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Scalable Asymmetric Total Syntheses of (+)-Psoracorylifol B and (+)-*ent*-Psoracorylifol C

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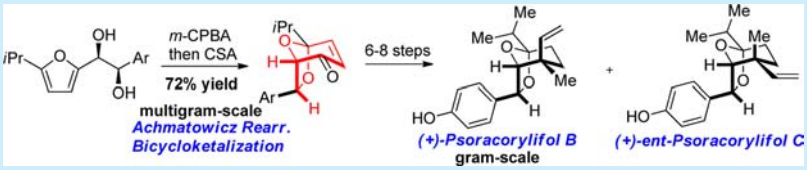
Supporting Information



ABSTRACT: The first, asymmetric total syntheses of potent antimicrobial Psoracorylifol B (>1.3 g obtained, dr 10.5:1) with a 9.4% overall yield on a gram scale in 14 steps and *ent*-Psoracorylifol C with a 4.3% yield in 16 steps were achieved. The key features of our synthesis include (i) sequential, rarely explored Achmatowicz rearrangement/bicycloketalization to construct the 6,8-dioxabicyclo[3.2.1]octane core, and (ii) Cu-mediated S_N2' methylation or Johnson–Claisen rearrangement to stereoselectively install the all-carbon quaternary stereocenter. This concise, highly efficient, and scalable synthetic route may provide expedited and practical access to psoracorylifols and their analogues for further biological activity evaluation.

Psoracorylifols A–C (Figure 1) were isolated from the seeds of *Psoralea corylifolia* L. (*Buguchi*, a well-known traditional

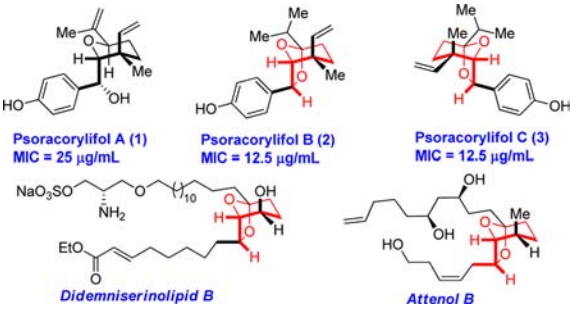


Figure 1. Psoracorylifols A, B, and C and structurally related didemniserinolipid B and attenol B.

Chinese medicine for treatment and cure of gynecological bleeding, vitiligo, psoriasis, and bone fractures)[1] by Yue et al. in 2006.[2] These compounds have shown significant antimicrobial activity *in vitro* as potent inhibitors against two strains of *Helicobacter pylori* (ATCC 43504 and SS1) with MICs of 12.5–25 μg/mL. The remarkable inhibition of H. *pylori*-ATCC 43504 holds great potential for clinical use because H. *pylori* infections causing diseases such as gastritis, peptic ulcer, and gastric cancer are often resistant to metronidazole (MIC = 128 μg/mL against H. *pylori*-ATCC43504), which is a main ingredient for combination therapies of various H. *pylori* infections.[3] In 2007, Yoshikawa et al. independently isolated psoracorylifols B and C again from the same seeds of *Psoralea corylifolia*, although both compounds did not show the expected inhibitory effects on the release of β-hexosaminidase from RBL-2H3 cells.[4]

Structurally, these psoracorylifols shared a common all-carbon quaternary stereocenter on the tetrahydropyran and a peripheral phenol substituent. Psoracorylifol A (PsA, **1**) was characterized by the presence of a 2,6-*trans*-substituted tetrahydropyran, while psoracorylifol B (PsB, **2**) and psoracorylifol C (PsC, **3**) feature a unique 6,8-dioxabicyclo[3.2.1]octane (6,8-DOBCO) framework. These structural differences might account for the greater antimicrobial potency of PsB and PsC when compared with that of PsA. In fact, simple alkylated 6,8-DOBCOs such as brevicomin, frontalin, and multistriatin are insect pheromones,[5] while more complicated substitution of 6,8-DOBCO exists in many biologically active and/or structurally diverse natural products (*cf.* didemniserinolipid B[6] and attenol B,[7] Figure 1). This privileged bicyclic acetal scaffold has been targeted as a platform for the development of new synthetic methods/strategies[8] and recently investigated by Ley et al. to expand the molecular diversity for drug-discovery programs.[9] The combination of potent antimicrobial activity and unique and interesting structures of PsB and PsC prompted us to undertake their total syntheses. Herein, we reported the first, asymmetric total syntheses of psoracorylifol B (**2**) and *ent*-psoracorylifol C (*ent*-**3**) by exploitation of the Achmatowicz rearrangement/bicycloketalization for the construction of the 6,8-DOBCO framework.

At the outset of our studies, we recognized that PsB was reported as a diastereomer of the enantiomer of PsC (*ent*-**3**) (except for the opposite all-carbon chiral center, Scheme 1).[2,4] To fully exploit this structural relationship and ease the synthetic work, we proposed to synthesize the enantiomer of PsC from a common intermediate (e.g., **4**, Scheme 1) used for the synthesis

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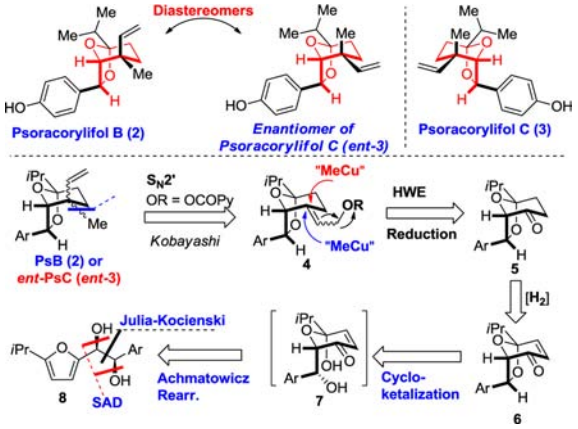
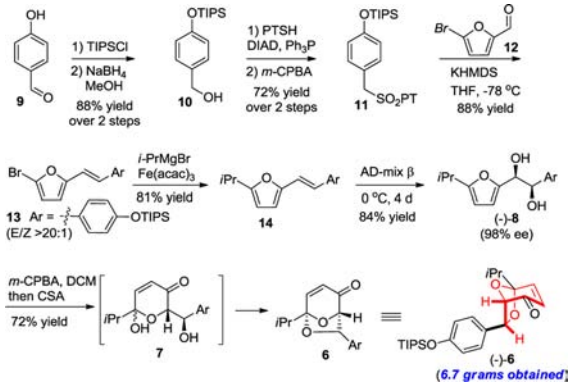
Scheme 1. Synthetic Plan for Psoracorylifol B (2) and *ent*-Psoracorylifol C (*ent*-3)



of PsB via divergent transformations. Structural analysis of PsB and *ent*-PsC clearly revealed that the primary synthetic challenges included (i) stereoselective construction of the all-carbon quaternary stereocenter[10] and (ii) efficient preparation of the unique 6,8-dioxabicyclo[3.2.1]octane (6,8-DOBCO) framework. For the first synthetic challenge, we envisioned that on the basis of elegant work by Kobayashi[11] the all-carbon quaternary stereocenter could be constructed by Cu-mediated S_N2' methylation of allyl picolinate **4** (Scheme 1), although the stereoselectivity and stereochemical outcome could not be predicted and controlled at this stage. However, it might be advantageous to access both PsB and *ent*-PsC from a nonselective reaction mixture if their separation by column chromatography was not difficult. For the 6,8-DOBCO framework of PsB and *ent*-PsC, it was noted that in 2010 Hashimoto[12] et al. reported an efficient Rh-catalyzed 1,3-dipolar cycloaddition[13] of α-diazocarbonyl compounds with aldehydes to construct the fully substituted 6,8-DOBCO framework of PsB and PsC. Unfortunately, this elegant strategy has not yet led to the total synthesis of PsB or PsC. Nonetheless, in continuation of our interest in the synthetic utilities of Achmatowicz rearrangement,[14] we envisioned that the 6,8-DOBCO core structure (**6**) could be constructed by sequential Achmatowicz rearrangement/bicycloketalization (AR/BCK, **8** → **6**), a protocol originally developed by Ogasawara[15] for the enantio- and diastereoselective synthesis of hexoses from furfural. To our surprise, this AR/BCK strategy has been rarely exploited in the synthesis of 6,8-DOBCO, which instead was prepared conventionally by dehydrative ketalization of the corresponding dihydroxyl ketone.[16] Given that the structure of type **8** could be synthesized straightforwardly through Julia–Kocienski olefination[17] and Sharpless asymmetric dihydroxylation,[18] we first explored this strategy for the synthesis of the 6,8-DOBCO framework of PsB and *ent*-PsC. If implementation of these two key tactics (S_N2' methylation and AR/BCK) were successful, we expected that the total syntheses of PsB and *ent*-PsC could be achieved in a concise, highly enantioselective fashion.

Our synthesis (Scheme 2) began with the preparation of sulfone **11** for Julia–Kocienski olefination. Specifically, 4-hydroxylbenzaldehyde (**9**) was converted to **11** in 4 steps through silylation with triisopropylsilyl chloride (TIPSCl), $NaBH_4$ reduction, Mitsunobu reaction[19] with 1-phenyl-1*H*-tetrazol-5-yl thiol (PTSH) in the presence of PPh_3/DIAD (diisopropyl azodicarboxylate), and oxidation with *m*-CPBA (3-chloroperbenzoic acid). The Julia–Kocienski olefination of **11**

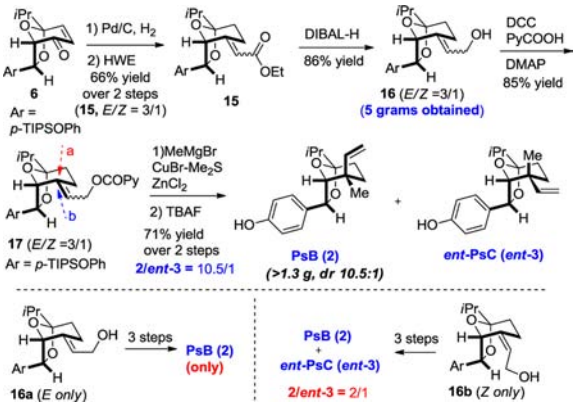
Scheme 2. Synthesis of the Key 6,8-DOBCO (6) on Multigram Scale



and 5-bromo-2-furaldehyde **12** was effectively promoted by KHMDS at −78 °C to give the alkene **13** in 88% yield with excellent E/Z selectivity (E/Z > 20/1). In the course of reproducing this olefination, the E/Z selectivity was found to be dependent on the reaction temperature as well as the counterion of the base, since NaHMDS and LiHMDS under various conditions gave lower E/Z selectivity.[20] Next, iron-catalyzed Kochi cross-coupling[21] of **13** with *i*-PrMgBr yielded the 2,5-disubstituted furan **14**, which underwent Sharpless asymmetric dihydroxylation with AD mix-β using *t*-BuOH/H_2O (1:1) as the mixed solvents at 0 °C for 4 days to provide the desired furyl diol **8** in 84% yield as the single diastereomer (98% ee by HPLC). Treatment of the furyl diol **8** with *m*-CPBA initiated the oxidative ring expansion (Achmatowicz rearrangement) and provided pyranone acetal **7**, which upon treatment of 10-camphorsulfonic acid (CSA) in the same reaction vessel underwent dehydrative bicycloketalization to give the key 6,8-DOBCO (**6**) in 72% yield, corresponding to the core bicyclic skeleton of PsB and *ent*-PsC. In particular, the efficiency and robustness of the synthetic route to the 6,8-DOBCO (6.7 g obtained) were demonstrated by performing these reactions on a multigram scale without a significant drop in yields as compared to the corresponding milligram-scale reactions.

To construct the all-carbon quaternary stereocenter via Kobayashi's S_N2' methylation, the 6,8-DOBCO (**6**) needed to be properly functionalized with the introduction of two carbons (Scheme 3). Specifically, Pd/C-mediated hydrogenation of **6** followed by Horner–Wadsworth–Emmons (HWE)[22] olefina-

Scheme 3. Completion of Total Syntheses of Psoracorylifol B and *ent*-Psoracorylifol C



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tion to provide the conjugated ester **15** in 66% combined yield over two steps as an *E*/*Z* mixture (3/1). Although separation of these two *E*/*Z* stereoisomers by flash column chromatography was difficult, the resulting allylic alcohols **16** (**16a** and **16b**) from reduction with diisobutylaluminum hydride (DIBAL-H) indicated noticeably different R_f values based on TLC and could be separated by careful flash column chromatography. However, the *E*/*Z* mixture **16** was used for subsequent transformations because Kobayashi et al. found that stereoselectivity in the course of S_N2' substitution was independent of the *E*/*Z* stereochemistry of the allyl picolinate.[11] DCC-mediated esterification of allylic alcohol **16** with picolinic acid provided quantitatively the desired picolinate **17** as the key substrate for the S_N2' methylation. To our delight, picolinate **17** underwent regio- and stereoselective S_N2' substitution with MeMgBr in the presence of CuBr-Me_2S/$ZnCl_2$ to furnish psoracorylifol B as a 10.5:1 diastereomeric mixture (**2**/*ent*-**3** = 10.5:1) after desilylation with TBAF. It was noteworthy that the S_N2' methylation on a gram-scale proceeded smoothly with similar efficiency and stereoselectivity to deliver 1.34 g of PsB (dr 10.5:1). The formation of PsB as the major product in the course of S_N2' methylation was unexpected and could not be fully rationalized because the methyl addition from the bottom face (concave, path b) of the bicyclic acetal **17** was seemingly disfavored. Suspicion of misassignment of PsC as PsB was eliminated by single crystal X-ray diffraction analysis of the 4-nitrobenzoate derivative of PsB (Figure 2.). The high

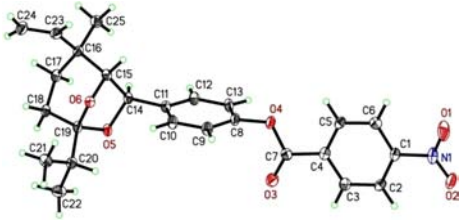


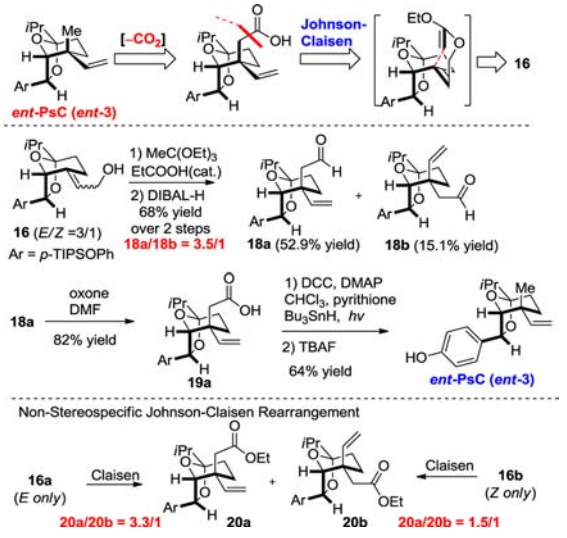
Figure 2. ORTEP diagram of 4-nitrobenzoate derivative of psoracorylifol B (**2**).

diastereoselectivity of S_N2' methylation for **17** (path b) might arise from blocking the top-face attack (path a) by coordination of Zn^{2+} with tetrahydropyran oxygen and picolinate. However, the dependence of diastereoselectivity on the alkene geometry (e.g., **16a** → PsB only, **16b** → PsB + *ent*-PsC, Scheme 3) was very surprising to us and in sharp contrast to Kobayashi's findings.[11] More studies are needed to address the stereoselectivity issues in the course of this S_N2' substitution. All spectroscopic data of synthetic PsB and *ent*-PsC were in good agreement with those reported for natural PsB and PsC,[20] except for the optical rotation. The opposite sign of optical rotation of *ent*-PsC supported the absolute configuration proposed for the natural PsC.

We recognized that *ent*-PsC (*ent*-**3**) was synthesized as a minor product from both **16b** and a 3:1 mixture of **16a**/**16b** in the final S_N2' substitution (Scheme 3). To achieve a more efficient synthesis of *ent*-PsC, we designed a new synthetic route that exploited the Johnson−Claisen[23] rearrangement of the allylic alcohol **16** and reductive decarboxylation[24] to construct the all-carbon quaternary stereocenter (Scheme 4).

Treatment of allylic alcohol **16** (*E*/*Z* = 3/1) with a catalytic amount of propionic acid in $MeC(OEt)_3$ under reflux and subsequent DIBAL-H reduction of the Johnson−Claisen rearrangement adducts produced a 3.5:1 diastereomeric mixture

Scheme 4. Total Syntheses of *ent*-PsC (*ent*-3) via Johnson−Claisen Rearrangement/Reductive Decarboxylation



of **18a** and **18b** in 68% combined yield, which could be separated by flash column chromatography (Scheme 4). Interestingly, Johnson−Claisen rearrangement of the single *E*-isomer **16a** was found to give surprisingly a 3.3:1 diastereomeric mixture of **20a** and **20b** favoring **20a**, while under the same conditions *Z*-isomer **16b** resulted in only a 1.5:1 mixture favoring **20a**. Oxidation of **18a** with oxone in DMF[25] gave an excellent yield of the desired carboxylic acid **19a**, which was subjected to the modified Barton's reductive decarboxylation[26] to furnish (+)-*ent*-PsC in 64% yield as the single diastereomer after desilylation.[20] In contrast to the S_N2' methylation method in Scheme 3, this route delivered *ent*-PsC as the major product in 5 steps from the common intermediate **16** with 27.6% overall yield. It was noteworthy that Kobayashi[11d] reported a conceptionally similar strategy to diastereoselectively install the opposite stereochemistry of the quaternary carbon via ester methylation and picolinate allylic S_N2' substitution.

In summary, we have achieved the first, asymmetric total syntheses of potent antimicrobial Psoracorylifol B with a 9.4% overall yield on a gram-scale in 14 steps and *ent*-Psoracorylifol C with a 4.3% yield in 16 steps. The conciseness and efficiency were enabled by exploitation of two key reactions to solve two major synthetic challenges: (i) the novel Achmatowicz rearrangement/bicycloketalization sequence to construct the core 6,8-dioxabicyclo[3.2.1]octane substructure and (ii) S_N2' methylation of allylic picolinate or Johnson−Claisen rearrangement of the allylic alcohol to stereoselectively install the all-carbon quaternary stereocenter. Our synthetic studies confirmed the relative and absolute configurations of PsB and PsC and provided expedited and practical chemical access to these structurally novel antimicrobial agents PsB and *ent*-PsC and their analogues for further biological activity evaluation.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterizations and copies of ^1H and ^{13}C NMR spectra of new compounds, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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