Notes

An Efficient Synthesis of the Cholinergic Channel Activator ABT-418

Steven J. Wittenberger

Process Chemistry, Department 45L/R8, Pharmaceutical Products Division, Abbott Laboratories, 1401 Sheridan Road, North Chicago, Illinois 60064−4000

Received May 30, 1995 (Revised Manuscript Received October 4, 1995)

Alzheimer's disease is a late-onset neurodegenerative disorder which manifests itself in afflicted individuals through the multifaceted loss of intellectual abilities and disturbances in thought content and behavior. Cholinergic channel activators (ChCAs), such as (*S*)-nicotine, have been demonstrated to exhibit intrinsic cognitive enhancing and anxiolytic activities presumably by selective interaction with central neuronal nicotinic acetylcholine receptors.[1] ABT-418, (*S*)-3-methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole, represents a new class of isoxazole-containing ChCAs[2] currently being evaluated as a safe and effective treatment for Alzheimer's disease-related personality changes and memory loss.[3]

The initial approach[2] to ABT-418 centered about a [3 + 2] nitrile oxide cycloaddition onto the (*S*)-proline-derived alkyne (eq 1). This route proved to be unsuitable for the preparation of kilogram quantities of compound: it was too lengthy, required several chromatographic purifications, and provided product in low overall yield. A series of second generation syntheses (eq 2) featured the strategy of the addition of a dianion derived from acetone oxime to the carboxylic ester of (*S*)-proline[4] or (*S*)-pyroglutamic acid.[5] Although convergent and high yielding overall, these approaches also had liabilities: the necessity of 2*n* equiv of *n*-butyllithium per mole of acetone oxime used, the highly exothermic deprotonation of the oxime OH, and the production of a 2,6-dimethylpyridine *N*-oxide **1** byproduct in the (*S*)-proline series. All of these problems were aggrandized upon scale-up.

Observations made in the context of another project inspired a new approach to ABT-418. Stuk et al. reported a synthesis of the diamino alcohol core unit of HIV protease inhibitor ABT-538.[6] Key to this synthesis was the addition of sodioacetonitrile to *N*,*N*-dibenzylphenylalanine benzyl ester **2** to give the α-cyano ketone **3** to which was added benzylmagnesium chloride providing the enamino ketone **4** in high enantiomeric excess

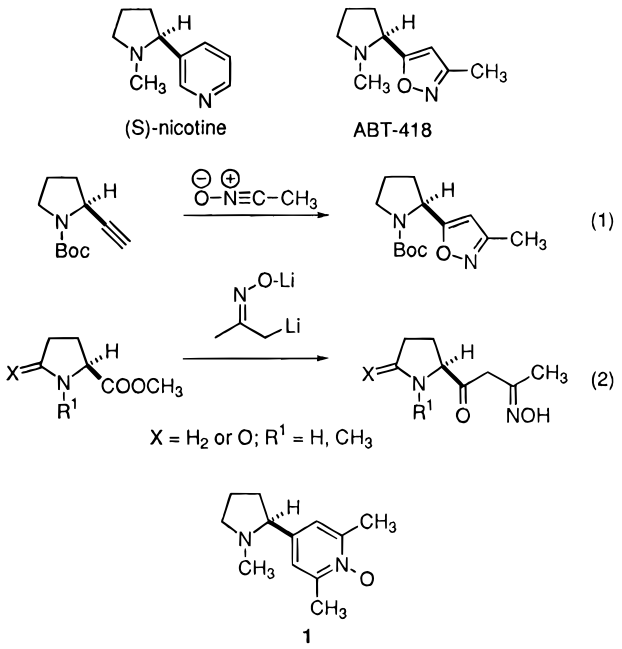


Figure 1. Key transformations in early routes to ABT-418.

(Scheme 1). In the course of studies related to the elaboration and reduction of this intermediate to the required diastereomer of the diamino alcohol core unit, it was found that treatment with 1 equiv of hydroxylamine hydrochloride selectively produced the ketooxime **5**.[7]

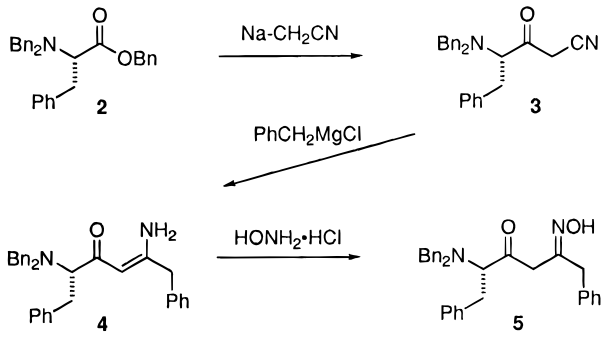
Implementation of this strategy[8] to the ABT-418 problem began with the condensation of *N*-methylproline methyl ester[4] (**6**) with sodioacetonitrile to give to the α-cyano ketone **7** (Scheme 2). Of paramount importance to the success of the new route was the maintenance of optical purity at the α-center. On the basis of experience gained in the HIV protease core unit synthesis, the most likely step to observe any erosion in optical purity was the sodioacetonitrile addition to the α-amino ester. HPLC analysis of the enantiomeric excess could not be accomplished on the α-cyano ketone **7** as no resolution was observed on any of the chiral supports that were screened. Fortunately the route is short and an established method existed[4] for the determination of enantiomeric excess of ABT-418, so trial runs were taken through to the final product and HPLC analyses were performed on ABT-418, and any degradation in optical purity was first assumed to occur in the acetonitrile anion condensation. Optimal overall yield and enantiomeric excess was achieved when the condensation was conducted in THF solvent. Trial runs done in solvent mixtures of THF/toluene gave ABT-418 in inferior yield and enantiomeric excess, and with methyl *tert*-butyl ether as solvent, a slightly lower (87%) enantiomeric excess was realized in comparable overall yield.

Reaction of the crude α-cyano ketone **7** with methylmagnesium chloride provided the enamino ketone **8** which was isolated following aqueous workup but not

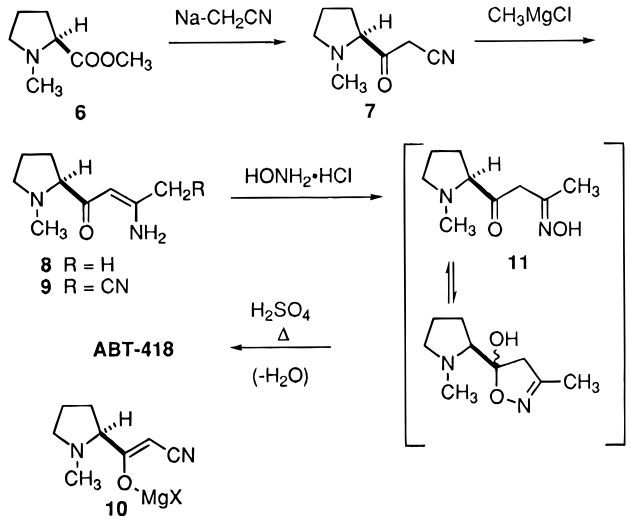
(1) Williams, M.; Sullivan, J. P.; Arneric, S. P. *DN&P*, **1994**, *7*, 205−223.
(2) Garvey, D. S.; Wasicak, J. T.; Decker, M. W.; Brioni, J. D.; Buckley, M. J.; Sullivan, J. P.; Carrera, G. M.; Holladay, M. W.; Arneric, S. P.; Williams, M. *J. Med. Chem.* **1994**, *37*, 1055−1059.
(3) Arneric, S. P.; Anderson, D. J.; Bannon, A. W.; Briggs, C. A.; Brioni, J. D.; Decker, M. W.; Donnelly-Roberts, D.; Gopalakrishnan, M.; Holladay, M. W.; Kyncl, J.; Marsh, K. C.; Radek, R. J.; Rodrigues, A. D.; Sullivan, J. P.; Buccafusco, J. J.; Pauly, J. *Cent. Nerv. Syst. Drug Rev.* **1995**, in press.
(4) Elliott, R. L.; Kopecka, H.; Lin, N.-H.; He, Y.; Garvey, D. S. *Synthesis* **1995**, 772−774.
(5) Lin, N.-H.; He, Y.; Kopecka, H. *Tetrahedron Lett.* **1995**, *36*, 2563−2566.
(6) Stuk, T. L.; Haight, A. R.; Scarpetti, D.; Allen, M. S.; Menzia, J. A.; Robbins, T. A.; Parekh, S. I.; Langridge, D. C.; Tien, J.-H. J.; Pariza, R. J.; Kerdesky, F. A. J. *J. Org. Chem.* **1994**, *59*, 4040−4041.
(7) Zhao, C., unpublished results.
(8) Lin, N.-H.; He, Y.; U.S. Patent 5,424,444, 1995.

0022-3263/96/1961-0356$12.00/0

Scheme 1. Stuk's Diamino Alcohol Core Unit Synthesis



Scheme 2. Synthetic Route to ABT-418 from *N*-Methylproline Methyl Ester



purified further. Interestingly, it was found that in the event that all traces of residual acetonitrile were not removed following the preparation of **7**, the bis-acetonitrile addition product, cyanomethyl enamino ketone **9** was formed. It was apparent that the methylmagnesium chloride deprotonated the residual acetonitrile faster than adding to the nitrile moiety of either the acetonitrile or the α-cyano ketone anion **10**, and this chloromagnesium acetonitrile anion, in turn, reacted with **10** faster than did methylmagnesium chloride. This unexpected reactivity precluded the sequential addition of sodioacetonitrile and methylmagnesium chloride.

Treatment of the enamino ketone **8** with hydroxylamine hydrochloride regioselectively produced the keto oxime **11**. Addition of aqueous sulfuric acid followed by gentle heating catalyzed *in situ* cyclodehydration to produce the isoxazole ring of ABT-418. By this novel regiospecific method of 3,5-disubstituted isoxazole preparation, ABT-418 was produced in 49% overall yield from *N*-methylproline methyl ester in >98% ee from economical reagents and reactions suitable for scale-up with a single purification, the distillation of the final product.

Experimental Section

General. Reactions were routinely performed under an inert atmosphere (nitrogen or argon). Solvents and reagents were used as received from commercial sources. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F-254 glass-backed plates, 250 μm thickness.

(*S*)-2-(Cyanoacetyl)-*N*-methylpyrrolidine (7). A 3-L three-neck round-bottom flask equipped with an overhead stirrer, addition funnel, internal temperature monitor, and N_2 inlet was charged with sodium amide (97.9 g, 2.25 mole) and tetrahydrofuran (HPLC grade, 1350 mL). The suspension was cooled to ca. −40 °C to −45 °C, and a solution of acetonitrile (135 mL, 2.58 mol) and tetrahydrofuran (75 mL) was added dropwise at such a rate that the internal temperature remained ≤−36 °C (ca. 22 min). The nearly homogeneous solution was stirred ca. 13 min and was then added via a dry ice cooled cannula to a 5-L three-neck round-bottom flask equipped with an overhead stirrer internal temperature monitor and nitrogen outlet and charged with a solution of *N*-methylproline methyl ester (**6**) (125.5 g, 0.876 mol) and tetrahydrofuran (1350 mL) cooled to ca. −40 °C to −45 °C. The internal temperature was maintained ≤−40 °C throughout the addition. After ca. 1 h the reaction was quenched by the addition of solid ammonium chloride (131 g, 2.45 mole). The cold bath was removed, and the reaction was allowed to warm to ca. +5 °C over about 1.5 h. Filter-aid (250 g) was added, and the mixture was filtered through a pad of filter-aid (250 g, 2 in. ht × 6 in diam.) topped with sand (500 g). The filter cake was washed with THF (ca. 1 L) to remove most of the color. The filtrate was concentrated in vacuo, and the foamy orange residue, 267.2 g, was used directly in the next step. (Theoretical yield is 133.4 g. The excess mass is presumably salts and does not appear to interfere with the following step.) TLC data: R_f (1:10:90, concd NH_4OH/MeOH/CH_2Cl_2): sm = 0.5, pdt = 0.2; iodine stain). MS (DCI/NH_3) m/z 153 $(M + H)^+$, 100%. IR ($CHCl_3$, cm^{-1}) 3000, 2790, 2180, 1727, 1570.

(*S*)-2-(3-Aminobut-2-enoyl)-*N*-methylpyrrolidine (8). A 3-L three-neck round-bottom flask equipped with an overhead stirrer, addition funnel, internal temperature monitor, and N_2 inlet was charged with the above crude keto nitrile **7** (267 g, ca. 0.87 mol) dissolved in tetrahydrofuran (1 L) and chilled to −5 °C to −10 °C. Methylmagnesium chloride (930 mL, 3 M THF, 2.79 mol) was added via addition funnel at such a rate as to maintain the internal temperature ≤+5 °C (ca. 90 min). Following the addition the cold bath was removed and the reaction allowed to warm to room temperature and stir overnight (ca. 15 h). The dark mixture was carefully poured into ice (1.5 kg) and stirred 5−10 min. The aqueous portion was exhaustively extracted with ethyl acetate (ca. 15 to 20 × 1 L). The combined organics were dried (Na_2SO_4), filtered, and evaporated leaving 158.2 g of dark oil used directly in the next step. Theoretical yield is 147.4 g for the two steps. TLC data: R_f (1:10:90, concd NH_4OH/MeOH/CH_2Cl_2): sm = 0.2, pdt = 0.15; iodine stain. Relative R_f's of starting material and product are very dependent upon the amount of concd NH_4OH in the developing solvent. MS (DCI/NH_3) m/z 169 $(M + H)^+$, 100%. ^{13}C NMR ($CDCl_3$) δ 22.29, 22.97, 30.68, 41.15, 56.71, 74.51, 91.79, 163.05, 199.33. ^1H NMR ($CDCl_3$) δ 1.70−1.90 (m, 3H), 1.96 (s, 3H), 2.00−2.30 (m, 2H), 2.33 (s, 3H), 2.70 (t, J = 7.5 Hz, 1H), 3.14 (dt, J = 2, 8 Hz, 1H), 5.31 (s, 1H), 5.45 (br s, 1H), 9.80 (br s, 1H).

(*S*)-2-(3-Amino-4-cyanobut-2-enoyl)-*N*-methylpyrrolidine 9. MS (DCI/NH_3) m/z 194 $(M + H)^+$, 100%. IR ($CHCl_3$, cm^{-1}) 3250, 3160, 2200. ^{13}C NMR ($CDCl_3$) δ 23.11, 24.16, 30.58, 41.12, 56.64, 74.40, 92.12, 115.08, 152.96, 200.98. ^1H NMR ($CDCl_3$) δ 1.70−1.95 (m, 3H), 2.05−2.15 (m, 1H), 2.20−2.40 (m, 1H), 2.33 (s, 3H), 2.76 (t, J = 7.5 Hz, 1H), 3.16 (dt, J = 2, 7 Hz, 1H), 3.38 (s, 2H), 5.35 (br s, 1H), 5.53 (s, 1H), 9.70 (br s, 1H).

(*S*)-3-Methyl-5-(*N*-methyl-2-pyrrolidinyl)isoxazole (ABT-418). A 2-L three-neck round-bottom flask equipped with an overhead stirrer, reflux condenser, internal temperature monitor, and N_2 inlet was charged with the above crude keto enamine **8** (158 g, ca. 0.87 mol), acetonitrile (HPLC grade, 1000 mL), and hydroxylamine hydrochloride (64.0 g, 0.92 mol) and stirred at room temperature for 6 h. Aqueous 50% sulfuric acid (9.4 M, 240 mL, 2.26 mol) was added, and the mixture was heated to reflux for ca. 1 h. After cooling, the bulk of the solvents were removed in vacuo. The residue was basified by the addition of saturated sodium carbonate solution (ca 1.2 L, to pH 9−10), saturated with sodium chloride, and extracted with ethyl acetate (4 x 500 mL). The combined organics were washed with brine (1 × 1 L) and then dried ($MgSO_4$ + activated carbon). The mixture was filtered, the filtrate was concentrated, and the residue was distilled at reduced pressure (10 mmHg, bp 98−101 °C) to give 71.97 g of light yellow oil (49% overall yield from ester, ≥98% ee, Chiralcel AD column with 3% ethanol/hexane at 1 mL/min, UV detection @ 214 nm. t_R: (S) = 7.1 min, (R) = 8.1 min). TLC data: R_f (1:10:90, concd NH_4OH/MeOH/CH_2-

Cl_2): sm = 0.15, oxime intermediate = 0.3, pdt = 0.4; iodine stain. MS (DCI/NH_3) *m*/*z* 167 $(M + H)^+$, 100%; 184 $(M + NH_4)^+$, 5%. ^{13}C NMR ($CDCl_3$) δ 11.03, 22.51, 31.28, 40.30, 56.22, 61.88, 101.12, 159.17, 173.83. ^1H NMR ($CDCl_3$) δ 1.80−2.03 (m, 3H), 2.18−2.43 (m, 2H), 2.28 (s, 3H), 2.34 (s, 3H), 3.14−3.21 (m, 1H), 3.45 (t, J = 7.5 Hz, 1H), 6.00 (s, 1H).

Acknowledgment. I am grateful to Mr. Michael Fitzgerald, Process Chemistry, Department 45L, for assistance with the chiral HPLC analyses, Dr. Chen Zhao, Antiviral Chemistry, Department 47D, for sharing preliminary results, Drs. William Bunnelle, B. A. Narayanan, and Pulla Reddy Singam, Abbott Laboratories, Chemical and Agricultural Product Division, for helpful discussion, and the Structural Chemistry Department at Abbott Laboratories for acquisition of spectral data.

JO9509723