Communications to the Editor

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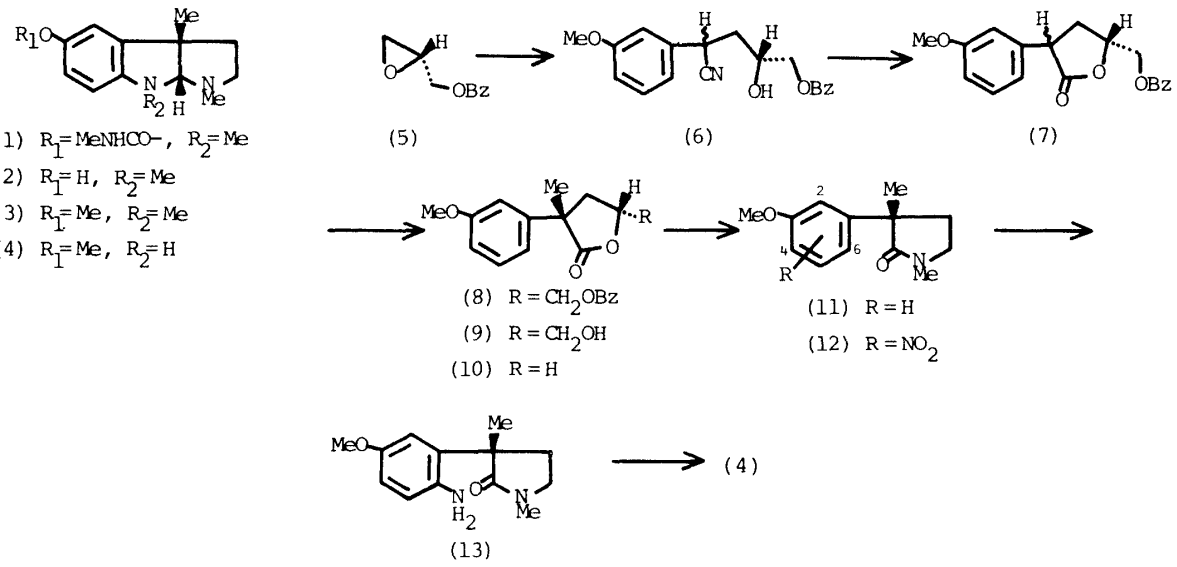
ENANTIOSELECTIVE SYNTHESIS OF (-)-PHYSOSTIGMINE

Seiichi Takano,* Emiko Goto, Michiyasu Hirama, and Kunio Ogasawara
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

The first enantioselective synthesis of (-)-physostigmine (1), a potent cholinesterase-inhibiting alkaloid from Physostigma venenosum Balf., has been accomplished using (S)-(-)-benzyl 2,3-epoxypropyl ether (5) as a chiral synthon.

KEYWORDS———chiral synthesis; chiral synthon; (-)-physostigmine; (-)-eseroline; (-)-esermethole; cholinesterase inhibitor

(-)-Physostigmine (1),[1] a major alkaloid of the fruit (Calabar bean) of Physostigma venenosum Balf., is a long-established compound and is being currently used as a cholinesterase inhibitor. Because of the medicinal importance of the alkaloid, a number of syntheses[2] have been reported since the first one by Julian and Pikl[3] in 1935. However, we know of no report to date of an enantioselective approach to this alkaloid. We report here the first enantioselective synthesis of (-)-physostigmine (1) in satisfactory optical purity using a readily accessible chiral synthon, (S)-(-)-benzyl 2,3-epoxypropyl ether (5).



Scheme

(S)-(-)-Benzyl 2,3-epoxypropyl ether (5),[4,5,6] obtained from (D)-mannitol-1,2:5,6-diacetonide, was treated with the carbanion prepared in situ from 3-methoxybenzyl cyanide and lithium diisopropylamide (LDA) in tetrahydrofuran (THF) (-78°C room temperature) to give the cyano-alcohol (6) as a mixture of epimers. Hydrolysis of the crude mixture with hot ethanolic potassium hydroxide (7h) afforded the γ-lactone (7)[7] as a mixture of epimers after acid work-up (dil. HCl). Overall yield of (7) from (5) was 63%. Alkylation of the mixture (7) with methyl iodide in the presence of LDA in THF (-78°C room temperature) led to a stereoselective introduction of the methyl group from the less hindered face of the molecule to give 80% yield of the desired compound (8), $[\alpha]_D$ -42.1° (c=1.34, MeOH), along with 11% yield of the undesired epimer after separation employing silica-gel column chromatography. The benzyl group of (8) was removed by hydrogenolysis under an atomospheric pressure of hydrogen in the presence of 10% palladized charcoal in methanol containing a trace of perchloric acid to give the hydroxy-lactone (9) in quantitative yield. Upon sequential one-pot treatment, viz., hydrolysis with methanolic potassium hydroxide, oxidative cleavage with sodium periodate, and reduction with sodium borohydride, followed by acid work-up (dil. HCl), the compound (9) furnished the lactone (10), $[\alpha]_D$ -72.1° (c=1.01, MeOH) in 96% overall yield. Condensation of the lactone (10) with 40% aqueous methylamine at 180°C using a sealed tube (12h) gave the lactam (11), $[\alpha]_D$ -79.9° (c=1.22, MeOH) in 82% yield.

Although we were unable to find optimal conditions for the regioselective introduction of the nitrogen group on the aromatic ring, the desired compound (13) was obtained from (11) in a pure state in 27% overall yield. Thus, treatment of (11) with cupric nitrate trihydrate in acetic anhydride[8] (5-10°C, 30min) furnished a mixture of three regio-isomeric compounds from which 19% of the 4-nitro isomer (12:4-NO_2) and 72% of a mixture of the 2- and 6-isomers were separated through silica-gel column chromatography. The latter mixture was then hydrogenated under an atomospheric pressure of hydrogen in the presence of platinum catalyst in methanol to give a mixture of the amino derivatives which could be separated by using a silica-gel column to give the desired 6-amino-lactam (13) in 38% yield accompanied by 30% yield of the unnecessary 2-amino derivative. Reduction of the lactam (13) with a 1.5 equivalent molar excess of lithium aluminum hydride in THF at room temperature (1h) afforded the tricyclic aminal (4), mp 68-69°C, $[\alpha]_D$ -101° (c=0.388, $CHCl_3$), in 60% yield. Reductive N-methylation with formalin and sodium cyanoborohydride in acidic media (pH 5-6) at room temperature gave (-)-esermethole (3),[9] $[\alpha]_D$ -123° (c=0.412, benzene) in 44% yield. Its spectroscopic data (IR, ^{1}H-NMR, MS) as well as chromatographic behavior (tlc on silica-gel and alumina plates) were completely identical with those of an authentic material (3), $[\alpha]_D$ -129° (c=0.326, benzene), prepared from a natural physostigmine (1).[10] O-Demethylation of (3) with boron tribromide in methylene chloride at -78 ∿ 10°C afforded (-)-eseroline (2), mp 175-178°C, $[\alpha]_D$ -82.1° (c=0.524, $CHCl_3$) (authentic (-)-eseroline (2),[10] mp 178-182°C, $[\alpha]_D$ -88.7° (c=0.284, $CHCl_3$) (mixed mp 178-182°C) in 76% yield. Since (-)-eseroline (2) has been nicely converted into (-)-physostigmine (1) in one step,[11] this is the first enantioselective synthesis.

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