United States Patent [19]

Okuhara et al.

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[54] METHOD FOR IMMUNOSUPPRESSION

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[21] Appl. No.: **868,749**

[22] Filed: **May 30, 1986**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 799,855, Nov. 24, 1985, Pat. No. 4,894,366.

[30] **Foreign Application Priority Data**

Dec. 3, 1984 [GB] United Kingdom 8430455
Feb. 5, 1985 [GB] United Kingdom 8502869
Apr. 1, 1985 [GB] United Kingdom 8508420

[51] **Int. Cl.**[5] **A61K 31/395**

[52] **U.S. Cl.** **514/183;** 514/63; 514/291; 514/411; 540/452; 540/456

[58] **Field of Search** 540/452, 456; 514/63, 514/291, 411, 183

[56] **References Cited**

U.S. PATENT DOCUMENTS

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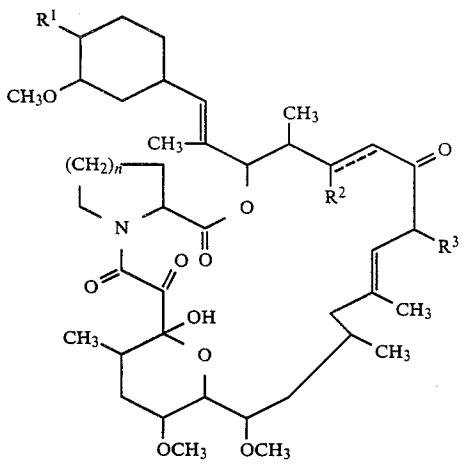
Primary Examiner—Robert T. Bond

Attorney, Agent, or Firm—Oblon, Spivak, McClelland, Maier & Neustadt

[57] **ABSTRACT**

This invention relates to tricyclo compounds useful for treatment and prevention of resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like, which can be represented by the following formula:



(I)

to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

5 Claims, No Drawings

METHOD FOR IMMUNOSUPPRESSION

RELATED APPLICATION

This application is a continuation-in-part of Ser. No. 06/799,855, filed Nov. 24, 1985, now U.S. Pat. No. 4,894,366.

This invention relates to novel tricyclo compounds having pharmacological activities, to a process for their production and to a pharmaceutical composition containing the same.

More particularly, it relates to novel tricyclo compounds, which have pharmacological activities such as immunosuppressive activity, antimicrobial activity, and the like, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

Accordingly, one object of this invention is to provide a novel tricyclo compounds, which are useful for treatment and prevention of resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

Another object of this invention is to provide a process for production of the tricyclo compounds by fermentation processes and synthetic processes.

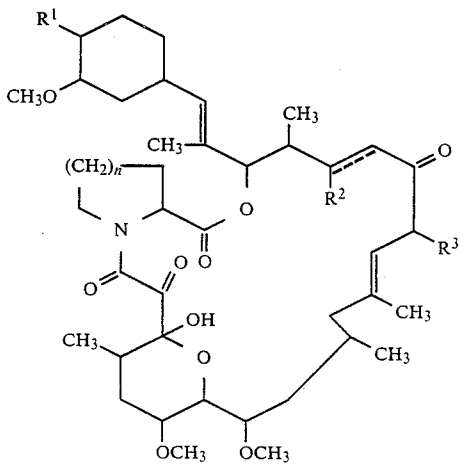
A further object of this invention is to provide a pharmaceutical composition containing, as active ingredients, the tricyclo compounds.

Still further object of this invention is to provide a use of the tricyclo compounds for manufacturing a medicament for treating and preventing resistance by transplantation, graft-versus-host diseases by medulla ossium transplantation, autoimmune diseases, infectious diseases, and the like.

With respect to the present invention, it is to be noted that this invention is originated from and based on the first and new discovery of new certain specific compounds, FR-900506, FR-900520, FR-900523 and FR-900525 substances. In more detail, the FR-900506, FR-900520, FR-900523 and FR-900525 substances were firstly and newly isolated in pure form from culture broths obtained by fermentation of new species belonging to genus Streptomyces.

And, as a result of an extensive study for elucidation of chemical structures of the FR-900506, FR-900520, FR-900523 and FR-900525 substances, the inventors of this invention have succeeded in determining the chemical structures thereof and in producing the tricyclo compounds of this invention.

The new tricyclo compounds of this invention can be represented by the following general formula:



(I)

wherein

R^1 is hydroxy or protected hydroxy,

R^2 is hydrogen, hydroxy or protected hydroxy,

R^3 is methyl, ethyl, propyl or allyl,

n is an integer of 1 or 2, and

the symbol of a line and dotted line is a single bond or a double bond,

and salts thereof.

Among the object compound (I), the following four specific compounds were found to be produced by fermentation.

(1) The compound (I) wherein R^1 and R^2 are each hydroxy, R^3 is allyl, n is an integer of 2, and the symbol of a line and dotted line is a single bond, which is entitled to the FR-900506 substance;

(2) The compound (I) wherein R^1 and R^2 are each hydroxy, R^3 is ethyl, n is an integer of 2, and the symbol of a line and dotted line is a single bond, which is entitled to the FR-900520 substance (another name: the WS 7238A substance);

(3) The compound (I) wherein R^1 and R^2 are each hydroxy, R^3 is methyl, n is an integer of 2, and the symbol of a line and dotted line is a single bond, which is entitled to the FR-900523 substance (another name: the WS 7238B substance); and

(4) the compound (I) wherein R^1 and R^2 are each hydroxy, R^3 is allyl, n is an integer of 1, and the symbol of a line and dotted line is a single bond, which is entitled to the FR-900525 substance.

With respect to the tricyclo compounds (I) of this invention, is to be understood that there may be one or more conformer(s) or stereoisomeric pairs such as optical and geometrical isomers due to asymmetric carbon atom(s) and double bond(s), and such isomers are also included within a scope of this invention.

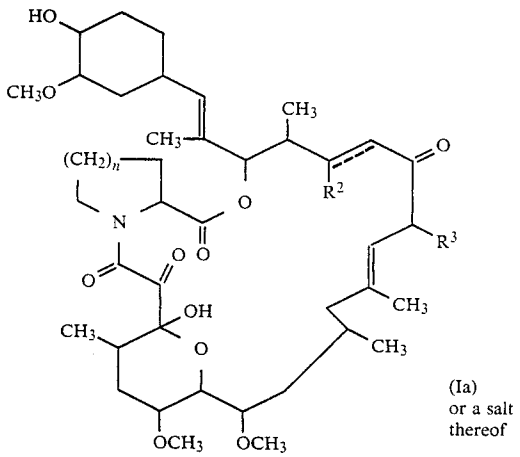
According to this invention, the object tricyclo compounds (I) can be prepared by the following processes.

[I] FERMENTATION PROCESSES

Species belonging to the genus Streptomyces —Fermentation→ FR-900506 substance, FR-900520 substance, FR-900523 substance and FR-900525 substance

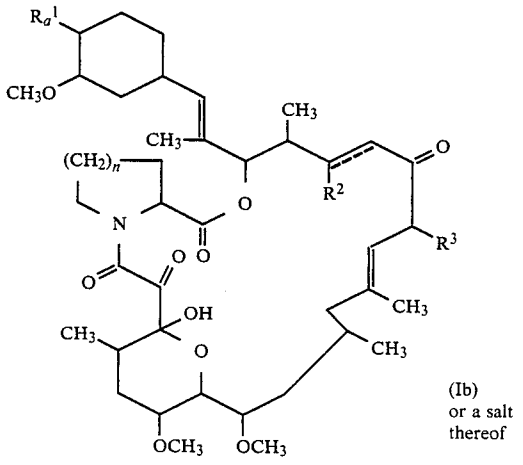
[II] SYNTHETIC PROCESSES

(1) Process 1 (Introduction of Hydroxy-Protective Group)



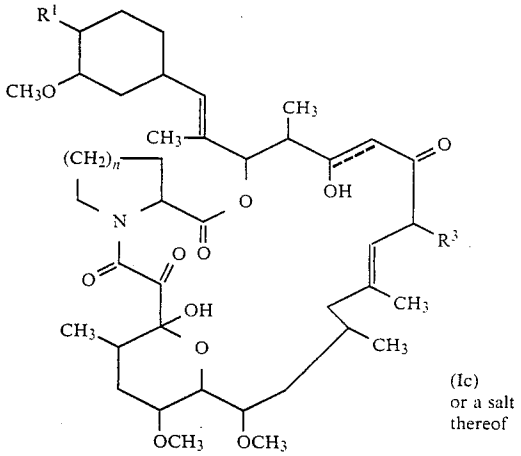
(Ia) or a salt thereof

Introduction of Hydroxy-Protective Group



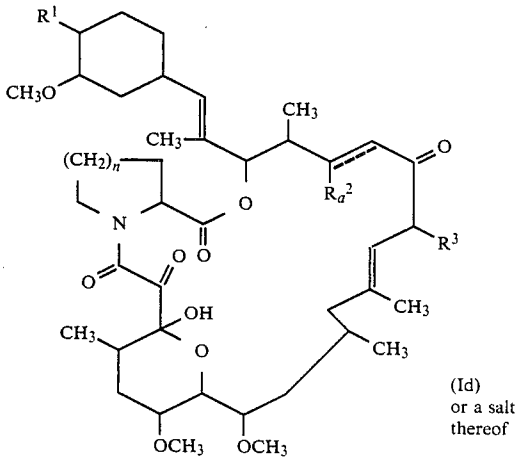
(Ib) or a salt thereof

(2) Process 2 (Introduction of Hydroxy-Protective Group)



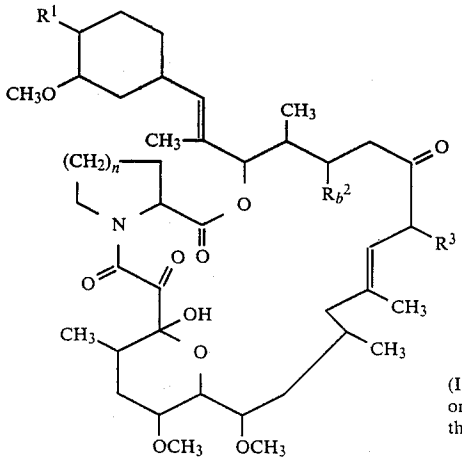
(Ic) or a salt thereof

Introduction of Hydroxy-Protective Group



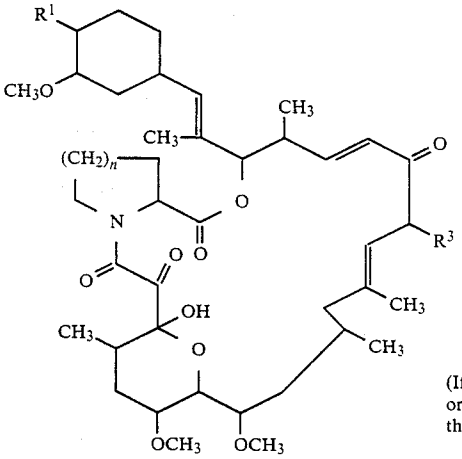
(Id) or a salt thereof

(3) Process 3 (Formation of Double Bond)



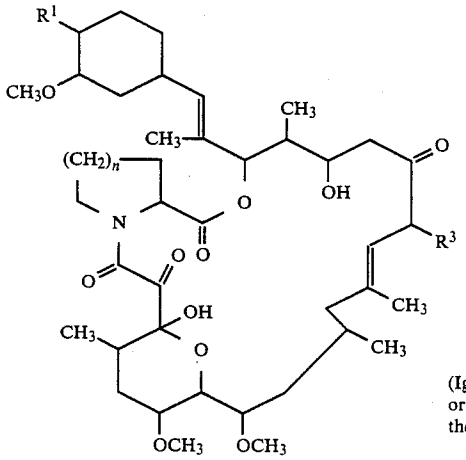
(Ie) or a salt thereof

Base



(If) or a salt thereof

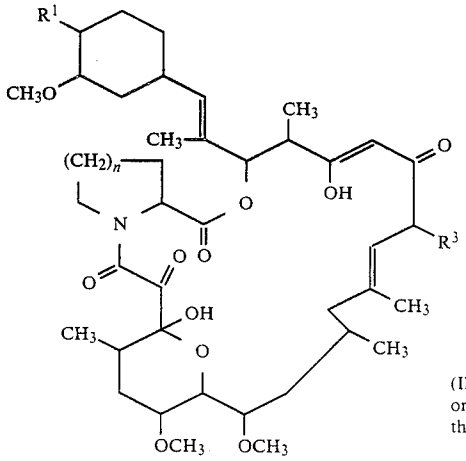
(4) Process 4 (Oxidation of Hydroxyethylene Group)



(Ig) or a salt thereof

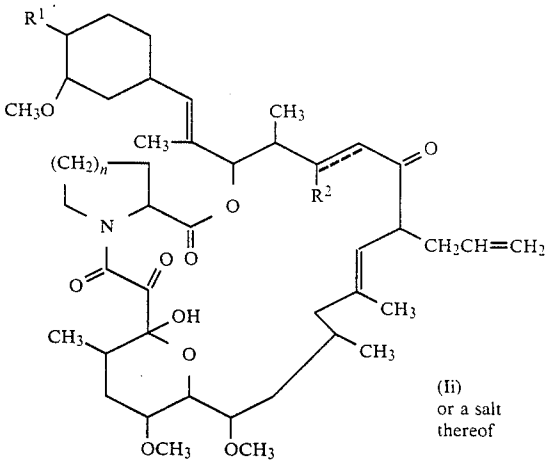
Oxidation of Hydroxyethylene Group

-continued



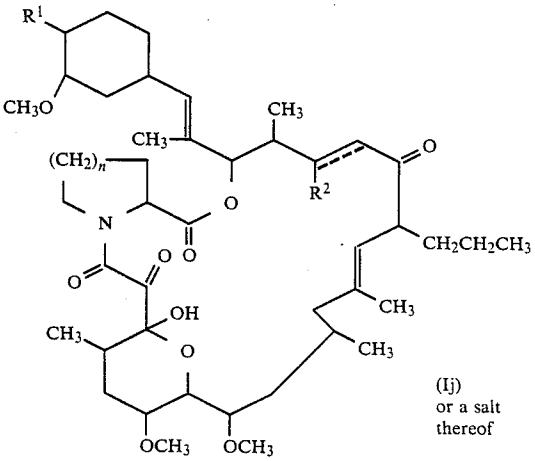
(Ih) or a salt thereof

(5) Process 5 (Reduction of Allyl Group)



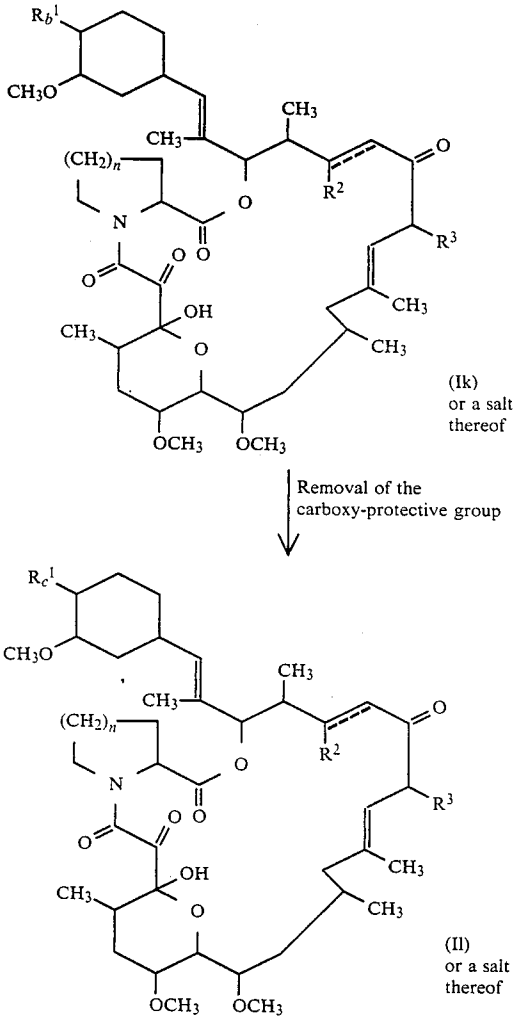
(Ii) or a salt thereof

Reduction



(Ij) or a salt thereof

(6) Process 6 (Removal of the carboxy-protective group)



in which

R^1, R^2, R^3, n and the symbol of a line and dotted line are each as defined above,

R_a^1 and R_a^2 are each protected hydroxy,

R_b^1 is protected carboxy(lower)alkylcarbamoyloxy,

R_c^1 is carboxy(lower)alkylcarbamoyloxy, and

R_b^2 is a leaving group.

Particulars of the above definitions and the preferred embodiments thereof are explained in detail as follows.

The term "lower" used in the specification is intended to mean 1 to 6 carbon atoms, unless otherwise indicated.

Suitable hydroxy-protective group in the "protected hydroxy" may include:

1-(lower alkylthio)(lower)alkyl such as lower alkylthiomethyl (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), and the like, in which the preferred one may be C_1–C_4alkylthiomethyl and the most preferred one may be methylthiomethyl;

trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, etc.), lower alkyldiarylsilyl (e.g. methyl-diphenylsilyl, ethyl-diphenylsilyl, propyl-diphenylsilyl, tert-butyl-diphenylsilyl, etc.), and the like, in which the preferred one may be tri(C_1–C_4)alkylsilyl and C_1–C_4alkyl-diphenylsilyl, and the most preferred one may be tert-butyl-dimethylsilyl and tert-butyl-diphenylsilyl;

acyl such as aliphatic acyl, aromatic acyl and aliphatic acyl substituted with aromtic group, which are derived from carboxylic, sulfonic and carbamic acids; and the like.

The aliphatic acyl may include lower alkanoyl which may have one or more suitable substituent(s) such as carboxy (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.), cyclo(lower)alkyloxy(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkyl (e.g. cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxyheptanoyl, menthyloxyhexanoyl, etc.), camphorsulfonyl, lower alkylcarbamoyl having one or more suitable substituent(s) such as carboxy and a protected carboxy, for example, carboxy(lower)alkylcarbamoyl (e.g. carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.) protected carboxy(lower)alkylcarbamoyl such as tri(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl (e.g. trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, trimethylsilylpropoxycarbonylbutylcarbamoyl, etc.), and the like.

The aromatic acyl may include aroyl which may have one or more suitable substituent(s) such as nitro (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.), arenesulfonyl which may have one or more suitable substituent(s) such as halogen (e.g. benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.), and the like.

The aliphatic acyl substituted with aromatic group may include ar(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkoxy and trihalo(lower)alkyl (e.g. phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.), and the like.

The more preferred acyl group thus defined may be C_1–C_4alkanoyl which may have carboxy, cyclo(C_5–C_6-alkyloxy(C_1–C_4)alkanoyl having two (C_1–C_4)alkyl groups on the cycloalkyl moiety, camphorsulfonyl, carboxy(C_1–C_4)-alkylcarbamoyl, tri(C_1–C_4)alkylsilyl(C_1–C_4)alkoxycarbonyl(C_1–C_4)alkylcarbamoyl, benzoyl which may have one or two nitro, benzenesulfonyl having halogen, phenyl(C_1–C_4)alkanoyl having C_1–C_4alkoxy and trihalo(C_1–C_4)alkyl, and the most preferred one may be acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

Suitable "protected carboxy(lower)alkylcarbamoyl" and "carboxy(lower)alkylcarbamoyl" moieties of the "protected carboxy(lower)alkylcarbamoyloxy" and

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