Methyltrioxorhenium catalysed synthesis of highly oxidised aryltetralin lignans with anti-topoisomerase II and apoptogenic activities

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Abstract—A novel and efficient procedure to prepare highly oxidised aryltetralin lignans, such as isopodophyllotoxone and (-)-aristolactone derivatives, by oxidation of podophyllotoxin and galbulin with methylrhenium trioxide (MTO) and novel MTO heterogeneous catalysts is reported. It is noteworthy that in the case of isopodophyllotoxone derivatives the functionalisation of the C-4 position of the C-ring and the ring-opening of the D-lactone moiety increased the activity against topoisomerase II while causing the undesired inhibition of tubulin polymerisation to disappear. The novel (-)-aristolactone derivatives showed apoptogenic activity against resistant human lymphoma cell lines.

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1. Introduction

Lignans are a family of natural products with a broad variety of biological and pharmacological activities.1 Among them, aryltetralin derivatives are of special interest owing to their powerful antitumoral, antimicrobial, antiviral, cardiovascular and immunosuppressive activity.2 Aryltetralin derivatives show also a selective nonredox inhibition of 5-lipoxygenase by interaction with the arachidonic acid binding site and could form a new class of therapeutic agents for the treatment of asthma and rheumatoid arthritis.3 Podophyllotoxin 1, isolated from different plants of the genus Podophyllum, is the most investigated aryltetralin derivative. It is a well-established inhibitor of cell division at the level of the microtubule assembly by freezing polymerisation of tubulin at the colchicine site.4 This activity has led to the design of semi-synthetic derivatives, such as etoposide (4′-demethyl-7-[4,6-O-ethylidene-β-D-glucopyranosyl]epipodophyllotoxin) and teniposide (4′-demethyl-7-[4,6-O-thienylidene-β-D-glucopyranosyl]epipodophyllotoxin), which have been widely used for the treatment of small-cell lung cancer, testicular cancer, lymphoma and acute lymphocytic leukaemia.5 Etoposide and teniposide show different side effect profiles compared to podophyllotoxin due to their action as selective inhibitors of DNA topoisomerase II, a key enzyme involved in DNA transcription, replication, recombination and possibly DNA repair.6 In recent years, several syntheses of podophyllotoxin and aryltetralin lignan derivatives have been reported in the literature which mainly focused on structural modifications of leader molecules to obtain less toxic analogues with high biological activities. On the other hand, a few data are available on oxidative functionalisation,7 a process that plays a relevant role in their biological mechanism of action. For example, it is known that etoposide undergoes oxidative ortho-demethylation by a cytochrome P450-dependent metabolic process to a 3′,4′-dihydroxy derivative.8 This derivative is further oxidised to the corresponding ortho-benzoquinone, a highly reactive intermediate responsible for the irreversible binding to proteins and DNA.9 In a similar way, a semibenzoquinone free radical intermediate of etoposide is responsible for DNA strand breakage.10 Since general and selective methods for the oxidation of aryltetralin lignans are still lacking,11 novel synthetic strategies are needed to

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