The synthesis of the new 3-piperidinol chiral building blocks from substituted pyridines and the synthesis of new vitamin C analogues

Dissertation

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The experimental part of this work was done from October 2001 to June 2005 in the Department of Chemistry and Pharmacy in the University of Regensburg.

To my supervisor, Prof. Dr. Oliver Reiser, I am very grateful to this interesting project, the chance to fulfil this work and his often support.

Table of contents

Abbreviations and symbols

AA	ascorbic acid
Ac	acetyl
AcOEt	ethyl acetate
AOS	active oxygen species
9-BBN	9-Borabicyclononane
BINAP	2,2’-bis(diphenylphorphino)-1,1’-binaphthyl
Bn	benzyl
br	broad
conc.	concentrated
COX-2	cyclooxygenase-2
dec.	decomposed
dd	double doublet
dt	double triplet
DIBAL	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMF	*N,N’*-dimethylformamide
DMP	Dess-Martin-Periodinane
DMSO	dimethylsulfoxide
ee	enantiomer excess
equiv.	equivalent
HRMS	high resolution mass spectrum
IR	infrared spectroscopy
MCPBA	*meta* chloroperoxybenzoic acid
Mp	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
PCC	pyridinium chlorochromate
PE	petroleum ether
Pg	protecting group
Ph	phenyl
p-TSA	*para* toluenesulfonic acid
rt	room temperature
s	singlet

SVCT2	sodium-dependent Vitamin C transporter 2
t	triplet
TBAF	*tert*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilylchloride
TBS	*tert*-butyldimethylsilyl
tert	tertial
Tf	trifluoromethanesulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*para*-toluenesulfonyl
TsCl	*para*-toluenesulfonyl chloride
UV	ultraviolet spectroscopy

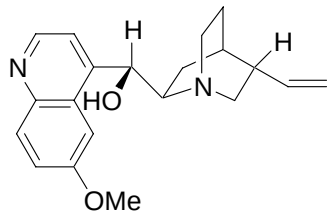
Part I

The synthesis of new 3-piperidinol chiral building blocks from substituted pyridines

1 Introduction

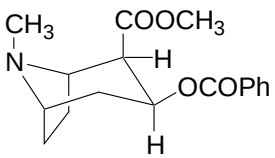
Alkaloids comprise numerous families of nitrogen-containing organic compounds which occur widely in the plant kingdom. Alkaloids are often considered to be “waste products” of the vital process in plants because they are accumulated in the easily detachable parts: the bark, leaves and fruits.

Quinine is a representative of the alkaloids. It has four asymmetric carbon atoms and can exist as a number of different stereoisomers. For example, a dextrorotatory diasteromer of quinine, called quinidine, is used as a powerful antiarrhythmic agent in the treatment of tachycardia [1] and ciliary arrhythmia.[2]

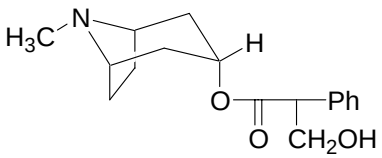


1 Quinine

Piperidine alkaloids widely present in natural compounds. Morphine [3] is well known as a pain killer and also is sometimes used as an adjunct in cancer chemotherapy. Cocaine [4] is present in the leaves of the coca shrub which grows in south America and elsewhere. Atropine [5] is found in belladonna, henbane, Jamestown weed and other plants of the nightshade family, and was at one time widely used in ophthalmic practice for diagnosis and treatment.



2 Cocaine



3 Atropine

3-piperidinols [6] play an important role in piperidine alkaloids and its derivatives have received much attention owing to a variety of their biological activities. Especially, 2,6-(*cis* or *trans*)-disubstituted-3-piperidinols, [7] such as Prosopis [8] and Cassia alkaloids, [9] have already displayed strong activities in biological and pharmaceutical test. Therefore, many methods leading to the synthesis of these compounds have been developed to date.[10]

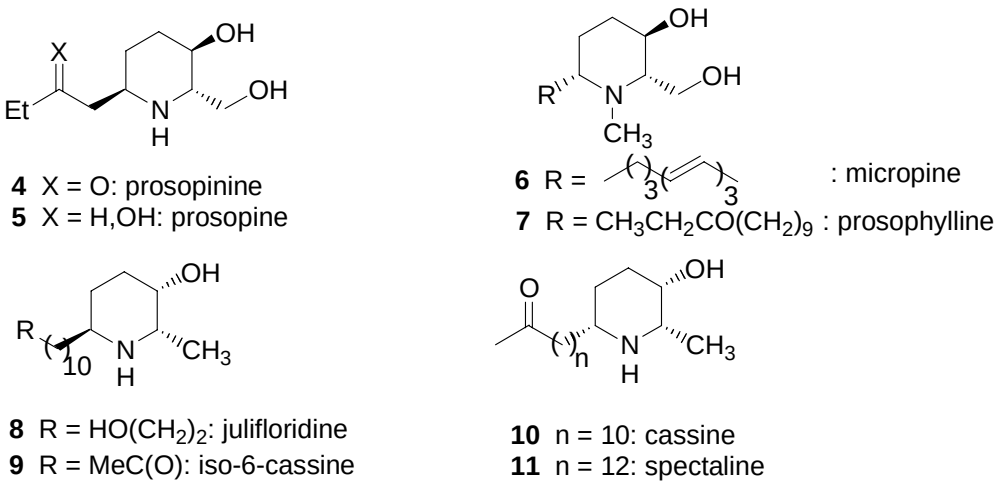
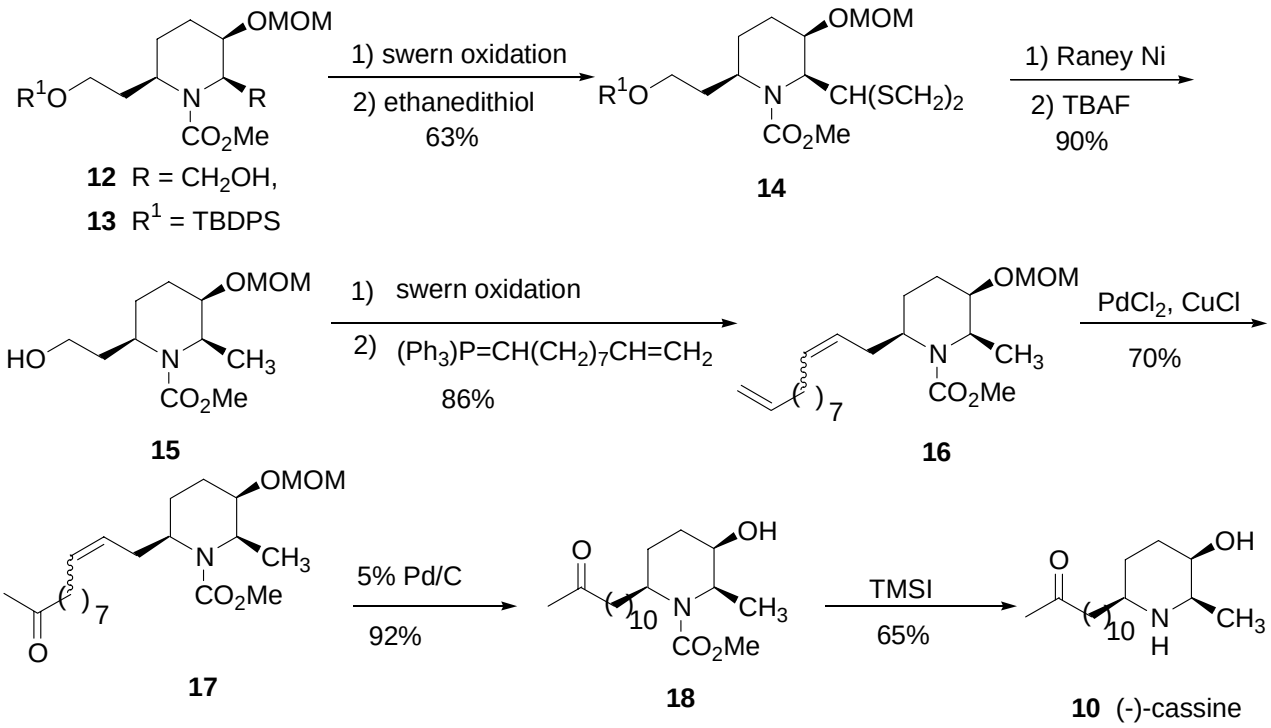


Figure 1. Summary of 3-piperidinols widely existed in nature

The construction of chiral building blocks provides us with powerful tools for the efficient synthesis of biologically active natural compounds. A large number of methods have already been developed for the synthesis of the piperidines, indolizidines, pyrrolizidines, quinolizidines and so on. Chiral 3-piperidinols have proved to be versatile chiral building blocks for the construction of many natural occurring alkaloids. [6-11]

For example, in 1993, (-)-Cassine [12] was for the first time synthesized by T. Momose and



Scheme 1. The first asymmetric synthesis of (-)-cassine

coworkers (Scheme 1).[13] In the same paper, the synthesis of the alkaloid (+)-Spectaline was also published using the same chiral building block **19** (Figure 2). This building block and its enantiomer can also be applied for the synthesis of the following compounds **20**-**24** (Figure 3).[14]

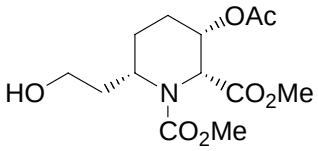


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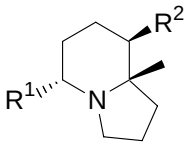
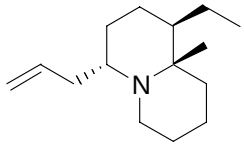
Figure 2.



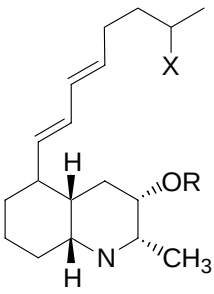
20 $R^1 = (CH_2)_3CH=CH_2$, $R_2 = CH_3$
21 $R^1 = (CH_2)_4CH_3$, $R_2 = CH_3$
22 $R^1 = (CH_2)_5CH=CH_2$, $R_2 = CH_3$
23 $R^1 = (CH_2)_3CH_3$, $R_2 = (CH_2)_2CH_3$



24

Figure 3.

Another example is the synthesis of decahydroquinoline alkaloids, lepadines A, B and C (Figure 4), isolated from the tunicate Clavelina lepadiformis by Steffan [15] and Andersen and co-workers,[16] showed significant cytotoxic activity toward a variety of murine and human cancer cell lines.[16]



25 Lepadin A: X= H_2, R= $COCH_2OH$
26 Lepadin B: X= H_2, R= H
27 Lepadin C: X= O, R= $COCH_2OH$

Figure 4. Lepadines A, B and C

Therefore, the lepadines have already attracted many organic chemists to engage in their total synthesis.[17] For example, N. Toyooka and coworkers developed a new strategy to thesynthesis of lepadin B in 1999 (Scheme 2).[18]

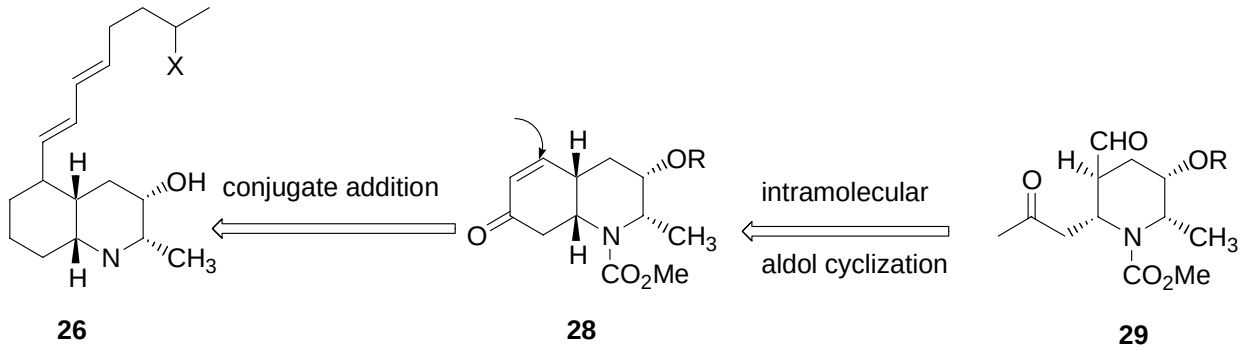
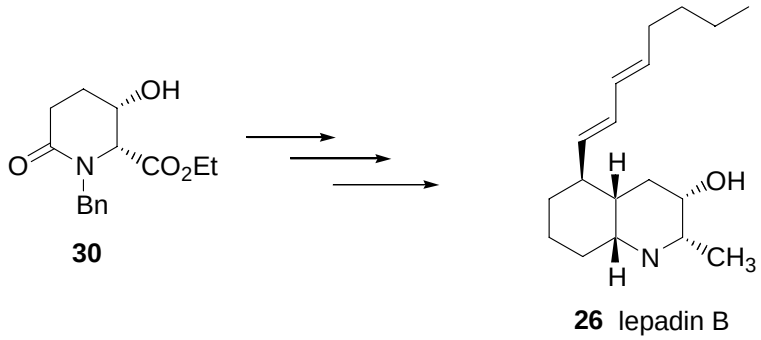


Figure 5. Retrosynthetic strategy for lepadin B



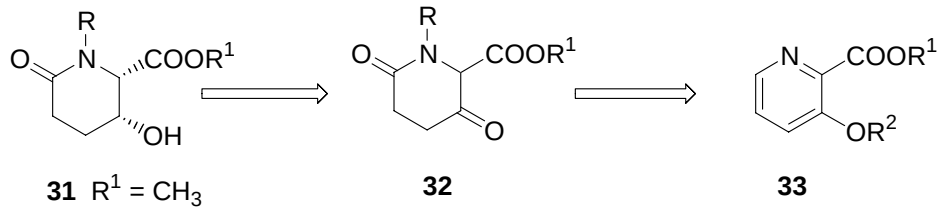
Scheme 2. Enantioselective total synthesis of lepadine B

In this synthetic route, the chiral 2-piperidone **30** [19] is used as the key starting material. Moreover, **30** also has been used in the synthesis of the marine alkaloid clavepictines A and B.[20]

Our interest is focused on the synthesis of these chiral building blocks from readily available pyridines.

2 Synthesis and discussion

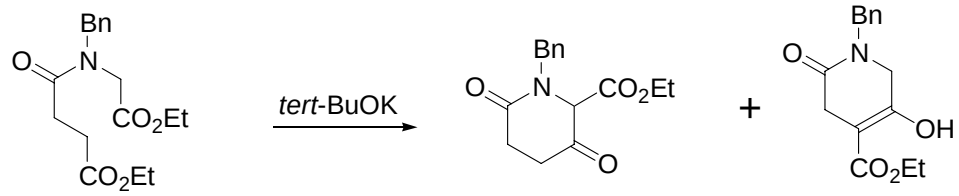
My project is to synthesize the chiral building block **31** and stereoisomers thereof. Our retro synthetic analysis envisioned 3, 6-piperidinedione-2-carboxylic acid methyl ester (**32**, R = H) as a suitable starting material, which in turn could be synthesized from picolic acid derivatives **33**. The β-keto-ester functionality could be enantioselectively reduced either with yeast [21] or with Ru-BINAP catalysts. [22]



31 $R^1 = CH_3$ **32** **33**

Figure 6. Retrosynthetic strategy for **31**

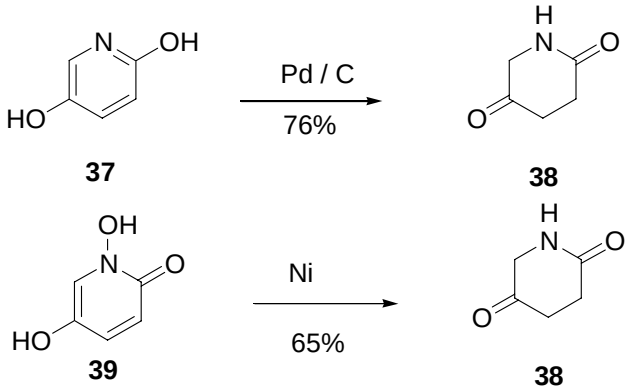
In the literature only one way to synthesize 3,6-piperidinedione **35** was reported. J. Bonjoch et al [23] used amido ester **34** as starting material, which was cyclized with potassium *tert*-butoxide to afford a mixture of **35** and **36** in a ratio of 4:3 in total 84% yield (Scheme 3). The separation of the two isomers, however, is difficult.



34 **35** **36**

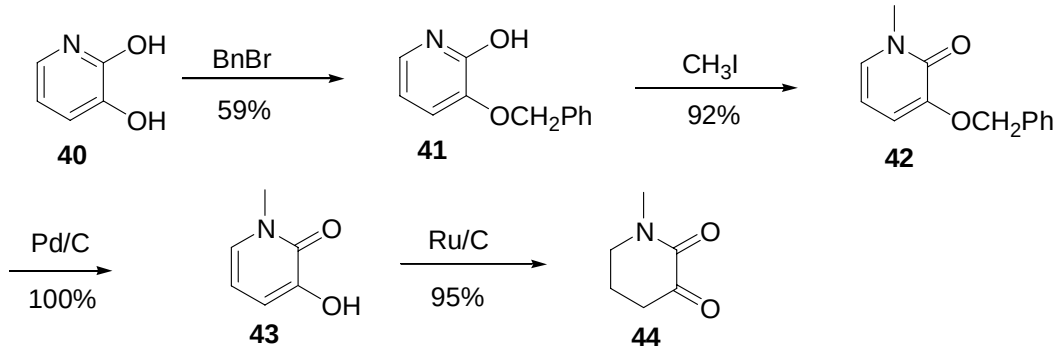
Scheme 3. Dieckmam cyclization to form piperidine-2,5-dione

Therefore, we want to develop a more convenient way to piperidine-2,5-dione **32**. C. Herdeis [24] and H. Takeya et al [25] have already reported that 2,5-piperidinedione **38** can be easily synthesized from 2,5-dihydroxypyridine **37** or 1,5-dihydroxy-2-pyridone **39** by hydrogenation in the presence of palladium/carbon (Pd/C) or Ni in 76% and 65% yield respectively (Scheme 4).



Scheme 4. Synthesis of 2,5-piperidinedione

They also reported that N-methyl-2,3-piperidione **44** can be prepared from N-methyl-2,3-dihydroxypyridine **43** by hydrogenation under the catalyse of Ru/C in 95% yield [26] (Scheme 5).



Scheme 5. Synthesis of N-substituted 2, 3-piperinedione **44**

These results suggested that it should be possible in a stereo-divergent manner to reduce substituted pyridine to make our target, 3, 6-piperidiones. Based on above research, the new procedure from substituted pyridine **47** should be developed in this work.

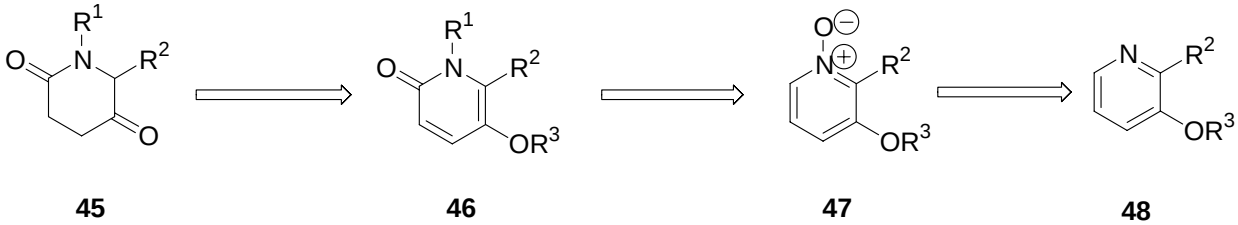


Figure 7. Retrosynthetic strategy of 3,6-piperidinedione **45**

As a key step in our synthetic strategy was envisioned rearrangement of pyridine-N-oxides to1*H*-pyridin-2-ones.[27] Katada first reported that pyridine N-oxide **49** is rearranged by acetic

anhydride to 2-acetoxy pyridine **52**. The product normally isolated is the α-oxo compound **53** because of the facile hydrolysis of α-acetoxy derivatives.[28]

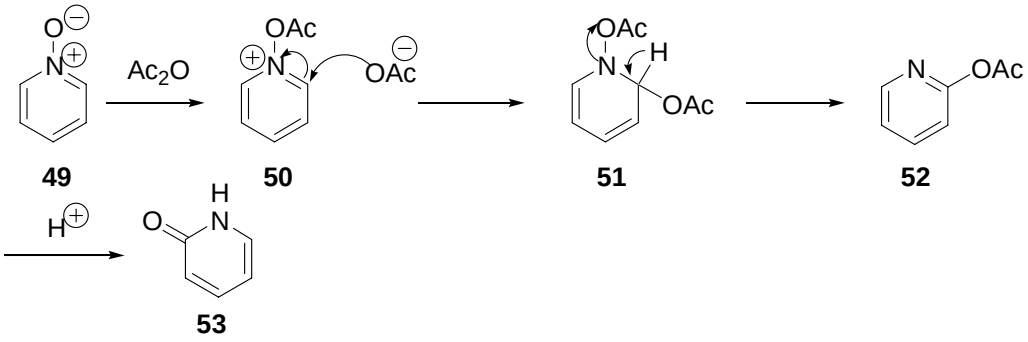
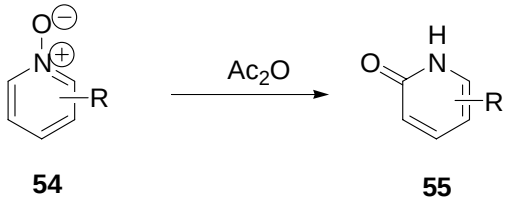


Figure 8. The mechanism of rearrangement reaction with acetic anhydride

In general, there is a very strong tendency for this rearrangement reaction to occur at the α position. For example, pyridine N-oxide **49** can be converted exclusively into 1*H*-pyridin-2-one (**53**) in quantitative yield. If one of the α positions is occupied, reaction will occur at the unsubstituted α position;[29] if both of the α positions are occupied, reaction will occur at γ position[30]. Especially, for 3-substituted pyridine 1-oxides, the rearrangement reaction will usually give a mixture of 2-and 6-pyridiones with a preponderance of 2-pyridones.[27] Many substituted pyridine 1-oxides **54** were examined for this rearrangement reaction, and the result is summarized in Table 1.

Table 1. The conversion of N-oxide into α-oxo-pyridine by reaction with acetic anhydride



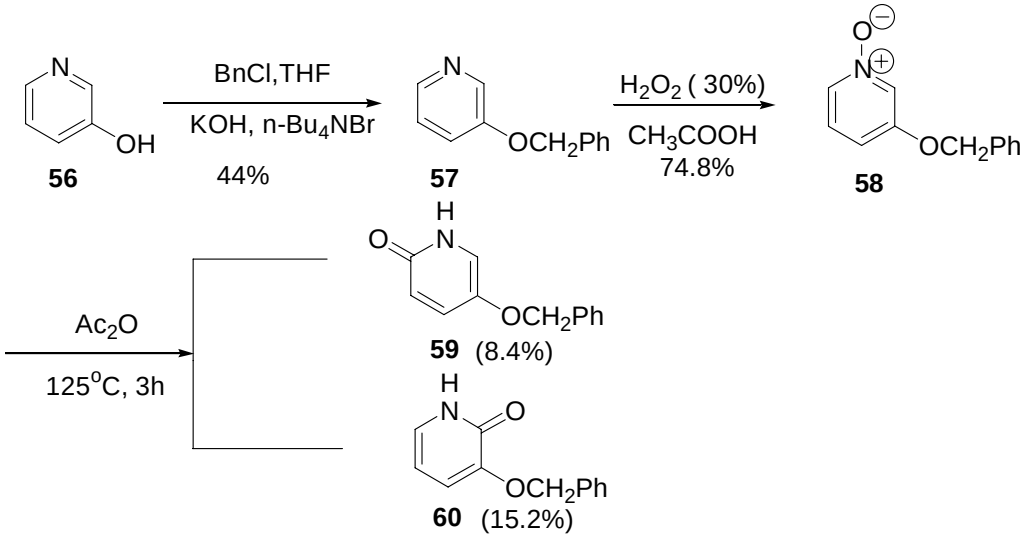
R	position of oxo group introduced	yield
H	2-	100%
3-COOH	2- and 6-	35% and 3%
4-OEt	2-	-
3-COOEt	2- and 6-	28% and 16%
3-X	6-	34%
2-OCH_3	6-	34%
4-OCH_3	2-	56%
3-CH_3	2- and 6-	40% and 40%

3-NO_2	2-	50%

2.1 Synthesis of 2, 5-piperidiones

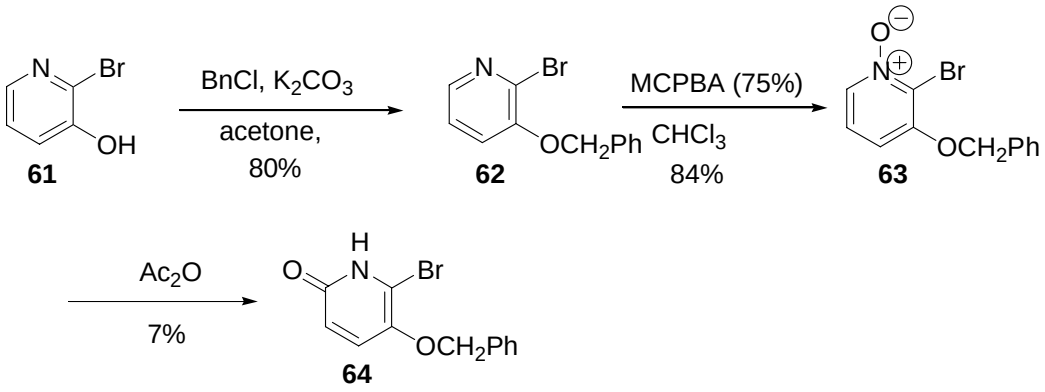
It is already known that 2,5-dihydroxypyridine can be prepared from 2 or 3-hydroxy pyridine by direct oxidation with potassium peroxy disulfate in 18% and 11% respectively.[31] Furthermore, two other routes, one seven step synthesis from 2-aminopyridine [32] and one eight step route from 3-bromopyridine [33] have also been described.

Therefore, according to our strategy, we started from the commercially available 3-hydroxypyridine (**56**), which was protected by reaction with benzyl bromide in DMF using small amounts of n-$Bu_4N^+Br^-$ to afford **57** in a moderate yield.[34] Then, **57** was converted to its oxide **58** by using perhydrol (30%) in acetic acid in good yield.[35] Unfortunately, a mixture of **59** and **60** was obtained in total 24% yield in a ratio of 1:2 in the subsequent rearrangement reaction with acetic anhydride (Scheme 6).



Scheme 6. The synthesis of 5-benzyloxy-2-pyridione

Next, we chose 2-bromo-3-hydroxypyridine (**61**), which could be easily prepared from 3-hydroxypyridine (**56**) through bromination in sodium hydroxide solution in 54% yield,[36] as our testing substrate (Scheme 7).



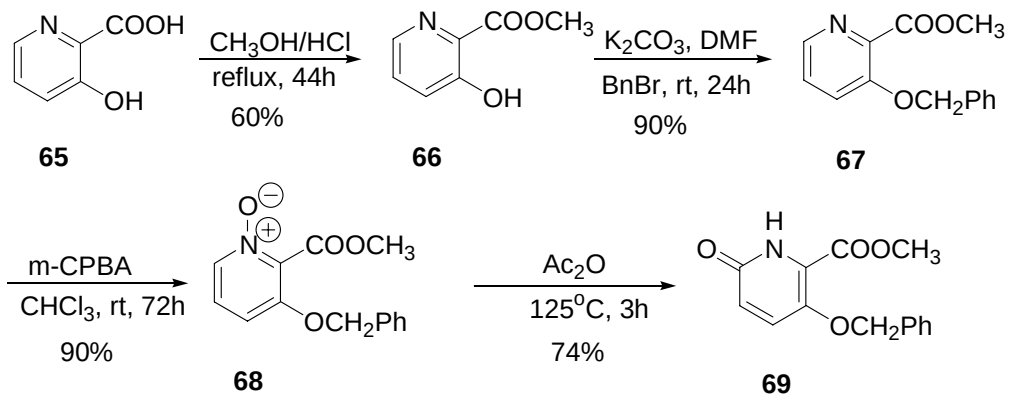
Scheme 7. Synthesis of 5-benzyloxy-6-bromo-1*H*-pyridin-2-one

Compound **61** reacted with benzyl chloride and potassium carbonate in acetone, to afford **62** in 80% yield. Subsequently, **62** was oxidized by MCPBA (75%) in $CHCl_3$ at room temperature to form **63** in 84% yield; **63** was rearranged with acetic anhydride at 125^{o}C for 3 h and converted to desired **64** in 7% yield.

Since the pyridine ring is a π-deficient system, nucleophile substitution will occur if there is a good leaving group in 2-or 6-position. 2-bromo-3-benzyloxy pyridine-1-oxide **63** can give 5-benzyloxy-6-bromo-1*H*-pyridin-2-one **64**, but in a low yield.

Next, we investigated 3-hydroxy-pyridine-2-carboxylic acid (**65**) as our next substrate. It is also a commercially available material.

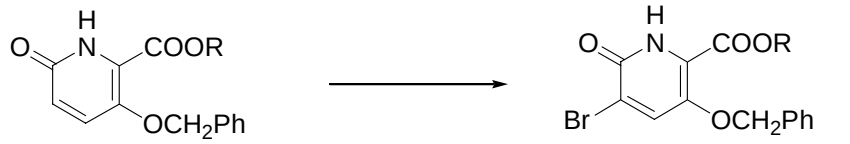
We started from 3-hydroxy-pyridine-2-carboxylic acid (**65**), which is to the synthesis of 5- and 6-disubstituted-pyridin-2-ones, converted into its methyl ester **66**.[37] Subsequent reaction with benzyl bromide yielded 3-benzyloxy-pyridine-2-carboxylic acid methyl ester (**67**) in high yield, which was oxidized by MCPBA to afford corresponding oxide **68**. Upon treatment with excess of anhydrous acetic anhydride, **69** was obtained in good yield following the established rearrangement sequence [38] (Scheme 8).



Scheme 8. The synthesis of the key intermediate **69**

2.2 Bromination

In order to functionalize **69**, a number of different reactions were tested. Firstly, compound **69** was reacted directly with bromine in aqueous solution at room temperature for 1 h. After purification, **70** was obtained as a white solid in 74% yield. Similarly, compound **71** also gave corresponding bromide **72** in 50% yield (Scheme 9).

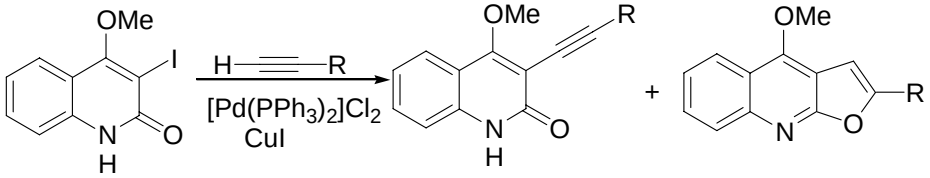


69 R = CH_3
71 R = Bn

70 R = CH_3 74%
72 R = Bn 50%

Scheme 9. The bromination of 1*H*-pyridin-2-ones

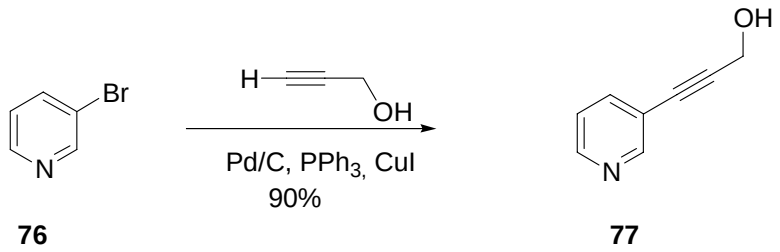
The intermediates **70** and **72** can subsequently be functionalized, using palladium-catalyzed cross coupling reactions as the key step. J. Reisch and coworkers [39] have reported that 3-iodo-4-methoxy-1*H*-2-quinolinone (**73**) could couple with alkynes in the catalysis of $[Pd(PPh_3)_2]Cl_2$, to afford a mixture of **74** and **75** in different ratio, depending on the substrate of alkynes. Furthermore, compound **74** could be transferred into **75** upon the treatment with $TBAF{\cdot}3H_2O$ in excellent yield [40] (Scheme 10).



73 **74** **75**

Scheme 10. $[Pd(PPh_3)_2]Cl_2$ catalyzed Sonogashira coupling reaction of **73**

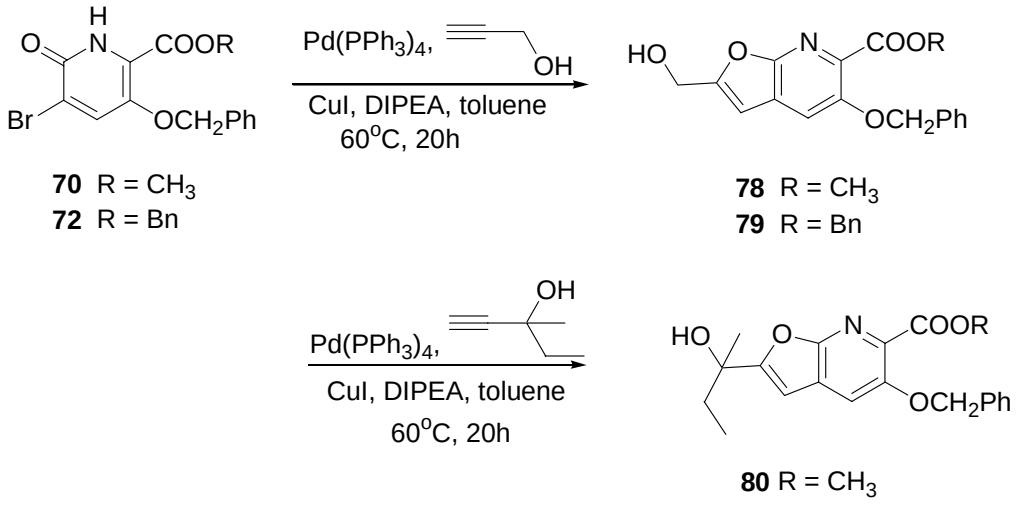
L. S. Bleicher and coworkers [41] also reported that the coupling of 3-bromo-pyridine (**76**) and propargyl alkohol in the presence of catalytic amounts of 10% Pd/C, PPh_3 and CuI (in a ratio of 1: 4: 2), and K_2CO_3 (2.5 equiv) in a DME-water mixture (1:1) could proceed smoothly in 90% yield (Scheme 11).



76 **77**

Scheme 11. Sonogashira coupling reaction of 3-bromopyridine (**76**)

Based on above research, we hoped to develop this method to the 3-bromo-pyridin-2-one system. As we expected, compound **70** and **72** were subjected to the conditions of palladium catalyzed Sonogashira coupling reaction [42] to afford **78**-**80** in quite good yield (Scheme 12). This is for the first time to form this new system.



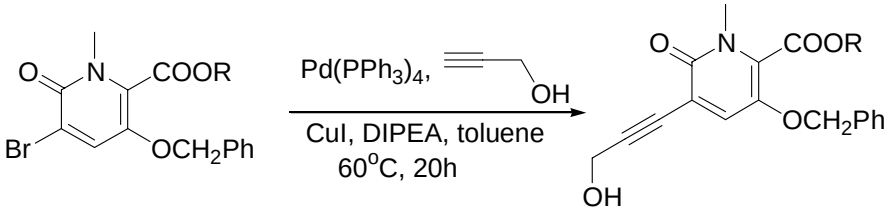
70 R = CH_3
72 R = Bn

78 R = CH_3
79 R = Bn

80 R = CH_3

Scheme 12. Sonogashira coupling reaction of 3-bromo-1*H*-pyridin-2-ones

Interestingly, N-alkylated intermediate **81**, was also subjected to this coupling reaction, afforded the substituted pyridione **83** in good yield, but no cyclization was observed (Scheme 13).



81

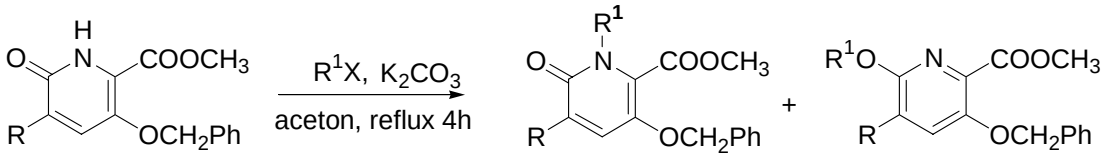
83 R = CH_3

Scheme 13. Sonogashira coupling reaction of **81**

2.3 Alkylation

Next, we needed to introduce protecting group onto nitrogen because N-protected 2-pyridiones may be more useful in the synthesis of alkaloids. At the beginning, we wanted to explore the possibility of alkylation, however, a mixture of *O*-alkylated and *N*-alkylated products were obtained. Table 2 shows the result of our research.

Table 2. Alkylation of 1*H*-pyridin-2-one



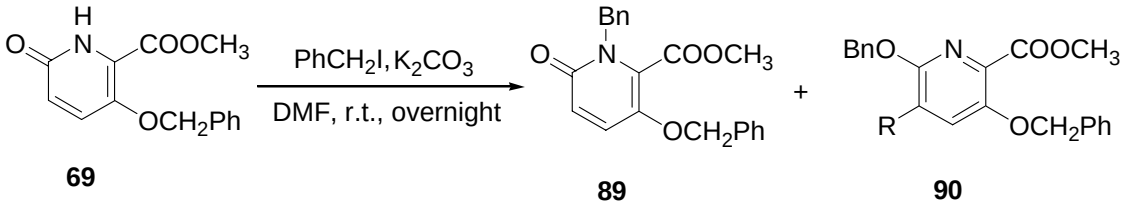
Entry	Substrate	R^1X	N-alkylation	O-alkylation
1	R = H **69**	CH_3I	66% **84**	34% **85**
2	R = Br **70**	CH_3I	65% **81**	33% **82**
3	R = H **69**	$CH_3CH_2CH_2CH_2Br$	6% **86**	24% **87**
4	R = H **69**	$BrCH_2COOCH_3$	-	86% **88**

For example, **69** was easily converted into **84** by alkylation with excess of methyl iodide in the presence of K_2CO_3 in acetone in 66% yield (Figure 15). Similarly, 3-benzyloxy-5-bromo-6-oxo-1, 6-dihydro-pyridine-2-carboxylic acid methyl ester (**70**) also gave the N-alkylated product **81** mainly under the same condition.

In contrast, employing 1-bromobutane and methyl ester bromoacetate, gave mainly *O*-alkylated products.

Unfortunately, also N-benzylation of **69** could not be achieved regioselectively under a variety of conditions. Various benzyl halides, reaction time, base and solvent were tested in order to optimize the condition (Table 3). The best condition were found to react **69** with benzyl iodide in the presence of K_2CO_3 in DMF, nevertheless, l-benzyl-3-benzyloxy-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (**89**) was obtained in only 40% yield, along with 60% of the O- alkylated product **90** (Table 3, Entry 5).

Table 3. Benzylation of intermediate **69**

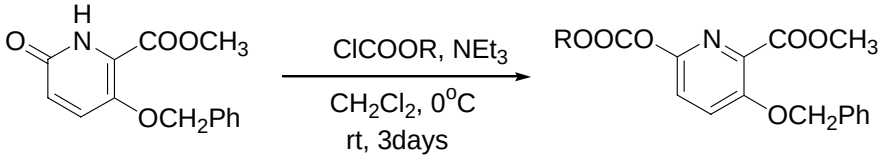


69 **89** **90**

Entry	BnX	Solvent	base	yield **89**	yield **90**
1	Br	DMF	NaH	19	70
2	Br	DMF	K_2CO_3	34	66
3	Br	acetone	K_2CO_3	25	72
4	Cl	DMSO	K_2CO_3 (TDA-1)	27	72
5	I	DMF	K_2CO_3	40	60
6	I	acetone	K_2CO_3	26	65
7	Br	1,4-dioxane	Cs_2CO_3	33	67
8	Br	CH_3CN	K_2CO_3 ($Bu_4N^+Br^-$)	34	66
9	I	DMSO	KOH	27	72

2.4 Alkoxycarbonylation [43]

In the following, the alkoxycarbonylation of the nitrogen atom or oxygen atom of the 1*H*-pyridin-2-one **69** was examined. Intermediate **69** was treated with triethylamine and chloroformate methyl ester, allyl ester or phenyl ester in CH_2Cl_2, to yield a single product. For chloroformate methyl ester, 90% of O-methoxycarbonylated compound (**91**) was obtained. For allyl ester, 58% of O-alkylated product and for phenyl ester, 74% of O-protected product was obtained, respectively (Scheme 14). The proposed structures **91-93** were supported by the ^{1}H NMR and ^{13}C NMR spectra**.**



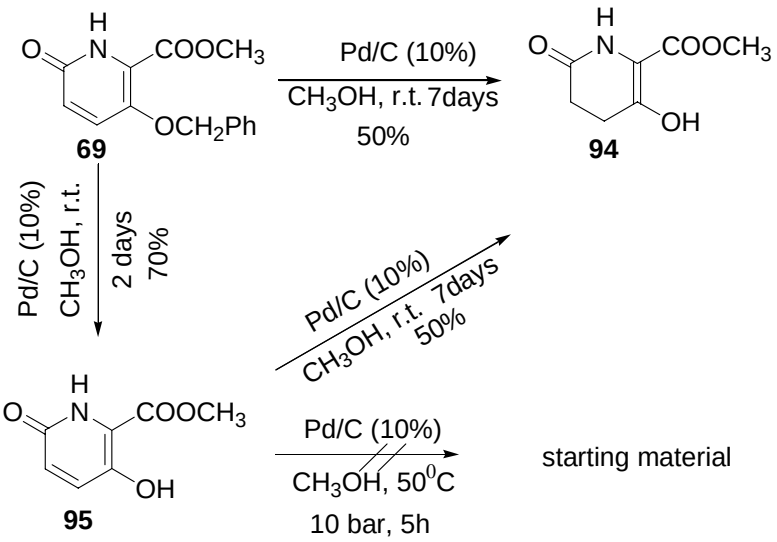
69

91 R = CH_3 90%
92 allyl 58%
93 Bn 74%

Scheme 14. The alkoxycarbonylation of **69**

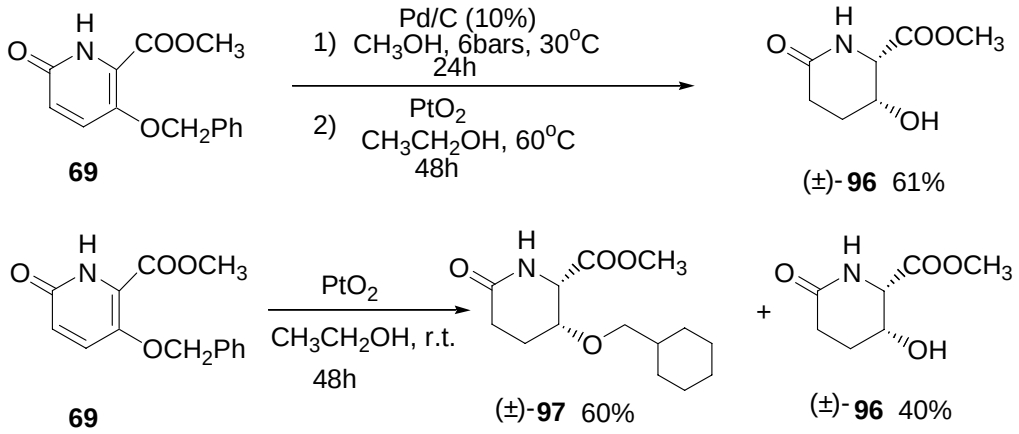
2.5 Hydrogenation

The 1*H*-pyridin-2-one derivatives described in the previous chapter were next investigated in hydrogenation reaction. The unprotected substrate **69**, using palladium on charcoal, proceeded very slowly. Even after 1 week, the conversion ratio was only 50%. Hydrogenation at elevated pressure (10 bar) and temperature (50°C) did not improve the yield of **94** (Scheme 15).



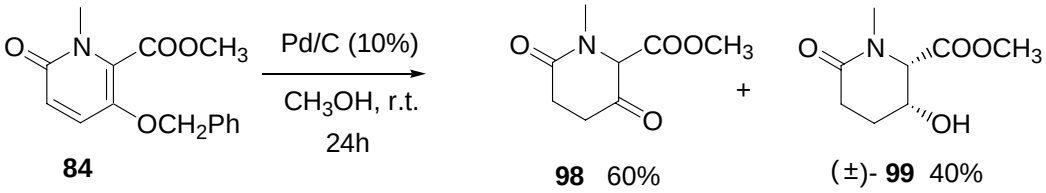
Scheme 15. Hydrogenation of **69** catalyzed by Pd/C

Because of the difficulties encountered with hydrogenation of **69** using Pd/C, we wanted to try the more active catalyst PtO_2. To our surprise, not only the double bonds in pyridine ring can be hydrogenated completely, but also those of in phenyl ring of the benzyloxy group. The new cyclohexyl derivative **97** was formed in 60% yield, along with 40% of the desired 3-pyridinol **96** (Scheme 16). The *cis* stereo-chemistry between the C-2 and C-3 substitutents was established via ^{1}H NMR data, using coupling constants of 3.8 Hz (**96**) and 3.4 Hz (**97**) between H-2 and H-3 as the indication.[44]



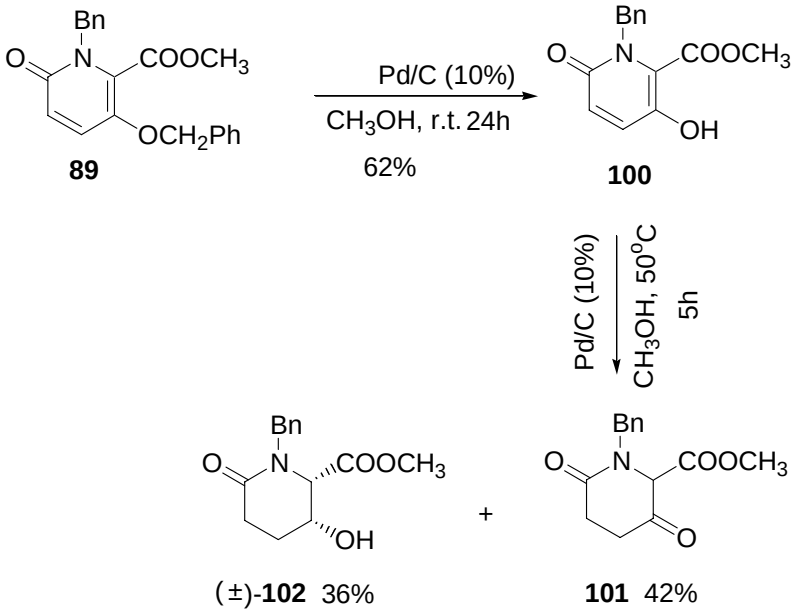
Scheme 16. Hydrogenation of **69** catalyzed by PtO_2

The N-protected substrates **84** and **89**, were more easily to be hydrogenated than the unprotected substrate **69**. Thus, **84** could be easily converted into **98** in 60% yield, along with **99** (40%) upon hydrogenation using 10% of Pd/C (Scheme 17).



Scheme 17. Hydrogenation of **84**

Compound **89** could only be hydrogenated to the pyridine **100** at room temperature. Sequently, **100** was hydrogenated at 50°C and 10bar hydrogen pressure to afford the expected compound **101,** along with **102** (36%) (Scheme 18).



Scheme 18. Hydrogenation of **89**

2.6 Oxidation reaction

Next, the side products **99** and **102** produced in the previously described hydrogenation, could be oxidized to the corresponding ketones **98** and **101**. Pyridinium chlorochromate (PCC) [45] and Dess-Martin-Periodinane (DMP) [46] both decomposed the substrate (Entry 1 and 2). Swern oxidation [47] afforded the corresponding ketone only in 54% yield (Entry 3).

Using modified Swern oxidation and choosing P_2O_5 as oxidant,[48] instead of oxalyl chloride, can afford the ketone also in a moderate yield (Entry 4). The results are shown down (Table 4). In contrast, compound **102**, could be oxidized easily by DMP in CH_2Cl_2 in 83% yield (Entry 6).

Table 4. The oxidation of 3-pyridinol **99** and **102**

Entry	substrate	reaction reagent	reaction condition	yield
1	**99**	DMP, CH_2Cl_2,	rt, 5days	destroyed
2	**99**	PCC, CH_2Cl_2	molecular sieves 4A	destroyed
3	**99**	DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2	-78	54%
4	**99**	DMSO, P_2O_5, Et_3N, CH_2Cl_2	rt, 2h	56%
5	**99**	PCC, NaOAc, CH_2Cl_2	rt, 2h	<40%
6	**102**	DMP, CH_2Cl_2,	rt, 2h	83%

2.7 Baker's yeast reduction

As the next step, the reduction of the piperidine-based β-keto ester was investigated by yeast reduction.[20] The most widely applied transformation using baker's yeast is the reduction of β-keto ester to the corresponding β-hydroxy esters, which often results in excellent chemical and optical yields. This methodology is shown below (Figure 9).

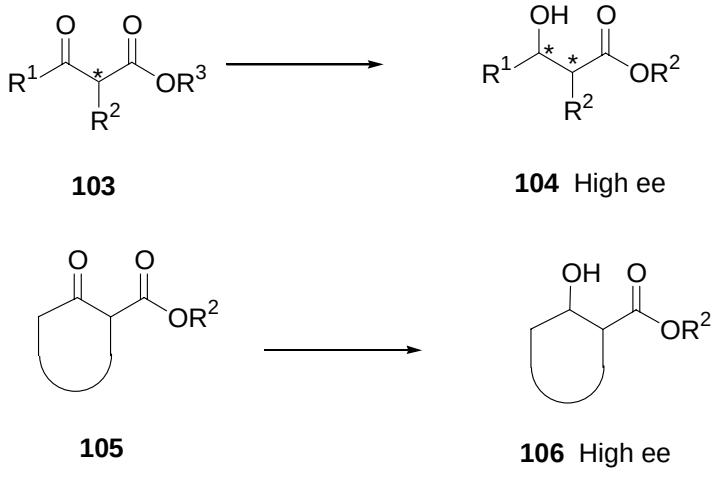
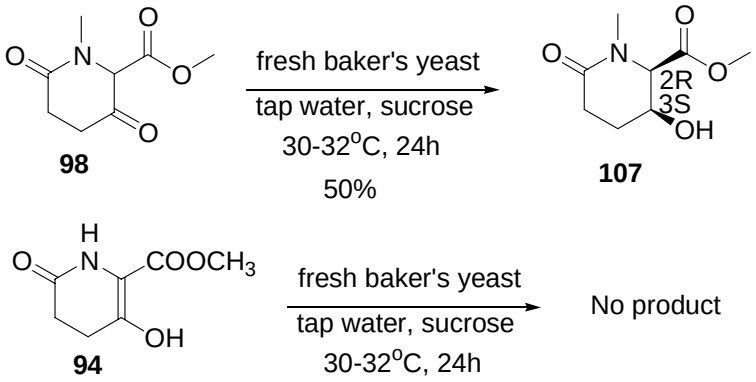


Figure 9.

In general, this methodology, at least with simple, saturated acetoacetate derivatives, has been superceded by the highly efficient Noyori hydrogenation methods using rhodium(I)-BINAP complexes as the catalysts.[21] However, for cyclic β-keto ester this latter method is

not so extensively explored. In such cases, baker's yeast has been shown to be particularly effective in delivering *cis*-β-hydroxy ester with good to excellent levels of enantiomeric enrichment.[49]

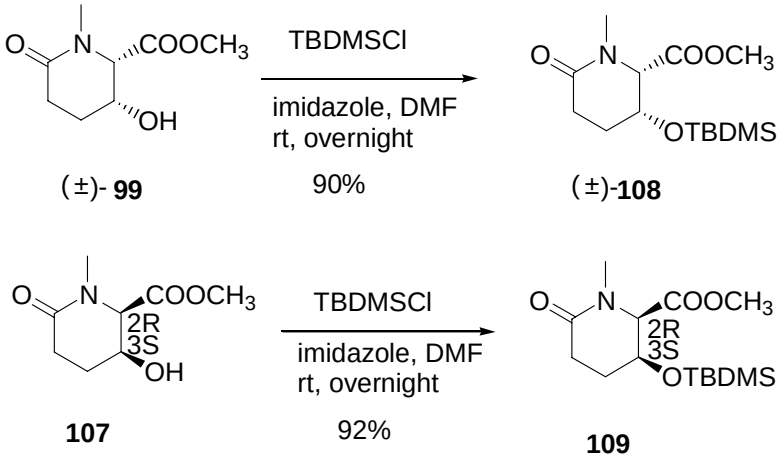
The yeast reductions are performed using the established method detailed by the Seebach group [50] using commercial baker's yeast available from a local supermarket and sucrose. The yeast reduction of 1-benzyl-3,6-dioxo-piperidine-2-carboxylic acid ethyl ester **101** was already reported. We succeeded to obtain our desired product β-hydroxy ester **107** in enantiomeric pure form (Scheme 19) from the β-keto ester **98**. But for the unprotected substrate **94**, we could not get the expected compound under the same condition.



Scheme 19. Baker's yeast reaction

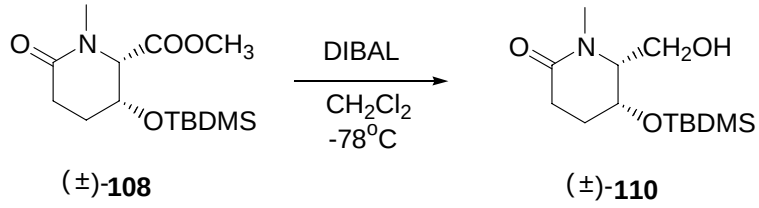
2.8 Protecting hydroxyl

Furthermore, the hydroxyl group of *cis*-3-pyridinol **99** could react with TBDMSCl and imidazole in DMF to form its silyl ether **108** in 90% yield. Similarly, the new resulting chiral building block **107** could also be converted to its corresponding more stable silyl ether **109** in the same condition in 92% yield (Scheme 20).



Scheme 20. Protecting with TBDMSCl

We also investigated the reduction of the TBDMS-protected 2-piperidinone **108** with 1M DIBAL hydride to convert the ester to alcohol **110** (Scheme 21), which may be more useful in the synthesis of other alkaloids.



(±)-**108** (±)-**110**

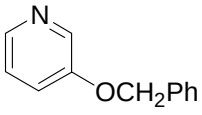
Scheme 21. The ester reduction of **108** by treating with DIBAL

In Conclusion, we have developed a new synthesis to the new chiral building blocks **107** and **109**, which could be applied furthermore for the synthesis of more complicated alkaloids.

3 Experimental Part

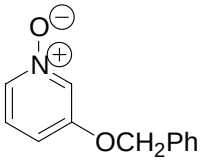
General

^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker ARX 250, ARX 300, ARX 400 or ARX 600, using TMS as internal reference. *J* Values were expressed in Hertz. TLC was performed on silica gel plate 60 F_{254} (Merck) coated on aluminium sheets. Melting point was determined on Büchi 510 and were uncorrected, and the heating speed was $3^{o}C$/min. IR spectra were measured as KBr pellets or liquid film. Optical rotation were measured on a Perkin Elmer 241 polarimeter at 589 nm. Column chromatography was performed on Merck silica gel 60 (Merck, 0.063-0.200 mm). Elemental analyse (Heraeus elementar vario EL III) and mass spectrometry (Finnigan Thermoquest TSQ 7000) were done by the central Analytical Laboratory (University of Regensburg).



57

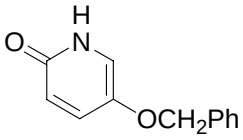
3-benzyloxypyridine (57) [34] A mixture of 3-hydroxypyridine (10 g), pulverized KOH (11.8 g), n-$Bu_4N^+Br^-$ (1.7 g) and benzyl chloride (19.4 ml) in THF was stirred at refluxing for 16 h. Water (400 ml) was added and the organic layer was extracted with 10% HCl (2 x 200 ml). The combined aqueous phases were basified with 25% NaOH and extracted with CH_2Cl_2 (2 x 300 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by chromatography through a silica gel column, using PE/AcOEt = 1/1 as eluent, to afford 8.53 g (44%) of product **57** as a clear liquid. TLC R_f 0.4 (PE/AcOEt = 1/9); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 2.7, 0.94, 1H), 8.23 (dd, *J* = 4.27, 1.75, 1H), 7.18-7.45 (m, 7H), 5.11 (s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.94, 142.35, 138.33, 136.16, 128.75, 128.33, 127.54, 123.88, 121.62, 70.34.



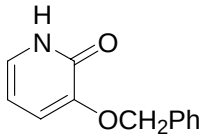
58

3-benzyloxypyridine 1-oxide (58) 3-benzyloxypyridine (**57**, 1.939 g) was dissolved in 9 ml of acetic acid and treated on the steambath with three 2.3 ml portions of perhydrol, the second

and the third of which were added after 0.75 and 1.25 h respectively. The mixture was left on the steambath for 5 h. After being cooled to the room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by chromatography through a silica gel column, eluting with $CH_3OH/CHCl_3$ = 1/9, to afford 1.575 g (74.8%) of product **58** as a white solid. TLC R_f 0.38 ($CH_3OH/CHCl_3$ = 1/9); ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.11 (dd, *J* = 1.82, 0.35, 1H), 7.88 (d, *J* = 6.3, 1H), 7.29-7.46 (m, 6H), 7.08 (dd, *J* = 8.64, 1.82, 1H), 6.62 (s, 1H), 5.17 (s, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 165.95, 156.77, 135.83, 133.96, 132.18, 128.53, 128.22, 127.94, 127.75, 126.08, 113.01, 70.19; PI-EIMS: m/z (relative intensity) 201.1 (M^+, 14.22%).



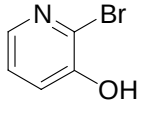
59



60

5-benzyloxy-1H-pyridin-2-one (59) and 3-benzyloxy-1H-pyridin-2-one (60) 1.5 g of 3-benzyloxypyridine 1-oxide (**58**) was dissolved in 15 ml of acetic anhydride and heated to 110^{o}C for 3 h. After being cooled to the room temperature, the reaction mixture was concentrated to dryness under reduced pressure. The residue was purified by chromatography, using $CH_3OH/CHCl_3$ = 1/9 as eluent, to afford a mixture of **59** and **60** in a ratio of 1:2, total weight: 0.36 g, yield: 24%. **59**: white solid. TLC R_f 0.15 (AcOEt/ethanol = 10/1); ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.30-7.50 (m, 6H), 7.12 (d, *J* = 3.2, 1H), 6.33 (d, *J* = 9.7, 1H), 4.92 (s, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 160.00, 142.28, 136.76, 134.03, 118.81, 116.56, 70.74; PI-EIMS: m/z (relative intensity) 201.1 (M^+, 17.21%).

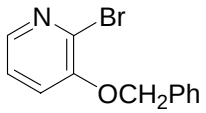
60: white solid. TLC R_f 0.18 (AcOEt/ethanol = 10/1); ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.43 (s, 1H), 7.31-7.43 (m, 5H), 6.91 (ddd, *J* = 5.94, 1.98, 1.58, 2H) 6.06 (t, *J* = 6.94, 1H), 4.99 (s, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 157.64, 148.49, 136.63, 128.33, 127.87, 127.85, 126.07, 116.56, 104.13, 69.52; PI-EIMS: m/z (relative intensity) 201.1 (M^+, 17.21%).



61

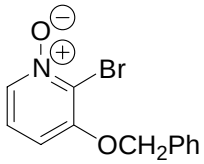
2-Bromo-pyridin-3-ol (61) [36] To a solution of 3-hydroxypyridine (5.262 g) in sodium hydroxide (2.169 g) in water (27.1 ml) was added dropwise with stirring a solution of bromine

(8.66 g) and NaOH (4.338 g) in water (32.5 ml) at 15°C. After stirring for 3 h, the pH was adjusted to 5 with concentrated hydrogenchloride. The solid was filtered and recrystallized from ethanol to give 5.12 g (54%) of the title compound **61**. TLC R_f 0.53 (PE/AcOEt = 1/1); ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.78 (s, 1H), 7.83 (dd, *J* = 4.08, 2.05, 1H), 7.21-7.45 (m, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 151.0907, 140.0903, 130.3860, 124.1702, 123.2063.



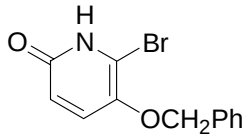
62

3-benzyloxy-2-bromo-pyridine (62) To a solution of 2-bromo-pyridin-3-ol (**61**, 4.092 g) and K_2CO_3 (4.57 g) in acetone (100 ml) was added dropwise benzyl chloride (3.2 ml). After refluxing for 24 h, the mixture was filtered and the filtration was concentrated to dryness. Water was added to the residue, and the resulting oil was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the crude residue was purified by chromatography to afford 4.95 g (80%) of product **62** as an oil. TLC R_f 0.81 (PE/AcOEt = 1/1); ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.97 (dd, *J* = 4.58, 1.45, 1H), 7.60 (dd, *J* = 4.58, 1.40, 1H), 7.31-7.50 (m, 6H), 5.26 (s, 2H); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ 151.46, 141.42, 135.97, 131.86, 128.54, 128.09, 127.50, 124.26, 121.47, 70.17.



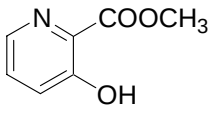
63

3-benzyloxy-2-bromo-pyridine 1-oxide (63) A solution of 3-benzyloxy-2-bromo-pyridine (**62,** 1.017 g) and *m*-chloroperoxybenzoic acid (70%, 1.14 g) in chloroform (12 ml) was stirred at room temperature. After 2.5 h, water was added and the organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography, using $CH_3OH/CHCl_3$ = 1/9 as eluent, to afford 906 mg (84%) of product **63** as a white solid. TLC R_f 0.4 ($CH_3OH/CHCl_3$ = 1/9); IR (KBr) 3084, 2923, 2871, 1589, 1549, 1448, 1427, 1218, 1201, 1070; ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.13 (dd, *J* = 6.45, 1.05, 1H), 7.31-7.49 (m, 6H), 7.21 (dd, *J* = 8.69, 1.06, 1H), 5.29 (s, 2H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 133.31, 128.53, 128.18, 127.53, 123.80, 110.02, 71.04; PI-EIMS: m/z (relative intensity) 278.9 (M^+, 3.33%).



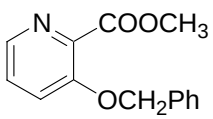
64

5-Benzyloxy-6-bromo-1H-pyridin-2-one (64) 2.05 g of 2-bromo-3-benzoxypyridine 1-oxide (**63**) was dissolved in 12 ml of acetic anhydride, and was heated to 125^{o}C for 3 h. The colour became dark. After being cooled to the room temperature, the excess acetic anhydride was removed under reduced pressure. Then the residue took up methanol 22 ml and conc. sulfuric acid 2 drops was added and the resulting reaction mixture was refluxed for 2 h. The solvent was evaporated in vacuum. The residue was neutralized with saturated sodium carbonate solution and extracted with $CHCl_3$, dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography through a silica gel column, eluting with PE/AcOEt = 1/1, to afford 135 mg (6.7%) of the title product **64** as a red crystal. TLC R_f 0.44 (PE/AcOEt = 1/1); Mp 144-145^{o}C; IR (KBr) 2922, 2856, 1618, 1481, 1450, 1269, 1236, 1086, 1027; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.98 (s, 1H), 7.28-7.45 (m, 5H), 7.27 (d, *J* = 8.79, 1H), 6.69 (d, *J* = 8.79, 1H), 5.09 (s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.74, 146.42, 136.02, 129.19, 128.69, 128.33, 127.71, 127.51, 109.92, 72.96; PI-EIMS: m/z (relative intensity) 278.9 (M^+, 1.85%); Anal. Calcd for $C_{12}H_{10}BrNO_2$: C, 51.45%; H, 3.60%; N, 5.00%. Found: C, 51.78%; H, 3.45%; N, 4.96%.



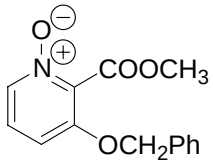
66

3-hydroxy-pyridine-2-carboxylic acid methyl ester (66) [37] 5 g of 3-hydroxypicolinic acid was added in 150 ml of saturated MeOH (HCl) solution. The mixture was stirred at reflux for 44 h. The solid dissolved slowly and finally it became a clear solution. The solvent was removed in vacuo. The saturated Na_2CO_3 solution was added. The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$. After removal of the solvent, 3.3 g (60%) of product **66** was obtained as a white solid. TLC R_f 0.48 (ethyl acetate); ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.45 (s, 1H), 8.15 (dd, *J* = 4.16, 1.39, 1H), 7.40-7.52 (m, 2H), 3.87 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 167.68, 155.43, 140.64, 133.17, 128.70, 125.41, 52.33.



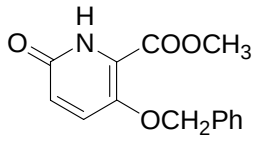
67

3-benzyloxy-pyridine-2-carboxylic acid methyl ester (67) [38] 2.4 g of 3-hydroxy-methyl picolinate (**66**), 3.25 g of K_2CO_3 and 2.81 ml of benzylbromide were dissolved in 30 ml of DMF. The mixture were stirred at rt overnight. Then the solvent was removed in vacuum. Water and CH_2Cl_2 were added together. The organic layer was washed with saturated NaCl, dried over $MgSO_4$. After removal of the solvent, an oil was obtained, which was purified by chromatography through a silica gel column, using PE/AcOEt = 1/1 as eluent to afford 3.67 g (96%) of the title product **67** as a clear liquid. TLC R_f 0.26 (PE/AcOEt = 1/1); ^{1}H NMR (250 MHz, DMSO-d_6) δ 8.18 (dd, *J* = 4.55, 1.05, 1H), 7.70 (dd, *J* = 8.57, 1.0, 1H), 7.28-7.55 (m, 6H), 5.25 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 165.52, 152.66, 140.89, 140.10, 136.22, 128.45, 127.89, 127.17, 126.80, 121.92, 69.68, 52.12.



68

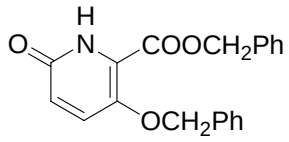
3-Benzyloxy-1-oxy-pyridine-2-carboxylic acid methyl ester (68) [38] To a solution of 3.67 g of **67** in 30 ml of $CHCl_3$, was added 4.47 g of MCPBA (70%). The solution was stirred at rt for 2 days. Then the reaction mixture was neutralized with saturated sodium carbonate aqueous solution. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was chromatographied through a silica gel column, eluting with $CH_3OH/CHCl_3$ = 1/9 to afford 3.62 g (93%) of product **68** as a white solid. TLC R_f 0.64 ($CH_3OH/CHCl_3$=1/9); Mp 104-106^{o}C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 6.51, 0.64, 1H), 7.31-7.43 (m, 5H), 7.16 (dd, *J* = 8.72, 6.51, 1H), 6.88 (dd, *J* = 8.72, 0.56, 1H), 5.17 (s, 2H), 4.30 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.92, 154.11, 134.83, 132.81, 128.81, 128.79, 128.76, 128.75, 128.50, 126.93, 125.45, 110.45, 71.35, 53.29; PI-EIMS: m/z (relative intensity) 258.9 (M^+, 9.63%).



69

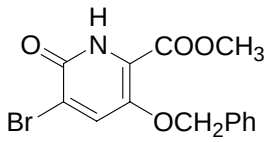
3-Benzyloxy-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (69) [38] 1.132 g of 3-Benzyloxy-1-oxy-pyridine-2-carboxylic acid methyl ester (**68**) was dissolved in 10 ml of acetic anhydride. The solution was stirred and heated in an oil bath at 125^{o}C for 3 h. The excess acetic anhydride was removed under reduced pressure and the residue took up in 20 ml

of methanol, conc. sulfuric acid (0.1 ml) was added, and the resulting mixture heated to reflux for 90 min. The solvent was evaporated in vacuum to afford a yellow solid, then saturated Na_2CO_3 aqueous solution was added to the residue. The mixture was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated to afford a 1.1 g of crude product, which was recrystallized with toluene to give 0.75 g (67%) of product **69** as a yellow solid. TLC R_f 0.46 ($CH_3OH/CHCl_3$ = 1/9); Mp 91-92^oC; ^1H NMR (250 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.28-7.59 (m, 5H), 7.37 (d, *J* = 9.91, 1H), 6.78 (d, *J* = 9.91, 1H), 5.07 (s, 2H), 3.94 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.38, 159.71, 144.89, 135.80, 129.04, 128.70, 128.53, 127.79, 127.74, 127.62, 74.68, 53.21.



71

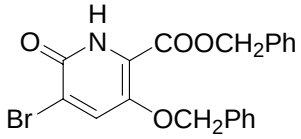
3-Benzyloxy-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid benzyl ester (71) This was prepared according to the procedure used for **69**, staring from 1.12 g of 3-benzyloxy-1-oxy-pyridine-2-carboxylic acid benzyl ester and 10 ml of acetic anhydride. After recrystallization from toluene, 0.72 g (64.3%) of product **71** was obtained as a pale yellow solid. TLC R_f 0.44 ($CH_3OH/CHCl_3$ = 1/9); IR (KBr) 3125, 3068, 1736, 1658, 1593, 1456, 1265, 1220, 1074, 1022; ^1H NMR (250 MHz, $CDCl_3$) δ 9.81 (br, 1H), 7.27-7.40 (m, 11H), 6.76 (d, *J* = 9.91, 1H), 5.36 (s, 2H), 5.00 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 160.85, 159.74, 145.06, 135.69, 135.47, 134.65, 129.02, 128.70, 128.68, 128.62, 128.41, 127.75, 127.73, 122.25, 74.45, 68.22; PI-EIMS: m/z (relative intensity) 336.2 (MH^+, 100%).



70

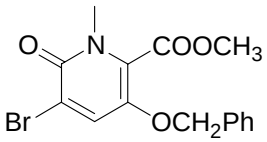
3-Benzyloxy-5-bromo-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (70) 0.5 g of 3-Benzyloxy-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester **(69)** was dissolved in 40 ml of 1,4-dioxane and 40 ml of H_2O. At rt, 0.308 g of bromine in 5 ml of water was added dropwise. Slowly, a yellow solid was precipitated from the solution. Stirring was continued for 14 h. The solid was collected by filtration. Weight: 280 mg; The filtration was extracted with CH_2Cl_2, dried over $MgSO_4$. After removal of the solvent, the residue was chromatographied through a silica gel column to afford additional 200 mg. Total 480 mg

(74%). TLC R_f 0.69 (ethyl acetate); Mp 178.5-179°C; IR (KBr) 3448, 3006, 2941, 2859, 1735, 1655, 1597, 1366, 1311, 1264, 1227, 1109, 953; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (br. 1H), 7.80 (s, 1H), 7.36-7.40 (m, 5H), 5.06 (s, 2H) 3.94 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.90, 156.34, 144.05, 137.78, 135.44, 128.75, 128.69, 127.84, 124.36, 122.05, 75.24, 53.29; PI-DCIMS: m/z (relative intensity) 338.1 (M^+, ^{79}Br, 100%), 340.1 (M^+, ^{81}Br, 98.85%); Anal. Calcd for $C_{14}H_{12}BrNO_4$: C, 49.73%; H, 3.58%; N, 4.14%; Br, 23.63%. Found: C, 49.62%; H, 3.51%; N, 4.04%; Br, 23.50%.

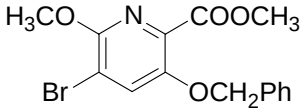


72

3-Benzyloxy-5-bromo-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid benzyl ester (72) 0.357 g of **71** was dissolved in 100 ml of H_2O and 1,4-dioxane (1/1). The bromine (0.054 ml) in 10 ml of H_2O was dropwise added to the mixture. After the addition, the mixture was stirred at rt for 4 h. Then the reaction mixture was extracted with $CHCl_3$, dried over $MgSO_4$, the crude product was purified by chromatography to afford 220 mg (50%) of the desired compound as a white solid (**72**). TLC R_f 0.43 (PE/AcOEt = 1/1); IR (KBr) 3442, 3122, 1728, 1647, 1596, 1222, 1100, 1026; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (br, 1H), 7.85 (s, 1H), 7.30-7.50 (m, 10H), 5.40 (s, 2H), 5.05 (s, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.50, 156.14, 144.18, 137.40, 135.20, 134.44, 128.84, 128.79, 128.76, 128.74, 128.63, 127.85, 124.73, 121.50, 74.92, 68.51; PI-DCIMS: m/z (relative intensity) 414.1 (MH^+,^{79}Br, 99.47%), 416.1 (MH^+, ^{81}Br, 100.0%).



81

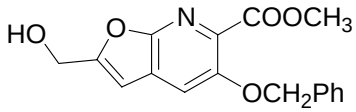


82

3-Benzyloxy-5-bromo-1-methyl-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (81) and 3-benzyloxy-5-bromo-6-methoxy-pyridine-2-carboxylic acid methyl ester (82) 0.5 g of 3-Benzyloxy-5-bromo-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (**70**), 0.3 g of K_2CO_3, 15 ml of dry acetone and 1.4 ml of methyl iodide were added into a dry flask. The mixture was stirred at reflux for 5 h. After being cooled to rt, the mixture was evaporated in vacuum. Then H_2O and CH_2Cl_2 were added. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography, eluting

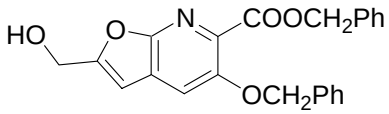
with PE/AcOEt = 1/1, to afford 340 mg (65.3%) of product **81** as a white solid. TLC R_f 0.51 (PE/AcOEt = 1/1); Mp 105-105.5^oC; IR (KBr) 3036, 1721, 1648, 1595, 1433, 1366, 1277, 1144, 1088, 1026; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.30-7.42 (m, 5H), 4.94 (s, 2H), 4.13 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.83, 156.88, 138.41, 135.99, 135.54, 130.80, 128.71,128.65, 128.00, 118.72, 75.75, 53.28, 35.11; EI-MS: m/z (relative intensity) 350.9 (M^+, ^{79}Br, 4.95%), 353.0 (M^+, ^{81}Br, 5.01%); HRMS: Calad for $C_{15}H_{14}BrNO_4$: 351.0106. Found: 351.0101.

Compound **82**: white solid, 169 mg (32.5%). TLC R_f 0.89 (PE/AcOEt = 1/1); Mp 75-75.5^oC; IR (KBr) 2951, 1734, 1553, 1479, 1455, 1416, 1376, 1288, 1230, 1113, 1027; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.30-7.45 (m, 5H), 5.11 (s, 2H), 4.01 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.93, 153.95, 149.60, 135.80, 134.29, 131.14, 128.69, 128.30, 127.30, 110.40, 72.98, 54.83, 52.54; PI-EIMS: m/z (relative intensity) 350.8 (M^+, ^{79}Br, 6.55%), 352.8 (M^+, ^{81}Br, 6.46%); Anal. Calcd for $C_{15}H_{14}BrNO_4$: C, 51.16%; H, 4.01%; N, 3.98. Found: C, 51.41%; H, 3.92%; N, 3.64%.



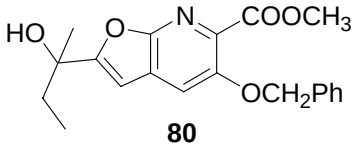
78

5-Benzyloxy-2-hydroxymethyl-furo[2,3-*b*]pyridine-6-carboxylic acid methyl ester (78) To a 50 ml of dry flask, 400 mg of 3-Benzyloxy-5-bromo-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester **(70)**, 4 ml of DIPEA, 4 ml of dry toluene and 40.9 mg of $Pd(PPh_3)_4$ were added together. The mixture was purged with nitrogen and vacuum several times, then heated to 60^oC. 4.5 mg of CuI and 0.17 ml of propargyl alcohol were added consequently. After 20 h, the reaction mixture was allowed to cool to rt, and 8 ml of Et_2O was added. The mixture was washed with dilute HCl, H_2O and brine, dried over $MgSO_4$, After removal of the solvent, a yellow solid was obtained (440 mg), which was recrystallized from toluene to afford 310 mg (84%) of product **78** as a yellow solid. TLC R_f 0.35 (ethyl acetate); Mp 101-101.5^oC; IR (KBr) 3416, 3135, 1727, 1603, 1443, 1402, 1228, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.49 (m, 7H), 6.57 (s, 1H), 5.20 (s, 2H), 4.76 (s, 2H), 3.98 (s, 3H), 3.08 (br, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.07, 161.23, 155.11, 152.49, 136.08, 132.88, 128.66, 127.11, 124.22, 116.22, 102.51, 72.27, 58.15, 52.60; PI-EIMS: m/z (relative intensity) 313.3 (M^+, 14.44%); Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17%; H, 4.83%; N, 4.47%. Found: C, 65.04%; H, 4.72%; N, 4.20%.



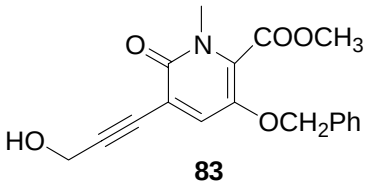
79

5-Benzyloxy-2-hydroxymethyl-furo[2,3-*b*]pyridine-6-carboxylic acid benzyl ester (79) This was prepared according to the procedure used for **78**, starting from 310 mg of compound **72**, 20 ml of dry toluene, 3 ml of DIPEA, 25.6 mg of $Pd(PPh_3)_4$, 104.8 mg of propargyl alcohol and 2.82 mg of CuI. After crystallization in toluene, the desired product **79** was obtained as a yellow solid (170 mg, 60%). TLC R_f 0.45 (ethyl acetate); Mp 129-132^oC**;** IR (KBr) 3328, 1715, 1606, 1398, 1245, 1010; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.70 (m, 11H), 6.53 (s, 1H), 5.42 (s, 2H), 5.14 (s, 2H), 4.73 (s, 2H), 3.08 (br, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.83, 161.02, 155.20, 152.27, 136.01, 135.73, 133.35, 128.64, 128.50, 128.41, 128.19, 128.12, 127.26, 124.03, 118.10, 115.92, 102.54, 72.19, 67.32, 58.12; PI-EIMS: m/z (relative intensity) 389.3 (M^+, 1.31%); Anal. Calcd for $C_{23}H_{19}NO_5 \cdot 0.25H_2O$: C, 70.06%; H, 4.95%; N, 3.55%. Found: C, 69.93%; H, 4.94%; N, 3.52%.



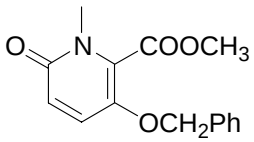
80

5-Benzyloxy-2-(1-hydroxy-1-methyl-propyl)-furo[2,3-*b*]pyridine-6-carboxylic acid methyl ester (80) To a 50 ml of dry flask, 470 mg of compound **70**, 5 ml of DIPEA, 10 ml of dry toluene and 48 mg of $Pd(PPh_3)_4$ were added together. The mixture was purged with nitrogen and vacuum several times, then heated to 60^oC. 5.3 mg of CuI and 0.4 ml of 3-methyl-1-pentin-3-ol were added consequently. After 20 h, the reaction mixture was allowed to cool to rt, and 60 ml of Et_2O was added. The mixture was washed with 5% HCl, H_2O and brine, dried over $MgSO_4$, After removal of the solvent, the residue was purified by chromatography, using PE/AcOEt = 1/1 as eluent to afford a yellow oil, which was recrystal1ized from toluene to afford 395 mg (80%) of product **80** as a yellow solid. TLC R_f 0.36 (PE/AcOEt = 1/1); Mp 79-80^oC; IR (KBr) 3415, 2970, 1726, 1605, 1578, 1448, 1408, 1357, 1313, 1173, 1222, 1084, 1020; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.55 (m, 3H), 7.29-7.44 (m, 3H), 6.53 (s, 1H), 5.14 (s, 2H), 3.91 (s, 3H), 2.08 (s, 1H), 1.77-2.06 (m, 2H), 1.52 (s, 3H), 0.86 (t, *J* = 7.49, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.91, 163.80, 153.92, 151.90, 135.12, 131.06, 127.67, 127.08, 126.07, 123.61, 115.18, 99.74, 71.70, 71.22, 51.57, 33.12, 25.53, 7.13; CI-MS: m/z (relative intensity) 356.1 (MH^+, 100.00%); Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59%; H, 5.96%; N, 3.94%. Found: C, 67.55%; H, 5.97%; N, 3.70%.

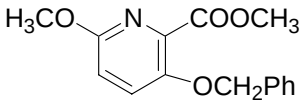


83

3-Benzyloxy-5-(3-hydroxy-prop-1-ynyl)-1-methyl-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (83) To a solution of 470 mg compound **81** in 20 ml of dry toluene , 3.4 ml of DIPEA, and 33.4 mg of $Pd(PPh_3)_4$ were added together. The mixture was purged with nitrogen and vacuum several times, then heated to 60°C. 3.7 mg of cuprous iodide and 0.14 ml of propargyl alcohol were added consequently. Then the solution was stirred at that temperature for 24 h. The reaction mixture was allowed to cool to rt, followed by the addition of 60 ml of Et_2O. The mixture was washed with 2% HCl, H_2O and brine, dried over $MgSO_4$, After removal of the solvent, an oil was obtained, which was purified by chromatography, using ethyl acetate as eluent to afford a yellow oil. The crude product was recrystallized from toluene to give the desired product **83** as a yellow solid in a quantitative yield. TLC R_f 0.18 (ethyl acetate); Mp 107-108°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.30-7.40 (m, 4H), 4.93 (s, 2H), 4.51 (s, 2H), 3.90 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.81, 158.59, 137.77, 134.68, 131.89, 131.12, 127.64, 127.60, 127.49, 127.44, 126.84, 116.32, 94.90, 79.07, 74.02, 52.26, 50.24, 33.37. PI-EIMS: m/z (relative intensity) 327.1 (M^+, 4.52%).



84

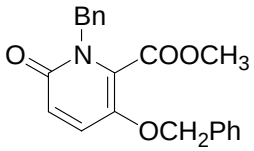


85

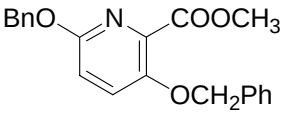
3-benzyloxy-1-methyl-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (84) and 3-benzyloxy-6-methoxy-pyridine-2-carboxylic acid methyl ester (85) To a dry 250 ml of flask, 4 g of compound **69**, 3.2 g of K_2CO_3, 160 ml of dry acetone were added. Then 1.5 ml of methyl iodide was added. The mixture was refluxed for 4 h. After being cooled to the room temperature, the reaction mixture was filtered and distilled in vacuum. H_2O and CH_2Cl_2 were added to the residue. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography through a silica gel column, eluting with ethyl acetate, to afford 2.74 g (65%) of product **84** as a clear liquid. TLC R_f 0.33 (ethyl acetate); IR (film) 3033, 2953, 1736, 1669, 1591, 1433, 1374, 1283, 1165, 1092, 1024, 939, 828, 748, 731, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.41 (m, 5H), 7.26 (d, J = 9.9, 1H), 6.61 (d, J = 9.9, 1H), 4.94 (s, 2H), 3.90 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.29, 160.20, 139.18, 135.98, 133.84, 131.19, 128.64, 128.46, 127.91, 122.61, 75.23, 53.14, 33.58;

PI-EIMS: m/z (relative intensity) 273.1 (M^+, 11.70%); HRMS: Calcd for $C_{15}H_{15}NO_4$ (M^+): 273.1001. Found: 273.0996.

Compound **85**: 1.47 g (35%) as a clear colourless liquid. TLC R_f 0.75 (ethyl acetate); IR (KBr) 2925, 2854, 1733, 1462, 1377, 1261, 1092, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.45 (m, 6H), 6.81 (d, 1H), 5.12 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.62, 157.88, 149.59, 136.38, 135.82, 128.61, 128.42, 128.10, 127.29, 114.71, 72.77, 53.84, 52.46; EI-MS: m/z (relative intensity) 273.1 (M^+, 14.60%); HRMS: Calcd for $C_{15}H_{15}NO_4$ (M^+): 273.1001. Found: 273.1000.



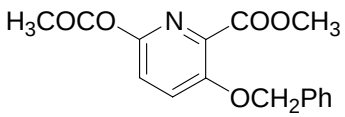
89



90

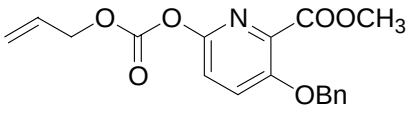
1-benzyl-3-benzyloxy-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (89) and **3,6-bis-benzyloxy-pyridine-2-carboxylic acid methyl ester (90)** 0.5 g of compound **69** was dissolved in 10 ml of DMF, 0.4 g of K_2CO_3 and 0.7 g of $PhCH_2I$ were added. The mixture was stirred at room temperature overnight. The solvent was evaporated in vacuum completely. Then H_2O and CH_2Cl_2 were added. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuum and the residue was purified by chromatography, using PE/ ethyl acetate = 1/1 as eluent, to afford 270 mg (40%) of product **89** as a clear liquid. TLC R_f 0.5 (ethyl acetate); IR (film) 3033, 2952, 1733, 1669, 1589, 1541, 1435, 1394, 1279, 1237, 1182, 1133, 1078, 1025, 940, 830, 730, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.39 (m, 11H), 6.68 (d, *J* = 10.0, 1H), 5.29 (s, 2H), 4.90 (s, 2H), 3.61 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.46, 160.16, 139.71, 136.17, 136.01, 134.02, 130.44, 128.62, 128.53, 128.42, 127.78, 127.75, 127.72, 123.19, 75.11, 52.77, 48.18; PI-EIMS: m/z (relative intensity) 349.4 (M^+, 18.14%); HRMS: Calcd for $C_{21}H_{19}NO_4$ (M^+): 349.1314. Found: 349.1308.

Compound **90**: 405 mg (60%). TLC R_f 0.78 (ethyl acetate); IR (film) 3032, 2950, 2884, 1731, 1601, 1450, 1372, 1328, 1256, 1223, 1138, 1092, 1016, 860, 824, 736; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.48 (m, 11H), 6.87 (d, *J* = 9.0, 1H), 5.35 (s, 2H), 5.12 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.54, 157.28, 149.83, 137.04, 136.37, 135.54, 128.62, 128.45, 128.42, 128.39,128.11, 127.94, 127.27, 115.11, 72.73, 68.22, 52.44; CI-MS: m/z (relative intensity) 349.4 (M^+, 13.91%); HRMS: Calcd for $C_{21}H_{19}NO_4$ (M^+): 349.1314. Found: 349.1310.



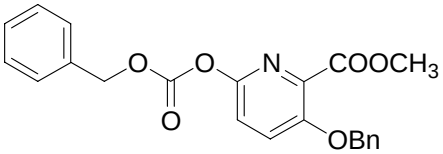
91

6-Acetoxy-3-benzoyloxy-pyridine-2-carboxylic acid methyl ester (91) 1 g of compound **69** and 0.64 ml of NEt_3 were dissolved in 20 ml of dichloromethane and a solution of 0.36 ml of methyl chloroformate was added dropwise at 0°C in 5 min. After stirring at rt for 48 h, 20 ml of water was added. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography, eluting with PE/AcOEt = 1/1, to afford 440 mg (90%) of the title product **91**. TLC R_f 0.39 (PE/AcOEt = 1/1); Mp 70-71°C; IR (KBr) 1759, 1727, 1580, 1437, 1318, 1284, 1217, 1099, 1017; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.49 (m, 6H), 7.21 (d, *J* = 9.06, 1H), 5.21 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.06, 153.62, 153.46, 149.82, 136.93, 135.58, 128.80, 128.48, 128.33, 127.02, 126.33, 119.49, 71.78, 55.59, 52.72; PI-DCIMS: m/z (relative intensity) 318.2 (MH^+, 100.00%); Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.57%; H, 4.77%; N, 4.41. Found: C, 60.48%; H, 4.54%; N, 4.38%.



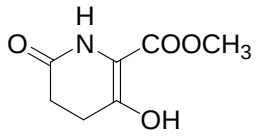
92

6-Allyloxycarbonyloxy-3-benzoyloxy-pyridine-2-carboxylic acid methyl ester (92) This was obtained following the procedure described for **91**, staring from allyl chloroformate (0.61 ml), 0.8 ml of NEt_3, and 0.5 g of compound **69** in 20 ml of CH_2Cl_2. After recrystallization from ethanol, 382 mg (57.8%) of product **92** was obtained as a white needle crystal. TLC R_f 0.68 (PE/AcOEt = 1/1); Mp 74-75°C; IR (KBr) 1757, 1584, 1468, 1364, 1220, 1097; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.49 (m, 6H), 7.22 (d, *J* = 8.88, 1H), 5.90- 6.03 (m, 1H), 5.41 (ddd, *J* = 17.18, 2.84, 1.44, 1H), 5.31 (ddd, *J* = 10.40, 2.38, 1.17, 1H), 5.21 (s, 2H), 4.72 (dd, *J* = 5.85, 1.33, 2H), 3.95 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.07, 153.46, 152.86, 149.81, 136.89, 135.57, 130.89, 129.23, 128.80, 128.48, 128.33, 127.02, 126.31, 119.67, 119.53, 71.76, 69.44, 53.44, 52.72, 45.84; PI-DCIMS: m/z (relative intensity) 344.2 (MH^+, 100.00%); HRMS: Calcd for $C_{18}H_{17}NO_6$ (M^+): 343.1056. Found: 343.1049.



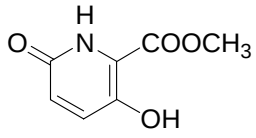
93

3-benzyloxy-6-benzyloxycarbonyloxy-pyridine-2-carboxylic acid methyl ester (93) To a solution of 0.56 g of compound **69** in 20 ml of CH_2Cl_2 and 0.9 ml of NEt_3, was added dropwise a solution of 0.91 ml chloroformate benzyl ester in 5 ml of CH_2Cl_2 in 5 min at 0^oC. The solution was kept at that temperature for 2 h then warmed to rt. After 2 days, the reaction mixture was washed with H_2O. The combined organic layers were dried over $MgSO_4$. After removal of the solvent, a white solid was obtained, which was recrystallized from ethanol to afford 0.63 g (74.3%) of the title product **93** as a white plate solid. TLC R_f 0.85 (ethyl acetate); Mp 126-127^oC; IR (KBr) 1753, 1583, 1451, 1381, 1283, 1215, 1099, 1012; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.56 (m, 11H), 7.19-7.25 (d, *J* = 8.9193, 1H), 5.25 (s, 2H), 5.21 (s, 2H), 3.96 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.99, 152.47, 151.99, 148.69, 135.65, 134.49, 133.40, 127.79, 127.77, 127.65, 127.54. 127.29, 125.94, 125.21, 118.59, 70.63, 69.63, 51.73; PI-DCIMS: m/z (relative intensity) 394.2 (MH^+, 100.00%); Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17%; H, 4.87%; N, 3.56. Found: C, 66.91%; H, 4.64%; N, 3.41%.



94

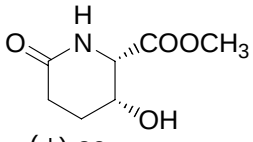
3-hydroxy-6-oxo-1,4,5,6-tetrahydro-pyridine-2-carboxylic acid methyl ester (94) 1.55 g of compound **69** was dissolved in 120 ml of methanol, and 150 mg of palladium carbon (10%) was added. The mixture was hydrogenated at room temperature for 7 days. After removal of the solvent, the residue was chromatographied through a silica gel column, eluting with $CH_3OH/CHCl_3$ = 1/30, to afford 500 mg (50%) of product **94** as a white solid. TLC R_f 0.33 (ethyl acetate); Mp 134-135°C; IR (KBr) 3196, 2913, 1661, 1487, 1444, 1363, 1320, 1255, 1205, 1165, 1082, 1024, 995, 957, 785, 750; ^1H NMR (300 MHz, $CDCl_3$) δ 10.60 (br, 1H), 6.84 (br, 1H), 3.87 (s, 3H), 2.56-2.71 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.28, 165.23, 158.12, 104.60, 52.29, 29.17, 25.56; PI-EIMS: m/z (relative intensity) 171.1 (M^+, 13.38%); Anal. Calcd for $C_7H_9NO_4$: C, 49.12%; H, 5.30%; N, 8.18%. Found: C, 49.05%; H, 5.32%; N, 8.21%.



95

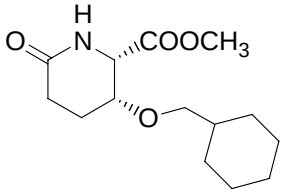
3-hydroxy-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (95) 0.6 g of compound **69** was dissolved in 50 ml of methanol and hydrogenated with 100 mg of

palladium carbon (10%) at room temperature for two days. Then the catalyst was removed by filtration. The solvent was removed in vacuum and purified by chromatography through a silica gel column, using $CH_3OH/CHCl_3$ = 30/1 as eluent to provide 274 mg (70%) of product **95** as a white solid. TLC R_f 0.3 ($CH_3OH/CHCl_3$ = 1/9); Mp 135-137^oC (dec.); IR (KBr) 3398, 3248, 1655, 1595, 1429, 1344, 1249, 1182, 1078, 893, 802, 712, 569; ^1H NMR (400 MHz, $CDCl_3$) δ 9.33-10.09 (br. 2H), 7.35 (br, 1H), 6.85 (d, *J* = 8.3, 1H), 3.99 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.87, 159.80, 149.19, 134.79, 129.63, 113.50, 53.15; PI-EIMS: m/z (relative intensity) 169.0 (M^+, 90.48%); Anal. Calcd for $C_7H_7NO_4$: C, 49.71%; H, 4.17%; N, 8.28%. Found: C, 49.67%; H, 4.23%; N, 8.23%.

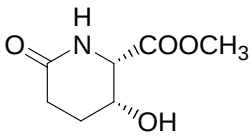


(±)-**96**

***cis*-(±)-3-hydroxy-6-oxo-piperidine-2-carboxylic acid methyl ester (96)** 1 g of compound **69** and 100 mg of Pd/C (10%) were suspended in 250 ml of methanol. The mixture was stirred under 6 bar at 30^oC for 24 h. The catalyst was filtered and the filtrate was concentrated completely in vacuum. The residue was dissolved in 250 ml of ethanol, and 170 mg of PtO_2 was added. The mixture was hydrogenated under 10 bar at 60^oC for 48 h. After removal of the catalyst by filtration, the filtrate was evaporated completely under reduced pressure. The residue was purified by chromatography, using $CH_3OH/CHCl_3$ = 1/15 as eluent to afford 410 mg (61%) of the title product **96** as a white solid. TLC R_f 0.12 ($CH_3OH/CHCl_3$ = 1/9); ^1H NMR (300 MHz, CD_3OD) δ 7865 (s, 3H), 4.39-4.43 (m, 1H), 4.26 (d, *J* = 3.84, 1H), 2.54 (ddd, *J* = 17.91, 10.63, 7.20, 1H), 2.29 (ddd, *J* = 18.04, 6.11, 3.50, 1H), 1.93-2.02 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 174.19, 171.48, 64.61, 60.95, 52.90, 27.72, 26.91; PI-CIMS: m/z (relative intensity) 174.0 (MH^+, 100.00%); Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55%; H, 6.40%; N, 8.09%. Found: C, 48.98%; H, 6.54%; N, 7.73%.



(±)- **97**

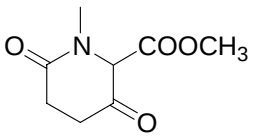


(±)- **96**

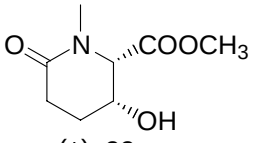
***cis*-(±)-3-cyclohexylmethoxy-6-oxo-piperidine-2-carboxylic acid methyl ester (97) and *cis*-(±)-3-hydroxy-6-oxo-piperidine-2-carboxylic acid methyl ester (96)** 1 g of compound

69 was dissolved in 250 ml of ethanol, and 170 mg of PtO_2 was added. The mixture was hydrogenated at 60°C under 10 bar for 48 h. The catalyst was removed by filtration. The filtrate was concentrated in vacuum to afford a white solid, which was purified by chromatography through a silica gel column, using $CH_3OH/CHCl_3$ = 1/15 as eluent to afford 623 mg (60%) of product **97** as a white solid. TLC R_f 0.6 ($CH_3OH/CHCl_3$ = 1/9); Mp 104-105°C; IR (KBr) 3179, 3078, 2920, 2849, 1731, 1663, 1448, 1407, 1333, 1268, 1196, 1082, 1024; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 1H), 4.17 (d, *J* = 3.35, 1H), 4.01-4.09 (m, 1H), 3.80 (s, 3H), 3.47 (dd, *J* = 8.62, 5.96, 1H), 3.10 (dd, *J* = 8.62, 6.56, 1H), 2.41-2.54 (m, 1H), 2.28-2.36 (m, 1H), 2.18-2.28 (m, 1H), 1.75-1.86 (m, 1H), 1.60-1.75 (m, 5H), 1.44-1.55 (m, 1H), 1.03-1.30 (m, 3H), 0.84-0.93 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.80, 169.38, 74.89, 70.92, 59.27, 52.51, 37.95, 29.89, 29.81, 26.49, 25.99, 25.81, 25.78, 23.04; EI-MS: m/z (relative intensity) 269.1 (M^+, 11.38%); HRMS: Calcd for $C_{14}H_{23}NO_4$ (M^+): 269.1627. Found: 269.1628.

Compound **96:** 267 mg (40%).



98

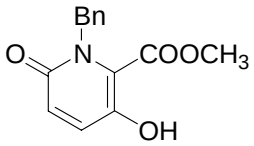


(±)- **99**

1-methyl-3,6-dioxo-piperidine-2-carboxylic acid methyl ester (98) and *cis*-(±)-3-hydroxy-1-methyl-6-oxo-piperidine-2-carboxylic acid methyl ester (99) 2.1 g of compound **84** was dissolved in 60 ml of methanol, and 210 mg of Pd/C (10%) was added. The mixture was hydrogenated at room temperature for 24 h. After the filtration, the filtrate was concentrated to dryness. The residue was purified by chromatography, eluting with ethyl acetate, to afford 854 mg (60%) of the title product **98** as a white solid. TLC R_f 0.3 (ethyl acetate); IR (KBr) 2958, 1733, 1664, 1435,1397, 1304, 1258, 1237, 1167, 1047, 986; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (s, 1H), 3.77 (s, 3H), 2.90 (s, 3H), 2.51-2.80 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.73, 169.30, 165.19, 70.42, 52.64, 34.55, 32.86, 27.68; EI-MS: m/z (relative intensity) 185.2 (M^+, 26.67%); HRMS: Calcd for $C_8H_{11}NO_4$ (M^+): 185.0688. Found: 185.0685.

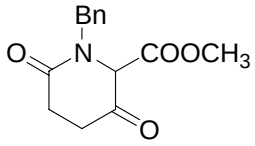
Compound **99**: white solid, 575 mg (40%). TLC R_f 0.11 (ethyl acetate); Mp 90-92°C; IR (KBr) 3398, 3198, 2957, 2701, 1746, 1611, 1500, 1451, 1402, 1357, 1259, 1202, 1154, 1109, 1041, 1014, 960, 752, 715, 663; ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.51 (br, 1H), 4.12-4.20

(m, 2H), 3.67 (s, 3H), 2.68 (s, 3H), 2.20-2.49 (m, 2H), 1.70-1.93 (m, 2H); ^{13}C NMR (75.5 MHz, DMSO) δ 170.32, 168.85, 65.89, 64.18, 51.79, 33.38, 28.32, 26.11; PI-EIMS: m/z (relative intensity) 187.1 (M^+, 13.82%); Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33%; H, 7.00%; N, 7.48%. Found: C, 50.70; H, 6.73; N, 7.44.

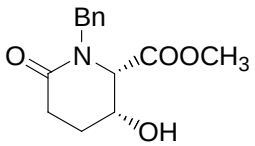


100

1-benzyl-3-hydroxy-6-oxo-1,6-dihydro-pyridine-2-carboxylic acid methyl ester (100) 1.25 g of compound **89** was dissolved in 50 ml of methanol, and 125 mg of Pd/C (10%) was added. The mixture was hydrogenated at room temperature for 24 h. After the filtration, the filtrate was concentrated to dryness. The residue was purified by chromatography, eluting with ethyl acetate, to afford 570 mg (62%) of the title product **100** as a white solid. TLC R_f 0.41 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (s, 1H), 7.19-7.31 (m, 4H), 7.04 (d, *J* = 6.86, 2H), 6.92 (d, *J* = 9.88, 1H), 5.58 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.56, 160.49, 150.38, 137.77, 133.67, 129.29, 128.52, 127.08, 126.37, 115.72, 52.84, 49.43.



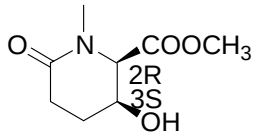
101



(±)-**102**

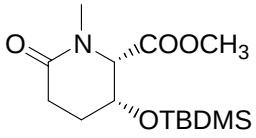
1-benzyl-3,6-dioxo-piperidine-2-carboxylic acid methyl ester (101) and *cis*-(±)-1-benzyl-3-hydroxy-6-oxo-piperidine-2-carboxylic acid methyl ester (102) To a solution of 569 mg of compound **90** in 100 ml of methanol, 57 mg of palladium carbon (10%) was added. The reaction mixture was hydrogenated at 50^{o}C under 10 bar pressure for 5 h. After being cooled to the room temperature, the reaction mixture was filtered. After removal of the solvent, the residue was purified by chromatography, eluting with petroleum ether/ethyl acetate = 1/1, to afford 240 mg (42%) of product **101** as a white crystal. TLC R_f 0.59 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.36 (m, 5H), 5.08 (d, *J* = 14.7, 1H), 4.42 (s, 1H), 4.16 (d, *J* = 14.7, 1H), 3.68 (s, 3H), 2.65-2.98 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 198.82, 170.10, 166.42, 135.17, 128.86, 128.76, 128.20, 68.44, 53.44, 49.10, 35.46, 28.89; PI-EIMS: m/z (relative intensity) 261.1 (M^+, 25.88%).

Compound **102**: 210 mg (36%). TLC R_f 0.28 (ethyl acetate); IR (film) 3366, 2953, 1740, 1627, 1448, 1415, 1357, 1208, 1179, 1096, 1053, 1018, 987, 917, 811, 758; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.34 (m, 5H), 5.21 (d, *J* = 14.8, 1H), 4.07-4.17 (m, 2H), 3.90 (d, *J* = 14.8, 1H), 3.69 (s, 3H), 2.44-2.75 (m, 2H), 1.88-2.09 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.57, 169.67, 136.03, 128.67, 128.54, 127.82, 66.29, 62.67, 52.56, 49.58, 29.11, 26.33; PI-EIMS: m/z (relative intensity) 263.3 (M^+, 21.23%); HRMS: Calcd for $C_{14}H_{17}NO_4$ (M^+): 263.1158. Found 263.1160.



107

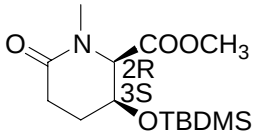
(2R, 3S)-3-hydroxy-1-methyl-6-oxo-piperidine-2-carboxylic acid methyl ester (107) To the flask contained 80 mg of compound **98**, was added 8 ml of tap water, 1.5 g of sucrose and 1 g of fresh baker's yeast. The resulting mixture was gently stirred at 30-32^{o}C for 48 h. Then 5 g of celite was added and stirred for another 5 min. After being cooled to the room temperature, the reaction mixture was filtered and washed with water. The filtrate was saturated with sodium chloride, and extracted with $CHCl_3$, washed with water. The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography through a silica gel column to afford 40 mg (50%) of product **107** as a white solid. TLC R_f 0.11 (ethyl acetate); $[\alpha]_D$ = - 8.23 (c = 0.79, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 4.27-4.32 (m, 2H), 3.77 (s, 3H), 2.83 (s, 3H), 1.84-2.60 (m, 4H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 172.96, 171.66, 67.87, 66.14, 52.80, 34.83, 29.38, 27.16; CI-MS: m/z (relative intensity) 205.3 (MNH_4^+, 21.77%), 188.2 (MH^+, 53.21%); Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33%; H, 7.00%; N, 7.48%. Found: C, 50.83%; H, 6.65%; N, 7.45%.



(±)-**108**

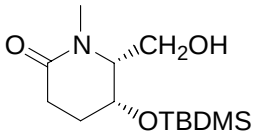
***cis*-(±)-3-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-6-oxo-piperidine-2-carboxylic acid methyl ester (108)** 0.519 g of *cis*-(±)-3-hydroxy-1-methyl-6-oxo-piperidine-2-carboxylic acid methyl ester (**99**) was dissolved in 8 ml of DMF, followed by the addition of 0.472 g of imidazole and 0.5 g of TBDMSCl. The solution was stirred at rt overnight. Then the solvent was evaporated completely in vacuum. H_2O and CH_2Cl_2 were added, and the organic layer

was dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography, eluting with ethyl acetate, to afford 0.75 g (90%) of product **108** as a white soft solid. TLC R_f 0.39 (ethyl acetate); IR (KBr) 2930, 1753, 1641, 1470, 1402, 1255, 1182, 1077, 999, 937, 833; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25-4.31 (m, 1H), 4.06 (d , *J* = 5.87, 1H) 3.76 (s, 3H), 2.85 (s, 3H), 2.63 (dt, *J* = 17.57, 5.39, 1H), 2.31-2.42 (m, 1H), 2.11-2.24 (m, 1H), 1.77-1.86 (m, 1H), 0.88 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.96, 169.80, 66.88, 66.60, 52.12, 34.31, 28.77, 27.04, 25.52, 17.89, -4.74, -5.14; PI-EIMS: m/z 301.2 (M^+); HRMS: Calcd for $C_{14}H_{27}NO_4Si$ (M^+): 301.1709. Found: 301.1702.



109

(2R,3S)-3-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-6-oxo-piperidine-2-carboxylic acid methyl ester (109) This procedure was similar to **108**, starting from (2R, 3S)-3-hydroxy-1-methyl-6-oxo-piperidine-2-carboxylic acid methyl ester (**107**). After chromatography, 125 mg (92%) of the desired product **109** was obtained as a white solid. TLC R_f 0.39 (ethyl acetate); $[\alpha]_D$ = - 78.64 (c = 0.22, $CHCl_3$); IR (film) 2858, 1746, 1651, 1463, 1397, 1300, 1254, 1207, 1116, 1047, 1013; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.25-4.31 (m, 1H), 4.06 (d , *J* = 5.87, 1H), 3.76 (s, 3H), 2.85 (s, 3H), 2.63 (dt, *J* = 17.57, 5.39, 1H), 2.31-2.42 (m, 1H), 2.11-2.24 (m, 1H), 1.77-1.86 (m, 1H), 0.88 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.99, 169.82, 66.90, 66.62, 52.15, 34.33, 28.79, 27.06, 25.54, 17.91, -4.72, -5.12; PI-EIMS: m/z 301.2 (M^+); HRMS: Calcd for $C_{14}H_{27}NO_4Si$ (M^+): 301.1709. Found: 301.1701.



(±)- **110**

***cis*-(±)-5-(*tert*-butyl-dimethyl-silanyloxy)-6-hydroxymethyl-1-methyl-piperidin-2-one (110)** To a solution of **(±)**-*cis*-3-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-6-oxo-piperidine-2-carboxylic acid methyl ester (**108**) in 15 ml of CH_2Cl_2, 0.66 ml of 1M DIBAL hydride was added. The solution was stirred under nitrogen for 2 h. Then, 0.66 ml of the same DIBAL solution was added. After 1 h, 1 ml of methanol and 0.2 ml of water were added. The reaction mixture was warmed to rt, and 25 ml of water was added. The mixture was extracted with CH_2Cl_2 several times. The combined organic layers were dried over $MgSO_4$. After removal of

the solvent, the residue was purified by chromatography through a silica gel column, eluting with ethyl acetate, to afford 17 mg (19%) of product **110** as a yellow solid. TLC R_f 0.13 (ethyl acetate); IR (KBr) 3387, 2931, 1628, 1473, 1401, 1254, 1045; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (dt, *J* = 10.24, 4.53, 1H), 3.97 (dd, *J* = 11.80, 7.41, 1H), 3.79 (dd, *J* = 11.66, 2.33, 1H), 3.38-3.45 (m, 1H), 2.98 (s, 3H), 2.54 (dddd, *J* = 6.72, 4.53, 1H), 2.38 (dddd, *J* = 9.06, 8.51, 7.96, 7.41, 1H), 2.11-2.18 (m, 1H), 1.81-1.93 (m, 1H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.50, 69.48, 62.59, 60.77, 33.97, 28.67, 26.45, 25.68, 17.94, -4.63, -5.11; PI-EIMS: m/z (relative intensity) 274.2 (MH^+, 16.05%); HRMS: Calcd for $C_{13}H_{28}NO_3Si$ (MH^+): 274.1835. Found: 274.1835.

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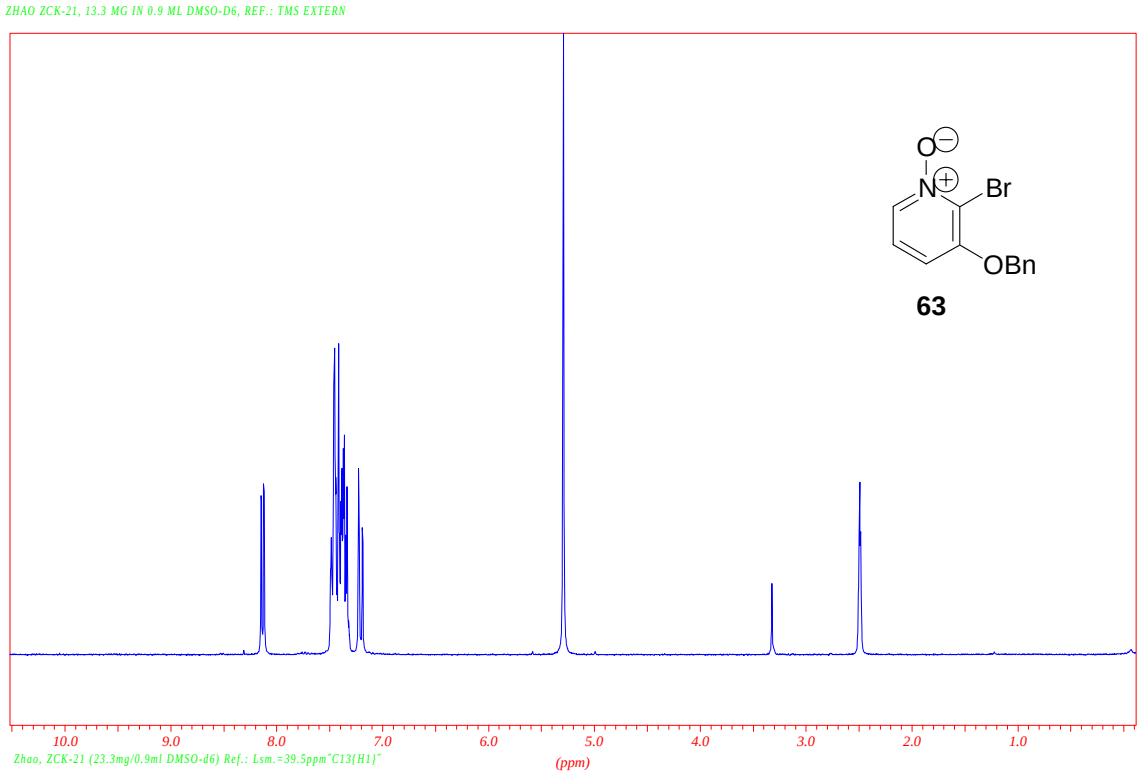
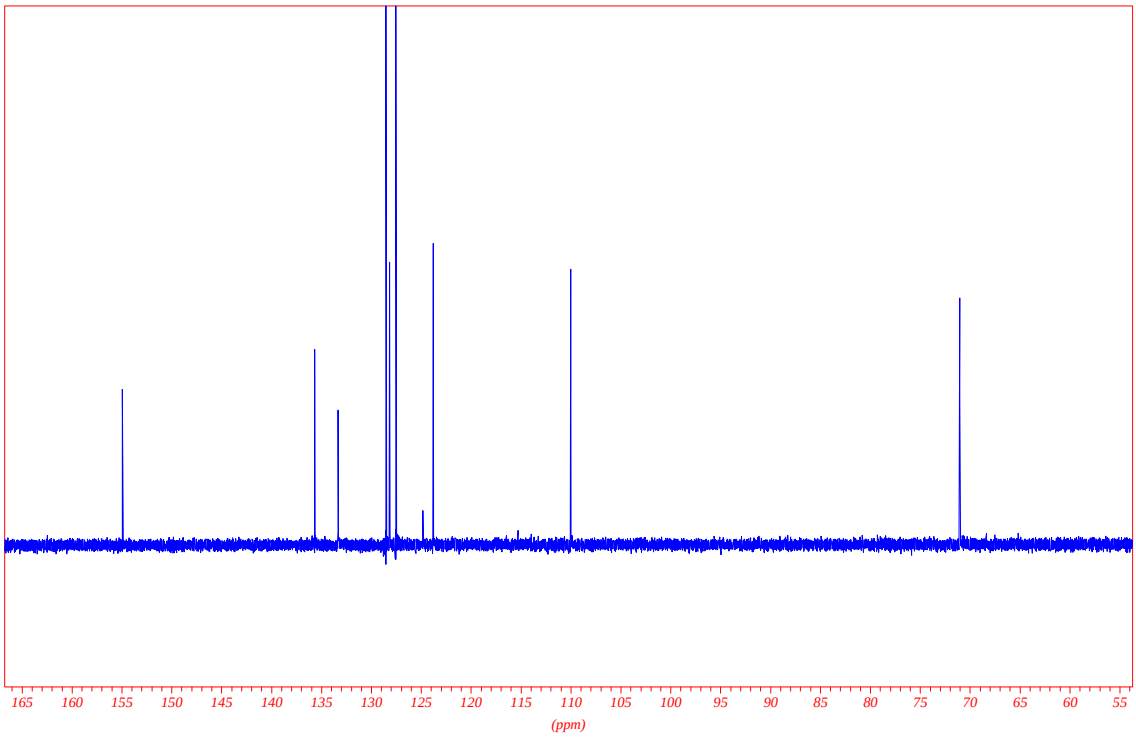
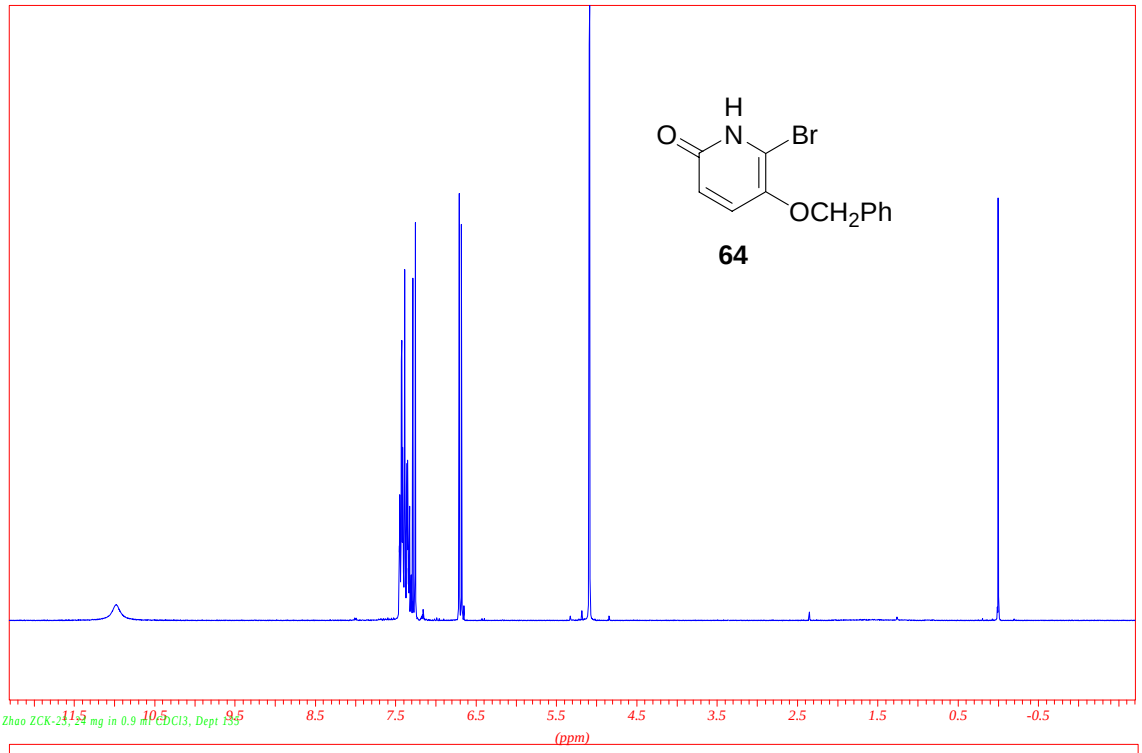
4 NMR-Spectra



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O
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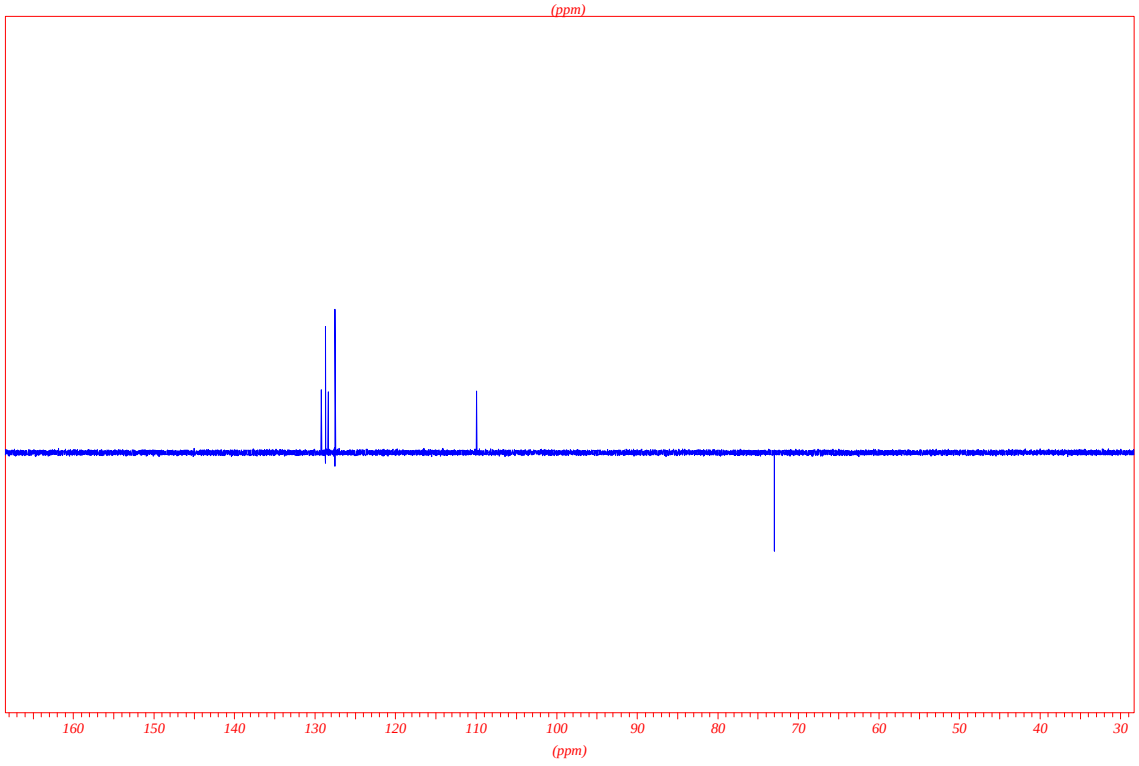
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
(ppm)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140
130
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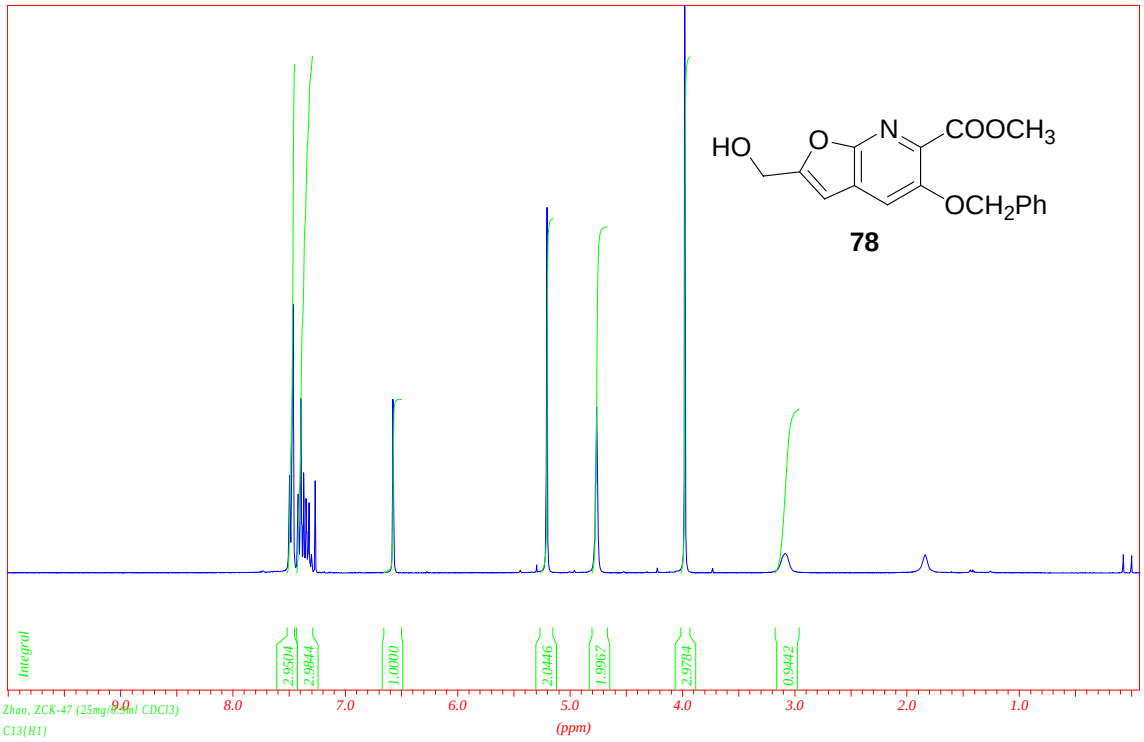
110
100
90
80
70
60
50
40
30
(ppm)


HO
O
N
COOCH3
OCH2Ph
78
Integral
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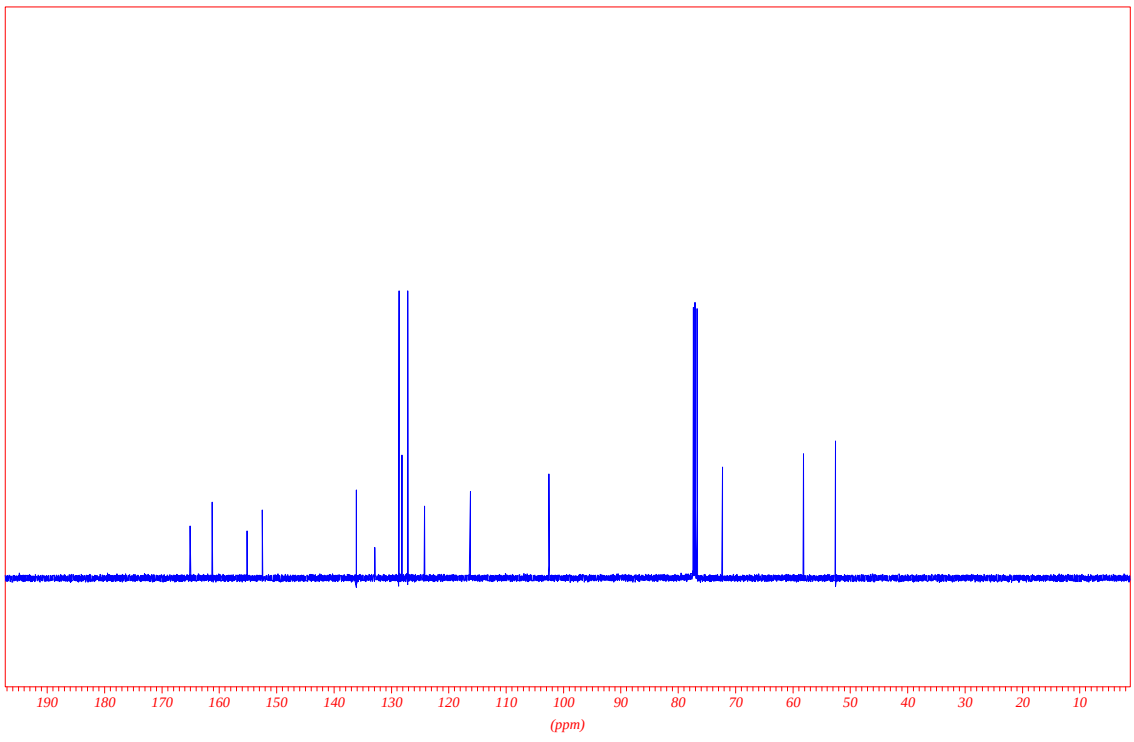
1.0000
2.0446
1.9967
2.9784
0.9442
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)
Zhao, ZCK-47 (25mg/0.5ml CDCl3)
C13{H1}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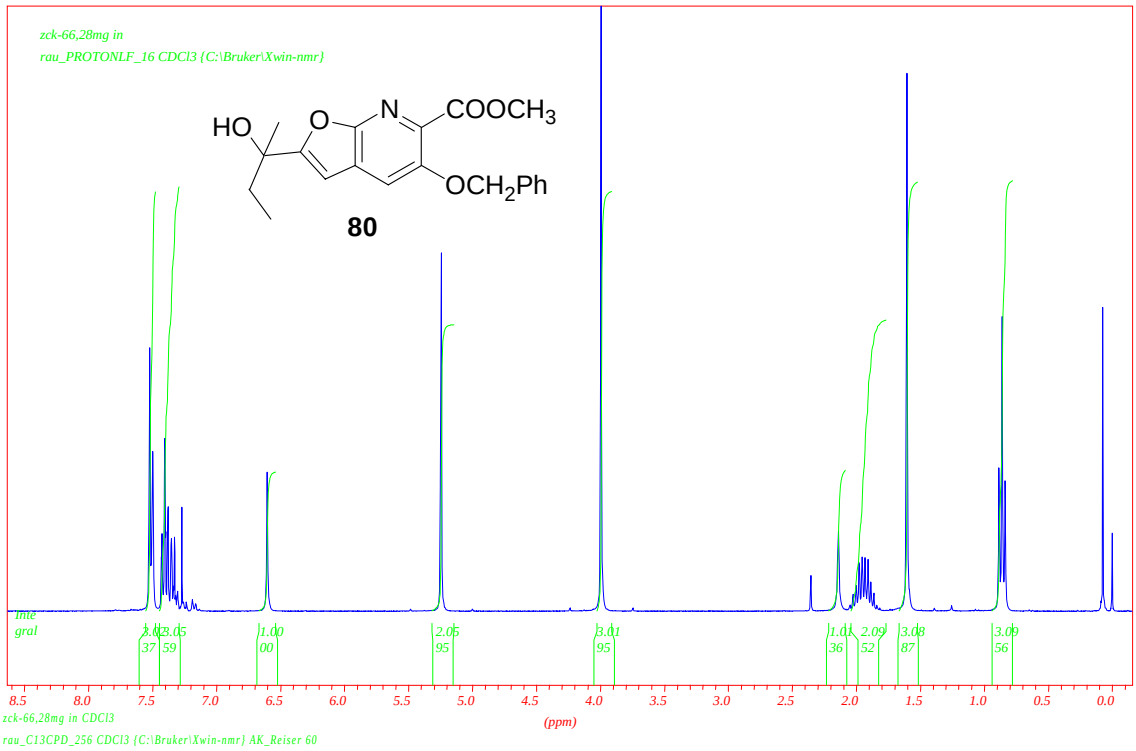
10
(ppm)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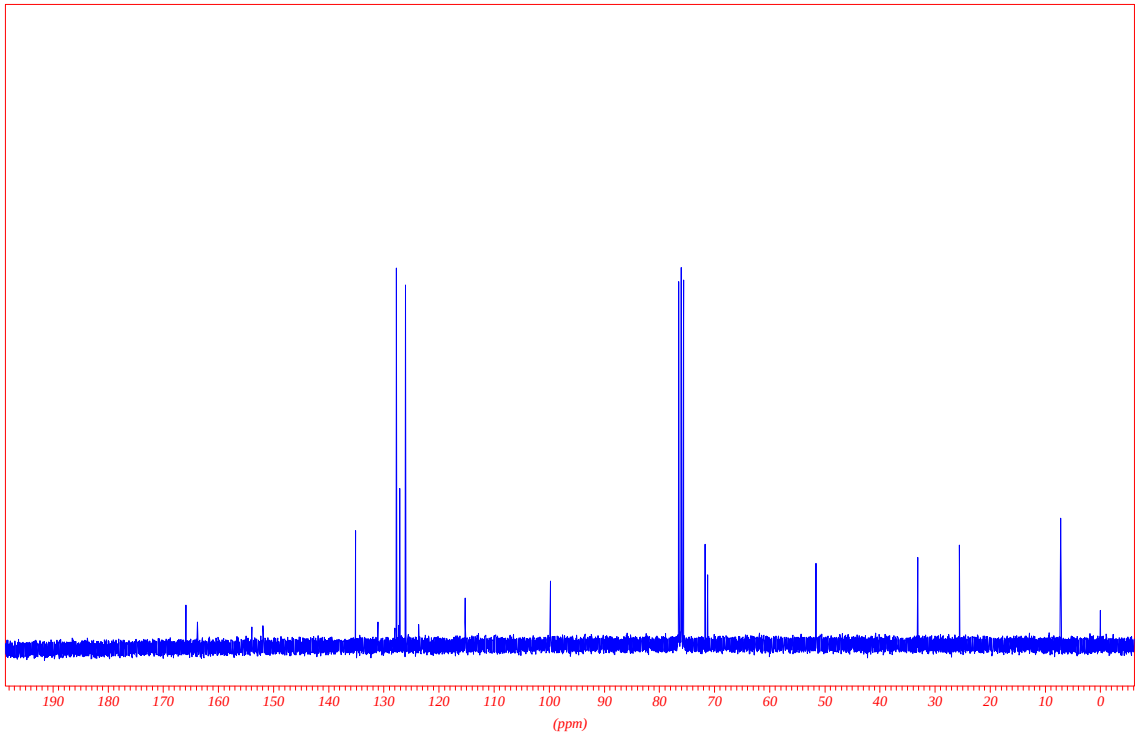
HO
O
N
COOCH3
OCH2Ph
80
inte
gral
3.00 3.05
37 59
1.00
00
2.05
95
3.01
95
1.01 2.09
36 52
3.08
87
3.09
56
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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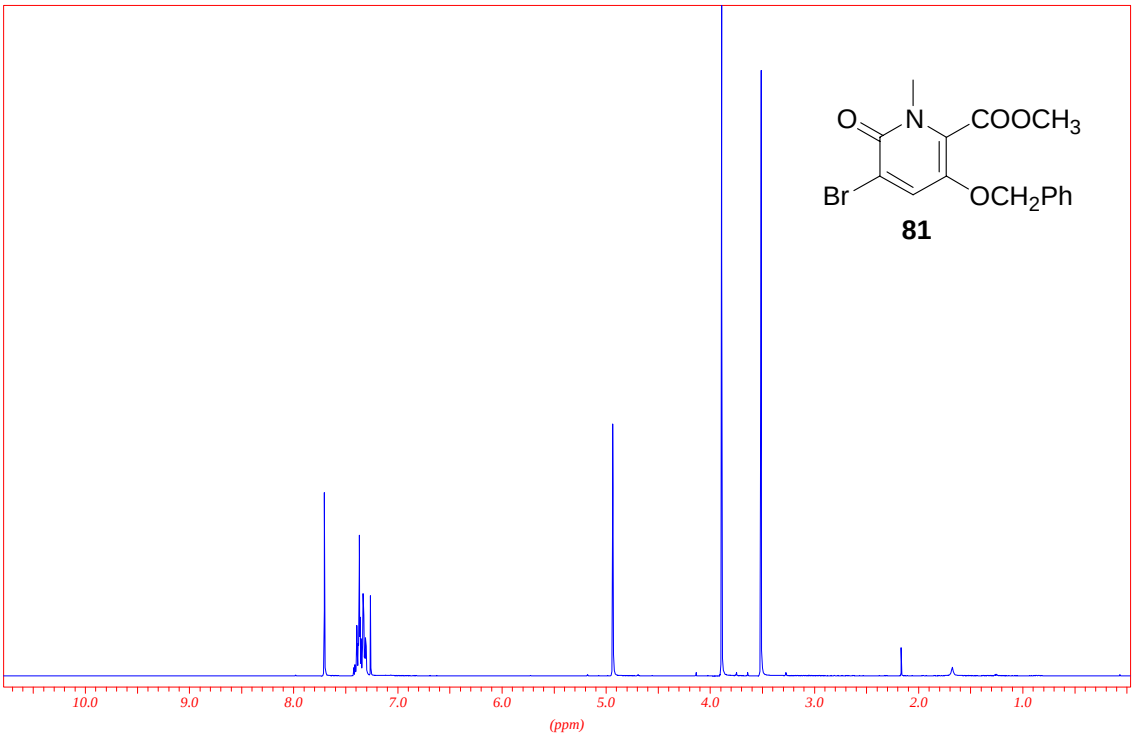
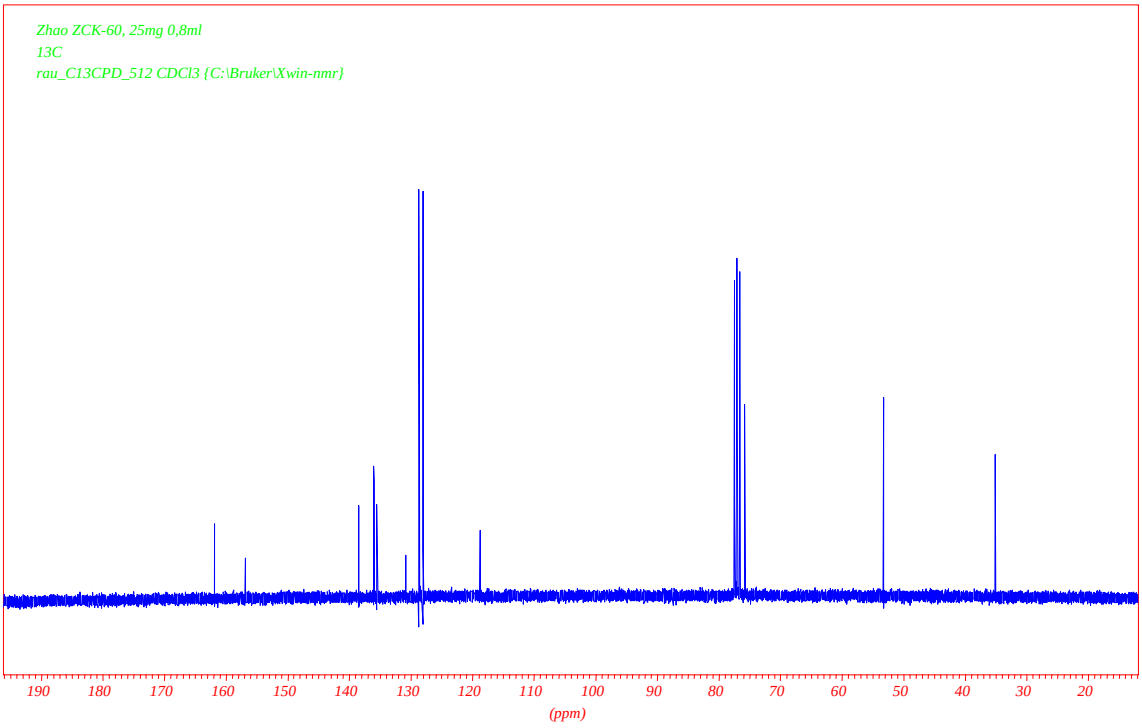
(ppm)


O
N
COOCH3
Br
OCH2Ph
81
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)


Zhao ZCK-60, 25mg 0,8ml
13C
rau_C13CPD_512 CDCl3 {C:\Bruker\Xwin-nmr}
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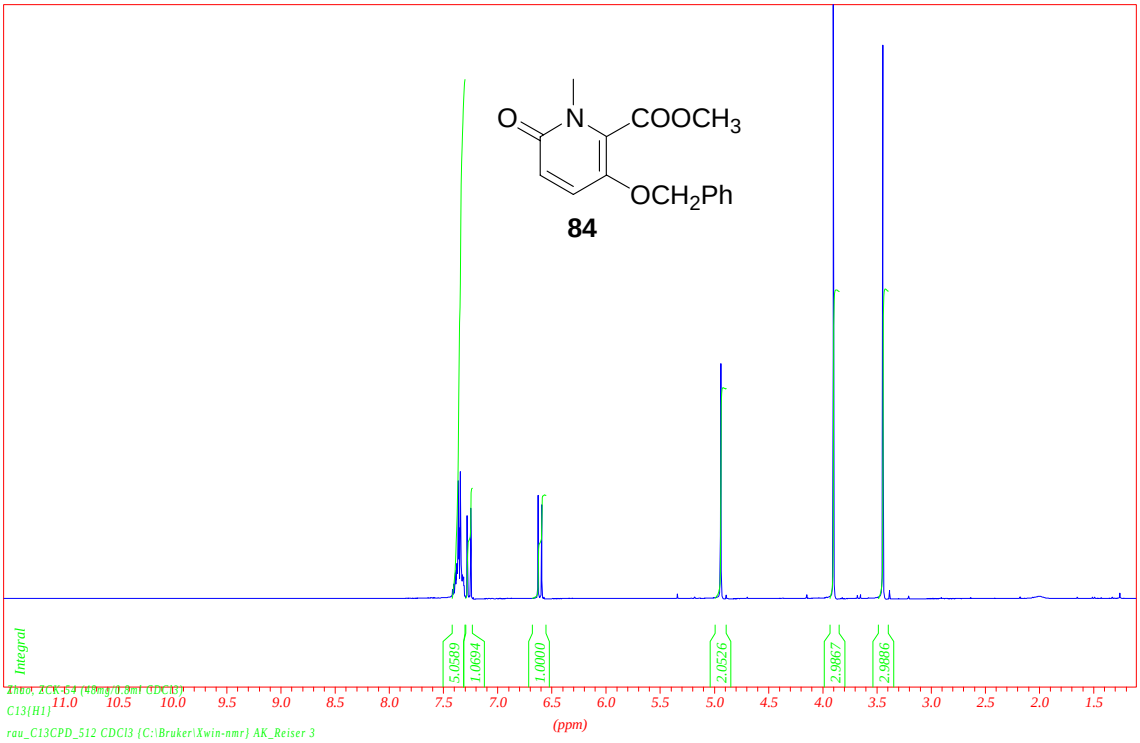
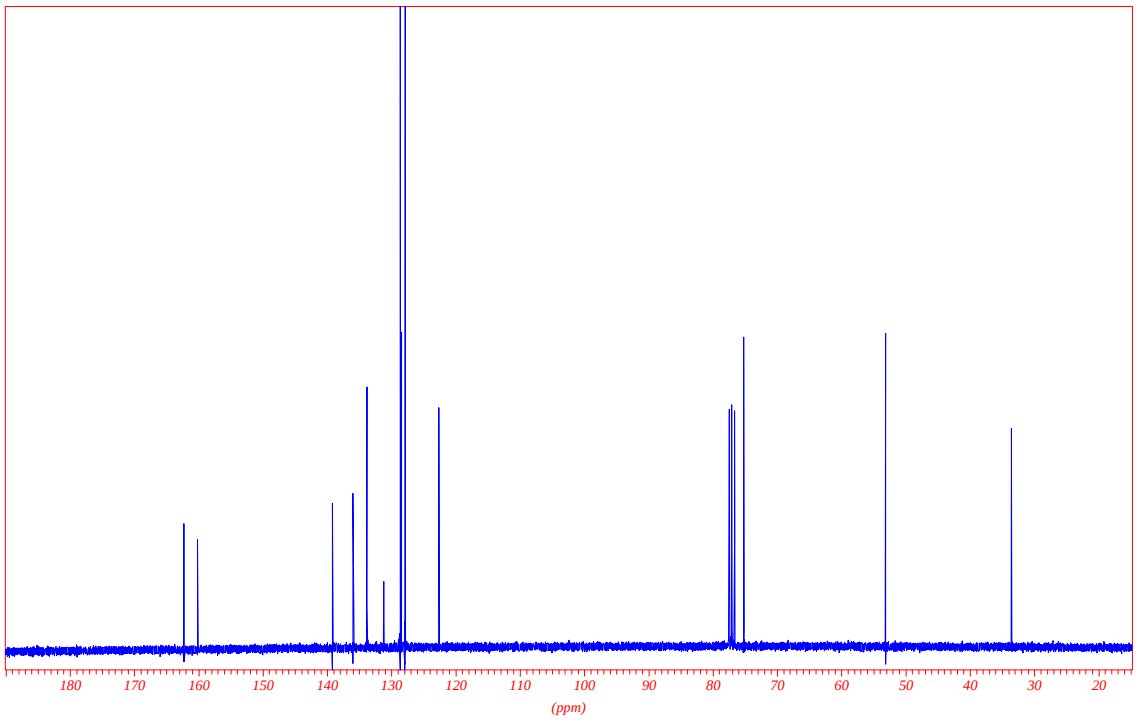
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


O
N
COOCH3
OCH2Ph
84
Integral
5.0589
1.0694
1.0000
2.0526
2.9867
2.9886
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
(ppm)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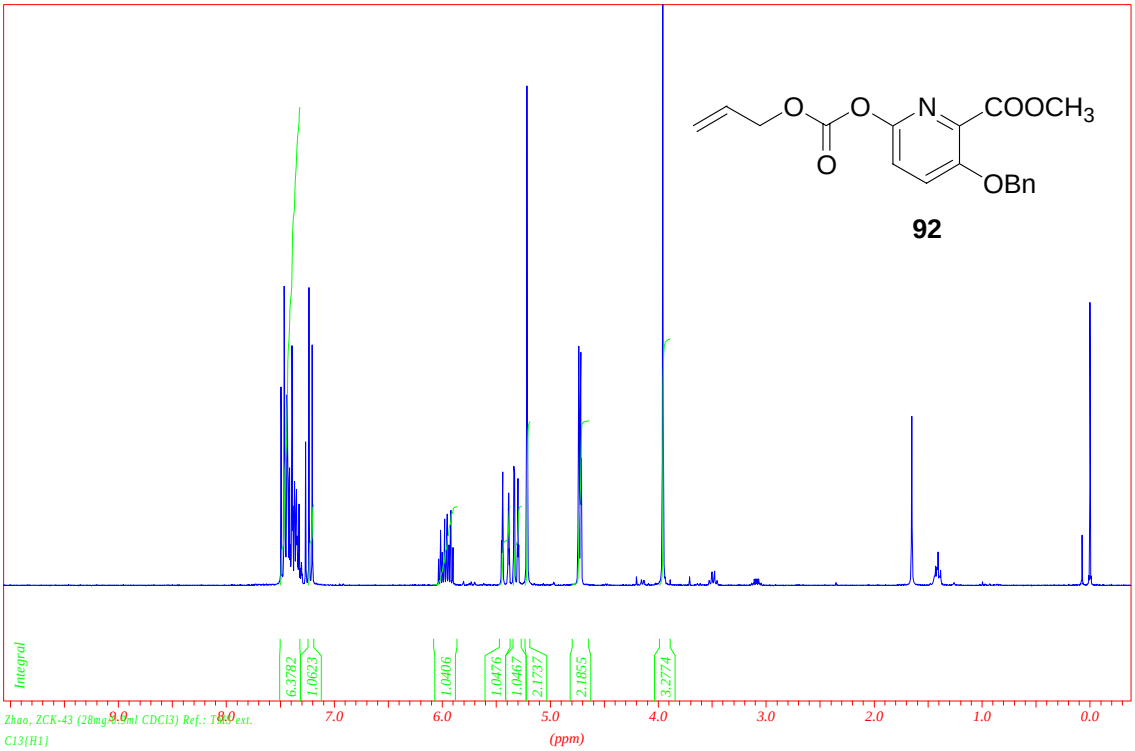
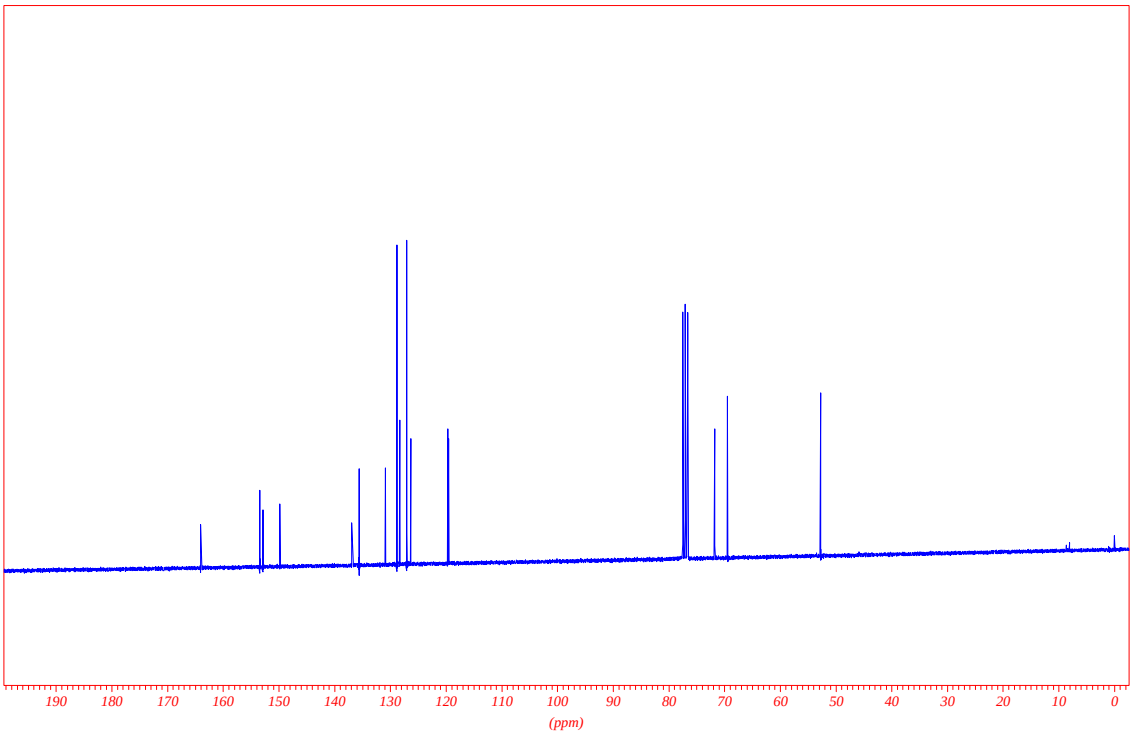
(ppm)


O
O
O
N
COOCH3
OBn
92
Integral
6.3782
1.0623
1.0406
1.0476
1.0467
2.1737
2.1855
3.2774
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


190
180
170
160
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140
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120
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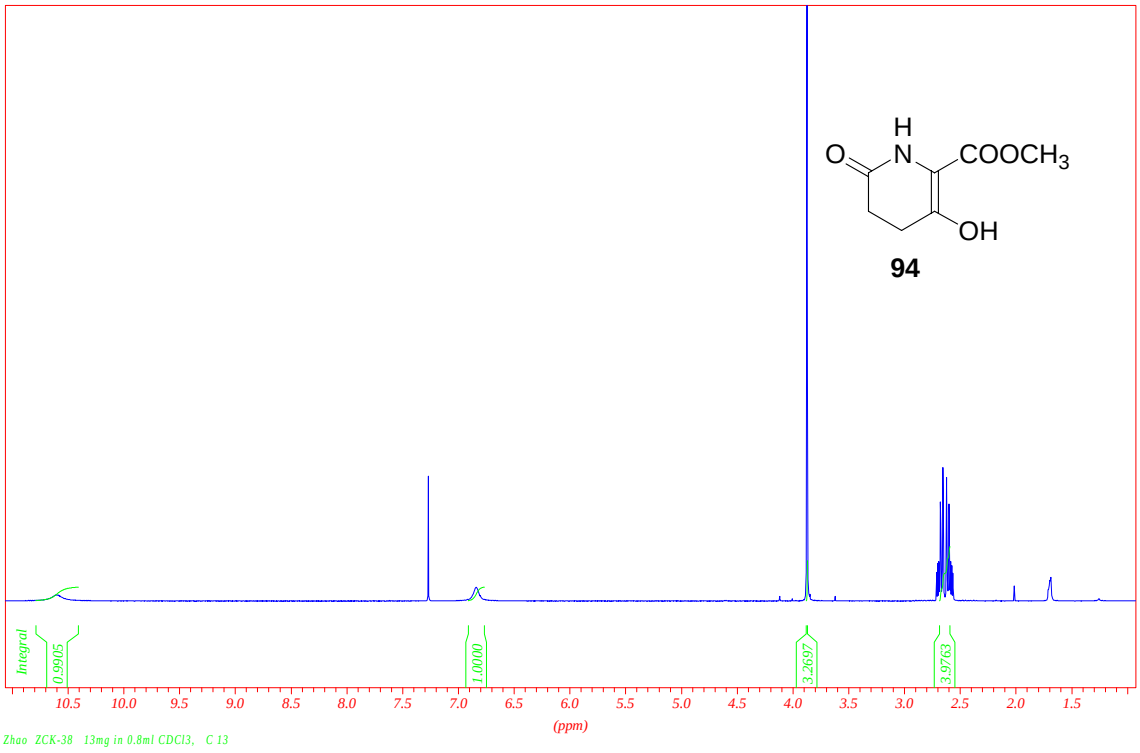
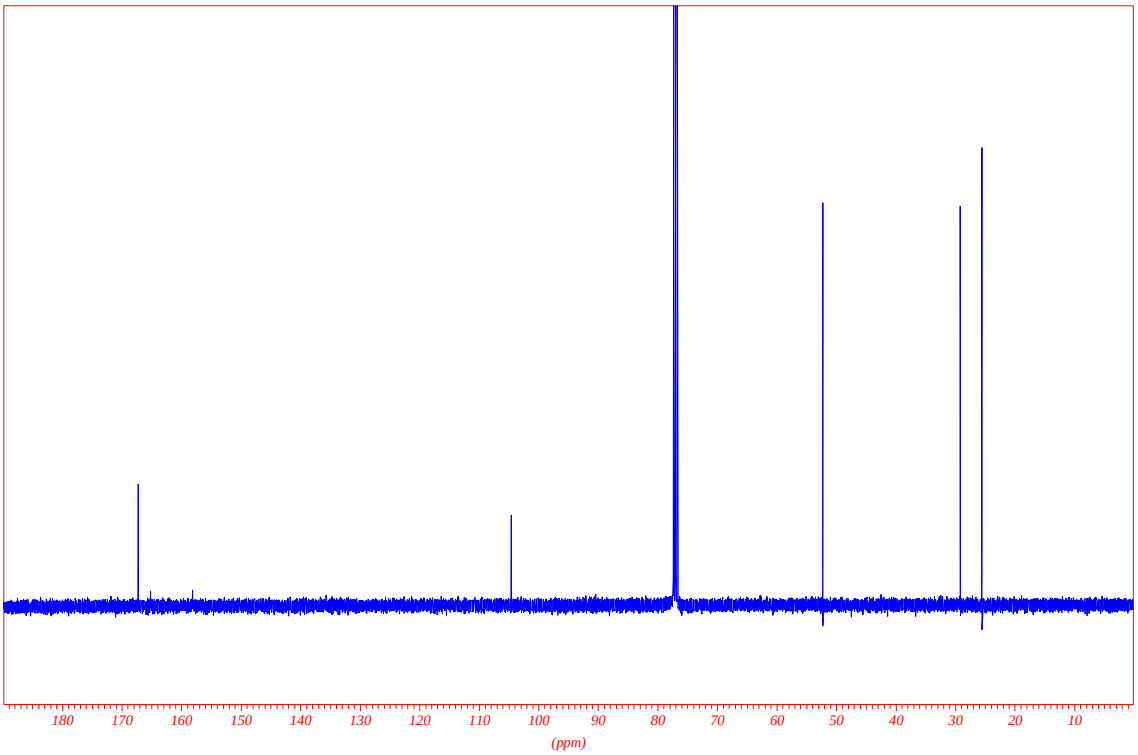
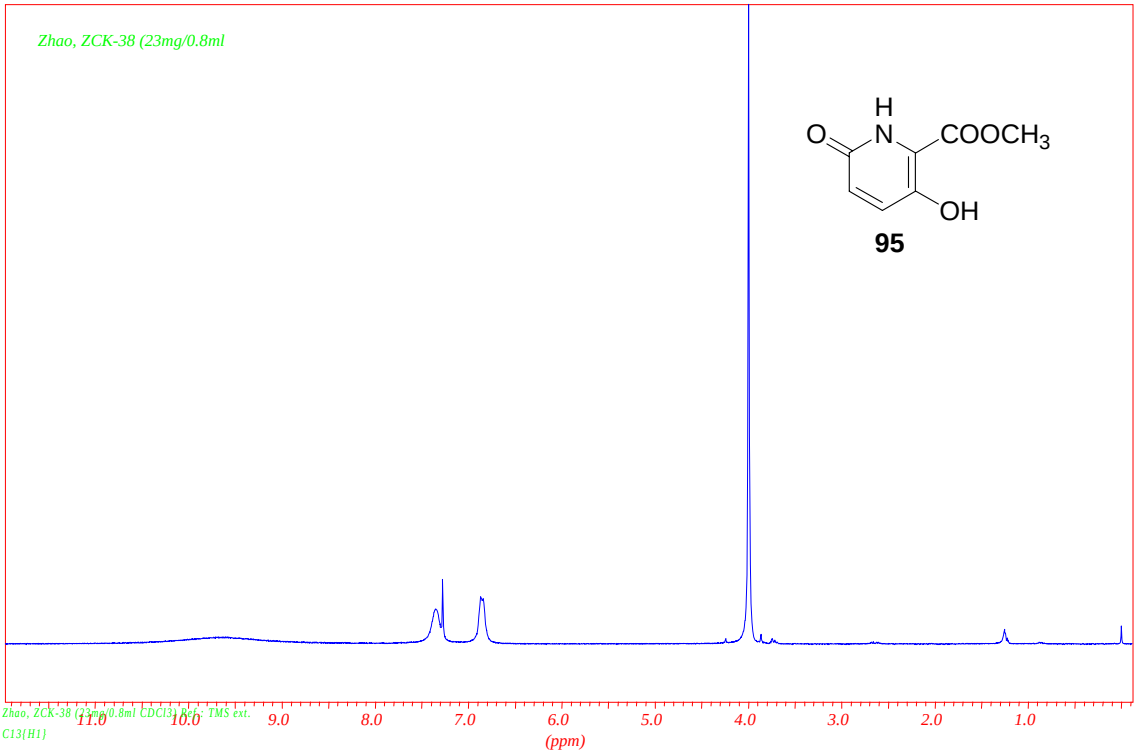
100
90
80
70
60
50
40
30
20
10
0
(ppm)



Zhao ZCK-38 13mg in 0.8ml CDCl3, C 13




Zhao, ZCK-38 (23mg/0.8ml
H
O
N
COOCH3
OH
95
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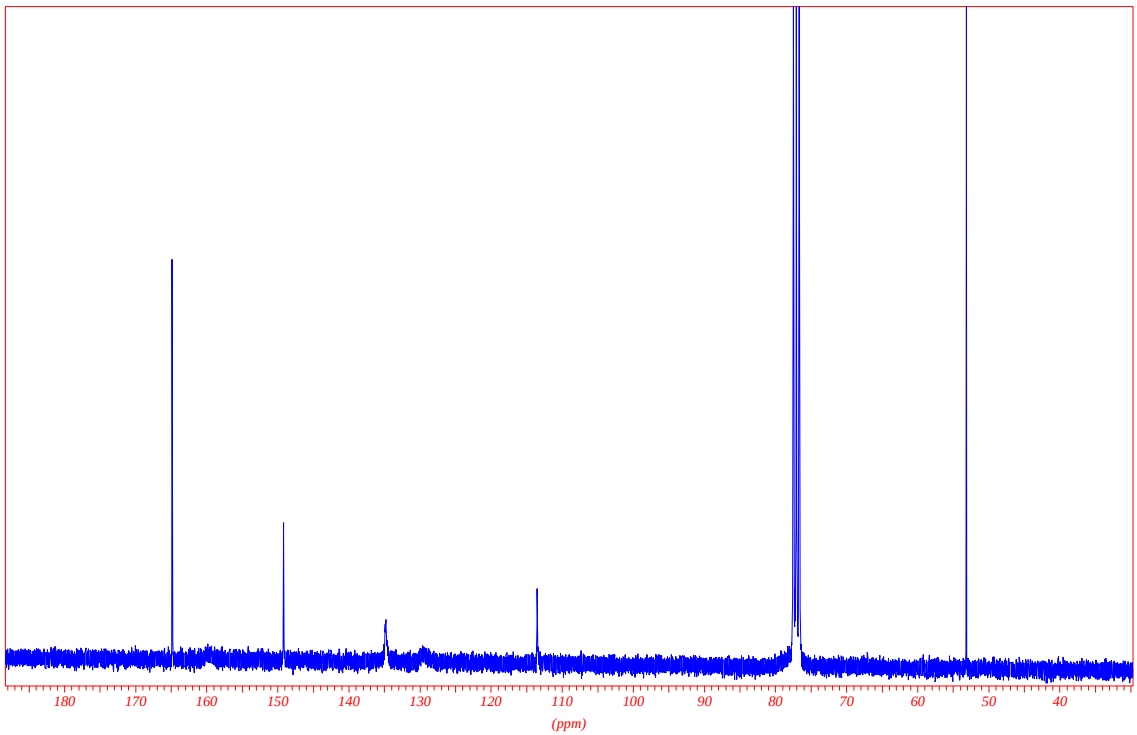
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)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160
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140
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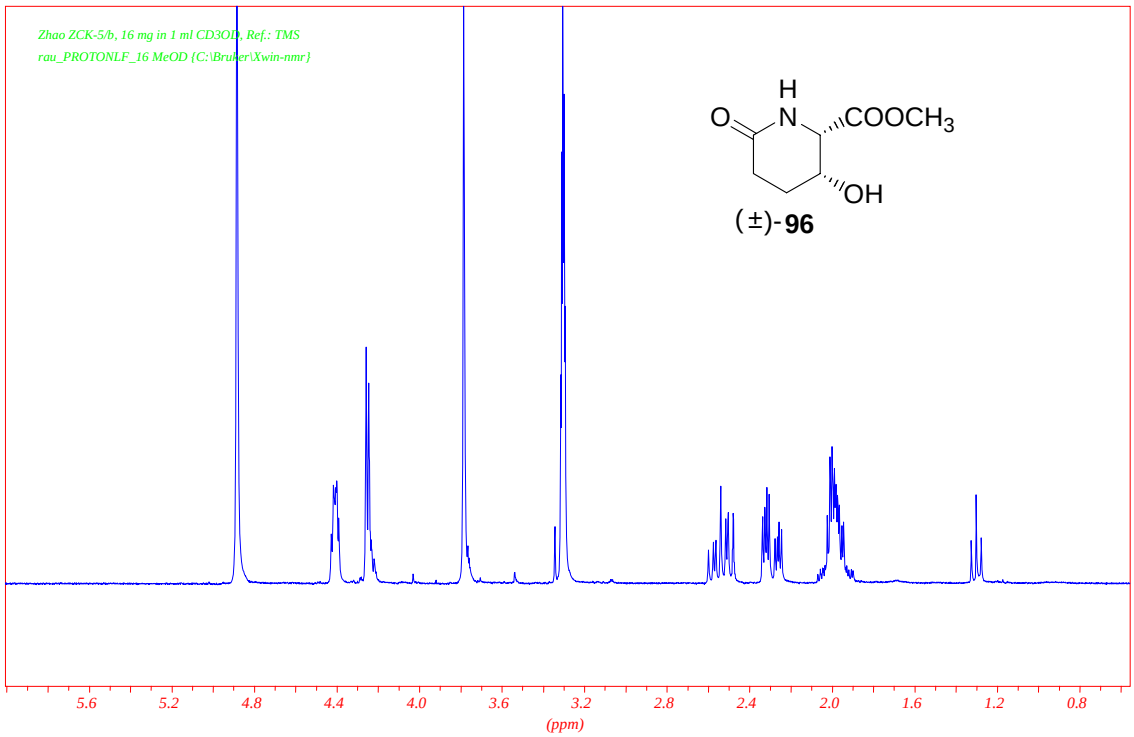
120
110
100
90
80
70
60
50
40
(ppm)


Zhao ZCK-5/b, 16 mg in 1 ml CD3OD, Ref.: TMS
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H
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N
COOCH3
OH
(±)-96
5.6
5.2
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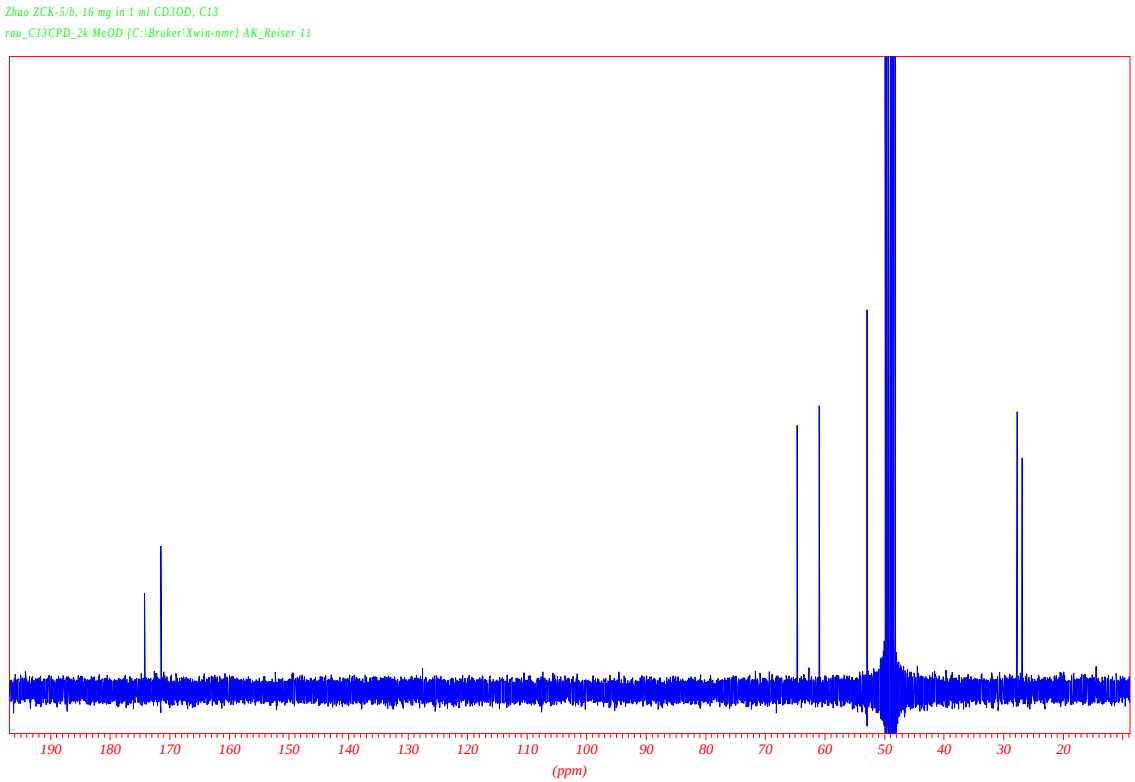
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
(ppm)


Zhao ZCK-5/b, 16 mg in 1 ml CD3OD, C13
rau_C13CPD_2k MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 11
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180
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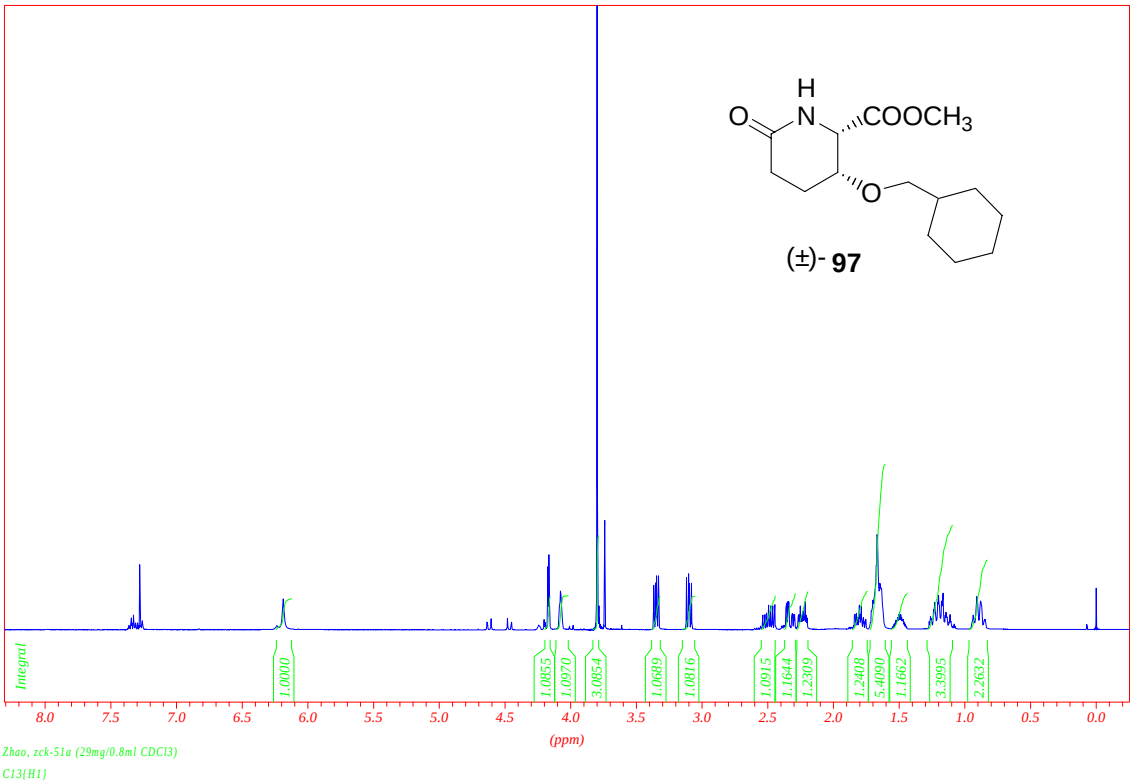
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)


H
O
N
COOCH3
O
(±)- 97
Integral
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1.0970
3.0854
1.0689
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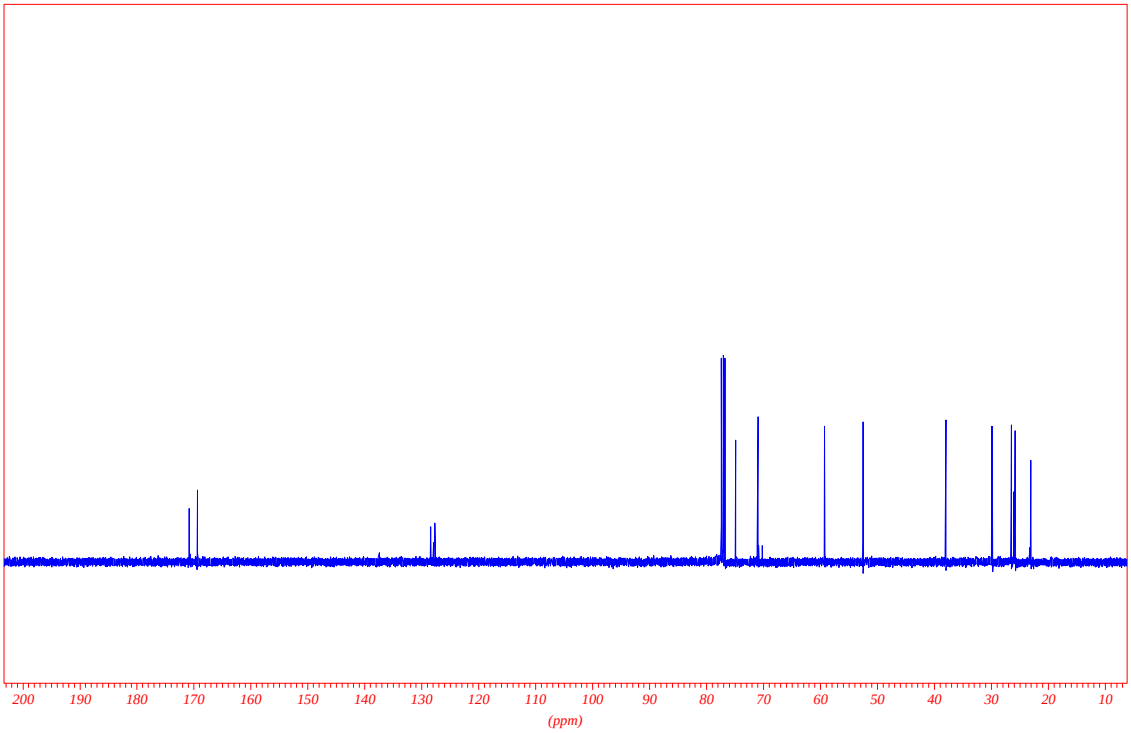
1.0915
1.1644
1.2309
1.2408
5.4090
1.1662
3.3995
2.2632
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)
Zhao, zck-51a (29mg/0.8ml CDCl3)
C13{H1}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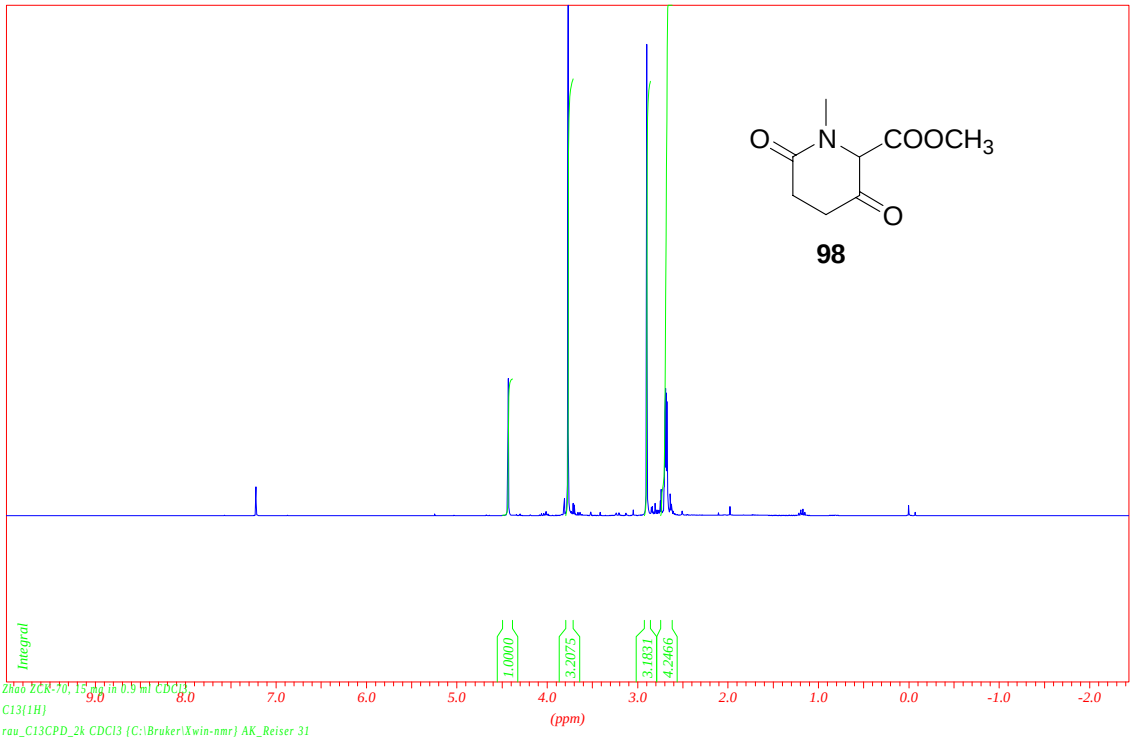
(ppm)


O
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COOCH3
O
98
Integral
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3.2075
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4.2466
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7.0
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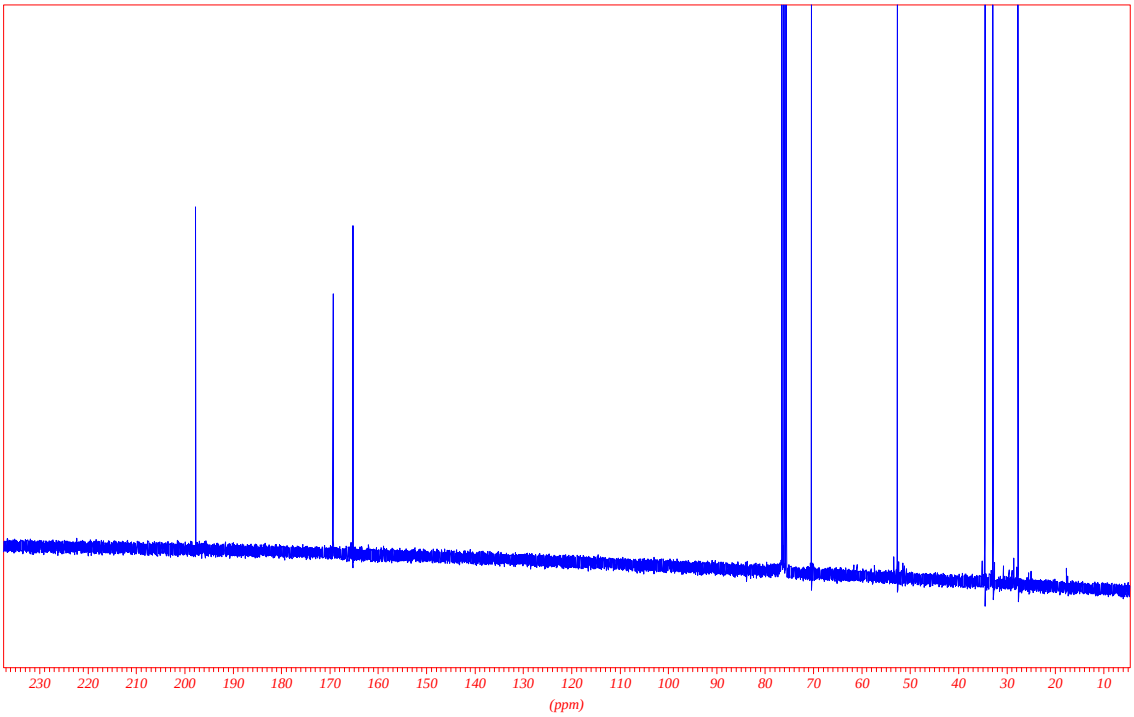
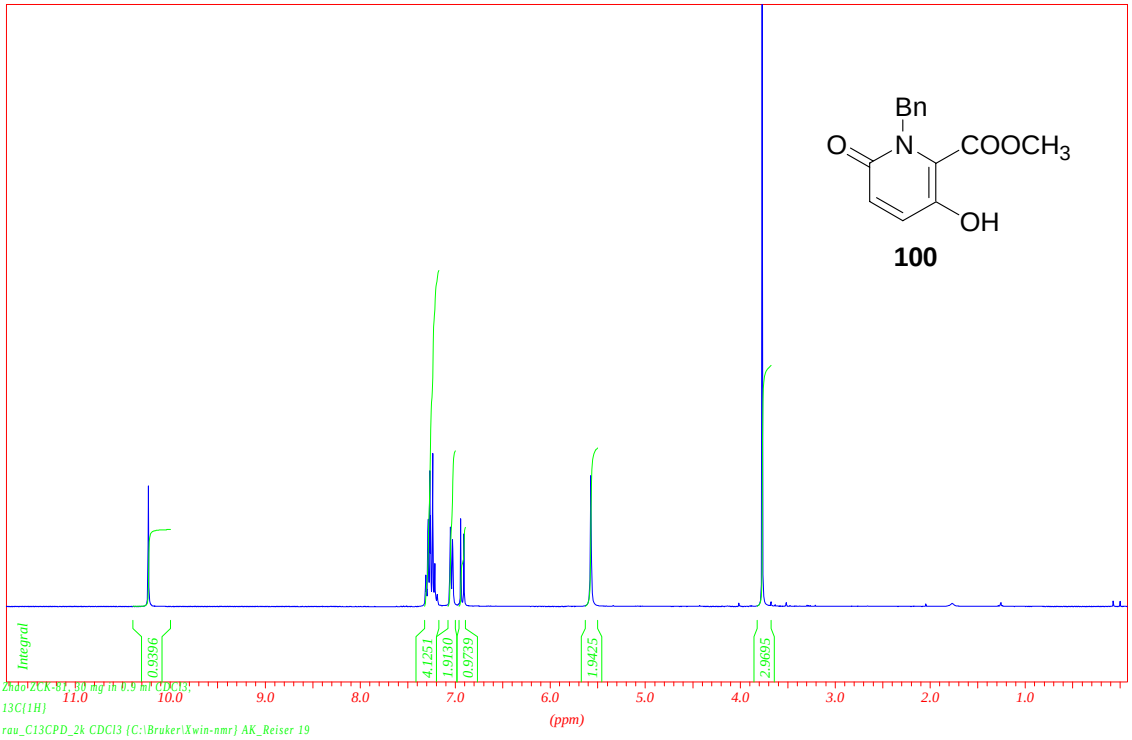
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
(ppm)


230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


Bn
O
N
COOCH3
OH
100
Integral
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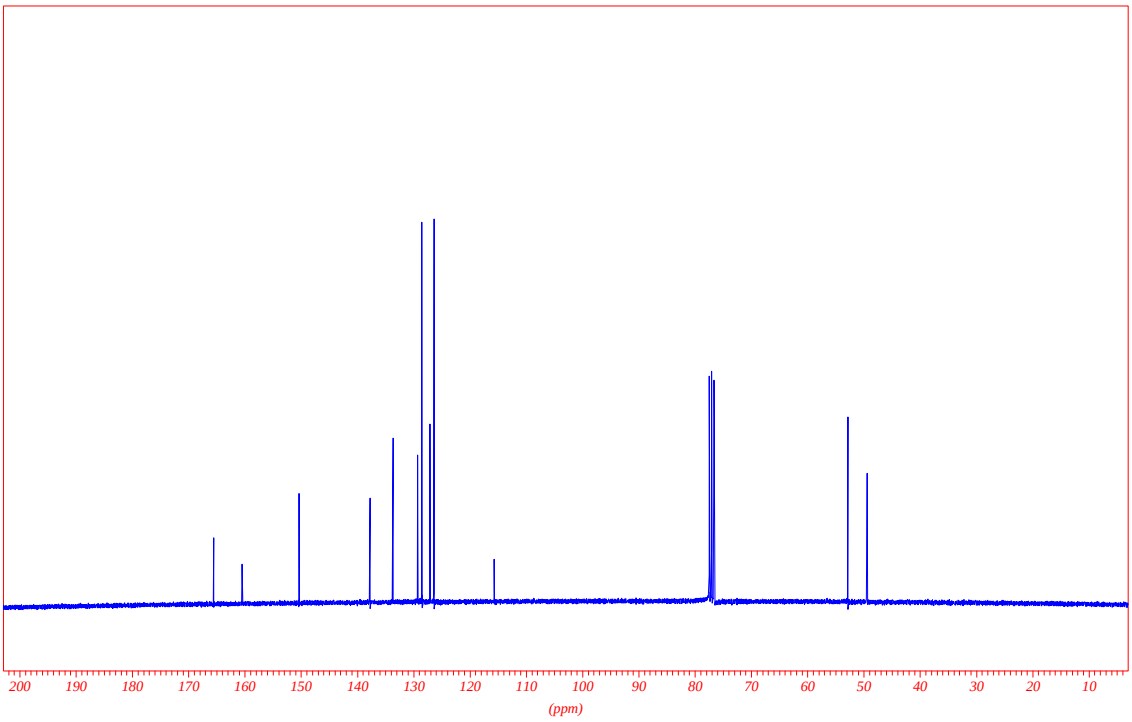
1.9130
0.9739
1.9425
2.9695
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
(ppm)


200
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180
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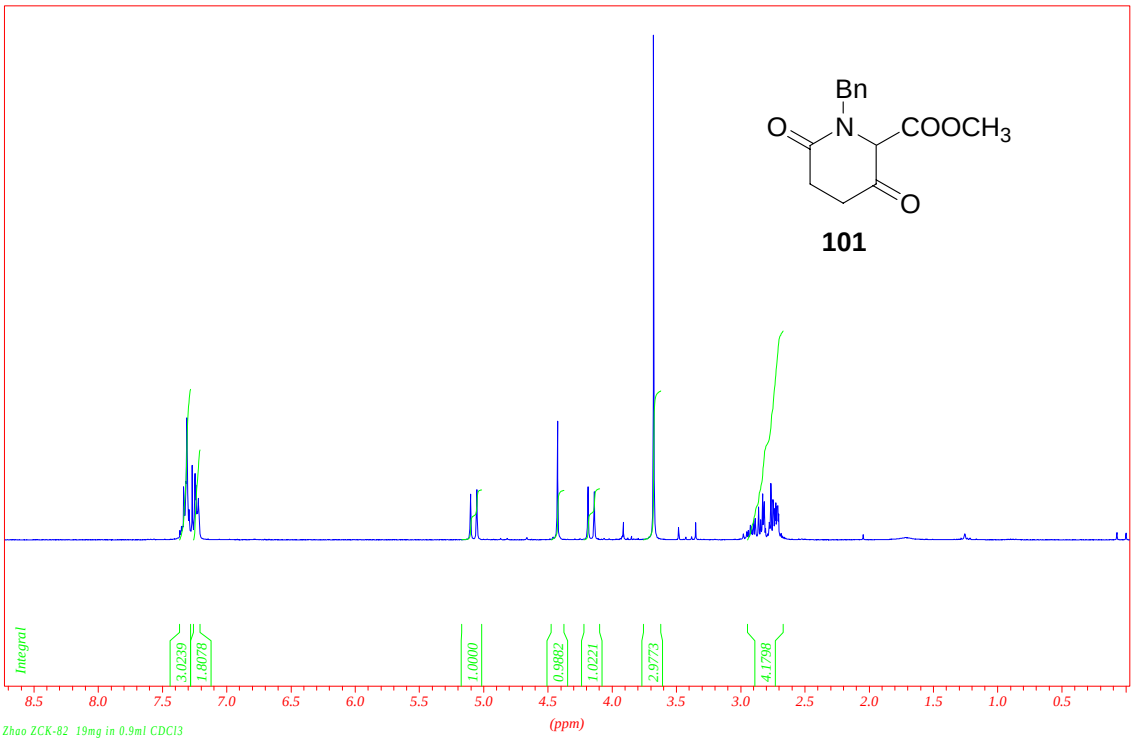
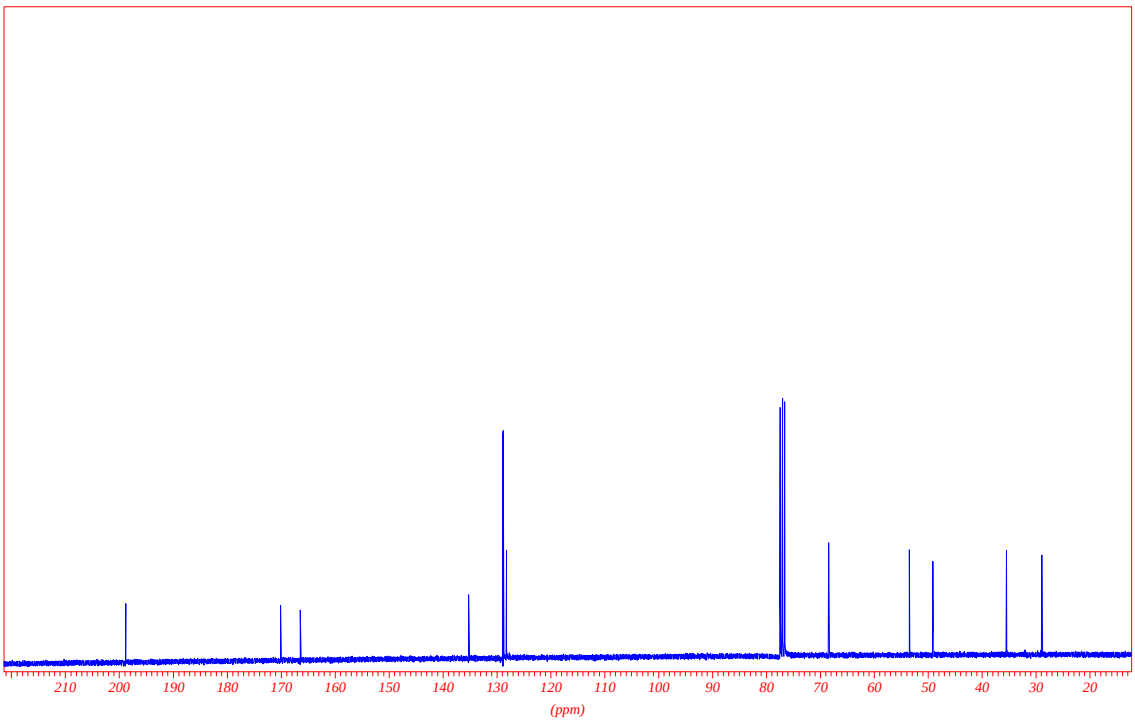
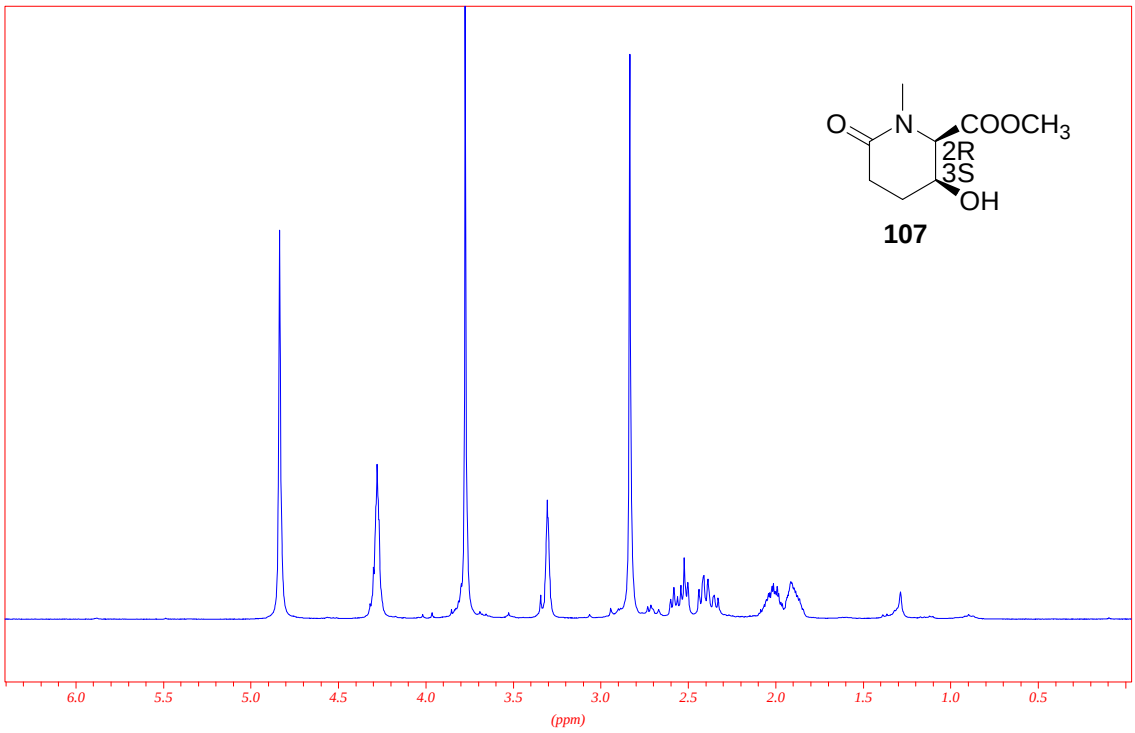
110
100
90
80
70
60
50
40
30
20
10
(ppm)



Zhao ZCK-82 19mg in 0.9ml CDCl3
C13{H1}
rau_C13CPD_2k CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 22

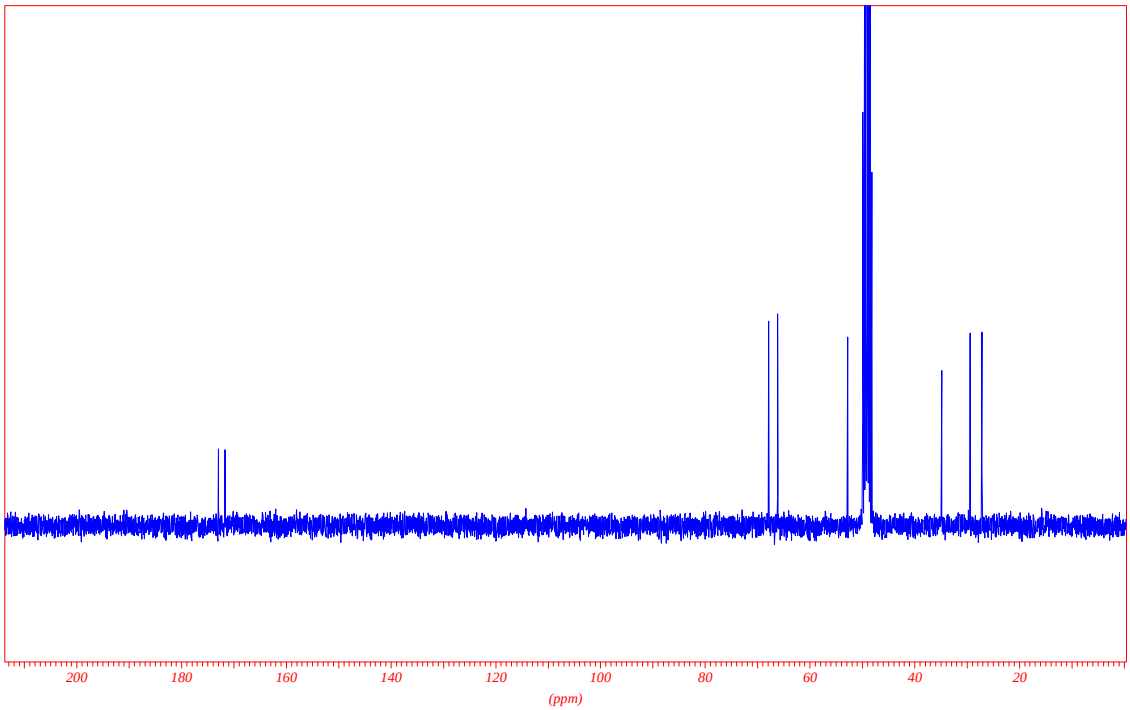


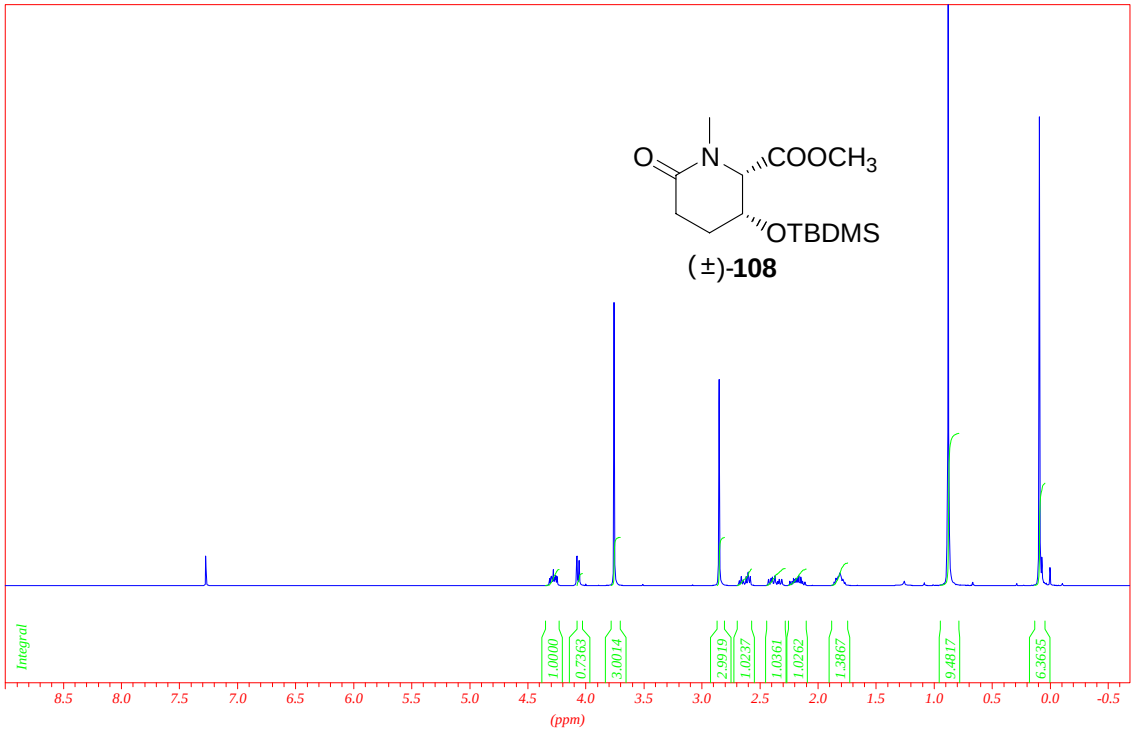
Zhao ZCK-73, 22 mg in 0.9 ml CD3OD, Ref.: TMS extern
rau_PROTONLF_16 MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 21



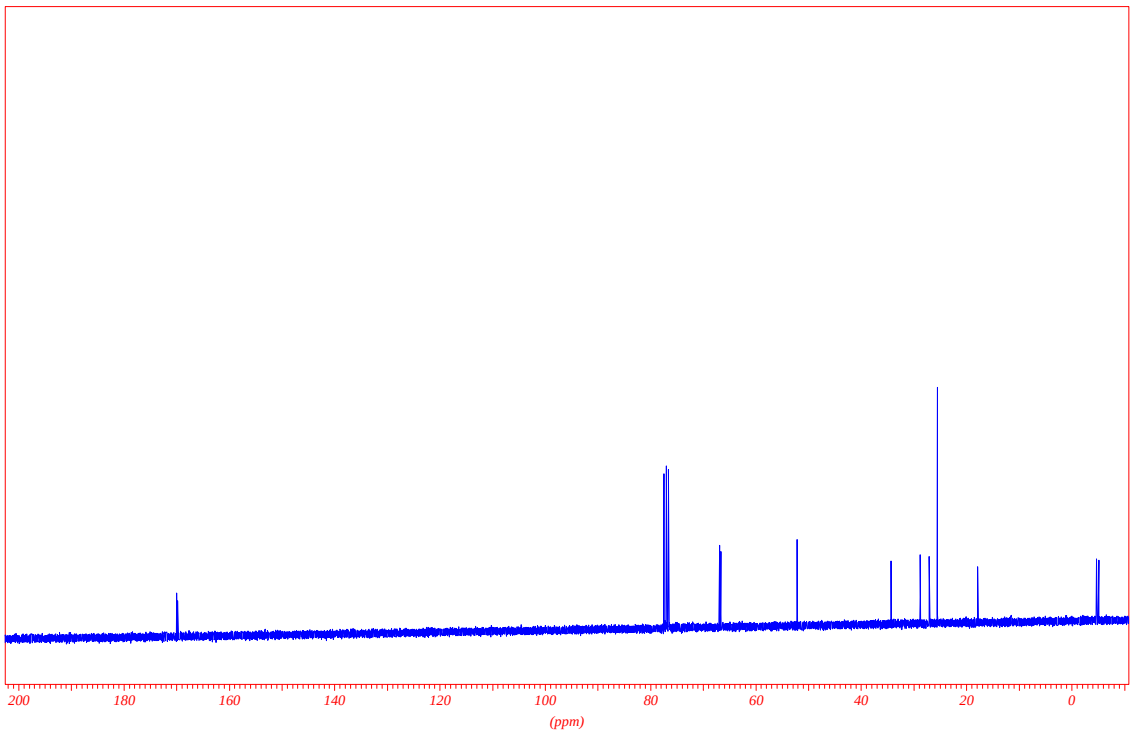
107

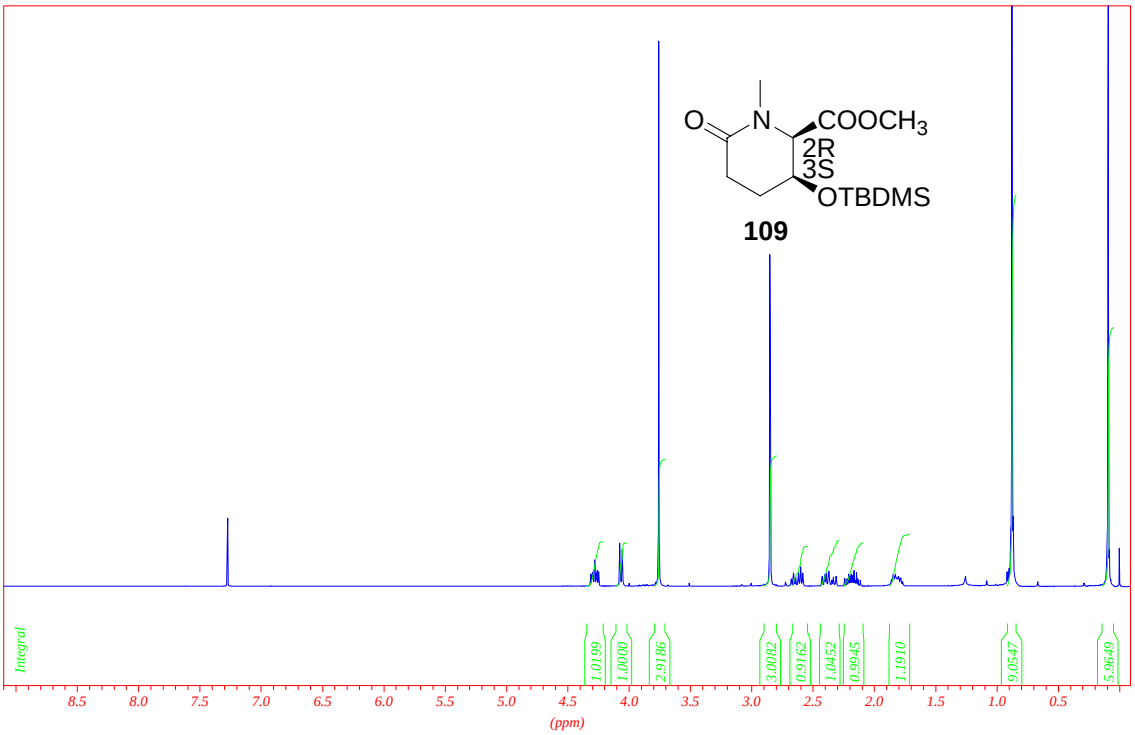
Zhao ZCK-73, 22 mg in 0.9 ml CD3OD
C13{H1}
rau_C13CPD_512 MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 21

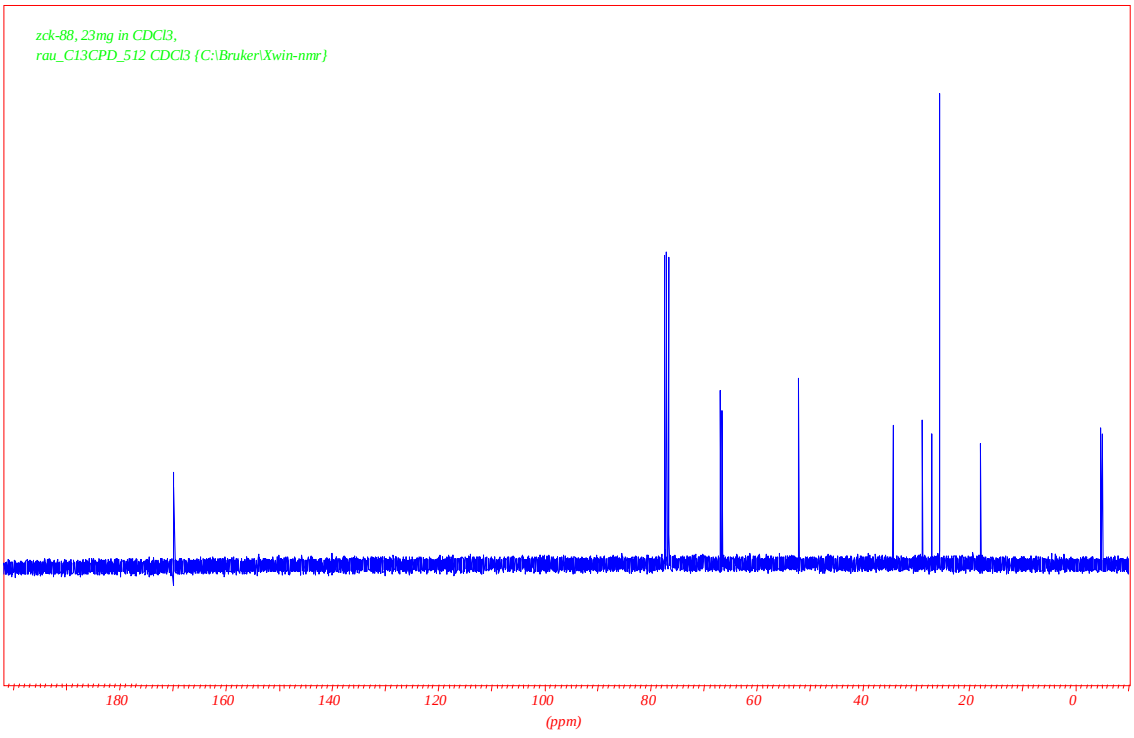




Zhao ZCK-83 21mg in 0.8ml CDCl3, C13{H1}
rau_C13CPD_512 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 32




O
N
COOCH3
2R
3S
OTBDMS
109
Integral
1.0199
1.0000
2.9186
3.0082
0.9162
1.0452
0.9945
1.1910
9.0547
5.9649
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


zck-88, 23mg in CDCl3,
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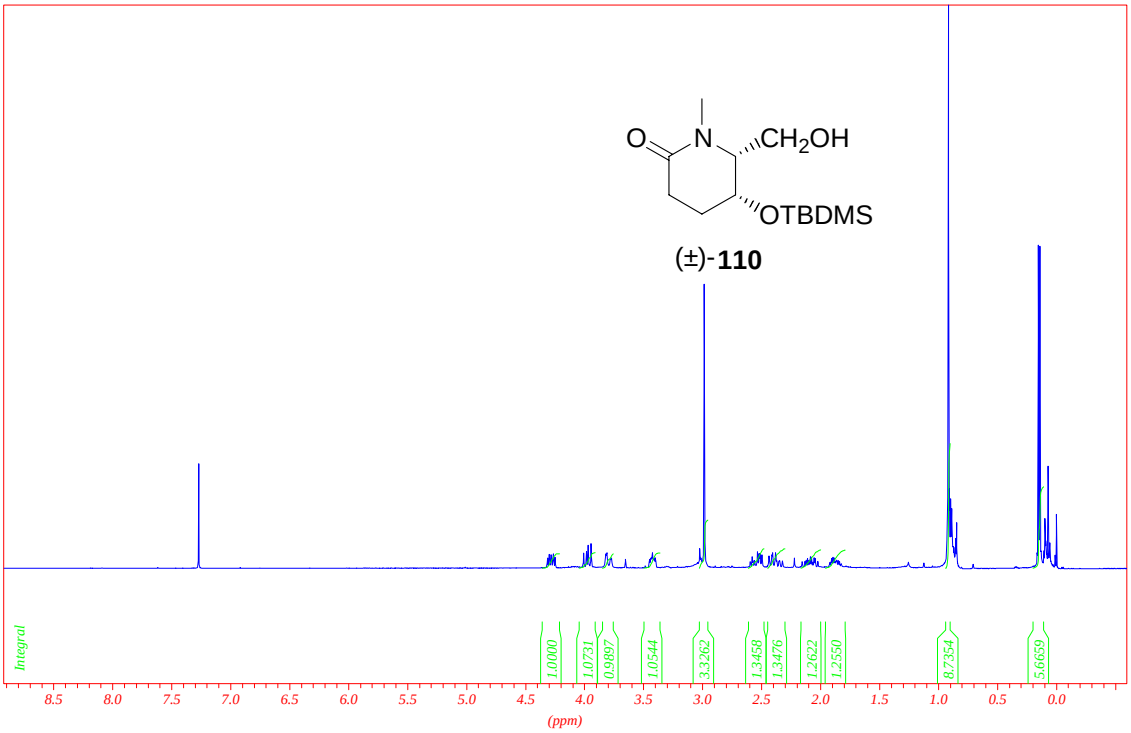
180 160 140 120 100 80 60 40 20 0
(ppm)



zhao zck85B CDCl3

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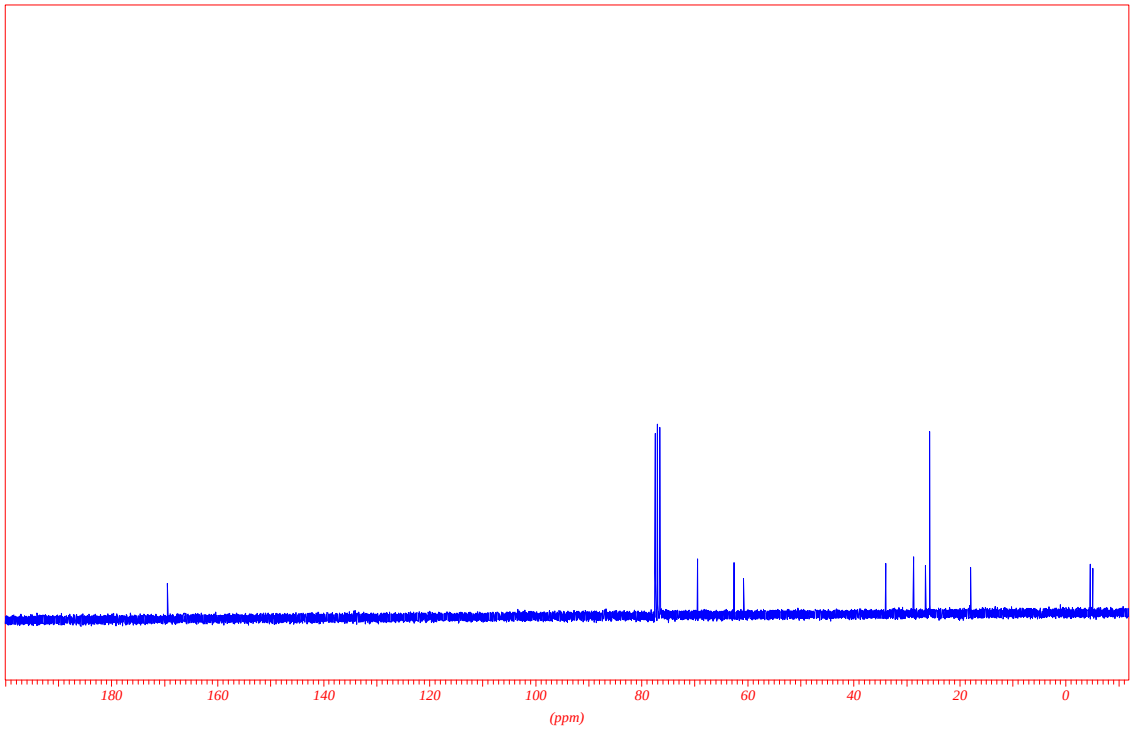


Part II

The synthesis of new vitamin C analogues

1 Introduction

Vitamin C, or L-ascorbic acid, is a vital nutrient for humans and has many important functions in the body. Vitamin C exhibits anti-scorbutic properties, since it contributes to the synthesis of collagen, the main constituent of the protein fibers in human tissue, which is important in maintaining healthy skin elasticity and texture, and also helps maintain the integrity of substances of mesechymal origin, such as connective tissue, osteoid tissue, and dentin.[1]

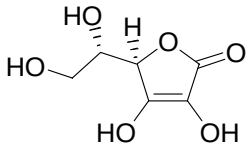


Figure 1. The structure of L-ascorbic acid **1**

In fact, Vitamin C allows hydroxylation of two amino acids, lysine and proline, by keeping the iron in the cofactor of the lysine and proline hydroxylases in the reduced state Fe^{2+}. Vitamin C is further essential for wound healing and facilitates recovery from burns.[2]

Vitamin C also plays a role in other oxidation and enzymatic hydroxylation processes, and, in particular, in the hydroxylation of the dopamine in noradrenaline catalyzed by β-hydroxylase, or in the hydroxylation of tryptophan in 5-hydroxytrypophan catalyzed by tryptophan hydroxylase.[3]

In addition, Vitamin C possesses reducing properties owing to the characterisic 1-oxo-2-ene-2,3-diol structure element. Being a strong reducing agent, ascorbic acid is reversibly oxidized and reduced in the body, functioning as a redox system in the cell and being useful in the treatment of cancer. It is involved in the metabolism of phenylalanine and tyrosine. Vitamin C facilitates the absorption of iron and protects folic acid reductase, which converts folic acid to folinic acid, and may help release free folic acid from its conjugates in food.

Vitamin C is one of the most potent naturally-occurring antioxidants in biological systems as it scavenges active oxygen species and free radicals as a chain breaking antioxidant to protect cellular components against oxidative damage by free radicals and active oxygen species (AOS).[4] AOS, including superoxide (O_2^-), hydrogen peroxide, the hydroxyl radical, and the ferryl radical are considered to be generated by, or formed subsequent to, reduction of molecular oxygen in living organism. The hydroxyl radical and ferryl radical, a complex of

oxygen radical and iron ion, are the most reactive and are thought to be the major species responsible for oxidatative injury of enzymes, lipid members, and DNA in living cells and tissues. Being a powerful antioxidant, Vitamin C protects against oxidative damage to DNA, membrane lipids and proteins. As mentioned above, it is involved in the synthesis of numerous substances such as collagen, and also of certain anabolic steroid hormones, and transmitters of the nervous system, lipids and proteins. It seemed to be required for proper immune function and its use has been recommended to prevent or treat colds. Although this has not been demonstrated by experimental studies, it seems that Vitamin C does shorten or reduce the severity of a cold.

Vitamin C is also a water-solvable celluar antioxidant that reacts with free radicals in the water compartment of cells and in intercellular fluids and can recycle Vitamin E by chemically regenerating it after it has been spent in terminating a free radical reaction.

Vitamin C has been used in recent years as an active ingredient of cosmetics.[5] It acts as antioxidant to against free radical attack and UV ray damage. Since free radicals are considered to be responsible for skin damage and premature ageing, cosmetics containing Vitamin C or derivatives thereof are currently marked as antiageing agents to prevent skin free-radical damage by UV rays, and to renew skin elasticity and firmness, through production of collagen, the body's intercellular cement, and other supporting structures.[6]

While, as just indicated, Vitamin C possesses numerous indispensable biological properties, it nevertheless has some disadvantages, since it is self-oxidizable, heat sensitive, and unstable in vitro in aqueous mediums, particularly, in an alkaline pH.[7] Upon storage or exposure to light, oxygen, moisture and /or high temperature, Vitamin C undergoes rapid degradation.

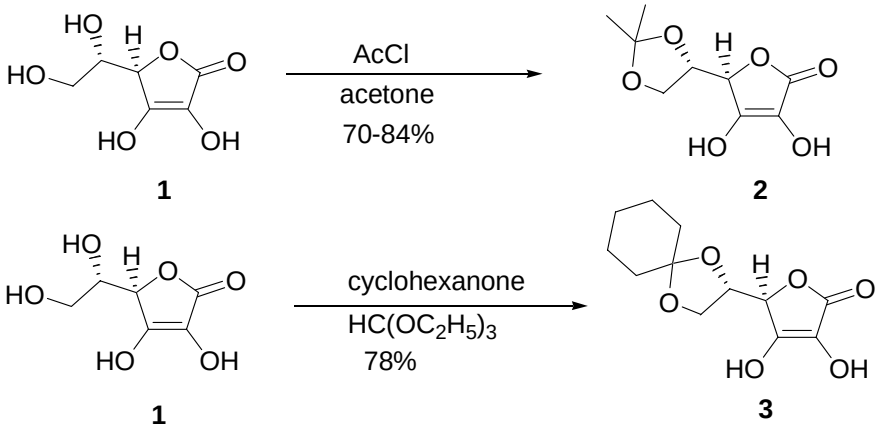
To solve the problem of self-oxidation, several approaches have been considered stabilizing Vitamin C. Among them, hybrids of ascorbic acid and, for example, gluconic or urocanic acid were discussed.[8] Another method consists in stabilizing vitamin C using physical techniques, for example, by incorporation in cyclodextrins zeolites or liposomes.[9] Furthermore, it has been suggested that Vitamin C derivatives should be used, for example, as phosphodiesters in combination with vitamin E.[10]

Another stabilization method would involve chemical functionlization of the enediol group of the Vitamin C. Ascorbic acid in its lactone form has four hydroxyl groups at carbons 2, 3, 5, 6. These hydroxyl groups have different chemical activities: the 2-and 3-hydroxyl groups, together with the double bond connecting carbons 2 and 3, form an enediol system that is very sensitive to oxidation and is responsible for the oxidative degradation of ascorbic acid, whereas the 5- and 6-hydroxyl groups form a rather a stable diol system. Naturally, the

selective chemical modification of the hydroxyl groups of **1** is of particular interest. Common derivatization of ascorbic acid converts the hydroxyl groups to alkyl-, acyl-, sulfo-, or phosphoryl-containing groups, which also affect the solubility of ascorbic acid in water or in oils. Known ascorbic acid derivatives fall into two main groups, water soluble and oil soluble ascorbic acid derivatives. These two groups differ in their potential uses.

1.1 5- or 6-hydroxyl groups modification

1.1.1 5,6-O, O-acetal

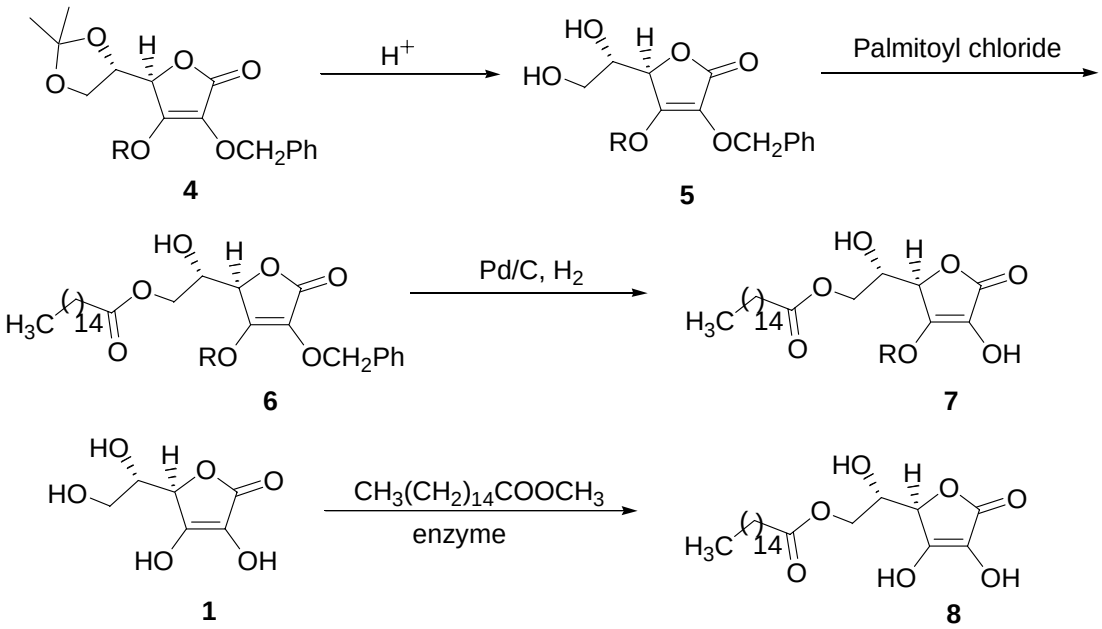


Scheme 1. The synthesis of 5,6-O,O-acetal

Acetone and cyclohexanone acetals **2** and **3** of ascorbic acid can be readily synthesized. Despite the poor stabilities and limited solubilities of **1**, the Vitamin acetals were isolated in good yield.[11] 5,6-O-isopropylidene-L-ascorbic acid (**2**) can be used for topical treatment of the skin for increasing the concentration of ascorbic acid in the dermal layer of the skin, for enhancing the synthesis of skin collagen, and for increasing the antioxidant potential of the skin.[12]

1.1.2 5-or 6-O-monoester

Various kinds of fatty acid esters of L-ascorbic acid **7** were synthesized by the esterification of ascorbic acid at 5- or 6- positions with palmitoyl chloride.[13-14]



Scheme 2. The synthesis of 6-O-monoester

Fatty acid esters of ascorbic acid at either 6- or both 5- and 6- positions are effective as antioxidant and suppressed the oxidation of methyl linoleate.

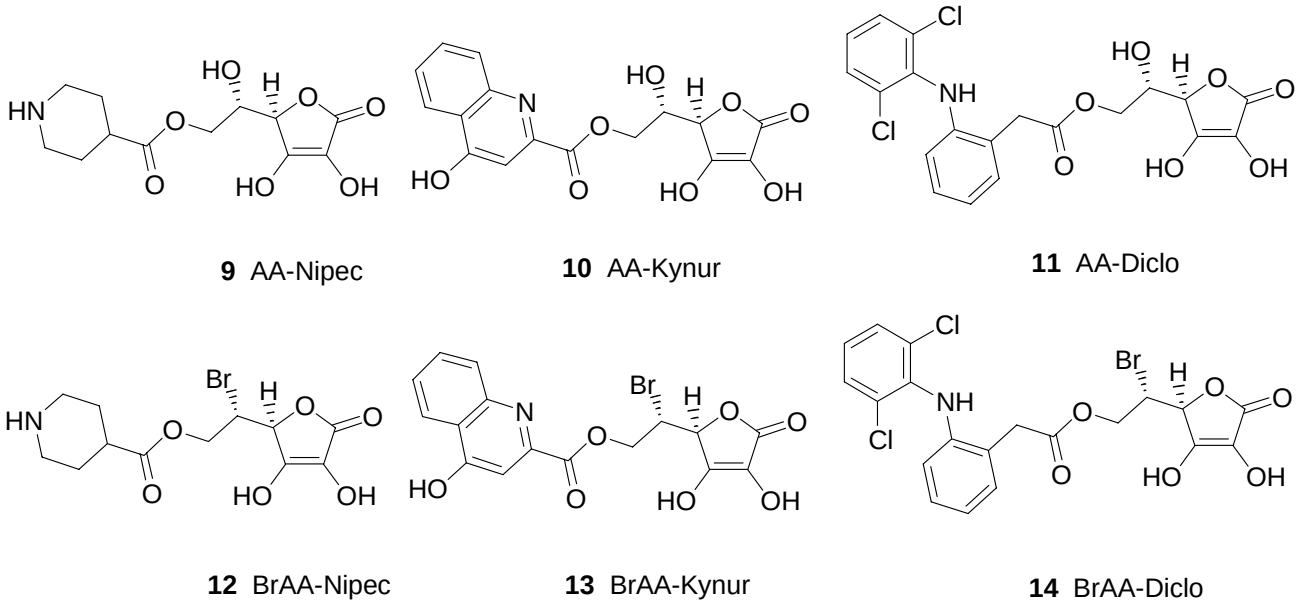


Figure 2. The structure of 6-Br-ascorbic acids

Recently, ascorbic acid (AA) or 6-Br-ascorbic acid (BrAA) conjugation has been investigated as a tool to improve brain drug delivery by the Vitamin C transfer SVCT2 (Figure 2). The result shows that nipecotic acid conjugates (AA-Nipec and BrAA-Nipec),

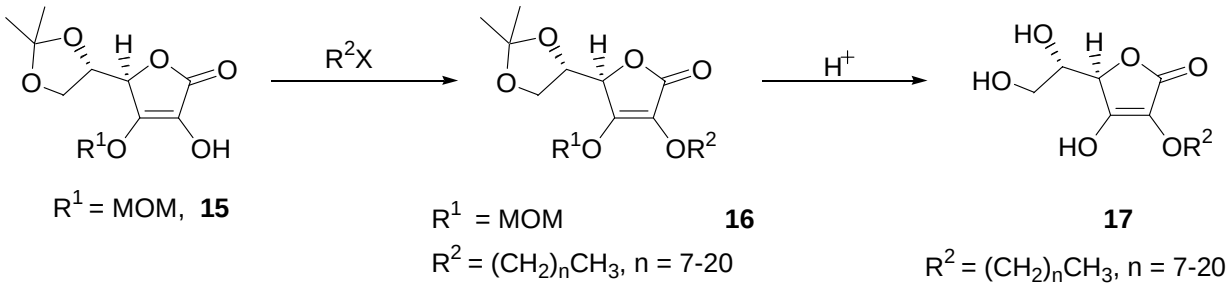
differently from the parent compound, show anticonvulsant effects whereas kynurenic acids derivatives do not.[15]

1.1.3 5,6-O,O-diesters [12]

5,6-O,O-diesters of L-ascorbic acids can also act as chain-breaking antioxidant.

1.2 2-hydroxyl group modification

1.2.1 2-O-alkyl-L-ascorbic acids



Scheme 3. The synthesis of 2-O-alkyl-L-ascorbic acids

Because the acidity in **1** of the hydroxy group at C-3 is stronger than that at C-2, 3-O-alkylation is favoured over 2-O-alkylation. As a result, 2-O-alkyl-ascorbic acids can be prepared from 3-O-alkyl-5,6-O-isopropylidene-L-ascorbic acid (**15**) through further alkylation followed by deprotection at C-2 (Scheme 3).[16-17]

In general, 2-O-alkyl ascorbic acid and 3-O-alkyl ascorbic acid exhibit almost the same reducing potency as ascorbic acid and α-tocopherol. Since no significant change in reducing ability are observed upon blocking either the 2-O or the 3-O enolic hydroxyl group of ascorbic acid, 2-O and 3-O-monoalkylascorbic acids appear to have an equal electron-donating potency.

2-O-alkylascorbic acid and their derivatives with high lipophilicity and electron –donating ability show strong AOS scavenging activity in vitro and in vivo. The longer, straight-chain alkyl moieties and the electron-donating activity of the enolic hydroxyl group may both be beneficial and essential in inhibiting the lipid peroxidation and subsequent cellular and tissue damage. The short alkyl and aromatic groups are found to be less active.[17]

1.2.2 2-phosphate [18]

The 2-phosphate esters are manufactured by treating L-ascorbic acid (**1**) (which may be protected at 5- or 6- position) with a phosphorylation agent, such as $POCl_3$.

2-phosphate derivatives of **1** show some biological activity. For example, magnesium L-ascorbic acid-2-phosphate, a water soluble, stable, non-poisonous and non-irritating derivative was used as an additive in the modern functional whitening cosmetics, and to eliminate free oxygen radical to remove wrinkles after the absorption by the skin.

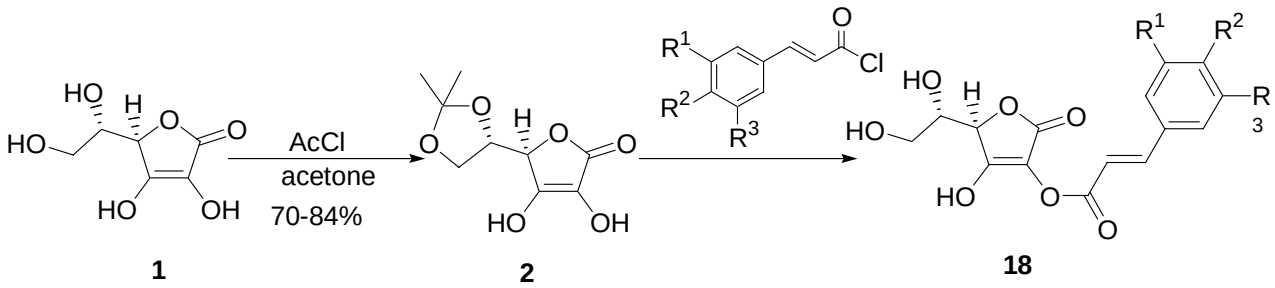
1.2.3 2-sulfate [18c, 19]

2-sulfate-L-ascorbic acid are not found to be an effective biological agent. In Contrast, their metal salts, such as sodium, potassium, and magnesium, are used in the fields of cosmetics, foods and medicines, etc.

1.2.4 2-monoarylester [20]

The effectiveness of the mono- and diesters of **1** has been studied in vitro by using keratinocytes from human epidermis in a first culture subjected to oxidizing stress, such as the hypoxanthine-xanthine oxidase system, the action of UV light, or the addition of iron salts.

The results obtained revealed that the compounds furnish an excellent protective activity at low concentrations, as compared with those of the compounds now used in cosmetic and pharmaceutical products, such as ascorbic acid and its principal derivatives.



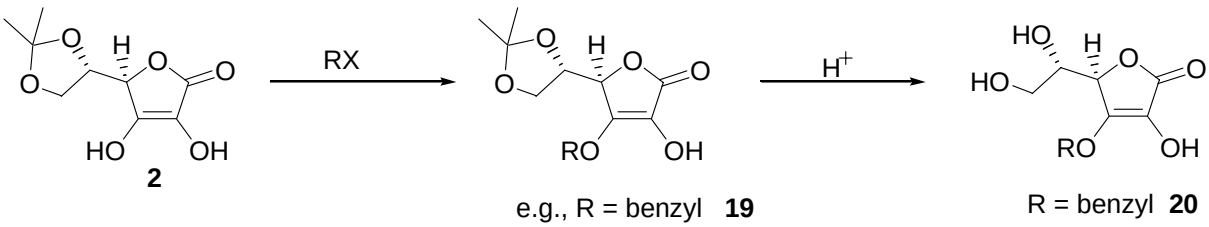
Scheme 4. The synthesis of 2-monoarylesters

1.2.5 2-monofatty acid ester [13a]

The ascorbic acid fatty acid esters at 2-position do not act as antioxidant.

1.3 3-hydroxyl group modification

1.3.1 3-O-alkyl ascorbic acid [17, 21]



Scheme 5. The synthesis of 3-O-alkyl-L-ascorbic acids

The 3-O-alkyl ascorbic acids with long alkyl chains exhibit a potent inhibitory effect on lipid peroxidation. However, the radical scavenging activity of the 3-O-alkyl ascorbic acids is lower than that of the 2-O-alkyl ascorbic acids and ascorbic acid.

Both 3-O-alkyl and 2-O-alkyl compounds require long alkyl moieties and the electron-donating activity of their enolic hydroxyl group in the suppression of lipid peroxidation.

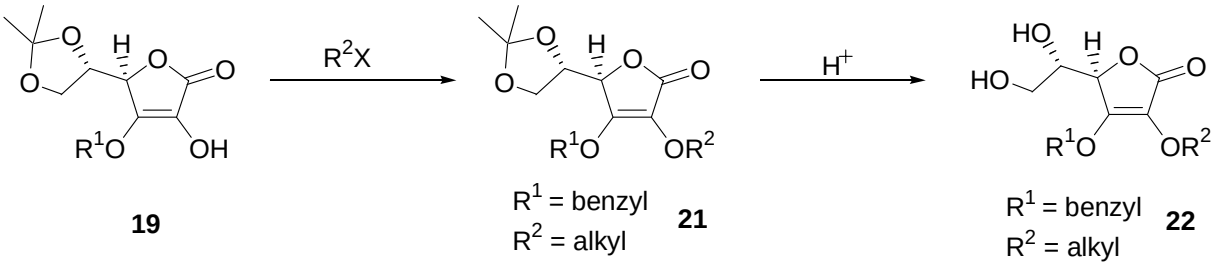
These findings taken together suggest that the long alkyl chain act as an essential anchor to the lipid bilayer and that a too long alkyl chain or too high hydrphobicity of the compounds resulted in the decreased mobility of the radical scavenger in the lipid bilayer.

3-O-alkyl ascorbic acid analogues with an appropriate hydrophobicity can easily penetrate and / or diffuse into the lipid bilayers and act as free radical quenchers that potently protect against the lipid peroxidation of the biomembrane.

1.3.2 3-phosphate-L-ascorbic acid [22]

The stability of 3-phosphate-L-ascorbic acid is improved, comparing to L-ascorbic acid. Its efficacy, however, is unchanged because of the ease of hydrolysis of this ester in vivo.

1.4 2,3-O-disubstituted ascorbic acid [23-24]



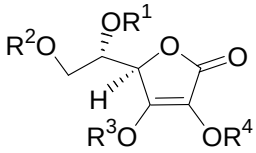
Scheme 6. The synthesis of 2,3-O-disubstituted ascorbic acids

These series compounds **22** have already lost the reducing activity and other bioavailability due to the low solubility of the products in water. Therefore, such compounds are practically useless for cosmetic, dermatological and other application.[24]

2 Synthesis and discussion

2.1 Introduction

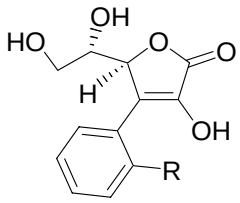
The general formula of ascorbic acids derivatives is described as **23**:



23

Figure 3. The general formula of vitamin C analogues

Vitamin C analogues with high lipophilicity may be potent antioxidants and could display improved stability. We therefore wanted to synthesize **24**.



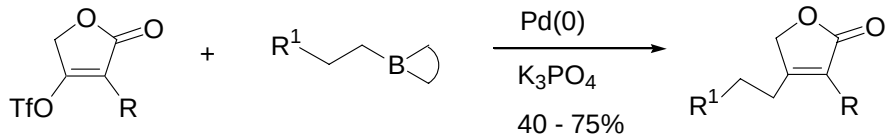
24 R = OH

Figure 4. The structure of new target molecule **24**

In this molecule, a 2-hydroxylphenyl group is introduced instead of the hydroxyl group in 3-position. We expect that through such a modification, the lipophilicity of the new Vitamin C analogue will be increased. Moreover, because 3-keto-enol tautomerism is not possible, the new designed compound should be more stable than Vitamin C.

So far, no Vitamin C analogues with aryl groups in 3-position have been reported. The synthetic strategy that was envisioned towards **24** involved the introduction of aryl groups into the 3-position of Vitamin C by Suzuki coupling reaction.

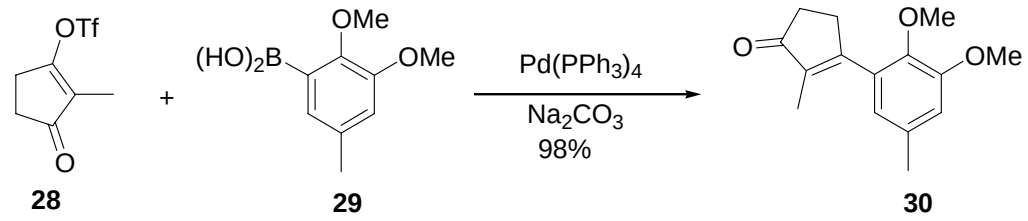
Suzuki reaction of teteronic acid triflate **25** with 9-alkyl-9-BBN was reported by Grigg group for the total synthesis of (-)-isoseiridine (Scheme 7).[25]



25 **26** **27**

Scheme 7. The first Suzuki reaction of teteronic acid triflate **25** with 9-alkyl-9-BBN **26**

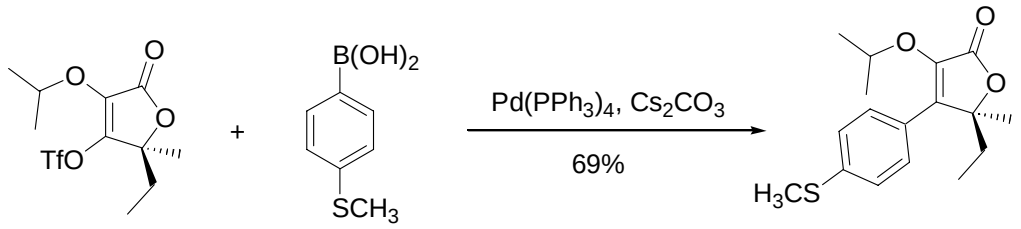
Antonia and coworkers have also reported that the Suzuki coupling reaction of the aryl boronic acid **29** with the enol triflate **28** in the presence of the $Pd(PPh_3)_4$/ aqueous Na_2CO_3 gave rise to the enone **30** in very high yield (Scheme 8).[26]



28 **29** **30**

Scheme 8. Suzuki coupling reaction of triflate **28**

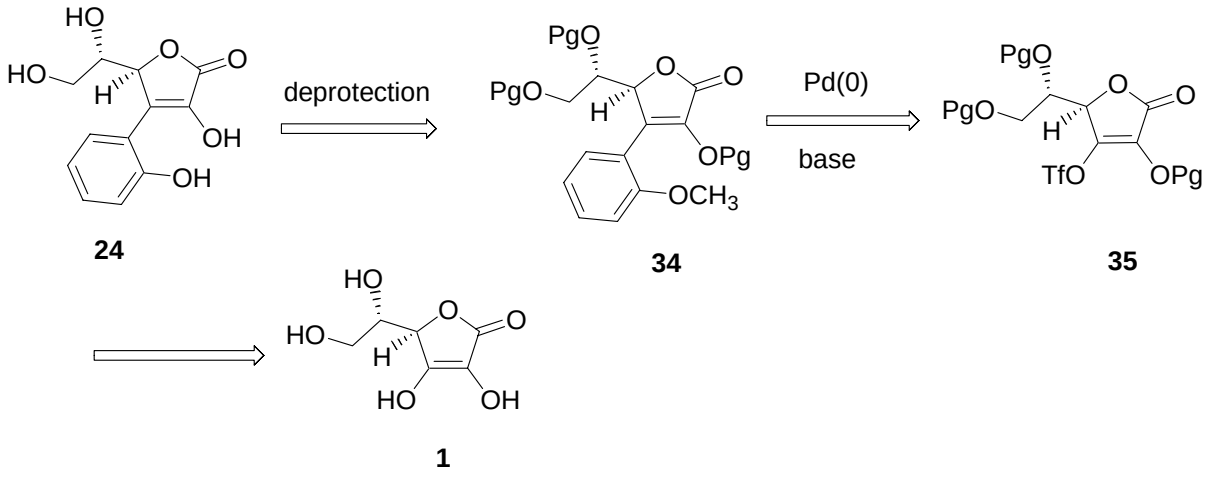
More closely to our target, L. S. Tan and co-workers synthesized the COX-2 specific inhibitor **33** in 69% yield upon the treatment of the enol triflate **31** and aryl boronic acid **32** catalyzed by $Pd(PPh_3)_4$ in the presence of Cs_2CO_3 (Scheme 9).[27]



31 **32** **33**

Scheme 9. Suzuki coupling reaction for the synthesis of COX-2 inhibitor **33**

As a result, we hoped that we can introduce aryl groups in Vitamin C in a similar way. Our retrosynthetic strategy is shown in Scheme 10. As key intermediate, the synthesis of **35** was envisioned, requiring the differentiation of the hydroxyl groups in **1**.



24 **34** **35**

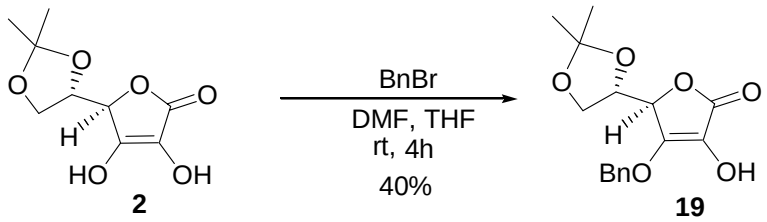
1

Scheme 10. Retrosynthetic strategy of new Vitamin C analogues

2.2 Choosing alkyl as protecting group

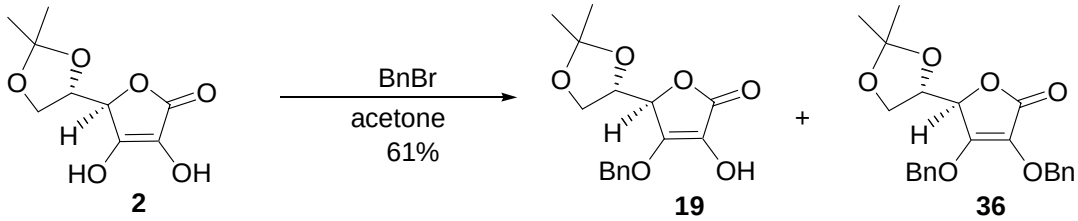
Following literature procedure, 5,6-O-isopropylidene ascorbic acid (**2**) was prepared from L-ascorbic acid (**1**) by treatment with acetone and acetyl chloride at rt for 14 h in 70-84% yield [11] (Scheme 1).

However, the selective alkylation of **2** was generally difficult to achieve, and **2** was fairly sensitive to the alkylation reagent, the base and the solvent as well as the reaction conditions employed. K. Kato and co-workers have already reported that 5,6-O-isopropylidene-3-O-benzyl-L-ascorbic acid (**19**) can be obtained in 40% yield, upon treatment with **2** and benzyl bromide in DMF-THF (Scheme 11).[17]



Scheme 11. Selective benzylation of **2** in DMF-THF

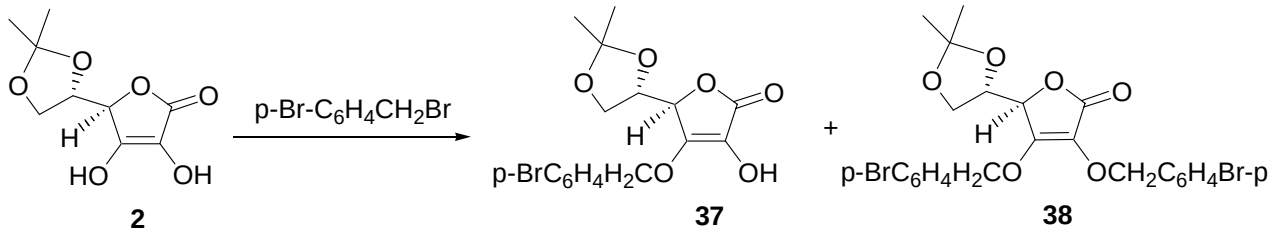
G. K. Mukund and R. T. Shankar have also reported that using BnBr as an alkylating agent, anhydrous potassium carbonate as a base and in dry acetone, **19** can be obtained in good yield (61%), along with 15% amounts of 2,3-disubstituted product **36** (Scheme 12).[21d]



Scheme 12. Selective benzylation of **2** in acetone

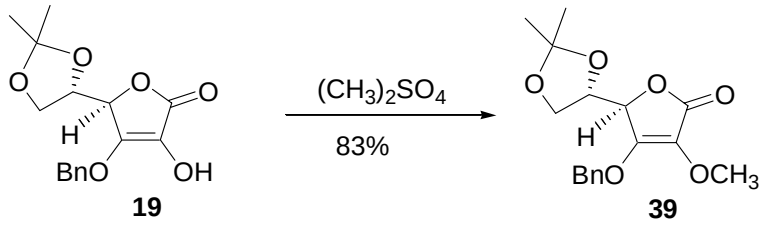
Since it is known that in THF-DMSO, generally 3-O-alkylation of **1** is favoured over 2-O-alkylation,[28] we tried this method on substrate **2**. Several bases were used to optimise this reaction. In our hands, the best result was obtained when 5,6-O-isopropylidene ascorbic acid (**2**) was reacted with p-Br-$C_6H_4CH_2Br$ in DMSO and $NaHCO_3$ at 50^oC for 20 h to afford the desired 3-O-alkylated product **37** in 50% yield, along with small amounts of 2,3-disubstituted product **38** (Table 1).

Table 1. The 3-alkylation of 5,6-O,O-acetal **2**



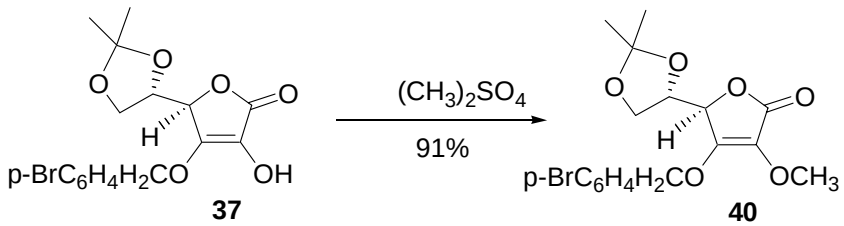
Entry	Reaction condition	Time	Yield **37**
1	DMSO, Na_2CO_3, 50°C	7h	45%
2	DMSO, Na_2CO_3, PTC, rt	20h	47%
3	DMSO, $NaHCO_3$, 50°C	20h	50%
4	DMSO, Na_2CO_3, PTC, 50°C	20h	40%

It is known that 5,6-O-isopropylidene 3-O-benzyl-L-ascorbic acid (**19**) can furnish **39** in refluxing acetone using anhydrous potassium carbonate as a base with excess of dimethylsulfate in excellent yield.[21d] We got similar result by repeating this protocol.



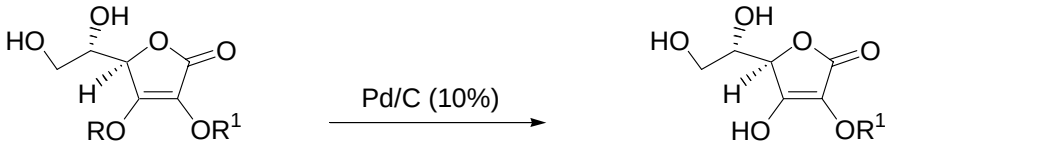
Scheme 13. Methylation of **19** using dimethylsulfate as reagent

Under the same condition, substrate **37** could also be converted to its 2,3-O-disubstituted product **40** in 91% yield (Scheme 14).



Scheme 14. Methylation of **37** using dimethylsulfate as reagent

U. Beifuss and co-workers [21f] have reported that 2-O-alkyl-l-ascorbic acid **43** can be obtained in very good yields by hydrogenolysis of benzyl ethers **41** and **42** (Scheme 15). Best results in the hydrogenolysis step are observed with the p-bromobenzyl derivatives **42** instead of the benzyl compounds **41**.

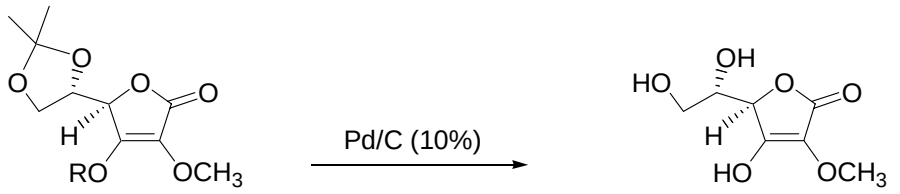


41: R = benzyl
42: R = p-Br-benzyl

43
43a: R = benzyl (69%)
43b: R = p-Br-benzyl (90-94%)

Scheme 15. Hydrogenation of **41**-**42**

Upon hydrogenolysis of benzyl ethers in **39** and **40** catalyzed by palladium carbon at rt, the 2-O-methyl-L-ascorbic acid **44** was obtained in very good yield, and we also found, the p-bromobenzyl group is removed with better results than the benzyl group. However, unfortunately, the 5,6-O,O-acetal function group was also cleaved during the hydrogenation.

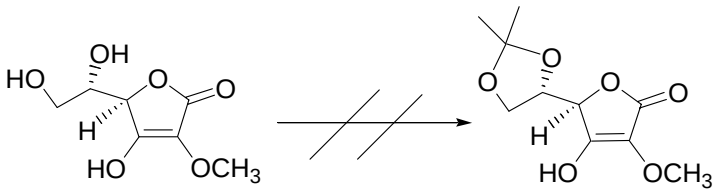


R = benzyl **39**
p-Br-benzyl **40**

44
R = benzyl **70%**
p-Br-benzyl **100%**

Scheme 16. The hydrogenation of **39** and **40**

The hydroxyl groups in 5 and 6-position should be protected before introducing the triflate group in 3-position. As a result, several ways were tried to protect the 5,6-diol in **44**. The results, however, were not satisfactory, mainly because of the poor solubility of **44**.



44 **45**

1. p-TSA, acetone, reflux 20h
2. acetone, AcCl, rt, 20h.

Scheme 17.

2.3 Choosing acetyl as protecting group

We next tried to introduce an acetyl group to 5,6-O-isopropylidene-L-ascorbic acid **2** in 2-postion. In 1988, J. Cabral and P. Haake [29] reported a selective acylation in 2-position on Vitamin C. Based on the discovery, that ascorbate anion **46** or **47** will react preferentially at the 3-position. Generally, short reaction times at room temperature are most effective in producing the 3-ester. Rapid mixing of the acid chloride with a mixture of triethylamine and **2**, followed by stirring for a brief time, gives the best yield for the 3-ester, but little preferentially of the desired 2-ester **48**. In the presence of small amounts of water or methanol, the 2-ester is formed as was reported by R. B. Paulssen and co-workers.[30] According to their method, a mixture of 2-O-acetyl-5,6-O-isopropylidene-L-ascorbic acid (**48**) and $Et_3N.HCl$ is obtained in a ration of 8:1, but no yield is given. Following their procedure, we succeeded to obtain the desired 2-O-acetyl-5,6-O-isopropylidene-L-ascorbic acid (**48**) in pure form in 60% yield (Scheme 18).

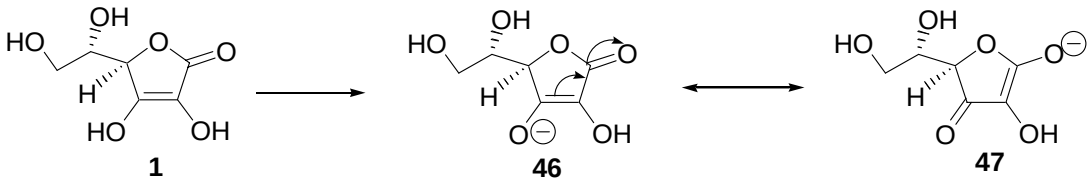
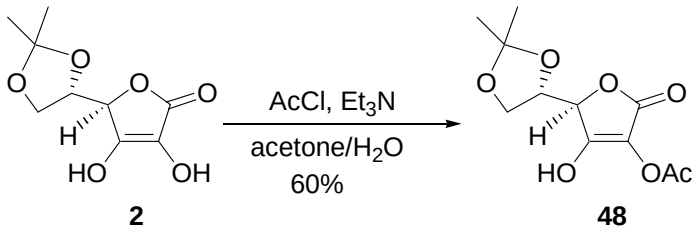


Figure 5.

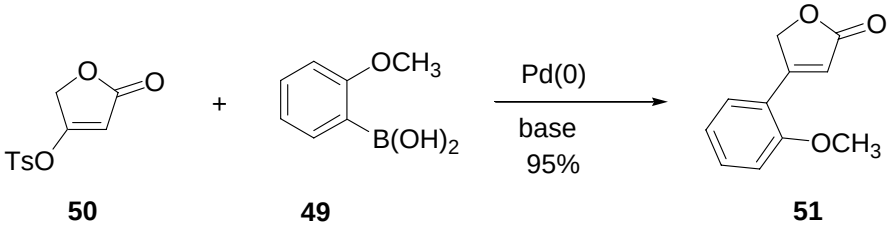


Scheme 18. The selective 2-acetylation of **2**

2.3.1 Tosylate as coupling substrate

With 2-O-acetyl-5,6-O-isopropylidene-L-ascorbic acid (**48**) in hand, our attention was turned towards the synthesis of its tosylate or triflate of the 3-hydroxyl group. Since our molecule contains mainly a furanone framework, and currently, the most frequently used methods for synthesizing 4-substituted 2(5H)-furanone derivatives are based on the transition metal catalyzed coupling reaction.[31] Wu and co-workers have already reported that under standard Suzuki conditions 4-tosyl-2(5H)-furanone (**50**) underwent coupling reaction with o-methoxy

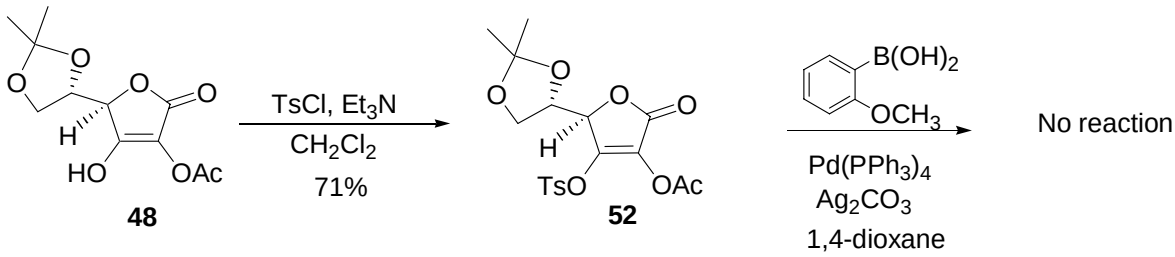
phenyl boronic acid (**49**) to provide a 95% yield of desired product **51** [32] (Scheme 19). A series of similar compounds were also synthesized in good yield under the same condition.



50 **49** **51**

Scheme 19. Tosylate-based Suzuki coupling reaction

Firstly, the tosylate **52** was prepared by simply mixing **48**, tosyl chloride, and triethylamine in dichloromethane at room temperature in 71% yield. In contrast to the corresponding triflate described later, the tosylate **52** was remarkably stable and could be isolated as a stable white solid. Unfortunately, the tosylate did not react with o-methoxy phenyl boronic acid under Suzuki coupling reaction (Scheme 20).



48 **52**

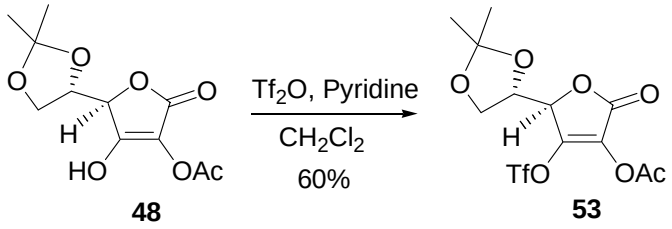
Scheme 20. Suzuki coupling reaction of Tosylate **52**

2.3.2 Triflate as coupling substrate

2.3.2.1 Suzuki coupling reaction

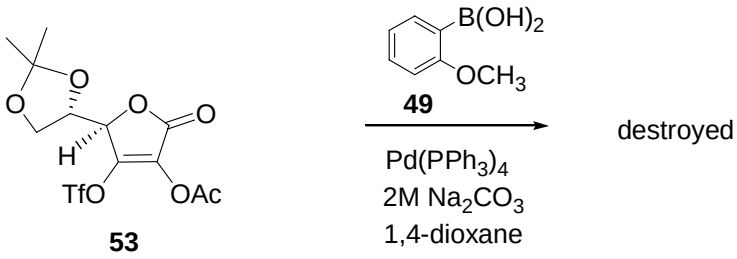
We therefore focused our attention to the corresponding triflate **53** as a substrate in the palladium catalyzed cross-coupling reaction.

As a key step in our synthetic route, Suzuki coupling reaction [33] is one of most useful approaches of introducing carbon carbon bond. It is based on Pd(0) catalyzed cross coupling reactions of various organoboron derivatives with aryl halides,[34] triflates [35] or diazonium salts [36] under basic conditions. The original procedure, using $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in benzene at reflux gives good yields with many substituted arylboronic acids.[37] Firstly, the 3-O-triflate-2-O-acetyl-5,6-O-isopropylidene-L-ascorbic acid (**53**) was easily prepared from 2-O-acetyl-5,6-O-isopropylidene-L-ascorbic acid (**48**) and pyridine in dichloromethane at 0^oC for 2 h in 60% yield (Scheme 21).



Scheme 21. Synthesis of 3-triflate **53**

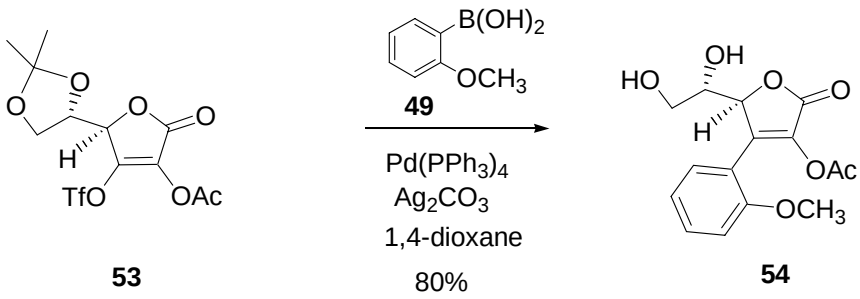
With **53** in hand, palladium catalyzed cross coupling reactions with aryl boronic acid were investigated. The required **49** was conveniently synthesized from commercially available 2-bromoanisole. However, our initial attempts to introduce 2-methoxyphenyl by using standard coupling condition, i.e., $Pd(PPh_3)_4$ and aqueous 2M Na_2CO_3 in 1,4-dioxane at reflux for 20h, did not give the desired compound (Scheme 22).



Scheme 22. Suzuki coupling reaction of triflate **53** under standard condition

It has been suggested that using carbonates as a base, the Suzuki-coupling reaction rate are strongly dependent on the nature of the cation. In fact, the nature of the cation and the strength of the base both play an important role in the course of the cross coupling reaction. Smith et al [38] have already claimed that for boronic acids a base of sufficient strength is needed to form the boronate anion to allow the transmetalation step to occur. The major influence of pH in cross coupling reaction reactions has also been demonstrated in detail. Zhang et al [39] have also reported that the rate of the cross coupling reaction increased with the size of the cation. An explanation is suggested that the larger cations are better solvated, resulting in a more nucleophilic, “naked” phenolate anion.

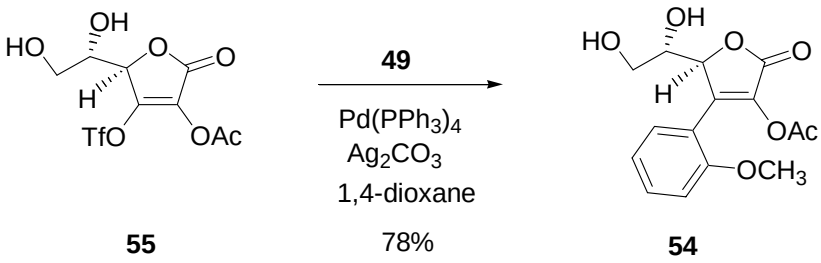
Indeed, the o-methoxy phenyl boronic acid (**49**) could be reacted with the enol triflate **53** in the presence of $Pd(PPh_3)_4/Ag_2CO_3$ in 1,4-dioxane at 80^oC for 20h to yield the desired compound **54** in 80% yield (Scheme 23).



53 **54**

Scheme 23. Suzuki coupling of triflate **53** in the catalyse of $Pd(PPh_3)_4/Ag_2CO_3$

We also examined the possibility of substrate **55** for Suzuki coupling reaction. Fortunately, the 5,6-diol-3-triflate **55** could also couple with **49** under the same condition as 5,6-acetal-3-triflate **53** to afford the desired compound **54** in 78% yield (Scheme 24). This suggested that it was not necessary to protect 5,6-diol before the coupling reaction. The amount of boronic acid



55 **54**

Scheme 24. Suzuki coupling of triflate **55**

also played an important role in Suzuki reaction. The coupling reaction yield would be improved by increasing the amount of boronic acid. The result are shown below (Table 2).

Table 2. Suzuki coupling reaction of **53** and **55**

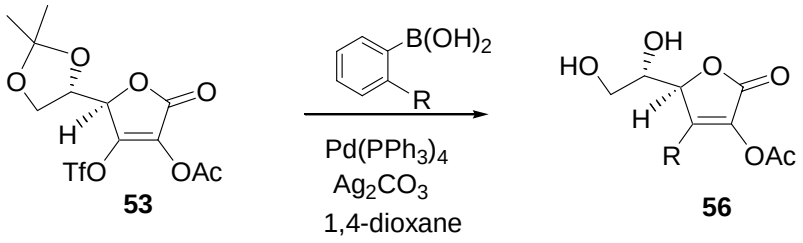
Entry	substrate	boronic acid	product	yield
1	**53**	2 equiv	**54**	80%
2	**55**	2 equiv	**54**	78%
3	**53**	1.1 equiv	**54**	50%
4	**55**	1.1 equiv	**54**	60%

Encouraged by these results, the scope of this reaction was investigated by using various boronic acids and substrate **53**. The results are shown in Table 3.

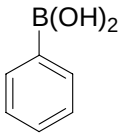
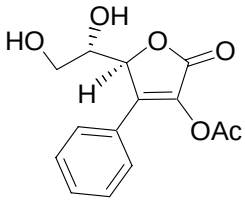
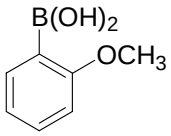
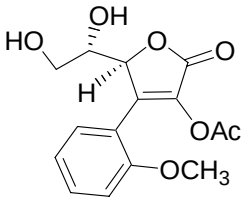
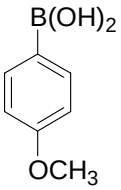
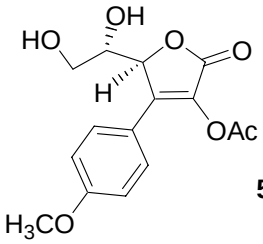
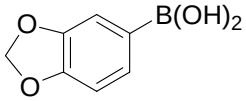
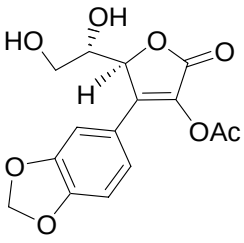
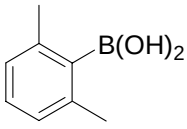
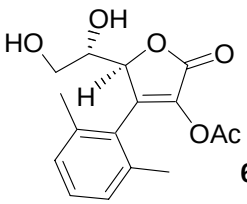
From the results listed in Table 3, we can make the following observations: (1) Triflate was more active than tosylate, and could couple with most of the selected boronic acids to provide the corresponding products in moderate and good yields. (2) When 2,5-dimethylphenyl

boronic acid coupled with substrate **53**, no product was detected, presumably due to the steric effect of the vicinal two methyl groups.

Table 3. Palladium–catalyzed Suzuki coupling reaction with various boronic acids



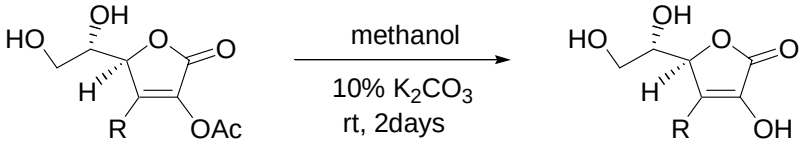
53 **56**

Entry	Boronic acid	Product	Yield
1		 **57**	80%
2		 **54**	78%
3		 **58**	74%
4		 **59**	64%
5		 **60**	0

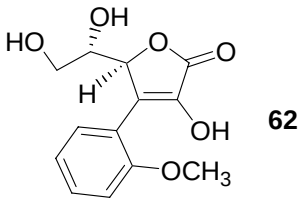
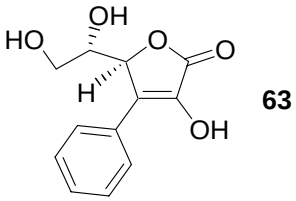
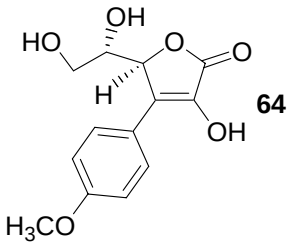
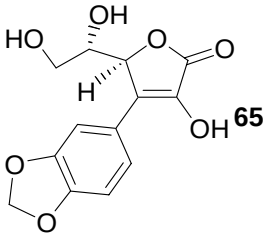
2.3.2.2 Deacylation

In the following, we also investigated the hydrolysis of esters **54**, **57-59** by treating them with potassium carbonate in methanol. Stronger bases could not be employed, because ascorbic acid is unstable in alkali aqueous solution. Moreover, we also found that greater excess of potassium carbonate will decrease the reaction yield. Employing a 10% K_2CO_3 aqueous solution in methanol, the deacylated products **62-65** could be obtained in good yield (Table 4).

Table 4. Potassium carbonate-catalyzed hydrolysis of esters

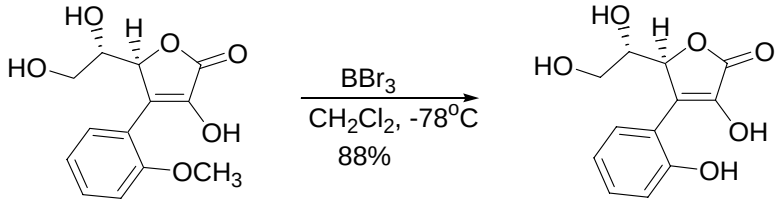


56 **61**

Entry	Starting material	Product	Yield
1	**54**	 **62**	60%
2	**57**	 **63**	58%
3	**58**	 **64**	55%
4	**59**	 **65**	54%

2.3.2.3 Demethylation

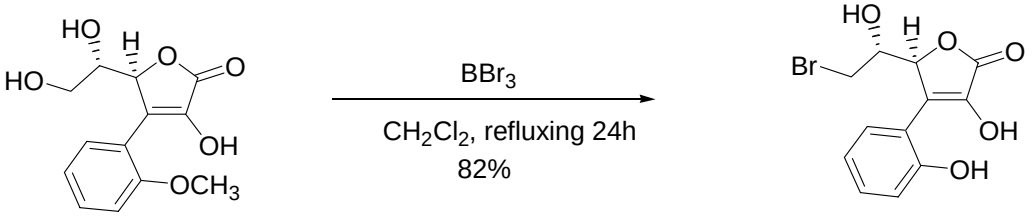
Finally, the methoxy group in compound **62** could be removed by treatment with BBr_3 in dichloromethane at –78°C to give target compound **24** in 88% (Scheme 25).



62 **24**

Scheme 25. Demethylation of compound **62**

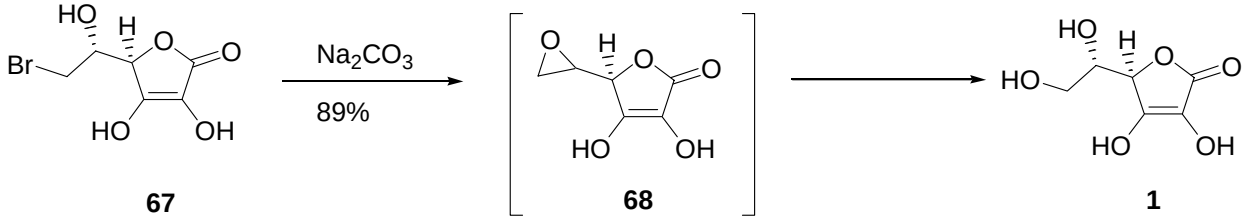
We once also tried to carry out this reaction at refluxing temperature. However, to our surprise, along with the demethylation, the bromination of 6-OH of substrate **62** also occurred (Scheme 26).



62 **66**

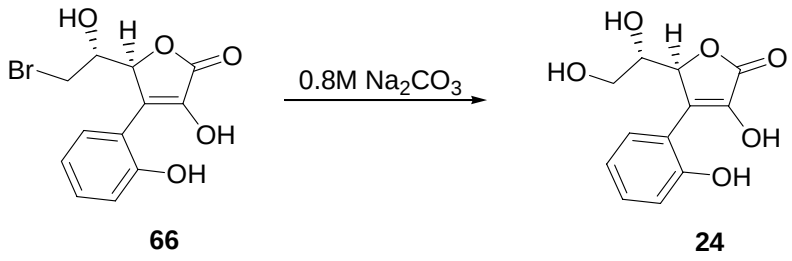
Scheme 26.

G. C. Andrews has reported that under mildly basic condition, the nucleophile substitution of 6-bromo-6-deoxy-L-ascorbic acid (**67**) will occur via direct displacement of the halogen group or via an intermediate 5,6-anhydro compound **68** to afford Vitamin C **1** in quite good yield [40] (Scheme 27). Therefore, 6-bromo-6-deoxy-3-(2-hydroxyphenyl)-3-deoxy-L-ascorbic acid (**66**) could also be converted to our target molecule **24** in good yield upon treatment with Na_2CO_3 aqueous solution (Scheme 28).



67 **68** **1**

Scheme 27. Nucleophile substitution of 6-bromo-6-deoxy-L-ascorbic acid (**67**)

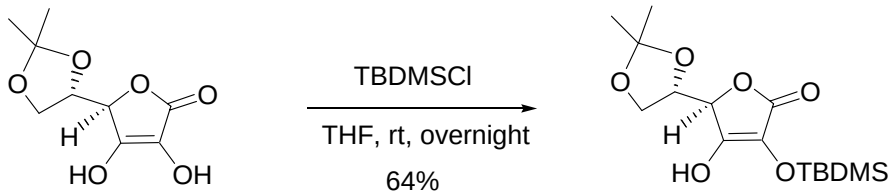


66 **24**

Scheme 28. Nucleophile substitution of **66**

2.4 Choosing TBS as protecting group

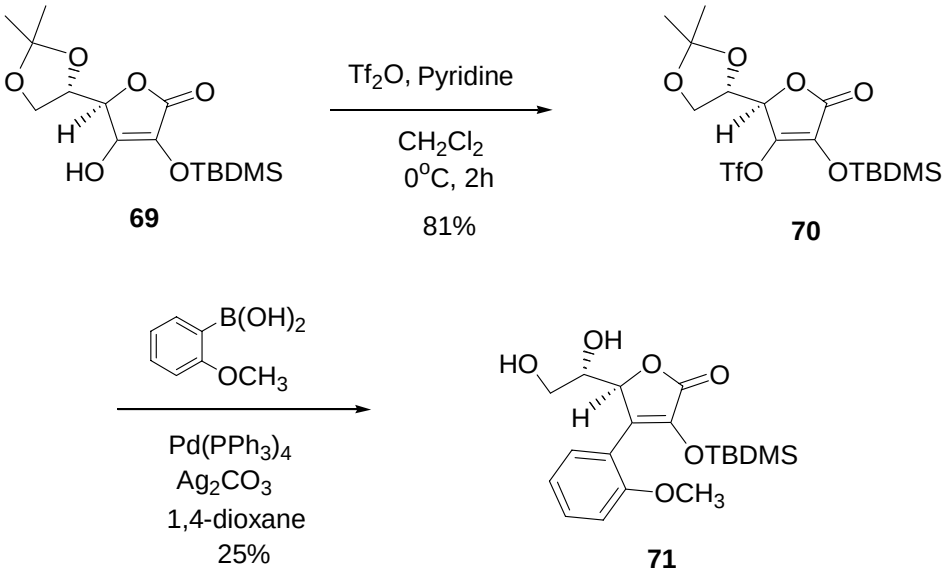
The target compound **24** was successfully synthesized by using acetyl as protecting group. An additional attempt was done to use TBS as protecting group. It has been reported that 5,6-O-isopropylidene- L-ascorbic acid (**2**) could be selectively silylated to **69** by using TBDMSCl as reagent in 92% yield.[41] Repeating this protocol, **69** was obtained in 64% yield as a white solid (Scheme 29).



2 **69**

Scheme 29. The selective silylation of **2**

Subsequently, triflation of compound **69** was carried out by using triflic anhydride in CH_2Cl_2 in 81% yield (Scheme 30). The following cross-coupling reaction of triflate **70** also afforded the desired compound **71**, however, in only low yield (25%), which could be explained by steric hindrance between the bulky group (TBDMS) and 2-methoxyphenyl group (Scheme 30).



Scheme 30. Choosing TBS as protecting group

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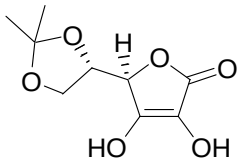
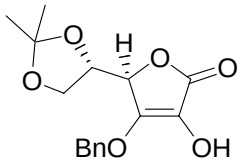
3 Experimental Part



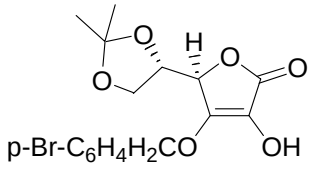
2

5,6-O-isopropylidene-L-ascorbic acid (2) [17] To a rapidly stirred suspension of L-ascorbic acid (**1,** 8.8 g) in acetone (88 ml) was added acetyl chloride (0.74 ml), and the mixture was stirred at ambient temperature for 14 h. The precipitate was collected by filtration, washed with ethyl acetate, and dried in vacuo to yield 9.07 g (84%) of the product **2** as a white solid. Mp 202-204^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.29 (br, 1H), 8.48 (br, 1H), 4.71 (d, *J* = 2.92, 1H), 4.26 (dt, *J* = 2.92, 6.64,1H), 4.10 (dd, *J* = 7.03, 8.37, 1H), 3.88 (dd, *J* = 6.33, 8.37, 1H), 1.25 (s, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 170.11, 152.27, 118.01, 108.85, 74.08, 73.30, 64.71, 25.68, 25.31.



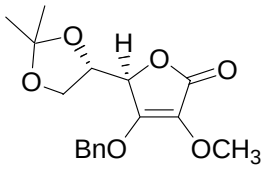
19

3-O-benzyl-5,6-O-isopropylidene-L-ascorbic acid (19) [17] 1 g of 5,6-O-isopropylidene-L-ascorbic acid (**2**) was dissolved in 5 ml of DMSO, and then 0.365 g of sodium hydrogencarbonate was added. The mixture was stirred at rt for 30 min. Then 0.516 ml of BnBr was added. The solution was stirred and warmed to 50^{o}C for 20 h. 20 ml of water was added. The reaction mixture was extracted with ethyl acetate, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography, eluting with PE/AcOEt = 2/1, to afford a clear liquid, which was recrystallized from petroleum ether to give 0.53 g (40%) of product **19** as a white solid. TLC R_f 0.2 (PE/AcOEt = 2/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.44 (m, 5H), 5.50 (s, 2H), 4.71 (d, *J* = 3.80, 1H), 4.21-4.42 (m, 3H), 1.38 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.97, 148.32, 135.68, 128.78, 128.68, 128.12, 119.45, 110.32, 75.70, 74.34, 73.56, 65.35, 25.92, 25.59.



37

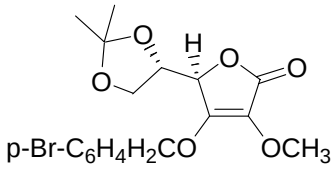
3-O-(4-bromo-benzyl)-5,6-O-isopropylidene-L-ascorbic acid (37) In 7 ml of DMSO was dissolved 1.34 g of 5,6-O-isopropylidene-L-ascorbic acid (**2**). Then, 0.489 g of sodium hydrogencarbonate was added. The resulting solution was stirred at rt for 30 min. Then 1.484 g of *p*-Br-$C_6H_4CH_2Br$ was added. The solution was stirred and warmed to 50^{o}C. After 20 h, 20 ml of water was added and then the reaction mixture was neutralized with 1N HCl. The reaction mixture was extracted with ethyl acetate, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography, eluting with PE/AcOEt = 4/1, to afford 1.153 g (50%) of compound **37** as a white solid. TLC R_f 0.63 (PE/AcOEt = 1/1); Mp 117-120^{o}C; $[\alpha]_D$ = - 27.07 (c = 1.47, CH_3OH); IR (KBr) 3379, 3286, 2986, 2933, 1756, 1695, 1487, 1373, 1337, 1258, 1220, 1161, 1117, 1059, 1009; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.40, 2H), 7.28 (d, *J* = 8.40, 2H), 6.05 (s, 1H), 5.45 (s, 2H), 4.57 (d, *J* = 3.46, 1H), 4.26 (ddd, *J* = 6.88, 6.72, 3.46, 1H), 4.11 (dd, *J* = 8.60, 6.88, 1H), 4.02 (dd, *J* = 8.60, 6.72, 1H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.96, 147.12, 133.63, 130.80, 128.73, 121.83, 118.51, 109.34, 74.55, 72.92, 71.63, 64.26, 24.83, 24.53; EIMS: m/z (relative intensity) 384.0 (M^+, ^{79}Br, 1.88%), 386.0 (M^+, ^{81}Br, 2.07%); HRMS: Calcd for $C_{16}H_{17}BrO_6$ (M^+): 384.0209. Found: 384.0207.



39

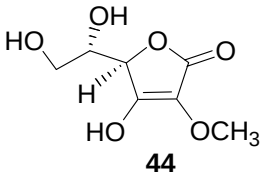
2-O-methyl-3-O-benzyl-5,6-O-isopropylidene-L-ascorbic acid (39) [21d] This was prepared according to the procedure used for **40**, staring from 1.24 g of 3-O-benzyl-5,6-O-isopropylidene-L-ascorbic acid, 0.694 g of K_2CO_3, 0.48 ml of dimethyl sulfate and 20 ml acetone. After chromatography through a silica gel column, eluting with PE/AcOEt = 3/1, 1.09 g (84%) product was obtained as a white solid. TLC R_f 0.26 (PE/AcOEt = 3/1); Mp 99-100^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.44 (m, 5H), 5.46 (s, 2H), 4.55 (d, *J* = 3.22, 1H), 4.31 (dt, *J* = 6.68, 3.22, 1H), 4.12 (dd, *J* = 8.52, 6.68, 1H), 4.04 (dd, *J* = 8.52, 6.68, 1H), 3.77

(s, 3H), 1.39 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.85, 155.33, 135.53, 128.73, 128.70, 127.67, 123.22, 110.35, 74.62, 73.97, 73.50, 65.32, 59.93, 25.88, 25.63.



40

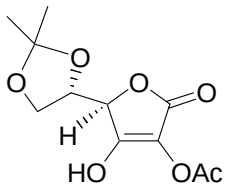
2-O-methyl-3-O-(4-bromobenzyl)-5,6-O-isopropylidene-L-ascorbic acid (40) To a refluxing mixture of 3-O-(4-bromobenzyl)-5,6-O-isopropylidene-L-ascorbic acid (**37**, 357 mg) and K_2CO_3 (165 mg) in 10 ml of acetone, was added 0.113 ml of dimethyl sulfate. The reaction mixture was refluxed for 30 min. Then the solvent was evaporated under reduced pressure. Brine was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized with PE/AcOEt = 1/1 to afford 338 mg (91.4%) of product **40** as a white solid. Mp 141-143^{o}C; $[\alpha]_D$ = - 28.71 (c = 1.47, $CHCl_3$); R_f 0.31 (PE/AcOEt = 4/1); IR (KBr) 2982, 2930, 1752, 1677, 1490, 1445, 1372, 1336, 1258, 1221, 1150, 1115, 1068; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 6.55, 1.95, 2H), 7.26 (dd, *J* = 6.55, 1.95, 2H), 5.41 (s, 2H), 4.55 (d, *J* = 2.98, 1H), 4.30 (dt, *J* = 6.68, 2.98, 1H), 4.12 (dd, *J* = 8.50, 6.69, 1H), 4.04 (dd, *J* = 8.50, 6.69, 1H), 3.78 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.65, 154.93, 134.53, 131.86, 129.31, 123.29, 122.77, 110.40, 74.47, 73.76, 72.65, 65.27, 59.90, 25.84, 25.62; PI-EIMS: m/z (relative intensity) 398.0 (M^+, ^{79}Br, 2.75%), 399.9 (M^+, ^{81}Br, 2.74%). Anal. Calcd for $C_{17}H_{19}BrO_6$: C, 51.14%; H, 4.80%; Br, 20.01%. Found: C, 51.07%; H, 4.88%; Br, 20.04%.



44

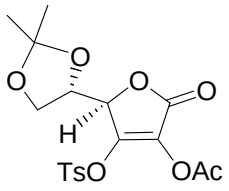
2-O-methyl-L-ascorbic acid (44) 0.647 g of 2-O-methyl-3-O-(4-bromobenzyl)-5,6-O-isopropylidene-L-ascorbic acid (**40**) was dissolved in 35 ml of warm ethanol. Then 65 mg of Pd/C (10%) was added. The mixture was hydrogenated under ambient atmosphere pressure for 20 h. The catalyst was filtered, and the filtrate was concentrated to dryness. The residue was purified by chromatography, eluting with ethyl acetate, to afford the title product **44** in a quantitative yield as a yellow solid. TLC R_f 0.66 (CH_3OH/CH_2Cl_2 = 1/2); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.55 (d, *J* = 2.10, 1H), 3.69 (dt, *J* = 6.79, 2.10, 1H), 3.60 (s, 3H), 3.42 (d, *J*

= 6.79, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 170.37, 121.13, 75.50, 69.02, 62.06, 58.94, 48.48; ES-MS: m/z (relative intensity) 191.0 (MH^+, 100.00%).



48

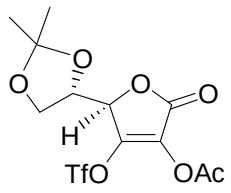
2-O-acetyl-5,6-O-isopropylidene-L-ascorbic acid (48) [29] Acetyl chloride (0.31 ml) was added slowly to a mixture of triethylamine (0.61 ml) and 5,6-O-isopropylidene-L-ascorbic acid (1 g, **2**) in 9.5 ml of acetone containing 1.1% H_2O at 22°C under nitrogen. After 2.5 min, triethylamine hydrochloride was filtered and the filtrate concentrated under reduced pressure. Then H_2O and ethyl acetate were added. The organic layer was dried over $MgSO_4$. After removal of the solvent, ether was added to the residue to effect the crystallization to provide 0.7 g (60%) of product **48** as a white solid. Mp 151-153°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.98 (d, *J* = 2.67, 1H), 4.35 (ddd, *J* = 7.10, 5.90, 2.67, 1H), 4.13 (dd, *J* = 8.47, 7.10, 1H), 3.93 (dd, *J* = 8.52, 6.04, 1H), 2.19 (s, 3H), 1.25 (s, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 167.53, 163.03, 112.22, 109.11, 74.81, 73.00, 64.70, 25.59, 25.18, 19.92; EIMS: m/z (relative intensity) 259.1 (M^+, 0.15%); Anal. Calcd for $C_{11}H_{14}O_7$: C, 51.16%; H, 5.46%. Found: C, 51.07%; H, 5.29%.



52

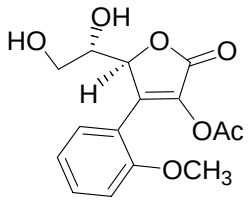
2-O-acetyl-3-O-(*p*-toluenesulfonyl)-5,6-O-isopropylidene-L-ascorbic acid (52) To a solution of 0.554 g 2-O-acetyl-5,6-O-isopropylidene-L-ascorbic acid (**48**) in 10 ml of CH_2Cl_2 were added 0.429 g of tosyl chloride and 0.36 ml of triethylamine. The solution was stirred at rt for 2.5 h. Then the solvent was evaporated under reduced pressure. The residue was purified by chromatography, using PE/AcOEt = 1/1 as eluent, to afford an oil, which was crystallized with the addition of diethyl ether. 0.63 g (71%) of the product **52** was obtained as a white solid. Mp 86-88°C; $[\alpha]_D$ = - 15.16 (c = 0.64, $CHCl_3$); TLC R_f 0.57 (PE/AcOEt =1/1); IR (KBr) 2995, 1773, 1713, 1595, 1389, 1342, 1264, 1136, 1010, 1057; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.40, 2H), 7.42 (d, *J* = 8.40, 2H), 4.90 (d, *J* = 2.30, 1H), 4.38 (ddt, *J* = 5.49, 2.30, 0.41, 1H), 4.17 (dd, *J* = 8.74, 6.96, 1H), 4.05 (dd, *J* = 8.64, 6.00, 1H), 2.49 (s, 3H),

2.13 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.82, 164.65, 150.53, 147.19, 131.37, 130.35, 128.61, 125.46, 110.93, 75.89, 72.54, 65.15, 25.57, 25.29, 21.88, 19.88; PI-EIMS: m/z (relative intensity) 412.1 (M^+, 22.51%); Anal. Calcd for $C_{18}H_{20}O_9S$: C, 52.42%; H, 4.89%. Found: C, 52.19%; H, 5.07%.



53

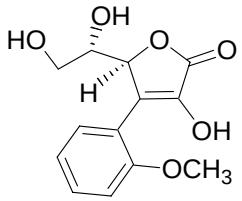
2-O-acetyl-3-O-(trifluoromethanesulfonyl)-5,6-O-isopropylidene-L-ascorbic acid (53) At 0^{o}C, 0.14 ml of pyridine was added to a mixture of 470 mg of 2-O-acetyl-5,6-O-isopropylidene-L-ascorbic acid (**48**) in 10 ml of CH_2Cl_2. Then 0.29 ml of triflic anhydride was added slowly by syringe. The solution was kept at 0^{o}C for 2 h. Then 2 ml of saturated ammonium chloride was added to quench the reaction. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography through a silica gel column, eluting with PE/AcOEt = 2/1, to afford 432 mg (61%) of product **53** as a clear liquid. $[\alpha]_D$ = - 23.29 (c = 1.46, $CHCl_3$); TLC R_f 0.76 (PE/AcOEt = 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (d, *J* = 2.20, 1H), 4.46 (ddd, *J* = 6.96, 5.76, 2.20, 1H), 4.24 (dd, *J* = 8.78, 6.96, 1H), 4.10 (dd, *J* = 8.78, 5.76, 1H), 2.33 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.41, 163.05, 148.81, 126.82, 118.3279 (q, *J* = 321.56), 111.33, 75.28, 72.12, 64.93, 25.49, 25.04, 19.90; PI-EIMS: m/z (relative intensity) 391.0 (MH^+, 100.00%); HRMS: Calcd for $C_{12}H_{14}F_3O_9S$ (MH^+): 391.0311. Found: 391.0308.



54

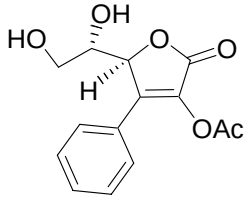
2-O-acetyl-3-deoxy-3-(2-methoxyphenyl)-L-ascorbic acid (54) 0.815 g of 2-O-acetyl-3-O-(trifluoromethanesulfonyl)-5,6-O-isopropylidene-L-ascorbic acid (**53**), 0.634 g of 2-methoxy phenyl boronic acid, 0.144 g of $Pd(PPh_3)_4$ and 1.15 g of silver carbonate were suspended in 30 ml of 1,4-dioxane. The mixture was purged with vacuum and nitrogen several times and

then heated to 80^{o}C for 20 h. After being cooled to the room temperature, the reaction mixture was filtered through celite and the filtrate was concentrated to dryness. H_2O and ethyl acetate were added together, and the combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography, using PE/ethyl acetate = 2/1 as eluent to afford 0.5 g (78%) of the title compound **54** as a viscous oil. $[\alpha]_D$ = - 114.12 (c = 0.25, CH_3OH); TLC R_f 0.39 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.45 (m, 2H), 6.92-7.04 (m, 2H), 5.77 (br, 1H), 3.80 (s, 3H), 3.64-3.78 (m, 3H), 3.48 (br, 2H), 2.23 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.78, 167.67, 156.85, 145.97, 133.90, 132.47, 130.35, 121.20, 116.90, 111.64, 80.89, 70.15, 63.67, 55.64, 20.36; PI-EIMS: m/z (relative intensity) 308.1 (M^+, 11.58%); HRMS: Calcd for $C_{15}H_{16}O_7$ (M^+): 308.0896. Found: 308.0898.



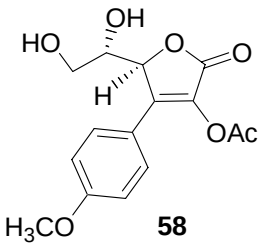
62

3-deoxy-3-(2-methoxyphenyl)-L-ascorbic acid (62) To a solution of 0.33 g of 2-O-acetyl-3-deoxy-3-(2-methoxyphenyl)-L-ascorbic acid (**54**) was added 0.44 g of potassium carbonate (10%) aqueous solution. The mixture was stirred at rt for 2 days. The solvent was removed in vacuo, and dilute HCl (1N) was added to adjust the pH to 6. The reaction mixture was then extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography through a silica gel column, eluting with ethyl acetate, to afford 0.17 g (60%) of the desired product **62** as a white solid. TLC R_f 0.28 (ethyl acetate); ^{1}H NMR (300 MHz, CD_3OD) δ 7.83 (dd, *J* = 7.74, 1.70, 1H), 7.34 (ddd, *J* = 8.47, 7.32, 1.73, 1H), 7.03-7.07 (m, 1H), 7.00 (dd, *J* = 7.47, 1.06, 1H), 5.84 (br, 1H), 3.84 (s, 3H), 3.59-3.74 (m, 3H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 172.01, 157.95, 139.88, 132.29, 131.45, 128.60, 121.91, 120.69, 112.45, 80.99, 71.31, 64.29, 55.97; PI-EIMS: m/z (relative intensity) 266.1 (M^+, 30.90%); HRMS: Calcd for $C_{13}H_{14}O_6$ (M^+): 266.0790. Found: 266.0788.



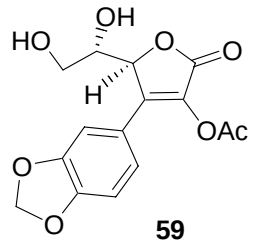
57

2-O-acetyl-3-deoxy-3-phenyl-L-ascorbic acid (57) This was prepared according to the procedure used for **54**, starting from 0.33 g of 2-O-acetyl-3-O-(trifluoromethanesulfonyl)-5,6-O-isopropylidene-L-ascorbic acid (**53**), 0.209 g of phenyl boronic acid, 59 mg of $Pd(PPh_3)_4$, 0.472 g of silver carbonate and 20 ml of 1,4-dioxane. After chromatography through a silica gel column, using ethyl acetate as eluent, 0.19 g (80%) of the title product **57** was obtained as a white solid. $[\alpha]_D$ = - 31.01 (c = 0.34, CH_3OH); TLC R_f 0.54 (ethyl acetate); IR (KBr) 1757, 1662, 1602, 1499, 1476, 1439, 1392, 1364, 1344, 1306, 1259, 1231, 1212, 1179, 1133, 1093, 1029, 990, 907, 766, 695, 643; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.66 (m, 5H), 5.59 (d, *J* = 2.13, 1H), 4.91 (ddd, *J* = 7.68, 6.79, 2.10, 1H), 4.48 (dd, *J* = 7.68, 0.65, 2H), 2.33 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.92, 166.10, 144.67, 134.88, 131.63, 130.85, 129.22, 128.06, 127.71, 127.61, 78.64, 74.78, 66.87, 20.42; Anal. Calcd for $C_{14}H_{14}O_6$: C, 60.43%; H, 5.07%. Found: C, 60.51%; H, 4.19%.



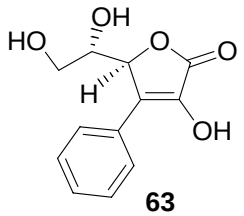
58

2-O-acetyl-3-deoxy-3-(4-methoxyphenyl)-L-ascorbic acid (58) This was prepared according to the procedure used for **54**, staring from 0.79 g of 2-O-acetyl-3-O-(trifluoromethanesulfonyl)-5,6-O-isopropylidene-L-ascorbic acid (**53**), 0.461 g of 4-methoxy phenyl boronic acid, 0.177 g of $Pd(PPh_3)_4$, 0.837 g of silver carbonate and 30 ml of 1,4-dioxane. After chromatography through a silica gel column, eluting with PE/AcOEt = 2/1, 0.5 g (74%) of the title product **58** was obtained as a white solid. TLC R_f 0.30 (ethyl acetate); $[\alpha]_D$ = - 35.36 (c = 0.14, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.61 (d, *J* = 8.88, 2H), 7.06 (d, *J* = 8.88, 2H), 5.83 (d, *J* = 0.86, 1H), 3.85 (s, 3H), 3.65-3.83 (m, 3H), 2.33 (s, 3H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 168.82, 163.41, 154.21, 147.18, 133.34, 130.89, 121.99, 115.75, 79.95, 71.64, 63.76, 56.02, 20.29; EIMS: m/z (relative intensity) 308.1 (M^+, 7.49%); HRMS: Calcd for $C_{15}H_{16}O_7$ (M^+): 308.0896. Found: 308.0896.



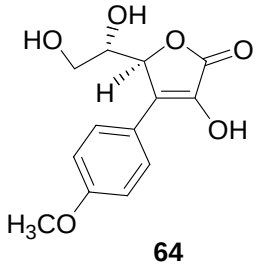
59

2-O-acetyl-3-deoxy-3-[3,4-(methylene-dioxy)phenyl]-L-ascorbic acid (**59**) This was prepared according to the procedure used for **54**, starting from 0.549 g of 2-O-acetyl-3-O-(trifluoromethanesulfonyl)-5,6-O-isopropylidene-L-ascorbic acid (**53**), 0.467 g of 3,4-methylene-dioxyphenyl boronic acid, 97 mg of $Pd(PPh_3)_4$, 0.775 g of silver carbonate and 30 ml of 1,4-dioxane. After chromatography through a silica gel column, eluting with PE/AcOEt = 2/1, to afford 0.29 g (64%) product **59** as a white solid. TLC R_f 0.45 (ethyl acetate); ^1H NMR (300 MHz, CD_3OD) δ 7.17 (d, *J* = 1.78, 1H), 7.14 (d, *J* = 1.13, 1H), 6.95 (dd, *J* = 1.78, 1.13, 1H), 6.04 (dd, *J* = 1.97, 1.05, 2H), 5.79 (d, *J* = 1.20, 1H), 3.89 (ddd, *J* = 7.34, 6.54, 1.14, 1H), 3.76 (dd, *J* = 10.68, 7.50, 1H), 3.68 (dd, *J* = 10.68, 6.59, 1H), 2.33 (s, 3H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 169.57, 168.74, 151.47, 149.95, 147.44, 133.79, 124.23, 123.39, 109.95, 108.86, 103.40, 80.09, 71.61, 63.76, 20.30; PI-EIMS: m/z (relative intensity) 322.0 (M^+, 13.04%); HRMS: Calcd for $C_{15}H_{14}O_8$ (M^+): 322.0689. Found: 322.0688.



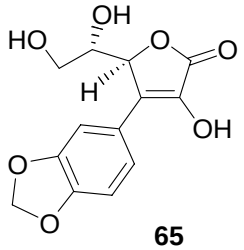
63

3-deoxy-3-phenyl-L-ascorbic acid (63) This was prepared according to the procedure used for **62**, staring from 0.18 g of 2-O-acetyl-3-deoxy-3-phenyl-5,6-O-isopropylidene-L-ascorbic acid (**57**), 10% of K_2CO_3 (0.152 g) aqueous solution and 10 ml of methanol. After chromatography through a silica gel column, eluting with ethyl acetate, 89 mg (58.2%) of the desired product **63** was obtained as a white solid. $[\alpha]_D$ = - 73.21 (c = 0.27, CH_3OH); TLC R_f 0.29 (ethyl acetate); IR (KBr) 3374, 3032, 1720, 1672, 1573, 1498, 1401, 1308, 1154, 1102, 1067, 1018, 986, 891, 759, 689; ^1H NMR (300 MHz, CD_3OD) δ 7.30-7.78 (m, 5H), 5.63 (d, *J* = 1.10, 1H), 3.94 (dt, *J* = 7.10, 0.82, 1H), 3.77 (dd, *J* = 10.72, 7.56, 1H), 3.69 (dd, *J* = 10.72, 6.55, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 171.82, 140.17, 132.14, 129.71, 129.63, 128.55, 128.09, 79.18, 71.19, 64.03; PI-EIMS: m/z (relative intensity) 236.0 (M^+, 8.39%); HRMS: Calcd for $C_{12}H_{12}O_5$ (M^+): 236.0685. Found: 236.0679.



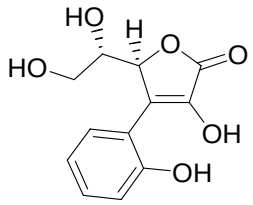
64

3-deoxy-3-(4-methoxyphenyl)-L-ascorbic acid (64) This was prepared according to the procedure used for **62**, staring from 78 mg of 2-O-acetyl-3-deoxy-3-(4-methoxyphenyl)-L-ascorbic acid (**58**), 10% of K_2CO_3 (59 mg) aqueous solution and 3 ml of methanol. After chromatography through a silica gel column, eluting with ethyl acetate, 227 mg (55%) of the desired product **64** was obtained as a white solid. $[\alpha]_D$ = - 92.22 (c = 0.09, CH_3OH); TLC R_f 0.33 (ethyl acetate); IR (KBr) 3273, 2926, 2843, 1672, 1606, 1518, 1460, 1381, 1294, 1191, 1122, 1054, 874, 814, 766, 719; ^{1}H NMR (300 MHz, CD_3OD) δ 7.69 (dd, *J* = 6.83, 2.16, 2H), 6.99 (dd, *J* = 6.83, 2.16, 2H), 5.57 (d, *J* = 1.10, 1H), 3.95 (ddd, *J* = 7.48, 6.56, 1.10, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 10.63, 7.48, 1H), 3.69 (dd, *J* = 10.63, 6.56, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 172.09, 161.44, 138.62, 130.09, 128.75, 124.66, 115.15, 79.13, 71.37, 64.06, 55.82; PI-EIMS: m/z (relative intensity) 266.2 (MH^+, 87.03%); Anal. Calcd for $C_{13}H_{14}O_6 \cdot 0.25\ H_2O$: C, 57.62%; H, 5.35%. Found: C, 57.88%; H, 5.55%.



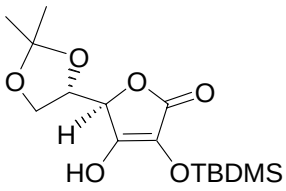
65

3-deoxy-3-[3,4-(methylene-dioxy)phenyl]-L-ascorbic acid (65) This was prepared according to the procedure used for **62**, starting from 74 mg of 2-O-acetyl-3-deoxy-3-[3,4-(methylene-dioxy)phenyl]-L-ascorbic acid (**59**), 10% of K_2CO_3 (53.9 mg) aqueous solution and 2.8 ml of methanol. After chromatography through a silica gel column, eluting with ethyl acetate, 35 mg (54.4%) of the title product **65** was obtained as a white solid. $[\alpha]_D$ = - 87.03 (c = 0.14, CH_3OH); TLC R_f 0.33 (ethyl acetate); IR (KBr) 3374, 2918, 1708, 1658, 1605, 1503, 1449, 1346, 1250, 1214, 1151, 1100, 1017, 927, 875, 831, 804, 769; ^{1}H NMR (300 MHz, CD_3OD) δ 7.36 (d, *J* = 1.54, 1H), 7.16 (dd, *J* = 8.18, 1.77, 1H), 6.89 (d, *J* = 8.18, 1H), 5.98 (dd, *J* = 1.61, 1.13, 2H), 5.54 (d, *J* = 1.10, 1H), 3.94 (ddd, *J* = 10.77, 6.77, 1.10, 1H), 3.76 (dd, *J* = 10.77, 7.44, 1H), 3.68 (dd, *J* = 10.77, 6.77, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 171.89, 149.46, 149.38, 139.03, 128.39, 126.16, 122.63, 109.40, 108.91, 102.79, 79.18, 71.34, 64.03; PI-EIMS: m/z (relative intensity) 280.0 (M^+, 100.00%); HRMS: Calcd for $C_{13}H_{12}O_7$ (M^+): 280.0583. Found: 280.0583.



24

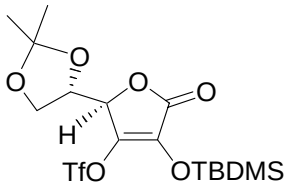
3-deoxy-3-(2-hydroxyphenyl)-L-ascorbic acid (24) 120 mg of 3-deoxy-3-(2-methoxyphenyl)-L-ascorbic acid (**62**) was suspended in 10 ml of CH_2Cl_2, then cooled to –78°C. BBr_3 (0.128 ml, 3 equiv) was added by syringe. After 1 h, the reaction mixture was allowed to warm to room temperature for 1 h and then cooled to –78°C again and quenched with H_2O. The reaction mixture was warmed to rt and the solvent was removed in vacuo. Then Dowex 50 (H^+) was added and the mixture was stirred at rt for 1 h. After removal of the solvent, the residue was purified by chromatography through a silica gel column, eluting with AcOEt/CH_3OH = 6/1, to afford 100 mg (88%) of the desired product **24** as a solid. TLC R_f 0.38 (ethyl acetate/methanol = 6/1); ^{1}H NMR (300 MHz, CD_3OD) δ 7.28 (d, *J* = 7.41, 1H), 7.13 (t, *J* = 7.27, 1H), 6.76-6.88 (m, 2H), 5.63 (br, 1H), 3.88 (t, *J* = 6.45, 1H), 3.61-3.78 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 173.21, 157.57, 146.55, 130.53, 129.07, 120.82, 120.53, 118.42, 112.61, 80.15, 71.29, 64.38.



69

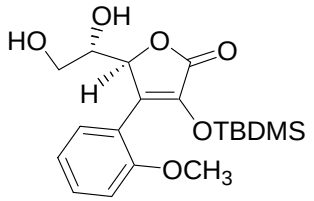
2-O-TBS-5,6-O-isopropylidene-L-ascorbic acid (69) [41] To a stirring suspension of 5,6-O-isopropylidene-L-ascorbic acid (**2**, 5 g) in 50 ml of THF was added *tert*-butyldimethylsilyl chloride (3.83 g) at rt followed by the addition of N,N-diisopropylethylamine (7.87 ml) over 30 min. The reaction mixture was stirred at rt overnight. After removal of the solvent under reduced pressure, the residue was dissolved in methyl *tert*-butyl ether (50 ml) and extracted with 1M potassium carbonate (50 ml). The aqueous layer was extracted with methyl *tert*-butyl ether 3 times, then the pH of the aqueous layer was adjusted to pH 6 using 2N HCl. The aqueous layer was extracted twice with isopropyl acetate (2 x 50 ml) and concentrated to dryness. The residue was purified by chromatography, eluting with PE/AcOEt = 1/2, to afford 4.885 g (64%) of product **69** as a white solid. Mp 68-71°C; $[\alpha]_D$ = - 8.26 (c = 1.18, $CHCl_3$); TLC R_f 0.43 (ethyl acetate); IR (KBr) 3432, 2935, 2860, 1738, 1686, 1465, 1373, 1259, 1121, 1151, 1016, 1062, 831, 786; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (d, *J* = 3.81, 1H), 4.44 (dt, *J*

= 6.62, 3.81, 1H), 4.10 (dd, *J* = 8.73, 6.87, 1H), 3.90 (dd, *J* = 8.64, 6.55, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 0.93 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.10, 153.38, 110.55, 110.54, 73.99, 73.98, 64.67, 25.83, 25.60, 25.39, 18.17, -3.63, -4.44; ESMS: m/z 329.1 ($M\text{-}H^+$).



70

2-O-TBS-3-O-trifloromethanesulfonyl-5,6-O-isopropylidene-L-ascorbic acid (70) 0.44 g of 2-O-TBS-5,6-O-isopropylidene-L-ascorbic acid (**69**) was dissolved in 8 ml of $ClCH_2CH_2Cl$, and cooled to 0^{o}C. Then 0.1 ml of pyridine and 0.22 ml of triflic anhydride were added. The reaction mixture was kept at 0^{o}C for 2 h. Then saturated NH_4Cl solution and dichloromethane were added together. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by chromatography through a silica gel column, eluting with PE/AcOEt = 4/1 to yield 0.5 g (81%) of product **70**. $[\alpha]_D$ = - 41.6 (c = 0.75, $CHCl_3$); TLC R_f 0.74 (PE/AcOEt = 4/1); IR (film) 2935, 1790, 1715, 1435, 1345, 1223, 1138, 1047, 841, 807; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.50 (d, *J* = 1.95, 1H), 4.40 (ddd, *J* = 1.95, 1.10, 7.24, 1H), 4.22 (dd, *J* = 8.58, 7.03, 1H), 4.07 (dd, *J* = 8.58, 5.93, 1H), 1.36 (s, 6H), 0.98 (s, 9H), 0.32 (s, 3H), 0.27 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.85, 140.93, 132.52, 120.53, 116.27, 110.92, 74.59, 72.20, 65.00, 25.62, 25.23, 25.17, 18.19, -4.31, -4.58; ESMS: m/z (relative intensity) 463.1 (MH^+, 100%).

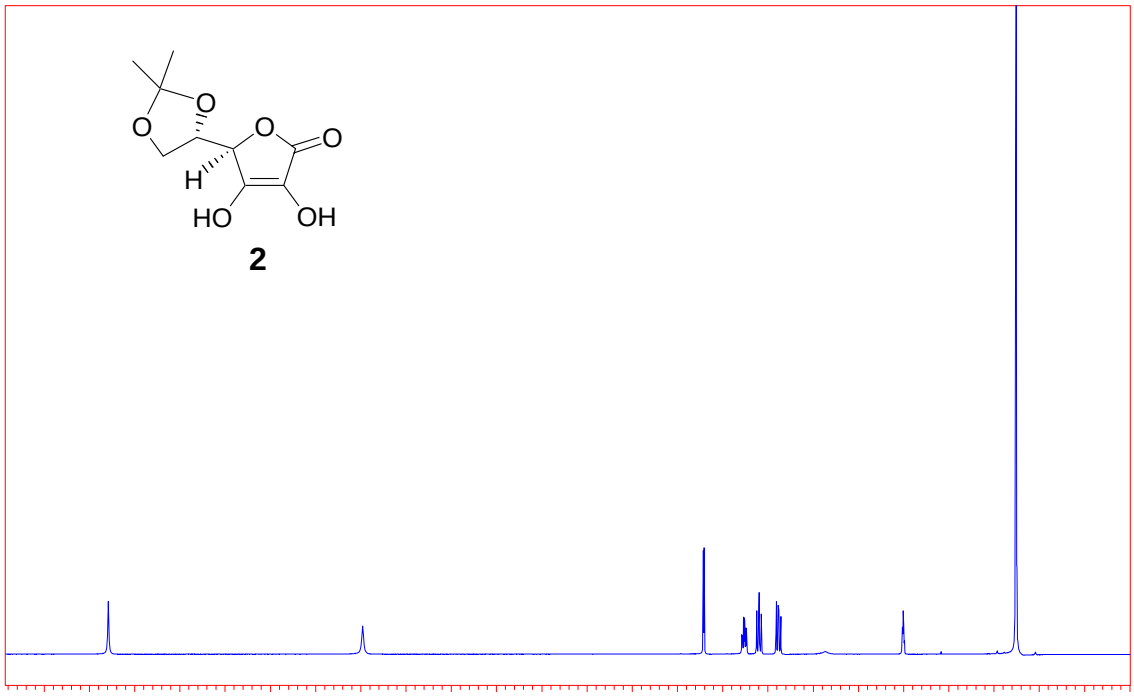


71

2-O-TBS-3-deoxy-3-(2-methoxyphenyl)-L-ascorbic acid (71) This was prepared according to the procedure used for **54**, starting from 0.41 g of 2-O-TBDMS-3-O-(trifluoromethanesulfonyl)-5,6-O-isopropylidene-L-ascorbic acid (**70**), 0.151 g of 2-methoxy phenyl boronic acid, 63 mg of $Pd(PPh_3)_4$, 0.275 g of silver carbonate and 10 ml of 1,4-dioxane. After chromatography through a silica gel column, eluting with PE/AcOEt = 3/1, 84

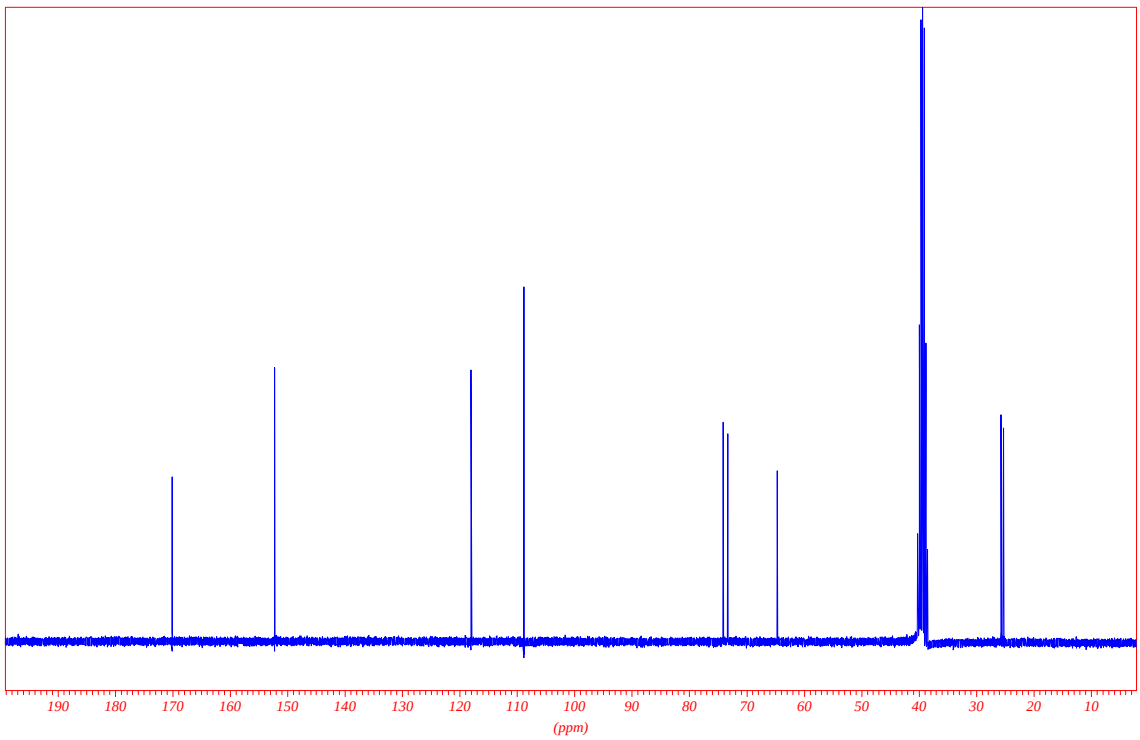
mg (25%) of the title product **71** was obtained as a yellow solid. $[\alpha]_D$ = - 81.09 (c = 0.46, CH_3OH); TLC R_f 0.8 (ethyl acetate); IR (KBr) 3294, 2931, 1730, 1598, 1491, 1463, 1437, 1386, 1286, 1246, 1161, 1116, 1019, 753; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.65, 1.65, 1H), 7.36 (ddt, *J* = 7.89, 1.75, 0.93, 1H), 7.02 (dt, *J* = 7.55, 1.03, 1H), 6.94 (dd, *J* = 8.45, 0.81, 1H), 5.61 (d, *J* = 1.71, 1H), 3.84 (s, 3H), 3.69-3.83 (m, 3H), 2.34 (br, 2H), 0.86 (s, 9H), 0.25 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.62, 156.24, 138.45, 134.09, 131.22, 130.90, 121.01, 118.73, 111.04, 79.96, 70.62, 64.05, 55.45, 25.44, 18.22, -4.16, -4.60; EIMS: m/z (relative intensity) 266.0 (M-TBDMS$^+$, 7.03%).

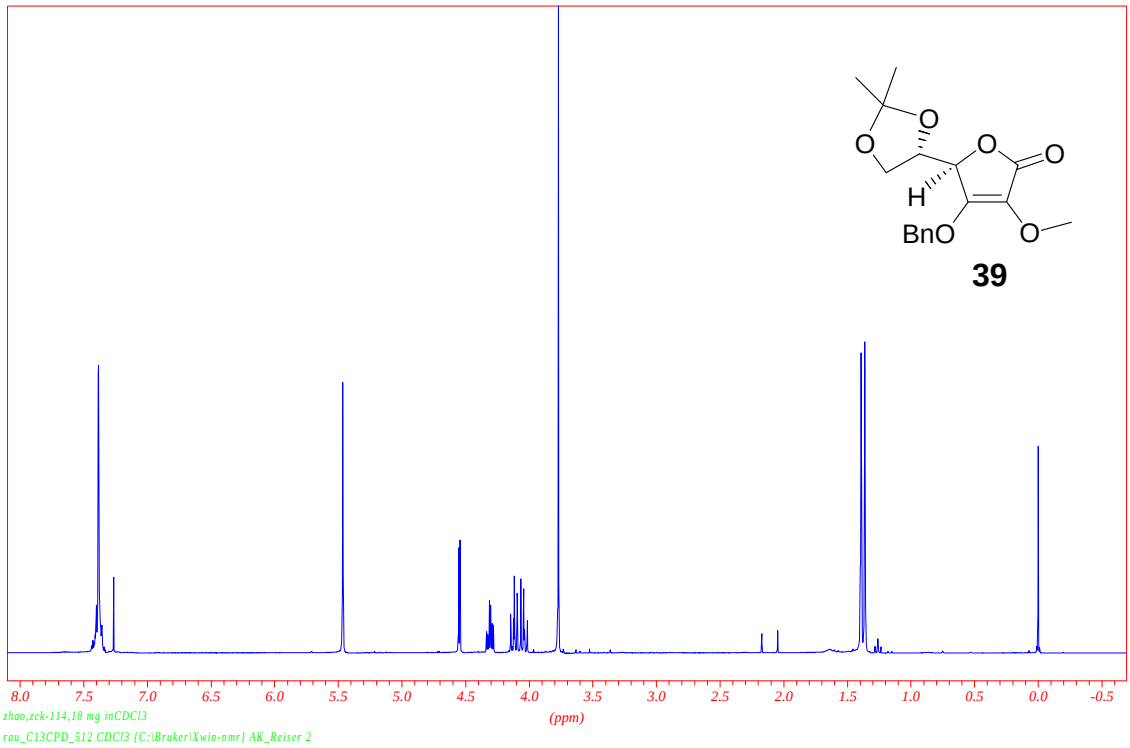
4 NMR-Spectra

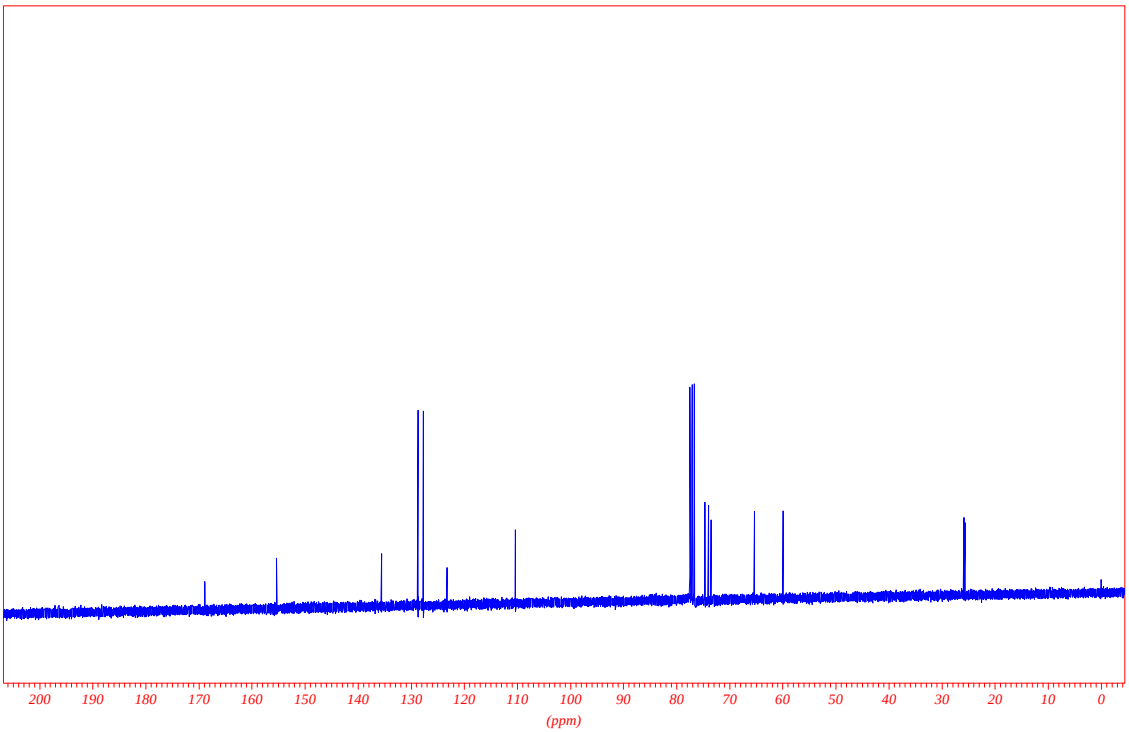


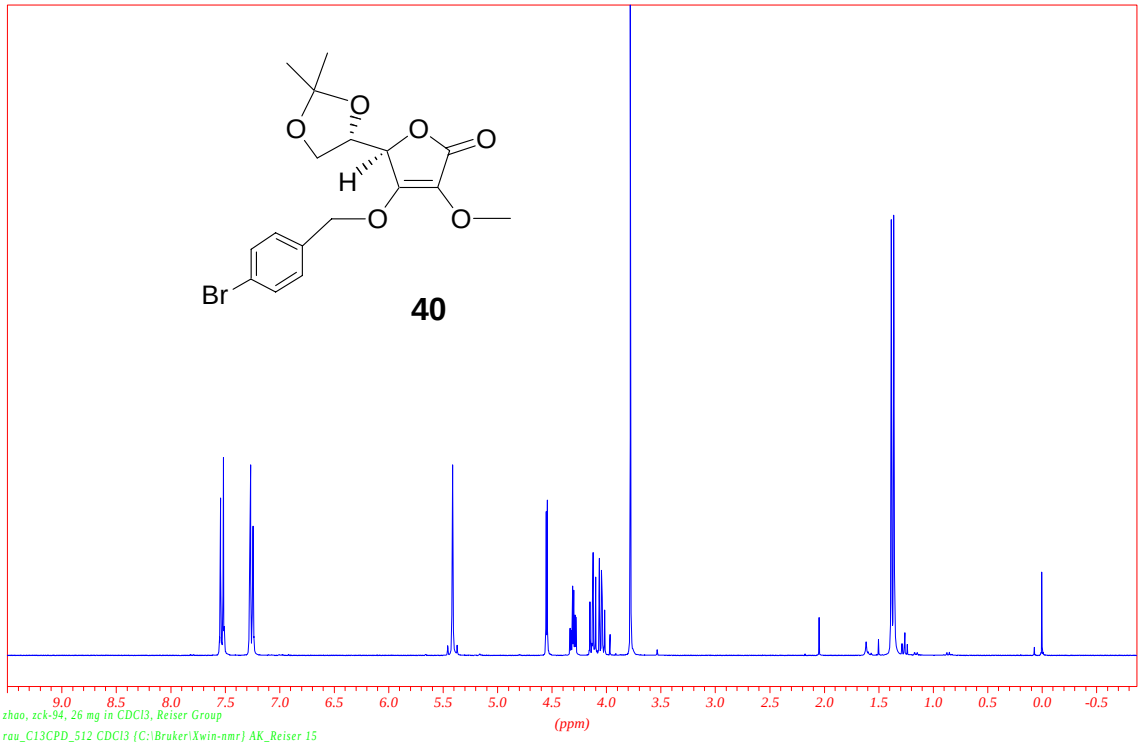
zck-90, 19mg in DMSO, reiser

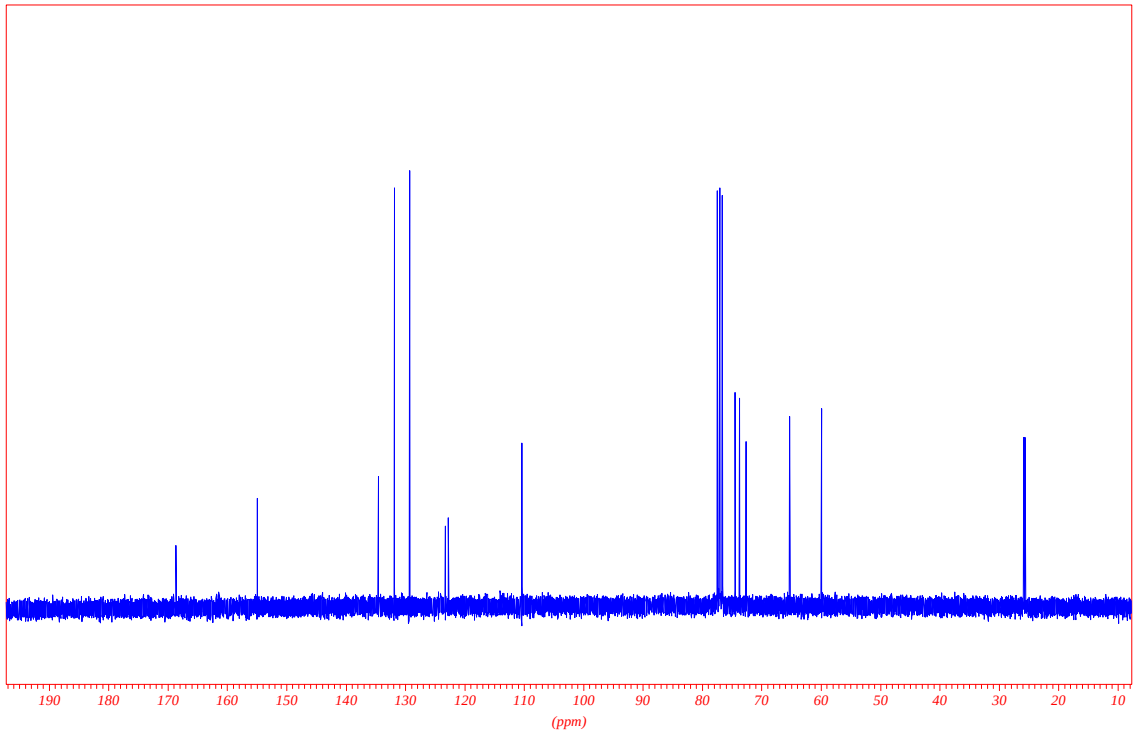
rau_C13CPD_2k DMSO {C:\Bruker\Xwin-nmr} AK_Reiser 12

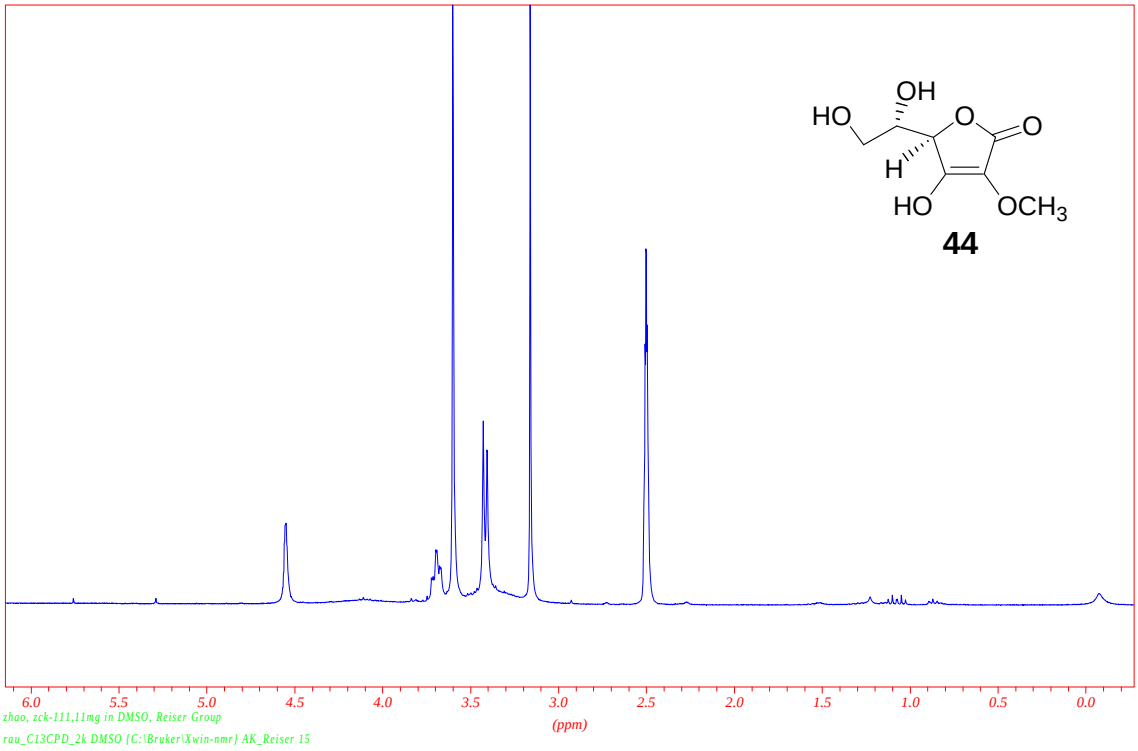


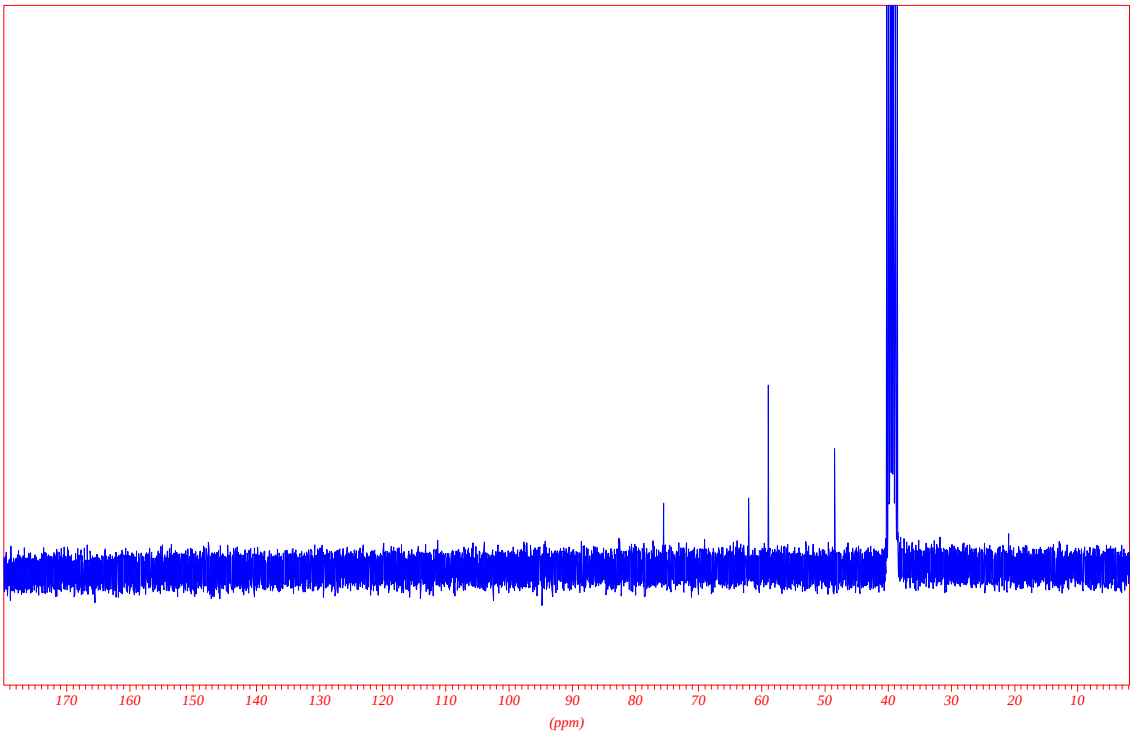

O
O
O
O
H
BnO
O
39
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)
zhao,zck-114,18 mg inCDCl3
rau_C13CPD_512 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 2

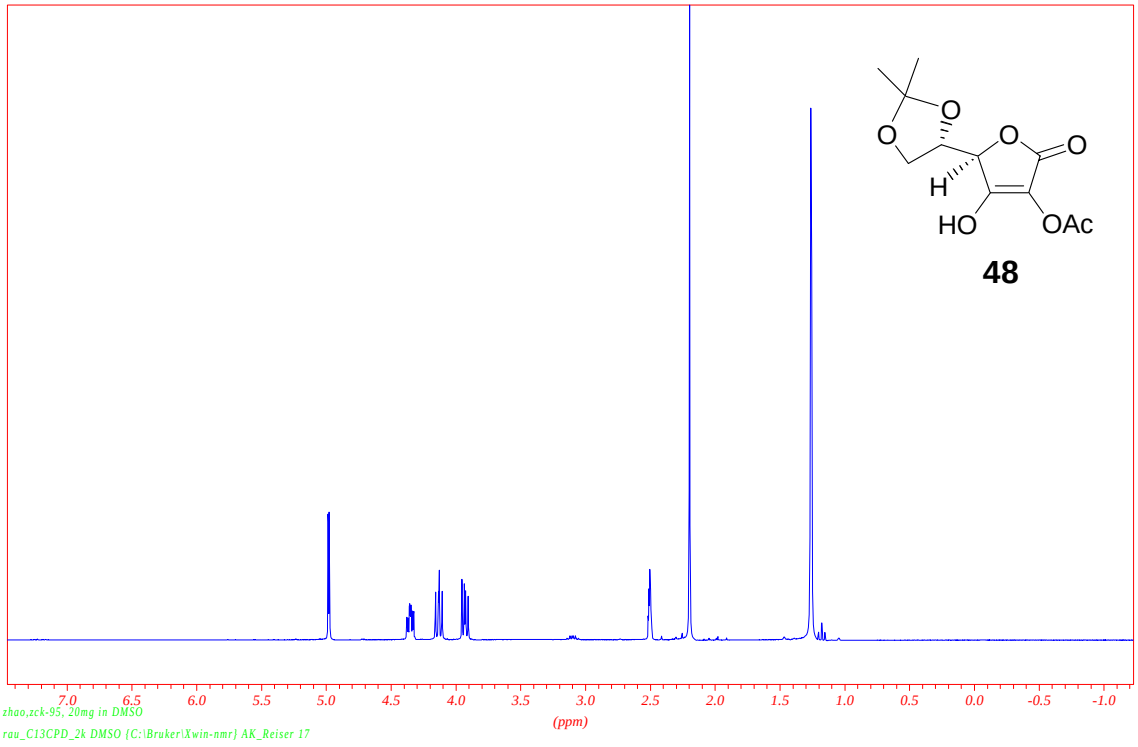

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

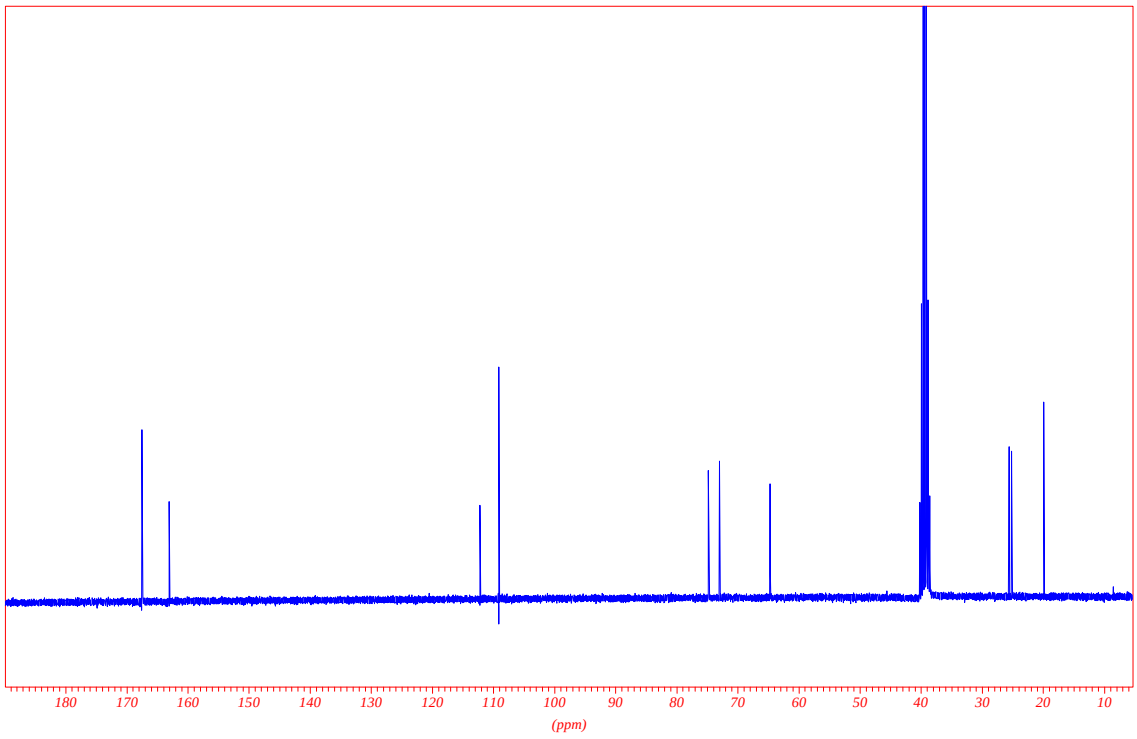

O
O
O
O
O
H
O
O
Br
40
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)
zhao, zck-94, 26 mg in CDCl3, Reiser Group
rau_C13CPD_512 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 15

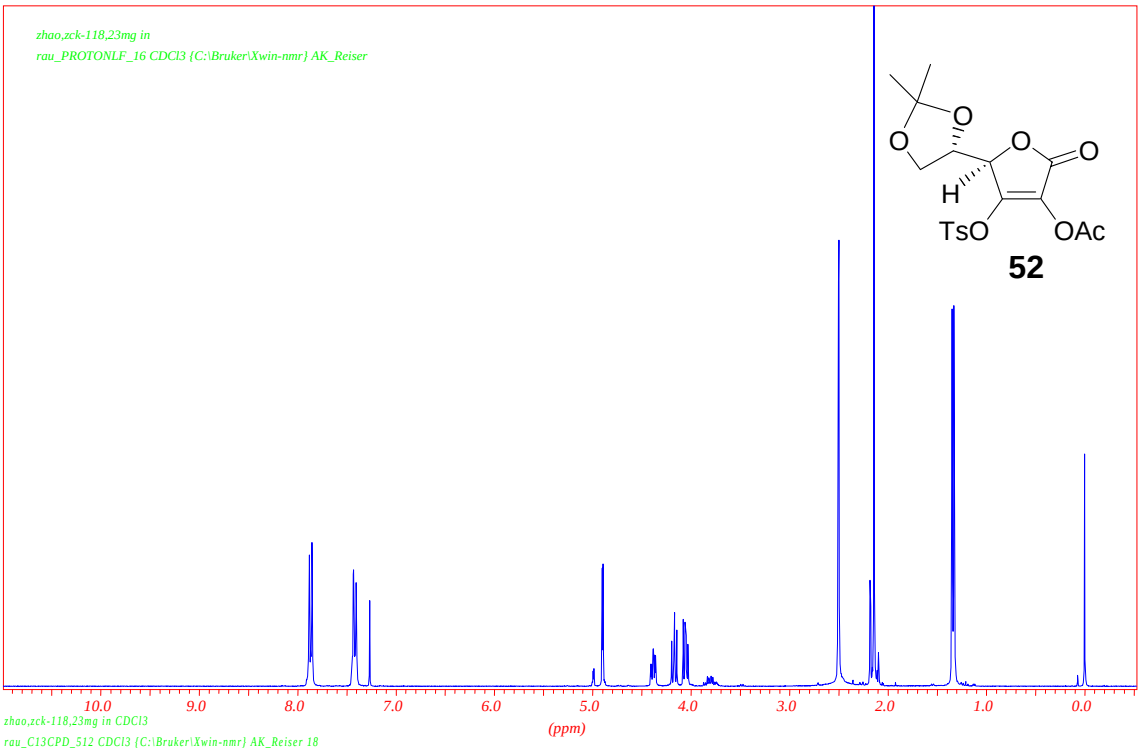

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

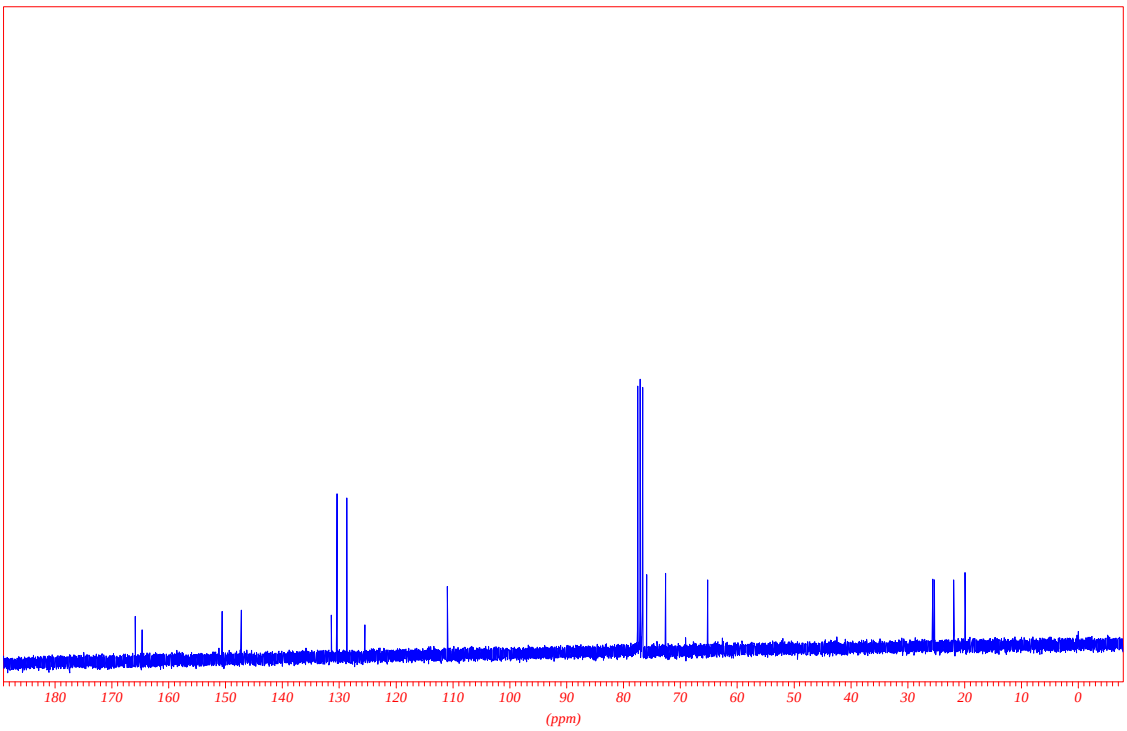

OH
HO
O
O
H
HO
OCH3
44
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)
zhao, zck-111,11mg in DMSO, Reiser Group
rau_C13CPD_2k DMSO {C:\Bruker\Xwin-nmr} AK_Reiser 15

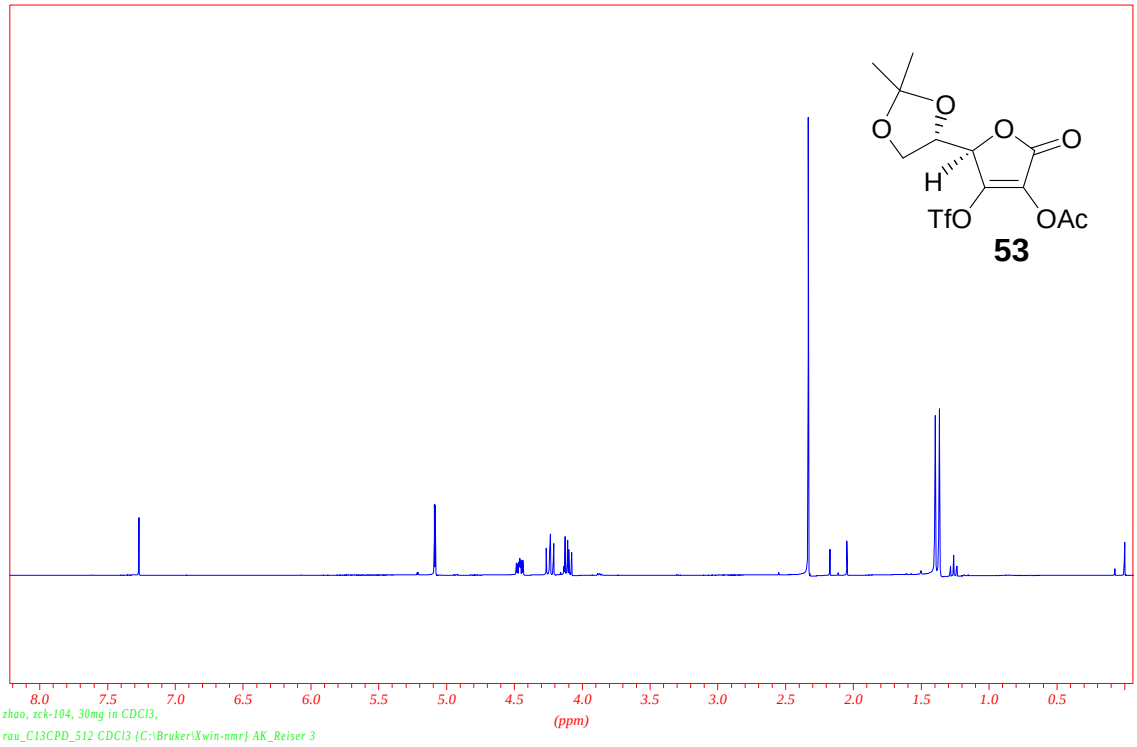

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

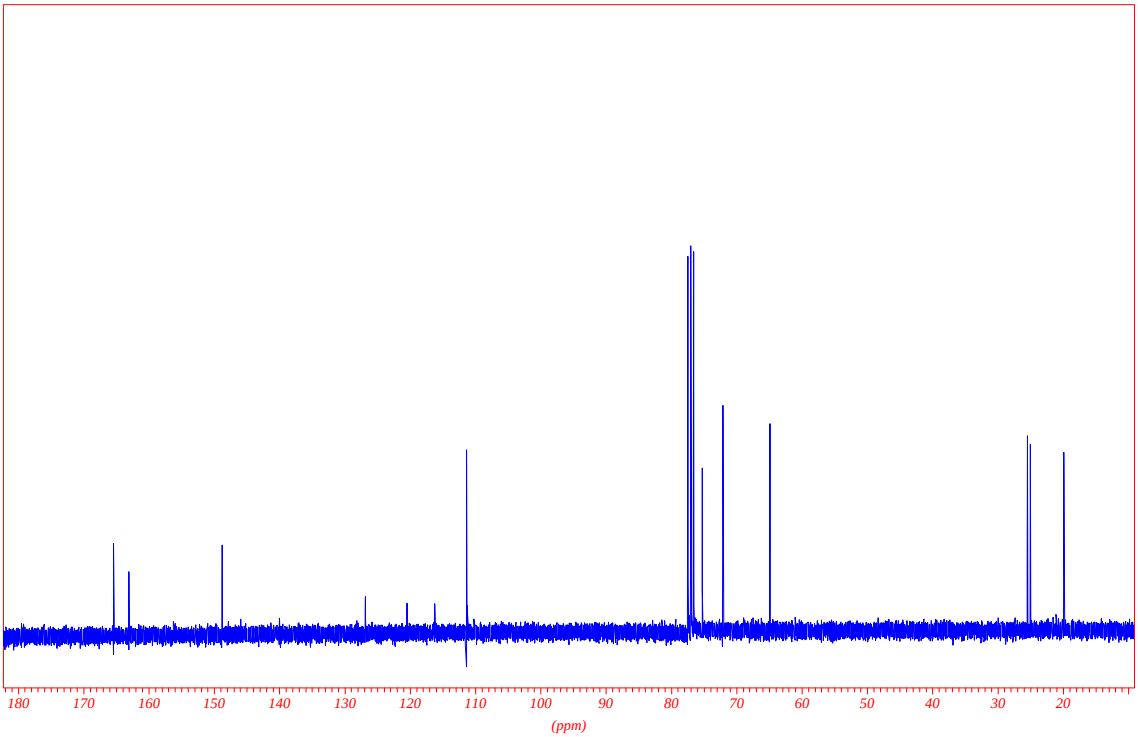

O
O
O
O
H
HO
OAc
48
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
(ppm)
zhao,zck-95, 20mg in DMSO
rau_C13CPD_2k DMSO {C:\Bruker\Xwin-nmr} AK_Reiser 17


180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

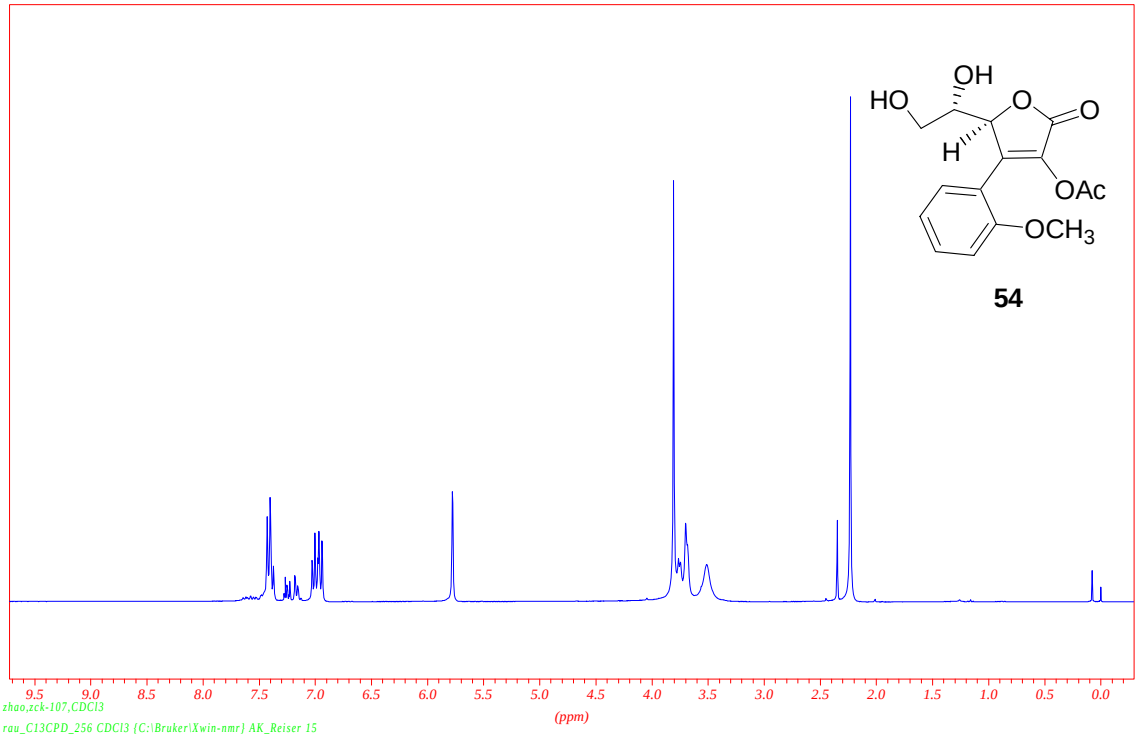

zhao,zck-118,23mg in
rau_PROTONLF_16 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser
O
O
O
O
H
TsO
OAc
52
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


zhao,zck-118,23mg in CDCl3
rau_C13CPD_512 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 18
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)


O
O
O
O
H
TfO
OAc
53
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)
zhao, zck-104, 30mg in CDCl3,
rau_C13CPD_512 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 3

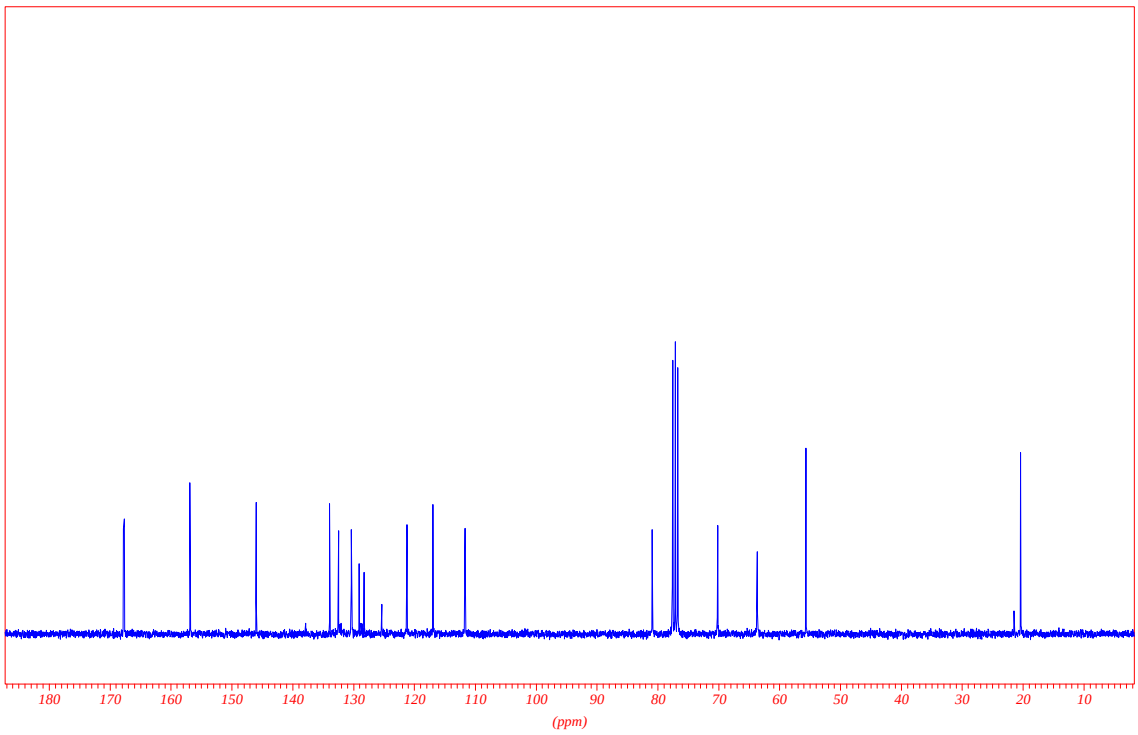

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
(ppm)

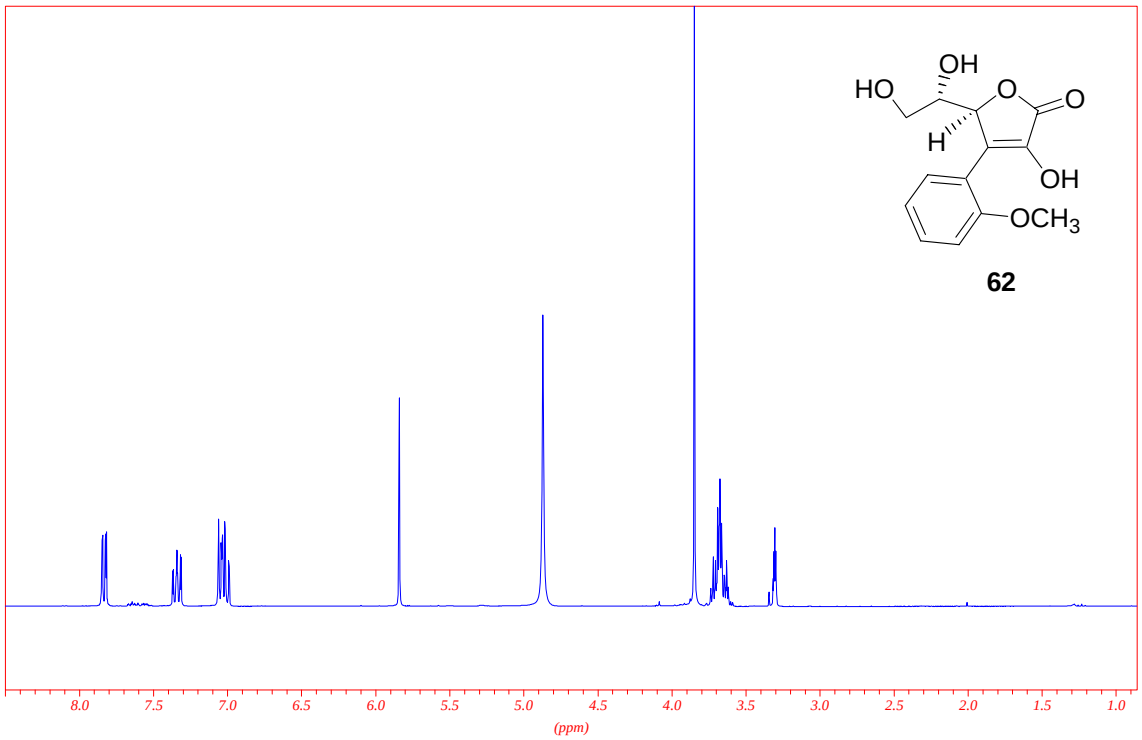
zhao,zck-107,CDCl3
rau_PROTONLF_16 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 15



54

zhao,zck-107,CDCl3
rau_C13CPD_256 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 15

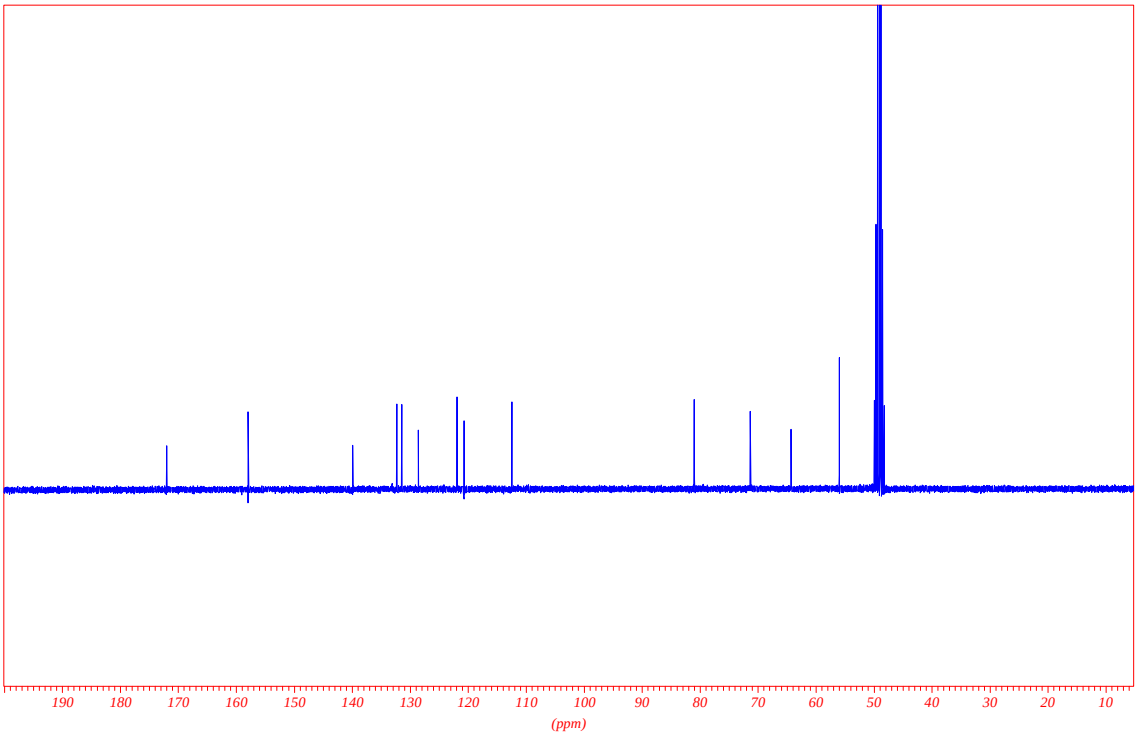


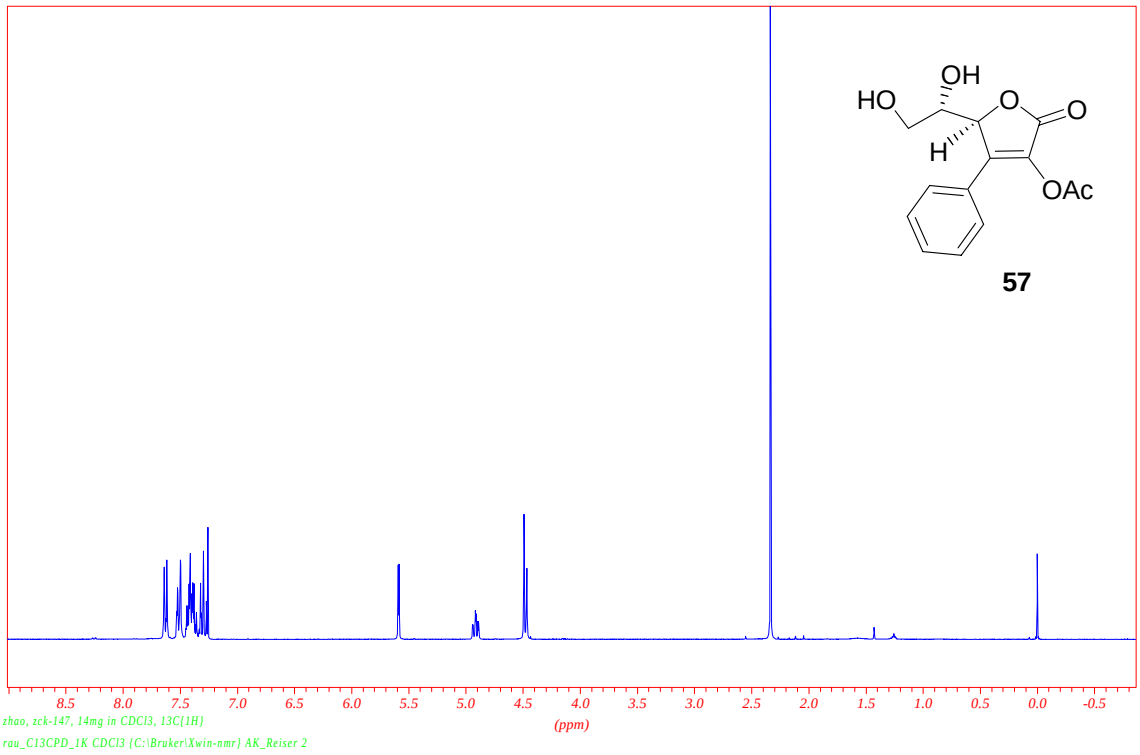


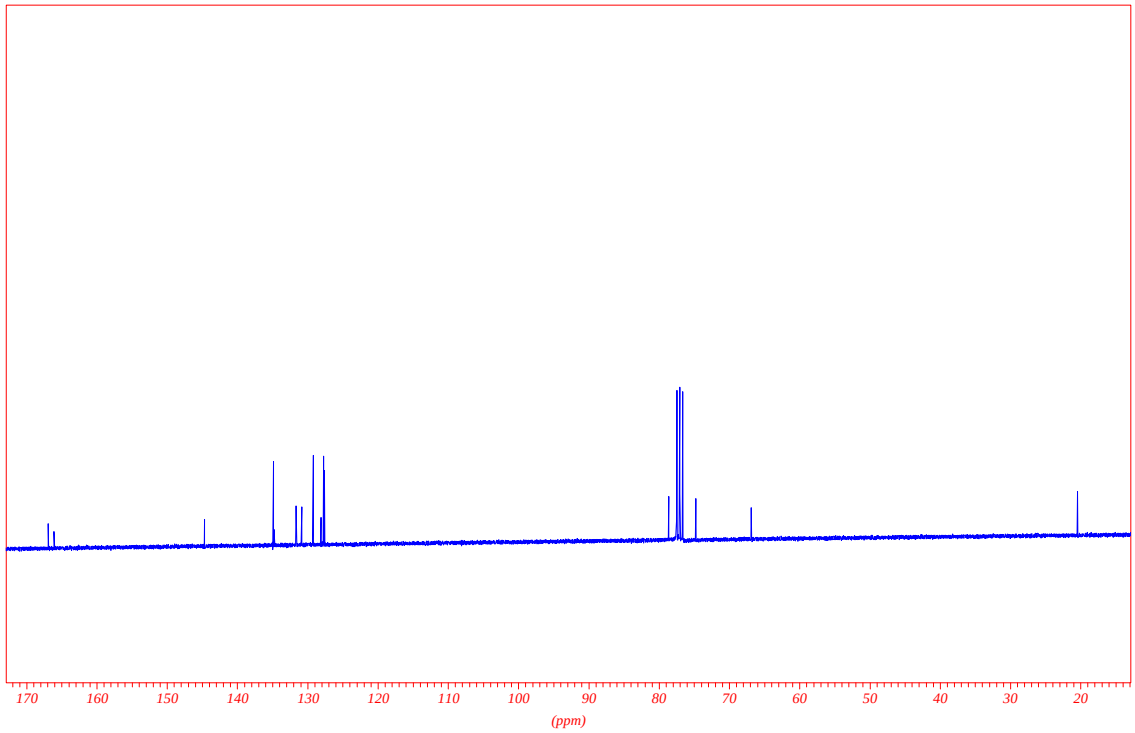
62

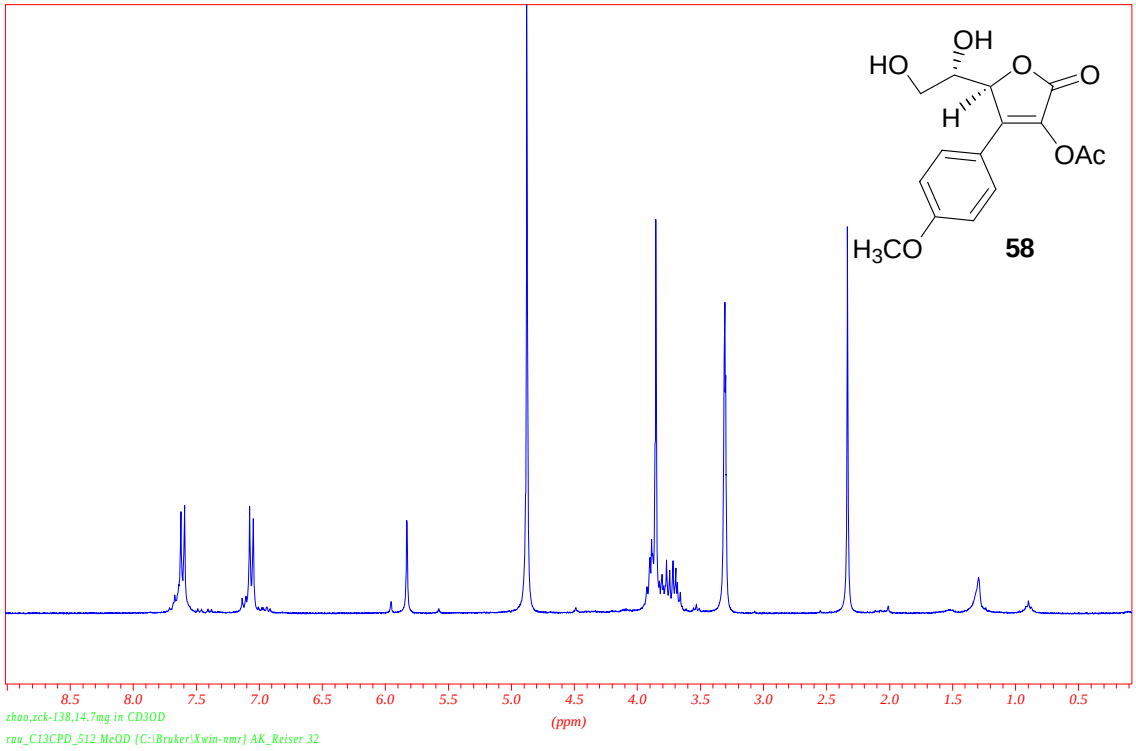
zhao, zck-120, CD3OD

rau_C13CPD_256 MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 2



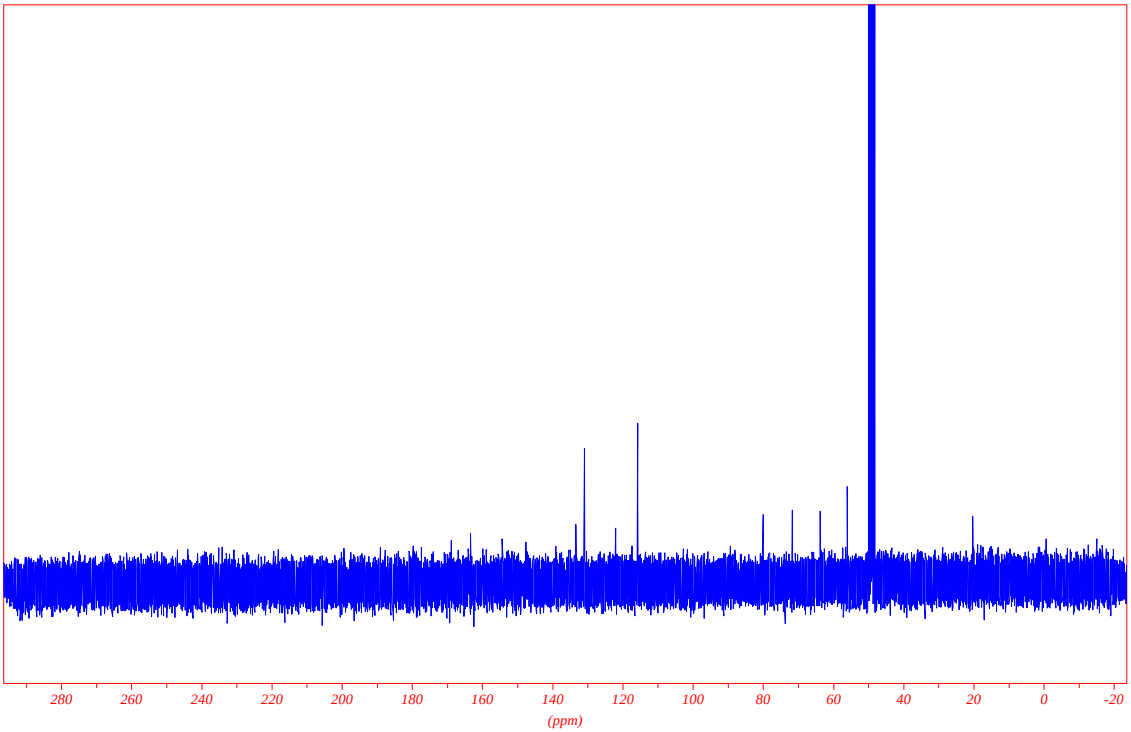

OH
HO
O
O
H
OAc
57
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)
zhao, zck-147, 14mg in CDCl3, 13C{1H}
rau_C13CPD_1K CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 2

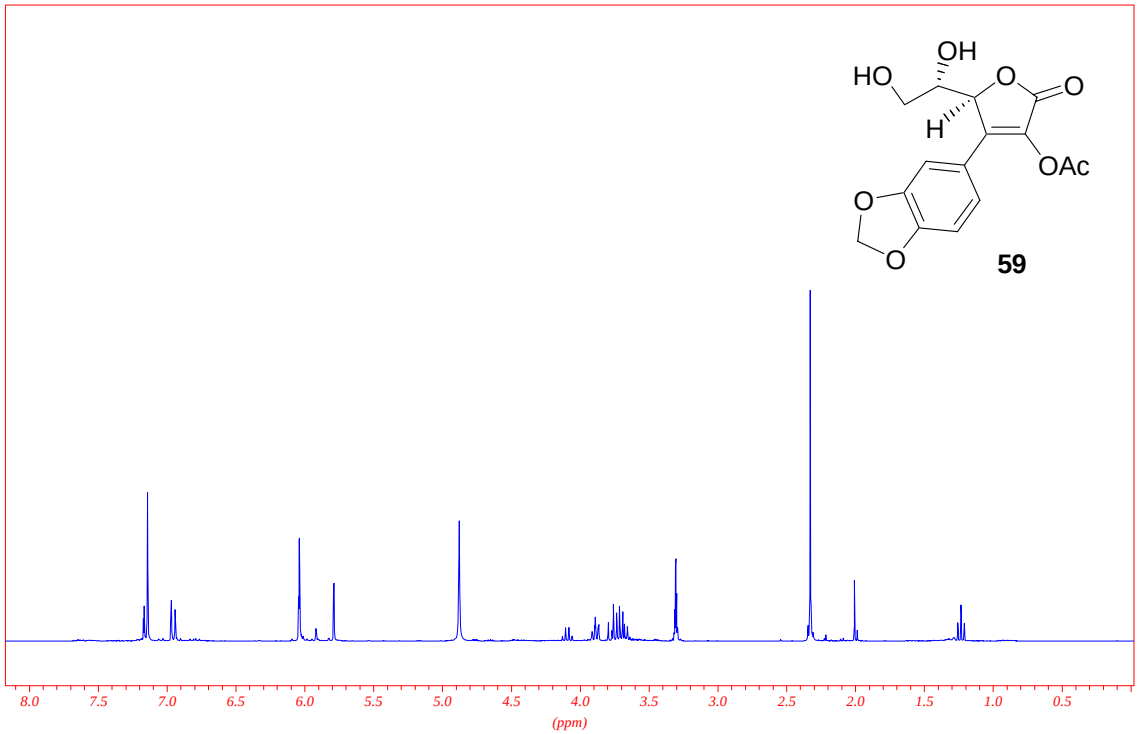

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
(ppm)



zhao,zck-138,14.7mg in CD3OD

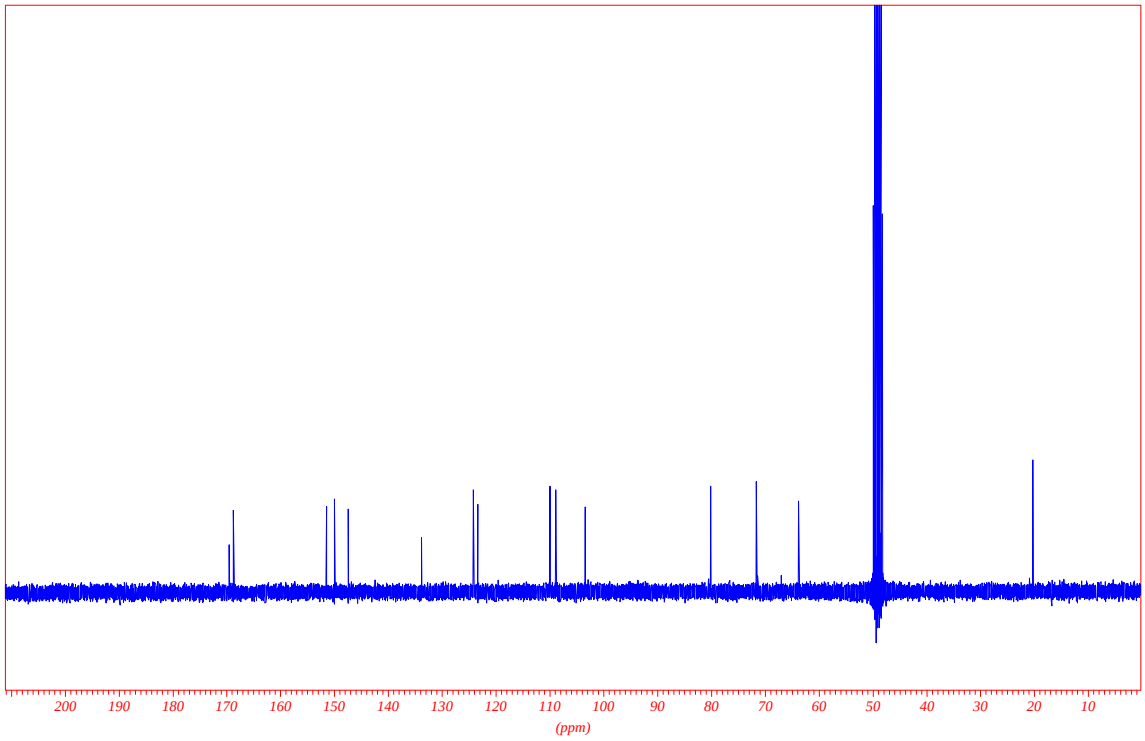
rau_C13CPD_512 MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 32

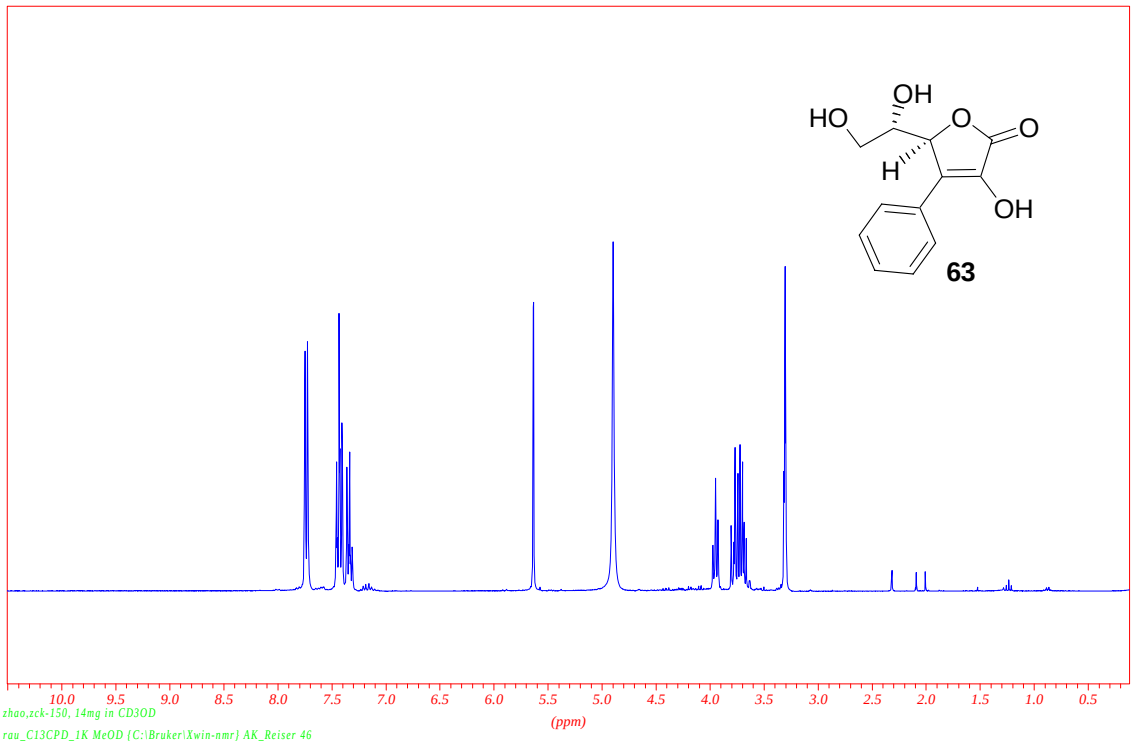




zck-146,32mg in CD3OD

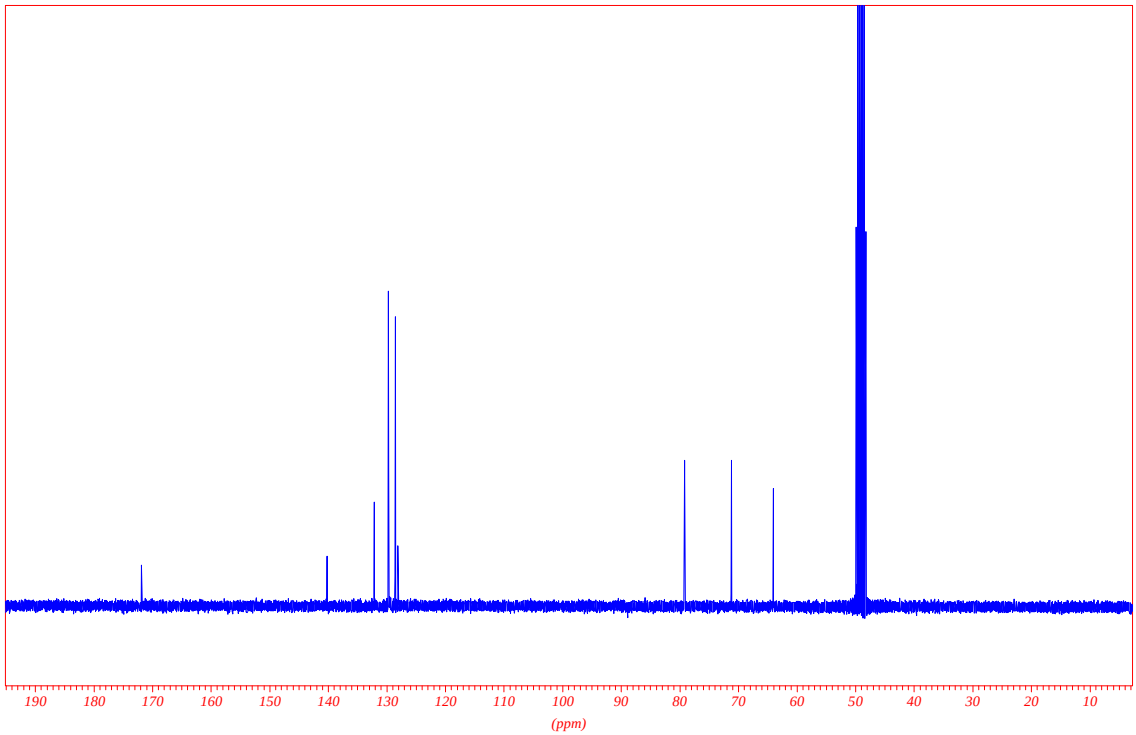
rau_C13CPD_256 MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 28





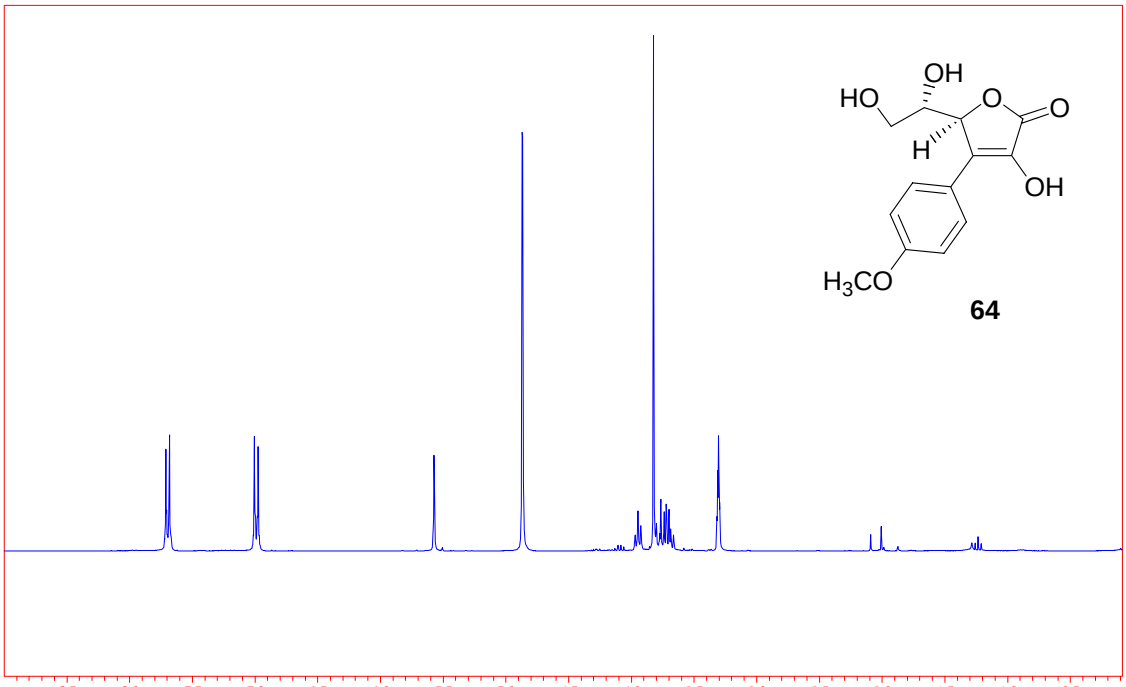
zhao,zck-150, 14mg in CD3OD

rau_C13CPD_1K MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 46



zhao,zck-143, CD3OD

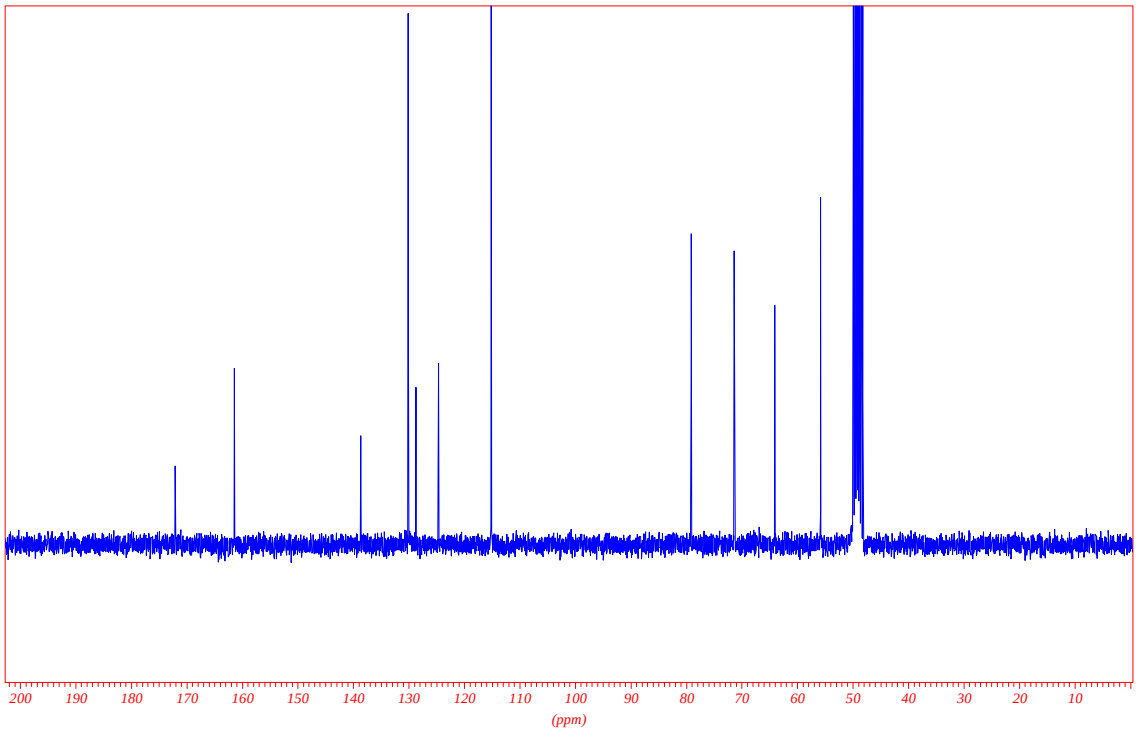
rau_PROTONLF_16 MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 36

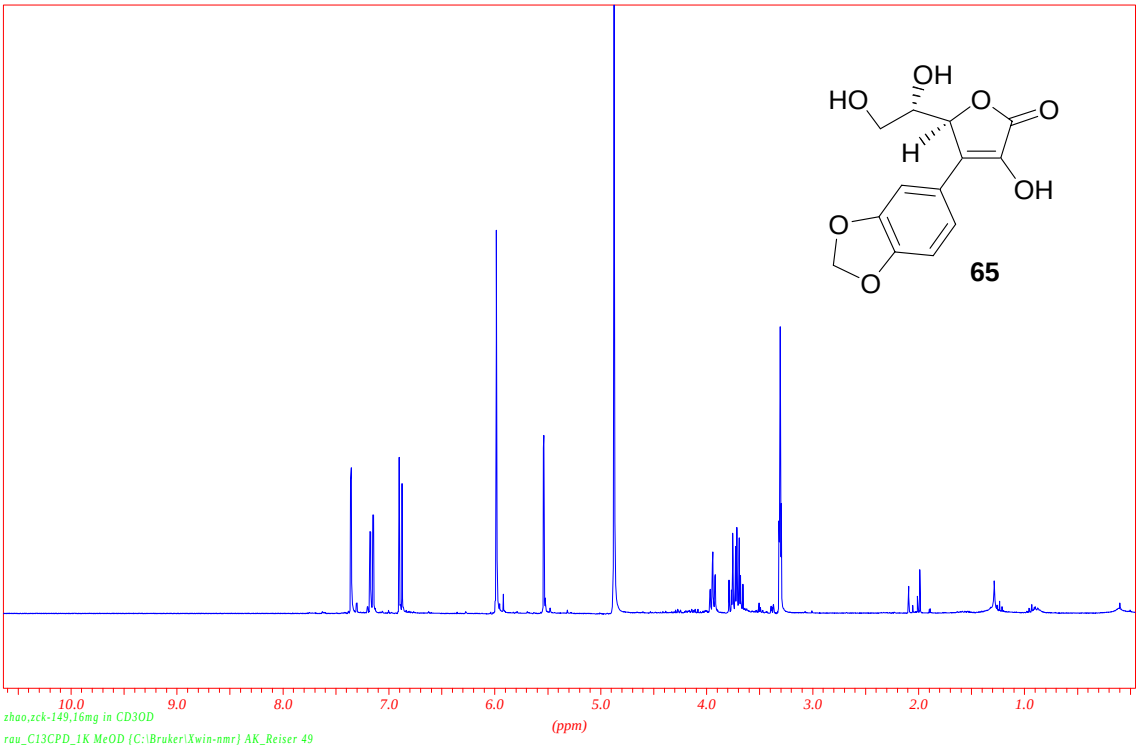


64

zhao,zck-143,CD3OD

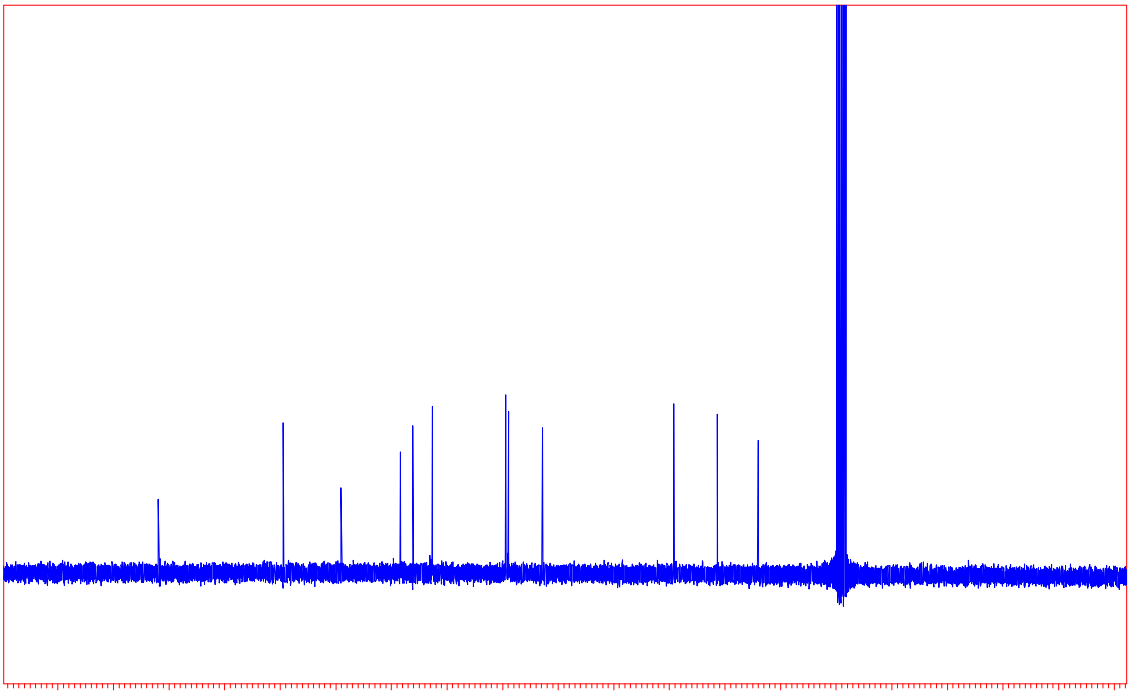
rau_C13CPD_1K MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 5



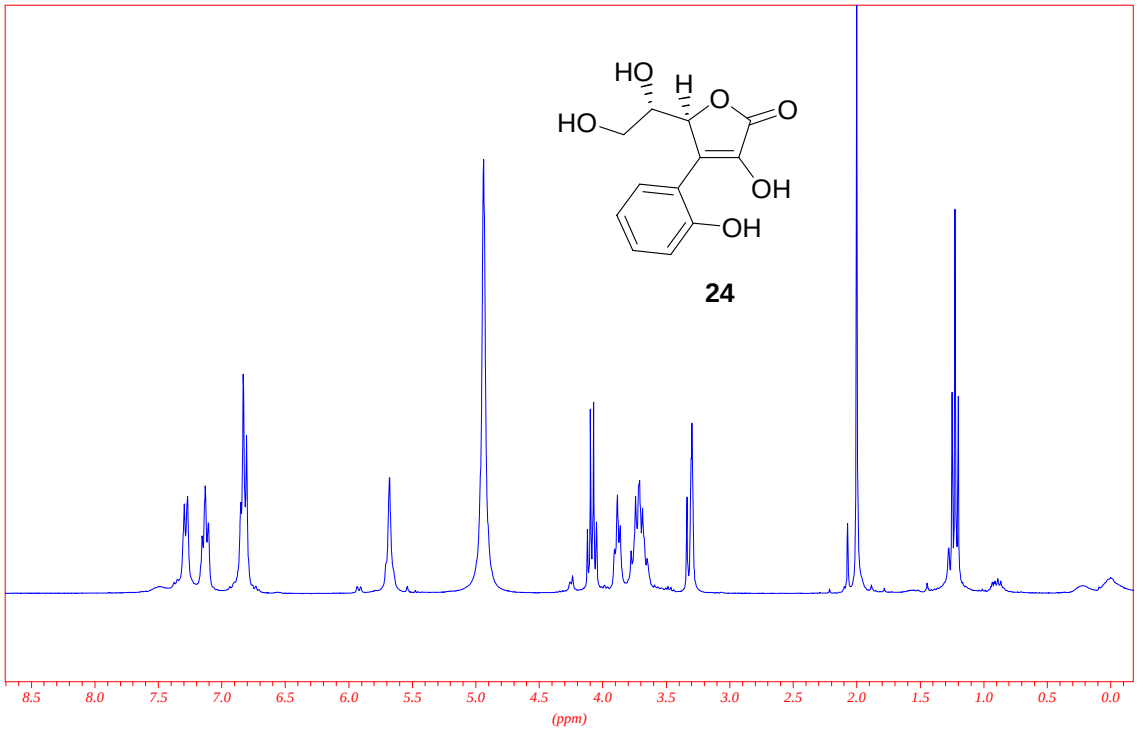


zhao,zck-149,16mg in CD3OD

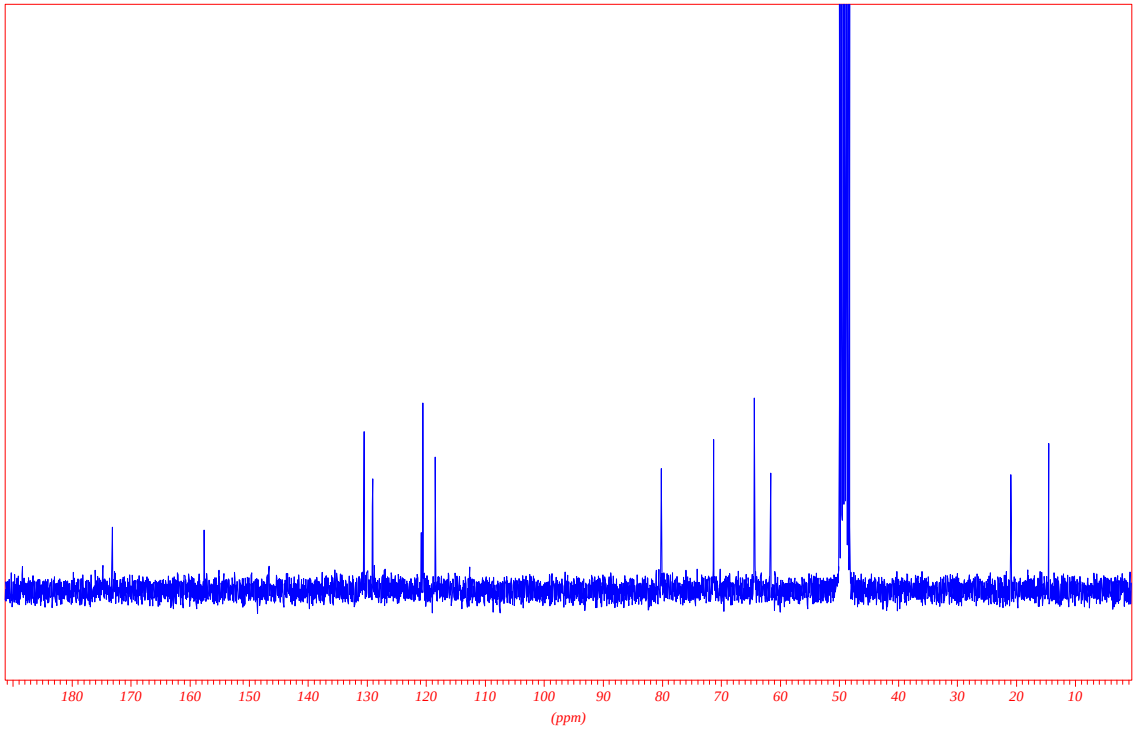
rau_C13CPD_1K MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 49

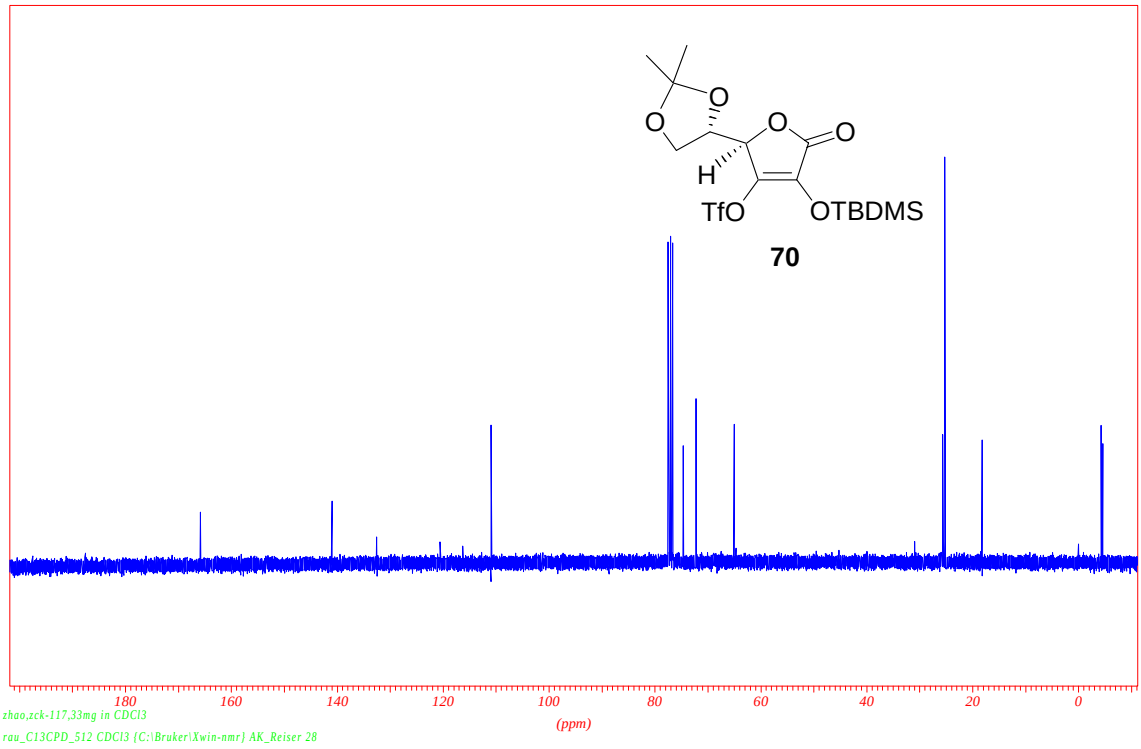


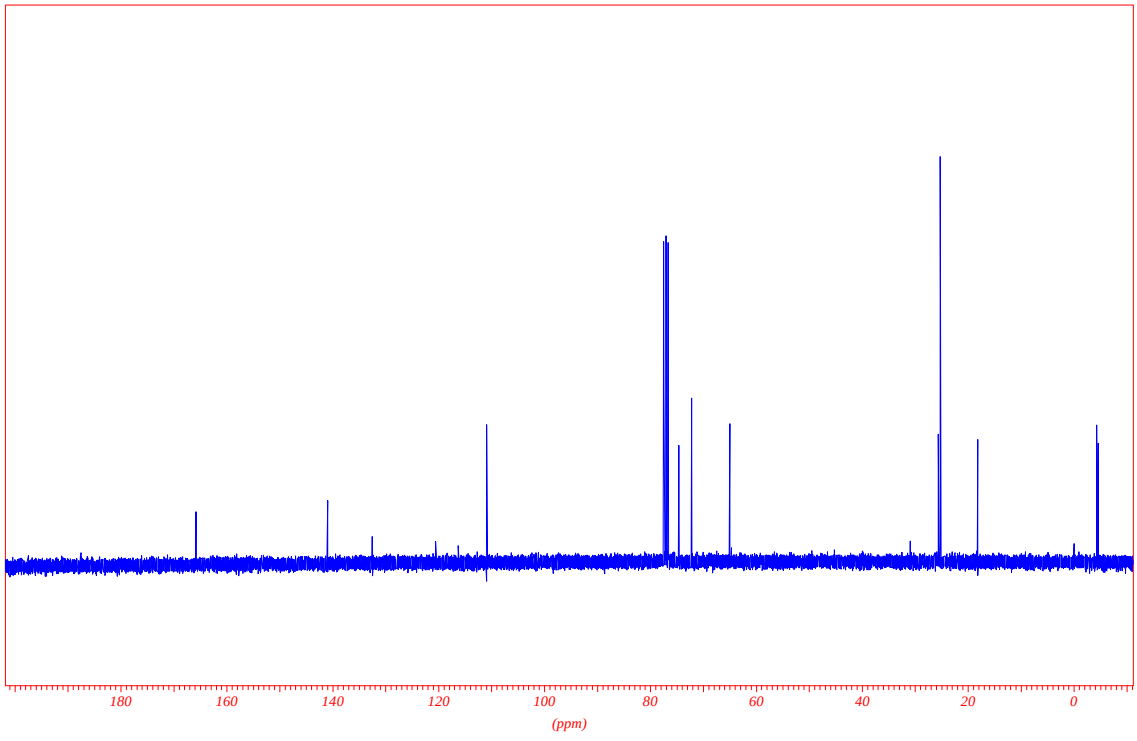
zhao,zck-133,52mg in CD3OD
rau_PROTONLF_16 MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 31

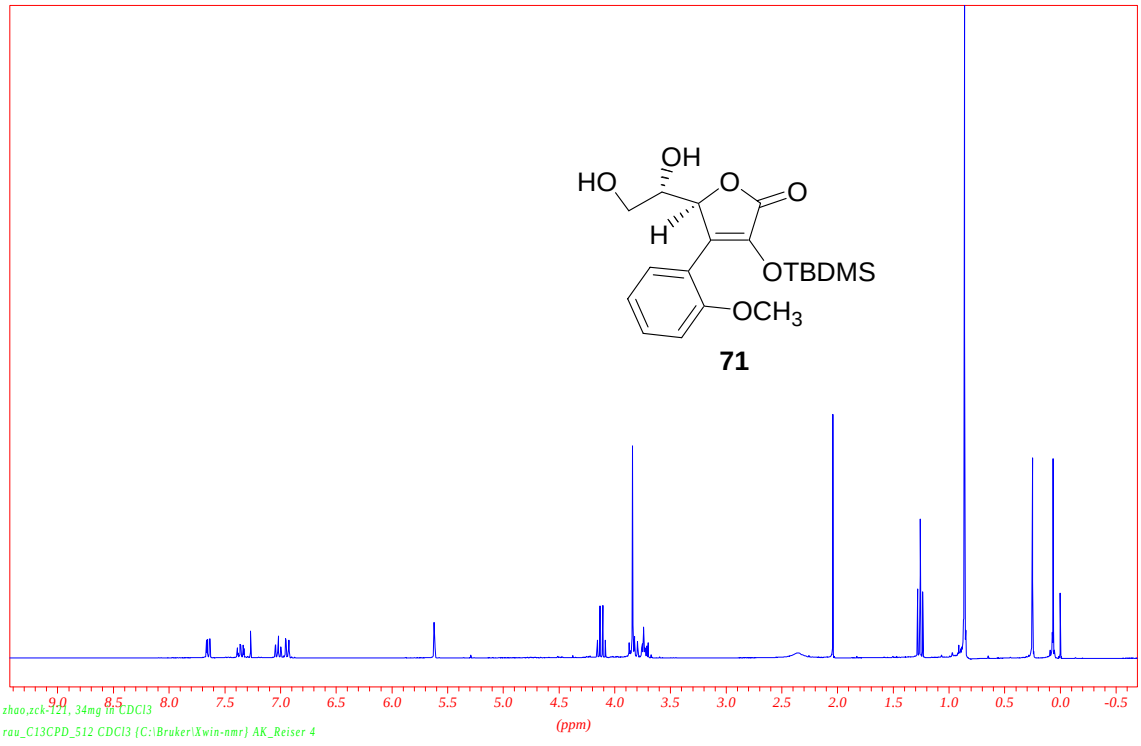


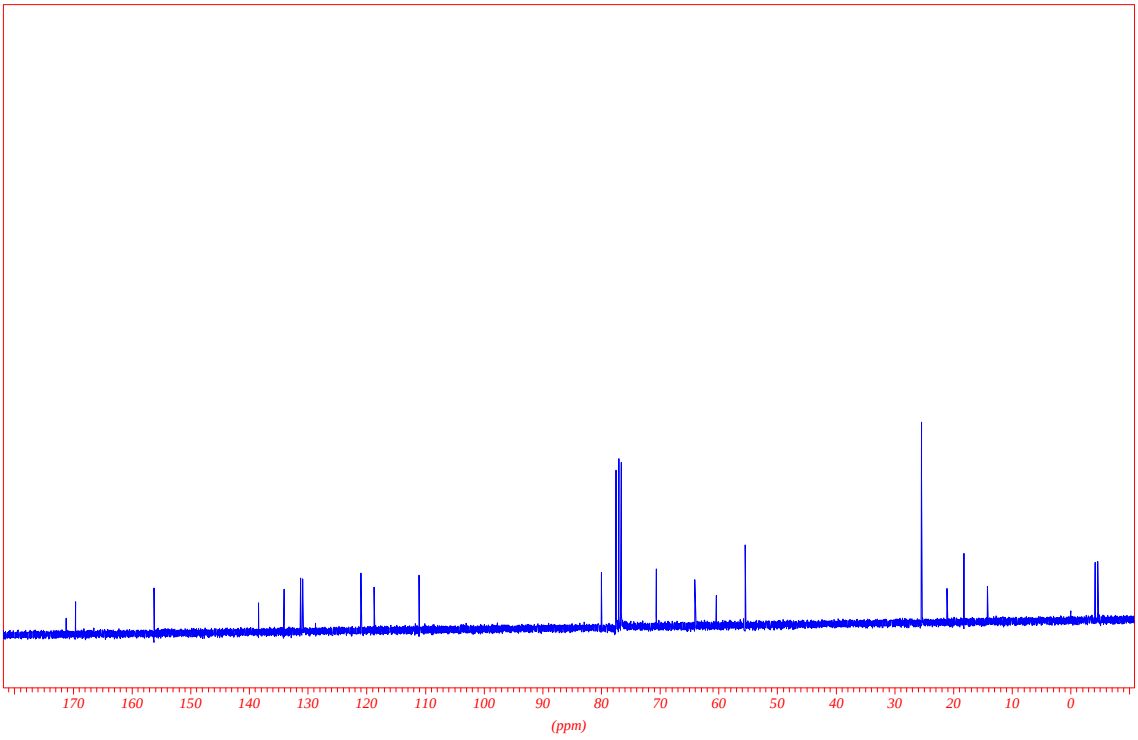
zhao,zck-133,52mg in CD3OD
rau_C13CPD_512 MeOD {C:\Bruker\Xwin-nmr} AK_Reiser 31




O
O
O
O
H
TfO
OTBDMS
70
180
160
140
120
100
80
60
40
20
0
(ppm)
zhao,zck-117,33mg in CDCl3
rau_C13CPD_512 CDCl3 {C:\Bruker\Xwin-nmr} AK_Reiser 28


180
160
140
120
100
80
60
40
20
0
(ppm)


OH
HO
O
O
H
OTBDMS
OCH3
71
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

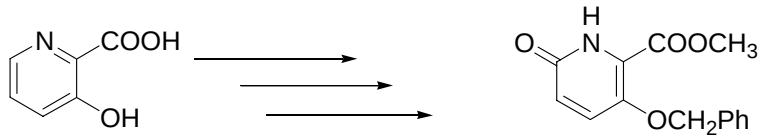
5 Summary

Two projects, one is the synthesis of chiral piperidine building blocks from substituted pyridines and the other is the synthesis of new Vitamin C analogues, were investigated in this thesis. In this thesis, the following results could be obtained:

Part 1:

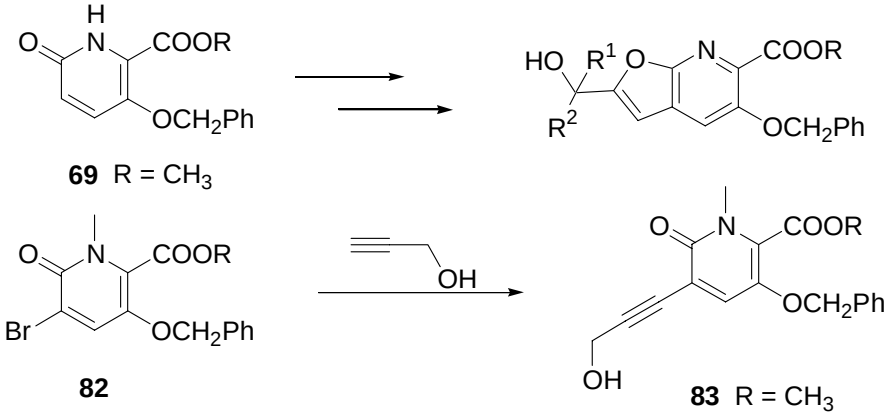
The aim of this project is to develop a new method towards the synthesis of chiral piperidine building blocks from available substituted pyridines. The following procedure was investigated in order to find a facile route.

Through esterification, benzylation, oxidation with m-CPBA and subsequent rearrangement reaction, 3-hydroxy-pyridine-2-carboxylic acid (**65**) could be converted to the key intermediate **69** in high yield.



65 **69**

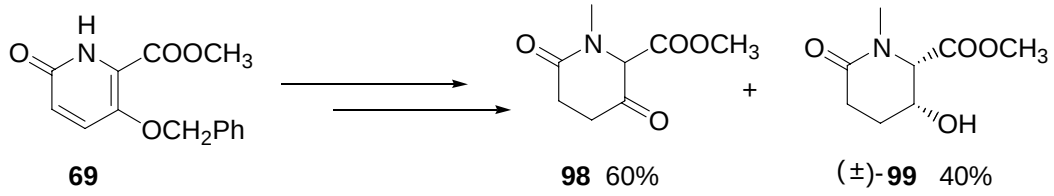
69 could be regional selectively brominated in 3-position, and the resulting compound could be furthermore coupled with propargyl alcohol in excellent yield in the presence of $Pd(PPh_3)_4$/CuI. In contrast, N-alkylated intermediate was also subjected to the coupling reaction, afforded the substituted pyridione **83** in good yields, but no cyclization was observed.



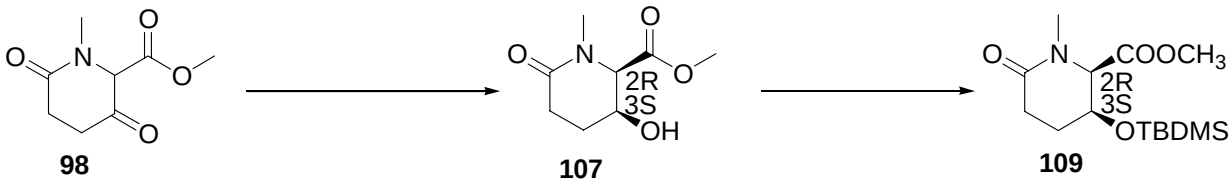
69 R = CH_3 **83** R = CH_3

82

69 could also be selectively N-alkylated to form **84**, which was easily hydrogenated under palladium/carbon to afford 2,5-piperidine-dione **98**, along with 3-piperidinol **99**.



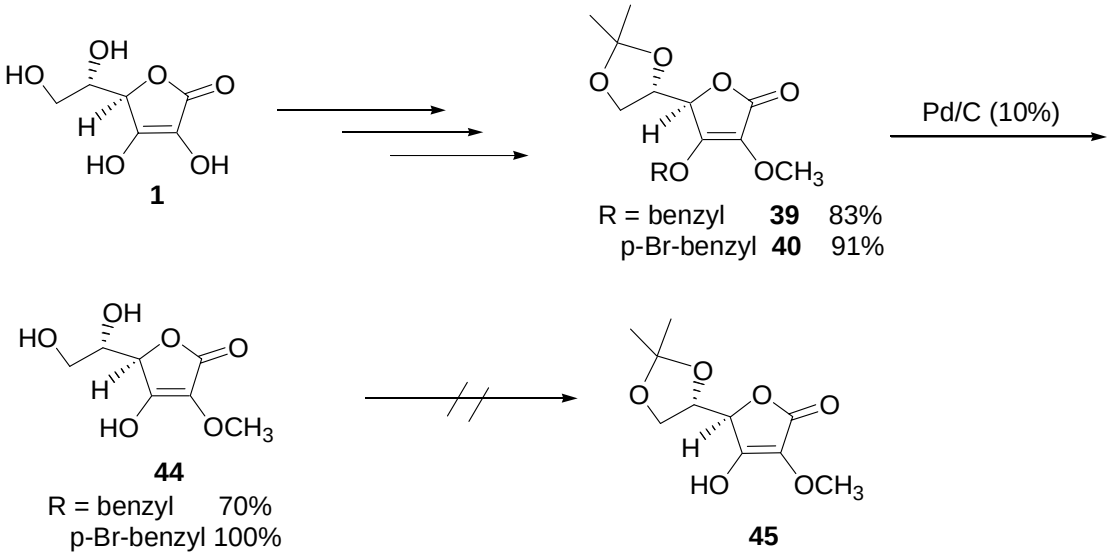
The β-keto ester **98** could be converted into a new chiral building block, (2R, 3S)-β-hydroxy ester **107**, which could be further transformed into another chiral building block **109**, upon treatment with TBDMSCl.



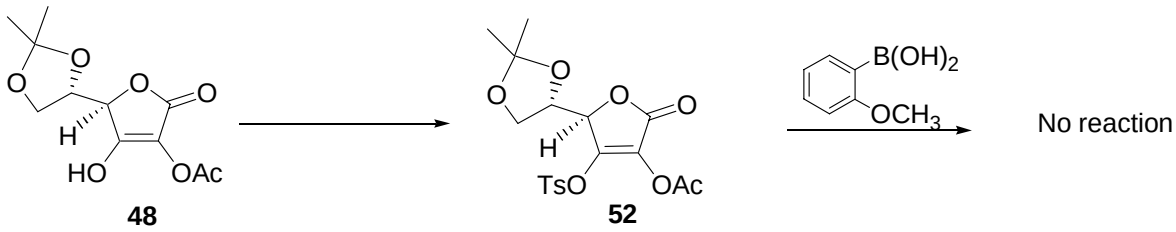
Part 2:

The aim is to develop a facile method to synthesize more stable Vitamin C analogues, which still have good antioxidant property.

Through selective protection 2,3,5,6-hydroxyl groups consequently, vitamin C **1** could be easily transformed into **39** and **40** in moderate yield. Upon hydrogenolysis of benzyl ethers in **39** and **40** catalyzed by palladium carbon, the 2-O-methyl-L-ascorbic acid (**44**) was obtained in excellent yield. However, the 5,6-O,O-acetal function group was also cleaved. Therefore, the corresponding triflate can not be obtained.

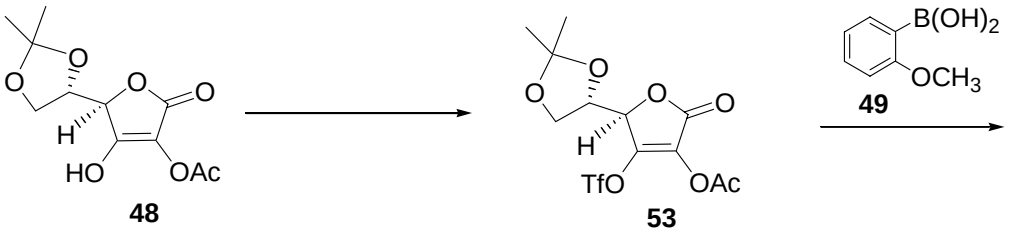


The tosylate **52** could also be easily obtained from 48 in good yield. However, **52** did no treact with 2-methoxy phenyl boronic acid **49** under the same condition as **53**.

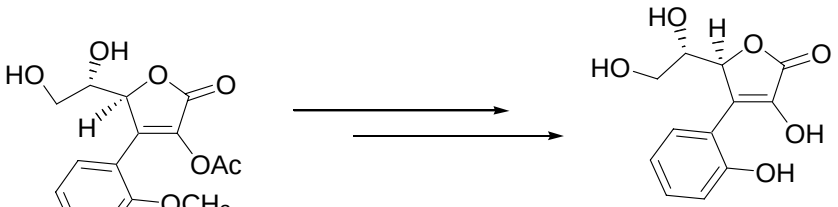


48 52

A new facile method for the synthesis of new Vitamin C analogue **24** was developed. After the regioselective protection for 5,6-diol from Vitamin C **1**, followed by the selective acetylation in 2-position, and subsequent triflation for the left 3-hydroxyl group, a key



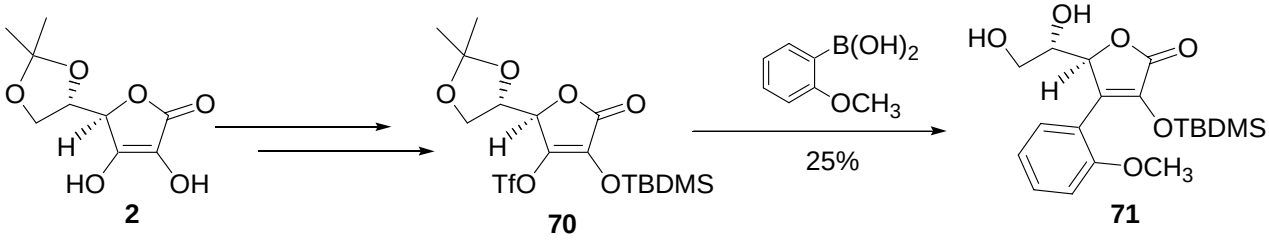
48 53



54 24

intermediate 3-triflate **53** was obtained in good yield. Then, after the Suzuki coupling reaction of **53** with 2-methoxy phenyl boronic acid **49** catalyzed by $Pd(PPh_3)_4/Ag_2CO_3$, and followed by the deacylation in 10% K_2CO_3, the resulting compound was finally demethylated upon treatment with BBr_3 in dichloromethane to afford the target compound **24** in good yield.

5,6-O-isopropylidene-L-ascorbic acid **2** could also be selective silylated in 2-position upon treatment with TBDMSCl and sequently converted into its triflate **70** in good yield, which could also couple with 2-methoxy phenyl boronic acid **49** to afford the desired compound, however, in only low yield (25%). This could be explained by steric hindrance between the bulky group (TBDMS) and 2-methoxyphenyl group.



2 70 71

6 Acknowledgement

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I want to thank Dr. T. Burgemeister, G. Stülher, A. Schramm, and F. Kastner for the testing of NMR spectra, G. Wandinger and his colleagues for the measuring of elemental analysis and Dr. K.K. Mayer, W. Söllner and J. Kiermaier for their measuring of MS spectra.

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