Organic LETTERS

Letter

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Total Synthesis of (−)-Melanthioidine by Copper-Mediated Cyclodimerization

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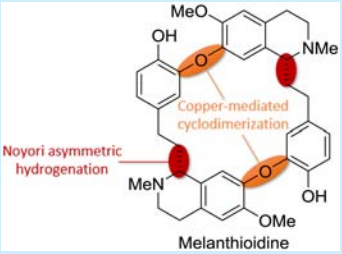
Supporting Information

ABSTRACT: An efficient asymmetric total synthesis of the dimeric macrocyclic diaryl ether phenethyltetrahydroisoquinoline alkaloid (−)-melanthiodine is reported. Key steps of the synthesis include an efficient Noyori asymmetric transfer hydrogenation to access the enantioenriched phenethyltetrahydroisoquinoline monomeric subunit and a copper-mediated cyclodimerization to form the two diaryl ether linkages with concomitant macrocyclization.



Dimeric macrocyclic diaryl ether tetrahydroisoquinoline alkaloids, whose general structure can be depicted such as **1** (head-to-tail dimers) or **2** (head-to-head dimers) (Figure 1), represent a large family of natural products that have been isolated from the leaves, roots, barks, and corms of a variety of plants throughout the world. From a structural point of view, they can be classified according to the nature of the monomeric tetrahydroisoquinoline subunit, which is in most cases a benzyl (**1** and **2**, $n = 1$) and, more rarely, a phenethyl (**1**, $n = 2$) derivative, and to the symmetry of the macrocycle which can be composed of two identical tetrahydroisoquinolines or not.[1,2] In addition to their interesting structures, they have been shown to possess a range of biological activities including antitumor,[3] anti-inflammatory,[4] antihypertensive,[5] antiplasmodial,[6] antimalarial,[7] and antileishmanial[2a,8] properties, just to mention a few, and were also shown to be potent molecules for the treatment of major diseases such as HIV[9] and Ebola.[10]

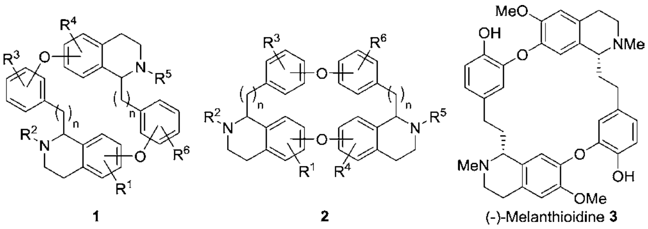
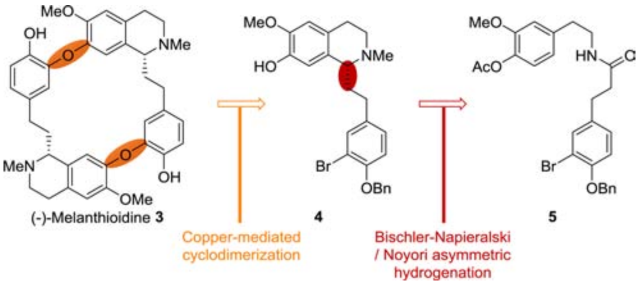


Figure 1. General structure of dimeric macrocyclic diaryl ether tetrahydroisoquinoline alkaloids **1** (head-to-tail) and **2** (head-to-head) and structure of melanthioidine **3**.

Scheme 1. Retrosynthetic Analysis of (−)-Melanthioidine



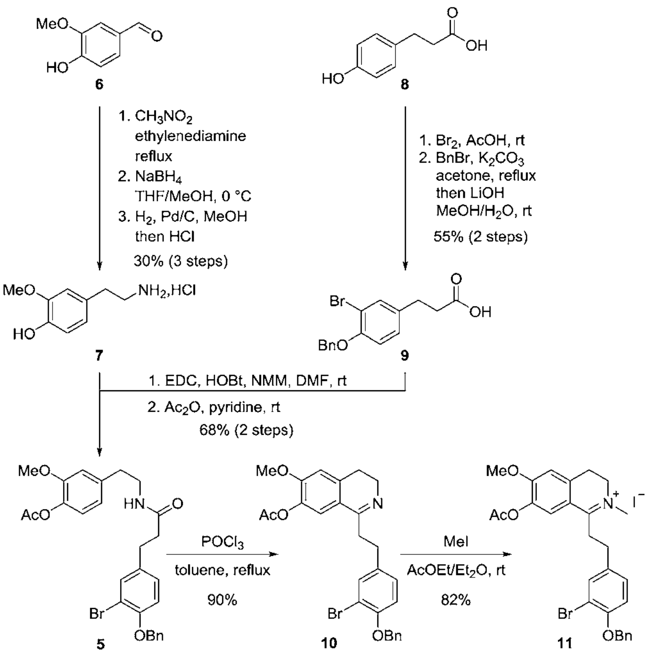
The interesting topology of these natural products coupled with their biological activities prompted immediate interest from the synthetic community, especially in the symmetrical dimeric series. However, most syntheses reported to date did not profit from the symmetrical nature of the target, which resulted in lengthy routes as well as reduced overall efficiencies.[11] Whenever this was taken into consideration, mostly by using a double Ullmann condensation reaction, the synthesis was hampered by the preparation of the enantio-enriched tetrahydroisoquinoline monomer which was usually based on a resolution step.[12]

Based on our long-standing interest in the use of copper-mediated cyclization reactions in natural product synthesis,[13,14] we became interested in this family of natural products and chose (−)-melanthioidine **3** (Figure 1) as a target. The bisphenethyltetrahydroisoquinoline alkaloid was isolated in 1962 by the Šantavý group[15] from the leaves and corms of *Androcymbium melanthioides*, a perennial flowering plant which grows in Southern and Eastern Africa that is extensively used in folk medicine for the treatment of many diseases. Its structure was elucidated in 1967 by the Šantavý and Battersby[12a] groups. To date, two syntheses of this natural product were reported, both based on a copper-catalyzed dimerization of a suitably functionalized phenethyltetrahydroisoquinoline possessing both a phenol and an aromatic bromide, the macrocyclization performing with little (4%)[12b] or moderate (30%)[12a] efficiency. While demonstrating the feasibility of this strategy, the efficiency of these

Received: May 24, 2016
Published: July 19, 2016

DOI: 10.1021/acs.orglett.6b01496
Org. Lett. 2016, 18, 3542−3545

Scheme 2. Synthesis of the Starting Dihydroisoquinoline/Dihydroisoquinolinium



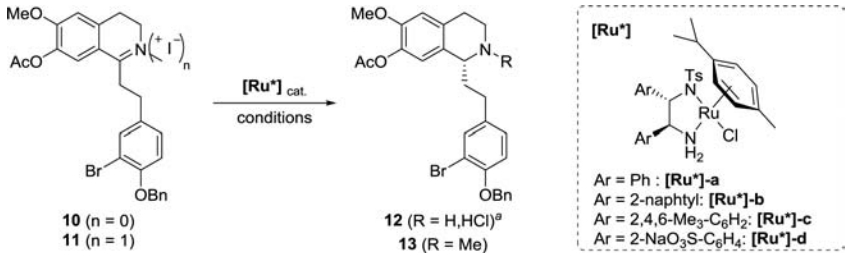
syntheses was however limited by either the resolution of the phenethyltetrahydroisoquinoline[12a] or the tedious separation of the diastereoisomeric macrocycles when such a step was not performed.[12b]

We therefore wondered if an efficient asymmetric total synthesis of (−)-melanthioidine could be designed based on a copper-mediated cyclodimerization[16] starting from enantio-enriched phenethyltetrahydroisoquinoline **4** possessing an aromatic bromide and a free phenol required for such a step in which both the macrocycle and the two diaryl ethers[17] of the target molecule would be formed in a single operation (Scheme 1). As for the tetrahydroisoquinoline **4**, it could be obtained in a straightforward and stereocontrolled manner using a Bieschler–Napieralski/Noyori asymmetric hydrogenation[18] sequence starting from suitably functionalized amide **5**.

Our synthesis started with the preparation of amide **5** in order to test the Bieschler–Napieralski/Noyori asymmetric hydrogenation sequence. This amide was readily prepared by an EDC/HOBt-mediated coupling of homobenzylic amine **7** and acid **9**, these substrates being prepared from vanillin[19] and 3-(4-hydroxyphenyl)propionic acid,[12b] respectively, using basic modifications of previously reported procedures (Scheme 2). Upon treatment with phosphorus oxychloride in refluxing toluene, a smooth Bieschler–Napieralski cyclization occurred, affording the desired sensitive dihydroisoquinoline **10** which, after further reaction with iodomethane, was converted to the corresponding dihydroisoquinolinium iodide **11**, both compounds being potential substrates for the asymmetric transfer hydrogenation reaction.[20]

Having in hand an efficient synthesis of dihydroisoquinoline derivatives **10** and **11**, this indeed set the stage for the study of their asymmetric transfer hydrogenation (Table 1). We initially focused our efforts on the reduction of cyclic iminium ion **11**: its reduction under standard conditions using 3 mol % of catalyst [**Ru***]-**a** and a mixture of formic acid and triethylamine as the reducing agent being totally inefficient (Table 1, entry 1), we then switched to the use of sodium formate as the reductant in water in combination with cetyltrimethylammonium bromide (CTAB) as the surfactant at room temperature.[20a] While we were pleased to note that the desired phenethyltetrahydroisoquinoline

Table 1. Optimization of the Asymmetric Transfer Hydrogenation Reaction of Dihydroisoquinoline 10/Dihydroisoquinolinium Ion 11

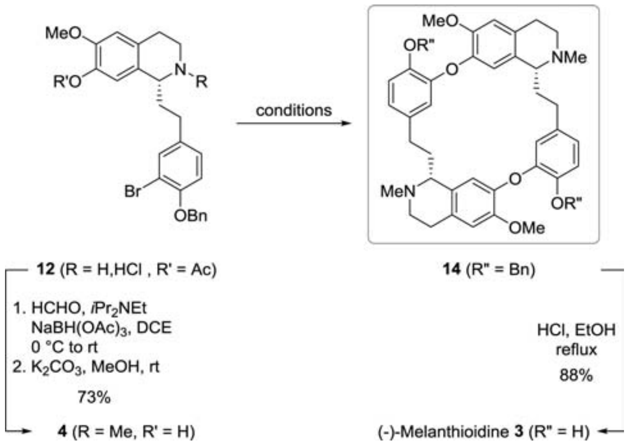


entry	substrate	[Ru*]$_{cat.}$	conditions	product	yield (%)	ee (%)
1	**11**	[**Ru***]-**a** (3 mol %)	HCO_2H/Et_3N (5:2), CH_3CN, rt, 24 h	**13**	–	–
2	**11**	[**Ru***]-**a** (3 mol %)	HCO_2Na, CTAB, H_2O, rt, 24 h	**13**	54	40
3	**11**	[**Ru***]-**a** (3 mol %)	HCO_2Na, CTAB, $AgSbF_6$ (4 mol %), H_2O, rt, 24 h	**13**	54	45
4	**11**	[**Ru***]-**a** (3 mol %)	HCO_2Na, CTAB, H_2O, 0 °C, 24 h	**13**	50	70
5	**11**	[**Ru***]-**a** (15 mol %)	HCO_2Na, CTAB, H_2O, 0 °C, 7 h	**13**	61	63
6	**11**	[**Ru***]-**b** (15 mol %)	HCO_2Na, CTAB, H_2O, 0 °C, 7 h	**13**	40	87
7	**11**	[**Ru***]-**c** (15 mol %)	HCO_2Na, CTAB, H_2O, 0 °C, 7 h	**13**	51	71
8	**11**	[**Ru***]-**d** (15 mol %)[b20b]	HCO_2Na, CTAB, H_2O, 0 °C, 30 h	**13**	10	0
9	**11**	[**Ru***]-**a** (15 mol %)	HCO_2Na, CTAB, H_2O, 40 °C, 7 h	**13**	78	0
10	**11**	[**Ru***]-**b** (15 mol %)	HCO_2Na, CTAB, H_2O, 40 °C, 7 h	**13**	84	0
11	**11**	[**Ru***]-**c** (15 mol %)	HCO_2Na, CTAB, H_2O, 40 °C, 7 h	**13**	97	0
12	**10**	[**Ru***]-**a** (15 mol %)	HCO_2H/Et_3N (5:2), CH_3CN, rt, 24 h	**12**	–	–
13	**10**	[**Ru***]-**a** (15 mol %)	HCO_2H/Et_3N (5:2), CH_2Cl_2, rt, 24 h	**12**	–	–
14	**10**	[**Ru***]-**a** (15 mol %)	HCO_2H/Et_3N (5:2), DMF, rt, 24 h	**12**	95	91

[a] Isolated as its hydrochloride after treatment with anhydrous HCl in diethyl ether. [b] In situ generated from $[RuCl_2(p\text{-cymeme})]_2$ and the corresponding chiral ligand.

DOI: 10.1021/acs.orglett.6b01496
Org. Lett. 2016, 18, 3542–3545

Table 2. Optimization of the Copper-Mediated Cyclodimerization and Completion of the Synthesis



entry	conditions	yield **14** (%)
1	$Cu(OTf)_2·C_6H_6$ (0.1 equiv), Cs_2CO_3 (1.1 equiv), pyridine (0.16 M), 110 °C, 24 h[22]	8
2	CuBr (0.1 equiv), picolinic acid (0.2 equiv), Cs_2CO_3 (2.0 equiv), DMSO (0.16 M), 90 °C, 24 h[23]	–
3	CuI (0.1 equiv), *N*-benzyl-*N*′-(5-methyl-[1,1′-biphenyl]-2-yl) oxalamide (0.2 equiv), K_3PO_4 (1.5 equiv), DMSO (0.16 M), 120 °C, 48 h[24]	–
4	CuCl (0.2 equiv), TMHD (0.4 equiv), Cs_2CO_3 (1 equiv), pyridine (0.16 M), 150 °C, 24 h[25]	–
5	CuCl (1 equiv), TMHD (2 equiv), Cs_2CO_3 (3 equiv), pyridine (0.16 M), 120 °C, 24 h	10
6	CuCl (1 equiv), TMHD (2 equiv), Cs_2CO_3 (3 equiv), pyridine (0.02 M), 120 °C, 24 h	–
7	Cu (3 equiv), K_2CO_3 (1.1 equiv), pyridine (0.16 M), 150 °C, 24 h[12a]	15
8	CuO (3 equiv), K_2CO_3 (1.1 equiv), pyridine (0.16 M), 120 °C, 24 h[26]	20
9	$CuBr·SMe_2$ (3 equiv), Cs_2CO_3 (9 equiv), pyridine (0.16 M), 150 °C, 10 h	30
10	$CuBr·SMe_2$ (1 equiv), Cs_2CO_3 (3 equiv), pyridine (0.16 M), 150 °C, 48 h	35

13 was formed in 54% yield, the enantioselectivity was found to be rather poor and the addition of silver hexafluoroantimony only gave a minor improvement of enantioselectivity. Cooling the reaction to 0 °C resulted in a significant improvement of the *ee* (70%) which was however still too low to be of any synthetic usefulness. At this stage, the yield could be improved to 61% by increasing the amount of the catalyst, and a brief screening of different ruthenium catalysts (Table 1, entries 5−8) revealed that both the yield and enantioselectivity could not be simultaneously improved. In addition, performing the reaction at 40 °C enabled a clean reaction with excellent conversion but was detrimental for the enantioselectivity, the phenethyltetrahydroisoquinoline **13** formed at this temperature being racemic, regardless of the nature of the ruthenium catalyst used (Table 1, entries 9−11). With the little success met for the asymmetric reduction of iminium **11**, we switched the substrate to dihydroisoquinoline **10**, which turned out to have an unexpected and unpredictable dramatically different behavior. In this case, the outcome of the asymmetric transfer hydrogenation was found to strongly depend on the nature of the solvent (Table 1, entries 12−14). To our delight, performing the reaction in DMF at rt afforded the anticipated phenethyltetrahydroisoquinoline **12** which could be isolated as its hydrochloride salt in 95% yield and 91% *ee*.[21]

Further methylation by reductive amination of **12** and subsequent cleavage of the acetate provided the properly substituted phenethyltetrahydroisoquinoline **4** possessing both the aromatic bromide and the phenol required for the cyclodimerization step (Table 2).

With an efficient enantioselective synthesis of monomeric precursor **4** in hand, we next moved to the crucial copper-mediated cyclodimerization step. Among all systems available for the formation of diaryl ethers mediated by copper complexes,[27] we first focused our efforts on catalytic systems (Table 2, entries 1−4). While we could detect minor amounts (8%) of the desired macrocyclic dimer **14** using the combination of $Cu(OTf)_2·C_6H_6$ and cesium carbonate in pyridine used in Cuny's total synthesis of verbanachalcone,[22] all other catalytic systems tested based on the use of a copper(I) halide in combination with picolinic acid,[23] *N*-benzyl-*N*′-(5-methyl-[1,1′-biphenyl]-2-yl)oxalamide,[24] or 2,2,6,6-tetramethylheptane-3,5-dione (TMHD)[25] failed to promote the cyclodimerization or only afforded a byproduct resulting from the reduction of the starting aromatic bromide. Switching to stoichiometric amounts of the copper complex turned out to be much more efficient, the concentration of the reaction mixture being crucial for the reaction to occur. Indeed, while the use of 1 equiv of copper(I) chloride in combination with 2 equiv of TMHD in pyridine at 0.16 M afforded the target macrocycle, although in a low yield (10%, Table 2, entry 5), diluting the reaction mixture to 0.02 M to avoid problems associated with oligomerization completely inhibited the reaction (Table 2, entry 6).

A brief screening of other copper complexes revealed that the system used in the Šantavý and Battersby synthesis[12a] was far from optimal and only gave 15% of *O*,*O*-dibenzylmelanthioidine **14** (Table 2, entry 7), which is in sharp contrast with the yield initially reported by the authors. A slightly superior result was obtained when switching to copper(II) oxide in pyridine, a system used for the synthesis of a variety of naturally occurring diaryl ethers[26] which gave **14** in 20% yield (Table 2, entry 8). A significant increase in the yield (30%) could be obtained by combining a more soluble copper salt, $CuBr·SMe_2$, and the more reactive cesium phenoxide generated from cesium carbonate in pyridine, acting as both a ligand for copper salts and the solvent (Table 2, entry 9). Finally, the desired macrocycle **14** could be obtained in 35% yield by decreasing the amount of both the copper complex and the base while increasing the reaction time (Table 2, entry 10). This yield compares rather well with the ones typically obtained for cyclodimerization reactions[16] and is actually more than acceptable when considering that a 20-membered ring macrocycle and two sterically hindered diaryl ethers are formed in a single operation and given the difficulties associated with the formation of macrocyclic ethers in general.

Simple deprotection of the two benzyl ethers in **14** by treatment with hydrochloric acid in refluxing methanol followed by purification on silica gel finally afforded the desired synthetic melanthioidine **3** (23 mg). The IR, NMR data and melting point for the synthetic compound were identical to the ones reported in the literature,[12] and a negative optical rotation was recorded. No O.R.D. was measured in the present study.

In conclusion, we have developed the first enantioselective total synthesis of the dimeric macrocyclic diaryl ether phenethyltetrahydroisoquinoline alkaloid (−)-melanthiodine. Key steps of the synthesis include an efficient Noyori asymmetric hydrogenation to access the enantioenriched phenethyltetrahydroisoquinoline monomeric subunit and a highly challenging copper-mediated cyclodimerization. Both the two diaryl ether

DOI: 10.1021/acs.orglett.6b01496
Org. Lett. 2016, 18, 3542−3545

linkages and the macrocycle are installed in a single operation using this strategy which highlights the efficiency of copper-mediated transformations in the synthesis of natural products and the impact of copper catalysis in the synthesis of complex molecules and macrocyclic ethers. Further applications of copper-mediated cyclodimerization reactions are under study and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01496.

Detailed experimental procedures and full characterization for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Our work was supported by the Université libre de Bruxelles (ULB). J.W. acknowledges the Chinese Scholarship Council for a graduate fellowship.

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