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Towards the total synthesis of Amphidinolide E: optimization of fragment I.

Optimització de la preparació del fragment I de l'amfidinolida E.

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June 2013

Universitat de Barcelona

Hi ha una força motriu més poderosa que el vapor, l'electricitat i l'energia atòmica: la voluntat.

Albert Einstein

REPORT

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SUMMARY

Amphidinolides are macrolides (macrocyclic lactones) that are produced by marine dinoflagellates. Most of these complex molecules exhibit strong anticancer properties, but they are difficult to isolate and only very low quantities are available for further studies. Therefore, they are good targets for a total synthesis.

Amphidinolide E is a 19-membered macrolide possessing a tetrahydrofuran ring, 8 stereogenic centres and 6 double bonds, four of which are stereogenic (Figure 1).

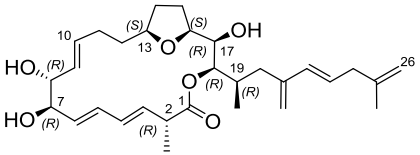
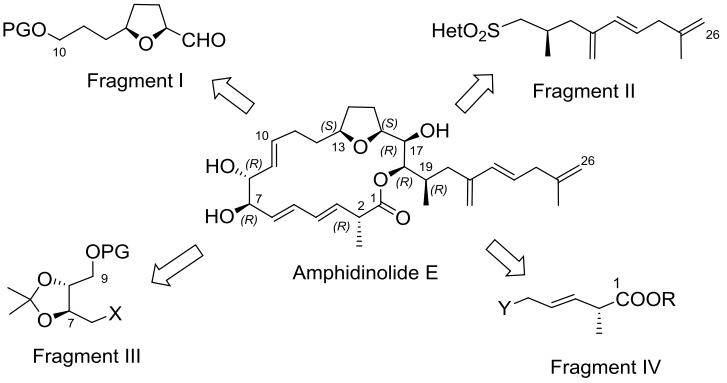


Figure 1: Amphidinolide E

In our research group, Jorge Esteban and Laura Mola have studied new approaches to synthesize Amphidinolide E in their Ph D Theses. The retrosynthetic analysis involves the disconnection of Amphidinolide E into four fragments (Scheme 1).



Scheme 1: Disconnection of Amphidinolide E into four fragments

In this work, compound **5**, precursor for Fragment I (Figure 2), was synthesized as a mixture of diastereomers by means of a new, five-step strategy that involves epoxidation of an alkene, allylation of an epoxide and formation of the tetrahydrofuran ring.

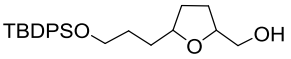
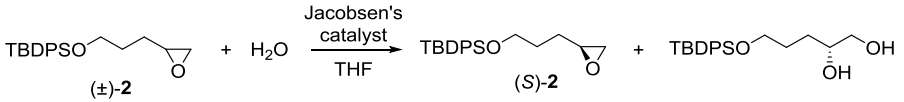


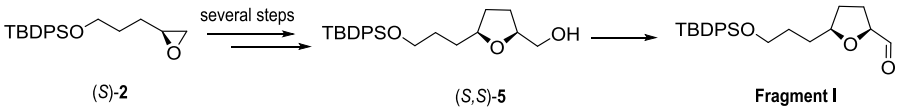
Figure 2: Compound **5**, precursor for Fragment I

Furthermore, Jacobsen's hydrolytic kinetic resolution (Jacobsen's HKR), a methodology that had not been used before in our group, was studied for the enantioselective synthesis of **5**. When racemic terminal epoxide (±)-**2** is treated with water in the presence of Jacobsen's (*S,S*)-(salen)-Co(III)-OTs catalyst, (*R*)-**2** reacts much more quickly to yield a diol. In contrast, (*S*)-**2** remains unaltered, enabling the resolution of (±)-**2** (Scheme 2).



Scheme 2: Jacobsen's HKR of racemic terminal epoxide (±)-**2**

This reaction is of vital importance because only (*S*)-**2** leads to the obtention of enantiopure Fragment I within several steps, including another Jacobsen's HKR (Scheme 3).



Scheme 3: Synthesis of enantiopure Fragment I

Very high enantiomeric excess (99%), determined by HPLC, was achieved in the Jacobsen's HKR reaction.

RESUM

Les amfidinolides són macròlids (lactones macrocícliques) produïdes per dinoflagel·lats marins. La major part d'aquestes molècules complexes exhibeixen una potent activitat antitumoral, però són difícils d'aïllar i n'hi ha poca quantitat disponible per a fer més estudis. Per aquests motius són unes bones candidates per a una síntesi total.

L'Amfidinolida E és un macròlid de 19 baules amb un anell de tetrahidrofurà, 8 centres estereogènics i 6 enllaços dobles, quatre dels quals són estereogènics (Figura 1).

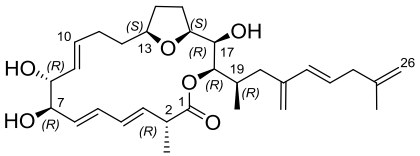
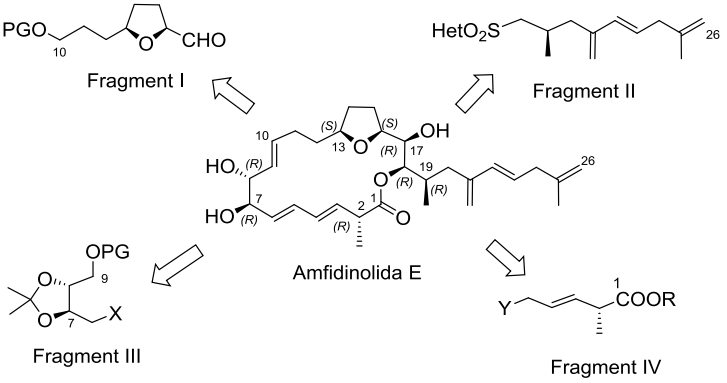


Figura 1: Amfidinolida E

Al nostre equip d'investigació, Jorge Esteban i Laura Mola han estudiat, a les seves tesis doctorals, noves estratègies per a sintetitzar l'Amfidinolida E. L'anàlisi retrosintètica desconnecta l'Amfidinolida E en quatre fragments (Esquema 1).



Esquema 1: Desconnexió de l'Amfidinolida E en quatre fragments

En aquest treball es va sintetitzar el compost **5**, precursor del Fragment I (Figura 2), com a barreja de diastereòmers mitjançant una nova estratègia de cinc etapes que inclou reaccions d'epoxidació d'un alquè, al·lilació d'un epòxid i formació de l'anell de tetrahidrofurà.

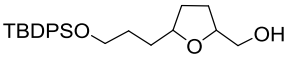
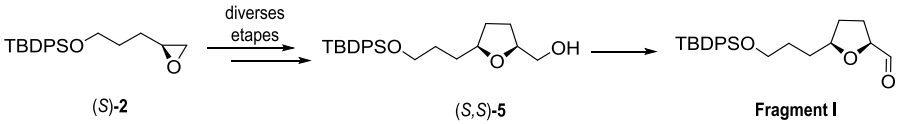


Figura 2: Compost **5**, precursor del Fragment I

A més, es va estudiar la resolució hidrolítica cinètica de Jacobsen (HKR de Jacobsen), una nova metodologia que no havia estat emprada al grup: quan es tracta l'epòxid terminal racèmic (±)-**2** amb aigua en presència del catalitzador de Jacobsen (*S,S*)-(salen)-Co(III)-OTs, (*R*)-**2** reacciona molt més ràpidament per fornir un diol. En canvi, (*S*)-**2** roman inalterat, fent possible la resolució de (±)-**2** (Esquema 2).

Esquema 2: HKR de Jacobsen de l'epòxid terminal racèmic (±)-**2**

Aquesta reacció és d'una gran importància perquè només (*S*)-**2** porta a l'obtenció del Fragment I enantiopur en diverses etapes, que inclouen una altra HKR de Jacobsen (Esquema 3).



Esquema 3: Síntesi del Fragment I enantiopur

Es va aconseguir, en la reacció de HKR de Jacobsen, un excés enantiomèric molt alt (99%), determinat per HPLC.

INTRODUCTION AND OBJECTIVES

Amphidinolides are a family of secondary metabolites produced by marine dinoflagellates of the genus *Amphidinium*. They are macrolides (macrocyclic lactones) and their importance lies in the fact that many of them possess powerful antitumor activity against murine lymphoma L1210 and human carcinoma KB cells.[1]

Even though the biosynthesis of macrolides starts mainly with acetate and propionate as precursors, a wide range of structures have been found. Divergent metabolic pathways produce either tetrahydrofuran or tetrahydropyran rings, epoxides, ketones and double bonds, as well as different macrolactone sizes. This diversity may suggest that different anticancer mechanisms of action are displayed.

Despite the current interest in such species, they are difficult to isolate from their natural sources and cultured cells produce a rather poor amount of these products. Therefore, since there is low availability of amphidinolides to perform further studies and because they are structurally very diverse, they are an attractive target for total synthesis.

Amphidinolide E (Figure 1) was first isolated by Kobayashi and coworkers in 1990,[2] who determined its absolute configuration in 2002.[3] It is a 19-membered macrolide possessing a tetrahydrofuran ring, 8 stereogenic centres and 6 double bonds (four of them stereogenic).

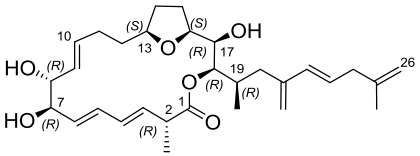
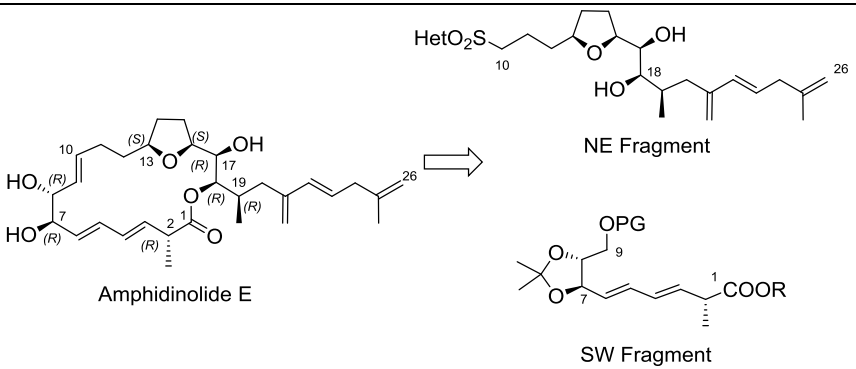


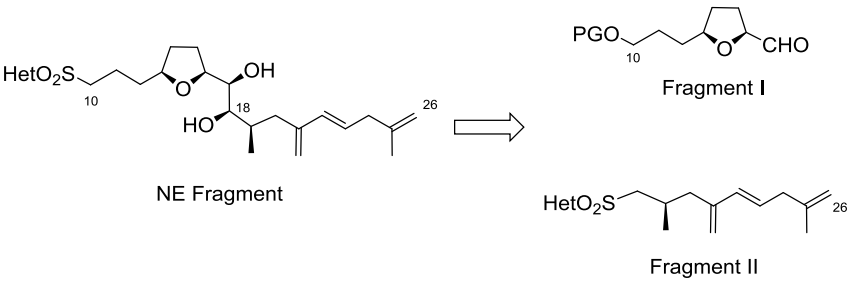
Figure 1: Amphidinolide E

So far, two total syntheses of Amphidinolide E have already been published. In our research group, Jorge Esteban and Laura Mola have studied new approaches to synthesize Amphidinolide E in their Ph D Theses.[4] The retrosynthetic analysis designed involves the disconnection of the target compound into the SW and NE Fragments (Scheme 1).

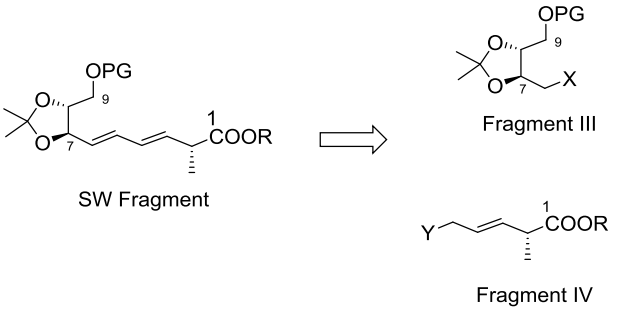


Scheme 1: Disconnection of Amphidinolide E

In turn, the SW and the NE Fragments are disconnected into two fragments apiece (Schemes 2 and 3).



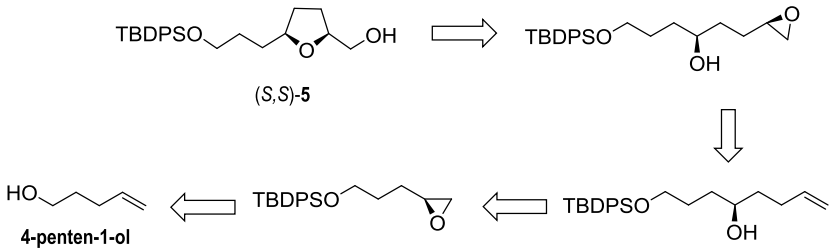
Scheme 2: Retrosynthetic analysis of the NE Fragment



Scheme 3: Retrosynthetic analysis of the SW Fragment

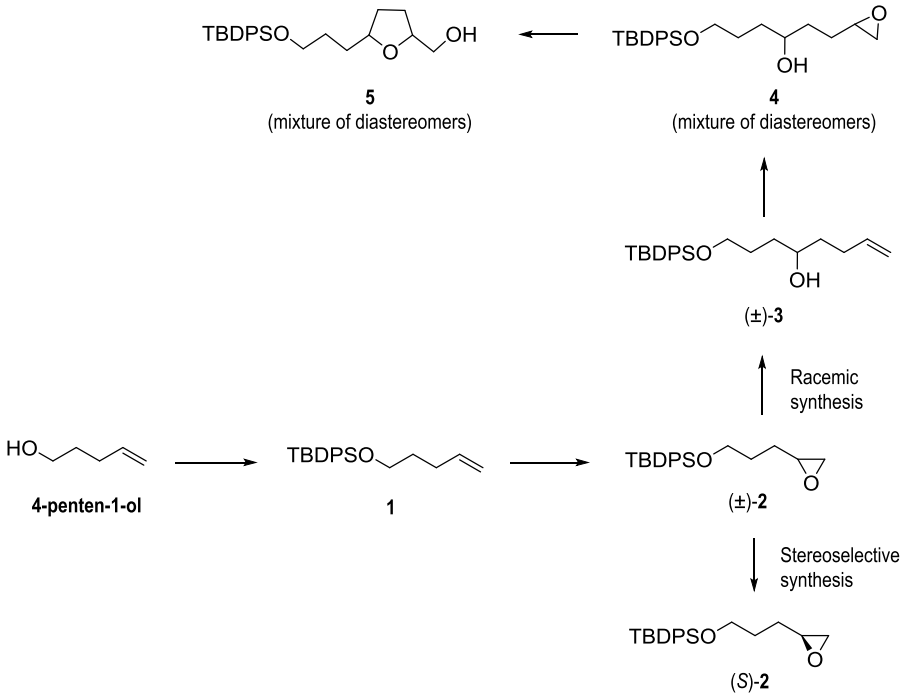
Fragments I and II are assembled *via* a Julia-Kocienski reaction to yield the NE Fragment, and so are Fragments III and IV to afford the SW Fragment.

This work is focused on key Fragment I, which is a *cis*-2,5-disubtituted tetrahydrofuran ring. Scheme 4 shows the retrosynthetic analysis for compound (*S,S*)-**5**, precursor for Fragment I.



Scheme 4: Retrosynthetic analysis of compound (*S,S*)-**5**

As the reaction conditions for the obtention of enantiopure epoxide (*S*)-**2** had to be optimized, the preparation of the tetrahydrofuran ring was first performed with racemic epoxide (±)-**2**. Hence, our work is divided in two main parts: the racemic synthesis and the stereoselective synthesis, focusing specially on the preparation of enantiopure (*S*)-**2** (Scheme 5).



Scheme 5: Racemic synthesis and stereoselective synthesis

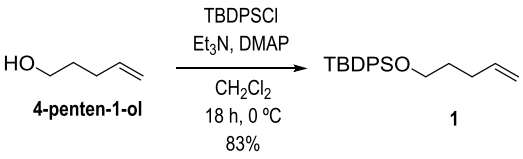
The main objectives are:

- The preparation of compound **5** as a mixture of diastereomers, by means of a new, five-step strategy, and the optimization of the reaction conditions (racemic synthesis).
- The study of Jacobsen's hydrolytic kinetic resolution (Jacobsen's HKR) to obtain enantiopure epoxide (*S*)-**2** and the determination of its enantiomeric excess by HPLC (stereoselective synthesis).

1. RESULTS AND DISCUSSION

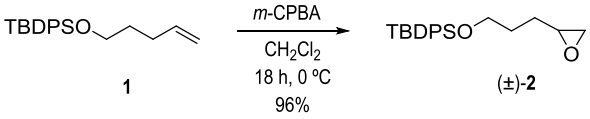
1.1 RACEMIC SYNTHESIS

The synthesis starts with 4-penten-1-ol, which was protected as its *tert*-butyldiphenylsilyl ether, **1**, in the presence of DMAP as a catalyst (Scheme 6).[5]



Scheme 6: Alcohol protection with TBDPSCl

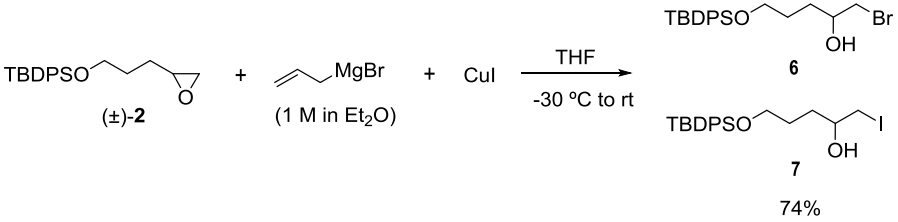
Then, the double bond was oxidized with *m*-CPBA and racemic epoxide (±)-**2** was obtained in 96% yield (Scheme 7).[6]



Scheme 7: Oxidation of the double bond

Under basic conditions, epoxide opening occurs by the attack of the nucleophile at the less hindered carbon atom. Allylmagnesium bromide is a common nucleophile in epoxide ring opening reactions in which a new C-C bond is created. However, when (±)-**2** was treated with

allylmagnesium bromide (1 M in Et_2O) and catalytic CuI,[7] undesired Br (**6**) and I (**7**) halohydrins were obtained as the main products (Scheme 8) instead of the desired allylation product.



Scheme 8: Obtention of undesired halohydrins **6** and **7**

Halohydrins **6** and **7** were characterized by ^1H NMR, ^{13}C NMR and mass spectrometry (Figure 2).

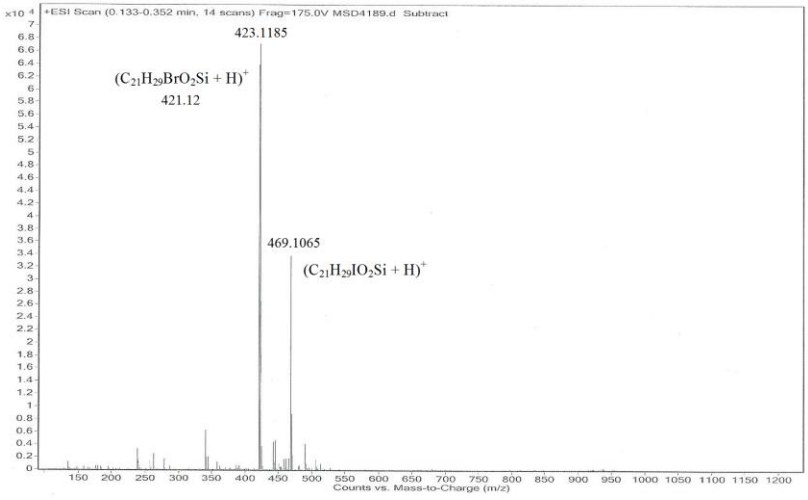
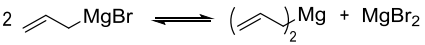


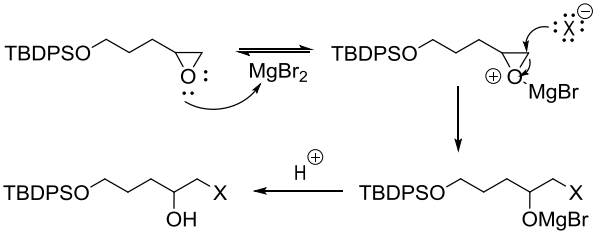
Figure 2: MS of undesired halohydrins **6** and **7**

The obtention of halohydrins **6** and **7** as the major products when (±)-**2** was reacted with allylmagnesium bromide was not completely unexpected.[7] Allylmagnesium bromide is in equilibrium with diallylmagnesium and magnesium bromide (Scheme 9).



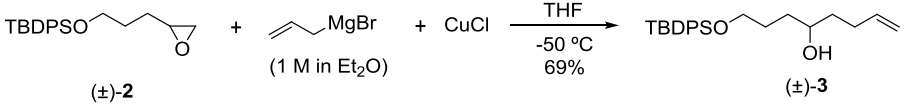
Scheme 9: Schlenk equilibrium

The epoxide oxygen atom coordinates to magnesium bromide, which is a good Lewis acid, and then bromide or iodide attacks the less substituted carbon atom (Scheme 10).



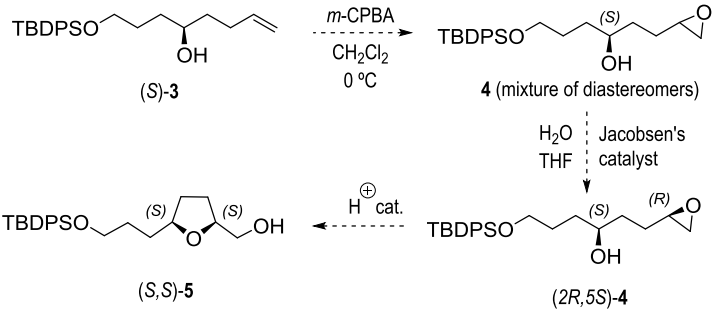
Scheme 10: Mechanism of halohydrin formation

In order to prevent the formation of such side-products, CuCl was used instead of CuI (chloride is a worse nucleophile than iodide) and the reaction was performed at -50 ºC.[7d] Under these conditions, alcohol (±)-**3** was obtained as the major product in 69% yield and only traces of halohydrins could be observed by tlc (Scheme 11).



Scheme 11: Allylation of racemic epoxide

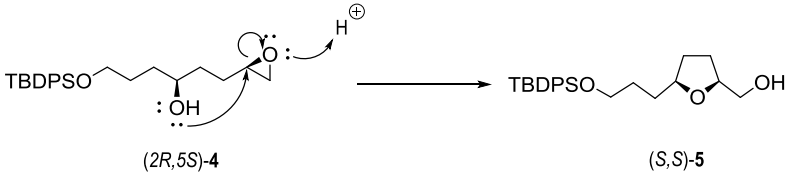
The next step was the oxidation of the double bond to yield compound **4** as a mixture of diastereomers. Although it was not necessary for the racemic synthesis, the isolation of the 5-hydroxy epoxide must be achieved because a new Jacobsen's HKR has to be performed to obtain enantiopure (*S,S*)-**5** (Scheme 12).



Scheme 12: Obtention of enantiopure (*S,S*)-**5**

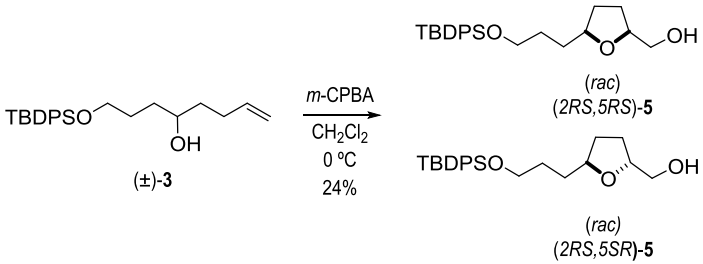
Under acidic conditions, the hydroxyl group attacks preferentially the most substituted carbon atom of the epoxide to yield a tetrahydrofuran ring (Scheme 13). Furthermore, it is a

favored 5-*exo-tet* cyclization, whereas the formation of a six-membered ring would be a disfavored 6-*endo-tet* cyclization according to Baldwin's rules.[8]



Scheme 13: Mechanism of the epoxide ring opening in acidic conditions

When compound (±)-**3** was treated with *m*-CPBA under standard conditions, **5** was directly obtained as a 1:1 mixture of diastereomers, even before the reaction could be quenched (Scheme 14).

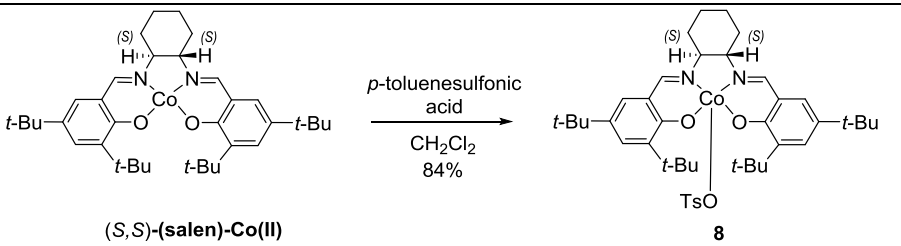


Scheme 14: Direct obtention of **5** as a mixture of diastereomers

Although there has been no time to explore this reaction further, we expect that modification of the reaction conditions can allow us to isolate epoxide **4**. Similar epoxide alcohols are known in the literature. Another possibility could be to temporarily protect the 2ary alcohol.

1.2 STEREOSELECTIVE SYNTHESIS

In order to obtain (*S*)-**2**, a Jacobsen's hydrolytic kinetic resolution (Jacobsen's HKR) was performed. (*R*)-**2** reacts with water much more quickly than (*S*)-**2** in the presence of (*S,S*)-(salen)-Co(III)-OTs (Jacobsen's catalyst) to afford the (*R*)-diol.[9] Jacobsen's catalyst **8** was prepared by stirring a solution of (*S,S*)-(salen)-Co(II) and *p*-toluenesulfonic acid in CH_2Cl_2 open to the air, which enables the oxidation of Co(II) to Co(III) (Scheme 15).[10] For the catalyst to be catalytically active and enantioselective it is very important that complete oxidation of Co(II) to Co(III) takes place, although further experimentation is still needed.



(*S*,*S*)-**(salen)-Co(II)** **8**

Scheme 15: Preparation of Jacobsen's catalyst

Once the catalyst was prepared, it was added to a mixture of (±)-**2**, water and THF (Scheme 16).

(±)-**2** (*S*)-**2**

Scheme 16: Jacobsen's hydrolytic kinetic resolution

Entry	H_2O equivalents	Catalyst's age	Reaction time	Yield	ee%
1	0.7	3 days	20 h	36%	99%
2	0.7	30 days	20 h	37%	79%
3	0.7	24 hours	20 h	15%	>99%
4	0.55	new	20 h	38%	>99%

Table 1: Results of the HKRs

Very high enantiomeric excess (99%) was achieved when the catalyst was recently prepared (entry 1). The catalyst loses its activity with time (entry 2). Better yields are obtained when 0.55 equiv. of water are used instead of 0.7 equiv. (compare entries 3 and 4). We are currently working on optimizing the reaction time.

1.3 CONCLUSIONS

- Compound **5**, precursor for Fragment I, was synthesized as a mixture of diastereomers with an overall yield of 13% (not optimised). However, we still have to work on the optimization of the epoxidation reaction of **4** in order to prevent its cyclization to tetrahydrofuran **5**, and enable its Jacobsen's HKR and ultimately obtain enantiopure (*S,S*)-**5**.
- Several Jacobsen's HKRs were performed and high enantiomeric excesses were achieved (99%). HPLC allowed us to determine the %ee of the *(S)*-**2** epoxide yielded in the different experiments. When the reaction was finished in less than 24 h and the catalyst's age was 3 days or less, the enantiomeric excess was 99%. The time the catalyst remains open to the air seems to play an important role on its activity.

EXPERIMENTAL SECTION

2.1 GENERAL EXPERIMENTAL METHODS

Analytical thin-layer chromatography (tlc) was performed on 0.25 mm silica gel plates (F254). The spots were visualized with UV light and exposure to *p*-anisaldehyde. Flash column chromatography was performed on silica gel 60 (0.040-0.063 nm).

^{1}H NMR spectra (400 MHz) were recorded on Varian Mercury-400 spectrometers. Chemical shifts are reported in ppm downfield from tetramethylsilane with the partially-deuterated solvent as the internal standard ($CDCl_3$ δ 7.26). ^{13}C spectra were recorded at 100.6 MHz with proton decoupling. Chemical shifts are indicated in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$ δ 7.26).

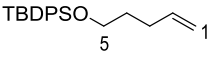
Optical rotations ($[\alpha]_D$) were measured on a Perkin-Elmer 241 MC polarimeter at 20 ºC using the sodium D line wavelength (589 nm). The concentration (% w/V) and the solvent are indicated in brackets.

2.2 EXPERIMENTAL PROCEDURES

2.2.1 Racemic synthesis

5-tert-Butyldiphenylsilyloxy-1-pentene (1)

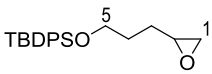
TBDPSCl (5.3 mL, 20 mmol) was added dropwise to a stirring solution of 4-penten-1-ol (1.48 g, 17.0 mmol), DMAP (98 mg, 0.80 mmol) and triethylamine (2.85 mL, 20.4 mmol) in anhydrous CH_2Cl_2 under a N_2 atmosphere at 0 ºC. After the addition, the ice bath was removed and the reaction mixture was stirred overnight at rt. HCl 1 M (100 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (100 mL), dried over $MgSO_4$ and filtered. The solvent was eliminated under reduced pressure and the crude was purified by column chromatography (hexanes/AcOEt 90:10) to afford **1** (4.59 g, 83%) as a clear oil.



Colorless oil. **R_f** (hexanes/AcOEt 90:10): 0.72. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, $OSi(Ph)_2{}^tBu$), 1.64-1.67 (m, 2H, H_4), 2.12-2.18 (m, 2H, H_3), 3.67 (t, 2H, *J* = 6.4, H_5), 4.91-4.95 (m, 1H, H_1), 4.97-5.03 (m, 1H, $H_{1'}$), 5.80 (ddt, 1H, *J* = 6.6, *J* = 10.1, *J* = 16.9, H_2), 7.38-7.67 (m, 10H, Ph).

5-*tert*-Butyldiphenylsilyloxy-1,2-epoxy-pentane ((±)-2)

m-CPBA (1.59 g, 9.20 mmol) was added in portions to a stirring solution of **1** (2.49 g, 7.67 mmol) in dry CH_2Cl_2 (47 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 $NaHCO_3$ (20 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL) and stirred for 30 minutes. The layers were separated and the organic phase was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$ and filtered. The solvent was eliminated under reduced pressure to give 2.50 g (96%) of (±)-**2** as a colorless oil.



Colorless oil. **R_f** (hexanes/AcOEt 80:20): 0.58. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, $OSi(Ph)_2{}^tBu$), 1.57-1.77 (m, 4H, H_3 + H_4), 2.45 (dd, 1H, *J* = 2.7, *J* = 5.0, H_1), 2.72-2.74 (m, 1H, H_2), 2.89-2.93 (m, 1H, $H_{1'}$), 3.66-3.75 (m, 2H, H_5), 7.38-7.67 (m, 10H, Ph). **HPLC** (Chiralpack AS-H, hexanes/isopropanol 99.5:0.5, 0.4 mL/min, λ = 254 nm): t_R = 10.2 min; t_S = 10.7 min.

Enantiomer	t_R (min)	Area	% Area
(*R*)-**2**	10.161	5759.7	48.764
(*S*)-**2**	10.739	6051.6	51.236

Table 2: HPLC parameters of (±)-**2**

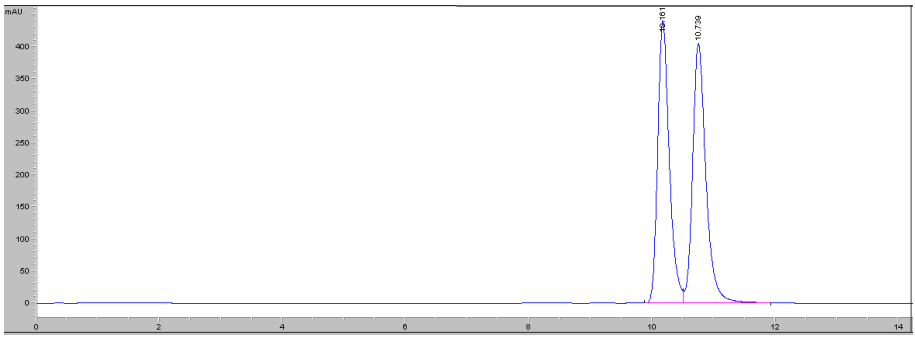
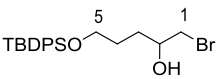


Figure 3: HPLC chromatogram of (±)-**2**

Addition of allylmagnesium bromide to (±)-2. Reaction at -30 ºC

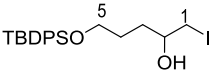
A solution of racemic epoxide (±)-**2** (202 mg, 0.593 mmol) in anhydrous THF (1.15 mL) was added to a stirring mixture of a solution of allylmagnesium bromide (1 M in Et_2O, 0.95 mL, 0.95 mmol) and CuI (18 mg, 0.095 mmol) in anhydrous THF (2.85 mL) under N_2 at -30 ºC. The mixture was stirred at -30 ºC for 20 min, and then at rt for 70 min. The reaction was quenched with a 5% solution of $NaHCO_3$ (25 mL), and the mixture was extracted with Et_2O (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was eliminated under reduced pressure and the crude liquid was purified by column chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 99:1) to yield 170 mg of a 3:1 mixture of **6** and **7** as a clear oil.

1-Bromo-5-*tert*-butyldiphenylsilyloxy-2-pentanol (**6**)



Clear oil. **R_f** (CH_2Cl_2): 0.46. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, OSi(Ph)$_2$^{t}Bu), 1.58-1.77 (m, 4H, H_3 + H_4), 2.64 (d, 1H, *J* = 4.9, OH), 3.39 (dd, 1H, *J* = 6.7, *J* = 10.3, H_1), 3.50 (dd, 1H, *J* = 3.9, *J* = 10.3, $H_{1'}$), 3.70 (m, 2H, H_5), 3.77-3.88 (m, 1H, H_2), 7.36-7.67 (m, 10H, Ph). **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 19.2 (C, ^{t}Bu), 26.8 (OSi(CH_3)$_3$(Ph)$_2$), 28.5 (C_4), 32.0 (C_3), 40.0 (C_1), 63.8 (C_5), 70.7 (C_2), 127.7 (CH, Ph), 129.7 (CH, Ph), 133.5 (C, Ph), 135.6 (CH, Ph). **MS** (ESI+): *m/z* 421.12 ($C_{21}H_{30}{}^{79}BrO_2Si$), 423.12 ($C_{21}H_{30}{}^{81}BrO_2Si$).

5-*tert*-Butyldiphenylsilyloxy-1-iodo-2-pentanol (**7**)

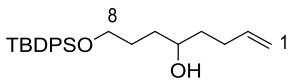


Clear oil. **R_f** (CH_2Cl_2): 0.46. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, OSi(Ph)$_2$^{t}Bu), 1.58-1.77 (m, 4H, H_3 + H_4), 2.57 (d, 1H, *J* = 5.1, OH), 3.24 (dd, 1H, *J* = 6.4, *J* = 10.1, H_1), 3.35 (dd, 1H, *J* = 4.1, *J* = 10.1, $H_{1'}$), 3.53-3.59 (m, 1H, H_2), 3.70 (m, 2H, H_5), 7.36-7.67 (m, 10H, Ph). **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 15.9 (C_1), 19.2 (C, ^{t}Bu), 26.8 (OSi(CH_3)$_3$(Ph)$_2$), 28.5 (C_4), 33.6 (C_3), 63.8 (C_5), 70.8 (C_2), 127.7 (CH, Ph), 129.7 (CH, Ph), 133.5 (C, Ph), 135.6 (CH, Ph). **MS** (ESI+): *m/z* 469.11 ($C_{21}H_{30}IO_2Si$).

8-*tert*-Butyldiphenylsilyloxy-1-octen-5-ol ((±)-3). Reaction at -50 ºC

A solution of racemic epoxide (±)-**2** (404 mg, 1.19 mmol) in anhydrous THF (2.35 mL) was added to a stirring mixture of a solution of allylmagnesium bromide (1 M in Et_2O, 3.0 mL, 3.0 mmol) and CuCl (31 mg, 0.31 mmol) in anhydrous THF (4.5 mL) under N_2 at -50 ºC for 30 min. The reaction was quenched with a 5% solution of $NaHCO_3$ (40 mL), and the mixture was extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was eliminated under reduced pressure and the liquid was purified by

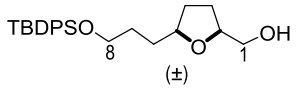
column chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 99:1) to yield 313 mg (69%) of (±)-**3** as a clear oil.



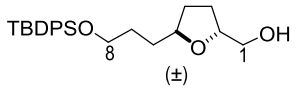
Colorless oil. $\mathbf{R_f}$ (CH_2Cl_2): 0.31. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, OSi(Ph)$_2$^{t}Bu), 1.45-1.62 (m, 6H, H_4 + H_6 + H_7), 2.08-2.18 (m, 2H, H_3), 3.62-3.66 (m, 1H, H_5), 3.68-3.71 (m, 2H, H_8), 4.95-4.99 (m,1H, H_1), 5.02-5.07 (m, 1H, $H_{1'}$), 5.85 (ddt, 1H, *J* = 6.7, *J* = 10.2, *J* = 17.0, H_2), 7.38-7.67 (m, 10H, Ph). **^{13}C NMR** ($CDCl_3$, 100.6 MHz): δ 19.2 (C, ^{t}Bu), 26.8 (OSi(CH_3)$_3$(Ph)$_2$), 28.7 (CH_2), 30.1 (CH_2), 34.3 (CH_2), 36.5 (CH_2), 64.2 (C_8), 71.1 (C_5), 114.6 (C_1), 127.6 (CH, Ph), 129.6 (CH, Ph), 133.6 (C, Ph), 135.6 (CH, Ph), 135.6 (CH, Ph), 138.7 (C_2).

(5-(3-(*tert*-Butyldiphenylsilyloxy)propyl)tetrahydrofuran-2-yl)methanol (5, mixture of diastereomers)

m-CPBA (27 mg, 0.16 mmol) was added in portions to a stirring solution of (±)-**3** (59 mg, 0.15 mmol) in dry CH_2Cl_2 (0.76 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 $NaHCO_3$ (1 mL) and saturated aqueous $Na_2S_2O_3$ (1 mL) and stirred at rt for 30 minutes. The layers were separated and the organic phase was washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$ and filtered. The solvent was eliminated under reduced pressure and the residue was purified on silica gel (hexanes/AcOEt 90:10) to give 15 mg (24%) of **5** as a 1:1 mixture of cis, trans diastereomers.



Colorless oil. $\mathbf{R_f}$ (CH_2Cl_2/MeOH 99:1): 0.27. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, OSi^{t}Bu(Ph)$_2$), 1.44-1.50 (m, 1H, H_4), 1.53-1.73 (m, 4H, H_6 + H_7), 1.84-2.00 (m, 3H, H_3 + H_4), 3.46 (dd, 1H, *J* = 5.6, *J* = 11.3, H_1), 3.67-3.70 (m, 3H, $H_{1'}$ + H_8), 3.83-3.88 (m, 1H, H_5), 3.96-4.01 (m, 1H, H_2), 7.38-7.67 (m, 10H, Ph).

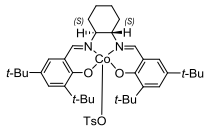


Colorless oil. $\mathbf{R_f}$ (CH_2Cl_2/MeOH 99:1): 0.27. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 1.05 (s, 9H, OSi^{t}Bu(Ph)$_2$), 1.44-1.50 (m, 1H), 1.53-1.73 (m, 4H), 1.84-2.00 (m, 3H), 3.61 (dd, 1H, *J* = 2.3, *J* = 11.2), 3.67-3.70 (m, 3H), 3.89-3.94 (m, 1H), 4.06-4.12 (m, 1H), 7.38-7.67 (m, 10H, Ph).

2.2.2 Stereoselective synthesis

Preparation of catalyst (*S,S*)-(Salen)-Co(III)-OTs (8)

CH_2Cl_2 (0.87 mL) was added to (*S,S*)-(salen)-Co(II) (40 mg, 0.066 mmol) and *p*-toluenesulfonic acid (14 mg, 0.073 mmol). The colour of the solution changed from bright red to dark green. The mixture was stirred for 1 hour open to the air, and then the solvent was evaporated under reduced pressure. **8** (42 mg, 83%) was obtained as a dark green solid. This solid was directly used in the next step.



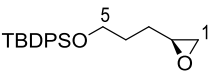
Dark green solid.

(*S*)-5-*tert*-Butyldiphenylsilyloxy-1,2-epoxy-pentane ((*S*)-2)

A small round-bottomed flask was charged with epoxide (±)-**2**, H_2O/THF 1:1 and (*S,S*)-salen-Co(III)-OTs (10^{-2} equivalents) in that order. The reaction mixture was stirred for the time indicated in Table 3 at rt. CH_2Cl_2 was then added and the reaction was quenched with anhydrous $MgSO_4$. The reaction mixture was filtered and purified on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to yield (*S*)-**2** as a colorless oil.

Entry	H_2O equivalents	Catalyst's age	Reaction time	Yield	ee%
1	0.7	3 days	20 h	36%	99%
2	0.7	30 days	20 h	37%	79%
3	0.7	24 hours	20 h	15%	>99%
4	0.55	new	20 h	38%	>99%

Table 3: Results of the HKRs



Colorless oil. $\mathbf{R_f}$ (CH_2Cl_2/MeOH 95:5): 0.92. $\mathbf{[\alpha]_D}$: -2.98 (*c* 1.08, $CHCl_3$); lit.[11] -2.1 (*c* 0.85, $CHCl_3$). **HPLC** (Chiralpack AS-H, hexanes/isopropanol 99.5:0.5, 0.4 mL/min, λ = 254 nm): t_R =10.2 min; t_S = 10.8 min

(±)-**2** (*S*)-**2**

Enantiomer	t_R (min)	Area	% Area
(*R*)-**2**	10.180	26.8	0.484
(*S*)-**2**	10.763	5499.7	99.516

Table 4: HPLC parameters of (*S*)-**2**

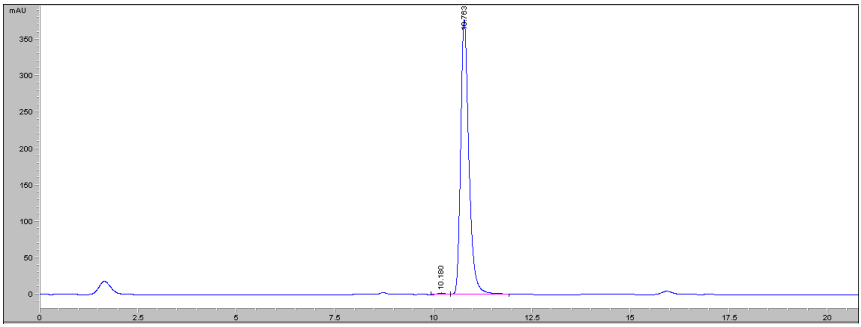


Figure 4: HPLC chromatogram of (*S*)-**2**

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APPENDICES

APPENDIX 1. ACRONYMS

m-CPBA	*meta*-chloro peroxybenzoic acid
DMAP	4-dimethylaminopyridine
HKR	hydrolytic kinetic resolution
HPLC	high performance liquid chromatography
PG	protecting group
t_R	retention time
rt	room temperature
TBDPS	*tert*-butyldiphenylsilyl
tlc	thin layer chromatography
THF	tetrahydrofuran