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(RESEARCH ARTICLE)

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Synthesis of biologically active lignan natural products via an Claisen rearrangement and an unusual 1.4 diaryl rearrangement

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Abstract

Biologically active natural products have been of increasing interest to chemists due to the growing demand for new medicines. Lignans are a family of secondary plant metabolites known to exhibit both interesting biological activities and immense structural variety. This thesis describes the synthesis of a number of lignan and neolignane natural products and analogues thereof, with the overall aim of synthesizing the complex dineolignane manassantin B 29. The interest in 29 originates from its potent inhibition of the transcription factor HIF-1, which is a potential target for a new class of selective anticancer drugs targeting the hypoxic region common in solid tumours. Initially, a series of 2,5-diaryl-3,4-dimethyl tetrahydrofuran lignans were synthesized via the strategy proposed for the synthesis of the more complex 29. During the course f this work, it was found that varying the substrates in the final cyclisation step could significantly influence the products formed. This serendipitous discovery led to extensive investigation into the mechanisms controlling the reaction and the different compounds synthesized. With this knowledge three different subclasses of lignan were successfully synthesized, with the relative and absolute stereochemistry of a number of the natural compounds determined for the first time. With the test synthesis proving successful the synthesis of 29 was undertaken via the envisaged convergent strategy, the three fragments syn-dimethyl compound 58 and two similar diaryl bromides 59 and 60 were synthesized enantioselectivity and in pleasing yields. Unfortunately the fragments could not be joined using the established aryl lithium addition methodology which had proved very successful on the test substrates. Despite several modifications to the syn-dimethyl compound and adjusted strategies, the synthesis of manassantin B 29 remains elusive. The diaryl bromides 59 and 60 were however successfully employed in the synthesis of a series of 8,4'-oxyneolignans using a Suzuki Miyaura strategy. Selected synthetic natural products and analogues were sent to NCI for testing against a panel of the sixty common cancer cell lines. Whilst a further series of natural and analogous 8,4'-oxyneolignans were sent to the Swiss Tropical and Public Health Institute for evaluation against both leishmania and malaria.

Keywords: Claisen rearrangement; Lignans; 1.4 Diaryl Rearrangement; anticancer drugs; HIF-1; Secondary plant metabolite; Dineolignane manassantin B 29

1. Introduction

Lignans comprise a family of secondary metabolites existing widely in plants and also in human food sources. As important components, these compounds play remarkable roles in plants' ecological functions as protection against herbivores and microorganisms. Meanwhile, foods rich in lignans have revealed potential to decrease of risk of cancers. To date, a number of promising bioactivities have been found for lignan natural products and their unnatural analogues, including antibacterial, antiviral, antitumor, antiplatelet, phosphodiesterase inhibition, 5-lipoxygenase inhibition, HIV reverse transcription inhibition, cytotoxic activities, antioxidant activities, immunosuppressive activities and antiasthmatic activities. Therefore, the synthesis of this family and also their analogues have attracted widespread

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interest from the synthetic organic chemistry community. Herein, we outline advances in the synthesis of lignan natural products in the last decade. Keywords: natural products, total synthesis, lignin.

Lignans are a family of secondary metabolites widely distributed in plants and human food sources. The story of lignans can traced back to 1942, when Harworth introduced the term for the first time to describe this family. It is known that lignans have remarkable ecological functions in plants, providing protection against herbivores and microorganisms]. The consumption of foods rich in lignans has potential to decrease of risk of cancers]. During its long research history, this family has exhibited attractive pharmacological activities. such as antibacterial, antiviral antitumor, antiplatelet, phosphodiesterase inhibition, 5-lipoxygenase inhibition, HIV reverse transcription inhibition, cytotoxic, antioxidant, immunosuppressive and antiasthmatic properties.

Lignan compounds have dimeric structures formed through a β,β′-linkage between two phenylpropane units with different degrees of oxidation on the side-chain and variable substitution patterns on the phenyl ring. Traditionally, lignans are divided into two classes: classical lignans and neolignans. It should be noted that the term lignan in the literature refers to classical lignans in most cases. Regarding the classification of classical lignans, four different types are reported. The first one arranged classical lignans into three subgroups: acyclic lignan derivatives, aryl naphthalene derivatives and dibenzo cyclooctadiene derivatives [41]. The second type includes six subgroups: dibenzyl butanes, dibenzyl butyrolactones, arylnaphthalenes, dibenzocyclooctadienes, substituted tetrahydrofuran's and 2,6-diarylfurofurans.

One is comprised of eight subgroups: furofurans, furans, dibenzyl butanes, dibenzyl butyrolactones, alterations, arylnaphthalenes, dibenzocyclooctadienes and dibenzylbutyrolactols. The fourth one includes seven subgroups of lignan scaffolds: cyclobutanes, tetrahydrofurans, furofurans, dibenzyl butanes, aryltetralins, cycloheptenes and dibenzocyclooctadienes. The synthesis of lignans and their analogues is an active field in the synthetic organic chemistry community. Tremendous synthetic efforts on this family have been well documented by reviews. In recent years, several nice reviews have outlined progress of particular topics related to the synthesis of furofuran lignans, aryl naphthalene lactone analogues and aryl tetralin glycosides. The present review will focus on the papers on the synthesis of lignans published from 2008–2018. In order to avoid unnecessary duplication, we will not discuss works already presented in previous reviews. For the convenience of introduction of advances in the synthesis of lignans, we discuss three subgroups in present review, namely, acyclic lignan derivatives, dibenzo cyclooctadiene derivatives and aryl naphthalene derivatives.

Lignans are a family of secondary metabolites widely distributed in plants and human food sources. The story of lignans can traced back to 1942, when Harworth introduced the term for the first time to describe this family. It is known that lignans have remarkable ecological functions in plants, providing protection against herbivores and microorganism. The consumption of foods rich in lignans has potential to decrease of risk of cancers. During its long research history, this family has exhibited attractive pharmacological activities, such as antibacterial [20], antiviral, antitumor, antiplatelet, phosphodiesterase inhibition, 5-lipoxygenase inhibition, HIV reverse transcription inhibition, cytotoxic, antioxidant, immunosuppressive and antiasthmatic properties. Lignan compounds have dimeric structures formed through a β,β -linkage between two phenylpropane units with different degrees of oxidation on the side-chain and variable substitution patterns on the phenyl ring. Traditionally, lignans are divided into two classes: classical lignans and neolignans. It should be noted that the term lignan in the literature refers to classical lignans in most cases. Regarding the classification of classical lignans, four different types are reported. The first one arranged classical lignans into three subgroups: acyclic lignan derivatives, aryl naphthalene derivatives and dibenzo cyclooctadiene derivatives.

1.1. Advances in the Synthesis of Acyclic Lignan Derivatives

In the last decade, synthetic progress in acyclic lignan derivatives is related to lignans featuring dibenzyl tetrahydrofuran, dibenzylbutyrol acetone, and diphenyltetrahydrofuranfurofuran skeletons.

The synthesis of the acyclic lignan derivative (±)-paulownia was accomplished by Angle and coworkers in 2008 [The key step is a formal [3 + 2]-cycloaddition between silyl ether 1 and aldehyde 2 in the presence of BF_3OEt_2 and 2,6-di-*tert*-butyl-4-methylphenol (DBMP), generating aryl tetrahydrofuran 3**.** After oxidation and removal of the protecting group, the resulting product 4 was connected with imitate **5**, generating lactone **6**. The synthesis of (±)-paulownia was finished through photocyclization under a medium-pressure Hanovia lamp.

In 2011, Barker and coworkers reported the total synthesis of (+)-galbelgin (Scheme 2) [54]. A stereoselective aza-Claisen rearrangement developed in their lab [55] afforded a reliable access to the original two stereocenters in chiral amide 8. The subsequent nucleophilic addition from 11, reduction, hydroxyl

2. Materials and methods

It sounds like you're working on a fascinating project! The synthesis of biologically active lignan natural products via a Claisen rearrangement and an unusual 1,4 diaryl rearrangement is an interesting area of research.

To get started, you'll need to plan out your experiment carefully. Here are some general steps to consider:

- Research: Begin by researching the specific lignan natural products you are interested in synthesizing. Understand their chemical structures, biological activities, and any previous synthetic methods that have been reported in the literature.
- Design a synthetic route: Based on your research, design a synthetic route that incorporates the Claisen rearrangement and the 1,4 diaryl rearrangement. Consider the starting materials, reagents, reaction conditions, and purification methods required for each step.
- Laboratory work: Set up your laboratory experiments according to your planned synthetic route. This may involve performing reactions, purifications, and characterization of intermediates and final products using techniques such as NMR, mass spectrometry, and chromatography.
- Optimization: As with any synthetic route, you may need to optimize reaction conditions to achieve high yields and selectivity. This could involve varying reaction parameters such as temperature, time, and stoichiometry.
- Data analysis: Once you have obtained your synthetic products, analyze them using various spectroscopic and analytical techniques to confirm their structures.
- Biological testing: If the goal of your project is to access biologically active compounds, you may need to perform biological assays to evaluate the activity of your synthesized lignan natural products.

It's important to keep detailed records of your experiments, including reaction conditions, observations, and analytical data. Additionally, be sure to follow all safety protocols when working in the laboratory.

If you have specific questions about any of these steps or need guidance on a particular aspect of your experiment work, feel free to ask!

The synthesis of various lignans via the rearrangements of 1,4-diarylbutane-1,4-diols is an intriguing area of organic chemistry research. The use of Claisen rearrangement and 1,4-diaryl rearrangement in the synthesis of lignans offers a versatile and efficient approach to accessing these biologically active natural products.

Here are some general steps to consider for the synthesis of various lignans via the rearrangements of 1,4-diarylbutane-1,4-diols:

- Design a synthetic route: Plan a synthetic route that utilizes the 1,4-diarylbutane-1,4-diol as a key intermediate. Consider the specific lignan natural products you are interested in synthesizing and how the rearrangements can be used to access their core structures.
- Synthesis of 1,4-diarylbutane-1,4-diol: Develop a method for synthesizing the 1,4-diarylbutane-1,4-diol starting material. This may involve the use of suitable coupling reactions or other synthetic strategies to construct the desired carbon-carbon bond connectivity.
- Claisen rearrangement: Explore conditions for the Claisen rearrangement of the 1,4-diarylbutane-1,4-diol to access key intermediates in the synthesis of lignans. Optimization of reaction conditions such as temperature, choice of base, and solvent may be necessary to achieve high yields and selectivity.
- 1,4-diaryl rearrangement: Investigate methods for the 1,4-diaryl rearrangement to further transform the Claisen rearrangement products into diverse lignan structures. This may involve the use of specific reagents or catalysts to facilitate the rearrangement process.
- Purification and characterization: Purify the synthesized compounds using appropriate chromatographic techniques and characterize them using spectroscopic methods such as NMR, mass spectrometry, and X-ray crystallography to confirm their structures.
- Biological evaluation: If the goal is to access biologically active lignans, conduct biological assays to assess the activity of the synthesized compounds. This may involve testing against specific biological targets or cell lines.

Throughout your research and experimentation, it's important to keep detailed records of your synthetic procedures, analytical data, and any observations made during the course of your work.

As you progress with your project, you may encounter specific challenges or questions related to experimental design, reaction optimization, or characterization techniques. Feel free to ask for assistance with any aspect of your research!

- **A: Acyl-Claisen-** To a stirred suspension of TiCl4·2THF (1 mmol) in CH2Cl2 (5 mL), under an atmosphere of nitrogen, was added a solution of allylic morpholine (1 mmol) in CH2Cl2 (2.5 mL) followed by dropwise addition of *i*Pr2NEt (1.5 mmol). After stirring for 10 min a solution of acid chloride (1.2 mmol) in CH2Cl2 (2.5 mL) was added dropwise and the resultant mixture stirred for the specified time. The reaction mixture was quenched with aqueous NaOH (12 mL, 1 M) and the aqueous phase extracted with CH2Cl2 (3 × 10 mL).
- The combined organic extracts were washed with brine (6 mL), dried (MgSO4), the solvent removed *in vacuo* and the crude product purified by column chromatography.
- **B: Dihydroxylation-** To a stirred solution of morpholine pentenamide (1 mmol) in *t*BuOH/H2O (1:1, 20 mL) or *t*BuOH/H2O/THF (1:1:1, 30 mL) was added NMO (3 mmol). A solution of OsO4 (0.08 mmol, 2.5% w/v in *t*BuOH) was then added dropwise and the resultant mixture stirred for the specified time. The mixture was quenched with saturated aqueous Na2SO3 (30 mL) and stirred for a further 1 h. The aqueous phase was extracted with ethyl acetate (3 × 20 mL), the combined organic extracts washed with aqueous KOH (5 mL, 1 M), dried (MgSO4), the solvent removed *in vacuo* and the crude product purified by column chromatography.
- **C: Lithium aluminium hydride reduction:** To a stirred suspension of LiAlH4 (1.4 mmol) in THF (10 mL), under an atmosphere of nitrogen at 0 °C, was added a solution of lactone (1 mmol) in THF (10 mL) and the mixture stirred for the specified time. After warming to room temperature, the mixture was quenched with the addition of water (30 mL) and the aqueous phase extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO4) and the solvent removed *in vacuo*.
- **D: Periodate cleavage:** To a stirred solution of triol (1 mmol) in MeOH/H2O (3:1, 50 mL) was added NaIO4 (1.2 mmol) and the resultant mixture stirred for the specified time. The reaction mixture was quenched with brine (40 mL) and extracted with ethyl acetate (3 × 80 mL). The organic layers were combined, washed with water (2 × 40 mL), dried (MgSO4) and solvent removed *in vacuo* to give the crude product which was purified by column chromatography if necessary.

3. Result and discussion

3.1. Molecular Descriptors

Using the aforementioned methods, ten molecular descriptors were calculated for each of the 160 compounds studied. Molecular weight, lipophilicty (LogP), the number of hydrogen bond donors, hydrogen bond acceptors and rotatable bonds and polar surface area (PSA) have been extensively used in the assessment of a molecules' suitability to be considered as a drug [68]. The other molecular descriptors—dipole moment, polarisability, ionisation potential and water solubility (LogS) have been used less extensively, however their association with desirable characteristics has led them to being increasingly examined in recent times [63,69,70].

To analyse the molecular descriptors, summary statistics–the mean, median and standard deviation for each of these parameters—for each compound type, as well as for all 160 compounds (all classical lignans, neolignans, flavonolignans and CLCs) were calculated and are in the table provided

3.2. Molecular Weight

The molecular weights of the compounds in this study are approximately normally distributed (**Figure 3**), with an overall mean of 381.5 g mol^{-1} and standard deviation of 70.4 g mol^{-1}

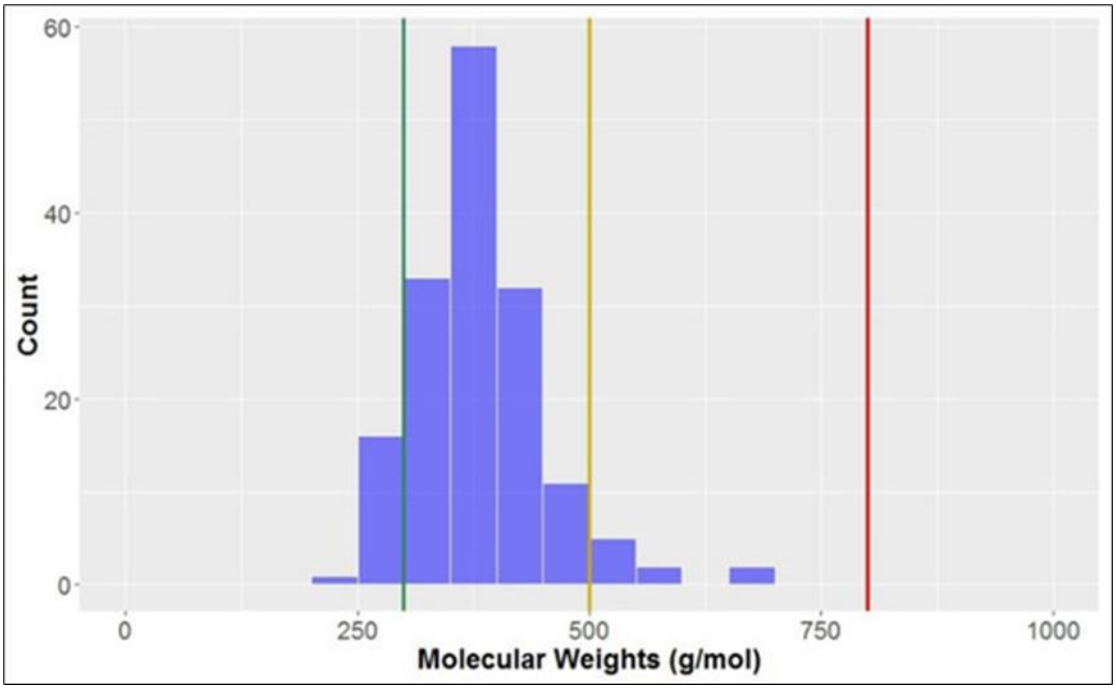

Figure 1 The statistical distribution of the molecular weight of all analyzed compounds (green = 300 g mol^{-1}, compounds < 300 g mol^{-1} are in the *lead-like* space; yellow = 500 g mol^{-1}, compounds < 500 g mol^{-1} are in the *drug-like* space; red = 800 g mol^{-1}, compounds < 800 g mol^{-1} are in the KDS). Total number of compounds = 160.

Unsurprisingly, the categories with the highest average molecular weights were CLCs and flavonolignans, with mean molecular weights of 567.4 ± 67.5 and 478.6 ± 7.0 g mol^{-1}, respectively. By definition, flavonolignans are the result of a dimerization of a phenyl propanoid unit and flavone nucleus, a flavone moiety having a higher molecular weight than another phenyl propanoid unit that forms the basis of a classical lignan/neolignane . The CLCs in this study are classical lignans/neolignans with a least one additional saccharide unit attached. Of all of the sub-classes, flavonolignans had the lowest standard deviation for molecular weight, indicative that the compounds of this type have very similar molecular composition. Of the classical lignans and neolignans, dibenzyocyclooctadienes had a significantly higher average than other classical lignans and neolignans (413.3 g mol^{-1} vs. 361.2 g mol^{-1}). Conversely, biphenyls (313.8 ± 62.6 g mol^{-1}) and biphenyl ethers (296.5 ± 27.4 g mol^{-1}) had the lowest molecular weights, on average. Looking at these compounds, they generally have lower numbers of substituents on the aromatic ring and less elaboration of the sidechains, which could account for this observation. Compounds in the KDS have molecular weights lower than 800 g mol^{-1} (red line in **1**); as can be seen, all of the compounds studied exist in KDS for this parameter. Almost all (94.5%) of the compounds would be considered to be *drug-like* when considering molecular weight, however only ~10% of compounds are also considered *lead-like* (<300 g mol^{-1}).

3.3. The Octanol–Water Partition Coefficient (LogP)

Like the molecular weights, the lipophilicites (LogP values)—the octanol-water partition coefficient of the molecules—are approximately normally distributed (mean = 3.0, standard deviation = 1.3, , Figure 4).All compounds studied have a calculated LogP less than the benchmark for KDS (LogP = 6.5), and all but one can be considered *drug-like* (LogP < 5) for this parameter. Approximately half of the compounds had a calculated lipophilicity allowing it to be in *lead-like* space. The compound classes that were calculated to exhibit the highest degree of lipophilicity were dibenzocyclooctadienes and cyclobutanes (LogP = 3.9 ± 0.7 and 3.7 ± 0.9, respectively). Contrastingly, CLCs have the lowest average calculated LogP (0.4 ± 1.1), thereby demonstrating a low affinity for non-aqueous systems and the highest degree of hydrophilicity. Flavonolignans also had low LogP values (mean = 1.6) which was notably lower than the classical lignans and neolignans studied(mean = 3.3).

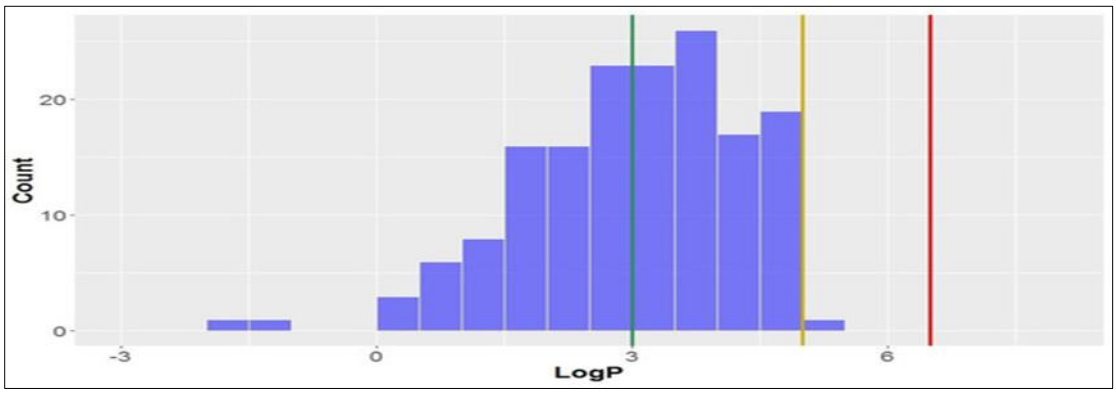

Figure 2 The statistical distribution of the octanol–water partition coefficient (LogP) of all analysed compounds (green = 3, compounds < 3 are in the *lead-like* space; yellow = 5, compounds < 5 are in the *drug-like* space; red = 6.5, compounds < 6.5 are in the KDS). Total number of compounds = 160

3.4. Hydrogen Bond Donors and Acceptors

Ideally, compounds should not have too many hydrogen bond donors and acceptors; the number of hydrogen bond donors should be lower than seven, five and three to be considered to be in KDS, *drug-like* space and *lead-like* space, respectively. On average, the compounds in this study conform reasonably well with the three aforementioned definitions used for the chemical spaces (mean = 3.0, standard deviation = 1.3, **Figure 5**, for hydrogen bond donors. As can be seen, most compounds have three or less hydrogen bond donors (81.3%), allowing them to be classified in *lead-like* space and the majority of compounds have less than two. There are a proportion of compounds that do have more than three hydrogen bond donors–these compounds were mainly CLCs and flavonolignans, with their mean number of hydrogen bond donors being 6.1 and 4.1, respectively. Dibenzylbutanes and alkyl aryl ethers also had a significant percentage of compounds excluded from *lead-like* space according to this parameter.

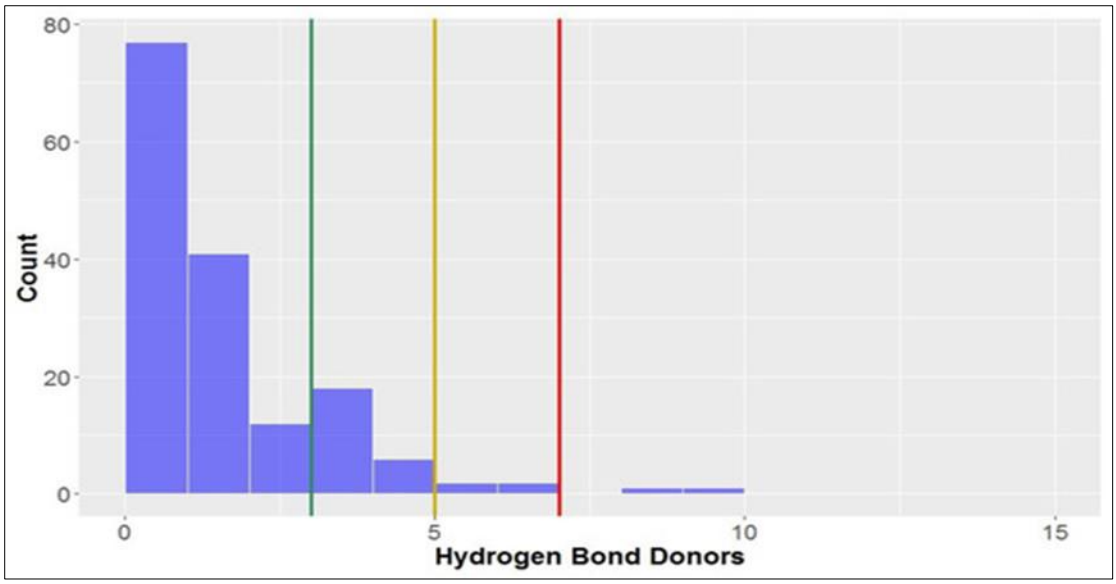

Figure 3 The statistical distribution of the hydrogen bond donors of all analysed compounds (green = 3, compounds < 3 are in the *lead-like* space; yellow = 5, compounds < 5 are in the *drug-like* space; red = 7, compounds < 7 are in the KDS). Total number of compounds = 160

Only 15% of compounds were classified as being *lead-like* in terms of the number of hydrogen bond acceptors (≤3 hydrogen bond acceptors)–much lower than that observed for the hydrogen bond donors, although greater than 90% of compounds had ≤10 hydrogen bond acceptors, classifying them as *drug-like.*

The number of hydrogen bond acceptors displayed a slightly-left skewed normal distribution (**Figure 6**)–far different to the strongly-skewed distribution seen for the aforementioned number of hydrogen bond donors (**Figure 5**). The

overall mean number of hydrogen bond acceptors was 6.3, although this was largely inflated due to the CLCs (hydrogen bond donors = 16.6 ± 3.8) and to a lesser degree, flavonolignans (hydrogen bond donors = 9.0 ± 0.8); without these two compound types included in the analysis, the mean decreased to 5.4 hydrogen bond acceptors. The only compounds studied with greater than 15 hydrogen bond acceptors, thus not in KDS, were CLCs.

3.5. Synthesis of Various Lignans *via* the Rearrangements of 1,4-diarylbutane-1,4-diols

Based upon these initial findings, it was decided to further investigate the uncommon126 1,4-diaryl rearrangement in order to prepare 4,4-diarylbutanal products containing other aromatic substitution patterns. Previous work had shown this rearrangement occurred only in the case where both aromatic rings were *para*-methoxybenzene rings.

The proposed mechanism for this unusual 1,4- to 4,4-aryl migration is *via* a 5-membered cyclic intermediate which undergoes subsequent TBS elimination and ring opening to give the 4,4- diarylbutanal (Figure 3.2). It was proposed that the aromatic ring at C-4 does not participate in the rearrangement and therefore was the first site examined for modifications to the rearrangement substrate.

Common aldehyde **6** was prepared in two steps, dihydroxylation followed by periodate cleavage, from alkene **7** which was prepared following literature procedures.126,127 A range of aryl organometallic reagents were then added to aldehyde **3.6**, giving alcohols **3.8a–f** in moderate to good yields as single diastereoisomers as predicted by the Felkin-Anh model.[127]

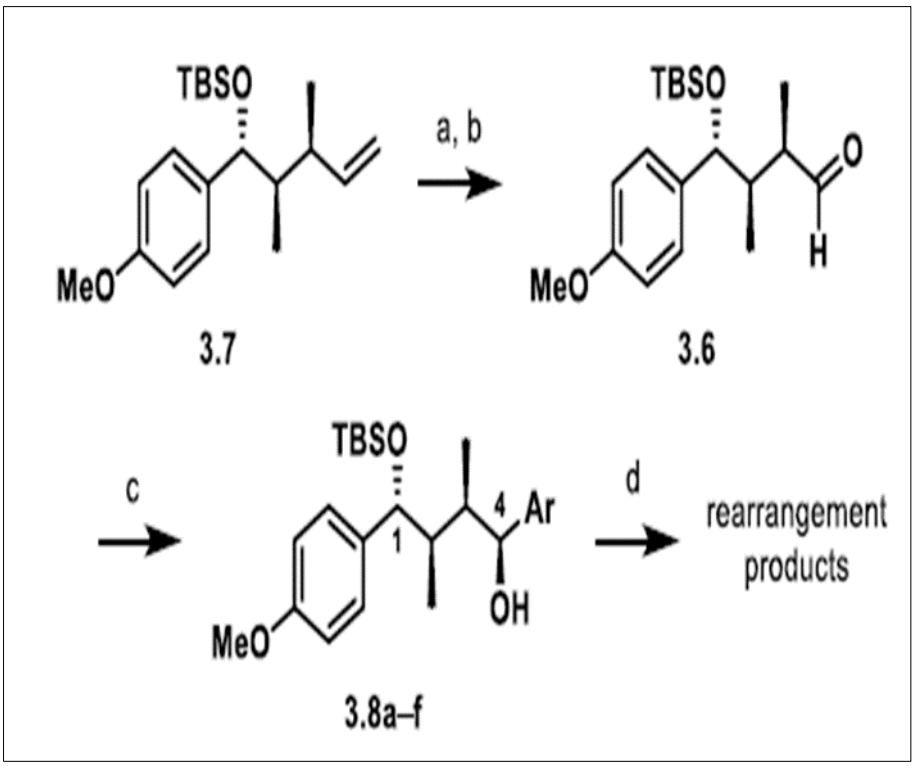

Figure 4 Reagents and conditions: (a) NMO, OsO4, tBuOH/H2O (1:1), 24 h, 83%; (b) NaIO4, MeOH/H2O (3:1), 1 h, quant.; (c) organometallic reagent, THF, -78 °C, 24 h, Ar = 4-methoxyphenyl 3.8a (33%), 3,4-dimethoxyphenyl 3.8b (22%), 3,4- methylenedioxyphenyl 3.8c (82%), 3,4,5-trimethoxyphenyl 3.8d (52%), phenyl 3.8e (23%), thienyl 3.8f (quant.); 3.8a–c, e–f

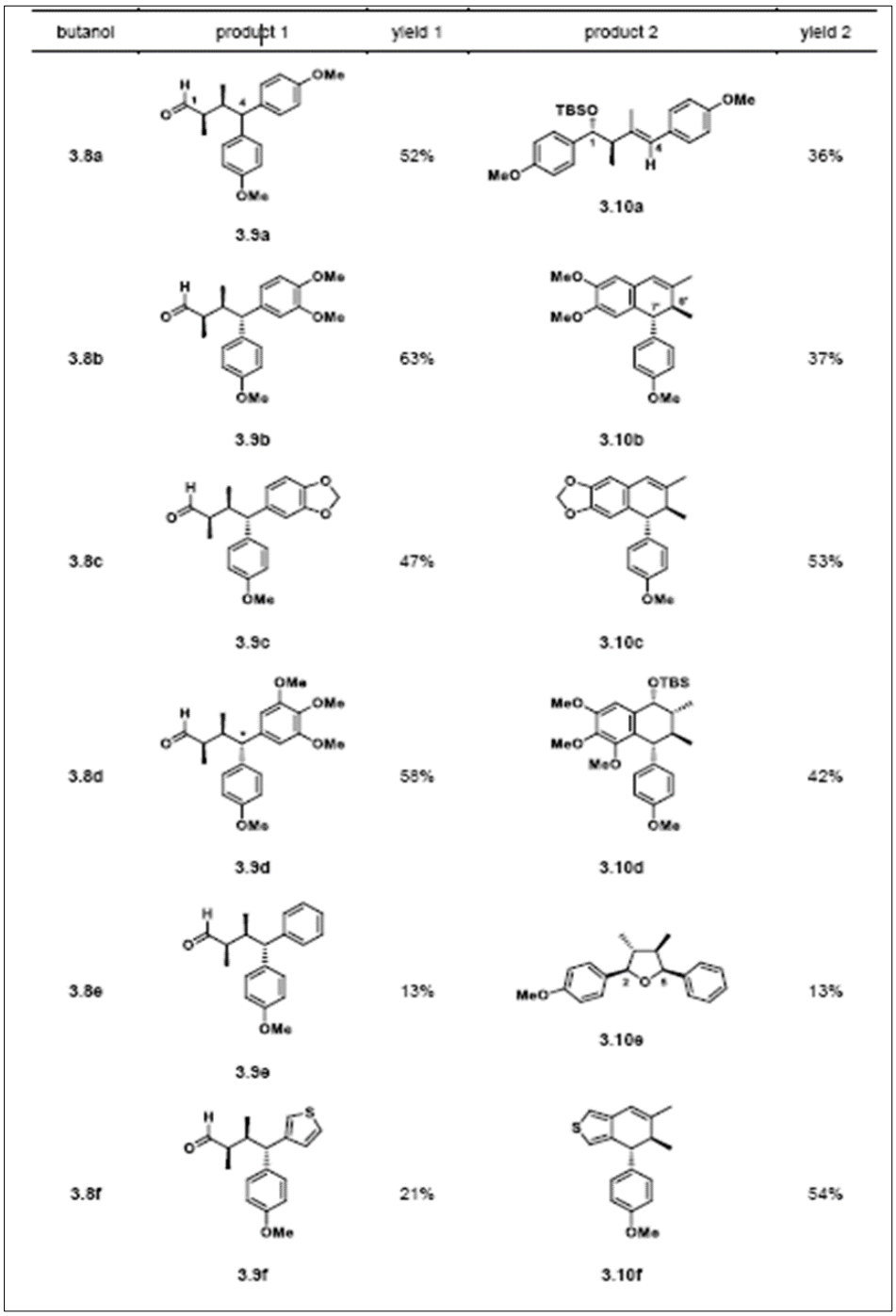

Figure 5 As expected, upon treatment with trimethylamine and methanesulfonyl chloride at 0 °C, all butanols 3.8a–f gave rise to 4,4-diarylbutanals 3.9a–f. The aryl migration was found to be stereoselective with 1H and 13C NMR showing that for all aldehydes except 3.9d (Table 3.1) a single diastereomer had formed. Whilst alcohol 3.8a with bis-*para*-methoxyphenyl rings gave only aldehyde 3.9a, in the cases of butanols 3.8b–f other products were also obtained. These were determined to be aryl tetralins 3.10b– d,f for butanols 3.8b–d,f and a 2,5-diaryl THF 3.10e from butanol 3.8e. The aryl tetralins 3.10b–d,f were also obtained as single diastereoisomers and by comparison to literature compounds,126,141,142 coupling constants between protons H-7′ and H-8′ determined a *trans*-relationship between these substituents.

The stereochemistry at position C-4 of the 4,4-diarylbutanals **3.9** was determined through cyclisation of butanal **3.9c**, using catalytic *p*TSA in toluene, which gave aryl tetralin 3.11 as a single isomer in 50% yield.143 Tetralin 3.11 had a coupling constant of 6.5 Hz between H-7′ and H-8′, suggesting a *CIS* relationship between the substituents at these positions, opposite to the tetralins formed from the rearrangement reaction.

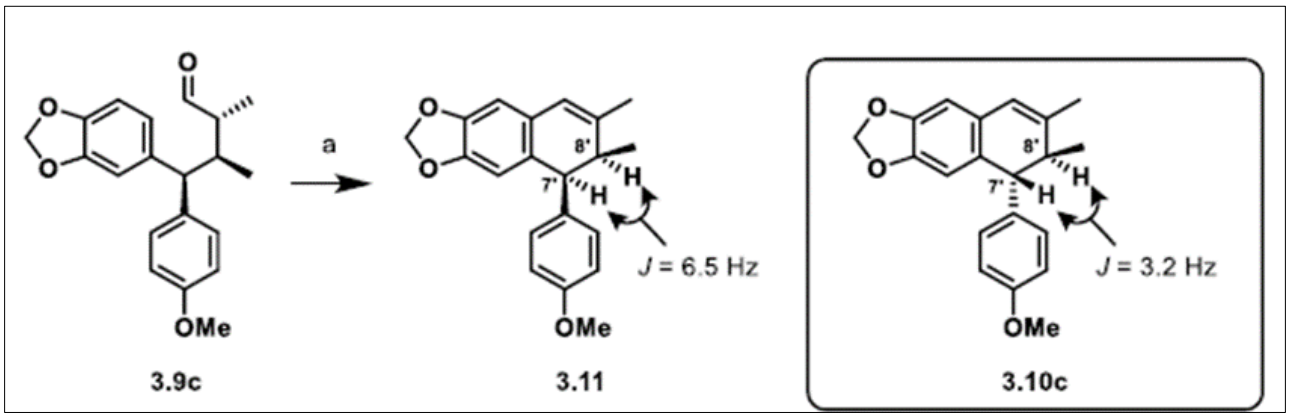

Figure 6 Reagent and conditions: (a) ***ρ***TSA toluene, reflux, 30 min, 50 %

Based on this information a mechanism was proposed for the stereoselective formation of both the 4,4- diarylbutanals 3.9 and aryl tetralins 3.10. It is proposed that the first step of the rearrangement is formation of a quinone-methide 3.12 which occurs *via* methanesulfonylation of the 8′-OH followed by elimination of methane sulfonate due to the electron donating properties of the adjacent aromatic ring (Figure 3.2). The next step involves *ipso*-attack of C-1, *via* donation from the C-4 methoxy group, onto C-7′ giving two diastereomeric 5-membered intermediates 3.13a and 3.13b.

From here it is suggested that the *cis-trans-trans* intermediate 3.13a would give rise to 4,4-diarylbutanal 3.9c through elimination of TBSCl whereas the *cis-trans-cis* intermediate 3.13b would give rise to aryl tetralin 3.10c. The formation of the aryl tetralins is proposed to occur due to the pseudo-axial position of the C-1′–C-6′ aromatic ring, allowing attack of C-6′, due to donation from the oxygen at C-3′, at C-7 resulting in formation of the tetralin structure and re-aromatization of the *para*-methoxyphenyl ring. A possible alternative pathway could proceed *via* breaking of the C-1–C-7 bond resulting in a charged intermediate then followed by cyclisation from C-6′ onto C-7 to give the aryl tetralin. However, if proposed for this step, the same mechanism could be applied to the formation of butanal 3.9c and from the charged intermediate it would be possible to form diastereomeric aryl tetralins thus suggesting an SN2 type mechanism. Subsequent elimination of TBSOH gives the final aryl tetralin 3.10c. Interestingly, the tetralin product 3.10d from the reaction of butanol 3.8d which contained a trimethoxybenzene ring did not match the expected product (Figure 3.3). The predicted product would have a proton at C-2 and a methoxy at C-5, and the isolated product 3.10d had the reverse arrangement. Furthermore, analysis of the 1H NMR spectrum of aldehyde 3.9d showed that diastereomers had formed at C-4, which was not observed for any of the other aldehydes tested.

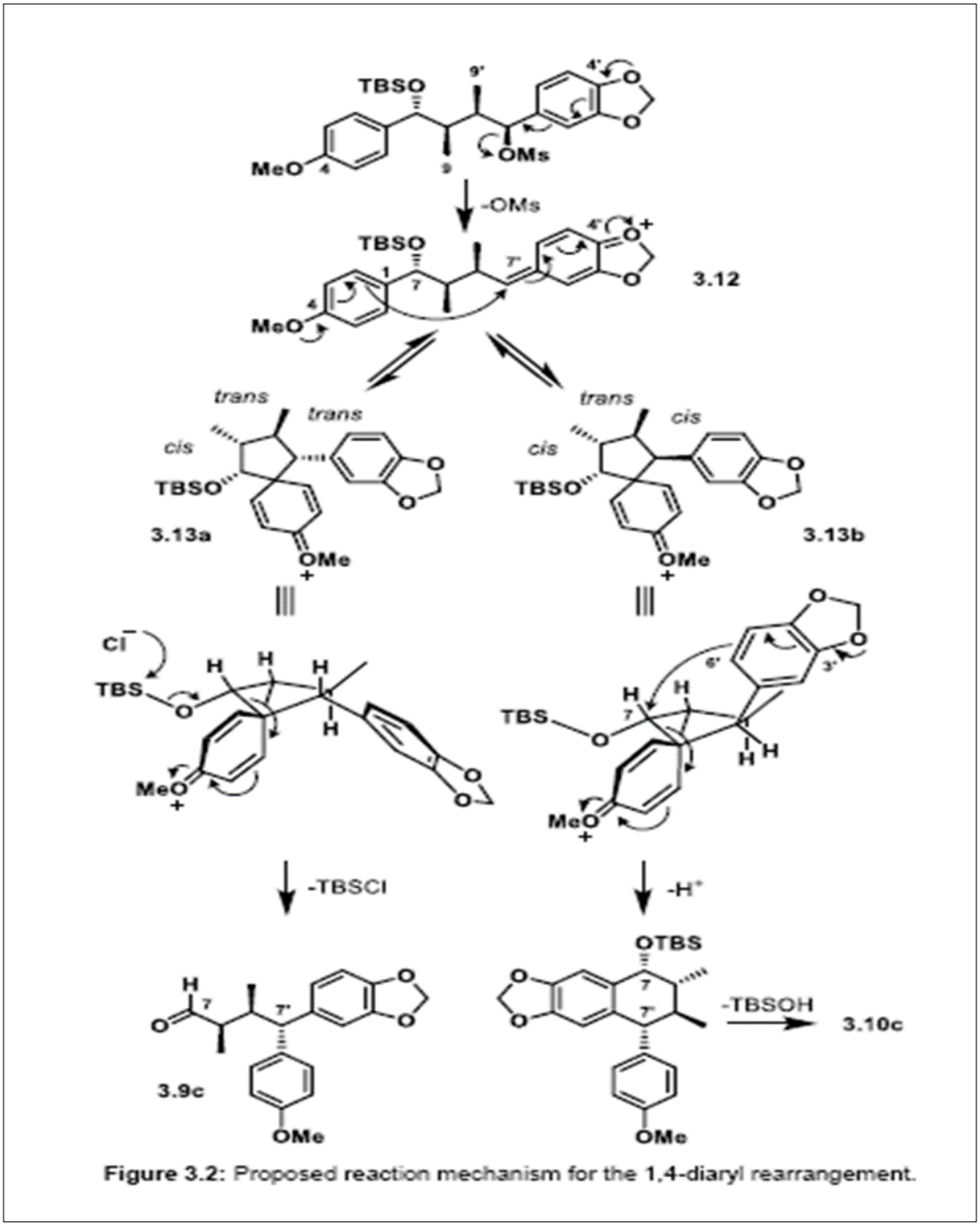

Figure 3.2: Proposed reaction mechanism for the 1,4-diaryl rearrangement.

Figure 7 Proposed reaction mechanism for the 1, 4- diaryl rearrangement

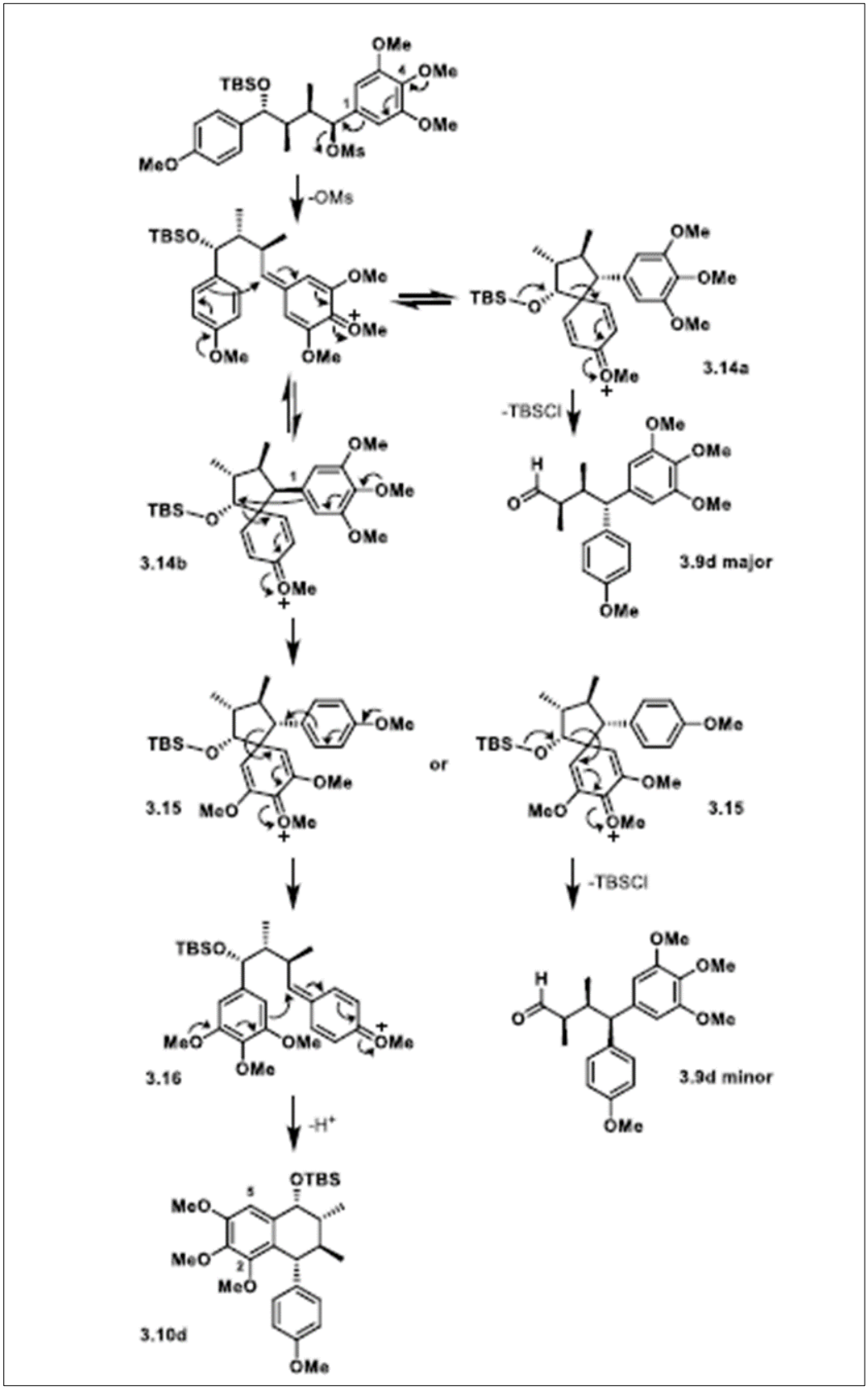

Figure 8 To account for this it is proposed that reaction of 3.8d initially forms diastereomeric 5-membered intermediates 3.14a and 3.14b

To account for this it is proposed that reaction of 3.8d initially forms diastereomeric 5-membered intermediates 3.14a and 3.14b. The cis-trans-trans intermediate 3.14a ring opens to form aldehyde 3.9d. However, the cis-trans-cis intermediate 3.14b does not form the tetralin but instead undergoes ipso-attack to form a second 5-membered intermediate 3.15. This intermediate being in the cis-tran trans configuration can then both ring open to either form the minor diastereomer of aldehyde 3.9d or quinone methide 3.16. From the quinonemethide, stereoselective attack from C-6 of the trimethoxybenzene ring onto C-7′ then gives the observed tetralin 3.10d with the correct geometry and accounts for the formation of diastereomeric aldehydes 3.9d. Aryl tetralin 3.10d was isolated as the TBS-ether, however previous reports have shown that some tetralins require stirring in mild acid or chloroform to give the unsaturated aryl tetralin.[126]

The reaction of butanol 3.8e does not form a tetralin product but instead forms THF 3.10e. This can be explained due to the lack of electron donating groups on the C-7′ phenyl ring. In this case the lack of an electron donating group at C-3′ does not allow formation of the tetralin product and competing THF formation becomes a favourable alternative.[127]

Previous seco-lignans have reported anti-proliferative activities against selected cell lines (e.g. Schisandra lignan 3.4 IC50 5.97 μM HL-60 cancer cell line).144 Aldehydes 3.9a–f were therefore reduced, using NaBH4 in methanol, giving 3.17a–f in moderate to good yields. Testing of 3.17a–f against the NCI-60 panel of human cancer cell lines showed considerably lower activity compared to that of Schisandra lignan 3.4. These results are consistent with the results of Wukirsari et al. who recently also showed that other 4,4-diaryl-butanols had low activity and that synthetic 3.4 was inactive.145 Our results combined with those of Wukirsari et al. has led to the conclusion that 4,4- diarylbutanols do not represent a cytotoxic scaffold.145

Scheme 3.4: Reagents and conditions: (a) NaBH4, MeOH, -78 °C, 24 h, Ar = 4-methoxyphenyl 3.17a (64%), 3,4-dimethoxyphenyl 3.17b (quant.), 3,4-methylenedioxyphenyl 3.17c (quant.), 3,4,5-trimethoxyphenyl 3.17d (70%), phenyl 3.17e (quant.), thienyl 3.17f (15%).

In summary, the rearrangement of 1,4-diarylbutane-1,4-diols has been investigated showing that the products formed are dependent on the substitution patterns of both aryl rings and can give rise to 4,4- diarylbutanals, aryl tetralins and THF moieties. All 4,4-diarylbutanals were reduced to give 4,4- diarylbutanols which contain the same structural motifs as some previously reported cytotoxic lignans and were tested for their anti-cancer activities.

The results and discussion section of a research report on the synthesis of lignans via the rearrangements of 1,4-diarylbutane-1,4-diols would typically include a detailed analysis of the experimental outcomes, characterization data, and the implications of the findings. Here's an example of what this section might look like:

3.5.1. Synthesis of 1,4-Diarylbutane-1,4-Diol

The synthesis of 1,4-diarylbutane-1,4-diol was achieved through a multistep synthetic route involving [describe key reactions and purification steps]. The final compound was obtained in [yield]

Claisen Rearrangement

The Claisen rearrangement of 1,4-diarylbutane-1,4-diol was successfully carried out using [selected conditions]. The desired rearrangement product, [product name], was obtained in [yield]

1,4-Diaryl Rearrangement

Subsequent to the Claisen rearrangement, the 1,4-diaryl rearrangement was explored to access various lignan structures. Initial investigations using [chosen reagents/catalysts] provided [product name] in [yield]

Purification and Characterization

The synthesized compounds were purified using [chromatographic method] to obtain analytically pure samples. Characterization by NMR spectroscopy confirmed the structures of the rearrangement products, with key peaks corresponding to the expected chemical shifts and coupling patterns. Additionally, mass spectrometry data supported the molecular weights of the compounds.

Biological Evaluation (Optional)

In collaboration with [biochemistry/pharmacology team], the synthesized lignan compounds were evaluated for their [specific biological activity or target]. Initial results indicate promising [activity/affinity] against [target], suggesting potential applications in [relevant field].

Data Analysis and Implications

The successful synthesis of diverse lignan structures via rearrangements of 1,4-diarylbutane-1,4-diols demonstrates the utility of this approach for accessing complex natural products. The optimized reaction conditions for the Claisen and 1,4-diaryl rearrangements provide efficient routes to various lignans with potential biological activities. The findings contribute to the development of new synthetic methodologies and expand the scope of lignan synthesis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Davin, L. B.; Wang, H.-B.; Crowell, A. L.; Bedgar, D. L.; Martin, D. M.; Sarkanen, S.; Lewis, N.G. Science 1997, 275 (5298), 362–367.

[2] Pickel, B.; Constantin, M.-A.; Pfannstiel, J.; Conrad, J.; Beifuss, U.; Schaller, A. Angew.Chem. Int. Ed. 2010, 49 (1), 202–204.

[3] von Heimendahl, C. B. I.; Schäfer, K. M.; Eklund, P.; Sjöholm, R.; Schmidt, T. J.; Fuss, E. Phytochemistry 2005, 66 (11), 1254–1263.

[4] Hemmati, S.; Heimendahl, C. B. I. von; Klaes, M.; Alfermann, A. W.; Schmidt, T. J.; Fuss, E. Planta Med. 2010, 76 (09), 928–934.

[5] Hemmati, S.; Schmidt, T. J.; Fuss, E. FEBS Lett. 2007, 581 (4), 603–610.

[6] D. Haworth, R.; Woodcock, D. J. Chem. Soc. Resumed 1939, 1054–1057.

[7] Pinto, M. M. M.; Kijjoa, A.; Mondranondra, I.; Gutiérrez, A. B.; Herz, W. Phytochemistry 1990, 29 (6), 1985–1988.

[8] Urones, J. G.; De Pascual Teresa, J.; Marcos, I. S.; Martín,D. D. Phytochemistry 1987,26 (5), 1540–1541.

[9] Briggs, L. H.; Cambie, R. C.; Hoare, J. L. Tetrahedron Lett. 1959, 1 (4), 14–15.

[10] D. Haworth, R.; Kelly, W. J. Chem. Soc. Resumed 1937, 1645–1649.

[11] D. Haworth, R.; Richardson, T. J. Chem. Soc. Resumed 1935, 633–636.

[12] Rahman, M. M. A.; Dewick, P. M.; Jackson, D. E.; Lucas, J. A. Phytochemistry 1990, 29 (6), 1971–1980.

[13] Kochetkov, N. K.; Khorlin, A.; Chizhov, O. S.; Sheichenko, V. I. Tetrahedron Lett. 1961, 2 (20), 730–734.

[14] Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H.; Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. Chem. Pharm. Bull. (Tokyo) 1979, 27 (6), 1383.

[15] Cho, J. Y.; Kim, A. R.; Park, M. H. Planta Med. 2001, 67 (04), 312–316.

[16] Cho, J. Y.; Park, J.; Yoo, E. S.; Yoshikawa, K.; Baik, K. U.; Lee, J.; Park, M. H. Arch. Pharm. Res. 1998, 21 (1), 12–16.

[17] Kuo, C.-C.; Chiang, W.; Liu, G.-P.; Chien, Y.-L.; Chang, J.-Y.; Lee, C.-K.; Lo, J.-M.; Huang, S.- L.; Shih, M.-C.; Kuo, Y.-H. J. Agric. Food Chem. 2002, 50 (21), 5850–5855.

[18] Kiso, Y. BioFactors 2004, 21 (1–4), 191–196.

[19] Chen, H.-H.; Chen, Y.-T.; Huang, Y.-W.; Tsai, H.-J.; Kuo, C.-C. Free Radic. Biol. Med. 2012, 52 (6), 1054–1066.

[20] Lee, J. S.; Kim, J.; Yu, Y. U.; Kim, Y. C. Arch. Pharm. Res. 2004, 27 (10), 1043–1047.

[21] Bussey, R. O.; Sy-Cordero, A. A.; Figueroa, M.; Carter, F. S.; Falkinham, J. O.; Oberlies, N. H.; Cech, N. B. Planta Med. 2014, 80 (6), 498–501.

[22] Nguyen, K. D. H.; Dang, P. H.; Nguyen, H. X.; Nguyen, M. T. T.; Awale, S.; Nguyen, N. T. Bioorg. Med. Chem. Lett. 2017, 27 (13), 2902–2906.

[23] Wang, K.-W.; Zhu, J.-R.; Shen, L.-Q. Nat. Prod. Res. 2013, 27 (6), 568–573.

[24] Wang, G. K.; Lin, B. B.; Rao, R.; Zhu, K.; Qin, X. Y.; Xie, G. Y.; Qin, M. J. Nat. Prod. Res. 2013, 27 (15), 1348–1352.

[25] Woo, K. W.; Suh, W. S.; Subedi, L.; Kim, S. Y.; Kim, A.; Lee, K. R. Bioorg. Med. Chem. Lett. 2016, 26 (3), 730–733.

[26] Pan, W.; Liu, K.; Guan, Y.; Tan, G. T.; Hung, N. V.; Cuong, N. M.; Soejarto, D. D.; Pezzuto, J. M.; Fong, H. H. S.; Zhang, H. J. Nat. Prod. 2014, 77 (3), 663–667.

[27] Xiao, X.; Ji, Z.; Zhang, J.; Shi, B.; Wei, S.; Wu, W. Chem. Nat. Compd 2013,49(1),21–23.

[28] Zhang, J.-W.; Hu, Z.; Gao, P.; Wang, J.-R.; Hu, Z.-N.; Wu, W.-J. Int. J. Mol. Sci. 2013, 14 (12), 24064–24073.

[29] Tan, Y. P.; Savchenko, A. I.; Broit, N.; Boyle, G. M.; Parsons, P. G.; Williams, C. M. Fitoterapia 2017.

[30] Li, J.-L.; Li, N.; Lee, H.-S.; Xing, S.-S.; Qi, S.-Z.; Tuo, Z.-D.; Zhang, L.; Li, B.-B.; Chen, J.-G.; Cui, L. Fitoterapia 2016, 109, 185–189.

[31] Albertson, A. K. F.; Lumb, J.-P. Angew. Chem. Int. Ed. 2015, 54 (7), 2204–2208.

[32] S. Lancefield, C.; J. Westwood, N. Green Chem. 2015, 17 (11), 4980–4990.

[33] DellaGreca, M.; R. Iesce, M.; Previtera, L.; Purcaro, R.; Rubino, M.; Zarrelli, A. Photochem. Photobiol. Sci. 2008, 7 (1), 28–32.

[34] Tran, F.; Lancefield, C. S.; Kamer, P. C. J.; Lebl, T.; Westwood, N. J. Green Chem. 2014, 17 (1), 244–249.

[35] Mori, N.; Furuta, A.; Watanabe, H. Tetrahedron 2016, 72 (51), 8393–8399.

[36] Inai, M.; Ishikawa, R.; Yoshida, N.; Shirakawa, N.; Akao, Y.; Kawabe, Y.; Asakawa, T.; Egi, M.; Hamashima, Y.; Kan, T. Synthesis 2015, 47 (22), 3513–3521.