

[A010]



UNITÉ DE PHYTOPHARMACIE ET MÉDIATEURS CHIMIQUES, INRA
ROUTE DE SAINT-CYR, 78026, VERSAILLES



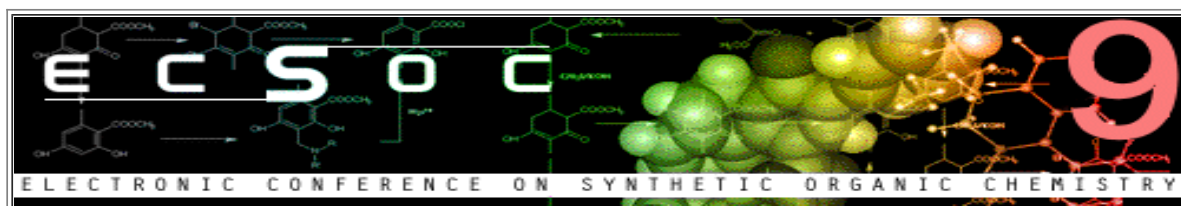
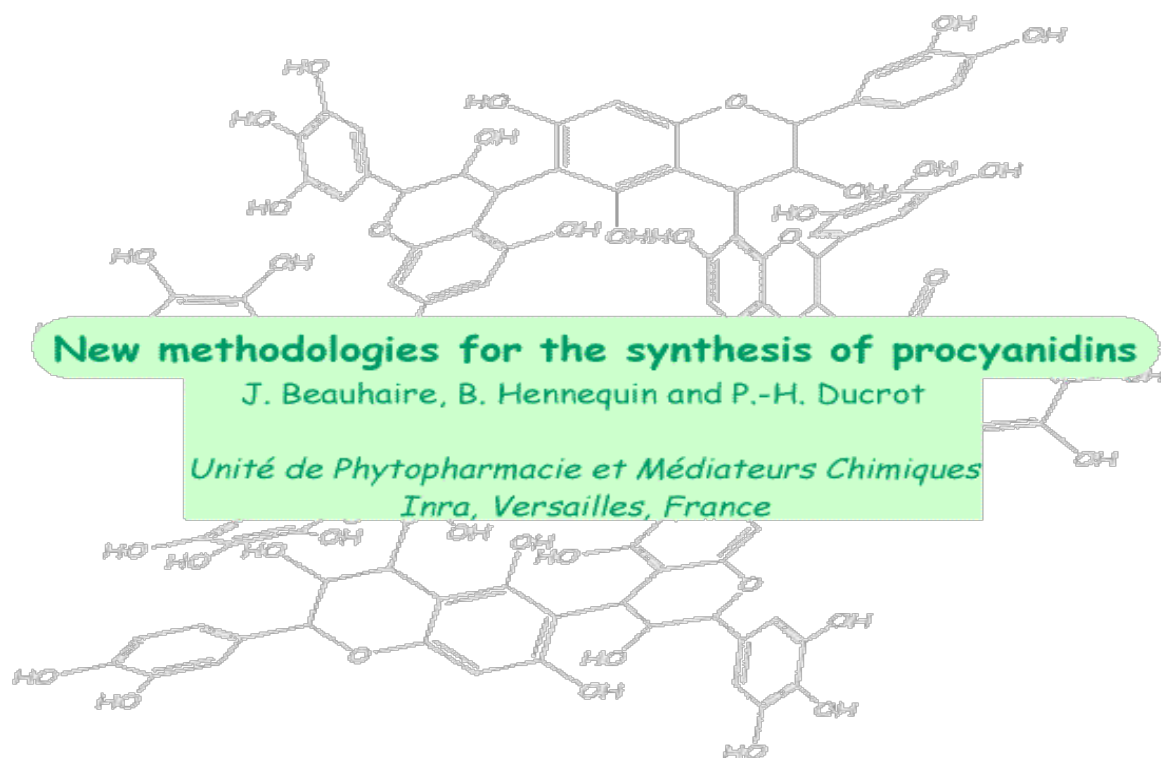
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FROM CINNAMIC ESTERS

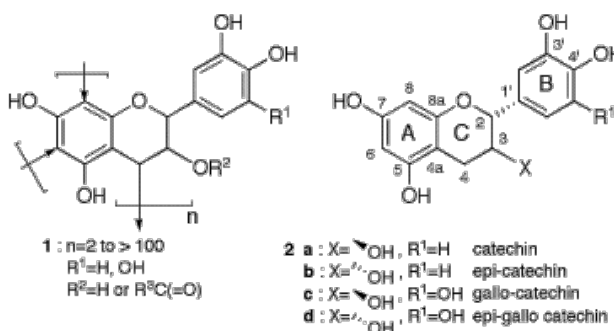
FROM CHALCONES

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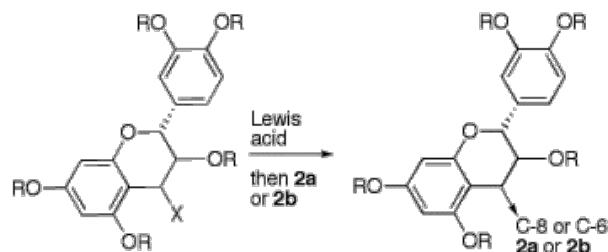
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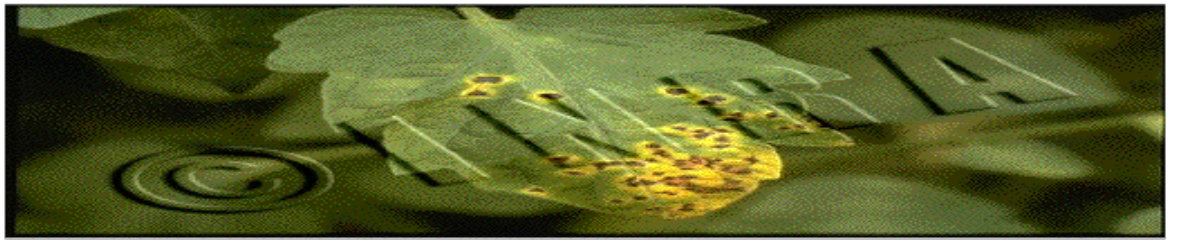
Proanthocyanidins are known as condensed or nonhydrolyzable tannins.[1–3] Many biological activities, and mainly a powerful free-radical scavenging activity[4-6], have been reported for flavonoids, and their investigation is now increasingly important. The flavan-3-ols protective effects on diseases involving oxidative stress like cancers,[7,8] cardiovascular,[9,10] and neurodegenerative[11] diseases have often been attributed to their antioxidative properties. Most of the described proanthocyanidins (procyanidins **1**) involve oligomerization of catechin derivatives **2a–d**. However, proanthocyanidins may be linked either through carbon–carbon and/or carbon–oxygen bonds. While the natural occurrence of dimeric procyanidins with a C–C interflavanyl linkage is well documented,[12–14] little is known about proanthocyanidin possessing an ether bond only as interflavanyl linkage. Natural compounds exhibiting this ether interflavanyl bond are relatively rare but some have been reported in species of *Acacia* heartwood and are not derived from catechins but from epioritin-4-ol. The first single ether-linked (C4-O-C4) dimeric promelacacinidins were indeed identified in *A. melanoxylon*[15] and were followed by similar bis-teracacinidins,[16] and the first (C4-O-C3) ether-linked bis-teracacinidins[17] from *A. galpinii*. Recently both C4-O-C4 and C4-O-C3 ether-linked dimers were also isolated from *A. coffra*. [18]



In an ongoing program aimed at the synthesis of modified proanthocyanidins, we were interested in the preparation of modified catechin derivatives involving introduction of substituents either at C6 and/or C8. This project prompted us to perform the synthesis of C4-O-C3 pseudo dimers of catechin derivatives[19], C6 and C8 hydroxylated catechin derivatives [20] and methylene linked catechin pseudo dimers [21].

Herein, we will show a new strategy aimed at the total synthesis of procyanidines. Indeed, all the reported strategies aimed at the same goal are until now derived from a unique methodology described in the following scheme. Depending on the nature of the substrate, of the leaving group X of the protecting groups R and on the Lewis acid used for the generating of the corresponding benzylic carbocation, the course of the reaction may be considerably affected. Therefore, we decided to investigate some other strategy for the synthesis of procyanidines, not derived from this widely documented "biomimetic" methodology.





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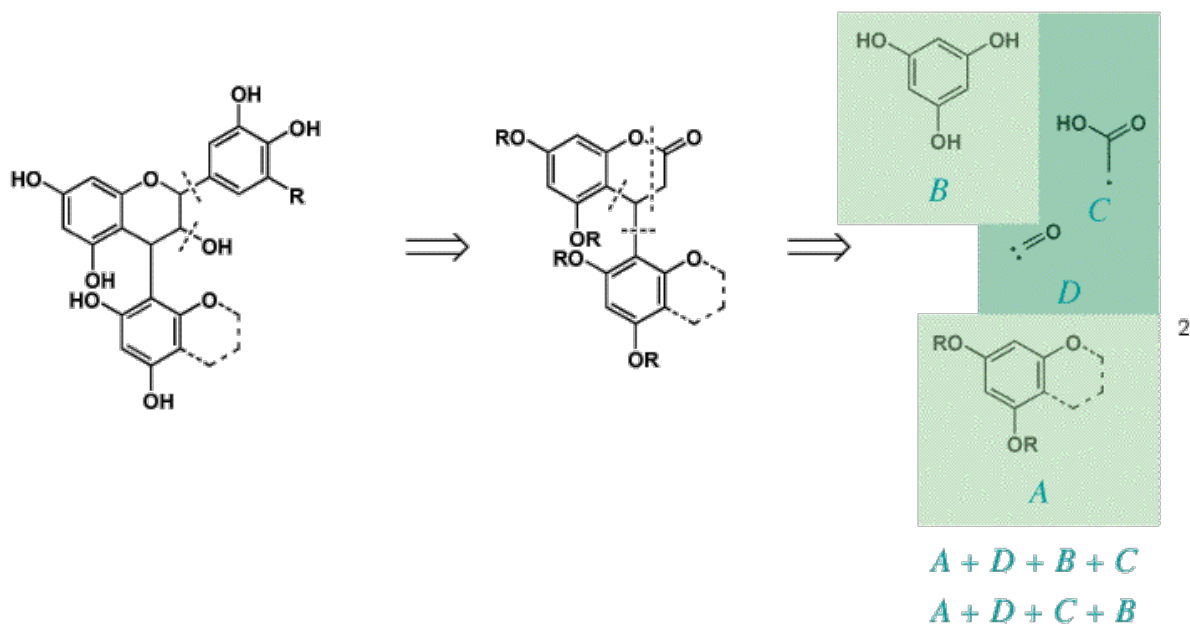
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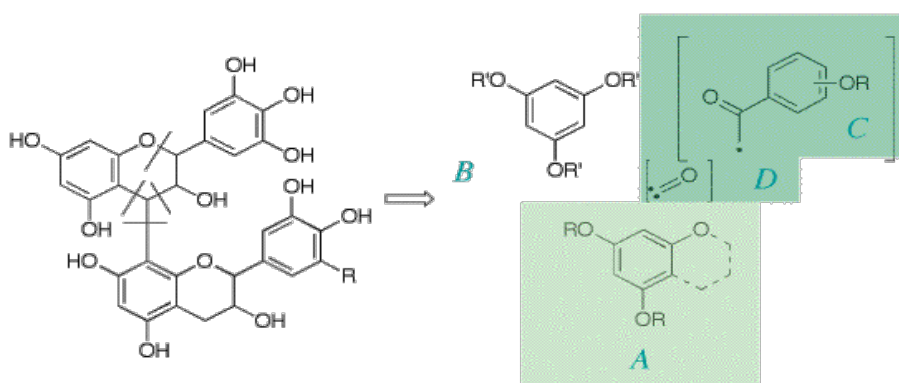
First retrosynthetic scheme through dehydrocoumarin pseudodimers



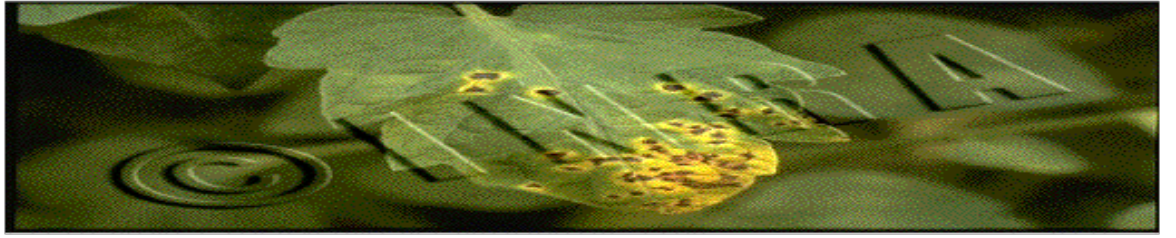
The first results concerning related to the "A+D+B+C" route, using catechin as fragment A, have already been published [20] and are summarized [here](#)

The main results related to the "A+D+C+B" route are described in the [From cinnamic esters](#) section, the A+D+C fragment being the desired cinnamic ester.

Second retrosynthetic scheme through condensation of phloroglucinol on chalcones



The difficulties encountered in the functionalisation of the carbonyl group of the dihydrocoumarins formed in the former part, prompted us to design a new method starting [from chalcones](#) (A+D+C)



Formation of the starting cinnamic esters

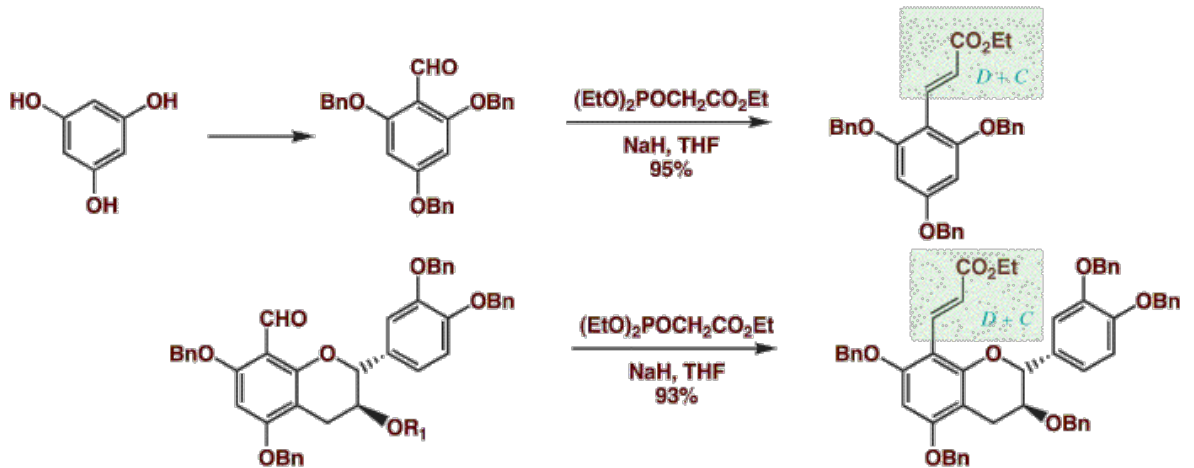
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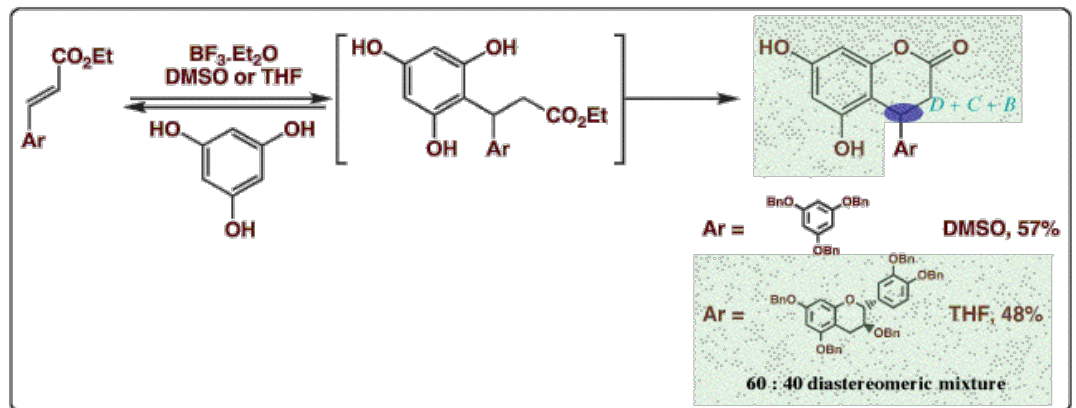
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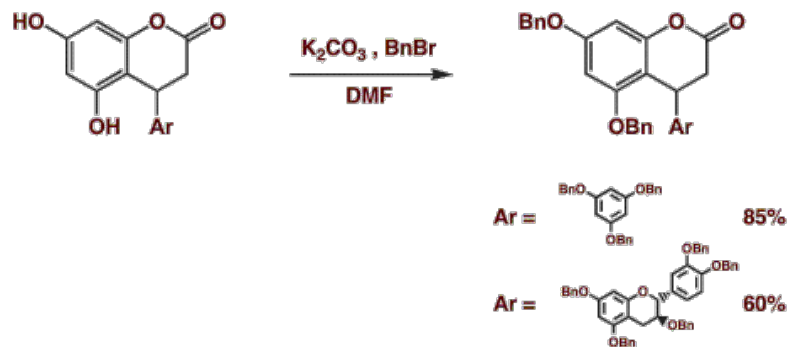
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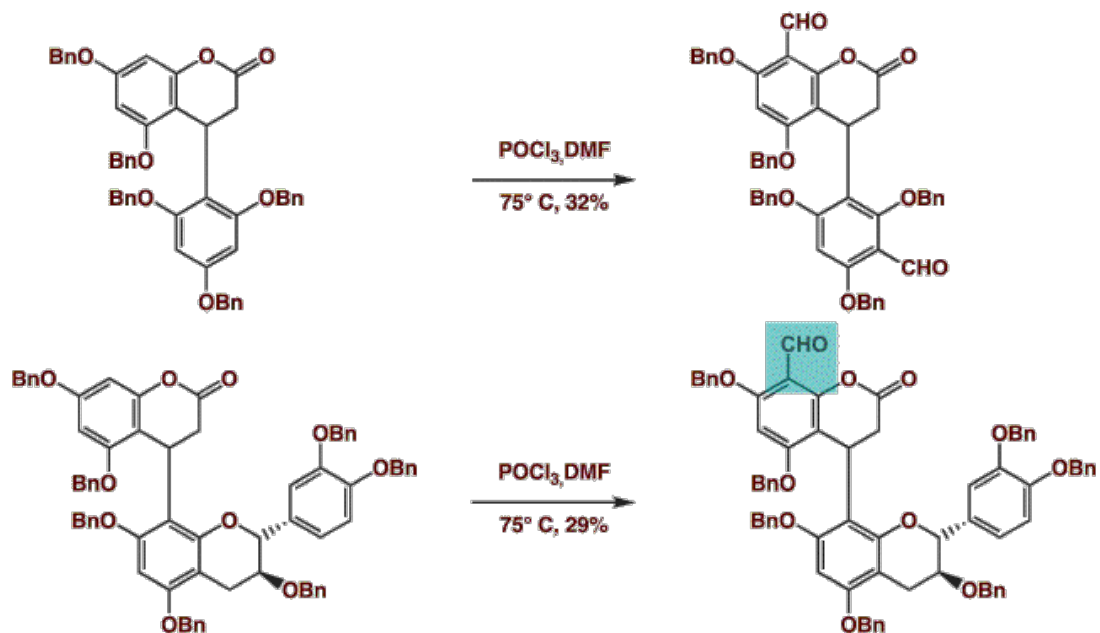


The key step: Lewis acid catalysed addition on phloroglucinol

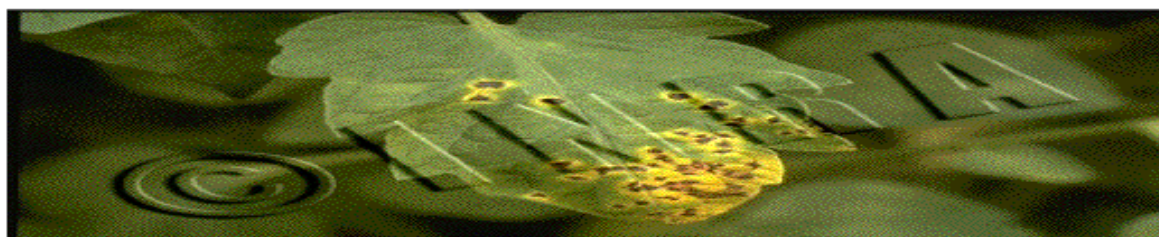
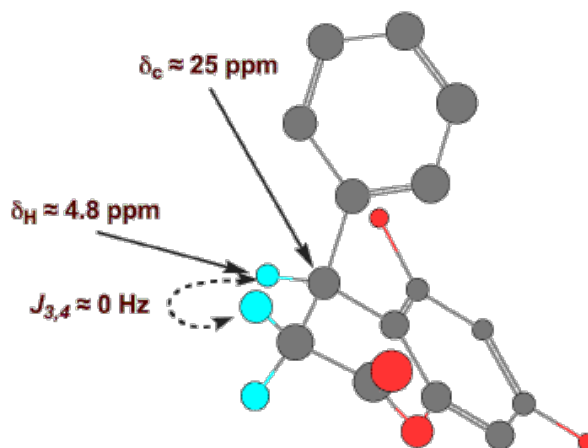


Further fonctionnailization of the dihydrocoumarins formed in the previous step





Pseudo boat conformation of the dihydrocoumarins



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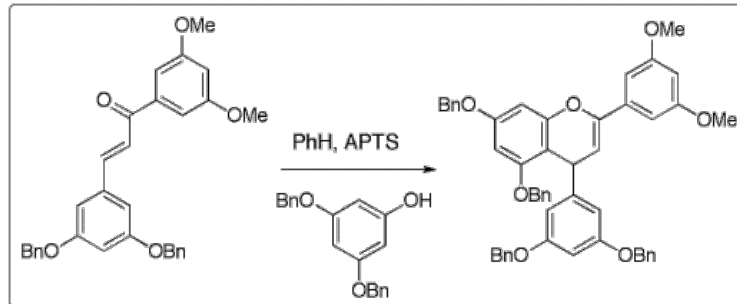
Lewis acid catalysed addition of chalcones on di-*O*-benzyl phloroglucinol

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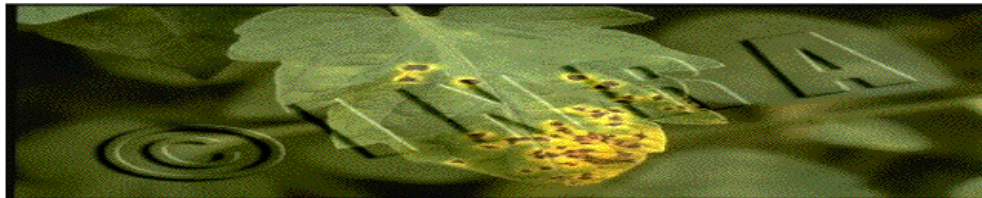
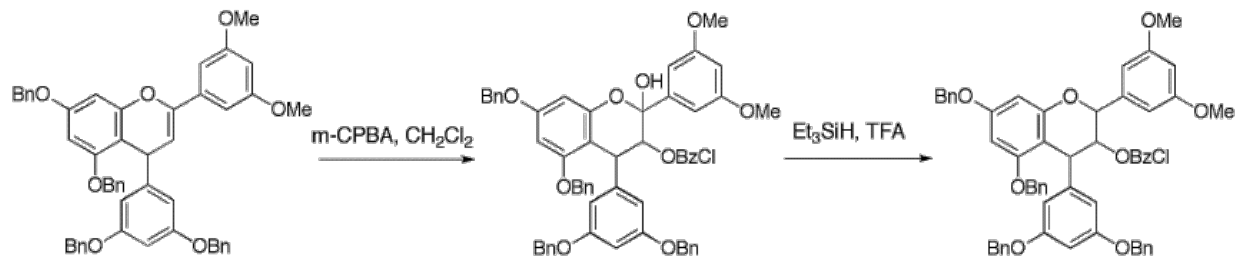
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Further fonctionnalisation at C-2 and C-3



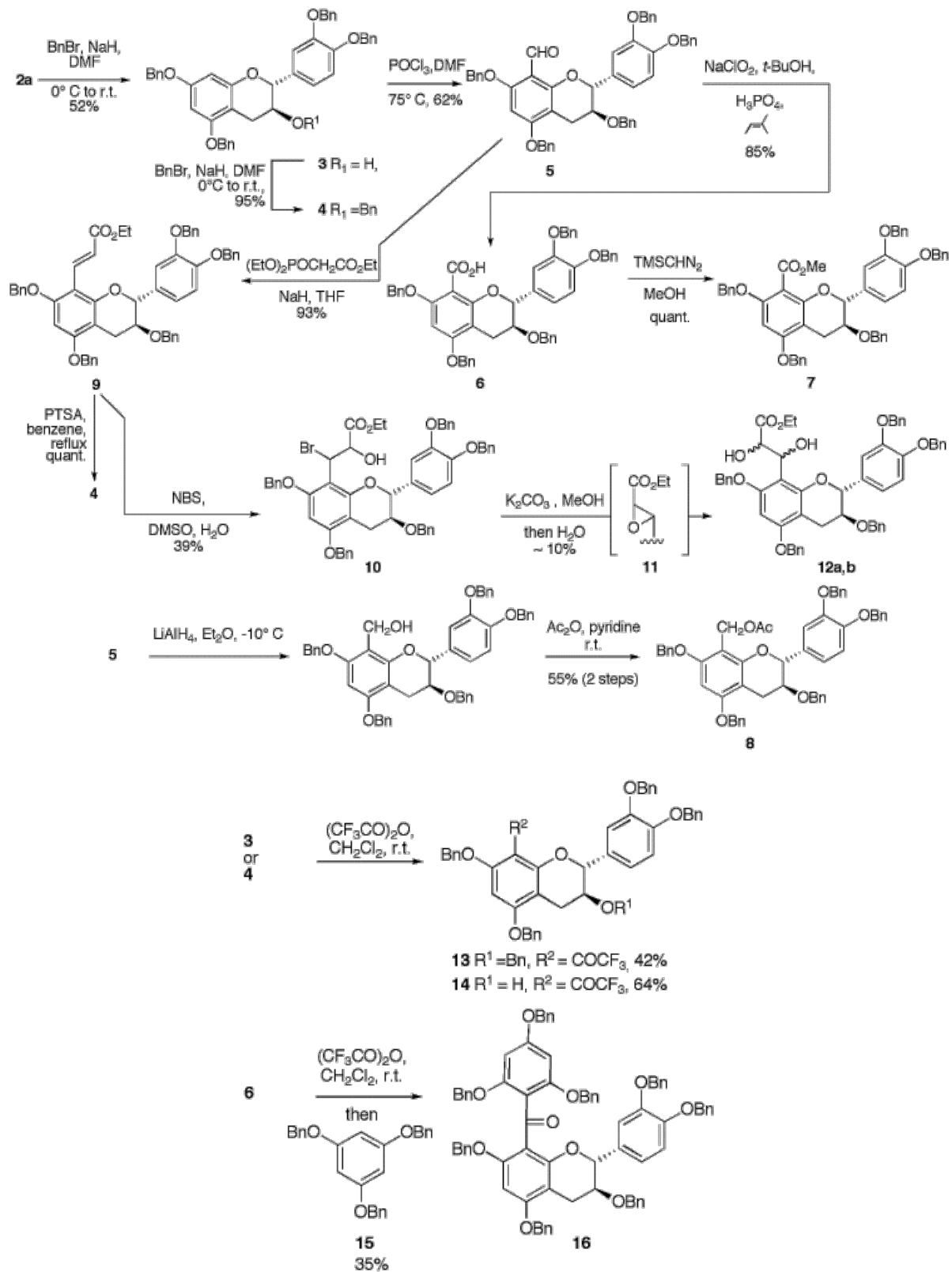
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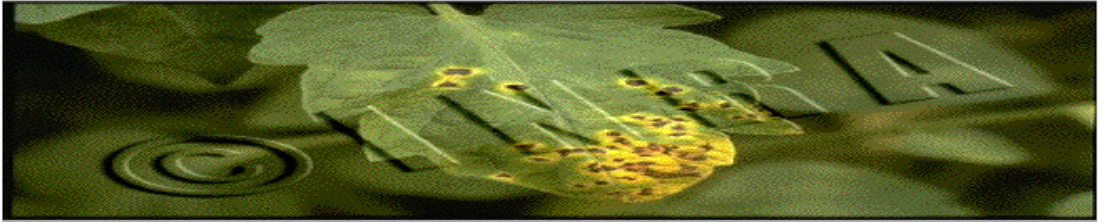
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