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Towards the total synthesis of Amphidinolide E: preparation of fragments I and II.

Cap a la síntesi total de l'anfidinolida E: preparació dels fragments I i II.

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June 2012

Universitat de Barcelona

Per als meus avis Josep Ramon i Lluïsa, de qui he tingut la sort d'heretar l'esperit químic que m'ha portat fins aquí.

REPORT

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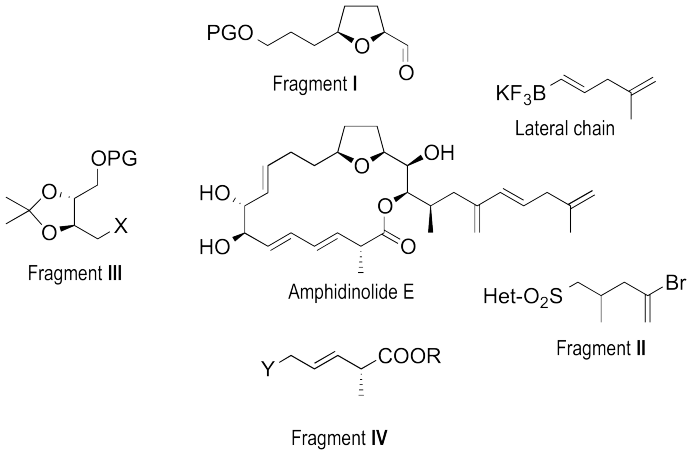
SUMMARY

Amphidinolides are a group of macrolides with interesting structures and biological activities isolated from marine microorganisms. Because of that, they are attractive targets for total synthesis as the number of synthetic approaches by different research groups testifies.

This work focuses on the synthesis of Amphidinolide E, and specifically on the preparation of fragments **I** and **II**.



Fragments involved in our synthesis of Amphidinolide E.

The synthetic route for the preparation of fragment **I** uses the chiral epoxide (*R*)-glycidol as the starting material. Fragment **I** was synthesised in 19% yield through a twelve-step route that involves diverse reactions such as oxidations, hydroborations, protections, deprotections, asymetric alkylations, reactions with organometallic compounds and alcohol activations.

Once the preparation of fragment **I** was complete we realised that the first step (protection of the hydroxyl group as a benzyl ether) was the one with the lowest yield (57%). Hence, we decided to optimise it. We tested the effect of the solvent and the leaving group but no improvement was achieved. Finally, we discovered that increasing the amount of base (from 1.0 to 1.8 equivalents) allowed us to prepare the desired benzyl ether in 92% yield.

Fragment **II** had been previously synthesised using Evans' asymmetric alkylation methodology with 1,3-oxazolidin-2-ones as chiral auxiliaries. We prepared the chiral imide auxiliary in the lab in 46% yield using the natural *L*-phenylalanine amino acid as the starting material. However, the asymmetric alkylation with this chiral auxiliary afforded a very low yield (15%) and was not reproducible. Even though both lithium and sodium bases and small and large scale reactions were run no improvement was noted.

We then decided to test another asymmetric alkylation methodology and used chiral amides derived from pseudoephedrine as chiral auxiliaries. In this case the yield was higher (60%) and acceptable for the synthesis of fragment **II**. The literature reports that alkylation reactions with this chiral auxiliary are highly diastereoselective, but this had to be assessed for our alkylation agent. For this analysis we used HPLC and followed two different strategies.

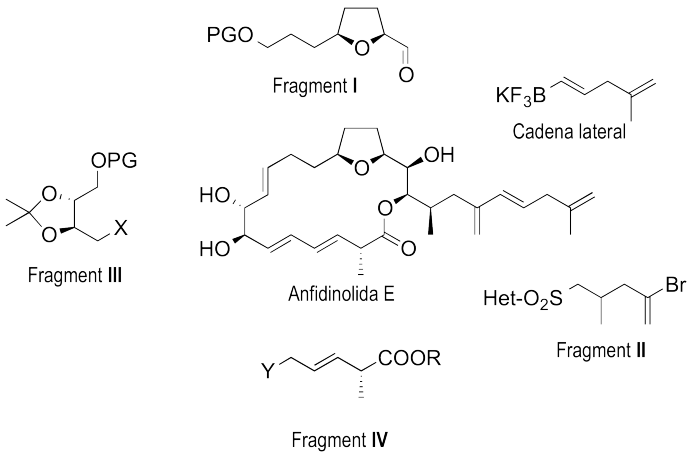
In the first strategy we tried to epimerise the alkylation product in order to have both diastereomers. This way we would be able to determine their retention times and analyse whether the undesired diastereomer had been formed during the alkylation reaction. Unfortunately, the epimerisation with a strong base such as LDA was not successful. On the other hand, in the HPLC analysis of the product formed during epimerisation under acidic conditions a new peak was observed. However, it was not possible to confirm that it corresponded to the undesired diastereomer.

In the second strategy the chiral auxiliary was eliminated from the molecule. We wanted to compare the alcohol obtained with its enantiomer by chiral HPLC. The undesired enantiomer was prepared with Evans auxiliary, whose selectivity had already been tested by the research group. Disappointingly, the retention time of both enantiomers was too similar under the set of HPLC conditions tested (different chiral columns and mobile phases), so once again we could not confirm that the reaction was completely selective.

RESUM

Les anfidinolides són un grup de compostos macrocíclics obtinguts de microorganismes marins amb certes característiques comunes i interessants estructures i activitats biològiques. Per això, la seva síntesi total ha estat àmpliament estudiada per diversos grups de recerca.

El present treball està centrat en la síntesi de l'anfidinolida E, en concret en la preparació dels fragments **I** i **II**.



Fragments implicats en la nostra síntesi de l'anfidinolida E.

La ruta emprada per a la síntesi del fragment **I** parteix de l'epòxid quiral (*R*)-glicidol. Aquest fragment ha estat sintetitzat a través d'una ruta de dotze passos, amb un rendiment global del 19%. Aquesta ruta inclou reaccions tan diverses com oxidacions, hidroboracions, proteccions i desproteccions, alquilacions asimètriques, reaccions amb compostos organometàl·lics i activacions d'alcohol.

Un cop sintetitzat el fragment **I** es va observar que el primer pas, corresponent a la protecció d'un grup alcohol en forma d'èter benzílic, era el de menor rendiment (57%) i ens vam proposar optimitzar-lo. Es van variar paràmetres com el dissolvent i el grup sortint, sense èxit. Finalment, es va trobar que la base emprada no era de la concentració teòrica indicada i es va aconseguir obtenir un 92% de rendiment utilitzant-ne 1.8 equivalents enlloc d'1.0.

Pel que fa al fragment **II**, aquest havia estat sintetitzat prèviament mitjançant una alquilació asimètrica emprant com a auxiliar quiral una 1,3-oxazolidin-2-ona desenvolupada per Evans. Aquest auxiliar va ser sintetitzat al laboratori a partir de l'aminoàcid natural *L*-fenilalanina amb un 46% de rendiment. A l'hora de dur a terme l'alquilació asimètrica amb aquest auxiliar, però, es va trobar que la reacció tenia un rendiment molt baix i a més era poc reproduïble tant amb bases de liti i sodi com a petita i gran escala.

Es va provar la reacció amb un auxiliar quiral alternatiu: la pseudoefedrina. Aquest cop el rendiment de l'alquilació va ser major, del 60%, i acceptable per ser utilitzada per a la síntesi del fragment **II**. A continuació, i tot i que la bibliografia ja indica que aquesta reacció és diestereoselectiva, ens vam proposar determinar la diastereoselectivitat de la reacció per a l'agent alquilant emprat en aquest cas. Per a aquesta anàlisi vam utilitzar la cromatografia líquida d'alta resolució (HPLC) i vam seguir dues estratègies diferents.

En la primera d'elles vam decidir epimeritzar la pseudoefedrina alquilada per tenir els dos diastereòmers i així conèixer quin temps de retenció té cadascun. D'aquesta forma en analitzar el producte de l'alquilació per HPLC podríem saber si el diastereòmer indesitjat s'havia format. No vam ser capaços d'epimeritzar el producte d'alquilació emprant una base forta com l'LDA. En medi àcid es va observar un nou pic per HPLC, però en aquests moments no podem assegurar amb certesa que correspongui al diastereòmer esperat.

En la segona estratègia es va eliminar l'auxiliar quiral i es va voler comparar el compost obtingut amb el seu enantiòmer per HPLC quiral. L'enantiòmer no desitjat es va preparar amb l'auxiliar d'Evans, la selectivitat del qual ja ha estat prèviament avaluada pel grup d'investigació. Malauradament, els temps de retenció dels dos enantiòmers eren massa semblants per a totes les columnes i eluents provats de forma que aquest experiment tampoc va permetre determinar la diastereoselectivitat de la reacció.

INTRODUCTION

Marine microorganisms (a diverse group of unicellular eukaryotes like bacteria, cyanobacteria and dinoflagellates) are an important source of marine toxins and bioactive substances. Amphidinolides, a group of macrolides with unique chemical structures and cytotoxic activity, have been isolated from marine dinoflagellates of the *Amphidinium* species, which are separated from the inside cells of Okinawan marine flatworms of the *Amphiscolops* species.[1] Their gross structures and absolute stereochemistry have been elucidated and confirmed by NMR data, X-ray diffraction analysis, characterisation of their degradation products and chemical interconversion.[1-4]

With some exceptions, amphidinolides have some unique structural features: odd-membered macrocyclic lactone rings, at least one exomethylene group, *E*-olefins and dienes, vicinally located one-carbon branches and a high number of chiral centres. Most of them have also an epoxide and either tetrahydrofuran or tetrahydropyran rings (*Figure 1*).

Amphidinolides A-H and J-Y have shown cytotoxic activity against murine lymphoma L1210 and human epidermoid carcinoma KB cells.[2] Among them, Amphidinolide N has proved to be the most active of all amphidinolides, exhibiting remarkably potent cytotoxicity against human tumour cell lines (with IC_{50} values lower than nM), and is expected to be a lead compound for new anticancer drugs.[4] Moreover, Amphidinolides B and D have potent cytotoxic activity against human colon tumour cell line HCT 116[5] and Amphidinolide H exhibits antitumour activity against murine leukemia P388 mice.[6]

The biosynthesis of amphidinolides has been studied by feeding marine dinoflagellates with ^{13}C-enriched sodium acetate, which has shown that they are biosynthesised through non-successive mixed polyketide and acetate units (either entire, C1 carbonyl or C2 methyl).[2-4] Much effort has been devoted to the culture of *Amphidinium* species for the production of these bioactive macrolides.[3,4] However, the quantity of macrolides in the extracts of the cultured cells is quite poor and the isolation yields are very low and scientists are, therefore, trying to identify the polyketide synthase in dinoflagellate of the *Amphidinium* species.

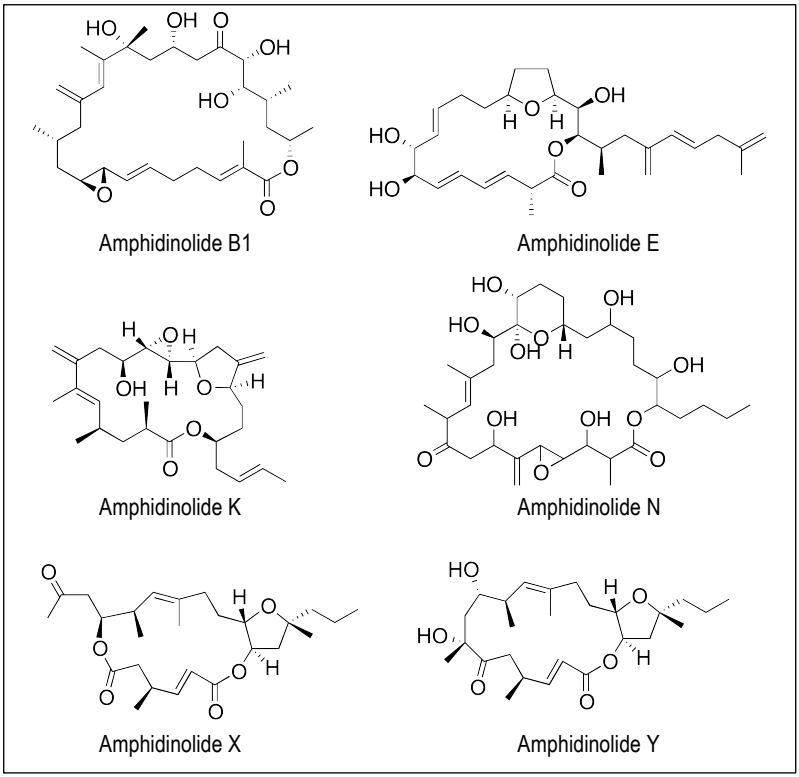
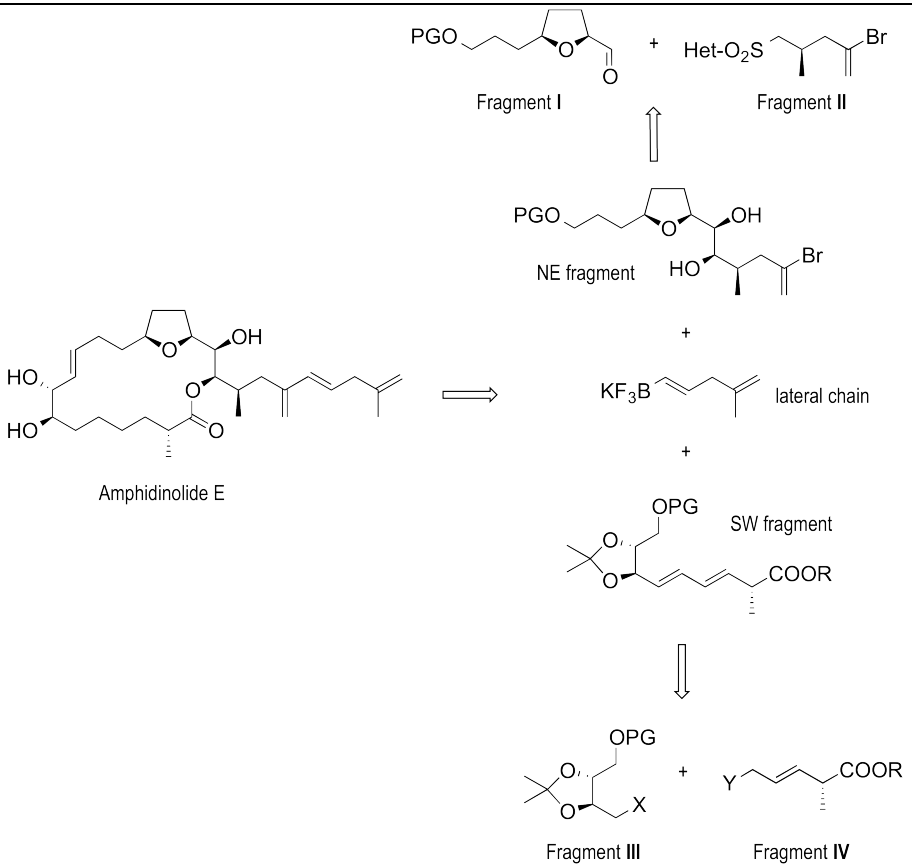


Figure 1. Structures of some representative amphidinolides.

Due to their unique structures and potent cytotoxicity together with the lack of enough sample to initiate complete biological studies, amphidinolides represent specially interesting targets for total synthesis. This project focuses on a synthetic approach to one of them: Amphidinolide E.

SYNTHETIC ANALYSIS OF AMPHIDINOLIDE E

Amphidinolide E is a 19-membered lactone with a tetrahydrofuran ring, four C1 branches (two exomethylene groups), three hydroxyl groups and eight chiral centres.[7,8] Different synthetic studies for Amphidinolide E have been carried out, including two total synthesis.[9,10,11] This work focuses on the retrosynthesis shown in *Scheme 1*, where the molecule is disconnected into four fragments.



Scheme 1. Retrosynthetic analysis of Amphidinolide E.

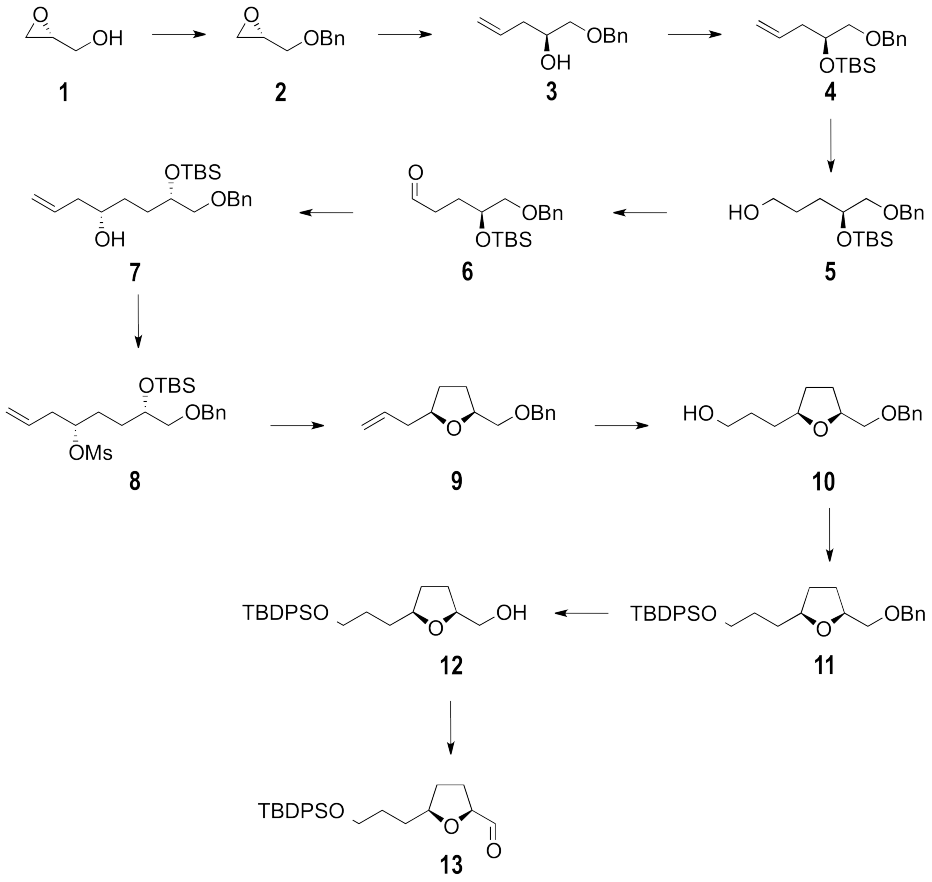
Both NE and SW fragments are prepared by a Julia-Kocienski reaction between fragments **I** and **II,** and **III** and **IV** respectively. Finally, the union of the NE and SW fragments by a Julia-Kocienski reaction, macrolactonisation and the incorporation of the side chain through a Suzuki-Molander coupling is expected to afford Amphidinolide E.[11]

OBJECTIVES

The main objective of this work was the preparation of fragments **I** and **II** of Amphidinolide E and the optimisation of some low-yielding and/or problematic steps along the synthetic routes already developed in the research group. Another objective was the spectroscopic characterisation of the newly synthesised products.

1. SYNTHESIS OF FRAGMENT I

The synthetic approach proposed by our group for the synthesis of fragment **I** uses commercial (*R*)-glycidol as the starting compound (*Scheme 2*) and is a twelve-step process.



Scheme 2. Synthetic approach to fragment **I**.

1.1. SYNTHETIC ROUTE

1.1.1. Step 1: Alcohol protection

The first step of the synthesis is the protection of the alcohol group in (*R*)-glycidol. This is necessary to avoid undesired reactions.

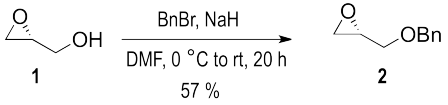
A protective group must be stable under the conditions of the synthesis. At the same time, its elimination must be mild enough not to affect the other groups in the molecule. *Table 1* shows that alkyl ethers are the only protective group for alcohols that are stable under all the conditions used in this synthesis. Among them, trityl ether and THP are especially labile under acidic conditions and we have, therefore, chosen benzyl ether as the best protecting group for our hydroxyl.

Protecting group		Organomagnesium	Oxidative conditions	Basic medium
Esters	Acetate	H[a]	L[b]	H
	Benzoate	H	L	H
	Pivaloate	M[c]	L	M
Alkyl ethers	Benzyl	L	L	L
	Trityl	L	L	L
	THP	L	L	L
Silicon ethers	TBS	L	L	H
	TBDPS	L	L	H
	TIPS	L	L	H

(a) *H* indicates that under these conditions the protective group is readily removed.
(b) *L* indicates that the protective group is stable under the reaction conditions.
(c) *M* indicates that the stability of the protecting group depends on the exact parameters of the reaction.

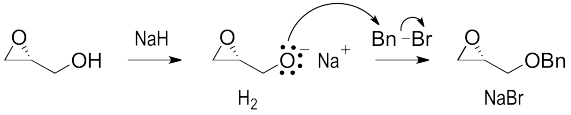
Table 1. Stability of common protecting groups for alcohols under different conditions. Taken from P. Wuts and T. Greene.[12]

When (*R*)-glycidol was treated with NaH and BnBr in THF a 57% yield of the corresponding benzyl ether was obtained (*Scheme 3*). This yield was later improved (*see 1.2. Optimization of the protection of (R)-glycidol*).



Scheme 3. Step 1 of the synthesis of fragment **I**.

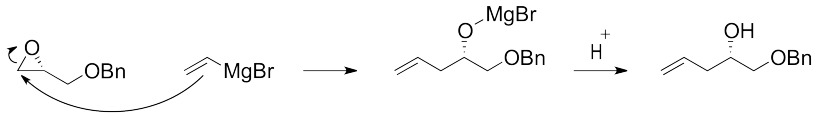
Alcohols are weak acids and sodium hydride, which is a strong base, has been used for the deprotonation of (*R*)-glycidol. Once the alkoxide is formed, it reacts with benzyl bromide *via* an S_N2 mechanism and the corresponding benzyl ether is formed (*Scheme 4*).



Scheme 4. Mechanism of step 1 of the synthesis of fragment **I**.

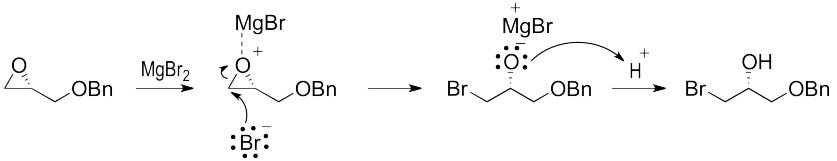
1.1.2. Step 2: Epoxide opening

Organometallic compounds are nucleophilic reagents that allow us to form new C-C bonds. In particular, organomagnesium compounds are common reagents for the opening of epoxide rings. In this case, vinylmagnesium bromide has been used. The attack takes places on the less sterically hindered carbon to give alcohol **3** (*Scheme 5*).



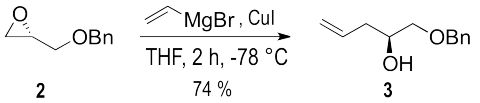
Scheme 5. Mechanism of step 2 of the synthesis of fragment **I**.

Catalytic amounts of a Cu(I) salt can be used to improve the yield of the ring-opening reaction of epoxides using Grignard reagents.[13] In this case, the reaction proceeds *via* an organocopper reagent formed *in situ.* It has been previously proved that this protocol minimises the formation of the major impurity of this reaction: 1-bromo-3-benzyloxy-2-propanol (*Scheme 6*), which forms due to the presence of $MgBr_2$ in the solutions of Grignard reagents.



Scheme 6. Formation of the undesired halohydrin.

When epoxide **2** was treated with organomagnesium bromide and catalytic amounts of CuI, alcohol **3** was isolated in 74% yield (*Scheme 7*).



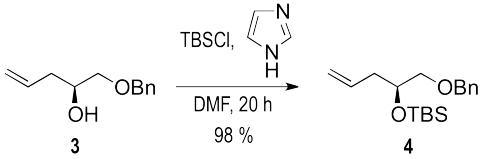
Scheme 7. Step 2 of the synthesis of fragment **I**.

By NMR analysis of the fractions obtained after chromatography purification of the crude reaction mixture we could isolate starting material **2**, and we determined that the conversion of the reaction had been 74%. In future experiments, this reaction could be run with more equivalents of vinylmagnesium bromide or with a longer reaction time. Since the undesired halohydrin has not been detected during the purification we consider that the amount of CuI used (0.25 equiv) is appropriate.

1.1.3. Step 3: Alcohol protection

After epoxide opening a new alcohol group was formed, which also needed protection in order to block its participation in the next steps of the synthesis. This new protecting group had to be orthogonal with the benzyl group, since its deprotection would be done while maintaining the alcohol protecting group at C_{17}. If the stabilities shown in *Table 1* are considered again, silicon ethers appear as a good choice. They are stable under oxidising conditions and mild acid and basic medium. The fact that they can be deprotected with fluoride, which does not affect most of the common functionalities, makes them useful protective groups. It is possible to eliminate them from the molecule without altering other protecting groups, for example benzyl ethers.

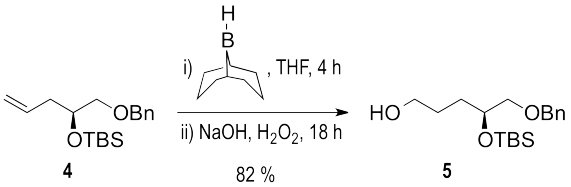
The use of protective groups adds two additional steps to the synthetic route, so one of their main requisites is that both their introduction and elimination reactions have to be high-yielding. The experimental results obtained (*Scheme 8*) indicate that the TBS group accomplishes this requisite.



Scheme 8. Step 3 of the synthesis of fragment **I**.

1.1.4. Step 4: Hydroboration

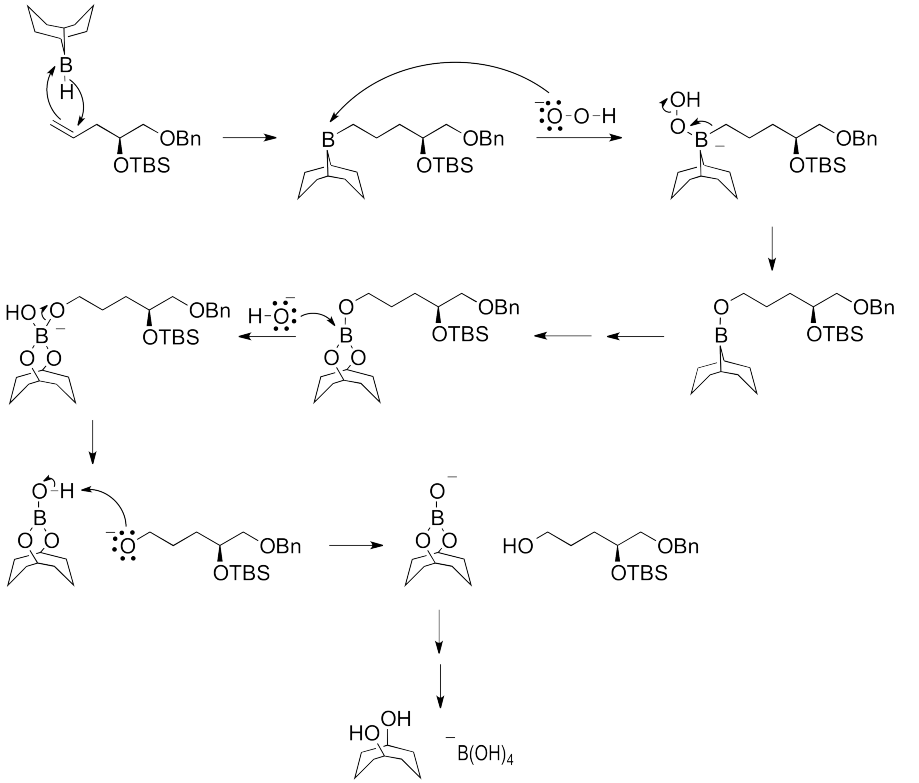
In the most common reactions for the transformation of double bonds to alcohols the hydroxyl group formed lies on the most substituted position. However, when the opposite regioselectivity is required, hydroboration of the double bond is the solution. In this case 9-BBN was used instead of borane, which is the most common hydroborating agent (*Scheme 9*). The reason is that the regioselectivities achieved with 9-BBN are higher than the ones afforded by borane, because of steric effects.[14]



Scheme 9. Step 4 of the synthesis of fragment **I**.

A highly polar compound was observed by TLC, which seemed to correspond to a secondary product that had lowered the yield of the reaction. However, ^{1}H NMR analysis showed the presence of starting material and indicated that the conversion of the reaction had been of 81%, which could justify the yield of this step. If the mechanism of the hydroboration is considered (*Scheme 10*), it is observed that this polar compound may correspond to 1,5-cyclooctanediol.

The fact that the yield obtained is due to a conversion lower than 100% and not to undesired secondary products may make it easier to increase it by using a larger amount of reactants or increasing the reaction time.



Scheme 10. Mechanism of step 4 of the synthesis of fragment **I**.

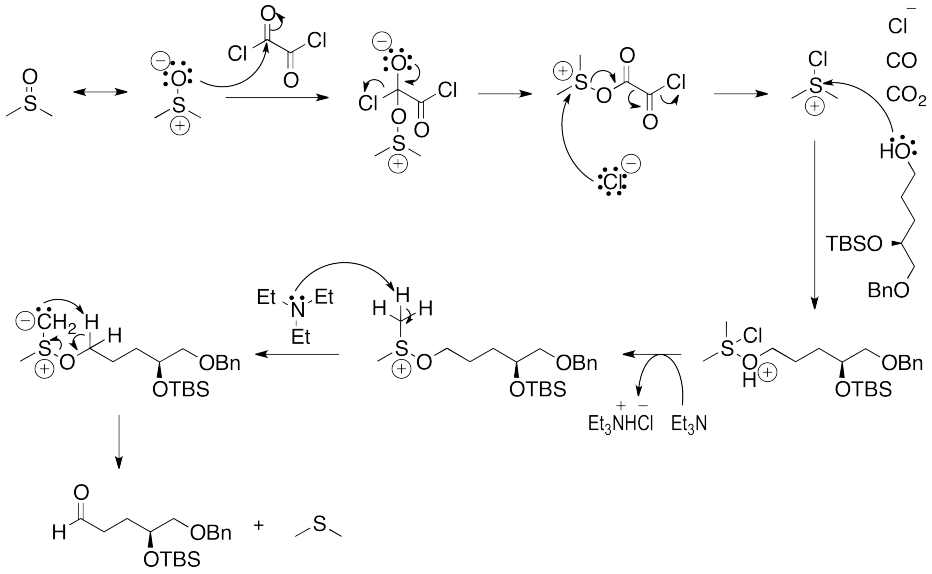
1.1.5. Step 5: Alcohol oxidation

Several reagents can be used to oxidise alcohols. When the product of the reaction is an aldehyde, though, the conditions must be controlled to avoid further oxidation to the carboxylic acid. In this case a Swern oxidation was used. It has already been shown in *Table 1* that the two protecting groups of the molecule are stable under these conditions.

There are some reactions in which the order of the addition of the reactants is crucial for the formation of the desired product. This is one of such cases since oxalyl chloride and DMSO must be added first in order to form the reactive species – the one able to oxidise the alcohol group.

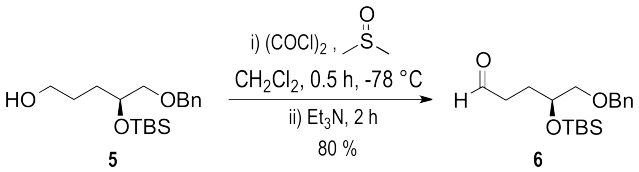
As it can be seen from its mechanism (*Scheme 11*), the Swern reaction is very clean: all the by-products formed are volatile and, consequently, easily removed from the reaction mixture.

This is one of its advantages. On the other hand, the unpleasant smell of dimethyl sulfide is one of its drawbacks.



Scheme 11. Mechanism of step 5 of the synthesis of fragment **I**.

When alcohol **5** was treated under the conditions of the Swern reaction, aldehyde **6** was isolated in 80% yield (*Scheme 12*).

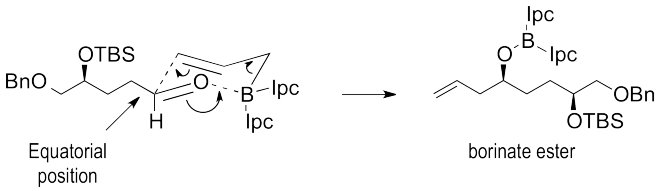


Scheme 12. Step 5 of the synthesis of fragment **I**.

1.1.6. Step 6: Stereoselective carbonyl allylation

The allylation of **6** implies the formation of a new stereogenic centre. In order to create only one of the two possible diastereomers an asymmetric alkylation is required and a chiral allylborane has been used: (+)-allyldiisopinocampheylborane. The reaction takes place through a six-membered transition state in which the alkyl group of the aldehyde (a bulky one) adopts an equatorial position (*Scheme 13*). The stereoselectivity of this reaction is dictated by which of the

two diastereotopic faces of the aldehyde is attacked by the chiral borane. In our case, (+)-allyldiisopinocampheylborane affords product with the desired stereochemistry.



Scheme 13. Transition state and product of the allylation reaction.

Apart from the desired compound, the only by-product observed after column chromatography was Ipc-OH (*Figure 2*). It is formed during the oxidative *work-up* (H_2O_2, NaOH) by hydrolysis of the borinate ester formed in the allylation reaction. The mechanism is analogous to the one indicated in *Scheme 10* for hydroboration with 9-BBN. The formation of this by-product, which had a similar polarity to our compound, impurified some of the fractions of the final product.

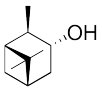
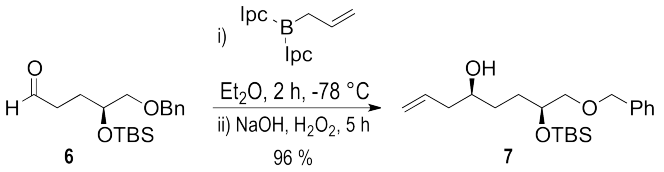


Figure 2. Secondary product formed in step 6.

In any case, the recovering of only these fractions meant that the undesired diastereomer was not formed and the carbonyl allylation was diastereoselective: only one diastereomer is observed in the NMR spectrum of the crude reaction mixture. Moreover, the conversion was quantitative (*Scheme 14*).



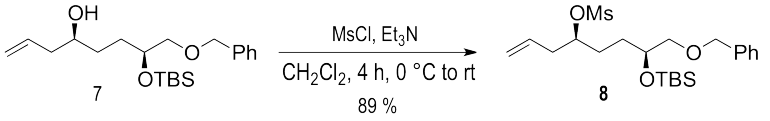
Scheme 14. Step 6 of the synthesis of fragment **I**.

1.1.7. Step 7: Alcohol activation

As it will be seen in step 8, the formation of the tetrahydrofuran ring involves an S_N2 displacement of a leaving group at C_{13}. Since alcohols are bad leaving groups, though, it is

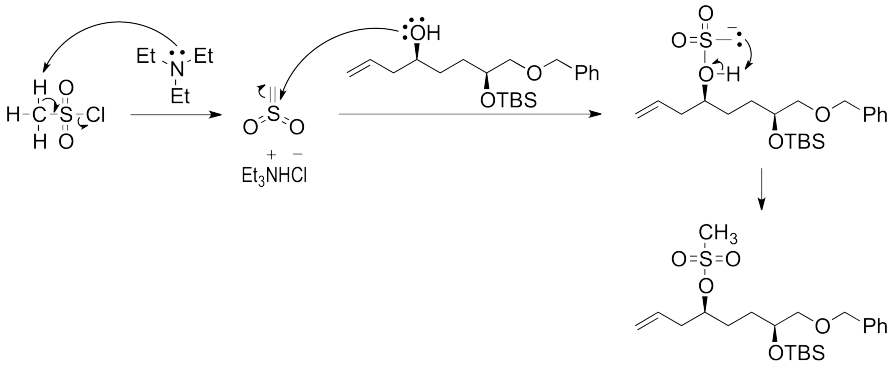
usually necessary to activate them. Halogens and sulfonates, which are better leaving groups, are among the most common groups used for this purpose. Some of the reactants used for halogenation, such as bromine, could affect the double bond present in our molecule. Therefore, activation as a sulfonate, and specifically as a mesylate, was proposed as the most suitable option. It can be easily obtained by reaction of the alcohol with mesyl chloride and with a weak base.

When alcohol **7** was treated with MsCl and Et_3N in CH_2Cl_2 at 0 °C an 89% yield of the corresponding mesylate **8** was obtained (*Scheme 15*).



Scheme 15. Step 7 of the synthesis of fragment **I**.

Because the crude NMR of the reaction was exceptionally clean no purification by column chromatography was needed. By analysing the mechanism of the reaction (*Scheme 16*) it can be seen that the additional products formed can be easily separated during the *work-up*.

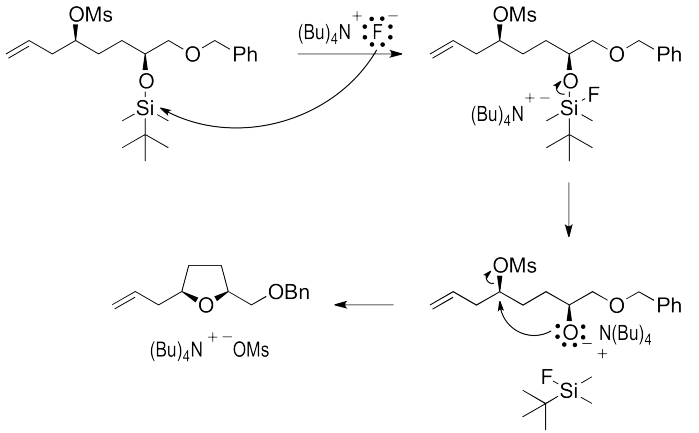


Scheme 16. Mechanism of step 7 of the synthesis of fragment **I**.

1.1.8. Step 8: Tetrahydrofuran ring formation

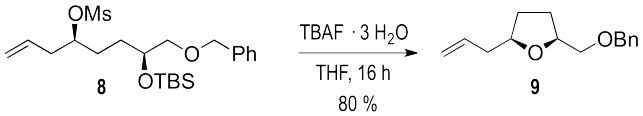
The tetrahydrofuran ring is formed by an intramolecular S_N2 reaction. The TBS group is deprotected by treatment with fluoride anion (in this case TBAF is used as the source of fluoride) and then the alkoxide formed attacks C_{13}. The use of fluoride is a suitable method for the elimination of silicon ethers because of the high affinity between fluorine and silicon. This

attack displaces the mesiloxy group intramolecularly and forms the tetrahydrofuran with both its substituents in a *cis* configuration (*Scheme 17*).



Scheme 17. Mechanism of step 8 of the synthesis of fragment **I**.

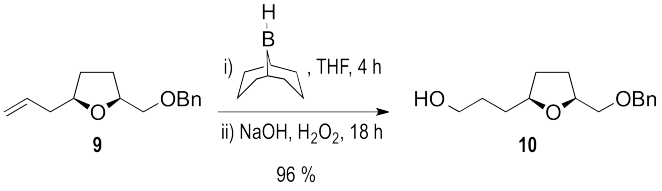
When compound **8** was treated with TBAF in THF for 16 h, tetrahydrofuran **9** was obtained in 80% yield (*Scheme 18*).



Scheme 18. Step 8 of the synthesis of fragment **I**.

1.1.9. Step 9: Hydroboration

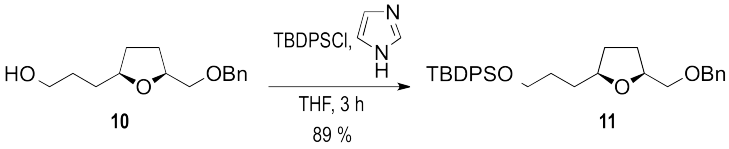
This process is equivalent to the one used for the conversion of **4** into **5**. In this case, though, after 4 h of reaction it was observed by TLC that there was still starting material in the reaction mixture so 0.5 equivalents more of 9-BBN were added. Consequently, the reaction was quantitative and a high yield was obtained: 96% (*Scheme 19*). This positive result indicates that the yield of step 4 will probably improve by adding 2.5 equiv of 9-BBN instead of 2.0.



Scheme 19. Step 9 of the synthesis of fragment **I**.

1.1.10. Step 10: Alcohol protection

Once again an alcohol group was formed and it had to be protected. By analysis of the next steps of the synthesis[15] it can be observed that the protective group used must be stable to acidic medium. A benzyl ether seemed to be a good option again but its deprotection, which is done by hydrogenolysis, is incompatible with the double bond present in the NE fragment. Among the silicon ethers, TBDPS is the most stable to acidic conditions[12] so it was the protective group used in this case (*Scheme 20*).

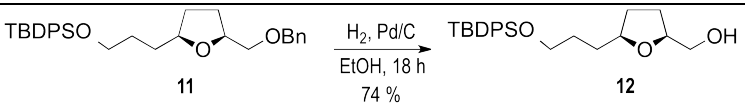


Scheme 20. Step 10 of the synthesis of fragment **I**.

1.1.11. Step 11: Alcohol deprotection

A benzyl ether can only be eliminated to afford the alcohol group by reduction with hydrogen catalysed with palladium or with a metal (lithium or sodium) in liquid ammonia. The other protecting group present in **11**, TBDPS, is stable to both reaction conditions. The second choice involves the use of higher temperatures and a more complex set-up in the lab. In our case the hydrogenation option was used.

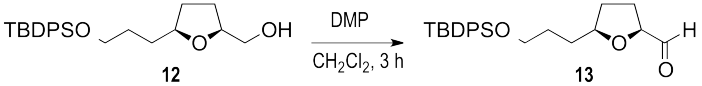
Treatment of benzyl ether **11** with H_2 and Pd/C afforded the desired alcohol in 74% yield (*Scheme 21*). Since the *work-up* of this reaction involves filtration with Celite® and purification by column chromatography is not necessary, the reason for the yield obtained has not been determined.



Scheme 21. Step 11 of the synthesis of fragment **I**.

1.1.12. Step 12: Alcohol oxidation

The final step of this synthesis is the oxidation of the terminal alcohol to an aldehyde. In this case Dess-Martin Periodinane is used (*Scheme 22*). This is a mild oxidative agent which is usually used for complex structures and for advanced stages of the synthesis. This is, therefore, a suitable reagent for the last step of the synthesis of fragment **I**.



Scheme 22. Step 12 of the synthesis of fragment **I**.

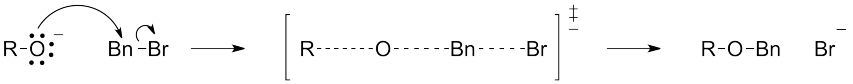
This reaction was not carried out in the lab because aldehydes are unstable. It will only be performed right before running the Julia-Kocienski reaction between fragments **I** and **II**.

1.2. OPTIMISATION OF THE BENZYLATION OF (*R*)-GLYCIDOL

Being the protection of (*R*)-glycidol the step with the lowest yield in the synthesis of fragment **I**, an additional objective we decided to accomplish was to optimise it and, consequently, improve the total yield. The benzyl ether is a good protecting group in this sequence both because of its stability and elimination conditions. Therefore, we focused our efforts on finding more suitable conditions for the introduction of the benzyl group.

1.2.1. Effect of the solvent

It can be seen in *Scheme 23* that in the binuclear nucleophilic substitution that takes place between our alkoxide and benzyl bromide one of the reactants is negatively charged. The transition state also has a negative charge but that charge is dispersed over two atoms (the O and the Br).



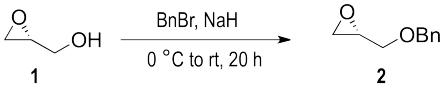
Scheme 23. Mechanism of the S_N2 reaction between an alkoxide and benzyl bromide.

A more polar solvent will, therefore, stabilise both reactants and transition state but the reactant will be stabilised to a greater extent. The activation energy in a more polar solvent will increase and the reaction rate decrease. Thus, we expected that the reaction would be faster in THF, which is a less polar solvent, than in DMF (*Table 2*).

Solvent	Structure	Dielectric constant (ε, 25 °C)
DMF		37
THF		7.6

Table 2. Dielectric constants of the solvents used.

The reaction with THF instead of DMF was tested but no improvement on the yield of the reaction was observed (*Table 3*).



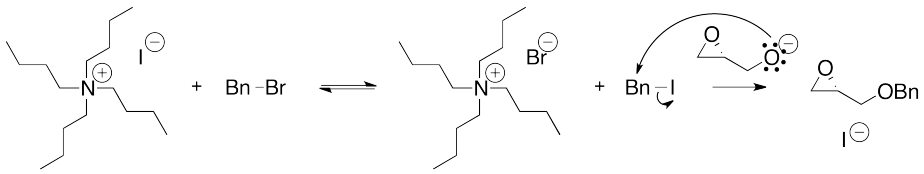
1 2

Entry	Solvent	Yield [%]
1	DMF	57
2	THF	54

Table 3. Effect of the solvent on the yield of (*R*)-glycidol's protection.

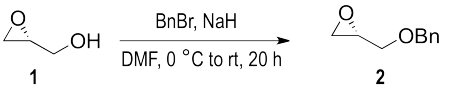
1.2.2. Effect of the leaving group

Catalytic amounts of TBAI are used in the literature to improve the outcome of this kind of reactions. In this case, small amounts of benzyl iodide are formed, which react faster with the alkoxide (*Scheme 24*). This is because iodide is a bigger anion than bromide, so it can distribute the negative charge better and is then less basic and a better leaving group.



Scheme 24. Benzylation of (*R*)-glycidol with TBAI.

However, once again, after trying the protection reaction with a catalytic amount of TBAI the yield of the reaction did not increase (*Table 4*).



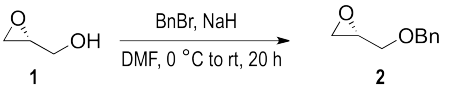
1 2

Entry	Solvent	TBAI [equiv]	Yield [%]
1	DMF	-	57
2	DMF	0.04	54

Table 4. Effect of TBAI on the yield of (*R*)-glycidol's protection.

1.2.3. Effect of the number of equivalents of NaH

Before quenching the reaction mixture we always checked by TLC that no starting material was still present. However, the reaction mixture was difficult to follow by TLC because (*R*)-glycidol is highly polar and the reaction was run in DMF, which complicates TLC analysis. It was thus difficult to assess whether the starting material had been completely consumed. Taking into account that NaH is sold as an emulsion in oil which is stated to be 60% in NaH and that it reacts easily with humidity we thought that is was possible that its concentration was less than 60%. Hence, we ran the reaction with more equivalents of NaH (*Table 5*), which finally resulted in an improvement of the benzylation yield.



1 2

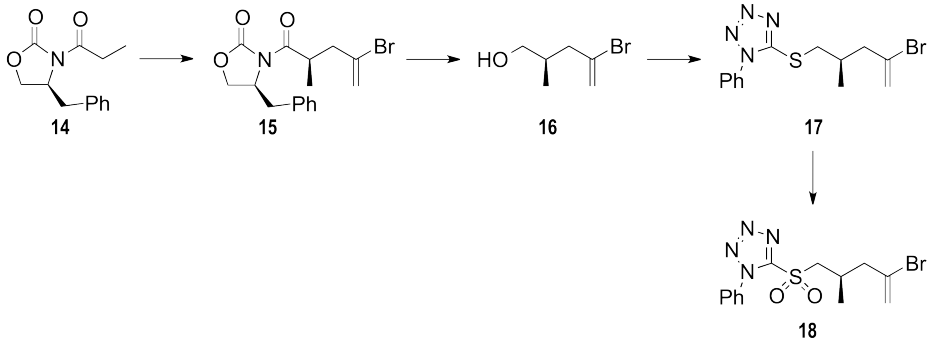
Entry	Solvent	TBAI [equiv]	NaH [equiv]	Yield [%]
1	DMF	-	1	57
2	DMF	-	1.3	77
3	DMF	-	1.8	92

Table 5. Effect of the number of equivalents of NaH on the yield of the protection of (*R*) glycidol.

In conclusion, to achieve high yields in the protection of (*R*)-glycidol as a benzyl ether it is necessary to quantitatively generate the alkoxide. It might be necessary to titrate the base used before running the reaction.

2. SYNTHESIS OF FRAGMENT II

Fragment **II**, which is also part of the NE fragment of Amphidinolide E, has been obtained by our research group following the synthetic route shown in *Scheme 25*.

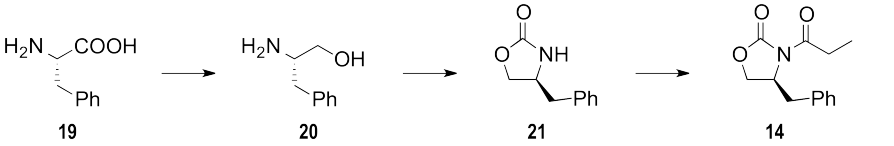


Scheme 25. Synthetic approach to fragment **II**.

One of the key steps of this synthesis is the formation of a chiral centre. This means that for the transformation of **14** to **15** an enantioselective reaction is required, obtaining only one of the two possible diastereomers. A chiral auxiliary, which induces the desired enantioselectivity and is afterwards eliminated from the molecule, is a good option in these cases. Evans' chiral 1,3-oxazolidin-2-ones have been reported to achieve stereoselectivities greater than 100:1 in alkylation reactions,[16] so they are apparently good candidates for this transformation.

2.1. SYNTHESIS OF EVANS AUXILIARY

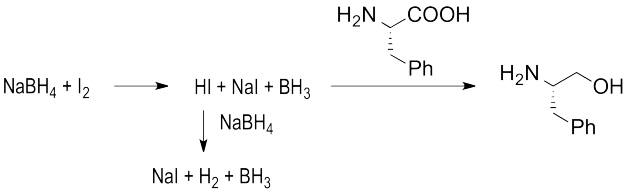
When obtaining an enantiomerically pure compound, amino acids are useful sources as its starting material. In this case, Evans auxiliary can be synthesised from phenylalanine (*Scheme 26*).



Scheme 26. Synthesis of Evans auxiliary.

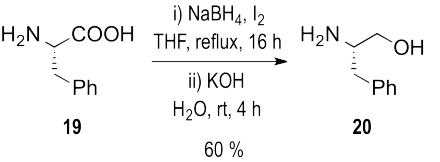
The first reaction of this three-step synthesis is the reduction of the acid to the alcohol. Carboxylic acids are usually reduced with borane, which is in this case prepared *in situ* with sodium borohydride activated with iodine.[17] Since this method was first described, it has been widely used for the reduction of α-amino acids.[18]

The mechanism of this reaction is based on the reaction of $NaBH_4$ with iodine to generate borane *in situ*, which is able to reduce carboxylic acids. H_2, which results from the oxidation of hydride, is the cause of the gas evolution observed during the reaction (*Scheme 27*).



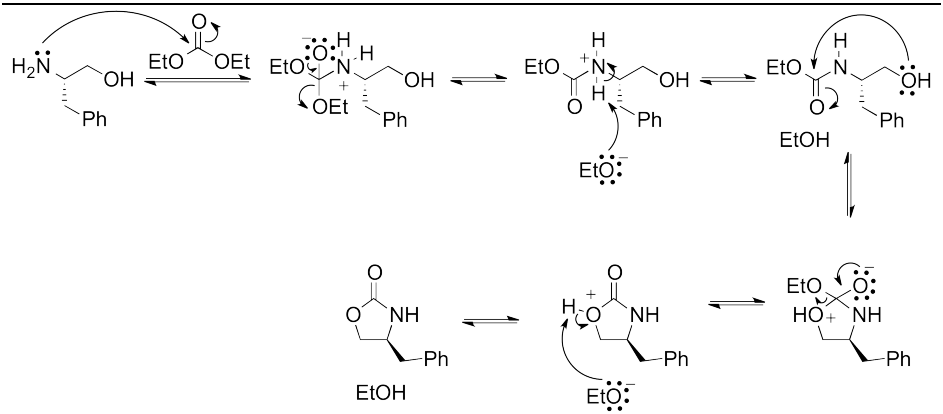
Scheme 27. Mechanism of the first step of the synthesis of Evans auxiliary.

Phenylalanine was reduced to the corresponding alcohol in 60% yield (*Scheme 28*).



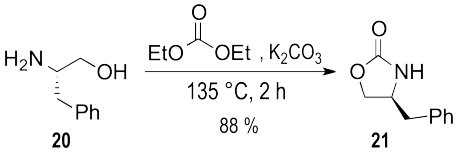
Scheme 28. First step of the synthesis of Evans auxiliary.

In the second step, both amine and alcohol attack the carbonyl group of diethyl carbonate, with ethoxides as leaving groups in this basic medium. As a result, a carbamate is formed. By analysing the mechanism of this reaction (*Scheme 29*) one can notice that the amine, which is more nucleophilic than the alcohol, is the first one to attack the carbonyl group. Secondly, even though there are amine groups from other molecules in the solution, the intramolecular reaction, where the alcohol group attacks the carbonyl, has a higher rate.



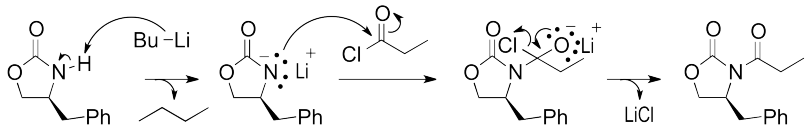
Scheme 29. Mechanism of the second step of the synthesis of Evans auxiliary.

The formation of the carbamate is an equilibrium reaction, so ethanol is distilled in order to displace it towards the formation of the desired product, which was obtained in 88% yield (*Scheme 30*).



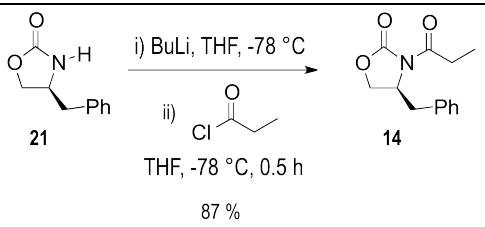
Scheme 30. Second step of the synthesis of Evans auxiliary.

For the final acylation reaction, a strong base (butyllithium) is used to deprotonate the nitrogen of the carbamate, which reacts with an acid chloride to give **14** (*Scheme 31*).



Scheme 31. Mechanism of the third step of the synthesis of Evans auxiliary.

The acylated oxazolidin-2-one was isolated in 87% yield (*Scheme 32*).

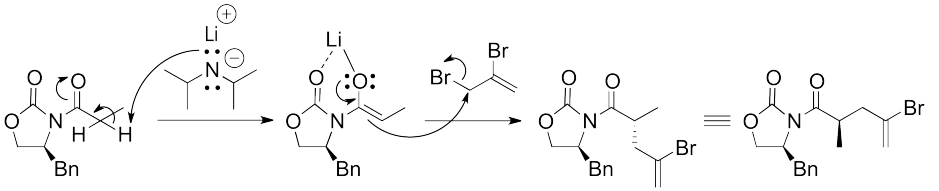


Scheme 32. Third step of the synthesis of Evans auxiliary.

2.2. ASYMMETRIC ALKYLATION WITH EVANS AUXILIARY

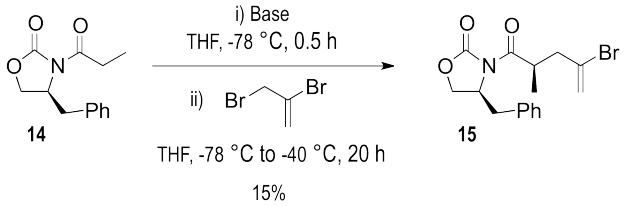
The next step was the asymmetric alkylation of the acyloxyzolidinone just described using the methodology developed by Evans.

The stereoselectivity of this alkylation step is interpreted by assuming that a metal-chelated *Z*(O)-enolate is formed (*Scheme 33*) and that the benzyl group, which is a bulky substituent, dictates the diastereoface that attacks 2,3-dibromopropene.



Scheme 33. Mechanism of the stereoselective alkylation with Evans auxiliary.

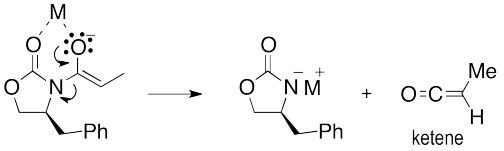
The reaction was run under the conditions described by Evans but the yield we obtained was very low: only 15%.



Scheme 34. Asymmetric alkylation of **14**.

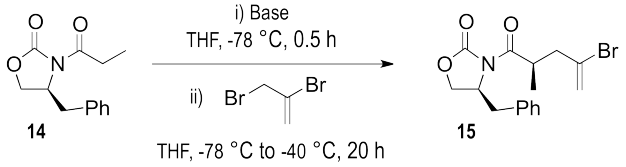
In spite of the high yields described in the literature for this transformation, the yields obtained in our research group are variable and not reproducible. This is why we decided to try to optimise this reaction.

The asymmetric alkylation using Evans auxiliaries works extremely well when the alkylating agents are reactive (MeI, benzylic or allylic). Even though 2,3-dibromopropene is an allylic bromide, we decided to study the reaction using different bases. This reaction has been described with both lithium and sodium bases. When a smaller and less electropositive cation like lithium is used, the bond between the metal and the oxygen atoms is tighter than with more electropositive metals like sodium or potassium. This means that the chelate formed will be more stable and less reactive. One the one hand, it means that it will have less tendency to react with the electrophile, but at the same time it will be more stable towards decomposition *via* a ketene (*Scheme 35*).



Scheme 35. Formation of the undesired ketene from Evans' chelate.

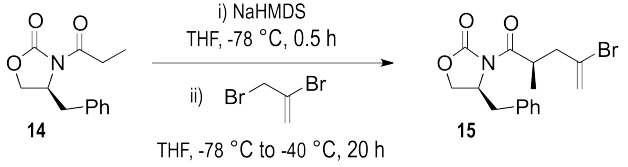
Conversely, the use of sodium bases affords more reactive chelates but these are only stable at temperatures below –20 °C (compared to 0 °C for lithium enolates). All the experiments conducted by our group so far had been performed with NaHMDS, so we decided to try a lithium base (LDA) and test if a more stable chelate results in a higher yield for the reaction. Unfortunately, the yield did not increase (*Table 6*).



Entry	Base	Yield [%]
1	NaHMDS	15
2	LDA	14

Table 6. Yield of Evans alkylation using different bases.

Some reactions afford better yields when run at a larger scale. However, after running the reaction with five times more starting material there was no improvement (*Table 7*).



Entry	Starting material [mg]	Yield [%]
1	200	15
2	1000	4

Table 7. Yield of Evans alkylation with NaHMDS using different amounts of starting material.

2.3. ASYMMETRIC ALKYLATION WITH PSEUDOEPHEDRINE

Having found no alternative way to increase the yield of the alkylation reaction using Evans auxiliary, we decided to try a different chiral auxiliary. Pseudoephedrine amides have also been used as auxiliaries for this kind of reactions and are inexpensive, commercially available and highly practical auxiliaries for asymmetric alkylation reactions.[19] Their high diastereoselectivities can be explained assuming that their enolate adopts the conformation shown in *Figure 3*. The solvent molecules (tetrahydrofuran in our case) that are coordinated to the lithium alkoxide sterically hinder the β-face of the enolate, so attack to the electrophile takes place from the α-face. The mnemonic used to know which absolute configuration the new centre has is to consider that the new alkyl group will be on a 1,4-syn configuration with respect to the methyl substituent on the carbon α to nitrogen.

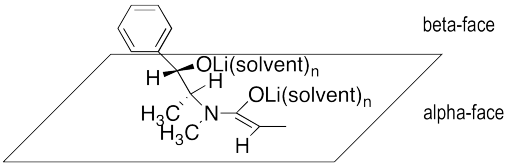
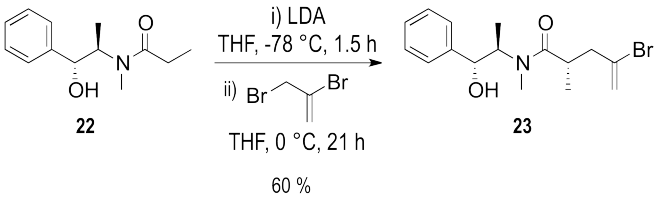


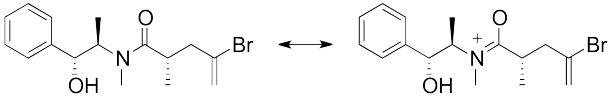
Figure 3. Proposed reactive conformation of pseudoephedrine amide enolates. Taken from A. G. Myers *et al.*[19]

We ran this reaction using (*R*,*R*)-pseudoephedrine and got a 60% yield of the desired product (*Scheme 36*), which is acceptable for our synthesis.



Scheme 36. Asymmetric alkylation of pseudoephedrine.

The yield is not the only aspect to take into account in this reaction: the diastereomeric excess must also be evaluated. While it has already been proved by our group that alkylation of Evans auxiliary with 2,3-dibromopropene affords diastereomeric ratios higher than 99:1, this still has to be evaluated with this new auxiliary. Even though this can be usually assessed by ^{1}H NMR, the fact that this molecule has rotamers makes it difficult to quantify the stereoselectivity with this technique. Many tertiary amides exist in two rotameric forms: the N-C(O) bond has a certain double bond character and rotation is restricted (*Scheme 37*). Since NMR is a slow technique, *E* and *Z* conformations of **23** can be distinguished, giving an NMR spectrum with two structures (a major and a minor one).



Scheme 37. Resonance structures of **23**.

We confirmed that the two species observed in the NMR spectrum of **23** are rotamers with 1D NOE spectra (*Figures 4-6*).[20]

Even though we confirmed the presence of rotamers, we could not exclude the possibility of small amounts of a minor diastereomer being present in the mixture. Hence, we decided to analyse our alkylation product using a different technique (HPLC). Two strategies were followed and these are described below.

2.3.1. Strategy A

We decided to analyse our alkylation product by HPLC to check whether only one signal was observed. This would mean that the reaction was selective.

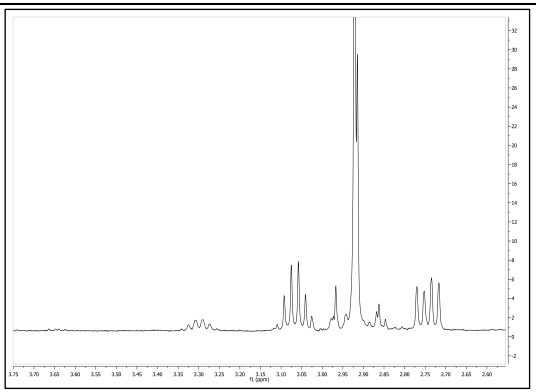


Figure 4. Part of the ^{1}H NMR spectrum of **23**.

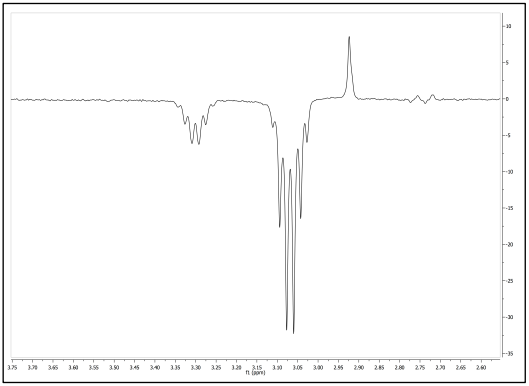


Figure 5. 1D NOE spectrum with irradiation of the signal at 3 ppm of **23**.

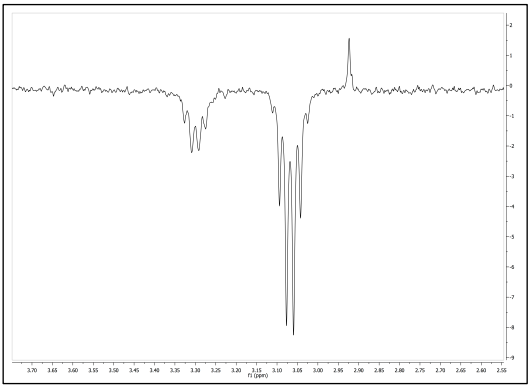
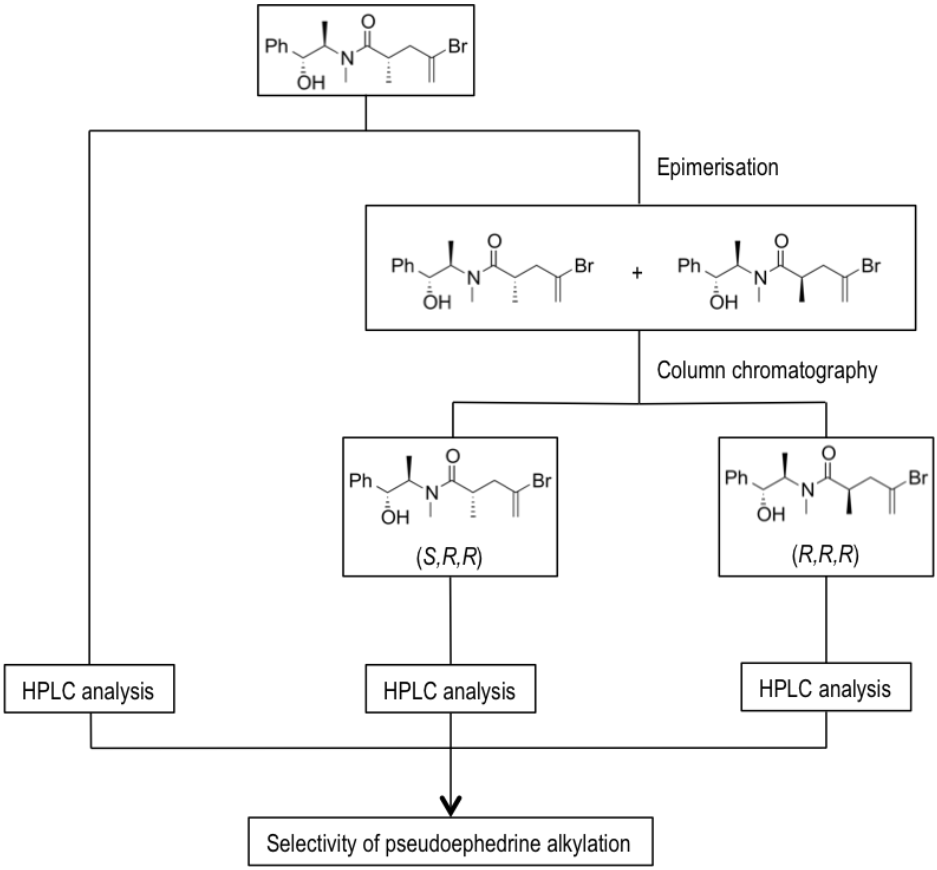


Figure 6. 1D NOE spectrum with irradiation of the signal at 3.3 ppm of **23**.

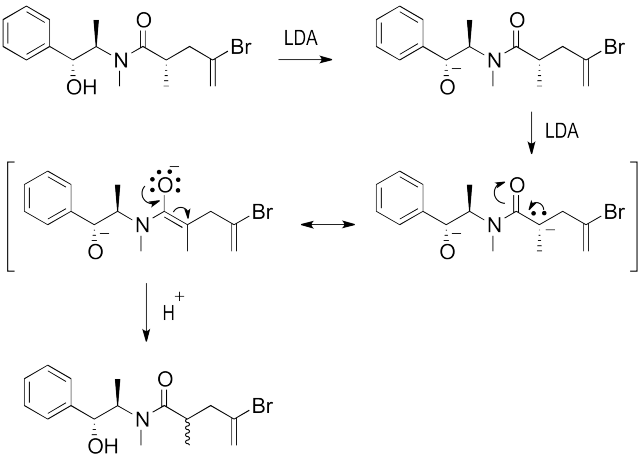
The first thing that had to be done was to prepare a sample of the undesired diastereomer (*S*,*R*,*R*) and then find HPLC conditions that allowed us to separate it from the (*R*,*R*,*R*)-isomer. We decided to epimerise our molecule at C_{19} and analyse it by HPLC as the authors of the original paper[19] had done for similar compounds. We hypothesised that we would obtain two main peaks, one for each epimer, or four peaks if the rotamers were also distinguished by HPLC. One of them should have the same retention time as the one obtained in the alkylation and the other one would correspond to the undesired epimer. In this way, we would be able to determine the diastereoselectivity of the alkylation reaction (*Scheme 38*).



Scheme 38. Procedure A followed to determine the selectivity of the pseudoephedrine alkylation.

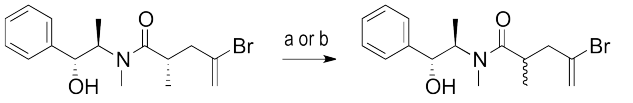
First, we tried to epimerise *S*,*R*,*R* with a strong base such as LDA. At least two equivalents of this base were needed (the most acidic proton in the molecule is the hydroxyl). Formation of

the amide enolate followed by aqueous quenching of the reaction would result in the loss of stereochemistry at C_{19} and consequent epimerization (*Scheme 39*).



Scheme 39. Epimerisation of **23** with LDA.

We followed the procedure described in the literature (*Scheme 40, conditions a*) for this reaction but, unfortunately, when analysing the reaction product by ^{1}H NMR we could not identify either the starting material nor the epimerisation product (*Figure 7*). Although some signals were common with **23**, there were no allylic protons (between 5 and 6 ppm). Some kind of cleavage seemed to have occurred, but we could not identify the product.



23 **23a, 23b**

a) LDA (5 equiv), THF, -78 °C to rt, 5 h; b) i) TFA (20 equiv), THF, reflux, 1 or 5 h, ii) $NaHCO_3$, rt, 24 h

Scheme 40. Epimerisation of **23**.

Since strong basic medium seemed not to be the appropriate conditions for our compound, we decided to try the epimerisation in acidic medium. This type of molecules can be epimerised with strong acids such as TFA as well, *via* a complex mechanism with an enol intermediate.

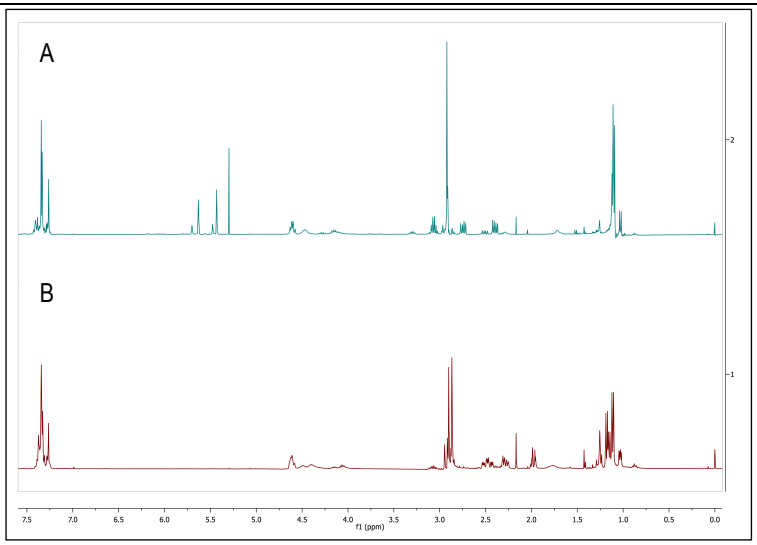


Figure 7. ^{1}H NMR spectra of **23** before (A) and after (B) treatment with LDA.

The epimerisation with TFA was run following the reaction conditions reported in the literature for similar compounds (*Scheme 40, conditions b*).

No reaction was observed in our case, as NMR analysis of the crude clearly showed (*Figure 8*).

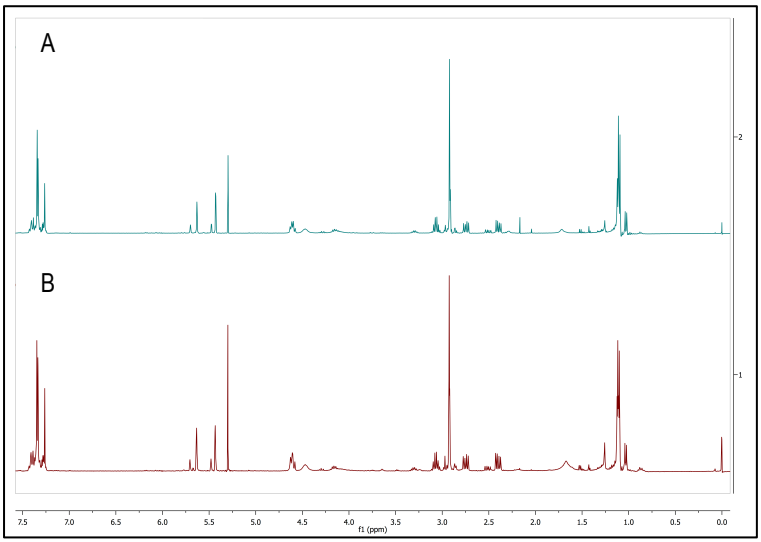


Figure 8. ^{1}H NMR spectra of **23** before (A) and after (B) treatment with TFA.

We then increased the reaction time and signals for a new compound were observed by ^{1}H NMR. However, when we tried to isolate it by column chromatography we obtained starting material as the major compound and small fractions of mixtures of different compounds. We analysed the major fraction by HPLC and compared it with the starting material (*Figure 9*).

A new signal at t_R = 15.4 min appeared. This could be assigned to the minor diastereomer. In this case, comparison with the initial spectrum would show that it was not formed during the alkylation. It would then mean that the reaction is selective. However, at this point we have not yet confirmed that this signal corresponds to our epimer so a second approach was pursued.

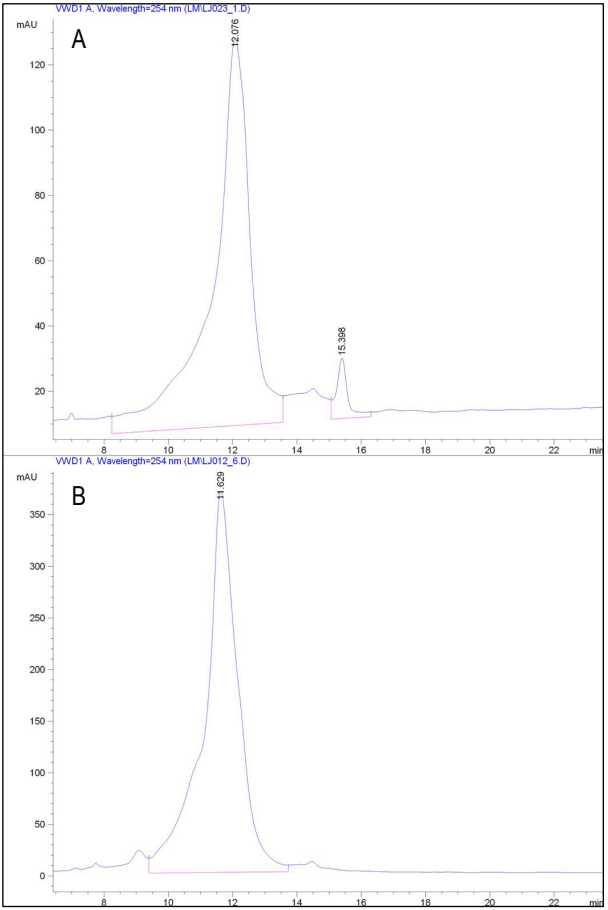
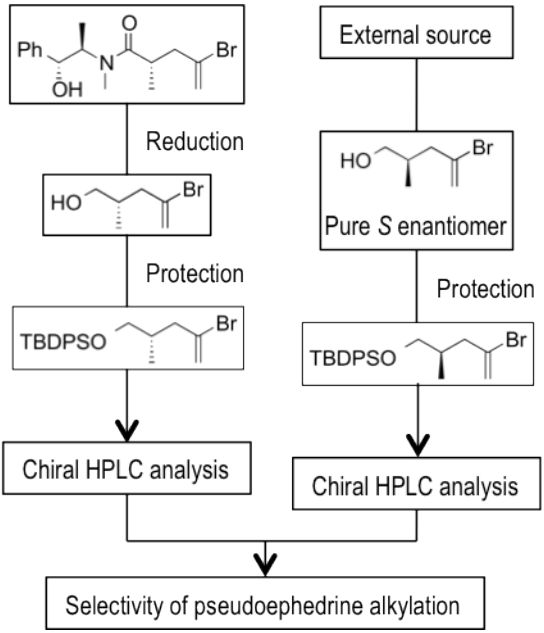


Figure 9. HPLC analysis of **23** before (A) and after (B) treatment with TFA.

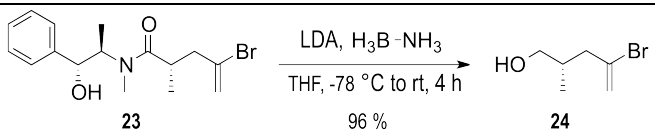
2.3.2. Strategy B

In our second strategy (*Scheme 41*), the chiral auxiliary was eliminated from the molecule. The resulting alcohol would be analysed by chiral HPLC in order to see if its enantiomer was present (which would mean that the alkylation with pseudoephedrine was not selective enough). Once again, we needed to have the enantiomeric form of the alcohol in order to know its retention time. It was obtained by alkylation with Evans auxiliary, whose selectivity had already been proved. Moreover, in both cases the alcohols had to be protected with a group containing a chromophore so that they could be detected by the HPLC apparatus used, which is coupled to a UV detector.



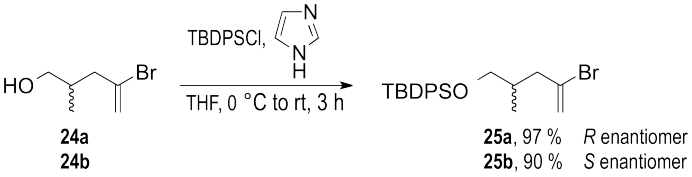
Scheme 41. Procedure B followed to determine the selectivity of pseudoephedrine alkylation.

The pseudoephedrine auxiliary was eliminated by reduction of the amide group with lithium amidotrihydroborate.[21] This reagent reduces tertiary amides to primary alcohols selectively and without epimerisation of the stereogenic centre. In addition to this, the yields of the reaction are high (96% in our case). Moreover, this reagent can be easily prepared *in situ* starting from a borane-ammonia complex, which can be converted to the hydride source by deprotonation with a strong base such as LDA (*Scheme 42*).



Scheme 42. Reduction of **23** to an alcohol with lithium amidotrihydroborate.

The last step was the protection of the alcohol group of both enantiomers as TBDPS ethers in order to detect them with the HPLC-UV technique. Similarly to most protection reactions, the yields were very high: 90 and 97% for the *S* and *R* enantiomers respectively (*Scheme 43*).



Scheme 43. Protection of alcohols **24a** and **24b** as TBDPS ethers.

The optical rotations of both structures were determined in order to check that they were enantiomers. If the experimental procedure had been followed correctly, these two structures should show the same absolute optical rotation but with opposite sign. In fact, this assumption agreed with the values obtained (*Table 8*). Nevertheless, it was later determined by HPLC that a certain amount of TBDPSOH still remained in the sample, so these values are not the ones of the pure compounds. In any case, their opposite signs do point to their stereogenic centres having opposite configurations.

	Enantiomer *R*	**Enantiomer *S***
Concentration [% g/V]	0.9	0.7
$[\alpha]_D$	+80.8	–75.4

Table 8. Optical rotations measured for **25a** and **25b**.

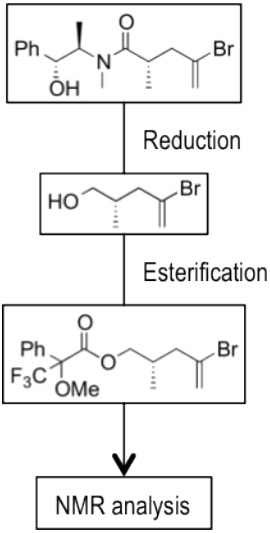
We then proceeded to analyse both enantiomers by chiral HPLC. A mixture of both enantiomers was prepared in order to find chromatographic conditions that allowed the separation of the enantiomers. However, for this racemic mixture only a single broad band was observed. Even though different columns (both normal and reverse phase), polarities and flux rates were tested all efforts were in vain.

Hence, even though both strategies followed seem to indicate that the reaction is diastereoselective, stronger evidence must still be found.

2.3.3. Strategy C

Although it has not been yet possible to experimentally test this approach, a new method is proposed for the determination of the diastereoselectivity of this alkylation reaction (*Scheme 44*). Since the research group needs to know whether this reaction is selective for the total synthesis of Amphidinolide E, it will be tested in the future.

The synthesis of Mosher esters has been used as a method to determine the enantiomeric composition of alcohols and amines.[22] This method consists of the preparation of an ester by reaction of the alcohol under study with α-methoxy-α-trifluoromethylphenylacetylchloride. The resulting ester has an additional chiral centre, so if the alcohol is enantiomerically pure only one diastereomer will be formed. Otherwise, it is known that the two possible diastereomers have some signals on NMR (both ^{1}H and ^{19}F) with considerably different chemical shifts. Thus, if we observe only one set of signals we will finally confirm that the pseudoephedrine alkylation is selective.



Scheme 44. Procedure C followed to determine the selectivity of pseudoephedrine alkylation.

3. CONCLUSIONS

Fragment **I** of Amphidinolide E has been synthesised in 19% yield with chiral (*R*)-glycidol as the starting material.

The yield of the first step of the synthesis of fragment **I** has been optimised from 67 to 92%. The effects of the solvent and the leaving group have been evaluated. However, the poor condition of the base used was the real cause of the low yield.

Evans auxiliary, widely used for asymmetric alkylation reactions, has been synthesised with L-phenylalanine as the starting material and in 46% yield. However, the complete synthesis of fragment **II** has not been achieved because of the low yield obtained on the alkylation of Evans auxiliary (15%), so we decided to use another auxiliary.

Pseudoephedrine is proposed as a better chiral auxiliary for the synthesis of fragment **II**. HPLC has been used to assess the selectivity of its asymmetric alkylation. The results obtained seem to indicate that it is highly selective but further studies still need to be done.

The results of this project will be useful to increase the yield of the total synthesis of Amphidinolide E. With high amounts of this compound available, biological studies will be undertaken to determine its pharmacological effects.

At this moment, the research group has synthesised the NE fragment by a Julia-Kocienski olefination with high regioselectivity. Fragment **IV** is being synthesised in order to study the Julia-Kocienski reaction between fragments **III** and **IV**.

4. EXPERIMENTAL PROCEDURE

All reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen and with anhydrous solvents, which were previously purified and dried according to standard methods.

Unless specified otherwise, all starting materials were obtained from commercial suppliers and used without further purification.

Analytical thin-layer chromatography was carried out on 0.25 mm silica gel plates (F254). The eluent used is specified in each case. The spots were visualised with UV (254 nm) and with exposure to *p*-anisaldehyde.

Flash column chromatography was performed on Merck silica gel 60 (0.040-0.063 mm). The eluents, which are specified in each case, were previously distilled.

^{1}H NMR spectra were recorded on a Varian Mercury-400 spectrometer. Chemical shifts (δ) are reported in ppm downfield from TMS. Coupling constants (*J*) are quoted in Hz and are indicated only in one of the protons involved (when applicable). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet and m = multiplet), coupling constant and integration.

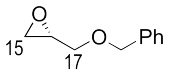
HPLC chromatograms were recorded on an Agilent 1100 Series Phenomenex chromatograph. The achiral column used was Agilent Prep-Sil 4.6 x 250 mm with hexanes and isopropanol as the eluents. The chiral column used was Lux 5u-Amylose-2 4.6 x 250 mm with water and acetonitrile as the eluents. The samples were eluted with a flow of 1 mL/min in both cases. The detections were done by UV at 246 nm.

Optical rotations ($[\alpha]_D$) were measured on $CHCl_3$ and at room temperature on a Perkin-Elmer 241 MC polarimeter. The wavelength used was the D line of sodium (589 nm).

All along the experimental part the compounds are numbered according to the numeration of Amphidinolide E.

(*S*)-2-(BENZYLOXYMETHYL)OXIRANE (2)

BnBr (1.3 equiv) and TBAI (when applicable) were added to a solution of **1** (1 equiv) in the solvent indicated in *Table 9* ([**1**] = 0.2 M) at 0 °C. 60% w/w NaH was then added and after 1 h at 0 °C the mixture was stirred for 20 h at room temperature Then, H_2O was added, the layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried with anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 80:20) to obtain **2**.



Colourless oil. $\mathbf{R_f}$ (hexanes/AcOEt 70:30): 0.31. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.62 (dd, 1H, $J_{15,16}$ = 2.7, $J_{15,15'}$ = 5.0, H_{15}), 2.80 (dd, 1H, $J_{15',16}$ = 4.2, $H_{15'}$), 3.19 (dddd, 1H, H_{16}), 3.45 (dd, 1H, $J_{16,17}$ = 5.8, $J_{17,17'}$ = 11.4, H_{17}), 3.77 (dd, 1H, $J_{16,17'}$ = 3.1, $H_{17'}$), 4.56 (d, 1H, J_{gem} = 11.9, $C\underline{H}_2Ph$), 4.62 (d, 1H, $C\underline{H}_2Ph$), 7.26-7.36 (m, 5H, Ph).

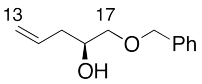
Entry	Solvent	NaH [equiv]	TBAI [equiv]	Yield [%]
1	DMF	1	–	57
2	DMF	1	0.04	54
3	THF	1	–	54
4	DMF	1.3	–	77
5	DMF	1.8	–	92

Table 9. Reaction conditions tested for the benzylation of **1.**

(*S*)-1-BENZYLOXYPENT-4-EN-2-OL (3)

A 1 M solution of vinylmagnesium bromide in THF (5.6 mL, 735 mg, 5.6 mmol) was added dropwise to a solution of **2** (759 mg, 4.62 mmol) and CuI (229 mg, 1.18 mmol) in THF at −78 °C. After 2 h at −78 °C the mixture was quenched by addition of a saturated NH_4Cl aqueous solution and the layers were separated. The aqueous phase was extracted with Et_2O (4 x 30 mL) and the combined organic extracts were washed with brine (2 x 40 mL). The organic layer was then dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue (980

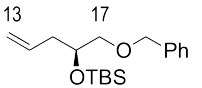
mg) was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 70:30) to afford **3** (661 mg, 3.44 mmol, 74%).



Colourless oil. **R_f** (hexanes/AcOEt 70:30): 0.38. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.24-2.30 (m, 2H, H_{15}), 2.33 (broad s, 1H, OH), 3.38 (dd, 1H, $J_{17,17'}$ = 9.5, $J_{16,17}$ = 7.4, H_{17}), 3.52 (dd, 1H, $J_{16,17'}$ = 3.4, $H_{17'}$), 3.85-3.93 (m, 1H, H_{16}), 4.56 (s, 2H, $C\underline{H_2}Ph$), 5.06-5.17 (m, 2H, H_{13}), 5.83 (ddt, 1H, $J_{13,14}$ = 17.2, $J_{13',14}$ = 10.2, $J_{14,15}$ = 7.1, H_{14}), 7.24-7.41 (m, 5H, Ph).

(*S*)-5-BENZYLOXY-4-(*TERT*-BUTYLDIMETHYLSILYLOXY)-1-PENTENE (4)

Imidazole (683 mg, 9.93 mmol) and TBS chloride (776 mg, 4.89 mmol) were added to a solution of **3** (634 mg, 3.30 mmol) in anhydrous DMF (8.2 mL) at 0 °C. After 3.5 h at room temperature, TLC showed that the reaction was not yet complete. More imidazole (116 mg, 1.69 mmol) and TBS chloride (250 mg, 1.58 mmol) were added. After 16 h the mixture was diluted with H_2O (40 mL) and Et_2O (40 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phases were washed with brine (2 x 50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product (1.27 g) was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 90:10), affording **4** (994 mg, 3.24 mmol, 98%).

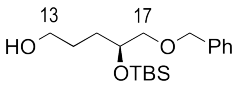


Colourless oil. **R_f** (hexanes/AcOEt 90:10): 0.68. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.03 (s, 3H, $OSi(C\underline{H_3})_2{}^tBu$), 0.04 (s, 3H, $OSi(C\underline{H_3})_2{}^tBu$), 0.87 (s, 9H, $OSi(CH_3)_2{}^t\underline{Bu}$), 2.21 (dddt, 1H, $J_{13,15}$ = 1.2, $J_{15,16}$ = 6.3, $J_{14,15}$ = 7.5, $J_{15,15'}$ = 13.8, H_{15}), 2.33 (dddt, 1H, $J_{13,15'}$ = 1.3, $J_{15',16}$ = 5.3, $J_{14,15'}$ = 6.7, $H_{15'}$), 3.38 (d, 2H, $J_{16,17}$ = 5.5, H_{17}), 3.82-3.91 (m, 1H, H_{16}), 4.51 (s, 2H, $C\underline{H_2}Ph$), 4.98-5.08 (m, 2H, H_{13}), 5.81 (ddt, 1H, $J_{13,14}$ = 10.2, $J_{13',14}$ = 17.2, H_{14}), 7.23-7.35 (m, 5H, Ph).

(*S*)-5-BENZYLOXY-4-(*TERT*-BUTYLDIMETHYLSILYLOXY)PENTAN-1-OL (5)

A 0.5 M solution of 9-BBN in THF (11.0 mL, 671 mg, 5.52 mmol) was added to a solution of **4** (846 mg, 2.76 mmol) in anhydrous THF (25 mL). After stirring for 4 h at room temperature, 33% H_2O_2 (5.5 mL, 1.8 g, 53 mmol) and 2 M NaOH (5.5 mL, 440 mg, 11 mmol) were added and the mixture was stirred for 18 h. Brine (50 mL) and CH_2Cl_2 (50 mL) were then added and the

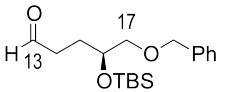
layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL) and the combined organic layers were washed with brine (2 x 40 mL). Then, they were dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The crude product (1.32 g) was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 70:30) to obtain **5** as a colourless oil (738 mg, 2.27 mmol, 82%).



Colourless oil. **R_f** (hexanes/AcOEt 70:30): 0.34. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.00 (s, 3H, OSi(C<u>H</u>$_3$)$_2$^{t}Bu), 0.01 (s, 3H, OSi(C<u>H</u>$_3$)$_2$^{t}Bu), 0.83 (s, 9H, OSi(CH$_3$)$_2$^{t}<u>Bu</u>), 1.31-1.84 (m, 5H, H_{14}+H_{15}+OH), 3.34 (dd, 1H, $J_{16,17}$ = 5.9, $J_{17,17'}$ = 9.5, H_{17}), 3.38 (dd, 1H, $J_{16,17'}$ = 5.6, $H_{17'}$), 3.52-3.62 (m, 2H, H_{13}), 3.80-3.88 (m, 1H, H_{16}), 4.42-4.50 (m, 2H, C<u>H</u>$_2$Ph), 7.21-7.32 (m, 5H, Ph).

(*S*)-5-BENZYLOXY-4-(*TERT*-BUTYLDIMETHYLSILYLOXY)PENTANAL (6)

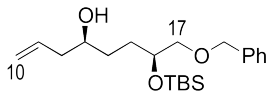
$(COCl)_2$ (230 μL, 335 mg, 2.64 mmol) was added to a solution of DMSO (375 μL, 410 mg, 5.25 mmol) in anhydrous CH_2Cl_2 (8.5 mL) at −78 °C. A solution of **5** (712 mg, 2.19 mmol) in anhydrous CH_2Cl_2 (6 mL) was then added *via* cannula. The temperature was maintained for 30 min before adding anhydrous Et_3N (1.6 mL, 1.2 g, 11 mmol). The mixture was warmed to room temperature and was allowed to react for 2 h. The solution was quenched with saturated aqueous $NaHCO_3$ (50 mL) and diluted with Et_2O (80 mL) to separate both layers. The organic phase was washed with saturated aqueous $NaHCO_3$ (2 x 50 mL) and brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue (729 mg) was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 70:30) to afford **6** (562 mg, 1.74 mmol, 80%).



Colourless oil. **R_f** (hexanes/AcOEt 70:30): 0.66. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.00 (s, 3H, OSi(C<u>H</u>$_3$)$_2$^{t}Bu), 0.01 (s, 3H, OSi(C<u>H</u>$_3$)$_2$^{t}Bu), 0.83 (s, 9H, OSi(CH$_3$)$_2$^{t}<u>Bu</u>), 1.76 (dq, 1H, $J_{14,15}$ = $J_{15,16}$ = 7.1, $J_{15,15'}$ = 14.1, H_{15}), 1.86 – 1.96 (m, 1H, $H_{15'}$), 2.45 (td, 2H, $J_{13,14}$ = 1.6, $J_{14,15'}$ = 7.4, H_{14}), 3.30 (dd, 1H, $J_{16,17}$ = 6.3, $J_{17,17'}$ = 9.5, H_{17}), 3.38 (dd, 1H, $J_{16,17'}$ = 5.3, $H_{17'}$), 3.82-3.89 (m, 1H, H_{16}), 4.45 (d, 1H, J_{gem} = 12.0, C<u>H</u>$_2$Ph), 4.49 (d, 1H, C<u>H</u>$_2$Ph), 7.22-7.35 (m, 5H, Ph), 9.73 (t, 1H, H_{13}).

(4*S*,7*S*)-8-BENZYLOXY-7-(*TERT*-BUTYLDIMETHYLSILYLOXY)OCT-1-EN-4-OL (7)

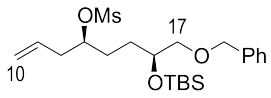
A solution of **6** (509 mg, 1.58 mmol) in Et_2O (2.8 mL) was added to a 1 M solution of (+)-allyldiisopinocampheylborane (2.2 mL, 718 mg, 2.2 mmol) in Et_2O (2.5 mL) at -78 °C. The mixture was allowed to react at this temperature for 1.5 h and then 3 M NaOH (650 μL, 78.0 mg, 1.95 mmol) and 33% H_2O_2 (620 μL, 205 mg, 6.00 mmol) were added. After stirring for 5 h, H_2O (10 mL) and Et_2O (10 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 20 mL) and the combined organic phases were washed with brine (30 mL). The organic extract was dried with anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product (1.14 g). It was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 70:30) to yield **7** (562 mg, 1.27 mmol, 96%).



Colourless oil. $\mathbf{R_f}$ (hexanes/AcOEt 70:30): 0.46 **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.00 (s, 3H, $OSi(C\underline{H_3})_2{}^tBu$) 0.01 (s, 3H, $OSi(C\underline{H_3})_2{}^tBu$), 0.83 (s, 9H, $OSi(CH_3)_2{}^t\underline{Bu}$), 1.44-1.64 (m, 4H, H_{14}+H_{15}), 1.74 (s, 1H, OH), 2.05-2.16 (m, 1H, H_{12}), 2.19-2.29 (m, 1H, $H_{12'}$), 3.32 (dd, 1H, $J_{16,17}$ = 5.7, $J_{17,17'}$ = 9.6, H_{17}), 3.37 (dd, 1H, $J_{16,17'}$ = 5.5, $H_{17'}$), 3.53-3.65 (m, 1H, H_{13}), 3.78-3.86 (m, 1H, H_{16}), 4.43-4.51 (m, 2H, $C\underline{H_2}Ph$), 5.03-5.07 (m, 1H, H_{10}), 5.07-5.13 (m, 1H, $H_{10'}$), 5.77 (dddd, 1H, $J_{11,12}$ = 6.7, $J_{11,12'}$ = 7.7, $J_{10,11}$ = 9.4, $J_{10',11}$ = 11.5, H_{11}), 7.19-7.33 (m, 5H, Ph).

(4*S*,7*S*)-8-BENZYLOXY-4-METHANSULFONYLOXY-7-(*TERT*-BUTYLDIMETHYLSILYLOXY)-OCT-1-ENE (8)

Et_3N (275 μL, 200 mg, 1.97 mmol) and MsCl (135 μL, 196 mg, 1.71 mmol) were added to a solution of **7** (479 mg, 1.31 mmol) in anhydrous CH_2Cl_2 (2.6 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then the temperature was raised to room temperature. After 2 h, H_2O (10 mL) and Et_2O (10 mL) were added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give **8** (505 mg, 1.14 mmol, 89%).

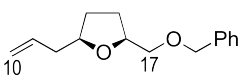


Colourless oil. $\mathbf{R_f}$ (hexanes/AcOEt 70:30): 0.54 **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.00 (s, 3H, $OSi(C\underline{H_3})_2{}^tBu$) 0.01 (s, 3H, $OSi(C\underline{H_3})_2{}^tBu$), 0.83 (s, 9H, $OSi(CH_3)_2{}^t\underline{Bu}$), 1.41-1.66 (m, 4H, H_{14}

+ H_{15}), 2.44 (t, 2H, $J_{11,12}$ = $J_{12,13}$ = 6.5, H_{12}), 2.92 (s, 3H, $OSO_2C\underline{H}_3$), 3.30 (dd, 1H, $J_{16,17}$ = 5.9, $J_{17,17'}$ = 9.6, H_{17}), 3.36 (dd, 1H, $J_{16,17'}$ = 5.4, $H_{17'}$), 3.80 (quint., 1H, $J_{15,16}$ = $J_{16,17}$ = 4.8, H_{16}), 4.47 (s, 2H, $C\underline{H}_2Ph$), 4.64-4.74 (m, 1H, H_{13}), 5.07-5.10 (m, 1H, H_{10}), 5.11-5.15 (m, 1H, $H_{10'}$), 5.67-5.81 (m, 1H, H_{11}), 7.20-7.34 (m, 5H, Ph).

(*2R,5S*)-2-ALLYL-5-(BENZYLOXYMETHYL)TETRAHYDROFURAN (9)

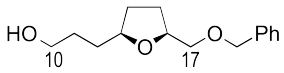
TBAF·3 H_2O (647 mg, 2.05 mmol) was added to a solution of **8** (505 mg, 1.14 mmol) in anhydrous THF (20 mL). After stirring for 16 h at room temperature the mixture was concentrated under reduced pressure. The residue (1.03 g) was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 70:30) to obtain **9** (213 mg, 0.92 mmol, 80%).



Colourless oil. $\mathbf{R_f}$ (hexanes/AcOEt 70:30): 0.56. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.49-1.60 (m, 1H, H_{14}), 1.64-1.73 (m, 1H, H_{15}), 1.87-1.99 (m, 2H, $H_{14'}$+$H_{15'}$), 2.20-2.29 (m, 1H, H_{12}), 2.35-2.44 (m, 1H, $H_{12'}$), 3.45 (dd, 1H, $J_{16,17}$ = 4.8, $J_{17,17'}$ = 10.0, H_{17}), 3.50 (dd, 1H, $J_{16,17'}$ = 5.8, $H_{17'}$), 3.90-3.98 (m, 1H, H_{16}), 4.05-4.12 (m, 1H, H_{13}), 4.56 (d, 1H, J_{gem} = 12.2, $C\underline{H}_2Ph$), 4.60 (d, 1H, $C\underline{H}_2Ph$), 5.00-5.12 (m, 2H, H_{10}), 5.82 (ddt, 1H, $J_{11,12}$ = 7.0, $J_{10,11}$ = 10.2, $J_{10',11}$ = 17.2, H_{11}), 7.23-7.38 (m, 5H, Ph).

3-((2*S*,5*S*)-5-(BENZYLOXYMETHYL)TETRAHYDROFURAN-2-YL)PROPAN-1-OL (10)

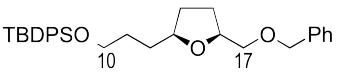
A 0.5 M solution of 9-BBN in THF (2.9 mL, 177 mg, 1.47 mmol) was added to a solution of **9** (171 mg, 0.74 mmol) in anhydrous THF (2.5 mL). After stirring for 4 h at room temperature, TLC showed that the reactant had not completely disappeared so more 9-BBN (700 μL, 42.7 mg, 0.350 mmol) was added and the mixture was stirred for an additional 1 h. Then, 2 M NaOH (1.4 mL, 110 mg, 2.8 mmol) and 33% H_2O_2 (1.4 mL, 460 mg, 14 mmol) were added and the mixture was stirred for 18 h more. Brine (15 mL) and CH_2Cl_2 (15 mL) were added to separate the layers and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product (350 mg), which was purified by *flash* column chromatography on silica gel (CH_2Cl_2/MeOH 95:5), gave **10** (177 mg, 0.71 mmol, 96%).



Colourless oil. **R_f** (CH_2Cl_2/MeOH 95:5): 0.26. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.48-1.76 (m, 6H, $2H_{11}$+$2H_{12}$+H_{14}+H_{15}), 1.89-2.02 (m, 2H, $H_{14'}$+$H_{15'}$), 3.47 (d, 2H, $J_{16,17}$ = 6.6, H_{17}), 3.59-3.72 (m, 2H, H_{10}), 3.86-3.95 (m, 1H, H_{13}), 4.07-4.15 (m, 1H, H_{16}), 4.55 (d, 1H, J_{gem} = 12.2, C$\underline{H}_2$Ph), 4.59 (d, 1H, C$\underline{H}_2$Ph), 7.25-7.36 (m, 5H, Ph).

(2*S*,5*S*)-5-BENZYLOXYMETHYL-2-(*TERT*-BUTYLDIPHENYLSILYLOXYPROPYL) TETRAHYDROFURAN (11)

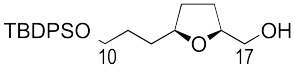
Imidazole (95 mg, 1.40 mmol) and TBDPS chloride (275 μL, 291 mg, 1.06 mmol) were added to a solution of **10** (173 mg, 0.69 mmol) in anhydrous THF (3.4 mL). After stirring for 3 h at room temperature the mixture was quenched with H_2O (15 mL) and diluted with CH_2Cl_2 (15 mL) to separate the phases. The aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain **11** (302 mg, 0.62 mmol, 89%).



Colourless oil. **R_f** (hexanes/AcOEt 70:30): 0.57. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.04 (s, 9H, OSi^t$\underline{Bu}$$(Ph)_2$), 1.04-1.72 (m, 6H, $2H_{11}$+$2H_{12}$+H_{14}+H_{15}), 1.88-1.96 (m, 2H, H_{14}+H_{15}), 3.43 (dd, 1H, $J_{16,17}$ = 4.9, $J_{17,17'}$ = 10.0, H_{17}), 3.47 (dd, 1H, $J_{16,17'}$ = 5.9, $H_{17'}$), 3.65-3.68 (m, 2H, H_{10}), 3.80-3.86 (m, 1H, H_{13}), 4.02-4.09 (m, 1H, H_{16}), 4.52-4.61 (m, 2H, C$\underline{H}_2$Ph), 7.26-7.42 (m, 10H, Ph).

((2*S*,5*S*)-5-(3-(*TERT*-BUTYLDIPHENYLSILYLOXYPROPYL)TETRAHYDROFURAN-2-YL)METHANOL (12)

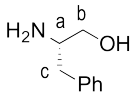
10% Pd/C (300 mg) was added to a solution of **11** (302 mg, 0.62 mmol) in absolute EtOH (4.1 mL). The mixture was stirred under a H_2 atmosphere for 20 h. The residue was filtered over Celite® and concentrated in *vacuo* to yield **12** (183 mg, 0.46 mmol, 74%).



Colourless oil. **R_f** (hexanes/AcOEt 70:30) = 0.26. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, OSi^{t}Bu(Ph)$_2$), 1.43-1.50 (m, 1H, H_{14}), 1.53-1.73 (m, 4H, H_{11}+H_{12}), 1.84-2.00 (m, 3H, H_{14}+H_{15}), 3.46 (dd, 1H, $J_{16,17}$ = 5.6, $J_{17,17'}$ = 11.3, H_{17}), 3.67-3.70 (m, 3H, H_{10}+$H_{17'}$), 3.83-3.89 (m, 1H, H_{13}), 3.96-4.01 (m, 1H, H_{16}), 7.35-7.42 (m, 6H, Ph), 7.65-7.68 (m, 4H, Ph).

(*S*)-2-AMINO-3-PHENYLPROPANOL (20)

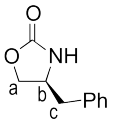
L-phenylalanine (10.0 g, 60.5 mmol) was added to a solution of $NaBH_4$ (5.70 g, 151 mmol) in anhydrous THF (160 mL). I_2 (15.4 g, 60.5 mmol) was then added dropwise at 0 °C. The mixture was stirred at reflux for 16 h and MeOH was added (20 mL). The solution was concentrated in *vacuo* to give a white paste to which a 20% solution of KOH in H_2O was added (120 mL). After stirring for 4 h at room temperature, the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated over reduced pressure. The white solid (9.87 g, 65.3 mmol) was recrystallized with toluene (6 mL) to give **20** (5.42 g, 35.9 mmol, 60%).



White solid. **R_f** (CH_2Cl_2/MeOH 95:5) = .0.40. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.73 (s, 1H, OH), 2.53 (dd, 1H, $J_{a,c}$ = 8.5, $J_{c,c'}$ = 13.4, H_c), 2.80 (dd, 1H, $J_{a,c'}$ = 4.5, $H_{c'}$), 3.08-3.17 (m, 1H, H_a), 3.33-3.44 (m, 1H, H_b), 3.59-3.69 (m, 1H, $H_{b'}$), 7.14-7.38 (m, 5H, Ph).

(*S*)-4-BENZYL-1,3-OXAZOLIDIN-2-ONE (21)

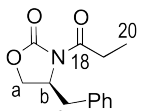
Potassium carbonate (0.47 g, 3.40 mmol) and diethyl carbonate (8.7 mL, 8.48 g, 71.8 mmol) were added to **20** (5.25 g, 34.7 mmol). The reaction was heated to 135 °C and the EtOH formed was distilled. H_2O (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic extracts were washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. **21** (5.42 g, 30.5 mmol) was obtained as a yellow solid (5.42 mg, 30.5 mmol, 88%).



Yellow solid. **R_f** (CH_2Cl_2/MeOH 96:4) = 0.42 **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 2.88 (d, 2H, J = 6.0, H_c), 4.06-4.18 (m, 2H, H_a), 4.43-4.49 (m, 1H, H_b), 5.38 (s, 1H, NH), 7.14-7.39 (m, 5H, Ph).

(*S*)-4-BENZYL-3-PROPANOYL-1,3-OXAZOLIDIN-2-ONE (14)

A 1.6 M solution of BuLi in hexanes (8.0 mL, 0.72 g, 13 mmol) was added dropwise to a solution of **21** (2.00 g, 11.2 mmol) in anhydrous THF (35.4 mL) at −78 °C. Then, propanoyl chloride (1.2 mL, 1.2 g, 14 mmol) was added at the same temperature. After stirring for 30 min the reaction mixture was quenched with saturated aqueous NH_4Cl (4.3 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were washed with H_2O (2 x 50 mL) and brine (50 mL), dried with anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The residue (2.96 g) was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 70:30) and **14** (2.26 g, 9.66 mmol, 87%) was obtained.



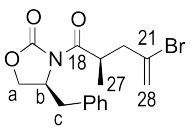
White solid. **R_f** (hexanes/AcOEt 70:30): 0.33. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.21 (t, 3H, $J_{19,20}$ = 7.4, H_{20}), 2.77 (dd, 1H, J_{bc} = 9.6, $J_{c,c'}$ = 13.4, H_c), 2.87-3.06 (m, 2H, H_{19}), 3.31 (dd, 1H, $J_{bc'}$ = 3.3, $H_{c'}$), 4.13-4.24 (m, 2H, H_a), 4.68 (ddt, 1H, $J_{a,b}$ = 3.3, $J_{a',b}$ = 6.9, H_b), 7.18-7.37 (m, 5H, Ph).

(*S*)-4-BENZYL-3-((*R*)-4-BROMO-2-METHYLPENT-4-ENOYL)-1,3-OXAZOLIDIN-2-ONE (15)

The base indicated in *Table 10* (1.1 equiv) was added to a solution of **14** in THF at −78 °C. After 40 min at the same temperature 2,3-dibromopropene (2 equiv) was added and the mixture was stirred for 1 h at −78 °C and for 20 h at −40 °C. Then, H_2O and CH_2Cl_2 were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with H_2O and brine. The organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated to obtain the crude product. It was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 70:30) to afford **15**.

Entry	Base	Yield [%]
1	NaHMDS	15
2	LDA	14

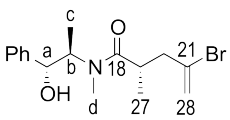
Table 10. Bases tested for the alkylation of **14**.



Colourless oil. **R_f** (hexanes/AcOEt 70:30): 0.38. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.23 (d, 3H, $J_{19,27}$ = 6.9, H_{27}), 2.53 (ddd, 1H, $J_{20,28'}$ = 0.8, $J_{19,20}$ = 6.7, $J_{20,20'}$ = 14.5, H_{20}), 2.75 (dd, 1H, $J_{b,c}$ = 9.6, $J_{c,c'}$ = 13.4, H_c), 3.01 (ddd, 1H, $J_{20',28'}$ = 0.8, $J_{19,20'}$ = 7.6, $H_{20'}$), 3.28 (dd, 1H, $J_{b,c'}$ = 3.3, $H_{c'}$), 4.15-4.23 (m, 3H, H_{19}+H_a), 4.69 (ddt, 1H, $J_{a,b}$ = $J_{a',b}$ = 7.6, H_b), 5.50 (d, 1H, $J_{28,28'}$ = 1.6, H_{28}), 5.69 (dt, 1H, $H_{28'}$), 7.18-7.37 (m, 5H, Ph).

(*S*)-4-BROMO-*N*-((1*R*,2*R*)-2-HYDROXY-1-METHYL-2-PHENYLETHYL)-*N*,2-DIMETHYL-4-PENTENAMIDE (23)

A 1.6 M solution of BuLi in hexanes (3.6 mL, 370 mg, 5.8 mmol) was added to a solution of LiCl (717 mg, 16.6 mmol) and ^{i}Pr$_2$NH (878 μL, 629 mg, 6.21 mmol) in anhydrous THF at −78 °C. The temperature was raised to 0 °C and after 10 min a solution of **22** (611 mg, 2.76 mmol) in anhydrous THF (6 mL) was added *via* cannula at −78 °C. The mixture was stirred for 1 h at −78 °C, for 15 min at 0 °C and for 15 min at room temperature. 2,3-Dibromopropene (684 μL, 1.10 g, 5.52 mmol) was then added at 0 °C and the mixture was stirred for 21 h at this temperature. The reaction was quenched with NH_4Cl (50 mL) and diluted with AcOEt (50 mL). The layers were separated and the aqueous phase was extracted with AcOEt (3 x 40 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue (1.46 g) was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 40:60) to obtain **23** (562 mg, 1.66 mmol, 60%).



Yellow oil. **R_f** (hexanes/AcOEt 40:60): 0.27. **^{1}H NMR** (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, $CDCl_3$, 400 MHz): δ 0.97-1.20 (m, 6H, H_c+H_{27}), 2.40 (dd, 1H, $J_{19,20}$ = 6.8, $J_{20,20'}$ = 14.3, H_{20}), 2.50* (dd, 1H, $J_{19,20}$ = 4.4, $J_{20,20'}$ = 12.6, H_{20}), 2.74 (dd, 1H, $J_{19,20'}$ = 7.2, $H_{20'}$), 2.83-2.91* (m, 1H, $H_{20'}$), 2.92 (s, 3H, H_d), 3.01-3.15 (m, 1H, H_{19}), 3.23-3.37* (m, 1H, H_{19}), 3.97-4.23 (m, 1H, H_b), 4.23-4.35* (m, 1H, H_b), 4.47 (broad s, 1H, OH), 4.56-4.70 (m, 1H, H_a), 5.43 (d, 1H, *J* = 1.6, H_{28}), 5.47* (d, 1H, *J* = 1.4, H_{28}), 5.63 (s, 1H, $H_{28'}$), 5.70* (s, 1H, $H_{28'}$), 7.22-7.45 (m, 5H, Ph).

EPIMERIZATION OF 23 WITH ACID

TFA (20 equiv) was added to a solution of **23** in THF ([**18**] = 0.1 M). The mixture was stirred at reflux for the time indicated in *Table 11* and neutralized with saturated aqueous $NaHCO_3$. After stirring for 24 h at room temperature CH_2Cl_2 was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. A colourless oil was obtained.

Entry	Reflux time [h]	Epimerization
1	1	No
2	4	?

Table 11. Reflux time tested for the epimerization of **23** with acid.

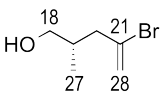
EPIMERIZATION OF 23 WITH BASE

A 1.6 M solution of BuLi in hexanes (540 μL, 49.4 mg, 0.864 mmol) was added to a solution of diisopropylamine (130 μL, 93.1 mg, 0.920 mmol) in THF (1 mL) at −78 °C. This mixture was transferred to a −78 °C solution of **23** (59 mg, 0.17 mmol) in THF (1 mL) *via* cannula. After stirring for 5 h at room temperature the mixture was quenched with NH_4Cl (1 mL). H_2O (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were washed with brine (2 x 20 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. ^1H NMR analysis of the residue (28 mg) showed the disappearance of the starting material and formation of multiple, undesired compounds.

(*S*)-4-BROMO-2-METHYLPENT-4-EN-1-OL (24)

A 1.6 M solution of BuLi in hexanes (460 μL, 42.0 mg, 0.736 mmol) was added to a solution of diisopropylamine (115 μL, 82.3 mg, 0.814 mmol) in THF (0.8 mL) at −78 °C. Then, borane-ammonia complex (27 mg, 0.73 mmol) was added at 0 °C. The mixture was stirred for 15 min at 0 °C and for 30 min at room temperature. A solution of **23** (62 mg, 0.18 mmol) in THF (1 mL) was then added *via* cannula at 0 °C and the mixture was stirred for 3 h at room temperature. Brine (10 mL) and Et_2O (10 mL) were added and the phases were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) and the organic extracts were washed with brine (20

mL). The organic phase was dried with anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to obtain the crude product (52 mg). It was was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 40:60) to afford **24** (31 mg, 0.17 mmol, 96%).



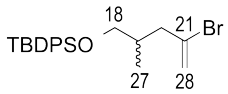
Colourless oil. $\mathbf{R_f}$ (hexanes/AcOEt) = 0.49. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.95 (d, 3H, $J_{19,27}$ = 6.8, H_{27}), 2.03-2.09 (m, 1H, H_{19}), 2.24 (ddd, 1H, $J_{20,28'}$ = 0.8, $J_{19,20}$ = 8.2, $J_{20,20'}$ = 14.2, H_{20}), 2.59 (ddd, 1H, $J_{20',28'}$ = 1.0, $J_{19,20'}$ = 6.0, $H_{20'}$), 3.54 (d, 2H, $J1_{8,19}$ = 5.7, H_{18}), 5.45 (d, 1H, $J_{28,28'}$ = 1.5, H_{28}), 5.60 (dt, 1H, $H_{28'}$).

2-BROMO-5-(*TERT*-BUTYLDIPHENYLSILYLOXY)-4-METHYLPENT-1-ENE (25)

Imidazole (2 equiv) and TBDPS chloride (1.5 equiv) were added to a solution of **(*R*)-24** or **(*S*)-24** in THF ([**19**] = 0.2 M) at 0 °C. The mixture was stirred for 3 h at room temperature. Then, H_2O and CH_2Cl_2 were added to separate the phases. The aqueous layer was extracted with CH_2Cl_2 and the organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue, which was purified by *flash* column chromatography on silica gel (hexanes/AcOEt 40:60), gave **25** (*Table 12*).

Entry	Enantiomer	Yield [%]
1	*R*	97
2	*S*	90

Table 12. Yields of the protection of **24a** and **24b**.



Colourless oil. $\mathbf{R_f}$ (hexanes/AcOEt) = 0.74. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 0.93 (d, 3H, $J_{19,27}$ = 6.7, H_{27}), 1.06 (m, 9H, OSi^{t}Bu(Ph)$_2$), 2.03-2.13 (m, 1H, H_{19}), 2.19 (dd, 1H, $J_{19,20}$ = 8.4, $J_{20,20'}$ = 14.1, H_{20}), 2,68 (dd, 1H, $J_{19,20'}$ = 5.5, $H_{20'}$), 3.51 (dd, 1H, $J_{18,19}$ = 5.6, $J_{18,18'}$ = 9.9, H_{18}), 3.56 (dd, 1H, $J_{18',19}$ = 5.4, $H_{18'}$), 5.40-5.41 (m, 1H, H_{28}), 5.52-5.54 (m, 1H, $H_{28'}$), 7.34-7.45 (m, 6H, Ph), 7.63-7.74 (m, 4H, Ph).

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APPENDICES

ACRONYMS

9-BBN	9-borabicyclo[3.3.1]nonane
Bn	Benzyl
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
HPLC	High Performance Liquid Chromatography
LDA	Lithium diisopropylamide
Ms	Mesyl
NaHMDS	Sodium hexamethyldisilazane
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
PG	Protecting Group
Ph	Phenyl
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldimethylphenylsilyl
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography