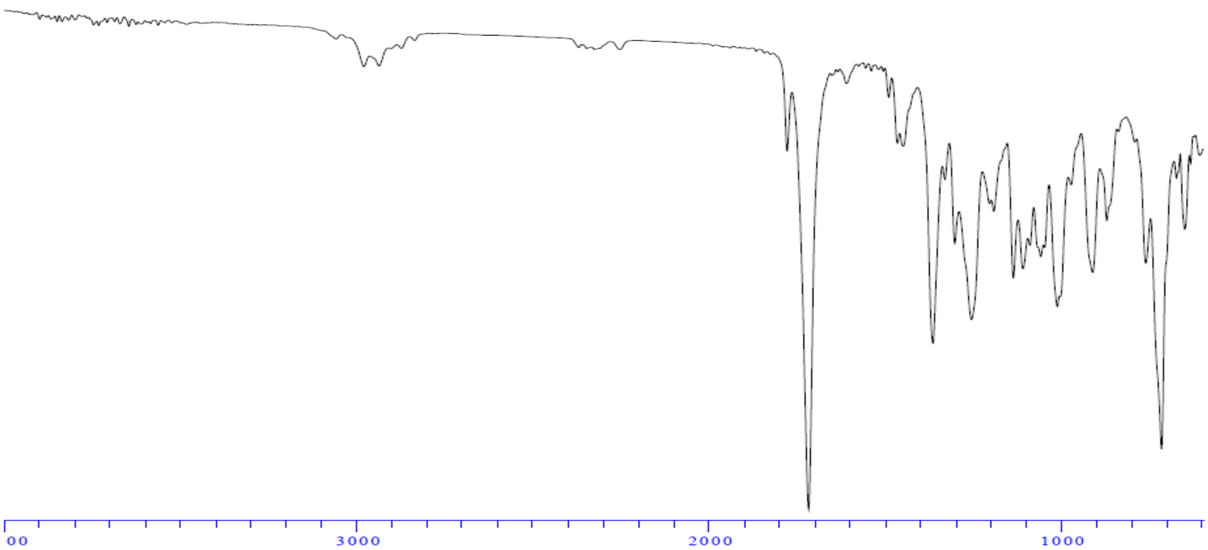

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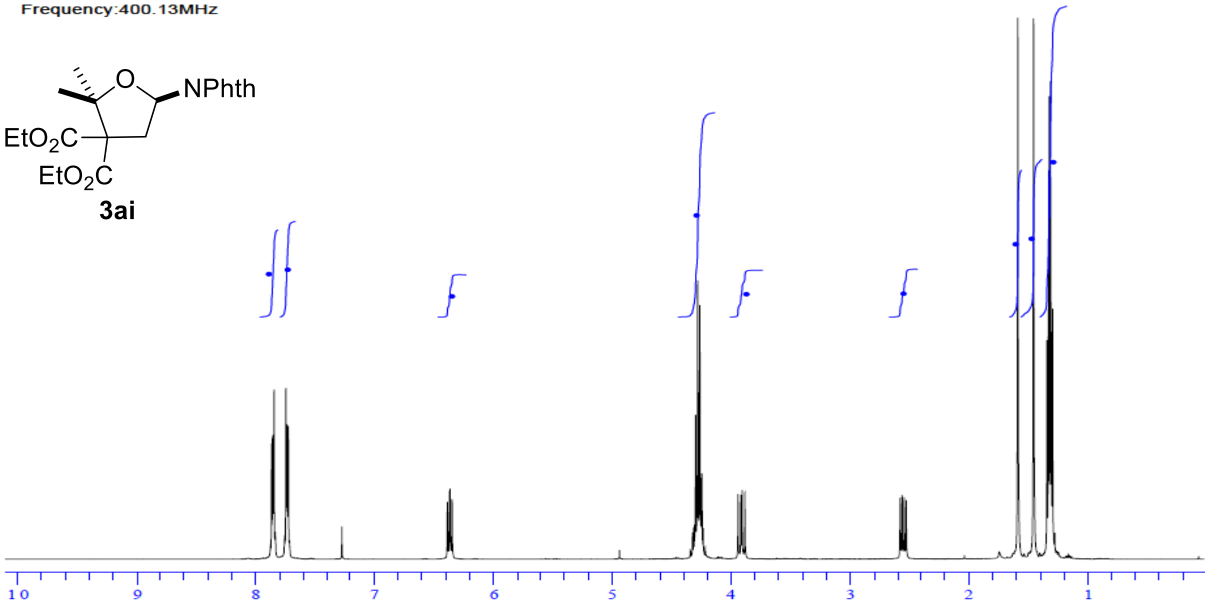

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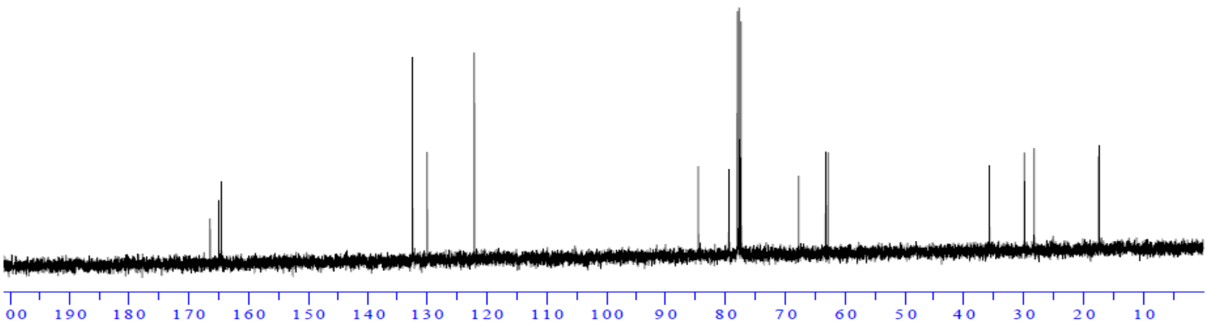

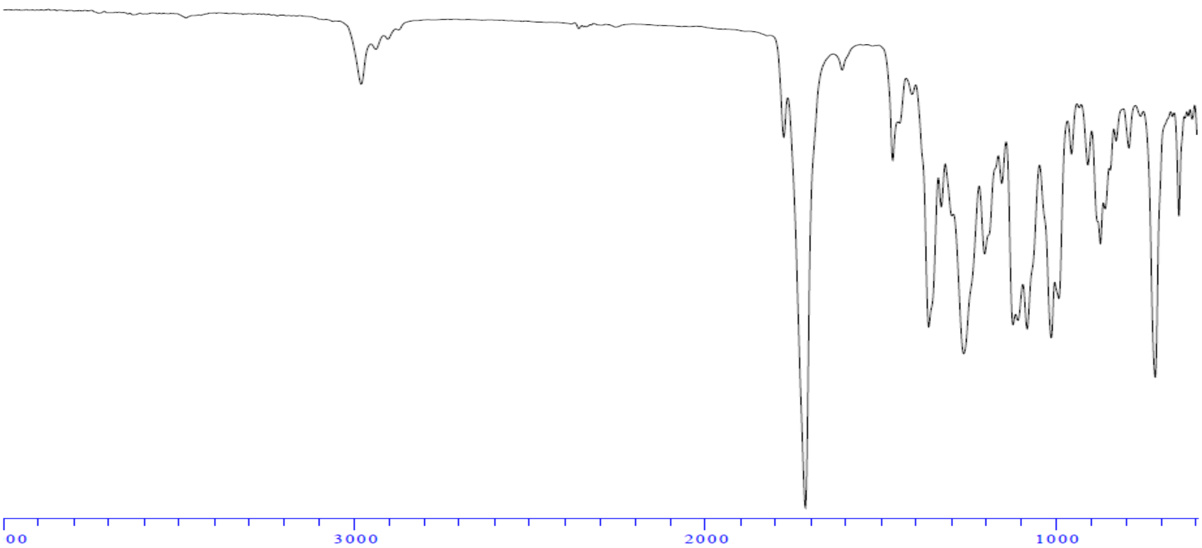

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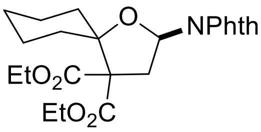

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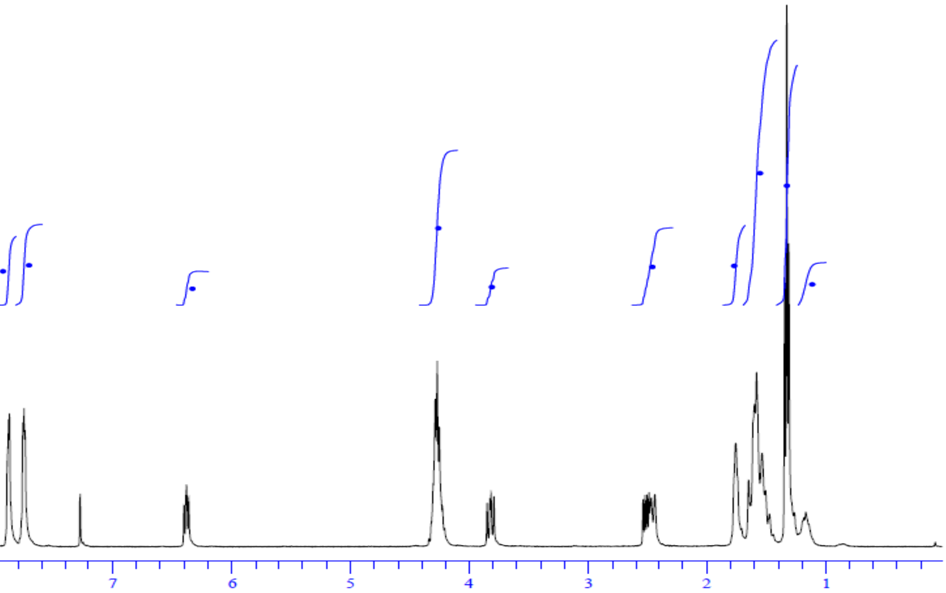

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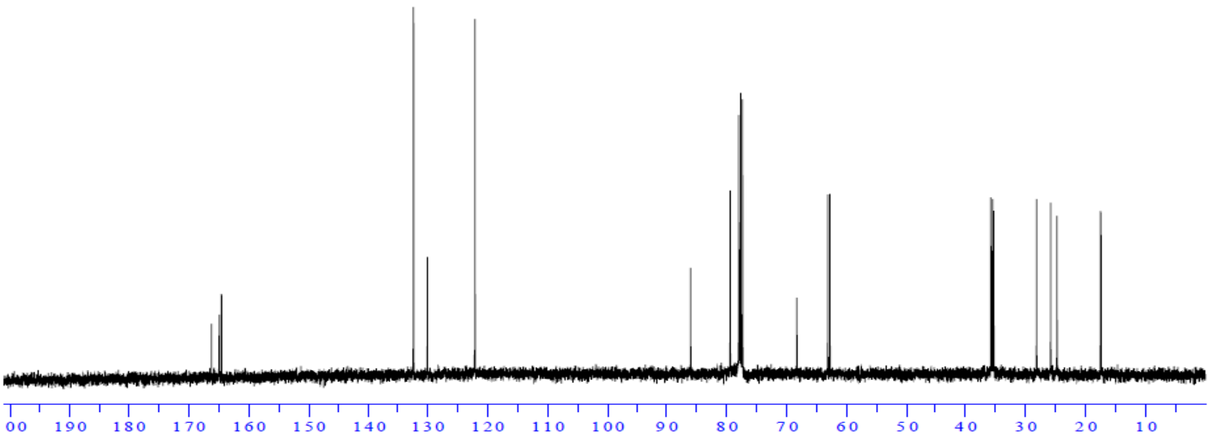

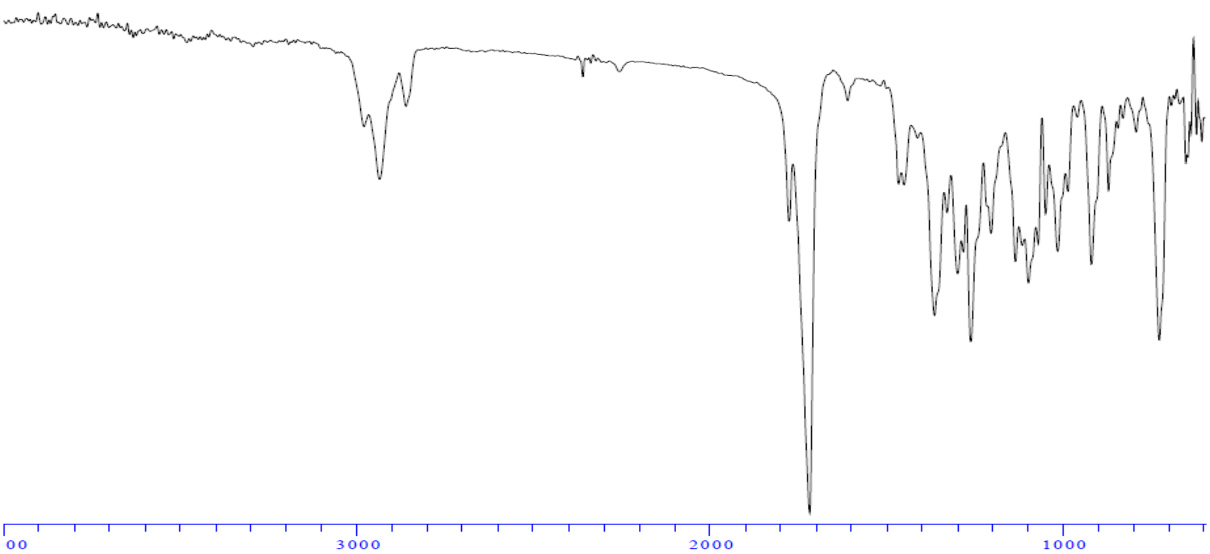

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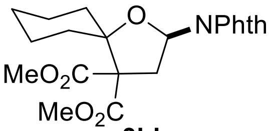
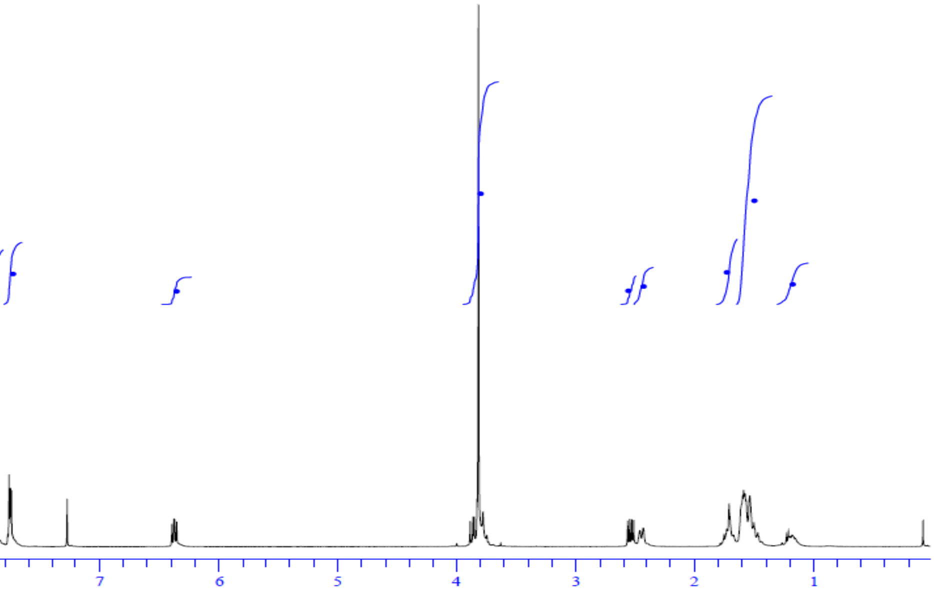


3bj



solvent:<CDCl3>
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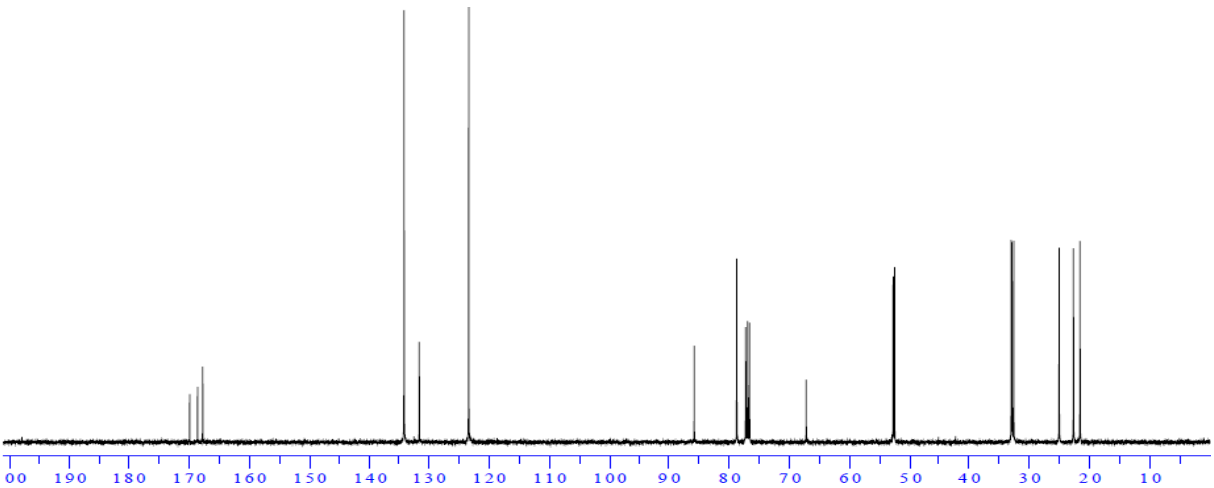

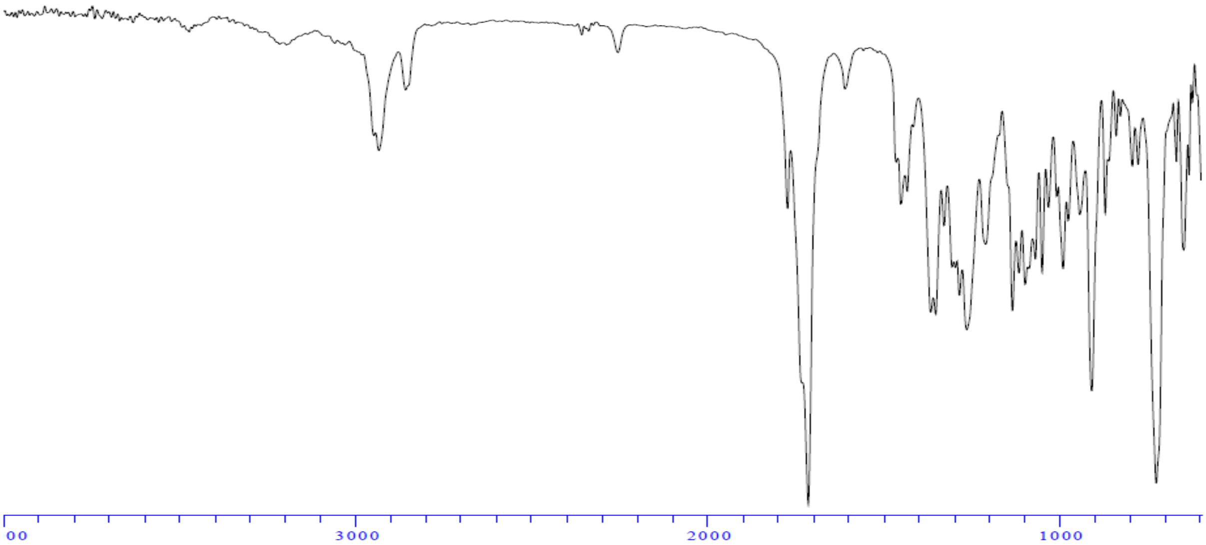

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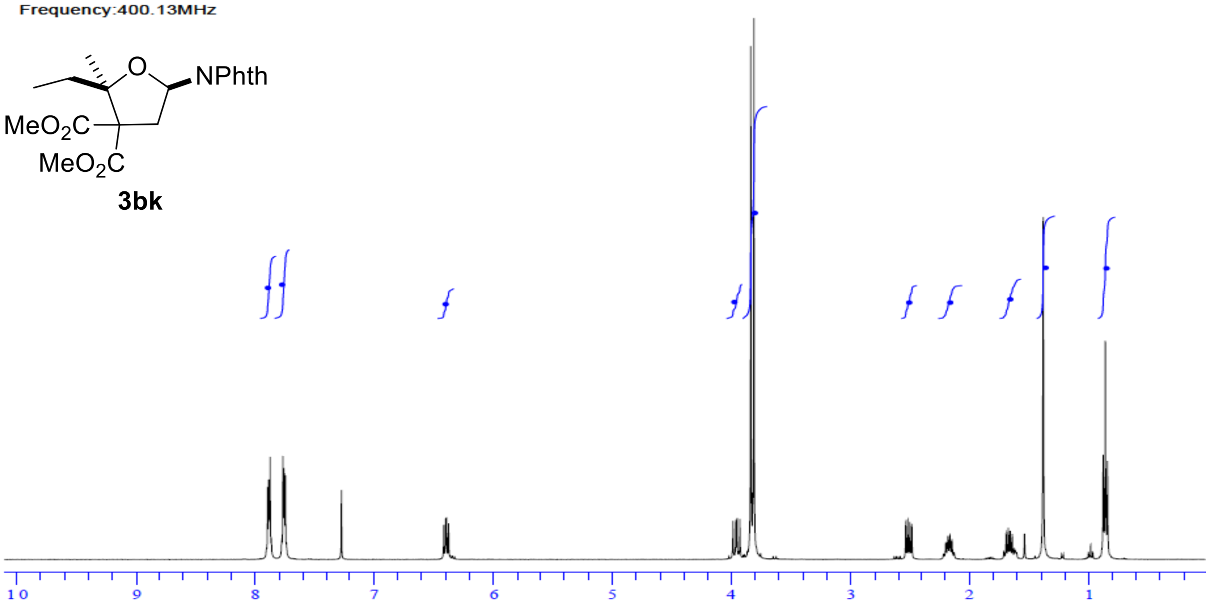

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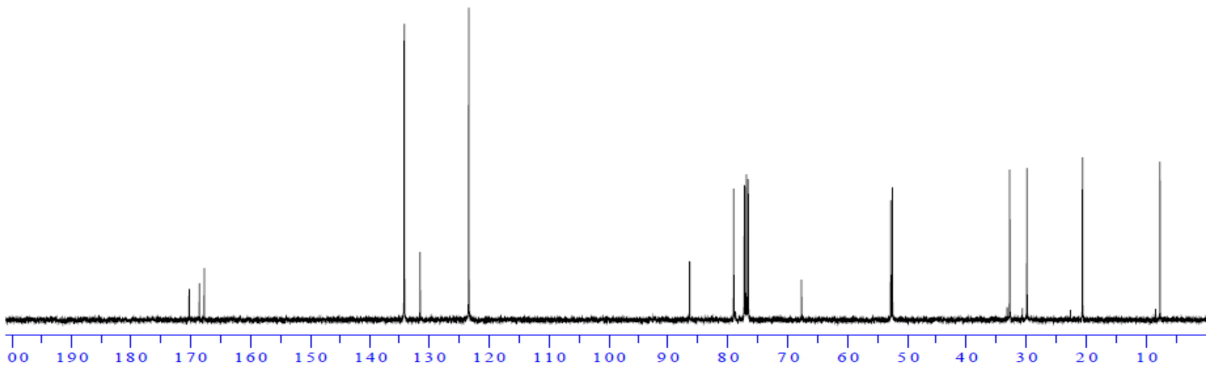

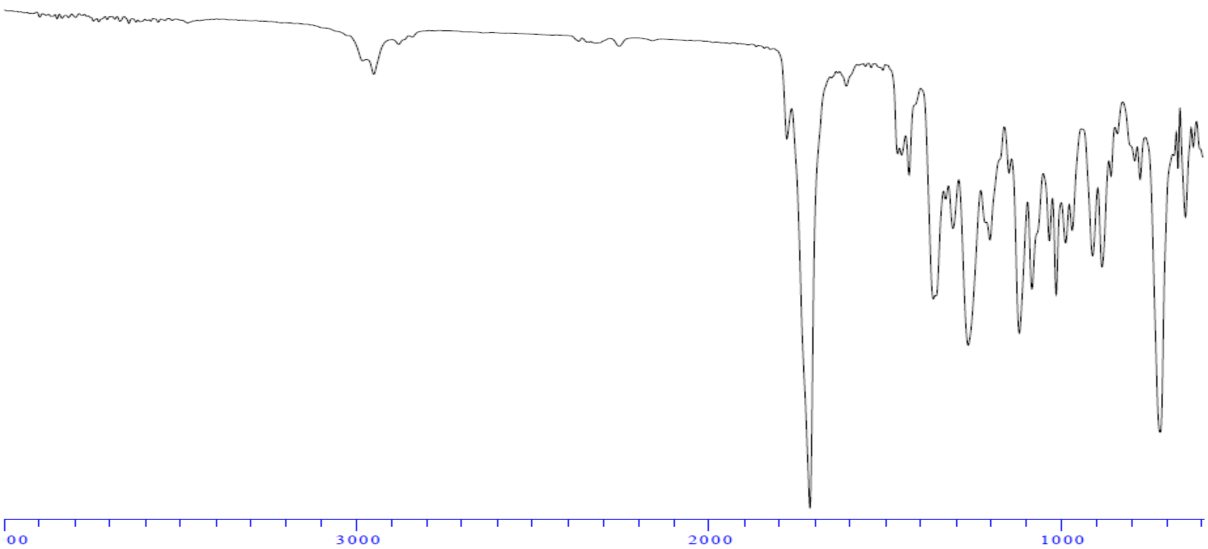

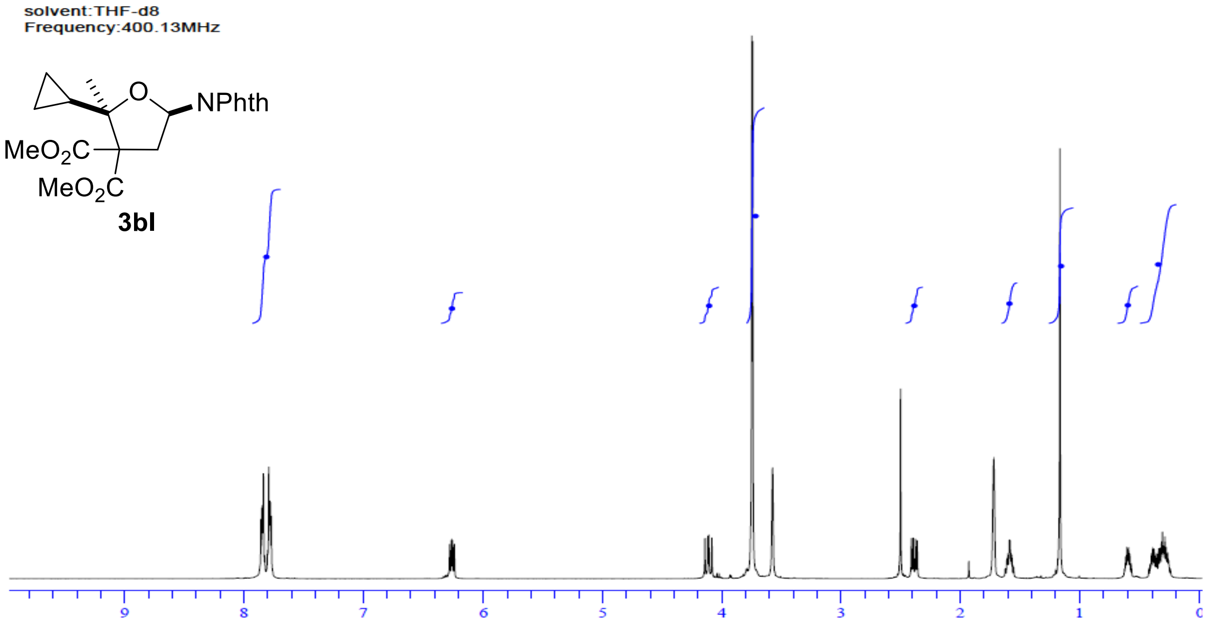
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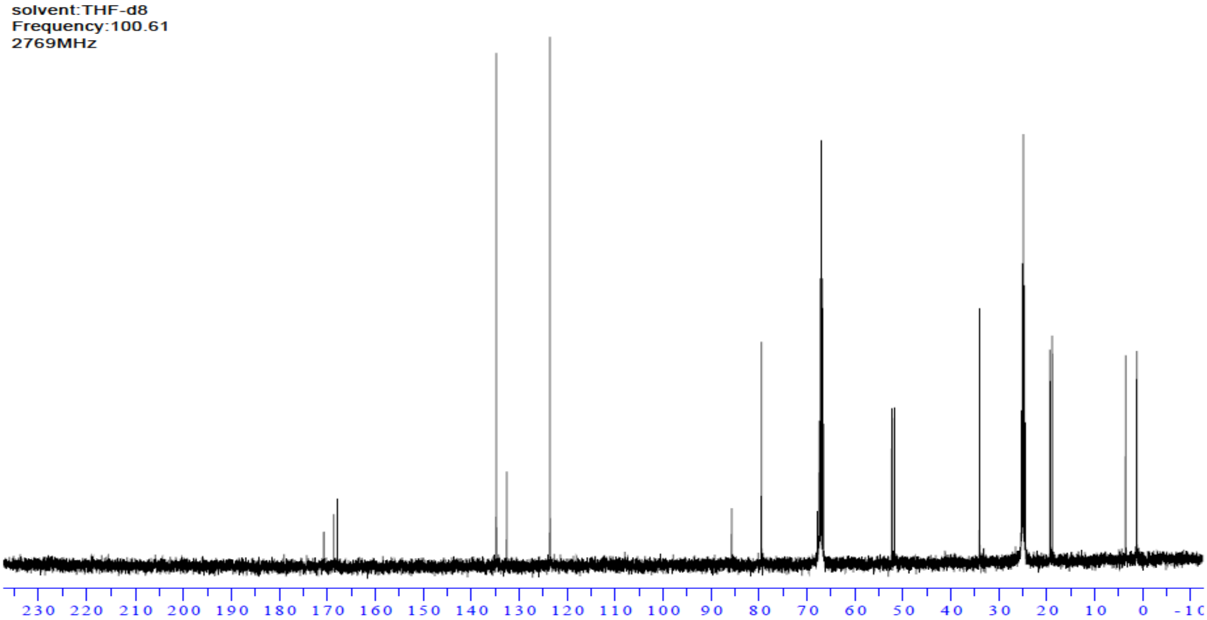
NPhth
MeO_2C
MeO_2C
3bl
9
8
7
6
5
4
3
2
1
0


solvent:THF-d8
Frequency:100.61
2769MHz
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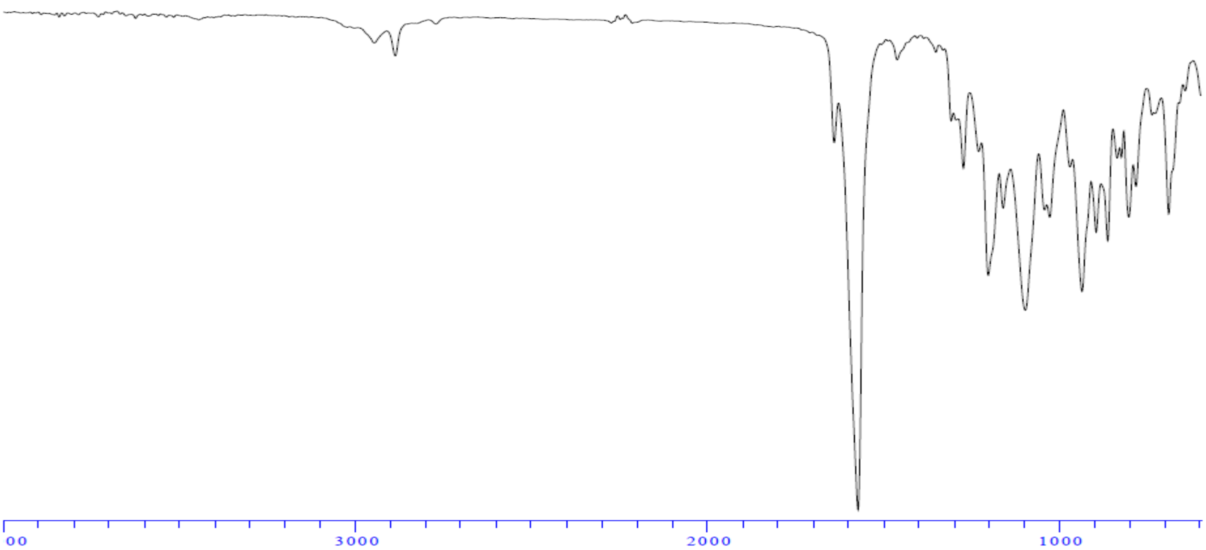
00
3000
2000
1000

solvent:<CDCl3>
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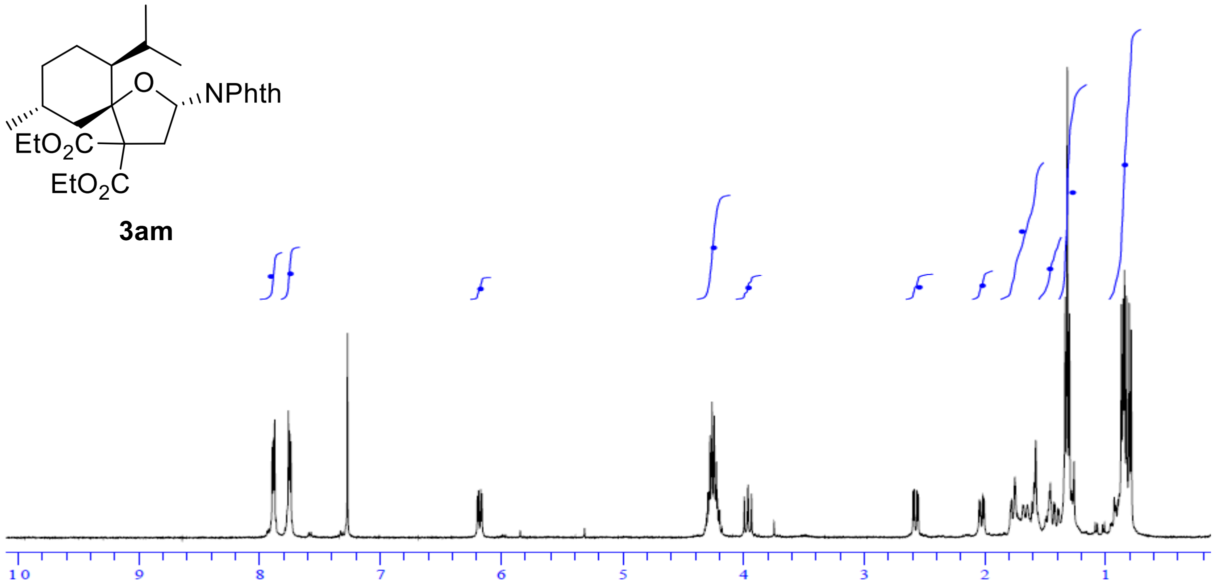
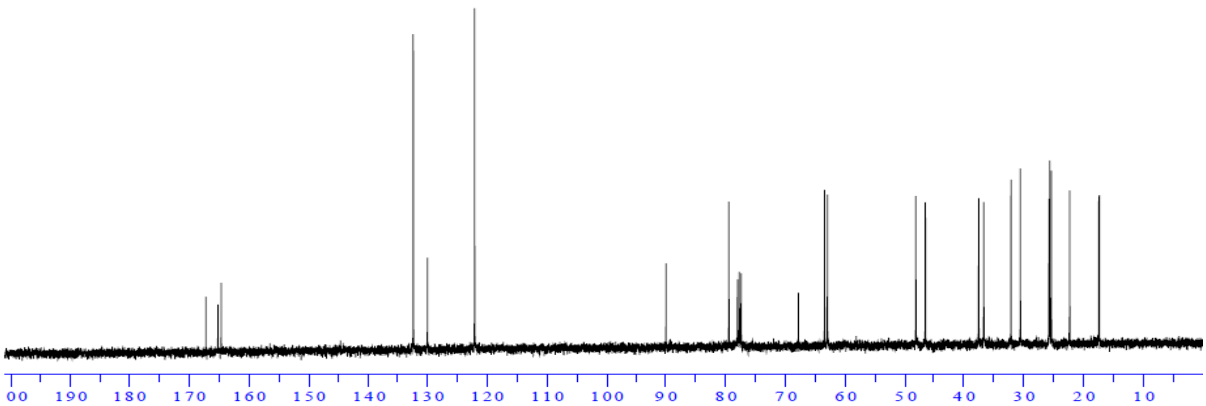
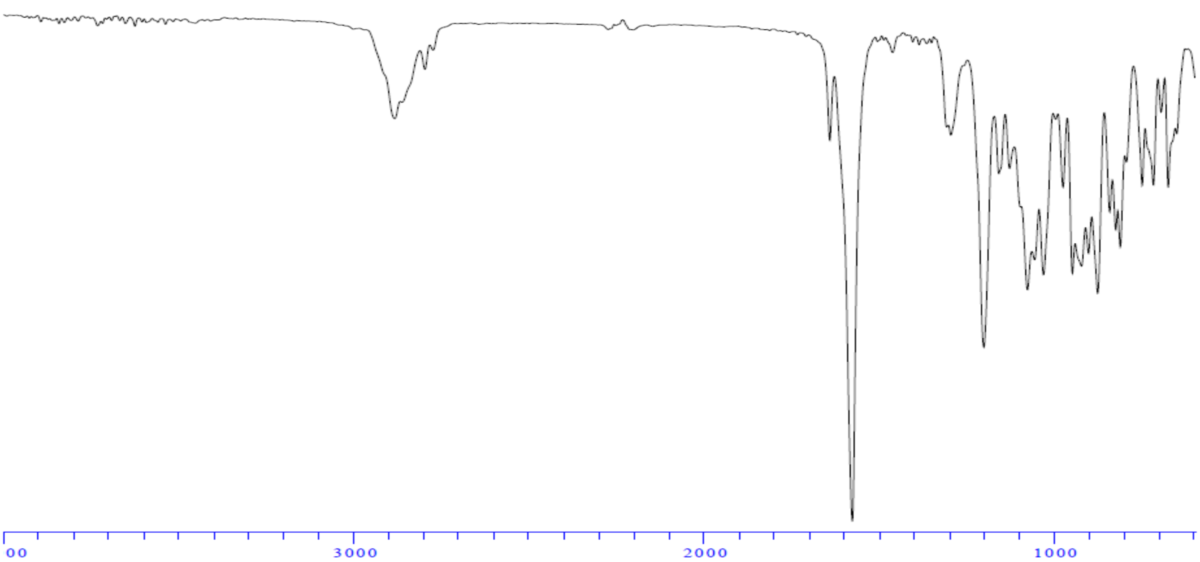


3am

solvent:<CDCl3>
Frequency:100.612769MHz

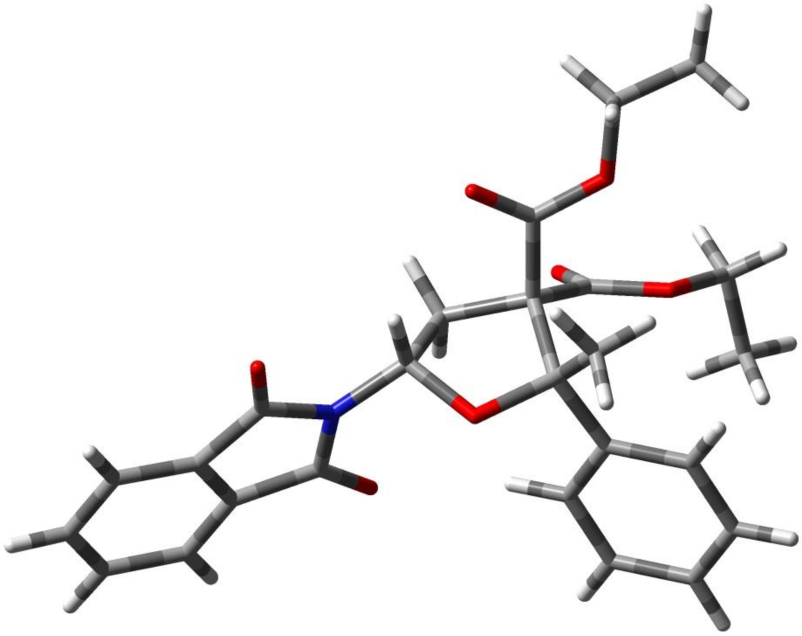




6 Crystallographic data

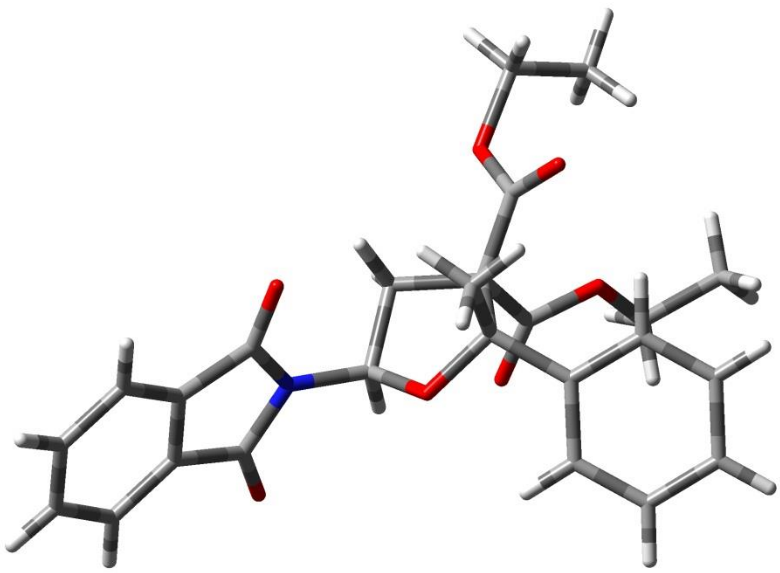
Compound **3aa** was crystallized from *i*PrOH.

The crystal structure of **3aa** (image below) has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number : CCDC 858768.



Compound *epi*-**3aa** was crystallized from *i*PrOH.

The crystal structure of *epi*-**3aa** (image below) has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number : CCDC 858769.



Compound **3am** was crystallized from *n*-hexane.

The crystal structure of **3am** (image below) has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number : CCDC 861951.