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Total Synthesis of Virgatolide B

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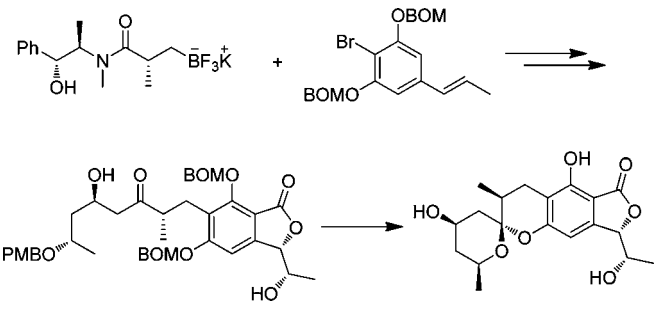
ABSTRACT



The first total synthesis of the benzannulated spiroketal virgatolide A is presented. Key features include sp^3-sp^2 Suzuki coupling of an enantiomerically enriched β-trifluoroboratoamide and an aryl bromide, regioselective intramolecular carboalkoxylation, and a 1,3-*anti*-selective Mukaiyama aldol reaction followed by global deprotection/cyclization with regioselectivity governed by internal hydrogen bonding.

In 2011, Che et al. reported the isolation and characterization of three novel structurally related spiroketals[1] from the endophytic fungus *Pestalotiopsis virgatula* (L147). Virgatolides A–C (**1**–**3**) (Figure 1) contain a common tetracyclic core and differ only in their stereochemistry and substitution at C-4 and C-13. The absolute stereochemical configurations of these natural products were inferred by comparison of their CD spectra to those of pestaphthalides A and B.[2] Preliminary biological data revealed that the compounds exhibit moderate cytotoxicity against HeLa (cervical epithelium) cells with IC_{50} values of 19.0, 22.5, and 20.6 μM, respectively.[1] To date, no total synthesis of the virgatolide family has been reported. Herein, we present the first enantioselective total synthesis of virgatolide B (**2**).

Disconnection of the spiroketal moiety in **2** affords the corresponding dihydroxyketone **4** (Scheme 1). In order to avoid acid-catalyzed elimination of the sensitive β-hydroxy moiety of **4**,[3] a synthetic route was developed that facilitated global deprotection/cyclization under mild conditions.

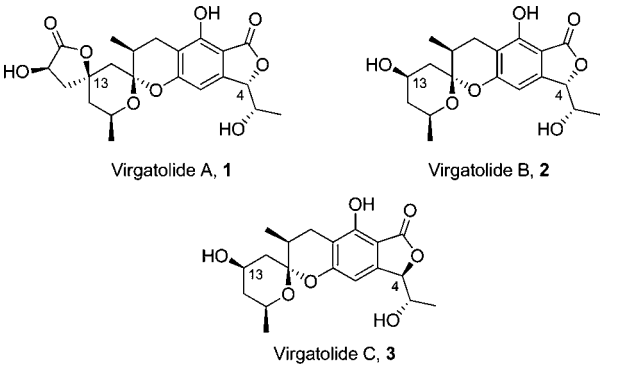


Figure 1. Virgatolides A–C, **1**–**3**.

We hypothesized that intramolecular hydrogen bonding between the phthalide carbonyl and the neighboring phenol would allow differentiation of the two possible spiroketal regiosiomers, facilitating selective formation of **2**. In turn, ketone **4** would be accessed by a 1,3-*anti*-selective Mukaiyama aldol reaction[4] between methyl ketone **6** and

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(2) Ding, G.; Liu, S.; Guo, L.; Zhou, Y.; Che, Y. *J. Nat. Prod.* **2008**, *71*, 615.

(3) (a) Yuen, T.-Y.; Yang, S.-H.; Brimble, M. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8350. (b) Initial studies toward **2** used ethoxymethyl (EOM) instead of benzyloxymethyl (BOM) as a protecting group for the phenolic OH groups. It was found that acid-catalyzed removal of the EOM groups caused degradation of the starting material.

(4) (a) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (b) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

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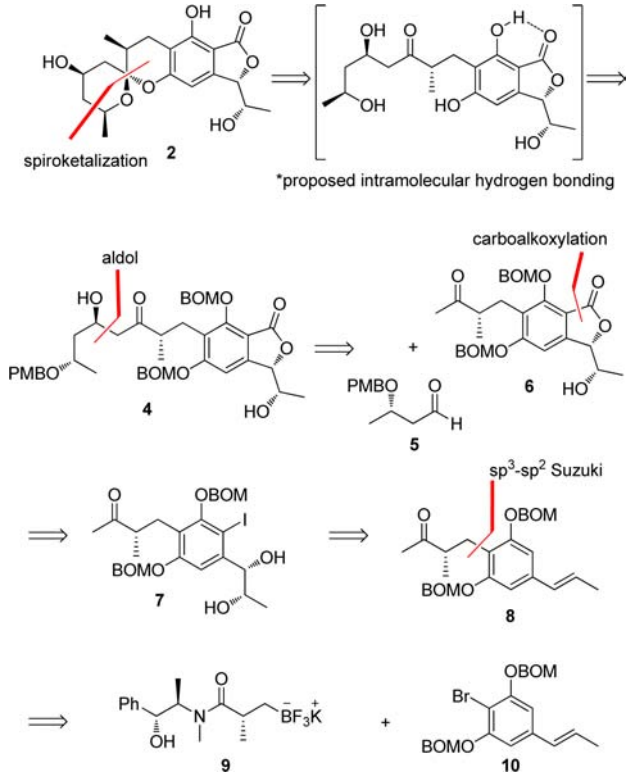
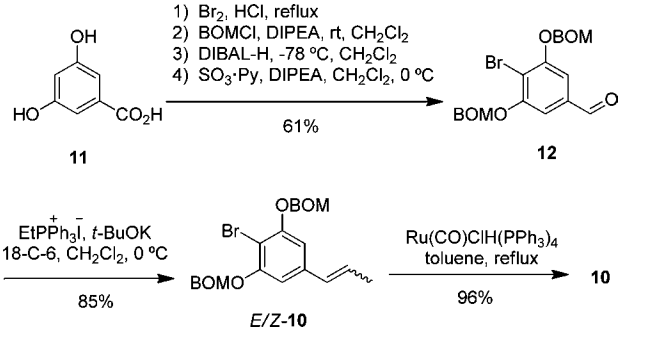
PMB protected (*S*)-3-hydroxybutanal **5**. The phthalide subunit present in **6** was to be constructed from iodide **7** by intramolecular carboalkoxylation.[5] Iodide **7** would be assembled *via* Sharpless asymmetric dihydroxylation[6] of alkene **8** followed by iodination.

Scheme 1. Retrosynthetic Analysis



Alkene **8** contains a synthetically challenging α-chiral *β*-arylated ketone. There is a scarcity of direct methods for the construction of such motifs,[7] which are most commonly accessed by benzylation of enolates,[8] conjugate addition of aryl organometallics,[9] Negishi cross-coupling,[10] or catalytic asymmetric hydrogenation of α,*β*-unsaturated carbonyls.[11] Each of these methods suffers from various drawbacks.[7] Our synthetic strategy sought to utilize methodology recently developed by Molander et al. for the Suzuki cross-coupling of enantiomerically enriched potassium *β*-trifluoroboratoamide **9**[7] with aryl bromide **10**.

Scheme 2. Synthesis of Bromide **10**



Construction of aryl bromide **10** began from commercially available 3,5-dihydroxybenzoic acid **11** (Scheme 2). Bromination,[12] BOM protection, and adjustment of the oxidation state gave aldehyde **12** in 61% yield over four steps. Wittig reaction of **12** with ethyltriphenylphosphonium iodide afforded **10** in 85% yield as an inseparable mixture of *E*/*Z* isomers. Isomerization of *E*/*Z*-**10** using catalytic $Ru(CO)ClH(PPh_3)_3$ in refluxing toluene[13] provided isomerically pure **10** in 96% yield.

Trifluoroboratoamide **9** has been prepared by Molander et al. by alkylation of amide **16** with iodide **15** and conversion of the pinacol boronate species **17** to the trifluoroborate salt **9**.[7] Preparation of iodide **15** by alkylation of isopropylpinacolboronate[14] proved inefficient and required two distillations. We were pleased to find that the use of Brown's method[15] provided **15** in sufficient purity simply by treatment of boronate **14** with pinacol, washing the organic layer with water, and subsequent concentration *in vacuo* (Scheme 3). Alkylation of amide **16**[16] with **15** followed by conversion to the trifluoroborate with KHF_2 according to Molander's procedure afforded **9** in high yield and excellent diastereoselectivity.[7] The diastereoselectivity was >95:5 by ^1H NMR analysis of **17**, and the values of the spectroscopic data and optical rotation value for **9** compared well to the literature values.[7]

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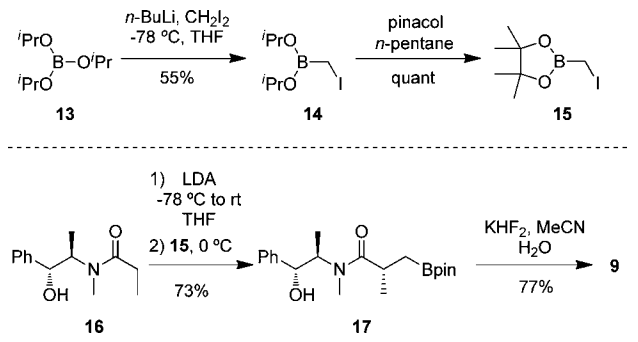
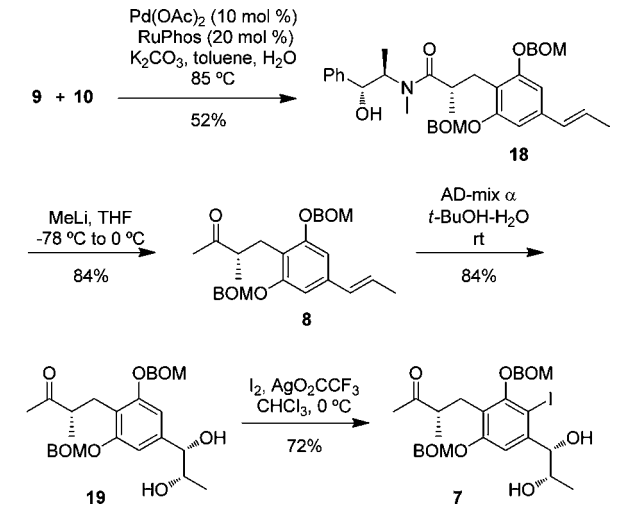
Scheme 3. Synthesis of Trifluoroboratoamide **9**



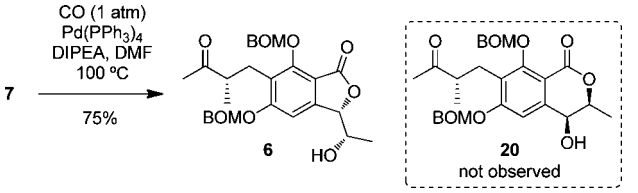
Scheme 4. Synthesis of Iodide **7**



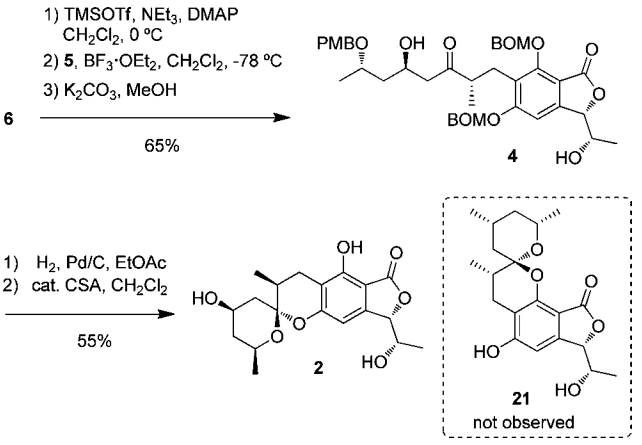
Gratifyingly, despite the use of a sterically demanding, electron-rich aryl bromide, Suzuki coupling of **9** and **10** proceeded cleanly using $Pd(OAc)_2$ and RuPhos,[17] furnishing amide **18** (Scheme 4). We believe this provides the first demonstrated use of Molander's trifluoroboratoamide Suzuki cross-coupling methodology in a total synthesis. Conversion of **18** to methyl ketone **8** with methyllithium[16] proceeded in high yield without significant loss of material due to double alkylation. Sharpless asymmetric dihydroxylation[6] of **8** using AD-mix α afforded diol **19** in high yield as a single diastereoisomer by ^1H NMR. Selective monoiodination of the aromatic ring afforded iodide **7** with a trace amount of the easily separable di-iodinated product.

Carbonylation of iodide **7** with concomitant intramolecular alkoxylation[5] afforded phthalide **6** in 75% yield (Scheme 5). Pleasingly, the intramolecular cyclization completely favored formation of phthalide **6** over isochromanone **20**, even at the elevated temperature at which the reaction was conducted, indicating a strong kinetic preference for 5-membered ring formation. To the best of our

Scheme 5. Formation of Phthalide **6**



Scheme 6. Synthesis of Virgatolide B, **2**



knowledge this is the first reported palladium-catalyzed carboalkoxylation where both 5- and 6-membered cyclization products are possible.

Attention next turned to the key aldol reaction to unite methyl ketone **6** with aldehyde **5** using a Mukaiyama protocol.[18] Simultaneous conversion of **6** to the TMS enol ether and protection of the secondary alcohol as a TMS ether was effected with TMSOTf (Scheme 6). The crude enol ether was then added to a preformed complex of aldehyde **5** and $BF_3 \cdot OEt_2$ in dichloromethane at −78 °C. On completion of the reaction, the crude aldol adduct was dissolved in methanol and treated with saturated aqueous potassium carbonate to liberate the latent alcohol functionality. Ketone **4** was isolated in 65% yield over three steps with excellent diastereoselectivity (single diastereomer by ^1H and ^{13}C NMR). Finally, global deprotection of the two BOM groups and the PMB group under hydrogenolysis followed by equilibration with a catalytic amount of CSA yielded virgatolide B, **2**, in 55% over two steps. Pleasingly, the spiroketal isomer **21** produced by cyclization of the other phenolic oxygen *peri* to the phthalide carbonyl was not observed.

Spectroscopic data (^1H NMR, ^{13}C NMR, and HRMS analyses) for synthetic virgatolide B, **2**, were in full agreement with those reported for the natural product.[1] Furthermore, the absolute stereochemistry of naturally occurring virgatolide B was confirmed by comparison of

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the optical rotation values ($[\alpha]^{25}_{D}$ +19.1 (*c* 0.25 in MeOH)), {lit. +25.0, (*c* 0.07 in MeOH)}.

In summary, the first total synthesis of virgatolide B, **2**, has been achieved *via* a highly convergent synthesis. Key features include the first example of Suzuki coupling of a chiral trifluoroboratoamide in a total synthesis,[7] the first example of an intramolecular carboalkoxylation to form a phthalide where formation of an isochromanone is also possible,[5] and a 1,3-*anti*-selective Mukaiyama aldol reaction.[4,18] Preservation of the rotational symmetry about the aromatic ring enabled the requirement for regioselectivity to be delayed until control could be governed by intramolecular hydrogen-bonding interactions. The overall approach is enantioselective, scalable, and highly amenable to the construction of analogues and the remaining members of this novel family of natural products.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.