**1._COMPARATIVE STUDY on the separation of diastereomeric-salts via diastereomer salt formation**.

COMPARATIVE STUDY on the separation of 8-phenylsulfinyl-1-naphthoic **1** using crystallization, liquid-liquid extraction and bulk liquid membranes in an innovative way that provides enough high separation constants (β = EDC = $\alpha_{op}$) was performed. These results can be used for the development of innovative technologies for industrial production of valuable chiral compounds using salting-out selective extraction (SOSE or ELLE), pH gradient effected membrane transport or 'heat facilitated diastereomeric crystallization ('HFR') techniques.[1]

The latter method may change the way of our thinking about crystallization: Here instead of cooling the freshly prepared mixture – of the sodium salt of the racemic acid **1** dissolved in water and the chiral base in form of its sulfate – was kept hot (near to boiling point of the solvent water) and stirred until the selective crystallization of one of the diastereomeric salts from their melted mixture was completed. The prolonged heating and stirring facilitated the firstly separated oily phase to change its composition from near to racemic composition to high diastereomeric excess due to anion-exchange ((+)-**1** and (-)-**1**) with the water phase ($\alpha_{op}$=170). The increased temperature of crystallization could also be inhibit the nucleation of the more soluble diastereomeric salt. The latter method may be named as "**Self-Extracting Crystallisation**".

Separation efficiency has already been quantified and named as *enantiomer distribution constant* (EDC),[2] *separation factor* (β),[3] or *operational selectivity* ($\alpha_{op}$)[4] by the researchers involved in *organic chemistry, separation science* or *process chemistry*. It is obvious that they are practically equal to each other, and we found that they can be estimated from specific rotation data of the appropriate analyte samples recovered from the equilibrated and separated phases according to the protocols of *heat facilitated crystallisation* (HFR), *enantioselective liquid-liquid extraction* or *enantioselective facilitated transport through bulk liquid membranes.*

*'Trennfaktor β'* (German) is defined[5] as $\beta = K_A/K_B$, where $K_A$ is the partition coefficient of compound A, and $K_B$ is the partition coefficient of compound B, the former showing preference to the extracting solvent (i.e. $K_A > K_B$). We earlier used *'Separation Constant β'* to describe the selectivity of the SOSE process which can be estimated by using specific rotation data of samples of the analyte recovered from the equilibrated liquid-liquid (extraction) or solid-liquid (crystallization) phases according to Equation 1. It is obvious that this term practically equal to *EDC* (*enantiomer distribution constant*) or to $\alpha_{op}$ (*operational selectivity*).

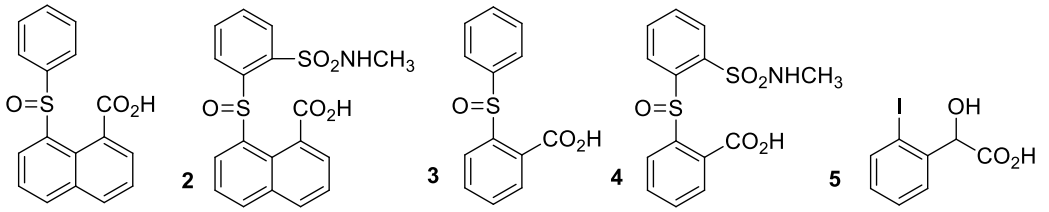
$$\beta^p = \frac{(\alpha_{Tp})+\alpha`}{(\alpha_{Tp})-\alpha`} \times \frac{(\alpha_{Tn})+\alpha}{(\alpha_{Tn})-\alpha} = \alpha_{op} = \text{EDC} \qquad \text{(Eq. 1)}$$

$\beta^p$: Separation (=*selectivity*) parameter for the preferred enantiomer; // $\alpha_{Tp}$: Maximal specific rotation of the *preferred* enantiomer (with + or – signs); // $\alpha_{Tn}$: Maximal specific rotation of the *non-preferred* (= other) enantiomer (with – or + signs); // $\alpha`$: Specific rotation of the sample recovered from the organic phase (= *extract phase*); // $\alpha$: Specific rotation of the sample recovered from the aqueous phase (= *raffinate phase*)

Below is given an example of calculation of $\beta$ from specific rotation data using the recovered acid samples of (+)-**1** and/or (-)-**1** from the crystalline phase ("*virtual extract*") and from the mother liquor phase ("*virtual raffinate*"), taking the whole process as a "*virtual extraction*" having thermodynamic phase equilibrium; and the specific rotation of the *pure enantiomer* ($\alpha_{Tp}$ and $\alpha_{Tn}$: which may be called as *maximal rotation*, or *absolute rotation*). Thus *'HFR'* of **1** with brucine gave: $\alpha_{Tp}$ :+795; $\alpha_{Tn}$: -795; $\alpha`$ :+736; $\alpha$ :-585; than by Eq.1 $\beta$ = EDC = $\alpha_{op}$ = **170.52**; while *'HFR'* of **1** with strychnine: $\alpha_{Tp}$ :+795; $\alpha_{Tn}$: -795; $\alpha`$ :-316; $\alpha$ :+249; than by Eq.1 $\beta$ = EDC = $\alpha_{op}$ =**4.43**.

For better understanding of the '*HFR-Self-Extracting Crystallisation*' process an X-ray study of solid state structures of the crystalline precipitates is planned for the near future.

Our preliminary tests showed that this methodology is effective not only for related chiral sulfoxide carboxylic acids (**1**, **2**, **3**, **4**), but can easily be applied for the resolution of racemic 2-iodomandelic acid (**5**). Results were published along with the determination of the absolute configuration the (-) and (+) enantiomers of **6**.[6] For **1** to **5** bases used are with ($\alpha_{Tp}$: / $\alpha_{Tn}$):




Brucine (+736/-585) Optochin (+127/-117) Cinchonine (-303/+334) Optochin (+100/-107) …. Strychnine (-130/+108)

Optical rotations were measured in DMF at 25 °C and c = 0.5 g/100 mL.

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[1] A. Nemes, et al., Tetrahedron: Asymmetry 28 (2017) 1078-1082; DOI: 10.1016/j.tetasy.2017.07.001

[2] D.J. Cram, et al., *J. Am. Chem. Soc.,* 1974,*96,* 7367-7369. DOI: 10.1021/ja00830a042

[3] J. Rábai, Angew. Chem., Int. Ed. Engl., 1992, 31 1631-1633. DOI: 10.1002/anie.199216311

[4] B. Schuur, et al., *Org. Biomol. Chem.,* 2011, *9,* 36-51. DOI: 10.1039/C0OB00610F

[5] *Houben-Weyl Methods of Organic Chemistry* Vol. I/1, 4th Edition: p 235. O. Jübermann – Partition and Extraction.

[6] A. Nemes, et al. *Chem. Pap.* 2019, 73, 47–54. DOI: 10.1007/s11696-018-0568-6

THE CHIRAL DISCRIMINATION MECHANISM in a given system is considered to include a large number of factors such as the structure of the racemate and the resolving agent, moreover the solvent and the temperature. Thus the efficiency of a resolving agent with optimal conditions for a target racemate is not foreseeable. Since it is obvious that the basic physico-chemical phenomena concerning the enantiomeric recognition processes are not the same in the case of crystallization and extraction methods, therefore we have been undertaking systematic studies on the resolution of (±)-**1** using three different methods: diastereomeric crystallization, enantioselective liquid-liquid extraction and chiroselective transport.

The optimal conditions for obtaining enantiomerically pure (-)-1 was diastereomeric crystallization using half equivalent of brucine as resolving agent. Enantiomerically enriched 1 was also afforded by enantioselective liquid-liquid extraction, using half equivalent of optochin in water / chloroform solvent system. Chiroselective transport gave similar results as the extraction experiments. Comparison of these results showed difference between the mechanism of the chiral recognition processes in the case of strychnine and quinoline alkaloids.

## 2. SYNTHESIS & DESIGN OF NOVEL CHIRAL SOLVATING AGENTS. NMR EXPERIMENTS & PROOF OF THE PRINCIPLE.

### 2.1 New fluorine containing amino acid based chiral NMR shift reagents.[7], [8]

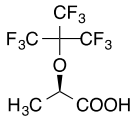
NMR spectroscopy is an advantageous possibility for chiral discrimination, because NMR instruments are usually available for routine structure determinations. The %ee determination by NMR spectroscopy is based on diastereomer formation, either as (1) derivatization in a separate step before the measurement, or (2) in situ complex formation (using lanthanide shift reagents or chiral solvating agents). These latter procedures have the advantage of fast optimization and data processing, as well as lacking racemization and purification.

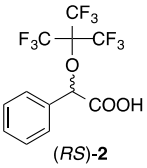
Since most of the active pharmaceutical ingredients (APIs) are optically active molecules, pharmaceutical industry needs simple, fast and accurate analytical methods for determination of enantiomeric ratios.

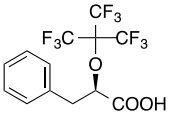
In our previous work we showed, that α-(nonafluoro-tert-butoxy)carboxylic acids, based on lactic acid (R)-1, mandelic acid (RS)-2 and 3-phenyllactic acid (R)-3,[9] display good chiral discrimination properties towards chiral amines.[10]

To extend these experiments, four new chiral carboxylic acid derivatives were synthesized, starting from natural α-amino acids. In order to introduce the nonafluoro-tert-butoxy moiety, the amino group was replaced by stereospecific nucleophilic substitution. In this paper we present the synthesis and chiral discrimination studies of carboxylic acids (*S*)-1, (*S*)-4, (*S*)-5 and (*S*)-6. We tested these compounds in $^{1}H$ and $^{19}F$ NMR experiments as chiral NMR shift reagents.

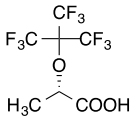
Previous work:

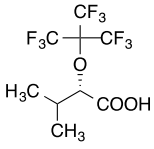

(*R*)-**1**

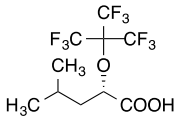

(*RS*)-**2**

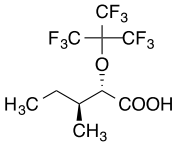

(*R*)-**3**

This work:


(*S*)-**1**


(*S*)-**4**


(*S*)-**5**


(*S*)-**6**

The starting materials of the synthesis of α-(nonafluoro-*tert*-butoxy)carboxylic acids are the natural amino acids alanine, valine, leucine and isoleucine. The first step is diazotization of amino group followed by hydrolysis to yield the optically active α-hydroxycarboxylic acids. In this reaction inversion of configuration occurs in a stereospecific way. Then the obtained carboxylic acids were reacted with $SOCl_2$ in the presence of methanol, to give the methyl α-hydroxycarboxylate intermediates (*R*)-**7**, (*R*)-**8**, (*R*)-**9** and (*R*)-**10**. Based on our previous experiments the ether bonds were formed with nonafluoro-*tert*-butanol under Mitsunobu reaction conditions which took place also with complete inversion of configuration.

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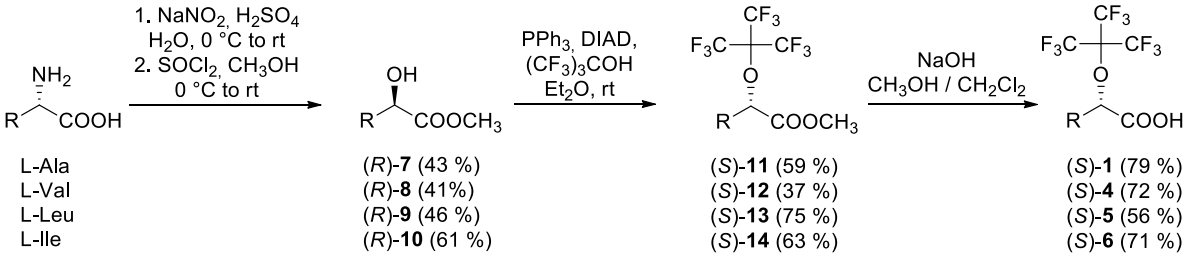
[7] Anikó Nemes, Tamás Csóka, Szabolcs Béni, Dénes Szabó, New fluorine containing amino acid based chiral NMR shift reagents. 19th European Symposium on Fluorine Chemistry, Warsaw, 2019. Abstract I-C19-page 222.

[8] Anikó Nemes, Tamás Csóka, Szabolcs Béni, József Rábai, Dénes Szabó; Chiral α-amino acid-based NMR solvating agents; Submitted to J Org. Chem. (2019) - under revision.

[9] T. Csóka, A. Nemes, D. Szabó, Tetrahedron Lett. (2013) 1730-1733

[10] A. Nemes, T. Csóka, Sz. Béni, V. Farkas, J. Rábai, D. Szabó, J. Org. Chem. 80 (2015) 6267-627.

In the last step the ester protecting group was hydrolyzed with NaOH in MeOH-$CH_2Cl_2$ solvent mixture, to give the target α-(nonafluoro-*tert*-butoxy)carboxylic acids(*S*)-**1**, (*S*)-**4**, (*S*)-**5** and (*S*)-**6** (*vide infra*).




| | | | |
|---|---|---|---|
| L-Ala | (*R*)-**7** (43 %) | (*S*)-**11** (59 %) | (*S*)-**1** (79 %) |
| L-Val | (*R*)-**8** (41%) | (*S*)-**12** (37 %) | (*S*)-**4** (72 %) |
| L-Leu | (*R*)-**9** (46 %) | (*S*)-**13** (75 %) | (*S*)-**5** (56 %) |
| L-Ile | (*R*)-**10** (61 %) | (*S*)-**14** (63 %) | (*S*)-**6** (71 %) |

These acids have good solubility in apolar solvents due to $CF_3$ groups and they form tight ion pair with chiral amines. In these diastereomeric salts methine protons have different chemical shifts in the $^1$H NMR spectra therefore they can be used to determine enantiomeric excess of amines. Due to the nine chemically equivalent fluorine atoms in $^{19}$F NMR spectra there is only one strong singlet, which is sensitive to the salt formation thus this method is also suitable to give %ee.

## 2.2 New fluorine containing chiral NMR shift reagents[11, 12]

Based on the fact that most of the APIs (Active Pharmaceutical Ingredients) are optically active molecules, pharmaceutical industry needs simple, fast and accurate chiral analytical methods. Applications of fluorine containing chiral NMR shift reagents are highly beneficial. We synthesized several α-(nonafluoro-*tert*-butoxy)carboxylic acid derivatives in order to develop new chiral solvating agents (CSAs). Our preliminary study showed that the most effective chiral recognition takes place, when an aromatic group is attached directly to the chiral center of the α-(nonafluoro-*tert*-butoxy)carboxylic acid. The present study is related to determine the importance of the π-π stacking in the chiral discrimination process.

We synthesized four new *O*-(nonafluoro-*tert*-butyl)mandelic acid derivatives with aromatic ring substituents and examined their chiral recognition by $^1$H NMR spectroscopy. Chiral discrimination values are shown in the Table below.

| Components: (*RS*)-acid // (*S*)-amine | 4-Q-$C_6H_4$-C**H**[$OC(CF_3)_3$]COOH | |
|---|---|---|
| | δ (ppm) | Δδ (ppm/Hz) |
| (*RS*)-*O*-perfluoro-*tert*-butyl-mandelic acid<br>1 eq. (*S*)-1-phenylethyl amine | 5.19<br>5.04 | 0.15/37.5 |
| (*RS*)-*O*-perfluoro-*tert*-butyl-4-bromomandelic acid<br>1 eq. (*S*)-1-phenylethyl amine | 5.08<br>5.17 | 0.09/22.5 |
| (*RS*)-*O*-perfluoro-*tert*-butyl-4-fluoromandelic acid<br>1 eq. (*S*)-1-phenylethyl amine | 5.08<br>5.17 | 0.09/22.5 |
| (*RS*)-*O*-perfluoro-*tert*-butyl-4-methylmandelic acid<br>1 eq. (*S*)-1-phenylethyl amine | 5.01<br>5.15 | 0.14/35 |

Our experiments show that the optically active acids form tight ion pairs with racemic amines in apolar solvents and the formed diastereomeric salts are distinguishable by NMR spectroscopy.

We used racemic and (*S*)-α-phenylethylamine as model substrate. Typical chemical shift difference in $^1$H NMR using chiral solvating agents reported in the literature is approximately 0.05 ppm. In the case of α-(nonafluoro-*tert*-butoxy)carboxylic acids chemical shift differences were observed for the methine and methyl protons of the analyte.

The measured Δδ for methine protons were 0.09 - 0.15 ppm. Although $^1$H NMR is the most commonly used analytical method, it suffers from several disadvantages, such as severe overlapping peaks due to signal multiplicity and narrow spectral window. Observing $^{19}$F nuclei the spectral overlap can be eliminated, and the 9 chemically equivalent fluorine atoms offer strong singlet signals. The measured Δδ for fluorine atoms were 0.006 - 0.026 ppm, which values are comparable to those of known chiral solvating agents.

[11] Anikó Nemes, Tamás Csóka, Szabolcs Béni, Viktor Farkas, József Rábai, Dénes Szabó, Chiral recognition properties of optically active α-(nonafluoro-tert-butoxy)carboxylic acids, European Symposium of Fluorine Chemistry, 2016_ESoFC_Kiev.

[12] Nemes Anikó, Szabó Dénes, Farkas Viktor, Rábai József: Királis felismerési folyamatok és alkalmazásaik: rezolválás és királis analitika, MKE Vegyészkonferencia, Hajdúszoboszló, 2017

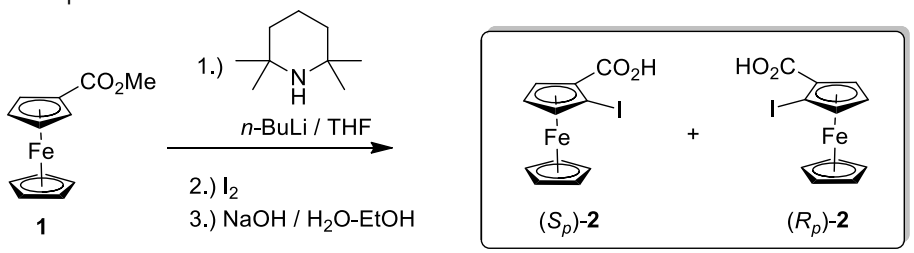
**3_SYNTHESIS OF CHIRAL BUILDING BLOCKS AND CHIRAL REAGENTS OR OTHER PRECURSORS FOR FURTHER STUDIES**

3.1 Synthesis of fluorous pyrrolidone derivatives.[13]

5-Perfluoroalkyl-pentane-1,4-diols obtained by the reduction of fluorinated γ-lactone precursors can easily be converted to 5-perfluoroalkyl-pentane-1,4-diiodides or 5-perfluoroalkyl-pentane-1,4-dimesylates. These novel bis-alkylating reagents were reacted with primary amines to afford fluorous *N*-substituted-pyrrolidines. The enantiomers of the latter fluorous pyrrolidines could be used as recoverable organocatalysts in some base induced reactions.

3.2 Synthesis of racemic 2-iodoferrocenecarboxylic acid

We prepared the title acid with directed regioselective lithiation of methyl ferrocenecarboxylate in position 2 followed iodination of the formed intermediate in good isolated yield (Cf. Scheme). This sample showed agreeable physical properties and spectral data to that reported in the literature. [14]




SOON WE LEARNED that the preparation of single enantiomers of this acid has been published by the same group. Thus the $S_P$-2-iodoferrocenecarboxylic acid was synthesized from 3-O-(ferrocenecarbonyl)-1,2:5,6-di-O isopropylidene-α-D-glucofuranose by (i) deprotonative metalation in THF using lithium (*S*)-bis(1-phenylethyl)amide (2 x 2 eq at 10 min interval) through a double asymmetric induction process in the presence of $ZnCl_2$·TMEDA (1 eq) as in situ trap, followed by iodolysis as described previously, and (ii) saponification of the ester.[15] FURTHER EXPERIMENTS with the racemic acid ($S_p$/$R_p$)-**2** has been reconsidered by us and postponed for a while.

3.3 Unusual reactivity of meso-tetrakis(trifluormethyl)porphin[16]

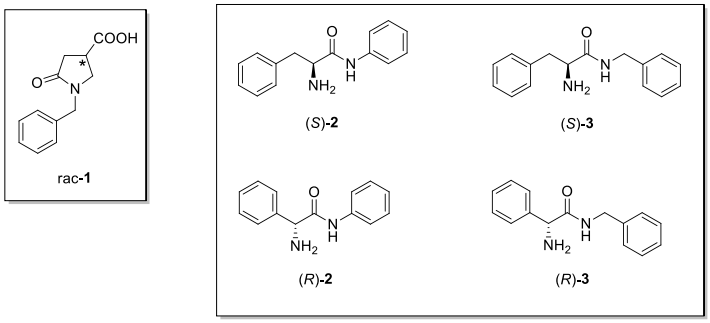
Based on the unusual reactivity of trifluoromethyl groups in nitrogen containing heterocycles, we synthesized the appropriate porphyrin mono-, di-, tri- or tetra-carboxylic ester derivatives by treatment of the precursor meso-tetrakis(trifluoromethyl)porphyrin with an excess of sodium- or potassium alkoxide in the respective alcohol.

This method offers an efficient route for the synthesis of LOWER SYMMETRY meso-substituted porphyrins compared to usual preparations utilizing stepwise condensation reactions. The structure of tetrakis(butyloxycarbonyl)porphyrin was determined by X-ray analysis.

3.4 Optical resolution of N-benzyl-5-oxo-3-pyrrolidinecarboxylc acid.[17]

Pyrrolidone derivatives are important compounds for the pharmaceutical industry because of their biological activity. There are several methods for the synthesis of pyrrolidine moiety, but they usually apply enantioselective transition metal catalysts, which are disadvantageous because of the costly purification methods. It is more economical to synthesize these compounds in racemic form and apply an optical resolution step at the end of the synthesis.

We optimized the resolution process of **rac-1**. Four α-amino acid amides were synthesized and tested for in four solvents. The most effective method was diastereomer crystallisation of **rac-1** with one eq of (S)-**3** from ethyl-methyl-ketone.




[13] László Orha, József Rábai, Fluorine Notes, 2017, 110, 1-2 , DOI 10.17677/fn20714807.2017.01.01

[14] G. Dayaker, A. Sreeshailam, F. Chevallier, T. Roisnel, P. R. Krishna, F. Mongin, Deprotonative metallation of ferrocenes using mixed lithium–zinc and lithium–cadmium combinations, Chem. Commun., 2010, 46, 2862–2864.

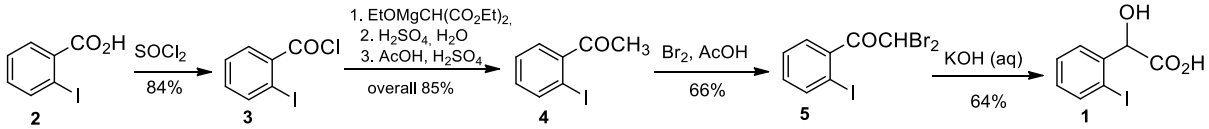
[15] P. Srinivas, S. Prabhakar, F. Chevallier, E. Nassar, W. Erb, V. Dorcet, V. Jouikov, P. R. Krishna, F. Mongin, Synthesis of ferrocene amides and esters from aminoferrocene and 2-substituted ferrocenecarboxylic acid and the properties thereof, New J. Chem., 2016, 40, 9441-9447.

[16] Anikó Nemes, Egmont Mérész, István Jalsovszky, Dénes Szabó, Zsolt Böcskei, József Rábai, Unusual reactivity of trifluoromethyl groups in meso-tetrakis(trifluoromethyl) porphyrin, J. Fluorine Chem. 203 (2017); DOI: 10.1016/j.jfluchem.2017.05.009

[17] Balázs Török, ELTE Master Thesis, 2017 (Supervisor Dr. Anikó Nemes).

3.5 Synthesis of enantiopure 2-iodomandelic acid and determination of its absolute configuration.[18]

Racemic 2-iodomandelic acid **1** was synthesized from commercially available 2-iodobenzoic acid **2**. Acyl chloride **3** was reacted with diethyl malonate, then the formed diester was hydrolysed and decarboxylated in a one-pot reaction. The obtained 2-iodoacetophenone **4** was reacted with bromine and the dibromoacetophenone derivative **5** was hydrolysed to give the racemic acid (±)-**1**. Optical resolution of (±)-**1** via diastereomeric crystallization with strychnine afforded enantiopure (R)-(−)-**1**. Absolute configuration of (−)-**1** and of its methyl ester (−)-**6** was determined by VCD spectroscopy.



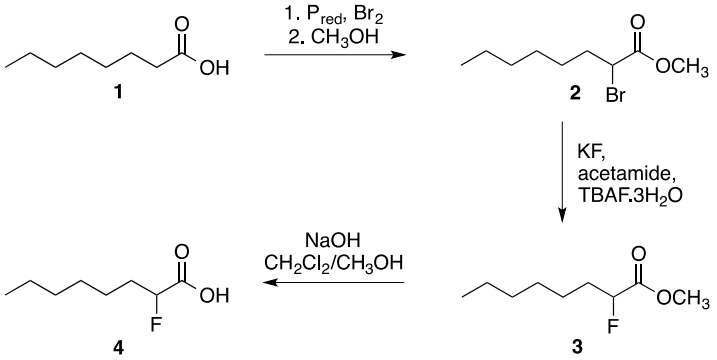

Optical resolution of racemic **1** was carried out by diastereomeric crystallization. To find the optimal conditions for the optical resolution of (±)-1 we tested several methods, using strychnine, brucine, optochin, quinine, quinidine, cinchonine, cinchonidine, (*S*)-1-methylbenzylamine and ephedrine as resolving agents. It is worthy to note, that although ephedrine was successful resolving agent for other mandelic acid derivatives, in the case of (±)-1, the crystallization trials did not give filterable precipitate. We obtained the enantiopure (−)-**1** using 0.5 eq of the organic base strychnine as a resolving agent in warm aqueous media (*Self-Extracting Crystallisation*). To one eq of (±)-**1** were added 1 eq of NaOH and 0.5 eq of strychnine nitrate (B × $HNO_3$). One of the diastereomeric salts [(−)-**1** × B] separated in crystalline form, from which (−)-**1** was regenerated with aq-NaOH solution. This method provided the enantiopure (−)-**1** {ee > 99%, $[\alpha]_{578}$ = − 130 (c = 0.5, DMF)}. (+)-**1** was isolated from the mother liquor after partial evaporation and acidification in 77% ee {$[\alpha]_{578}$ = + 108 (c = 0.5, DMF)}.

After crystallization from toluene, the ee of **1** was 94% {$[\alpha]_{578}$ = + 115 (c = 0.5, DMF)}. The calculated separation efficiency is very high ($\alpha_{op} \geq 500$). Enantiomeric excess (ee) of the products was determined by $^1$H NMR spectroscopy using (*S*)-1-methylbenzylamine as chiral solvating agent. The calculated ee values of the products based on the measured optical rotation are slightly different from that obtained by $^1$H NMR method, due to the presence of impurities in the crude products.

The absolute configuration of this acid was determined by comparison of the experimental VCD spectra of (-)-1 and its methyl ester with that obtained by quantum chemical calculations. Thus for this (-)-1 acid (*R*)-configuration was assigned.

3.6 Synthesis of racemic 2-fluorooctanoic acid.[19]

A multiple step synthesis of 2-fluorooctanoic acid as individual project in Advanced Organic Chemistry Laboratory course is described. As theoretical background students need to know about enolate chemistry (Hell-Volhard-Zelinsky reaction), nucleophilic substitution and elimination reactions as well. During their practical work, advanced laboratory techniques such as slow addition of reactants, in situ reagent formation and vacuum distillation were introduced. After each step the products were characterized using boiling point or melting point determination and NMR spectroscopy ($^1$H, $^{13}$C, $^{19}$F).




3.7 Synthesis of aryl trifluorethyl sulfides.[20]

Aryl 2,2,2-trifluoroethyl sulfides were synthesized by copper(I)-catalyzed nucleophilic aromatic substitution reaction (Goldberg-Ullmann coupling). The method requires aryl iodides and 2,2,2-trifluoroethyl thioacetate as starting materials, benzylamine as solvent and base, and copper(I) bromide as a catalyst. The reaction mixture was stirred at 110 °C for 6 h under inert atmosphere to afford the targeted aryl 2,2,2-trifluoroethyl sulfides in moderate to good yield.

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[18] Anikó Nemes, Elemér Vass, István Jalsovszky, Dénes Szabó, Synthesis of enantiopure 2-iodomandelic acid and determination of its absolute configuration by VCD spectroscopy, Chem. Pap. 73, 47–54 (2019). DOI: 10.1007/s11696-018-0568-6

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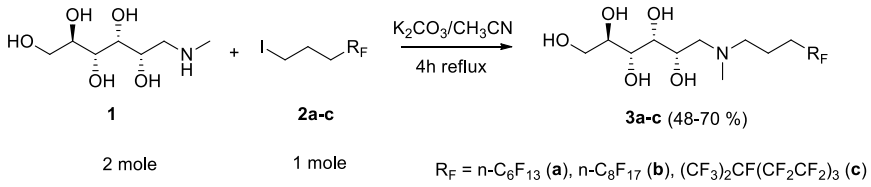
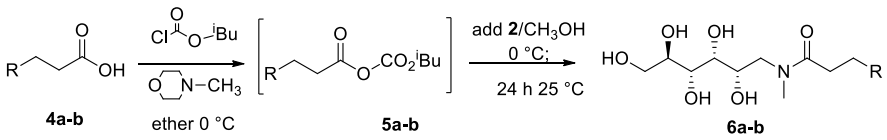
[20] Bálint Menczinger, Anikó Nemes, Dénes Szabó, Gitta Schlosser, Tamás Jernei, Antal Csámpai, József Rábai, Synthesis of aryl 2,2,2-trifluoroethyl sulfides, Journal of Fluorine Chemistry, 231, 2020, No 109464; DOI: 10.1016/j.jfluchem.2020.109464

3.8 Synthesis of *N*-methyl-glucamine based fluorous chiral auxiliaries.[21]

The selective *N*-alkylation or *N*-acylation of D-glucamine using (perfluoroalkyl)propyl iodides, mesylates or fluorinated carboxylic acids allowed the synthesis of novel fluorous chiral resolving agents. These compounds were designed to exploit the unique effects of perfluoroalkyl-groups[22] on the substituted molecules' microscopic[23] and macroscopic [24] properties. The synthesis of amines **3a-c** and amides **6a-b** are shown below. All new compounds were characterized with mp, specific rotation data, and HRMS, $^{1}H$, $^{19}F$ and $^{13}C$ NMR spectroscopy.



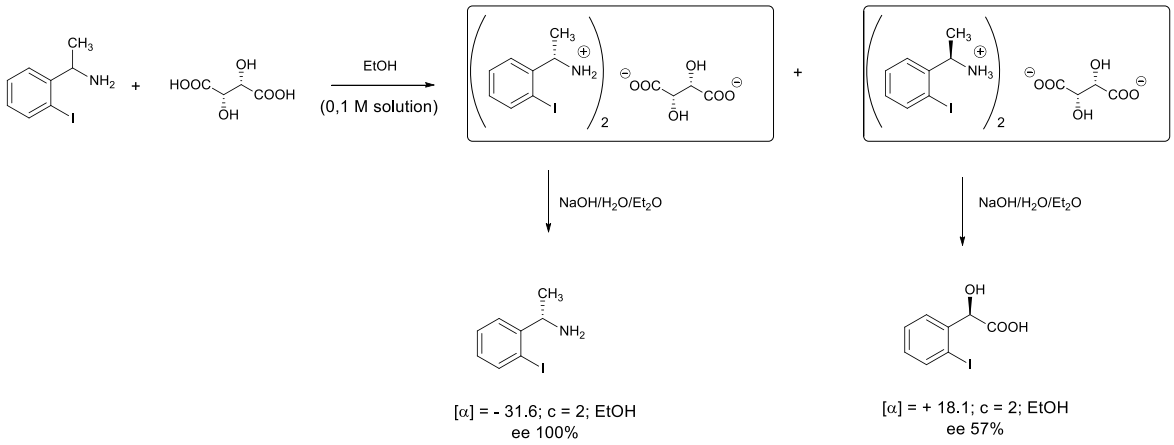

**Scheme 1**. Preparation of N-methyl-N-[3-(perfluoroalkyl)propyl]-D-glucamines **1a-c.**




**Scheme 2**. Selective *N*-acylation of *N*-methyl-D-glucamine **1** with *in situ* generated mixed anhydrides **5a-b**.

3.8 Synthesis of enantiopure 2-iodo-α-phenylethylamine and an X-ray study of the less soluble tartrate salt.[25]

The reaction of 2-iodoacetophenone with ammonium formate, and the subsequent hydrolysis resulted in the formation of racemic 2-iodo-α-phenylethylamine in 46% yield as pale yellow liquid. Optical resolution of this amine was carried out by diastereomeric crystallization. To find the optimal conditions several methods were tested, using tartaric acid, *O*,*O*'-dibenzoyl tartaric acid and camphene-10-sulfonic acid as resolving agents. The enantiopure (−)-amine was obtained using 1 eq of (L)-tartaric acid in warm 96% ethanol. One of the diastereomeric salts separated in crystalline form, from which the enantiopure (−)-amine {ee > 99%, $[\alpha]_{546}$ = −31.6 (c = 2, EtOH)} was liberated by aq-NaOH. The (+)-amine was isolated from the mother liquor after partial evaporation and acidification in 57% ee {$[\alpha]_{546}$ = + 18.1 (c = 2, EtOH)}. Enantiomeric excess (ee) of the products was determined by $^{1}H$ NMR spectroscopy using (*S*)-mandelic acid as chiral solvating agent

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