Tetrahedron 69 (2013) 7285–7289

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Biomimetic synthesis of an antitumour indole sesquiterpene alkaloid, 12-epi-*ent*-pentacyclindole

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ARTICLE INFO

Article history:
Received 16 May 2013
Accepted 21 June 2013
Available online 28 June 2013

Keywords:
ent-Halimic acid
Indole sesquiterpenes
Pentacyclindole
Polyalthenol
Antitumour

ABSTRACT

Biomimetic synthesis of 12-epi-*ent*-pentacyclindole **7**, using as key step the cyclization of 12-epi-*ent*-polyalthenol acetate has been carried out. This way, the structure and absolute configuration of the natural product pentacyclindole **1** has been confirmed. The synthesized indole sesquiterpenes **7**, **11** and **12** show cellular proliferation inhibition of a number of human leukaemic and solid tumour cell lines.

1. Introduction

Indole sesquiterpenes represent a group of terpene-alkaloids with diverse biological activities.[1] Pentacyclindole **1**[2] (Fig. 1), is an indole sesquiterpene that shows a new carbon skeleton, being the only natural product with that framework (defined to be all ring systems and the linkers that connect them). In an exhaustive study made throughout the CAS Registry analysing pentacyclindole frameworks,[2,3] 213 compounds with the same graph structure were found, and only 7 that have the same heteroframework. Compound **1** has been recently isolated from *Greenwayodendron suaveolens* roots,[2] along with polyalthenol **2**, suaveolindole **3** and its derivatives **4** and **5** (Fig. 1). In addition, pentacyclindole **1** and polyalthenol **2** present activity against clinical isolates of *Staphylococcus aureus* (MIC_{90} of 8 and 4 μg/ml). Williams and co-workers[2] suggest that **1** is a product of the biosynthetic cyclization between C-2 and C-17 of polyalthenol **2**.

The structural novelty of pentacyclindole **1** and its remarkable antibiotic activity prompted us to start the synthesis of **7** with the aim to add new evidences for the biogenetic route of **1** new framework. In this work we communicate the synthesis of **7** from *ent*-halimic acid methyl ester **8**[4] (Fig. 1). This compound is a natural product with a very well-known structure and stereochemistry that has been used as starting material for the synthesis of a wide variety of natural products,[5] for instance, indole diterpene thiersindole C **9**[6] and the indole sesquiterpene 12-epi-*ent*-polyalthenol **6**,[7] which synthesis confirmed the structure and absolute configuration of the natural product **2**.

2. Results and discussion

The synthesis of **7** using **6** as key intermediate was carried out according to the synthetic route depicted in Scheme 1. Acetylation of **6** with acetic anhydride in pyridine gave the acetylderivative **10** that by treatment with hydroiodic acid in refluxing benzene[8] led to **11**. The HRESMS of **11** shows the same signal at *m*/*z* 402 as **10**, corresponding to the ion with identical atomic mass than the precedent compound **10**. This indicates that the cyclization has taken place between C-2 and C-17, as expected in the reaction of a 3-(but-3-enyl) indole in acidic media,[8] generating three new stereocenters in a single step with total diastereoselection.

Effectively, in the ^1H NMR spectra of **11**, in comparison with the one of **10**, can be appreciated the absence of the signals corresponding to H-2 of the indole ring and the signal corresponding to the olefinic hydrogen at C-17 of **10**. The hexahydrocarbazole structure of **11** and the stereochemistry of the three new stereogenic centres formed was determined by NMR bidimensional experiments $^1H/^{13}C$ (HMQC, HMBC and ROESY). The shield of H-17,

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0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.06.075

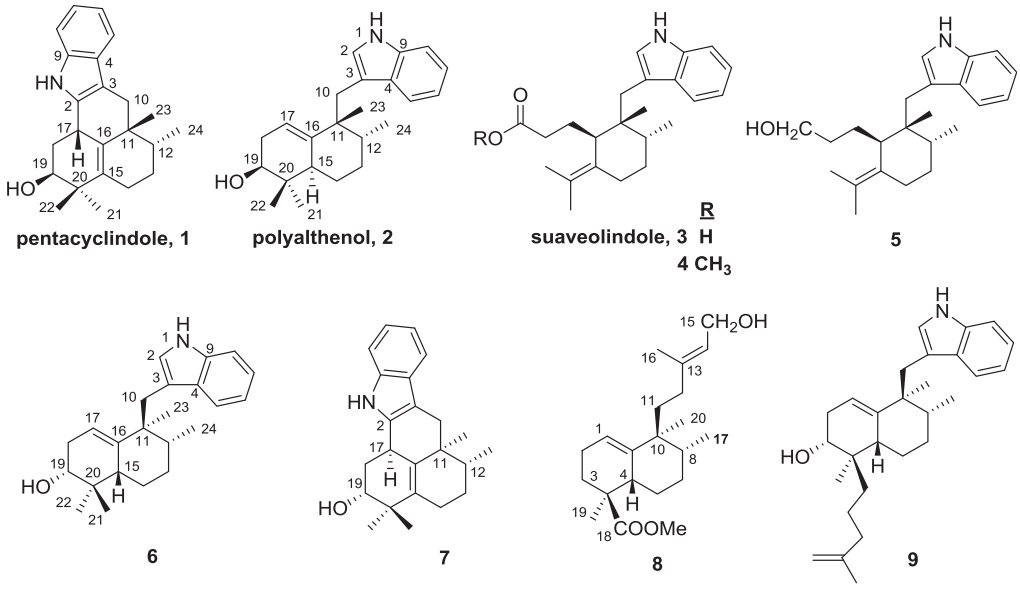
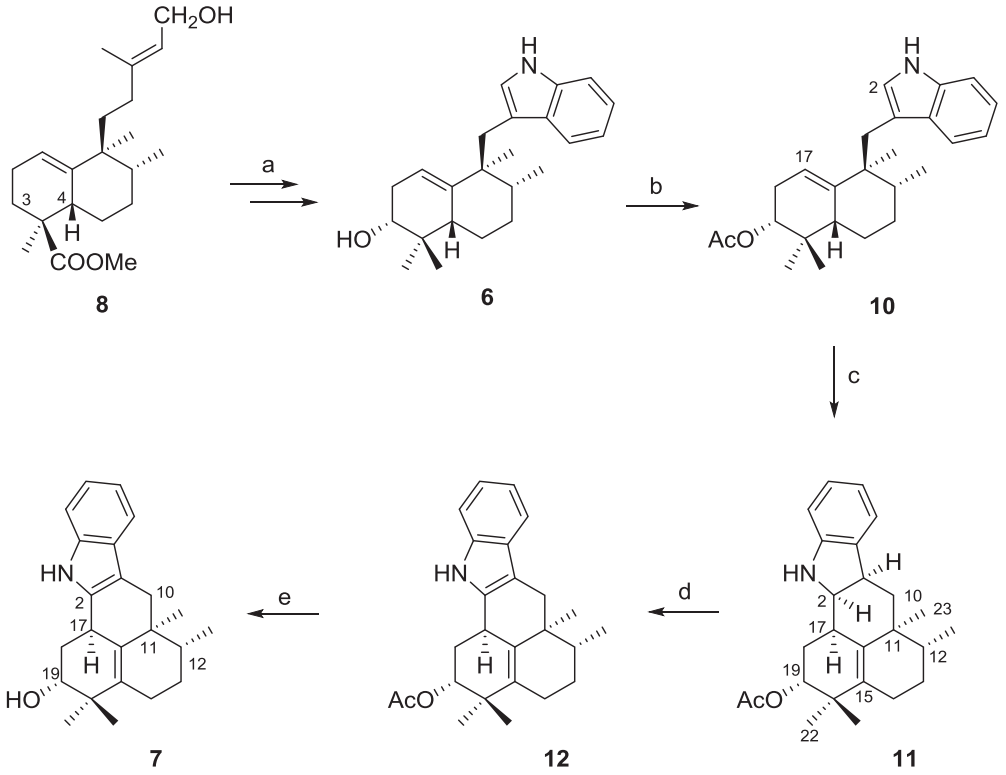


Fig. 1. Pentacyclindole and several structurally related indole sesquiterpenes **1**–**5**, 12-epi-*ent*-polyaltenol **6**, 12-epi-*ent*-pentacyclindole **7**, *ent*-halimic acid methyl ester **8** and thiersindole C **9**.



Scheme 1. Reagents and conditions: (a) Ref. 7. (b) Ac_2O, Py, rt, 20 h, 99%. c) HI 57%, C_6H_6, 85 °C, 75 min, 93%. d) TPAP, NMO, 4 Å molecular sieves, DCM, rt, 15 min, 66%. e) 10% KOH/MeOH, rt, 3 h, 93%.

the correlation between C-2 with H-18 and the appearance in the ^{13}C NMR spectra of two quaternary carbons signals at 136.6 and 131.9 ppm corresponding the tetra-substituted olefin Δ^{15} for they show 1,3 correlations with Me-21, Me-22 and Me-23, indicate that the new pentacyclic system was formed. The observed NOEs (Fig. 2) between H-2 with H-3 and H-17, indicate that these hydrogens are located by the same side of the molecule and the NOEs between Me-23 with H-3 and H-17 permit the stereochemistry to be determined as 2*R*, 3*R*, 17*R* for the new stereocentres.

This cyclization reaction can be considered the key step in this biomimetic synthesis of pentacyclindole analogues, and could be used to corroborate other biogenetic routes of other sesqui and diterpeno indoles, such as tubingensin A and B that have been proposed to derive from anominina.[8,9]

Once obtained the pentacyclic system, we proceeded with the oxidation of the indoline **11** to obtain the tetrahydrocarbazolic structure. To achieve this, several methods were tested, such as oxygen, Swern oxidation[10] or CrO_3/Py,[11] but the one that gave