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Biomimetic Enantioselective Total Synthesis of (−)-Mycoleptodiscin A

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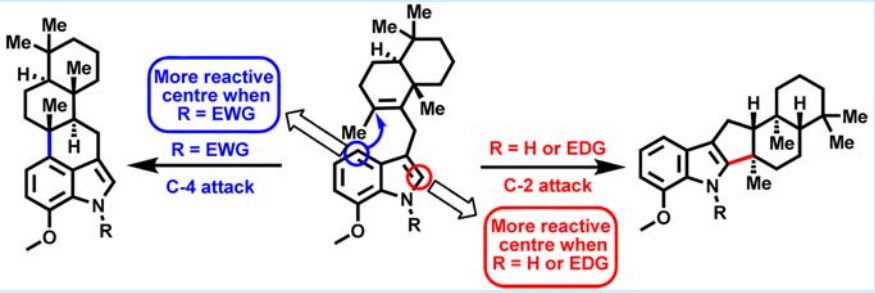
Supporting Information



ABSTRACT: Biomimetic total synthesis of (−)-mycoleptodiscin A (**1**) was achieved starting from the enantiopure key intermediate, which was prepared by Friedel−Crafts reaction between 7-methoxyindole and chiral primary allylic alcohol. The crucial step in this synthesis was an intramolecular Friedel−Crafts reaction at C-4 of the indole derivative driven by the EDG/EWG within a compound that was rationally designed to prevent the cyclization reaction at the C-2 positon of indole, thereby successfully providing the complete carbon framework of **1**. This intramolecular Friedel−Crafts reaction at C-4 of indole derivative could be applied for the synthesis of other C-4-substituted indole alkaloid natural products.

Tropical endophytic fungi have been demonstrated to be rich and reliable sources of structurally novel compounds with a wide range of biological activities.[1] Some of these are promising leads to clinical drugs.[2] Mycoleptodiscins A (**1**) and B (**2**) (Figure 1) are a pair of natural products isolated from the

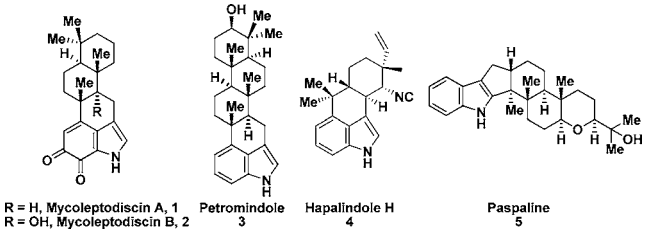
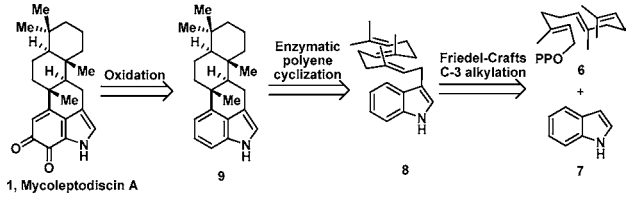


Figure 1. Mycoleptodiscins A and B and related C-4 alkylated and C-2 alkylated indole terpenoids.

endophytic fungus *Mycoleptodiscus* sp. by Cubilla-Rios et al. in 2013.[3] Mycoleptodiscins bear resemblance to indoloterpenes such as petromindole (**3**) and hapalindoles (**4**), which contain sesquiterpenoid framework connected to the C-3 and C-4 positions of the indole moiety.[4,5] Other types of indoloterpenoids are paspaline (**5**) and related natural products where the terpenoid framework is connected to the C-2 and C-3 positions of indole.[6] Mycoleptodiscin B (**2**) is an inhibitor of cell growth of four cancer cell lines H460, A2058, H522-T1, and PC-3, with IC50 values ranging from 0.60 to 0.78 μM, while the biological activity of mycoleptodiscin A (**1**) is unknown, possibly due to its natural source scarcity.

The biosynthesis of indoloterpenes is believed to proceed by condensation of farnesyl pyrophosphate (**6**) with an indole (**7**) to give 3-farnesylindole (**8**), followed by enzymatic polyene cyclization initiated by attack from C-4 of farnesylindole (**8**) to generate the pentacyclic carbon framework **9**. Finally, oxidation of indole moiety to *o*-indoloquinone affords mycoleptodiscin A (**1**) (Scheme 1). The presence of an interesting carbon

Scheme 1. Possible Biosynthetic Pathway for Mycoleptodiscin A



framework composed of four contiguous stereocenters and an *o*-indoloquinone moiety coupled with its low natural abundance has made mycoleptodiscin an important synthetic target. In 2015, Li and co-workers reported an elegant first total synthesis of **1** via 26 steps (longest linear sequence) using asymmetric Carreira polyene cyclization as a key step.[7] Recently, Chandrasekhar and co-workers reported protecting group free synthesis of **1** from sclareolide.[8] Our attention was drawn to

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these molecules because of their intriguing structures, which are fascinating from both topological and biosynthetic perspectives. As described previously, biosynthetically a Friedel–Crafts reaction may be responsible for the indole C-4 alkylation. However, the selective functionalization of the less nucleophilic C-4 position of 3-substituted indole is extremely difficult since most electrophiles prefer to attack the C-2 position. Unlike indole, there are some previous reports where direct C-4 cyclization on indoline derivatives have been reported.[9] There is one report in the literature where intramolecular direct C-4 cyclization on indole was carried out in Michael fashion using molten NaCl–$AlCl_3$.[10] This method was further applied to the total synthesis of bruceolline and hapalindoles by Badenock et al.[11a] and Johnston et al.,[11b] respectively. Although functionalization at the C-4 position of indole has been studied for a long time, no successful method except the Witkop photocyclization has been reported.[12] Reductive Heck reaction using 4-bromoindole is another alternative for the synthesis of 4-substituted indole.[13] Both of these strategies are nontrivial in case of mycoleptodiscin A (**1**). Our synthetic strategy was guided by speculations concerning biosynthesis of these natural products, i. e. selective inter and intramolecular Friedel–Crafts alkylation of indole derivative at C-3 and C-4 positions, respectively. It was envisioned that intermolecular Friedel–Crafts alkylation at C-3 position of indole could be achieved without much difficulty but as discussed earlier, the major challenge is activation of C-4 of indole in the presence of C-2. For this, we resorted to electrophilic aromatic substitution reaction and effect of EWG/EDG on indole. It was contemplated that EWG group such as $-SO_2Ph$ on nitrogen of 7-methoxyindole (**10**) would deactivate both C-2 and C-3 positions of indole and in turn C-4 would become most nucleophilic position due to the resonance effect of methoxy group at C-7 of indole, hence generating the 4-alkylation product under Friedel–Crafts reaction conditions. To explore whether this proposed biosynthetic pathway could be achieved in absence of enzymatic catalysis, model studies were conducted. Lewis acid catalyzed Friedel–Crafts reaction of 7-methoxyindole (**10**) and cyclogeraniol (**11**) was attempted. After screening various Lewis and Bronsted acids, mixture of 7-methoxyindole (**10**) and cyclogeraniol (**11**) on treatment with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature for 1 h afforded coupling product **12** with 81% yield in highly regioselective manner. Next, to effect the intramolecular Friedel–Crafts reaction by activation of C-4 position of indole, nitrogen of indole derivative **12** was converted to corresponding sulfonamide **13** by treatment with benzenesulfonyl chloride under basic conditions (Scheme 2). Various Lewis acids were screened for intramolecular Friedel–Crafts reaction to form C–C bond between C-4 of indole moiety with olefin in cyclohexene ring. The compound **13** was treated with 3 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 as solvent at room temperature. To our disappointment, it did not provide the desired cyclization product, and the starting material was recovered (Table 1, entry 1). Similar results were obtained when 3 equiv of *p*TSA was used in CH_2Cl_2 or toluene at room temperature (Table 1, entry 2). Among the catalysts tested $Cu(OTf)_2$, $Bi(OTf)_3$, and $Fe(OTf)_3$ in CH_2Cl_2 failed to generate cyclization product, and the starting material was recovered in each case (Table 1, entries 3–5). Finally, compound **13**, on treatment with 1 equiv of $SnCl_4$ in CH_2Cl_2, afforded cyclization product (confirmed by ^1H NMR of the crude sample) which after desulfonylation by using Na–Hg in a MeOH/THF mixture afforded the C-4-cyclized indole **14** as a single diastereomer in 30% overall yield (Table 1, entry 6). Although the yield was moderate, this was the first time the desired tetracyclic ring system was observed, and thus, further optimization of the reaction was carried out. Treatment of the compound **13** with 1 equiv of $AlCl_3$ also resulted in the formation of C-4-cyclized product with 35% overall yield after desulfonylation (Table 1, entry 7). To our delight, treatment of compound **13** with 1.5 equiv of TMSOTf followed by desulfonylation afforded the desired compound **14** in 63% overall yield (Table 1, entry 11). To further check the scope and generality of the intramolecular Friedel–Crafts reaction, several diverse examples were carried out. First, various 3-substituted indole derivatives **15a–h** were prepared by known literature procedures (see the Supporting Information). As shown in Scheme 3, compounds **15a–d** having different substituents underwent smooth intramolecular Friedel–Crafts cyclization at C-4 to provide **16a–d** with moderate to good yields. Further, compounds **15e–h** also reacted efficiently to generate C-4 cyclization product **16e–h** in highly diastereoselective fashion. The trans diequatorial conformation of phenyl and methyl groups of the cyclization product **16g** was established by ^1H NOE experiments as a strong NOE interaction was observed between the H_a proton and C-11 proton. A more general substrate **17** also underwent smooth cyclization, which on subsequent desulfonylation afforded compound **18** in 68% overall yield.

Scheme 2. Synthesis of C-4 Cyclization Precursor

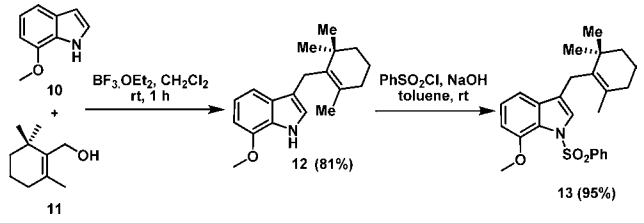
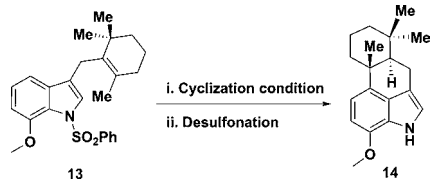


Table 1. Optimization Table for Lewis Acid Catalyzed Friedel–Crafts C-4 Cyclization Reaction of indole



entry	catalyst	equiv	solvent	yield (%)
1	$BF_3{\cdot}OEt_2$	3	CH_2Cl_2	NR[a]
2	*p*TSA	3	CH_2Cl_2[b]	NR[a]
3	$Cu(OTf)_2$	0.1	CH_2Cl_2	NR[a]
4	$Bi(OTf)_3$	0.1	CH_2Cl_2	NR[a]
5	$Fe(OTf)_3$	0.1	CH_2Cl_2	NR[a]
6	$SnCl_4$	1	CH_2Cl_2	30
7	$AlCl_3$	1	CH_2Cl_2	35
8	$SnCl_4$	2	toluene	NR[a]
9	$AlCl_3$	2	toluene	NR[a]
10	TMSOTf	1	CH_2Cl_2	45
11	TMSOTf	1.5	CH_2Cl_2	63

[a]NR = no reaction. [b]Toluene was also used for the same reaction.

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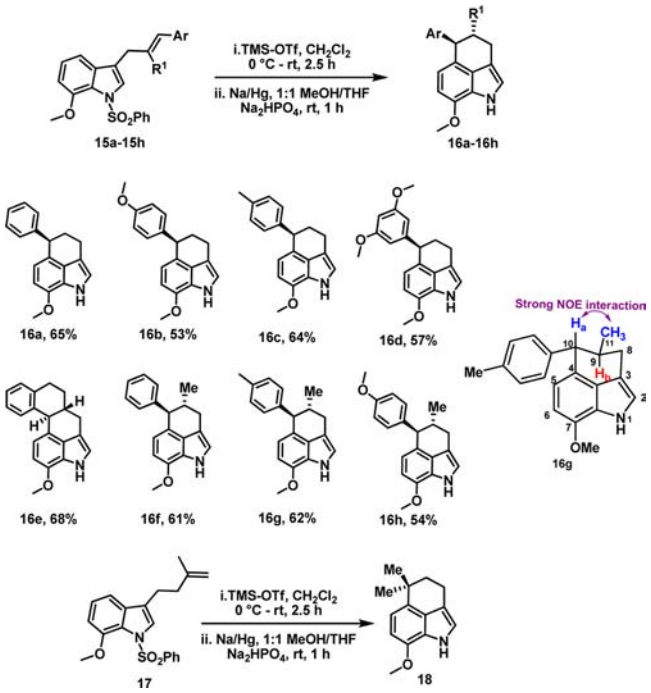
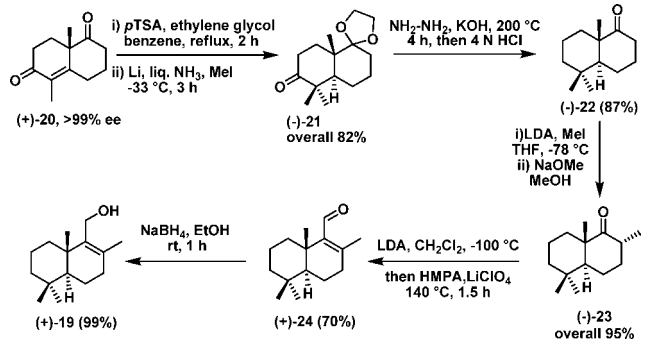
Scheme 3. Synthesis of Various C-4 Cyclization Products



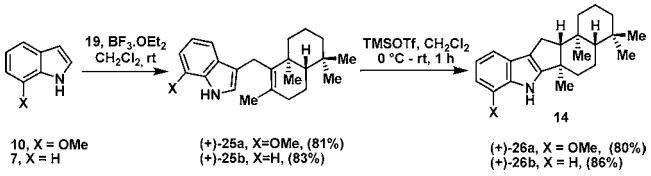
After successful achievement of the novel C-4 cyclization of indole, we directed our attention toward biomimetic total synthesis of **1**. To access **1**, 7-methoxyindole (**10**) and alcohol (+)-**19** were identified as appropriate precursors for the key inter- and intramolecular Friedel−Crafts reactions. The alcohol **19** was prepared in six steps from Wieland−Mischer ketone derivative **20** (Scheme 4).[14] Selective ketalization of **20** with

Scheme 4. Synthesis of Alcohol (+)-19



ethylene glycol and *p*-toluenesulfonic acid followed by reductive methylation with methyl iodide in lithium−liquid ammonia afforded *trans*-decalone **21** in 82% overall yield.[15] Wolff−Kishner reduction of ketone **21** followed by hydrolysis of the ketal using aqueous HCl afforded ketone **22** in 87% yield. Methylation of **22** using LDA/MeI and subsequent epimerization with NaOMe at the newly generated stereocenter resulted in the formation of **23** as a single diastereomer in 95% yield. The ketone **23** was converted to α,β-unsaturated aldehyde **24** by using dichloromethyllithium, generated in situ from dichloromethane and LDA at −100 °C followed by treatment with HMPA, lithium perchlorate, and $CaCO_3$ at 140 °C.[16] The aldehyde **24** was reduced to the corresponding alcohol **19** with $NaBH_4$ in EtOH in 98% yield. After having both precursors in hand, total synthesis of **1** was initiated by treating 7-methoxyindole (**10**) and primary allylic alcohol **19** with $BF_3{\cdot}OEt_2$ in dichloromethane to furnish 3-alkylated indole **25a** in 81% yield. At this stage, to investigate the effect of an −OMe group at the C-7 position of indole on C-2 vs C-4 cyclization, compound **25a** was treated with TMSOTf, and as expected, it smoothly underwent cyclization at C-2 to furnish **26a**. Similarly, 3-alkylated indole **25b** (prepared by coupling indole **7** and alcohol **19** using $BF_3{\cdot}OEt_2$) on exposure to TMSOTf afforded C-2 cyclization product **26b** (Scheme 5).

Scheme 5. Lewis Acid Catalyzed C-2 Cyclization



Absolute stereochemistry of the compound **26b** was established by single-crystal X-ray analysis (Figure 2).[17] Thus, it is clear

Figure 2. ORTEP of compound **26b**.

that the presence of an electron-donating substituent at C-7 might increase the nucleophilicity at C-4, but C-2 remains the most nucleophilic position for an unprotected 3-substituted indole. The above-mentioned C-2 cyclization could be used for synthesis of paspaline (**5**) type indoloterpenes using the appropriately C-3-substituted indole derivatives. Having appropriately functionalized C-3-alkylated indole derivative **25a** in hand, the next objective became intramolecular Friedel−Crafts reaction at C-4 of indole **25a** and elaboration of the resulting product to give **1**. As mentioned previously, to facilitate C-4 cyclization over C-2, the indole nitrogen of **25a** was protected using $PhSO_2Cl$ under basic conditions to afford the key intermediate **27**. Compound **27** on exposure to TMSOTf for 2 h at room temperature afforded the desired cyclized product **28** in 75% yield with high regio- and diastereoselectivity. Compound **28** represents the complete carbon framework of **1**. Reductive desulfonylation of **28** using Na/Hg provided **29** in almost quantitative manner. Finally, demethylation of **29** using BBr_3 followed by immediate treatment with IBX in DMF to oxidize the resulting 7-hydroxyindole derivative **30** to *o*-indoloquinone afforded **1** in only 10% overall yield. Gratifyingly, use of Fremy's salt,[18] a radical oxidant instead of IBX to oxidize **30**, enhanced the yield to 75% for the targeted natural product mycoleptodiscin A (**1**) (Scheme 6). The spectral data (NMR, IR, HRMS, etc.) and physical properties of the synthetic sample were in complete agreement with those reported for the natural product.[3]

In summary, we have achieved the total synthesis of (−)-mycoleptodiscin A, which stands out with respect to brevity and overall efficiency as a biomimetic key step and for the convergent nature of our synthetic plan. Two Friedel−

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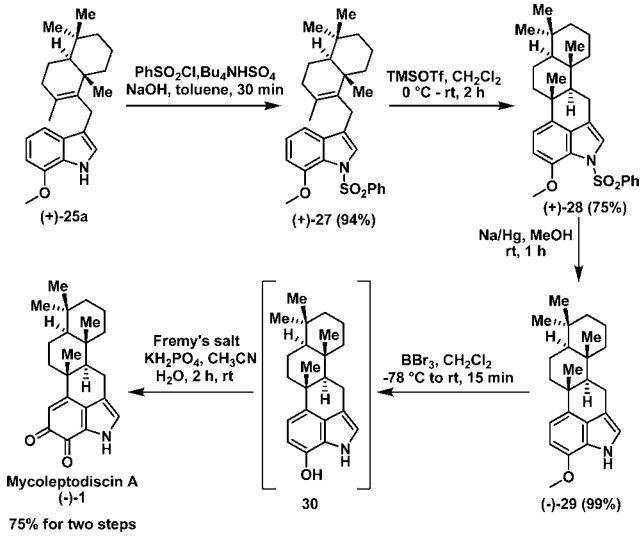
Scheme 6. Synthesis of (−)-Mycoleptodiscin A (1)



Crafts reactions were used for a highly regioselective intermolecular coupling of primary allylic alcohol with an indole derivative and an unprecedented intramolecular C-4 cyclization of indole derivative with olefin in a highly diastereoselective fashion to assemble the complete carbon framework of natural product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03292.

X-ray data for (+)-**26b** (CIF)
Experimental procedures and spectral data for all the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor K. C. Nicolaou on the occasion of his 70th birthday.

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