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New Recurrent Synthetic Method for the Synthesis of Functionalized Oligomeric β-O-4 Lignin Model Compounds.

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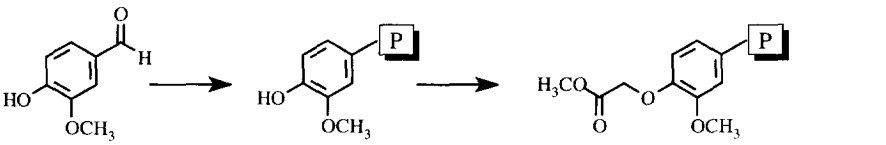
Abstract : β-O-4 lignin model compounds have been synthesized using a new recurrent method affording dimers and trimers with controlled stereochemistry and bearing an aldehyde group.

Lignins are complex polyphenolic vegetal polymers[1,2] which valorization is still a challenge. Lignin model compounds are therefore very useful in the studies of mechanisms and structures dealing with biosynthesis[3], degradation and complexation processes.[4] However, lignin models frequently used are either synthetic lignin which are almost as complex as native lignin or small molecules like dimers which can not mimic the polymeric characters of lignin. It would be interesting to develop a method for the preparation of oligomeric β-O-4 structure type (aryl-alkyl-ether) which is the most abundant structural patterns of lignins.[2,4] The recurrent synthetic method we have developed consists on the formation of β-O-4 dimer or trimer structures containing a masked aldehyde. The aldehyde function can allow a further access to higher molecular weight polymers; it also can be used to anchor phenolic lignin models to solid support for a better biodegradation process[5] mimic.

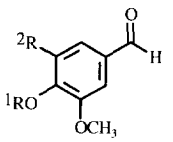
This synthetic method was based on a repetitive sequence: aldolic condensation[6,7] between a phenolic aldehyde moiety (**3**[8] or **6**) and a guaiacyl ester enolate bearing a masked aldehyde function (**2**), reduction of the ester group, liberation of the protected aldehyde and protection of the β-diol (**6**) (scheme 1). The results were dependent on the protective groups retained for masking the aldehyde function. If the condensation reaction is carried out using dioxolane **2a**, the β-aryl ether compound is not formed ; in contrast the corresponding cinnamic aldehyde was isolated.[9]

The dimethyl acetal **2b** synthesized from trimethyl orthoformate proved to be unstable on silica gel and readily decomposed to the corresponding aldehyde. Finally, the protection by 2,2-dimethyl propanediol allowed us to synthesize the dioxane **2c**[10] which exhibits all the stability requirement for further reactions and purification steps.



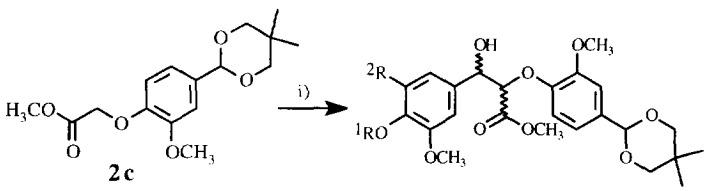
1a : P = dioxolane
1b : P = dimethyl acétal
1c : P = 4,4-dimethyl dioxane

2a : P = dioxolane
2b : P = dimethyl acétal
2c : P = 4,4-dimethyl dioxane

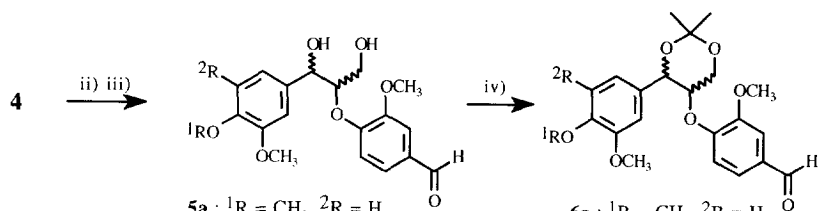


3a : $^1R = CH_3$, $^2R = H$
3b : ^1R = benzyl, $^2R = H$
3c : ^1R = benzyl, $^2R = OCH_3$

After aldolic condensation of compound **2c** with **3**, the ester group was reduced using DIBAH. The aldehyde moiety was then deprotected in acidic media. In order to perform a second aldolic condensation, the intermediate diol was then protected with acetone to give the dioxanes **6**.



4a : $^1R = CH_3$, $^2R = H$
4b : ^1R = benzyl, $^2R = H$
4c : ^1R = benzyl, $^2R = OCH_3$



5a : $^1R = CH_3$, $^2R = H$
5b : ^1R = benzyl, $^2R = H$
5c : ^1R = benzyl, $^2R = OCH_3$

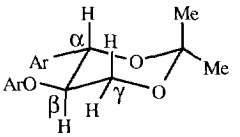
6a : $^1R = CH_3$, $^2R = H$
6b : ^1R = benzyl, $^2R = H$
6c : ^1R = benzyl, $^2R = OCH_3$

Scheme 1 : synthetic sequences for β-O-4 structure elaboration.
i) : LDA/THF -78°C 45 min, then **3** (~50%) ; ii) : DIBAH/THF 0°C (~75%) ;
iii) : oxalic ac. THF/MeOH/H_2O (5/3/2) RT (~100%) ; iv) $CuSO_4$/acetone RT (~80%).

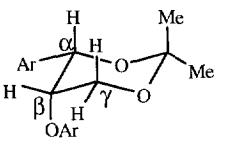
An erythro/threo ratio of 65:35 (**4a**) and 70:30 (**4b**) was determined from ^1H NMR analysis based on previous studies from Lundquist and al.[11] A diastereoisomeric control can occur using a more sterically crowded ester enolate[12]. Erythro and threo compounds **4** could not be separated on silica gel column. However,

compounds **4b** and **4c**, bearing a protective benzyl ether, crystallize (iPr_2O/Et_2O; 3/1) as a mixture in which erythro isomers largely predominate (over 90%). The residue results in a yellow oil containing the threo isomer and an impurity which was isolated and identified as a benzyl alcohol compound. Its formation might be due to the reduction of the carbonyl function in compound **3** by an hydride transfer[13] from LDA present in excess. The structure of this by-product has been confirmed carrying out the reduction of **3** with $NaBH_4$. In order to preclude this secondary reaction and to increase the yield of the condensation step, a base like hexamethyldisilazane which lacks an α proton to the nitrogen atom, would be helpful in further studies.

While the protection of hydroxyl groups with trimethylsilyl chloride was found troublesome, the reaction of 1,3-diol **5** with acetone allowed us a facile separation of erythro and threo isomers by HPLC.[14] The structural assignment was easily deduced from ^1H NMR chemical shift and coupling constants values found for the dioxanes **6** erythro and threo.



6-erythro



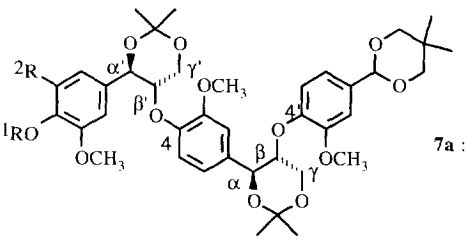
6-threo

Table 1[15]: ^1H NMR (250 MHz) data for identification of erythro and threo diastereoisomers **6**[a].

	α-H	β-H	γ_{ax}-H	γ_{eq}-H
6b-erythro	4.93 (9.0)	4.32 (9.0; 8.9; 5.2)	4.16 (11.6; 5.2)	4.01 (11.6; 8.9)
6b-threo	5.07 (2.0)	4.28 ([b])	4.20 (13.0; 2.0)	4.18 (13.0; 2.0)

[a] Chemical shifts from TMS measured in $CDCl_3$ (J in Hz). [b] multiplet: Jax-eq ≅ Jeq-eq.

The erythro dimer **6a** was further reacted with compound **2c** in a second aldol condensation. The aldol adduct was then reduced and the β-diol protected to afford the trimer **7a** with still a predominant erythro-erythro structure.[16] This repetitive sequence could as well be applied to **6b** and **6c**.



7a : $^1R = CH_3$, $^2R = H$

Scheme 3 : di-β-O-4 erythro-erythro protected trimer.

The originality of the synthetic scheme developed above lies on the presence of a free aldehyde function on a β-O-4 dimer. This functionality allows us to access to oligomers of higher molecular weight. For this purpose, the use of protective discriminating group for the aldehyde and β-diol functions are currently under investigation. The β-diol protection must resist to the aldehyde deprotection and also facilitate the erythro and threo isomers purification for further steps. Nevertheless an anchorage on solid support could be realized using an amino linker

between the aldehyde and the support. The same synthetic approach has been developed to a dialdehyde resulting from an oxidative coupling of vanillin at the C_5 position and allow the synthesis of a mixt aryl-aryl β-O-4 tetramer.[17] The fully elucidation of its structure by NMR and MS data is currently under investigation.

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8. **3a** is commercially available. Benzyloxy derivatives **3b** and **3c** were prepared from vanillin and syringaldehyde by benzylation (benzyl chloride / K_2CO_3 / KI in refluxing acetone) followed by filtration on silica gel using mixture of methylene chloride/petroleum ether (80/20) to eliminate excess of benzyl chloride. Yields were over 80%.
9. Duran, H.; Roblin, J.-Ph.; Gorrichon, L. *C.R. Acad. Sci. Paris*, submitted for publication.
10. **1c** was prepared from vanilline by acetalization (2,2-dimethyl propanediol/*p*-TsOH in refluxing benzene using Dean-Stark apparatus). **2c** was prepared following the procedure described by Nakatsubo (ref. 6 above). Overall yield was 80%.
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14. HPLC purifications of **6** were performed on a Jobin-Yvon miniprep apparatus using silica gel 15-40 mm column and methylene chloride/ethyl acetate/petroleum ether (4/1/5) as eluent.
15. Chemical shift and coupling constant J for diastereoisomers erythro/threo **6a** and **6c** are similar to those for **6b**.
16. In the ^{1}H NMR domain from 4.5 to 6.0 ppm, we observed a singlet at 5.24 ppm corresponding to the acetal proton of the masked aldehyde and two doublets corresponding to α-H and α'-H at 4.88 ppm (J = 8.34 Hz) and 4.81 ppm (J = 8.35 Hz) respectively. These values are in accordance with an erythro-erythro stereochemistry. Signals for β-H, β'-H, γ-H and γ'H are overlapped.
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