Chemistry in the Ambient Field of the Alkaloid Epibatidine, 1

2-(Het)aryl-Substituted 7-Azabicyclo[2.2.1]heptane Systems

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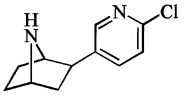
Epibatidine (**1**) is a recently discovered trace alkaloid found in the skin of a Latin-American poisonous frog. Its remarkably high analgetic activity is accompanied by high toxicity. Therefore, in order to tune its biological activity, a convergent and efficient synthetic pathway was sought to synthesize epibatidine derivatives with different (het)aryl substituents. The hydro(het)arylation of the key intermediate 7-azabicycloheptene (**10**) represents such an approach. The synthesis of **10** by a Diels–Alder reaction of an *N*-activated pyrrole (**7**) with ethynyl *p*-tolyl sulfone (**6**) and subsequent steps has been optimized. The crucial last step, the reductive cleavage of the vinyl sulfone **9**, has been replaced by a high-yield fluoride-induced degradation of the β-silylated sulfone **12** to give **10**. A number of structurally different racemic epibatidine analogs (**16b–e**) can be prepared by palladium-catalyzed hydro(het)arylation of **10** with iodo(het)arenes **15b–e** in good yields.

The isolation[1] and complete spectroscopic characterization[2] of the the novel, structurally simple trace alkaloid epibatidine (**1**), which is obtained from the skin of the Latin-American poisonous frog *epipedobates tricolor*, was reported by Daly in 1992. This work has given rise to numerous pharmaceutical investigations and great hopes after the extremely high analgetic activity of this compound in the "hot-plate test" had been discovered. This was especially important as epibatidine seemed to work in a different way to current painkillers, thus binding to hitherto unknown nonopiodic receptors in the brain[3]. From a chemical point of view it is remarkable that, for the first time, an azabicyclo[2.2.1]heptane system has been found in nature and that, to date, only the second time that a 2-chloropyridyl system has been detected as part of a natural product, an antitumor antibiotic[4]. A structural similarity to the natural product nicotine (**2**) is evident. Indeed, up to now epibatidine is the most effective of all known agonists of nicotinergic acetylcholine receptors. A pharmaceutical application of epibatidine in human medicine is not feasible due to its high toxicity, which exceeds that of nicotine.

Scheme 1



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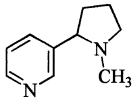

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Variations of the epibatidine structure are feasible in terms of the (het)arene substituent, the ring size of the bicyclic system, and the position and nature of the hetero atom. In this first publication of a series of articles we report a general synthesis of (het)arylated epibatidine analogs.

Results and Discussion

Among the published syntheses of racemic epibatidine[5] that proceed in a convergent manner, the synthesis by Clayton and Regan[6] appeared most interesting. The key step of that synthesis is a hydroarylation of an *N*-protected 7-azabicycloheptene **10** with 2-chloro-5-iodopyridine (**15a**) (Scheme 3). This reaction type should also allow the hydroarylation by other (het)arenes; our own hydroarylation experiments with norbornene[7] gave us confidence to try this synthetic procedure, although due to the presence of a second donor center, there is always the problem of a competitive complexation of the palladium catalyst. The difficult synthetic access to the key compound **10** proved to be a serious problem for the general applicability of the hydroarylation reaction. In particular, the reductive cleavage of the sulfonyl group in the heterogenous phase led to a distinct decrease in yield and low reproducibility in the last step. Therefore, the whole synthesis was improved in such a manner that the synthesis of **10** is now possible in gram quantities without problems.

Synthesis of *N*-Methoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene (10)

The aluminum trichloride mediated reaction of bis(trimethylsilyl)acetylene[8] (**3**) with *p*-toluenesulfonyl chloride gave 2-(trimethylsilyl)ethynyl *p*-tolyl sulfone (**5**) in 97% yield (ref.[9] 80%). The direct [4 + 2] cycloaddition of *N*-(methoxycarbonyl)pyrrole (**7**) with **5** did not succeed, even under high-pressure conditions (13 kbar). Therefore, in order to en-

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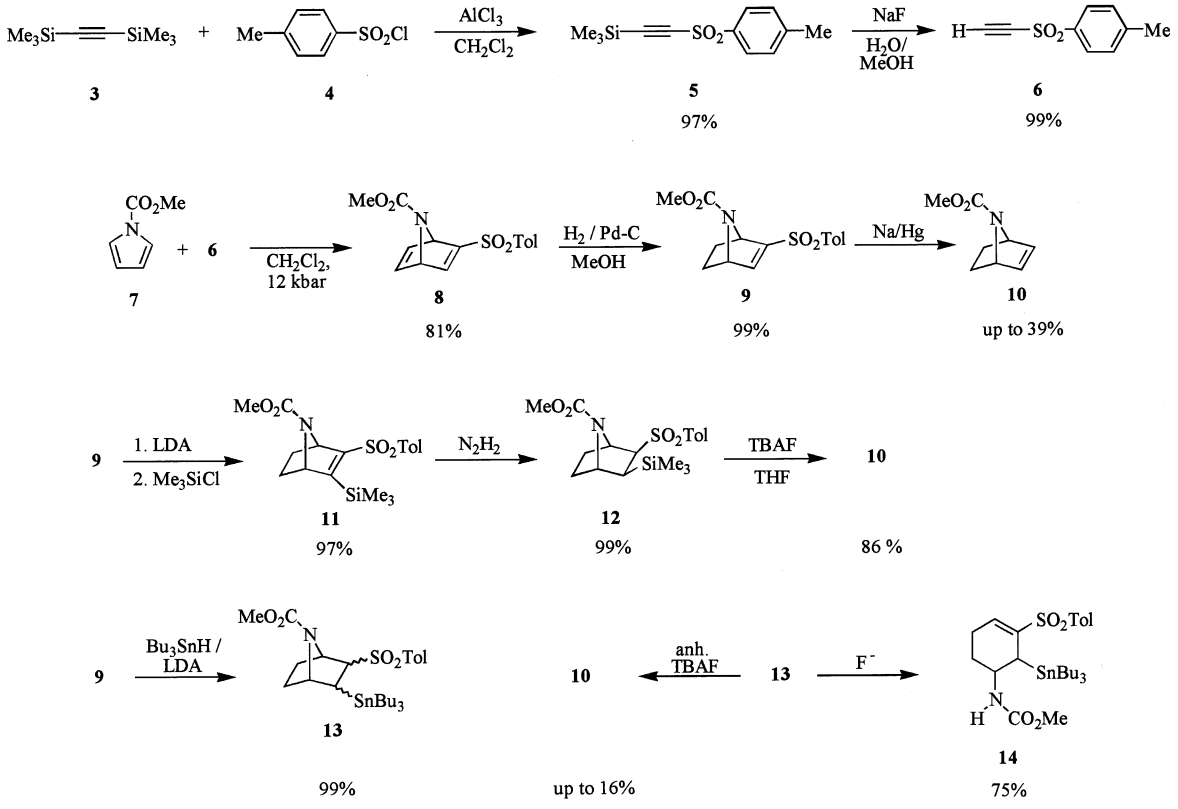
hance the activity of **5** the silyl group had to be split off first. The best desilylation method towards **6** proved to be the reaction with a methanol/water solution of sodium fluoride[10] (99% yield; ref.[9] 83%). The subsequent Diels–Alder reaction with **7** to give the azabicyclic vinyl sulfone[11] **8** is strongly dependent on the reaction conditions. By careful control of the reaction temperature over a small range (85–87 °C, yield 74%) or under high-pressure conditions (12 kbar, yield 81%) the reported yield[6] (36%) could be increased markedly. The subsequent catalytic hydrogenation of the less hindered double bond[12] proceeded almost quantitatively (99%). A number of literature methods are known for the reductive degradation of vinyl sulfones[13]. However, employment of aluminum amalgam[14], potassium/graphite[15], lithium/ethylamine[16] (ring opening of the bicycle), samarium iodide[17], tri-*n*-butyltin hydride[18] or sodium dithionite[19] all proved to be unsuccessful. Only in the heterogenous reaction with sodium amalgam[12] could **10** be obtained in a yield ranging from 20 to 39%.

Therefore, an alternative synthetic approach was required. The β-elimination of a saturated silylated or stannylated sulfone[20] looked promising. The formal hydrosilylation of **9** was achieved in a two-step reaction: the anion in the β-position to the sulfonyl group was formed selectively by reaction of **9** with lithium diisopropylamide, followed by almost quantitative silylation to **11** (yield 97%). The subsequent hydrogenation to **12** proceeded in a more reproducible way (yield 99%) and with complete *endo* selectivity with diimide, generated from dipotassium azodicarboxylate[21], than with a heterogenous catalyst (palladium on charcoal). The use of a Pd/C hydrogenation catalyst, which had not been washed acid-free with triethylamine before use, gave rise to a 2,3-bis-*exo/endo,exo/exo,endo* mixture of **12** in the ratio 2:1:1. It also proved possible to add a tri-*n*-butylstannyl anion to obtain the β-stannylated sulfone **13** (yield 99%) in a Michael-analogous reaction by using a mixture of tri-*n*-butylstannane/lithium diisopropylamide. A number of synthetic methods were tried for the subsequent β-elimination. In the case of the silylated sulfone, cleavage with TBAF (tetra-*n*-butylammonium fluoride) proved to be the best method. For the bis-*exo* isomer **12**, cleavage of the silyl and the sulfonyl group to give **10** was achieved with TBAF trihydrate (yield 86%), whereas the *cis/trans* mixture of **12** could be degraded completely with anhydrous TBAF[22] only. This synthetic methodology is distinctly superior to the reductive cleavage, with a total yield of 83%. In contrast, degradation of the stannylated sulfone **13** with anhydrous TBAF proceeded only in a low yield (up to 16%). Another problem encountered in the synthesis of the pure azabicycloheptene **10** on a preparative scale using the stannyl route was the difficulty in completely separating the tri-*n*-butylstannyl fluoride by column chromatography. The use of inorganic fluorides, like potassium fluoride on silica gel in methanol, led to ring opening of the bicyclic system to give the substituted cyclohexene system **14**. In conclusion, the synthetic pathway using the silylated sulfone is well suited to the generation of adequate amounts of **10** for a subsequent chemical study.

Scheme 2

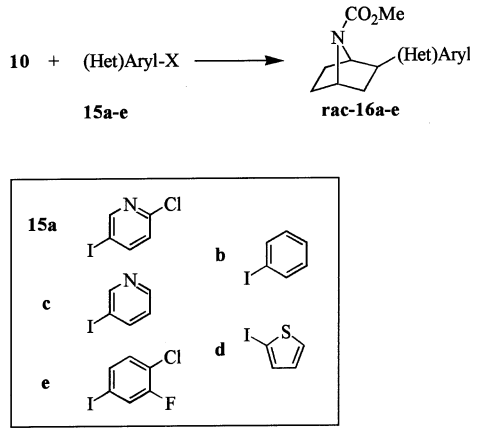


Palladium-Catalyzed Hydroarylation of *N*-Methoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene (10)

The palladium-catalyzed reductive hydroarylation reaction opens up a valuable way for the C−C coupling of (het) aromatic compounds with bicyclic alkenes, in cases where a Heck reaction is not feasible, as the rigid bicyclic system cannot rotate around the newly formed C−C bond, to form a conformation required for the subsequent *syn* elimination of the hydridopalladium species.

All hydroarylation reactions were performed in dimethylformamide with 10 mol-% of bis(triphenylphosphane)palladium diacetate as catalyst and piperidinium formate as a reducing agent.

Scheme 3



The reaction temperature was optimized in the case of the epibatidine precursor **16a**. This optimization is important as reduction of the leaving group of the aromatic system[7], which always occurs in parallel with the hydroarylation reaction, shows a different temperature dependence. In this way an increase in the yield of **16a** from 35%[6] to 77% was achieved mainly by lowering the reaction temperature from 75 to 50°C. Under identical reaction conditions iodobenzene (**15b**), 3-iodopyridine (**15c**), 2-iodothiophene (**15d**) and 4-chloro-3-fluoro-1-iodobenzene (**15e**) were allowed to react with **10**. In all cases C−C coupling proceded exclusively with formation of the *exo*-aryl-substituted azabicyclic systems **16a**−**e**. The isolated yields varied between 44% in the case of the thienyl compound **16d** and 85% in the case of the phenyl-substituted system **16b**. The amino group, deactivated by the methoxycarbonyl group, did not strongly inhibit the reaction rate or influence the yield. These new alkaloid analogs are currently being tested for their biological effects.

We gratefully acknowledge the support of this work by the *Bayer AG*, Leverkusen, the *Fonds der Chemischen Industrie*, the *Degussa AG*, Frankfurt, and the *Chemetall GmbH*, Langelsheim. We are indebted to Dr. *G. Remberg* (Universität Göttingen) for MS measurements.

Experimental Section

All reactions were carried out under dry nitrogen using Schlenk techniques. All solvents were carefully dried by standard procedures. Amines were dried with calcium hydride. Other reagents are commercially available and were used as received. − NMR: Bruker AMX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) with $CDCl_3$ as solvent and TMS as internal standard. − Bis(trimethylsilyl)acetylene[8] (BTMSA) (**3**), 2-(trimethylsilyl)ethynyl *p*-tolyl sulfone[9] (**5**), *N*-(methoxycarbonyl)pyrrole[23] (**7**), and 2-chloro-5-iodopyridine[24] (**15a**) were synthesized as described in the literature.

Ethynyl p-Tolyl Sulfone (**6**): A solution of 3.72 g (88.6 mmol) of sodium fluoride in degassed water (60 ml) was added dropwise to a solution of 14.9 g (59.7 mmol) of **5** in degassed methanol (120 ml) at 10°C. After complete addition, the resulting suspension was stirred for another 15 min. Water was added and the mixture was extracted with ether (3 × 100 ml). The combined ether layers were treated with sodium hydrogen carbonate, washed with brine, and then dried with anhydrous $MgSO_4$. After concentration to dryness, a white product was obtained. In most cases purification by flash column chromatography was unnecessary. Yield: 10.5 g (99%) **6**, m.p. 74°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3), 3.45 (s, 1 H, $H_{alkynyl}$), 7.39 (d, J = 8.3 Hz, 2 H, 3,5-H_{aryl}), 7.89 (d, J = 8.3 Hz, 2 H, 2,6-H_{aryl}). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8 (+, Ar-CH_3), 80.4 (+, $HC_{alkynyl}$), 81.0 ($C_{quat.}$, CSO_2), 127.7 (+, C_{aryl}-2,6), 130.1 (+, C_{aryl}-3,5), 137.8 ($C_{quat.}$, C_{aryl}-4), 146.0 ($C_{quat.}$, C_{aryl}-1). − GC-MS (70eV); *m/z* (%): 180 (42) [M^+], 139 (48), 115 (100).

N-(Methoxycarbonyl)-2-(p-tolylsulfonyl)-7-azabicyclo[2.2.1]hepta-2,5-diene (**8**): This compound was obtained by cycloaddition of **6** to **7** (4.0 equiv. used) during 24 h keeping the reaction temperature between 85 and 87°C. After concentration of the excess diene under mild conditions, column chromatography on silica gel with petroleum ether/AcOEt (2:1) (R_f = 0.20) as the eluent afforded the desired Diels−Alder product on a 10-g scale (yield: 74%): white solid, m.p. 95°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H, Ar-CH_3), 3.42 (br. s, 3 H, OCH_3), 5.21 (s, 1 H, 4-H), 5.42 (s, 1 H, 1-H), 6.85−7.05 (m, 2 H, 5,6-H), 7.35 (d, J = 8.0 Hz, 2 H, 3′,5′-H_{aryl}), 7.59 (br. s, 1 H, 3-H), 7.74 (d, J = 8.0 Hz, 2 H, 2′,6′-H_{aryl}).

7-(Methoxycarbonyl)-2-(p-tolylsulfonyl)-7-azabicyclo[2.2.1]hept-2-ene (**9**): This compound was prepared from the corresponding diene in almost quantitative yield (99%) by hydrogenation of a solution of the bicyclic diene **8** in ethyl acetate or methanol, with the calculated volume of hydrogen (catalyst: 10% palladium on charcoal). All data were in accordance with the literature. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (m, 2 H), 2.00 (m, 2 H), 2.44 (s, 3 H, Ar-CH_3), 3.45 (br. s, 3 H, OCH_3), 4.82 (d, J = 3.5 Hz, 1 H, 1-H), 4.88 (m, 1 H, 4-H), 7.02 (d, 1 H, 3-$H_{olefin.}$), 7.35 (d, J = 8.3 Hz, 2 H, 3′,5′-H_{aryl}), 7.78 (d, J = 8.3 Hz, 2 H, 2′,6′-H_{aryl}).

N-(Methoxycarbonyl)-3-(p-tolylsulfonyl)-2-trimethylsilyl-7-azabicyclo[2.2.1]hept-2-ene (**11**): To an ice-cold solution of 1.19 ml (8.40 mmol) of diisopropylamine in anhydrous THF (28 ml) was added dropwise 5.25 ml (8.40 mmol) of 1.6 M *n*-butyllithium in hexane and the solution was stirred for an additional 15 min at 0°C. The resulting solution of lithium diisopropylamide was then added at −78°C to 2.46 g (8.00 mmol) of the vinyl sulfone **9**, dissolved in 150 ml of anhydrous THF, during 90 min by syringe. The mixture was stirred for 2 h and the anion formed was quenched at −78°C with 1.11 ml (8.80 mmol) of freshly distilled chlorotrimethylsilane. The reaction mixture was allowed to warm up to room temperature overnight and a saturated solution of ammonium chloride was added. After addition of ether (200 ml) and separation, the aqueous layer was extracted twice with ether. The organic extract was treated with sodium hydrogen carbonate, washed twice with brine and was then dried with anhydrous $MgSO_4$. The solid product obtained after evaporation of the sol-

vent and finally drying in vacuo (2.95 g, 97%) was slightly yellow (100% pure by GC; mp. 83°C). An analytical sample was obtained by further purification by short column chromatography with petroleum ether/ethyl acetate (2:1; R_f = 0.53). White solid, m.p. 86°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.35 (s, 9 H, $SiMe_3$), 1.07 and 1.28 (ddd, *J* = 11.7, 8.7, 3.0 Hz, 2 H, 5,6-H_{endo}), 1.83−1.92 (m, 1 H), 1.93−2.02 (m, 1 H), 2.44 (s, 3 H, Ar-CH_3), 3.37 (br. s, 3 H, CO_2CH_3), 4.71 (d, *J* = 3.8 Hz, 1 H, 1-H), 4.92 (d, *J* = 3.8 Hz, 1 H, 4-H), 7.34 (d, *J* = 8.1 Hz, 2 H, 3′,5′-H_{aryl}), 7.76 (d, *J* = 8.1 Hz, 2 H, 2′,6′-H_{aryl}). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = −0.5 (+, $SiMe_3$), 21.6 (+, CH_3), 24.0 (−), 52.5 (+, OCH_3), 62.3 (+), 66.5 (+), 127.8 (+, C_{aryl}-2′,6′), 129.8 (+, C_{aryl}-3′,5′), 137.1 ($C_{quat.}$, C_{aryl}-4′), 144.5 ($C_{quat.}$, C_{aryl}-1′), 153.3 ($C_{quat.}$), 155.7 ($C_{quat.}$, C=O), 160.3 ($C_{quat.}$). − GC-MS (70eV); *m/z* (%): 351 (1) [M^+ − C_2H_4], 336 (100) [M^+ − C_2H_4 − CH_3], 304 (10). − $C_{18}H_{25}NO_4SSi$ (379.55): calcd. C 56.96, H 6.64, N 3.69, S 8.45; found C 56.89, H 6.65, N 3.38, S 8.48.

N-(Methoxycarbonyl)-3-exo-(p-tolylsulfonyl)-2-exo-trimethylsilyl-7-azabicyclo[2.2.1]heptane (**12**) *by Diimide Reduction:* 3.55 g (18.3 mmol) of dipotassium azodicarboxylate, freshly prepared by saponification of azodicarboxamide with 40% aqueous potassium hydroxide,[20] was added to a stirred solution of 2.32 g (6.10 mmol) of the silylated bicyclic vinyl sulfone **11** in anhydrous methanol (60 ml) at 0°C. The reduction was initiated by adding sufficient acetic acid (50% in water) to neutralize the solution (pH = 6−7). The ice bath was removed and the suspension stirred at room temperature overnight. After 12 h, the bright yellow color of the azodicarboxylic acid salt had disappeared. Water was added and the mixture extracted three times with ether (150 ml). GLC indicated complete conversion (100%). The combined ether layers were washed with brine (2 × 10 ml) and dried (anhydrous $MgSO_4$). The solvent was evaporated under reduced pressure to yield the desired sulfone as a pale yellow solid, 2.30 g (99%). An analytical sample was purified by short column chromatography with petroleum ether/ethyl acetate (3:1) (R_f = 0.35). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.30 (s, 9 H, $SiMe_3$), 1.20 (t, *J* = 7.0 Hz, 1 H, 2-H_{endo}), 1.55−1.90 (m, 4 H), 2.45 (s, 3 H, Ar-CH_3), 2.65−2.78 (m, 1 H), 3.62 (s, 3 H, CO_2CH_3), 3.74−3.91 (m, 1 H, 1-H), 4.31−4.43 (m, 1 H, 4-H), 7.36 (d, *J* = 8.3 Hz, 2 H, 3′,5′-H_{aryl}), 7.73 (d, *J* = 8.3 Hz, 2 H, 2′,6′-H_{aryl}). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.5 (+, $SiMe_3$), 13.8 (+), 14.2 (+), 21.6 (+, CH_3), 23.7 (−), 27.3 (−), 52.6 (+, OCH_3), 59.0 (+), 62.0 (+), 127.8 (+, C_{aryl}-2′,6′), 130.1 (+, C_{aryl}-3′,5′), 137.1 ($C_{quat.}$, C_{aryl}-4′), 144.7 ($C_{quat.}$, C_{aryl}-1′), 155.2 ($C_{quat.}$, C=O). − GC-MS (70eV); *m/z* (%): 366 (30) [M^+ − CH_3], 226 (100) [M^+ − SO_2Ar]. − $C_{18}H_{27}NO_4SSi$ (381.56): calcd. C 56.66, H 7.13, N 3.67, S 8.40; found C 56.26, H 6.93, N 3.51, S 8.49.

N-(Methoxycarbonyl)-7-azabicyclo[2.2.1]hept-2-ene (**10**) *by Desilylation/Detosylation of* **12**: The fluoride-induced degradation of the silyl compound **12** to the bicyclic alkene **10** was performed with 5−7 equiv. of tetra-*n*-butylammonium fluoride trihydrate in anhydrous THF at room temperature during 16 h. GLC indicated complete conversion without the formation of any byproducts. After the usual work up with water and extraction with ether/pentane, the solvents were removed from the resulting alkene, which was then purified by rapid filtration through a short column (basic alumina, activity 1) with ether/pentane (1:1) [R_f = 0.53 (SiO_2; ether/pentane, 1:1)]. Yield: 237 mg (86%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (dd, *J* = 10.9, 3.4 Hz, 2 H, 5,6-H_{endo}), 1.77−1.90 (m, 2 H, 5,6-H_{exo}), 3.62 (s, 3 H, OCH_3), 4.72 (s, 2 H, 1,4-H), 6.22 (s, 2 H, 2,3-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9 (−, C-5,6), 52.4 (+, OCH_3), 59.5 (+, C-1,4), 134.7 (+, C-2,3), 154.9 ($C_{quat.}$, C=O). − MS (CI, CH_4); *m/z* (%): 154 (100) [M^+ + 1].

N-(Methoxycarbonyl)-3-(p-tolylsulfonyl)-2-exo-tributylstannyl-7-azabicyclo[2.2.1]heptane (**13**): To a solution of lithium diisopropylamide (4.15 mmol in 15 ml of anhydrous THF) was added dropwise 1.10 ml (4.15 mmol) of tributyltin hydride at 0°C. After complete addition, the mixture was stirred at 0°C for another 15 min and then cooled to −78°C. A solution of 1.16 g (3.77 mmol) of **9** in anhydrous THF (5 ml) was added by syringe. The mixture was allowed to warm up to room temperature overnight. 20 ml of water was added and the aqueous layer was extracted with ether (3 × 30 ml). The combined ether layers were washed with brine (2 × 10 ml), dried ($MgSO_4$), and the solvent evaporated under reduced pressure to yield crude **13** as a brown oil, 2.24 g (99%). As the product is unstable to column chromatography it was used without further purification [R_f = 0.42 (SiO_2; petroleum ether/AcOEt, 2:1)]. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70−1.10 {m, 15 H, $Sn(CH_2[CH_2]_2CH_3)_3$ }, 1.18−1.95 {m, 18 H, $Sn(CH_2[CH_2]_2CH_3)_3$ and 2,3,5,6-H}, 2.41 (s, 3 H, Ar-CH_3), 3.60 (s, 3 H, CO_2CH_3), 4.25−4.52 (m, 2 H, 1,4-H), 7.36 (d, *J* = 8.0 Hz, 2 H, 3′,5′-H_{aryl}), 7.70−7.80 (m, 2 H, 2′,6′-H_{aryl}). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.8 (−, $SnCH_2CH_2$), 13.5−13.6 (+, C-2,3 and $Sn[CH_2]_3CH_3$), 21.4 (+, CH_3), 24.4 and 27.3 (−, $Sn[CH_2]_2CH_2CH_3$ and C-5,6), 29.0 (−), 30.5 (−, $SnCH_2CH_2$), 52.5 (+, OCH_3), 57.0 (+), 58.0 (+), 127.9 (+, C_{aryl}-2′,6′), 130.0 (+, C_{aryl}-3′,5′), 137.0 ($C_{quat.}$, C_{aryl}-4′), 144.7 ($C_{quat.}$, C_{aryl}-1′), 155.3 ($C_{quat.}$, C=O). − MS (DIP, 70eV); *m/z* (%): 542 (100) [M^+ + 1 − C_4H_9].

The destannylation was performed with 10 equiv. of dried TBAF[22]. Yield: 16% of **10**. Reaction of **13** with potassium fluoride on silica gel in anhydrous methanol led, under ring opening, to 5-(methoxycarbonylamino)-1-(*p*-tolylsulfonyl)-6-tri-*n*-butyltincyclohex-1-ene (**14**) (yield 75%) [R_f = 0.48 (SiO_2, petroleum ether/AcOEt, 3:1)]. The structure of **14** was confirmed by H/D exchange at the carbamate, NOE and 2D-NMR experiments, including HMBC and HMQC techniques. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 {t, *J* = 7.3 Hz, 9 H, $Sn[(CH_2)_3CH_3]_3$}, 0.95−1.10 {m, 6 H, $Sn[CH_2(CH_2)_2CH_3]_3$}, 1.28−1.39 {m, 7 H, $Sn[(CH_2)_2CH_2CH_3]_3$ and 4-$H_{ax.}$}, 1.86 (m, 1 H, 4-$H_{eq.}$), 2.41 (s, 3 H, Ar-CH_3), 2.45 (m, 2 H, 3-H), 2.64 (m, 1 H, 6-H), 3.60 (s, 3 H, OCH_3), 3.81 (m, 1 H, NC*H*), 4.59 (m, 1 H, NH), 6.63 (m, 1 H, 1-$H_{olefin.}$), 7.30 (d, *J* = 8.1 Hz, 2 H, 3′,5′-H_{aryl}), 7.68 (d, *J* = 8.1 Hz, 2 H, 2′,6′-H_{aryl}). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 [−, $^1J(^{119}Sn, CH_2)$ = 315 Hz, $SnCH_2CH_2$], 13.7 (+, $Sn[CH_2]_3CH_3$), 21.6 (+, CH_3), 25.4 (−, C-3), 27.4 (−, $Sn[CH_2]_2CH_2CH_3$), 28.9 (−, $SnCH_2CH_2$), 29.2 (−, C-4), 32.6 [+, $^1J(^{119}Sn, CH)$ = 240 Hz, C-6], 50.7 (+, NHCH), 52.0 (+, OCH_3), 127.6 (+, C_{aryl}-2′,6′), 129.8 (+, C_{aryl}-3′,5′), 131.3 (+, $SO_2C=CH$), 136.6 ($C_{quat.}$, C_{aryl}-1′), 143.7 ($C_{quat.}$, $SnCCSO_2$), 144.0 ($C_{quat.}$, C_{aryl}-4′), 155.9 ($C_{quat.}$, C=O). − MS (DIP, 70eV); *m/z* (%): 599 (3) [M^+ + 1], 542 (100) [M^+ + 1 − C_4H_9].

Heck-Type Hydroarylation Reactions to Racemic Epibatidine Analogs. − General Procedure: 0.05 equiv. of bis(triphenylphosphane)palladium(II) acetate was dissolved in 1.5 ml of anhydrous dimethylformamide and 1.5 equiv. of the alkene, 1.0 equiv. of the aryl compound, and 3.5 equiv. of piperidine were added. Finally, 3.0 equiv. of formic acid was added rapidly in one portion. After stirring until conversion was complete (usually 16 h), the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted three times with ethyl acetate and then the combined organic layers were washed with brine. After drying with anhydrous $MgSO_4$ and evaporation of the volatile components, the crude products were purified by flash column chromatography (SiO_2, 40−63 μm; Macherey-Nagel, Düren, Germany).

2-(6′-Chloro-3′-pyridyl)-N-methoxycarbonyl-7-azabicyclo[2.2.1]heptane (**16a**): Colorless oil, 800 mg (77%) [R_f = 0.29 (SiO_2;

petroleum ether/AcOEt, 2:1)]. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48–1.66 (m, 2 H), 1.75–1.84 (m, 3 H), 1.99 (dd, *J* = 12.7, 9.1 Hz, 1 H, 3-H_{endo}), 2.87 (dd, *J* = 9.1, 4.6 Hz, 1 H, 2-H_{endo}), 3.64 (s, 3 H, CO_2CH_3), 4.18 (br. s, 1 H, 1-H), 4.42 (br. s, 1 H, 4-H), 7.22 (d, *J* = 8.4 Hz, 1 H, 5′-$H_{pyridyl}$), 7.58 (dd, *J* = 8.4, 2.3 Hz, 1 H, 4′-$H_{pyridyl}$), 8.20 (d, *J* = 2.3 Hz, 1 H, 2′-$H_{pyridyl}$). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7 (–, C-5 or C-6), 29.6 (–, C-5 or C-6), 40.2 (–, C-3), 44.7 (+, C-2), 52.4 (+, OCH_3), 56.1 (+, C-4), 62.0 (+, C-1), 124.1 (+, $C_{pyridyl}$-5′), 137.1 (+, $C_{pyridyl}$-4′), 139.8 ($C_{quat.}$, $C_{pyridyl}$-3′), 148.6 (+, $C_{pyridyl}$-2′), 149.3 ($C_{quat.}$, $C_{pyridyl}$-6′), 156.0 (C=O). – MS (70eV); *m/z* (%): 266 (28) [M^+], 237 (7) [M – C_2H_5], 192 (8), 140 (28) [Cl–C_5NH_3–CH=CH_2^+], 127 (100). – HRMS: $C_{13}H_{15}ClN_2O_2$: calcd. 266.0822; found 266.0822. – $C_{13}H_{15}ClN_2O_2$ (266.72): calcd. C 58.54, H 5.67, Cl 13.29, N 10.50; found C 58.08, H 5.60, Cl 13.15, N 10.37.

N-Methoxycarbonyl-2-phenyl-7-azabicyclo[2.2.1]heptane (**16b**): Colorless oil, 786 mg (85%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 7.1 Hz, 1 H), 1.50–1.65 (m, 1 H), 1.70–2.05 (m, 4 H), 2.89 (dd, *J* = 8.2, 5.7 Hz, 1 H, 2-H_{endo}), 3.64 (s, 3 H, CO_2CH_3), 4.26 (br. s, 1 H, 1-H), 4.43 (br. s, 1 H, 4-H), 7.15–7.30 (m, 5 H, H_{aryl}) . – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.8 (–, C-5 or C-6), 29.6 (–, C-5 or C-6), 40.0 (–, C-3), 48.3 (+, C-2), 52.3 (+, OCH_3), 56.1 (+, C-4), 62.2 (+, C-1), 126.2 (+, C_{aryl}-4′), 127.0 (+, C_{aryl}-2′,6′), 128.4 (+, C_{aryl}-3′,5′), 145.5 ($C_{quat.}$, C_{aryl}-1′), 156.0 (C=O). – MS (70eV); *m/z* (%): 231 (24) [M^+], 127 (100). – HRMS: $C_{14}H_{17}NO_2$: calcd. 231.1259; found 231.1259. – $C_{14}H_{17}NO_2$ (231.29): calcd. C 72.70, H 7.41, N 6.06; found C 72.09, H 7.42, N 5.98.

N-Methoxycarbonyl-2-(3′-pyridyl)-7-azabicyclo[2.2.1]heptane (**16c**): Colorless oil, 743 mg (80%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48–2.10 (m, 6 H), 2.92 (dd, *J* = 9.1, 4.2 Hz, 1 H, 2-H_{endo}), 3.67 (s, 3 H, CO_2CH_3), 4.25 (br. s, 1 H, 1-H), 4.46 (br. s, 1 H, 4-H), 7.40–7.80 (m, 4 H, H_{aryl}). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.6 (–, C-5 or C-6), 29.5 (–, C-5 or C-6), 40.3 (–, C-3), 45.5 (+, C-2), 52.2 (+, OCH_3), 56.0 (+, C-4), 61.9 (+, C-1), 123.3 (+, $C_{pyridyl}$-5′), 133.9 (+, $C_{pyridyl}$-4′), 140.6 ($C_{quat.}$, $C_{pyridyl}$-3′), 147.6 (+, $C_{pyridyl}$-6′), 148.8 (+, $C_{pyridyl}$-2′), 155.8 (C=O). – MS (70eV); *m/z* (%): 232 (19) [M^+], 127 (100). – HRMS: $C_{13}H_{16}N_2O_2$: calcd. 232.1212; found 232.1212. – $C_{13}H_{16}N_2O_2$ (232.27): calcd. C 67.22, H 6.94, N 12.06; found C 66.73, H 6.84, N 11.88.

N-Methoxycarbonyl-2-(2′-thienyl)-7-azabicyclo[2.2.1]heptane (**16d**): Colorless oil, 209 mg (44%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32–2.05 (m, 6 H), 3.19 (dd, *J* = 7.9, 5.5 Hz, 1 H, 2-H_{endo}), 3.66 (s, 3 H, CO_2CH_3), 4.25 (br. s, 1 H, 1-H), 4.41 (br. s, 1 H, 4-H), 6.82 (d, *J* = 3.2 Hz, 1 H, 3′-$H_{thienyl}$), 6.88 (dd, *J* = 5.1, 3.2 Hz, 1 H, 4′-$H_{thienyl}$), 7.11 (d, *J* = 5.1 Hz, 1 H, 5′-$H_{thienyl}$). – MS (70eV); *m/z* (%): 237 (26) [M^+], 162 (7), 139 (9), 127 (100). – HRMS: $C_{12}H_{15}NO_2S$: calcd. 237.0823; found 237.0823. – $C_{12}H_{15}NO_2S$ (221.32): calcd. C 65.12, H 6.83, N 6.33; found C 64.92, H 6.85, N 6.23.

2-(4′-Chloro-3′-fluorophenyl)-N-methoxycarbonyl-7-azabicyclo[2.2.1]heptane (**16e**): Colorless oil, 345 mg (61%). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–2.05 (m, 6 H), 2.85 (dd, *J* = 8.2, 5.7 Hz, 1 H, 2-H_{endo}), 3.67 (s, 3 H, CO_2CH_3), 4.22 (br. s, 1 H, 1-H), 4.42 (br. s, 1 H, 4-H), 6.96 (d, *J* = 8.3 Hz, 1 H, H_{aryl}), 7.06 (m, 1 H, H_{aryl}), 7.27 (m, 1 H, H_{aryl}). – HRMS: $C_{14}H_{15}ClFNO_2$: calcd. 283.0776; found 283.0776. – $C_{14}H_{15}ClFNO_2$ (282.79): calcd. C 59.46, H 5.35, N 4.95; found C 58.92, H 5.29, N 4.88.

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