ORGANIC LETTERS

2011
Vol. 13, No. 17
4494–4497

A Concise Approach to the Dalesconol Skeleton

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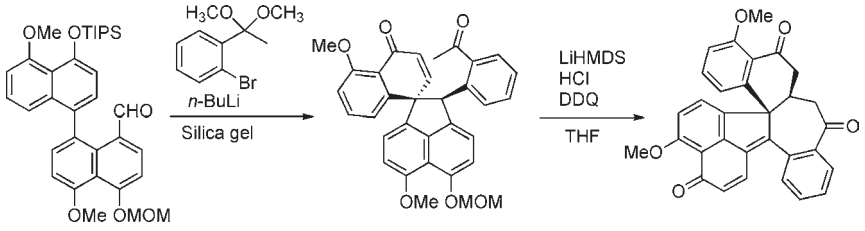
Received June 13, 2011

ABSTRACT



A rapid approach to the skeleton of dalesconol A and B, unprecedented immunosuppressants, has been achieved through a convergent strategy featuring a carbocation-mediated dearomatization−cyclization and a following one-pot consecutive operation.

Polyketides dalesconol A and B (Scheme 1) were initially isolated by Tan and co-workers in 2008 from *Daldinia eschscholzii*, and they were revealed to possess promising immunosuppressive activity, which is comparable to that of clinically used cyclosporine A, but with a significantly superior selectivity index (SI) (**1**, IC_{50} = 0.16 μg mL^{-1}, SI > 500; **2**, IC_{50} = 0.25 μg mL^{-1}, SI > 320; cyclosporine A, IC_{50} = 0.06 μg mL^{-1}, SI = 187).[1] It was found that the racemates of **1** and **2** have better immunosuppressive activity than that of their enantiomers. These compounds were also isolated by She, Lin, and co-workers from a marine-based endophytic fungus (Sporothrix sp. #4335) and named sporothrin A and B.[2] Compound **1** was found to be a potent acetylcholine esterase (AChE) inhibitor. In addition, both **1** and **2** showed modest antitumor activity against hepG2 cell lines. These biological activities make **1** and **2** attractive lead compounds for the development of pharmaceutical agents. Structurally, dalesconol A and B have an unprecedented carbon skeleton with seven fused 5-, 6-, and 7-membered rings. All these features make dalesconol A and B attractive synthetic targets. During the course of our synthetic studies toward dalesconol A and B, Snyder and co-workers reported the first and elegant total synthesis of these natural products.[3] Herein, we wish to report our own synthetic approach to the skeleton of dalesconol A and B (compound **3** in Scheme 1).

One of our retrosynthetic plans is shown in Scheme 1. The 7-membered ring ketone in **3** was envisioned to form via an intramolecular Michael addition of spiro enone **4**. Compound **4** might be obtained through a dearomatization−cyclization process from an intermediate such as **5**, which could be constructed by coupling of **6**, **8**, and **9**.

The synthesis of fragments **8** and **9** is described in Scheme 2. Both **8** and **9** can be obtained from **11**, which can be prepared on a multigram scale from commercially available **10**. Heating **10** in melted potassium hydroxide at 260 °C gave naphthalene-1,8-diol in 73% yield.[3,4] Naphthalene-1,8-diol was monomethylated with MeI

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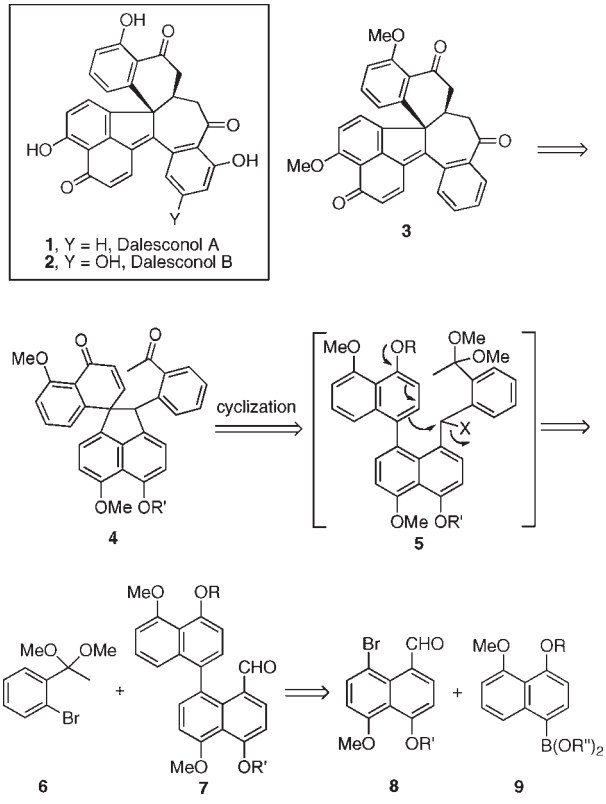
10.1021/ol2015847
Published on Web 08/01/2011

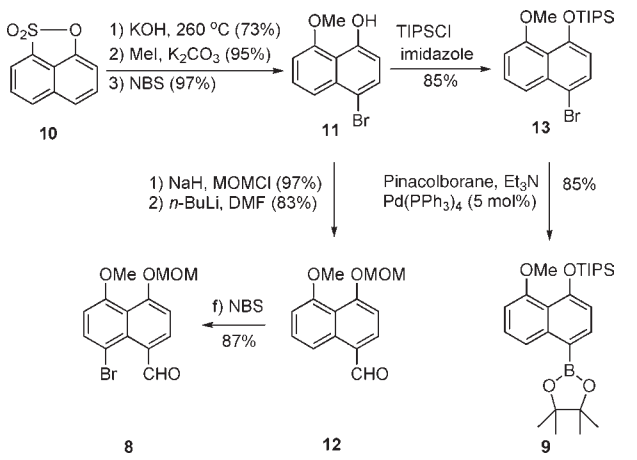
and K_2CO_3, and subsequently regioselectively brominated with NBS[3,5] in 95% and 97% yield, respectively. Upon protection with a MOM group (97% yield),[3] compound **11** was treated with *n*-BuLi and DMF to provide aldehyde **12** in 83% yield.[3] Fragment **8** was formed in 87% yield by a regioselective bromination of **12** with NBS in DMF at room temperature.[6] Alternatively, compound **11** was protected with chlorotriisopropylsilane to provide **13** in 85% yield,[7] which was then boronated with pinacolborane, triethylamine, and $Pd(PPh_3)_4$ at 90 °C to afford fragment **9** in 85% yield.[8] Fragment **6** was prepared from *o*-bromoacetophenone in 97% yield by ketalization.[9]

Scheme 1. Retrosynthetic Analysis of the Dalesconol Skeleton

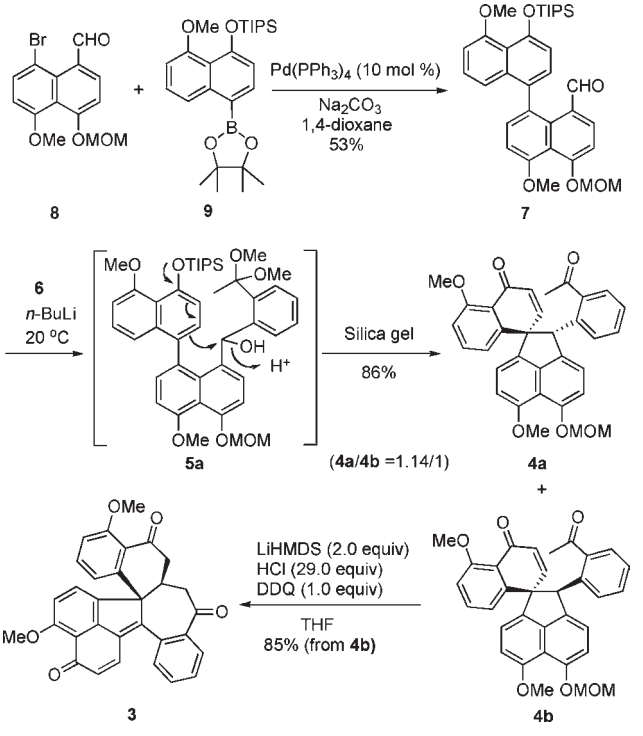


The synthesis of dalesconol skeleton **3** is outlined in Scheme 3. Fragments **8** and **9** were combined to give compound **7** in 53% yield via Suzuki–Miyaura coupling with 10 mol % $Pd(PPh_3)_4$ in the presence of Na_2CO_3.[8,10] Reacting aldehyde **7** with the anion generated from compound **6** by halogen–lithium exchange led to the formation

Scheme 2. Synthesis of Compounds **8** and **9**



Scheme 3. Synthesis of Compound **3**



of alcohol **5a**, which cyclized smoothly with concomitant deprotection of the methoxy ketal[11] to give two diastereoisomers **4a** and **4b** (**4a**:**4b** = 1.14:1) in 86% yield upon treatment with silica gel. The structures of **4a** and **4b** were confirmed by X-ray diffraction (Figures 1 and 2). Further studies showed that **4a** and **4b** behaved differently toward the subsequent intramolecular Michael addition reaction. No cyclization was observed for **4a** under various reaction conditions. However, to our delight, **4b** was readily

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converted to dalesconol skeleton **3** in overall 85% yield in one pot via intramolecular Michael addition (2.0 equiv of LiHMDS in THF at rt),[12] removal of MOM (concentrated HCl), and oxidation with DDQ.[13] The structure of compound **3** was established by X-ray diffraction (Figure 3).

The alkylative dearomatization of compound **5a** is the key step for the synthetic sequence, and its success is highly dependent upon the protecting groups and acid catalysts used. Various reaction conditions have been examined for this step, and some of them are shown in Table 1. For example, treating **5b** with various acids, such as HCl, TsOH, HOAc, led to a messy mixture (Table 1, entry 1). No cyclization was observed when **5a** was first desilylated with TBAF and subsequently treated with *n*-Bu_3P and DEAD (Table 1, entry 2).[14] However, the cyclization products **4a** and **4b** were obtained in 51% yield when **5a** was desilylated and then treated with silica gel (Table 1, entry 3). Subsequently, it was found that a higher yield (86%) was obtained when **5a** was directly treated with silica gel in CH_2Cl_2 at 40 °C (Table 1, entry 4). The dearomatization–cyclization process likely proceeded via a carbocation generated from the cleavage of the benzylic hydroxy group assisted by the weakly acidic silica gel. In this process, the Friedel–Crafts-type alkylation occurred at the *para*-position of the OTIPS group to form the spiro 5-membered ring.[15–19]

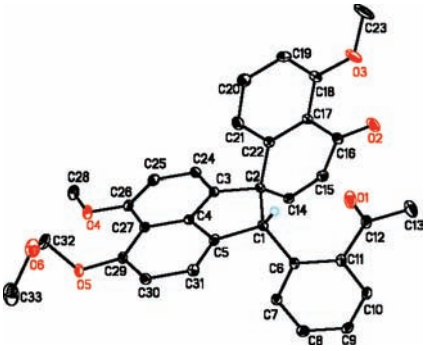


Figure 1. X-ray structure of compound **4a**.

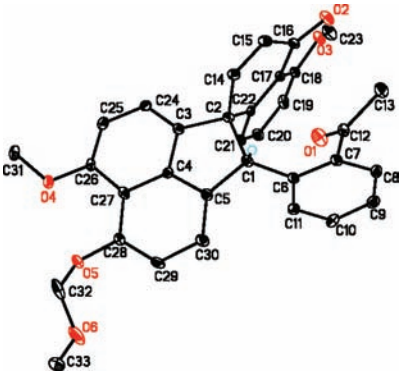


Figure 2. X-ray structure of compound **4b**.

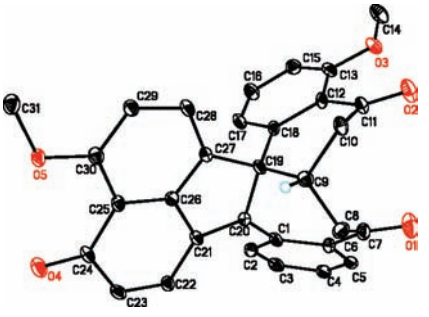
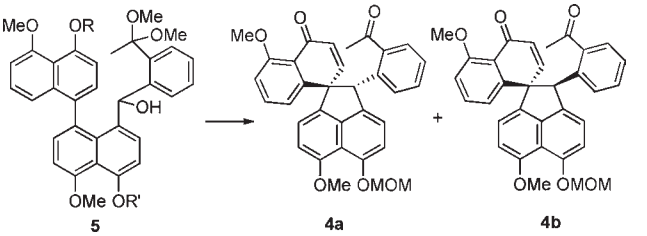


Figure 3. X-ray structure of compound **3**.

Table 1. Studies on the Alkylative Dearomatization



5 4a 4b

entry	5	protective group	reagent	yield (%) (4a+4b)
1	**5b**	R = MOM R′ = MOM	Acid[a]	0
2	**5a**	R = TIPS R′ = MOM	TBAF (*n*-Bu)$_3$P DEAD	0
3	**5a**	R = TIPS R′ = MOM	TBAF Silica gel	51
4	**5a**	R = TIPS R′ = MOM	Silica gel	86

[a] Such as HCl, TsOH, HOAc.

In summary, we have developed a convergent and concise synthetic approach to the dalesconol skeleton.

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The key ring structure and the quaternary carbon are constructed via a carbocation-mediated alkylative dearomatization and subsequent intramolecular Michael addition. Further improvement of this strategy and its application to the total synthesis of dalesconol A, B and their derivatives as well as biological activity studies are currently underway.

Acknowledgment. The authors gratefully acknowledge the National Basic Research Program of China (973 program, 2011CB808600) and the Chinese Academy of Sciences for financial support.

Supporting Information Available. Experimental procedure, characterization data, and X-ray structures of **4a**, **4b**, **3** along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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