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SYNTHESIS OF AN ABIOTIC DITOPIC RECEPTOR MOLECULE

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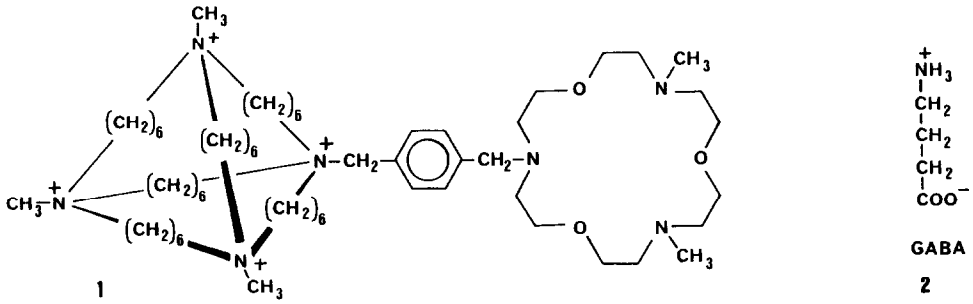
The synthesis of the ditopic host molecule 1 is described, which binds aminocarboxylates with preference over simple ammonium salts.

Enzymatic selectivity in substrate binding appears to be the result of the concerted binding action of a multitude of anchor groups, which are arranged in a precise spatial relationship within the active site. A reasonable approach to adapt this enzymic principle for the creation of selectivity in artifical host guest systems is the incremental construction of polytopic receptors i.e. the construction of host molecules composed of covalently linked anchor groups, which by themselves are only capable of binding functional substructures of the substrate[1].

Here I report on the synthesis of a ditopic receptor molecule 1, consisting of a macrotricyclic quaternary ammonium moiety for complexing an anionic substrate function, and an azacrown macrocycle serving as an anchorgroup for a prim. ammonium cationic substructure. The binding characteristics of these anchor groups have been thoroughly investigated [2,3], so that their combination can be expected to be suitable for binding aminocarboxylates like the neurotransmitter GABA 2



1

GABA

2

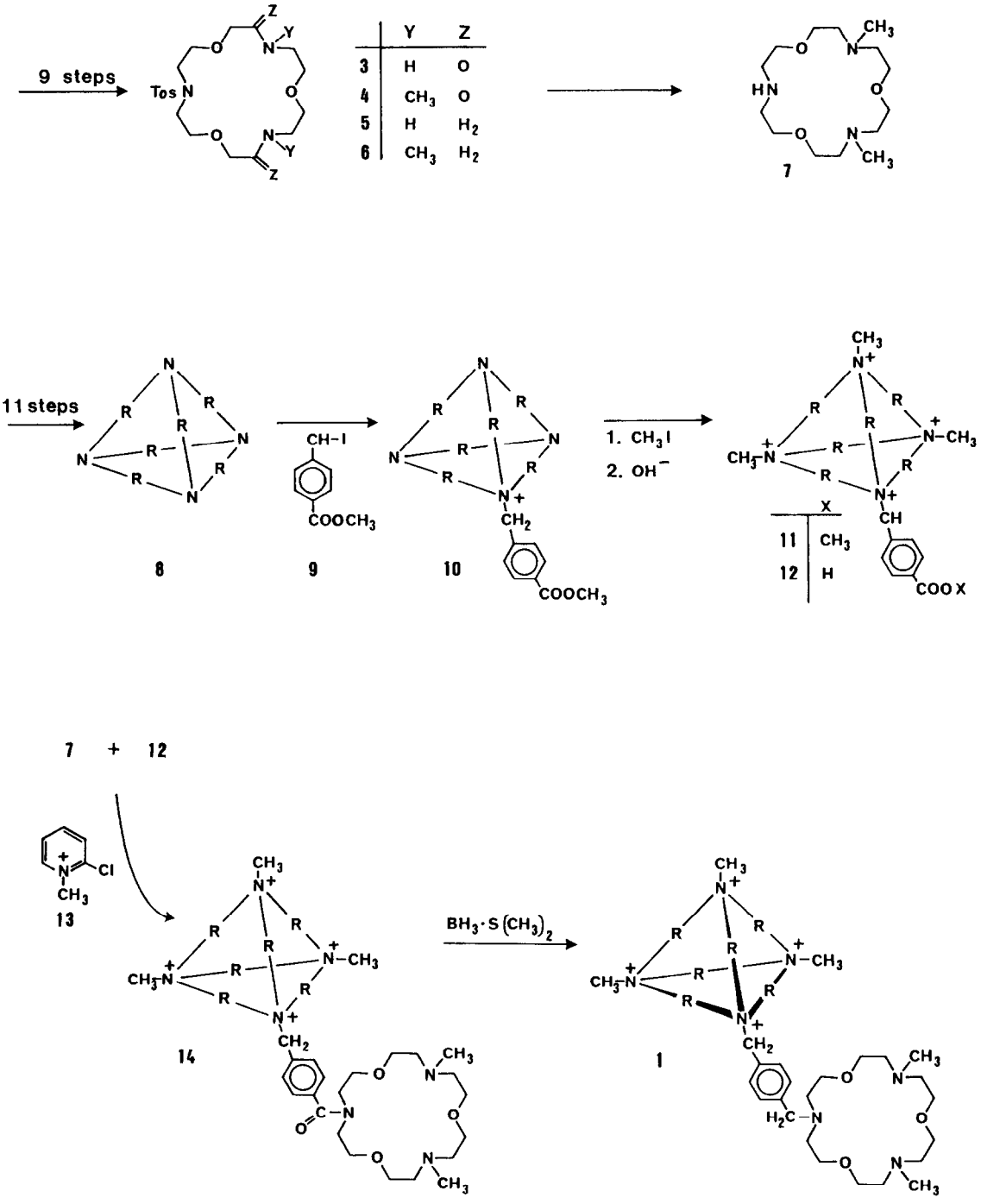
The synthesis of 1 called for a convergent strategy thus preparing the receptor functions independent from each other and linking the two parts in the last steps. The tert. amine structure of 1 suggested to take advantage of an amide formation reaction as the coupling process followed by amide reduction.

This strategy required the two substructures of 1 to be prepared as a monofunctional carboxylic acid and a secondary amine , respectively, which was achieved according to the following routes (scheme 1).

The Tos protected macrocycle 3, itself obtainable in 9 steps from commercial starting material [4], can be transformed to the desired macrocyclic amine 7 via either of two pathways: Amide 3 can be N-alkylated ($KH/DMSO/CH_3I$; 80%) and then reduced by BH_3/THF (95%) to yield the tert. amine 6 [5]. Alternatively, reduction to the secondary amine 5 (BH_3/THF, 90%) can preceed an Eschweiler-Clarke methylation step ($HCOOH/HCHO$, 95%). Both routes are comparable in yields and purity of product 6. Detosylation of 6 ($HBr/CH_3COOH/C_6H_5OH$, 85%) completed the synthesis of the azacrown moiety 7.
The synthesis of the carboxylic acid coupling component started with the macrotricyclic tert. amine 8 , itself being the product of a multistep synthetic sequence [6]. In principle the alkylation of a molecule possessing four nucleophilic centers of similar reactivity should lead to a mixture of products. The reaction of 8 and 9, however, could be conducted to produce 85% of the monoalkylated species 10. Permethylation of the remaining tert. nitrogen centers (CH_3I/CH_3CN, 80%) and alkaline hydrolysis of the ester function (85%) furnished the carboxylic acid 12, which is ready for attachment of amine 7.
The reagent of choice for promoting the amide coupling between 7 and 12 was found in Mukaiyama's compound 13 [7]. The smooth and almost quantitative reaction observed on application of this reagent in DMF contrasted sharply to the sluggish conversions found with half a dozen other reagent combinations. To complete the synthesis the amide 14 had to be reduced to a tert. amine. Hydride reductions usually successful in this type of reactions failed at first with compound 14 because of its insolubility in organic solvents. Fortunately the solubility of the BF_4-salt of 14 and the stability of the $BH_3 \cdot S(CH_3)_2$ complex in nitromethane were sufficient to allow the reduction to 1 in resonable yield (65%). Thus, the sequence described opens a way to obtain the artifical ditopic receptor molecule 1 in 28 steps from commercial material in a calculated overall yield of ca. 2%.

The physical properties of 1 (solubilities in different solvents, precipition by anions) and its basic complexation features resemble those of the parent components. Halide anions are complexed by 1 via inclusion into the macrotricyclic cavity and potassium ion and prim. ammonium cations are bonded likewise although with a different selectivity pattern than displayed by the parent azacrown compound [3]. Since we failed to directly view the complexation process of a bifunctional guest molecule (like GABA 2) interacting with both anchor groups of 1 simultaneously, one has to rely on more indirect evidence. The association constants of ammonium guests with 1 (tab. 1) are enhanced by a factor of 5 if the guest molecule carries an additional negative charge.

Scheme 1 (R in the tetrahedral structures represents $-(CH_2)_6-$; Counteranions are omitted throughout)



Obviously the supplementary possibility of an interaction of the anionic moiety of the guest with 1 aids in binding, so that the preferential complexation of aminocarboxylates versus simple ammonium cations can be considered to emerge from a double recognition process. In view of the fact that there is no rigid geometric relationship between the two receptor sites in 1 and any twist around a single bond in the spacing unit could paralyze the binding of a bifunctional guest molecule, an observed selectivity factor of 5 encourages us to follow this line to receptors with a more rigorously defined spatial arrangement of anchor groups.

Tab. 1: Conditional association constants (M^{-1}) of 1 with ammonium guests at optimal pH (methanol/H_2O 9:1 v/v; 25°C, measured by a K^+ sensitive glas electrode)

K^+	195 (9.10);	290 (9.40)
Tyramine		143 (9.10)
6-Amino-1-hexanol		48 (9.10)
6-Amino hexanoic acid		233 (9.40)
4-Amino butanoic acid		250 (9.40)

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