SYNTHESIS OF DESMETHYL TIAGABINE†

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Abstract-The title compound has been investigated as one in a series of novel and selective GABA uptake inhibitors that exhibit potent anti-convulsant effects. Versatile syntheses have been developed for the preparation of this compound in excellent yields. Key steps are a Grignard reaction followed by ring opening with simultaneous dehydration and bromination of a hydroxymethyl cyclopropane with bromotrimethylsilane; displacement of bromine with ethyl R-(-)-piperidine-3-carboxylate and an acid or base catalyzed hydrolysis of the ester moiety.

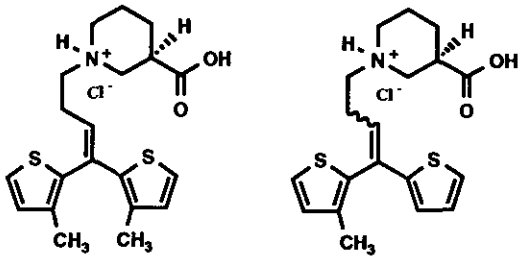
Epilepsy is a disorder characterized by recurrent spontaneous electrical discharges within the brain which are manifested by clinical seizures. Four million patients in the USA are afflicted with this ailment. Current targets for therapeutic intervention include blocking of receptors of excitatory amino acids, modulating excitatory membrane ion channels and enhancing the neurotransmittory effect of γ-aminobutyric acid (GABA).[1,2]

Tiagabine **(I)**,[3] currently in phase III clinical trials, works by retarding the neuronal reuptake of GABA into the presynaptic terminal. Maintaining the extra cellular concentration of GABA leads to calming of excitatory synaptic currents thereby preventing seizures. The synthesis of several novel GABA uptake inhibitors, Tiagabine[4] and its 5-hydroxy human metabolite[5] have already been reported.

We now report the synthesis of desmethyltiagabine **(II)**. This and other regioisomers have been tested for clinical efficacy as part of a screening program for anti-convulsants.[4,6] This compound has a nipecotic acid residue linked by an aliphatic

† **This paper is dedicated to Professor A. R. Katritzky.**

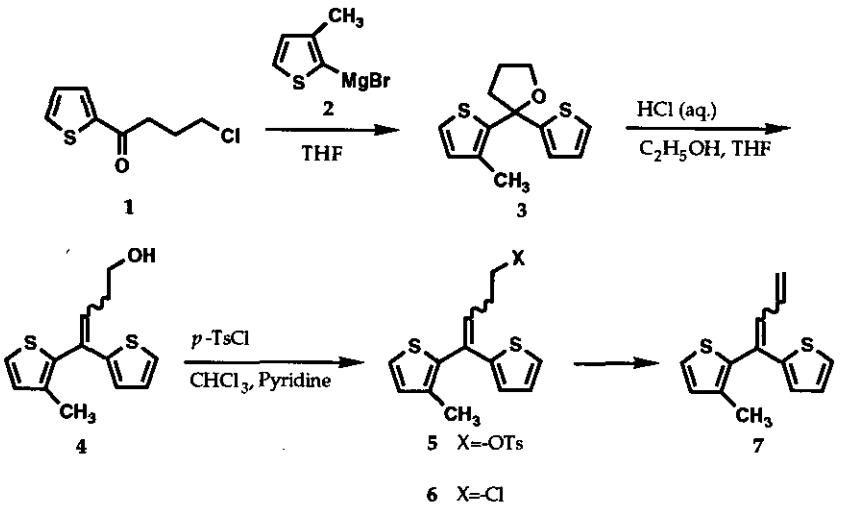
chain to a lipophilic anchor thus making the transport of the very hydrophilic nipecotic acid over the blood brain barrier possible.



I II

Retrosynthetic analysis of the target molecule would suggest a strategy of alkylating a nipecotic acid residue (protected as the ester derivative) with a 4-halo- or 4-tosyl-1,1-diaryl-1-butene. Such an approach is shown in Scheme 1.

Scheme 1



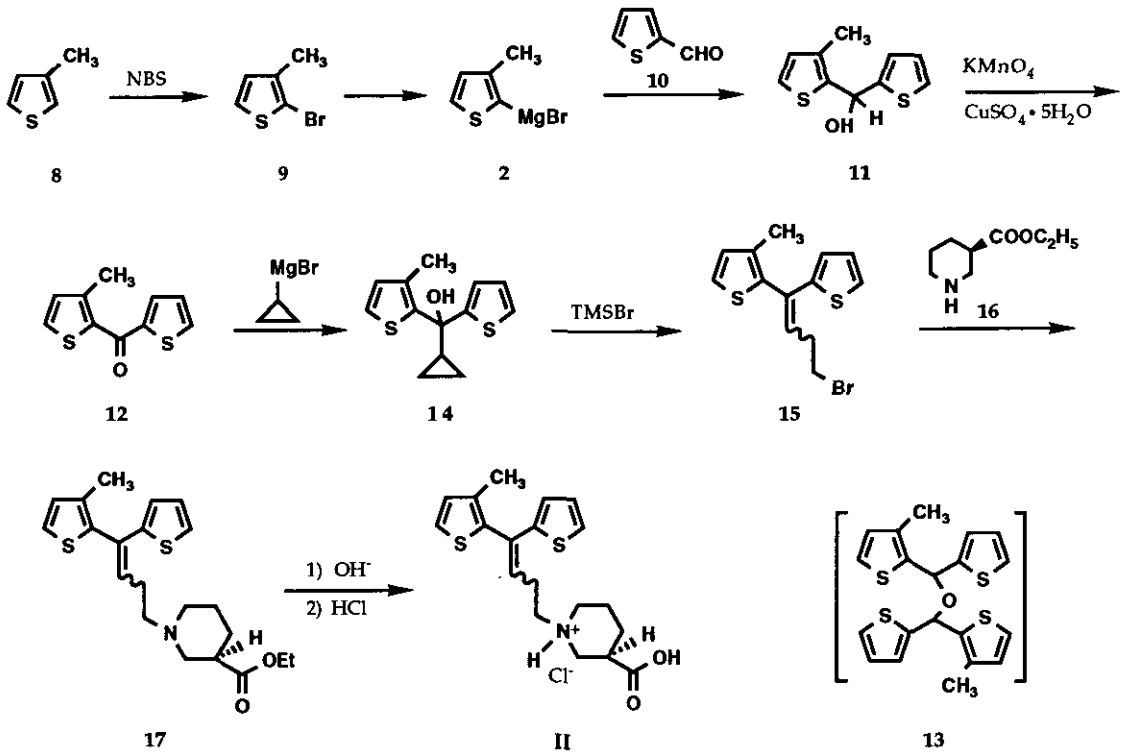
Reaction of 4-chloro-1-(2-thienyl)-1-butanone (**1**) with the Grignard reagent (**2**) provided the 2,2-disubstituted tetrahydrofuran (**3**) in good yield. The tetrahydrofuran ring could be opened with concomitant dehydration to provide the unsymmetrical butenol (**4**). Conversion to the *p*-toluene sulfonate derivative (**5**) with *p*-toluenesulfonyl chloride in pyridine/chloroform at 45 °C was a facile process; at reflux temperature, the corresponding chloride derivative (**6**) was obtained. These derivatives could be used to alkylate nipecotic acid esters but the yields were variable. The chloride

displacement in particular was not amenable to catalysis by crown ethers, DMAP etc. Elimination to the diene (7) was also a frequent problem.

We now report technically superior syntheses that were amenable to scale up. Scheme II depicts the first of two methods that appeared to be particularly successful.

Scheme II

(Method A)



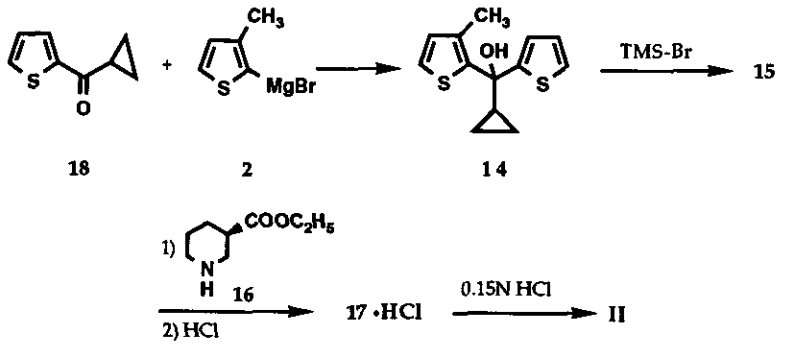
3-Methylthiophene (8) was brominated with *N*-bromosuccinimide by standard procedures[7] to yield 2-bromo-3-methylthiophene (9). No product arising from the bromination of the methyl group was discernible. Grignard reagent (2) was prepared in high yield[7] and condensed with 2-formylthiophene (10) to yield the carbinol (11). This carbinol is unstable to storage and is readily converted to the corresponding ether dimer (13) after standing even at -10 °C or on contact with acids. The ether dimer (13) is a crystalline compound; it's structure was confirmed by nmr and mass spectra. The Grignard reagent was superior to the aryl lithium reagent; with the latter, more isomeric products were

obtained. Carbinol (**11**) was oxidized with a mixture of potassium permanganate and copper sulfate pentahydrate to the ketone (**12**).[8] The reaction was slow and necessitated the addition of fresh portions of the reagent after 24 hour periods. A small amount of (**13**) was formed in this reaction. Oxidation with numerous other reagents such as MnO_2, pyridinium chlorochromate on alumina, or oxidation under phase transfer conditions yielded the ketone in much lower yields which were difficult to reproduce. It is useful to note that the ketone (**12**) could not be directly prepared by reaction of the Grignard reagent (**2**) with 2-cyanothiophene or the acid chloride of thiophene-2-carboxylic acid.[9] The carbonyl carbon of the dithienyl ketone (**12**) was refractory to attack by Grignard reagents designed to introduce the straight chain 3-carbon fragment. Reaction with cyclopropyl magnesium bromide furnished the carbinol (**14**) in high yields.[10] The cyclopropyl ring was opened with simultaneous dehydration and bromination with hydrobromic acid in acetic acid or with bromotrimethylsilane to yield the 4-bromo-1,1-diaryl-1-butene (**15**).[11]

Ethyl R-(-)-piperidine-3-carboxylate was resolved by literature procedures[12] to furnish the R-enantiomer as the L-(+)-tartrate. Conversion to the free base (**16**) was followed by condensation with (**15**) in acetone to yield (**17**). Hydrolysis of the ester residue with base followed by extraction and acidic workup yielded the hydrochloride salt of desmethyl-tiagabine(**II**). It is important to note the crystallization of the product as a methylene chloride solvate. The material revealed a slow loss of methylene chloride on standing, and was shown to be a 90:10 mixture of the Z and E isomers respectively by nmr.

Scheme III

(Method B)



Further improvements in the synthesis are shown in Scheme III (Method B). Cyclopropyl thien-2-yl ketone (**18**), available commercially, was subjected to a Grignard reaction with (**2**) to yield the carbinol (**14**) in excellent yield.

Bromotrimethyl- silane mediated opening of the cyclopropyl ring led to the 4-bromo derivative **(15)**. Condensation with ethyl R-(-)-piperidine-3-carboxylate **(16)** was conducted in isopropyl acetate as solvent with anhydrous lithium carbonate as the base. The transformation was cleaner and did not provide any of the diene **(7)** arising from elimination of hydrogen bromide. The alkylation of the nipecotate residue could also be directly effected with a mixture of tartrate salt of **(16)**, lithium carbonate and isopropyl acetate. The yields were however, marginally lower. Compound **(17)** was readily isolated as the hydrochloride; isopropyl acetate was superior to all other solvents used in this reaction.
Acid catalyzed hydrolysis with aqueous hydrochloric acid was a facile process; the hydrochloride salt of the product could be crystallized out of the same solution. 0.15N hydrochloric acid was found to be optimally effective in cleaving the ester without racemizing the chiral center. In conclusion, the methods developed here are general ones that can be adapted to the synthesis of several analogues of Tiagabine.

EXPERIMENTAL SECTION

General Procedures. ^{1}H and ^{13}C Nmr spectra were obtained on a Bruker 200 MHz or General Electric QE300 MHz nmr spectrometer and are reported in parts per million (ppm) down field from tetramethylsilane (TMS). Infrared spectra were recorded on a Nicolet 5-SXC FT-IR spectrophotometer using potassium bromide pellets or nujol mull films. Data are reported in wave numbers (cm^{-1}). Mass spectra were obtained by Desorption Chemical Ionization (DCI) method on Finnigan MAT95 or SSQ700 systems. Microanalysis was performed with a Carlo Erba Elemental Analyzer. The reactions were monitored by thin layer chromatography (tlc) using silica gel $60F_{254}$ on Merck 0.25mm plates and/or high performance liquid chromatography using Shimadzu LC-6A with Waters C-18 or Merck-Hitachi equipped with 3.9 mm x 30 cm Microbondapack column; 50/50 0.05M citric acid / CH_3CN as eluent, 2.0 ml/min flow, and a Shimadzu spectrophotometric detector operating at 254 nm. Tetrahydrofuran (THF) and dichloromethane were dried over 4 Å molecular sieves. 2-Bromo-3-methylthiophene was purchased from the Shell Chemical Co.; all other chemicals were purchased from the Aldrich Chemical Co.

Method A:

3-Methylthien-2-yl(thien-2-yl)methanol(11). Magnesium turnings (15.2 g, 0.625 mol) were covered with dry THF (30 ml). A crystal of iodine was added, followed by 2-bromo-3-methylthiophene **(9)** (4.4 g, 0.025 mol). The Grignard reaction was initiated by heating to reflux and continued by dropwise addition of 2-bromo-3-methylthiophene **(9)** (84.1

g, 0.475 mol) in dry THF (570 ml). When addition was completed, the reaction mixture was maintained at reflux temperature for 1 h and then cooled to 5 °C. A solution of freshly distilled 2-formylthiophene (**10**) (50.4 g, 0.45 mol) in dry THF (50 ml) was added, dropwise, keeping the temperature below 15 °C. Stirring was continued for 1 h at room temperature. The Grignard reaction mixture was carefully added, with vigorous stirring, to a solution of saturated ammonium chloride (500 ml) in ice water (500 ml). Excess magnesium turnings were removed by filtration of the aqueous solution. The aqueous layer was extracted with dichloromethane (2x300 ml). The combined organic phases were washed with water (2x100 ml) and brine (50 ml). The organic layer was dried over magnesium sulfate for 30 min. After filtration, the solvent was removed in vacuo to furnish an oil (95.6 g, 91%). Hplc analysis revealed a purity of 93%; this was sufficient for further reaction. ^{1}H Nmr ($CDCl_3$, 200 MHz): 2.18 (3H, s), 2.90 (1H, s), 6.22 (1H, s), 6.79 (1H, d, J=4.5 Hz), 6.92 (2H, m), 7.15 (1H, d, J=4.5 Hz), 7.22 (1H, m). For ether dimer (**13**), ^{1}H Nmr ($CDCl_3$, 200 MHz): 2.05 (3H, s), 2.09 (3H, s), 5.95 (2H, s), 6.80 (3H, m), 6.92 (3H, m), 7.25 (4H, m); ms (m/z): 402 (M^+).

3-Methylthien-2-yl(thien-2-yl)methanone(12). To a solution of **(11)** (88.8 g, 0.423 mol) in benzene (1000 ml), finely ground potassium permanganate (133.7 g, 0.846 mol) and finely ground copper sulfate pentahydrate (53.0 g, 0.212 mol) were added. After the mixture had been mechanically stirred for 24 h at 70 °C, 40 % conversion to the ketone was observed by hplc analysis. The mixture was filtered. The filtrate was treated with fresh portions of potassium permanganate (133.7 g, 0.846 mol) and copper sulfate pentahydrate (53.0 g, 0.212 mol) and the reaction continued at 70 °C for an additional 24 h. Hplc showed 70% conversion to the ketone. The mixture was filtered again and treated with fresh aliquots of potassium permanganate (133.7 g, 0.846 mol) and copper sulfate pentahydrate (53.0 g, 0.212 mol) at 70 °C for another 24 h. After filtration, the organic phase was washed with water (2x100 ml), 5% aqueous sodium bicarbonate (50 ml), water (100 ml) and brine (50 ml). After drying over magnesium sulfate, the solvent was removed in vacuo to provide an oil (75.8 g, 86%). The product with an hplc assay of 91% was used without further purification. ^{1}H Nmr ($CDCl_3$, 200 MHz): 2.47 (3H, s), 6.90 (1H, d, J=4.5 Hz), 7.04 (1H, dd, J=5.0 Hz, J=0.5 Hz), 7.35 (1H, d, J=4.5 Hz), 7.56 (1H, dd, J=5.0 Hz, J=0.5 Hz), 7.80 (1H,dd, J=5.0 Hz, J=0.5 Hz), ms (m/z): 208 ((M^+- 1) / M^+ / (M^+ + 2) / (M^+ + 4) 12:14:5:2), gc analysis also revealed 3-5% of the ether dimer (**13**).

Cyclopropyl(3-methylthien-2-yl)(thien-2-yl)methanol(14). Magnesium turnings (16.1 g, 0.664 mol) were covered with dry THF (30 ml). A crystal of iodine was added together with bromocyclopropane (3.0 g, 0.025 mol). The Grignard

reaction was initiated by heating to reflux and the reaction was continued by dropwise addition of bromocyclopropane (57.5 g, 0.475 mol) in dry THF (450 ml). When addition was complete the reaction mixture was kept at reflux temperature for 1 h and then cooled to 15 °C. A solution of **(12)** (69.0 g, 0.332 mol) in dry THF (40 ml) was added slowly, keeping the temperature below 25 °C. The mixture was stirred overnight at room temperature. A solution of saturated ammonium chloride (800 ml) in ice water (800 ml)was prepared; the Grignard reaction mixture was carefully added with good stirring. Excess magnesium turnings were removed by filtration and the aqueous solution was extracted with dichloromethane (2x400 ml). The combined organic phases were washed with water (2x200 ml) and brine (100 ml). Drying (magnesium sulfate) and evaporation of the solvents in vacuo yielded (69.1 g, 83%) a viscous, tea-colored oil. Hplc assay 87%. This material was used without further purification. ^{1}H Nmr ($CDCl_3$, 200 MHz): 0.60 (4H, m), 1.75 (1H, m), 1.97 (3H, s), 2.30 (1H, s), 6.80 (1H, d, J=4.5 Hz), 6.91 (2H, m), 7.10 (1H, d, J=4.5 Hz), 7.25 (1H, dd, J=5.0 Hz, J=2.0 Hz), ms (m/z): 250 (M^+ / (M^+ + 1) / (M^+ + 2) 33:5:3).

E/Z-4-Bromo-1-(3-methylthien-2-yl)-1-(thien-2-yl)-1-butene(15). To a solution of **(14)** (69.0 g, 0.28 mol) in anhydrous dichloromethane (500 ml), under a nitrogen atmosphere, was added dropwise a solution of bromotrimethylsilane (46.5 g, 0.3 mol) in anhydrous dichloromethane (50 ml). The temperature was maintained below 10 °C. When addition was complete, the solution was allowed to warm to room temperature, stirred for an additional 15 min and water (200 ml) was added carefully. The solution was treated with activated charcoal (10.0 g) for 30 min and filtered through filter aid. The organic phase was separated and washed with 5% aqueous sodium bicarbonate (100 ml) and water (100 ml). After drying over magnesium sulfate and filtration, the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (600 g, 40-63 µm, n-heptane) to give the title compound (65.9 g, 77%) as an oil. Hplc assay 98%. ^{1}H Nmr ($CDCl_3$, 200 MHz), major isomer: 2.07 (3H, s), 2.60 (2H, q, J=7.0 Hz), 3.39 (2H, t, J=7.0 Hz), 6.32 (1H, t, J=7.0 Hz), 6.69 (1H, dd, J=4.5 Hz, J=1.5 Hz), 6.89 (2H, m), 7.16 (1H, dd, J=4.5 Hz, J=1.5 Hz), 7.27 (1H, d, J=4.5 Hz).

E/Z-(R)-1-[4-(3-methylthien-2-yl)-4-(thien-2-yl)-3-butenyl]-3-piperidinecarboxylic acid hydrochloride(II). A suspension of **(15)** (64.0 g, 0.21 mol), ethyl R-(-)-piperidine-3-carboxylate-L-(+)-tartrate (87.0 g, 0.28 mol), potassium carbonate (60.0 g, 0.43 mol) and potassium iodide (2.5 g, 10 mmol) in acetone (1000 ml) was stirred at room temperature for 48 h. The reaction mixture was filtered over a pad of filter aid and the solvent from the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica gel (500 g, 40-63 µm, n-heptane/ethyl acetate gradient 20/1 to 1/1) to give the ethyl carboxylate **(17)** (50.5 g) as an oil. This was dissolved in ethanol (100 ml) and 0.5 M

sodium hydroxide (400 ml) was added. The mixture was refluxed for 45 min whereupon a clear solution was obtained. Ethanol was removed from the solution by evaporation under reduced pressure and the aqueous solution was acidified (pH=1.5) with 6N hydrochloric acid. Extraction of the aqueous solution with dichloromethane (200 ml), drying over magnesium sulfate, filtration and cooling of the filtrate provided the title compound as a crystalline hemi solvate with dichloromethane. The crystals were washed with diethylether (400 ml) and dried. Yield: 51.4 g (52% calc. from (15)). The substance consists of a E/Z mixture in a 1/9 ratio according to nmr. ^{1}H Nmr (DMSO-d_6, 200 MHz), major isomer: 2.03 (3H, s), 5.75 (1.6H, s (CH_2Cl_2)), 6.34 (1H, t, J=7.0 Hz), 6.82 (1H, d, J=4.5 Hz), 6.95-7.05 (2H, m), 7.45 (1H, d, J=4.5 Hz), 7.57 (1H, d, J=4.5 Hz), ms (m/z): 361 (M^+), dsc: Onset of melting at 179.6 °C.

During the storage the substance loses dichloromethane as a function of time. Anal. Calcd for $C_{19}H_{24}NO_2ClS_2$ C, 51.25; H, 5.52; N, 3.03; S, 13.83. Found C, 51.57; H, 5.74; N, 3.42;, S, 13.85.

Method B:

Cyclopropyl(3-methylthien-2-yl)(thien-2-yl)methanol(14). A heterogeneous mixture of magnesium turnings (2.1 g, 84.7 mmol), iodine crystals (50.0 mg) and THF (134 ml) was refluxed for 15 min under nitrogen and a mixture of 2-bromo-3-methylthiophene (9) (15.0 g, 84.7 mmol) and THF (18 ml) was slowly added via a pressure equalizing addition funnel to maintain a steady exothermic reaction. The reaction was completed after 2 h of reflux. Cyclopropyl thien-2-yl ketone (18) (10.7 g, 70.6 mmol) in THF (10 ml) was added dropwise over a period of 30 min. The reaction was completed after 2 h of reflux. The mixture was cooled to room temperature. Saturated ammonium chloride solution (135 ml) was added and stirring continued for 15 min. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 75 ml), the combined organic layers were dried over magnesium sulfate. Evaporation of the solvent(s) in vacuo gave the title compound (18.6 g, 88%) as a clear yellow oil: Tlc(20% ethyl acetate in hexane) R_f 0.47; ir (film) υ_{max}: 3550, 3000, 2900, 1470, 1440, 1400, 1380, 1360, 1280, 1050, 700 cm^{-1}; ^{13}C nmr (DMSO-d_6) δ: 15, 23, 72, 122, 124, 124.5, 126, 131.5; ms m/z (DCI/NH_3): 233 $(M + H - H_2O)^+$, 250 $(M + NH_4 - H_2O)^+$.

E/Z-4-Bromo-1-(3-methylthien-2-yl)-1-(thien-2-yl)-1-butene(15). To a solution of (14) (9.1 g, 36.2 mmol) in methylene chloride (120 ml) was added dropwise, bromotrimethylsilane (13.9 g, 90.5 mmol) in methylene chloride (60 ml). The mixture was stirred under nitrogen at 25 °C for 30 min. A catalytic amount of *p*-toluenesulfonic acid was added to the mixture. Evaporation of the solvent under reduced pressure gave the product (10.3 g, 86%) as a viscous, brown oil:

Tlc(20% ethyl acetate in hexane) R_f 0.62 ; ir (film) υ_{max}: 3100, 2900, 1600, 1430, 1250, 850, 700 cm^{-1}; ^{13}C nmr (DMSO-d_6) δ: 14, 32.5, 33, 124.5, 125.5, 128, 129, 129.5, 132.5, 135; ms m/z (DCI/NH_3): 313 $(M + H)^+$, 330 $(M + NH_4)^+$.

Ethyl R-(-)-piperidine-3-carboxylate(16). A suspension of ethyl R-(-)-piperidine-3-carboxylate-L-tartrate (30.0 g, 97.6 mmol) and ethyl acetate (300 ml) was stirred at 4 °C and 3.5N NaOH solution (51 ml) was added dropwise. The mixture was stirred for 30 min. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (150 ml). The combined organic layers were washed with H_2O (2 x 30 ml), dried over magnesium sulfate and concentrated under reduced pressure to yield a pale yellow oil (11.0 g, 72%).

Ethyl E/Z-(R)-1-[4-(3-methylthien-2-yl)-4-(thien-2-yl)-3-butenyl]-3-piperidinecarboxylate hydrochloride(17·HCl). A 250 ml 3 necked round bottomed flask equipped with a stirrer, condenser and a Dean Stark apparatus was charged with **15** (10.3 g, 31.0 mmol) and isopropyl acetate (144 ml). Ethanol-water mixture (25 ml) was distilled under nitrogen. The mixture was cooled to 25 °C; ethyl R-(-)-piperidine-3-carboxylate **(16)** (5.9 g, 37.2 mmol) and lithium carbonate (11.5 g, 155.0 mmol) were added in one portion. The mixture was refluxed for 96 h. The reaction mixture was filtered; HCl(gas) (1.5 g) was bubbled into the filtrate. Evaporation of solvents furnished a viscous brown oil. Trituration with ethyl acetate yielded a solid. The product was washed with cold ethyl acetate and dried in vacuo to yield a brown solid. (4.5 g, 34%): Tlc (20% THF in heptane) R_f 0.07; ir (KBr) υ_{max}: 3440, 2900, 1750, 1620, 1210 cm^{-1}; ^{13}C nmr (DMSO-d_6) δ: 14, 21, 25, 51, 55, 61, 124.5, 125.5, 126.5, 127.5, 130, 171.5; ms m/z (DCI/NH_3): 390 $(M + H)^+$.

E/Z-(R)-1-[4-(3-methylthien-2-yl)-4-(thien-2-yl)-3-butenyl]-3-piperidinecarboxylic acid hydrochloride(II). A 250 ml 3 necked round bottomed flask equipped with a magnetic stirrer, condenser and a Dean Stark apparatus was charged with **(17·HCl)** (4.0 g, 9.39 mmol) and 0.15 N HCl (60 ml). A ethanol-water mixture (20 ml) was distilled under nitrogen. The reaction was complete after 11 h of reflux. The mixture was cooled to 50 °C, toluene (10 ml) was added and the mixture was stirred for 15 min. The aqueous layer was separated, 3 drops of concentrated HCl were added and the mixture was stirred in an ice bath for 1 h. The product separated as an oil. The aqueous layer was decanted. The oil was dissolved in methanol (25 ml). The solution was evaporated to dryness. The viscous, brown oil was kept in a refrigerator for 24 h whereupon the product crystallized. The product was washed with cold methanol. Yield (1.6 g, 42%): Tlc (70:20:5:5 / EtOAc:MeOH:H_2O:HOAc) R_f 0.61; ir (KBr) υ_{max}: 3420, 2920, 2600, 1720, 1620, 1450, 1200, 700;

^{13}H nmr (DMSO-d_6) δ: 14, 21, 24, 51, 55, 124.5, 125.5, 126.5, 127.5, 130, 173; ms m/z (DCI/NH_3): 362 $(M + H)^+$. The substance consists of a E/Z mixture in a 3/97 ratio according to hplc.

REFERENCES

1. P. Krogsgaard-Larsen, O. M. Larsson, and A. Schousboe, 'GABA Mechanism in Epilepsy,' Wiley-Liss, Inc., 1991, pp. 165-187.
2. J. P. Chambon, V. N'Goka, J. M. Linget, G. Schlewer, and C. G. Wermuth, *J. Med. Chem.*, 1991, **34**, 2547.
3. K. E. Andersen, P. H. Andersen, C. Braestrup, K. Frederiksen, J. A. Jansen, L. J. S. Knutsen, A. Mortensen, E. B. Nielsen, U. Sonnewald, and P. D. Suzdak, *J. Neurochem.*, 1990, **54**, 639.
4. K. E. Andersen, C. Braestrup, F. C. Grønvald, A. S. Jørgensen, L. J. S. Knutsen, E. B. Nielsen, U. Sonnewald, P. O. Sørensen, and P. D. Suzdak, *J. Med. Chem.*,1993, **36**, 1716.
5. K. E. Andersen, M. Begtrup, M. S. Chorghade, J. Lau, E. C. Lee, B. F. Lundt, H. Petersen, P. O. Sørensen, and H. Thøgersen, *Tetrahedron*, submitted for publication.
6. C. Braestrup and F. C. Grønwald, '*N*-(Butenyl substituted)azaheterocyclic carboxylic acids,' U.S. Patent 5,010,090 (*Chem Abst.*, 1991, **107**, 11549k).
7. E. T. Harper, R. M. Kellog, A. P. Schaap, and H. Wynberg, *J. Org. Chem.*, 1968, **33**, 2902.
8. C. Lee and S. M. Menger, *J. Org. Chem.*, 1979, **44**, 3446.
9. T. Fujisawa, T. Kawara, K. Sakata, and T. Sato, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1052.
10. R. Giegan, M. Julia, and S. Julia, *Bull. Soc. Chim. Fr.*, 1960, 1072.
11. G. Balme, G. Fournet, and J. Gore, *Tetrahedron Lett.*, 1986, **27**, 1907.
12. i) A. M. Akkerman, D. K. DeJongh, and H. Veldstra, *Recl. Trav. Chim. Pays-Bas*, 1951, **70**, 899. ii) G. Bettoni, E. Duranti, and V. Tortorella, *Gazz. Chim. Ital.*, 1972, **102**, 189. iii) P. Magnus and L. Thurston, *J. Org. Chem.*, 1991, **56**, 1166. iv) Dr. Gary Callen (Abbott Laboratories) personal communication; formic acid / isopropyl acetate mixture was used as solvent.

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