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Towards the Total Synthesis of Peperomin D
Aproximació a la Síntesi Total de la Peperomina D

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L'èxit és la suma de petits esforços repetits dia rere dia.

Robert Collier

Dedicat a totes aquelles persones que m'han aconsellat, ajudat i format, tant a nivell professional com personal, per arribar a ser el que sóc avui; així com també ho dedico a aquella persona amb la qual he viscut tants bons moments durant aquests quatre anys. Remarcar amb especial èmfasis el suport incondicional que he rebut sempre dels meus pares, guies i exemple a seguir, als quals mai podré suficientment agrair tot el que han fet per mi.

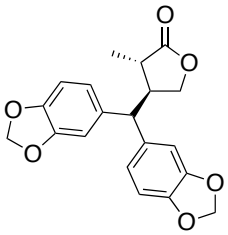
Per a vosaltres.

REPORT

CONTENTS

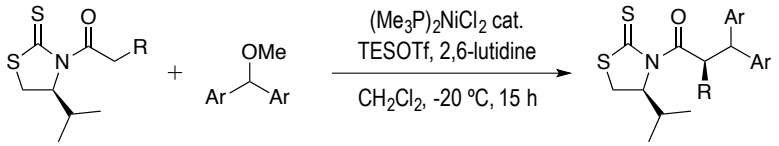
1. SUMMARY

Peperomins A – E are a class of novel and unusual type of secolignans with a common structure except for the different substituents of the aromatic rings. Extracted from different *Peperomia* type plants found in Taiwan, Venezuela or India, these molecules present a broad range of significant biological activities, from antitumor to anti-HIV, and therefore they are considered as potential chemotherapeutic agents. Thus, it is highly desirable any efficient synthesis of these natural compounds.



Peperomin D

From all types of peperomins, peperomin D has been described in the literature as the most complicated to synthesize. Therefore, it is an excellent target to challenge new synthetic methods. Keeping in mind this idea, the key step of our approach, and the major improvement compared to other syntheses, involves a catalytic nickel(II) reaction recently developed in our research group.

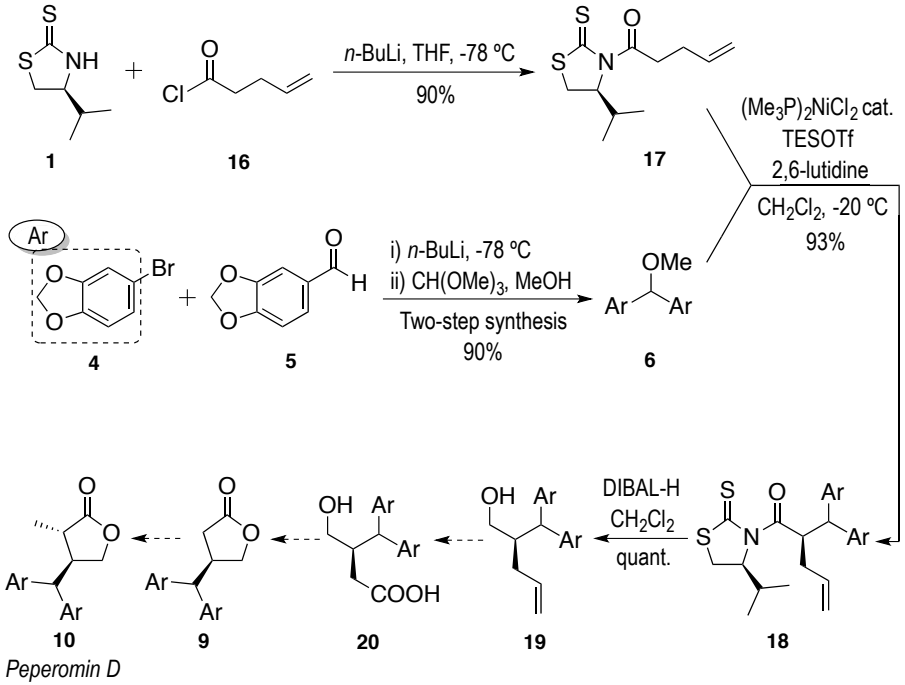


> 90%

Key reaction for the total synthesis of peperomin D

The strength of this reaction is the use of a nickel(II) complex, which is structurally simple, robust, and commercially available. The reaction is highly stereoselective and efficient, as only one of the two possible diastereomers is observed and isolated in excellent yields.

After some studies with an N-acyl thioimide containing an ester group, the removal of the chiral auxiliary turned out to be too difficult and, as a consequence, we were forced to modify our synthetic plan. Instead, a new approach based on the reaction of an N-acyl thioimide possessing a terminal olefin was assessed. Preliminary results have been promising.



Best synthetic approach to achieve peperomin D

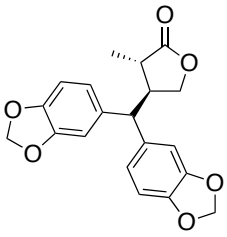
Double bonds are much more resistant to hydride reagents and thus DIBAL-H can be used to reduce the chiral auxiliary. The synthetic approach shown in the former scheme has provided alcohol **19** in an overall yield of 84% over 3 steps. Moreover, it was possible to avoid chromatographic purification of product **6**, as well as in the reaction of **18** to give **19**.

In order to complete the synthesis, further steps involving ozonolysis, cyclization and substrate-controlled α-methylation will be applied. By completing the synthesis with the most complicated peperomin among all of them, the synthetic pathway might also be applied to synthesize all other peperomins. Work is in process.

Keywords: peperomin D, total synthesis, stereoselective, catalytic, single diastereomer, nickel enolates.

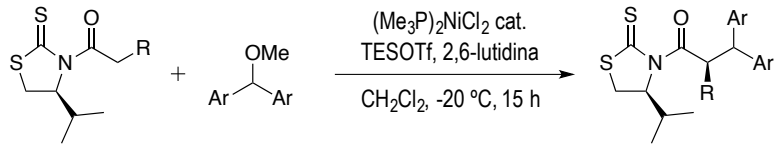
2. RESUM

Les peperomines A – E són una nova i inusual classe de secolignans. Posseeixen una estructura comuna, a excepció dels diferents substituents de l'anell aromàtic. Extretes de diferents plantes *Peperomia* de Taiwan, Veneçuela o la India, aquestes molècules presenten un gran ventall d'activitats biològiques, com són propietats antitumorals o contra el VIH. Com a conseqüència, estan considerades com a agents quimioterapèutics potencials i es desitjable trobar una ruta sintètica eficient per a obtindré aquests productes naturals.



Peperomin D

De tots els tipus de peperomines, la peperomina D esta descrita a la literatura com la més complicada de sintetitzar. Per aquest motiu aquesta molècula és un objectiu sintètic excel·lent per a encarar nous mètodes sintètics. Tenint en compte aquesta idea, el pas clau del nostre enfocament, i la principal millora respecte altres síntesis, implica una reacció catalítica de níquel(II) recentment desenvolupada al nostre grup de recerca.

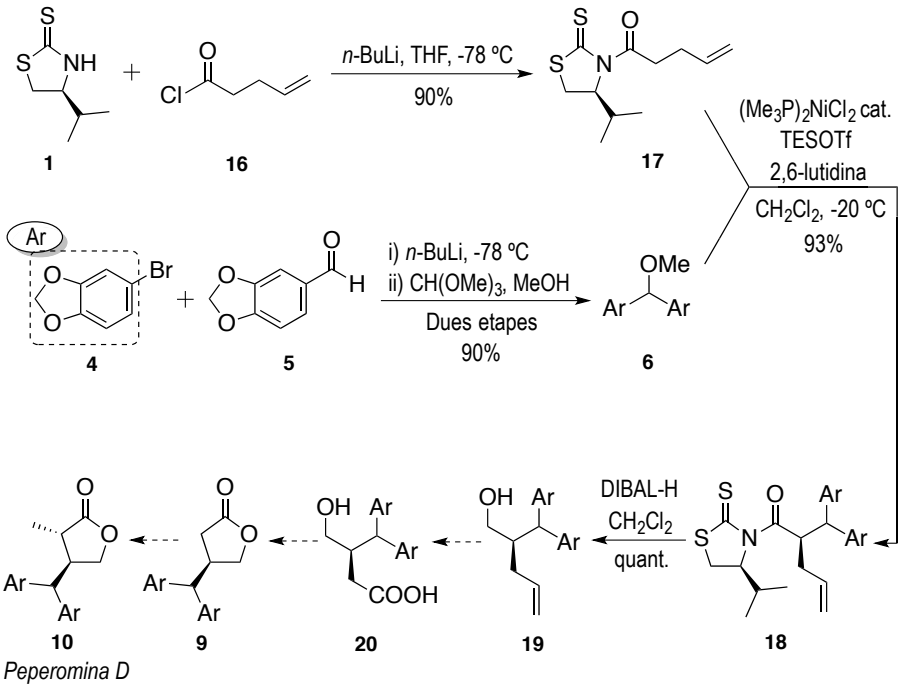


> 90%

Reacció clau en la síntesi total de la peperomina D

El punt fort d'aquesta reacció es l'ús d'un complex de níquel(II) estructuralment simple, robust, i comercialment disponible. La reacció és altament estereoselectiva i eficient, ja que només un dels dos possibles diastereomers es observat i aïllat amb rendiments excel·lents.

Després d'alguns estudis amb una N-acil tioimida contenint un grup ester, la eliminació de l'auxiliar quiral va resultar ser massa difícil i, com a conseqüència, vam estar obligats a modificar la ruta sintètica. Un nou enfocament basat en la reacció d'una N-acil tioimida amb una olefina terminal va ser estudiat. Els resultats obtinguts són prometedors.



Millor enfocament sintètic per arribar a la peperomina D

Els dobles enllaços són molt més resistents als hidrurs i, per tant, DIBAL-H pot ser utilitzat per a reduir l'auxiliar quiral. La síntesi proposada anteriorment ha proporcionat l'alcohol **19** amb un rendiment global del 84% després de 3 etapes de reacció. A més a més, ha estat possible evitar l'ús de columnes cromatogràfiques durant l'obtenció del producte **6**, així com en la reacció del compost **18** per donar **19**.

Per a completar la síntesi seran portades a terme noves etapes d'ozonòlisis, ciclació i α-metilació per control de substrat. Al completar la síntesi amb la peperomina més complicada de totes, la ruta sintètica podria ser aplicada per a la síntesis de tota la resta de peperomines. El treball està en curs.

Paraules clau: peperomina D, síntesi total, estereoselectiu, catalític, únic diastereomer, enolats de níquel.

3. INTRODUCTION

Natural products have played a central role in the development of the field of organic chemistry by providing challenging synthetic targets. Special attention is paid to natural products that exhibit pharmacological or biological activity, which could be potentially used for therapeutic benefit in treating diseases.

This present work is focused on secolignans, a novel and unusual class of lignans. Among all the secolignans discovered to date, peperomins A – E are the best-known representatives. As seen in Figure 1, all these compounds contain a common pharmacophore, with little differences on the aromatic ring substituents.

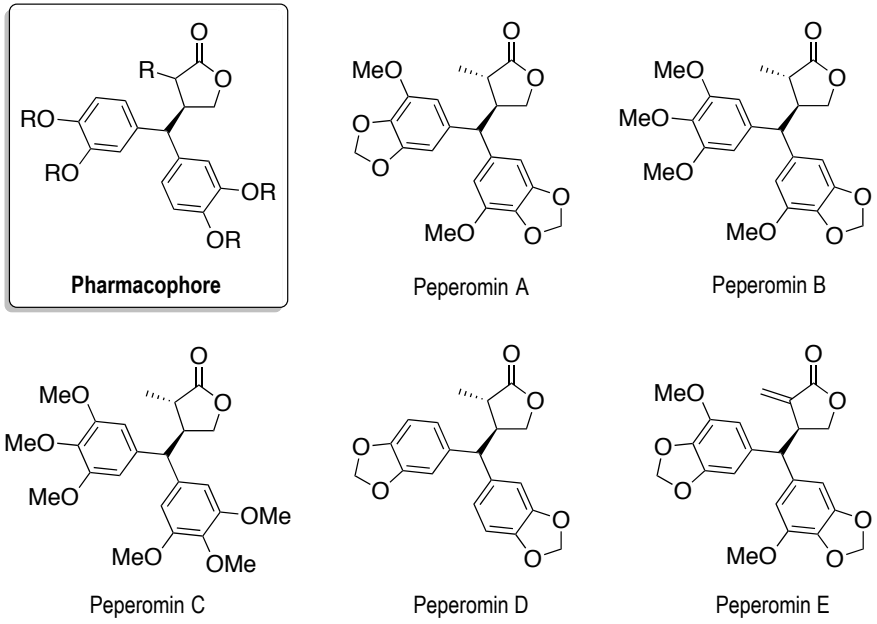


Figure 1: Most representative peperomin-type compounds

Peperomin-type metabolites were first isolated in 1989 by Chen et al. from *Peperomia japonica makino*, a perennial herb growing on wet rocks and trees at low altitudes of up to 1500 m in Taiwan.[1] In purpose of studying the Formosan antitumor plants, fully characterization and absolute configuration of peperomin A, B and C were performed. Another type of secolignan, peperomin D, was isolated a few years later, in 1996, by Monache et al. from *Peperomia glabella*, an epiphyte plant from Venezuela.[2] Finally, peperomin E was isolated in 1998 from *Peperomia dindigulensis* in India.[3]

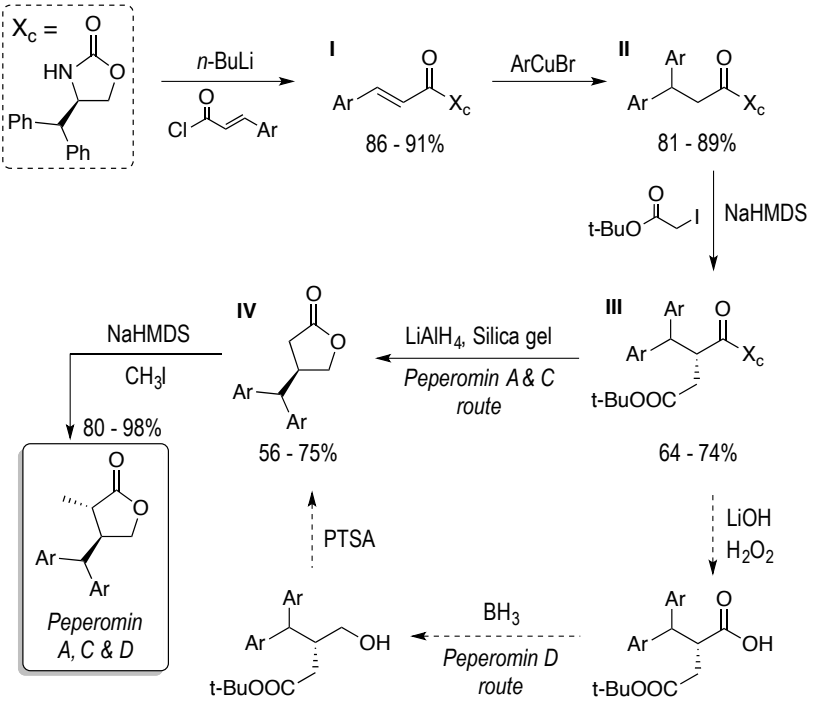
Figure 2: Peperomia glabella in Osaka, Japan

Kenpei, 30/01/11 via Wikimedia Commons, Creative Commons Attribution

It is well known that aqueous and alcoholic infusions of the whole herbs are used in Chinese folk medicine for the treatment of malignant tumours. Furthermore, they are used as an antiasthmatic remedy in Venezuelan folk medicine. These compounds have structural features that are present in combretastatins[4] and podophyllotoxins[5]. In view of the high tubulin inhibitory activity of both, the evaluation of the biological activity of peperomins and their analogs could be important. In fact, peperomins have shown in different studies a broad range of potent biological activities, from antitumor[6] to anti-HIV[7]. As a result, these types of secolignans have received considerable attention as potential chemotherapeutic agents.[8]

Due to their broad range of biological activities and therapeutic potential, the development of a stereoselective approach that would allow a practical synthesis of naturally occurring secolignans and their derivatives is highly desirable. In spite of this, only a few syntheses have been reported yet.[9-11]

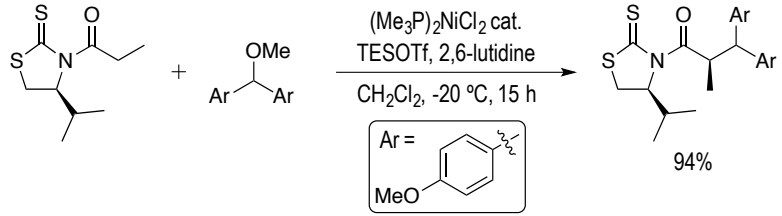
Since the first total synthesis of a racemic mixture of peperomin C by Cruz-Almanza et al.,[9] the best enantioselective synthesis so far has been reported by Sibi et al., which achieves an overall yield of 28% for both peperomin A and C, involving 5 synthetic steps (see Scheme 1). Unexpectedly, peperomin D seems to be much more complicated to synthesize and the synthetic approach is slightly different, involving 7 steps and an overall yield of 27%.[10]



Scheme 1: Synthetic pathway by Sibi et al.[10]

With this present synthesis in mind, this project is focused on the development of a more efficient synthesis applying a recent methodology developed in our research group (see Scheme 2),[12] ideal for the synthesis of these aromatic molecules.

The methodology developed is based on the catalytic formation of a nickel(II) enolate, which performs an attack to the electrophile *sp3* carbon between the aromatic groups, previously activated to the carbenium cation with TESOTf. Altogether, such a reaction leads to the formation of a new carbon-carbon bond with a complete stereocontrol. The product is obtained in excellent yields and as a single diastereomer.



Scheme 2: C-C bond formation via enolate S_N1 alkylation

The outcome of the reaction relies on the substituents of the aromatic rings, as only electrophiles with electronically rich aromatic rings react (see Figure 3). This information suggests that an S_N1 type alkylation takes place, as only aromatic rings with electron donor groups provide stable carbenium intermediates due to its multiple resonance forms.

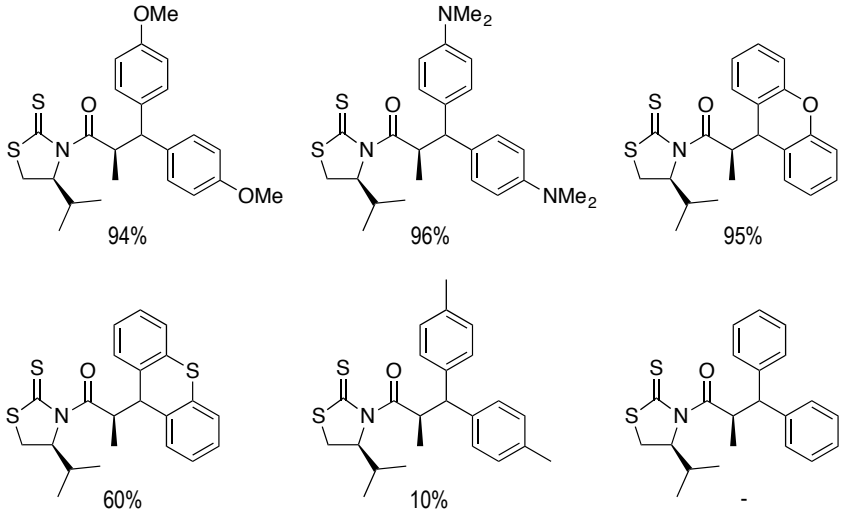


Figure 3: Outcome of the reaction depending on the aromatic substituents

While the reaction is strongly dependent of the aromatic substituents, the alkylation was not affected by the steric hindrance of the side chain (see Figure 4) and a lot of different groups, including ester, double bonds, or even heteroatoms at the α-position can be used without loss of yield.

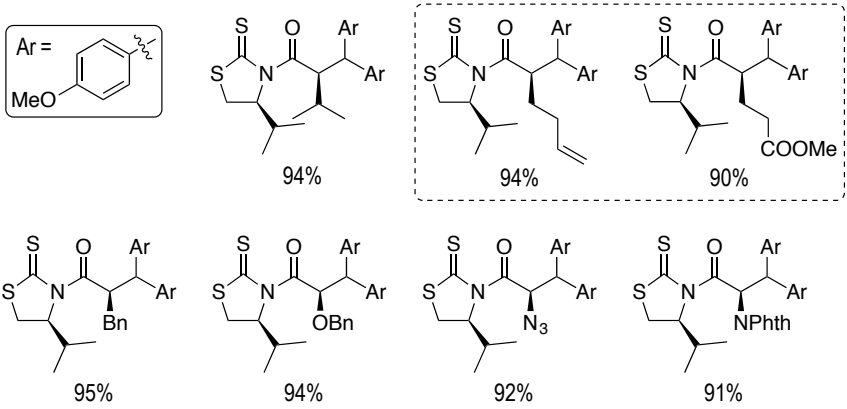


Figure 4: Outcome of the reaction depending on the side chain

For all these reasons, such natural products were targeted as potential candidates for this type of synthesis, due to the multiple electron donor groups bound to the aromatic rings (hyphened box indicates the side chains involved in our synthetic pathway). Thanks to this, an easier and more efficient approach is envisaged to achieve a compound similar to product III of Scheme 1. Afterwards, a comprehensive study of reduction conditions could provide a successful pathway to remove the chiral auxiliary, and therefore lead to the formation of the lactone.

As our method builds the pharmacophore structure, the proposed synthetic pathway in section 5 and 6 could be easily applied to the total synthesis of all peperomin-type molecules displayed in Figure 1. In terms of complexity, peperomin D has been chosen to demonstrate the high efficiency of this synthesis, as it has the largest room for improvement compared to previous synthesis.

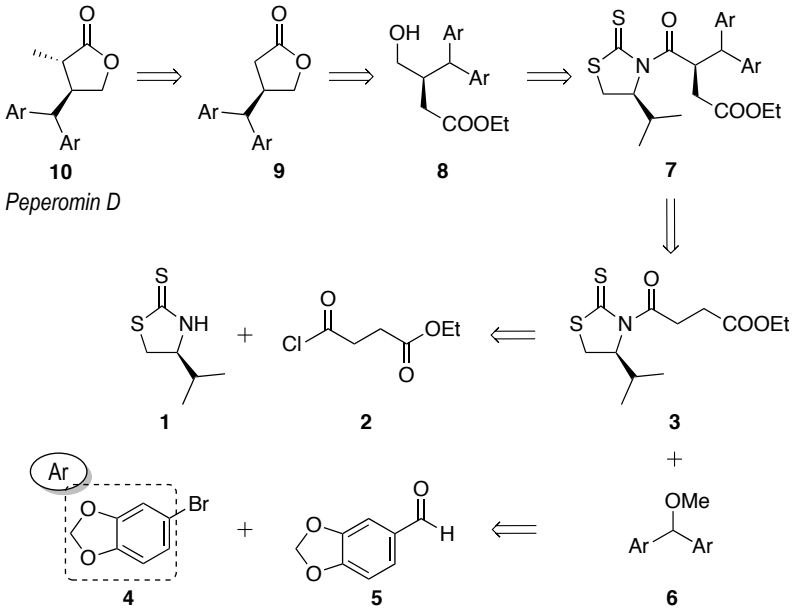
4. OBJECTIVES

The main objective of the present project is the synthesis of peperomin D. The synthetic approach can be divided into minor objectives, as follows:

- Synthesis and subsequent acylation of the thiazolidinethione chiral auxiliary.
- Synthesis of the electrophile via an organolithium compound to form a benzylic alcohol, followed by the conversion to a methyl ether.
- Study of the nickel(II) catalytic reaction already developed in our research group to form stereoselectively the desired C-C bond.
- Removal of the chiral auxiliary via reductive conditions.
- Final steps, involving cyclization and α-carbon methylation.

Another objective, inherent to this study, is the spectroscopic characterization of the synthesized products.

5. TOWARDS THE TOTAL SYNTHESIS OF PEPEROMIN D FIRST APPROACH



Scheme 3: Retrosynthetic analysis of peperomin D. First approach

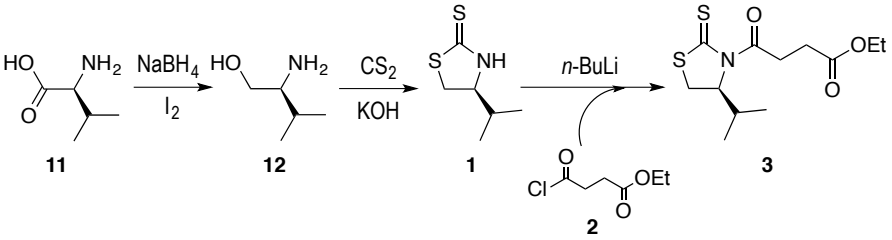
The proposed retrosynthetic analysis to obtain peperomin D is represented in Scheme 3. It was planned to use the chiral thiazolidinethione auxiliary **1**, after an acylation with the acid chloride **2**. The key step of the sequence involves the direct reaction of **3** and methyl ether **6**, catalyzed by a nickel(II) complex. The configuration of the new stereocenter is completely controlled due to the presence of the isopropyl group on the thiazolidinethione, which provides the single diastereomer **7**.

After the catalytic reaction, removal of the auxiliary should be possible using reductive conditions to give an alcohol, and the resultant γ–hidroxy ester **8** should spontaneously produce the desired lactone. A final reaction to insert the methyl group into the α-carbon of the carbonyl would be conducted. Due to substrate control, stereocontrol of such an alkylation would not be a major problem due to the bulky substituent at the β-position.[10]

5.1. SYNTHESIS AND ACYLATION OF THE CHIRAL AUXILIARY

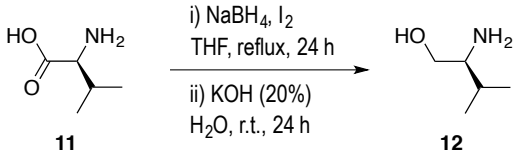
In order to control the stereochemical outcome of a synthesis, chiral auxiliaries have been widely used in all types of synthetic pathways. This chemical unit is temporarily incorporated into a prochiral substrate, and then, after the desired reaction, can be easily removed from it. Chiral thiazolidinethiones present considerable advantages because the removal can be done using a wide range of reaction conditions, which give access to a variety of functional groups and facilitate the use of this type of chiral auxiliaries. Moreover, the chiral auxiliary can be easily recovered for re-use.

For the total synthesis peperomin D, the thiazolidinethione derived from the natural amino acid L-valine **11** has been used (Scheme 4).



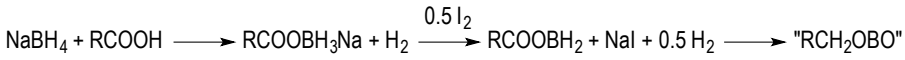
Scheme 4: Synthesis and acylation of the chiral auxiliary

The first reaction of this three-step synthesis is the reduction of the carboxylic acid to the alcohol.



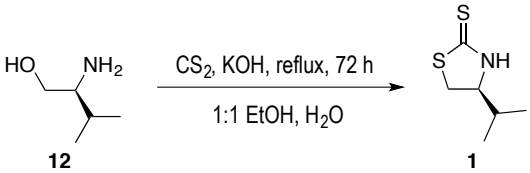
Scheme 5: First step of the chiral auxiliary synthesis

Carboxylic acids can be reduced with $NaBH_4/I_2$, as it is a safe and chemoselective method, easy to scale up and with the main advantage of not epimerising the α–carbon. The reduction takes advantage of the reductive species $RCOOBH_2$ produced *in situ* with sodium borohydride activated with iodine (Scheme 6). This intermediate is much less reactive and subsequent more selective than others, for instance, $BH_3 \cdot THF$. Since this method was first described, it has been widely used for the reduction of α–amino acids.[13]



Scheme 6: Chemical pathway for carboxylic acid reductions

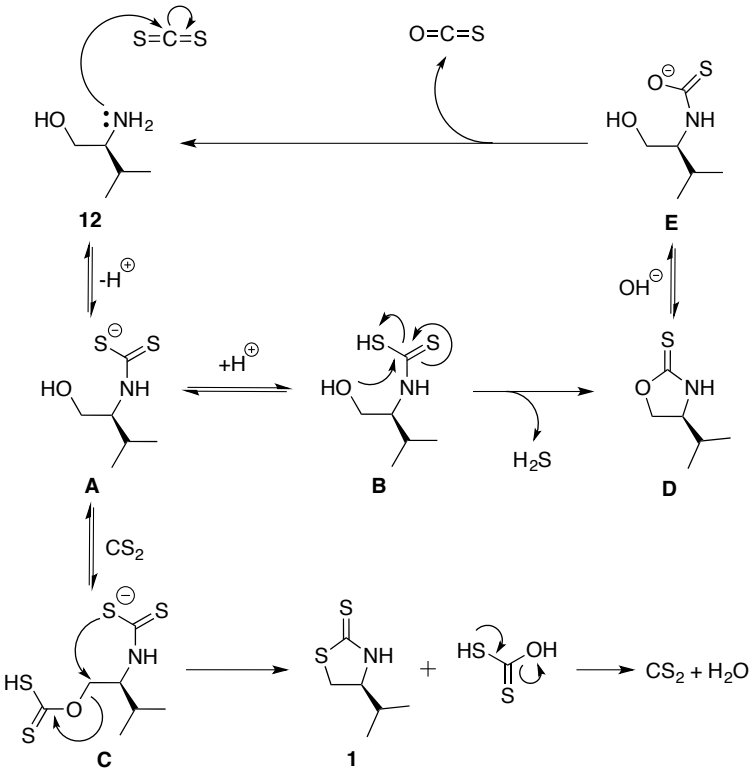
In the second step, the thiazolidinethione **1** was obtained using a process first described by Le Corre.[14] This method requires a long reflux reaction of L-valinol (**12)** in the presence of CS_2 in excess and a strong basic solution generated with KOH.



Scheme 7: Second step of the chiral auxiliary synthesis

These conditions are well known. If CS_2 is employed under stoichiometrical conditions, or weaker bases are used, like Et_3N, the main product achieved is an oxazolidinethione (D). The amino group is more nucleophilic than the alcohol and it attacks the carbon disulfide first to form intermediate A. Then, the alcohol group performs another nucleophilic attack to the same carbon disulfide (intermediate B) or to a new one (intermediate C). Depending on this, the resulting product will be an oxazolidinethione (D) or a thiazolidinethione **1** (see Scheme 8).

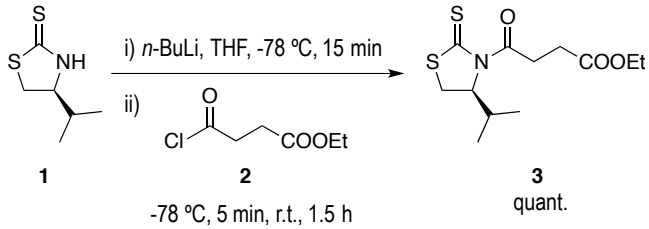
To achieve the quantitative formation of **1**, a strong basic solution is needed. These conditions favour the ring opening of D, without affecting our desired product. After the ring opening, equilibrium is achieved to recover L-valinol (**12)**. Thiazolidinethione is the most stable product, and the spontaneous decomposition of the carbonodithioic O,S-acid shifts the equilibrium towards **1**.



Scheme 8: Mechanism of the heterocycle formation

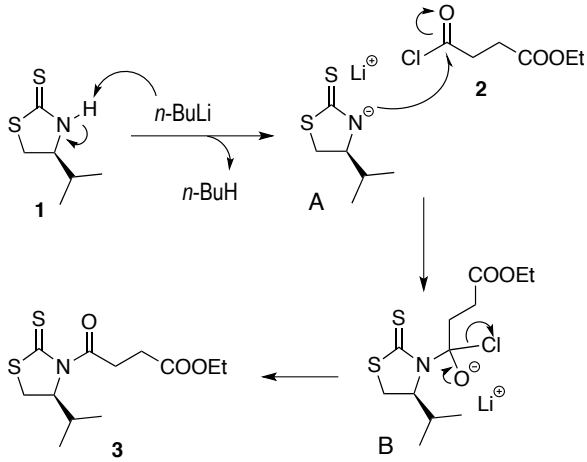
Over the two steps explained before, thiazolidinethione **1** was obtained with 63% yield. The reaction was performed in a considerably large scale of 43 mmol, which demonstrates the robustness of the method.

The final step is an acylation reaction. A strong base, in this case *n*-butyllithium, is used to deprotonate the nitrogen of the thiazolidinethione, which reacts with the acid chloride **2** to give **3** (Scheme 9). *n*-Butyllithium is very useful to remove weakly acid hydrogens due to its extremely basic pKa, but also for its ease and clean reaction. Indeed, the protonation of *n*-butyllithium produces butane, which, as a gas, is easily removed. The reaction was performed at a 6 mmol scale, presenting a quantitative yield as a result.



Scheme 9: Chiral auxiliary acylation

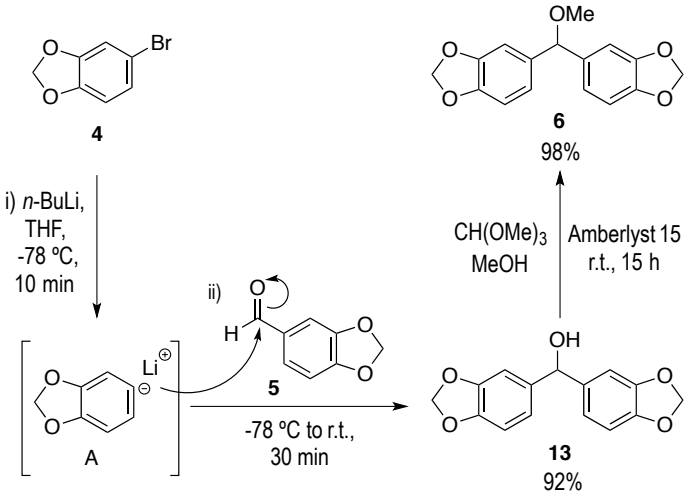
As shown below, deprotonation of the chiral auxiliary produces a highly nucleophilic species (A) that is easily acylated with the commercially available acid chloride. After the attack to the carbonyl, the reaction occurs via a tetrahedral intermediate (B), which quickly collapses expelling the chlorine atom (Scheme 10).



Scheme 10: The acylation mechanism

5.2. SYNTHESIS OF THE ELECTROPHILE

As previously found in our research group, to perform efficiently the nickel(II) catalytic reaction, the electrophile must be a methyl ether group instead of an alcohol. For this reason, formation of the electrophile involves a two-step synthesis.



Scheme 11: Synthesis of the electrophile

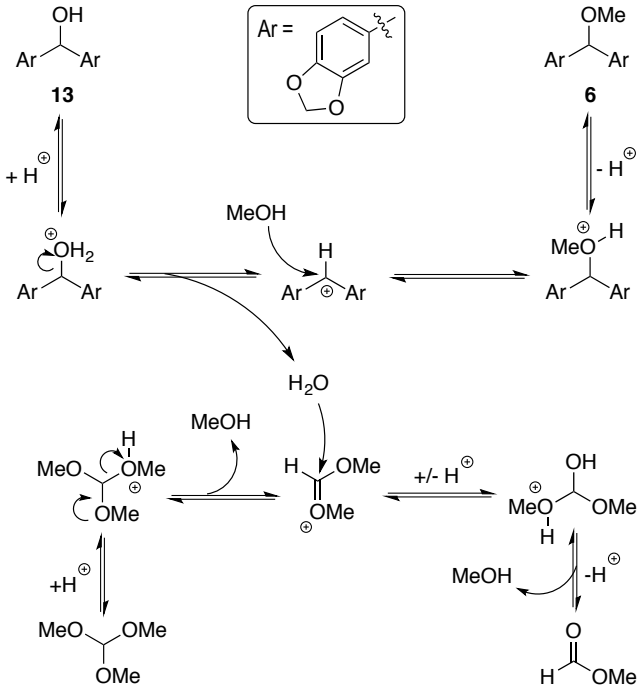
Compound **13** was obtained following a procedure described by Diederich et al.[15] Aryl bromide can be easily metalated by treatment of aryl bromide **4** with *n*-BuLi, and the resultant nucleophilic intermediate (A) attacks the carbonyl of piperonal (**5**) to afford the dibenzylic alcohol **13**. After running some ^{1}H-NMR experiments, it was clearly established that the alcohol was not stable in air, reacting up to 65% in less than 4 days.

Some experiments proved that the alcohol was stable only under a nitrogen atmosphere. It was clear to us that the presence of oxygen or water caused the degradation. Alcohol **13** was stored under N_2 atmosphere and, to provide safer conditions, it was also kept in the freezer at -20 ºC. Once the reaction was fully controlled, it was possible to obtain a 92% yield of alcohol **13** without a column chromatography.

Compared to the alcohol, the methyl ether **6** is much more stable in air, although it is also kept under a nitrogen atmosphere and in the freezer. **6** was not purified by column chromatography and it was used directly in the next reaction, due to the high purity obtained.

Even so, column chromatography should be avoided due to the ease of degrading the ether bond.

A plausible mechanism to explain the formation of the methyl ether is proposed in Scheme 12. The sulfonic group of the Amberlyst structure is essential to catalyse the reaction acting as acid catalyst. Once the alcohol from the aromatic molecule is protonated, water is replaced via an S_N1 or reaction by methanol, which is employed as the solvent of the reaction. All these reactions are equilibria, which can be displaced to quantitative conversion because of the presence of trimethyl orthoformate. This reagent captures the water released from the ether formation and gives inert methyl formate.

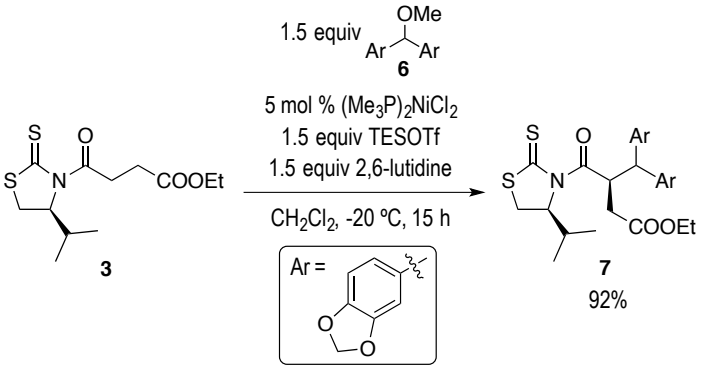


Scheme 12: Proposed mechanism of the methyl ether formation

5.3. STEREOSELECTIVE ALKYLATION CATALYZED BY NI(II)

The stereocontrolled construction of C-C bonds is one of the main goals of organic synthesis. As explained in the Introduction, our approach hinges on an alkylation reaction recently developed by our group,[12] based on the catalytic formation of a nickel(II) enolate. One of the main points in favour of this method is that the nickel(II) complex used is structurally simple, robust, and commercially available.

As expected, the stereoselective catalytic reaction proceeded in high yields to afford the desired product as a single diastereomer. Moreover, the reaction is proved to be robust and consistent, as it was performed at a significant 3 mmol (1.6 g) scale with a 92% yield (Scheme 13).

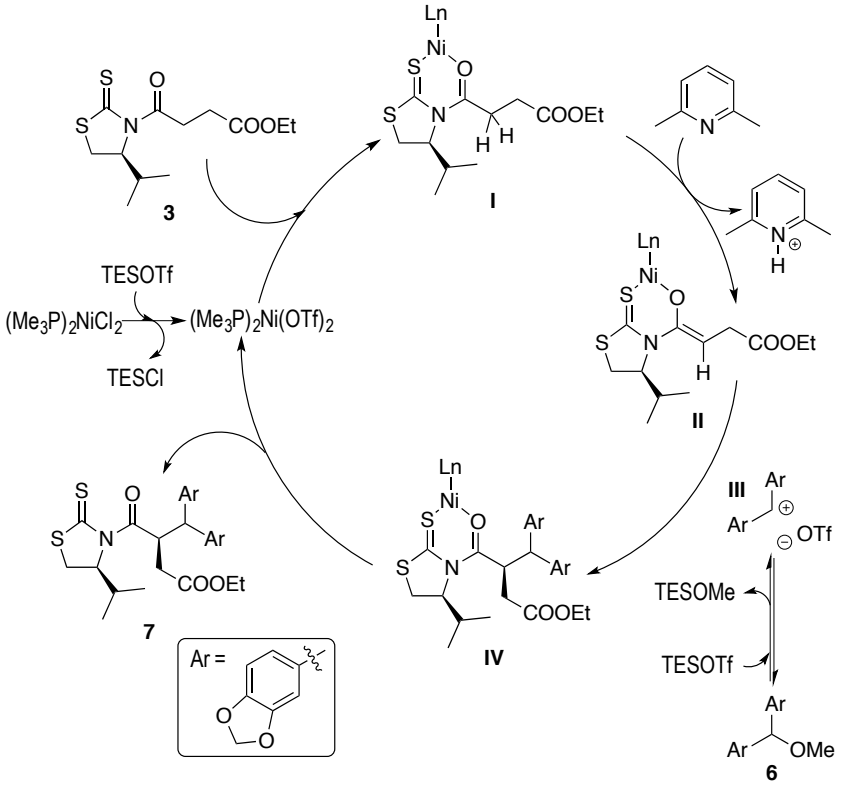


Scheme 13: Stereoselective alkylation catalyzed by Ni(II)

A plausible catalytic cycle for the above alkylation is outlined in Scheme 14. Since Sodeoka uncovered the formation of nickel(II) triflate complexes by treatment of the corresponding nickel(II) chlorides with TESOTf,[16] $(Me_3P)_2Ni(OTf)_2$ is believed to be the true catalyst of the alkylation reaction. Thus, addition of this complex to **3** gives rise to complex I, which can be deprotonated by 2,6-lutidine to produce chelated Z enolate II.

The crucial step in the overall cycle involves the production of the carbenium III. In the same reaction mixture, the activation of the previously synthesized electrophile **6** with TESOTf triggers the formation of the carbenium intermediate III. Once species II and III are formed, the isopropyl group of the chiral auxiliary forces the approach of III from the *Re* face of the enolate, and an S_N1-type reaction takes place, leading to the formation of a new carbon-carbon bond with a

complete stereocontrol in complex IV. Finally, product dissociation regenerates the catalyst, while achieving the pure diastereomer **7**.

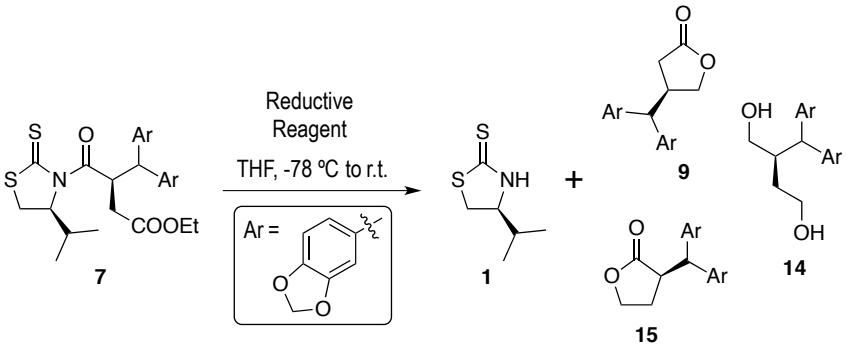


Scheme 14: Plausible mechanism for the stereocontrolled catalytic alkylation

5.4. REMOVAL OF THE CHIRAL AUXILIARY

Once product **7** is obtained after the stereoselective alkylation, the chiral auxiliary has to be removed. Removal of the chiral auxiliary can be done in different ways, such as substitution or reduction. Reduction and substitution were performed before in our research group with very similar substrates, affording excellent yields.[12] In our case, a reduction could afford the desired alcohol.

As anticipated, this reaction turned to be the most complicated step of the synthesis, due to the potential reduction of the ester group. Furthermore, the bulky substituents around hinder the desired chemoselective reduction. Different conditions were studied, which have been summarized in Table 1:



Entry	Reductive Reagent	Equiv.	Time	Conv. [%]	Yield [%] 9	Yield [%] 14	Yield [%] 15
1	$LiBH_4$	1	2 h	32	12	-	-
2	$LiBH_4$	1	5 h	41	9	-	-
3	$LiBH_4$	2	5 h	55	17	35	-
4	$LiBH_4$	1	17 h	80	15	28	-
5	$NaBH_4$	7	24 h	87	15	13	-
6	DIBAL-H	1	20 min	100	-	-	19

(a) All conversions and entries 2 & 3 yields are given from ^{1}H-NMR analysis
(b) 1, 4, 5 & 6 yield are given after chromatographic purification
(c) All reactions were performed in a scale of 0.1 or 0.2 mmol
(d) CH_2Cl_2 was used instead of THF as solvent for the DIBAL-H reaction

Table 1: Testing conditions for the reduction reaction

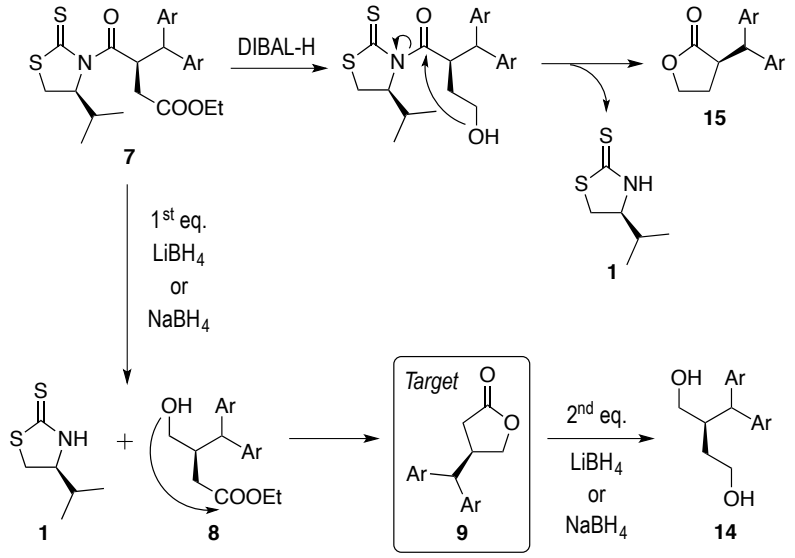
The analysis of the results summarized in Table 1 suggests some general trends. On the one hand, as the starting material is really bulky, a long reaction time was needed to afford a considerable conversion of **7** (compare entries 1-4 in Table 1). Surprisingly, the potential γ-hydroxy ester **8** was never isolated, which indicates that the five-membered lactone **9** is formed easily.

In order to know if the lactone was being formed directly in the reaction mixture, or in the subsequent work up, a sample of the $LiBH_4$ reaction mixture was extracted and was analysed by ^{1}H-NMR. Unexpectedly, lactone signals were easily recognised, which indicates that cyclization was indeed produced in the reaction mixture. Unfortunately, advantageous conditions to generate the lactone in high yields were not found, due to the formation of the diol over time.

After all these tests with $LiBH_4$, a softer reducing reagent such as $NaBH_4$ was next assessed. The ester group should be much more stable to this new reducing agent and therefore better results were expected. After a 24 h reaction, a high conversion was achieved, although after a column chromatography, little amount of the lactone was isolated (see entry 5 in Table 1). Even worse was the isolation of a significant 13% of the diol **14**, which proves that the ester group can be also reduced with $NaBH_4$ at long time reactions.

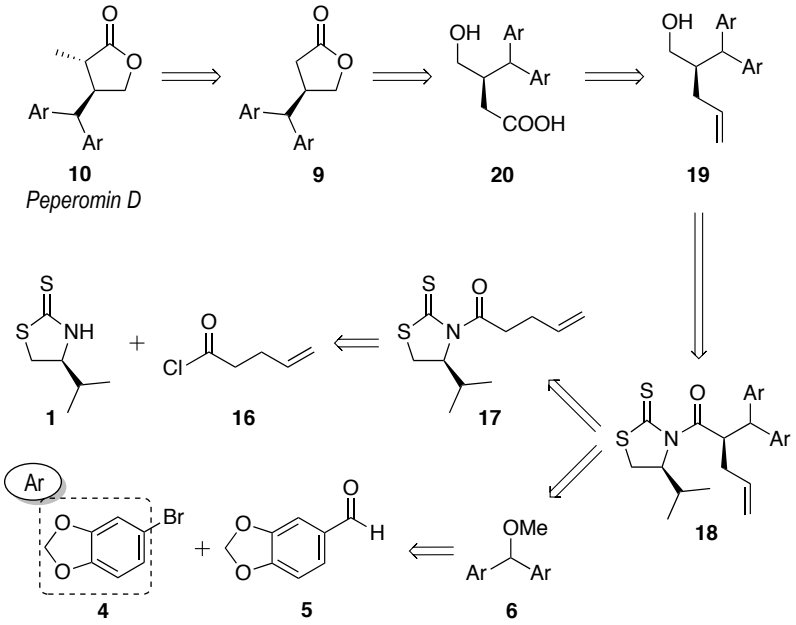
One last reaction was proposed using a much more powerful reducing reagent. DIBAL-H is much more reactive than boron hydrides, although it is sterically hindered. This fact is easily demonstrated in entry 6, where it was achieved a total conversion in only 20 minutes. Even though there was a total conversion of **7**, no evidence of formation of our desired lactone **9** was observed. Instead of the chiral auxiliary, the ester group was completely reduced for being more accessible. The resulting alcohol attacks the only carbonyl of the molecule left, giving the non-desired lactone **15**, while releasing the chiral auxiliary (see Scheme 15). Other intermediates where isolated after a column chromatography without the ester group but containing the chiral auxiliary still bonded.

To sum up, two general trends were observed depending of what reduction takes place first: reduction of the chiral auxiliary or the ester group. Considering the lack of chemoselectivity and the low yield of the required lactone, we were forced to modify the initial plan.



Scheme 15: Reduction trends depending on the reductive reagent

6. TOWARDS THE TOTAL SYNTHESIS OF PEPEROMIN D SECOND APPROACH

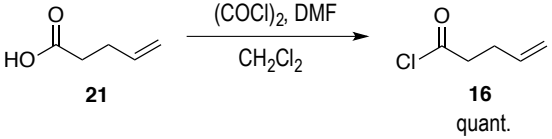


Scheme 16: Retrosynthetic analysis of peperomin D. Second approach

Due to the problems found in the removal of the chiral auxiliary, we envisaged that the replacement of the ester group by an olefin could override the lack of chemoselectivity in the removal of the thiazolidinethione. Thus, it was planned to adapt the original plan to a different acyl group containing a terminal olefin. Once the chiral auxiliary was removed, an oxidative ozonolysis applied to the double bond would generate a carboxylic acid, and the subsequent cyclization would be promoted to form the desired lactone. As in the original synthetic route, final methylation in the α-carbon by substrate control would provide peperomin D.

6.1. ACYLATION OF THE CHIRAL AUXILIARY

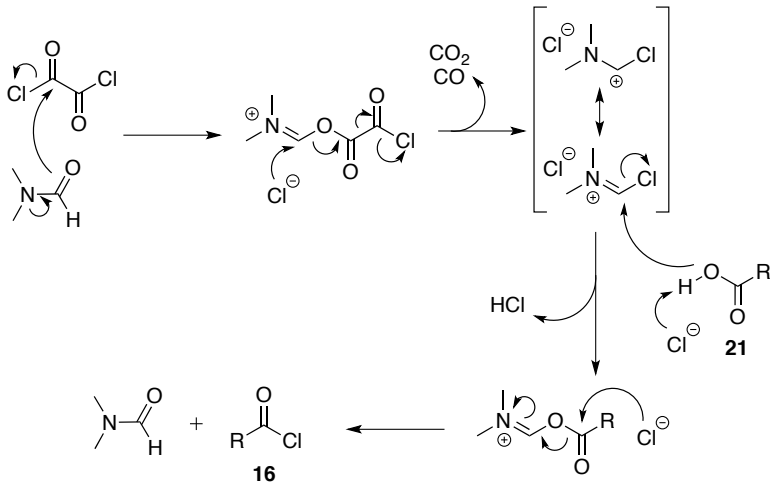
In section 5.1 the acylation of the chiral auxiliary was performed with an inexpensive and commercially available acid chloride. In this case, the desired acid chloride **16** was prepared from the carboxylic acid, using oxalyl chloride and DMF as a catalyst.



Scheme 17: Synthesis of the acid chloride

Oxalyl chloride is very useful to prepare acid chlorides because all by-products of the reaction are volatile, and the desired product can be easily and pure isolated in a high yield. Furthermore, the end of the reaction can be easily monitored because no more bubbles are released from the reaction mixture. Once the reaction is completed, all solvents and volatile compounds are eliminated *in vacuo* with a rotary evaporator.

Scheme 18 provides a detailed mechanism of the conversion of the carboxylic acid into the acid chloride. As can be seen, DMF acts as a catalyst, forming an intermediate, which can be attacked by the carboxylic acid more easily.



Scheme 18: Mechanism of the acid chloride formation, catalyzed by DMF

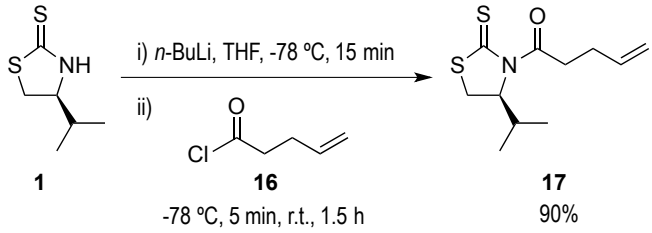
Initially, the reaction was not reproducible and important losses of material were observed. Apart from rotary evaporation, no further treatment of the reaction mixture was carried out. Thus, the high amount of lost material could only be explained due to the volatility of the resultant acid chloride. To verify our hypothesis, the pressure of the pump was measured at 40 mm Hg and an estimation of the boiling point in that vacuum could be established.

Compound	Boiling Point at 760 mm Hg (ºC)	Expected Boiling Point at 40 mm Hg (ºC)
Carboxylic Acid (**21**)	189	101
DMF	153	65
Acid Chloride (**16**)	130	44
Oxalyl Chloride	63	< 0
CH_2Cl_2	40	< 0

Table 2: Summary of compounds' boiling point at different pressure

With all these new information in hand, the evaporation of the volatiles was carefully controlled. The water bath was kept at 0 ºC and the mixture reaction was only left for 20 minutes instead of 1.5 h. With all these changes, it was finally achieved a quantitative yield. Once all the procedure was well established, a 10 mmol scale reaction was performed also achieving quantitative yields.

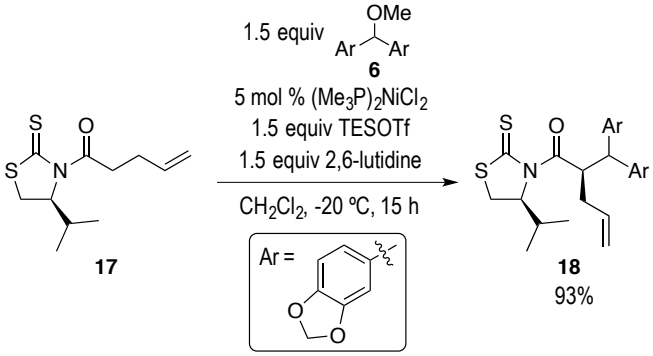
Once the acid chloride was formed, it was immediately used in an acylation reaction as explained in section 5.1. As well as in the acylation of the chain with the ester group, this acylation also exhibited an excellent yield at a 6 mmol scale.



Scheme 19: Acylation of the chiral auxiliary

6.2. STEREOSELECTIVE ALKYLATION CATALYZED BY NI(II)

The electrophile **6** (section 5.2) was used without any changes, and therefore the catalytic reaction with nickel(II) was performed as previously. The reaction was carried out at a significant scale of 3.5 mmol (1.7 g) and, once again, a single diastereomer was obtained in an excellent 93% yield.



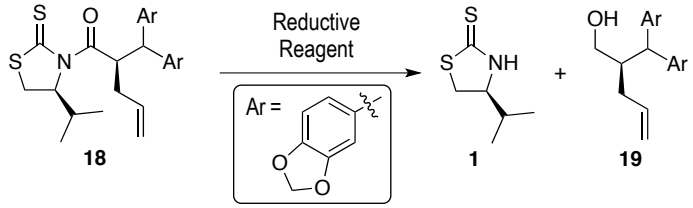
Scheme 20: Stereoselective alkylation catalyzed by Ni(II)

6.3. REMOVAL OF THE CHIRAL AUXILIARY

Due to the unsuccessful reduction reaction obtained with **7**, a new study was launched to find suitable conditions to remove the chiral auxiliary from **18** efficiently. Now, the double bond allows the use of stronger reducing reagents, while increasing the scope of potential reaction conditions.

After unsuccessful reactions with $NaBH_4$ and $LiBH_4$, DIBAL-H turned out to be an efficient reagent (see Table 3). With only 20 minutes the desired alcohol could be obtained quantitatively. A simple wash with 2 M NaOH was enough to separate the thiazolidinethione from alcohol **19**, resulting in a pure product. Therefore it was not necessary to perform a column chromatography. Acidification of the basic aqueous phase and subsequent extraction with an organic solvent could retrieve the free chiral auxiliary for re-use.

DIBAL-H reaction was repeated again at a 1 mmol scale. Alcohol **19** was also isolated in quantitative yield and for the chiral auxiliary **1** was obtained a recovery of 98%.



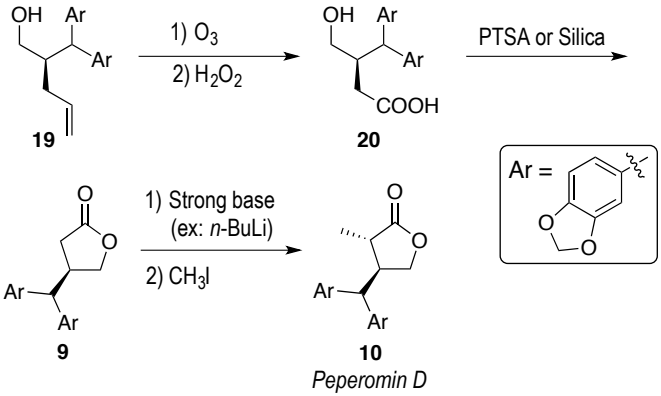
Entry	Reductive Reagent	Solvent	Equiv.	Time	Conv. [%]	Yield [%] 19
1	$NaBH_4$	THF : H_2O (98:2)	5	20 h	45	< 5
2	$LiBH_4$	THF anh.	2	24 h	76	16
3	DIBAL-H	CH_2Cl_2	2.2	20 min	100	quant.

(a) All reactions were performed in a scale of 0.15 - 0.2 mmol
(b) All conversions and yields are given from ^{1}H-NMR analysis, except yield from entry 2, given after chromatographic purification

Table 3: Testing conditions for the reduction reaction

6.4. FUTURE REACTIONS

The alkylation and the removal of the chiral auxiliary have been proved to work successfully. Oxidative ozonolysis of the olefin followed by spontaneous cyclization of the resultant γ-hydroxyacid **20** should provide the desired lactone **9**. Finally, α-carbon methylation by substrate control should allow us to complete the enantioselective synthesis of peperomin D.



Scheme 21: Proposed future reactions

7. EXPERIMENTAL SECTION

7.1. MATERIALS AND METHODS

Unless otherwise specified, reactions were conducted in oven-dried glassware under inert atmosphere of nitrogen with anhydrous solvents. The solvents and reagents were dried and purified when necessary according to standard procedures.[17] Dichloromethane from Scharlab, in synthesis grade quality, was distilled before use. All commercial reagents were obtained from registered suppliers and used without further purification.

Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F254 plates and analysed by UV (254 nm) and stained with phosphomolybdic acid or *p*-anisaldehyde. The eluent used is specified in each case.

Column chromatographies were carried out under low pressure (*flash*) conditions and performed on Aldrich silica gel, pore size 60 Å (40 – 63 μm).

Melting points (mp) were determined with a Bibby Stuart Scientific SMP10.

Specific rotations ($[\alpha]_D$) were determined at 20 ºC on a Perkin-Elmer 241 MC polarimeter. They were measured on $CHCl_3$ and the wavelength used was the D line of sodium (589 nm).

IR spectra were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer using ATR technique. Only the more representative frequencies (ν) are reported.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer. Chemical shifts (δ) are reported in ppm and referenced to internal TMS (δ 0.00 for ^{1}H NMR) or (δ 77.0 for ^{13}C NMR). Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, oct = octet, m = multiplet, br = broad (and their corresponding combinations); when necessary, 2D techniques (COSY, HSQC) were also used to assist on structure elucidation.

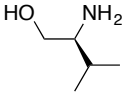
Mass spectra were obtained with an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

7.2. TOWARDS THE TOTAL SYNTHESIS OF PEPEROMIN D. FIRST APPROACH

7.2.1. Synthesis of *(S)*-Valinol (12)

L-Valine (5.0 g, 42.7 mmol) and $NaBH_4$ (3.9 g, 102.6 mmol) were purged with N_2 and dissolved afterwards in THF (100 mL). A solution of I_2 (10.8 g, 42.7 mmol) in THF (50 mL) was added dropwise while the reaction was stirring at 0 ºC and was heated at reflux for 24 h.

The day after, the mixture was cooled to r.t. and MeOH was added until no more bubbles of H_2 were released. Solvent was removed *in vacuo* and a solution of KOH 20% (80 mL, 16.5 g) was added. The mixture was stirred at r.t. for another 24 h. The aqueous solution was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give 4.1 g of L-valinol (**12**), which was used in the following step without purification.



12

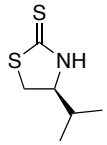
Colorless Oil; $\mathbf{R_f}$ = 0.05 (CH_2Cl_2); $\mathbf{[\alpha]_D}$= +21.9 (c 2.0, $CHCl_3$); **IR** (film): 3400 br, 2980, 1580, 1485, 1465, 1390, 1370 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.64 (1H, dd, *J* = 10.6, 4.0 Hz CH_aH_bOH), 3.28 (1H, dd, *J* = 10.6, 8.6 Hz, CH_aH_bOH), 2.55 (1H, ddd, *J* = 8.6, 6.5, 4.0 Hz, NCH), 2.05 (3H, br s, OH, NH_2), 1.56 (1H, oct, *J* = 6.5 Hz, $CH(CH_3)_2$), 0.93 (3H, d, *J* = 6.5 Hz, $CH(CH_3)_a(CH_3)_b$), 0.92 (3H, d, *J* = 6.6 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 64.9, 58.8, 31.5, 19.8, 18.8.

7.2.2. Synthesis of *(S)*-4-isopropyl-1,3-thiazolidine-2-thione (1)

Carbon disulfide (6.3 mL, 103.8 mmol) was added to a solution of *(S)*-valinol (**12**) (4.1 g, prepared in section 7.2.1.) in EtOH (15 mL) under N_2. To the yellow mixture, a solution of 1.75 M of KOH (6.1 g, 107.8 mmol) in 1:1 EtOH:H_2O (50 mL) was added dropwise at r.t. over 20 min, turning the solution red. The reaction mixture was stirred and heated at reflux for 72 h.

After cooling, volatiles were removed and the resulting residue was acidified with 0.5 M HCl (200 mL), which produced the formation of a yellow solid. The suspension was washed with

CH_2Cl_2 (3 x 50 mL), and the combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the resulting oil was purified by flash column chromatography on silica gel (CH_2Cl_2) to give 4.3 g of **1** (26.7 mmol, 63% yield over 2 steps).



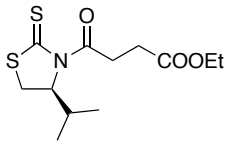
1

White Solid; **mp** = 69 - 70 ºC; [lit.[18] **mp** = 68 – 69 ºC]; $\mathbf{R_f}$ = 0.28 (hexanes/EtOAc 8:2); **[α]D**= -35.5 (c 1.00, $CHCl_3$) [lit.[19] **[α]D** = -34.9 (c 1.10, $CHCl_3$); **IR** (ATR): 3150, 2954, 1490, 1383, 1277, 1027, 974, 663 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.99 (1H, br s, NH), 4.06 (1H, td, *J* = 8.3, 6.8 Hz, NCH), 3.51 (1H, dd, *J* = 11.1, 8.3 Hz, SCH_aH_b), 3.33 (1H, dd, *J* = 11.1, 8.3 Hz, SCH_aH_b), 1.91 − 2.06 (1H, oct, *J* = 6.8 Hz, $CH(CH_3)_2$), 1.04 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 1.01 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 201.2, 70.1, 36.0, 32.1, 18.9, 18.3; **HRMS** (+ESI): m/z calculated for $[M+H]^+$ $C_6H_{12}NS_2$: 162.0406, found: 162.0402.

7.2.3. Synthesis of *(S)*-N-(4-ethoxy-4-oxobutanoyl)-4-isopropyl-1,3-thiazolidine-2-thione (3)

A 1.6 M solution of *n*-BuLi in hexanes (4.1 mL, 6.6 mmol) was added dropwise to a solution of the thiazolidinethione **1** (0.97 g, 6.0 mmol) in THF (1.6 mL) at −78 ºC under N_2. The reaction mixture was stirred for 15 min and ethyl 4-chloro-4-oxobutanoate (**2**) (1.1 mL, 7.8 mmol) was carefully added. The resulting clear solution was stirred for 30 min at −78 ºC and 2 h at r.t.

The reaction mixture was cooled to 0 ºC and quenched with sat NH_4Cl (2.4 mL) and water (6 mL). This mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were washed with 0.5 M NaOH (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The resultant oil was purified by flash column chromatography on silica gel (CH_2Cl_2) to afford 1.7 g (6.0 mmol, quant. yield) of the thioimide **3** as a yellow oil.



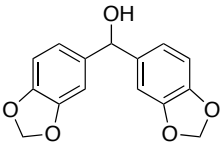
3

Yellow Oil; $\mathbf{R_f}$ = 0.44 (hexanes/EtOAc 8:2); **[α]D**= +255.0 (c 1.0, $CHCl_3$); **IR** (ATR) 2959, 1731, 1686, 1357, 1254, 1148, 1090, 1023, 845 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.15 (1H, ddd, *J* = 8.0, 6.2, 1,1 Hz, NCH), 4.15 (2H, q, *J* = 7.2 Hz, $COOCH_2CH_3$), 3.61 (1H, ddd, J= 18.5, 6.8, 5.1 Hz, $NCOCH_aH_b$), 3.54 (1H, dd, *J* = 11.4, 8.0 Hz, SCH_aH_b), 3.48 (1H, ddd, *J* = 18.5, 8.1, 5.2 Hz, $NCOCH_aH_b$), 3.02 (1H, dd, *J* = 11.4, 1.1 Hz, SCH_aH_b), 2.71 (1H, ddd, *J* = 17.0, 8.1, 5.1 Hz, $NCOCH_2CH_aH_b$), 2.62 (1H, ddd, *J* = 17.0, 6.8, 5.2 Hz, $NCOCH_2H_aH_b$), 2.42 − 2.30 (1H, m, $CH(CH_3)_2$), 1.26 (3H, t, *J* = 7.2 Hz, $COOCH_2CH_3$), 1.06 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.97 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.8, 172.7, 172.4, 71.7, 60.6, 33.9, 30.8, 30.5, 29.1, 19.0, 17.7, 14.2; **HRMS** (+ESI): m/z calculated for $[M+Na]^+$ $C_{12}H_{19}NO_3S_2Na$: 312.0699, found: 312.0697.

7.2.4. Synthesis of di(3,4-methylenedioxyphenyl)methanol (13)

1-bromo-3,4-(methylenedioxy)benzene (**4**) (2.0 g, 10 mmol) was dissolved in THF (15 mL) under N_2 and cooled to −78 ºC. A 2.33 M solution (verified by titration) of *n*-BuLi in hexanes (4.5 mL, 10.5 mmol) was added dropwise. After 10 min, piperonal (**5**) (1.5 g, 10 mmol) was dissolved in THF (4 mL) and added dropwise.

After 30 min, 1 mL MeOH was added at r.t. and solvents were removed *in vacuo*. The resulting solid was dissolved in CH_2Cl_2 and washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*, to afford 2.6 g of alcohol **13** (9.4 mmol, 92% yield).

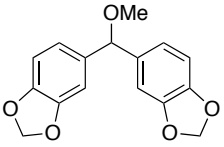


13

White Solid; **mp**[14] = 82 − 85ºC; $\mathbf{R_f}$ = 0.60 (hexanes/EtOAc 6:4); **IR**[14] ($CHCl_3$): 3601, 3023, 2892, 1504, 1487, 1443, 1243, 1041, 934 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.86 − 6.82 (4H, m, ArH), 6.78 − 6.74 (2H, m, ArH), 5.94 − 5.92 (4H, m, OCH_2O), 5.68 (1H, s, $CH(Ar)_2$), 2.10 (1H, s, OH); **^{13}C NMR**[14] ($CDCl_3$, 100.6 MHz) δ 147.8, 147.0, 138.0, 119.8, 108.1, 107.0, 101.1, 75.8.

7.2.5. Synthesis of di(3,4-methylenedioxyphenyl)methyl methyl ether (6)

Product **13** (2.5 g, 9.4 mmol) and Amberlyst® 15 in catalytic amount were purged under N_2. Trimethyl orthoformate (3.8 mL, 35 mmol) and methanol (2.4 mL, 58 mmol) were added and the resultant mixture was stirred for 15 h. The reaction mixture was filtered and the solvents were removed *in vacuo* to give 2.6 g (9.2 mmol, 98% yield) of methyl ether **6**.



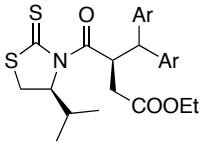
6

Orange Solid; **mp** = 46 – 50 ºC; $\mathbf{R_f}$ = 0.67 (hexanes/EtOAc 8:2); **IR** (ATR): 2892, 2813, 1686, 1603, 1483, 1432, 1230, 1090, 1027, 922, 777 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.82 – 6.78 (4H, m, ArH), 6.75 – 6.74 (2H, m, ArH), 5.92 – 5.90 (4H, m, OCH_2O), 5.06 (1H, s, $CH(Ar)_2$), 3.34 (3H, s, OCH_3); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 147.8, 146.9, 136.2, 120.3, 108.0, 107.2, 101.0, 84.8, 56.8; **HRMS** (+ESI): m/z calculated for $[M\text{-}OMe]^+$ $C_{15}H_{11}O_4$: 255.0652, found: 255.0654.

7.2.6. Synthesis of *(S)*-N-[*(R)*-2-(2-ethoxy-2-oxoethyl)-3,3-di(3,4-methylenedioxyphenyl) propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (7)

Solid $(Me_3P)_2NiCl_2$ (14.1 mg, 50 µmol) was added to a solution of thioimide **3** (289 mg, 1.0 mmol) and diaryl methyl ether **6** (429 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to −20 ºC. TESOTf (339 µmL, 1.5 mmol) and 2,6-lutidine (174 µmL, 1.5 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at −20 ºC for 15 h.

The reaction was quenched with sat. NH_4Cl (2.4 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography on silica gel (hexanes/EtOAc 8:2) to afford 505 mg (0.93 mmol, 92% yield) of the corresponding alkylated product **7**.



7

Yellow Solid; **mp** = 69 – 70 ºC; $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 8:2); **[α]**$_D$= +183.1 (c 1.0, $CHCl_3$); **IR** (ATR) 2959, 2879, 1722, 1682, 1481, 1437, 1357, 1237, 1148, 1028, 921 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.00 (1H, d, *J* = 1.7 Hz, ArH), 6.91 (1H, dd, *J* = 8.0, 1.7 Hz, ArH), 6.83 (1H, d, *J* = 1.7 Hz, ArH), 6.80 (1H, dd, *J* = 8.0, 1.7 Hz, ArH), 6.73 (1H, d, *J* = 8.0 Hz, ArH), 6.64 (1H, d, *J* = 8.0 Hz, ArH), 6.43 (1H, ddd, *J* = 11.0, 10.1, 4.1 Hz, NCOCH), 5.92 – 5.89 (2H, m, OCH_2O), 5.84 (2H, s, OCH_2O), 5.23 (1H, ddd, *J* = 8.4, 5.4, 1.0 Hz, NCH), 4.10 (1H, d, *J* = 11.0 Hz, $CH(Ar)_2$), 4.05 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 3.43 (1H, dd, *J* = 11.4, 8.4 Hz, SCH_aH_b), 2.84 (1H, dd, *J* = 11.4 Hz, 1.0 Hz, SCH_aH_b), 2.60 (1H, dd, *J* = 15.5, 10.1 Hz, $NCOCHCH_aH_b$), 2.47 (1H, dd, *J* = 15.5, 4.1 Hz, $NCOCHCH_aH_b$), 1.82 – 1.69 (1H, m, $CH(CH_3)_2$), 1.22 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 0.76 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.68 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 204.1, 174.7, 171.2, 148.0, 147.5, 146.5, 146.2, 135.9, 135.7, 121.7, 121.3, 109.1, 108.5, 108.3, 108.0, 101.0, 100.8, 71.8, 60.9, 55.3, 42.2, 37.9, 30.8, 28.8, 18.7, 17.1, 14.1; **HRMS** (+ESI): m/z calculated for $[M+Na]^+$ $C_{27}H_{29}NO_7S_2Na$: 566.1278, found: 566.1270.

7.2.7. Reduction of 7

7.2.7.1. Reduction with $LiBH_4$

Compound **7** (109 mg, 0.2 mmol) was purged with N_2, dissolved in THF (1 mL) and then cooled to −78 ºC. A 2 M solution of $LiBH_4$ in THF (100 µL, 0.2 mmol) was added dropwise. The reaction mixture was stirred for 30 min at −78 ºC and then 17 h at r.t.

The reaction mixture was quenched with sat. NH_4Cl (2 mL). After 30 min, the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was washed with 0.5 M NaOH, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/EtOAc from 9:1 to EtOAc) to afford 12 mg (0.03 mmol, 15% yield) of lactone **9** and 19 mg (0.06 mmol, 28% yield) of diol **14**.

7.2.7.2. Reduction with $NaBH_4$

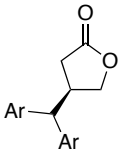
Compound **7** (109 mg, 0.2 mmol) and $NaBH_4$ (52 mg, 1.4 mmol) were purged with N_2, cooled to −78 ºC, and dissolved in THF (1 mL). The reaction mixture was stirred for 30 min at −78 ºC and then 24 h at r.t.

The reaction mixture was quenched with sat. NH_4Cl (2 mL). After 30 min, the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was washed with brine (30 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc from 7:3 to EtOAc) to afford 10 mg (0.03 mmol, 15% yield) of lactone **9** and 9 mg (0.03 mmol, 13% yield) of diol **14**.

7.2.7.3. Reduction with DIBAL-H

A solution of **7** (100 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was cooled to −78 ºC and a 1 M solution of DIBAL-H in toluene (184 µmL, 0.18 mmol) was added dropwise. The reaction mixture was stirred for 5 min at −78 ºC and then 20 min at r.t.

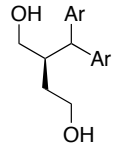
The reaction mixture was first quenched with MeOH (0.5 mL) and then a 1 M solution of sodium potassium tartrate was added (2 mL). After 1 h, the aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL) and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel (hexanes/EtOAc from 9:1 to EtOAc) to afford 12 mg (0.04 mmol, 19% yield) of lactone **15**.



9

(R)-4-[di(3,4-methylenedioxyphenyl)methyl]butyrolactone

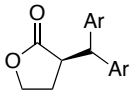
White solid; **mp**[10] = 66 − 67 ºC; $\mathbf{R_f}$[10] = 0.44 (hexanes/EtOAc 1:1); $\mathbf{[\alpha]_D}^{10}$ = -4.3 (c 1.0, CH_2Cl_2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.76 − 6.67 (6H, m, ArH), 5.93 − 5.91 (4H, m, OCH_2O), 4.28 (1H, dd, *J* = 9.5, 7.3 Hz, OCH_aH_b), 3.96 (1H, dd, *J* = 9.5, 6.9 Hz, OCH_aH_b), 3.65 (1H, d, *J* = 11.7 Hz, $CH(Ar)_2$), 3.33 – 3.22 (1H, m, $CHCH(Ar)_2$), 2.58 (1H, dd, *J* = 17.8, 8.4 Hz, $COCH_aH_b$), 2.25 (1H, dd, *J* = 17.8, 7.8 Hz, $COCH_aH_b$); **^{13}C NMR**[10] ($CDCl_3$, 100.6 MHz) δ 176.7, 148.2, 146.7, 146.6, 136.4, 135.9, 128.4, 120.6, 120.5, 108.6, 107.7, 101.2, 72.2, 54.8, 40.0, 34.1, 31.1; **HRMS** (+ESI): m/z calculated for $[M+Na]^+$ $C_{19}H_{16}O_6Na$: 363.0839, found: 363.0837.



14

(R)-2-[di(3,4-methylenedioxyphenyl)methyl]-1,4-butanediol

Brown Oil; $\mathbf{R_f}$ = 0.45 (EtOAc); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.79 − 6.68 (6H, m, ArH), 5.91 − 5.87 (4H, m, OCH_2O), 3.73 (1H, ddd, *J* = 11.0, 7.4, 3.7 Hz, $HOCH_aH_bCH_2$), 3.70 (1H, d, *J* = 11.6 Hz, $CH(Ar)_2$), 3.66 (1H, dd, *J* = 11.0, 3.0 Hz, $HOCH_aH_bCH$), 3.61 (1H, ddd, *J* = 11.0, 7.2, 4.0 Hz, $HOCH_aH_bCH_2$), 3.44 (1H, dd, *J* = 11.0, 6.0 Hz, $HOCH_aH_bCH$), 2.82 (2H, br s, OH), 2.40 (1H, dddt, *J* = 11.6, 8.9, 6.0, 3.0 Hz, $CHCH(Ar)_2$), 1.75 – 1.66 (1H, m, $HOCH_2CH_aH_b$), 1.58 (1H, dddd, *J* = 11.4, 8.3, 7.4, 4.0, $HOCH_2CH_aH_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 147.9, 146.0, 145.9, 137.7, 137.6, 121.0, 120.7, 108.4, 108.3, 108.0, 107.8, 100.9, 63.9, 61.0, 53.0, 42.7, 33.6; **HRMS** (+ESI): m/z calculated for $[M+Na]^+$ $C_{19}H_{20}O_6Na$: 367.1152, found: 367.1157.



15

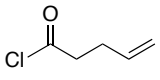
(R)-3-[di(3,4-methylenedioxyphenyl)methyl]butyrolactone

Colourless Oil; $\mathbf{R_f}$ = 0.22 hexanes/EtOAc 8:2); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.78 – 6.70 (4H, m, ArH), 6.67 – 6.59 (2H, m, ArH), 5.94 (2H, q, *J* = 1.5 Hz, OCH_2O), 5.91 (2H, dd, *J* = 5.1, 1.4 Hz, OCH_2O), 4.49 (1H, d, *J* = 5.3 Hz, $CH(Ar)_2$), 4.17 (1H, ddd, *J* = 8.9, 8.2, 7.5 Hz, $HOCH_aH_b$), 3.98 (1H, td, *J* = 8.7, 4.2 Hz, $HOCH_aH_b$), 3.29 (1H, td, *J* = 9.1, 5.3 Hz, COCH), 2.46 – 2.36 (1H, m, $COCHCH_aH_b$), 2.11 (1H, dq, *J* = 12.9, 8.4 Hz, $COCHCH_aH_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 177.9, 147.8, 147.8, 146.5, 146.3, 136.0, 135.1, 122.0, 120.8, 109.1, 108.7, 108.2, 108.1, 101.0, 101.0, 66.3, 49.9, 43.7, 26.3.

7.3. TOWARDS THE TOTAL SYNTHESIS OF PEPEROMIN D. SECOND APPROACH

7.3.1. Synthesis of 4-pentenoyl chloride (16)

Oxalyl chloride (1.1 mL, 11.7 mmol) previously micro-distilled was added dropwise to a solution of 4-pentenoic acid (1.0 g, 10.0 mmol) and DMF in catalytic amount (2 drops) in CH_2Cl_2 (9 mL) under N_2. After 3 h volatiles were removed *in vacuo* during 20 min in an ice-bath to afford the desired acid chloride **16** quantitatively (1.2 g, 10.0 mmol) and is used straightway in the following step.



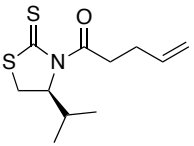
16

Colorless oil; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.79 (1H, ddt, *J* = 16.9, 10.2, 6.5 Hz, $(CH_2)_2C\underline{H}$), 5.11 (1H, ddt, *J* = 16.9, 1.5, 1.4 Hz, $(CH_2)_2CHC\underline{H_a}H_b$), 5.09 (1H, ddt, *J* = 10.2, 1.5, 1.4 Hz, $(CH_2)_2CHCH_a\underline{H_b}$), 2.99 (2H, t, *J* = 7.3 Hz, $ClCOC\underline{H_2}$), 2.46 (2H, tdt, *J* = 7.3, 6.5, 1.4 Hz, $ClCOCH_2C\underline{H_2}$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 173.2, 134.7, 117.0, 46.3, 29.0.

7.3.2. Synthesis of *(S)*-4-isopropyl-N-4-pentenoyl-1,3-thiazolidine-2-thione

A 2.5 M solution of *n*-BuLi in hexanes (2.6 mL, 6.4 mmol) was added dropwise to a solution of the thiazolidinethione **1** (0.94 g, 5.8 mmol) in THF (4 mL) at −78 ºC under N_2. The reaction mixture was stirred for 15 min and a solution of **16** (1.2 g, 10.0 mmol) in THF (3 mL) was carefully added. The resulting mixture was stirred for 30 min at −78 ºC and 2 h at r.t.

The reaction mixture was cooled to 0 ºC and quenched with sat. NH_4Cl (2.5 mL) and water (5 mL). This mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The resultant oil was purified by flash column chromatography on silica gel (hexanes/EtOAc 95:5) to afford 1.3 g (5.2 mmol, 90% yield) of the thioimide **17** as a yellow oil.



17

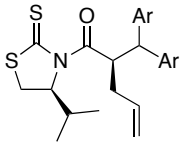
Yellow oil; **R_f** = 0.48 (hexanes/EtOAc 9:1); **$[\alpha]_D$**= +353.2 (c 1.0, $CHCl_3$); **IR** (ATR) 3074, 2959, 1691, 1637, 1352, 1250, 1157, 1085, 1032, 912 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.86 (1H, ddt, *J* = 16.9, 10.2, 6.5 Hz, $CO(CH_2)_2C\underline{H}$), 5.16 (1H, ddd, *J* = 8.0, 6.2, 1.2 Hz, $NC\underline{H}$), 5.07 (1H, dq, *J* = 16.9, 1.5 Hz, $CO(CH_2)_2CHC\underline{H_a}H_b$), 5.01 (1H, ddd, *J* = 10.2, 2.9, 1.5 Hz, $CO(CH_2)_2CHCH_a\underline{H_b}$), 3.51 (1H, dd, *J* = 11.5, 8.0 Hz, $SC\underline{H_a}H_b$), 3.46 (1H, ddd, *J* = 17.4, 8.3, 6.2 Hz, $NCOC\underline{H_a}H_b$), 3.27 (1H, ddd, *J* = 17.4, 8.2, 6.6 Hz, $NCOCH_a\underline{H_b}$), 3.02 (1H, dd, *J* = 11.5, 1.2 Hz, $SCH_a\underline{H_b}$), 2.52 – 2.30 (3H, m,

$COCH_2CH_2$, $CH(CH_3)_2$), 1.06 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.97 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 202.7, 173.2, 136.8, 115.5, 71.6, 37.5, 30.8, 30.5, 28.8, 19.1, 17.7; **HRMS** (+ESI): m/z calculated for $[M+H]^+$ $C_{11}H_{18}NOS_2$: 244.0824, found: 244.0828.

7.3.3. Synthesis of *(S)*-N-[*(R)*-2-(2-propenyl)-3,3-di(3,4-methylenedioxyphenyl)propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (18)

Solid $(Me_3P)_2NiCl_2$ (48.9 mg, 174 μmol) was added to a solution of thioimide **17** (0.85 g, 3.5 mmol) and diaryl methyl ether **6** (1.5 g, 5.2 mmol) in CH_2Cl_2 (7 mL) under N_2 at r.t. The resulting mixture was purged with N_2 again and then cooled to −20 ºC. TESOTf (1.2 mL, 5.2 mmol) and 2,6-lutidine (0.61 mL, 5.2 mmol) were added dropwise after 3 and 7 min respectively. The reaction mixture was stirred at −20 ºC for 15 h.

The reaction was quenched with sat. NH_4Cl (7 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* and the crude oil was purified by flash column chromatography on silica gel (from hexanes to hexanes/EtOAc 6:4) to afford 1.6 g (3.2 mmol, 93% yield) of the corresponding alkylated product **18**.



18

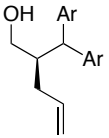
Yellow Solid; **mp** = 71 – 72 ºC; **R_f** = 0.40 (hexanes/EtOAc 8:2); **[α]$_D$**= +336.9 (c 1.0, $CHCl_3$); **IR** (ATR) 2959, 2870, 1686, 1602, 1481, 1437, 1241, 1143, 1085, 1032, 925 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.99 – 6.94 (2H, m, ArH), 6.80 – 6.76 (2H, m, ArH), 6.72 (1H, d, *J* = 7.9 Hz, ArH), 6.65 (1H, d, *J* = 7.9 Hz, ArH), 6.25 (1H, ddd, *J* = 11.4, 9.3, 4.2 Hz, NCOCH), 5.90 (2H, dd, *J* = 6.7, 1.4 Hz, OCH_2O), 5.87 – 5.75 (1H, m, $CO(CH_2)_2CH$), 5.84 (2H, dd, *J* = 6.7, 1.4 Hz, OCH_2O), 5.12 (1H, ddd, *J* = 8.0, 6.2, 0.8 Hz, NCH), 5.00 – 4.91 (2H, m, $CO(CH_2)_2CHCH_aH_b$), 4.13 (1H, d, *J* = 11.4 Hz, $CH(Ar)_2$), 3.32 (1H, dd, *J* = 11.4, 8.0 Hz, SCH_aH_b), 2.86 (1H, dd, *J* = 11.4 Hz, 0.8 Hz, SCH_aH_b), 2.32 (1H, ddd, *J* = 13.8, 5.5, 4.2 Hz, $NCOCHCH_aH_b$), 2.15 (1H, dt, *J* = 13.8, 9.3 Hz, $NCOCHCH_aH_b$),1.95 – 1.81 (1H, m, $CH(CH_3)_2$), 0.85 (3H, d, *J* = 6.8 Hz, $CH(CH_3)_a(CH_3)_b$), 0.64 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_a(CH_3)_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 204.0, 174.9, 147.9, 147.6, 146.3, 145.9, 137.6, 136.5, 134.3, 121.3, 121.0, 117.3, 108.8, 108.4, 108.1, 108.1, 101.0, 100.8, 71.7, 54.3, 45.9, 37.5, 30.6, 29.7, 18.5, 17.7; **HRMS** (+ESI): m/z calculated for $[M+H]^+$ $C_{26}H_{28}NO_5S_2$: 498.1403, found: 498.1404.

7.3.4. Synthesis of *(R)*-2-di[(3,4-methylenedioxyphenyl)methyl]-4-penten-1-ol (19)

A solution of **18** (498 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was cooled to −78 ºC and a 1 M solution of DIBAL-H in toluene (2.2 mL, 2.2 mmol) was added dropwise. The reaction mixture was stirred for 5 min at −78 ºC and then 20 min at r.t.

The reaction mixture was first quenched with MeOH (1 mL) and then a 1 M solution of sodium potassium tartrate was added (10 mL). After 1 h, the aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with 2 M NaOH (3 x 30 mL), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford alcohol **19** quantitatively (346 mg, 1.0 mmol).

The basic aqueous phase was acidified with HCl to pH = 1. The aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL), dried over $MgSO_4$, filtered and solvents were removed *in vacuo* to recover thiazolidinethione **1** (157 mg, 98% recovery).



19

Colourless Oil; $\mathbf{R_f}$ = 0.51 (hexanes/EtOAc 7:3); $\mathbf{[\alpha]_D}$ = -26.7 (c 1.0, $CHCl_3$); **IR** (ATR) 3576, 3395 br, 3072, 2886, 1635, 1606, 1483, 1435, 1239, 1179, 1030, 916 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 6.79 – 6.69 (6H, m, ArH), 5.90 (2H, dd, *J* = 4.0, 1.5 Hz, OCH_2O), 5.89 (2H, dd, *J* = 5.6, 1.5 Hz, OCH_2O), 5.82 (1H, dddd, *J* = 19.7, 9.5, 8.4, 6.1 Hz, $HOCH_2CHCH_2CH$), 5.06 – 4.99 (2H, m, $HO(CH_2CH)_2CH_aH_b$), 3.73 (1H, d, *J* = 11.4 Hz, $CH(Ar)_2$), 3.63 (1H, dt, *J* = 7.5, 3.4 Hz, $HOCH_aH_b$), 3.52 – 3.45 (1H, m, $HOCH_aH_b$), 2.36 – 2.27 (1H, m, $CHCH(Ar)_2$), 2.24 – 2.15 (1H, m, $CH_2CHCH_aH_b$), 2.06 (1H, dt, *J* = 14.3, 8.4 Hz, $CH_2CHCH_aH_b$); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ 147.9, 147.8, 146.0, 145.9, 137.7, 137.6, 136.7, 121.0, 120.7, 116.7, 108.4, 108.3, 108.1, 107.9, 100.9, 100.9, 62.5, 52.6, 43.8, 33.8; **HRMS** (+ESI): m/z calculated for $[M+Na]^+$ $C_{20}H_{20}O_5Na$: 363.1203, found: 363.1200.

8. CONCLUSIONS

As expected, starting materials **1**, **3, 6** & **17** have been obtained in high yields. Catalytic nickel(II)-mediated alkylation reactions have afforded the corresponding products **7** & **18** as a single diastereomer in excellent yields, amplifying even more the existent scope for this S_N1 enolate reactions.

The first proposed synthetic pathway could not be completed due to the lack of chemoselectivity between the reduction of the ester group and the chiral auxiliary, which gave as a result low yields of lactone **9**.

The second approach of the proposed synthesis has afforded product **19** in an overall yield of 84% over 3 steps, increasing considerably intermediate yields of the reported to date best synthesis. Soft reductive agents such as $NaBH_4$ or $LiBH_4$ have been proved to be not useful, achieving low yields of the desired product. In comparison, DIBAL-H has proceeded smoothly and with the desired efficiency.

This project has found a solution to all the expected major problems of this synthesis, such as possible difficulties in the nickel(II) reaction, as well as removal of the thiazolidinethione chiral auxiliary in reductive conditions. From now on, further reactions of ozonolysis and cyclization have to be applied. If high yields are obtained, one last reaction of methylation following the reaction applied by Sibi et al. will be conducted to achieve the desired peperomin D. Work is in progress.

9. REFERENCES AND NOTES

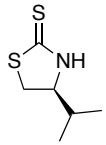
1. Chen, C.-M.; Jan, F.-Y.; Chen, M.-T.; Lee, T.-J., *Heterocycles,* **1989**, *29*, 411-414.
2. Monache, F. D.; Compagnone, R. S., *Phytochemistry,* **1996**, *43*, 1097-1098.
3. Govindachari, T. R.; Kumari, G. N. K.; Partho, P. D., *Phytochemistry,* **1998**, *49*, 2129-2131.
4. Lin, C. M.; Singh, S. B.; Chu, P. S.; Dempcy, R. O.; Schmidt, J. M.; Pettit, G. R.; Hamel, E., *Mol. Pharmacol.,* **1988**, *34*, 200-208.
5. Loike, J. D.; Brewer, C. F.; Sternlicht, H.; Gensler, W. J.; Horwitz, S. B., *Cancer. Res.,* **1978**, *38*, 2688-2693.
6. Wu, J.-L.; Li, N.; Hasegawa, T.; Sakai, J.-I.; Mitsui, T.; Ogura, H.; Kataoka, T.; Oka, S.; Kiuchi, M.; Tomida, A.; Turuo, T.; Li, M.; Tang, W.; Ando, M., *J. Nat. Prod.*, **2006**, *69*, 790-794.
7. Zhang, G.-L.; Li, N.; Wang, Y.-H.; Zheng, Y.-T.; Zhang. Z.; Wang, M.-W., *J. Nat. Prod.*, **2007**, *70*, 662-664.
8. Wang, X.-Z.; Liang, J.-Y.; Wen, H.-M.; Shan, C.-X.; Liu, R., *J. Pharm. Biomed. Anal.*, **2014**, *94*, 1-11.
9. Cruz-Almanza, R.; Higareda, F. P., *Heterocycles,* **1992**, *34*, 2323-2330.
10. Sibi, M. P.; Johnson, M. D.; Punniyamurthy, T., *Can. J. Chem.,* **2001**, *79*, 1546-1555.
11. Soorukram, D.; Panmuang, J.; Tuchinda, P.; Kuhakarn, C.; Reutrakul, V.; Pohmakotr, M., *Tetrahedron,* **2014**, *70*, 7577-7583.
12. Fernández-Valparís, J.; Romo, J. M.; Romea, P.; Urpí, F.; Kowalski, H.; Font-Bardia, M., *Org. Lett.,* **2015**, *17*, 3540-3543.
13. McKennon, M.; Meyers, A.; Drauz, K.; Schwarm, M., *J. Org. Chem.,* **1993**, *58*, 3568-3571.
14. Delaunay, D.; Toupet, L.; Le Corre, M., *J. Org. Chem.,* **1995**, *60*, 6604-6607.
15. Betschmann, P.; Sahli, S.; Diederich, F., *Helv. Chim. Acta,* **2002**, *85*, 1210-1245.
16. (a) Suzuki, T.; Hamashima, Y.; Sodeoka, M., *Angew. Chem., Int. Ed.,* **2007**, *46*, 5435. (b) Hamashima, Y.; Nagi, T.; Shimizu, R.; Tsuchimoto, T.; Sodeoka, M., *Eur. J. Org. Chem.,* **2011**, *20-21*, 3675-3678.
17. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R., *Purification of Laboratory Chemicals*. Pergamon Press: Oxford, **1986**.
18. Galvez, E.; Romea, P.; Urpí, F.; Jewett, J. C.; Rawal, V. H., *Org. Synth.,* **2009**, *86*, 70-80.
19. Baiget, J.; Cosp, A.; Galvez, E.; Gomez-Pinal, L.; Romea, P.; Urpí, F., *Tetrahedron,* **2008**, *64*, 5637-5644.

10. ACRONYMS

HIV	Human Immunodeficiency Virus
n-BuLi	*n*-Butyllithium
NaHMDS	Sodium bis(trimethylsilyl)amide
TESOTf	Trimethylsilyl trifluoromethanesulfonate
NPhth	Phthalimide
THF	Tetrahydrofuran
r.t.	Room Temperature
EtOH	Ethanol
Et_3N	Triethylamine
n-BuH	Butane
NMR	Nuclear Magnetic Resonance
MeOH	Methanol
DIBAL-H	Diisobutylaluminum hidryde
DMF	Dimethylformamide
PTSA	*p*-Toluenesulfonic acid
TLC	Thin-Layer Chromatography
UV	Ultraviolet
IR	Infrared Spectroscopy
ATR	Attenuated Total Reflectance
mp	Melting Point
TMS	Tetramethylsilane
COSY	Correlation Spectroscopy

HSQC	Heteronuclear Single Quantum Coherence Spectroscopy
HRMS	High-Resolution Mass Spectrometry
Rf	Retention Factor
EtOAc	Ethyl Acetate
ESI	Electrospray Ionization

APPENDICES



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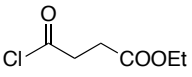

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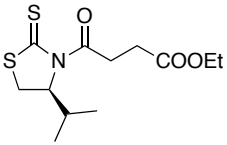

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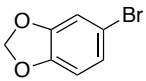

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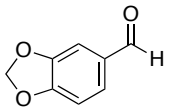

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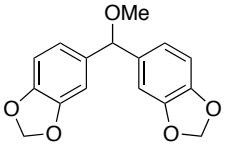

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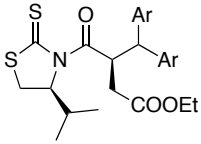

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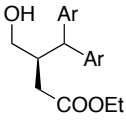

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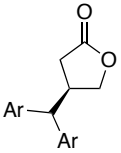

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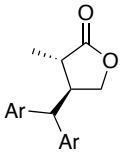

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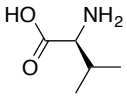

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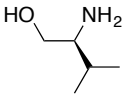

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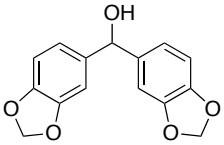

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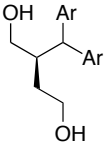

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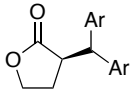

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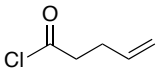

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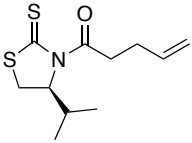

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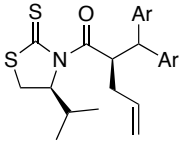

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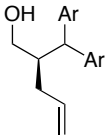

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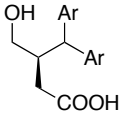

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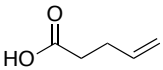

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