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Corso di Laurea magistrale in Chimica Industriale

Tesi di Laurea

Alkoxyallene based synthesis of enantiopure tetrahydrofuranol derivatives;
a novel approach to the synthesis of Jaspine B

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ABBREVIATIONS

Alox	aluminum oxide
aq.	aqueous
Bu	butyl
c	concentration (g/mL)
calcd.	calculated
cat.	catalyst
COSY	correlated spectroscopy
δ	chemical shift
DAG	diacetone-D-glucose
d	doublet
DMF	N,N-dimethylformamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
EA	elemental analysis
equiv.	equivalents
ESI	electro spray ionization
Et	ethyl
h	hour(s)
q	quartet
HMQC	heteromolecular multiple quantum coherence
HPLC	High-performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared
J	coupling constant (Hz)
M	molar
m	multiplet
Me	methyl
m_c	center of multiplets
min	minute(s)
µ	micro
MHz	mega Hertz
MS	mass spectroscopy
MTBE	methyl tert-butyl ether
m/z	mass to charge ratio
N	normal
NBS	N-bromosuccinimide
NMR	nuclear magnetic
Ph	phenyl
Py	pyridine
ppm	parts per million
quant.	quantitative
quint.	quintet
R	organic substituent
R_f	retention factor
r.t.	room temperature
s	singlet

TBDPSCl	tert-Butylchlorodi-phenylsilane
TFA	trifloroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSOTf	trimethylsilyl trifluoromethanesulfonate

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1 INTRODUCTION

1.1 Motivation and aim

The development of new synthetic methods is considered as one of the primary goals in organic chemistry. Despite all the methodologies developed so far, construction of highly functionalized heterocyclic compounds still remains a challenging field. Nitrogen and oxygen containing heterocyclic compounds such as imidazoles, pyridines and furans play a fundamental role in synthetic and medicinal chemistry. These heterocycles can be found in many natural products, *e.g.* penicillin, vitamins, morphine, nicotine. More than 80% of drugs on the market are heterocyclic compounds, supported by the fact that 90% of drug research is focused on these molecules.

One of these natural compounds is Jaspine B (**1**) (Fig. 1), whose enantiopure synthesis has been attracting some attention in the recent years. Natural Pachastrissamine (**1**) (Jaspine B) was first isolated in 2001 by Higa and co-workers[1] from the marine sponge *Pachastrissa sp.* (calthropellidae family). Later in 2003 Debitus and co-workers[2] isolated the same compound from a vanuatuan marine sponge genus *Jaspis.* This natural product is a 18 carbons anhydrophytosphingosine derivative in which the C-1 and C-4 position are connected through an ether linkage forming a tetrahydrofuran ring bearing three contiguous different substituents in an all-*cis* arrangement: an amino group, a hydroxyl group and an aliphatic chain.[3a,b]

It was found that this compound exhibits a significant cytotoxic activity against P388, A549, HT29, and MEL28 carcinoma cells,[4] indicating the potential usage in cancer treatment.

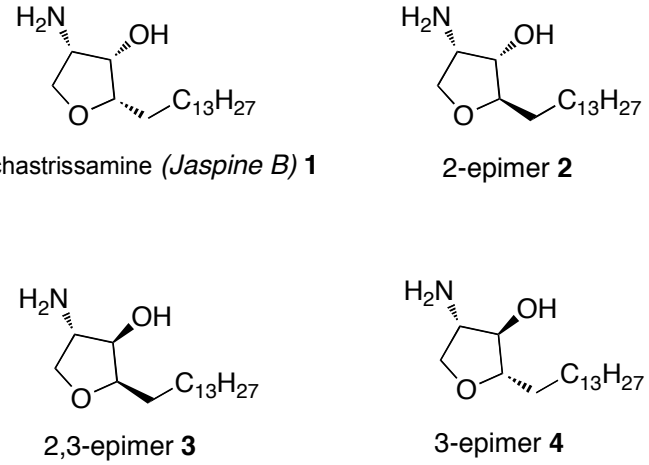
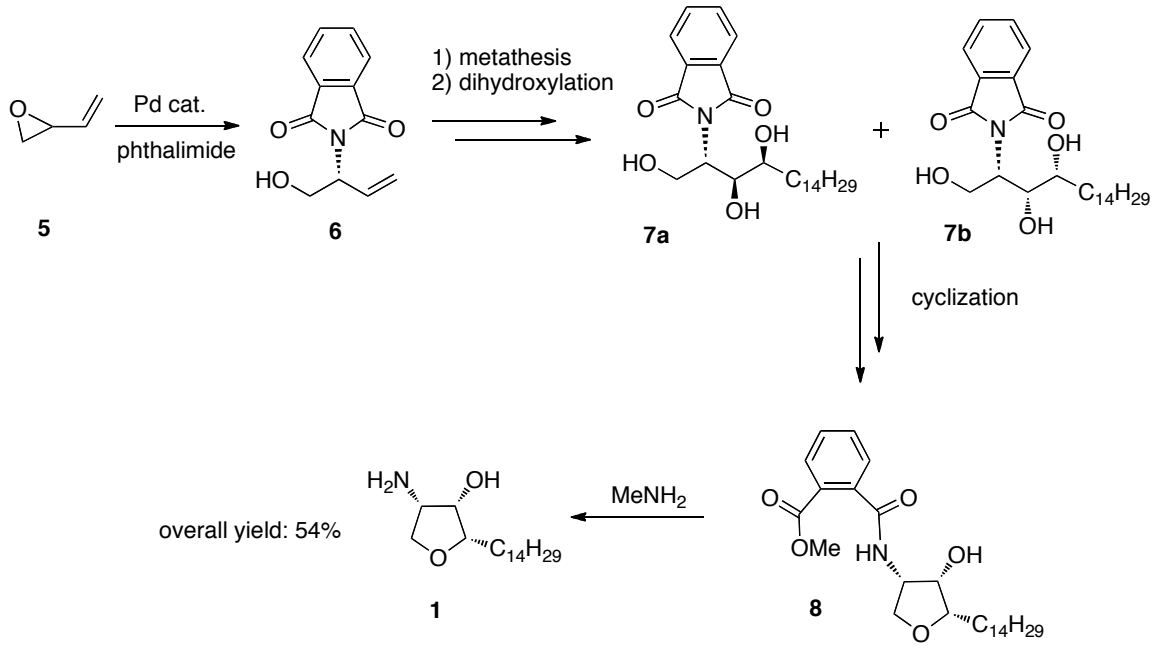


Figure 1: Structures of Pachastrissamine and its three diastereomers **2**-**4**.

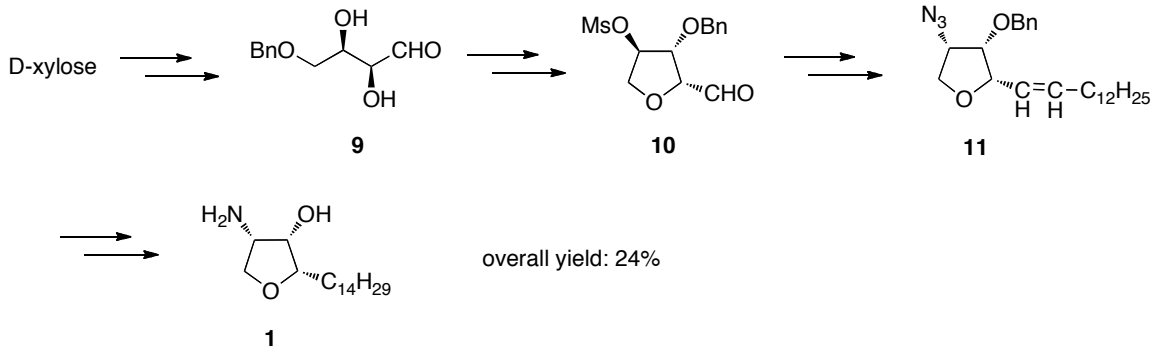
Due to the promising biological activity, the development of methods to stereoselectively synthesize Jaspine B gains more importance. From the many approaches described in the literature, Delgado and co-workers[5a] as well as Ohno and co-workers[6] have synthesized four diastereomers of Pachastrissamine (Figure 1; **1**, **2**, **3**, **4**), however, other publications present the synthesis only of Jaspine B (**1**), using starting materials from the chiral pool: *e.g.* L-xylose, D-glucose and L-tartaric acid.[7a-b-c]

Castillòn *et al.* reported a suitable strategy (Scheme 1) that can provide enantiopure Jaspine B **1** in 6 steps with an overall yield of 54% starting from racemic butadiene mono-epoxide.[7d] The key steps are the enantioselective palladium-catalyzed allylic amination of the epoxide **5** providing intermediate **6**, followed by a cross-metathesis reaction with a ruthenium catalyst.



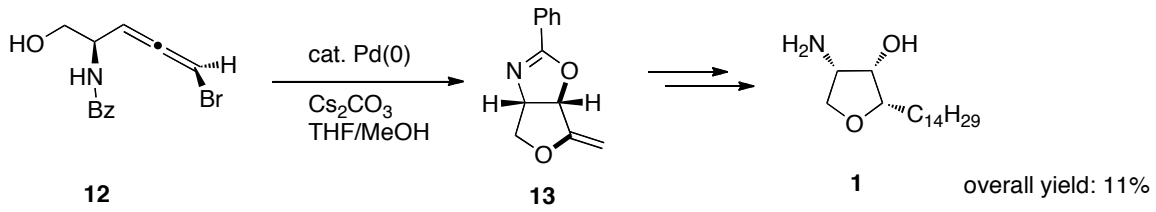
Scheme 1: Castillòn´s approach for the synthesis of Jaspine B.

Liu´s research group synthetized Jaspine B (**1**) from D-xylose in 11 linear steps with 24% overall yield (Scheme 2).[7b] The key steps in the synthesis involves a Wittig reaction of hydroxyaldehyde **9** with $Ph_3P{=}CH_2$ followed by iodine-induced debenzylation and a subsequent stereoselective 2,5-cyclization affording the desired configuration.



Scheme 2: Liu´s approach for the synthesis of Jaspine B.

Allene derivatives are versatile starting materials for the synthesis of heterocycles. Ohno *et al.* have described a strategic synthesis of Jaspine B (**1**) employing an allene (Scheme 3).[5b] The palladium(0)-catalyzed cascade cyclization of bromoallene **12** bearing hydroxyl and benzylamine groups as internal nucleophiles, could regio- and stereoselectively provide an appropriately functionalized tetrahydrofuran **13** for the synthesis of the target molecule. Starting from Garner´s aldehyde as the chiral source for the preparation of bromoallene **12**, this strategy provides Jaspine B (**1**) in 11 steps with 11% overall yield.

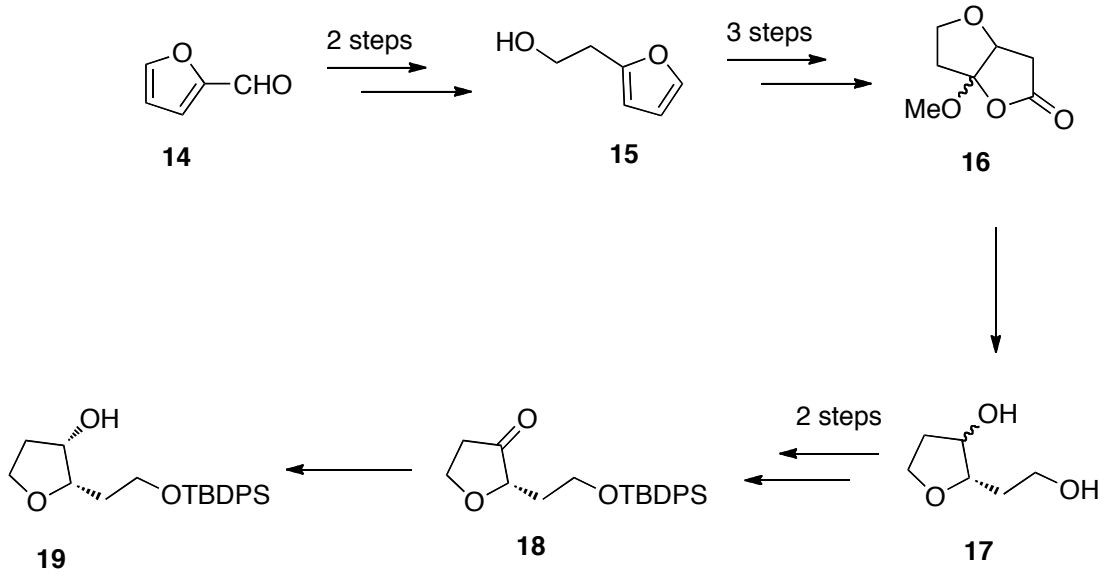


Scheme 3: Ohno´s approach to the synthesis of Jaspine B (**1**).

1.2 Comparable literature for a novel synthesis of a tetrahydrofuranol derivative

Recently Fall and coworkers reported a tedious 9-steps synthesis of tetrahydrofuranol **19** (Scheme 4) starting from a furan derivative. Compound **19** was used as precursor of isonucleoside analogues.[8a] Isodideoxynucleosides derivatives easily obtained from tetrahydrofuranol **19** exhibit interesting biological activities and in particular, a potent anti-HIV activity. Fall started the synthesis from 2-(furan-2yl)ethanol **15** which was prepared in two steps from commercially available furfural **14**.[8b] Oxidation of **15** followed by treatment with tetrabutylammonium fluoride, provided the corresponding bicyclic lactone **16.** The

ring was opened with lithium aluminum hydride affording a diastereomeric mixture of diol **17.** A selective monoprotection of **17** followed by oxidation afforded the furanone derivate **18**. A stereoselective reduction with L-Selectride provided the enantiomeric pure *cis*-configured tetrahydrofuranol **19**. The similarity between the configuration of tetrahydrofuranol **19** and the structure of Jaspine B (**1)**, prompted us to start this work focus our attention seeking an easier methodology to achieve this target molecule.



Scheme 4: Fall´s approach to the synthesis of tetrahydrofuranol **19**.

1.3 Alkoxyallenes for the synthesis of natural products

Within the Reissig group it has been shown that alkoxyallenes **20** proved to be very useful three-carbon building blocks for the construction of functionalized heterocycles e.g. furans, pyrroles, pyridines and 1,2-oxazines.[9a,b] The synthetic potential of allenic intermediates is substantially supported by the fact that they have been used in numerous natural product syntheses.[10] Among the different types of allenic compounds, donor- and alkoxy-substituted allenes in particular proved to be the most versatile, as they are characterized by a unique triple

reactivity pattern (Figure 2). The γ-carbon can be attacked by nucleophiles, the β-carbon shows typical enol-ether reactivity and the hydrogen at the α-carbon can be abstracted by strong bases such as alkyl lithiums, generating highly reactive C-3-nucleophiles as lithiated alkoxyallenes **21**. These types of compounds easily undergo additions at C-1 to electrophiles leading to a broad range of synthetically diverse intermediates bearing an alkoxyallenyl moiety.

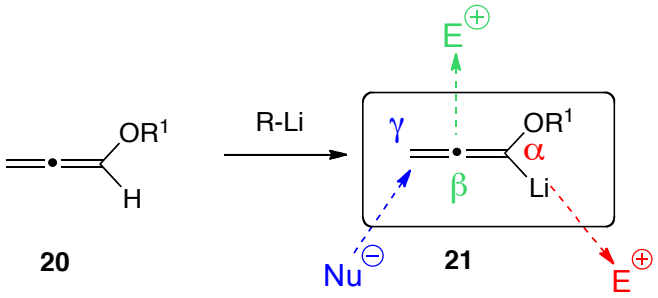
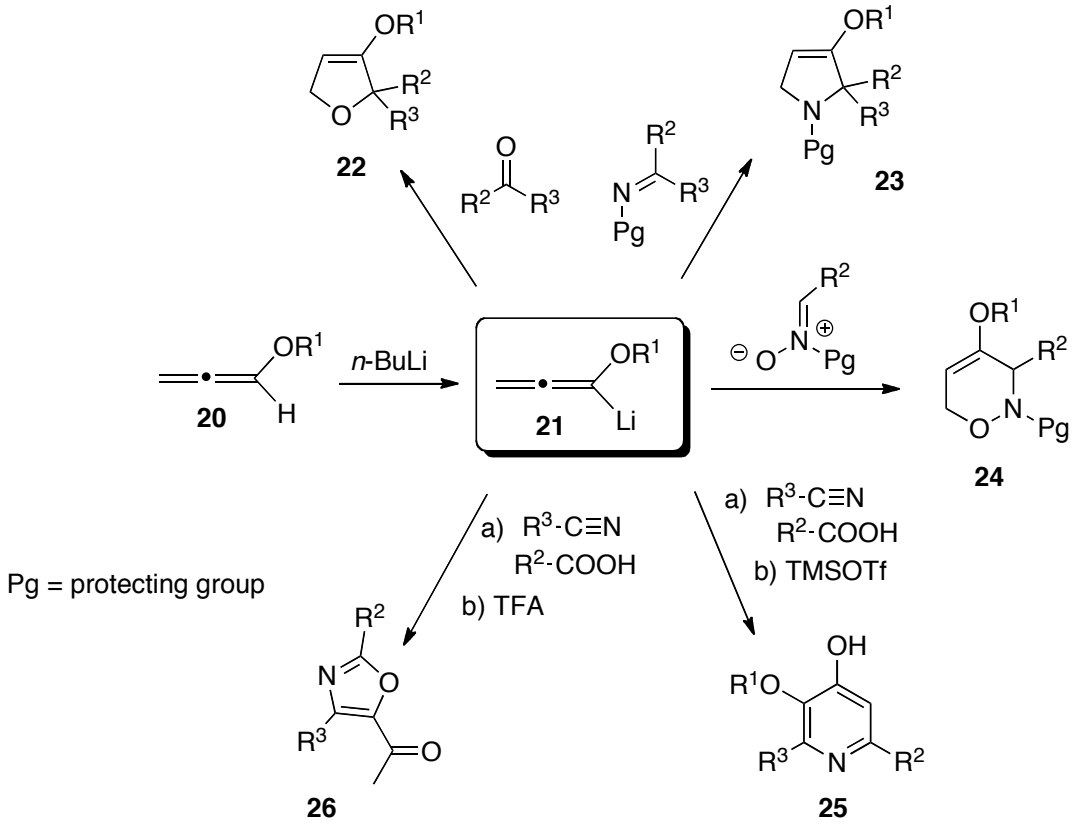


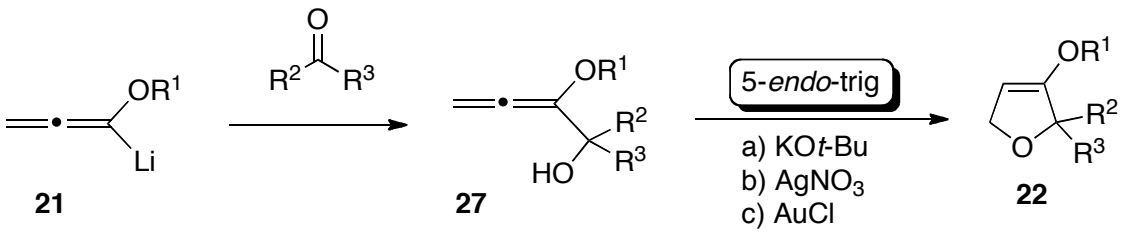
Figure. 2: Alkoxyallene reactivity.

The synthetic potential of allenic intermediates has been exploited in natural product syntheses due to the unique and versatile reactivity of the moiety. In Scheme 4 are depicted some examples which demonstrate the high potential of alkoxyallenes as building blocks for the synthesis of heterocycles. The addition of lithiated alkoxyallene **21** to an aldehyde or ketone provides α-allenyl alcohols, that can easily be converted into dihydrofuran derivatives **22**.[10a-c] Similarly, 2,5-dihydropyrrole **23** can be synthesized starting from an imine.[11a-c] The addition product to aldonitrones can spontaneously cyclize to 3,6-dihydro-2*H*-1,2-oxazines **24**.[12a,b] Furthermore, alkoxyallenes can be used as moiety in a three component reaction with a nitrile and a carboxylic acid followed by reaction with TMSOTf to provide hydroxypiridine **25**.[13] When replacing TMSOTf with TFA the final product is 5-acetyl oxazole derivative **26**.[14]



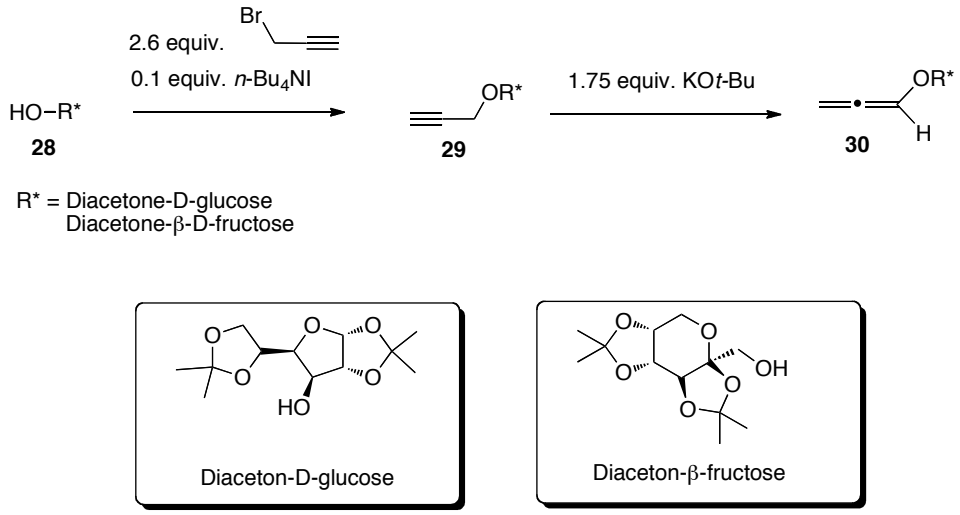
Scheme 5: Alkoxyallene based synthesis of different heterocycles.

The above mentioned two-step synthesis of 3-alkoxy-substituted dihydrofurans **22** starting from alkoxyallenes was first reported in 1969 by Brandsma and Arens.[10a] The addition of lithiated alkoxyallenes **21** to aldehydes or ketones quantitatively furnish alcohols **27** which can easily cyclize under basic conditions (Scheme 6).[15a,b] Recently, two new procedures for the required 5-*endo*-trig cyclization were described employing either $AgNO_3$[16] or AuCl[17a-c] as a catalyst.



Scheme 6: Two-step protocol for preparation of 3-alkoxy-substituted dihydrofuran derivatives.

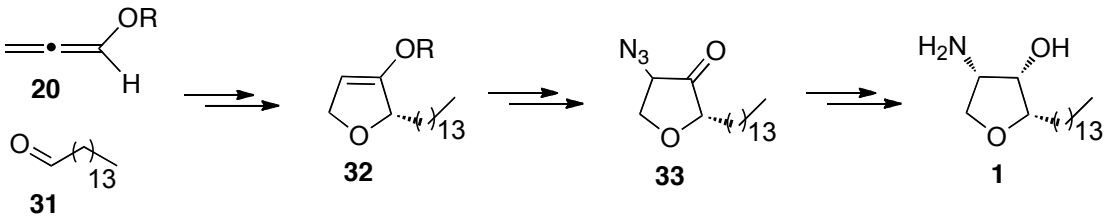
The formation of 3-alkoxy-substituted dihydrofurans creates a new challenge for the search of a convenient method for the enantiopure synthesis of this type of compounds. In this context, alkoxyallenes are of particular of interest to be explored as a chiral starting material, whose chirality may be transferred to newly created stereogenic center.[18a-c] Goré *et al.* published the synthesis of a series of enantiopure alkoxyallenes bearing carbohydrate based auxiliaries.[19] Simultaneously to this work, Hausherr described in his PhD thesis an interesting stereoselective synthesis of the natural product (-)-Preussin using a carbohydrate based alkoxyallene.[20] In accordance with these publications, enantiopure alcohol **28** can smoothly react with propargyl bromide in a Williamson ether synthesis to furnish the propargyl ether **29** in good yields (Scheme 7). Base catalyzed isomerization of the alkyne **29** to allene **30** was induced by KO*t*-Bu.



Scheme 7: Synthesis of alkoxyallene derivatives from enantiopure carbohydrates.

Since this pathway provided an easy access to activated enantiopure dihydrofuran derivatives, we focused our research first on these key steps to find an efficient approach for the synthesis of enantiopure tetrahydrofuranol **19**. The synthesis of Jaspine B (**1**) was the second goal due the similarity with **19**. Once the corresponding dihydrofuranone **32** is obtained from the addition of alkoxyallene **20** to 1-pentadecanal **31**, the insertion of the amino group in the 4-

position should be realized by bromination followed by azidation reaction to provide the 4-azidofuranone derivate **33**.[21] The selective reductions of the keto- and amino-group should finally provide the target molecule Jaspine B (**1**) (Scheme 8).

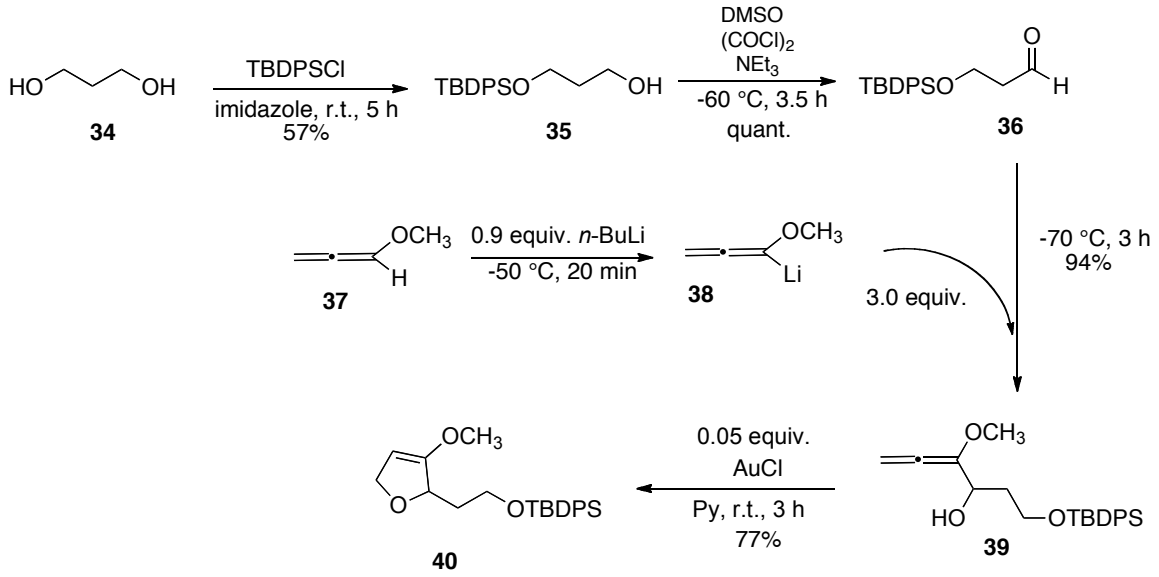


Scheme 8: Anticipated pathway for the synthesis of Jaspine B (**1**).

2 RESULTS AND DISCUSSION

2.1 First model studies for the synthesis of a racemic tetrahydrofuranol derivative.

In order to find an efficient pathway for the synthesis of enantiopure Jaspine B (**1**), the research first focused on the synthesis of racemic tetrahydrofuranol **rac-19** using methoxyallene and a protected aldehyde as precursors. Commercially available 1,3-propandiol (**34**) was treated with *tert*-butylchlorodiphenylsilane and imidazole providing mono-protected alcohol **35**, that under Swern oxidation conditions, was quantitatively transformed into the corresponding aldehyde **36** (Scheme 9). Lithiation of methoxyallene **37** with *n*-butyllithium and subsequent addition of unpurified aldehyde **36** provided primary allenyl adduct **39**. Due to the instability of intermediate **39** during purification it was employed in subsequent reactions as crude material. The 5-*endo*-trig cyclization afforded the desired racemic 2,5-dihydrofuran derivative **40** with 72% overall yield (based on **35**).



Scheme 9: Synthesis of the racemic 3-methoxy-2,5-dihydrofuran **40**.

The choice of the reaction conditions is crucial for the cyclization step. Adopting Arens´s strongly basic conditions (KO*t*-Bu in DMSO)[10a] or the electrophilic activation with a silver(I) catalyst[16] no satisfying results could be obtained (Tab. 1, entries 1 and 2). The use of catalytic amounts of gold(I) chloride and pyridine emerged as the best condition for the cyclization to 3-methoxy-2,5-dihydrofuran derivative **40** (Tab. 1, entry 3).[17a]

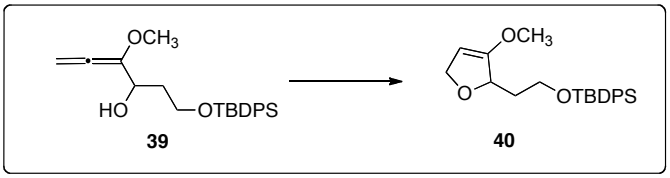


Figure. 3: Cyclization of primary allenyl adduct **39**.

Table. 1: Reaction conditions for the 5-*endo*-trig cyclization of **39**.

Entry	**Reaction conditions**	**Solvent**	**Time (h)**	**Temperature (°C)**	**Yield (%)** of **40**
1	0.50 equiv. KO*t*-Bu	DMSO	1.5	60	28
2	0.20 equiv. $AgNO_3$, 5.0 equiv. K_2CO_3	CH_3CN	4	r.t.	0
3	0.05 equiv. AuCl, 0.15 equiv. Pyridine	CH_2Cl_2	3	r.t.	77

A possible mechanism for the gold(I)-catalyzed 5-*endo*-trig cyclization is proposed in Figure 4. The Lewis acidic character of this catalyst allows the formation of a complex with an allene. Gold(I)-chloride and pyridine generate the active catalyst species **I** that can interact with the substrate **27** to form a π-

complex **II**; which in presence of an alkoxy group in 3-position, is in equilibrium with the σ-complex **III**. After nucleophilic attack of the hydroxy group to the allene, this moiety cyclizes affording the corresponding furan intermediate **IV**. An hydrodemetallation closes the catalytic cycle forming the alkoxy-2,5-dihydrofuran **22** with recovering of the gold(I) complex **I**.

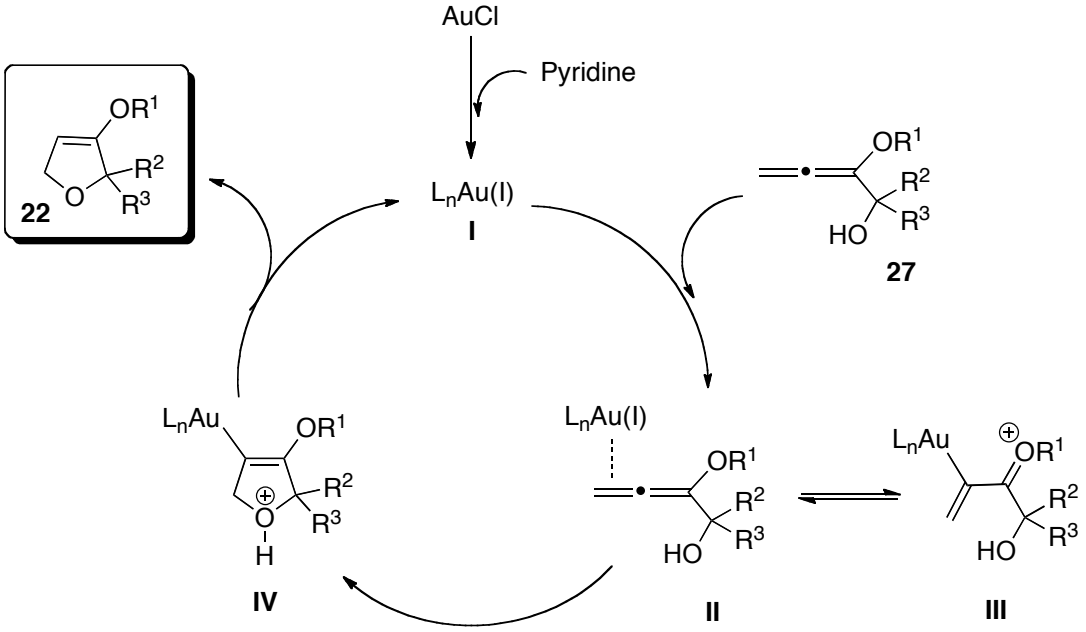
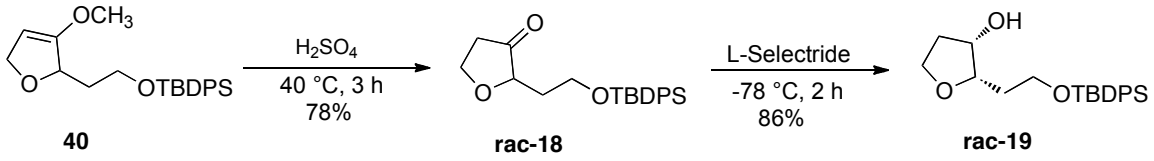


Figure 4: Possible mechanism for the gold(I) catalyzed cyclization.

The *cis*-configured tetrahydrofuranol **rac-19** was obtained first by hydrolysis of dihydrofuran **40** with strong acid followed by diastereoselective reduction of **rac-18** with L-Selectride (Scheme 10). The steric hindrance induced by the three *sec*-butyl groups of L-Selectride is essential for the formation of the *cis*-diastereomer. The attack of L-Selectride was, as expected, preferred on the opposite side of the chain in α-position of the carbonyl group.

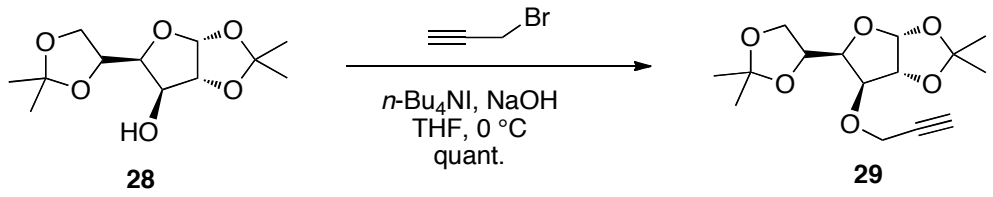


Scheme 10: Synthesis of racemic tetrahydrofuranol **rac-19**.

The reduction of ketone **rac-18** was also performed with $NaBH_4$ as reducing agent, but only a 1:1 mixture of the *cis/trans* isomers was obtained with 50% yield.

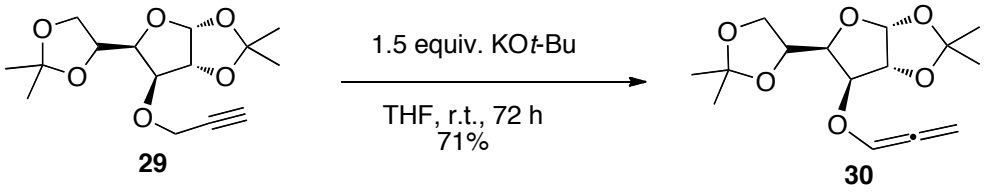
2.2 Synthesis of an enantiopure tetrahydrofuranol derivative

In order to be prepared for the synthesis of enantiopure Jaspine B (**1**), a similar synthetic route as for the synthesis of racemic tetrahydrofuranol derivative **rac-19** was tested using suitable chiral starting materials. Therefore, we decide to use the literature-known carbohydrate-alkoxyallene derivative **30** as chiral starting material,[18a-c, 19] which is easily accessible by a two-step reaction sequence.
The commercially available enantiopure alcohol diacetone-D-glucose **28** smoothly reacted in the first step with propargyl bromide to furnish the corresponding propargyl ether **29** in quantitative yield (Scheme 11).



Scheme 11: Reaction of diacetone-D-glucose **28** with propargyl bromide.

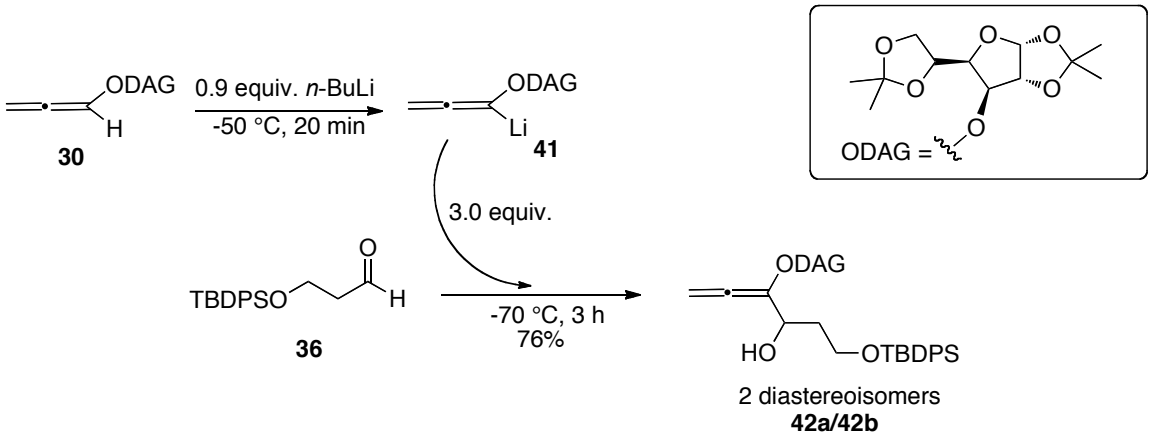
The subsequent base catalyzed isomerization of alkyne **29** to allene **30** was achieved with KO*t*-Bu in THF at room temperature (Scheme 12) with 71% yield.



Scheme 12: Base catalyzed isomerization of alkyne **29** to allene **30**.

Several experiments were performed to optimize the yield of this transformation. Applying literature procedures,[18a-c] this reaction was performed using 1.5 to 2.0 equivalents of KO*t*-Bu under reflux of toluene giving yields between 12% and 56%. The low yields may be explained by decomposition of the sugar moiety at high temperature. The reaction conditions could be optimized by carrying out this step at room temperature with 1.5 equivalents of base for 72h affording the alkoxyallene **30** in 71% yield.

Subsequent addition of protected aldehyde **36** to lithiated alkoxyallene **41** (Scheme 13) provided the two diastereomers **42a** and **42b** (ratio ca. 1:1) in good yield, which could be separated by HPLC.

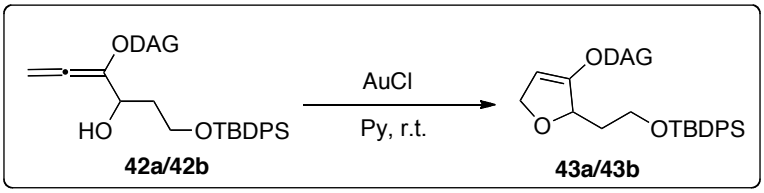


Scheme 13: Addition of aldehyde **36** to lithiated alkoxyallene **41**.

Further steps were carried out independently with the both separated diastereomers, but also with a mixture of these isomers. Since the correct

configuration is still unknown and for numbering simplification, **a** and **b** will be used for products derived from the different diastereomers **42a** and **42b**, respectively.

The allenyl alcohols **42a/b** were cyclized to alkoxy-2,5-dihydrofuran derivatives **43a/b** in the presence of catalytic amounts of gold(I) chloride and pyridine, (Scheme 13). Comparing the reaction efficacy of the separated isomers **42a** and **42b** (Tab. 2, entries 1 and 2) with the mixture of diastereoisomers (Tab. 2, entry 3), it is evident that the 5-*endo*-trig cyclization was favored when the isolated compounds were used. The higher purity of separated isomers **42a** and **42b** may be responsible for higher yields obtained. The observed yields for diastereomers **43a** and **43b** were in the same range as for the racemic compound **40** (see above).



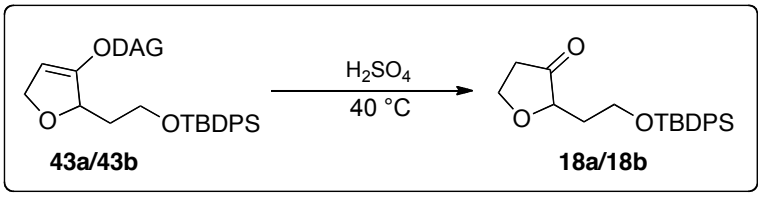
Scheme 14: Cyclization of primary allenyl adduct **42a/42b**.

Table 2: Reaction performance for the 5-*endo*-trig cyclization of **42a/b**.

Entry	Substrate	Conditions	Time (h)	Yield (%) of 43a/b
1	**42a**	0.2 equiv. AuCl 0.15 equiv. Pyridine	1	73
2	**42b**	0.2 equiv. AuCl 0.15 equiv. Pyridine	1	77
3	Mixture of **42a/b**	0.2 equiv. AuCl 0.15 equiv. Pyridine	4	27

The hydrolysis of the enol ether in **43a/b** providing the corresponding ketones **18a/b**, proved to be a crucial step of this synthesis (Scheme 15). The cleavage of the carbohydrate moiety did not occur smoothly as with the methoxy-substituted derivative (chapter *2.1*). This might be due to the possibility that the acid can coordinate to the oxygen atoms in the carbohydrate structure. This is supported by the longer reaction time and larger amount of acid needed to obtain good yields. The reaction temperature was not raised higher than 40°C since this can lead to racemization of the final product.

Better yields were obtained when the substrate **43b** is used in comparison to substrate **43a** and the mixture of diastereomers (Tab. 3). After 48 h complete conversion of the substrate **43b** was observed (entry: 2), as confirmed by the ^{1}H NMR spectrum of the crude product. The yield of only 71% can be explained by purification problems during the column chromatography. The conversion of substrate **43a** after 72 h was not quantitative (entry 1) and after the chromatography purification 64% yield was obtained. The opposite values of the optical rotation between the two enantiomers produced **43a** and **43b** indicated that probably no racemization occurred under these conditions. As in the previous cyclization reactions, the comparison of the reaction efficacy of the pure diastereomers **43a** and **43b** (entries 1 and 2) with that of the mixture of diastereomers (entry 3) shows that the yields were higher when the enantiopure compounds were used.

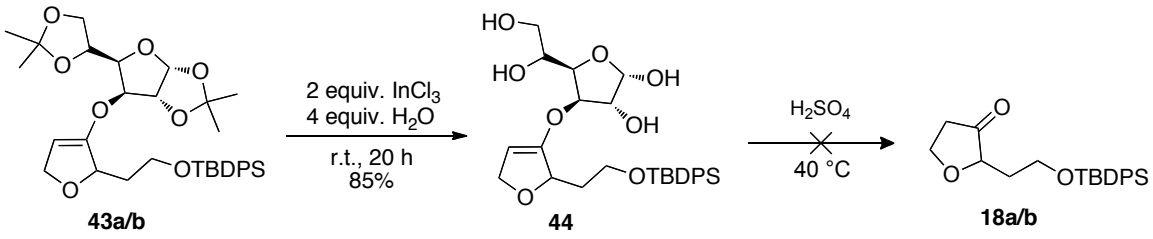


Scheme 15: Hydrolysis of ether bond.

Table 3: Hydrolysis of the enol ether moiety of dihydrofurans **43a/b**.

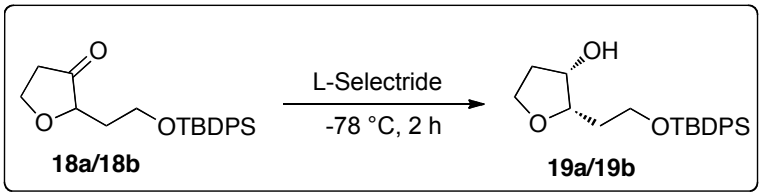
Entry	Substrate	Reaction condition	Time (h)	$[\alpha]_D$	Yield (%) of 18
1	**43a**	6 mL/mmol of 1:1 2 N H_2SO_4/THF	72	+42.4	64
2	**43b**	6 mL/mmol of 1:1 2 N H_2SO_4/THF	48	-47.3	71
3	mixture of **43a/b**	4 mL/mmol of 1:1 2 N H_2SO_4/THF	54	0	27

An alternative method has been checked for the cleavage of ketals of the carbohydrate moiety. Therefore alkoxy-2,5-dihydrofuran **43a/b** was treated with $InCl_3$ and water in order to afford the expected deprotected **44** (Scheme 15).[22] However, acidic hydrolysis of **44**, did not provide the desired ketone **18a/b**.



Scheme 16: Cleavage of the ketals of **43a/b** and attempted hydrolysis of the enol ether unit.

Stereoselective reduction of tetrahydrofuranone **18a/b** with L-Selectride provided the *cis*-configured tetrahydrofuranol **19a/b** with acceptable yields (Scheme 17). No significant difference in the yields comparing the reactions of pure substrate **18a** and **18b** (Tab. 4; entries 1 and 2) with that of the mixture of diastereomers (entry 3) was observed for this step.

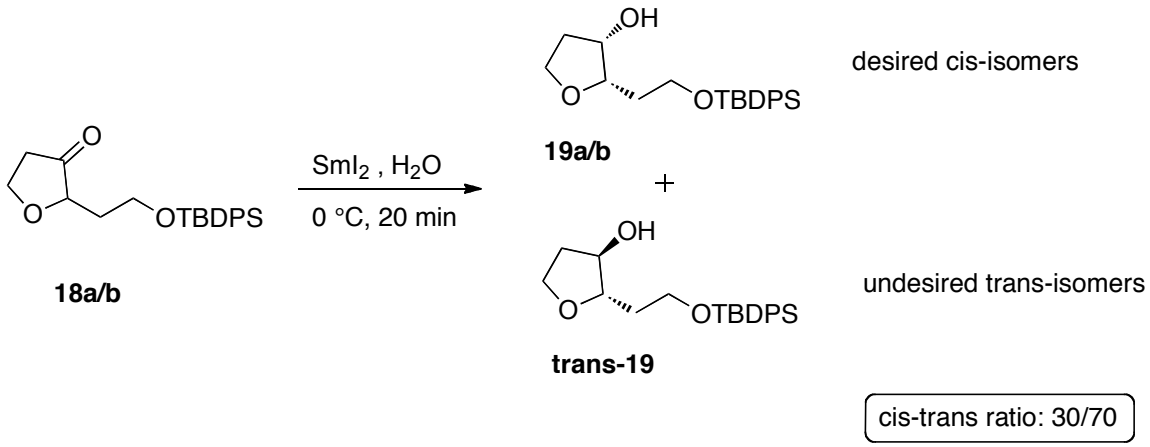


Scheme 17: Stereoselective reduction of ketone **18a/b** to alcohol **19a/b**.

Table 4: Reduction of ketone **18a/b** to alcohol **19a/b**.

Entry	Substrate	Yield (%) of 19a/b
1	**18a**	52
2	**18b**	40
3	mixture of **18a/b**	57

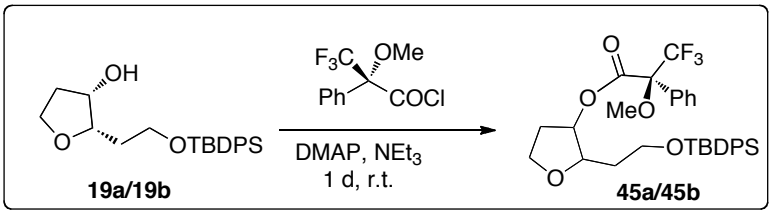
The stereoselective reduction of **18a/b** with samarium diiodide in presence of water was also tested.[23] The yield of **19a/b** was almost quantitative, but a 30:70 mixture of *cis/trans*-isomers was obtained, showing a low selectivity of SmI_2 employing this substrate.



Scheme 18: Reduction of ketone **18a/b** with SmI_2.

An efficient method for the determination of the enantiomeric excess is based on chemical derivatisation. Since diastereomers have different physical properties a reliable route to determine the enantiopurity of a chiral substrate is its transformation into diastereomers by introducing a chiral group bearing a fixed stereogenic center. The formed diastereomers can then either be separated by chromatography or be distinguished by other physical experiments such as NMR spectroscopy. A commonly used chiral substrate for this purpose is α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher´s chloride).[24]

The two *cis*-configured tetrahydrofuranols **19a** and **19b** were converted into the corresponding Mosher esters **45a** and **45b** (Scheme 19).



Scheme 19: Reaction between tetrahydrofuranols **19a and 19b** with Mosher´s chloride.

As expected, after reaction with the Mosher chloride both diastereoisomers **19a** and **19b** provided only the diastereomerically pure esters **45a** and **45b**, respectively, easily distinguishable by ^{1}H NMR spectra (Figure 5). This fact confirms that the synthesized tetrahydrofuranols **19a** and **19b** were enantiopure (within the experimental error of the NMR method of ca. 3%), and that no racemization has occurred during enol ether hydrolysis and subsequent reduction. This result confirms the validity of the synthetic pathway chooses for these transformations.

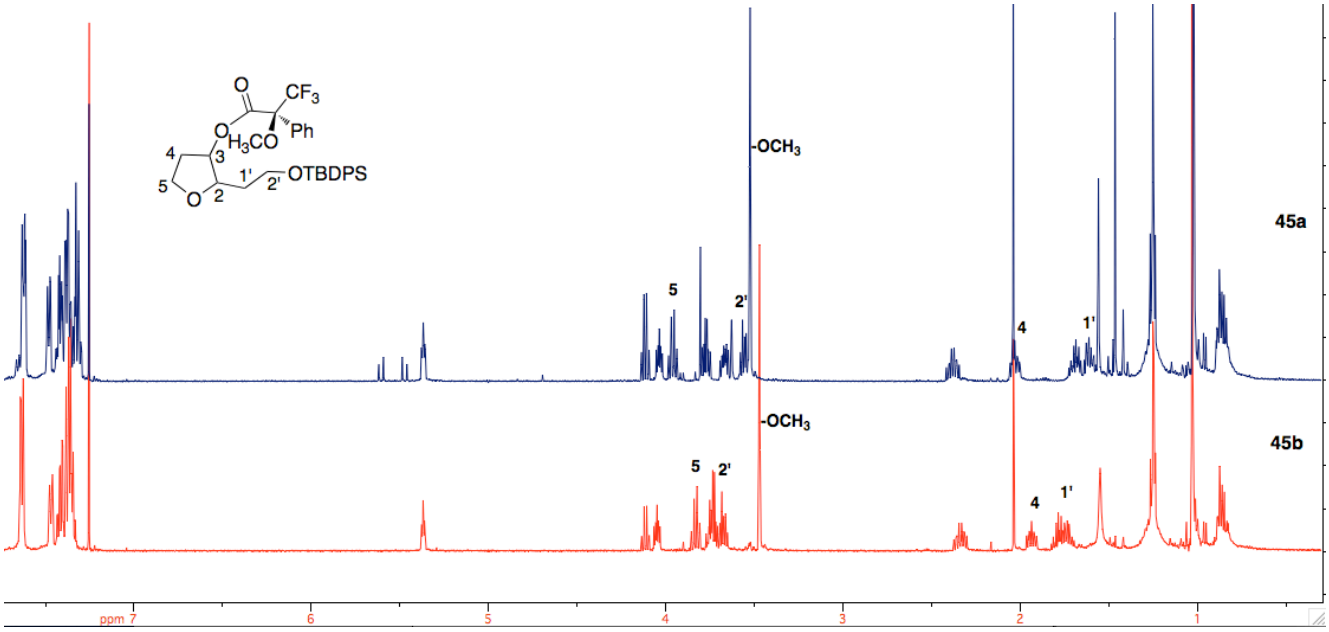


Figure 5: ^{1}H NMR spectra (CDCl3, 500 MHz) of the Mosher ester **45a** and **45b**.

The ^{1}H NMR spectrum, illustrated in Figure 5, unambiguously prove the enantiopurity of the synthetized diastereoisomers **45a** and **45b**.

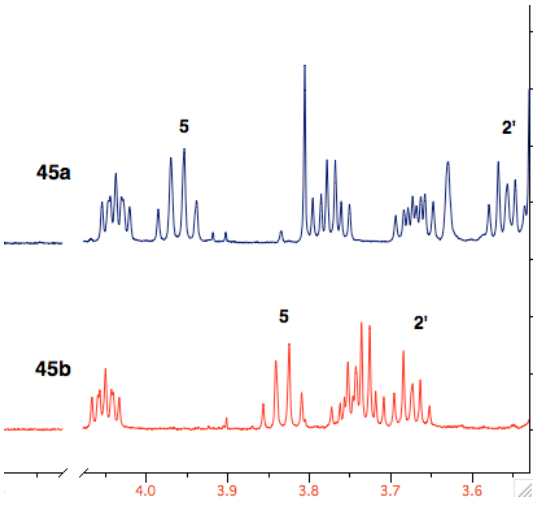


Figure 6: Enlargement of ^{1}H NMR spectra (CDCl3, 500 MHz) of the Mosher ester **45a** and **45b**

Focusing on the spectra's area between 3.5 and 4.0 ppm (Figure 6), it is possible to evaluate the different signals chemical shift of the proton in 5 position of the furan moiety between the two diasteromers **45a** and **45b**. The same strong difference appear for the proton signals 2' associated to the second carbon of the alkyl substituent.

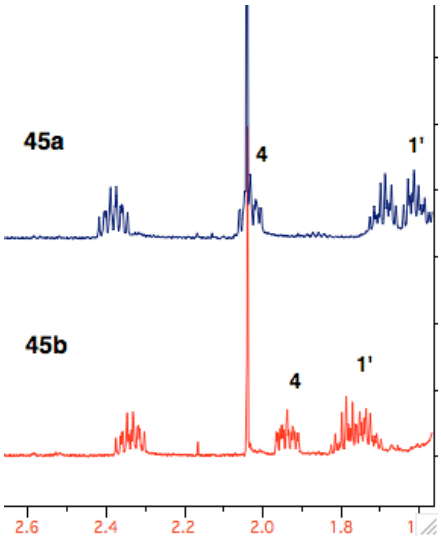


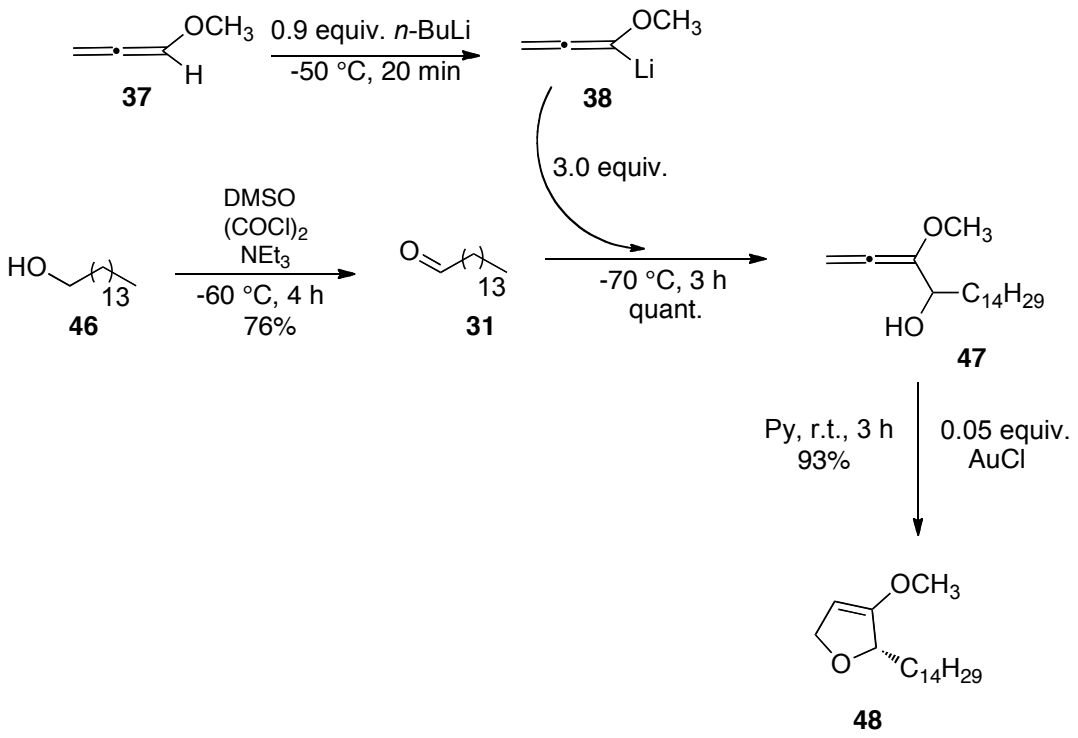
Figure 7: Enlargement of ^{1}H NMR spectra (CDCl3, 500 MHz) of the Mosher ester **45a** and **45b**

Significant differences are easily recognized in the spectra between 1.6 and 2.1 ppm (Figure 7). The disagreement chemical shift of the signals of the proton in 4 position of the furan moiety, and the protons 1' associated to the first carbon of the alkyl substituent, can unambiguously prove the expected enantiopurity of **45a** and **45b**.

2.3 Synthesis of racemic Jaspine B

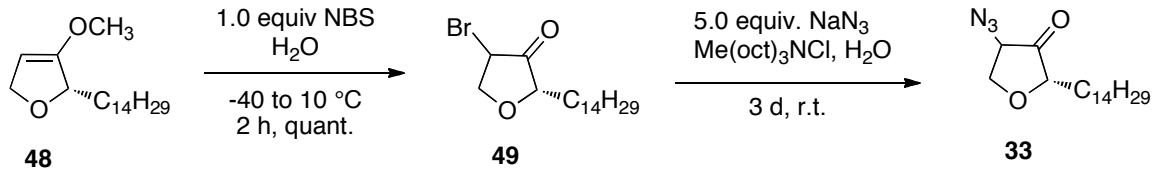
The last part of this work was focused on the synthesis of racemic Jaspine B (**1**). Commercially available 1-pentadecanol (**46**) was converted under Swern reaction conditions in good yield into the corresponding 1-pentadecanal (**31**) (Scheme 20). Lithiation of methoxyallene **37** with *n*-butyllithium and subsequent addition of unpurified aldehyde **31** quantitatively provided primary allenyl adduct **47**, which was used as a crude material, due to the instability of this compound during the purification process, for the following reaction.

Using the optimized conditions of the gold(I)-catalyzed reaction tested in the previous experiments, **47** was cyclized affording after chromatographic purification the corresponding 2,5-dihydrofuran derivative **48** (71% overall yield based on **46**).



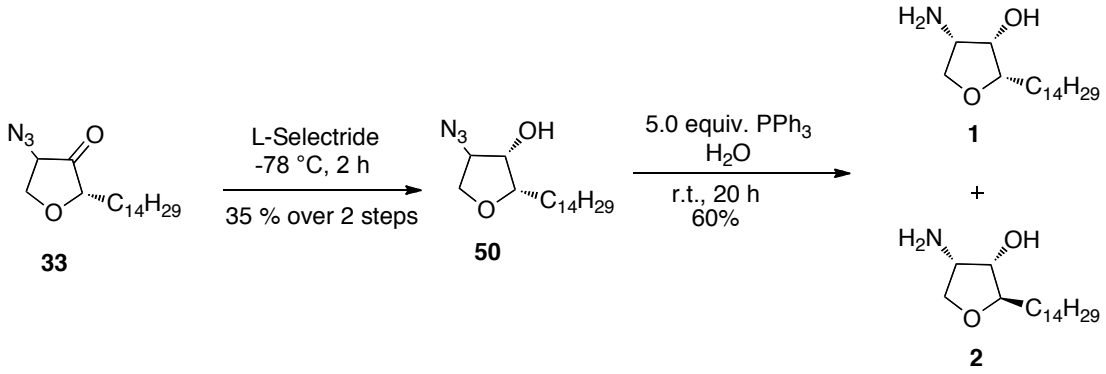
Scheme 20: Synthesis of racemic 2,5-dihydrofuranol derivative **48**.

The introduction of the amino group in 4-position was the crucial step of this synthesis. In order to find an efficient pathway, it was decided to start the transformation from the 2,5-dihydrofuran derivative **48**, where the carbon in the 4-position is activated by the enol ether moiety. Treating 3-methoxydihydrofuran **48** with NBS quantitatively produced the two diastereomers (ratio 1:1.5) of the corresponding 4-brominated furan-3-one derivate **49** (Scheme 21). Due to the high instability, this compound was directly used for the following reaction without the determination of the relative configuration of the two formed isomers. The azidation reaction proved to be the most delicate step of the sequence.[21] Bromine derivative **49** was treated with 5.0 equivalents of NaN_3 to afford the two corresponding diastereomers of azide derivatives **33** (ratio: 1:1.5), which again were used as crude compounds for the next step without any purification.



Scheme 21: Bromination and azidation reactions to obtain the 4-azido furan-3-one **33**.

A stereoselective reduction of the keto group of **33** with L-Selectride provided the corresponding alcohol **50** (two diastereomers) (Scheme 22). This intermediate was reduced under Staudinger conditions employing triphenylphosphine/water[25] furnishing a mixture of Jaspine B (**1**) and 2-epi-Jaspine B (**2**) [1:1.6 ratio deduced by ^{1}H NMR spectra (Figure 9)] in good yield. After a first chromatographic purification, it was not possible to separate the mixture of the two synthesized epimers by routine HPLC or reversed phase HPLC. The very high polarity of the products apparently require more specific separation techniques.



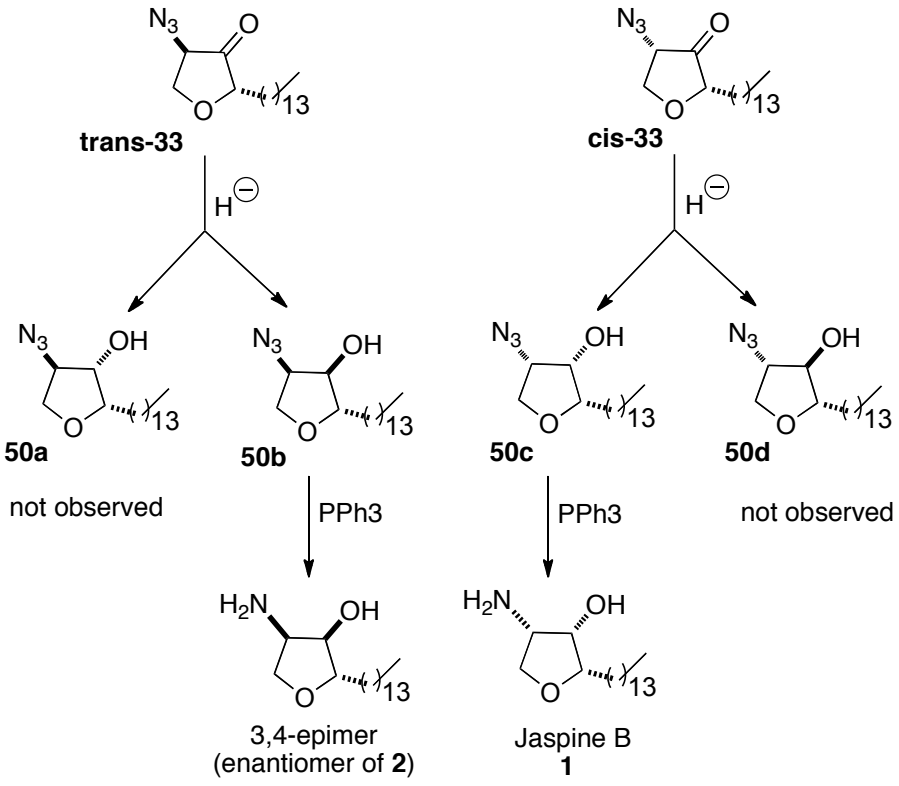
Scheme 22: Reductions to provide the target molecule Jaspine B (**1**).

A possible explanation of the results obtained in this pathway, leading to Jaspine B (**1**) and one of its epimer **2**, is shown in Scheme 23.

After bromination and azidation of **48**, two diasteromers (**cis-33**, **trans-33**) were formed. Regarding the reduction of the keto group of the furan moiety, it should be notice that the addition of hydride might form four different diasteromers (**50a**, **50b**, **50c**, **50d**) (Scheme 23).

For the **cis-33**, only all-cis configured moiety **50c** was obtained. This was the expected result since the highly bulky L-selectride must approach ketone from less hindered direction. No traces of the unfavorable product **50d** were observed. More investigations are needed to explain the results obtained after reduction of **trans-33** that leads exclusively to **50b**. For this case it seems that the steric hindrance of the azide group is more bulking than the alkyl substituent during the addition of the hydride.

A following reduction of the azide group (under Staudinger conditions) of the two diasteromers formed can easily provide the Jaspine B (**1**) and the corresponding 3,4-epimer (enantiomer of **2**).



Scheme 23: Possible isomers formed after reductions of cis-33 and trans-33.

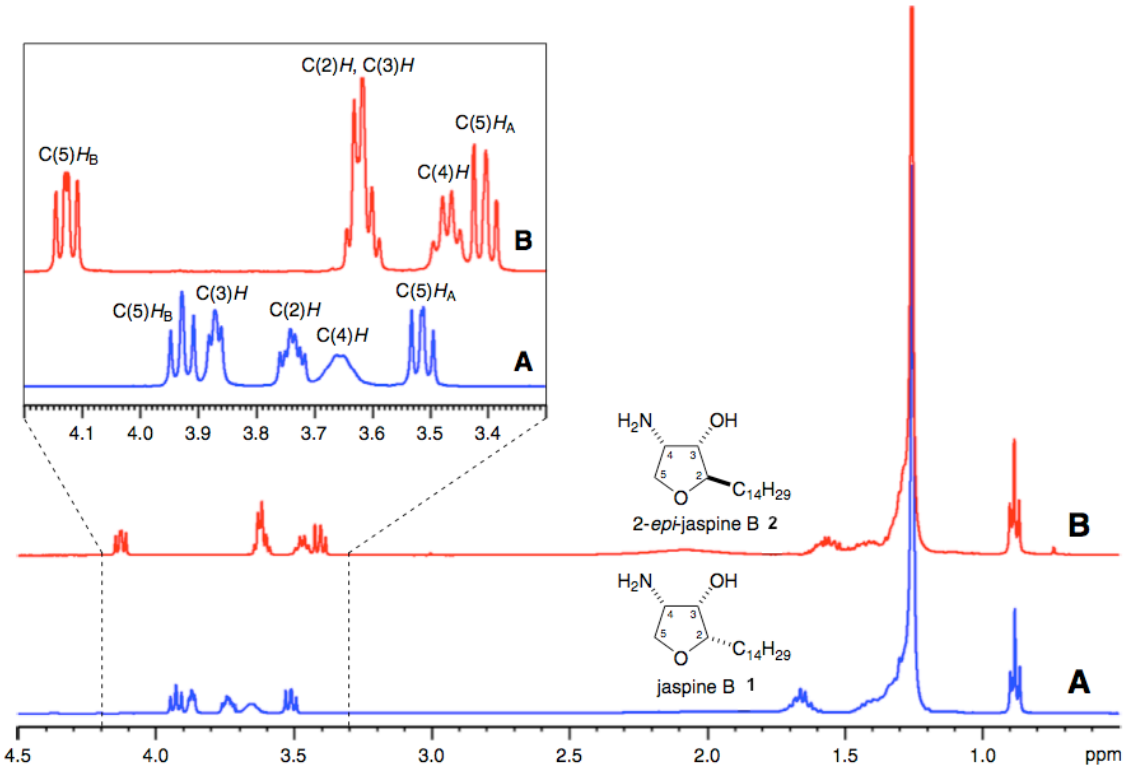


Figure 8. 400 MHz ^{1}H NMR literature spectra for (A) jaspine B (**1**) and (B) 2-epi-jaspine B (**2**) in $CDCl_3$.[26]

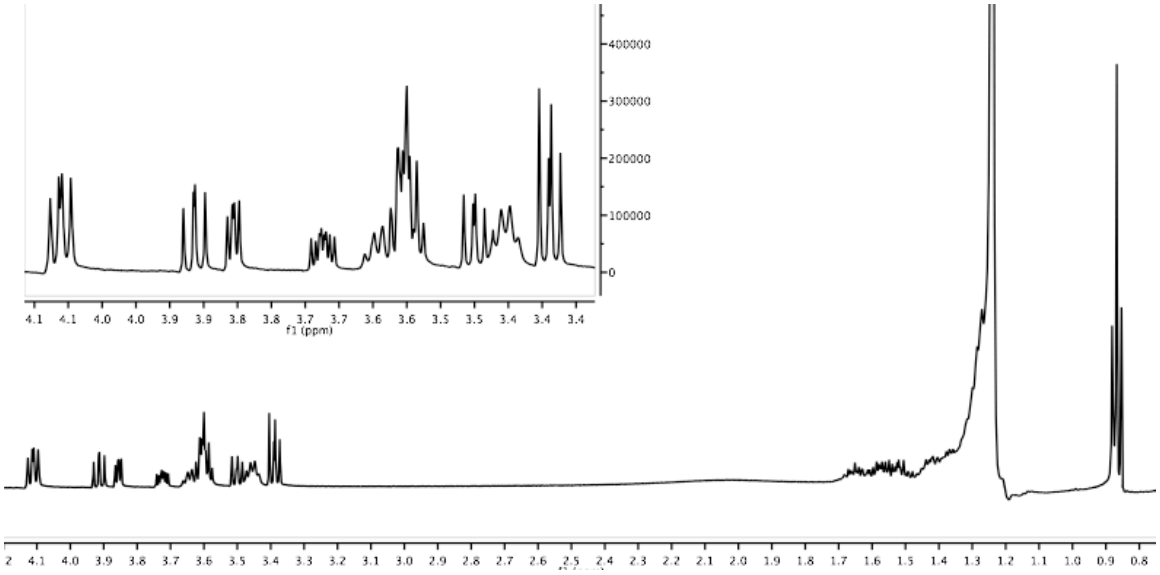


Figure 9. 500 MHz ^{1}H NMR spectra of the synthetized mixture of jaspine B (**1**) and 2-epi-jaspine B (**2**).

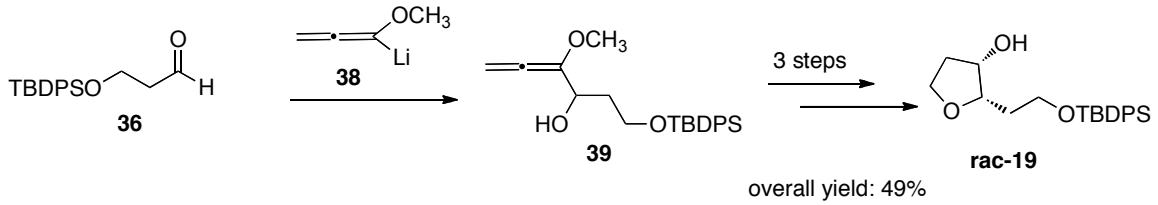
The purity of the synthetized mixture of the Jaspine B (**1**) and 2-epi-Jaspine B

(**2**), allowed to compare the ^{1}H NMR spectrum obtained (Figure 9) with a literature known ^{1}H NMR spectra of the isolated epimers (**1** and **2**) (Figure 8) and to affirm that the synthetic pathway successfully provide Jaspine B (**1**) and one epimer (2-epi-Jaspine B) (**2**) in 1:1.6 ratio with 15% overall yield (based on **46**).

3 SUMMARY AND PERSPECTIVES

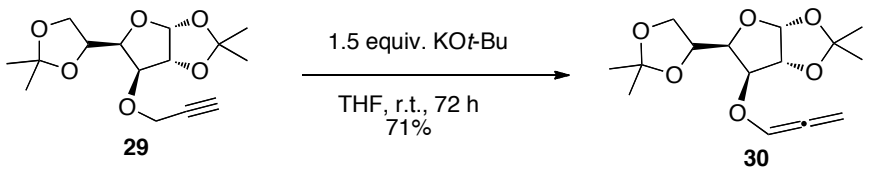
3.1 Summary

The versatility of alkoxyallenes as building block for the synthesis of heterocyclic compounds has been demonstrated. The addition of aldehyde **36** to the lithiated alkoxyallene **38** followed by the gold(I)-catalyzed cyclization of the primary allenyl compound forming **39** has been optimized providing the corresponding 2,5-dihydrofuran in excellent yield (Scheme 24). The stereoselective reduction employing L-Selectride easily provided the corresponding *cis*-configured tetrahydrofuranol **rac-19** with 49% overall yield (based on **36**), which confirmed the efficacy of this pathway for the synthesis of isodideoxynucleotides derivatives.



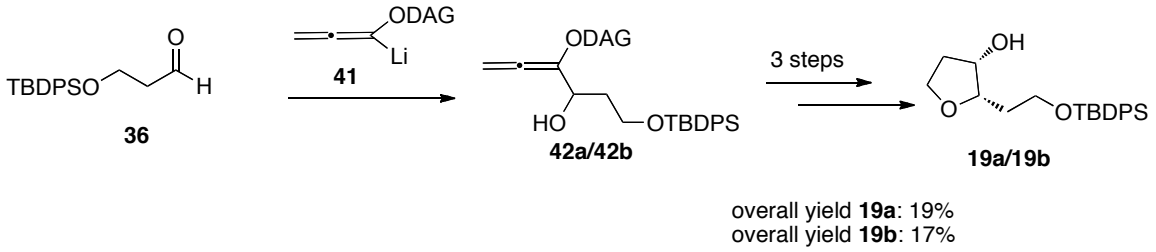
Scheme 24: Scheme for the synthesis of **rac-19**.

The use of an alkoxyallene with a chiral auxiliary has demonstrated to be an feasible pathway for the construction of enantiopure compounds. The carbohydrate moiety diacetone-D-glucose proved to be an excellent chiral source. Treating propargyl ether **29** with KO*t*-Bu at room temperature for 72h smoothly provide the corresponding alkoxyallene **30** in 71% yield (Scheme 25).



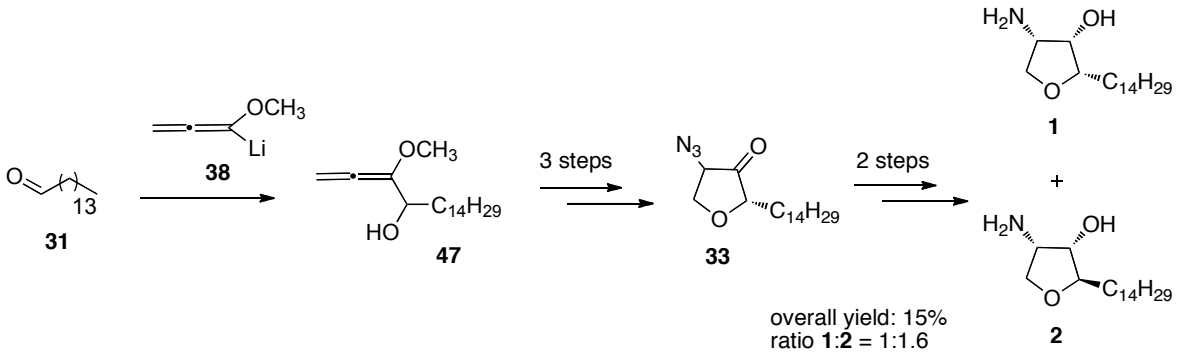
Scheme 25: Base catalyzed isomerization of alkyne **29** to allene **30**

The use of alkoxyallene **30** in the previously described synthesis of tetrahydrofuranol derivatives, allowed us to obtain the two pure diastereoisomers *cis*-configured of the target molecules **19a** and **19b**, respectively with 19% and 17% overall yield (Scheme 26).



Scheme 26: Scheme for the synthesis of **19a** and **19b**

Applying the previously optimized conditions we have described a novel synthesis of racemic Jaspine B (**1**) and 2-*epi*-Jaspine B (**2**) starting from 1-pentadecanal **31** and lithiated methoxyallene **38** (Scheme 27).

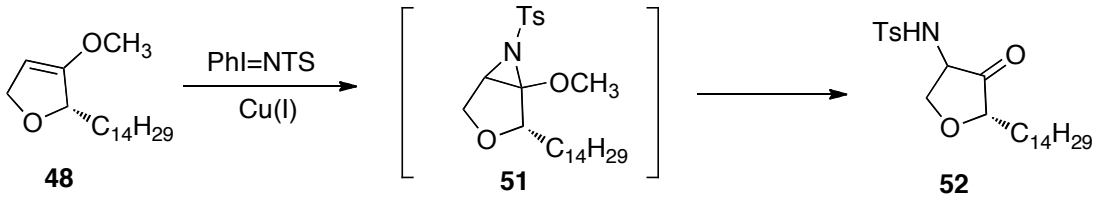


Scheme 27: Scheme for the synthesis of racemic Jaspine B (**1**) and 2-epi-Jaspine B (**2**).

3.2 Perspectives

The enantiopure synthesis of Jaspine B (**1**) should be explored employing the chiral alkoxyallene as it was described here for the synthesis of enantiopure

tetrahydrofuranols **19a** and **19b**. In addition, a more efficient method for the introduction of the amino group at the furan moiety needs be investigated. Aziridation of 2,5-dihydrofuran **48** in the presence of (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane,[21] could provide the corresponding aziridine intermediate **51**, that due the high instability of the moiety, should form the corresponding α-amino-ketone by ring opening (Scheme 28).



Scheme 28: Possible pathway for the introduction of the amino group at the furan moiety.

The same synthetic pathway discussed in this work can be employed in the synthesis of pyrroles. Treating lithiated alkoxyallenes with imines instead of aldehydes can easily provide the corresponding pyrrole derivatives (Scheme 5).
The potential and the versatility of the investigated pathway could open an interesting challenge for the synthesis of new heterocyclic compounds.

4 EXPERIMENTAL PART

4.1 General experimental methods

Reactions involving moisture or oxygen sensitive reagents were performed under an atmosphere of dry argon in flame dried glass flasks. Solvents and reagents were handled and added by standard Schlenk-techniques. The reaction temperatures stated were those of the external bath.

The solvents THF, Et_2O, CH_2Cl_2, CH_3CN and toluene were purified using the solvent purification system SPS 800 of M. Braun. Anhydrous DMF was purchased from Aldrich and stored under an argon atmosphere in sure seal® bottles. Pyridine was distilled from calcium hydride and stored over molecular sieves 4 Å. Triethylamine was heated with calcium hydride, distilled and stored over KOH pellets. Hexane and ethyl acetate were distilled from calcium hydride. All other reagents were used as purchased without further purification unless otherwise stated.

All proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR spectra) were recorded using a Bruker AC 250 (250 MHz), Bruker AC 500 (500 MHz), Bruker ECP 400 (400 MHz) or Joel Eclipse 500 (500 MHz) instruments at ambient temperature. Chemical shifts (δ) for all compounds are listed in parts per million (ppm) and refer to solvent residual peaks (^{1}H NMR: $CDCl_3$, 7.21 ppm; ^{13}C NMR: $CDCl_3$, 77.0 ppm) as internal standard. Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C NMR spectra were recorded proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMQC).

Mass spectra and HRMS analyses were recorded with an Agilent 6210 (ESI-ToF, 4 kV), a Varian Ionspec QFT-7 (ESI-FT ICRMS) or a Finnigan MAT 711 (EI, 80 eV, 8 kV) instrument.

IR spectra were recorded as KBr pellets for solid samples or as film between KBr

plates for liquid samples with a Nicolet 5 SXC FT-IR interferometer equipped with a DTGS-detector.

Elemental analyses were recorded with a CHN analyzer 2400 by Perkin-Elmer. On analytical scale chiral compounds were analyzed using a DAICEL Chiralpak IC column. Optical rotations were measured with a Perkin Elmer 241 polarimeter in 2 mL micro cuvettes with the Na_D line.

Thin layer chromatography (TLC) was performed with aluminium coated TLC plates purchased from Merck (Merck silica gel 60). Preparative column chromatography was performed with silica gel 60 (230-400 mesh, 40-63 µM, Merck- Schuchardt).

Names for all compounds were generated using the nomenclature program connected to CS ChemBioDraw Ultra. Only for the diacetone-D-glucose moiety, the carbon numeration was chosen for ease arbitrarily, therefore sometimes is not corresponding with the numeration generated by the nomenclature program.

4.2 General procedures

General procedure 1 for Swern oxidation (GP1): $(COCl)_2$ (1.1 equiv.) and DMSO (2.0 equiv.) were added to CH_2Cl_2 (5 mL/mmol alcohol) at -60 °C. The resulting solution was stirred for 5 min in a flame dried flask. A solution of the alcohol (1.0 equiv.) dissolved in CH_2Cl_2 (5 mL/mmol alcohol) was added and subsequently stirred for 20 min followed by addition of NEt_3 (5.0 equiv.). The resulting mixture was stirred for 3 h at the indicated temperature and 1 h at r.t., quenched with water (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The obtained residue was not purified due to the sensitivity of the produced aldehyde, and directly used for the subsequent reaction.

General procedure 2 for the addition of aldehydes to lithiated alkoxyallenes (GP2): In a flame dried glass at -50 °C the corresponding alkoxyallene (3.0 equiv.) was dissolved in Et_2O or THF (2 mL/mmol aldehyde) and *n*-BuLi (2.9 equiv.) was added drop-wise. The resulting solution was stirred for 20 min, followed by cooling to -70 °C and addition of the corresponding aldehyde (1.0 equiv). The mixture was stirred for 3 h, quenched with water (2 mL/mmol aldehyde) and warmed up to r.t. The layers were separated and the aqueous phase was extracted with Et_2O or THF (3x). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure.

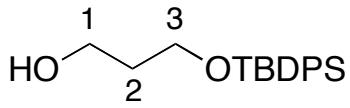
General procedure 3 for gold(I) catalyzed cyclization (GP3): To a solution of the corresponding allenyl alcohol in CH_2Cl_2 (15 mL/mmol) and pyridine (0.15 equiv.) was added AuCl (0.05-0.20 equiv.). The mixture was stirred for 1-3 h at r.t. and quenched by addition of H_2O (15 mL/mmol) and sat. aq. $NaHCO_3$ solution (15 mL/mmol) was added. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure.

General procedure 4 for hydrolysis of dihydrofurans (GP4): At 40 °C a mixture of 2 N H_2SO_4 and THF (1:1) was added to the dihydrofuran. The reaction mixture was stirred at the indicated temperature and the conversion was monitored by TLC. The mixture was quenched with water (7 mL/mmol) and sat. aq. $NaHCO_3$ solution (7 mL/mmol) was added. The aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (Alox).

General procedure 5 for the reduction of furan-3-ones (GP5): To a solution of the furan-3-one in THF (25 mL/mmol of ketone) at -78 °C was added dropwise L-selectride (1.0 M in THF, 2.5 equiv.). The mixture was stirred for 1.5 h at -78 °C followed by the addition of sat. aq. NH_4Cl solution (80 mL/mmol). The resulting solution was stirred at r.t. for 30 min, the water phase was extracted with EtOAc and the combined organic phases were dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel.

4.3 Synthesis of starting materials

3-(*tert*-Butyldiphenylsiloxy)propan-1-ol (35)

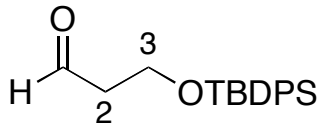


1,3-Propandiol (3.58 mL, 50.0 mmol) was dissolved in DMF (100 mL) at r.t. under inert atmosphere, followed by addition of imidazole (3.54 g, 52.0 mmol,). The resulting mixture was stirred for 10 min before adding TBDPSCl (12.2 mL, 52.0 mmol). The solution was stirred for 4 h and subsequently quenched with water (100 mL). The organic phase was separated and the aqueous phase was extracted with MTBE (3 x 100 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc-hexane, 1:6) affording alcohol **(35)** (9.24 g, 57%) as yellow crystals; R_f= 0.30 (EtOAc-hexane, 1:6).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75-7.63 (m, 4H, Ph), 7.49-7.32 (m, 6H, Ph), 3.84, 3.82 (t, *J* = 5.7 Hz, 2H each, 1-H, 3-H), 2.35 (s, 1H, OH), 1.81 (quint, *J* = 5.7 Hz, 2H, 2-H), 1.06 (s, 9H, *t*-Bu) ppm.

Spectroscopic and physical properties agree with previously published data.[27]

3-(*tert*-Butyldiphenylsiloxy)propanal (36)

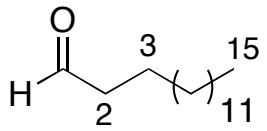


According to **GP1**: $(COCl)_2$ (0.97 mL, 11.0 mmol) and DMSO (1.42 mL, 20.0 mmol) were dissolved in CH_2Cl_2 (50 mL) at -60 °C and stirred for 5 min. Alcohol **35** (3.14 g, 10.0 mmol) and after 20 min NEt_3 (6.96 mL, 50.0 mmol) were added to the solution. The mixture was stirred for 3 h at -60 °C, 1 h at r.t. and worked up as stated above, affording aldehyde **36** (2.87 g, quant.) as yellow oil containing residual DMSO.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (t, *J* = 2.2 Hz, 1H, CHO), 7.73-7.57 (m, 4H, Ph), 7.49-7.32 (m, 6H, Ph), 4.02 (t, *J* = 6.0 Hz, 2H, 3-H), 2.65-2.52 (m, 2H, 2-H), 1.04 (s, 9H, *t*-Bu) ppm.

Spectroscopic and physical properties agree with previously published data.[27]

1-Pentadecanal (31)

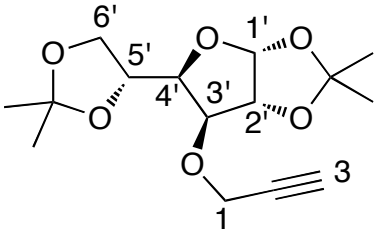


According with **GP1**: $(COCl)_2$ (0.82 mL, 9.5 mmol) and DMSO (1.23 mL, 17.3 mmol) were dissolved in CH_2Cl_2 (45 mL) at -60 °C and stirred for 5 min. 1-pentadecanol (2.50 g, 8.72 mmol) and after 20 min NEt_3 (6.0 mL, 43.3 mmol) were added to the solution. The mixture was stirred for 3 h at -60°C and 1h at r.t. and worked up as stated above, affording aldehyde **31** (2.83 g, 80%) as yellow oil containing residual DMSO.

^{1}H NMR (400 MHz $CDCl_3$): δ = 9.75 (t, *J* = 1.9 Hz, 1H, CHO), 2.72 (s, 1H, OH), 2.40 (td, *J* = 7.1, 1.9 Hz, 2H, 2-H), 1.66-1.50 (m, 2H, 3-H), 1.24 (m_c, 22H, CH_2-chain), 0.87 (t, *J* = 7.1 Hz, 3H, 15-H) ppm.

Spectroscopic and physical properties agree with previously published data.[28]

(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-(prop-2-yn-1-yloxy)tetrahydrofuro[2,3-d][1,3]dioxol (29)



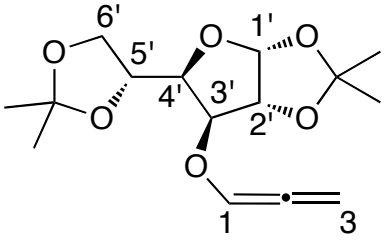
To a solution of diacetone-D-glucose (15.6 g, 60.0 mmol) in THF (60 mL) were subsequently added *n*-Bu_4NI (2.22 g, 6.00 mmol), NaOH (w/w 60% in water, 60 mL) and propargyl bromide (80% in toluene) (17.4 mL, 156 mmol). The mixture was stirred for 5 h at 0 °C and overnight at r.t. The solution was washed with water (3 x 60 mL) and the combined aqueous phase extracted with Et_2O (3 x 60 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by

chromatography on silica gel (EtOAc-hexane, 1:6) affording ether **29** 15.8 g (93%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (d, *J* = 3.7 Hz, 1H, 1'-H), 4.62 (d, *J* = 3.7 Hz, 1H, 2'-H), 4.30-4.20 (m, 2H, 5'-H), 4.28 (d, *J* = 2.3 Hz, 2H, 1-H), 4.13 (dd, *J* = 7.6, 3.0 Hz, 1H, 4'-H), 4.11-4.05 (m, 1H, 6'-H), 4.09 (d, *J* = 3.0 Hz, 1H, 3'-H), AB part of an ABX system (δ_b = 3.98, J_{AB} = 8.6 Hz, J_{BX} = 5.4 Hz, 1H, 6'-H), 2.46 (t, *J* = 2.3 Hz, 1H, 3-H), 1.49, 1.41, 1.34, 1.30 (4 s, 3H each, CH_3) ppm.

Spectroscopic and physical properties agree with previously published data.[18-b]

(3a*R*,5*R*,6*S*,6a*R*)-5-(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-(propa-1,2-dienyloxy)tetrahydrofuro[2,3-*d*][1,3]dioxole (30)



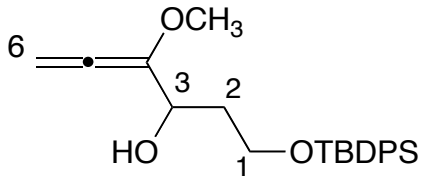
To a solution of propargyl ether **29** (7.00 g, 23.5 mmol) in THF (120 mL) was added KO*t*-Bu (3.96 g, 35.3 mmol, 1.5 equiv.) and stirred for 72 h at r.t. The mixture was quenched with water (50 mL) and sat. $NaHCO_3$ (50 mL) and the aqueous phase was washed with EtOAc (3 x 80 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (EtOAc-hexane, 1:3, +1% NEt_3) affording alkoxyallene **30** 4.94 g (71%) as yellow oil. R_f = 0.50 (EtOAc-hexane, 1:6).

^{1}H NMR (400 MHz, $CDCl_3$): δ = ABX system (δ_X = 6.69, δ_A = 5.58, δ_B = 5.54, J_{AB} = 8.6 Hz, J_{AX} = J_{BX} = 6.0 Hz, 3H, 1-H, 3-H), 5.86 (d, J = 3.8 Hz, 1H, 1'-H), 4.58 (d, J = 3.8 Hz, 1H, 2'-H), 4.33 (ddd, J = 7.6, 6.1, 5.3 Hz, 2H, 5'-H), 4.24 (d, J = 3.0 Hz, 1H, 3'-H), 4.17 (dd, J = 7.6, 3.0 Hz, 1H, 4'-H), AB part of an ABX system (δ_A = 4.08, δ_B = 4.03, J_{AB} = 8.7 Hz, J_{AX} = 6.1 Hz, J_{BX} = 5.3 Hz, 2H, 6'-H), 1.50, 1.42, 1.34, 1.30 (4 s, 3H each, CH_3).

Spectroscopic and physical properties agree with previously published data.[18b]

4.4 Synthesis of racemic tetrahydrofuranol

1-(*tert*-Butyldiphenylsiloxy)-4-methoxyhexa-4,5-dien-3-ol (39)



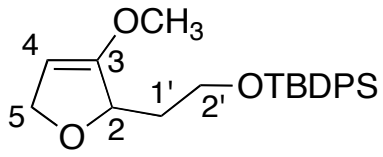
According to **GP2**: Methoxyallene (1.32 g, 18.8 mmol) and *n*-BuLi (2.5 M in THF, 6.77 mL, 16.1 mmol) were added to Et_2O (10 mL) at -50 °C and stirred for 20 min. Aldehyde **36** (2.50 g, 8.70 mmol) was added, the mixture was stirred for 3 h at -70 °C and worked up as stated above, affording crude allenyl alcohol **39** (1.95 g, 94%) as yellow oil which was directly used for the subsequent reaction.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73-7.58 (m, 4H, Ph), 7.47-7.32 (m, 6H, Ph), 5.57-5.52 (m, 2H, 6-H), 4.51 (m_c, 1H, 3-H), 3.94-3.74 (m, 2H, 1-H), 3.45 (s, 3H, OCH_3), 3.11 (d, J = 4.8 Hz, 1H, OH), 1.97-1.86 (m, 2H, 2-H), 1.04 (s, 9H, *t*-Bu) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.1 (s, C-5), 135.6 (d, Ph), 133.2* (s, C-4, Ph), 129.8 (d, Ph), 127.8 (d, Ph), 92.2 (t, C-6), 69.8 (d, C-3), 61.9 (t, C-1), 56.2 (q, OCH_3), 36.3 (t, C-2), 27.0, 19.2 (q, s, *t*-Bu) ppm; the signal marked with * has double intensity.

No further analyses were carried out due the instability of this compound.

***tert*-Butyl[2-(3-methoxy-2,5-dihydrofuran-2-yl)ethoxy]diphenylsilane (40)**



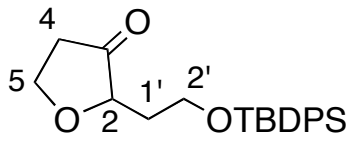
According to **GP3**: Allenyl alcohol **39** (1.00 g, 2.62 mmol) was dissolved in CH_2Cl_2 (40 mL) and pyridine (33.2 μL, 0.43 mmol) was added. AuCl (32.0 mg, 0.14 mmol, 0.05 equiv.) was added to the mixture, the solution was stirred for 3 h at r.t. and worked up as described above. The crude product was purified by column chromatography on (Alox, EtOAc-hexane, 1:20) affording 686 mg of dihydrofuran **40** (77%) as yellow oil. R_f = 0.45 (EtOAc-hexane, 1:20).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77-7.61 (m, 4H,Ph), 7.48-7.32 (m, 6H,Ph), 4.73 (td, *J*= 7.3, 3.5 Hz, 1H, 4-H), 4.63-4.49 (m, 3H, 2-H, 5-H), 3.88-3.76 (m, 2H, 2'-H), 3.62 (s, 3H, OCH_3), 2.02 (dtd, *J*= 14.7, 7.3, 3.5 Hz, 1H, 1'-H), 1.75 (td, *J*= 14.7, 7.3 Hz, 1H, 1'-H), 1.04 (s, 9H, *t*-Bu) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.6 (s, C-3), 135.7 (d, Ph), 133.3 (s, Ph), 129.8 (d, Ph), 127.8 (d, Ph), 89.4 (d, C-4), 78.9 (d, C-2), 73.6 (t, C-5), 60.3 (t, C-2'), 57.4 (q, OCH_3), 37.9 (t, C-1'), 27.6, 19.2 (q, s, *t*-Bu) ppm.

No further analyses were carried out due the instability of this compound.

2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]-2,5-dihydrofuran-3(2*H*)-one (18)

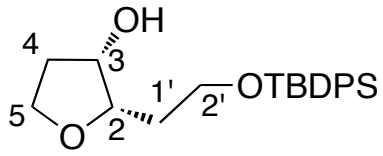


According to **GP4**: To a solution of dihydrofuran **40** (250 mg, 0.65 mmol) was added a mixture of 2 N H_2SO_4 and THF (1:1) (1.3 mL) and THF (5 mL). The mixture was stirred for 4 h at 40 °C and worked up as stated above. The crude product was purified by column chromatography (Alox, EtOAc-hexane, 1:15) affording furanone **18** (186 mg, 78%) as yellow oil. R_f = 0.30 (EtOAc-hexane, 1:15) on Alox TLC.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71-7.58 (m, 4H, Ph), 7.45-7.30 (m, 6H, Ph), 4.28 (d, *J* = 4.6 Hz, 1H, 2-H), 4.07 (td, *J* = 9.0, 7.4 Hz, 1H, 5-H), 3.94-3.73 (m, 3H, 5-H, 2'-H), 2.62-2.41 (m, 2H, 4-H), 2.05-1.93 (m, 1H, 1'-H), 1.88-1.77 (m, 1H, 1'-H), 1.04 (s, 9H, *t*-Bu) ppm.

Spectroscopic and physical properties agree with previously published data.[8a]

***cis*-2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]tetrahydrofuran-3-ol rac-(19)**



According to **GP5:** To furanone **18** (170 mg, 0.46 mmol) in THF (12 mL) at -78 °C was added L-Selectride (1.0 M in THF, 1.16 mL, 1.16 mmol). The mixture was stirred for 1.5 h at this temperature followed by addition of sat. aq. NH_4Cl solution (35 mL). The mixture was stirred at r.t. for 30 min and worked up as stated above. The crude product was chromatographed on silica gel (EtOAc-hexane,

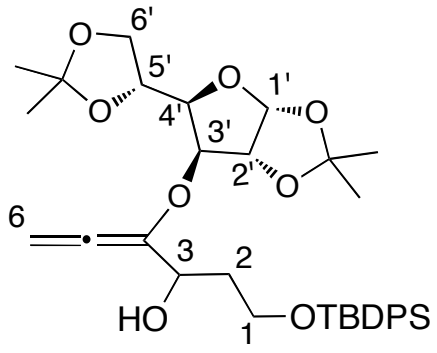
1:4) affording alcohol **rac-(19**) (146 mg, 86%) as a colorless oil. R_f = 0.20 (EtOAc-hexane, 1:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.60 (m, 4H, Ph), 7.47-7.35 (m, 6H, Ph), 4.45-4.38 (m, 1H, 3-H), 4.04 (q, *J* = 7.9 Hz,1H, 5-H), 3.82-3.65 (m, 4H, 5-H, 2-H, 2'-H), 3.21 (s, 1H, OH), 2.25-1.85 (m, 4H, 4-H, 1'-H), 1.08 (s, 9H, *t*-Bu) ppm.

Spectroscopic and physical properties agree with previously published data.[8a]

4.5 Synthesis of enantiopure tetrahydrofuranol 19a/b

1-(*tert*-Butyldiphenylsiloxy)-4-{[(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl]oxy)}hexa-4,5-dien-3-ol (42a/b)



According to **GP2**: Allene (**30**) (4.90 g, 16.4 mmol) and *n*-BuLi (2.5 M in THF, 6.70 mL, 15.9 mmol) were added to Et_2O (15 mL) at -50 °C and stirred for 20 min. At -70 °C aldehyde (**36**) (1.72 g, 5.48 mmol) was added, the mixture was stirred for 3 h at -70 °C and worked up as stated above. The crude product was purified by column chromatography on silica gel (EtOAc-hexane, 1:10, then EtOAc-$CHCl_3$, 1:6) affording a mixture of the two diastereomers **42a/b** (2.55 g,

74%, d.r.= 1:1) as yellow oil. Separation by HPLC provided diastereomer **42a** (980 mg, 29%) and diastereomer **42b** (1.01 g, 30%) as yellowish oils.

Diastereomer 42a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75-7.60 (m, 4H, Ph), 7.52-7.31 (m, 6H, Ph), 5.84 (d, *J* = 3.7 Hz, 1H, 1'-H), AB part of an ABX system (δ_A = 5.68, δ_B = 5.61, J_{AB} = 8.3 Hz, J_{BX} = 2.2 Hz, J_{AX} = 2.0 Hz, 2H, 6-H,), 4.56 (d, *J* = 3.7 Hz, 1H, 2'-H), 4.50-4.42 (m, 1H, 3-H), 4.28 (t, *J* ≈ 3.7 Hz, 1H, 3'-H), 4.27-4.23 (m, 1H, 5'-H), 4.15 (dd, *J* = 8.1, 3.7 Hz, 1H, 4'-H), 4.09-4.04 (m, 1H, 6'-H), 3.99 (dd, *J* = 8.6, 5.4 Hz, 1H, 6'-H), 3.96-3.89 (m, 1H, 1-H), 3.76 (dt, *J* = 10.6 Hz, 5.5 Hz, 1H, 1-H), 3.37 (d, *J* = 6.1 Hz, 1H, OH), 2.02-1.94 (m, 1H, 2-H), 1.91-1.81 (m, 1H, 2-H), 1.50, 1.36, 1.30, 1.22 (4 s, 3H each, CH_3),1.04 (s, 9H, *t*-Bu) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.3 (s, C-5), 135.8 (d, Ph), 133.8 (s, C-4), 133.2 (s, Ph), 130.0 (d, Ph), 127.9 (d, Ph), 112.2, 109.3 [2 s, $C(CH_3)_2$], 105.5 (d, C-1'), 93.3 (t, C-6), 82.5, 81.0, 80.9 (3 d, C-2', C-3', C-4'), 73.6 (d, C-5'), 69.7 (d, C-3), 67.5 (t, C-6'), 62.0 (t, C-1), 36.3 (t, C-2), 26.7, 26.4, 26.3, 25.3 (4 q, CH_3), 26.9, 19.3 (q, s, *t*-Bu) ppm.

No further analyses were carried out due the instability of this compound.

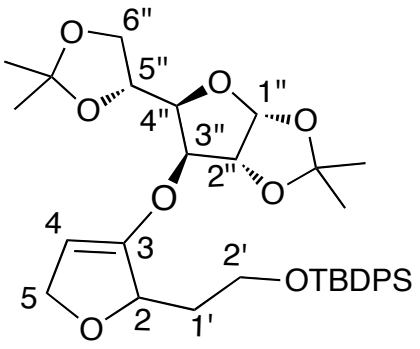
Diastereomer 42b

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71-7.60 (m, 4H, Ph), 7.47-7.33 (m, 6H, Ph), 5.84 (d, *J* = 3.8 Hz, 1H, 1'-H), AB part of an ABX system (δ_A = 5.63, δ_B = 5.60, J_{AB}= 8.4 Hz, J_{BX}= 2.0 Hz, J_{AX} = 1.9 Hz, 2H, 6-H), 4.55 (d, *J* = 3.8 Hz, 1H, 2'-H), 4.52-4.45 (m, 1H, 3-H), 4.36-4.30 (m, 1H, 5'-H), 4.27 (d, *J* ≈ 3.5 Hz, 1H, 3'-H), 4.19 (dd, *J* = 7.8, 3.8 Hz, 1H, 4'-H), 4.10-4.07 (m, 1H, 6'-H), 4.01 (dd, *J* = 8.6, 5.3 Hz, 1H, 6'-H), 3.91-3.75 (m, 2H, 1-H), 3.12 (d, *J* = 4.5 Hz, 1H, OH), 1.95-1.80 (m, 2H, 2-H), 1.50, 1.40, 1.30, 1.20 (4 s, 3H each, CH_3), 1.04 (s, 9H, *t*-Bu) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.9 (s, C-5), 135.6 (d, Ph), 133.8 (s, C-4), 133.4 (s, Ph), 130.0 (d, Ph), 128.0 (d, Ph), 112.2, 111.9 [2 s, $C(CH_3)_2$], 105.5 (d, C-1'), 93.8 (t, C-6), 82.6, 81.4, 81.0 (3 d, C-2', C-3', C-4'), 73.7 (d, C-5'), 69.3 (d, C-3), 67.5 (t, C-6'), 61.8 (t, C-1), 36.3 (t, C-2), 26.9, 26.5, 26.4, 25.4 (4 q, CH_3), 27.0, 19.3 (q, s, *t*-Bu) ppm.

No further analyses were carried out due the instability of this compound.

tert-Butyl{2-[3-((3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)-2,5-dihydrofuran-2-yl]ethoxy}diphenylsilane (43a/b)



Diastereomer 43a

According to **GP3**: Allenyl alcohol **42a** (875 mg, 1.43 mmol) was dissolved in CH_2Cl_2 (30 mL) and pyridine (18.0 μL, 0.21 mmol). AuCl (67 mg, 0.28 mmol, 0.20 equiv.) was added to the mixture. The solution was stirred for 1 h at r.t. and worked up as stated above. The crude product was purified by column chromatography (silica gel, EtOAc-hexane, 1:6) affording 640 mg of **43a** (73%) as yellow oil.

$[\alpha]_D$ = -8.8 (*c* = 1.15, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72-7.63 (m, 4H,Ph), 7.46-7.31 (m, 6H, Ph), 5.84 (d, *J* = 3.8 Hz, 1H, 1''-H), 4.78 (m_c, 1H, 2-H), 4.76-4.69 (m, 1H, 4-H), 4.64 (d, *J* = 3.8 Hz, 1H, 2''-H), 4.63-4.53 (m, 2H, 5-H), 4.39 (d, *J* ≈ 3.1 Hz, 1H, 3''-H), 4.30-4.23 (m, 1H, 5''-H), 4.20 (dd, *J* = 7.9, 3.1 Hz, 1H, 4''-H), AB part of an ABX system (δ_A = 4.10, δ_B = 3.98, J_{AB} =8.7 Hz, J_{BX} = 6.0 Hz, J_{AX} = 5.6 Hz, 2H, 6''-H), 3.84 (t, *J* = 7.0 Hz, 2H, 2'-H), 2.08-1.81 (m, 2H, 1'-H), 1.53, 1.41,1.33, 1.28 (4 s, 3H each, CH_3),1.04 (s, 9H, *t*-Bu) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.4 (s, C-3), 136.0 (d, Ph), 134.0 (s, Ph), 128.5 (d, Ph), 127.0 (d, Ph), 112.3, 109.3 [2 s, $C(CH_3)_2$], 105.1 (d, C-1''), 100.0 (d, C-4), 82.2, 81.9, 80.1 (3 d, C-2'', C-3'', C-4''), 78.4 (d, C-2), 72.6 (t, C-5), 72.2 (d, C-5''), 67.5 (t, C-6''), 60.5 (t, C-1'), 37.2 (t, C-2'), 26.9, 26.8, 26.4, 25.3 (4 q, CH_3), 27.0, 19.4 (q, s, *t*-Bu) ppm.

IR (KBr): ν (cm^{-1}) = 3070-3050 (=C-H), 2990-2860 (C-H), 1690-1650 (C=C), 1100-1020 (C-O).

MS (ESI-TOF): calcd. for $C_{34}H_{46}O_8Si$: 633.2854 $[M + Na]^+$; found: 633.2846.
EA: calcd. (%) for $C_{34}H_{46}O_8Si$ (610.3): C 66.86, H 7.59; found: C 66.92, H 7.64.

Diastereomer 43b

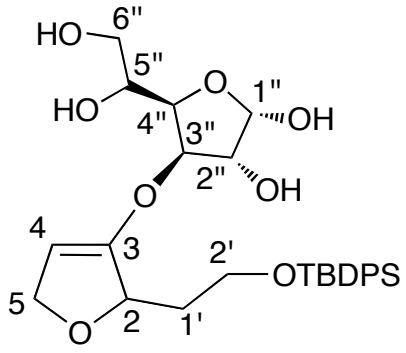
According to **GP3**: Allenyl alcohol **42b** (932 mg, 1.52 mmol) was dissolved in CH_2Cl_2 (30 mL) and pyridine (19.2 μL, 0.23 mmol). AuCl (71 mg, 0.30 mmol, 0.20 equiv.) was added to the mixture. The solution was stirred for 1 h at r.t. and worked up as stated above. The crude product was purified by column chromatography (silica gel, EtOAc-hexane, 1:6) affording 714 mg of **43b**] (77%) as yellow oil.

$[\alpha]_D^{20}$= -20.7 (*c* = 1.29, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72-7.57 (m, 4H, Ph), 7.45-7.32 (m, 6H, Ph), 5.72 (d, *J* = 3.8 Hz, 1H, 1''-H), 4.80-4.72 (m, 2H, 2-H, 4-H), 4.64-4.56 (m, 2H, 5-H), 4.50 (d, *J* = 3.8 Hz, 1H, 2''-H), 4.39 (d, *J* ≈ 3.1 Hz, 1H, 3''-H), 4.33-4.25 (m, 1H, 5''-H), 4.21 (dd, *J* = 7.6, 3.1 Hz, 1H, 4''-H), AB part of an ABX system ($\delta_A = \delta_B$ = 4.05, J_{AB} = 7.7 Hz, J_{BX} = 5.9 Hz, J_{AX} = 3.6 Hz, 2H, 6''-H), 3.86-3.71 (m, 2H, 2'-H), 2.00-1.90 (m, 1H, 1'-H), 1.77-1.67 (m, 1H, 1'-H), 1.51, 1.44,1.33, 1.30 (4 s, 3H each, CH_3), 1.04 (s, 9H, *t*-Bu) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.0 (s, C-3), 135.5 (d, Ph), 133.9 (s, Ph), 129.6 (d, Ph), 127.6 (d, Ph), 112.1, 109.1 [2 s, $C(CH_3)_2$], 105.1 (d, C-1''), 92.0 (d, C-4), 82.0, 81.7, 80.1 (3 d, C-2'', C-3'', C-4''), 78.2 (d, C-2), 72.7 (t, C-5), 72.1 (d, C-5''), 67.0 (t, C-6''), 60.4 (t, C-2'), 37.1 (t, C-1'), 26.8, 26.7, 26.4, 25.8 (4 q, CH_3), 27.0, 19.3 (q, s, *t*-Bu) ppm.

(2*S*,3*R*,4*R*,5*R*)-4-{[2-(2-(*tert*-Butyldiphenylsiloxy)ethyl)-2,5-dihydrofuran-3-yl]oxy}-5-(*R*)-1,2-dihydroxyethyltetrahydrofuran-2,3-diol (44a/b])

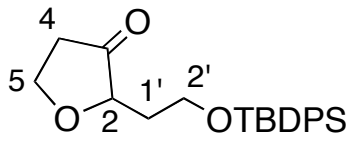


Dihydrofuran 44a/b

To a solution of alkoxydihydrofuran diastereomers **43a/b** (100 mg, 0.16 mmol) in CH_3CN (4 mL) and H_2O (11.5 μL) was added $InCl_3$ (70 mg, 0.36 mmol). The resulting mixture was stirred at rt. for 20 h. After the addition of H_2O (5 mL) and CH_2Cl_2 (4 mL) the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2x 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure providing 85 mg of **44a/b** as colorless oil directly used for the subsequent reaction without purification (purity determined by ^{1}H NMR spectroscopy ≈ 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75-7.52 (m, 4H, Ph), 7.47-7.28 (m, 6H, Ph), 5.98 (dd, *J* = 5.3, 3.8 Hz, 1H, 1''-H), 4.66 (dd, *J* = 3.8, 2.1 Hz, 1H, 2''-H), 4.45-4.35 (m, 1H, 5''-H), 4.21 (t, *J* = 3.9 Hz, 1H, 4''-H), 4.03-3.55 (m, 8H, open chain tautomer), 2.23-2.08 (m, 1H, 1'-H), 1.87-1.74 (m, 1H, 1'-H), 1.06 (s, 9H, *t*-Bu) ppm.

2-[2-(*tert*-Butyldiphenylsiloxy)ethyl]dihydrofuran-3(2*H*)-one (18a/b)



Diastereomer (18a)

According to **GP 4**: To a solution of dihydrofuran **43a** (100 mg, 0.16 mmol) was added a mixture of 2 N H_2SO_4 and THF (1:1) (1.60 mL). The resulting mixture was stirred for 72 h at 40 °C and worked up as stated above. The crude product was purified by column chromatography (Alox, EtOAc-hexane, 1:15) affording **18a** (37.0 mg, 64%) as yellow oil. R_f = 0.30 (EtOAc-hexane, 1:15) on Alox TLC.

$[\alpha]_D^{20}$ = +42.4 (*c* = 1.24, $CHCl_3$)

The ^1H NMR spectrum of the sample obtained here agrees with that of the racemic compound **rac-18** (see above).

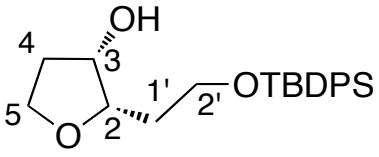
Diastereomer 18b

According to **GP 4**: To a solution of dihydrofuran **43b** (100 mg, 0.16 mmol) was added a mixture of 2 N H_2SO_4 and THF (1:1) (1.60 mL). The resulting mixture was stirred for 72 h at 40 °C and worked up as stated above. The crude product was purified by column chromatography (Alox, EtOAc-hexane, 1:15) affording **18b** (41 mg, 71%) as yellow oil. R_f = 0.30 (EtOAc-hexane, 1:15) on Alox TLC.

$[\alpha]_D^{20}$ = -47.3 (*c* = 1.40, $CHCl_3$)

The ^1H NMR spectrum of the sample obtained here agrees with that of the racemic compound **rac-18** (see above).

***cis*-[2-*tert*-Butyl(diphenylsiloxy)ethyl]tetrahydrofuran-3-ol (19a/b)**



Diastereomer 19a

According to **GP5**: To dihydrofuranone **18a** (28 mg, 0.076 mmol) in THF (2.5 mL) at -78 °C was added L-Selectride (1.0 M in THF, 0.19 mL, 0.19 mmol). The mixture was stirred for 1.5 h at this temperature, followed by addition of sat. aq. NH_4Cl solution (10 mL). The mixture was stirred at r.t. for 30 min and worked up

as stated above. The crude product was purified by column chromatography on silica gel (EtOAc-hexane, 1:4) affording furanol **19a** (14.6 mg, 52%) as colorless oil. R_f = 0.20 (EtOAc-hexane, 1:4).

$[\alpha]_D^{20}$ = -7.9 (*c* = 0.73, $CHCl_3$)

The ^{1}H NMR spectrum of the sample obtained here agrees with that of the racemic compound **rac-19** (see above).

Diastereomer 19b

According to **GP5**: To dihydrofuranone **18b** (25 mg, 0.068 mmol) in THF (2.5 mL) at -78 °C was added L-Selectride (1.0 M in THF, 0.14 mL, 0.14mmol). The mixture was stirred for 1.5 h at this temperature followed by addition of sat. aq. NH_4Cl solution (10 mL). The mixture was stirred at r.t. for 30 min and worked up as stated above. The crude product was purified by column chromatography on silica gel (EtOAc-hexane, 1:4) affording furanol **19b** (10.0 mg, 40%) as colorless oil; R_f = 0.20 (EtOAc-hexane, 1:4).

$[\alpha]_D^{20}$ = +6.4 (*c* = 0.39, $CHCl_3$)
The ^{1}H NMR spectrum of the sample obtained here agrees with that of the racemic compound **rac-19** (see above).

Reduction with SmI_2: Dihydrofuranone **18a/b** (9.0 mg, 24 μmol) was added to a solution of NEt_3 (17.0 μL, 123 μmol), H_2O (3.5 μL, 153 μmol) and THF (3 mL) and argon was bubbled through the solution for 3 h. The resulting mixture was added in one portion to a solution of SmI_2 (0.1 M in THF, 612 μL, 61.2 μmol) at 0°C and was stirred for 20 min. The mixture was quenched with sat. aq. NaH_4Cl solution (4 mL) and the aqueous phase was extracted with EtOAc (3 x 5 mL).

The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc-hexane, 1:6) affording a *cis/trans* mixture of furnanols **19** (8.0 mg, 93%) as a colorless oil. The *cis/trans* ratio of ca. 70:30 was determined by ^{1}H NMR spectroscopy comparing the signals of the hydroxyl group.

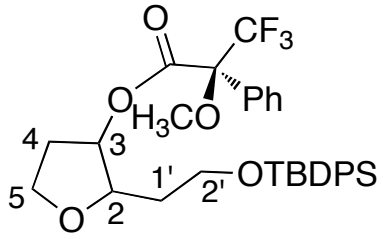
The ^{1}H NMR spectrum for the *cis*-**19** agreed with that described above.

***trans*-[2-*tert*-Butyl(diphenylsiloxy)ethyl]tetrahydrofuran-3-ol (*trans*-19)**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72-7.60 (m, 4H, Ph), 7.47-7.35 (m, 6H, Ph), 4.15-4.09 (m, 1H, 3-H), 4.04 (t, *J* = 7.1 Hz, 2H, 5-H), 3.82-3.76 (m, 2H, 2'-H), 3.72-3.68 (m, 2H, 1-H), 2.88 (s, 1H, OH), 2.25-1.85 (m, 4H, 4-H, 1'-H), 1.08 (s, 9H, *t*-Bu) ppm.

The spectroscopic and physical data agree with previously published data.[8a]

Mosher ester 45a of furanol 19a



Furanol **19a** (19.5 mg, 0.053 mmol) was dissolved in CH_2Cl_2 (1.9 mL) and 4-dimethylaminopyridine (26.0 mg, 0.212 mmol), NEt_3 (14.8 μL, 0.106 mmol) and (*S*)-Mosher´s chloride (29.9 μL, 0.159 mmol) were added. The mixture was

stirred at r.t. for 24 h. The mixture was diluted with CH_2Cl_2 (2.7 mL) and the organic layer was washed with sat. aq. $NaHCO_3$ solution (0.8 mL), 2 N HCl (0.8 mL) and H_2O (0.8 mL). The organic layer was dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure. To remove traces of remaining pyridine the product was dried in high vacuum. The crude product was purified by column chromatography on silica gel (EtOAc-hexane, 1:10) affording ester **45a** (30.0 mg, 97%) as a colorless oil.

$[\alpha]_D^{20}$ = -36.1 (*c* = 1.16, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70-7.59 (m, 4H, Ph), 7.52-7.28 (m, 11H, Ph), 5.40-5.34 (m, 1H, 3-H), 4.07-4.02 (m, 1H, 2-H), 3.97 (q, *J* ≈ 8 Hz, 1H, 5-H), 3.78 (td, *J* = 8.7, 5.1 Hz, 1H, 5-H), 3.71-3.65 (m, 1H, 2'-H), 3.60-3.54 (m, 1H, 2'-H), 3.53 (s, 3H, OCH_3), 2.44-2.33 (m, 1H, 4-H), 2.09-1.99 (m, 1H, 4-H), 1.75-1.66 (m, 1H, 1'-H), 1.66-1.58 (m, 2H, 1'-H), 1.03 (s, 9H, *t*-Bu) ppm.

IR (KBr): ν (cm^{-1}) = 3070 (=C-H), 2955-2930 (C-H), 1750 (C=O), 1560-1530 (C=C), 1255 (C-F), 1170-1010 (C-O).

MS (ESI-TOF): calcd. for $C_{32}H_{37}F_3O_5Si$: 609.2255 $[M + Na]^+$; found: 609.2222.

EA: calcd. (%) for $C_{32}H_{37}F_3O_5Si$ (586.7): C 65.51, H 6.36; found: C 65.45, H 6.34.

Mosher ester 45b of furanol 19b

Furanol **19b** (8.00 mg, 0.022 mmol) was dissolved in CH_2Cl_2 (1.1 mL) and 4-dimethylaminopyridine (15.0 mg, 0.12 mmol), NEt_3 (8.3 μL, 0.06 mmol) and (S)-Mosher´s chloride (16.7 μL, 0.09 mmol) were added. The mixture was stirred at r.t. for 24 h. The mixture was diluted with CH_2Cl_2 (1.5 mL) and the organic layer was consecutively washed with sat. aq. $NaHCO_3$ solution (0.5 mL), 2 N HCl (0.5 mL) and H_2O (0.5 mL). The organic layer was dried with Na_2SO_4, filtered and the

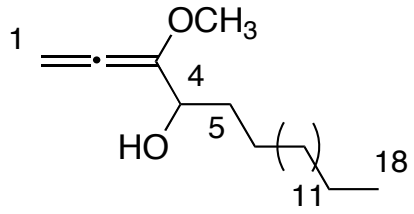
solvent was removed under reduced pressure. To remove traces of remaining pyridine the product was dried in high vacuum. The crude product was purified by column chromatography on silica gel (EtOAc-hexane, 1:10) affording ester **45b** (10.0 mg, 80%) as a colorless oil.

$[\alpha]_D^{20}$ = +4.5 (*c* = 0.66, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67-7.61 (m, 4H, Ph), 7.50-7.31 (m, 11H, Ph), 5.40-5.35 (m, 1H, 3-H), 4.06 (ddd, *J* = 8.4, 4.8, 3.7 Hz, 1H, 2-H), 3.84 (q, *J* ≈ 8 Hz, 1H, 5-H), 3.79-3.64 (m, 3H, 5-H, 2'-H,), 3.48 (s, 3H, OCH_3), 2.40-2.28 (m, 1H, 4-H), 1.99-1.89 (m, 1H, 4-H), 1.85-1.68 (m, 2H, 1'-H), 1.05 (s, 9H, *t*-Bu) ppm.

4.6 Synthesis of racemic Jaspine B

3-Methoxyoctadeca-1,2-dien-4-ol (47)



According to **GP2**: Methoxyallene (1.81 g, 20.8 mmol) and *n*-BuLi (2.35 M in THF, 8.5 mL, 20.1 mmol) were added to THF (14 mL) at -50 °C and stirred for 20 min. At -70 °C aldehyde **31** (2.00 g, 6.93 mmol) was added, the reaction mixture was stirred for 3 h at -70 °C and worked up as stated above, affording allenyl

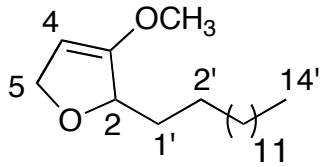
alcohol **47** (3.16 g, quant.) as colorless solid directly used for the subsequent reaction.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.56-5.49 (m, 2H, 1-H), 4.14 (dtt, *J* = 7.4, 5.8, 1.7 Hz, 1H, 4-H), 3.44 (s, 3H, OCH_3), 2.03-1.97 (m, 1H, OH), 1.61-1.50 (m, 2H, 5-H), 1.25 (s, 24H, CH_2-chain), 0.87 (t, *J* = 6.9 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.1 (s, C-2), 136.2 (s, C-3), 92.3 (t, C-1), 63.2 (d, C-4), 56.7 (q, OCH_3), 34.5-29.8 (several t, CH_2-chain), 14.4 (q, CH_3) ppm.

No further analyses were carried out due the instability of this compound.

3-Methoxy-2-tetradecyl-2,5-dihydrofuran (48)



According to **GP3**: Allenyl alcohol **47** (2.05 g, 6.93 mmol) was dissolved in CH_2Cl_2 (100 mL) and pyridine (84.0 μL, 1.04 mmol). AuCl (80.0 mg, 0.35 mmol, 0.05 equiv.) was added to the mixture. The solution was stirred for 3 h at r.t. and worked up as stated above. The crude product was purified by column chromatography (Alox, EtOAc-hexane, 1:40) affording dihydrofuran **48** (1.90 g, 93%) as a brownish solid.

^{1}H NMR (500 MHz, C_6D_6): δ = 4.81-4.74 (m, 1H, 4-H), 4.65-4.56 (m, 2H, 5-H), 4.21 (q, *J* = 1.6 Hz, 1H, 2-H), 3.19 (s, 3H, OCH_3), 1.95-1.83 (m, 1H, 1'-H), 1.76-1.49 (m, 3H, 1'-H, 2'-H), 1.29 (s, 22H, CH_2-chain), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3) ppm.

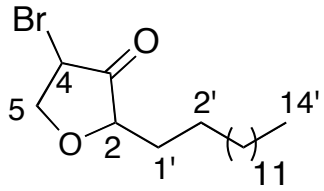
^{13}C NMR (101 MHz, C_6D_6): δ = 159.1 (s, C-3), 90.5 (d, C-4), 81.8 (d, C-2), 72.9 (t, C-5), 56.9 (q, OCH_3), 34.6 (t, C-1'), 34.2-29.5 (several t, CH_2-chain), 14.3 (q, CH_3) ppm.

IR (KBr): ν (cm^{-1}) = 2990-2860 (C-H), 1650 (C=C), 1110-1090 (C-O).

MS (ESI-TOF): calcd. for $C_{19}H_{36}O_2$: 335.5744 $[M + K]^+$; found: 335.2437
No better HRMS analysis could be obtained.

EA: calcd. (%) for $C_{19}H_{36}O_2$ (296.5): C 77.97, H 12.24; found: C 77.20, H 11.22.

4-Bromo-2-(tetradecyl)dihydrofuran-3(2*H*)-one (49)



To a solution of CH_3CN (30 mL), THF (30 mL) and H_2O (3 mL) was added drop-wise at -40 °C *N*-bromosuccinimide (1.01 g, 5.70 mmol). Under vigorous stirring, dihydrofuran **48** (1.68 g, 5.70 mmol) was added and the mixture was stirred for 2 h at this temperature and 1 h at 10 °C. The reaction was quenched by addition of H_2O (25 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude product was dissolved in hexane in which NBS is not soluble. The solution was filtered and the solvent evaporated under reduced pressure affording a mixture of two diastereoisomers of crude **49**

(2.08 g, quant.) as yellow oil which was used directly for the following reaction due the instability of this compound (d.r. **a**:**b** ≈ 1:1.5).

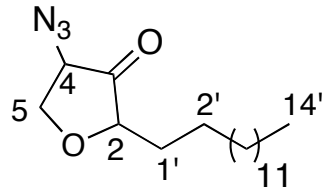
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.58 (dd, *J* = 10.3, 7.9 Hz, 1H, 5-H^{a}), 4.40-4.33 (m, 2H, 4-H^{a}, 5-H^{b}), 4.32-4.22 (m, 2H, 4-H^{b},5-H^{b}), 4.01 (dd, *J* = 10.3, 7.9 Hz, 1H, 5-H^{a}), 3.92 (dd, *J* ≈ 8, 4.2 Hz, 1H, 2-H^{a}), 3.78 (dd, *J* ≈ 8, 4.3 Hz, 1H, 2-H^{b}), 1.88-1.79 (m, 1H, 1'-H^{b}), 1.78-1.69 (m, 1H, 1'-H^{b}), 1.65-1.53 (m, 2H, 1'-H^{a}),1.51-1.43 (m, 2H, 2'-H), 1.25 (m$_c$, 22H, CH_2-chain), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 209.1 (s, C-3), 79.9, 78.8 (2 d, C-2^{b}, C-2^{a}), 72.1, 71.4 (2 t, C-5^{b}, C-5^{a}), 43.0, 42.3 (2 d, C-4^{a}, C-4^{b}), 32.0 (t, C-1'), 31.5-29.2 (several t, CH_2-chain), 14.1 (q, C-CH_3) ppm.

IR (KBr): ν (cm^{-1}) = 2925-2850 (C-H), 1755 (C=O), 1120 (C-O), 540 (C-Br)

MS (ESI-TOF): calcd. for $C_{18}H_{33}BrO_2$: 360.3574 $[M]^+$; found: 360.3183.
No better HRMS analysis could be obtained.

4-Azido-2-(tetradecyl)dihydrofuran-3(2*H*)-one (33)



Bromofuranon **49** (2.08 g, max. 5.70 mmol) was dissolved in CH_2Cl_2 (15 mL) and H_2O (7.7 mL), sodium azide (1.88 g, 28.9 mmol) and methyltrioctylammonium chloride (60.5 mg, 0.15 mmol) were added. The mixture was stirred for 3 d at r.t. The layers were separated and the organic phase was washed with H_2O (3 x 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford **33** (1.80 g, 96%) as yellow solid (d.r. **a**:**b** ≈ 1:1.5). This crude product used without further purification due to its instability.

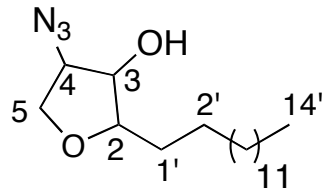
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.45 (q, *J* = 9.0 Hz, 1H, 5-H^b), 4.23 (dd, *J* = 10.4, 6.9 Hz, 1H, 5-H^a), 4.10 (t, *J* = 9.0 Hz, 1H, 4-H^b), 4.06 (t, *J* = 6.9 Hz, 1H, 4-H^a), 3.92 (dd, *J* = 8.1, 4.4 Hz, 1H, 2-H^a), 3.87 (dd, *J* = 10.4, 6.9 Hz, 1H, 5-H^a), 3.82 (dd, *J* = 8.1, 4.4 Hz, 1H, 2-H^b), 3.61 (q, *J* = 9.0 Hz, 2H, 5-H^b), 1.80-1.68 (m, 2H, 1'-H), 1.68-1.51 (m, 2H, 2'H), 1.24 (m_c, 22H, CH_2-chain), 0.87 (t, *J* = 6.9 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.4 (s, C-3), 80.0, 79.3 (2 d, C-2^b, C-2^a), 68.2, 68.0 (2 t, C-5^a, C-5^b), 61.3, 60.3 (2 d, C-4^b, C-4^a) 32.0 (t, C-1'), 30.0-25.4 (several t, CH_2-chain), 14.3 (q, CH_3) ppm.

IR (KBr): ν (cm^{-1}) = 2940-2860 (C-H), 2120 (N_3), 1725 (C=O), 1100 (C-O).

MS (ESI-TOF): calcd. for $C_{18}H_{33}N_3O_2$: 362.5718 $[M + K]^+$; found: 362.6315.
No better HRMS analysis could be obtained.

4-Azido-2-(tetradecyl)tetrahydrofuran-3-ol (50)



According to **GP5:** To furanone **33** (1.73 g, 5.36 mmol) dissolved in THF (120 mL) was added at -78 °C L-selectride(1.0 M in THF, 13.4 mL, 13.4 mmol). The mixture was stirred for 1.5 h at this temperature followed by addition of sat. aq. NH_4Cl solution (250 mL). The mixture was stirred at r.t. for 30 min and worked up as stated above. The crude product was purified by column chromatography on silica gel (EtOAc-hexane, 1:20) affording a mixture of two diastereoisomers **50** (650 mg, 37%, (d.r. ≈ 1:1.5) as colorless crystals. R_f = 0.30 (EtOAc-hexane, 1:6).

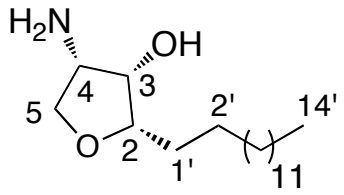
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.22-4.17 (m, 1H, 3-H^b), 4.12 (dd, *J* = 9.9, 5.9 Hz, 1H, 5-H^b), 4.09 (dd, *J* = 7.1, 4.4 Hz, 1H, 3-H^a), 4.03 (dd, *J* = 9.9, 5.9 Hz, 1H, 4-H^b), 3.97 (dd, *J* = 9.1, 7.1 Hz, 1H, 5-H^a), 3.92-3.87 (m, 1H, 4-H^b), 3.84 (dd, *J* = 9.1, 7.1 Hz, 1H, 5-H^a), 3.79 (dd, *J* = 9.9, 5.9 Hz, 1H, 5-H^b), 3.75 (td, *J* = 7.1 Hz, 4.4 Hz, 1H, 2-H^a), 3.65-3.58 (m, 1H, 2-H^b), 2.41 (s_{br}, 1H, OH), 2.30 (s_{br}, 1H, OH), 1.67-1.58 (m, 2H, 1'-H), 1.30-1.22 (m, 24H, CH_2-chain), 0.86 (q, *J* = 7.1 Hz, 3H, CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) : δ = 83.0, 82.2 (2 d, C-2^b, C-2^a), 76.2, 72.6 (2 d, C-3^b, C-3^a), 69.5, 68.5 (2 t, C-5^b, C-5^a), 63.7, 63.1 (2 d, C-4^b, C-4^a), 32.1 (t, C-1'), 31.3-29.9 (several t, CH_2-chain), 14.3 (q, CH_3) ppm.

IR (KBr): ν (cm^{-1}) = 3330 (-OH), 2915-2850 (C-H), 2105 (N_3), 1100 (C-O).

MS (ESI-TOF): calcd. for $C_{18}H_{35}N_3O_2$: 348.2622 $[M + Na]^+$; found: 348.2637.

cis-cis-4-Amino-2-(tetradecyl)tetrahydrofuran-3-ol (Jaspine B) (1)



Azidofuranol **50** (650 mg, 2.00 mmol) was dissolved in THF (80 mL) and H_2O (29 mL). Triphenylphosphine (2.62 g, 10.0 mmol) was added and the mixture was stirred for 2 d at r.t. The reaction was quenched with H_2O (20 mL) and the aqueous phase was extracted with Et_2O (3 x 40 mL), the combined organic phases were dried with $MgSO_4$, filtered and the solvents were evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel [100% CH_2Cl_2, CH_2Cl_2 + 10% MeOH , CH_2Cl_2-NH_3 (7N in MeOH), 10/1] affording a mixture of two diastereomers **1** and **2** (Jaspine B : 2-epi-Jaspine B ≈ 30 : 70, 312 mg, 60%) as colorless solids.

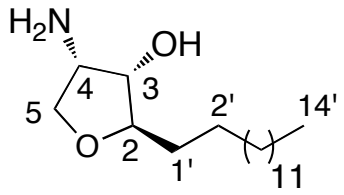
Due to the high polarity of the compounds it was not possible to separate the two diastereomers by routine HPLC or by reversed phase HPLC,.It was possible to interpret the ^{1}H NMR spectrum of the mixture of the two diastreomers by comparison with the reported ^{1}H NMR spectra of the two isolated epimers.

Data for Jaspine B **(1)**:

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.92 (dd, *J* = 8.5, 7.4 Hz, 1H, 5-H), 3.86 (dd, *J* = 5.1, 3.5 Hz, 1H, 3-H), 3.73 (ddd, *J* = 7.6, 6.2, 3.5 Hz, 1H, 2-H), 3.67-3.62 (m, 1H, 4-H), 3.51 (dd, *J* = 8.5, 6.8 Hz, 1H, 5-H), 1.72-1.60 (m, 2H, 1'-H), 1.24 (s, 24H, CH_2-chain), 0.87 (t, *J* = 7.0 Hz, 3H, CH_3) ppm.

The spectroscopic and physical properties agree with previously published data.[26]

***trans-cis*-4-Amino-2-(tetradecyl)tetrahydrofuran-3-ol (2-epi-Jaspine B) (2)**



^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.12 (dd, *J* = 8.8, 6.5 Hz, 2H, 5-H), 3.62-3.57 (m, 2H, 2-H, 3-H), 3.49-3.43 (m, 1H, 4-H), 3.39 (dd, *J* = 8.8, 6.8 Hz, 1H, 5-H), 1.60-1.48 (m, 2H, 1'-H), 1.24 (s, 24H, CH_2-chain), 0.87 (t, *J* = 7.0 Hz, 3H, CH_3) ppm.

Spectroscopic and physical properties agree with previously published data.[26]

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