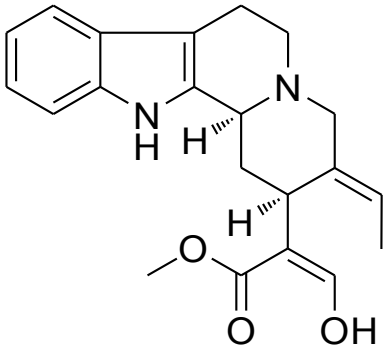
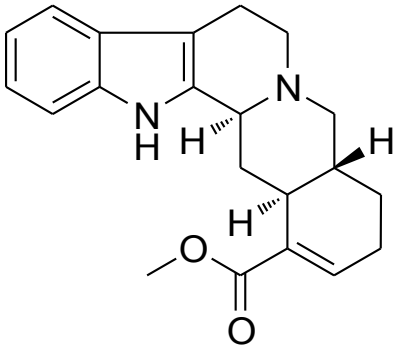
Approach to the synthesis of indole-alkaloids by phosphonate-based chemistry.





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Bachelor Thesis

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Abstract

A synthetic route towards apo-yohimbine and geissoschizine, based on phosphonate chemistry and enantioselective catalytic Pictet-Spengler reactions has been explored. The phosphonate functional group containing aldehyde needed for this route has been synthesized, and proved able to undergo Pictet-Spengler reactions with different N-allyl-tryptamine derivatives. The ee's of these reactions covered a very wide range, from a (nearly) racemic mixture up to 84% ee, depending on both the catalyst and tryptamine-derivative.
The targeted final products apo-yohimbine and geissoschizine could not be obtained, due to problems with the cyclizations steps (e.g. a Heck-reaction) required for their synthesis.

Also, a novel route towards some spiro-compounds was explored. For this route, the synthesis of a bis-sulphone containing C_4-aldehyde was prepared. A bis-phosphonate analogue could not be synthesized. The bis-sulphonic aldehyde was then used in a Pictet-Spengler reaction, which yielded the normal β-carboline Pictet-Spengler product, instead of the spiro-product.

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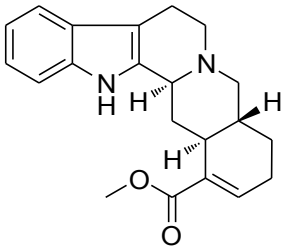
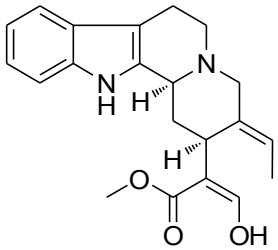
Introduction

Indole-alkaloids are natural compounds often found in plants, and with a very diverse range of bio-activities. Some examples of indole containing bio-active compounds are serotonin, a neurotransmitter, and different kinds of painkillers and drugs like ajmaline, vincamine and ergotamine.

Some indole-alkaloids can be synthesized by a condensation reaction between an aldehyde and a tryptamine-derivative. This reaction is known as the *Pictet-Spengler* reaction, and was first discovered in 1911 in it's racemic form.[1] Since 2007, several catalytic enatioselective methods have been developed,[2] resulting in the total synthesis of (-)-arboricine in 2009.[3]



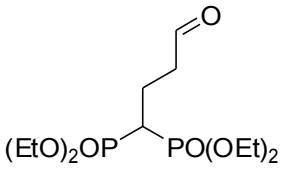
Apo-yohimbine **(1)**



Geissoschizine **(2)**

This report describes the approach to the synthesis of β-carboline alkaloids apo-yohimbine **1** and geissoschizine **2**. The approach of the synthesis is quite similar to the work done by Claveau on the synthesis of mitragynine[4], although this work has a focus on the diethyl phosphonate functional group incorporated in the aldehyde molecule, instead of a sulphone functional group. The synthesis of indole-alkaloids with phosphonate functional groups present in it has not yet been reported in any content found in SciFinders database. Therefore, all steps of this synthesis are important, though the focus will be on achieving Pictet-Spengler condensation, and later on the final cyclization to yield the target compounds.

Also, this report describes the first few steps of a synthetic route towards spiro-compounds, which are precursors for vindoline-alkaloids. The C_4-aldehyde **21**, containing a bis-sulphonate group, was synthesized, but the analogue **20**, containing a bis-phosphonate group, could not be synthesized.



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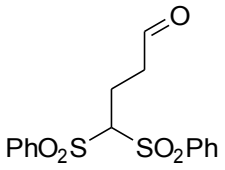
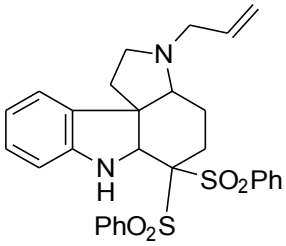


(21)

Aldehyde **21** was then used to do a Pictet-Spengler reaction, the goal of which was to obtain the desired spiro-compound **23**, but the β-carboline alkaloid **23a** was found instead.



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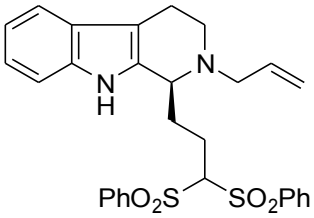
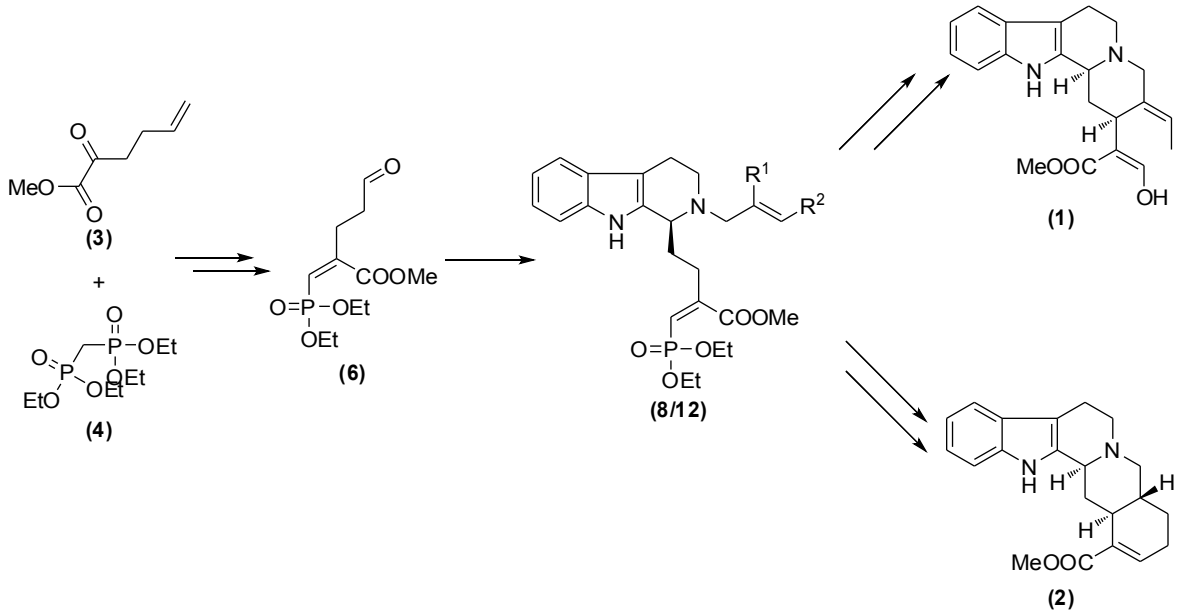


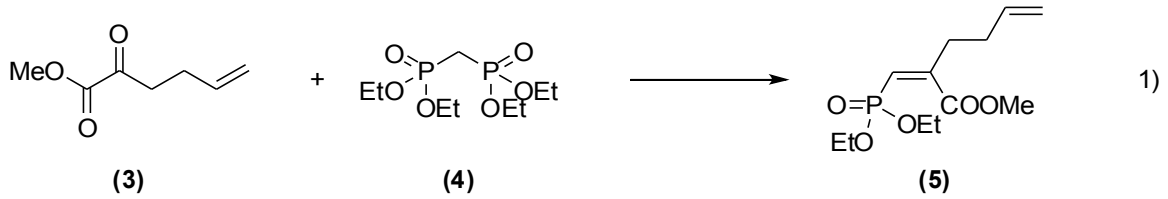
(23a)

Results and discussion



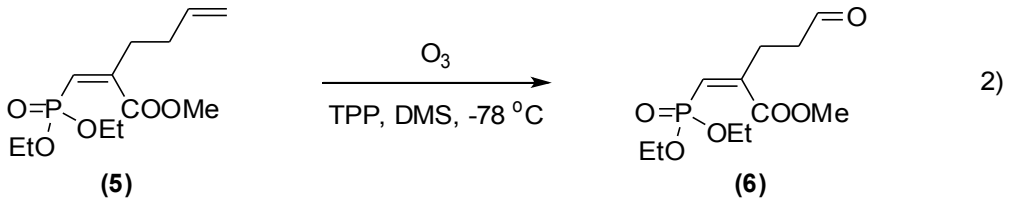
The synthesis of the targeted compounds apo-yohimbine **1** and geissoschizine **2** is done in a similar way. Both routes start of with the coupling of α-keto ester **3** and bisphosphonate **4** to form alkene **5**, followed by oznolysis to yield the phosphonate containing aldehyde **6**. This aldehyde will be used in Pictet Spengler reactions with different N-allyl-tryptamines **7** and **11** to yield products **8** and **12**. After these reactions, different routes are taken to get to the ring closure steps, which yield apo-yohimbine **1** and a precursor to geissoschizine **2**.

*General synthetic route towards aldehyde **(6)**.*



First, out of keto-ester **3** and bisphosphonate **4**, alkene **5** is synthesized by a *Horner-Wadsworth-Emmons reaction*, the mechanism can be seen in reaction scheme 1. This reaction was carried out in THF at 0 °C and gave a yield of 29% for the main product, but side reactions were also noticeable on TLC. The spots on TLC were also quite smeared on TLC, which could be due to interactions between the polar phosphonate group and the silica on the TLC plates. NMR analysis of the

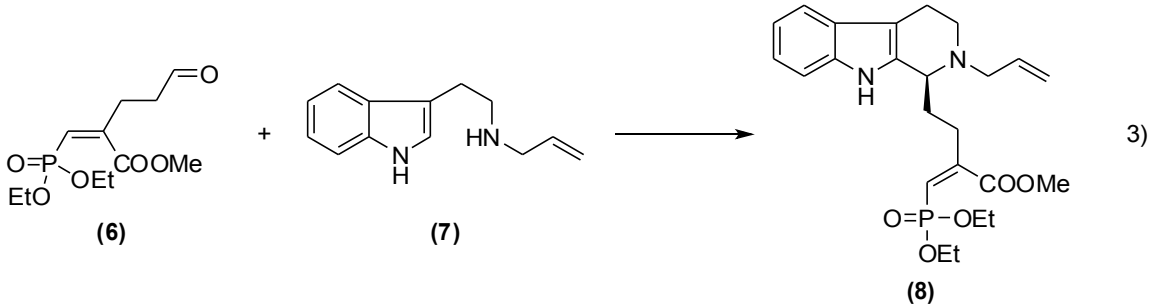
obtained product showed an E:Z ratio of 20:80, though once a ratio of 8:92 was observed, though this reaction was quenched when conversion was not yet reached. However, this might indicate that the E-isomer is the thermodynamically stable product of the reaction, whereas the desired Z-isomer would thus be the kinetically stable product. It has to be noted, though, that decreasing the temperature did not show any effect on either the yield or the E:Z ratio of the product. Isomerisation might therefore occur by a nucleophilic attack of the phosphate formed during the coupling onto the double bond between the phosphonate and the ester present in **5**.

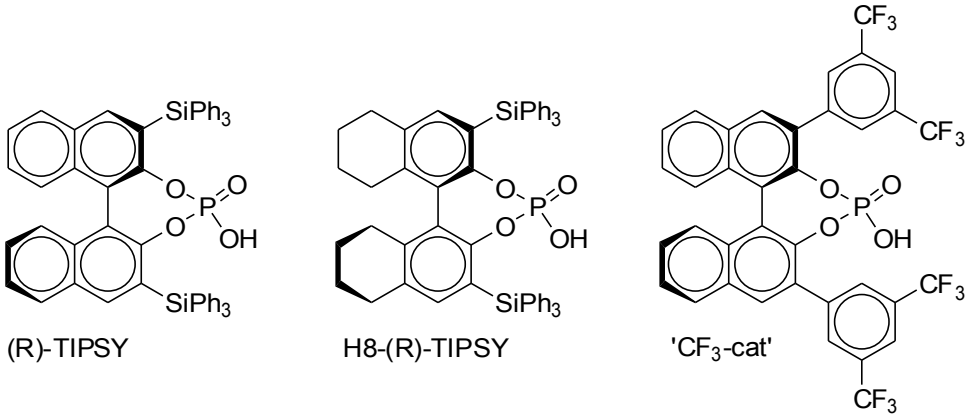


2)

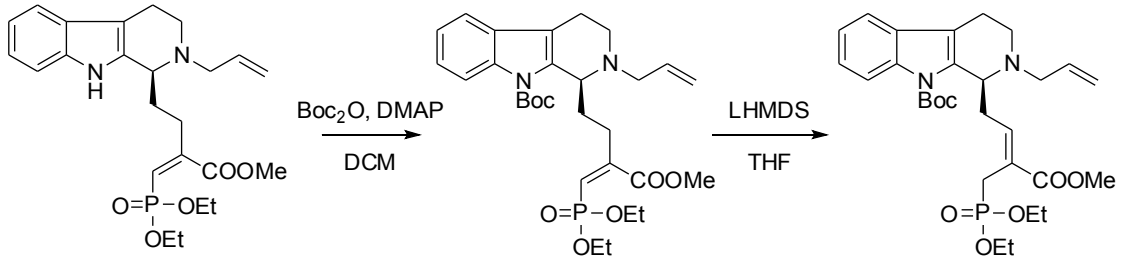
Alkene **5** is subsequently used to form the desired aldehyde **6**. This is achieved by dissolving **5** in DCM and bubbling ozone through the solution at -78 °C. When the solution turns blue, the reaction is stopped by removing the O_3 flow, and DMS is added as a reducing agent, to obtain aldehyde **6**. The yield of this reaction was 40%, but when TPP is used as an extra reducing agent, the yield is lower (37%), due to smearing of TPPO (a product of the reduction) through the spot of the desired product. Also, multiple spots were again witnessed on TLC. This may partially be explained by the E/Z isomer mixture, and partially by overoxidation which could lead to oxidation of the double bond next to the ester in **5**.

*Continuation of synthesis specific for apo-yohimbine **(1)**.*





Aldehyde **6** is reacted with tryptamine derivative **7** and chiral catalyst H8-(R)-TIPSY in an enantioselective Pictet Spengler reaction. This reaction gave a yield of 31%. The reaction was also tested with the (R)-TIPSY catalyst and a CF_3-containing binolic chiral catalyst. The yields were comparable, but the ee's were lower. For the H8-(R)-TIPSY catalyst, the ee was 84%, for the (R)-TIPSY it was 74% and for the CF_3-catalyst, the product was a racemic mixture (ee <0.5%).

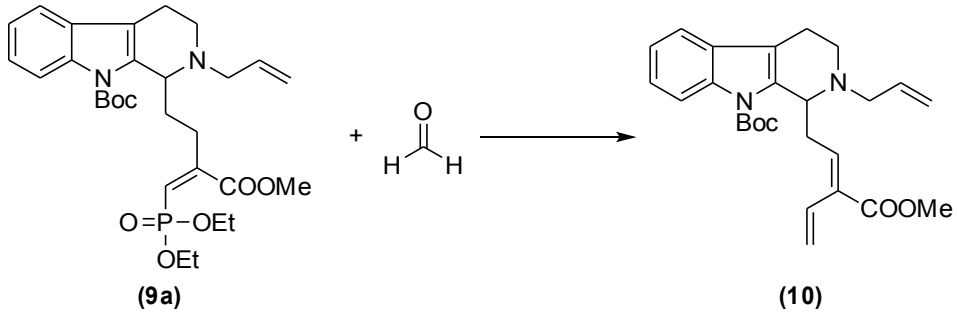


4)

T

he product **8** of the Pictet Spengler reaction was than prepared for the final ring closure reaction. First, the free NH of the indole-moiety has to be protected. This is done by adding Boc-anhydride to a solution of **8** and DMAP in DCM. After workup, the Boc-protected product **9** was obtained with a yield of 73%.

Second, the double bond located next to the phosphonate- and methylester-groups was shifted to the other side of the ester-group by producing the anion with LHMDS in THF. Then, the anion was protonated again to obtain the product **9a** with the shifted double bond.



5)

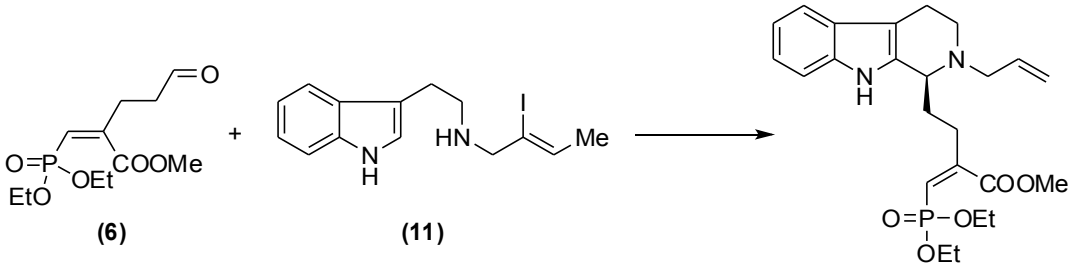
N

ext, a second *Horner-Wadsworth-Emmons* reaction was done between formaldehyde and the phosphonate group of **9a**, producing diene **10**. This diene would than be heated to reflux in toluene, to achieve 4+2 cycloaddition, forming apo-yohimbine **1**.

However, a crude NMR showed that the formation of the anion was not fully achieved, thus there was no full conversion. Also, the *HWE* reaction did not occur, according to TLC and NMR spectra. It should be noted that both the anion-formation and the formation of formaldehyde out of paraformaldehyde was to be done by LHMDS, which was added in 1.5 eq. The incomplete conversion of **9** to it's

shifted form **9a** might be indicatory for a loss of LHMDS due to acidic residues on the flask or in the reaction mixture. This might then also explain why there was no reaction between **9** and the formaldehyde. However, formaldehyde is also known for its low reactivity, and this may thus be another explanation of why the desired product is not observed.

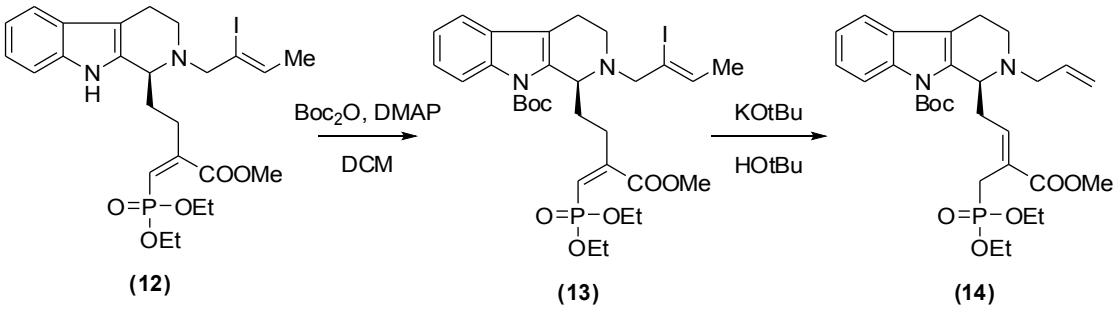
*Continuation of synthesis specific for geissoschizine **(2)**.*



6)

A

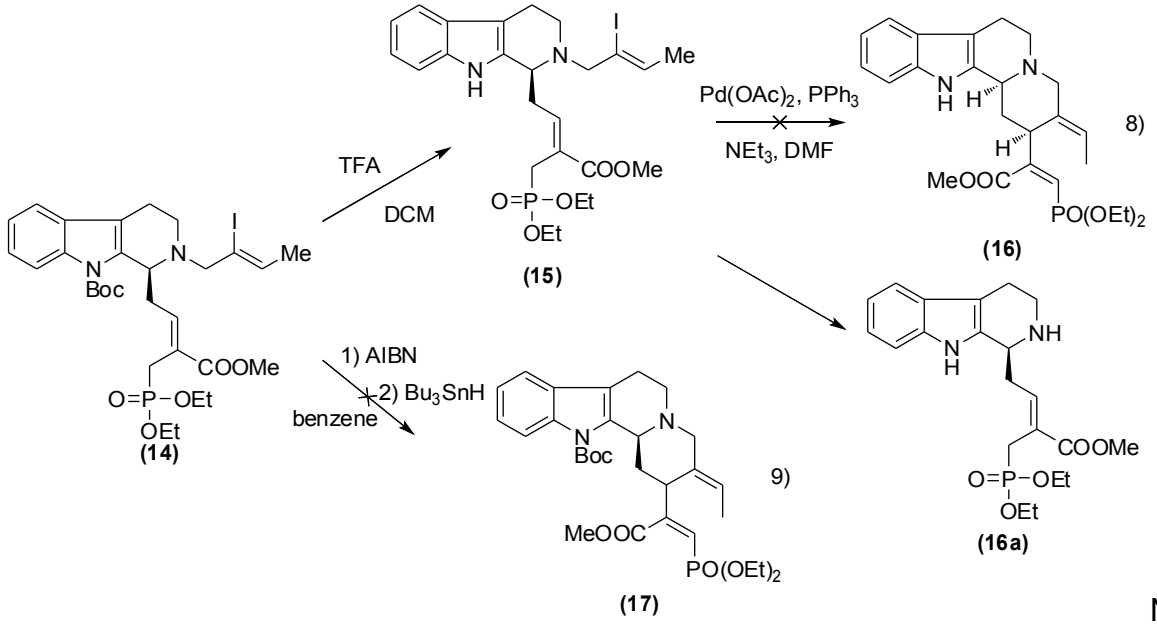
fter aldehyde **6** has been obtained, it reacted with N-allyl-tryptamine derivative **11** in a Pictet-Spengler reaction, to form product **12**, containing an allylic side chain substituted with an I- and a Me-group. This reaction proved to less regioselective than its equivalent with tryptamine-derivative **7**, because the ee was much lower, 54% for product **12** against 84% for product **8**. However, the yield was better, 64% against 30%.



7)

Subsequently, **12** was protected by letting it react with Boc_2O and DMAP in DCM, yielding **13** in 54%, which however may be due to short reaction times (only several hours). Next, **13** was dissolved in *t*BuOH and 0.75 eq. of KO*t*Bu was added to shift the C=C double bond close to the phosphonate in **13** to the other side of

the methyl-ester in **14**. This reaction was carried out at 50 °C. This reaction gave a yield of 60%.



N

ext, **14** was deprotected of the Boc-group by dissolving it in DCM and adding TFA. The yield of this reaction was 65% of **15**.

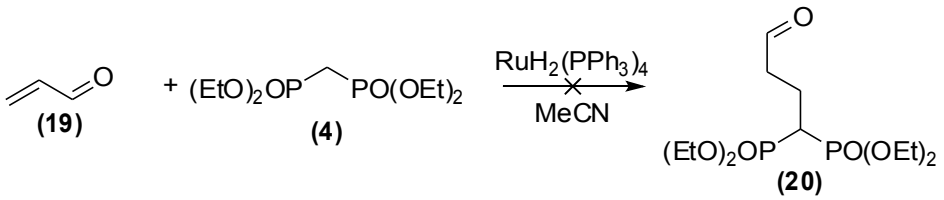
Next, cylization of **14** was attempted by the Heck-reaction. $Pd(OAc)_2$, PPh_3 and NEt_3 were added to **14** in DMF, argon was flushed through the solution and the reaction was heated up to 80 °C under argon atmosphere. After 2.5 hours, the reaction was stopped, but an NMR after purification showed only the starting compound. Either no product was formed, or it does not come off the column. When the same reaction was done again, but then for four hours instead of 2.5, some products did come of the column. In LC-MS, these products appeared as peaks of [M+1] at 575, 577 and 523. The first of these peaks has the right mass for the desired cyclized product **16**, but can also be due to formation of a triple carbon-carbon bond out of the N-allyl side chain. The 577 peak can be explained by either a substitution of the I-group for a proton, or the reduction of one of the double bonds that are present in **16**, but neither one of these compounds is the desired one. Finally, the mass peak at 523 can be explained by a complete loss of the allylic side chain of the tryptamine derivative, resulting into compound **16a**. The peak of free NH is also seen in NMR spectra.

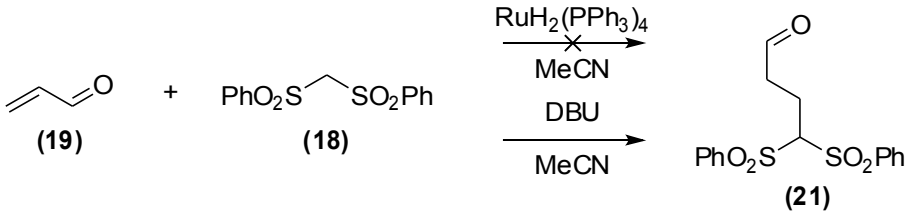
Beside the cyclization of **14**, cyclization reactions were also tried with **15** as a starting material. First, a Pd-catalyzed ring closure was attempted, just like described for the cyclization of **14**, but the desired product **17** was not observed in NMR spectra.

Second, a radical-induced ring closure reaction was attempted. AIBN was added to a solution of **15** in benzene, and after reflux was reached, Bu_3SnH was added to the solution. This was left for one hour, after which the reaction was worked up. After purification, an NMR was taken of the product. This NMR showed traces of the desired product **17**, but the yield could only be estimated, based on NMR combined with the low weight of the acquired product, to be well below 0.1%

Unfortunately, this result concludes the search for a way to incorporate phosphonate groups in the synthesis of apo-yohimbine and geissoschizine, because the necessary ring-closure could not be achieved.

Synthesis-route towards spiro-compounds and their precursors.

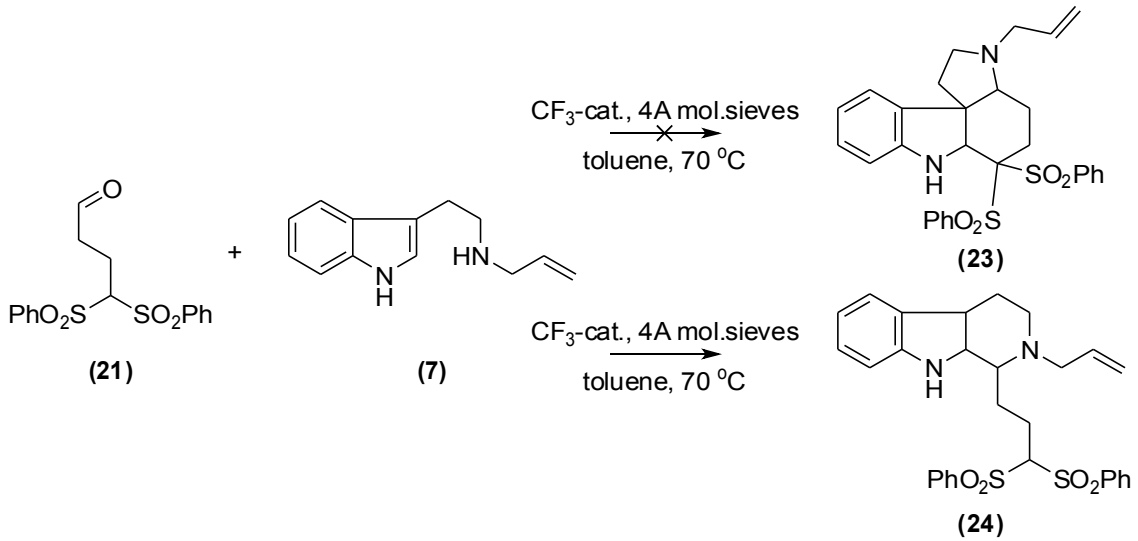




9)

For the synthesis of spiro-compounds **22** and **23**, which are also products of Pictet-Spengler reactions, aldehydes **20** and **21** are synthesized by reacting acrolein **19** with either bisphosphonate **4** or disulphone **18**. In both cases, this was done by adding $RuH_2(PPH_3)_4$ as a catalyst (15 mol%) to a solution of both reagents in acetonitrile. The reaction of **4** and **19** proved to be difficult. After 24 hours of reacting at 25 ^oC, there was still no conversion on TLC, even though comparable reactions showed reaction times of 15 hours.[5] It was therefore concluded that this

reaction would not go at the standard conditions, and it was thus not further investigated. The reaction of **18** and **19** also proved difficult under standard conditions, because after 18 hours there was only a yield of 0.6%. From this result, it was concluded that the ruthenium-catalyst might be unusable in the state it was. The literature describes a yellow-ish catalyst, whereas the one used was black, even though it came straight out of an unopened bottle. However, due to logistical reasons, no further investigation was made for the activity of the catalyst. Instead, the same reaction of **18** and **19** was tried again, but with 10 mol% DBU instead of $RuH_2(PPh_3)_4$ as a catalyst. All other conditions were kept the same, although a check by TLC showed almost complete conversion after already 1.5 hours. This reaction was than stopped, and after purification, aldehyde **21** was obtained in 30% yield.



10)

Aldehyde **21** was then used in a Pictet-Spengler reaction with **7** and 10 mol% of the same CF_3-containing catalyst as used before, to obtain product **23**. This reaction was carried out in toluene at 70 °C for 21 hours. The TLC showed almost complete conversion, but also three different visible spots, indicating at least one side reaction. Also, the TLC showed that catalyst and product have almost the same retention times, making them almost inseparable on a column. Therefore, only the most purest of fractions that came out of the column were put together,

which yielded a product with 10.5% yield. However, NMR analysis showed that not product **23**, but the 'normal' Pictet-Spengler product **24** was formed.

Conclusions and Future prospects

Phosphonate-based chemistry poses some problems in the approach to synthesis of apo-yohimbine. Besides the difficult purification, possibly due to smearing of the products because of the phosphonate group, the phosphonate group also seems to have some influence on the reactivity of the compounds. This is illustrated by the low yields that are reported for all reactions, even though according to TLC (almost) full conversion was achieved for every reaction. This might indicate problems with the purification, for example some kind of intolerance for the silica used for column purification. Also, some kind of oxygen sensitivity can be a good explanation for low yields. It has to be noted that, starting with the Pictet-Spengler reactions in schemes 3 and 6, the colour of the reaction mixtures and products was always ranging between dark yellow and brown, which may be due to oxidation of the N-C bond to yield a conjugated iminium-salt. This conjugation between an electron rich ring system and an electron poor 'tail' explains the colouring. Also, iminium salts in conjugation with an indole system are known to be yellow.

Still, beside the fact that a lot of the compound is lost throughout the synthesis, which should be solved, the original aim of this research still has some prospects as well. It was shown in scheme 7 that shifting the C=C double bond next to the methyl-ester is possible. This opens up another chance to obtain **9a**, which could be purified and then reacted with formaldehyde. This might lead to the synthesis of **10**, which would increase the chances of finally obtaining apo-yohimbine **1.**

Experimental

General remarks

All chemicals were obtained from Sigma-Aldrich, Acros and/or Merck, and used without further purification, unless stated otherwise.

For purification, flash column chromatography was done on silica gel (0.032-0.063 µm, flash). Analytical thin layer chromatography was done on *plastic plates coated with* silica gel 60 F_{254}*.* Visualization was done under UV light, followed by dipping the plate into an anise aldehyde solution and heating.

NMR spectra were recorded on a Brücker 400 MHz spectrometer. The data are listed as follows: chemical shift in ppm, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants in Hz, integration and assignment.

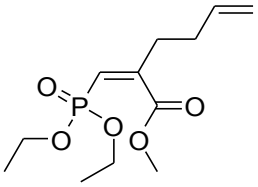
For ^{13}C-NMR APT spectra, the type of C-atom (primary/tertiary or secondary/quaternary) is reported with p/t or s/q. This assignment is based on the quaternary peaks of $CDCl_3$.

The enantiomeric excess (ee) was measured using a chiral HPLC, equiped with a chiral column AD00CE-GI150. The eluent used was heptane:iso-propanol 90:10.

The compounds used and synthesized are prone to oxidation. Therefore, working with dry glasswork and under N_2 or Ar atmosphere is recommended.

*General synthesis of alkene **5** and aldehyde **6**, precursor for Pictet-Spengler reactions.*

1. Synthesis of (Z)-methyl 2-((diethoxyphosphoryl)methylene)hex-5-enoate.



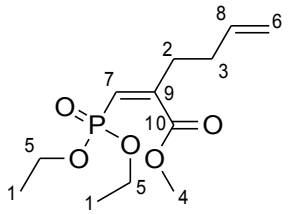
(5)

In a 50 ml roudbottomflask, equipped with a magnetic stirrer, tetraethyl methylenebis(phosphonate) **4** (11.0 mmol, 3171 mg) was added to 30 ml of pre-distilled THF. To this solution, NaH (60% dispersed in oil 400 mg, 10.0 mmol) was added. The solution was cooled in an ice bath, and methyl 2-oxohex-5-enoate **3**

(1422 mg, 10.0 mmol, 90% purity) was added dropwise. The reaction was left stirring for 3 hours, after which it was quenched by adding a saturated NH_4Cl solution to it. The mixture was then washed with Et_2O, dried with Na_2SO_4 and subsequently filtered on a glass filter. Et_2O and THF were evaporated, after which a column was done with eluent Petroleum ether (PE)/Ethyl Acetate (EA) in an initial ratio of 3:1, which was changed towards 1:1 after approximately 1 column volume.

^{1}H-NMR

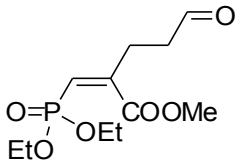
1.33 (q, 6H, CH_3CH_2OP) 7.6 Hz; 2.26 (d, 3H, $CH_2CH_2CHCH_2$) 6.8 Hz; 2.49 (d, 3H, $MeOOCCH_2CH_2$) 7.6 Hz; 3.828 (s, 3H, $COOCH_3$); 4.10 (q, CH_3CH_2OP) 7.2 Hz; 5.04 (dd, 2H, *HH*CCH) 10.6 Hz, 18 Hz; 5.73 (d, 1H, P*CH*C) 14.4 Hz; 5.80 (m, 1H, CHH*CH*CH_2) 1.2 Hz



^{13}C-NMR (APT)

16.0 *(1)*; 30.90 *(2)*; 34.93 *(3)*; 52.10 *(4)*; 61.73 *(5)*; 115.81 *(6)*; 119.59 *(7)*; 135.96 *(8)* ; 152.89 *(9)* ; 167.98 *(10)*

2. Synthesis of (Z)-methyl 2-((diethoxyphosphoryl)methylene)-5-oxopentanoate.



(6)

In a 100 ml roundbottom flask with magnetic stirrer, compound **5** (3695 mg, 13.37 mmol)* was dissolved in DCM, then cooled to -78 °C with dry ice in acetone. Ozone was then bubbled through this solution. The ozone flow was stopped when the solution turned blue, and dimethylsulfide (DMS) was added (20 eq, 267 mmol,

20 ml). The reaction was allowed to warm up to room temperature and was left stirring for 21 hours. Next, the solvents were evaporated and the residue was columned with PE/EA 1:2 as eluent. After 3 column volumes, the eluent was changed to EA only.

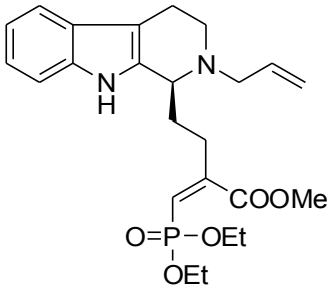
*: This was non-purified product of synthesis step 1.

^{1}H-NMR:

1.30 (t, 6H, CH_3CH_2OP) 7Hz; 3.823 (s, 3H, COO*Me*); 4.0 (m, 4H, $(CCH_3CH_2O)_2P$); 5.78 (d, 1H, P*CH*COOMe) 13.7 Hz; 9.77 (s, 1H, C*H*OCH_2)

Specific synthesis towards apo-yohimbine.

3. (Z)-methyl 4-(2-allyl-2,3,4,4a,9,9a-hexahydro-1H-pyrido[3,4-b]indol-1-yl)-2-((diethoxyphosphoryl)methylene)butanoate.



(8)

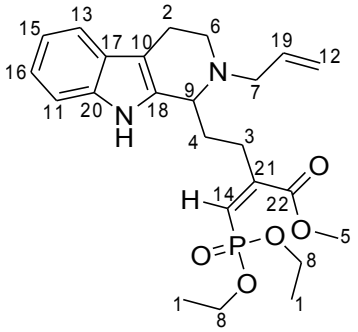
In 10 ml roundbottom flasks with magnetic stirrer, compound **7** (0.100 gr, 0.5 mmol), 4Å molecular sieves and different catalysts* (3 mol%) were added to toluene pre-dried on 4Å molecular sieves. The mixtures were stirred for 10 minutes, after which aldehyde **6** (0.125 gr, 0.5 mmol) was added. The mixtures were then flushed with N_2, the flasks were closed and the reactions were heated to 70 ^oC for 17 hours. The mixtures were then filtered over celite on a glass filter and washed with EA. Subsequently, the solvent is evaporated and the crude products are purified on a column. The eluent used is EA.

^{1}H-NMR:

1.32 (m, 6H, ($CH_3CH_2O)_2P$) 7.1 Hz

; 1.95 (q, 2H, $NCHCH_2CH_2$) 7.1 Hz; 2.60 (t, 2H, $NCHCH_2CH_2$) 7.9 Hz; 2.8-3.24 (m, 4H, NCH_2CH_2) 3 Hz; 3.25 (d, 2H, NCH_2CHCH_2) 6.2 Hz; 3.73 (t, 1H, $NCHCH_2CH_2$), 6.0 Hz; 4.1 (m, 4H, $(CH_3CH_2O)_2P$) 3 Hz; 5.17 ('t', 2H, CH_2CHCHH) 11.4 Hz, 4.9 Hz; 5.77 (d, 1H, PCHCOOMe) 14.8 Hz; 5.9 (m, 1H, NCH_2CHCH_2) 4 Hz; 7.1-7.5 (m, 4H, aromatic protons); 8.55 (s, 1H, indole-proton)

^{13}C-NMR (APT)



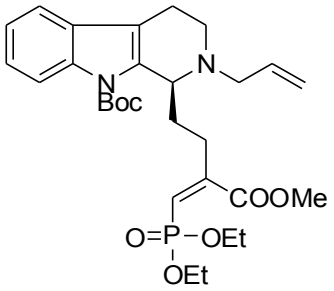
16.15 *(1)*; 17.62 *(2)*; 31.39 *(3)*; 32.42 *(4)*; 52.31 *(5)*; 55.12 *(6)*; 56.18 *(7)*; 61.89 *(8)*; 107.56 *(10)*; 110.88 *(11)*; 117.17 *(12)* ; 117.71 *(13)* ; 118.90 *(14)* ; 121.06 *(16)* ; 127.33 *(17)* ; 128.42 ** ; 131.86 ** ; 134.38 *(18)* ; 134.89 *(19)* ; 135.98 *(20)* ; 136.47 ** ; 136.76 ** ; 154.27 *(21)* ; 168.57 *(22)*

*The different catalysts are the ones described in scheme 3 of the apo-yohimbine synthesis.

** An assignment of these peaks could not be made, based on *ChemDraw* ^{13}C-NMR predictions.

NB: In the ^{13}C-NMR APT, C *(9)* and C *(15)* could not be assigned to peaks, based on *ChemDraw* ^{13}C-NMR predictions.

4. (Z)-tert-butyl 2-allyl-1-(4-(diethoxyphosphoryl)-3-(methoxycarbonyl)but-3-en-1-yl)-2,3,4,4a-tetrahydro-1H-pyrido[3,4-b]indole-9(9aH)-carboxylate.



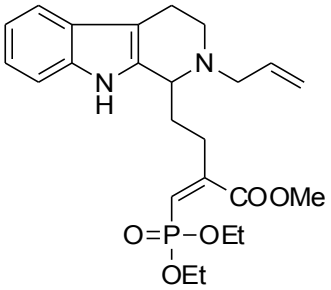
(9)

Compound **8** (341 mg, 0.740 mmol), Boc_2O (274 mg, 1.26 mmol) and DMAP (18.1 mg, 0.148 mmol) were put in a 50 ml roundbottom flask and dissolved in 10 ml DCM. The mixture was stirred at room temperature for 18 hours, after which the solvent was evaporated and the product was columned with an initial 4:1 mixture of PE/EA, which was changed to only EA after one column volume.

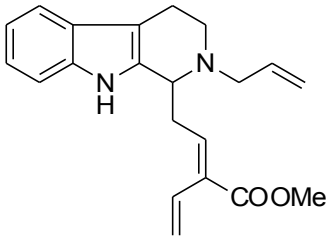
^{1}H-NMR:

1.32 (t, 6H, $(CH_3CH_2O)_2P$ 7.1 Hz; 1.68 (s, 9H, $(CH_3)_3COCN$); 1.7 (td, 2H, $NCHCH_2CH_2$) 4 Hz; 2.0 (td, 1H, $MeOOCCHCH_2$) 3 Hz; 2.68-2.95 (m, 2H NCH_2CH_2C) 4 Hz; 3.2 (m, 2H, NCH_2CH_2C) 4 Hz; 3.83 (s, 3H, $COOCH_3$); 4.1 (m, 4H, $(CH_3CH_2O)_2P$ 1Hz, 4.7 Hz; 4.26 (broad d, 1H, $NCHC^{ar}N^{indole}$) ~6Hz; 5.11 (d, 1H, NCH_2CHCH_2 *(H-trans)*) 4.5 Hz; 5.15 (s, 1H, NCH_2CHCH_2 *(H-cis)*); 5.78 (d, 1H, $PCHCCOOMe$) 14.7 Hz; 5.9-6.0 (m, 1H, NCH_2CHCH_2); 7.2-8.1 (m, 4H, aromatic protons)

5. (Z)-tert-butyl 2-allyl-1-(3-((diethoxyphosphoryl)methyl)-4-methoxy-4-oxobut-2-en-1-yl)-2,3,4,4a-tetrahydro-1H-pyrido[3,4-b]indole-9(9aH)-carboxylate (9a) *and* **(E)-tert-butyl 2-allyl-1-(3-(methoxycarbonyl)penta-2,4-dien-1-yl)-2,3,4,4a-tetrahydro-1H-pyrido[3,4-b]indole-9(9aH)-carboxylate (10).**



(9a)



(10)

In a 10 ml roundbottom flask compound **9** (150 mg, 0.268 mmol) was dissolved in 3 ml of THF. To this solution, LHMDS (Lithium bis(trimethylsilyl)amide, 67.2 mg, 0.401 mmol) was added. Next, a TLC and a crude NMR sample were taken to confirm formation of the anion of **9***. Subsequently, paraformaldehyde (9.6 mg, 0.32 mmol) was added. When conversion is reached according to TLC, the reaction is quenched with NH_4Cl. After washing with Et_2O, column chromatography is done.

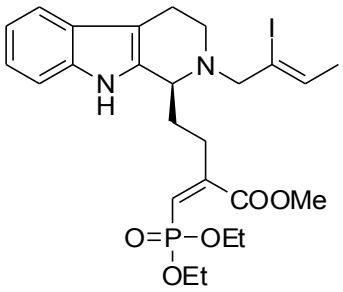
*When quenched, this anion of **9** would become **9a**.

^{1}H-NMR:

1.32 (t, 6H, $(CH_3CH_2O)_2P$ 7.1 Hz; 1.68 (s, 9H, $(CH_3)_3COCN$); 1.7 (td, 2H, $NCHCH_2CH_2$) 4 Hz; 2.0 (td, 1H, $MeOOCCHCH_2$) 3 Hz; 2.68-2.95 (m, 2H NCH_2CH_2C) 4 Hz; 3.2 (m, 2H, NCH_2CH_2C) 4 Hz; 3.83 (s, 3H, $COOCH_3$); 4.1 (m, 4H, $(CH_3CH_2O)_2P$ 1Hz, 4.7 Hz; 4.26 (broad d, 1H, $NCHC^{ar}N^{indole}$) ~6Hz; 5.11 (d, 1H, NCH_2CHCH_2 *(H-trans)*) 4.5 Hz; 5.15 (s, 1H, NCH_2CHCH_2 *(H-cis)*); 5.9-6.0 (m, 1H, NCH_2CHCH_2); 6.57 (d, 1H, PCHCCOOMe) 14.7 Hz; 7.2-8.1 (m, 4H, aromatic protons).

Specific synthesis towards geissoschizine.

6. (S,Z)-methyl 4-(2-allyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-2-((diethoxyphosphoryl)methylene)butanoate.



(12)

This procedure is almost the same as procedure 3, which yields compound **8**. The only differences are that only H8-(R)-TIPSY is used as a catalyst, and that the tryptamine derivative is different. In this case, tryptamine **11** is used, instead of **7**.

The amounts are as follows:

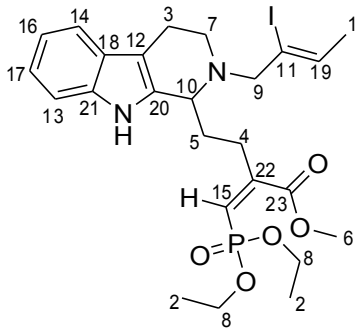
compound **6** (87.7 mg, 0.33 mmol); tryptamine **11** (112 mg, 0.33 mmol); catalyst (8.7 mg, 3 mol%)

^{1}H-NMR:

1.33 (m, 6H, ($CH_3CH_2O)_2P$) + impurities* (total 7H) 7.1 Hz; 1.97 (m, 2H, $NCHCH_2CH_2$) 6.3 Hz; 2.58+3.18 (2x d, 2H, $NCHCH_2CH_2$) ~10Hz; 2.77 (m, 3H, $CH_3CHClCH_2$); 3.29+3.67 (2x m, 2H, $NCHCH_2CH_2$) 4.1 Hz; 3.40 (t, 2H, $NCH_2ClCHMe$) 4.3 Hz; 3.86 (s, 3H, COO*Me*); 4.1 (m, 4.5H, $(CH_3CH_2O)_2P$ + impurities*; 5.8 (dd, 2H, P*CH*COOMe) 6.5, 15.0 Hz + impurities; 7.1-7.7 (m, 5H, aromatic protons); 8.59 (ds, 1H, NH-indole) + impurity*

*Impurity is most likely starting material **11.**

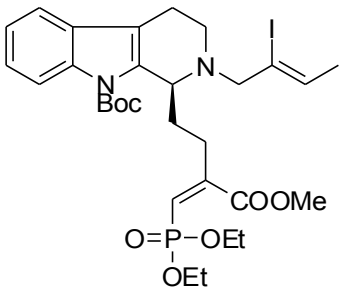
^{13}C-NMR (APT):



14.06 *(1)* ; 16.21 *(2)* ; 21.30 *(3)* ; 22.21 *(4)* ; 31.90 *(5)* ; 52.39 *(6)* ; 53.37 *(7)* ; 61.87 *(8)* ; 64.88 *(9)* ; 107.83 *(12)* ; 110.82 *(13)* ; 117.57 *(14)* ; 119.05 *(15)* ; 119.39 *(16)* ; 121.35 *(17)* ; 127.24 *(18)* ; 132.46 *(19)* ; 135.89 *(20)* ; 169.2 *(21)* ; 170.9 *(22)*

NB: C-10 and C-11 could not be identified in the spectrum, based on *ChemDraw* predictions.

7. (S)-tert-butyl 1-((Z)-4-(diethoxyphosphoryl)-3-(methoxycarbonyl)but-3-enyl)-2-((Z)-2-iodobut-2-enyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-9(2H)-carboxylate.



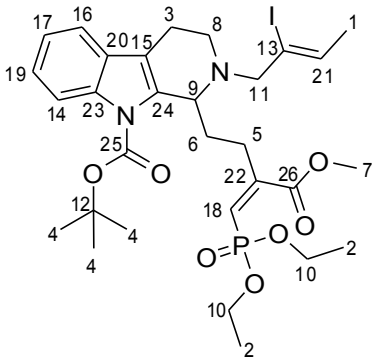
(13)

In a 50 ml roundbottom flask, equipped with a magnetic stirrer, compound **12** (68 mg, 0.113 mmol) was dissolved in DCM and DMAP (2.8 mg, 0.026 mmol) and Boc_2O (78 mg, 0.357 mmol) were added to the solution. The mixture was left stirring for 2.5 hours at room temperature, after which the solvent was evaporated and the product was purified by column, with EA as eluent.

^{1}H-NMR:

1.34 (m, 8H, ($CH_3CH_2O)_2P$) + ethyl acetate 7.3 Hz; 1.66 (t, 9H, CH_3CCOO) excess Boc; 1.80 (d, 3H, CH_3CHCl) 6.4 Hz; 2.47-3.25 (6x m, 6H, $NCH\mathit{CH_2}CH_2$ + $N\mathit{CH_2CH_2}C$); 3.84 (ds, 3H, COO*Me*) (double singlet, no full conversion); 4.12 (m, 4H, ($CH_3\mathit{CH_2}O)_2P$) with impurities, 6.4 Hz; 5.8 (d + q, 2H, P*CH*C + C*H*MeCl) 6.4 Hz, 14.9 Hz; 7.2-7.6 (4H, aromatic protons); 8.14 (d, 0.7 H, unprotected NH-indole)

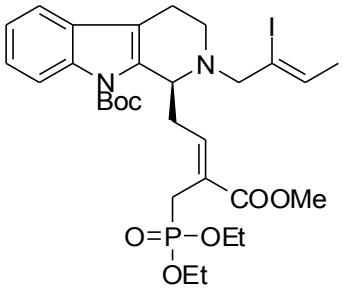
^{13}C-NMR (APT):



13.8 *(1)*; 16.44 *(2)*; 20.48 *(3)*; 27.71 *(4)*; 31.59 *(5)*; 33.65 *(6)*; 51.73 *(7)*; 56.01 *(8)*; 61.36 *(10)*; 64.44 *(11)*; 83.16 *(12)*; 109.71 *(13)*; 113.79 *(15)*; 115.22 *(14)*; 117.38 *(16) ;* 118.54 *(17)* ; 123.60 *(19)* ; 128.80 *(20)* ; 131.98 *(21)* ; 135.37 *(22)*; 154.19 *(25)*; 167.85 *(26)*;

NB: C-9, C-18, C-23 and C-24 could not be identified in the spectrum, based on the prediction made by *ChemDraw*.

8. (S,Z)-tert-butyl 2-allyl-1-(3-((diethoxyphosphoryl)methyl)-4-methoxy-4-oxobut-2-enyl)-3,4-dihydro-1H-pyrido[3,4-b]indole-9(2H)-carboxylate.



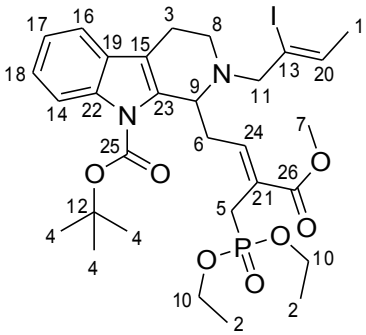
(14)

In a 25 ml roundbottom flask, compound **13** (100 mg, 0.214 mmol) was dissolved in *t*BuOH. To this solution, KO*t*Bu (160 µl 1M solution, 0.160 mmol) was added and the reaction was heated to 50 °C while stirring. After 1.5 hours, EA and water were added to quench the reaction. The layers were separated, and the organic layer was washed with brine, while the aqueous layer was washed wit EA. Next, the organic layers were combined, the solvent was evaporated and a crude NMR was taken. Further purification was unnecessary.

^{1}H-NMR:

*Fingerprint-peaks are identical to the spectrum of **13**, but the COOMe-ester peak has shifted from 3.84 ppm to 3.76 ppm*.

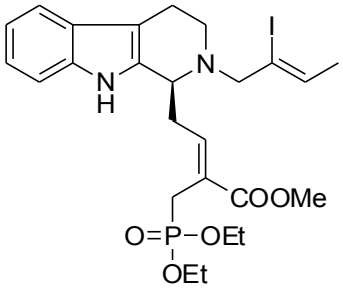
^{13}C-NMR (APT):



14.0 *(1)*; 16.27 *(2)*; 20.96 *(3)*; 25.88 *(5)*; 28.20 *(4)*; 34.08 *(6)*; 40.70 *; 40.96 *; 51.84 *(7)*; 52.20 *; 56.61 *(9)*; 60.30 *; 61.82 *(10)*; 64.97 *(11)*; 83.49 *(12)*; 109.54 *(13)*; 114.68 *(14)*; 115.72 *(15)*; 122.65 *(16)*; 122.90 *; 124.07 *(18)*; 129.30 *(19)*; 132.39 *(20)*; 135.66 *(21)*; 135.95 *(22/23)*; 145.40 *(24)*; 150.14 *(25)*; 167.30 *(26)*;

NB: C-8 and C-17 could not be found in the spectrum, based on *ChemDraw* predictions. * Could not be assigned, based on *ChemDraw* predictions.

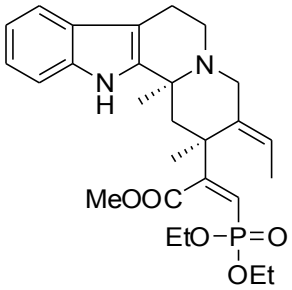
9. (Z)-methyl 2-((diethoxyphosphoryl)methyl)-4-((S)-2-((Z)-2-iodobut-2-enyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)but-2-enoate.



(15)

In a 10 ml roundbottom flask, equipped with a magnetic stirrer, compound **14** (157 mg, 0.224 mmol) was dissolved in DCM, after which TFA (1.5 ml) was added. The solution was left stirring at room temperature for 2 hours, after which the reaction was quenched with a saturated NH_4Cl solution. The mixture was diluted with EA, and the layers were separated, after which the organic layer was washed with $NaHCO_3$, water and brine (all 2x). The water layer was washed with EA, and after washing all organic layers were put together, then dried with Na_2SO_4 and filtered, after which the solvent was evaporated. No further purification was done, for the product was used immediately in a next step.

10. (Z)-methyl 3-(diethoxyphosphoryl)-2-((2S,12bS,E)-3-ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acrylate.



(16)

In a 10 ml roundbottom flask, equipped with a magnetic stirrer, compound **15** (67 mg, 0.11 mmol) was dissolved in DMF, after which $Pd(OAc)_2$ (2.5 mg, 10 mol%),

PPh_3 (5.9 mg, 20 mol%) and NEt_3 (28 mg, 0.28 mmol) were added. The solution was bubbled through with argon for 15 minutes, and was then left under argon atmosphere. The reaction was heated to 80 °C, and was left stirring for 4 hours. A column separation was done next, with EA as the eluent. Different fractions were collected, of which an LC-MS sample was measured for preliminary identification based on mass peaks.

LC-MS:

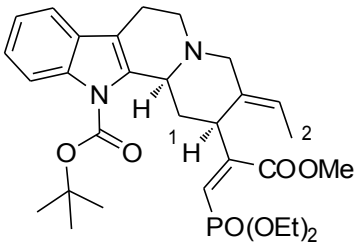
One fraction showed the main [M+1] peak at 573.4, the other fraction showed [M+1] at 575.4 as the main peak. *The 573.4 peaks has the right mass, so an NMR spectrum was recorded of that fraction. However, this fraction contains only traces of interesting compound. Mostly, it consists of what is probably TPP or TPPO, for the aromatic proton peaks are very large.*

Peaks of interest:

5.82 (d, 1H*, P*CH*C of the E-isomer) ~15 Hz

6.04 (d, 1H*, P*CH*C of the Z-isomer) ~15 Hz

11. (12bS,E)-tert-butyl 2-((Z)-1-(diethoxyphosphoryl)-3-methoxy-3-oxoprop-1-en-2-yl)-3-ethylidene-1,2,3,4,6,7-hexahydroindolo[2,3-a]quinolizine-12(12bH)-carboxylate.



(17)

In a 50 ml roundbottom flask, equipped with a magnetic stirrer, compound **14** (60 mg, 0.086 mmol) was dissolved in purified benzene (10 ml), after which AIBN (17 mg, 0.103 mmol) was added. The mixture was first heated while under argon atmosphere to reflux, and then Ph_3SnH (72 mg, 0.206 mmol) dissolved in benzene (1 ml) was added. The reaction was left to reflux for 45 minutes, after which the solvents were evaporated. The product was then diluted with *DCM (remark, don't do this, use EA or another relatively high boiling solvent.)* after which it was washed with water and a saturated $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4, filtered and then columned with EA, which was eventually enriched with a MeOH gradient, as eluent.

^{1}H-NMR:

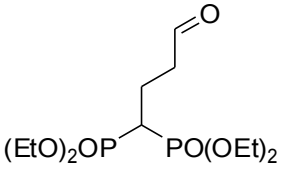
Only Ethyl acetate, dichloromethane, and excess AIBN and Ph_3SnH peaks are visible. However, when zoomed in, some very minuscule peaks appear, of what is probably the desired product. If they really belong to the desired product, the ascription will be as follows.

2.85 *this peak belongs to the proton 1*

5.31 *these peaks belong to the methyl group-protons 2*

Synthesis of spiro-compounds and their precursors.

12. tetraethyl (4-oxobutane-1,1-diyl)bis(phosphonate).

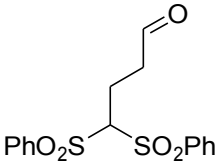


(20)

In a 50 ml roundbottom flask, equipped with a magnetic stirrer, bisphosphonate **4** (1500 mg, 5.2 mmol) was dissolved in acetonitrile, together with $RuH_2(PPh_3)_4$, and acrolein **19** (347 µl, 5.2 mmol) was added to the solution. This reaction was left stirring at room temperature for 21 hours. The solvent was evaporated, and the product was columned with a PE/EA mixture in a 1:1 ratio.

An NMR could not be taken, due to the fact that the reaction did not produce any product.

13. 4,4-bis(phenylsulfonyl)butanal.



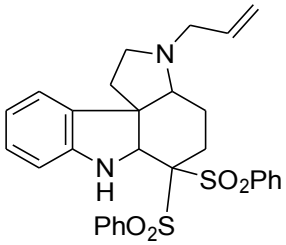
(21)

In a 50 ml roundbottom flask, equipped with a magnetic stirrer, bis-sulphonate **18** (296 mg, 1.0 mmol) and DBU (15 µl, 0.1 mmol) were dissolved in MeCN. Next, acrolein (67 µl, 1.0 mmol) was added dropwise. The reaction was left stirring for 1.5 hours at 25 ^{o}C, after whihch it was purified by column.

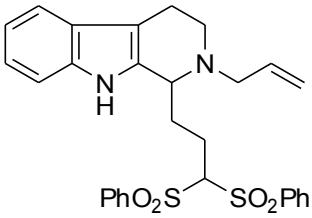
^{1}H-NMR:

2.47 (q, 2H, $CHOCH_2C\mathit{H}_2CHR_2$), 6.3 Hz; 3.02 (t, 2 H, $CHOC\mathit{H}_2CH_2CHR_2$), 6.9 Hz; 4.69 (t, 1H, $C\mathit{H}R_2CH_2CH_2$), 6.3 Hz; 7.28-7.72 (m, 10H, aromatic protons); 9.73 (s, 1H, $C\mathit{H}OCH_2CH_2$)

14. 3-allyl-6,6-bis(phenylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole (23).



(23)



(23a)

In a 50 ml roundbottom flask, equipped with a magnetic stirrer, compounds **21** (106 mg, 0.30 mmol) and **7** (60 mg, 0.30 mmol) were dissolved in dry toluene (dried over mol. sieves, 4Å), together with the CF_3-catalyst (23 mg, 10 mol%) also used in *procedure 3*, and described in scheme 3 of this report. The reaction mixture was flushed with N_2, and was then heated to 70 °C for 21 hours while stirring.

The mixture was then filtered over celite and washed well with EA. The solvent was evaporated, and the product was columned with PE/EA 1:1 as eluent.

^{1}H-NMR:

1.72 ('q', 2H, NCH*CH*$_2$CH$_2$CHR$_2$); 2.34 (q, 2H, NCH CH$_2$*CH*$_2$CHR$_2$), 3.5, 5.6 Hz; 2.80 (m, 2H, NCH$_2$CH$_2$C); 3.15 (t, 2H, N*CH*$_2$CHCH$_2$); 3.27 (dd, 1H, NC*H*CH$_2$CH$_2$); 4.74 (t, 1H, NC*H*CH$_2$CH$_2$); 5.18 (q, 2H, NCH$_2$CHC*HH*) (cis and trans), 4.1, 9.2 Hz; 5.77 (m, 1H, NCH$_2$C*H*CHH); 7.14-8.06 (m, 14H, aromatic protons in indole- and sulphone-groups)

Note: This spectrum is not assigned to the desired product, but to product ***23a.***

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