Natural Products

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Total Syntheses of Dalesconol A and B**

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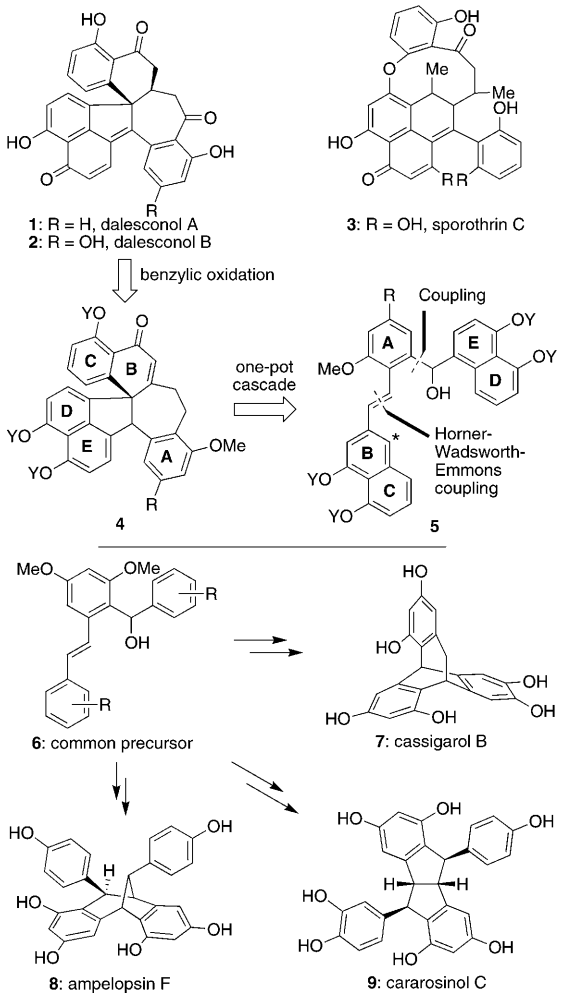
As part of a program seeking to identify new classes of potent immunosuppressants, Tan and co-workers recently isolated and characterized dalesconol A and B (**1** and **2**, respectively; Scheme 1) from a culture of *Daldinia eschsholzii* IFB-TL01 residing inside the gut of the mantis species *Tenodora aridifolia*.[1] Apart from possessing an unprecedented carbon-based skeleton containing seven fused rings of various sizes, these isolates indeed possessed immunosuppressive activity levels (IC_{50} values of 0.16 $\mu g\,mL^{-1}$ and 0.25 $\mu g\,mL^{-1}$ for **1** and **2**, respectively) comparable to that of the clinically utilized cyclosporine A ($IC_{50} = 0.06\ \mu g\,mL^{-1}$), but with significantly reduced background cytotoxicity.[2] Intriguingly, racemic mixtures of either **1** or **2** were found to be more potent than their separated enantiomers.[3] Subsequently, She, Lin, and co-workers obtained the same natural products **1** and **2**, from a marine-based endophytic fungus (*Sporothrix* sp. #4335) that grows on the inshore mangrove tree *Kandelia candel*, and named them sporothrin A and B;[4] they also isolated and characterized the related metabolite sporothrin C (**3**). Their activity screens revealed that **1** was a potent acetylcholinesterase inhibitor and that both **1** and **2** possessed modest antitumor activity. As such, members of this structurally novel natural product family could serve as valuable leads for future pharmaceutical development. In this communication, we describe the first total syntheses of dalesconol A and B (**1** and **2**) through an expedient and scalable route capable of providing the material supplies needed for more thorough biochemical applications.

As revealed in Scheme 1, our synthetic approach to **1** and **2** was based primarily on the idea that an appropriately protected form of **5** could be converted into the desired core (such as that represented by **4**) in a single, cascade operation. The key step would employ among its operations a Friedel–Crafts cyclization initiated by ionization of its hydroxy function and a subsequent oxidative C–C bond-forming event; these processes would utilize the starred carbon atom within **5** as both a nucleophile and electrophile to transform it into the lone quaternary center of the natural products. Subsequent adjustments in the oxidation state would then complete the target molecules. This overall analysis was inspired by our earlier studies towards members of the resveratrol class of oligomeric polyphenols,[5] wherein cascade operations using the structurally similar precursor **6** enabled the preparation of a number of architectures, including the [3.2.2]-, [3.2.1]-, and [3.3.0]-bicyclic frameworks of natural products **7**–**9**.[6] Therefore, if the envisioned cascade could be achieved (**5**→**4**), then the power of the general structural



Scheme 1. Retrosynthetic analysis of the dalesconols (**1** and **2**) based on an attempt to utilize key intermediate **5**, a variant of **6** which has already led to a variety of resveratrol-derived polycyclic natural products (**7**–**9**).

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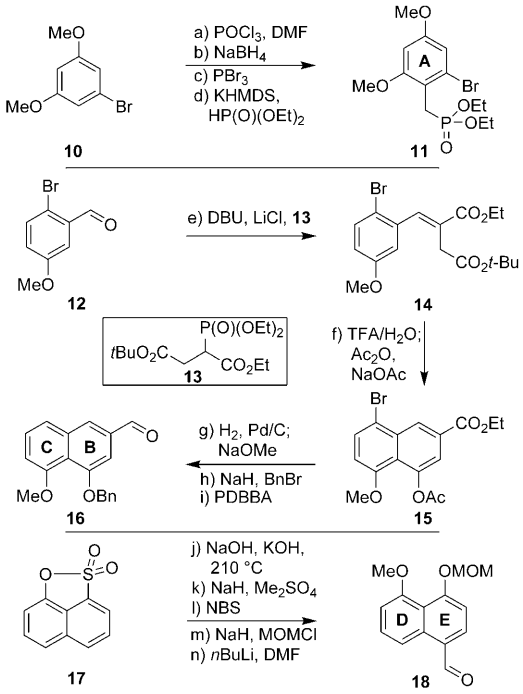
subtype represented by **5** and **6** as precursors to controllably access structurally and biosynthetically diverse architectures would be enhanced.

Our explorations to test this overall hypothesis began with the preparation of three phenolic precursors, which were anticipated to come together to form **5** through the retrosynthetic disconnections indicated in Scheme 1; dalesconol B (**2**) was specifically targeted. After several rounds of protecting group selections to achieve proper reactivity in later steps (see below), fragments **11**, **16**, and **18** were smoothly prepared from commercial materials in four, five, and five linear steps, respectively (Scheme 2). Given the conventional nature of many of these operations, a detailed discussion of the entire sequence is not warranted. However, we do wish to note the following: 1) each fragment was readily synthesized on multigram scale; 2) extensive efforts to form a variant of **14** by Stobbe condensations (with a free carboxylic acid instead of the *tert*-butyl ester) proved low yielding and capricious, particularly on scale;[7] 3) attempted DIBAL-H reduction of the ester within **15** into the aldehyde failed, with only PDBBA (formed by admixing DIBAL-H with KO*t*Bu)[8] giving the desired chemoselectivity;[9] and 4) commercial sultone **17** had to be recrystallized prior to use to achieve a high yielding alkali fusion reaction en route to **18**.[10]

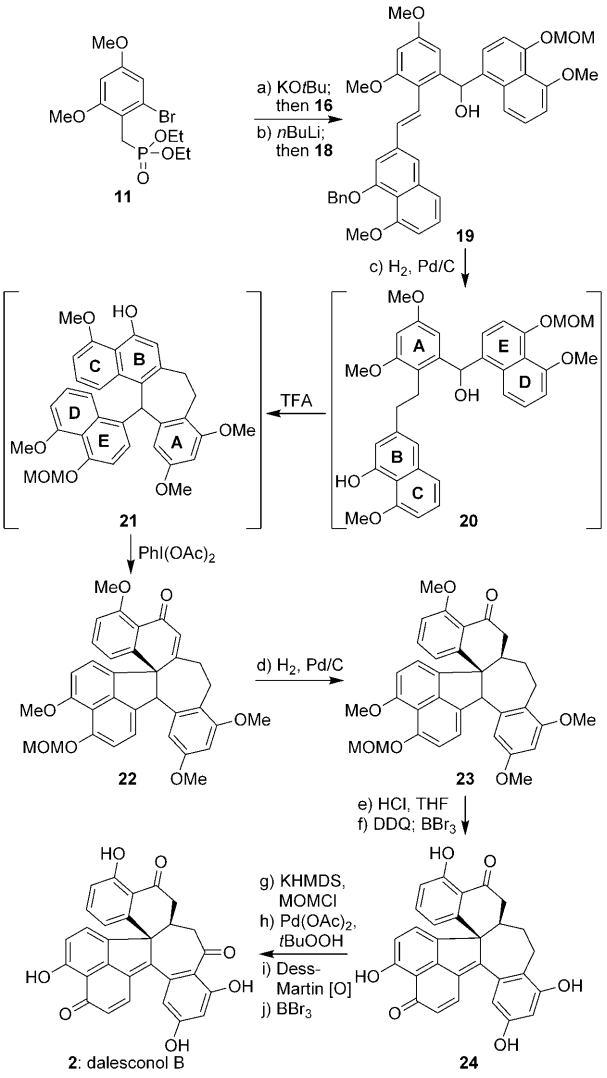


Scheme 2. Synthesis of key phenolic building blocks **11**, **16**, and **18**: a) $POCl_3$ (3.0 equiv), DMF (6.0 equiv), 90 °C, 6 h; aq. KOH, 0→25 °C, 12 h, 99%; b) $NaBH_4$ (2.0 equiv), MeOH, 0 °C, 30 min, 96%; c) PBr_3 (1.0 equiv), pyridine (cat.), Et_2O, 25 °C, 4 h, 96%; d) KHMDS (0.5 M in toluene, 1.8 equiv), $HP(O)(OEt)_2$ (2.0 equiv), 0 °C, 15 min; then starting material added, THF, 0→25 °C, 12 h, 94%; e) LiCl (1.3 equiv), DBU (1.0 equiv), **13** (1 equiv), CH_3CN, 25 °C, 12 h, 99%; f) TFA/H_2O (9:1), 25 °C, 90 min; NaOAc (1.4 equiv), Ac_2O, 140 °C, 1 h, 83%; g) H_2 (1 atm), Pd/C (10%), MeOH/CH_2Cl_2 (2:1), 25 °C, 24 h; filter, NaOMe (3.0 equiv), 0→25 °C, 2 h, 99%; h) NaH (2.0 equiv), BnBr (2.0 equiv), DMF, 0→25 °C, 1 h, 77%; i) PDBBA (0.9 equiv), THF, −20→0 °C, 1.5 h, 67%; j) NaOH/KOH/**17** (1:5:1 by weight), 210 °C, 40 min, 53%; k) NaH (1.0 equiv), THF, 0 °C, 10 min; Me_2SO_4 (1.0 equiv), 0→25 °C, 14 h, 99%; l) NBS (1.0 equiv), CH_3CN, 25 °C, 1 h, 98%; m) NaH (1.2 equiv), MOMCl (1.5 equiv), DMF, 0 °C, 1.5 h, 99%; n) *n*BuLi (1.6 M in hexanes, 1.2 equiv), THF, −78 °C, 20 min; DMF (4.0 equiv), THF, −78 °C, 1.5 h, 96%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N*,*N*-dimethylformamide, NBS = *N*-bromosuccinamide, PDBBA = potassium diisobutyl-*tert*-butoxyaluminum hydride, KHMDS = potassium bis(trimethylsilyl)amide, MOM = methoxymethyl, THF = tetrahydrofuran.

With these fragments in hand, they were then united into key intermediate **19** (a defined form of retron **5**, see Scheme 1) in 58% overall yield by an initial Horner–Wadsworth–Emmons olefination between the anion derived from **11** and aldehyde **16**, and subsequent halogen–lithium exchange and nucleophilic attack onto the aldehyde function of **18** (Scheme 3). As such, we could now test our ability to convert this material into the entire dalesconol framework. After extensive studies, this goal was indeed realized; Scheme 3 presents the sequence in its current level of optimization.

In the event, compound **19** was taken up in a mixture of EtOAc and EtOH (2:3) and subjected to 1 atmosphere of H_2 gas in the presence of a full equivalent of Pd/C (10%); under these specific conditions, the benzyl protecting group was excised and the double bond uniting the A and B rings was reduced in quantitative yield. Use of any other solvent combinations or ratios, as well as catalytic loadings of palladium, led to significant amounts of material in which the alcohol group on the carbon atom bridging the A and E rings was reduced as well. After filtration and solvent removal, the crude residue was resuspended in 2,2,2-trifluoroethanol and treated with a full equivalent of TFA at −45 °C for 15 minutes. During this time, the alcohol function was ionized, thereby initiating a Friedel–Crafts reaction which generated the seven-membered ring within **21**.[11] Subsequent addition of 1.1 equivalents of $PhI(OAc)_2$ to the same pot at −45 °C, and then 20 minutes of additional reaction time converted the strategically deprotected phenol (B ring) into an oxidized material with a *para*-disposed carbocation that was engaged by the D ring to fashion the complete dalesconol core as expressed in **22**.[12] Globally, these operations provided **22** in 32% yield upon isolation, thereby accounting for an overall efficiency level of 75% per step based on its four distinct operations.

Having completed this critical operation, the completion of dalesconol B (**2**) required several adjustments in oxidation state prior to removal of the phenolic protecting groups. The first of these events, hydrogenation of the double bond within **22**, occurred chemoselectively when performed in a 3:1 mixture of EtOH and EtOAc at 25 °C. This step provided **23** as a single diastereomer of unknown configuration in 84% yield;[13] other solvents or prolonged reaction times led to unwanted conversion of the benzylic ketone into the corresponding alcohol as well. After removal of the MOM-protecting group (HCl, THF) and DDQ-mediated oxidation[14] into the corresponding *para*-quinone methide, an X-ray crystal structure of the resultant intermediate (not shown, see the Supporting Information) confirmed the stereochemistry as that desired for the target structure and as drawn in

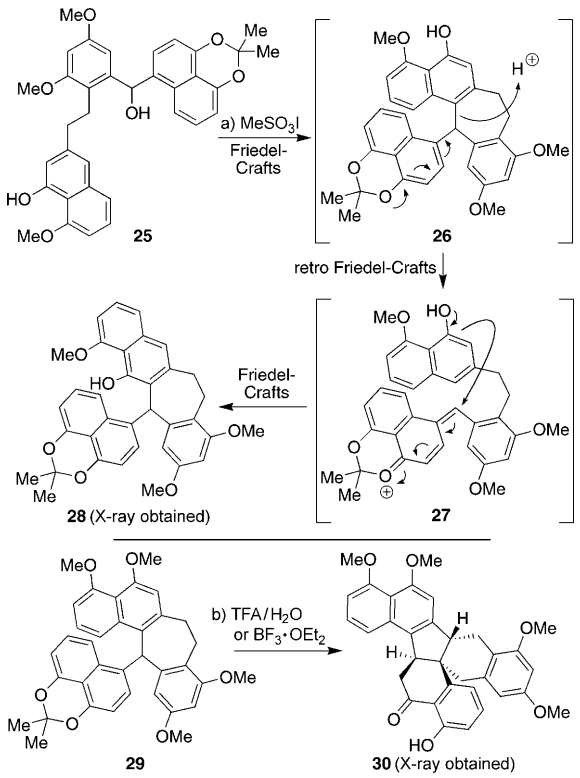


Scheme 3. Total synthesis of dalesconol B (**2**): a) KO*t*Bu (1.0 M in THF, 1.1 equiv), THF, −78 °C, 20 min; **16** (1.0 equiv), −78→25 °C, 2 h, 87%; b) *n*BuLi (1.6 M in hexanes, 1.5 equiv), THF, −78 °C; **18** (2.0 equiv), −78→25 °C, 4 h, 67%; c) H_2 (1 atm), Pd/C (10%, 1 equiv), EtOAc/EtOH (2:3), 25 °C, 45 min; filter, solvent removal, TFA (1.0 equiv), 2,2,2-trifluoroethanol, −45 °C, 15 min; $PhI(OAc)_2$ (1.1 equiv), −45 °C, 20 min, 32% overall; d) H_2 (1 atm), Pd/C (10%, 1.0 equiv), EtOH/EtOAc (3:1), 25 °C, 3–10 h, 84%; e) conc. HCl (40 equiv), THF, 0→25 °C, 3 h, 99%; f) DDQ (0.97 equiv), CH_2Cl_2, 25 °C, 1 h; −78 °C, BBr_3 (1.0 M in CH_2Cl_2, 25 equiv), −78→0 °C, 12 h, 73%; g) KHMDS (0.5 M in THF, 5.0 equiv), MOMCl (20 equiv), THF, 0 °C, 20 min, 91%; h) $Pd(OAc)_2$ (1.0 equiv), *t*BuOOH (25 equiv), K_2CO_3 (10 equiv), CH_2Cl_2, 72 h, 25 °C, 42%; i) Dess–Martin periodinane (5.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 2 h, 99%; j) BBr_3 (1.0 M in CH_2Cl_2, 25 equiv), CH_2Cl_2, −78 °C, 15 min, 73%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

compound **23**. In practice, however, the DDQ oxidation step was followed directly by exposure to BBr_3 in the same pot to unveil all the phenols, thereby providing **24**, which required a benzylic oxidation adjacent to the A ring to reach the target structure.

Though simply stated, this final operation proved challenging to effect as no oxidation protocol with the free phenols of **24** led to the desired product; either the starting material was recovered unchanged or complete decomposition was observed. After reprotection of all the phenols as MOM ethers, however, exposure of the resultant material to $Pd(OAc)_2$, K_2CO_3, and *tert*-butylhydrogen peroxide in CH_2Cl_2 in an open flask at 25 °C over 3 days[15] uniquely effected conversion of the desired methylene into a benzylic alcohol.[16] Interestingly, no ketone or hydroperoxide products were observed for this transformation, a result counter to previous literature reports; this result, we believe, is indicative of the truly unique nature of the seven-membered ring within these molecules and perhaps explains the numerous failed attempts in achieving its oxidation. In any event, with an alcohol finally installed, additional oxidation with Dess–Martin periodinane and MOM removal with BBr_3 in CH_2Cl_2 completed the target molecule **2** in 73% overall yield.[17] Therefore, a total of 15 linear operations, with only half of these occurring after the preparation of key intermediate **19**, were needed to achieve the total synthesis. To date, over 20 mg of dalesconol B (**2**) have been prepared.

It is important to stress, however, that the sequence delineated above, particularly the cascade-based sequence converting **19** into **22**, required several generations of approaches to achieve. The main challenge, as we observed on numerous occasions, was that subtle alteration of reaction conditions or the mere alteration or absence of a single protecting group afforded a number of unanticipated skeletal rearrangements. For instance, exposure of a molecule with a free phenol on the B ring (**25**, Scheme 4) to a stronger acid



Scheme 4. Selected challenges encountered in executing the cascade-based construction of the dalesconol core: skeletal rearrangements deriving from differential protection of the phenols: a) $MeSO_3H$ (10 equiv), CH_2Cl_2, −78→0 °C, 1 h, 77%; b) TFA/H_2O (9:1), 25 °C, 24 h or BF_3·OEt_2 (10 equiv), CH_2Cl_2, −78→25 °C, 7 h, 59%.

than used above ($MeSO_3H$ in CH_2Cl_2) led to an alternate seven-membered ring adduct (**28**). As indicated, we believe this structure, one whose connectivities were confirmed by X-ray crystallographic analysis, is the product of a retro-Friedel–Crafts/Friedel–Crafts sequence as **26** was observed during the course of the reaction, though it could not be isolated in any significant quantity. On the basis of the evaluation of a number of X-ray crystal structures of related intermediates, materials of general architecture **28** appear to have significantly less steric strain than those like **26**.[18] Indeed, even **21** (see Scheme 3) can rearrange into such products if appropriate care is not taken (in terms of total reaction time, temperature, or equivalents of acid used). Similarly, when efforts were made to deprotect the ketal within compound **29** and similar materials having a protected B ring (which prevented their initial rearrangement into materials like **28**), both protic and Lewis acidic conditions led to deprotection and concomitant rearrangement to unique polycycle **30**. The exact mechanism for this event is the subject of current investigations.

Finally, we wished to determine if the developed sequence could be applied to prepare dalesconol A (**1**) as well. As shown in Scheme 5, that goal was achieved starting with phosphonate **31**,[19] obtained from *ortho*-anisaldehyde, through the same general sequence of events as described above for dalesconol B (**2**). Interestingly, though there is one fewer phenol in the A ring within all of these intermediates, no fundamental change in reactivity was observed, though some differences in reaction time and temperature were required for individual steps to reach completion. As a testament to the strength of the developed chemistry, our first attempt to execute this sequence, in which we started with just 100 mg of *ortho*-anisaldehyde, led to the preparation of a characterizable amount of dalesconol A (**1**). The yields and experimental description for this synthesis in the Supporting Information represent additional, larger pushes of material.

In conclusion, we have developed a short, direct route to dalesconols A and B (**1** and **2**) that is capable of providing both natural products, as well as several analogues, to enable a more comprehensive evaluation of their biochemical potential. Key elements of the sequence include a one-pot cascade which sequentially forged two rings and the lone quaternary carbon to complete the entire polycyclic core of the targets from an acyclic material, a unique benzylic oxidation to fashion the final oxygen atoms of the targets, and the demonstration that alteration in phenol protecting group or reaction conditions could afford a number of unique structures in addition to the target molecules. Indeed, the ability to obtain not only **22**, but also **28** and **30** from intermediates having the general structures **5** and **6**, reaffirms their power as privileged starting materials for the controlled generation of a variety of distinct architectures.[20]

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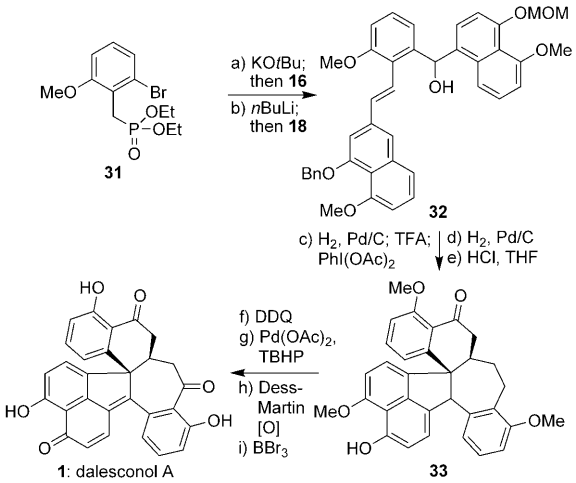

Scheme 5. Total synthesis of dalesconol A (**1**): a) KO*t*Bu (1.0 M in THF, 1.1 equiv), THF, −78 °C, 20 min; **16** (1.0 equiv), −78→25 °C, 3 h, 79%; b) *n*BuLi (1.6 M in hexanes, 1.5 equiv), THF, −78 °C; **18** (2.0 equiv), −78→25 °C, 4 h, 51%; c) H_2 (1 atm), Pd/C (10%, 1 equiv), EtOAc/EtOH (2:3), 25 °C, 1 h; filter, solvent removal, TFA (1.0 equiv), 2,2,2-trifluoroethanol, −45 °C, 15 min; $PhI(OAc)_2$ (1.1 equiv), −45 °C, 20 min, 27% overall; d) H_2 (1 atm), Pd/C (10%, 1.0 equiv), EtOH/EtOAc (3:1), 25 °C, 3–10 h, 65%; e) conc. HCl (30 equiv), THF, 0→25 °C, 2 h, 99%; f) DDQ (1.1 equiv), benzene, 25 °C, 30 min, 77%; g) $Pd(OAc)_2$ (1.0 equiv), *t*BuOOH (25 equiv), K_2CO_3 (10 equiv), CH_2Cl_2, 72 h, 25 °C, 41%; i) Dess–Martin periodinane (5.0 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 2 h, 99%; j) BBr_3 (1.0 M in CH_2Cl_2, 15 equiv), CH_2Cl_2, −78→25 °C, 5 h, 66%.

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[2] For a recent total synthesis of cyclosporin A, see: X. Wu, J. L. Stockdill, P. Wang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 4098–4100.

[3] This unique biological activity can perhaps be explained if both enantiomers can enter the binding pocket, a phenomenon that was only just recently observed: M. Mentel, W. Blankenfeldt, R. Breinbauer, *Angew. Chem.* **2009**, *121*, 9248–9251; *Angew. Chem. Int. Ed.* **2009**, *48*, 9084–9087.

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[7] For a related Stobbe condensation, see: a) J. L. Bloomer, K. W. Stagliano, J. A. Gazzillo, *J. Org. Chem.* **1993**, *58*, 7906–7912. The preparation and use of phosphonate **13** was inspired by the following article: b) M. Tamiya, K. Ohmori, M. Kitamura, H. Kato, T. Arai, M. Oorui, K. Suzuki, *Chem. Eur. J.* **2007**, *13*, 9791–9823.

[8] a) M. Chae, J. Song, D. An, *Bull. Korean Chem. Soc.* **2007**, *28*, 2517–2518. The sodium and lithium analogs have been made as well: b) J. I. Song, D. K. An, *Chem. Lett.* **2007**, *36*, 886–887;

c) M. S. Kim, Y. M. Choi, D. K. An, *Tetrahedron Lett.* **2007**, *48*, 5061 – 5064.

[9] A sequence using $LiAlH_4$ to completely reduce the ester of **15**, followed by Dess–Martin oxidation, afforded a commensurate yield of product, albeit at the cost of an additional synthetic step.

[10] For recent uses of the alkali fusion reaction, see: a) M. Poirier, M. Simard, J. D. Wuest, *Organometallics* **1996**, *15*, 1296 – 1300; b) S. A. Snyder, Z.-Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744 – 5745.

[11] With the double bond present, or with any oxidized form of the double bond, the desired Friedel–Crafts cyclization could not be achieved. Therefore, a reduction was required before a penultimate oxidation event to complete the targets. This change proved absolutely necessary in this case.

[12] The use of $PhI(OAc)_2$ to forge such types of systems is, of course, well known. For selected examples, see: a) Y. Kita, T. Takada, M. Gyoten, H. Tohma, M. H. Zenk, J. Eichhorn, *J. Org. Chem.* **1996**, *61*, 5857 – 5864; b) Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada, H. Tohma, T. Takada, *J. Org. Chem.* **1998**, *63*, 6625 – 6633; c) H. Tohma, H. Morioka, S. Takizawa, M. Arisawa, Y. Kita, *Tetrahedron* **2001**, *57*, 345 – 352; d) I. R. Baxendale, S. V. Ley, C. Piutti, *Angew. Chem.* **2002**, *114*, 2298 – 2301; *Angew. Chem. Int. Ed.* **2002**, *41*, 2194 – 2197; e) C. J. Lion, D. A. Vasselin, C. H. Schwalbe, C. S. Matthews, M. F. G. Stevens, A. D. Westwell, *Org. Biomol. Chem.* **2005**, *3*, 3996 – 4001; f) I. R. Baxendale, J. Deeley, C. M. Griffiths-Jones, S. V. Ley, S. Saaby, G. K. Tranmer, *Chem. Commun.* **2006**, 2566 – 2568; g) D. R. Kelly, S. C. Baker, D. S. King, D. S. de Silva, G. Lord, J. P. Taylor, *Org. Biomol. Chem.* **2008**, *6*, 787 – 796. However, to the best of our knowledge, the transformation has never been used in such a cascade event as described here. For excellent reviews on such reactions in synthesis, see: h) L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235 – 2261; i) S. Quideau, L. Pouységu, D. Deffieux, *Curr. Org. Chem.* **2004**, *8*, 113 – 148.

[13] Molecular modeling suggested that there would be a preference for the desired approach of hydrogen in this reaction, though the overall bias was not profound. For precedent that the desired hydrogenation could be achieved without loss of the benzylic ketone, see: a) T. Kametani, H. Kondoh, M. Tsubuki, T. Honda, *J. Chem. Soc. Perkin Trans. 1* **1990**, 5 – 10; b) D. H. Miles, D.-S. Lho, V. Chittawong, A. M. Payne, *J. Org. Chem.* **1990**, *55*, 4034 – 4036. Nevertheless, this reaction could be capricious, with over-reduction easily achieved if the reaction was not carefully monitored, particularly on scale-up.

[14] For a general reference on DDQ, see: D. R. Buckle in *Encyclopedia of Reagents for Organic Synthesis*, *Vol. 3* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 1299 – 1704.

[15] a) J.-Q. Yu, E. J. Corey, *Org. Lett.* **2002**, *4*, 2727 – 2730; b) J.-Q. Yu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 3232 – 3233.

[16] Only one other oxidant, $Mn(OAc)_3$, delivered similar material without the formation of significant amounts of by-products: T. K. M. Shing, Y.-Y. Yeung, P. L. Su, *Org. Lett.* **2006**, *8*, 3149 – 3151. Other oxidants that failed to effect this transformation include DDQ (in the presence and absence of water), the Jones reagent, Ag_2O, *N*-bromosuccinimide, and ceric ammonium nitrate (CAN).

[17] The permethylated form of **24** could also be oxidized into a ketone over two steps under the reported conditions; however, despite numerous attempts, it could never be fully deprotected to give dalesconol B (**2**); the nonhydrogen-bound phenol within ring A proved resistant to cleavage over several attempts.

[18] See the Supporting Information section for these structures. Based on MMFF94 calculations, rearranged compound **28** is approximately 6.8 kcal mol^{-1} more stable than **26**.

[19] See the Supporting Information section for the synthetic route.

[20] For a recent review on the concept of privileged architectures in drug discovery and development, see: M. Welsch, S. A. Snyder, B. S. Stockwell, *Curr. Opin. Chem. Biology* **2010**, *14*, 347 – 361.

