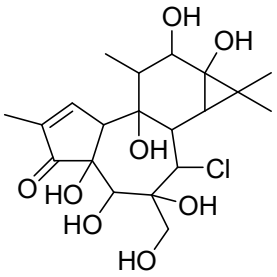
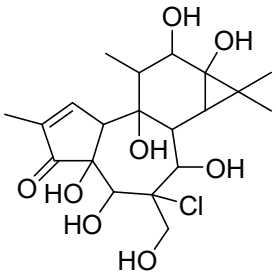
compound undergoing ring opening of the 6,7-epoxide ring to form hydrochloride adducts such as:



and



Compound A Compound B.

These compounds are considered toxic impurities and are difficult to remove from the desired 6,7-epoxytigliane compounds and result in loss of desired compound and low yields during chromatographic purification steps.

Although purification of the product 6,7-epoxytigliane compounds by crystallization has been attempted, these compounds appear particularly resistant to crystallization.

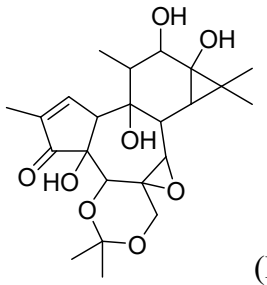
There is a need for methods of manufacturing 6,7-epoxytigliane compounds that result in high yields and high purity therapeutic product.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

Summary

The present disclosure is based at least in part on the discovery that a key intermediate in the synthetic preparation of therapeutically useful 6,7-epoxytigliane compounds crystallizes to form a high purity product and allows the preparation of the desired 6,7-epoxytigliane compounds in high yield and high purity.

In a first aspect, there is provided a crystalline form of a compound of formula (I):

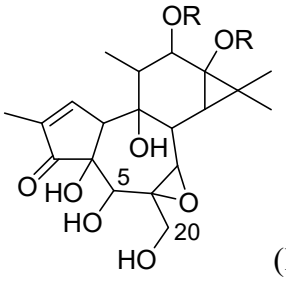


(I)

or a stereoisomer, pharmaceutically acceptable salt or solvate thereof.

In another aspect, there is provided a method of making a crystalline form of a compound of formula (I) comprising the steps of:

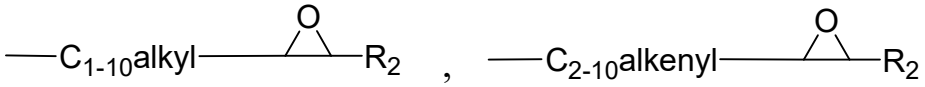
i) providing a mixture comprising one or more compounds of formula (II):



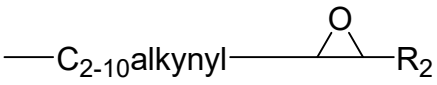
(II)

wherein each R is independently selected from H and -C(O)R_1, wherein when only one compound of formula(II) is present in the composition, at least one R group is not hydrogen; and

R_1 is selected from C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, cycloalkyl, aryl, C_{1-10}alkylcycloalkyl; C_{2-10}alkenylcycloalkyl, C_{2-10}alkynylcycloalkyl, C_{1-10}alkylaryl, C_{2-10}alkenylaryl, C_{2-10}alkynylaryl, C_{1-10}alkylC(O)R_2, C_{2-10}alkenylC(O)R_2, C_{2-10}alkynylC(O)R_2, C_{1-10}alkylCH(OR_2)(OR_2), C(O)C_{2-10}alkenylCH(OR_2)(OR_2), C_{2-10}alkynylCH(OR_2)(OR_2), C_{1-10}alkylSR_2, C_{2-10}alkenylSR_2, C_{2-10}alkynylSR_2, C_{1-10}alkylC(O)OR_2, C_{2-10}alkenylC(O)OR_2, C_{2-10}alkynylC(O)OR_2, C_{1-10}alkylC(O)SR_2, C_{2-10}alkenylC(O)SR_2, C_{2-10}alkynylC(O)SR_2,



or

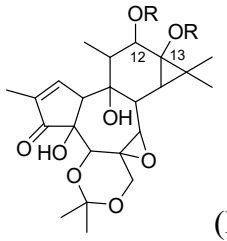


;

R_2 is hydrogen, -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{2-10}alkynyl, cycloalkyl or aryl;

wherein each alkyl, alkenyl, alkynyl, cycloalkyl or aryl group is optionally substituted;

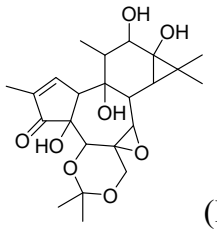
ii) forming a 5,20-acetonide of formula (III):



(III)

by treating the compound of formula (II) with 2,2-dimethoxypropane and a weakly acidic catalyst;

iii) de-esterifying the esters at C12 and C13 of formula (III) to provide a compound of formula (I):



(I)

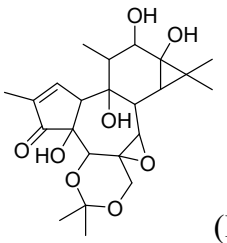
by treating the compound of formula (III) with a base; and

iv) crystallizing the compound of formula (I).

In yet a further aspect, there is provided 12-tigloyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one (compound 1) or 12,13-dihexanoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one (compound 2) in substantially pure form.

In yet a further aspect, there is provided 12-tigloyl-13-(2-methylbutanoyl)-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one produced by the method as described herein. In yet a further aspect, there is provided 12,13-dihexanoyl-6,7-epoxy-4,5,9,12,13,20-hexahydroxy-1-tigliaen-3-one produced by the method as described herein.

In yet a further aspect, there is provided a process for making a crystalline form of a compound of formula (I):



(I)