# Synthesis of benzofurans via acid catalysed transacetalisation/ Fries-type O→C rearrangement/ Michael addition/ ring-opening aromatisation cascade of β-pyrones

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*A dissertation submitted for the partial fulfillment of BS-MS dual degree in science*

**Indian Institute of Science Education and Research Mohali,**
**April 2016**

# Certificate of Examination

This is to certify that the dissertation titled "Synthesis of benzofurans via acid catalysed transacetalisation/ Fries-type O→C rearrangement/ Michael addition/ ring-opening aromatisation cascade of β-pyrones" submitted by Mr. Jopaul Mathew. (Reg. No. MS11027) for the partial fulfillment of BS-MS dual degree program of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

| | | |
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Dated: April 22, 2016

# Declaration

The work presented in this dissertation has been carried out by me under the guidance of **Dr. S. S. V. Ramasastry** at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussion. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

Jopaul Mathew

(Candidate)

Dated: April 22, 2016

In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge

Dr. S. S. V. Ramasastry

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# Acknowledgement

It is my privilege to express my sincere gratitude to my supervisor, **Dr. S. S. V. Ramasastry** for his invaluable discussion, guidance and supervision throughout the work. The confidence and dynamism with which he guided the work requires no elaboration. Additionally, I am very thankful to him for exposing me to this interesting field of research. Without his guidance, compiling the project report in this form would have been impossible.

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I am in short of words in expressing my heartfelt thanks to my family, always standing behind me with their love and support.

Jopaul Mathew

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# Notations and Abbreviations

| | |
|---|---|
| Pd | Palladium |
| NBS | N-Bromosuccinimide |
| mCPBA | *meta*-Chloroperoxybenzoic acid |
| TLC | Thin layer chromatography |
| NMR | Nuclear magnetic resonance |
| TBAOH | Tetrabutylammonium hydroxide |
| δ | Chemical shift in ppm |
| Ppm | Parts per million |
| MeCN | Acetonitrile |
| EtOAc | Ethyl acetate |
| IR | Infra-red |
| s | Singlet |
| d | Doublet |
| t | triplet |
| m | multiplet |
| dd | Doublet of doublet |
| dt | Doublet of triplet |
| td | Triplet of doublet |
| M.P. | Melting point |
| HRMS | High Resolution Mass spectrometry |
| ESI | Electron Spray Ionization |

# Contents

# Abstract

An unusual and facile approach for the synthesis of 2-benzofuranyl-3-hydroxyacetones from 6-acetoxy-*β*-pyrones and phenols is presented. The synthetic sequence involves a cascade transacetalisation, Fries-type O→C rearrangement followed by Michael addition and ring opening aromatisation. Versatility of this method was further demonstrated via the synthesis of 4,4*a* dihydropyrano[3,2-*b*]benzofuran-3-ones, furo[3,2-*c*]coumarins, and spiro[benzofuran-2,2'-furan]-4'-ones. The unexpected cascade event would also provide new possible considerations in the *β*-pyrone-involved organic synthesis.

# Chapter 1

# Introduction

Heterocycles constitute the largest divisions of organic compounds and are of immense biological importance. More than 90% of existing drugs are heterocylic in nature and hence reflecting the drug-likeness of this scaffold. One key structural feature inherent to heterocycles, lies in their ability to accommodate a variety of substituents around a core scaffold in defined three dimensional representations. Among these, benzofurans constitute a major group and these compounds have engrossed substantial attention due to their role as building blocks in bioactive natural products. These compounds also exhibit wide range of pharmacological activities. Further, benzofuran is an acclaimed privileged scaffold in drug discovery. Due to its clinical importance medicinal chemists are actively involved in the synthesis of these heterocycles and their diverse derivatives. Some of the drugs having benzofuran core are listed below (Figure 1).[1]

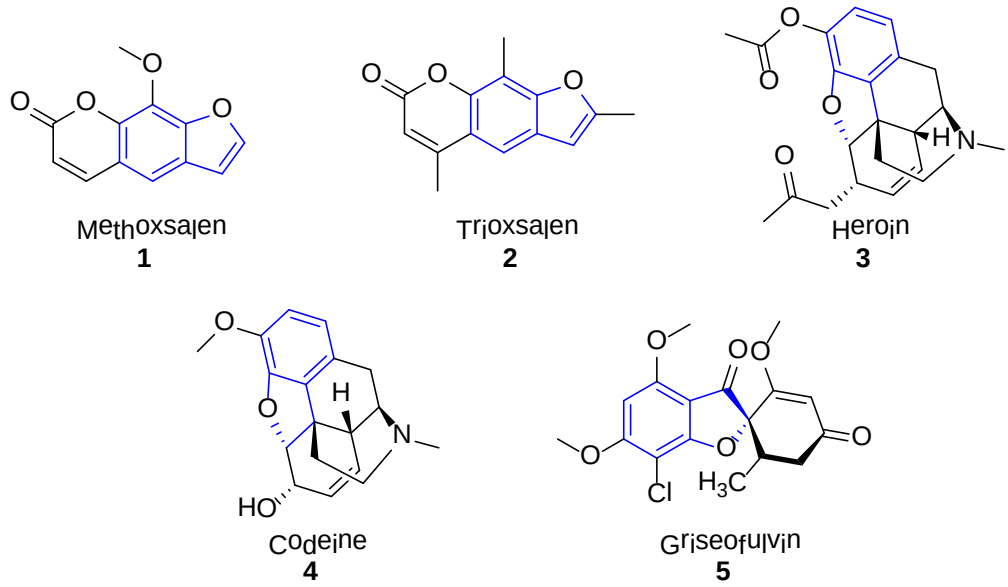



**Figure 1.** Representative examples of drugs or natural products containing benzofuran as a core structure.

Methoxsalen[2] **1** is a drug which is potent to treat diseases like psoriasis, Eczema, Vitiligo and Cutaneous lymphomas. Compound Trioxsalen[3] **2** is a photosensitizer which is used to increase skin tolerance to sunlight and enhance pigmentation of skin. Heroin[4] **3** is an opioid painkiller. Heroin is prescribed as an analgesic, and less commonly as a cough suppressant and as an antidiarrhoeal.

Codeine[5] **4**, also known as 3-methylmorphine, is an opiate used to treat pain, as a cough medicine, and for diarrhea. It is typically used to treat mild to moderate degrees of pain. It also possess hypnotic ability. Griseofulvin[6] **5** is used both in animals and humans to treat fungal infections of the skin and nail fungus.

Substituted benzofurans find application such as fluorescent sensor, antioxidants, brightening agents, and in other fields of chemistry and agriculture. They exhibit physiological and pharmacological properties. These substituted benzofurans offer a high degree of diversity that has proven useful in the development of new therapeutic agents. For example some substituted benzofurans are active against bacterial and fungal species, some show antimicrobial activities which yields better results than known antibiotics like Pencillin,[7] inhibition of several enzymes like glycogen synthase kinase 3 (GSK-3) which takes part in cancer, diabetes and neurodegenerative disorders,[8] activation of enzymes like Glucokinase which is a promising target for treatment of type-2 diabetes mellitus,[9] high percentage of inhibition against pro-inflammatory agents such as cytokines,[10] expresses high performance against cancer cell lines, activity against influenza virus[11] and also participation in Alzheimer's disease treatment.[12] A brief idea about biological activities of benzofurans and their derivatives can be analyzed from the diagram below (Figure 2).[13]

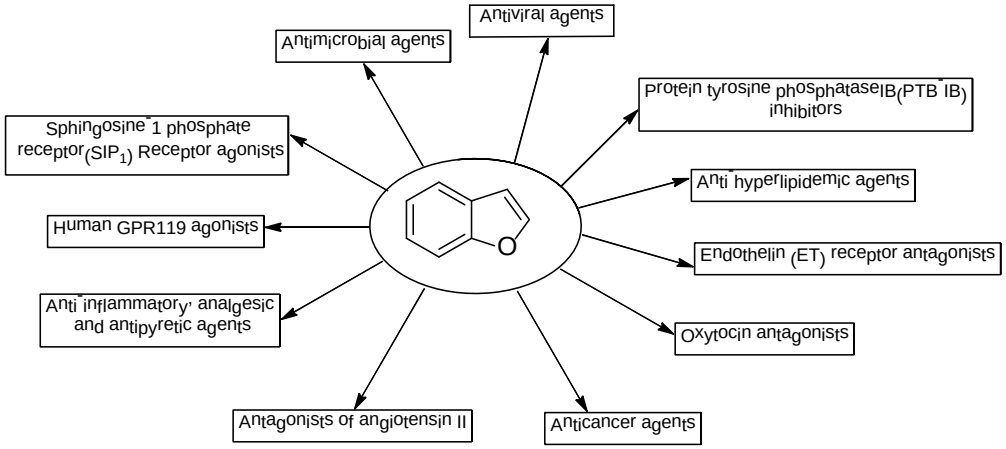
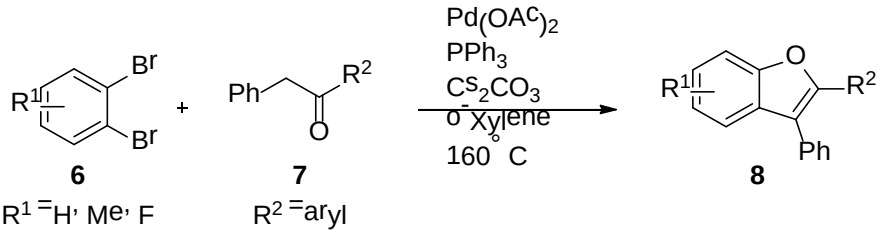



**Figure 2**. The biological activity spectrum of benzofuran derivatives.

Considering the prevalence of this skeleton in many biologically active molecules, various methods for the assemblage of substituted benzofurans have been documented. Some of the literature reports regarding the benzofuran synthesis are the following.

In 1999, Miura and coworkers reported the synthesis of aromatic heterocycles via palladium-catalyzed α-arylation reactions of carbonyls (Scheme 1). Coupling of benzyl ketones **6** with o-dibromobenzenes **7** yielded benzofurans **8** in moderate to good yields.[14]

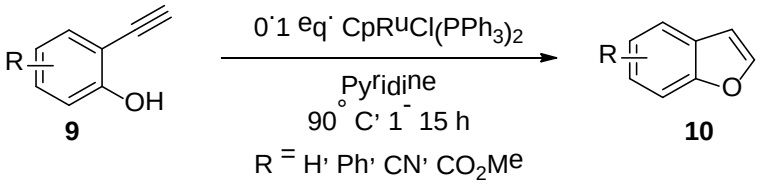



**6** **7** **8**

$R^1$ = H, Me, F $R^2$ = aryl

**Scheme 1.** Synthesis of benzofurans from benzyl ketones using Palladium catalyst

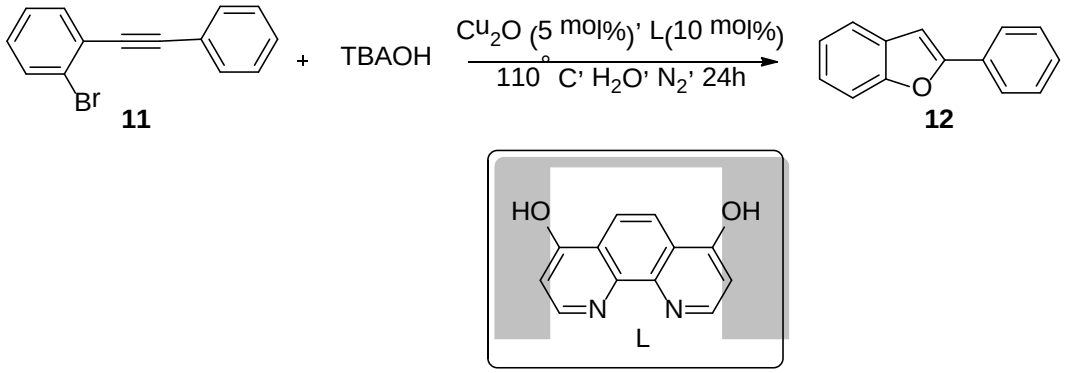
Ru-catalyzed cycloisomerizations of aromatic homopropargylic alcohols **9** effectively afford benzofurans **10** (Scheme 2). This was reported by Saa and group in 2009. These processes proved to be chemo and regioselective (5-*endo*-*dig* cyclization) derived from key Ru vinylidene intermediate. The presence of an amine/ammonium base−acid pair is crucial for the catalytic cycle.[15]




**9** **10**

**Scheme 2**. Synthesis of benzofuran via Ru-catalyzed cycloisomerisation.

Recently in 2015, Wang *et al.* also reported a methodology for the substituted benzofuran **12** synthesis. It consists of hydroxylation of different aryl bromides **11** and electron-deficient aryl chlorides by water solution of tetrabutylammonium hydroxide catalyzed by $Cu_2O$/4,7-dihydroxy-1,10-phenanthroline (L) (Scheme 3).[16]

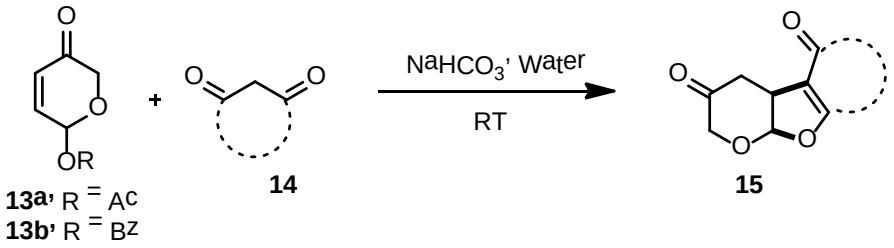



**11** **12**

**Scheme 3.** Synthesis of substituted benzofuran **12** from 2-bromoarylalkyne **11** using Copper catalyst.

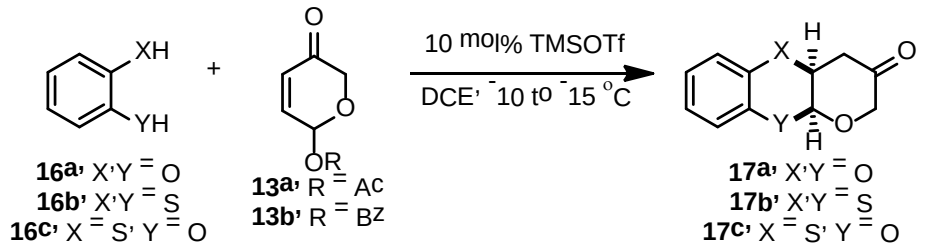
Most of the reported protocols involve the use of metal catalysts. The Pd catalysed synthesis of benzofurans required high temperature for reaction. Moreover, Ru-catalysed benzofuran construction require strong basic environment. The high cost of metal and its difficulty in recycling at the end of reaction renders the overall operation cumbersome and environmentally non-benign. Even though, owing to the limitations of the conventional approaches pertaining the reactivity and selectivity, further hampered by the harsh reaction conditions and limited functional-group tolerance, there still exists ample scope for exploring new approaches for the synthesis of benzofuran and its derivatives. Considering this as an opportunity we focused our attention to develop a methodology for the synthesis of benzofuran derivatives that will be accessible easily and can be obtained under mild conditions.

Development of novel cascade processes has received great attention owing to their exceptional ability to rapidly assemble intricate molecular scaffolds often associated with pot, step, and atom economy. Several efforts have been attempted for the synthesis O, S-containing heterocycles. One among those is reported by our research group in 2014. It described the synthesis of functionalized polycyclic acetals **15** under mild aqueous conditions (Scheme 4). This diversity oriented approach involves cascade Michael addition and cycloacetalization.[17]



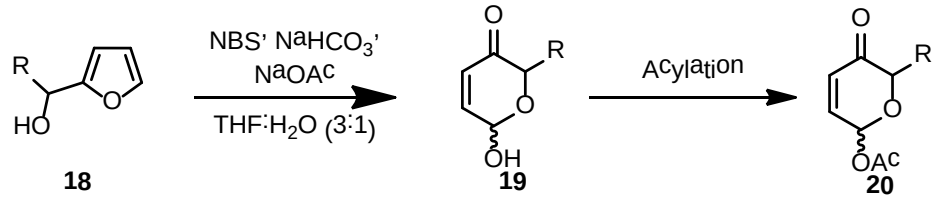

**Scheme 4.** Facile approach for the synthesis of furopyrans.

Later in 2015, another methodology for the synthesis of heterocycles such as pyrano-1, 4- dioxinones, pyrano-1,4-dithiinones and pyrano-1,4-oxathiinones **17a,b,c** was reported by our group. Cascade Michael addition–cycloacetalization of acetoxy-, alkoxy-, and aryloxypyranones **13a,b** and 1, 2-dinucleophiles **16a,b,c** under mild Lewis acidic conditions provided a direct access to oxygen and sulfur-containing complex heterocycles (Scheme 5).[18]

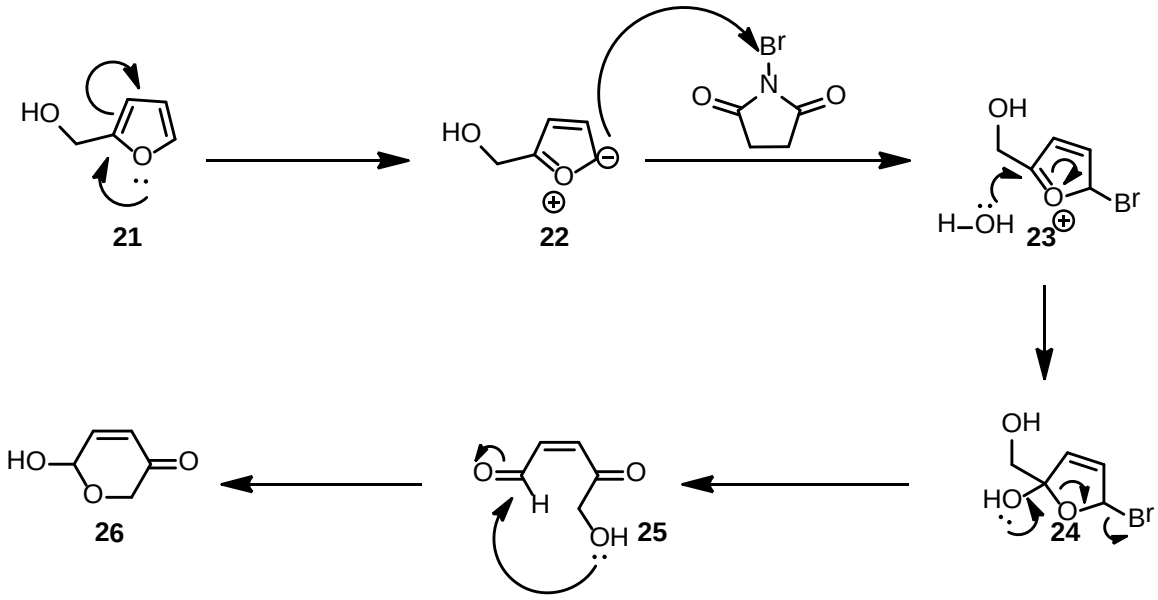



**Scheme 5.** Synthesis of O, S-containing polycycles.

These strategies necessitated to have rapid and efficient access to 6-acetoxy-*β*-pyrones **20**. This was synthesized using a well-known name reaction 'Achmatowicz reaction'. This was first reported by Osman Achmatowicz Jr. in 1971 wherein the conversion of furfuryl alcohol **18** to 6-hydroxy-*β*-pyrones **19** using bromine in methanol was reported.[19] N-bromosuccinimide (NBS)/methanol or mCPBA are the other reagents which are commonly used to effect this transformation (Scheme 6).




**Scheme 6**. Achmatowicz rearrangement mediated by NBS followed by acylation.

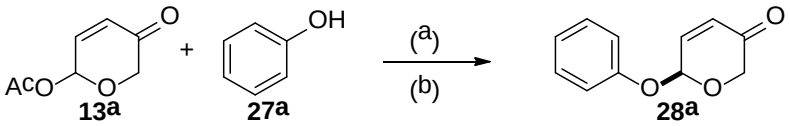



**Scheme 7**. Mechanism of Achmatowicz reaction mediated by NBS.

The mechanism of Achmatowicz rearrangement is depicted in Scheme 7. Due to the progress of reaction in a highly atom-economic fashion, it has been widely employed in the total synthesis of several natural products such as D-swainsonine,[20] diterpene phorbol[21] and C27-C38 and C44-C53 subunits of norhalochondrin B[22] and

also in synthesis of carbohydrates like all-α-L-heptamannoside[23] and L-cymarose.[24] The tolerance of this rearrangement towards sensitive functionalities widens its generality and application.

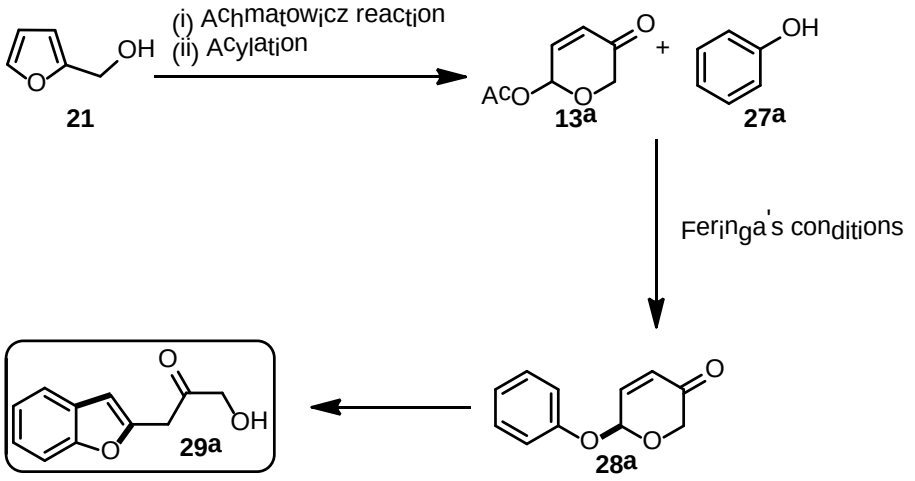
The synthesis of 6-phenoxy-*β*-pyrones **28a** was accessed with the Lewis acid catalyzed protocols of Grynkiewicz[25a] and Feringa[25b] from 6-acetoxy-*β*-pyrone **13a** and phenol **27a**. Scheme of protocols of Grynkiewicz (a) and Feringa (b) are demonstrated below (Scheme 8).




(a) Grynkiewicz conditions: $SnCl_4$, 1,2-dichloroethane, 0-5 °C, 10 min
(b) Feringa conditions: $BF_3{\cdot}OEt_2$, 1,2-dichloroethane, 0-5 °C, 5 min

**Scheme 8.** Protocol of Grynkiewicz's and Feringa's reaction conditions.

Required product **28a** was isolated in both the cases but in lower yields.[26] A detailed study of these reactions under close monitoring via Thin Layer Chromatography (TLC) revealed the formation a polar spot. Further study of the reaction under Feringa's conditions revealed that the concentration of the initially formed phenyl ether **28a** started diminishing and simultaneous build-up of the unanticipated product was observed. Thus, we have drawn the conclusion at this stage that the unexpected product **29a** formed via the intermediacy of **28a** (Scheme 9). The structure of the unexpected product **29a** was deduced from $^{1}H$ and $^{13}C$ NMR data.




**Scheme 9.** Theme of this work: Unprecedented cascade reaction of 6-acetoxy-*β*-pyrones **13a** and phenols **27a** leading to the synthesis of 1-(2-benzofuranyl)-3-hydroxyacetones **29a**.

# Chapter 2

# Results and Discussion

The reaction of **13a** and **27a** in the presence of 10 mol% TMSOTf was monitored by TLC. It can be observed from the above TLCs that **13a** transforms initially to the non-polar phenyl ether **28a** (TLC-1) [**Note**: $R_f$ of **27a** and **28a** are same]. Phenyl ether **28a** then slowly transforms to the pyran-fused benzofuran **29a'** and **29a'** converts to the benzofuran derivative **29** eventually (TLC-5), leaving behind little excess of the phenol **27a** employed in the reaction (TLCs-4&5).

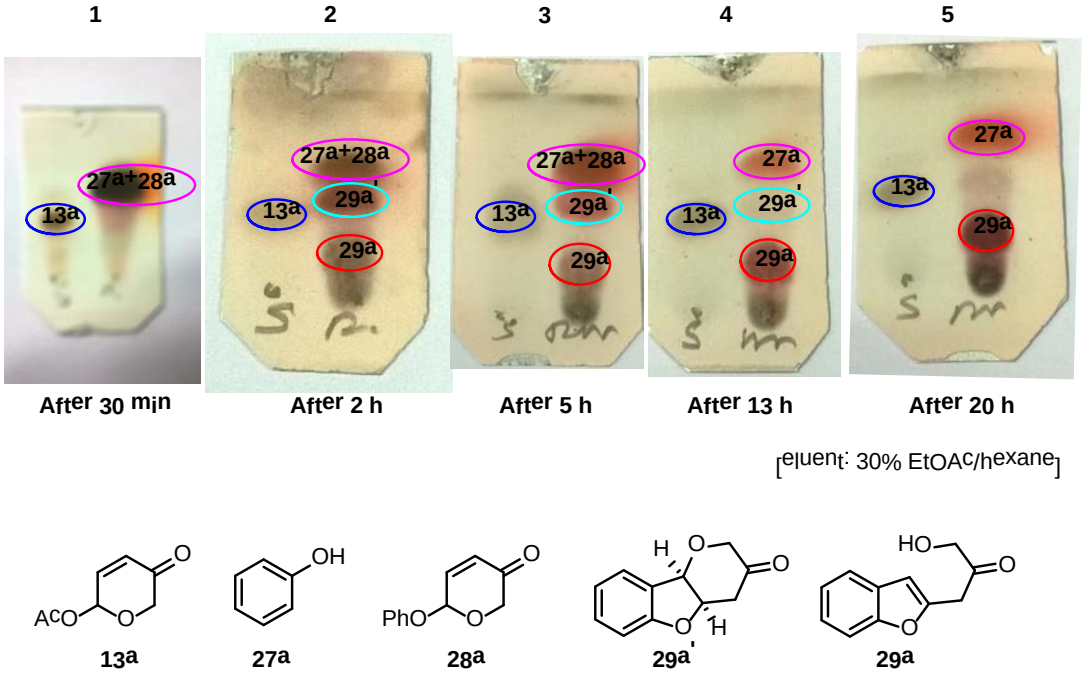


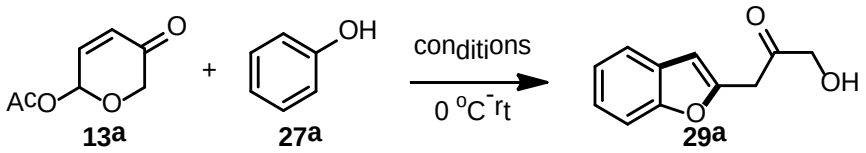

**Figure 3.** TLC monitoring of the reaction between **13a** and **27a**.

While **28a** is reasonably stable upon isolation; isolated samples of the pyran-fused benzofuran **29a'** were found to convert to benzofuran **29a** even at room temperature over a period of time. Apart from NMR, structure of **29a** was further confirmed by single-crystal X-ray diffraction analysis (*vide infra*).[27] Since the 6-acetoxy-*β*-pyrone **13a** can be accessed from furyl carbinol **21** in two straightforward steps, this protocol thus represents a unique three-step conversion of furans to benzofurans.

Having realized the significance of benzofurans, especially generated under mild Lewis acidic conditions from readily accessible starting compounds, and

considering the potential implications of this rearrangement in organic synthesis, we turned to optimizing the reaction conditions. Towards this, various Lewis/Brønsted acids and solvent combinations were investigated, and the representative results are compiled in Table 1.

**Table 1**. Optimization of the reaction parameters.[a]



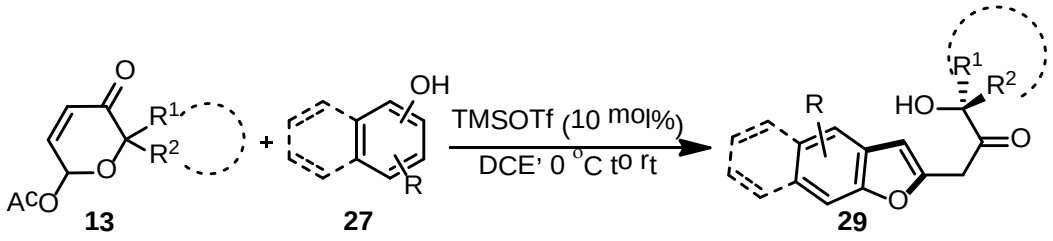

| Entry | Acid (10 mol %) | Solvent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $La(OTf)_3$ | DCE | 48 | 74[c] |
| 2 | $SnCl_4$ | DCE | 3 | 50 |
| 3 | $BF_3OEt_2$ | DCE | 18 | 55 |
| 4 | $FeCl_3$ | DCE | 18 | 45 |
| 5 | $In(OTf)_3$ | DCE | 20 | 48 |
| 6 | $Zn(OTf)_2$ | DCE | 20 | 45 |
| 7 | $Bi(OTf)_3$ | DCE | 20 | 61 |
| 8 | AgOTf | DCE | 21 | 40 |
| **9** | **TMSOTf** | **DCE** | **20** | **74** |
| 10[d] | TMSOTf | DCE | 20 | 47 |
| 11[e,f] | TMSOTf | DCE | 30 | 45 |
| 12[g] | TMSOTf | DCE | 72 | - |
| 13 | TfOH | DCE | 20 | 63 |
| 14 | PTSA | DCE | 20 | 51 |
| 15 | TMSOTf | $CH_3CN$ | 21 | 48 |
| 16 | TMSOTf | Toluene | 72 | 25 |
| 17 | TMSOTf | THF | 72 | - |

[a]A 5 mL glass vial was filled with **13a** (0.2 mmol), **27a** (0.22 mmol), and a solvent (1 mL). A catalyst (0.02 mmol) was then added at 0-5 °C. After stirring at the same temperature for about 30 min, continued the reaction at room temperature until **13a** and **28a** disappeared (by TLC). [b]Isolated yield after column chromatography. [c]**28a** exclusively formed. [d]20 mol % TMSOTf was employed. [e]5 mol % TMSOTf was employed. [f]**13a** and **28a** were also recovered. [g]In the presence of 2,6-di-*tert*-butyl-4-methylpyridine (1 equiv).

The reaction catalyzed by $La(OTf)_3$ generated exclusively the 6-phenoxy-*β*-pyrone **28a** even after extended reaction times, thereby establishing a high-yielding method for its selective synthesis (Table 1, entry 1). Most of the Lewis acids employed during the screening otherwise furnished the desired product **29a** in varied yields, with TMSOTf delivering the best result (Table 1, entries 2-9). Reaction with higher TMSOTf loading (20 mol %) gave a poor result due to the formation of undesired side products (Table 1, entry 10). On the other hand, reaction in the presence of 5 mol % TMSOTf was found to be sluggish (Table 1, entry 11). So, 10 mol % TMSOTf loading was realized to be optimal for this transformation (Table 1, entry 9).

Interestingly, the reaction in the presence of a proton sponge such as 2,6-di-*tert*-butyl-4-methylpyridine completely inhibited the product formation, indicating most likely that catalytic amounts of TfOH generated *in situ* might be promoting this process (Table 1, entry 12). However, despite repeated attempts, TfOH furnished the required product in lower yields when compared to TMSOTf (Table 1, entry 13). Among few other Brønsted acids employed, PTSA generated **29a** in satisfactory yield (Table 1, entry 14). So, considering its mild nature and ease of handling, TMSOTf was identified as the catalyst of choice for this study. Brief solvent screening with TMSOTf offered no further improvement in the yield (Table 1, entries 15-17).

With the optimized reaction conditions in hand (Scheme 10), the scope of the reaction was subsequently investigated, and the results are summarized in Table 2. Since the 6-benzoyloxy-*β*-pyrones (**13b** and **13g**) delivered the respective products (**29b, 29d** and **29g**) consistently in low yields under the optimized conditions, so acetates of *β*-pyrones **13** were preferred over benzoates during this study. List of diverse phenols and acetoxy & benzoyloxy pyaranones are shown in Figure 4 and Figure 5 respectively.




**Scheme 10.** General reaction scheme with optimized conditions.

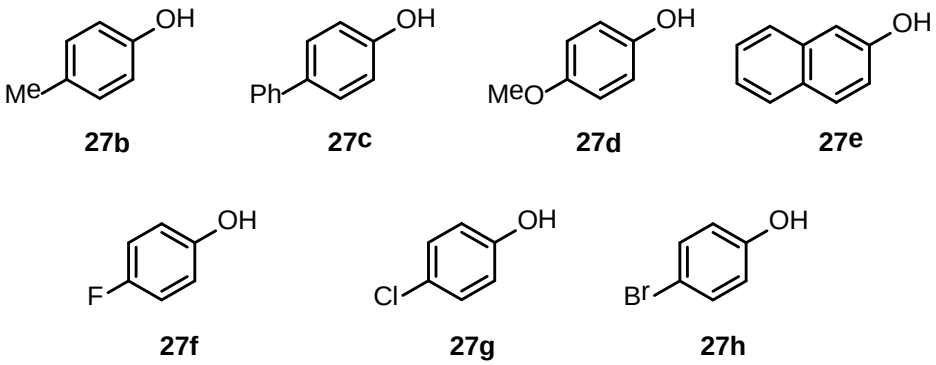



**Figure 4.** List of phenols employed in the study.

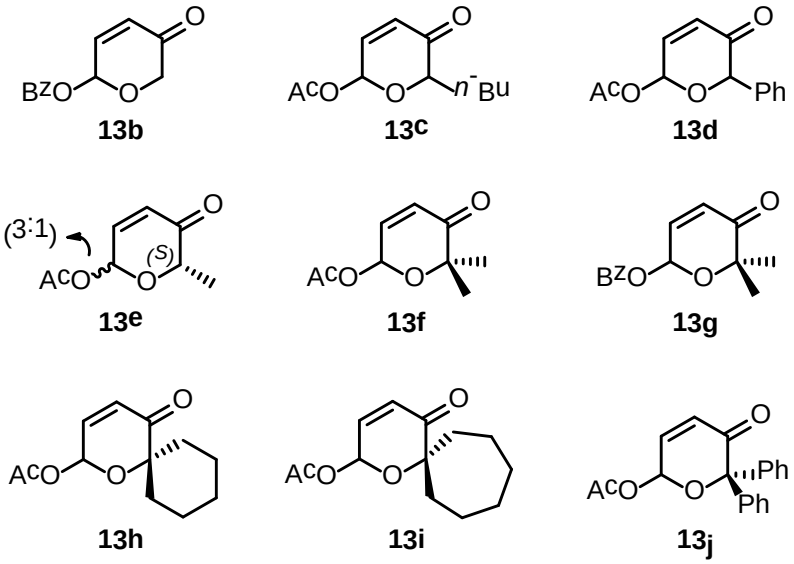
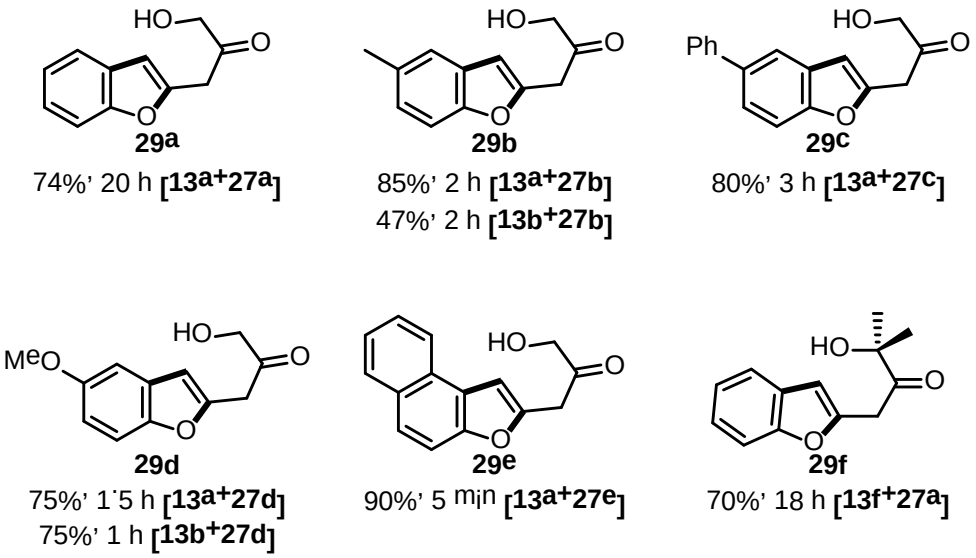
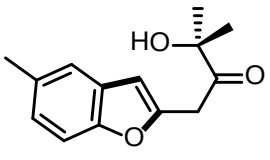


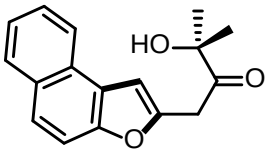

**Figure 5.** List of acetoxy and benzoyloxy pyranones employed in the study.

**Table 2**. Substrate scope[a,b]

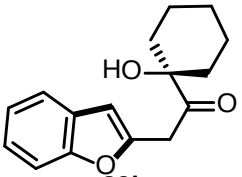




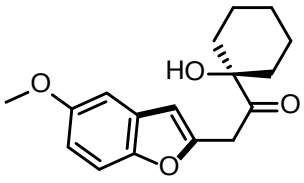
**29g**
70%, 2 h **[13f+27b]**[c]
40%, 2 h **[13g+27b]**



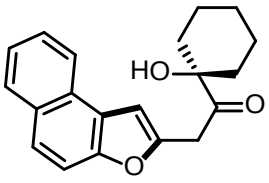
**29h**
92%, 5 min **[13f+27e]**



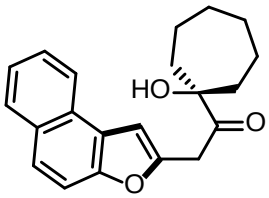
**29i**
60%, 2 h **[13h+27a]**



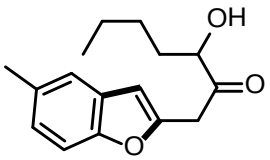
**29j**
66%, 2 h **[13h+27d]**



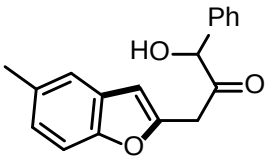
**29k**
90%, 7 min **[13h+27e]**



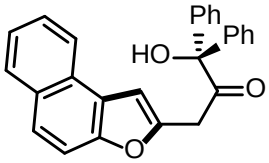
**29l**
92%, 8 min **[13i+27e]**



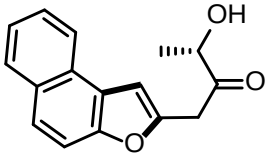
**29m**
78%, 6 h **[13c+27b]**



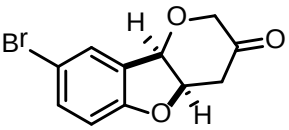
**29n**
85%, 20 min **[13d+27b]**



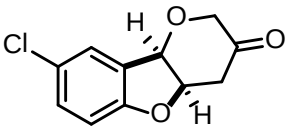
**29o**
80%, 20 min **[13j+27e]**



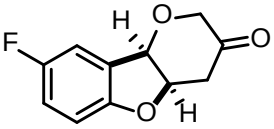
**29p**
$[\alpha]_D^{23}$ +6.327, *c* 0.06, $CHCl_3$
90%, 3 h **[13e+27e]**



**29q**
75%, 24 h **[13a+27h]**



**29r**
78%, 24 h **[13a+27g]**



**29s**
70%, 25 h **[13a+27f]**

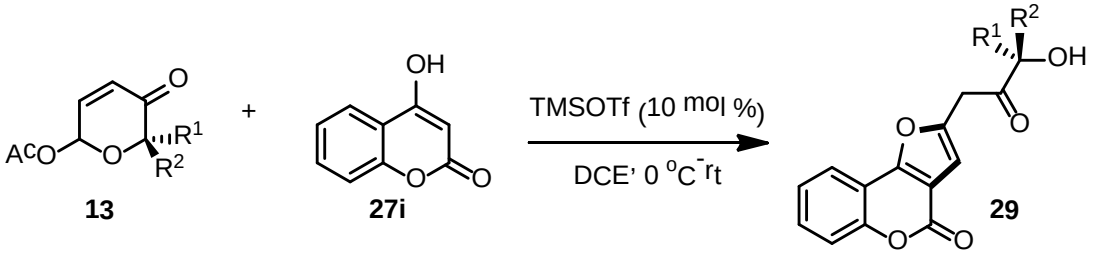
[a]A 5 mL glass vial was filled with **13** (0.2 mmol), **27** (0.22 mmol), and DCE (1 mL). TMSOTf (0.02 mmol) was then introduced at 0-5 °C. After stirring at the same temperature for 30 min, continued the reaction at room temperature until **13** and **28** disappeared (by TLC). [b]Isolated yield after column chromatography. [c]Structure confirmed by single crystal X-ray diffraction analysis[27].

A variety of 6-acetoxy-*β*-pyrones and phenols conveniently generated the respective benzofurans in good to excellent yields.[28] A range of possible substitution patterns on the pyrones were considered that provided 2-benzofuranyl propanones possessing 1°, 2° and 3°-alcoholic centres. Notably, chiral hydroxyacetones such as

**29p** can be easily assembled by employing this strategy. In particular, isolation of the alcohol **29p** in 93% ee, indicates the involvement of a non-racemizing process during the transformation which in turn signifies the mildness of the reaction conditions.

Interestingly, the reaction of the pyrone **13a** with halogenated phenols **27f-27h** generated only the 4,4a-dihydropyrano[3,2-*b*]benzofurans **29s**, **29r**, and **29q**. Even prolonged reaction times did not yield the expected 2-benzofuranyl-3-hydroxyacetones. This result has two-fold significance; it not only provided mechanistic insights about the conversion of **13** to **29**, but also provided a new entry for the synthesis of pyrano[3,2-*b*]benzofuran-3-ones.[29] In addition, the presence of halides on one end and ketone on the other end serve as excellent handles for further synthetic maneuvers.

Apart from phenols, strikingly, enols such as 4-hydroxycoumarin **27i** also proved to be a distinctive reactive partner in producing furocoumarins **29t-29v** in one simple step from 6-acetoxy-*β*-pyrones, Scheme 11. Furocoumarins are part of several bioactive natural products and medicinally interesting compounds (Figure 6).[30] Most of the synthetic approaches have focused on the construction of coumestanes. Only a few methods have been described for the synthesis of furo[3,2-*c*]coumarins.[31] In this regard, our approach depicted herein (Scheme 11) provides an unprecedented access for the synthesis of 2-alkylated furo[3,2-*c*]coumarins. (Table 3)




**Scheme 11**. Unprecedented approach for the synthesis of furo[3,2-*c*]coumarins **29**.

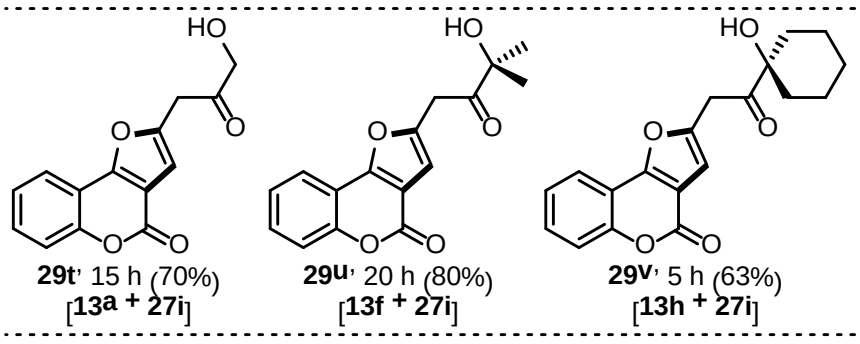



**Table 3.** List of furocoumarins synthesized.

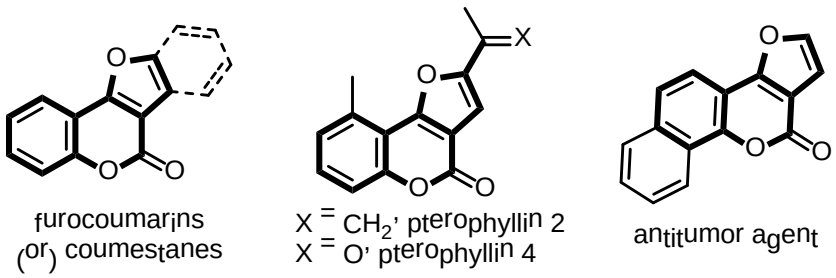
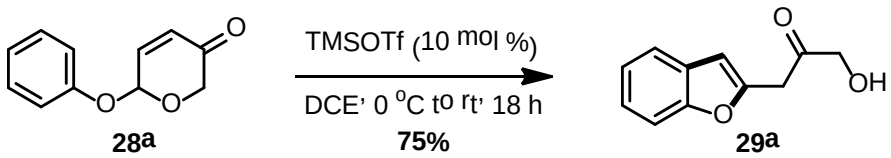


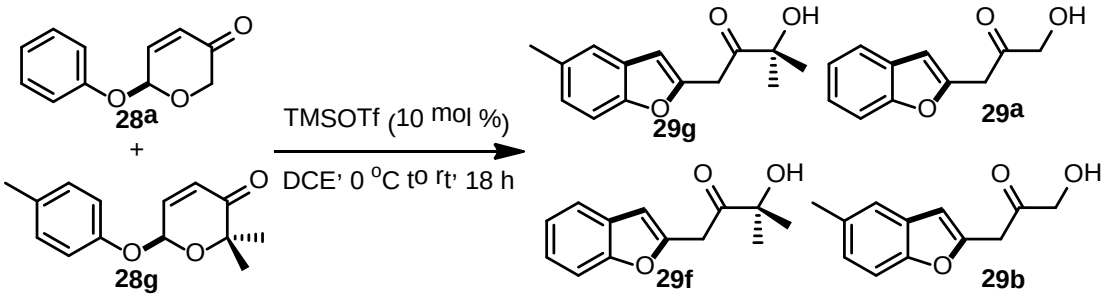

**Figure 6.** Representative examples of natural products having furocoumarin backbone.

To understand the mechanistic part, intermediate phenyl ether **28a** during the transformation of **13a** to **29a** was isolated and subjected to the optimized conditions. Benzofuran **29a** was obtained in 75% (Scheme 12).




**Scheme 12**. Conversion of phenyl ether **28a** to benzofuran **29a**.

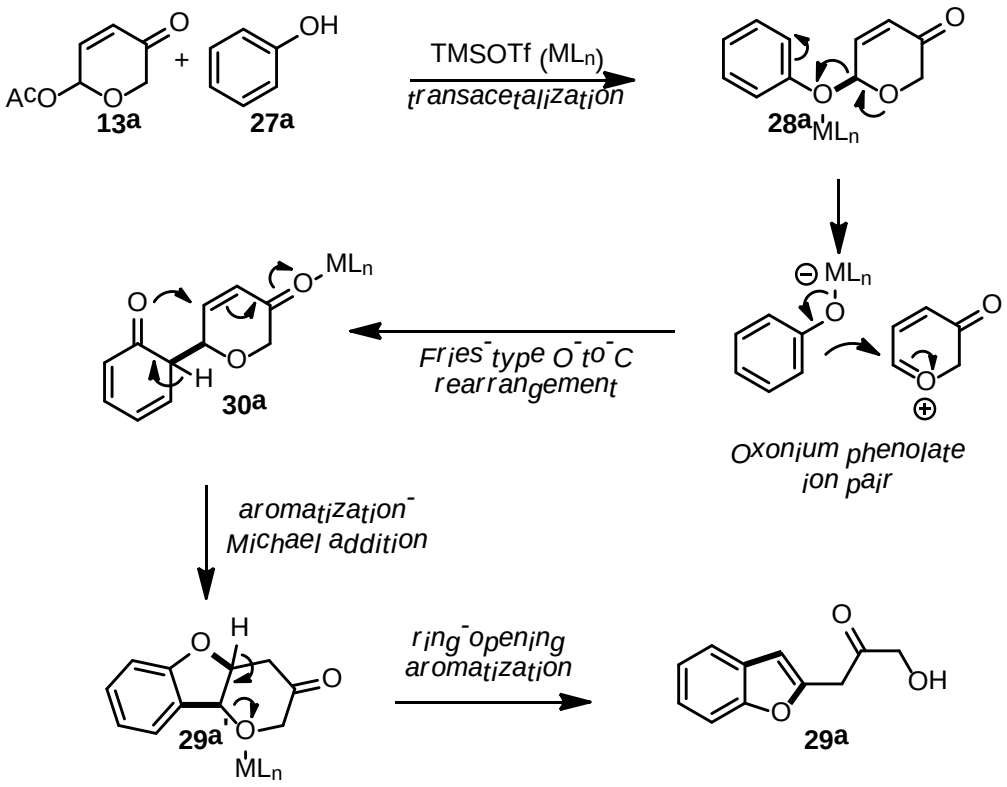
In order to validate the intermolecular nature of the Fries-type O→C rearrangement step during the conversion of **28a** to **29a**, a cross-over experiment between the phenyl ethers **28a** and **28g** was planned. Accordingly, a 1:1 mixture of the phenyl ethers **28a** and **28g** was subjected to the optimized conditions (Scheme 13). Crude reaction mixture and the fractions obtained after column chromatography purification were subjected to $^{1}$H-NMR analysis, which gave conclusive information regarding the intermolecular nature of the Fries-type O→C rearrangement step.




**Scheme 13**. Cross-over experiment between **28a** and **28g.**

Based on the experimental observations, a plausible mechanism has been proposed in Scheme 14. The cascade process begins with an acid catalyzed

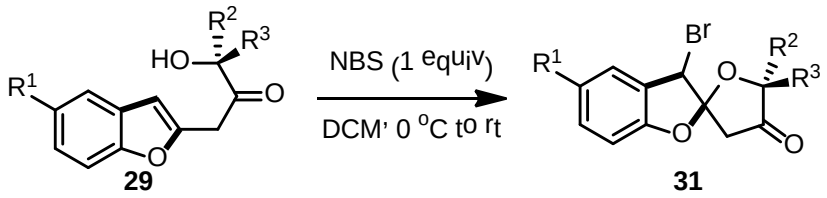
transacetalization followed by an unusual Fries-type O→C rearrangement[32] which leads to the formation of a neutral but unstable intermediate **30a** in a highly regio- and chemoselective manner.[33] Subsequently, **30a** undergoes aromatization and a concomitant oxa-Michael addition to form the 4,4a-dihydropyrano[3,2-*b*]benzofuran-3-one **29a'**. Further, acid-induced ring-opening aromatization of **29a'** delivers the 2-benzofuranyl-3-hydroxyacetone **29**.




**Scheme 14**. Plausible mechanism.

To further illustrate the generality and synthetic utility of this methodology, we considered an elaboration, Scheme 15. We intended to exploit the presence of alcohol functionality in the side chain in an intramolecular haloetherification reaction which would potentially generate spiro[benzofuran-2,2'-furan]-4'-ones.[34] Accordingly, reaction of the keto-alcohols **29a** and **29g** with NBS at room temperature conveniently furnished the respective 5,5-spiroketals **31a** and **31g** in excellent yields, thereby establishing a mere two-step unprecedented access from readily accessible 6-acetoxy-*β*-pyrones. List of these spiro compounds are depicted in Table 4. Prevalence of several bioactive natural products possessing the 5,5-spiroketal scaffold renders this

an attractive strategy for their easy synthesis.[35] Examples of natural products with a spiroketal backbone are shown in Figure 7.




**Scheme 15**. An unusual two-step synthetic approach for spiro[benzofuran-2,2'-furan]-4'-ones from *β*-pyrones.

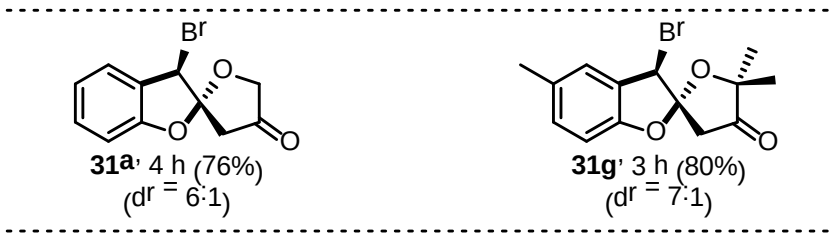



**Table 4.** List of Spiroketals synthesized.

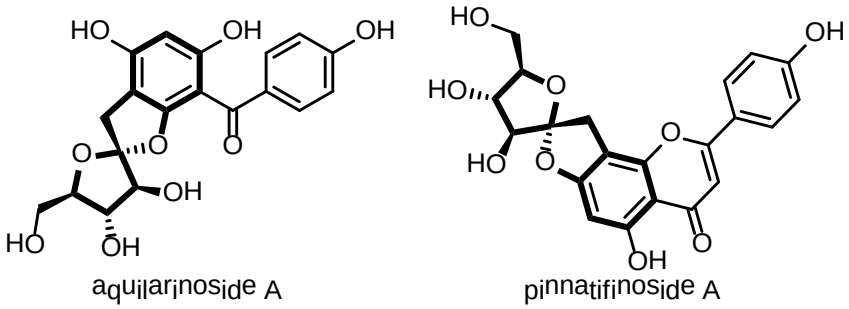
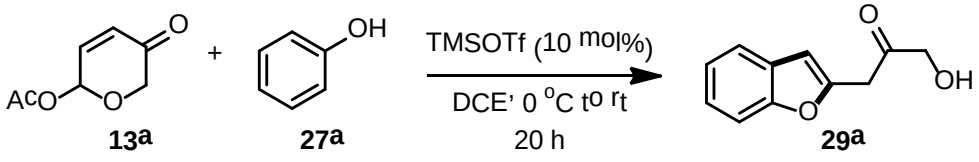



**Figure 7.** Representative examples of natural products having spiroketal backbone.

Two 'gram' scale reactions were carried out to demonstrate the scalability and practicality of the cascade process (Scheme 16). Reactions performed on 0.5 g (3.2 mmol) of **13a** and 1 g (6.4 mmol) scale of **27a** under the optimized conditions resulted in the formation of **29a** consistently in about 70% yield indicating the robustness of the present method.




0.5 g (3.2 mmol)
1.0 g (6.4 mmol)

0.461 g, **75%**
0.845 g, **70%**

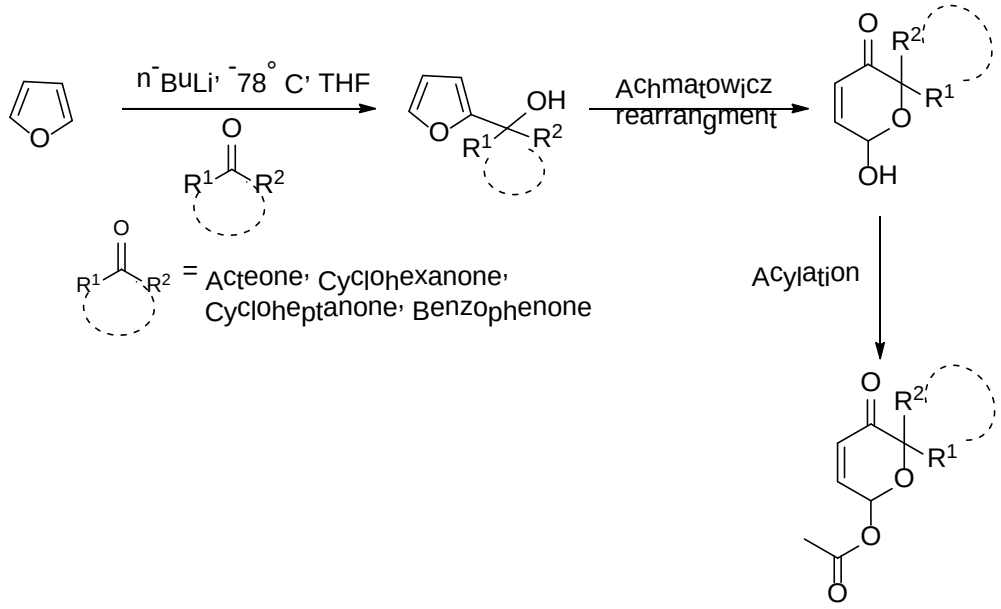
**Scheme 16**. Large scale reactions to verify the scalability of the present method.

# Chapter 3

# Experimental

**General experimental methods**: Starting compounds such as furan, furfural, (*S*)-1-(furan-2-yl) ethanol, phenols, and Lewis/Brønsted acids etc., were purchased from Sigma-Aldrich and were used without further purification. For thin layer chromatography (TLC), silica aluminum foils with fluorescent indicator 254 nm (from Aldrich) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. $H_2SO_4$ (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Column chromatography was performed using SD Fine silica gel 100-200 mesh (approximately 15–20 g per 1 g of the crude product). Dry THF was obtained by distillation over sodium and stored over sodium wire. IR spectra were recorded on a Perkin–Elmer FT IR spectrometer as thin films or KBr pellet, as indicated, with $\nu_{max}$ in inverse centimetres. Melting points were recorded on a digital melting point apparatus Stuart SMP30 and were uncorrected. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on a 400 MHz Bruker Biospin Avance III FT-NMR spectrometer. NMR shifts are reported as delta (δ) units in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are utilized to describe peak patterns when appropriate: br=broad, s=single, d=doublet, t=triplet, q=quartet and m=multiplet. Proton chemical shifts are given in δ relative to tetramethylsilane ($\delta$ 0.00 ppm) in $CDCl_3$ or in $(CD_3)_2SO$ ($\delta$ 2.50 ppm). Carbon chemical shifts are internally referenced to the deuterated solvent signals in $CDCl_3$ ($\delta$ 77.1 ppm) or in $(CD_3)_2SO$ ($\delta$ 39.5 ppm). Single crystal X-ray analysis was carried on an XtaLabmini diffractometer. High-resolution mass spectra were recorded on a Waters QTOF mass spectrometer. Optical rotations were recorded on Rudolph APIII/2W.

**Procedures:**



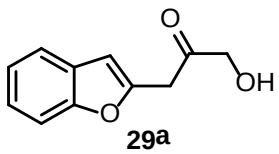

**Procedure A: Synthesis of substituted furfuryl alcohols.** To a stirred solution of furan (2 equiv) in dry THF at -78 °C under inert conditions, was added *n*-BuLi (1.6 M solution in cyclohexane, 2 equiv) dropwise (over a period of maximum 30 minutes). The reaction mixture was stirred for 30-45 following which dry acetone (1.2 equiv) was introduced and continued stirring for 30 minutes. The reaction was warmed to 0 °C. Upon completion, aq.$NH_4Cl$ was added to quench the reaction and diluted with EtOAc, and the layers were separated. The organic layer was washed with brine, the aqueous layers were extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield Substituted furfuryl alcohol (more than 90 % yield) as clear, colorless oil. An aliquot was removed and matched literature data. This material was used in the next reaction without further purification.

**Procedure B: Achmatowicz rearrangement**. To a stirred solution of furfuryl alcohol (1.00 equiv) in THF and water at 0 °C in a 50 mL pear flask were sequentially added sodium bicarbonate (2.00 equiv), sodium acetate (1.00 equiv), and NBS (1.00 equiv). Upon initial addition of NBS, the solution turned yellow and then orange after complete addition of solids. After 10 min, reaction was quenched at 0 °C with dil.HCl, diluted with EtOAc, and the layers were separated. The organic layer was

washed with brine, the aqueous layers were extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield Pyranone alcohol (100% yield) as a clear, colorless oil. An aliquot was removed and matched literature data. This material was used in the next reaction without further purification.

**Procedure C: Acetylation of 6-hydroxy-*β*-pyrone**. To a stirred solution of 6-hydroxy-*β*-pyrones (1 equiv) in dry $CH_2Cl_2$ was added acetic anhydride (1.1 equiv) and pyridine (1.1 equiv). The reaction mixture was stirred at $0^0$ C for 3 hours. The solvent was removed under vacuum and the residue was purified via column chromatography on silica. The product was colorless oil (95 %) that crystallized on cooling.

**General procedure for the optimization of reaction parameters.** An oven-dried 5 mL glass vial was charged with acetoxy pyranone **13a** (0.2 mmol, 1 equiv), phenol **27a** (0.22 mmol, 1.1 equiv) and an appropriate solvent (1 mL). A catalyst (10 mol%, 0.1 equiv) was then introduced at 0-5 $^oC$. The reaction mixture was stirred at the same temperature for 30 min, and continued stirring at room temperature until starting material disappeared as monitored by TLC. The reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with ethyl acetate (1-2 mL) and the layers were separated. The aqueous layer further extracted with ethyl acetate (1-2 mL) The organic layers were combined, dried over anhydrous $Na_2SO_4$, concentrated, and purified by silica gel column chromatography (hexanes/ethyl acetate) to afford the product **29a** as a pale yellow oil**.**



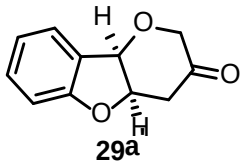

**29a**

**1-(Benzofuran-2-yl)-3-hydroxypropan-2-one (29a).**

This compound was isolated as pale yellow oil. $R_f$ = 0.2 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3454, 2923, 1738, 1454, 1365, 1228, 1216. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.30-7.35 (m, 2H), 6.67 (s, 1H), 4.42 (s, 2H), 3.94 (s, 2H), 3.01 (s, 1H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ

204.6, 155.0, 149.2, 128.2, 124.3, 123.0, 120.8, 111.1, 105.9, 67.9, 38.9**. HRMS (ESI):** *m/z* calcd for $C_{11}H_{11}O_3$ $(M+H)^+$: 191.0708; Found: 191.0711.

An intermediate during the transformation of **13a** to **29a**, the pyran-fused benzofuran **29a'** is isolable. The spectral data is given below.

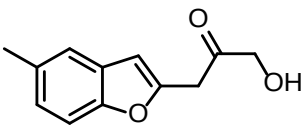



**29a**

**4,4a-Dihydro-2*H*-pyrano[2,3-*b*]benzofuran-3(9a*H*)-one (29a').**

This compound was isolated as pale yellow oil. Following the general procedure, in a separate reaction, 30 mg of **13a** afforded 18 mg of 29**a'** (50% yield). $R_f$ = 0.4 (EtOAc/Hexane = 3/7). **IR (thin film, neat):** $\nu_{max}/cm^{-1}$ 2969, 1737, 1494, 1434, 1365, 1228, 1216, 995, 909. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 3.0 Hz, 1H), 7.35-7.31 (m, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 5.54 (d, *J* = 7.3 Hz, 1H), 5.19 (dt, *J* = 7.4 and 3.6 Hz, 1H), 3.94 (d, *J* = 18.1 Hz, 1H), 3.55 (d, *J* = 18.1 Hz, 1H), 3.10-3.05 (m, 2H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 207, 160.6, 131.6, 126.9, 122.6, 121.8, 110.2, 79.2, 75.8, 68.7, 39.7. **HRMS (ESI):** *m/z* calcd for $C_{11}H_9O_3$ $(M-H)^+$: 189.0552; Found: 189.0547.

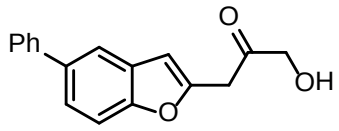
**General procedure for the substrate screening.** An oven-dried 5 mL glass vial was charged with the acetoxy pyranones **13** (0.2 mmol, 1 equiv), phenols **27** (0.22 mmol, 1.1 equiv), 1,2-dichloroethane (1 mL) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 10 mol%, 0.1 equiv) was added at 0-5 $^o$ C. Then the reaction mixture was stirred at same temperature for 30 min, and continued at room temperature until starting material disappeared as monitored by TLC. The reaction mixture was quenched with aqueous sodium bicarbonate solution, diluted with ethyl acetate (1-2 mL) and the layers were separated. The aqueous layer further extracted with ethyl acetate (1-2 mL) The organic layers were combined, dried over anhydrous $Na_2SO_4$, concentrated, and purified by silica gel column chromatography (hexanes/ethyl acetate) to afford the respective product (**29**).




**29b**

**1-Hydroxy-3-(5-methylbenzofuran-2-yl)propan-2-one (29b).**

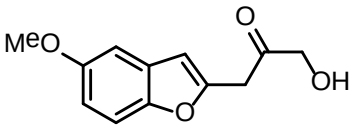
This compound was isolated as colourless solid. Following the general procedure, 30 mg of **13a** afforded 33 mg of **29b** (85% yield). M.P. = 103-104 $^{o}$C. $R_f$ = 0.2 (Hexane/EtOAc = 7/3). **IR** (thin film, neat): $\nu_{max}$ /cm$^{-1}$ 3352, 2923, 2855, 1723, 1471, 1261, 1050, 800. **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 7.35-7.34 (m, 2H), 7.11-7.09 (m, 1H), 6.59 (q, *J* = 1.0 Hz, 1H), 4.41 (s, 2H), 3.92 (s, 2H), 3.02 (s, 1H), 2.45 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ, 204.7, 153.4, 149.3, 132.5, 128.3, 125.5, 120.7, 110.5, 105.7, 67.9, 39.0, 21.5. **HRMS (ESI):** *m/z* calcd for $C_{12}H_{11}O_3$ $(M–H)^+$: 203.0708; Found: 203.0709.




**29c**

**1-Hydroxy-3-(5-phenylbenzofuran-2-yl)propan-2-one (29c).**

This compound was isolated as colourless solid. Following the general procedure, 30 mg of **13a** afforded 41 mg of **29c** (80% yield). M.P = 97-99 $^{o}$C. $R_f$ = 0.2 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}$/cm$^{-1}$ 3453, 2924, 2855, 1737, 1460, 1365, 1216, 764. **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.75-7.74 (m, 1H), 7.64-7.61 (m, 2H), 7.53-7.50 (m, 2H), 7.49-7.47 (m, 2H), 7.39-7.37 (m, 1H), 6.72 (d, *J* = 0.5 Hz, 1H), 4.44 (s, 2H), 3.96 (s, 2H), 3.10 (s, 1H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 204.5, 154.6, 150.0, 141.4, 136.8, 128.8, 128.7 (2C), 127.4 (2C), 126.9, 124.0, 119.4, 111.2, 106.2, 68.0, 38.9. HRMS (ESI): *m/z* calcd for $C_{17}H_{13}O_3$ $(M–H)^+$: 265.0865; Found: 265.0858.

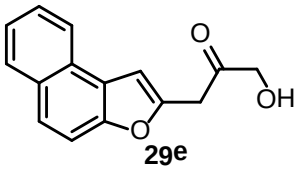



**29d**

**1-Hydroxy-3-(5-methoxybenzofuran-2-yl)propan-2-one (29d).**

This compound was isolated as pale yellow liquid. Following the general procedure, 30 mg of **13a** afforded 32 mg of **29d** (75% yield).$R_f$ = 0.2 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}$/cm$^{-1}$ 3424, 2924, 1730, 1476, 1206, 1030. **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.8 and 2.4

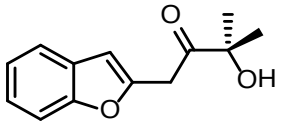
Hz, 1H), 6.60 (d, *J* = 0.7 Hz, 1H), 4.41 (s, 2H), 3.91 (s, 2H), 3.86 (s, 3H), 3.01 (s, 1H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 204.6, 156.0, 150.05, 150.02, 128.8, 112.9, 112.5, 106.1, 103.3, 67.9, 55.9, 39.0 **HRMS (ESI):** *m/z* calcd for $C_{12}H_{13}O_4$ $(M+H)^+$: 221.0814; Found: 221.0838




**29e**

**1-Hydroxy-3-(naphtho[2,1-*b*]furan-2-yl)propan-2-one (29e).**

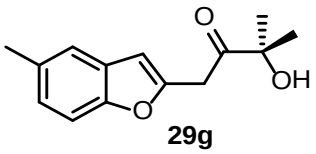
This compound was isolated as light brown solid. Following the general procedure, 30 mg of **13a** afforded 42 mg of **29e** (90% yield). M.P. = 97-99 $^oC$. $R_f$ = 0.2 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3410, 2892, 1727, 1394, 1155, 1040, 944, 809. **$^1$H NMR** (400 MHz, $(CD_3)_2SO$): δ 8.24 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.77 (q, *J* = 8.90 Hz, 2H), 7.61 (td, *J* = 7.60 Hz, 1H), 7.53-7.51 (m, 1H), 7.36 (s, 1H), 4.28 (s, 2H), 4.16 (s, 2H), 3.50 (s, 1H). **$^{13}$C NMR** (100 MHz, $(CD_3)_2SO$): δ 206.6, 152.0, 151.8, 130.3, 129.0, 127.4, 126.8, 125.0, 124.9, 124.0, 123.9, 112.6, 105.0, 67.9, 38.5. HRMS (ESI): *m/z* calcd for $C_{15}H_{13}O_3$ $(M+H)^+$: 241.0865; Found: 241.0869.




**29f**

**1-(Benzofuran-2-yl)-3-hydroxy-3-methylbutan-2-one (29f).**

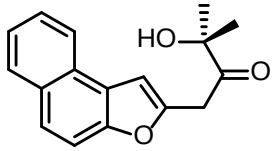
This compound was isolated as pale yellow oil. Following the general procedure, 30 mg of **13f** afforded 25 mg of **29f** (70% yield). $R_f$ = 0.3 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3446, 2926, 1719, 1454, 1366, 1194, 1051, 1252, 794. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.56-7.54 (m, 1H), 7.47-7.45 (m, 1H), 7.28-7.25 (m, 2H), 6.66 (q, *J* = 1.0 Hz, 1H), 4.11 (d, *J* = 1.0 Hz, 2H), 3.48 (s, 1H), 1.51(s, 6H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 209.1, 154.8, 150.4, 128.4, 124.0, 122.8, 120.7, 111.0, 105.6, 76.9, 35.9, 26.5 ($2CH_3$). HRMS (ESI): *m/z* calcd for $C_{13}H_{13}O_3$ $(M–H)^+$: 217.0865; Found: 217.0860.




**29g**

**3-Hydroxy-3-methyl-1-(5-methylbenzofuran-2-yl)butan-2-one (29g).**

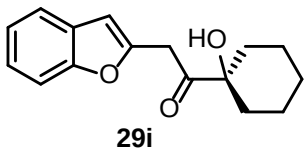
This compound was isolated as pale yellow solid. Following the general procedure, 30 mg of **13f** afforded 28 mg of **29g** (74% yield). M.P. = 63-68 $^{o}$C. $R_f$ = 0.4 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3440, 2925, 2855, 1719, 1474, 1377, 1265, 1204, 1051, 952, 798. **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.33 (m, 2H), 7.09 (d, *J* = 0.5 Hz, 1H), 6.58 (q, *J* = 0.8 Hz, 1H), 40.8 (d, *J* = 0.8 Hz, 2H), 3.47 (s, 1H), 2.45 (s, 3H), 1.49 (s, 6H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 209.1, 153.2, 150.5, 132.2, 128.5, 125.2, 120.6, 110.5, 105.3, 76.8, 36.0, 26.5, 21.3 (2C). HRMS (ESI): *m/z* calcd for $C_{14}H_{15}O_3$ $(M–H)^+$: 215.1072; Found: 215.1060.




**29h**

**3-Hydroxy-3-methyl-1-(naphtho[2,1-*b*]furan-2-yl)butan-2-one (29h).**

This compound was isolated as light yellow solid. Following the general procedure, 30 mg of **13f** afforded 40 mg of **29h** (92% yield). M.P. = 89-91 $^{o}$C. $R_f$ = 0.3 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3500, 2922, 1713, 1463, 1385, 1191, 952, 802. **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 8.13-8.10 (m, 1H), 7.96 (d, *J* = 8 Hz, 1H), 7.73-7.64 (m, 1H), 7.62-7.59 (m, 2H), 7.58-7.50 (m, 1H), 7.16 (d, *J* = 0.8 Hz, 1H), 4.20 (s, 2H), 3.49 (s, 1H), 1.53 (s, 6H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 209.2, 152.3, 149.6, 130.3, 128.7, 127.4, 126.2, 124.9, 124.5, 123.6, 123.4, 112.1, 104.7, 76.9, 36.1, 26.5 (2C). HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_3$ $(M–H)^+$: 267.1021; Found: 267.1008.

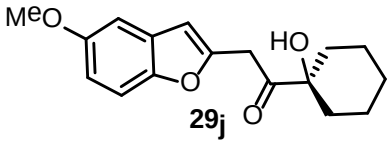



**29i**

**2-(Benzofuran-2-yl)-1-(1-hydroxycyclohexyl)ethanone** (**29i**).

This compound was isolated as pale yellow oil. Following the general procedure, 30 mg of **13h** afforded 21 mg of **29i** (60% yield). $R_f$ = 0.4 (Hexane/EtOAc = 7/3). IR

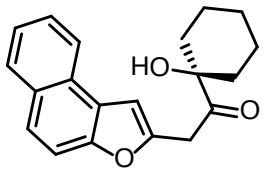
(thin film, neat): $\nu_{max}$ /cm$^{-1}$ 3440, 2933, 2857, 1713, 1595, 1453, 1251, 986, 955. **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.55-7.53 (m, 1H), 7.46-7.44 (m, 1H), 725-7.24 (m, 2H), 6.64 (d, *J* = 0.8 Hz, 1H), 4.13 (d, *J* = 0.5 Hz, 2H), 3.15 (s, 1H), 1.86-1.69 (m, 10H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 209.3, 154.8, 150.8, 128.5, 123.9, 122.7, 120.7, 111.0, 105.5, 78.6, 36.1, 33.7 (2C), 25.1, 20.9 (2C). HRMS (ESI): *m/z* calcd for $C_{16}H_{17}O_3$ $(M–H)^+$: 257.1178; Found: 257.1170.



**29j**

**1-(1-Hydroxycyclohexyl)-2-(5-methoxybenzofuran-2-yl)ethanone (29j).**

This compound was isolated as pale brown solid Following the general procedure, 30 mg of **13h** afforded 26 mg of **29j** (66% yield). M.P. = 93-95 $^{o}$C. $R_f$ = 0.4 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}$/cm$^{-1}$ 3409, 2927, 1714, 1510, 1206, 1034, 827. **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 2.7 Hz, 1H), 6.86 (dd, *J* = 8.90 and 2.60 Hz, 1H), 6.57 (s, 1H), 4.09 (s, 2H), 3.85 (s, 3H), 3.17 (s, 1H), 1.79-1.59 (m, 10H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 209.4, 155.9, 151.6, 149.8, 129.1, 112.4, 111.4, 105.6, 103.3, 78.6, 55.9, 36.2, 33.6 (2C), 25.1, 20.9 (2C). HRMS (ESI): *m/z* calcd for $C_{17}H_{19}O_4$ $(M–H)^+$: 287.1284; Found: 287.1278.

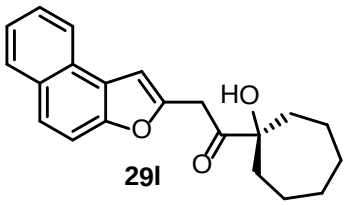


**29k**

**1-(1-Hydroxycyclohexyl)-2-(naphtho[2,1-*b*]furan-2-yl)ethanone (29k).**

This compound was isolated as white solid. Following the general procedure, 30 mg of **13h** afforded 37 mg of **29k** (90% yield). M.P. = 125-127 $^{o}$C. $R_f$ = 0.5 (Hexane/EtOAc = 1/4). IR (thin film, neat): $\nu_{max}$ /cm$^{-1}$ 3489, 2941, 1696, 1379, 1150, 993, 799. **$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.73-7.70 (m, 1H), 7.64-7.57 (m, 2H), 7.52-7.48 (m, 1H), 7.15 (d, *J* = 0.5 Hz, 1H), 4.23 (d, *J* = 6.5 Hz, 2H) 3.17 (s, 1H) 1.89-1.70 (m, 10H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 209.5, 152.3, 150.0, 130.2, 128.7, 127.4, 126.2, 124.8, 124.4, 123.7,

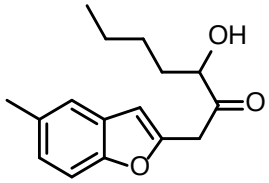
123.4, 112.1, 104.6, 78.7, 36.3, 33.7 (2C), 25.1, 21.0 (2C). HRMS (ESI): *m/z* calcd for $C_{20}H_{19}O_3$ $(M–H)^+$: 307.1334; Found: 307.1342




**29l**

**1-(1-Hydroxycycloheptyl)-2-(naphtho[2,1-*b*]furan-2-yl)ethanone (29l).**

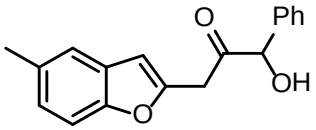
This compound was isolated as light brown solid. Following the general procedure, 30 mg of **13i** afforded 40 mg of **29l** (92% yield). M.P. = 110-112 $^oC$. $R_f$ = 0.5 (Hexane/EtOAc = 4/1). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3405, 2925, 1711, 1629, 1602, 1385, 1211, 1046, 846. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.13-8.10 (m, 1H), 7.97-7.94 (m, 1H), 7.73-7.71 (m, 1H), 7.64-7.57 (m, 2H), 7.52-7.48 (m, 1H), 7.15 (d, *J* = 0.8 Hz, 1H), 4.21 (d, *J* = 0.8 Hz, 2H), 3.23 (s, 1H), 2.07-2.01 (m, 2H) 1.88-1.68 (m, 10H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 209.5, 152.3, 150.1, 130.2, 128.7, 127.5, 126.2, 124.8, 124.4, 123.7, 123.4, 112.1, 104.6, 81.5, 37.7 (2C), 36.2, 29.2 (2C), 22.9 (2C). HRMS (ESI): *m/z* calcd for $C_{21}H_{21}O_3$ $(M–H)^+$: 321.1491; Found: 321.1501.




**29m**

**3-Hydroxy-1-(5-methylbenzofuran-2-yl)heptan-2-one (29m).**

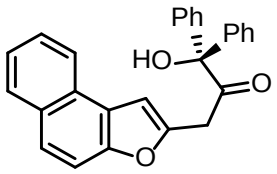
This compound was isolated as pale yellow oil. Following the general procedure, 30 mg of **13c** afforded 29 mg of **29m** (78%). $R_f$ = 0.5 (EtOAc/Hexane = 1/4). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3429, 2925, 2856, 1721, 1515, 1472, 1267, 1082, 822. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.32 (m, 2H), 7.09 (dd, *J* = 8.6 and 1.2 Hz, 1H), 6.58 (d, *J* = 0.7 Hz, 1H), 4.37-4.35 (m, 1H), 3.98 (s, 2H), 3.33 (d, *J* = 4.6 Hz, 1H), 2.45 (s, 3H), 1.94-1.90 (m, 1H), 1.68-1.63 (m, 2H) 1.47-1.40 (m, 3H) 0.95-0.91 (m, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 207.2, 153.3, 149.8, 132.3, 128.4, 125.4, 120.6, 110.5, 105.5, 76.2, 38.2, 33.2, 26.8, 22.4, 21.3, 13.9. **HRMS (ESI):** *m/z* calcd for $C_{16}H_{21}O_3$ $(M+H)^+$: 261.1491; Found: 261.1496.




**29n**

**1-Hydroxy-3-(5-methylbenzofuran-2-yl)-1-phenylpropan-2-one (29n**).

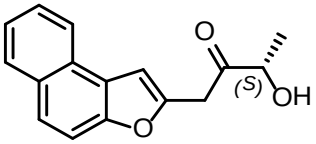
This compound was isolated as Pale yellow oil. Following the general procedure, 30 mg of **13d** afforded 29 mg of **29n** (80% yield). $R_f$ = 0.3 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3467, 2923, 2853, 1724, 1452, 1261, 1044, 800. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.44-7.36 (m, 5H), 7.32-7.30 (m, 2H), 7.09 (dd, *J* = 8.4 and 1.6 Hz, 1H), 6.44 (d, *J* = 0.7 Hz, 1H) 5.31 (s, 1H), 4.26 (s, 1H), 3.92-3.75 (m, 2H), 2.45 (s, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 204.3, 153.3, 149.5, 137.2, 132.3, 129.1, 129.0, 128.43, 128.41, 127.6, 125.3, 120.6, 110.5, 105.6, 79.4, 38.0, 21.3. **HRMS (ESI):** *m/z* calcd for $C_{18}H_{15}O_3$ $(M–H)^+$: 279.1021; Found: 279.1025.




**29o**

**1-Hydroxy-3-(naphtho[2,1-*b*]furan-2-yl)-1,1-diphenylpropan-2-one (29o).**

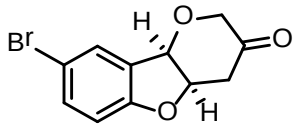
This compound was isolated as pale yellow oil. Following the general procedure, 30 mg of **13j** afforded 31 mg of **29o** (80% yield). $R_f$ = 0.3 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3500, 2922, 1713, 1463, 1385, 1191, 952, 802. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.3 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.74-7.70 (m, 1H), 7.63-7.57 (m, 2H), 7.51-7.44 (m, 11H), 6.99 (s, 1H), 4.56 (s, 1H), 4.21 (s, 2H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 206.1, 152.3, 149.6, 141.0, 130.2, 128.7, 128.5, 128.1, 127.5, 126.2, 124.8, 124.4, 123.6, 123.4, 112.2, 104.6, 86.0, 38.4. HRMS (ESI): *m/z* calcd for $C_{27}H_{20}NaO_3$ $(M+Na)^+$: 415.1310; Found: 415.1299.




**29p**

***(S)*-3-Hydroxy-1-(naphtho[2,1-*b*]furan-2-yl)butan-2-one (29p).**

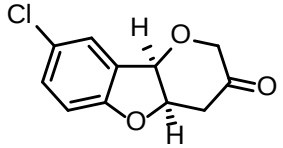
This compound was isolated as Pale yellow semisolid. Following the general procedure, 30 mg of **13e** afforded 41 mg of **29p** (90% yield). $R_f$ = 0.2 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3434, 1721, 1577, 1383, 951, 807. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 8.12-8.10 (m, 1H), 7.97-7.95 (m, 1H), 7.74-7.72 (m, 1H), 7.64-7.60 (m, 2H), 7.51 (ddd, *J* = 8.2, 6.9, and 1.3 Hz, 1H), 7.154-7.150 (m, 1H), 4.52-4.45 (m, 1H), 4.10 (dd, *J* = 2.8 and 0.8 Hz, 2H), 3.46 (s, 1H), 1.51-149 (m, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 207.5, 152.4, 149.0, 130.3, 128.7, 127.4, 126.3, 125.1, 124.6, 123.6, 123.4, 112.1, 104.9, 72.5, 38.0, 19.7. HRMS (ESI): *m/z* calcd for $C_{16}H_{13}O_3$ $(M–H)^+$: 253.0865; Found: 253.0870. **Optical rotation:** $[\alpha]_D^{23}$ +6.327 (*c* 0.06, $CHCl_3$) for a sample with *ee* 93%. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak AS column (90:10 *n*-Hexane/2-Propanol, 1.0 mL/min, 254 nm, $\tau_{major}$ = 63.7 min, $\tau_{minor}$ = 21.8 min).




**29q**

**8-Bromo-4,4a-dihydro-2*H*-pyrano[3,2-*b*]benzofuran-3(9*bH*)-one (29q).**

This compound was isolated as a pale brown oil. Following the general procedure, 30 mg of **13a** afforded 39 mg of **29q** (75 % yield). $R_f$ = 0.5 (EtOAc/Hexane = 3/7). **IR (thin film, neat):** $\nu_{max}/cm^{-1}$ 1731, 1587, 1489, 1470, 1233, 1087, 823, 605. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 2.2 Hz, 1H), 7.43 (dd, *J* = 8.6 and 2.2 Hz, 1H), 6.76-6.73 (m, 1H), 5.52 (d, *J* = 7.3 Hz, 1H), 5.23 (dt, *J* = 7.3 and 3.7 Hz, 1H), 3.98 (d, *J* = 18.1 Hz, 1H), 3.26 (d, *J* = 18.1 Hz, 1H), 3.10-2.99 (m, 2H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 207.1, 183.6, 134.5, 129.8, 113.5, 111.9, 109.7, 79.9, 75.4, 68.7, 39.5**.** HRMS (ESI): *m/z* calcd for $C_{11}H_8BrO_3$ $(M–H)^+$: 266.9657; Found: 266.9649.

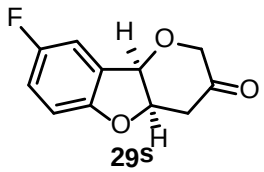



**29r**

**8-Chloro-4,4a-dihydro-2*H*-pyrano[3,2-*b*]benzofuran-3(9b*H*)-one (29r).**

This compound was isolated as colourless oil. Following the general procedure, 30 mg of **13a** afforded 34 mg of **29r** (78 % yield. $R_f$ = 0.5 (EtOAc/Hexane = 3/7). **IR**

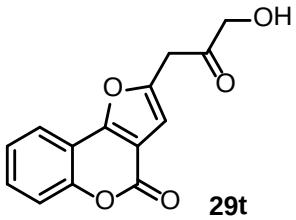
**(thin film, neat):** $\nu_{max}/cm^{-1}$ 1731, 1587, 1489, 1470, 1233, 1087, 823, 605. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 2.2 Hz, 1H), 7.31-7.27 (m, 1H), 6.80-6.76 (m, 1H), 5.23 (dt, *J* = 7.3 and 3.7 Hz, 1H), 3.99-3.64 (m, 1H), 3.58-3.54 (m, 1H), 3.10-2.99 (m, 2H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 207.4, 159.2, 131.6, 129.4, 126.9, 116.6, 111.4, 80.0, 75.5, 68.7, 39.5**.** HRMS (ESI): *m/z* calcd for $C_{11}H_8ClO_3$ $(M–H)^+$: 223.0162; Found: 223.0163.



**29s**

**8-Fluoro-4,4a-dihydro-2*H*-pyrano[3,2-*b*]benzofuran-3(9b*H*)-one (29s).**

This compound was isolated as colorless oil. Following the general procedure, 30 mg of **13a** afforded 28 mg of **29s** (70% yield). $R_f$ = 0.5 (EtOAc/Hexane = 3/7). **IR (thin film, neat):** $\nu_{max}/cm^{-1}$ 1738, 1510, 1484, 1221, 1194, 794, 835. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 7.5 and 2.8 Hz, 1H), 7.04-7.03 (m, 1H), 6.80-6.77 (m, 1H), 5.52 (d, *J* = 7.3 Hz, 1H), 5.24-5.22 (m, 1H), 3.97 (d, *J* = 18.1 Hz, 1H), 3.56 (d, *J* = 18.1 Hz, 1H), 3.05 (dd, *J* = 6.0 and 3.5 Hz, 2H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 207.3, 157.8 (d, *J* = 238.12 Hz, 1C), 156.6, 118.5 (d, *J* = 24.60 Hz, 1C), 116.0, 113.4 (d, *J* = 24.05 Hz, 1C), 110.8, 79.9, 75.8, 68.7, 39.6. **HRMS (ESI):** *m/z* calcd for $C_{11}H_{10}FO_3$ $(M+H)^+$: 209.0614; Found: 209.0608.

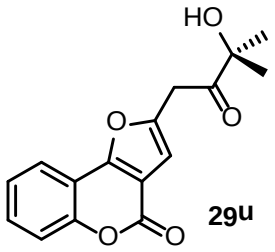


**29t**

**2-(3-Hydroxy-2-oxopropyl)-4*H*-furo[3,2-*c*]chromen-4-one (29t).**

This compound was isolated as pale yellow liquid. Following the general procedure, 30 mg of **13a** afforded 35 mg of **29t** (70% yield). $R_f$ = 0.2 (Hexane/EtOAc = 7/3). **IR** (thin film, neat): $\nu_{max}/cm^{-1}$ 3427, 2929, 1733, 1632, 1059, 897. **$^1$H NMR (400 MHz, $CDCl_3$):** δ 7.84 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.56-7.52 (m, 1H), 7.46-7.44 (m, 1H), 7.36 (td, *J* = 7.5 and 1.1 Hz, 1H), 6.89 (s, 1H), 4.45 (s, 2H), 4.01 (s, 2H) 3.01 (s, 1H). **$^{13}$C NMR (100 MHz, $CDCl_3$):** δ 203.6. 158.0, 157.7, 152.5, 149.8, 130.9, 124.6,

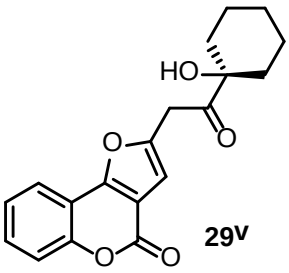
120.8, 117.4, 112.4, 111.5, 107.6, 68.1, 38.0. **HRMS (ESI):** *m/z* calcd for $C_{14}H_9O_5$ $(M–H)^+$: 257.0450; Found: 257.0451.




**29u**

**2-(3-Hydroxy-3-methyl-2-oxobutyl)-4*H*-furo[3,2-*c*]chromen-4-one (29u).**

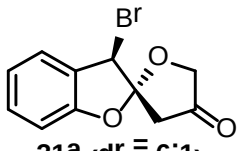
This compound was isolated as pale yellow solid. Following the general procedure, 30 mg of **13f** afforded 37 mg of **29u** (80% yield). M.P. = 132-135 $^oC$. $R_f$ = 0.3 (Hexane/EtOAc = 7/3). IR (thin film, neat): $\nu_{max}/cm^{-1}$ 3428, 2934, 2856, 1732, 1461, 1062, 974, 795. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.52-7.43 (m, 2H), 7.36-7.32 (m, 1H), 6.87 (s, 1H), 4.19 (d, *J* = 0.7 Hz, 2H), 3.26 (s, 1H), 1.52 (s, 6H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 208.3, 158.2, 157.4, 152.4, 151.2, 130.6, 124.5, 120.8, 117.3, 112.6, 112.5, 107.3, 76.9, 35.4, 26.6 (2C). HRMS (ESI): *m/z* calcd for $C_{16}H_{14}NaO_5$ $(M+Na)^+$: 309.0739; Found: 309.0729.




**29v**

**2-(2-(1-Hydroxycyclohexyl)-2-oxoethyl)-4H-furo[3,2-*c*]chromen-4-one (29v).**

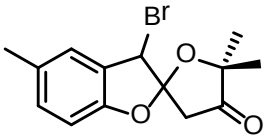
This compound was isolated as Pale yellow solid. Following the general procedure, 30 mg of **13h** afforded 28 mg of **29v** (63% yield). M.P. = 131-133 $^oC$. $R_f$ = 0.5 (Hexane/EtOAc = 4/1). IR (thin film, neat): $\nu_{max}$ /cm$^-$ 3457, 2934, 1734, 1632, 1448, 1164, 1100, 947. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 7.8 and 1.5Hz, 1H), 7.54-7.50 (m, 1H), 7.45-7.43 (m, 1H), 7.36-7.32 (m, 1H), 6.84 (s, 1H), 4.20 (s, 2H), 3.20 (s, 1H), 1.86-1.65 (m, 10H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 208.7, 158.2, 157.3, 152.4, 151.6, 130.6, 124.5, 120.8, 117.3, 112.6, 111.5, 107.1, 78.7, 35.7, 33.7 (2C), 25.1, 20.9 (2C). **HRMS (ESI):** *m/z* calcd for $C_{19}H_{19}O_5$ $(M+H)^+$: 327.1232; Found: 327.1222.




**31a (dr = 6:1)**

**3-Bromo-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-4'(5'*H*)-one (31a).**

This compound was isolated as pale yellow oil. Following the general procedure, 30 mg of **29a** afforded 31 mg of **31a** (73% yield. $R_f$ = 0.6 (EtOAc/Hexane = 2/8). **IR (thin film, neat**): $\nu_{max}/cm^{-1}$ 2918, 1770, 1594, 1467, 1322, 1284, 1166, 1034, 906, 880, 751, 672. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 8.9 Hz, 1H), 7.08-7.05 (m, 1H), 6.93-6.90 (m, 1H), 5.49 (s, 1H), 4.34-4.33 (m, 2H), 3.29-3.24 (m, 1H), 3.04 (d, *J* = 18.8 Hz, 1H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 209.5, 157.3, 134.2, 131.2, 126.0, 122.7, 117.5, 111.1, 72.5, 50.6, 46.2. **HRMS (ESI)**: *m/z* calcd for $C_{11}H_{10}BrO_3$ $(M+H)^+$: 268.9813; Found: 268.9802.




**31g (dr = 7:1)**

**3-Bromo-5,5',5'-trimethyl-3*H*,3'*H*-spiro[benzofuran-2,2'-furan]-4'(5'*H*)-one (31g).**

This compound was isolated as white solid. Following the general procedure, 30 mg of **29g** afforded 32 mg of **31g** (80% yield.) M.P. = 103-104 $^oC$ $R_f$ = 0.6 (EtOAc/Hexane = 1/9). **IR (thin film, neat):** $\nu_{max}/cm^{-1}$ 2923, 1761, 1489, 1304, 1108, 839, 814. **$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.26-7.25 (m, 1H), 7.11-7.02 (m, 1H), 6.80-6.77 (m, 1H), 5.39 (s, 1H), 3.41-3.36 (m, 1H), 3.11-3.06 (m, 1H), 2.34 (s, 3H), 1.45 (s, 3H) 1.33 (s, 3H). **$^{13}$C NMR** (100 MHz, $CDCl_3$): δ 213.5, 155.3, 132.0, 131.8, 126.8, 126.1, 115.0, 110.6, 85.3, 52.3, 45.3, 25.1, 25.0, 20.8**.** HRMS (ESI): *m/z* calcd for $C_{14}H_{14}BrO_3$ $(M-H)^+$: 309.0127; Found: 309.0138.

**Crystal structure of 29g (CCDC 1437901):** Structure of the benzofuran derivative **29g** was confirmed by single crystal X-ray diffraction analysis.

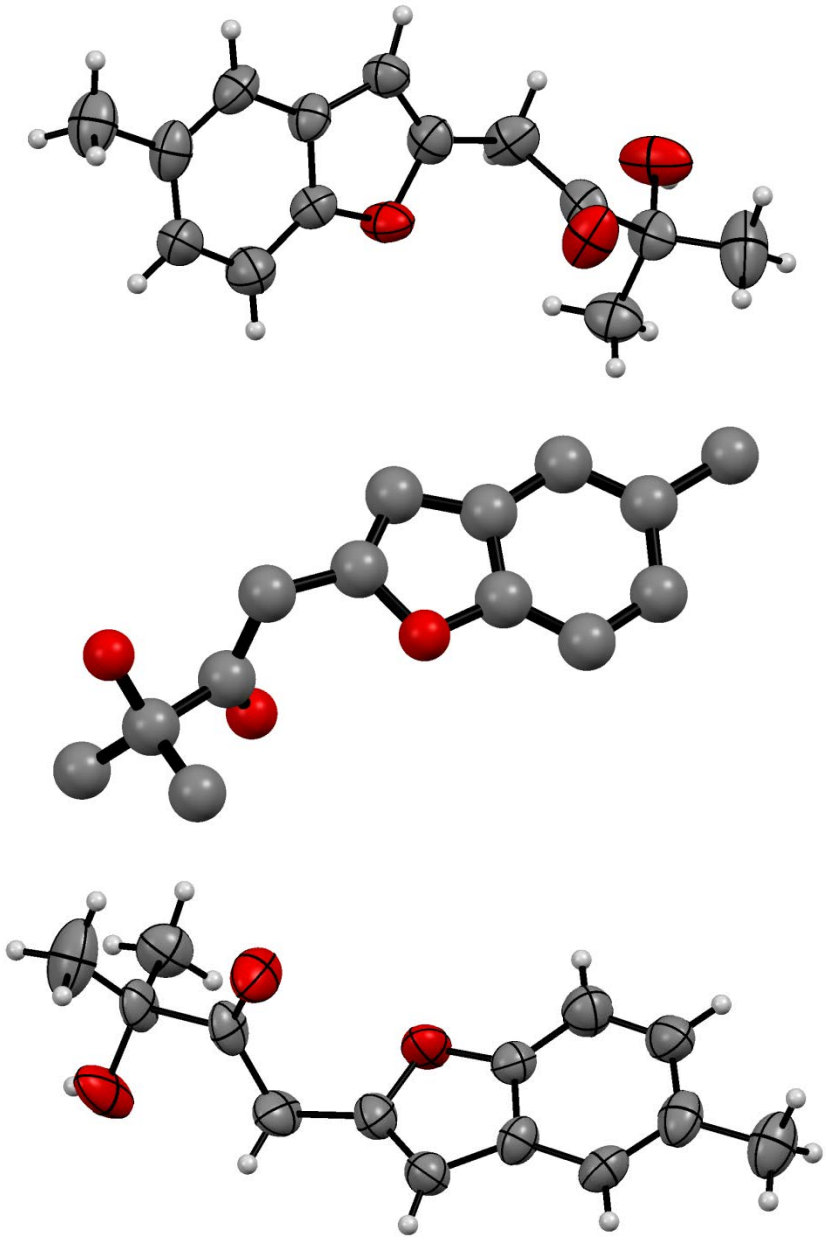


**Figure 8:** ORTEP diagram of **29g** with 30% ellipsoidal probability.

Crystal Data for $C_{14}H_{16}O_3$ ($M$ =232.28 g/mol): monoclinic, space group $P2_1/n$ (no. 14), $a$ = 14.498(2) Å, $b$ = 5.9876(8) Å, $c$ = 14.857(2) Å, $\beta$ = 103.208(7)°, $V$ = 1255.6(3) Å$^3$, $Z$ = 4, $T$ = 293 K, μ(Mo Kα) = 0.086 mm$^{-1}$, $Dcalc$ = 1.2287 g/cm$^3$, 12978 reflections measured (7.08° ≤ 2Θ ≤ 54.94°), 2864 unique ($R_{int}$ = 0.0530, $R_{sigma}$ = 0.0293) which were used in all calculations. The final $R_1$ was 0.0546 (I>=2u(I)) and $wR_2$ was 0.1671 (all data).

| **Table 5.1**. Crystal data and structure refinement for JP-02-10. (**29g**) | |
|---|---|
| **Identification code** | JP-02-10 |
| **Empirical formula** | $C_{14}H_{16}O_3$ |
| **Formula weight** | 232.28 |
| **Temperature/K** | 293 |
| **Crystal system** | monoclinic |
| **Space group** | $P2_1/n$ |
| **a/Å** | 14.498(2) |
| **b/Å** | 5.9876(8) |
| **c/Å** | 14.857(2) |
| **α/°** | 90 |
| **β/°** | 103.208(7) |
| **γ/°** | 90 |
| **Volume/Å$^3$** | 1255.6(3) |
| **Z** | 4 |
| **$\rho_{calc}$g/cm$^3$** | 1.2287 |
| **μ/mm$^{-1}$** | 0.086 |
| **F(000)** | 496.3 |
| **Crystal size/mm$^3$** | 0.3 × 0.22 × 0.16 |
| **Radiation** | Mo Kα (λ = 0.71075) |
| **2Θ range for data collection/°** | 7.08 to 54.94 |
| **Index ranges** | $-18 \leq h \leq 18$, $-7 \leq k \leq 7$, $-19 \leq l \leq 19$ |
| **Reflections collected** | 12978 |
| **Independent reflections** | 2864 [$R_{int}$ = 0.0530, $R_{sigma}$ = 0.0293] |
| **Data/restraints/parameters** | 2864/0/157 |

| | |
|---|---|
| **Goodness-of-fit on $F^2$** | 1.033 |
| **Final R indexes [I>=2σ (I)]** | $R_1$ = 0.0546, $wR_2$ = 0.1515 |
| **Final R indexes [all data]** | $R_1$ = 0.0688, $wR_2$ = 0.1671 |
| **Largest diff. peak/hole / e $Å^{-3}$** | 0.22/-0.17 |

**Table 5.2.** Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for JP-02-10.

| Atom | ***X*** | ***Y*** | ***z*** | **U(eq)** |
|---|---|---|---|---|
| O1 | 1776.5(5) | 4548.3(6) | 3605.2(5) | 52.7(3) |
| O2 | -363.8(5) | 3694.0(6) | 3063.8(5) | 70.4(4) |
| O3 | -225.5(5) | -1828.9(6) | 3735.3(5) | 72.5(4) |
| C4 | 2341.1(5) | 6873.3(6) | 4809.8(5) | 46.9(3) |
| C5 | -437.1(5) | -270.7(6) | 2995.2(5) | 50.0(4) |
| C6 | -21.1(5) | 1955.1(6) | 3399.4(5) | 49.0(4) |
| C7 | 1727.0(6) | 5241.0(6) | 5081.6(5) | 52.4(4) |
| C8 | 2884.6(5) | 8678.2(6) | 5227.0(5) | 54.2(4) |
| C9 | 1415.0(5) | 3906.6(6) | 4346.5(5) | 49.3(4) |
| C10 | 3399.7(5) | 9914.3(6) | 4726.9(6) | 55.6(4) |
| C11 | 2339.7(5) | 6369.5(6) | 3903.1(5) | 47.7(3) |
| C12 | 3984.2(6) | 11874.8(6) | 5163.0(6) | 76.9(6) |
| C13 | 57.5(6) | -928.2(6) | 2237.2(6) | 64.8(5) |
| C14 | 3367.4(6) | 9335.4(6) | 3814.6(6) | 61.3(4) |
| C15 | 2838.9(6) | 7568.1(6) | 3382.1(5) | 59.0(4) |
| C16 | 827.1(6) | 1862.9(6) | 4195.7(6) | 57.2(4) |
| C17 | -1492.0(6) | -81.2(6) | 2623.3(6) | 81.4(6) |

**Table 5.3.** Anisotropic displacement parameters ($Å^2 \times 10^3$) for JP-02-10. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|---|---|---|---|---|---|---|
| O1 | 63.6(7) | 48.0(6) | 46.6(6) | -6.3(5) | 12.5(5) | -4.9(4) |
| O2 | 78.0(8) | 33.6(5) | 87.1(9) | 3.0(5) | -7.0(7) | 3.3(5) |
| O3 | 120.5(11) | 34.6(6) | 65.5(8) | -9.1(6) | 27.6(7) | 4.1(5) |
| C4 | 49.1(8) | 44.5(7) | 45.8(8) | 4.3(6) | 8.0(6) | -0.2(5) |
| C5 | 59.6(9) | 33.2(7) | 57.8(9) | -2.5(6) | 15.0(7) | -0.8(6) |
| C6 | 58.5(9) | 32.2(7) | 56.7(9) | 0.5(6) | 14.0(7) | 0.4(6) |
| C7 | 60.2(9) | 52.5(8) | 44.5(8) | -1.6(7) | 11.8(6) | 2.1(6) |
| C8 | 54.0(8) | 53.5(8) | 52.2(9) | 0.9(7) | 6.5(7) | -7.6(7) |
| C9 | 55.6(8) | 41.9(7) | 48.8(8) | 1.2(6) | 8.5(6) | 4.4(6) |
| C10 | 43.1(8) | 46.9(8) | 71.8(11) | 1.3(6) | 2.5(7) | -0.8(7) |
| C11 | 49.4(8) | 43.6(7) | 48.4(8) | -0.6(6) | 7.7(6) | -0.5(6) |
| C12 | 60.9(11) | 58.5(10) | 104.4(16) | -9.4(8) | 4.5(10) | -12.3(10) |
| C13 | 76.6(12) | 54.7(9) | 65.4(10) | 8.7(8) | 21.5(9) | -3.8(8) |
| C14 | 53.2(9) | 61.5(9) | 68.8(11) | -6.8(7) | 13.1(7) | 8.2(8) |
| C15 | 62.9(9) | 65.8(9) | 49.5(9) | -6.3(8) | 15.2(7) | 2.4(7) |
| C16 | 68.3(10) | 39.8(7) | 59.6(9) | -2.7(7) | 6.9(7) | 6.0(6) |
| C17 | 59.0(11) | 69.0(11) | 117.1(18) | -10.4(9) | 22.3(11) | -20.8(11) |

**Table 5.4.** Bond lengths for JP-02-10.

| Atom | **Atom** | **Length/Å** | | **Atom** | **Atom** | **Length/Å** |
|---|---|---|---|---|---|---|
| O1 | C9 | 1.3781(11) | | C5 | C17 | 1.5070(11) |
| O1 | C11 | 1.3735(7) | | C6 | C16 | 1.5000(10) |
| O2 | C6 | 1.2109(7) | | C7 | C9 | 1.3454(9) |
| O3 | C5 | 1.4212(9) | | C8 | C10 | 1.3825(11) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C4 | C7 | 1.4406(9) | | C9 | C16 | 1.4788(8) |
| C4 | C8 | 1.3964(8) | | C10 | C12 | 1.5050(8) |
| C4 | C11 | 1.3800(11) | | C10 | C14 | 1.3894(12) |
| C5 | C6 | 1.5281(7) | | C11 | C15 | 1.3761(11) |
| C5 | C13 | 1.5186(12) | | C14 | C15 | 1.3765(8) |

**Table 5.5.** Bond angles for JP-02-10.

| Atom | **Atom** | **Atom** | **Angle/°** | | **Atom** | **Atom** | **Atom** | **Angle/°** |
|---|---|---|---|---|---|---|---|---|
| C11 | O1 | C9 | 105.70(6) | | C10 | C8 | C4 | 119.67(7) |
| C8 | C4 | C7 | 136.29(8) | | C7 | C9 | O1 | 111.37(6) |
| C11 | C4 | C7 | 105.20(5) | | C16 | C9 | O1 | 114.89(6) |
| C11 | C4 | C8 | 118.51(7) | | C16 | C9 | C7 | 133.61(8) |
| C6 | C5 | O3 | 105.81(6) | | C12 | C10 | C8 | 120.42(7) |
| C13 | C5 | O3 | 110.40(5) | | C14 | C10 | C8 | 119.27(5) |
| C13 | C5 | C6 | 107.86(6) | | C14 | C10 | C12 | 120.31(7) |
| C17 | C5 | O3 | 110.77(6) | | C4 | C11 | O1 | 110.87(6) |
| C17 | C5 | C6 | 110.78(5) | | C15 | C11 | O1 | 125.67(7) |
| C17 | C5 | C13 | 111.05(6) | | C15 | C11 | C4 | 123.46(5) |
| C5 | C6 | O2 | 120.00(6) | | C15 | C14 | C10 | 122.56(7) |
| C16 | C6 | O2 | 122.80(5) | | C14 | C15 | C11 | 116.53(7) |
| C16 | C6 | C5 | 117.18(4) | | C9 | C16 | C6 | 115.43(5) |
| C9 | C7 | C4 | 106.86(7) | | | | | |

**Table 5.6.** Hydrogen atom coordinates (Å×$10^4$) and isotropic displacement parameters (Å$^2$×$10^3$) for JP-02-10.

| Atom | ***X*** | ***Y*** | ***Z*** | **U(eq)** |
|---|---|---|---|---|
| H3 | -164.3(5) | -3077.7(6) | 3530.0(5) | 108.8(6) |
| H7 | 1575.2(6) | 5130.9(6) | 5655.3(5) | 62.9(5) |
| H8 | 2900.0(5) | 9046.9(6) | 5838.4(5) | 65.0(5) |
| H12a | 4172.6(6) | 11657.6(6) | 5819.7(6) | 115.3(9) |
| H12b | 4537.5(6) | 12000.8(6) | 4914.1(6) | 115.3(9) |
| H12c | 3615.3(6) | 13216.7(6) | 5033.4(6) | 115.3(9) |
| H13a | 726.1(6) | -1057.8(6) | 2492.5(6) | 97.1(7) |
| H13b | -186.0(6) | -2335.6(6) | 1977.3(6) | 97.1(7) |
| H13c | -55.0(6) | 193.0(6) | 1762.8(6) | 97.1(7) |
| H14 | 3716.6(6) | 10174.5(6) | 3483.2(6) | 73.6(5) |
| H15 | 2820.1(6) | 7203.2(6) | 2769.8(5) | 70.9(5) |
| H16a | 611.5(6) | 1552.8(6) | 4754.8(6) | 68.6(5) |
| H16b | 1223.0(6) | 622.5(6) | 4097.2(6) | 68.6(5) |
| H17a | -1736.0(6) | -1480.5(6) | 2354.9(6) | 122.0(9) |
| H17b | -1790.0(6) | 291.5(6) | 3117.9(6) | 122.0(9) |
| H17c | -1622.1(6) | 1065.9(6) | 2160.1(6) | 122.0(9) |

# Summary

Benzofurans and its derivatives constitute an important space in organic chemistry. It enjoys application in wide range of fields, like medicine, pharmaceuticals etc. This makes the synthesis of these organic compounds under mild conditions as a challenge. Literature reports are known for the synthesis but through harsh conditions or by the use of metal catalysts which are toxic in nature. In this report we have described a cascade event of *β*-pyrones and phenols, originated out of serendipity, leading to the synthesis of 2-benzofuranyl-3-hydroxyacetones by Lewis acid catalysis. The versatility of this strategy lies in its ability to establish unprecedented access for medicinally significant scaffolds such as 4,4*a*-dihydropyrano[3,2-*b*]benzofuran-3-ones, furo[3,2-*c*]coumarins, and spiro[benzofuran-2,2'-furan]-4'-ones in short and efficient manner.

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(26) **29a** was obtained in <10% yield when performed the reaction at room temperature as suggested in the original protocols of Grynkiewicz and Feringa. Reaction at reduced temperature (0-5 $^{o}$C) only delivered **29a** in reasonable yields.

(27) See the Chapter 3 for details. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 1437901 (for **29g**) has been assigned.

(28) The observed regioselectivity (C-1 vs C-3) during the Friestype rearrangement of 2-naphthyl derivatives (**29e, 29h, 29k, 29l, 29o** and **29p**) is in agreement with literature reports, see: C. Cui, X. Wang, R. G.; Weiss, *J. Org. Chem.*, **1996,** *61*, 1962.

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# Publications resulted out of the present research

(1) Bankar, S. K.; Mathew, J.; Ramasastry, S. S. V. *Chem. Comm.* **2016**, *52*, 5569

# Appendix

**Determination of enantiomeric excess (ee) of 29p by chiral HPLC.**

Empower 3 SOFTWARE

Vishnu

SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sb-04-48 np chir-AS10% | Acquired By: | System |
| Sample Type: | Unknown | Sample Set Name | |
| Vial: | 1 | Acq. Method Set: | Bishnu MBH |
| Injection #: | 5 | Processing Methoc | sb448naprac |
| Injection Volume: | 10.00 ul | Channel Name: | 254.0nm |
| Run Time: | 120.0 Minutes | Proc. Chnl. Descr.: | PDA 254.0 nm |
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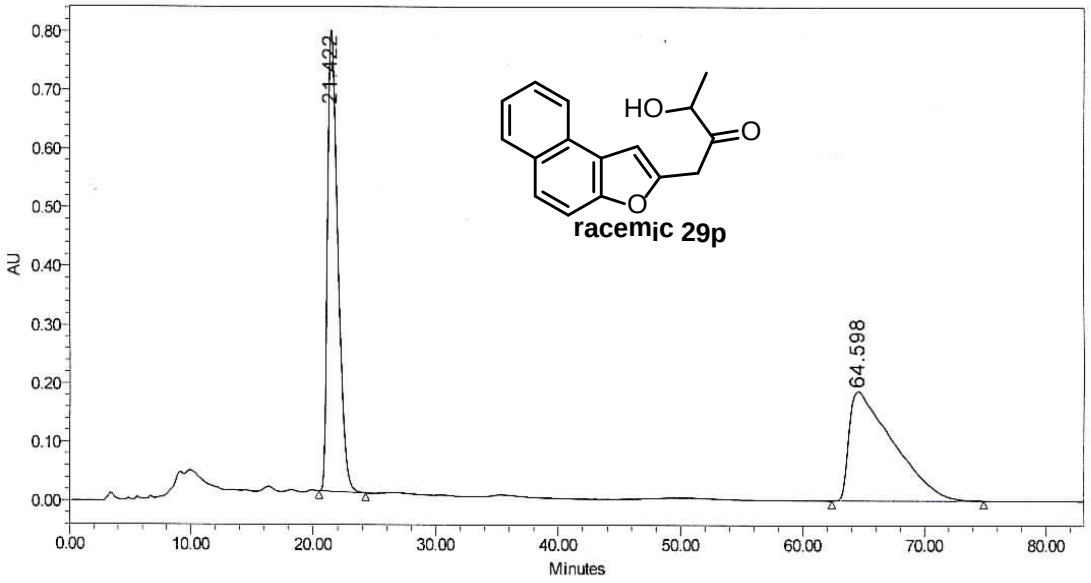
| Date Processed: | 04-11-2015 20:54:15 IST | | |




| | RT | Area | % Area | Height |
|---|---|---|---|---|
| 1 | 21.422 | 46302803 | 49.54 | 785844 |
| 2 | 64.598 | 47160151 | 50.46 | 186658 |

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Report Method ID: 4230
Page: 1 of 1

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Date Printed:
04-11-2015
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Empower 3 SOFTWARE

Vishnu

## SAMPLE INFORMATION

| | | | |
|---|---|---|---|
| Sample Name: | sb-04-48 np chir-AS10% | Acquired By: | System |
| Sample Type: | Unknown | Sample Set Name | |
| Vial: | 1 | Acq. Method Set: | Bishnu MBH |
| Injection #: | 6 | Processing Method | sb448npchiral |
| Injection Volume: | 10.00 ul | Channel Name: | 254.0nm |
| Run Time: | 120.0 Minutes | Proc. Chnl. Descr.: | PDA 254.0 nm |
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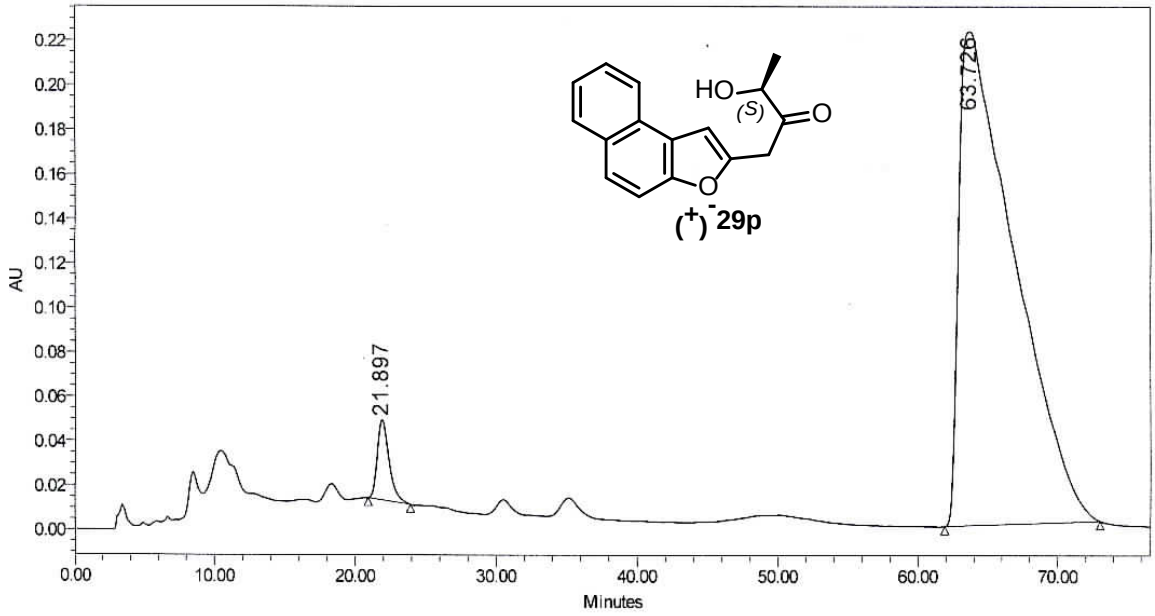
| Date Processed: | 04-11-2015 20:55:20 IST | | |

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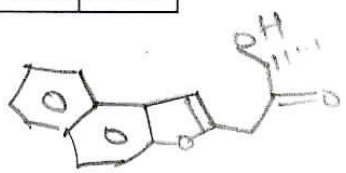

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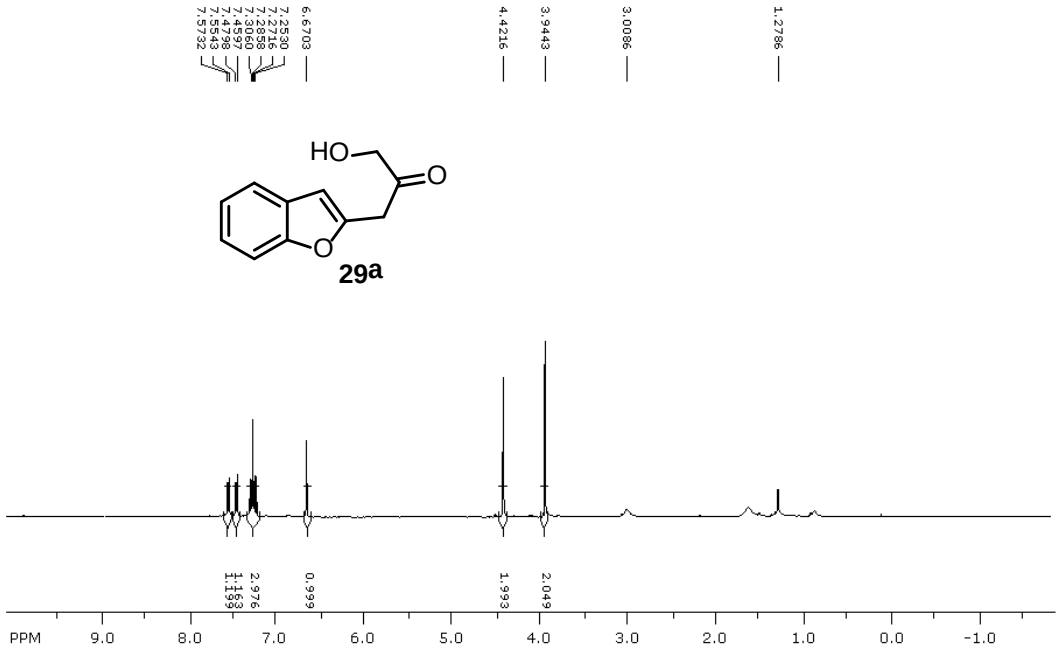
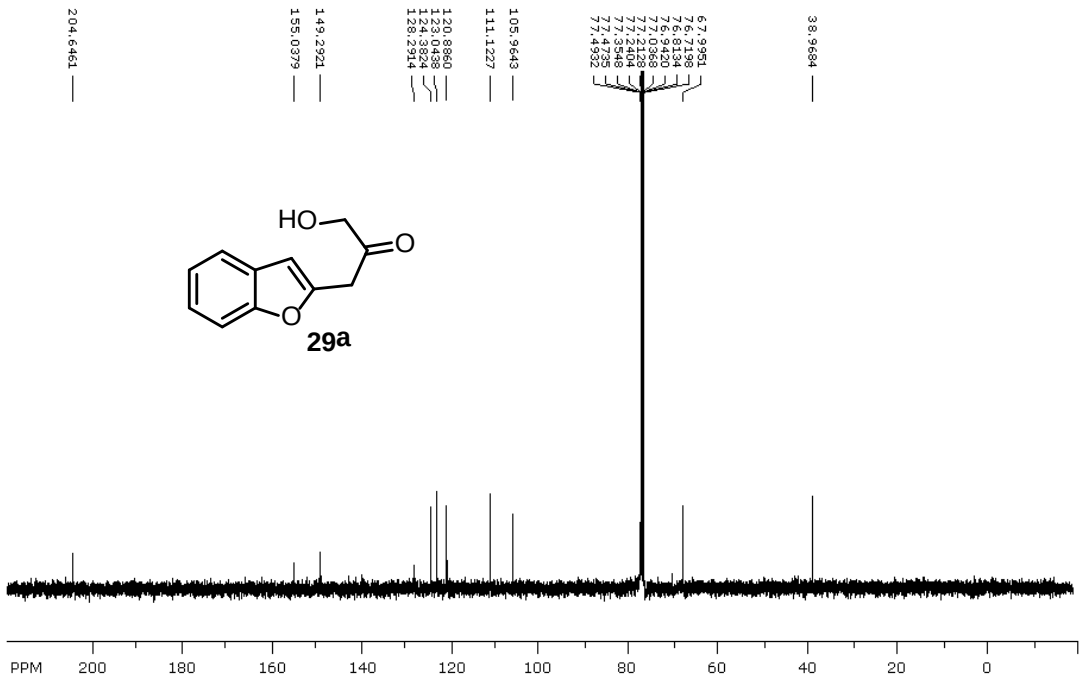
**$^{1}$H and $^{13}$C-NMR spectra of representative compounds reported in this study**

(**Note**: In general, in a $^{1}$H NMR spectrum recorded in $CDCl_3$, a peak at around δ 1.6 refers to moisture in the solvent/sample and a peak at about δ 1.2 refers to oil/grease present in the sample. In a $^{13}$C NMR spectrum recorded in $CDCl_3$, a peak at about δ 29.7 usually represents oil/grease)

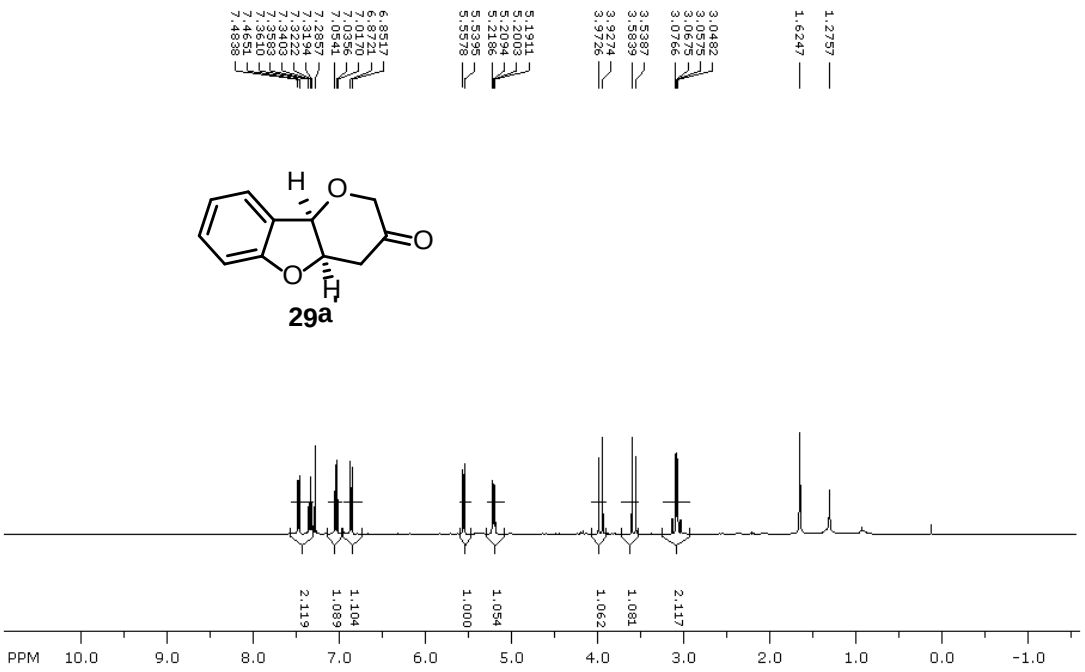
$^{1}$H NMR of **29a**



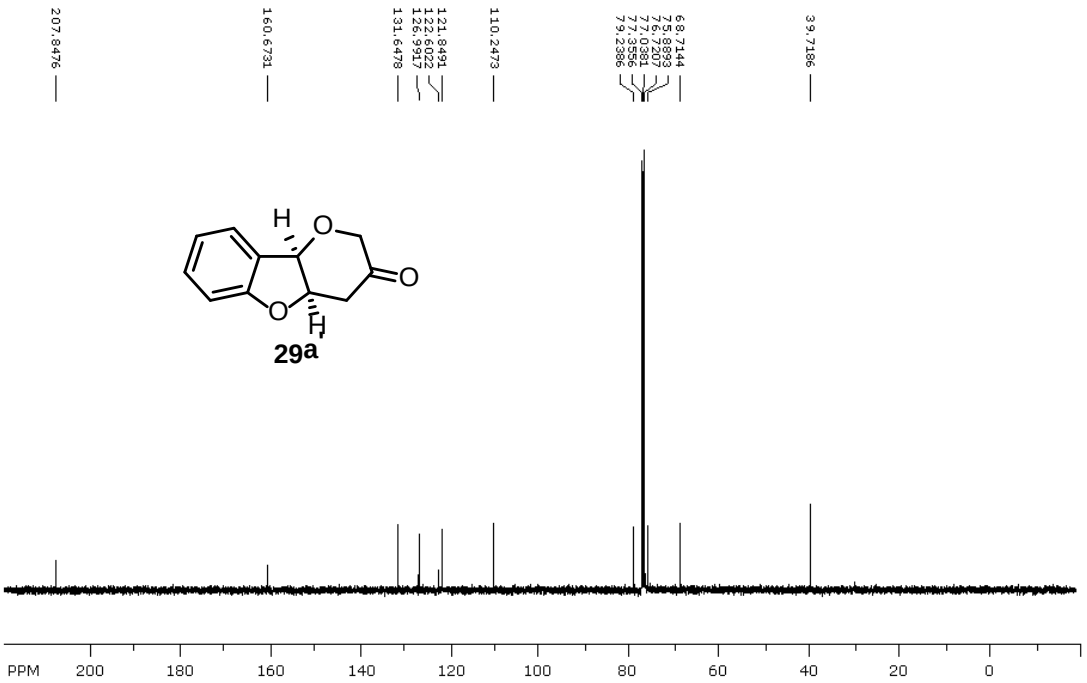

$^{13}$C NMR of **29a**



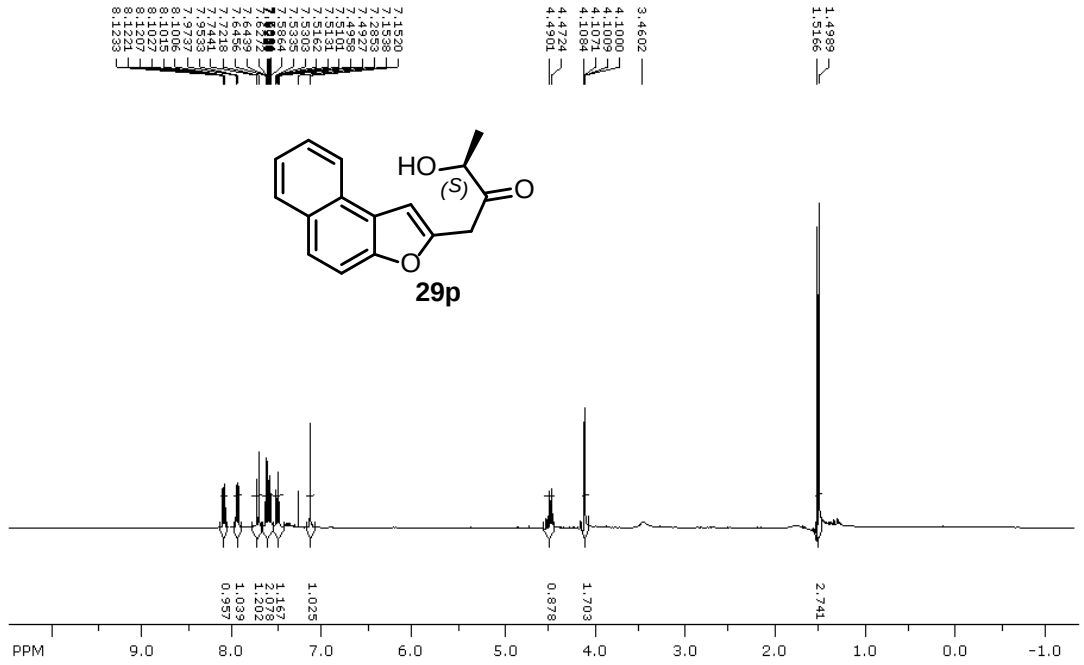
$^{1}$H NMR of **29a'**




$^{13}$C NMR of **29a'**



$^{1}$H NMR of **29p**

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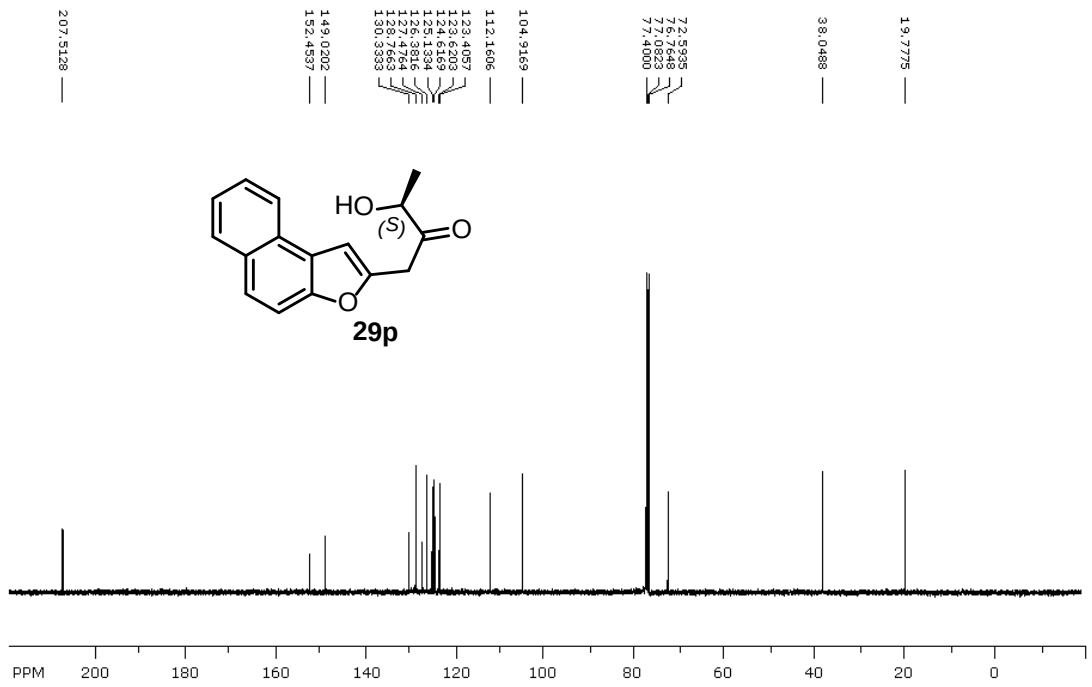
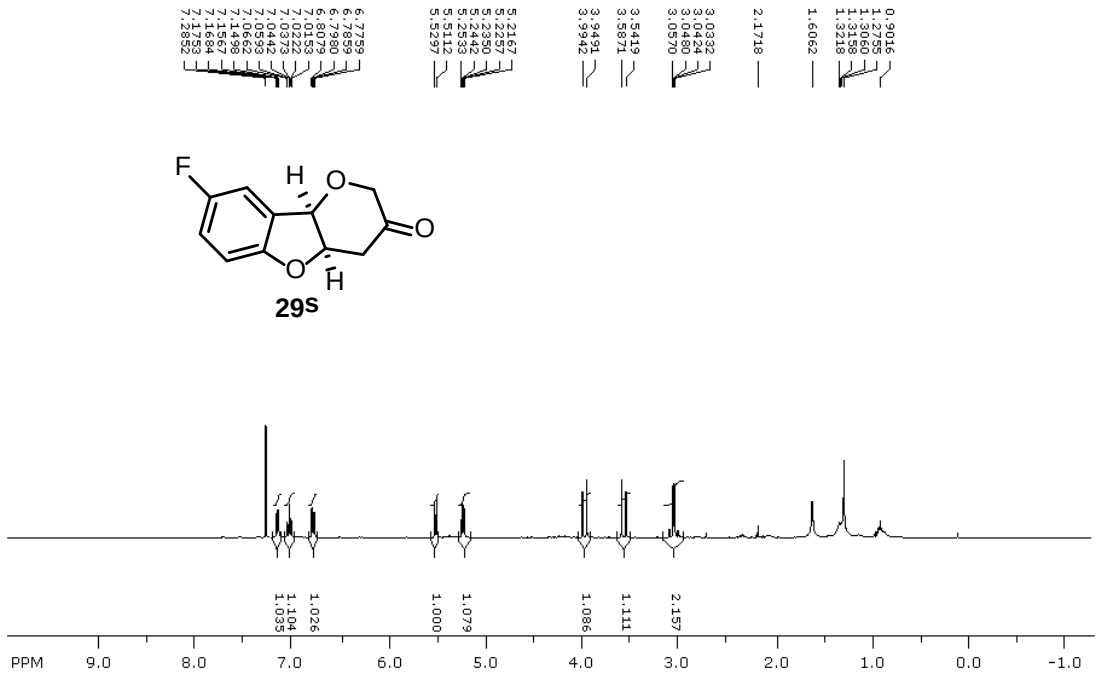
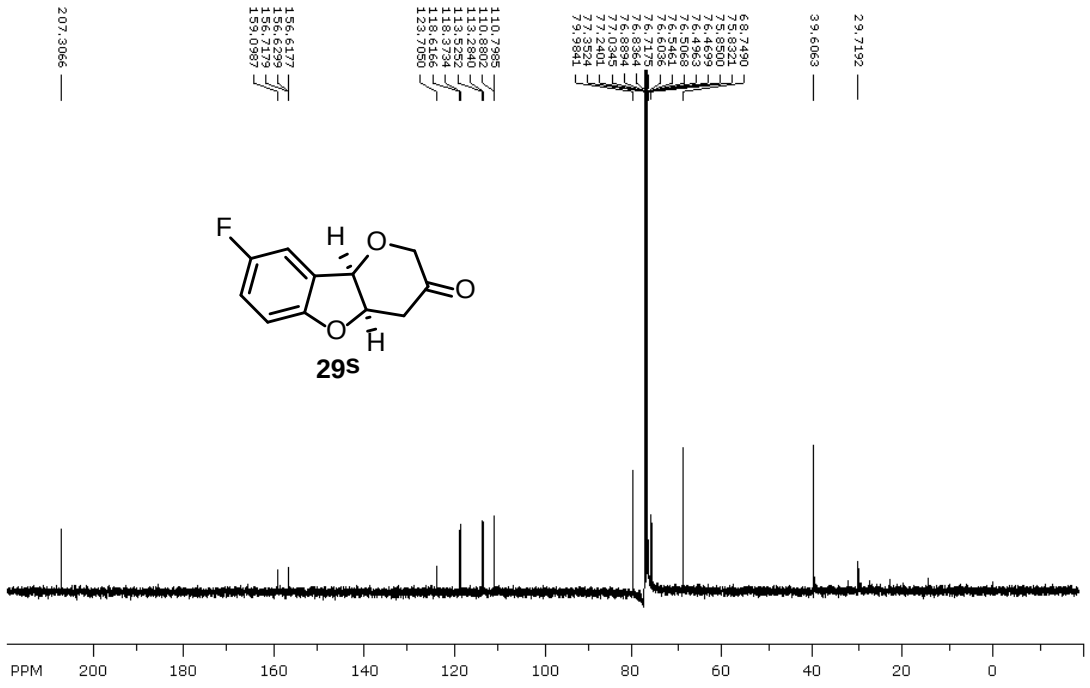


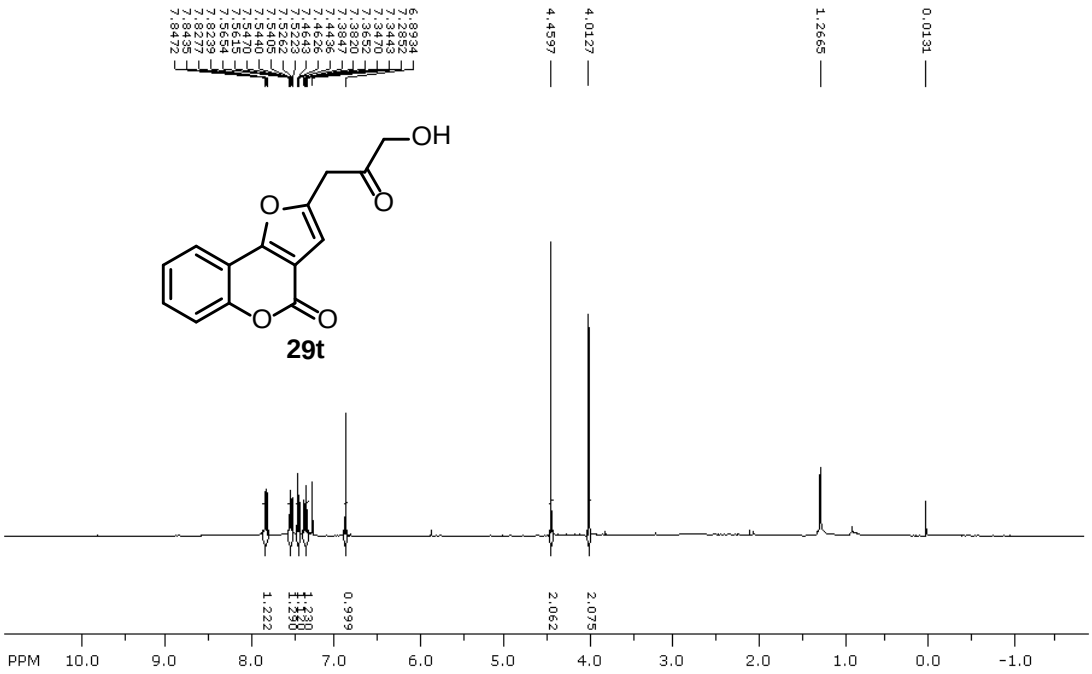
$^{1}$H NMR of **29s**



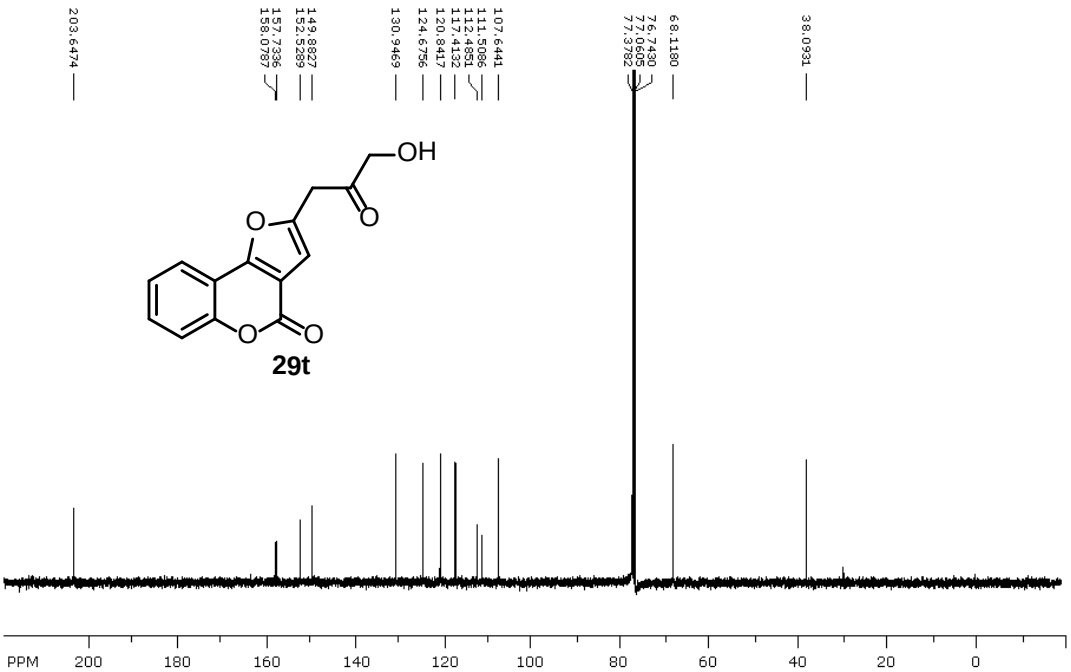

$^{13}$C NMR of **29s**



$^{1}$H NMR of **29t**




$^{13}$C NMR of **29t**



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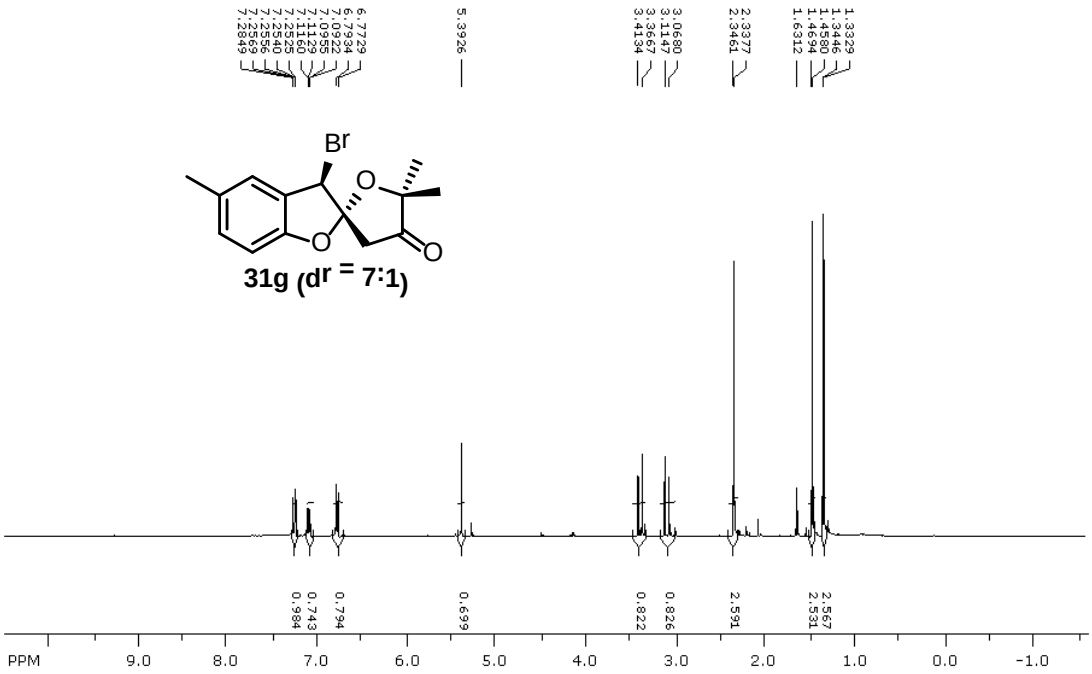


$^{13}$C NMR of **31g**