groups for the hydroxyl group and the synthesis thereof may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981, or Fiser & Fiser. Exemplary hydroxyl protecting groups include methoxymethyl, 1-ethoxyethyl, benzyloxymethyl, (β-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, t-butyl(diphenyl)silyl, trialkyl-silyl, trichloromethoxycarbonyl and 2,2,2-trichloroethoxymethyl.

Starting Materials

The starting materials for the present resolution methods may be obtained as described in the Examples herein, or by methods analogous to those described in European Patent Application No. 93300241.2 (EP-A-552041).

The starting mixtures I or IV may contain, for example, the diastereomers of the compounds Ia and Ib or IVa and IVb, although it is preferred that such compounds are separated prior to conducting the enzymatic resolution methods of the present invention.

Preferred Compounds

Cis compounds of the formula I have a stereoisomeric configuration which is preferred in compounds employed as intermediates in the preparation of C-13 sidechain-bearing taxanes. Compounds of the mixtures I and II having the same absolute stereoconfiguration corresponding to that of a compound Ia where R^1 is acetyloxy, R^2 is furyl and R^3 is hydrogen in the 3R,4S configuration are particularly preferred.

itself, may impart an increased or more desirable pharmacological activity to the taxane product, or may form a taxane product which is more readily converted to a taxane having an increased or more desirable pharmacological activity than the starting compound.

The compounds resolved according to the methods of the present invention may be modified prior to use in side chain formation. For example, resolved compounds containing an azide group N_3 as the group W may be treated by a reducing agent to form an amine group which may be substituted.

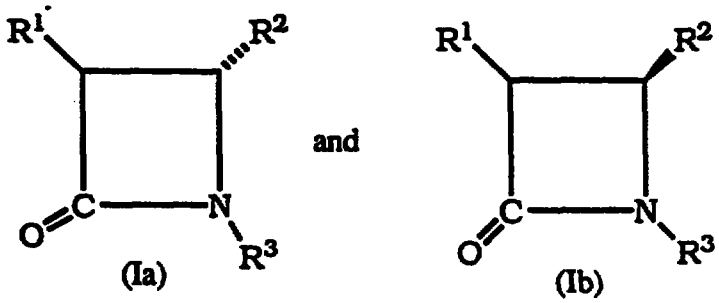
Exemplary methods for side chain formation, and taxane products which may be formed employing such methods, include those described in European Patent Application No. 534,708; U.S. Patent Application Serial No. 08/080,704, filed June 28, 1993; U.S. Patent Application Serial No. 08/029,819, filed March 11, 1993; U.S. Patent Application Serial No. 07/996,455, filed December 24, 1992; U.S. Patent Application Serial No. 08/062,687, filed May 20, 1993; U.S. Patent Application Serial No. 07/981,151, filed November 24, 1992; and U.S. Patent Application Serial No. 07/995,443, filed December 23, 1992; all of which aforementioned documents are incorporated herein by reference. See also EP-A-590267, EP-A-577082, EP-A-577083 and EP-A-558959.

Salts or solvates of reactants or products may be employed or prepared as appropriate or desired in the methods of the present invention.

The methods of the present invention are further described by the following examples. These examples are illustrative only, and are in no way intended to limit the scope of the instant claims.

CLAIMS

1. A method for the resolution of a mixture I comprising the enantiomers Ia and Ib, where R^1 is in the cis position relative to R^2 in both Ia and Ib, or where R^1 is in the trans position relative to R^2 in both Ia and Ib:



where

R^1 is hydroxyl; halo; or -O-C(O)-R^4, where R^4 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl or heterocyclo;

R^2 is heterocyclo or cycloalkyl;

R^3 is hydrogen; R^4; -C(O)-OR^4; or -C(O)-R^4, where R^4 is independently selected from those groups recited for R^4 above;

comprising the step of contacting said mixture I with an enzyme or microorganism capable of catalyzing the stereoselective conversion of one of said compounds Ia or Ib to a non-enantiomeric form, and effecting said conversion.

2. The method of claim 1, wherein said stereoselective conversion is selected from stereoselective hydrolysis and stereoselective esterification.

R^1 is alkanoyloxy or hydroxy;
R^2 is furyl or thienyl; and
R^3 is hydrogen, phenyl or substituted phenyl.

5. The method of claim 4, wherein a lipase is employed.

6. The method of any preceding claim, wherein, further, the non-enantiomeric compounds obtained are separated by a separation step.

7. The method of claim 6, wherein said separation step is an extraction, distillation, crystallization, or column chromatography step.

8. The method of any preceding claim, wherein, further, a product of said method is employed in the preparation of a taxane bearing a C-13 sidechain.

9. A method for the resolution of a mixture IV comprising the enantiomers IVa and IVb:

$$R^2\text{-}T^a\text{-}C(O)\text{-}OR^6 \qquad \text{(IVa)}$$

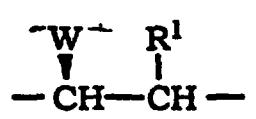
and

$$R^2\text{-}T^b\text{-}C(O)\text{-}OR^6 \qquad \text{(IVb)}$$

where
T^a is



and T^b is



; or

capable of catalyzing the stereoselective hydrolysis of mixture IV to provide said mixture VI; or

(iii) where R^6 is R^4, where R^4 is independently selected from those groups recited for R^4 above; and one of R^{6a} or R^{6b} is the same as R^6 and the other of R^{6a} or R^{6b} is R^7, where R^7 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl or heterocyclo, except that R^7 is not the same as R^6;

the step of contacting said mixture IV, in the presence of an organic alcohol of the formula VIII:

$$R^7\text{-OH} \quad \text{(VIII)}$$

where R^7 is as defined above, with an enzyme or microorganism capable of catalyzing the stereoselective transesterification of mixture IV to provide said mixture VI.

12. The method of claim 9, 10 or 11, wherein, further, the non-enantiomeric compounds obtained are separated by a separation step.

13. The method of claim 12, wherein said separation step is an extraction, distillation, crystallization, or column chromatography step.

14. The method of any one of claims 9-13, wherein, further, a product of said method is employed in the preparation of a taxane bearing a C-13 sidechain.