THE APPLICATION OF THE TITANIUM-CATALYZED HYDROAMINATION OF ALKYNES TOWARD THE SYNTHESIS OF BENZYLISOQUINOLINE DERIVATIVES

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THE APPLICATION OF THE TITANIUM-CATALYZED HYDROAMINATION OF ALKYNES TOWARD THE SYNTHESIS OF BENZYLISOQUINOLINE DERIVATIVES

Referent:	Prof. Dr. S. Doye
Koreferent:	Prof. Dr. J. Blümel
Tag der mündlichen Prüfung:	26.05.2006

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfsmittel durchgeführt habe. Zudem erkläre ich, dass ich an keiner anderen Stelle die Promotionsprüfung beantragt habe.

Heidelberg, den 22.05.2006

ABSTRACT

The enantioselective synthesis of (+)-(*S*)-laudanosine (**101**) and (–)-(*S*)-xylopinine (**102**) were achieved successfully in 7 steps from commercially available homoveratylamine (**86**) in 62% and 51% yield, respectively. The key intermediate aminoalkyne **123** was accessed easily by coupling aryl iodide **115** and alkyne **121** using a Sonogashira reaction. Dihydroisoquinoline **124** was obtained by intramolecular hydroamination of the aminoalkyne **123**. Employing Noyori´s reduction protocol, the absolute configuration at C-1 of the benzylisoquinoline was introduced with 93% *ee*. Finally, methylation of norlaudanosine (**146**) by a reductive amination protocol afforded (+)-(*S*)-laudanosine (**101**). Alternatively, formation of the berberin-bridge using a Pictet-Spengler reaction afforded (–)-(*S*)-xylopinine (**102**).

The strategy was also applied to synthesize benzylisoquinolines with electron-deficient A-rings. 5-Trifluoromethyl-benzylisoquinoline (**174**) was successfully synthesized in 8 steps from commercially available 4-bromo-trifluorotoluene (**162**) in 20% yield. Both Sonogashira reaction and hydroamination gave the desired products in excellent yields. Moreover, 6,7-difluoro-benzylisoquinoline (**182**)**,** was synthesized following a similar route from commercially available *o*-bromo-benzoic acid (**175**) in 19% yield for the seven steps.

KURZZUSAMMENFASSUNG

Die enantioselektiven Synthesen von (+)-(*S*)-Laudanosin (**101**) und (–)-(*S*)-Xylopinin (**102**) wurden ausgehend von Homoveratrylamin (**86**) in 7 Stufen mit Ausbeuten von 62% und 51% erfolgreich durchgeführt. Das Aminoalkin **123** wurde leicht aus Aryliodid **144** und Alkin **121** durch die Sonogashira Kupplungsreaktion hergestellt. Das Dihydroisochinolin **124** wurde durch eine intramolekulare Hydroaminierung von Aminoalkin **123** erhalten. Die *S*-Konfiguration an C-1 wurde durch eine enantioselektive Reduktion des Imins **124** nach Noyori mit 93%-*ee* erhalten. Eine reduktive Aminierung des erhaltenen Norlaudanosins (**146**) lieferte schlichßlich (+)-(*S*)-Laudanosin (**101**). Herstellung der Berberin-Brücke durch eine Pictet-Spengler-Reaktion ergab (–)-(*S*)-Xylopinin (**102**).

Die Strategie wurde auch zur Synthese von Benzylisochinolinen mit einem elektronenarmen A-Ring verwendet. So wurde 5-Trifluormethylbenzylisochinolin (**174**) über 8 Stufen mit einer Ausbeute von 20% aus dem im Handel erhältlichen 4-Bromtrifluortoluol (**162**) erfolgreich synthetisiert. Die Schlüsselschritte, die Sonogashira-Reaktion und die Hydroaminierung, verliefen mit sehr guten Ausbeuten. Außerdem wurde 6,7-Difluorbenzylisochinolin (**182**) über 7 Stufen mit einer Ausbeute von 19% aus der im Handel erhältlichen *o*-Brombenzoesäure (**175**) synthetisiert.

To My Parents and My Family

ACKNOWLEDGMENT

First of all, I would like to thank Prof. Sven Doye for his excellent and patient supervision and also for the exciting research theme and his encouragements throughout the course of this work. Many thanks to Prof. Dr. Janet Blümel for his kind assumption of the co-reference. Special thanks to Prof. Dr. H. M. R. Hoffmann D. Sc. for the generous support. I also thank the DAAD for the scholarship since 2002. Many thanks to the former member of the Doye´s group: Holger Siebeneicher, Frauke Pohlki and Andreas Heutling for useful and pleasant discussions. I thank all my colleagues: Sven Riedel, Klaudia Marcseková, Carsten Müller, Michael Huwe, Nikola Gaidzik and Christian Loos in for their unfailing support and very good working conditions. Finally, I would like to thank my parents for their moral support and also my beloved wife, Dewi Meliati Agustini and our children, Nur Abdillah Ifhamuddin and Nur Atqiya Maulidia for their patience and support during my study in Hannover and Heidelberg.

CONTENTS:

I INTRODUCTION

1.1. HYDROAMINATION

Nitrogen-containing organic compounds are wide spread in nature and they are therefore of great importance for fundamental research and chemical industry. Many amines, enamines and imines have well-defined biological functions that are important and even essential for life. Many of them are also useful as pharmaceuticals, herbicides, fungicides and insecticides, as well as bulk and fine chemicals. With respect to industry, several hundred thousand tons of amines are produced worldwide per year.[1] The classical well-developed methods for their synthesis are the reduction of nitrogen-containing functionalities in higher oxidation states (e.g., reduction of nitriles, imines, azides, nitroso and nitro compounds), nucleophilic substitution of halogen atoms or other potential leaving groups at sp^3-carbons by ammonia and amines, the Ritter-reaction and reductive aminations of carbonyl compounds.[2] Among these methods, only the reductive amination is a highly atom efficient process, that applies versatile and inexpensive starting materials and produces a minimal amount of waste. Unfortunately, other mentioned, potentially useful processes such as the substitution at sp^3-carbons by nitrogen nucleophiles often lead to the formation of a mixture of products (primary, secondary and tertiary amines, quaternary ammonium salts).

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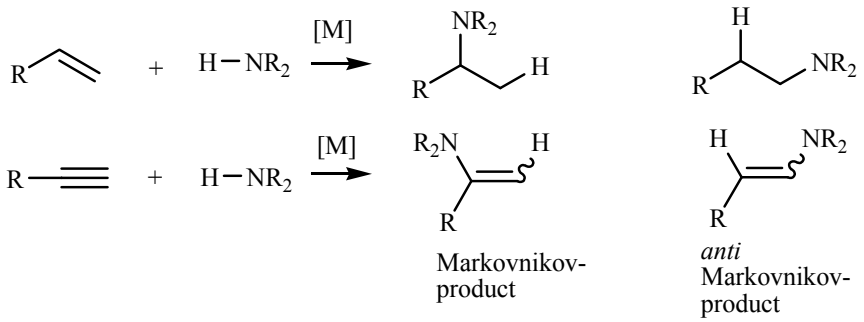
[1] G. Heilen, H. J. Mercker, D. Frank, R. A. Reck, R. Jäckh, *Ullmann´s Encyclopedia of Industrial Chemistry*, 5th ed., VCH, Weinheim, **1985**, vol. A2, p. 1–36.

[2] J. R. Malpass, *Comprehensive Organic Chemistry* (Eds.: D. Barton, W. D. Ollis), Pergamon Press, Oxford, **1979**, vol. 2, p. 1−59.

The hydroamination of alkenes and alkynes, which constitutes of a formal addition of an N-H bond across a carbon-carbon multiple bond (Scheme 1),[3] is a transformation of fundamental simplicity and would offer the most attractive route to numerous classes of organo-nitrogen molecules such as alkylated amines, enamines or imines. This fundamentally simple transformation proceeds with 100 % atom efficiency and without waste formation. It would offer environmental and economical benefits to chemical industry.



Scheme 1. Hydroamination of alkenes and alkynes.

Thermodynamic considerations indicate that the synthesis of alkylamines by direct addition of amines to alkenes is slightly exothermic or approximately thermoneutral.[4] The free energy for the addition of NH_3 to $H_2C{=}CH_2$ is estimated to be $\Delta G° \approx$ -15 kJ/mol. The hydroamination of alkynes is thermodynamically more favorable. The free energy for the addition of NH_3 to acetylene is estimated (AM1-semiempirical calculation) to be ~ 63 kJ/mol more exothermic than the addition to ethylene.[5] In general, nucleophilic attack of the amine nitrogen bearing the lone electron pair on the electron-rich nonactivated alkene leads to electrostatic repulsion. A [2 + 2] cycloaddition of N-H to the alkene would be an orbital symmetry-forbidden process and is unfavorable because of the high-energy difference between π (C=C) and σ (N-H). At higher temperatures, the reaction equilibrium is shifted toward the starting materials because of

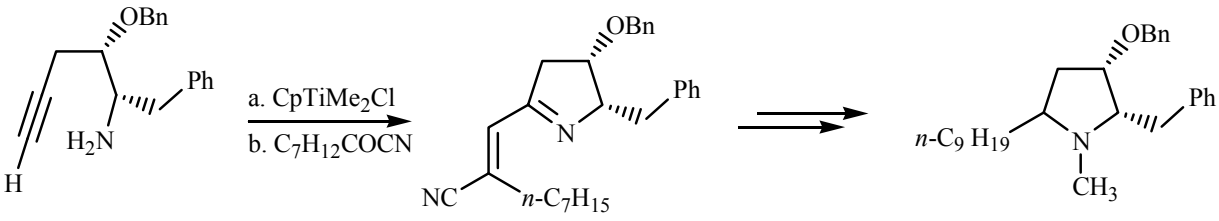
[3] a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675−703; b) E. Haak, S. Doye, *Chem. Unserer Zeit* **1999**, *33*, 296–303; c) M. Nobis, B. Drießen-Hölscher, *Angew. Chem.* **2001**, *40*, 3983–3985; d) F. Pohlki, S. Doye, *Chem. Soc. Rev.* **2003**, *32*, 104−114; e) M. Beller, A. Tillack, J. Seayed, in: *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), 2nd ed., VCH, Weinheim, **2004**, vol. 2, p. 403–414; f) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159.
[4] D. M. Roundhill, *Chem. Rev.* **1992**, *92*, 1–27.
[5] T. Straub, A. Haskel, T. G. Neyroud, M. Kapon, M. Botoshansky, M. S. Eisen, *Organometallics* **2001**, *20*, 5017−5035.

a highly negative reaction entropy. However, amines will undergo direct nucleophilic addition to a carbon-carbon triple bond if the π-system is electron-deficient (e.g., in perfluoroalkynes) or activated by neighboring functional groups (e.g., OR, COR, COOR, C≡CH).[3]

The hydroamination can be assisted or catalyzed by alkali metal ions,[6] transition metal[7] or lanthanide complexes,[8] which allow the processes to be performed under milder conditions. Corresponding hydroaminations have been extensively used for the generation of small libraries of various classes of biological interesting compounds. Hydroamination reactions have also been applied to synthesize natural products.

1.1.1. HYDROAMINATION IN NATURAL PRODUCTS SYNTHESIS

The regioselective titanium promoted intramolecular addition of amines to alkynes has been applied to the total synthesis of the antifungal agent (+)-preussin (**1**),[9] which contains a central pyrrolidine ring. The key step of the synthesis is the cyclization of a 1-amino-4-alkyne. The 1-amino-4-alkyne **2** was cyclized in the presence of a stoichiometric amount of $CpTiMe_2Cl$. Subsequently, the octyl side chain was introduced by quenching the intermediate azatitanacyclobutene with octanoyl cyanide to yield **3**. Two further steps led to (+)-preussin (**1**) in 33-44% overall yield from aminoalkyne **2**.

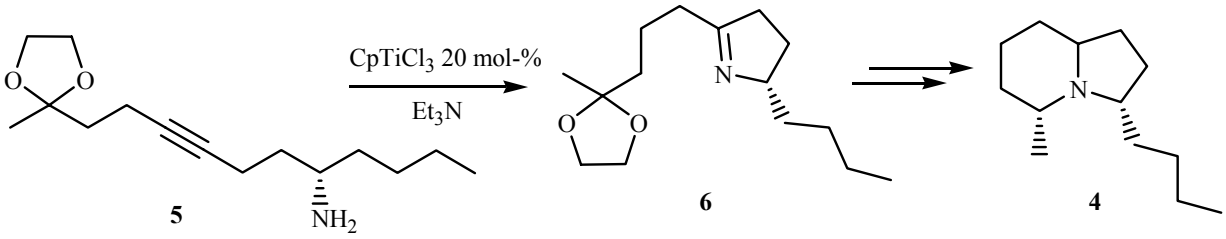


2 **3** **1**

Scheme 2. The total synthesis of (+)-preussin (**1**) by Livinghouse et. al.

[6] For reviews on base catalyzed hydroamination, see: J. Seayad, A. Tillack, C. G. Hartung, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 795−813.
[7] For a review on Group 4 complexes as hydroamination catalysts, see: I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2003**, 935–946.
[8] For review on organolathanide complexes as hydroamination catalyst, see: S. Hong, T. J. Marks, *Acc. Chem. Res.* **2004**, *37*, 673–689.
[9] P. L. McGrane, T. Livinghouse, *J. Am. Chem. Soc.* **1993**, *115*, 11485–11489.

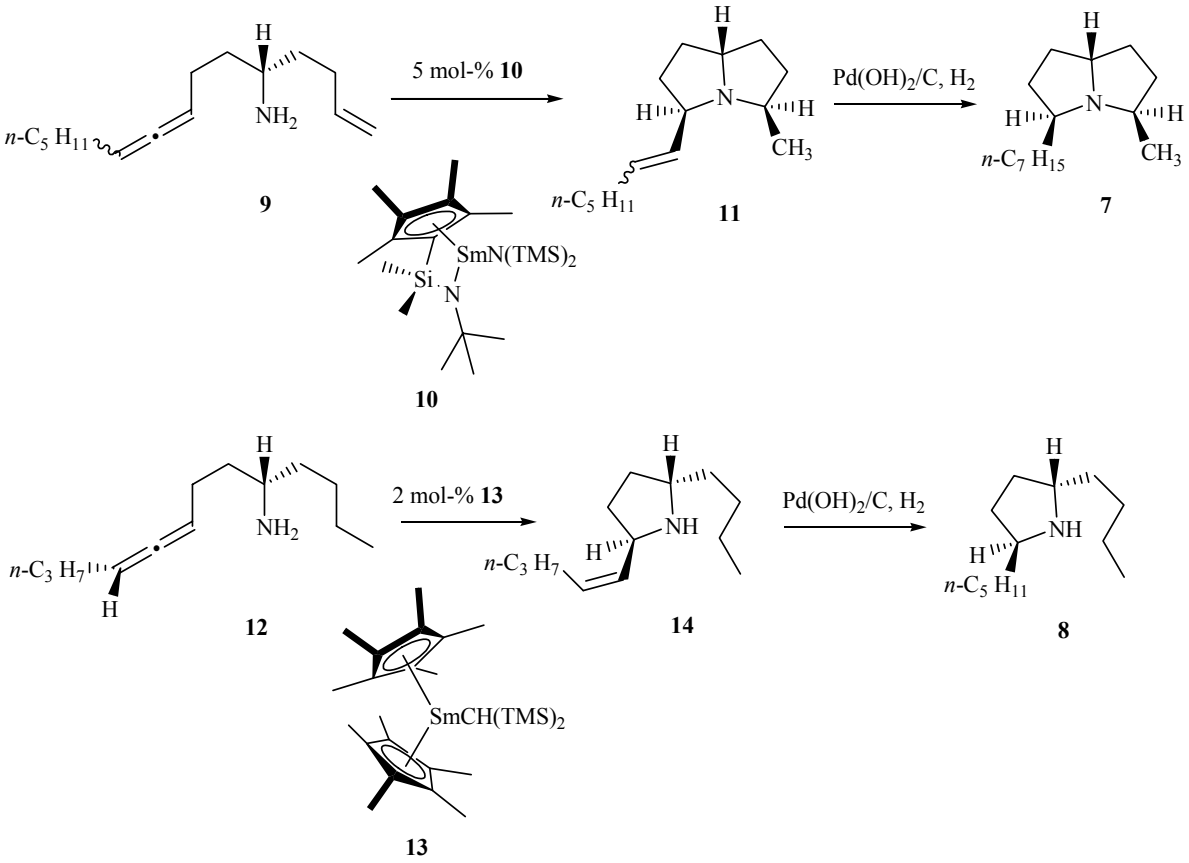
A titanium-catalyzed hydroamination reaction was utilized in the total synthesis of (±)-monomorine (**4**).[10] The key intermediate, γ-amino alkyne **5**, was cyclized with $CpTiCl_3$ (20 mol-%) in 93% yield and four further steps converted Δ^1- pyrroline **6** to (±)-monomorine (**4**) in 53% overall yield.



Scheme 3. The total synthesis of (±)-monomorine (**4**) by Livinghouse et. al.

The efficiency and high diastereoselectivity of organolantanide-catalyzed hydroaminations/cyclizations of aminoallenes were highlighted by Marks et.al.[11] in the total synthesis of (+)-xenovenine (**7**), isolated from *Solenopsis xenoveneum*, and pyrrolidine 197B (**8**), which was detected in a skin extract of *Dendrobates histonicus*. The constrained geometric organolantanide complex $Me_2Si(Me_4C_5)$(*t*-Bu-N)$SmN(TMS)_2$ (**10)** efficiently catalyzed the stereoselective tandem bicyclization of acyclic compound **9** to the bicyclic pyrrolizidine intermediate **11** under mild conditions. Following reduction of the unsaturation using hydrogen in the presence of $Pd(OH)_2/C$, (+)-xenovenine (**7**) was furnished in 78% yield (two steps). In the synthesis of pyrrolidine 197B (**8**), the catalytic ring closure of aminoallene **12** was effected by $Cp^*_2SmCH(TMS)_2$ (**13)** in pentane solution at 23°C, yielding the expected *trans*-pyrrolidine bearing an carbon-carbon double bond **14** with excellent *Z*-selectivity. Hydrogenation led to pyrrolidine 197B (**8**) in 88% yield (two steps).

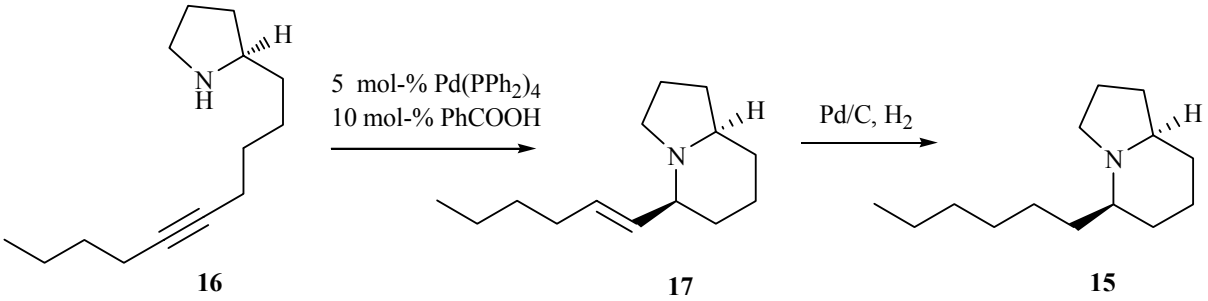
[10] P. L. McGrane, T. Livinghouse, *J. Org. Chem.* **1992**, *57*, 1323–1324.
[11] V. M. Arredondo, S. Tian, F. E. McDonald, T. J. Marks, *J. Am. Chem. Soc.* **1999**, *121*, 3633–3639.



Scheme 4. The total synthesis of (+)-xenovenine (**7**) and (+)-pyrrolidine (**8**) by Marks et. al.

Indolizidine alkaloids, isolated from the skin secretion of certain neotropical frogs, represent a class of pharmacologically important compounds. Yamamoto et. al.[12] has applied the Pd(0)/benzoic acid catalyzed intramolecular hydroamination of alkynes to synthesize indolizidine 209D (**15**). This structurally simple example of an indolizidine alkaloid acts as a noncompetitive blocker of neuromuscular transmission. The ε-amino alkyne **16** was treated with 5 mol-% $Pd(PPh_3)_4$ and 10 mol-% benzoic acid and Et_3N (2 equiv) in 1,4-dioxane at 100°C for 12 h to give one diastereoisomer of indolizidine **17** in 74% yield. Hydrogenation of **17** smoothly gave indolizidine(–)-209D (**15**) in 85% yield.

[12] N. T. Patil, N. K. Pahadi, Y. Yamamoto, *Tetrahedron Lett.* **2005**, *46*, 2101–2103.



16 **17** **15**

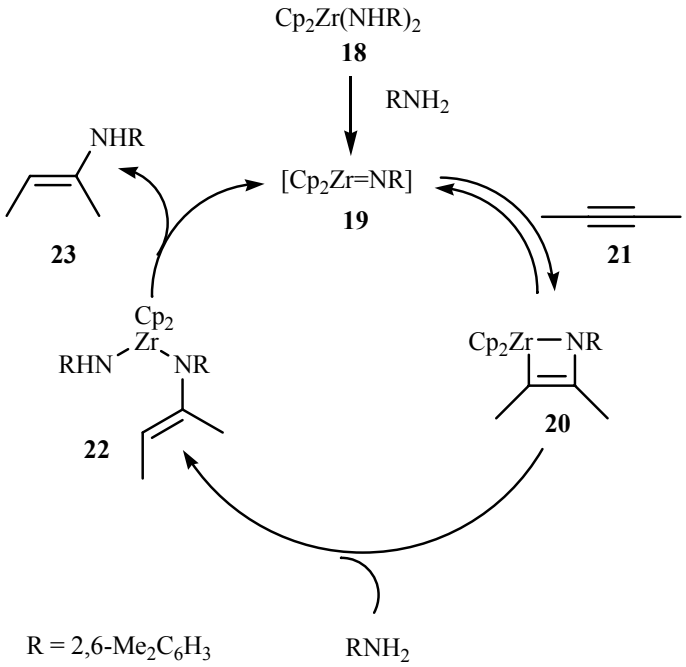
Scheme 5. The total synthesis of (–)-indolizidine 209D (**15**) by Yamamoto et.al.

1.1.2. TITANIUM-CATALYZED HYDROAMINATION

Catalysis based on titanium complexes in the filed of hydroamination has significant advantages compared to processes which are based on toxic (Hg, Tl) or more expensive metals (Ru, Rh, Pd, U, Th).[3a,3f] Inspired by a study on the zirconium-catalyzed hydroamination of alkynes by Bergman et. al.[13] and the fact that the titanium-catalyzed intramolecular hydroamination reaction has already been reported by the Livinghouse group,[9,10,14] Doye et. al. developed a general method for the catalytic intermolecular hydroamination of alkynes.[15]

As suggested by Bergman, the catalytic-cycle of the Zr-catalyzed hydroamination of alkynes,[13] involves the catalytically active Zr-imido complex **19**, which is formed at a temperature above 85°C from the catalyst precursor **18** by reversible and rate determining α-elimination of the sterically demanding amine. The imido complex **19** then undergoes a reversible [2+2]cycloaddition with the employed alkyne **21** yielding an azazirconacyclobutene **20**. Rapid protonation of the Zr-C bond by excess amine gives the bisamide **22**, which finally undergoes α-elimination of the enamine product **23** generating the catalytically active species **19** (Scheme 6).

[13] P. J. Walsh, A. M. Baranger, R. G. Bergman, *J. Am. Chem. Soc*. **1992**, *114*, 1708–1719; b) A. M. Baranger, P. J. Walsh, R. G. Bergman, *J. Am. Chem. Soc*. **1993**, *115*, 2753–2763.
[14] P. L. McGrane, M. Jensen, T. Livinghouse, *J. Am. Chem. Soc.* **1992**, *114*, 5459–4560.
[15] For an account, see: S. Doye, *Synlett* **2004**, 1653–1672.



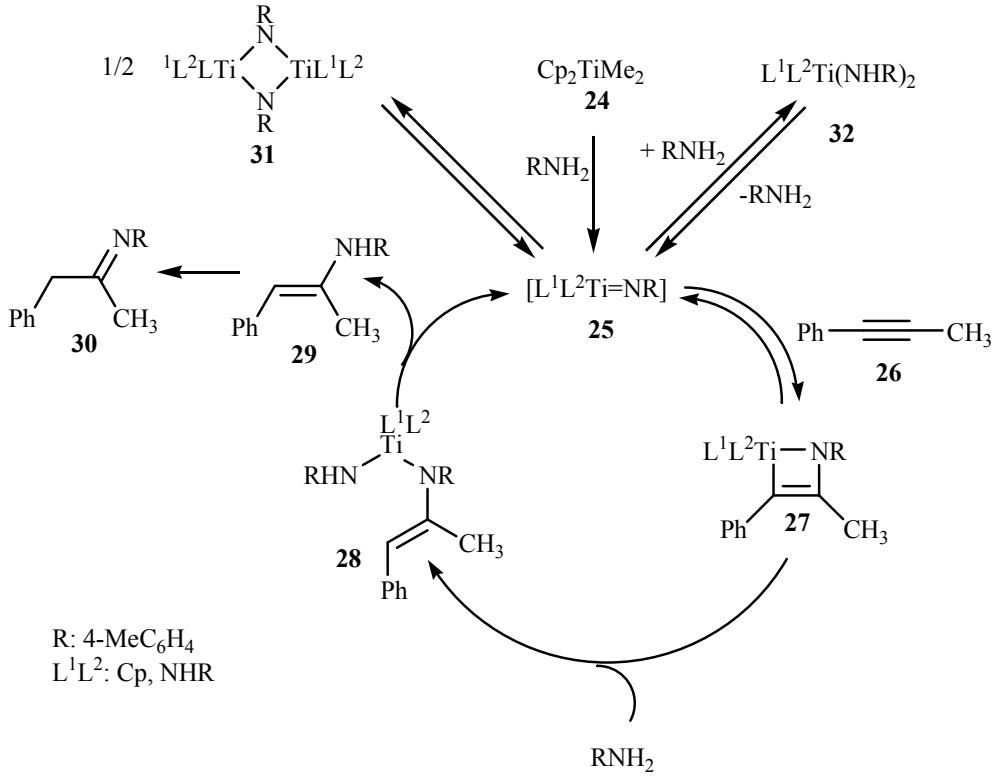
Scheme 6. Mechanism of the Zr-catalyzed hydroamination suggested by Bergman.

Doye´s strategie to improve the Bergman catalytic cycle, which was limited to the use of 2,6-dimethylaniline, was to make sure that the equilibrium between complex **19** and the corresponding bisamide **18** is on the side of the imido complex **19** and to avoid the dimerization of the imido complex **19** to form a catalytically inactive dimer, if the amine is smaller than 2,6-dimethylamine. The first improvement should undoubtly result in increased reaction rates and should also avoid the inhibition of the catalytic reaction by the amine starting material. The second improvement should secure the possible use of the catalytic cycle for reactions of any amine.

Doye´s group reported that Cp_2TiMe_2 (**24**) is a very efficient catalyst for the intermolecular hydroamination on alkynes.[16] By using Cp_2TiMe_2 (**24**) as catalyst, primary aryl amines, *t*-alkyl and *sec*-alkyl amines can be reacted with alkynes in high yields. The reactions occurred with high regioselectivity for unsymmetricly substituted

[16] A) E. Haak, I. Bytschkov, S. Doye, *Angew. Chem.* **1999**, *111*, 3584–3586; b) E. Haak, H. Siebeneicher, S. Doye, *Org. Lett.* **2000**, *2*, 1935–1937.

alkynes. Cp_2TiMe_2 also catalyzed intramolecular hydroaminations/ cyclyzations of amino alkynes.[17] Unfortunately, *n*-alkyl- and benzyl amines are poor substrates for the Cp_2TiMe_2 catalyzed intermolecular hydroamination. It has also been observed that the hydroamination step was responsible for a partial racemization if enantiometrically pure amines were employed.[18]



Scheme 7. Mechanism of Cp_2TiMe_2 catalyzed hydroamination.

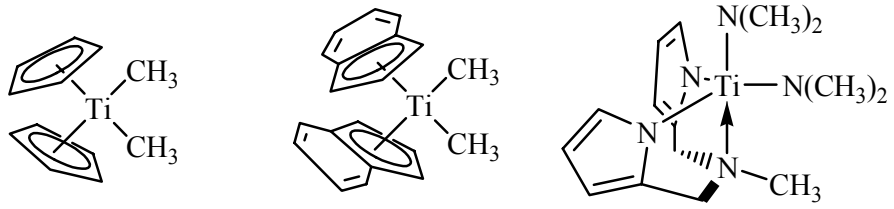
According to a kinetic study,[19] the catalytic cycle includes a reversible dimerization of the catalytically active imido complex **25** and a reversible addition of the amine to **25** yielding the bisamide **32**. The equilibrium between the catalytically active imido complex **25** and the bisamide **32** is far on the side of **32** and not on the side of the imido complex **25** (see scheme 7). DFT calculations by Bergmann and Straub[20] strongly

[17] I. Bytschkov, S. Doye, *Tetrahedron Lett.* **2002**, *43*, 3715–3718.
[18] F. Pohlki, I. Bytschkov, H. Siebeneicher, A. Heutling, W. A. König, S. Doye, *Eur. J. Org. Chem.* **2004**, 1967–1972.
[19] F. Pohlki, S. Doye, *Angew. Chem.* **2001**, *113*, 2361–2364.
[20] B. F. Straub, R. G. Bergman, *Angew. Chem.* **2001**, *113*, 4768–4771.

support this interpretation of the kinetic study. It was found that using Cp_2TiMe_2 as catalyst precursor obviously did not avoid the dimerization of the catalytically active imido complex.

To reach the targets, Doye applied then a bigger ligand than cyclopentadienyl (Cp). Using $Cp^*_2TiMe_2$ as catalyst, hydroamination reactions between *n*-alkyl-, or benzylamines and alkynes took place to give the desired products, unfortunately, with low regioselectivities, when unsymmetrically substituted 1-aryl-2-alkylalkynes were employed.[21]

After a screening of hydroamination catalysts based on Ti-complexes,[22] Doye´s group found that Ind_2TiMe_2 (**33**) catalyzed the intermolecular hydroamination of internal and terminal alkynes with primary-aryl-, *t*-alkyl-, *sec*-alkyl-, *n*-alkylamines, and even benzylamines with modest to excellent regioselectivity. Using Ind_2TiMe_2 (**33**) as a catalyst no dimerization of the catalytically active imido complex was observed. Ind_2TiMe_2 (**33**) could be claimed as the first general catalyst with improved activity that can be used efficiently for all substrate combinations in intermolecular hydroamination reaction.[23]



24 **33** **34**

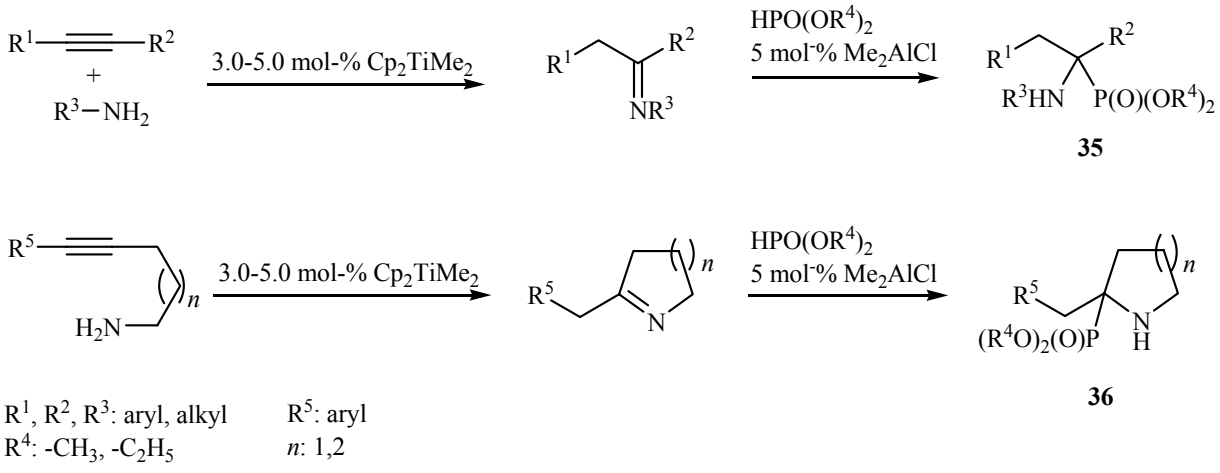
Figure 1. Titanium complexes which have already been used as catalysts of hydroamination reaction.

[21] A. Heutling, S. Doye, *J. Org. Chem.* **2002**, *67*, 1961–1964.
[22] F. Pohlki, A. Heutling, I. Bytschkov, T. Hotopp, S. Doye, *Synlett* **2002**, 799–801.
[23] A. Heutling, F. Pohlki, S. Doye, *Chem. Eur. J.* **2004**, *10*, 3059–3071.

Titanium-catalyzed hydroaminations of alkynes are not only limited to metallocene or Cp-based systems. Odom et. al.[24] reported that even the simple complex $Ti(NMe_2)_4$ could be applied as precatalyst for the hydroamination of alkynes. The new Ti-pyrrolyl complex $Ti(NMe_2)_2$(dmpa) (**34**) which can be generated from $Ti(NMe_2)_4$ and di-(pirrolyl-α-methyl)methylamine (H_2-dmpa) catalyzed also hydroamination reactions of alkynes. This catalyst, having a bulky ancillary ligand, was more efficient and selective than $Ti(NMe_2)_4$ in hydroaminations with aliphatic and aromatic amines. Using this catalyst, new methods for the synthesis of imines, hydrazones, *α,β*-unsaturated imines, pyridines, indoles and pyrroles have been developed.[25]

1.1.3. TITANIUM-CATALYZED HYDROAMINATIONS USED FOR SYNTHESIS OF BIOLOGICALLY INTERESTING COMPOUNDS.

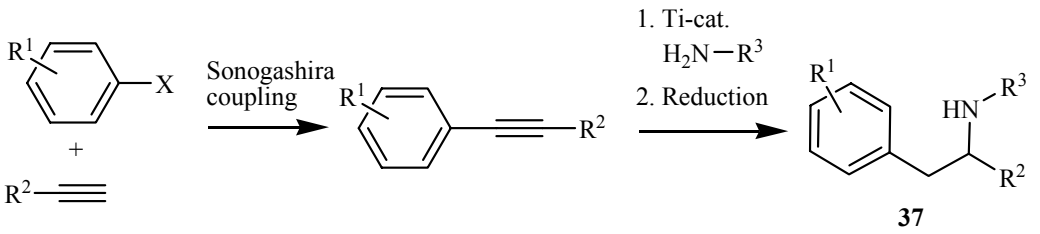
Titanium catalyzed hydroaminations of the alkynes and a subsequent Lewis-acid catalyzed nucleophilic addition of diethyl- or dimethyl-phosphite have been applied to a one-pot procedure for the synthesis of α-amino phosphonic acid derivatives **(35** and **36**).[26] Using this method, both acyclic and cyclic α-amino phophonates could be easy synthesized.



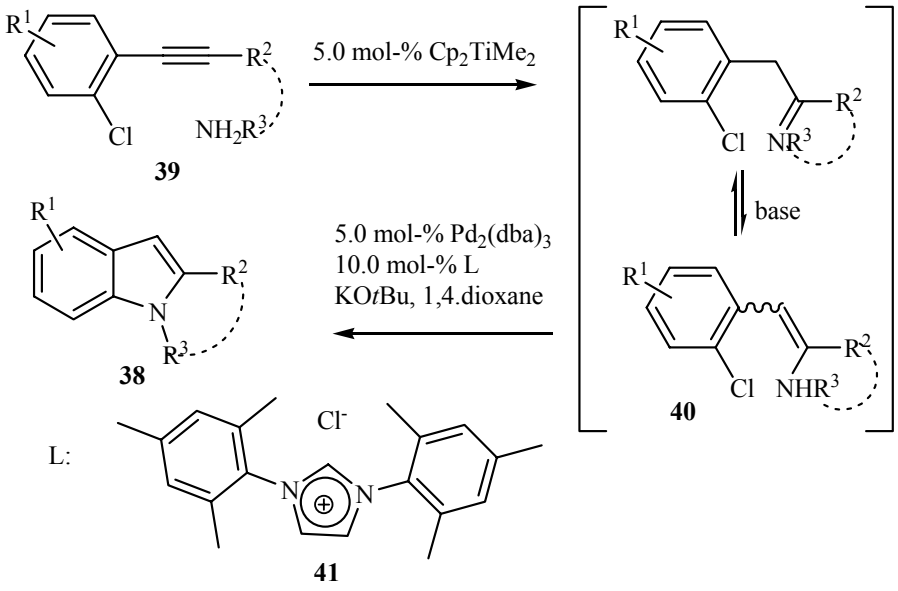
Scheme 8. Synthesis of α-amino phosphonate derivatives.

[24] a) Y. Shi, J. T. Ciszewski, A. L. Odom, *Organometallics* **2001**, *20*, 3967–3969; b) Y. Shi, J. T. Ciszewski, A. L. Odom, *Organometallics* **2002**, *21*, 5148–5148.
[25] Recent resume of Odom´s works, see: A. L. Odom, *Dalton Trans.* **2005**, 225–233.
[26] E. Haak, I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2002**, 457–463.

A highly flexible procedure to synthesize 2-arylethylamine derivatives (**37**) has also been developed involving a Ti-catalyzed hydroamination.[27] The reaction starts with a Pd-catalyzed coupling between an aryl halide and a terminal alkyne (Sonogashira reaction). A subsequent regioselective Ti-catalyzed hydroamination of the alkynes, followed by a final reduction of the obtained imines gave 2-arylethylamines in good to excellent yields. From a mathematical point of view, 20 aryl halide, 20 terminal alkynes and 20 primary amines could be converted into 8000 different 2-arylethylamine derivatives by the synthetic approach.



Scheme 9. Synthesis of 2-arylethylamine.

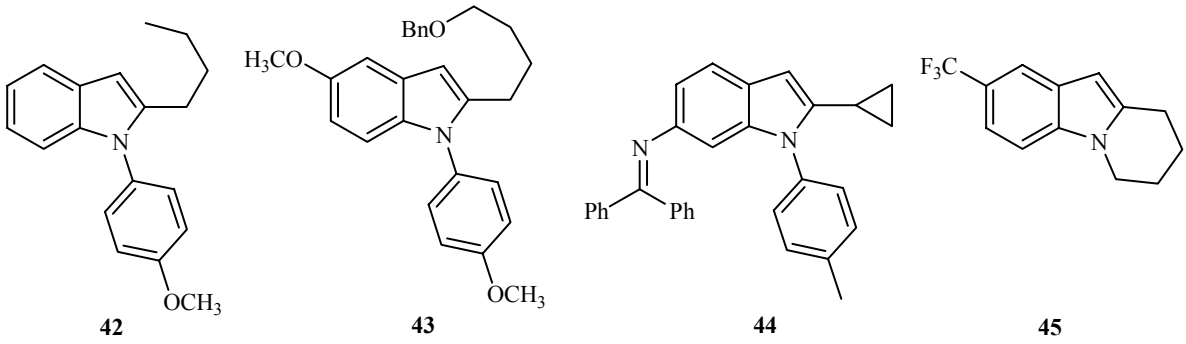


R^3: *t*-Bu-, *p*-Tol, 4-$MeOC_6H_4$, *rac*-CH(Ph)Me

Scheme 10. The one pot procedure of synthesis of indole derivatives by Doye.

[27] a) H. Siebeneicher, S. Doye, *Eur. J. Org. Chem.* **2002**, 1213–1220; b) A. Heutling, R. Severin, S. Doye, *Synthesis*, **2005**, 1200–1204.

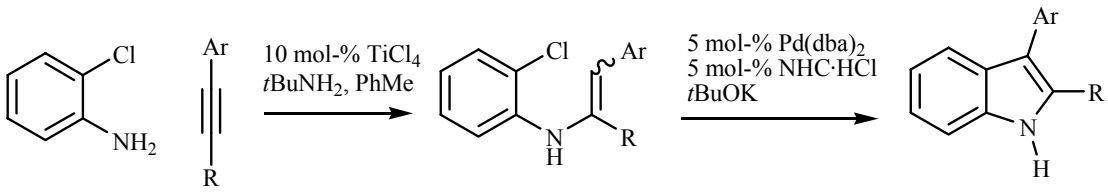
Doye et. al. demonstrated a combination of a Titanium-catalyzed hydroamination and a subsequent Palladium-catalyzed Buchwald-Hartwig reaction in one-pot to give 1,2-; 1,2,5- and 1,2,6-substituted indoles (e.g.: **42**, **43**, **44** respectively) in good yields. This procedure offers a great deal of synthetic flexibility, since the employed starting materials are easily accessible from 1-chloro-2-iodobenzenes and terminal alkynes by Sonogashira coupling reactions.[28]



42 **43** **44** **45**

Figure 2. Several indoles synthesized applying Doye´s procedure.

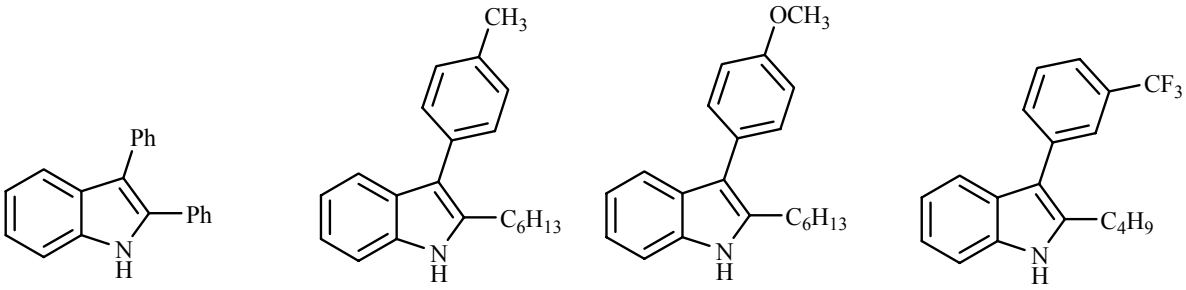
Ackermann et.al. has also achieved a one-pot indole synthesis consisting of a highly regioselective $TiCl_4$-catalyzed hydroamination and a 5-*endo* Heck cyclization.[29] The reaction between an internal alkyne and 2-chloroaniline (**47**) in the presence of $TiCl_4$ and *t*$BuNH_2$ at 105°C leads to an enamine **49**. After the addition of $Pd(OAc)_2$, an *N*-heterocyclic carbene (NHC) ligand and *t*BuOK, the 2,3-disubstituted indoles **46** were obtained with complementary regiosectivity of Larock´s annulations indole products.[30]



47 **48** **49** **46**

Scheme 11. The one pot procedure of synthesis of indoline derivatives by Ackermann.

[28] H. Siebeneicher, I. Bytschkov, S. Doye, *Angew. Chem.* **2003**, *115*, 3151–3153.
[29] L. Ackermann, L. T. Kaspar, C. J. Gschrei, *Chem. Comm.* **2004**, 2824–2825.
[30] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652-7662.



50 **51** **52** **53**

Figure 3. Several 2,3-substituted indoles synthesized applying Ackermann procedure.

1.2. BENZYLISOQUINOLINE ALKALOIDS

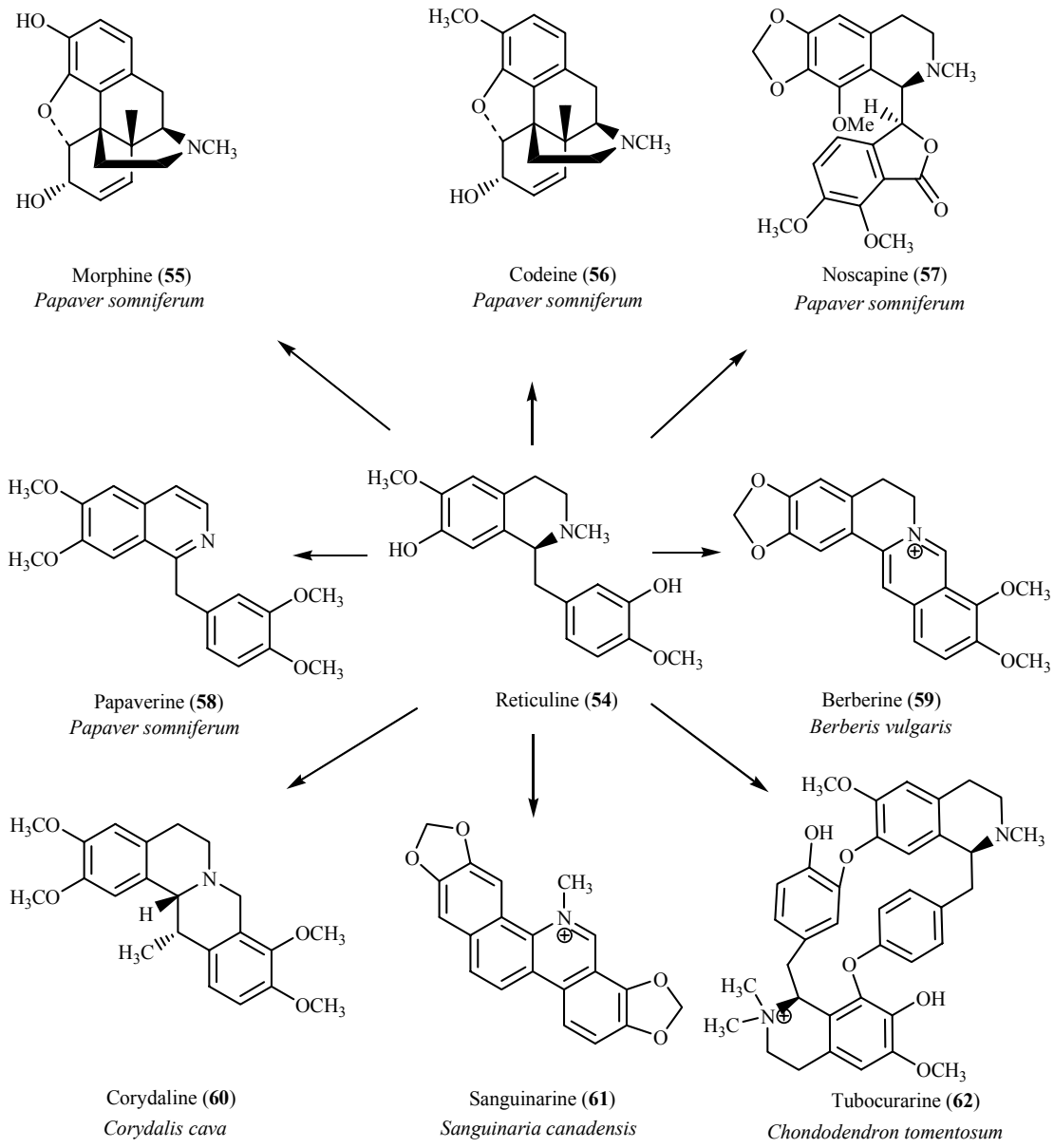
Benzylisoquinoline alkaloids are a large and diverse group of secondary metabolites found mainly in five related plant families, including *Papaveraceae* and *Ranunculaceae*, with more than 2500 defined structures. Several benzylisoquinoline alkaloids play important ecophysiological roles in the interaction between plants and other organisms, especially pathogens and herbivores. The pharmacological activity of benzylisoquinoline alkaloids renders many of them useful as pharmaceuticals and is often a clue to their biological role in the plant.

1.2.1. USES OF BENZYLISOQUINOLINE ALKALOIDS

The benzylisoquinoline class of alkaloids contains such varied physiologically active members of opium alkaloids as the narcotic analgesic morphine (**55**), the antitussive and narcotic codeine (**56**), the antitussive noscapine (**57**), and the vasodilator papaverine (**58**).[31] The antibacterial berberine (**59**) is used in treatment of eye and intestinal infection. The form of an extract of *Carydalis cava* contains the sedative corydaline (**60**). The form of an extract from *Sanguinaria canadenses* that is used in a toothpaste and oral rinse additive contains the antibacterial sanguinarine (**61**). Tubocurarine (**62**), a non-depolarizing muscle relaxant, is used as an adjuvant to anesthesia to produce temporary paralysis from *Chondodendron tomentosum*. From the collection of pharmaceuticals, only papaverine (**58**) is synthetically produced for industrial uses. The remaining alkaloids presented (see scheme 12) are either purified from plants or are used

[31] For review of opium alkaloids, see: P. L. Schiff Jr., *Am. J. Pharm. Educ.* **2002**, *66*, 186–194.

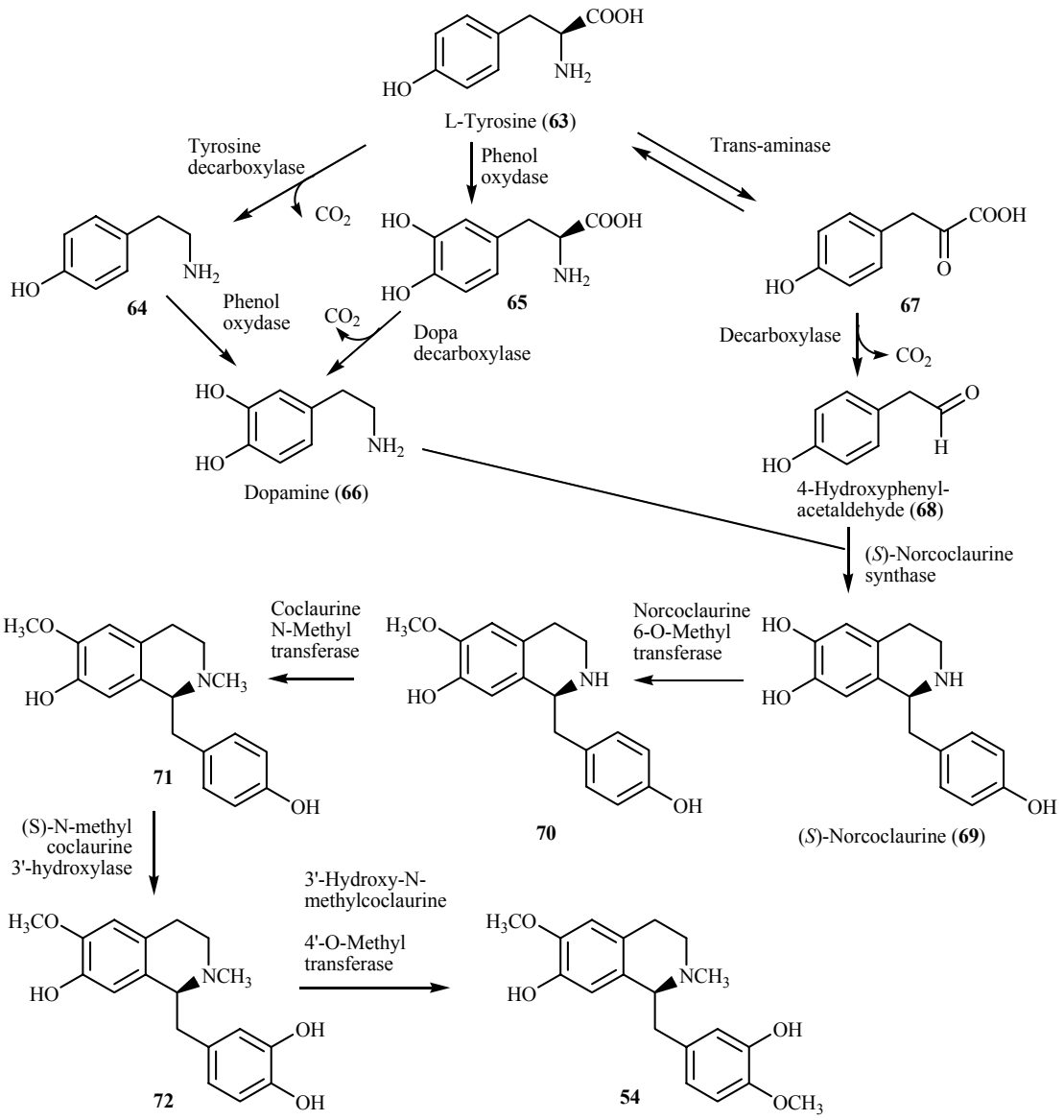
in the form of a crude extract. All of these industrially useful natural products are biosynthetically intermediated by (*S*)-reticuline **(54)**.[32]



Scheme 12. Pharmaceutically useful alkaloid derivatives formed from the benzylisoquinoline alkaloid (*S*)-reticuline (**54**).

[32] For review, see: T. M. Kutchan, in: *The Alkaloids: Chemistry and Biology* (Eds.: G. A. Cordell), Academic Press, San Diego, **1998**, vol. 50, 258–316.

1.2.2. BIOSYNTHESIS OF BENZYLISOQUINOLINE ALKALOIDS



Scheme 13. Biosynthetic pathway leading to (*S*)-reticuline (**54**).

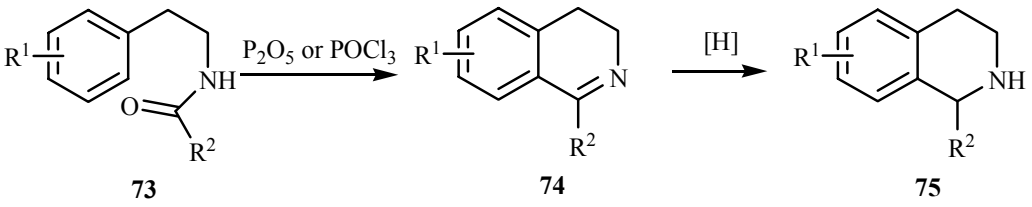
All benzylisoquinoline alkaloids share a common biosynthetic origin beginning with a lattice of decarboxylations, *o*-hydroxylations, and deaminations that convert L-tyrosine

(**63**) into both dopamine (**66**) and 4-hydroxyphenyl acetaldehyde (**68**).[33] The first committed step in benzylisoquinoline alkaloid biosynthesis is catalyzed by (*S*)-norcoclaurine synthase, which condenses dopamine (**66**) and 4-hydroxyphenylacetaldehyde (**68**) to form the trihydroxylated alkaloid (*S*)-norcoclaurine (**69**) (see scheme 13).[34] Sequential 6-*O*-methylation of (*S*)-norcoclaurine (**69**), followed by *N*-methylation, a P450-dependent 3' hydroxylation, and subsequent 4'-*O*-methylation lead to the formation of (*S*)-reticuline **(54)**, an important branch-point intermediate in benzylisoquinoline alkaloid biosynthesis.[35] Major strides have been made in the elucidation of the enzymatic synthesis of tetrahydrobenzylisoquinoline alkaloids due in large part to the use of plant cell suspension cultures that have been optimized for the production of selected alkaloids.

1.2.3. SYNTHESIS OF ISOQUINOLINE DERIVATIVES.

The frequent occurrence of the isoquinoline nucleus in alkaloids has led to considerable interest in the synthesis of isoquinoline derivatives. The traditional and classical methods (Bischler-Napieralski-, Pictet-Spengler- and Pommeranz-Fritsch cyclization) have been modified to asymmetric synthesis.[36]

BISCHLER-NAPIERALSKI CYCLIZATION/REDUCTION

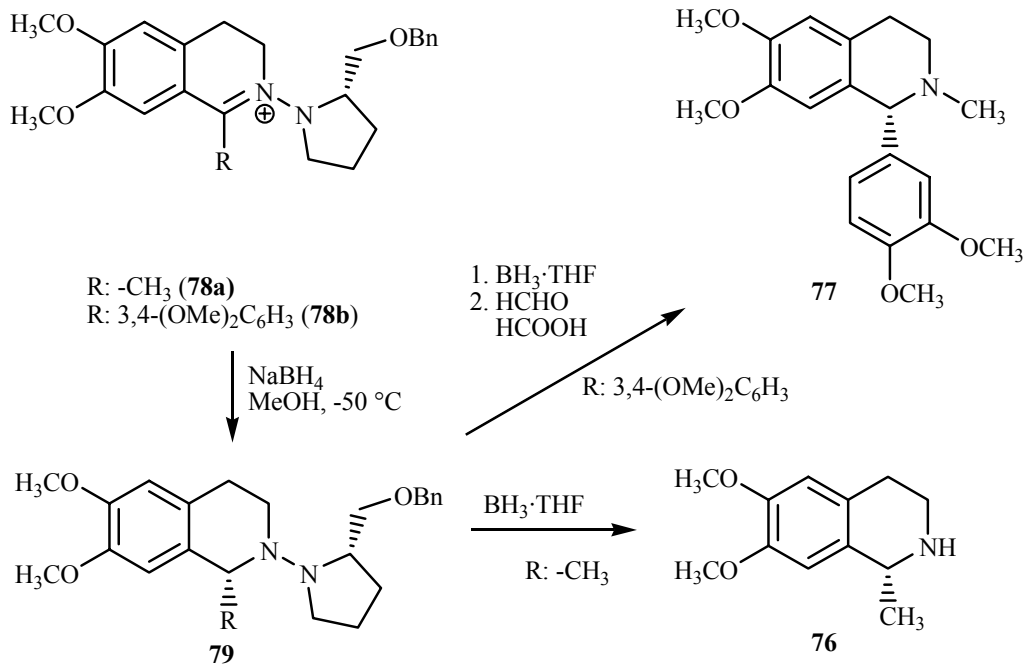


73 **74** **75**

Scheme 14. Bischler-Napieralski Cyclization/Reduction.

[33] a. M. Rueffer, M. H. Zenk, *Z. Naturforsch.* **1987**, *42*, 319–332; b. N. Samanani, P.J. Facchini, *J. Biol. Chem.* **2002**, *277*, 33878-33883..
[34] a) R. Stadler, T. M. Kutchan, S. Löffler, N. Nagakura, B. K. Cassels, M. H. Zenk, *Tetrahedron Lett.* **1987**, *28*, 1251–1254; b) R. Stadler, T. M. Kutchan, M. H. Zenk, *Phytochemistry* **1989**, *28*, 1083–1086.
[35] For recent review: P. J. Facchini, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **2001,** *52*, 29–66.
[36] For reviews, see: M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004,** *104,* 3341–3370.

The Bischler-Napieralski reaction involves the cyclization of phenylethyl amides (**73**) in the presence of dehydrating agents such as P_2O_5 or $POCl_3$ to afford 3,4-dihydroisoquinoline products (**74**).[37] Since the yields are very poor under the conditions original described for the reaction, modifications using lower temperature and milder condensing agents has improved the reaction.[38] Reduction of the imines **74** yields tetrahydroisoquinoline derivatives (**75**). The stereochemical outcome of the sequential Bischer-Napieralski cyclization/reduction can be determined in the reduction process either by diastereoselective or enantioselective methods.



Scheme 15. The synthesis of (+)-(*R*)-salsolidine (**76**) and (–)-(*R*)-cryptostyline II (**77**) by Kibayashi et.al.

Numerous modifications of this reaction sequence have been reported.[35] In one of them, Kibayashi et. al.[39] used dihydroisoquinoline salts **78a** and **78b** containing a chiral hydrazonium functionality in the synthesis of (+)-(*R*)-salsolidine (**76**) and (–)-(*R*)-cryptostyline II (**77**). Reduction of **78a** and **78b** employing sodium borohydride as well

[37] A. Bischler, B. Napieralski, *Ber.* **1893**, *26*, 1903–1908.
[38] W. M. Whaley, T. R. Govindachari, in: *Organic Reaction* (ed.: R. Adams), John Wiley & Sons, London, **1951**, vol. VI, 74–150.
[39] H. Suzuki, S. Aoyagi, C. Kibayashi, *Tetrahedron Lett.* **1995**, *36*, 6709–6712.

as other metal hydride reagents resulted in the formation of tetrahydroisoquinolines with excellent diastereoselectivities (90-96% *de*). Reductive N-N bond cleavage converted **79** into the alkaloids (+)-(*R*)-**76** and (–)-(*R*)-**77**, respectively. The efficiency of the asymmetric induction was postulated to arise from the pyramidal stability of the pyrrolidine sp^3-hybridized nitrogen atom and hydride-ion approach to the imine double bond from the sterically less shielded side.[40]

Enantioselective synthesis of isoquinoline alkaloids according to a Bischler-Napieralski cyclization/reduction approach is based on an enantioselective reduction of prochiral 3,4-dihydroisoquinolines. For this purpose chiral hydride reducing agents or chiral hydrogenation-catalysts are used to introduce the desired chiral centers. Excellent results have been described by Buchwald and Willoughby,[41] in which chiral titanocene catalysts **80** (see figure 4) were introduced to control the stereoselectivity of the hydrogenation of cyclic imines with excellent levels of enantiomeric excess (95-99% *ee*).

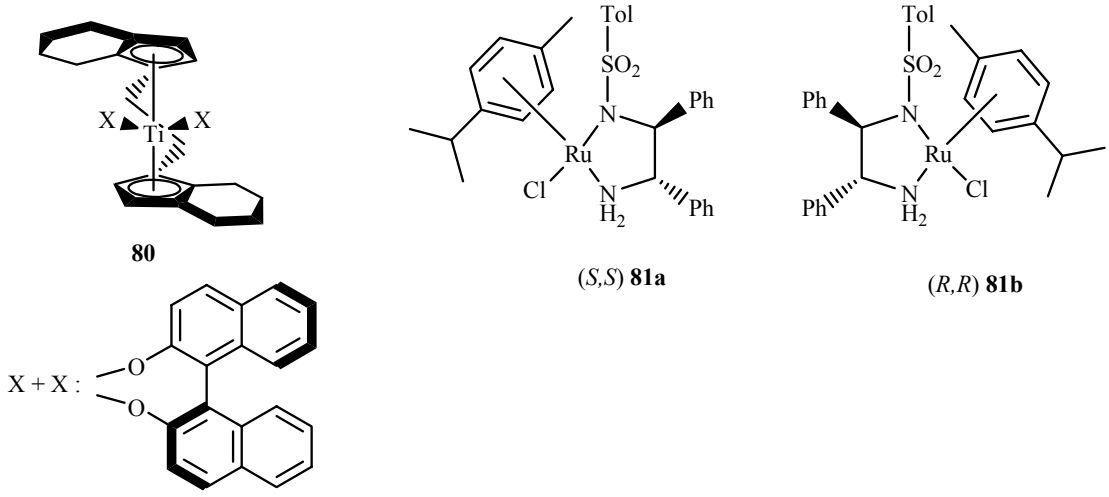
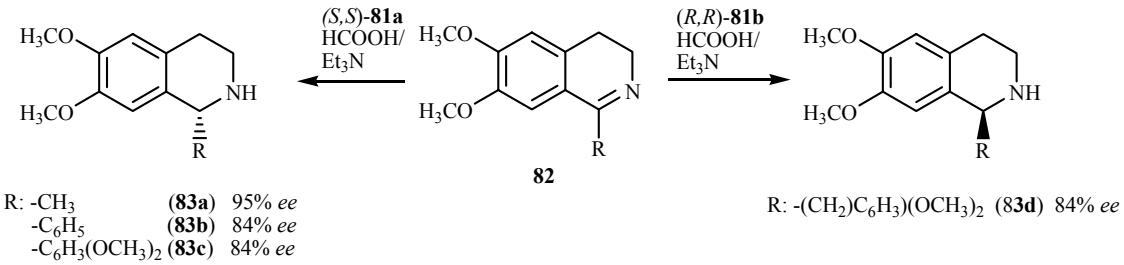


Figure 4. Some enantioselective catalysts for hydrogenation of imines.

The prime procedure of asymmetric imine reduction was reported by Noyori et.al.[42] under the conditions of a transfer hydrogenation with an azeotrope mixture of formic

[40] H. Suzuki, S. Aoyagi, C. Kibayashi, *J. Org. Chem.* **1995**, *60*, 6114-6122.
[41] a) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1992**, *114*, 7562–7564; b) C. A. Willoughby, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 8952–8962.
[42] a) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916–1417; b) for reviews using the Ru-catalyst, see: R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97–102.

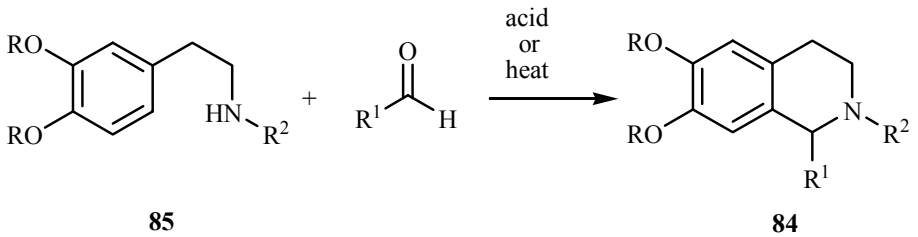
acid/triethylamine in the presence of the chiral diamine-Ru(II)-η^6arene complexes **81a** and **81b**. Currently, this procedure has become the preferred method for enantioselective reductions of cyclic imines. As described by Noyori's group, several isoquinoline derivatives have been prepared in high yields with high *ee* values, starting from cyclic imines **82** (R: CH_3-, C_6H_5-, 3,4-$(OMe)_2C_6H_3(CH_2)_2$-, and 3,4-$(OMe)_2C_6H_3$). It has been shown that the absolute configuration of the catalyst determined that of the resulting amine. Accordingly, products with (1*R*) configuration were obtained when the catalyst (*S,S*)-**81a** was used, whereas the (1*S*) isomers were obtained when the catalyst (*R,R*)-**81b** was applied, as illustrated in scheme 16.



Scheme 16. The enantioselective imine reduction of dihydroisoquinolines following Noyori´s procedure.

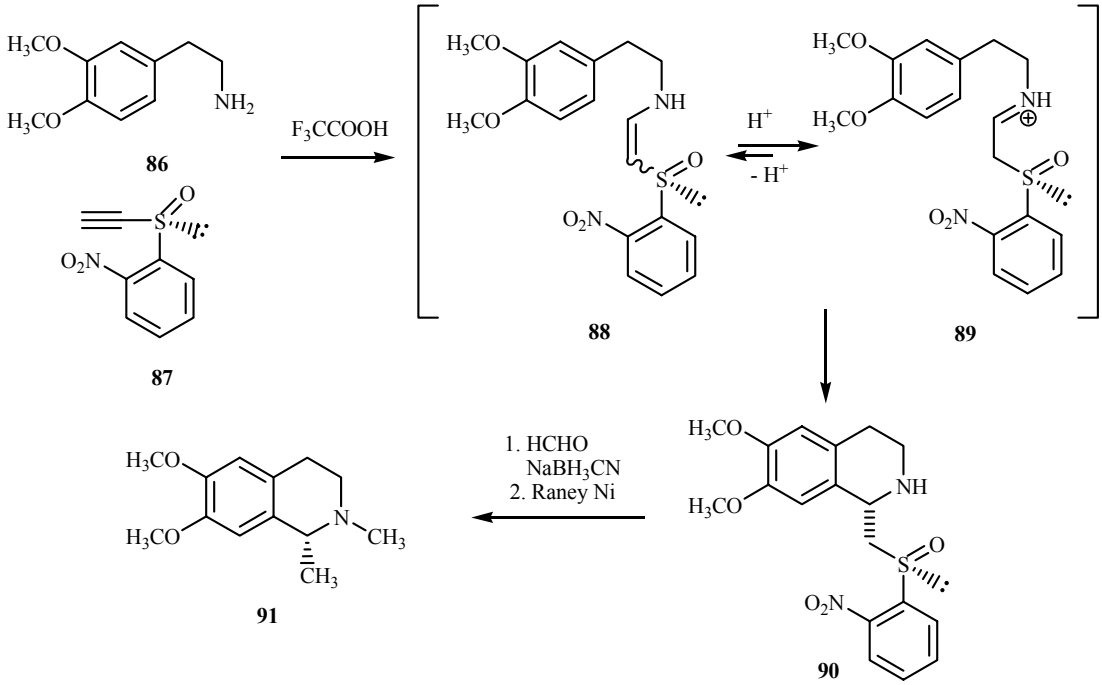
PICTET-SPENGLER REACTION

The Pictet-Spengler reaction involves the condensation of a *β*-arylehtylamine **85** with a carbonyl compound to give the corresponding tetrahydroisoquinoline **84**. These reactions are generally catalyzed by protic or Lewis acids, although numerous thermally-mediated examples are found in the literature. Aromatic compounds containing electron-donating substituents are the most reactive substrates for this reaction



Scheme 17. Pictet-Spengler isoquinoline synthesis.

Stereoselective Pictet-Spengler reactions have been developed in various modifications. Among them, Chan et.al.[43] used a chiral synthetic equivalent of acetaldehyde **87** to obtain a single tetrahydroisoquinoline diastereomer **90** as a result of a one-pot Michael addition cyclization process. *N*-Methylation and subsequent desulphurization with Raney nickel gave enantiomerically pure (+)-(*R*)-carnegine (**91**) in good yield (see scheme 18).



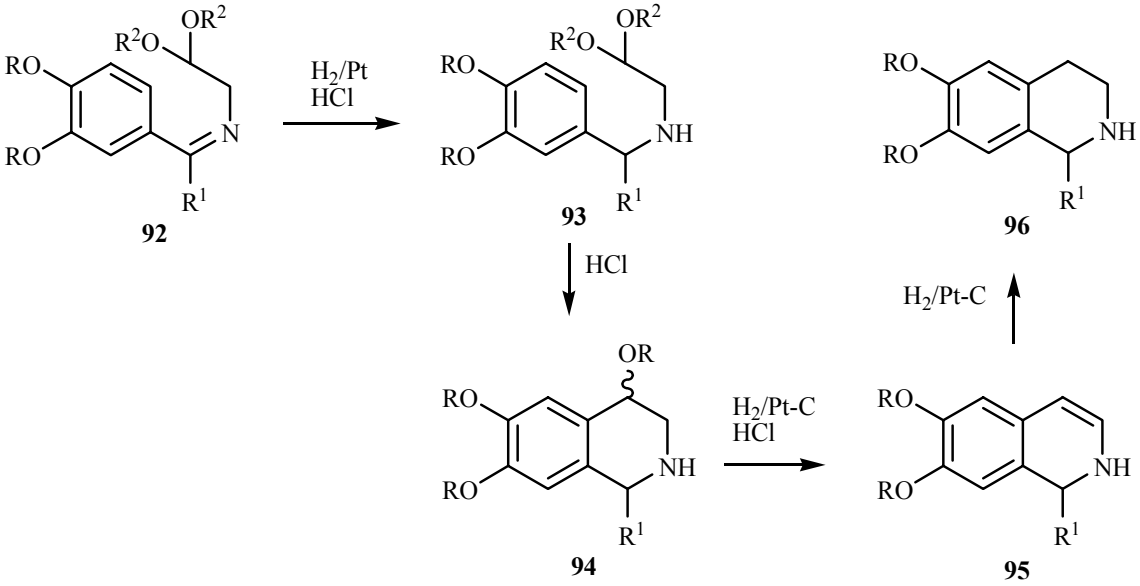
Scheme 18. The synthesis of (+)-(*R*)-carnegine (**91**) via Pictet-Spengler cyclization by Chan et. al.

POMERANZ-FRITSCH REACTION

The Pomeranz-Fritsch reaction involves the preparation of isoquinolines via the acid mediated cyclization of an appropriate iminoacetal intermediate **92.**[44] A modification by

[43] a) W. Chan, A. W. M. Lee, L. Jiang, *Tetrahedron Lett.* **1995**, *36*, 715–718; b) A. W. M. Lee, W. H. Chan, Y. Tao, Y. K. Lee, *J. Chem. Soc., Perkin Trans. 1* **1994**, 477–481.
[44] a) C. Pommeranz, *Monatsh.* **1893**, *14*, 116; b) P. Fritsch, *Ber.* **1893**, *18*, 419–422; c) W. J. Gesler, in: *Organic Reactions* (ed.: R. Adams), John Wiley and Sons, London, **1951**, vol. VI, 191–206.

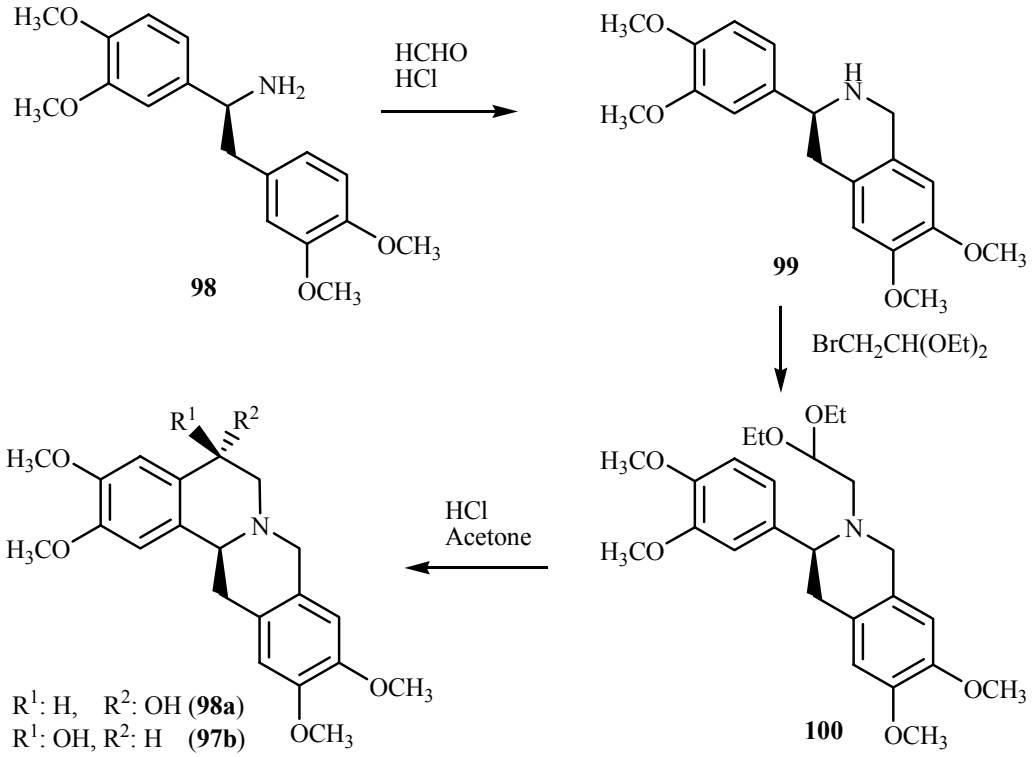
Bobbit is the most widely used variation of the Pomeranz-Fritsch reaction. [45] This modification involves cyclization of benzylaminoacetal **93**, usually prepared from classical Pomeranz-Fritsch imine **92**, to yield 4-hydroxy derivatives **94**. Tetrahydroisoquinoline **96** can be otained after removing hydroxyl group. With this method, the C-1 stereocenter can be prepared before cyclization takes place.



Scheme 19. Pomeranz-Fritsch-Bobbit cyclization.

Badia´s group[46] used optically active benzylamine **98** as the starting material for the synthesis of (5*S*)- and (5*R*)-hydroxyxylopinine (**97a** and **97b**). The approaches used two consecutive classical steps involving the Pictet-Spengler and the Pomeranz-Fritsch-Bobbitt cyclization. First, amine **98** was converted to tetrahydroisoquinoline **99** under the action of formaldehyde/HCl. In the second step, the tetracyclic protoberberine carbon skeleton was obtained by cyclization of aminoacetal **100** in concentrated HCl as a separable 1:1 mixture of (5*R*)-**97a** and (5*S*)-**97b** hydroxyxylopinine (see scheme 20).

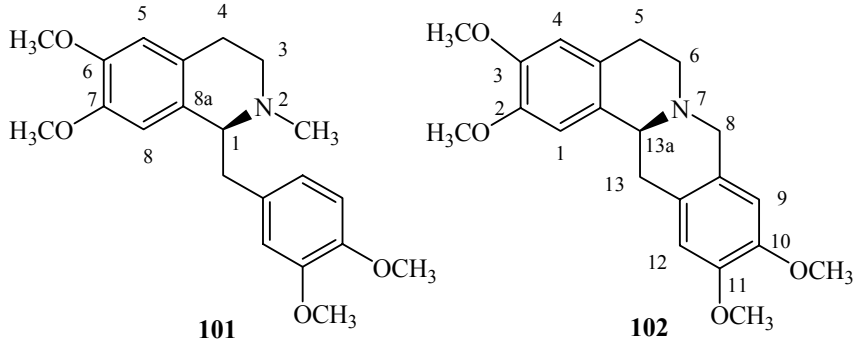
[45] M. Bobbitt, J. M. Kiely, K. L. Khanna, R. Eberman, *J. Org. Chem.* **1965**, *30*, 2247–2250.
[46] L. Carrillo, D. Badia, E. Dominguez, E. Anakabe, I. Osante, I. Tellitu, J. L. Vicario, *J. Org. Chem.* **1999**, *64*, 1115–1120.



Scheme 20. The synthesis of 5-hydroxyxylopinine (**97**) by Badia et. al.

2. ENANTIOSELECTIVE SYNTHESIS OF (+)-(*S*)-LAUDANOSINE AND (–)-(*S*)-XYLOPININE

2.1. INTRODUCTION

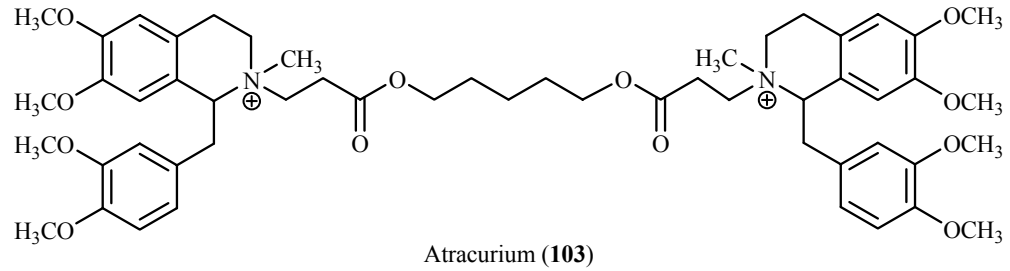


101 **102**

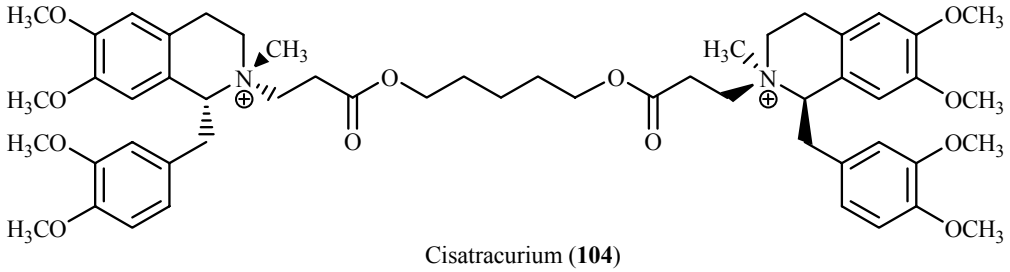
Figure 5. Structures of (+)-(*S*)-laudanosine (**101**) and (–)-(*S*)-xylopinine (**102**)

Laudanosine (**101**) is a substructure of the muscle relaxant atracurium (**103**). This recently developed muscle relaxant contains two quaternary nitrogen atoms in the benzyltetrahydroisoquinoline structures. It is used as a complement of tubocurarine (**62**). In addition to enzymatic ester hydrolysis, atracurium (**103**) is also degraded in the body by non-enzymatic E2 Hofmann elimination, which is independent of liver or kidney function. Normally, this elimination would require strongly alkaline conditions and a high temperature. However, the presence of the ester groups increases the acidity and thus facilitates the deprotonation. The elimination can proceed readily under

physiological conditions, giving atracurium (**103**) a half life of about 20 minutes. This is particularly valuable when patients have low or atypical pseudocholinesterase enzymes. Atracurium (**103**) contains four chiral centers (including the two quaternary nitrogen atoms) and is supplied as a mixture of stereoisomer. The single isomer cisatracurium (**104**) has recently been introduced. This isomer is more potent than the mixture, has a slightly longer duration of action, and causes fewer cardiovascular side effects.[47]



Atracurium (**103**)

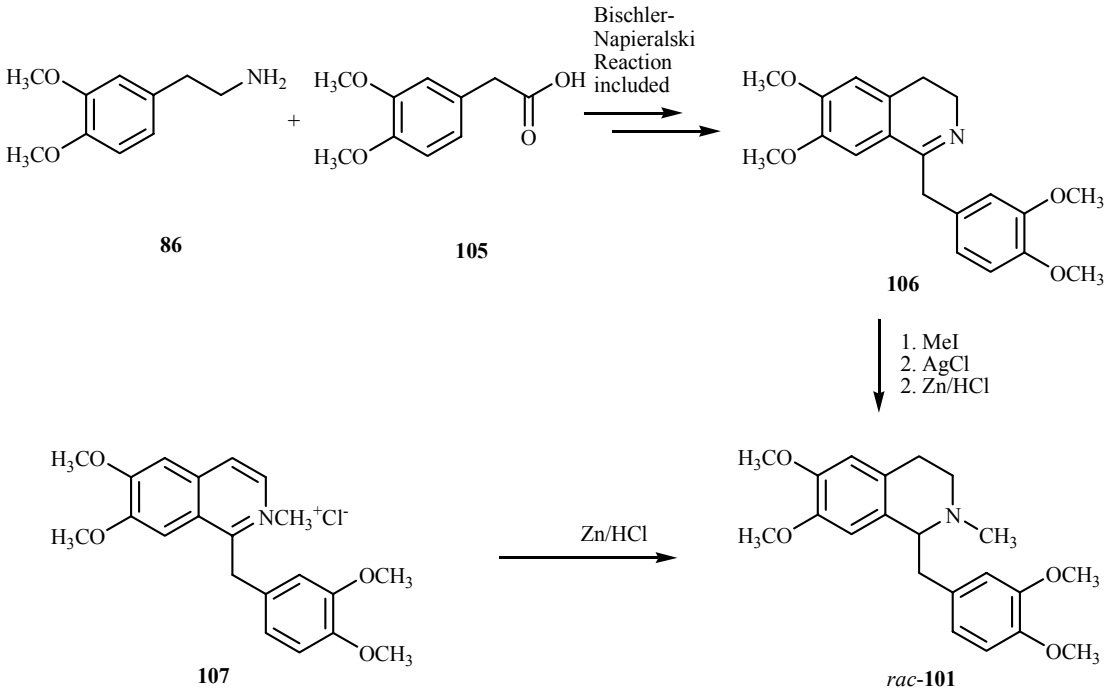


Cisatracurium (**104**)

Figure 6. Structure of atracurium (**103**) and cisatracurium (**104**).

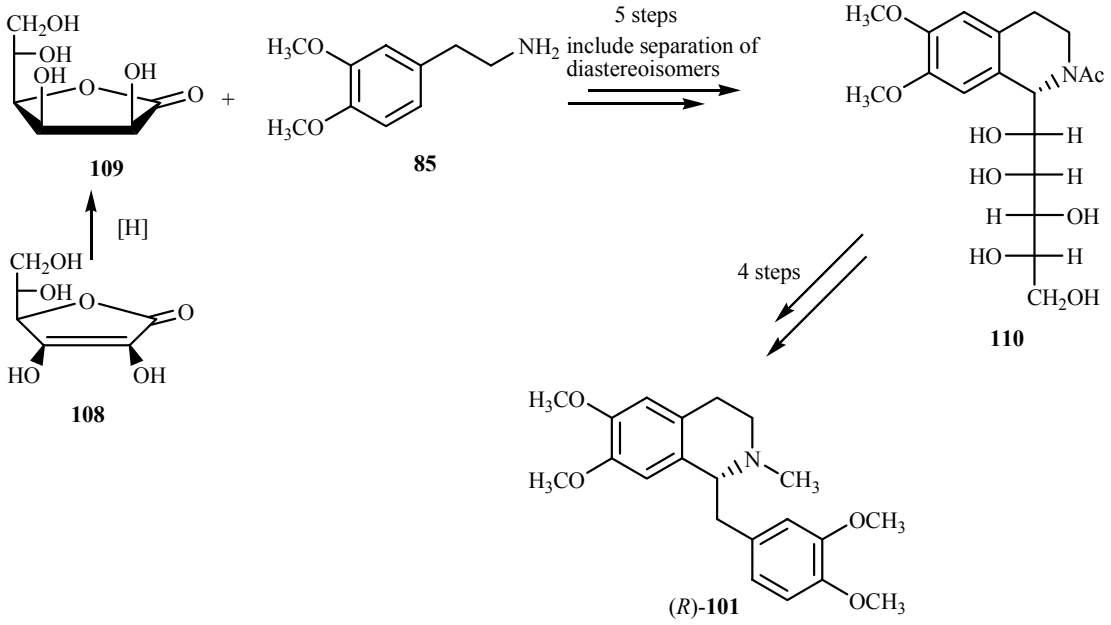
The synthesis of *rac*-laudanosine (**101**) has been reported first by Pictet and Finkelstein[48] using the Bischler-Napieralski cyclization/reduction sequence. Treatment of homoveratrylamine (**86**) and dimethoxyphenylacetic acid (**105**) with PCl_5 and subsequent reduction of the dihydroisoquinoline **106** in the presence of HCl/Zn furnished the product (*rac*-laudanosine), which was obtained as an identical compound with the reduction product of chloromethylate papaverine (**107**) (see scheme 20, **107** → **101**).

[47] P. M. Dewick, *Medicinal natural products : a biosynthetic approach,* 2nd ed., John Wiley & Sons, New York, **2002**, p. 324.
[48] A. Pictet, M. Finkelstein, *Ber.* **1909**, *42*, 1979.



86 **105** **106** **107** *rac*-**101**

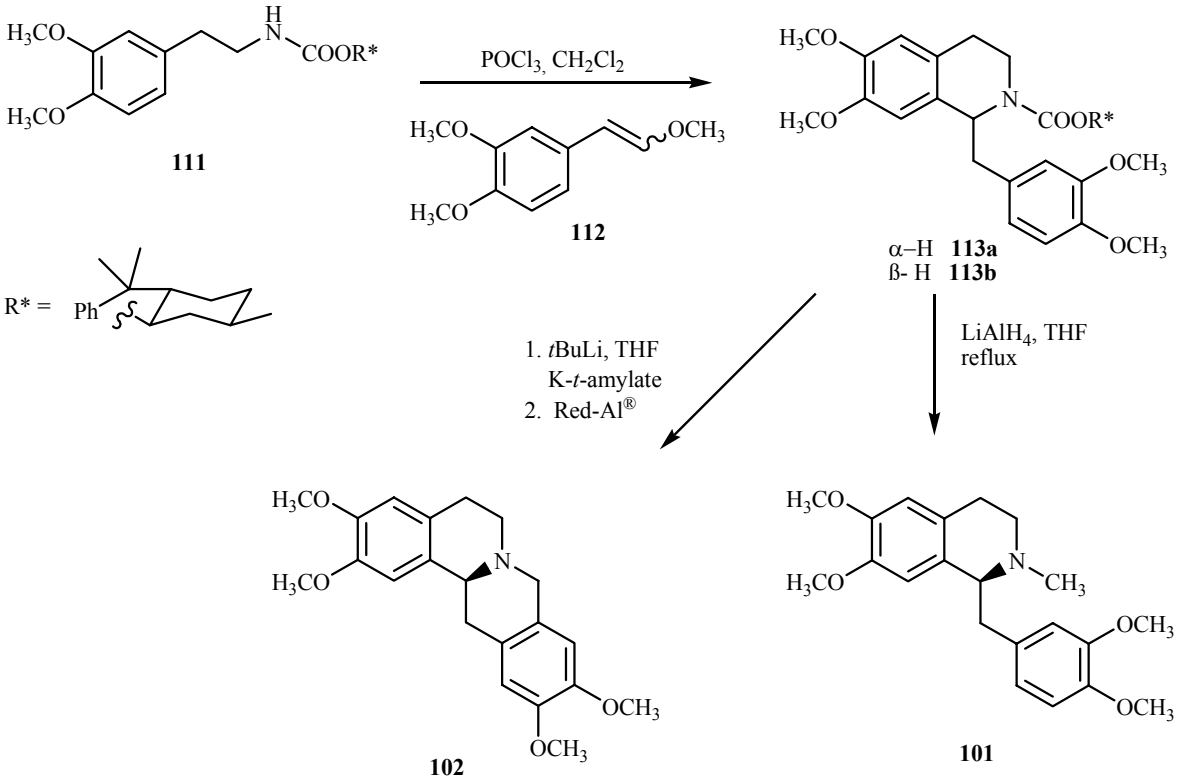
Scheme 21. The synthesis of *rac*-laudanosine (**101**) by Pictet and Finkelstein.



109 **85** **110** **108** (*R*)-**101**

Scheme 22. The synthesis of (–)-(*R*)-laudanosine (**101**) by Czarnocki.

Czarnocki[49] used (+)-*L*-ascorbic acid (**108**) as chiral starting material to synthesize (–)-(*R*)-laudanosine (**101**) *via* Bischler-Napieralski cyclization/diastereoselective reduction. Using this method, laudanosine (**101**) has been synthesized with good enantioselective excess. First, (+)-*L*-ascorbic acid (**108**) was converted to *L*-gulano-1,4-lacton (**109**) by catalytic hydrogenation. After treatment with homoveratrylamine (**86**) at an elevated temperature and several subsequent steps including the Bischler-Napieralski reaction using PCl_5, pentahydroxy compound **110** was obtained. Several further transformations of tetrahydroisoquinoline **110** gave unnatural (–)-(*R*)-laudanosine (**101**) with 94% *ee* (Scheme 22).

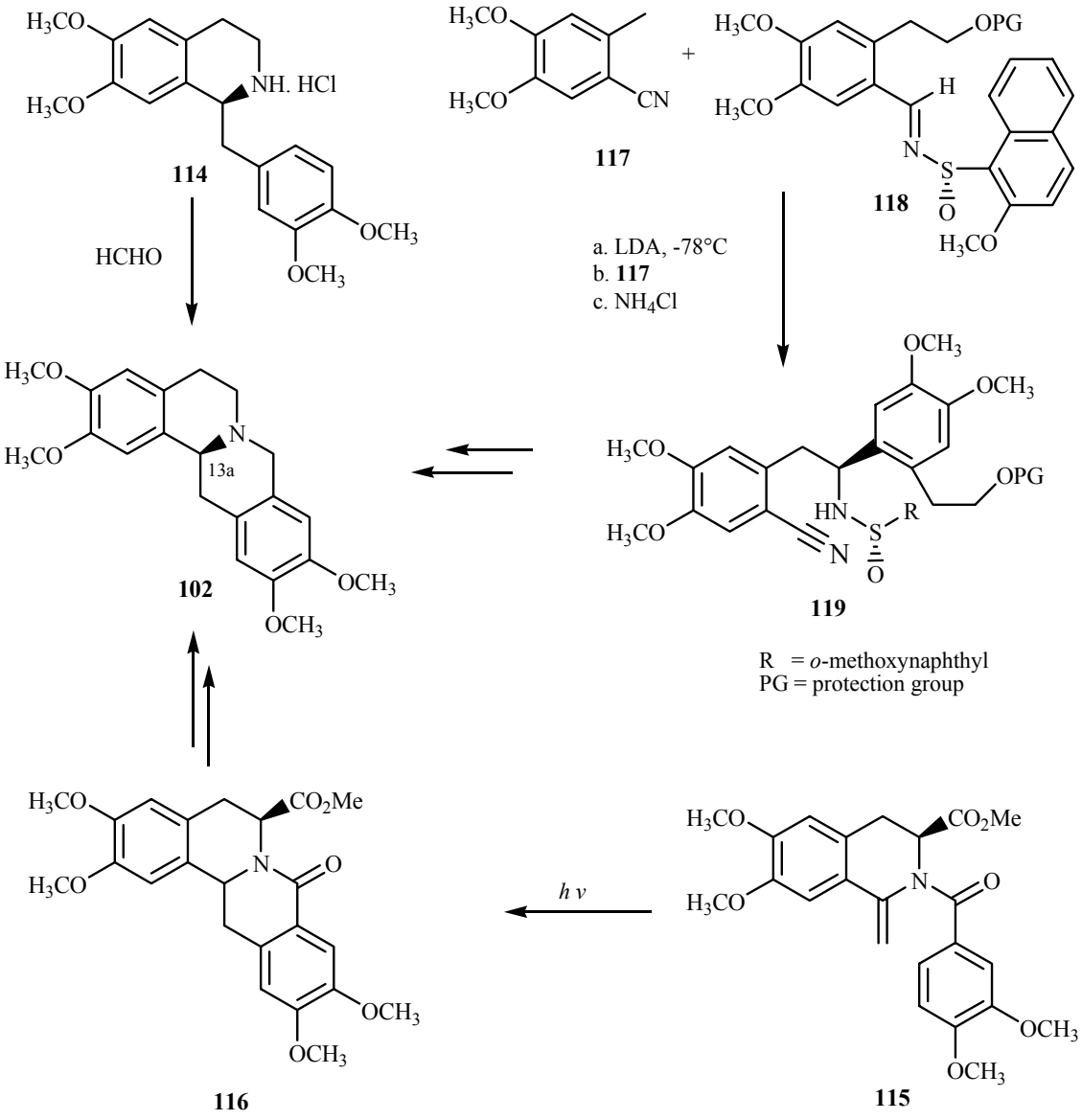


Scheme 23. The synthesis of (–)-(*S*)-laudanosine (**102**) and (+)-(*S*)-xylopinine (**102**) by Comins et.al.

A cyclohexyl-based chiral auxiliary has been used by Comins et.al.[50] in concise asymmetric synthesis of laudanosine (**101**) and xylopinine (**102**). A condensation of the

[49] Z. Czarnocki, J. B. Mieczkowski, M. Ziolkowski, *Tetrahedron Asymmetry* **1996**, *7*, 2711–2720.
[50] D. L. Comins, P. M. Thakker, M. F. Baevsky, M. M. Badawi, *Tetrahedron* **1997**, *53*, 16327–16340.

chiral carbamate **111**, with vinyl ether **112** gave diastereoisomeric benzylisoquinolines **113a** and **113b** in a 83:17 ratio. Unfortunately, the diastereoisomers **113a** and **113b** could not be conveniently separated by chromatography, so the mixture was finally reduced with $LiAlH_4$ to give laudanosine (**101**) in 73% with only 63% *ee*. Alternatively, transformation of the product by treatment with *t*BuLi/potassium *t*-amylate and subsequent reduction using Red-Al® afforded xylopinine (**102**) (Scheme 23).



Scheme 24. Several synthetic routes to (–)-(*S*)-xylopinine (**102**).

Xylopinine (**102**) is a prototypical member of the protoberberines, a large family of naturally occurring alkaloids characterized by a tetracyclic ring skeleton containing a tetrahydroisoquinoline core. In higher plant, the "berberine bridge" is formed by the enzyme-catalyzed conversion of an *N*-methyl group in (*S*)-reticuline (**54**).[51] Xylopinine (**102**) was first isolated from *Xylopia discreta* (Annonaceae) by J. Schmutz in 1959.[52]

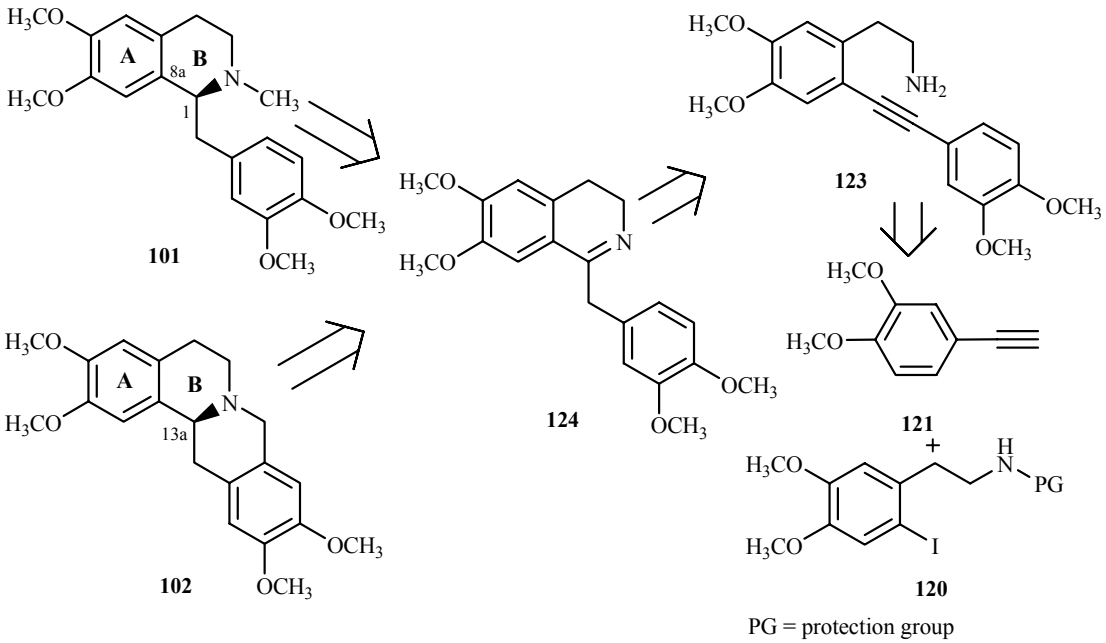
Several synthesis of xylopinine (**102**) have been reported. Before xylopinine was isolated as a natural product, Corrodi and Hardegger synthesized this molecule by heating (–)-tetrahydropapaverine hydrochloride (**114**) with aqueous formaldehyde.[53] Comins[49] and Czarnocki[54] used a chiral auxiliary mediated Pictet-Spengler reaction to get the desired configuration at C13a of xylopinine (**102**). A photochemical cyclization strategy using an enatiomerically pure enamide (**115**) was employed by Kametani.[55] Davis reported the asymmetric synthesis of (−)-(*S*)-xylopinine (**102**) using enantiopure sulfinimines.[56] The benzyl-protected 2-methoxynaphthylsulfinimine (+)-(*S*)-**118** was reacted with the lithiated nitrile of **117** affording the major diastereoisomer (–)-(S_S,*S*)-**119** in 68% yield with 96% *de*. This key intermediate **119** was then converted to (–)-(*S*)-xylopinine (**102**) (Scheme 24).

2.2. RETROSYNTHETIC ANALYSIS

The *S*-configuration of C1 of (+)-(*S*)-laudanosine (**101**) and C13a of (–)-(*S*)-xylopinine (**102**) should be constructed by an enantioselective reduction of imine **124**, which has already been described by Noyori et al. In contrast to the common synthesis of benzylisoquinoline alkaloids, the imine **124** was planned to arise from an intramolecular hydroamination reaction of amino alkyne **123**. Using this approach, the C1–C8a bond

[51] For Reviews see: a) T. M. Kutchan, in *The Alkaloids: Chemistry and Biology*, (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, vol. 50, 258–316. b) P. J. Facchini, *Annu. Rev. Plant Physiol. Plant Mol. Biol.* **2001**. *52*, 29–66.
[52] J. Schmutz, *Helv. Chim. Acta* **1959**, 335–343.
[53] H. Corrodi, E. H. Hardegger, *Helv. Chim. Acta* **1956**, 889–897.
[54] Z. Czarnocki, Z. Arazny, *Heterocycles* **1999**, *51*, 2871–2879.
[55] T. Kametani, N. Takagi, M. Toyota, T. Honda and K. Fukumoto, *J. Chem. Soc. Perkin I* **1981**, 2830–2834.
[56] F. A. Davis, P. K. Mohanty, *J. Org. Chem*. **2002**, *67*, 1290–1296.

can be formed by a Sonogashira coupling reaction[57] between the aryl iodide **120** and alkyne **121**. Correspondingly, the typical electrophilic aromatic substitution reaction which is usually employed for the formation of the C1–C8a bond of benzylisoquinolines can be avoided. An obvious advantage of this strategy is the fact that in contrast to electrophilic aromatic substitutions, the Pd-catalyzed Sonogashira coupling is facilitated by electron-withdrawing substituents located in the A-ring (Scheme 25).

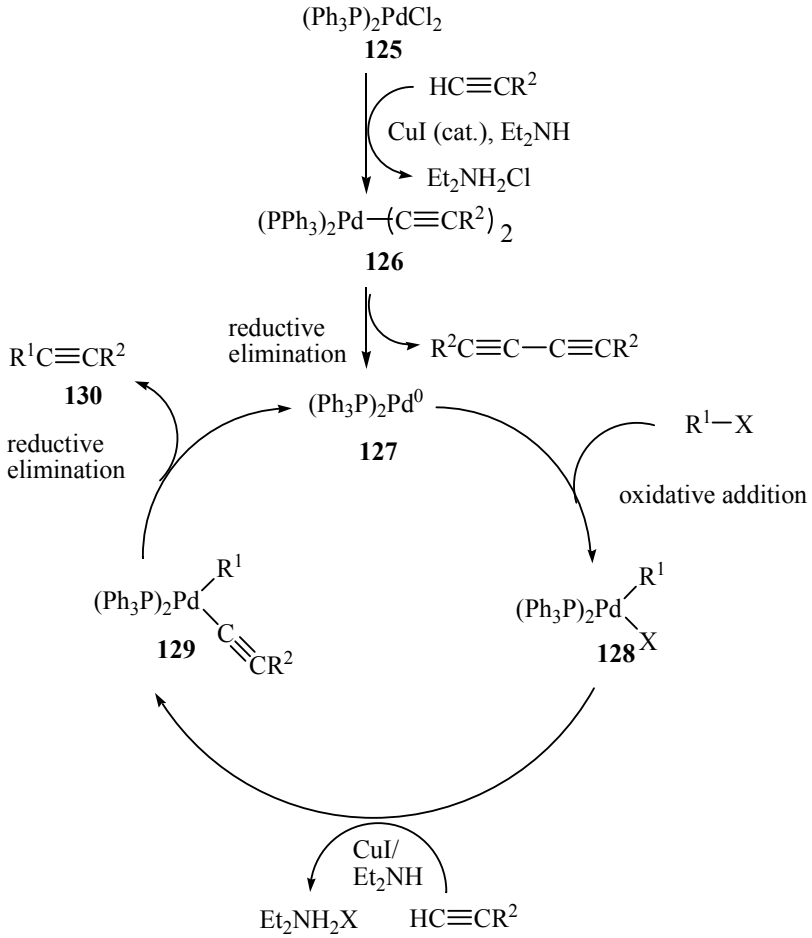


Scheme 25. Retrosynthesis of both (+)-(*S*)-laudanosine (**101**) and (–)-(*S*)-xylopinine (**102**).

Sonogashira demonstrated that terminal alkynes react smoothly with haloalkenes and aryl halides in the presence of catalytic amounts of bis(triphenylphosphine)palladium dichloride and cuprous iodide in diethylamine at room temperature. This mild process has performed very well in a variety of contexts in organic synthesis. The presumed catalytic cycle for this Pd^0/Cu^I-catalyzed coupling of sp- and sp^2-carbon atoms is shown in scheme 26. Bis(triphenylphosphine)palladium(0), the putative active catalyst, could conceivably be formed in situ through sequential copper(I) iodide-catalyzed bis-

[57] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; b) K. Sonogashira, in: *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 3, p. 521–549.

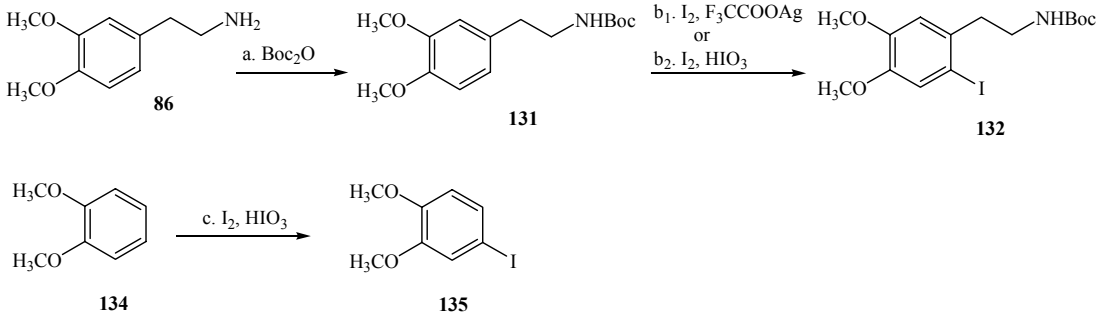
alkynylation and reductive elimination reaction (**125→126→127**). Once formed, the highly coordinatively unsaturated 14-electron palladium(0) complex **127** participates in an oxidative addition reaction with the aryl- or vinyl halide to the give 16-electron palladium(II) complex **128**. A cooper(I)-catalyzed alkynylation of **128** then furnishes an aryl- or vinyl palladium(II) complex **129**. Finally, a terminating reductive elimination step liberates the coupling product **130** and regenerates the active palladium catalyst **127**.



Scheme 26. Catalytic cycle for the Sonogashira reaction.

2.3. SYNTHESIS OF AMINO ALKYNES

Homoveratrylamine (**86**) and Boc-anhydride were reacted in methanol in the presence of the strong base NaOH at room temperature. After purification, the Boc-protected amine (**131**) was isolated in 85% yield. Iodination of the product with iodine in the presence of silver trifluoroacetate gave aryl iodide (**132**) in 93% yield. Because the silver salt is relatively expensive, a modified Konigstein procedure,[58] using a mixture of iodine and HIO_3 in methanol/water (3:1), was used in further experiments. This procedure also gave the product in a satisfactory yield (79%). Iodoveratrol (**135**), the desired Sonogashira coupling partner, was also syntheiszed by using this modified Konigstein procedure in 92% yield from veratrol (**134**).

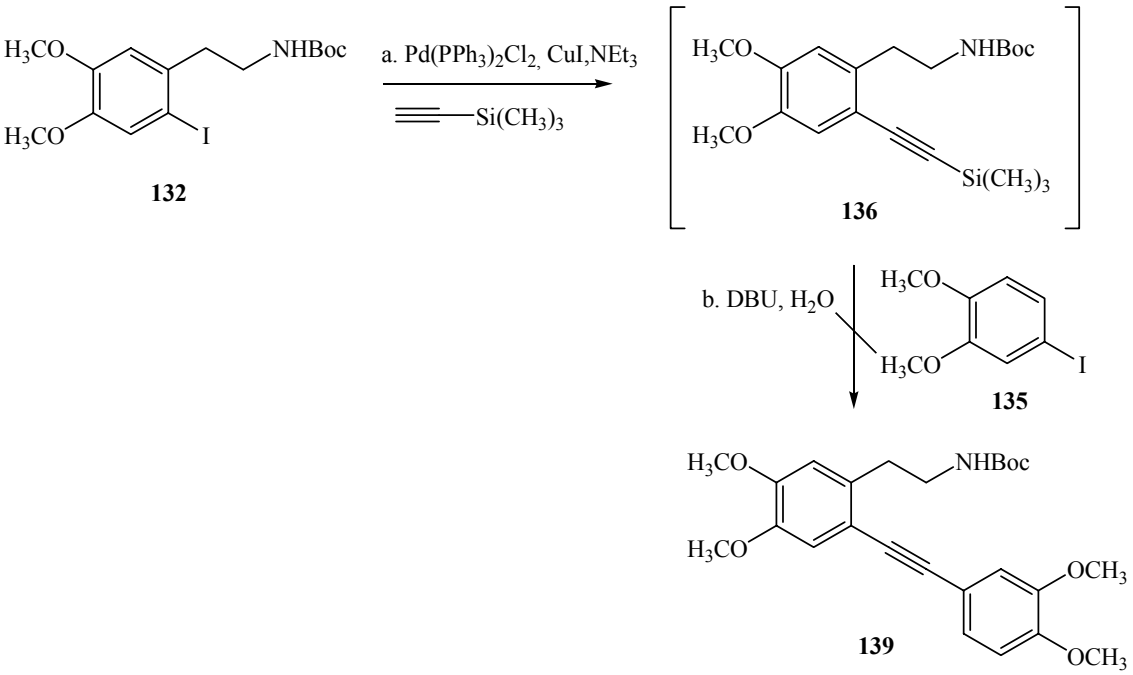


Scheme 27. Synthesis of aryl iodides **132** and **135**. Reagents and conditions: a. Boc_2O 1.3 equiv, NaOH 2.0 equiv, MeOH, 0°C → 25°C, 18 h, 85%; b_1. I_2 1.1 equiv, $F_3CCOOAg$ 1.1 equiv, CH_2Cl_2, 25°C, 4 h, 93%, b_2. I_2 0.4 equiv, HIO_3 0.2 equiv, MeOH/H_2O (3:1), 85°C, 48 h, 79%; c. I_2 0.4 equiv, HIO_3 0.2 equiv, MeOH-H_2O (3:1), 85°C, 48 h, 92%.

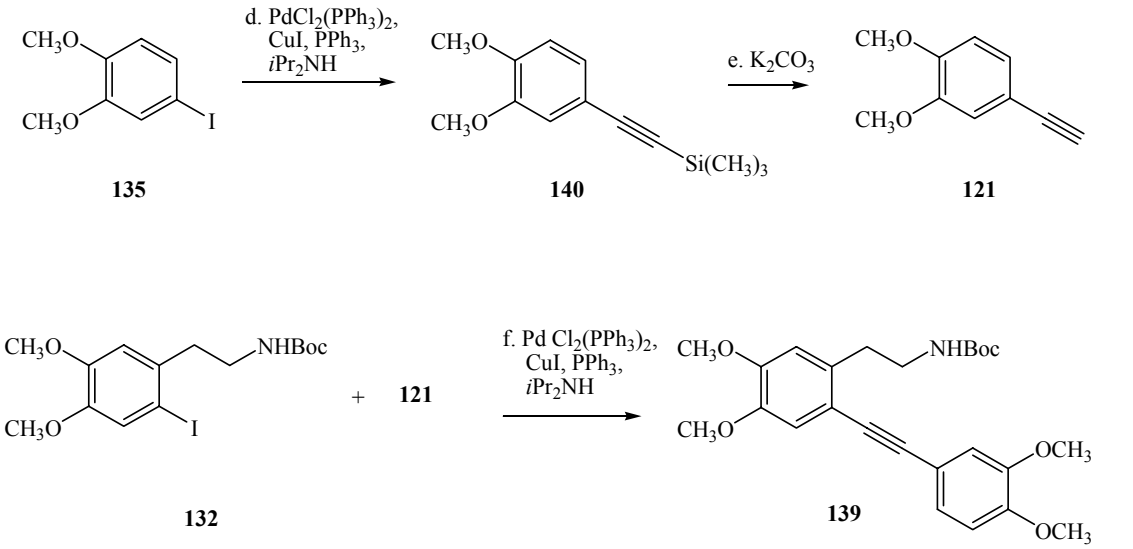
In an initial experiment to construct bisarylacetylene **139**, aryl iodides **132** and **135** were subjected to a one-pot Sonogashira coupling reaction that was reported to give bisarylacetylenes from TMS-acetylene and two different aryl iodides.[59] Aryl iodide **132** was first added to a flask containing 6 mol-% $PdCl_2(PPh_3)_2$ and 10 mol-% CuI. Subsequently, 6.0 equivalents of Et_3N and TMS-acetylene were added, in order to obtain the standard Sonogashira product. Unfortunately, subsequent addition of 1.0 equivalent of the second aryl iodide **135**, 12.0 equivalents of DBU and 40 mol-% of water did not

[58] a) L. F. Tietze, R. Schimpf, *Synthesis* **1993**, 876–880; b) H. O. Wirth, O. Königstein, W. Kern, *Justus Liebigs Ann. Chem.* **1960**, *634*, 84–104.
[59] M. J. Mio, L. C. Kopel, J. B. Braun, T. L. Gadzikwa, K. M. Hull, R. G. Brisbois, C. J. Markworth, P. A. Grieco, *Org. Lett*. **2002**, *4*, 3199–3202.

result in the formation of the desired bisarylethyne (**139**). As the product, only aryl alkyne **136** was isolated in 81% yield (Scheme 28).



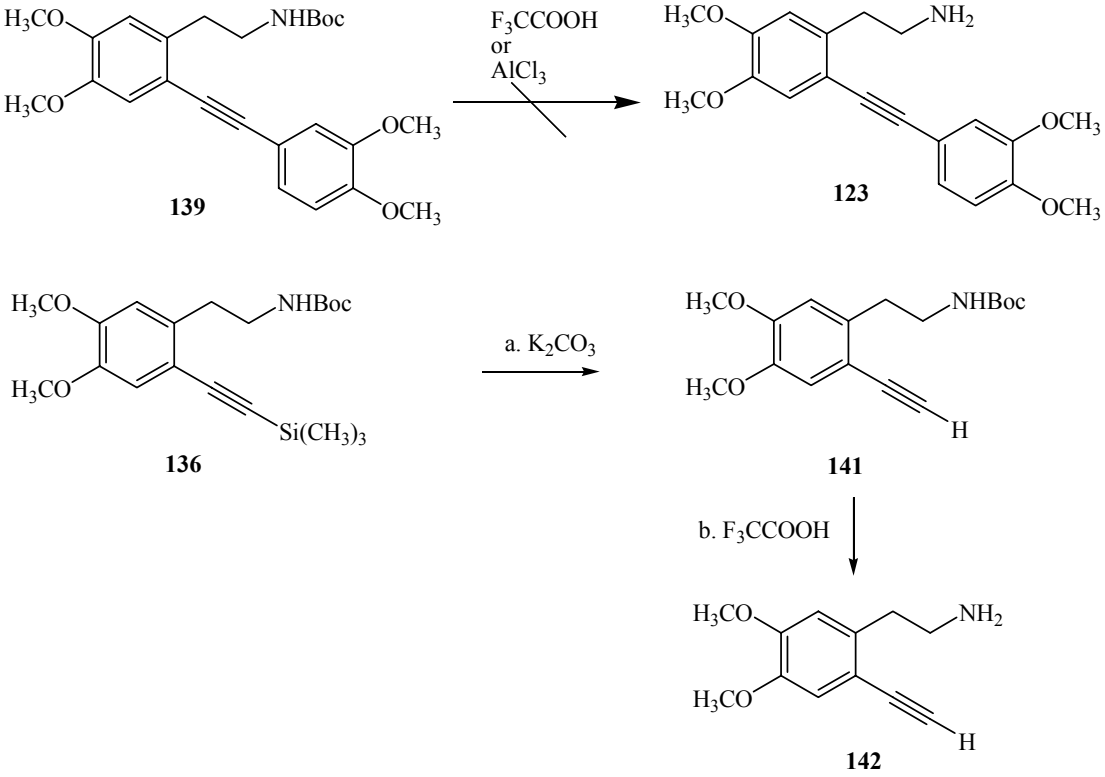
Scheme 28. One-pot procedure of synthesis of bisarylacetylene **110**. Reagents and conditions: a. 6 mol-% $PdCl_2(PPh_3)_2$, 10 mol-% CuI, NEt_3, TMS-acetylene, 25 °C, 18 h; b. DBU 12.0 equiv, 40 mol-% H_2O, **135**, 25 °C, 24 h.



Scheme 29. Synthesis of alkyne **139**. Reagents and conditions: d. 2 mol-% $PdCl_2(PPh_3)_2$, 4 mol-% CuI, 4 mol-% PPh_3, *i*Pr_2NH, 25°C, 16 h, 92%; e. K_2CO_3 0.1 equiv, MeOH, 25°C, 16 h, 82%; f. 2 mol-% $PdCl_2(PPh_3)_2$, 4 mol-% CuI, 4 mol-% PPh_3, *i*Pr_2NH, 25°C, 16 h, 95%.

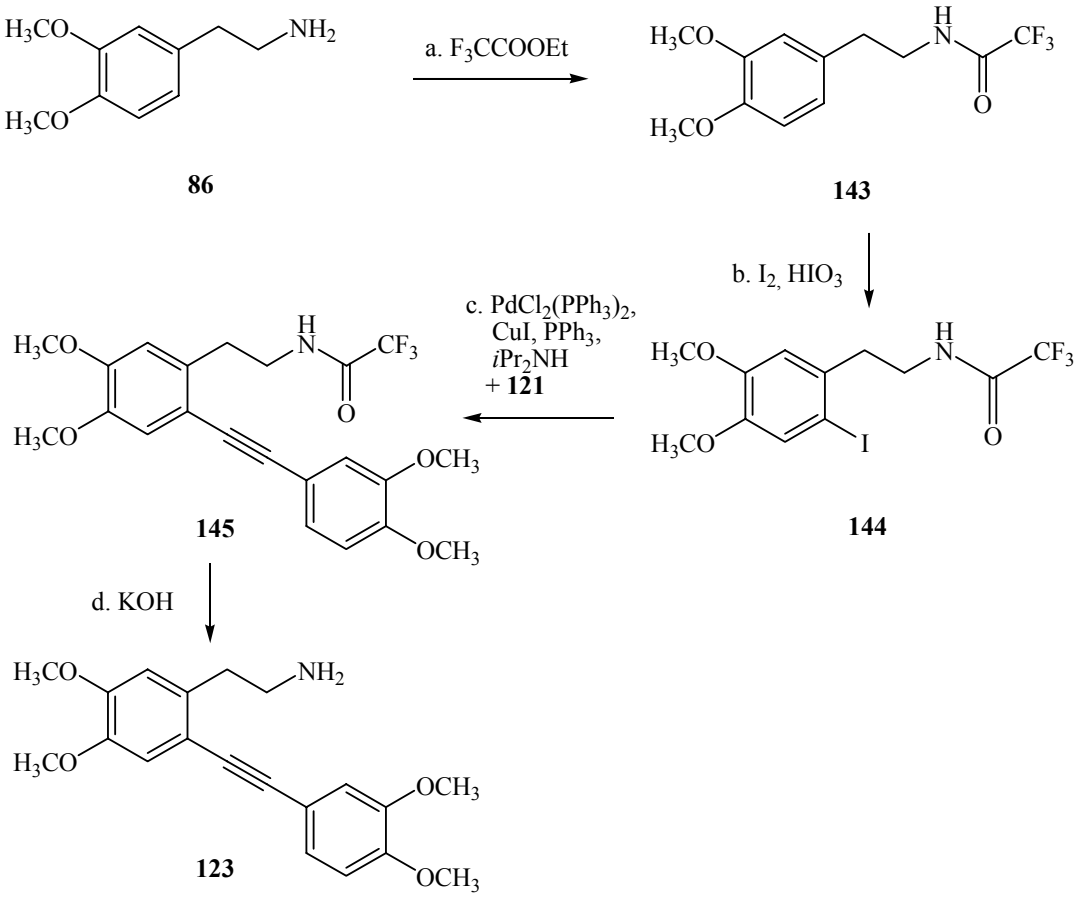
Alternatively, the bisarylacetylene **139** was then planned to be synthesized step by step. Coupling between TMS-acetylene and iodoveratrol (**135**) under standard Sonogashira conditions afforded TMS-protected alkyne **140** in 92% yield. Subsequently, removal of the TMS group of arylalkyne **140** under basic conditions gave terminal alkyne **121** in 82% yield. Then, a second coupling reaction between alkyne **121** and **132** using the standard Sonogashira conditions gave the Boc-protected amino alkyne **139** in 95% yield (Scheme 29).

Surprisingly, cleavage of the Boc-group of **139** to afford the desired amino alkyne **123** failed. The usual procedure using trifluoroacetic acid at room temperature gave a dark brown solution. According to TLC, there was still protected amine left in solution after 6 h. However, no significant product formation could be observed. The use of $AlCl_3$ as Lewis-acid catalyst for the deprotetion also resulted in a dark brown solution and no amine formation.



Scheme 30. Deprotection of Boc-group. Reagents and condition: a. K_2CO_3 0.1 equiv, MeOH, 25°C, 3 h, 88%; b. F_3CCOOH 6.5 equiv, CH_2Cl_2, 25°C, 20 h, 86%.

In contrast, amino alkyne **142** can easily be obtained from **141** under standard condition for the deprotection of Boc-groups. The electron rich alkyne **139**, which is substituted by two donating electron rich 3,4-dimethoxyphenyl-groups, might be protonated under the reaction conditions. Then, the protonated form can cause side reactions to give an unseparable mixture of products. A neural deprotection method (for example: using TBDPSOTf or TMSI) was avoided since CO_2 is released. CO_2 should contact in neutral condition with primary amines to form carbamides. So we decided to use the trifluoroacetamide protecting group.



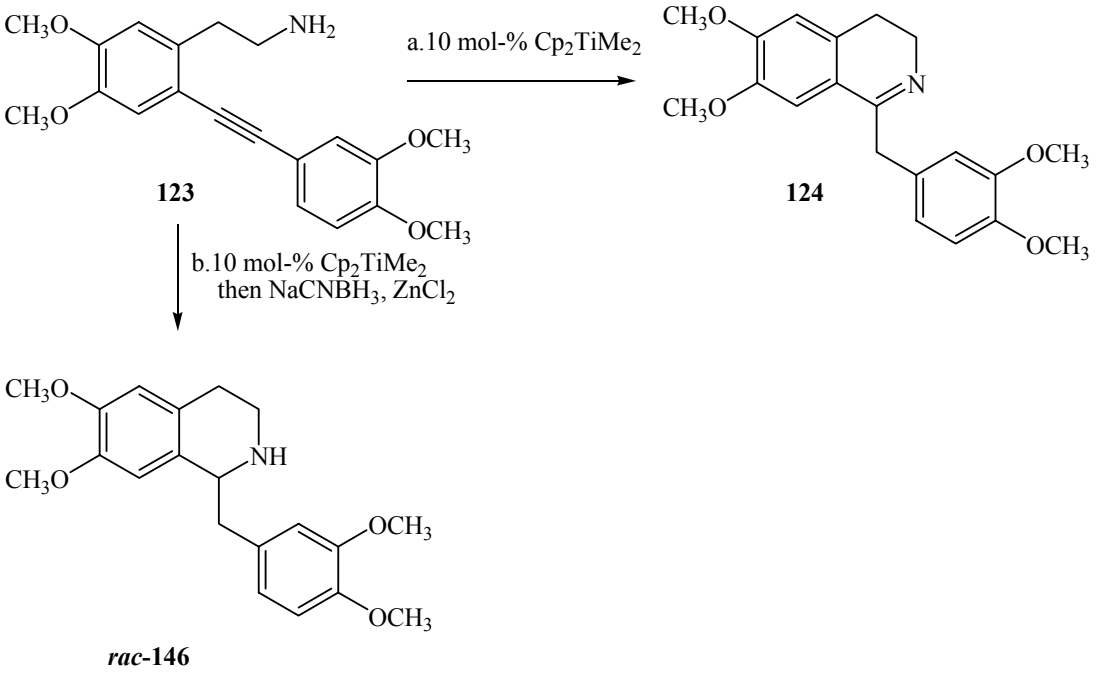
Scheme 31. Synthesis of amino alkyne **123**. Reagents and conditions: a. $F_3CCOOEt$ 1.1 equiv, THF, 25°C, 4 h; b. I_2 0.4 equiv, HIO_3 0.2 equiv, MeOH/H_2O (3:1), 85°C, 48 h, 93% (two steps); c. 4 mol-% $PdCl_2(PPh_3)_2$, 8 mol-% CuI, 8 mol-% PPh_3, *i*Pr_2NH, 25 °C, 16 h, 84%; d. KOH 10.0 equiv, MeOH, 25 °C, 8 h, 90%.

The synthesis of the amino alkyne **123** was accomplished as depicted in scheme 31. The reaction of homoveratrylamine **86** with ethyl trifluoroacetate in THF at 25°C gave the *N*-protected trifluoroacetaamide **143** cleanly. After evaporation of the solvent, without further purification, the product **143** was obtained in high purity. Subsequently, aryl amine **143** was iodinated to give **144** in the presence of I_2 and HIO_3 at 85°C in a mixture of water and methanol (modified Konigstein method) in 93% yield. Aryl iodide **144** was then subjected to the standard Sonogashira conditions to give the TFA-protected amino alkyne **145** in 84% yield. In this context, it is worth mentioning that in alkyne **145** the C1-C8a bond (*vide supra*) has already been established. Liberation of the NH_2-group under basic condition (KOH, MeOH) delivered amino alkyne **123** in 90% yield.

2.4. INTRAMOLECULAR HYDROAMINATION CYCLIZATION

The key intermediate **123** was subjected to the hydroamination reactions at 105°C in toluene in the presence of 5 mol-% of a Ti-complex as the catalyst. The reaction was stopped after 48 h and a subsequent reduction performed with $NaCNBH_3$ and $ZnCl_2$ in methanol at 25°C for 20 h was performed. As can be seen from table 1 (entry 1-4), under these conditions, the desired product **146** was only obtained in 34% yield, when Cp_2TiMe_2 was used as the catalyst. The product was not detected, when Ind_2TiMe_2, $Ti(NMe_2)_4$ or (*rac*-EBTHI)$TiMe_2$ were used. These results showed that for this reaction it was necessary to find a special and optimized conditions. Norlaudanosine (*rac*-**146**) was obtained from amino alkyne **123** in 96% yield under hydroamination conditions in the presence 10 mol-% Cp_2TiMe_2 after 16 h of reaction time.

To produce imine **124**, the key intermediate **123** was subjected in the same conditions. The hydroamination reaction proceeded smoothly within 16 h in 98% yield after chromatography. It is necessary to note that aqueous workup should be avoided because the imine product is easily converted to the more stable enamine under aqueous conditions.



Scheme 32. Hydroamination of amino alkyne **123**. Reagents and conditions: a. 10 mol-% Cp_2TiMe_2, toluene, 105°C, 16 h, 98%; b. 10 mol-% Cp_2TiMe_2, toluene, 105°C, 16 h; then $NaCNBH_3$ 2.0 equiv, $ZnCl_2$ 1.0 equiv, MeOH, 25°C, 20 h, 96%

Table 1. Hydroamination of amino alkyne (**123**).

Entry	Mol- %	Catalyst	Time	Yields of **124** (%)
1	5	Cp_2TiMe_2	48 h	34[a]
2	5	Ind_2TiMe_2	48 h	-
3	5	Ti $(NMe_2)_4$	48 h	-
4	5	(*rac*-EBTHI)$TiMe_2$	48 h	-
5	10	Cp_2TiMe_2	16 h	96
6	20	$CsOH•H_2O$	7 d	not isolated
7	40	$CsOH•H_2O$	7 d	66[b]

a. Product **146** after reduction with $NaCNBH_3/ZnCl_2$; b. as a 1:2 mixture imine and enamine.

Knochel et. al.[60] reported that $CsOH•H_2O$ catalyzed hydroaminations of alkynes in NMP at 90-120°C. A corresponding cyclization of amino alkyne **123** took place in the presence of 20 mol-% $CsOH•H_2O$ in NMP at 150°. However, according to TLC, the reaction was not completed even after 7 days under the reaction conditions and the product could not be isolated by flash chromatography. However, when the catalyst of $CsOH•H_2O$ was 40 mol-%, the product could be isolated in 66% yield as a 1:2 mixture of imine and enamine.

The enantioselective transfer hydrogenation under Noyori conditions employing 1 mol-% (η^6-*p*-cymene)[(1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine]RuCl (**81b**) as the catalyst in an azeotropic mixture of formic acid and triethylamine furnished norlaudanosine (**146)** in 92% yield with 93% *ee* (*S*-configuration), in good agreement with Noyori´s results (scheme 33).

Using formic acid as a stable organic hydrogen donor is an alternative to the flammable molecular hydrogen. Although Ru(II)-complexes are known to catalyze the reversible process,

$$HCO_2H \overset{\text{Ru-cat.}}{\rightleftharpoons} H_2 + CO_2$$

the reduction of the imine is a result of transfer hydrogenation by formic acid. Interference of molecular hydrogen does not take place.

A chiral Ru hydride **147** is formed and it is assumed that the hydrogen transfer occurs via metal-ligand bifunctional catalysis. The N-H linkage may stabilize a transition state **148** by formation of a hydrogen bond to the nitrogen atom. The stereochemical outcome of the reaction is determined by discrimination of the enantiofaces of the imine double bond of the cyclic imine.

[60] D. Tzalis, C. Koradin, P. Knochel, *Tetrehedron Lett*. **1999**, *40*, 6193-6195.

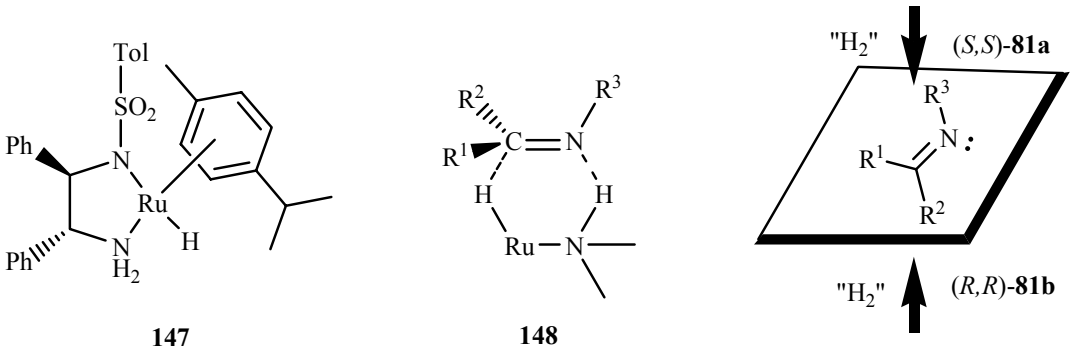
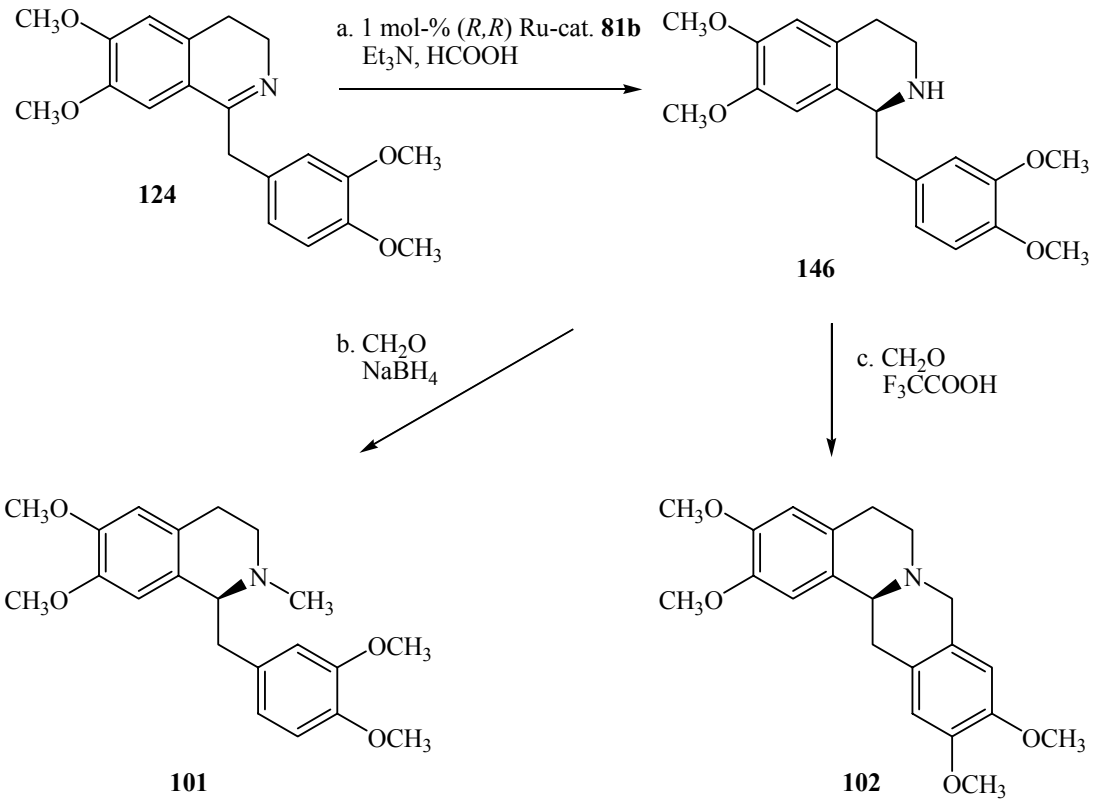


Figure 7. Asymmetric Ru-catalyzed transfer hydrogenation.



Scheme 33. Synthesis of (+)-(*S*)-laudanosine (**101**) and (–)-(*S*)-xylopinine (**102**). Reagents and conditions: a. 1 mol-% (*R,R*)-Ru-cat. **81b**, HCOOH : NEt_3 (5:2), DMF, 25°C, 7 h, 92%, 93% *ee*; b. CH_2O, $NaBH_4$ 10 equiv, H_2O, MeOH, 25°C, 2 h, 99%; c. CH_2O, F_3CCOOH, 25°C, 16 h, 82%.

The final step of the synthesis of (+)-(*S*)-laudanosine (**101**) was the methylation of the N-2 atom of norlaudanosine **146**. Treatment of **146** with formaldehyde (37%) and subsequent borohydride-reduction at 25 °C (16 h) furnished (+)-(*S*)-laudanosine (**101**) in

99% yield. Optical rotation of the product was $[\alpha]_D^{25}$ = + 87 (c = 0.7, in ethanol) (Lit.[61] $[\alpha]_D^{25}$ = + 103, in ethanol).

Alternatively, the formation of a berberin bridge from **146** by regioselective Pictet-Spengler reaction employing aqueous formaldehyde (37%) and trifluoroacetic acid afforded (–)-(*S*)-xylopinine (**102**) in 82% yield. Optical rotation of product was $[\alpha]_D^{25}$ = -262 (c = 0.1, in chloroform) (Lit.[50] $[\alpha]_D^{25}$ = - 297, in chloroform).

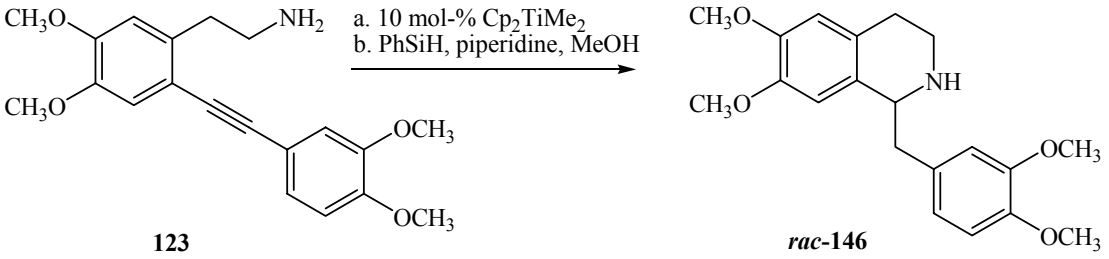
2.5. ENATIOSELECTIVE ONE-POT SYNTHESIS OF ISOQUINOLINE BY A HYDROAMINATION/ ENATIOSELECTIVE REDUCTION SEQUENCE

Modern synthesis design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity. As a result, one-pot procedures have been developed to avoid the decrease of yields caused by workup and purification. With such procedures, intermediates do not need to be stable enough for isolation, because they are quickly transformed by a subsequent reaction into the desired products.

In the Doye group, the borohydride reduction system $NaCNBH_3$, $ZnCl_2$[62] has become the method of choise to reduce imines which are obtained by hydroamination reaction of alkynes to the desired amines. Both reactions can be conveniently performed as a one-pot operation. Using this two-steps method, amino alkyne **123** was converted into *rac*-norlaudanosine **146** in 96% yield.

Alternatively, the amino alkyne **123** could also be cyclized to give *rac*-norlaudanosine **146** in 79% yield using a one pot protocol consisting of Cp_2TiMe_2-catalyzed hydroamination/hydrosilylation sequence.[63]

[61] *Römpp Lexikon Naturstoffe*, 10th ed. (Eds.: B. Fugmann, S. Lang-Fugmann, W. Steglich), Georg Thieme Verlag, Stuttgart, **1997**, p. 79–80.
[62] S. Kim, C. H. Oh, J. S. Ahn, Y. J. Kim, *J. Org. Chem*. **1985**, *50*, 1927–1932.
[63] A. Heutling, F. Pohlki, I. Bytschkov, S. Doye, *Angew. Chem.* **2005**, *117*, 3011–3013.



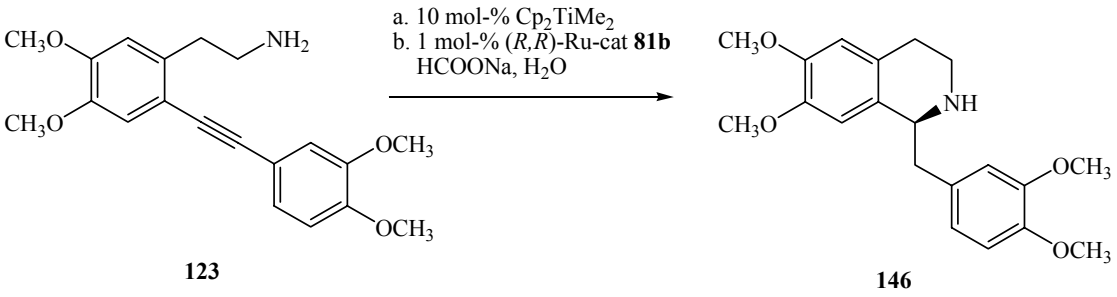
Scheme 34. Hydroamination/hydrosilylation of amino alkyne **123**. Reagents and conditions: a. 10 mol-% Cp_2TiMe_2, toluene, 105°C, 16 h; b. $PhSiH_3$ equiv, 40 mol-% piperidine, 40 mol-% MeOH, 105°, 24 h, 79% (two steps).

Inspired by the work of Odom who has reported that Ti-catalyzed hydroaminations could be followed by further transformations catalyzed by other metals in one-pot, the asymmetric transfer hydrogenation by Noyori´s procedure was attempted to be employed subsequently to the Ti-catalyzed hydroamination reaction. Amino alkyne **123** was subjected to 10 mol-% Cp_2TiMe_2 in toluene at 105°C until amino alkyne **123** was completely consumed. The Noyori´s reduction system (1 mol-% (*R,R*)-Ru-cat **81b**, NEt_3:HCOOH = 5:2, DMF) was then directly added to the hydromination reaction mixture at room temperature. However, after further stirring for 48 h, the desired amine product was not observed according to TLC. The titanium catalyst might be interfering with the Ruthenium–catalyzed transfer hydrogenation process. The same result has also been reported by Siebeneicher,[64] even with high concentrations of the Ru-catalyst. Consequently, the Ti-catalyst must be decomposed before reduction.

Since Cp_2TiMe_2 can be consumed by the methylenation of amides,[65] we thought that if the hydroamination mixture is quenched with DMF (solvent for the reduction process) followed by heating for several hours, the reduction process should work afterwards. Correspondingly, DMF was added to the hydroamination mixture and then the mixture was heated to 65°C for 24 h. Subsequently, under Noyori´s conditions the dihydroisoquinoline **124** could be reduced completely into (*S*)-norlaudanosine (**146**). After purification by flash chromatography, (*S*)-norlaudanosine (**146**) was isolated in 61% yield and, unfortunately, with only 26% *ee*.

[64] H. Siebeneicher, *Dissertation,* Universität Hannover, **2004**, p. 78.
[65] N. A. Petasis, S-P. Lu, *Tetrahedron Lett.* **1995**, *36*, 2393–2396.

Xiao et. al.[66] reported a recent modification of the Noyori system. He described a degassed aqueous system in the presence of HCOONa as the hydrogen source. With this method, unfunctionalized aromatic ketones were easily reduced into alcohols by a Ru-catalyzed transfer-hydrogenation with HCOONa in neat water with good to excellent enantioselectivities. A one-pot hydroamination/modified asymmetric transfer hydrogenation sequence was performed with the amino alkyne **123** as starting material. Cyclization using Cp_2TiMe_2 as the catalyst was complete after 16 h (10 mol-% Cp_2TiMe_2, toluene, 105 °C). Subsequently, water containing (*R,R*)-Ru-catalyst **81b** and HCOONa were added at 40°C. After the resulting mixture had been degassed three times, the solution was allowed to react at 40°C for 7 h. After the solution had been cooled to 25°C and a worked up with ether, (*S*)-norlaudanosine (**146**) was isolated by flash chromatography in 93% yield and with 60% *ee* (Scheme 35).



Scheme 35. One-pot procedure of Cp_2TiMe_2-catalyzed hydroamination/asymmetric Ru-catalyzed transfer hydrogenation reduction.

[66] X. Li, X. Wu, W. Cheng, F. E. Hancock, F. King, J. Xiao, *Org. Lett*. **2004**, *6*, 3321–3324.

III INTRAMOLECULAR HYDROAMINATION OF ALKYNES AS A GENERAL METHOD FOR THE SYNTHESIS OF BENZYLISOQUINOLINES

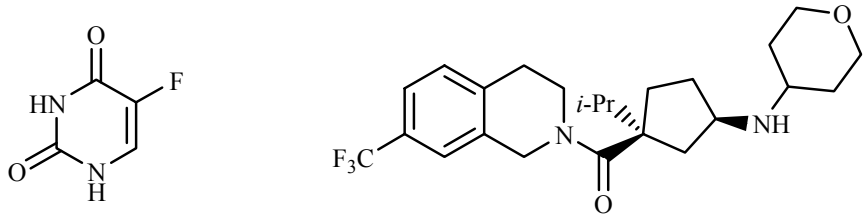
3.1. INTRODUCTION

The successful synthesis of (+)-(*S*)-laudanosine (**101**) and (–)-(*S*)-xylopinine (**102**) motivated us to apply the intramolecular hydroamination of alkynes towards the synthesis of benzylisoquinolines with an electron-deficient A-ring. To our best knowledge today, there are not simple methods to synthesize these molecules. We choose fluorinated benzylisoquinolines as molecular targets.

The organofluorine chemistry contributes to great advances in modern medical treatments. With the aid of the known influence of a fluorine atom on physical, chemical and biological phenomena, therapeutic efficacy has been increased and pharmacological properties have been improved. A significant finding in the late 1950s was that 5-fluoro urasil (5-FU) **148** exhibits significant tumor-inhibiting activity. Since then, 5-FU (**148**) has been employed with success for treatment of human breast cancer and several other types of malignancies.[67] A wide variety of effective fluoromedicines have been

[67] T. Hiyama, *Organofluoride Compounds Chemistry and Application*, Springer, Berlin, **2000**, p. 137.

developed and put into the pharmaceutical marketplace, including steroid- and non-steroid antiviral agents, antihypertensive agents and central nervous system drugs for the management of mental illnesses such as depression and psychoses. Recently, some fluorinated isoquinolines have been patented as compounds, which are useful as modulators of chemokine receptor activity. Tetrahydropyranyl cyclopentyl tetrahydroisoquinoline **150** is the simplest member of this interesting pharmacologically class of molecules.[68]

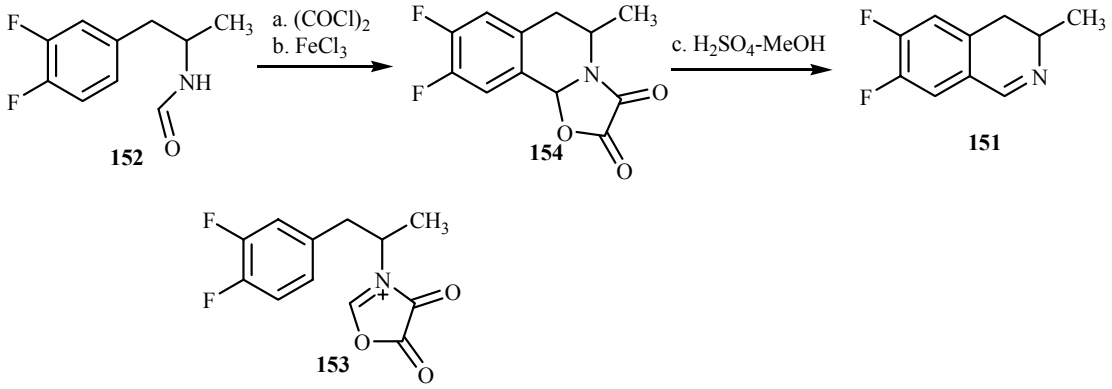


149 **150**

Figure 8. 5-Fluorouracil and a fluorinated isoquinoline.

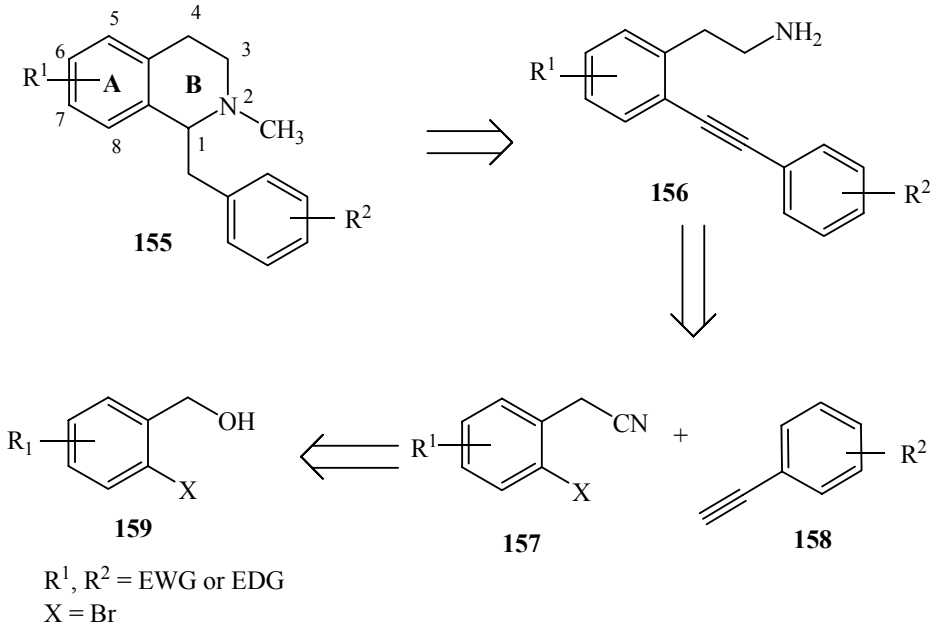
Mitscher et. al.[69] demonstrated the synthesis of 6,7.difluoro dihydroisoquinoline **151** employing the modified Bischler-Napieralski conditions. Reaction of **152** with oxalyl chloride followed by cyclization in the presence of iron(III) chloride produced the oxalyl ester amide **154** in 85% yield for the two steps. The success of this process was via the presumed cyclic oxazolidinedione intermediate which forms a highly reactive *N*-acyliminium ion **153** further polarized in the presence of iron(III) chloride.[70] Compound **154** was immediately hydrolyzed and dehydrated with acidic methanol to give the previously elusive **151** in 73% yield.

[68] R. Jiao, S. D. Goble, S. G. Mills, G. Morriello, A. Pasternak, L. Yang, C. Zhou, G. Butora, S. Kothandaraman, D. Guiadeen, C. Moyes, *PCT Int. Appl.* **2003**, WO 2003-US13121 20030425.
[69] R. A. Fecik, P. Devasthale, S. Pillai, A. Keschavarz-Shokri, L. Shen, L. A. Mitscher, *J. Med. Chem.* **2005**, *48*, 1229-1236.
[70] R. D. Larsen, R. A. Reamer, E. G. Corley, P. Davis, E. J. J. Grabowski, P. J. Reider, I, Shinkai, *J. Org. Chem.* **1991**, **56**, 6034-6038.



Scheme 36. The synthesis of dihydroisoquinoline **151**.

3.2. GENERAL RETROSYNTHESIS ANALYSIS OF BENZYLISOQUINOLINES



Scheme 37. Retrosynthesis of benzylisoquinolines.

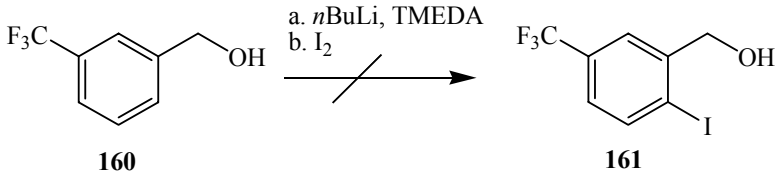
In analogy to the synthesis of laudanosine (**101**), the synthesis of benzylisoquinoline derivatives with electron-deficient A-rings commenced with the preparation of the key intermediate amino alkyne (**156**), as shown in scheme 37. The significant processes in this context are the cross coupling between the aryl bromide **157** and the terminal alkyne **158** which can be achieved by a Sonogashira reaction, and subsequently an

intramolecular Ti-catalyzed hydroamination. The coupling partner *o*-bromo-benzylnitrile **157** should be accessable via cyanation of *o*-bromo benzylalcohol (**159**).

3.3. SYNTHESIS OF 6-TRIFLUOROMETHYLBENZYLISOQUINOLINE

The first goal in this synthesis was to obtain an *o*-halogenated-benzylnitrile. In principle, this could be achieved by halogenation of a deactivated aromatic **160** (scheme 38). Usual methods for this transformation are carried out under harsh conditions. A convenient method, however, is a directed *ortho*-lithiation, followed by a quenching with an electrophile. Several examples have been reported using this method for the metalation of EWG-substituted aromatic system.[71]

Seebach has reported the synthesis of several *ortho*-substituted benzylalcohols via formation of *ortho*-lithiated benzyloxylithium compounds using a direct *ortho* lithiation procedure.[72] We attempted to iodinate *m*-trifluoromethyl benzylacohol (**160**), employing Seebach´s procedure (*n*BuLi 2.0 equiv, TMEDA 2.0 equiv, petrolether, reflux, 16 h). The resulting mixture was cooled to −78°C and then treated with an iodine solution in THF. After the mixture was allowed to reach room temperature, it was found that the desired product **161** was not obtained. The unsuccessful trial of this method was probably caused by side reactions of the lithium alkoxide group, which tends to aggregate with themselves to form oligomeric or polymeric clusters. The oxygen-functionalized side chain is thus converted into a huge and voluminous substituent that sterically shields the neighboring ortho position.[73]



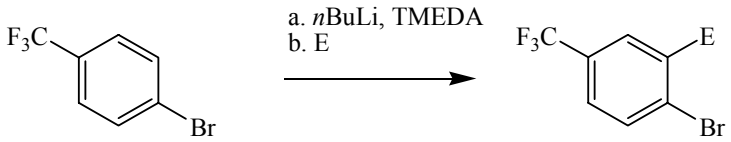
160 **161**

Scheme 38. Application of Seebach´s procedure to the synthesis of **161**.

[71] For reviews, see: a) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933; b) C. G. Hartung, V. Snieckus, in *Modern Arene Chemistry* (Ed.: D. Astruc), VCH, Weinheim, **2002**, p. 330.
[72] N. Meyer, D. Seebach, *Angew. Chem.* **1978**, *90*, 553–554.
[73] For further studies of a similar problem, see: E. Marzi, A. Spitalari, F. Mongin, M. Schlosser, *Eur. J. Org. Chem.* **2002**, 2508–2517.

Since the directed *ortho*-lithiation strategy starting from benzylacohol **160** was unsuccessful, *p*-bromo-trifluorotoluene (**162**) was chosen as the starting material. We thought that removing the benzylic moiety could facilitate the directed *ortho* lithiation and avoid any aggregation problems. As subsequent reaction with formaldehyde should give the desired *o*-halogenated-benzylalcohol **163**. Treatment of *p*-bromo-trifluorotoluene (**162**) with *n*BuLi and TMEDA followed by the addition of monomeric formaldehyde in THF did not give the desired product. Variation of the temperature did not improve the results.

Table 2. Functionalization of aryl bromide **162** via directed *ortho*-lithiation.



162 **163**

	Reagent	Temperature (°C)	Electrophile	Yields (%)
1	*n*BuLi, THF	-78	HCHO	-
2	*n*BuLi, THF	-20	HCHO	-
3	*n*BuLi/TMEDA, THF	-78	HCHO	-
4	*n*BuLi/TMEDA, THF	-20	HCHO	-
5	*n*BuLi/TMEDA, THF	-78	CO_2	17
6	*n*BuLi/TMEDA, THF	-78	I_2	60*
7	*n*BuLi/TMEDA, THF	-20	I_2	63*

* As a mixture (3:2) with starting material.

In contrast to the results obtained with formaldehyde, reactions with CO_2 or I_2, took place succesfully, although with poor yields. The very poor yield obtained after treatment with CO_2 might be evoked by wet CO_2 granula. A better yield was obtained when I_2 was employed as the electrophile. Unfortunately, the obtained mixture between product **163** and starting material **162** could not be separated by flash chromatography or vacuum distillation.

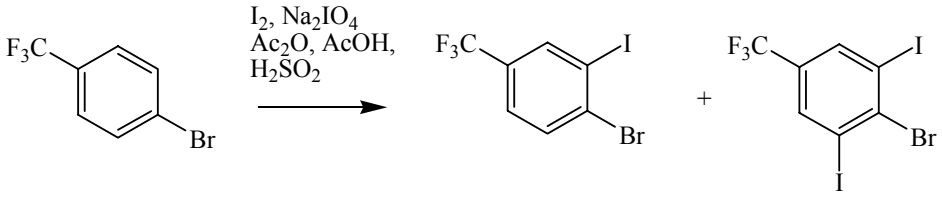
We choose an oxidative aromatic iodination procedure by Lulinski and Skulsky[74] to obtain 3-iodo-4-bromo-trifluorotoluene (**164**). Deactivated aromatic compounds can be iodinated with an anhydrous system of I_2/$NaIO_4$/acetic anhydride/glacial acetic acid, acidified with conc. sulfuric acid. The Author suggested that this reaction follows:

$$14\ Ar\text{-}H + 4\ I_2 + 6\ NaIO_4 + 24\ Ac_2O + 17\ H_2SO_4 \xrightarrow{AcOH/Ac_2O} 14\ Ar\text{-}ISO_4 + 3\ Na_2SO_4 + 48\ AcOH$$

The anhydrous and strongly acidic conditions are indispensable to attain the possible highest yield of the assumed organic iodine (III) intermediates, Ar-ISO_4 or O_4SI-Ar-ISO_4 (undesired product) derived from the reacted deactivated arenes by their electrophilic substitution with I^{3+}. After completion of the main iodination reactions, the resulting reaction mixtures were poured into an excess of aqueous Na_2SO_3 solution (which also destroys the rest of iodine and any oxidizing species).

$$Ar\text{-}ISO_4 + Na_2SO_3 + H_2O \longrightarrow Ar\text{-}I + Na_2SO_4 + H_2SO_4$$

The treatment of *p*-bromo-trifluorotoluene (**162**) under these conditions, surprisingly, gave 4-bromo-3-iodo-trifluorotoluene **164** in 96% yield with 0.5% impurity of 3,5-diiodo-4-bromo-trifluorotoluene (**165**).

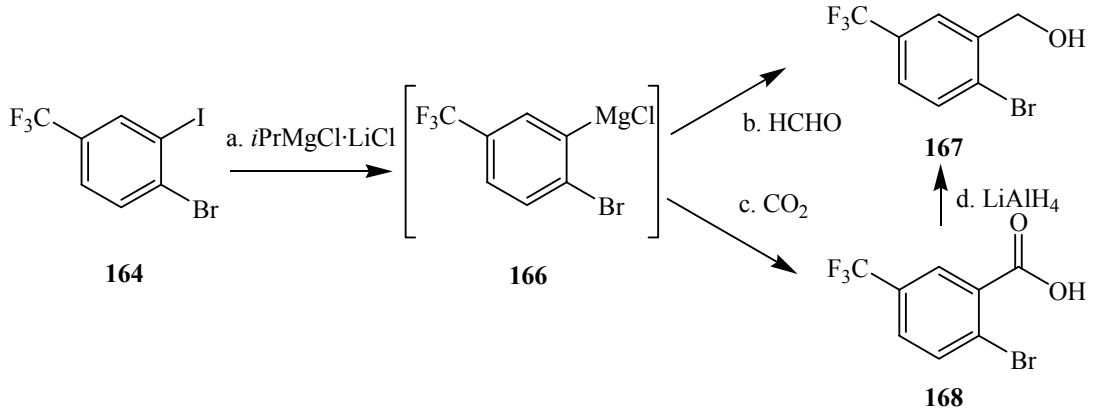


162 **164** **465** impurity

Scheme 39. Iodination of *p*-bromo-trifluorotoluene (**162**). Reagents and condition: I_2 1.1 equiv, $NaIO_4$ 1.1 equiv, CH_3COOH, $(CH_3CO)_2O$, H_2SO_4, 5→25°C, 21 h, 96%.

[74] P. Lulinski, L. Skulski, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 951–956.

At this stage, a chemoselective halogen-magnesium exchange by Knochel,[75] followed by the addition to formaldehyde seems to be a convenient way to obtain *o*-bromo-benzylalcohol derivatives (**167**). Treatment of *o*-bromo-aryliodide **164** with 1.0 equivalent of *i*PrMgCl•LiCl, followed by quenching the resultant aryl magnesium derivative **166** with freshly distilled monomeric formaldehyde in THF[76] at 40°C and aqueous workup provided the expected *o*-bromo-benzylalcohol **167** in 72% yield. Alternatively, using CO_2 as the electrophile, *o*-bromo benzoic acid derivative **168** was obtained in only 34% yield. The carboxylic group of **168** was then reduced easily with $LiAlH_4$ to give **168** in 62% yield.



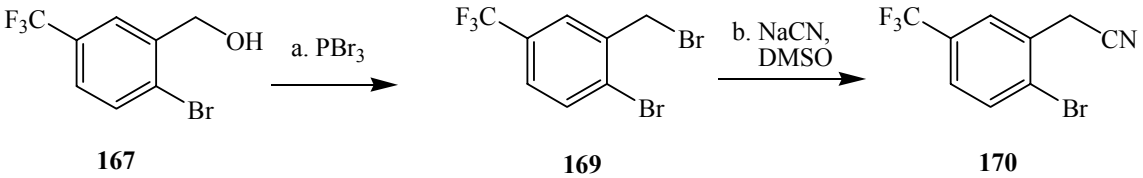
164 **166** **167** **168**

Scheme 40. Synthesis of fragment **167**. Reagents and conditions: a. *i*PrMgCl•LiCl in THF 1.0 equiv, - 20°C, 2 h; b. HCHO in THF 1.1 equiv, - 20°C, 1 h, 72%; c. CO_2 granule, - 20°C, 1 h, 34%; d. $LiAlH_4$ 2.2 equiv, ether, 25°C, 3 h, 62%.

With the alcohol group in the right place, attempts could begin to substitute the alcohol group by a nitrile group. It was desirable to perform this conversion in a single step, in order to avoid a second process at the benzylic position. Initially, we chose a simple procedure reported by Davis and Untch,[77] using NaCN/Me_3SiCl and a catalytic amount of NaI in DMF/CH_3CN, to be employed to the benzyl alcohol **167**. Unfortunately, this procedure did not give the desired product. Alternatively, we focused on a standard procedure for the transformation of an alcohol. The benzylic alcohol **167** was first

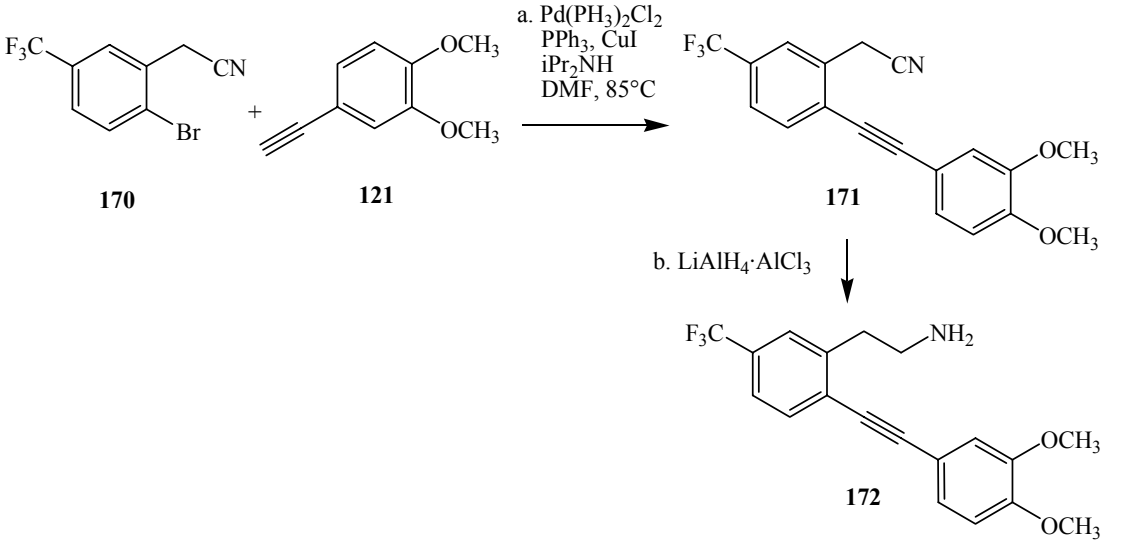
[75] For an example of a chemoselective halogen-magnesium exchange, see: C-Y. Liu, P Knochel, *Org. Lett.* **2005**, *7*, 2543–2546.
[76] Preparation of monomeric formaldehyde in THF, see: M. Schlosser, D. Coffinet, *Synthesis* **1971**, 380–381.
[77] R. Davis, K. G. Untch, *J. Org. Chem .Soc.* **1981**, *46*, 2985–2987.

transformed into the bromide **169**, by reaction with PBr_3 in 69% yield. Nucleophilic substitution employing bromobenzyl derivative **169** and NaCN in DMSO afforded *o*-bromo-benzylnitrile **170** in 62% yield.



167 **169** **170**

Scheme 41. Transformation of the alcohol group to a nitrile group. Reagents and conditions: a. PBr_3 0.5 equiv, CH_2Cl_2, 25°C, 16 h, 69%; b. NaCN 2.0 equiv, DMSO, 90 → 50°C, 62%.



170 **121** **171** **172**

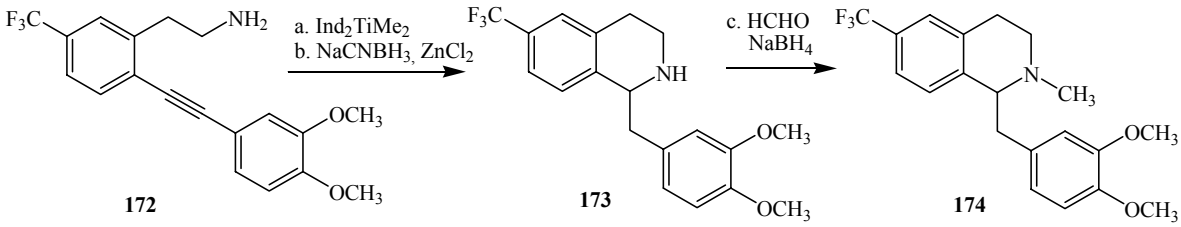
Scheme 42. Synthesis of amino alkyne **176**. Reagents and conditions: a. 4 mol-% $Pd(PPh_3)_2Cl_2$, 8 mol-% PPh_3, 8 mol-% CuI, *i*$PrNH_2$, DMF, 85°C, 16 h, 96 %; b. $LiAlH_4$•$AlCl_3$ 1.0 equiv, ether, 25°C, 2 h, 93%.

The synthesis of the key intermediate amino alkyne **172** from **170** required a cross coupling with the terminal alkyne **121** under Sonogashira conditions. Under the standard conditions (4 mol-% $Pd(PPh_3)_2Cl_2$, 8 mol-% PPh_3, 8 mol-% CuI, i$PrNH_2$, DMF, 85°C, 16 h), bisarylacetylene **171** was obtained in 96% yield. It is important to note that with the arylbromide as the coupling partner, DMF was found to be the best solvent for the cross coupling reactions.[78] Finally, amino alkyne **172** was obtained in 93% yield by a

[78] a) I. Saito, K. Yamaguchi, R. Nagata, E. Murahashi, *Tetrahedron Lett.* **1990**, *31*, 7469–7472; b) F. Makra, J. C. Rohloff, A.V. Muehldorf, J. Link, *Tetrahedron Lett.* **1995**, *36*, 6815–6818; c) D. H.

reduction of the nitrile using a strong hydride reducing agent ($LiAlCH_4 \cdot AlCl_3$, ether, 2 h).

The tetrahydroisoquinoline **173** was formed by cyclization of amino alkyne **172**. The key intermediate **172** was subjected to an intramolecular hydroamination reaction employing 5 mol-% Ind_2TiMe_2 as the catalyst in toluene at 110°C for 16 h. Subsequently, reduction of the imine using the hydride reagent $NaCNBH_3$, $ZnCl_2$ afforded tetrahydroisoquinoline **173** in 96% yield. Finally, methylation of the amino group of **173** applying a reductive amination protocol with formaldehyde 37% and $NaBH_4$, furnished CF_3-substituted benzylisoquinoline **174** in 69% yield.

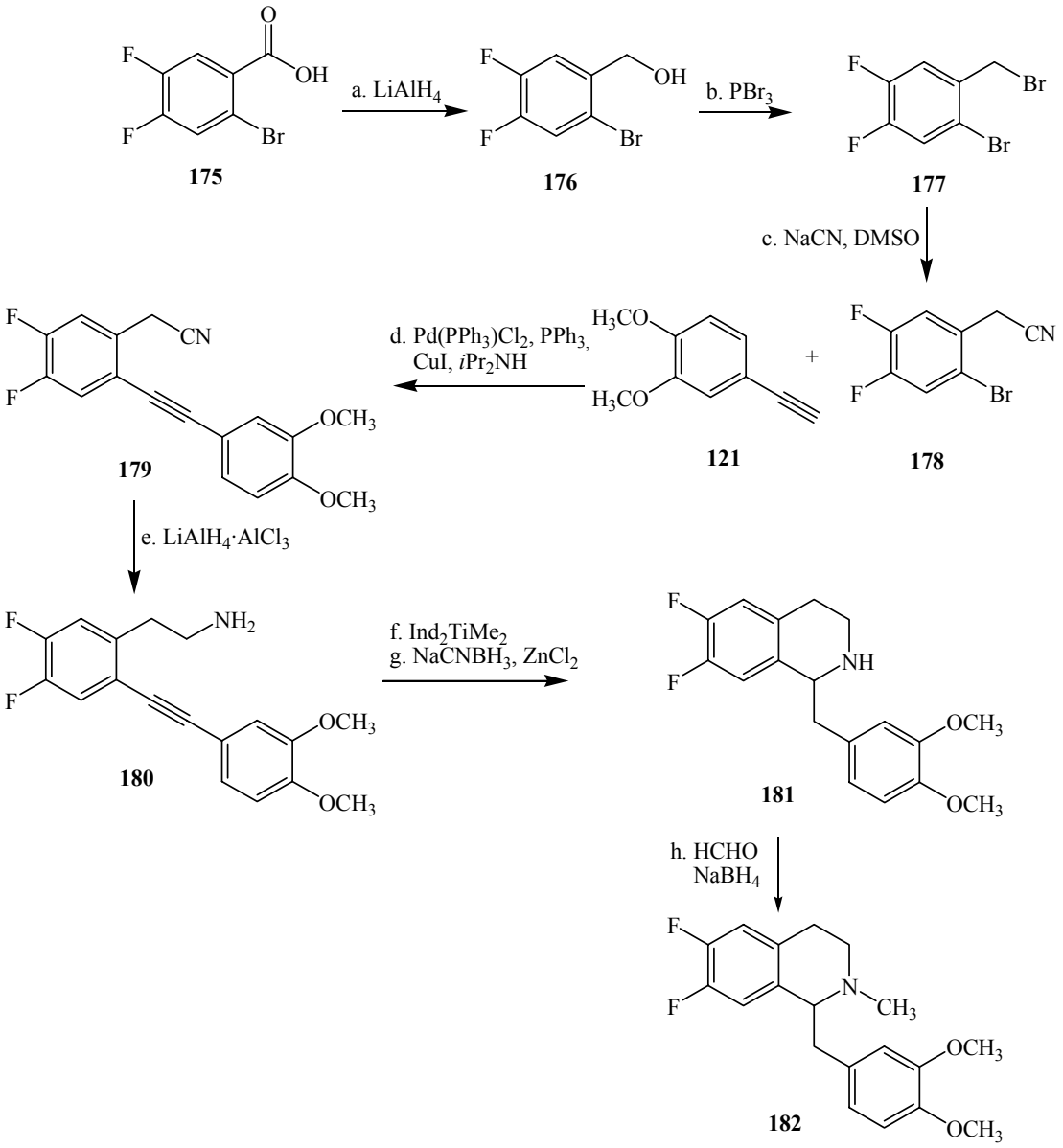


Scheme 43. The synthesis of tetrabenzylisoquinoline **174**. Reagents and conditions: a. 5 mol-% Ind_2TiMe_2, toluene, 110°C, 16 h; b. $NaCNBH_3$ 2.0 equiv, $ZnCl_2$ 1.0 equiv, MeOH, 25°C, 20 h, 96% (two steps); c. CH_2O, $NaBH_4$ 10 equiv, H_2O, MeOH, 25 °C, 2 h, 68%.

3.4. SYNTHESIS OF 6,7-DIFLUOROBENZYLISOQUINOLINE

With the experience obtained in the synthesis of amino alkyne **172**, we used the same conditions to synthesize amino alkyne **180** from commercially available 2-bromo-4,5-difluorobenzoic acid **175** (see scheme 44). First, the carboxylic group was reduced using $LiAlH_4$ to furnish benzylalcohol **176** in 59% yield. Treatment of benzylalcohol **176** with PBr_3 transformed the alcohol group into the bromide group to give benzyl bromide **177** in 94% yield. Nucleophilic substitution using benzylbromide **177** and NaCN in DMSO furnished 2-bromo-4,5-difluorobenzylnitrile (**178**) in 58% yield.

Turkenburg, A. A. Antipov, M. B. Thathagar, G. Rothenberg, G. B. Sukhorukov, E. Eiser, *Phys. Chem. Chem. Phys*. **2005**, *7*, 2237–2240.



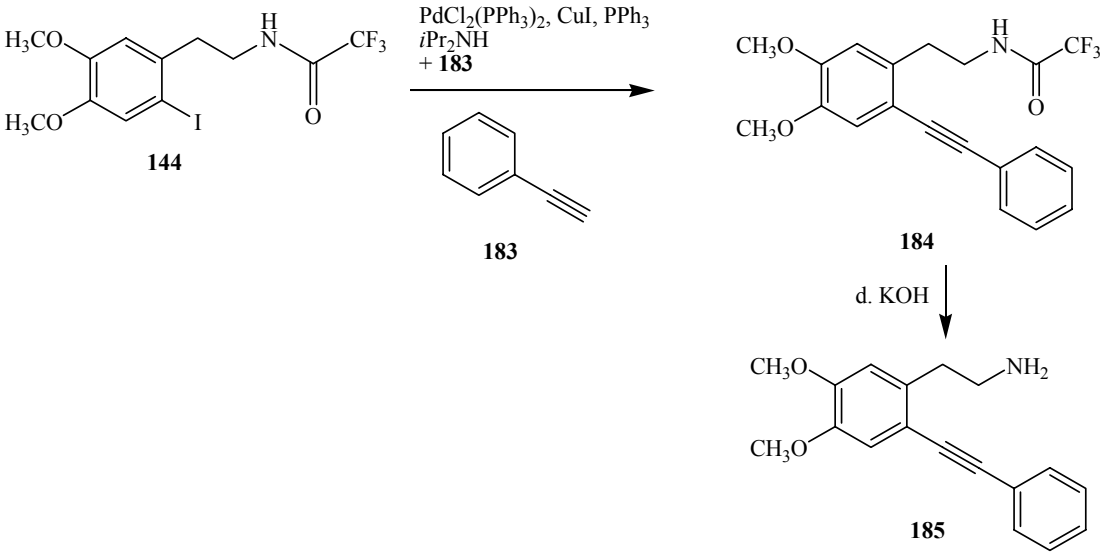
Scheme 44. Synthesis of tetrahydrobenzylisoquinoline **182**. Reagents and conditions: a. $LiAlH_4$ 1.1 equiv, ether, 25°C, 2 h, 59%; b. PBr_3 0.5 equiv, CH_2Cl_2, 25°C, 24 h, 94%; c. NaCN 2.0 equiv, DMSO, 90→50°C, 58%; d. 4 mol-% $PdCl_2(PPh_3)_2$, 8 mol-% CuI, 8 mol-% PPh_3, iPr_2NH, DMF, 80°C, 16 h, 79%; e. $LiAlH_4$•$AlCl_3$ 1.0 equiv, ether, 25°C, 2 h, 91%; f. 5 mol-% Ind_2TiMe_2, toluene, 110°C, 16 h; g. $NaCNBH_3$ 2.0 equiv, $ZnCl_2$ 1.0 equiv, MeOH, 25°C, 20 h, 96% (two steps); h. CH_2O, $NaBH_3$, H_2O, MeOH, 25°C, 2 h, 84%.

The arylbromide **178** was then coupled with alkyne **121** under Sonogashira conditions to give alkyne nitrile **179** in 79% yield. Finally, the key intermediate amino alkyne **180** was obtained after reduction with $LiAlH_4 \cdot AlCl_3$ in 91% yield.

The key intermediate **180** was then subjected to an intramolecular hydroamination reaction employing 5 mol-% Ind_2TiMe_2 as the catalyst in toluene at 110°C for 16 h. Subsequently, reduction of the imine using hydride reagent $NaCNBH_3$, $ZnCl_2$ afforded tetrahydroisoquinoline **181** in 96% yield over two steps. Finally, the methylation of the amino group of **182** using a reductive amination protocol with formaldehyde 37% and $NaBH_4$, furnished benzylisoquinoline **182** in 84% yield.

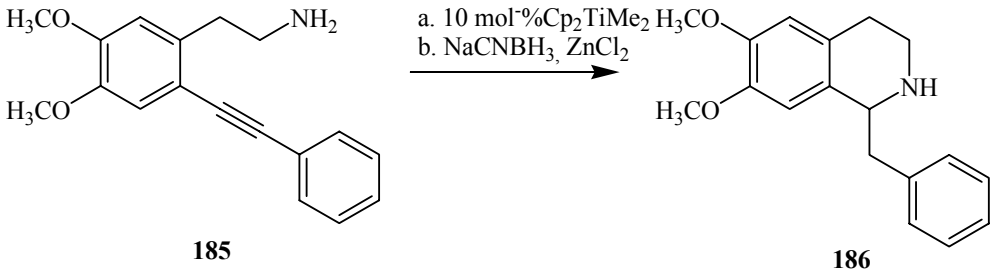
3.5. SYNTHESIS OF 3′,4′-DEDIMETHOXYNORLAUDANOSINE

During the synthesis of laudanosine (**101**) we had already synthesize aryliodide **144**. With this aryl iodide in hand, another alkyne **184** was synthesized from phenylacetylene **183** under the standard Sonogashira conditions (2 mol-% $Pd(PPh_3)_2Cl_2$, 8 mol-% PPh_3, 8 mol-% CuI, iPr_2NH, 25°C, 16 h) in 81% yield. Liberation of the NH_2-group under basic conditions (KOH, MeOH, H_2O, 25°C, 20 h) delivered amino alkyne **185** in 83% yield.



Scheme 45. Synthesis of amino alkyne **185**. Reagents and conditions: a. 4 mol-% $PdCl_2(PPh_3)_2$, 8 mol-% CuI, 8 mol-% PPh_3, iPr_2NH, 25°C, 16 h, 81%; d. KOH 10.0 equiv, MeOH, 25°C, 8 h, 83%.

The key intermediate **185** was subjected to an intramolecular hydroamination reaction employing 10 mol-% Cp_2TiMe_2 as the catalyst in toluene at 110°C for 16 h, and subsequently, reduction of the imine using hydride reagent $NaCNBH_3$, $ZnCl_2$ afforded tetrahydroisoquinoline **186** in 96% yield over two steps.

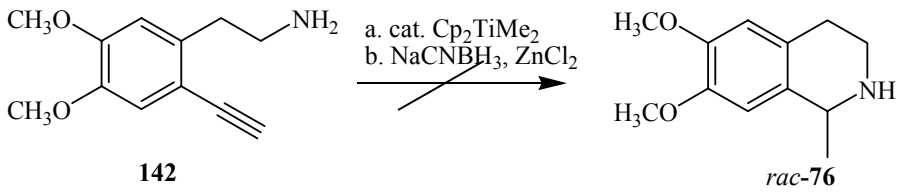


185 **186**

Scheme 46. Synthesis of tetrahydrobenzylisoquinoline **186**. Reagents and conditions: a. 10 mol-% Cp_2TiMe_2, toluene, 110°C, 16 h; b. $NaCNBH_3$ 2.0 equiv, $ZnCl_2$ 1.0 equiv, MeOH, 25°C, 20 h, 82% (two steps).

3.6. ATTEMPS TO SYNTHESIZE OF SALSOLIDINE

Starting from amino alkyne **142**, we attempted to synthesize salsolidine (**76**). The amino alkyne **142** was subjected to hydroamination conditions in the presence of 10 mol-% Cp_2TiMe_2 at 105°C for 24 h. However, after a standard reduction in the presence $NaCNBH_3$ and $ZnCl_2$, we did not find the desired product of **76** by flash chromatography. The same result was obtained, when 20 mol-% Cp_2TiMe_2 was employed.



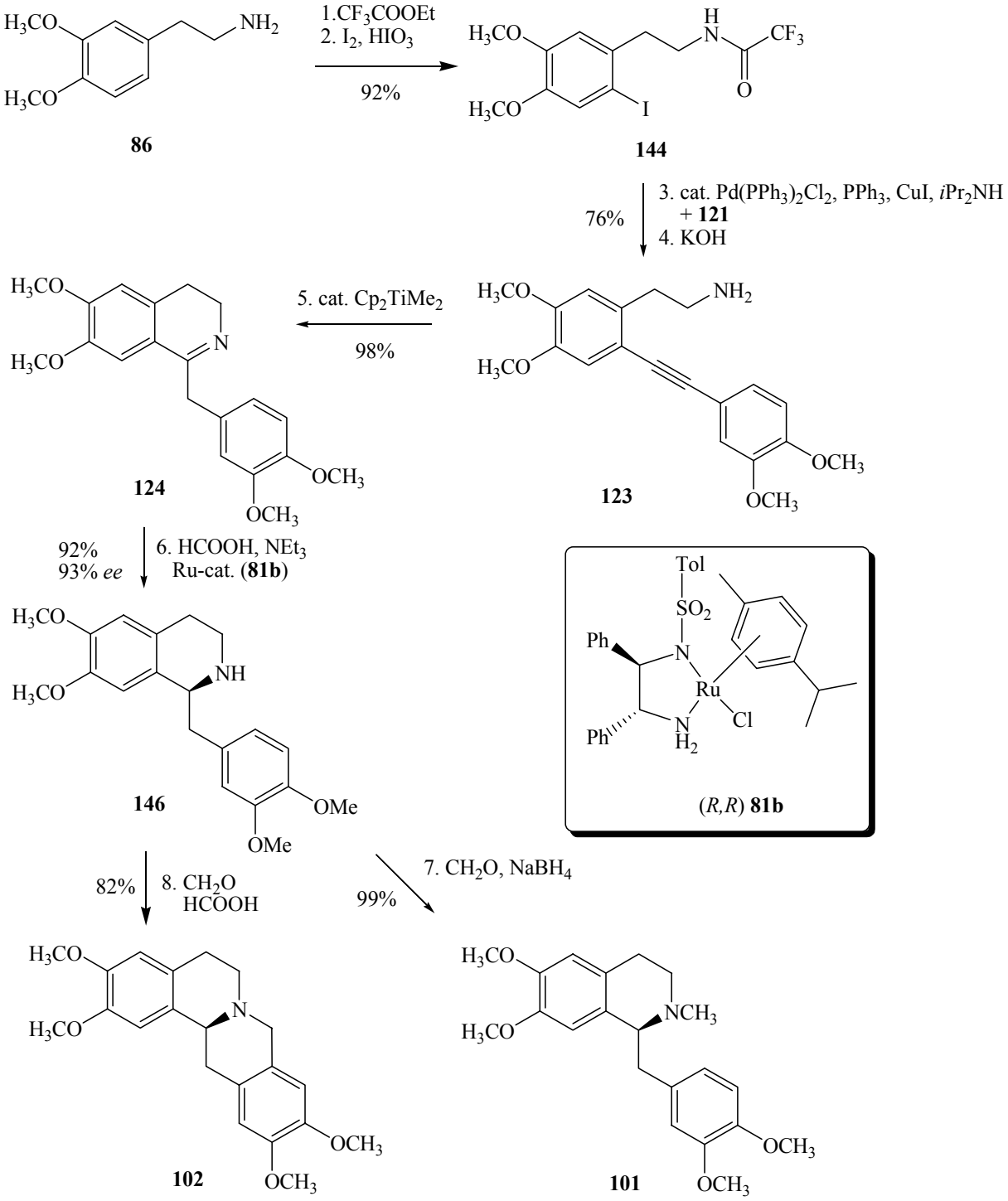
142 *rac*-**76**

Scheme 47. Attempts to synthesize salsolidine (**76**) using a Ti-catalyzed hydroamination.

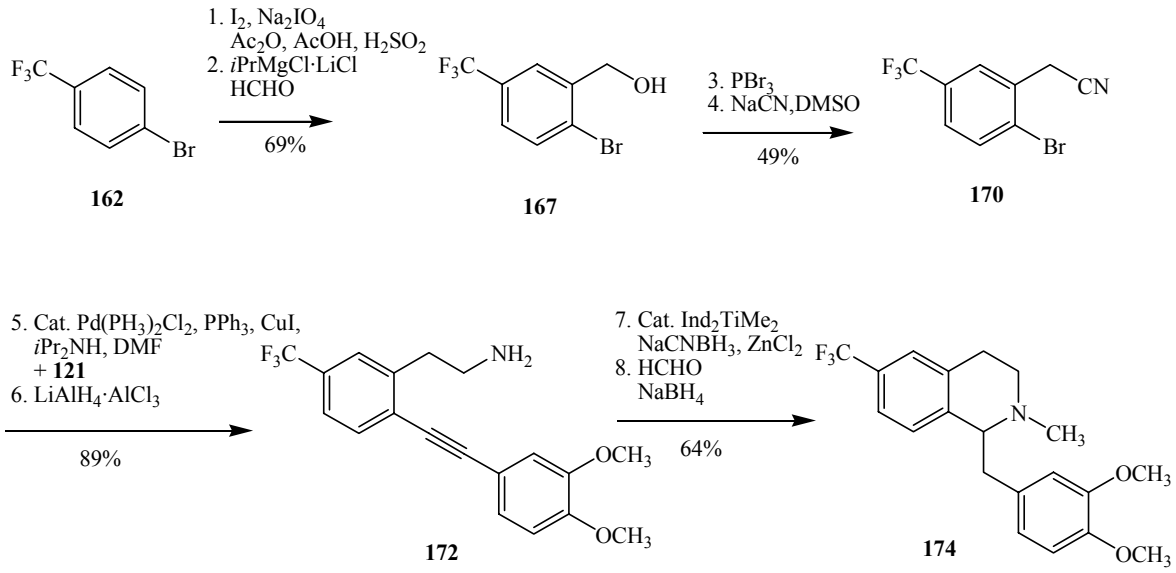
IV SUMMARY

We have demonstrated a new and general method for the synthesis of benzylisoquinolines. The Sonogashira reaction and an intramolecular alkyne-hydroamination are used as key steps in our strategy. Using this new method, benzylisoquinolines containing both electron-rich and electron-deficient A-rings can be synthesized successfully.

The attempts to synthesize (–)-(*S*)-laudanosine (**101**) and (+)-(*S*)-xylopinine (**102**) were successful in 7 steps from commercially available homoveratylamine (**86**) in 62% and 51% yields, respectively. The key intermediate amino alkyne **123** was accessed easily by the coupling of arylhalide **144** and alkyne **121** using the Sonogashira protocol. Dihydroisoquinoline **124** was obtained by intramolecular hydroamination of amino alkyne **123**. Employing Noyori´s protocol, *S*-configuration at C-1 of the benzylisoquinoline was constructed in 93% *ee*. Finally, the methylation of norlaudanosine (**146**) under the conditions of a reductive amination afforded (–)-(*S*)-laudanosine (**101**). Alternatively, the formation of the berberin bridge using a Pictet-Spengler reaction afforded (+)-(*S*)-xylopinine (**102**).

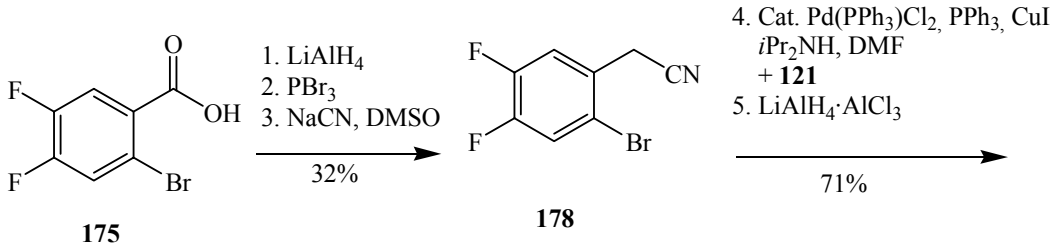

1.CF3COOEt
2. I2, HIO3
92%
86
144
76%
3. cat. Pd(PPh3)2Cl2, PPh3, CuI, iPr2NH
+ 121
4. KOH
5. cat. Cp2TiMe2
98%
124
123
92%
93% ee
6. HCOOH, NEt3
Ru-cat. (81b)
146
(R,R) 81b
82%
8. CH2O
HCOOH
7. CH2O, NaBH4
99%
102
101

The success of the synthesis of laudanosine (**101**) and xylopinine (**102**) motivated us to apply this strategy toward the synthesis of benzylisoquinolines with electron-deficient A-rings. The first molecular target in this context was 6-trifluoromethyl-benzylisoquinoline (**174**). Applying the described method, 6-trifluoromethyl-benzylisoquinoline (**174**) was successfully synthesized in 20% yield over 8 steps from commercially available 4-bromo-trifluorotoluene (**162**).

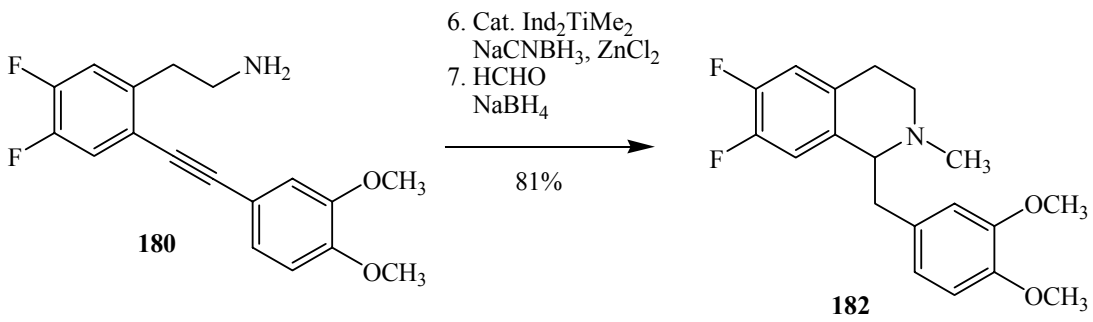


162 **167** **170** **172** **174**

With the experience of the synthesis of **174**, the next target was synthesized following a similar route. Again, both the Sonogashira reaction and the intramolecular hydroamination worked successfully to give the desired products in excellent yields. The 6,7-difluoro-benzylisoquinoline **182** was obtained in 19% yield from commercially available *o*-bromo-benzoic acid **175** over 8 steps.



175 **178**



180 **182**

V EXPERIMENTAL SECTION

5.1. GENERAL REMARKS:

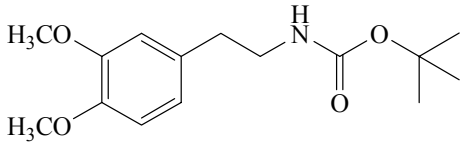
All reactions were performed under argon in flame dried Duran glassware (e.g. Schlenk tubes equipped with Teflon stopcocks). Toluene, diethylether and THF were distilled under argon from molten sodium. CH_2Cl_2 and triethylamine were distilled from calcium hydride. Formic acid was distilled from phthalic anhydride. Cp_2TiMe_2 was synthesized according to ref.[79] (η^6-*p*-cymene)[(1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylene-diamine)]RuCl was synthesized according to ref.[41a] All other reagents were purchased from commercial sources and were used without further purification. For the chromatographic purification of products, glass columns of different widths and lengths were used depending on the purification problem. Silica gel 60 (0.040-0.063 nm) was used as stationary phase and acid washed sea sand was used as filling material. The eluent was chosen after preliminary thin layer chromatography experiments. For the separation, a light pressure was applied. After isolation of the fractions, the solvents were evaporated under reduced pressure, and the resulting purified product was dried under high vacuum. Unless otherwise noted, yields refer to isolated yields of pure compounds as gauged by thin layer chromatography (TLC) and ^{1}H and ^{13}C NMR spectroscopy. All products were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, and mass spectrometry (MS). Additional characterization data were obtained by high-resolution mass spectrometry (HRMS) and/or CHN elemental analysis. NMR spectra were recorded with the following spectrometers: Bruker Avance ARX 250, Bruker Avance DRX 300, Bruker AC 300, Bruker Avance DRX 400, Bruker Avance DRX 500. All ^{1}H NMR spectra are reported in δ units ppm downfield from tetramethylsilane as internal standard or to the singlet of $CDCl_3$ at δ = 7.26 ppm. All ^{13}C NMR spectra are reported in δ units ppm relative to the central line of the triplet of CDC_{l3} at δ = 77.0 ppm. IR spectra were recorded with a Bruker Vector 22 spectrometer using an attenuated total reflection (ATR) method or KBr pellet. Mass spectra were recorded with

[79] N. A. Petasis, in: *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. A. Paquette), John Wiley & Sons, New York, **1995**, vol. 1, p. 470–473.

a JEOL JMS-700 or a Finnigan TSQ 700 (EI) spectrometer with an ionization potential of 70 eV. Elemental analyses were carried out with an Elementar Vario EL machine. *ee* values were determined by HPLC analysis carried out with a Surveyor HPLC System Thermo (Chiralcel OD column). Optical rotations were recorded with a Perkin–Elmer 241 polarimeter at the indicated temperature with the sodium-D-line (λ = 589 nm) in a cell of length l = 1 dm. Melting points were determined in an open capillary using a mercury thermometer by Tottoli melting point apparatus Büchi 510 and were uncorrected. PE: light petroleum ether, b.p. 40–60 °C. MTBE: methyl *tert*-butyl ether. EE: ethyl acetate.

5.2. DESCRIPTION OF THE EXPERIMENTS, ANALYTICAL DATA

ENANTIOSELECTIVE SYNTHESIS OF (+)-(S)-LAUDANOSINE AND (−)-(S)-XYLOPININE



131

[2-(3′,4′-Dimethoxy-phenyl)-ethyl]-carbamic acid *t*-butyl ester (**131**): At 0°C, Boc_2O (8.41 g, 38.5 mmol) and NaOH (2.40 g, 60.0 mmol) were added to a suspension of homoveratrylamine (**86**) (5.44 g, 30.0 mmol) in water (60 mL). After the mixture has been stirred at 25°C for 18 h, ethyl acetate (60 mL) was added. The mixture was coolded to 0°C and the pH was adjusted to 2-3 with 2 N HCl. After washing with a solution of $KHSO_4$ (1 M, 100 mL) and brine (100 mL), the organic layer was dried with Na_2SO_4 and the solvent was removed under vacuum. Recrystallization of the residue from MTBE/PE gave **131** (7.11 g, 84%) as colourless crystals. Further purification of the mother liquor by flash chromatography (SiO_2, MTBE/PE = 1:1) provided additional **131** (1.13 g, 13%).

M.p.: 57-58°C.

^{1}H-NMR (400 MHz, $CDCl_3$, TMS): δ = 1.44 (s, 9 H); 2.74 (t, J = 7.0, 2 H); 3.38-3.33 (m, 2 H); 3.86 (s, 3 H); 3.87 (s, 3 H); 4.58 (br. s, 1 H); 6.72 (s, 1 H); 6.73 (d, J = 8.6 Hz, 1 H); 6.81 (d, J = 8.0 Hz, 1 H) ppm.

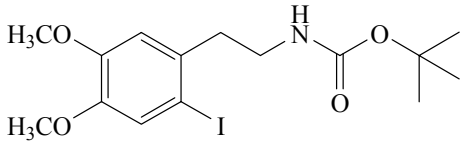
^{13}C-NMR (100 MHz, DEPT, $CDCl_3$, TMS): δ = 28.4 (CH_3), 35.8 (CH_2), 41.9 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 79.2 (C), 111.4 (CH), 112.0 (CH), 120.7 (CH), 131.5 (C), 147.6 (C), 149.0 (C), 155.9 (C) ppm.

IR (Golden Gate ATR): $\tilde{\upsilon}$ = 3373, 2988, 2967, 2939, 2874, 2837, 1684, 1592, 1518, 1464, 1419, 1389, 1365, 1268, 1233, 1170, 1144, 1027, 849, 813, 766, 609 cm^{-1}.

MS: *m/z* (%) = 281 (22) [M^+], 264 (13), 226 (43), 208 (13), 180 (16), 164 (89), 151 (100), 149 (9), 121 (9), 107 (12), 94 (14), 91 (8), 79 (8), 77 (9), 66 (7).

HRMS: calcd. ($C_{15}H_{23}NO_4$) 281.1627, found 281.1623.

$C_{15}H_{23}NO_4$ (281.3): calcd. C 64.03, H 8.24, N 4.98; found C 63.75, 8.20, N 4.95.



132

[2-(2´-Iodo-4´,5´-dimethoxy-phenyl)-ethyl]-carbamic acid *t*-butyl ester (**132**): A solution of **131** (1.53 g, 5.4 mmol), I_2 (0.50 g, 2.2 mmol) and HIO_3 (0.19 g, 1.1 mmol) in a 3:1 mixture of MeOH/H_2O (55.0 mL) was heated to 85°C for 48 h. Then, aqueous Na_2SO_3 (5%) was added the colour of iodine disappeared. The mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed under vacuum. Recrystallization of residue from MTBE/PE gave **132** (1.20 g, 55%) as pale-yellowish crystals and further purification by flash chromatography (SiO_2, MTBE/PE = 1:1) of the mother liquor provided additional **132** (0.52 g, 24%).

M.p.: 83-84°C.

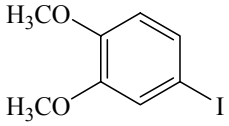
^{1}H-NMR (400 MHz, $CDCl_3$, TMS): δ = 1.44 (s, 9 H); 2.87 (t, J = 7.1 Hz, 2 H); 3.36-3.31 (m, 2 H); 3.85 (s, 6 H); 4.62 (br. s, 1 H); 6.74 (s, 1 H); 7.21 (s, 1 H) ppm.

^{13}C-NMR (100 MHz, DEPT, $CDCl_3$): δ = 28.5 (CH_3), 40.4 (CH_2), 40.7 (CH_2), 56.0 (CH_3), 56.2 (CH_3), 79.3 (C), 88.1 (C), 112.8 (CH), 121.8 (CH), 134.1 (C), 148.3 (C), 155.9 (C) ppm.

IR (Golden Gate ATR): $\tilde{\upsilon}$ = 3335, 3003, 2970, 2932, 2871, 2843, 1686, 1541, 1509, 1498, 1458, 1442, 1379, 1367, 1302, 1291, 1253, 1221, 1164, 1030, 861 cm^{-1}.

MS: *m/z* (%) = 407 (40), 351 (49), 333 (13), 290 (100), 277 (74), 263 (10), 233 (10), 224 (28), 207 (25), 180 (91), 164 (28), 151 (37), 135 (12), 121 (11), 107 (17), 91 (9), 79 (10), 77 (13).

HRMS: calcd. ($C_{15}H_{23}NO_4I$) 407.0594, found 407.0584.



135

4-Iodo-1,2-dimethoxy-benzene (**135**): A solution of veratrol (**134)** (13.82 g, 100 mmol), I_2 (10.12 g, 40.0 mmol), and HIO_3 (3.52 g, 20.0 mmol) in a 3:1 mixture of MeOH/H_2O (1000 mL) was heated to 85°C for 48 h. Then, aqueous Na_2SO_3 (5%) was added until the iodine color disappeared. The mixture was extracted with CH_2Cl_2 (3×150 mL) and the combined organic layers were dried with Na_2SO_4. After concentration under vacuum and purification by Kugelrohr distillation, **135** (24.32 g, 92.1 mmol, 92%) was isolated as a yellow oil.

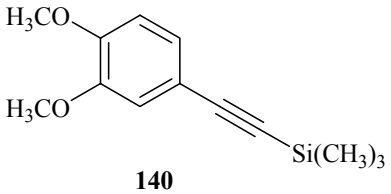
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 3.85 (s, 3 H), 6.61 (d, J = 8.5 Hz, 1 H), 7.11 (d, J = 1.8 Hz, 1 H), 7.22 (dd, J = 1.8, 8.5 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 55.9 (CH_3), 56.1 (CH_3), 82.3 (C), 113.2 (CH), 120.4 (CH), 129.8 (CH), 149.2 (C), 149.9 (C) ppm.

IR: $\tilde{\nu}$ = 2955, 2930, 2836, 1583, 1503, 1460, 1439, 1393, 1321, 1250, 1229, 1177, 1157, 1022, 838, 797, 762, 614 cm^{-1}.

MS: m/z (%) = 264 (83) [M^+], 249 (26), 221 (31), 218 (18), 203 (17), 122 (19), 94 (100), 79 (33), 77 (23), 66 (24).

HRMS: calcd. ($C_8H_9IO_2$) 263.9647; found 263.9647.



140

(3,4-Dimethoxy-phenylethynyl)-trimethyl-silane (**140**): $Pd(PPh_3)_2Cl_2$ (282 mg, 0.40 mmol, 2 mol-%), CuI (160 mg, 0.84 mmol, 4 mol-%), PPh_3 (208 mg, 0.80 mmol, 4 mol-%), and iPr$_2$NH (60 mL) were placed in a round-bottomed flask. After addition of 4-iodoveratrol (**135)** (5.28 g, 20.0 mmol), the mixture was stirred at 25°C for 30 min, and trimethylsilylacetylene (1.96 g, 20.0 mmol) was then added. After this mixture has been stirred at 25°C for an additional 16 h, a saturated NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/MTBE, 3:1), **140** (4.31 g, 18.4 mmol, 92%) was isolated as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.24 (s, 9 H), 3.87 (s, 3 H), 3.87 (s, 3 H), 6.76 (d, J = 8.3 Hz, 1 H), 6.96 (d, J = 1.8 Hz, 1 H), 7.07 (dd, J = 1.9, 8.3 Hz, 1 H) ppm.

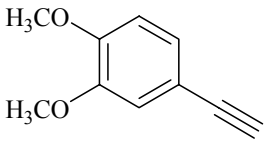
^{13}C NMR (100 MHz, DEPT, $CDCl_3$): δ = 0.0 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 92.3 (C), 105.2 (C), 110.8 (CH), 114.6 (CH), 115.3 (C), 125.4 (CH), 148.5 (C), 149.7 (C) ppm.

IR: $\tilde{\nu}$ = 3001, 2958, 2835, 2156, 1599, 1577, 1514, 1464, 1442, 1409, 1322, 1266, 1243, 1197, 1163, 1137, 1027, 951, 855, 765 cm^{-1}.

MS: m/z (%) = 234 (58) [M^+], 219 (100), 203 (11), 162 (14), 151 (13), 138 (10), 113 (10), 109 (4), 95 (4), 77 (8).

HRMS: calcd. ($C_{13}H_{18}O_2Si$) 234.1076; found 234.1058.

$C_{13}H_{18}O_2Si$ (234.4): calcd. C 66.62, H 7.74; found C 66.57, H 7.82.



121

4-Ethynyl-1,2-dimethoxy-benzene (**121**): Anhydrous K_2CO_3 (138 mg, 1.00 mmol) was added to a solution of **140** (2.41 g, 10.3 mmol) in MeOH (25 mL). After this mixture had been stirred at 25°C for 4 h, the solvent was evaporated under vacuum. A saturated aqueous $NaHCO_3$ was added to the residue and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/MTBE, 1:1), **121** (1.37 g, 8.45 mmol, 82%) was isolated as a white crystalline solid.

M.p.: 70-71°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.00 (s, 1 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 6.79 (d, J = 8.3 Hz, 1 H), 6.98 (d, J = 1.8 Hz, 1 H), 7.10 (dd, J = 1.8, 8.3 Hz, 1 H) ppm.

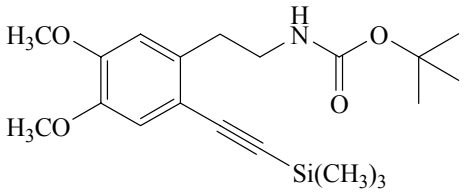
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 55.9 (CH_3), 75.6 (CH), 83.7 (C), 110.9 (CH), 114.2 (C), 114.7 (CH), 125.4 (CH), 148.6 (C), 149.9 (C) ppm.

IR: $\tilde{\nu}$ = 3428, 3259, 3250, 3007, 2971, 2939, 2843, 1597, 1579, 1511, 1452, 1446, 1408, 1323, 1263, 1240, 1152, 1138, 1035, 1026, 860, 821, 810, 730, 621 cm^{-1}.

MS: m/z (%) = 162 (100) [M^+], 147 (21), 119 (10), 91 (14), 76 (8), 65 (6).

HRMS: calcd. ($C_{10}H_{10}O_2$) 162.0681; found 162.0659.

$C_{10}H_{10}O_2$ (162.2): calcd. C 74.06, H 6.21; found C 73.66, H 6.14.



136

[2-(4′,5′-Dimethoxy-2′′-trimethylsilanylethynyl-phenyl)-ethyl]-carbamic acid *t*-butyl ester (**136**): $Pd(PPh_3)_2Cl_2$ (141 mg, 0.2 mmol, 2 mol-%), CuI (76 mg, 0.4 mmol, 4 mol-%), PPh_3 (105 mg, 0.4 mmol, 4 mol-%) and *i*-Pr_2NH (60.0 mL) were placed in a round-bottomed flask. After addition of **132** (4.07 g, 10.0 mmol), the mixture was stirred at 25°C for 30 min, and trimetylsilylacetylene (0.98 g, 10.0 mmol) was added. After this mixture had been stirred at 25°C for additional 16 h, a saturated NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2 (3x 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE:PE, 1:1), **136** (2.64 g, 70%) was isolated as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.24 (s, 9 H) 1.41 (s, 9 H); 2.91 (t, J = 6.8 Hz, 2 H); 3.41-3.37 (m, 2 H); 3.84 (s, 3 H); 3.86 (s, 3 H); 4.64 (br. s, 1 H); 6.67 (s, 1 H); 6.92 (s, 1 H) ppm.

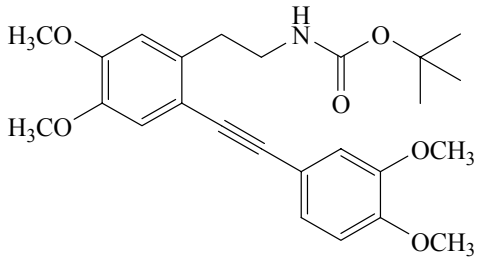
^{13}C-NMR (100 MHz, DEPT, $CDCl_3$): δ = 0.0 (CH_3), 28.4 (CH_3), 34.3 (CH_2), 41.1 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 79.0 (C), 96.6 (C), 103.9 (C), 112.2 (CH), 114.4 (C), 114.7 (CH), 135.1 (C), 147.1 (C), 149.6 (C), 155.8 (C) ppm.

IR (film): $\tilde{\upsilon}$ = 3386, 2961, 2147, 1713, 1604, 1511, 1465, 1392, 1365, 1343, 1250, 1227, 1200, 1172, 1112, 1005, 861, 760 cm^{-1}.

MS: *m/z* (%) = 377 (74) [M^+], 321 (42), 288 (4), 276 (19), 262 (19), 248 (34), 247 (100), 245 (27), 233 (14), 217 (9), 189 (6), 188 (20), 162 (13), 131 (4), 113 (9).

HRMS: calcd. ($C_{20}H_{31}NO_4Si$) 377,2022 found 377.2007.

$C_{20}H_{31}NO_4Si$ (377.5): calcd. C 63.62, H 8.28, N 3.71; found C 63.70, H 8.50, N 3.74.



139

{2-[2-(3,4-Dimethoxy-phenylethynyl)-4,5-dimethoxy-phenyl]-ethyl}-carbamic acid *t*-butyl ester (**139**): $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol, 2 mol-%), CuI (38 mg, 0.2 mmol, 4 mol-%), PPh_3 (52 mg, 0.2 mmol, 4 mol-%) and *i*-Pr_2NH (15 mL) were placed in a round-bottomed flask. After addition of aryl iodide **132** (2.04 g, 5.0 mmol), the mixture was stirred at 25°C for 30 mi, and alkyne **121** (0.81 g, 5.0 mmol) was then added. After this mixture had been stirred at 25°C for additional 16 h, a saturated NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2 (3x50). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE:PE, 1:1), **139** (2.11 g, 4.8 mmol, 96%) was isolated as a pale-yellowish solid.

M.p.: 113-114°C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H); 2.98 (t, J = 6.9 Hz, 2 H); 3.43-3.45 (m, 2 H); 3.87 (s, 3 H); 3.88 (s, 3 H); 3.89 (s, 3 H); 3.91 (s, 3 H); 6.71 (s, 1 H); 6.82 (d, J = 8.3 Hz, 1 H); 6.99 (s, 1 H); 7.02 (d, J = 1.7 Hz, 1 H); 7.11 (dd, J = 1.9, 8.3 Hz, 1 H) ppm.

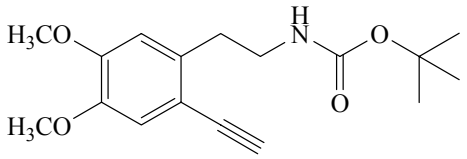
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 28.38 (CH_3), 34.65 (CH_2), 40.1 (CH_2), 55.90 (CH_3), 55.95 (CH_3), 55.98 (CH_3), 79.3 (C), 86.44 (C), 91.79 (C), 111.06 (CH), 112.32 (CH), 114.11 (CH), 114.58 (CH), 115.63 (C), 124.71 (CH), 134.19 (C), 147.27 (C), 148.70 (C), 149.25 (C), 149.42 (C), 155.87 (C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3374, 2964, 2935, 2857, 1690, 1598, 1575, 1517, 1465, 1413, 1392, 1365, 1346, 1323, 1244, 1171, 1136, 1092, 1027, 855, 816, 807 cm^{-1}.

MS : *m/z* (%) = 441 (20) [M^+], 407 (8), 385 (4); 367 (3), 351 (14), 340 (5), 324 (14), 322 (23), 311 (20) 299 (14), 289 (18), 281 (28), 276 (33), 262 (44), 251 (10), 225 (33), 208 (22), 183 (27), 180 (15), 165 (20), 164 (81), 151 (100), 131 (4), 113 (6), 107 (7), 91 (5), 77 (6).

HRMS: calcd. ($C_{25}H_{31}NO_6$) 441.2151; found 441.2178.

$C_{25}H_{31}NO_6$ (441.5): calcd. C 68.01, H 7.08, N 3.17; found C 67.70, H 6.96, N 3.25.



141

[2-(2-Ethynyl-4′, 5′-dimethoxy-phenyl)-ethyl]-carbamic acid *t*-butyl ester (**141**): Anhydrous K_2CO_3 (97 mg, 0.7 mmol) was added to a solution of **136** (2.06 g, 5.4 mmol) in MeOH (13.5 mL). After this mixture has been stirred at 25°C for 3 h, the solvent was evaporated under vacuum. A saturated aqueous $NaHCO_3$ was added to the residue and the mixture was extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE:PE, 1:1) **141** (1.46 g, 4.8, 88%) was isolated as a colourless solid.

M.p.: 105-107°C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9 H); 2.95 (t, J = 6.8 Hz, 2 H); 3.17 (s, 1 H); 3.34-3.41 (m, 2 H); 3.84 (s, 3 H); 3.86 (s, 3 H); 6.68 (s, 1 H); 6.94 (s, 1 H) ppm.

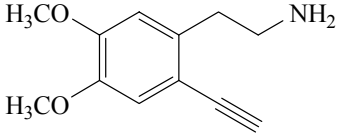
^{13}C-NMR (100 MHz, DEPT, $CDCl_3$): δ = 28.4 (CH_3), 34.3 (CH_2), 41.0 (CH_2), 55.9 (CH_3), 79.0 (C), 79.4 (CH), 82.3 (C), 112.2 (CH), 113.4 (C), 115.2 (CH), 131.0 (C), 135.1 (C), 147.2 (C), 149.7 (C), 155.8 (C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3417, 3237, 3006, 2976, 2935, 2873, 2097, 1702, 1604, 1515, 1440, 1390, 1366, 1356, 1330, 1285, 1266, 1229, 1168, 1102, 1018, 1007, 855 cm^{-1}.

MS: *m/z* (%) = 305 (65) {M^+], 249 (62), 232 (31), 204 (10), 188 (64), 175 (100), 173 (4), 161 (11), 145 (9), 131 (10), 115 (6), 113 (9), 102 (6), 89 (4), 77 (3), 57 (34).

HRMS: calcd. ($C_{17}H_{23}NO_4$) 305.1627; found 305.1619.

$C_{17}H_{23}NO_4$ (305.4): calcd. C 66.86, H 7.59, N 4.59; found C 66.59, H 7.55, N 4.72.



142

2-(2-ethynyl-4,5-dimethoxyphenyl)ethanamine **(142)**: At 0°C, F_3CCOOH (1,5 mL, 1.5 mmol) was added to a solution of **141** (1.14 g, 3.0 mmol) in CH_2Cl_2 (18 mL). After this mixture has been stirred at 25°C for 18 h, the solution was neutralized by saturated $NaHCO_3$ solution and the mixture was extracted with CH_2Cl_2 (3x 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, EtOAc + 3% NH_3) gave **142** (529 mg, 2.6 mmol, 86%) as a very hygroscopic pale yellowish solid.

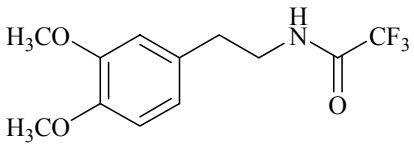
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.88 (t, J = 6.2 Hz, 2 H), 2.95-2.95 (m, 2 H), 3.17 (s, 1 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 6.69 (s, 1 H), 6.96 (s, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 38.3 (CH_2), 43.0 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 79.2 (CH), 82.5 (C), 112.2 (CH), 113.5 (C), 115.3 (CH), 136.0 (C), 147.0 (C), 149.7 (C) ppm.

IR (film): $\tilde{\upsilon}$ = 3280, 3001, 2936, 2850, 2096, 1604, 1573, 1512, 1464, 1396, 1344, 1261, 1222, 1193, 1098, 1030, 995, 861, 810, 747, 657 cm^{-1}

MS: *m/z* (%) = 205 (16) [M^+], 176 (100), 162 (10), 151 (16), 131 (5), 113 (10).

HRMS: calcd. ($C_{12}H_{15}NO_2$) 205.1103; found 250.1098.



143

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2,2,2-trifluoro-acetamide (**143**): At 25°C, ethyl trifluoroacetate (10.58 g, 74.5 mmol) was added dropwise to a solution of homoveratrylamine (**86**) (**7**, 11.75 g, 65.0 mmol) in THF (325 mL). The mixture was stirred at 25°C for 2 h. Evaporation of the solvent under vacuum gave **143** (17.98 g, 64.9 mmol, 99%) as a white solid. For the subsequent iodination, the product was used without further purification.

M.p.: 81–82°C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.82 (t, J = 7.0 Hz, 2 H), 3.57–3.61 (m, 2 H), 3.86 (s, 6 H), 6.36 (br. s, 1 H), 6.68 (d, J = 1.4 Hz, 1 H), 6.72 (dd, J = 1.7, 8.4 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H) ppm.

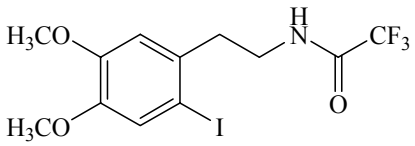
^{13}C NMR (125 MHz, DEPT, $CDCl_3$): δ = 34.5 (CH_2), 41.1 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 111.5 (CH), 111.7 (CH), 115.8 (q, J = 288 Hz, CF_3), 120.6 (CH), 130.0 (C), 148.2 (C), 149.2 (C), 157.1 (q, J = 37 Hz, C) ppm.

IR: $\tilde{\nu}$ = 3426, 3319, 3116, 3009, 2966, 2943, 2840, 1700, 1591, 1566, 1515, 1469, 1460, 1454, 1444, 1264, 1250, 1238, 1215, 1201, 1181, 1160, 1137, 1029, 805 cm^{-1}.

MS: m/z (%) = 277 (29) [M$^+$], 164 (42), 151 (100), 113 (7), 107 (6), 91 (3), 78 (3).

HRMS: calcd. ($C_{12}H_{14}F_3NO_3$) 277.0926; found 277.0944.

$C_{12}H_{14}F_3NO_3$ (277.2): calcd. C 51.99, H 5.09, N 5.05; found C 51.77, H 4.96, N 5.05.



144

2,2,2-Trifluoro-N-[2-(2-iodo-4,5-dimethoxy-phenyl)-ethyl]-acetamide (**144**): A solution of **143** (17.98 g, 64.9 mmol), I_2 (6.57 g, 25.9 mmol), and HIO_3 (2.29 g, 13.0 mmol) in a 3:1 mixture of MeOH/H_2O (650 mL) was heated to 85°C for 48 h. After concentration under vacuum, the residue was dissolved in CH_2Cl_2 (150 mL). The solution was washed with aqueous Na_2SO_3 (5%, 50 mL), H_2O (100 mL) and brine (100 mL). The combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, PE/EtOAc, 4:1), **144** (24.42 g, 60.6 mmol, 93%) was isolated as a white solid.

M.p.: 122–123°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.97 (t, J = 7.0 Hz, 2 H), 3.55–3.64 (m, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 6.39 (br. s, 1 H), 6.69 (s, 1 H), 7.22 (s, 1 H) ppm.

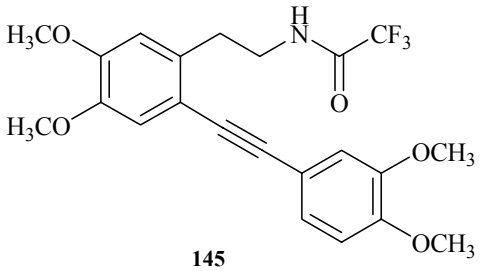
^{13}C NMR (125 MHz, DEPT, $CDCl_3$): δ = 39.0 (CH_2), 40.0 (CH_2), 55.9 (CH_3), 56.2 (CH_3), 87.9 (C), 112.6 (CH), 115.7 (q, J = 288 Hz, CF_3), 121.9 (CH), 132.6 (C), 148.6 (C), 149.6 (C), 157.1 (q, J = 37 Hz, C) ppm.

IR: $\tilde{\nu}$ = 3434, 2941, 2844, 1708, 1636, 1627, 1599, 1561, 1508, 1465, 1457, 1441, 1380, 1256, 1218, 1181, 1163, 1028, 858, 786, 727 cm^{-1}.

MS: m/z (%) = 403 (62) [M$^+$], 290 (50), 277 (100), 179 (3), 164 (5), 151 (8), 113 (6), 91 (2), 77 (4).

HRMS: calcd. ($C_{12}H_{13}F_3INO_3$) 402.9892; found 402.9866.

$C_{12}H_{13}F_3INO_3$ (403.1): calcd. C 35.75, H 3.25, N 3.47; found C 35.97, H 3.34, N 3.51.



145

N - {2 - [2 - (3,4 - Dimethoxy-phenylethynyl) - 4,5 – dimethoxy - phenyl] - ethyl} - 2,2,2 – trifluoro - acetamide (**145**): $Pd(PPh_3)_2Cl_2$ (186 mg, 0.26 mmol, 4 mol-%), CuI (101 mg, 0.53 mmol, 8 mol-%), PPh_3 (138 mg, 0.51 mmol, 8 mol-%), and iPr$_2$NH (19 mL) were placed in a round-bottomed flask. After addition of aryl iodide **144** (2.66 g, 6.60 mmol), the mixture was stirred at 25°C for 30 min, and alkyne **121** (1.07 g, 6.60 mmol) was then added. After this mixture had been stirred at 25°C for an additional 16 h, saturated NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/EtOAc, 1:1), **145** (2.41 g, 5.51 mmol, 84%) was isolated as a yellow crystalline solid.

M.p.: 164–165°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.10 (t, J = 6.6 Hz, 2 H), 3.66–3.74 (m, 2 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 3.91 (s, 3 H), 6.48 (br. s, 1 H), 6.68 (s, 1 H), 6.85 (d, J = 8.3 Hz, 1 H), 7.02 (s, 1 H), 7.04 (d, J = 1.7 Hz, 1 H), 7.11 (dd, J = 1.8, 8.2 Hz, 1 H) ppm.

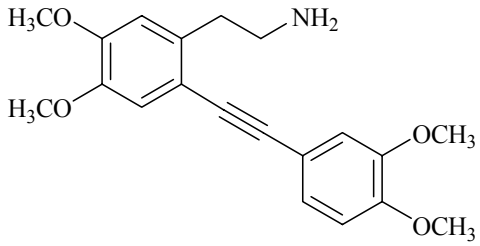
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 33.2 (CH_2), 40.9 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 85.9 (C), 92.3 (C), 111.1 (CH), 112.1 (CH), 114.2 (CH), 114.8 (CH), 115.1 (C), 115.2 (C), 115.8 (q, J = 287 Hz, CF_3), 124.7 (CH), 132.7 (C), 147.8 (C), 148.8 (C), 149.6 (C), 149.7 (C), 157.2 (q, J = 37 Hz, C) ppm.

IR: $\tilde{\nu}$ = 3331, 3008, 2934, 2836, 1704, 1603, 1576, 1518, 1467, 1452, 1352, 1323, 1245, 1227, 1215, 1179, 1157, 1137, 1092, 1023, 1001, 809 cm^{-1}.

MS: m/z (%) = 437 (100) [M$^+$], 369 (3), 324 (6), 311 (54), 281 (2), 267 (4), 253 (4), 213 (4), 201 (5), 161 (10), 150 (11), 113 (8).

HRMS: calcd. ($C_{22}H_{22}NO_5F_3$) 437.1450; found 437.1445.

$C_{22}H_{22}NO_5F_3$ (437.4): calcd. C 60.41, H 5.07, N 3.20; found C 60.14, H 5.15, N 3.24.



123

2-[2-(3,4-Dimethoxy-phenylethynyl)-4,5-dimethoxy-phenyl]-ethylamine (**123**): Aqueous KOH (5 M, 11.0 mL, 55.0 mmol) was added to a solution of **146** (2.37 g, 5.42 mmol) in MeOH (55 mL) at 0°C. The cooling bath was removed and the mixture was stirred at 25°C for 20 h. Then, the MeOH was removed under vacuum and the residue was diluted with H_2O (50 mL). After extraction with CH_2Cl_2 (4×50 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (SiO_2, EtOAc/MeOH, 1:1 + 3% NH_3) gave **123** (1.66 g, 4.86 mmol, 90%) as a very hygroscopic pale brown solid. Amino alkyne **123** was stored as a solution in CH_2Cl_2 (100 mg/mL) at 4°C.

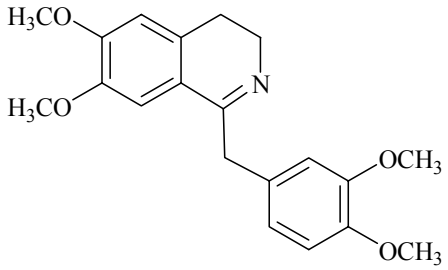
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 (s, 2 H), 2.90–2.97 (m, 2 H), 3.01–3.08 (m, 2 H), 3.88 (s, 3 H), 3.89 (s, 6 H), 3.90 (s, 3 H), 6.73 (s, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 7.01 (s, 2 H), 7.11 (dd, J = 1.9, 8.3 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 37.2 (CH_2), 42.2 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 55.8 (CH_3), 86.4 (C), 91.6 (C), 111.0 (CH), 112.4 (CH), 114.0 (CH), 114.6 (CH), 114.8 (C), 115.5 (C), 124.6 (CH), 134.1 (C), 147.1 (C), 148.6 (C), 149.1 (C), 149.3 (C) ppm.

IR: $\tilde{\nu}$ = 3360, 3003, 2939, 2830, 1599, 1576, 1517, 1465, 1348, 1322, 1244, 1224, 1181, 1156, 1089, 1022, 996, 854, 813, 805, 764 cm^{-1}.

MS: m/z (%) = 341 (90) [M^+], 326 (19), 312 (100), 297 (22), 281 (6), 267 (7), 253 (11), 225 (4), 216 (5), 204 (15), 190 (20) 161 (11), 151 (12), 113 (8).

HRMS: calcd. ($C_{20}H_{23}NO_4$) 341.1627; found 341.1630.



124

1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline (**124**): A solution of **123** in CH_2Cl_2 (6.83 mL, *c* = 100 mg/mL, 2.00 mmol) was transferred to a Schlenk tube and the solvent was removed under vacuum. Then, toluene (0.5 mL) and a solution of Cp_2TiMe_2 (0.54 mL, *c* = 0.37 mol/L in toluene, 0.20 mmol, 10 mol-%) were added. The reaction mixture was heated to 110°C for 16 h. After the obtained brown liquid had been allowed to reach room temperature, the solvent was removed under vacuum. Purification of the residue by flash chromatography (SiO_2, EtOAc + 4% NEt_3) provided **124** (669 mg, 1.96 mmol, 98%) as a yellow solid.

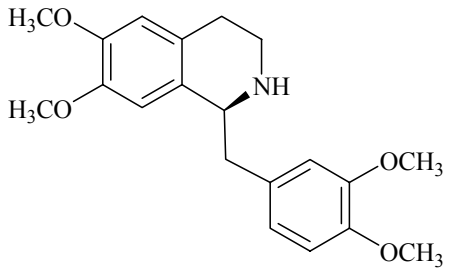
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.63 (t, *J* = 7.7 Hz, 2 H), 3.71 (t, *J* = 7.7 Hz, 2 H), 3.74 (s, 3 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 3.87 (s, 3 H), 3.97 (s, 2 H), 6.64 (s, 1 H), 6.74–6.86 (m, 3 H), 6.98 (s, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 25.3 (CH_2), 40.3 (CH_2), 43.7 (CH_2), 55.6 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 110.5 (CH), 110.7 (CH), 111.4 (CH), 111.7 (CH), 119.6 (C), 120.7 (CH), 128.5 (C), 132.7 (C), 147.7 (C), 148.1 (C), 149.3 (C), 153.0 (C), 169.6 (C) ppm.

IR: $\tilde{\nu}$ = 2992, 2934, 2832, 2803, 1609, 1589, 1515, 1465, 1449, 1416, 1374, 1326, 1301, 1262, 1233, 1173, 1154, 1138, 1154, 1138, 1111, 1026, 983, 950, 862, 821, 805, 787, 766, 698, 546 cm^{-1}.

MS: *m*/*z* (%) = 341 (3) [M^+], 340 (4), 326 (4), 194 (7), 193 (79), 192 (100), 177 (14), 176 (33), 151 (19), 148 (15), 147 (10), 131 (8), 118 (6), 106 (4).

HRMS: calcd. ($C_{20}H_{23}NO_4$) 341.1627; found 341.1592.



146

(–)-(*S*)-Norlaudanosine (**146**): A 5:2 mixture of HCOOH and NEt_3 (1.5 mL) was added to a suspension of imine **124** (1.02 g, 3.00 mmol) and (η^6-*p*-cymene)[(1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine)]RuCl (19 mg, 0.03 mmol) in DMF (6.0 mL). After the mixture had been stirred at 25°C for 7 h, a saturated aqueous Na_2CO_3 solution (30 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, EtOAc/MeOH, 4:1 + 1% NH_3), **146** (951 mg, 2.77 mmol, 92%, 93% *ee*, HPLC: hexane/2-propanol/diethylamine, 55:45:0.1, 0.5 mL/min) was isolated as a yellow oil.

$[\alpha]_D^{25}$ = –23.6 (*c* = 0.85, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.65–2.76 (m, 2 H), 2.82–2.95 (m, 2 H), 3.14–3.24 (m, 2 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.13 (dd, *J* = 4.4, 9.2 Hz, 1 H), 6.59 (s, 1 H), 6.66 (s, 1 H), 6.75–6.84 (m, 3 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 29.5 (CH_2), 41.0 (CH_2), 42.2 (CH_2), 55.9 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 56.8 (CH_3), 78.7 (CH), 101.7 (C), 109.4 (CH), 111.3 (CH), 111.8 (CH), 112.4 (CH), 121.4 (CH), 127.4 (C) 131.4 (C), 147.0 (C), 147.5 (C), 147.7 (C), 148.6 (C) ppm.

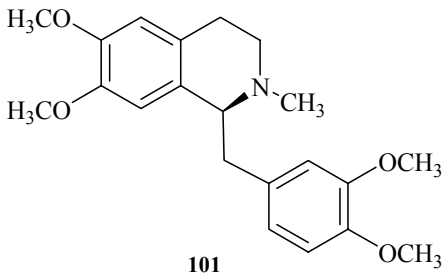
IR: $\tilde{\nu}$ = 3330, 2997, 2934, 2833, 1509, 1585, 1515, 1464, 1412, 1379, 1320, 1266, 1157, 1140, 112, 1028, 945, 859, 811, 729 cm^{-1}.

MS: *m*/*z* (%) = 343 (2) [M^+], 342 (9), 341 (24), 326 (15), 266 (3), 206 (17), 193 (74), 192 (100), 177 (12), 176 (27), 162 (5), 151 (16), 131 (6).

HRMS: calcd. ($C_{20}H_{25}NO_4$) 343.1784; found 343.1717.

One-pot procedure of Cp_2TiMe_2-catalyzed hydroamination/asymmetric Ru-catalyzed transfer hydrogenation reduction to synthesize norlaudanosine (**146**): A solution of **123**

in dichloromethane (1.71 mL, *c* = 100 mg/mL, 0.50 mmol) was transferred to a Schlenk tube and the solvent was removed under vacuum. Then, toluene (0.5 mL) and a solution of Cp_2TiMe_2 (0.14 mL, *c* = 0.37 mol/L in toluene, 0.05 mmol, 10 mol-%) were added. The reaction mixture was heated at 110°C for 16 h. The hydroamination product was then allowed to reach room temperature. In the other flash, $[RuCl_2(p\text{-cymene})]_2$ (1.5 mg, 0.0025 mmol) and TsDPEN (25.0 mg, 0.005 mmol) were dissolved in 1 mL of water and stirred at 40°C for 1 h. The Ru-TsDPEN solution and HCOONa (170 mg, 2.5 mmol) were then added the resulted hydroamination mixture. Following degassing three times, the solution was stirred at 40°C for 24 h. A saturated aqueous Na_2CO_3 solution (30 mL) was added to the solution. The resulting mixture was extracted with diethylether (3×30 mL) and the combined organic layers were dried with $MgSO_4$. After concentration under vacuum and purification by flash chromatography (SiO_2, EtOAc/MeOH, 4:1 + 1% NH_3), **146** (160 mg, 0.47 mmol, 93%, 60% *ee*) was isolated as a yellow oil. The *ee* value was determined by HPLC with ODH column, hexane/2-propanol, 60:40, 0.5 mL/min, time retention 23.9 min (*S*) and 31.8 min (*R*).



101

(+)-(*S*)-Laudanosine (**101**): Aqueous CH_2O (2.0 mL, *c* = 37%) was added to a solution of **146** (330 mg, 0.96 mmol) in MeOH (6.0 mL). After this mixture had been stirred at 25°C for 3 h, $NaBH_4$ (400 mg, 10.57 mmol) was slowly added. Subsequently, the reaction mixture was stirred at 25°C for an additional 16 h. Then, saturated aqueous NH_4Cl (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 95:3:3), (+)-(*S*)-laudanosine (**101**) (340 mg, 0.95 mmol, 99%) was isolated as a cream-colored solid.

M.p.: 88–89°C.

$[\alpha]_D^{25}$ = +87 (*c* = 0.70, EtOH).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53 (s, 3 H), 2.56–2.60 (m, 1 H), 2.71–2.85 (m, 3 H), 3.10–3.18 (m, 1 H), 3.56 (s, 3 H), 3.66–3.70 (m, 1 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 6.04 (s, 1 H), 6.54 (s, 1 H), 6.58–6.63 (m, 2 H), 6.75 (d, *J* = 8.1 Hz, 1 H) ppm.

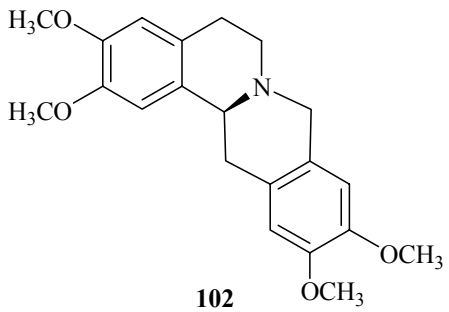
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 25.5 (CH_2), 40.8 (CH_2), 42.6 (CH_3), 47.0 (CH_2), 55.5 (CH_3), 55.7 (CH_3), 55.7 (CH_3), 55.9 (CH_3), 64.8 (CH), 111.0 (CH), 111.1 (CH), 111.2 (CH), 113.0 (CH), 121.8 (CH), 126.0 (C), 129.2 (C), 132.5 (C), 146.3 (C), 147.2 (C), 147.3 (C), 148.5 (C) ppm.

IR: $\tilde{\nu}$ = 2993, 2915, 2789, 1607, 1516, 1466, 1451, 1374, 1334, 1281, 1265, 1227, 1204, 1155, 1142, 1104, 1029, 1018, 861, 818 cm^{-1}.

MS: *m*/*z* (%) = 358 (80) [M^+ + H], 342 (3), 307 (22), 289 (11), 222 (3), 206 (100), 204 (18), 190 (10).

HRMS: calcd. ($C_{21}H_{28}NO_4$) 358.2018; found 358.2000.

$C_{21}H_{27}NO_4$ (357.4): calcd. C 70.56, H 7.61, N 3.92; found C 70.28, H 7.61, N 3.98.



102

(–)-(*S*)-Xylopinine (**102**)**:** A mixture of aqueous CH_2O (0.8 mL, *c* = 37 %), HCOOH (1.2 mL), and **146** (52 mg, 0.15 mmol) was heated to 90°C for 2 h. After the resulting mixture had cooled to 25°C, saturated aqueous $NaHCO_3$ was added until pH 7 was reached. The mixture was then extracted with dichloromethane (3×15 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vacuum. After purification by flash chromatography (SiO_2, EtOAc/NEt_3, 99:1), (–)-(*S*)-xylopinine (**102**) (44 mg, 0.12 mmol, 82%) was isolated as a cream-colored solid.

M.p.: 178–180°C.

$[\alpha]_D^{25}$ = –262 (*c* = 0.10, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.57–2.69 (m, 2 H), 2.84 (dd, J = 11.5, 15.1 Hz, 1 H), 3.09–3.16 (m, 2 H), 3.24 (dd, J = 3.7, 15.8 Hz, 1 H), 3.59 (dd, J = 3.7, 11.4 Hz, 1 H), 3.67 (d, J = 14.3 Hz, 1 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.95 (d, J = 14.7 Hz, 1 H), 6.58 (s, 1 H), 6.62 (s, 1 H), 6.66 (s, 1 H), 6.74 (s, 1 H) ppm.

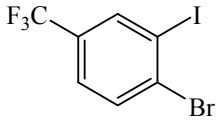
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 29.1 (CH_2), 36.4 (CH_2), 51.4 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 58.3 (CH_2), 59.6 (CH), 108.6 (CH), 109.1 (CH), 111.4 (CH), 111.5 (CH), 126.3 (C), 126.4 (C), 126.8 (C), 129.8 (C), 147.4 (C), 147.5 (C), 147.5 (C), 147.7 (C) ppm.

IR: $\tilde{\nu}$ = 3435, 2931, 2833, 1612, 1518, 1464, 1384, 1350, 1329, 1260, 1241, 1205, 1144, 1102, 1005, 856, 787, 769 cm^{-1}.

MS: m/z (%) = 355 (94) [M^+], 354 (34), 340 (11), 316 (4), 267 (5), 251 (5), 206 (10), 199 (7), 190 (22), 164 (100), 151 (14), 121 (10), 112 (12).

HRMS: calcd. ($C_{21}H_{25}NO_4$) 355.1784; found 355.1778.

SYNTHESIS OF 6-TRIFLUOROMETHYLBENZYLISOQUINOLINE



164

1-Bromo-2-iodo-4-trifluoromethyl-benzene (**164**): Concentrated H_2SO_4 (75.0 mL) was added dropwise to a solution of $NaIO_4$ (12.83 g, 60.0 mmol) and I_2 (15.23 g, 60.0 mmol) in a 2:1 mixture AcOH/ Ac_2O (75 mL) at 5-10°C. Then, 4-bromo-trifluorotoluene **162** (11.25 g, 50.0 mmol) was added dropwise and the mixture was stirred at 25°C for 21 h. The mixture was poured into ice-water containing Na_2SO_3 and the crude products were extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE), arylhalide **164** was isolated as a yellowish oil (16.92 g, 48.22 mmol, 96%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (ddd, J = 0.6, 1.0, 8.3 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 8.08-8.09 (m, 1 H) ppm.

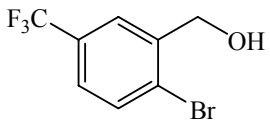
^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.4 (C), 122.6 (q, J = 273 Hz, CF_3), 126.1 (q, J = 4 Hz, CH), 130.6 (q, J = 34 Hz, C), 133.0 (CH), 134.0 (C), 137.0 (q, J =4 Hz, CH) ppm.

IR: $\tilde{\upsilon}$ = 1591, 1459, 1377, 1317, 1257, 1173, 1132, 1102, 1074, 1074, 1012, 893, 825, 800,705, 653, 615 cm^{-1}.

MS: *m/z* (%) = 352 (100) [M^+, ^{81}Br], 350 (34) [M^+, ^{79}Br], 333, 302, 271, 238, 223, 208, 144, 143, 75, 74.

Preparation of a solution of monomeric formaldehyde in THF: The mixture of dried paraformaldehyde (3.00 g) (two days in exicator with phosphor pentoxide as drying agent), THF (100 mL) and some drops of a solution of BF_3 in diethylether was refluxed at 70°C for 2 h. Then, a slow distillation of the mixture was maintained and the solution of monomeric formaldehyde in THF was collected into a two-necked flask in -70°C. The concentration of the solution is ~0.8 M.

Preparation of a solution of *i*Pr-MgCl•LiCl: Magnesium turning (5.36 g, 220.0 mmol) and anhydrous LiCl (8.48 g, 200.0 mmol) were placed in an Ar-flushed flask and THF (50 mL) was added. After a solution of *i*PrCl (18.3 mL, 200.0 mmol) in THF (50 mL) has been slowly added, the reaction mixture was stirred at 25°C 20 h. The deep grey solution of *i*PrMgCl•LiCl was transferred via syringes to another flask under Ar atmosphere. The solution is stored at -20°C. Concentration of the solution of *i*PrMgCl•LiCl is ~2.0 M.



167

(2-Bromo-5-trifluoromethyl-phenyl)-methanol (**167**): At -20°C, a solution of *i*PrMgCl•LiCl in THF (12.5 mL, 25.0 mmol, 2.0 M) was slowly added to a solution of 2-bromo aryl iodide **164** (8.75 g, 25.0 mmol) in THF (12.5 mL). After the mixture has been stirred at -20°C for 2 h, a solution of monomeric formaldehyde in THF (35.0 mL, 28.0 mmol, 0.8 M) was added. After the mixture has been stirred for additional 1 h, water (50 mL) was then added and the mixture was extracted with diethylether (5x30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO2, PE:EE, 9:1) benzylalcohol **167** was isolated as a white solid (4.60 g, 18.04 mmol, 72%).

M.p.: 66-67°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (br. s, 1 H), 4.37 (s, 2 H), 7.40 (dd, *J* = 1.9, 8.3 Hz, 1 H), 7.65 (d, *J* = 8.3 Hz, 1 H), 7.79 (d, *J* = 1.3 Hz, 1 H).

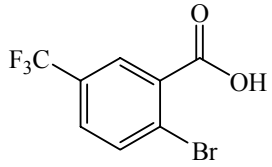
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 64.3 (CH_2), 123.8 (q, *J* = 272 Hz, C), 125.1 (q, *J* = 4 Hz, CH), 125.5 (q, *J* = 4 Hz, CH), 125.7 (q, *J* = 1Hz, C), 130.1 (q, *J* = 33 Hz, C), 132.9 (CH), 140.8 (C) ppm.

IR: $\tilde{\upsilon}$ = 3300, 2913, 1605, 1583, 1474, 1413, 1372, 1330, 1257, 1184, 1120, 1083, 157, 1023, 897, 834, 829, 745, 716, 435 cm^{-1}.

MS: *m/z* (%) = 256 (35) [M^+, ^{81}Br], 254 (34) [M^+, ^{79}Br], 237 (15), 175 (100), 145 (41), 127 (51), 113 (7), 77 (11).

HRMS: calcd. ($C_8H_6{}^{79}BrF_3O$) 253.9554; found 253.9559.

$C_8H_6BrF_3O$ (255.0) calcd.: C 37.68, H 2.37; found C 37.49, H 2.41.



168

2-Bromo-5-(trifluoromethyl)benzoic acid (**168**): At -20°C, a solution of *i*PrMgCl•LiCl in THF (5.0 mL, 25.0 mmol, 2.0 M) was slowly added to a solution of 2-bromo aryl iodide **164** (3.50 g, 10.0 mmol) in THF (5.0 mL). After the mixture has been stirred at -20°C for 2 h, dried ice (1.0 g, 22.0 mmol) was added. After the mixture has been stirred for additional 1 h, water (50 mL) was then added and the mixture was extracted with diethylether (5x30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE:EE, 9:1) the benzoic acid **168** was isolated as white solid (0.91 g, 3.39 mmol, 34%).

M.p. 105-106°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (dd, J = 3.4, 8.4 Hz, 1 H), 7.87 (d, J = 8.5 Hz, 1 H), 8.28 (d, J = 2.1 Hz, 1 H), 10.94 (br. s, 1 H) ppm.

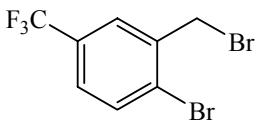
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 123.2 (q, J = 272 Hz, C), 126.8 (q, J = 1 Hz, C), 129.5 (q, J = 4 Hz, CH_2), 129.9 (q, J = 3 Hz, CH), 130.1 (q, J = 34 Hz, C), 135.7 (C), 170.05 (C) ppm.

IR: $\tilde{\upsilon}$ = 3431, 3056, 1718, 1689, 1609, 1577, 1476, 1417, 1391, 1370, 1331, 1268, 1188, 1127, 1084, 1033, 920, 837, 760,700 cm^{-1}.

MS: *m/z* (%) = 270 (100) [M^+, ^{81}Br], 268 (97) [M^+, ^{79}Br], 253 (97), 251 (99), 249 (10), 225 (25), 223 (20), 144 (30), 125 (6), 74 (9)

HRMS: calcd. ($C_8H_4{}^{79}BrF_3O_2$) 267.9347; found 267.9337.

$C_8H_4BrF_3O_2$ (269.0): C 35.72, H 1.50; found C 35.87, H 1.61.



169

1-Bromo-2-bromomethyl-4-trifluoromethyl-benzene (**169**): PBr_3 (0.68 g, 2.5 mmol) was added to a solution of benzylalcohol **167** (1.27 g, 5.0 mmol) in CH_2Cl_2 (25 mL). After the solution has been stirred at 25°C for 24 h, a saturated aqueous Na_2CO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (5x30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE), bromobenzyl **169** was isolated as a colorless oil (1.25 g, 3.93 mmol, 79%).

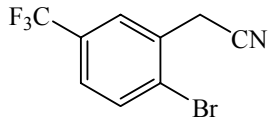
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.61 (s, 2 H), 7.42 (dd, J = 1.0, 8.4 Hz, 1 H), 7.71 (s, 1 H), 7.72 (d, J = 7.5 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 32.0 (CH_2), 123.4 (q, J = 272 Hz, C), 126.6 (q, J = 4 Hz, CH), 127.9 (q, J = 4 Hz, CH), 128.8 (C), 130.5 (q, J = 33 Hz, C), 134.0 (CH), 138.1 (C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 2834, 1605, 1580, 1479, 1440, 1409, 1333, 1276, 1220, 1198, 1173, 1131, 1081, 1032, 949, 908, 829, 908, 829, 758, 728, 588 cm^{-1}.

MS: *m/z* (%) = 320 (8) [M^+, ^{81}Br+^{81}Br], 318 (16) [M^+, ^{81}Br+^{79}Br], 316 (10) [M^+, ^{79}Br+^{79}Br], 284 (17), 239 (100), 237 (100), 158 (42), 151 (12), 113 (8), 107 (7), 89 (8), 63 (8)

HRMS: calcd. ($C_8H_5{}^{79}Br_2F_3$) 315.8710; found 315.8703



170

(2-Bromo-5-trifluoromethyl-phenyl)-acetonitrile (**170**): A solution of NaCN (0.49 mg, 10.0 mmol) in DMSO (2.5 mL) was heated to 90°C. The oil bath was removed and bromobenzyl **169** (1.59 g, 5.0 mmol) was slowly added. After the mixture had been allowed to reach 50°C, water (25 mL) was added. The mixture was extracted with CH_2Cl_2 (5×40 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vacuum. After purification by flash chromatography (SiO_2, PE/EE, 95:5), *o*-bromo-benzylnitrile **170** (0.81 mg, 3.1 mmol, 62%) was isolated as a white solid.

M.p.: 61-62°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 2 H), 7.50 (dd, J = 1.5, 8.9 Hz, 1 H), 7.76 (d, J = 8.7 Hz, 1 H), 7.78 (s, 1 H) ppm.

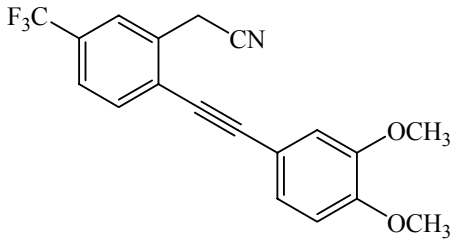
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 24.9 (CH_2), 116.0 (C), 123.3 (q, J = 273 Hz, C), 126.5 (q, J = 4 Hz, CH), 126.7 (q, J = 4 Hz, CH), 127.6 (C), 130.8 (q, J = 34 Hz, C), 131.2 (C), 133.8 (CH) ppm.

IR: $\tilde{\upsilon}$ = 3080, 2914, 2252, 1607, 1476, 1425, 1403, 1331, 1322, 1286, 1263, 1187, 1167, 1129, 1085, 1032, 937, 877, 739, 747, 715, 421 cm^{-1}.

MS: *m/z* (%) = 265 (75) [M^+, ^{81}Br], 263 (78) [M^+, ^{79}Br], 246 (9), 244 (11), 184 (100), 183 (21), 157 (13), 144 (4), 134 (11), 114 (6), 89 (3), 75 (4).

HRMS: calcd. ($C_9H_5{}^{79}BrF_3N$) 262.9557; found 262.9533.

$C_9H_5BrF_3N$ (264.0): calcd. C 40.94, H 1.91, N 5.30; found C 40.71, H 1.96, N 5.20.



171

[2-(3,4-Dimethoxy-phenylethynyl)-5-trifluoromethyl - phenyl] - acetonitrile (**171**): $Pd(PPh_3)_2Cl_2$ (85 mg, 0.12 mmol, 4 mol-%), CuI (46 mg, 0.24 mmol, 8 mol-%), PPh_3 (63 mg, 0.24 mmol, 8 mol-%) and a 3:1 mixture of *i*Pr_2NH//DMF (12.0 mL) were placed in a round-bottomed flask. After the addition of aryl bromide **170** (789 mg, 3.00 mmol), the mixture was stirred at 25°C for 1 h, and alkyne **121** (486 mg, 3.00 mmol) was then added. After the mixture had been stirred at 80°C for additional 16 h, saturated NH_4Cl solution was added. The mixture was extracted with MTBE (3×50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/EtOAc, 9:1), alkyn **171** (994 mg, 2.88 mmol, 96%) was isolated as a white crystalline solid.

M.p.: 79-80°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 6 H), 4.01 (s, 2 H), 6.87 (d, J = 8.3 Hz, 1 H), 7.06 (d, J = 1.9 Hz, 1 H), 7.20 (dd, J = 1.9, 8.3 Hz, 1 H), 7.60 (d, J = 8.1 Hz, 1 H), 7.67 (d, J = 8.1 Hz, 1 H), 7.74 (s, 1 H) ppm.

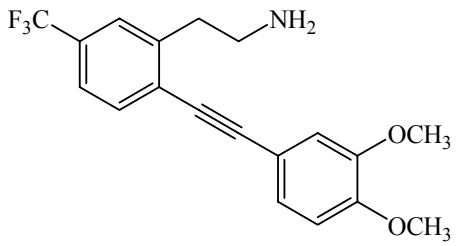
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 22.9 (CH_2), 56.0 (CH_3), 83.6 (C), 98.7 (C), 111.1 (CH), 113.8 (C), 114.2 (CH), 116.6 (C), 123.5 (q, J = 272 Hz, C), 125.1 (q, J = 4 Hz, CH), 125.4 (CH), 127.0 (C), 130.4 (q, J = 33 Hz, C), 132.3 (C), 132.5 (CH), 149.9 (C), 150.4 (C) ppm.

IR: $\tilde{\upsilon}$ = 3079, 2972, 2942, 2915, 2842, 2249, 2208, 1600, 1578, 1518, 1499, 1463, 1442, 1426, 1320, 1273, 1251, 1229, 1165, 1137, 1105, 1076, 1020, 871, 834, 817 cm^{-1}.

MS: *m/z* (%) = 345 (100) [M^+], 330 (6), 302 (8), 275 (13), 190 (6) 151 (5).

HRMS: calcd. ($C_{19}H_{14}F_3NO_2$) 345.0977; found 345.1010.

$C_{19}H_{14}F_3NO_2$ (345.3): calcd. C 66.09, H 4.09, N 4.06; found C 65.91, H 4.16, N 4.03.



172

2-[2-(3,4-Dimethoxy-phenylethynyl)-5-trifluoromethyl-phenyl]-ethylamine (**172**): A solution of $AlCl_3$ (339 mg, 3.0 mmol) in diethylether (4.5 mL) was rapidly added to a solution of $LiAlH_4$ (114 mg, 3.0 mmol) in diethylether (3.0 mL) and the mixture was stirred at 25°C for 30 minutes. A solution of nitrile **171** (1.04 mg, 3.0 mmol) in diethylether (6.0 mL) was then slowly added to the mixture. After the mixture has been stirred at 25°C for additional 2 h, water was added dropwise to decompose the excess of hydride and a solution of KOH (5.0 mL, 5 M) was then added to make a basic condition. The colloidal mixture was extracted with diethylether (10x30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 9:1:0.01), aminoalkyne **172** (980 mg, 2.8 mmol, 93%) was isolated as a yellowish solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (br. s, 2 H), 3.08-3.11 (m, 4 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 6.84 (d, J = 8.3 Hz, 1 H), 7.15 (dd , J = 1.9, 8.3 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1 H), 7.49 (s, 1 H), 7.60 (d, J = 7.9 Hz, 1 H) ppm.

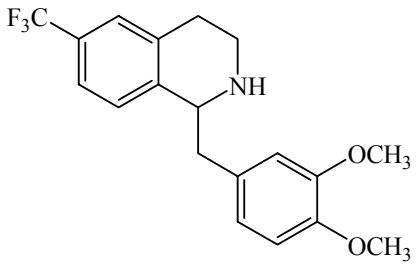
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 38.3 (CH_2), 42.2 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 85.3 (C), 95.8 (C), 111.1 (CH), 114.1 (CH), 114.7 (C), 123.1 (q, J = 4 Hz, CH), 123.9 (q, J = 272 Hz, C), 125.1 (CH), 126.0 (q, J = 4 Hz, CH), 127.1 (C), 129.7 (q, J = 33 Hz, C), 132.5 (CH), 141.8 (C), 148.8 (C), 150.01 (C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3386, 2999, 2946, 2838, 2206, 1615, 1598, 1577, 1518, 1471, 1456, 1441, 1412, 1327, 1256, 1229, 1173, 1125, 1020, 860, 844, 833, 815, 807 cm^{-1}.

MS: *m/z* (%) = 349 (100) [M^+], 334 (16), 330 (21), 318 (25), 273 (8), 233 (16), 212 (27), 198 (22) 166 (20), 161 (16), 151 (54), 113 (12), 86 (17).

HRMS: calcd. ($C_{19}H_{18}F_3NO_2$) 349.1290; found 349.1270.

$C_{19}H_{18}F_3NO_2$ (349.3) calcd.: C 65.32, H 5.19, N 4.01; found C 65.31, H 5.46, N 4.28.



173

1-(3,4-Dimethoxy-benzyl)-6-trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline (**173**): A mixture of amino alkyne **172** (175 mg, 0.5 mmol) and Ind_2TiMe_2 (9 mg, 0.025 mmol, 5 mol-%) in toluene (0.25 mL) in a Schlenk tube was stirred at 105°C for 16 h. After the obtained brown liquid had been allowed to reach room temperature, a solution of $NaCNBH_3$ (63 mg, 1.0 mmol) and $ZnCl_2$ (68 mg, 0.5 mmol) in MeOH (5.0 mL) was added. The reaction mixture was stirred at 25°C for 24 h. Then, saturated aqueous NH_4Cl (25 mL) was added and the mixture was extracted with MTBE (5×25 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 20:1:0.01), tetrahydrobenzylisochinoline **173** was isolated as a yellowish solid (169 mg, 0.48 mmol, 96%).

M.p.: 92-94°C

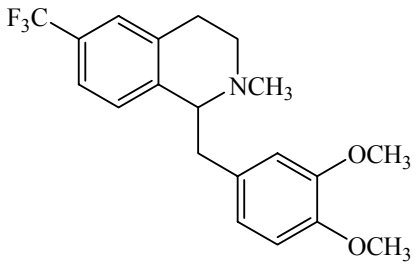
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.81-2.96 (m, 4 H), 3.19-3.26 (m, 2 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.21 (dd, J = 3.2, 9.5 Hz, 1 H), 6.71 (d, J = 1.7 Hz, 1 H), 6.79 (dd, J = 1.7, 8.1 Hz, 1 H), 6.84 (d, J = 8.0 Hz, 1 H), 7.33-7.43 (m, 3 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 29.9 (CH_2), 40.5 (CH_2), 41.8 (CH_2), 55.6 (CH_3), 55.8 (CH_3), 57.1 (CH), 111.2 (CH), 112.1 (CH), 121.3 (CH), 122.2 (q, J = 4 Hz, CH), 124.2 (q, J = 272 Hz, C), 126.1 (q, J = 4 Hz, CH), 126.6 (CH), 128.3 (C), 130.7 (C), 136.2 (C), 142.5 (C), 147.7 (C), 148.9 (C) ppm.

IR: $\tilde{\upsilon}$ = 2936, 2835, 1621, 1590, 1516, 1466, 1425, 1338, 1323, 1266, 1237, 1160, 1126, 1077, 1030, 828, 813, 764, 646 cm^{-1}.

MS: *m/z* (%) = 351 (1) [M^+], 334 (4), 332 (11), 214 (6), 201 (94), 200 (100), 198 (22), 185 (22), 173 (7), 151 (35), 131 (11), 113 (7), 107 (7).

HRMS: calcd. ($C_{19}H_{20}F_3NO_2$) 351.1446; found 351.1401.



174

1-(3,4-Dimethoxy-benzyl)-2-methyl-6-trifluoromethyl - 1,2,3,4 - tetrahydro-isoquinoline (**174**): Aqueous CH_2O (0.5 mL, *c* = 37%) was added to a solution of **173** (88 mg, 0.25 mmol) in MeOH (1.5 mL). After this mixture had been stirred at 25°C for 3 h, $NaBH_4$ (95 mg, 2.5 mmol) was slowly added. Subsequently, the reaction mixture was stirred at 25°C for an additional 16 h. Then, saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 95:5:1), benzylisoquinoline **174** (62 mg, 0.17 mmol, 68%) was isolated as a yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3 H), 2.63-2.94 (m, 4 H), 3.08-3.22 (m, 2 H), 3.72 (s, 2 H), 3.72 (s, 3 H), 3.82 (t, J = 6.0 Hz, 1 H), 3.85 (s, 3 H), 6.45 (d, J = 1.8 Hz, 1

H), 6.63 (dd, J = 2.0, 8.7 Hz, 1 H), 6.76 (d, J = 8.3 Hz, 1 H), 6.82 (d, J = 8.1 Hz, 1 H), 7.26 (d, J = 7.9 Hz, 1 H), 7.32 (s, 1 H) ppm.

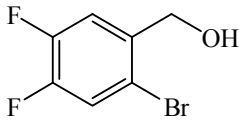
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 26.3 (CH_2), 40.4 (CH_2), 42.8 (CH_3), 46.9 (CH_2), 55.6 (CH_3), 55.8 (CH_3), 65.0 (CH), 110.9 (CH), 112.8 (CH), 121.7 (CH), 121.8 (q, J = 2 Hz, CH), 124.2 (q, J = 272 Hz, C), 125.5 (q, J = 4 Hz, CH), 128.2 (q, J = 32 Hz, C), 128.4 (CH), 131.5 (C), 135.4 (C), 141.7 (C), 147.4 (C), 148.4 (C) ppm.

IR: $\tilde{\upsilon}$ = 2937, 2836, 2787, 1661, 1590,1516, 1465, 1428, 1324, 1265, 1239, 1159, 1077, 1030, 976, 894, 803, 764, 738, 645 cm^{-1}.

MS: *m/z* (%) = 363 (3) [M^+-H_2], 348 (4), 346 (7), 215 (75), 214 (100), 212 (24), 199 (15), 195 (8), 186 (7), 151 (12), 113 (6).

HRMS: calcd. ($C_{20}H_{22}F_3NO_2$-H_2) 363.1446; found 363.1481.

SYNTHESIS OF 6,7-DIFLUOROBENZYLISOQUINOLINE



176

(2-Bromo-4,5-difluoro-phenyl)-methanol (**176**): To a suspension of $LiAlH_4$ (835 mg, 22.0 mmol) in diethylether (30 mL) in a two-necked flask with reflux condenser was slowly added a solution of benzoic acid **175** (4.74 g, 20.0 mmol) in diethylether (30 mL) at the rate such as to produce gentle reflux. After the mixture had been stirred at room temperature for 2 h, water was added dropwise to decompose the excess of hydride and then a solution of H_2SO_4 (25 mL, 2 M) was added to make acid condition. The mixture was extracted with diethylether (5x50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, ethyl acetate/PE 1:9), benzylalcohol **176** was isolated as a white solid (2.61 g, 11.7 mmol, 59%).

M.p.: 70-71°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (t, J = 5.8 Hz, 1 H), 4.68 (d, J = 5.3 Hz, 1 H), 7.36 (d, J = 7.5 Hz, 1 H), 7.39 (d, J = 7.4 Hz, 1 H) ppm.

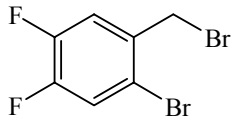
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 63.9 (CH_2), 114.9 (dd, J = 4, 8 Hz, C), 117.0 (d, J = 19 Hz, CH), 121.6 (d, J = 20 Hz, CH), 136.8 (dd, J = 4, 5 Hz, C), 149.3 (dd, J = 13, 251 Hz, C), 149.8 (dd, J = 12, 249 Hz, C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3303, 3061, 2917, 1614, 1600, 1494, 1471, 1443, 1399, 1362, 1293, 1219, 1185, 1138, 1066, 981, 881, 809, 629, 527 cm^{-1}.

MS: *m/z* (%) = 224 (72) [M^+, ^{81}Br], 222 (34) [M^+, ^{79}Br], 207 (11), 203 (11), 193 (11), 162 (10), 143 (100) 141 (22), 125 (14), 115 (68), 114 (71), 113 (37), 112 (20), 95 (27), 74 (6), 63 (18).

HRMS: calcd. ($C_7H_5{}^{79}BrF_2O$) 221,9492; found 221.9491.

$C_7H_5BrF_2O$ (223.0): calcd. C 37.70, H 2.26; found C 37.75, H 2.39.



177

1-Bromo-2-bromomethyl-4,5-difluoro-benzene (**177**): PBr_3 (1.49 g, 5.5 mmol) was added dropwise to a solution of benzylalcohol **176** (2.45 g, 11.0 mmol) in CH_2Cl_2 (55 mL). After the mixture had been stirred at 25°C for 24 h, a saturated aqueous Na_2CO_3 solution (50 mL) was added. The mixture was extracted with CH_2Cl_2 (5x30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE), bromobenzyl **177** was isolated as oil (2.96 g, 10.3 mmol, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.5 (s, 2 H), 7.3 (dd, J = 7.9, 10.4 Hz, 1 H), 7.4 (dd, J = 7.4, 9.6 Hz, 1 H) ppm.

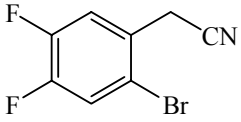
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 31.70 (CH_2), 117.99 (dd, J = 4, 8 Hz, CH), 119.53 (d, J = 18 Hz, CH), 122.15 (d, J = 20 Hz, CH), 133.90 (dd, J = 4, 5 Hz, C), 149.55 (dd, J = 13, 250 Hz, C), 150.01 (dd, J = 14, 255 Hz, C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3051, 2977, 2590, 1602, 1499, 1441, 1395, 1306, 1289, 1218, 1193, 1152, 1115, 994, 883, 815, 737, 703, 670, 629, 575, 553 cm^{-1}.

MS: *m/z* (%) = 288 (7) [M^+, ^{81}Br+^{81}Br], 286 (11) [M^+, ^{81}Br+^{79}Br], 284 (6) [M^+, ^{79}Br+^{79}Br], 207 (97), 205 (100), 125 (33), 125 (19), 113 (8), 75 (4).

HRMS: calcd. ($C_7H_4{}^{79}Br_2F_2$) 283.8648; found 283.8633.

$C_7H_4Br_2F_2$ (285.9): calcd. C 29.41, H 1.41; found C 29.31, H 1.46.



178

(2-Bromo-4,5-difluoro-phenyl)-acetonitrile (**178**): A solution of NaCN (980 mg, 20.0 mmol) in DMSO (5.0 mL) was heated to 90°C. The oil bath was then removed and bromobenzyl **177** (2.86 g, 10.0 mmol) was slowly added. After the mixture had been allowed to reach 50°C, water (25 mL) was added. The mixture was extracted with CH_2Cl_2 (5×40 mL). The combined organic layers were dried with $MgSO_4$ and

concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/EE, 9:1), cyanobenzyl **178** (1.34 mg, 5.8 mmol, 58%) was isolated as a white solid.

M.p.: 53-54°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.79 (s, 2 H), 7.40 (dd, J = 7.3, 10.0 Hz, 1 H), 7.56 (dd, J = 7.3, 9.3 Hz, 1 H) ppm.

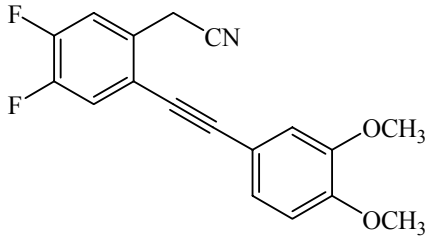
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 24.3 (CH_2), 116.1 (C), 117.1 (dd, J = 4, 7 Hz, C), 118.5 (d, J = 19 Hz, CH), 122.2 (d, J = 20 Hz, CH), 126.8 (dd, J = 4, 6 Hz, C), 149.8 (dd, J = 12, 252 Hz, C), 149.9 (dd, J = 13, 253 Hz, C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3055, 2972, 2939, 2257, 1602, 1586, 1502, 1412, 1399, 1286, 1206, 1188, 1149, 993, 915, 887, 859, 806, 756, 626, 578 cm^{-1}.

MS: *m/z* (%) = 233 (96) [M^+, ^{81}Br], 231 (97) [M^+, ^{79}Br], 152 (100), 125 (47), 112 (5), 75 (9).

HRMS: calcd. ($C_8H_4{}^{79}BrF_2N$) 230.9495; found 230.9488.

$C_8H_4BrF_2N$ (232.0): calcd. C 41,41, H 1,74, N 6.04; found C 42.14, H 1.97, N5.87.



179

[2-(3,4-Dimethoxy-phenylethynyl)-4,5-difluoro-phenyl]-acetonitrile (**179**): $Pd(PPh_3)_2Cl_2$ (155 mg, 0.22 mmol, 4 mol-%), CuI (84 mg, 0.44 mmol, 8 mol-%), PPh_3 (115 mg, 0.44 mmol, 8 mol-%) and a mixture of iPr$_2$NH (5.5 mL)/DMF (5.5 mL) were placed in a round-bottomed flask. After addition of aryl bromide **178** (1.28 g, 5.52 mmol), the mixture was stirred at 25°C for 1 h, and alkyne **121** (0.90 g, 5.55 mmol) was added. After this mixture had been stirred at 80°C for an additional 16 h, saturated NH_4Cl solution was added. The mixture was extracted with MTBE (3×50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/EE, 5:1), **179** (1.36 mg, 4.34 mmol, 79%) was isolated as a white crystalline solid.

M.p.: 113-114°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.92 (s, 5 H), 3.92 (s, 3 H), 6.86 (d, J = 8.5 Hz, 1 H), 7.03 (d, J = 1.9 Hz, 1 H), 7.15 (dd, J = 1.8, 8.2 Hz, 1 H), 7.33 (dd, J = 7.7, 10.6 Hz, 1 H), 7.37 (dd, J = 7.7, 10.6 Hz, 1 H) ppm.

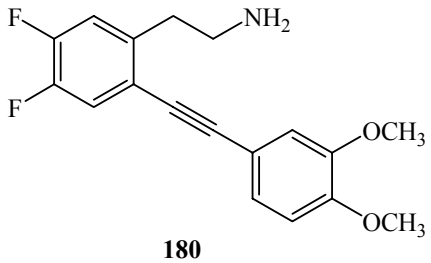
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 22.3 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 82.7 (C), 96.6 (C), 111.1 (CH), 113.9 (C), 114.1 (CH), 116.7 (C), 117.6 (d, J = 19 Hz, CH), 119.9 (dd, J = 4, 8 Hz, C), 120.9 (d, J = 19 Hz, CH), 125.2 (CH), 128.6 (dd, J = 4,8 Hz, C), 148.2 (dd, J = 13, 35 Hz, C), 148.8 (C), 150.34 (C), 151.6 (dd, J = 13, 38 Hz, C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3005, 2966, 2939, 2839, 2257, 2214, 1600, 1578, 1517, 1466, 1445, 1424, 1413, 1346, 1320, 1251, 1224, 1173, 1137, 1023, 882, 869, 815, 754 cm^{-1}.

MS: *m/z* (%) = 313 (100) [M^+], 298 (9), 270 (10, 243 (12), 226 (12), 212 (5), 200 (5), 161 (11), 150 (10), 112 (6), 91 (6).

HRMS: calcd. ($C_{18}H_{13}F_2NO_2$) 313.0914; found 313.0930.

$C_{18}H_{13}F_2NO_2$ (313.3) calcd. C 69.01, H 4.18, N 4.47; found C 69.79, H 4.24, N 4.41.



180

2-[2-(3,4-Dimethoxy-phenylethynyl)-4,5-difluoro-phenyl]-ethylamine (**180**): A solution of $AlCl_3$ (467 mg, 3.50 mmol) in diethylether (4.5 mL) was rapidly added to a solution of $LiAlH_4$ (133 mg, 3.50 mmol) in diethylether (3.5 mL). After the mixture had been stirred at 25°C for 30 minutes, a suspension of nitrile **179** (1.10 g, 3.50 mmol) in diethylether (7.0 mL) was slowly added. After the mixture had been stirred at 25°C for 2 h, water was added dropwise to decompose the excess of hydride and then a solution of KOH (5 mL, 5 M) was added to make basic conditions. The colloidal mixture was extracted with diethylether (10x30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 9:1:0.01), aminoalkyne **180** (1.01 g, 3.18 mmol, 91%) was isolated as a yellowish crystalline solid.

M.p.: 60-61°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.95 (t, J = 6.4 Hz, 2 H), 3.05 (t, J = 6.1 Hz, 2 H), 3.91 (s, 6 H), 7.00 (d, J = 1.7 Hz, 1 H), 7.05 (dd, J = 8.0,11 Hz, 1 H), 7.12 (dd, J = 1.9, 8.3 Hz, 1 H), 7.31(7dd, J = 7.9, 11 Hz, 1 H) ppm.

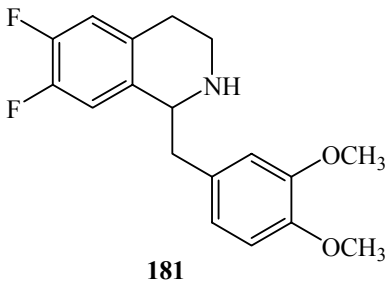
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 38.3 (CH_2), 42.5 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 111.1 (CH), 114.1 (CH), 114.9 (C), 118.0 (d, J = 18 Hz, CH), 119.7 (dd, J = 3, 7 Hz, CH_2), 120.6 (d, J = 19 Hz, CH), 124.9 (CH), 138.96 (dd, J = 4, 5 Hz, C), 148.4 (dd, J = 3, 247 Hz, C), 148.8 (C), 149.9 (C), 149.9 (dd, J = 3, 251 Hz, C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3441, 3040, 3012, 2935, 2834, 2794, 1609, 1591, 1517, 1461, 1417, 1329, 1303, 1259, 1241, 1208, 1155, 1137, 1102, 1029, 861, 807, 766, 634, 622 cm^{-1}.

MS: *m/z* (%) = 317 (100) [M$^+$], 302 (12), 288 (27), 286 (21), 273 (7), 243 (10), 241 (11), 225 (12), 201 (36), 180 (21), 175 (12), 166 (20), 151 (75), 138 (8), 113 (6).

HRMS: calcd. ($C_{18}H_{17}F_2NO2$) 317.1227; found 317.1234.

$C_{18}H_{17}F_2NO_2$ (317.3): calcd. C 68.13, H 5.40, N 4.41; found C 67.89, H 5.47, N 4.36.



181

1-(3,4-Dimethoxy-benzyl)-6,7-difluoro-1,2,3,4-tetrahydro-isoquinoline (**181**): A mixture of aminoalkyn **180** (159 mg, 0.50 mmol), Ind_2TiMe_2 (9 mg, 0.025 mmol, 5 mol-%) in toluene (0.25 mL) in a Schlenk tube was stirred at 105°C for 16 h. After the obtained brown liquid had been allowed to reach room temperature, a solution of $NaCNBH_3$ (63 mg, 1.00 mmol) and $ZnCl_2$ (68 mg, 0.50 mmol) in MeOH (5 mL) was added. The reaction mixture was stirred at 25°C for 24 h. A saturated aqueous NH_4Cl solution (25 mL) was then added and the mixture was extracted with MTBE (5×25 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 20:1:0.01), tetrahydrobenzylisoquinoline **181** (154 mg, 0.48 mmol, 96%) was isolated as a yellowish solid.

M.p.: 60-61°C.

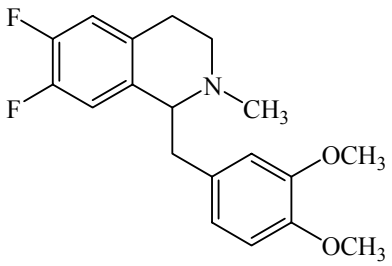
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (br. s, 1 H), 2.67-2.92 (m, 4 H), 3.12-3.22 (m, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.08 (dd, J = 3.3, 9.5 Hz, 1 H), 6.74 (d, J = 1.7 Hz, 1 H), 6.78 (dd , J = 1.7, 8.1 Hz, 1 H), 6.84 (d, J = 8.1 Hz, 1 H), 6.89 (dd, J = 8.5, 10.6 Hz, 1 H), 7.03 (dd, J = 8.3, 11.2 Hz, 1 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 29.3 (CH_2), 40.7 (CH_2), 41.9 (CH_2), 55.8 (CH_3), 55.9 (CH_3), 56.7 (CH), 111.4 (CH), 112.3 (CH), 114.6 (dd, J = 2, 16 Hz, CH), 117.3 (dd, J = 3, 14 Hz, CH), 121.3 (CH), 130.7 (C), 131.9 (dd, J = 4, 5 Hz, C), 135.0 (dd, J = 3, 4 Hz, C), 147.8 (C), 148.3 (dd, J = 13, 249 Hz, C), 148.5 (dd, J = 12, 248 Hz, C), 149.0 (C) ppm.

IR (KBr): $\tilde{\upsilon}$ = 3007, 2944, 2840, 2211, 1698, 1678, 1517, 1465, 1442, 1407, 1342, 1283, 1266, 1248, 1221, 1189, 1174, 1134, 1023, 882, 863, 808, 765 cm^{-1}.

MS: *m/z* (%) = 319 (2) [M^+], 267 (4), 182 (17), 169 (41, 168 (100), 166 (15), 153 (16), 151 (17),141 (7), 113 (6), 72 (11).

HRMS: calcd. ($C_{18}H_{19}F_2NO_2$) 319.1384; found 319.1399.



182

1 - (3,4 - Dimethoxy-benzyl) - 6,7 - difluoro - 2 - methyl- 1,2,3,4 – tetrahydrobenzyl-isoquinoline (**182**): Aqueous CH_2O (0.5 mL, *c* = 37%) was added to a solution of **181** (80 mg, 0.25 mmol) in MeOH (1.5 mL). After this mixture had been stirred at room temperature for 3 h, $NaBH_4$ (95 mg, 2.5 mmol) was slowly added. Subsequently, the reaction mixture was stirred at 25°C for an additional 16 h. Then, saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 95:5:1), tetrahydro-benzylisoquinoline **182** was isolated as a yellowish oil (70 mg, 0.21 mmol, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 2.54-2.54 (m, 1 H), 2.69-2.84 (m, 3 H), 3.03-3.16 (m, 2 H), 3.69 (t, *J* = 6.0 Hz, 1 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 6.49 (dd, *J* = 8.2, 11.2 Hz, 1 H), 6.57 (d, *J* = 1.9 Hz, 1 H), 6.61 (dd, *J* = 1.7, 8.1 Hz, 1 H), 6.76 (d, *J* = 8.1 Hz, 1 H), 6.84 (dd, *J* = 8.1, 10.9 Hz, 1 H) ppm.

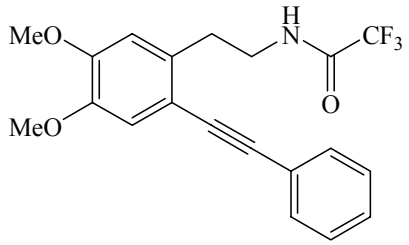
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 25.5 (CH_2), 40.3 (CH_2), 42.6 (CH_3), 46.6 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 64.5 (CH), 111.0 (CH), 112.8 (CH), 116.3 (d, *J* = 17 Hz, CH), 116.7 (d, *J* = 16 Hz, CH), 121.7 (CH),130.9 (dd, *J* = 4, 6 Hz, C), 131.6 (C), 134.0 (dd, *J* = 4, 4 Hz, C), 147.5 (C), 147.9 (dd, *J* = 18, 250 Hz, C), 148.5 (dd, *J* = 16, 249 Hz, C), 148.5 (C) ppm.

IR: $\tilde{\upsilon}$ = 2936, 2836, 2798, 1608, 1591, 1516, 1465, 1417, 1375, 1315, 1264, 1238, 1212, 1157, 1140, 1085, 1030, 881, 807, 764 cm^{-1}.

MS: *m/z* (%) = 333(5) [M^+], 332 (6), 316 (9), 198 (9), 183 (100), 182 (100), 180 (93), 167 (84), 151 (40), 139 (22), 133 (10), 127 (13), 119 (16), 107 (13), 106 (14), 86 (29), 78 (9), 65 (12).

HRMS: calcd. ($C_{19}H_{21}F_2NO_2$) 333.1540; found 333.1523.

SYNTHESIS OF 3´,4´-DEDIMETHOXYNORLAUDANOSINE



184

N-{2 - [2 - (3,4 - Dimethoxy - phenylethynyl) - 4,5 - dimethoxy-phenyl]-ethyl}-2,2,2-trifluoro -acetamide (**184**): $Pd(PPh_3)_2Cl_2$ (112 mg, 0.16 mmol, 2 mol-%), CuI (61 mg, 0.32 mmol, 4 mol-%), PPh_3 (83 mg, 0.32 mmol, 4 mol-%), and iPr$_2$NH (24 mL) were placed in a round-bottomed flask. After addition of aryl iodide **144** (3.22 g, 8.00 mmol), the mixture was stirred at 25°C for 30 min, and phenylacetylene **183** (0.82 g, 8.00 mmol) was then added. After this mixture had been stirred at 25°C for an additional 16 h, saturated NH_4Cl solution was added. The mixture was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. After purification by flash chromatography (SiO_2, PE/EtOAc, 1:1), **184** (2.44 g, 6.47 mmol, 81%) was isolated as a yellow crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.09 (t, J = 6.6 Hz, 2 H), 3.71-3.73 (m, 2 H), 3.88 (s, 3 H), 3.90 (s, 3 H), 6.54 (br. s, 1 H), 6.68 (s, 1 H), 7.03 (s, 1 H), 7.34-7.38 (m, 3 H), 7.48-7.52 (m, 2 H) ppm.

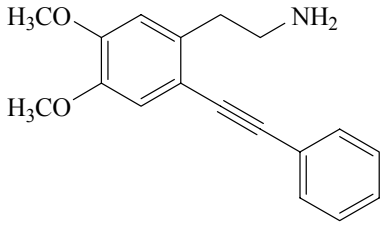
^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 33.1 (CH_2), 40.7 (CH_2), 55.9 (CH_3), 56.0 (CH_3), 87.4 (C), 92.2 (C), 112.1 (CH), 114.7 (C), 114.8 (CH), 115.7 (q, J = 288 Hz, C), 122.9 (C), 128.4 (CH), 131.3 (CH), 132.9 (C), 147.7 (C), 149.7 (C), 157.3 (q, J = 37 Hz, C) ppm.

IR: $\tilde{\upsilon}$ = 3431, 2940, 1707, 1628, 1605, 1562, 1514, 1444, 1353, 1250, 1220, 1180, 1093, 1001, 862, 757, 691 cm^{-1}.

MS: *m/z* (%) = 377 (87) [M^+], 312 (4), 281 (8), 264 (15), 252 (17), 251 (100), 236 (4), 201 (5), 188 (5), 178 (10), 162 (14), 151 (11), 112 (9).

HRMS: calcd. ($C_{20}H_{18}F_3NO_3$) 377.1239; found 377.1257.

$C_{20}H_{18}F_3NO_3$ (377.4): calcd. C 63.66, H 4.81, N 3.71; found C 63.54, H 4.89, N 3.79.



185

2-(4,5-Dimethoxy-2-(phenylethynyl)phenyl)ethanamine (**185**): At 0°C, aqueous KOH (5 M, 16.0 mL, 80.0 mmol) was added to a solution of **184** (3.04 g, 8.1 mmol) in MeOH (80 mL). The cooling bath was removed and the mixture was stirred at 25°C for 20 h. Then, the MeOH was removed under vacuum and the residue was diluted with H_2O (50 mL). After extraction with CH_2Cl_2 (4×50 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (SiO_2, EtOAc + 3% NH_3) gave **185** (1.90 g, 6.8 mmol, 83%) as a very hygroscopic pale brown solid.

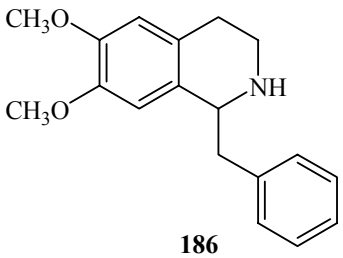
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.93-3.07 (m, 4 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 6.74 (s, 1 H), 7.01 (s, 1 H), 7.30-7.36 (m, 3 H), 7.48-7.52 (m, 2 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 38.2 (CH_2), 42.7 (CH_2), 55.7 (CH_3), 55.8 (CH_3), 88.0 (C), 91.4 (C), 112.2 (CH), 114.5 (CH), 114.6 (C), 123.3 (C), 127.8 (CH), 128.2 (CH), 131.1 (CH), 135.0 (C), 146.9 (C), 149.2 (C) ppm.

IR: $\tilde{\upsilon}$ = 3366, 2935, 2851, 2006, 1596, 1571, 1514, 1464, 1442, 1400, 1349, 1249, 1217, 1189, 1168, 1092, 1071, 1027, 1001, 859, 757, 692 cm^{-1}.

MS: *m/z* (%) = 281 (26) [M^+], 253 (16), 252 (100), 251 (30), 237 (6), 212 (5), 207 (5), 201 (6), 163 (6), 151 (12), 132 (4),

HRMS: calcd. ($C_{18}H_{19}NO_2$) 281.1416; found 281.1415.



186

1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**186**): A mixture of aminoalkyne **185** (283 mg, 1.00 mmol), Cp_2TiMe_2 (0.27 mL, 0.37 mmol/mL, 0.10 mmol, 10 mol-%) in toluen (0.50 mL) in a Schlenk tube was stirred at 105°C for 16 h. After the obtained brown liquid had been allowed to reach room temperature, a solution of $NaCNBH_3$ (126 mg, 2.00 mmol) and $ZnCl_2$ (136 mg, 1.00 mmol) in MeOH (10 mL) was added. The reaction mixture was stirred at room temperature for 24 h. A saturated aqueous NH_4Cl (25 mL) was then added and the mixture was extracted with MTBE (5×25 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was evaporated under vacuum. After purification by flash chromatography (SiO_2, MTBE/MeOH/NEt_3, 9:1:0.01), tetrahydrobenzylisoquinoline **186** (233 mg, 0.82 mmol, 82%) was isolated as a yellowish viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.71-2.78 (m, 2 H), 2.90-2.98 (m, 2 H), 3.18-3.24 (m, 2 H), 3.80 (s, 3 H), 3.86 (s, 3 H), 4.17 (dd, J = 4.6, 9.4 Hz, 1 H), 6.60 (s, 1 H), 7.22-7.36 (m, 5 H) ppm.

^{13}C NMR (75 MHz, DEPT, $CDCl_3$): δ = 29.41 (CH_2), 40.64 (CH_2), 42.79 (CH_2), 55.84 (CH_3), 55.95 (CH_3), 56.85 (CH), 109.57 (CH), 111.89 (CH), 126.45 (CH), 127.26 (C), 128.59 (CH), 129.42 (CH), 130.39 (C), 139.10 (C), 147.03 (C), 147.53 (C) ppm.

IR: $\tilde{\upsilon}$ = 3333, 2933, 2831, 1610, 1515, 1464, 1453, 1261, 1223, 1113, 1031, 859, 750, 701 cm^{-1}.

MS: *m/z* (%) = 283 (3) [M^+], 282 (17), 280 (19), 266 (10), 250 (5), 220 (7), 206 (21), 193 (100), 192 (100), 177 (37), 176 (84), 165 (6), 161 (7), 148 (35), 147 (24), 134 (10), 131 (19).

HRMS: calcd. ($C_{18}H_{21}NO_2$) 283.1572; found 283.1531.