Ce projet est cofinancé par l'Union européenne
L'Europe s'engage en Picardie avec le Fond européen de développement régional

SYNTHESIS OF FLUORENES WITH POTENTIAL BIOACTIVITIES

Jérémy SCHNEIDER[1*], Alexandra DASSONVILLE-KLIMPT[1], Pascal SONNET[1]
(1) LG2A, UMR 7378, UFR de Pharmacie, Université de Picardie Jules Verne, 1 rue des Louvels, 80037 Amiens Cedex, France.
* jeremy.schneider@etud.u-picardie.fr

Introduction

Fluorenone and fluorene containing natural products display diverse structural features due to their various ring junctions and chiral centers. Both have potential bioactivities and this family of natural products aroused considerable attention from synthetic chemists. They have interesting physicochemical properties and could be used as fluorescent probes[1]. They display also high therapeutic activities as anti-oxidant, anti-bacterial, anti-cancer, anti-malarial, anti-myocardial ischemia or anti-Alzheimer[2-7].

For example, dendroflorin (**1**) and denchysan A (**2**) isolated from *Dendrobium chrysotoxum species*, inhibit the growth of human hepatoma BEL-7402 cells with IC_{50} values of 0.97 μg/mL, and 1.38 μg/mL respectively[3]. Dendroflorin has also an antimigratory effect at 1.0 µg/mL in 24h for H 460 cells (lungs cancer)[4]. 9-oxo-9*H*-fluorene (**3**) induces apoptosis and inhibits the tubulin polymerization in cells. This compound is active in the range of 0.15 to 0.29 µM for many cancer cells (T47D (breast), HCT 116 (colon), SNU 398 (carcinoma))[5] and represents thus interesting pharmacophore for the research of new anti-tumoral drugs.

Isolated from the radix of *Caulophyllum robustum* Maxim, Caulophine (**4**) has an anti-myocardial ischemia activity as a calcium antagonist[6]. Interestingly, some amino-fluorenes (**5**) have also shown a capacity to reduce the amyloid burden which induces severe neurodegeneration and cognitive deficits in Alzheimer's disease[7].

Fluorenes are very attractive scaffolds for the design of new therapeutic agents. In our laboratory, we focus on the design and the preparation of novel asymmetric 2,4,7-trisusbtituted fluorenes (**6**). Herein, we describe the first steps of a synthesis able to lead to a new library of enantiopure fluorenes with high potential bioactivities.

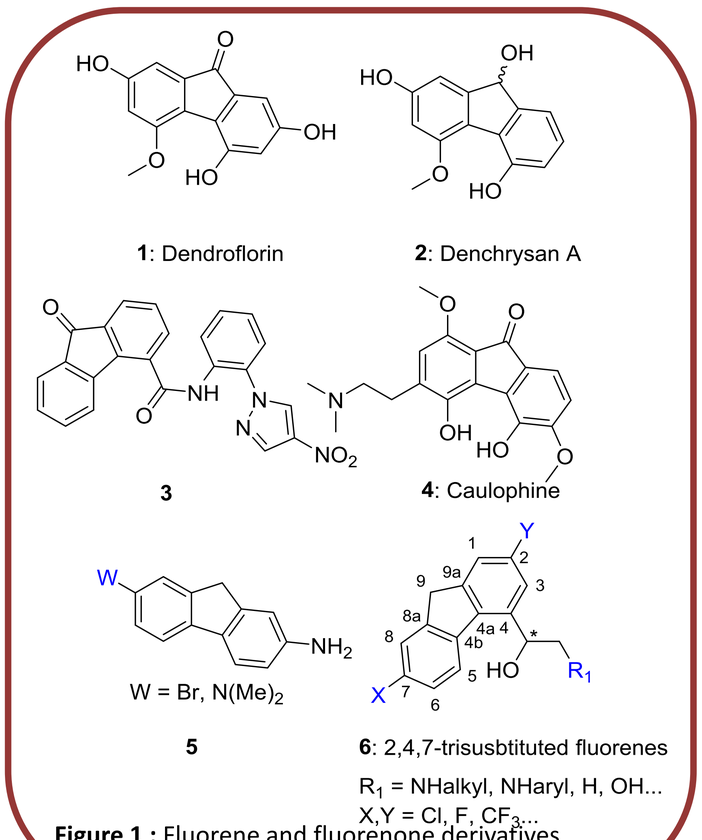


Figure 1 : Fluorene and fluorenone derivatives

Synthesis

Two **routes A** and **B** were envisaged to synthesize **2,4,7 – trisubstituted fluorene** derivatives (**Fig. 2**). These routes have a common intermediate **8** which can be prepared from fluorene through a radical Wohl-Ziegler reaction or a Friedel-Craft reaction (**Fig. 3**). We have synthesized four intermediates **8a-d**. Iodine compound **8d** can also be synthesized from **8b** by an halide exchange . It was obtained on two steps with 28 % of global yield.

The next step for the two routes was a Friedel-Craft chloroacylation realized in the presence of $AlCl_3$. Compounds **9a** and **11a** were obtained with respectively quantitative and 82 % yields. After reduction and dehydration of **11a**, vinyl compound **12a** was synthesized with 94 % yields (**Fig. 4**).

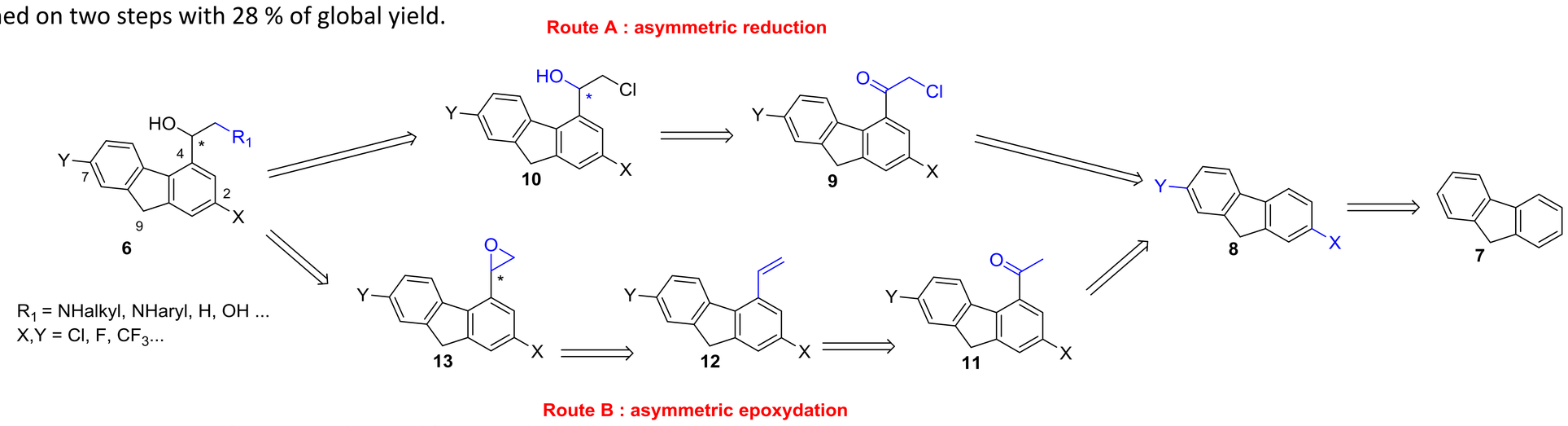


Figure 2 : Retrosynthesis of 2,4,7 – trisubstituted fluorenes derivatives **6**

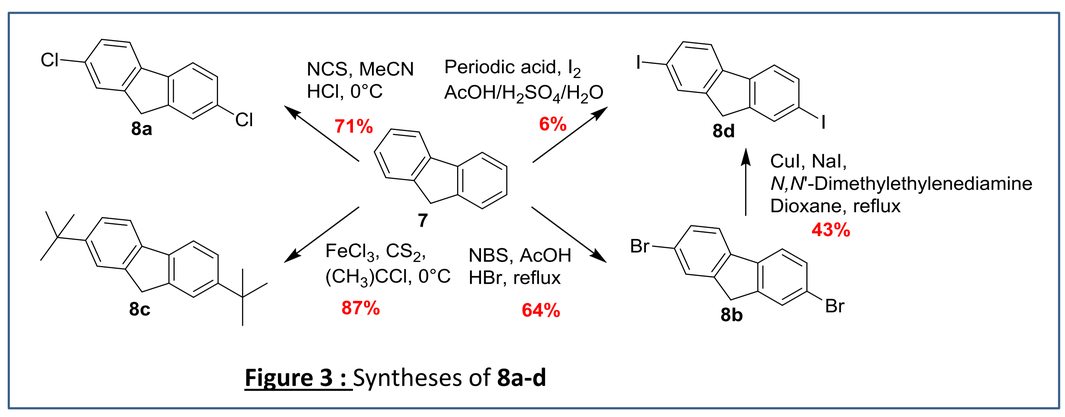


Figure 3 : Syntheses of **8a-d**

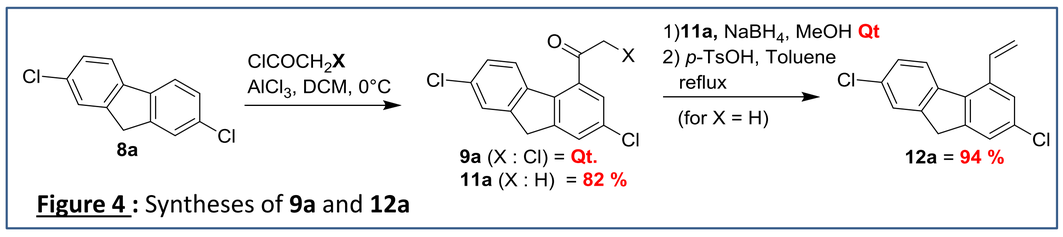
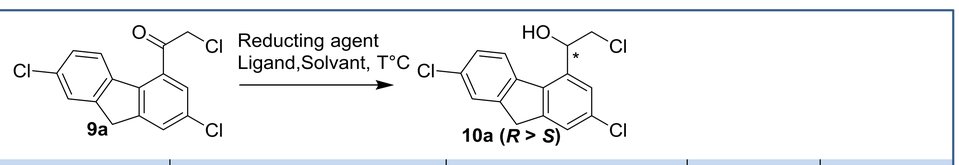


Figure 4 : Syntheses of **9a** and **12a**

In order to obtain a chiral chlorhydrine **10a** (**route A**) a Corey-Bakshi-Shibata reduction was accomplished on the compound **9a** (**table 1**). According to the solvent, the temperature and the quantities of reducing agent and/or ligand (*S*)-CBS, **10a** was obtained with 30 % to quantitative yield (entries 1-5, **table 1**) but unfortunately no enantioselectivity was observed. However, the use of BINOL as a ligand and $LiAlH_4$ as reducing agent (entry 6, **table 1**) has allowed to obtain **(*R*)-10a** with 53 % yield and 51 % enantiomeric excess.



Entry	Solvent	T°C	Reducing agent(eq.)	Ligand (eq.)	Yield(%)	ee. (%)
1	THF	0 – 23	BH_3.THF (0.7)	(*S*)-CBS (0.1)	30	22
2	THF	23	BH_3.THF (0.7)	(*S*)-CBS (0.5)	30	13
3	Toluene	23	BH_3.DMS (4)	(*S*)-CBS (0.1)	91	4
4	THF	0 – 23	BH_3.DMS(1.3)	(*S*)-CBS (0.01)	Qt	2
5	Toluene	-78 - 0	BH_3.DMS (4)	(*S*)-CBS (0.1)	Qt	9
6	THF	-78	$LiAlH_4$ (1)	(*S*)-BINOL (1)	53	51

Table 1: Synthesis of **10a** (**Route A**)

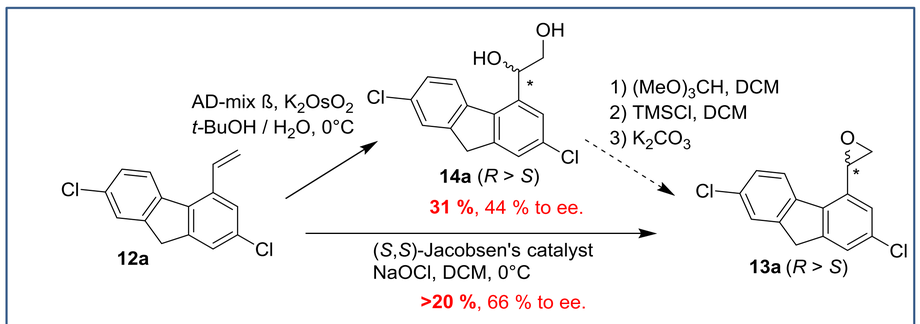


Figure 5 : Synthesis of **13a** (**Route B**)

Concerning the **route B,** the vinyl **12a** underwent an asymmetric Sharpless dihydroxylation to give the diol **(*R*)-14a** with 44 % of enantiomeric excess. The next step will be the epoxydation of the diol **14a** to give **13a**. We realized also a direct asymmetric Jacobsen epoxydation on the vinyl **12a** and obtained **(*R*)-13a** with a first promising 66 % enantiomeric excess (**Fig. 5**). Finally, we will achieve an enantiopure fluorenic platform with **10a** or **13a**. Fluorene **6** compounds will be synthesized after a direct S_N2 on **10** or *via* a nucleophilic addition on epoxyde **13**.

Conclusion

In this work, two enantiopure and synthetic routes to **6** have been investigated. At this time we have synthesized the compounds **13a** and **10a** with respectively a 66 % and a 53 % enantiomeric excess. Efforts are currently in progress to improve enantioselective steps. The synthesis of the epoxyde **13** or the chloro-alcohol **10** from common intermediates **8**, will allow us to obtain novels 2,4,7-trisusbtituted fluorenes with potential bioactivities**.**

[1.] Kucherak O. A. *et al.*, *J. Phys. Chem. Lett.* , 1, **2010**, 616–620. [2.] (a) Shi Y. *et al., Tetrahedron* 72, **2016**, 1717-1735. (b) Makanga M., *Malaria Journal*, **2014**, 13:291. [3.] Lam Y. et al., *Evidence-Based Complementary and Alternative Medicine*, **2015**, 1-25. [4.] Klongkumnuankarn P. *et al.*, *Evidence-Based Complementary and Alternative Medicine*, **2015**, 1-10. [5.] Kemnitzer W. *et al.*, *Bioorg. & Med. Chem. Lett.,* 20, **2010**, 1288-1292. [6.] Si K. W. *et al., Basic & Clinical Pharmacology & Toxicology*, 107, **2010**, 976-981. [7.] Hong H. S. *et al.*, *Neurobiology of Aging 31*, **2010**, 1690-1699.