# ChemInform Abstract: Enantioselective Highly Efficient Synthesis of (−)-Cephalotaxine Using Two Palladium-Catalyzed Transformations.

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# Enantioselective Highly Efficient Synthesis of (−)-Cephalotaxine Using Two Palladium-Catalyzed Transformations

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**Abstract:** Cephalotaxine (**1**), the major alkaloid isolated from *Cephalotaxus* species, has attracted considerable attention due to the promising antitumor activity of several of its derivatives and its unique structural features. Herein we describe a highly efficient enantioselective synthesis of **1** employing two successive Pd-catalyzed transformations starting from **25** to give the pentacyclic product **6**. The controlling stereogenic center in **25** was introduced by an enantioselective reduction of the enone **16**.

Cephalotaxine (**1**) is the parent compound of a group of alkaloids called harringtonines. They occur in about eight known species of the genus *Cephalotaxus* (Cephalotaxaceae), evergreen plum yews, which are indigenous to south-east Asia.[1] Cephalotaxine has become an interesting synthetic target, not only because of its unique ring skeleton containing a 1-azaspiro[4.4]-nonane moiety fused to a benzazepine system but also as a result of the antileukemic activity of several of its 2-alkylhydroxysuccinates at C-3, especially harringtonine (**2**), deoxyharringtonine (**3**), isoharringtonine (**4**), and homoharringtonine (**5**); cephalotaxine (**1**) itself is biologically largely inactive. Clinical trials have reached phase II−III,[1,2] and more recently, homoharringtonine (**5**) has been investigated in the treatment of chloroquine-resistant malaria.[3]

Since the first isolation of **1** in 1963 by Paudler[4] and its characterization[5] in the 1960s and 1970s, about a dozen total syntheses of racemic cephalotaxine (**1**) have been reported[6] and even more approaches have been devised for the construction of its pentacyclic skeleton.[7] On the other hand, until now only two syntheses of enantiopure (−)-cephalotaxine (**1**) have been published. In the synthesis of Mori,[8] optically pure D-(+)-proline has been used as starting material, whereas Nagasaka[9] employed a resolution of a racemic key intermediate by the formation of diastereomeric acetals. Here we describe a highly efficient enantioselective synthesis of (−)-cephalotaxine (**1**) by two successive Pd-catalyzed reactions in which chirality is intro-

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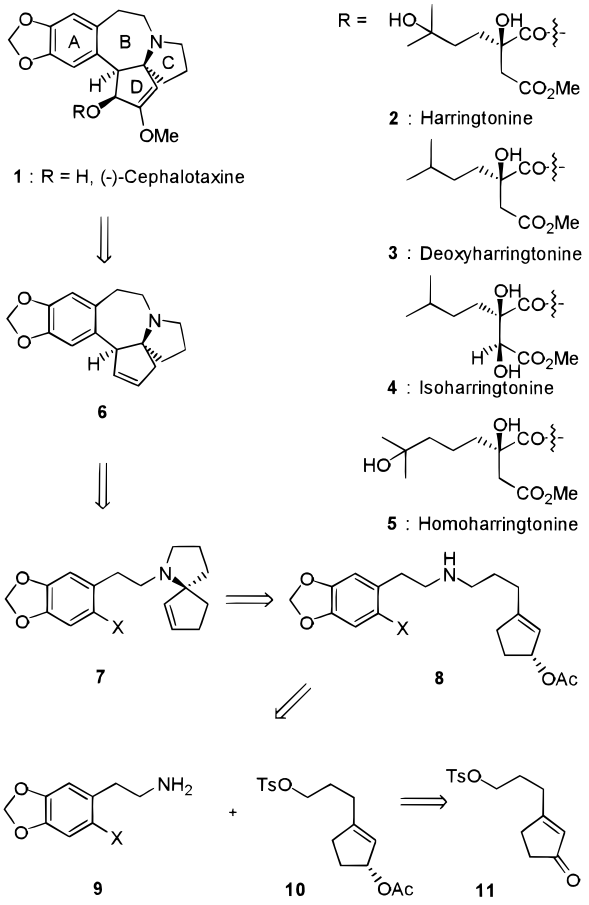
**Scheme 1.** Retrosynthetic Analysis of (−)-Cephalotaxine




duced by a catalytic enantioselective reduction. A communication on the synthesis of racemic cephalotaxine has already appeared.[6o]

Our retrosynthesis of **1** led to the pentacyclic core **6**, whereby the transformation of **6** into the naturally occurring alkaloid **1** had already been accomplished by Mori[8] using the procedure developed by Kuehne.[6i] It was our assumption that **6** should be available by a combination of a Heck reaction[10] and a Tsuji-Trost allylation[11] starting from the secondary amine **8**. The intramolecular Pd-catalyzed substitution of an allyl acetate with an amine had already been reported by Godleski.[12] Moreover, we had developed a stereoselective entrance to benzazepines by an intramolecular Heck reaction.[13] The secondary amine **8** where X represents an iodine or bromine atom should be available by the alkylation of the primary amine **9** with **10**, which contains a cyclopentenyl acetate moiety.

Following an established procedure, we synthesized the cyclopentenone **11**[12a] from cyclopentane-1,3-dione **12** via **13**.[14] By reaction of **13** with a Grignard reagent generated from 3-chloropropanol (**15**) in which the alcohol function was protected as the magnesium salt[15] and tosylation of the crude product, the enone **11** was obtained in 50% yield.

In the racemic series, **11** was reduced with DIBALH and treated with acetic anhydride to give *rac*-**10** in 93% yield. For the synthesis of the (−)-enantiomer of cephalotaxine (**1**), the allyl acetate **10** with the (*R*)-configuration of the stereogenic center was necessary, since it was known from the work of Trost[16] that the formation of the Pd-allyl complex and the nucleophilic addition of an amine as a soft nucleophile should proceed with inversion, resulting in an overall retention of the configuration of the used substrate. For the enantioselective synthesis of **10**, we intended to carry out an enantioselective reduction of the cyclopentenone **11**. However, no satisfying catalytic procedure had been reported for this type of substrate. Thus, we anticipated that the reduction of **11** using Corey's oxazaborolidine method[17] would give only a low ee, as we found for the corresponding cyclohexenone. We therefore introduced a sterically demanding bromine atom as a removable dummy[18] in the 2-position of **11** to give **16**, which was then reduced using diborane in the presence of catalytic amounts of the oxazaborolidine **18**. By this way, **17** was obtained after acetylation of the formed allylic alcohol in 96% overall yield and 87% ee. The enantioselective reduction was performed in THF as solvent with 0.7 equiv of borane−tetrahydrofuran complex in the presence of 0.1 equiv of *B*-methyloxazaborolidine **18**.[19] The enantiomeric excess was determined by NMR experiments using $Eu(hfc)_3$ as chiral shift reagent.[20] Although slightly elevated temperatures are most often reported to show the best results,[21] we found the highest ee of 87% and the best yields when the reduction was carried out at −15 °C. Thus, reaction at 50 °C afforded **16** in only 51% yield without a positive effect on the enantioselectivity. In addition, when the *B*-butyloxazaborolidine[22] was used as the chiral ligand, the ee value could not be improved. The allylic alcohol was very sensitive to decomposition, and for this reason, the crude product was acetylated without any purification.

The substrate **16** employed in the reduction could also be prepared by an alternative way from **12** in an overall yield of

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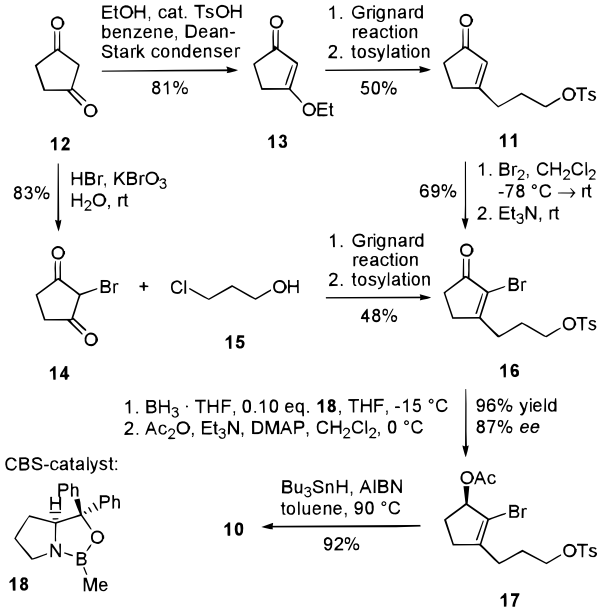
40%. Reaction of **12** with bromine generated in situ from potassium bromate and hydrogen bromide[23] gave **14**,[24] which was subsequently treated with a large excess of the Grignard reagent obtained from **15** and afterward with tosyl chloride. To improve the enantioselectivity in the reduction step, we intended to use an iodine instead of a bromine atom in the 2-position of **16**; several methods to iodinate enones in the α-position had been developed in the last 10 years.[25] However, in our hands the yields were quite low, the best one being only 21%.

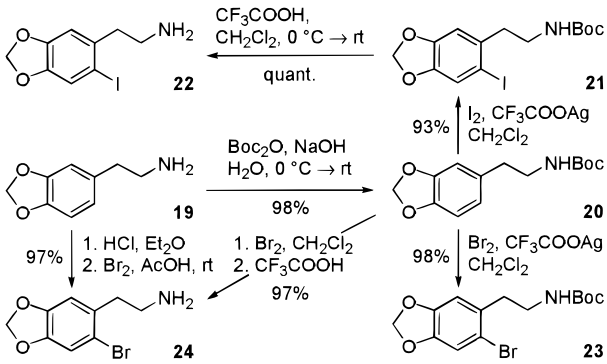
The removal of the bromo atom in **17** to give **10** in 92% yield was performed as a radical reaction using AIBN and tributyltin hydride as the hydride source. Other methods to achieve a debromination[26] of **17** such as hydrogenolysis in the presence of Pd on charcoal[27] or Wilkinson's catalyst[28] or the use of tris(trimethylsilyl)silane (TTMSS) as the hydride source[29] failed. The absolute configuration of the stereogenic center in **10** was determined in analogy to the products obtained by reduction of enones with oxazaborolidine **18** prepared from L-proline and later confirmed by a comparison of the optical rotation of the final pentacyclic compound with the known value.

As the second building block, the primary amines **22** and **24**, respectively, were prepared from piperonal via phenylethylamine **19**.[30] Protection with di-*tert*-butyl dicarbonate, iodination with iodine in the presence of silver trifluoroacetate,[31] and deprotection gave **22** in almost quantitative yield; iodination of **20** with the usual reagents as iodine and iodic acid according to the procedure of Königstein[32] to give **21** was unsatisfactory. At the first sight, this is surprising, but it can be understood taking into account that the steric arrangement of the methylenedioxy group restricts an overlap of the nonbonding electron pairs of the oxygens with the π-orbitals of the arene.[7i] The formation of the bromo compound **24** was much easier; either the protected **20** was treated with bromine followed by work up with trifluoroacetic acid or **19** was transformed into the hydrochloride and then reacted with bromine in acetic acid.[33] The bromination of **20** to give **23** could also be performed in the presence of one equivalent of silver trifluoroacetate; in this case a partial deprotection as in the reaction of **20** with bromine in dichloromethane does not take place.

**Scheme 2.** Enantioselective Preparation of Allylic Acetate **10**




**Scheme 3.** Halogenation of Phenylethylamines




The alkylation of the primary amines **22** and **24**, respectively, with the tosylate **10** after in situ transformation into the corresponding iodo compound was performed in the absence of any additional base. Several attempts were made with varying amounts of triethylamine and Hünig's base, but the yields were best if simply a 2−3-fold excess of the primary amine was applied. In this way we obtained the secondary amines **25a** and **25b**, respectively, in 70−90% yield.

However, the Pd-catalyzed reaction of **25a** with an iodoaryl moiety did not lead to the desired spiro compound. This result may be explained by an insufficient reactivity of the allyl acetate in comparison to the iodoaryl moiety; thus, the Pd seems to undergo preferably an oxidative addition at the aromatic ring. Consequently, we tried the same reaction using the bromo compound **25b** and were able to isolate the spirocyclic amine **26** in 88% yield. Here the use of tetramethylguanidine (TMG) as a base as described by Fuchs[34] for similar reactions was advantageous; however triethylamine can also be applied. Interestingly the reaction stops if the temperature exceeds 50 °C, which was interpreted as a further hint toward a competing reaction at the haloaryl moiety. Thus, the best results were obtained if the reaction temperature was kept at 45 °C and strictly controlled.

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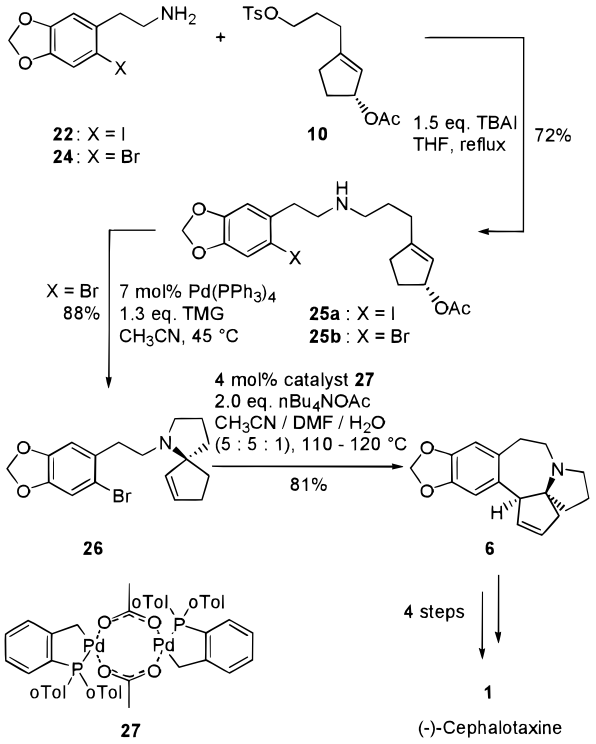
**Scheme 4.** Synthesis of (−)-Cephalotaxine Precursor **6**




The Heck reaction of **26**, which gives the pentacyclic core **6** of cephalotaxine (**1**) in 81% yield, was performed using 4 mol % of the palladacycle **27**, being described by Herrmann and Beller;[35] under the usual conditions, for example, with $Pd(PPh_3)_4$ as catalyst, no transformation was observed. The cyclization occurs highly stereoselectively; thus, the double bond in **26** is attacked exclusively from Re face syn to the nitrogen and furthermore no double bond isomers were detected. A comparison of the optical rotation of **6** with that described by Mori[8] shows that the allylation of **25b** to give **26** has occurred with an overall retention as anticipated and that a racemization did not take place. We also tried to perform the transformation from **25b** to **6** in a domino-type fashion[36] using the palladacycle **27**; however, the reaction of **25b** to give **26** was not possible employing **27**. The transformation of **6** into cephalotaxine (**1**) by bishydroxylation of the cyclopentene moiety using $OsO_4$, oxidation of the diol to the diketone, formation of the methyl enol ether, and diasteroselective reduction of the remaining keto group had been described by Mori.[8]

## Conclusion

A novel highly efficient strategy for the enantioselective synthesis of (−)-cephalotaxine (**1**) with two palladium-catalyzed reactions as key steps starting from the secondary amine **25b** to give the pentacyclic product **6** has been developed. Chirality was introduced by an enantioselective reduction of **16** with diborane in the presence of a catalytic amount of *B*-methyloxazaborolidine **18**. The Pd-catalyzed allylation of **25b** proceeds with complete retention, and the following Heck reaction gives a single diastereomer.

At the moment, the developed concept is used for the synthesis of skeleton-modified analogues.

## Experimental Section

**4-Toluenesulfonic Acid 3-(2-Bromo-3-oxo-cyclopent-1-enyl)-propyl Ester (16).** Method A: Bromination of the enone **11**. To a solution of the enone **11** (1.62 g, 5.52 mmol) in $CH_2Cl_2$ (25 mL) at −78 °C was added a solution of bromine (970 mg, 6.07 mmol, 1.1 equiv) in $CH_2Cl_2$ (15 mL). After the mixture was stirred at room temperature for 4 h, triethylamine (2.90 g, 28.7 mmol, 5.2 equiv) was added and the mixture stirred again for 2 h. Water was added, and the aqueous layer was extracted twice with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by chromatography on silica gel (100 g of $SiO_2$, petroleum ether/MTBE = 1:2) to give **16** (1.42 g, 3.79 mmol, 69%). Method B: Grignard reaction with 2-bromo-cyclopentane-1,3-dione (**14**). 3-Chloropropanol (**15**) (2.65 g, 28.0 mmol, 4.9 equiv) dissolved in THF (30 mL) was cooled to −78 °C. Methylmagnesium chloride (3.6 M in THF, 28.0 mmol) was added dropwise. After the addition was complete, the solution was allowed to warm to room temperature. When the gas production stopped, magnesium turnings (750 mg, 30.8 mmol, 5.3 equiv) were added, and the solution was heated at reflux for 3 h. The reaction mixture was then cooled to 0 °C, and 2-bromo-cyclopentane-1,3-dione (**14**) (1.01 g, 5.73 mmol) was added. The reaction mixture was stirred overnight, and then saturated $NH_4Cl$ solution (6 mL) was added. The mixture was partitioned between 100 mL of cold ethyl acetate and 50 mL of cold 2 N HCl. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic fractions were dried over $Na_2SO_4$ and concentrated at reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (12 mL) and cooled to −10 °C. Tosyl chloride (1.81 g, 9.49 mmol, 1.7 equiv), triethylamine (944 mg, 9.34 mmol, 1.6 equiv), and DMAP (70.0 mg, 573 $\mu$mol, 0.1 equiv) were added, and the mixture was stirred at −10 °C for 18 h, then partitioned between ethyl acetate and a saturated solution of $NaHCO_3$. After separation, the organic layer was washed with 1 N HCl and brine, dried over $Na_2SO_4$, and concentrated in vacuo. Purification by column chromatography (100 g of $SiO_2$, petroleum ether/ethyl acetate = 1:1) afforded 1.03 g (2.76 mmol, 48%) of **16**. $R_f$ = 0.64 (petroleum ether/ethyl acetate = 1:2); UV ($CH_3CN$) $\lambda_{max}$ (lg $\epsilon$) 193.5 (4.704), 227.5 (4.254), 272.5 (2.670); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.98 (tt, $J$ = 7.7, 6.1 Hz, 2 H), 2.46 (s, 3 H), 2.48−2.66 (m, 6 H), 4.09 (t, $J$ = 6.1 Hz, 2 H), 7.36 (d, $J$ = 8.3 Hz, 2 H), 7.79 (d, $J$ = 8.3 Hz, 2 H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.6, 25.8, 28.9, 30.3, 33.0, 69.3, 123.6, 127.8, 129.9, 132.6, 145.0, 174.5, 201.1. Anal. calcd for $C_{15}H_{17}BrO_4S$ (373.3): C, 48.27; H, 4.59. Found: C, 48.43; H, 4.64.

**4-Toluenesulfonic Acid 3-(2-Iodo-3-oxo-cyclopent-1-enyl)-propyl Ester.** The enone **11** (305 mg, 1.04 mmol) was dissolved in $CH_2Cl_2$ (1.5 mL) at 0 °C. Trimethylsilyl azide (265 mg, 2.28 mmol, 2.2 equiv) was added dropwise, and the mixture was stirred for 2.5 h at 0 °C. A solution of iodine (510 mg, 2.01 mmol, 1.9 equiv) in $CH_2Cl_2$ (1.5 mL) and pyridine (1.5 mL) was added slowly. The mixture was allowed to warm to room temperature and stirred for 24 h, then diluted with MTBE, washed with water, 2 N HCl, $Na_2S_2O_3$ solution, and $NaHCO_3$ solution, and dried over $Na_2SO_4$. Concentration and chromatography (30 g of $SiO_2$, petroleum ether/ethyl acetate = 1:1) gave 89.4 mg (213 $\mu$mol, 21%) of the iodo compound as colorless crystals. $R_f$ = 0.32 (petroleum ether/ethyl acetate = 1:1); mp 82 °C; UV ($CH_3CN$) $\lambda_{max}$ (lg $\epsilon$) 193.5 (4.771), 225.5 (4.207), 253.0 (3.888); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.97 (tt, $J$ = 7.8, 6.2 Hz, 2 H), 2.47 (s, 3 H), 2.57 (mc, 2 H), 2.62 (t, $J$ = 7.8 Hz, 2 H), 2.72 (mc, 2 H), 4.11 (t, $J$ = 6.2 Hz, 2 H), 7.38 (d, $J$ = 8.3 Hz, 2 H), 7.81 (d, $J$ = 8.3 Hz, 2 H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 21.7, 26.1, 31.9, 32.5, 32.8, 69.3, 103.6, 127.9, 130.0, 132.8, 145.1, 180.6, 203.3; EI HRMS *m/z* 419.9892, $C_{15}H_{17}IO_4S$ requires 419.9892. Anal. calcd for $C_{15}H_{17}IO_4S$ (420.3): C, 42.87; H, 4.08. Found: C, 42.69; H, 4.02.

**Acetic Acid 2-Bromo-3-[3-(toluene-4-sulfonyloxy)-propyl]-cyclopent-2-enyl Ester (17).** To a mixture of the oxazaborolidine **18** (152

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mg, 0.55 mmol, 0.1 equiv) and borane (3.90 mmol, 0.74 equiv) in THF at −15 °C was added dropwise a 0.3 M solution of the enone **16** (1.96 g, 5.26 mmol) in THF. At the same temperature MeOH was added. The solvents were removed, and after a second addition of MeOH, the solution was concentrated in vacuo. The crude allylic alcohol as a 0.3 M solution in $CH_2Cl_2$ was acetylated at 0 °C with acetic anhydride (1.20 g, 11.6 mmol, 2.2 equiv), triethylamine (650 mg, 6.50 mmol, 1.2 equiv), and DMAP (80.0 mg, 650 $\mu$mol, 0.1 equiv). After being stirred at 0 °C for 1.5 h, the mixture was poured into a cold, half saturated solution of $NaHCO_3$. The organic layer was extracted three times with $CH_2Cl_2$. The combined organic fractions were dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (120 g of $SiO_2$, petroleum ether/MTBE = 3:2) to give 2.11 g (5.06 mmol, 96%) of the allylic acetate as a colorless oil. $R_f$ = 0.54 (petroleum ether/MTBE = 1:3); [α] +12.5° (*c* = 1.0, $CHCl_3$); UV ($CH_3CN$): $\lambda_{max}$ (lg $\epsilon$) 194.0 (4.772), 223.5 (4.130), 255.5 (2.688), 261.5 (2.768), 266.0 (2.732), 272.5 (2.660); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.79−1.87 (m, 3 H), 2.09 (s, 3 H), 2.20−2.29 (m, 3 H), 2.36−2.45 (m, 2 H), 2.46 (s, 3 H), 4.05 (t, *J* = 6.4 Hz, 2 H), 5.67 (dtd, *J* = 7.7, 3.0, 0.7 Hz, 1 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 7.81 (d, *J* = 8.3 Hz, 2 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 21.2, 21.7, 26.3, 26.3, 29.3, 32.4, 69.8, 81.7, 116.0, 127.9, 129.9, 133.0, 144.9, 146.5, 170.7. Anal. calcd for $C_{17}H_{21}BrO_5S$ (417.3): C, 48.93; H, 5.07. Found: C, 49.14; H, 5.19.

**Acetic Acid 3-[3-(Toluene-4-sulfonyloxy)-propyl]-cyclopent-2-enyl Ester (10).**[12] Method A: DIBALH reduction of enone **11** to racemic **10**. To a solution of enone **11** (512 mg, 1.74 mmol) in toluene (10 mL) at −45 °C was added slowly a solution of DIBALH in toluene (1.5 M, 2.5 mL, 3.0 mmol). Celite (0.5 g) and a 1:1 mixture of water and methanol (1 mL) was added. It was warmed to room temperature and filtered. The solution was dried over $Na_2SO_4$, and volatile components were removed in vacuo. The crude allylic alcohol as a 0.3 M solution in $CH_2Cl_2$ was acetylated at 0 °C with acetic anhydride (176 mg, 1.72 mmol, 1.0 equiv), triethylamine (176 mg, 1.74 mmol, 1.0 equiv), and DMAP (20.0 mg, 164 $\mu$mol, 0.1 equiv). After being stirred at 0 °C for 1.5 h, the mixture was poured into a cold, half saturated solution of $NaHCO_3$. The organic layer was extracted three times with $CH_2Cl_2$. The combined organic fractions were dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (70 g of $SiO_2$, petroleum ether/MTBE = 3:2) to give 549 mg (1.62 mmol, 93%) of the racemic allylic acetate **10** as a colorless oil. Method B: Dehalogenation of allylic acetate **17**. To a solution of bromide **17** (230 mg, 550 $\mu$mol) in toluene (9 mL) was added azobis(isobutyronitrile) (100 mg, 605 $\mu$mol, 1.1 equiv) and tributyltin hydride (176 mg, 605 $\mu$mol, 1.1 equiv), and the mixture was stirred at 90 °C for 3 h. Removal of the volatile components in vacuo and purification by column chromatography afforded 171 mg (504 $\mu$mol, 92%) of **10** as a colorless oil. $R_f$ = 0.66 (petroleum ether/ethyl acetate = 1:2); [α] +57.5° (*c* = 1.0, $CHCl_3$); UV ($CH_3CN$) $\lambda_{max}$ (lg $\epsilon$) 194.0 (4.740), 224.5 (4.069), 255.5 (2.702), 261.5 (2.758), 266.0 (2.706), 272.5 (2.614); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.75−1.95 (m, 2 H), 2.01 (s, 3 H), 2.05−2.43 (m, 6 H), 2.46 (s, 3 H), 4.04 (d, *J* = 6.4 Hz, 2 H), 5.39 (br. s, 1 H), 5.54−5.65 (br. s, 1 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.79 (d, *J* = 8.1 Hz, 2 H);$^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.3, 21.6, 26.6, 26.9, 30.2, 33.5, 69.8, 80.6, 123.1, 127.8, 129.8, 132.9, 144.8, 150.5, 171.0. $C_{17}H_{22}O_5S$ (338.4).

**(2-Benzo[1,3]dioxol-5-yl-ethyl) Carbaminic Acid *tert*-Butyl Ester (20).** Homopiperonylamine (**19**) (4.02 g, 24.4 mmol) was suspended in water (50 mL) and cooled with an ice bath, and carbonic acid *tert*-butyl ester (6.76 g, 31.0 mmol, 1.3 equiv) and sodium hydroxide (1.94 g, 48.4 mmol, 2.0 equiv) were added. The ice bath was removed, and the mixture was stirred overnight. Then the same volume of ethyl acetate was added and cooled to 0 °C, and the pH was adjusted to 2−3 with 2 N HCl. The organic layer was separated with a 1 M solution of $KHSO_4$ and brine, dried over $Na_2SO_4$, and concentrated in vacuo. Recrystallization from MTBE/petroleum ether yielded colorless crystals of **20** (5.03 g, 19.0 mmol, 78%). Concentration of the mother liquor and column chromatography (70 g of $SiO_2$, petroleum ether/MTBE = 1:1) afforded additionally 1.29 g (4.86 mmol, 20%) of **20** as a colorless solid. $R_f$ = 0.60 (petroleum ether/MTBE = 1:1); mp 60 °C; UV ($CH_3CN$) $\lambda_{max}$ (lg $\epsilon$) 199.5 (4.604), 234.5 (3.600), 286.5 (3.575); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.44 (s, 9 H), 2.71 (t, *J* = 7.0 Hz, 2 H), 3.32 (dt, *J* = 7.0, 5.3 Hz, 2 H), 4.53 (br. s, 1 H), 5.93 (s, 2 H), 6.61 (dd, *J* = 7.8, 1.5 Hz, 1 H), 6.68 (d, *J* = 1.5 Hz, 1 H), 6.75 (d, *J* = 7.8 Hz, 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 28.4, 35.9, 42.0, 79.2, 100.8, 108.3, 109.1, 121.6, 132.7, 146.0, 147.7, 155.8; EI HRMS *m*/*z* 265.1314, $C_{14}H_{19}NO_4$ requires 265.1314. Anal. calcd for $C_{14}H_{19}NO_4$ (265.3): C, 63.38; H, 7.22. Found: C, 63.28; H, 7.33.

**2-(6-Bromo-benzo[1,3]dioxol-5-yl)-ethyl Carbamininic Acid *tert*-Butylester (23).** The Boc-protected amine **20** (494 mg, 1.86 mmol) was suspensed together with silver trifluoroacetate (453 mg, 2.05 mmol, 1.1 equiv) in $CH_2Cl_2$ (20 mL). Bromine (361 mg, 2.26 mmol, 1.2 equiv) was added slowly. After filtration over Celite, the solution was washed with 5% $Na_2SO_3$ solution until decolorization and dried over $Na_2SO_4$. The solvent was removed in vacuo. Column chromatography (50 g of $SiO_2$, petroleum ether/MTBE = 3:1) afforded 626 mg (1.82 mmol, 98%) of the brominated compound. $R_f$ = 0.58 (petroleum ether/MTBE = 1:1); mp 96 °C; UV ($CH_3CN$) $\lambda_{max}$ (lg $\epsilon$) 203.0 (4.579), 238.0 (3.681), 294.0 (3.639); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.44 (s, 9 H), 2.85 (t, *J* = 7.0 Hz, 2 H), 3.33 (dt, *J* = 7.0, 6.0 Hz, 2 H), 4.60 (br. s, 1 H), 5.95 (s, 2 H), 6.71 (s, 1 H), 6.99 (s, 1 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 28.4, 36.2, 40.4, 79.2, 101.6, 110.4, 112.7, 114.5, 131.3, 146.9, 147.3, 155.8. Anal. calcd for $C_{14}H_{18}BrNO_4$ (344.2): C, 48.85; H, 5.27. Found: C, 49.04; H, 5.20.

**2-(6-Brom-benzo[1,3]dioxol-5-yl)-ethylamin (24).**[37] Method A: Bromination of the hydrochloride of homopiperonylamine. Homopiperonylamine hydrochloride (9.12 g, 45.2 mmol) was dissolved in acetic acid (50 mL), and bromine (14.5 g, 90.7 mmol, 2.0 equiv) was added. The solution was stirred for 3 h at room temperature. Then it was washed with 5% $Na_2SO_3$ solution until decolorization. It was cooled with an ice bath and made strongly basic with 20% NaOH solution. The aqueous phase was extracted four times with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo; 10.7 g (44.0 mmol, 97%) of the amine was obtained. Method B: Bromination and deprotection of the Boc-protected amine. The Boc-protected amine **20** (420 mg, 1.58 mmol) was dissolved in $CH_2Cl_2$ (20 mL), and bromine (373 mg, 2.34 mmol, 1.5 equiv) was added. After 2 h the mixture was cooled to 0 °C, and trifluoroacetic acid (1.49 g, 13.1 mmol, 8.3 equiv) was added. The mixture was stirred for 1 h at room temperature and then poured into 2 N HCl and extracted with $CH_2Cl_2$. The aqueous phase was made basic (pH > 10) with 25% $NH_3$ solution and was extracted three times with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo; 374 mg (1.53 mmol, 97%) of the brominated amine was obtained. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.37 (br. s, 2 H), 2.76−2.97 (m, 4 H), 5.95 (s, 2 H), 6.72 (s, 1 H), 7.00 (s, 1 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 40.1, 42.3, 101.6, 110.3, 112.7, 114.6, 132.0, 146.8, 147.3; $C_9H_{10}BrNO_2$ (244.1).

**2-(6-Iodo-benzo[1,3]dioxol-5-yl)-ethylamine (22).**[38] To a solution of **21** (394 mg, 1.01 mmol) in $CH_2Cl_2$ (5.0 mL) was added trifluoroacetic acid (740 mg, 6.49 mmol, 6.4 equiv). After being stirred for 7 h, the solution was poured into water and made strongly basic with $NH_3$ solution. The aqueous phase was extracted four times with $CH_2Cl_2$. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo; 294 mg (1.01 mmol, 100%) of the amine **22** was obtained. This compound was typically carried on without purification. An analytical sample was purified as hydrochloride, which was recrystallized from ($CH_2Cl_2$/MTBE). mp (hydrochloride) 217 °C (decomp.); UV ($CH_3CN$) $\lambda_{max}$ (lg $\epsilon$) 207.0 (4.508), 241.5 (3.831), 295.0 (3.588); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.40 (br. s, 2 H), 2.67−2.95 (m, 4 H), 5.95 (s, 2 H), 6.75 (s, 1 H), 7.24 (s, 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 42.6, 44.5, 88.1, 101.5, 109.7, 118.7, 135.6, 146.9, 148.4. Anal. calcd for $C_9H_{10}INO_2$·HCl (327.6): C, 33.00; H, 3.38. Found: C, 33.21; H, 3.35.

**Acetic Acid 3-{3-[2-(6-Bromo-benzo[1,3]dioxol-5-yl)-ethylamino]-propyl}-cyclo-pent-2-enyl Ester (25b).** To a refluxing solution of **24** (741 mg, 3.04 mmol, 2.0 equiv) and TBAI (804 mg, 2.18 mmol, 1.5

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equiv) in THF (5 mL) was dropped a solution of tosylate **10** (505 mg, 1.49 mmol) in THF (3 mL) with an infusion pump for 8 h. The reaction mixture was poured into MTBE. After the addition of cold 5% NaOH solution, the aqueous layer was extracted four times with MTBE. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. Purification by column chromatography (90 g of $SiO_2$, gradient column: 150 mL of ethyl acetate; 300 mL of ethyl acetate/MeOH = 15:1, 1% $Et_3N$; then ethyl acetate/MeOH = 5:1, 1% $Et_3N$) afforded **25b** as a pale yellow oil (438 mg, 1.07 mmol, 72%). $R_f = 0.54$ (ethyl acetate/MeOH = 5:1, 1% $Et_3N$); mp 42 °C; [α] +48.6° ($c = 1$, $CHCl_3$); UV ($CH_3CN$) $\lambda_{max}$ (lg $\epsilon$) 201.0 nm (4.633), 236.5 (3.677), 294.0 (3.628); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.70 (br. s, 1 H), 1.71 (tt, $J = 7.3$, 7.2 Hz, 2 H), 1.83 (dddd, $J = 14.0$, 8.7, 3.9, 3.2 Hz, 1 H), 2.02 (s, 3 H), 2.12−2.26 (m, 3 H), 2.32 (dddd, $J = 14.0$ Hz, 8.7 Hz, 7.6 Hz, 5.1 Hz, 1 H), 2.41−2.49 (m, 1 H), 2.68 (t, $J = 7.2$ Hz, 2 H), 2.86 (mc, 4 H), 5.47 (m, 1 H), 5.95 (s, 2 H), 6.62−6.66 (m, 1 H), 6.74 (s, 1 H), 6.99 (s, 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.4, 27.8, 29.0, 30.4, 33.5, 36.5, 49.4, 49.6, 80.9, 101.6, 110.2, 112.7, 114.4, 122.5, 132.3, 146.8, 147.3, 152.2, 171.1. Anal. calcd for $C_{19}H_{24}BrNO_4$ (410.3): C, 55.62; H, 5.90. Found: C, 55.31; H, 5.80.

**1-[2-(6-Bromo-benzo[1,3]dioxol-5-yl)-ethyl]-1-aza-spiro[4.4]non-6-ene (26).** To a degassed solution of **25b** (625 mg, 1.52 mmol) in $CH_3CN$ (6 mL) was added tetramethylguanidine (230 mg, 1.99 mmol, 1.3 equiv) and $Pd(PPh_3)_4$ (130 mg, 112 $\mu$mol, 7 mol %). The mixture was stirred at 45 °C for 15 h. It was diluted with MTBE and extracted twice with 1 N HCl. The aqueous phase was washed twice with MTBE and then made basic with 10% NaOH. It was extracted four times with MTBE. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (70 g of $SiO_2$, ethyl acetate) to give 471 mg (1.35 mmol, 88%) of the spirocyclic amine. $R_f = 0.57$ (ethyl acetate/MeOH = 5:1, 1% $Et_3N$); [α] −44.0° ($c = 1$, $CHCl_3$); UV ($CH_3CN$) $\lambda_{max}$ (lg $\epsilon$) 201.0 (4.592), 294.0 (3.639); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.61 (dt, $J = 13.6$, 6.8 Hz, 1 H), 1.74−1.98 (m, 5 H), 2.30 (tdd, $J = 7.1$, 2.2, 2.1 Hz, 2 H), 2.38, 2.56 (m, 2 H), 2.69−2.85 (m, 3 H), 2.88−3.02 (m, 1 H), 5.56 (dt, $J = 5.6$, 2.1 Hz, 1 H), 5.80 (dt, $J = 5.6$, 2.2 Hz, 1 H), 5.93 (s, 2 H), 6.71 (s, 1 H), 6.96 (s, 1 H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 21.3, 29.6, 31.5, 36.4, 38.2, 49.7, 51.2, 101.5, 110.2, 112.5, 114.3, 132.1, 133.1, 134.7, 146.6, 147.1; EI HRMS *m*/*z* 349.0677, $C_{17}H_{20}BrNO_2$ requires 349.0677.

**3,5,6,8,9,14b-Hexahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]-pyrrolo[2,1-*b*][3]-benzazepine (6).**[8] A mixture containing $CH_3CN$ (5 mL), DMF (5 mL), water (1 mL), **26** (179 mg, 511 $\mu$mol), tetra-*n*-butylammonium acetate (310 mg, 1.03 mmol, 2.0 equiv), and palladium catalyst **27** (19.0 mg, 20.0 $\mu$mol, 4 mol %) was stirred for 7 h at 120 °C. The solution was poured into MTBE and washed with diluted NaOH. The organic phase was extracted three times with 1 N HCl. The acidic phase was made basic with 10% NaOH and extracted four times with MTBE. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo. Purification by column chromatography (25 g of $SiO_2$, ethyl acetate) afforded **6** (112 mg, 416 $\mu$mol, 81%) as a colorless oil. $R_f = 0.22$ (ethyl acetate/MeOH = 5:1, 1% $Et_3N$); [α] −200.4° ($c = 1.0$, $CHCl_3$; lit.[8] −230.8°, $c = 1.22$, $CHCl_3$); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.66−1.87 (m, 2 H), 1.91−2.07 (m, 3 H), 2.34 (dd, $J = 14.2$, 6.1 Hz, 1 H), 2.43 (ddd, $J = 9.3$, 9.3, 6.8 Hz, 1 H), 2.58 (dd, $J = 11.7$, 7.3 Hz, 1 H), 2.76 (ddd, $J = 17.8$, 4.9, 2.4 Hz, 1 H), 2.96 (ddd, $J = 12.7$, 11.7, 6.1 Hz, 1 H), 3.11 (ddd, $J = 9.3$, 7.6, 4.9 Hz, 1 H), 3.20 (ddd, $J = 14.2$, 12.7, 7.3 Hz, 1 H), 3.88 (br. s, 1 H), 5.52 (dddd, $J = 5.9$, 2.4, 2.2, 2.2 Hz, 1 H), 5.79 (dddd, $J = 5.9$, 2.7, 2.7, 2.1 Hz, 1 H), 5.88 (d, $J = 1.5$ Hz, 1 H), 5.89 (d, $J = 1.5$ Hz, 1 H), 6.59 (s, 1 H), 6.65 (s, 1 H); $^{13}$C NMR (50.3 MHz, $CDCl_3$) $\delta$ 19.8, 30.4, 34.9, 42.9, 48.9, 53.5, 62.1, 68.3, 100.7, 109.8, 110.7, 128.6, 131.6, 132.0, 133.5, 146.0, 146.3; $C_{17}H_{19}NO_2$ (269.3).

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**Supporting Information Available:** General Experimental Section and complete characterization of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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