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**Phytopathogens**

# Asymmetric Synthesis of the Phytopathogen (+)-Fomannosin**

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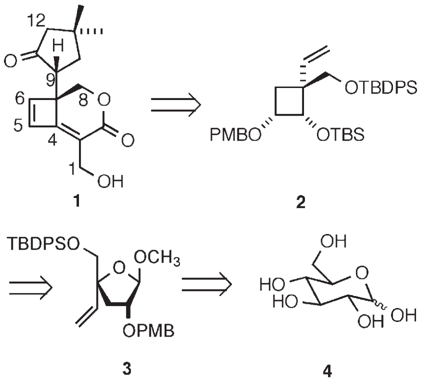
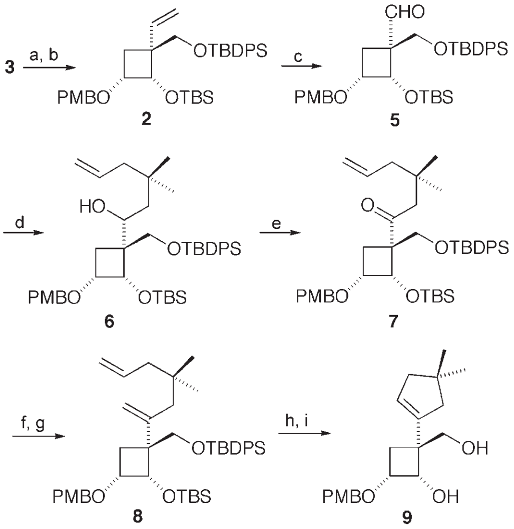
In 1967, the wood-rotting basidiomycete fungus *Fomes annosus* (Fr.) Karst became recognized as the agent responsible for generating a powerful phytopathogenic metabolite called fomannosin (**1**; Scheme 1 shows the naturally occuring + form).[1] This sesquiterpene lactone causes the death of host cells prior to hyphal invasion and is particularly toxic to *Pinus taeda* seedlings.[1b] The substantial adverse economic impact associated with infestations of this bacterial growth in pine stands located in the southeastern United States has been noted.[2,3] The quite unusual structural features of **1**, in tandem with the biological profile outlined above, have prompted detailed studies of its biogenesis.[2,4] A synthesis of racemic fomannosin has also been documented.[5] The lability of this noncrystalline methylenecyclobutene toxin led to its structural definition by virtue of two X-ray crystallographic studies involving 5,6-dihydro derivatives.[1b,6]

From the outset, we targeted a convergent, enantioselective approach featuring D-glucose (**4**) as starting material (Scheme 1). Retrosynthetically, the plan entailed the transformation of **4** into enantiomerically pure **2** by application of zirconocene-based deoxygenative ring contraction technology.[7] The step leading from **3** to **2** was intended to serve as a branch point from which other stereoisomers of the fomannosin family could be accessed. For this strategy to be successful, viable tactics would be required for attaching the dimethyl-substituted cyclopentanone to the four-membered ring and for fusing the lactone ring across C-4 and C-7. We reasoned further that the particular configuration at C-9 might well be subject on thermodynamic grounds to controlled epimerization in either the *R* or *S* direction as a function of overall substitution. Since we had earlier developed a preparatively attractive route from **3** to **2**,[8] the crafting of more advanced intermediate **9** was next pursued (Scheme 2).



**Scheme 1.** Retrosynthetic analysis of (+)-fomannosin (**1**). TBDPS = *tert*-butyldiphenylsilyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.



**Scheme 2.** Synthesis of **9**. Reagents and conditions: a) $[Cp_2ZrCl_2]$, *n*BuLi; THF, −78 °C→RT (60 % plus 25 % of the diastereomer); b) TBSCl, imidazole, $CH_2Cl_2$, RT (90 %); c) $O_3$, Sudan III, $CH_2Cl_2$, −78 °C, then $PPh_3$ (91 %); d) $H_2C{=}CHCH_2C(CH_3)_2CH_2I$, *t*BuLi, THF, −78 °C, (96 %); e) PDC, 4-Å MS, $CH_2Cl_2$, RT, 24 h (83 %); f) $(CH_3)_3SiCH_2Li$, pentane/toluene (1:1), −78 °C; g) PTSA, $C_6H_6$, RT, 5 h (83 % over two steps); h) Grubbs-2, $C_6H_6$, reflux, 4 h (91 %); i) TBAF, THF, RT, overnight (76 %). PDC = pyridinium dichromate, PTSA = *p*-toluenesulfonic acid, TBAF = tetrabutylammonium fluoride.

The acquisition of **2** was followed by ozonolysis with Sudan III serving as internal indicator.[9] The hindered, nonenolizable aldehyde **5** so produced was reacted in turn with the lithium reagent directly available by metalation of 5-iodo-4,4-dimethyl-1-pentene to provide carbinol **6** in near-quantitative yield. While **6** was uneventfully oxidized with PDC, the projected olefination of **7** as a route to diene **8** proved problematic, a likely consequence of prevailing steric congestion. The blockade existing on the faces of the carbonyl double bond inhibited customary operation of the Wittig, Tebbe, and Nysted reagents. When Peterson olefination conditions[10] were implemented instead, the targeted con-

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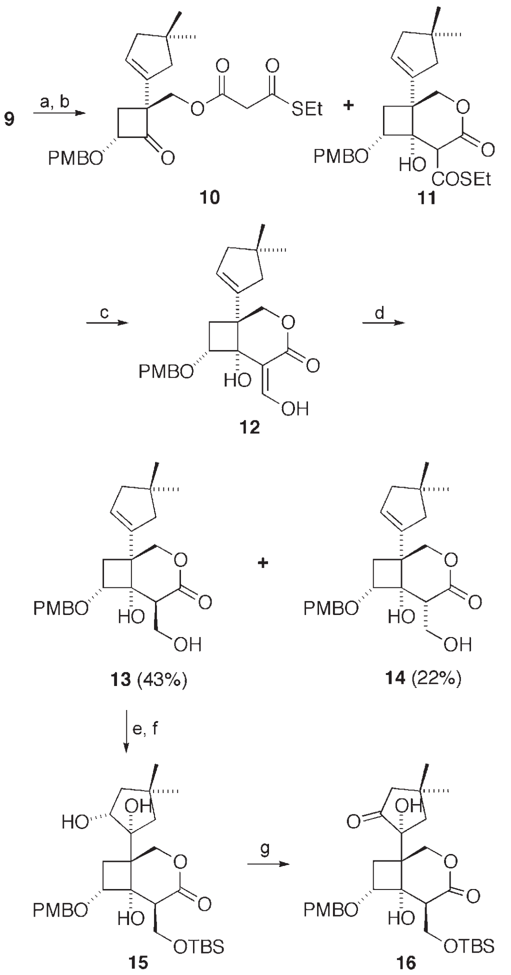
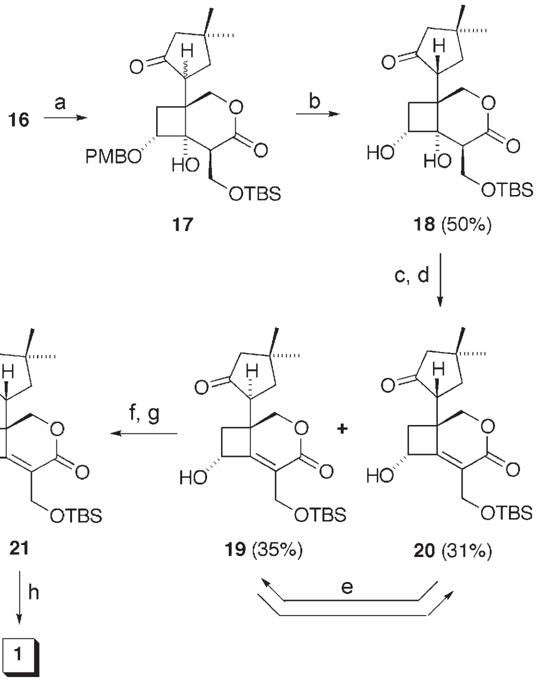
version to **8** proceeded remarkably well. The latter diene was cyclized under mandatory high-dilution conditions through the action of the Grubbs-2 ruthenium catalyst.[11] Generation of the cyclopentene ring in this manner set the stage for effective desilylation to give diol **9**.

Introduction of the lactone sector was next addressed. Highlights of the sequence ultimately developed include the regioselective monoesterification of **9** with ethylsulfanylcarbonyl acetic acid[12] as promoted by EDCI[13] (Scheme 3). Ethylsulfanylcarbonyl acetic acid was selected because it held the prospect, once incorporated into **9**, of allowing for chemoselective reduction in the presence of the labile lactone functionality. Direct oxidation of the esterification product with IBX afforded **10** and **11**. Chemical homogeneity was reinstalled through their combined treatment with 10% Pd/C in the presence of triethylsilane.[14] Not only did these conditions lead to aldol ring closure (in the case of **10**) but to subsequent reductive desulfurization as well with formation of **12** (74%). Ultimately, we found that the hydroxymethylene group could be chemoselectively reduced with $NaBH_4$ at 0°C in methanol containing $KH_2PO_4$.[15] The coformation of **13** and **14** proved not to be problematic as these diastereomers can be independently transformed by a comparable route into **21**. The pathway, exemplified for **13**, began with monoprotection as the TBS ether in advance of hydroxy-directed osmylation[16] to generate **15**. That the three hydroxy groups in **15** had been installed in an all-*cis* relationship was strongly supported by NOESY experiments performed on its Swern oxidation product **16**.

With this stereochemical assignment secure, the objectives that remained consisted of serial removal of the unneeded OH group in the cyclopentane ring, proper introduction of the two sites of unsaturation resident in the target, and ultimate desilylation. The first of these goals was met by treating **16** with samarium diiodide in the presence of *tert*-butyl alcohol as the proton source[17] (Scheme 4). This process afforded in 64% yield an inseparable mixture of the tricyclic keto lactone diastereomers **17**. Although **17** proved resistant to many conditions for PMB deprotection, the desired unmasking of the cyclobutanol OH group could be accomplished with trifluoroacetic acid in anhydrous $CH_2Cl_2$.[18] Pure samples of **18** (50%) were separated from its C-9 diastereomer (8%) by chromatography. The chemical-shift values and coupling patterns of the C-8 lactonic methylene protons in these isomers are distinctively different (in $CDCl_3$). Although these characteristics are evident in many 5,6-dihydrofomannosins,[19] we did not consider the



*Scheme 3.* Synthesis of lactone **16**. Reagents and conditions: a) $HOOCCH_2COSEt$, EDCI, $CH_2Cl_2$, −40°C→RT; b) IBX, DMSO, RT, 3 h (44% over two steps); c) Pd/C, $Et_3SiH$, $CH_2Cl_2$, then silica gel (74%); d) $NaBH_4$, MeOH, $KH_2PO_4$, HOAc, 0°C; e) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78°C (89%); f) $OsO_4$, THF/py (4:1), 0°C, then $H_2S$ (76%); g) ClCOCOCl, DMSO, $CH_2Cl_2$, $Et_3N$, −78°C→RT (78%). EDCI = 1-dimethoxyaminopropyl-3-ethylcarbodiimide hydrochloride, IBX = *o*-iodoxybenzoic acid.



*Scheme 4.* Completion of the (+)-fomannosin (**1**) synthesis. Reagents and conditions: a) $SmI_2$, *tert*-butyl alcohol/THF (1:4), 15 min (64%); b) $CF_3CO_2H$, $CH_2Cl_2$, RT, 8 min; c) $SOCl_2$, $Et_3N$, $CH_2Cl_2$, RT; d) DBU, $CH_2Cl_2$, 0°C, 20 min; e) DBU, $CH_2Cl_2$ (see text); f) $(CF_3SO_2)_2O$, $CH_2Cl_2$, 0°C; g) DBU, $C_6H_6$, RT (35% over two steps); h) TBAF, THF, 0°C (86%).

existing correlation to be sufficiently developed to form a reliable basis for configurational assignment to C-9. In the present examples, the presence of a C-5 hydroxy group, and particularly its capacity for intramolecular hydrogen bonding, could have an unforeseen effect.

Formation of the cyclic sulfites[20] of **18** or ist diastereomer proceeded uneventfully, thereby allowing subsequent elimination as promoted by DBU. Monitoring of each of these reactions by thin layer chromatography revealed that the respective conversions to **19** and **20** were occurring rapidly (< 10 min). After 45 min, equilibration of the isomers had taken place with ultimate production of near-identical two-component mixtures in a 1:1 ratio. By the proper adjustment of reaction parameters, funneling of all material through **19** was made practical. Introduction of the cyclobutene double bond was next accomplished by conversion of **19** to its triflate and elimination within this activated intermediate. In addition, epimerization occurred to set the H-9 configuration β as in **21** ($^1$H NMR analysis). Desilylation was achieved uneventfully by treatment with TBAF in THF at 0 °C. When chromatographed, the resulting dextrorotatory carbinol exhibited spectroscopic properties that matched those reported for formannosin.[2,4] The configurations of **18**–**21** could now be assigned unequivocally.

An enantioselective synthesis of **1** has been achieved in a convergent manner that features novel modes of construction of the fused cyclobutene ring, the pendant cyclopentanone, and the functionalized six-membered lactone. The flexibility provided by the modes of assembly of the structural components should also allow the synthesis of analogues and antipodes. From such compounds might well arise a fuller definition of the structural requirements for phytopathogenicity.

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