Tetrahedron: Asymmetry Vol 1, No. 7, pp. 441-444, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

RESEARCHES ON ANTIVIRAL AGENTS.2[1]. ENANTIOSPECIFIC SYNTHESIS OF 1,3-DIMETHYL-6-OXIRANYLPYRIMIDIN-2,4-DIONE WITH ANTI-ASFV ACTIVITY.

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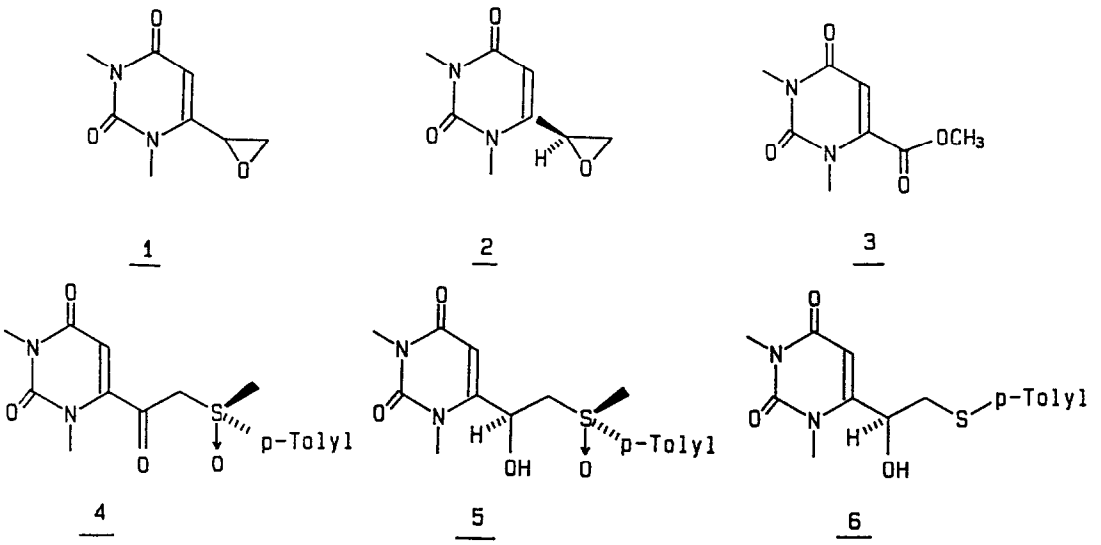
(*Received* 8 *May* 1990)

Abstract : Chiral epoxide (+)2 has been synthetized in very good yield and high enantiomeric excess via a modified Solladié procedure starting from commercially available orotic acid. Chiral HPLC chromatographic analysis and 300 MHz ^{1}H-NMR with the addition of chiral shift reagent Eu(hfc)$_3$ of compound (+)2 are also reported.

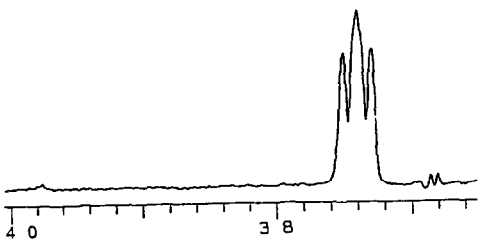
We have been involved in the last few years in the synthesis and biological evaluation of new pyrimidine derivatives as potential antitumor and antiviral agents[2]. The racemic epoxide 1 showed a remarkable anti-ASFV (African Swine Fever Virus) activity[3]. ASFV is the agent of an important disease of wild and domestic pigs that threatens the swine industry of many countries. So far, no effective means of eradication have been found, and the control of the disease is still confined to recognition, quarantine, slaughter and decontamination procedures.
It is well known that, due to the ability to bind to cellular macromolecules, the most electrophilically reactive epoxides can give rise to many kind of effects[4] to extents that can be markedly dependent on their stereochemistry[5]. Therefore we deemed interesting in the antiviral evaluation of a pure enantioner of 1 to see whether the anti-ASFV activity might increase.
To the best of our knowledge no records are available in the literature dealing with a chiral synthesis or a resolution into the enantiomers of compounds similar to 1. This communication deals with the synthesis of the chiral epoxide (+) 2 in high yield and in very good enantiomeric excess using a modified Solladié procedure[6].
Starting material 3[7] was prepared in a single step (93%) from commercial orotic acid using an excess of diazomethane in MeOH at room temperature. Condensation of 3 with (R)-methyl-p-tolyl sulfoxide[8] at -78°C[9], in spite of the presence of the possible competitive reactive centers[1], gave only the expected product 4 as a foam in very good yield (90%) with $[\alpha]_D$ 66 (c 1.5,$CHCl_3$).
DIBAH reduction of the β-ketosulfoxide 4 gave a single product 5 (95%), as shown by chromatography (SiO_2, $CHCl_3$/MeOH = 9/1) and by 300 MHz ^{1}H-NMR (the sharp singlet at δ3.26 , 6H, 2xN-CH_3 and the AB part of the ABX system of the methylene at δ2.82-3.14 do not show traces of the diastereoisomer); $[\alpha]_D$ 113.9 (c 1,$CHCl_3$).
PBr_3 reduction[10] of the β-hydroxysulfoxide 5 afforded a single sulfide 6 (75%, $[\alpha]_D$ -18.3 , c 1.4,$CHCl_3$, mp 165-66° C) which showed at the 300 MHz ^{1}H-NMR all the expected resonance signals and a FAB-MS spectrum

SCHEME

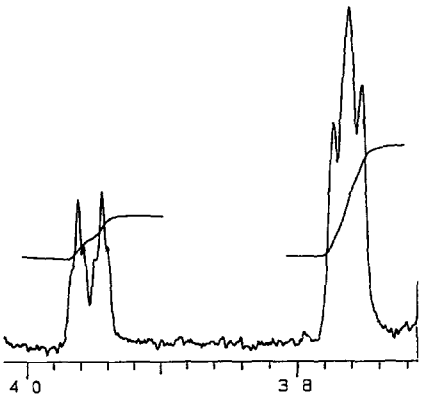


(Gly+TDEG) of m/e 307 (M^++1). Methylation at the sulfur atom operated with MeI in the presence of $AgBF_4$ followed by *in situ* epoxidation NaOH (10% aqueous solution) with catalytic amount of TBAF afforded clean epoxide (+)2 (75%) which was further purified for analytical purposes, $[\alpha]_D$ 51.6 (c 1,$CHCl_3$).
The ^{1}H-NMR spectrum of (+)2[11], after the addition of a small amount (three drops of a 1M $CDCl_3$ solution) of the chiral shift reagent tris-3-(heptafluorpropyl-hydroxymethylen)-d-camphorato europium (III), Eu $(hfc)_3$ did not detect the enantiomer (see fig.1).
Similarly, HPLC analysis of (+)2 performed on a chiral column of chiralcel OD 250x4 mm eluting with hexane/isopropanol=90/10 (flow rate 1.0 ml/min.) in comparison with the chromatogramme of the racemic epoxide 1 gave an enantiomeric excess of 98.05% (see fig. 2).
With the purpose to obtain the other isomer (-)2 we operated the reduction of the β-ketosulfoxide 4 with DIBAH+$ZnCl_2$ as described[6]. In this case we obtained a diastereoisomeric mixture of alcohols of difficult chromatographic separation. Using a very large concentration of $ZnCl_2$ (6 mole equivalents) we obtained only part of the diastereoisomer with the OH inverted as shown by the ^{1}H-NMR of the mixture. Without further purification we prepared the epoxide and we obtained an enantiomeric excess of 30% of the (+)2 enantiomer as shown by the 300 MHz ^{1}H-NMR of the mixture after the addition of chiral shift reagent Eu $(hfc)_3$ (see fig.1). The lack of inversion of the configuration expected[6] during the reduction of 4 with DIBAH+$ZnCl_2$ is probably due to the many possible site of complexation of the β-ketosulfoxide 4 and to the extremely poor rotation of the side chain in C-6 of a N-1 methylated pyrimidine[12].
The biological results of (+) 2 will be published elsewhere, more effort will be devoted to obtain the enantiomer (-) 2 if necessary soon after the biological tests.

FIG. 1



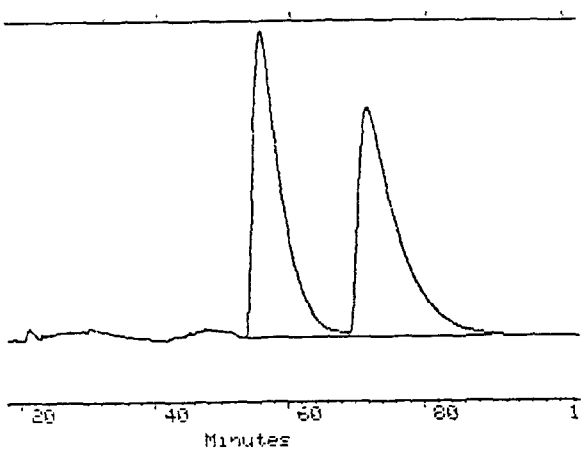
Part of the 300-MHz ^{1}H-NMR spectrum of (+)2 in $CDCl_3$ after the addition $Eu(hfc)_3$, proton on asymmetric carbon



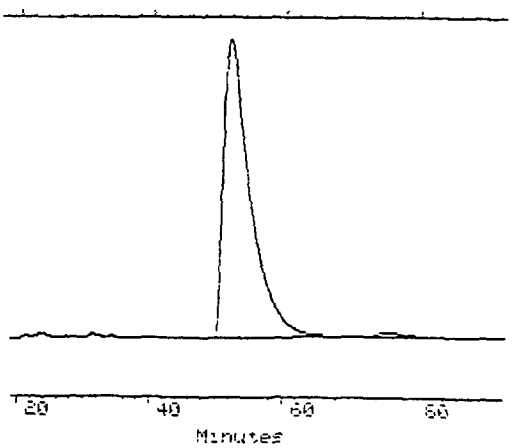
Part of 300-MHz ^{1}H-NMR spectrum of the mixture of (+)2 and (-)2 from DIBA+$ZnCl_2$ reduction, proton on asymmetric carbon

The good overall yield calculated from orotic acid and the extremely high asymmetric induction of this route make this synthesis very attractive to prepare optically active 6-substituted pyrimidines (lactones, glucosides), which have been not extensively investigated, in spite of their potential interest as anti-AIDS and/or antitumor agents; work in this direction is already in progress in our laboratory.

FIG. 2



Chiral HPLC chromatogramme of 1



Chiral HPLC chromatogramme of (+)2

Acknowledgment. Thanks are due to prof. F.Gasparrini, Dip. di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università "La Sapienza" for the HPLC experiments and to dr. R. Di Fabio, Dept. of Chemistry, University of Montreal, Quebec, Canada for ^{1}H-NMR spectra with chiral shift reagent.

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7. Satisfactory microanalyses and spectroscopic data were obtained for all new compounds described.

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10. Reduction of the β-ketosulfoxide 5 with $LiAlH_4$ tried at different temperatures gave a complex mixture of products.

11. Data in our hands do not allow to assign the correct absolute stereochemistry of (+)2. Although an (S) stereochemistry can be assigned to the epoxide (+)2 on the basis of the results reported by G.Solladié, C.Greck, G.Demailly, A.Solladié Cavallo, Tetrahedron Lett. 23, 5047, (1982).

12. Steric inhibition operated by C-6 substituents on N-1 position is well known. See for example V.Niedballa and H.Vorbruggen, J.Org.Chem. 39, 3660 (1974). H.Tanaka, I.Nasu, T.Miyasaka Tetrahedron Lett., 49, 4755, (1979).