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A novel chemo-enzymatic synthesis of the stable and separable C-C dimeric atropoisomers of the bioactive natural sesquiterpene 8-trans-hydroxycalamenene

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PURPOSE OF THE ABSTRACT

Terpenes are a class of compounds characterized by carbon backbones of a variable number of isoprene units which can be rearranged into cyclic structures. Among these, sesquiterpenes are formed by three isoprene units and display a wide range of biological activities such as antimicrobial, antimycobacterial, analgesic, anti-inflammatory and anti-protozoal properties, as evidenced by in vitro assays of constituents in essential oils extracted from different plant species [1-3]. 8-hydroxycalamenene (mainly in trans configuration) is an important natural product representative of this group, whose (+)-form represents the major toxic constituent of Dysoxylum acutangulum seeds [4]. Moreover, a minor component of the same plant was characterized as an unsymmetrical C-C- dimer of (+)-8-hydroxycalamenene, existing as a discrete atropoisomer [5]. Interestingly, to the best of our knowledge, no further investigations on its chemical synthesis and pharmacological profile have been carried out in more recent years. Thus, a new chemo-enzymatic entry was considered to prepare these peculiar structures characterized by a conformationally-constrained stereogenic axis.

Accordingly, the two enantiomers of 8-trans-hydroxycalamenene (1 and 2, Figure 1) were chemically prepared through stereoselective syntheses starting from naturally occurring (-) and (+)-menthol, both easily available from the chiral pool. The obtained sesquiterpene isomers were thus used as substrates in a laccase-mediated oxidative C-C coupling. A synthetic protocol, previously described by us for the preparation of 1 [6], has been successfully adapted for the synthesis of 2. Subsequently, aiming at enzymatically generating the C-C dimers of the two substrates, laccase from Trametes versicolor was selected, based on our expertise with this enzyme in analogues transformations [7]. Laccases are multi-copper oxidases known for being able to activate normally inert Csp2-H bonds of phenol – or aniline – substrates by generating organic radicals at the expense of molecular oxygen, generating water as the only reduction byproduct [8].

The oxidation of 1 and 2 was studied using different reaction media and conditions and, finally, the optimized biotransformations allowed to isolate in good yields the target C-C dimers 3 and 4 (Figure 1), as a stereoenriched mixture of stable and separable atropoisomers.

Thanks to this chemo-enzymatic approach, the C-C dimeric metabolites of both the enantiomers 8-trans-hydroxycalamenene were obtained and fully characterized. Their bioactive profiles, starting from potential antiprotozoal activity [2,3,9] and/or cytotoxicity, is now under investigation.

FIGURES

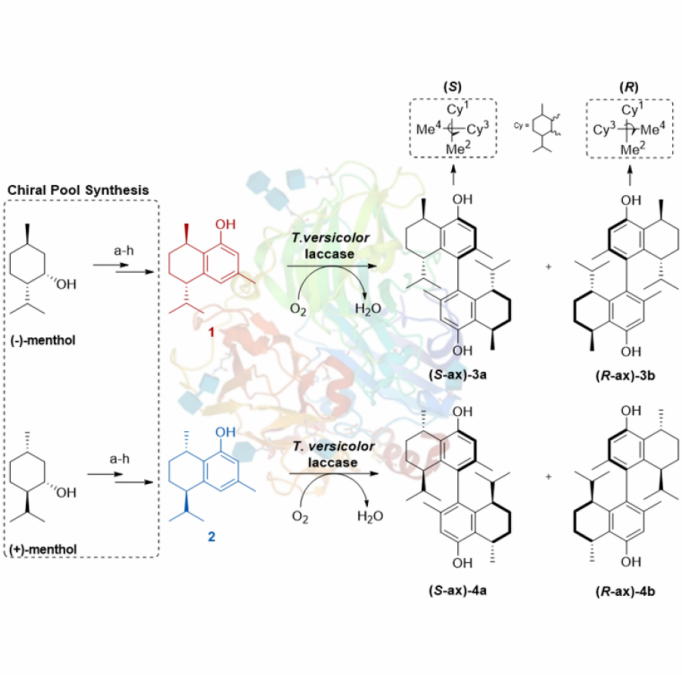

FIGURE 1

Chemo-enzymatic synthesis of bicalamenene atropoisomers.

Reagents and conditions: a) CrO3/H2SO4, Et2O-H2O, 25 deg; b) TsNHNH2, DCM, 0 deg; c) BuLi, hexane/TMEDA, -78 deg - Rt; d) DMF, -78 deg; e) DMS, LDA, THF, -60 deg; f) (CF3CO)2O, TEA, THF, 0 deg; g) LiAlH4, Et2O, 0 deg; h) H2, Pd/C, MeOH

FIGURE 2

KEYWORDS

chemo-enzymatic synthesis | T. versicolor laccase | terpenoids and natural products | biocatalysis

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