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Gold catalysis in stereoselective natural product synthesis: (+)-linalool oxide, (−)-isocyclocapitelline, and (−)-isochrysotricine

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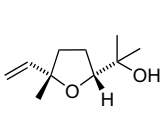
ABSTRACT

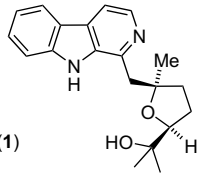
A stereoselective synthesis of the tetrahydrofuran-containing natural products (2*S*,5*R*)-(+)-linalool oxide (**1**), (−)-isocyclocapitelline (**2**), and (−)-isochrysotricine (**3**) is reported. Key steps are the copper-mediated S_N2'-substitution of propargyl oxiranes **7** and the gold-catalyzed cycloisomerization of dihydroxyallenes **8**/**17**, resulting in a highly efficient center-to-axis-to-center chirality transfer. The enantioselective total synthesis of (−)-isocyclocapitelline (**2**) and (−)-isochrysotricine (**3**) allowed the elucidation of the absolute configuration of these β-carboline natural products.

1. Introduction

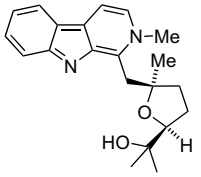
Due to their presence in many biologically active natural products, chiral tetrahydrofurans continue to be of high interest in preparative and medicinal chemistry.[1] Recently, 2,5-substituted tetrahydrofurans have attracted much attention since they occur in annonaceous acetogenins, which exhibit highly diverse biological properties.[2] Various other natural products also contain this heterocyclic system, including the terpenoid linalool oxide (**1**), the β-carboline alkaloids, (−)-isocyclocapitelline (**2**), and (−)-isochrysotricine (**3**).



(2*S*,5*R*)-(+)-Linalool Oxide (**1**)



(−)-Isocyclocapitelline (**2**)



(−)-Isochrysotricine (**3**)

Furanoid linalool oxide (**1**) is an important constituent of oolong, black and green tea and is also found in many essential oils[3] and fruit aromas (e.g., in papaya).[4] It is used in perfumery (e.g., for lavender notes) and for the reconstitution of essential oils.[5] For these applications, control of the stereochemistry is crucial since the fragrance properties of linalool oxide depend on the absolute configuration at C-2: the (2*R*)-isomers have a leafy earthy note whereas the (2*S*)-isomers exhibits a sweet floral creamy flavor.[6,7] Although many syntheses of linalool oxide have been reported,[8] most of them are not stereoselective; only two diastereo- and enantioselective routes have been disclosed so far.[9]

Isocyclocapitelline (**2**) and isochrysotricine (**3**) were isolated (together with their diastereomers cyclocapitelline and chrysotricine) in 1999 from the Rubiaceae plant *Hedyotis capitellata*, which has been widely used in traditional Chinese and Vietnamese herb medicine.[10] The constitution and relative configuration of these β-carboline alkaloids were confirmed by NMR data and an X-ray analysis; the absolute configuration was unknown at the beginning of our work. Studies of the biological activity of isochrysotricine and isocyclocapitelline were hampered by the minute amounts of the alkaloids available from natural sources; for chrysotricine, however, an interesting in vitro activity against the growth of HL-60 leukemia cells has been observed.[11] Previous synthetic studies were devoted to (+)-chrysotricine,[12] racemic isocyclocapitelline/isochrysotricine,[13] and norisocyclocapitelline.[8g]

Taking into account that all three natural products contain a chiral 2,5-trisubstituted tetrahydrofuran ring of the same relative configuration,[14] we reasoned that related synthetic routes should lead to these target molecules. Based on our experience with the gold-catalyzed[15] cycloisomerization of α-hydroxyallenes[16]

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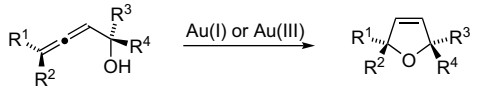
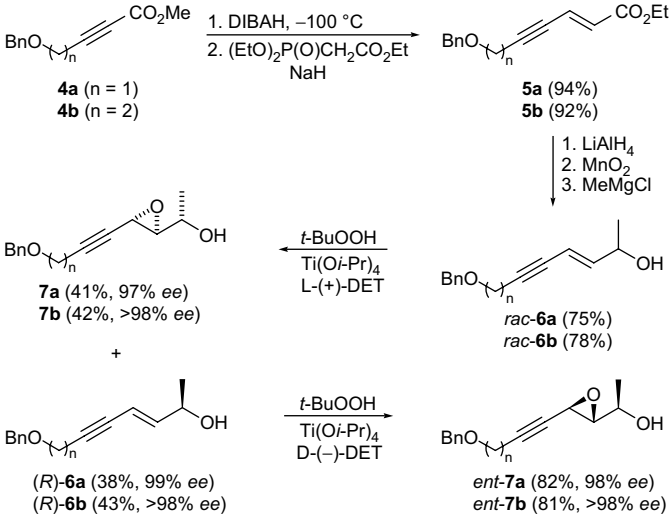
(Scheme 1) and other functionalized allenes[17] to five- or six-membered heterocycles, we planned to use this reaction (which takes place with efficient axis-to-center chirality transfer) as the key step for the synthesis of the natural products **1**–**3**. In this paper, we report on our synthesis of (2*S*,5*R*)-(+)-linalool oxide (**1**), as well as the first total syntheses of (−)-isocyclocapitelline (**2**) and (−)-isochrysotricine (**3**).[18]



Scheme 1. Gold-catalyzed cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans.

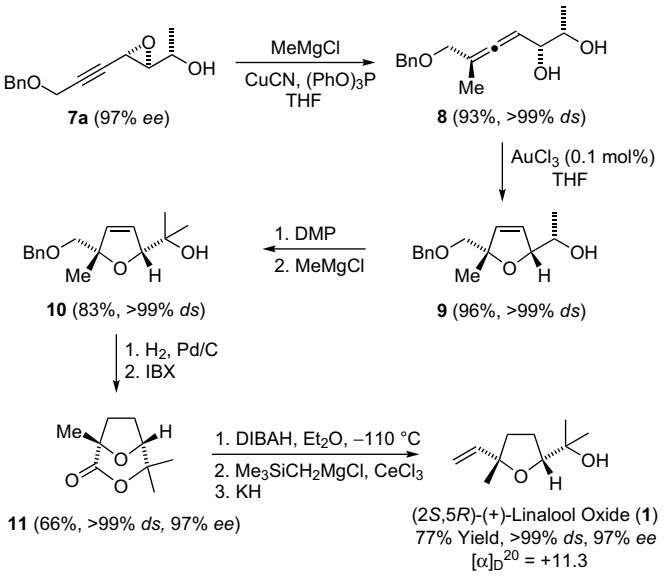
2. Results and discussion

Our approach started from the known esters **4a**[19] and **4b**,[20] which were converted into the enynoates **5** by a one-pot reduction–olefination sequence (Scheme 2).[21] Efficient transformation into the racemic secondary alcohols *rac*-**6** was achieved by standard reduction–oxidation–Grignard addition. Both enynes turned out to be excellent substrates for a kinetic resolution by Katsuki–Sharpless epoxidation;[22] with L-(+)-diethyl tartrate, both the epoxides **7** and the unreacted starting materials (*R*)-**6** (configuration assigned according to the Katsuki–Sharpless mnemonic device[22]) were obtained with high enantiomeric excess.[23] The enynes (*R*)-**6** were converted into oxiranes *ent*-**7**[23] by a matched Katsuki–Sharpless epoxidation using D-(−)-diethyl tartrate. It should be noted that the corresponding tertiary epoxyalcohols are not accessible by Katsuki–Sharpless epoxidation, due to the low reactivity of tertiary allylic alcohols.[22] With both enantiomers of the epoxyalcohols **7** at hand, either enantiomer of the target molecules **1**–**3** is accessible.



Scheme 2. Stereodivergent synthesis of propargyl oxiranes **7** by Katsuki–Sharpless epoxidation (DET=diethyl tartrate).

The key steps of the synthesis of (2*S*,5*R*)-(+)-linalool oxide (**1**) are the *anti*-selective copper-mediated S_N2'-substitution of propargyl oxirane **7a** and the gold-catalyzed cycloisomerization of the dihydroxyallene **8** thus formed (Scheme 3). Treatment of **7a** with a methylmagnesium cyanocuprate in the presence of triphenylphosphite as ligand to copper (in order to prevent epimerization of the allene[24]) afforded **8** with excellent chemical yield (93%) and diastereoselectivity (>99% ds).[25] The subsequent gold-catalyzed cycloisomerization was achieved in the presence of only 0.1 mol % $AuCl_3$ in THF, which gave the 2,5-dihydrofuran **9** with 96% yield (960 turnovers on a 2 g scale) as a single diastereomer, completing the key center-to-axis-to-center chirality transfer. As expected from previous results,[16,17e] only the hydroxy group in α-position participates in the cyclization.



Scheme 3. Stereoselective synthesis of (2*S*,5*R*)-(+)-linalool oxide (**1**) from propargyl oxirane **7a** (DMP=Dess–Martin periodinane; IBX=2-iodoxybenzoic acid).

Conversion of the secondary alcohol **9** into the tertiary alcohol **10** by oxidation with Dess–Martin periodinane (DMP; 94% yield)[26] or with 2-iodoxybenzoic acid (IBX) in DMSO[27] (63% yield) and subsequent Grignard addition proceeded smoothly. One-pot hydrogenation–debenzylation of **10** using palladium on charcoal as the catalyst furnished the desired diol with 81% yield; however, all attempts to selectively oxidize this to the corresponding lactol failed. Rather, we obtained mixture of the lactol and lactone **11**, regardless whether PCC, PDC, DMP, or IBX was used as the oxidizing agent. Therefore, we decided to completely oxidize the diol to lactone **11**, which was obtained with 66% yield over two steps when 2 equiv of IBX were used. For the final conversion of **11** into (2*S*,5*R*)-(+)-linalool oxide (**1**), we initially utilized a one-pot procedure consisting of the reduction of **11** with DIBAH at −110 °C and subsequent treatment of the lactol thus formed with freshly prepared $Ph_3P{=}CH_2$.[28] Since the yield of **1** was only 20% (33% for a stepwise process), we switched to a modified Peterson olefination using trimethylsilylmethylmagnesium chloride/cerium chloride and potassium hydride.[29] Under these conditions, the target molecule **1** was obtained with 77% overall yield for the reduction–olefination sequence. Gratifyingly, the high stereochemical purity was maintained overall steps, so that (2*S*,5*R*)-(+)-linalool oxide (**1**) was obtained with >99% ds and 97% ee (determined by GC; see Scheme 4). Comparison of the optical rotation of our product {$[\alpha]_D^{20}$ +11.3 (*c* 0.065, $CHCl_3$)} with the literature value[7] {$[\alpha]_D^{20}$ +4.0 (*c* 0.028, $CHCl_3$)} confirms the absolute configuration.

In contrast to linalool oxide, the absolute configuration of the other two target molecules, (−)-isocyclocapitelline (**2**) and (−)-isochrysotricine (**3**), was unknown at the onset of our study. We randomly selected epoxyalcohol *ent*-**7b** for our synthesis (Scheme 5). The first step matches with those used for linalool oxide: *anti*-selective copper-mediated S_N2'-substitution with MeMgCl/CuCN/$(PhO)_3P$ afforded the allenic diol **12** with high diastereoselectivity (>98% ds), and the chemo- and stereoselective gold-catalyzed cycloisomerization furnished the desired 2,5-dihydrofuran **13** with excellent yield and center-to-axis-to-center chirality transfer. With a catalyst loading of only 0.05 mol % $AuCl_3$ in