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SYNTHESIS OF BENZOBICYCLO[2.2.1]HEPTYLIMIDAZOLES AS CONFORMATIONALLY CONSTRAINED ADRENERGIC RECEPTOR ANTAGONISTS

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Abstract – A facile method for the preparation of conformationally rigid analogues of the adrenergic α-2 receptor antagonist atipamezole and the adrenergic α-2 receptor agonist medetomidine has been developed. The efficient benzyne [4+2] cycloaddition reaction was used to give the core 7-acetylbenzonorbornadiene structure, which was subsequently elaborated to the corresponding imidazole-based *syn* and *anti* isomers by means of the classical Bredereck's method.

INTRODUCTION

Atipamezole (**1**, 4-(2,3-dihydro-2-ethyl-1*H*-inden-2-yl)-1*H*-imidazole) is a potent and selective α-2 adrenergic receptor antagonist.[1] It is currently used for reversing the sedation and other effects produced by the veterinary sedative medetomidine (**2**, 4-[1-(2,3-dimethylphenyl)ethyl]-1*H*-imidazole hydrochloride) that is, in turn, a highly potent and selective adrenergic α-2 receptor agonist (Figure 1).[2] There are few reports in the literature that describe the synthetic procedures for preparing conformationally restricted analogues of medetomidine focusing on the preparation of naphthyl and tetralin and 3,4-dihydronaphthalene analogues of medetomidine.[3,4] We studied the synthesis of even more

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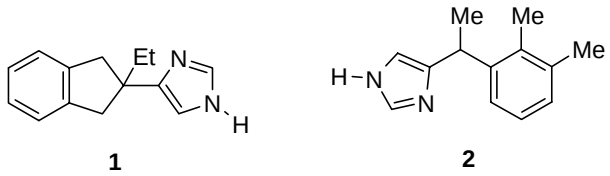
rigid analogues of atipamezole and medetomidine. We now describe a concise synthesis of *syn*-**3** and *anti*-**4** isomers of conformationally constrained imidazolyl-substituted benzobicyclo[2.2.1]heptane.

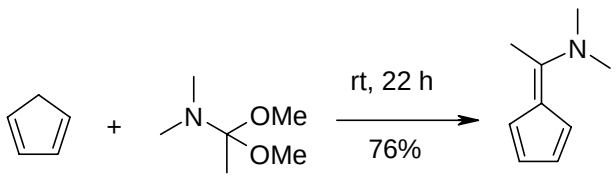


1 **2**

Figure 1. Chemical structures of atipamezole (**1**) and medetomidine (**2**).

RESULTS AND DISCUSSION

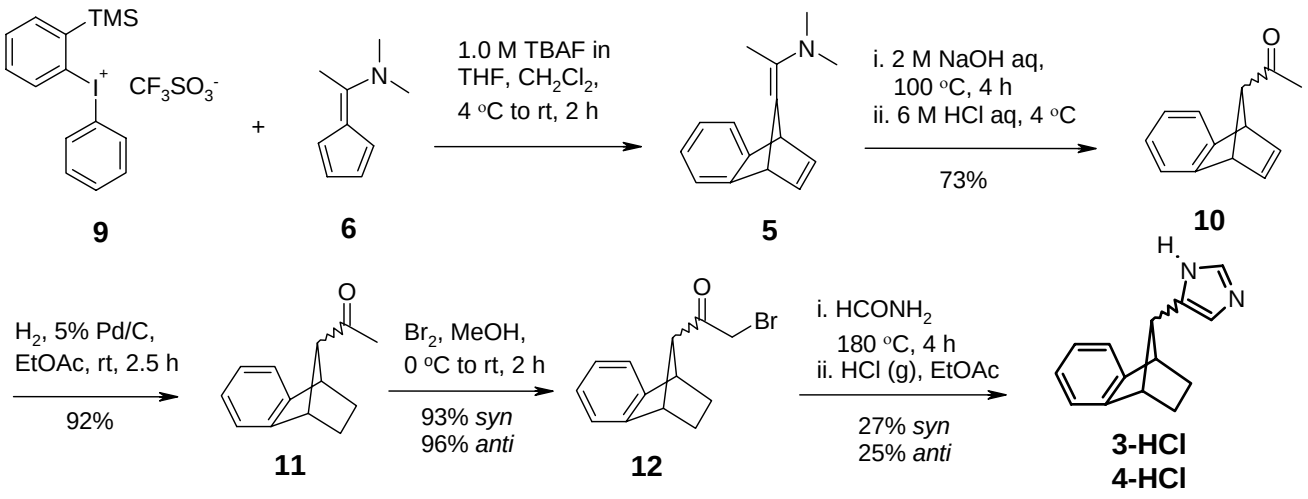
The bridged enamino benzobicyclo[2.2.1]heptene cycloadduct (**5**) was synthesized as a key intermediate by a straightforward benzyne-Diels–Alder reaction. The *in situ* generated benzyne acted as a dienophile and an enamino-6-dimethylamino-6-methylfulvene (**6**) as a diene in the [4+2] cycloaddition reaction. First, fulvene (**6**) was prepared by allowing cyclopentadiene (**7**) to react with *N*,*N*-dimethylacetamide dimethyl acetal (**8**) (Scheme 1).[5,6]



7 **8** **6**

Scheme 1.

Second, the Diels–Alder reaction between the enaminofulvene (**6**) and benzyne, generated *in situ* from (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflate[7–9] (**9**) in the presence of tetra-*n*-butylammonium fluoride in dichloromethane, gave the bridged enamine cycloadduct (**5**) (Scheme 2). The recently reported hypervalent iodine triflate[7] (**9**) proved to be a superb and highly efficient benzyne precursor in the Diels–Alder reaction in comparison with the other benzyne precursors studied in the early phase of this investigation. For example, the enaminofulvene (**6**) failed to give the desired cycloadduct when dienophilic benzyne was generated from benzenediazonium-2-carboxylate and 2-bromofluorotoluene in the presence of isoamyl nitrite and methylmagnesium bromide, respectively.



Scheme 2.

The bicyclic enamine cycloadduct (**5**) was subsequently hydrolysed by means of aqueous sodium hydroxide to give a moderate yield of 7-acetylbenzonorbornadiene (**10**) as a 55:45 *syn/anti* mixture. The isomers were chromatographically (SiO_2) separable but were carried as a mixture to the next step. An isomeric mixture of 7-acetylbenzonorbornadienes (**10**) was catalytically (5% Pd/C) hydrogenated in ethyl acetate to give benzonorbornene (**11**) with a 55:45 *syn/anti* ratio in a good yield of 92%. The isomers of 7-acetylbenzobicyclo[2.2.1]heptane (**11**) were chromatographically (SiO_2) separable. The structural characterization of the *syn* and *anti* isomers of **11** was carried out by means of NOE experiments (NOESY). A strong NOE was observed between the protons *H*1-a and *H*3 in the *syn* isomer (**11a**). No such effect was observed in the *anti* isomer (**11b**) (Figure 2). A mild regioselective bromination of isomers (**11a**) and (**11b**) with bromine in methanol afforded the 7-bromoacetylbenzonorbornanes (**12a**) and (**12b**) in a good yield of 93 and 96%, respectively.[10] No isomerisation was found to take place during the regioselective bromination.

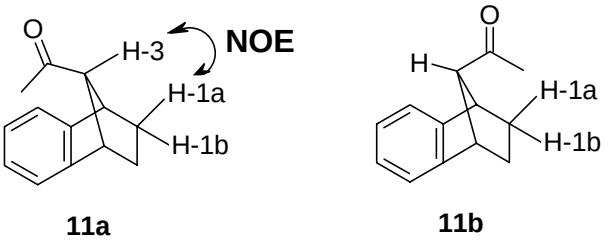


Figure 2. NOE was observed in *syn*-**11a** but not in *anti*-**11b**.

Finally, the combined isomeric mixture of bromobenzonorbornanes (**12a**) and (**12b**) was cyclised to imidazoles (**3**) and (**4**) in formamide at 180 °C by means of Bredereck's method (Scheme 2).[11] The

Bredereck reaction was carried out using the mixture of α-bromo ketones, because it was observed that isomerisation takes place during the cyclisation reaction. The *syn* and *anti* 7-imidazolylbenzonorbornanes (**3**) and (**4**) were isolated as hydrochlorides and recrystallized in good yields from mixtures of ethyl acetate and isopropanol or acetonitrile and isopropanol, respectively. A strong NOE was observed between the protons *H*-1a and *H*-3 in the *syn* isomer (**3**). No such effect was observed in the *anti* isomer (**4**).

In conclusion, a facile method for the preparation of conformationally rigid analogues of atipamezole and medetomidine has been developed. The efficient benzyne [4+2] cycloaddition reaction was used to give the core 7-acetylbenzonorbornadiene structure, which was subsequently elaborated to the corresponding imidazole-based *syn* and *anti* isomers by means of the classical Bredereck's method.

EXPERIMENTAL

General Procedures. Unless otherwise stated, reactions were carried out in oven-dried glassware under a positive atmosphere of argon or nitrogen. Reagents were transferred with plastic syringes and oven-dried or disposable needles. Dichloromethane was continuously distilled from calcium hydride. All reagents were purchased from Aldrich Chemical Company and Fluka Chemie Ag. All chromatography solvents were obtained commercially and used without further purification. The R_f values refer to the TLC developed using 0.25 mm Merck silica gel F-254 aluminum foil-supported plates visualised with either ethanolic phosphomolybdic acid (5%), Pauly's reagent[12] specific for unsubstituted imidazole ring systems or ultraviolet lamp. Yields are for unoptimised procedures and refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise noted. All ^{1}H NMR spectra (300 MHz) were obtained in CD_3OD, $CDCl_3$, DMSO-d_6 or D_2O at ambient temperature on a Varian Mercury 300 instrument. Chemical shifts (δ) are reported in parts per million relative to the internal reference tetramethylsilane and coupling constants (*J*) are given in Hz. FTIR spectra were recorded as potassium bromide tablets with the Bruker Equinox 55 instrument. High and low resolution MS spectra were provided by the mass spectrometry facilities of VTT Processes, Espoo, Finland.

6-Dimethylamino-6-methylfulvene (6). A mixture of freshly distilled cyclopentadiene (**7**) (12.10 g, 183.0 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (**8**) (24.37 g, 183.0 mmol) was stirred at rt for 22 h. The resulting brownish orange crystals were filtered and washed with cold ether (3×10 mL) to give **6** as light orange crystals (18.71 g, 76%). TLC (EtOAc/*n*-hexane 1:1) R_f 0.48; mp 87–88 °C, recrystallized from ether/*n*-hexane (lit.,[6] 88–89 °C).

7-(Dimethylaminoethylidene)benzonorbornadiene (5). To a solution of (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflate (**9**) (5.92 g, 11.78 mmol) and 6-dimethylamino-6-methylfulvene (**6**) (7.95 g, 58.80 mmol, 5 equiv.) in dichloromethane (70 mL) was added dropwise a 1.0 M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (14.5 mL, 14.5 mmol) at 4 °C, and the reaction mixture was stirred at room temperature for 2 h. Then, water (50 mL) was added to the reaction mixture, and the resulting mixture was extracted with dichloromethane (1×100 mL and 2×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give crude **5** as a dark oil (23.03 g), which was used without further purification in the next step. TLC (PhMe/CH_2Cl_2/TEA (20:2:1) R_f 0.42.

7-Acetylbenzonorbornadiene (10). A mixture of crude **5** (23.03 g) and aqueous 2 M sodium hydroxide solution (300 mL, 600 mmol) was refluxed for 4 h. The reaction mixture was cooled to 4 °C. 6 M Hydrochloric acid (70 mL) was added to the solution until pH was 1-2. The resulting mixture was extracted with ether (3×100 mL). The combined organic layers were washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to give crude **10** as a red oil (7.73 g). The crude product was chromatographed on silica (EtOAc/*n*-hexanes 1:5) to give 7-acetylbenzonorbornadiene (**10**) as a mixture of *syn* and *anti* isomers (1.14 g, 73%, *syn*:*anti* 55:45). *anti* isomer: R_f 0.68 (EtOAc–hexane 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 (s, 3 H), 3.41 (br s, 1 H), 4.21 (br s, 1 H), 6.87 (obsc., 1 H), 6.95–7.05 (m, 2 H), 7.28–7.30 (m, 2 H); GC–MS t_{ret} 25.5 min, *m/z* 184 [M^+], 169 [$M\text{-}CH_3$]$^+$, 141[$M\text{-}CH_3CO$]$^+$, 115, 89, 63, 43. *syn* isomer: R_f 0.66 (EtOAc–hexane 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3 H), 3.35 (br s, 1 H), 4.29 (br s, 1 H), 6.77 (obsc., 1 H), 6.97–7.03 (m, 2 H), 7.25–7.33 (m, 2 H); GC–MS t_{ret} 26.5 min, *m/z* 184 [M^+], 169 [$M\text{-}CH_3$]$^+$, 141[$M\text{-}CH_3CO$]$^+$, 115, 89, 63, 43. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H 6.57. Found: C, 83.06; H, 6.52. The *syn* and *anti* isomers were carried as a mixture to the next step.

7-Acetylbenzonorbornene (11). To a mixture of **10** (0.530 g, 2.88 mmol) in ethyl acetate (30 mL) was added 5% palladium on activated carbon (0.100 g). A hydrogen balloon was attached to the reaction vessel, and the reaction mixture was stirred at rt for 2.5 h. The reaction mixture was filtered through Celite and evaporated to dryness. The crude product was purified by flash chromatography (EtOAc/*n*-hexane 1:50) providing the separable *syn* isomer (**11a**) (0.263 g) and *anti* isomer (**11b**) (0.228 g) as yellow oils, the total yield being 92%. *syn* isomer (**11a**): R_f 0.50 (EtOAc–hexane 1:2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14–1.23 (m, 2 H), 1.86 (s, 3 H), 1.96–2.00 (m, 2 H), 2.66 (t, *J* 1.5, 1 H), 3.58 (m, 2 H), 7.00–7.04 (m, 2 H), 7.09–7.13 (m, 2 H); NOESY cross peak at δ (2.66, 1.98); *m/z* 186 [M^+]; FTIR (KBr/cm^{-1}) 2956, 1697, 1469, 1180, 1110, 756; *anti* isomer (**11b**): R_f 0.64 (EtOAc–hexane 1:2); ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 1.09–1.12 (m, 2 H), 1.84–1.91 (m, 2 H), 2.10 (s, 3 H), 2.68 (app. quintet, *J* 1.5, 1 H), 3.53 (app. dd, *J* 1.6, 2 H), 7.00–7.06 (m, 2 H), 7.07–7.12 (m, 2 H); NOESY no cross peak at δ (2.68, 1.86); *m/z* 186 [M^+]; FTIR (KBr/cm^{-1}) 2975, 2875, 1707, 1471, 1361, 1112, 751. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H 7.58. Found: C, 83.69; H, 7.60.

***syn*-7-Bromoacetylbenzonorbornene (12a).** *syn*-7-Acetylbenzonorbornene (**11a**) (0.217 g, 1.17 mmol) was dissolved in methanol (10 mL), and the resulting solution was cooled to 0 °C. Then, a solution of bromine (65.0 μL, 1.26 mmol) in methanol (0.50 mL) was added, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with an equimixture of *n*-hexane and ether (50 mL). The resulting solution was washed with distilled water (10 mL), a saturated solution of $NaHCO_3$ (10 mL) and 10% solution of Na_2SO_3 (15 mL), dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to give *syn*-**12a** (0.290 g; 93%) as a yellowish oil. R_f 0.77 (EtOAc–hexane 1:2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25–1.29 (m, 2 H), 2.06–2.09 (m, 2 H), 3.04 (t, *J* 1.5, 1 H), 3.68 (s, 2 H), 3.64–3.68 (app. quintet, *J* 1.5, 2 H), 7.08–7.11 (m, 2 H), 7.17–7.20 (m, 2 H). *m/z* 265 [M^+]; FTIR (KBr/cm^{-1}) 2947, 1721, 1707, 1468, 1392, 1060, 754, 645. Anal. Calcd for $C_{13}H_{13}OBr$: C, 58.89; H, 4.94; Br, 30.14. Found: C, 58.81; H, 4.97; Br, 30.10. The product was carried to the next step without additional purification.

***anti*-7-Bromoacetylbenzonorbornene (12b).** *anti*-7-acetylbenzonorbornene (**11b**) (0.250 g, 1.34 mmol) was dissolved in methanol (10 mL), and the resulting solution was cooled to 0 °C. Then, a solution of bromine (75.0 μL, 1.46 mmol) in methanol (0.50 mL) was added, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with an equimixture of *n*-hexane and ether (50 mL). The resulting solution was washed with distilled water (10 mL), a saturated solution of $NaHCO_3$ (10 mL) and 10% solution of Na_2SO_3 (15 mL), dried with anhydrous Na_2SO_4, filtered and evaporated *in vacuo* to give *anti*-**12b** (0.342 g; 96%) as a yellowish oil. R_f 0.72 (EtOAc–hexane 1:2); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18–1.24 (m, 2 H), 1.96–2.00 (m, 2 H), 3.07 (t, *J* 1.5, 1 H), 3.63 (app dd, *J* 1.6, 2 H), 3.96 (s, 2 H), 7.08–7.12 (m, 2 H), 7.15–7.18 (m, 2 H). *m/z* 265 [M^+]; FTIR (KBr/cm^{-1}) 2975, 2875, 1709, 1460, 1392, 1068, 754. Anal. Calcd for $C_{13}H_{13}OBr$: C, 58.89; H, 4.94; Br, 30.14. Found: C, 58.83; H, 4.89; Br, 30.09.

7-Imidazolylbenzonorbornenes (3 and 4). A mixture of *syn* and *anti* bromides (**12**) (0.603 g, 2.27 mmol) in formamide (25 mL) was heated at 180 °C for 4 h. The reaction mixture was cooled to rt and diluted with distilled water (60 mL). The resulting mixture was acidified with 6 M hydrochloric acid (5 mL) and washed with ethyl acetate (2×20 mL). The aqueous layer was made alkaline with a concentrated solution of ammonia (20 mL) and extracted with ethyl acetate (1×40 mL, 2×20 mL). The combined

EtOAc layers were washed with distilled water (15 mL) and brine (15 mL), dried with Na_2SO_4, filtered and evaporated *in vacuo* to give the dark brown oil as a crude mixture of *syn*-**3** and *anti*-**4** isomers (0.270 g). The crude product (0.270 g) was dissolved in EtOAc (1 mL). The resulting solution was triturated with a saturated solution of hydrogen chloride in EtOAc (10 mL) to give a crude mixture of imidazole hydrochlorides. The crystallization of the crude hydrochloride from EtOAc/*i*-PrOH gave the *syn* imidazole (**3**) hydrochloride (153 mg, 27%) and the crystallization of the residual mother liquor from MeCN/*i*-PrOH in the refrigerator gave the corresponding *anti* imidazole (**4**) hydrochloride (137 mg, 25%) both as colorless crystals. *syn*-(**3**) hydrochloride: R_f 0.26 (CH_2Cl_2–MeOH–NH_3 9:1:0.05); mp 209–211 °C, from EtOAc/*i*-PrOH; ^{1}H NMR (D_2O, 300 MHz) δ 1.13 (dd, *J* 4.9, 12, 2 H), 2.03 (d, *J* 7.5, 2 H), 3.12 (s, 1 H), 3.55 (app s, 2 H), 6.57 (s, 1 H), 7.02 (m, 2 H), 7.18 (m, 2 H), 8.20 (s, 1 H); NOESY cross peak at δ (2.03, 3.12); FABMS 211 $[M+1]^+$; FTIR (KBr/cm^{-1}) 3093, 2806, 2613, 1617, 1404, 853, 753; Anal. Calcd for $C_{14}H_{15}N_2Cl$: C, 68.15; H, 6.13; N, 11.35. Found: C, 67.93; H, 6.08; N, 11.38. *anti*-(**4**) hydrochloride: R_f 0.28 (CH_2Cl_2–MeOH–NH_3 9:1:0.05); mp 193–195 °C, from MeCN/*i*-PrOH; ^{1}H NMR (D_2O, 300 MHz) δ 1.01 (m, 2 H), 1.72 (m, 2 H), 2.94 (s, 1 H), 3.58 (app s, 2 H), 7.08 (m, 2 H), 7.19 (m, 2 H), 7.22 (s, 1 H), 8.39 (s, 1 H); NOESY no cross peak at δ (1.72, 2.94); FABMS 211 $[M+1]^+$; FTIR (KBr/cm^{-1}) 3096, 2772, 2674, 1616, 1460, 842, 755. Anal. Calcd for $C_{14}H_{15}N_2Cl$: C, 68.15; H, 6.13; N, 11.35. Found: C, 68.99; H, 6.06; N, 11.41.

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