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Steroidal guanidinium receptors for the enantioselective recognition of *N*-acyl α-amino acids

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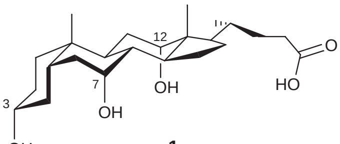
Guanidinium cations 4 and 5 extract *N*-acetyl α-amino acids into $CHCl_3$ from an aqueous medium with enantiomeric excesses of up to 80%.

Enantioselective recognition is of continuing interest in supramolecular chemistry,[1] especially where relevant to the large-scale resolution of racemates. Enantioselective phase transfer is particularly attractive, raising the possibility of 'catalytic' resolutions based on the transport of substrates through otherwise impermeable barriers.[2] Carboxylates/carboxylic acids are suitable targets for this approach, because of their ability to partition between aqueous and organic phases. Amino acids, and their *N*-acyl derivatives, are attractive substrates because of their biological significance and practical importance.[3]

Herein we describe a new strategy for the enantioselective extraction of chiral carboxylates from aqueous into organic media, and its realisation in the form of receptors which show significant enantiodiscrimination in the case of *N*-acetyl α-amino acids. In common with previous work on carbohydrate[4] and anion recognition,[5] our design exploits cholic acid **1** as a starting material. The secondary hydroxy groups in **1** can be independently modified to give differentiated, co-directed substituents as in **2**.[6] Groups A–C are spaced so as to allow, in



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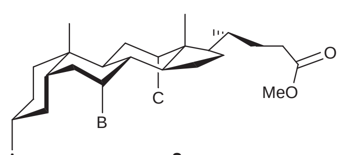

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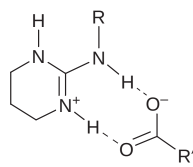
a typical case, cooperative effects on a substrate with minimum interference from intramolecular interactions. The design is suggestive of 'three-point contact', as required for the classical model of enantioselective recognition.[7]

For carboxylate extraction, it is useful that one of groups A–C should form a specific, electroneutral complex with the anionic centre. To serve this purpose we have chosen the guanidinium unit **3**, capable of binding carboxylates as shown.[8] Of the possible variations on our general theme, we report the synthesis and properties of two initial examples; the bisphenylcarbamate **4** and its asymmetrically-substituted relative **5**. Receptor **4** was accessible from 3α-azide **6**[9] as shown in Scheme 1, while receptor **5** was prepared *via* a longer sequence with alcohol **7** as the penultimate intermediate.

As anticipated, solutions of **4**·Cl^- and **5**·Cl^- in $CHCl_3$ were capable of extracting carboxylic acids from neutral or basic aqueous solutions, presumably through exchange of carboxylate for chloride. In the case of *N*-acetyl α-amino acids the ^1H NMR spectra of the complexed substrates were enantiomer-



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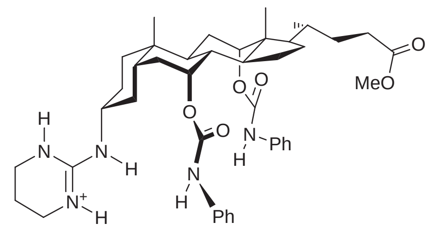

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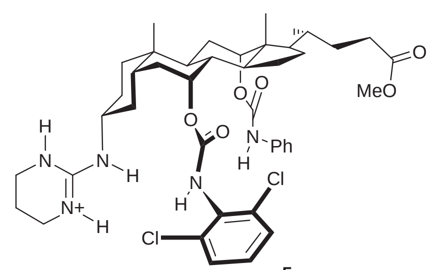

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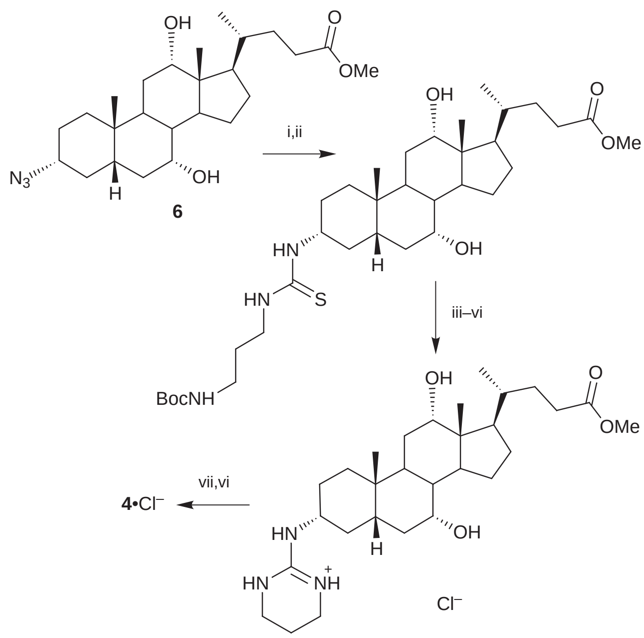
dependent, allowing the determination of enantioselectivities, as well as extraction efficiencies, by simple integration. The results are shown in Table 1. Extraction efficiencies were moderate to good for substrates with non-polar side-chains, although neither receptor was effective with the polar asparagine derivative. Receptor **4** proved remarkably consistent in its



Scheme 1 *Reagents and conditions*: i, Zn dust, AcOH, room temp., 24 h; ii, $SCN(CH_2)_3NHBoc$, $Pr^i{}_2NEt$, dry CH_2Cl_2, room temp., 72 h; iii, MeI, MeOH, reflux; iv, TFA, CH_2Cl_2, room temp.; v, $Pr^i{}_2NEt$, MeOH, room temp., 24 h; vi, aq. NaOH then aq. HCl; vii, PhNCO, conc. aq. HCl (cat.), CH_2ClCH_2Cl, reflux, 72 h.

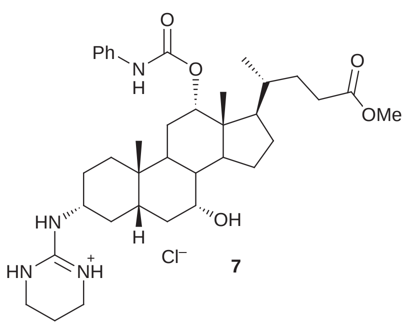
Table 1 Extractions by $4{\cdot}Cl^-$ and $5{\cdot}Cl^-$ of racemic *N*-acetyl α-amino acids from aqueous buffer (pH 7.4) into $CHCl_3$[a]

Substrate	Receptor **4** Extraction efficiency (mol%)[b]	Receptor **4** Enantio-selectivity (L:D)[c]	Receptor **5** Extraction efficiency (mol%)[b]	Receptor **5** Enantio-selectivity (L:D)[c]
N-Ac-alanine	52	7:1	76	6:1
N-Ac-phenylalanine	87	7:1	93	9:1
N-Ac-tryptophan	83	7:1	92	6:1
N-Ac-valine	71	7:1	89	9:1
N-Ac-*tert*-leucine	[d]	[d]	82	5:2
N-Ac-methionine	[d]	[d]	93	9:1
N-Ac-proline	[d]	[d]	74	4:1
N-Ac-asparagine	0	—	0	—

[a] Solutions of receptor in $CHCl_3$ (6 mM, 1 ml), and substrate in phosphate buffer (7–8 mM, 5 ml), were stirred vigorously for 2 h. The organic phases were isolated, dried by passage through hydrophobic filter paper, then evaporated. The residues were dissolved in $CDCl_3$ (0.6 ml) and analysed by ^1H NMR spectroscopy. [b] Determined by ^1H NMR integration of substrate α-C*H* and N*H* *vs*. 7/12β-*H* of receptor. [c] Determined by ^1H NMR integration of α-C*H* and N*H* signals for enantiomers of substrates. Assignments confirmed through control experiments with enantiopure substrates. [d] Not determined.

ability to differentiate between enantiomers, irrespective of side-chain bulk. Receptor **5** showed generally higher extraction abilities, possibly due to the greater acidity of the dichlorophenylcarbamoyl NH, and was more sensitive to side-chain structure. Perhaps surprisingly, the substrate with the most sterically hindered asymmetric centre (*N*-Ac-*tert*-leucine) gave the lowest selectivity.

^1H NMR spectroscopy and molecular modelling combined to suggest plausible models for the binding geometries. A Monte Carlo Molecular Mechanics (MCMM) search† on the complex between **5** and *N*-acetyl-L-valinate **8** yielded the configuration shown in Fig. 1. The carboxylate accepts H-bonds from the 7-carbamoyl and two guanidinium NH groups, while the acetyl oxygen is bound to the 12-carbamoyl NH. In support of this structure, the receptor carbamate and 2 of the 3 guanidinium N*H* signals moved downfield on complex formation, while a weak



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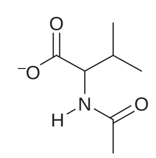

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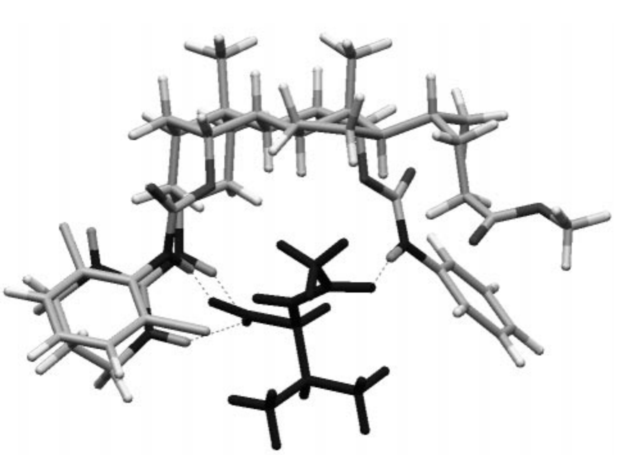

Fig. 1 Structure of **5** + L-**8** (black) derived from computer-based molecular modelling. Intermolecular hydrogen bonds are shown as broken lines.

intermolecular NOE was observed from the α-C*H* in L-**8** to the *ortho* protons of **5**-NH*Ph* (consistent with Fig. 1, allowing for some rotational freedom about the N–Ph bond‡). A similar MCMM search† on **5** + D-**8** yielded a higher-energy structure in which the acetyl O···HN interaction is missing, the 12-carbamoyl NH forming a fourth (apparently strained) hydrogen bond to the carboxylate.

Viewed as forerunners of an extended family of receptors, **4** and **5** show encouraging levels of enantioselectivity. Many variants are within easy reach, a majority with much greater differentiation between the three substituents. We hope to report examples with improved performance in the foreseeable future.

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Notes and references

† Calculations employed MacroModel V5.5 (ref. 10), the Amber* force field, $CHCl_3$ GB/SA solvation, and 5000 steps of MCMM. Six and three separate searches were conducted for the L and D substrates respectively, all from widely differing starting geometries and all yielding essentially similar final structures.

‡ Rotation about N–Ph allows an *ortho* proton to make van der Waals contact with the substrate α-CH.

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