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ENANTIOSELECTIVE SYNTHESIS OF FOUR ISOMERIC BUILDING BLOCKS USEFUL IN THE SYNTHESIS OF 2-NOR-LEUKOTRIENE ANALOGUES

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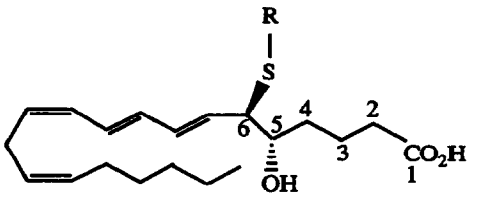
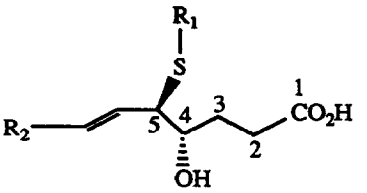
Abstract : We report, in this letter, the enantioselective synthesis of four isomeric functionalized epoxides (**3a, 3b, 3c** and **3d**) which are useful building blocks for the synthesis of 2-nor-leukotriene analogues. All four epoxides are formally derived from a single non chiral starting material, the 2-butyne-1,4-diol **7**.

The peptidoleukotrienes (LTC_4, LTD_4 and LTE_4) exert profound pharmacological effects on respiratory smooth muscle contractility and microvascular permeability, thus implying a possible role in allergic asthma[1]. So, the discovery of selective peptidoleukotriene antagonists remains a major focus for pharmaceutical research.

Previous studies in our laboratories[2] as well as in other groups[3-5], have resulted in the identification of antagonists obtained by modification of the backbone of the natural LTD_4. A flip from agonist to antagonist was observed when shortening the distance between the peptide and the carboxylate moieties, resulting in 2-nor-leukotrienes analogues **2** (Figure 1). In the natural series, all four isomers at chiral centers C5 to C6 have been prepared, firstly in order to assist in determining the exact stereochemistry of the natural leukotrienes and secondly for a better understanding of the structure-activity relationships[6]. In the course of an ongoing programm aimed at the discovery of novel leukotrienes antagonists we were interested in preparing a series of nor-LTD_4 analogues **2**. The synthesis of these derivatives required a short, efficient, stereo- and enantio-specific access to the four isomeric intermediate aldehydes **3a** to **3d** (Figure 2). We anticipated that all four isomers **3a** to **3d** could formally derive form a single non chiral precursor, the butynediol **7** (Figure 3). The synthesis of the trans-aldehydes **3a** and **3b** was first accomplished as depicted in Figure 4 (Schemes 1 and 3) : LAH reduction of **7** gave the butenediol **8** which was monoprotected as its p-bromobenzylderivative **9**[7]. Subsequent enantioselective epoxidation using Sharpless's reagent afforded **10a** and **10b**[8]. The enantiomeric purity of these enantiomers have been established to be greater than 95% by 400 MHz NMR on the Mosher's ester derivatives. Smooth oxydation of the free alcohols gave the corresponding aldehydes[9] which were submitted to a Wittig-type reaction to afford the unsaturated compounds **11**. The next key step required the reduction of the double bond without opening of the epoxide. This was nicely accomplished by diimide, using Cusack's procedure[10]. Then, removal of the protecting benzyl group of **12** followed by oxidation gave us the trans, optically active aldehydes **3a** and **3b**. Their enantiomeric purity have been found to be greater than 95% by ^1H and ^{13}C NMR analysis

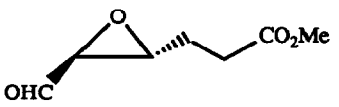


1 : Natural peptidoleukotrienes

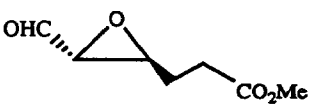


2 : 2-nor-peptidoleukotrienes analogs

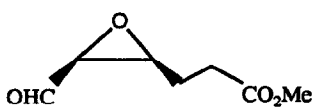
Figure 1 : Peptidoleukotrienes and norpeptidoleukotriene analogs



4 (R), 5(S) **3a**



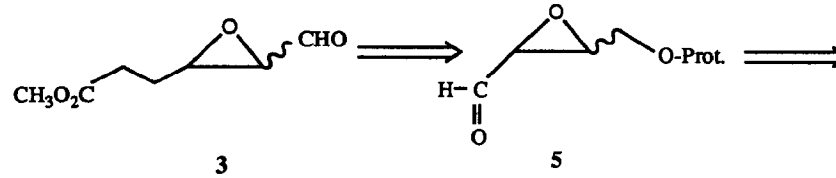
4 (S), 5 (R) **3b**



4 (S), 5 (S) **3c**

4 (R), 5 (R) **3d**

Figure 2 : Chiral epoxy-aldehyde intermediates



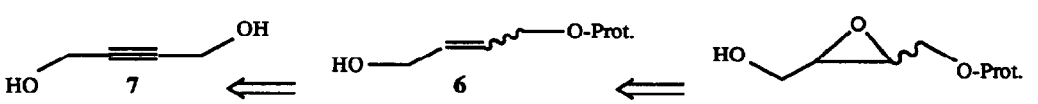
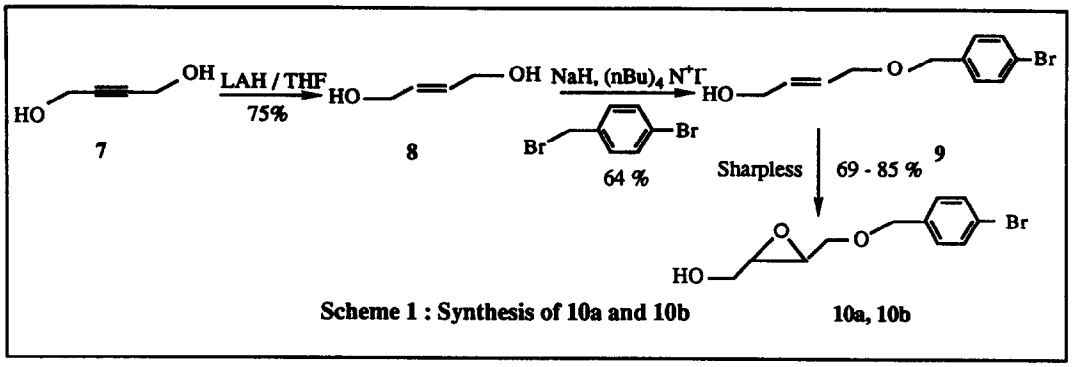
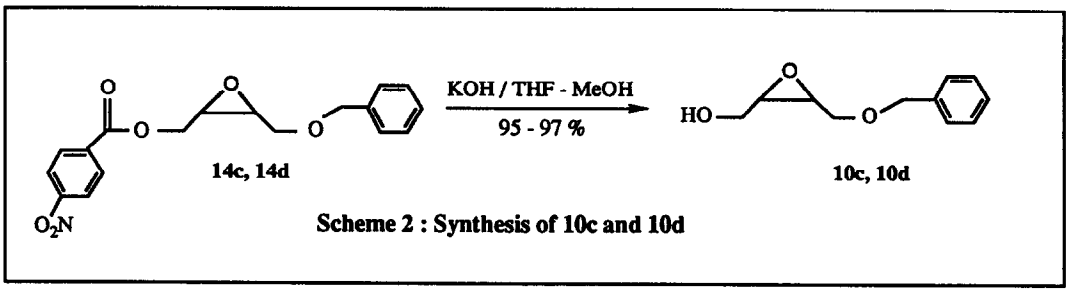


Figure 3 : Retrosynthetic scheme

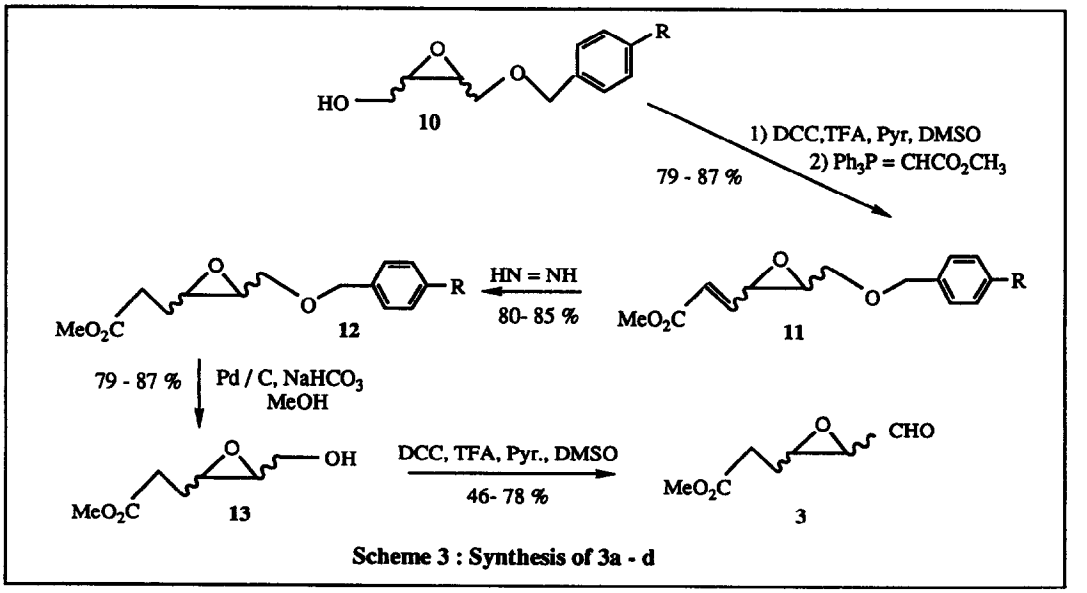
FIGURE 4



Scheme 1 : Synthesis of 10a and 10b



Scheme 2 : Synthesis of 10c and 10d



Scheme 3 : Synthesis of 3a - d

(300 MHz) after derivatization with a chiral diamine[11] (Peaks due to the other diastereoisomer were not detected).

Although the cis-alcohols **10c** and **10d** corresponding to **10a** and **10b** should also be available from butynediol **7**[7], it was more convenient to prepare **10c** and **10d** (R = H) by saponification of the paranitrobenzoates derivatives **14c** and **14d** commercially available in high enantiomeric purity[12] (Scheme 2). The same sequence of reactions allowed us to obtain the isomeric aldehydes **3c** and **3d**. As for the trans isomers, the optical purity of the trans aldehydes has been checked by ^{1}H and ^{13}C NMR analysis of the corresponding imidazolidines and found to be greater than 95%.

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References and Footnotes

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   b) Boubia, B., Thesis, Université Louis Pasteur, Strasbourg, 1990.
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6. See reference 1 p. 38
7. In order to get crystalline, easy to purify compounds, we used a procedure described for the corresponding cis-derivatives :
   Chong, J.M., Wong, S., *J. Org. Chem.*, **1987**, *52*, 2596-2598.
8. One enantiomer of the trans family has been described by Chong and al.[7] ; it has been obtained by Sharpless epoxidation of the corresponding monoprotected trans butynediol.
9. We did not try to isolate the corresponding aldehydes but we carried out the olefination reaction in the same pot.
10. Cusack, N.J., Reese, C.B., Roozpeikar, B., *J. Chem. Soc. Chem. Commun.*, **1972**, *20*, 1132-1133.
11. Mangeney, P., Alexakis, A., Normant, J.F., *Tetrahedron Letters*, **1988**, *29*, 2677-2680.
12. Both enantiomers are commercially available from FLUKA.
13. $[\alpha]_D$ values mesured in $CHCl_3$: **10a** : $[\alpha]_D^{22}$ = +17.7 (c = 2.12); **10b** : $[\alpha]_D^{22}$ = -17.7 (c = 2.07); **10c** : $[\alpha]_D^{22}$ = -26 (c = 1.055); **10d** : $[\alpha]_D^{22}$ = +26 (c = 0.91). **12a** : $[\alpha]_D^{24}$ = +19.3 (c = 2.45); **12b** : $[\alpha]_D^{24}$ = -19.6 (c = 2.5); **12c**: $[\alpha]_D^{24}$ =-19.7 (c = 1.40); **12d** : $[\alpha]_D^{24}$ = +19.3 (c = 1.20). **11a** : $[\alpha]_D^{20}$ = +17.6 (c = 2.3); **11b** : $[\alpha]_D^{20}$ = -17.1 (c = 2.07); **11c** : $[\alpha]_D^{20}$ = +15.3 (c = 1.24); **11d** : $[\alpha]_D^{20}$ = -15.6 (c = 1.14). **13a** : $[\alpha]_D^{20}$ = +42 (c = 1.32); **13b** : $[\alpha]_D^{20}$ = -42.9 (c = 1.62); **13c** : $[\alpha]_D^{20}$ = -14.1 (c = 0.82); **13d** : $[\alpha]_D^{20}$ = +13.8 (c = 0.84). **3a** : $[\alpha]_D^{23}$ = -82.8 (c = 1.15); **3b**: $[\alpha]_D^{23}$ = +84.6 (c = 1.30); **3c** : $[\alpha]_D^{25}$ = -118.9 (c = 0.98); **3d** : $[\alpha]_D^{25}$ = +125.0 (c = 1.20).