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(54) Title: PROCESS FOR PREPARATION OF TAXANE DERIVATIVES AND β-LACTAM INTERMEDIATES THEREFOR

(57) Abstract

Taxol (I) is a complex diterpene which is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. However, taxol has a problem with solubility in aqueous media, which may impose some serious limitation in its use. TAXOTERE (III) seems to have antitumor activity superior to taxol with better bioavailability. Taxotère has a modified taxol structure with a modified C-13 side chain. This fact strongly indicates that modification on the C-13 side chain would provide a new series of taxol and TAXOTERE analogues which may have higher potency, better bioavailability and less unwanted toxicity. The present invention provides efficient and practical methods for the syntheses of TAXOTERE and its analogues through β-lactam intermediates and their coupling with baccatin III.

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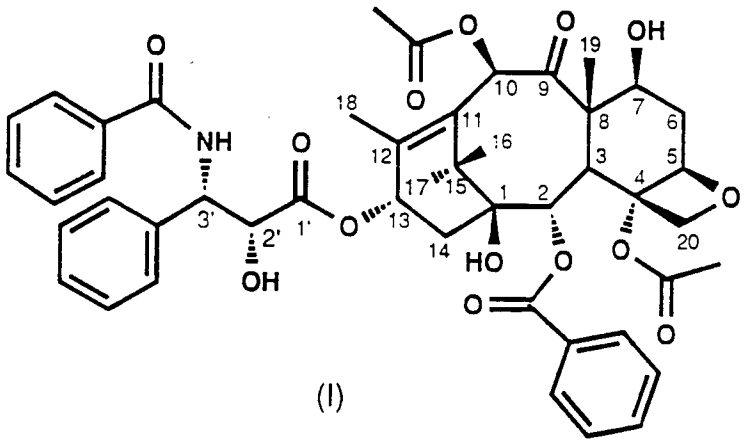
PROCESS FOR PREPARATION OF TAXANE DERIVATIVES AND ß-LACTAM INTERMEDIATES THEREFOR

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of taxoid(s) including TAXOTÈRE and its analogs and the ß-lactam intermediates useful in this process.

BACKGROUND OF THE INVENTION

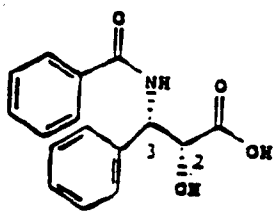
Taxol (I) is a complex diterpene which is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity against different cancers which have not been effectively treated by existing antitumor drugs. For example, taxol is currently in phase III clinical trials for advanced ovarian cancer, phase II for breast cancer, and phase I for lung cancers, colon cancer and acute leukemia.



(I)

Although taxol is an extremely important "lead" in cancer chemotherapy, taxol has a problem with solubility in aqueous media, which may impose some serious limitation in its use. It is common for improved drugs to be derived from naturally occurring lead compounds. In fact, French researchers, Potier, Guéritte-Voegelein,

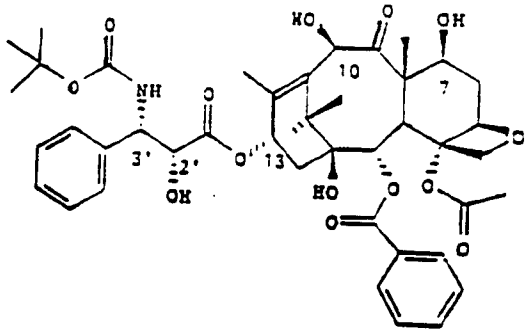
Guénard et al. have discovered that a modification of the C-13 side chain of taxol brought about a new anticancer agent which seems to have antitumor activity superior to taxol with better bioavailability. This synthetic compound was named "TAXOTÈRE (II)", which has t-butoxycarbonyl instead of benzoyl on the amino group of (2R,3S)-phenylisoserine moiety at the C-13 position and a hydroxyl group instead of an acetoxy group at C-10. [Colin, M. et al. Eur. Pat. Appl. EP253,738 (1988)]. Taxotère is currently in phase II clinical trial in both United States and Europe. TAXOTÈRE has been synthesized by a semisynthetic process, including a coupling of N-tert-butoxycarbonyl-(2R,3S)-3-phenylisoserine with 10-deacetylbaccatin III with proper protecting groups. (Denis, J.-N. recently reported (Commercon, A. et al., Tetrahedron Letters, 1992, 33 5185)).



(II)

It is known that the C-13 side chain of taxol, i.e., N-benzoyl-(2R, 3S)-3-phenylisoserine (III) moiety, is crucial for the strong antitumor activity of taxol. (Senilh et al., C.R. Séancas Acad. Sci. Ser. 2 1984, 299, 1039; Guéritte-Voegelein et al., Tetrahedron, 1986, 42, 4451, and Mangatal et al., Tetrahedron, 1989, 45, 4177; Guéritte-Voegelein et al. J. Med. Chem. 1991, 34, 992; and Swindell et al., J. Med. Chem. 1992, 35, 145; Mathew, A.E. et al., J. Med. Chem. 1992, 35, 145). Moreover, some modification of the C-13 side chain can provide a new series of taxol analogs which may have higher potency, better bioavailability and less unwanted toxicity, as

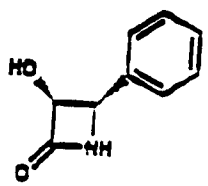
exemplified by the discovery of TAXOTÈRE (II).



(III)

Accordingly, the development of an efficient method which can be applied to various analogs of taxol and TAXOTÈRE and analogs thereof, i.e., a method having flexibility and wide applicability, is extremely important and of current demand. It has been shown that such a new and efficient method with flexibility can be developed by using enantiomerically pure ß-lactams as key-intermediates [Ojima, I. et al., J. Org. Chem., 1991, 56, 1681; Ojima et al., Tetrahedron, 1992, 48, 6985; Holton, R.A., Eur. Patent Appl. EP 400,971 (1990)].

Lithium chiral ester enolate-imine cyclocondensation strategy has been applied to the asymmetric synthesis of the side chain of taxol via a (3*R*,4*S*)-3-hydroxy-4-phenylazotidin-2-one (IV) as the key-intermediate. (Ojima, I. et al., J. Org. Chem., 1991, 56, 1681; Ojima et al., Tetrahedron, 1992, 48, 6985)



(IV)

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