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Synthesis of tri- and tetracyclic diterpenes. Cyclisations promoted by SmI_2

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Abstract—Several tri- and tetracyclic diterpenes have been synthesised from zamoranic acid. The key step is the cyclisation of a dicarbonyl 13,14-secoderivative by SmI_2.

1. Introduction

Tri- and tetracyclic diterpenes are very common in nature, showing a variety of skeletons, and many of them are very important not only due to their structures but also from the biological point of view.[1] Abietanes, pimaranes, isopimaranes, cassanes, cleistanthanes, totaranes and the trinor-derivatives, podocarpanes, are tricyclic diterpenes. Among the tetracyclic systems are kauranes, beyeranes or hibaenes and isohibaenes (Fig. 1). They show biological profiles as antifungal,[2] antiinflamatory,[3] antioxidant,[4] antibiotic,[5] antitumoural,[6] antimalarial,[7] cardioactive,[8] and antiviral[9] compounds and are inhibitors of nitric oxide.[10] Additionally some of this class of species are active as phytoalexines,[11] making these compounds particularly interesting. Due to their wide distribution and interesting bioactivities many synthetic studies have been reported.[12]

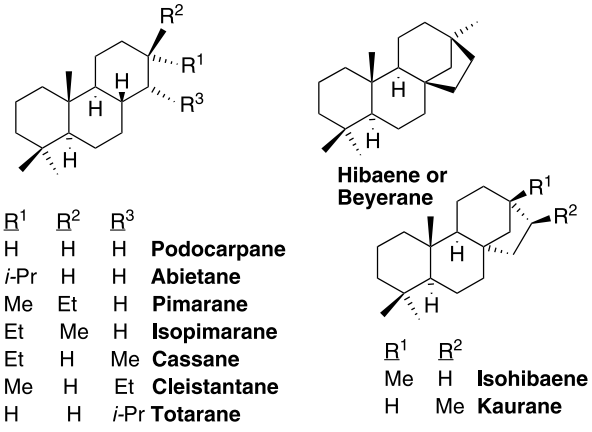

Figure 1. Diterpene tri- and tetracyclic skeletons.

As part of our continuing efforts to synthesise this kind of biologically active compound, a series of tri-and tetracyclic diterpenes were synthesised from zamoranic acid. This compound is a labdane diterpene,[13] which has already been used to prepare biologically active natural products, such as sesquiterpene drimanes,[14] labdanolides, such as limonidilactone,[15] diterpenes with the isofregenedane skeleton, such as chrysolic acid and isofregenedol.[16] Recently we have reported the synthesis of tri- and tetracyclic diterpenes[17] and (+)-totarol.[18]

In this paper we show that when the trinorderivative of zamoranic acid, the dialdehyde (14,15,16-trinorlabdan-13,17-dial), **23**, is treated with SmI_2, it gives rise to the podocarpanic diol **36** as the major product, an advanced intermediate for the synthesis of tricyclic compounds with the isopimarane, cassane, cleistanthane and rearranged abietane skeletons.

2. Results and discussion

Our general approach to the tricyclic diterpenes from zamoranic acid is outlined in Scheme 1. To allow access to tricyclic diterpenes of diverse skeletons such as **II**, our plan

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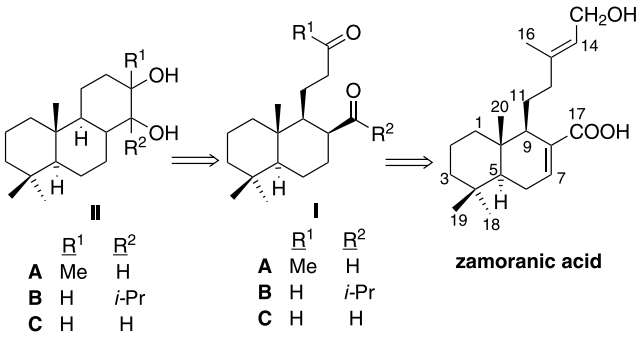


Scheme 1.

leads to the corresponding dicarbonyl compounds **I** as intermediates for subsequent cyclisation by SmI_2. The synthesis of the dicarbonyl compounds **I** was planned as resulting from the degradation of the side chain of zamoranic acid and then adjustment of the functionalisation or substitution at C-17. The synthesis of tricyclic diterpenes, such as pimaranes, or tetracyclic species, such as hibaenes **IIA**, was planned via an intermediate obtained by cyclisation of **IA**. The synthesis of totaranes, and particularly (+)-totarol, can be envisaged from diol **IIB** as intermediate, this being obtained by cyclisation of **IB** with SmI_2. As highlighted above in order to obtain tricyclic diterpenes with a range of different skeletons, the synthesis of the podocarpanic diol **IIC** was planned from the dialdehyde **IC**.

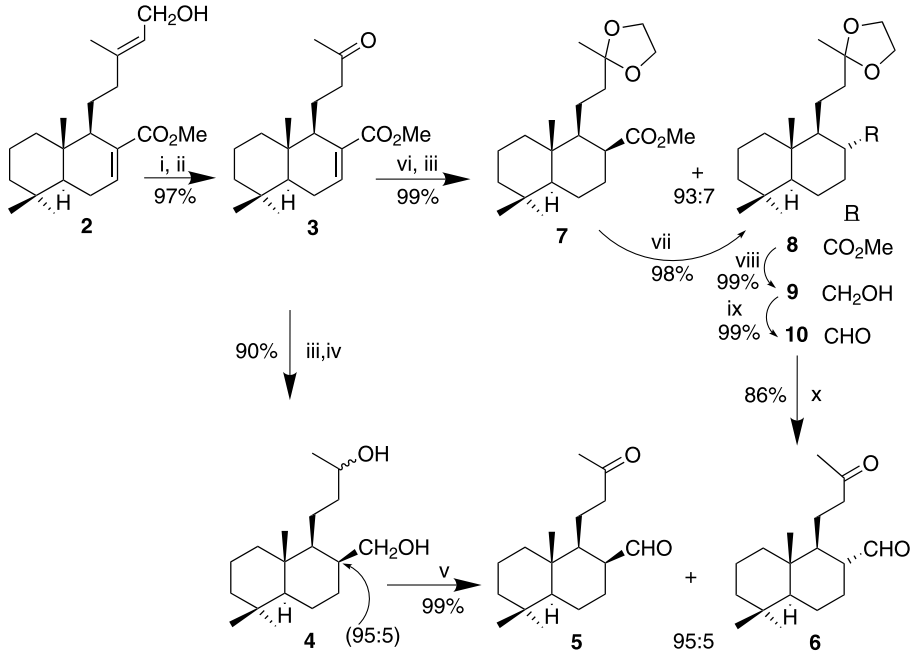
In the paper we describe the synthesis of compounds with pimarane and hibaene skeletons and of (+)-totarol, and demonstrate the potential of the podocarpanic diol **36** as an intermediate for the synthesis of different tricyclic diterpene skeletons. Initially, we describe the synthesis of the dicarbonyl compounds, then the cyclisation with SmI_2 of each of these, and finally the synthesis of the diterpenes.

2.1. Degradation of the side chain and synthesis of dicarbonyl compounds

2.1.1. Synthesis of dicarbonyl compounds 5 and 6. The synthesis of the intermediates **5** and **6** is shown in Scheme 2. Chemoselective oxidation of the allyl alcohol olefin unit of zamoranic acid **2** with OsO_4[19] afforded the corresponding diol, which was subsequently cleaved with LTA (lead tetracetate)[20] to yield the methyl ketone **3**. Hydrogenation of **3** in the presence of PtO_2,[21] followed by reduction with DIBAL-H[22] led to compound **4** with very good diastereoselectivity, we realised that LAH could also be used for the latter part of this transformation. Oxidation of **4** using Swern technique[23] gave **5** and **6**; Collins's reagent[24] could also facilitate this transformation.

However, aldehyde **6** was alternatively synthesised from **7** in an excellent yield (Scheme 2). Hydrogenation of the dioxolane derivative of **3** gives **7** and **8** stereoselectively (93:7, 98%). The coupling constants of H-8 in the ^{1}H NMR spectra for **7** (J=1.6, 4.8 Hz) and **8** (J=4.3, 11.8 Hz) confirm the stereochemical assignment for C-8. Treatment of **7** with NaOMe[25] gave diastereomer **8**, which was easily converted to **6** by a reduction–oxidation sequence through the intermediates **9** and **10**, these transformations confirm the C-8 stereochemistry of **5** and **6**.

2.1.2. Synthesis of dicarbonylic compound 19. Addition of isopropylmagnesium chloride[26] to aldehyde **10** (Scheme 3) proceeded with complete stereoselectivity to give exclusively the 14*R*-hydroxy derivative **11**, in excellent yield. The structure of **11** was confirmed by X-ray analysis of one of its derivatives (compound **15**, Scheme 3), showing that the reaction of the nucleophile has taken place from the less hindered *Si* face of the carbonyl group.



Scheme 2. (i) OsO_4, NMO, ^{t}BuOH/THF/H_2O, rt, 18 h; (ii) LTA, benzene, rt, 2 h; (iii) H_2/PtO_2/Et_2O, rt, 36 h for **3** to **4** and 10 h for **3** to **7** and **8**; (iv) DIBAL-H, toluene, −78 °C, 30 min; (v) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 30 min; (vi) $(CH_2OH)_2$, *p*-TsOH, benzene, reflux, 21 h; (vii) (a) NaOMe/MeOH, reflux 12 h; (b) CH_2N_2; (viii) LAH, Et_2O, rt, 1 h; (ix) CrO_3/Py, DCM, rt, 30 min; (x) *p*-TsOH/acetone, rt, 14 h.