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Synthetic Approach to Wortmannilactone C

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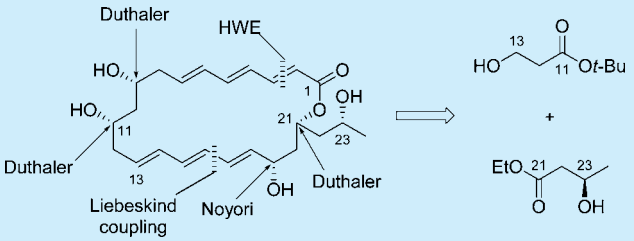
Supporting Information

ABSTRACT: A diastereomer of wortmannilactone C has been synthesized according to a convergent and versatile strategy from *tert*-butyl 3-hydroxypropanoate and ethyl (*R*)-3-hydroxybutanoate. The key steps are a Liebeskind cross-coupling and a Horner–Wadsworth–Emmons (HWE) reaction to construct the macrolactone. The stereogenic centers at C9, C11, and C21 were controlled by enantioselective allyltitanations, and the C19 stereocenter was controlled by using a Noyori reduction of an acetylenic ketone.



Biologically active compounds can be of different origins such as plants, animals, or fungi and particularly soil filamentous fungi which are prolific sources of bioactive natural products.[1,2] In 2006, it was reported that an isolate of the fungus *Talaromyces wortmannii*, which was collected from the soil in Xishuangbanna in the Yunnan province in China, contains four novel 22-membered lactones, wortmannilactones A–D.[3] Later on, *Talaromyces wortmannii* was cultured in Erlenmeyer flasks, and after 14 days at 27 °C, the solid culture was extracted with ethyl acetate; the extract was separated to afford wortmannilactones A–D in a ratio of 71:9:13:7 (Figure 1).

As part of our work on the synthesis and on the establishment of structure of natural products by total synthesis,[4,5] we became interested in the synthesis of wortmannilactone C which presents cytotoxic activity against a panel of human cancer cell lines.[6] The planar structure of wortmannilactone C was established by NMR (^{1}H, ^{13}C, COSY, HMQC, HMBC); however, the configuration of the stereogenic centers at C9, C11, C19, C21, and C23 was not established. Arbitrarily, we decided to attribute the *R*, *S*, *S*, *R*, *R* configuration respectively to the C9, C11, C19, C21, and C23 stereogenic centers based on the stereogenic centers at the same positions of dolabelide B which is also a 22-membered ring lactone (Figure 2).[7]

Here, we would like to report a convergent strategy and a potential modular access to all the stereoisomers of wortmannilactone C from **Fragments A** and **B** which would be assembled using a Liebeskind cross-coupling and by employing a Horner–Wadsworth–Emmons (HWE) olefination to construct the macrocycle. The synthesis of **Fragment A** was planned from *tert*-butyl 3-hydroxypropanoate **2**, and the stereogenic centers at C9 and C11 would be controlled using enantioselective allyltitanations. **Fragment B** would be synthesized from ethyl (*R*)-3-hydroxybutanoate **12**. The stereogenic center present in **12** would correspond to the C23 stereogenic center of wortmannilactone C, and the stereogenic centers at C21 and C19 would be respectively controlled by utilizing an enantioselective allyltitanation and a Noyori reduction of an acetylenic ketone (Scheme 1).

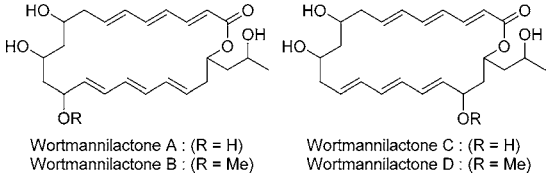


Figure 1. Structures of wortmannilactones A–D.

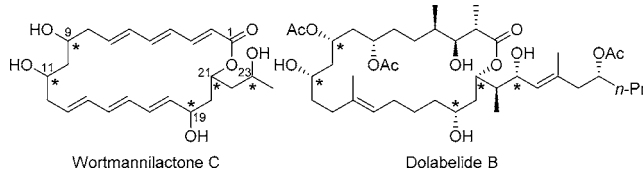
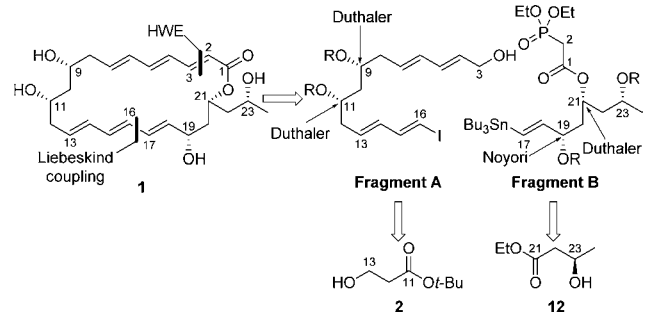


Figure 2. Structures of wortmannilactone C and dolabelide B.

Scheme 1. Retrosynthetic Analysis



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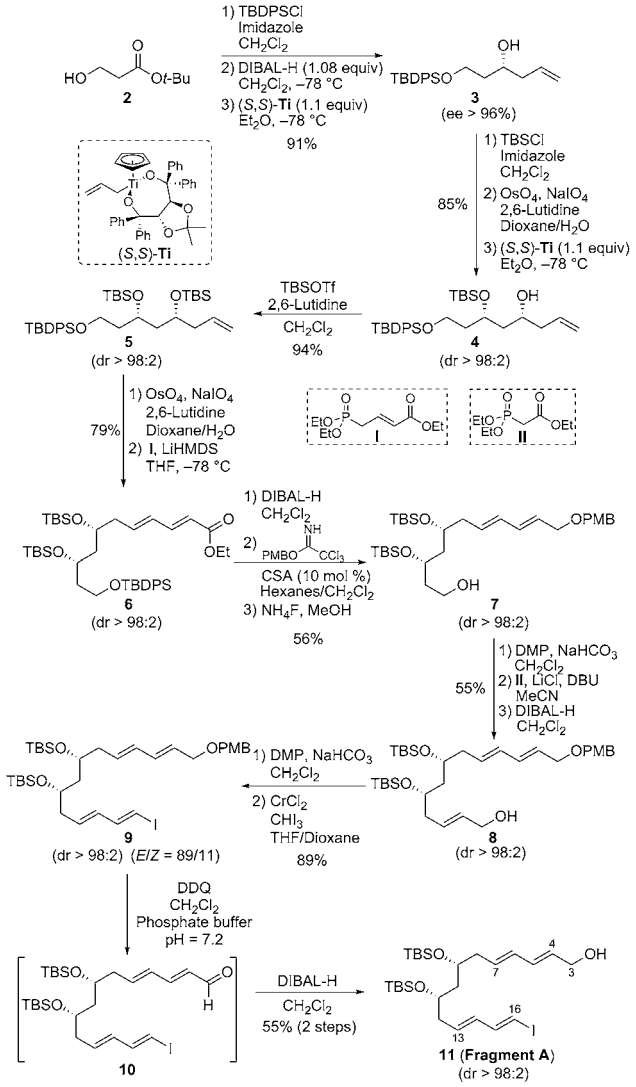
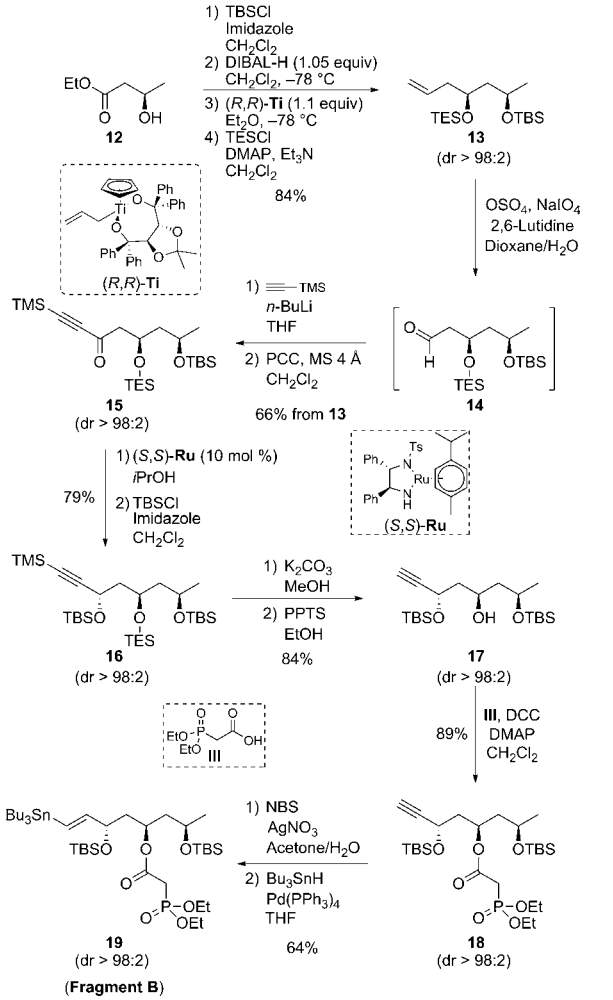
Scheme 2. Synthesis of Compound 11 (Fragment A)



Scheme 3. Synthesis of Compound 19 (Fragment B)



The synthesis of **Fragment A** started with the transformation of *tert*-butyl 3-hydroxypropanoate **2** to the optically active homoallylic alcohol **3** in three steps. After protection of the hydroxyl group [TBDPSCl (1.2 equiv), imidazole (2 equiv), CH_2Cl_2, 0 °C to rt], followed by reduction by DIBAL-H (1.08 equiv, CH_2Cl_2, −78 °C, 2 h), the obtained unstable aldehyde was treated with the allyltitanium complex (*S*,*S*)-**Ti** (1.1 equiv, Et_2O, −78 °C, 12 h) to furnish **3** in 91% yield and with an enantiomeric excess superior to 96%.[8,9] This homoallylic alcohol **3** was then transformed into the protected 1,3-diol **5** in four steps. The first step was the protection of the hydroxyl group [TBSCl (2.5 equiv), imidazole (4 equiv), CH_2Cl_2, 0 °C to rt] followed by the oxidative cleavage of the unsaturation [OsO_4 (3 mol %), $NaIO_4$ (4 equiv), 2,6-lutidine (2 equiv), dioxane/H_2O]. The resulting aldehyde was treated directly with (*S*,*S*)-**Ti** (1.1 equiv, Et_2O, −78 °C, 12 h) to furnish the expected monoprotected *syn*-1,3-diol **4** (85% over 3 steps) which was protected [TBSOTf (1.9 equiv), 2,6-lutidine (1.9 equiv), CH_2Cl_2, −78 °C, 2 h] as a TBS ether (compound **5**) (Scheme 2).

To access the C4−C7 diene, the protected 1,3-diol **5** was transformed into the conjugated dienic ester **6** by oxidative cleavage of the terminal double bond [OsO_4 (3 mol %), $NaIO_4$ (4 equiv), 2,6-lutidine (2 equiv), dioxane/H_2O] and treatment of the resulting aldehyde with the unsaturated phosphonoester **I** (2 equiv) [LiHMDS (1.9 equiv), THF, 2 h]. After a sequence of reduction by DIBAL-H (3 equiv) in CH_2Cl_2, protection of the primary alcohol as a PMB ether [PMBOC(NH)CCl_3 (1.67 equiv), CSA (10 mol %), CH_2Cl_2, rt, 18 h], and selective deprotection of the alcohol protected as a TBDPS ether [NH_4F (15 equiv), MeOH, reflux, 1.5 h],[10] alcohol **7** was isolated and transformed into the allylic alcohol **8** after an oxidation step, an HWE olefination with phosphonoester **II** (1.2 equiv) [LiCl (1.3 equiv), DBU (1.2 equiv), MeCN, rt, 20 h],[11] and a reduction (55% over the 3 steps). The obtained allylic alcohol **8** was then converted to iododiene **11** in four steps. After oxidation of **8**, the obtained aldehyde was submitted to the Takai conditions [$CrCl_2$ (20 equiv), CHI_3 (2 equiv), THF/dioxane, rt][12] to produce iododiene **9** in 89% yield which, after deprotection/oxidation of the primary hydroxyl group with DDQ, led to aldehyde **10** which was reduced by DIBAL-H. The obtained iododiene **11** corresponds to **Fragment A** and was formed from *tert*-butyl 3-hydroxypropanoate **2** in 19 steps with an overall yield of 8.7% (Scheme 2).

The synthesis of the second fragment, **Fragment B**, started with the transformation of ethyl (*R*)-3-hydroxybutanoate **12** into the protected diol **13**. After a protection step [TBSCl (1.2 equiv), imidazole (2 equiv), CH_2Cl_2, 0 °C to rt] followed by a reduction with DIBAL-H (1.05 equiv), the resulting aldehyde

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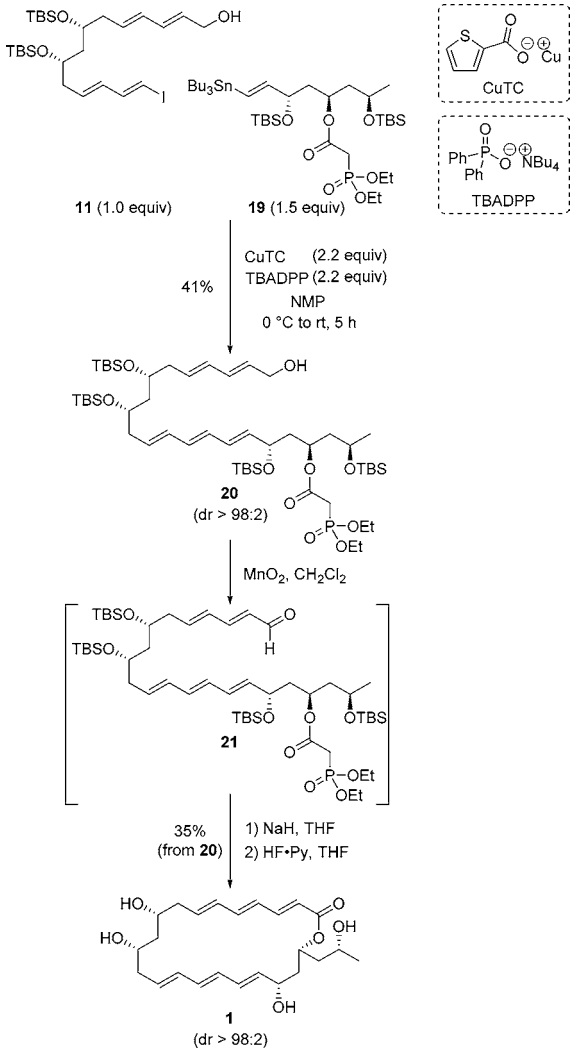
Scheme 4. Coupling of Fragments 11 and 19 and End of the Synthesis



was directly treated with the allyltitanium complex (*R*,*R*)-**Ti** (1.1 equiv, Et_2O, −78 °C, 12 h) to provide the *syn*-1,3-diol with an excellent dr superior to 98:2. This *syn*-1,3-diol was then protected as a TES ether [TESCl (1.5 equiv), DMAP (0.1 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C to rt]. To transform diol **13** into the desired protected triol **16**, diol **13** was oxidatively cleaved [OsO_4 (3 mol %), $NaIO_4$ (4 equiv), 2,6-lutidine (2 equiv), dioxane/H_2O] and the resulting aldehyde **14** was treated with trimethylsilylethynyl lithium to produce the corresponding propargylic alcohol with poor diastereoselectivity (dr = 56:44). However, after oxidation [PCC (1.5 equiv), MS 4 Å, CH_2Cl_2, rt] and reduction with the highly face selective Noyori ruthenium complex, (*S*,*S*)-**Ru** (10 mol %) in *i*PrOH,[13] the desired *anti*,*syn*-triol was isolated (dr > 98:2) and then protected as a TBS ether to produce **16**. In order to form phosphonoester **18**, acetylenic triol **16** was selectively deprotected by treatment with K_2CO_3 (1.5 equiv) in MeOH (rt, 5 h) and then with PPTS (10 mol %) in EtOH (rt, 3 h) to furnish **17**. The resulting hydroxyl group at C21 was then esterified with phosphonoacid **III**[14] (1.5 equiv) [DCC (2.25 equiv), DMAP (0.45 equiv), CH_2Cl_2, rt, 24 h][15] to produce the phosphonoester **18** in 89% yield. The formation of vinylstannane **19**, corresponding to **Fragment B**, was obtained in two steps from **18** via an acetylenic bromide intermediate [NBS (1.2 equiv), $AgNO_3$ (10 mol %), acetone/H_2O] which was hydrostannylated [$Pd(PPh_3)_4$ (5 mol %), Bu_3SnH (3 equiv), THF, −78 °C to rt, 2 h] (Scheme 3).

Having **11** and **19** in hand, these two fragments were coupled using Liebeskind conditions, i.e. copper thiophencarboxylate (CuTC) (2.2 equiv) and tetrabutylammonium diphenylphosphinate (TBA-DPP) (2.2 equiv) in NMP (0 °C to rt, 5 h),[16] and the (*E*,*E*,*E*)-triene **20** was isolated in a moderate yield of 41%. It is worth noting that other coupling reactions such as a Heck and a Stille coupling have been tried to access fragment C3−C24, but were unsuccessful.

After oxidation of the primary allylic alcohol in **20** with MnO_2 (30 equiv, CH_2Cl_2, rt, 18 h), the sensitive aldehyde **21** was directly treated with NaH (100 equiv, THF) to produce the macrocyclic lactone which was deprotected with HF·Py (64% yield). By comparison of the ^1H and ^{13}C NMR spectra and the α_D described in the literature,[17] the obtained macrolactone **1** revealed to be a diastereomer of wortmannilactone C (Scheme 4).[18]

In summary a diastereomer of wortmannilactone C was synthesized in 23 steps from **2**, with an overall yield of 1.5%, using a convergent strategy. The key steps were a Liebeskind coupling and an HWE olefination. In addition as the allyltitanium complexes and the Noyori ruthenium complexes are highly face selective reagents, all the diastereomers of wortmannilactone C should be accessible by the strategy that has been developed.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and spectroscopic 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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(6) Active on HCT-5 (colon cancer, IC_{50} = 56.3 μM), HCT-115 (colon cancer, IC_{50} = 52.4 μM), A549 (lung cancer, IC_{50} = 118.5 μM), MDA-MB-231 (breast cancer, IC_{50} = 120.4 μM), and K562 (leucocythemia, IC_{50} = 130.5 μM).

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(17) Macrolactone **1**: $[\alpha]_D^{20}$ −42.1 (*c* 0.145, MeOH); wortmannilactone C: $[\alpha]_D^{20}$ lit.[3] −9.2 (*c* 0.85, MeOH).

(18) Comparison of the NMR data of the natural product with those of the synthetic one did not allow the prediction of the configuration of the stereogenic centers.

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