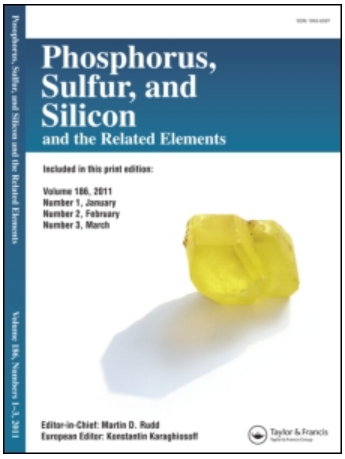

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Asymmetric Synthesis of Biologically Active Compounds Bearing a Chiral Sulfinyl Group

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ASYMMETRIC SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS BEARING A CHIRAL SULFINYL GROUP.

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Abstract The asymmetric synthesis of $\underset{\sim}{3}(\underline{R}_C,\underline{S}_S)$ and $\underset{\sim}{3}(\underline{S}_C,\underline{R}_S)$, important intermediates in the synthesis of optically pure Sparsomycin analogs, is discussed. The enantioselective synthesis of both isomers, R and S, of Oxisuran and three of their bioisosters is also described. In both strategies o.p. methanesulfinate esters of DAG were used as starting material.

INTRODUCTION

The utility of o.a. sulfoxides as auxiliaries in highly asymmetric synthesis is now well documented.[1] Additionally, chiral nonracemic alkylsulfoxides occur in a variety of biologically active molecules such as: Sparsomycin [2a], Oxisuran and analogs[2b], Carpetimycin A[2c] and the potassium channel activator RP49356.[2d]

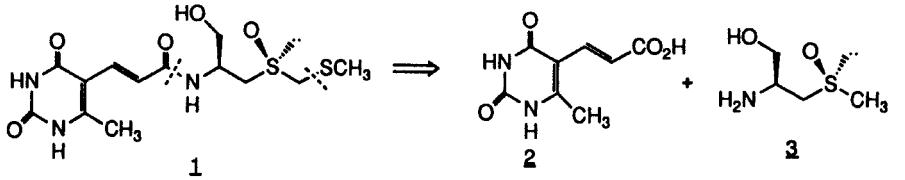
RESULTS AND DISCUSSION

In this communication we present our preliminary results on the asymmetric synthesis of N-protected $\underset{\sim}{3}(\underline{R}_C,\underline{S}_S)$ and $\underset{\sim}{3}(\underline{S}_C,\underline{R}_S)$, important intermediates in the synthesis of Sparsomycin analogs, and the enantioselective synthesis of both R and S isomers of Oxisurane and three of their bioisosters.

Asymmetric synthesis of N-protected $\underset{\sim}{3}(\underline{R}_C,\underline{S}_S)$ and $\underset{\sim}{3}(\underline{S}_C,\underline{R}_S)$.

Sparsomycin $\underset{\sim}{1}$ has received considerable attention because of its biological activity against various tumors, bacteria, fungi and viruses.

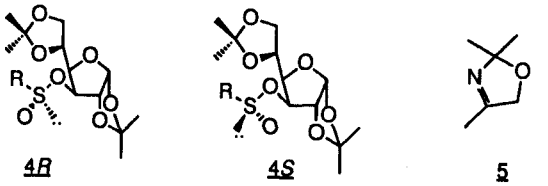
From a retrosynthetic analysis, sparsomycin $\underset{\sim}{1}$ can be viewed as an amide consisting of β-(6-methyluracyl)acrylic acid $\underset{\sim}{2}$ and the chiral amine $\underset{\sim}{3}$.



1 2 3

SCHEME 1 Retrosynthetic scheme of Sparsomycin $\underset{\sim}{1}$.

The acid 2 is easily obtained from the commercial available 6-methyluracil. More challenging is the synthesis of the hydroxyamine 3. Our asymmetric synthesis of N-protected 3(R_C,S_S) and 3(S_C,R_S) was achieved by combining two new methodologies that we have recently developped: (i) The synthesis of o.p. R and S methanesulfinates of DAG (4R and 4S), Fig. 1, and (ii) The synthesis of 3-oxazolines 5, Fig. 1.



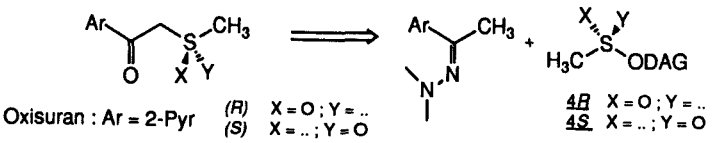
4R 4S 5

FIGURE 1 Methanesulfinates of DAG, 4R and 4S, and 3-oxazolines, 5.

Enantioselective synthesis of R and S Oxisuran and bioisosters.

The Oxisuran 6 is a synthetic immunosuppressive drug used in organ and tissue transplants to supress cell-mediated immunity without inhibiting humoral antibody formation.

Optically active oxisuran , 6R and 6S, and bioisosters, 7-9(R and S), can be obtained from the enolate of the corresponding aryl methyl ketone and the adequate methanesulfinate ester of DAG, 4R or 4S, Scheme 2. In order to avoid epimerization at sulfur, the N,N-dimethylhydrazone of the starting ketones were used.



SCHEME 2 Retrosynthetic scheme of o.p. Oxisuran and bioisosters.

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