Golden opportunities in natural product synthesis: first total synthesis of (−)-isocyclocapitelline and (−)-isochrysotricine by gold-catalyzed allene cycloisomerization†

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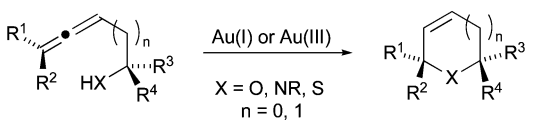
The first enantioselective total syntheses of the β-carboline alkaloids (−)-isochrysotricine (1) and (−)-isocyclocapitelline (2) are reported which confirm the absolute configuration of these natural products. Key steps are the copper-mediated S_N2'-substitution of propargyl oxiranes 13/14 and the gold-catalyzed cycloisomerization of α-hydroxyallene 15, resulting in a highly efficient center-to-axis-to-center chirality transfer.

Homogeneous gold catalysis is an emerging area of transition metal catalysis with tremendous potential for the synthesis of complex target molecules.[1] Based on their ability to activate C–C double or triple bonds as soft, carbophilic Lewis acids, gold salts are ideally suited for the formation of C–C and C–heteroatom bonds by nucleophilic attack at these activated substrates. Additionally, reactive C–H bonds can be directly activated by gold catalysts, opening a second efficient pathway for gold-catalyzed bond formation. In spite of its utility, however, applications of homogeneous gold catalysis in (stereoselective) natural product synthesis are still scarce.[2] In this paper, we report the first total syntheses of the β-carboline alkaloids (−)-isochrysotricine and (−)-isocyclocapitelline, taking advantage of the gold-catalyzed cycloisomerization of α-hydroxyallenes.

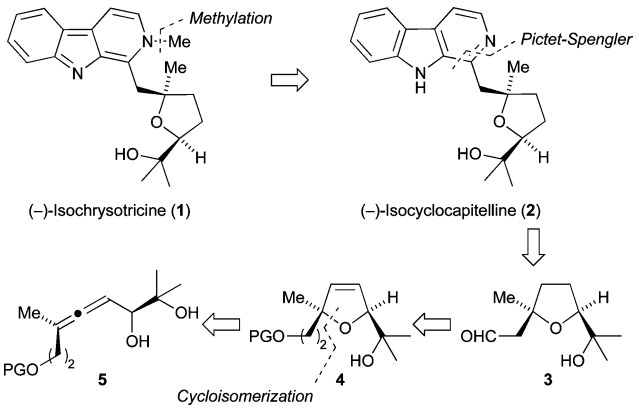
Our group has been interested in the stereoselective synthesis and transformation of functionalized allenes[3] for some time. Recently, we have reported the gold-catalyzed cycloisomerization of α-hydroxyallenes to 2,5-dihydrofurans[4] which combines a high reactivity and excellent axis-to-center chirality transfer with a tolerance to many functional groups. Moreover, the method could be extended to the *endo*-cyclization of β-hydroxyallenes,[5] α-/β-aminoallenes,[5,6] and α-thioallenes[7] to the corresponding 5- or 6-membered O-, N-, or S-heterocycles (Scheme 1). These transformations are perfect examples for atom economy.[8]



Scheme 1 Gold-catalyzed cycloisomerization of α- or β-heterosubstituted allenes to 5- and 6-membered heterocycles.

Isochrysotricine (**1**) and isocyclocapitelline (**2**) were isolated (together with their diastereomers chrysotricine and cyclocapitelline) in 1999 from the Rubiaceae plant *Hedyotis capitellata* which has been widely used in traditional Chinese and Vietnamese herb medicine.[9] The constitution and relative configuration of these β-carboline alkaloids were confirmed by NMR data and an X-ray analysis; the absolute configuration has not been determined so far. Studies of the biological activity of isochrysotricine and isocyclocapitelline have been 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 found.[10] Previous synthetic studies have been limited to racemic chrysotricine/isochrysotricine[11] and norisocyclocapitelline.[12]

Since the absolute configuration of isochrysotricine and isocyclocapitelline is unknown, we decided to design a stereodivergent route which should allow a rapid access to both enantiomers of **1** and **2** (Scheme 2). Retrosynthetically, isochrysotricine (**1**) can be traced back to isocyclocapitelline (*N*-methylation–deprotonation), and the β-carboline moiety should be accessible by Pictet–Spengler-cyclization–aromatization of the aldehyde **3** and tryptamine.[11] As precursor of tetrahydrofuran **3**, we envisaged the 2,5-dihydrofuran **4** which should be accessible by chemo- and stereoselective gold-catalyzed cycloisomerization of the allene **5**.



Scheme 2 Retrosynthesis of (−)-isochrysotricine (**1**) and (−)-isocyclocapitelline (**2**); PG = protecting group.

Our approch started from the known ester **6**[13] which was converted into the enynoate **7** by a one-pot reduction–olefination sequence[14] (Scheme 3). Efficient transformation into the secondary alcohol **8** was achieved by standard reduction–oxidation–Grignard addition. This enyne turned out to be an excellent substrate for a kinetic resolution by Katsuki–Sharpless epoxidation;[15]

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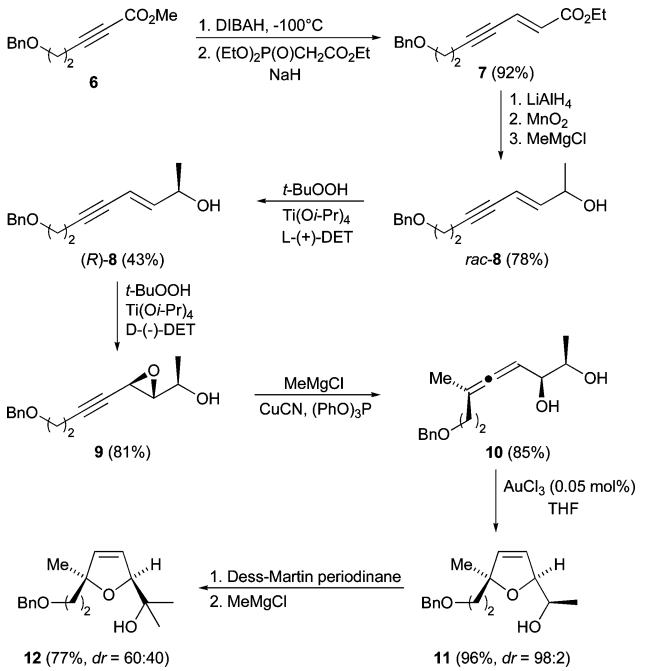
† Electronic supplementary information (ESI) available: NMR data of compounds **1–3** and **7–16**. See DOI: 10.1039/b703995f



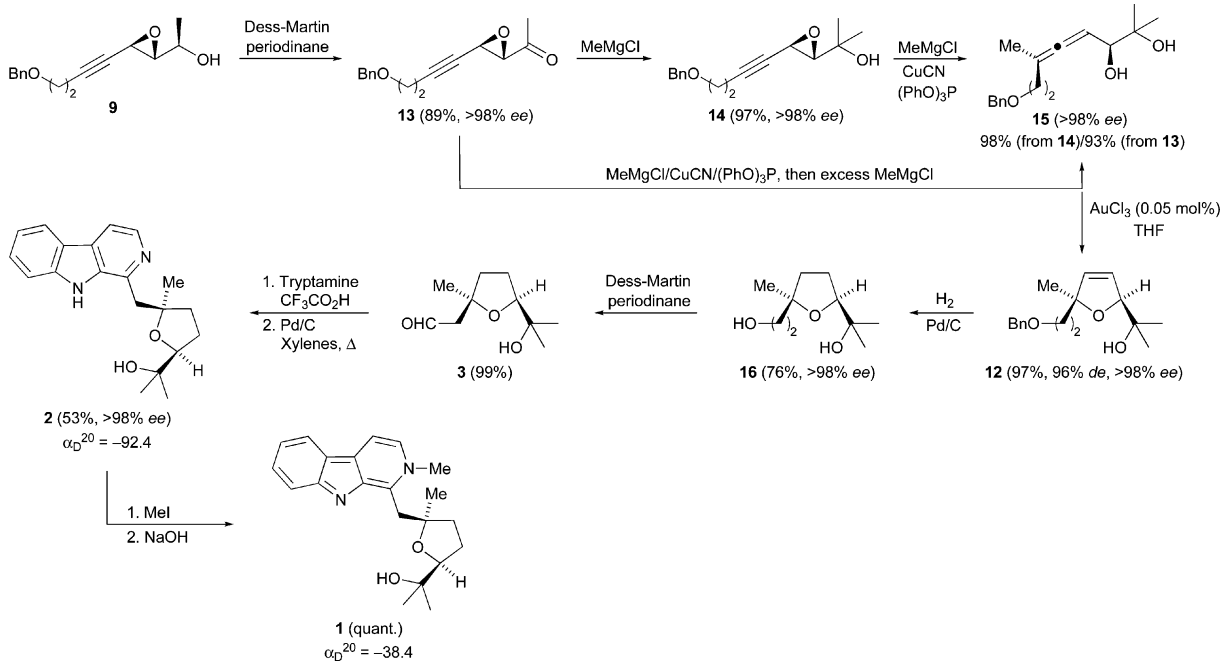
Scheme 3 Copper-mediated and gold-catalyzed synthesis of 2,5-dihydrofuran **11** and conversion into tertiary alcohol **12**.

with L-(+)-diethyl tartrate, both the epoxide *ent*-**9** (42% yield, not shown) and the unreacted starting material (*R*)-**8** (43% yield; configuration assigned according to the Katsuki–Sharpless mnemonic device[15]) were obtained with >98% ee. The enyne (*R*)-**8** was then converted into oxirane **9** by a matched Katsuki–Sharpless epoxidation using D-(−)-diethyl tartrate. With both enantiomers of the epoxyalcohol at hand, we decided to continue our synthesis with the (*R*,*R*,*R*)-isomer **9** first.

The key steps of the synthesis are the *anti*-selective copper-mediated S_N2'-substitution of propargyl oxirane **9**, using a methylmagnesium-cyanocuprate and triphenylphosphite as ligand to copper,[16] and the gold-catalyzed cycloisomerization of the dihydroxyallene **10** thus formed. This center-to-axis-to-center chirality transfer proceeds with excellent stereoselectivity (dr = 98 : 2 for **11**) and good yield. As expected from previous results,[4,5] only the hydroxy group in α-position participates in the cyclization. With a catalyst loading of only 0.05 mol% $AuCl_3$ in THF,[17] the cycloisomerization of **10** (over 1900 turnovers on a 2 g-scale!) belongs to the most efficient transformations reported so far in homogeneous gold catalysis.

In contrast to these unproblematic steps, the conversion of the secondary alcohol **11** into the tertiary alcohol **12** turned out to be tricky. The oxidation of **11** to the corresponding ketone could be achieved with IBX (2-iodoxybenzoic acid) in DMSO (79% yield) or with Dess–Martin periodinane[18] in CH_2Cl_2 (91% yield). Unfortunately, this ketone undergoes a very facile epimerization (probably *via* the corresponding enol), so that the subsequent Grignard addition afforded alcohol **12** as a 60 : 40 mixture of diastereomers. The ease of this epimerization was surprising to us because the corresponding ketone with a benzyloxymethyl instead of the benzyloxyethyl side chain is configurationally stable under the same conditions.[19]

In order to circumvent this pitfall, we decided to change the order of events (Scheme 4). Treatment of epoxyalcohol **9** with Dess–Martin periodinane[18] (or with IBX; 88% yield) gave the ketone **13** which turned out to be configurationally stable. Subsequent Grignard addition and S_N2'-substitution of the tertiary alcohol **14** to allene **15** proceeded with excellent yield and without any loss of stereochemical information (>98% ee). Alternatively, the conversion of **13** into **15** can be carried out in a tandem S_N2'-substitution–1,2-addition by treating the substrate first with the methylmagnesium cuprate and then with excess



Scheme 4 Synthesis of (−)-isocyclocapitelline (**2**) and (−)-isochrysotricine (**1**) *via* 2,5-dihydrofuran **12**.

Grignard reagent in a one-pot procedure. Also this sequence afforded allenic diol **15** with 93% yield and excellent stereocontrol (>98% ee). The subsequent axis-to-center chirality transfer by gold-catalyzed cycloisomerization (0.05 mol% $AuCl_3$ in THF) proceeded as for allene **10** to give the key intermediate with excellent yield (97%) and high stereochemical purity (96% de, >98% ee).

The next steps to the target molecules, hydrogenation–debenzylation of **12** using palladium on charcoal as the catalyst, as well as oxidation of **16** with Dess–Martin periodinane,[18] gave the aldehyde **3** with good yield. We then carried out a Pictet–Spengler cyclization[20] of **3** with tryptamine as has been reported for the synthesis of chrysotricine;[11] (−)-isocyclocapitelline (**2**) was obtained with 53% yield over 2 steps and >98% de/ee after aromatization of the crude tetrahydro-β-carboline with palladium on charcoal in refluxing xylenes. Comparison of the optical rotation of our product ($a_D^{20} = -92.4$, $CHCl_3$, $c = 0.525$) with that of the natural product ($a_D^{20} = -75$, $CHCl_3$, $c = 0.50$) suggests that the latter was not isolated as an enantiomerically pure compound. More importantly, it confirms the absolute configuration of (−)-isocyclocapitelline (**2**) to be (2*S*,5*R*). Finally, methylation of the β-carboline with MeI in refluxing acetone and deprotonation with aqueous NaOH[11] afforded (2*S*,5*R*)-(−)-isochrysotricine (**1**) with an optical rotation of $a_D^{20} = -38.4$ (MeOH, $c = 1.020$; no literature value reported). The spectroscopic data of synthetic **1** and **2** are in excellent agreement with those described in the literature.[9]

In summary we have developed the first enantioselective total syntheses of the β-carboline alkaloids (−)-isochrysotricine (**1**) and (−)-isocyclocapitelline (**2**) which also confirm the hitherto unknown absolute configuration of these natural products. Due to the regiodivergent nature of our approach, both enantiomers are accessible *via* the same route, consisting of a crucial center-to-axis-to-center chirality transfer by copper-mediated S_N2'-substitution of propargyl oxiranes **13**/**14** and gold-catalyzed cycloisomerization of α-hydroxyallene **15**. Our synthesis clearly demonstrates that homogeneous gold catalysis is a perfect tool for the stereoselective construction of complex natural products, and we are currently pursuing the application of our methods to further interesting target molecules.

Acknowledgements

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