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An alternative improved synthesis of (–)-norferruginine, a potent nAChR agonist

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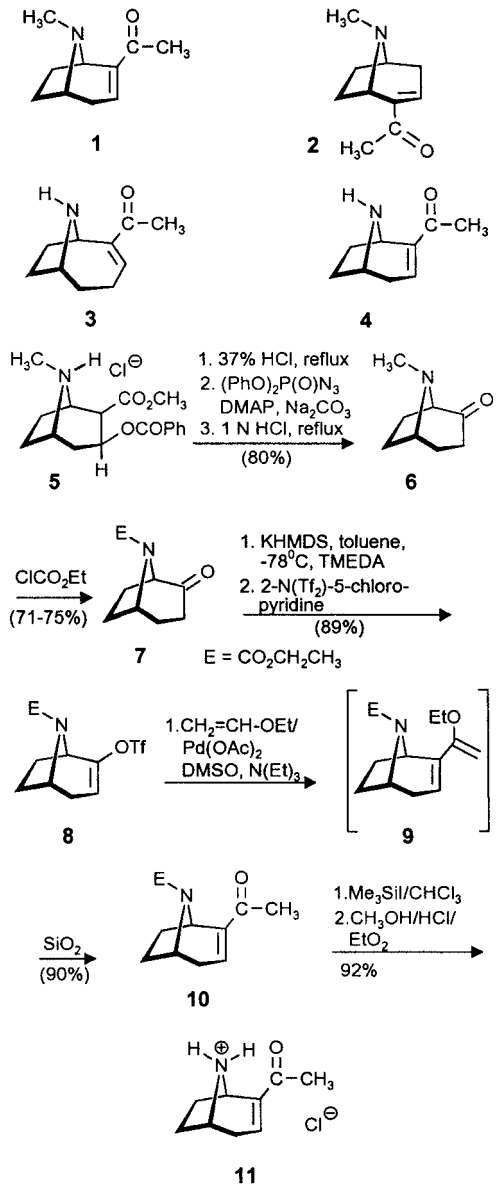
In our program aimed at the creation of novel semisynthetic variants of highly potent nicotinic acetylcholine receptor (nAChR) ligands that possibly show a separation of antinociception from toxic effects, we were interested in an efficient asymmetric synthesis of (–)-norferruginine (**4**). (–)-Ferruginine (**1**) is the unnatural enantiomer of (+)-ferruginine (**2**), a potent neurotoxin from the two arboreal species *Darlingia ferruginea* (J. F. Bailey) and *darlingiana* (F. Muell.), characterized by an 8-aza-bicyclo[3.2.1]octane skeleton [1–2]. The structural relationship of **1** and **2** to the highly potent semirigid nAChR agonist anatoxin-a (**3**) [3] has aroused increasing interest in these tropane alkaloids because the design, synthesis and biological evaluation of novel (–)-ferruginine analogues might achieve selectivity for central versus ganglionic nAChRs and possibly contribute to a further understanding of the structure/activity relationship at this receptor familiy [4–6].

Because of the close structural similarity particulary of (–)norferruginine (**4**) with anatoxin-a (**3**) – both exhibit equal absolute configurations at the two stereogenic centers (C-1 and C-5 or C-1 and C-6, respectively) and are characterized by a secondary amine moiety – we focused our efforts on a short and efficient synthesis of the enantiopure tropane derivative **4**, which compares favorably to previously described asymmetric syntheses [2, 7–9]. A particularly attractive feature for the asymmetric synthesis of enantiomerically pure **4** was the opportunity for its ready preparation from confiscated grade (–)-cocaine hydrochloride as starting material from the "chiral pool". Unfortunately the known multistep syntheses utilizing this useful precursor only afforded moderate overall yield of **4** [1, 2]. Thus we undertook an alternative asymmetric synthesis of (–)-norferruginine (**4**) starting from enantiomerically pure (+)-2-tropinone (**6**) as key intermediate and chiral building block. This is easily accessible from (–)-cocaine hydrochloride (**5**) by an improved synthetic method published recently by Trudell et al. [10].

As illustrated in Scheme 1 (+)-2-tropinone (**6**) could easily be converted in good yield to the N-protected bicyclic ketone **7** with ethyl chloroformate in the presence of potassium carbonate [11]. For the introduction of the ketonic side chain, characteristic for the target compound **4**, the enol triflate **8** seemed to be an appropriate precursor. This was easily accessible using KHMDS in toluene at −78 °C to prepare the corresponding potassium enolate of **7**, which was converted to the ketone-derived enol triflate **8** in nearly 89% yield with Comins' *N*-(5-chloro-2-pyridyl-triflimide) [12]. The enol triflate **8** appeared as an ideal starting material for the introduction of the acetyl side chain in mask form by a palladium-catalyzed cross-coupling with ethyl vinyl ether as an acetyl anion equivalent [13]. The reaction was accomplished under traditional Heck reaction conditions using triethylamine as the base in DMSO and in the presence of 8% palladium acetate as the catalyst precursor. The vinylation expectedly occurred at the oxygen-substituted carbon of the ethyl vinyl ether providing the 2-alkoxy diene **9** in high yield, thus constituting the key step of the new (–)-norferruginine approach. Hydrolysis of the diene **9** resulting from vinylation e.g. by flash chromatography on silica gel at ambient temperature provided the desired acetyl compound **10** in 90% yield without isolation of the intermediate **9**. Deprotection of the carbamate **10** using Me_3SiI in chloroform generated the target molecule as the hydrochloride **11** after treatment with HCl/Et_2O. This exhibits spectroscopic data in accord with structure **11**.

In conclusion, we have performed an alternative efficient and improved synthesis of enantiomerically pure (–)-norferruginine (**4**) in six steps and 44% overall yield. The novel route, utilizing (–)-cocaine hydrochloride as starting material from the "chiral pool", constitutes a remarkable simple procedure for the construction of (–)-norferruginine (**4**). Key step of the efficient synthesis is the introduction of the required acetyl side chain in masked form by reacting of the enol triflate of (+)-2-tropinone (**6**) with ethyl

Scheme



vinyl ether/$Pd(OAc)_2$ under Heck reaction conditions. Additionally the enol triflate **8** should allow ready access to a variety of (–)-ferruginine analogues.

Experimental

1. (–)-(1R,5S)-2-(Trifluoromethanesulfonyloxy)-8-azabicyclo[3.2.1]non-2-ene-8-carboxylic acid ethyl ester (**8**)

To a stirred solution of the ketone **7** (788 mg, 4.00 mmol) in dry THF (10 ml) was added a solution of TMEDA (750 µl, 5.00 mmol) in dry dimethoxyethane (DME, 25 ml). The solution was cooled to −78 °C and a solution of potassium hexamethyldisilazide (KHMDS, 10 ml, 0.5 M in toluene) added dropwise (1 ml/min) under Argon. After stirring for 30 min at −78 °C a solution of *N*-(5-chloro-2-pyridyl)triflimide (1.90 g, 4.80 mmol, freshly Kugelrohr distilled) in dry DME (5 ml) was added. The resulting solution was stirred at −78 °C for 2 h and than allowed to warm to 0 °C. Diethyl ether (40 ml) and then saturated aqueous $NaHCO_3$-solution (10 ml) were added, the organic phase separated and the aqueous phase reextracted with diethyl ether (2 × 5 ml). The combined organic phase was dried (K_2CO_3) filtered and evaporated in vacuo. The resulting yellow oil was purified by cc on silica gel (column 15 × 2 cm with *n*-hexane/ethyl acetate 4 : 1) to provide **8** as a colorless oil (1.19 g, 89%) $R_f = 0.39$ (*n*-hexane/ethyl acetate 4 : 1), $[\alpha]_D^{20} = -29.7$ °C (c = 1.7 in CH_2Cl_2). IR (film) $\nu = 2987$ cm^{-1}, 1712, 1421, 1318, 1208. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.19$ (t, $^3J = 6.9$ Hz, 3 H, CH_2CH_3), 1.63 (bs, 1 H, 6α-H), 1.90 (d, $^2J_{7\alpha,7B} = 17.4$ Hz, 1 H, 7a-H), 2.05 (bs, 1 H, 4α-H), 2.13 to 2.22 (m, 2 H, 6β-H, 7β-H), 2.82 (bs, 1 H, 4β-H), 4.08 (q, $^3J = 6.9$ Hz, 2 H, CH_2CH_3), 4.28–4.38 (m, 2 H, 1-H, 5-H), 5.48–5.51 (m, 1 H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.47 (CH_2CH_3), 29.13 (C-4), 31.91 (C-6), 34.44 (C-7), 51.47 (C-5), 55.63 (C-1), 61.55 (CH_2CH_3), 113.89 (C-3), 118.4 (CF_3, $^1J_{C,F} = 320.5$ Hz), 151.08 (C-2), 154.28 (C=O). EI-MS (70 eV): m/z (%) = 329 (7, M^+), 281 (7), 59 (100). HR-MS (M^+): $C_{11}H_{14}F_3NO_5S$, calcd 329.0545 found 329.0508

2. (–)-(1R,5S)-2-Acetyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid ethyl ester (**10**)

To a solution of the triflate **8** (132 mg, 0.40 mmol) in dry DMSO (1.0 ml), containing triethylamine (90 µl, 0.64 mmol) and ethyl vinyl ether (0.4 ml, 4.0 mmol) was added a solution of $Pd(OAc)_2$ (3.5 mg, 15 µmol) in dry DMSO (1.0 ml). The resulting yellow solution was saturated with Ar and stirred under Ar at 65 °C for 3 h. After cooling to room temperature the black slurry was quenched with ice water (15 ml) and the resulting mixture extracted with ethyl acetate (3 × 20 ml). The combined organic phase was evaporated in vacuo and the resulting residue purified by chromatography on silica gel [column 15 × 2 cm with *n*-hexane/ethyl acetate 3 : 1 (saturated with water containing one drop of HBr/HOAc 30%)] to provide ketone **10** as a colorless oil (83 mg, 90%). $R_f = 0.35$ (*n*-hexane/ethyl acetate 4 : 1) $[\alpha]_D^{25}$ −110.4° (c = 0.13 in CH_2Cl_2). UV (CH_2Cl_2): λ_{max} (lgε) = 230 nm (3.78). IR (film): 2978 cm^{-1}, 1701, 1666, 1420, 1106. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16 (t, $^3J = 6.9$ Hz, 3 H, CH_2CH_3), 1.48–1.55 (m, 1 H, 6α-H), 1.75 (dt, $^2J_{7\alpha,7\beta} = 9.5$ Hz, $^3J_{7\alpha,b} = 2.5$ Hz, 1 H, 7α-H), 1.98–2.03 (m, 2 H, 6β-H, 7β-H), 2.05–2.14 (m, 1 H, 4α-H), 2.20 (s, 3 H, $COCH_3$), 2.86 (bs, 1 H, 4β-H), 4.04 (q, $^3J = 6.9$ Hz, 2 H, CH_2CH_3), 4.37 (bs, 1 H, 5-H), 4.92 (d, $^3J_{1,7\alpha} = 5.9$ Hz, 1 H, 1-H), 6.59 (s, 1 H, 3-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.65 (CH_2CH_3), 24.88 (CH_3), 29.66 (C-4), 34.71 (C-6), 35.16 (C-7), 51.41 (C-5), 51.83 (C-1), 61.05 (OCH_2), 137.40 (C-2), 145.32 (C-3), 154.93 (COOEt), 196.42 ($COCH_3$). EI-MS (70 eV): m/z (%) = 223 (100, M^+), 208 (49), 122 (64). HR-MS (M^+):
$C_{12}H_{17}NO_3$, calcd 223.1208 found 223.1207.

3. (–)-(1R,5S)-2-Acetyl-8-azabicyclo[3.2.1]oct-2-ene-hydrochloride (**11**)

To a stirred solution of the carbamate **10** (91 mg, 0.41 mmol) in dry $CHCl_3$ (0.4 ml) was added TMSI (205 µl, 1.51 mmol). The resulting solution was heated in a closed vessel at 85 °C (oil bath) under Ar for 3.5 h. After cooling to room temperature the solvent and excess TMSI was removed in vacuo. To the residue a mixture of CH_3OH (3 ml) and 2 M HCl in Et_2O (0.6 ml, Aldrich) was added dropwise under Ar and the resulting solution stirred for 5 min at room temperature. Then the solvent was evaporated in vacuo and the red brown residue purified by chromatography on silica gel [(ICN silica RP C18, 32–63 µm, 60 Å), column 20 × 1 cm, eluting with 1. THF 2. THF/CH_3OH 95 : 5, with 0.2% 2 M HCl in Et_2O] to provide **4** as its crystalline hydrochloride **11** (70 mg, 92%). m.p.: >150 °C dec., $R_f = 0{,}24$ (streaking, $CH_3OH : CH_2Cl_2 : NH_3 = 5 : 95 : 0.1$/silica gel), $[\alpha]_D^{20} = -66.7$ °C (c = 0.25 in CH_3OH). UV (CH_3OH) λ_{max} (lg ε) = 224 nm (3.66). IR (KBr) $\nu = 3413$ cm^{-1}, 2925, 1662. ^{1}H NMR (500 MHz, CD_3OD): δ = 1.86–1.93 (m, 1 H, 6α-H), 2.06–2.12 (m, 1 H, 7α-H), 2.16–2.23 (m, 1 H, 6β-H), 2.24–2.32 (m, 1 H, 7β-H), 2.33 (s, 3 H, CH_3), 2.49 (dd, $^2J = 20.5$ Hz, $^3J = 4.6$ Hz, 1 H, 4α-H), 2.99 (dd, $^2J = 20.5$ Hz, $^3J = 2.5$ Hz, 1H, 4β-H), 3.31–3.29 (m, 2 H, $NH_2^{\oplus}$), 4.20 (t, broad, $^3J = 6.2$ Hz, 1 H, 5-H), 4.73 (d, $^3J = 6.0$ Hz, 1 H, 1-H), 7.01 (t, $^3J = 3.4$ Hz, 1 H, 3-H). ^{13}C NMR (125 MHz, CD_3OD): δ = 23.69 (C-4), 27.62 (CH_3), 32.61 (C-6), 33.21 (C-7), 52.12 (C-5), 53.23 (C-1), 136.83 (C-2), 139.55 (C-3), 195.70 (C=O). EI-MS (70 eV): m/z (%) = 151 (4, M^+), 149 (5), 128 (20), 44 (100). HR-MS (M^+-2):
$C_9H_{11}NO$, calcd 149.080780 found 149.084064.

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