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Enantioselective Synthesis of (R)- and (S)-5-Dimethylaminomethyl-4,5-dihydro-2(3*H*)-furanone Methobromide - Constrained Analogues of Acetylcholine

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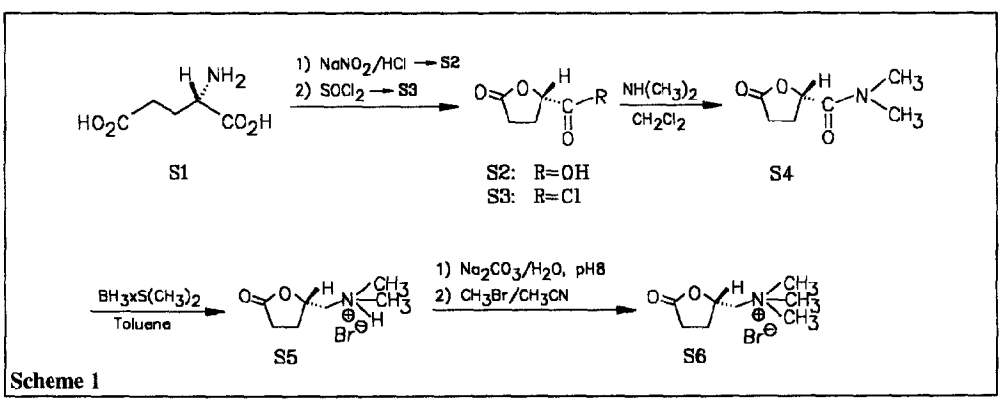
Abstract: **S6** and **R6** represent constrained analogues of acetylcholine. Two effective routes to synthesize the enantiopure title compounds starting from either D- or L- glutamic acid are reported.

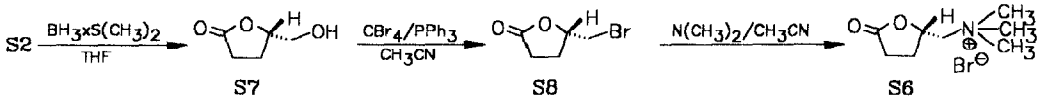
Rothstein et al. prepared racemic 5-dimethylaminomethyl-4,5-dihydro-2(3*H*)-furanone methobromide (**6**)[1], where the ester moiety of acetylcholine is configurationally fixed by lactonization. Pharmacological experiments showed cholinergic activity for this compound, but lower than for acetylcholine[2]. Moreover, nmr studies suggest, that acetylcholine adopts a lactone-like conformation when interacting with a nicotinic or muscarinic receptor[3]. For these reasons the pharmacological effects of **R6** and **S6** are of great interest.
We now demonstrate two different routes to synthesize **S6** and **R6** in enantiomerically pure form. For simplicity, only the S-enantiomers are graphically represented. Nevertheless all the corresponding R-enantiomers are obtained in the same manner.



Scheme 1

In each case either L-glutamic acid (**S1**) or D-glutamic acid (**R1**) serves as starting material. According to Scheme 1, **S1** is converted to the lactone **S2** by reaction with $NaNO_2$/HCl (59% yield for **S2**, 55% yield for **R2**)[4]. On treating **S2** with $SOCl_2$, **S3** is obtained in 91% yield (**R3**: 95%)[5]. **S4** is available by stirring **S3** with 2 eq. of dimethylamine in CH_2Cl_2 (-78°C to r.t. overnight) (70% yield for **S4**, colourless needles, mp. 73 -

74°C, $[\alpha]_D^{25}$ = +34.4 (*c*=1, CH_3OH), 62% for **R4**, mp. 74.5-75°C, $[\alpha]_D^{25}$ = -35.9 (*c*=1, CH_3OH)). Subsequently the amide moiety is selectively reduced with 2/3 mol borane-dimethylsulfide-complex by refluxing in toluene followed by hydrolysis with HBr (33 % in acetic acid). Recrystallization twice from *tert.*-butyl-methylether/acetonitrile gives **S5** as hygroscopic colourless crystals (27% for **S5**, mp. 177-179°C, $[\alpha]_D^{23}$ = +62.7 (*c*=1, CH_3OH), 15% for **R5**, mp. 178-180°C, $[\alpha]_D^{23}$ = -61.5 (*c*=1, CH_3OH)). Treating **S5** with aqueous Na_2CO_3, extraction with CH_2Cl_2 and subsequent quaternization with CH_3Br in acetonitrile gives **S6** in 70% yield (hygroscopic crystals, $[\alpha]_D^{20}$ = +49.4 (*c*=1, CH_3OH), 46% for **R6**, $[\alpha]_D^{20}$ = -45.6 (*c*=1, CH_3OH)).



S7 S8 S6

Scheme 2

The second route for the synthesis of the rigid acetylcholine **S6** is demonstrated in Scheme 2. Here, the lactone **S2** is easily reduced by borane-dimethylsulfide-complex to give **S7** in 76% yield (57% for **R7**)[6]. Treating **S7** with CBr_4/PPh_3 in acetonitrile yields **S8** (64% for S-, 58% for R-enantiomer)[7], which is used to quaternize trimethylamine by stirring both compounds in acetonitrile at r.t. over night. Recrystallization twice from *tert.*-butyl-methylether gives **S6** in 12% yield (34% for **R6**).

In summary the first route (Scheme 1) is more successful for **S6** (overall yield 7.1%) than for **R6** (overall yield 2.24%). Following Scheme 2, **R6** is available in 6.18% overall yield, whereas **S6** is synthesized in only 3.44% overall yield.

Nmr spectra of S-enantiomers agree with those of the corresponding R-enantiomers. The $[\alpha]_D$ values of the target compounds **S6** synthesized by the two represented routes are almost identical. This also proved true for **R6.**

Structure and purity of all new compounds (**S4**, **S5**, **S6** and corresponding R-enantiomers) were confirmed by ir-, nmr-data and elemental analysis. Nmr-spectroscopy after addition of (S)-(+)-1-(9-anthryl)-2,2,2-trifluorethanol demonstrates the enantiopurity of **S6** and **R6**. Further synthetic and pharmacological investigations are in progress and will be published later.

References and Notes

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