Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 1405–1410

TETRAHEDRON: *ASYMMETRY*

A new and efficient synthetic route to enantiopure (+)-anatoxin-a from (–)-cocaine hydrochloride

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Received 31 January 2000; accepted 9 February 2000

Abstract

The potent nAChR agonist (+)-anatoxin-a was efficiently synthesized in enantiomerically pure form starting from a readily available confiscated grade (–)-cocaine hydrochloride. The eight-step synthesis providing novel extensions to existing methodology proceeded with 26% overall yield and with stereochemical integrity of the relevant original stereogenic centers. Key steps were an effective ring expansion of the (+)-2-tropinone **2** to the 9-azabicyclo[4.2.1]nonanone **5** with $TMSCHN_2/Al(CH_3)_3$ and the introduction of the required methyl ketone side chain in masked form by reacting the corresponding enol triflate **6** with ethyl vinyl ether/$Pd(OAc_2)$ under Heck reaction conditions.

1. Introduction

Since the alkaloidal toxin from strains of the fresh blue–green algae *Anabaena flos-aquae* (Lyngb.) de Bréb., referred to as 'very fast death factor', has been recognized as the azabicyclic alkaloid (+)-anatoxin-a **9**,[1,2] a number of elegant synthetic routes have been reported leading to numerous racemic and asymmetric syntheses.[3] Most of the asymmetric syntheses of enantiomerically pure (+)-anatoxin-a **9** and *ent*-**9** have been devised utilizing a starting material from the 'chiral pool' or by constituting a de novo asymmetric synthesis.

(+)-Anatoxin-a represents one of the most potent nicotinic agonists known[4] for the nicotinic acetylcholine receptor (nAChR), thus providing an attractive lead for the design of novel structural variations of the alkaloid, possibly selective, high affinity-ligands of the various nAChRs with improved safety and pharmacokinetic and pharmacodynamic profiles. Interestingly natural (+)-anatoxin-a **9** is a stereospecific agonist[4] (*ent*-**9** is inactive), providing strong evidence that a high level of stereodiscrimination is exhibited by the nAChRs.

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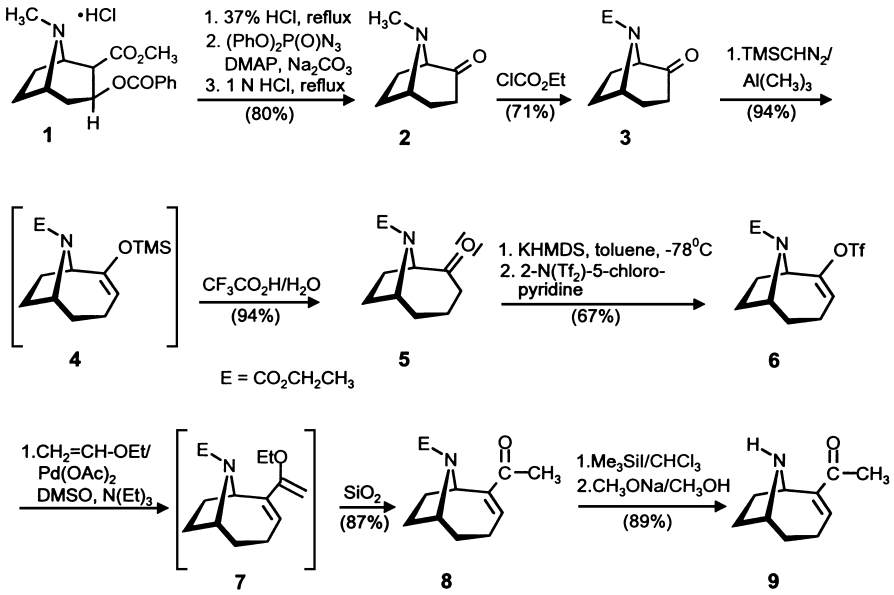
0957-4166/00/$ - see front matter
PII: S0957-4166(00)00059-8

Thus, in order to explore the pharmacological activities of new variants of the potent enantiomer (+)-anatoxin-a sufficient quantities of the natural toxin (–)-**9** as starting material were needed. Advantageously the requisite quantities of precursors for the construction of (+)-anatoxin-a and of enantiomerically pure analogues could be prepared from (–)-cocaine hydrochloride **1**. Because the earliest asymmetric synthesis, starting with (–)-cocaine hydrochloride,[2] furnished rather low overall yield, we tried to develop an efficient and improved asymmetric synthesis of (+)-anatoxin-a, again utilizing (–)-cocaine hydrochloride as starting material from the 'chiral pool' with stereochemical integrity of the relevant original stereogenic centers of the natural precursor, which are not directly involved in the various subsequent reactions.

2. Results and discussion

A particularly attractive feature for the asymmetric synthesis of enantiomerically pure natural (+)-anatoxin-a was the opportunity for its ready preparation from (+)-2-tropinone, which is easily available by degradation of (–)-cocaine hydrochloride **1** in a high-yielding two step synthesis, published recently.[5]

As illustrated in Scheme 1, treatment of (+)-2-tropinone **2** with ethyl chloroformate under reflux afforded the *N*-protected bicyclic ketone **3** in good yield. The one-carbon homologation of the 2-tropinone **3** with insertion of a methylene group exclusively at the less hindered side of the carbonyl group was achieved regioselectively with trimethylsilyldiazomethane ($TMSCHN_2$) promoted by the organoaluminum Lewis acid $Al(CH_3)_3$.[6] This effective ring expansion proved one of the key steps of our successful new (+)-anatoxin-a synthesis. The ring-enlarged product, initially formed under the conditions employed, is the trimethylsilyl enol ether **4**, which is easily transformed to the 9-azabicyclo[4.2.1]nonan-2-one **5** with 94% yield by mild acidolysis with aqueous trifluoroacetic acid.[7]



Scheme 1.

With the *N*-protected bicyclic ketone **5** in hand, we required a concise reaction sequence which would allow introduction of the ketonic side chain, characteristic of (+)-anatoxin-a. Most promising seemed to be an approach with the enol triflate **6**[8] as precursor. This was readily available using KHMDS in toluene at –78°C to prepare the corresponding potassium enolate of **5**, which was advantageously trapped with Comins' *N*-(5-chloro-2-pyridyl)triflimide to furnish the ketone-derived enol triflate in more than 60% yield. The enol triflate **6** proved to be a synthetically versatile intermediate, only recently used to prepare UB-165, an interesting novel anatoxin-a/epibatidine hybrid,[7] retaining the aza-bicyclo[4.2.1]nonane moiety of anatoxin-a and the pyridyl unit of epibatidine. This sensitive intermediate **6** was then subjected to Hallberg's methodology[9] providing a convenient synthesis of 2-alkoxy 1,3-dienes by reacting cyclic enol triflates with alkyl vinyl ethers in the presence of a palladium catalyst, and in this case allowing the introduction of the desired methyl ketone side chain in masked form.

Thus, the reaction of the enol triflate **6** with ethyl vinyl ether in the presence of 8% palladium acetate—performed under traditional Heck reaction conditions, using triethylamine as the base in DMSO—gave the 2-ethoxydiene **7** in high yield, establishing the second key step of our new (+)-anatoxin-a approach.

Under comparatively mild conditions, e.g. by flash chromatography on silica gel at ambient temperature, compound **7** was easily hydrolyzed to furnish the corresponding α,β-unsaturated methyl ketone, the *N*-protected (+)-anatoxin-a **8**. Deprotection of **8** using Me_3SiI in chloroform generated the natural (+)-anatoxin-a as the free base **9** after treatment with CH_3ONa/CH_3OH. This exhibits spectroscopic data (^1H NMR, ^{13}C NMR and MS) in accord with those reported by the group of Rapoport[3i,10] for the natural toxin and with specific rotation of equal magnitude.

In conclusion we have performed a new and efficient synthesis of enantiomerically pure (+)-anatoxin-a in eight steps and 26% overall yield, starting from a readily available confiscated grade (–)-cocaine hydrochloride. The route utilizing a starting material from the chiral pool constitutes a remarkably simple procedure for the construction of natural anatoxin-a through a series of routine reactions. Key steps are on the one hand the effective ring expansion of the (+)-2-tropinone **2** to the 9-azabicyclo[4.2.1]nonanone **5** with $TMSCHN_2/Al(CH_3)_3$ and on the other hand the introduction of the required methyl ketone side chain in masked form by reacting the corresponding enol triflate with ethyl vinyl ether/$Pd(OAc)_2$ under Heck reaction conditions. In addition our procedure should be amenable to scale up and compares favorably to the previously described synthesis from (–)-cocaine hydrochloride **1**.[2] Versatile intermediates are the ketone **5** and the enol triflate **6**, which should allow ready access to various (+)-anatoxin-a analogues.

3. Experimental

General procedures: standard vacuum techniques were used in handling of air sensitive materials. Melting points are uncorrected: 'Leitz–Heiztischmikroskop' HM-Lux. Solvents were dried and freshly distilled before use according to literature procedures. IR: Perkin–Elmer 257, 398 and FT-IR spectrometer 510-P (Nicolet). Liquids were run as films, solids as KBr pellets. ^1H NMR and ^{13}C NMR: Jeol JNM-GX 400 and LA 500; δ/ppm = 0 for tetramethylsilane, 7.26 for chloroform. MS: vacuum generators 7070 (70 eV; ^{11}B). Column chromatography: purification were carried out on Merck silica gel 60 (70–260 or 200–400 mesh) flash chromatography. Reactions were monitored by thin-layer chromatography (TLC) by using plates of silica gel (0.063–0.200

mm, Merck) or silica gel-60-F_{254} microcards (Riedel de Haen). Optical rotations: Mod. Dip-370 polarimeter (Jasco). UV: UV–vis scanning spectrophotometer UV-2101 (PC, Shimadzu).

3.1. (+)-(1R)-2-Oxo-tropane-8-carboxylic acid ethyl ester **3**

To a stirred solution of the ketone **2**[5] (1.50 g, 10.0 mmol) in benzene (20 mL) was added ethyl chloroformate (2.0 mL, 20 mmol) and K_2CO_3 (280 mg, 2.00 mmol). The mixture was heated at reflux under Ar for 12 h, cooled to room temperature and filtered. The filtrate was washed with 2.0 M aqueous HCl (10 mL), the aqueous wash back-extracted with benzene (10 mL) and the combined organic layers washed with saturated aqueous $NaHCO_3$ (20 mL) and with brine (10 mL), then dried over $MgSO_4$ (10 g), filtered and evaporated. The residue was purified by flash chromatography on silica gel (column 15×2 cm with *n*-hexane:ethyl acetate 4:1) to afford the ketone **3** as a pale yellow oil (1.55 g, 71%): R_f 0.19 (*n*-hexane:ethyl acetate 4:1); $[\alpha]_D^{20}$ +32 (c 0.02, CH_3OH); IR (film) 2980, 1700, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3H), 1.74–2.46 (m, 8H), 4.06–4.14 (m, 2H), 4.36–4.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 27.0, 27.8, 30.5, 32.4, 52.7, 61.4, 64.0, 154.1, 205.5. Anal. calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10; found: C, 60.79; H, 7.42; N, 6.91.

3.2. (1R)-2-Trimethylsilyloxy-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic acid ethyl ester **4**

To a –78°C solution of Me_3Al (2.0 M, 3.2 mL in *n*-hexane) in dry CH_2Cl_2 (50 mL) was added (3 mL/min) a solution of the ketone **3** (985 mg, 5.0 mmol) in dry CH_2Cl_2 (15 mL) followed by a solution of $TMSCHN_2$ (2.0 M, 3.2 mL in *n*-hexane). The resulting solution was allowed to warm to room temperature, kept at ambient temperature for 12 h, and after diluting with *n*-pentane (120 mL) ice-cooled aqueous $NaHCO_3$ (2.5%, 12 mL) was added slowly at 0°C. Stirring was continued for 5 min and the colorless precipitate removed by filtration. The aqueous layer was separated and the organic phase washed rapidly with ice-cooled aqueous $NaHCO_3$ (2.5%, 10 mL) and with brine (10 mL), then dried over $MgSO_4$ (10 g), filtered and rotary evaporated leaving 1.43 g of an oil which was chromatographed on silica gel (column 10×3.5 cm with *n*-hexane:ethyl acetate:$N(Et)_3$ 6:3:0.1) to provide **4** as a colorless oil (1.33 g, 94%): R_f 0.50 (*n*-hexane:ethyl acetate:$N(Et)_3$ 6:3:0.1); IR (film) 2960, 1705, 1650, 1464 cm^{-1}. Exact mass calcd for $C_{14}H_{25}NO_3Si$: 283.1603; found: 283.1599. Because of low stability the enol ether **4** was not further characterized and used directly in the next reaction.

3.3. (–)-(1R)-2-Oxo-9-azabicyclo[4.2.1]nonane-9-carboxylic acid ethyl ester **5**

Aqueous trifluoroacetic acid (70%, 20 mL) was degassed for 5 min with Ar and then compound **4** (611 mg, 2.16 mmol) added. The solution was stirred at 50°C for 3 h. Then the solvent was evaporated in vacuo, the residue was resolved in CH_2Cl_2 (20 mL), the solution washed with saturated aqueous $NaHCO_3$ (10 mL), dried over $MgSO_4$ (5 g), filtered and evaporated. The residue was purified by flash chromatography on silica gel (column 15×2 cm with *n*-hexane:ethyl acetate 2:1) to provide ketone **5** as a colorless oil (433 mg, 94%): R_f 0.38 (*n*-hexane:ethyl acetate 2:1); $[\alpha]_D^{20}$ –23.1 (c 0.01, $CHCl_3$). IR (film) 2956, 1700, 1424 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 2 rotamers, ratio ca. 2:1) δ 1.16 (t, J = 7.0 Hz, 2H), 1.23 (t, J = 7.0 Hz, 1H), 1.45–1.76 (m, 3H), 1.78–1.96 (m, 2H), 2.03–2.17 (m, 2H), 2.33 (dd, J = 7.0 Hz, J = 7.0 Hz, 2H), 2.51 (dd, J = 2.4 Hz, J = 1.4 Hz, 1H), 4.09 (q, J = 7.0 Hz, 1.33H), 4.12 (q, J = 7.0 Hz, 0.66 H), 4.29 (d, J = 10.1 Hz, 0.66H), 4.38 (d, J = 10.1

Hz, 0.33H), 4.46 (d, broad, J = 7.1 Hz, 0.33H), 4.54 (d, broad, J = 7.1 Hz, 0.66H); ^{13}C NMR (100 MHz, $CDCl_3$, 2 rotamers) δ (major rotamer) 14.7, 19.2, 26.5, 30.1, 32.9, 41.7, 56.8, 61.3, 64.6, 153.5, 215.0; δ (minor rotamer) 14.7, 19.1, 27.1, 29.6, 33.9, 41.7, 56.3, 61.3, 64.8, 154.1, 215.2; MS (70 eV) m/z (%) 211 (M^+, 24), 140 (100). Exact mass calcd for $C_{11}H_{17}NO_3$: 211.1208; found: 211.1207.

3.4. (+)-(1R)-2-(Trifluoromethanesulfonyloxy)-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic acid ethyl ester **6**

To a stirred solution of the ketone **5** (211 mg, 1.00 mmol) in dry THF (5 mL), cooled to –78°C under Ar, was added dropwise a solution of potassium hexamethyldisilazide (KHMDS) (2.20 mL, 0.5 M in toluene). After stirring for 1 h, a solution of *N*-(5-chloro-2-pyridyl)triflimide (392 mg, 1.00 mmol, freshly Kugelrohr distilled) in dry THF (2 mL) was added in one portion. The resulting solution was stirred at –78°C for 3 h and then allowed to warm to room temperature. Water (5 mL) was added and the mixture extracted with CH_2Cl_2 (3×5 mL). The combined organic phase was dried (K_2CO_3), filtered and evaporated in vacuo leaving a pale yellow oil, which was purified by column chromatography on silica gel (column 15×2 cm with *n*-hexane:ethyl acetate 2:1) to provide **6** as a colorless oil (230 mg, 67%): R_f 0.59 (*n*-hexane:ethyl acetate 2.5:1); $[\alpha]_D^{20}$ +28.2 (c 0.28, $CHCl_3$); IR (film) 2958, 1709, 1419 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 2 rotamers, ratio 2:1) δ 1.19 (t, J = 7.0 Hz, 3H), 1.54–1.78 (m, 3H), 1.95–2.25 (m, 5H), 4.09 (q, J = 7.0 Hz, 2H), 4.35 (s, broad, 0.33H), 4.40 (s, broad, 0.66H), 4.50 (d, J = 8.0 Hz, 0.66H), 4.60 (d, J = 8.0 Hz, 0.33H), 5.72 (t, J = 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 2 rotamers) δ (major rotamer) 14.7, 19.8, 28.0, 30.7, 30.8, 55.2, 58.4, 61.5, 118.4 (q, J = 319.5 Hz, CF_3), 120.8, 153.6, 154.0; δ (minor rotamer) 14.8, 19.8, 29.2, 29.9, 31.9, 54.8, 58.6, 61.5, 118.4 (q, J = 319.5 Hz, CF_3), 120.6, 153.8, 154.0. MS (70 eV) m/z (%) 343 (M^+, 4), 210 (100). Exact mass calcd for $C_{12}H_{16}F_3NO_5S$: 343.0701; found: 343.0692.

3.5. (+)-(1R)-2-Acetyl-9-azabicyclo[4.2.1]non-2-ene-9-carboxylic acid ethyl ester **8**

To a solution of the triflate **6** (135 mg, 0.39 mmol) in dry DMSO (1 mL), containing triethylamine (90 μL, 0.64 mmol) and ethyl vinyl ether (0.4 mL, 4 mmol), was added a solution of $Pd(OAc)_2$ (3.5 mg, 15 μmol) in dry DMSO (1 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 **8** as a colorless oil (82.5 mg, 87%): R_f 0.18 (*n*-hexane:ethyl acetate 3:1); $[\alpha]_D^{20}$ +55.9 (c = 0.16, $CHCl_3$); IR (film) 2932, 1702, 1666, 1423 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 2 rotamers, ratio 2:1) δ 1.10 (t, J = 7.0 Hz, 1H), 1.18 (t, J = 7.0 Hz, 2H), 1.55–1.67 (m, 3H), 1.96–2.15 (m, 2H), 1.97–2.29 (m, 1H), 2.22 (s, 3H), 2.34–2.42 (m, 2H), 3.99 (q, J = 7.0 Hz, 1.33H), 4.04 (q, J = 7.0 Hz, 0.66H), 4.29–4.34 (s, broad, 0.33H), 4.38–4.42 (m, 0.66H), 5.16 (t, J = 9.0 Hz, 1H), 6.77 (t, J = 5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 2 rotamers) δ (major rotamer) 14.6, 24.2, 25.4, 28.6, 30.6, 31.6, 53.0, 55.8, 60.8, 142.4, 149.5, 153.8, 197.8; δ (minor rotamer) 14.8, 24.2, 25.6, 29.3, 30.9, 32.1, 54.2, 55.2, 60.8, 141.5, 148.6, 153.8, 197.8; MS (70 eV) m/z (%) 237 (M^+, 100). Exact mass calcd for $C_{13}H_{19}NO_3$: 237.1365; found: 237.1371.

3.6. (+)-(1R)-2-Acetyl-9-azabicyclo[4.2.1]non-2-ene **9**

To a solution of carbamate **8** (73 mg, 0.3 mmol) in dry $CHCl_3$ (0.8 mL) was added freshly distilled TMSI (140 μL, 1.00 mmol). The solution was stirred in a sealed tube under Ar for 4 h at 80°C and after cooling to room temperature a solution of sodium methanolate (81 mg, 1.50 mmol) in dry methanol (1 mL) was added. Then the mixture was evaporated in vacuo and to the remaining material water (1 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (2×2 mL) and with CH_2Cl_2:2-propanol 3:1 (2×3 mL). The combined organic phase was dried ($MgSO_4$), filtered, evaporated in vacuo and the residue purified by chromatography on silica gel [column 10×2 cm eluting with: (1) *n*-hexane:CH_2Cl_2 1:4 (100 mL); (2) CH_2Cl_2:MeOH 9:1 (100 mL); (3) CH_2Cl_2:MeOH:Et_2NH 90:10:0.1] to provide the free base **9** (44 mg, 89%): R_f 0.07 (streaking), CH_2Cl_2:MeOH:aqueous NH_3 95:15:0.1; $[\alpha]_D^{20}$ +41.0 (c 0.20, abs. ethanol [lit.[10] $[\alpha]_D^{24}$ +43.2, c 0.676, abs. ethanol]); ^1H and ^{13}C NMR data for the free base are in full accordance with those reported in the literature:[3i,10] ^1H NMR (free base, 500 MHz, $CDCl_3$) δ 1.6–2.2 (m, 6H), 2.26 (s, 3H), 2.4–2.5 (m, 2H), 3.74 (m, 1H), 4.62 (m, 1H), 6.85 (m, 1H) (NH-proton not detectable); ^{13}C NMR (free base, 125 MHz, $CDCl_3$) δ 25.0, 25.5, 30.3, 32.9, 33.4, 54.2, 57.8, 143.2, 152.3, 198.6.

Acknowledgements

This work was generously supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We also wish to thank the Bayer AG, Degussa AG and the Merck AG for generous gifts of various chemicals.

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