# Enantioselective Synthesis of (+)-(*S*)-Laudanosine and (–)-(*S*)-Xylopinine

**Didin Mujahidin[a] and Sven Doye*[a]**

**Keywords:** Alkaloids / Alkynes / Asymmetric Synthesis / Hydroamination / Titanium

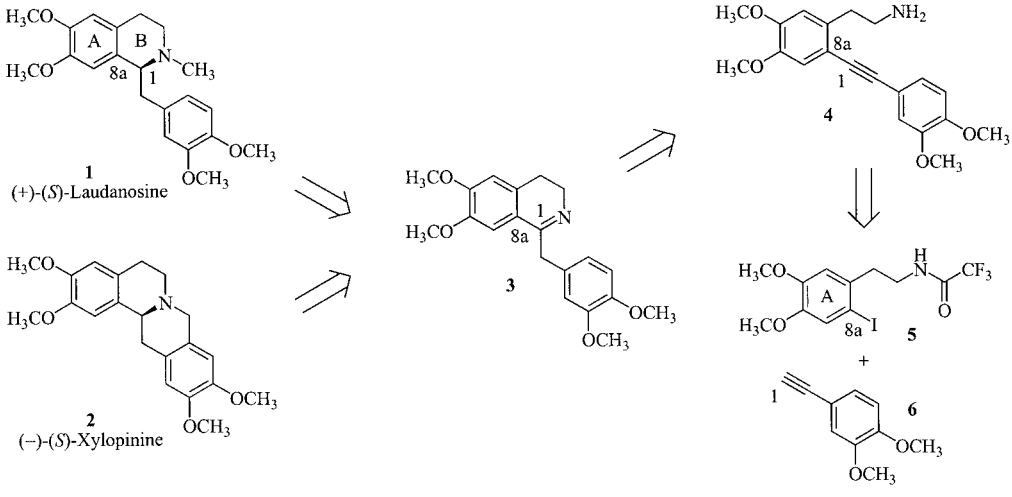
The study presents a new pathway for the enantioselective synthesis of benzylisoquinoline alkaloids. The key steps of the synthesis of (+)-(*S*)-laudanosine (**1**) and (–)-(*S*)-xylopinine (**2**) are a Sonogashira coupling that builds up the C1–C8a bond of the benzylisoquinoline skeleton, an intramolecular Ti-catalyzed hydroamination of an alkyne, and a subsequent enantioselective imine reduction according to Noyori's protocol.


## Introduction

Ti-catalyzed hydroaminations of alkynes have attracted much attention during the last few years.[1] While corresponding reactions have extensively been used for the generation of small libraries of various classes of biologically interesting compounds such as arylethylamines,[2] indoles,[3] and tryptamine homologs,[4] to the best of our knowledge, only one example of a natural product synthesis that applies a Ti-catalyzed hydroamination of an alkyne has been reported.[5,6]

Since benzylisoquinoline alkaloids play an outstanding role among the various classes of natural products, we focused on a synthetic approach towards the benzylisoquinoline framework that employs a Ti-catalyzed hydroamination of an alkyne as the key step.[7] As the first two prominent target molecules, we chose the opium alkaloids (+)-(*S*)-laudanosine (**1**)[8] and (–)-(*S*)-xylopinine (**2**).[9] For both compounds, several asymmetric syntheses have been described in the past.[10] However, in most cases, the benzylisoquinoline framework was formed by Pictet–Spengler, Bischler–Napieralski, or Pomeranz–Fritsch synthesis.

As outlined retrosynthetically in Scheme 1, our approach relies on the enantioselective reduction of imine **3**, which has already been described by Noyori et al.[11] In contrast to the common synthesis of benzylisoquinoline alkaloids, the imine **3** was planned to arise from an intramolecular hydroamination reaction of aminoalkyne **4**. Using this approach, the C1–C8a bond can be formed by a Sonogashira




Scheme 1. Retrosynthesis of (+)-(*S*)-laudanosine (**1**) and (–)-(*S*)-xylopinine (**2**).

[a] Organisch-Chemisches Institut, Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg, Germany
Fax: +49-6221-54-4205
E-mail: sven.doye@urz.uni-heidelberg.de

coupling[12] between the aryl iodide **5** and alkyne **6**. 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

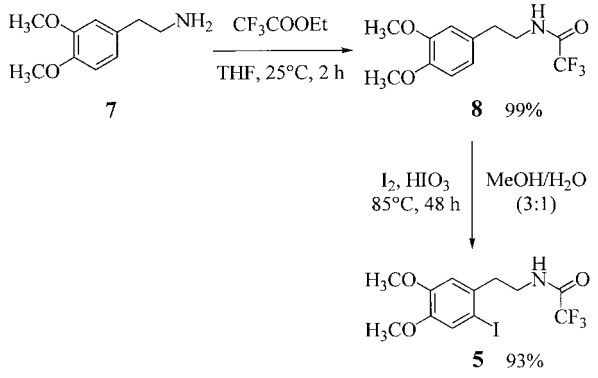
 **DOI: 10.1002/ejoc.200500095**  

obvious advantage of this strategy is the fact that in contrast to electophilic aromatic substitutions, the Pd-catalyzed Sonogashira coupling is facilitated by electron-withdrawing substituents located in the A-ring. Therefore, the Sonogashira coupling/hydroamination approach is somehow complementary to the common electrophilic substitution approach. For future synthesis of benzylisoquinoline derivatives with electron-deficient A-rings the new strategy might be even superior to the old substitution-based procedures.

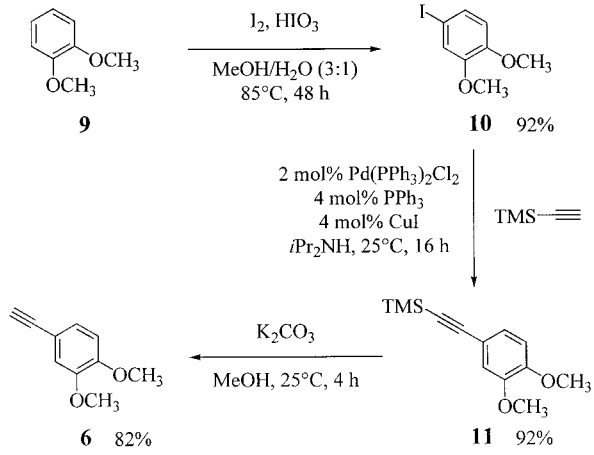
## Results and Discussion

The synthesis of aryl iodide **5** was accomplished as depicted in Scheme 2, according to Tietze's procedure.[13] Reaction of commercially available homoveratrylamine (**7**) with ethyl trifluoroacetate in THF at room temperature gave the *N*-protected trifluoroacetamide **8** cleanly in 99% yield. Subsequently, **8** was converted into **5** in 93% yield by iodination in the presence of $I_2$ and $HIO_3$ at 85 °C in a mixture of water and methanol.

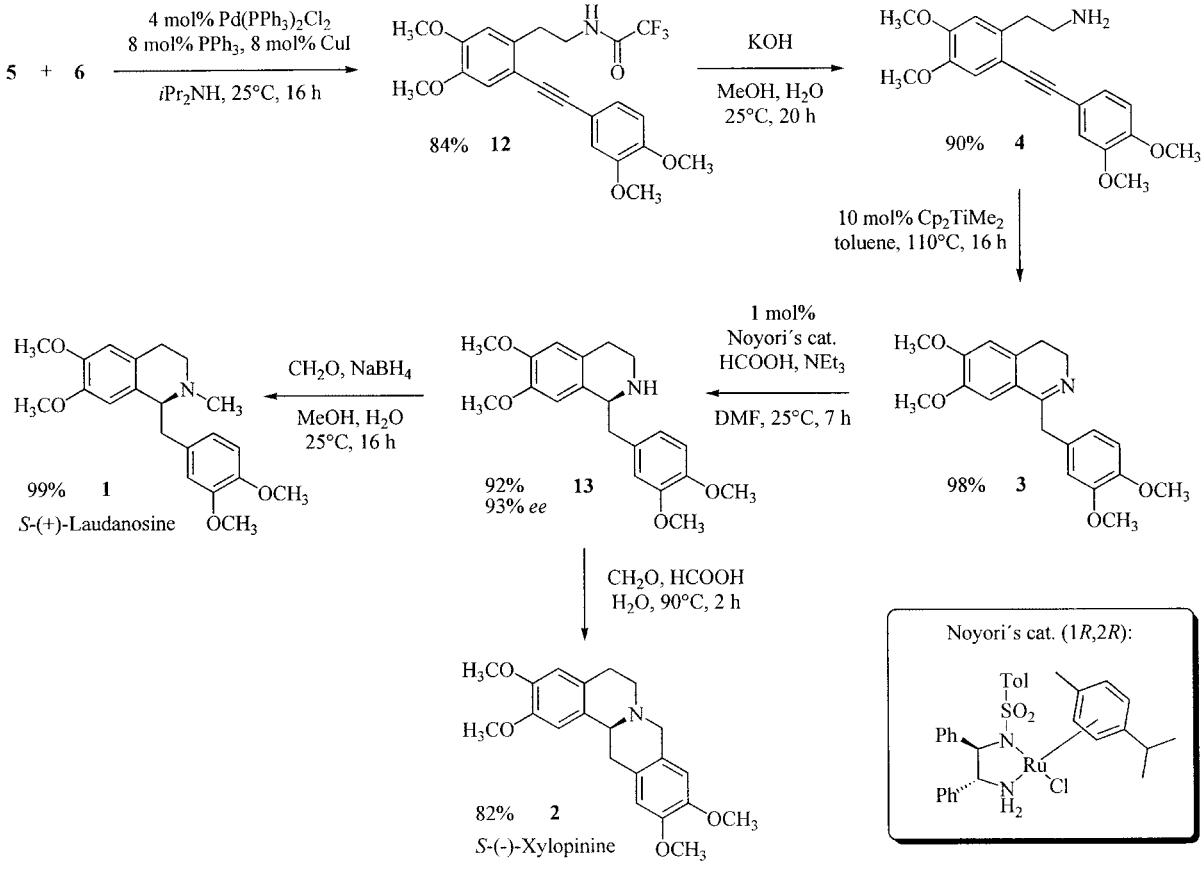
The synthesis of alkyne fragment **6** is summarized in Scheme 3. Iodination of veratrol (**9**) in the presence of $I_2$ and $HIO_3$ at 85 °C in a mixture of water and methanol afforded 4-iodoveratrol (**10**) in 92% yield. Subsequent stan-




Scheme 2. Synthesis of aryl iodide **5**.




Scheme 3. Synthesis of terminal alkyne **6**.




Scheme 4. Final steps in the synthesis of laudanosine (**1**) and xylopinine (**2**).

dard Sonogashira coupling [2 mol-% $Pd(PPh_3)_2Cl_2$, 4 mol-% $PPh_3$, 4 mol-% CuI, $iPr_2NH$, 25 °C, 16 h] employing TMS–acetylene (TMS = trimethylsilyl) led to the formation of TMS-protected alkyne **11** in 92% yield. The desired building block **6** was finally obtained in 82% yield by deprotection of **11** with $K_2CO_3$ in methanol at room temperature.

With **5** and **6** in hand, attention was now directed towards the completion of the synthesis, as shown in Scheme 4. Aryl iodide **5** and alkyne **6** were subjected to standard Sonogashira coupling conditions [4 mol-% $Pd(PPh_3)_2Cl_2$, 8 mol-% $PPh_3$, 8 mol-% CuI, $iPr_2NH$, 25 °C, 16 h] to give the trifluoroacyl-protected alkyne **12** in 84% yield. In this context, it is worth mentioning that in alkyne **12** the C1–C8a bond (vide supra) has already been established. Liberation of the $NH_2$ group under basic conditions (KOH, MeOH, $H_2O$, 25 °C, 20 h) delivered aminoalkyne **4** in 90% yield. This key intermediate was then subjected to an intramolecular hydroamination reaction at 110 °C in toluene by employing 10 mol-% $Cp_2TiMe_2$[14] as the catalyst. To our delight, the hydroamination reaction proceeded smoothly to produce imine **3** in 98% yield. After purification by flash chromatography, imine **3** was enantioselectively reduced according to Noyori's protocol by employing 1 mol-% ($\eta^6$-*p*-cymene)[(1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine)]RuCl as the catalyst.[11] In good agreement with Noyori's results, the corresponding secondary amine **13** was obtained in 92% yield with 93% *ee* [(*S*) configuration]. Amine **13** represents a single precursor for the synthesis of both target molecules. (+)-(*S*)-Laudanosine (**1**) was obtained from **13** by reductive amination ($CH_2O$, $NaBH_4$, MeOH, $H_2O$, 25 °C, 16 h) in 99% yield. Alternatively, a final Pictet–Spengler cyclization of **13** by employing aqueous $CH_2O$ and formic acid afforded (–)-(*S*)-xylopinine (**2**) in 82% yield.

## Conclusions

In summary, we have presented a new pathway for the enantioselective synthesis of benzylisoquinoline alkaloids. The key steps of the synthesis of (+)-(*S*)-laudanosine (**1**) and (–)-(*S*)-xylopinine (**2**) are a Sonogashira coupling that builds up the C1–C8a bond of the benzylisoquinoline skeleton, an intramolecular Ti-catalyzed cyclization of an aminoalkyne, and a subsequent enantioselective imine reduction according to Noyori's protocol.

## Experimental Section

**General Remarks:** All reactions were performed under argon in flame dried Duran glassware (e.g. Schlenk tubes equipped with Teflon stopcocks). Toluene was 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.[14] ($\eta^6$-*p*-cymene)[(1*R*,2*R*)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylenediamine)]RuCl was synthesized according to ref.[11] All other reagents were purchased from commercial sources and were used without further purification. Unless otherwise noted, yields refer to isolated yields of pure compounds as gauged by thin layer chromatography (TLC) and $^1H$ and $^{13}C$ NMR spectroscopy. All products were characterized by $^1H$ 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 $^1H$ NMR spectra are reported in $\delta$ units ppm downfield from tetramethylsilane as internal standard. All $^{13}C$ NMR spectra are reported in $\delta$ units ppm relative to the central line of the triplet of $CDCl_3$ at $\delta$ = 77.0 ppm. IR spectra were recorded with a Bruker Vector 22 spectrometer using an attenuated total reflection (ATR) method. Mass spectra were recorded with 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. Melting points are uncorrected. PE: light petroleum ether, b.p. 40–60 °C. MTBE: methyl *tert*-butyl ether.

**Trifluoroacetamide 8:** At 25 °C, ethyl trifluoroacetate (10.58 g, 74.5 mmol) was added dropwise to a solution of homoveratrylamine (**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 **8** (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. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**Aryl Iodide 5:** A solution of **8** (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), **5** (24.42 g, 60.6 mmol, 93%) was isolated as a white solid. M.p. 122–123 °C. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**4-Iodoveratrol (10):** A solution of veratrol (**9**, 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 mix-

ture 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, **10** (24.32 g, 92.1 mmol, 92%) was isolated as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**TMS–Alkyne 11:** $Pd(PPh_3)_2Cl_2$ (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 $i$Pr$_2$NH (60 mL) were placed in a round-bottomed flask. After addition of 4-iodoveratrol (**10**, 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 had been stirred at 25 °C for additional 16 h, a saturated $NH_4Cl$ solution was added. The mixture was extracted with $CH_2Cl_2$ (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), **11** (4.31 g, 18.4 mmol, 92%) was isolated as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**Alkyne 6:** Anhydrous $K_2CO_3$ (138 mg, 1.00 mmol) was added to a solution of **11** (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), **6** (1.37 g, 8.45 mmol, 82%) was isolated as a white crystalline solid. M.p. 70–71 °C. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**Alkyne 12:** $Pd(PPh_3)_2Cl_2$ (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 $i$Pr$_2$NH (19 mL) were placed in a round-bottomed flask. After addition of aryl iodide **5** (2.66 g, 6.60 mmol), the mixture was stirred at 25 °C for 30 min, and alkyne **6** (1.07 g, 6.60 mmol) was then added. After this mixture had been stirred at 25 °C for 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), **12** (2.41 g, 5.51 mmol, 84%) was isolated as a yellow crystalline solid. M.p. 164–165 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**Aminoalkyne 4:** Aqueous KOH (5 M, 11.0 mL, 55.0 mmol) was added to a solution of **12** (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 **4** (1.66 g, 4.86 mmol, 90%) as a very hygroscopic pale brown solid. Aminoalkyne **4** was stored as a solution in $CH_2Cl_2$ (100 mg/mL) at 4 °C. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**Imine 3:** A solution of **4** 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 **3** (669 mg, 1.96 mmol, 98%) as a yellow solid. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**(–)-(*S*)-Norlaudanosine (13):** A 5:2 mixture of HCOOH and $NEt_3$ (1.5 mL) was added to a suspension of imine **3** (1.02 g, 3.00 mmol) and ($\eta^6$-*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% $NH_3$), **13** (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, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**(+)-(*S*)-Laudanosine (1):** Aqueous $CH_2O$ (2.0 mL, *c* = 37%) was added to a solution of **13** (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 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 (**1**, 340 mg, 0.95 mmol, 99%) was isolated as a cream-colored solid. M.p. 88–89 °C. $[\alpha]_D^{22}$ = +87 (*c* = 0.70, EtOH) {ref.[8]: $[\alpha]_D$ = +103 (EtOH)}. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

**(–)-(*S*)-Xylopinine (2):** A mixture of aqueous $CH_2O$ (0.8 mL, *c* = 37%), HCOOH (1.2 mL), and **13** (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 $CH_2Cl_2$ (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 (**2**, 44 mg, 0.12 mmol, 82%) was isolated as a cream-colored solid. M.p. 178–180 °C. $[\alpha]_D^{22}$ = –262 (*c* = 0.10, $CHCl_3$) {ref.[9]: $[\alpha]_D$ = –297 ($CHCl_3$)}. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 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, $CDCl_3$): $\delta$ = 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.

## Acknowledgments

Generous support by Professor E. Winterfeldt and Professor H. M. R. Hoffmann is most gratefully acknowledged. We further thank the Deutscher Akademischer Austausch Dienst (DAAD Fellowship for D. M.), the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the Dr. Otto Röhm Gedächtnisstiftung, Darmstadt for financial support of our research.

[1] For reviews, see: a) I. Bytschkov, S. Doye, *Eur. J. Org. Chem.* **2003**, 935–946; b) S. Doye, *Synlett* **2004**, 1653–1672; c) A. Odom, *Dalton Trans.* **2005**, 225–233.
[2] a) H. Siebeneicher, S. Doye, *Eur. J. Org. Chem.* **2002**, 1213–1220; b) I. Bytschkov, H. Siebeneicher, S. Doye, *Eur. J. Org. Chem.* **2003**, 2888–2902.
[3] H. Siebeneicher, I. Bytschkov, S. Doye, *Angew. Chem.* **2003**, *115*, 3151–3153; *Angew. Chem. Int. Ed.* **2003**, *42*, 3042–3044.
[4] V. Khedkar, A. Tillack, M. Michalik, M. Beller, *Tetrahedron Lett.* **2004**, *45*, 3123–3126.
[5] P. L. McGrane, T. Livinghouse, *J. Org. Chem.* **1992**, *57*, 1323–1324.
[6] For a synthesis of (+)-preussin based on a stoichiometric imidotitanium–alkyne [2+2]-cycloaddition, see: P. L. McGrane, T. Livinghouse, *J. Am. Chem. Soc.* **1993**, *115*, 11485–11489.
[7] A synthesis of the isoquinoline framework that involves a Pictet–Spengler reaction of an imine obtained by Ti-catalyzed hydroamination of 1-hexyne has been described: Z. Zhang, L. L. Schafer, *Org. Lett.* **2003**, *5*, 4733–4736.
[8] *Römpp Lexikon Naturstoffe*, 10th ed. (Eds.: B. Fugmann, S. Lang-Fugmann, W. Steglich), Georg Thieme Verlag, Stuttgart, **1997**, p. 79–80.
[9] J. Schmutz, *Helv. Chim. Acta* **1959**, *42*, 335–343.
[10] For a recent review on the asymmetric synthesis of isoquinoline alkaloids, see: M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370.
[11] N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917.
[12] 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.
[13] 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.
[14] 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.

Received: February 4, 2005