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Total syntheses of the sesquiterpenes β-corymbolol and corymbolone

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This paper is dedicated to Professor Nicola Petragnani, for his invaluable contribution to the development of the Brazilian Organic Synthesis

Abstract—The first total synthesis of racemic corymbolone, an eudesmane sesquiterpene isolated from *Cyperus* species used in traditional medicine to treat many diseases, is reported. In the developed sequence, the immediate precursor of corymbolone is the diol β-corymbolol, an epimer at C_1 of the natural α-corymbolol. Thus, starting from the readily available Wieland–Miescher Ketone, the title compounds were achieved in 11 and 12 steps, respectively, in ca. 3% overall yield.

1. Introduction

Corymbolone (**1**) is a sesquiterpenic keto-alcohol first isolated in 1985, in South America, from the rhizomes of *Cyperus corymbosus* Rottboll.[1] Some years later, corymbolone was isolated in Cameroon, from *Cyperus articulatus* L., along with another eudesmane sesquiterpene, the diol α-corymbolol (**2a**).[2] Since 1994, *C. articulatus* L. and *C. corymbosus* Rottb. are treated as synonymous.[3] This cyperaceae is a tropical sedge widely distributed in southern and western Africa, where it is known as 'mandassi',[2] as well as in the Amazonian region, where it is called 'piripiri'.[4] The crude drug prepared from the rhizomes of this plant has been used in traditional medicine as contraceptive[5,6] and for treating many other diseases.[7,8]

Both corymbolone and corymbolol (Fig. 1) bear an axial hydroxyl group at the C_5 position, which is not an usual feature of the eudesmane sesquiterpenes.

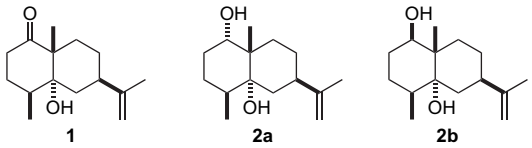
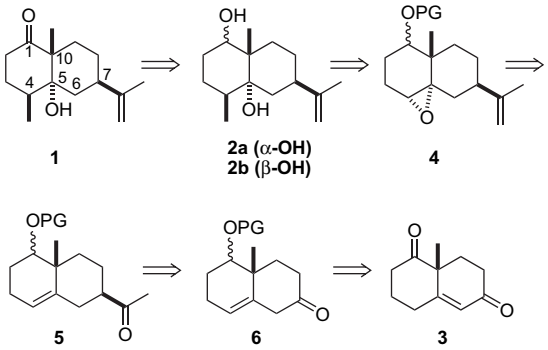


Figure 1. Corymbolone (**1**), α-corymbolol (**2a**) and β-corymbolol (**2b**).

The reported biological activity and the rare presence of an angular hydroxyl group, as well as the lack in the literature of any described synthesis of these compounds, stimulated us to investigate some approaches for their total synthesis. Thus, starting from the readily available Wieland–Miescher Ketone (**3**), we designed the retrosynthetic analysis depicted in Scheme 1.



Scheme 1. Retrosynthetic approach for **1** and **2**.

The functionalization of the A ring of **1** involves a nucleophilic opening of the α-epoxide **4**, by means of an adequate organometallic reagent, followed by oxidation of the secondary hydroxyl group of **2a** or **2b**. Since it is well known that the S_N2-type opening of cyclohexyl oxiranes is a trans-diaxial process, it can be foreseen that the organometallic reagent would attack the less substituted center (C_4) of **4** from the β-face. Therefore, the stereoselective α-epoxidation of **5** is a requirement to ensure the correct introduction of the axial methyl and hydroxyl groups at C_4

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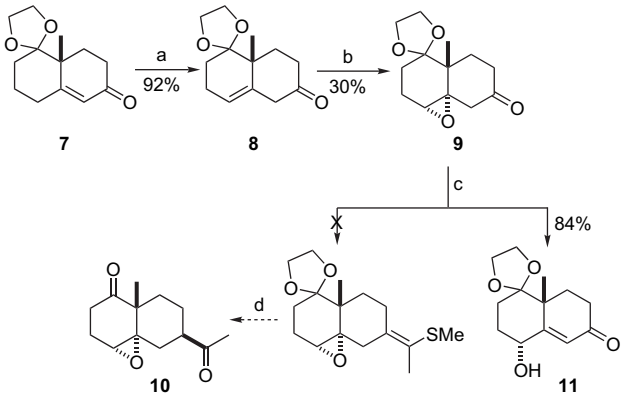
and C_5, respectively. A preferential epoxidation from the α-face could be expected, due to the steric hindrance offered by the C_{10} β-methyl group.

Concerning the B ring, the retrosynthetic analysis suggests that the isopropenyl unit could be introduced by homologation of the carbonyl group of **6**, followed by an olefination reaction of the resulting acetyl group present in **5** (or in some synthetic equivalent).

Finally, the migration of the double bond from the C_5–C_6 to the C_4–C_5 position, in an appropriate stage of the synthesis, would complete the retrosynthetic approach. The experimental results further described confirm the feasibility of the proposed sequence.

2. Results and discussion

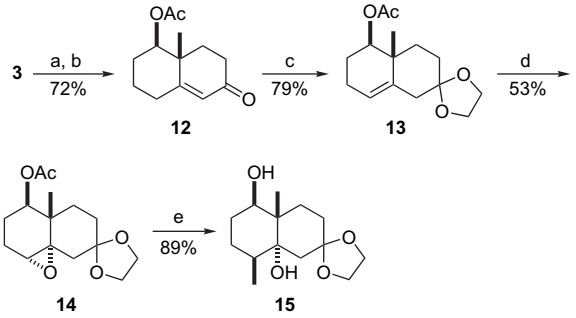
In a previous paper,[9] we presented the results of our attempts to promote the stereoselective α-epoxidation of the β,γ-unsaturated ketone **8**, obtained by deconjugation of **7**. By this first proposed protocol, the resulting product **9** would be submitted to a Horner–Emmons olefination, followed by hydrolysis, to furnish the advanced intermediate **10**. However, this sequence could not be achieved, since the desired epoxide **9** was obtained in very low yield (30%), accompanied by the reconjugated ketone **7** as the major product. Moreover, the epoxide **9** showed to be very unstable, even at 0 °C, and when submitted to the olefination reaction gave exclusively the allylic alcohol **11**, in 84% yield (Scheme 2). The formation of this alcohol can be rationalized on the basis of a deprotonation at C_6, with subsequent opening of the epoxide ring.



Scheme 2. Reagents and conditions: (a) i: *t*-BuOK/*t*-BuOH, 1 h, rt; ii: NaH_2PO_4 0.3 M; (b) *m*-CPBA, CH_2Cl_2, 2 h, rt; (c) $(EtO)_2P(O)CHCH_3(SMe)$, THF, 4 h, −78 °C and (d) H_3O^+.[9]

In view of these disappointing results, we formulated a second synthetic approach,[10] where none of the intermediates has acidic protons at C_6, for circumventing the undesirable reactions mentioned above. The envisaged key-intermediate of the new sequence was the α-epoxide **14**, which could be obtained from the ketone **3** (Scheme 3).

Thus, the acetate **12** was easily obtained by reduction[11] and acetylation[12] of **3**. The deconjugative ketalization of **12** was undertaken by treatment with ethylene glycol in the presence of *p*-TSA, leading to **13**[12] as a white crystalline solid.



Scheme 3. Reagents and conditions: (a) $NaBH_4$, EtOH, 0 °C, 92%; (b) Ac_2O, py, DMAP, rt, 78%; (c) ethylene glycol, *p*-TSA, PhH, 12 h, reflux; (d) *m*-CPBA, CH_2Cl_2, 3 h, rt and (e) MeMgI, CuI, Et_2O, 8 h, rt.[10]

It must be noted that some years after the publication of the above mentioned results,[10] the same sequence of reactions (from **3** to **13**) was employed by Danishefsky et al. in the total syntheses of baccatin III and taxol.[13]

The epoxidation of **13** was performed by classical conditions (*m*-CPBA in dichloromethane), giving a diastereomeric mixture (ca. 7:3, by ^1H NMR analysis) of the epoxides, which were separated by silica column chromatography into the pure α-isomer **14** (53%) and the corresponding β-isomer (19%). The correct structure of **14** was determined by NMR spectroscopy, and confirmed by X-ray analysis.[14]

Although a greater ratio of the desired α-epoxide had been expected a priori, the lower assessed α/β ratio can be probably attributed to a competitive hindrance between the C_{10} β-methyl group and the α-oxygen of the ketal group at C_7. Other epoxidizing reagents (DMD and TBHPMo) were then tried, not only on the intermediate **13**, but also on other related substrates.[15] The results thus obtained were more unfavourable, since the major isomers were always the β-epoxides. We have then decided to pursuit the synthetic route using the earlier protocol (*m*-CPBA-promoted epoxidation of **13**), in spite of the moderate yield of **14**.

The trans-diaxial opening of the epoxide **14** was best performed employing methylmagnesium iodide in the presence of 10% of cuprous iodide, although with loss of the protecting group at C_1. Eventually, the presence of the copper salt should preserve the chemoselectivity towards the epoxide ring, therefore avoiding the attack to the acetyl group. Nevertheless, a great excess of the Grignard reagent was required to achieve good results in the epoxide opening, since 2 equiv were consumed by the acetate group, giving the diol **15** as final product. At this point, the synthetic problems concerning the construction of the ring A of the target molecule were solved.

The introduction of the isopropenyl unit at C_7, as stated in the retrosynthetic analysis, would be possible following a sequence of reactions already employed by Heathcock et al.,[12] and by de Groot et al.,[16] in their syntheses of other eudesmane sesquiterpenes. The approach consists in a Wittig reaction at the C_7 carbonyl group, followed by hydroboration of the C_7–C_{11} double bond, oxidation of the hydroxyl group at C_{11} and, finally, another olefination of the resulting methyl ketone.