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Synthesis of (−)-agathic acid and (−)-copalic acid from andrographolide via a regioselective Barton-McCombie reaction

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ABSTRACT

The first synthesis of the *ent*-labdane diterpenoid (−)-agathic acid (**1**) with antibacterial activity is described. A chiral pool approach was employed with a linear sequence of 14 steps starting from readily available and inexpensive andrographolide. The regioselective deoxygenation in terms of Barton-McCombie free radical reaction completed a key step in the synthesis. (−)-Copalic acid (**2**), an analogue of (−)-agathic acid, has been conveniently synthesized from the key intermediate **7** in five steps.

1. Introduction

Natural products have served as the source of leads for the development of drugs, and have played a significant role in drug discovery: most clinically approved drugs are either natural products or inspired by a natural compound.[1] Copaiba oil, which was obtained from the trunk of several *Copaifera* L. species, has been widely used in cosmetics and pharmaceutical industries.[2] Diterpenic carboxylic acids present in Copaiba oil, including (−)-agathic acid (**1**), (−)-copalic acid (**2**), (−)-kaurenoic acid (**3**), (−)-hardwickiic acid (**4**) and others, comprise an important class of diterpenoid natural products, since they show promising antibacterial[2,3] and anti-cancer activities (Fig. 1).[4] (−)-Agathic acid and (−)-copalic acid, two *ent*-labdane type diterpene acids firstly reported by Ferreira[5] and Djerassi[6] respectively, attracted our attention not only because of their antibacterial activities but also due to their *ent*-labdane structures. Especially for (−)-agathic acid, which was recently named as platencin SL1 by Ben Shen and his co-workers since the deficiency of its physicochemical data in the literature for comparison,[7] it seems essential to clarify its structural characterization further by means of synthesizing this natural product.

To the best of our knowledge, there has not been any attempt reported to synthesize (−) or (+)-agathic acid yet so far, although the preparation of (−)-copalic acid was accomplished, based on a lipase-catalyzed resolution of racemic albicanol to afford (−)-albicanol as chiral building block.[8] Here we reported the first synthesis of (−)-agathic acid and the synthesis of (−)-copalic acid with a chiral pool strategy.

2. Results and discussion

Inspection of the structure of (−)-agathic acid revealed it to be an *ent*-labdane type diterpene with four chiral centers. For the synthesis of a natural product with a couple of chiral centers, chiral pool approach is usually believed more efficient and economic. Andrographolide, a readily available and inexpensive *ent*-labdane type diterpene, was naturally considered as the starting material. A retrosynthetic analysis of our approach to (−)-agathic acid based on chiral pool strategy is presented in Scheme 1. In this approach, 3,19-isopropylidenedioxy-12-oxo-13,14,15,16-teranor-*ent*-labda-8(17)-ene (**9**), which could be obtained from andrographolide (**10**), was selected as the chiral building block. We sought to generate **1** through the oxidation of 19-hydroxy precursor (**5**), which was to be prepared from aldehyde **9**, via Henry reaction of **9**, Nef reaction of **8**, selective removal of 3-hydroxy group of **7**, and

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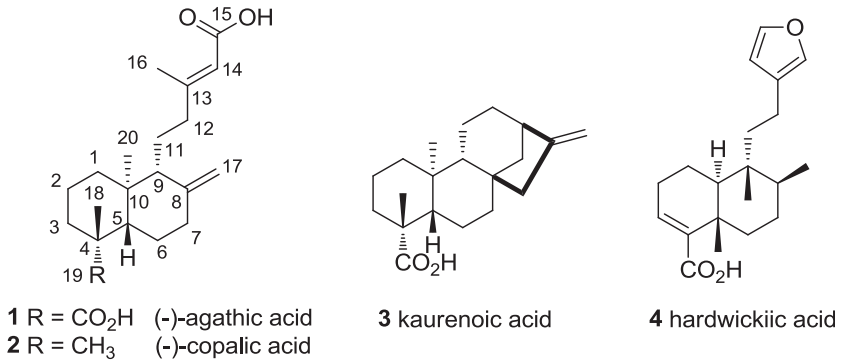
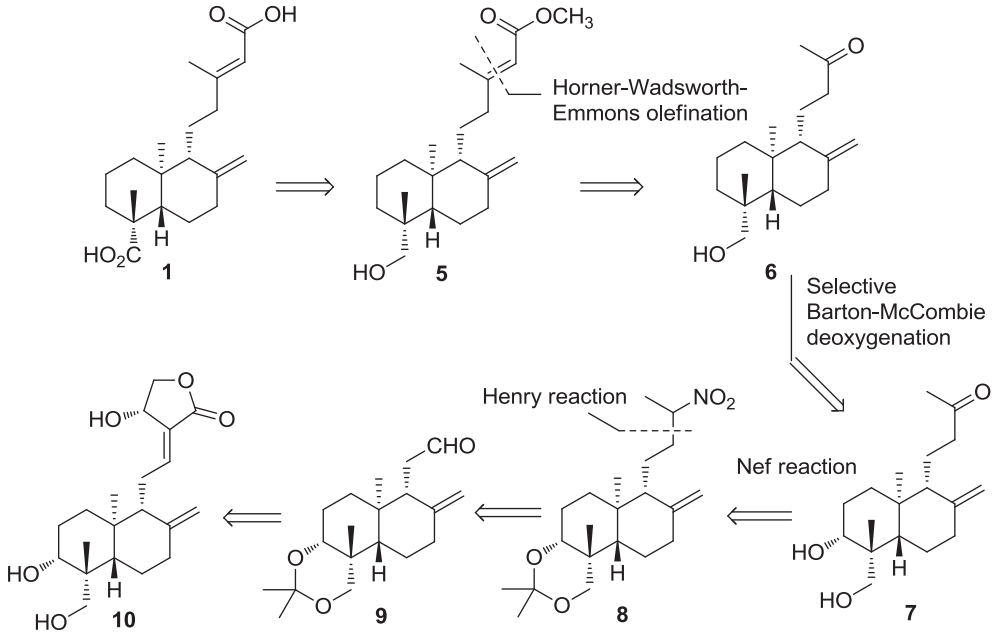


Fig. 1. Diterpenic carboxylic acids in Copaiba oil.

Horner–Wadsworth–Emmons olefination of **6**, as illustrated in Scheme 1.

The first part of the synthesis, which consisted in the transformation of andrographolide into the 3,19-dihydroxy tetranorlabdane methylketone **7** via isopropylidene-protected 3,19-dihydroxy tetranorlabdane aldehyde **9**, was carried out in an eight step sequence (Scheme 2). The key chiral building block **9** was prepared through a modified literature method.[9] The hydroxyl groups at C3 and C19 of andrographolide were firstly protected as described in the literature, followed by the elimination of the hydroxyl at C14 by reacting with acetic anhydride and DMAP in one step to furnish $\Delta^{14,15}$-andrographolide **11** in 76% yield, which was further oxidized selectively with $KMnO_4/MgSO_4$ to provide **9** in 60% yield. It is necessary to point out that the literature method for the oxidation of **11** with KMnO4 in aqueous THF could not be scaled up to more than 0.1 g since the formed aldehyde was very easily converted into carboxylic acid via further oxidation during work up. However, with our modified approach, the oxidation of **11** with $KMnO_4/MgSO_4$ in acetone could be scaled up to multi-grams scale. The condensation of aldehyde **9** with nitroethane under typical Henry reaction conditions with potassium *tert*-butoxide as base,[10] gave the α-hydroxynitro compound **12** as a mixture of four diastereomers. Fortunately, since the two newly generated chiral centers in α-hydroxynitro compound **12** would be removed during the subsequent reactions, the diastereomeric mixture of **12**, could be directly used for next elimination reaction without further purification. Thus, treatment of **12** (in its crude form) with acetic anhydride and DMAP in methylene chloride under 0 °C to room temperature afforded the nitroolefin **13** as an inseparable mixture of *E* and *Z* isomers in 70% yield for two steps. Reduction of **13** with sodium borohydride in chloroform at room temperature,[11] provided a 1.13:1 epimeric mixture of nitro compound **8** with an 80% yield. Finally, Nef reaction of epimeric mixture of **8** with oxidizing agent $KMnO_4$ in THF under basic condition,[12] immediately followed by the deprotection reaction with aqueous sulfuric acid, provided 3,19-dihydroxy tetranorlabdane methylketone **7** in 83% yield.

Selective deoxygenation of 3-hydroxyl group in 3,19-dihydroxy-13-oxo-15,16-dinor-*ent*-labda-8(17)-ene (**7**) was achieved through Barton-McCombie free radical deoxygenation reaction.[13] Accordingly, dihydroxyl compound **7** was treated with 1,1′- thio-



Scheme 1. Retrosynthetic analysis of (−)-agathic acid (**1**).