THREE CARBON HOMOLOGATION OF ALDEHYDES

SYNTHESIS OF THREE CARBON HOMOLOGATED UNSATURATED ALDEHYDES USING REGIOSELECTIVE WITTIG OLEFINATION CHEMISTRY

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TITLE: Synthesis of three carbon homologated unsaturated aldehydes using regioselective Wittig olefination chemistry

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Abstract

Unsaturated aldehydes are widely used in the synthesis of natural products and pharmaceutical molecules.[18,19,20] Among various methods available in the literature, carbon homologation is a common reaction employed for the synthesis of unsaturated aldehydes. Wittig reaction has emerged as a very useful method for making homologated unsaturated aldehydes. The use of classical Wittig reaction is not desirable on a commercial scale due to the formation of the by-product triphenylphosphine oxide which is insoluble in water and generally difficult to remove.

Use of alkyl phosphine reagents is one of the research interests in our group. Previously in our group, alkylphosphonium salts were successfully used in the Wittig reaction for the one and two carbon homologations.[15] The trialkylphosphine oxide by-product is water soluble and can be easily removed.

In this thesis, the three carbon homologation of aldehydes using (2-(1, 3-dioxolan-2-yl)ethyl)tripropylphosphonium bromide is described. The ylide formation is highly regioselective. A variety of aromatic and hetero aromatic aldehydes are homologated with good stereo selectivity. An attempt to synthesize the cytotoxic natural product (2*R*,3*R*,4*R*)-3,4-dihydro-3,4-dihydroxy-2-(3-methylbut-2-enyl)-1(2*H*)-naphthalenone using the homologated aldehyde is also illustrated.

Finally, the development of new synthetic routes for tricyclohexylphosphine is described. Tricyclohexylphosphine is used as a ligand in many important complexes which include the olefin metathesis Grubbs' catalyst and the homogeneous hydrogenation Crabtree's catalyst. It is synthesized generally from phosphorus trichloride and cyclohexylmagnesium bromide. It is also synthesized by hydrogenation of triphenyl phosphine with a niobium catalyst. Nevertheless, a new commercially viable synthesis possesses greatest advantage in the use of tricyclohexylphosphine.

Acknowledgements

First and foremost I would like to thank my supervisor Dr. James McNulty for accepting me into his research group. . It was a difficult transition to academic research after having spent three years working for AstraZeneca. However, the mentorship of Prof. McNulty was instrumental in helping me successfully transition to the academic environment. I would like to acknowledge my committee member, Dr. Harrison for his intellectual contributions to my thesis research. Much of the incentive, and funding for this work came about through our collaboration with Solvay (formerly Cytec). I would like to take this opportunity to acknowledge not only the financial support from Solvay, but the many useful discussions with our collaborator Dr. Dino Amoroso.

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List of Abbreviations

Ac = acetate

AcO = acetoxy

AD = asymmetric dihydroxylation

AcOEt = ethyl acetate

Bz = benzoyl

Bu = butyl

^{t}Bu = *tert*-butyl

^{n}BuLi = n-butyl lithium

$CDCl_3$ = deuterated chloroform

CH_3COOH = acetic acid

calc. = calculated

Conc. = concentration

CI = chemical ionization
DABCO = 1,4-diazabicyclo[2,2,2]octane
DCM = dichloromethane

DIBAL = DIBAL-H = diisobutylaluminium hydride

DMAP = 4-dimethylaminopyridine
DMF = dimethylformamide

DMP = Dess-Martin periodinane

DMSO = dimethyl sulfoxide

Et = ethyl

ES^+/ESI^+: electrospray mass spectrometry (positive mode)

EtOAc = ethyl acetate

Et_2O = diethyl ether

$FeCl_3$ = ferric chloride

g = gram

h = hours

HPLC = high pressure liquid chromatography

HOMO = highest occupied molecular orbital

HCl = hydrochloric acid

HRES MS = high resolution electrospray mass spectrometry

HREI MS = high resolution electron ionization mass spectrometry

^{i}Pr = *iso*-propyl

KOH = potassium hydroxide

KHMDS = potassium bis(trimethylsilyl)amide

LiHMDS = lithium bis(trimethylsilyl)amide

L = liter

Me = methyl

MHz = mega hertz

mmol = milli mole

min = minutes

NAOH = sodium hydroxide

OPA = oxaphosphetane

Ph = phenyl

Pr = propyl

PPTS = pyridinium p-toluenesulfonate

p-TSA = *p*-toluenesulfonic acid

PBu_3 = tributylphosphine

PMHS = polymethylhydrosiloxane

PG = protecting group

$PhI(OAc)_2$ = (diacetoxyiodo)benzene

RBF = round bottom flask

RT = room temperature

SDS = sodium dodecyl sulfate

S_N2 = nucleophilic substitution second order

TEA = triethylamine

TFA = trifluroacetic acid

TFSA = trifluromethylsulfonic anhydride

mg = milli gram

sat. = saturated

LiBr = lithium bromide

Zn (Hg) = zinc in mercury

^{31}P NMR = phosphorous NMR

^{1}H NMR = hydrogen NMR

^{13}C NMR = carbon NMR

NH_2NH_2 = hydrazine

Na_2SO_4 = sodium sulfate

$NaSO_4$ = sodium sulphate

NH_4Cl = ammonium chloride

$Na_2S_2O_3$ = sodium thiosulfate

$NaHCO_3$ = Sodium bicarbonate

NMR = nuclear magnetic resonance

NaH = sodium hydride

$NaBH_4$ = sodium borohydride

NaI = sodium iodide

TLC = thin layer chromatography

Tol = toluene

Ts = tosyl = 4-methylbenzenesulfonate

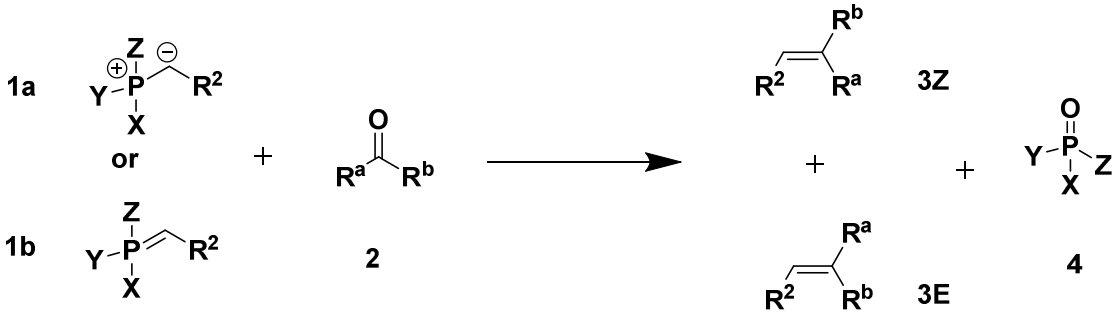
UV = ultraviolet light

w/w = weight by weight

1. The Wittig Reaction

Olefination of aldehydes and ketones is a commonly employed transformation in organic synthesis.[1] Prior to the development of the Wittig Reaction the positional and stereo chemical selectivity of double bond formation were the greatest challenges associated with the synthesis of alkenes. In 1953, Wittig and co-workers discovered a synthetic method using phosphonium ylides to obtain the olefins with explicit positional, and to some extent, stereoselectivity.[2]

The classical Wittig reaction utilised a stoichiometric quantity of phosphonium ylide and a carbonyl compound to furnish the olefin. Phosphine oxide is produced as a major by-product of the reaction.[3] (**Scheme-1**)

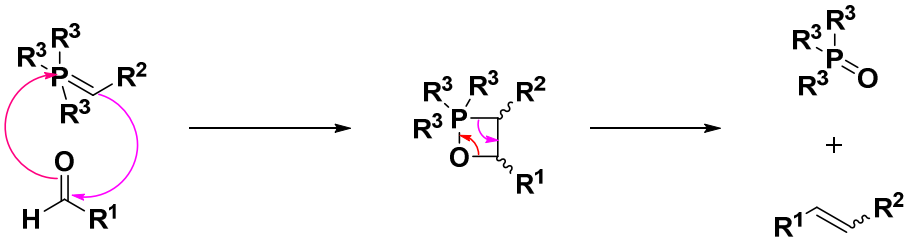


Scheme-1: **The Wittig Reaction (adapted from Gilheany)[3]**

1a and **1b** represent the ylide and ylene forms respectively. X, Y and Z may each be alkyl, aryl or alkoxy and need not necessarily be the same. R^2 may be alkyl, aryl, vinyl, or an electron withdrawing group. The carbonyl reactant (**2**) may be formaldehyde (R^a = R^b = H), an aldehyde (R^a = alkyl/aryl, R^b = H) or a ketone (R^a = alkyl/aryl, R^b = alkyl/aryl). **3** is the *E* or *Z* olefin and **4** is the phosphine oxide by-product.

1.1 Mechanism

Over the years substantial efforts have been devoted to elucidate the mechanism of the Wittig reaction.[4-9] Among many mechanisms proposed, the most widely accepted one invoked the direct formation of the oxaphosphetane ring. Vedejs and Snoble were the first to propose the mechanism involving [2+2] cycloaddition to form an oxaphosphetane, pseudorotation at phosphorus, and decomposition of the cyclic intermediate to yield the olefin and phosphine oxide. [10,11]



Scheme-2: Irreversible [2+2] cycloaddition mechanism by Vedejs (adapted from Gilheany)[3]

According to Vedejs, the stereochemistry of the alkene depends on the Transition State (TS) of the cycloaddition step. [10,11] Once the alkene is formed, it always retains the stereochemistry. The substituent on the carbonyl compound has very little effect on the stereo outcome. The alkene geometry is highly dependent on the type of the ylide used. Generally the Wittig ylides are classified into non-stabilized, semi stabilized and stabilized ylides. Due to the difference in the P-C bond angle, the stabilized and non-stabilized ylides approach the C=O bond differently resulting in two variable TS which decides the outcome of the stereochemistry.

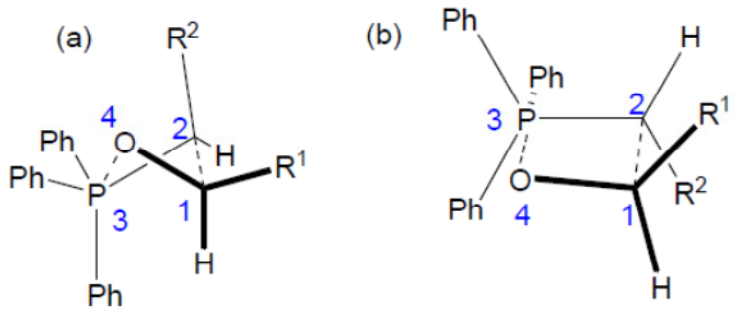


Figure- 1: Proposed transition states leading to *cis* & *trans* olefin products (adapted from Gilheany)[3]

Figure (1a) represents the TS of the reaction between an aldehyde and triphenylphosphine alkyl ylide. It suggests that the C=O bond and P-C bond approach each other with a wide angle; this results in an early transition state. The intermediate is puckered in shape and the bond formation happens at this stage.

The four substituents on the phosphorus are arranged in a near-tetrahedral shape disfavouring the straight planar approach. In a planar approach, one of the P-phenyl groups would project directly towards the forming P-O bond and there can be possible 1, 3 steric interactions between various substituents. The puckered transition state eliminates the unwanted interactions by placing the substituents in a wider angle to each other. The kinetically formed puckered TS normally favour the *cis*-OPA, which decompose irreversibly and stereospecifically to give *Z*- olefin.

The transition state for the reaction with stabilized ylides is considered to be a late stage one. Vedejs proposed that the geometry around the phosphorous is trigonal bipyramidal which the 1-3- steric interactions have negligible effect (**Figure (1b)**). Because of this the

approach for bond formation would be planar. Since 1, 2 interactions are higher in a *cis*-selective TS, the *trans*-selective with minor 1, 2 interactions is favoured. As a result, *trans*-OPA is formed selectively and *E* olefin is observed after the cycloreversion of the OPA.

It is clear from the above mechanistic details that the stereo outcome of the Wittig reaction is predominantly dictated by the type of ylide used.

1.2 Types of Wittig Ylides

In general, the Wittig ylides are widely classified as non-stabilized, semi-stabilized and stabilized ylides based on the substituent(s) on the α-carbon. [3]

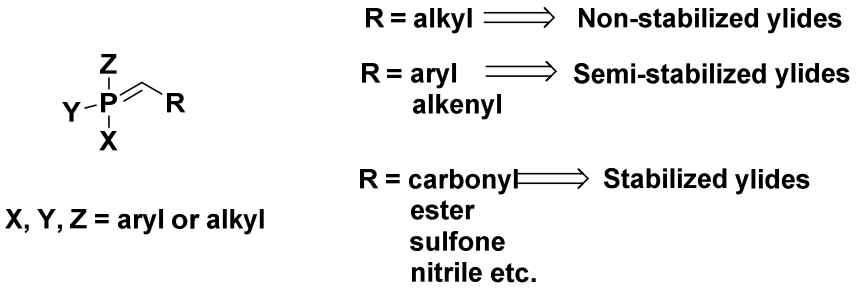


Figure-2: Classification of Wittig ylides

In the non-stabilized ylides the R is generally an alkyl group which are very reactive and quite unstable in the air. If R is aryl or alkenyl group which somewhat stabilizes the ylide with conjugation. Such type of partially stable ylide is classified as semi-stabilized. Triphenylphosphine derived ylides with an electron withdrawing group such as ester, carbonyl, nitrile etc. are typically stable to hydrolysis in the air. As a result these are termed as stabilized ylides.

Since the reaction is carried out in different solvents and temperatures, the exact calculation of reaction rates varies. However, in general, the non-stabilized ylides are known to react instantaneously at lower temperature while semi-stabilized ylides react in minutes with aldehydes at lower temperature. On the other hand, some stabilized ylides do not undergo Wittig reaction at lower temperature and requires heating. But, when an aryl group (X, Y, and Z) on the phosphorous is replaced with an alkyl group, stabilized ylides also react quickly at lower temperature.

As discussed earlier (**Section 1.1**), the nature of the ylide dictates the stereoselectivity of the reaction. The prediction of the *E* or *Z* selectivity in case of triphenylphosphine-derived ylides is very common based on the α-substituent **(Figure -3).**[6] However, predicting the stereo outcome with ylides derived from other phosphines is strenuous and it can be sophisticated in presence or absence of dissolved counter anions such as Lithium.[12]

Figure 3 - Summarizes the observed selectivity trends for reactions of representative ylides. Alkylidenetriphenylphosphoranes are the most frequently used for generating non-stabilized ylides. They predominantly show *Z* selectivity (**a**) except in the case of one alkyl substitution (**b**). Replacing one phenyl with tert-butyl group increases the *Z* selectivity considerably (**c**). In contrast, (alkylidene)alkyl-dibenzophospholanes (**d**) show extremely high *E*-selectivity.

The semi-stabilized ylides, derived from triphenylphosphine, are generally not very selective for one isomer or another. Thus allylidene or benzylidene triphenylphosphoranes (**e**) generally react to give approximately equal proportions of *E*

and *Z* alkene, while semi-stabilised alkyldiphenylphosphine-derived ylides (**f**) show moderate and in some cases very high *E*-selectivity. Semi-stabilised ylides with two or more of the *P*-phenyl groups replaced by alkyl groups (**g**) and also those derived from methyldibenzophosphole (**h**) show exceptionally high *E*-selectivity. As with non-stabilised ylides, the general observation applies that for a given semi-stabilised ylide *Z*-selectivity is highest for reactions with tertiary aldehydes, and *E*-selectivity is highest for reactions with primary aldehydes.

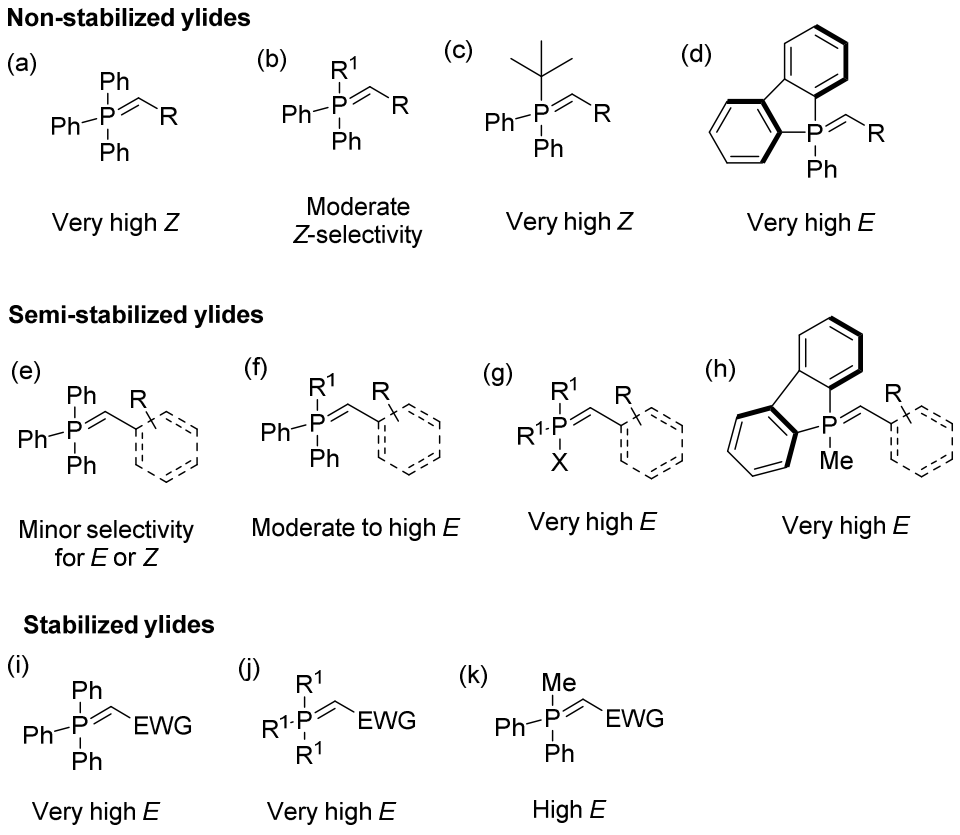


Figure- 3: Summary of observed selectivity trends for reactions of representative ylides. EWG = electron-withdrawing group: R, R^1 = alkyl; X = aryl. (Adapted from Gilheany)[3]

Wittig reactions of stabilised ylides derived from both triphenylphosphine (**i**) and trialkylphosphine (**j**) generally show very high selectivity for *E*-alkene in polar aprotic solvents. Methyldiphenylphosphine-derived ester stabilised ylides (**k**) show drop in stereoselectivity although still predominantly gives *E*-selective olefin. In many cases diminished *E*-selectivity and even predominant *Z*-selectivity is observed in reactions of stabilised ylides in alcoholic solvents.

1.3 Wittig reaction using trialkylphosphine ylides

It is clear from **Figure-3** that the stereo outcome of the Wittig reaction of non-stabilized and semi-stabilized ylides is highly dependent on the substituents on the phosphorous. Vedejs and Marth have mechanistically proved that replacing the phenyl group on phosphorous with an alkyl group alters the alkene stereochemistry.[11] It was shown that the alkylphosphonium ylides predominantly favours the formation of *E* alkene.

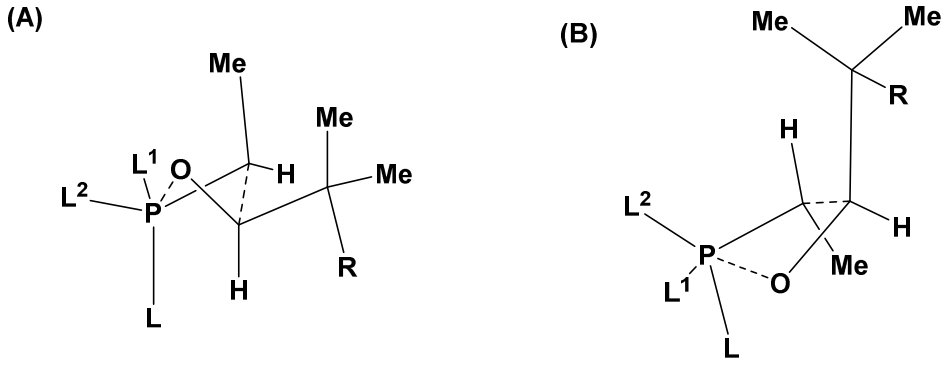
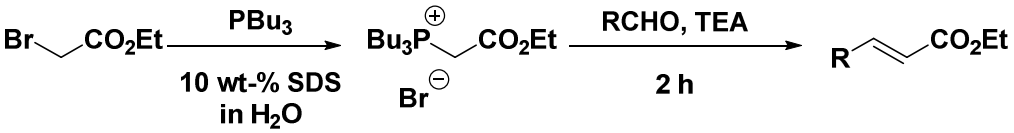


Figure- 4: (A) Cis-selective transition state; (B) Trans-selective transition state L, L^1, L^2 = alkyl or phenyl (adapted from Vedejs and Marth)[11]

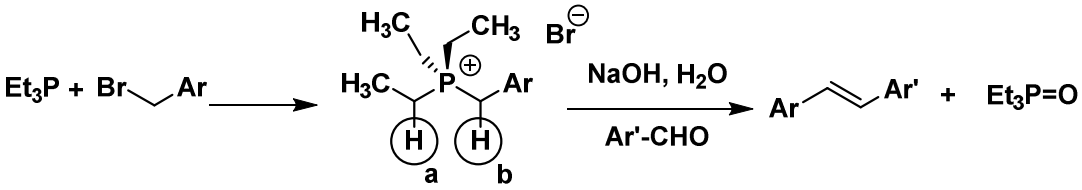
The transition state in both the triphenylphosphine and trialkylphosphine ylide cases is early, and the change in selectivity can be understood by comparing **(A)** (cis-selective) and **(B)** (*trans*-selective). The 1-3 interactions that destabilize **(A)** depend on the steric nature of the aldehyde, and also on the profile of the nearest phosphorus ligand $\mathbf{L^2}$. When P-phenyls are replaced by an alkyl group, the 1-3 interactions with $\mathbf{L^2}$ decreases and the cis selectivity with tertiary aldehyde is reduced as the stability of **(B)** improves relative to **(A).** A further decrease in 1-3 interactions occurs if the aldehyde R-CHO has a α-hydrogen (R unbranched or singly branched at the α-carbon). Under these circumstances, it is possible to orient R such that a C-H bond points toward phosphorus ligands. The trend toward **(B)** is also increased if the nearest phosphorus ligand $\mathbf{L^2}$is compact, and the combination results in a modestly trans-selective reaction under kinetic control in the case of the unbranched aldehyde.

Since the triphenylphosphine show limited stereo control with non-stabilized and semi-stabilized ylides, the use of trialkyl phosphines as an alternative is highly desirable. The formation of triphenylphosphine oxide as by-product which is not easy to remove in the work-up also possesses a huge challenge. The trialkyl phosphines on the other hand offer greater stereo selectivity with non-stabilized ylides and most of the trialkyl phosphine oxides are water soluble and can be easily removed during aqueous work-up.[13]

In 2006, Fulvia Orsini et al. used Tributylphosphine ylides to synthesize α, β -unsaturated esters in water (**Scheme 3**).[14] In 2009 the McNulty group developed an aqueous Wittig reaction (**Scheme 4**)[13] using alkylphosphine salts to synthesize *E* stilbens and alkenes.



Scheme- 3: Synthesis of unsaturated ester using trialkylphosphines (adapted from Orsini *et al*)[14]



Scheme- 4: Synthesis of stilbenes and alkenes by aqueous Wittig reaction[13]

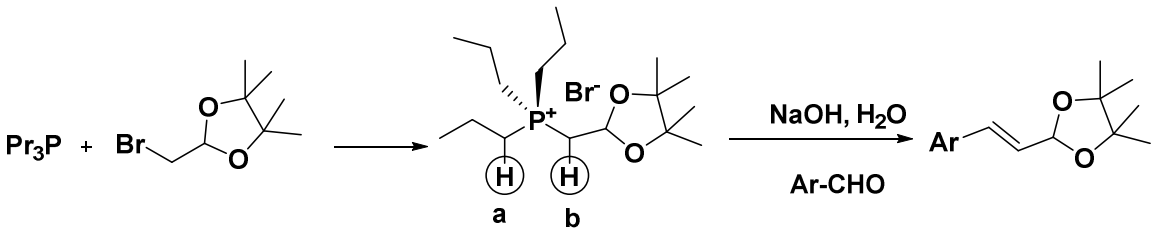
Wittig reaction of semi-stabilized ylides derived from trialkyl(benzyl)phosphonium salts (**Scheme 4**) offer chemoselective deprotonation at the benzylic[13] position (**b**) over the alkyl positions (**a**). Similar chemoselectivity was also demonstrated with trialkyl(allyl)phosphonium salts.[13] The use of trialkylphosphine- derived ylides in Wittig olefination is of limited applicability but typically provides a higher ratio of (*E*)-olefins.[13,15] Phosphine oxides containing small alkyl groups, such as trimethyl, triethyl and tripropylphosphine oxide are highly soluble in water.[15]

1.4 Two carbon homologation of aldehydes using Wittig reaction

Synthesis of α, β - unsaturated aldehydes is highly desirable transformation in organic synthesis.[16, 17] Especially, converting carbonyl compounds to corresponding homologated unsaturated counterparts is always a convenient option. The transformation is problematic, due to the presence of free alkenal in the reaction which can lead to

oligomerization. As such this transformation is typically carried out via a multistep process involving homologation to the unsaturated ester through a Horner–Wadsworth–Emmons (HWE) or related Wittig process, DIBAL-H mediated reduction to the allylic alcohol followed by Swern or Dess–Martin oxidation leading to the homologated alkenal.[15]

In 2013, the McNulty group developed an efficient and robust Wittig reaction using trialkylphosponium salt for the synthesis of alkenals in water **(Scheme 5)**.



Scheme-5: Synthesis of *α, β* - unsaturated aldehydes using aqueous Wittig reaction[15]

The fascinating aspect of the above reaction is the regio-selective formation of ylide. The phosphonium salt (**Scheme 5**) has two α-protons (**a, b**) with comparatively close acidities adjacent to the phosphorous. The probability of formation of ylide/anion on the propyl chain is higher than that of pinacol chain. However, the anion/ylide is generated by abstracting the proton (**b**) exclusively. The reason for this regio-selectivity may be attributed to the presence of two oxygen atoms on the pinacol which can interact with the metal atom of the base used through chelation.

Unlike the usual non-stabilized ylides, the (2-(1, 3-dioxolan-2-yl)ethyl)tripropylphosphonium bromide (**Scheme 5**) is highly stable for hydrolysis in air. The synthesis of the salt is straightforward and it crystallizes out from the reaction mass.[15]

By employing the phosphonium salt, various aromatic, aliphatic and hetero-aromatic aldehydes were successfully homologated to alkenals in excellent yields.

2. Three carbon homologation of aldehydes

2.1 Introduction

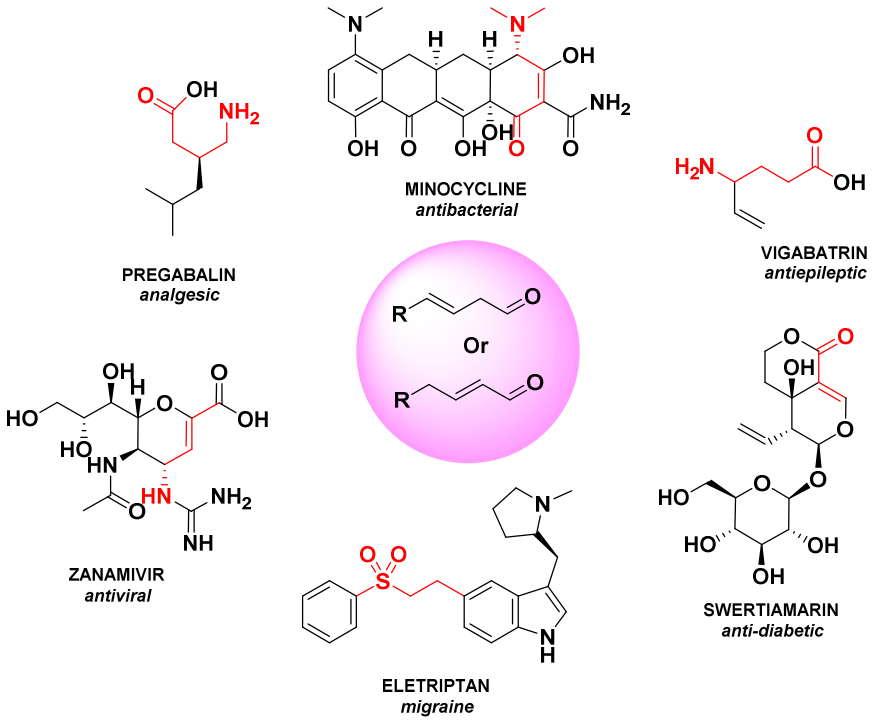
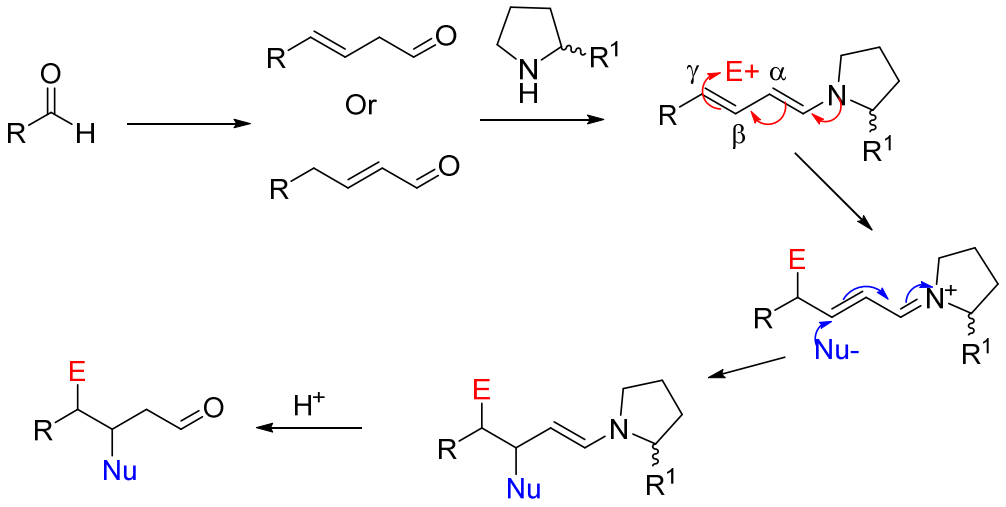


Figure- 5: Common drug molecules synthesized using unsaturated aldehydes[21]

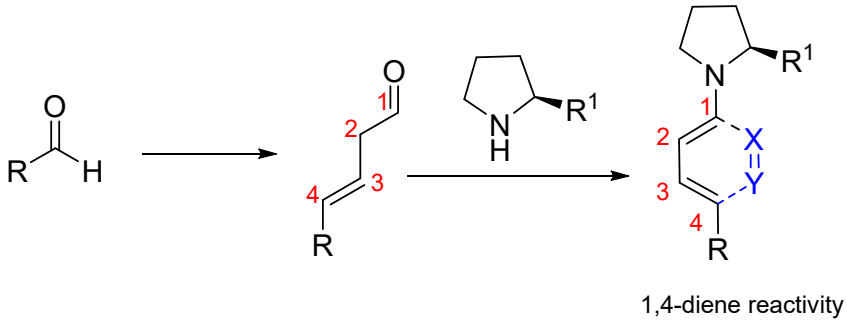
Unsaturated aldehydes are often employed as highly crucial intermediates in fine chemicals and pharmaceutical synthesis.[18,19,20] Especially, α, β and β, γ - unsaturated aldehydes gained significance after the evolution of organocatalysis. The conversion of aldehydes to homologated unsaturated aldehydes provides an easy and effective way to access important reaction intermediates. Several important pharmaceuticals are

synthesized using the homologated unsaturated aldehydes (**Figure 5**).[21] Therefore, an efficient and robust methodology is highly desirable for the streoselective carbon homologation of aldehydes.

One of the significant advancements in organocatalysis is the development of dienamine catalysis.[22] Dienamines differ from simple enamines in three main aspects : i) in an additional nucleophilic site at the δ-position and an electrophilic site at the γ-position for 1-aminobuta-1,3-dienes, ii) three types of reactivity modes (diene reactivity, vinylogous reactivity and enamine reactivity) exist for dienamines both of 1-aminobuta-1,3-dienes and of 2-aminobuta-1,3-dienes (**Scheme 6**),[22,23] and iii) dienamines can act as electron-rich olefin sources in inverse-electron demand Diels-Alder reactions by increasing the energy of the olefin HOMO (**Scheme 7**).[22,23] As a result of these novel properties, dienamine chemistry has become an important field of study in organic chemistry which in turn resulted in a huge demand for three carbons homologated unsaturated aldehydes.



Scheme- 6: Dual reactivity under dienamine catalysis: E- electrophile, Nu- nucleophile, R- alkyl/aryl/alkenyl, R^1- Chiral auxiliary[22,23]



Scheme- 7: Reactivity under Diels-Alder conditions[22]

The unsaturated aldehydes containing α or δ acidic hydrogen has been used extensively in organocatalysis (**Scheme 6 & 7**). Many organic chemists use these compounds as starting materials for methodology development and total synthesis.[23] They have been used in reactions like Diels-Alder cyclization for synthesizing heterocyclic molecules,[24] α / γ amination/alkylation of unsaturated aldehydes etc.[25,26] Therefore, developing a robust and efficient synthesis of these three carbon unsaturated aldehydes has prime importance in organic synthesis.

Over the years a variety of three carbon homologating methods are developed.[27] Most of the available methods for the three carbon homologation of aldehydes are often multistep and non-stereo selective. The reagents employed often suffered with poor yields and robustness.[27]

As mentioned in **Scheme-5**, Wittig reaction has been employed for the two carbon homologation.[15] Previously Triphenylphosphorane salt was used as a three carbon homologating agent.[28] But, the reaction predominantly gave *Z*- olefins and only few

aliphatic aldehydes were used as substrates. The generation of triphenylphosphine oxide as impurity which is insoluble in water possess a major challenge in purification. We envisioned a similar phosphonium salt which carries a protected propanal functionality (**Figure 6**).

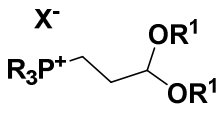
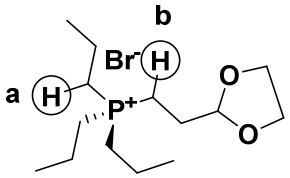


Figure- 6: Trialkylphosponium salt; R- Propyl or isobutyl, R^1-alkyl/oxolane, X- Cl or Br

2.2 Discussion of Results

For the synthesis of the phosphonium salt, 2-(2-bromoethyl)-1, 3-dioxolane was selected as the protected propanal equivalent. The possibility of regio selective ylide generation was considered while choosing the alkyl phosphine. The tripropylphosphine was successfully employed previously in our group.[15] Since the directing group for deprotonation (in this case the dioxolane group) is further away from the reactive hydrogen, regio selective ylide generation with tripropylphosphine possess a huge challenge (**Figure 7**). The hydrogen (**a**) in the propyl side chain and the hydrogen (**b**) in the dioxalane side chain exhibit similar acidities making the selective ylide formation difficult. Also, the presence of three propyl side chains means that there are four competing hydrogens in the ylide formation. Expecting this challenge, we also tried to use tri-isobutyl phosphine as the hydrogen next to phosphorous in the isobutyl chain is

sterically hindered for deprotonation than the hydrogen in the dioxolane side chain (**Figure 8**).



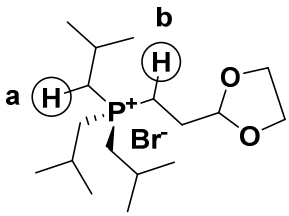
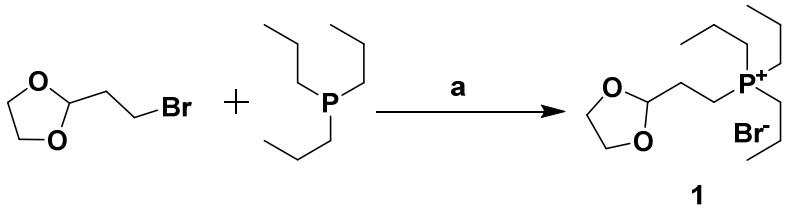


Figure- 7: Tripropylphosphonium salt **Figure- 8: Triisobutylphosphonium salt**

a, b = protons available for the ylide generation

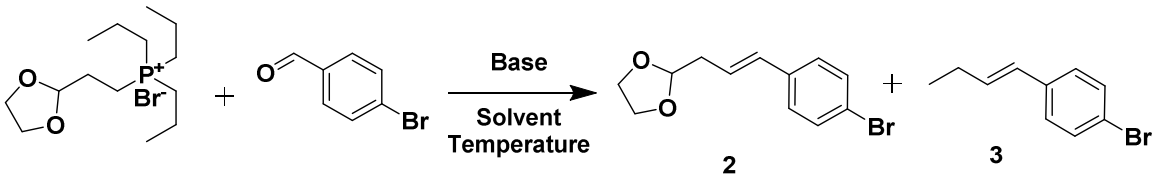
The phosphonium salt was synthesized according to the **Scheme 8** (see experimental section). The reaction with the tripropylphosphine was clean and afforded the phosphonium salt in 95% yield. The salt **1** is a white crystalline solid and hygroscopic. It is stable at room temperature when stored under inert atmosphere. However, tri-isobutyl phosphine did not form the required phosphonium salt with 2-(2-bromoethyl)-1, 3-dioxolane under neat reaction conditions at 100 °C.



Scheme- 8: Synthesis of Phosphonium salt 1

a) NaI (5 mol %), THF, 70 °C, 24h, 95 %

The phosphonium salt **1** was used to develop the three carbon Wittig homologation (**Scheme 9**). 4-bromobenzaldehyde was chosen as the carbonyl component for optimization of the reaction.



Scheme- 9: Wittig reaction optimization

Table 1 - Optimization of the Wittig reaction conditions

S. No	Salt (eq.)	Aldehyde (eq.)	Base(eq.)	Solvent	Temperature/ Time	Isolated Yield 2+3 (%)	% of (2:3)
1	1.1	1.0	LiHMDS 1.1	THF	0 °C-25 °C /10 h	70	60:40
2	1.1	1.0	NaOH 3	Water	120 °C /24 h	30	95:5
3	1.1	1.0	KOH 3	Water	120 °C /24 h	50	95:5
4	1.1	1.0	KOH 5	Water	120 °C /24 h	40	95:5
5	1.5	1.0	KOH 3	Water	120 °C /24 h	50	95:5
6	1.1	1.0	LiHMDS 1.1	THF/DMF 2:1	0 °C-25 °C /10 h	70	80:20

7	1.1	1.0	LiHMDS 1.1	THF/DMF 1:1	0 °C-25 °C /10 h	70	90:10
8	1.1	1.0	LiHMDS 1.1	DMF	0 °C-25 °C /10 h	55	90:10
9	1.1	1.0	KHMDS 1.1	THF/DMF 1:1	0 °C-25 °C /10 h	60	90:10

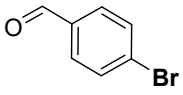
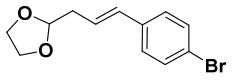
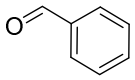
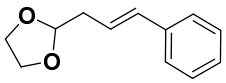
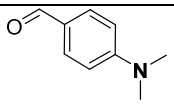
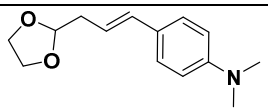
Table-1 summarises the important conditions screened for the optimization of the reaction. We anticipated two products after the reaction (**Scheme 9**). The product **2** which is formed by the ylide from the dioxolane chain and the product **3** from the propyl side chain. If the ylide generation is not selective, the ration of the two products would be 4:1.

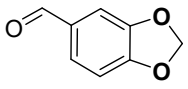
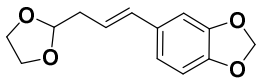
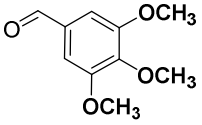
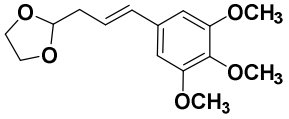
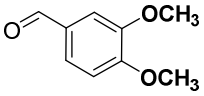
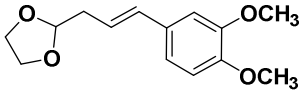
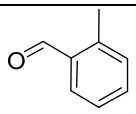
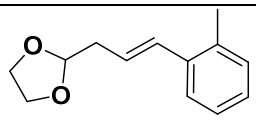
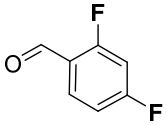
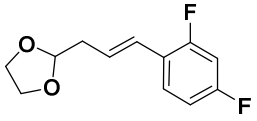
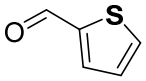
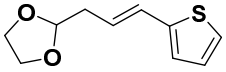
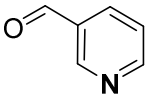
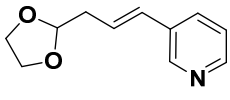
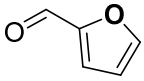
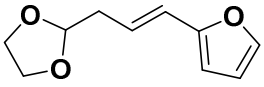
Inspired by the aqueous Wittig reaction developed in our group,[15] the reaction was carried out in water using NaOH as a base at 120 °C (**S.No 2**). To our delight greater selectivity was observed with 95% of product **2**. However the yield was only 30% and changing the base to KOH resulted in formation of the desired olefin up to 50% with identical stereo selectivity (**S.No 3**). Using higher amounts of base or the phosphonium salt did not enhance the yield (**S.No 4, 5**). The reason for the lower yield may be attributed to the degradation of the aldehyde or the salt at higher temperatures. Since the reaction under aqueous conditions gave poor yields, we explored the reaction in organic solvent. At first, the ylide was generated at 0 °C by the addition of LiHMDS in THF and the aldehyde was added at the same temperature (**S.No.1**). Then the reaction was slowly warmed to RT. Crude NMR shows 3:2 mixture of **2** and **3** with 70% yield. Performing the reaction at a temperature range of -78 °C to RT did not improve the selectivity. The

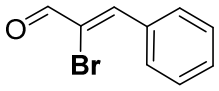
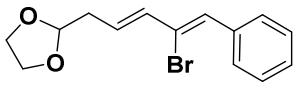
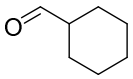
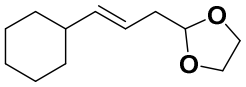
selectivity under aqueous conditions suggests that the polar solvent has a positive effect on the ylide formation. Also, the cation (Na^+ or K^+) may coordinate with the oxygen of the dioxolane and the ylide carbon driving the reaction towards the formation of the product **2**. Encouraged by this selective behaviour of ylide generation in water, we used a polar solvent (DMF) in addition to THF. To our surprise, we observed a considerable increase of selectivity (80:20) with 2:1 THF: DMF mixture as solvent (**S.No 6**). The selectivity was further enhanced to 90:10 with 70% yield when THF and DMF were used in equal quantities (**S.No 7**). Performing the reaction only in DMF or using KHMDS as base resulted in decrease of yield (**S.No 8, 9**). With the optimized conditions (**S.No. 7**) in hand, we then examined the substrate scope of the reaction.

2.2.1 Substrate scope

Table 2- Various aldehydes screened and their corresponding homologated products

Entry	Aldehyde	Product	Isolated Yield %	*E*:*Z* ratio
1			80	95:5
2			75	95:5
3			74	94:6

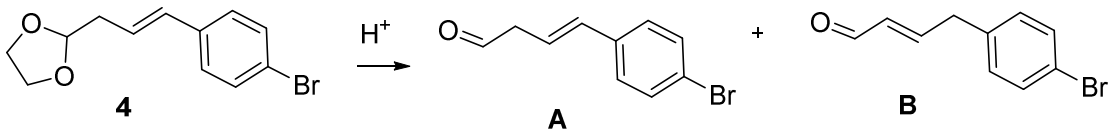
4			73	95:5
5			74	95:5
6			75	95:5
7			77	90:10
8			71	70:30
9			76	96:4
10			75	95:5
11			75	96:4

12			61	75:25
13			70	90:10

The reaction is well tolerated by aromatic, hetero aromatic, cinnamic and aliphatic aldehydes. **Table 2** shows the various aldehydes screened and the respective homologated products with the isolated yield and *E*, *Z* ratio. All the aromatic aldehydes gave the products from 70 -80% isolated yield. The stereoselectivity in most cases was excellent (95:5) and it is *E* in major (**Entry 1 to 6**). It is known that ortho substituted aldehydes generally show poor stereoselectivity in the Wittig reaction.[29] As expected 2-methyl benzaldehyde (**Entry 7**) and 2, 4-difluro benzaldehyde (**Entry 8**), gave the products with *E*, *Z* ratio of 90:10, 70:30 respectively. All the hetero aromatic aldehydes such as 2-furyl, 2-thianyl and 3-pyridyl carboxaldehydes rendered Wittig olefination products in good yields and excellent stereoselectivity (**Entries 9, 10, 11**). Interestingly, *α*- bromo cinnamaldehyde (**Entry 12**) also underwent the homologation smoothly in moderate yields with notable *E* selectivity. Finally the aliphatic cyclohexylcarboxaldehyde (**Entry 13**) was homologated in 70% yield with excellent *E* selectivity (90:10).

2.2.2 Deprotection of the dioxolane

After successfully developing the methodology to synthesize highly streoselective *β*, *γ*- unsaturated dioxolane derivatives, we are all set to synthesize *β*, *γ*- unsaturated aldehydes by the deprotection of dioxalane group. In general dioxalane groups are very easy to deprotect under mild acidic conditions. In this case of *β*, *γ*- unsaturated dioxolane derivatives, after deprotection we expected to have two aldehydes being *β*, *γ*- unsaturated aldehyde and *α, β*-unsaturated aldehyde which is resulted by the migration of the double bond (**Scheme 10**).



Scheme 10 - Acid mediated deprotection of the cyclic acetal

Table 3 - Acidic Conditions screened for the dioxolane deprotection

S.No	Acid (Eq)	Solvent	Temperature	Time (h)	Isolated yield
1	HCl (0.1 M)	Water	25 °C	2	70% B
2	TFA (1)	Water	25 °C	8	75% B
3	TFA (1)	DCM	25 °C	24	90% B
4	CH_3COOH (5)	Water	25 °C	24	10% A
5	CH_3COOH (5)	Water	60 °C	48	90 % (A&B)
6	*p*TSA (1)	DCM	25 °C	24	90% (A&B)

7	*p*TSA (1)	Acetone	60 °C	3	95% (A&B)

A variety of acids at various temperatures were employed for the deprotection of dioxolane group (**Table 3**). The dioxalane group was deprotected in 2 h and 8 h respectively at RT in water when we used 0.1 N HCl, TFA (**S.No 1, 2**). However these reactions produced **B** as a major product in 70% yield. Reaction in organic solvent like DCM with TFA was sluggish (24 h) at RT. Using milder acid like acetic acid at RT was not successful (**S.No 4**) while the reaction was warmed to 60 °C furnished the mixture of aldehydes in 90% yield (**S.No 5**). Using *p*-TSA as a catalyst was effective in DCM at RT with 90% mixture of aldehydes **A** and **B** in 24 h (**S.No 6**). Finally *p*-TSA under refluxing acetone conditions furnished the mixture of aldehydes in 95% yield in 3 h (**S.No 7**). Even though the reaction gave mixture of aldehydes at shorter duration the β, γ -unsaturated aldehyde **B** gradually isomerises to the more stable α, β -unsaturated aldehyde **A** over a period of time at RT.

3. Application of the Methodology

3.1. Introduction

The chemically sensitive keto-diol **5** and corresponding monomethyl ether **5a** motifs are present in many natural products, some of which show promising biological profiles (**Figure 9**). Examples of such natural products include the phytotoxic *cis*-6-deoxy-4-hydroxyscytalone (**8a**) and 4-hydroxyscytalone (**8b**),[30] cladosporol (**9**),[31] which shows hyper parasitic activity, and the antiangiogenic chrysanthone A (**10**).[32]

Two cytotoxic natural products, (2*R*,3*R*,4*R*)-3,4-dihydro-3,4-dihydroxy- 2-(3-methylbut-2-enyl)-1(2*H*)-naphthalenone (**6**) and (2*S*,3*R*,4*R*)-3,4-dihydro-3,4-dihydroxy-2-(3 methylbut-2- enyl)-1(2*H*)-naphthalenone (**7**) which were isolated by Kinghorn et al. from the chloroform-soluble extract of the roots of *Ekmanianthe longiflora.*[34] Interestingly, both compounds **6** and **7** exhibited in vitro cytotoxicity to a small panel of human tumor cell lines.[34]

A stereo selective synthesis of the *cis or trans* keto diol **5** is highly desirable since it can be used as a key intermediate to synthesise various biologically active molecules. Couche et al developed a strategy for synthesis of **8** and **8a** [35] exclusively, which involves long synthetic sequence including resolution step. In 2010, Tarun et al developed a diversity oriented synthesis for the common intermediate **5.**[33] However, the method involves expensive reactions like ring-closing metathesis (RCM) and commercially non-viable oxidation reactions.

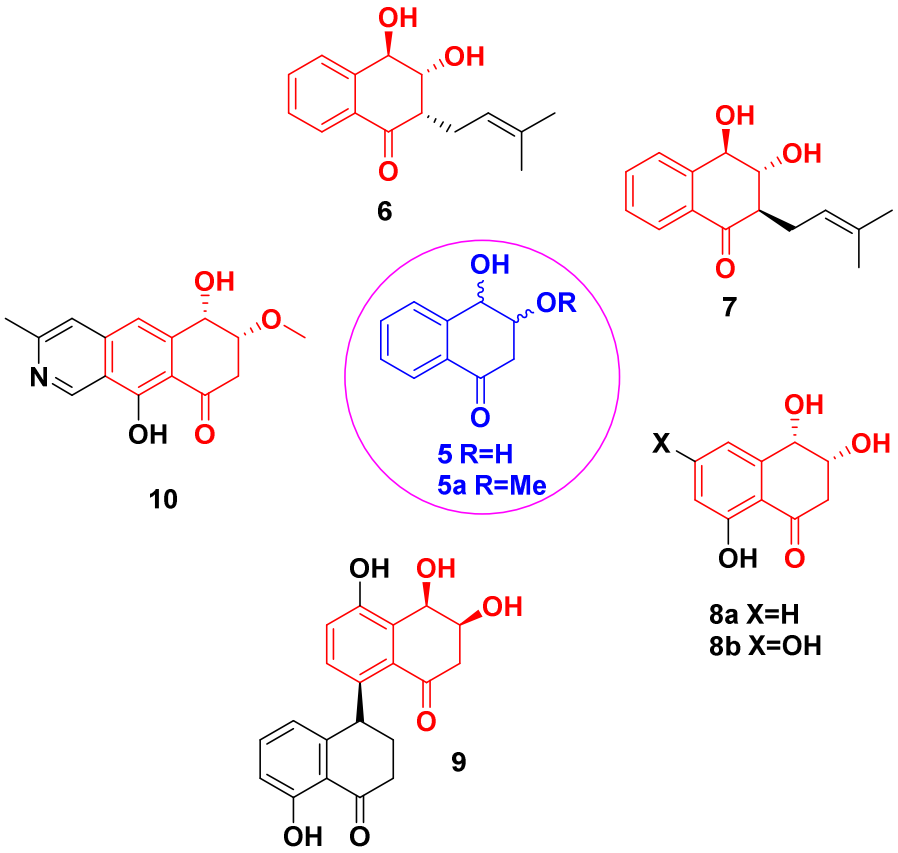


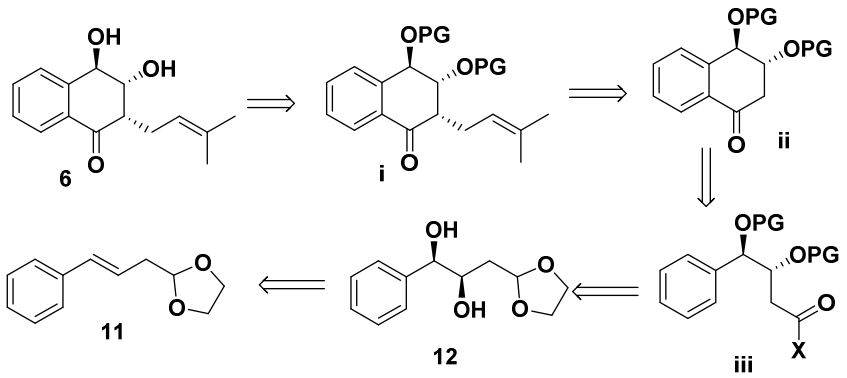
Figure 9 - Some biologically active natural products containing keto diol motifs (adapted and modified from Tarun.K.Sarkar Etal).[33]

We envisioned a simple strategy using the homologated aldehydes to synthesise the keto diol **5** and subsequently converting the diol into its biologically active derivatives. The results of the synthesis are outlined below.

3.2 Efforts for the total synthesis of (*2R*,*3R*,*4R*)-3,4-dihydro-3,4-dihydroxy-2-(3-methylbut-2-enyl)-1(*2H*)-naphthalenone (6).

The naphthalenone derivatives **6** and **7** (**Figure 9**) can be synthesised in one step from the keto diol intermediate **5**. In 2010 the racemic synthesis of **6** and **7** was reported by

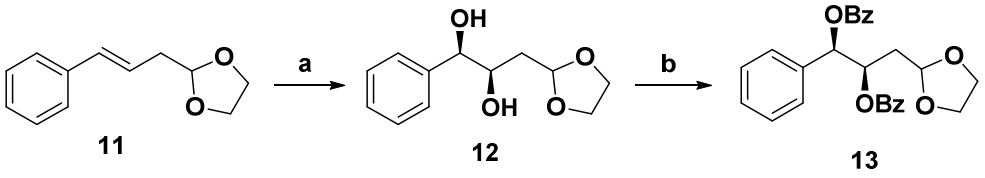
Venkateswarlu et al.[40] We have planned to synthesize enantiomerically pure natural product **6** via 2-cinnamyl- 1,3-dioxolane **(11).** According to our retrosynthesis, compound **6** was envisaged by the deprotection of diol (**i**), which in turn could be synthesized by the alkylation of ketone (**ii**). Ketone (**ii**) could be anticipated by the Friedel-Crafts acylation of **(iii)** which could be derived from cinnamyl dioxalane **11** through diol **12** (**Scheme 11**). It is important to note that the ketone (**ii)** is a key part of the synthesis and can be employed in the synthesis other derivatives as mentioned in **Figure 9**.



Scheme- 11: Retro-synthetic route for the target molecule 6

3.2.1 Discussion of results

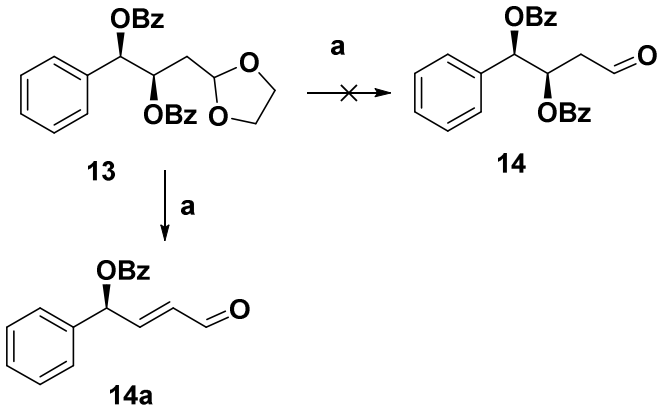
The synthesis was started by the Sharpless asymmetric dihydroxylation of the alkene in **11** with AD mix-β to diol (**12**) in 90% yield. The diol was protected as its benzoyl diester (**13**) by treatment with benzoyl chloride in the presence of triethylamine as a base. Then we have attempted the deprotection of the dioxalane group. Both the products **12** and **13** were isolated as white solids (**Scheme 12**).



Scheme- 12: Synthetic route for the molecule 13

a) AD-Mix- β, Me-Sulfonamide, *t*-BuOH/Water, 25 °C, 24h, 90% ; b) Benzoyl-Cl, TEA, DMAP, Pyridine, 0-25 °C, 18 h, 90% ;

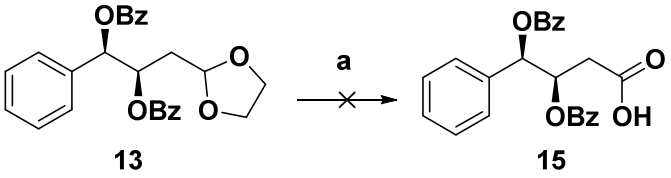
The deprotection of the dioxolane was initially carried out in water with dil.HCl as catalyst. Under these reaction conditions we were surprised to see the formation of *α*, *β*-unsaturated aldehyde **14a** through *β*- benzoyloxy elimination in **14.** Even though the reaction was screened using different acids like *p*-TSA, PPTS, $FeCl_3$, TFA, Acetic acid and Amberlite IR 120 resin in various solvents and at different temperatures, **14a** was obtained as sole product (**Scheme 13**).



Scheme- 13: Deprotection of the dioxolane group with various acids

(a) *p*-TSA, PPTS, $FeCl_3$, TFA, Acetic acid and Amberlite IR 120 resin.

Since the deprotection of dioxolane did not result in desired product, direct oxidation of the dioxolane to the carboxylic acid (**15**) was attempted by treatment with Oxone as an oxidant in THF and Water solvent mixture (**Scheme 14**).[36] Unfortunately, the oxidation reaction using oxone did not work with **13** and the carboxylic acid **15** was never observed in the reaction.

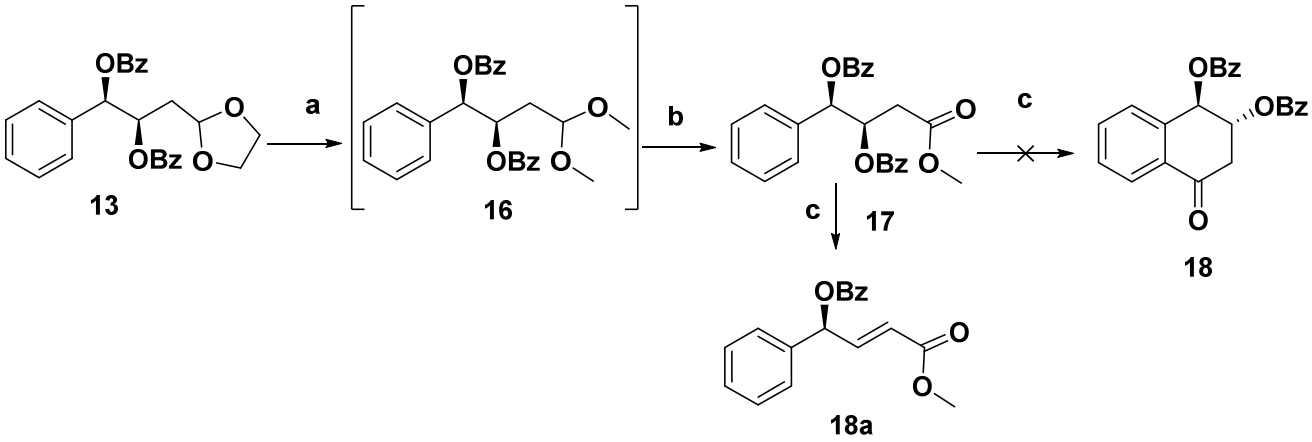


13 15

Scheme- 14: Oxidation of dioxolane to carboxylic acid

a) Oxone, THF/Water, 0-25 °C

While performing the oxidation reaction we came across an interesting reaction of oxone with dimethyl acetals. The dimethyl acetals react with oxone in alcoholic solvents to give corresponding methyl esters.[37] At this stage we have planned to take detour to the synthesis of intermediate **18.** We thought of converting dioxalane group to dimethyl acetal (**16**) in a single step followed by oxidation to methyl ester (**17**) which could deliver required ketone **18** (**Scheme 15**).



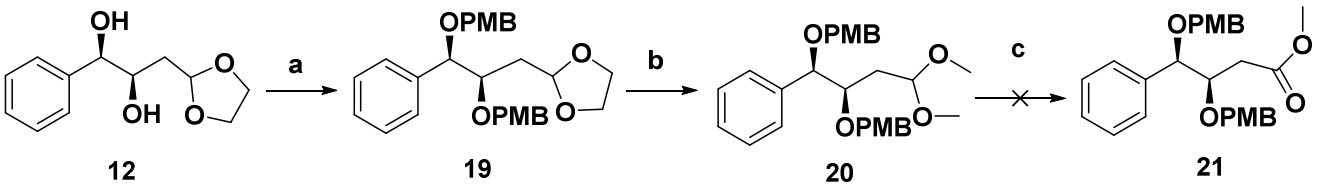
Scheme- 15: Alternate approach for the synthesis of the key intermediate 18

a) *p*-TSA, methanol, reflux, 2 h, 95% ; b) Oxone, methanol/water, reflux, 24 h, 60% ; c) Triflic acid, DCM, 0-25 °C, 1 h

As expected the dioxolane was converted into dimethyl acetal by refluxing in methanol using *p*-TSA as a catalyst.[38] The dimethyl acetal was not isolated and oxone was added directly to the reaction. After refluxing for 24 h the methyl ester (**17**) was isolated in 60% yield for two consecutive steps.

The cyclization was carried out by known literature procedure[38] in DCM utilizing trifluromethyl sulfonic acid (TFSA) as a catalyst. To our surprise we could even see trace amounts required ketone **18** instead we are able to isolate α, β-unsaturated ester (**18a**) which is resulted by the elimination of β-benzoyloxy group.

By taking the unsuccessful results into consideration, we thought of changing the protecting group from electron withdrawing benzoyl protection group to electron donating *p*-methoxy benzyl (PMB) group. We expected that an electron donating group would disfavour the β-elimination while benzoyl group was prone to elimination.



Scheme- 16: Synthesis of the ester 21 with PMB protected diol

a) PMB-Cl, NaH, THF/DMF, 0-25 °C, 24 h, 90% ; b) *p*-TSA, methanol, reflux, 2h, 90% ; c) Oxone, methanol/water, reflux, 24 h / $PhI(OAc)_2$, LiBr, water RT

The diol **12** was successfully protected with PMB-Cl by using NaH as a base in 90% yield. Once again the efforts which we put forward to get the aldehyde by the deprotection of dioxolane were futile and resulted in the formation of to *β*-eliminated product. The PMB protected dioxolane derivative (**19**) was converted into its corresponding dimethyl acetal (**20**) with *p*TSA in methanol. However the oxidation of methyl acetal to the corresponding ester was unsuccessful with oxone. The oxidation was also carried out by employing hypervalent iodine(III)/LiBr combination in water according to literature.[39] But, the reaction did not produce the required ester (**21**).

3.2.2 Conclusion and future work

In conclusion, the three carbon homologation of aldehydes using (2-(1, 3-dioxolan-2-yl)ethyl)tripropylphosphonium bromide is successfully developed. The ylide formation is highly regioselective. A variety of aromatic and hetero aromatic aldehydes are homologated with good stereo selectivity. The purification of the phosphine oxide

impurity is highly convenient as it is removed using water wash. The deprotection of the dioxolane is straightforward affording the aldehydes in remarkable yield.

The future work would be developing an organocatalytic method to synthesize biologically active molecules using the homologated molecules. The *E* selective β, γ - unsaturated aldehydes can be used to synthesise some useful natural products.

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4. New Synthetic Routes for Tricyclohexyl Phosphine

4.1 Introduction

Tricyclohexylphosphine is used in important complexes as ligand which includes the 2005 Nobel Prize winning Grubbs' catalyst[1] and the homogeneous hydrogenation Crabtree's catalyst.[2] It is also used as a ligand in various metal catalyzed coupling reactions. The evolution of palladium catalyzed chemistry has created a huge demand for the phosphine ligands and tricyclohexylphosphine is a vital member in that group.

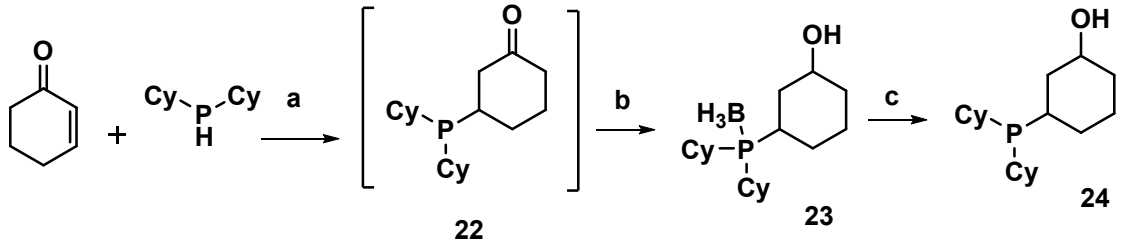
It is synthesized generally from phosphorus trichloride and cyclohexylmagnesium bromide. It is also synthesized by hydrogenation of triphenylphosphine oxide with a niobium catalyst or catalytic hydrogenation. The process is very tedious and has many technical hitches. Nevertheless, a new commercially viable synthesis possesses greatest advantage in the use of tricyclohexylphosphine.

The McNulty group has been working with alkylphosphines for more than a decade. The group has developed many new methodologies in organic synthesis using alkylphosphines.[3] With a great deal of expertise in handling the alkylphosphines, we took the challenge of developing a new synthetic process for tricyclohexylphosphine.

Over the past two years we have been working with Cytec Solvay Ltd. on novel methodologies for the synthesis of the ligand. Herein we present the three significant routes that were proposed and developed for the synthesis of tricyclohexylphosphine and its derivatives.

4.2. Route 1: 3-(dicyclohexylphosphino)cyclohexanol synthesis

This route was proposed in a vision of developing a solid supported tricyclohexylphosphine catalyst. Solid-supported reagents are easily removed from reactions by filtration. Excess reagents can be used to drive reactions to completion without difficulties in purification. Recycling of recovered reagents is economical, environmentally-sound, and efficient. Ease of handling is especially important when dealing with expensive or time-intensive catalysts which can be incorporated into flow reactors and automated processes. Reagents on solid-support react differently, more selectively, than their unbound counterpart.[4] The free hydroxyl group on 3-(dicyclohexylphosphino)cyclohexanol **(24)** can be attached to a solid support which in turn could be used to access the desired catalyst. The target molecule (**24**) is synthesized according to **Scheme 17.** The synthesis begins with a Michael addition of dicyclohexylphosphine on to 2-cyclohexen-1-one to give the ketone intermediate (**22**).



Scheme- 17: Synthesis of 3-(dicyclohexylphosphino)cyclohexanol (24)

a) Diethylene glycol, 85-90 °C, 2 h ; b) $NaBH_4$, Acetic acid, 0-25 °C, 2 h , 85 % over **a** and **b**; c) DABCO, toluene, 110 °C 24 h, 99% conversion based on ^{31}P NMR. Cy-Cyclohexyl

The reaction was done in diethylene glycol at 90 °C. The ketone **22** was not isolated and it was reduced using $NaBH_4$ in acetic acid according to the literature procedure.[5] The borane alcohol (**23**) was isolated as a white solid in 85% yield over two steps.

The removal of the boronate group has previously been accomplished by treatment with a large excess of a strongly nucleophilic amine,[6] such as diethylamine, DABCO, morpholine, or by treatment with tetrafluoroboric acid.[7] The latter method was not suitable in this current study, as subsequent product purification necessitates an aqueous workup.

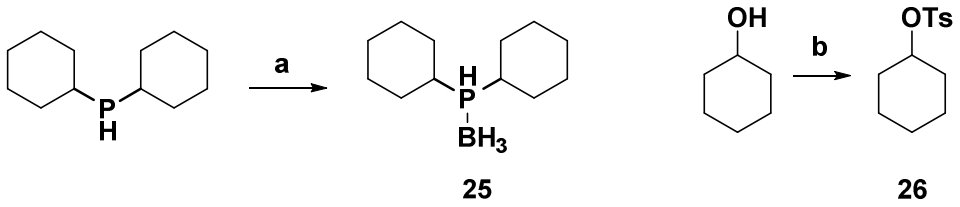
The de-boronation was initially performed in toluene using DABCO at 110 °C for 24 h.[6b] The reaction was also done by refluxing in morpholine at 110 °C for 2 h.[8] The conversion was 99% in both the cases. The reaction was monitored using the ^{31}P NMR (see experimental section). 3-(dicyclohexylphosphino)cyclohexanol (**24**) is highly unstable in the air and was very tedious to isolate under the normal laboratory conditions. The reaction was performed on 5 g scale and it is very robust. Efforts for isolating the alcohol (**24**) and subsequent synthesis of solid supported tricyclohexylphosphine are currently underway in our laboratory.

4.3. Route 2: Tricyclohexylphosphine synthesis through S_N2 reaction

Phosphine-borane complexes[9] have recently been used as intermediates in the synthesis of phosphine derivatives not accessible by other methods.[10] They are typically prepared via the reaction of a free phosphine with borane. Borane-protected phosphines are stable to metalation with lithium reagents and can subsequently be reacted with various

electrophiles under mild conditions to yield functionalized phosphine boranes. Notably, the borane group acts as both a protecting group and an activating group. In fact, hydrogen, methyl, and methylene groups adjacent to the phosphorus atom are activated towards deprotonation by strong bases.[11]The borane moiety can be removed quantitatively, and with retention of configuration, by treatment with either large excess of a nucleophilic amine[9] or tetrafluoroboric acid.[10]

In this route, the dicyclohexylphosphine was converted into its borane complex (**25**) by treatment with $NaBH_4$ in acetic acid in 95% yield (**Scheme 18**).[5]



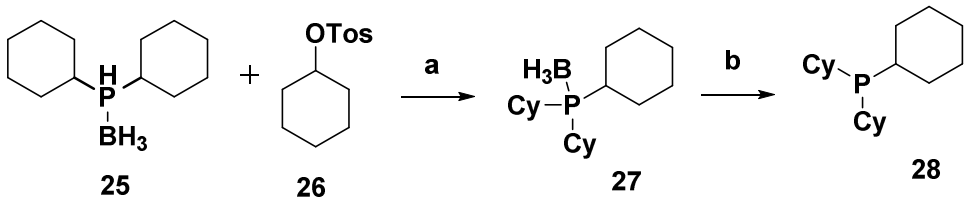
25 **26**

Scheme- 18: Boronation of dicyclohexylphosphine and tosylation of cyclohexanol

a) $NaBH_4$, Acetic acid, 0-25 °C, 2 h, 95% ; b) *p*-toluenesulfonyl chloride, Pyridine/THF, 4 h, 25 °C, 90%

Tosylated cyclohexanol (**26**) was used as a cyclohexane equivalent. The tolsylation was performed in Pyridine/THF to get **26** in 90% yield. The nucleophilic substitution reaction ($\mathbf{S_N2}$) was performed according to the procedure reported by Grubbs.[8] Compound **25** was metalated with ^{n}BuLi at -70 °C in THF and the generated phosphide anion was allowed to react with the electrophile **26** at 70 °C to yield the tricyclohexylphosphine borane.

Unfortunately, there was only 10% conversion observed (through ^{31}P NMR) and the phosphide was oxidised to phosphine oxide.



Scheme- 19: Synthesis of tricyclohexylphosphine through S_N2 reaction

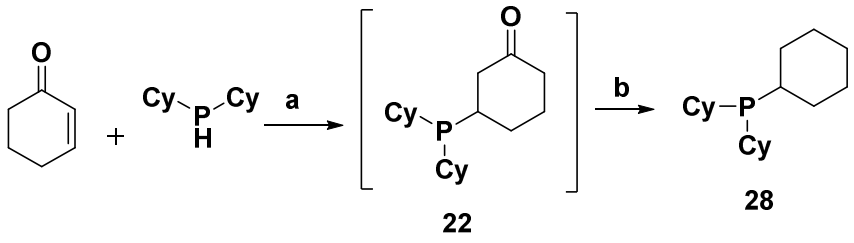
a) n-Butyl Lithium, DMF, -70 to 120 °C, 24 h, 40% ; b) Morpholine, 110 °C, 4 h, 99% conversion.

The reaction was later performed using DMF as solvent and the S_N2 reaction was done at 120 °C. The conversion was about 60% and the tricyclohexylphosphine borane was isolated in 40% yield as a white solid.

The deprotection of borane was carried out using the same method as in **Route -1**. Treatment of the tricyclohexylphosphine borane with morpholine at 110 °C for 2 h resulted in quantitative deprotection as monitored by ^{31}P NMR. Isolation of tricyclohexylphosphine form the reaction mixture was very tedious due to its high oxophilic nature. The isolation of the free phosphine from the reaction mass is currently pursued in our lab.

4.4. Route 3: Tricyclohexylphosphine synthesis through ketone reduction

In **Route -1**, Michael addition of dicyclohexylphosphine to 2-cyclohexen-1-one yields 3-(dicyclohexylphosphino)cyclohexanone (**22**). The ketone can be reduced to alkane to get tricyclohexylphosphine directly. Reduction of carbonyl compounds to the corresponding alkanes is a commonly known transformation. The important reactions used for this transformation are Clemmensen[12] and Wolff-Kishner reduction.[13] The conditions employed in the usual reactions are normally very harsh and requires strong reducing reagents like Zn (Hg)/HCl and NH_2NH_2/KOH. Using classical conditions for reducing the ketone present in **22** to give tricyclohexylphosphine is not economically viable. Also, use of water work-up for purification wherein the phosphine is unstable in such conditions limits the usage of traditional reduction. Recently very mild and inert strategies for ketone reduction have been developed. Among these reactions, the use of catalytic amounts of Lewis acid in the presence of polymethylhydrosiloxane (PMHS), a by-product of the silicone industry which is inexpensive, easy to handle, and environmentally friendly reducing agent.[14]



Scheme- 20: Tricyclohexylphosphine synthesis through ketone reduction

a) THF, 80-90 °C, 12 h; b) PMHS, Diethyl Zinc, LiBr, 24 h, 25 °C, 60 % conversion

In 2008, Jean-Marc Campagne *et al*. reported the $FeCl_3$ catalyzed reduction of ketones and aldehydes to alkanes using PMHS as reducing agent. But, the reaction was done under microwave conditions by using iron catalyst which possesses the formation undesired metal-phosphine complex.[15] In 2015, Hans Adolfsson and co-workers used diethyl zinc as a Lewis acid catalyst for the reduction of *tert*-amides to amines at room temperature.[16] Inspired by the reactivity of the catalyst, we used the strategy for reducing ketone **22** to tricyclohexylphosphine (**28**).

The ketone **22** was synthesised through Michael addition of dicyclohexylphosphine onto 2-cyclohexen-1-one at 80 °C in THF. The ketone was not isolated and the reduction was carried out in the same reaction flask at RT (**Scheme 20**). The conversion in the first step was quantitative and it was about 60% in the reduction step (based on ^{31}P NMR). The reaction sample was spiked with standard tricyclohexylphosphine and the ^{31}P NMR confirmed the formation of the required product. The reaction is still in preliminary stage and further optimization is under progress.

4.5. Conclusion and future work

In conclusion, three synthetic strategies for tricyclohexylphosphine derivatives were developed. Route-1 can be used to synthesize a solid supported catalyst through the free alcohol functionality in Cy_3P. Both route-2 and route-3 can be employed to access tricyclohexylphosphine in its pure form. The S_N2 reaction of the dicyclohexylphosphine borane on tosylated cyclohexanol requires cryogenic conditions which is a major concern

on industrial scale. Although initial attempts for borane deprotection using DABCO was sluggish, using morpholine reduced the reaction time to 2 h. Finally, the reduction of ketone to alkane offer easy access to tricyclohexylphosphine. The reactions are performed in one-pot at mild conditions. Further optimization of the reduction step is necessary for commercialization of the process.

Even though all the routes are promising on lab scale, large scale synthesis still requires great amount of work. The oxophilic nature of tricyclohexylphosphine makes the isolation very complicated. Highly inert atmosphere and apparatus is required for the isolation.

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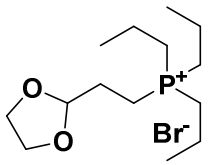
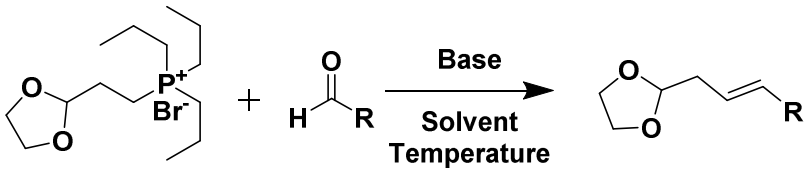
5. Experimental procedure

(2-(1, 3-dioxolan-2-yl)ethyl)tripropylphosphonium bromide (1)



To a 25 mL flame dried RBF with magnetic stir bar, charged, 2-(2-bromoethyl)1,3-dioxalane (3 g, 16.573 mmol, 1 eq) and sodium iodide (12.42 mg, 0.82 mmol, 0.05 eq) under nitrogen atmosphere. 10 mL of freshly distilled THF and Tri-n-propylphosphine (3.315 mL, 16.5 mmol, 1 eq) was added. The contents were stirred at 60-70 °C. After 24 h, the reaction was cooled to room temperature. The solvent was evaporated under *vacuo* at 50 °C and the white residue was washed with 10 mL of hexanes. The residue was dissolved in 10 mL of DCM and filtered over a celite bed under vacuum. The filtrate was evaporated at 40 °C. The obtained pasty solid was kept in a refrigerator for 12 h. White solid was formed after cooling and the same was washed with 10 mL of hexanes. The solid was dried under nitrogen flow to obtain the salt as a free flowing white solid (5.38 g, 95% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.99 (t, J = 3.6 Hz, 1H), 4.04 – 3.97 (m, 2H), 3.92 – 3.86 (m, 2H), 2.53 – 2.43 (m, 8H), 2.03 – 1.97 (m, 2H), 1.70 – 1.60 (m, 6H), 1.14 (td, J = 7.2, 1.4 Hz, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 101.84 (d, J = 13.3 Hz), 65.26, 25.64, 21.42 (d, J = 47.0 Hz), 15.66 (dd, J = 21.9, 10.1 Hz), 13.07 (d, J = 50.2 Hz). ^{31}P NMR (243 MHz, $CDCl_3$) δ 33.36.

Wittig reaction



R = Aryl, Heteroaryl

Procedure A

To a Microwave reaction tube with stir bar, charged, the corresponding aldehyde (1 eq.) and the phosphonium salt (1.1 eq.). To the tube, base (3-5 eq) and H_2O (1 mL) were added. The tube was sealed and heated at 110 °C overnight. The tube was cooled to room temperature and 5 mL of water was added. The aqueous solution was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mass was purified by silica gel column chromatography using EtOAc/Hexane as eluent.

Procedure B

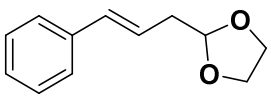
To a Microwave reaction tube with stir bar, charged, the corresponding aldehyde (1 eq.) and the phosphonium salt (1.1 eq.). To the tube, base (3-5 eq) and water (1 mL) were added. The tube was sealed and heated at 120 °C for 10 min in a Microwave reactor. The tube was cooled to room temperature and 5 mL of water was added. The aqueous solution was extracted with EtOAc (2x5 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mass was purified by silica gel column chromatography using EtOAc/Hexane as eluent.

Procedure C

To a 25 mL RBF with stir bar, charged, the phosphonium salt **1** (1.1 eq) under nitrogen. 5 mL of THF/DMF (1:1) mixture was added; the contents were purged with nitrogen and sealed with rubber septum and was cooled to 0 °C. The corresponding base (LiHMDS or KHMDS) was added through a syringe at 0 °C and was stirred at same temperature for 30 min. After that, solution of aldehyde (1 eq) in DMF and THF (2 mL) was added drop wise under nitrogen at 0 °C and the temperature was raised to 25 °C. The reaction was monitored using TLC and after the completion of the reaction, the reaction mass was evaporated under vacuum to give crude residue. The crude mass was dissolved in DCM, washed with water, followed by sat. NH_4Cl solution. The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mass was purified by silica gel column chromatography using EtOAc/Hexane as eluent. The fractions were concentrated under vacuum to afford the corresponding homologated product.

Substrate synthesis:

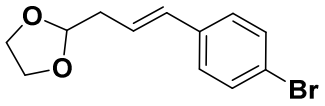
2-cinnamyl- 1,3-dioxolane



Synthesized using the general procedure **C**. 1.1 eq. of LiHMDS, and benzaldehyde (106 mg, 0.99 mmol) was used. 2-cinnamyl- 1,3-dioxolane (143.25 mg, 75%) was obtained as

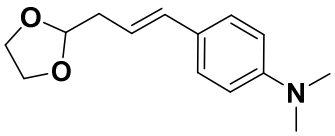
yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.23 (t, J = 7.3 Hz, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.27 (dt, J = 15.9, 7.2 Hz, 1H), 5.02 (t, J = 4.7 Hz, 1H), 4.05 – 4.02 (m, 2H), 3.91 (td, J = 6.4, 4.1 Hz, 2H), 2.64 – 2.61 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.34, 133.20, 129.08 – 128.04, 127.22, 126.19, 123.76, 103.86, 65.06, 37.94. HREI MS (M+) cald. for $C_{12}H_{14}O_2$: 190.0994, found 190.0985.

(*E*)-2-(3-(4-bromophenyl)allyl)-1,3-dioxolane



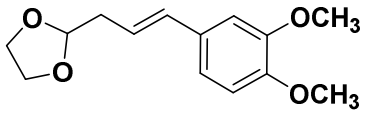
Synthesized using the general procedure **C**. 1.1 eq. of LiHMDS, and 4-bromo-benzaldehyde (100 mg, 0.54 mmol) was used. (*E*)-2-(3-(4-bromophenyl)allyl)-1,3-dioxolane (116.56 mg, 80%) was obtained as pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 6.37 (d, J = 15.9 Hz, 1H), 6.16 (dt, J = 15.8, 7.2 Hz, 1H), 4.91 (t, J = 4.6 Hz, 1H), 3.93 (dd, J = 8.8, 5.1 Hz, 2H), 3.83 – 3.80 (m, 2H), 2.51 (ddd, J = 6.9, 4.7, 1.3 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.27, 132.03, 131.55, 127.72, 124.68, 120.92, 103.63, 65.07, 37.86. HRES MS (M+H) cald. for $C_{12}H_{13}BrO_2$: 268.0099, found 268.0104.

(*E*)-4-(3-(1,3-dioxolan-2-yl)prop-1-en-1-yl)-*N*,*N*-dimethylaniline



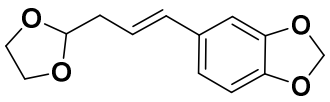
Synthesized using the general procedure C. 1.1 eq. of LiHMDS and 4-(Dimethylamino) benzaldehyde (100 mg, 0.67 mmol) was used. (*E*)-4-(3-(1,3-dioxolan-2-yl)prop-1-en-1-yl)-*N*,*N*-dimethylaniline (116.21 mg, 74%) was obtained as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 2H), 6.70 (d, *J* = 7.9 Hz, 2H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.05 (dt, *J* = 15.7, 7.2 Hz, 1H), 4.99 (t, *J* = 4.7 Hz, 1H), 4.04 – 4.01 (m, 2H), 3.92 – 3.89 (m, 2H), 2.97 (s, 3H), 2.59 (ddd, *J* = 7.0, 4.7, 1.3 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 149.85, 132.97, 127.09, 126.13, 119.34, 112.52, 104.22, 65.01, 40.63, 38.04. HRES MS (M+H) cald. for $C_{14}H_{20}NO_2$: 234.1481, found 234.1478.

(*E*)-2-(3-(3,4-dimethoxyphenyl)allyl)-1,3-dioxolane



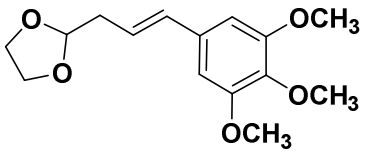
Synthesized using the general procedure **C**. 1.1 eq. of LiHMDS and 3,4-Dimethoxybenzaldehyde (120 mg, 0.72 mmol) was used. (*E*)-2-(3-(3,4-dimethoxyphenyl)allyl)-1,3-dioxolane (180.73 mg, 75%) was obtained as yellow oil.^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86 (d, *J* = 1.8 Hz, 1H), 6.82 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.74 – 6.71 (m, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 6.02 (dt, *J* = 15.7, 7.2 Hz, 1H), 4.90 (t, *J* = 4.7 Hz, 1H), 3.96 – 3.92 (m, 2H), 3.84 – 3.78 (m, 8H), 2.53 – 2.49 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.96, 148.54, 132.87, 130.49, 121.72, 119.30, 111.06, 108.60, 103.97, 65.03, 55.86 (d, *J* = 14.5 Hz), 37.91. HRES MS (M+H) cald. for $C_{14}H_{19}O_4$: 251.1283, found 251.1284.

(*E*)-5-(3-(1,3-dioxolan-2-yl)prop-1-en-yl)benzo[*d*][1,3]dioxole



Synthesized using the general procedure **C**. 1.1 eq. of LiHMDS and piperonal (100 mg, 0.66 mmol) was used. (*E*)-5-(3-(1,3-dioxolan-2-yl)prop-1-en-yl)benzo[*d*][1,3]dioxole (113.41 mg, 73%) was obtained as yellow oil.^{1}H NMR (600 MHz, $CDCl_3$) δ 6.85 (d, J = 1.5 Hz, 1H), 6.71 (dd, J = 8.0, 1.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.34 (d, J = 15.8 Hz, 1H), 6.03 – 5.95 (m, 1H), 5.86 (s, 2H), 4.89 (t, J = 4.7 Hz, 1H), 3.95 – 3.91 (m, 2H), 3.84 – 3.79 (m, 2H), 2.49 (ddd, J = 6.9, 4.7, 1.3 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.93, 146.89, 132.72, 131.89, 121.96, 120.69, 108.18, 105.59, 103.88, 100.97, 65.05, 37.81. HRES MS (M+H) cald. for $C_{13}H_{15}O_4$: 235.0970, found 235.0964.

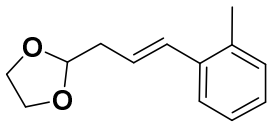
(*E*)-2-(3-(3,4,5,-trimethoxyphenyl)allyl)-1,3-dioxolane



Synthesized using the general procedure **C**. 1.1 eq. of LiHMDS and 3,4,5-Trimethoxybenzaldehyde (100 mg, 0.50 mmol) was used. (*E*)-2-(3-(3,4,5,-trimethoxyphenyl)allyl)-1,3-dioxolane (105.15 mg, 74%) was obtained as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.62 (s, 2H), 6.46 (d, J = 15.8 Hz, 1H), 6.17 (dt, J = 15.7, 7.2 Hz, 1H), 5.00 (t, J = 4.7 Hz, 1H), 4.06 – 4.00 (m, 2H), 3.94 – 3.90 (m, 2H), 3.89 (s, 6H), 3.86 (s, 3H), 2.61 (ddd, J = 7.0, 4.7, 1.3 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.26,

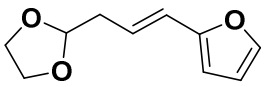
137.59, 133.15, 133.09, 123.25, 103.86, 103.26, 65.05, 60.93, 56.08, 37.85. HREI MS (M+) cald. for $C_{15}H_{20}O_5$: 280.1311, found 280.1303.

(*E*)2-(3-(o-tolyl)allyl)-1,3-dioxolane



Synthesized using the general procedure **C**. 1.1 eq. of LiHMDS and o-tolualdehyde (100 mg, 0.83 mmol) was used. (*E*)2-(3-(o-tolyl)allyl)-1,3-dioxolane (131.23 mg, 77%) was obtained as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, J = 7.0, 5.0 Hz, 1H), 7.02 – 6.96 (m, 3H), 6.57 (d, J = 15.8 Hz, 1H), 5.98 (dt, J = 15.7, 7.2 Hz, 1H), 4.86 (t, J = 4.6 Hz, 1H), 3.90 – 3.86 (m, 2H), 3.77 – 3.73 (m, 2H), 2.49 (ddd, J = 7.1, 4.6, 1.4 Hz, 2H), 2.21 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.47, 135.10, 131.04, 130.18, 127.15, 126.00, 125.51 (d, J = 23.2 Hz), 125.06, 103.97, 65.07, 38.20, 19.84. HREI MS (M+) cald. for $C_{13}H_{16}O_2$: 204.1150, found 204.1131.

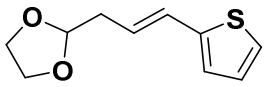
(*E*)-2-(3-(furan-2-yl)allyl)-1,3-dioxolane



Synthesized using the general procedure **C**. 1.1 eq. of LiHMDS and furfural (100 mg, 1.04 mmol) was used. (*E*)-2-(3-(furan-2-yl)allyl)-1,3-dioxolane (140.23 mg, 75%) was obtained as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (d, J = 1.5 Hz, 1H), 6.36 (ddd, J = 13.6, 6.7, 3.1 Hz, 2H), 6.19 (dt, J = 15.8, 7.1 Hz, 2H), 5.00 (t, J = 4.7 Hz, 1H), 4.05 –

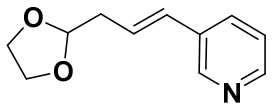
4.01 (m, 2H), 3.92 – 3.89 (m, 2H), 2.59 (ddd, *J* = 7.1, 4.7, 1.3 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.09 – 152.65, 141.56, 122.64, 121.67, 111.10, 106.90, 103.67, 65.05, 37.67. HREI MS (M+) cald. for $C_{10}H_{12}O_3$: 180.0780, found 180.0776.

(*E*)-2-(3-(thiophen-2-yl)allyl)-1,3-dioxolane



Synthesized using the general procedure **C**. 1.1 eq. of LiHMDS, 2-Thiophenecarboxaldehyde (100 mg, 0.89 mmol) was used. (*E*)-2-(3-(thiophen-2-yl)allyl)-1,3-dioxolane (132.55 mg, 76%) was obtained as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (d, *J* = 5.0 Hz, 1H), 6.96 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.93 (d, *J* = 3.3 Hz, 1H), 6.66 (d, *J* = 15.7 Hz, 1H), 6.09 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.00 (t, *J* = 4.6 Hz, 1H), 4.04 – 4.01 (m, 2H), 3.92 – 3.89 (m, 2H), 2.58 (ddd, *J* = 7.1, 4.6, 1.4 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.50, 127.20, 126.36, 124.96, 123.66, 123.56, 103.66, 65.07, 37.77. HREI MS (M+) cald. for $C_{10}H_{12}O_2S$: 196.0558, found 196.0556.

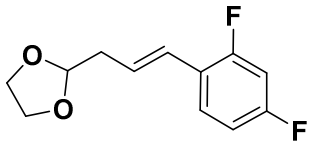
(*E*)-3-(3-(1,3-dioxolan-2-yl)prop-1-en-1-yl)pyridine



Synthesized using the general procedure **C**. 1.1 eq of LiHMDS, 3-Pyridinecarboxaldehyde (100 mg, 0.93 mmol) was used. (*E*)-3-(3-(1,3-dioxolan-2-yl)prop-1-en-1-yl)pyridine (134.58 mg, 75%) was obtained as yellow oil. ^{1}H NMR (600

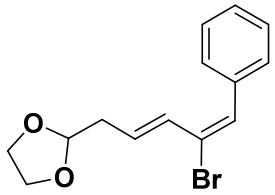
MHz, $CDCl_3$) δ 8.61 (d, J = 1.8 Hz, 1H), 8.47 (dd, J = 4.8, 1.3 Hz, 1H), 7.73 (dt, J = 7.9, 1.8 Hz, 1H), 7.27 (dd, J = 7.9, 4.8 Hz, 1H), 6.52 (d, J = 16.0 Hz, 1H), 6.35 (dt, J = 16.0, 7.1 Hz, 1H), 5.02 (t, J = 4.6 Hz, 1H), 4.06 – 4.01 (m, 2H), 3.95 – 3.89 (m, 2H), 2.65 (ddd, J = 7.0, 4.6, 1.4 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.89, 147.74, 133.08, 132.99, 129.51, 126.62, 123.51, 103.46, 65.10, 37.92. HRES MS (M+H) cald. for $C_{11}H_{14}NO_2$: 192.1095, found 192.1022.

(*E*)-2-(3-(2,4-difluorophenyl)allyl)-1,3-dioxolane



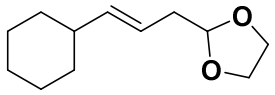
Synthesized using the general procedure **C**. 1.1 eq of LiHMDS, 2,4-Difluorobenzaldehyde (100 mg, 0.70 mmol) was used. (*E*)-2-(3-(2,4-difluorophenyl)allyl)-1,3-dioxolane and (*Z*)-2-(3-(2,4-difluorophenyl)allyl)-1,3-dioxolane (112.27 mg, 71%) was obtained as yellow oil in 70:30 mixture. ^{1}H NMR (600 MHz, $CDCl_3$) (Major isomer *E*) δ 7.23 (dq, J = 8.2, 6.4 Hz, 1H), 7.13 (tt, J = 8.3, 6.3 Hz, 1H), 6.93 – 6.83 (m, 1H), 6.35 (d, J = 11.4 Hz, 1H), 6.05 (dt, J = 11.4, 1H), 5.05 (t, J = 4.6 Hz, 1H), 4.06 – 4.02 (m, 2H), 4.00 (ddd, J = 6.2, 5.2, 2.7 Hz, 2H), 2.66 (t, J = 5.1 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.67 (d, J = 7.7 Hz), 160.00 (d, J = 7.7 Hz), 131.37 (t, J = 7.7 Hz), 131.06, 128.70 (t, J = 10.2 Hz), 127.61 (t, J = 10.7 Hz), 119.64, 118.02, 111.57, 103.58, 65.10, 39.24. HREI MS (M+) cald. for $C_{12}H_{12}O_2F_2$: 226.0808, found 226.0805.

2-((2*E*,4*E*)-4-bromo-5-phenylpenta-2,4-dien-1-yl)-1,3-dioxolane



Synthesized using the general procedure C. 1.1 eq of LiHMDS, α-Bromocinnamaldehyde (100 mg, 0.47 mmol) was used. 2-((2*E*,4*E*)-4-bromo-5-phenylpenta-2,4-dien-1-yl)-1,3-dioxolane (85.28 mg, 61%, *E*:*Z* = 25:25) was obtained as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) Major isomer: δ 7.49 – 7.46 (m, 2H), 7.35 – 7.31 (m, 3H), 6.30 – 6.22 (m, 1H), 6.07 (dt, *J* = 10.8, 7.3 Hz, 1H), 5.90 – 5.82 (m, 1H), 5.04 (t, *J* = 4.8 Hz, 1H), 4.07 – 4.01 (m, 2H), 3.91 (ddd, *J* = 4.5, 4.1, 2.3 Hz, 2H), 2.84 (ddd, *J* = 7.2, 4.8, 1.5 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.64, 136.60, 133.60, 131.49, 129.47, 128.29, 128.18, 128.03, 123.40, 113.08, 112.05, 103.27, 65.04, 35.26.

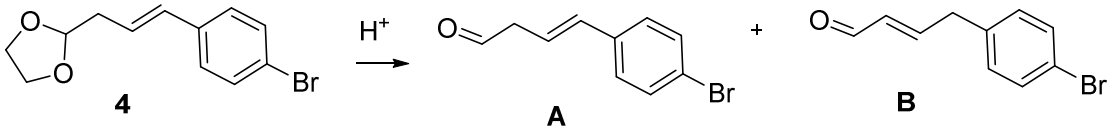
(*E*)-2-(3-cyclohexylallyl)-1,3-dioxolane



Synthesized using the general procedure C. 1.1 eq of LiHMDS, cyclohexanecarboxaldehyde (100 mg, 0.89 mmol) was used. (*E*)-2-(3-cyclohexylallyl)-1,3-dioxolane (123.56 mg, 70%) was obtained as yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.46 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.31 (dtd, *J* = 15.3, 6.9, 1.2 Hz, 1H), 4.79 (t, *J* = 4.8 Hz, 1H), 3.91 – 3.89 (m, 2H), 3.80 – 3.78 (m, 2H), 2.30 – 2.28 (m, 2H), 1.90 – 1.83 (m, 1H),

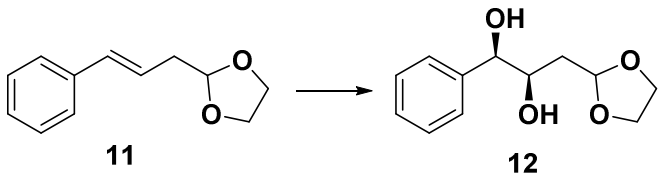
1.67 – 1.61 (m, 5H), 1.23 – 1.14 (m, 3H), 1.04 – 0.95 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.29, 120.75, 104.39, 64.94, 40.69, 37.67, 32.96, 26.21, 26.08.

Deprotection of the dioxolane



The compound **4** (0.18 mmol, 50 mg) in corresponding solvent and acid, was stirred at the appropriate temperature for a given time (**Table 3**). TLC indicated the disappearance of the dioxolane compound. The solvent was removed under vacuum and the crude was dissolved in EtOAc and washed with sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and purified through silica gel column using 4:1 EtOAc/Hexane. The concentration of the fractions gave a mixture of A and B as pale yellow liquid. Compound **A** (α, β-unsaturated aldehyde) ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.47 (d, J = 7.8 Hz, 1H), 7.41 – 7.38 (m, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.85 (dt, J = 15.6, 6.7 Hz, 1H), 6.03 (ddt, J = 15.6, 7.8, 1.6 Hz, 1H), 3.54 (dd, J = 6.6, 1.3 Hz, 2H).

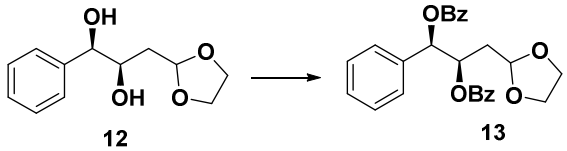
(1*R*,2*R*)-3-(1,3-dioxolan-2-yl)-1-phenylpropane-1,2-diol (12)



11 12

To a solution of alkene (**11)** (900 mg, 4.73 mmol) (prepared according to the general procedure **C**) in aq. *t*-BuOH (1:1 v/v, 60 mL) at 0 °C was added AD-mix-*β* (10.15 g, 1.5 eq). To the mixture, added methyl sulfonamide (450 mg, 1 eq.) and stirred for 24 h at room temperature. The reaction was monitored using TLC and after completion, the mixture was treated with sat. $Na_2S_2O_3$ and extracted with EtOAc, and the organic layer was washed with brine. The extract was dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by silica gel column chromatography (EtOAc/Hexane, 1:1) to give the diol **12** (957 mg, 90%) as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.36 (m, 4H), 7.32 (ddt, *J* = 8.9, 6.4, 2.3 Hz, 1H), 5.04 – 5.03 (m, 1H), 4.55 (dd, *J* = 6.6, 2.7 Hz, 1H), 4.07 – 3.98 (m, 3H), 3.93 – 3.84 (m, 2H), 3.38 (d, *J* = 2.3 Hz, 1H), 3.03 (d, *J* = 3.2 Hz, 1H), 1.88 – 1.78 (m, 2H).

(1*R*,2*R*)-3-(1,3-dioxolan-2-yl)-1-phenylpropane-1,2-diyl dibenzoate (13)

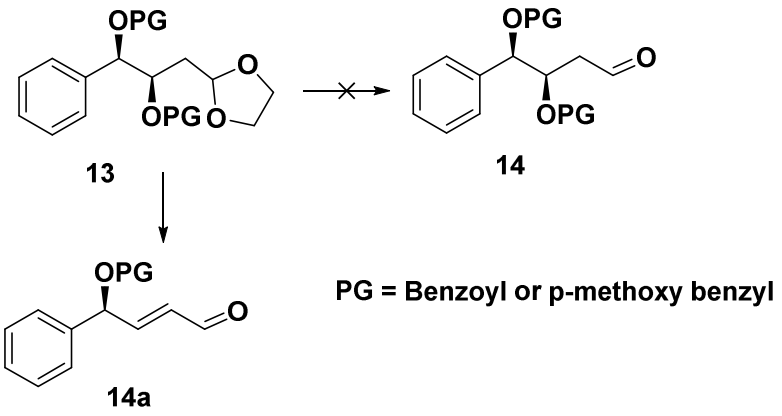


12 13

Triethylamine (361 mg, 4 eq.) and benzoyl chloride (376 mg, 3 eq.) were added drop wise to a stirred solution of the diol **12** (200 mg, 0.89 mmol)**,** and 4-(dimethylamino) - pyridine

(217 mg, 2 eq.) in dry dichloromethane at room temperature. The reaction was stirred for 18 h, quenched with water, extracted with dichloromethane, dried and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica with 2: 1 EtOAc– Hexane as eluent gave the diester **13** (347 mg, 90%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.4, 1.3 Hz, 2H), 7.93 (dd, J = 8.2, 1.1 Hz, 2H), 7.46 – 7.41 (m, 4H), 7.35 – 7.30 (m, 4H), 7.29 – 7.21 (m, 3H), 6.15 (d, J = 6.9 Hz, 1H), 5.86 (ddd, J = 8.9, 7.0, 3.5 Hz, 1H), 4.91 (dd, J = 5.1, 4.3 Hz, 1H), 3.88 – 3.78 (m, 2H), 3.74 – 3.69 (m, 2H), 2.05 (ddd, J = 14.5, 8.9, 4.2 Hz, 1H), 1.92 (ddd, J = 14.6, 5.2, 3.6 Hz, 1H).

Deprotection of the dioxolane:



Method 1:

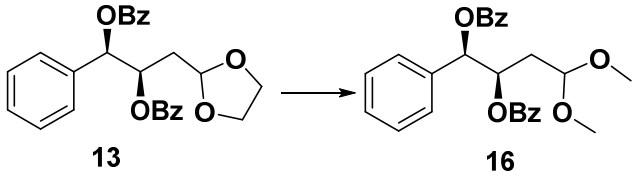
The protected diol **13** (0.23 mmol, 100 mg) or **19** (0.21 mmol, 100 mg) was dissolved in acetone (10 mL) and corresponding acid *p*-TSA (0.3 eq.) or PPTS (0.3 eq.) was added. The reaction was monitored at room temperature for 8 h and there was no deprotection observed. The reaction was then refluxed for 4 h. TLC indicated the disappearance of the

dioxolane compound. The acetone was removed under vacuum and the crude was dissolved in EtOAc and washed with sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and purified through silica gel column using 4:1 EtOAc/Hexane. The concentration of the fractions gave a pale yellow liquid (45 mg, 50%). The obtained aldehyde was analyzed using ^{1}H NMR and which indicated that the product obtained was **14a** and not **14** as expected. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.55 (d, J = 7.8 Hz, 1H), 8.03 (dd, J = 8.3, 1.2 Hz, 2H), 7.56 – 7.51 (m, 1H), 7.40 (dd, J = 8.7, 7.4 Hz, 4H), 7.37 – 7.33 (m, 2H), 7.33 – 7.29 (m, 1H), 6.92 (dd, J = 15.7, 4.5 Hz, 1H), 6.68 (dd, J = 4.5, 1.6 Hz, 1H), 6.34 (ddd, J = 15.7, 7.8, 1.7 Hz, 1H).

Method 2:

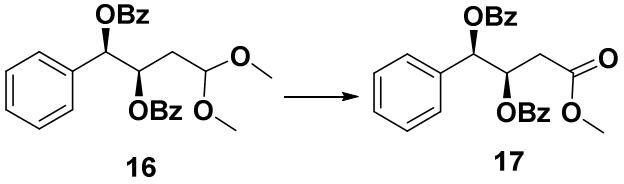
The protected diol **13** (0.23 mmol, 100 mg) or **19** (0.21 mmol, 100 mg) was dissolved in 0.1M HCl in water (5 mL). The reaction was monitored at room temperature for 8 hrs. TLC indicated the disappearance of the dioxolane compound but the product was matching with **14a**. The reaction was extracted EtOAc and washed with sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and purified through silica gel column using 4:1 EtOAc/Hexane. The concentration of the fractions gave a pale yellow liquid (42 mg, 46%). The obtained aldehyde was analyzed using ^{1}H NMR and which indicated that the product obtained was **14a** and not **14** as expected.

(1*R*,2*R*)-4,4-dimethoxy-1-phenylbutane-1,2-diyl dibenzoate (16):



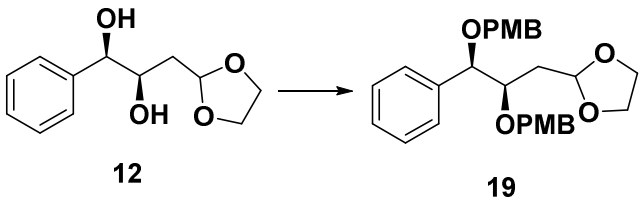
To a solution of diester **13** (50 mg, 0.011 mmol) in 5 mL methanol added, *p*-TSA (4.2 mg, 0.2 eq) and refluxed for 2 h. TLC indicated the absence of the starting material and the crude ^{1}HNMR indicated the presence of desired product **16**.

(1*R*,2*R*)-4-methoxy-4-oxo-1-phenylbutane-1,2-diyl dibenzoate (17):



To a solution of dimethyl acetal **16** (50 mg, 0.0115 mmol) in 6 mL methanol/water (4:1) added, Oxone (424 mg, 6 eq) and stirred at 70 °C. After 24 h, TLC indicated the absence of the acetal and the crude ^{1}HNMR indicated the presence of desired product **17**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, J = 7.8 Hz, 2H), 7.91 (d, J = 7.7 Hz, 2H), 7.44 (d, J = 7.7 Hz, 4H), 7.35 – 7.24 (m, 7H), 6.22 (d, J = 7.0 Hz, 1H), 5.98 (q, J = 6.6 Hz, 1H), 3.53 (s, 3H), 2.65 (d, J = 6.3 Hz, 2H).

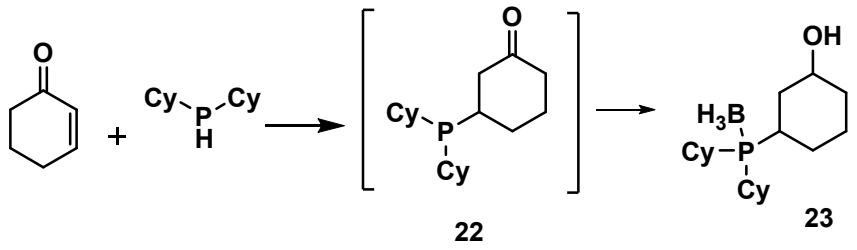
2-((2*R*,3*R*)-2,3-bis((4-methoxybenzyl)oxy)-3-phenylpropyl)-1,3-dioxolane (19)



To diol **12** (200 mg, 0.89 mmol) dissolved in THF/DMF (1:2 mixture 12 ml) added, (44.9 mg, 2.1 eq.) at 0 °C. After 30 min, added, *p*-methoxybenzyl chloride (294 mg, 2.1 eq.). The reaction was stirred at RT for 24 h, quenched with water, extracted with dichloromethane, dried and evaporated under reduced pressure to give the crude product. Purification by column chromatography on silica with 2: 1 EtOAc– Hexane as eluent gave the protected diol **19** (374 mg, 90%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 – 7.37 (m, 4H), 7.34 – 7.31 (m, 1H), 7.27 – 7.24 (m, 2H), 7.23 – 7.18 (m, 2H), 6.89 – 6.87 (m, 2H), 6.86 – 6.84 (m, 2H), 4.88 (dd, J = 7.1, 3.4 Hz, 1H), 4.60 (d, J = 10.8 Hz, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.45 (dd, J = 13.2, 8.2 Hz, 2H), 4.27 (d, J = 11.5 Hz, 1H), 3.90 – 3.86 (m, 3H), 3.83 (d, J = 5.3 Hz, 6H), 3.81 – 3.77 (m, 2H), 1.82 (ddd, J = 13.5, 9.8, 3.4 Hz, 1H), 1.56 (ddd, J = 14.1, 7.1, 3.5 Hz, 1H).

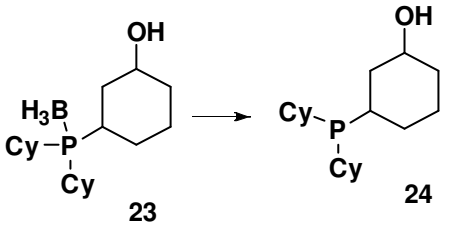
Route -1:

3-(dicyclohexylphosphino)cyclohexanol borane



To a 25mL flame dried Schlenk flask, with magnetic stirrer, purged with argon three times. Under Argon, charged, diethylene glycol (7.5 mL, 6 eq.) and dicyclohexylphosphine (0.95 g, 1 eq.). The contents were stirred at 85 °C for 15 min on a pre-heated oil bath. Charged, 2-cyclohexen-1-one (0.644 g, 1.4 eq.) under argon. The contents were stirred at 85-90 °C for 2.5 h. The reaction was analysed using ^{31}P NMR, which indicated complete conversion (^{31}P NMR (243 MHz, $CDCl_3$) δ 11.54) to **22**.The mass was cooled to 25°C and freshly distilled THF (10 mL) was added. The vessel was cooled to 0°C using an Ice bath. Sodium borohydride (362 mg, 2 eq.) and glacial acetic acid (684 mg, 1.7 eq.) were added. The temperature was raised to 25 °C and stirred for 6 h. The mass was analyzed using ^{31}P NMR and the reaction was found complete. The reaction mass was evaporated under vacuum at 50 °C resulting in an oily mass. To the oily mass added, 10 mL of water. White precipitate was formed and filtered under suction to give the product (**23**) in 85 % overall yield. ^{31}P NMR (243 MHz, $CDCl_3$) δ 29.45.

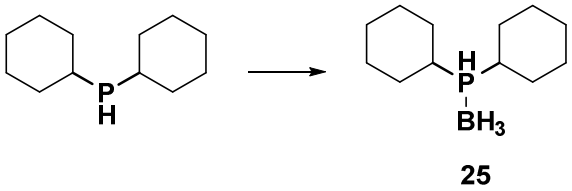
3-(dicyclohexylphosphino)cyclohexanol



To a flame dried Schlenk flask, under argon, charged, compound **23** (5 g, 1 eq.) and DABCO (1.44 g, 4 eq.). The flask was purged with argon and freshly distilled toluene (10 mL) was added. The flask was sealed and stirred at 110 °C for 30 h. ^{31}P NMR analysis indicated the complete deprotection of the borane to the required compound **24**. ^{31}P NMR (243 MHz, Tol) δ 9.61.

Route-2

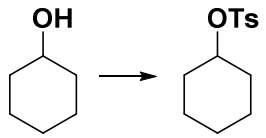
Boronation of dicyclohexylphosphine



To a solution of dicyclohexylphosphine (4.03 g, 20.3 mmol) in dry THF (20 mL) at 0 °C under nitrogen was added solid sodium borohydride (1.15 g, 30.5 mmol) in one portion followed by a solution of glacial acetic acid (2.1 g, 34.5 mmol) in THF (8.0 mL) drop wise over 30 min. Frothing occurs but is readily controllable through magnetic or overhead stirring of the solution. Subsequent to the acid addition, the reaction mixture

was stirred at room temperature for 1 h at which time TLC analysis indicated complete conversion. TLC: hexane/EtOAc 85:15, Cy_2PH Rf ¼ 0:85, $Cy_2PH–BH_3$ Rf ¼ 0:73. Water (20 mL) was slowly added to the reaction followed by acetic acid (2.0 g) in water (25 mL). Crystallization occurred by storing in the refrigerator for 12 h. The crystals were filtered by suction, washed with water and dried to give $Cy_2PH–BH_3$ (**25**) in 95% yield. ^{31}P NMR (243 MHz, Tol) δ 19.11 (d, J = 51.6 Hz)

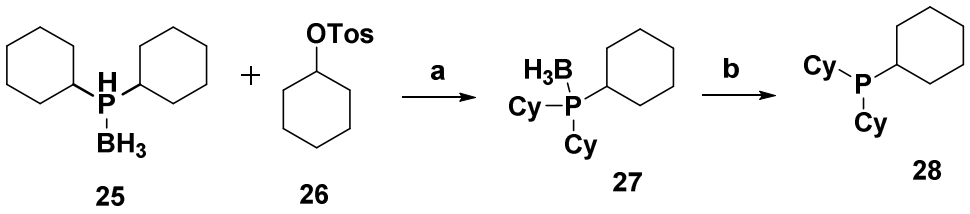
Tosylation of cyclohexanol



26

p-Toluenesulfonyl chloride (2.47 g, 1.29 mmol, 1.3 eq.) was slowly added to a solution of cyclohexanol (1 g, 0.99 mmol) and pyridine (5 mL) in 10 mL of dry THF at RT. The reaction mixture was stirred for 18 h. TLC indicated the completion of the reaction (*p*-anisaldehyde staining). The solvent was evaporated under vacuum and a saturated aqueous solution of sodium bicarbonate (10 mL) was added to the residue, and the resulting dark red slurry was extracted with ethyl acetate (2x 10 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution and water and dried over Na_2SO_4, and the solvent was evaporated *in vacuo* to yield (**26**) 2.3 g (90%) of a white solid.

Synthesis of tricyclohexylphosphine through S_N2 reaction



25 26 27 28

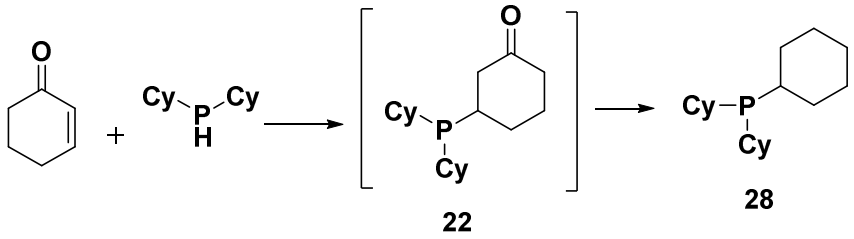
(a) S_N2 Reaction

Compound **25** (100 mg, 0.47 mmol) in THF (3 mL) was placed into a Schlenk flask and purged with argon. The solution was cooled to -78 °C, and *n*-butyl lithium (0.11 mL of a 1.6 M solution in hexane, 0.51 mmol, 1.1 eq.) was added drop wise *via* syringe. The colorless reaction mixture was stirred for 2 h while slowly warming to room temperature. Upon cooling of the solution to -78°C, compound **26** (144 mg, 0.56 mmol, 1.2 eq.) in DMF (5 mL) was slowly added *via* syringe. The reaction mixture was kept for 2 h at RT and then stirred at 120 °C overnight. The reaction was analysed using ^{31}P NMR which showed the absence of **25** and a new peak corresponding to **27**. Water (10 mL) was slowly added to the reaction. Crystallization occurred by storing in the refrigerator for 12 h. The crystals were filtered by suction, washed with water and dried to give $Cy_3P–BH_3$ (**27**) 60 mg in 43 % yield. ^{31}P NMR (243 MHz, Tol) δ 29.45 (d, J = 64.2 Hz).

(b) Borane deprotection

To a flame dried Schlenk flask, under argon, charged, compound **27** (100 mg, 0.51 mmol) and morpholine (10 mL). The flask was sealed and stirred at 110 °C for 1 h. ^{31}P NMR analysis indicated the complete deprotection of the borane to the required compound **28**. ^{31}P NMR (243 MHz, Tol) δ 9.65.

Route -3

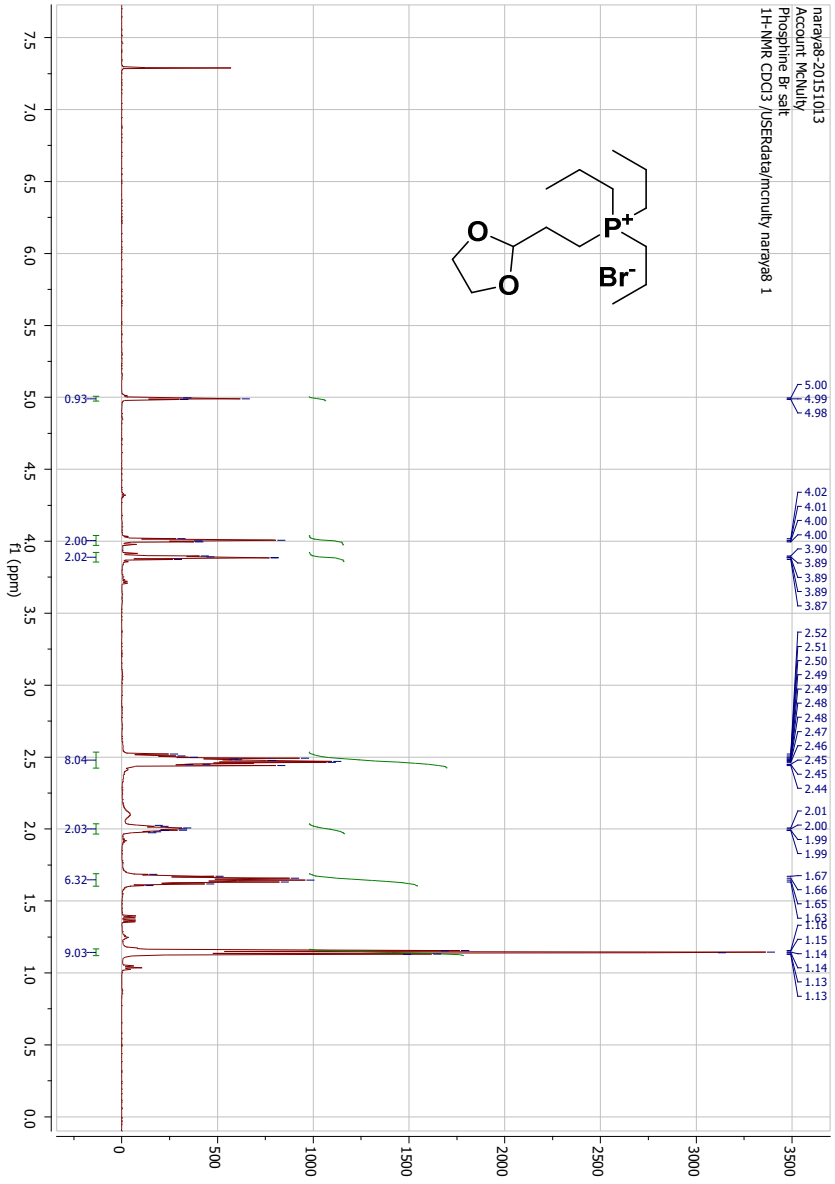


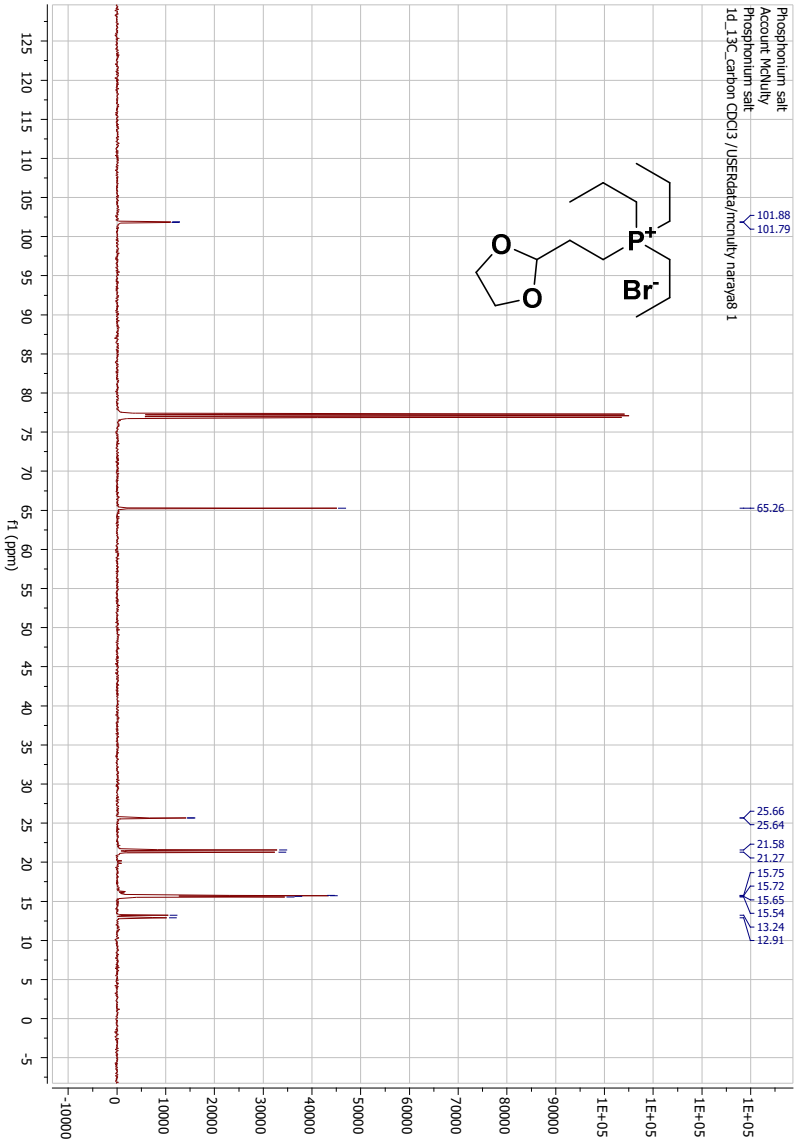
22 28

To a 25 mL flame dried Schlenk flask, with magnetic stirrer, purged with argon three times. Under Argon, charged, THF (5 mL) and dicyclohexylphosphine (0.95 g, 0.47 mmol, 1 eq.). The contents were stirred at 85 °C for 15 min on a pre-heated oil bath. Charged, 2-cyclohexen-1-one (0.6 g, 1.3 eq.) under argon. The contents were stirred at 85-90 °C for 10 h. The reaction was analysed using ^{31}P NMR, which indicated complete conversion to **22** (Cy_2PH - 30 ppm, Cy_3P Ketone (**22**) 11.6 ppm). The reaction was cooled to RT, added, PMHS (0.86 mL, 3 eq.), LiBr (54 mg, 0.1 eq.) and diethyl zinc (0.21 mL, 0.05 eq.). The reaction was stirred at RT for 24 h and ^{31}P NMR shows the disappearance of peak at 11.6 ppm and new peak at 10.64 ppm (10.6 ppm corresponds to Cy_3P). The NMR showed about 60 % conversion to tricyclohexylphosphine (**28**). The reaction mass was spiked with standard tricyclohexylphosphine which confirmed the formation of the product.

Appendix B - Selected Spectra:

(2-(1, 3-dioxolan-2-yl)ethyl)tripropylphosphonium bromide (1)




Phosphonium salt
Account McNulty
Phosphonium salt
1d_13C_carbon CDCl3 /USERdata/mcnulty narayan8 1
101.88
101.79
65.26
25.66
25.64
21.58
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15.65
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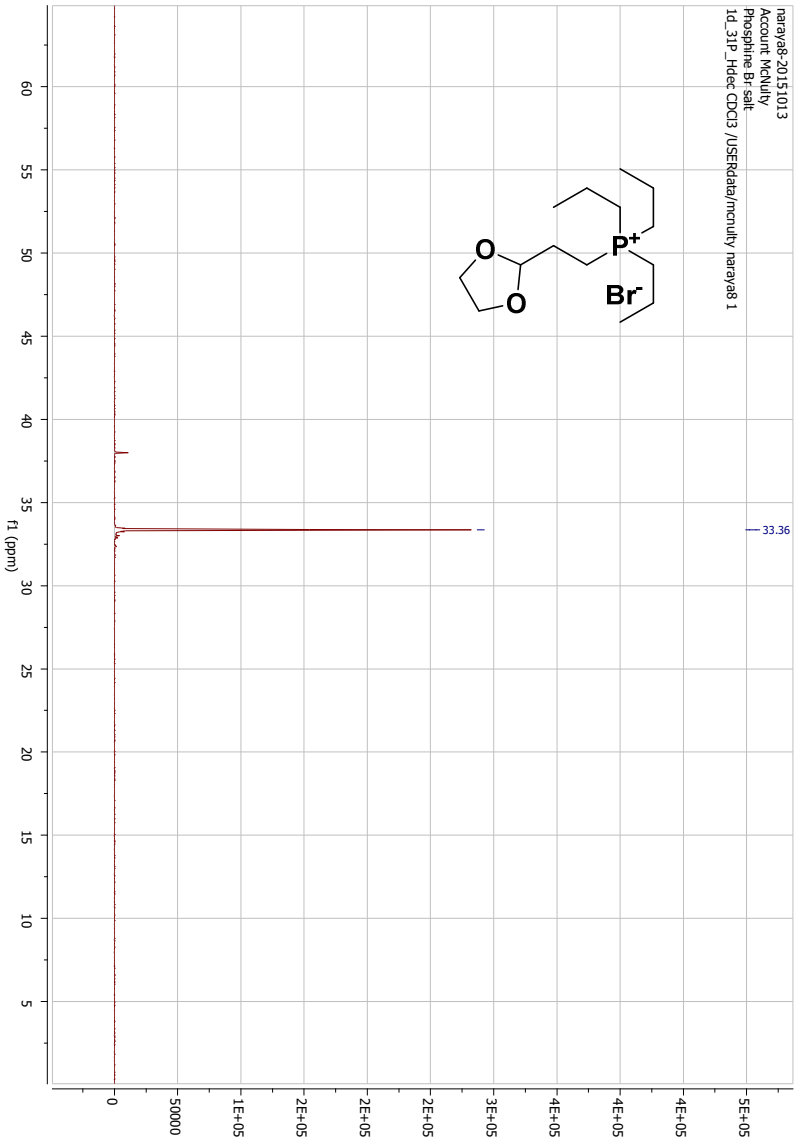
13.24
12.91
O
O
P+
Br-
f1 (ppm)


naraya8-20151013
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O
O
P+
Br-
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f1 (ppm)
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55
50
45
40
35
30
25
20
15
10
5
0
50000
1E+05
2E+05
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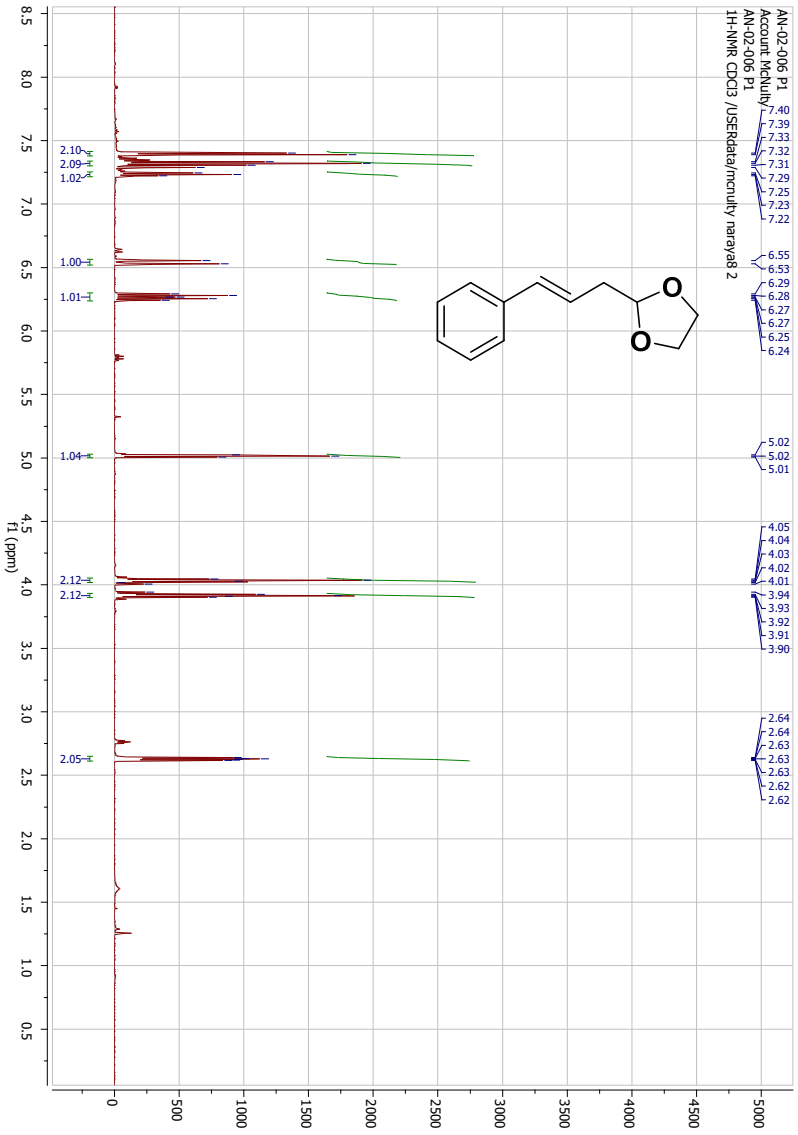
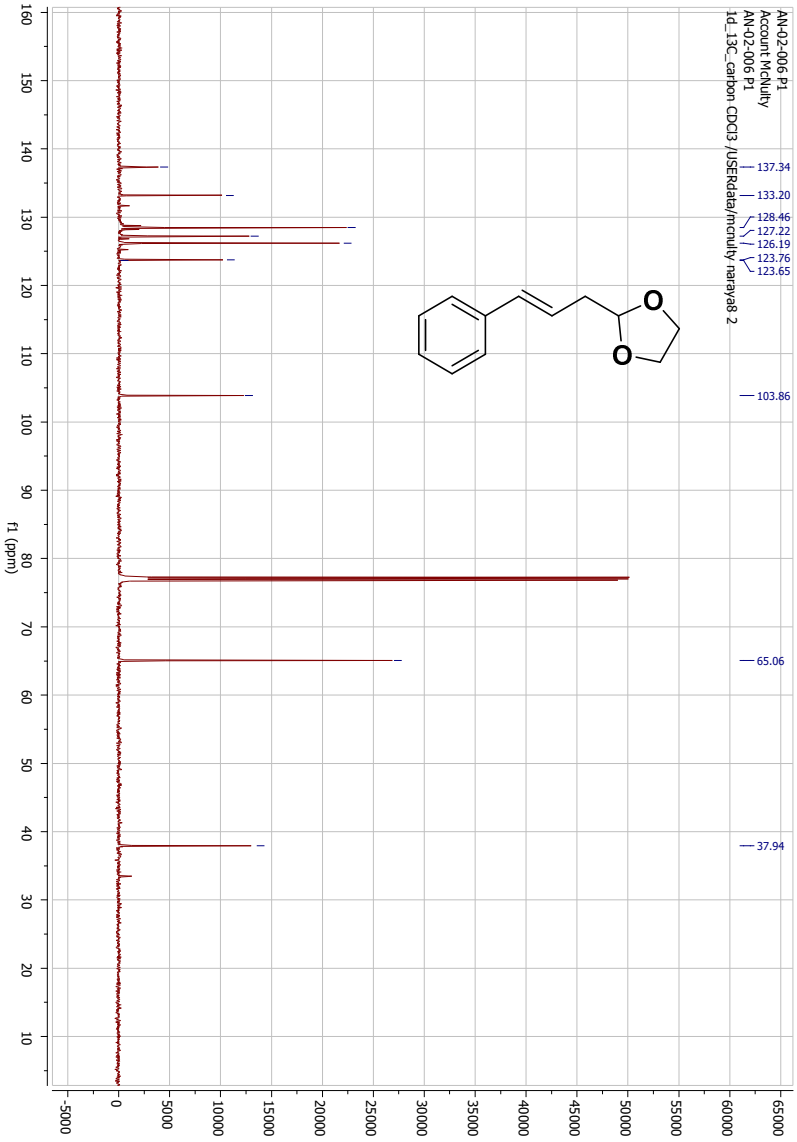
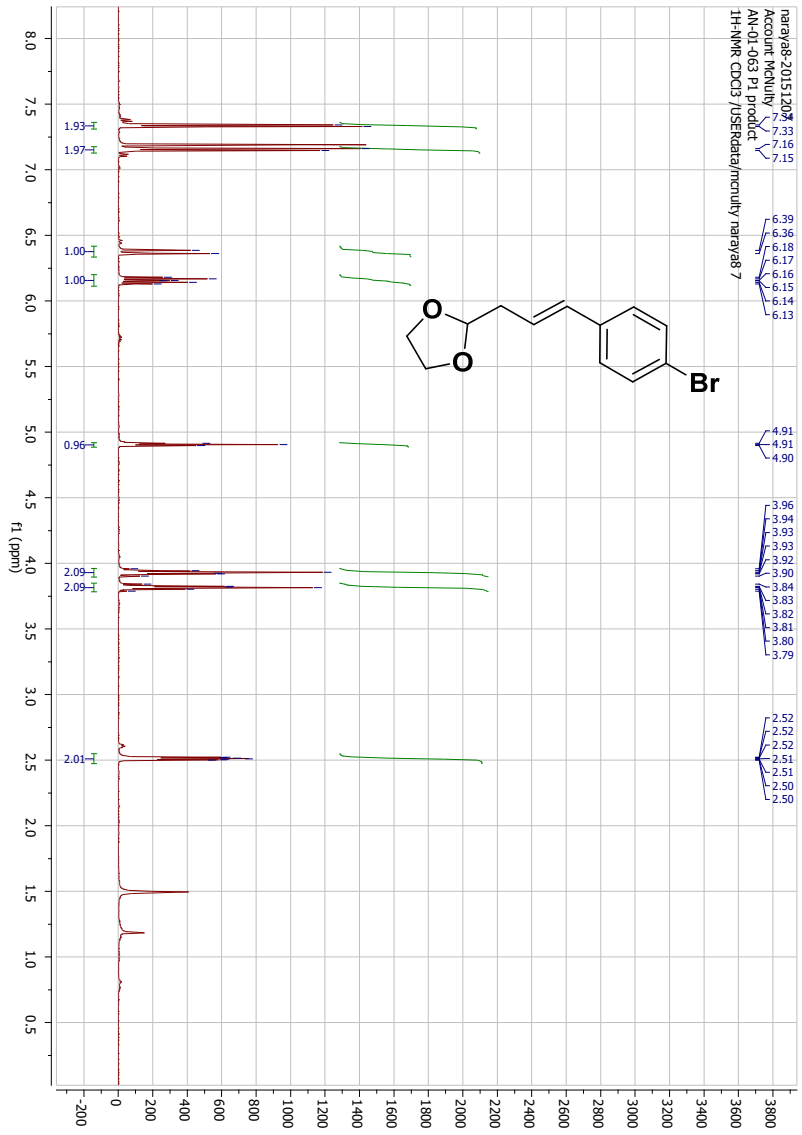
4E+05
4E+05
4E+05
5E+05

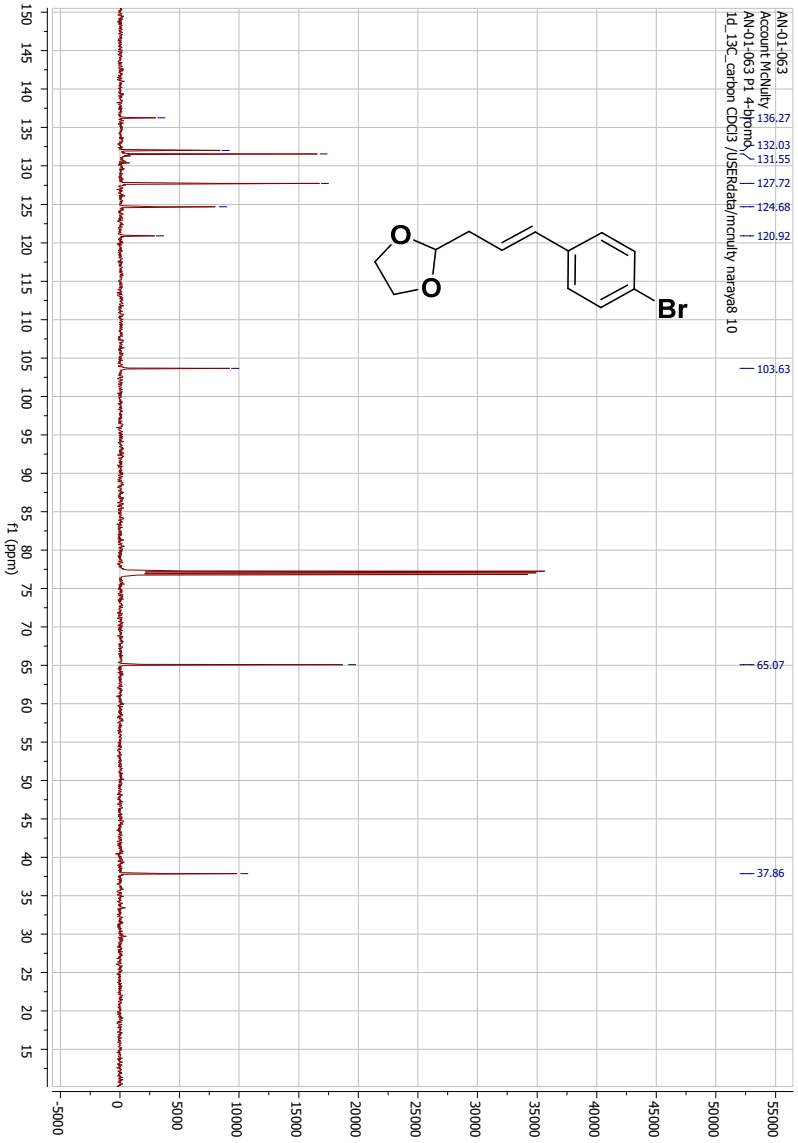
2-cinnamyl- 1,3-dioxolane



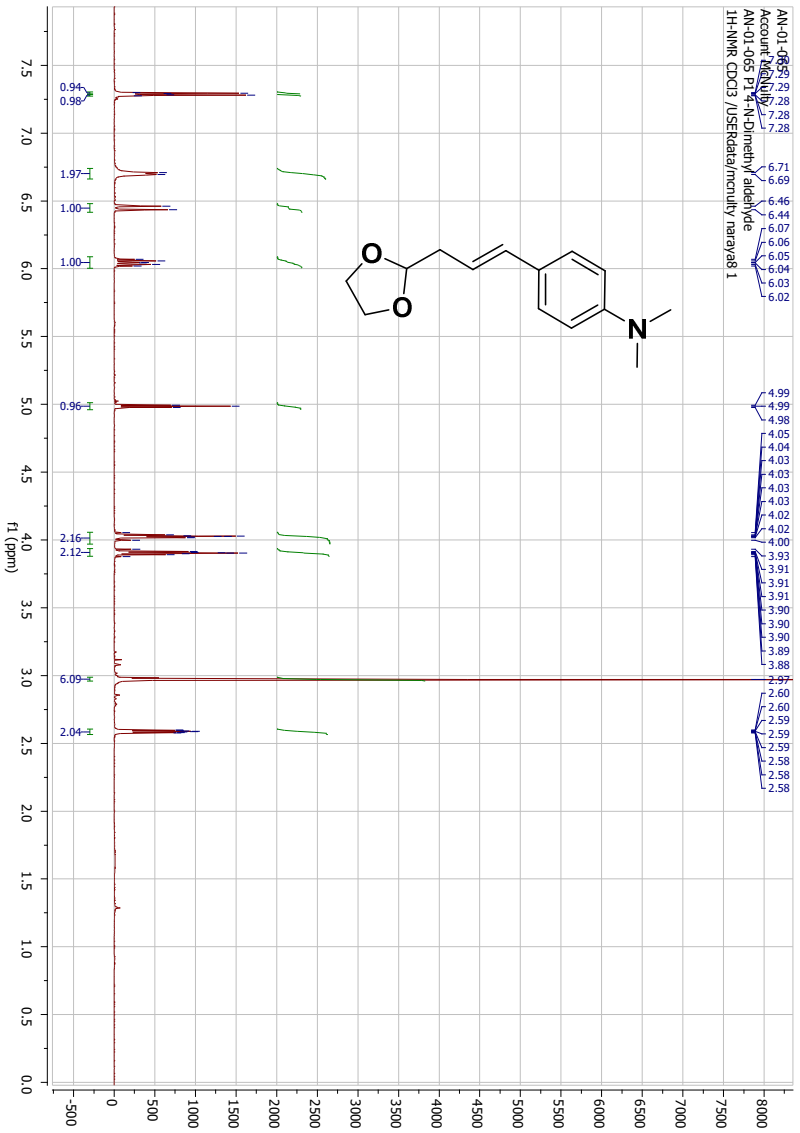

AN-02-006 P1
Account McNulty
AN-02-006 P1
1d_13C_carbon CDCl3 /USERdata/mcnulty narayan8 2
137.34
133.20
128.46
127.22
126.19
123.76
123.65
103.86
65.06
37.94
f1 (ppm)
O
O

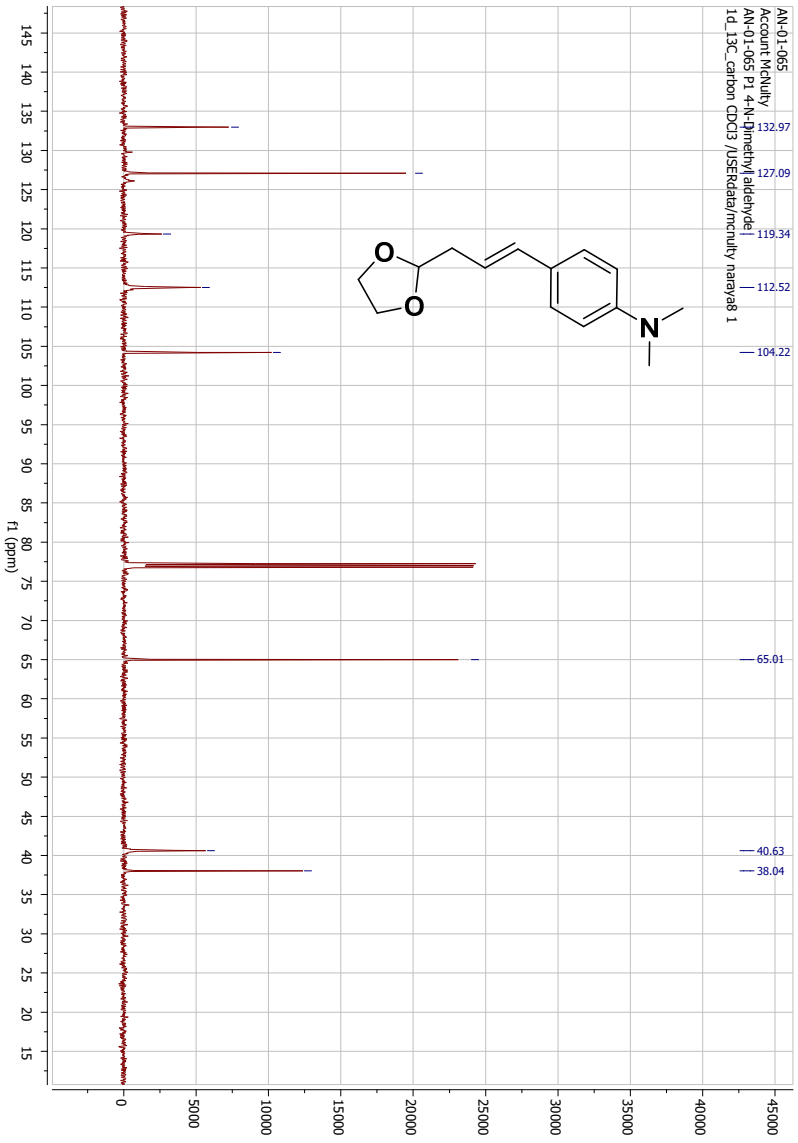
(*E*)-2-(3-(4-bromophenyl)allyl)-1,3-dioxolane



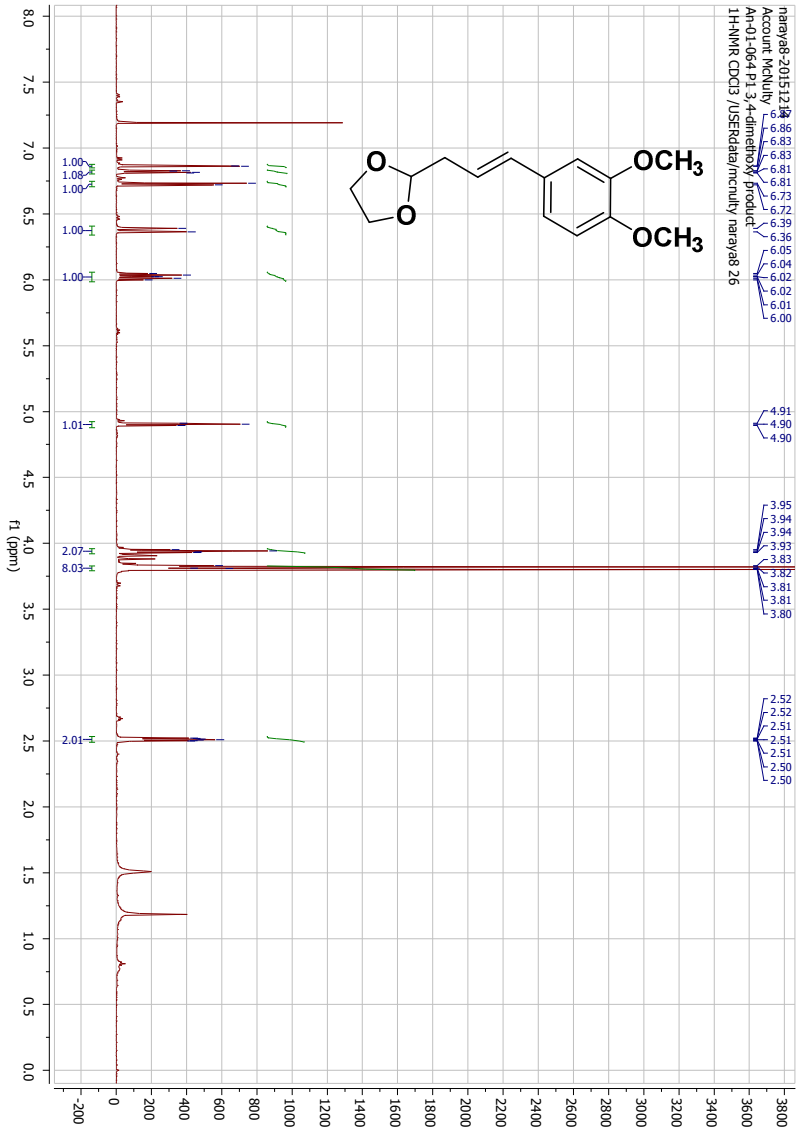

AN-01-063
Account McNulty
AN-01-063 P1 4-bromo
1d_13C_carbon CDCl3 /USERdata/mcnulty narayan8 10
136.27
132.03
131.55
127.72
124.68
120.92
103.63
65.07
37.86
O
O
Br
f1 (ppm)

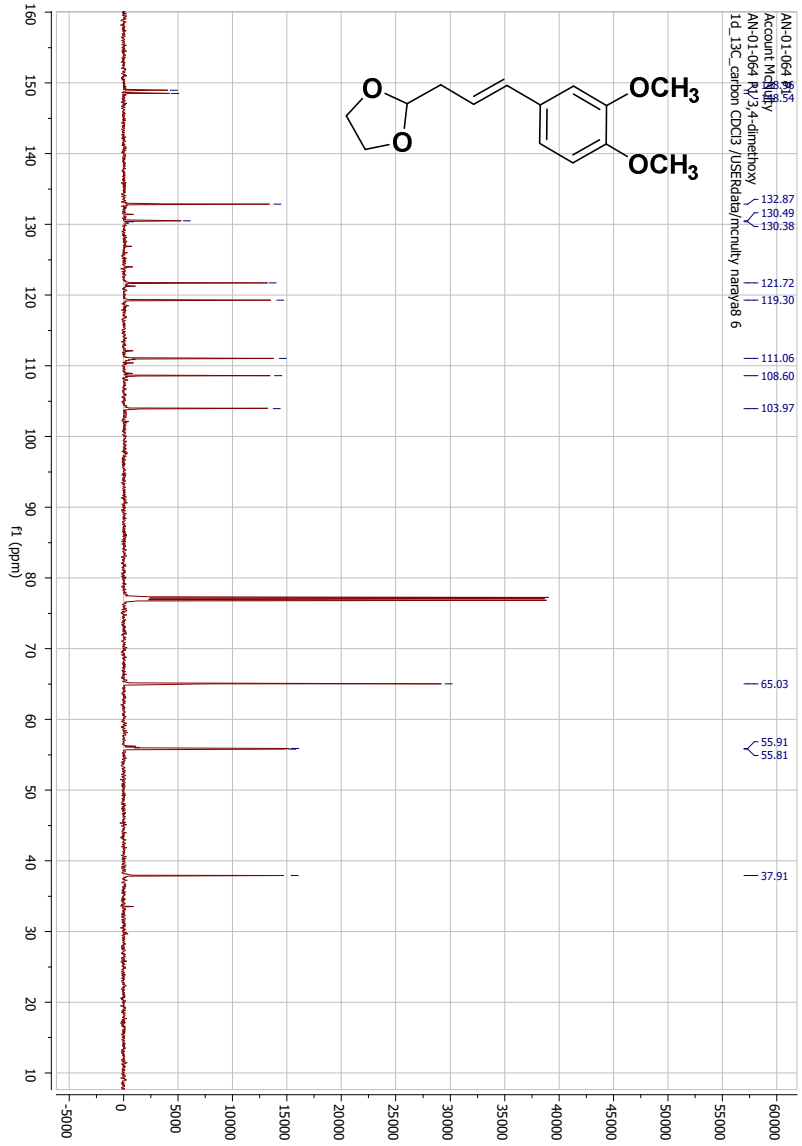
(*E*)-4-(3-(1,3-dioxolan-2-yl)prop-1-en-1-yl)-*N*,*N*-dimethylaniline



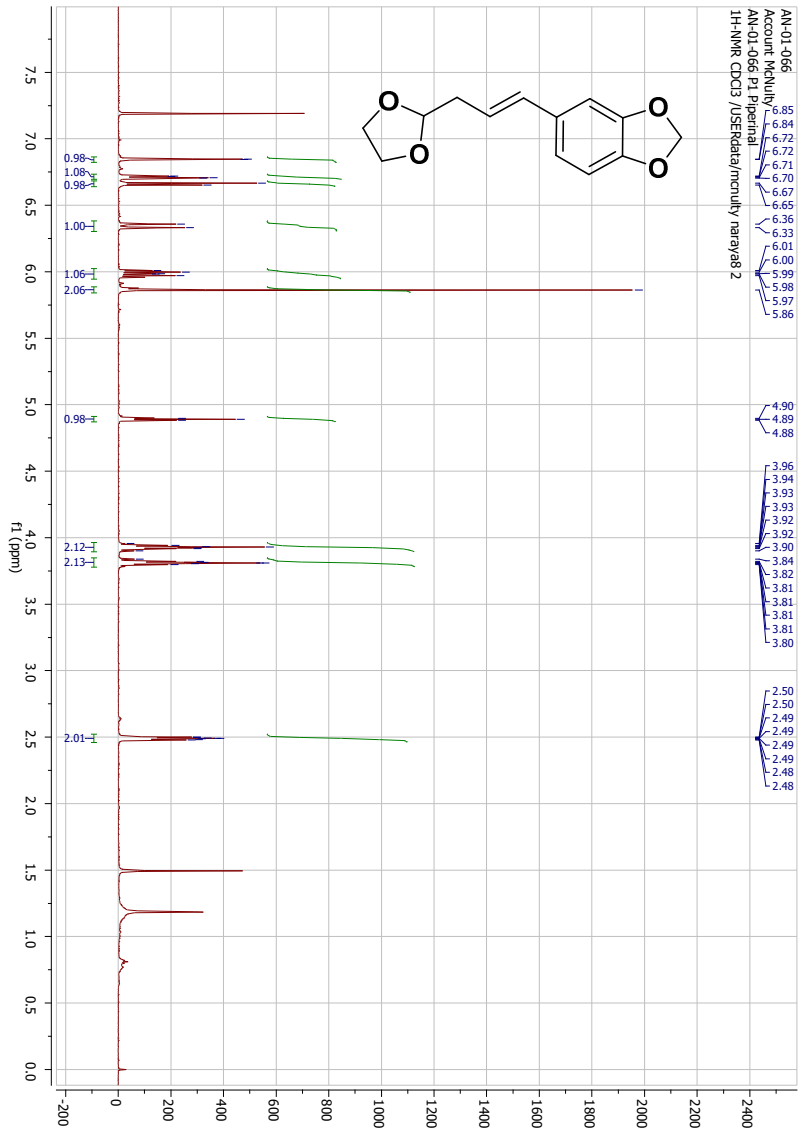

AN-01-065
Account McNulty
AN-01-065 P1 4-N-Dimethyl aldehyde
1d_13C_carbon CDCl3 /USERdata/mcnulty narayа8 1
132.97
127.09
119.34
112.52
104.22
65.01
40.63
38.04
O
O
N
f1 (ppm)

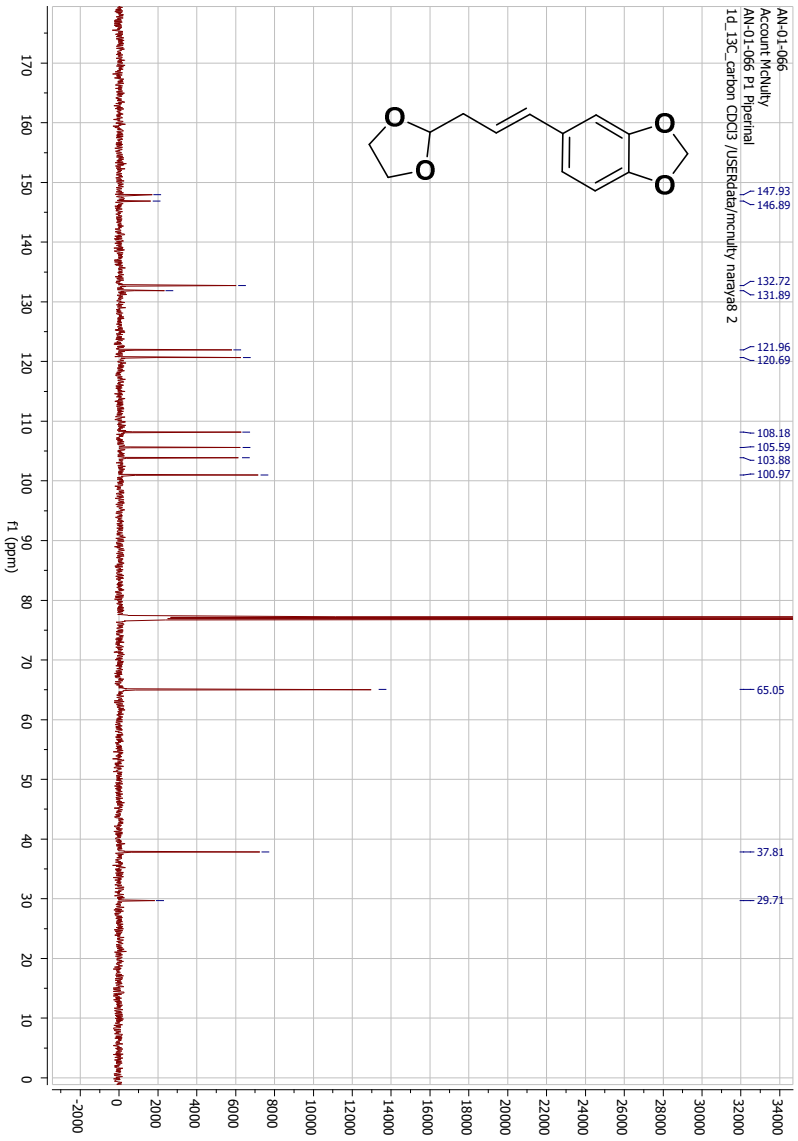
(*E*)-2-(3-(3,4-dimethoxyphenyl)allyl)-1,3-dioxolane



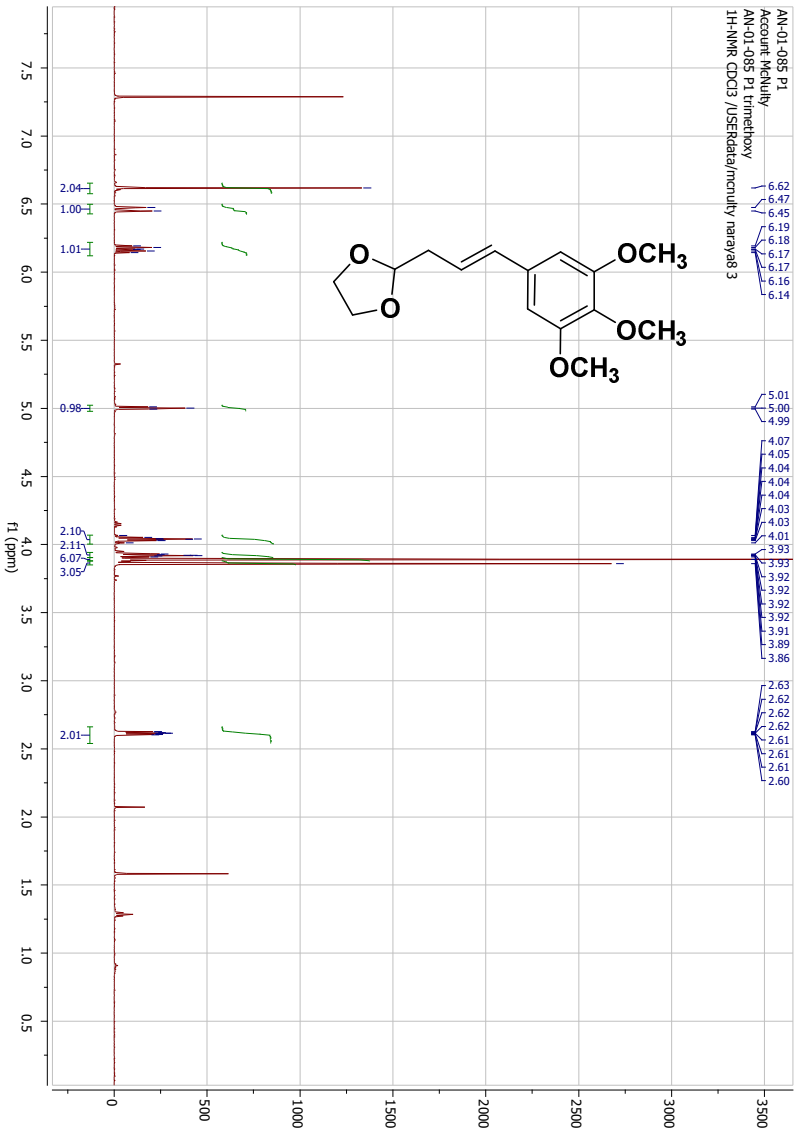

AN-01-064
Account McNulty
AN-01-064 Py 3,4-dimethoxy
1d_13C_carbon CDCl3 /USERdata/mcnulty narayan8 6
132.87
130.49
130.38
121.72
119.30
111.06
108.60
103.97
65.03
55.91
55.81
37.91
f1 (ppm)

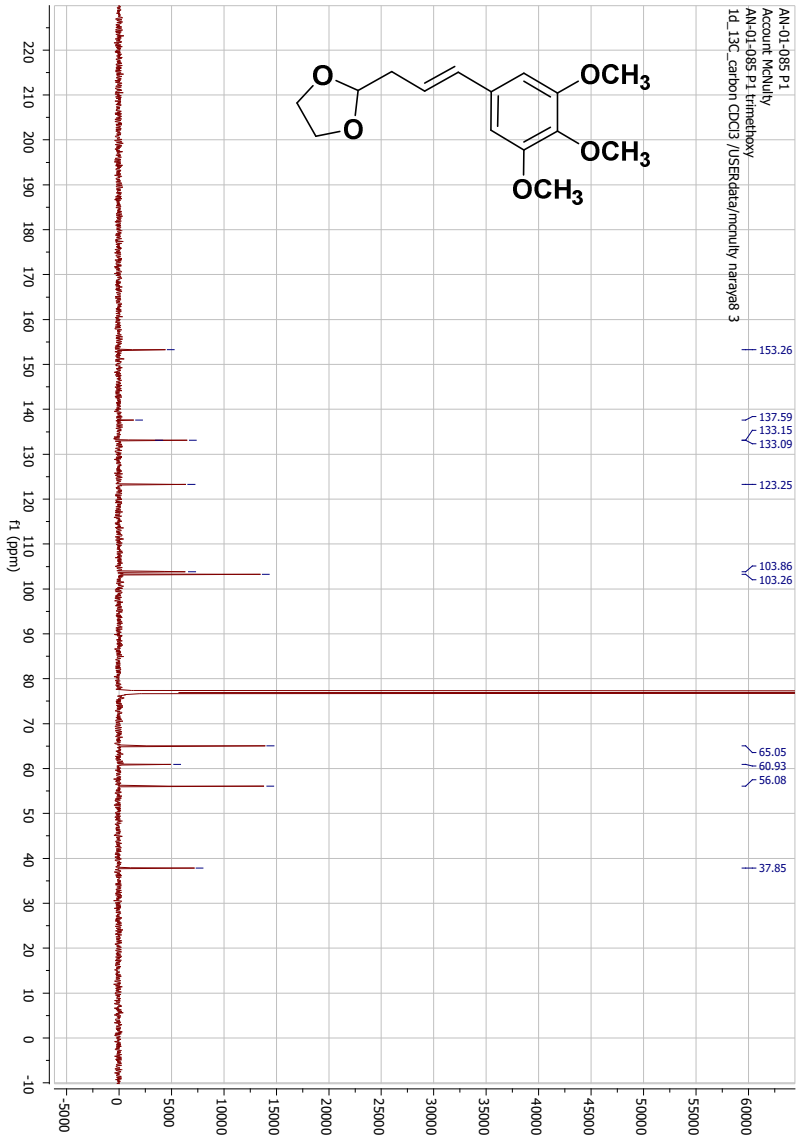
(*E*)-5-(3-(1,3-dioxolan-2-yl)prop-1-en-yl)benzo[*d*][1,3]dioxole



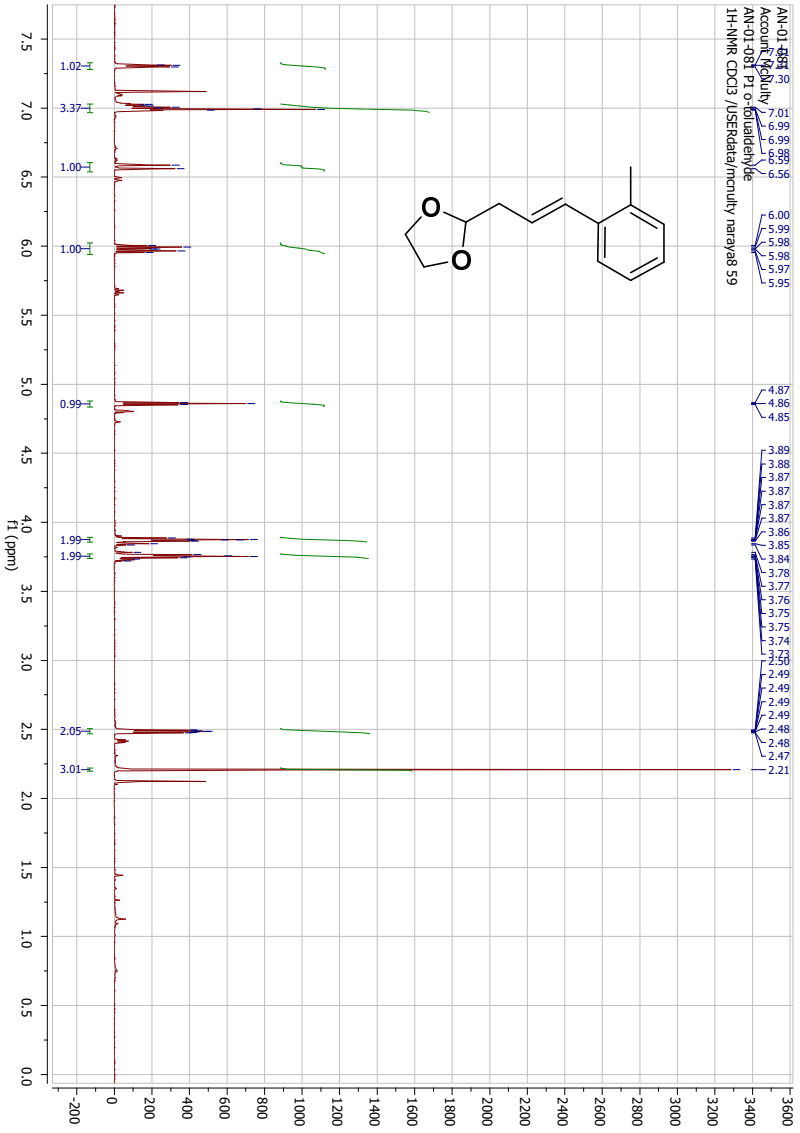

AN-01-066
Account.McNulty
AN-01-066 P1 Piperinal
1d_13C_carbon CDCl3 /USERdata/mcnulty narayan8 2
147.93
146.89
132.72
131.89
121.96
120.69
108.18
105.59
103.88
100.97
65.05
37.81
29.71
f1 (ppm)

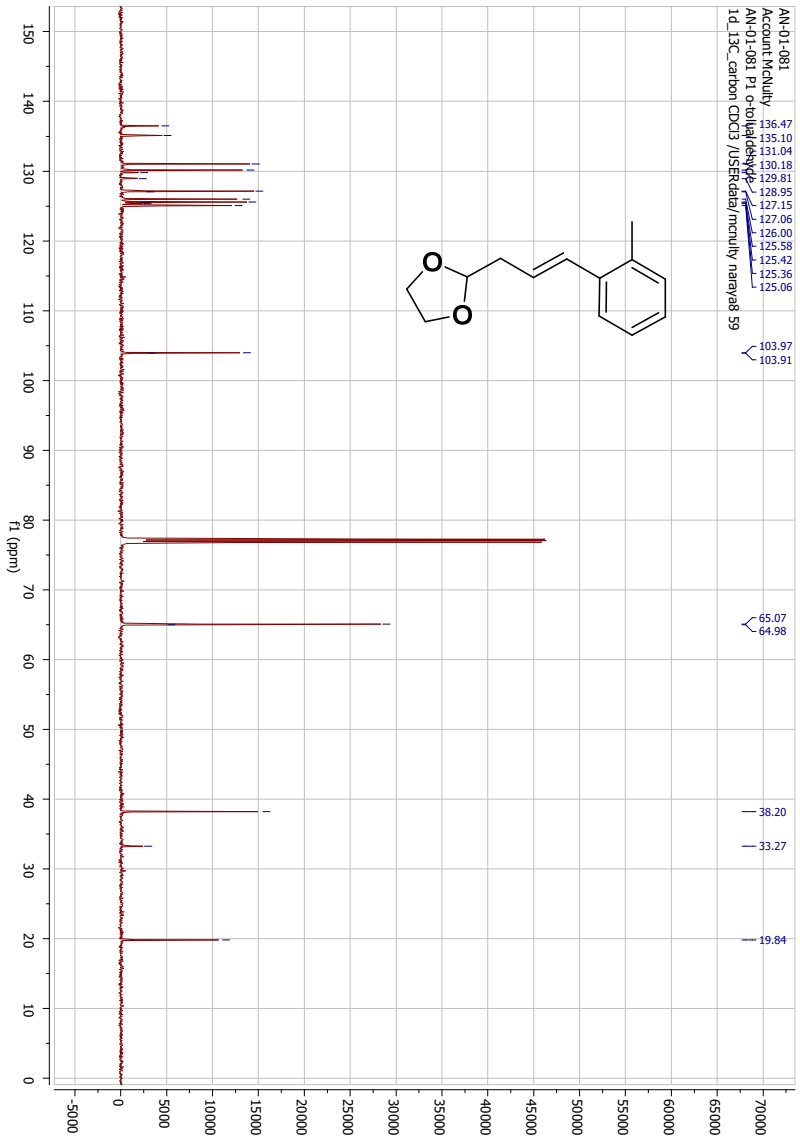
(*E*)-2-(3-(3,4,5,-trimethoxyphenyl)allyl)-1,3-dioxolane



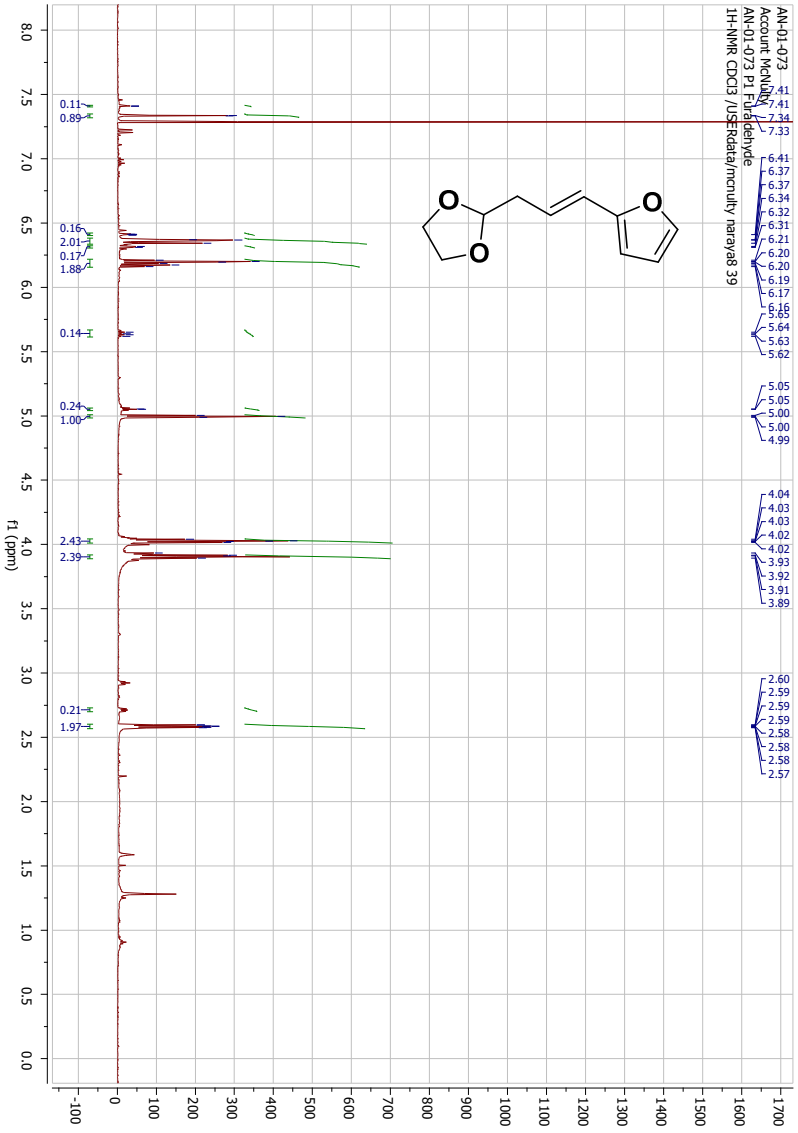

AN-01-085 P1
Account McNulty
AN-01-085 P1 trimethoxy
1d_13C_carbon CDCl3 /USERdata/mcnulty narayan8 3
153.26
137.59
133.15
133.09
123.25
103.86
103.26
65.05
60.93
56.08
37.85
f1 (ppm)

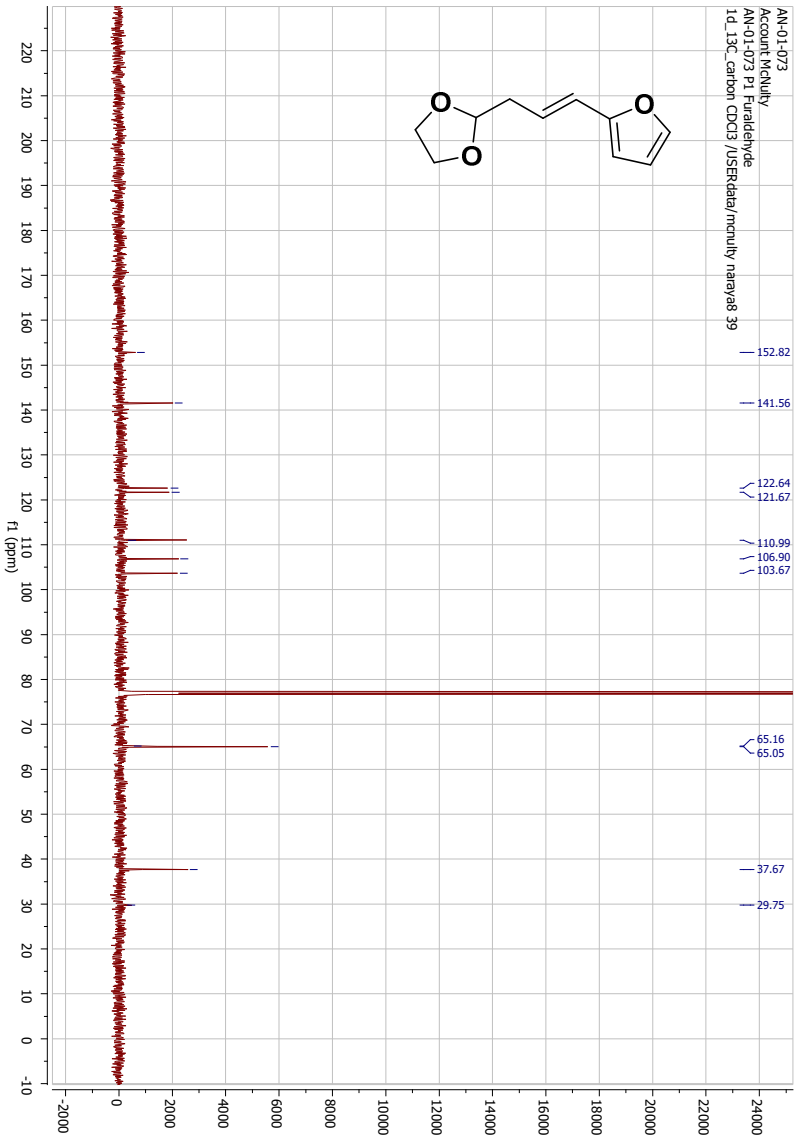
(*E*)2-(3-(o-tolyl) allyl)-1,3-dioxolane



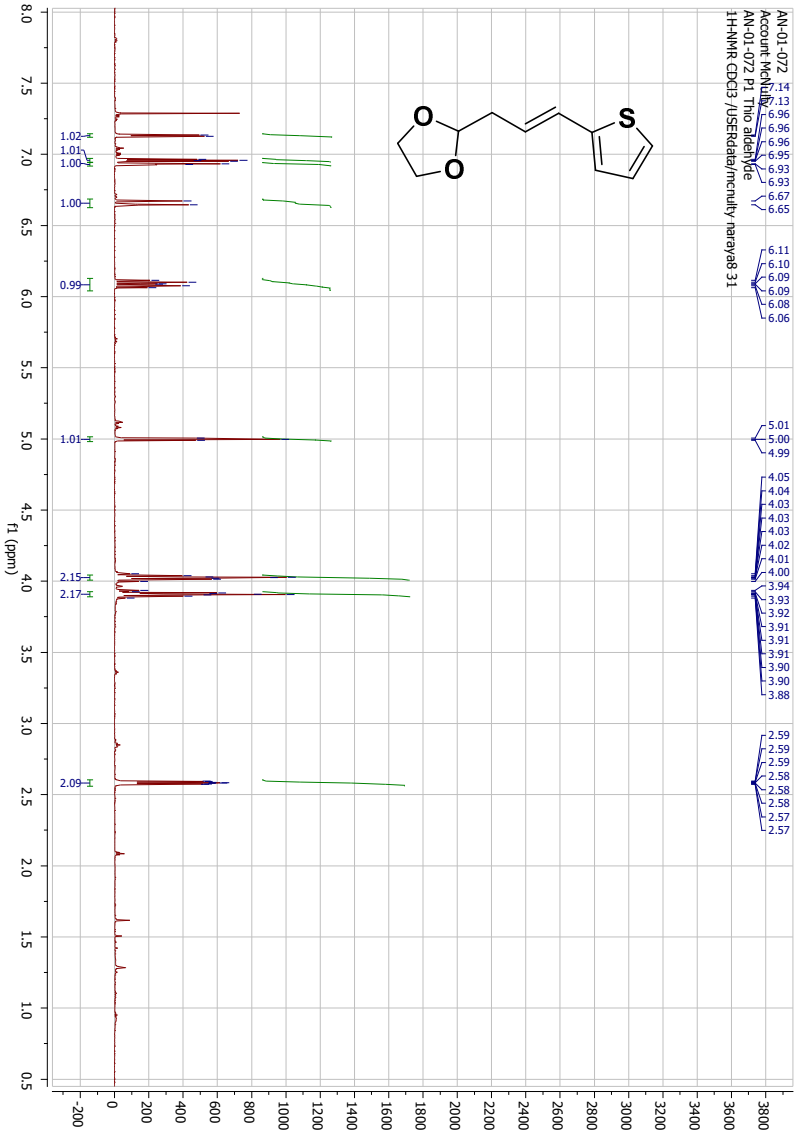

AN-01-081
Account.hcNulty
AN-01-081 P1 o-tolualdehyde
1d_13C_carbon CDCl3 /USERdata/mcnulty narayа8 59
136.47
135.10
131.04
130.18
129.81
128.95
127.15
127.06
126.00
125.58
125.42
125.36
125.06
103.97
103.91
65.07
64.98
38.20
33.27
19.84
O
O
f1 (ppm)

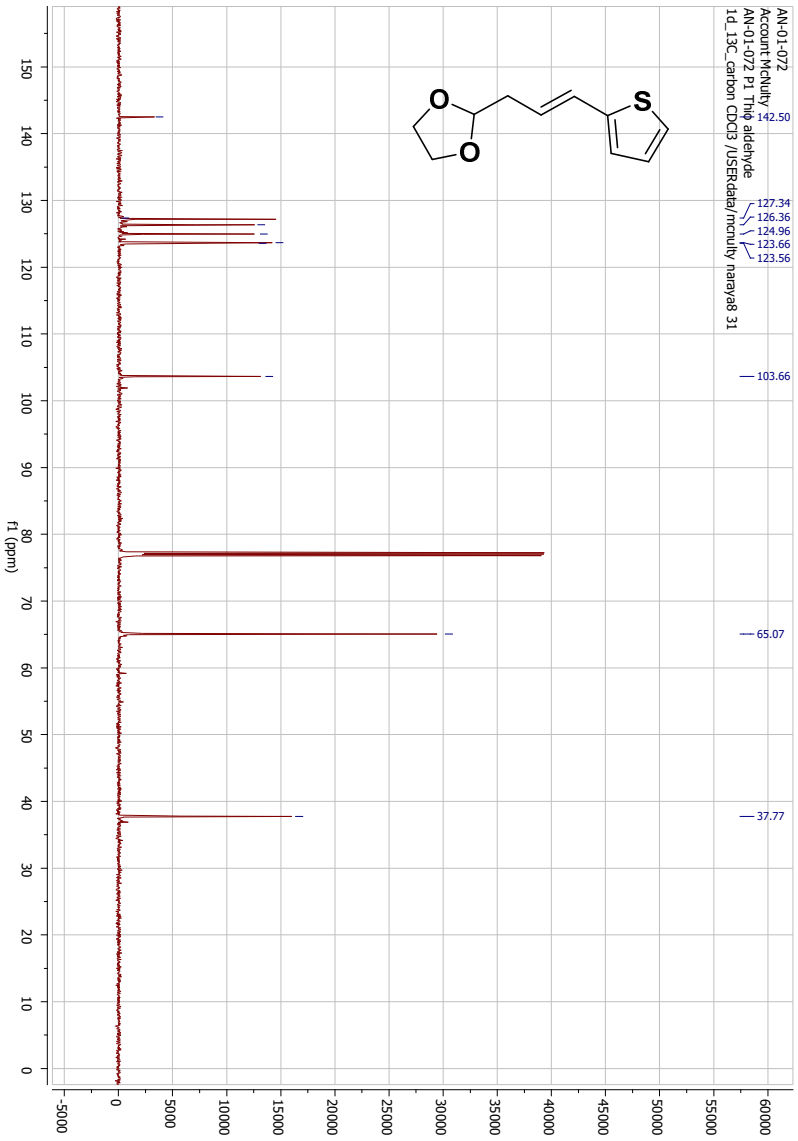
(*E*)-2-(3-(furan-2-yl)allyl)-1,3-dioxolane



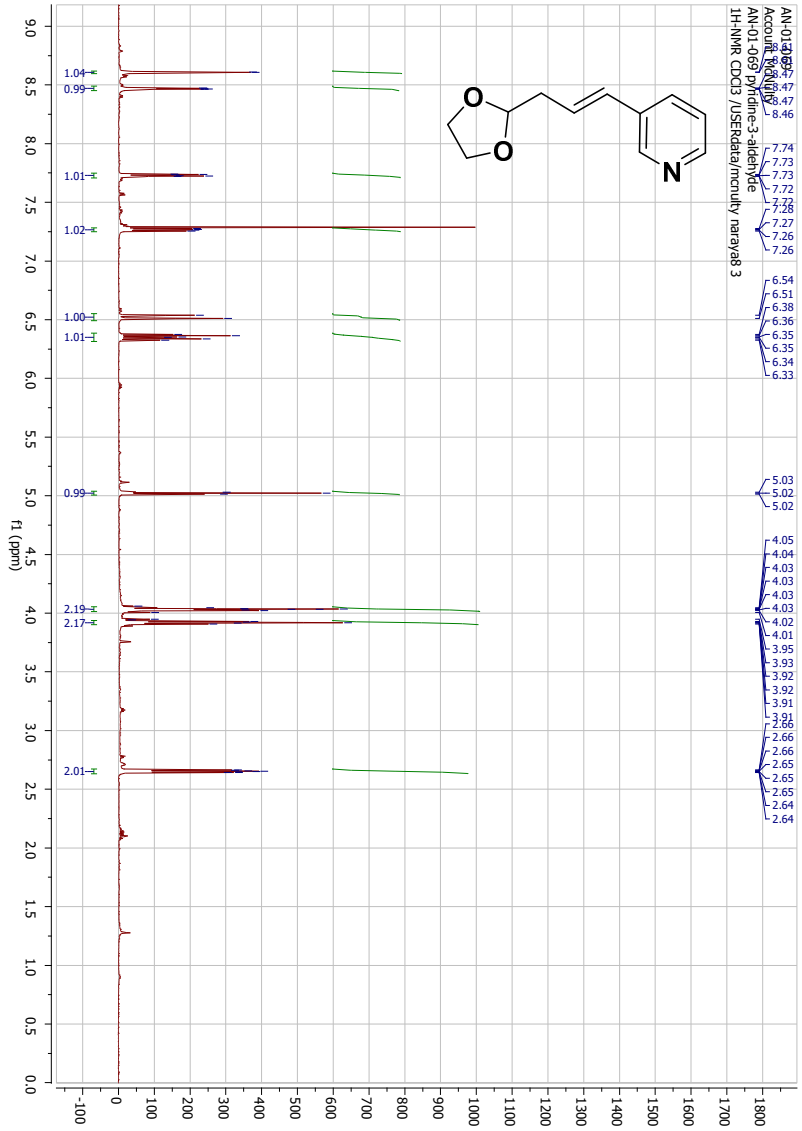

AN-01-073
Account.hcNulty
AN-01-073 P1 Furaldehyde
1d_13C_carbon CDCl3 /USERdata/mcnulty narayа8 39
152.82
141.56
122.64
121.67
110.99
106.90
103.67
65.16
65.05
37.67
29.75
f1 (ppm)

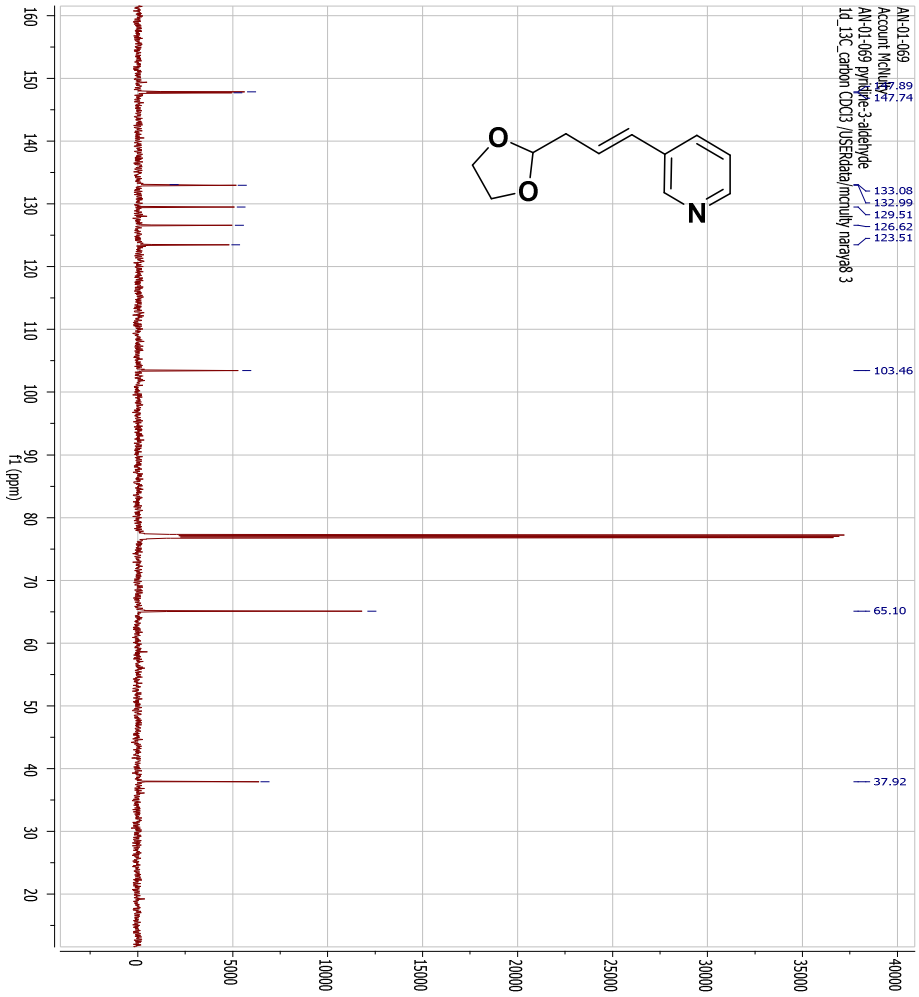
(*E*)-2-(3-(thiophen-2-yl)allyl)-1,3-dioxolane



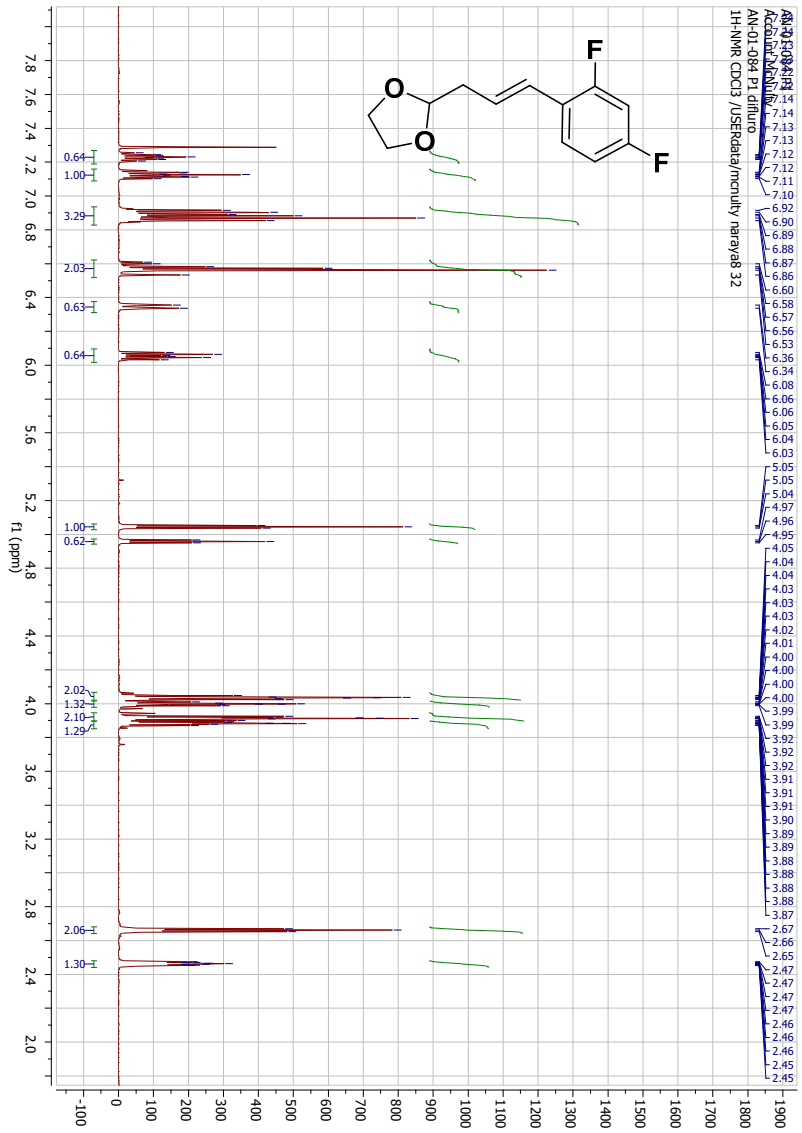

AN-01-072
Account.hCNulty
AN-01-072 P1 Thio aldehyde
1d_13C_carbon CDCl3 /USERdata/mcnulty_naraya8 31
142.50
127.34
126.36
124.96
123.66
123.56
103.66
65.07
37.77
f1 (ppm)
O
O
S

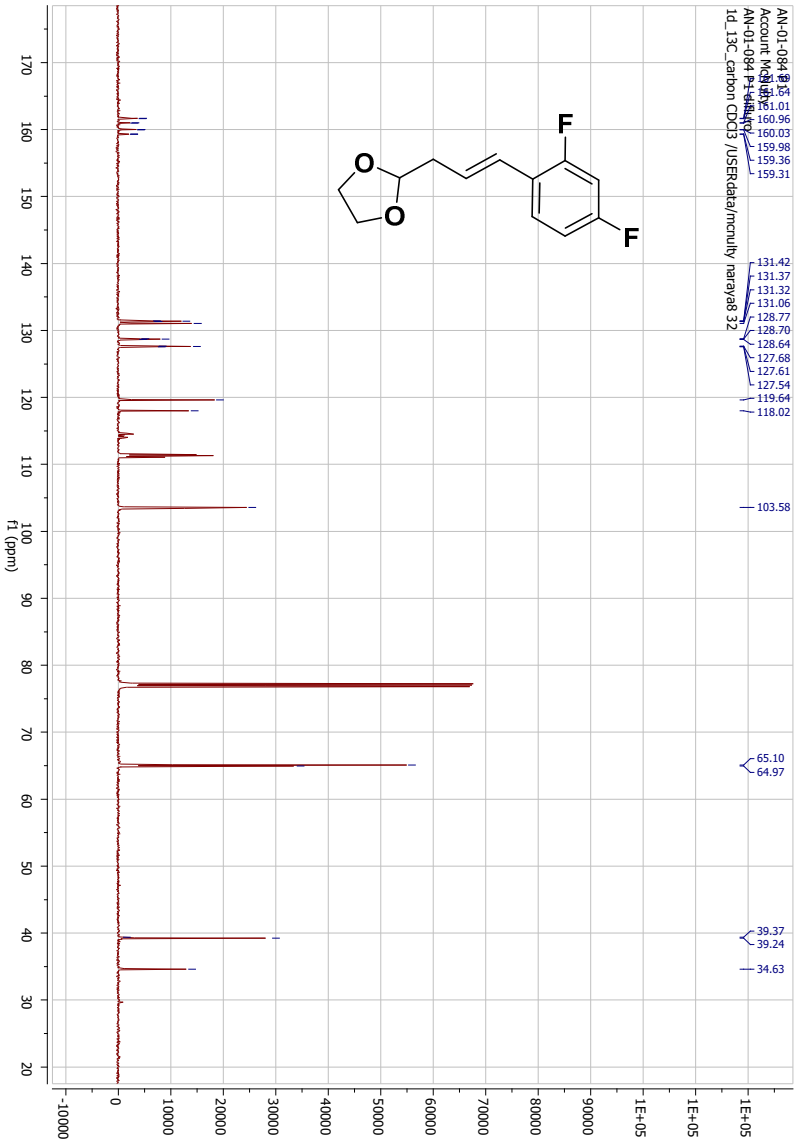
(*E*)-3-(3-(1,3-dioxolan-2-yl)prop-1-en-1-yl)pyridine



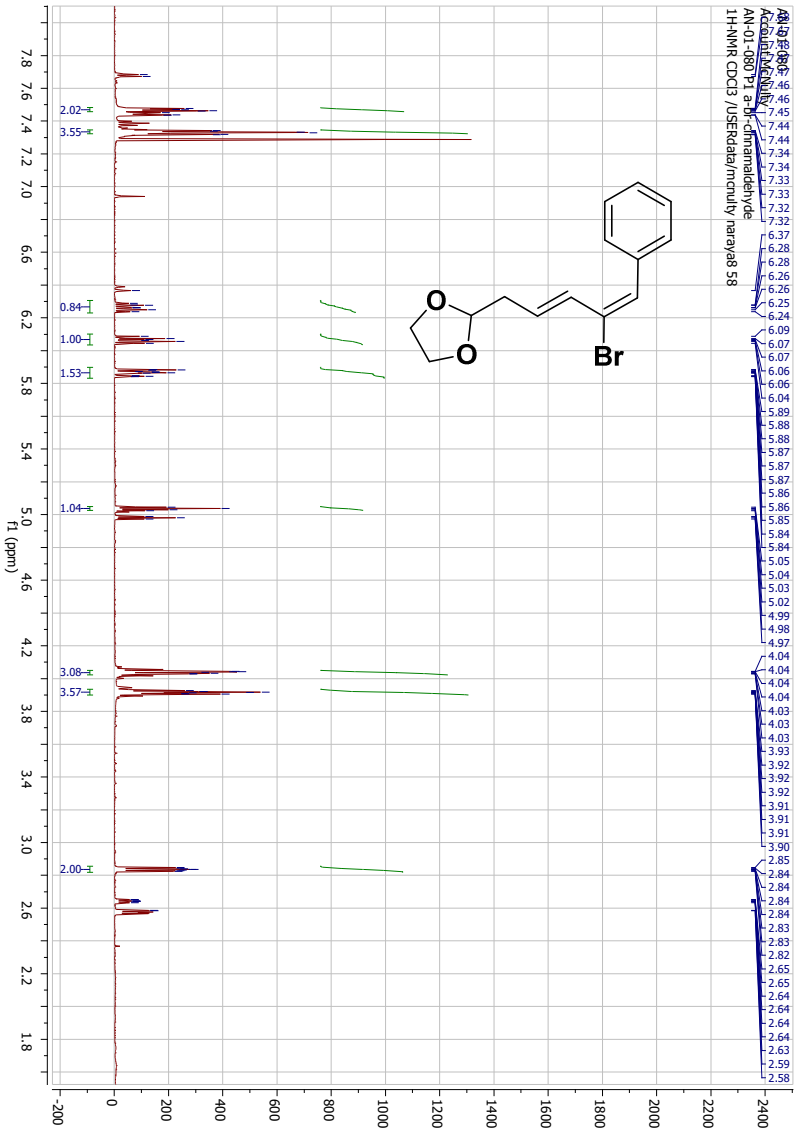

AN-01-069
Account Mcnulty
AN-01-069 pyridine-3-aldehyde
1d_13C_carbon CDCl3 /USERdata/mcnulty narayab8 3
147.89
147.74
133.08
132.99
129.51
126.62
123.51
103.46
65.10
37.92
O
O
N
f1 (ppm)

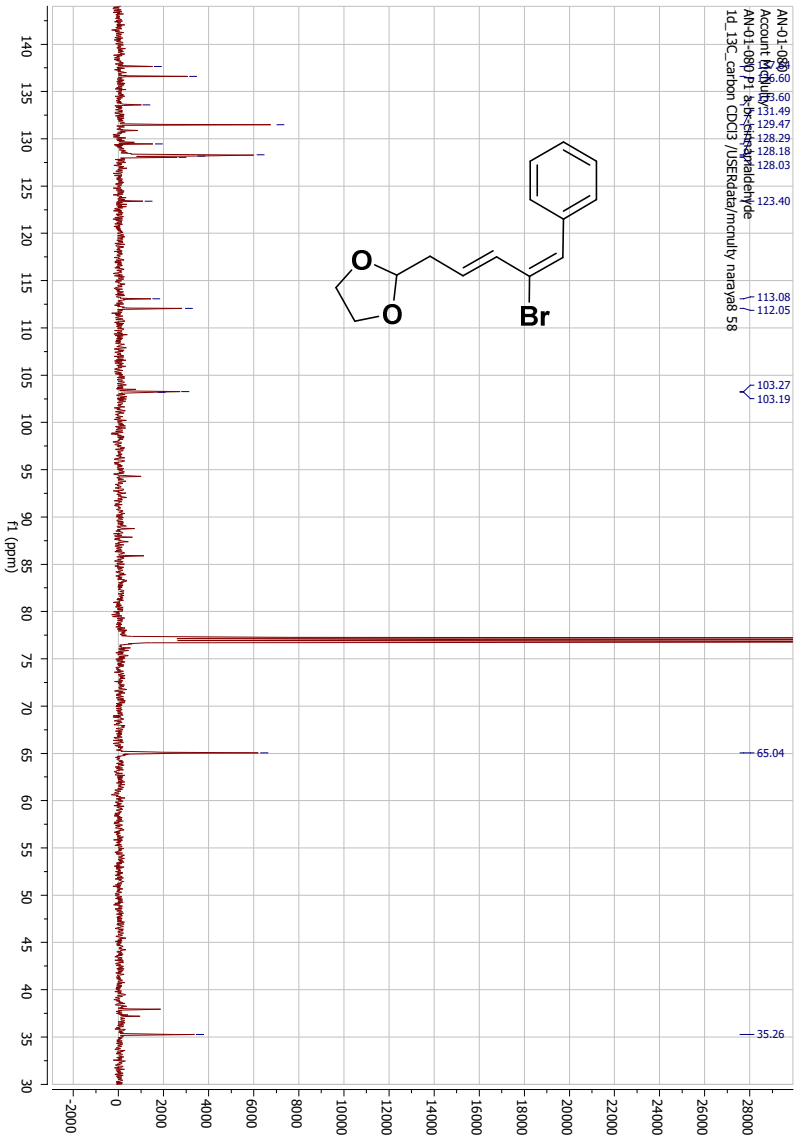
(*E*)-2-(3-(2,4-difluorophenyl)allyl)-1,3-dioxolane (*E*: *Z* /70:30)



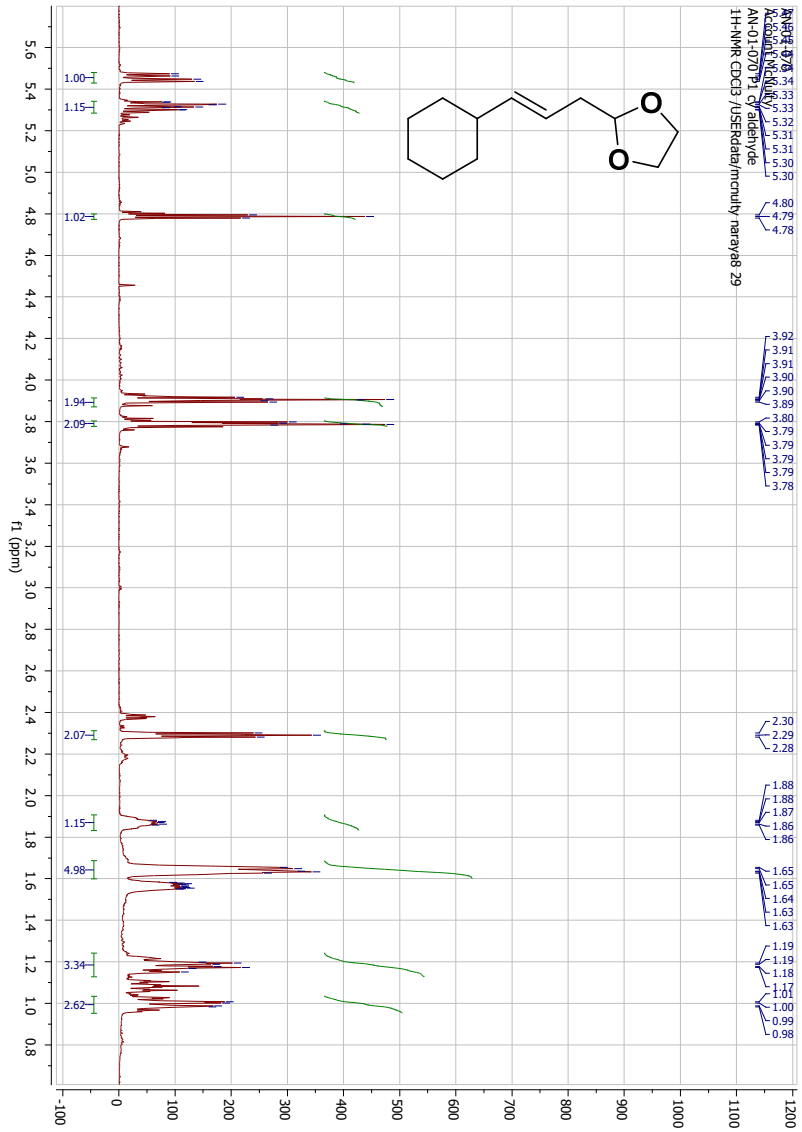

F
O
O
F
f1 (ppm)
AN-01-084
Account mcnulty
AN-01-084 P1 1d_13C_carbon CDCl3 /USER/data/mcnulty narayan8 32
161.01
160.96
160.03
159.98
159.36
159.31
131.42
131.37
131.32
131.06
128.77
128.70
128.64
127.68
127.61
127.54
119.64
118.02
103.58
65.10
64.97
39.37
39.24
34.63

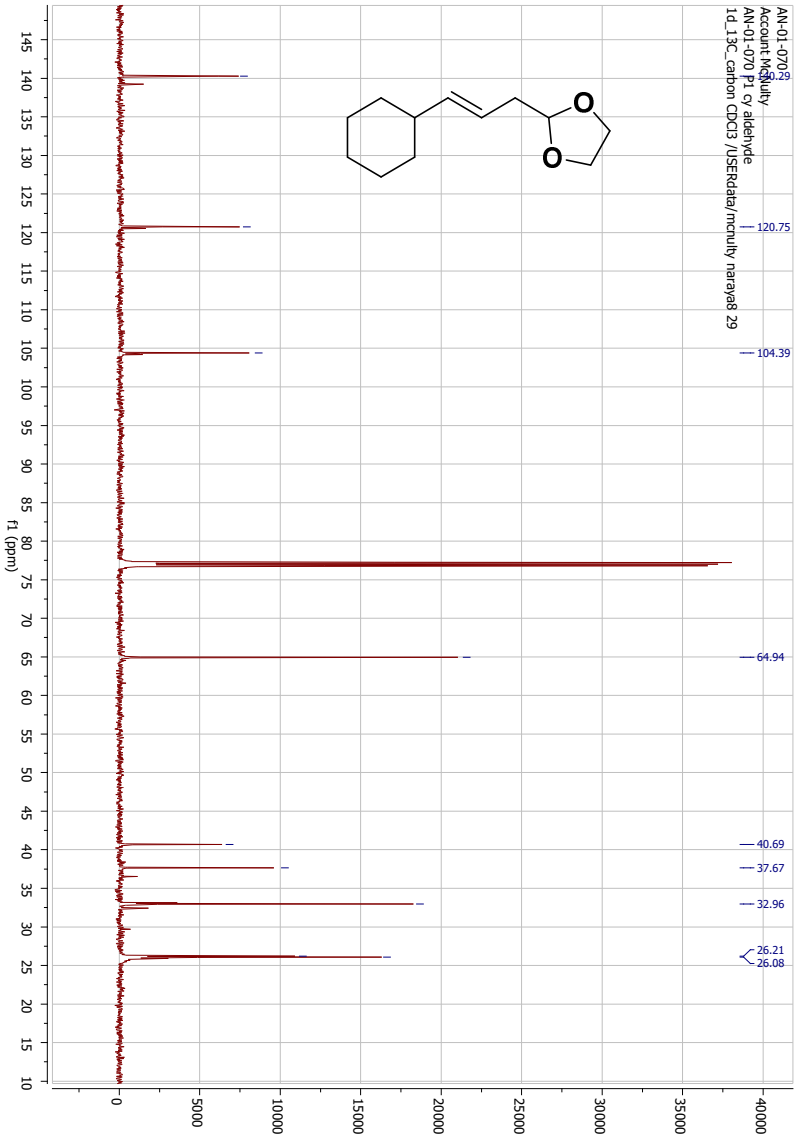
2-((2*E*,4*E*)-4-bromo-5-phenylpenta-2,4-dien-1-yl)-1,3-dioxolane (2*E*,4*E* : 2*E*,4*Z* **/** 75:25)

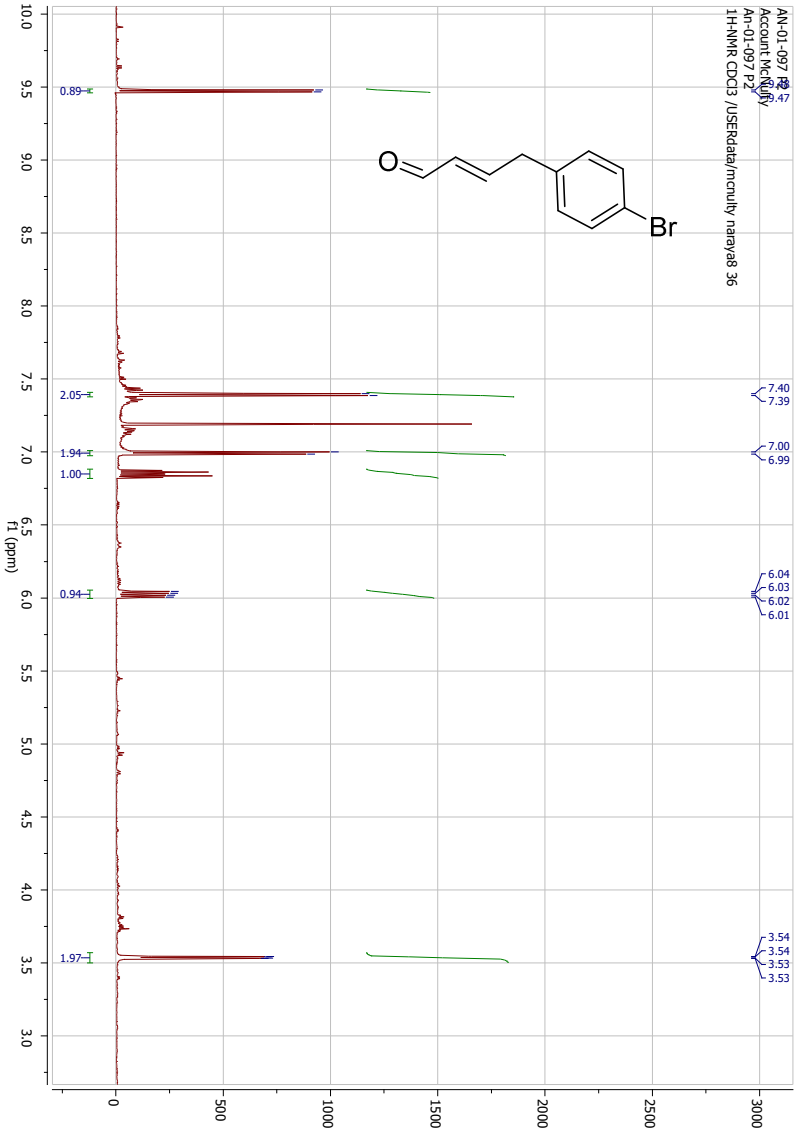


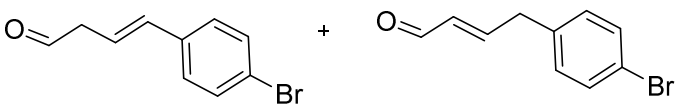

O
O
Br
f1 (ppm)
65.04
35.26
103.27
103.19
113.08
112.05
123.40
128.03
128.18
128.29
129.47
131.49

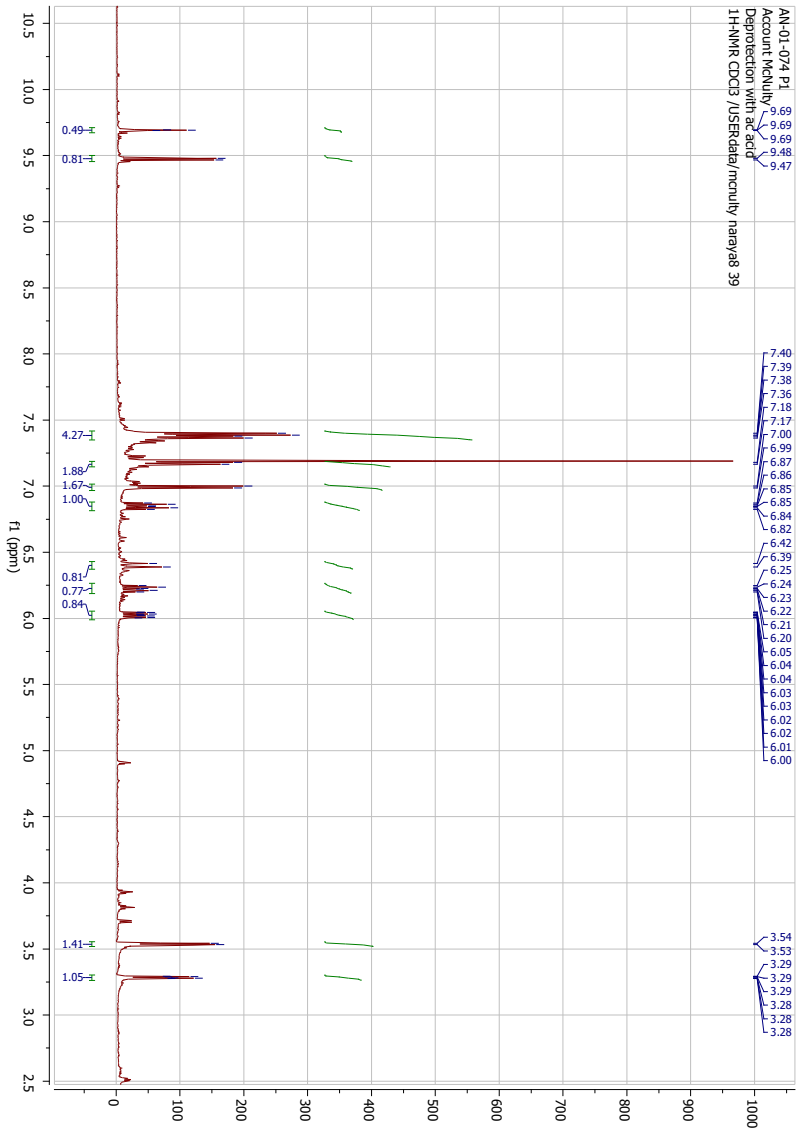
(*E*)-2-(3-cyclohexylallyl)-1,3-dioxolane



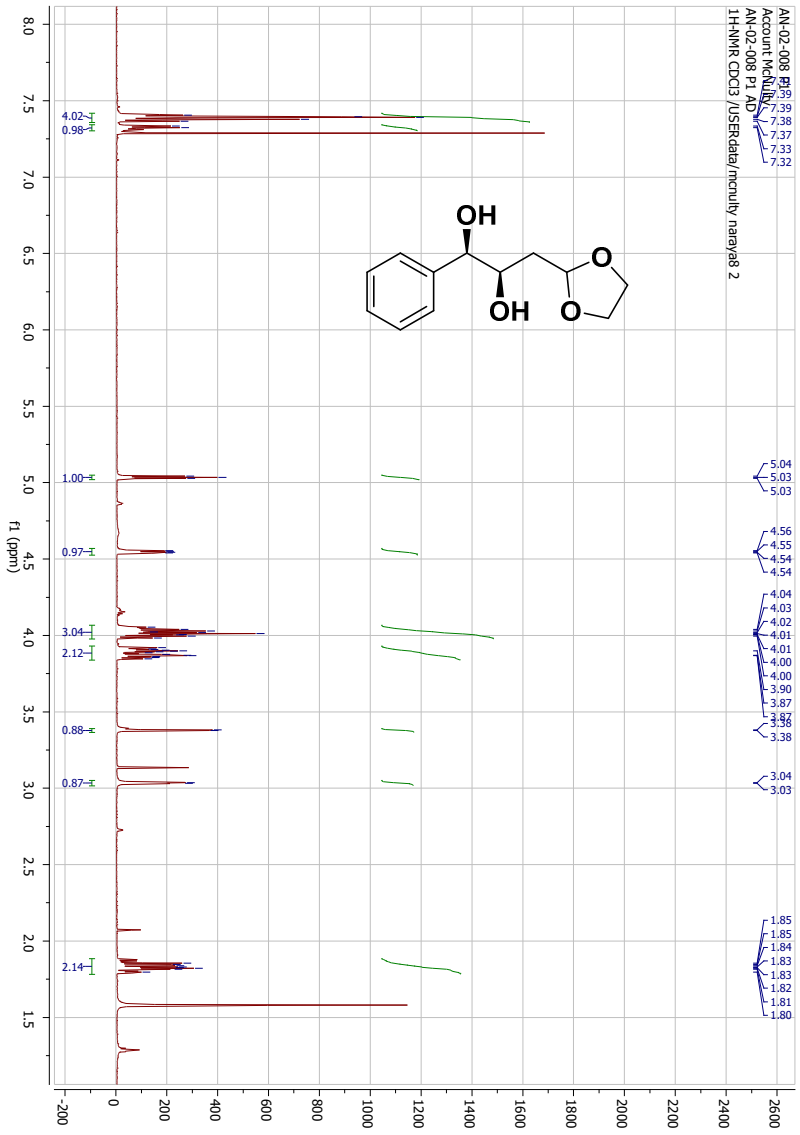

AN-01-070
Account.McNulty
AN-01-070 P1 cy aldehyde
1d_13C_carbon CDCl3 /USERdata/mcnulty/ narayan8 29
140.29
120.75
104.39
64.94
40.69
37.67
32.96
26.21
26.08
f1 (ppm)
O
O


O
Br
0.89
2.05
1.94
1.00
0.94
1.97
7.40
7.39
7.00
6.99
6.04
6.03
6.02
6.01
3.54
3.54
3.53
3.53
f1 (ppm)

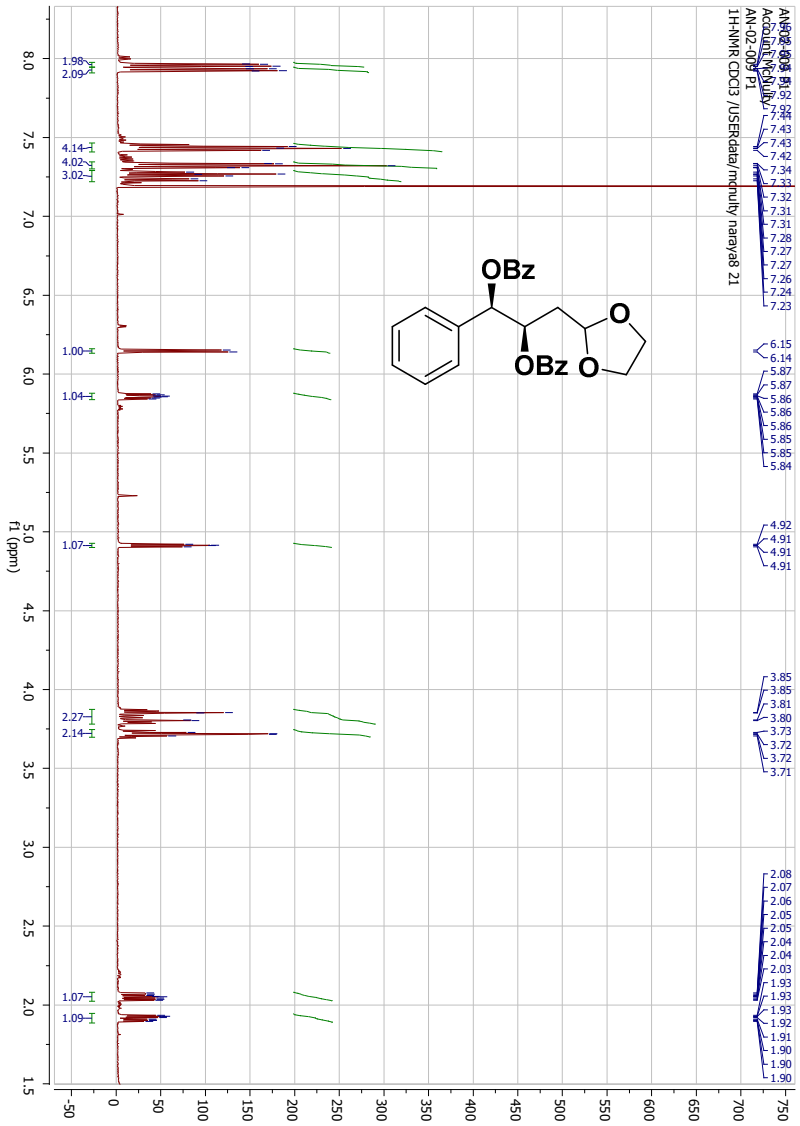

O
Br
+
O
Br


AN-01-074 P1
Account McNulty
Deprotection with ac acid
1H-NMR CDCl3 /USERdata/mcnulty narayan8 39
f1 (ppm)
0.49
0.81
4.27
1.88
1.67
1.00
0.81
0.77
0.84
1.41
1.05
9.69
9.69
9.69
9.48
9.47
7.40
7.39
7.38
7.36
7.18
7.17
7.00
6.99
6.87
6.86
6.85
6.85
6.84
6.82
6.42
6.39
6.25
6.24
6.23
6.22
6.21
6.20
6.05
6.04
6.04
6.03
6.03
6.02
6.02
6.01
6.00
3.54
3.53
3.29
3.29
3.29
3.28
3.28
3.28

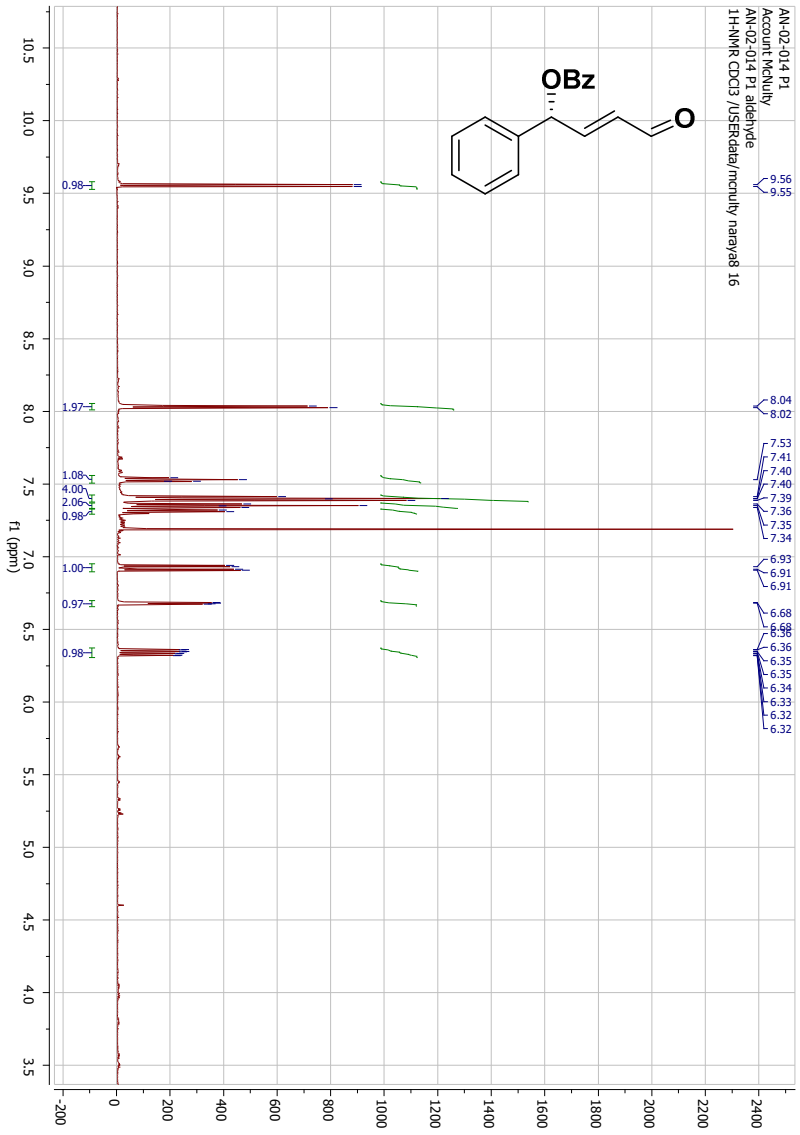
(1*R*,2*R*)-3-(1,3-dioxolan-2-yl)-1-phenylpropane-1,2-diol (12)



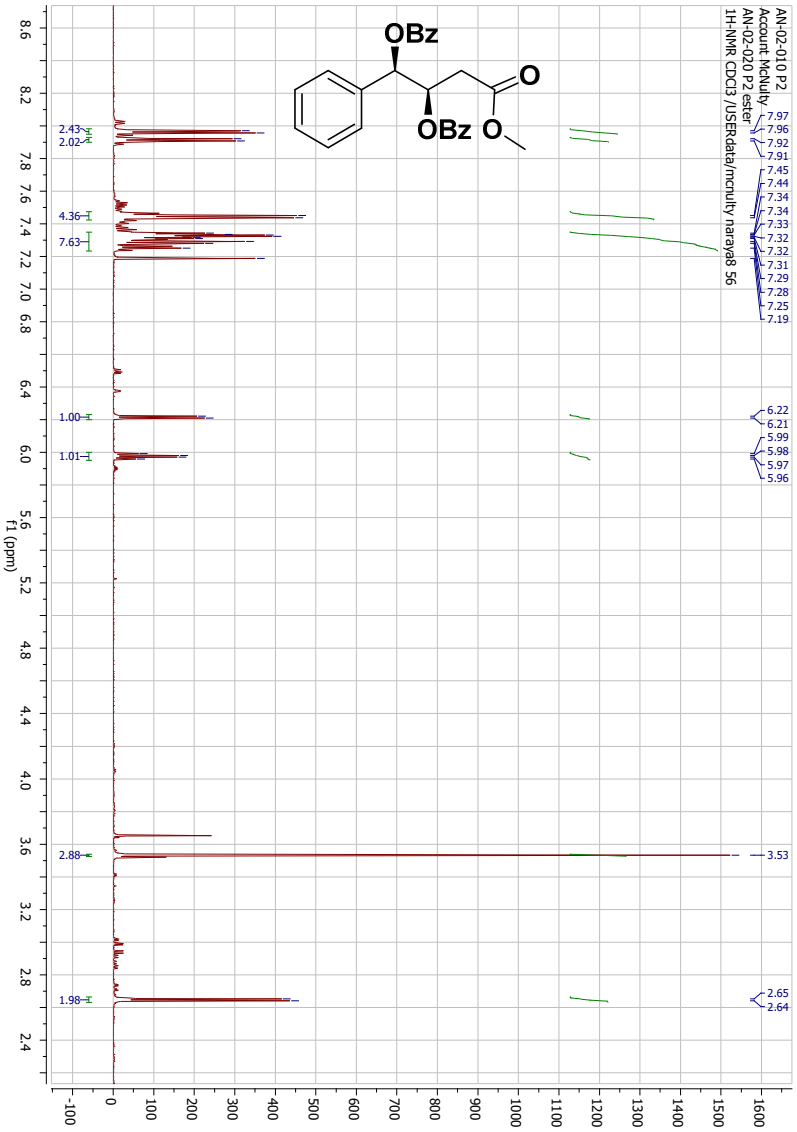
(1*R*,2*R*)-3-(1,3-dioxolan-2-yl)-1-phenylpropane-1,2-diyl dibenzoate (13)



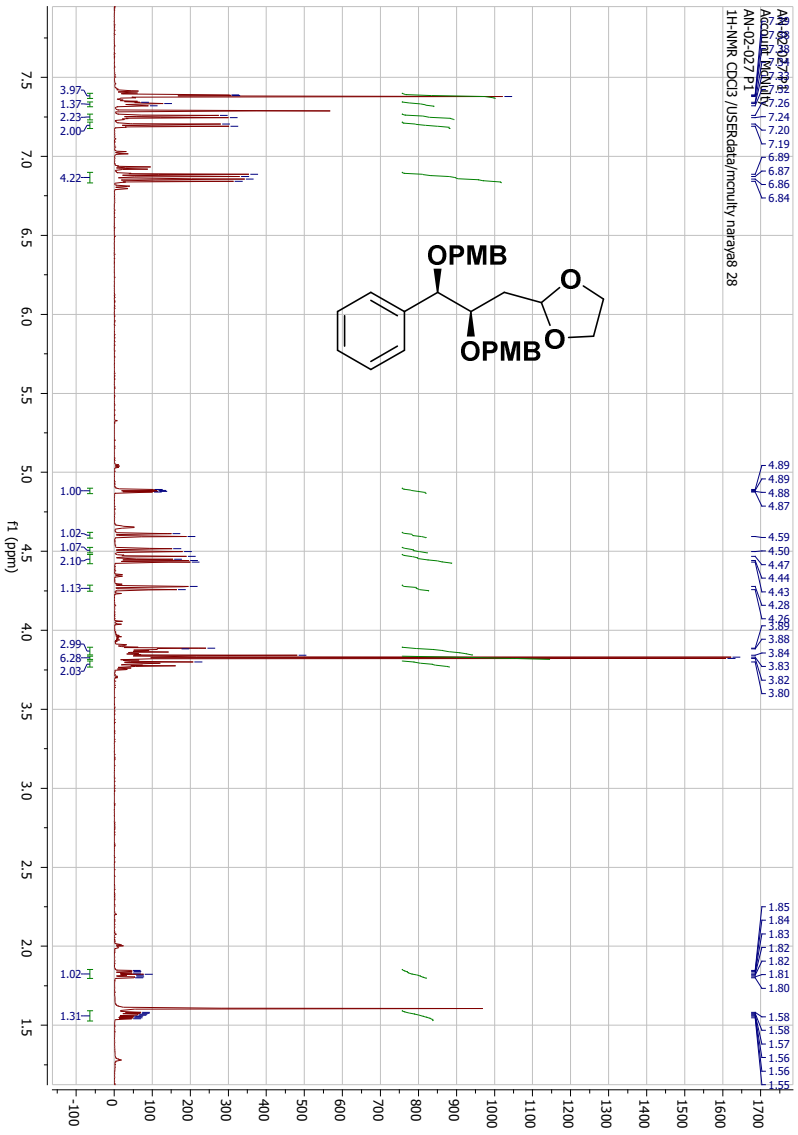
(*R*,*E*)-4-oxo-1-phenylbut-2-en-1-yl benzoate (14a)



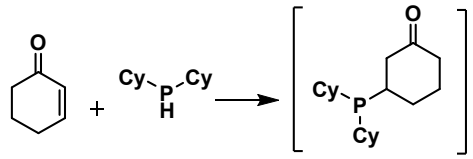
(1*R*,2*R*)-4-methoxy-4-oxo-1-phenylbutane-1,2-diyl dibenzoate (17)

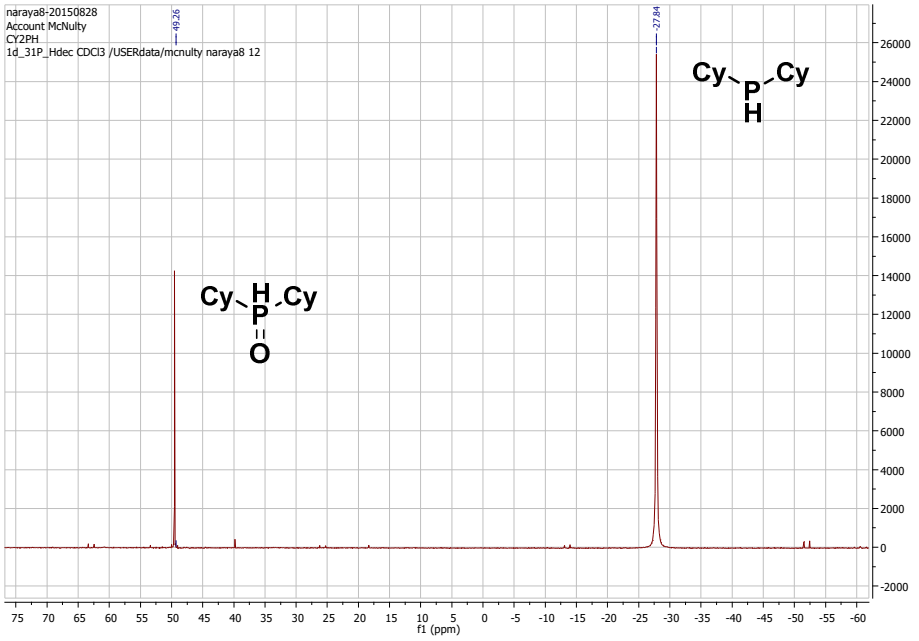


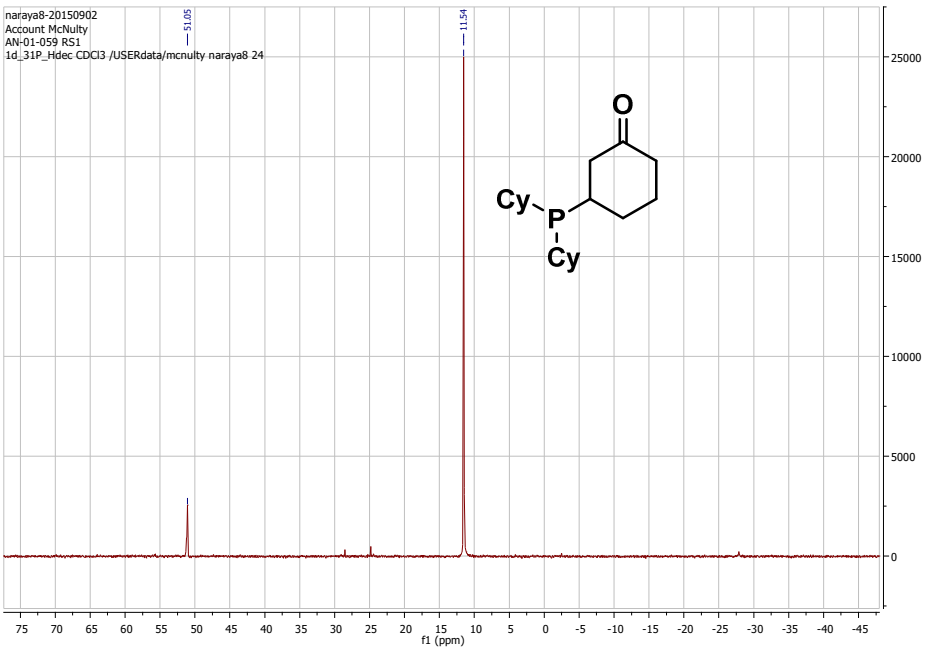
2-((2*R*,3*R*)-2,3-bis((4-methoxybenzyl)oxy)-3-phenylpropyl)-1,3-dioxolane (19)



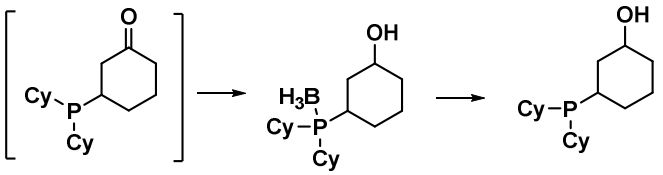
Route -1: 3-(dicyclohexylphosphino)cyclohexanone (22)

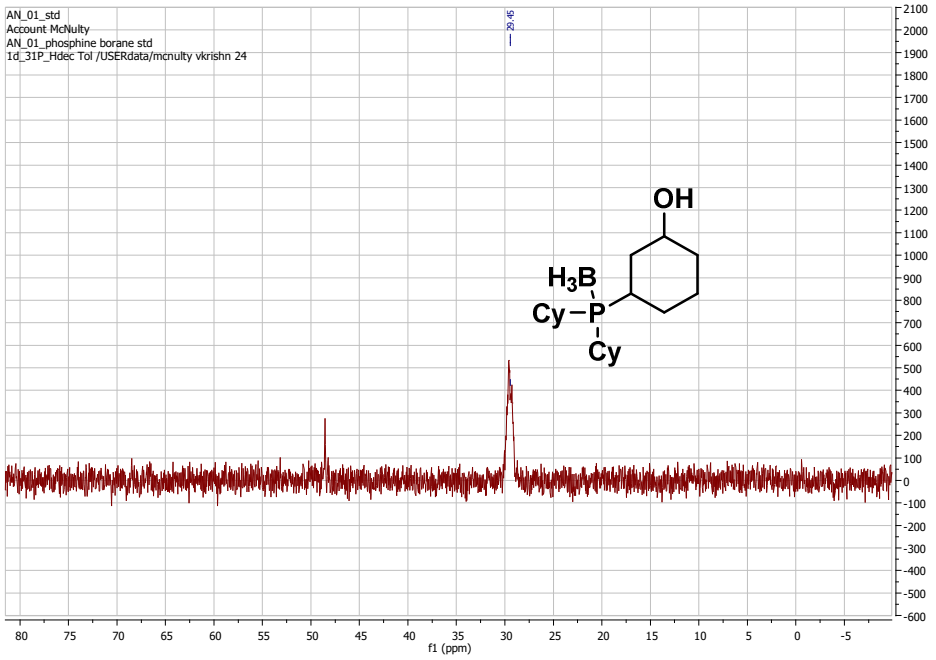


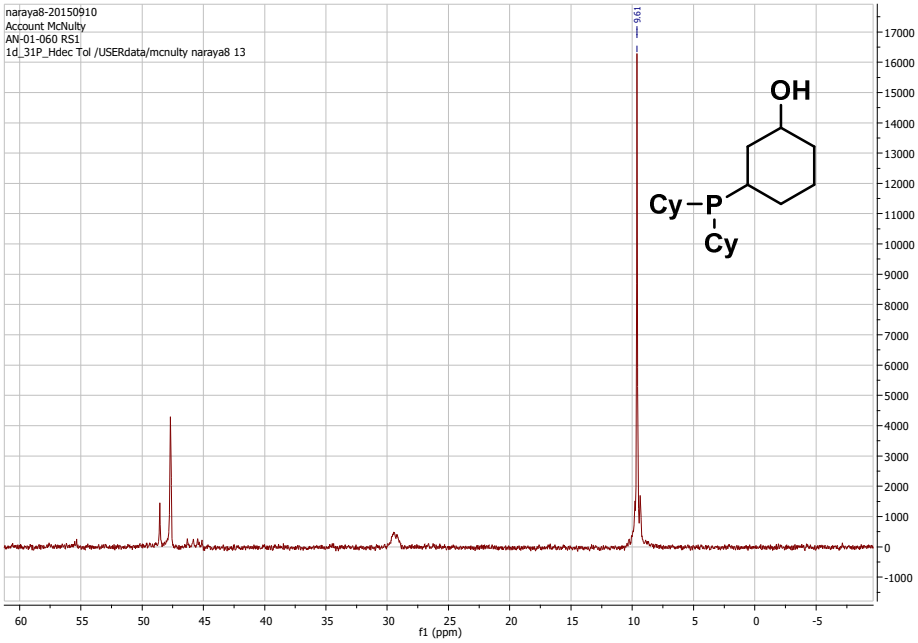




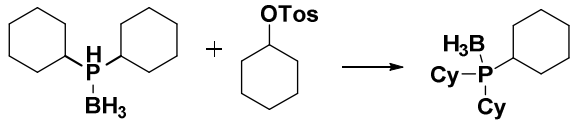
3-(dicyclohexylphosphino)cyclohexanol (23)

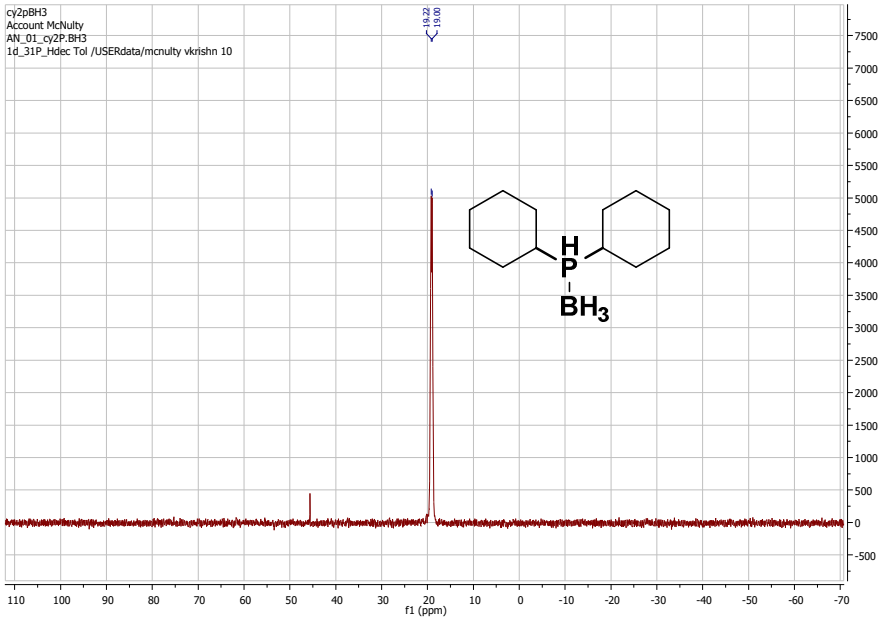


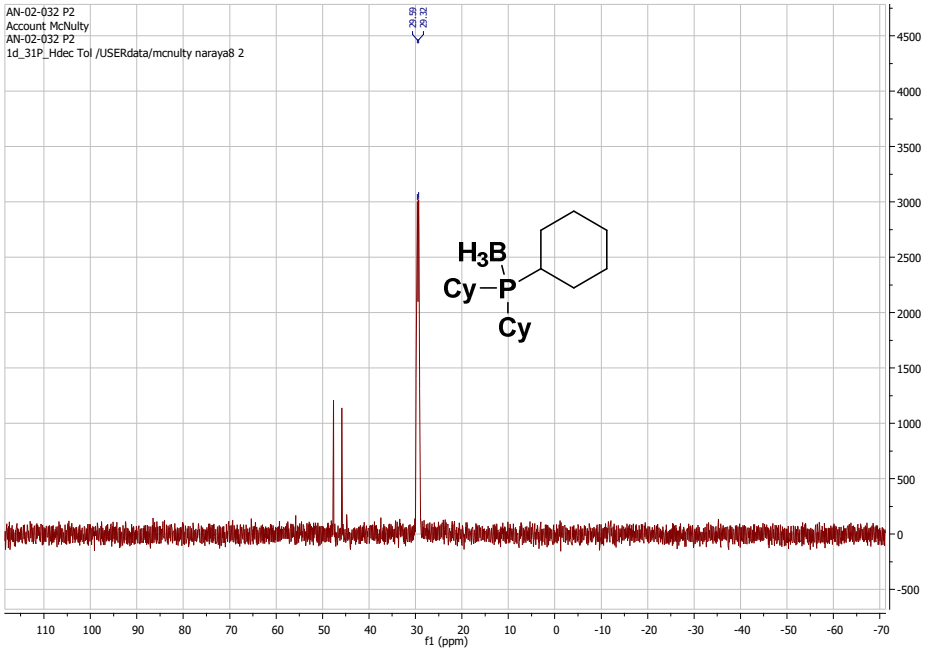




Route- 2: Synthesis of tricyclohexylphosphine (28) through S_N2 reaction







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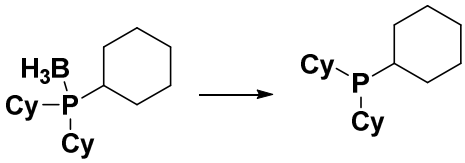
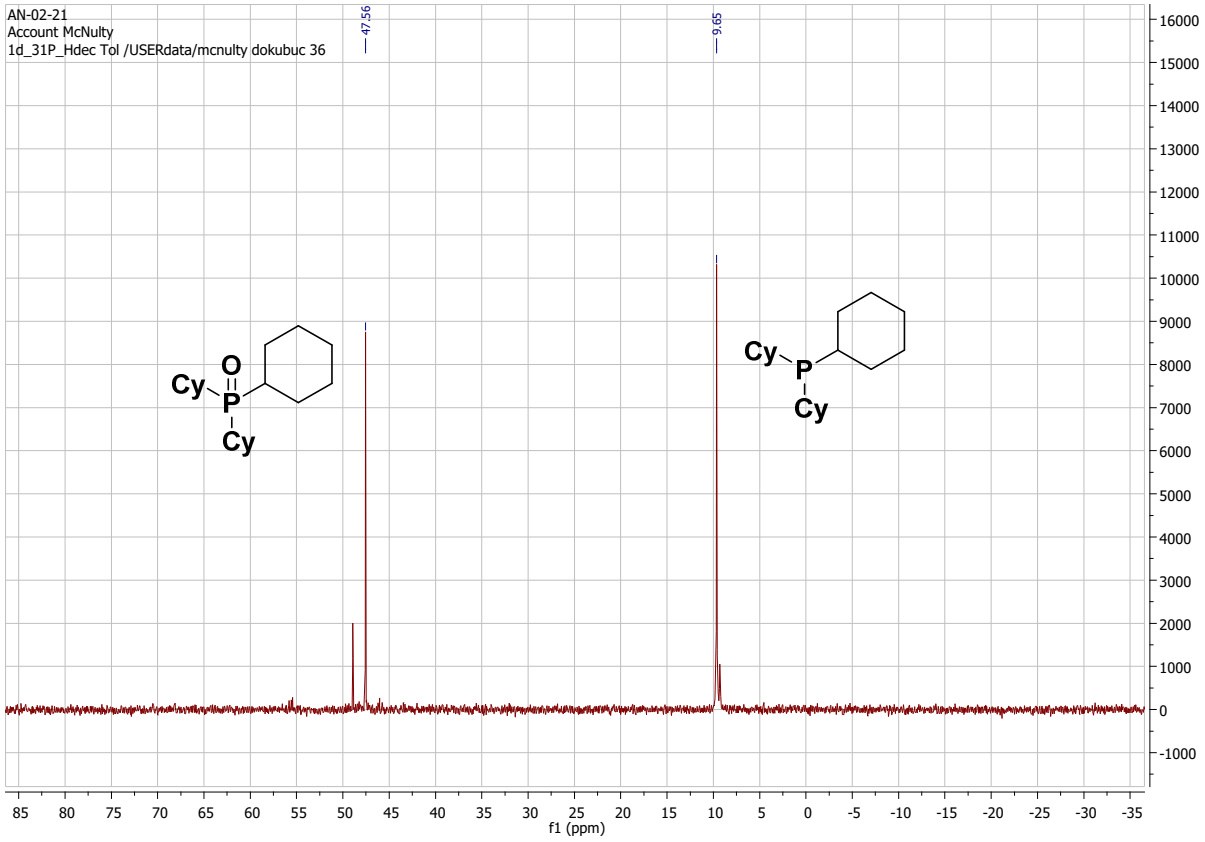
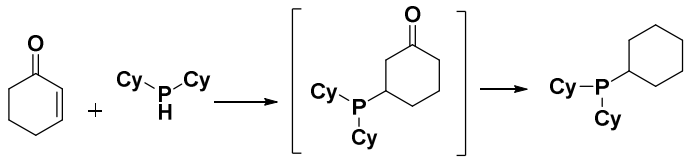
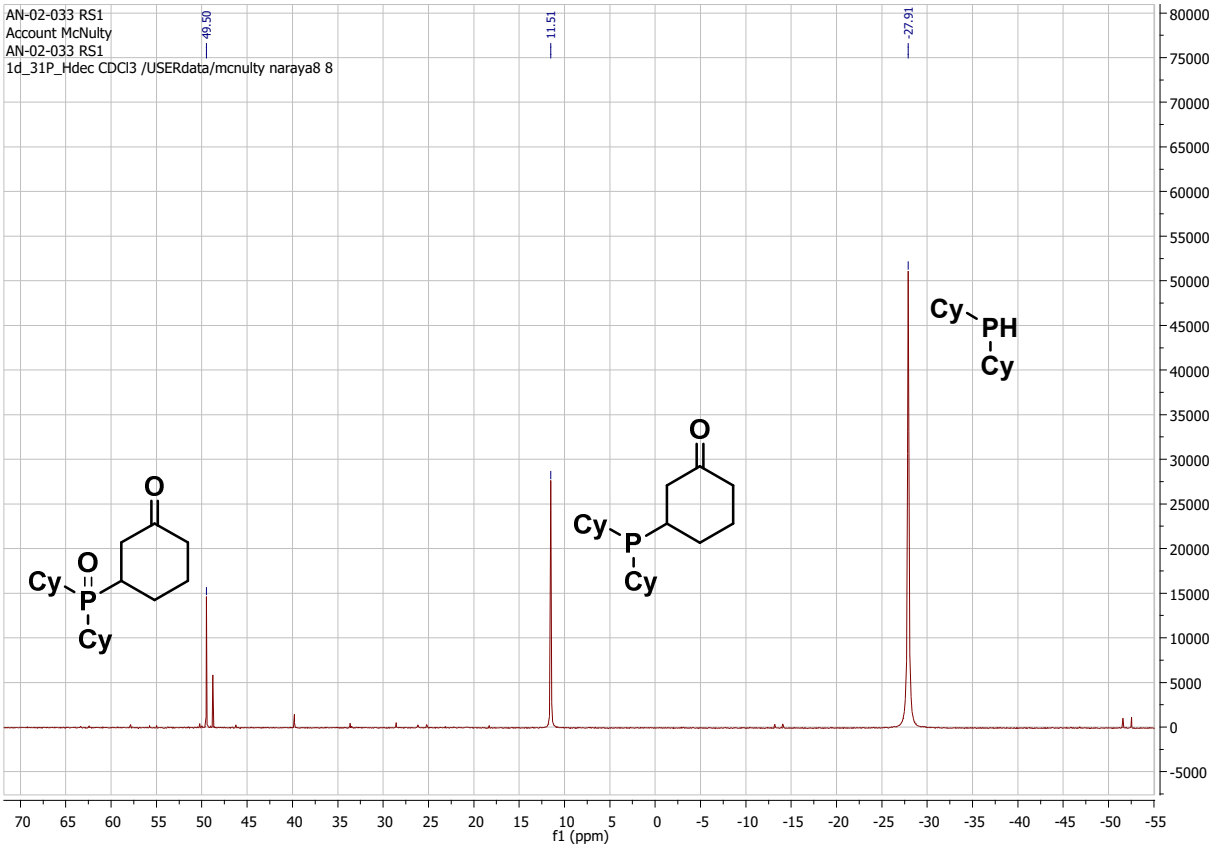
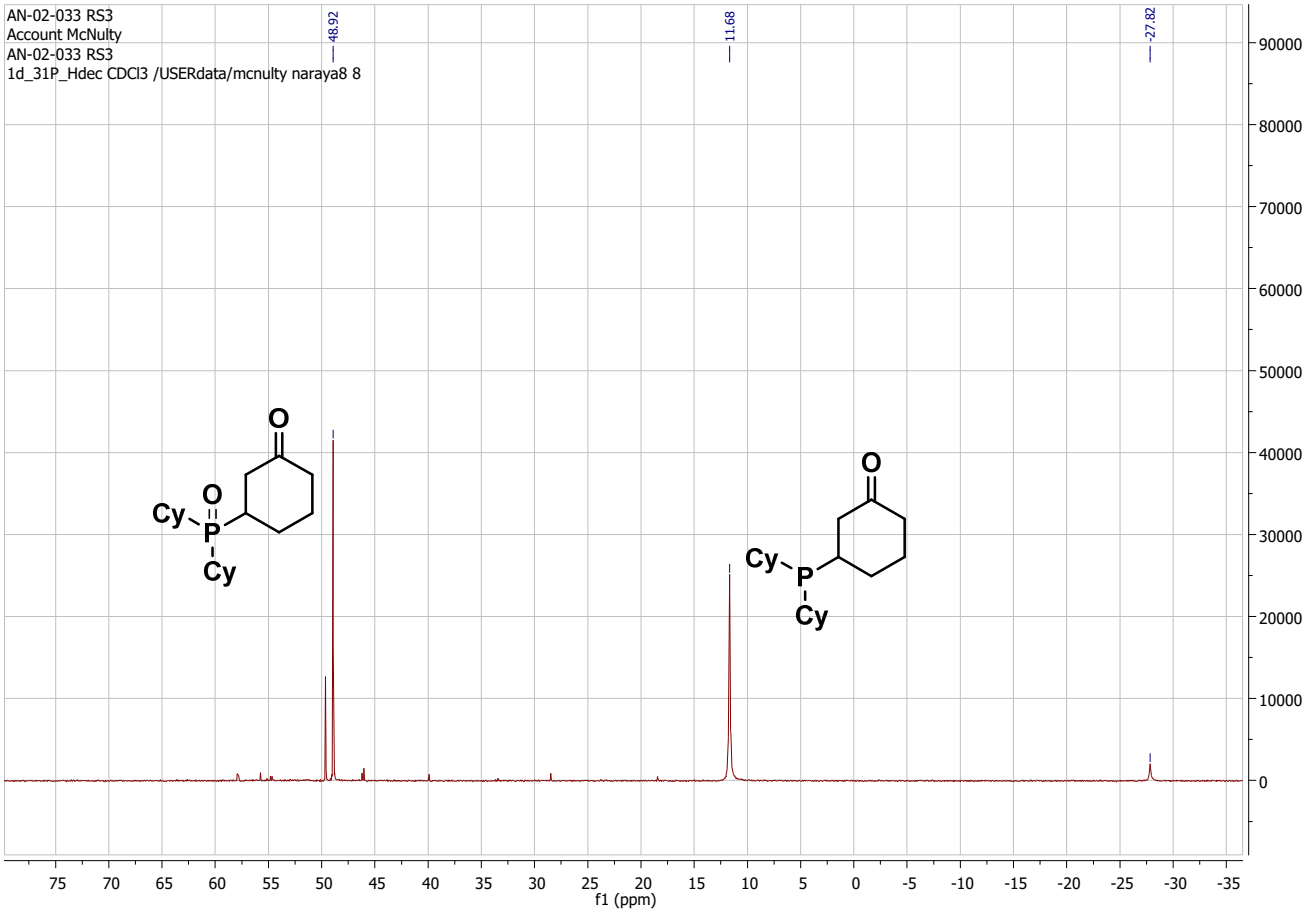




Route- 3: Tricyclohexylphosphine (28) synthesis through ketone reduction



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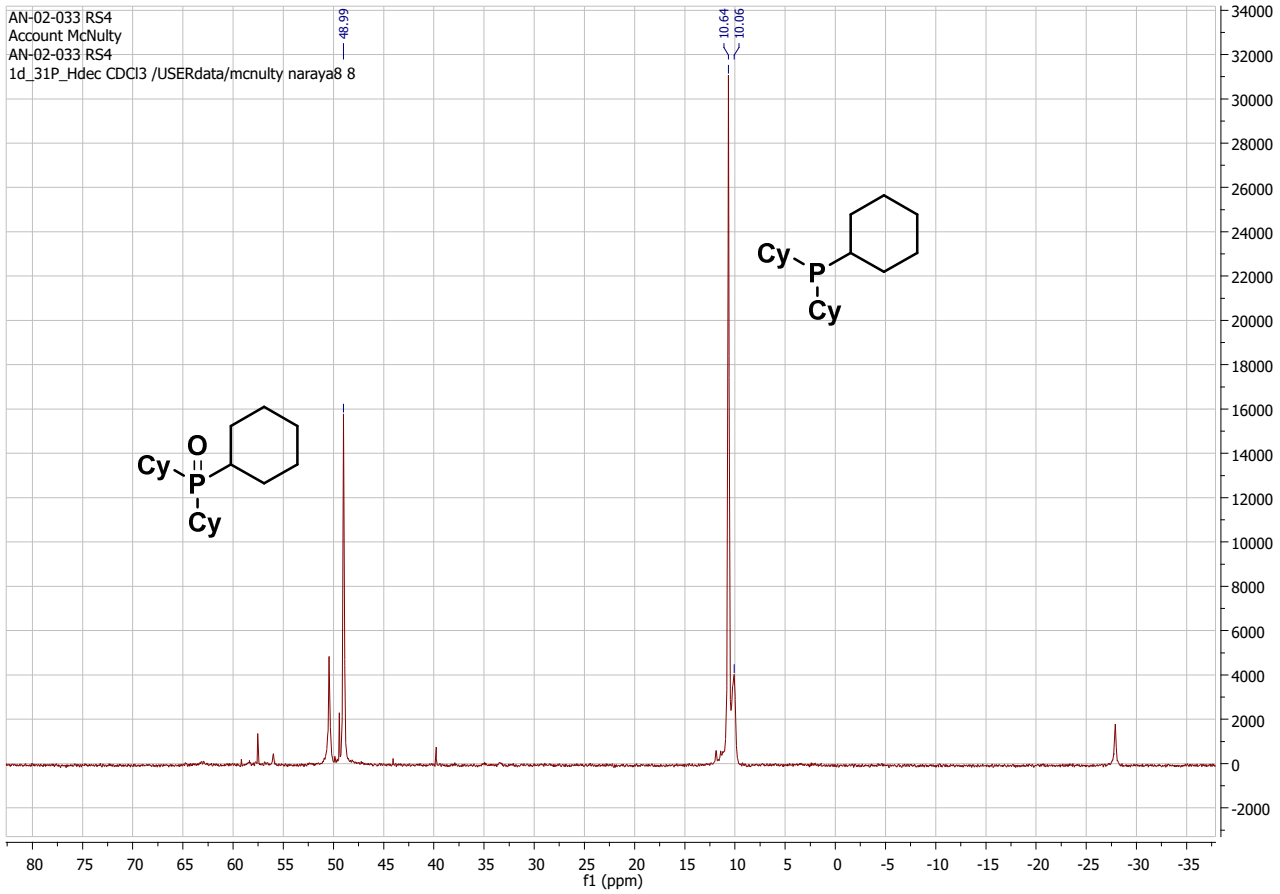
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