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Efficient Enantioselective Syntheses of (+)-Dalesconol A and B

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Supporting Information

ABSTRACT: We herein report the first enantioselective syntheses of immunosuppressants (+)-dalesconol A and B in a highly efficient and concise manner, which features an efficient palladium-catalyzed enantioselective dearomative cyclization−kinetic resolution cascade to install the chiral all-carbon quaternary center, an effective sterically hindered Stille coupling, a powerful 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation to furnish all requisite unsaturation, and a tandem hydrolysis−ring closure sequence.

Initially isolated by Tan and co-workers[1] in 2008 from mantis-associated fungus *Daldinia eschscholzii*, Dalesconol A (**1**, IC_{50} = 0.16 μg mL^{-1}, SI > 500) and B (**2**, IC_{50} = 0.25 μg mL^{-1}, SI > 320) are two unusual polyketides that exhibit strong immunosuppressive activities comparable to that of clinically used cyclosporine A[2] (IC_{50} = 0.06 μg mL^{-1}, SI = 187), but with superior selective index (SI) values for their noncytotoxic nature. Interestingly, both natural dalesconol A and B are scalemic mixtures with an excess of their (−)-enantiomers (ratios of (−)/(+) ≈ 2/1), a consequence dictated by laccase during the atropselective coupling of naphthol radicals in their biosynthesis.[3] Intriguingly, both scalemic mixtures of natural dalesconol A and B provided more potent immunosuppressive activities than their enantiomers.[1] Subsequently, these two compounds were also isolated by She, Lin, and co-workers from a mangrove endophtic fungus (Sporothrix sp. #4335) and named as sporothrin A and B.[4] Compound **1** exhibited strong inhibition of acetylcholine esterase (IC_{50} = 1.05 μM) while both compounds showed modest antitumor activities. Structurally, dalesconol A and B possess an architecturally unique and highly dense carbon skeleton containing seven fused rings of various sizes and two stereogenic centers including one sterically congested all-carbon quaternary center. The only total syntheses of racemic dalesconol A and B were accomplished beautifully by Snyder and co-workers[5] by employing a key one-pot cationic cyclization−intramolecular oxidative coupling cascade through a sequence of 15 linear steps and 25 overall steps. Later, Shi and co-workers reported a concise method for constructing the dalesconol skeleton by using a carbocation-mediated dearomatization−cyclization strategy.[6] An efficient enantioselective syntheses of dalesconol A and B would not only help provide ample optically pure samples for further elucidation of their biological mechanism but also provide valuable analogs for discovering new immunosuppressants. Herein we report the concise and first enantioselective syntheses of (+)-dalesconol A and B (**1** and **2**).

The major challenge in synthesizing **1** and **2** (Figure 1a) is to establish the highly congested all-carbon quaternary center within the densely fused ring systems. Instead of using an oxidative or cationic cyclization approach adopted by Snyder[5] or Shi[6] in their synthetic studies, we envisioned implementing a palladium-catalyzed intramolecular enantioselective dearomative cyclization,[7,8] a strategy that had been applied successfully for the

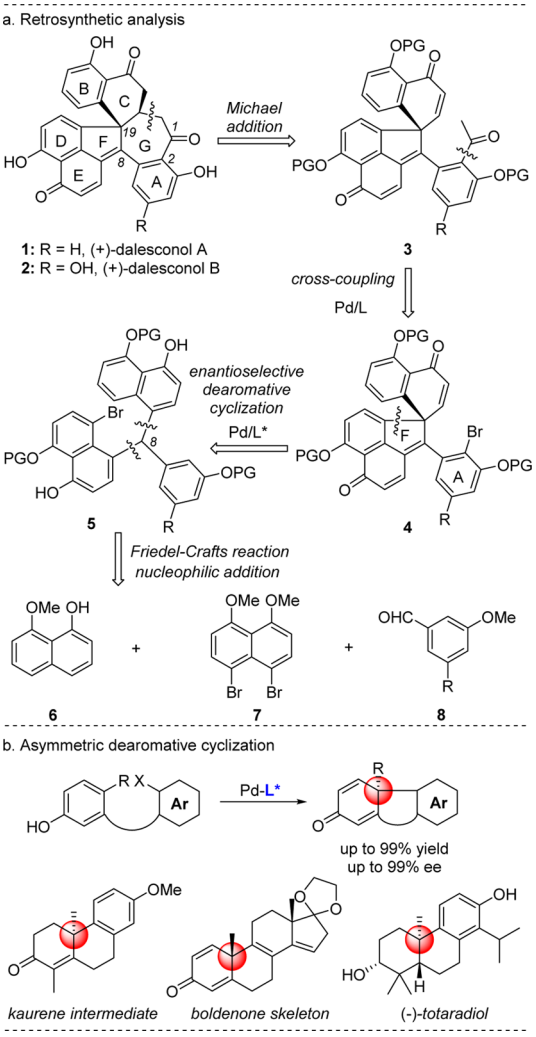

Figure 1. Retrosynthetic analysis of dalesconol A (**1**) and B (**2**) on the basis of an enantioselective dearomative cyclization.

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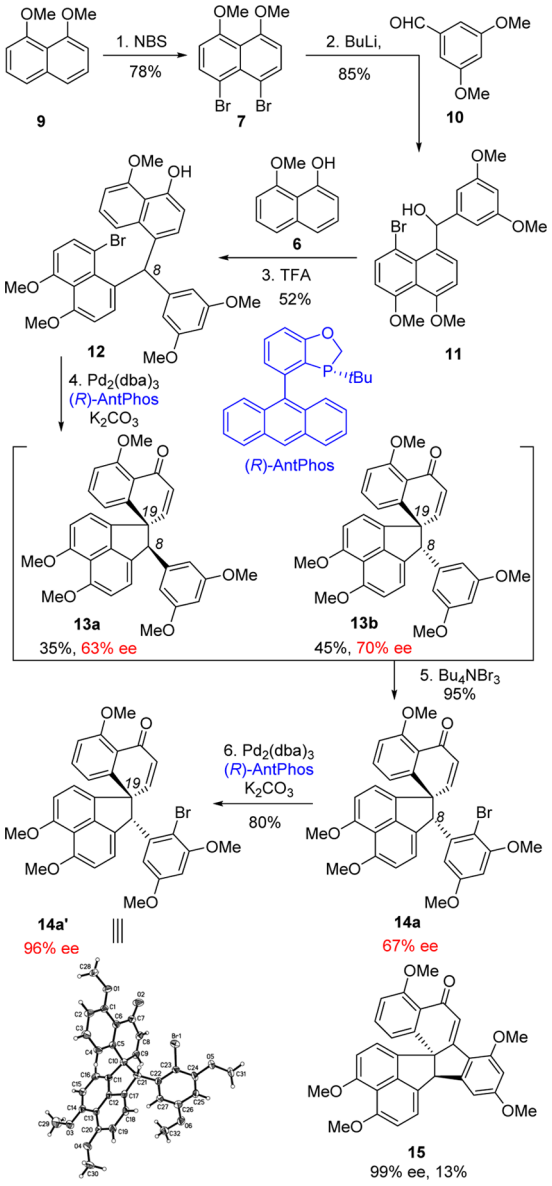
synthesis of terpenes and steroids in our laboratory (Figure 1b).[9] Thus, dalesconol A and B could be derived from spiroenone **3** through an intramolecular Michael addition to fuse the seven-membered G ring. The installation of the acetyl group in **3** could be accomplished by a palladium-catalyzed sterically demanding cross-coupling from aryl bromide **4**. The key spiroenone skeleton in **4** could be constructed from a racemic aryl bromide **5** through an unprecedented enantioselective dearomative cyclization affected by a chiral palladium catalyst. The stereocenter at position 8 could be eliminated by a subsequent oxidation. The bromo naphthol **5** would be easily prepared from readily available aromatic compounds **6**, **7**, and **8** by a Friedel–Crafts reaction and a nucleophilic addition.

We commenced our synthesis from commercially available starting material 1,8-dimethoxynaphthalene (**9**), which was treated with NBS to provide the dibromo compound **7** in 78% yield (Scheme 1). Lithium–bromide exchange of **7** with 1.05 equiv of BuLi followed by an *in situ* nucleophilic addition with aldehyde **10** provided alcohol **11** in 85% yield. The next step was to install another naphthalene moiety on **11**. This was accomplished by a Friedel–Crafts alkylation of naphthol **6** with alcohol **11** in the presence of TFA to afford bromo naphthol **12** in 52% yield. The stage was set for the crucial enantioselective intramolecular dearomative cyclization of racemic **12** with a chiral palladium catalyst. We envisioned that a P-chiral mono-phosphorus ligand developed in our laboratory could be effective for this unprecedented enantioselective intramolecular cyclization to afford the spiroenones **13a** and **13b**. The challenge was the highly acidic nature of the proton at position 8 in **12**, which might complicate the outcome of the cyclization. After many experimentations,[10] we found that both the enantioselectivities and the diastereomeric ratios of **13a**/**b** were highly sensitive to the choice of the ligand as well as the base. (*R*)-AntPhos[11] proved to be most effective and provided preferentially the 19*S* isomers **13a** (63% ee) and **13b** (70% ee). This palladium-catalyzed asymmetric reaction was proposed to proceed through the conformation A depicted in Figure 2a during reductive elimination, favoring the formation of 19*S* products. With K_2CO_3 as the base, a good combined yield (80% yield) was achieved. Employment of a stronger base such as Cs_2CO_3 (~40% ee's) and KO*t*Bu (~20% ee's) led to preferentially the formation of the thermodynamically more stable isomer **13b**, however with a diminished ee (~20% ee's). We thus chose K_2CO_3 as the base for the synthesis. Interestingly, the diastereomeric mixture of **13a** and **13b** (~1:1.3) was transformed to a single diastereomeric aryl bromide **14a** in 95% yield and in 67% ee upon treatment of Bu_4NBr_3. Apparently, a facile proton shift took place at position 8 during the electrophilic aromatic substitution, resulting in the sole formation of the thermodynamically more stable isomer **14a**.[12] The next challenge was to enhance the optical purity of **14a**. We considered that the sterically hindered aryl bromide **14a** bearing a vicinal enone moiety could proceed in an intramolecular Heck cyclization by employing a chiral palladium catalyst in a kinetic resolution fashion. Excitingly, when **14a** was treated with the same chiral catalyst (Pd-(*R*)-AntPhos) used for dearomative cyclization, an effective kinetic resolution (S = 15) was observed[13] and the 19*S* enantiomer proceeded at a much lower rate than its antipode, resulting in the formation of bromide **14a′** in 96% ee and in 80% isolated yield along with the heptacyclic Heck product **15** in 13% yield and 99% ee. It was believed that the steric interaction between the A ring and the *tert*-butyl group of AntPhos caused the less favorable conformation of the Pd complex B required for olefin insertion (Figure 2b), leading to a relatively lower rate of the 19*S* enantiomer for Heck cyclization. The absolute configuration of **14a′** was confirmed by X-ray crystallography.[14]

Scheme 1. Enantioselective Synthesis of Spiroenone 14a′[a]



[a]Reagents and conditions: (1) NBS (1.05 equiv), DCM, −15 °C; then NBS (1.05 equiv), DMF, 20 °C (78%); (2) *n*BuLi (1.05 equiv), THF, −78 °C; then **10** (1.1 equiv), −78 °C (85%); (3) **6** (1.1 equiv), TFA (1.8 equiv), DCM, −40 °C to rt (52%); (4) $Pd_2(dba)_3$ (3.0 mol %), (*R*)-AntPhos (8.0 mol %), K_2CO_3 (2.0 equiv), toluene, 80 °C (80%); (5) Bu_4NBr_3 (1.05 equiv), rt (95%, 67% ee); (6) $Pd_2(dba)_3$ (3.0 mol %), (*R*)-AntPhos (8.0 mol %), K_2CO_3 (2.0 equiv), toluene, 80 °C (80%, 96% ee); NBS = *N*-bromosuccinimide, dba = dibenzylidene acetone.

To complete the synthesis of dalesconol B, the next mission was to install a two carbon unit at the C2 position (Scheme 2). To avoid a Heck side reaction, the carbon–carbon double bond in **14a′** was hydrogenated over PtO_2 to form **16** in 84% yield. It should be noted that the spirocyclic unit of **14a′** underwent a Wagner–Meerwein rearrangement to form a planar aromatized side product under conditions of H_2/Pd/C.[15] Next, a sterically hindered Stille coupling between bromide **16** and trimethyl-

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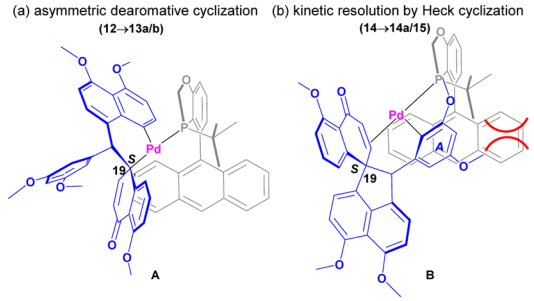
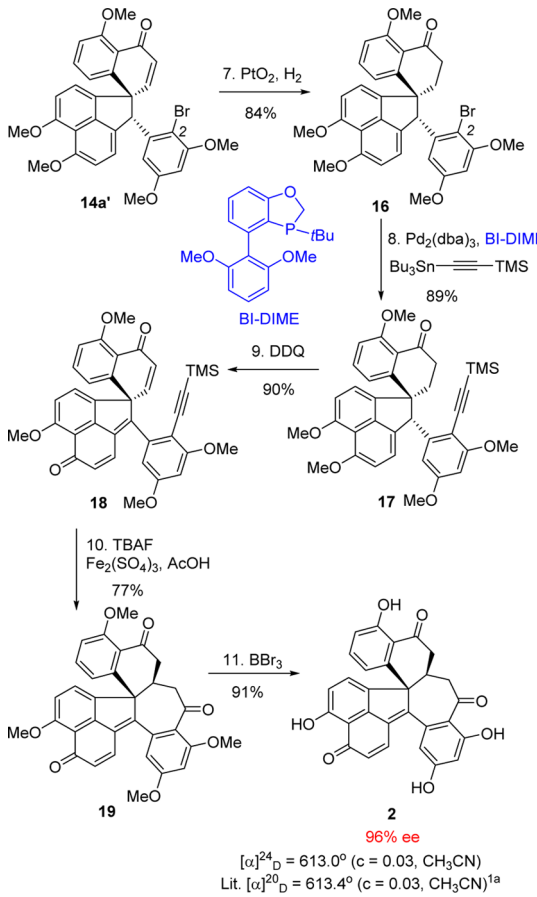


Figure 2. (a) Stereochemical model of asymmetric dearomative cyclization during reductive elimination: The formation of 19*S* isomers was favored with (*R*)-AntPhos. (b) Stereochemical model of kinetic resolution–Heck cyclization: The Heck cyclization of the 19*S*-enantiomer was slower due to the less favorable conformation of the Pd complex B during insertion.

Scheme 2. Completion of (+)-Dalesconol B (2)[a]

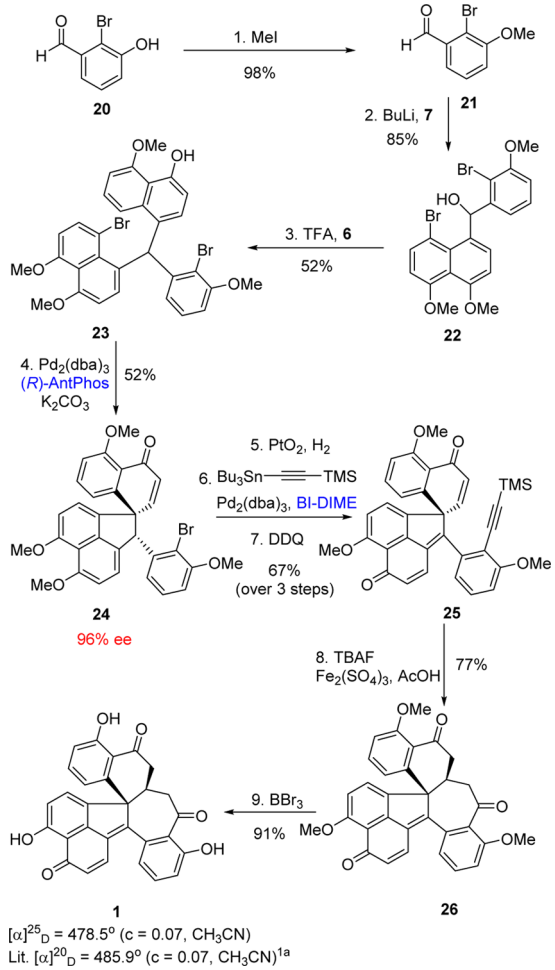


[a]Reagents and conditions: (7) PtO_2 (30 mol %), H_2 (10 atm), 25 °C (84%); (8) TMSC≡CSnBu_3 (3.0 equiv), $Pd_2(dba)_3$ (2.5 mol %), BI-DIME (5 mol %), toluene, 100 °C (89%); (9) DDQ (2.2 equiv), DCE, 80 °C (90%); (10) TBAF (2.0 equiv), THF, rt; then $Fe_2(SO_4)_3$ (10 mol %), AcOH/DCE, 60 °C (77%); (11) BBr_3 (1.5 M in DCM, 43 equiv), DCM, 35 °C (91%); DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBAF = tetrabutylammonium fluoride.

((tributylstannyl)ethynyl)silane proceeded smoothly with a Pd-BI-DIME catalyst[16] (5 mol %) to form compound **17** in 89% yield. Low conversions were observed when ligands PPh_3, *t*Bu-DPPF, and *t*Bu_3P were employed. A powerful 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation[17] of **17** formed both the enone and the *p*-naphthoquinone methide moieties of **18** in an excellent yield. Treatment with TBAF followed by hydrolysis under conditions of $Fe_2(SO_4)_3$/HOAc[18] automatically forged the seven-membered ring and formed **19** containing the full skeleton of dalesconol B. Finally, a global demethylation with BBr_3 completed the enantioselective synthesis of (+)-dalesconol B (**2**) from 1,8-dimethoxynaphthalene (**9**) through 11 linear steps and in 10% overall yield.

We then pursued the synthesis of (+)-dalesconol A (**1**), whose structure lacked only one hydroxyl group compared to that of dalesconol B (Scheme 3). However, the strategy of cyclization–bromination–kinetic resolution to form the enantiomerically pure all-carbon quaternary center employed in the synthesis of dalesconol B would not be well suited for the synthesis of dalesconol A due to a regioselectivity issue during the bromination step. Because of the same catalyst employed in both catalytic steps, we therefore implemented a one-pot enantioselective cyclization–kinetic resolution cascade of

Scheme 3. Completion of (+)-Dalesconol A (1)[a]



[a]Reagents and conditions: (1) MeI (3.0 equiv), K_2CO_3 (2.0 equiv), acetone, rt (98%); (2) **7** (1.0 equiv), *n*BuLi (1.05 equiv), THF, −78 °C; then **21** (1.1 equiv), −78 °C (85%); (3) **6** (1.1 equiv), TFA (1.8 equiv), DCM, −40 °C to rt (52%); (4) $Pd_2(dba)_3$ (3.0 mol %), (*R*)-AntPhos (8.0 mol %), K_2CO_3 (2.0 equiv), toluene, 100 °C (52%); (5) PtO_2 (30 mol %), H_2 (10 atm), 25 °C (84%); (6) TMSC≡CSnBu_3 (3.0 equiv), $Pd_2(dba)_3$ (2.5 mol %), BI-DIME (5 mol %), toluene, 100 °C (89%); (7) DDQ (2.2 equiv), DCE, 80 °C (90%); (8) TBAF (2.0 equiv), THF, rt; then $Fe_2(SO_4)_3$ (10 mol %), AcOH/DCE, 70 °C (77%); (11) BBr_3 (1.5 M in DCM, 40 equiv), DCM, 35 °C (91%).

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dibromide **23** by using a Pd-(*R*)-AntPhos catalyst. Thus, aldehyde **21** was prepared in 98% yield from phenol **20** by methylation. A nucleophilic addition followed by a Friedel–Crafts reaction with **6** furnished the dibromide **23** in 52% yield. Gratifyingly, the cyclization–kinetic resolution cascade proceeded smoothly at 100 °C for 20 h with K_2CO_3 as the base providing product **24** in 52% yield and 96% ee. It should be noted that the formation of only a single diastereomer **24** was observed in the reaction, and its optical purity started at ∼50% ee and reached 96% ee after the kinetic Heck process proceeded. The following steps for the synthesis of (+)-dalesconol A were similar to those for (+)-dalesconol B. Thus, a sequence of hydrogenation–Stille coupling–DDQ oxidation–hydrolysis cyclization cascade–global demethylation completed the enantioselective synthesis of dalesconol A, which consisted of 9 linear steps and an 11% overall yield from commercially available starting material **20**. Furthermore, the one-pot enantioselective cyclization–kinetic resolution cascade was also successfully applied to the synthesis of (+)-dalesconol B, leading to only 9 linear steps in its overall synthesis.

In conclusion, we have accomplished the first enantioselective syntheses of immunosuppressants (+)-dalesconol A and B in a highly efficient and concise manner, which features an unprecedented enantioselective palladium-catalyzed dearomative cyclization–kinetic resolution cascade to install the sterically congested chiral all-carbon quaternary center, an effective sterically hindered Stille coupling, a powerful DDQ oxidation to furnish all requisite unsaturation, and a tandem hydrolysis–Michael addition ring closure sequence. Both Dalesconol A and B can be prepared within 9 steps from commercially available starting materials with a scalable synthetic route, which should facilitate the discovery and the development of new immunosuppressants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00783.

Full experimental details, characterization data, NMR spectra of **1**, **2**, and related intermediates, chiral HPLC trace of **1** and related chiral intermediates (PDF)

Crystallographic data of **14a′** (CIF)

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†G.Z. and G.X. contributed equally.

Notes

The authors declare no competing financial interest.

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(12) See Supporting Information for rationale.

(13) Racemic **14a** was also subjected for kinetic resolution with a Pd-(*R*)-AntPhos catalyst. At 61% conversion of Heck cyclization, the enantiomerically enriched aryl bromide **14a′** was collected in 96% ee (S = 15).

(14) CCDC 1528560 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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