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Total Synthesis of Integrastatin B Enabled by a Benzofuran Oxidative Dearomatization Cascade

Atul A. More and Chepuri V. Ramana*

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India

Supporting Information

ABSTRACT: The first total synthesis of integrastatin B, a potent HIV-1 integrase inhibitor, has been accomplished in seven steps with a 17.9% overall yield employing easily accessible starting compounds. The Oxone-mediated oxidative benzofuran dearomatization cascade has been employed as the key skeletal construct to forge the central tetracyclic nucleus.

The endophytic fungal metabolites integrastatins A (**1**) and B (**2**) (Figure 1) having an unprecedented [6/6/6/6] tetracyclic skeleton have been isolated from an unnamed fungal source (ATCC74478) and from the *Ascochtya* species (ATCC74477).[1] A preliminary screening against the recombinant HIV-1 integrase enzyme revealed that the integrastatins inhibited the strand-transfer reaction (IC_{50} = 1.1 μM shown by **1** and 2.5 μM shown by **2**). The unique structural features, when taken together with an urgent need for the development of new agents for disabling HIV-viral replicative processes, have led to the study of integrastatins as fascinating targets. Despite the efforts of several groups, the total synthesis of the integrastatins has not yet been reached.[2−4] In addition, the recent addition of epicoccolide A (**3**)[5] and epicocconigrone A (**4**)[6] as new members of this family and their broad-spectrum biological activities (anticancer, antimicrobial, and antifungal) revealed the significance of this structural core as a new clinically relevant scaffold. There are four preliminary reports currently documented that address the assembly of the key tetracyclic skeleton.[2−4,7] These include the construction of the bicyclic ketal core either by $SnCl_2$-mediated cycloetherification of a suitably functionalized stilbene reported by Taylor's group[2] and the Pd-catalyzed oxidative ketalization of a terminal alkene documented by Stoltz's group.[4] We have documented two different approaches that are apparently biomimetic.[3,7] Our first report proposed and established the possibility of the dimerization of a phthalaldehyde via a pinacol coupling as the central event in the construction of this tetracyclic core.[3] The benzoin variant of this sort of dimerization has been put forward as a possible biosynthetic path for **3** and **4** by the Laatsch group.[5] Very recently, taking clues from the common biogenetic partner "epicoccolide B" of **3** and **4**, the oxidation of a benzofuran unit to the transient *o*-quinone methides (*o*-QMs)[8,9] and its subsequent cycloaddition with the carbonyl group present on the C2-aryl ring has been established as a general approach for the construction of the central tetracyclic core of all these natural products (Figure 1).[7]

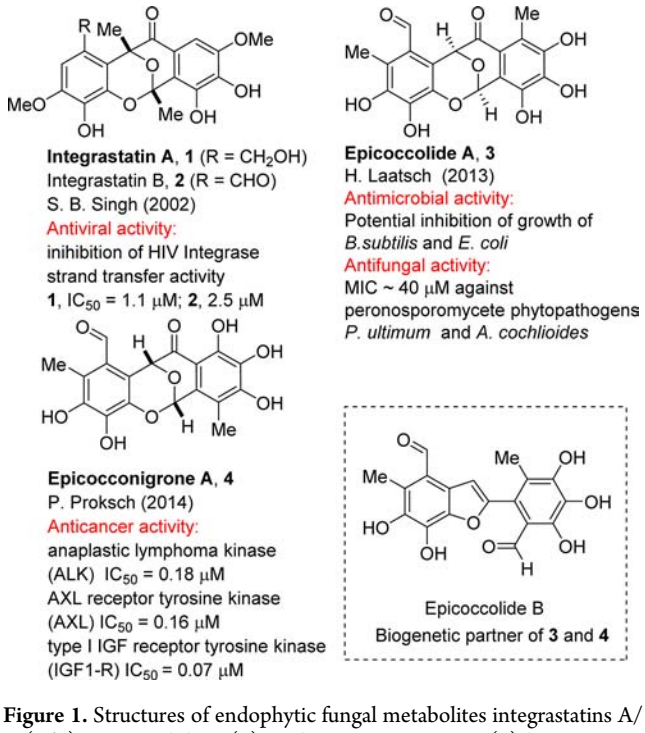

Figure 1. Structures of endophytic fungal metabolites integrastatins A/B (**1**/**2**), epicoccolide A (**3**), and epicocconigrone A (**4**) having a rare [6,6,6,6]-tetracyclic core and epiococcolide B, a biogenetic partner isolated along with **3** and **4**.

In this paper, we document the first total synthesis of integrastatin B employing this benzofuran oxidative dearomatization cascade as the key reaction.

Scheme 1 reveals the salient features of our retrosynthetic disconnection of integrastatins nucleus. Structurally, integrastatins are highly oxygenated and densely populated with the quaternary carbons. Other than the pendant methyl groups, out of the 15 carbons present in the main framework, 13 are quaternary carbons and the remaining two are tertiary carbons

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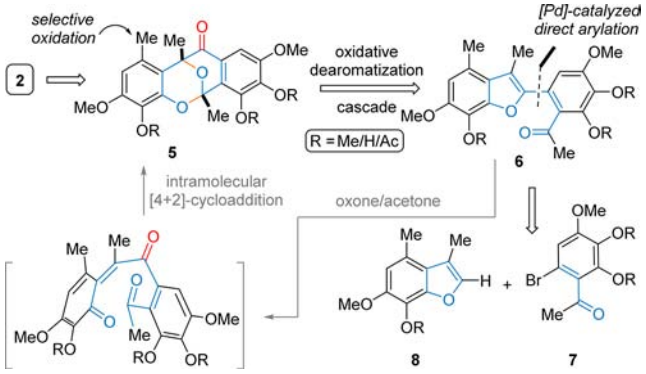
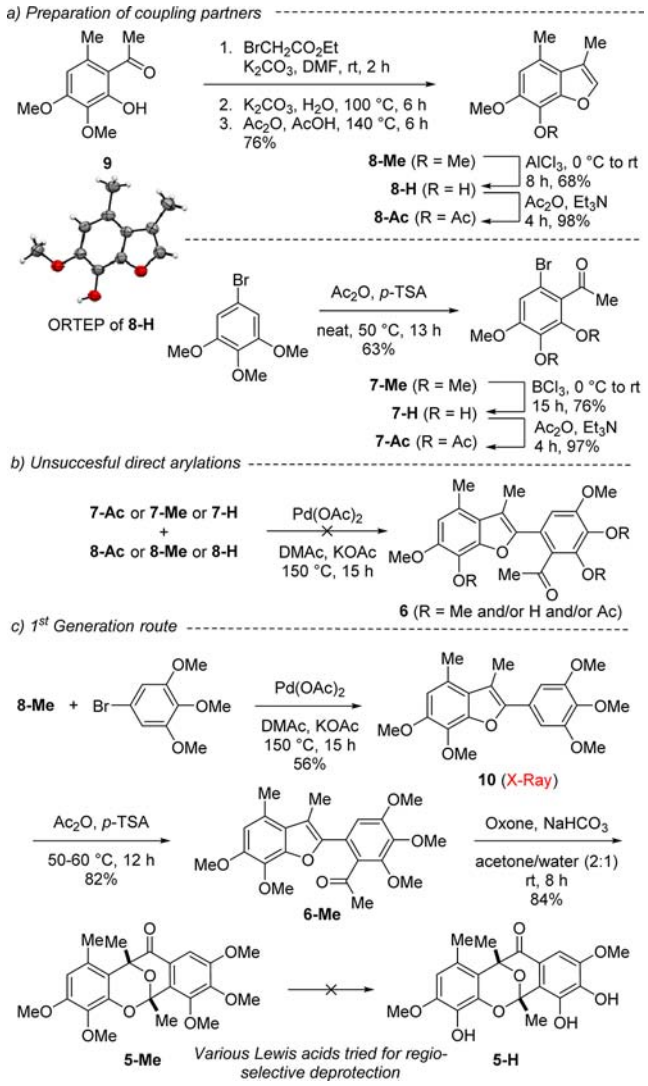
Scheme 1. Key Retrosynthetic Disconnections for Integrastatins B (2) Featuring Benzofuran Oxidative Dearomatization/[4 + 2]-Cycloaddition Cascade



that are distributed one on each aromatic ring. It is not only the dense substitution on each aromatic ring but also the differentiation of the three phenolic −OH groups present on each aromatic ring that is another critical component that required serious thought during the design of the retrosynthetic path. In a forward sense, we identified that these critical issues had to be addressed before the established key skeletal construct could be conducted. At the outset of our retrosynthetic design, we thought to place a methyl group as a surrogate for the key aldehyde group present in the integrastatin B (**2**). Keeping these issues in mind and employing our key transform, the benzofuran **6** has been identified as the key substrate.

Our first objective was set for the synthesis of the advanced benzofuran intermediate **6** employing Pd chemistry that we established in the model studies.[7,10,11] In this direction, the benzofurans **8** and their coupling partners **7** have been identified as starting precursors. The differentially protected benzofuran compounds **8** were accessed from the easily available 2-hydroxy-3,4-dimethoxy-6-methylacetophenone **9**.[12] The sequence involved the benzofuran formation[13] followed by selective monodemethylation with Lewis acid ($AlCl_3$) in CH_2Cl_2.[14] Indeed, the expected compound **8-H** was obtained exclusively when the compound **8-Me** was treated with 1 equiv of $AlCl_3$ in CH_2Cl_2 at 0 °C. The free hydroxyl group was protected as its acetate **8-Ac** (Scheme 2a). The synthesis of compound **7-Ac** was started from 5-bromo-1,2,3-trimethoxybenzene. The Friedel−Crafts acylation protocol gave 1-(6-bromo-2,3,4-trimethoxyphenyl)ethan-1-one (**7-Me**), which was subjected to the carbonyl-directed/Lewis acid mediated selective demethylation in the presence of BCl_3 in CH_2Cl_2 solvent. The resulting phenol **7-H** was protected as its acetate **7-Ac** (Scheme 2a). Our next concern was the coupling of benzofuran **8-Ac** and its partner **7-Ac** to obtain the advanced intermediate **6**. This was found to be a difficult proposition in this proposed synthetic plan. Several possibilities employing the other intermediates **7-Me**/**7-H**/**7-Ac** and **8-Me**/**8-H**/**8-Ac** have been attempted without any success (Scheme 2b). Additionally, we have explored various ligands, temperature conditions, and bases along with solvents such as DMF, THF, and DMSO, etc. Unfortunately, in all cases, either the starting materials remained intact or the aryl bromides and benzofurans self-dimerized. The difficulties in the direct coupling with the aryl bromides having bulky *ortho* substituents revealed that these events should be postponed. Thus, the coupling of benzofuran **8-Me** with the starting 5-bromo-1,2,3-trimethoxybenzene was

Scheme 2. Synthesis of Differentially Protected Building Blocks of 7/8, Examination of their Pd-Catalyzed Direct Coupling To Prepare the Key Intermediate 6, and Failure Route



attempted, and the required coupling product **10** was obtained in 56% yield under established conditions (Scheme 2c).

Next, benzofuran **10** was subjected to the Friedel−Crafts acylation by heating in acetic anhydride (Ac_2O) in the presence of catalytic amounts of *p*-TSA.[15] The acylation occurred exclusively on the pendant aryl ring giving the benzofuran **6-Me**. The key Oxone-mediated cascade process of benzofuran **6-Me** proceeded smoothly in the presence of 2 equiv of Oxone in acetone/water (2:1) at room temperature over 8 h and provided the tetracyclic compound **5-Me** in very good yield.[7,16] Next, one of the last key events in our synthesis was the selective hydrolysis of three out of five methoxy groups. To achieve this, several Lewis acid and other demethylating agents were screened; unfortunately, none of the conditions gave desired intermediate **5-H** except the decomposition of compound **5-Me** (Scheme 2c).

The failure of the first generation route prompted us to revise our approach. The sequence of Oxone- mediated benzofuran dearomatization cascade followed by selective deprotection of the methyl ethers (in case of **7** and **8**) was reversed. Also,

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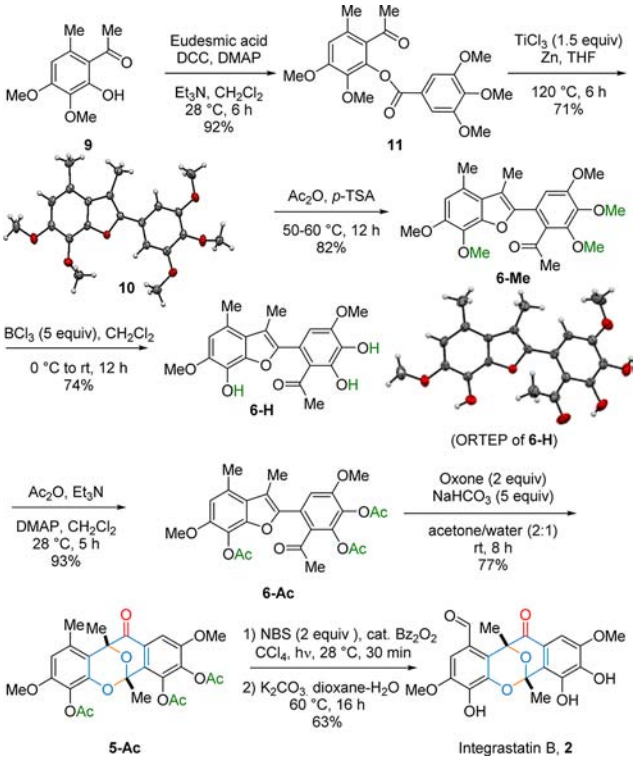
considering the moderate yield in the coupling event and the lengthy route for the intermediate **10** that was explored as an off-shoot from the attempted synthesis of the originally planned substrate **6** via direct benzofuran coupling, we opted to develop an alternative route for the preparation of **10**. To this end, this intermediate benzofuran compound **10** was synthesized in better yields (65% over two steps) by employing $TiCl_3$-mediated intramolecular Fürstner–McMurry coupling[17] of ester **11** that was prepared by coupling of previously synthesized **9** with the commercially available eudesmic acid. The benzofuran **10** was subjected to Friedel–Crafts acylation to form **6-Me**. Next, one of the key events in our synthesis was the selective hydrolysis of three out of five methoxy groups. This could be achieved with commendable selectivity by a prolonged exposure of compound **6-Me** to 5 equiv of boron trichloride (BCl_3) in CH_2Cl_2.[14] The regioselectivity of this hydrolysis reaction has been established by a simple comparison of the spectral data of the resulting product **6-H** with the data of the fragments **7-H** and **8-H** and was further confirmed by the single-crystal X-ray structural analysis of **6-H** (Scheme 3).

Scheme 3. Second-Generation Route: Completion of Total Synthesis of Integrastatin B (2)



Finally, the acetylation of three phenolic –OH groups present in **6-H** with Ac_2O in Et_3N gave the key benzofuran intermediate **6-Ac**. The oxidative skeletal reorganization of benzofuran **6-Ac** using Oxone–$NaHCO_3$ in acetone/water (2:1) at room temperature over 8 h provided the tetracyclic compound **5-Ac** in 77% yield. With the advanced intermediate **5-Ac** in hand, we next proceeded to the selective oxidation of the aryl-CH_3 group to the corresponding aldehyde followed by deacetylation to acquire the natural product. For this purpose, compound **5-Ac** was initially subjected to radical bromination by employing catalytic benzoyl peroxide as a radical initiator and bromide (NBS) in carbon tetrachloride (CCl_4) under sunlight. The resulting *gem*-dibromide intermediate was immediately subjected for the base-mediated hydrolysis using potassium carbonate (K_2CO_3) in a mixture of water–dioxane.[18] This provided integrastatin B (**2**) in 61% isolated yield over two steps. The spectral and analytical data of **2** compare well with the data reported for the natural product.[1] Overall, the synthetic integrastatin B was obtained in a total yield of 17.9% over seven steps.

In summary, the first total synthesis of integrastatin B has been successfully executed in seven steps in a highly efficient manner. The indigenous Oxone-mediated oxidative dearomatization/[4 + 2]-cycloaddition cascade has been successfully applied for the construction of the central bicycle [3.3.1]octane ring system. The key advanced C2-aryl benzofuran intermediate could be accessed either by Pd-catalyzed C2-arylation or by a Fürstner–McMurry coupling. The Lewis acid mediated selective demethylation is praiseworthy in accessing the key benzofuran intermediate having differentially protected phenolic –OH groups. The overall approach is practical and scalable. In addition, the easy generation of *o*-QM that we have disclosed here has its own potential to emerge as the strategy of choice in related natural products synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00404.

Full experimental procedures, characterization data, and NMR/mass spectra of all new compounds (PDF)
Crystallographic data for compound **8-H** (CIF)
Crystallographic data for compound **10** (CIF)
Crystallographic data for compound **6-H** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vr.chepuri@ncl.res.in.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor M. Nagarajan on the occasion of his 65th birthday.

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