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Stereospecific 1,2-Aryl Migration in 2-Hydroxy Alkyl Aryl Acetals with PPh_3/CCl_4. Syntheses of Optically Active Ibuprofen and Naproxen*

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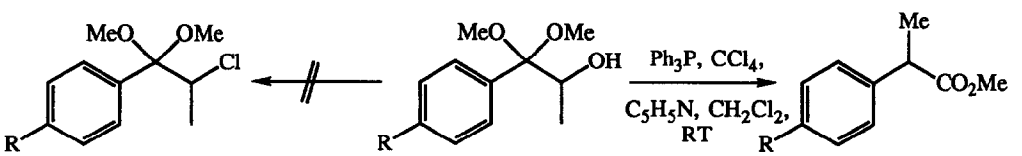
Abstract: Treatment of 2-hydroxy acetals (R)-(-)-**1** and (R)-(-)-**3** with PPh_3 and CCl_4 resulted in a stereospecific 1,2-aryl migration leading to the asymmetric synthesis of (R)-(-)-**2** and (R)-(-)-**4** respectively.

The use of enantiomerically pure drugs in chemotherapy is almost becoming mandatory not only to realize the enhanced specificity of drug action[1] but to avert the possible toxicity and undesirable load on the metabolism by the other enantiomer [1]. Currently, the synthesis of optically active α-arylpropanoic acids has emerged as an area of intense research[2] owing to their marked anti-inflammatory action. In this context, the rearrangement reactions of propiophenone derivatives are merited for their propensity for stereospecific 1,2-aryl migration and utilized in obtaining optically active acids on a practical scale[3].

Generally, the reactions of alcohols with PPh_3/CCl_4 are known to offer alkyl halides without any rearrangement[4]. However, we reported recently[5] that such a treatment of (±)-2-hydroxy propiophenone dimethylacetals in the presence of pyridine resulted in a rearrangement, furnishing (±)-methyl-2-arylpropanoates in high yields, to the total exclusion of the expected chloro-ketones (eqn. 1). We wish to demonstrate herein the potential of this reaction in realizing the synthesis of optically active Ibuprofen and Naproxen in high yields.

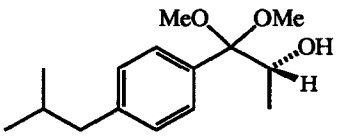


Equation 1

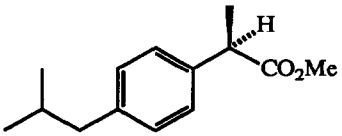
The optically active α-hydroxy acetals[6-8] (R)-(-)-**1** (82% ee) and (R)-(-)-**3** (70% ee), when subjected to the reaction conditions shown in eqn. 1 furnished the corresponding optically active esters (R)-(-)-**2** (82% ee) and (R)-(-)-**4** (70% ee), without any significant loss of optical purity[9], thus indicating the occurrence of stereospecific rearrangement with inversion of configuration at the carbon bearing the hydroxyl group. These results further provide an experimental support to the mechanism proposed earlier by us for the rearrangement.

In this context, the isolated report[7] of obtaining (-)-**2** by the treatment of (-)-**1** with SO_2Cl_2 in the presence of base, especially at low temperatures, deserves to be mentioned. Nevertheless, the presently observed efficient and stereospecific rearrangement represents one of the very few examples of asymmetric processes with the use of PPh_3/CCl_4. Finally, this transformation provides an efficient and convenient route to optically active Ibuprofen and Naproxen.

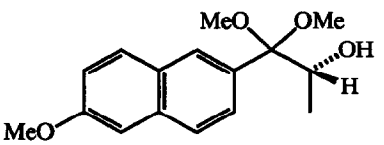
In a typical experiment, to a premixed solution of (R)-(-)-**1** (5 mmol), PPh_3 (7.5 mmol), pyridine (10 mmol) in CH_2Cl_2 (10 ml), dropwise addition of CCl_4 (25 mmol) was made at room temperature. After stirring the reaction mixture for 15 hours, the product was isolated[5] in 78% yield. Similarly, the reaction of (R)-(-)-**3** afforded (R)-(-)-**4** in 81% yield.



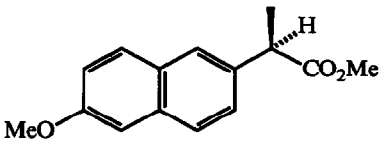
(R)-(-)-1



(R)-(-)-2



(R)-(-)-3



(R)-(-)-4

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Reference and notes

* NCL communication number 5122.

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6. (R)-(-)-**1** and (R)-(-)-**3** were preparerd in five steps from (S)-ethyl lactate following known procedures (refs. 7, 8). Higher enantiomeric purities of **1** and **3**, however, could not be realized owing to known slight racemization occurring during the preparation of the α-hydroxy acetal.

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9. The optical purity of (R)-(-)**1** and (R)-(-)-**3** as well as that of the products has been determined by a direct comparison of their specific rotations with those reported[7] and by their PMR data using the Chiral shift reagent, $Eu(hfc)_3$.