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Grau de Química

Treball Final de Grau

Preparation of precursors for the synthesis of the C_{18}–C_{28} fragment of Iriomoteolide-2a.

Preparació de precursors per a la síntesi del fragment C_{18}–C_{28} de la Iriomoteolida-2a.

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June 2016

Universitat de Barcelona

B:KC Barcelona Knowledge Campus
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S'ha de fer de la vida un somni i d'un somni una realitat.

Pierre Curie

A l'Anna Mª, en Cristian i a tota la gent del laboratori, gràcies de tot cor per tot l'ajut, suport i bons moments que m'heu donat en el transcurs d'aquest TFG.

A l'Isaac, la Judit, la Laura i la Lídia, gràcies per haver-me acompanyat en aquest viatge. Ningú em coneix millor que vosaltres, gràcies per fer-me entendre el que significa realment la paraula amistat i per il·luminar els moments més foscos amb un raig de llum. "*Nos quedan muchos más regalos por abrir*".

A la meva mare. Mare, amiga, confident, companya de viatge, el motiu de la meva felicitat. Gràcies per haver-me ensenyat tant, per haver-me fet tal i com sóc, per fer-me entendre el valor de l'esforç, per donar-me tot el teu amor, per fer-me sentir el fill més afortunat del món. Aquest treball (i tot el que queda per venir) va per tu.

REPORT

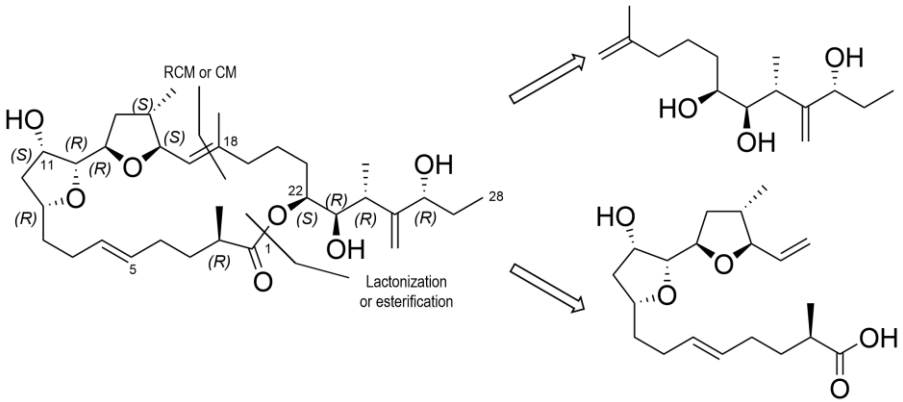
CONTENTS

SUMMARY

Marine dinoflagellates of the genus *Amphidinium* produce a great diversity of secondary metabolites, among them macrolides with very diverse and interesting structures, such as Amphidinolides and Iriomoteolides. These metabolites have potent anticancer activity, a fact that, together with their low availability from natural resources, makes them interesting targets for total synthesis in order to further study and evaluate their biological activity.

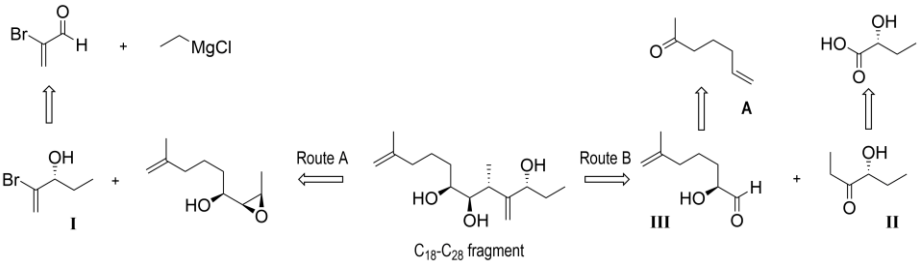
Iriomoteolide-2a is a potent cytotoxic 23-membered macrolide of polyketide origin. This macrolide contains 11 stereogenic centers and features a structurally complex side chain.

To date, only the structure of iriomoteolide-2a is known. No total synthesis has been reported yet. The retrosynthesis designed in the group for Iriomoteolide-2a disconnects the molecule into two major fragments (**Scheme S1).** This TFG focuses on the preparation of precursors that can be applied to the stereoselective preparation of the C_{18}–C_{28} fragment.



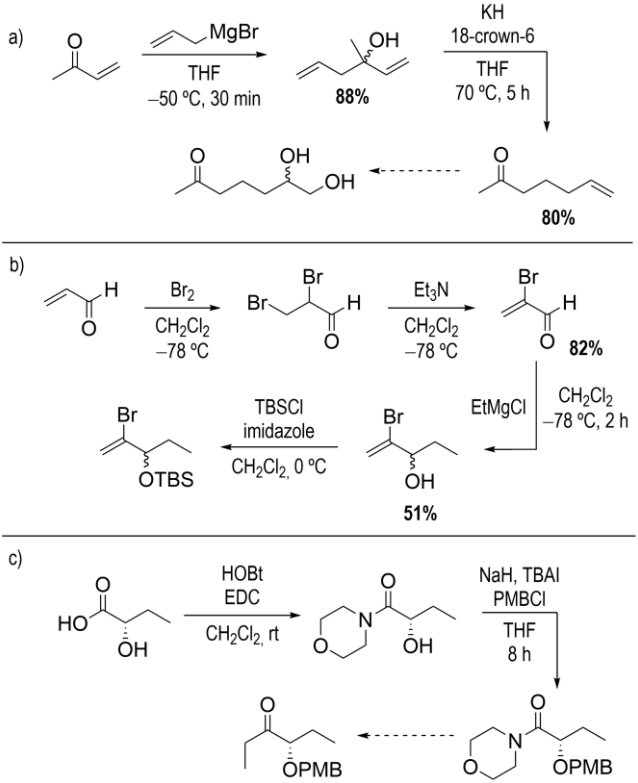
Scheme S1. Retrosynthetic analysis for Iriomoteolide-2a.

Two routes have been proposed for the synthesis of the C_{18}–C_{28} fragment as shown in **Scheme S2.**



Scheme S2. Retrosynthetic analysis for C_{18}–C_{28} fragment.

In this work ketone **A** has been prepared following the route shown in **Scheme S3a**. Its dihydroxylation under different conditions has been studied. TBS-protected vinyl bromide **I** has also been prepared following the route shown in **Scheme S3b.** Finally, the first steps towards the preparation of ketone **II** have been explored (**Scheme S3c**).



Scheme S3. Synthetic routes studied in this work.

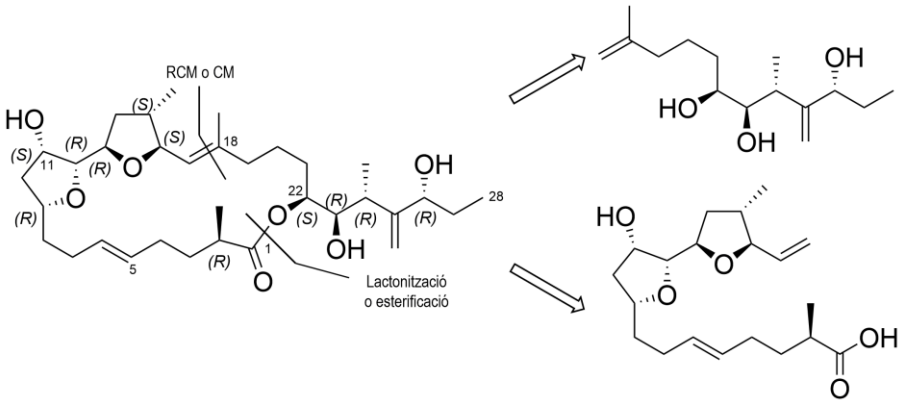
Keywords: precursors, total synthesis, asymmetric synthesis, macrolides.

RESUM

Els dinoflagel·lats marins del gènere *Amphidinium* produeixen una gran diversitat de metabòlits secundaris, entre ells macròlids amb estructures diverses i interessants, com les Amfidinolides i les Iriomoteolides. Aquests metabòlits tenen una activitat anticancerosa potent, fet que, conjuntament amb poca disponibilitat de fonts naturals, fet que els fa interessants com a objectiu per a la síntesi total al laboratori a fi d'avaluar després la seva activitat biològica.

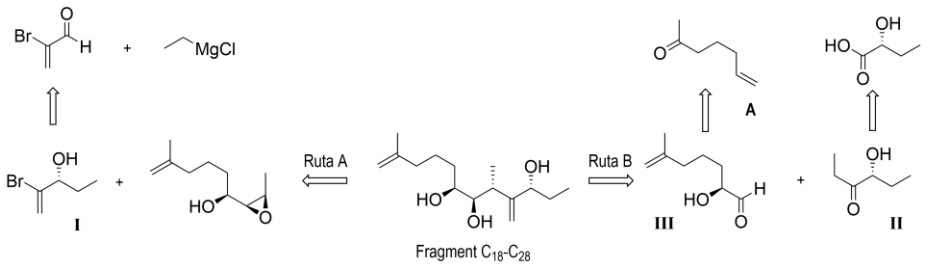
La Iriomoteolida-2a és un macròlid de 23 membres i potent agent citotòxic d'origen policètid. Aquest macròlid conté 11 centres estereogènics i una cadena lateral estructuralment complexa.

Fins avui, només es coneix l'estructura de la Iriomoteolida-2a. No s'ha publicat cap síntesi total encara. La retrosíntesi dissenyada en el grup per a la Iriomoteolida-2a desconnecta la molècula en dos fragments principals (**Esquema R1**). Aquest TFG se centra en la preparació de precursors que es poden utilitzar en la preparació estereoselectiva del fragment C_{18}–C_{28}.



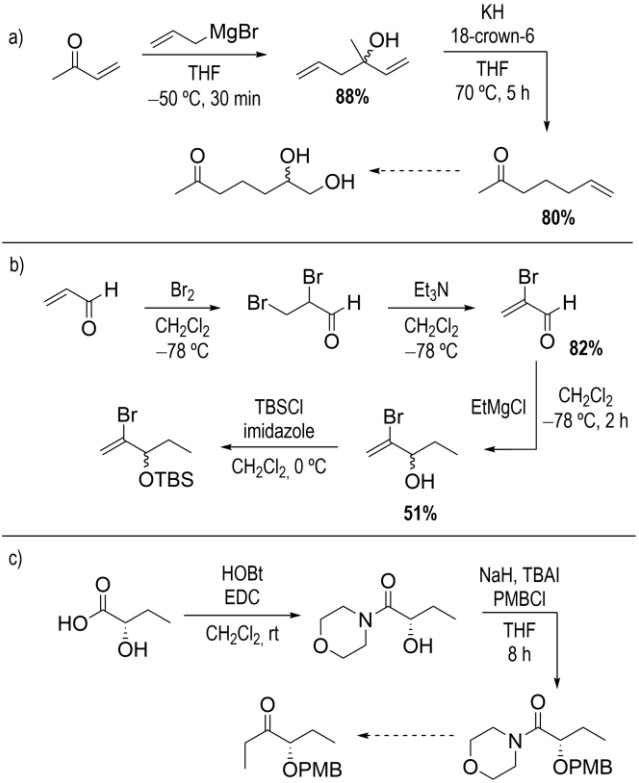
Esquema R1. Anàlisi retrosintètica de la Iriomoteolida-2a.

S'han proposat dues rutes per a la síntesi del fragment C_{18}-C_{28}, com es mostra a l'**Esquema R2.**



Esquema R2. Anàlisi retrosintètica del fragment C_{18}-C_{28}.

En aquest treball s'ha preparat la cetona **A** seguint la ruta de l'**Esquema R3a** i s'ha estudiat la seva dihidroxilació sota diferents condicions. El bromur de vinil protegit amb TBS **I** també s'ha preparat seguint la ruta de l'**Esquema R3b**. Finalment, s'han explorat els primers passos per a la preparació de la cetona **II** (**Esquema R3c**).



Esquema R3. Rutes sintètiques estudiades.

Paraules clau: precursors, síntesi total, síntesi asimètrica, macròlids.

INTRODUCTION AND OBJECTIVES

Iriomoteolides, like Amphidinolides, are a family of secondary metabolites produced by marine benthic dinoflagellates of the genus *Amphidinium.* These secondary metabolites are macrolides, or macrocyclic lactones, with a potent cytotoxic activity.

Iriomoteolide-2a is a 23-membered macrolide with an interesting structure, which includes two tetrahydrofuran rings, a complex side chain, three double bonds (two of them stereogenic) and eleven stereogenic centres. It exhibits potent cytotoxic activity in vitro and in vivo.

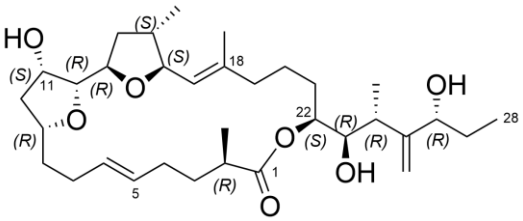


Figure 1. Iriomoteolide-2a.

Its isolation, structural elucidation and study of biological activity was reported by Tsuda and co-workers in 2015.[1] Iriomoteolide-2a was isolated from algal cells from marine dinoflagellates of the genus *Amphidinium*. Only a 0.032% dry weight was obtained from 15.3 g of algal cells. Complex structural determination techniques (^{1}H–^{1}H COSY & TOCSY, HMBC, ROESY, CH_2-selected E-HSQC-TOCSY, HRESIMS…) were used in its structure elucidation.

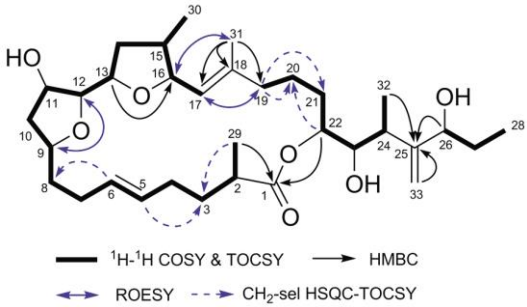
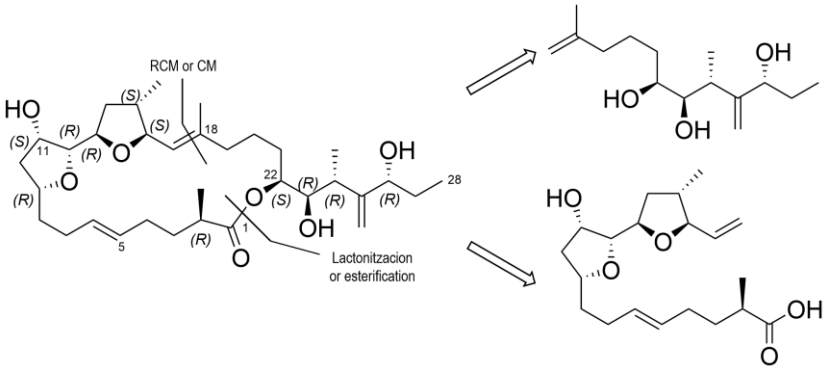


Figure 2. Selected 2D NMR correlations for Iriomoteolide-2a.[1]

*(image taken from Masashi Tsuda et al. Heterocycles **2015**, 91, 265-274)*

Due to its exciting structure and its low availability from natural resources, Iriomoteolide-2a is an interesting synthetic target. The retrosynthesis designed in the group for the total synthesis of Iriomoteolide-2a disconnects the molecule into two major fragments (**Scheme 1**).



Scheme 1. Retrosynthetic analysis for Iriomoteolide-2a.

This project focuses on the preparation of precursors for the synthesis of fragment C_{18}–C_{28} with an unprecedented **1,2,5-trihydroxy-3-methyl-4-methyleneheptyl** chain (**Figure 3**).

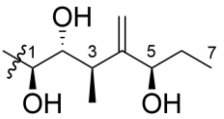
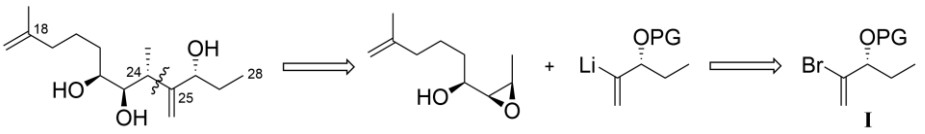


Figure 3. 1,2,5-Trihydroxy-3-methyl-4-methyleneheptyl substructure.

1. RETROSYNTHETIC ANALYSIS OF FRAGMENT C_{18}–C_{28}

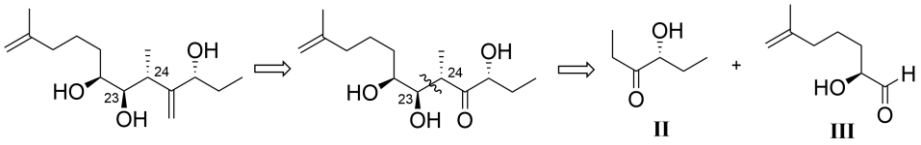
Two routes have been proposed for the synthesis of fragment C_{18}–C_{28}, as discussed below.

In route **A**, the nucleophilic attack of an organolithium compound to an epoxide forms the C_{24}–C_{25} bond.



Scheme 2. Route **A**.

Route B is based on an aldol reaction to form the C_{23}–C_{24} bond.

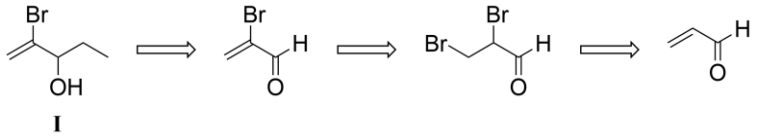


Scheme 3. Route **B**.

In this work we have focused on the preparation of synthons **I**, **II** and **III** from readily available starting materials.

1.1. Retrosynthesis of I

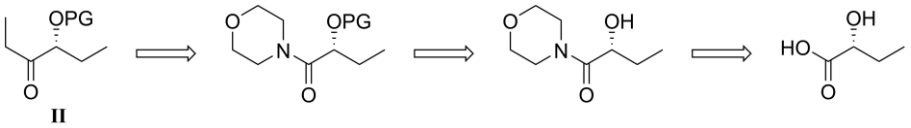
For the synthesis of **I**, the following retrosynthesis has been designed. The starting material was acrolein, which was transformed into **I** in three steps: bromination of the alkene, elimination and ethyl addition to the aldehyde.



Scheme 4. Retrosynthesis for synthon **I**.

1.2. Retrosynthesis of II

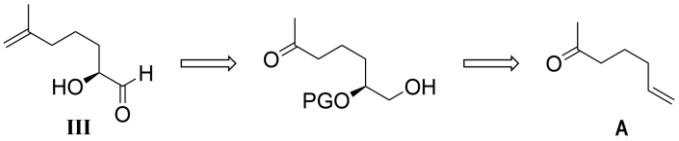
The chosen staring material for the preparation of **II** was commercially available (*R*)-2-hydroxybutanoic acid, which was transformed into **II** by morpholine amide formation, alcohol protection and reaction with ethylmagnesium bromide.



Scheme 5. Retrosynthesis for synthon **II**.

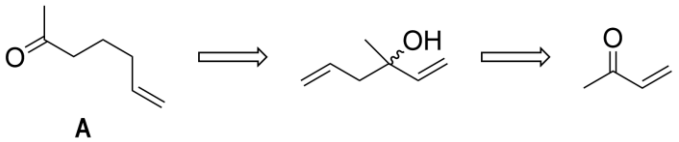
1.3. Retrosynthesis of III

We considered the possibility to prepare **III** from ketone **A** via alkene dihydroxylation, methylenation of the ketone and selective oxidation of the primary alcohol.



Scheme 6. Retrosynthesis for synthon **III**.

We plan to prepare ketone **A** from methyl vinyl ketone (**Scheme 7**).



Scheme 7. Retrosynthesis for ketone **A**.

2. OBJECTIVES

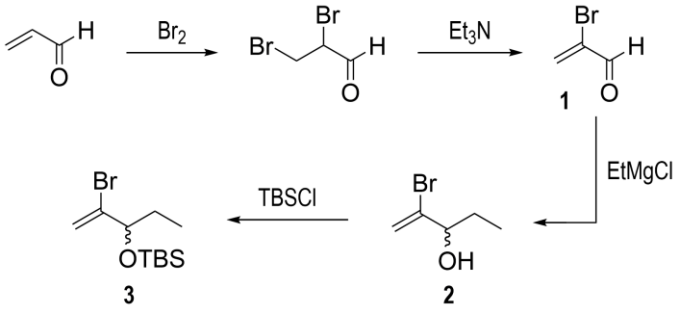
The main objectives of this project are:

- The preparation of synthon **I** from acrolein.
- The preparation of ethyl ketone **II** from (*R*)-2-hydroxybutanoic acid.
- The preparation of ketone **A**.
- To study the best approach for the transformation of **A** into synthon **III**.

RESULTS AND DISCUSSION

A. SYNTHESIS OF 2-BROMO-3-*tert*-BUTYLDIMETHYLSILYLOXYPENT-1-ENE (3)

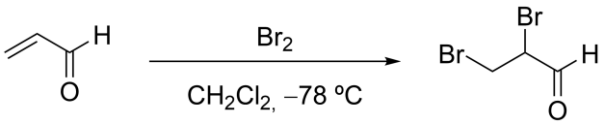
For the synthesis of alkene **3**, the following synthetic route was planned, starting from acrolein (**Scheme 8**).



Scheme 8. Synthetic route to **3**.

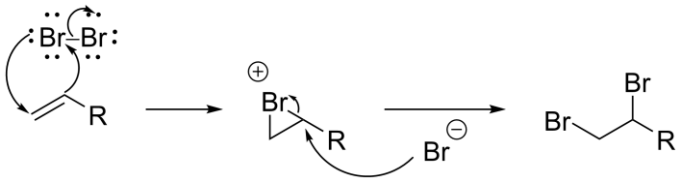
1. Alkene bromination and elimination

Bromination of acrolein (propenal) was performed according to a literature procedure.[2]



Scheme 9. Bromination of acrolein.

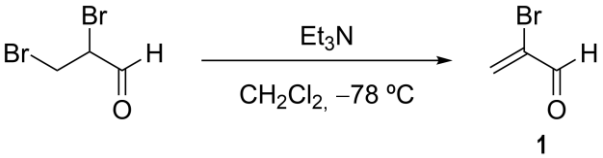
The bromination of an alkene with molecular bromine proceeds through a cyclic intermediate, called a **bromonium ion**. Then, the bromide anion just formed attacks this cyclic intermediate and the 1,2-dibromo product is obtained as shown in **Scheme 10**.



Scheme 10. Mechanism for the bromination of an alkene.

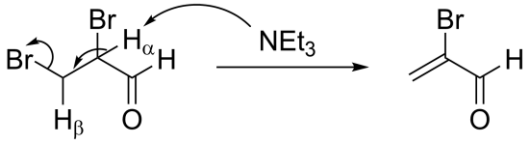
Another bromine source to perform the bromination of an alkene is pyridinium tribromide, which is safer than molecular bromine. The presence of water is deleterious for this reaction because it can act as a nucleophile and attack the bromonium ion, forming the corresponding halohydrin.

The dibromo product was not isolated and was directly treated with Et_3N to perform an E2 elimination.



Scheme 11. E2 elimination.

The elimination was performed with triethylamine. Because it is a poor nucleophile, the competition S_N2 vs E2 is shifted towards elimination.



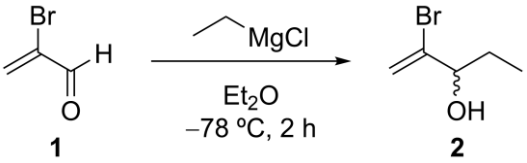
Scheme 12. E2 mechanism.

Usually E2 eliminations are performed with strong bases but in this case a weak base, such as Et_3N, is necessary because we want to deprotonate C_α and not C_β. The C_α proton, adjacent to the carbonyl group, which is an electron withdrawing group, is more acidic than the C_β proton and is removed selectively.

2-Bromoacrolein (2-bromoprop-2-enal) (**1**) was isolated in 82% yield for the two steps, and it was sufficiently pure so that no column chromatography was necessary. It has to be stored at 0 ºC to prevent decomposition.

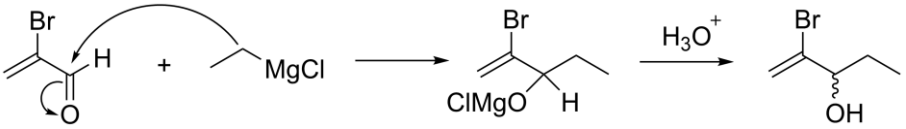
2. Organomagnesium addition to 2-bromoacrolein

The next step was the addition of ethylmagnesium chloride to **1** to give **2** in 51% yield.[3]



Scheme 13. Organomagnesium addition to **7**.

A simplified reaction mechanism is shown in **Scheme 14**:

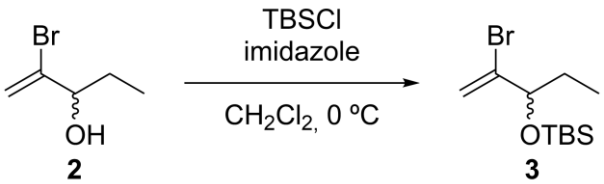


Scheme 14. Organomagnesium addition mechanism.

The product isolated was sufficiently pure and no purification by column chromatography was necessary.

3. Alcohol protection with TBSCl

This step features the protection of alcohol **2** with *tert*-butyldimethylsilyl chloride to obtain TBS-protected alcohol **3**. A protecting group stable to strong bases (which will be needed for the lithiation of **3**) was chosen. For the actual synthesis, other protecting groups will probably have to be evaluated.



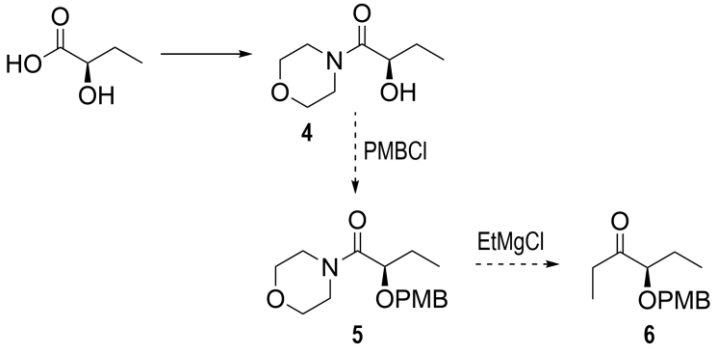
Scheme 15. Alcohol protection of **2**.

The role of imidazole in this reaction is to eliminate the produced hydrochloric acid. Also, it may make TBSCl more electrophilic acting as a catalyst, although imidazole is not the best Lewis base that can perform this role.[4]

Protected alcohol **3** was isolated only in 18% yield, although we are confident that this yield can be easily increased.

B. TOWARDS THE PREPARATION OF (4*R*)-4-*p*-METHOXYBENZYLOXYHEXAN-3-ONE (6)

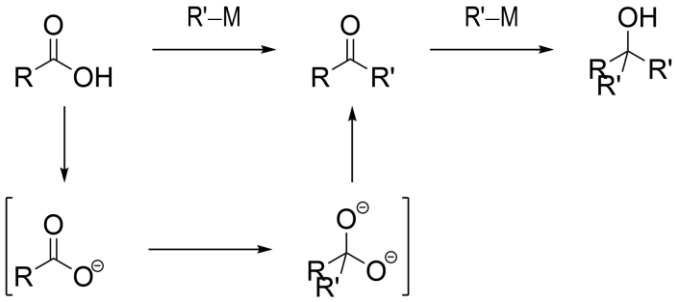
The synthesis designed for the preparation of ketone **6** from commercially available (2*R*)-2-hydroxybutanoic acid is shown in **Scheme 16**.



Scheme 16. Synthetic route for **6**.

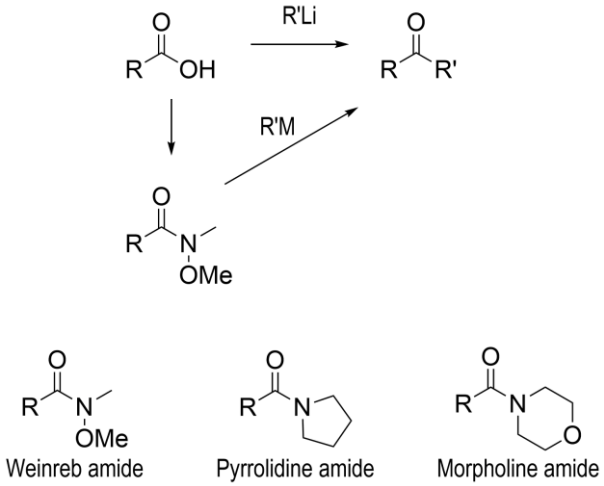
The first step is the formation of a morpholine amide. Next, the hydroxyl group is protected as a PMB ether. Finally, the reaction between the protected morpholine amide and ethylmagnesium bromide should afford the ketone in good yield.

Although ketones can be obtained from carboxylic acids by reaction with alkyllithiums, it is a transformation that uses harsh reaction conditions and is not indicated when there is an epimerizable centre in the carboxylic acid, as is our case. Also, an excess of the organometallic compound is needed because it first reacts with the acidic hydrogen.



Scheme 17. Organometallic addition to a carboxylic acid.

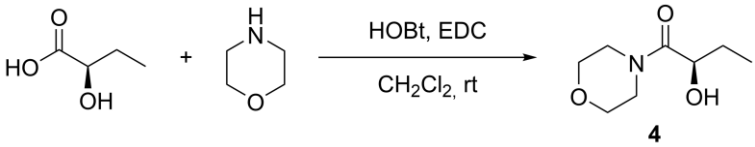
Another possibility is to transform the carboxylic acid into an amide, which can then react with an organometallic reagent to form the ketone. One of the most widely used amides is the Weinreb amide.[5,6] Although it is a method that works very well, the required reagent (*N,O*-dimethylhydroxylamino hydrochloride) is expensive. Another solution is to use pyrrolidine[7] or morpholine[8] amides developed in our group. In this work, we decided to use the morpholine amide.



Scheme 18. General synthetic scheme and available amides.

1. Formation of the morpholine amide

The formation of the morpholine amide was performed using EDC and HOBt as coupling agents, according to a literature procedure.[9]



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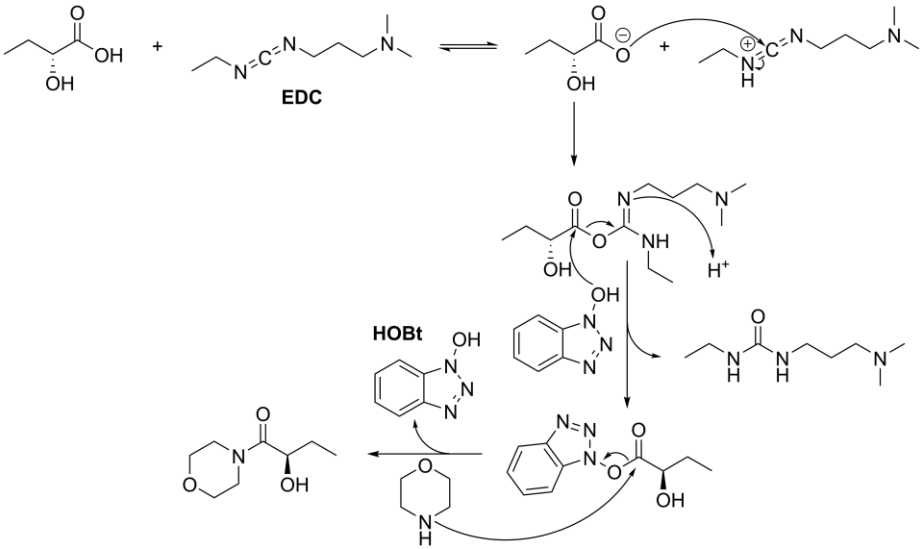
Scheme 19. Morpholine amide formation.

The mechanism for this reaction is shown in **Scheme 20**.



Scheme 20. Mechanism for morpholine amide formation.

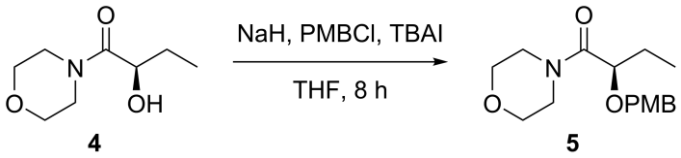
We tried to follow the course of the reaction by TLC but the amide couldn't be visualized using stains such as $KMnO_4$ or *p*-anisaldehyde. Tolidine, a stain specific for amides was also tested, although tertiary amides (like **4**) not having an NH group, usually can't be visualized with this method.

Finally, a phosphomolybdic acid stain was used. PMA is a general stain that reacts with a lot of functional groups. Although a new dark green spot appeared using the PMA stain, the compound wasn't easy to visualize.

Analysis of the ^{1}H-NMR spectrum of the crude reaction mixture revealed that the morpholine amide had been obtained so, considering the difficulty to visualize the compound by TLC, it was decided to carry on the next reaction without purification to avoid product loss.

2. Alcohol protection with PMBCl

The next step was the protection of **4** with PMBCl to give **5** (**Scheme 21**).[10] Because the PMB protecting group contains a phenyl group, the product should be easily visualized by TLC with UV light.



Scheme 21. Alcohol protection with PMBCl.

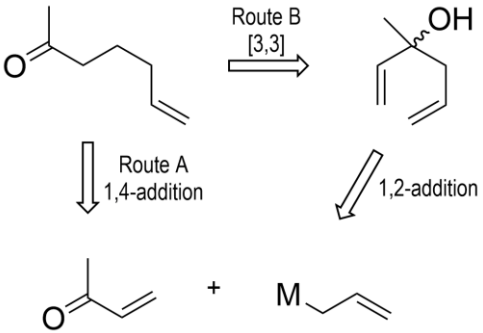
Due to time constraints we haven't been able to purify **5**, although the ^{1}H-NMR spectrum of the crude reaction mixture indicates that the protection has been successful. No starting material is detected in the crude mixture and signals of a new compound, compatible with the desired structure, appear.

C. TOWARDS THE SYNTHESIS OF (*S*)-2-HYDROXY-6-METHYLHEPT-6-ENAL

For the preparation of aldehyde **III**, ketone **8** was chosen as the starting material. It could be transformed into target aldehyde **III** by asymmetric dihydroxylation, methylenation and selective oxidation. The preparation of ketone **8** and the attempts to transform it into the ketodiol **10** are discussed in the next sections.

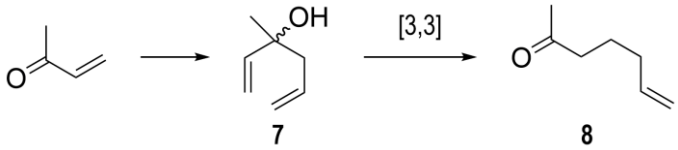
1. Preparation of hept-6-en-2-one

In our research group, Cristian Marco, in the course of his PhD thesis, tried to prepare ketone **8** by conjugate addition (or 1,4-addition) of an allyl–metal to methyl vinyl ketone with no success (**Scheme 22,** route **A**). In the best case, and using Cu(I), a 1:1 mixture of 1,2- and 1,4-addition products were obtained. With allylmagnesium bromide, the product obtained was exclusively the 1,2-addition product, as expected.



Scheme 22. Retrosynthetic analysis for ketone **A**.

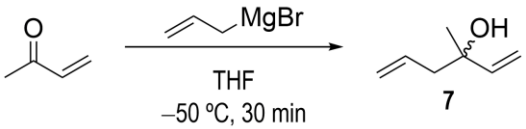
As this can be transformed into ketone **8** through an oxy-Cope reaction, we decided to explore this via.



Scheme 23. Synthetic route to ketone **8**.

1.1. Allylmagnesium bromide addition to methyl vinyl ketone

Allylmagnesium bromide reacted with methyl vinyl ketone in a 1,2-addition (or direct addition) to the carbonyl, to furnish **7** in 88% yield.



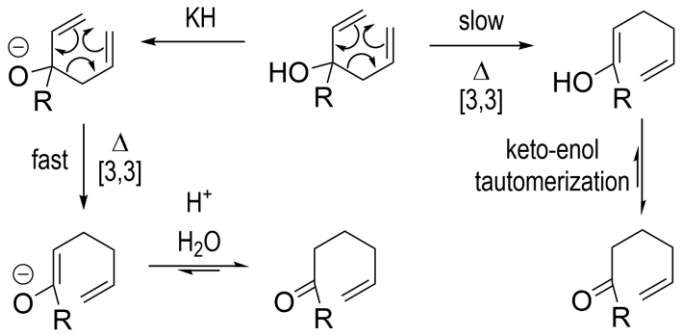
Scheme 24. Direct addition to methyl vinyl ketone.

1.2. Oxy-Cope rearrangement of 7

The Cope rearrangement is a [3,3] sigmatropic rearrangement of a 1,5-diene that takes place through a six-membered cyclic transition state (**Scheme 25**).

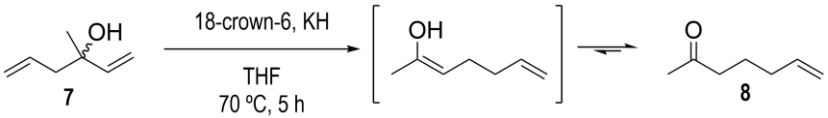
Scheme 25. Cope rearrangement.

In our case, and because there is a hydroxyl group at C_3, the product obtained is an enol that tautomerizes to the corresponding ketone (**Scheme 26**). This reaction is strongly accelerated by the presence of base and is called an **oxy-Cope rearrangement**.[11]



Scheme 26. Oxy-Cope rearrangement.

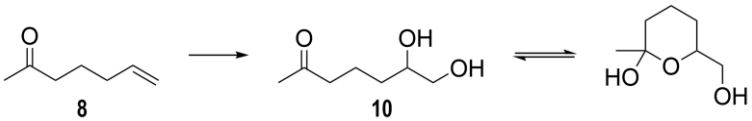
When alcohol **7** was treated with KH, in the presence of 18-crown-6 at 70 ºC, ketone **8** was isolated in 80% yield.[12]



Scheme 27. Oxy-Cope rearrangement of **7**.

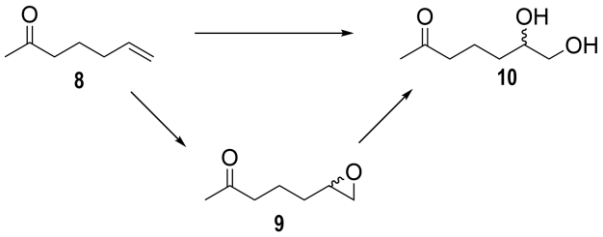
2. Dihydroxylation assays

With ketone **8** in our hands, the next step was to study the dihydroxylation of the double bond to form the corresponding 1,2-diol. It is plausible that our product is in equilibrium with the corresponding hemiketal.



Scheme 28. Dihydroxylation and hemiketal formation.

Different reaction conditions have been tested for the preparation of **10**, as described below.

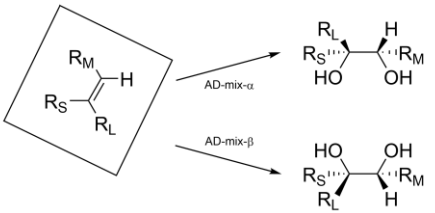


Scheme 29. General synthetic scheme for dihydroxylation of **8**.

2.1. Sharpless asymmetric dihydroxylation

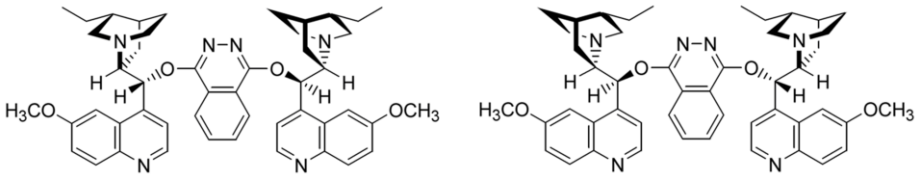
The Sharpless asymmetric dihydroxylation[13,14] is a method for the enantioselective preparation of 1,2-diols from prochiral olefins. A catalytic amount of OsO_4 and a stoichiometric oxidant (*e.g.* $K_3Fe(CN)_6$ or *N*-methylmorpholine (NMO)) are needed, while enantioselectivity is achieved through the addition of chiral ligands (like $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$)).

This combination of reagents is also available as stable, pre-packaged mixtures (AD-mix-α and AD-mix-β) for either enantiopreference (**Scheme 30**).



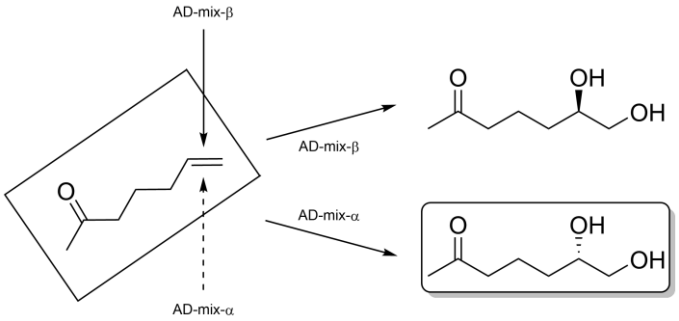
AD-mix-α:
$K_2OsO(OH)_4$ (cat), K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2PHAL$ (cat)

AD-mix-β:
$K_2OsO(OH)_4$ (cat), K_2CO_3, $K_3Fe(CN)_6$, $(DHQD)_2PHAL$ (cat)



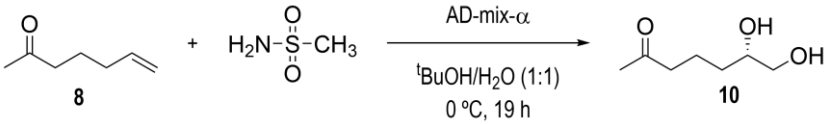
Scheme 30. Sharpless asymmetric dihydroxylation and reactants.

In our particular case, the preparation of **10** requires the use of AD-mix-α to obtain the desired configuration, as it is shown in **Scheme 31**.



Scheme 31. Ketone dihydroxylation scheme.

When ketone **8** was submitted to the conditions of Sharpless asymmetric dihydroxylation using AD-mix-α, the starting material disappeared after 8 h of reaction. Unfortunately, analysis of the crude reaction mixture by ^{1}H-NMR showed a complex mixture from which ketodiol **10** couldn't be identified. Attempts to purify this mixture by column chromatography were unsuccessful. At this point, we concentrated our efforts in the preparation of racemic **10**, as discussed in the following sections.

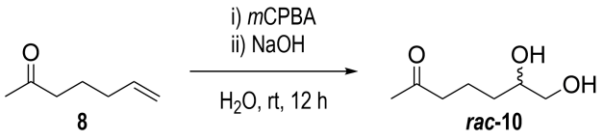


Scheme 32. Sharpless asymmetric dihydroxylation of ketone **8**.

3.2. One-pot epoxidation and ring opening

In order to determine the enantiomeric excess of the Sharpless asymmetric dihydroxylation, a racemic mixture of ketodiol **10** was needed. To obtain it, we decided to epoxidize the double bond and then hydrolyze the epoxide just formed.

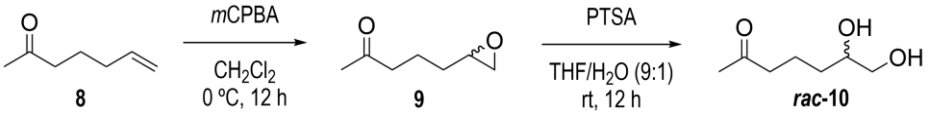
The first attempt was performed with *m*CPBA and the epoxide opening was done *in situ* in basic medium (NaOH) in a one-pot reaction.[15]



Scheme 33. Epoxidation and epoxide opening in basic medium.

After work-up and purification, a very small amount of material, with a complex ^{1}H-NMR spectrum, was isolated. Possibly, the high polarity of **10**, coupled with the possibility that it exists in equilibrium with its hemiketal complicates the isolation of this compound.

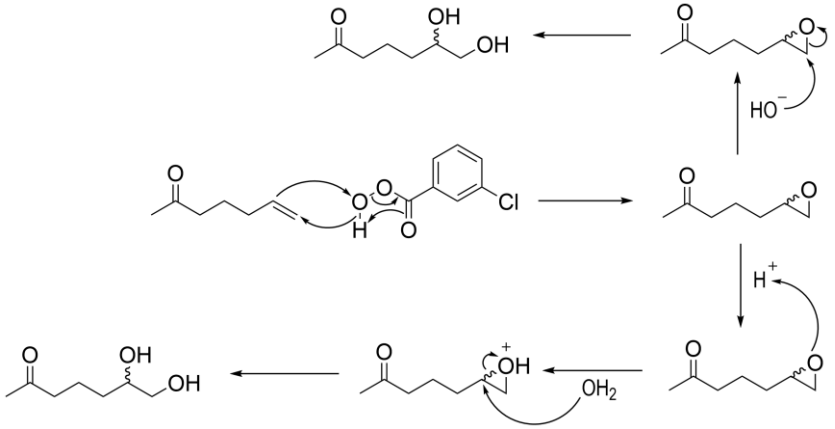
At this point we decided to isolate the epoxide and then, hydrolize it under acidic conditions. When ketone **8** was treated with *m*CPBA, epoxide **9** was satisfactorily obtained and could be characterized by ^{1}H-NMR. It was directly submitted, without purification, to ring opening in acidic medium (TsOH, PTSA).



Scheme 34. Formation and opening of epoxide **9**.

Again, a very small amount of material was isolated, with a complex NMR spectrum.

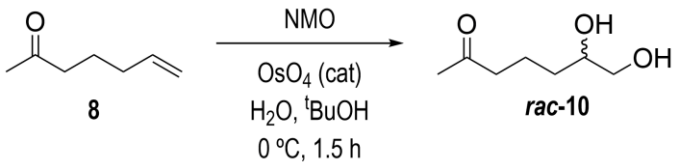
Scheme 35 shows the mechanism of these reactions. As can be seen, the epoxide opening is different under acidic or basic conditions.



Scheme 35. Epoxidation and ring opening mechanism.

3.3. Osmium(VIII) oxide

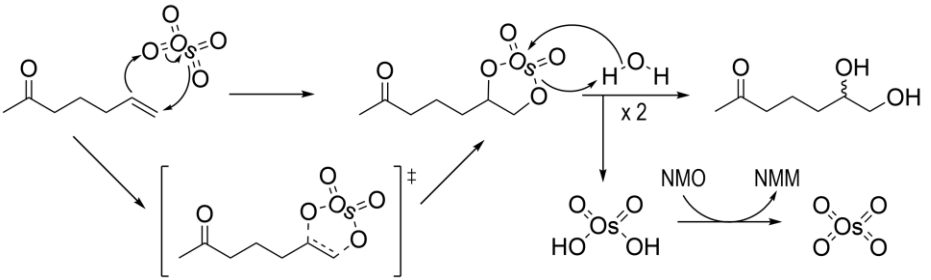
As a final attempt, we tried the dihydroxylation of ketone **8** using OsO_4.[16]



Scheme 36. Dihydroxylation with OsO_4 of **8**.

As before, the product couldn't be detected in the complex reaction mixture.

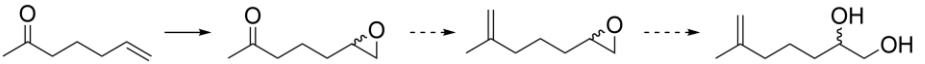
Scheme 37 shows the mechanism of dihydroxylation using OsO_4, where an oxidant is needed (NMO = *N*-methylmorpholine *N*-oxide) in order to recover the dihydroxylation agent, which is used in catalytic amounts.



Scheme 37. Mechanism for the dihydroxylation using OsO_4.

As discussed before, the high polarity of ketodiol **10**, combined with the possible formation of the hemiketal is complicating the isolation and characterization of the desired product.

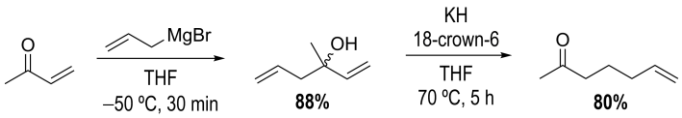
In the future, methylenation of the epoxyketone before epoxide hydrolysis will be tested (**Scheme 38**).



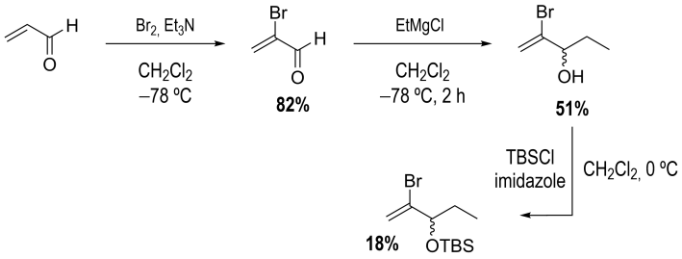
Scheme 38. Methylenation of epoxyketone and further dihydroxylation.

CONCLUSIONS

- Ketone **A** has been prepared in two steps with an overall yield of **69%**.



- TBS-protected vinyl bromide **I** has been successfully obtained in three steps.



- The two first steps of the synthesis of ketone **II** have been examined. These steps require further optimization to improve yield and isolation.

- Dihydroxylation of ketone **A** has been studied without success. Probably the best choice for the preparation of aldehyde **III** would be the epoxidation of ketone **A**, followed by methylenation of the carbonyl group and epoxide opening. In this way, we will avoid the difficulties derived from the formation of the hemiketal and the high polarity of the ketodiol.

EXPERIMENTAL PROCEDURES

GENERAL EXPERIMENTAL METHODS

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

Analytical thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates (F254). The spots were visualized with UV light, exposure to potassium permanganate, *p*-anisaldehyde, tolidine or phosphomolybdic acid.

Flash column chromatography was performed on Merck silica gel 60 (0.040–0.063 nm). The eluents are specified in each case.

^{1}H-NMR spectra (400 MHz) were recorded on a Varian Mercury-400 spectrometer. Chemical shifts (δ) are reported in ppm downfield from TMS (tetramethylsilane) with the partially-deuterated solvent as the internal standard ($CDCl_3$, δ 7.26). Coupling constants (*J*) are quoted in Hz. ^{13}C spectra were recorded at 100.6 MHz with proton decoupling. Chemical shifts are indicated in ppm from TMS with the partially-deuterated solvent as the internal standard ($CDCl_3$, δ 77.0). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet and m = multiplet), coupling constant, number of protons, proton number.

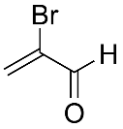
Along the experimental section, the compounds are numbered according to the numeration in the results and discussion section.

EXPERIMENTAL PROCEDURES

2-Bromoprop-2-enal (1)

Br_2 (5.20 mL, 100 mmol) was added dropwise to a stirring solution of acrolein (7.0 mL, 100 mmol) in CH_2Cl_2 (150 mL) at –78 ºC over 10 min. After an additional 30 min at –78 ºC, Et_3N (14 mL, 100 mmol) was added and the mixture was warmed to rt for 2 h. The reaction was then quenched by the addition of H_2O (120 mL), the layers were separated, and the aqueous layer

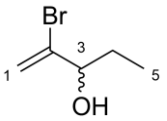
was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with a 9:1 mixture of brine and 1 M HCl (100 mL), dried ($MgSO_4$), filtered and concentrated at rt and 300 torr to obtain **1** (82%).



Yellowish oil; **Rf** 0.76 (Hexanes/AcOEt 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 2.2, 1H, H_3), 6.89 (d, *J* = 2.2, 1H, $H_{3'}$), 9.26 (s, 1H, CHO).

2-Bromo-1-penten-3-ol (2)

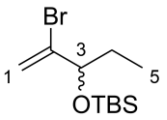
Ethylmagnesium bromide (2.0 mL, 4.9 mmol) was added dropwise to a stirring solution of **1** (600 mg, 4.45 mmol) in Et_2O (45 mL) at –78 ºC and stirred for 2 h. The reaction mixture was left to warm to rt and was quenched with H_2O (10 mL). The layers were separated, the aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases dried ($MgSO_4$) and concentrated under reduced pressure at rt to obtain **2** (51%)



Yellowish oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.4, 3H, H_5), 1.62–1.75 (m, 2H, H_4), 4.02 (t, *J* = 6.5, 1H, H_3), 5.57 (d, *J* = 1.9, 1H, H_1), 5.87 (dd, *J* = 1.8, 0.6, 1H, $H_{1'}$).

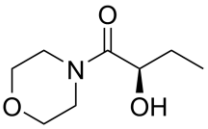
2-Bromo-3-*tert*-butyldimethylsilyloxypent-1-ene (3)

TBSCl (420 mg, 2.70 mmol) was added to a stirring solution of imidazole (370 mg, 5.40 mmol) and **2** (370 mg, 2.25 mmol) in CH_2Cl_2 (9 ml) at 0 ºC. After stirring at this temperature for 4 h, it was allowed to warm to rt and brine was added (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated at rt. The residue was purified on silica gel (hexanes) to give **3** (18 %).



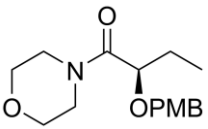
Yellowish oil; **Rf** 0.69 (hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.07 (s, 6H, Me), 0.86 (t, *J* = 7.4, 3H, H_5), 0.91 (s, 9H, ^{t}Bu), 1.56–1.67 (m, 2H, H_4), 4.07 (t, *J* = 5.4, 1H, H_3), 5.50 (s, 1H, H_1), 5.85 (s, 1H, $H_{1'}$).

(2*R*)-2-Hydroxy-1-morpholinobutan-1-one (4)



(2*R*)-2-Hydroxybutanoic acid (300 mg, 2.88 mmol), morpholine (301 mg, 3.46 mmol), HOBt (882 mg, 5.76 mmol) and EDC (670 mg, 4.32 mmol) were combined in CH_2Cl_2 (9 mL) and then stirred at rt for 5 h. The mixture was then filtered, washed with 1 M HCl (15 mL) and sat. $NaHCO_3$ (15 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to obtain a residue which was analysed by ^{1}H-NMR. The spectrum showed the presence of **4**, along with impurities, and was directly used in the next step.

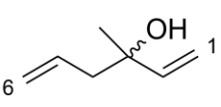
(2*R*)-2-hydroxy-1-(4-morpholinyl)-1-butanone (5)



p-Methoxybenzyl chloride (206 mg, 1.30 mmol) and tetrabutylammonium chloride (22 mg, 0.060 mmol) were added to the alkoxide generated from alcohol **4** (216 mg, 1.20 mmol) and NaH (32 mg, 1.32 mmol) in THF (5 mL) and stirred at rt for 8 h. The reaction mixture was quenched with sat. NH_4Cl (5 mL) and extracted with AcOEt (2 x 10 mL). The combined organic layers were washed with brine and the solvent was concentrated under reduced pressure. ^{1}H-NMR analysis of the residue obtained showed the absence of starting material and the presence of new signals, compatible with **5**.

3-Methyl-1,5-hexadien-3-ol (7)

A 1.0 M solution of allylmagnesium bromide in THF (30.5 mL, 30.5 mmol) was added dropwise to a stirring solution of 3-buten-2-one (1.0 mL, 12 mmol) in anhydrous THF under a N_2 atmosphere at –50 ºC. After the addition, the reaction mixture was stirred for 30 minutes at the same temperature. The solution was quenched by addition of saturated NH_4Cl aqueous solution (100 mL). The layers were separated, the aqueous layer extracted with Et_2O (2 x 50mL) and the combined organic phases dried over $MgSO_4$, filtered and concentrated under reduced pressure (0 ºC, 100 mbar). The residue was purified by flash column chromatography (hexanes/AcOEt 75:25) to obtain compound **7** (88%).

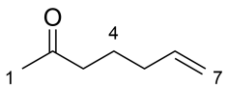


Brownish oil; **Rf** 0.63 (hexanes/AcOEt 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.26 (s, 3H, Me), 2.24 (dd, *J* = 13.4, 7.8, 1H, $H_{4'}$), 2.32 (dd, *J* = 13.6, 6.9, 1H, H_4), 5.04 (dd, *J* = 10.7, 1.2, 1H, H_1), 5.07–5.14 (m, 2H, H_6), 5.19 (dd, *J* = 17.3, 1.3, 1H, $H_{1'}$), 5.78 (dddd, *J* = 17.0, 10.4, 8.1, 6.7, 1H, H_5),

5.91 (dd, *J* = 17.3, 10.3, 1H, H_2); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 27.6 (Me), 47.0 (C_4), 72.5 (C_3), 112.0 (C_6), 119.1 (C_1), 133.7 (C_5), 144.8 (C_2).

6-Hepten-2-one (8)[12]

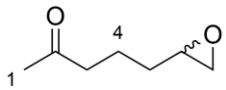
A solution of **7** (0.9 g, 8 mmol) in anhydrous THF (9 mL) was added via cannula to a stirring solution of potassium hydride (2.12 g, 52.0 mmol; previously washed with Et_2O) and 18-crown-6 (1.6 g, 6.1 mmol) in anhydrous THF (9 mL). After the addition, the reaction mixture was stirred at reflux for 5 h at 70 ºC, obtaining a brownish green solution. The solution was left to cool at rt and was quenched by slow addition of distilled H_2O (20 mL). The layers were separated, the aqueous layer extracted with Et_2O (2 x 10 mL) and the combined organic phases dried with $MgSO_4$. The residue was purified by flash column chromatography (hexanes/AcOEt 75:25) to obtain compound **2** (78 %).



Yellowish oil; **Rf** 0.56 (hexanes/AcOEt 7:3); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.66 (q, *J* = 7.5, 2H, H_4), 2.03–2.08 (m, 2H, H_5), 2.11 (s, 3H, H_1), 2.42 (t, *J* = 7.4, 2H, H_3), 4.93–5.03 (m, 2H, H_7), 5.75 (ddt, *J* = 16.8, 10.1, 6.7, 1H, H_6); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 22.8 (C_4), 29.2 (C_1), 33.2 (C_5), 42.9 (C_3), 115.3 (C_7), 138.0 (C_6), 208.9 (C_2).

6,7-Epoxy-2-pentanone (9)

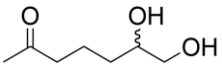
m-CPBA (330 mg, 1.90 mmol) was added in portions to a stirring solution of **8** (180 mg, 1.60 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 ºC. The ice bath was then removed and the reaction mixture was stirred overnight at rt. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL) and stirred at rt for 30 min. The layers were separated and the organic phase was washed with brine (5 mL), dried over $MgSO_4$ and filtered. The solvent was eliminated under reduced pressure.



Whitish oil; **Rf** 0.26 (hexanes/AcOEt 8:2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38–1.47 (m, 1H, CH_aH_b), 1.56–1.64 (m, 1H, CH_aH_b), 1.68–1.77 (m, 2H, CH_2), 2.12 (s, 3H, H_1), 2.43 (dd, *J* = 5.0, 2.7, 1H, H_7), 2.49 (t, *J* = 7.2, 2H, H_3), 2.71 (dd, *J* = 5.0, 4.0, 1H, $H_{7'}$), 2.87 (dtd, *J* = 7.0, 4.2, 2.7, 1H, H_6).

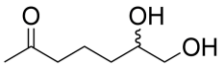
DIHYDROXYLATION ASSAYS

PTSA hydrolysis of 9



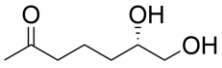
PTSA (95 mg, 0.5 mmol) was added to a solution of **9** (50 mg, 0.4 mmol) in THF/H_2O 9:1 (5 mL) and the mixture was stirred overnight at rt. AcOEt (2 x 10 mL) was added, the layers were separated, the aqueous phase was extracted with AcOEt (3 x 5 mL), dried over $MgSO_4$ and the solvent was eliminated under reduced pressure. A complex mixture was obtained as evidenced by ^{1}H-NMR analysis of the reaction mixture.

One-pot epoxidation + epoxide hydrolysis



*m*CPBA (220 mg, 0.96 mmol) was added to a solution of **8** (100 mg, 0.87 mmol) in H_2O (6 mL) at 0 ºC and the reaction mixture was stirred for 12 h at 30 ºC. After that, NaOH (155 mg, 3.88 mmol) was added to the mixture and it was stirred at reflux for 3 h. The aqueous phase was extracted with AcOEt (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Analysis of the ^{1}H-NMR showed a complex mixture.

Sharpless asymmetric dihydroxylation



AD-mix-α (3.8 g) and methanesulfonamide (260 mg, 2.73 mmol) were added to a stirring solution of **8** (100 mg, 0.89 mmol) in ^{t}BuOH/H_2O 1:1 (9 mL) at 0 ºC and stirred for 12 h. The reaction was quenched by $Na_2S_2O_3$, extracted with AcOEt (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Analysis of the ^{1}H-NMR spectrum showed a complex mixture.

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APPENDICES

APPENDIX 1: ABBREVIATIONS AND ACRONYMS

CM	Cross metathesis
COSY	Correlation spectroscopy
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HOBt	Hydroxybenzotriazole
HRESIMS	High-resolution electrospray ionisation mass spectrometry
mCPBA	*m*-chloroperbenzoic acid
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine oxide
NMR	Nuclear magnetic resonance
PG	Protecting group
PMA	Phosphomolybdic acid
PMBCl	*p*-methoxybenzyl chloride
PTSA	*p*-toluenesulfonic acid
RCM	Ring closing metathesis
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
rt	Room temperature
TBAI	Tetrabutylammonium iodide
TBSCl	*tert*-butyldimethylsilyl chloride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TOCSY	Total correlation spectroscopy