

# SYNTHESIS OF POLYFLUOROKETONES CONTAINING AN INDOLE RING AS INHIBITORS OF HUMAN $\text{Ca}^{2+}$ - INDEPENDENT PHOSPHOLIPASE $\text{A}_2$

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## Introduction

Phospholipase  $\text{A}_2$  ( $\text{PLA}_2$ ) enzymes catalyze the hydrolysis of the *sn*-2 ester bond of glycerophospholipids producing free fatty acids and lysophospholipids.<sup>1</sup> The main representative of these fatty acids is arachidonic acid, which can be transformed into eicosanoids (prostaglandins, leukotriens, etc) by the action of other enzymes. Lysophospholipids are precursors for other bioactive compounds, such as platelet-activating factor (PAF). PAF and eicosanoids constitute basic mediators of inflammation and other pathophysiological routes. In the superfamily of  $\text{PLA}_2$  enzymes, three are the predominant groups found in human tissues; the cytosolic  $\text{PLA}_2$  ( $\text{cPLA}_2$ ), the calcium-independent  $\text{PLA}_2$  ( $\text{iPLA}_2$ ) and the secreted  $\text{PLA}_2$  ( $\text{sPLA}_2$ ).<sup>1</sup> We have recently demonstrated that  $\text{Ca}^{2+}$ -independent phospholipase  $\text{A}_2$  (GVIA  $\text{iPLA}_2$ ) plays a key-role in experimental autoimmune encephalomyelitis and that GVIA  $\text{iPLA}_2$  is a novel target for the development of new therapies for multiple sclerosis.<sup>2</sup>

A series of fluoroketones of the general structure **1** has been presented as  $\text{iPLA}_2$  inhibitors and the structure-activity relationship has been evaluated.<sup>3,4</sup> Polyfluoroketones **FKGK11** and **FKGK18** proved to be potent and selective inhibitors of GVIA  $\text{iPLA}_2$  (Table 1). Therefore, to extend this research, we synthesized a variety of polyfluoroketones containing an indole ring and a four carbon atom chain between the ring and the polyfluoroketone group.

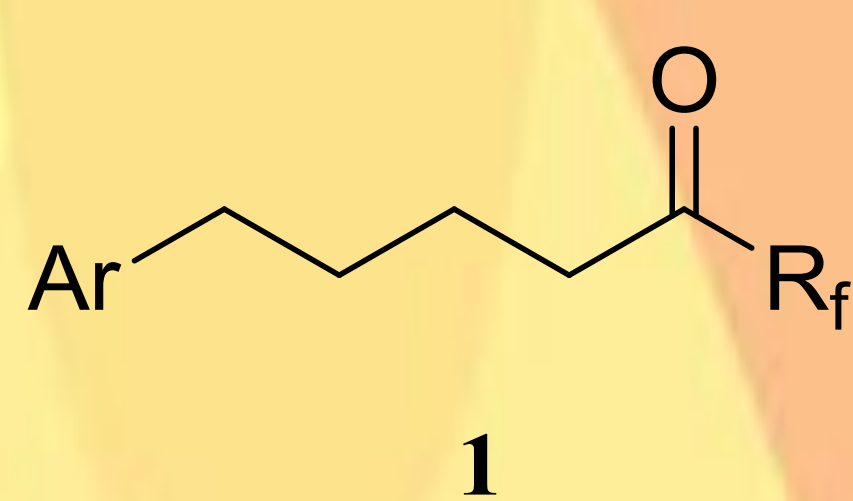


Table 1<sup>4</sup>

No	Ar	R <sub>f</sub>	X <sub>1</sub> (50) for $\text{iPLA}_2$
FKGK11		$\text{C}_2\text{F}_5$	$0.0014 \pm 0.0001$
FKGK18		$\text{CF}_3$	$0.0002 \pm 0.0000$

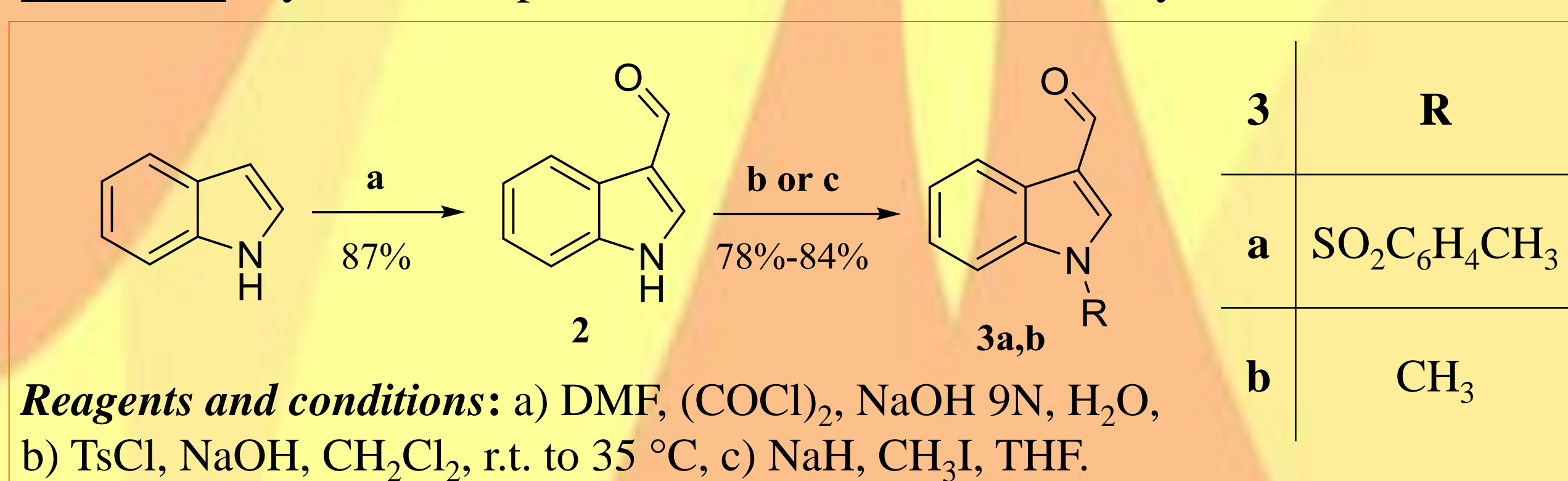
## Synthesis

Indole-3-carboxaldehyde (**2**) was obtained from indole using the Vilsmeier - Haack reaction and then it was protected with the tosyl or the methyl group (Scheme 1). These two protected aldehydes along with commercially available indole-5-carboxaldehyde underwent a Horner - Wadsworth - Emmons reaction with triethyl-4-phosphonocrotonate in the presence of a strong base (1,1,3,3-tetramethyl guanidine or NaH) to produce the corresponding unsaturated esters **4a-c** (Scheme 2). After catalytic hydrogenation, we received the saturated esters **5a-d**; in the case of ester **5d** the indole ring was also hydrogenated along with the double bonds. After saponification with NaOH 1N in ethanol, we acquired the corresponding carboxylic acids **6a-d** which were converted to acyl chlorides with the method of oxalyl chloride/DMF. In situ, the acyl chlorides were treated with pyridine and trifluoroacetic anhydride or pentafluoropropionic anhydride to provide the trifluoromethyl ketone **8d**, and pentafluoroethyl ketones **7a-c**. In the case of pentafluoroethyl ketone **7c** the reaction conditions of the last step were in consistency with the Vilsmeier - Haack reaction and as a result we obtained the aldehyde derivative (Scheme 3).

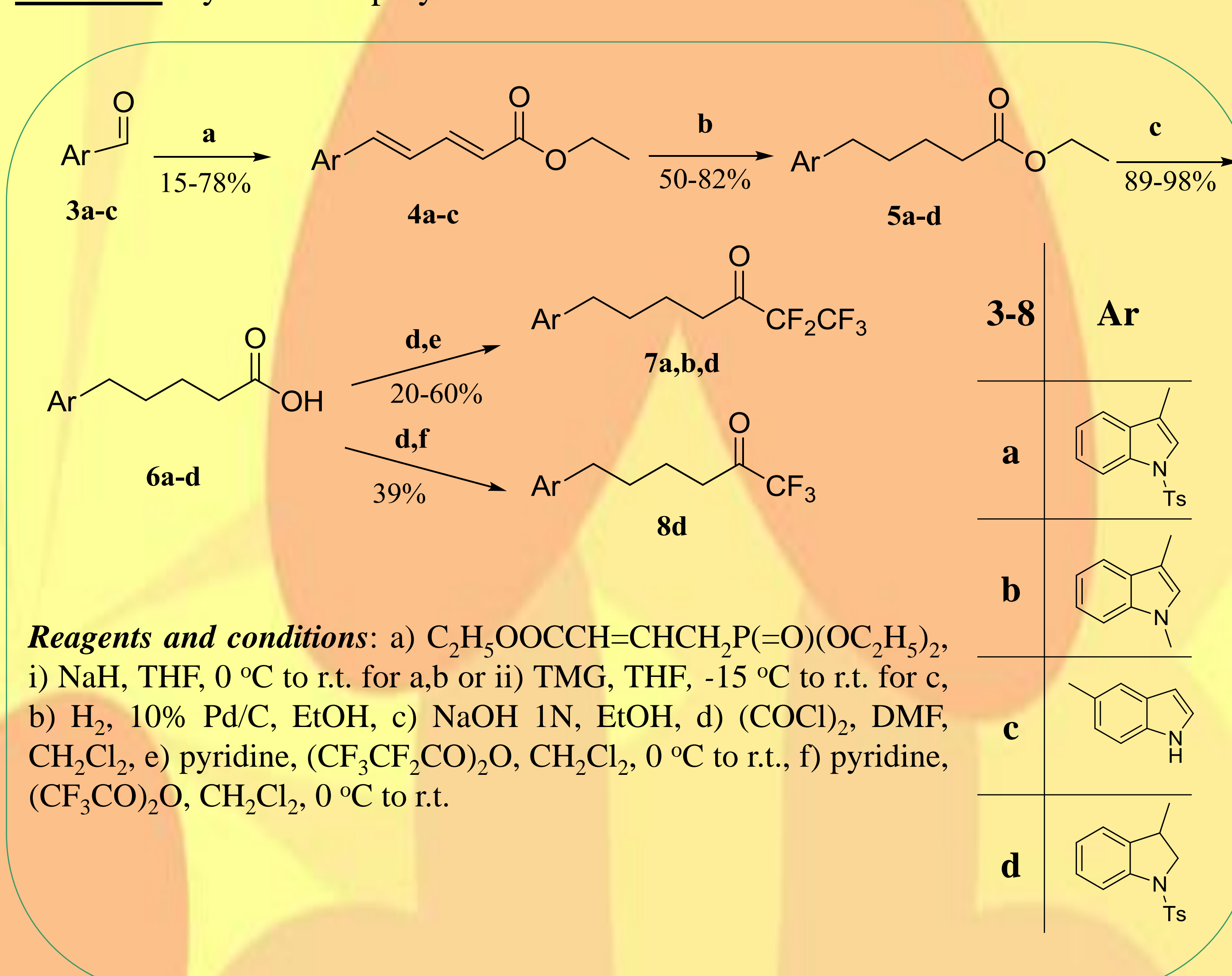
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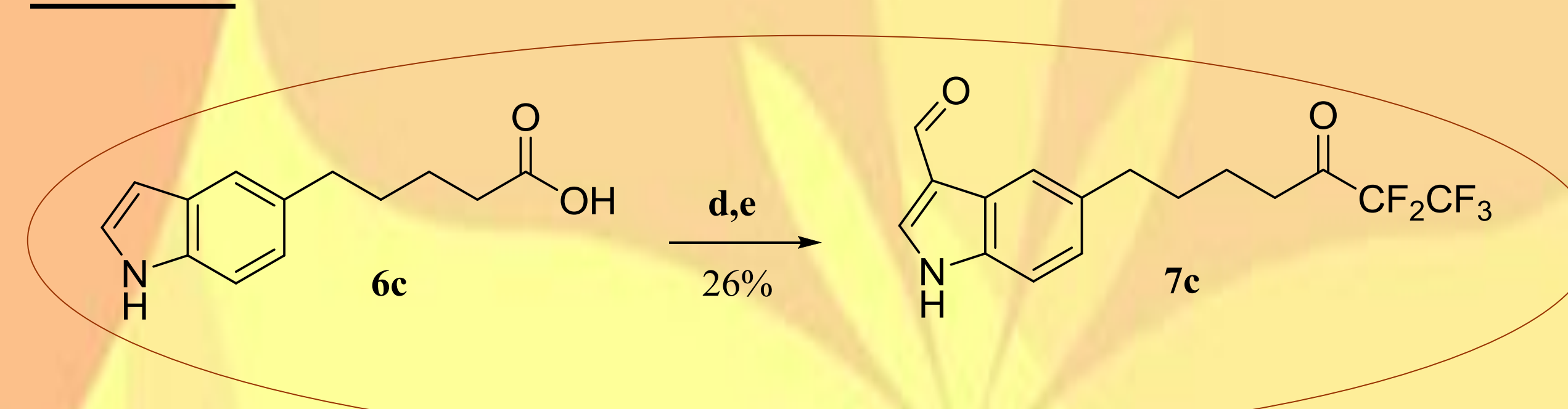
## Scheme 1: Synthesis of protected indole-3-carboxaldehyde



## Scheme 2: Synthesis of polyfluoroketones



## Scheme 3



## Conclusion

Five novel polyfluoroketones were synthesized containing an indole ring and the evaluation of their inhibitory activity is in progress.

## References

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