Organic LETTERS

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Expanding Diversity without Protecting Groups: (+)-Sclareolide to Indolosesquiterpene Alkaloid Mycoleptodiscin A and Analogues

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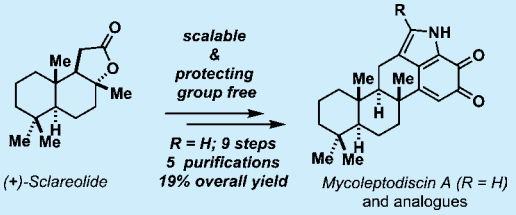
Supporting Information

ABSTRACT: Short and scalable synthesis of the complex pentacyclic indolosesquiterpene natural product mycoleptodiscin A has been achieved from commercially available diterpenoid (+)-sclareolide in 19% overall yield. This approach allows one to prepare various analogues of mycoleptodiscin using McMurry cyclization as a key reaction with just three chromatographic purifications.



Polycyclic sp^3-rich carbon-containing natural products are the preferred starting points in drug discovery due to the diversity, spatial arrangement, and natural tendency to bind to target receptors. Several FDA approved drugs in this class are a testimony to this.[1] Natural products with hybridized skeletons derived from terpenes, alkaloids, sugars, and amino acids have imparted better value to their druggability.[2] Indolosesquiterpenoids with built-in terpene and alkaloid characteristics have been generating attention from followers of natural product synthesis.[3] The International Cooperative Biodiversity Group (ICBG)−Panama consortium isolated two novel reddish orange alkaloids from the endophytic fungus *Mycoleptodiscus* sp. in 2013 and named them mycoleptodiscin A and B.[4] The structural features of these include tricyclic sesquiterpene ABC rings fused onto indole-6,7-dione DE rings, thus making a pentacyclic hybrid terpene indole. Interestingly, the BCDE ring skeleton of these natural products is closely related to structurally fascinating indole terpenoids such as hapalindoles, xiamycin A, and petromindoles (Figure 1).[5,6]

The limited availability of mycoleptodiscin A (≤1 mg) from a natural source was inadequate for the screening of bioassays. The submicromolar anticancer activities of mycoleptodiscin B and scarcity of mycoleptodiscin A along with our own interest in exploiting bioactive complex natural products prompted us to initiate the total synthesis of mycoleptodiscin A and its close analogues. The first total synthesis of mycoleptodiscin A was reported starting from farnesyl acetate by Li et al.,[7] involving elegant Carreira cationic cyclization[8] and copper-mediated intramolecular C−N bond formation as key steps with an overall yield of <1%.

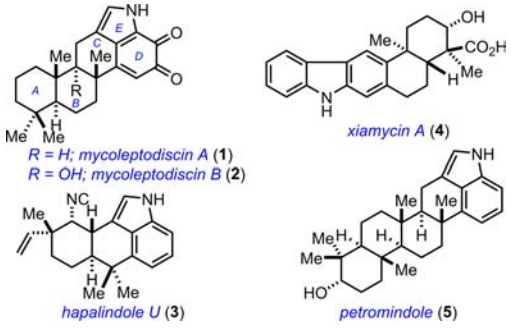


Figure 1. Mycoleptodiscins A and B and related natural products.

The protecting-group-free, scalable, and divergent synthesis toward natural and non-natural bioactives has been a challenge to the research groups engaged in total synthesis.[9] The multicomponent coupling reactions, domino processes, convergence of building blocks to complex skeletons, diversity-oriented synthesis, biology-oriented synthesis, diverted total synthesis, etc., are the outcomes of efforts toward this objective.[10] Including additional functionalities on abundantly available natural products to generate scarcely available complex natural products is yet another strategy.[11] A careful survey of commercially available natural products that have an embedded skeleton of mycoleptodiscins revealed (+)-sclareolide (**9**) to be the best starting point for enhancing the remaining rings to achieve the target synthesis with ease. Recently, the utility of this natural product was demonstrated in meroterpenoid synthesis by Baran's group and in the synthesis of (+)-chlorolissoclimide by Alexanian et al.[12]

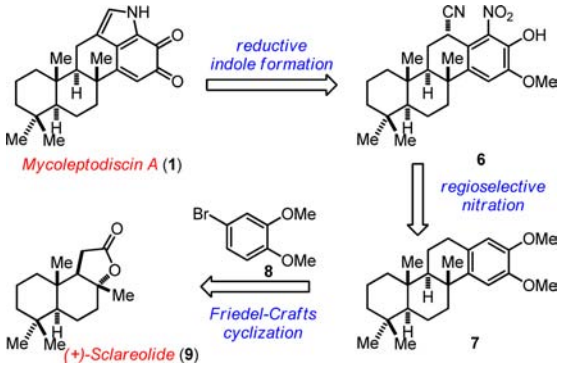
We relied on Friedel−Crafts cyclization, regioselective nitration, and reductive cyclization as key operations to build indole toward the synthesis of mycoleptodiscin A (**1**) from commercially available terpenoid **9** (Scheme 1). The *ortho*-benzoquinone **1** could be constructed through the reductive indole formation of nitrophenol **6** followed by in situ aerobic oxidation. Synthesis of **6** was planned from cationic cyanation and selective nitration on tetracycle **7**, which is accessible from the coupling of **9** with bromoveratrole **8**.

Lithiated 3,4-dimethoxybenzene (generated by adding *n*-BuLi to bromoveratrole **8**) was added onto (+)-sclareolide (**9**) to furnish aryl ketone **10** in 64% yield. The next objective was to

Received: April 20, 2016
Published: May 16, 2016

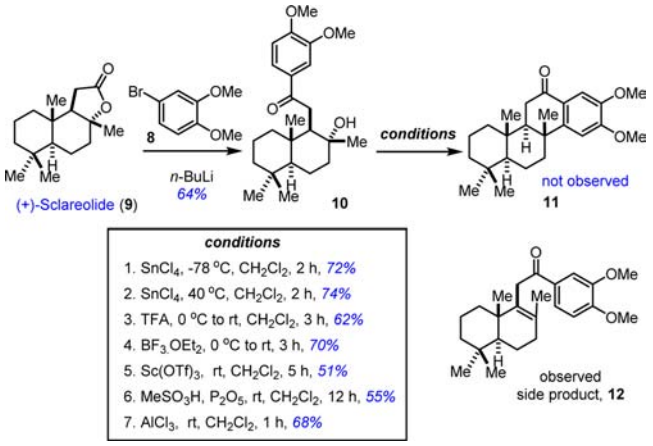
DOI: 10.1021/acs.orglett.6b01145
Org. Lett. 2016, 18, 2684−2687

Scheme 1. Retrosynthetic Analysis of Mycoleptodiscin A



engage Friedel−Crafts cyclization triggered by the tertiary alcohol group in **10** with the dimethoxy phenyl ring (Scheme 2). Attempts with various Lewis acids ($SnCl_4$, $BF_3{\cdot}OEt_2$, TFA,

Scheme 2. Initial Attempts of Friedel−Crafts Cyclization



$AlCl_3$, P_2O_5−$MeSO_3H$, $Sc(OTf)_3$) failed to achieve the target **11**, and dehydration of **10** was observed as the sole product **12**.

Due to the presence of negative electronic factors on the aryl ring bearing a carbonyl group, compound **10** was converted to deoxy derivative **13** using Pd−C/H_2 in PEG-400 in a single step with excellent yield (Scheme 3).[13] Highly electron-rich arene **13** underwent smooth intramolecular Friedel−Crafts cyclization with $SnCl_4$ at −78 °C by trapping carbocation intermediate **A** in 94% optimized yield (see Table 1 for optimization conditions) to furnish tetracyclic core **7** with a *trans*-fused ring junction.[14] Due to the axial orientation of the C-15 methyl group, the phenyl ring preferred a bottom face attack at the C-9 position. The benzylic site C-17 was functionalized via selective PCC oxidation to give benzylic ketone **11** in 89% yield.[15] The carbonyl-assisted selective nitration of the phenyl ring was achieved with a nitrating mixture (HNO_3/H_2SO_4)[16] followed by $NaBH_4$ reduction to give nitro alcohol **14** as a single isomer in excellent yield. Cyanation of benzylic alcohol in **14** was possible with TMSCN catalyzed by $In(OTf)_3$ to afford **15** in 82% yield along with trace amounts of eliminated product.[17] The relative stereochemistry of compounds **14** and **15** was characterized by single X-ray crystallography (Figure 2).[18] Other Lewis acids, such as $InBr_3$ and $InCl_3$, gave moderate yields. The selective demethylation of **15** with BBr_3 to nitrophenol **6** was achieved in 85% yield. Reductive construction of indole was achieved on **6** with Pd−C and ammonium formate,[19] which underwent

Scheme 3. Total Synthesis of Mycoleptodiscin A

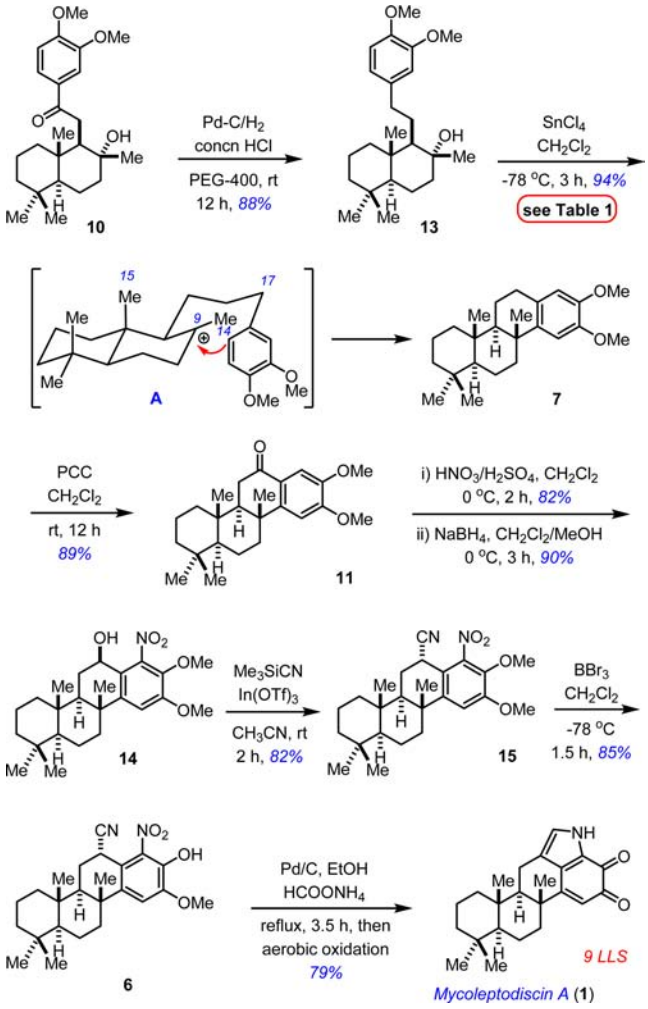
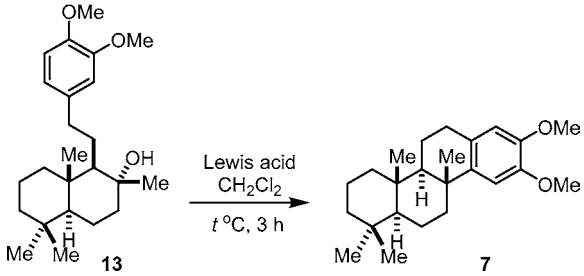


Table 1. Lewis Acid Screening for Friedel−Crafts Cyclization[a]



entry	Lewis acid (3 equiv)	t (°C)	yield (%)[b]
1	**$SnCl_4$**	**−78**	**94**
2	I_2	reflux	75
3	$BF_3{\cdot}OEt_2$	−78	80
4	TFA	−78	63
5	$MeSO_3H$	−78	61
6	$P_2O_5/MeSO_3H$	0	55
7	$AlCl_3$	0	70
8	$Sc(OTf)_3$	rt	78

[a]Reactions were carried out with **13** (0.2 mmol) and Lewis acid (0.6 mmol) in 0.1 M CH_2Cl_2. [b]Yields determined by ^1H NMR analysis with an internal standard of 1,1,2,2-tetrachloroethane.

DOI: 10.1021/acs.orglett.6b01145
Org. Lett. 2016, 18, 2684−2687

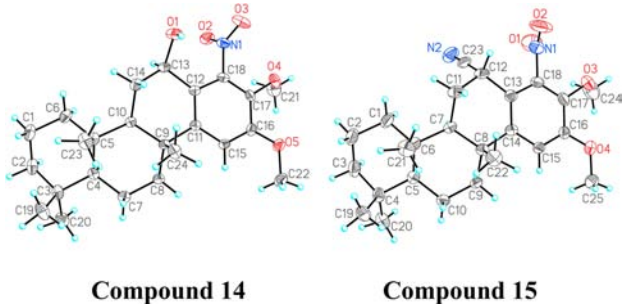
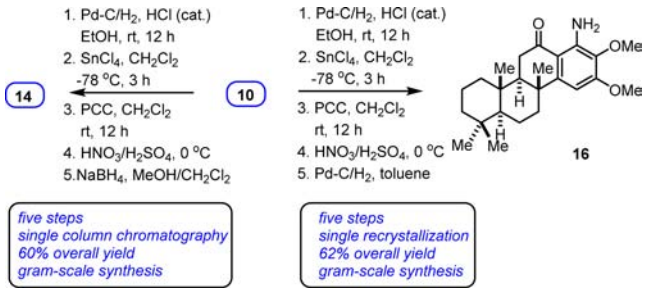


Figure 2. ORTEP diagrams of compounds **14** and **15**.

spontaneous aerobic oxidation to furnish mycoleptodiscin A (**1**) in 79% yield.

The strategy adapted was further optimized to five-step sequential transformations, such as hydrogenation, Friedel–Crafts cyclization, oxidation, nitration, and $NaBH_4$ or Pd–C reduction to generate advanced key intermediates **14** and **16** without purification (Scheme 4). To prove the fact that the

Scheme 4. Gram-Scale Syntheses of Key Intermediates 14 and 16

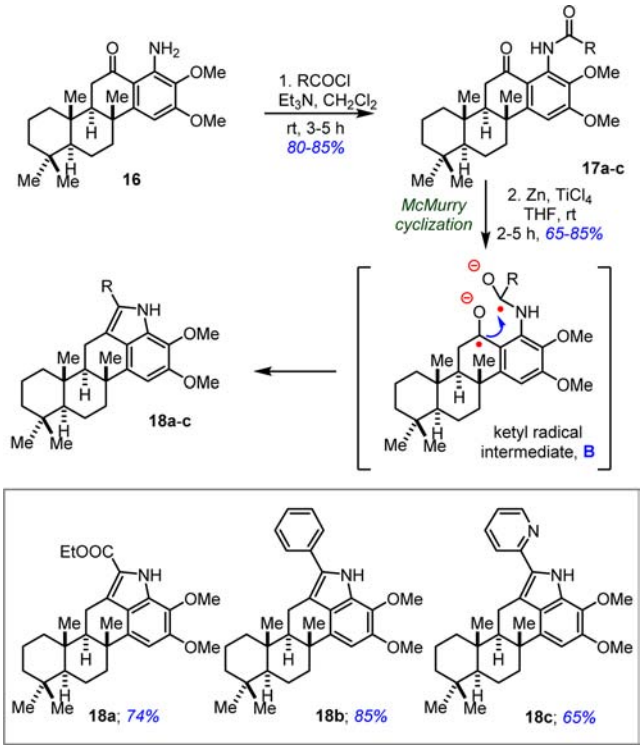


present strategy allows scalability for the synthesis of mycoleptodiscin A, compound **10** was transformed to **14** in five straight steps in an overall yield of 60%, which involved only single-column chromatography (Scheme 4). Similarly, aryl ketone **10** was also converted to another advanced key intermediate **16** in five steps with 62% overall yield, which involved only single crystallization without chromatography (Scheme 4).

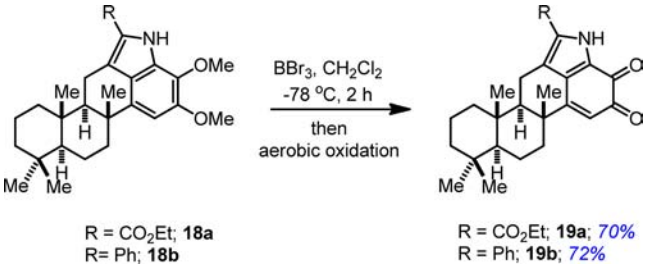
Intermediate **16** allowed us to synthesize analogues of natural product **1** with ease using McMurry cyclization as a key step. It is well-demonstrated that methoxyaniline **16** would undergo McMurry cyclization through oxo amide intermediates **17** (Scheme 5). Diversity of the indole ring was achieved rather easily. Acylation of aniline **16** with different acid chlorides provided **17a–c**, which on treatment with $Zn/TiCl_4$ under McMurry cyclization conditions provided 2-substituted indole analogues **18a–c** via ketyl radical intermediate B (Scheme 5).[20] This sesquiterpenoid framework is also present in other bioactive indole alkaloid natural products, such as hapalindoles and pertromindole (Figure 1). Unfortunately, *N*-formyl derivative **16** did not yield a corresponding indole in McMurry cyclization for the synthesis of **1**. Demethylation of methyl ethers **18a,b** and spontaneous aerobic oxidation provided the mycoleptodiscin analogues **19a,b** in good yields (Scheme 6).

In summary, the present strategy describes an enhancement of (+)-sclareolide, which allowed a very short synthesis of mycoleptodiscin A and its analogues. The protecting-group-free total synthesis in fewer than nine steps with five

Scheme 5. Synthesis of Mycoleptodiscin A Analogues



Scheme 6. Synthesis of Mycoleptodiscin A Analogues



chromatographic purifications is the noteworthy point of this strategy.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01145.

Experimental procedures, characterization details, and ^1H and ^{13}C NMR spectra of all new compounds (PDF)
X-ray data for **14** (CIF)
X-ray data for **15** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.6b01145
Org. Lett. 2016, 18, 2684–2687

■ ACKNOWLEDGMENTS

K.N. thanks the University Grants Commission (UGC), New Delhi, for a research fellowship. R.C. thanks CSIR-Senior Research Associateship (Scientists' Pool Scheme) for financial assistance. We thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for financial support as part of XII five-year programme project under ORIGIN (CSC-108). We gratefully acknowledge Prof. Ashwini Nangia and Sudhir Mittapalli, School of Chemistry, University of Hyderabad, for X-ray analysis.

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(18) CCDC-1454907 (**14**) and CCDC-1454906 (**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.

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DOI: 10.1021/acs.orglett.6b01145
Org. Lett. 2016, 18, 2684−2687