Asymmetric synthesis of enantiomerically pure drugs involving organobrominated intermediates

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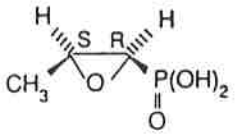
The neglet of stereochemistry in the development and application of drugs in general leads to serious misconceptions and is a source of problems in pharmacokinetics [1].

Chirality is not a requirement for bioactivity, but in those cases, and there are many, in which a chiral center is present in the bioactive molecule, usually great differences are found for the activities of the enantiomers [2].

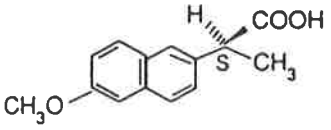
For the above reasons the asymmetric synthesis of enantiomerically pure drugs is a target of synthetic methodology [3].

Recently, practical asymmetric syntheses, involving key organobrominated intermediates, of enantiomerically pure drugs have been described. It is the case of the synthesis of enantiomerically pure (1R, 2S)-(-)-(1,2-epoxypropyl)-phosphonic acid 1, the antibiotic Fosfomycin [4-5], of (S) - (+) - 2 - (6-methoxy-2-naphthyl)-propanoic 2, the antiinflammatory Naproxen [6-7] and of Anthracyclinones 3 (R = H, X = OCH_3 ; R = OH, X = OCH_3 ; R = H, X = H ; R = OH, X = H) [8-9], the Aglycones of antineoplastic Anthracyclines.



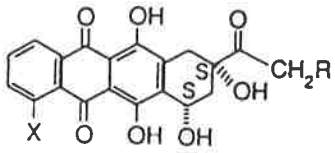
1

Fosfomycin



2

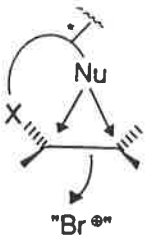
Naproxen



3

Anthracyclinones

The use of tartaric acid as chiral auxiliary in directing an appropriate highly diastereoselective bromination of prochiral olefins is the common strategy for the asymmetric synthesis of 1, 2 and 3.



X = O, P, C

The anchimeric assistance of a nucleophilic site, in the auxiliary, to the positive charge developed in the transition state can be accounted for the diastereofacial selection, in the kinetically controlled attack of electrophilic bromine on the double bond. The basic knowledge drawn from the present study has been very useful for the scaling up of an entirely new enantioselective process for the industrial production [10] of Naproxen.

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Free radical bromination internal and external return

The importance of reversible hydrogen atom transfer (external return), (-1), has been established as a kinetically significant process since the early studies of the mechanism of free radical bromination [1]. Only recently [2-4], however, has the reversible reaction been recognized as a significant cage process, (2), which takes place during solution phase brominations. It has been shown that the rate of internal return (-1) is competitive with diffusion (3) and that this competition is viscosity dependent [5].

$$RH + Br\bullet \underset{}{\overset{k_1}{\rightleftharpoons}} R\bullet + HBr \qquad (1, -1)$$

$$RH + Br\bullet \underset{k_2}{\overset{k_2}{\rightleftharpoons}} (R\bullet + HBr)_{cage} \qquad (2, -2)$$

$$(R\bullet + HBr)_{cage} \xrightarrow{k_{diff}} R\bullet \qquad (3)$$

The viscosity dependence of the kinetic deuterium isotope effect for benzylic bromination at a constant temperature has been determined. As the relative viscosity decreases the deuterium isotope effect increases. Since the viscosity decreases as the temperature increases the magnitude of the TDKIE was determined at constant viscosity. The mechanistic interpelation of the TDKIE for these brominations is therefore subject to modification.

It has been reported that the temperature dependence of the Hammett linear free energy relationship obtained from the competitive bromination of a series of substituted toluenes increases in magnitude as the temperature increases [6]. This observation has been rationalized as being due to entropic control of the free energy of activation. This conclusion was arrived at, however, without considering viscosity dependent internal cage return. When the temperature is held constant and the viscosity is changed, the Hammett ϱ value does increase in magnitude (i.e. becomes more negative). However, when a plot of ϱ *vs.* temperature is constructed from values of ϱ determined in solvents, which at those temperatures had constant viscosities, the slope of the plot describes normal enthalpy control ; *i.e.*, as the magnitude of ϱ became smaller.

The effect of internal and external return on the interpretation of the results of kinetic studies of reversible homolytic reactions will be discussed.

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