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TOTAL SYNTHESIS OF AN OPTICALLY ACTIVE 8-CARBA-PHYSOSTIGMINE ANALOG: A POTENT ACETYLCHOLINESTERASE INHIBITOR

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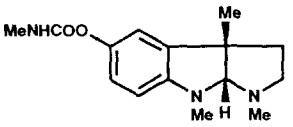
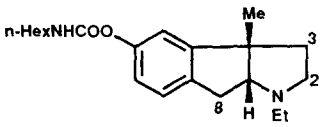
Abstract: Syntheses of 8-carba-physostigmine enantiomers **2a** and **2b** via optically active intermediates **9a** and **9b** are described. The key synthetic intermediate **9** was prepared via a [2 + 2] cycloaddition of indene **4** and dichloroketene, followed by Beckmann rearrrangement, reduction and resolution.

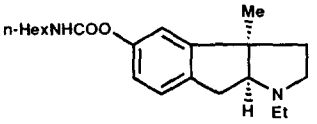
(−)-Physostigmine (**1**) is a naturally occuring acetylcholinesterase inhibitor which has been evaluated extensively in patients with Alzheimer's disease[1,2]. The short half-life and high toxicity of physostigmine may account for the inconsistent efficacy shown in clinical studies[3]. In an attempt to decrease the potential for both side effects and metabolic and chemical lability, we sought to replace the central NMe group of the physostigmine nucleus with a methylene to provide the closely related 8-carba-physostigmine analog **2**. We report herein the total synthesis of the optically pure 1,2,3,3a,8,8a-hexahydro-1-ethyl-3a-methyl-5-hexylcarbamoyloxy-indeno[2,1-b]pyrrole enantiomers, **2a** and **2b**.



(-)
1, physostigmine



(-)
2a



(+)
2b

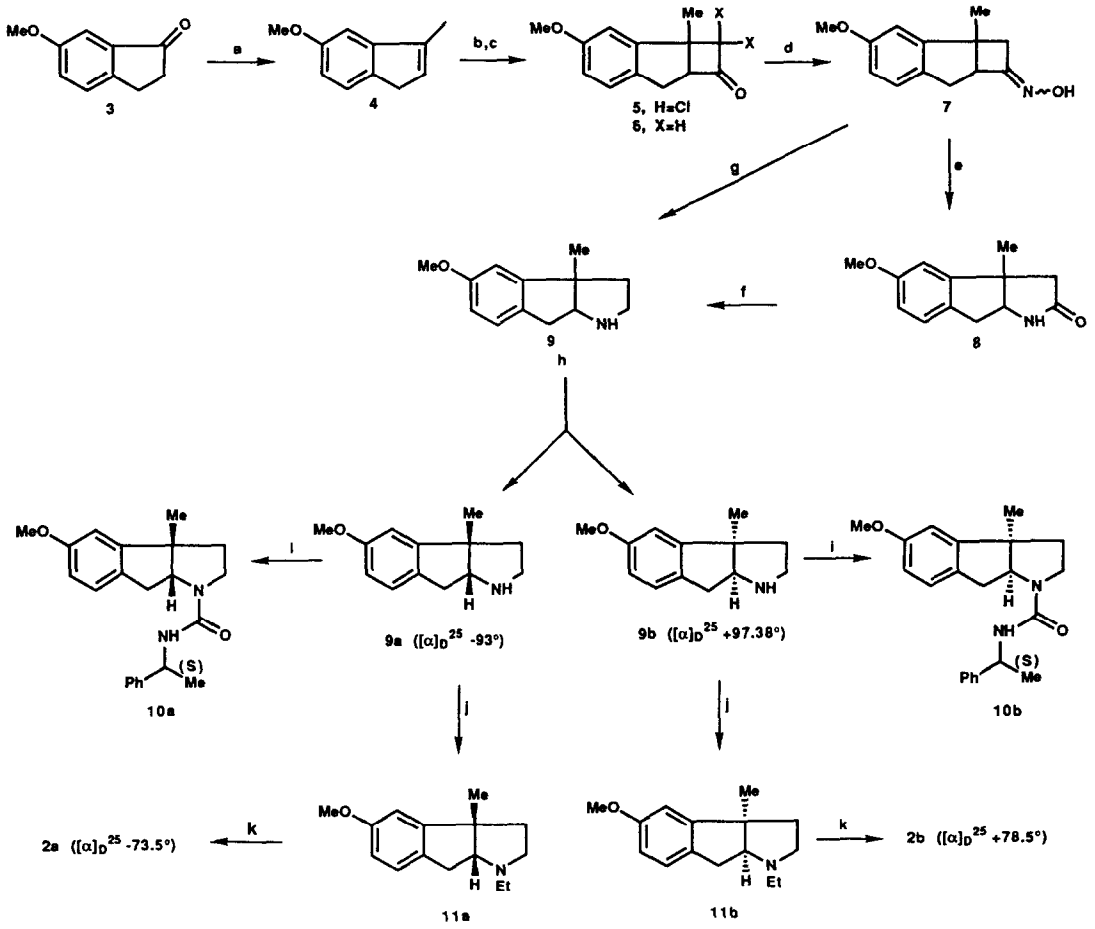
Our synthesis proceeds as illustrated in Scheme I by way of the key synthetic intermediate **9**, which can be resolved into its pure enantiomers. A solution of 6-methoxy-1-indanone (**3**) was added[4] dropwise to a solution of MeMgBr in dry THF at 0°C to give indene **4** in 83% yield after silica column chromatography. [2 + 2] Cycloaddition of indene **4** and dichloroketene[5], generated from trichloroacetylchloride, $POCl_3$, and activated Zn in refluxing anhydrous ether afforded dichlorocyclobutanone derivative **5**, which was subsequently dechlorinated without purification. Dehalogenation of **5** with activated Zn and NH_4Cl in MeOH at 40-45°C gave cyclobutanone **6** in 73% overall yield as white crystals, mp 71-72°C, after silica gel column chromatography. Compounds **5** and **6** are thermolabile; e.g., when the reduction of **5** is conducted with Zn in refluxing acetic acid, indene **4** and several unidentified products are observed. Treatment of **6** with $NH_2OH.HCl$ and sodium acetate in MeOH afforded a 1:1 mixture of E and Z isomers of oxime **7** as evidenced by ^{13}C NMR. Beckmann rearrangement[6] of the oxime mixture **7** by the use of several different reagents (e.g., $SOCl_2$,

H_2SO_4, TsCl/THF-H_2O-NaOH, TsCl/NEt_3, MsCl/NEt_3, etc.) in each case led to a mixture of lactam regioisomers as well as other unidentified products. The best conditions found for conversion to the desired regioisomer **8** were the use of 1.0 eq each of NaH and tosyl chloride in CH_2Cl_2 at 0°C, followed by stirring at r.t. for 15 hr. The desired lactam **8** was produced as a white solid, mp 197-198°C, in 60% yield after triturating the crude residue with ether. Reduction of **8** with $LiAlH_4$ gave amine **9** as an oil in quantitative yield. Compound **9** was also generated directly by reaction of oxime **7** with 5 eq. of DIBAL[7] at 0°C; however, column purification was required and compound **9** was isolated in only 30% yield. Resolution[8] of **9** was achieved by several recrystallizations of the corresponding di-p-toluoyl-L-tartaric acid salts. Base treatment of each salt provided enantiomers **9a** and **9b** as oils with >97% ee. Both enantiomers were converted to the corresponding N_1 carbamate diastereomers, **10a** and **10b**, by reaction with (S)-1-(phenyl)ethyl isocyanate, and the optical purity was determined by ^1H NMR. The absolute configuration of **9b** at C_{3a} and C_{8a} was determined by X-ray crystal structure analysis of the corresponding salt and found to be the same as that of unnatural (+)-physostigmine.

Both **9a** and **9b** were independently converted to the final products **2a** and **2b**. N-Ethyl derivative **11** was obtained in quantitative overall yield by acetylation ($Ac_2O/NEt_3/CH_2Cl_2$), followed by reduction with 3 eq. BH_3.DMS. Demethylation followed by reaction with hexyl isocyanate afforded (−) and (+)-8-carba-physostigmine analogs **2a** and **2b**[9] as oils in 90% overall yield. The corresponding di-p-toluoyl-L-tartrate salts were prepared as a form suitable for biological studies. The (−) isomer **2a** (IC_{50} of 20 ± 7 nM), having the same absolute configuration as that of physostigmine (IC_{50} of 128 ± 14 nM), is about 12 fold more potent than the (+) isomer **2b** (IC_{50} of 233 ± 22 nM) in the acetylcholinesterase inhibition assay.[10]

In summary, replacement of the central NMe of the physostigmine nucleus by a methylene group affords a more potent, longer half-life and less toxic acetylcholinesterase inhibitor[11]. It is reported[12] that (−)-physostigmine is more potent than (+)-physostigmine, which is similar to our result in which compound **2a**, which possesses the same absolute configuration as that of physostigmine, is more potent than **2b**.

Scheme I



a) i, MeMgBr/THF, 0°C (1 hr), rt (0.5 hr); ii, HCl (aq.); b) 1.05 eq. CCl_3COCl, 1.1 eq. Zn, 1.05 eq. $POCl_3$/ether, reflux (4 hr), rt (15 hr); c) 5 eq. Zn, 5 eq. NH_4OH/MeOH, 40-45°C (15 hr); d) 1.5 eq. NH_2OHHCl, 1.6 eq. NaOAc/MeOH, rt (1 hr); e) NaH, 0°C (5 min), TsCl/CH_2Cl_2, 0°C (2 hr), rt (15 hr), 2N NaOH, extracted with CH_2Cl_2, trituated with ether; f) $LiAlH_4$/THF, reflux (5 hr); g) i, 5 eq. DIBAL, 0°C (2 hr); ii, NaF; h) i, di-p-toluoyl-L-tartaric acid, recrystallizations; ii, basified to pH 11, then extracted with $CHCl_3$; i) (S)-Ph(Me)CHNCO/CH_2Cl_2; j) i, Ac_2O, NEt_3, CH_2Cl_2; ii, 3 eq. BH_3 DMS/THF; k) i, 48% HBr, reflux (3 hr), evaporated, basified to pH 10, extracted with $CHCl_3$; ii, 0.1 eq. NaH, rt (30 min), 1.05 eq. hexyl isocyanate.

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References and Notes:

1. Davis, K.L.; Mohs, R.C. *Am. J. Psychiatry* **1982**, *139*, 1421.

2. Christie, J.E.; Shering, A.; Ferguson, J.; Glen, A.I. *Brit. J. Psychiat.* **1981**, *138*, 46.

3. Gibson, M.; Moore, T.; Smith, C.M.; Whelpton, R. *Lancet* **1985**, 695.

4. Reverse addition (in which Grignard reagent was added to a solution of 6-methoxy-1-indanone) led to incomplete reaction, perhaps due to deprotonation.

5. a) Krepski, L.R., Hassner, A. *J. Org Chem.* **1978**, *43*, 2879. b) Brady, W.T. *Tetrahedron* **1981**, *37*, 2949.

6 a) Oppolzer, W., Fehr, C.; Warneke, J. *Helv. Chim. Acta.* **1977**, *60*, 48. b) Maruoka, K., Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am Chem. Soc.* **1983**, *105*, 2831. c) P_2O_5-CH_3SO_3H or polyphosphoric acid gave the undesired regioisomer exclusively: Jeffs, P W.; Molina, G.; Cortese, N.A.; Hauck, P.R.; Wolfram, J. *J. Org. Chem.* **1982**, *47*, 3876.

7. Sasatani, S.; Miyazaki, T., Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4711

8. We were unable to resolve compound **9** with several different chiral acids (eg., mandelic acid and camphor sulfonic acid salts gave an oil, and tartaric acid salts of both isomers co-crystallized out and in a hydroscopic form). We were also unable to separate two diastereomers, generated from **9** and (S)-1-phenyl or (naphthyl)ethyl isocyanate.

9 ^{1}H NMR ($CDCl_3$, 300 MHz) of **2a** and **2b**: 0.86 (m, 3H), 1.08 (t, 3H), 1.2-1.4 (m, 9H), 1.4-1.6 (m, 2H), 1.85-2.15 (m, 2H), 2.2-2.4 (m, 2H), 2.7-3 16 (m, 5H), 3.2 (q, 2H), 5.1 (t, 1H, NH), 6.8-7.0 (m, 2H), 7.0 (d, 1H) ppm; ^{13}C NMR ($CDCl_3$, 300 MHz) 13.7, 14.0, 22.6, 26.4, 27.5, 29.8, 31.4, 35.4, 39.4, 41.2, 48.8, 53.0, 55.6, 77.2, 116.4, 120.0, 125.5, 137.6, 150.5, 153.1, 154.9 ppm.

10. Acetylcholinesterase activity was determined by the method described by Ellman (Ellman, G.L.; Courtney, D.K.; Andres, V., Jr ; Featherstone, R.M. *Biochem, Pharmacol.* **1961**, *7*, 88.). The assay solution consists of a 0.1 M sodium phosphate buffer, pH 8.0, with the addition of 100 μM tetraisopropylpyrophosphoramide, 100 μM dithiobisnitrobenzoic acid (DTNB), 0.02 units/ml AChE (Sigma Chemical Co. — from human erythrocytes), and 200 μM acetylthiocholine iodide. The final assay volume was 0.25 ml. Test compounds were added to the assay solution prior to enzyme addition, and a 20 min preincubation period was followed by addition of the test substrate. Changes in absorbance at 412 nM were recorded for 5 min for the control o. d. test solutions. The reaction rates were compared and the present inhibition due to the presence of test compounds was calculated.

11. Detailed biological data will be reported elsewhere.

12. Yu, Q.; Brossi, A. *Heterocycles* **1988**, *27*, 745.