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Synthetic Efforts Towards the Total Synthesis of Furanolactone Cembranoids and Discovery of Antimicrobial and Anticancer Benzyloxylated Congeners

Dissertation

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Dedication

To God

To my dearest Papang Melecio

To my dearest Mamang Natividad

To my siblings Editha, Estrella, Alexander, Evangeline,

Tita and Narcisa

……..with love immortalized.

I have no patience with attempts to identify science with measurement, which is but one of its tools, or with any definition of the scientist which would exclude a Darwin, a Pasteur or a Kekulé. The scientist is a practical man and his are practical aims. He does not seek the ultimate but the proximate. He does not speak of the last analysis but rather of the next approximation. His are not those beautiful structures so delicately designed that a single flaw may cause the collapse of the whole. The scientist builds slowly and with a gross but solid kind of masonry. If dissatisfied with any of his work, even if it be near the very foundations, he can replace that part without damage to the remainder. On the whole, he is satisfied with his work, for while science may never be wholly right it certainly is never wholly wrong; and it seems to be improving from decade to decade.

— Gilbert Newton Lewis
***The Anatomy of Science* (1926), 6-7.**

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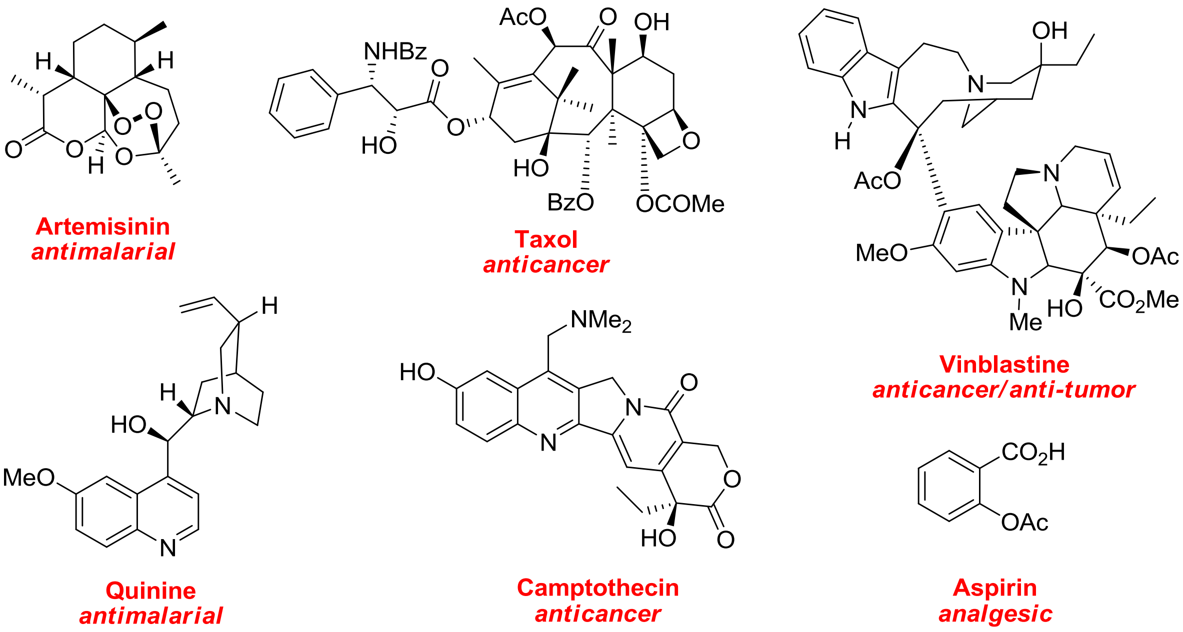
C. MAIN PART - DISCOVERY OF ANTIMICROBIAL AND ANTI-CANCER BENZYLOXYLATED KETOARYL ALDEHYDES AND 2-ARYLIMIDAZOLINES

A. INTRODUCTION

1. Harnessing Chemistry and Biology from Natural Product Structures

The mountains, the seas and even the microscopic hideouts remain as brewing pots for current pharmaceuticals and future drug candidates. Whether directly isolated from nature or chemically-transformed in the laboratory, these compounds are at the helm of being the source molecules for directed, knowledge-based medicinal chemistry. If secondary metabolites serve as biological guardians for plant and marine organism to ward off pathogens or insect predators, in humans, natural products are used to cure some of the deadly diseases. A variety of past and current bioactive compounds from plants can easily illustrate the point e.g. artemisinin, taxol, vinblastine, quinine, camptothecin and the salicylic acid-derived, aspirin. Many, if not, have been significant challenges to the synthetic chemist to prepare in the laboratory.[1]



Artemisinin *antimalarial*

Taxol *anticancer*

Vinblastine *anticancer/anti-tumor*

Quinine *antimalarial*

Camptothecin *anticancer*

Aspirin *analgesic*

Figure 1. Representative biologically active natural products.

The science of synthesis is a field that is vital to all areas of chemistry. It embraces the unique ability of chemists to create new reactions and to design molecules or molecular systems with a required (or predicted) set of properties. Explorations aimed at the synthesis of natural products has its origin in structure elucidation, which in decades prior to the dawn of modern physical and spectroscopic methods was accomplished by degradation and partial synthesis of chemical fragments or, in some cases, by the relay and/or total synthesis of the natural product itself. However, in spite of the modern techniques available to the natural products chemist, the complete stereochemical assignment of a novel metabolite on the basis of spectroscopic methods is still a challenging aspect. In such cases, organic synthesis continues to play a significant role in structure determination. Growing interest in natural products synthesis has also been propelled by the fact that many classes of important pharmaceutical agents isolated from natural products - lactam antibiotics, macrolide antibiotics, and steroid hormones are three illustrative classes of natural products that have given rise to important medicinal agents.[2] Fascination with the role that secondary metabolites play in regulating cellular and other biological processes continues to provide the stimulus for natural products synthesis, as well as research on the creation of small-molecule libraries and ultimately drug candidates based on natural product prototypes. In many cases, the amount of natural products available from natural sources is so limited that total synthesis is needed in order to provide material for further pharmacological evaluation.

As time progressed in the 20th century, the chemical community has witnessed the explosion of landmark and cutting edge advances in synthetic methods and strategies that have pushed the construction of biologically important complex molecular targets to be synthesized in the laboratory with minimal challenge.[3-5] With organic synthesis boasting a rich history and perpetual recognition, a practicing chemist on this field has within his grasp the possibility of being able to create nearly any target with enough time and effort. An important remaining puzzle is to achieve syntheses with heightened levels of efficiency. To tackle this concern, the formal conceptualization of “economies” in synthetic designs involving the ideas of atom-,[6] step-[7] and redox-economy[8] were spurred to streamline laborious synthetic sequences.

Parallel to this success thus came the resurgence of new technologies available for the discovery of chemical leads to counter the increasing demands for drugs against emerging and neglected diseases. Functional genomics studies has led to the unearthing of a record breaking number of potential therapeutic protein targets; combinatorial chemistry has stretched out the size of compound collections; and high-throughput screening (HTS) has enabled the screening of million-compound libraries. However, despite these breakthroughs, the number of hits entering development has remained more or less slow while pharmaceutical research productivity has continued to drop.[9] Evidently, there is a need for new strategies for the production of new chemical leads with a better rate of success in clinical development.

Fragment-based drug discovery is recognized recently as one of the stirring methods for lead generation. Fragments are small, low molecular weight molecules that usually form part of a natural product or biologically active compound. They are combined or optimized to generate lead compounds. Thus, during the past two years, fragment-based chemistry has caused a revolution in drug discovery by establishing a new route to lead compounds which have progressed into clinical trials.[10]

2. Organic Synthesis with Renewable Resources

The world is approaching a time where scarcity of petrochemical resources used to provide energy and chemical materials needed by the society is taking its toll. To address this dilemma, abundant biomass resources have been thought as promising alternatives for the sustainable supply of valuable, functionalized starting materials to the chemical industry (e.g. alcohols, aldehydes, ketones, and carboxylic acids) for manufacturing drugs and polymeric materials. In this perspective, the presence of highly oxidized functional groups in carbohydrates - the main compounds in biomass - poses an advantage over difficulties encountered to convert such functionality to organic fuels.[11]

Current chemical investigations have been focused on the production of platform chemicals to design consistently structured compounds as useful and versatile chemical building blocks. Such platform chemicals have been reported to be biologically and chemically fashioned from sugar. The building-block chemicals can be realized by subsequent transformation into a variety of highly important bio-based chemicals and materials. Building-block chemicals are defined as polyfunctionalized compounds that reveal a potential to be converted into new types of useful molecules. A well-reported method for the degradation of hyperfunctionality in carbohydrates is an acid-catalyzed process for the selective removal of functional groups and formation of defined building blocks.[12]

Furoic acid and furfuryl alcohol are among the monofunctionalized furan derivatives produced from furfural, a product of sugar dehydration.[13] Over the past years, significant contributions arising from the Reiser group have defined the use of these chemical building blocks in organic synthesis. A number of stereocontrolled synthetic approaches have been laid down towards various natural products and their building blocks,[14-20] as well as syntheses aimed at unnatural amino acids and peptides which are useful probes for secondary structure explorations and pharmacologic investigations.[21-24] Thus, a development of novel strategy for *trans*-annulated γ-lactone synthesis opened doors towards the first enantioselective total synthesis of the anti-cancer sesquiterpenoid arglabin™,[14] and accordingly, is a testament and shining achievement on the potential of furan derivatives in complex molecule synthesis.

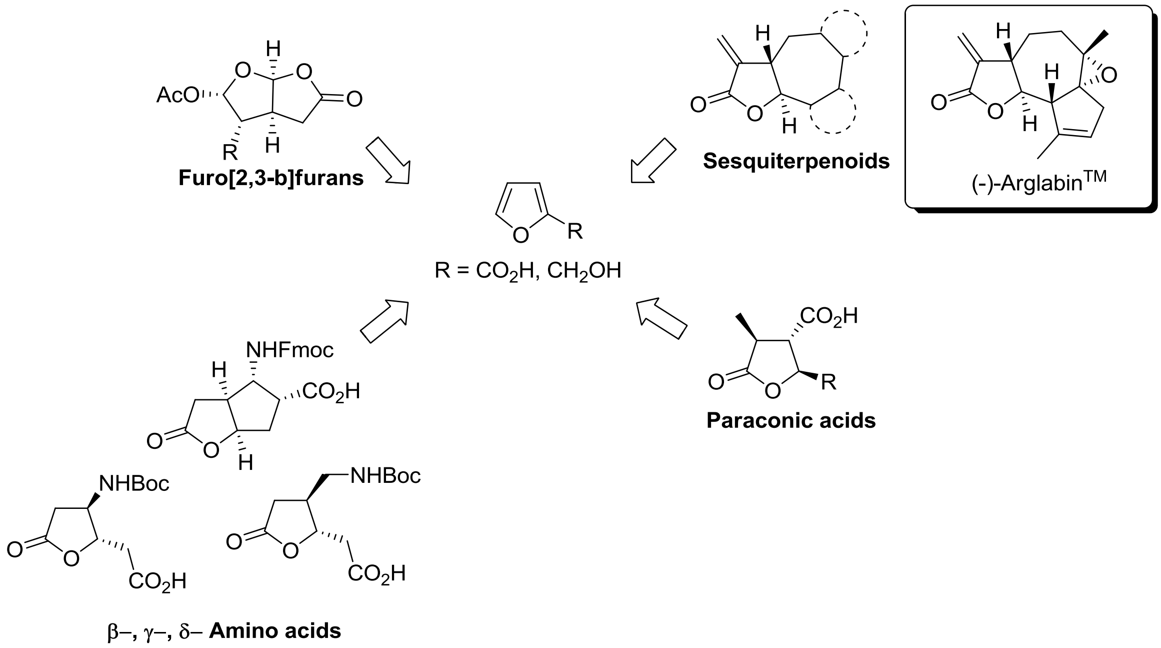


Figure 2. Several organic compounds derived from furan derivatives according to Reiser et al.

References

1. Lesney, M. S. *ACS Today's Chemist at Work*. **2004**, 26.
2. Roush, W. R. *J. Am. Chem. Soc*. **2008**, *130*, 6654.
3. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657.
4. (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley: New York, 1989. (b) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis: Targets, Strategies, Methods*; VCH: Weinheim; New York, 1996.
5. Newhouse, T.; Baran, P. S.; Hoffmann,R.W. *Chem. Soc. Rev.* 2009, 38, 3010.
6. (a) Trost, B. M. *Science* 1991, 254, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* 1995, 34, 259.
7. (a) Wender, P. A.; Croatt, M. P.;Witulski, B. *Tetrahedron.* 2006, *62*, 7505. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* 2008, 41, 40. (c) Wender, P. A.; Miller, B. L. *Nature* 2009, 460, 197.
8. (a) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* 2008, 130, 17938. (b) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* 2009, 48, 2854.
9. Bohacek, R. S.; McMartin, C.; Guida, W.C. *Med. Res. Rev.* **1996**,*16*, 3.
10. (a) Schulz, M. N.; Hubbard, R. E. *Curr. Opin. Pharm*. **2009**, *9*, 615-621. (b) Murray, C. W.; Rees, D. C. *Nature Chem.* **2009**, *1*, 187.
11. Román-Leshkov, Y.; Chheda, J. N.; Dumesic, J. A. *Science.* **2006**, *312*, 1933.
12. Bicker, M.; Hirth, J.; H. Vogel, *Green Chem.* **2003**, ***5***, 280.
13. Ulbrich, K.; Kreitmeier, P.; Reiser, O. *Synlett.* **2010**, 2037.
14. Kalidindi, S.; Jeong, W. B.; Schall,A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem. Int. Ed.* **2007**, *46*, 6361.
15. Weisser, R.; Yue, W.; Reiser, O. *Org. Lett.* **2005**, *7*, 5353.
16. Jezek, E.; Schall, A.; Kreitmeier, P.; Reiser, O. *Synlett.* **2005**, 915.
17. Nosse, B.; Bandichhor, R.; Jeong, W. B.; Böhm, C.; Reiser, O. *Org. Lett.* **2003**, *5*, 941.
18. Bandichhor, R.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem. Eur. J.* **2003**, *9*, 260.
19. Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315-1318.
20. Böhm, C.; Schinnerl, M.; Bubert, C. Zabel, M.; Labahn, T. Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955.
21. Haque, M. M. Ph.D. Dissertation, **2005**.
22. Bordessa, A. Ph.D. Dissertation, **2008**.
23. Delatouche, R. Ph.D. Dissertation, **2008**.
24. Sahr, F. *PhD Dissertation*. **2009**.

B. MAIN PART - SYNTHETIC STUDIES TOWARDS LACTONE-CONTAINING FURANOCEMBRANOIDS FROM FURANS

1. Isolation and identification of highly oxidized furanolactone cembrane diterpenoids from the octocoral genus *Pseudopterogorgia*

Gorgonian octocorals (phylum Cnidaria, order Gorgonacea) living in the Caribbean waters are inexhaustible machinery of chemically and biologically fascinating secondary metabolites.[1,2] Terpenoid natural products especially abound in number, and these include the sesquiterpenes, diterpenes, *bis*-diterpenes, steroids and carotenoids. [1,2]

The genus *Pseudopterogorgia* comprised of over 20 species are located in the West Indies region from Bermuda to the Bahamas, the Florida Keys, the Greater and Lesser Antilles, and the northern coast of South America to Brazil (Figure 1). They are best known as “sea plumes” based on their large, highly plumose and physically soft forms.[3] Species of this genus are well-known for the production of diterpenoids with complex molecular architecture that exhibit a wide array of biological activities including antibacterial, anti-inflammatory, antimalarial, and cytotoxic properties.[4]

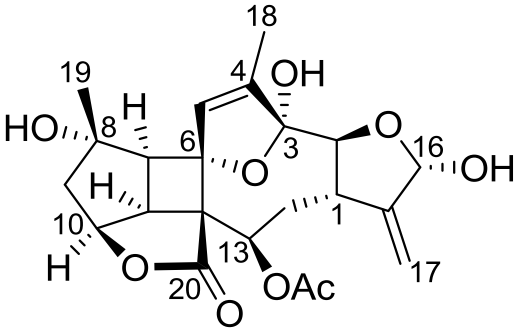
Figure 1. The Caribbean sea (photo credits from T. Laughlin, www.Shipdetective.com).

Pioneering studies on the marine natural product chemistry of *Pseudopterogorgia kallos* (Bielschowsky, 1918) (Figure 2) showed that it is a rich source of pseudopterane diterpenoids.[5] However, during 2003–2008 subsequent chemical inspection has demonstrated that this gorgonian species also contains several minor bioactive diterpenes that are based on highly distinct novel carbon frameworks.[6] Another noteworthy species that also mines structurally fascinating furan-based carbocyclic structures is *Pseudopterogorgia bipinnata* (Verrill, 1864) (Figure 2). This octocoral is well-known to contain cembranes, gersolanes and pseudopteranes which are also thoroughly investigated for their pharmacologic effects.[7]

Figure 2. The Gorgonian octocorals – *Pseudopterogorgia kallos* (left) and *Pseudopterogorgia bipinnata* (right) (photo credits from from Robert Fenner and Dr. Juan Armando Sanchez).

1.1 Bielschowskysin (1) from *Pseudopterogorgia kallos*[6c]

As a result of continuing explorations of the Rodriguez group (University of Puerto Rico) on marine invertebrate natural products chemistry of species from the West Indian region, they studied the extracts of *P. kallos* collected near the Old Providence Island located in the Southwestern Caribbean Sea in 2003. From this specimen, they were able to isolate and elucidate the highly oxygenated hexacyclic diterpene, bielschowskysin (**1**) (Figure 3). The structure is highlighted by a tricyclo[9.3.0.02,10]tetradecane ring system which was extensively established through spectroscopic evidences and single-crystal X-ray diffraction analysis. A distinguishing attribute of **1** is a *cis*-fused [5,5] oxa-bicycle as well as a dihydrofuran unit that is sometimes camouflaged as a 1,4 diketone moiety. Bielschowskysin is perhaps one of the most structurally daunting members of the furanocembranoid series due to its highly strained cage-like structure featuring a quaternary stereocenter in the tetrasubstituted cyclobutane which is also fused to a substituted oxocane ring. This skeletal carbocylic platform is unprecedented in the field of natural products. The X-ray crystal structure which defined only the relative configuration of 10 chiral centers were assigned as 1*S**,2*S**,3*S**,6*S**,7*S**,8*S**, 10*S**,11*S**,12*R**,13*R**.



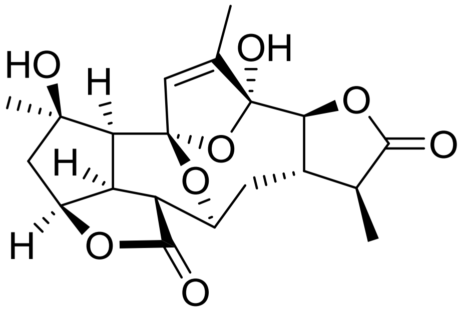
bielschowskysin (**1**)

Figure 3. Structure of bielschowskysin (**1**).

Terpenoid **1** was found to exhibit antiplasmodial activity (IC_{50} = 10 μg/mL) when tested against *Plasmodium falciparum*. Being able to prevent the growth of *P. falciparum*, **1** was also tested for anticancer screen using the NCI's *in vitro* cell-based assays. Thus, **1** was observed to display strong and specific *in vitro* cytotoxicity against the EKVX non-small cell lung cancer (GI_{50} < 0.01 μM) and CAKI-1 renal cancer (GI_{50} = 0.51 μM).

1.2 Verrilin (2) from *Pseudopterogorgia bipinnata*[8]

In accord to the interest of the Rodriguez group to discover new antituberculosis agent, they were able to isolate and identify verrillin (**2**) (Figure 4) from a Colombian collection of *P. bipinnata*. Verrillin is a hexacyclic diterpene associated in structure to some bipinnatins, but possesses a novel carbon skeleton. Since the bipinnatins and **2** were purified within the same source, the latter is assumed to be generated from a significantly different biosynthetic pathway that affords a novel cyclization pattern. Results of the structure elucidation paved the way towards the establishment of the relative stereochemistry of **2** with the tetrahydropyran ring and the eight-membered cyclic ketal having the chair and distorted crown conformation, respectively. In such conformation, verrillin (**2)** assumes an additional molecular stability *via* intramolecular hydrogen bonding between the C8 hydroxyl proton and the tetrahydropyran oxygen. Thus, the overall relative stereochemistry of **2** was assigned as *1S*,2S*, 3S*,6S*,7S*,8R*,10S*,11S*,12R*,13R*,15S**.



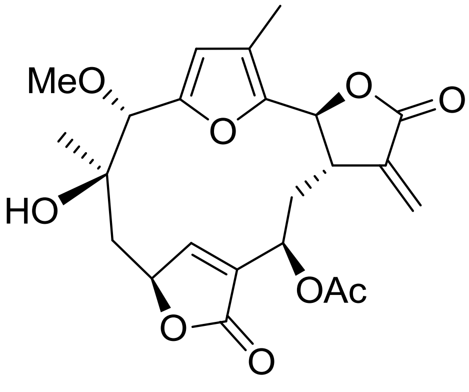
verrilin (**2**)

Figure 4. The structure of verrillin (**2**).

Verrillin (**2**) is characterized as a new class of regular diterpenes. The name verrillane was proposed for its structurally unique carbon framework. Although not yet proven, the carbobicyclic ring system appears to be produced by subsequent transannular cyclization of a suitable cembranoid precursor. The purification of both skeletal classes from the same specimen of *P. bipinnata* provides indirect support that the verrillane ring system could be synthesized *in vivo* by subsequent cyclization of the cembrane skeleton via a C7-C11 bond formation. In an *in vitro* colorimetric assay against *Mycobacterium tuberculosis* $H_{37}Rv$ at 6.25 μg/mL, diterpenoid **2** was found to be insignificantly proliferative.

1.3 Bipinnatin K from *Pseudopterogorgia kallos*[9]

A further chemical study of the terpenoid metabolites from the crude organic extract of the gorgonian octocoral *P. kallos* in 2008 has led to the isolation of bipinnatin K (**3**) (Figure 5) in addition to other six related furanocembranoid compounds. It is feasible that **3** might be an isolation artifact, and its presence in the crude gorgonian extract implies that the true natural product present in this animal bears a highly reactive furanyl epoxide array (as in **9**) that is susceptible to S_N2-type methanolysis at C7. Such a transient epoxide would also be the most plausible biogenetic precursor to the rearranged furanocembrane bielschowskysin (**1**). Compound **3** was also evaluated to exhibit inhibitory action against an acetylcholine-binding protein (AChBP) from *Aplysia californica*.



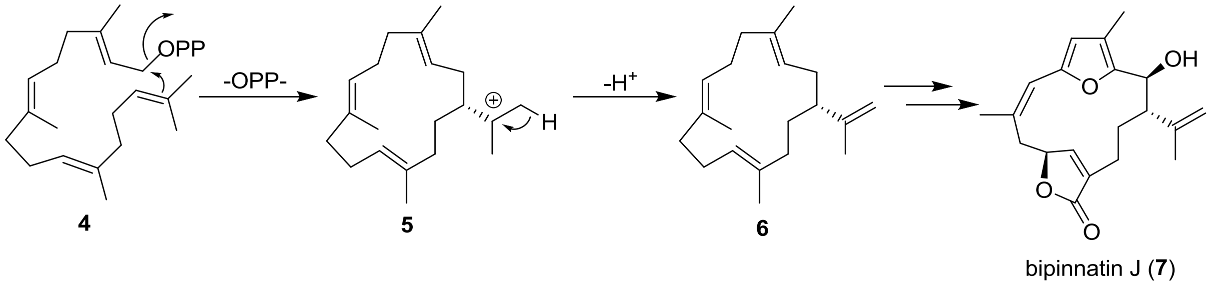
bipinnatin K (**3**)

Figure 5. *S*tructure of bipinnatin K (**3**).

2. Proposed Biogenetic Pathways for Oxidized Furanolactone Cembranoid Metabolites

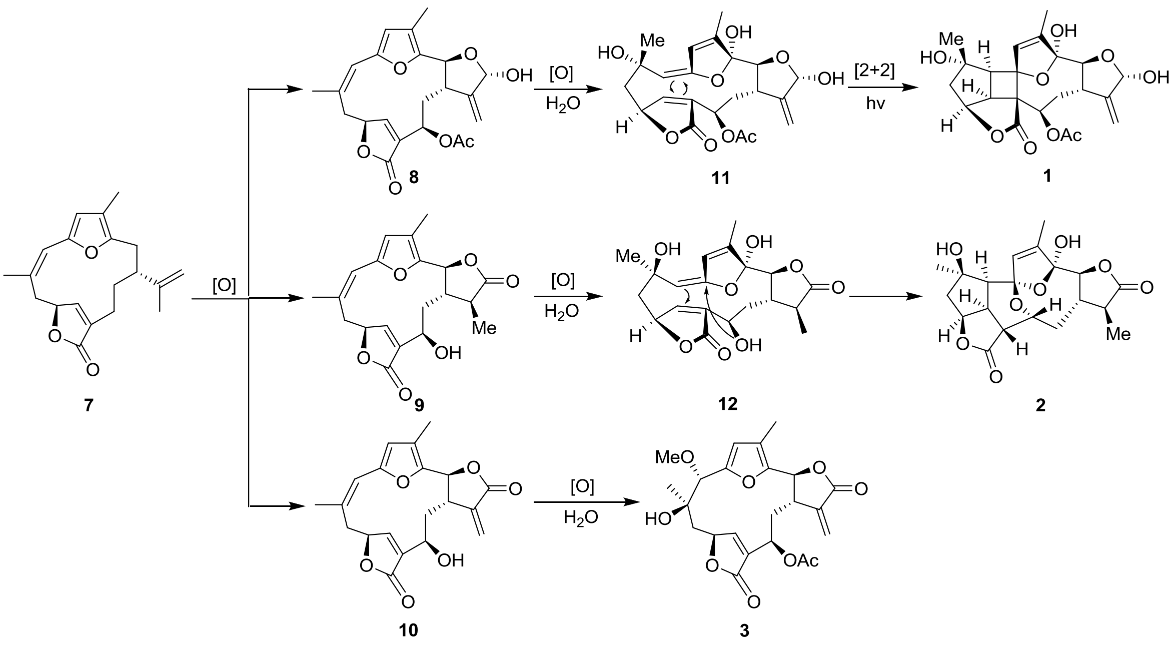
The furanocembranoids and their derivatives are structurally variegated natural products that not only display a wide variety of oxidation patterns but also display a highly diverse carbon skeleton.[9,10]

Their biosynthesis (Scheme 1) starts with a type A cyclization of geranylgeranyl diphosphate (**4**) to furnish the 14-membered macrocycle and yield a carbocation (**5**). At this point, the biosynthetic routes may vary depending on how the intermediary carbocation is trapped. In the case of the furanocembranoids, a simple loss of a proton from the isopropyl side chain affords the natural product neo-cembrene (**6**). From neo-cembrene **6**, a series of regioselective oxidations with concurrent cyclization of the furan ring, as well as a $\Delta^{7,8}$ double bond isomerization and an ensuing hydroxylation at C2 would afford bipinnatin J (**7**). Not much is known about the participating enzymes. Presumably cytochrome P450 monooxygenases are involved in the oxidative reactions. The oxidative opening of the furan ring, which is frequently observed in furanocembranoids and their derivatives, is another area of interest.[10]



Scheme 1. Biogenetic pathways to bipinnatin J (**7**) from geranylgeranyl pyrophosphate (**4**).

Biosynthetic speculations accounted for the formation of bielschowskysin (**1**), verrillin (**2**) and other related polycyclic furanocembranoid derivatives may involve enzymatic oxidations, and transannular (cyclo)additions (Scheme 2). It is can be presumed that these natural products ultimately originated from simple furanocembranoids such as rubifolide or bipinnatin J (**7**). The *exo*-alkylidene dihydrofuran intermediates **8, 9** and **10** are all likely intermediates in the biosynthesis of **1, 2** and **3**, respectively. These intermediates could be spawned by epoxidation of the $\Delta^{7,8}$ double bond, followed by ‘‘doubly vinylogous’’ hydrolysis,or by hydration of an ene-dione stemming from the oxidative opening of the furan moiety. It is important to mention that the biosynthetic pathways conferred in Scheme 2 are merely speculative. The exact steps under which most the proposed steps occur remain unidentified. The carbon-skeleton of bielschowskysin **1** is thought to be obtained *via* a transannular [2+2]-cycloaddition of **11**, which again comes from the opening of the benzylic epoxide by the furan ring. The proposed route to verrillin **2** involves the synthesis of the higher oxidized precursor **12**. Again epoxidation of the benzylic double bond induces the cascade, but this time a transannular 1,4-addition with acetal formation leads to verrillin **2**. The route to **3** may initially involve a regioselective epoxidation of $\Delta^{7,8}$ in **10** followed by a regioselective methoxide attack on the resulting oxirane.[10]



Scheme 2. Oxidative biogenetic proposals for **1-3.**

3. Aim of this study

Despite the large body of oxidized and highly functionalized furanocembranoids reported in the literature, relatively little synthetic work has been carried out until recently. A handful of research groups reported several synthetic explorations towards furanocembranoids that culminated in semi- and total syntheses. With attention given to compounds **1-3**, their total synthesis up to the present time has remained elusive. For the purpose of establishing their absolute configuration and further evaluation of their biological activity, studies aimed at their enantiocontrolled synthesis are wanting. Therefore, this study was designed to provide synthetic strategies towards **1-3**, especially for bielschowskysin (**1**).

This chapter is divided into two parts. The first part as outlined in Figure 6 is focused on three approaches aimed towards the enantiocontrolled construction of the northeastern segment of furanolactone cembranoid diterpenes **1-3** *via* intermediate **13** which is presumed to be a viable synthon for macrocyclic retron **14**. A common synthon for the first two approaches was a furan ester-derived cyclopropane carbaldehdehyde **15** which, after the addition of either nucleophiles **16** or **17**, and *retro*-aldol-lactonization sequences, leads to γ-substituted furan lactone of type **13**. The third approach features a Michael addition of furansiloxynitrile **18** to dimethylmaleate **19** which, after subsequent transformations involving enantioselective β-keto ester reduction and lactonization provided also *trans*-lactone **13**.

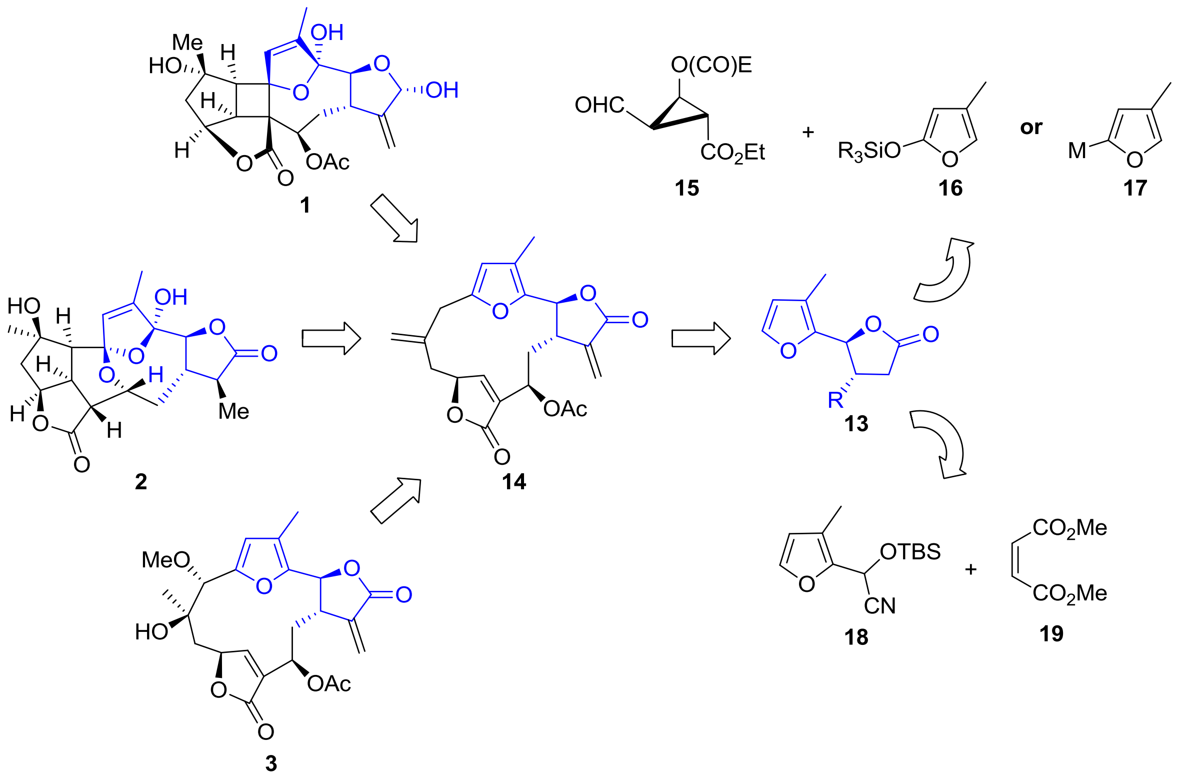


Figure 6. General retrosynthetic analysis of **1-3**.

The second part of the study was an attempt to explore a facile, simplified approach towards the total synthesis of bielschowskysin (**1**) as illustrated in Figure 7 starting (again) from furan derivatives such as furfuryl alcohol **20** and furan ester-derived cyclopropane **15**. The furfuryl alcohol **20** was proposed to undergo manipulations leading to olefinic ester **21** which is then subjected to photocycloaddition, methylenation and allylic oxidation to provide the western cyclobutane sector **22**. For the other side, Hosumi-Sakurai allylation of **15** followed by lactonization, homologation and allylic oxidation as key transformations was expected to deliver lactol carbaldehyde **23** for the eastern sector.

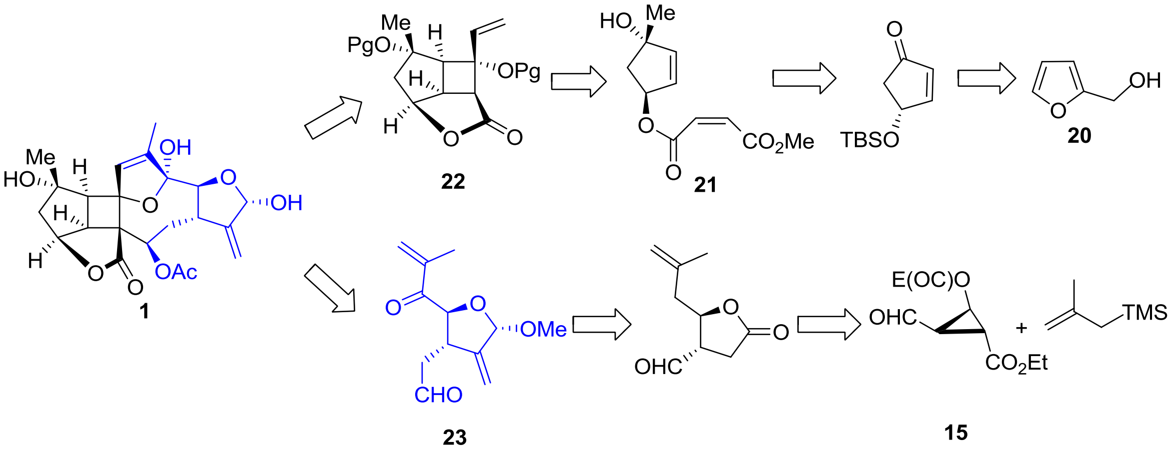
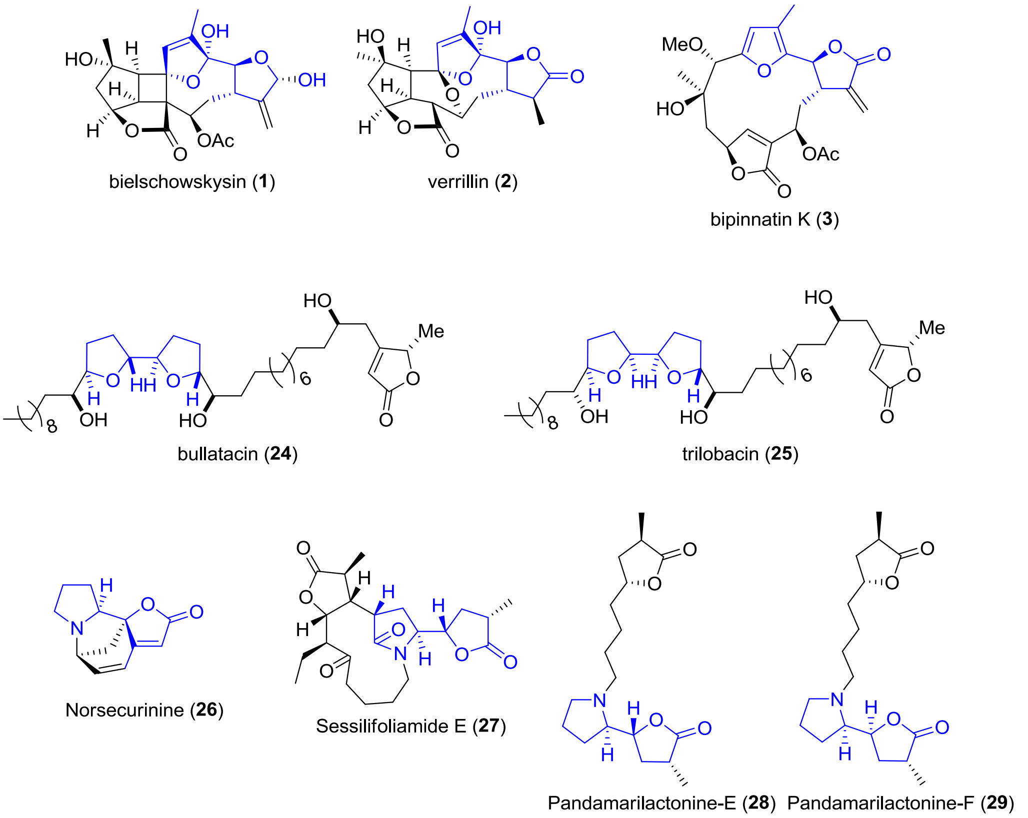


Figure 7. Retrosynthesis of bielschowskysin (**1**).

4. Stereoselective approaches towards the northeastern sectors of 1-3

4.1 Diastereocontrolled vinylogous Mukaiyama aldol addition of heterosiloxydienes to trifunctionalized cyclopropane 15

Adjacently linked five-membered heterocycles and γ-butyrolactone motifs are privileged substructures in a number of complex marine and plant natural products. These moieties are well-prominent in various furanocembranoid diterpenes (e.g. **1-3**)[6c,8,9] isolated from *Pseudopterogorgia* species, cytotoxic Annonaceous acetogenins (**24** and **25**)[11] and alkaloids from the genera *Securinega* (e.g. **26**),[12] *Stemmona* (e.g. **27**)[13] and *Pandanus* (e.g. **28** and **29**)[14]. The segments highlighted in the structures in Figure 8 feature *bis*-tetrahydrofuran motifs or, oxocane or azacane rings attached to a 4,5-disubstituted butyrolactol or butyrolactone.



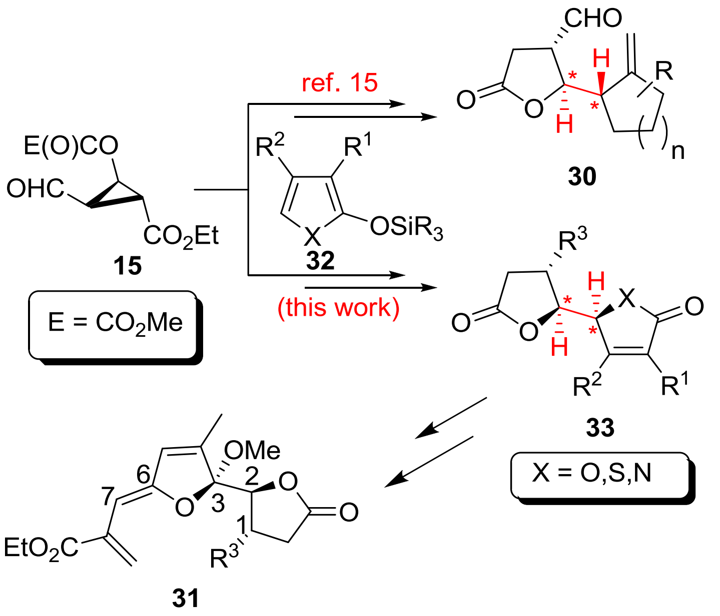
bielschowskysin (**1**) verrillin (**2**) bipinnatin K (**3**)

bullatacin (**24**) trilobacin (**25**)

Norsecurinine (**26**) Sessilifoliamide E (**27**) Pandamarilactonine-E (**28**) Pandamarilactonine-F (**29**)

Figure 8. Representative natural products with *bis*-heterocycle framework.

Previous investigations in the Reiser group demonstrated that addition of various siloxyenol ethers and allylsilanes to cyclopropyl aldehyde **15** from enantiopure cyclopropanated heterocyclic esters afford *anti*-addition adducts of the type **30** under high Felkin-Ahn 1,2 and 1,3-stereocontrol (Scheme 3).[15]



Scheme 3. Addition of silane and siloxy nucleophiles to cyclopropane **15**.

In accord to our interest in providing a suitable strategy to construct the northeastern segment(s) (ex. **31**) of furanolactone cembranoid natural products **1-3** from cyclopropane carboxaldehyde **15**, we first envisioned a vinylogous Mukaiyama aldol reaction (VMAR) with heterosiloxydiene **32** as a key step to build the *trans*-butanolide γ-butenolide moiety **33** (where X = O) (Figure 9). A butenolide could be pictured as a masked furan which can be afforded through DIBALH reduction at -78 ^{o}C[16] (ex. conversion of **33** to **34**). With a furan moiety, oxidative transformations[17] and carbon homologation reactions are possible *en route* **35** or **36**.

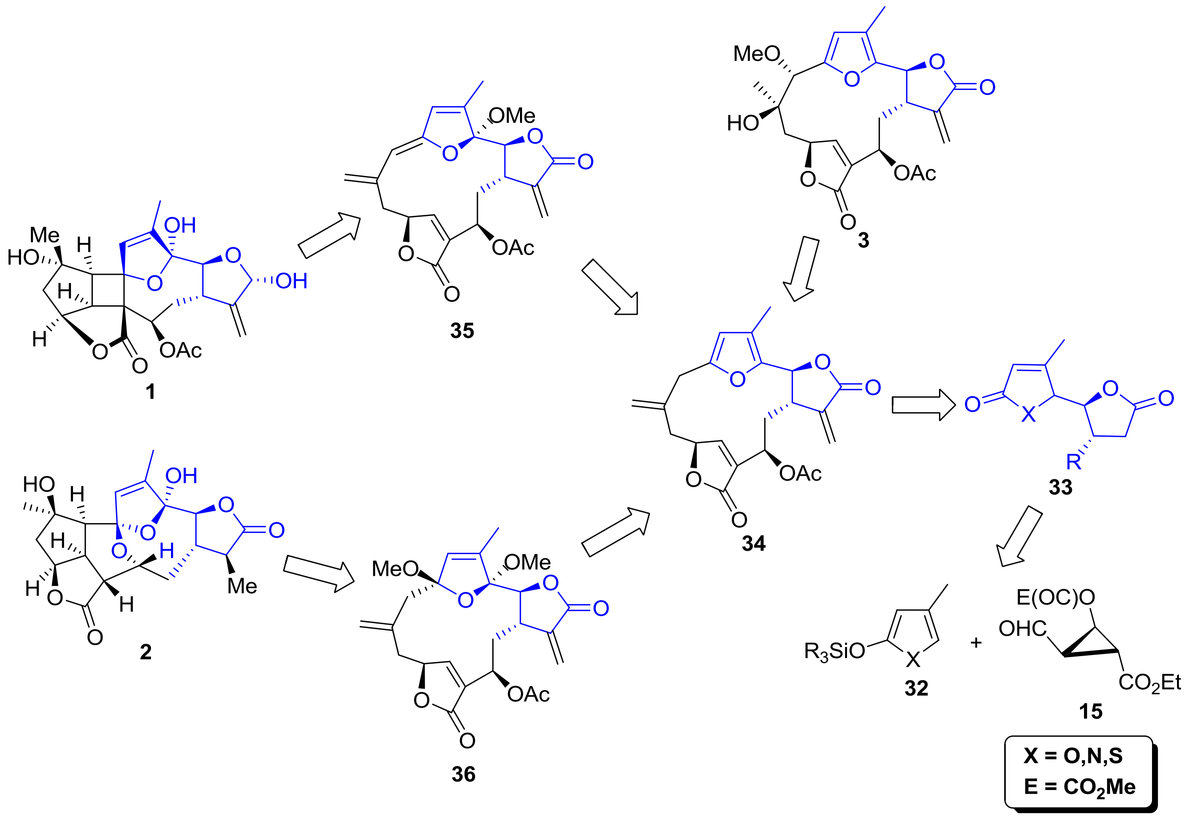
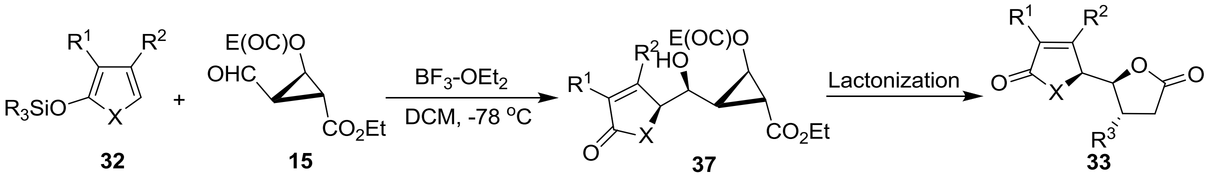


Figure 9. Retrosynthesis starting from a VMAR approach.

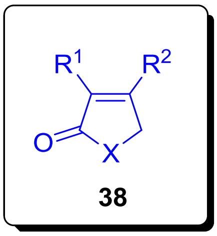
The general scheme for the synthesis of the γ-heterocyclic *trans*-lactone **33** is shown in Scheme 4. The sequence starts with VMAR of siloxydiene **32** and cyclopropane **15** which affords cyclopropane platform **37**, followed by an established lactone synthesis featuring a one-pot *retro*-aldol and lactonization reactions.[15b] To allow studies for the substrate scope of this methodology, various furanones including pyrrolidene and thiophenone-derived heterosiloxydienes were used for this purpose.



Scheme 4. General synthetic scheme for lactone **33**.

4.1.1 Synthesis of butenolide derivatives and N-Boc pyrrolidene

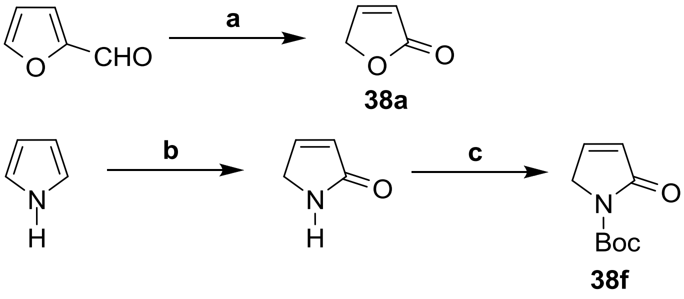
The synthesis of several 2-heterocyclic precursors **38** (Figure 10) were carried out as described in the literature by



X = O; R^1 = H; R^2 = H (**38a**)
X = O; R^1 = Me; R^2 = H (**38b**)
X = O; R^1 = H; R^2 = Me (**38c**)
X = O; R^1 = Ph; R^2 = Ph (**38d**)
X = O; R^1 = 4'-^{t}BuPh; R^2 = 4'-^{t}BuPh (**38e**)
X = *N*-Boc; R^1 = H; R^2 = H (**38f**)
X = S; R^1 = H; R^2 = H (**38g**)

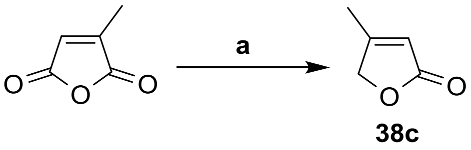
Figure 10. Siloxydiene precursors **38a-38g** for VMAR.

a) oxidative transformation from the corresponding aromatic heterocycle.[18]



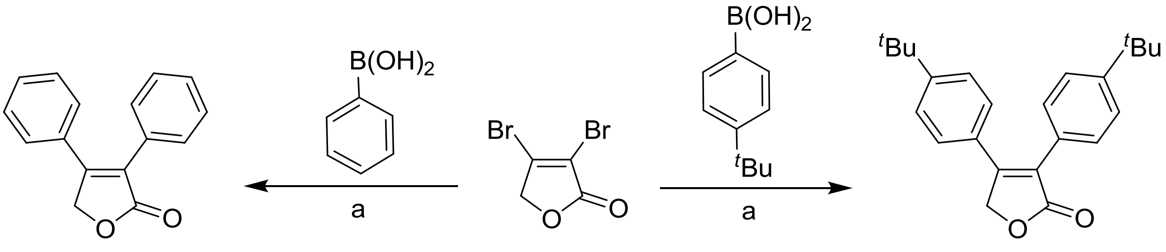
Scheme 5. Conditions. a) HCO_2H, 30% H_2O_2, *N,N*-dimethylethanolamine, reflux, 6 h, 23%; b) PbO_2, $BaCO_3$, 30% H_2O_2, H_2O, 4 h, reflux; c) Boc_2O, DMAP, MeCN, SiO_2,45 min, rt, 28% in two steps.

b) regioselective carbonyl reduction.[19]



Scheme 6. Condition: a) $NaBH_4$, THF, 1 h, 0 ^{o}C, 40%.

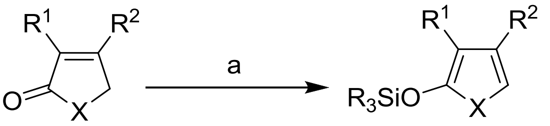
c) Suzuki-Miyaura arylation of α,β-dibromobutenolide.[20]



38d **38e**

Scheme 7. Conditions. a) 5 mol% $Pd(PPh_3)_2Cl_2$, TEBAC, CsF, H_2O-PhMe (1:1), 18 h, reflux, 64% (**38d**); 74% (**38e**).

The rest of the oxoheterocyclics were purchased commercially. The siloxydiene nucleophiles were prepared by deprotonation of oxoheterocycles **38a-38g** with triethylamine (TEA) followed by addition of either trialkylsilyl chloride (for **38a**) or trialkylsilyl triflate (TMSOTf or TBSOTf) (Scheme 8).[20]



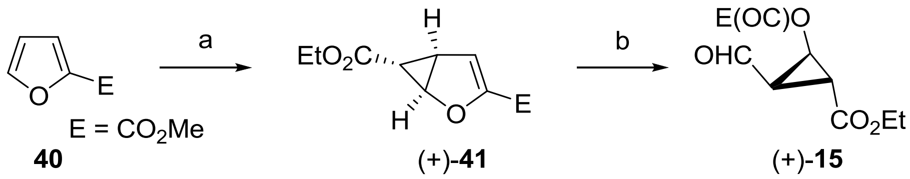
38a-38g **32a-32g**

Scheme 8. Heterosiloxydiene synthesis. Conditions: a) TMSCl or R_3SiOTf, TEA, DCM, 0 °C.

4.1.2 Synthesis of the cyclopropylcarbaldehyde

The gram-scale synthesis of the highly functionalized cyclopropane **15** from furan 2-carboxymethyl ester **39** has been previously described in the literature.[15b,21] The variety of chemical transformations possible with this scaffold has shuttled the birth of several synthetic applications towards natural product[14-18] and peptide synthesis.[22] Both cyclopropane enantiomers are easily afforded with high enantiomeric purity after iterative recrystallizations (>99% ee) of the resulting product from a two-step procedure.

The stereochemical fate of **15** derived- *trans* lactone is a consequence of reactions relying on asymmetric cyclopropanation with bis(oxazoline)-ligand (BOX) and Felkin-Ahn addition of nucleophiles.[21] Since a *4S, 5S* stereochemistry is desired (*1S,2S* in biogenetic numbering; see Figure 8 for reference), the *R,R*-isopropyl BOX-ligand derived from D-valine was used in the cyclopropanation procedure applied to **40** to afford (+)-**41** (Scheme 9).



Scheme 9. Cyclopropanation and ozonolysis: a) (i) ethyl diazoacetate (1.05 equiv), $Cu(OTf)_2$ (0.66 mol%), (+)-^{i}PrBOX ligand (0.92 mol%), $PhNHNH_2$ (0.82 mol%), DCM, 0 °C, 5 days; (ii) recrystallization (CH_2Cl_2, pentane), >99% *ee*, 45%; b) (i) O_3, DCM, -78 °C; (ii) DMS (2.50 equiv.), 16 h, -78 °C - rt, 89%.

The asymmetric induction observed for oxobicyclic (+)-**41** can be explained from the mechanistic proposals of Pfaltz[23] and Andersson[24] for the stereoselective cyclopropanation of alkenes. The reactive copper complex **42** (Figure 11) is thought to be approached by furan **40** at the less hindered region in such a way that steric repulsions with the isopropyl group are minimized which consequently drives a [2+1] addition of the carbene ethyl ester to the presumably more electron rich alkene moiety.

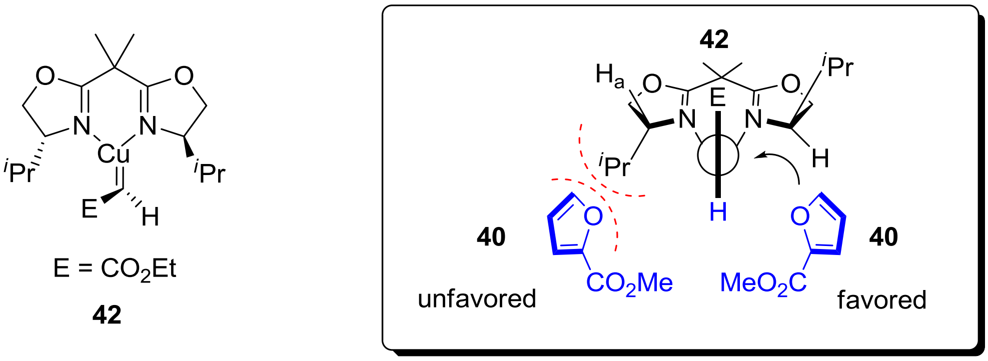
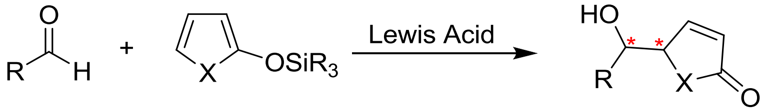


Figure 11. Mechanistic model for asymmetric cyclopropanation.

Finally, reductive ozonalysis of (+)-**41** provided cyclopropylcarbaldehyde (+)-**15** in 90% yield (Scheme 9). A white to very slightly yellowish solid product was afforded after treatment of the yellow syrup with diethyl ether. This two-step procedure can be scaled up to 50-100 g and the final product is stable for months when stored under nitrogen at -20 °C.

4.1.3 Vinylogous Mukaiyama aldol reaction (VMAR) of heterosiloxydienes to cyclopropane carboxaldehyde 15

Within the realm of carbon-carbon bond-forming reactions, the vinylogous Mukaiyama aldol reaction of heterocyclic silyloxy dienes to aldehydes and ketones which involves chirality transmittal from a chiral (racemic or nonracemic) carbonyl a^1-acceptor has been regarded as one of the powerful approaches to gain entry to highly functionalized β-hydroxylated carbonyl architectures. In addition to regioselectivity issues, the generation of two adjacent stereocenters at the γ-butenolide and at the C-OH positions also poses a challenging task (Scheme 10).[25] Several studies have been generated from the Casiraghi and Rassu laboratories that exploited, during the past decade, the addition of furan-, pyrrole-, and thiophene-based 2-silyloxy dienes with a variety of chiral pool-derived aldehyde synthons.[26]

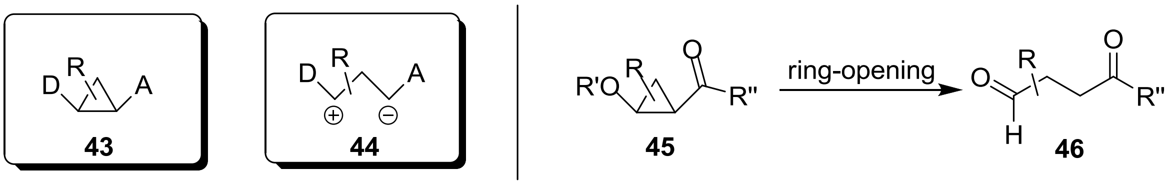


Scheme 10. Vinylogous Mukaiyama aldol reaction (VMAR).

Our investigation thus started by reacting trimethylsiloxyfuran (**38a**, entry 1) with cyclopropane (+)-**15** in the presence of BF_3•OEt_2 following the original protocol described for the addition of silane derivatives.[25] Boron trifluoride is an excellent Lewis acid which can effect very good yields and 1,4 stereoinduction.[15b] Based on the NMR spectra of intermediate cyclopropyl butenolide carbinol **37a-37g**, an almost complete conversion was achieved. Addition of other siloxydiene nucleophiles rendered no problems.

4.1.4 Synthesis of beta-substituted γ-(2-oxoheterocyclic)butyrolactones

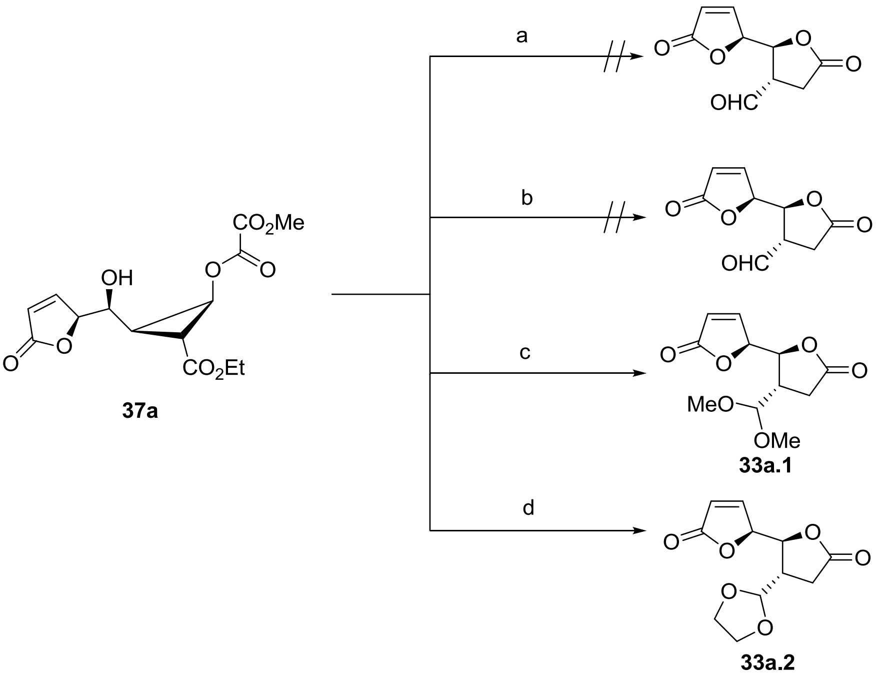
Aside from being small, strained organic fascination, cyclopropane derivatives have been utilized as versatile building blocks in a number of organic synthetic studies. Proper activation of the strained three-membered ring is a requirement, and generally, electron-donating or -accepting moieties are involved in their reactions to make polar reactions more favorable. Cleavage or enlargement of rings may then occur under relatively mild conditions. Nevertheless, synthetically useful aspects of these transformations most frequently involve precursor cyclopropanes containing functional groups that often ease out the rearrangement and allow further chemistries of the products obtained. Cyclopropane derivatives adorned with donor and acceptor groups are particularly amenable for synthetic operations, since electronic effects of these substituents assure activation of the cyclopropanes and a high versatility of the products after ring cleavage. Vicinally donor-acceptor-substituted cyclopropanes (**43**) serve as 1,3-dipolar synthon in many synthetically valuable transformations. Since the two charges of synthon **44** are in 1,3-relationship, many reactions utilizing **43** may be regarded as reactions involving a formal *umpolung of reactivity* and, therefore, often afford products not easily accessible by alternative methods. Most of the acceptor groups applied in a majority of studies reported in the literature are carbonyl groups, and therefore, most of the donor-acceptor cyclopropanes (D-A cyclopropanes) can be described by general structure **45** (Scheme 11). The simplest ring cleavage products of type **46** are very useful intermediates due to the 1,4-distance of the two carbonyl groups.[27]



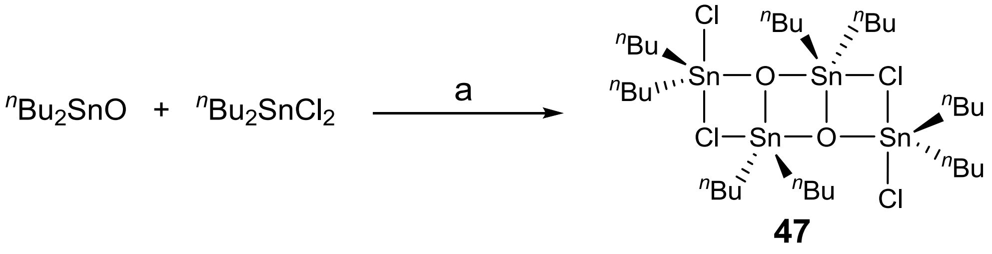
Scheme 11. Donor-acceptor cyclopropane structure and chemistry.

It was previously reported that unpurified allylated cyclopropyl carboxaldehydes such as **15,** can be smoothly transformed into functionalized γ-lactones. Barium hydroxide-assisted cyclopropane ring cleavage and lactonization yields a *trans*-lactone β-aldehyde. Alternatively, Otera's tin(IV) catalyst-facilitated ring opening followed by acetalization with 1,2-ethanediol or methanol could also provide protected aldehydes in good yields.[15,21,28]

Several lactonization conditions were evaluated to prepare the desired oxoheterocyclic lactones (Scheme 12). Treatment of **37a** with $Ba(OH)_2.8H_2O$ and TEA, produced substantial decomposition as evidenced by a number of spots on TLC. When an Otera tin catalyst **47** (see Scheme 13 for preparation) was used, the methanol or ethylene glycol protected aldehyde **33** was yielded. A slightly lower yield was obtained for the methyl acetal **33a.1** compared to the 1,2-dioxolane derivative **33a.2** (entry 3) with good diastereoselectivity. Hence, ethylene glycol was decided as the protecting alcohol. To check the effect of changing the silyl component in reaction diastereoselectivity, the TMS group was switched to a bulky TBS. An improvement in the selectivity was observed for **33a.2** (*dr* 99:1 entry 4).

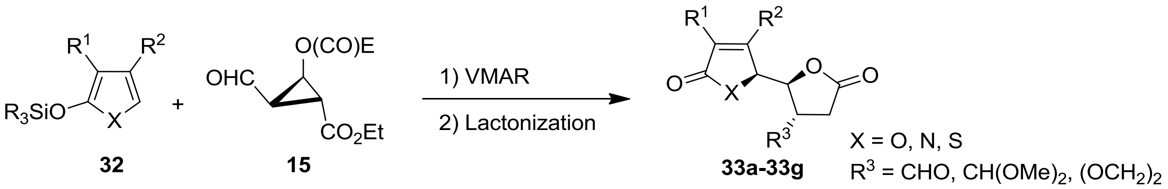


Scheme 12. Lactonization of **37a** under a variety of conditions. a) $Ba(OH)_2.8H_2O$, MeOH, 0 °C, 2 h; b) TEA, DCM, 0 °C, 2 h; c) 5 mol % cat. **47**, MeOH, reflux, 12 h, 38%; d) 5 mol % cat. **47**, ethylene glycol, PhMe, reflux, 12 h, 40%.



Scheme 13. Synthesis of Otera tin catalyst **47**. a) Benzene, reflux, 12 h, 90%.

Table 1. Ketoheterocycle-Lactone **33** synthesis from sequential VMAR and *retro*-aldol – lactonization cascades



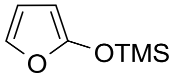
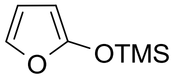
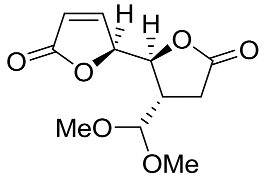
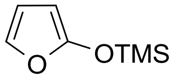
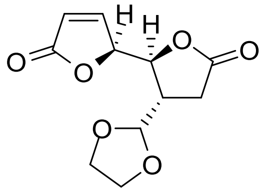
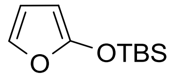
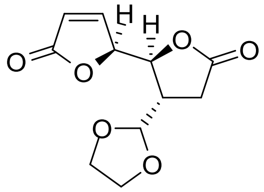
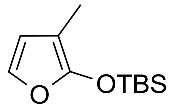
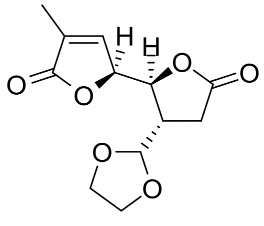
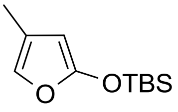
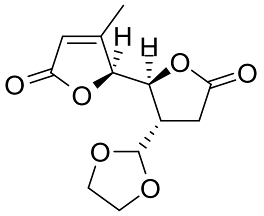
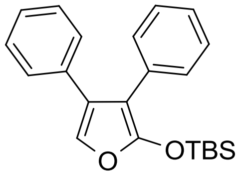
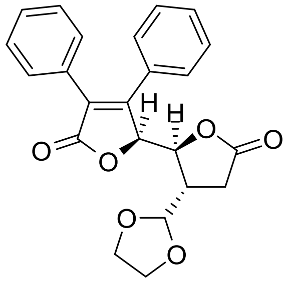
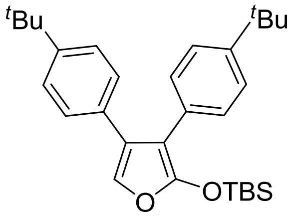
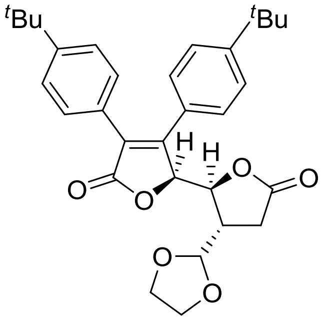
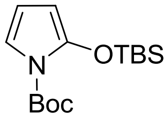
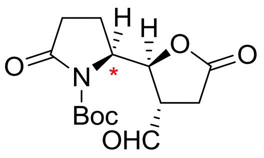
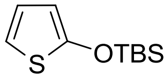
Entry	Heterosiloxydiene **32**	Lactonization Reagent	Lactone **33** Structure	Isolated Yield (%)	*dr*^{d,e}
1	 **32a**	A	-	-	-
2	 **32a**	B	 **33a.1**	38	83:17
3	 **32a**	C	 **33a.2**	40	86:14
4	 **32a**	C	 **33a.2**	40	99:1
5	 **32b**	C	 **33b**	44	87:13

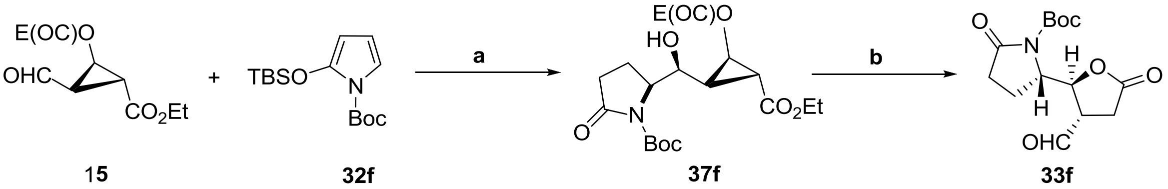
Table 1 continuation...........

6	 **32c**	C	 **33c**	65	>99
7	 **32d**	C	 **33d**	42	91:9
8	 **32e**	C	 **33e**	50	90:10
9	 **32f**	A,C	 **33f**[b]	43[c]	91:9
10	 **32g**	A or C	-	-	91:9[f]

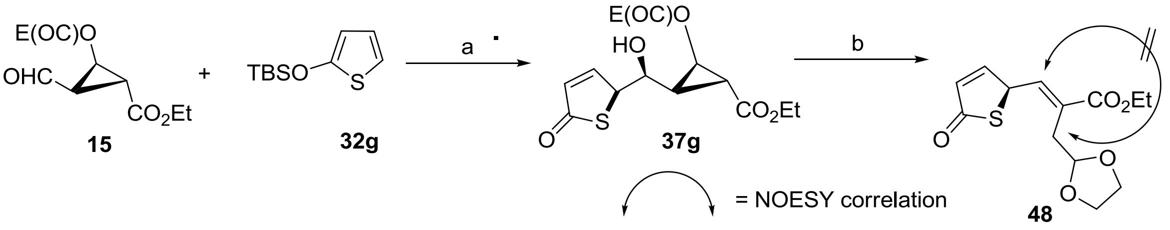
[a]A: $Ba(OH)_2.8H_2O$; B: catalyst **47** (5 mol %), MeOH, reflux, 12 h; C: catalyst **47** (5 mol %), ethylene glycol, PhMe, reflux, 12 h. [b]C5' stereochemistry is arbitrary. [c]Performed after conjugate reduction with Pd/C, NaOAc, THF; Yield after three steps. [d]Ratio of *4S,5S,5'S* and *4S,5S,5'R* diastereomers. [e]Determined by ^1H NMR integral analysis. [f]Determined from the ^1H NMR spectrum of crude cylopropane thiophenone carbinol **37f.**

Having established the reaction sequence (TBS and ethylene glycol as enol and aldehyde protecting groups, respectively), several substituted siloxylated furan nucleophiles including a *Boc*-protected pyrrole and thiophene were further investigated for the substrate scope experiments (Table 1, entry 5-10). Good to moderate yields (38-65%) were obtained for **33a-33f** with good to excellent diastereoselectivity (*dr* 84-99). In general, moderate to good yields were obtained.

Due to the instability of cyclopropane pyrrolidenone **37f** under method C conditions, a sequence involving conjugate reduction (H_2, Pd/C) and barium hydroxide/MeOH lactonization (entry 9) was carried out to give pyrrolidenone lactone β-carbaldehyde in moderate yield (Scheme 14). Thiophenone cyclopropane **37h** was not stable in any of the lactonization reagents employed (entry 10). Purification of the major product (9%) obtained using condition C was identified to be an elimination compound **48** (Scheme 15).

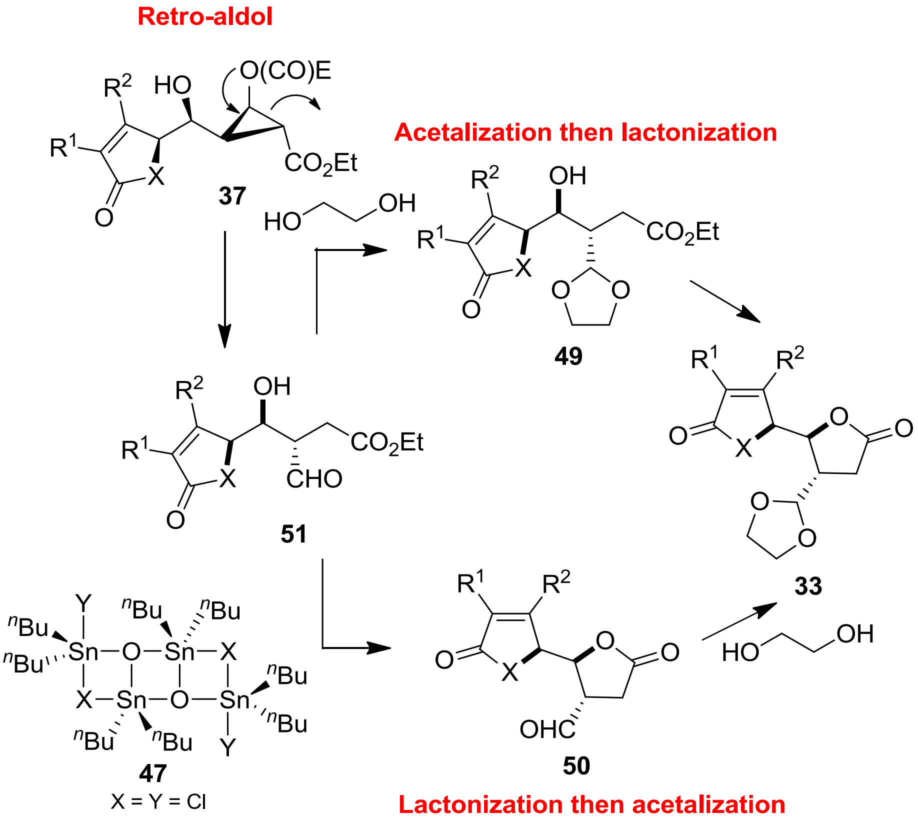


Scheme 14. Synthesis of Lactone **33f**. Conditions: a) i. BF_3-OEt_2, DCM, -78 °C, 16 h (93%); ii. H_2 (1 atm), NaOAc, THF, 24 h, quantitative; b) $Ba(OH)_2.8H_2O$, MeOH, 0 °C, 2 h, 43%.



Scheme 15. VMAR and attempted lactonization of **37g**. Condition: a) i. $BF_3•OEt_2$, DCM, 78 °C, 16 h (95%); b) catalyst **10** (5 mol %), ethylene glycol, PhMe, reflux, 12 h, 9%.

Large scale preparation of lactone **33c** yielded two other minor products. LC-MS examination showed molecular ions (M^+ = *m/z* 300; M^+ = *m/z* 210) which can be directly corroborated to intermediates **49** and **50** (Scheme 16). This only suggests that *retro*-aldol product **51** enters into two different pathways prior to the formation of the end product **33c** – one being the acetalization-lactonization sequence and the other being the lactonization-acetalization sequence where the latter is more favored due to the separation of considerable amounts of semi-pure intermediate **50** (about 4%).



Scheme 16. Plausible Otera tin-catalyzed lactonization pathway *en route* lactone **33**.

4.1.5 Establishment of stereochemistry of the oxoheterocyclic butyrolactones

In relation to previously reported stereoinductions under BF_3-catalyzed Mukaiyama addition of siloxyenol ethers to **15**, the expected *trans*-4,5-disubstitution in the butyrolactone moiety was also observed. This finding was ascertained by the absence of a spatial correlation between H4 and H5 and the presence of a long distance correlation between the acetal proton and H5 in the NOESY spectrum (Figure 12).

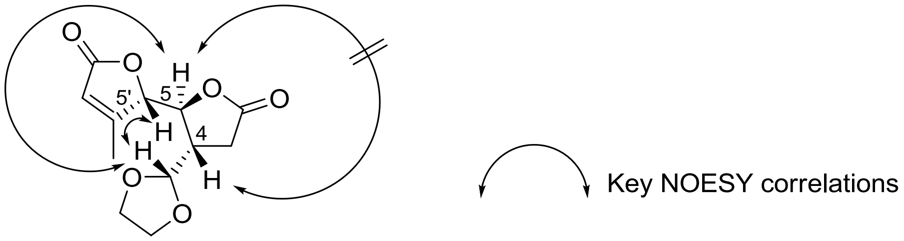


Figure 12. NOESY correlations in lactone **33c**.

The C5’ butenolide configuration was established based on single X-ray crystal structure of **33c** (Figure 13) and chiro-optical ellipticity evidences. The absolute configuration at C5 of butenolides can be readily and unequivocally established from the CD spectrum. It can be directly correlated to the sign of the n-π^* and π-π^* Cotton effect (Figure 14). The validity of the helicity rule has been observed for simple 2(5H)-furanones substituted at C5 and to products of various VMAR-related studies.[29]

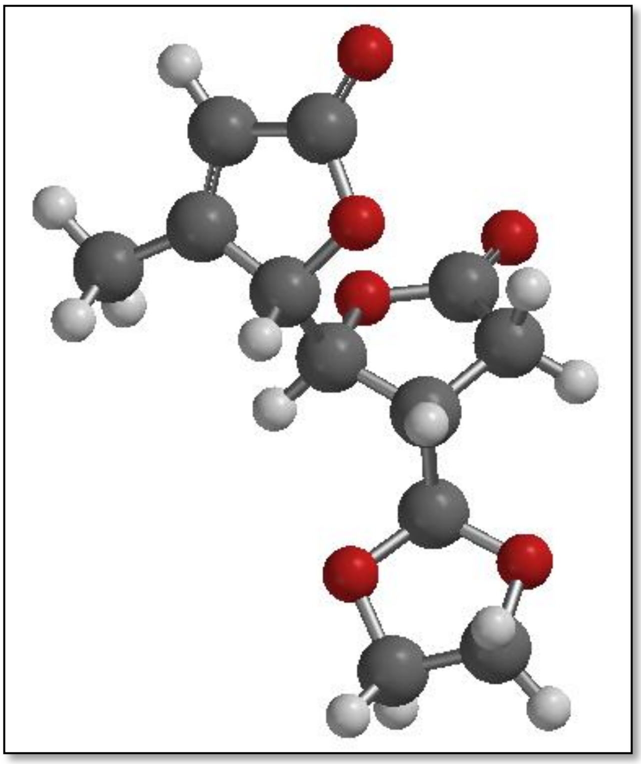


Figure 13. Single X-ray crystal structure of **33c**.

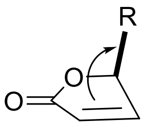
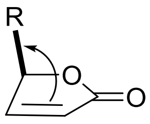
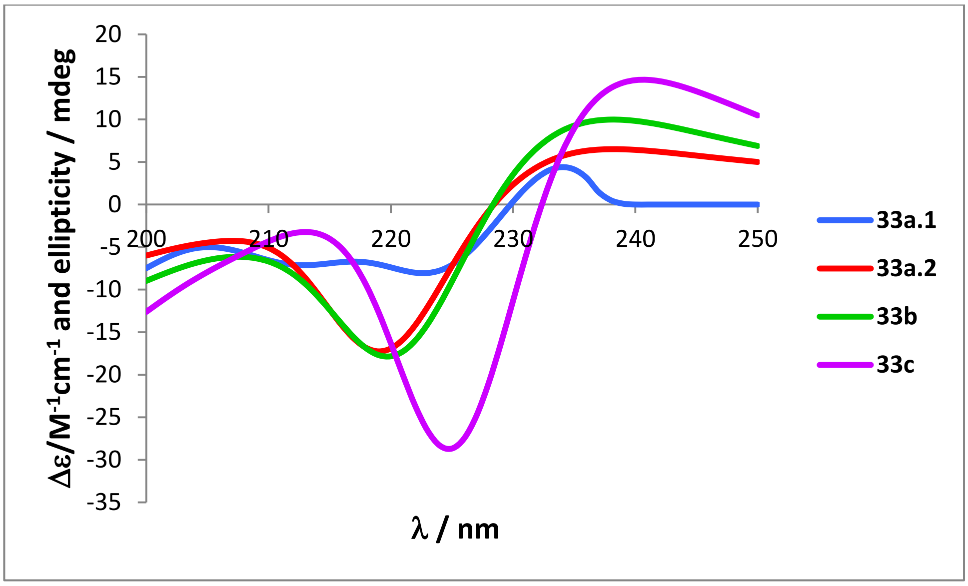
	 **P**	 **M**
n- π * (235 - 250 nm)	Δε < 0	Δε > 0
π-π* (200 – 215 nm)	Δε > 0	Δε < 0

Figure 14. Correlation of butenolide hellicity with molar ellipticity values and absorption wavelengths.

As reflected in the CD spectrum of **33a-e** in MeOH (Figure 15), the butenolide lactones display negative and positive Cotton shifts for the π-π* and n-π* transitions, respectively, which is readily ascribable for derivatives with C5'*S* stereochemistry exhibiting M helicity. Noteworthy, the 2,3-diaryl butenolides produced bathochromic shifted bands associated to π-π*. The shift is presumably caused by the increased conjugation between the aryl rings and the α,β-unsaturated system.



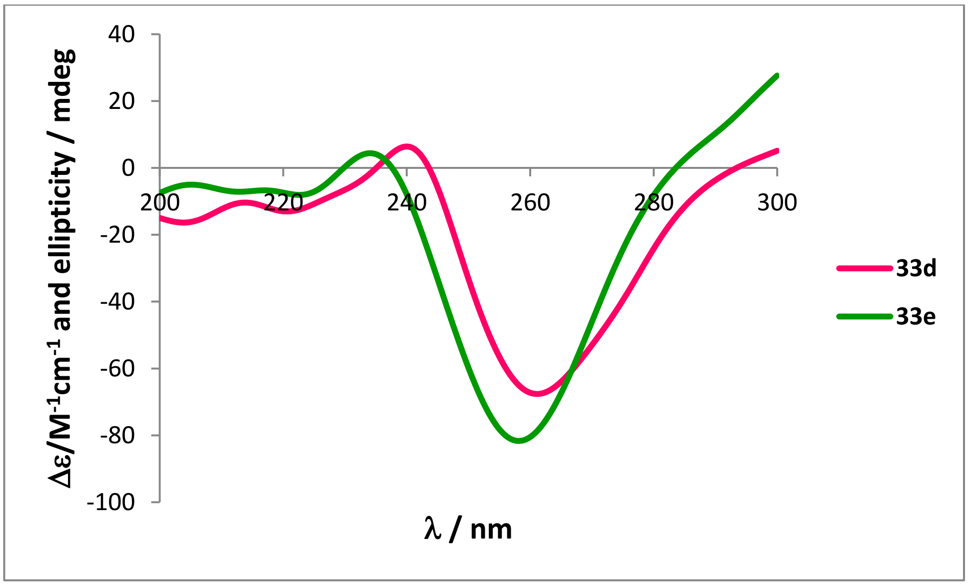
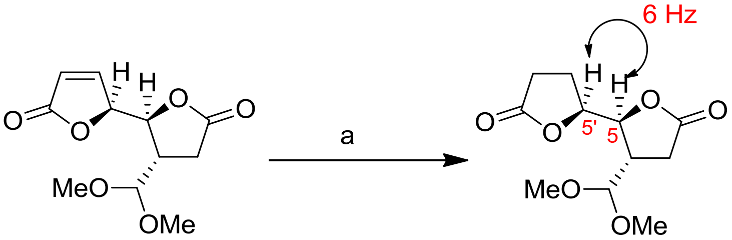


Figure15. CD spectra of lactones **33a-33e.**

The H5-H5’ vicinal coupling ($^{3}J_{5,5'}$) was also studied for this purpose. The coupling constant information is also a credible guide for assigning the 5,5’-*syn/anti* relative disposition of the two heteroatom substituents, with *syn* compounds exhibiting larger *J* values compared to their *anti* counterparts. In this respect, the saturated *bis*-butyrolactone **52** formed through conjugate reduction by treating lactone **33a.1** with $NaBH_4/NiCl_2$ reagent system displayed a 6 Hz $^{3}J_{5,5'}$ coupling value, indicating a *syn* relationship between H5 and H5’ (Scheme 15).



33a.1 **52**

Scheme 15. Conjugate reduction of lactone **33a.1**. Conditions: a) $NaBH_4$, $NiCl_2$, THF, 0 °C, 1 h, 84%.

4.1.6 Proposed mechanism of heterosiloxydiene addition

It has been well-established that addition pathways described for siloxyenol ethers, trimethylsilyl cyanide (TMSCN) and allylsilanes (cyclic and acyclic variants) to 1,2,3-trifunctionalized cyclopropane carbaldehydes abide very well with the Felkin Ahn paradigm.[15] Under this mechanism, it was suggested that the reactive conformer of **15** is *s-cis* and that by high Felkin Ahn stereocontrol, allows the addition of sterically demanding nucleophiles at the *Re* face where unfavorable interactions are avoided (Figure 16).[15b,31]

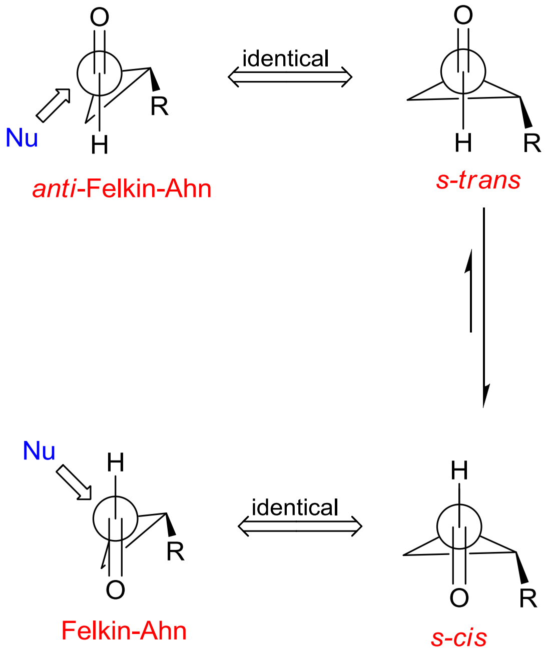


Figure 16. Mode of nucleophilic additions to cyclopropane carbaldehydes.

Under Lewis acid-mediated VMAR of heterosiloxydienes with chiral prochiral aldehydes, two new stereocenters are formed which results into four diastereomeric condensation products. The ratio of the aldol products provides a measure of the preference for the respective transition structure. It was proposed that under this catalytic condition, either a '*Diels-Alder-like*' transition-state model **TS1** or an open-chain transition **TS2** could be operative, accounting for the formation of *syn* or *anti* compounds (Figure 17). The aldehyde diastereofacial preference will mainly depend upon Lewis acid-carbonyl complexation, whereas discrimination of the siloxydiene π-face will be dictated by the *syn*clinical/*anti*periplanar preference for the corresponding transition structures and favorable/unfavorable orbital overlap between the diene reagent and the incoming aldehyde π-system.

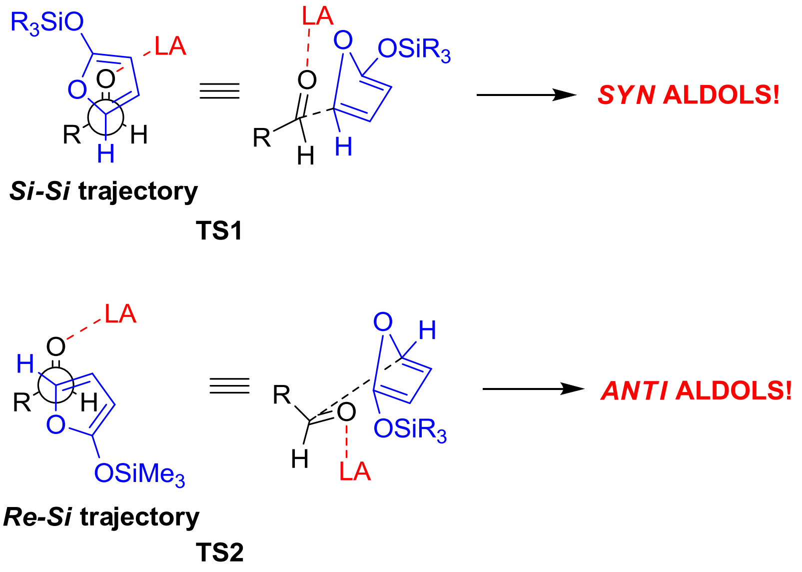
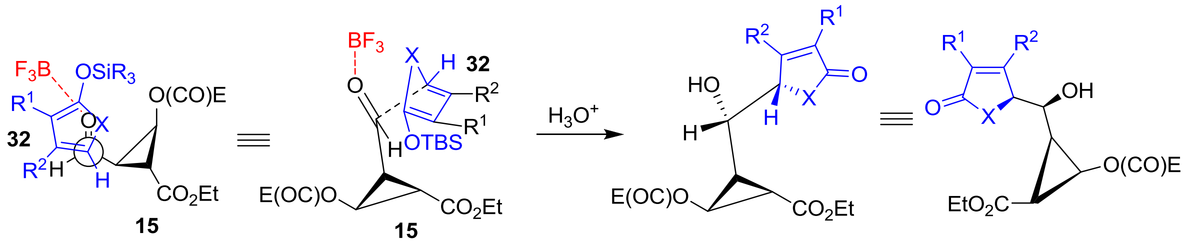
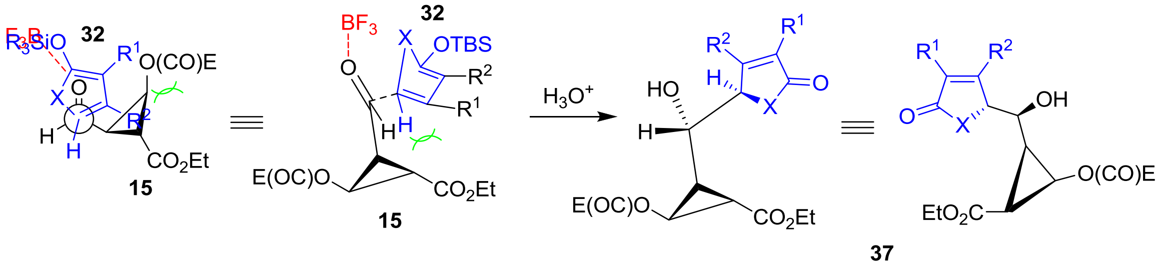


Figure 17. Transition states for VMAR of heterosiloxydienes with aldehydes.

With these stereochemical observations, noteworthy the *trans* arrangement of substituents in the γ-butyrolactone moiety, it is clear that addition pathways leading to the cyclopropyl carbinol butenolides is identical with those of the cyclic allylsilanes in accordance to the Felkin-Ahn philosophy. The high *syn* stereopreference was accounted from the *syn*periplanar orchestrated orbital overlap between the heterodiene and the aldehyde π system which may also feature a '*Diels-Alder like*' transition state (Scheme 16). It was reported in a previous study that addition of prochiral cyclohexenol silyl ether to **15**, gave a 1:1 mixture of diastereomers.[15b] In this study, a successful 1,4-stereoinduction was achieved affording up to >99 diastereoselectivity. Clearly, steric effects play a significant role in the observed stereoselectivity. This can be explained from the substitution pattern effects at C2 and C3 of the oxoheterocyclic nucleophiles. With hydrogens or the presence of a methyl group at C-4, a high selectivity is observed. The decrease in selectivity observed with methyl or aryl moieties at C3 can be attributed to unfavorable interactions of the substituents with the methyl oxallyl group in *cis* relationship with the aldehyde.



Favored TS *en route* to *syn* adducts



Less favored TS *en route* to *anti* adducts

Scheme 16. Plausible model for transition state addition of siloxydienes **32** to cyclopropanealdehyde **15**.

4.1.7 Synthesis of the model *exo*-enol furan lactone unit of bielschowskysin

A more elaborate retrosynthetic analysis of bielschowskysin starting from butenolide lactone **33c** is illustrated in Figure 18. A key 2+2 photocycloaddition reaction was first envisaged from retron **53**. The synthesis of a model segment that is reminiscent for **53** (ex. acrylate *exo*-enol lactone **54**) would be a very significant task. The introduction of the *exo*-enol functionality was thought to be possible via 2,5-furan oxidation and acid-catalyzed selective elimination at C6 and C7 in retron **55**. The C12/C13 connection can be established by intramolecular Baylis-Hilmann reaction from retron **56**. Homologation and elaborative functionalizations (*en route* to butenolide construction) of C9 and C14 from lactone **33c** should generate acrylate lactone **57**. The methacryl arm was proposed to be introduced via a Pd-catalyzed coupling of methacrylate ester with the furan moiety.

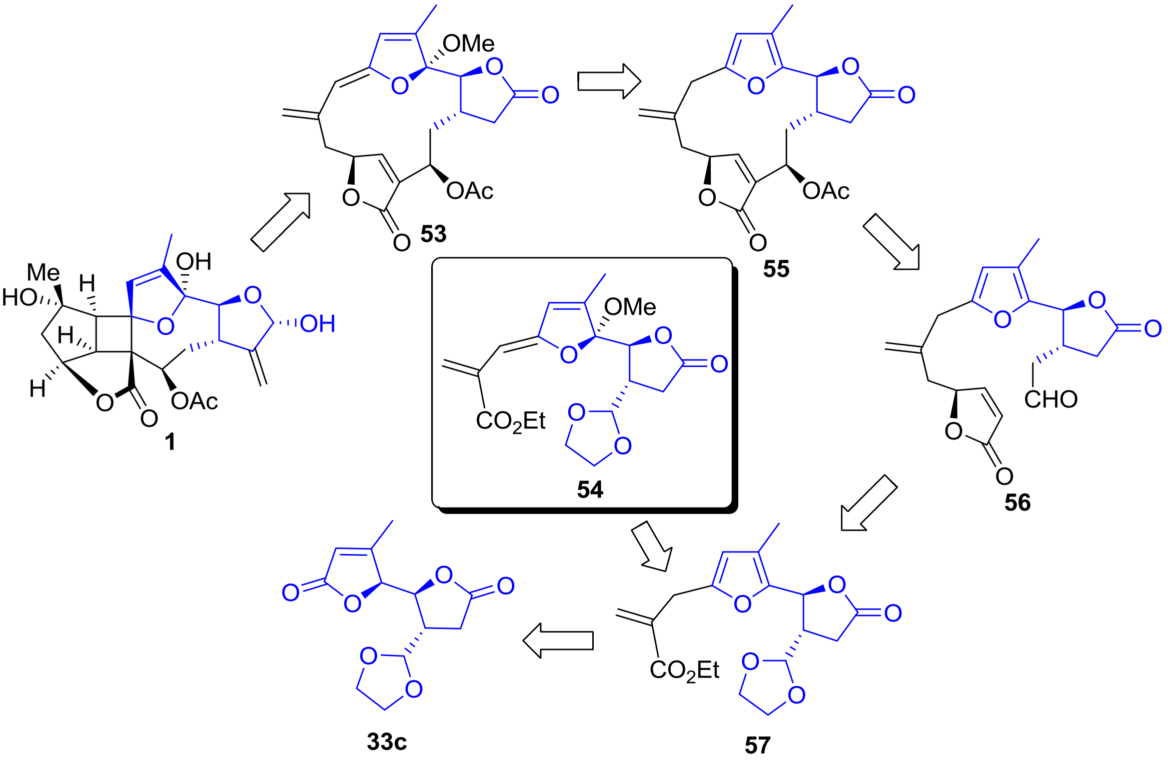
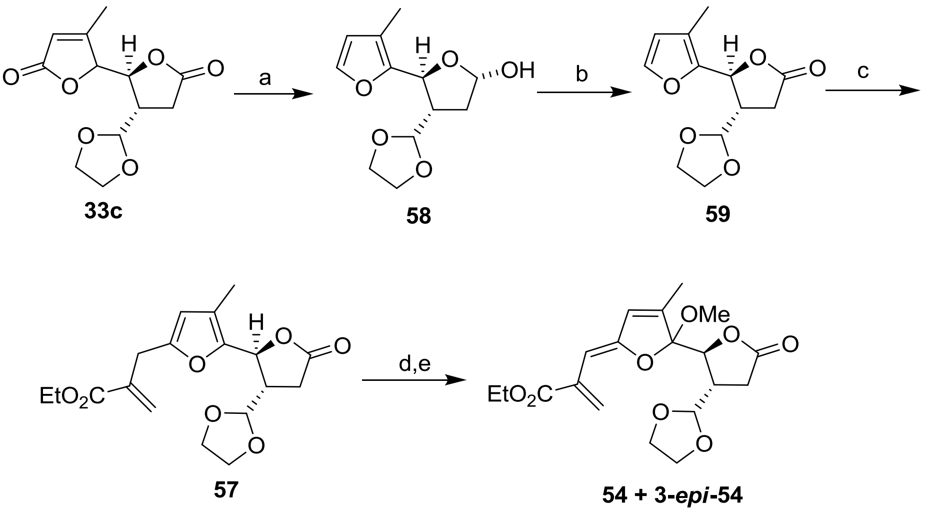


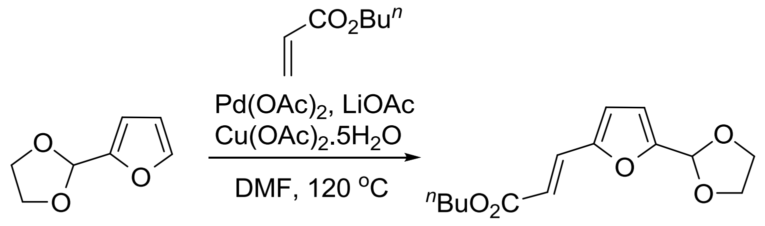
Figure 18. Retrosynthetic analysis of bielschowskysin from lactone **33c**.

Beginning with butenolide-lactone **33c**, the task was set to perform a global reduction with DIBALH to deliver lactol-furan **58** in a moderate yield (63%) (Scheme 17). Reoxidation of **58** under Ley's condition furnished furan lactone **59** quantitatively. In this form, the installation of the C17 *exo*-methylene moiety is possible.



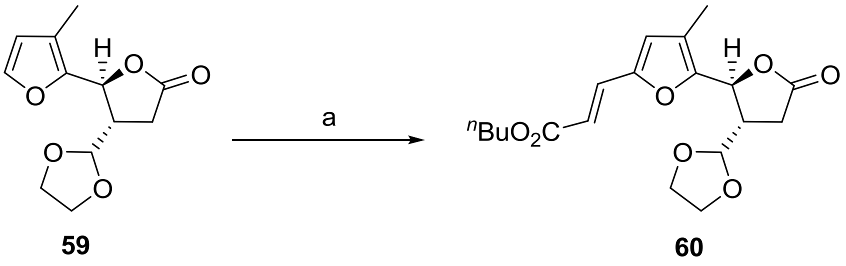
Scheme 17. Conditions. a) DIBALH, DCM, -78 °C (63%); b) TPAP, NMO, mol. sieve 4A, DCM, rt (quant.); c) ethyl methacrylate, $Pd(OAc)_2$, LiOAc, $Cu(OAc)_2.5H_2O$, DMF, 117 °C (52%); d) Br_2, MeOH, $NH_3(g)$, -40 °C; e) silica gel CC (55%).

The next steps were centered towards the extension of C6. One-carbon homologation using the Vielsmeier Haack reaction was unsuccessful. A number of studies recently reported direct intermolecular arylation of five-membered heteroarenes via C-H bond cleavage under the influence of palladium catalysts. These reactions are effective and straightforward tactics for making hetaryl-aryl platforms.[32] Inspired by this concept, the direct vinylation of furans and thiophenes at the 2- and 5-position under palladium catalytic conditions have also been described (Scheme 18).[33]



Scheme 18. Pd-catalyzed furan-acrylate coupling accdg. to Miura et al.

Adapting the procedure described by Miura and co-workers, a trial reaction was first performed between *n*-butyl acrylate and lactone **59**. A moderate conversion (52%) to acrylate lactone **60** was observed (Scheme 18). Coupling of methacrylate ethyl ester with furan lactone **59** in the presence of 2 mol % Pd(OAc)$_2$, LiOAc and CuOAc under aerobic conditions afforded acrylate lactone **57** (55% isolated yield) (Scheme 17). Referring to the mechanism proposed for this reaction (Figure 18), a strong preference for β-elimination at the least hindered carbon was observed (Figure 19). This Csp^2-Csp^2 coupling protocol presents the first synthetic application of this carbon-carbon bond forming reaction in complex molecule setting.



Scheme 19. Conditions: a) *n*-butyl acrylate, Pd(OAc)$_2$, LiOAc, Cu(OAc)$_2$•2H$_2$O, DMF, 120 °C, 12 h, 49%.

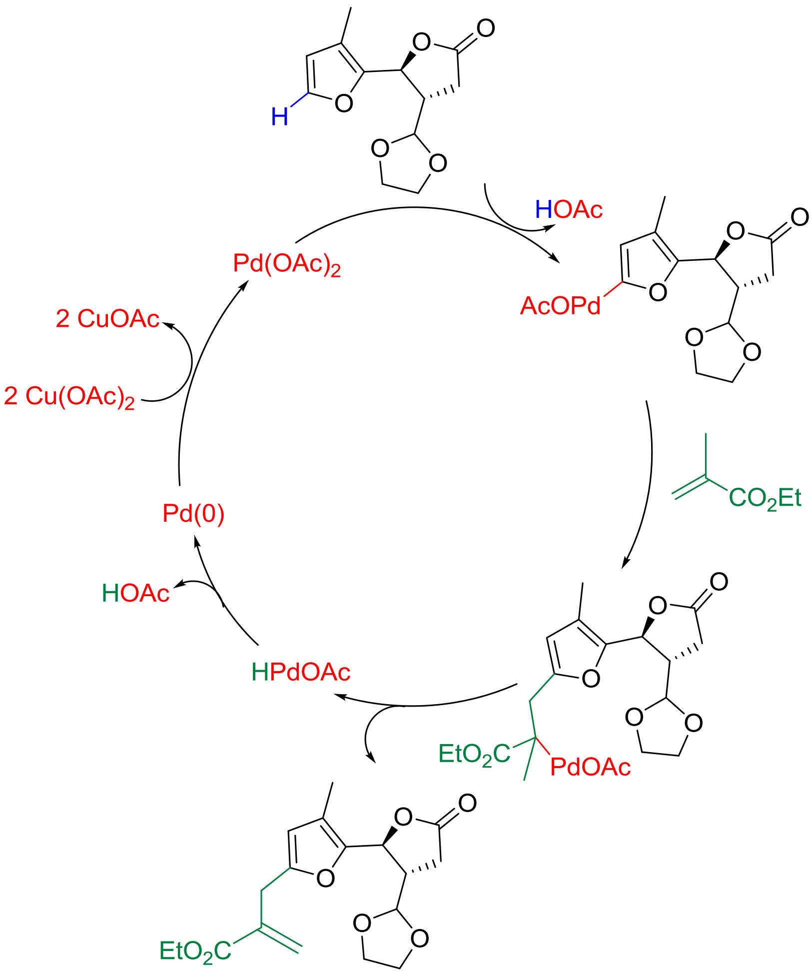
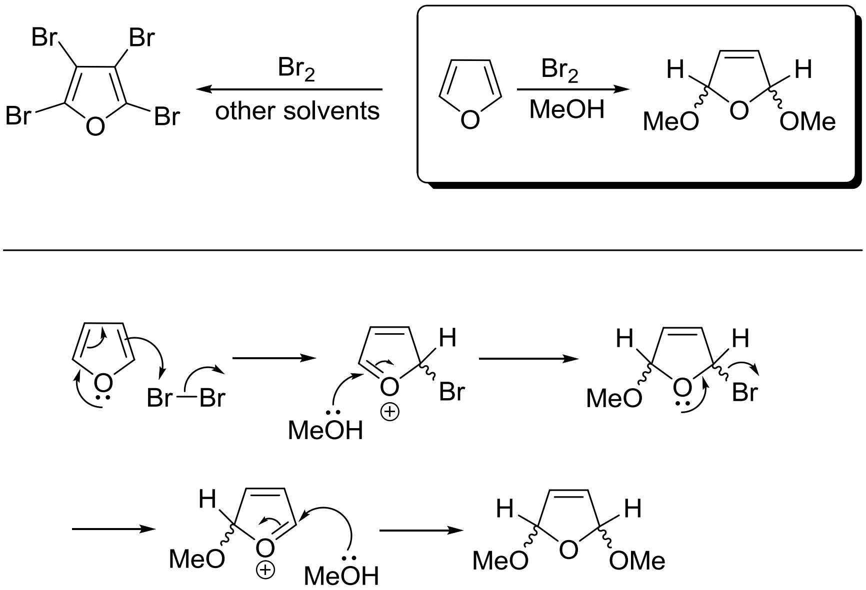


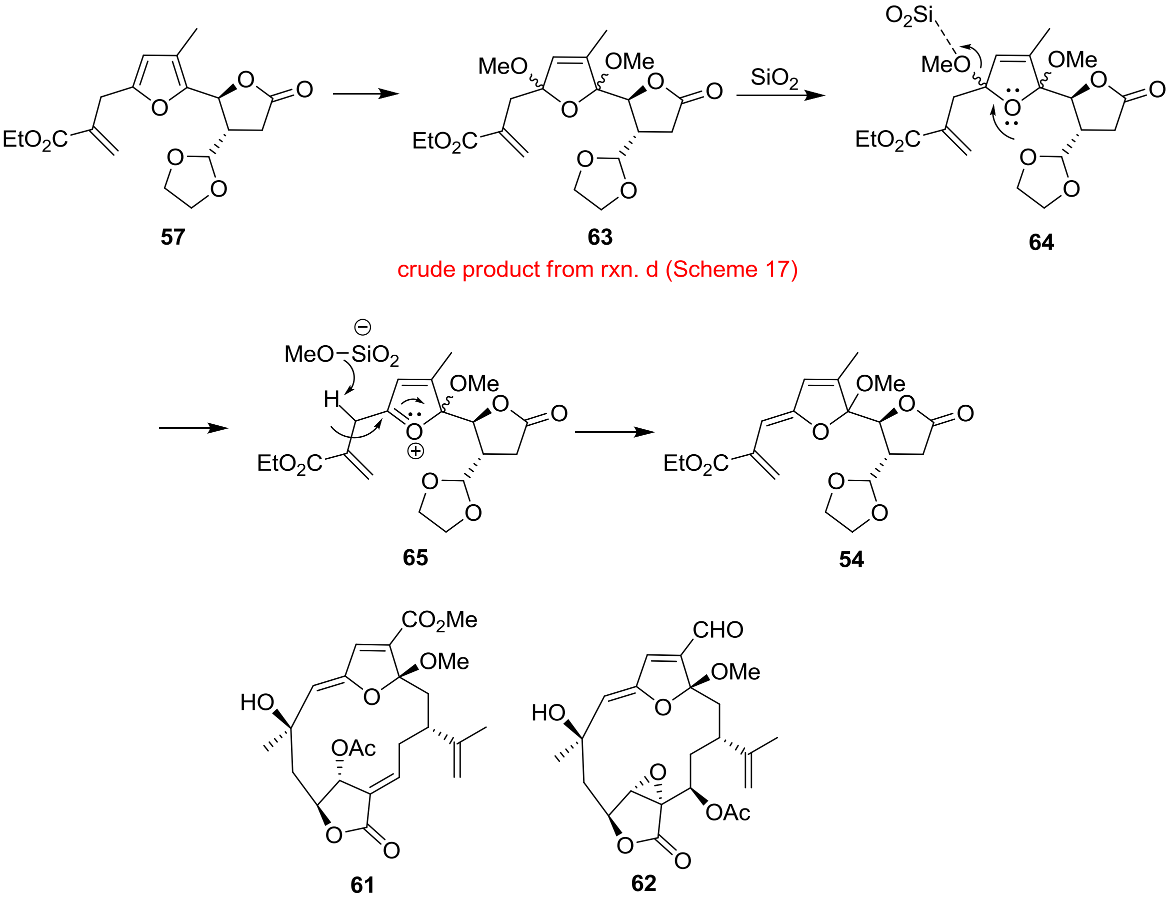
Figure 19. Mechanistic pathway for the Pd-catalyzed coupling of methacryl ester with lactone **59**.

The fascination of structural variations in furanocembranoid metabolites stems from the wide array of oxidative chemistry encompassed in the biosynthesis of the furan moiety. The new structural platforms afforded in these transformations triggers the creation of novel polycyclic derivatives which in turn lead to unprecedented biogenetic skeletons. This very behavior of furanocembranoids has sparked a number studies inspired from biogenetic hypotheses and has therefore, led to biomimetic total synthesis.[17] For example, the Trauner (Germany)[34] and Pattenden (United Kingdom)[35] groups have explicitly studied bioinspired reaction pathways to install functionalities essential for the synthesis of highly oxidized furanocembranoid compounds.

Thus, oxidative transformation of **57** was undertaken to study the installment of the *exo*-enol furan moiety. For this reaction, 2,5-methoxylation with Br_2/MeOH followed by a base work-up was employed. Under such oxidative chemistry, a regioselective methoxylation at α–carbons of furans is rather ensued instead of the usual electrophilic addition of bromine taking place using methanol as solvent (Scheme 20).[36] With Na_2CO_3, the reaction proceeded very slow and an incomplete conversion was achieved. However in a separate experiment, when gaseous ammonia was bubbled into the solution after 30 minutes of stirring at 0 ^{o}C, a crude mixture of diastereomeric dimethoxylated products was afforded (Scheme 21). Interestingly, after purification of the products in a silica gel column, a less polar (major) spot was noted on TLC. Unambiguous NMR analysis of the isolated compound revealed a structure corroborative to a methyl protected *Z*-*exo*-trienolfuran lactone **54** (along with its C3 epimer). The cyclic ketal motiffed product features a *Z*-olefinic geometry which was elucidated based on H5/H7 NOESY correlation. Other related coral natural products such as **61** and **62** also exhibit this oxidized moiety. Enol **54** was also found susceptible to decomposition when exposed to $CDCl_3$ overnight.



Scheme 20. Bromination of furan in methanol.



Scheme 21. Silica-assisted conversion of lactone diketal **63** to *exo*-enol furanlactone **54** and structure of exo-enol ether diterpenoids **61**and **62**.

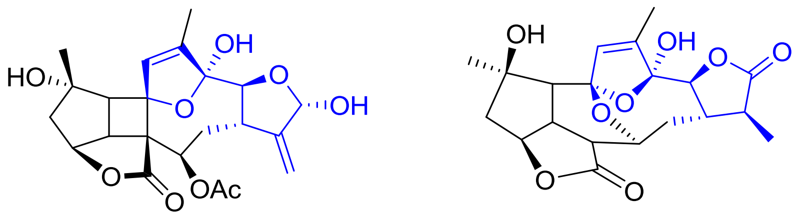
The partial and regioselective deacetalization observed during the silica-mediated reaction may have stemmed from the silica-induced elimination of the C6 methoxy group to give intermediate **64** followed by the formation of a 1,3-furyldienium ion intermediate **65**, which, after H7 eviction, is subsequently quenched through bond reorganization or resonance stabilization to finally furnish **54**. In relation to this interesting finding, we would also like to propose the possibility of a furanocembranoid with 2,5-dimethoxytetrahydrofuran moiety as plausible intermediate in the biosynthesis of furanocembranoids **1, 2, 61** and **62**[34,35] in addition to previously published biogenetic speculations.[10] The *Z* olefin thus observed should be amenable with the requisite double geometry for [2+2] photocycloaddition to install the cyclobutane core in accordance to Sulikowski's study.

4.1.8 Conclusion

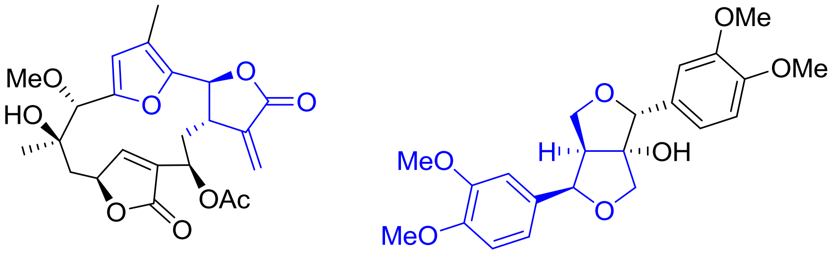
In conclusion, we have developed a new diastereocontrolled strategy to approach the heterocycle-butyrolactone units of several complex natural product structures through vinylogous Mukaiyama addition of heterosiloxydienes to highly functionalized cyclopropane carbaldehyde **15** and lactonization sequences. In addition, the first synthesis of a *Z*-*exo*-trienolfuran lactone substructure **54** representing the northeastern sector of bielschowskysin **1** was also accomplished.

4.2 Diastereocontrolled addition of organotitanium reagents to trifunctionalized cyclopropane 15 – synthesis of γ-arylbutyrolactones

Highly substituted γ-arylbutyrolactone motifs are profusely present in many synthetic intermediates and biologically active structures.[37] In general, their enantiomeric purity and absolute configuration play a significant role on their purported pharmacologic properties.[38] Thus, much effort has been invested in their asymmetric synthesis.[39] Among the derivatives thus far reported, less attention has been devoted to the stereoselective synthesis of *trans* and especially, *cis* γ-aryl- or heteroarylbutyrolactones.[40] Construction of the two stereocenters in β.γ-disubstituted-γ-butyrolactone requires laborious, step-wise procedures. Thus, lactone-based synthons prepared in this respect may serve as intermediates for the synthesis of highly oxidized furanocembranoids (e.g. **1-3**)[6c,8,9] and lignan natural products (e.g. **66**)[41] (Figure 20).



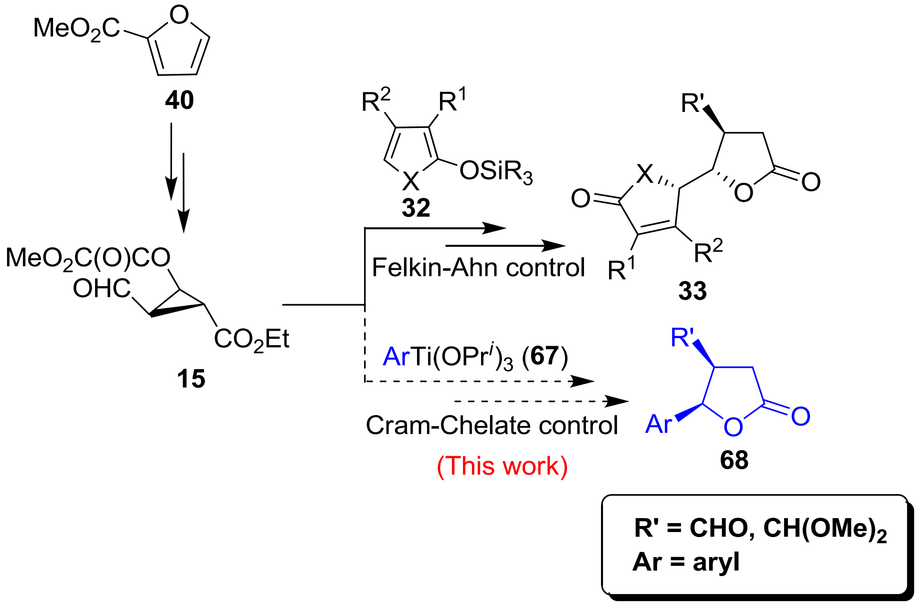
bielschowskysin (**1**) verrillin (**2**)



bipinnatin K (**3**) gmelinol (**66**)

Figure 20. Representative γ-aryllactone-derived natural products.

In the previous section, a vinylogous Mukaiyama addition of siloxydienes to cyclopropyl aldehyde **15** which affords *trans*-lactones **33** with high diastereoselectivity following the Felkin-Ahn paradigm[15,21] was described. As a useful alternative would appear is the addition of nucleophiles through a substrate-controlled Cram chelate addition pathway that should lead to the corresponding *cis*- and *trans*-lactones. In this section, the addition of aryl- and heteroarylltitanium nucleophiles **67** to **15** giving rise to either *cis*- or *trans*-lactones **68,** which appear to be useful building blocks towards the synthesis of **1-3** and **66** (Scheme 22) is discussed.[42]



Scheme 22. Chelate-controlled addition of aryl nucleophiles to cyclopropane **15**.

Among all the possible means of introducing a heterocyclic entity (ex. furan) into a more complex organic structure is the straightforward use of metaloorganic reagent prepared by metalation of a heterocycle.[43] The installation of a furan moiety into a system has a particular impact, not only due to its reactivity, but also because of a wide range of functional groups that can be harnessed through a one- or two-step sequence from the heterocycle. Inspired by the successful installation of butenolide units to cyclopropane carbaldehyde (see previous section), the addition of a furyl nucleophile was also envisaged as an alternative strategy. The furyl nucleophile in this concept is proposed to be in the form of metalofuran **69** (Figure 21). Such straightforward introduction of furan in the lactone (obtained after the usual retro-aldol/lactonization sequences), should streamline the steps *en route* to intermediate **70** skipping reduction and reoxidation steps (see Scheme 17 for reference). Furanlactone **70** should be a convenient synthon for **71** and **72**.

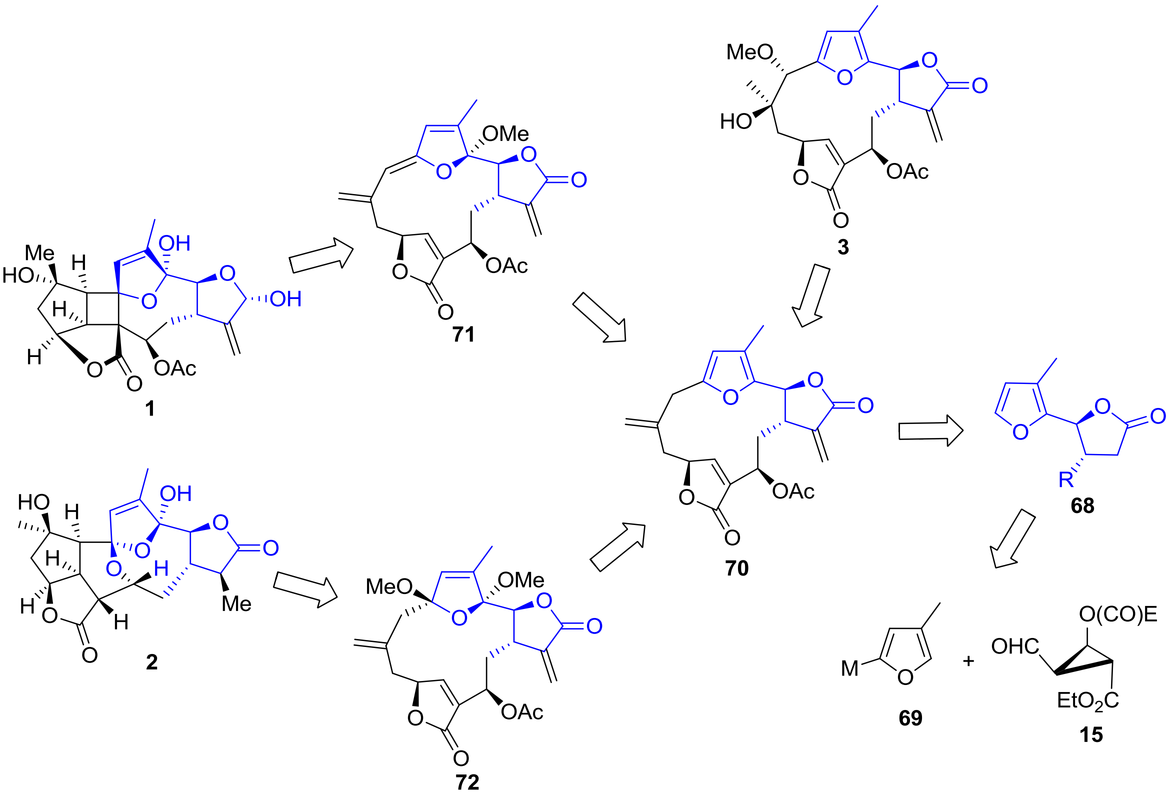
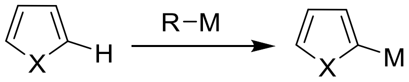


Figure 21. Retrosynthesis based on metalofuran addition to **15**.

4.2.1 Synthesis of Metalofurans

Over the past years, several metaloorganics have been prepared. Their reactivity is enhanced with the iconicity of the carbon-metal bond, thus giving a difference in electronegativity between the metal component and carbon.

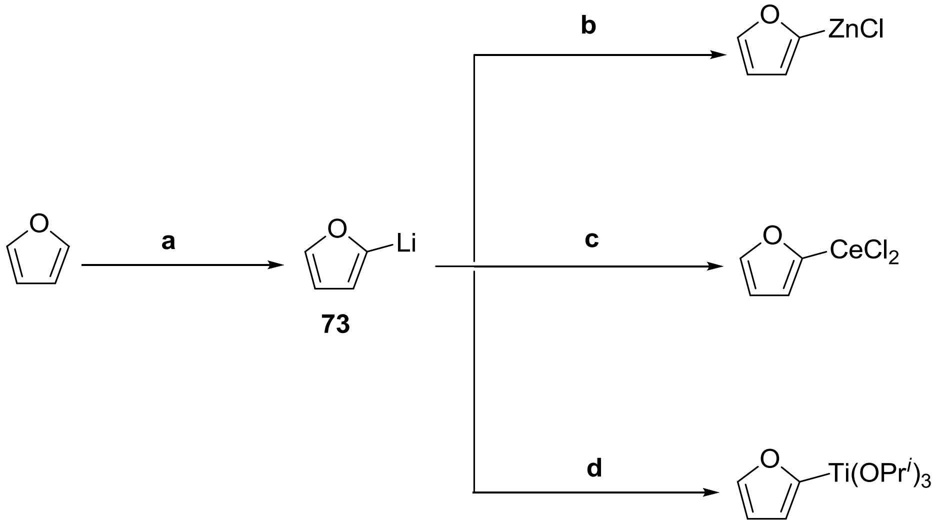
One of the most important procedures considered towards metalated heterocycles is dehydrometalation (Scheme 23). This reaction works if the acidity of the generated R-H from R-M is lower than that of the Het-H. Hydrogen-metal exchange reactions are highly direct methods being used mainly (but not exclusively) for the synthesis of hetaryllithiums using lithium alkyls.[44]



Scheme 23. Dehydrometalation of heterocycles.

Hetaryllithiums are one of the most useful metalated heterocycles. They are usually obtained by direct deprotonotation of acidic hydrogens using strong bases or, by halogen exchange at the less acidic sites of aromatic rings. Thus, the preparation of 2-lithiofuran **73** serves as a convenient gateway towards the synthesis of various transition metal-bearing furan reagents via transmetalation reactions.[44]

The preparation of 2-lithiofuran **73** was performed by dehydrolithiation of furan with *n*-BuLi in THF at -78 ^{o}C. Treatment of cyclopropane **15** with **73** resulted to substantial decomposition as expected. The highly labile methyloxallyloyx group and the two electrophilic carbonyl functionalities were not tolerated in this reaction because of the high basicity and poor selectivity conferred by hetaryllithium **73**. The highly polarized carbon-metal bond and the high reactivity that is imparted by organolithium reagents preclude the presence of functional groups in an organic molecule. Nevertheless, a covalent bond formed between transition metals and carbon tolerates a variety of functional groups such as amide, ester, nitro functionalities, etc. Thus, screening of other transition metal-bearing furyl nucleophiles were undertaken considering the sensitive nature of the methyl oxalate moiety in **15** under basic nucleophilic conditions. The metalofurans were prepared by transmetalation with $CeCl_3$, $CuCl_2$ and $ZnCl_2$. Nevertheless, efforts to add several different 2-furyl metal reagents ($ArCeCl_2$, ArCuCl, ArZnCl) (Scheme 24) alone or in combination with $BF_3{\cdot}OEt_2$ to aldehyde **16** were also unsuccessful. Either decomposition or no reaction of the starting material was observed.



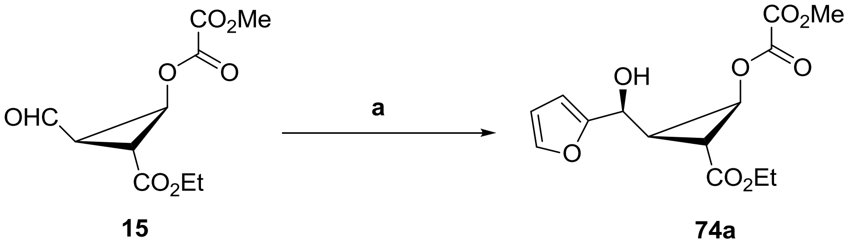
73

67a

Scheme 24. Dehydrolithiation and transmetalation of furan. Conditions: a) *n*-BuLi, THF, 2 h, -78 ^oC; b) $ZnCl_2$, THF, 2 h, -78 ^oC; c) $CeCl_3$, THF, 2h, -78 ^oC; d) $TiCl(OPr^i)_3$, THF, 2 h, -78 ^oC.

We next turned our attention to a titanofuryl nucleophile (furyltris(2-propoxo)titanium) **67a**. Organotitanium reagents display high chemo- and diastereoselectivity towards aldehydes in comparison to other carbonyl functionalities and are considered as "well-behaved reagents" because of their ability to mitigate chemical reactivity and basicity.[45] Despite studies describing additions of organotitanium reagents, direct asymmetric additions to carbonyls have been demonstrated in only a few investigations.[46]

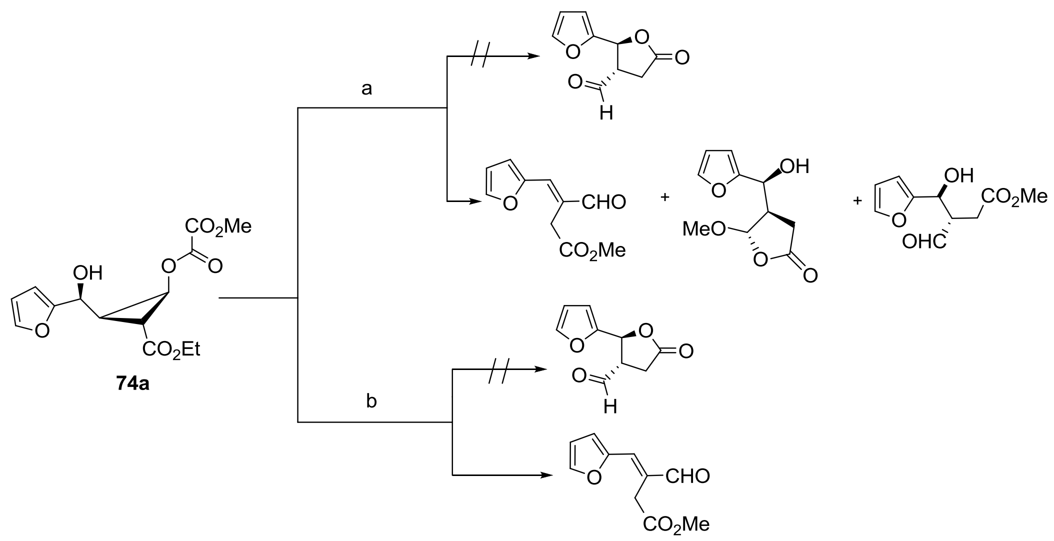
Reaction of the 2-furyltitanium reagent **67a** with **15** was also unsuccessful, however, when $BF_3{\bullet}OEt_2$ was additionally employed, the desired furyl transfer was finally achieved to give rise to **74a** (>90% conversion) (Scheme 25). It is well-established that coordination of carbonyl groups to Lewis acids exerts a dramatic effect on the rates and selectivities of reactions at the carbonyl centers.[47]



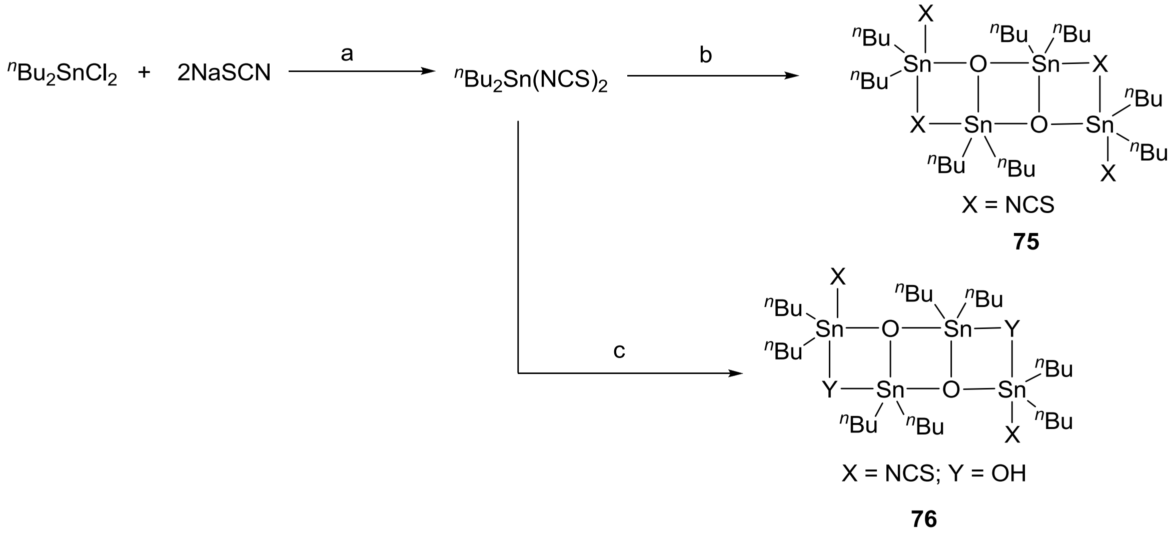
Scheme 25. Addition of titanium furan **67a** to **15**. Conditions: a) 67a (4 equiv), BF_3•OEt_2, THF, 16 h, -78 °C.

4.2.2 Synthesis of γ-arylated and γ-alkylated lactones

While **74a** can be isolated, due to its sensitive nature, we opted to directly convert it to the corresponding lactone **68a** through a *retro*-aldol and lactonization sequence upon saponifying the oxalylic ester, making use of 1,2-donor-acceptor relationship in the cyclopropane ring[15,21,48] (see also section 1.4.1.4). Treatment of **74a** with $Ba(OH)_2{\cdot}8H_2O$ and triethylamine however, failed to give the expected furyllactone carbaldehyde (Scheme 26). Lactonization experiments with several stannoxanes were carried out next. Stannoxane catalysts **75** and **76** were prepared according to Scheme 27.[49] After screening, catalyst **47** proved to be the most effective catalyst with an overall yield of the two-step sequence from **15** to **68a** to 40% (Table 2, entry 1).

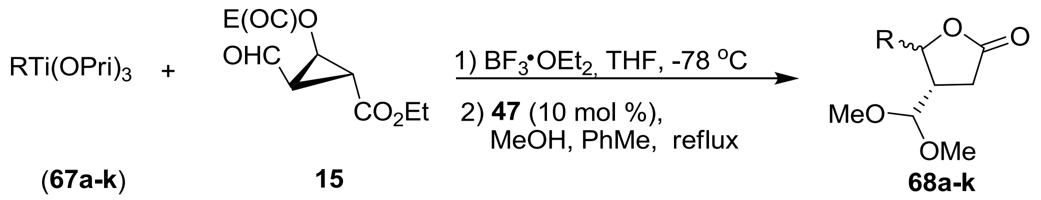


Scheme 26. Base-catalyzed lactonization of **74a**/Products detected from MS analysis. Conditions: a) $Ba(OH)_2$•$8H_2O$ (0.55 equiv), MeOH, 2 h, 0 °C; b) TEA (2 equiv), MeOH, 2 h, 0 °C.



Scheme 27. Preparation of Otera catalysts **75** and **76**. Conditions: a) benzene, 12 h, reflux (77%); b) dibutyltin oxide (1 equiv), PhMe, 12 h, reflux (90%); c) dibutyltin oxide (3 equiv), PhMe, 12 h, reflux (83%).

Table 2. γ-Aryl and alkyl lactone synthesis from cyclopropane aldehyde, **15**.



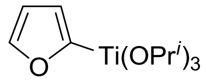
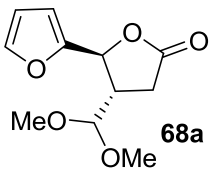
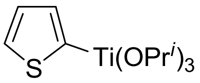
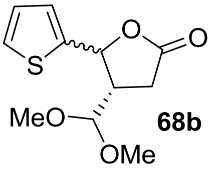
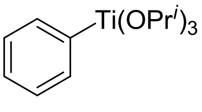
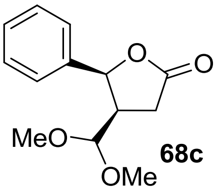
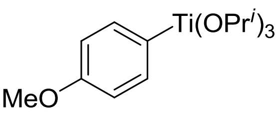
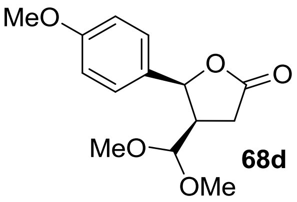
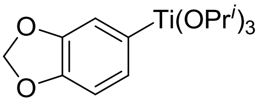
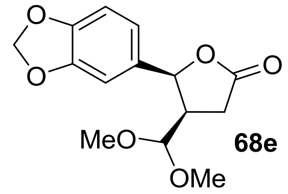
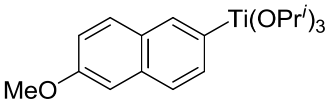
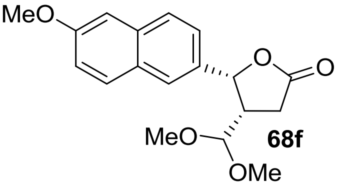
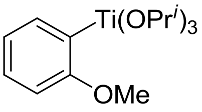
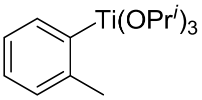
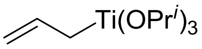
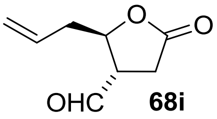
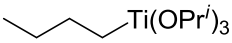
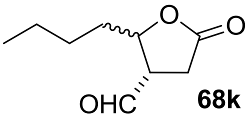
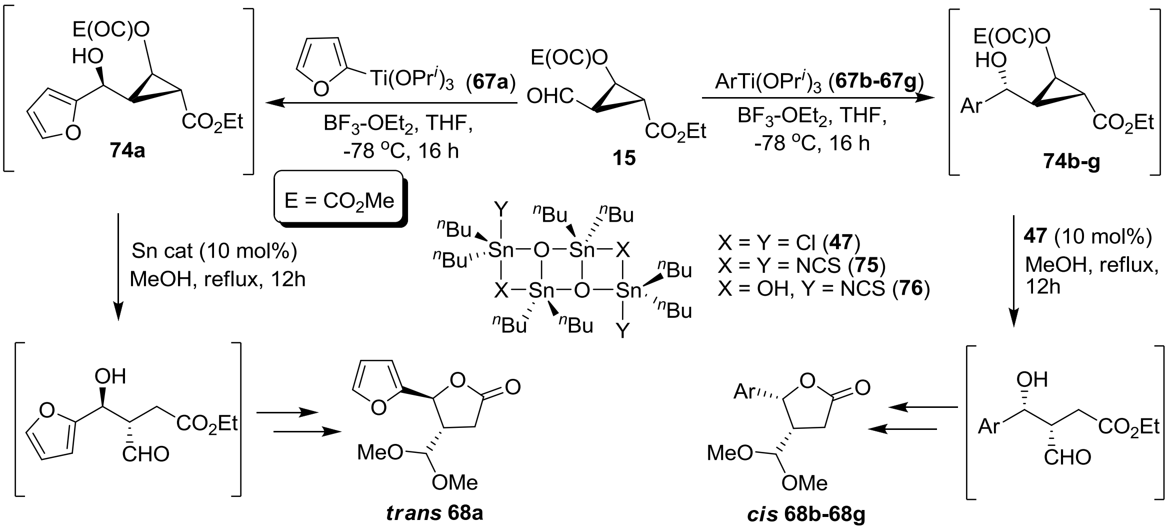
Entry	Titanium Nucleophile **67**	Lactone Structure **68**[b]	Isolated Yield[c]	*cis*:*trans* ratio[f]
1	 **67a**	 **68a**	40 23[d] 29[e]	14:86
2	 **67b**	 **68b**	38	54:46
3[a]	 **67c**	 **68c**	45	>99:1
4[a]	 **67d**	 **68d**	38	82:18
5[a]	 **67e**	 **68e**	33	76:24

Table 2 continuation..........

6	 **67f**	 **68f**	37	6:94
7	 **67g**	-	-	-
8	 **67h**	-	-	-
9	 **67i**	 **68i**	29[g]	6:94
10	 **67j**	-	-	-
11	 **67k**	 **68k**	Traces[g]	-

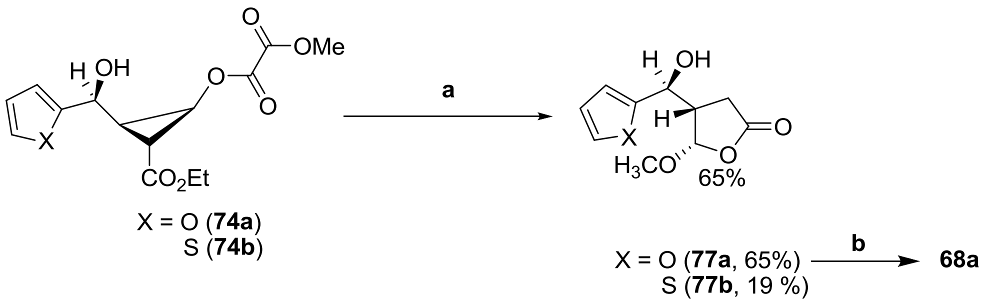
[a] Ent-15 was used. [b]Major diastereomer shown. [c]Unless otherwise stated, **47** was used as catalyst. Overall yield in two steps. [d] **75** was used. [e] **76** was used. [f] Based on relative integrals in the ^{1}H NMR spectrum. [g] Lactonization was carried out with $Ba(OH)_2$•$8H_2O$.

A representative number of other aryltitanium reagents, being readily prepared by dehydrolithiation or dehalolithiation of aryl derivatives followed by titanation with $ClTi(OPr^i)_3$, were tested for the synthesis of lactones of the type **68** (Scheme 28).[50] Besides 2-thienyl (entry 2) and phenyl (entry 3), alkoxy substituted aryl groups (entries 4-6) being especially relevant towards naturally occuring compounds such as **66** were successfully introduced. However, aryltitanium nucleophiles bearing substitutions at the *ortho* position, e.g those derived from 2-bromoanisole **67g** and 2-bromotoluene **67h** (entries 7 and 8), were not amenable with this reaction sequence due to sterical hindrance.[51] On the other hand, a number of unidentified products were observed with vinyltitanium **67j**.



Scheme 28. Pathways *en route* to *cis*- and *trans*-γ-aryllactones.

Interestingly, when the reaction was subjected to 10 mL per 100 mg dilution, the formation of a different rearrangement product was observed (Scheme 29). The structure was identified as a γ-methoxy-β-carbinolfuranelactone **77a** after extensive NMR spectroscopic analysis in 65% yield. The elucidated structure was further evidenced by characteristic fragment ions from the EIMS spectrum (Figure 22). The product can be converted to furanlactone **68a** almost quantitatively after stirring in methanolic PTSA. The reaction also works with thienyl cyclopropyl carbinol to provide the corresponding γ-methoxylactone **77b** albeit, in 19% overall yield. The mechanism of this rearrangement can be traced plausibly by the initial formation of the *retro*-aldol intermediate **78** (Scheme 30). Following the formation of γ-arylatedlactone aldehyde **79**, a concomitant yielding of hemiacetal **80** followed by intramolecular transesterification reaction leads to the hetaryllactone adducts **77a** and **77b**.



Scheme 29. Unusual rearrangement product of **74a**. Conditions: a) 47 (10 mol %), MeOH (10 mL/ 100 mg), 12 h, reflux.

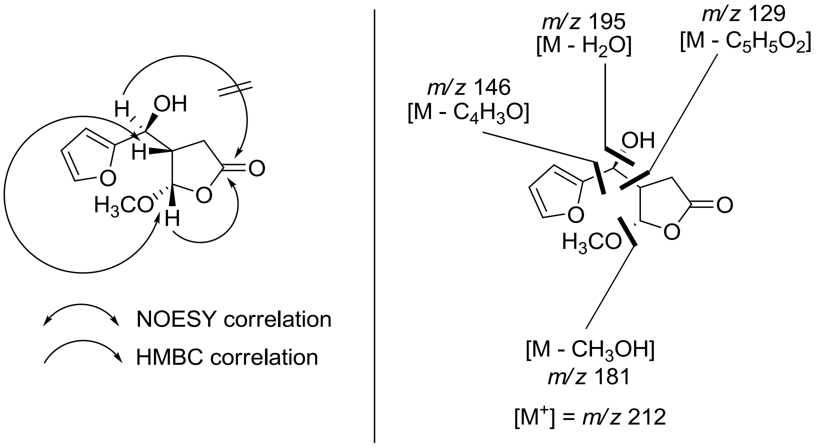
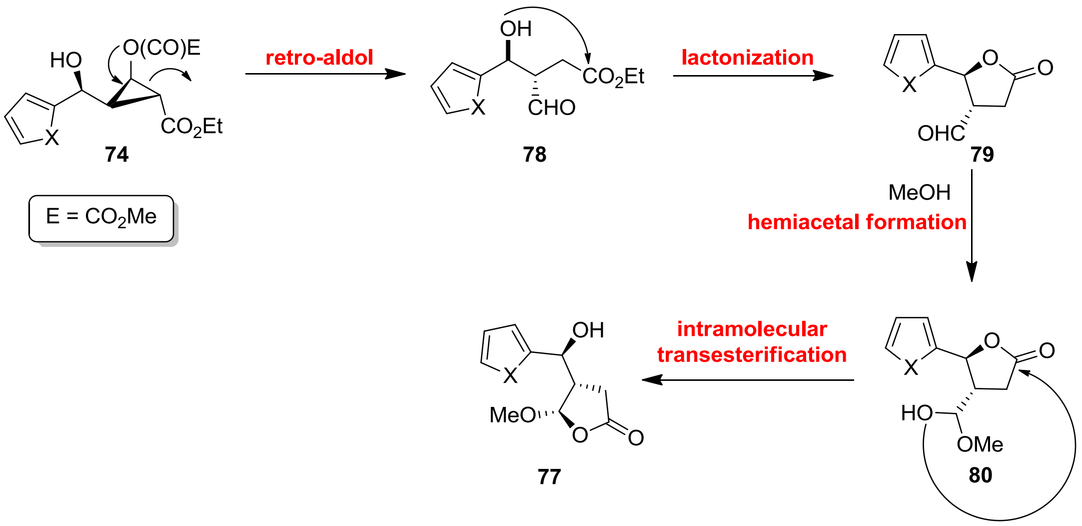
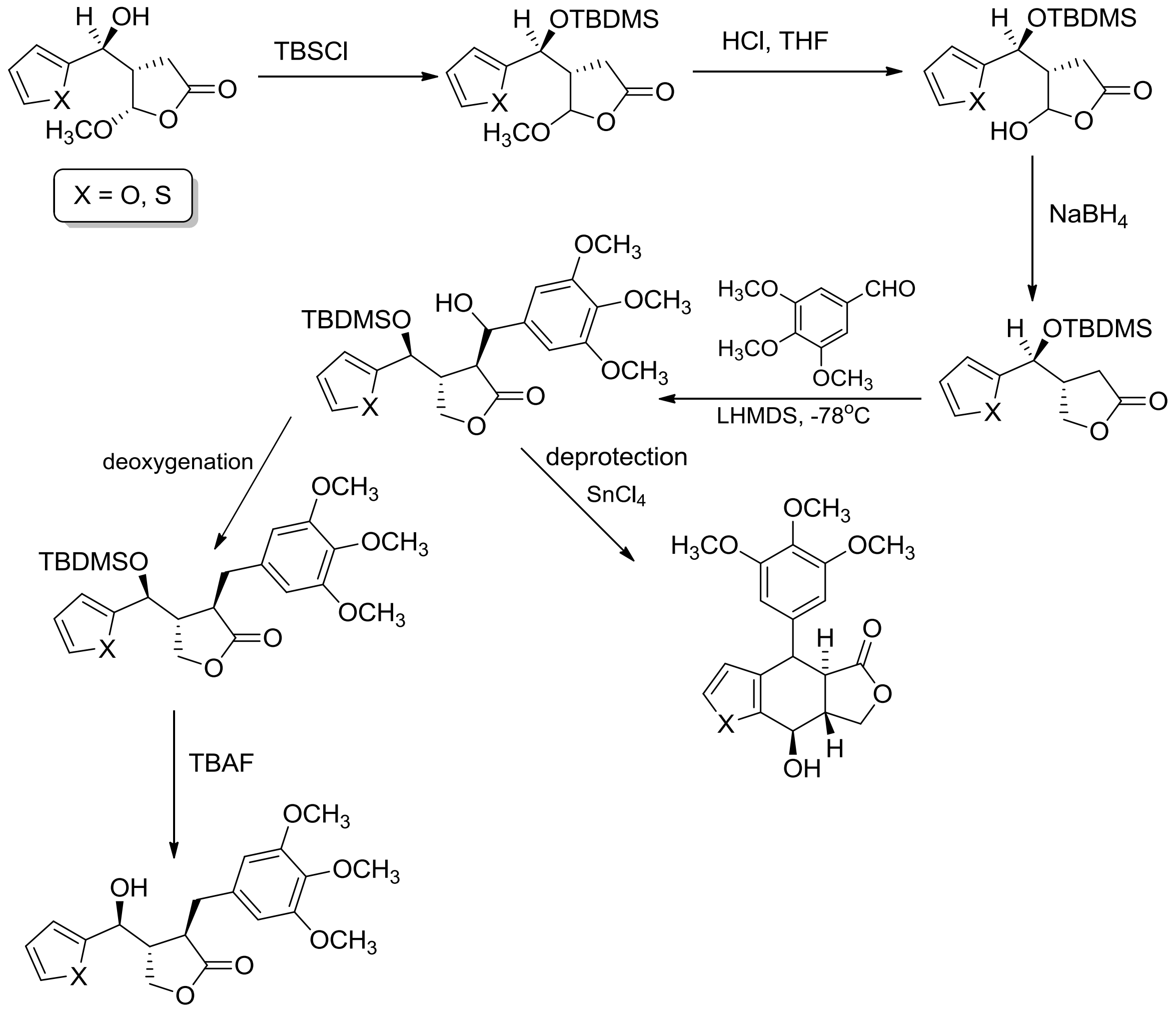


Figure 22. Spectroscopic analysis of lactone **77a**.



Scheme 30. Plausible formation of rearrangement product **77**.

The hetarylcarbinol lactones **77** could be useful synthons for the facile formal synthesis of cytotoxic heterolignanolides **81** and **82**[52] as outlined in Scheme 31.



Scheme 31. Proposed synthesis of heterolignanolides **81** and **82**.

4.2.3 Determination of stereochemistry

The stereochemistry of **68a-f** was confirmed through 2D-NOESY correlation experiments and X-ray analysis of **68c** (Figure 23). Thus, it was revealed that the diastereoselectivity of this reaction sequence was greatly influenced by the type of aryl nucleophile being used. While the 2-furyltitanium **67a** gave rise predominantly to the *trans*-lactone **68a** (*dr* 86:14), the aryl substituted lactones **68c-68f** were obtained with moderate to excellent *cis*-selectivity (*dr* 3:1 to >99:1), demonstrating for the first time that addition of nucleophiles to **15** can ultimately lead to *cis*-lactone of type **68** as the major products.

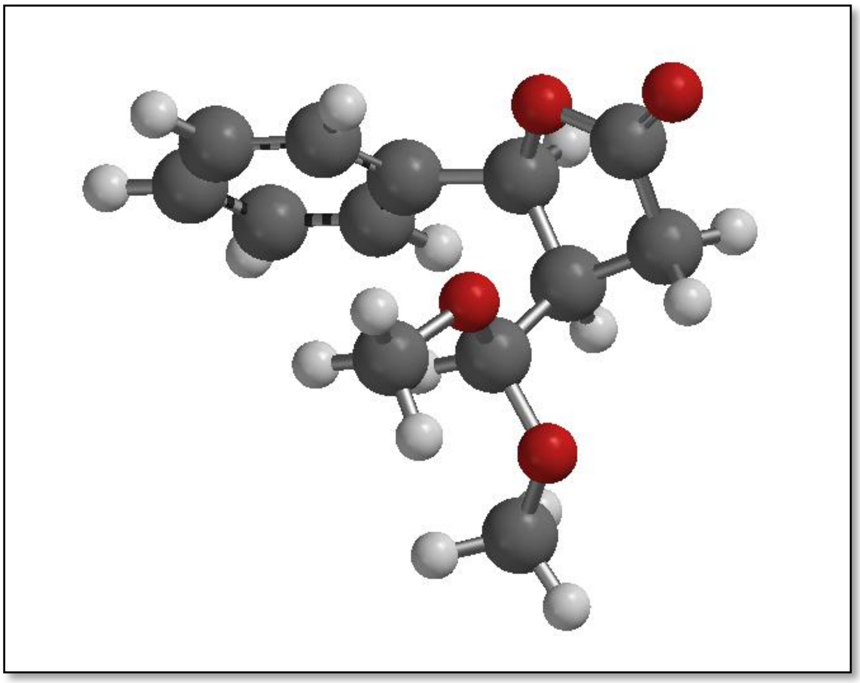
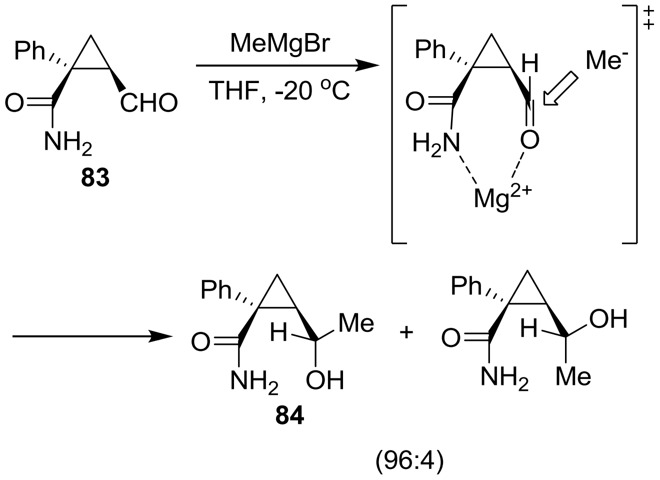


Figure 23. Single crystal X-ray structure of *cis*-lactone **68c**.

4.2.4 Proposed mechanism of metaloorganic nucleophile addition to cyclopropane aldehyde 15

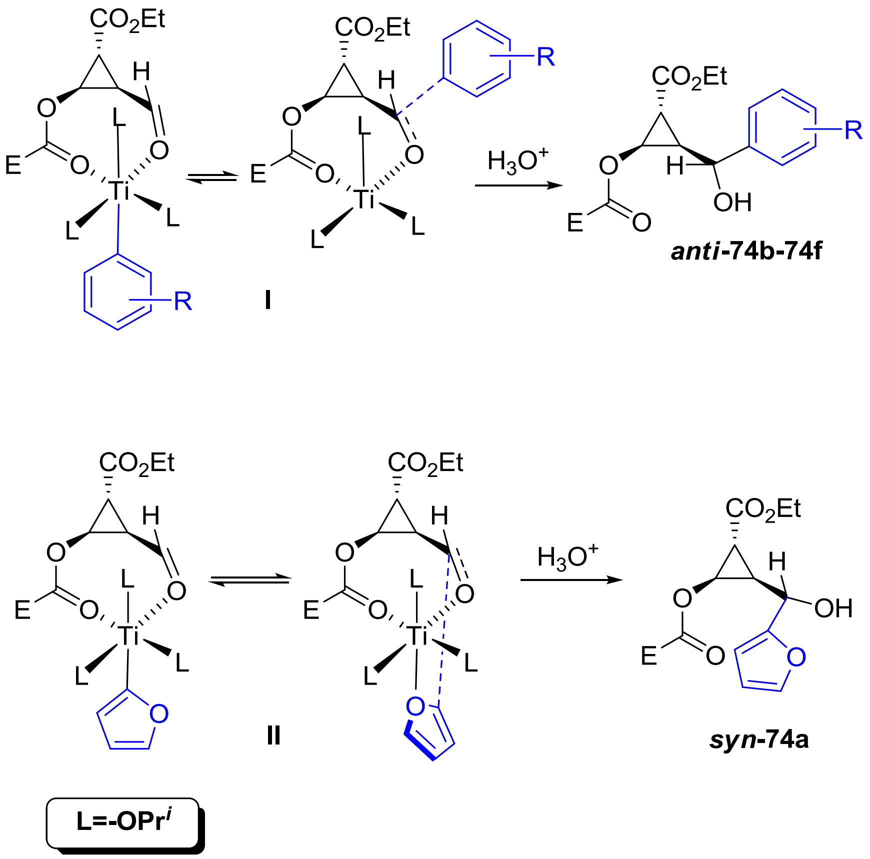
In a previous related study, Shuto and co-workers[53] discovered that nucleophilic addition of Grignard reagents on a cyclopropane carbaldehyde derivative **83** proceeds with high stereoselectivity to give *anti*-product **84** in excellent yield and selectivity (Scheme 32). Initially, the proposed pathway was ascribed to a bisected-conformational transition state stabilized by the characteristic electron donating effect of the cyclopropane moiety. In the end, they found that the *anti*-selectivity of the Grignard addition to *cis*-substituted cyclopropane carbaldehydes occurred through an unusual 7-membered 1,4-chelation controlled pathway which agreed well with the proposed mechanism of Reiser for such Cram chelate-controlled addition reactions.[54]



Scheme 32. Addition of methyl Grignard reagent to cyclopropyl aldehyde **83**.

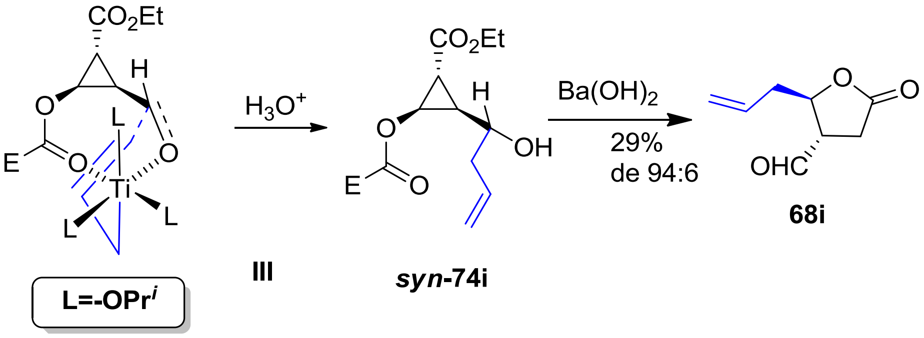
In agreement to this mechanistic hypothesis, the *cis*-selectivity observed in the formation of **68c-68f** with aryltitanium/BF_3·OEt_2 reagents, contrasting the high *trans*-selectivity achieved in the corresponding transformations with allyl-silanes/BF_3·OEt_2 and the excellent oxygen-chelating capabilities of titanium reagents led to the proposal of a cyclic Cram chelate-type featuring a rather unusual 8-membered titanium complex under 1,5-stereocontrol .

The aryl nucleophile is delivered externally from the sterically less hindered face of the carbonyl group, giving rise to **74c-g** as the major diastereomer (Scheme 33, pathway I).[55] In contrast, the *syn*-selectivity observed with furan titanate **67a** results through the formation of an incipient bond between the furyl nucleophile and the electrophilic aldehyde carbon while the oxygen atom in the furan ring is coordinated with titanium, favoring the formation of *syn* addition product **74a** (Scheme 33, pathway II).



Scheme 33. Chelate-controlled addition of organotitanium **67a-67f** to cyclopropyl aldehyde **15**.

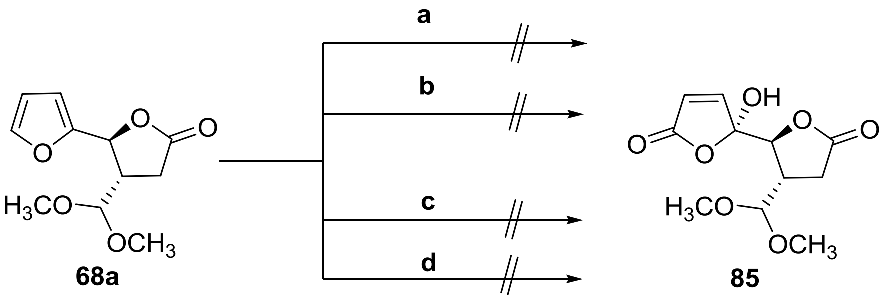
The poor diastereoselectivity achieved with the thienyl nucleophile **67b** could be explained by the weaker coordination ability of sulfur to titanium, thus resulting in no preference either for pathway I or II. The lower diastereoselectivity for oxygenated aryltitanium reagents leading to **68d-68f** compared to **68c** might reflect different degrees of internal delivery of the nucleophile via coordination of titanium to the oxygen substituents in the aryl rings. In agreement with this proposal is the highly selective addition of allyltitanium **67i** to **15** (Table 2, entry 9), leading to **68i** by directed delivery of the allyl nucleophile via a Zimmerman-Traxler-like transition state (Scheme 34, pathway III).



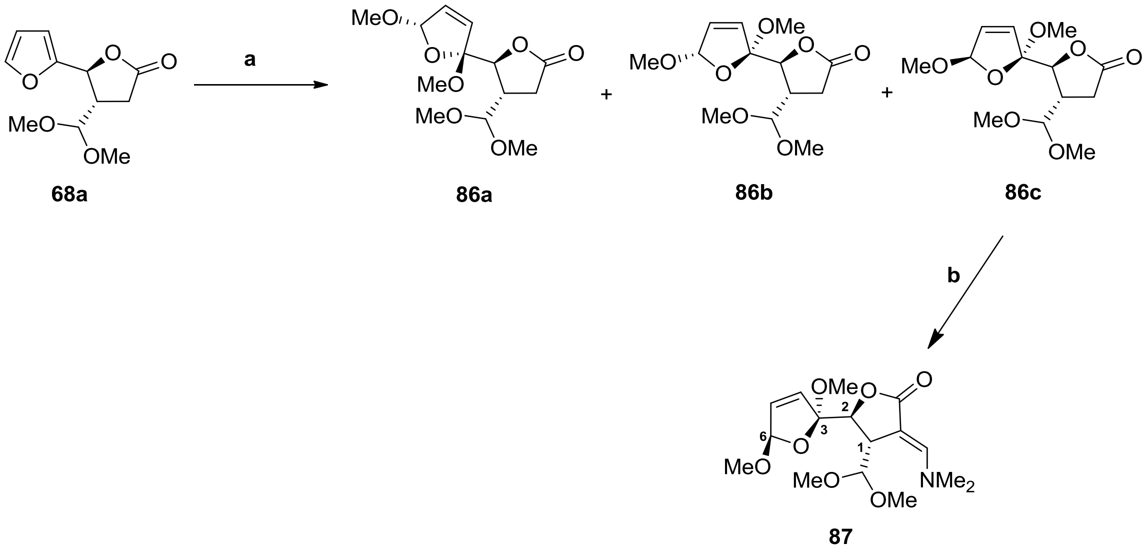
Scheme 34. Chelate-controlled addition of organotitanium **67i** to cyclopropyl aldehyde **15**.

4.2.5 Synthesis of model fragment for the northeastern segment of furanolactonecembranoids 1 and 2

Lactone **68a** seemed to be a suitable precursor to study the synthesis of the northeastern segments of diterpenoids **1** and **2**. Initial attempts to perform oxidative transformations on the furane ring using a number of methods known for that moiety, i.e. singlet oxygen oxidation, mCPBA or Jones oxidation[56] to furnish a γ-hydroxybutenolide **85** were unsuccessful (Scheme 35). Using bromine[57] in methanol, however, afforded the 2,5-dimethoxy-2,5-dihydrofuran **86** in 75% yield, albeit as a mixture of three diastereomers in a 1:1:2 ratio, from which **86c** could be separated by chromatography (Scheme 36). From the mixture of **86a** and **86b** the former was obtained in pure form by crystallization and its structure could be assigned unambiguoulsy by X-ray structural analysis (Figure 24). The major diastereomer **86c** was heated with Bredereck's reagent[58] to install the α-dimethylaminomethylene handle, furnishing **87** in good yield (81%). The model precursor product thus obtained satisfies the needed *1S,2S,3S* (and *6S*) stereochemistries required in furanocembranoids **1** and **2**.



Scheme 35. Attempted oxidative transformations of lactone **68a**. Reagents/Conditions: a) $NaClO_2$, KH_2PO_4, $^{t}BuOH$, H_2O; b) MMPP; c) mCPBA; d) $^{1}O_2$, rose Bengal, $h\nu$ (254 nm).



Scheme 36. Methoxylation of lactone **68a**. Conditions: a) Br_2, MeOH, $NH_{3(g)}$ (pH 8), 30 min., 0 °C (75%). b) Bredereck's rgt. ($(Me_2N)_3CH$), PhMe, 24 h, 70 °C, 81%.

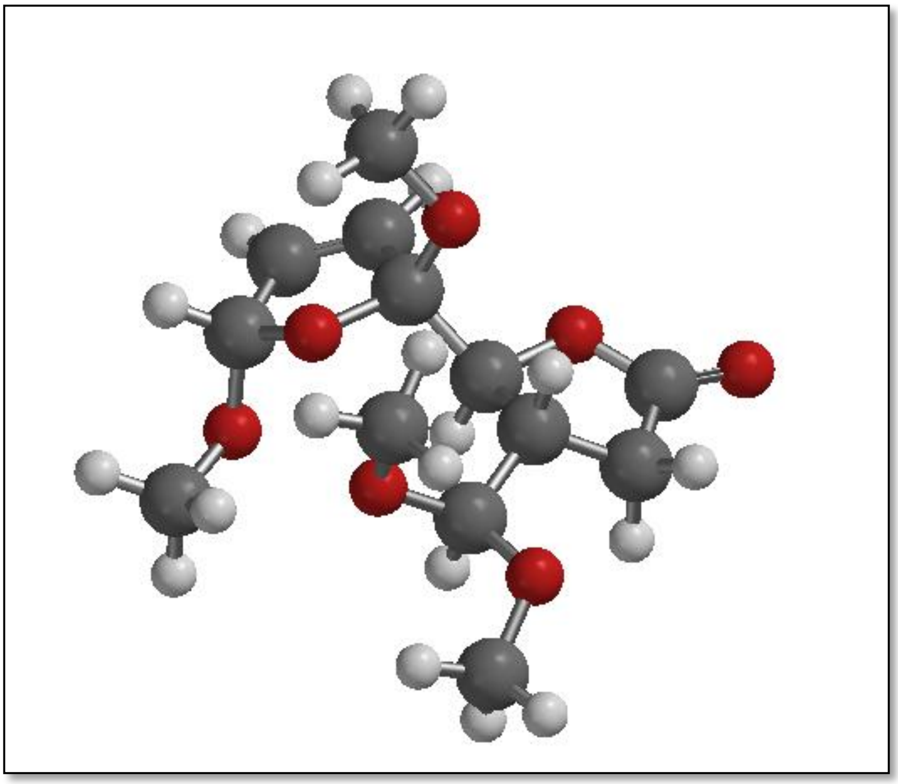
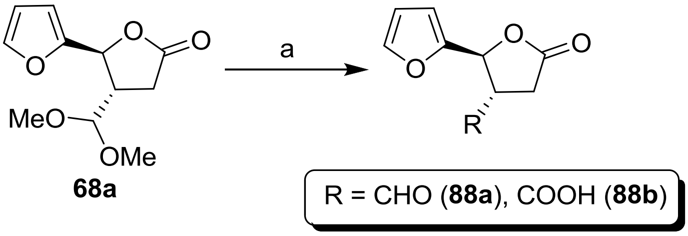


Figure 24. Single X-ray crystal structure of **86a**.

Attempts to deprotect the *O*-methyl acetal protecting group in **68a** proved to be a very challenging task. A number of known deprotecting methods (including oxidative deprotection conditions, see Table 3) were tried but only pyridinium *p*-toluene sulfonate (PPTS) in aqueous acetone showed considerable conversion (ca. >60%) to furyllactone β-carbaldehyde **88a**.

Table 3. Deprotection of lactone **68a**.



Entry	Deprotection Condition	Conversion
1	TFA-$CHCl_3$-H_2O (3:3:1)	NR
2	TFA-THF-H_2O (3:3:1)	NR
3	1M HCl/THF	NR
4	HCO_2H (150 equiv.), 0 °C	NR
5	PPTS/H_2O-Acetone (8:2), reflux	>60% conversion
6	$SnCl_2$, $C_{10}H_8$, PhMe	NR
7	$ZnBr_2$, DCM	NR
8	BBr_3, DCM	NR
9	Otera catalyst **75**, acetone, PhMe, reflux	NR
10	Jones rgt., acetone, 0 °C	NR
11	$FeCl_3$, HCl, H_2O_2	NR

NR = no reaction.

4.2.6 Conclusion

In conclusion, a new diasteroselective approach was developed towards γ-aryl lactones utilizing aryltitanium reagents in combination with the readily available cyclopropanecarbaldehyde **15**. This methodology extends the previously reported functionalization of **15** with allylsilanes in substrate scope, but also offers for the first time a reversal of stereochemistry. Thus, *cis*-disubstituted γ-aryl-β-methyl acetal lactones with good diastereoselectivity in enantiomerically pure form can be obtained, which compares well with previously reported methods.[39,40]

4.3 Synthetic approach employing diastereoselective reduction of furylated β-keto esters

Chiral paraconic acids or 5-oxo-tetrahydro-3-furancarboxylic acid derivatives are a small class of highly substituted γ-butyrolactones are commonly found metabolites in mosses, lichens and fungi.[59] The non-natural paraconic acid **89**, 5-oxo-tetrahydro-3-furancarboxylic acid, is a first member of the series and considered as an important precursor in the synthesis of A-factor[60], an inducer of the biosynthesis of streptomycin in non-active mutants of *Streptomyces griseus*. Paraconic acid esters have many industrial applications particularly in the perfume and solvent industries.[61] Aside from the presence of a carboxylic group at the β-carbon atom, naturally occurring paraconic acid derivatives also contain an alkyl side chain at the γ-carbon atom and a methyl or *exo*-methylene group at the α-position.[62] Several examples of natural paraconic acid metabolites are rocellaric acid **90**, phaseolinic acid **91** and methylenolactocin **92** (Figure 25).[63,64]

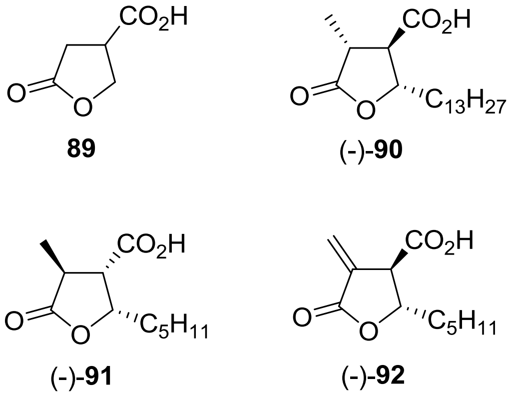
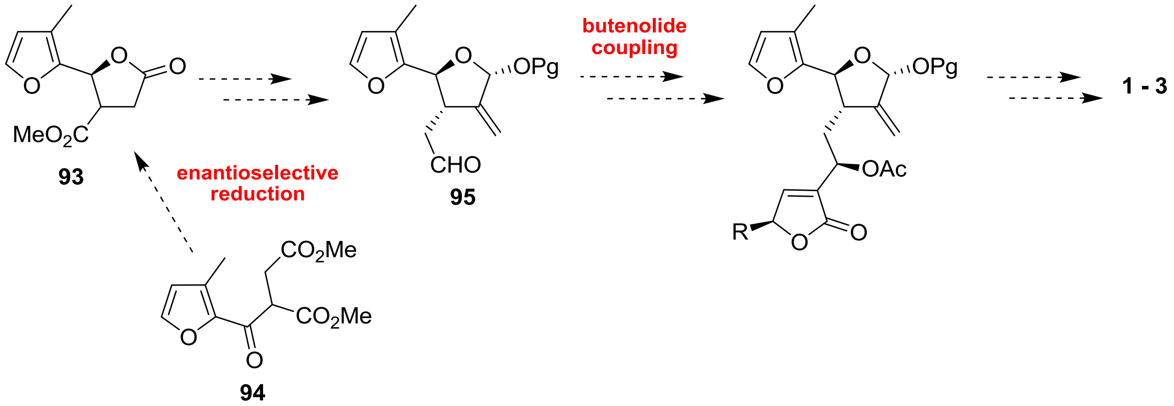


Figure 25. Structure of several paraconic acids.

To address the challenge in their enantioselective synthesis, the development of different methods towards **89** and its analogues using chiral auxiliaries, enzymatic methods, and asymmetric catalysis by transition metal complexes has gathered interests.[65] Its chiral derivatives have been demonstrated to be useful building blocks for the synthesis of compounds which may exhibit a different pharmacological activity pattern.[66] Acids of type **89** bearing two stereocenters are difficult to synthesize according to known procedures, which usually include several steps with the involvement of organometallic or difficult to handle reagents.[65] The asymmetric reduction of acylsuccinates offers a promising route to chiral 2-alkylparaconic acids.

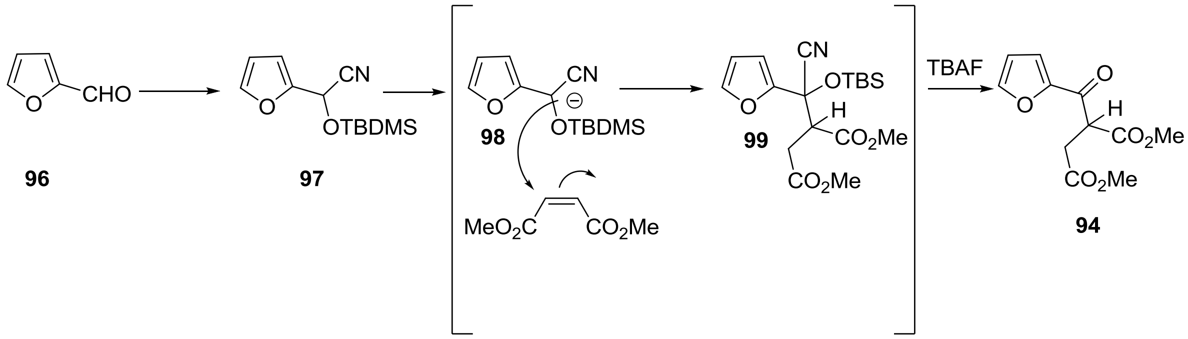
Within the frame of this study to provide strategies towards the stereocontrolled synthesis of the furan lactone backbone of furanocembranoids **1-3**[6c,8,9] from furan derivatives, attention was further envisioned to synthesize a γ-furyllactone β-carboxy ester **93** by way of diastereoselective reduction of β-keto furoylsuccinic diester **94** (Scheme 37). Lactone **93** was envisaged as a suitable derivative to further study homologation reactions leading to aldehyde **95** and subsequently provides opportunities for coupling with γ-alkylbutenolides as illustrated in Scheme **37**.



Scheme 37. Proposed synthesis of furanocembranoids **1-3** from furanlactone **93**.

4.3.1Synthesis of furylsuccinyl diester 94

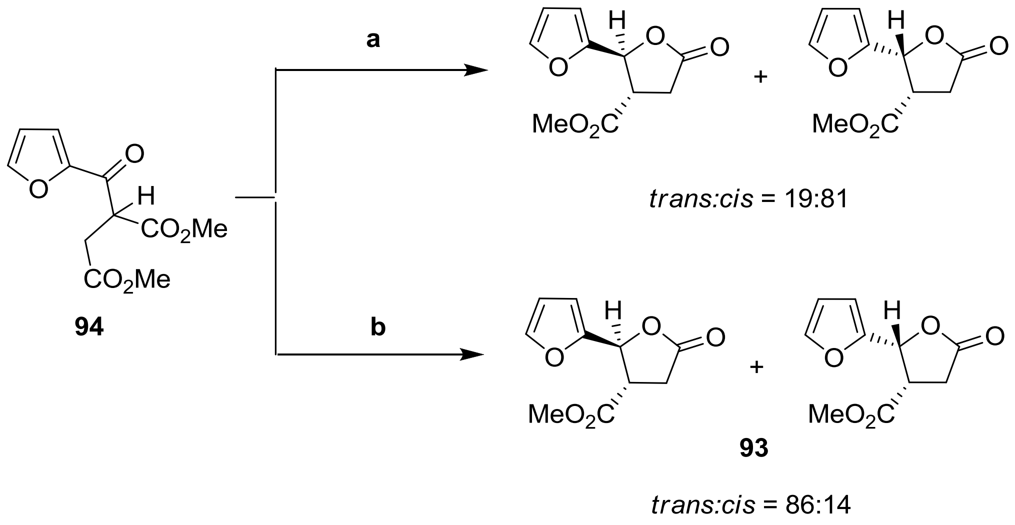
The synthesis of diester **94** started from furfural **96.**[67] Thus, treatment of **96** with TBSCl, KCN and ZnI$_2$ (catalyst) furnished siloxynitrile derivative **97** in excellent yield (96%). Umpolung manipulation of **97** via LDA assisted deprotonation at -78 °C provided the nucleophile intermediate **98** which subsequently undergone Michael addition to dimethylmaleate to provide diester nitrile **99** (Scheme 38).[68] TBAF accelerated removal of the TBS group followed with concurrent eviction of the nitrile group furnished **94** in moderate yield (61%).



Scheme 38. Synthesis of furan diester **94**. Conditions: a) TBSCl, KCN, ZnI_2, MeCN, 12 h, rt (96%); b) (i) LDA, THF, 1 h, -78 ^{o}C; (ii) TBAF, HAc, THF, rt, 4h (61%).

4.3.2 Diastereoselective lactone synthesis by Hydride Reduction of 94

The hydride reduction of arylsuccinyl diesters has been previously reported. Treatment of furylsuccinyl diester with $NaBH_4$ and $Zn(BH_4)_2$ followed by exposure in TFA afforded *cis* and *trans*, respectively, with different degrees of selectivity. A high preference to form the *cis*- and *trans*-lactones was observed with $NaBH_4$ and $Zn(BH_4)_2$, respectively (Scheme 39).[68] This partiality can be explained on the basis of the Felkin-Ahn and Cram Chelate principles as shown in Figure 26.



Scheme 39. Conditions: a) (i) $NaBH_4$, MeOH, 2h, 0 ^{o}C; (ii) PTSA (79%); b) (i) $Zn(BH_4)_2$, THF, 2 h, 0 ^{o}C; (ii) HAc (52%).

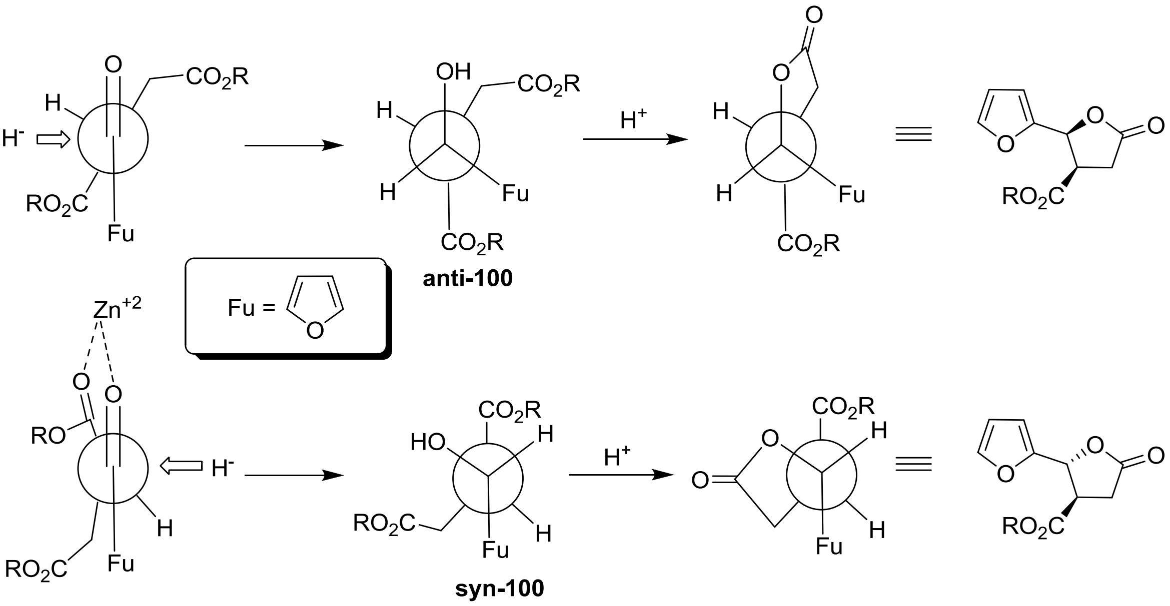


Figure 26. Addition of hydride in Felkin-Ahn and Chelate controlled conditions.

Under the Felkin-Ahn control, the hydride (H^-) is delivered at the least congested site to give *anti*-**100** while the 1,3-stereocontrolled $Zn(BH_4)_2$ addition drives the hydride addition at the other side to furnish *syn*-**100**. Subsequently, the *cis*- and *trans*- lactones were generated from *anti* and *syn* intermediates respectively, under acidic conditions.

4.3.3 Enantioselective reduction of 94 by dynamic kinetic resolution (DKR)

As shown in Figure 27, substrate enantiomers S_R and S_S react at different rates, k_R and k_S, affording products P_R and P_S under certain chiral conditions. This dichotomy allows chemical and biological kinetic resolution of racemic mixtures. Chirally sensitive stereocenters that racemize during reaction can, in principle, be transformed in 100% yield to enantiomerically pure products regardless of the extent of substrate conversion.[69]

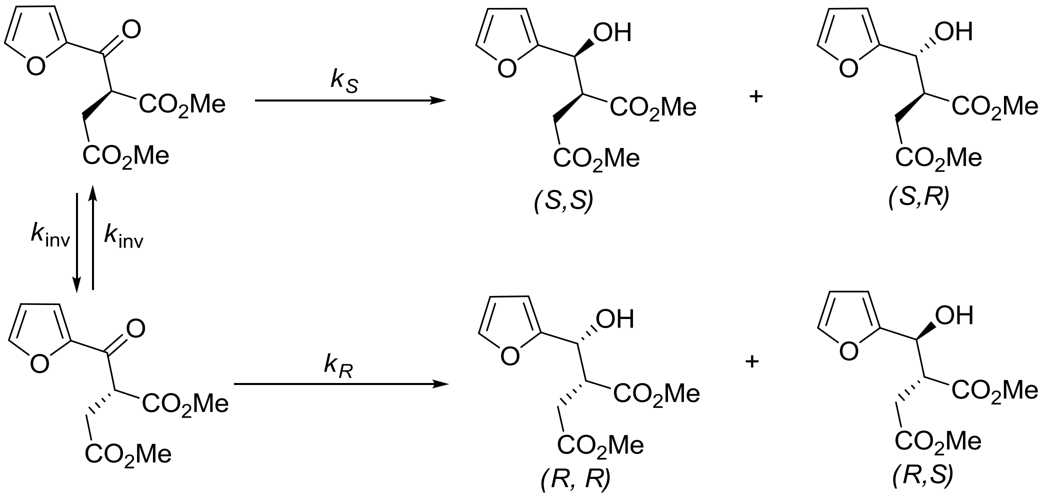
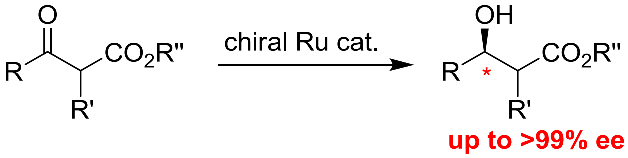


Figure 27. Pathways in DKR controlled reactions.

The reduction of α-substituted β-keto esters is among the most common DKR reaction. The chiral substrates that undergo ready racemization passing through the enol form are converted to a series of important β-hydroxy esters. Although four stereoisomers are furnished in this reaction, the selection of appropriate conditions may result in a single product with high stereoselectivity.

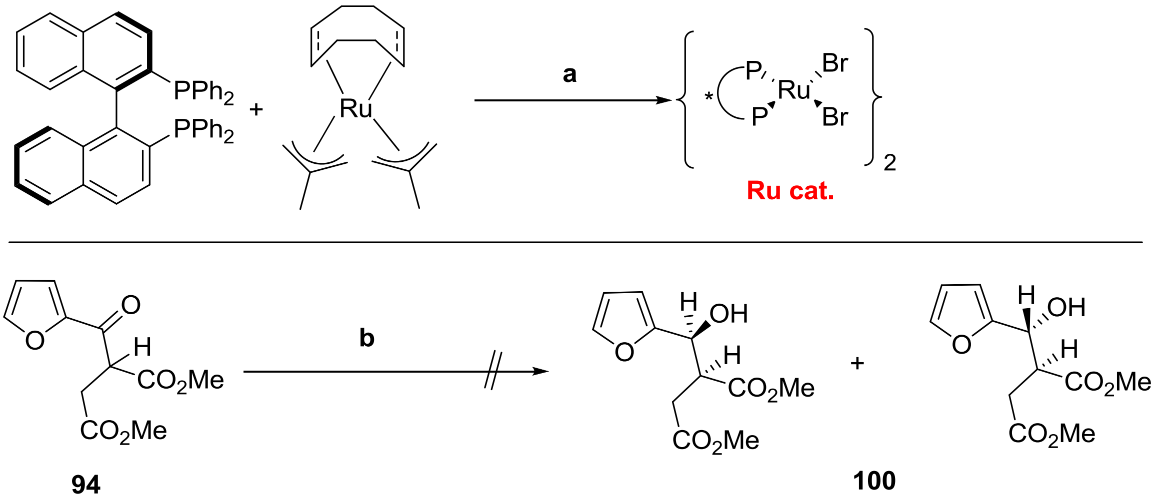
4.3.3.1 Ruthenium-catalyzed asymmetric hydrogenation

Established after the pioneering studies of Noyori and co-workers, asymmetric hydrogenation of β-keto esters with chiral ruthenium catalysts has emerged as a powerful approach which can be often combined with dynamic kinetic resolution (DKR) methods to synthesize α-substituted β-hydroxy esters and related compounds (Scheme 40).[70]

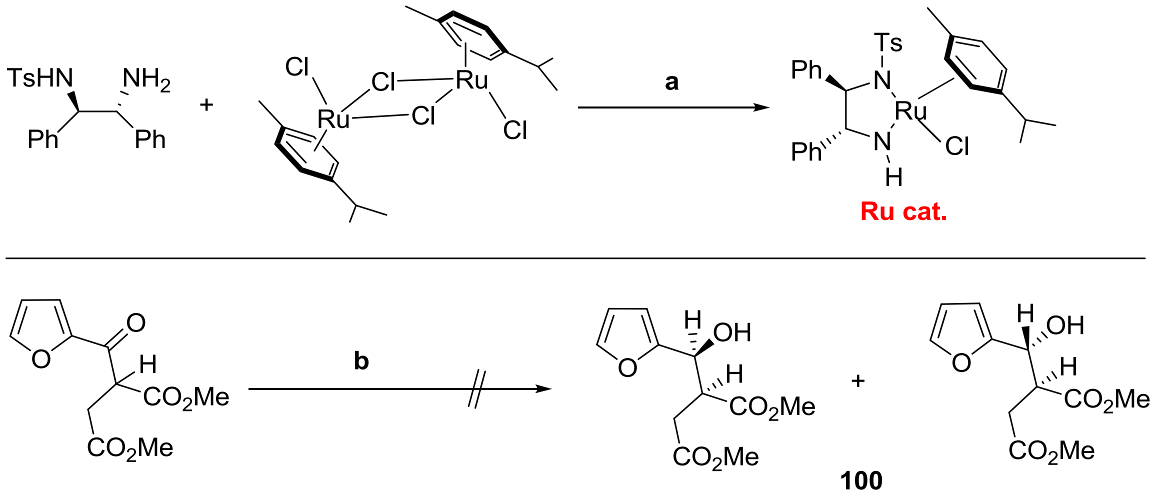


Scheme 40. Ruthenium catalyzed enantioselective carbonyl reduction.

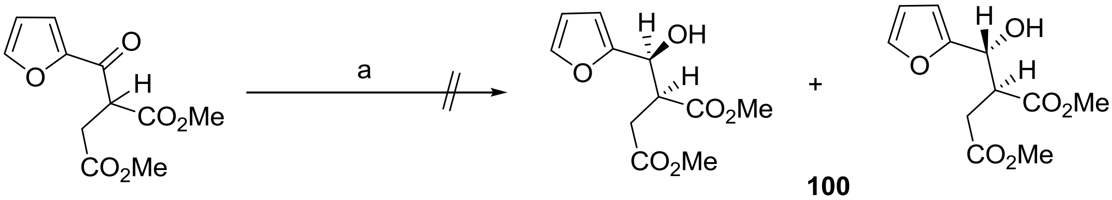
Asymmetric hydrogenation of **94** with $RuBr_2[(R)\text{-BINAP}]$ in methanol and asymmetric transfer hydrogenation with the Noyori/Ikariya's [(*R,R*)-RuCl(TsDPEN)(*p*-cymene)] and 5:2 HCO_2H/Et_3N as solvent and hydrogen source proved to be futile and challenging (Scheme 41 and 42). Recently, Vinogradov and co-workers described the asymmetric hydrogenation of acylsuccinates in the presence of a $RuCl_3$–BINAP catalyst system.[71] This study has allowed the synthesis of chiral 2-alkylparaconic acid esters in preparative yields and excellent enantioselectivities (Scheme 43). Nevertheless, subjection of furylsuccinate **94** with $RuCl_3$/*R*-BINAP in absolute MeOH and 40 bar of H_2 at 50 °C did not promote conversion to the desired β-hydroxy product **100** (Scheme 43).



Scheme 41. Conditions: a) HBr, acetone, rt; b) Ru cat., MeOH, H_2 (75 atm), 50 °C.



Scheme 42. Conditions: a) KOH (98%); b) Ru cat., $HCO_2H\text{-}Et_3N$ (5:2), 4 days, rt.



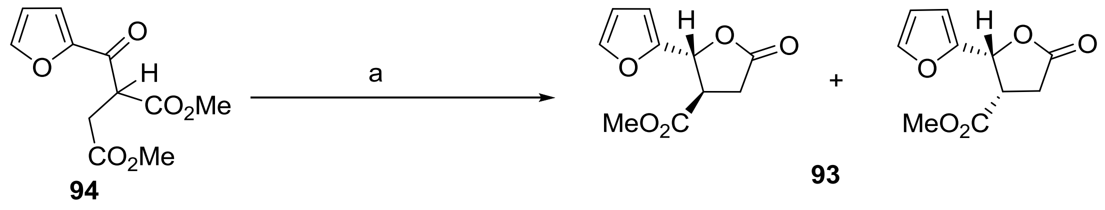
100

Scheme 43. Conditions: a) $RuCl_3$ (1 equiv), (*R*)-BINAP, H_2 (40 atm), MeOH, 12 h, 60 °C.

4.3.3.2 Biocatalytic reduction using yeast

A number of microorganisms and enzymes are also known to catalyze the stereoselective reduction of β-keto esters to β-hydroxy esters. The use of a baker's yeast is probably one of the most convenient biological methods to carry out this protocol.[69,72]

Bioreduction of furylsuccinate **94** with *Saccharomyces cerevisiae* (Baker's yeast) biomass furnished a 25% combined yield of 3:1 *cis*- and *trans*-**93** lactones (Scheme 44). Plagued with difficulty on their separation in silica, the β-hydroxysuccinate intermediates were directly treated with PTSA to afford the lactones. The low yield can be attributed to complications brought about by the high hydrolytic activity of *S. cerevisiae* enzymes and concomitant decarboxylation reactions occurring on many intermediates. Multifunctional substrates are particularly labile to decompositions owing to various membrane and/or cytoplasmic enzymes present in microbial whole cell systems. Figure 28 summarizes the possible pathways of the transformations involved. Pathway a, is the most common for all yeast strains. It involves the hydrolysis of the secondary ester group of **94** to give the corresponding hemiester **101**, whose subsequent fate is decarboxylation and hydrolysis *en route* to γ-hydroxyoacids **102**. Pathway b involves the hydrolysis of the primary ester group and reduction of the carbonyl group of the ketodiester to give **100**. Pathway c involves a *retro* Claisen reaction driving the formation of heteroaromatic acid **103**.[73]



Scheme 44. Conditions: a) (i) Dr. Oetcker's Yeast, H_2O, 12 h; (ii) PTSA, THF, 4 h, 0 °C (25%).

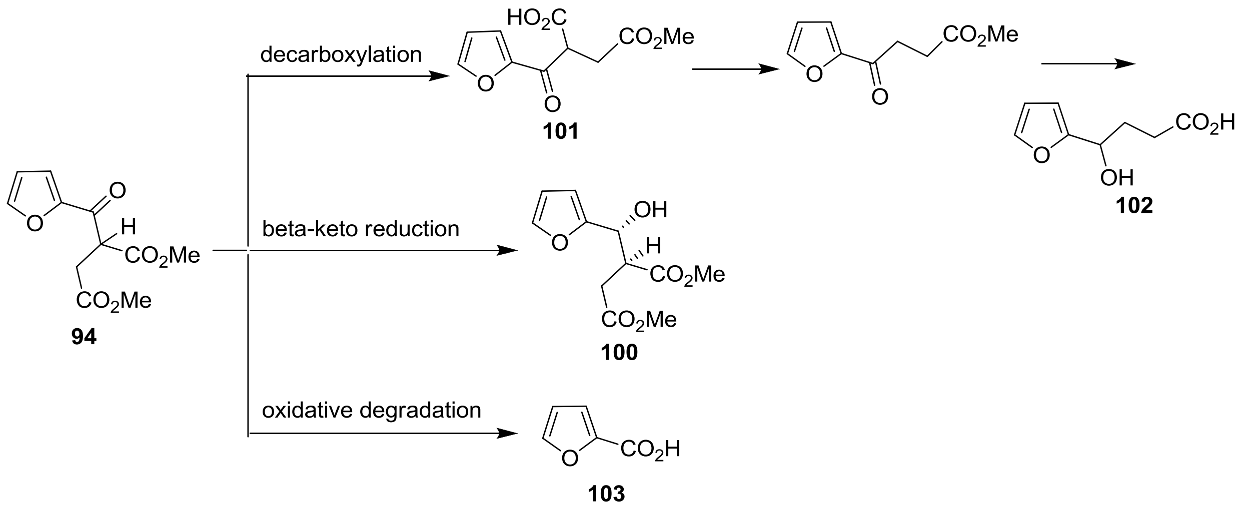


Figure 28. Degradative pathways in yeast reductions.

The absolute stereochemistry of *cis*-lactone **93** was established from its single X-ray structure (Figure 29). Thus, the C4 and C5 stereocenters were assigned the *4S,5R* configuration. The *trans*-lactone **93** on the other hand was given the *4R,5R* stereochemistry based on its negative Cotton effects around 210 nm which readily corroborated for n-π* transition of (*R*) γ-arylated-β-carboxylactones (Figure 30).[73]

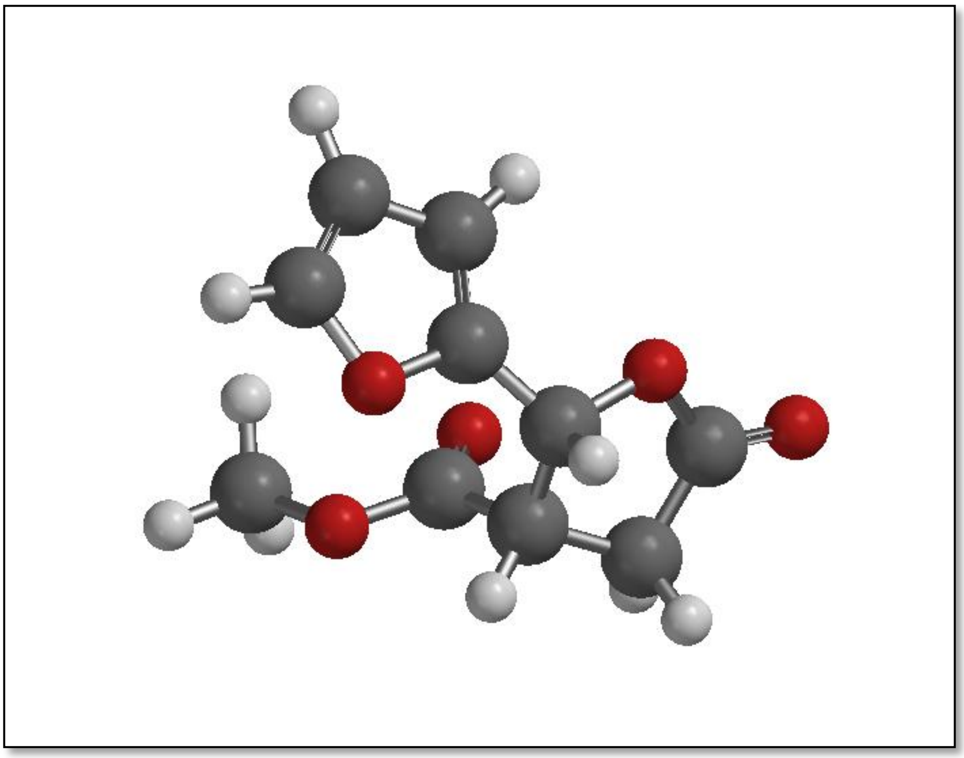


Figure 29. Single X-ray crystal of *cis*-lactone (-)-**93**.

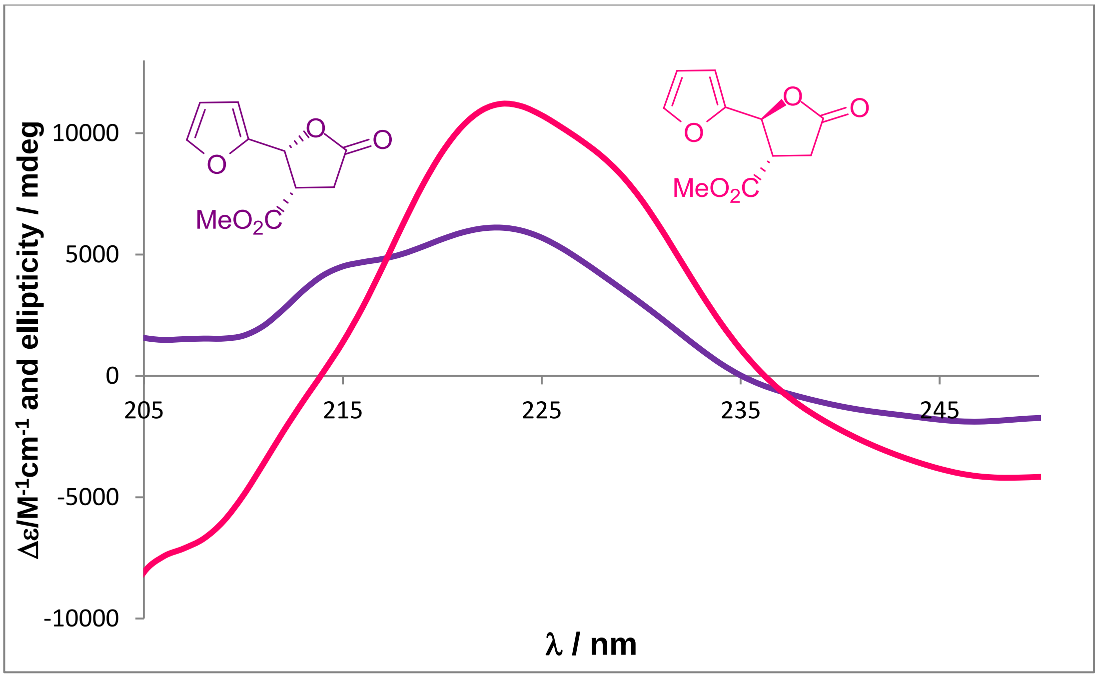


Figure 30. CD spectrum of *cis*-**93** and *trans*-**93.**

4.3.4 Conclusion

Enantioselective reduction of a furylated β-keto succinate ester **94** was successfully carried out using yeast to furnish *cis*- and *trans*- lactones albeit in small yield. Thus, further investigations and optimizations on this aspect are still needed. Although the afforded *trans* stereochemistry was opposite to what is originally required, it can be a useful template for the synthesis *en route* the enantiomer of **1-3**.

4.4 A Simplified Approach Towards the Total Synthesis of Bielschowskysin

4.4.1 Synthetic Efforts towards Bielschowskysin (1)

Although there are no reported total syntheses of bielschowskysin, there have been two reported syntheses of the cyclobutane core found in the natural product.

As the key step towards bielschowskysin (**1**) (Figure 31) the Sulikowski[74] and Lear[75] groups envisaged along the lines of the proposed biosynthetic pathway a photostimulated [2+2] cycloaddition by constructing the C6/C12 and C7/C11 junctions in building up the cyclobutane core, aiming at intermediates **104** and **105**, respectively.

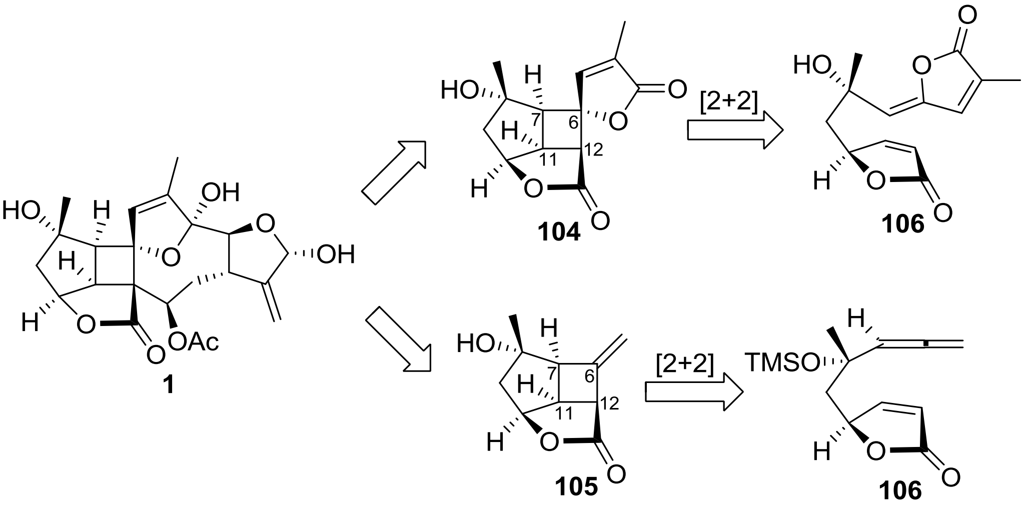
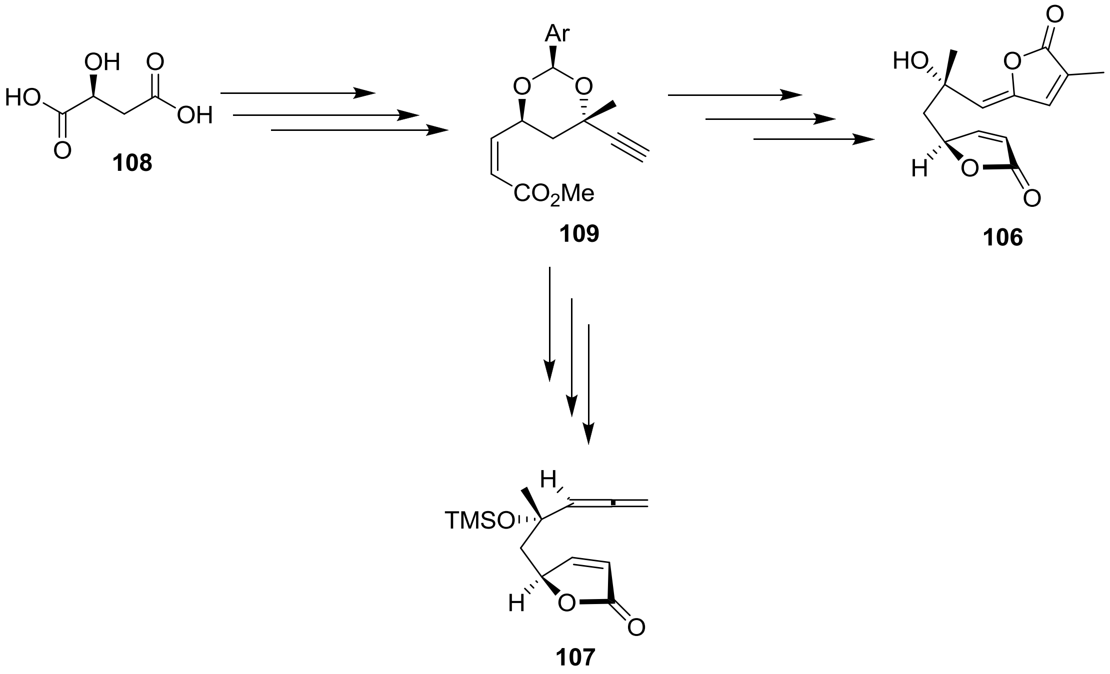


Figure 31. Retrosynthetic strategies for the synthesis of **1**.

Both synthetic routes towards the photocyclization precursors **106** and **107** started from (*L*)-malic acid (**108**), going to the common intermediate **109** (Scheme 44). The alkynyl group was manipulated in a different way by both groups: Elongation was carried out by Doroh and Sulikowski via a palladium-catalyzed cross coupling reaction**,** followed by oxidation of the alcohol and ultimately acid catalyzed 5-*exo-dig* cyclization of the carboxylic acid onto the acetylene moiety. Lear and coworkers converted the acetylene to an allene utilizing a copper-catalyzed addition of formaldehyde followed by dehydration.



Scheme 44. Synthesis of furanones **106** and **107**.

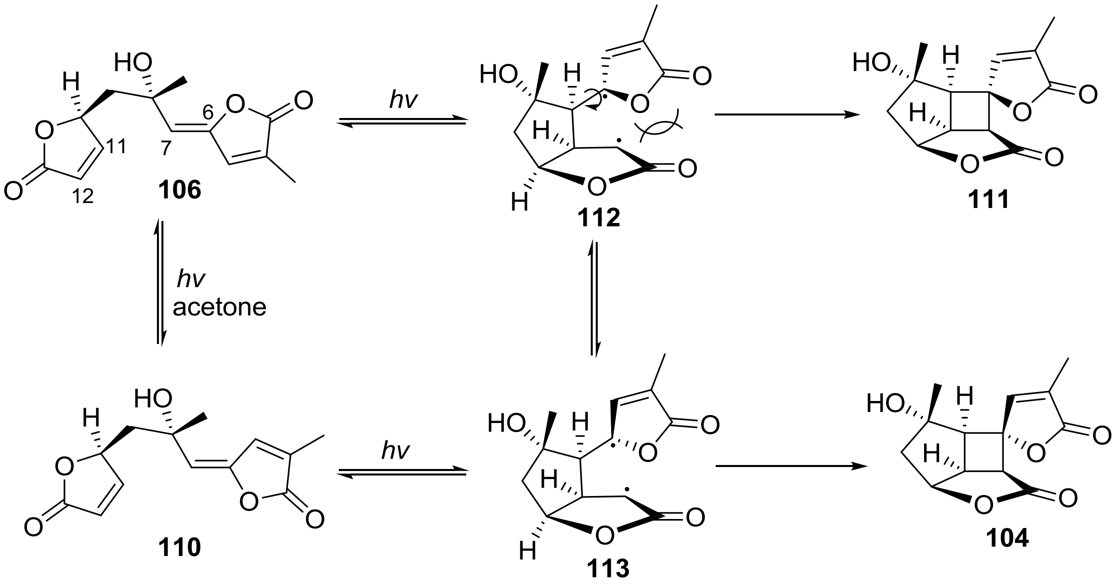
[2+2] Photoaddition. According to the study done by Doroh and Sulikowski, photoirradiation of **106** was first done in chloroform using a 275 W sun lamp, however double bond isomerization in the alkylidene moiety of the forming furanone **110** was observed to a considerable extent. Further irradiation of the solution provided a complex mixture of products. Switching the solvent to acetone showed a dramatic effect (Scheme 45). A similar isomerization phenomenon occurred but this time prolonged exposure of the solution using a daylight lamp afforded a 5:1 mixture of two compounds (50%) with **104** being the major and **111** as the minor [2+2] photoadduct. Sulikowski and Doroh postulated that the formation of **104** adheres with the norm of the 'rule of five[76] *vis-à-vis* [2+2] photoinduced addition of alkene derivatives to furanones.[77] According to this rule, intramolecular 1,5-photocyclization events occur and are preferentially geared towards the formation of a five-membered ring. High regioselectivity is usually achieved when two reacting olefins are separated by two to four atoms.[78] Hence, in accordance with this rule, a plausible formation of a 1,4-biradical[79] **112** and **113** intermediates rather than a concerted reaction mechanism may be operating in this photoaddition. It was envisaged that a photochemical equilibriation effected

a) *cis-trans* isomerization of **106** to **110** and vice versa;

b) rotation of the C6 - C7 bond which triggered the interconversion of **112** to **106** and **113** to **110**; and

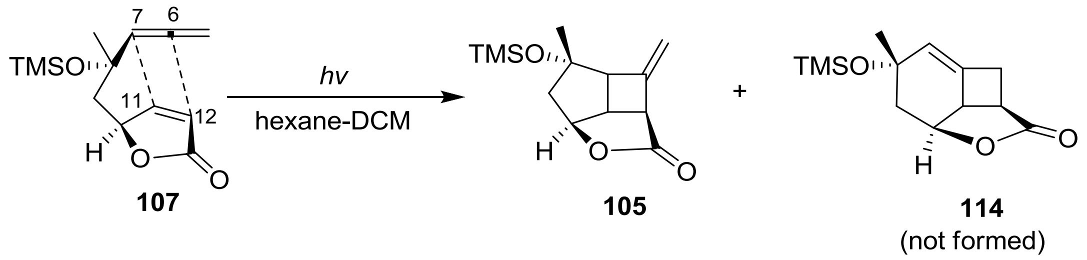
c) stereochemical mutation of triplet radicals, i.e. rotation around C6 and C12 interconverts **112** to **113**.

The path favoring the formation of photoadduct **104** from these series of photoinduced equilibriation processes were ascribed by the authors to a more preferable dipole interaction in **113** during radical combination.



Scheme 45. Photochemical phenomena leading to photoadduct **2**.

On a separate study, subjection of the dichloromethane/hexane solution of furanone **107** under UV-irradiation (254 nm) afforded **105** (70%) exclusively (Scheme 46). They suggest that the regiocontrolled [2+2] addition of the internal double bond of the allenyl moiety is attributed to the presence of a tertiary alcohol center at C8. Such favors the creation of a five-membered ring and averts the formation of a six-membered cyclic structure, hence, illustrating a photochemical system that is governed solely by the 'rule of five' as applied to [2+2] photoadditions of tethered allenes to enones.[80] It has been reported that some allene photosubstrates possessing an oxygenated C3 substituent (in this case C7) have the propensity to form both straight photoadduct (as in **105**) and bridgehead olefinic (as in **114**).[81] Therefore, Lear and co-workers ascribed the regioselectivity and high stereocontrol of the photoreaction on the presence of a chiral quaternary center connected to C7 and on the conformation of the 1,3-allene moiety.



Scheme 46. Photochemical cycloaddition *en route* to photoadduct **3**.

4.4.2 Retrosynthetic analysis

Although the three previously discussed strategies present viable approaches to construct the northeastern sector of furanocembranoids **1-3**, some unforeseen challenges might arise along the way especially when the synthesis will approach to its completion, noteworthy for **1**. For example, a number of steps to build up the lower sector may be required which invokes refunctionalization and protection-deprotection sequences. To address this potential problem, the synthetic approach has been simplified for **1** through a convergent approach. The interest to pursue bielschowskysin (**1**) is mainly related to its structural complexity and pharmacological activity (antimalarial and anti-cancer).[6c]

The retrosynthetic analysis (Figure 32) starts through a lateral scission of the middle portion of **1** affording retron **115** and **116**. It was envisioned that connections between C3/C6, C4/C5 and C12/C13 can be installed via acetalization, RCM and aldol addition, respectively. The synthesis of **115** can be achieved from methallyl lactone aldehyde **117**. The latter can be obtained from chiral cyclopropane **15** and methallyl TMS **118** through an established protocol for γ-allyl lactone synthesis. On the other hand, cyclobutane **116** was envisaged to be made from cyclopentenol maleate **119** through a [2+2] photocycloaddition as key step. The synthesis of **119** can be accomplished by way of Mitsunobo reaction of the known cyclopentene diol **120** with methylmaleate **121**. The commonality among the starting materials can be traced on the fact that most of them are readily made from furan compounds.

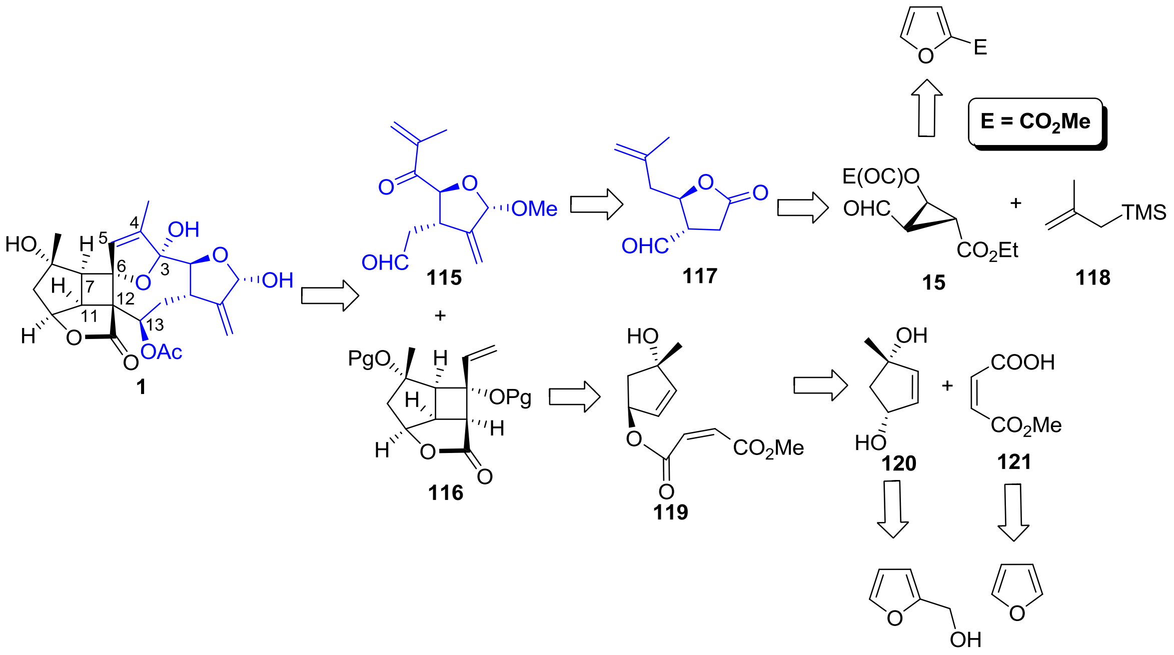
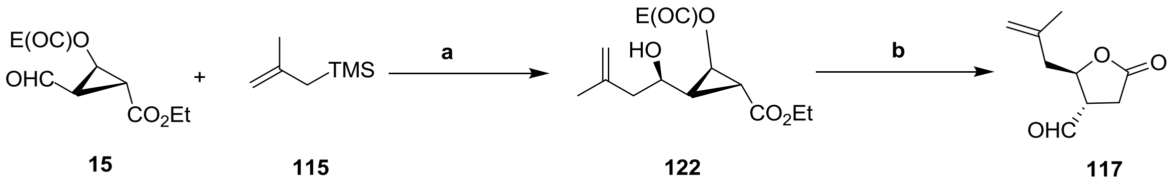


Figure 32. Retrosynthesis of bielschowskysin (**1**).

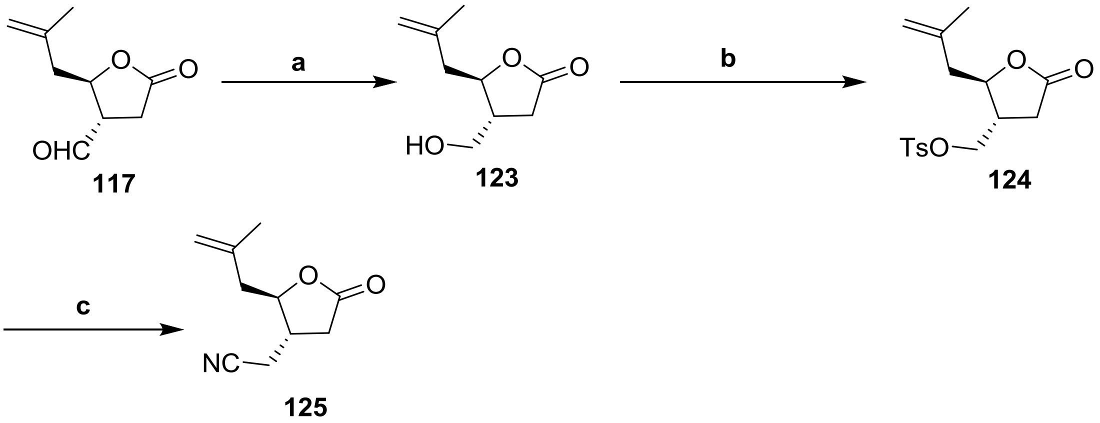
4.4.3 Synthesis towards ketolactol synthon 115

Allylsilanes are convenient nucleophilic equivalents for Hosumi-Sakurai allylation reactions. In this sequence, a methallyl TMS **118** was used as a building block for the C3/C4/C18 segment.[15] Thus, allylation of cyclopropane carboxaldehyde **15** with **115** under $BF_3 \cdot OEt_2$ catalysis provided cyclopropane carbinol **122** in 97% (Scheme 47). One-pot *retro*-aldol and lactonization of **122** under basic conditions (methanolic $Ba(OH)_2 \cdot 8H_2O$) delivered *trans*-methallyllactone **117** in moderate yield. Lactone **117** is now a suitable platform for further functionalizations. Moreover, it features the *trans-1S,2S* configuration required in furanocembranoid **1**.



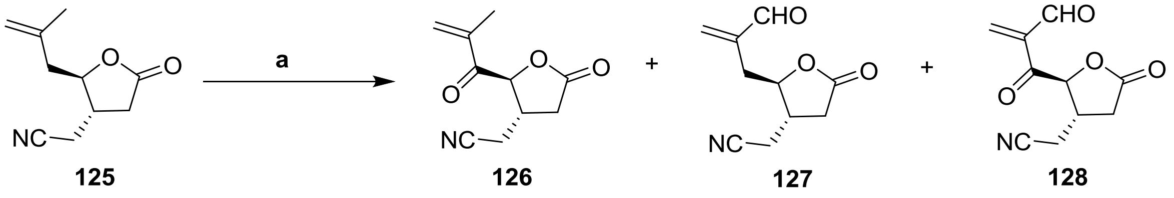
Scheme 47. Synthesis of lactone **117**. Conditions: a) $BF_3 \cdot OEt_2$, DCM, 16 h, 78 °C (97%); b) $Ba(OH)_2 \cdot 8H_2O$, MeOH, 0 °C (44%).

The next planned sequence was the one-carbon homologation of the β-carbaldehyde functionality. Originally, an Arndt-Eistert reaction was proposed as the homologation strategy. However, this reaction requires toxic transformations and work-ups. Therefore, a less elegant incorporation of a nitrile group was proposed as alternative strategy. The nitrile group on the latter stage can be easily converted directly to an aldehyde functionality by DIBALH reduction. Thus, to carry out such chain extension chemistry, the β-carbaldehyde was reduced first to an alcohol. Treatment of lactone **117** with $NaBH_4$ in MeOH yielded methallyl lactone methanol **123** (Scheme 48). Tosylation of the resulting alcohol **123** with tosyl chloride in the presence of triethylamine and catalytic amounts of DMAP furnished the tosylated derivative **124** in a moderate yield. The tosylate group now opens an opportunity for S_N2 reaction with nitrile as the nucleophilic component. Thus, treatment of tosylated lactone **124** with KCN in refluxing DMF afforded methallylated acetonitrile lactone **125** in good yield.



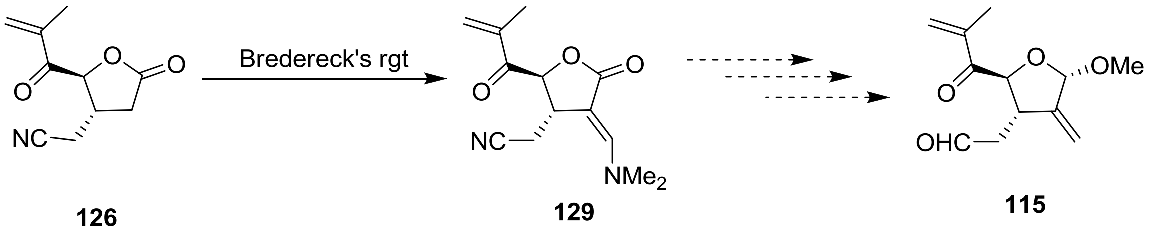
Scheme 48. Synthesis of lactone **125**. Conditions: a) $NaBH_4$, MeOH, 1 h, 0 °C 56%; b) TsCl, Et_3N, DMAP, DCM, 12 h, 0 °C 44%. (c) KCN, DMF, 48 h, reflux, 85%.

The next critical step was the incorporation of a hydroxyl or keto group at the saturated methylene carbon in the methallyl arm of the lactone by way of allylic oxidation. Reaction of nitrile **125** with SeO_2 in a biphasic solution (H_2O-dioxane) resulted in the formation of three compounds with the keto derivative **126** as the main product in moderate yield (Scheme 49). The drawback in this reaction is the possibility of undergoing over and non-regioselective oxidation thus the co-formation of products **127** and **128**.



Scheme 49. Allylic oxidation of lactone 125. Conditions: a) SeO_2, dioxane-H_2O (1:1), 12 h, reflux (31% for **126**; 22% **127** and 10% for **128**).

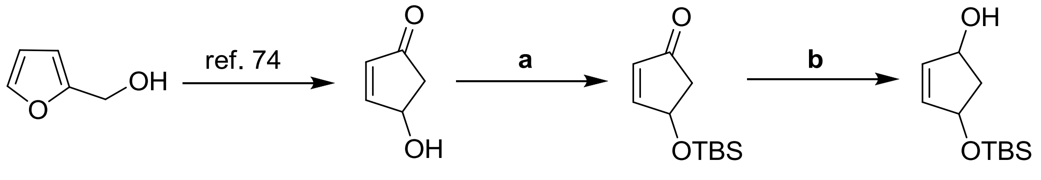
Installation of the *exo*-olefinic component by heating nitrile lactone **126** with Bredereck's reagent to yield **129** and reduction with excess DIBALH should lead to the desired lactol **115** (Scheme 50).



Scheme 50. Synthesis of lactol methyl ether **115**.

4.4.4 Synthesis towards cyclobutane synthon 116

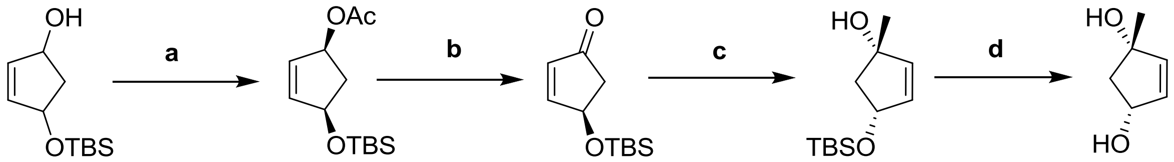
The asymmetric preparation of cyclopentene diol **120** has been already described in the literature. The synthesis was carried out following the well-established procedure of Curran and co-workers for the macroscale preparation of optically active *cis*-2-cyclopenten-1,4-diols.[82] The synthesis started with the acid-catalyzed rearrangement of furfuryl alcohol **130** to racemic 4-hydroxy cyclopent-2-enone **131** with improved modifications from Reiser and co-workers.[83] This rearrangement presents an interesting mechanism that is well-reported in several studies.[82] The introduction of a bulky protecting group in the free hydroxyl group in **131** (ex. TBS group) drives the subsequent LAH reduction of **132** to occur in a highly diastereoselective fashion yielding the *cis*-substituted product **133** in a good yield (Scheme 51).



130 **131** **132** **133**

Scheme 51. Synthesis of alcohol **133**. Conditions: a) TBDMSCl, NEt_3, DMAP (5 mol %), THF, 0 °C - rt, 83%; b) $LiAlH_4$ (0.70 eq.), LiI (0.50 eq.), toluene/TBME, -30 °C, 3 h, 79%.

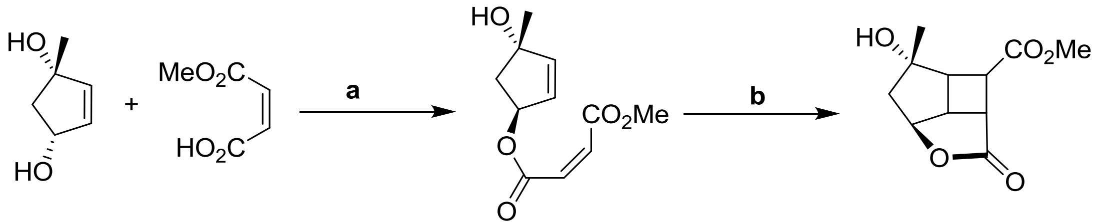
The next step was delved on the kinetic enzymatic resolution of racemate **133** using a porcine pancreas lipase (PPLE).[84] The interest TBS-protected acetoxycyclopentene **134** was readily separated from the unreacted cyclopentenol (Scheme 52). Through a series of protection-deprotection transformations involving saponification and oxidation sequences known for this chiral cyclopentenol, a smooth conversion towards cyclopentenone **135** was achieved. Addition of the methyl nucleophile at the less hindered face of the cyclopentenone delivered tertiary alcohol **136** with good diastereoselectivity (92% *dr*). TBS removal under non-nucleophilic basic conditions using TBAF furnished chiral methylcyclopentendiol **120**.



133 **134** **135** **136** **120**

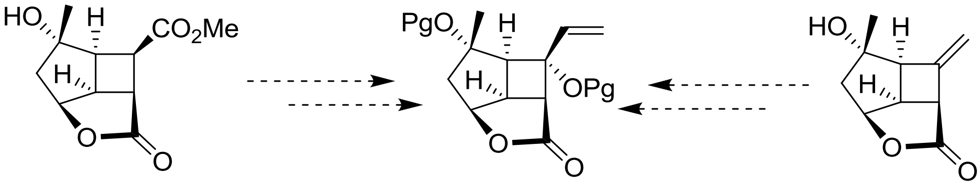
Scheme 52. Enzymatic resolution: a) porcine pancreas lipase PPLE, vinylacetate, Et_3N (0.68 eq.), TBME, rt, 48 h, 78%; b) (i) LiOH, THF:MeOH:H_2O (3:1:1), rt, 2 h, 93%; (ii) PCC, DCM, 2 h, 0 °C, 85%. c) MeLi, THF, 3 h, -78 °C, 63%; d) TBAF, NEt_3, THF, rt, 24 h, 79%.

Since the required stereoconfiguration at C10 is *S*, a Mitsunobo inversion was the next sensible step to perform. To further simply and accelerate the synthesis of the requisite diene, methylmaleate **121** was chosen as the nucleophilic component in the reaction. Thus, treatment of cyclopentendiol with methylmaleate in the presence of DIAD and PPh_3 provided diene ester **119** in 94% yield (Scheme 53). The maleate moiety and the olefin in the cyclopentene handle now constitute the electron-poor and electron-rich alkenes suitable for a photodriven [2+2] cycloaddition. Thus, a trial photoirradiation of **119** in acetone[74] afforded a crude mixture of diasteromeric cyclobutane products **137** as evidenced from the ^{1}H and ^{13}C NMR spectra (Figure 33). Due to the observation of many diastereomeric adducts, further optimization on this reaction is recommended. Further manipulations on cyclobutane **137** (e.g. conversion of carbomethoxy ester to aldehyde, Wittig olefination and allylic oxidation) should lead to intermediate cyclobutane **116**. Alternatively, transformation of the Lear cyclobutane **105** to **116** should also be investigated (Scheme 54).



120 **121** **119** **137**

Scheme 53. Conditions: a) **121**, PPh_3, DIAD, MeCN, 4 h, 0 °C, 85%; b) acetone, $h\nu$ (254 nm), 24 h, >80% conversion.



137 **116** **105**

Scheme 54. .Synthesis of **116** from **137**or **105**.

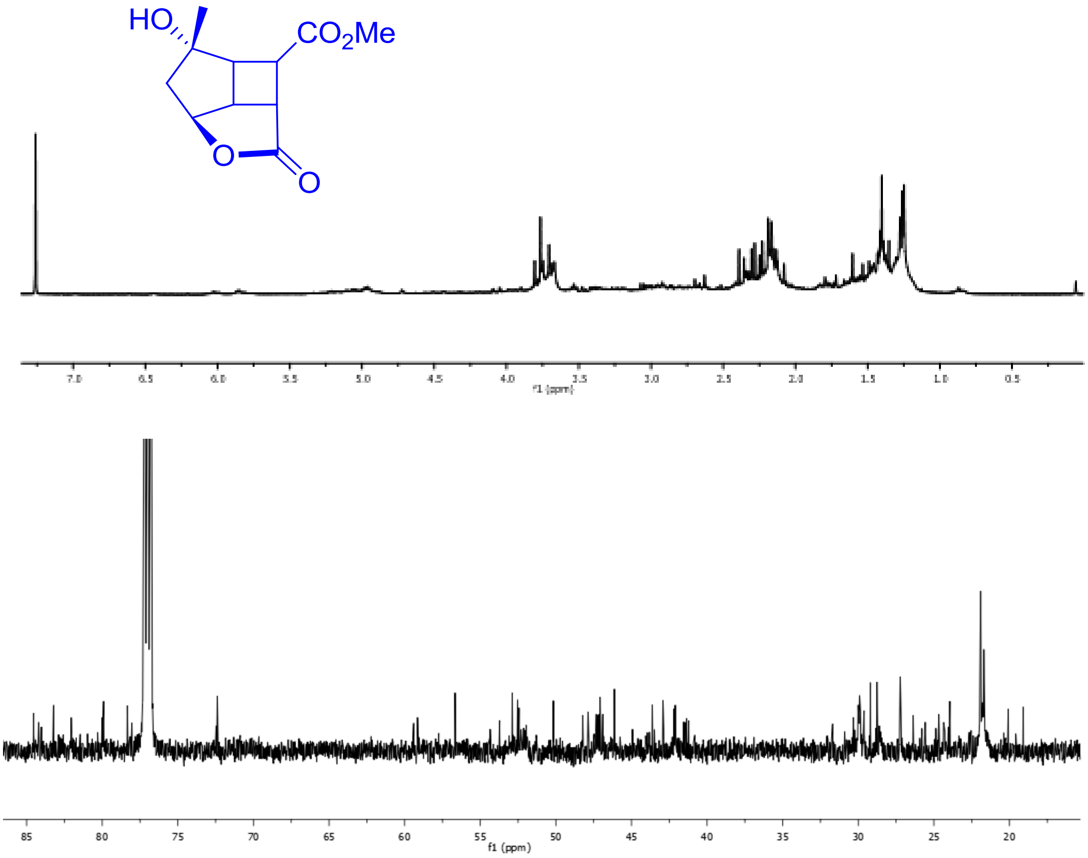
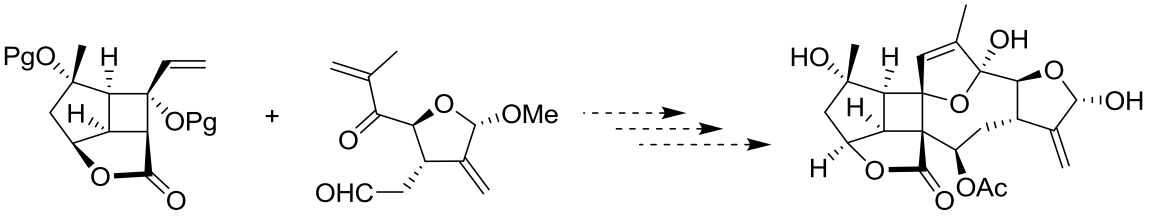


Figure 33. ^{1}H and ^{13}C NMR spectra of cyclobutane **137**.

Once the eastern segment **115** and western segment **116** have been successfully synthesized, coupling of these two intermediates followed by deprotection should lead to bielschowskysin (**1**) (Scheme 55).



Scheme 55. Proposed completion of **1**.

4.4.5 Conclusion

Starting from furan derivatives as starting materials, two intermediates **119** and **126** relevant for constructing the two key building blocks **115** and **116** were successfully prepared. Further synthetic transformations of these compounds may potentially lead to the completion of bielschowskysin (**1**).

References

1. Blunt, J.; Copp, B.; Munro, M.; Northcote, P.; Prinsep, P. *Nat. Prod. Rep.* **2004**, *21*, 1.
2. Rodriguez, A. D. *Tetrahedron.* **1995**, *51*, 4571.
3. Bayer, F. M. *The Shallow-Water Octocorallia of the West Indian Region*; Martinus Nijhoff: The Hague, 1961.
4. Heckrodt, T. J.; Mulzer, J. *Top. Curr. Chem.* **2005**, *244*, 1.
5. Look, S. A.; Burch, M. T.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1985**, *50*, 5741.
6. (a) Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G. *J. Org. Chem.* **2003**, *68*, 4977. (b) Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G. *Org. Lett.* 2**003**, *5*, 2551. (c) Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega- Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661. (d) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G. *Eur. J. Org. Chem.* **2004**, 3909. (e) Marrero, J.; Rodríguez, A. D.; Barnes, C. L. *Org. Lett.* **2005**, *7*, 1877. (f) Marrero, J.; Ospina, C. A.; Rodríguez, A. D.; Baran, P.; Zhao, H.; Franzblau, S. G.; Ortega-Barria, E. *Tetrahedron.* **2006**, *47*, 6998.
7. (a) Fenical, W. *J. Nat. Prod*. **1987**, *50*, 1001. (b) Rodriguez, A. D.; Shi, J.-G. *J. Org. Chem*. **1998**, *63*, 420. (c) Rodriguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Org. Chem*. **1998**, *63*, 4425. (d) Rodriguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Nat. Prod.* **1999**, *62*, 1228. (e) Rodriguez, A. D.; Shi, J.-G.; Shi, Y.-P. *J. Org. Chem*. **2000**, *65*, 3192.
8. Rodriguez, A. D.; Shi, Y. P. *J. Org. Chem.* **2000,** *65,* 5839.
9. Marrero, J.; Benitez, J.; Rodriguez, A.; Zhao, H.; Raptis, R. G.. *J. Nat. Prod.* **2008,** *71,* 381.
10. Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298.
11. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275.
12. (a) Iketubosin, G. O.; Mathieson, D. W. *J. Pharm. Pharmacol*. **1963**, *15*, 810. (b) Saito, S.; Tanaka, T.; Kotera, K.; Nakai, H.; Sugimoto, N.; Horii, Z.; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull*. **1965**,*13*, 786.
13. Hitotsuyanagi, Y.; Hikita, M.; Oda, T.; Kakuta, D.; Fukaya, H; Takeya, K.. *Tetrahedron.* **2007**, *63*, 1008.
14. Tan, M. A.; Kitajima, M.; Kogure, N.; Nonato, M. G.; Takayama, H. *Tetrahedron Lett.* **2010**, *51*, 4143.
15. (a) Kalidindi, S.; Jeong, W. B.; Schall, A.; Bandichhor, R.; Nosse, B.; Reiser, O. *Angew. Chem. Int., Ed.* **2007**, *46*, 6361. (b) Bandichhor, R.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem. Eur. J.* **2003**, *9*, 260.
16. Vassilikogiannakis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. *Chem. Eur. J*. **2005**, *11*, 5899.
17. Montagnon, T.; Noutsias, D.; Alexopoulou, I.; Tofi, M.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2011**, *9*, 2031.
18. (a) Nasman, J. H. *Org. Syn.* **1990,** *68*, 162. (b) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Burreddu, P.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **2008**, *73*, 5446.
19. Sharma, V.; Kelly, G. T.; Watanabe, C. M. H. *Org Lett.* **2008**, *10*, 4815.
20. Brimble, M. A.; Brimble, M. T.; Gibson, J. J. Org. Bio-Org. Chem. (1972-1999). **1989**, *1*, 179. (b) Curti, C.; Battistini, L.; Zanardi, F.; Rassu, G.; Zambrano, V.; Pinna, L.; Casiraghi, G. *J. Org. Chem.* **2010**, *75*, 8681.
21. Böhm, C.; Schinnerl, M.; Bubert, C. Zabel, M.; Labahn, T. Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000**, 2955.
22. (a) Haque, M. M. Ph.D. Dissertation, **2005**. (b) Bordessa, A. Ph.D. Dissertation, **2008**. (c) Delatouche, R. Ph.D. Dissertation, **2008**. (d) Sahr, F. PhD Dissertation. **2009**.
23. Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Helvetica Chimica Acta* **1988**, *71*, 1553.
24. Temme, O.; Taj, S. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 6007.

25. Nosse, B.; Bandichhor, R.; Jeong, W. B.; Böhm, C.; Reiser, O. *Org. Lett.* **2003**, *5*, 941.
26. (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Denmark, S. E.; Heemstra Jr., J. R.; Beutner, G. L. *Angew. Chem.* **2005**, *117*, 4760; *Angew. Chem. Int. Ed.* **2005**, *44*, 4682. (c) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43. d) Hosokawa, S.; Tatsuta, K. *Mini-Rev. Org. Chem.* **2008**, *5*, 1. (e) Zanardi, F.; Battistini, L.; Curti, C.; Casiraghi, G. *Chemtracts*. **2010**, 123.
27. (a) Reißig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Brückner, C.; Reißig, H.-U. *J. Org. Chem.* **1988**, *53*, 2440. (*c*) Kunz, H.; Lindig, M. *Chem. Ber.***1983**, *116*, 220.
28. Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315-1318.
29. (a) Gawronski, J. K.; Chen, Q. H.; Geng, Z.; Huang, B.; Martin, M. R.; Mateo, A. I.; Brzotowska, M.; Rychilewska, U.; Feringa, B. L. *Chirality*. **1997**, *9*, 537. (b) Gawrosnki, J. K.; van Oeveren, A.; van der Deen, H.; Leung, C. W.; Feringa, B. L. *J. Org. Chem.* **1996**, *61*, 1513. (c) Zanardi, F.; Battistini, L.; Rassu, G.; Pinna, L.; Mor, M.; Culeddu, N.; Casiraghi, G. *J. Org. Chem.* **1998**, *63*, 1368. (d) Jefford, C. W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037. (e) Figadere, B.; Chaboche, C.; Peyrat, J. F.; Cave, A. *Tetrahedron Lett.* **1993**, *34*, 8093. (e) Zanardi, F.; Battistini, L.; Rassu, G.; Auzzas, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 2048.
30. Zanardi, F.; Battistini, L.; Rassu, G.; Auzzas, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000,** *65*, 2048.
31. (a) Casiraghi, G.; Rassu, G. *Synthesis***.** **1995**, 607. (b) Lopez, C. S.; Alvarez, R.; Vaz, B.; Faza, O. N.; de Lara, A. R. *J. Org. Chem*. **2005***,* *70*, 3654. (c) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Burreddu, P.; Zanardi, F.; Casiraghi, G. *J. Org. Chem***.** **2008***,* *73*, 5446. (d) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem***.** **2004***,* *69*, 261.
32. (a) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002,** *219*, 211. b) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55. (c) Miura, M.; Satoh, T. Handbook of C-H Transformations; Dyker, G., Ed.; Wiley-VCH:Weinheim, 2005; Vol. 1, p 223. (d) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (e) Schnürch,M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (g) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200.
33. Maehara, A.; Satoh, T.; Miura, M. *Tetrahedron*. **2008**, *64*, 5982.
34. (a) Kimbrough, T. J.; Roethle, P. A.; Mayer, P.; Trauner, D. *Angew. Chem. Int. Ed*. **2010**, *49*, 2619. (b) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298.
35. Li, Y.; Pattenden, G.; Rogers, J. *Tetrahedron Lett.* **2010**, *51*, 1280.
36. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. Organic Chemistry; Oxford University Press, 2006.
37. (a) Brenna, E.; Fuganti, C.; Serra, S. *Tetrahedron: Asymmetry*. **2003**, *14*, 1. (b) Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *59*, 365. (c) Ghosh, A. K.; Swanson, L. J. *J. Org. Chem.* **2003**, *68*, 9823. (*d*) Lipshutz, B. H. ; Lower, A. ; Kucejko, R. J.; Noson, K. *Org. Lett.* **2006**, *8*, 2969; (*e*) Stangeland, E. L.; Sammaki, T. *J. Org. Chem.* **2004**, *69*, 2381.; (*f*) Hilborn, J. W.; Lu, Z.-H.; Jurgens, A. R.; Fang, O. K.; Byers, H. ; Wald, S. A. ; Senanayake, C. H. *Tetrahedron Lett.* **2001**, *42*, 8919.
38. (a) Russell, G. F. ; Hills, J. I. *Science*. **1971**, *172*, 1043. (b) Friedmann, L. ; Miller, J. G. *Science*. **1971**, *172*, 1044. (c) Otsuka, K.; Zenibayashi, Y.; Itoh, M.; Totsuka, A. *Agric. Biol.Chem.* **1974**, *38*, 485. (d) Tumlinson, J. H.; Klein, M. G.; Doolittle, R. E.; Ladd, T. L.; Proveaux, A. T. *Science*. **1977**, *197*, 789.
39. (a) Schall, A.; Reiser, O. *Eur. J. Org. Chem.* **2008**, *14*, 2353. (b) Seitz, M.; Reiser, O. *Curr. Opin. Chem. Biol.* **2005**, *9*, 285. (c) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43.

40. (a) Ramachandran, P. V.; Padiya, K. J.; Rauniyar, V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2004**, *45*, 1015. (b) Ozeki, M.; Hashimoto, D.; Nishide, K.; Kajimoto, T.; Node, M. *Tetrahedron: Asymmetry*. **2005**, *16*, 1663 and references cited therein.
41. Cambie, R. C.; Lal, A. R.; Rutledge, P. S.; Wellington, K. D. *Biochem. Syst. Ecol.*, **1997**, *25*, 565.
42. Macabeo, A. P. G.; Kreuzer, A.; Reiser, O. *Org. Biomol. Chem.* **2011**, DOI: 10.1039/c1ob05113j.
43. Tanis, S. P.; Deaton, M. V.; Dixon, L. A.; McMillis, M. C.; Raggon, J. W.; Collins, M. A. *J. Org. Chem.* **1998**, *63*, 6914.
44. Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667.
45. (a) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421. (b) Reetz, M. T.; Steinbach, R.; Westermann, J. ; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441. (*c*) Haarmann, H.; Eberbach, W. *Tetrahedron Lett.* **1991**, *32*, 903. (d) Zhou, S.; Chen, C. R.; Gau, H. M. *Org. Lett*, **2010**, *12*, 48. (e) Macabeo, A. P. G. *Synlett*, **2008**, *20*, 3247.
46. Zhou, S.; Chen, C.-R.; Gau, H.-M. *Org. Lett.* **2010**, *12*, 48.
47. Asao, N.; Asano, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 3206.
48. Daniewski, A. R.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1992**, *57*, 7133.
49. (a) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.*, **1991**, *56*, 5307. (b) Orita, A.; Sakamoto, K.; Hamada, Y.; Mitsutome, A.; Otera, J. *Tetrahedron*, **1999**, *55*, 2899.
50. (a) Takahashi, H.; Tanahashi, K.; Higashiyama, K.; Onishi, H. *Chem. Pharm. Bull.*, **1986**, *34*, 479. (b) Yoshida, K.; Hayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 2872. (c) Lee, H. W.; Lam, F. L.; So, C. M.; Lau, C. P. Chan, A. S. C.; Yee, F. *Angew. Chem., Int. Ed.*, **2009**, *48*, 7436.
51. Weber, B.; Seebach, D. *Tetrahedron.* **1994**, *50*, 7473.
52. Ramos, A. C.; Pelaez, R.; Luis Lopez, J.; Caballero, E.; Medarde, M.; San Feliciano, A. *Tetrahedron*, **2001**, *57*, 3963.
53. Ono, S.; Shuto, S.; Matsuda, A. *Tetrahdron Lett.* **1996**, *37*, 221.
54. Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.
55. (a) Bubert, C.; Reiser, O. *Tetrahedron Lett.***1997**, *38*, 4985. (b) Kazuta, Y.; Abe, H.; Yamamoto, T.; Matsuda, A.; Shuto, S. *Tetrahedron*. **2004**, *60*, 6689; (c) Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.*, **2004**, *69*, 9143. (d) Reetz, M. T. *Acc. Chem.Res.* **1993**, *26*, 462.
56. (*a*) Patil, S.; Stephens, B. E.; Liu, F.*Tetrahedron*. **2008**, *64*, 10831. (*b*) Maeba, I.; Suzuki, M.; Hara, O.; Takeuchi, T.; Iijima, I.; Furukawa, H. *J. Org. Chem.* **1987**, *52*, 4521.
57. Du, W.; Hu, Y. *Carbohydr. Res.*, **2006**, *341*, 725.
58. Wassermann, H. H.; Ives, J. L. *J. Org. Chem.*, **1978**, *43*, 3238.
59. (a) Mori, K.; Chiba, N. *Liebigs Ann. Chem.* **1989**, 957. (b) Mori, K.; Yamane, K. *Tetrahedron*. **1982**, *38*, 2919. (c) Mori, K. *Tetrahedron*. **1983**, *39*, 3107.
60. Crawforth, J. M.; Fawcett, J.; Rawlings, B. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1721.
61. Patrick, T. M. Jr.; Erikson, F. B. U.S.P. 2, 926, 173, 1960. (C.A.N. 54:P11999d).
62. (a) Maier, M. S.; Marimon, D. I. G.; Stortz, C. A.; Adler, M. T. *J. Nat. Prod*. **1999**, *62*, 1565. (b) Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem.* **1998**, *63*, 2385. (c) Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron: Asymmetry.* **1993**, *4*, 457. (d) Huneck, S.; Tonsberg, T.; Bohlmann, F. *Phytochemistry*. **1986**, *25*, 453.
63. Mandal, P. K.; Roy, S. C. *Tetrahedron.* **1999**, *55*, 11395. (b) Mahato, S. B.; Siddiqui, K. A. I.; Bhattacharya, G.; Ghosal, T.; Miyahara, K.; Sholichin, M.; Kawasaki, T. *J. Nat. Prod.* **1987**, *50*, 245.
64. Park, B. K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *Agric. Biol. Chem.* **1987**, *51*, 3443.

65. Drioli, S.; Felluga, F.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *J. Org. Chem.* **1998**, *63*, 2385.
66. Comini, A.; Forzato, C.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2004**, *15*, 617. (b) Berti, F.; Felluga, F.; Forzato, C.; Furlan, G.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry.* **2006**, *17*, 2344.
67. Rawal, V. H.; Rao, J. A.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4275.
68. Yoshida, S.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 310.
69. Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36.
70. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144.
71. Turova, O. V.; Starodubtseva, E. V.; Vinogradov, M. G.; Ferapontov, V. A.; Struchkova, M. I. *Tetrahedron: Asymmetry*. **2009**, *20*, 2121.
72. Seebach, D.; Rogo, S.; Maetzke, T.; Braunschweiger, H.; Cercus, J.; Krieger, M. *Helv. Chim. Acta.* **1987**, *70*, 1605.
73. Forzato, C.; Furlan, G.; Nitti, P.; Pitacco, G.; Valentin, E.; Zangrando, E.; Buzzini, P.; Goretti, M.; Turchetti, B. *Tetrahedron: Asymmetry.* **2008**, *19*, 2026.
74. Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903.
75. Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, *50*, 173.
76. (a) Liu, R. S.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4936. (b) Carlough, K.; Srinivasan, R. *J. Am. Chem. Soc*. **1967**, *89*, 4932.
77. (a) Busque, F.; de March, P.; Figueredo, M.; Font, J.; Margaretha, P.; Raya, J. *Synthesis.* **2001**, *8*, 1143. (b) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1994**, *50*, 12829. (c) Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Tetrahedron.* **1998**, *54*, 4873. (d) Rustullet, A.; Racamonde, M.; Alibes, R.; de March, P.; Figueredo, M.; Font, J. *Tetrahedron.* **2008**, *64*, 9442. (e) Alibes, R.; Bourdelande, J. L.; Font, J. *Tetrahedron: Asymmetry.* **1991**, *2*, 1391.
78. Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.
79. Maradyn, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 5359.
80. Hue, B. T. B.; Dijkink, J.; Kuiper, S.; Larson, K. K.; Guziec, F. S. Jr.; Goubitz, K.; Fraanje, J.; Schenk, H.; van Maarseveen, J. H.; Hiemstra, H. *Org. Biomol. Chem.* **2003**, *1*, 4364.
81. Dauben, W. G.; Rocco, V. P.; Shapiro, G. J. *J. Org. Chem.* **1985**, *50*, 3155.
82. (a) Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron.* **1997**, *53*, 1983. (b) Curran, T. T.; Hay, D. A. *Tetrahedron: Asymmetry*. **1996**, *7*, 2791.
83. Schall, A. Ph.D. Dissertation, **2007**.
84. L3126 Lipase from porcine pancreas, Type II, 8100-400 units/mg protein (using olive oil (30 min incubation)), 30-90 units/mg protein (using triacetin), purchased from Sigma-Aldrich.

C. MAIN PART - DISCOVERY OF ANTIMICROBIAL AND ANTI-CANCER BENZYLOXYLATED KETOARYL ALDEHYDES AND 2-ARYLIMIDAZOLINES

One aspect of modern drug discovery involves the evaluation of small molecular weight compounds for their ability to modulate a biological pathway in cells or organisms. This approach is likely to benefit in the future from an evolving forward analysis of synthetic pathways used in diversity-oriented synthesis that leads to structurally complex and diverse small molecules. One of the aims of diversity-oriented syntheses is to synthesize efficiently a collection of small molecules capable of perturbing any disease-related biological pathway, leading eventually to the identification of therapeutic protein targets capable of being modulated by small molecules.[1]

Nowadays, the driving force to contribute to the library of these compounds is to produce certain derivatives which may either contain a pharmacophore, a certain functional group or a substituent which enhances bioactivity. More often than not, some of these compounds may not be active to the target disease but rather to another type of disease.

1. Antimicrobial drug discovery

The discovery of antimicrobial agents to treat infectious diseases has been one of the most notable achievements of the past century.[2] However, the rise of infective diseases caused by bacteria resistant to multiple antibacterial drug classes represents a serious world-wide health problem.[3] The methicillin-resistant *Staphylococcus aureus* (MRSA) is considered as one of the most resistant bacterial strain and is now the causative agent for the majority of staphylococcal infections in hospitals, as well as a leading cause of serious infections in the community. Other problematic resistant Gram-positive bacteria include vancomycin-resistant enterococci (VRE) and penicillin resistant *Streptococcus pneumoniae* (PRSP). The stimulated use of antimicrobial agents available in the market has resulted in the emergence of resistance to the commonly used drugs with important implications for morbidity, mortality and health care costs.[4,5] Inspite of a large number of antibiotics and chemotherapeutics available for medical use, the antimicrobial resistance has created a substantial need for design of new class of antimicrobials and this area will always remain of immense significance.

1.1 Discovery of antituberculosis agents

Chronic pulmonary tuberculosis is a disease which continues to spread scare particularly to people in developing countries. It stays as a major global concern in the health sector despite the accessibility of efficient treatment regimens. According to the 2010/2011global fact sheet of the World Health Organization (WHO), TB causes a mortality rate of about 1.7 million deaths although the rate has decreased to 35% since 1990.[6-8] This escalated condition has been aggravated by the emergence of multi-drug resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*.[9,10] With much consideration to the seriousness of this pandemic health problem, the need to explore and develop new compounds that may exhibit novel inhibitory mechanism is timely and significant in TB drug discovery research.

Ideal TB drug targets should have three characteristics: they should be required for bacterial growth and persistence; it should be possible to inhibit their activity using small molecules; and they should be accessible to these modulatory compounds. Theoretically, the simplest way to locate targets that have these ideal characteristics is to discover an active compound and then define its target.[11]

2. Anti-cancer drug discovery

Cancer is a disease that is characterized by uncontrolled growth and spread of abnormal cells. It accounts for nearly 8 million deaths each year, and this is estimated to reach 12 million deaths by 2030. Current trend of the disease accounts that one out of every four males will die of cancer in the same manner as one out of every five females.[12,13]

Traditional anticancer drug discovery follows the main dichotomy of current drug discovery in general, which is largely molecular-target-based. Global genomic and proteomic approaches that are being employed in conjunction with bioinformatic tools to elucidate novel drug discovery targets and to probe mechanisms of action and toxicity of potential drug molecules have been reviewed recently. Combinatorial chemistry and high-throughput screening against pure molecular targets and cancer cells are established methods for primary anti-cancer drug discovery. Most of the potential novel molecular targets for anti-cancer drug discovery can be grouped into the following categories: growth factor receptor tyrosine kinases (RTKs) and serine/threonine kinase signal transduction pathway targets; cell cycle targets; apoptosis-related targets; extracellular matrix targets, tumor angiogenesis and metastasis targets; and cell life-span targets.[14]

3. Biological activity of benzyloxy aldehyde derivatives

Despite the simplicity and thus, lack of complexity in their structure, benzyloxybenzaldehyde and a number of its substituted derivatives have shown biological effects in a number of screening assays. They have been observed to exhibit significant inhibitory activity toward neutrophil superoxide formation and were also evaluated for *c*AMP-elevating capability equivalent to forskolin.[15] In a cytotoxicity assay against Hela cells, several benzyloxy benzaldehyde derivatives were observed to arrest the cell cycle progression at G2/M phase and thus, induced cell apoptosis.[16] In addition, they have been evaluated to possess superoxide dismutase-1 activity linked to familial amyotropic lateral sclerosis.[17]

4. Biological activity of 2-imidazolines

2-Imidazolines are found in the structures of various natural products and bioactive compounds. For example, the marine alkaloid 4,5-dihydro-6'-deoxybromotopsentin was isolated from a *Spongosorites* sp. marine sponge with high cytotoxicity.[18] Since the discovery of the imidazoline receptor (imidazoline binding site, IBS) in 1984,[19] many bioactive 2-imidazoline-containing molecules have been synthesized and used as ligands. In addition, 2-imidazolines have also been investigated to exhibit antihyperglycemic, anti-inflammatory, antihypertensive, antihypercholesterolemic, and antidepressant reagents.[20]

5. Aim of this work

It was previously described in a Chinese patent that α-benzylidene-β-carboxyl-γ-heptyl derivative^{TM} (**1**)[21] exhibits potent antimycobacterial activity. Based on previous investigations where compounds with shikimate kinase activity display antimicrobial properties[22-24] and that several derivatives of benzyloxylated benzaldehydes demonstrate promising inhibitory effect against *Helicobacter pylori* kinases,[25] further explorations on the antituberculosis activity of the benzylidene substructure, in the form of benzaldehyde derivative **2a** was carried out. The study was engaged to prepare several derivatives of **2a** in an intention to discover more biologically potent derivative(s) based on the modification of rings A (**2** series) and B (**3** series) and aldehyde group C (**4** series) (Figure 1, structure **2**). To compare the activity of **2a** with the other substructure, lactone acid **5** was also prepared to examine if the purported inhibitory activity will be sustained. Several highly substituted γ-lactone derivatives[26-29] have been reported to exhibit antimycobacterial properties.

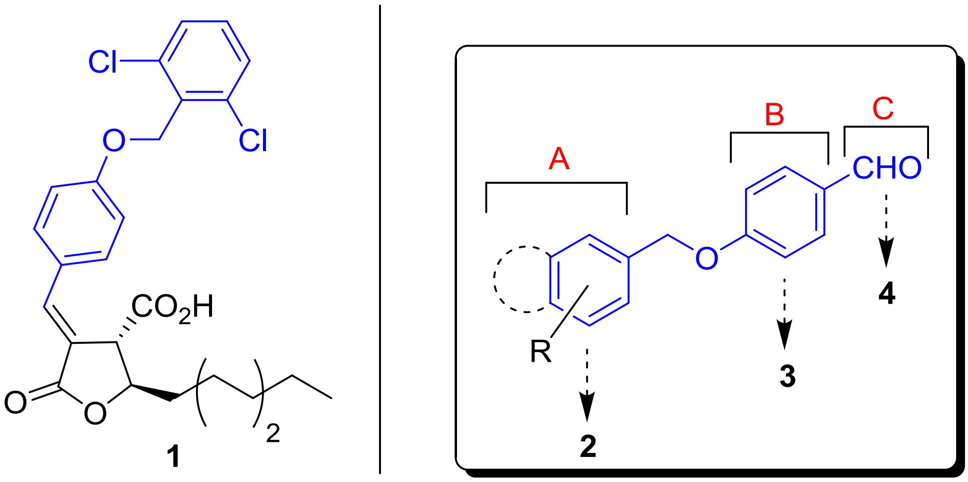
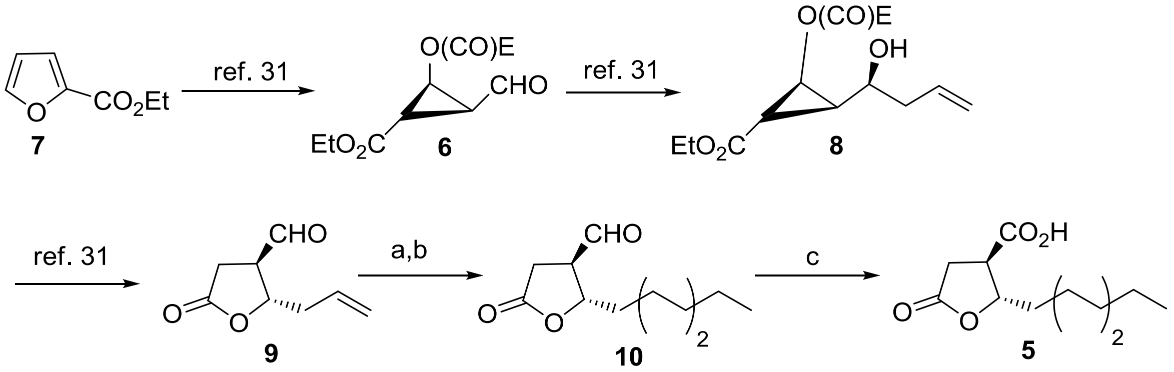


Figure 1. a) Antimycobacterial benzylidene 1^{TM}. b) Ring modifications leading to series **2-4**.

6. Synthesis and antituberculosis activity of γ-heptyl paraconic acid and benzyloxy benzaldehyde derivatives

6.1 Synthesis of γ-heptyl paraconic acid 5

The synthesis of paraconic acid **5** started from cyclopropanealdehyde **6** (prepared from furan ester **7**) following previous methods reported for rocellaric acid and other paraconic acids (Scheme 1).[30-32] Allylation with ally TMS in the presence of $BF_3 \bullet OEt_2$ provided cyclopropyl carbinol **8** which underwent immediately *retro*-aldol and lactonization (using $Ba(OH)_2.8H_2O$) to give γ-allyl-lactone β-aldehyde **9** in 45%. The allyl moiety of **9** was transformed to a heptyl group to furnish lactone aldehyde **10** in two steps by employing ruthenium-catalyzed crossed-metathesis (CM) with 1-hexene and hydrogenation reactions. Finally, Jones oxidation of **10** afforded paraconic acid **5**.

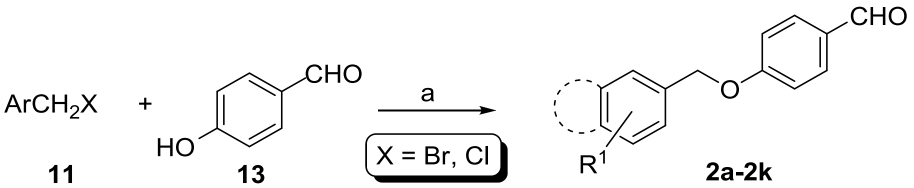


Scheme 1. Synthesis of γ-heptyl paraconic acid **3**. Conditions: (a) 1-hexene, Grubbs I catalyst (20 mol %), DCM, reflux, 8 h, 61% b) H_2, Pd/C (10%), THF, rt, 12 h, quant. c) Jones reagent, DCM, 0 °C, 30 mins, 95%.

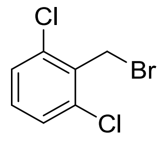
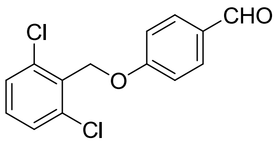
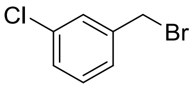
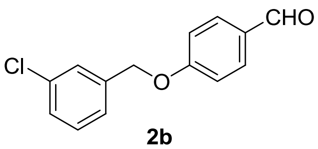
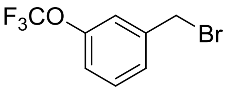
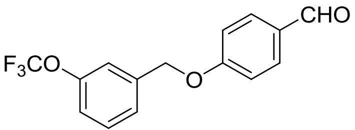
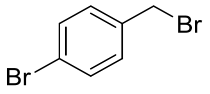
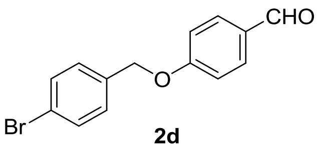
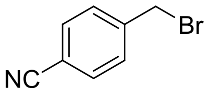
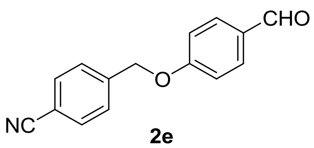
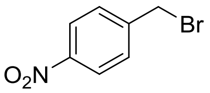
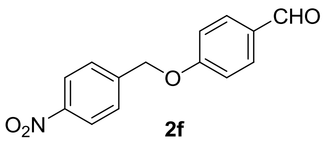
6.2 Synthesis of benzyloxy benzaldehyde derivatives 2a-2k and 3a-3e

4-(2’, 5’-Dichlorobenzyloxy)benzaldehyde **2a** and other derivatives (**2b-2k**) and **3a-e**) based on the modification of rings A and B were prepared through Williamson ether synthesis between several benzylic halides (**11** or **12**) and aromatic hydroxyaldehydes (**13** or **14**) (Scheme 2 and 3).[15]

Table 1. Synthesis of ring A modified derivatives.



Scheme 2. Conditions: a). Reagents and conditions: K_2CO_3, acetone, 18 h, rt.

Entry	**ArCH$_2$X 11**	**Product 2**	**Isolated Yield**
1		 **2a**	97
2		 **2b**	86
3		 **2c**	56
4		 **2d**	23
5		 **2e**	77
6		 **2f**	75

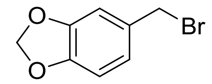
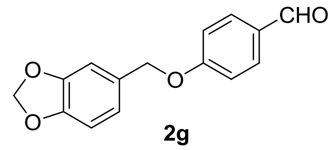
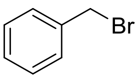
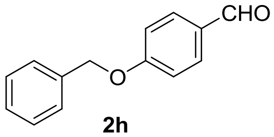
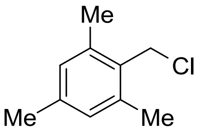
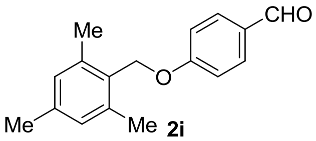
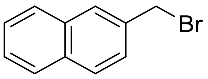
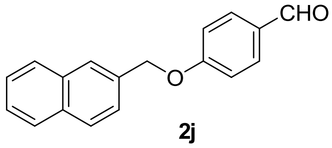
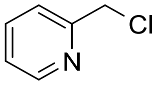
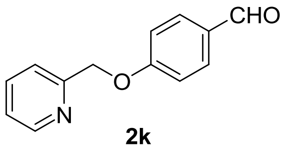
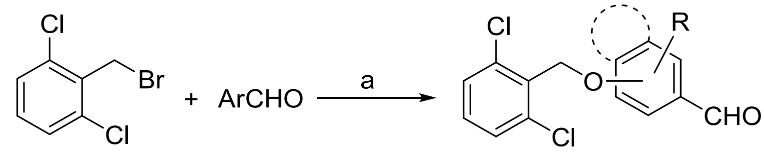
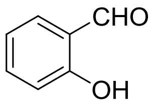
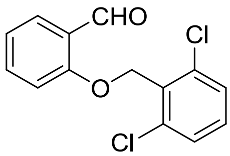
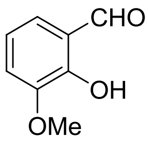
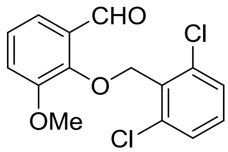
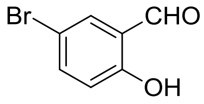
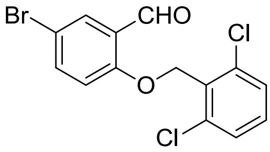
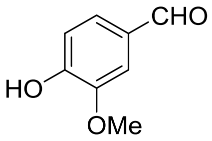
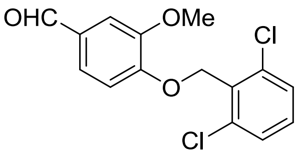
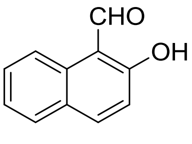
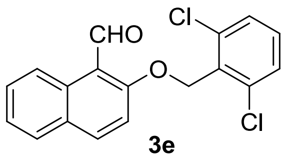
7		 **2g**	74
8		 **2h**	98
9		 **2i**	43
10		 **2j**	75
11		 **2k**	98

Table 2. Synthesis of B modified derivatives.



12 **14** **3a-3e**

Scheme 3. Conditions: a) Reagents and conditions: K_2CO_3, acetone, 18 h, rt.

Entry	**ArCHO 14**	**Product 3**	**Isolated Yield**
1		 **3a**	19
2		 **3b**	13
3		 **3c**	7
4		 **3d**	20
5		 **3e**	9

6.3 Antituberculosis activity

The compounds were screened in assays to quantify their antitubercular activity under both aerobic and anaerobic conditions. Briefly, the 8 day microplate-based assay using Alamar blue reagent (added on day 7) for determination of growth (MABA)[33] gave an assessment of activity against replicating *M. tb*, while the 11 day high-throughput, luminescence-based low-oxygen-recovery assay (LORA)[34] measured activity against bacteria in a non-replicating state that models clinical persistence. Minimum inhibitory concentrations (MICs) are defined as the lowest compound concentration effecting >90% growth inhibition, and the values recorded in the Tables represent the mean of at least two independent determinations. For comparison purposes, several anti-TB drugs were used as standards ex. rifampin (RMP), isoniazid (INH) and streptomycin (SM).

Based on the MABA and LORA MIC data (Table 3), benzaldehyde **2a** showed the lowest MIC value while **2b**, **2c**, **2f**, **2i**, **2j**, and **3c** gave considerable MIC data. The presence of halogenic substituents in **2a-c** and **3c** was observed to conjure antitubercular activity. The presence of a 2,6-dichloro substitution was found critical for a more potent activity along the compound **2** series. The insertion of chlorine atom in an aromatic system has been reported to be essential for antitubercular activity.[35,36] The substitution pattern in ring B was also significant for inhibitory activity. Compared to the 1,4-substituted **2** series, the 1,2-substitution featured in **3** series seemed to have diminishing effects as observed in **3a**-**3c** and **3e**. The presence of a methoxy group in ring B (e.g. **3d**) also caused inactivity although a 1,4-substitution is exemplified. The poor inhibitory activity observed for paraconic acid **5** suggest that the bioactive segment in **1** may lie in the benzyloxyarylidene fragment.

Table 3. MABA and LORA MIC of **2** and **3** series, and acid **5** against *M. tb.* $H_{37}Rv$

Compound	MABA MIC (μg/mL) (% inh)	LORA MIC (μg/mL) (% inh)
2a[a]	18.5	>20 (39%)
2b	49.3	>100 (84%)
2c	48.4	99.7
2d	>100 (80%)	nd
2e	>100 (39%)	nd
2f	>100 (2%)	nd
2g	81.2	>100(81%)
2h	96.4	>100 (65%)
2i	47.2	>100(86%)
2j	>100 (15%)	nd
2k	>100 (80%)	nd
5[a]	>20% (0%)	nd
3a	>100 (32%)	nd
3b	>100 (32%)	nd
3c	>100 (33%)	nd
3d	>100 (88%)	nd
3e[b]	>50 (9%)	nd
RMP	0.15	0.84
INH	0.68	>128
SM	0.83	33.2

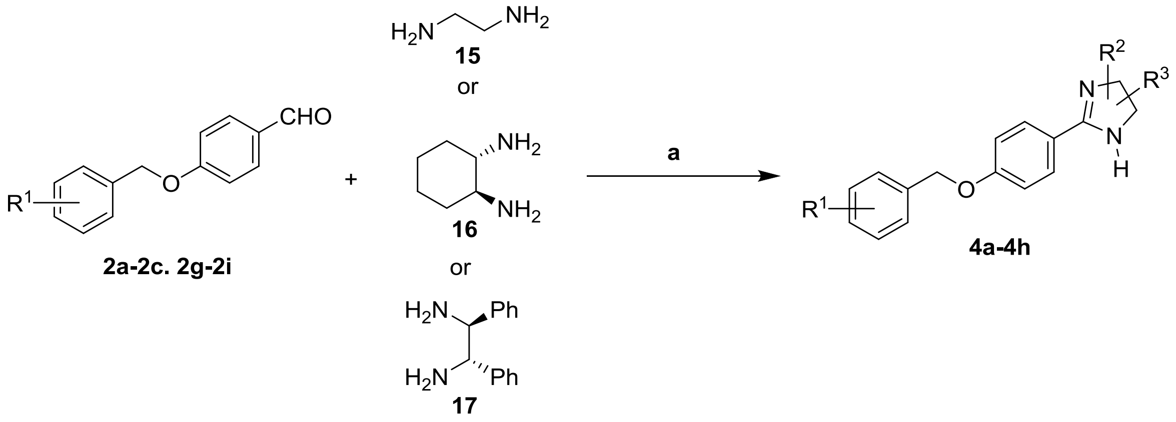
[a]initially screened at 20 μg/mL; [b]initially screened at 50 mg/mL. nd = not determined. RMP = rifampin; INH = isoniazid; SM = streptomycin sulfate.

7. Synthesis, antimicrobial and anticancer activity of benzyloxylated 2-arylimidazolines

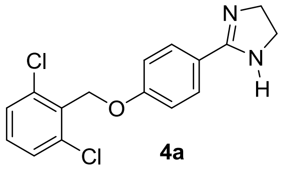
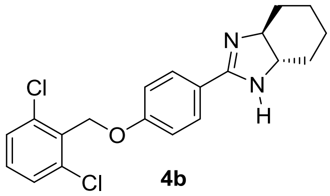
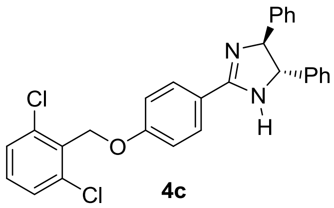
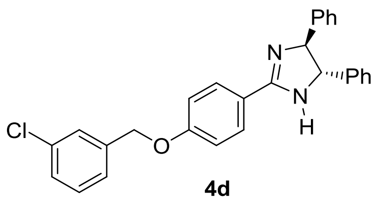
7.1 Synthesis of benzyloxylated 2-arylimidazolines and benzophenone 18

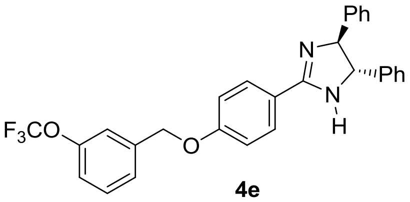
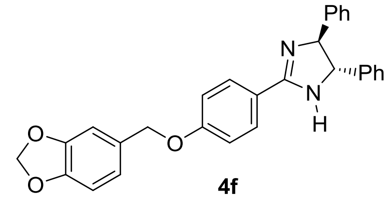
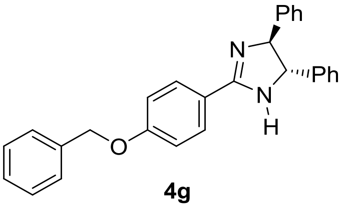
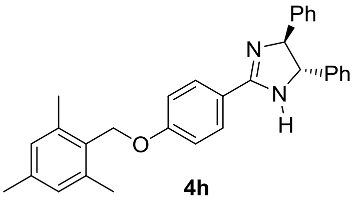
Taking into account the inhibition values of **2a** in the first series which present a 2,6-dichlorobenzyl group in ring A and a 1,4 structural pattern in Ring B, further efforts were aimed at modifying the aldehyde warhead. Modifications were done by changing the carbaldehyde moiety to 2-imidazolines and to a ketone. Thus, oxidative conversion of **2a** was done with diamines **15-17** in the presence of molecular iodine and potassium carbonate under warming conditions to prepare the **4** series (Scheme 4).[37] Compound **18** was synthesized from 4-hydroxybenzophenone and 2,6-dichlorobenzyl bromide using reaction conditions stated for the **2** and **3** series (Scheme 5).[15]

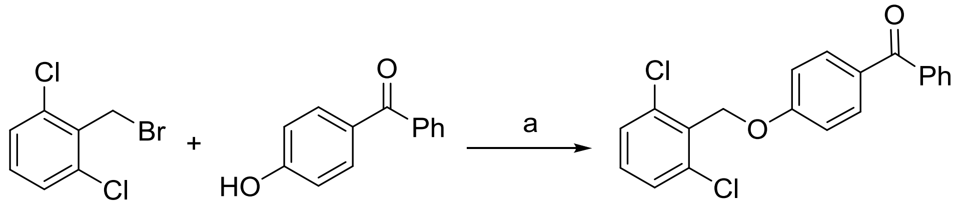
Table 4. Synthesis of 2-arylimidazoline **4** and benzyoxylated acetophenone **20**.



Scheme 4. a) I_2, K_2CO_3, ${}^{t}BuOH$, 70 °C.

Entry	ArCHO	Diamine	Product	Isolated Yield
1	**2a**	**15**	 **4a**	33
2	**2a**	**16**	 **4b**	20
3	**2a**	**17**	 **4c**	58
4	**2b**	**17**	 **4d**	99

5	**2c**	**17**	 **4e**	84
6	**2g**	**17**	 **4f**	70
7	**2h**	**17**	 **4g**	75
8	**2i**	**17**	 **4h**	66



20

Scheme 5. Conditions: a) Reagents and conditions: K_2CO_3, acetone, 18 h, rt, 61%.

7.2 Antimicrobial and anticancer activity of benzyloxylated 2-arylimidazolines

According to Table 5, an improved activity was observed in the **4** series when the aldehyde functionality was transformed into a 2-imidazoline platform. Noteworthy, **4c**, which features a *trans*-diphenyl configuration and 2,6-dichloro substitution showed the lowest MIC value. When other bioactive **2** derivatives were transformed to this 1,3-diazacyclopentene moiety, significant improvement of inhibition was also observed in **4d**, **4e**, **4g** and **4h**. It seemed that halogenated and hydrophobic characters in A ring are relevant for activity against *M. tb.* In addition, MIC values against slow-replicating *M. tb.* based on the LORA assay suggested high activity for chlorinated **4c** and **4d** and the highly hydrophobic **4h**.

Table 5. Antimicrobial activity of imidazoline **4** series and ketone **18**.

Compound	**MABA MIC (µg/mL)**	**LORA MIC [µg/mL]**	***M. smeg***	***Staph. aureus***	***Escherichia coli***	***Candida albicans***
4a	39.1	-	-	-	-	-
4b	11.1	12.9	11.4	50.0	>50 (21)	>50
4c	3.0	2.9	2.5	>50 (76%)	>50	>50
4d	6.1	2.8	2.3	2.9	>50 (22)	>50
4e	5.8	12.3	2.6	2.9	>50 (9)	>50
4f	10.7	11.0	2.6	5.9	>50 (8)	>50
4g	7.9	11.1	4.9	-	>50	>50
4h	6.1	3.1	4.5	4.6	>50 (11)	>50
20	>100 (82%)	-	-	-	-	-
RMP	0.15	0.84	18.08			
INH	0.68	>128	89.03			
MOX			0.11			
SM	0.83	33.2	0.12			
TMC			<0.008			
MET			>512			
Amp				2.37	18.96	
Genta				0.57	1.10	
Amphotericin B						0.36
Ketoconazole						0.03

MOX = moxifloxacin.; AMP = ampicillin; GENTA = gentamycin; MET = methicillin.

Owing to the continual emergence of multi-drug resistance to clinically available antibiotics against bacterial and fungal pathogens,[38,39] the bioactive congeners were also tested for antimicrobial activity against *Mycobacterium smegmatis*, *Staphylococcus aureus* (Gram-positive bacteria), *Escherichia coli* (Gram-negative bacteria) and *Candida albicans* (a fungus). The well-established antibiotics cited in Table 5 were used as positive controls. Against *M. smegmatis*, all *trans*-diphenyl derivatives showed good inhibition rates with the halogenated compounds **4c**-**4e** and the methylenedioxyphenyl bearing **4f** exhibiting the most potent activity. Versus *S. aureus,* the monosubstituted halogenic **4d** and **4e** displayed the highest selectivity. No activity was observed for all compounds against *E. coli* and *C. albicans* which suggested non-selectivity to Gram-negative bacteria and fungi.

To investigate the cytotoxic activity of the imidazoline compounds against Hela cell line (cervic cancer cells), an MTT cell proliferation assay was performed. Xanthohumol (**19**) was used as a positive control for cytotoxicity assay since it has been demonstrated to inhibit the growth of Hela cells.[40,41] The approximate IC_{50} value for **19** was 9.4 μM (Table 6). The most non-polar derivative **4h** showed the best anticancer activity with 4.5 μM IC_{50} value followed by **4c**-**4e** and **4g**. The presence of the *trans*-diphenyl in the imidazoline moiety seemed to be an important factor for cytotoxic activity. The electron-donating methylenedioxy substituent in 4f effected decreased activity along the *trans*-arylated congeners.

Table 6. Cytotoxicity data for **4** (HeLa cells, 150.000 cells/mL, 72 h incubation,IC_{50} values in lM ± SD, n = 8).

Compound	IC_{50} (μM)
4a	54.2 ± 12.5
4b	31.5 ± 5.6
4c	5.12 ± 1.3
4d	7.4 ± 0.4
4e	7.6 ± 1.0
4f	13.6 ± 4.8
4g	7.9 ± 0.7
4h	4.5 ± 0.6
Xanthohumol	9.4 ± 1.4

8. Conclusion

A series of benzyloxylated ketoaryl aldehydes and 2-arylimidazoline analogues based on the benzylidene fragment of the known antimicrobial lactone acid (**1**) have been synthesized and evaluated for antimicrobial and anti-cancer activity. Results evidenced that inhibition against *Mycobacteria* and Gram-positive bacteria (*S. aureus*) is dependent on the presence of halogens in ring A and substitution pattern in ring B, whereas conversion of the aldehyde functionality to 2-imidazoline with *trans*-diphenyl moiety dramatically effects enhanced activity. In the course of anti-cancer investigation against Hela cells, the cytotoxic activity of the bioactive imidazoline congeners was attributed to the presence of electron-withdrawing groups and non-polar substituents in ring A, and *trans*-diphenyl imidazoline.

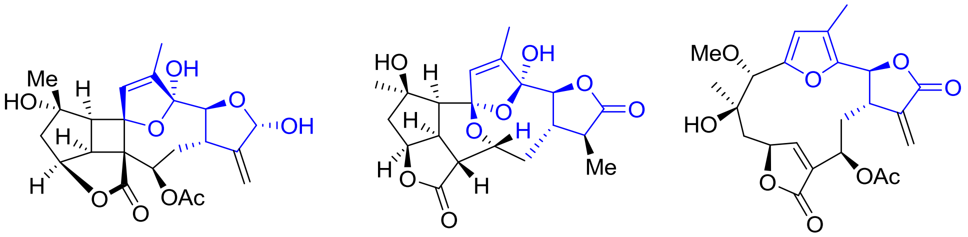
References

1. Schreiber, S. *Science*. **2000**, *282*, 1964.
2. Qadri, F.; Svennerholm, A. M.; Faruque, A. S. G.; Sack, R. B.; *Clin. Microbiol. Rev.* **2005**, *18*, 465.
3. Devasia, R. A.; Jones, T. F.; Ward, J.; Stafford, L.; Hardin, H.; Bopp, C.; Beatty, M.; Mintz, E.; Schaffner, W. *Am. J. Med.* **2006**, *119*, 168.
4. Boucher, H. W.; Talbot, G. H.; Bradley, J. S.; Edwards, J. E.; Gilbert, D.; Rice, L. B.; Scheld, M; Spellberg, . B.; Bartlett, J. *Clin. Infect. Dis.* **2009**, *48,*1.
5. Moellering Jr., R. C. *Clin. Infect. Dis.* **2008**, *46*,1032.
6. Dye, C. *Nat. Rev. Microbiol* **2009***, 7,* 81.
7. Boogard, J.; Kibiki, G. S.; Kisanga, E. R.; Boeree, M. J.; Aarnoutse, R. E. *Antimicrob. Agents Chemother.* **2009**, *53,* 849.
8. World Health Organization, Tuberculosis Facts (2010/2011). http://www.who.int/tb.
9. Maher, D.; Ravioglione, M. *Clin. Chest. Med.* **2005**, *26,* 168.
10. Tomioka, H. *Curr. Pharma. Des.* **2006,** *12*, 4047.
11. Sacchettini, J. C.; Rubin, E. J.; Freundlich, J. S. *Nat. Rev. Microbiol.* **2008**, *6*, 41.
12. Pezzuto, J. M.; Kosmeder, J. W.; Park, E. J. Characterization of natural product as chemopreventive agents. In *Cancer Chemoprevention*, Kelloff GJ, Hawk ET, Sigman CC (eds). Humana Press Inc.: Totowa, NJ; **2:** 3–37.
13. Guilford, J. M.; Pezzuto, J. M. *Expert Opin Investig Drugs* **2008**, *17***,** 1341.
14. Buolamwini, J. K. *Curr. Opin. Chem. Biol.* **1999**, *3*, 500.
15. Chang, C. Y.; Kuo, S. C.; Lin, Z. L.; Lin, Y. L.; Wang, J. P.; Huang, L. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1971.
16. Lin, C. F.; Yang, J. S.; Chang, C. Y.; Kuo, S. C.; Lee, M. R.; Huang, L. J. *Bioorg. Med. Chem.* **2005**, *13*, 1537.
17. Nowak, R. J.; Cuny, G. D.; Choi, S.; Lansbury, P. T.; Ray, S. S. *J. Med. Chem.* **2010**, *53*, 2709.
18. Tsujii, S.; Rinehart, K. L.; Kashman, Y.; Cross, S. S.; Lui, M. S.; Pomponi, S. A.; Diaz, M. C. *J. Org. Chem.* **1988**, *53*, 5446.
19. Bousquet, P.; Feldman, J.; Schwartz, J. *J. Pharmacol. Exp. Ther.* **1984**, *230*, 232.
20. Dardonville, C.; Rozas, I. *Med. Res. Rev.* **2004**, *24*, 639.
21. Li, S.; Yu, H.; Zhang, X.; Wang, L.; Xiao, J.; Zheng, Z.; Zhong, W. PCT Int. Appl. (**2008**), 31pp. Application: WO 2006-CN3403 20061213.
22. Segura-Cabrera, Y.; Rodriguez-Perez, M. A. *Bioorg. Med. Chem. Lett.* **2008**, *18,* 3152.
23. Kapnik, S. M.; Zhang, Y. *Expert Opin. Drug Discov.* **2008**, *3,* 565.
24. Mulabagal, V.; Calderon, A. I. *Anal. Chem.* **2010**, *82*, 3616.
25. Han, C.; Zhang, J.; Chen, L.; Chen, K.; Chen, X.; Jiang, H. *Bioorg. Med. Chem.* **2007**, *15,* 656.
26. Yuan, H.; He, R.; Wan, B.; Wang, Y.; Pauli, G. F.; Franzblau, S. G.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2008**, *18,* 2008, 5311.
27. Ma, C.; Case, R. J.; Wang, Y.; Zhang, H. -J.; Tan, G.T.; Van Hung, N.; Cuong, N.M.; Franzblau, S. G.; Soejarto, D. D.; Fong, H. H. S.; Pauli, G.F. *Planta Med.* **2005**, *71*, 261.
28. Pan, P. -C.; Cheng, M. -J.; Peng, C- .F.; Huang, H. -Y.; Chen, J. -J.; Chen, I. -S. *J. Nat. Prod.* **2010**, *73*, 890.
29. Chang, S. -Y.; Cheng, M. -J.; Peng, C. -F.; Chang, H. -S.; Chen, I. -S. *Chem. Biodiv.* **2008**, *5*, 2690.
30. Nosse, B.; Chhor, R. B.; Jeong, W. B.; Böhm, C.; Reiser, O. *Org. Lett.* **2003**, *5,* 941.
31. Chhor, R. B.; Nosse, B.; Sörgel, S.; Böhm, C.; Seitz, M.; Reiser, O. *Chem. Eur. J.* **2003**, *9*, 260.
32. Böhm, C.; O. Reiser, *Org. Lett.* **2001**, *3,* 1315.

33. Collins, L. A.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **1997**, *41*, 1004.
34. Cho, S. H.; Warit, S.; Wan, B.; Hwang, C. H.; Pauli, G. F.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **2007**, *51*, 1380.
35. Moreno, E.; Ancizu, S.; Silanes, S.; Torres, E.; Aldana, I.; Monge, A. *Eur. J. Med. Chem.* **2010**, *45*, 4418.
36. Kmentova, I.; Sutherland, H. S.; Palmer, B. D.; Blaser, A.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W. A.; Thompson, A. M. *J. Med. Chem.* **2010**, *53*, 8421.
37. Payne, D. J.; Gwynn, M. N.; Holmes, D. J.; Pompliano, D. J.; *Nat. Rev. Drug Discov.* **2006**, *6*, 29.
38. Wallace, R. J.; Nash, D. R.; Steele, L. C.; Steingrube, V. *J. Clin. Microbiol.* **1986**, 976.
39. Ishihara, M.; Togo, H. *Synlett.* **2006**, 227.
40. Vogel, S.; Ohmayer, S.; Brunner, G.; Heilmann, J. *Bioorg. Med. Chem.* **2008**, 16, 4286.
41. Heilmann, J.; Wasecha, M. R.; Schmidt, T. J. *Bioorg. Med. Chem.* **2001**, *9*, 2189.

D. SUMMARY

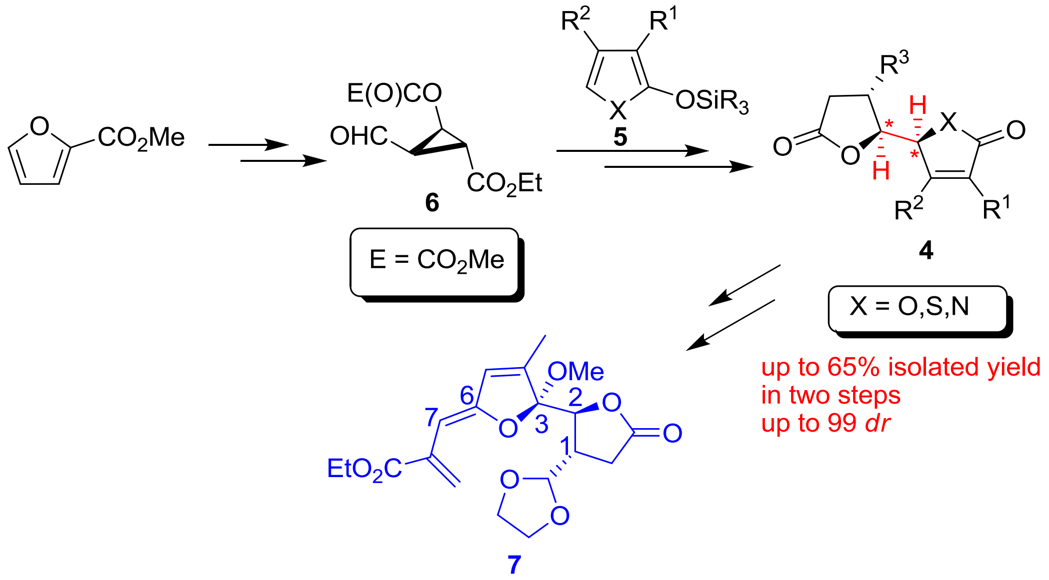
Within the framework of the study's interest on bioactive structure synthesis and discovery, chemical explorations have been undertaken to develop methods to synthesize complex, highly oxidized furanolactone cembranoids and antiproliferative benzyloxylated derivatives. Bulk of the study has been centered on synthetic strategies *en route* to the furanocembranoids bielschowskysin (**1**), verrillin (**2**) and bipinnatin K (**3**) starting from furan derivatives (Figure 1). Three approaches have been developed for their northeastern segments and in addition, a simplified approach for the total synthesis of **1** was also investigated.



bielschowskysin (1) **verrillin (2)** **bippinatin K (3)**

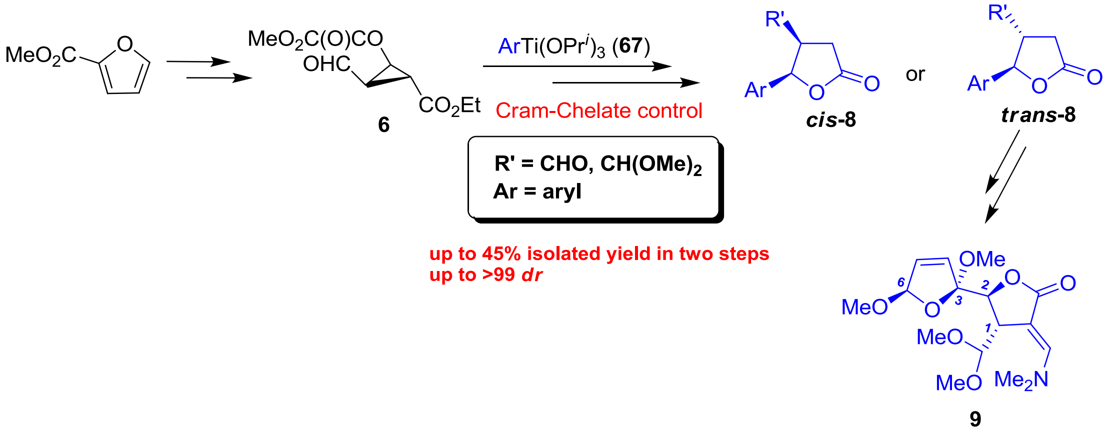
Figure 1. Furanolactone cembranoids **1-3**.

The first approach led to the development of a new diastereocontrolled strategy towards heterocycle-butyrolactone scaffolds **6** of several complex natural product structures in particular **1-3** through vinylogous Mukaiyama addition of heterosiloxydienes **5** to furan ester-derived highly functionalized cyclopropane carbaldehyde **6** and lactonization sequences. In addition, the first synthesis of a *Z*-*exo*-trienolfuran lactone substructure **7** representing the northeastern sector of bielschowskysin **1** was also accomplished.



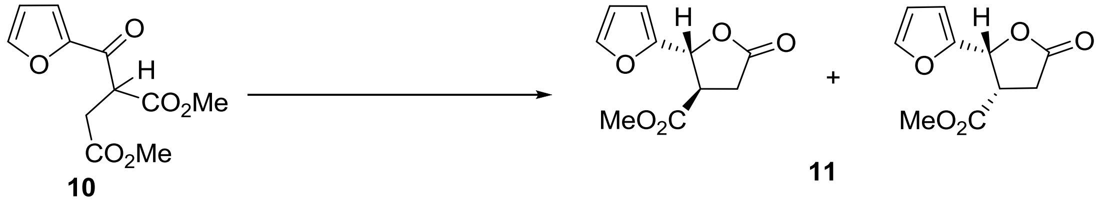
Scheme 1. Studies based on siloxydiene addition to cyclopropane **6**.

In the second approach, a new diasteroselective methodology was developed towards γ-aryl lactones utilizing aryltitanium reagents in combination with the readily available cyclopropanecarbaldehyde **6**. This methodology extends the previously reported functionalization of **6** with allylsilanes in substrate scope, but also offers for the first time a reversal of stereochemistry. Thus, *cis*-disubstituted γ-aryl-β-methyl acetal lactones **8** with good diastereoselectivity in enantiomerically pure form can be obtained, which compares well with previously reported methods. In addition, a two-step transformation of the *trans*-furan lactone derivative furnished a model compound **9** reminiscent of the oxidized northeastern sector of **1** and **2**.



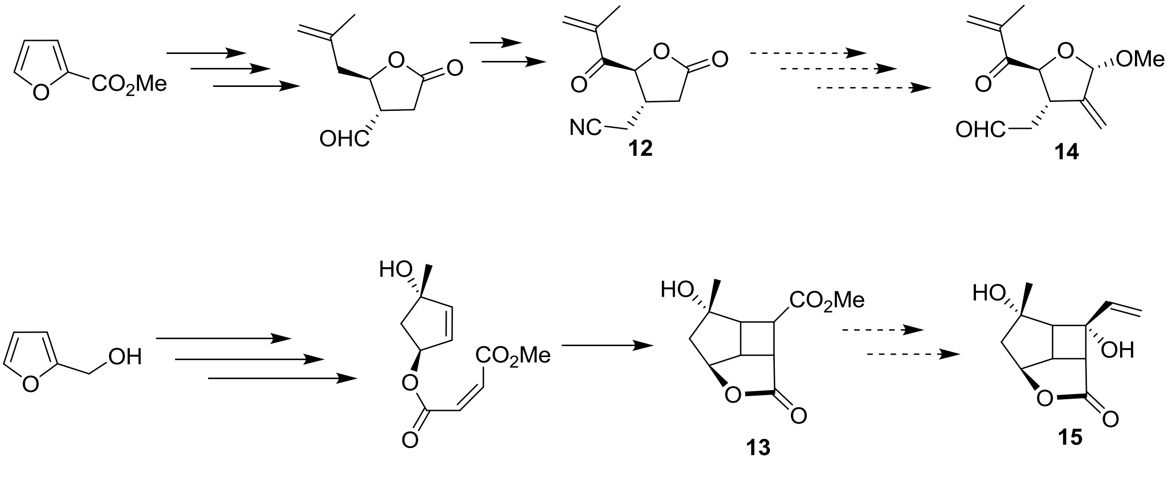
Scheme 2. Studies based on organotitanium addition to cyclopropane **6**.

The third approach was about the enantioselective reduction of a furylated β-keto succinate ester **10** using yeast to furnish *cis-* and *trans-* lactones **11**. Further investigations and optimizations on this aspect are still needed. Although the afforded *trans* stereochemistry was opposite to what is originally required, it can be a useful platform for the synthesis of the enantiomer of **1-3**.



Scheme 3. Yeast reduction of diester **10.**

In an attempt to synthesize bielschowskysin (**1**), two intermediates **12** and **13** relevant for constructing the two key building blocks **14** and **15** were successfully prepared starting from furan derivatives. Further synthetic transformations of these compounds may potentially lead to the completion of **1**.



Scheme 4. A simplified approach towards bielschowskysin **1**.

Finally, a series of benzyloxylated ketoaryl aldehydes (**16** and **17** series) and 2-arylimidazoline (**18** series) analogues based on the benzylidene fragment of the known antimicrobial lactone acid (**19**) were synthesized and biologically evaluated. Results indicated that inhibition against *Mycobacteria* and Gram-positive bacteria (*S. aureus*) is dependent on the presence of halogenic moieties in ring A and 1,4 substitution in ring B, whereas conversion of the aldehyde functionality to 2-imidazoline with *trans*-diphenyl moiety dramatically leads to increased activity. In the course of anti-cancer investigation, the cytotoxic activity of the bioactive imidazoline congeners against Hela cells was attributed to the presence of electron-withdrawing groups and non-polar substituents in ring A, and *trans*-diphenyl imidazoline.

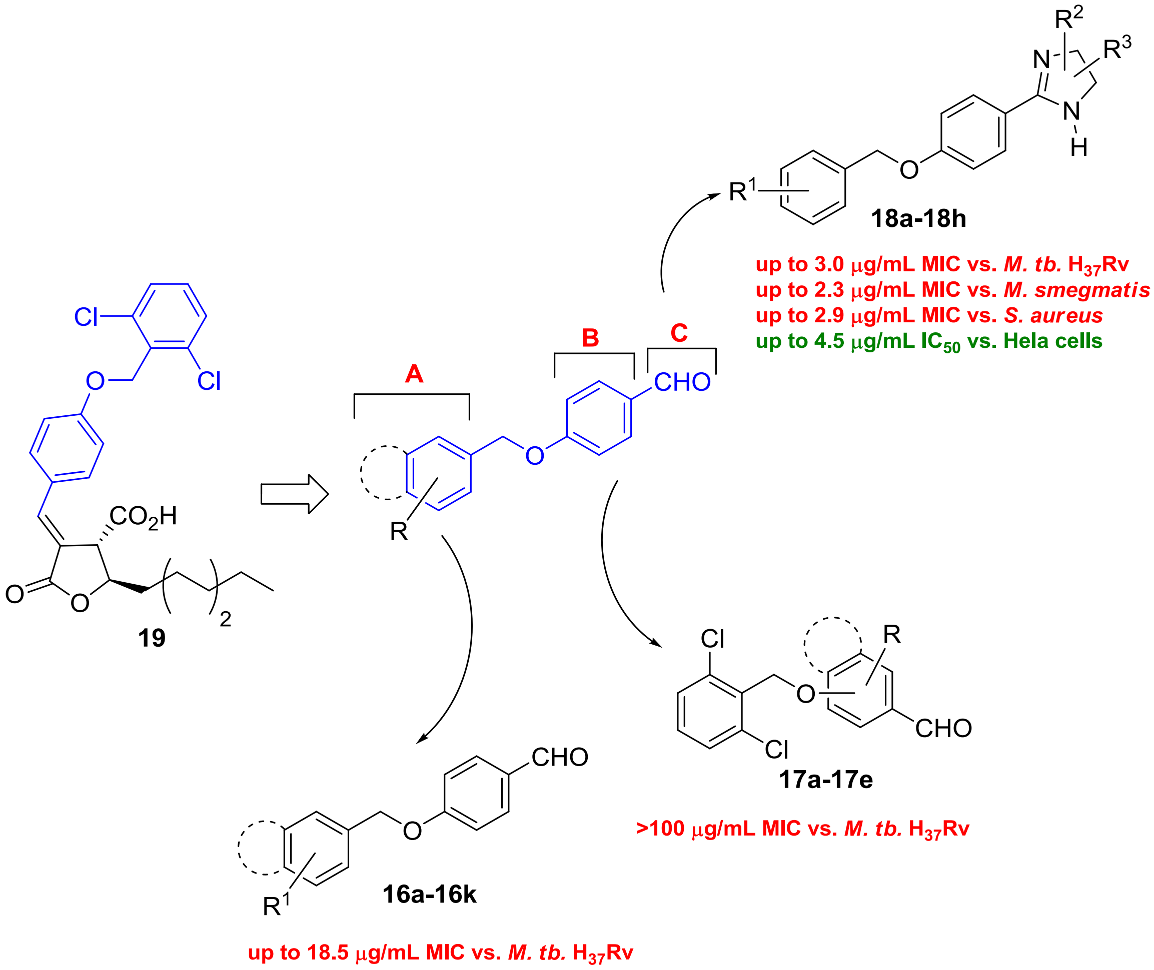


Figure 2. Synthesis and biological activity of benzyloxylated derivatives.

E. EXPERIMENTAL PART

1. General

1.1 Materials and methods

Unless otherwise stated, reactions were performed at ambient temperature (typically 20–22 ºC) in flame-dried glassware under a nitrogen atmosphere using dry solvents. Abs. solvents were prepared according to usual lab procedures or taken from the MB-SPS solvent purification system. Ethyl acetate, hexanes (bp 40-60 °C) and dichloromethane were purified by distillation before use. Further solvents and reagents were of pure, analytical quality. All other commercially available reagents were used as purchased from the supplier. Reactions performed at above room temperature were controlled by a Heidolph EKT 3001 temperature modulator. For reactions which require cooling to temperatures < -40 °C, a cryostat Haake EK 90 or dry ice/*iso*-propanol (or acetone) mixture was used. For carrying out ozonalysis, ozone was generated using a Fischer process technology ozone generator OZ 500 MM and oxygen was supplied from a gas tank.

1.2 Analytics

Optical rotations were measured with a 241 MC Perkin-Elmer polarimeter at a wavelength of 589 nm (Na-D) in a 1 dm. The concentration is given in [g/100 ml].

CD spectra were measured on a JASCO model J-710/720 at the Institut für Bioanalytic und Sensorik of the University of Regensburg (AK Prof. Dr. O. Wolfbeis) at 21° C between 300 and 200-180 nm in the specified solvent, the number of scans ranging between 10 and 50. The length of the cylindrical cuvettes was 1 cm, the resolution was 0.2 nm, the band width 1.0 nm, the sensitivity 20 mdeg, the response 0.25 s, the speed 20 nm/min. The background was subtracted to each spectrum. The absorption value is measured as Molar Ellipticity per Residue (deg cm^2 dmol^{-1}).

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300, Bruker Avance 400, Bruker Avance 600 and Bruker Avance 600 Kryo and are reported relative to residual solvent for ^{1}H NMR ($CHCl_3$ = 7.27 ppm) and ^{13}C NMR ($CDCl_3$ = 77.0

ppm). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicitiy, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, td = triplet of doublets, dd = doublet of doublets, m = multiplet, bs = broad singlet.

IR spectra were recorded on a Bio-Rad Excalibur FTS 300 spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR-System and are reported in frequency of absorption (cm^{-1}).

Mass spectrometric measurements were performed on Varian MAT 311A, Finnigan MAT 95 and Thermoquest Finnigan TSQ 7000..

Single crystal X-ray crystallographic analyses were carried out on Stoe Imaging Plate Diffraction System (IPDS) (Stoe & Cie GmbH, Darmstadt). Measurements of extremely small crystals (esp. for compound **33c**) were performed using Bruker AXS FR591 equipped with Montel focusing mirrors and a four circle Mach3 goniometer supporting a Pt135 CCD-detector at the Chemical Crystallography and Electron Microscopy Department, Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr c/o Prof. Dr. Christian W. Lehmann.

Melting points were measured on a Büchi SMP 20 in a silicon oil bath. The melting points are uncorrected.

Elemental analysis was prepared by the Microanalytical Department of the University of Regensburg using a Vario EL III or Mikro-Rapid CHN (Heraeus).

1.3 Chromatography

Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching (short and long λ), staining with I_2, mostain, molybdatophosphoric-acid (5% in ethanol), $KMnO_4$ solution or vanillin-sulfuric acid.

Column chromatography was performed in glass columns (wet or dry packing). As a stationary phase silica gel Merck 60 (0.063-0.200 mm) or flash silica gel Merck 60 (0.040-0.063 mm) was used.

Preparative HPLC was performed at the Analytical Department for HPLC and GC of the University of Regensburg (AK König, c/o Fr. S. Strauss) on a Autosampler Agilent 1100 Series (Diode array detector, 61361A Prep pump, λ = 254 nm, Phenomenex Luna 10 mM C18 (2) 100A (250x21.2 mm, 10 µm, flow rate: 21 mL/min, 25 °C, @ 0 min, 5% MeCN/H_2O (0.006% TFA w/w); @ 17 min, 84% MeCN/H_2O (0.006% TFA w/w); @ 18 min, 98% MeCN/H_2O (0.006% TFAw/w); @ 28 min, 98% MeCN/H_2O (0.006% w/w)).

2. List of abbreviations

abs	absolute
BOX	bisoxazoline
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bu	*n*-butyl
BuLi	*n*-butyl lithium
cat	catalytic
CD	circular dichroism
dr	diastereomeric ratio
DCM	dichloromethane
DIAD	diisopropylazodicarboxylate
DIBALH	diisobutyl aluminum hydride
DMAP pyridine	*N,N*-dimethylamino
DMF	dimethyl formamide
DMS	dimethyl sulfide
ee	enantiomeric excess
equiv	equivalents
EI	electronic ionization
Et	ethyl
h	hour
HPLC	high pressure liquid chromatography
HRMS	high resolution mass Spectrometry
HTS	high-throughput screening
^{i}Pr	*iso*-propyl
IR	infra red
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LORA	low-oxygen recovery assay
M	metal
MABA	microplate Alamar blue assay
*m*CPBA	*m*-chloroperbenzoic acid
MDR	multi-drug resistant
Me	methyl
MeCN	acetonitrile
MIC	minum inhibitory concentration
min	minute
MS	molecular sieve
NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholin-*N*-oxide
NOESY	Nuclear Overhauser Effect Spectroscopy
Nu	nucleophile
PCC	pyridinium chlorochromate
Pg	protecting group
Ph	phenyl
PMB	*p*-methoxy-benzyl
PPLE	porcine pancreas lipase Enzyme
PPTS	pyridinium –p-toluene sulfonate
PRSP	penicillin-resistant *Streptococcus pneumoniae*
PTSA	p-toluene sulfonic acid
pyr	pyridine
quant	quantitative
RCM	ring closing metathesis
rt	room temperature
SAR	structure-activity relationship
TBAF	tetrabutylammonium fluoride
TBME	*tert*-butyl-methyl-ether
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
^{t}Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilane
TMSCN	trimethylsilyl cyanide
TPAP	tetrapropylammonium perruthenate
Tf	trifluormethanesulfonate
Ts	tosyl
TsDPEN	tosyldiphenylamine
TS	transition-state
VMAR	vinylogous Mukaiyama aldol reaction
VRE	vancomycin-resistant enterocci

3. Synthetic preparation of literature-known compounds

The compounds used in Chapter B (see list below) were prepared according to literature/theses procedure/s:

Cpd number	Compound Name	Reference
15	(*1S,2S,3S*)-(-)-oxalic acid 2-ethoxycarbonyl-3-formyl-cyclopropyl ester methyl ester	Geyer, G. Ph.D. Dissertation. Universität Regensburg. 2008.
38a	2(5H)-furanone	Nasman, Jan H. Organic Syntheses (1990), 68 162.
38c	2(5H)-Furanone, 4-methyl-	Sharma, Vasudha; Kelly, Gilbert T.; Watanabe, Coran M. H. Organic Letters (2008), 10(21), 4815-4818.
38d	2(5H)-Furanone, 3,4-diphenyl-	Zhang, Ji; Blazecka, Peter G.; Belmont, Daniel; Davidson, James G. Organic Letters (2002), 4(25), 4559-4561.
38f	1H-Pyrrole-1-carboxylic acid, 2,5-dihydro-2-oxo-, 1,1-dimethylethyl ester	Curti, Claudio; Sartori, Andrea; Battistini, Lucia; Rassu, Gloria; Burreddu, Paola; Zanardi, Franca; Casiraghi, Giovanni. Journal of Organic Chemistry (2008), 73(14), 5446
41	(*1S,2S,3S*)-(-)-Oxalic acid 2-ethoxycarbonyl-3-formylcyclopropylester methyl	Geyer, G. Ph.D. Dissertation. Universität Regensburg. 2008 (with slight modification e.g. using R,R-iPrBox Ligand)
97	2-Furanacetonitrile, α-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-	Rawal, Viresh H.; Rao, J. Appa; Cava, Michael P. Tetrahedron Letters (1985), 26(36), 4275-8.

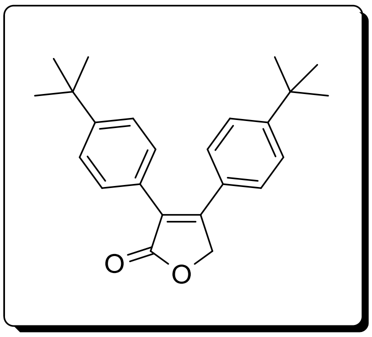
115	Silane, trimethyl(2-methyl-2-propen-1-yl)-	Hagen, Gisela; Mayr, Herbert. Journal of the American Chemical Society (1991), 113(13), 4954-61.
121	2-Butenedioic acid (*2Z*)-, 1-methyl ester	Pospisil, Jiri; Potacek, Milan. Tetrahedron (2006), Volume Date 2007, 63(2), 337-346.
134	4-Cyclopentene-1,3-diol, 1-acetate, (*1R,3S*)-	Schall, A. Ph.D. Dissertation. Universität Regensburg. 2008

4. Syntheses and spectral data of relevant compounds

4.1 Diastereocontrolled vinylogous Mukaiyama aldol addition of heterosiloxydienes to trifunctionalized cyclopropane 15

Synthesis of aromatic furanone 38e

3,4-Bis-(4-tert-butyl-phenyl)-5H-furan-2-one



3,4-Dibromofuranone (500 mg, 2.07 mmol, 1 equiv) was combined with 4-*tert*-butylphenylboronic acid (3.0 equiv), cesium fluoride (4.0 equiv.), $PdCl_2(PPh_3)_2$ (5 mol%), $BnEt_3NCl$ (5 mol %) and 10 mL each of degassed toluene and water. The reaction mixture was refluxed for 18 h. The reaction mixture was partitioned between 10 mL 1.5N hydrochloric acid and 100 mL toluene. The toluene extract was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with 8:1 hexanes-EtOAc to afford furanone **38e** as a crystalline solid.

Yield 532.8 mg,74%.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 8H), 5.16 (s, 2H),1.37 (s, 9H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 155.4, 154.2, 151.7, 128.9, 127.2, 125.9, 125.7, 70.6, 34.9, 34.8, 31.4, 31.1. EI-HRMS: *m/z* calcd for $C_{24}H_{28}O_2$ 348.2089 $[M]^+$; found: 348.2091. IR (neat) $\tilde{\nu}$ 1750, 1657, 1601, 1483, 1438, 1341, 1157, 1119, 1029, 959, 784 cm^{-1}.

Preparation of heterosiloxydienes

TMSO-Furan. A mixture of triethylamine (1.7 mL, 12.32 mmol, 2 equiv) and trimethylchlorosilane (0.82 g, 6.47 mmol,1.05 equiv) was added to a pre-cooled (0 ^{o}C) 2(5H)-furanone (517.5 mg, 6.16 mmol, 1 equiv) under nitrogen. The reaction mixture was allowed to stay at room temperature for 24 h. The mixture was filtered and the residue was washed three times with n-pentane. The filtrate was concentrated and the remaining liquid was fractionally distilled under reduced pressure to afford TMSO-furan (**32a.1**) with a small amount of triethylammonium chloride, which was removed by redistillation (595.3 mg, 62%), b.p. 44-46 ^{o}C/15 mmHg (lit. 34.35 ^{o}C/ mmHg).

General Procedure: Preparation of TBS-Heterocycles (32a.2-32g)

As a representative procedure, to a stirring solution of 2(5*H*)-furanone (258.3 mg, 3.08 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL), cooled to 0 °C, were sequentially added Et_3N (0.64 mL, 4.62 mmol, 1.5 equiv) and TBSOTf (0.78 mL, 3.38 mmol, 1.1 equiv) under argon atmosphere. After ambient temperature was reached, the reaction mixture was stirred for 2 h and the solvent was removed under vacuum. The oily residue was shaken with pentane (3x10 mL), the top organic layer pipetted off, washed with water (pH 7) and concentrated. The resulting light yellow oil was adjudged to be >95% pure in ^{1}H NMR and was used without further purification. Typical yield of the semi-pure TBS-protected product is 70-75% which is sufficient for the next step.

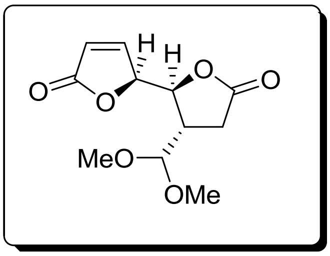
General procedure: Addition of heterosiloxydienes to cyclopropane aldehyde 15 – VMAR

Under a nitrogen atmosphere, a solution of cyclopropylcarbaldehyde (+)-**15** (500 mg, 2.05 mmol, 1 equiv) in anhydrous DCM (20 ml) was added via canula to a flame-dried three-necked flask and was cooled to -78 °C. $BF_3{\bullet}OEt_2$ (0.28 mL, 2.25 mmol, 1.1 equiv) was added via syringe and after stirring for 30 min, *tert*-butyldimethylsiloxyfuran solution in DCM (2.15 mmol, 1.05 equiv) was added slowly resulting to an orange-colored solution. After stirring for 16 h at -78 °C, saturated $NaHCO_3$ (45 mL) was added and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted three times with DCM (45x2 mL). The combined organic layers were washed with brine (45 mL), H_2O (45 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the carbinol cyclopropane **37** which was used for the next step without further purification.

General procedure: Synthesis of butenolide lactone

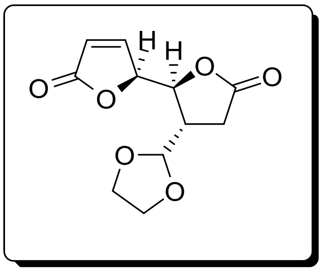
A round–bottomed flask, equipped with Dean–Stark trap was charged with cyclopropyl carbinol **37** (1 equiv) followed by ethylene glycol (224 μL, 4.02 mmol, 2 equiv), Sn–catalyst **47** (5 mol %) and 15 mL toluene. The mixture was gently refluxed for 12 h. Afterwhich, the crude mixture was evaporated and purified by chromatography on silica gel (ethyl acetate-hexanes 3:1) to yield γ-heterocyclic lactone β-dioxolane, **33**.

(2S,3S,2'S)-3-Dimethoxymethyl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33a.1)



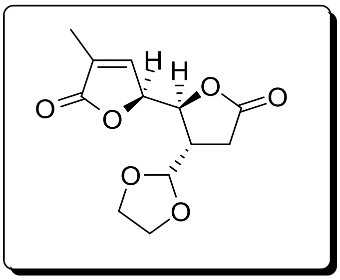
Yield 188.1 mg, 38%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 1H), 6.13 (m, 1H), 5.13 (dd, *J* = 3.8, 1.9 Hz, 1H), 4.68 (m, 1H), 4.33 (t, *J* = 7.1 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 2.95 (m, 1H), 2.68 (m, 1H), 2.38 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 172.2, 152.3, 122.4, 105.1, 83.2, 77.1, 56.2, 54.5, 39.4, 29.8. EI-HRMS: *m/z* calcd for $C_{11}H_{15}O_6$ 243.0869 $[M+H]^+$; found: 243.0869. IR (neat) $\tilde{\nu}$ 2945, 2837, 1783, 1745, 1603, 1451, 1361, 1159, 1112, 1054, 827 cm^{-1}.

(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33a.2)



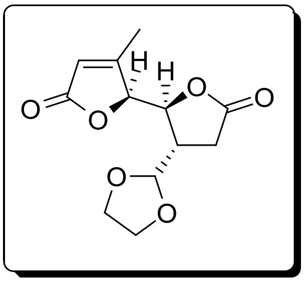
Yield 196.3 mg, 40%. ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.46 (m, 1H), 6.19 (dt, *J* = 13.3, 6.6 Hz, 1H), 5.18 (m, 1H), 4.93 (m, 1H), 4.70 (m, 1H), 4.01 (m, 2H), 3.92 (m, 2H), 2.99 (m, 1H), 2.76 (dt, *J* = 15.2, 7.6 Hz, 1H), 2.50 (m, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 174.8, 171.8, 152.1, 123.3, 103.3, 83.1, 76.3, 65.5, 65.3, 39.9, 29.2. LSI-HRMS: *m/z* calcd for $C_{11}H_{12}O_6$ 241.0712 [M+H]$^+$; found: 241.0711. IR (neat) $\tilde{\nu}$ 2945, 2837, 1754, 1603, 1159, 1113, 1066, 896, 826 cm^{-1}.

(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-4'-methyl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33b)



Yield 103.5 mg, 40% (based on 1.02 mmol **15**). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.01 (m, 1H), 5.04 (m, 1H), 4.97 (m, 1H), 4.94 (m, 1H), 4.71 (m, 1H), 4.67 (m, 1H), 4.04 (m, 1H), 3.94 (m, 1H), 2.94 (m, 1H), 2.78 (s, 3H), 2.52 (m, 1H), 1.97 (m, 1H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 174.8, 173.1, 143.9, 132.2, 103.3, 80.8, 76.8, 65.5, 65.4, 39.9, 29.3, 10.8. LSI-HRMS: *m/z* calcd for $C_{12}H_{15}O_6$ 255.0869 [M+H]$^+$; found: 255.0870. IR (neat) $\tilde{\nu}$ 2957, 2890, 1754, 1660, 1576, 1174, 1062, 1024, 943, 632 cm^{-1}.

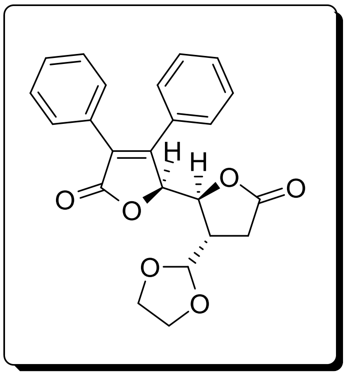
(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-3'-methyl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione ((33c)



Yield 338.4 mg, 65%. $[\alpha]_D^{25}$ +3.6 (*c* 0.3, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 1H), 4.94 (d, *J* = 4.1 Hz, 2H), 4.69 (dt, *J* = 11.7, 5.8 Hz, 1H), 3.98 (m, 4H), 3.03 (td, *J* = 9.9, 4.4 Hz, 1H), 2.79 (m, 1H), 2.49 (dd, *J* = 18.0, 5.4 Hz, 1H), 2.16 (dd, *J* = 12.3, 1.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 172.2, 164.3, 118.3, 103.3, 84.5, 75.7, 65.8, 40.1, 29.4, 14.0. EI-HRMS: *m/z* calcd for $C_{12}H_{13}O_6$ 253.0712 [M-H]$^+$; found: 253.0710. IR (neat) $\tilde{\nu}$ 2932, 2902, 2864, 1779, 1730, 1646, 1402, 1266, 1188, 1147, 1089, 1019, 975, 899 cm^{-1}.

EI-HRMS: *m/z* calcd for $C_{12}H_{13}O_6$ 253.0712 [M-H]$^+$; found: 253.0710. IR (neat) $\tilde{\nu}$ 2932, 2902, 2864, 1779, 1730, 1646, 1402, 1266, 1188, 1147, 1089, 1019, 975, 899 cm^{-1}.

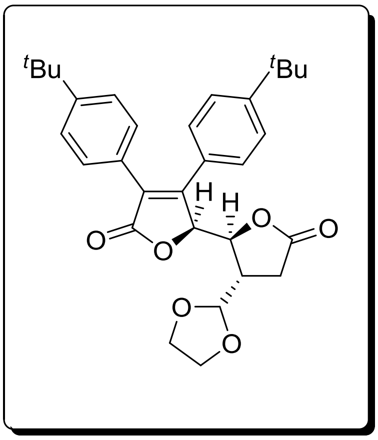
(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-3',4'-diphenyl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33d)



Yield 337.2 mg, 42%.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 10H), 5.57 (d, *J* = 1.4 Hz, 1H), 4.94 (m, 1H), 4.53 (dt, *J* = 8.2, 4.1 Hz, 1H), 3.96 (m, 4H), 3.16 (m, 1H), 2.86 (m, 1H), 2.50 (dd, *J* = 18.0, 6.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 173.1, 143.9, 132.2, 103.3, 80.9, 76.8, 65.5, 65.4, 39.9, 29.3, 10.8. LSI-HRMS:

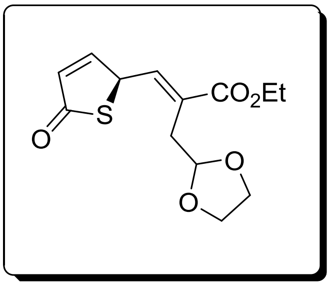
m/z calcd for $C_{23}H_{21}O_6$ 393.1338 $[M+H]^+$; found: 393.1328. IR (neat) $\tilde{\nu}$ 2960, 2893, 1789, 1750, 1643, 1446, 1355, 1156, 1027, 981, 910 cm^{-1}.

(2S,3S,2'S)-3',4'-Bis-(4-tert-butyl-phenyl)-3-[1,3]dioxolan-2-yl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33e)



Yield 458.1 mg, 49%.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 6H), 7.25 (m, 2H), 5.55 (d, *J* = 1.4 Hz, 1H), 4.94 (d, *J* = 4.4 Hz, 1H), 4.57 (dd, *J* = 5.4, 1.4 Hz, 1H), 3.94 (m, 4H), 3.14 (m, 1H), 2.84 (m, 1H), 2.50 (m, 1H), 1.31 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 172.2, 153.8, 151.8, 128.9, 127.8, 127.6, 126.5, 126.1, 125.4, 103.7, 81.4, 76.2, 65.6, 65.4, 40.4, 34.9, 34.7, 31.2, 31.2, 29.8. EI-HRMS: *m/z* calcd for $C_{31}H_{36}O_6$ 504.2512 $[M]^+$; found: 504.2501. IR (neat) $\tilde{\nu}$ 2962, 2868, 1791, 1756, 1608, 1363, 1160, 1027, 982, 837 cm^{-1}.

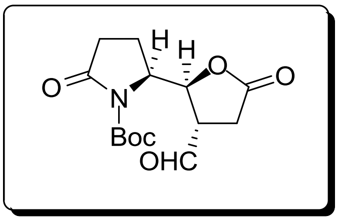
(E)-3-[1,3]Dioxolan-2-yl-4-((S)-5-oxo-2,5-dihydro-thiophen-2-yl)-but-3-enoic acid ethyl ester (48)



Yield 25.8 mg, 9% (based on 1.02 mmol **15**). ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.54 (m, 1H), 6.39 (m, 1H), 6.21 (m, 1H), 4.99 (m, 1H), 4.11 (m, 2H), 3.97 (m, 2H), 3.88 (m, 2H), 2.74 (m, 1H), 2.51 (m, 1H), 1.22 (m, 1H), 0.89 (m, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 171.2, 149.5, 141.0, 133.6, 130.5, 103.9, 65.4, 65.4, 60.8, 43.4, 34.0, 25.8, 14.1. EI-HRMS: *m/z* calcd for $C_{13}H_{16}SO_6$ 284.0718 $[M]^+$; found: 284.0724. IR (neat) $\tilde{\nu}$ 2926, 2850, 2322, 1733, 1685, 1259, 1182, 1038, 895 cm^{-1}.

Synthesis of pyrrolidenone lactone β-aldehyde

(S)-2-((S)-3-Formyl-5-oxo-tetrahydro-furan-2-yl)-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (33f)



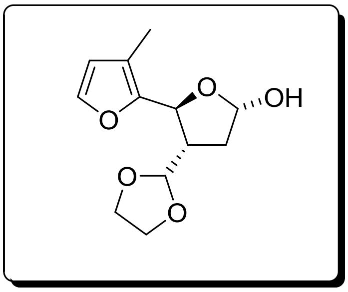
Palladium on carbon (10%, 74 mg) was added to a solution of α,β-unsaturated lactam cyclopropyl carbinol **37g** (854 mg, 2 mmol) in anhydrous THF (10 mL) in the presence of a small amount of NaOAc (31 mg) at room temperature. The reaction vessel was evacuated by aspirator and thoroughly purged with hydrogen (three times), and the resulting heterogeneous mixture was stirred under a balloon of hydrogen. After 24 h, the hydrogen was evacuated, the catalyst filtered off, and the filtrate was concentrated under vacuum to give a crude residue which was used for the next step without further purification.

The crude alcohol (1.0 equiv) was dissolved in MeOH (10 mL/mmol) and cooled to 0 °C. $Ba(OH)_2 \cdot 8H_2O$ (0.55 equiv) was added in small portions over 1 h. After 1 h stirring at 0 °C, DCM (10 ml/mmol) and H_2O (10 mL/mmol) were added and the layers were separated. The aqueous layer was again extracted with DCM (3x10 ml/mmol). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on silica gel (hexanes:ethylacetate 1:4) afforded the corresponding lactam lactone aldehyde **37f** as colorless syrup.

Yield 130.2 mg, 43% (based on 1.02 mmol **15**).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.75 (d, *J* = 1.4 Hz, 1H), 5.01 (ddd, *J* = 28.6, 14.3, 4.3 Hz, 1H), 4.38 (m, 1H), 3.47 (m, 1H), 3.30 (m, 1H), 3.01 (m, 1H), 2.86 (m, 1H), 2.72 (m, 1H), 2.47 (m, 1H), 1.59 (m, 1H), 1.54 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.9, 172.8, 150.2, 84.3, 78.4, 59.4, 49.2, 31.5, 28.9, 28.0, 28.0, 18.4. Anal. calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71 Found: C, 55.68; H, 6.72; N, 4.71. IR (neat) $\tilde{\nu}$ 2974, 2934, 1781, 1253, 1712, 1462, 1369, 1291, 1147, 1021, 971, 844, 797, 775 cm^{-1}.

Synthesis of lactolfuran dioxolane 58

(2S,3S,5S)-3-[1,3]Dioxolan-2-yl-2,3,4,5-tetrahydro-[2,2']bifuranyl-5-ol

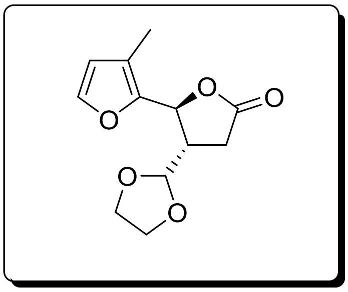


To a solution of **33c** (1.25 g, 4.92 mmol,1 equiv) in CH_2Cl_2 (75 mL) at −78 °C, DIBAL-H (11.8 mL of 1 M solution in DCM, 11.80 mmol, 2.4 equiv) was added under nitrogen. After 30 min the mixture was warmed to 0 °C, quenched with wet Et_2O and at room temperature, Et_2O, Na_2SO_4 (1.0 g) and $NaHCO_3$ (1.0 g) were added and the solution was stirred for 1 h, filtered through silica gel eluting with Et_2O and EtOAc, and concentrated to afford a crude oil which was purified with 1:1 hexanes-EtOAc to afford lactol **58**.

Yield 743.5 mg, 63% (*dr* 75:25, *16S/16R*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (m, 1H), 6.16 (m, 1H), 5.54 (m, 1H), 5.16 (dd, *J* = 5.7, 3.5 Hz, 1H), 4.98 (t, *J* = 3.4 Hz, 1H), 4.52 (m, 1H), 4.06 (m, 1H), 3.94 (m, 1H), 2.91 (dddd, *J* = 11.0, 8.3, 5.5, 2.8 Hz, 1H), 2.48 (m, 1H), 2.03 (s, 3H), 1.97 (d, *J* = 1.5 Hz, 2H, 1.61 (m, 1H)). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 141.6, 117.8, 113.0, 103.9, 98.6, 71.3, 65.5, 65.3, 44.4, 35.0, 9.7. EI-HRMS: *m/z* calcd for $C_{12}H_{16}O_5$ 240.0098 $[M]^+$; found: 240.0098. IR (neat) $\tilde{\nu}$ 3430, 2959, 2886, 1738, 1556, 1454, 1405, 1152, 1091, 942, 783 cm^{-1}.

Synthesis of lactonefuran dioxolane 59

(2S,3S)-3-[1,3]Dioxolan-2-yl-3,4-dihydro-2H-[2,2']bifuranyl-5-one

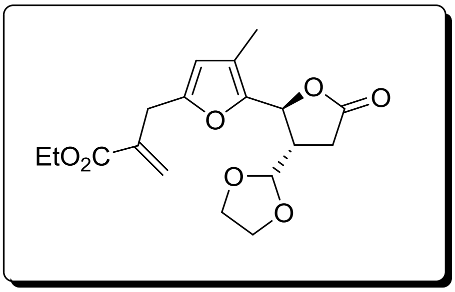


To a mixture of furanlactol **58** (79 mg, 0.335 mmol, 1 equiv), *N*-methylmorpholine *N*-oxide (NMO) (58.2 mg, 0.497 mmol, 1.5 equiv), 1.5 equiv and MS (4*Å*) (170 mg) in dry CH_2Cl_2 (10 mL) was added TPAP (17.4 mg, 0.05 mmol, 0.15 equiv). The reaction mixture was stirred at room temperature for 3 h under nitrogen and then was filtered through silica gel and Celite® eluting with EtOAc. The solvent was evaporated to give a crude oil, which was chromatographed on silica gel with 1:1 hexanes-EtOAc to afford furanlactone **59**.

Yield 83 mg, 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 1H), 6.24 (m, 1H), 5.48 (m, 1H), 4.92 (m, 1H), 4.02 (m, 2H), 3.92 (m, 2H), 3.15 (m, 1H), 2.92 (ddd, J = 17.7, 7.7, 5.2 Hz, 1H), 2.66 (m, 1H), 2.08 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 145.5, 142.4, 120.1, 113.3, 102.9, 72.6, 65.6, 65.4, 42.3, 29.6, 9.6. EI-HRMS: *m/z* 238.0841 calcd for $C_{12}H_{14}O_5$ $[M]^+$; found: 238.0843. IR (neat) $\tilde{\nu}$ 2900, 1775, 1348, 1175, 1136, 1031, 945, 767 cm^{-1}.

Synthesis of furanlactone methacrylate ethyl ester 57

2-((2'S,3'S)-3'-[1,3]-Dioxolan-2-yl-3-methyl-5'-oxo-2',3',4',5'-tetrahydro-[2,2']bifuranyl-5-ylmethyl)-acrylic acid ethyl ester

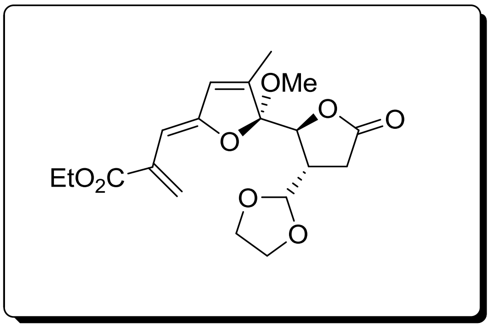


A mixture of **59** (50 mg, 0.21 mmol, 1 equiv), ethyl methacrylate (105 μL, 0.84 mmol, 4 equiv), $Pd(OAc)_2$ (2.4 mg, 0.011 mmol, 0.05 equiv), $Cu(OAc)_2.H_2O$ (84 mg, 0.42 mmol, 2 equiv) and LiOAc (55 mg, 0.84 mmol, 4 equiv) was stirred in DMF (1 mL) at 117 ^oC under air. After cooling, the reaction mixture was extracted with ethyl acetate and dried with anhydrous sodium sulfate. Compound **57** was purified by preparative reversed-phase HPLC using a gradient elution method with increasing amounts of acetonitrile in water.

Yield 38 mg, 52%. $[\alpha]_D^{25}$ +54.4 (*c* 0.4, DCM). ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (t, *J* = 3.3 Hz, 1H), 5.91 (s, 1H), 5.52 (t, *J* = 4.2 Hz, 1H), 5.41 (m, 1H), 4.92 (t, *J* = 3.9 Hz, 1H), 4.22 (m, 2H), 3.96 (m, 4H), 3.57 (d, 2H), 3.13 (m, 1H), 2.87 (m, 1H), 2.63 (m, 1H), 2.03 (t, 3H), 1.30 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 165.8, 152.1, 143.0, 135.9, 125.5, 119.8, 109.5, 101.6, 72.2, 64.3, 59.4, 41.2, 29.6, 28.3, 13.0, 8.9. EI-HRMS: *m/z* calcd for $C_{18}H_{22}O_7$ $[M]^+$: 350.1366; found: 350.1364. IR (neat): 2962, 2904, 1779, 1714, 1634, 1406, 1260, 1196, 1024, 947, 795 cm^{-1}.

Synthesis of trienol methyl ketal 54

2-[(2S,2'S,3'S)-3'-[1,3]Dioxolan-2-yl-2-methoxy-3-methyl-5'-oxo-2',3',4',5'-tetrahydro-2H-[2,2']bifuranyl-(5Z)-ylidenemethyl]-acrylic acid ethyl ester

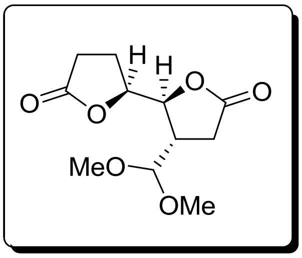


A solution of **57** (15 mg, 0.042 mmol, 1 equiv) in a mixture of MeOH (50 μL) and diethyl ether (35 μL) was stirred and cooled to -40°C. Liquid bromine (7.1 μL, 0.044 mmol, 1.03 equiv) in dry MeOH (0.1 mL) was added dropwise over 5 min. After addition, stirring was continued for an additional 10 min. The mixture was saturated with ammonia gas to pH 8, allowed to warm to room temperature, diluted with ether and evaporated. The residue was purified by flash chromatography (silica, 1:1 EtOAc–hexanes) to afford a mixture of 1:1 **54** and 3-*epi*-**54**.

Yield 8.8 mg, 55% (*dr* 50:50, 3S/3R). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (s, 1H), 6.18 (q, *J* = 1.4 Hz, 1H), 5.41 (d, *J* = 5.1 Hz, 1H), 4.85 (d, *J* = 3.5 Hz, 1H), 4.50 (d, *J* = 2.1 Hz, 1H), 4.23 (m, 2H), 3.92 (m, 4H), 3.47 (s, 2H), 3.14 (s, 2H), 2.84 (m, 1H), 2.68 (m, 1H), 2.42 (m, 1H), 1.95 (s, 3H), 1.31 (t, *J* = 3.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 166.9, 157.6, 141.2, 133.7, 127.1, 124.1, 115.0, 103.9, 94.0, 81.1, 65.8, 61.3, 50.9, 50.4, 38.4, 28.9, 14.1, 12.4. EI-HRMS: *m/z* calcd for $C_{19}H_{24}O_8$ $[M]^+$: 380.1471; found: 380.1478. IR (neat): 2904, 1782, 1710, 1636, 1447, 1366, 1244, 1130, 1021, 957, 942, 852 cm^{-1}.

Synthesis of bislactone 52

(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-tetrahydro-[2,2']bifuranyl-5,5'-dione



A solution of lactone **33a.1** (177 mg, 0.731 mmol, 1 equiv) in 7 mL of absolute MeOH was cooled to 0 °C and treated with $NiCl_2 \cdot 6H_2O$ (0.91 g, 3.8 mmol, 0.25 equiv). The resulting mixture was stirred at the same temperature for 15 min before the addition of $NaBH_4$ (0.29 g, 7.6 mmol, 1 equiv). After 30 min, further portion of $NaBH_4$ (0.14 g, 3.8 mmol, 0.5 equiv) was added, and the reaction was allowed to stir for additional 10 min. The reaction was quenched with saturated NH_4Cl solution and extracted with 3x10 mL CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated under vacuum. Silica gel flash chromatographic purification (1:1 hexanes-EtOAc) afforded saturated compound **52** as a colorless oil.

Yield 149.6 mg, 84% (*dr* 76:24, 3S/3R). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (m, 1H), 4.44 (m, 1H), 4.27 (m, 1H), 3.37 (s, 3H), 3.32 (s, 3H), 2.85 (dt, J = 10.1, 4.5 Hz, 1H), 2.47 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 175.3, 105.2, 80.6, 79.9, 55.9, 54.2, 39.7, 30.2, 27.9, 23.8. EI-HRMS: *m/z* calcd for $C_{11}H_{16}O_6$ $[M-H]^+$: 243.0689; found: 243.0866. IR (neat): 2947, 2838, 1768, 1457, 1367, 1152, 1121, 1052, 981, 876 cm^{-1}.

4.2 Diastereocontrolled addition of organotitanium reagents to trifunctionalized cyclopropane 15 – synthesis of γ-arylbutyrolactones

General Procedure A: Preparation of Aryltitanium Nucleophiles

From five-membered heterocyles. As representative procedure, to a THF (26 mL) solution of furan (1.5 mL, 8.04 mmol) at –78 °C, *n*-BuLi (5.27 mL, 8.44 mmol) was added slowly. The mixture was stirred for 2 h at this temperature, and the resulting solution was treated with a solution of chlorotriisopropoxytitanium in hexane (8.84 mL, mmol, 1.1 eq) dropwise over 5 min and stirred further for 30 min.

From bromophenyl derivatives. As representative procedure, to a solution of 4-methoxyphenyllithium was prepared by slow addition of *n*-butyllithium in hexane (1.6 M, 5.27 mL, 8.44 mmol, 1.05 eq) to 4-bromoanisole (1.0 mL, 8.04 mmol, 1 eq) in THF (mL) under a nitrogen atmosphere and was stirred for 2h at –78 °C. Chlorotriisopropoxytitanium in hexane (1 M, 8.84 mL, 8.84 mmol, 1.1 eq) was added dropwise over 5 min at –78 °C under nitrogen. After completion of the addition, the mixture was stirred further for 30 min.

General Procedure B: Addition of Aryltitanium Nucleophiles to Cyclopropanecarbaldehyde, 15

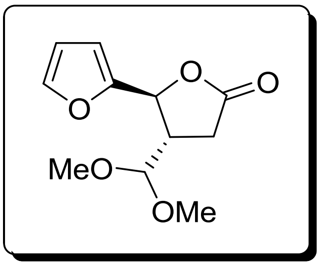
Under a nitrogen atmosphere, a solution of cyclopropylcarbaldehyde (+)-**15** (500 mg, 2.01 mmol, 1 equiv) in anhydrous THF (20 mL) was added via canula to a flame-dried three-necked flask and was cooled to -78 °C. $BF_3 \cdot OEt_2$ (0.28 mL, 2.21 mmol, 1.1 equiv) was added via syringe and after stirring for 30 min., the aryltitanium nucleophile solution (8.04 mmol, 4 equiv) was added slowly resulting to a color change (typically yellow-orange to reddish-orange).

After stirring for 16 h at -78 °C, saturated $NaHCO_3$ (45 mL) was added and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted three times with ethyl acetate (45x2 mL). The combined organic layers were washed with brine (45 mL), H_2O (45 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the arylcarbinol cyclopropane **10** which was used for the next step without further purification.

General Procedure C: Synthesis of γ-Aryllactone Methyl Acetals 68a-68f

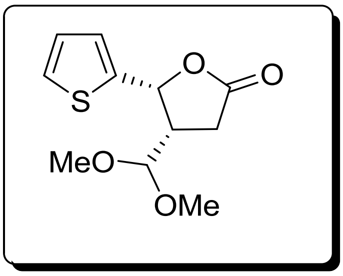
A round–bottomed flask, equipped with Dean–Stark trap was charged with arylcyclopropyl carbinol **74** (1 equiv) followed by methanol (2 mL per mmol) and Sn–catalyst **47** (10 mol%). The mixture was gently refluxed for 12 h. Afterwhich, the crude mixture was evaporated and purified by chromatography on silica gel (ethyl acetate-hexanes 1:2) to yield the protected aryllactone aldehyde, **68**.

(2S,3S)-3-Dimethoxymethyl-3,4-dihydro-2H-[2,2']bifuranyl-5-one (68a)



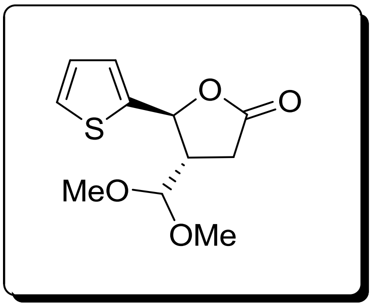
According to general procedure B, 181 mg (40%, 86:14 *trans-cis* ratio). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.25 (m, 2H), 5.40 (d, *J* = 4.6 Hz, 1H), 4.35 (d, *J* = 5.7 Hz, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.10 (m, 1H), 2.83 (dd, *J* = 17.9, 9.4 Hz, 1H), 2.61 (dd, *J* = 17.9, 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 151.0, 143.6, 110.5, 109.2, 104.3, 74.9, 55.4, 54.5, 42.2, 30.1. HR-EIMS: calcd for $C_{11}H_{14}O_5$ [M]$^+$: 226.0841, found: 226.08422. IR**:** $\tilde{\nu}$ = 2937, 1738, 1734, 1591, 1445, 1372, 1253, 1172, 1067, 748, 632, 537, 497 cm^{-1}.

(4S,5R)-4-Dimethoxymethyl-5-thiophen-2-yl-dihydro-furan-2-one (68b)



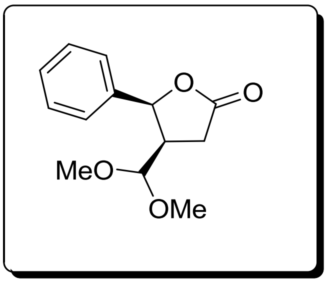
According to general procedure B, 184 mg (38%, 55:45 *cis-trans* ratio)^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.5 Hz, 1H), 7.03 (m, 2H), 5.84 (d, *J* = 7.7 Hz, 2H), 3.93 (d, *J* = 7.3 Hz, 2H), 3.59 (m, 1H), 3.25 (s, 3H), 3.21 (s, 3H), 2.73 (dd, *J* = 23.5, 13.4 Hz, 1H), 2.56 (dd, *J* = 17.6, 8.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 141.9, 126.9, 126.2, 125.9, 104.3, 78.3, 54.9, 54.8, 52.7, 43.2, 29.1. HR-EIMS: calcd for $C_{11}H_{14}O_4S$ $[M]^+$: 242.0613, found: 242.06144 IR**:** $\tilde{\nu}$ = 2940, 2834, 1782, 1732, 1441, 1169, 1062, 953, 712, 632, 540, 495 cm^{-1}.

(4S,5S)-4-Dimethoxymethyl-5-thiophen-2-yl-dihydro-furan-2-one (minor trans-68b)



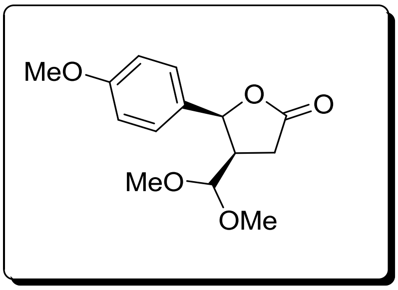
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 2.5 Hz, 1H), 7 (m, 2H), 5.65 (d, *J* = 5.1 Hz, 1H), 4.39 (d, *J* = 5.4 Hz, 1H), 3.41 (s, 3H), 3.37 (s, 3H), 3.14 (m, 2H), 2.91 (dd, *J* = 11.1, 5.8 Hz, 1H), 2.77 (dd, *J* = 19.3, 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 138.2, 127.0, 126.1, 125.8, 105.1, 78.0, 55.2, 54.9, 46.6, 29.9.

(4R,5S)-4-Dimethoxymethyl-5-phenyl-dihydro-furan-2-one (68c).



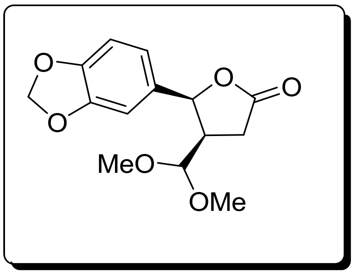
According to general procedure B, 214 mg (45%, >99% *cis*). Mp 86-89^{o}C, $[\alpha]_{20}^{D}$ -17 (*c* 0.12, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H), 5.60 (d, *J* = 7.7 Hz, 1H), 3.63 (d, *J* = 6.1 Hz, 1H), 3.35 (m, 1H), 3.12 (s, 3H), 3.10 (s, 3H), 2.71 (dd, *J* = 17.7, 7.6 Hz, 1H), 2.58 (dd, *J* = 17.7, 9.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 135.7, 128.7, 125.8, 103.9, 81.9, 55.1, 52.9, 43.0, 29.7. HR-EIMS: calcd for $C_{13}H_{16}O_4$ $[M]^+$: 236.104, found: 236.10469. IR**:** $\tilde{\nu}$ = 3008, 2936, 2879, 2836, 1747, 1606, 1500, 1454, 1379, 1306, 1222, 1166, 1118, 1051, 972, 879, 737, 688, 562, 510, 429 cm^{-1}.

(4R,5S)-4-Dimethoxymethyl-5-(4-methoxy-phenyl)-dihydro-furan-2-one (68d).



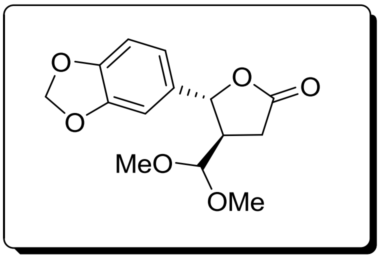
According to general procedure B, 203 mg (38%, 82:18 *cis-trans* ratio).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 5.58 (d, *J* = 7.7 Hz, 1H), 3.82 (s, 3H), 3.40 (d, *J* = 6.1 Hz, 1H), 3.17 (s, 3H), 3.13 (s, 3H), 3.08 (m, 1H), 2.70 (dd, *J* = 16.8, 7.4 Hz, 1H), 2.57 (dd, *J* = 17.7, 9.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 159.7, 127.6, 113.8, 103.8, 81.5, 55.5, 54.9, 52.9, 43.2, 29.5. HR-EIMS: calcd for $C_{14}H_{18}O_5$ $[M]^+$: 266.1154, found: 266. 11558. IR**:** $\tilde{\nu}$ = 2962, 2836, 1779, 1613, 1515, 1462, 1254, 1176, 1020, 797, 632, 537, 497 cm^{-1}.

(4R,5S)-5-Benzo[1,3]dioxol-5-yl-4-dimethoxymethyl-dihydro-furan-2-one (68e)



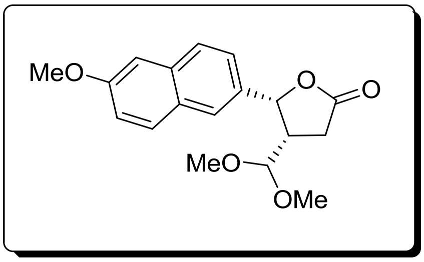
According to general procedure B, 186 mg (33%, 76:24 *cis-trans* ratio). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (m, 3H), 5.93 (s, 1H), 5.47 (d, *J* = 7.6 Hz, 1H), 3.67 (d, *J* = 6.1 Hz, 1H), 3.14 (s, 1H), 3.11 (s, 1H), 3.00 (m, 1H), 2.64 (dd, *J* = 18.1, 7.4 Hz, 1H), 2.51 (dd, *J* = 16.8, 9.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 148.0, 147.6, 129.6, 119.6, 108.2, 106.7, 103.6, 101.3, 81.4, 54.9, 53.4, 43.3, 29.5. HR-EIMS: calcd for $C_{14}H_{16}O_6$ $[M]^+$: 280.0947, found: 280.09519. IR: $\tilde{\nu}$ = 2936, 1776, 1612, 1492, 1445, 1243, 1177, 1036, 930, 632, 539, 495 cm^{-1}.

(4R,5R)-5-Benzo[1,3]dioxol-5-yl-4-dimethoxymethyl-dihydro-furan-2-one (minor trans-68e)



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (m, 3H), 5.92 (s, 1H), 5.27 (d, *J* = 4.9 Hz, 1H), 4.31 (d, *J* = 5.1 Hz, 1H), 3.34 (s, 3H), 3.28 (s, 3H), 2.98 (m, 1H), 2.63 (m, 1H), 2.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 148.2, 147.7, 133.3, 119.3, 108.3, 106.1, 104.8, 101.3, 81.8, 65.4, 54.7, 53.4, 46.4, 29.9.

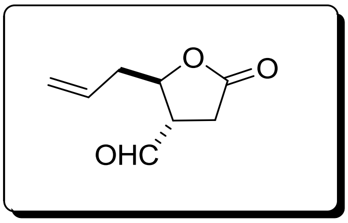
(4S,5R)-4-Dimethoxymethyl-5-(6-methoxy-naphthalen-2-yl)-dihydro-furan-2-one (68f)



According to general procedure B, 235 mg (37%, 92:8 *cis-trans* ratio).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 6H), 5.75 (d, *J* = 7.6 Hz, 1H), 3.93 (s, 3H), 3.66 (d, *J* = 6.1 Hz, 1H), 3.17 (m, 1H), 3.12 (s, 3H), 3.09 (s, 3H), 2.78 (dd, *J* = 17.7, 7.7 Hz, 1H), 2.63 (dd, *J* = 17.6, 9.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 158.2, 134.3, 130.8, 129.5, 128.4, 127.0, 125.1, 124.3, 119.5, 105.7, 103.7, 81.6, 55.3, 54.9, 53.4, 43.4, 29.7. HR-EIMS: calcd for $C_{18}H_{20}O_5$ $[M]^+$: 316.1311, found: 316.13092. IR**:** $\tilde{\nu}$ = 2999, 2929, 2837, 1772, 1609, 1487, 1458, 1384, 1302, 1265, 1182, 1119, 1054, 983, 859, 783, 704, 474 cm^{-1}.

Synthesis of trans-allyllactone 68i.

(2R,3S)-2-Allyl-5-oxo-tetrahydro-furan-3-carbaldehyde

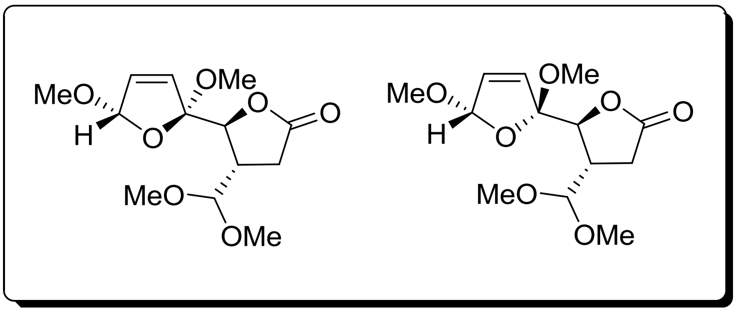


To a THF (26 mL) solution of allymagnesium bromide in THF (4.02 mL, 2M, 4.02 mmol, 1 equiv) at –78 °C, chlorotriisopropoxytitanium in hexane (8.84 mL, 1 M, 8.84 mmol, 1.1 equiv) was added dropwise over 5 min under nitrogen atmosphere. After completion of the addition, the mixture was stirred further for 30 min. Under a nitrogen atmosphere, a solution of cyclopropylcarbaldehyde (-)-**15** (500 mg, 2.01 mmol, 1 equiv) in anhydrous THF (20 mL) was added via canula to a flame-dried three-necked flask and was cooled to -78 °C. $BF_3 \cdot OEt_2$ (0.28 mL, 2.21 mmol, 1.1 equiv) was added via syringe and after stirring for 30 min., the allyltitanium nucleophile solution (8.04 mmol, 4 equiv) was added slowly resulting to a color change (orange-red). After stirring for 16 h at -78 °C, saturated $NaHCO_3$ (45 mL) was added and the mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted three times with ethyl acetate (45x2 mL). The combined organic layers were washed with brine (45 mL), H_2O (45 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the allylcarbinol cyclopropane **74i** which was used for the next step without further purification. Crude alcohol **74i** (1.0 equiv) was dissolved in MeOH (10 mL/mmol) and cooled to 0 °C. $Ba(OH)_2{\cdot}8H_2O$ (0.55 equiv) was added in small portions over 1 h. After 1 h stirring at 0 °C, DCM (10 mL/mmol) and H_2O (10 mL/mmol) were added and the layers were separated. The aqueous layer was again extracted with DCM (3x10 mL/mmol). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography on silica gel (hexanes:ethylacetate 1:1) afforded the corresponding lactone aldehyde **68i** as a very light yellow oil.

Yield 90 mg (29%, 94:6 *trans-cis* ratio).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 7.9 Hz, 1.1 Hz, 1H), 7.33 (td, *J* = 7.6 Hz, 1.3 Hz, 1H), 7.10 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.07- 6.97 (m, 1H), 5.60 (d, *J* = 4.7 Hz, 1H), 4.48 (d, *J* = 4.4 Hz, 1H), 2.45 (tt, *J* = 11.3 Hz, 3.5 Hz, 1H), 1.99 (m, 1H), 1.69 (m, 3H), 1.23 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 211.0, 139.4, 139.0, 129.3, 127.9, 127.6, 99.3, 80.1, 45.4, 28.9, 26.6, 24.7, 24.5, 24.0.

Synthesis of lactone acetals 86a-86c from 68a.

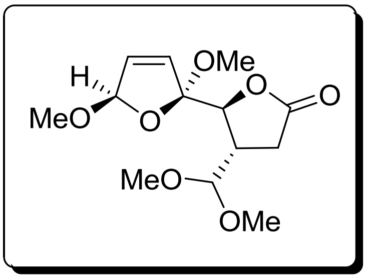
(2S,3S,2'R,5'S)-3-Dimethoxymethyl-2',5'-dimethoxy-3,4,2',5'-tetrahydro-2H-[2,2']bifuranyl-5-one (14a) and (2S,3S,2'S,5'S)-3-Dimethoxymethyl-2',5'-dimethoxy-3,4,2',5'-tetrahydro-2H-[2,2']bifuranyl-5-one (86b, relative stereochemistry assigned)



A solution of **68a** (40 mg, 0.388, 1 equiv) in a mixture of MeOH (0.1 mL) and diethyl ether (70 μL) was stirred and cooled to -40 °C. Liquid bromine (7.1 μL, 0.1429 mmol, 1.03 equiv) in dry MeOH (0.1 mL) was added dropwise over 5 min. After addition, stirring was continued for an additional 10 min. The mixture was saturated with ammonia gas to pH 8, allowed to warm to room temperature, diluted with ether and evaporated. The residue (2:1:1 mixture of three stereoisomers) was purified by flash chromatography (silica, 1:1 EtOAc–hexanes) to afford a mixture of **86a** and **86b** (19 mg) and pure **86c** (19 mg).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.13 (d, *J* = 2.8 Hz, 1H), 6.09 (d, *J* = 0.9 Hz, 1H), 6.07 (d, *J* = 0.8 Hz, 1H), 5.81 (s, 1H), 5.48 (s, 1H), 4.40 (d, *J* = 2.0 Hz, 1H), 4.26 (d, *J* = 5.5 Hz, 1H), 4.23 (d, *J* = 1.5 Hz, 1H), 3.51 (s, 2H), 3.46 (s, 1H), 3.40 (s, 3H), 3.38 (d, *J* = 1.0 Hz, 3H), 3.19 (s, 1H), 3.12 (s, 1H), 2.98 (m, 1H), 2.72 (ddd, *J* = 17.9, 10.0, 5.7 Hz, 1H), 2.40 (dt, *J* = 18.0, 2.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.6, 132.7, 132.4, 132.1, 130.9, 113.4, 112.4, 108.5, 107.4, 105.5, 105.3, 83.7, 83.4, 56.5, 55.5, 55.3, 54.9, 54.6, 53.9, 50.7, 50.1, 37.9, 30.0. HR-LSIMS: calcd for $C_{13}H_{21}O_7$ $[M+H]^+$: 289.1287, found: 289.13011. IR: $\tilde{\nu}$ = 2944, 2838, 1769, 1632, 1444, 1373, 1188, 1118, 1075, 1017, 972, 829, 697, 625 cm^{-1}.

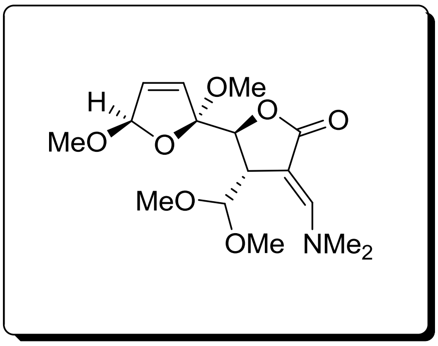
(2S,3S,2'S,5'R)-3-Dimethoxymethyl-2',5'-dimethoxy-3,4,2',5'-tetrahydro-2H-[2,2']bifuranyl-5-one (86c)



^{1}H NMR (600 MHz, $CDCl_3$) δ 6.18 (dd, J = 5.9, 0.9 Hz, 1H), 5.87 (dd, J = 5.9, 1.3 Hz, 1H), 5.76 (s, 1H), 4.49 (d, J = 2.1 Hz, 1H), 4.27 (d, J = 5.6 Hz, 1H), 3.45 (s, 3H), 3.39 (s, 6H), 3.16 (s, 3H), 3.00 (m, 1H), 2.67 (dd, J = 18.0, 10.0 Hz, 1H), 2.43 (dd, J = 18.0, 2.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.7, 133.7, 129.9, 114.2, 109.3, 104.6, 80.7, 56.5, 54.9, 54.4, 50.0, 38.0, 29.5. HR-LSIMS: calcd for $C_{13}H_{21}O_7$ $[M+H]^+$: 289.1287, found: 289.13010. IR: $\tilde{\nu}$ = 2942, 2835, 1780, 1632, 1450, 1374, 1247, 1193, 1117, 1076, 1016, 981, 834, 631, 536, 497 cm^{-1}.

Synthesis of compound 87

(2S,3S,2'S,5'R)-3-Dimethoxymethyl-4-dimethylaminomethylene-2',5'-dimethoxy-3,4,2',5'-tetrahydro-2H-[2,2']bifuranyl-5-one



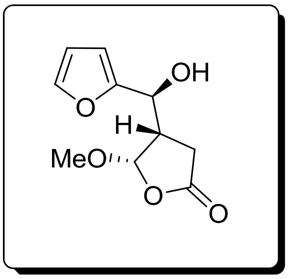
A mixture of 7 mg **86c** (0.0243 mmol, 1 equiv) and 5.9 μL (0.0340 mmol, 1.4 equiv) of tris-(dimethylamino)methane was heated under nitrogen with stirring at 70 °C for 48 h. The crude product was dried under vacuum for 2 h and filtered on silica gel with 2:1 hexanes-ethyl acetate to give 7 mg (81%) of **87**.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.17 (d, *J* = 0.8 Hz, 1H), 6.07 (dd, *J* = 5.9, 0.8 Hz, 1H), 5.88 (dd, *J* = 5.9, 1.2 Hz, 1H), 5.76 (s, 1H), 4.49 (s, 1H), 4.15 (d, *J* = 6.7 Hz, 1H), 3.75 (d, *J* = 6.7 Hz, 1H), 3.44 (s, 3H), 3.41 (s, 3H), 3.41 (s, 3H), 3.15 (s, 3H), 3.04 (s, 6H). ^{13}C NMR (150 MHz, CDCl$_3$) δ 175.0, 147.9, 132.5, 130.5, 114.8, 109.1, 107.2, 88.1, 79.0, 57.2, 56.3, 53.9, 50.0, 41.9, 29.7. HR-EIMS: calcd for $C_{16}H_{25}NO_7$ $[M]^+$: 343.1631, found: 343.16316. IR**:** $\tilde{\nu}$ = 2923, 2851, 1722, 1616, 1444, 1375, 1193, 1119, 1015, 771, 697, 622, 575, 437 cm^{-1}.

General Procedure D: Synthesis of Hetarylcarbinol lactone methyl acetals 77a and 77b

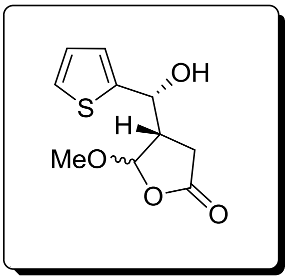
A round–bottomed flask, equipped with Dean–Stark trap was charged with arylcyclopropyl carbinol **74** (1 equiv) followed by methanol (10 mL per mmol) and Sn–catalyst **47** (10 mol%). The mixture was gently refluxed for 12 h. Afterwhich, the crude mixture was evaporated and purified by chromatography on silica gel (ethyl acetate-hexanes 1:2) to yield the hetarylcarbinols **77**.

(4S,5S)-4-((S)-Furan-2-yl-hydroxy-methyl)-5-methoxy-dihydro-furan-2-one (77a)



Yield 140.1 mg, 65%. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.35 (m, 2H), 5.51 (d, *J* = 5.1 Hz, 2H), 4.64 (m, 1H), 3.452 (s, 3H), 2.76 (m, 1H), 2.25 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.8, 153.3, 142.9, 110.4, 107.9, 106.4, 67.6, 56.8, 46.1, 30.4. LR-EIMS: m/z (%) 230.1 [M+NH$_4$]$^+$, 212 [M]$^+$, 198.1 (94), 195 (41), 181 (5), 170 (21), 146 (5), 129 (2). IR**:** $\tilde{\nu}$ = 1756, 1448, 1359, 1112, 1158, 1066, 896, 826 cm^{-1}

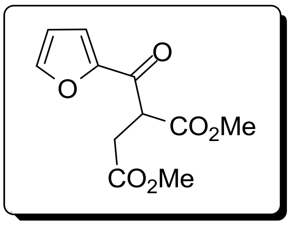
(4S,5S)-4-((R)-Hydroxy-thiophen-2-yl-methyl)-5-methoxy-dihydro-furan-2-one (77b)



Yield 22.0 mg, 19% (<u>*dr*</u> 60:40). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.25 (dd, *J* = 4.8, 1.5 Hz, 1H), 6.93 (dt, *J* = 3.5, 1.2 Hz, 1H), 5.46 (t, *J* = 5.1 Hz, 1H), 4.77 (m, 1H), 3.42 (s, 3H), 2.67 (m, 2H), 2.16 (m, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.9, 144.9, 127.0, 125.9, 125.3, 106.6, 70.0, 56.9, 48.8, 30.7. LR-EIMS: m/z (%) 228.0 [M]$^+$, 196 (10), 168 (8), 123 (29), 113 (100), 85 (48), 71 (24).

5. Synthetic approach employing diastereoselective reduction of furylated β-keto esters

2-(Furan-2-carbonyl)-succinic acid dimethyl ester 94

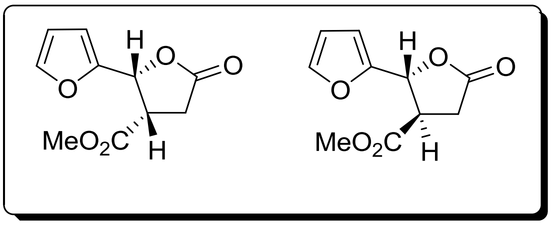


To LDA (13.92 mmol, 1.1 equiv) in toluene (200 mL) were added dropwise successively the cyanohydrin **97** (3 g, 12.7 mmol, 1 equiv) in toluene (20 mL) and dimethyl maleate (1.91 g, 13.3 mmol, 1.05 equiv) in toluene (20 mL) at -78 °C under nitrogen atmosphere. The mixture was quenched by addition of aqueous AcOH (15%, 11 mL, 25.3 mmol). The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layer was washed with brine (100 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residue was dissolved in THF (100 mL), and then AcOH (1.2 mL, 19 mmol) and TBAF (1.0 M in THF, 17 mL) were added to the solution at room temperature. After 30 min, the solution was washed with water (100 mL), 10% citric acid (100 mL), and brine (100 mL) and then dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography using hexane/EtOAc (1:1) as an eluent to afford **94** as a brown syrup.

Yield 1.86g, 61%.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, J = 1.7, 0.7 Hz, 1H), 7.29 (m, 1H), 6.52 (m, 1H), 4.53 (m, 1H), 3.60 (dd, J = 8.6, 3.5 Hz, 6H), 2.96 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.3, 171.4, 168.8, 151.5, 147.4, 119.2, 112.8, 52.8, 52.0, 49.4, 32.4. HR-EIMS: calcd for $C_{11}H_{12}O_6$ $[M]^+$: 240.0634, found: 240.0636. IR: $\tilde{\nu}$ = 1738, 1677, 1466, 1262, 1165, 1016, 890 cm^{-1}.

Diastereoselective reduction of furan diester 94

5-Oxo-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carboxylic acid methyl ester



$Zn(BH_4)_2$ reduction of 94

To a suspension of $NaBH_4$ (190 mg, 5 mmol, 2 equiv) in diethyl ether (3 mL) was added $ZnCl_2$ (1M in diethyl ether, 2.5 mL, 2.5 mmol, 1 equiv), at room temperature. The mixture was stirred for 5 h and the insoluble materials were filtered off. The filtrate was poured into a solution of **94** (2.45 mmol) in diethyl ether (50 mL) at -20 ^{o}C. The solution was allowed to warm to 0 ^{o}C and stirred for 2 h. The reaction was quenched by the addition of acetic acid (40 mmol). The mixture was washed with brine and dried and concentrated *in vacuo*. The residue was chromatographed on silica gel using hexane-EtOAc (2:1) to afford lactone **93** in 52% yield (267.5 mg, 86:14 *trans/cis*).

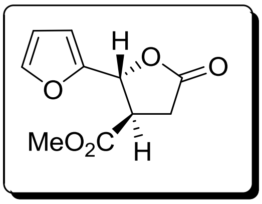
$NaBH_4$ reduction of 94

To a suspension of $NaBH_4$ (190 mg, 5 mmol, 2 equiv) in methanol (20 mL) at 0 ^{o}C, was added **94** (2.45 mmol) in methanol (10 mL). The solution was allowed to warm to 0 ^{o}C and stirred for 2 h. The reaction was quenched with water and concentrated. The aqueous layer was extracted with EtOAc (3x10 mL) and concentrated. The residue was dissolved in 25 mL THF and catalytic PTSA was added. The solution was stirred further for 3 h and water was added (25 mL). The solution was extracted with 20 mL EtOAc (3x). The combined organic layers were washed with saturated $NaHCO_3$, brine and dried (Na_2SO_4). After concentration, the residue was chromatographed on silica gel using hexane-EtOAc (2:1) to afford lactone **93** in 79% yield (406 mg, 19:81 *trans/cis*).

Yeast reduction

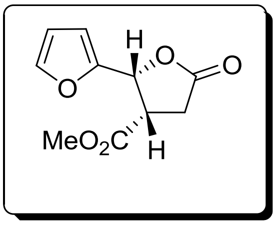
In a 1 L Erlenmeyer flask, 300 mg of furan succinate **94** in 5 mL ethanol and 100 mL water were added. Eight packs of Dr. Oetcker's yeast were added and the flask was shaken. Fermentation was signaled by the evolution of gas (CO_2) and the flask was set aside for 3 days. The yeast mixture was mixed with Celite 535 and filtered under vacuum and the residue was washed with some volumes of ethanol. The collected filtrate was concentrated *in vacuo* until ethanol was completely removed. The aqueous mixture was partitioned with diethyl ether (3x100 mL) and the combined organic layers were washed with brine (100 mL) and concentrated. The residue was chromatographed in silica using hexanes-EtOAc (4:1) to furnish *cis* **93** and *tran*s **93** (75:25) in 25 % combined yield.

(2R,3R)-5-Oxo-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carboxylic acid methyl ester (trans-93)



Yield 16.3 mg. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 10.2, 9.2 Hz, 1H), 6.35 (d, *J* = 3.3 Hz, 1H), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.67 (d, *J* = 8.5 Hz, 1H), 3.74 (m, 1H), 3.49 (s, 3H), 3.26 (dd, *J* = 17.7, 9.9 Hz, 1H), 2.69 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 169.1, 148.6, 143.6, 110.5, 110.1, 74.2, 52.4, 44.7, 30.2. HR-EIMS: calcd for $C_{10}H_{10}O_5$ $[M]^+$: 210.0528, found: 210.0527. IR**:** $\tilde{\nu}$ = 1781, 1733, 1437, 1260, 1189, 1154, 984, 923, 885, 751 cm^{-1}.

(2R,3S)-5-Oxo-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carboxylic acid methyl ester (cis-93)

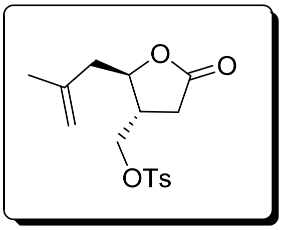


Yield 49.1 mg. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.39 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.42 (d, *J* = 3.3 Hz, 1H), 6.32 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.59 (d, *J* = 6.3 Hz, 1H), 3.70 (s, 3H), 3.63 (m, 1H), 2.94 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.98, 171.29, 144.21, 110.99, 110.73, 75.65, 53.21, 44.52, 32.30. HR-EIMS: calcd for $C_{10}H_{10}O_5$ [M]$^+$: 210.0528, found: 210.0526. IR**:** $\tilde{\nu}$ = 2954, 1773, 1773, 1737, 1441, 1369, 1211, 1166, 1099, 945, 737 cm^{-1}

6. A Simplified Approach Towards the Total Synthesis of Bielschowskysin

Synthesis of lactone tosylate 124

Benzenesulfonic acid (2R,3R)-2-(2-methyl-allyl)-5-oxo-tetrahydro-furan-3-ylmethyl ester

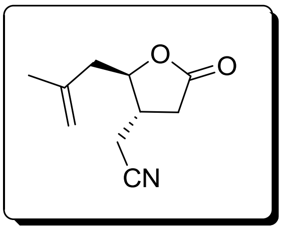


To a solution of methallyllactone alcohol **123** (200 mg, 1.18 mmol) in dry DCM (6 mL) were added *p*-toluenesulfonyl chloride (336 mg, 1.74 mmol, 1.5 equiv), Et_3N (1.77 mL, 11.8 mmol, 10 equiv), and DMAP (20 mg, 0.84 mmol, 15 mol %) at 0 °C. After 4 h at room temperature, the mixture was poured into ice-water and extracted with DCM (30 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, and brine, dried over anhydrous $MgSO_4$, and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give tosylate **124**.

Yield160.2.4 mg, 42%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.67 (m, 1H), 5.13 (m, 1H), 5.09 (dt, *J* = 4.6, 1.5 Hz, 1H), 4.27 (dt, *J* = 9.2, 4.1 Hz, 1H), 3.99 (dd, *J* = 4.4, 1.6 Hz, 2H), 2.63 (m, 1H), 2.54 (m, 1H), 2.42 (m, 3H), 2.36 (ddd, *J* = 5.7, 3.8, 2.5 Hz, 2H), 2.28 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 145.5, 132.2, 131.3, 130.1, 127.9, 119.8, 80.5, 69.0, 38.9, 38.6, 31.1, 21.7. HR-EIMS: calcd for $C_{16}H_{20}SO_5$ $[M]^+$: 324.1031, found: 324.1030. IR**:** $\tilde{\nu}$ = 2945, 2855, 232, 1778, 1734, 1444, 1376, 1179, 1022 cm^{-1}

Synthesis of lactone nitrile 125

[(2R,3S)-2-(2-Methyl-allyl)-5-oxo-tetrahydro-furan-3-yl]-acetonitrile

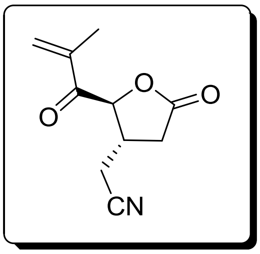


To a stirred solution of tosylate **124** (200 mg, 0.617 mmol) in DMF (10 mL) at room temperature was added potassium cyanide (80 mg, 1.23 mmol, 2 equiv). The resulting mixture was warmed to 90 °C and stirred for 30 h before it was cooled to room temperature, quenched with H_2O (10 mL) and diluted with Et_2O (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (silica gel, hexanes:EtOAc 2:1) afforded nitrile **125** as a colorless oil.

Yield 93.7 mg, 85%.^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (m, 1H), 4.88 (d, J = 7.6 Hz, 1H), 4.42 (ddd, J = 11.8, 6.0, 2.6 Hz, 1H), 2.83 (m, 1H), 2.50 (m, 5H), 1.81 (s, 3H), 1.78 (d, J = 7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 139.7, 116.6, 115.0, 81.7, 42.4, 36.9, 33.8, 22.7, 20.6. LR-EIMS = m/z 179.1[M]$^+$, 124.0(100), 97.0(78), 68.1(47), 41.1(52). IR**:** $\tilde{\nu}$ = 2920, 2851, 2163, 1778, 1651, 1425, 1183, 896 cm^{-1}

Synthesis of ketolactone nitrile 126

[(2S,3S)-2-(2-Methyl-acryloyl)-5-oxo-tetrahydro-furan-3-yl]-acetonitrile

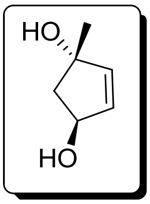


The methallyllactone nitrile **125** (60 mg, 0.335 mmol, 1 equiv) was dissolved in dioxane (3 mL). Selenium dioxide (39 mg, 0.352 mmol, 1.05 equiv) was dissolved in dioxane (3 mL) and added to the other solution. Finally, 0.25 mL of water was added and the mixture was heated at 60 °C and stirred for 16 h under reflux. The solvent was evaporated, water was added and the product was extracted with ether (3x20 mL). Combined organic layers were dried by Na_2SO_4. The product was purified by flash chromatography (PE/EA 1:1) to give **126** as a yellowish oil.

Yield 19.9 mg, 31%.^{1}H NMR (300 MHz, $CDCl_3$) δ 6.24 (d, *J* = 4.1 Hz, 1H), 6.13 (q, *J* = 1.4 Hz, 1H), 5.31 (d, *J* = 4.4 Hz, 1H), 5.30 (s, 1H), 2.86 (m, 1H), 2.65 (m, 1H), 2.42 (m, 1H), 1.94 (m, 3H), 1.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 172.9, 141.6, 129.6, 114.6, 79.8, 34.7, 31.8, 20.6, 17.4. LR-EIMS = *m/z* 193.1$[M]^+$, 124.0(20), 97.0(25), 69.1(100), 41.1(79). IR**:** $\tilde{\nu}$ = 2930, 2248, 1774, 1686, 1420, 1372, 1157, 1011, 907 cm^{-1}

Synthesis of cyclopentene diol 120

(1S,4R)-1-Methylcyclopent-2-ene-1,4-diol

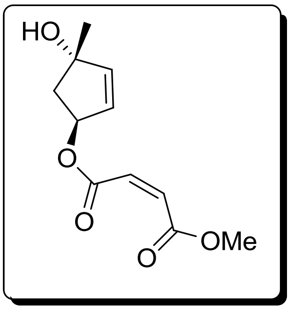


A solution of TBS-protected **136** (183 mg, 0.80 mmol) in anhydrous THF (5 mL) and Bu_4NF (1.0 M solution in THF, 1.5 mL, 1.5 mmol) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, and the residue was purified via column chromatography eluting with EtOAc/MeOH (49:1) to afford of **120** as a colorless syrup.

Yield 54.8 mg, 55%. ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 2H), 4.62 (d, *J* = 6.8 Hz, 1H), 3.48 (d, *J* = 26.9 Hz, 1H), 2.32 (dd, *J* = 14.4, 7.1 Hz, 1H), 1.77 (m, 1H), 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 134.2, 81.2, 75.4, 49.6, 27.5.

Synthesis of maleic ester 119

(Z)-But-2-enedioic acid (1S,4S)-4-hydroxy-4-methyl-cyclopent-2-enyl ester methyl ester

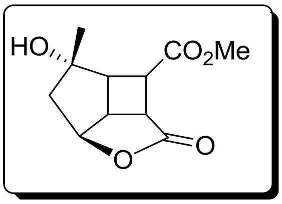


A solution of triphenyphosphine (88.5 mg, 0.338 mmol, 2 equiv) in toluene (3 mL) and diisopropylazodicarboxylate (75 µL, 0.338mmol, 2 equiv) was added over a period of 10 min. This mixture was stirred at rt for 20 min to yield a white precipitate of the triphenylphosphine-diisopropyl azodicarboxylate complex. To this latter complex as a suspension were added methylmaleate (28.5 mg, 0.219 mmol, 1.3 equiv) and a solution of **120** (19 mg, 0.0.168 mmol, 1 equiv) in toluene (3 mL). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure, and the residue was purified via column chromatography eluting with hexanes/EtOAc (3:1) to afford of **119** as a yellowish oil.

Yield 19.1 mg, 54%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (m, 2H), 5.96 (m, 1H), 5.83 (m, 2H), 3.71 (s, 3H), 2.34 (m, 1H), 1.96 (m, 1H), 1.89 (d, *J* = 18.5 Hz, 1H), 1.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 165.0, 144.1, 130.2, 130.0, 129.4, 82.1, 79.9, 52.2, 46.2, 28.6. LR-EIMS = m/z 211.1 $[M\text{-}CH_3]^+$, 131(18), 113(100), 97.1(23), 81.0(44), 43.1(31). IR: $\tilde{\nu}$ = 3411, 2980, 1725, 1643, 1437, 1374, 1218, 1163 cm^{-1}

Photoinduced synthesis of cyclobutane 137

(2S,3aS)-2-Hydroxy-2-methyl-5-oxo-octahydro-4-oxa-cyclobuta[cd]pentalene-1-carboxylic acid methyl ester



The maleic ester **119** (7 mg, 0.031 mmol) was dissolved in acetone (8 mL), and the resulting solution was bubbled with N_2 for 15 min. This solution was then irradiated with a high pressure UV lamp (254 nm) in a quartz test tube with stirring for 72 h. After consumption of the starting material, as indicated by TLC, the solvent was removed and the residue was purified by chromatography (4:1 hexane/ethyl acetate) to give photoadduct **137** as a yellowish oil and a mixture of diastereomers (>80% conversion).

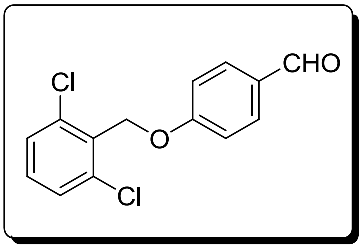
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (m), 2.26 (m), 1.32 (m). ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.8, 174.2, 170.4, 168.3, 84.5, 83.4, 81.7, 80.0, 59.7, 56.5, 52.3, 50.2, 48.8, 47.1, 46.0, 44.0, 30.0, 29.0, 27.2, 23.7, 21.3, 19.8, 18.8. IR**:** $\tilde{\nu}$ = 3479, 2981, 1715, 1623, 1436, 1373, 1227, 1165, 1045, 941 cm^{-1}.

7. Discovery of antimicrobial and anti-cancer benzyloxylated ketoaryl aldehydes and 2-arylimidazolines

A. General procedure for the synthesis of benzyloxylated ketoaryl derivatives (2a-2k, 3a-3e, 20)

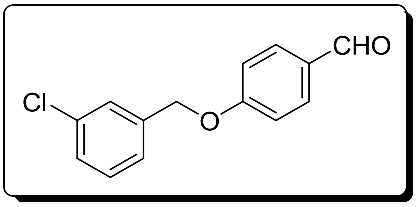
Phenol carbaldehydes (**13** or **14**) (1 equiv) or 4-hydroxybenzophenone (**16**) were dissolved in acetone (8 mL per mmol). To the solution was added the substituted benzyl bromides (or chlorides) (**11** or **12**) (1 equiv), and K_2CO_3 (1.5 equiv). The resulting mixture was stirred at room temperature for 12 h. In the case of reactions with benzyl chlorides, warming at 40°C was necessary. The reaction mixture was concentrated under reduced pressure and filtered on a 3 cm silica column eluting with hexanes/EtOAc to give the corresponding benzyloxylated ketoaryls derivatives (**2a-2k, 3a-3e, 20**).

4-(2,6-Dichloro-benzyloxy)-benzaldehyde (2a)



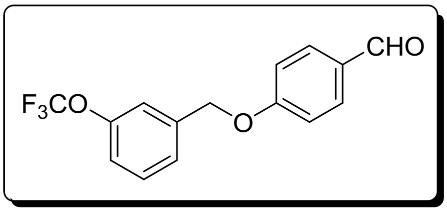
97% from 2,6-dichlorobenzyl bromide (1 mmol) and 4-hydroxybenzaldehyde **13** (1.01 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.86 (m, 2H), 7.38 (m, 2H), 7.28 (m, 1H), 7.12 (m, 2H), 5.36 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 163.8, 137.0, 132.0, 131.3, 130.8, 130.4, 128.6, 115.1, 65.3. LRMS (EI, 75 eV): *m/z* 280.0 $[M]^+$.

4-(3-Chloro-benzyloxy)-benzaldehyde (2b)



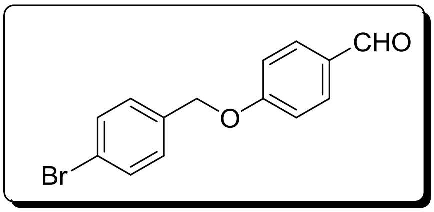
86% from 3-chlorobenzyl bromide (0.97 mmol) and 4-hydroxybenzaldehyde **13** (1.07 mmol) according to procedure A. ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.83 (s, 1H), 7.76 (m, 2H), 7.39 (d, *J* = 0.5 Hz, 1H), 7.26 (t, *J* = 1.9 Hz, 3H), 6.98 (m, 2H), 5.04 (s, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 190.7, 163.3, 138.1, 134.6, 132.0, 130.3, 130.1, 128.4, 127.4, 125.5, 115.1, 69.3. LRMS (EI, 75 eV): m/z 246.1 [M]$^+$.

4-(4-Trifluoromethoxy-benzyloxy)-benzaldehyde (2c)



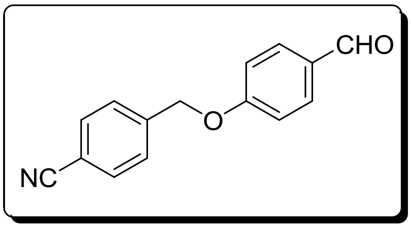
56% from 4-trifluoromethoxybenzyl bromide (0.78 mmol) and 4-hydroxybenzaldehyde **13** (0.86 mmol) according to procedure A. ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.85 (s, 1H), 7.81 (m, 2H), 7.37 (m, 3H), 7.16 (t, *J* = 10.3 Hz, 1H), 7.00 (m, 2H), 5.12 (s, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 190.7, 163.3, 149.5, 149.5, 138.4, 132.0, 130.4, 130.2, 125.6, 120.6, 119.8, 115.1, 69.2. LRMS (EI, 75 eV): m/z 296.1 [M]$^+$.

4-(4-Bromo-benzyloxy)-benzaldehyde (2d).



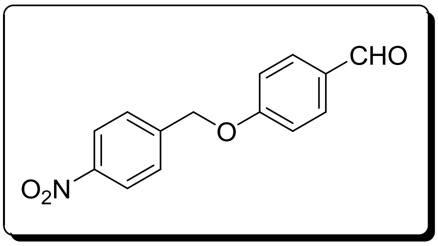
23% from 4-bromobenzyl bromide (0.80 mmol) and 4-hydroxybenzaldehyde **13** (0.88 mmol) according to procedure A.^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (d, *J* = 11.3 Hz, 1H), 7.84 (m, 2H), 7.52 (m, 2H), 7.32 (m, 2H), 7.05 (m, 2H), 5.08 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 163.4, 135.0, 132.1, 131.9, 130.2, 129.1, 122.3, 115.2, 69.4. LRMS (EI, 75 eV): m/z 290.0 $[M]^+$.

4-(4-Cyano-benzyloxy)-benzaldehyde (2e)



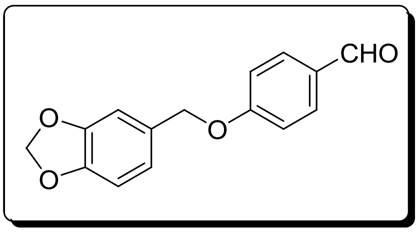
77% from 4-cyanobenzyl bromide (1.02 mmol) and 4-hydroxybenzaldehyde **13** (1.12 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.86 (m, 2H), 7.67 (m, 2H), 7.55 (dd, *J* = 13.5, 5.5 Hz, 2H), 7.01 (m, 2H), 5.20 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 163.0, 141.4, 132.5, 132.1, 130.5, 127.6, 118.6, 115.1, 112.1, 69.1. LRMS (EI, 75 eV): m/z 296.1 $[M]^+$.

4-(4-Nitro-benzyloxy)-benzaldehyde (2f).



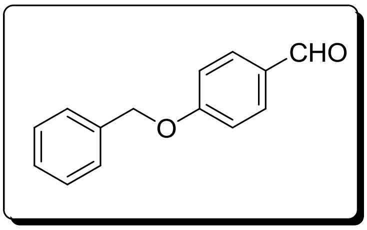
75% from 4-nitrobenzyl bromide (0.92 mmol) and 4-hydroxybenzaldehyde **13** (1.01 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.23 (m, 2H), 7.83 (m, 2H), 7.60 (m, 2H), 7.06 (m, 2H), 5.25 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 163.5, 147.7, 144.1, 132.1, 130.8, 124.1, 115.1, 68.6. LRMS (EI, 75 eV): m/z 257.1 $[M]^+$.

4-(Benzo[1,3]dioxol-5-ylmethoxy)-benzaldehyde (2g)



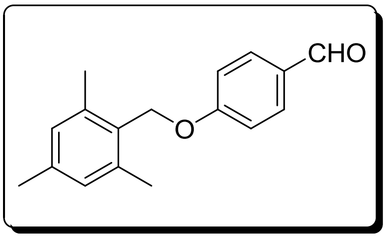
74% from 3,4-methylenedioxybenzyl bromide (0.93 mmol) and 4-hydroxybenzaldehyde **13** (1.02 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.80 (m, 2H), 7.04 (m, 2H), 6.82 (m, 3H), 5.95 (s, 2H), 5.01 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 163.7, 148.1, 147.7, 132.0, 130.1, 129.6, 121.4, 115.2, 108.4, 108.3, 101.3, 70.2. LRMS (EI, 75 eV): m/z 256.0 $[M]^+$.

4-benzyloxybenzaldehyde (2h)



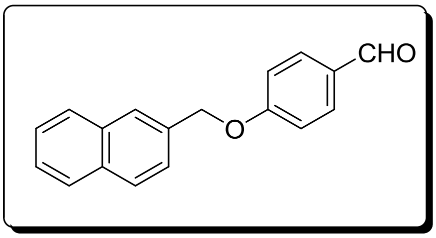
98% from benzyl bromide (1.17 mmol) and 4-hydroxybenzaldehyde **13** (1.28 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.86 (m, 2H), 7.42 (m, 5H), 7.06 (t, J = 5.6 Hz, 2H), 5.12 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 163.8, 136.0, 132.1, 130.2, 128.8, 128.4, 127.6, 115.20, 70.3. LRMS (EI, 75 eV): m/z 212.1 $[M]^+$.

4-(2,4,6-Trimethyl-benzyloxy)-benzaldehyde (2i)



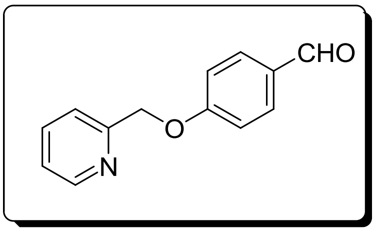
43% from 2,4,6-triemethylbenzyl chloride (1.19 mmol) and 4-hydroxybenzaldehyde **13** (1.30 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.92 (m, 2H), 7.16 (m, 2H), 6.98 (s, 2H), 5.14 (s, 2H), 2.41 (s, 6H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 162.8, 137.0, 136.3, 130.4, 128.2, 127.5, 127.2, 114.4, 113.2, 63.2, 19.3, 17.7. HRMS (EI, 50 eV) calculated for $C_{17}H_{18}O_2$: 254.1307, found: 254.1313. IR ($\tilde{\nu}$): 2191, 2051, 1612, 1568, 1515, 1450, 1373, 1244, 1171, 1108, 990, 835, 758, 696 cm^{-1}.

4-(Naphthalen-2-ylmethoxy)-benzaldehyde (2j)



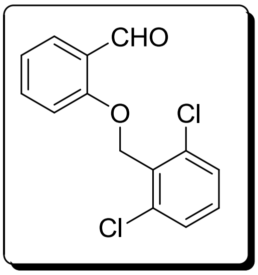
75 % from bromomethylnapthalene (0.90 mmol) and 4-hydroxybenzaldehyde **13** (0.99 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.91 (m, 6H), 7.54 (m, 3H), 7.12 (m, 2H), 5.27 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 163.8, 133.5, 133.3, 133.2, 132.1, 130.2, 128.7, 128.0, 127.8, 126.6, 126.5, 126.4, 125.2, 115.2, 70.4. LRMS (EI, 75 eV): m/z 262.1 $[M]^+$.

4-(Pyridin-2-ylmethoxy)-benzaldehyde (2k)



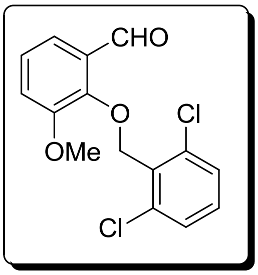
98 % from 2-pyridine chloromethane (1.57 mmol) and 4-hydroxybenzaldehyde **7** (1.73 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.57 (m, 2H), 8.53 (m, 1H), 7.78 (m, 1H), 7.68 (m, 1H), 7.45 (t, J = 9.2 Hz, 1H), 7.21 (m, 1H), 7.05 (m, 1H), 5.23 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.8, 163.3, 156.0, 149.3, 137.1, 132.0, 130.3, 123.1, 121.5, 115.2, 70.7. LRMS (EI, 75 eV): m/z 237.1 $[M]^+$.

2-(2,6-Dichloro-benzyloxy)-benzaldehyde (3a)



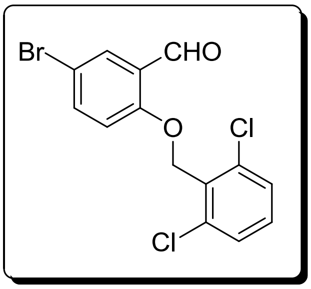
19% from 2,6-dichlorobenzyl bromide (1.55 mmol) and 2-hydroxybenzaldehyde (1.63 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.42 (d, *J* = 0.8 Hz, 1H), 7.89 (m, 1H), 7.59 (m, 1H), 7.39 (t, *J* = 2.1 Hz, 1H), 7.37 (s, 1H), 7.25 (m, 2H), 7.06 (m, 1H), 5.41 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 161.2, 136.9, 135.9, 131.4, 130.8, 128.6, 128.2, 121.5, 113.5, 65.9. HRMS (EI, 50 eV) calculated for $C_{14}H_{10}C_{l2}O_2$: 280.0058, found: 280.0062. IR ($\tilde{\nu}$): 2877, 1685, 1597, 1581, 1564, 1483, 1456, 1433, 1377, 1281, 1100, 1001, 865, 784,754 cm^{-1}.

2-(2,6-Dichloro-benzyloxy)-3-methoxy-benzaldehyde (3b)



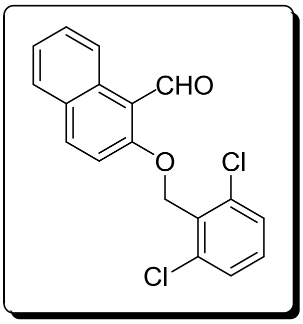
13% from 2,6-dichlorobenzyl bromide (1.25 mmol) and 3-methoxy-2-hydroxybenzaldehyde (1.31 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.34 (m, 3H), 7.16 (m, 3H), 5.54 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 153.2, 151.0, 137.2, 132.1, 130.7, 128.6, 128.6, 124.5, 118.7, 117.9, 69.9, 56.2. HRMS (EI, 50 eV) calculated for $C_{15}H_{12}Cl_2O_3$: 310.0164, found: 310.0162. IR ($\tilde{\nu}$): 3008, 2869, 1690, 1582, 1435, 1369, 1266, 1245, 1089, 969, 858, 779 cm^{-1}.

5-Bromo-2-(2,6-dichloro-benzyloxy)-benzaldehyde (3c).



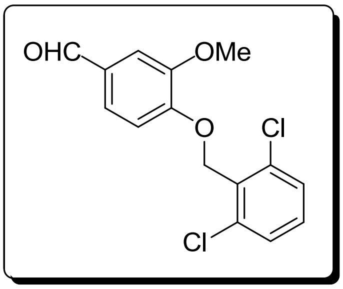
7% from 2,6-dichlorobenzyl bromide (0.94 mmol) and 5-bromo-2-hydroxybenzaldehyde (0.99 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.94 (t, *J* = 3.7 Hz, 1H), 7.66 (dt, *J* = 5.9, 2.9 Hz, 1H), 7.39 (t, *J* = 2.9 Hz, 1H), 7.37 (s, 1H), 7.28 (t, *J* = 3.1 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.39 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 160.1, 138.2, 136.9, 131.0, 130.9, 130.9, 128.7, 126.8, 115.6, 114.4, 66.2. HRMS (EI, 50 eV) calculated for $C_{14}H_9BrCl_2O_2$: 357.9163, found: 357.9162. IR ($\tilde{\nu}$): 2859, 1682, 1589, 1476, 1437, 1267, 1122, 1004, 820, 766 cm^{-1}.

2-(2,6-Dichloro-benzyloxy)-naphthalene-1-carbaldehyde (3d)



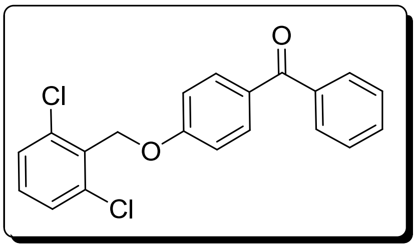
9% from 2,6-dichlorobenzyl bromide (1.10 mmol) and 2-hydroxynapthalene carbaldehyde (1.16 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.81 (s, 1H), 9.28 (d, *J* = 8.3 Hz, 1H), 8.11 (t, *J* = 6.5 Hz, 1H), 7.81 (m, 1H), 7.64 (m, 1H), 7.50 (d, *J* = 9.1 Hz, 1H), 7.44 (m, 2H), 7.38 (s, 1H), 7.31 (m, 1H), 5.55 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 163.4, 137.4, 136.9, 131.3, 130.9, 129.9, 129.1, 128.7, 128.3, 125.1, 117.9, 114.7, 67.1. HRMS (EI, 50 eV) calculated for $C_{18}H_{12}Cl_2O_2$: 330.0214, found: 330.0220. IR ($\tilde{\nu}$): 2872, 1667, 1510, 1436, 1243, 1051, 815, 759, 665 cm^{-1}.

4-(2,6-Dichloro-benzyloxy)-3-methoxy-benzaldehyde (3e).



20% from 2,6-dichlorobenzyl bromide (1.25 mmol) and vanillin (1.31 mmol) according to procedure A.^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.44 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.39 (d, *J* = 1.9 Hz, 1H), 7.31 (t, *J* = 2.3 Hz, 1H), 7.29 (s, 1H), 7.20 (m, 1H), 7.14 (m, 1H), 5.34 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 153.8, 150.3, 137.1, 131.3, 130.8, 130.7, 128.5, 126.5, 112.9, 109.8, 66.2, 56.1. LRMS (EI, 75 eV): m/z 310.0 $[M]^+$.

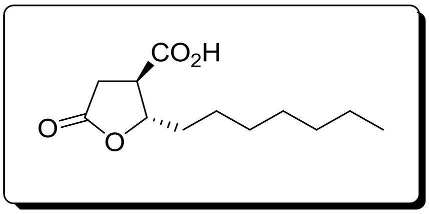
[4-(2,6-Dichloro-benzyloxy)-phenyl]-phenyl-methanone (20)



61% from 2,6-dichlorobenzyl bromide (0.95 mmol) and 4-hydroxybenzophenone (1.01 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (m, 2H), 7.76 (m, 1H), 7.56 (m, 1H), 7.45 (m, 1H), 7.35 (m, 1H), 7.23 (m, 2H), 7.09 (m, 2H), 5.35 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 160.8, 136.3, 135.1, 130.8, 130.2, 129.6, 128.9, 128.7, 127.9, 126.7, 126.4, 112.7, 63.5. HRMS (EI, 50 eV) calculated for $C_{20}H_{14}Cl_2O_2$: 356.0371, found: 356.0377. IR ($\tilde{\nu}$): 2898, 1650, 1595, 1506, 1438, 1243, 1172, 1008, 847, 765, 696 cm^{-1}.

Synthesis of heptyl-γ-lactone acid 3

(*2R,3S*)-2-Heptyl-5-oxo-tetrahydro-furan-3-carboxylic acid (5)



The synthesis of **3** was carried out following the method for the preparation of paraconic acids previously reported by our group. Under a nitrogen atmosphere, a DCM solution of allyllactone aldehyde **4** (100 mg, 0.59 mmol) was canulated to a three-necked round bottom flask and was degassed three times using a freeze-thaw method. 1-Hexene (1.05 equiv) was added and the solution was heated to 40 ^{o}C. A solution (10 mL) of Grubbs I catalyst (20 mol %) contained in a syringe was slowly added to the reaction mixture via canula. After complete addition, the reaction mixture was further refluxed for 8 h. The solution was evaporated *in vacuo* and chromatographed on a silica gel using 3:1 hexanes-ethyl acetate to afford an oily compound which was directly dissolved in MeOH (10 mL). Hydrogenation was carried out next using 10% Pd/C under a hydrogen atmosphere (1 atm). After 24 h, the solution was filtered on Celite and the filtrate was evaporated to give an oily compound **5**, which was directly oxidized with Jones reagent in acetone at 0 ^{o}C. After a conventional work-up, lactone acid 3 was afforded as a white solid

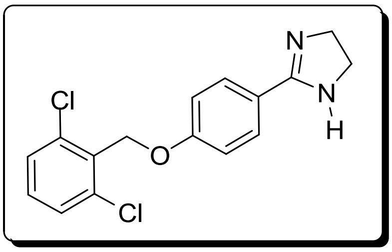
.

57% (in three steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.67 (s, 1H), 4.61 (m, 1H), 3.11 (m, 1H), 2.87 (m, 2H), 1.76 (m, 2H), 1.39 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.37, 174.63, 81.94, 45.45, 35.36, 31.91, 31.69, 29.13, 29.05, 25.18, 22.60, 14.07. HRMS (EI, 50 eV) calculated for $C_{12}H_{21}O_4$: 229.1440 $[M+H]^+$ found: 229.1445. IR ($\tilde{\nu}$): 3083, 1692, 1610, 1578, 1508, 1249, 1160, 1002, 874, 831, 767 cm^{-1}.

B. General procedure for the synthesis of benzyloxylated 2-arylimidazolines (4a-4h)

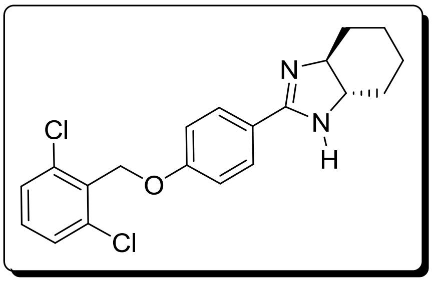
To a solution of the benzyloxybenzaldehydes **2a-2c**, **2g-2i** (1 equiv) in *t*-BuOH (8 mL per mmol) was added the diamines **15** or **16** or **17** (1.05 equiv). The obtained mixture was stirred at room temperature for 30 min. on a covered scintillation vial and K_2CO_3 (2.5 equiv) and I_2 (1.1 equiv) were added next to the reaction mixture and magnetically stirred at 70 ^oC. After 3h, the mixture was quenched with aqueous Na_2SO_3 until the deep orange disappeared and was extracted with DCM. The organic layer was washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. After filtration in a silica gel column (3 cm) eluting first with hexanes/EtOAc (to remove unreacted aldehydes) followed by DCM/MeOH (19:1), the second fraction was evaporated *in vacuo* to afford the benzyloxylated 2-arylimidazolines **(4a-4h)** in an almost pure state.

2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4,5-dihydro-1H-imidazole (4a)



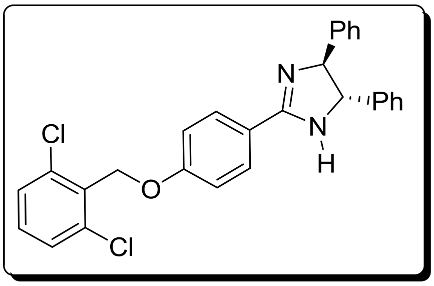
33% from aryl aldehyde derivative **2a** (1.51 mmol) and diamine **15** (1.66 mmol) according to procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 13.5, 5.5 Hz, 2H), 7.34 (t, *J* = 2.2 Hz, 1H), 7.31 (s, 1H), 7.23 (m, 2H), 7.01 (dd, *J* = 11.8, 5.5 Hz, 2H), 5.28 (d, *J* = 10.8 Hz, 2H), 3.86 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 136.9, 131.2, 130.8, 130.7, 128.5, 115.2, 65.4, 46.3. HRMS (EI, 50 eV) calculated for $C_{16}H_{14}Cl_2N_2O$: 320.0483 $[M]^+$, found: 320.0482. IR ($\tilde{\nu}$): 3115, 2959, 1607, 1557, 1507, 1437, 1257, 1186, 1090, 983, 835, 783, 766 cm^{-1}.

(7S,7aS)-2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole (4b)



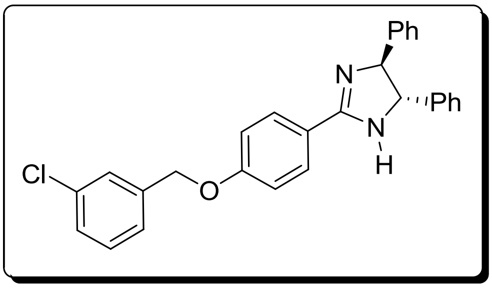
20% from aryl aldehyde derivative **2a** (0.88 mmol) and diamine **16** (0.97 mmol) according to procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.36 (m, 2H), 7.26 (m, 2H), 7.02 (m, 2H), 5.30 (m, 2H), 3.12 (m, 2H), 2.32 (dd, *J* = 16.9, 10.7 Hz, 2H), 1.82 (m, 2H), 1.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 160.9, 137.4, 131.6, 130.8, 128.4, 114.6, 69.1, 65.4, 30.6, 24.8. HRMS (EI, 50 eV) calculated for $C_{20}H_{20}Cl_2N_2O$: 374.0953, found: 374.0949. IR ($\tilde{\nu}$): 2933, 2858, 1610, 1564, 1510, 1438, 1244, 1007, 779 cm^{-1}.

(S)-2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5-phenyl-4-(R)-phenyl-4,5-dihydro-1H-imidazole (4c)



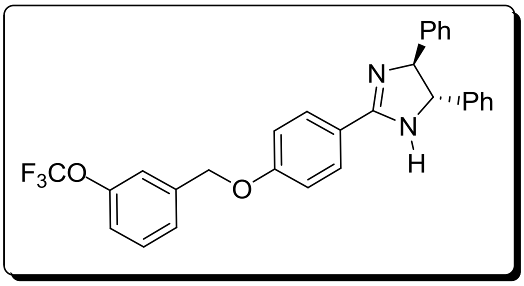
58% from aryl aldehyde derivative **2a** (0.214 mmol) and diamine **17** (0.23 mmol) according to procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (m, 1H), 7.38 (m, 15H), 7.07 (m, 2H), 5.35 (d, *J* = 9.5 Hz, 2H), 4.87 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 161.2, 143.6, 137.0, 131.8, 130.6, 129.2, 128.7, 128.5, 127.5, 126.6, 122.8, 114.7, 65.4. HRMS (EI, 50 eV) calculated for $C_{28}H_{22}Cl_2N_2O$: 472.1109, found: 472.1108. IR ($\tilde{\nu}$): 3380, 2890, 1611, 1565, 1514, 1437, 1244, 1172, 1009, 836, 762 cm^{-1}.

(S)-2-[4-(3-Chloro-benzyloxy)-phenyl]-5-phenyl-4-(R)-phenyl-4,5-dihydro-1H-imidazole (4d)



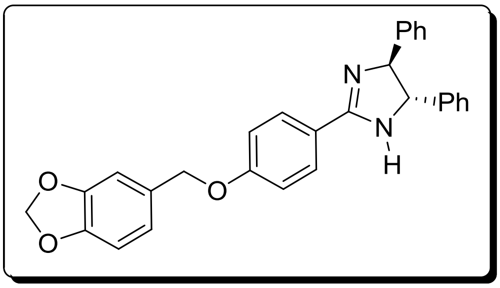
99% from diamine **17** (0.12 mmol) and aryl aldehyde derivative **2b** (0.11 mmol) according to procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (m, 2H), 7.46 (ddd, J = 7.1, 4.2, 1.8 Hz, 2H), 7.32 (m, 13H), 7.01 (m, 2H), 5.07 (d, J = 7.6 Hz, 2H), 4.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 160.6, 143.5, 138.6, 134.6, 131.1, 130.1, 129.9, 129.2, 128.7, 128.6, 128.3, 127.5, 127.4, 126.6, 125.3, 122.8, 115.0, 114.8, 69.2. HRMS (EI, 50 eV) calculated for $C_{28}H_{23}ClN_2O$: 438.1499, found: 438.1496. IR ($\tilde{\nu}$): 2918, 2869, 1612, 1572, 1514, 1451, 1245, 1172, 837, 756, 697 cm^{-1}.

(S)-5-Phenyl-4-(R)-phenyl-2-[4-(4-trifluoromethoxy-benzyloxy)-phenyl]-4,5-dihydro-1H-imidazole (4e)



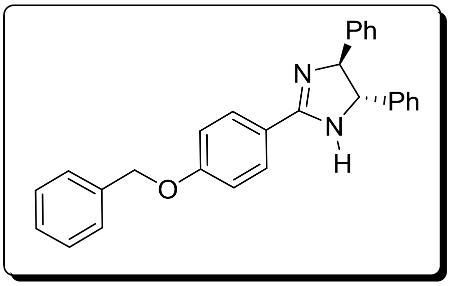
84% from diamine **17** (0.13 mmol) and aryl aldehyde derivative **2c** (0.12 mmol) according to procedure 3.3. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (m, 2H), 7.34 (m, 15H), 7.00 (m, 2H), 5.13 (s, 2H), 4.87 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 160.8, 143.3, 138.8, 130.1, 129.2, 128.7, 127.6, 126.6, 125.6, 120.4, 119.9, 114.8, 69.1. HRMS (EI, 50 eV) calculated for $C_{29}H_{23}F_3N_2O$: 488.1712, found: 488.1709. IR ($\tilde{\nu}$): 3402, 2898, 1613, 1519, 1449, 1251, 1171, 1029, 835, 757, 696 cm^{-1}.

(S)-2-[4-(Benzo[1,3]dioxol-5-ylmethoxy)-phenyl]-5-phenyl-4-(R)-phenyl-4,5-dihydro-1H-imidazole (4f)



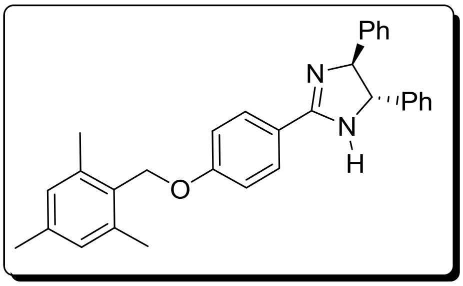
70% from diamine **17** (0.19 mmol) and aryl aldehyde derivative **2g** (0.18 mmol) according to procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (m, 2H), 7.28 (m, 11H), 6.89 (m, 5H), 5.97 (d, *J* = 4.3 Hz, 2H), 5.00 (s, 2H), 4.88 (d, *J* = 12.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.8, 161.1, 148.0, 147.6, 143.2, 130.1, 129.3, 128.8, 127.6, 126.6, 121.4, 114.8, 108.4, 101.2, 70.1. HRMS (EI, 50 eV) calculated for $C_{29}H_{24}N_2O_3$: 448.1787, found: 446.1795. IR ($\tilde{\nu}$): 3185, 2873, 1606, 1519, 1419, 1349, 1250, 1172, 1035, 924, 825, 758, 695 cm^{-1}.

(S)-2-(4-Benzyloxy-phenyl)-5-phenyl-4-(R)-phenyl-4,5-dihydro-1H-imidazole (4g)



75% from diamine **17** (0.11 mmol) and aryl aldehyde derivative **2h** (0.10 mmol) according to procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (m, 2H), 7.36 (s, 16H), 6.98 (m, 2H), 5.13 (d, *J* = 5.6 Hz, 2H), 4.88 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 161.0, 143.2, 136.9, 129.2, 128.7, 128.7, 128.6, 128.2, 127.5, 127.5, 126.6, 122.5, 114.6, 69.9. HRMS (EI, 50 eV) calculated for $C_{28}H_{24}N_2O$: 404.1889, found: 404.1894. IR ($\tilde{\nu}$): 3876, 2926, 1611, 1517, 1451, 1260, 1172, 1027, 839, 735, 694 cm^{-1}.

(S)-5-Phenyl-4-(R)-phenyl-2-[4-(2,4,6-trimethyl-benzyloxy)-phenyl]-4,5-dihydro-1H-imidazole (4h)



66% from diamine **17** (0.20 mmol) and aryl aldehyde derivative **2i** (0.19 mmol) according to procedure B. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.96 (m, 2H), 7.34 (m, 11H), 7.08 (m, 2H), 6.95 (m, 2H), 5.10 (m, 2H), 4.90 (d, *J* = 5.6 Hz, 2H), 2.39 (d, *J* = 4.8 Hz, 6H), 2.34 (d, *J* = 8.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.9, 161.8, 143.6, 138.6, 138.1, 129.4, 129.2, 129.2, 128.8, 127.5, 126.6, 122.3, 114.6, 64.8, 21.1, 19.5. HRMS (EI, 50 eV) calculated for $C_{31}H_{30}N_2O$: 446.2358, found: 446.2355. IR ($\tilde{\nu}$):2957, 1690, 1602, 1575, 1508, 1244, 1160, 980, 837, 807, 648 cm^{-1}.

F. APPENDICES

Appendix 1 - NMR Spectra

1.1 Spectra of compounds from Chapter B

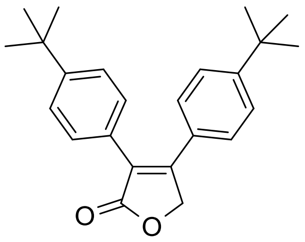
General Note:

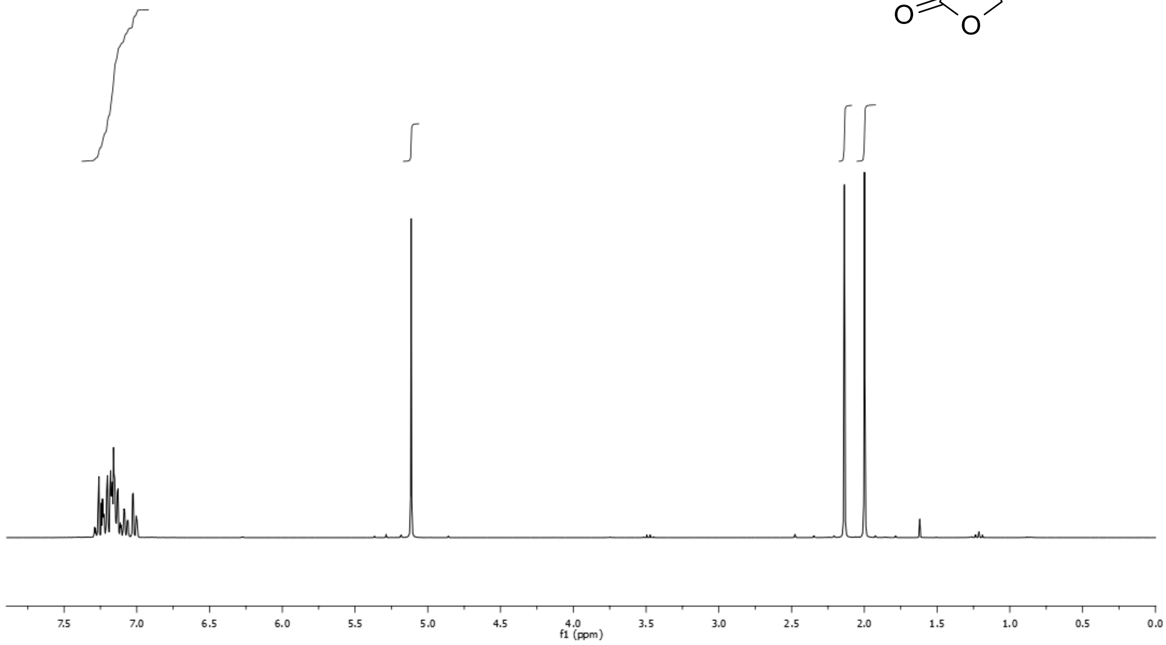
- ***The upper image is the ^{1}H NMR spectrum***

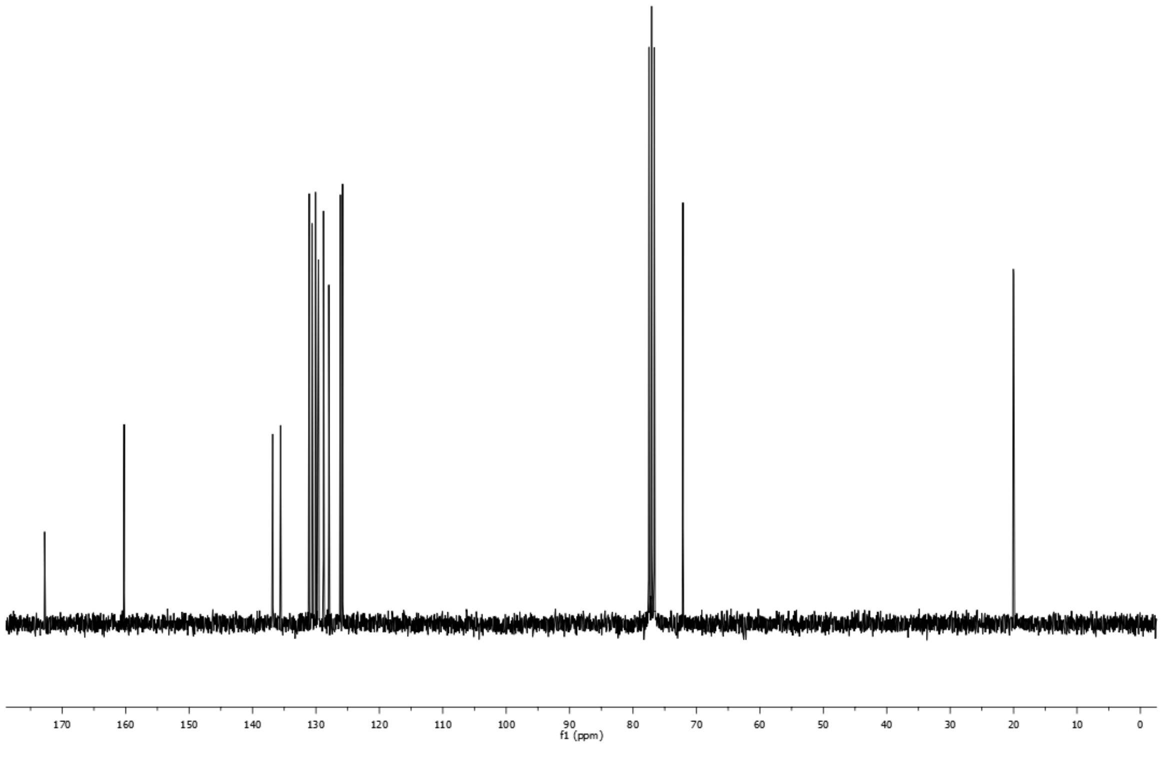
- ***The lower image is the ^{13}C NMR spectrum***

- ***All compounds were measured in $CDCl_3$***

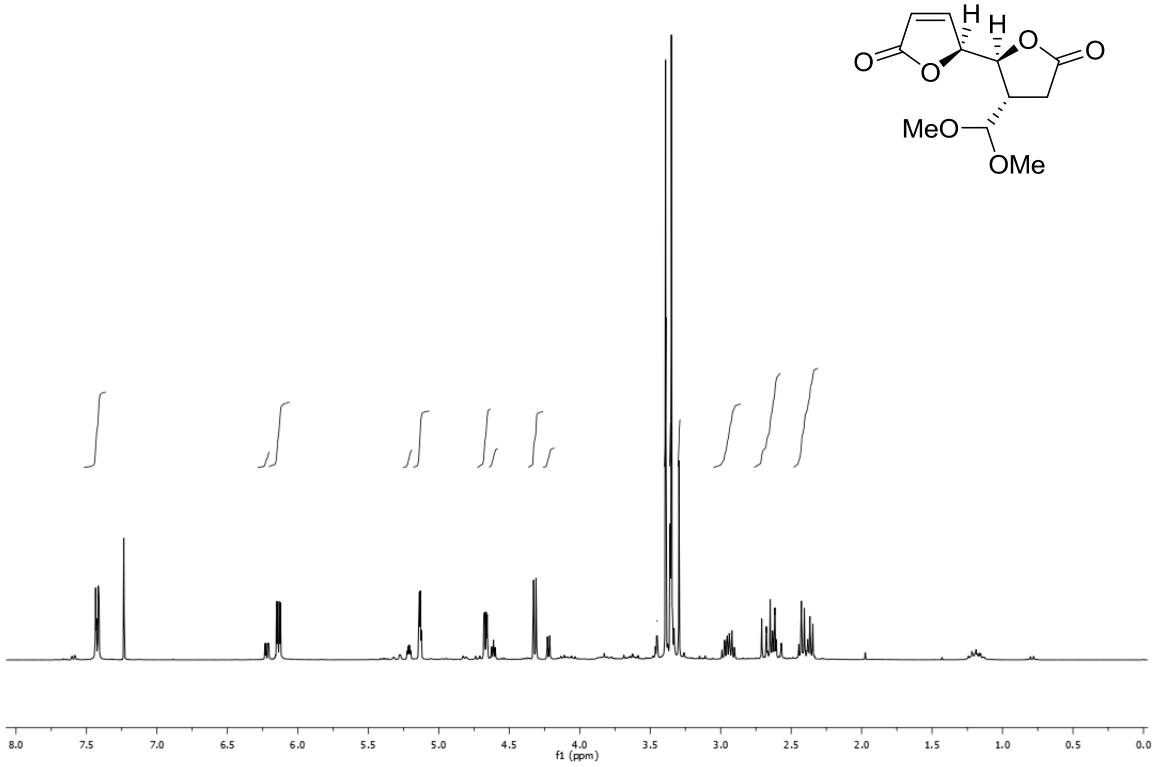
3,4-Bis-(4-tert-butyl-phenyl)-5H-furan-2-one (38e)

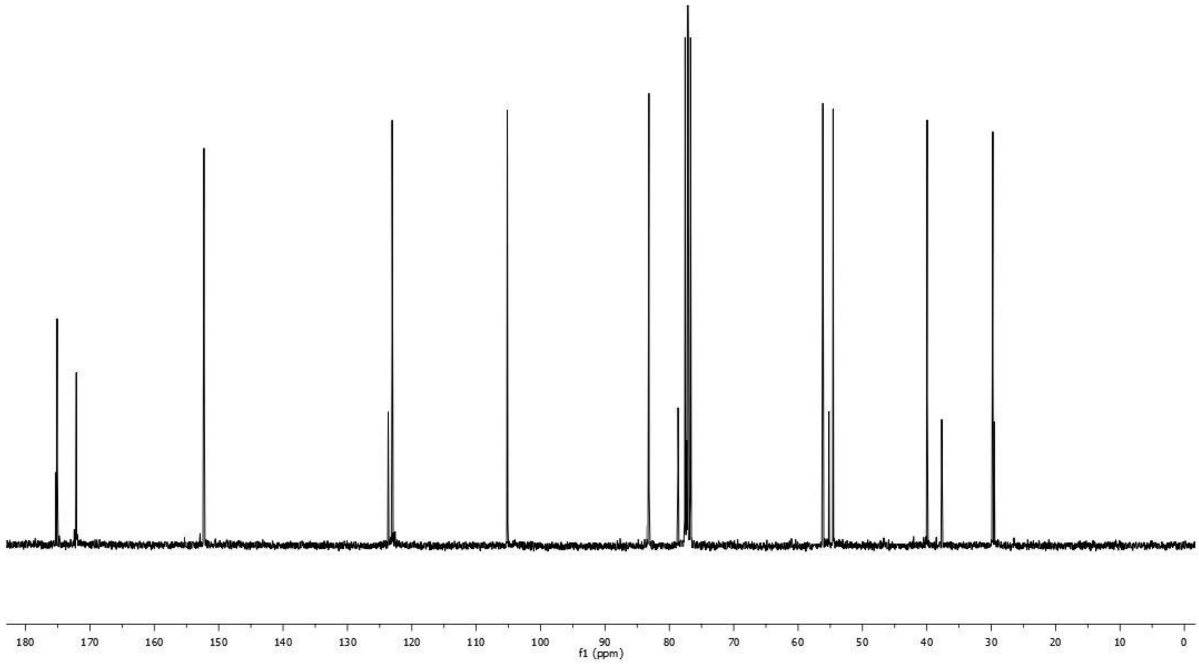




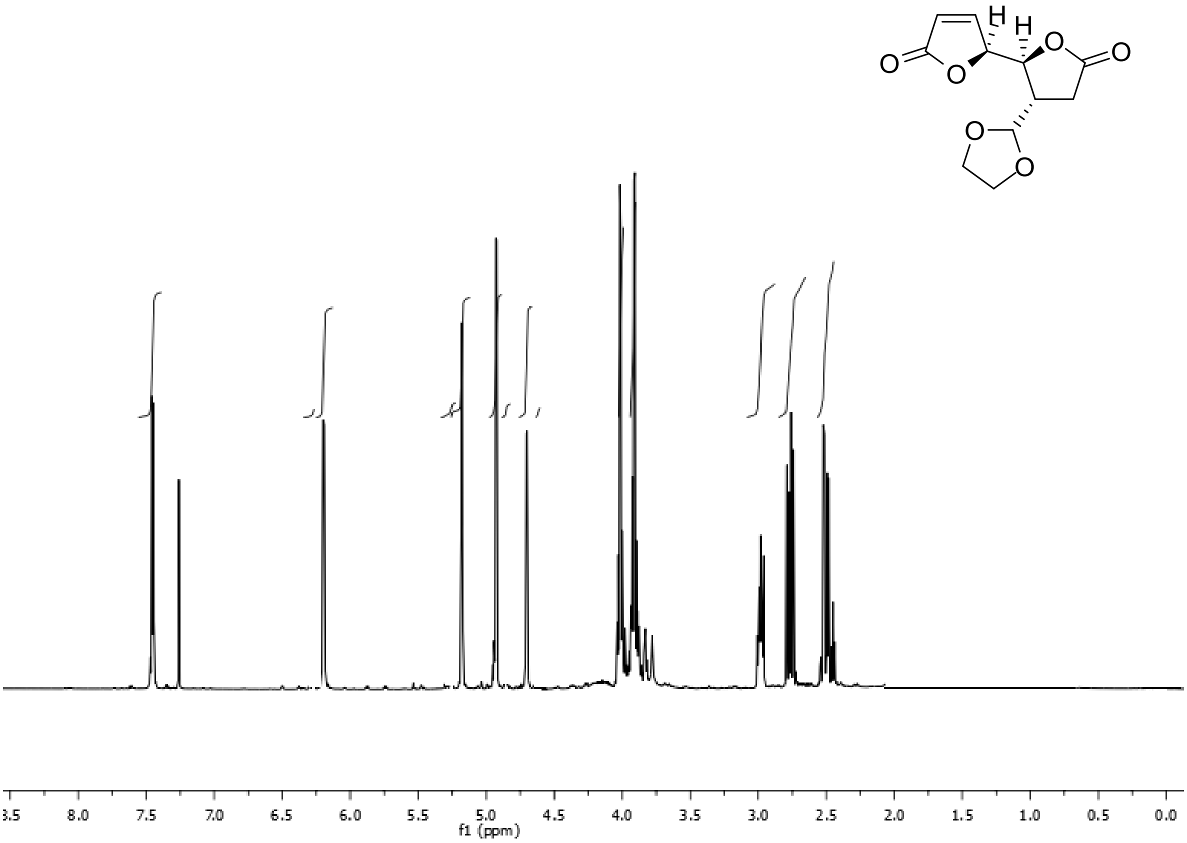


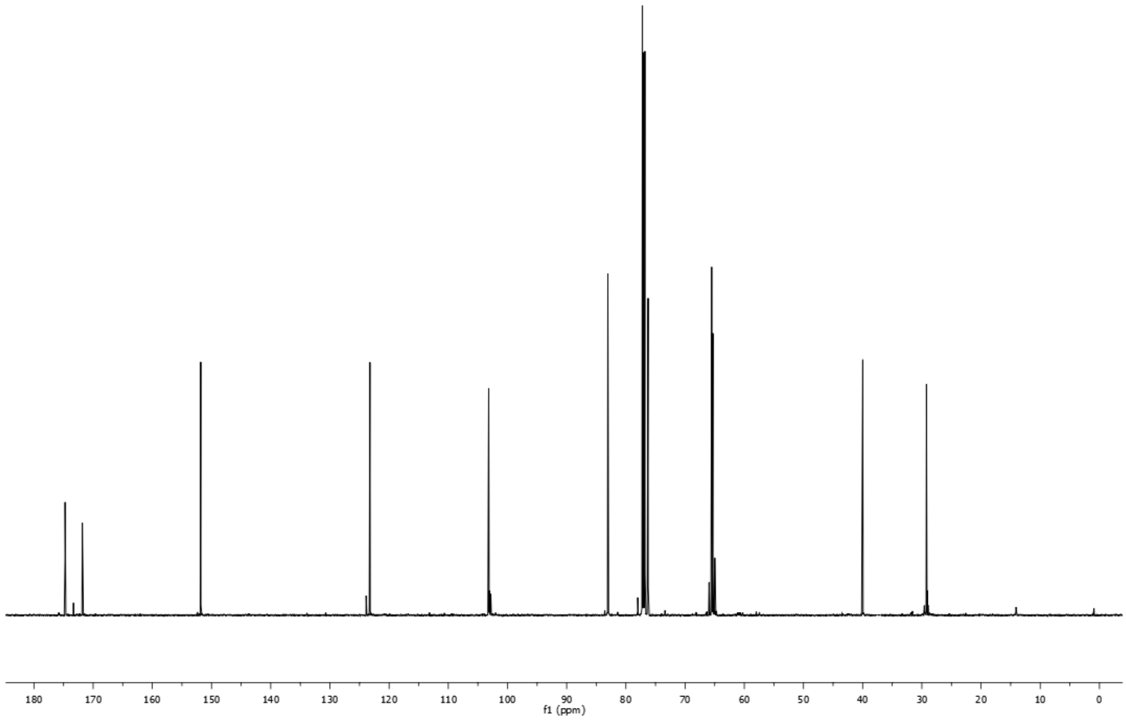
(2S,3S,2'S)-3-Dimethoxymethyl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33a.1)



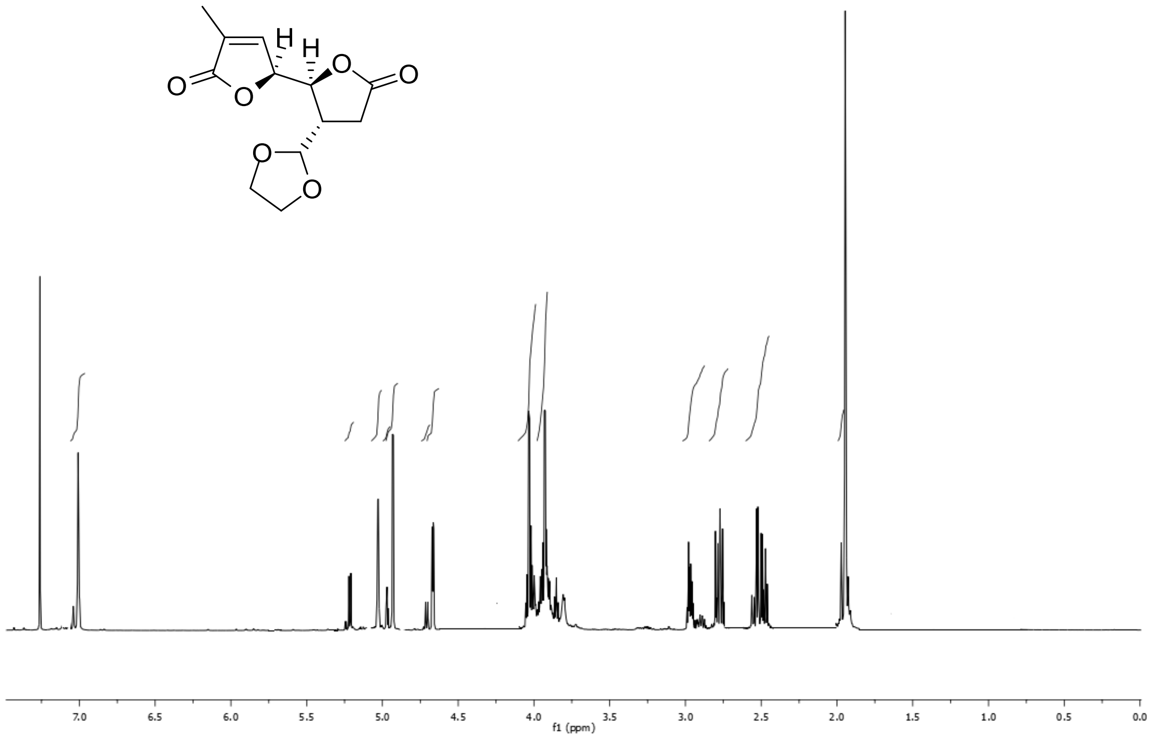


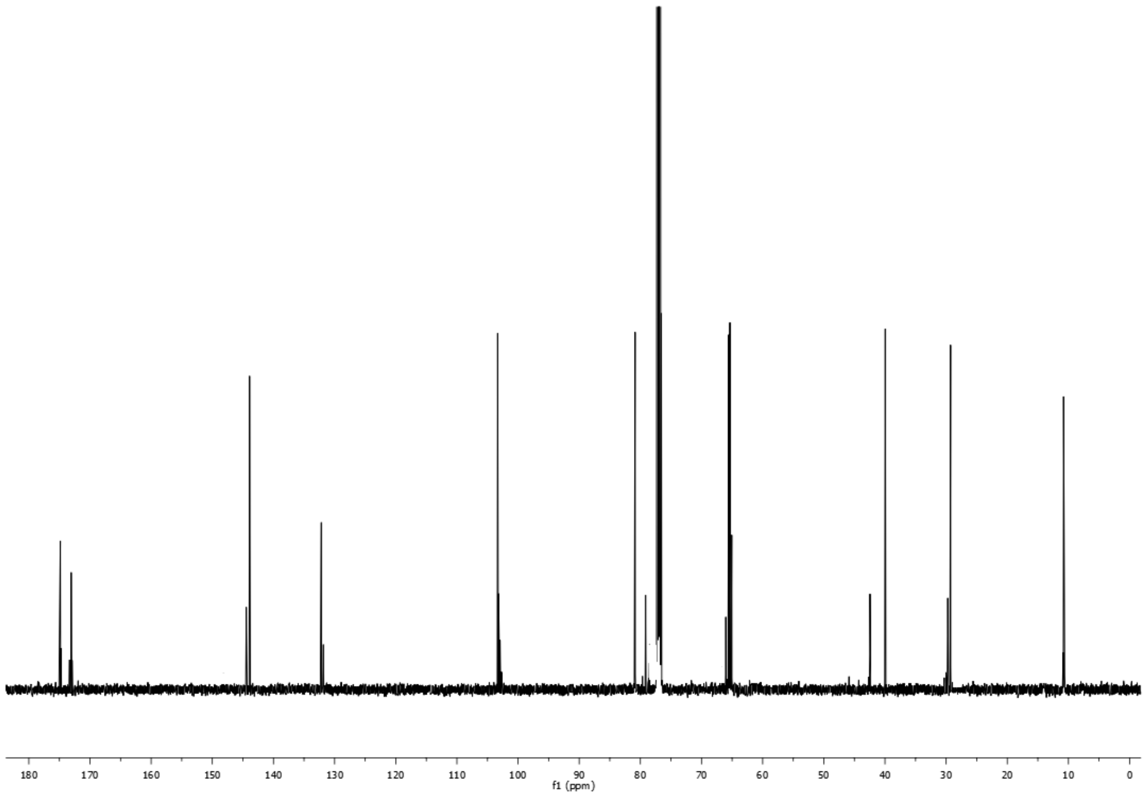
(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33a.2)



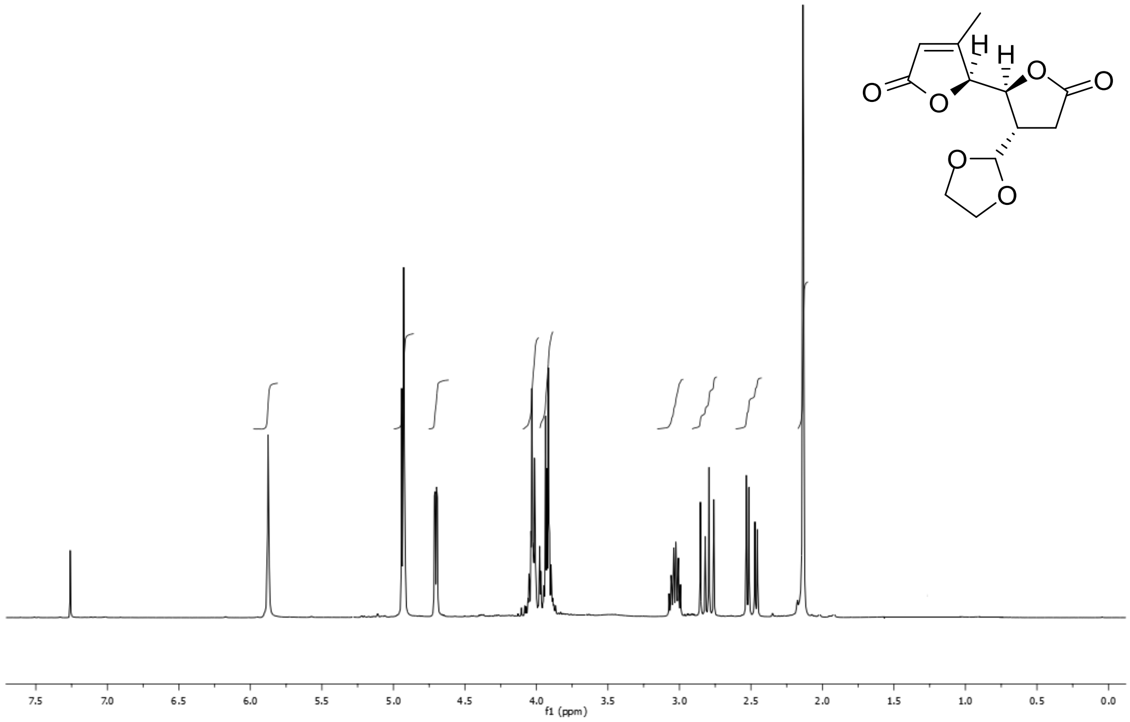


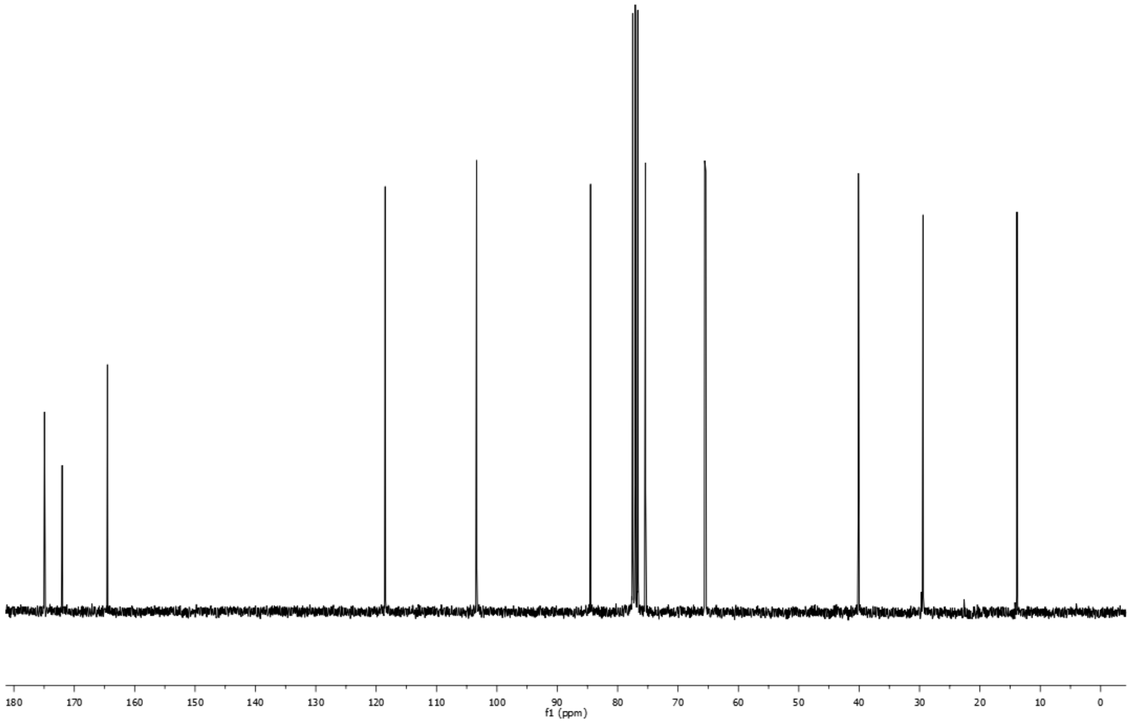
(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-4'-methyl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33b)



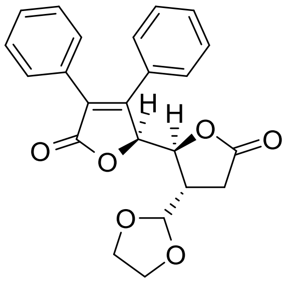


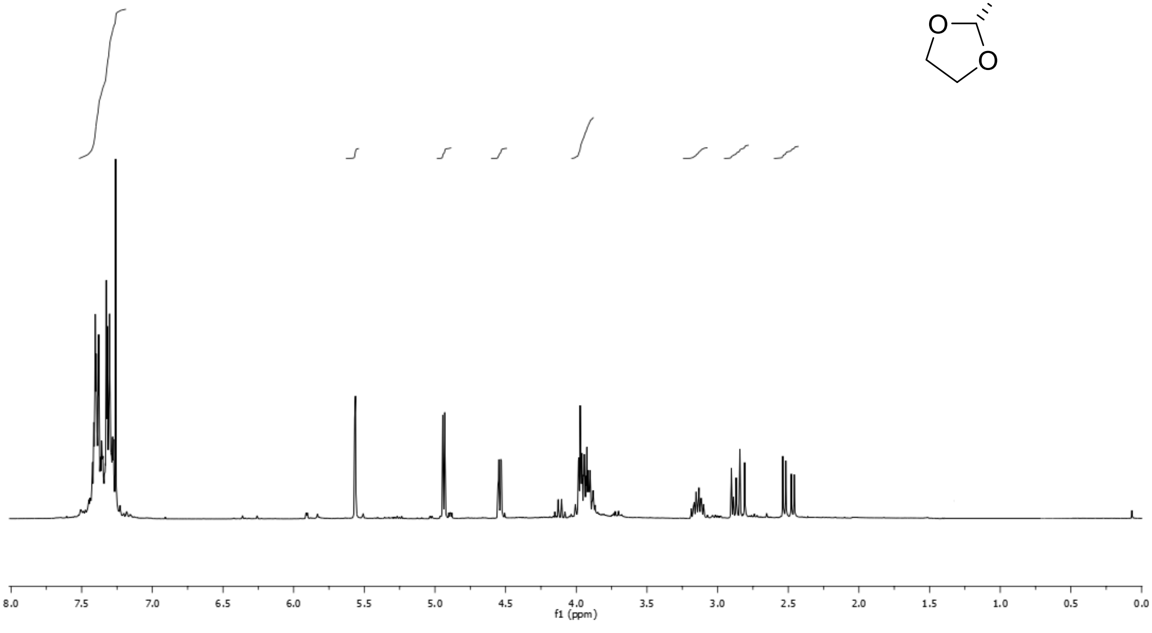
(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-3'-methyl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33c)

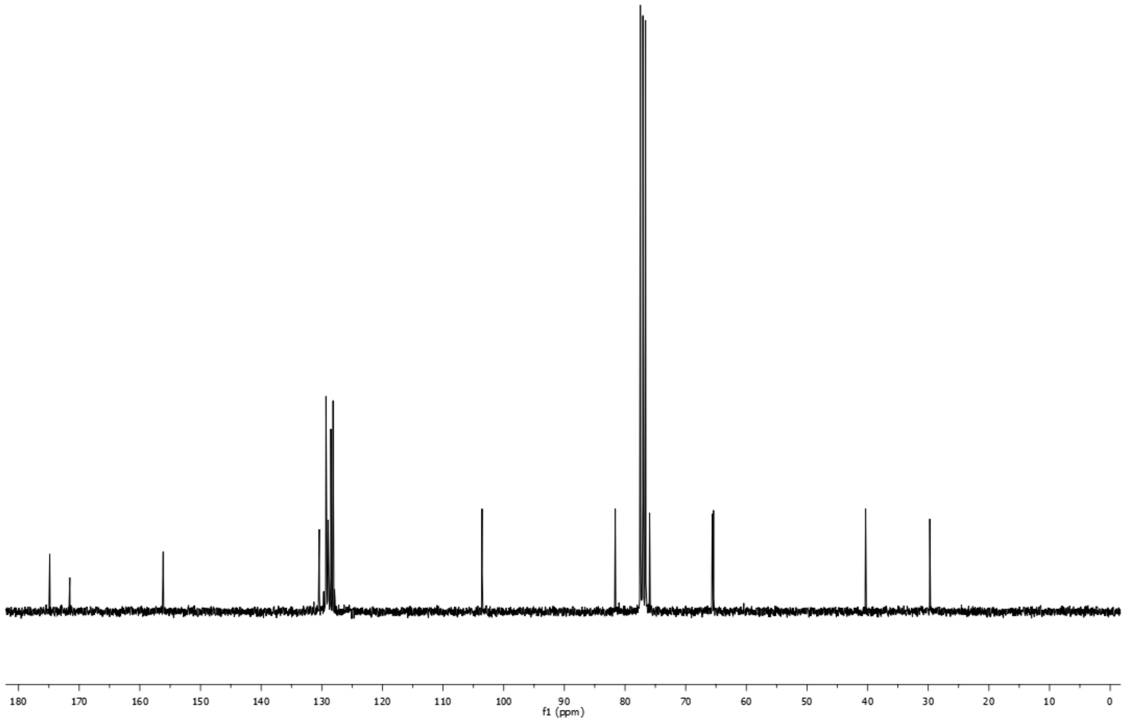




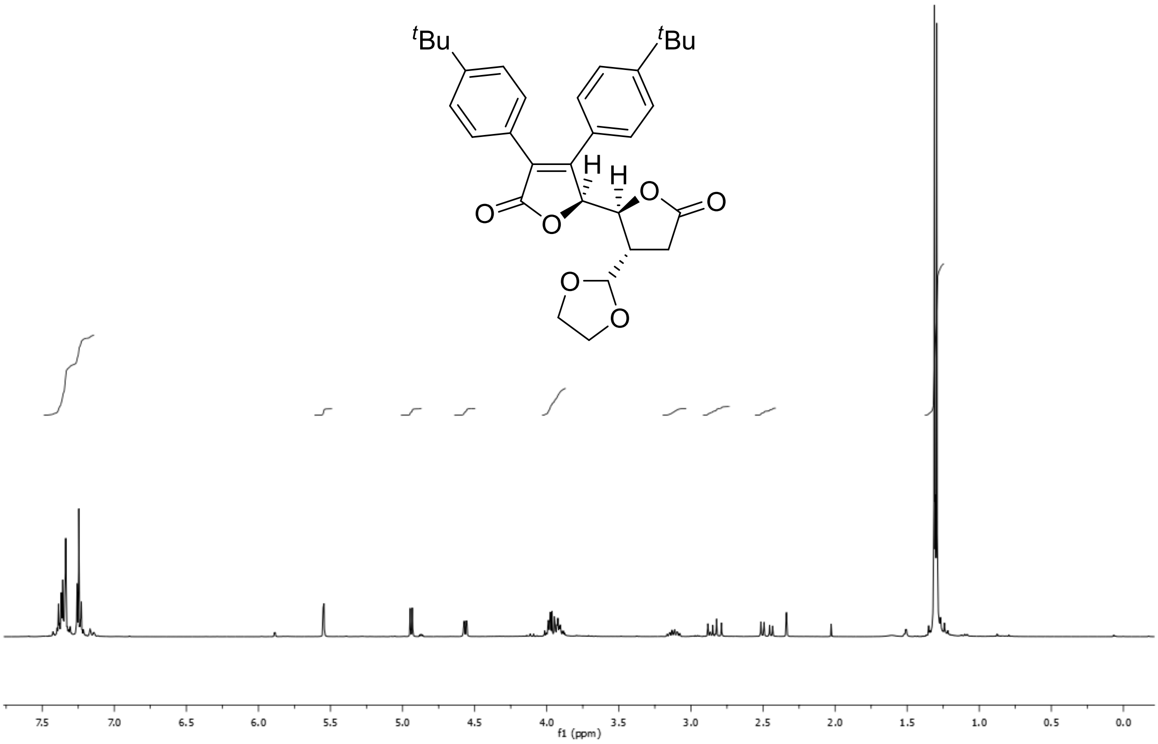
(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-3',4'-diphenyl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33d)

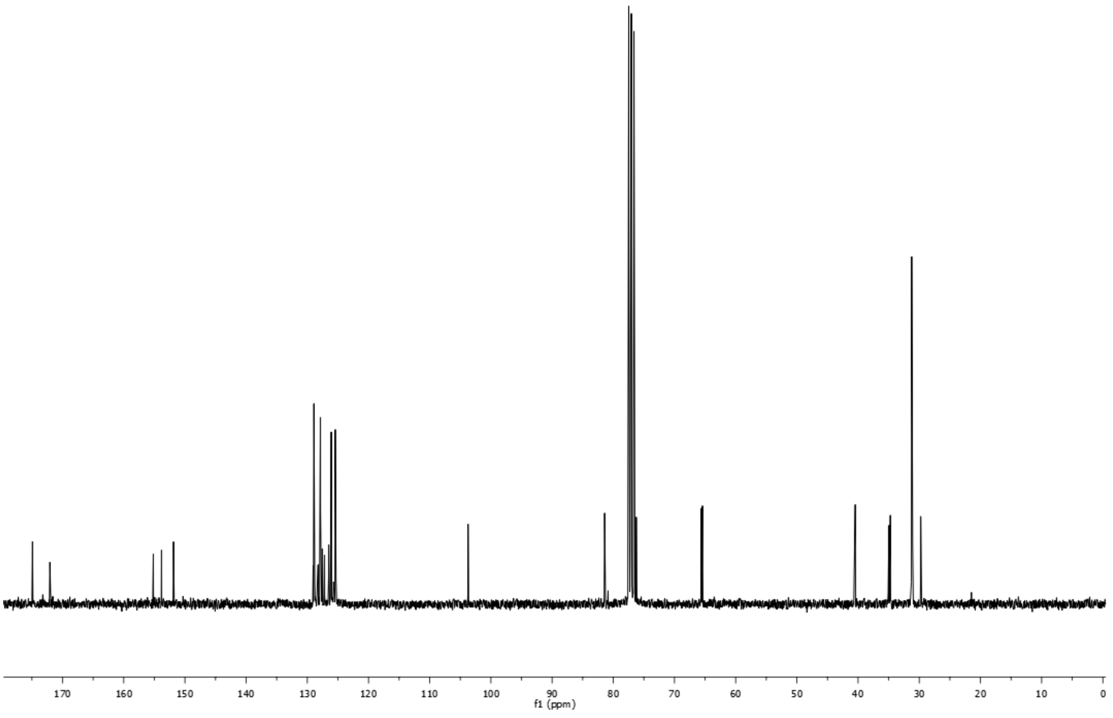




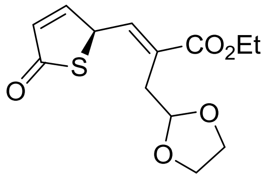


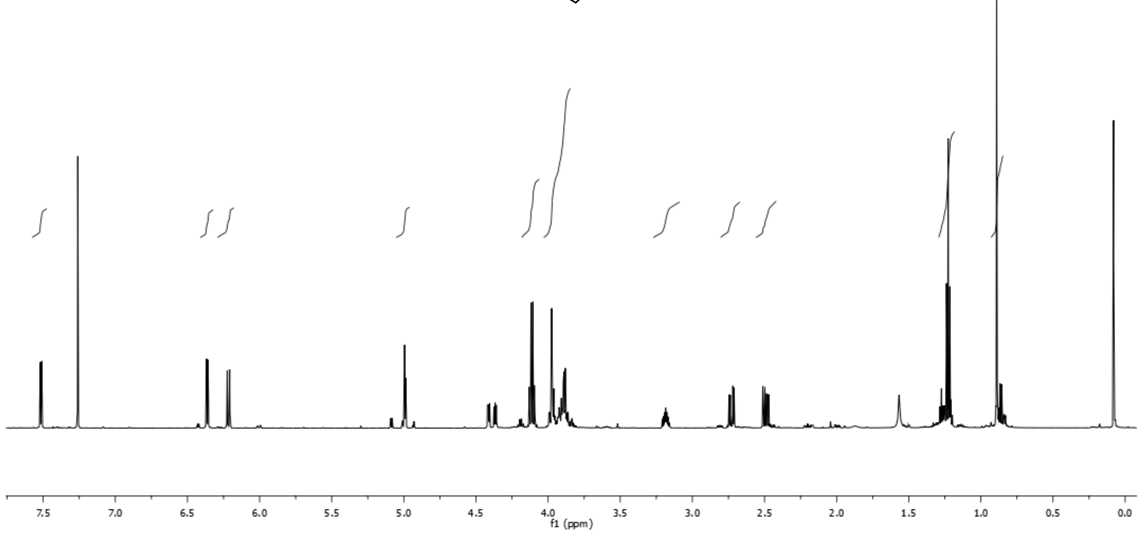
(2S,3S,2'S)-3',4'-Bis-(4-tert-butyl-phenyl)-3-[1,3]dioxolan-2-yl-3,4-dihydro-2H,2'H-[2,2']bifuranyl-5,5'-dione (33e)

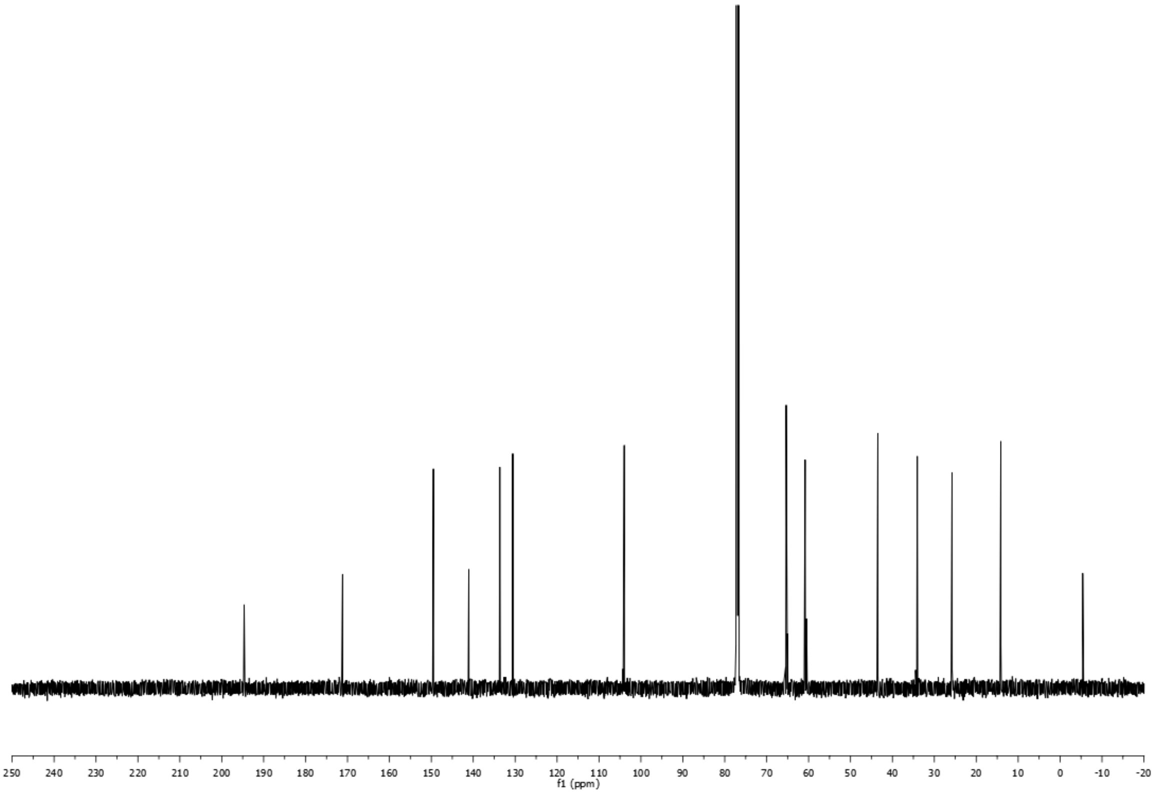




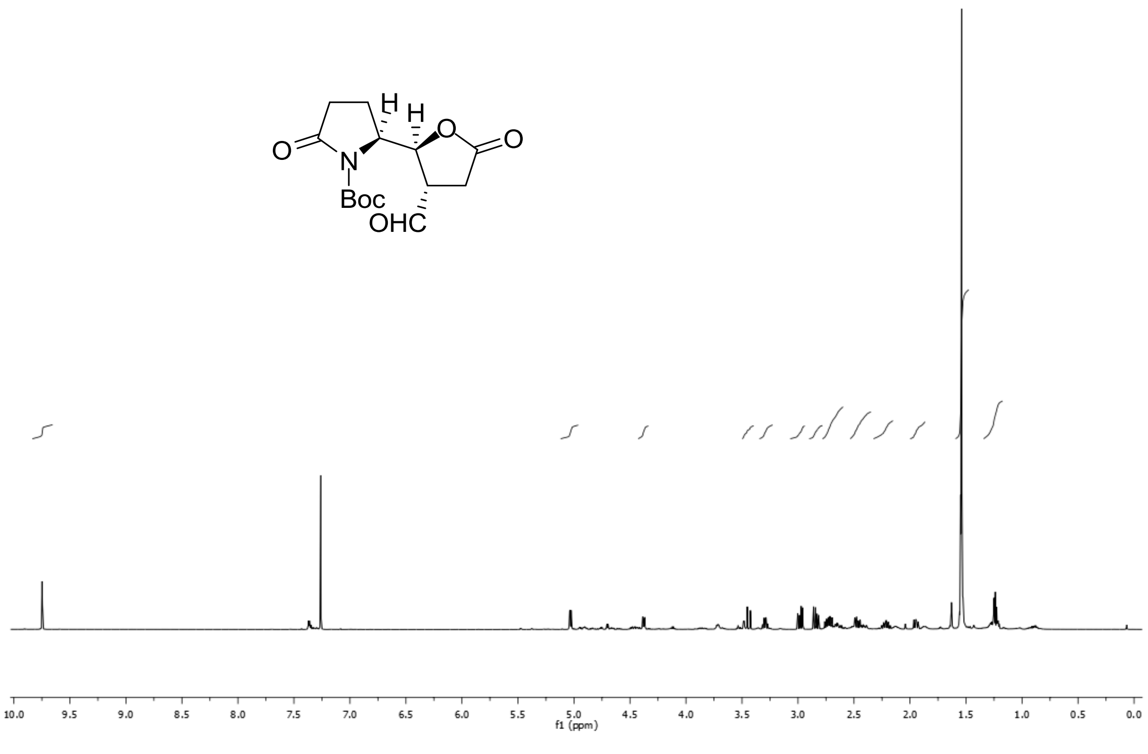
(E)-3-[1,3]Dioxolan-2-yl-4-((S)-5-oxo-2,5-dihydro-thiophen-2-yl)-but-3-enoic acid ethyl ester (48)

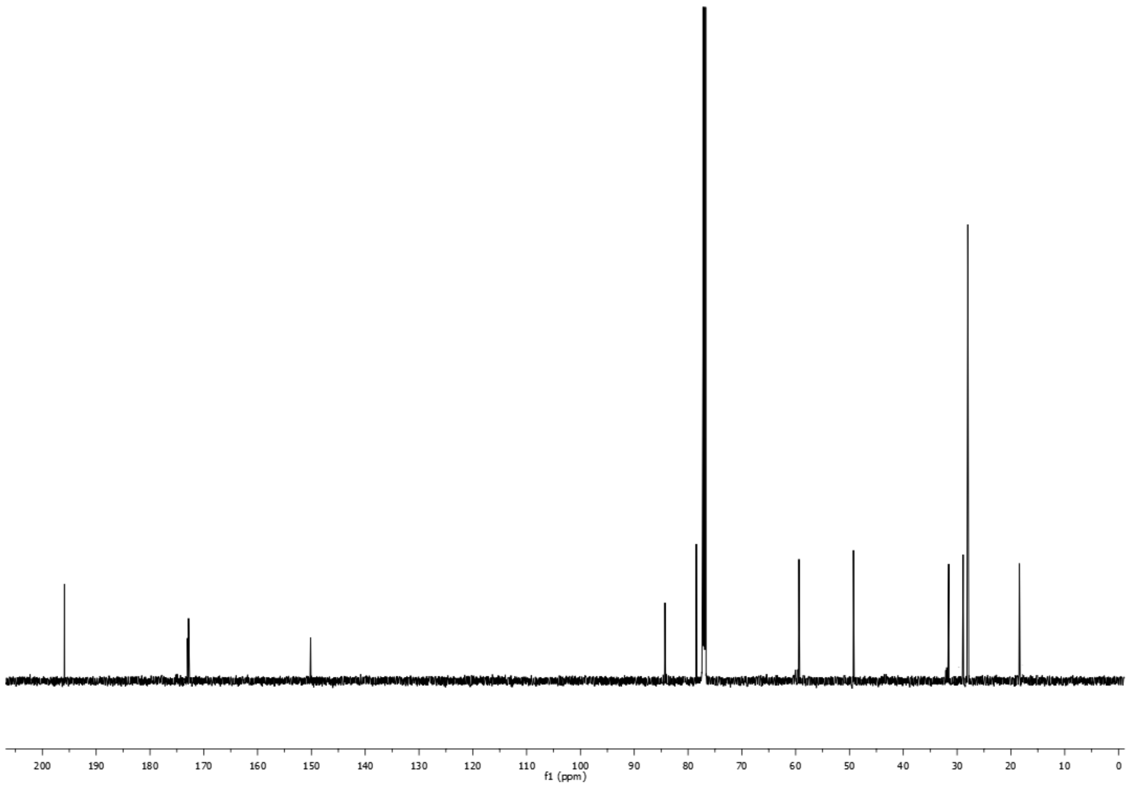




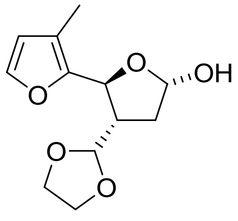


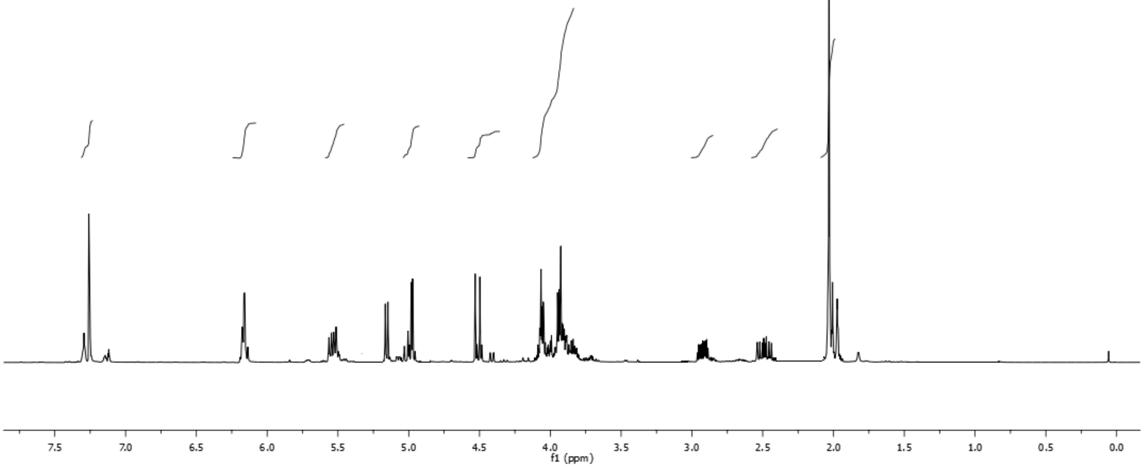
(S)-2-((S)-3-Formyl-5-oxo-tetrahydro-furan-2-yl)-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (33f)

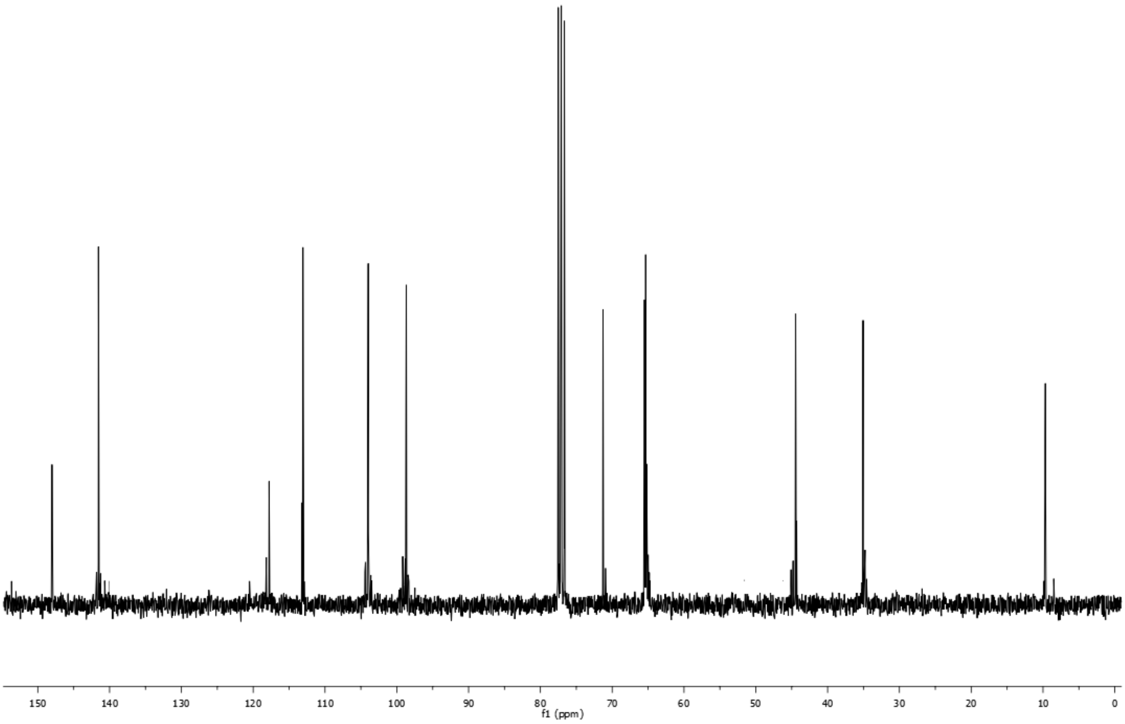




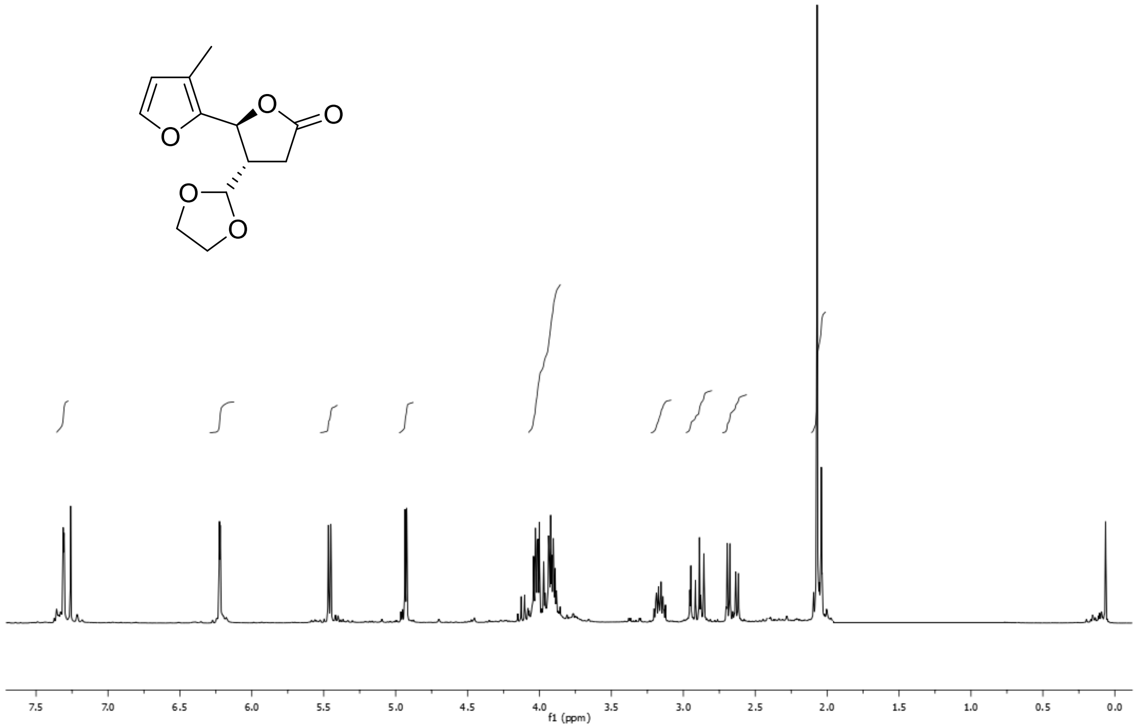
(2S,3S,5S)-3-[1,3]Dioxolan-2-yl-2,3,4,5-tetrahydro-[2,2']bifuranyl-5-ol (58)

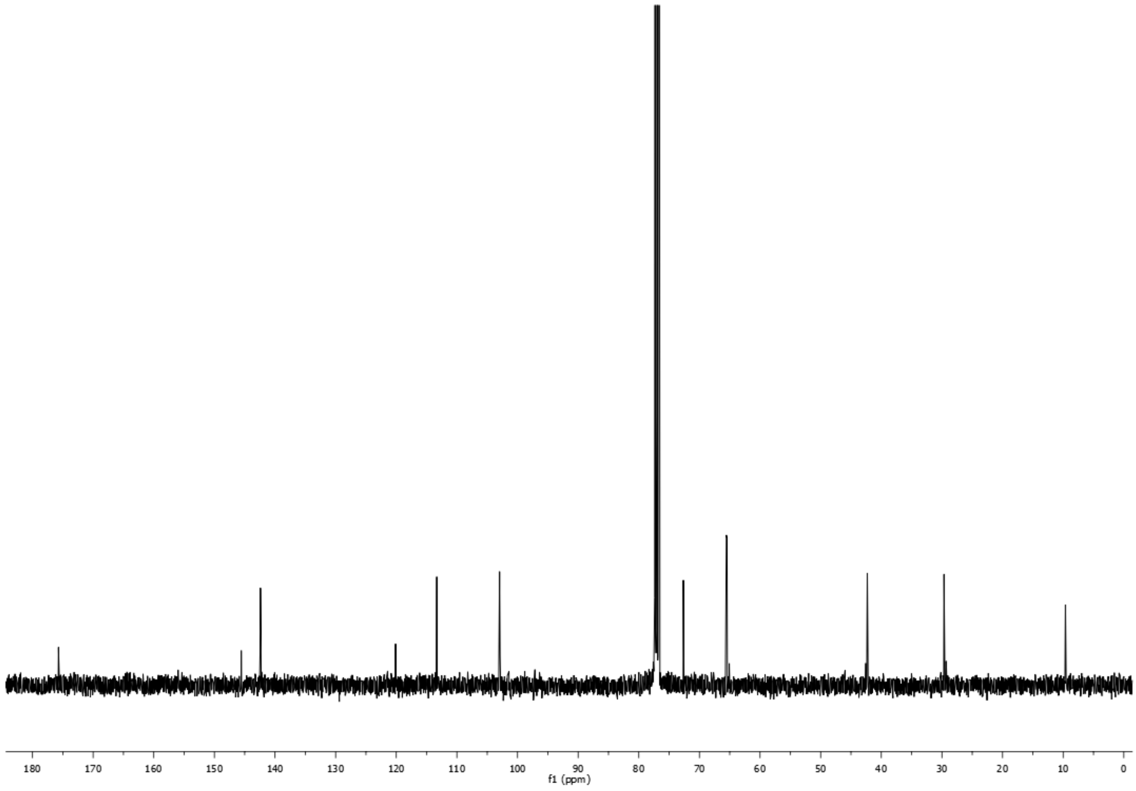




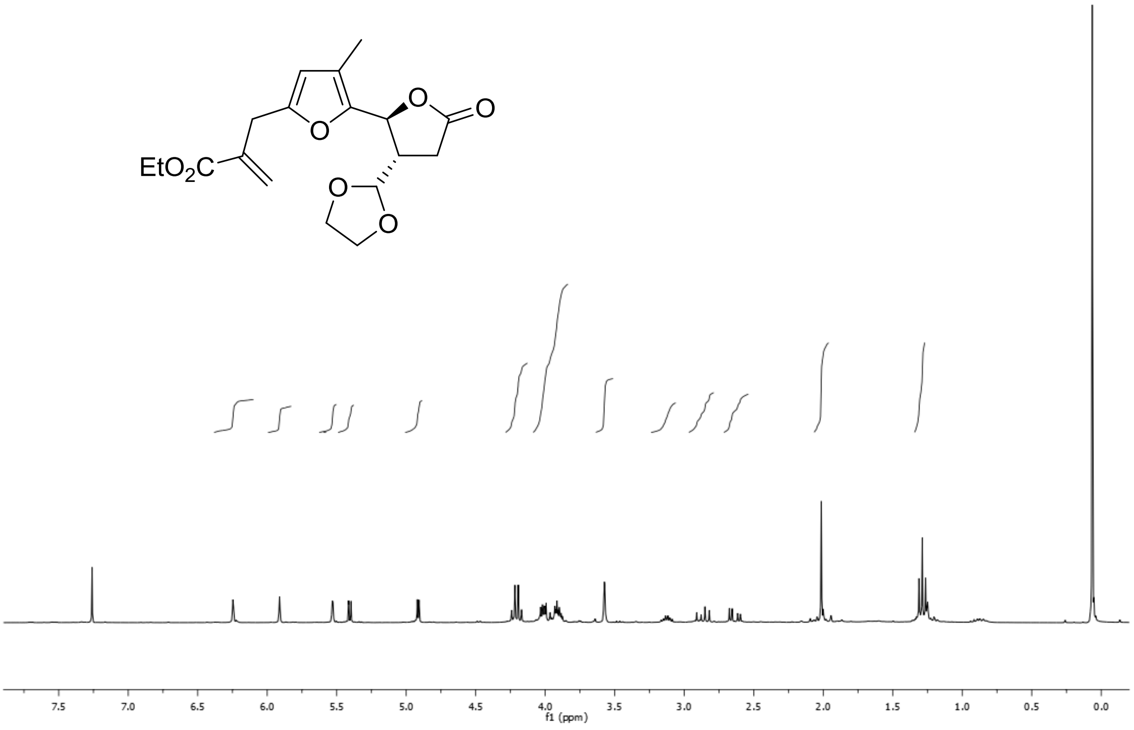


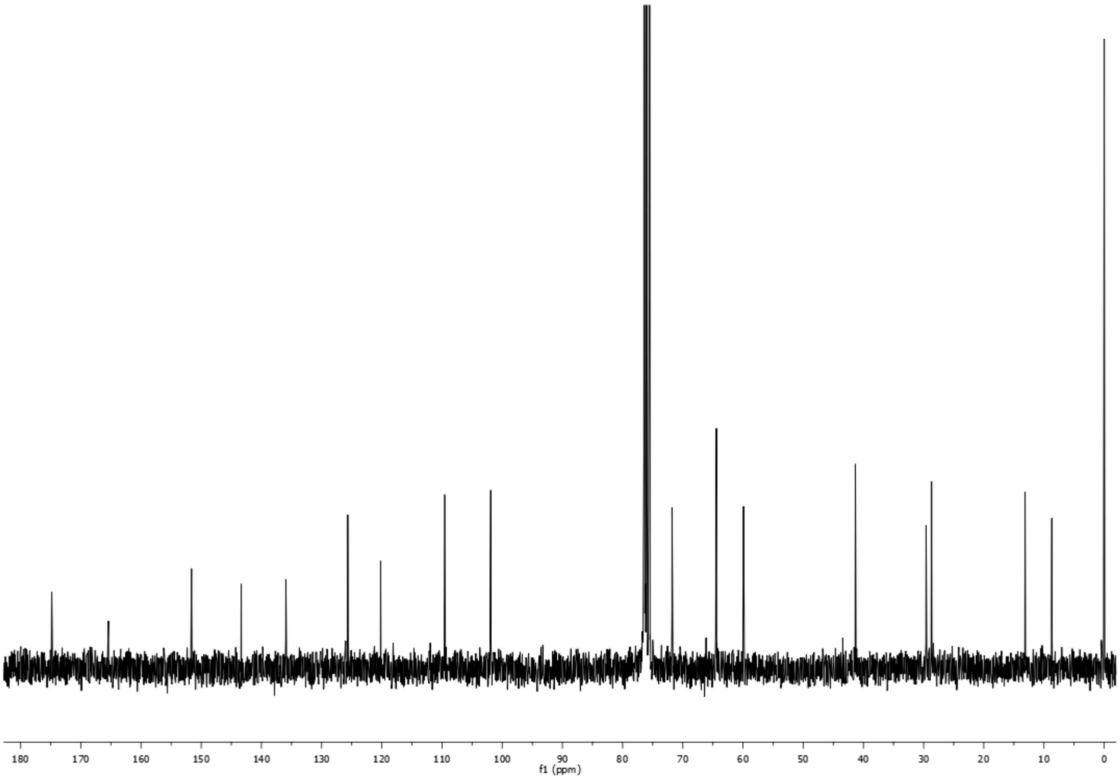
(2S,3S)-3-[1,3]Dioxolan-2-yl-3,4-dihydro-2H-[2,2']bifuranyl-5-one (59)



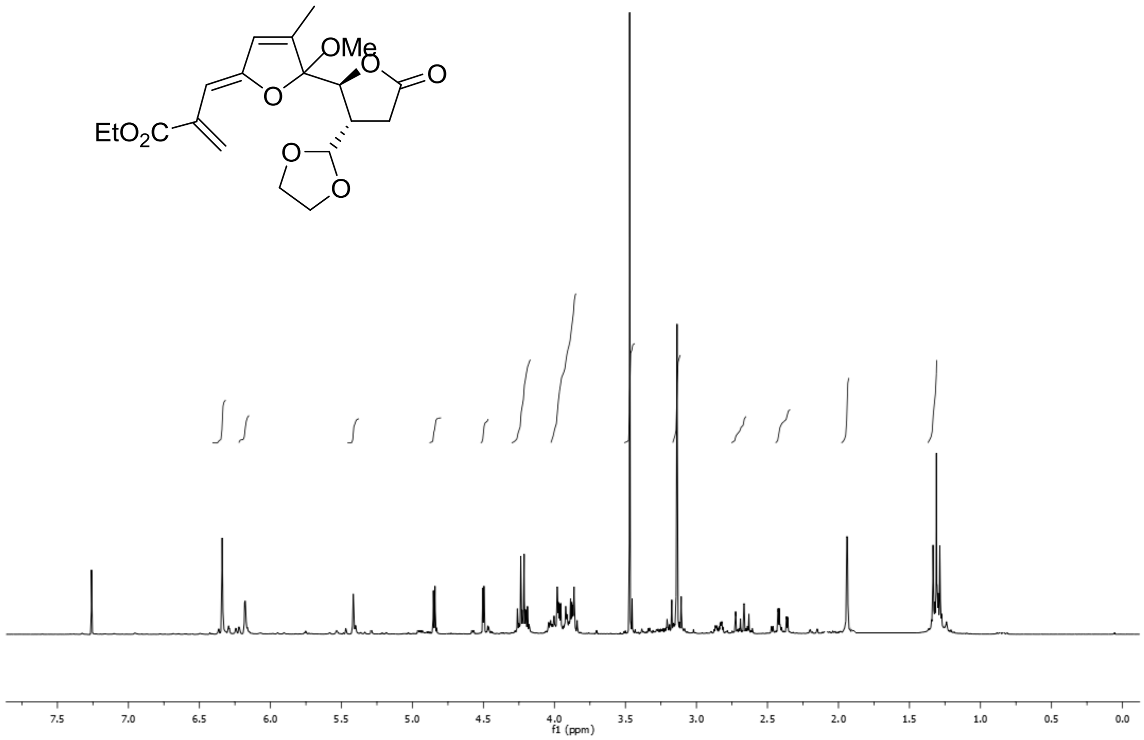


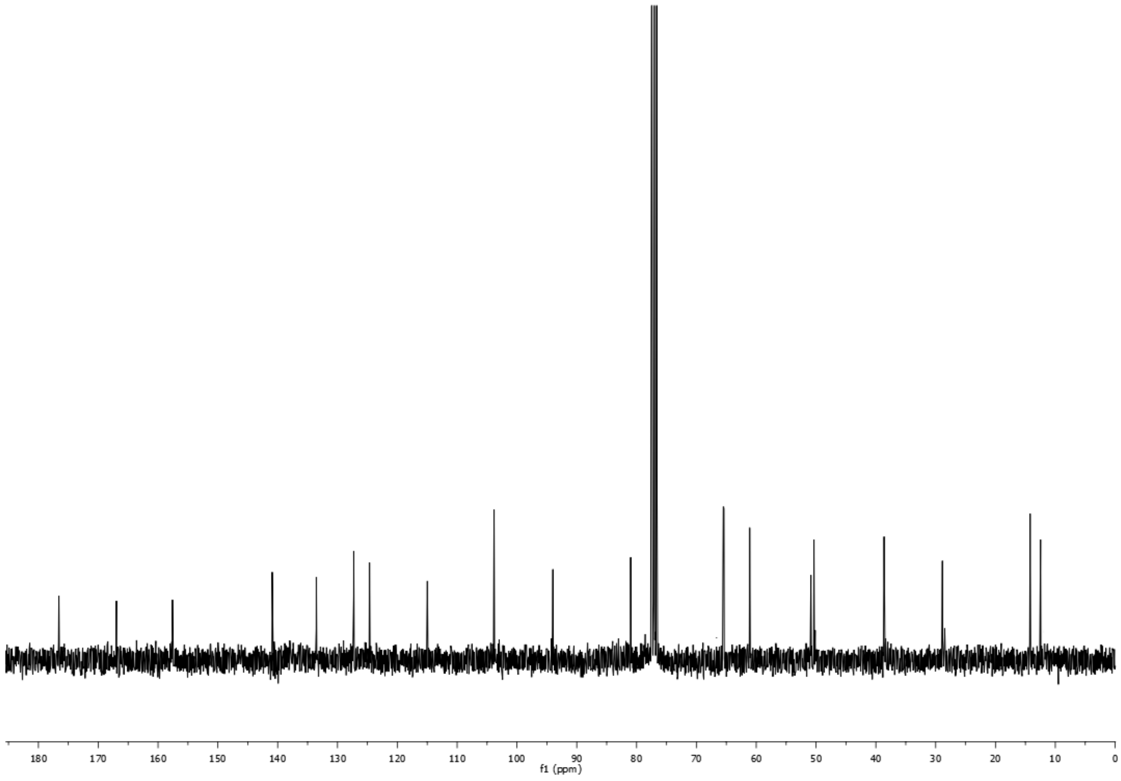
2-((2'S,3'S)-3'-[1,3]-Dioxolan-2-yl-3-methyl-5'-oxo-2',3',4',5'-tetrahydro-[2,2']bifuranyl-5-ylmethyl)-acrylic acid ethyl ester (57)

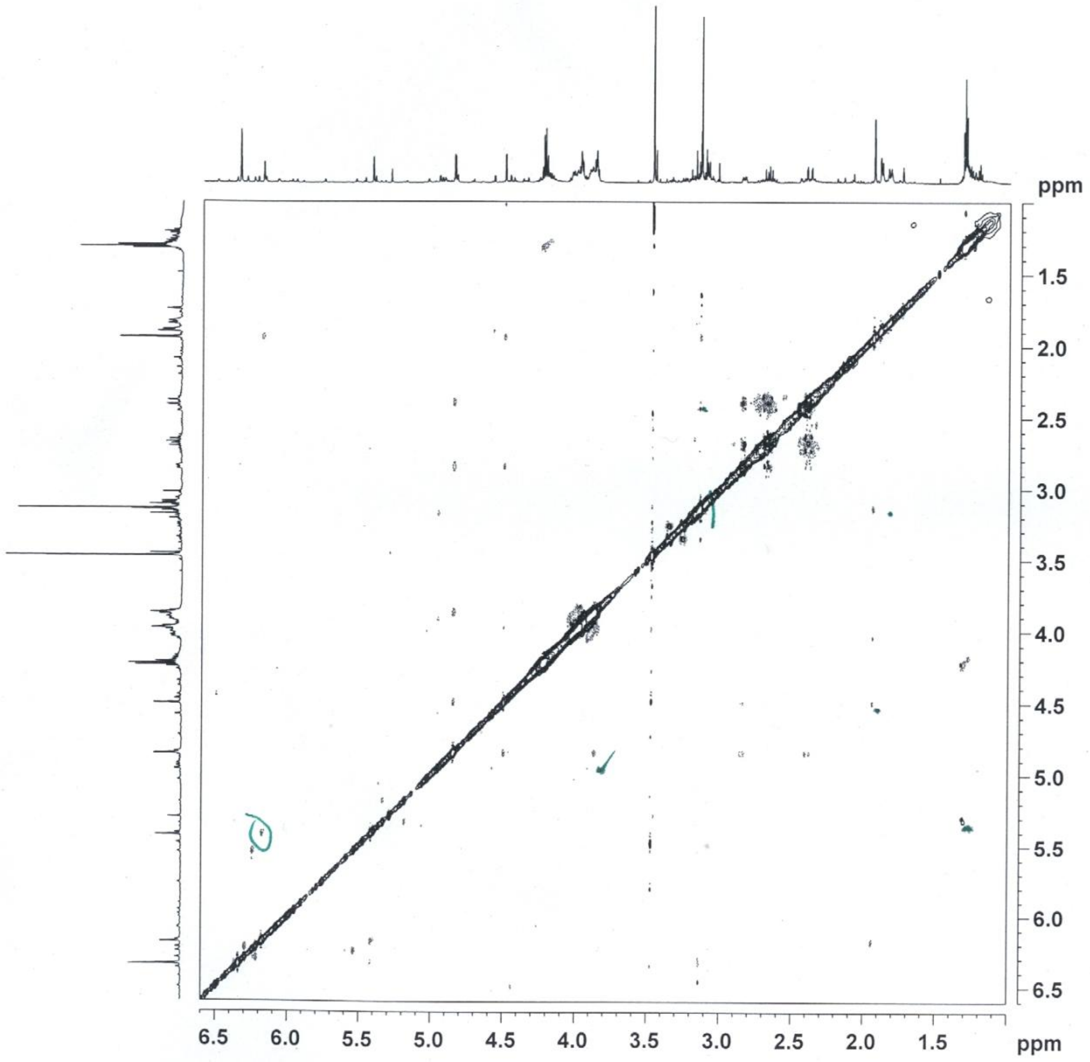




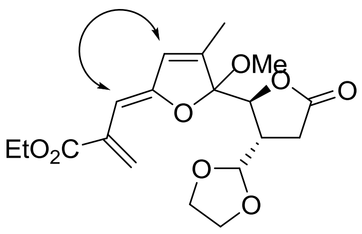
2-[(2S,2'S,3'S)-3'-[1,3]Dioxolan-2-yl-2-methoxy-3-methyl-5'-oxo-2',3',4',5'-tetrahydro-2H-[2,2']bifuranyl-(5Z)-ylidenemethyl]-acrylic acid ethyl ester (54)





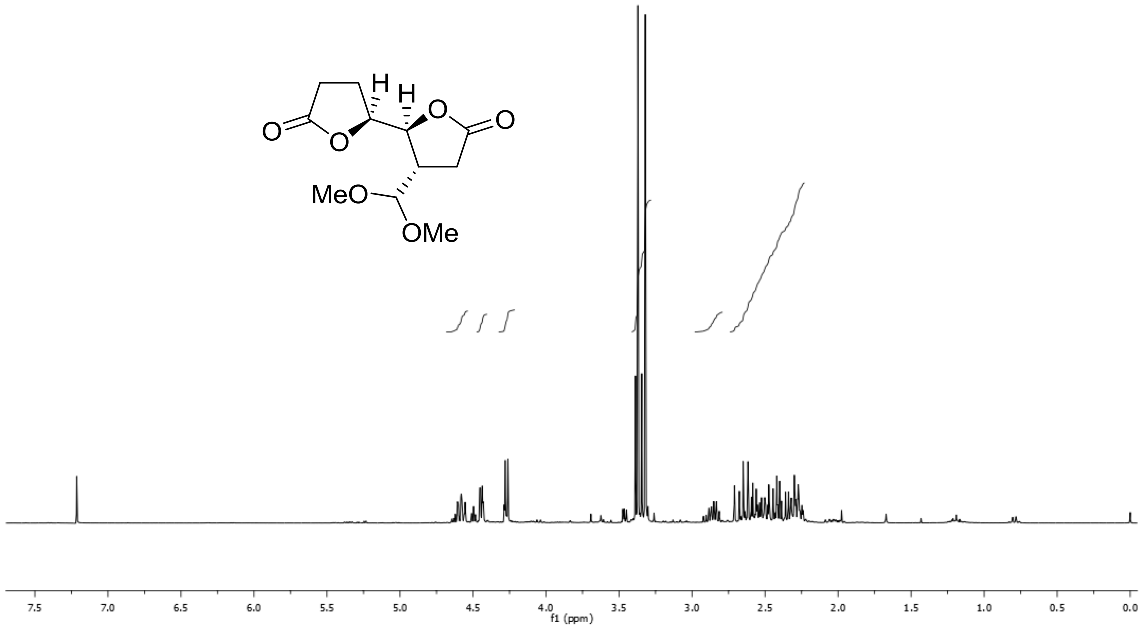


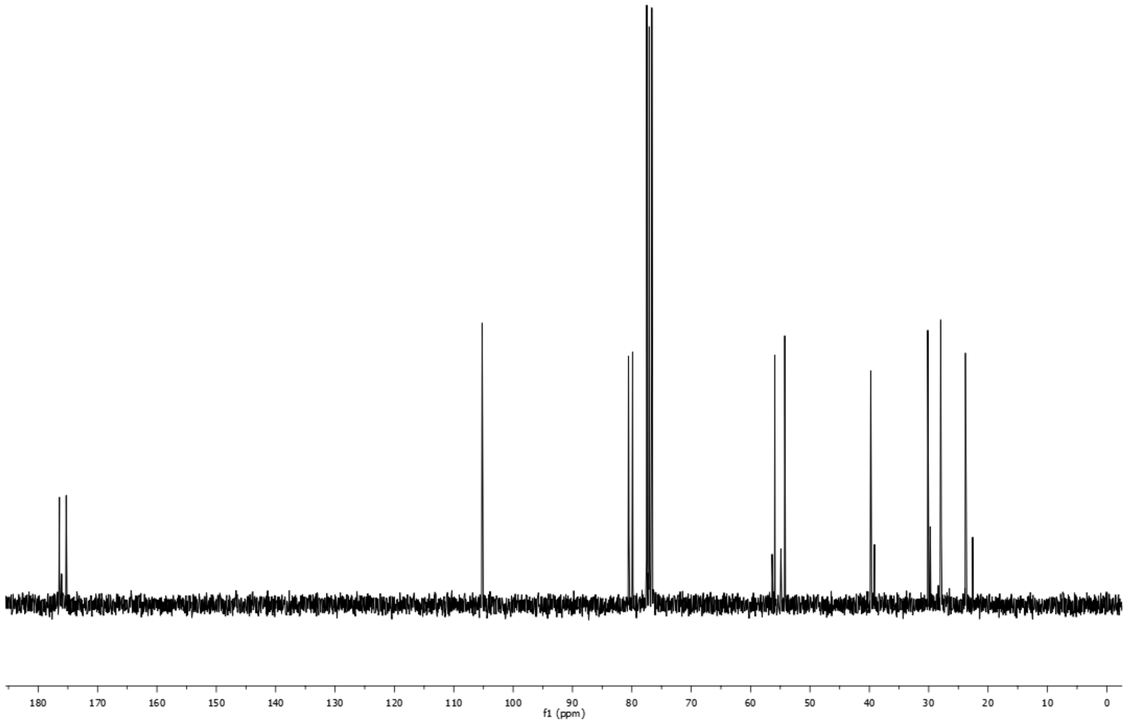
2D NOESY spectrum of lactone 54



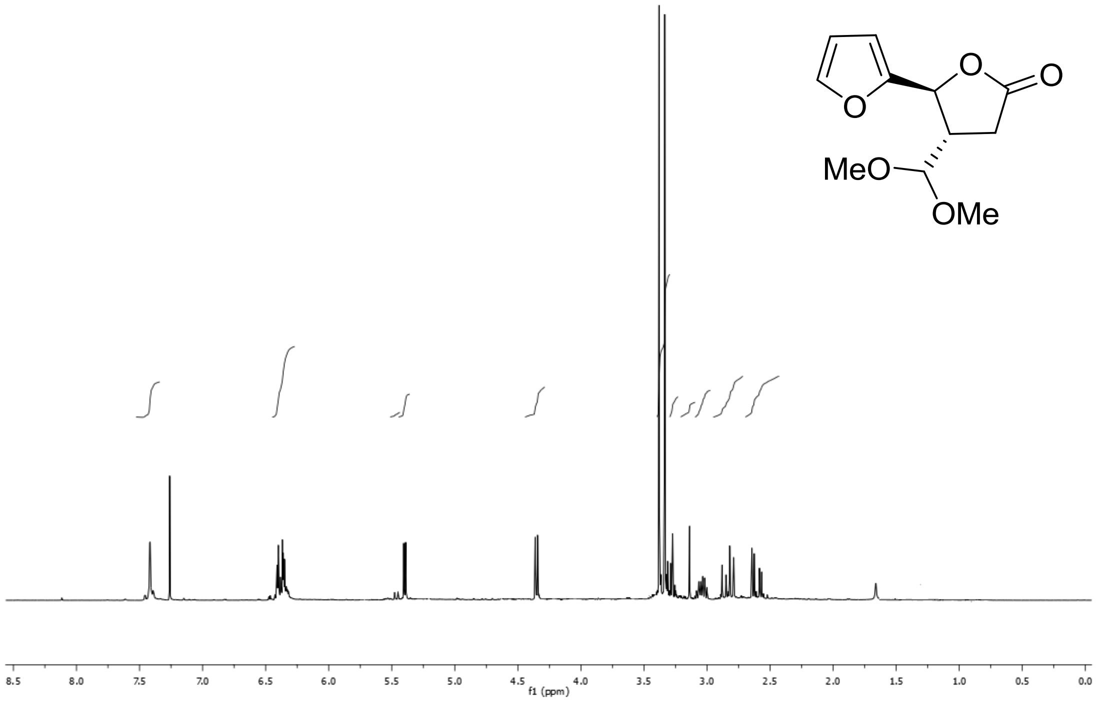
Key NOESY correlations in 54

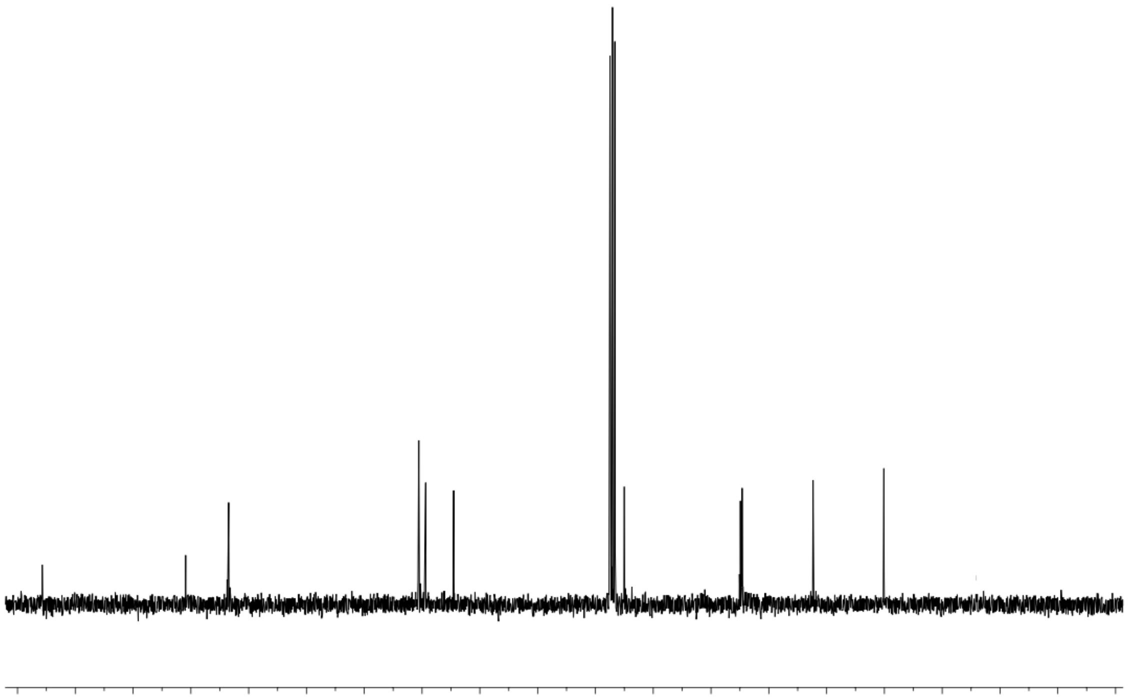
(2S,3S,2'S)-3-[1,3]Dioxolan-2-yl-tetrahydro-[2,2']bifuranyl-5,5'-dione (52)

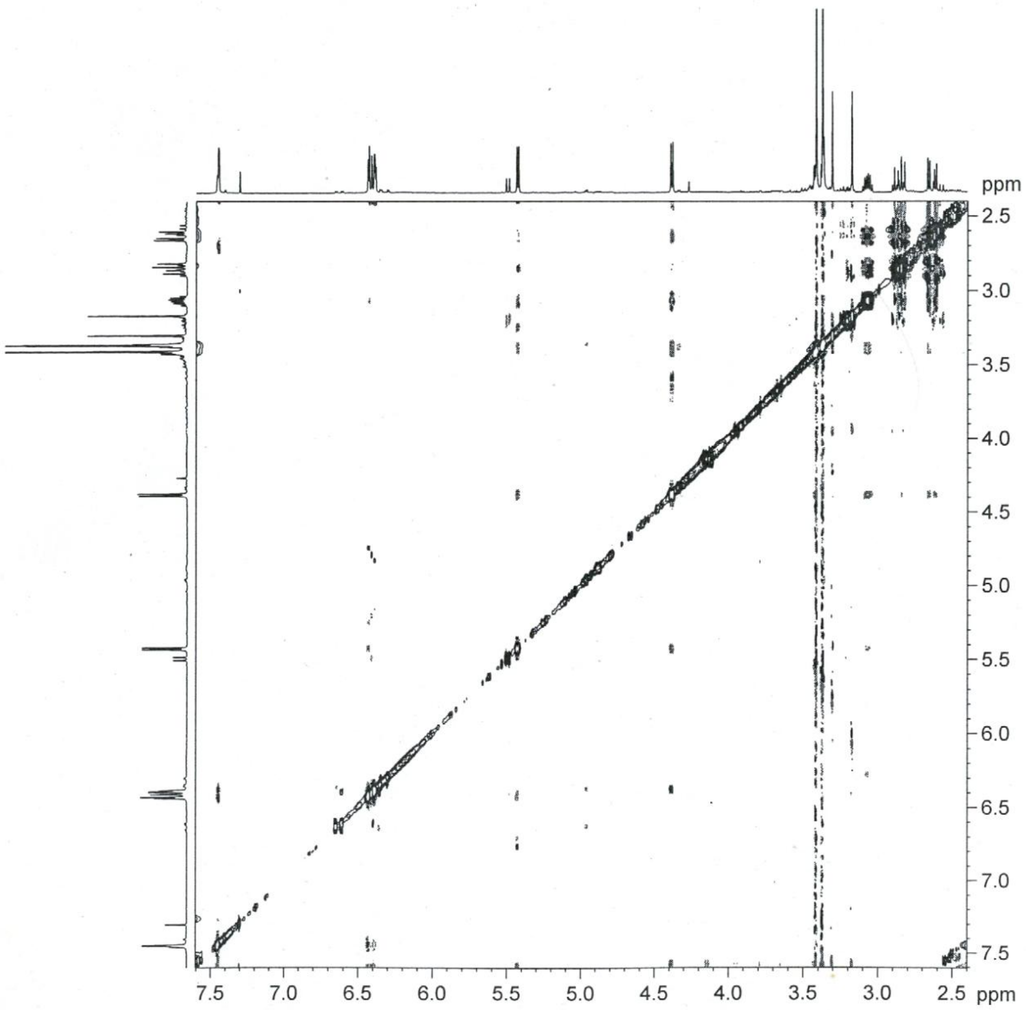




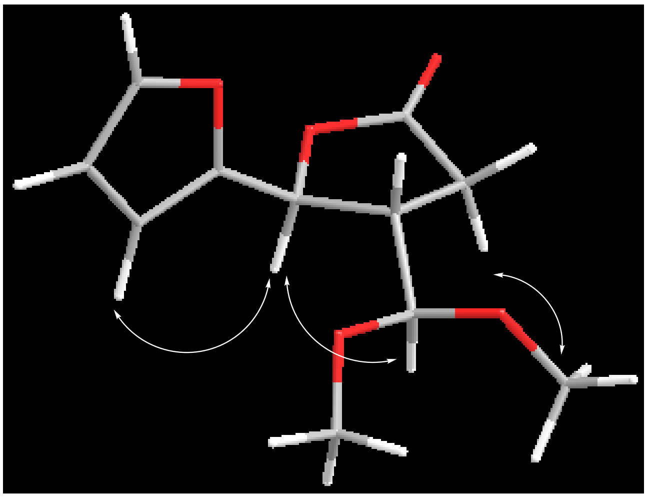
(2S,3S)-3-Dimethoxymethyl-3,4-dihydro-2H-[2,2']bifuranyl-5-one (68a)





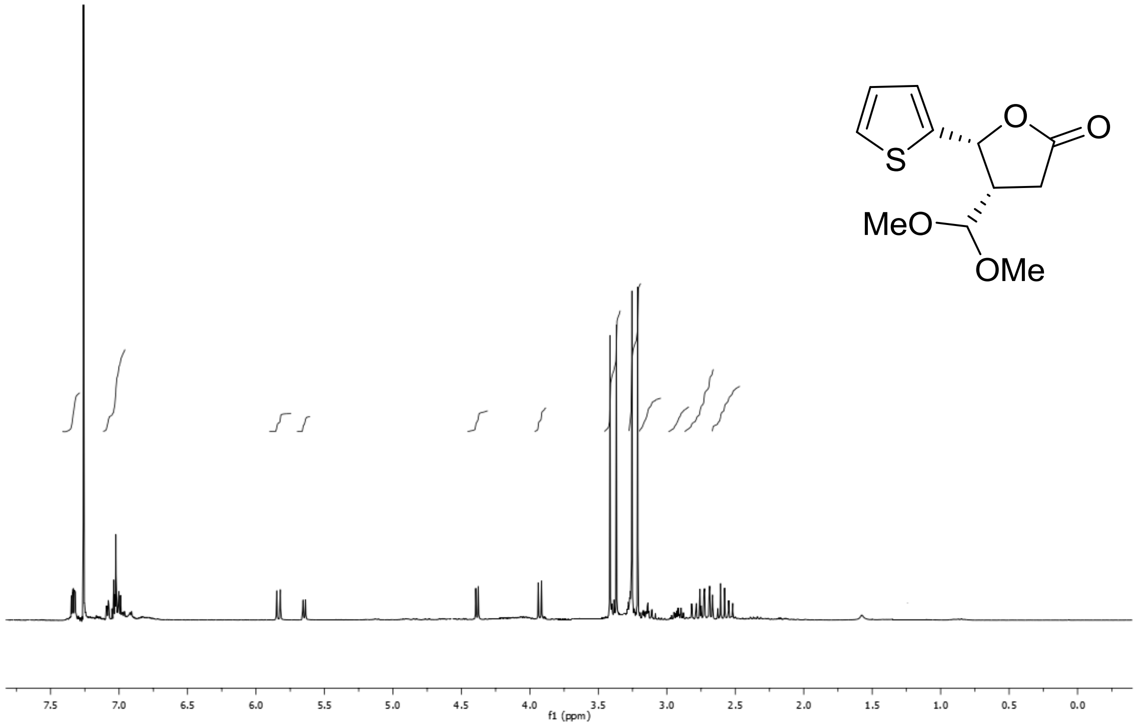


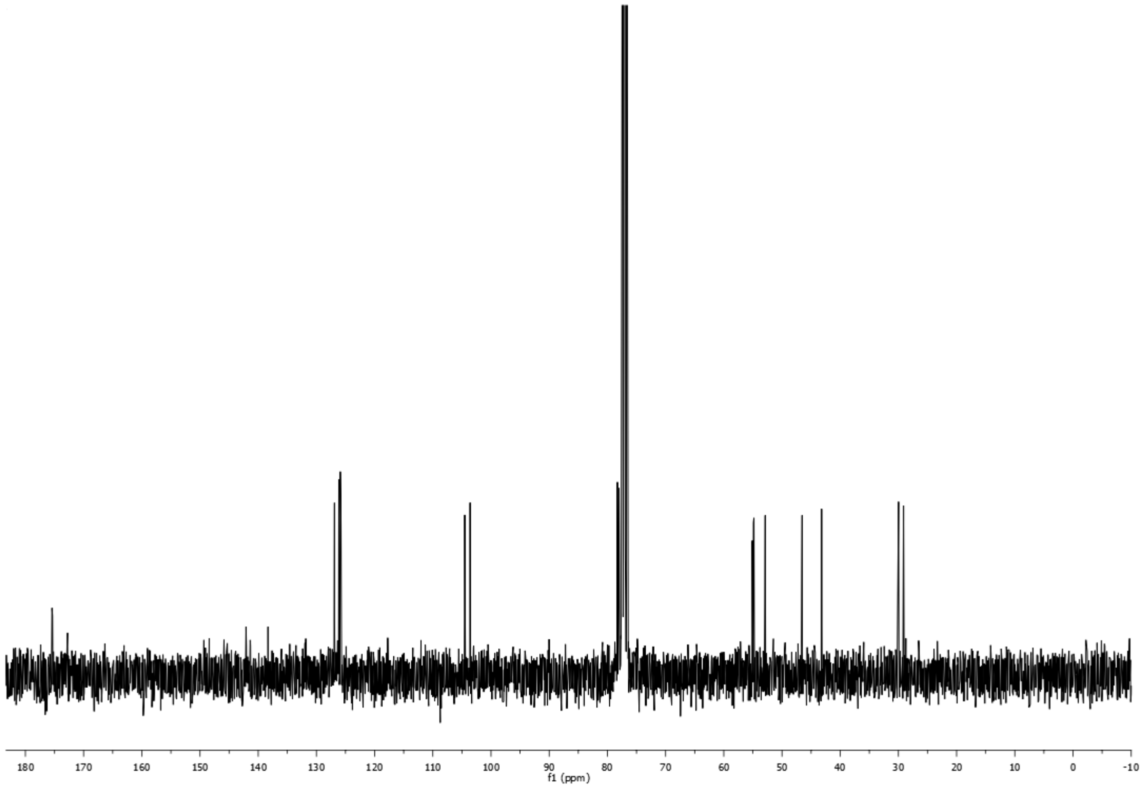
2D NOESY spectrum of lactone 68a



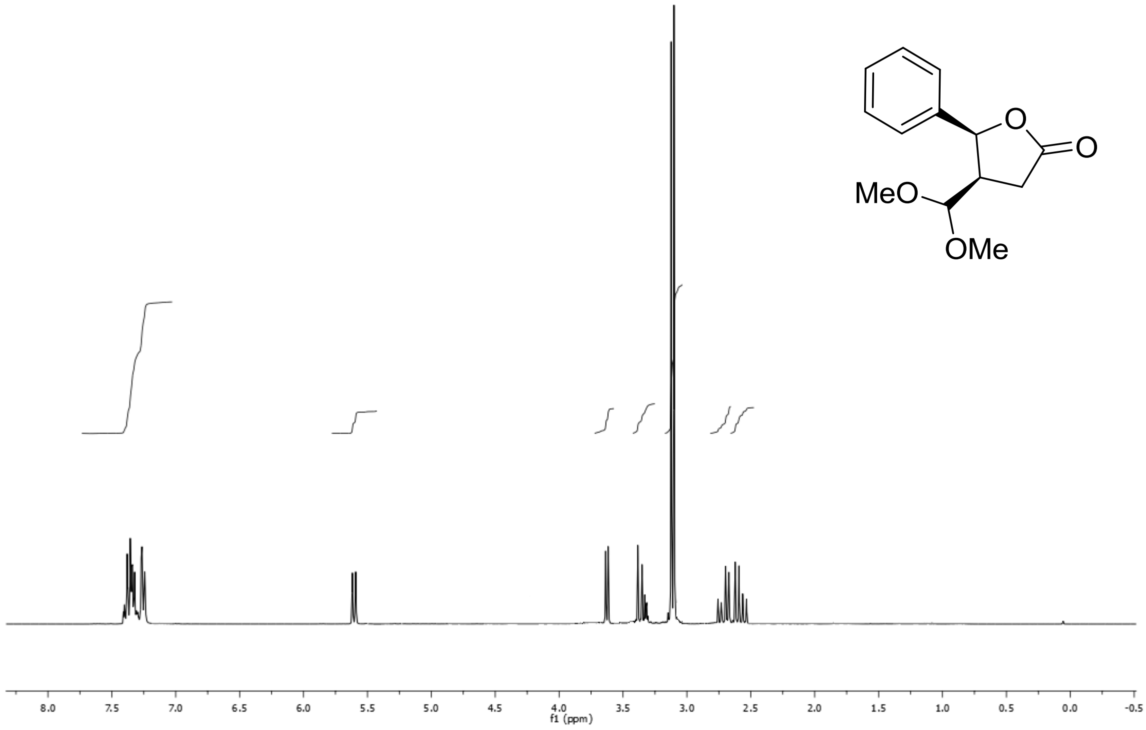
Key NOESY correlations in 68a

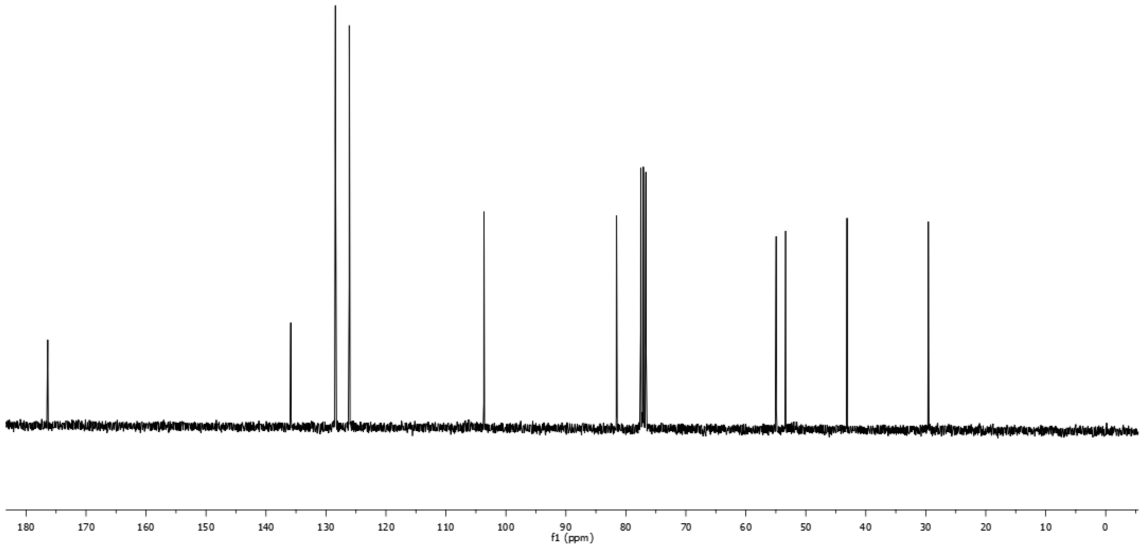
(4S,5R)-4-Dimethoxymethyl-5-thiophen-2-yl-dihydro-furan-2-one (68b)



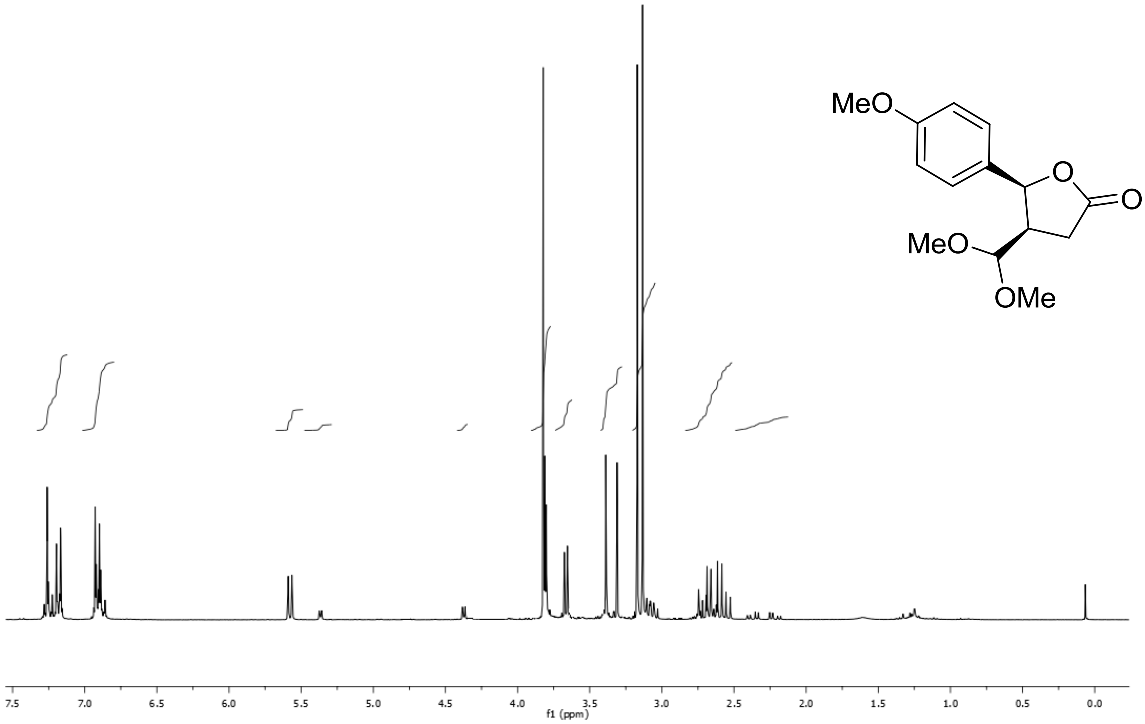


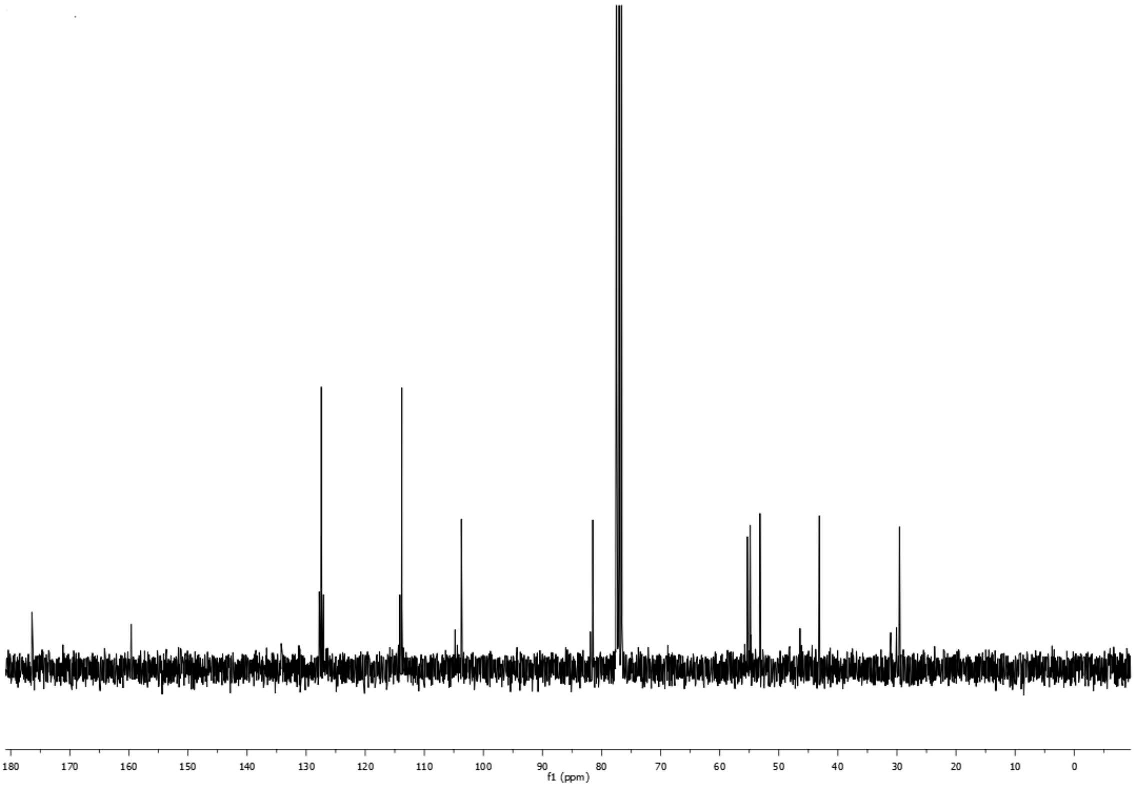
(4R,5S)-4-Dimethoxymethyl-5-phenyl-dihydro-furan-2-one (68c)



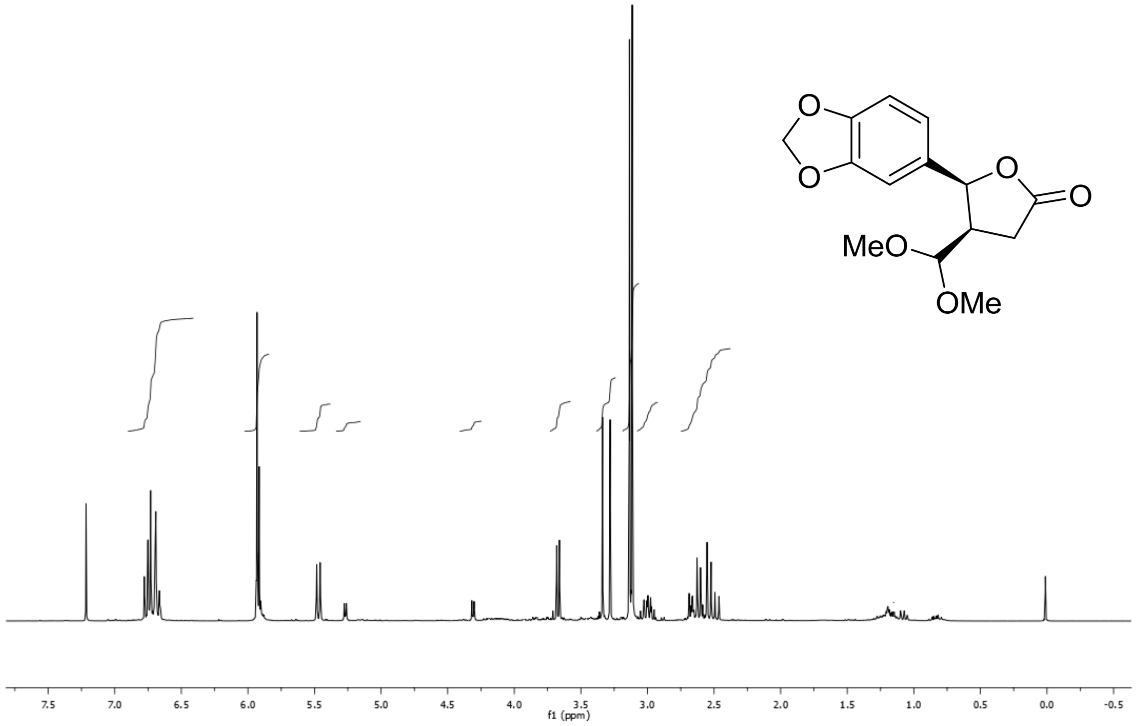


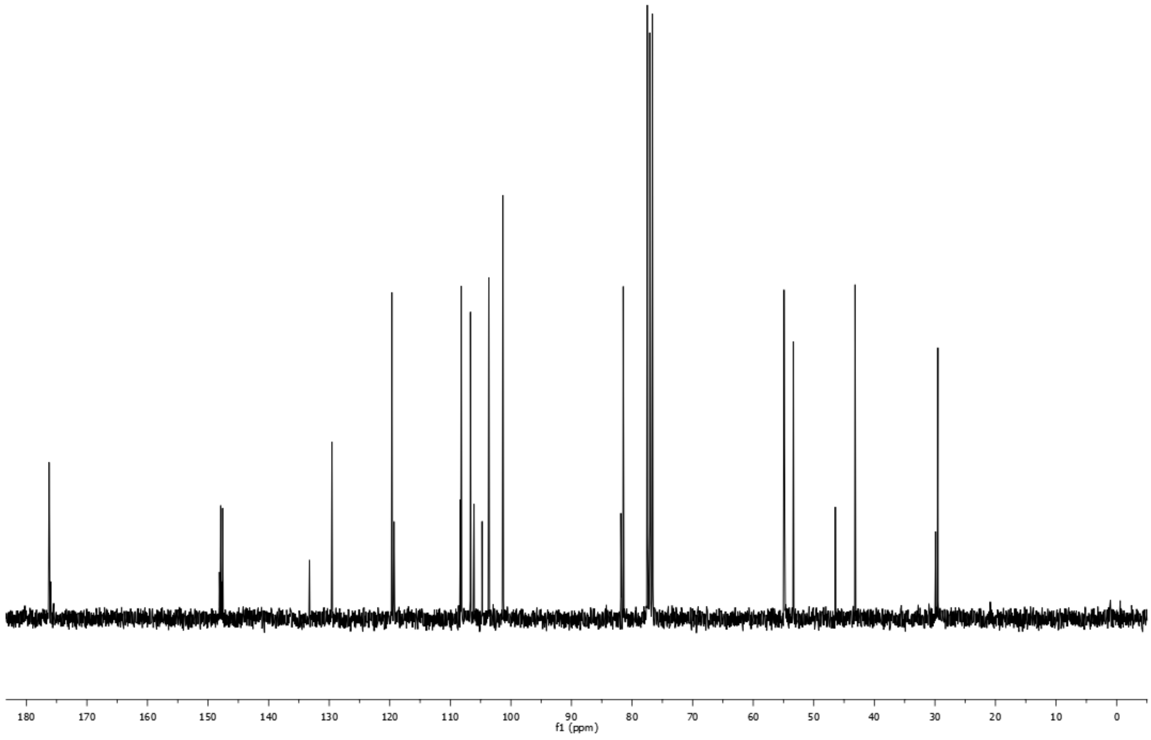
(4R,5S)-4-Dimethoxymethyl-5-(4-methoxy-phenyl)-dihydro-furan-2-one (68d).



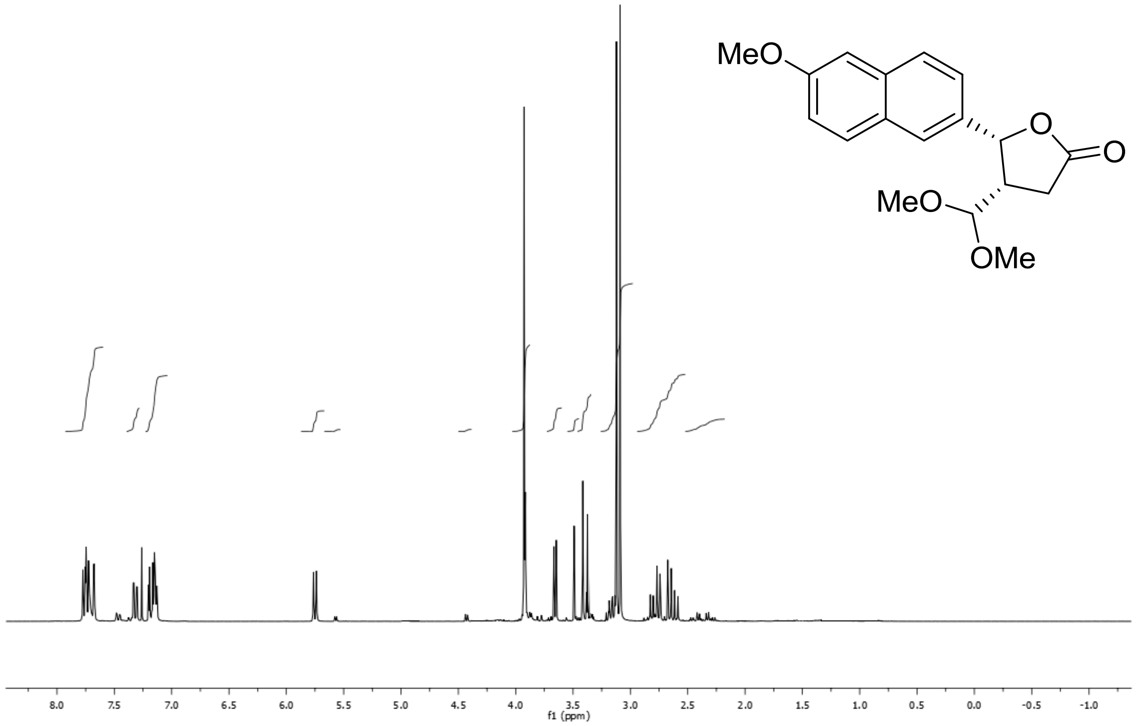


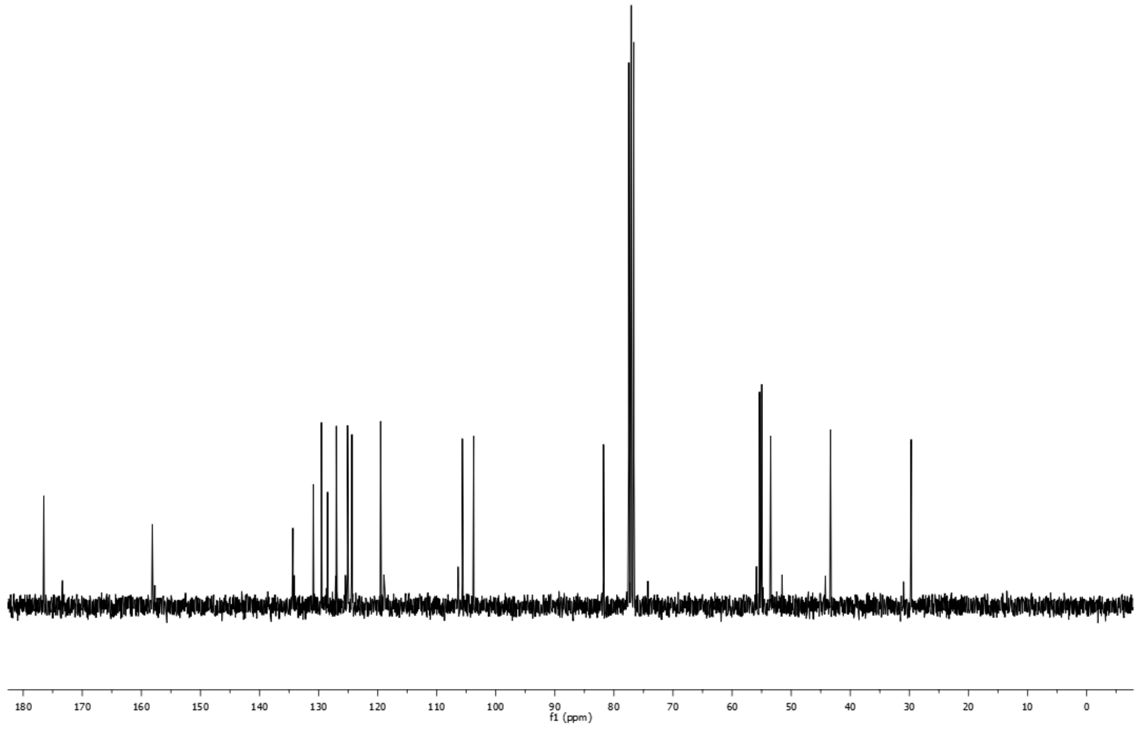
(4R,5S)-5-Benzo[1,3]dioxol-5-yl-4-dimethoxymethyl-dihydro-furan-2-one (68e)



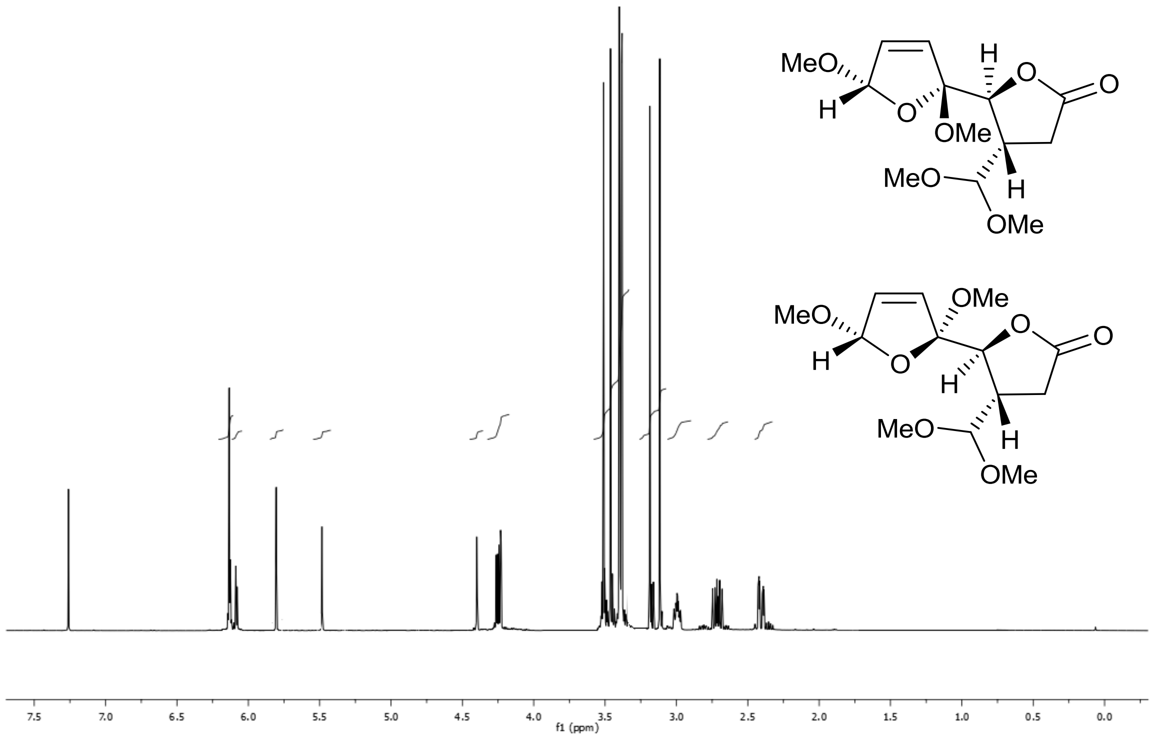


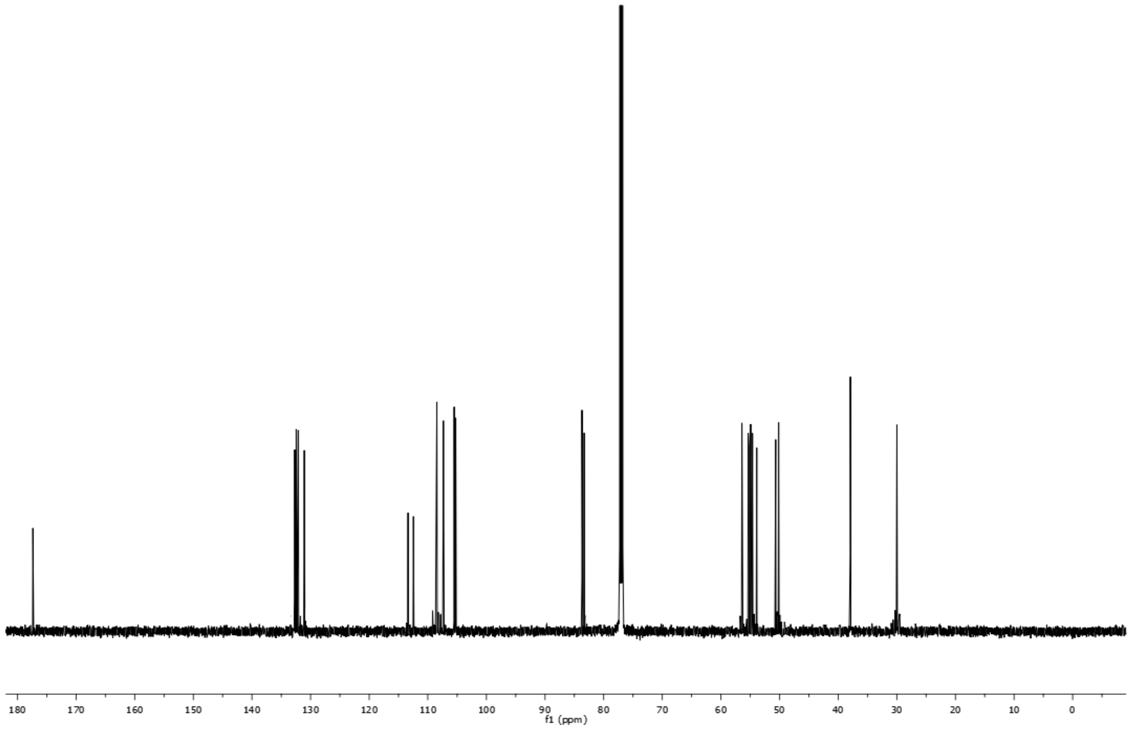
(4S,5R)-4-Dimethoxymethyl-5-(6-methoxy-naphthalen-2-yl)-dihydro-furan-2-one (68f)

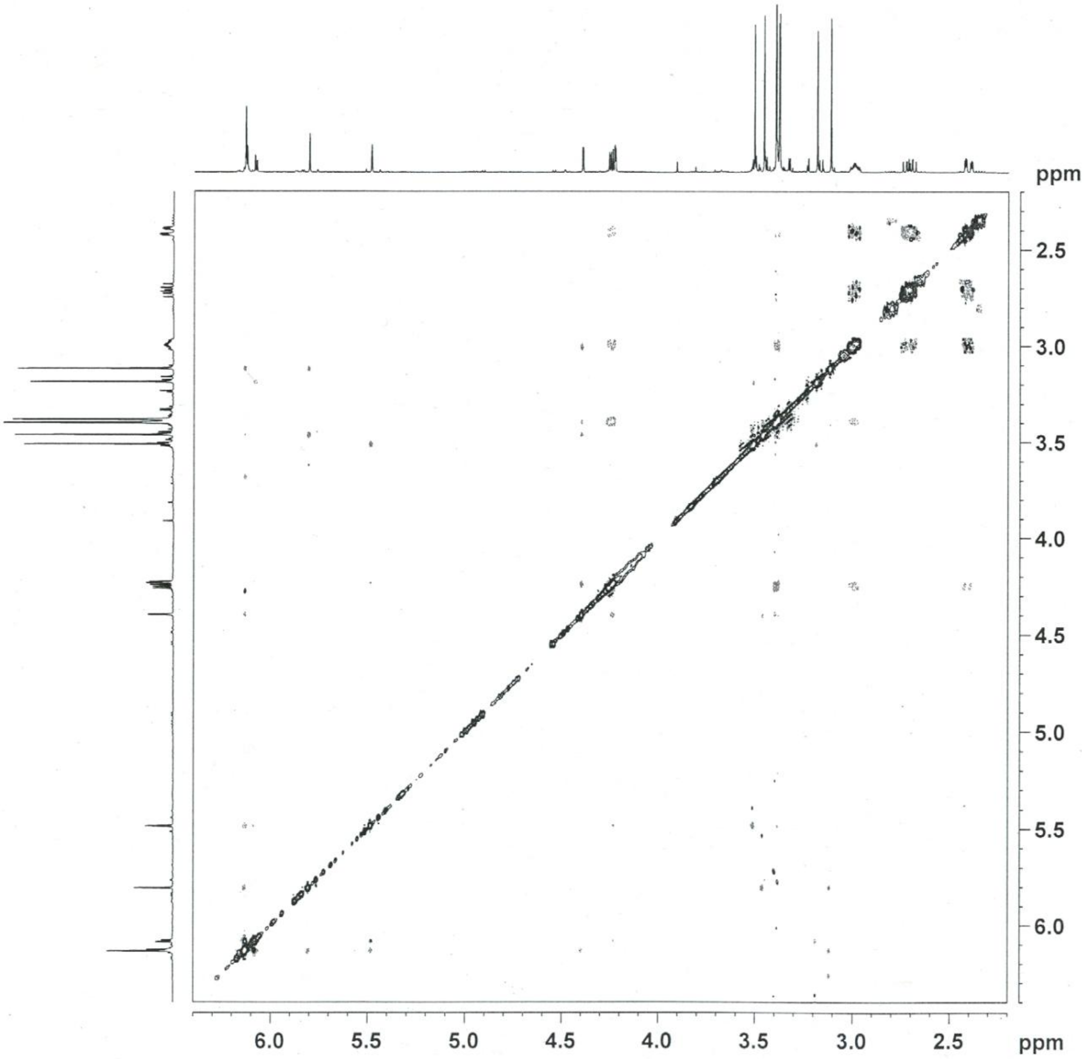




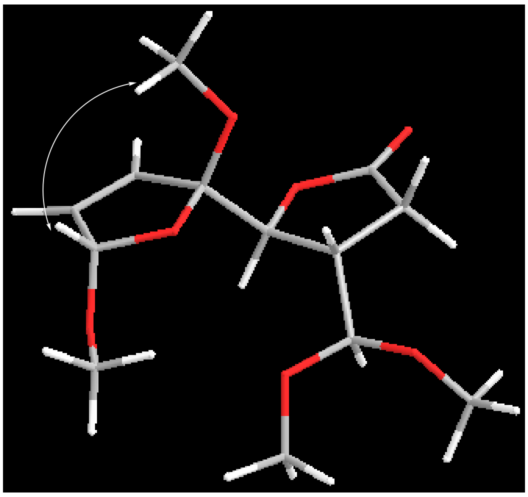
(2S,3S,2'R,5'S)-3-Dimethoxymethyl-2',5'-dimethoxy-3,4,2',5'-tetrahydro-2H-[2,2']bifuranyl-5-one (86a) and (2S,3S,2'S,5'S)-3-Dimethoxymethyl-2',5'-dimethoxy-3,4,2',5'-tetrahydro-2H-[2,2']bifuranyl-5-one (86b, relative stereochemistry assigned)

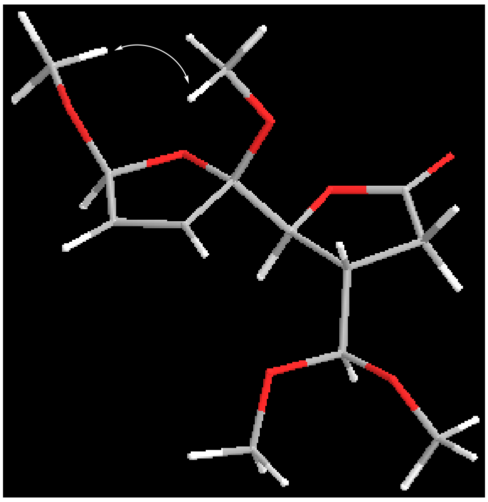






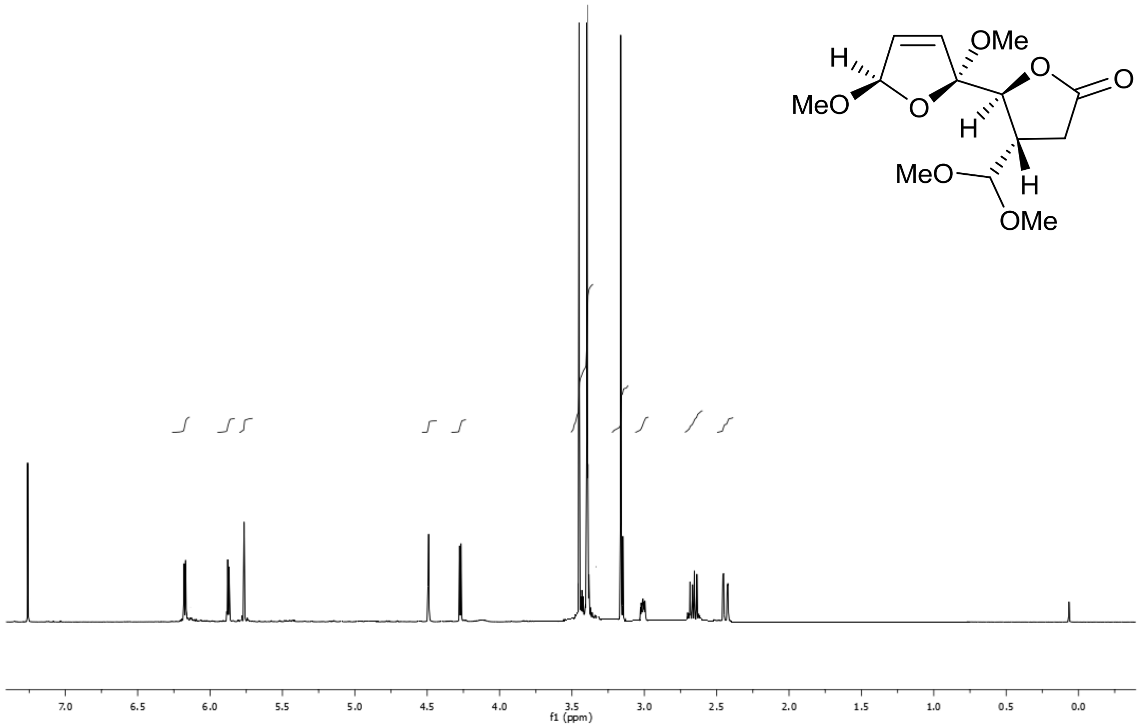
2D NOESY spectrum of 86a and 86b

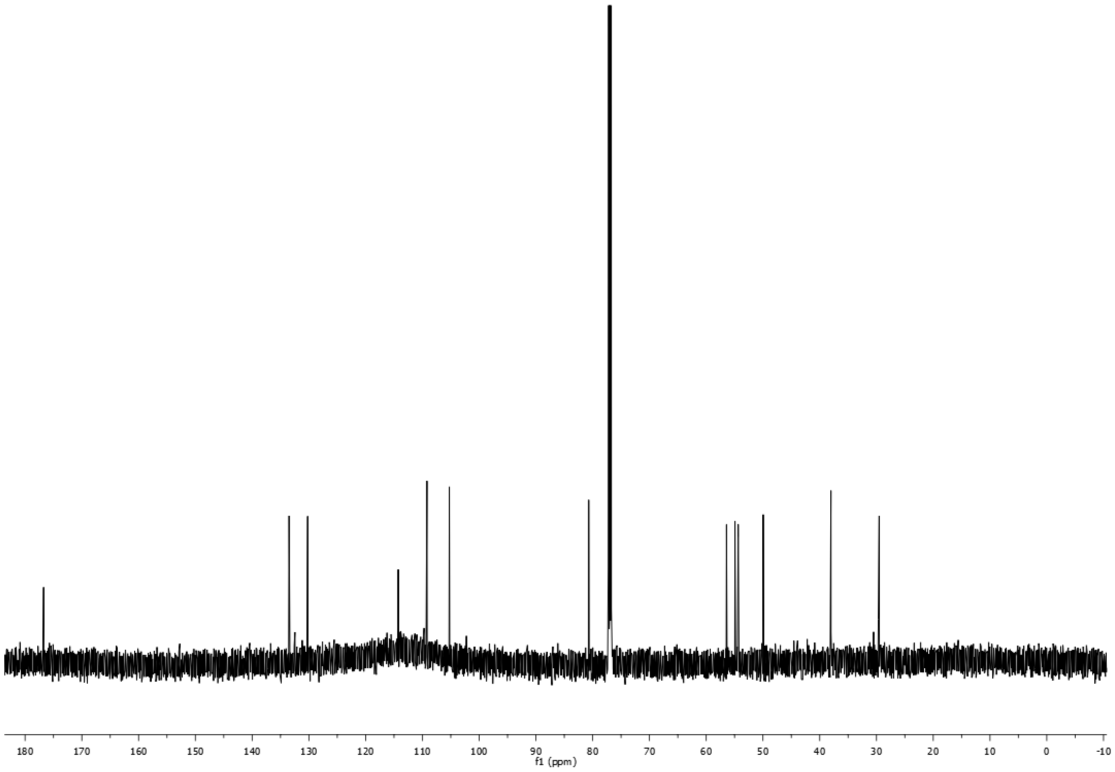


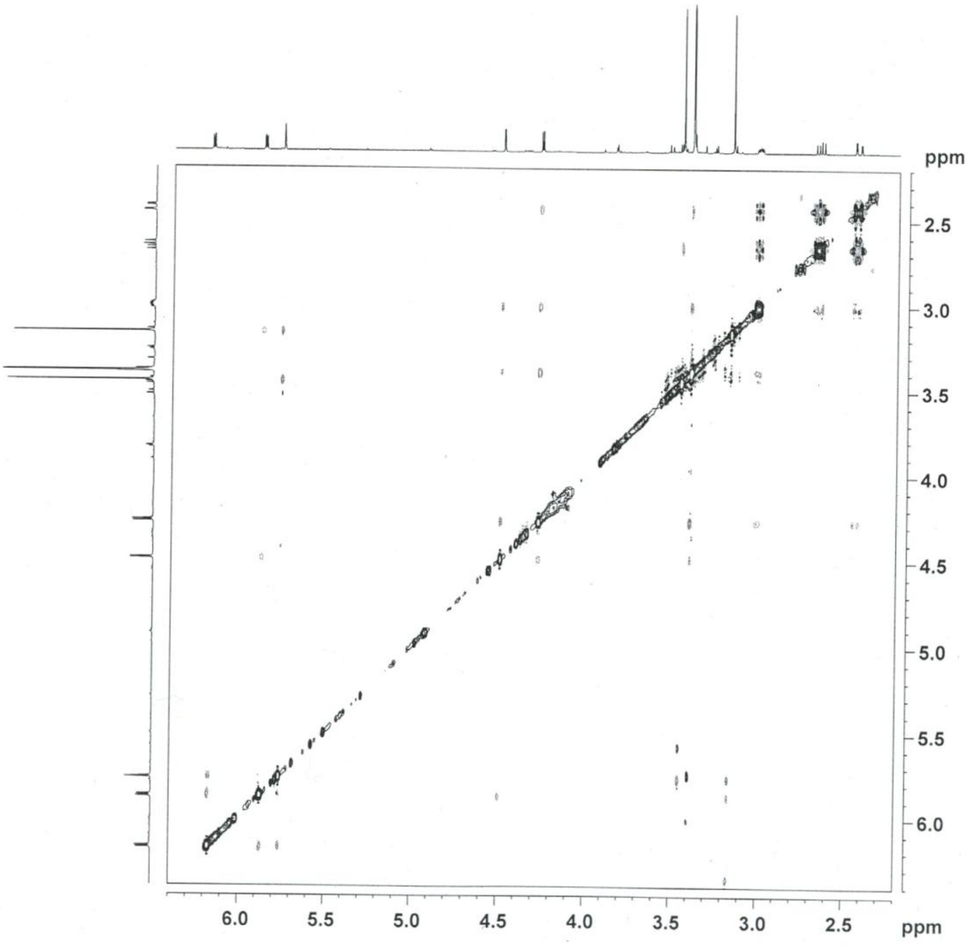


Key NOESY correlations in 86a and 86b

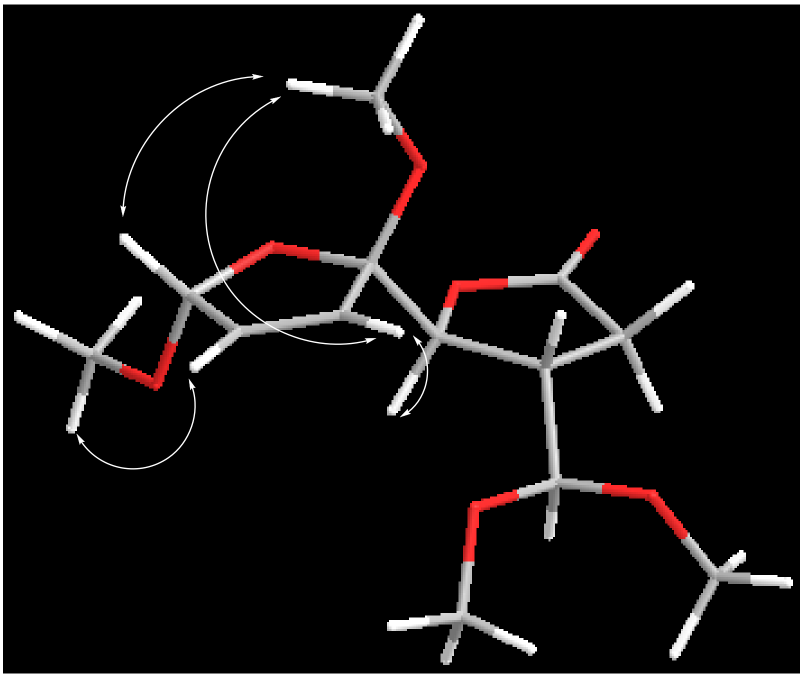
(*2S,3S,2'S,5'R*)-3-Dimethoxymethyl-2',5'-dimethoxy-3,4,2',5'-tetrahydro-2H-[2,2']bifuranyl-5-one (86c)





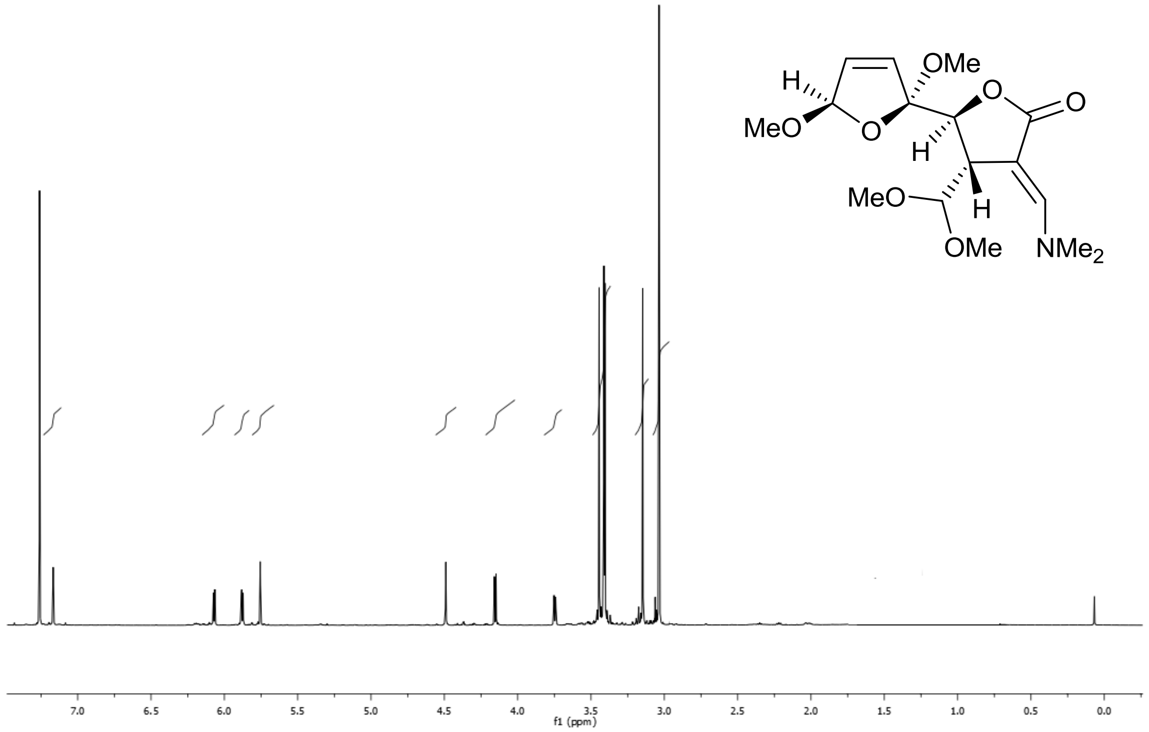


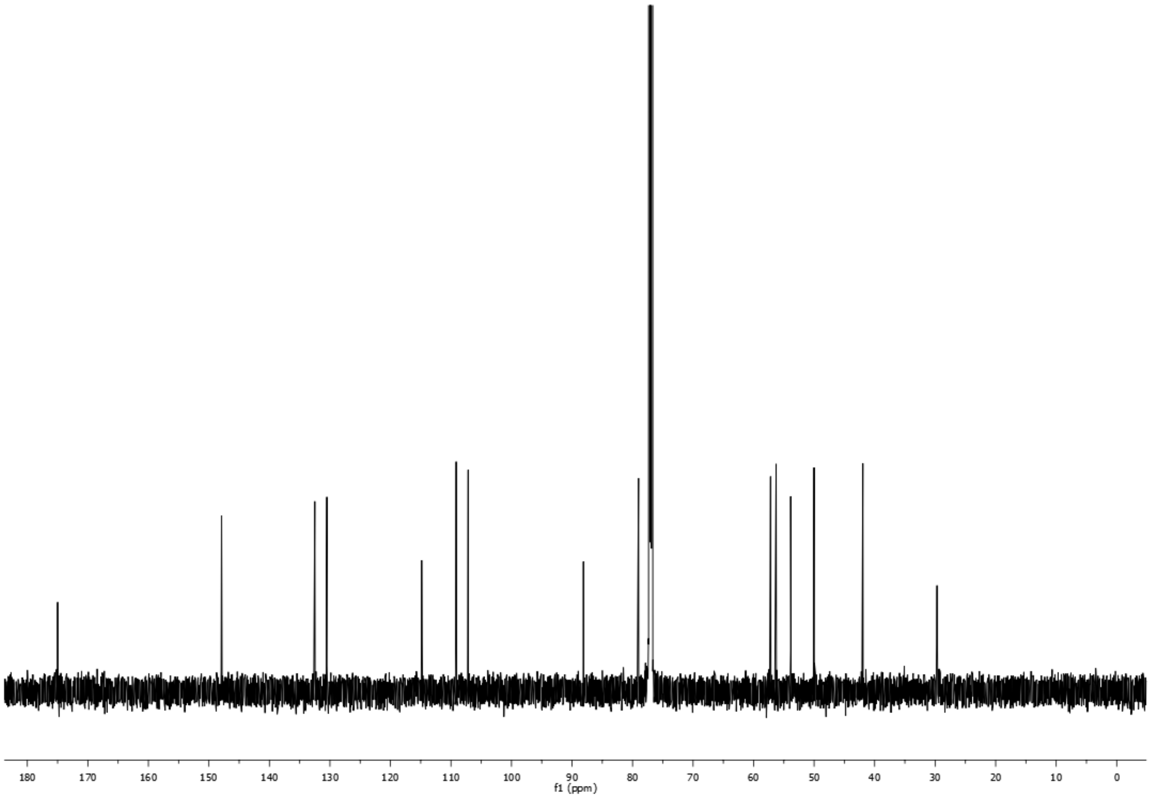
2D NOESY spectrum of 86c



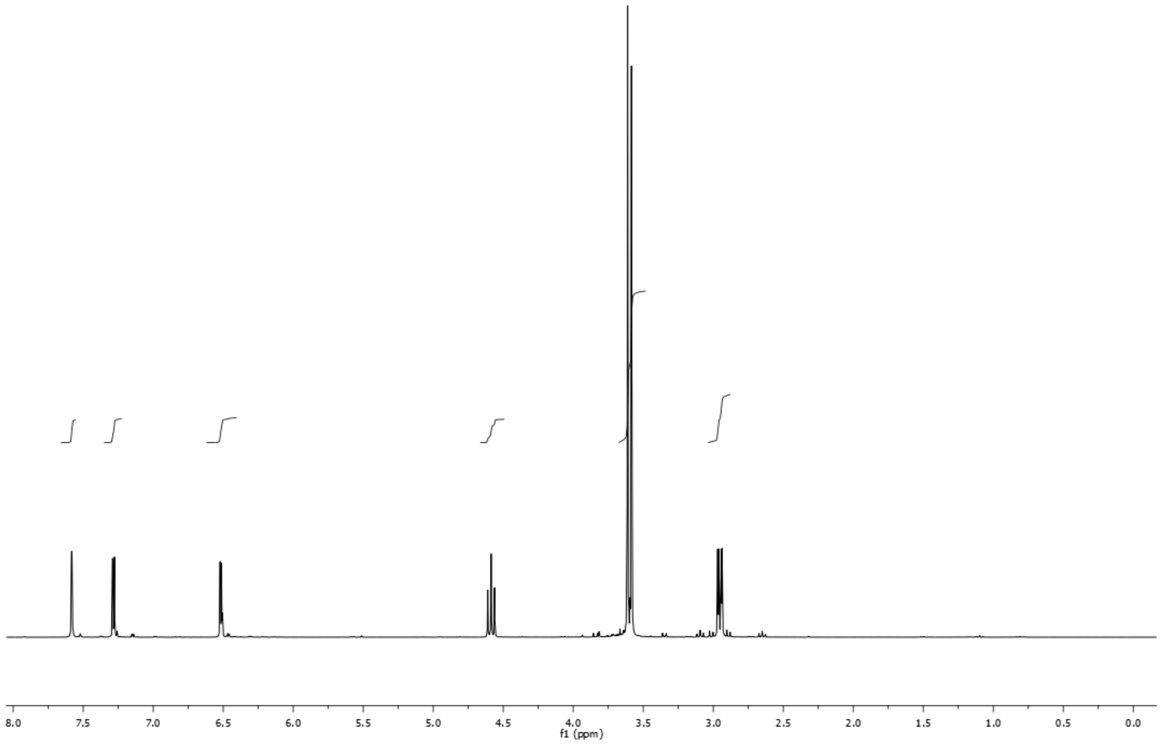
Key NOESY correlations in 86c

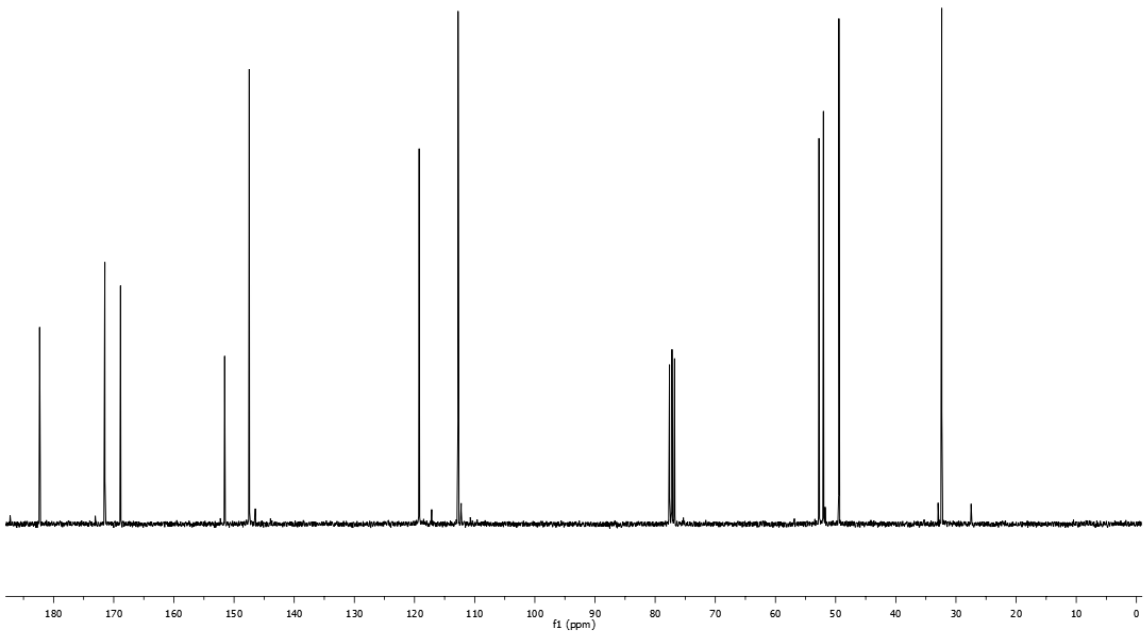
(*2S,3S,2'S,5'R*)-3-Dimethoxymethyl-4-dimethylaminomethylene-2',5'-dimethoxy-3,4,2',5'-tetrahydro-2H-[2,2']bifuranyl-5-one (87)



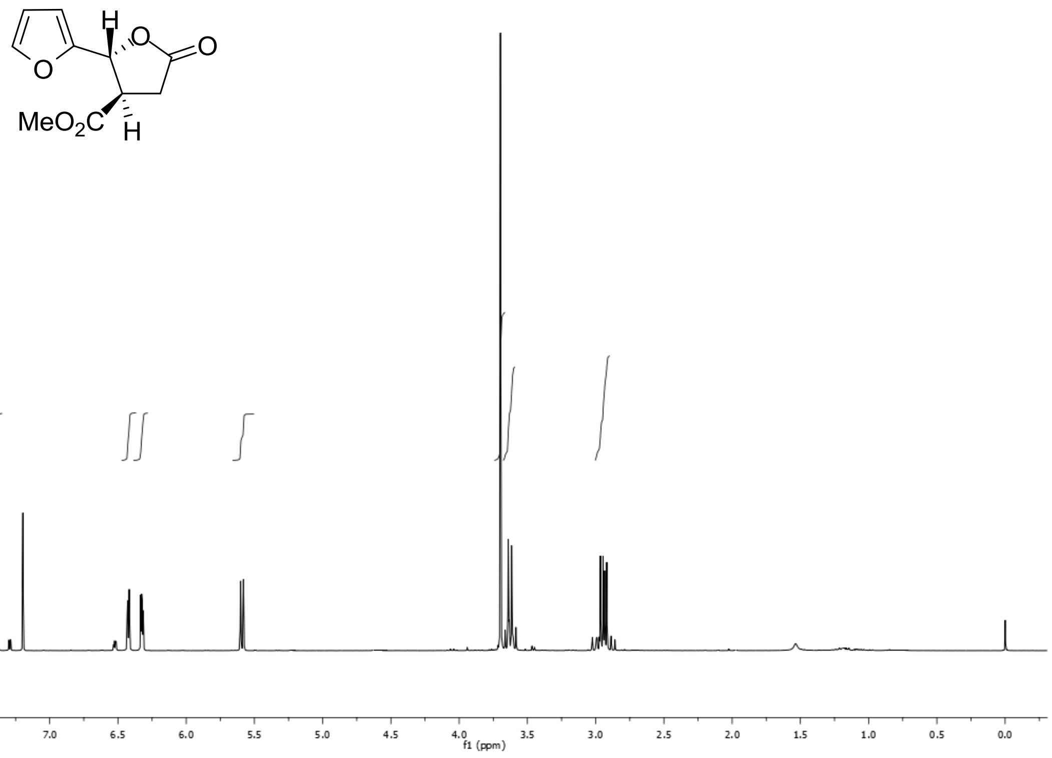


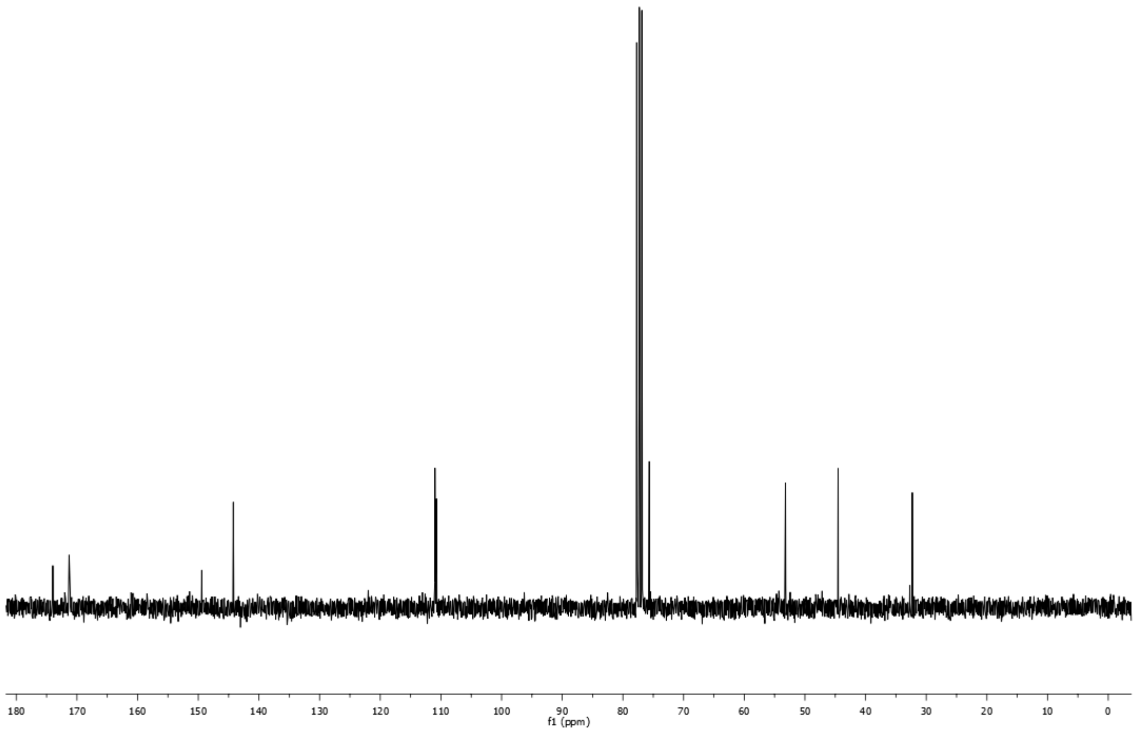
2-(Furan-2-carbonyl)-succinic acid dimethyl ester (94)



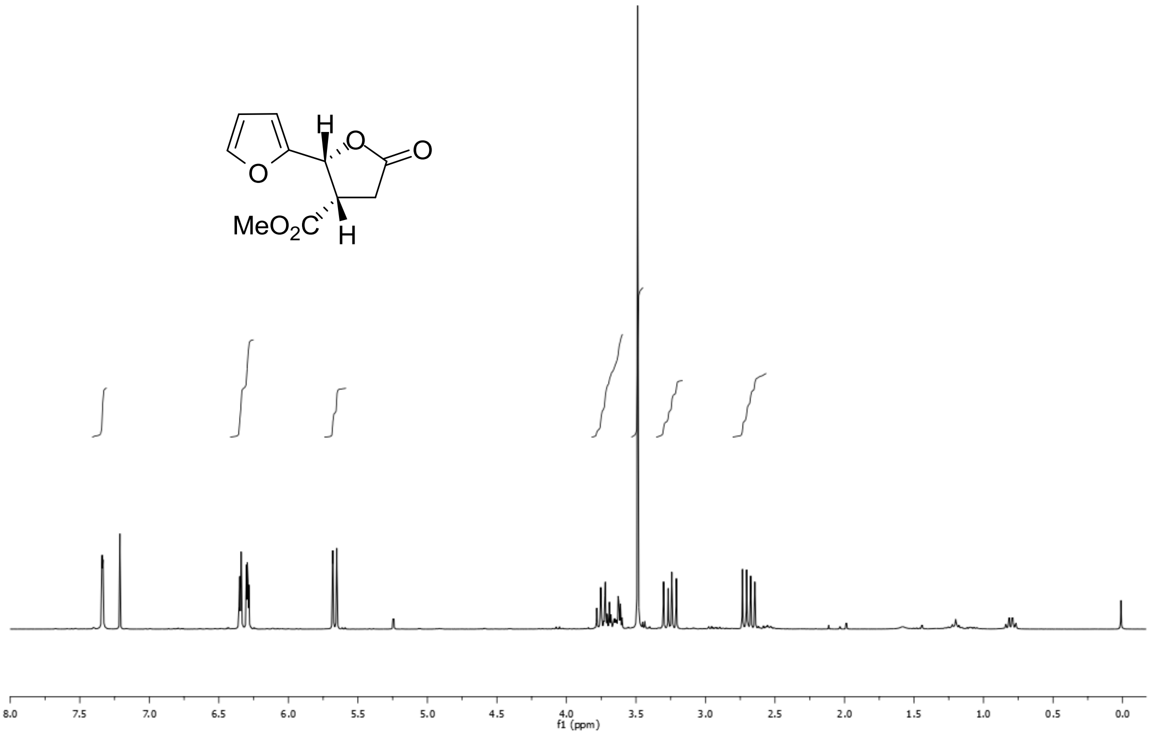


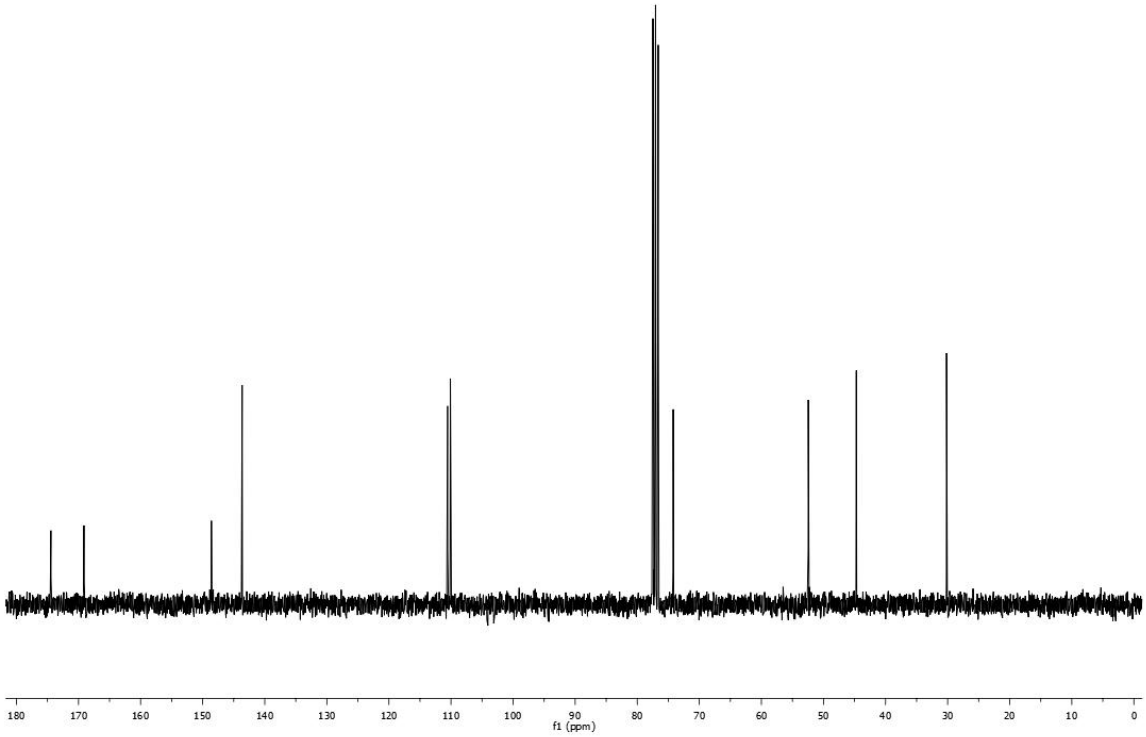
(2R,3R)-5-Oxo-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carboxylic acid methyl ester (trans-93)



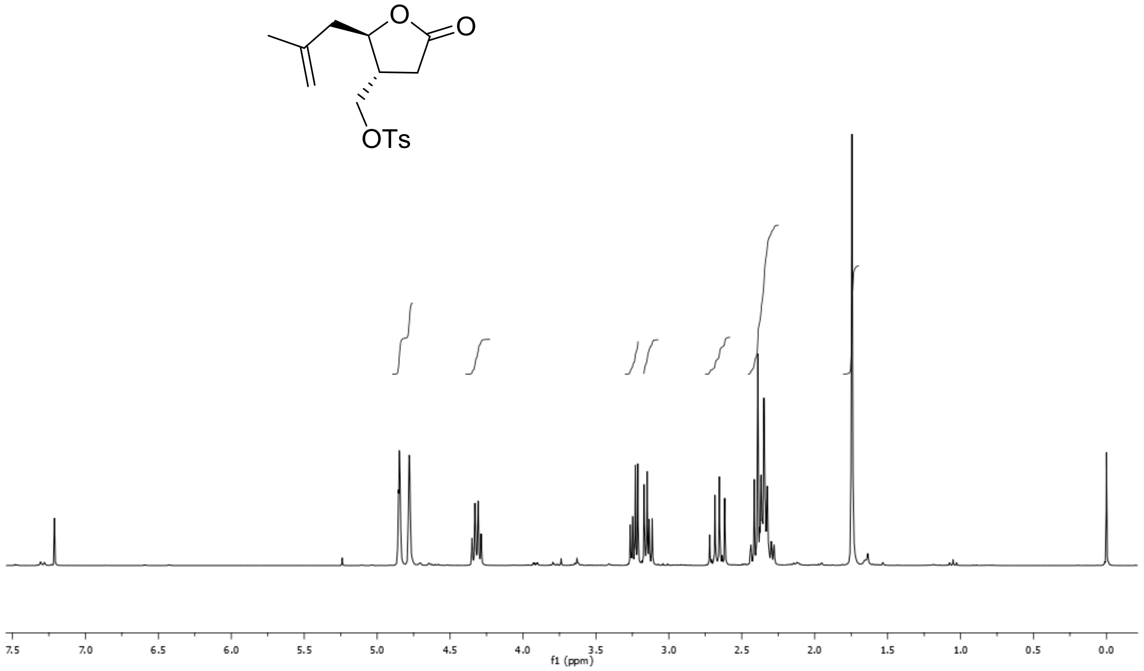


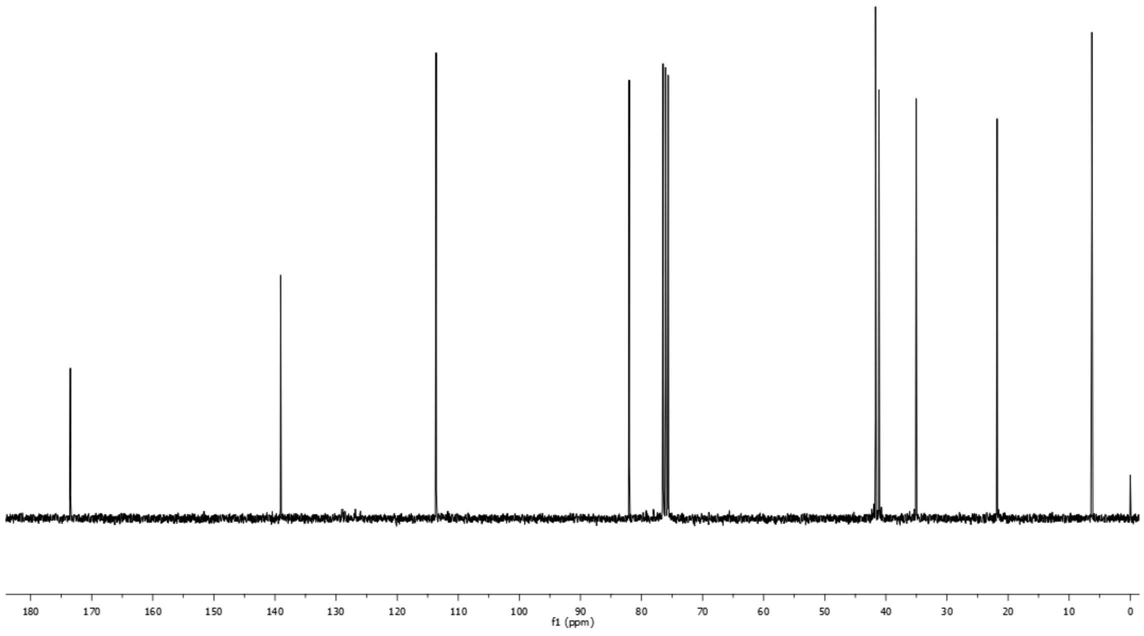
(2R,3S)-5-Oxo-2,3,4,5-tetrahydro-[2,2']bifuranyl-3-carboxylic acid methyl ester (cis-93)



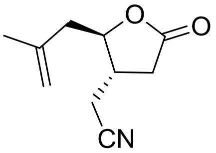


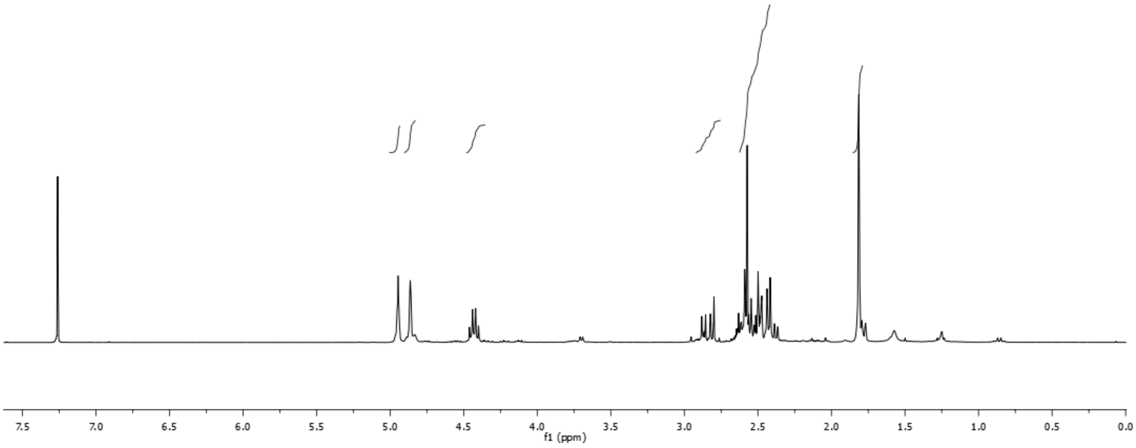
Benzenesulfonic acid (2R,3R)-2-(2-methyl-allyl)-5-oxo-tetrahydro-furan-3-ylmethyl ester (124)

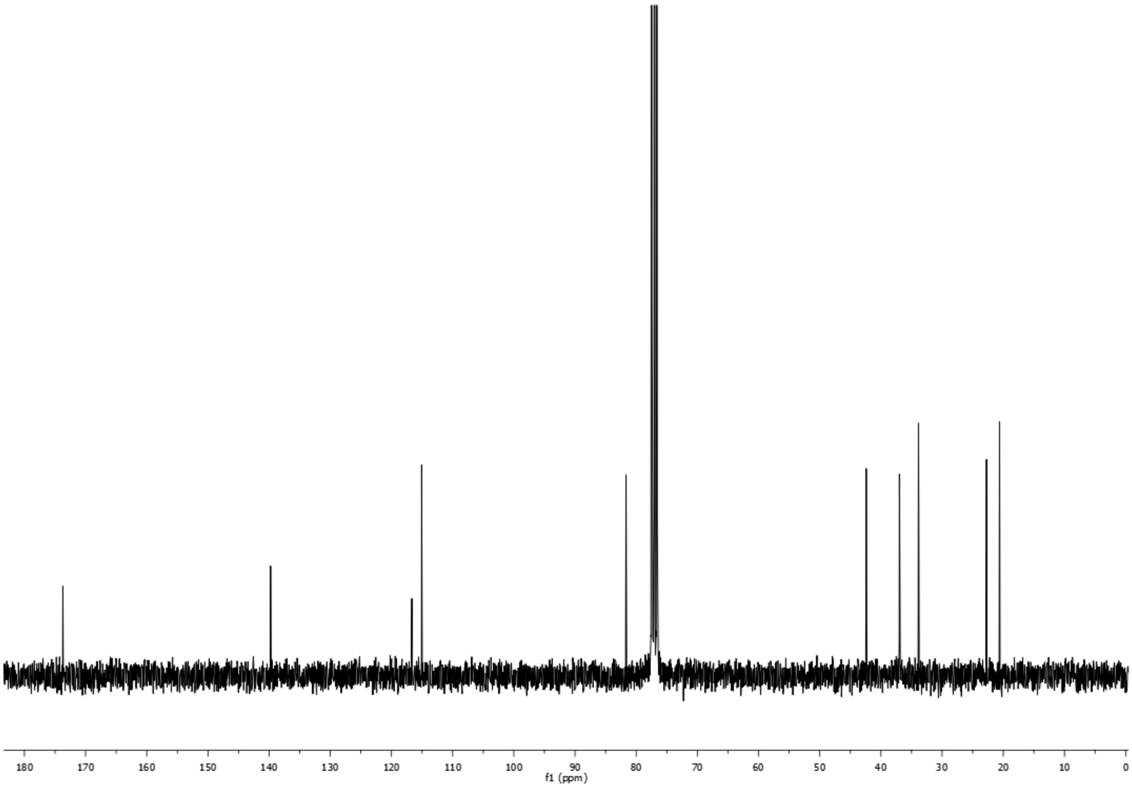




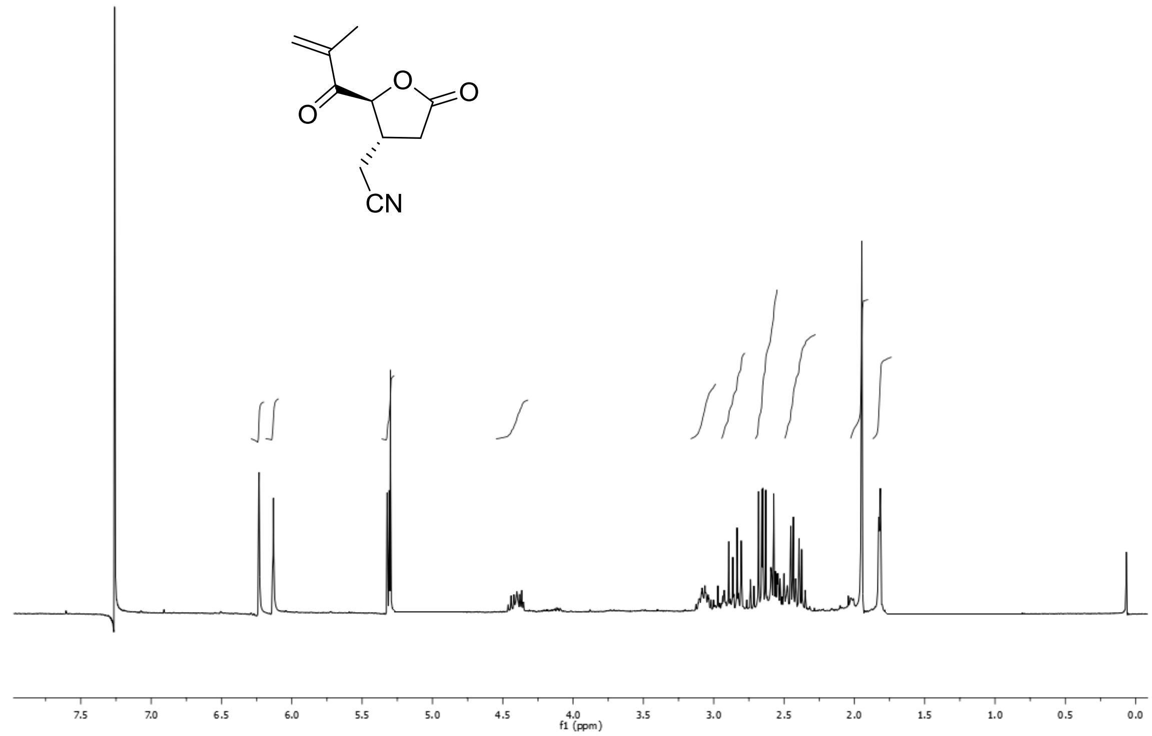
[(2R,3S)-2-(2-Methyl-allyl)-5-oxo-tetrahydro-furan-3-yl]-acetonitrile (125)

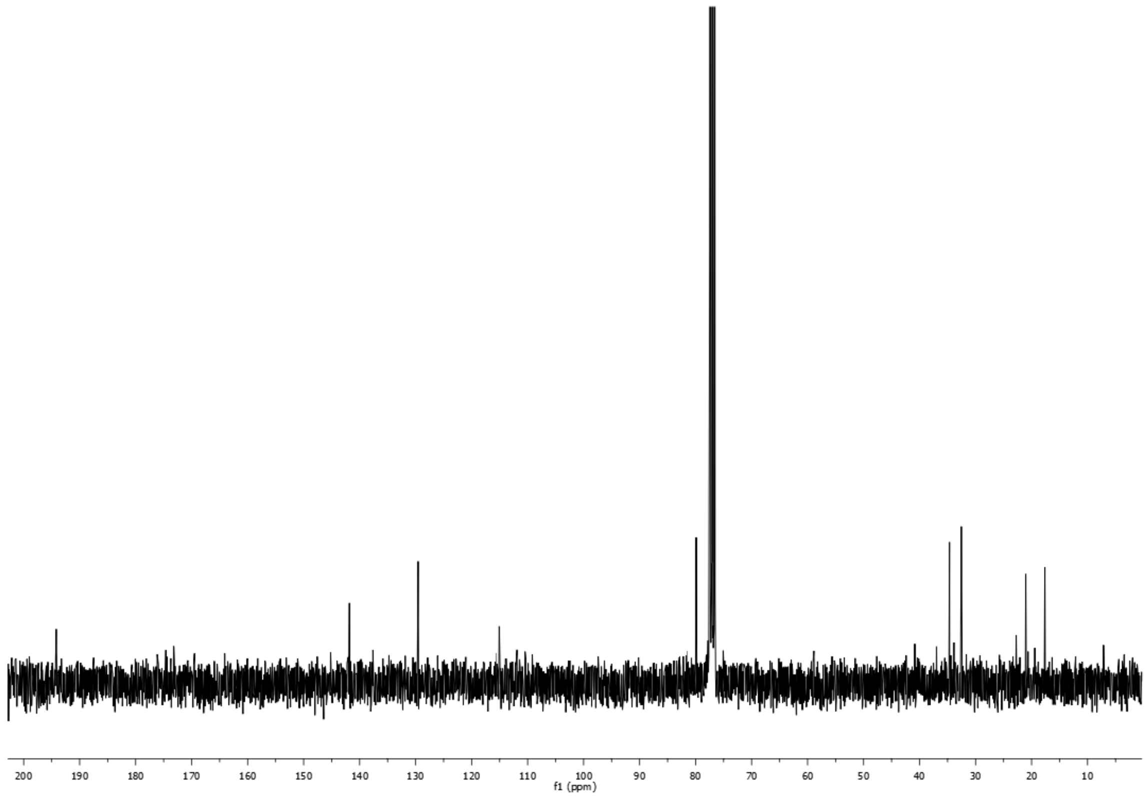




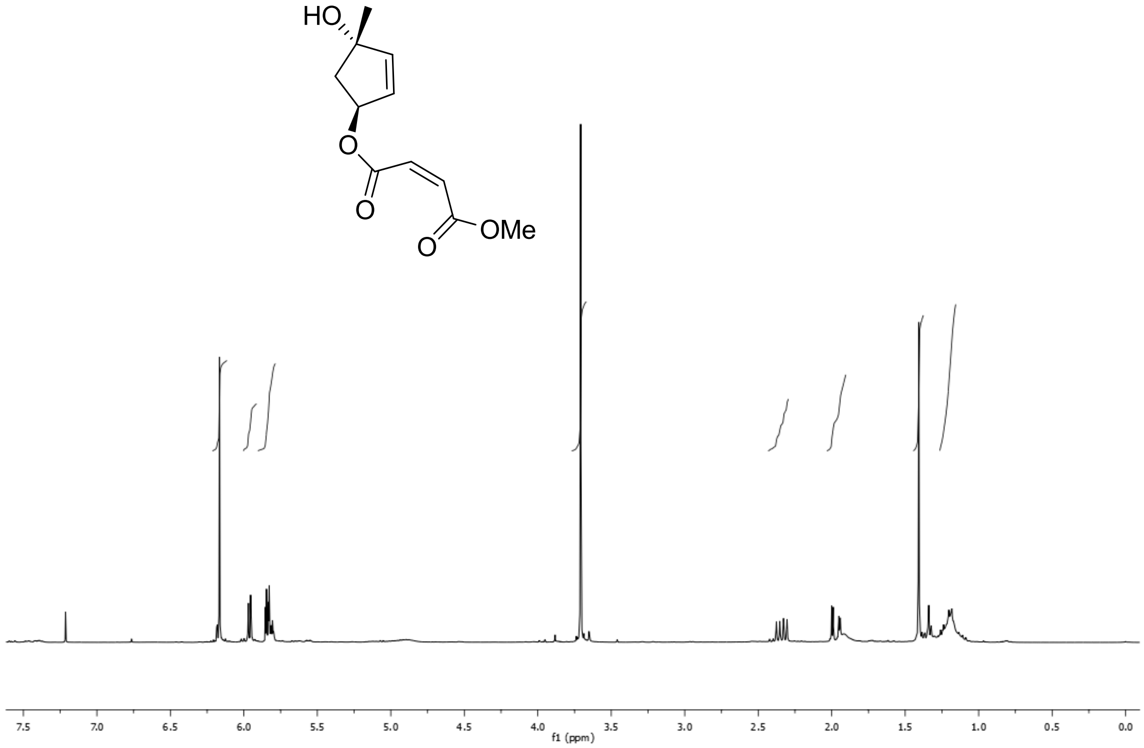


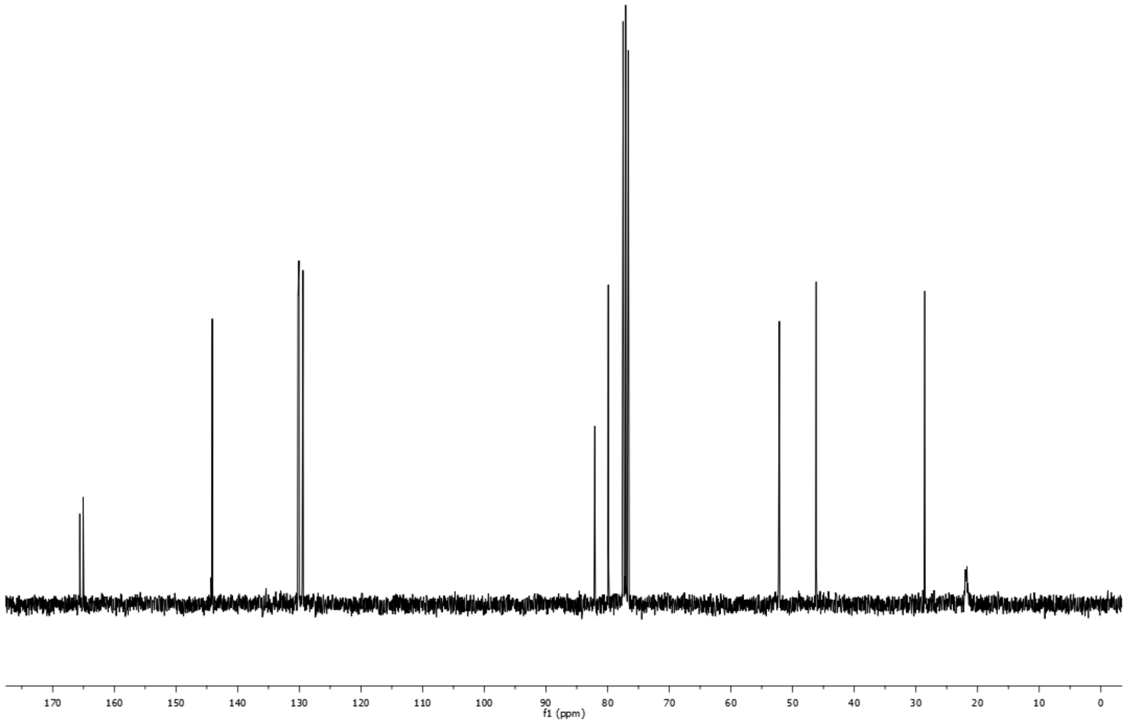
[(2S,3S)-2-(2-Methyl-acryloyl)-5-oxo-tetrahydro-furan-3-yl]-acetonitrile (126)





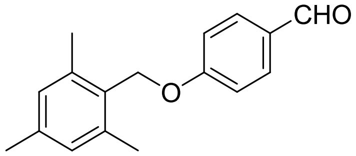
(Z)-But-2-enedioic acid (1S,4S)-4-hydroxy-4-methyl-cyclopent-2-enyl ester methyl ester (119)

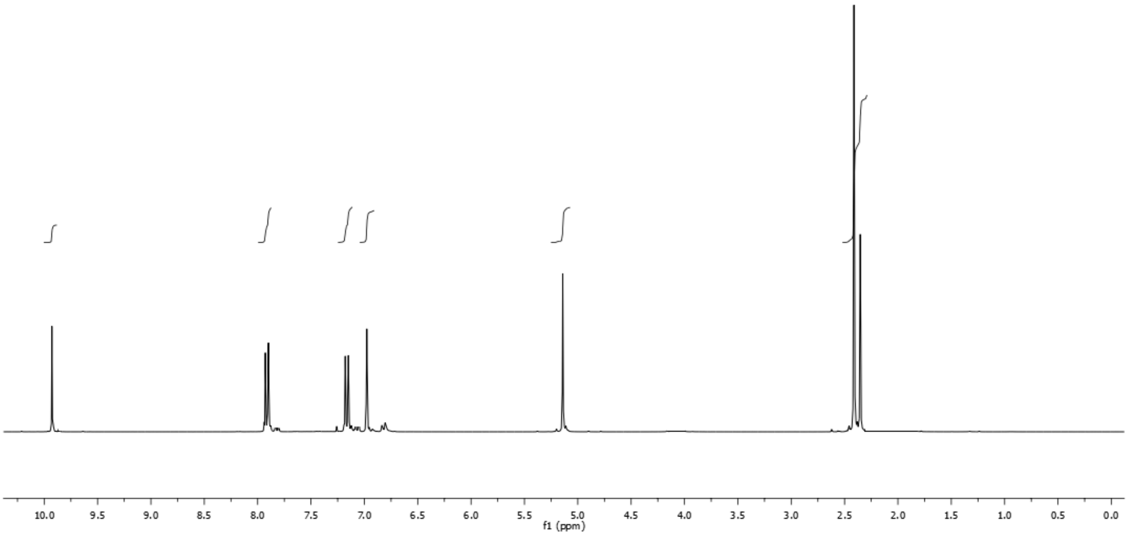


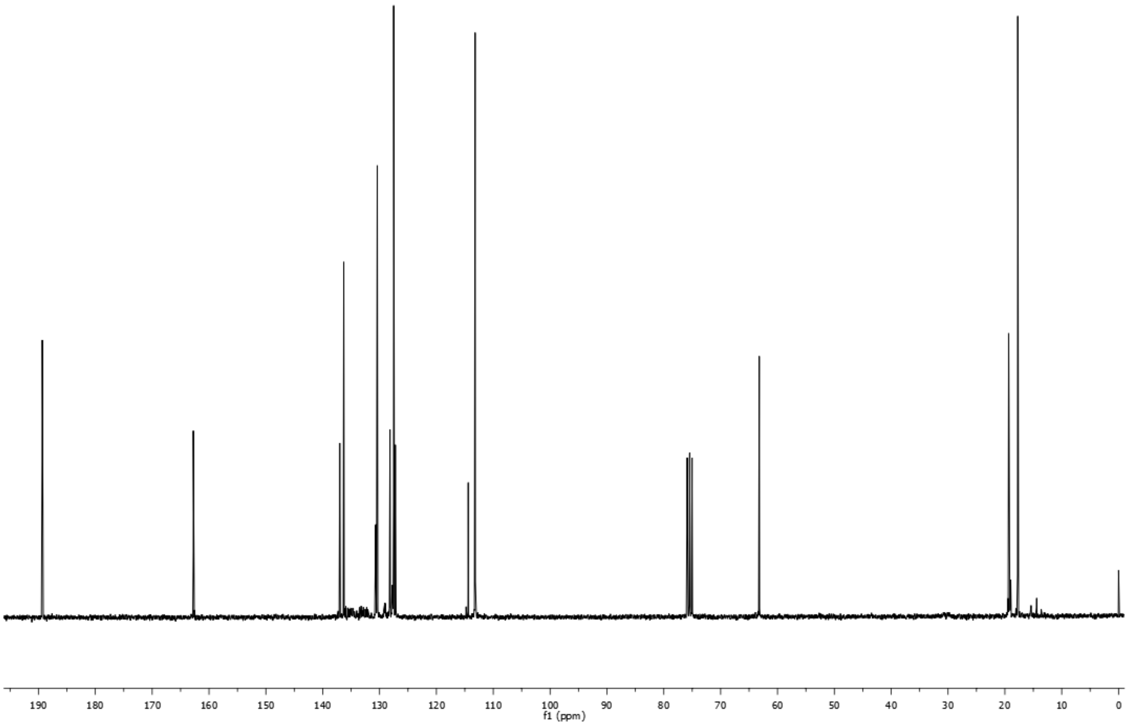


1.2 Spectra of compounds from Chapter C

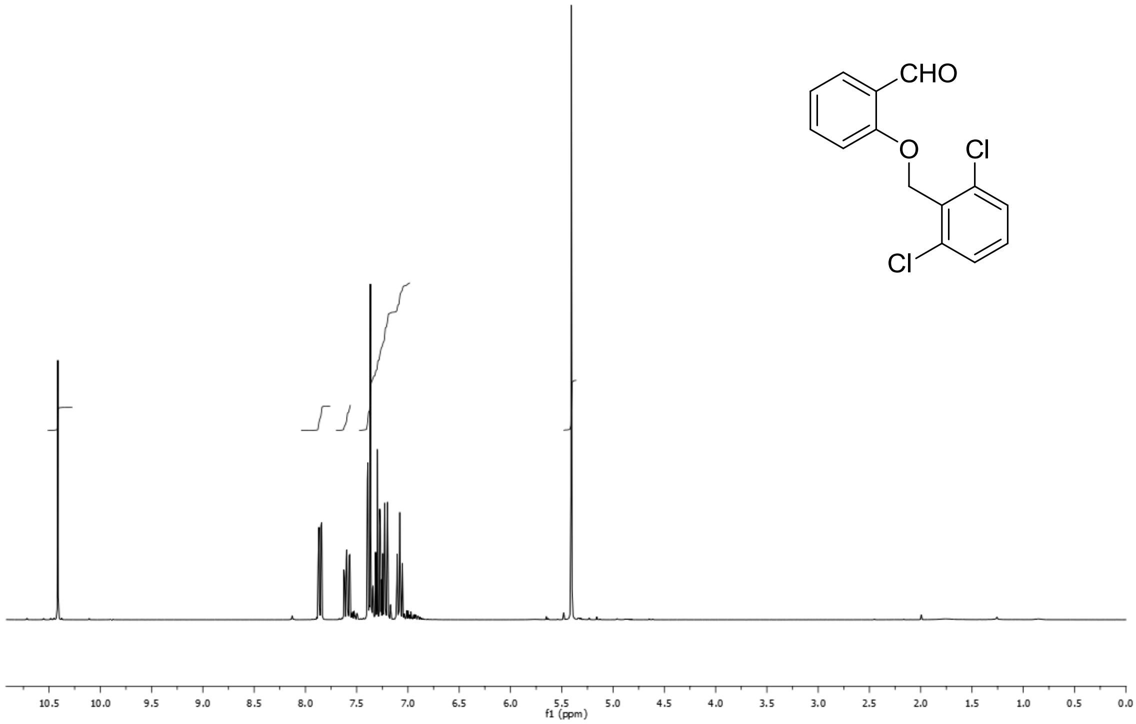
4-(2,4,6-Trimethyl-benzyloxy)-benzaldehyde (2i)

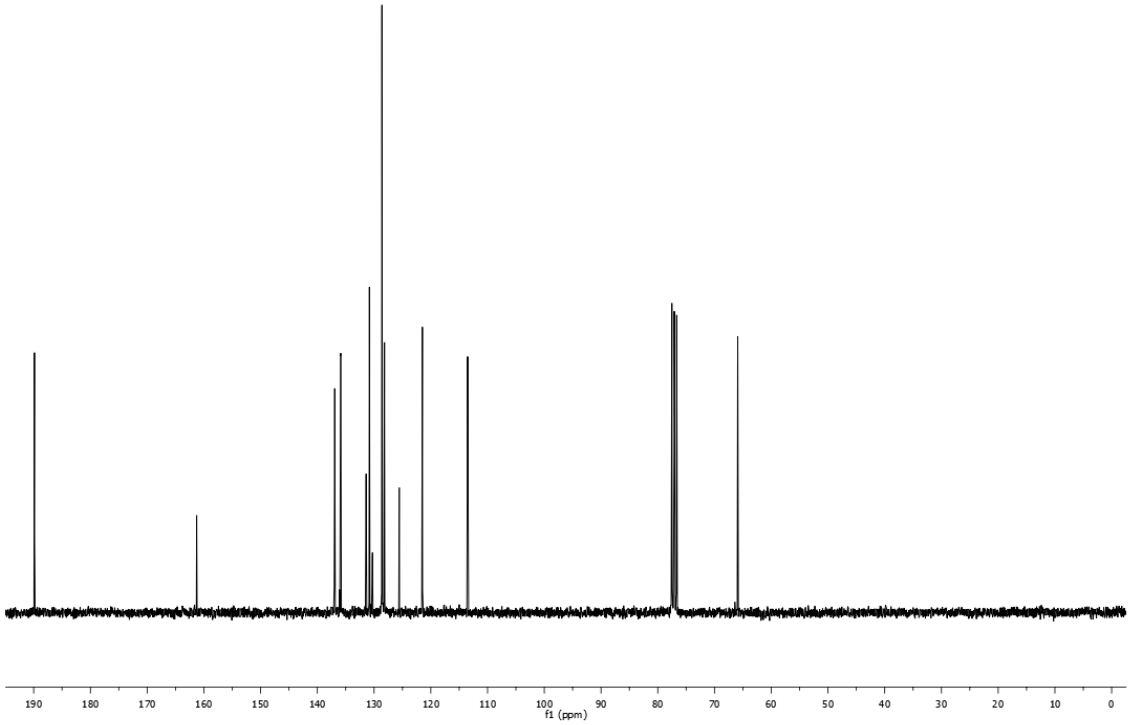




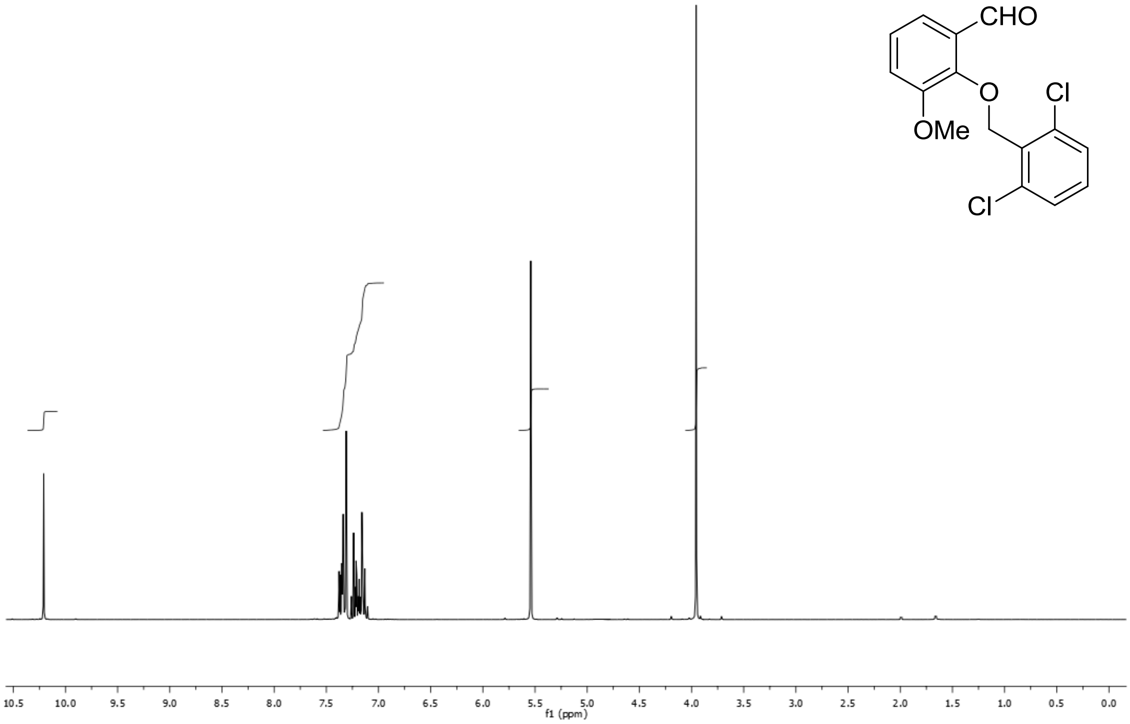


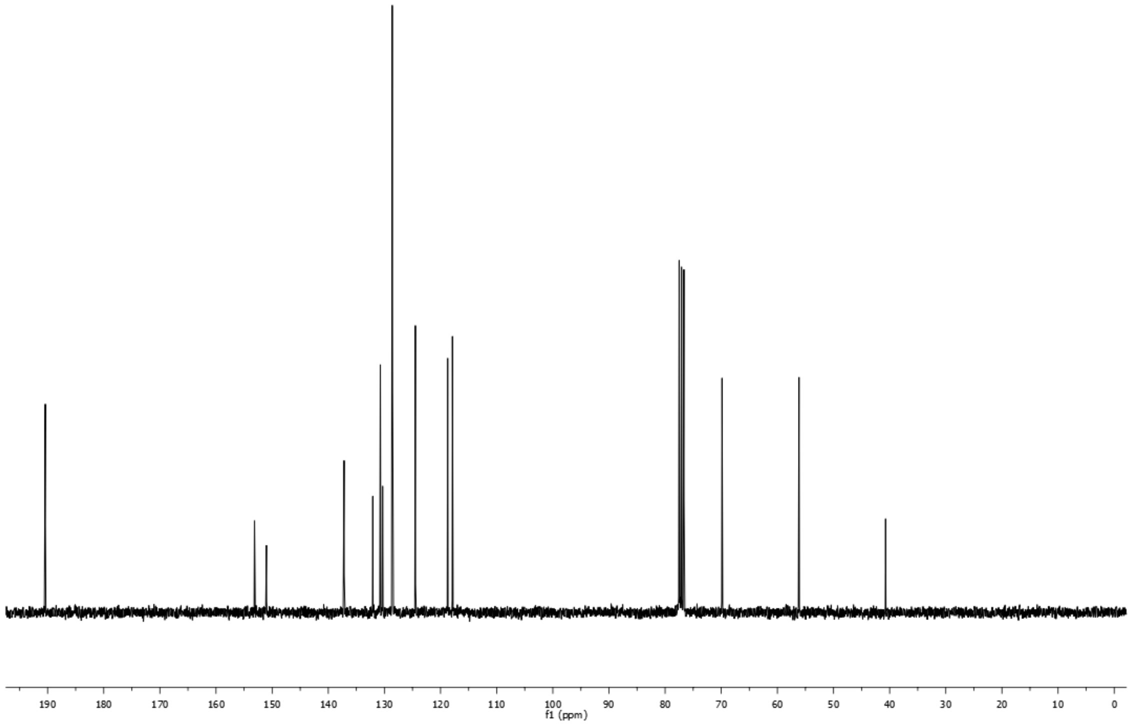
2-(2,6-Dichloro-benzyloxy)-benzaldehyde (3a)



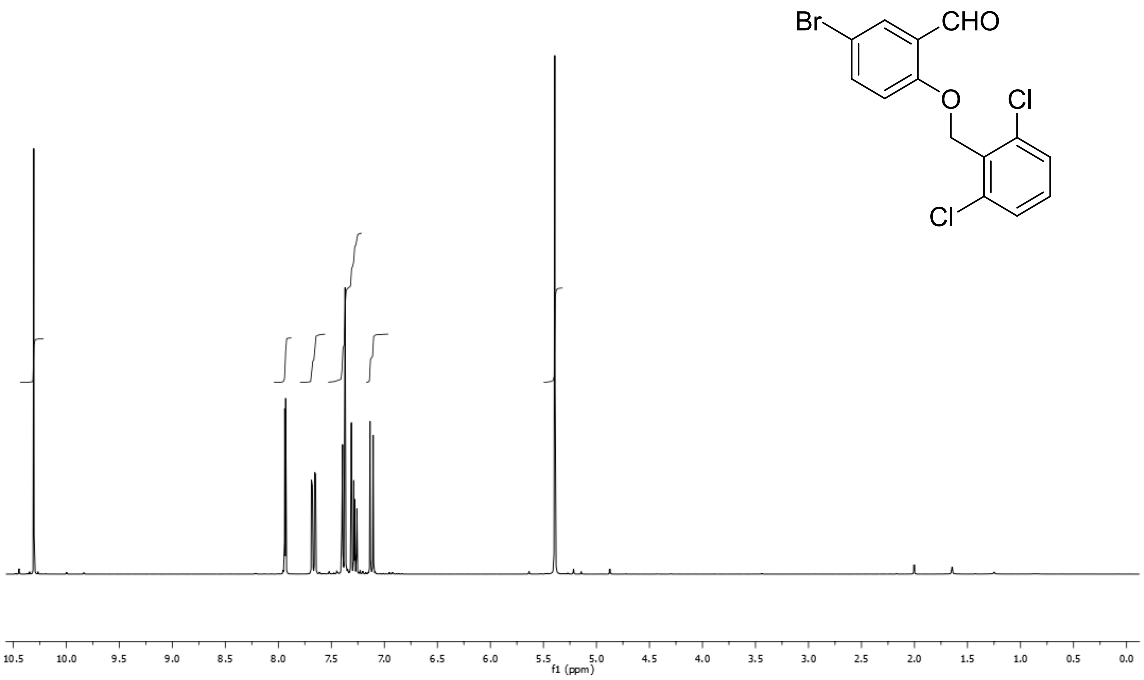


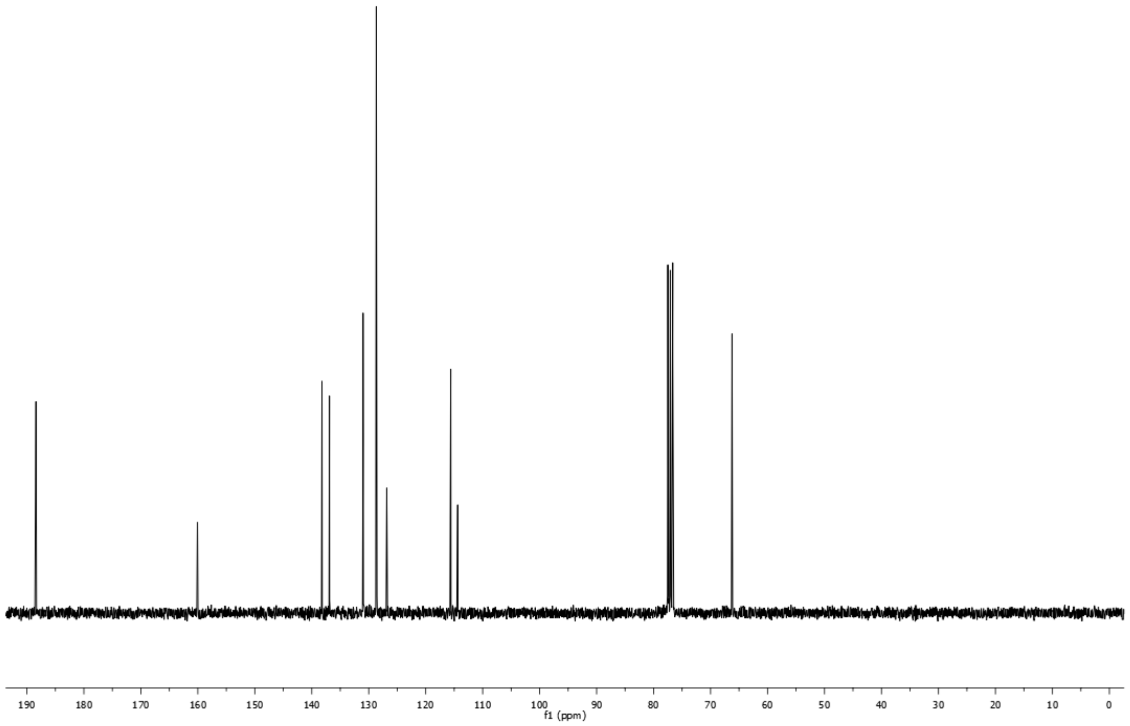
2-(2,6-Dichloro-benzyloxy)-3-methoxy-benzaldehyde (3b)



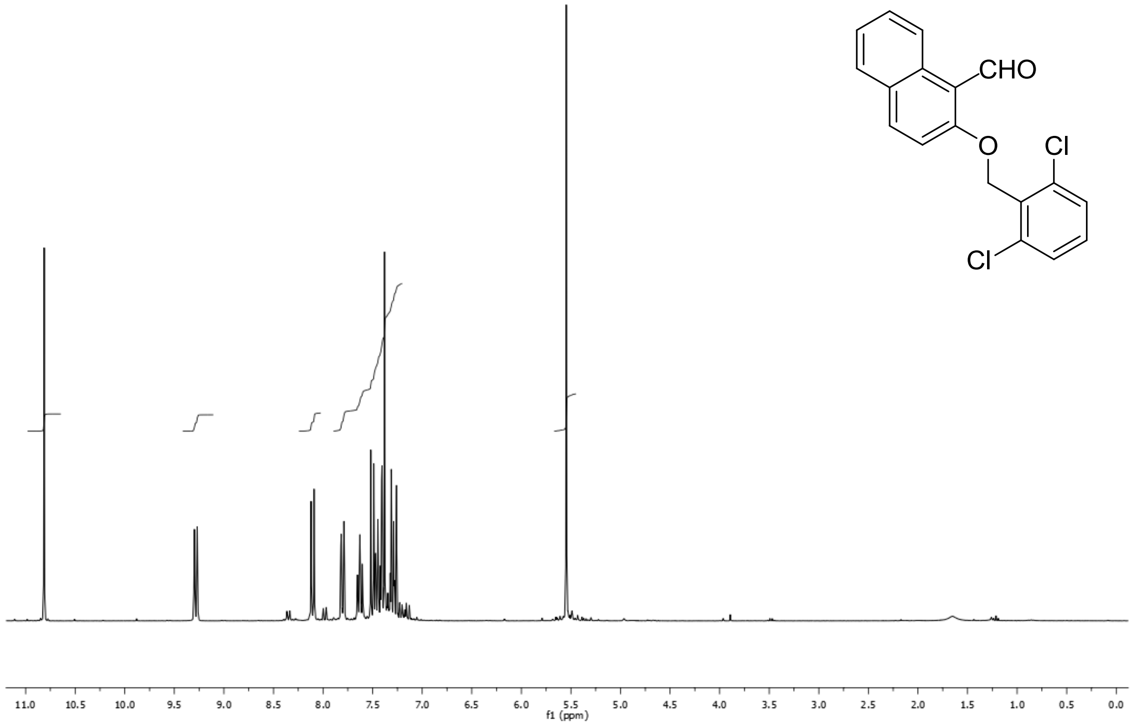


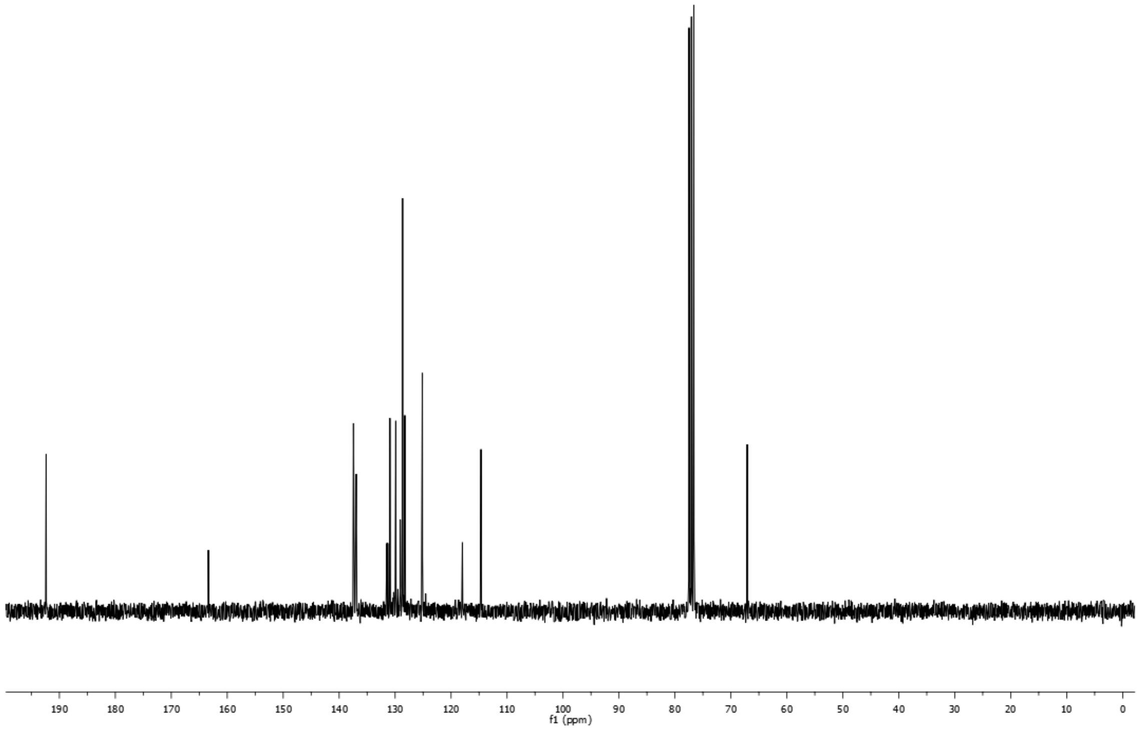
5-Bromo-2-(2,6-dichloro-benzyloxy)-benzaldehyde (3c)



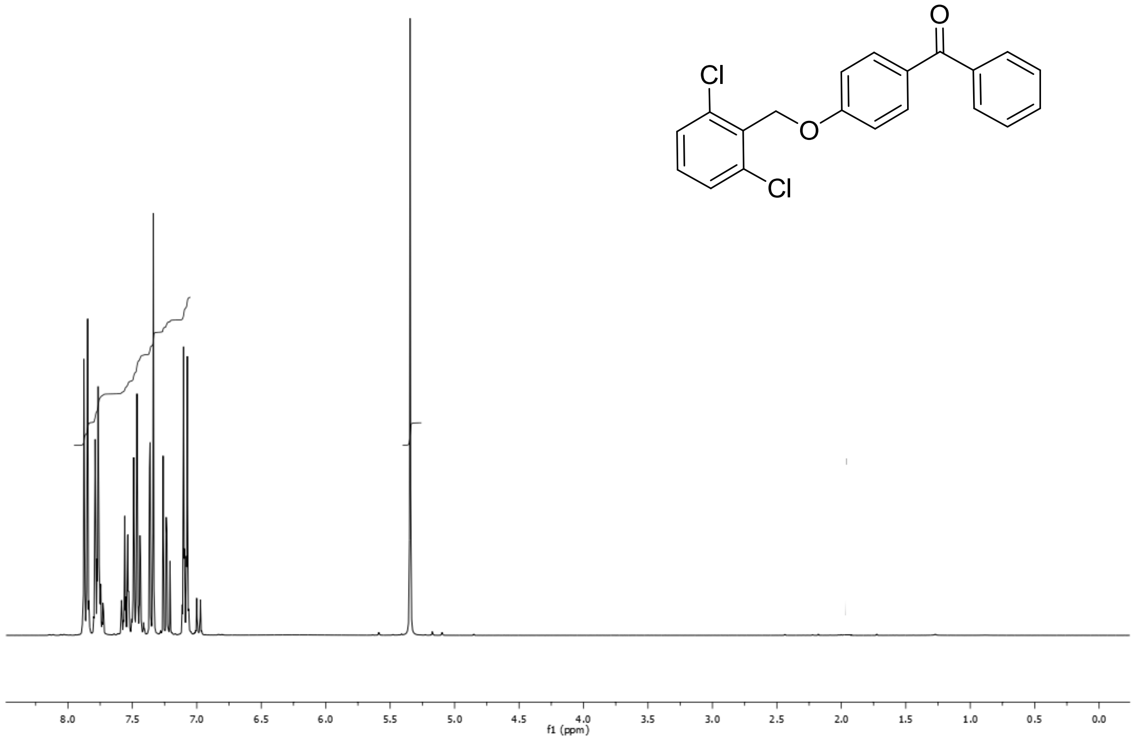


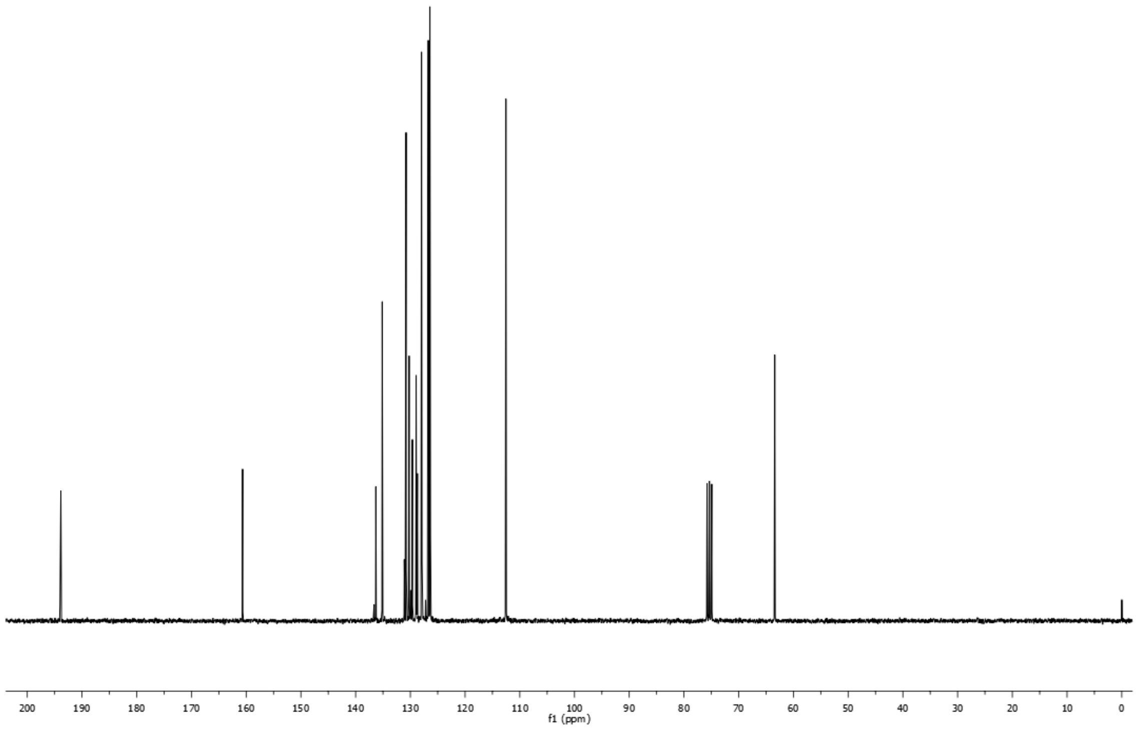
2-(2,6-Dichloro-benzyloxy)-naphthalene-1-carbaldehyde (3d)



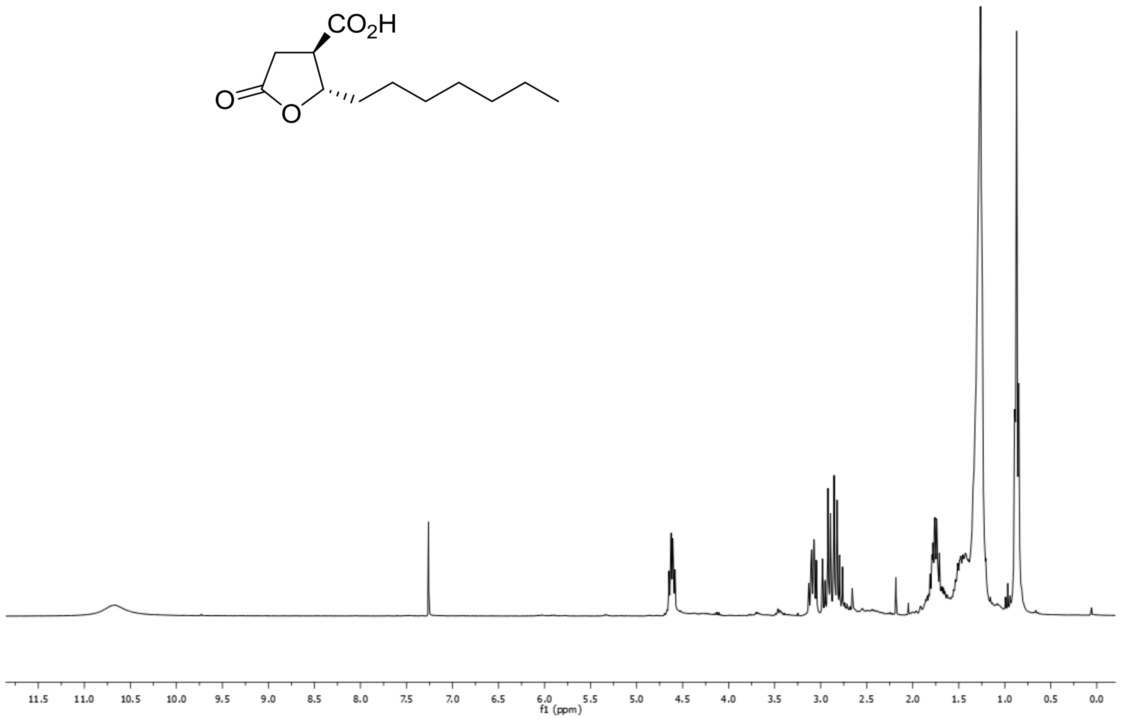


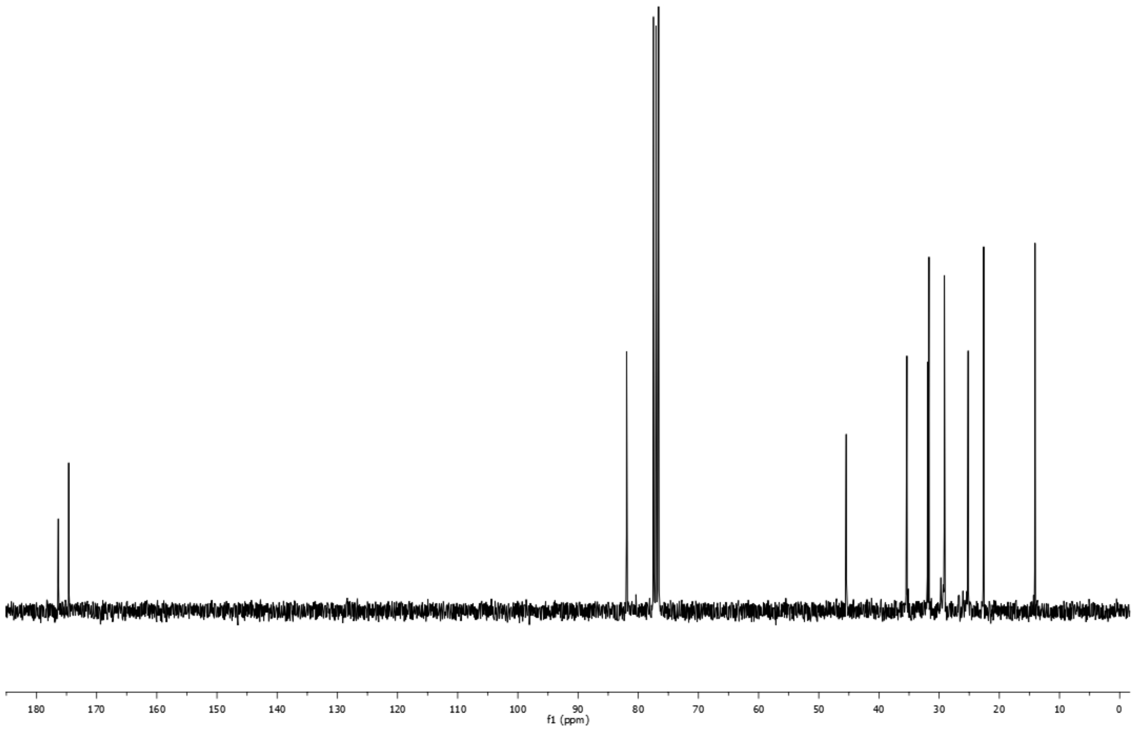
[4-(2,6-Dichloro-benzyloxy)-phenyl]-phenyl-methanone (20)



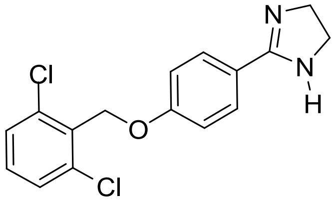


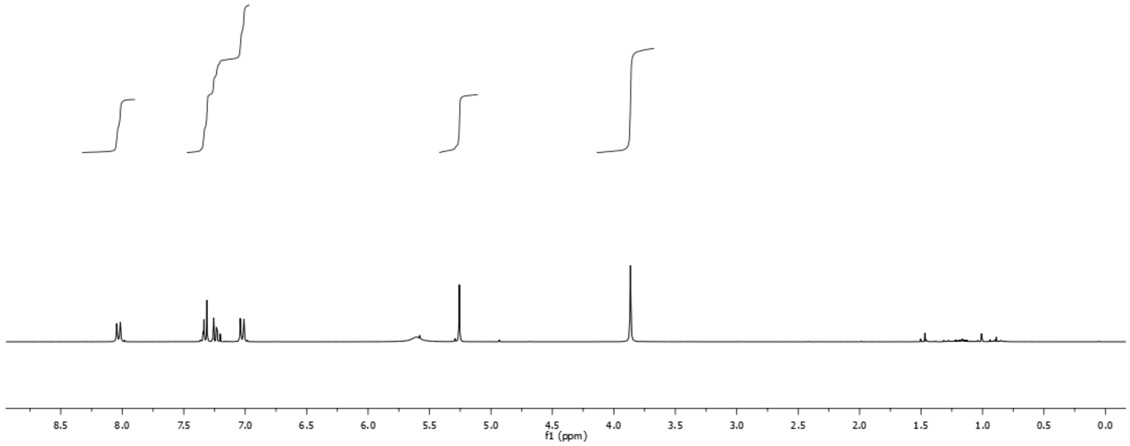
(2R,3S)-2-Heptyl-5-oxo-tetrahydro-furan-3-carboxylic acid (5)

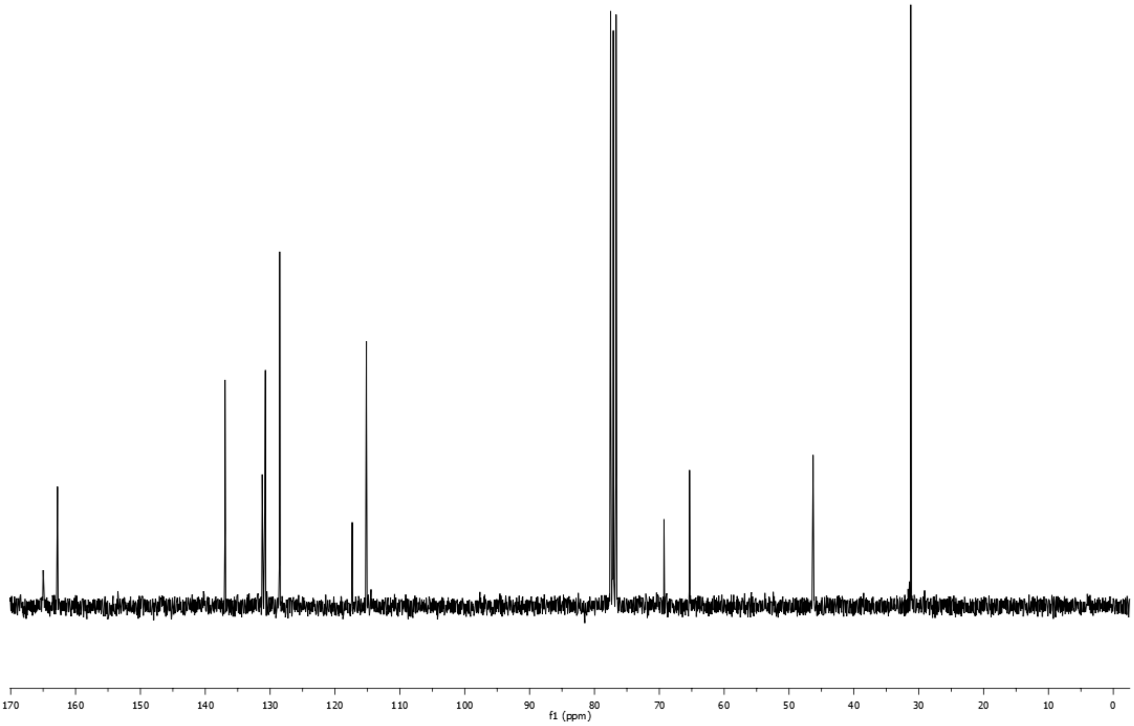




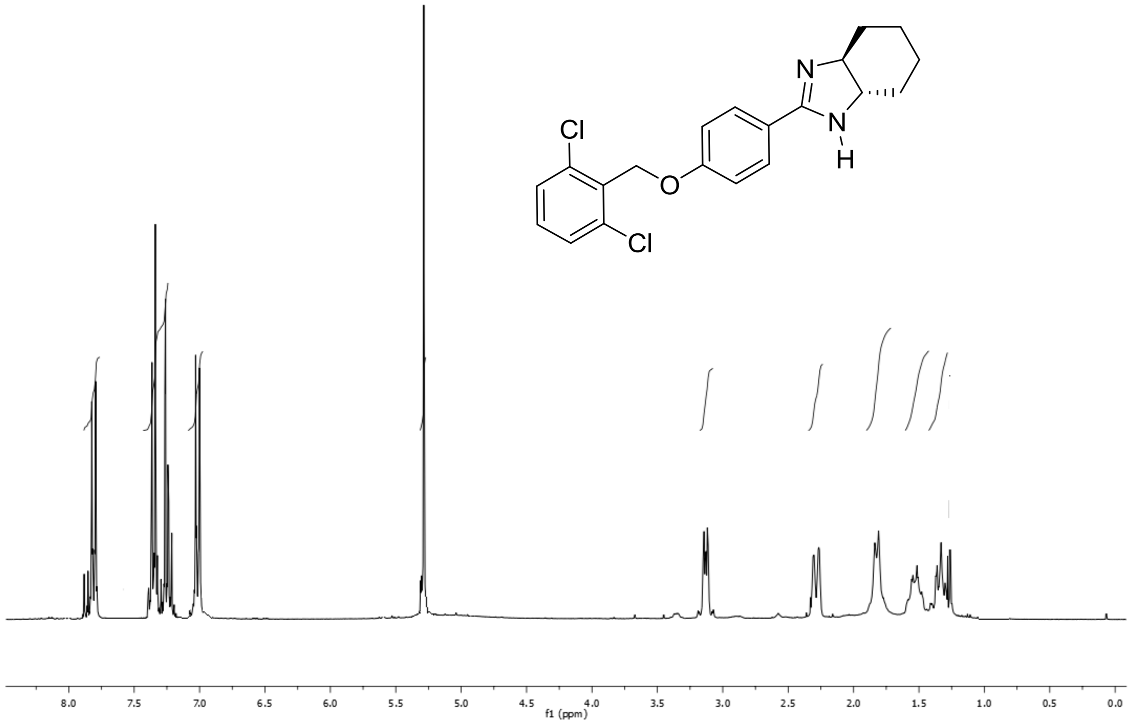
2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-4,5-dihydro-1H-imidazole (4a)

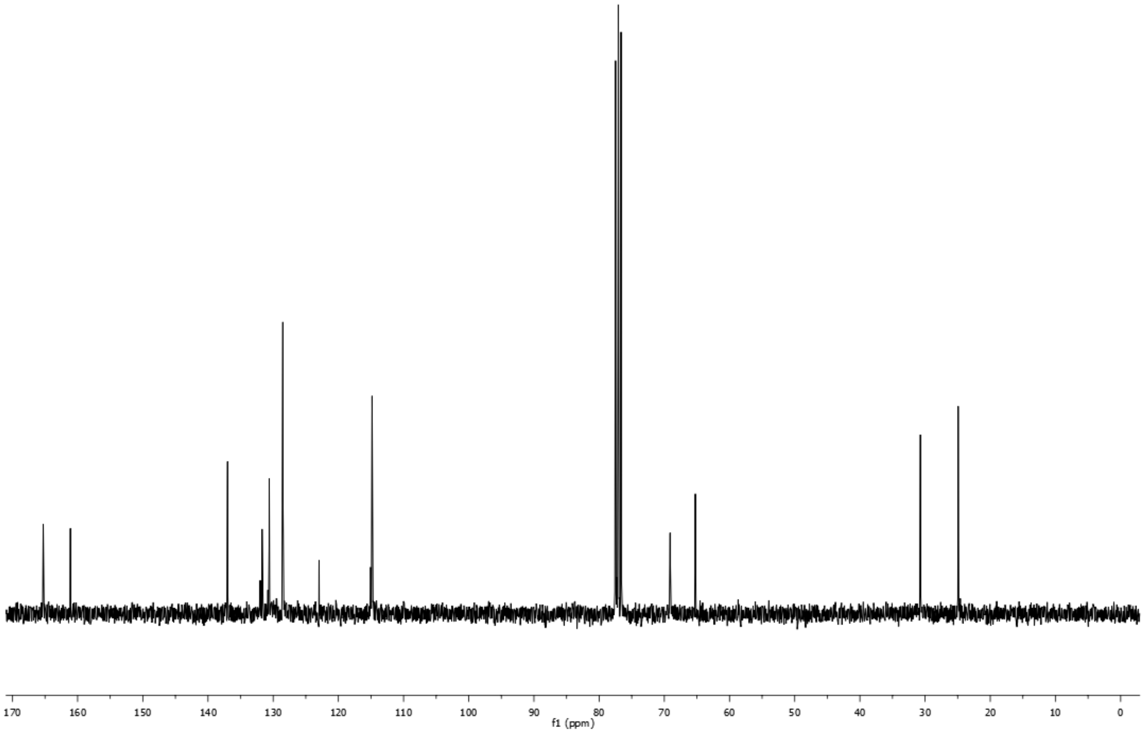




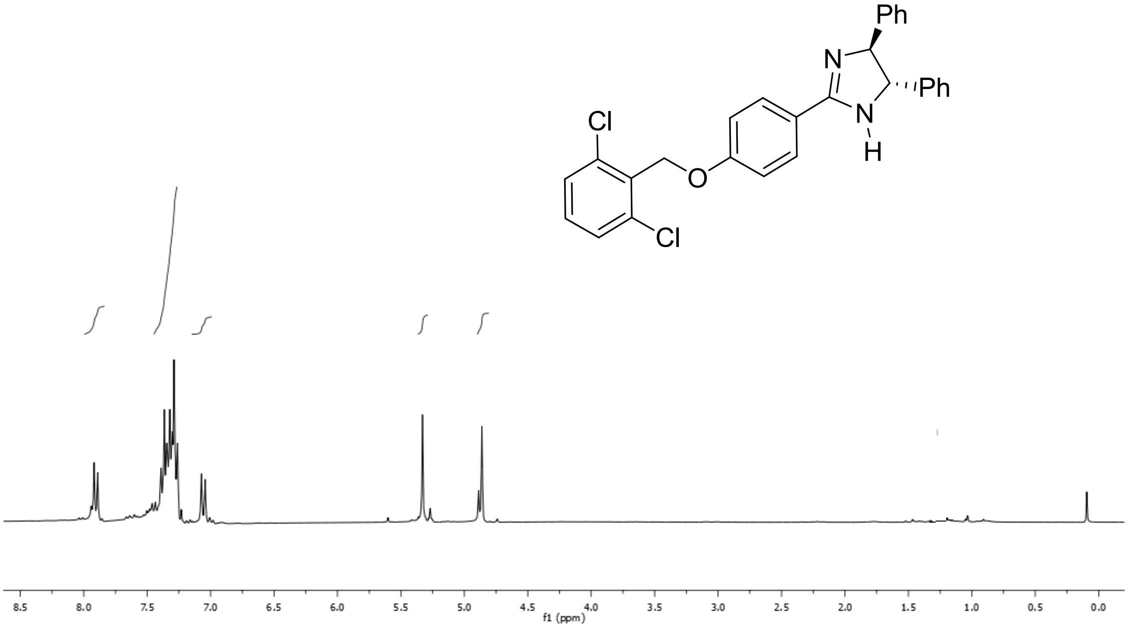


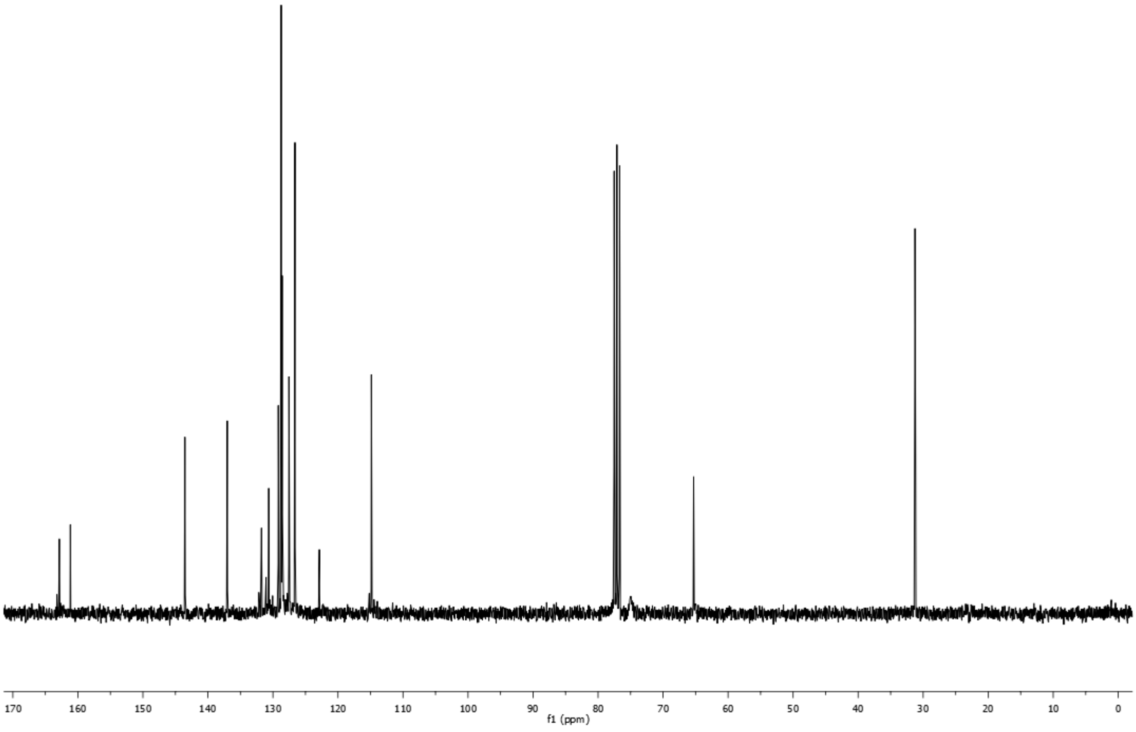
(7S,7aS)-2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-3a,4,5,6,7,7a-hexahydro-1H-benzoimidazole (4b)



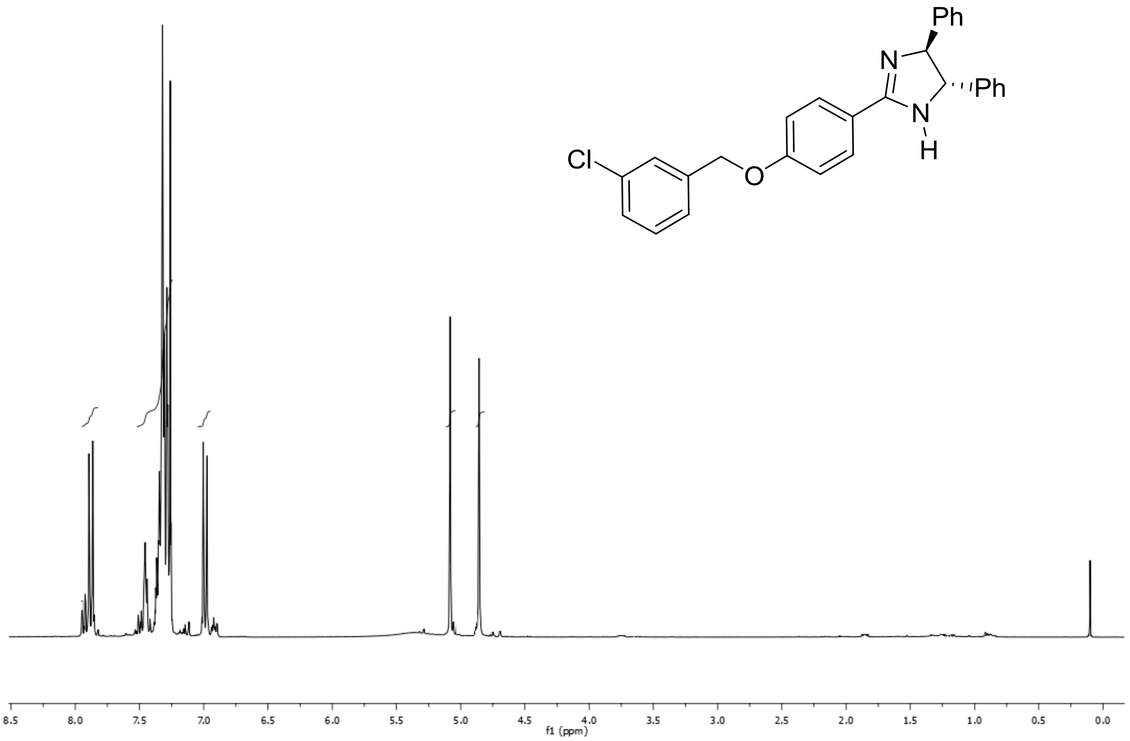


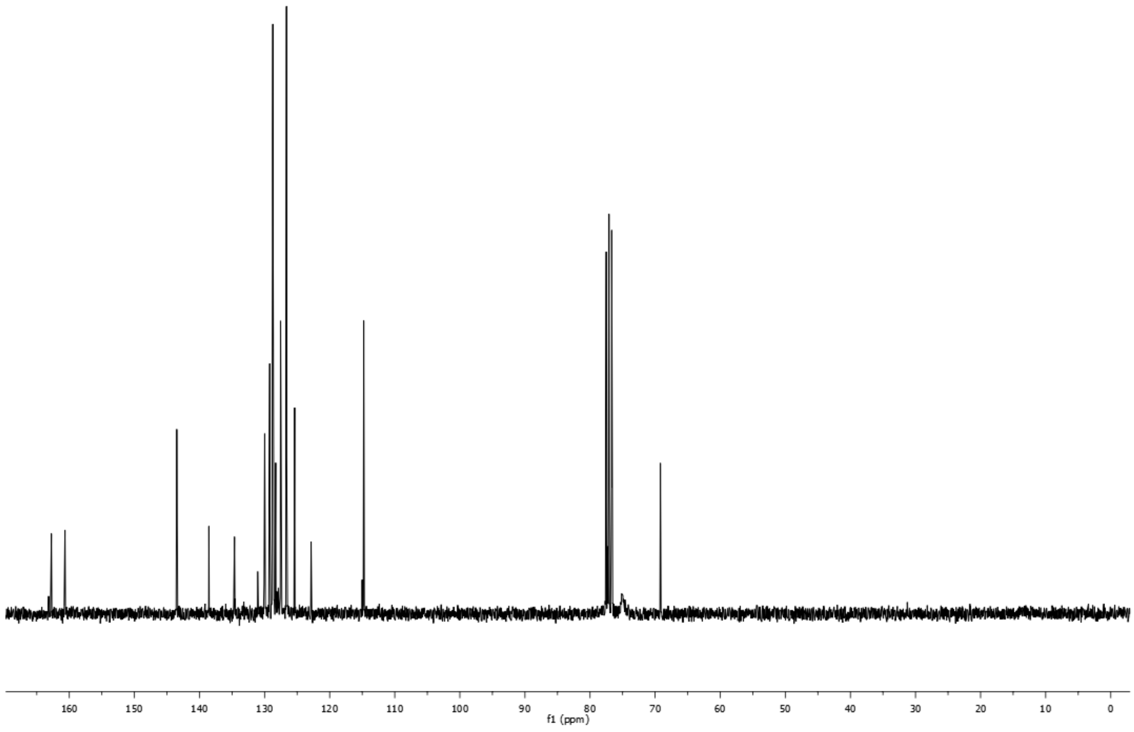
(S)-2-[4-(2,6-Dichloro-benzyloxy)-phenyl]-5-phenyl-4-(R)-phenyl-4,5-dihydro-1H-imidazole (4c)



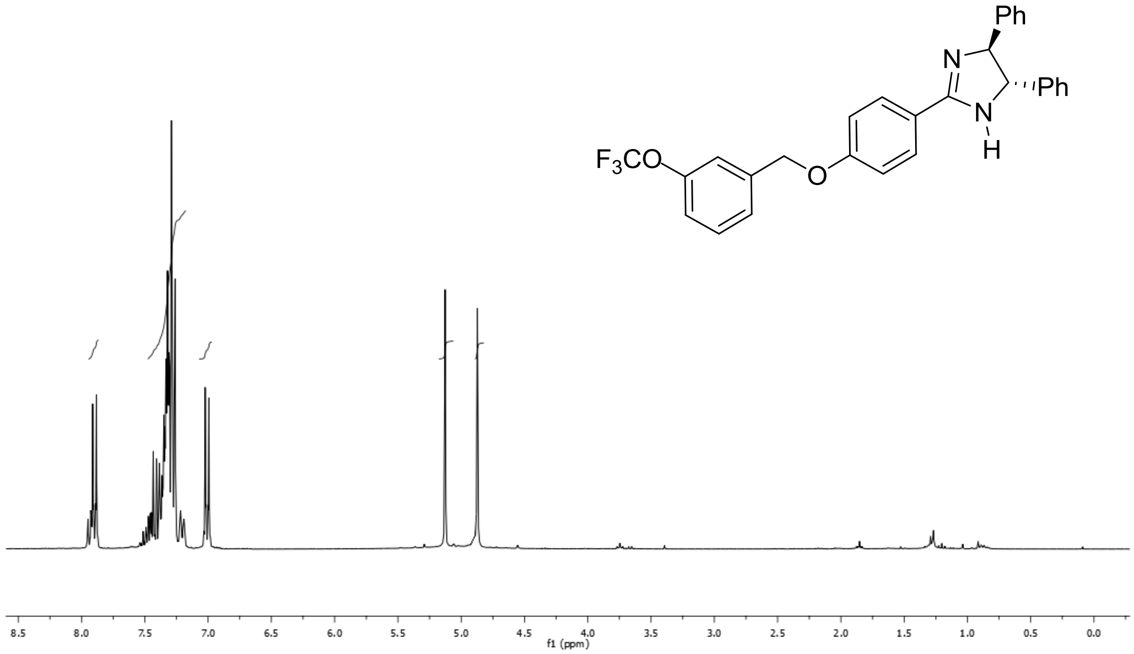


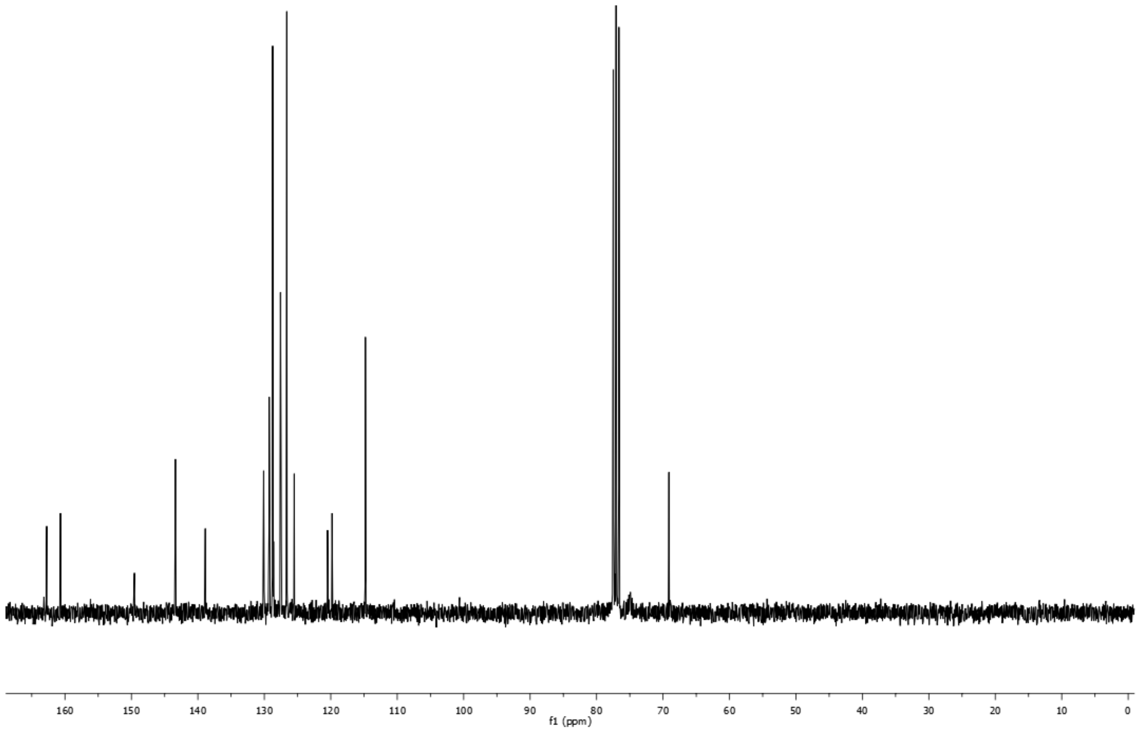
(S)-2-[4-(3-Chloro-benzyloxy)-phenyl]-5-phenyl-4-(R)-phenyl-4,5-dihydro-1H-imidazole (4d)



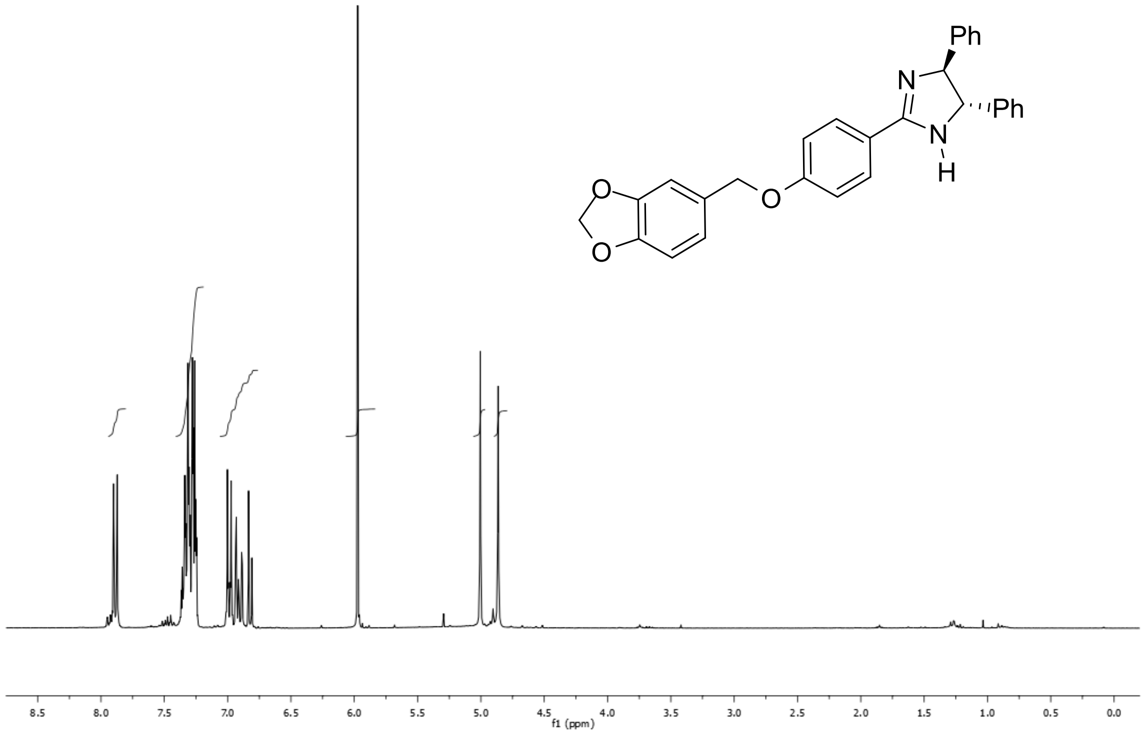


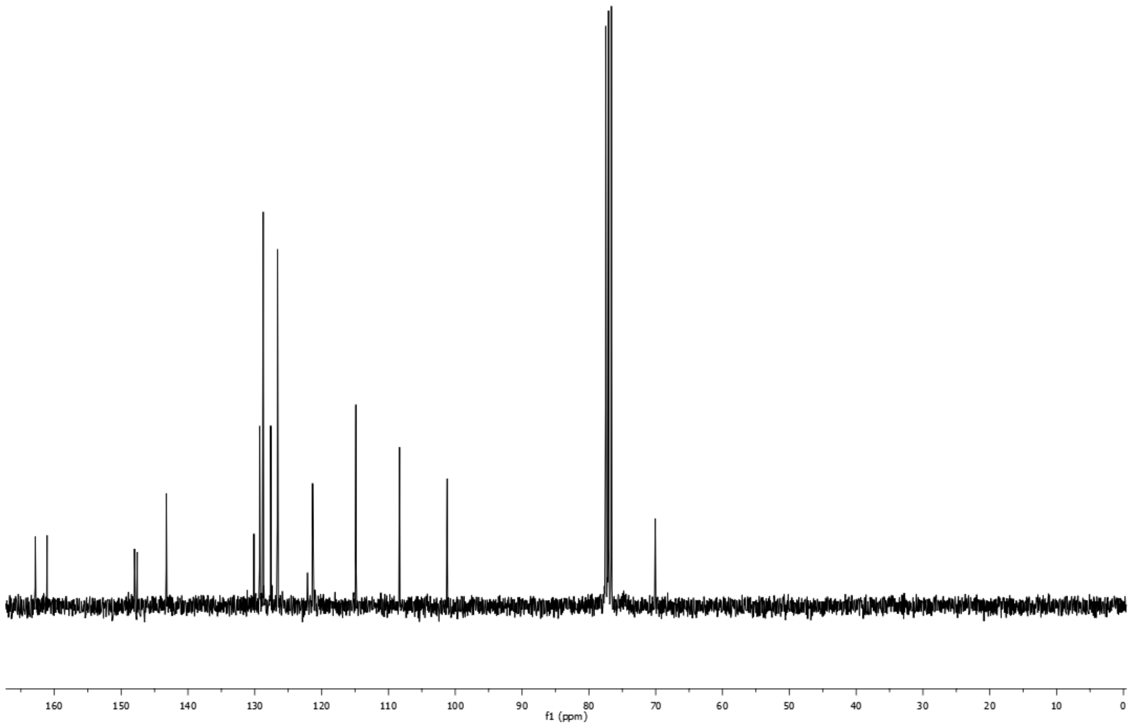
(S)-5-Phenyl-4-(R)-phenyl-2-[4-(4-trifluoromethoxy-benzyloxy)-phenyl]-4,5-dihydro-1H-imidazole (4e)



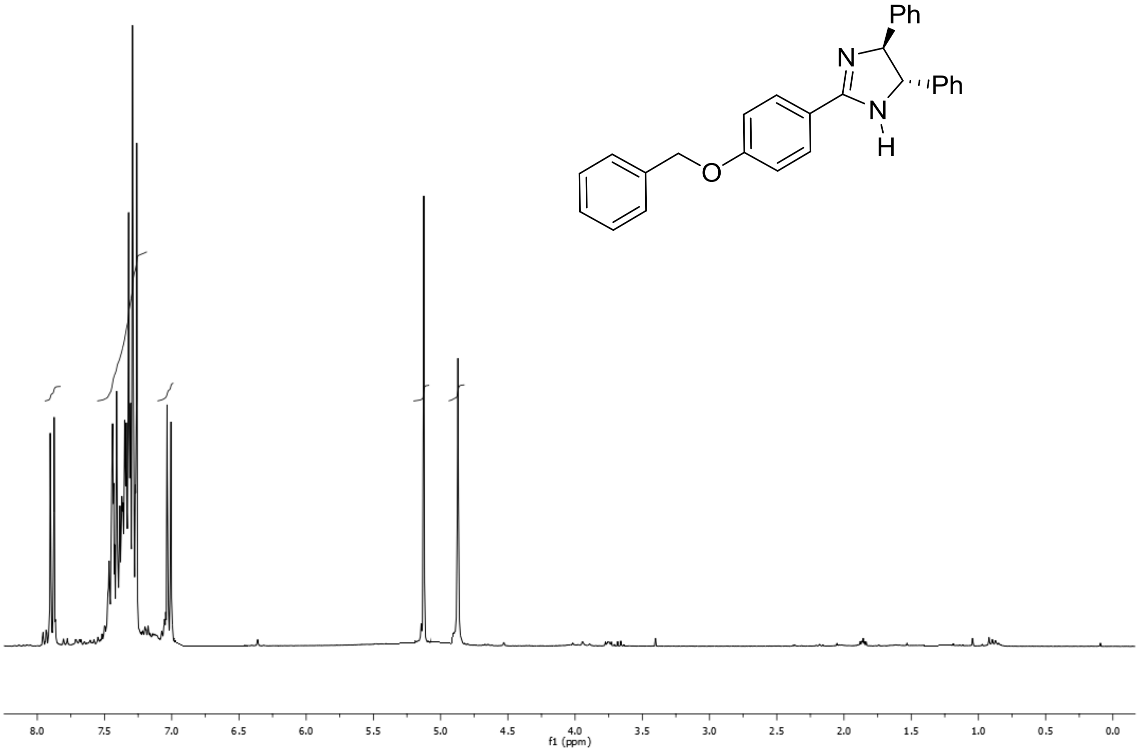


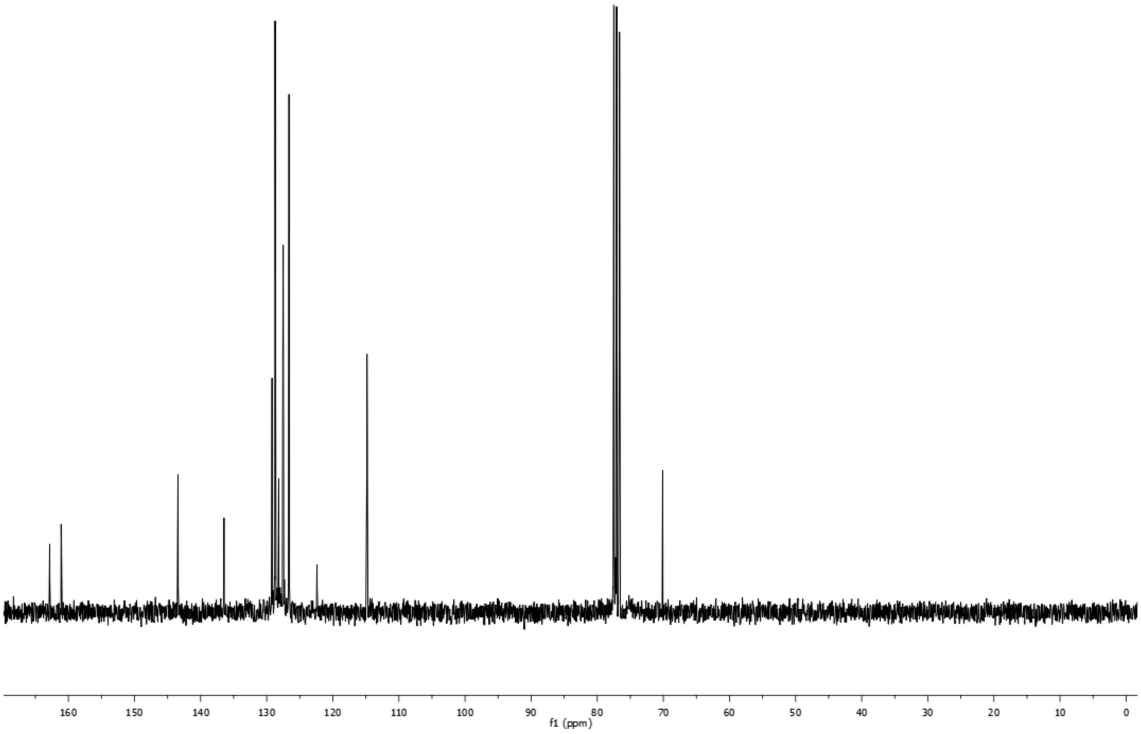
(S)-2-[4-(Benzo[1,3]dioxol-5-ylmethoxy)-phenyl]-5-phenyl-4-(R)-phenyl-4,5-dihydro-1H-imidazole (4f)



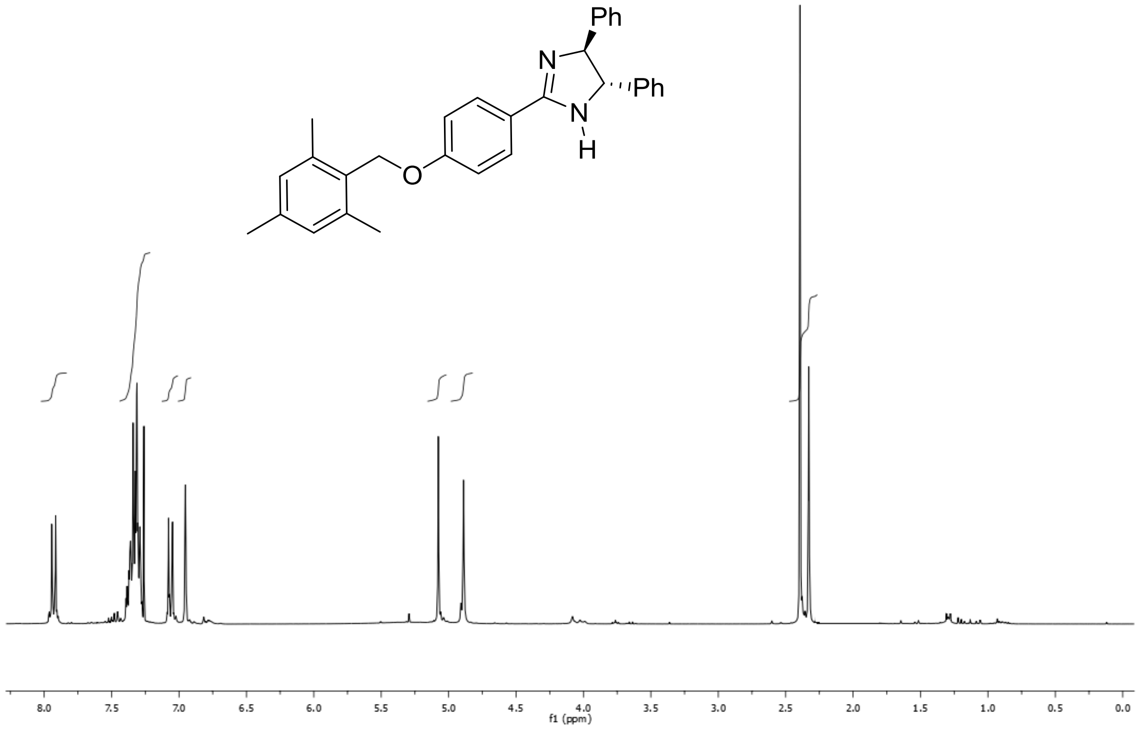


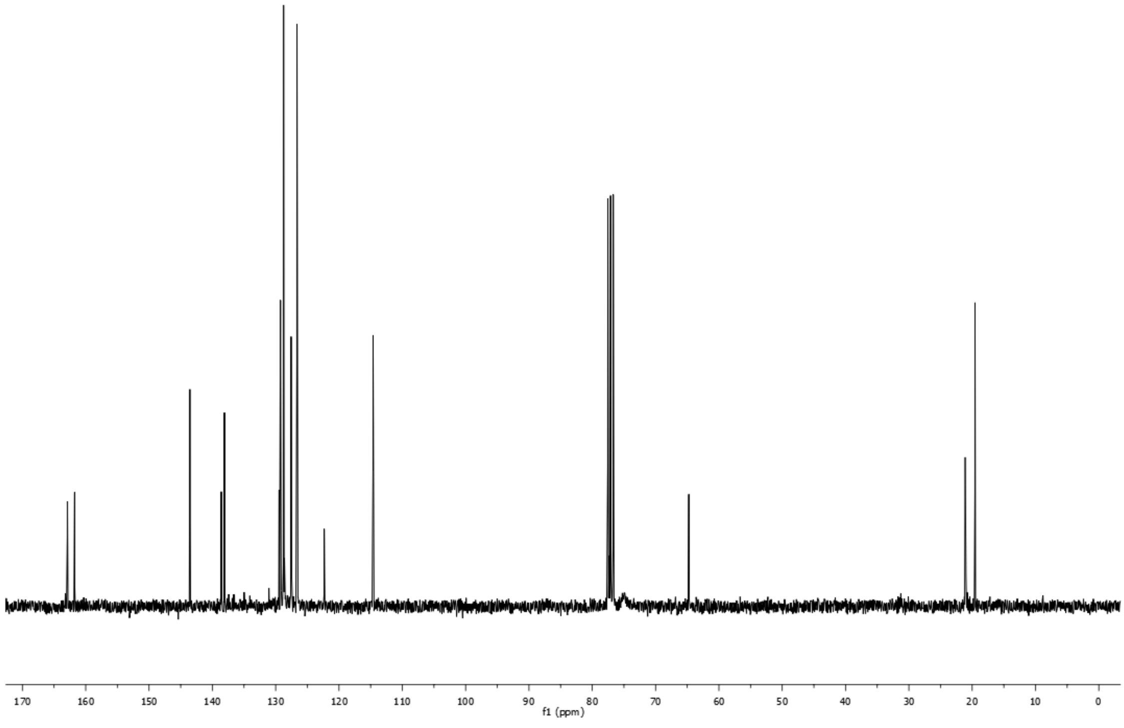
(S)-2-(4-Benzyloxy-phenyl)-5-phenyl-4-(R)-phenyl-4,5-dihydro-1H-imidazole (4g)



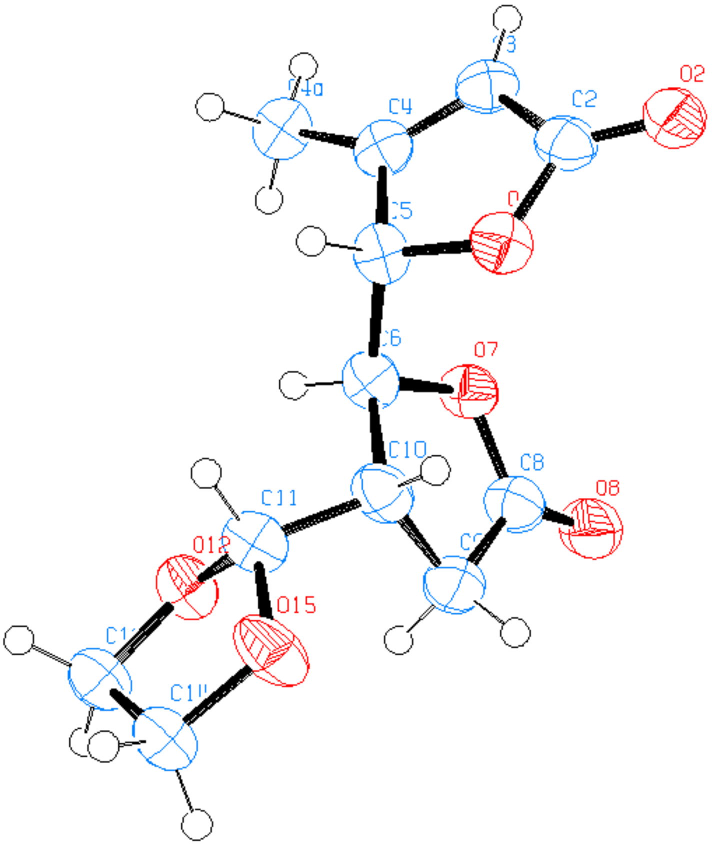


(S)-5-Phenyl-4-(R)-phenyl-2-[4-(2,4,6-trimethyl-benzyloxy)-phenyl]-4,5-dihydro-1H-imidazole (4h)





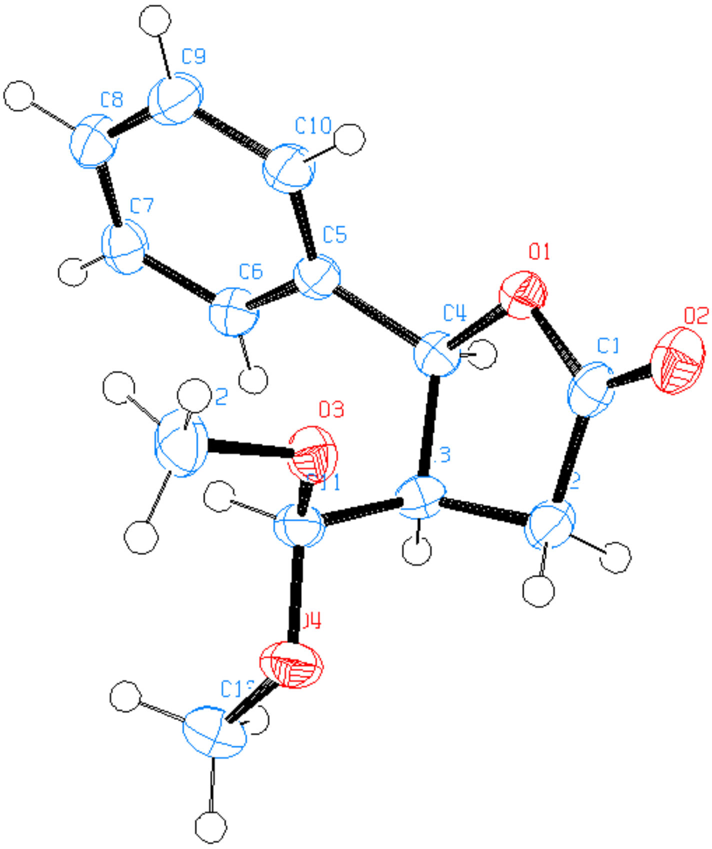
Appendix 2 – X-ray structure and data



Crystal data and structure refinement for compound 33c.

Identification code	7301	
Empirical formula	$C_{12}H_{14}O_6$	
Color	colourless	
Formula weight	254.23 g · mol^{-1}	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal system	ORTHORHOMBIC	
Space group	**$P2_1 2_1 2_1$, (no. 19)**	
Unit cell dimensions	a = 5.4669(6) Å	α= 90°.
	b = 10.3228(11) Å	β= 90°.
	c = 20.605(2) Å	γ = 90°.

Volume	1162.8(2) Å^3	
Z	4	
Density (calculated)	1.452 Mg · m^{-3}	
Absorption coefficient	1.002 mm^{-1}	
F(000)	536 e	
Crystal size	0.25 x 0.05 x 0.03 mm^3	
θ range for data collection	4.29 to 54.43°.	
Index ranges	$-5 \leq h \leq 5$, $-10 \leq k \leq 10$, $-21 \leq l \leq 21$	
Reflections collected	36878	
Independent reflections	1429 [R_{int} = 0.0827]	
Reflections with $I>2\sigma(I)$	1342	
Completeness to θ = 54.43°	99.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	0.97 and 0.87	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1429 / 0 / 165	
Goodness-of-fit on F^2	1.006	
Final R indices [$I>2\sigma(I)$]	R_1 = 0.0432	wR^2 = 0.1016
R indices (all data)	R_1 = 0.0467	wR^2 = 0.1053
Absolute structure parameter	-0.1(3)	
Extinction coefficient	0.027(3)	
Largest diff. peak and hole	0.311 and -0.236 e · Å^{-3}	

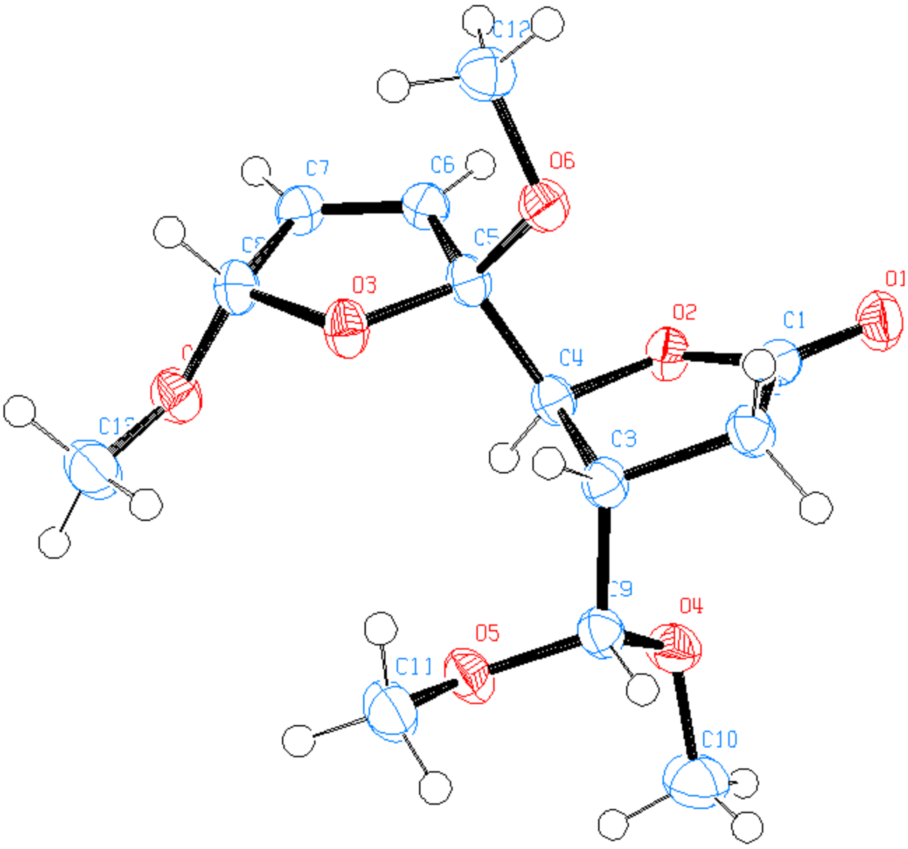


Crystal data and structure refinement for lactone 68c.

Empirical formula	$C_{13}H_{16}O_4$	
Formula weight	236.26	
Crystal size	0.467 x 0.148 x 0.050 mm	
Crystal description	needle	
Crystal colour	colourless	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.9224(2) A	alpha = 90 deg.
	b = 11.4859(4) A	beta = 90 deg.
	c = 17.6998(5) A	gamma = 90 deg.
Volume	1204.01(7) A^3	
Z, Calculated density	4, 1.303 Mg/m^3	
Absorption coefficient	0.96 mm^-1	
F(000)	504	

Measurement device type	Goniometer Xcalibur, detector: Ruby (Gemini ultra Mo)
Measuremnet method	w scans
Temperature	123 K
Wavelength	1.54184 A
Monochromator	graphite
Theta range for data collection	4.59 to 66.57 deg.
Index ranges	$-6 \le h \le 7$, $-10 \le k \le 13$, $-20 \le l \le 20$
Reflections collected / unique	5996 / 2090 [R (int) = 0.0182]
Reflections greater I>2\s(I)	2043
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.962 and 0.784

Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	
Data / restraints / parameters	2090 / 0 / 156
Goodness-of-fit on F^2	1.074
Final R indices [I> 2sigma (I)	R1 = 0.0292, wR2 = 0.0746
R indices (all data)	R1 = 0.0296, wR2 = 0.0749
Absolute structure parameter	0.07(15)
Largest diff. peak and hole	0.104 and -0.181 e.A^-3

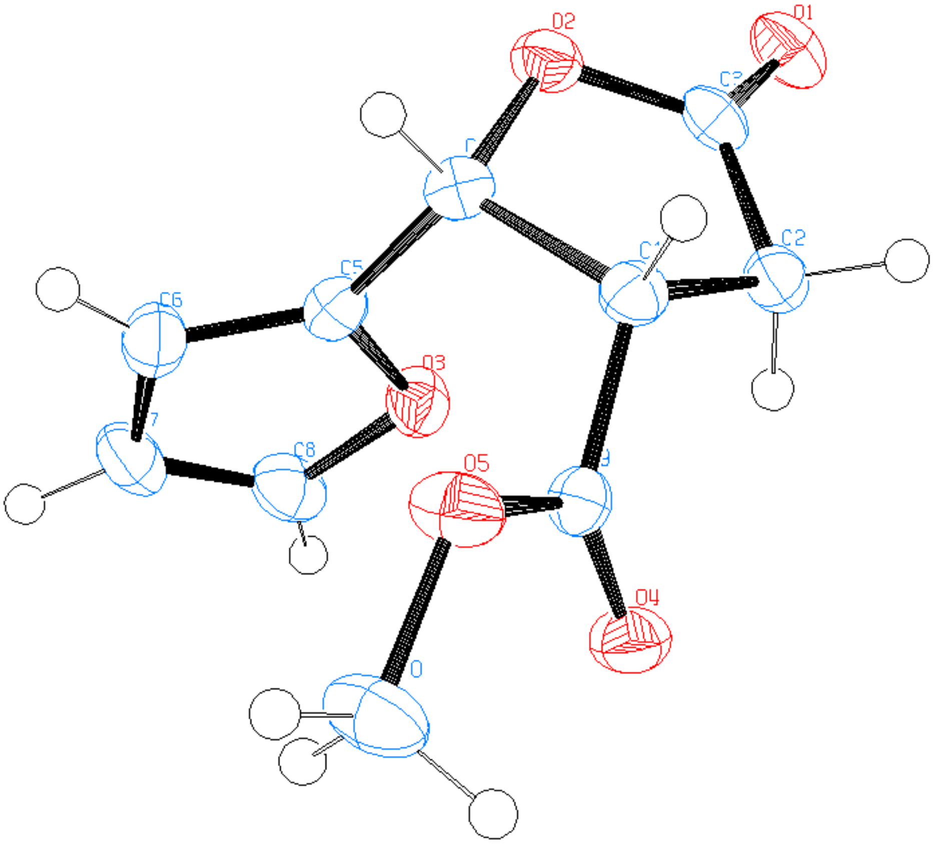


Crystal data and structure refinement for compound 86a.

Empirical formula	$C_{13}H_{20}O_7$	
Formula weight	288.29	
Crystal size	0.2359 x 0.1897 x 0.1102 mm	
Crystal description	plate	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 7.8226(2) A	alpha = 90 deg.
	b = 10.0497(2) A	beta = 102.925(2) deg.
	c = 9.1628(2) A	gamma = 90 deg.
Volume	702.08(3) A^3	
Z, Calculated density	2, 1.364 Mg/m^3	
Absorption coefficient	0.943 mm^-1	
F(000)	308	

Measurement device type	Goniometer Xcalibur, detector: Ruby (Gemini ultra Mo)
Measuremnet method	w scans
Temperature	123 K
Wavelength	1.54184 A
Monochromator	graphite
Theta range for data collection	4.95 to 66.79 deg.
Index ranges	-9 ≤ h ≤8, -11 ≤ k ≤ 11, -10 ≤ l ≤ 10
Reflections collected / unique	6700 / 2377 [R (int) = 0.0245]
Reflections greater I>2\ s(I)	2308
Absorption correction	Analytical
Max. and min. transmission	0.916 and 0.864

Refinement method	Full-matrix least-squares on F^2
Hydrogen treatment	
Data / restraints / parameters	2377 / 1 / 181
Goodness-of-fit on F^2	1.080
Final R indices [I> 2sigma(I)]	R1 = 0.0282, wR2 = 0.0739
R indices (all data)	R1 = 0.0289, wR2 = 0.0742
Absolute structure parameter	0.06(15)
Largest diff. peak and hole	0.238 and -0.150 e.A^-3



Crystal data for compound *cis*-93

Bond precision C-C = 0.0023 A Wavelength=1.54184
Cell a=16.6289(13) b=5.7810(4) c=10.2054(9)
alpha=90 beta=98.362(8) gamma=90
Temperature 123 K
Calculated Reported
Volume 970.63(13) 970.63(13)
Space group C 2 C 2
Hall group C 2y C 2y
Moiety formula C10 H10 O5 C10 H10 O5
Sum formula C10 H10 O5 C10 H10 O5
Mr 210.18 210.18
Dx,g cm -3 1.438 1.438
Z 4 4
Mu (mm-1) 1.000 1.000
F000 440.0 440.0
F000’ 441.66
h,k,l max 19,6,12 19,6,12
Nref 945[1705] 1396
Tmin,Tmax 0.919,0.961 0.928,1.000
Tmin’ 0.803

Appendix 3 - Biological assays

Alamar blue susceptibility test (MABA). Antimicrobial susceptibility testing was performed in black, clear-bottomed, 96-well microplates (black view plates; Packard Instrument Company, Meriden, Conn.) in order to minimize background fluorescence. Outer perimeter wells were filled with sterile water to prevent dehydration in experimental wells. Initial drug dilutions were prepared in either dimethyl sulfoxide or distilled deionized water, and subsequent twofold dilutions were performed in 0.1 ml of GAS (no Tween 80) in the microplates.

BACTEC 12B-passaged inocula were initially diluted 1:2 in GAS, and 0.1 ml was added to wells. Subsequent determination of bacterial titers yielded 1 3 106, 2.5 3 106, and 3.25 3 105 CFU/ml in plate wells for H_{37}Rv, H_{37}Ra, and *M. avium*, respectively. Frozen inocula were initially diluted 1:20 in BACTEC 12B medium followed by a 1:50 dilution in GAS. Addition of 1/10 ml to wells resulted in final bacterial titers of 2.0 3 105 and 5 3 104 CFU/ml for H_{37}Rv and H_{37}Ra, respectively. Wells containing drug only were used to detect auto fluorescence of compounds. Additional control wells consisted of bacteria only (B) and medium only (M). Plates were incubated at 37°C. Starting at day 4 of incubation, 20 ml of 103 alamar Blue solution (Alamar Biosciences/Accumed,

Westlake, Ohio) and 12.5 ml of 20% Tween 80 were added to one B well and one M well, and plates were reincubated at 37°C. Wells were observed at 12 and 24 h for a color change from blue to pink and for a reading of $50,000 fluorescence units (FU). Fluorescence was measured in a Cytofluor II microplate fluorometer PerSeptive Biosystems, Framingham, Mass.) in bottom-reading mode with excitation at 530 nm and emission at 590 nm. If the B wells became pink by 24 h, reagent was added to the entire plate. If the well remained blue or #50,000 FU was measured, additional M and B wells were tested daily until a color change occurred, at which time reagents were added to all remaining wells. Plates were then incubated at 37°C, and results were recorded at 24 h post-reagent addition. Visual MICs were defined as the lowest concentration of drug that prevented a color change. For fluorometric MICs, a background subtraction was performed on all wells with a mean of triplicate M wells. Percent inhibition was defined as 1 2 (test well FU/mean FU of triplicate B wells) 3 100. The lowest drug concentration effecting an inhibition of >90% was considered the MIC.

Relevant literature: L. Collins and S.G. Franzblau, Microplate alamar blue assay versus BACTEC 460 system for high-throughput screening of compounds against Mycobacterium tuberculosis and Mycobacterium avium, Antimicrobial Agents and Chemotherapy ***41*** *(1997). 1004–1009.*

Low-Oxygen Recovery Assay. The potential of samples to target the subpopulation of *Mycobacterium tuberculosis* in the non-replicating persistent (NRP) state was assessed using a low oxygen recovery assay (LORA). This employed *Mycobacterium tuberculosis* $H_{37}Rv$ (pFCA-luxAB) which synthesises luciferase when actively growing. The strain was cultured in 300mL of Dubos Tween–albumin broth (supplier) in a BioStatQ fermentor with a head space ratio of 0.5 and agitated at 120rpm with no detectable perturbation of the medium surface. The dissolved oxygen concentration (DOC) was monitored with an Ingold oxygen sensor probe. Cells were harvested when the OD at 570 nm indicated achievement of the desired growth phase (i.e. late non-replicating persistence). Aliquots of bacterial culture (50 mL) were centrifuged at 2700×g for 30 min, washed once with phosphate buffered saline (PBS), suspended in PBS (1 mL), and stored at −80 ^{o}C. Prior to use, cultures were thawed, diluted in Middlebrook 7H12 broth and sonicated for 15 s. Cultures were diluted to obtain an OD at 570nm of 0.03–0.05 and 2000–5000 relative light units (RLU) per 100 μL (i.e. 5×105 to ~2×106 CFU/mL). Twofold serial dilutions of compounds were prepared in 100 μL in black 96-well plates, and 100 μL of the cell suspension was subsequently added. The microplate cultures were placed under anaerobic conditions (oxygen < 0.16%) using an Anoxomat Model WS-8080, three cycles of evacuation and filling with amixture of 10% H_2, 5% CO_2, balance N_2. Plates were incubated at 37 ◦C for 7 days and then transferred to an ambient gaseous condition (5% CO_2-enriched air) incubator for a 24 h “recovery”. On day 7 and 8, 100 μL of culture were transferred to white opaque 96-well plates. A 10% solution of n-decanal in ethanol was freshly diluted 10-fold in PBS and 100 μL added to each well with an auto-injector. Luminescence was measured in a Victor2 multi-label reader (1 s reading time). Samples reducing viability under these non-growth conditions led to a decreased luciferase signal following aerobic recovery. Pure compounds were tested at 50 and 10 μg/mL and MICs were determined.

*Relevant Literature: S.H. Cho, S. Warit, B. Wan, C.H. Hwang, G.F. Pauli and S.G. Franzblau, Low-oxygen-recovery assay for high-throughput screening of compounds against nonreplicating Mycobacterium tuberculosis, Antimicrobial Agents and Chemotherapy **51** (2007) 1380–1385.*

Cytotoxicity study using HeLa cells. The cytotoxicity of the compounds was determined using the HeLa cells (ATCC CCL17). The test was carried out with some modifications according to the screening technique of Swanson and Pezzuto in 96-well plates (Falcon) with an inoculum of 2.5-104 cells/ mL. Test solutions were made as stocks in ethanol. Test concentrations were freshly prepared by diluting the stock solution with water to the required concentration. Final ethanol concentration was 1% (v/v) or less. Total assay volume was 150 μL. STLs and GSH/l-cys were added simultaneously. For quantification of the cytotoxicity, 15 μL of an aqueous solution of methylthiazolyltetrazolium chloride (MTT, Fluka, 5 mg/mL in PBS) was added after 72 h. During incubation at 37 °C for 4 h, the surviving cells metabolized MTT into an insoluble formazan dye. The culture medium was drawn off and the formazan dye was dissolved using 150 μL of 10% SDS (sodium dodecylsulfate) in water. After 24 h of incubation at room temperature, the optical density was measured at 540 nm using a microplate reader. For determination of the IC_{50} values, the optical density was plotted against the log concentration and six different concentrations have been tested. Every test was performed at least in duplicates and all experiments have been repeated at least twice. Maximal observed standard deviation was about 20% (absolute). Positive control measurements were performed with xanthohumol.

Relevant literatures:

J. Heilmann, M.R. Wasescha and T J. Schmidt. Bioorg. Med. Chem. ***9*** *(2001) 2189–2194.*

S. M. Swanson and J. M. Pezzuto. In Drug Bioscreening.Drug Evaluation Techniques in Pharmacology; Thompson, E.B. Ed.; VCH:New York, Weinheim, Cambridge, 1990; pp 273–297.

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Writing the acknowledgement has always been emotional for me. This is because expressing gratitude involves feelings that come straight from the heart. And before pouring things out, I would like to uncork some of my recollections prior to my arrival in Germany. So here it goes. At the time when the DAAD office in Bonn belt it out in an e-mail that I got selected as one of the successful applicants I suddenly got transfixed and petrified. Not because I didn't believe it. But it's because I would be leaving my family and friends very soon (in a matter of a month as I remember). And so when I told my mom and dad about the great news, we got ourselves into a tear-jerking situation. But then, as dad would always put it, "*That is life son. Just go on and follow what God has laid upon you. We are just here…..waiting for you*………*no worries*." And so, I went on to realize my dream of having a German education. As I sailed on, I met Oliver, I met friends, I did ultra-high ATP requiring experiments, I wandered through Europe (not all silly) and now (sigh), I am about to seal my European adventure. And thinking what it has been, my four-year stay in Germany is a collection of wonderful memories - memories that I would always want to rewind and share with family, friends and future students. And for this reason, I would like to thank all the people and groups who made my stay fruitful and worth remembering.

First, to **Prof. Dr. Oliver Reiser**. I found Oliver's name while wandering through the world-wide web as I was searching for a German professor in *synthetic medicinal chemistry* (those were my Google keywords). Out of the 30 Professors who I e-mailed (just a rough estimate), he gave the best response. What made it best actually was his expression of interest and willingness to have me in his lab although I warned him that I am no synthetic student by experience. So, I just appreciate Oliver for daring to have me. "*Oliver, thank you for accommodating me in your group. Thank you for giving me the opportunity to experience organic synthesis – tough and heart-breaking it may have been.☺ It has been a great pleasure to be mentored by you. Thank you for all the support, patience (esp. when I give you headache plus a list of shortcomings) and the unwavering guidance. Just… thank you!!!"*

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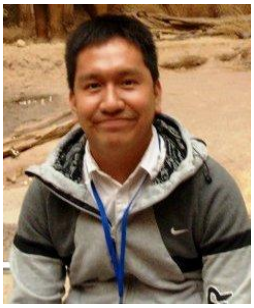
-Allan Patrick Macabeo-

CURRICULUM VITAE

Allan Patrick Gose Macabeo



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Education

since 10/2007	**PhD Thesis** in Organic Chemistry (with Prof. Dr. Oliver Reiser), Institute of Organic Chemistry, Univesity of Regensburg, Germany. “*Synthetic efforts towards the total synthesis of furanolactone cembranoids and discovery of antimicrobial and cytotoxic benzyloxylated congeners”*
10/2003	**Master of Science in Chemistry** (Magna Cum laude)
06/2001 - 10/2003	**Masters Thesis** (with Prof. Dr. Ma. Alicia M. Aguinaldo), Phytochemistry Laboratory, Research Center for the Natural Sciences, University of Santo Tomas, Manila, Philippines. “*Indole alkaloids from the leaves of Alstonia scholaris (L.) R. Br., photoinduced synthesis of 6,7-seco-angustilobine B-fullerene[*C_{60}*] adduct/s and comparison of their antituberculosis activity*”
06/1999 - 03/2001	**Master of Science in Chemistry Studies**, Faculty of the Graduate School, University of Santo Tomas, Manila, Philippines.
03/1999	**Bachelor of Science in Chemistry**
03/1998 - 03/1999	**Bachelors Thesis** (with Prof. Dr. Ma. Alicia M. Aguinaldo), Phytochemistry Laboratory, Research Center for the Natural Sciences, University of Santo Tomas, Manila, Philippines. “*The indole alkaloids from the leaves of Alstonia scholaris (L.) R. Br., and Catharanthus roseus (L.) G. Don. (Apocynaceae) – I. Isolation and structure elucidation of the major alkaloid using one-dimensional NMR spectroscopy; II. Comparative antimycobacterial activity and anticarcinogenicity against human oral-epidermoid carcinoma cell-lines*”

06/1995 - 03/1999	**Bachelor of Science in Chemistry Studies**, Department of Chemistry, College of Science, University of Santo Tomas, Manila, Philippines.
06/1991 - 03/1995	**Divine Word College of Vigan – High School Department**, Vigan City, Philippines High School Graduation (First Honorable Mention/Rank Three Overall).

Collegiate and Professional Awards

12/2010	**Pacifichem Young Scholars Award** sponsored by Merck Company USA and the Chemical Societies of the Pacific Basin (Honolulu, Hawaii, USA).
08/2007	**Best Research Paper**, Gruppo Medica Award for Outstanding Research in Herbal Medicine sponsored by the Gruppo Medica, Inc. and the Philippine Council for Health Research and Development (Manila, Philippines). *“Extracts and alkaloids from Voacanga globosa display high inhibitory activity to a human virulent strain of Mycobacterium tuberculosis and other related Mycobacteria in vitro. Structure identification of a new spirocyclic bisaspidospermidine indole alkaloid with potent antituberculosis property”*
12/2006	**Best Scientific Poster**, 11th Annual Convention of the Natural Products Society of the Philippines (Silliman University, Dumaguete City, Philippines). *“An antimycobacterial indole alkaloid from Voacanga globosa”*
07/2001	**Travel Award** sponsored by the International Union of Pure and Applied Chemistry and the World Chemistry Congress Committee (Brisbane, Queensland, Australia).
09/1999	**Best Research Paper** (3rd Place), Gruppo Medica Award for Outstanding Research in Herbal Medicine sponsored by Gruppo Medica, Inc. and the Philippine Council for Health Research and Development (Manila, Philippines). *“Potential Antitubercular Indole Alkaloids from Alstonia scholaris and Catharanthus roseus (Apocynaceae)”*
02/1999	**Champion Team Member**, Philippine National Chemistry Quiz Contest sponsored by the Philippine Association of Chemistry Students (PACS) (Manila, Philippines).

CURRICULUM VITAE

Employment History

04/2007 - *present*	*on-study leave status*
06/2003 - 03/2007	Tenured Instructor 4/Junior Science Researcher, Department of Chemistry, College of Science, University of Santo Tomas, Manila, Philippines
06/2001 - 03/2003	Instructor 1, Department of Chemistry, College of Science, University of Santo Tomas, Manila, Philippines
06/1999 - 03/2001	Teaching Assistant, Department of Chemistry, College of Science, University of Santo Tomas, Manila, Philippines

Scholarships

06/1995 - 03/1996	St. Martin de Porres Scholarship for Undergraduate Studies
06/1998 - 03/1999	CHED-COE Scholarship for BSc Chemistry
06/1999 - 10/2003	CHED-COE Scholarship for MSc Chemistry
04/2007 - 09/2007	Study Grant for German Language Course
10/2007 - 03/2011	German Academic Exchange Service/Deutscher Akademischer Austauschdienst (DAAD) Graduate Fellowship

Languages

Ilocano (native) Filipino (native) English (fluent) German (fair)

Additional Activities

German Chemical Society (student member)
Organic and Medicinal Chemistry Division, American Chemical Society (student member)
National Research Council of the Philippines (associate member)
Integrated Chemists of the Philippines (regular member)
International Editorial Board member, Pharmacognosy Magazine, Medknow Publications (Mumbai, India)

Presentations Related to Doctoral Work

1) Macabeo, A.P.G.; Reiser, O. Stereoselective synthesis of the northeastern sector of bielschowskysin from a functionalized cyclopropanecarbaldehyde. PACIFICHEM 2010, December 15-20, **2010**, Honolulu, HI, USA.
2) Macabeo, A.P.G.; Kreuzer, A.; Reiser, O. Diastereoselective routes to γ-aryl and γ-alkyl lactones: Mechanistic insights and model synthetic studies towards highly oxidized marine diterpenoids. 240th ACS National Meeting, August 22-26, **2010,** Boston, MA, USA.
3) Macabeo, A.P.G.; Reiser, O. Vinylogous Mukaiyama approaches towards the stereoselective synthesis of bielschowskysin and norsecurinines. 240th ACS National Meeting, August 22-26, **2010**, Boston, MA, USA.

4) Macabeo, A.P.G.; Reiser, O. Vinylogous Mukaiyama entry to γ-butenolidyl and γ-lactamyl butyrolactones – useful building blocks for natural product synthesis. 12th Belgian Organic Synthesis Symposium (BOSS XII), July 11-16, **2010**, Namur, Belgium.
5) Macabeo, A.P.G.; Kreuzer, A.; Reiser, O. Diastereoselective Synthesis of γ-Aryl and γ-Alkyl Lactones and their Application towards the Synthesis of Biologically Active Marine Diterpenoids and Antimycobacterial Paraconic Acid. GdCH Medicinal Chemistry Symposium, March, **2010**, Münster, Germany.

Publications

Refereed Journals

1. Macabeo, A.P.G.; Franzblau, S. G.; Cordell, G.A.; Aguinaldo, M.A.M. A Plumeran indole alkaloid from the antitubercular alkaloid extract of *Catharanthus roseus* (Linn.) G. Don (Apocynaceae). *Acta Manilana*. **1999**, 36, 51-54.

2. Macabeo, A.P.G.; Krohn, K.; Gehle, D.; Cordell, G.A.; Franzblau, S.G.; Aguinaldo, M.A.M. Indole alkaloids from the leaves of Philippine *Alstonia scholaris*. *Phytochemistry.* **2005**, 66 (10), 1158-1162.

3. Macabeo, A.P.G.; Byrne, L.T.; Franzblau, S.G.; Aguinaldo, M.A.M. 19,20*E*-Akuammidine from the bioactive alkaloid fraction of *Alstonia scholaris* leaves. *ACGC Chemical Research Communications*. **2006**, 20, 11-13.

4. Tudla, F.A.; Aguinaldo, M.A.M.; Krohn, K.; Hussain, H.; Macabeo, A.P.G. Highly oxygenated cyclohexene metabolites from *Uvaria rufa*. *Biochemical Systematics and Ecology*. **2007**, 35 (1), 45-47.

5. Aguinaldo, M.A.M.; Dalangin-Mallari, V.; Macabeo, A.P.G.; Byrne, L.T.; Yamauchi, T.; Abe, F.; Franzblau, S.G. Quinoline alkaloids from *Lunasia amara* inhibit *Mycobacterium tuberculosis* $H_{37}Rv$ *in vitro*. *International Journal of Antimicrobial Agents*. **2007**, 27(6), 744-746.

6. Mandap, K.; Marcelo, R.; Macabeo, A.P.G.; Franzblau, S.G.; Aguinaldo, M.A.M. Phenyldecanoids from the antitubercular fractions of the Philippine ginger (*Zingiber officinale*. *ACGC Chemical Research Communications*. **2007**, 21, 20-22.

7. Villafranca, M.; Aguinaldo, M.A.M.; Krohn, K.; Hussain, H. Clerosterols from *Clerodendrum quadriloculare*. *Biochemical Systematics and Ecology*. **2008**, 36(8), 659-660.

8. Macabeo, A.P.G.; Read, R.W.; Brophy, J.J.; Cordell, G.A.; Krohn, K.; Gehle, D.; Franzblau, S.G.; Aguinaldo, M.A.M. Activity of the extracts and indole alkaloids from *Alstonia scholaris* against *Mycobacterium tuberculosis* $H_{37}Rv$. *The Philippine Agricultural Scientist*. **2008**, 91(3), 348-351.

9. Macabeo, A.P.G. Synthetic uses of $ClTi(O\text{-}Pr^i)_3$ in C-C(N) Bond Formation. *Synlett*. **2008**, 20, 3247-3248.

10. Macabeo, A.P.G.; Aguinaldo, M.A.M. Chemical and phytomedicinal investigations in *Lunasia amara*. *Pharmacognosy Reviews*. **2008**, 2(4), 317-325.

11. Macabeo, A.P.G.; Alejandro, G.J.D.; Hallare, A.V.; Vidar, W.S; Villaflores, O.B. Phytochemical survey and pharmacological activities of the indole alkaloids in the genus *Voacanga* Thouars (Apocynaceae) - an update. *Pharmacognosy Reviews*. **2009**, 3(5), 132-142.
12. Villaflores, O.B.; Macabeo, A.P.G.; Gehle, D.; Krohn, K.; Franzblau, S.G.; Aguinaldo, M.A.M. Phytoconstituents from *Alpinia purpurata* and their *in vitro* inhibitory activity against *Mycobacterium tuberculosis*. *Pharmacognosy Magazine*. **2010**, 6(24), 339-344.
13. Barbic, M.; Macabeo, A.P.G.; Kreft, S.; Heilmann, J. Astragalosides from *Astragalus illyricus*. *Biochemical Systematics and Ecology*. **2010**, 38, 140-142.
14. Macabeo, A.P.G.; Tudla, F.A.; Alejandro, G.J.D.; Kouam, S.F.; Krohn, K.; Hidayat, H. Benzoylated derivatives from *Uvaria rufa*. *Biochemical Systematics and Ecology*. **2010**, 38, 857-860.
15. Macabeo, A.P.G.; Kreuzer, A.; Reiser, O. Diastereoselective Approaches towards Arylated γ-Butyrolactones and their Application towards Highly Oxidised *Pseudopterogorgia* Diterpenoids. *Organic and Biomolecular Chemistry*. **2011**, 9, 3146-3150.
16. Macabeo, A.P.G, Vidar, W.S., Wan, B., Franzblau, Chen, X., Decker, M., Heilmann, J., Aguinaldo, A. M., Cordell, G. A. *Mycobacterium tuberculosis* $H_{37}Rv$ and cholinesterase inhibitors from *Voacanga globosa*. *European Journal of Medicinal Chemistry.* **2011**, *in press*.

Published Proceedings

1. Macabeo, A.P.G.; Franzblau, S.G.; Read, R.W.; Brophy, J.J.; Aguinaldo, M.A.M. Vallesamine-type indole alkaloid derivatives from the antitubercular fractions of the leaves of *Alstonia scholaris* (Linn.) R. Brown. Proceedings of the Asia-Pacific Conference on Analytical Science. Philippine Federation of Chemistry Societies. Manila, Philippines. February 19-23, **2003**.
2. Macabeo, A.P.G.; Krohn, K.; Gehle, D.; Franzblau, S.G.; Aguinaldo, M.A.M. Alkaloids from the antitubercular fraction of *Alstonia Scholaris* (Linn.) R. Brown Leaves. Transactions of the National Academy of Science and Technology Philippines. **2003**, 25 (1), 128-129.
3. Macabeo, A.P.G.; Kreuzer, A.; Reiser, O. Diastereoselective routes to γ-aryl and γ-alkyl lactones: Mechanistic insights and model synthetic studies towards highly oxidized marine diterpenoids. Abstracts of Papers, 240th ACS National Meeting, Boston, MA, USA. August 22-26, **2010**.
4. Macabeo, A.P.G.; Reiser, O. Vinylogous Mukaiyama approaches towards the stereoselective synthesis of bielschowskysin and norsecurinines. Abstracts of Papers, 240th ACS National Meeting, Boston, MA, USA. August 22-26, **2010**.
5. Macabeo, A.P.G.; Vidar, W.S.; Barbic, M.; Aguinaldo, M.A.M.; Franzblau, S.G.; Cordell, G.A. Globospiramine, a new antituberculosis bisaspidospermidine indole alkaloid from *Voacanga globosa*. Abstracts of Papers, 240th ACS National Meeting, Boston, MA, USA, August 22-26, **2010**.

6. Macabeo, A. G.; Tudia, F.; Paragas, E.; Vidar, W.; Galvez, E.; Galang, G.; Inocencio, L.; Panlilio, B.; Villaflores, O.; Dalangin-Mallari, V.; Marcelo, R.; Yamauchi, T.; Abe, F.; Krohn, K.; Franzbalu, S.; Aguinaldo, A. In vitro antituberculosis activity of crude drugs and natural products from selected Philippine medicinal plants. Pacifichem 2010, International Chemical Congress of Pacific Basin Societies, Honolulu, HI, United States, December 15-20, 2010 (2010), HEALTH-286.

Laboratory Manual

Menguito, C.A.; Albano, P.B.S.; Macabeo, A.P.G.; Santiago, K.S. Laboratory Experiments in Biochemistry. Department of Chemistry, College of Science, University of Santo Tomas, Manila. May, **2003**.

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