JOC Article

The Carbohydrate−Sesquiterpene Interface. Directed Synthetic Routes to Both (+)- and (−)-Fomannosin from D-Glucose

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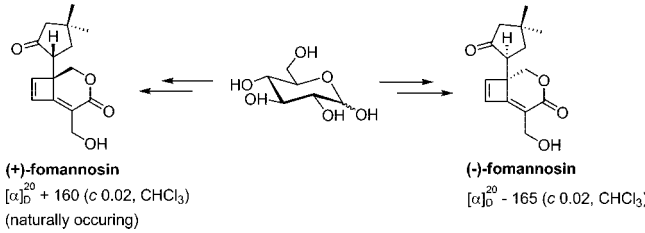
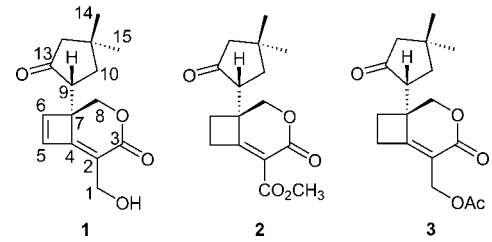


An enantiodivergent strategy for the total chemical synthesis of both naturally occurring (+)-fomannosin (**1**) and its (−)-antipode (*ent*-**1**) from α-D-glucose has been developed and successfully implemented. The key steps in the overall pathway include the following: (i) application of the zirconocene-mediated ring contraction of vinyl furanosides for the construction of highly substituted cyclobutanols; (ii) the use of ring-closing metathesis to form the pendant five-membered ring; (iii) making recourse to a monothio malonic ester to allow for chemoselective reduction to sensitive lactone intermediate **45**; (iv) hydroxyl-directed dihydroxylation with OsO_4 to generate **48**; and (v) sequential elimination via a cyclic sulfite and a cyclobutyl triflate. The bridge between the enantiomeric series consisted of a six-step linkup involving the structural modification of **22** so as to generate *ent*-**30b**. Optical activity was fully preserved throughout.

Introduction

In 1967, Bassett and co-workers succeeded in growing from still cultures of the wood-destroying Basidiomycetes fungus *Fomes annonsus* (Fr.) Karst a sesquiterpene metabolite named fomannosin.[1] *F. annonsus* causes the death of host cells and does so prior to hyphal invasion. The pathogen involved was ultimately shown to be **1**, the toxicity of which toward *Pinus tadea* seedlings and select bacteria aroused considerable economic concern, principally in the southeastern United States. Since pure **1** had been characterized as an unstable semisolid, definitive structural characterization was initially achieved by X-ray diffraction analysis involving the *p*-bromobenzoylurethane of the 5,6-dihydro derivative.[2] Ten years later, the absolute configuration of fomannosin was established by a second crystallographic study involving the (−)-camphanate ester of dihydro-**1**.[3]



^{13}C-labeling experiments have implicated a biosynthetic pathway in which mevalonate is first converted to humulene via intermolecular cyclization of *trans*,*trans*-farnesyl pyrophosphate. Subsequent ring closure to the protoilludyl cation presumably sets the stage for oxidative cleavage of a carbon−carbon bond to afford fomannosin (Scheme 1).[4] Although relatively small in size and endowed with only two stereogenic centers, **1** represents a significant challenge to synthetic chemists because of its inherent instability under both acidic and basic conditions, its methylenecyclobutene substructure, and its other unprecedented architectural features. The Matsumoto group was the first to engage in a quest of **1**, but their photochemical [2 + 2]

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(1) Bassett, C.; Underwood, R. T.; Kepler, J. A.; Hamilton, P. B. *Phytopathology* **1967**, *57*, 1046.

(2) Kepler, J. A.; Wall, M. S.; Mason, J. E.; Bassett, C.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1967**, *89*, 1260.

(3) Cane, D. E.; Nachbar, R. B.; Clardy, J.; Finer, J. *Tetrahedron Lett.* **1977**, 4277.

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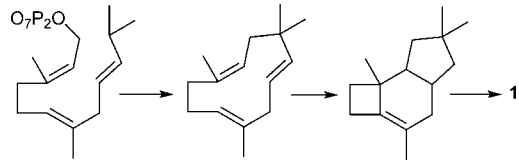

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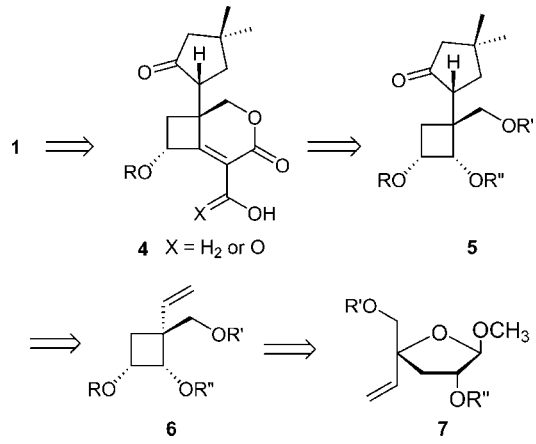

route was arrested at the stage of **2**.[5] This development was followed closely by the Kasugi/Uda approach to (±)-dihydrofomannosin acetate (**3**).[6] In 1981, Semmelhack et al. reported an innovative synthesis of (±)-**1**.[7] This hallmark development constitutes the only successful route to the target phytopathogen disclosed to the present time. In this full paper, we describe the evolution of a chemical strategy based upon the zirconocene-mediated ring contraction of a vinylated furanoside derived from α-D-glucose that has culminated in the companion total syntheses of (+)- and (−)-fomannosin.[8]

Retrosynthetic Analysis

The delicate nature of fomannosin directed us to consider installation of one or both of its constituent double bonds at a late stage. With this in mind, the retrosynthetic plan given in Scheme 2 was devised. Thus, the unsaturated center linking C5 to C6 was to be masked in the form of a protected hydroxyl group, with further disconnection across the C2−C4 double bond in **4** to lead back to intermediate **5**. In the constructive direction, ring-closing metathesis and intramolecular Knoevenagel condensation were regarded to constitute two processes having the potential for crafting the α,β-unsaturated lactone ring of the target. For the sake of maximum convergency, construction of the cyclopentanone subunit could take possible advantage of several options. These included, but were not limited to, [2 + 2] cycloaddition of a suitably reactive ketene to **6** followed by ring expansion, McMurry or related pinacol coupling of an

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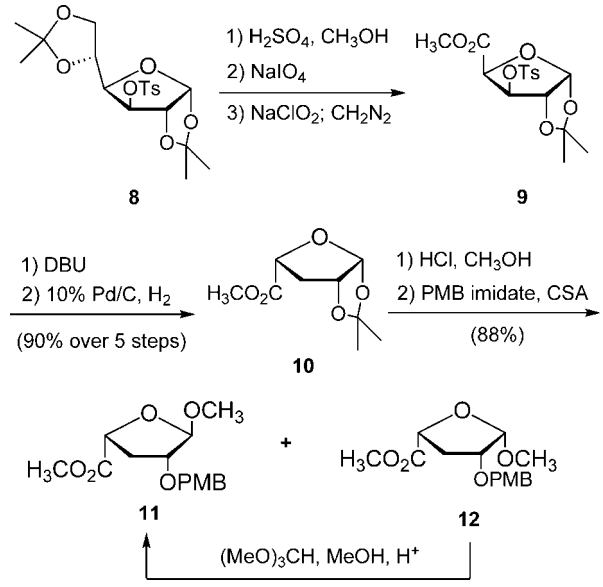

appropriate dicarbonyl precursor, or ring-closing metathesis of a suitably substituted diene generated from **6**.

The acquisition of this cyclobutane, which features three contiguous stereogenic centers along the periphery of its four-membered ring, was to exploit the capability of zirconocene[9] to deoxygenate **7**stereoselectively.[10] This tactic would allow for the generation of **7** from D-glucose and provide desirable linkage of the carbohydrate realm to the sesquiterpene domain.

Results and Discussion

Vinylated Furanoside Preparation and the Ring-Contraction Reaction. The synthesis commenced with the known tosylate **8**, which is readily available in enantiomerically pure form from D-glucose.[12] Selective hydrolysis of one of the two acetonide units in **8** with acidified methanol[13] generated a vicinal diol whose glycolic C−C bond was oxidatively cleaved with sodium periodate (Scheme 3). The resulting aldehyde was oxidized further to the methyl ester. When attempts to effect this transformation directly with bromine in methanol[14] proved unsuccessful, recourse was made to sequential treatment with sodium chlorite[15] and diazomethane. For the purpose of deoxygenation at C3, **9** was subjected to E_2 elimination in the presence of DBU, thereby making possible stereocontrolled catalytic hydrogenation to deliver **10**. Saturation exclusively from the β face takes place because steric blockade by the acetonide ring prohibits approach from the alternative direction. The efficiency of this five-step sequence is noteworthy in that chromatographic purification needs to be performed only once and the overall yield is 90%.

(4) (a) Cane, D.; Nachbar, R. B. *Tetrahedron Lett.* **1976**, 2097. (b) Cane, D.; Nachbar, R. B. *J. Am. Chem. Soc.* **1978**, *100*, 3208.
(5) Miyano, K.; Ohfune, Y.; Azume, S.; Matsumoto, T. *Tetrahedron Lett.* **1974**, 1545.
(6) (a) Kosugi, H.; Uda, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 160. (b) Kosugi, H.; Uda, H. *Chem. Lett.* **1977**, 1491.
(7) (a) Semmelhack, M. F.; Tomoda, S.; Nagaoka, H.; Boelter, S. D.; Hurst, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 747. (b) Semmelhack, M. F.; Tomoka, S. *J. Am. Chem. Soc.* **1981**, *103*, 2427. (c) Semmelhack, M. F. *Strategies Tactics Org. Synth.* **1984**, 201–222.
(8) (a) Paquette, L. A.; Peng, X.; Yang, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7817. (b) Paquette, L. A.; Kang, H.-J. *Tetrahedron* **2004**, *60*, 1353.
(9) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
(10) (a) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835. (b) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299.
(11) (a) Paquette, L. A.; Cuniere, N. *Org. Lett.* **2002**, *4*, 1927. (b) Paquette, L. A.; Kim, I. H.; Cuniere, N. *Org. Lett.* **2003**, *5*, 221.
(12) (a) Schmidt, O. T. *Methods Carbohydr. Chem.* **1963**, *2*, 320. (b) Hwang, C. K.; Li, W. S.; Nicolaou, K. C. *Tetrahedron Lett.* **1984**, *25*, 2295.
(13) Just, G.; Luthe, C. *Can. J. Chem.* **1980**, *58*, 2286.
(14) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087.
(15) Hase,T.; Wähälä, K. *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 7, pp 4533−4534.

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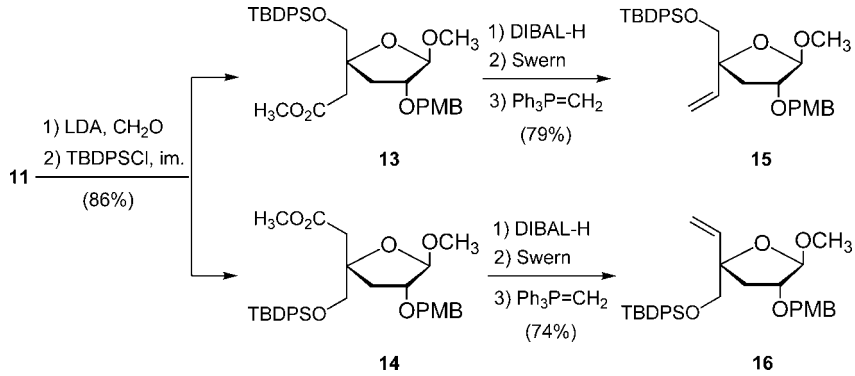

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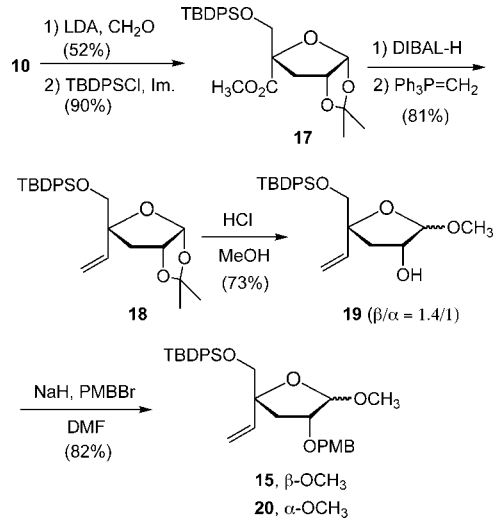

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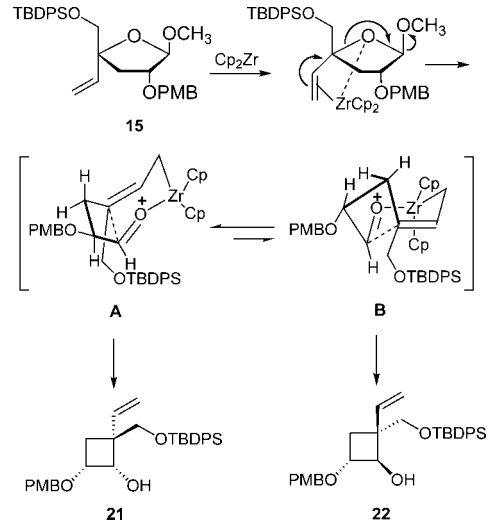

We next directed our efforts toward more advanced functionalization of furanoside **10**. During initial exploratory studies, it was noted that its hydrolysis with hydrochloric acid in methanol and subsequent exposure to *p*-methoxybenzyl trichloroacetimidate[16] afforded a 3.5:1 mixture of anomers **11** and **12** in 88% yield. The minor component could be readily epimerized by heating to 55 °C in a solvent system constituted of methanol and trimethyl orthoformate containing a catalytic quantity of HCl. As expected on steric grounds, alkylation of the lithium enolate of **11** with monomeric formaldehyde[17] gave rise to diastereoisomers **13** and **14** in a ratio of 1.7:1 after hydroxyl protection as the *tert*-butyldiphenylsilyl ethers (Scheme 4).[18] Although this pair of intermediates proved chromatographically separable and amenable to efficient conversion to **15** and **16**,[8b] the generation of anomers at each of two steps was not considered time-efficient.

Consequently, the hydroxymethylation was performed on **10** at an earlier stage (Scheme 5). By taking advantage of the steric screening offered by the acetonide substructure, we were able to achieve the exclusive production of **17** although in more modest yield. Sequential Dibal-H reduction and Wittig olefination of **17** to afford **18** proceeded in 81% yield without any concern for epimerization. Hydrochloric acid-promoted opening of the acetonide ring in **18** followed by base-promoted coupling to *p*-methoxybenzyl bromide delivered the anomeric methyl glycosides **15** and **20**.

The time had now arrived to examine the zirconocene-mediated ring contractions. While several successful examples featuring vinylated furanosides as substrates have appeared,[10,11] **15** and **20** represent members of a modified structural class where conversion to a cyclobutane would be accompanied with the generation of a quaternary center. This structural feature proved not to be an impediment to this reaction, as controlled exposure of **15** to "Cp_2Zr" gave rise in 85% yield to a diastereomeric mixture of **21** and **22** (2.4:1) (Scheme 6). The relative stereochemistries of the two products were unequivocally assigned on the basis of NOESY experiments performed on the corresponding TBS ethers, which were similarly prepared.[8b] Rationalization of the product distribution rests upon consideration of the ring-closure transition states. Initial coordination of the zirconium atom to the vinylic double bond and furanoside oxygen guarantees *E* geometry for the developing allylzirconium intermediate. Advancement along the pathway to transition state **A** eventuates in the formation of **21**, while passage through transition state **B** leads to **22**. Presumably, the adoption of **B** is less favored as a consequence of existing steric interaction between the methylene group of the developing cyclobutane and the allylic methylene group α to the zirconium, as well as dipole−dipole interactions between the oxygen atoms resident in the *p*-methoxybenzyl and *tert*-butyldiphenylsilyl ethers. Thus, **22** arises as the less dominant product. When C4-

(16) (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481.

(17) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

(18) The NOE data on which the stereochemical assignments rest have been provided earlier.[8b]

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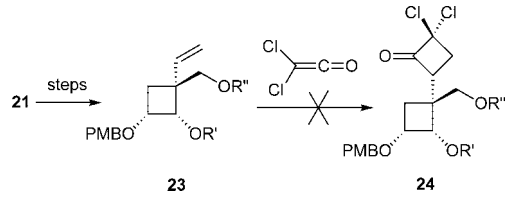

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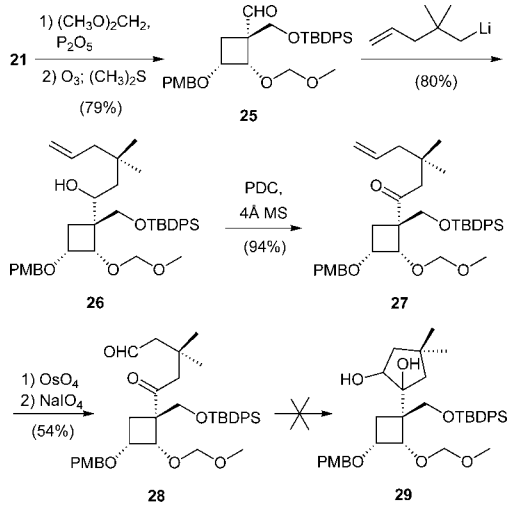
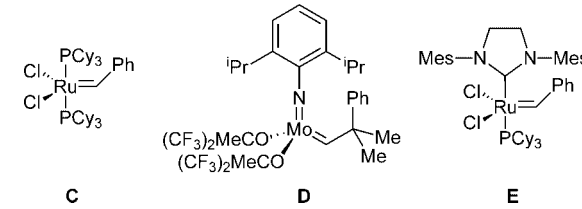


epimer **16** was treated in parallel fashion, very similar yields and product distributions were realized. This outcome is consistent with the proposed mechanistic pathway in which **A** and **B** are again involved in formation of the cyclobutanols.

Assembly of the Cyclopentanone Ring. The critical role to be played by the vinyl substituent in **21** was to serve as the cornerstone of the cyclopentanone subunit (constituted of C9−C15) in fomannosin (**1**). Several possible convergent solutions to this challenge suggested themselves. Of these, three approaches were accorded attention, the first of which consisted of dichloroketene in a [2 + 2] cycloaddition strategy followed by one-carbon ring expansion. However, this ploy was abandoned when extensive efforts[19] to induce the envisioned generation of **24** from differently protected **23** were universally met with failure (Scheme 7).

We therefore turned next to adaptation of the McMurry reaction[20] or related pinacol couplings[21] for elaboration of the cyclopentanone subunit. To this end, cyclobutanol **21** was initially protected as a methoxymethyl ether under acidic conditions[22] (Scheme 8).

Homologation of the vinyl side chain was achieved via ozonolysis and subsequent union with the lithium reagent derived from 5-iodo-4,4-dimethylpent-1-ene. Oxidation of the resulting carbinol with pyridinium dichromate in the presence of 4 Å molecular sieves delivered ketone **27** efficiently. It was soon uncovered that keto aldehyde **28** was a rather sensitive substance. Following a series of experiments designed to maximize its availability, recourse was eventually made to dihydroxylation with 1 equiv of OsO_4 and subsequent oxidative cleavage of the glycolic C−C bond with sodium periodate. We were disappointed to find, however, that no trace of the intramolecular cyclization product **29** was found when **28** was subjected to low-valent titanium- or samarium(II) iodide-based reductive conditions.



To avoid the above problem while maintaining a closely related tactical approach, ring-closing olefin metathesis[23] was selected as a potential means for construction of the five-membered ring. The original Grubbs catalyst **C**[24] is known to be sensitive to the structural environment and is not particularly effective for the formation of C=C double bonds in crowded surroundings. Although Schrock's catalyst **D**[25] is more active, it is less compatible with select functional groups of the type presently at hand. In contrast, the second-generation Grubbs catalyst **E** has been reported to be both tolerant of a wide range of functional groups and highly effective in the elaboration of tetrasubstituted olefinic bonds.[26] Our expectation was that **E** would prove effective in the fomannosin setting, where installation of a trisubstituted double bond adjacent to a quaternary center must be accomplished (Scheme 9).

Before proceeding, the hydroxyl group in **21** was protected as its methoxyethoxymethyl (MEM) ether.[27] The most effective way to accomplish this task involved coupling to MEM chloride in the presence of tetrabutylammonium chloride. The conversion of **21** to **31a** via **30a** profited from our earlier experience with this series of reactions. However, the carbonyl methylenation associated with advancement to **32a** proved to be problematic. Conventional tools for effecting this transformation, including the Wittig,[28] Tebbe,[29] and Nysted reagents,[30] proved to be uniformly ineffective, likely due to steric congestion imposed by the neighboring quaternary carbon. A modicum of success was achieved in the form of 1,2-addition with methyllithium followed by dehydration with thionyl chloride. However, this approach gave **32a** in only 24% yield and was accompanied by

(19) (a) Danheiser, R. L.; Savariar, S.; Cha, D. D. *Org. Synth.* **1990**, *68*, 32. (b) Johnston, B. D.; Czyzervska, E.; Oehlschlager, A. C. *J. Org. Chem.* **1987**, *52*, 3693. (c) Mehta, G.; Rao, H. S. P. *Synth. Commun.* **1985**, 991. (d) Krepski, L. R.; Hessner, A. *J. Org. Chem.* **1978**, *43*, 2879. (e) Greene, A. E.; Luche, M. J.; Depres, J.-P. *J. Am. Chem. Soc.* **1983**, *105*, 2435.

(20) (a) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748. (b) McMurry, J. R. *Chem. Rev.* **1989**, *89*, 1513. (c) Lectka, T. In *Active Metals*; Fürstner,A., Ed.; Wiley-VCH: Weinheim, 1995; p 85.

(21) (a) McMurry, J. E.; Lectka, T.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169. (b) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; p 563.

(22) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.

(23) (a) Reviews: Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. (d) Philips, A. J.; Arbell, A. D. *Aldrichchim. Acta* **1999**, *32*, 75. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (g) Ivin, K. J. *J. Mol. Catal. A* **1998**, *133*, 1. (h) *Alkene Metathesis in Organic Synthesis*; Fürstner, A., Ed.; Springer: Berlin, 1998. (i) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A* **1998**, *113*, 29. (j) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.

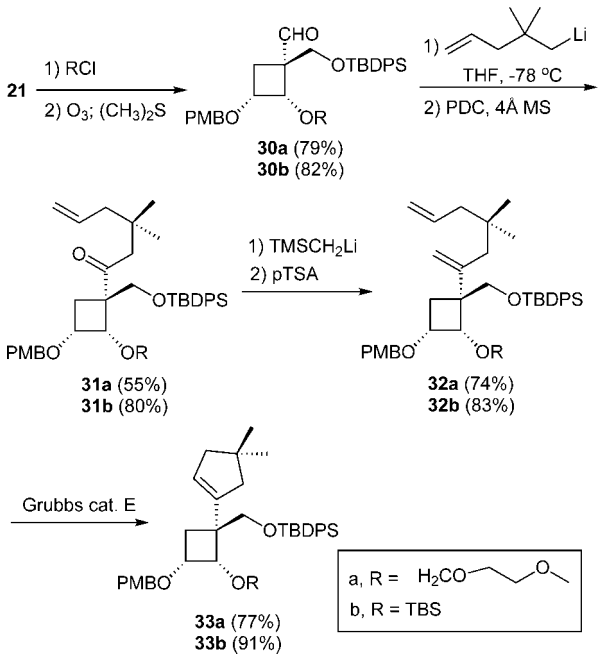
(24) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1996**, *118*, 100.

(25) (a) Schrock, R. L. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; O'Regan, M. B. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Regan, M. B.; Thomas, J. K.; Davis, W. M. J. *Am. Chem. Soc.* **1990**, *112*, 8378. (c) Bazan, G. C.; Oskam, J. H.; Cho, H. N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

(26) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(27) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999; p 41.

SCHEME 9



significant levels of the $\Delta^{9,10}$ regioisomer. This complication was bypassed when recourse was alternatively made to the Peterson olefination.[31] Treatment of **31a** with freshly prepared (trimethylsilyl)methyllithium[32] followed by *p*-toluenesulfonic acid monohydrate-promoted elimination in benzene furnished **32a** as the sole product. With pure diene in hand, the time had come to explore the ring-closing metathesis strategy. High-dilution conditions were necessary to deter intermolecular coupling. When proper consideration was accorded to this parameter, the use of **E** as catalyst gave **33a** in 77% yield.

At this point, hydroboration−oxidation was investigated as a means for introducing the carbonyl functionality at C13. This effort quickly made us aware of the sluggish reactivity of the cyclopentene double bond toward this class of reagents. For example, no reaction was observed when **33a** was heated to 90 °C with 9-borabicyclo[3.3.1]nonane[33] or exposed to catecholborane in the presence of ruthenium(III) chloride.[34] Even with hydroborating reagents as reactive as the borane−tetrahydrofuran and borane−dimethyl sulfide complexes, [35] neither elevated temperatures nor prolonged reaction times resulted in the complete consumption of **33a**. Beyond that, the desired product was isolated as an inseparable mixture of diastereomeric alcohols in only 36% yield.

We next opted to assess the influence of a free hydroxyl group on the hydroboration process. For this purpose, **27** was converted in the predescribed manner to **34**, which was desilylated in

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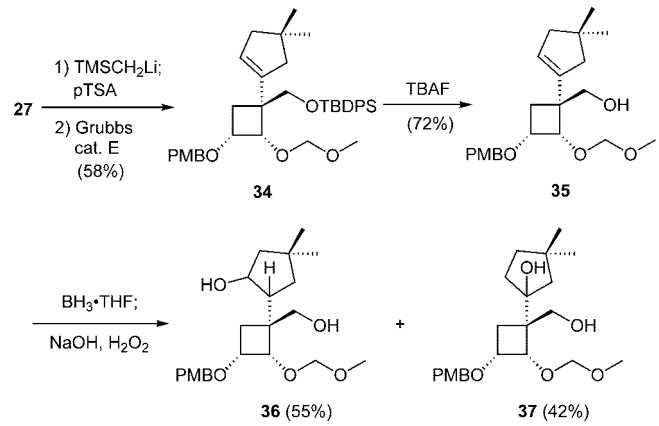

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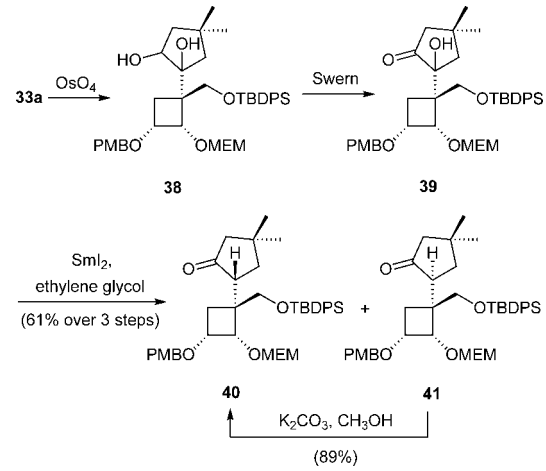


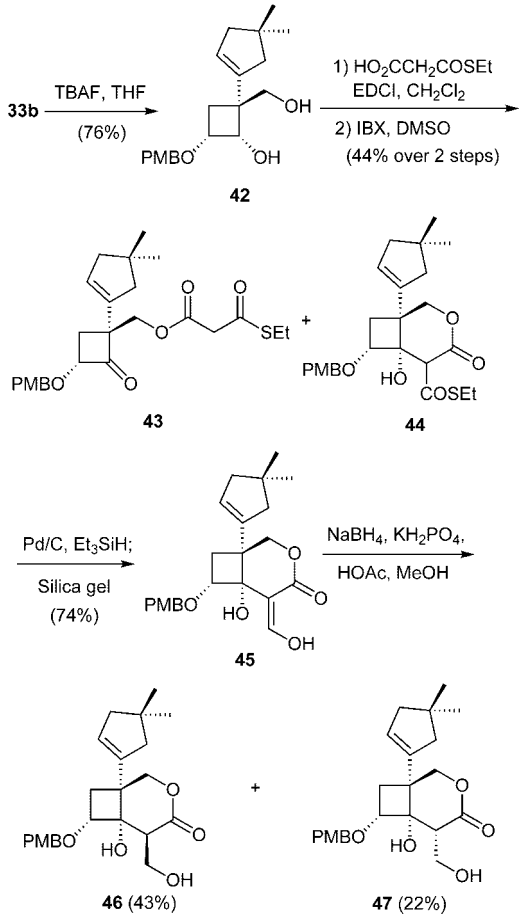
conventional fashion to arrive at **35** (Scheme 10). The hydroboration of **35** with the BH_3•THF complex was indeed appreciably accelerated, reaching completion within 30 min at room temperature. In addition, the efficiency was significantly improved to above 90%. However, this transformation is poorly regioselective, with tertiary carbinol **37** being formed competitively with **36**. The high proportion of **37** (42%) is attributed to the directing influence of the unmasked hydroxyl substituent. This state of affairs, in combination with concerns over reasonable differentiation of the two OH groups in **36**, prompted the search for an alternative approach to the problem.

Significant advancement came in the form of a three-step sequence that began with osmium tetraoxide-promoted dihydroxylation to give **38** (Scheme 11). Oxidation of this mixture of diols under Swern conditions resulted in conversion to the α-ketols **39** without measurable cleavage of the glycolic C−C bond.[36] To our delight, admixture of **39** with samarium(II) iodide[37] proceeded smoothly to generate the cyclopentanone diastereomers **40** and **41** in 61% overall yield for the three steps. Our inability to separate **39** into its two constituent isomers precluded an evaluation of the stereochemistry of the α-ketol reduction maneuver. The ketone diastereomers **40** and **41** were amenable to chromatographic purification.

Of special interest here was not only the 10:1 ratio of **40** to **41** but the obviously greater thermodynamic stability of the 9β

(28) (a) Maercker, A. *Org React.* **1965**, *14*, 270. (b) Maryanoff, B. E.; Reits, A. B. *Chem. Rev.* **1989**, *89*, 863.
(29) Review Pine, S. H. *Org. React.* **1993**, *43*, 1.
(30) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313, and references cited therein.
(31) Review: Ager, D. J. *Org. React.* **1990**, *38*, 1.
(32) Sommer, L. H.; Mitch, F. A.; Goldberg, G. M. *J. Am. Chem. Soc.* **1949**, *72*, 2746.
(33) Scouten, G. G.; Brown, H. C. *J. Org. Chem.* **1973**, *38*, 4092.
(34) Review Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, 4957.
(35) (a) Reviews: Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988. (b) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972. (c) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975. (d) Cragg, G. M. L. *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973.
(36) This was not the case with 2-iodoxybenzoic acid, which was prone to overoxidize **38** despite claims to the contrary: Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
(37) Review: Molander, G. A. *Org. React.* **1994**, *46*, 211.

SCHEME 12

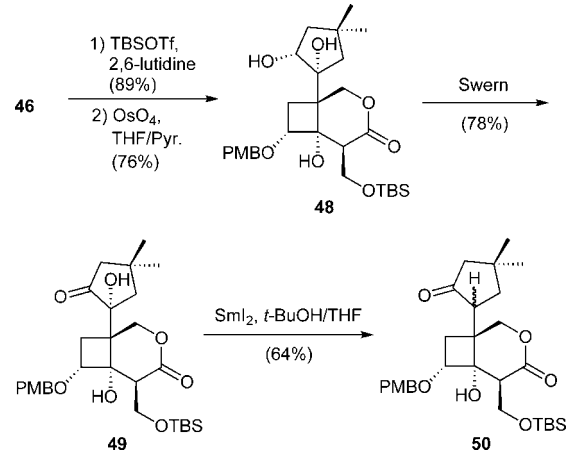


isomer as gauged from our ability to epimerize **41** in methanol containing K_2CO_3 to the identical mixture rich in **40**. This observation greatly simplified the throughput from **33a** to **40** since the intermediate steps could be usefully carried out on diastereomeric mixtures without any need for tedious chromatographic separation until arrival at **40**. The assignment of stereochemistry to the cyclopentanones was tentatively based on the method suggested by Kosugi and Uda.[6] According to their diagnostic model, the epimer with the larger ^{1}H NMR chemical shift difference between the two methylene protons at C8 possesses a β-hydrogen at C9. These characteristics are manifested by **40** and **41** ($\Delta\delta = 0.11$ and 0.05, respectively).

Construction of the Unsaturated Lactone Sector and the End Game for Production of the Natural Enantiomer of Fomannosin. With construction of the cyclobutane and cyclopentanone sectors now completed, attention was turned to generation of the unsaturated lactone ring. We soon became aware that the necessary step of MOM or MEM deprotection in more advanced intermediates could not be achieved by any of the known methods.[27] To circumvent this difficulty, recourse was made to alternative masking of the C4 hydroxyl with the *tert*-butyldimethylsilyl group as in **30b** (Scheme 9). Our expectations were that forward progress to **33b** would pose no complications, and this proved to be the case.

From this point, the conversion of **33b** to diol **42** proceeded quite smoothly (Scheme 12). We next undertook the regioselective monoesterification of **42** with ethylsulfanylcarbonyl acetic acid[38] as promoted by EDCI.[39] The *S*-ester of monothiomalonic acid was selected because it held the prospect, once

SCHEME 13



incorporated into **42**, of allowing for chemoselective reduction in the presence of the labile lactone functionality. After oxidation of the coupled product with IBX, an inseparable mixture of cyclobutanone **43** and its cyclized aldol counterpart **44** was obtained. Chemical homogeneity was regained when this two-component system was treated with 10% palladium on carbon in the presence of triethylsilane.[40] These conditions drove the six-membered ring closure to completion and effectively accomplished reduction to the aldehyde level, which materialized in its enol form as in **45** (74%). Caution was required to bring about the more advanced reduction of **45** because of the susceptibility of its lactone ring to cleavage. Ultimately, it was determined that sodium borohydride in cold (0 °C) methanol containing potassium dihydrogen phosphate[41] was reasonably effective in delivering diols **46** and **47**. Following chromatographic separation, stereochemical assignments were made on the basis of NOESY measurements. The coformation of **46** and **47** proved not to be problematic as these diastereomers can be independently transformed into **54** via a comparable route.

Once the hydroxymethyl group in **46** had been selectively silylated (Scheme 13),[42] we set out to functionalize the sterically congested cyclopentene double bond properly. The deployment of a hydroboration step again proved ineffective. The process was neither regioselective nor stereochemically definitive, giving rise to all four possible isomers. Alternative treatment with stoichiometric levels of osmium tetroxide followed by cleavage of the osmate ester with hydrogen sulfide resulted in the almost exclusive (>95 de) formation of triol **48**, which was readily purified. The outstanding diastereofacial selectivity of this step may stem from the nearby presence of a tertiary carbinol.[43,44] Subsequent to the Swern oxidation of **48**, recourse to NOESY experiments confirmed that the configuration at C9 in **49** was indeed *R*. Reductive cleavage of this unneeded C−O bond was

(38) (a) Imamoto, T.; Kodera, M.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2303. (b) Beaulieu, P. L.; Deziel, R.; Brunet, M. L.; Moss, N.; Plante,R. U.S. cont.-in-part of U.S. 5,574,015, 1998, 24 pp.

(39) Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996.

(40) (a) Takayama, H.; Fujiwara, R.; Kasai, Y.; Kitajima, M.; Aimi, N. *Org. Lett.* **2003**, *5*, 2967. (b) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

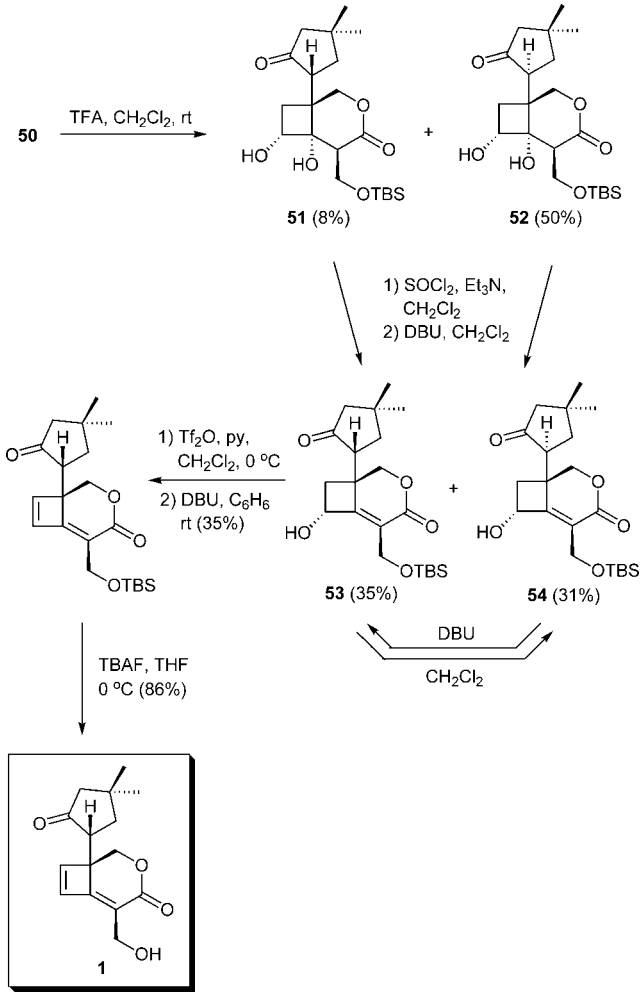
(41) (a) Fujii, H.; Hirano, N.; Uchiro, H.; Kawamura, K.; Nagase, H. *Chem. Pharm. Bull.* **2004**, *52*, 747. (b) Rabiczko, J.; Urbanczyk-Lipkowska, Z.; Chemielewski, M. *Tetrahedron* **2002**, *58*, 1433.

(42) Askin, D.; Angst, D.; Danishefsky, S. J. *J. Org. Chem.* **1987**, *52*, 622.

(43) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2899.

(44) (a) Hodgson, R.; Mahid, T.; Nelson, A. *Chem. Commun.* **2001**, 2076. (b) Donohoe, T. J.; Fisher, J. W.; Edwards, P. J. *Org. Lett.* **2004**, *6*, 465.

SCHEME 14



next accomplished by exposure of **49** to the action of samarium iodide in the presence of *tert*-butyl alcohol as the proton source.[45] The inseparable diastereomers **50** were thereby generated in 64% yield.

The availability of **50** set the stage for introduction of the diene unsaturation resident in the target molecule. However, removal of the PMB group proved not to be as readily accomplished as expected. When **50** was admixed with DDQ in a mixture of CH_2Cl_2 and pH 7 buffer,[46] the benzylic position experienced oxidation to furnish the benzoate.[47] The alternative deprotection procedure involving the use of ceric ammonium nitrate in aqueous acetonitrile[46] resulted in removal of the TBS group. The desired transformation was ultimately realized with trifluoroacetic acid under anhydrous conditions.[48] Recourse to this protocol made available a chromatographically separable two-component mixture consisting of **51** (8%) and **52** (50%) (Scheme 14). We were not surprised to observe that the chemical shift difference between the methylene protons at C8 in these diastereomers are quite distinctive. For **51**, the $\Delta\delta$ value is rather large (1.12 ppm) when compared to that for **52** (0.18 ppm). Notwithstanding, we were reluctant to make configurational assignments to C9 on this basis alone. The Kosuki−Uda correlation[6] was viewed to be insufficiently developed to be universally applicable and error-free. Reversals could materialize unexpectedly such as in the present examples where the presence of a C5 hydroxyl and particularly its capacity for intramolecular hydrogen bonding could induce major conformational changes. For this reason, we pressed on with both stereoisomeric series.

In the event, **51** and **52** were subjected to a two-step sequence consisting of initial conversion to their respective cyclic sulfites, as promoted by triethylamine, followed by DBU-promoted elimination. Formation of the cyclic sulfites proceeded uneventfully. Monitoring of the progress of each of the second reactions by thin-layer chromatography revealed that a single product, considered to be **53** and **54**, respectively, was being formed rapidly (5−10 min) in each instance. As time passed, equilibration of these isomers took place such that similar 1:1 mixtures of **53** and **54** were in hand after 30 min at rt. *Relevantly, the proper adjustment of reaction conditions permitted the funneling of all material through* **53** *in a high state of purity*. In the ^{1}H NMR spectrum of **53**, the chemical shift differences between methylene C8 protons proved to be unusually small (0.09 ppm). Direct comparison with the spectral data for **54** showed the $\Delta\delta$ in this instance (0.65 ppm) to be somewhat more pronounced than that for **53**. The narrowness of this gap could be a reflection of intramolecular hydrogen bonding operative between the OH functionality and C13 carbonyl group in both tricyclic intermediates as suggested upon inspection of molecular models.

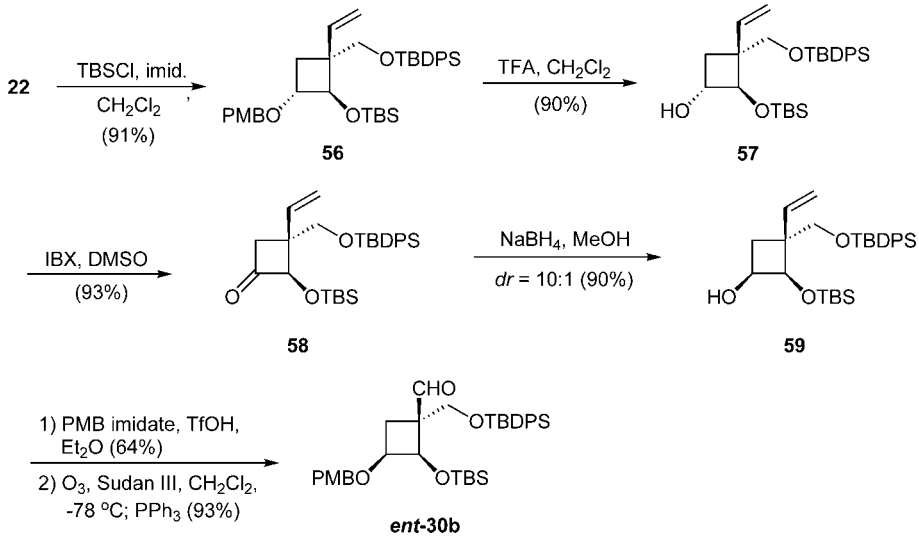
The dehydration of the C5 hydroxy group to afford the cyclobutane double bond proved to be a task as daunting as expected. No trace amount of cyclobutene product could be isolated with either Martin sulfurane or Burgess reagent. Recourse was finally made to formation of the triflate of **53**. Surprisingly, the triflate of **53** was amenable to chromatographic purification on silica gel. Two chemical events occurred upon its exposure to DBU in benzene, one being elimination with introduction of the cyclobutene double bond and the second being wholesale epimerization to set the C9 configuration as β. Although we were initially wary of our ability to control stereochemistry at C9, the significant thermodynamic advantage inherent in **55** greatly facilitated matters at this advanced stage of progress.

The conversion to (+)-fomannosin (**1**) was successfully achieved through the use of TBAF in THF at 0 °C. The resulting primary alcohol, dissolved in purified $CDCl_3$ (stored overnight with K_2CO_3 (s) before being filtered through basic alumina prior to use) to minimize solvent-induced degradation, exhibited a 500 MHz ^{1}H NMR spectrum very closely matching that reported for fomannosin at lower field strengths.[3,4] Synthetic **1** proved to be dextrorotatory. With these data in hand, it was possible to make absolute configurational assignments to **51–55** with confidence.

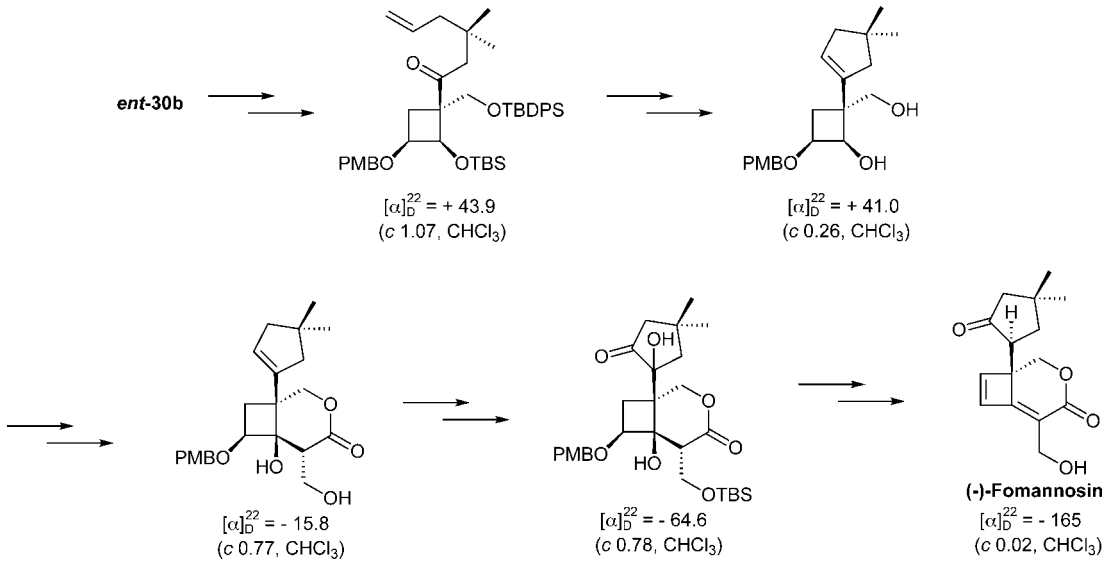
Total Synthesis of (−)-Fomannosin. En route to (+)-**1**, cyclobutanol **22** was produced as the minor constituent (25%) of the two-component mixture formed upon the zirconocene-promoted ring contraction of **15**. In line with the reactivity of its diastereomeric counterpart, the hydroxyl group proved amenable to silylation as in **56**, thus allowing for chemoselective removal of the PMB group and arrival at **57** (Scheme 15). With this result in hand, we recognized that configurational inversion at the carbinol center would provide a means for ultimately delivering (−)-fomannosin. The acquisition of **59** was efficiently realized by sequential IBX oxidation of **57** followed by reduction

(45) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424.
(46) Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468.
(47) Blakemore, P. R.; Kim, S.-K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831.
(48) (a) Yan, L.; Kahne, D. *Synlett* **1995**, 523. (b) Bonzide, A.; Sauvé, G. *Tetrahedron Lett.* **1999**, *40*, 2883.

SCHEME 15



SCHEME 16



with sodium borohydride. The preponderance of **59**, a likely reflection of steric control operating in **58**, was 10:1. The subsequent critical conversion of **59** into *ent*-**30b** was realized uneventfully, thereby affording a six-step bridge suitable for the production of unnatural fomannosin.

Ultimately, *ent*-**30b** was converted to levorotatory fomannosin via the synthetic protocol developed earlier for (+)-**1** (Scheme 16). The routes to these antipodes feature highly efficient functionalization reactions of extensively substituted cyclobutanes.

In summary, we have achieved asymmetric syntheses of (+)- and (−)-fomannosin from a common carbohydrate precursor. The key steps involved the initial elaboration of **21** from α-D-glucose, assembly of the cyclopentene subunit by ring-closing metathesis, and construction of the unsaturated lactone sector in advance of functional group manipulation. Atoms C4 to C9 of the fomannosin backbone arise from the glucose starting material as a result of zirconocene-promoted deoxygenative ring contraction. A great deal of stereochemical control seems available and it should prove feasible to modify configuration at C7 and C9 appropriately as desired for assessing structure/activity relationships.

Experimental Section

(−)-(3a*S*,5*S*,6*R*,6a*S*)-Methyl Dihydro-5-*tert*-butyldiphenylsiloxymethyl)-2,2-dimethyl-5*H*-furo[3,2-*d*][1,3]dioxole-6-carboxylate (17). To a THF solution (10 mL) of diisopropylamine (1.40 mL, 10 mmol) cooled to −30 °C was added *n*-butyllithium (1.5 M in hexanes, 3.33 mL, 5.0 mmol), and the resulting solution was stirred for 20 min in the cold before proceeding to −78 °C. Ester **10** (1.01 g, 5.00 mmol) in 6 mL of THF was quickly introduced, and 1 h was allowed to elapse before a THF solution (15 mL) of monomeric formaldehyde was added. The resulting mixture was warmed to −10 °C, quenched with saturated NH_4Cl solution (1 mL), and partitioned between ethyl acetate (300 mL) and water (50 mL). The separated aqueous phase was evaporated, the residue was dissolved in 1:1 methanol/ethyl acetate, and this solution was filtered through Celite. After drying and evaporation of the filtrate, the residue was subjected to MPLC on silica gel (elution with 2:3 hexanes/ethyl acetate) to give the alcohol (550 mg, 52% based on recovered **10**) as a white solid: mp 103−104 °C; IR (film, cm^{-1}) 3499, 1751, 1257; ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (d, J = 3.4 Hz, 1 H), 4.70 (t, J = 4.0 Hz, 1 H), 3.80−3.71 (m, 1 H), 3.74 (s, 3 H), 3.54 (dd, J = 7.2, 11.6 Hz, 1 H), 2.65 (d, J = 14.2 Hz, 1 H), 2.56 (t, J = 6.7 Hz, 1 H), 2.19 (dd, J = 4.7, 14.2 Hz, 1 H), 1.42

(s, 3 H), 1.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 112.6, 106.5, 88.2, 80.2, 66.1, 52.4, 35.8, 25.6, 25.5; HRMS (ES) *m/z* (M + Na)$^+$ calcd 255.0839, obsd 255.0861; $[\alpha]^{22}_D$ −66.6 (*c* 1.49, $CHCl_3$).

To a DMF solution (15 mL) of the above alcohol (900 mg, 3.88 mmol) and imidazole (1.32 g, 19.4 mmol) was added *tert*-butyldiphenylsilyl chloride (1.28 g, 4.66 mmol), and the reaction mixture was stirred overnight at rt before being quenched with water (100 mL) and extracted with ethyl acetate (3 − 100 mL). After drying and evaporation of the combined organic layers, the product was chromatographed on silica gel (elution with 7:1 hexanes/ethyl acetate) to furnish **17** (1.64 g, 90%) as a colorless oil: IR (film, cm^{-1}) 1766, 1732. 1428; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4 H), 7.45−7.35 (m, 6 H), 5.90 (d, *J* = 3.5 Hz, 1 H), 4.74 (dd, *J* = 3.5, 4.9 Hz, 1 H), 3.85 (d, *J* = 10.4 Hz, 1 H), 3.74 (s, 3 H), 3.69 (d, *J* = 10.4 Hz, 1 H), 2.72 (d, *J* = 14.2 Hz, 1 H), 2.29 (dd, *J* = 4.9, 14.2 Hz, 1 H), 1.48 (s, 3 H), 1.31 (s, 3 H), 1.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.7, 135.6 (2 C), 132.9, 132.7, 129.8, 127.8, 112.5, 106.8, 88.6, 80.3, 67.6, 52.3, 36.5, 26.6, 26.0, 25.9, 19.2; HRMS (ES) *m/z* (M + Na)$^+$ calcd 493.2017, obsd 493.2027; $[\alpha]^{22}_D$ −28.2 (*c* 1.43, $CHCl_3$).

(+)-((3a*S*,5*S*,6*R*,6a*S*)-Dihydro-2,2-dimethyl-6-vinyl-5*H*-furo[3,2-*d*][1,3]dioxol-5-yl)methanol *tert*-Butyldiphenylsilyl Ether (18). To a CH_2Cl_2 solution of **17** (905 mg, 1.92 mmol) cooled to −78 °C was added diisobutylaluminum hydride (4.8 mL of 1.0 M in hexanes). The reaction mixture was stirred at this temperature for 2 h prior to being quenched with methanol (1 mL) and 20% sodium potassium tartrate solution (20 mL). Stirring was maintained until clear phase separation was achieved. The aqueous layer was extracted with CH_2Cl_2 (3 × 00 mL), and the combined organic phases were washed with brine, dried, and evaporated to leave the aldehyde that was used directly without purification.

To a solution of methyltriphenylphosphonium bromide (2.13 g, 5.97 mmol) in THF (15 mL) was added *n*-butyllithium (3.3 mL of 1.5 M in hexanes) at −30 °C, and stirring was maintained for 20 min before the above aldehyde dissolved in THF (10 mL) was introduced. The reaction mixture was allowed to warm to rt, stirred for 3 h, and quenched with saturated $NaHCO_3$ solution (5 mL). Dilution with ethyl acetate (300 mL) and washing with brine followed. The organic phase was dried and freed of solvent, and the residue was purified by chromatography on silica gel (elution with 15:1 hexanes/ethyl acetate) to provide 682 mg (81% over two steps) of **18** as a colorless oil: IR (film, cm^{-1}) 1428, 1213, 1113; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4 H), 7.46−7.35 (m, 6 H), 5.99 (d, *J* = 3.9 Hz, 1 H), 5.95 (dd, *J* = 10.9, 17.4 Hz, 1 H), 5.33 (dd, *J* = 1.3, 17.4 Hz, 1 H), 5.10 (dd, *J* = 1.3, 10.9 Hz, 1 H), 4.90−4.86 (m, 1 H), 3.58 (d, *J* = 10.6 Hz, 1 H), 3.37 (d, *J* = 10.6 Hz, 1 H), 2.54 (dd, *J* = 6.5, 13.8 Hz, 1 H), 2.14 (dd, *J* = 1.4, 13.8 Hz, 1 H), 1.51 (s, 3 H), 1.34 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 135.6 (2 C), 133.2, 132.9, 129.7 (2 C), 127.7, 114.8, 112.5, 106.7, 88.6, 82.0, 69.4, 38.0, 26.9, 26.8, 19.2; HRMS (ES) *m/z* (M + Na)$^+$ calcd 461.2119, obsd 461.2123; $[\alpha]^{22}_D$ +0.40 (*c* 1.97, $CHCl_3$). Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.30; H, 7.82.

Acid Hydrolysis of 18. To a solution of **18** (370 mg, 12.2 mmol) in methanol (92 mL) was added a solution of concentrated HCl (2.0 mL) in methanol (8 mL) at rt. The reaction mixture was stirred for 1.5 h, quenched with solid $NaHCO_3$, and freed of methanol. The residue was dissolved in CH_2Cl_2, dried, and concentrated. Flash chromatography of the residue on silica gel (elution with 6:1 to 5:1 hexanes/ethyl acetate) afforded 151 mg (43%) of the β-isomer and 106 mg (30%) of the α-isomer.

For **19*β***: IR (film, cm^{-1}) 3438, 1472, 1428; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4 H), 7.46−7.34 (m, 6 H), 6.20 (dd, *J* = 17.8, 17.3 Hz, 1 H), 5.48 (dd, *J* = 1.6, 17.2 Hz, 1 H), 5.18 (dd, *J* = 1.6, 10.7 Hz, 1 H), 4.94 (s, 1 H), 4.16−4.09 (m, 1 H), 3.60 (s, 2 H), 3.28 (s, 3 H), 2.34 (dd, *J* = 5.2, 13.7 Hz, 1 H), 1.95 (d, *J* = 13.6 Hz,1 H), 1.09 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 135.78, 135.75, 133.5, 133.4, 129.8, 127.7, 113.5, 110.1, 87.0, 76.9, 70.5, 54.6, 39.6, 26.9, 19.5; HRMS (ES) *m/z* (M + Na)$^+$ calcd 435.1962, obsd 435.1961; $[\alpha]^{22}_D$ −21.5 (*c* 1.05, $CHCl_3$).

For **19α**: IR (film, cm^{-1}) 3558, 1428; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4 H), 7.46−7.35 (m, 6 H), 5.93 (dd, *J* = 10.8, 17.4 Hz, 1 H), 5.26 (dd, *J* = 1.4, 17.3 Hz, 1 H), 5.05 (dd, *J* = 1.4, 10.8 Hz, 1 H), 4.89 (d, *J* = 4.6 Hz, 1 H), 4.52−4.45 (m, 1 H), 3.50 (d, *J* = 10.4 Hz, 1 H), 3.49 (s, 3 H), 3.44 (d, *J* = 10.4 Hz, 1 H), 2.58 (dd, *J* = 8.1, 12.1 Hz, 1 H) 1.78 (dd, *J* = 9.4, 12.1 Hz, 1 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 135.8, 135.7, 133.3, 129.9, 129.8, 127.8, 113.6, 103.1, 85.6, 72.7, 69.4, 55.3, 39.4, 27.0, 19.4; HRMS (ES) *m/z* (M + Na)$^+$ calcd 435.1962, obsd 435.1966; $[\alpha]^{22}_D$ +78.4 (*c* 0.84, $CHCl_3$).

O-Benzylation of 19*β*. Sodium hydride (1.15 g of 60% mineral oil dispersion, 28.6 mmol) was added in one portion into a solution of **19*β*** (9.85 g, 23.9 mmol) in 220 mL of DMF at 0 °C. After 2 min, a solution of *p*-methoxybenzyl bromide (5.28 g, 26.3 mmol) in 30 mL of DMF was introduced dropwise, and stirring was maintained at rt for 4 h. After quenching with saturated $NaHCO_3$ solution and dilution with ethyl acetate and water, the separated aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with brine, dried, and concentrated to afford **15** (10.85 g, 82%) as a colorless oil spectroscopically identical to the material described in the Supporting Information.

O-Benzylation of 19α. Sodium hydride (1.08 g of 60% mineral oil dispersion, 26.9 mmol) was added in one portion into a solution of **19α** (8.54 g, 20.7 mmol) in 200 mL of DMF at 0 °C. After 2 min, a solution of *p*-methoxybenzyl bromide (4.99 g, 24.8 mmol) in 25 mL of DMF was added dropwise, and stirring was maintained at rt for 1 h. Following the introduction of 0.2 equiv each of additional sodium hydride and the bromide, agitation was prolonged for 2 h and the predescribed workup protocol was followed. There was isolated 9.06 g (82%) of **20** as a colorless oil: IR (film, cm^{-1}) 1613, 1512; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.61 (m, 4 H), 7.45−7.34 (m, 6 H), 7.27−7.25 (m, 2 H), 6.87−6.82 (m, 2 H), 5.91 (dd, *J* = 10.9, 17.4 Hz, 1 H), 5.21 (dd, *J* = 1.3, 17.4 Hz, 1 H), 5.03 (dd, *J* = 1.3, 10.9 Hz, 1 H), 4.80 (d, *J* = 4.3 Hz, 1 H), 4.52 (m, 2 H), 4.26−4.18 (m, 1 H), 3.79 (s, 3 H), 3.50−3.41 (m, 5 H), 2.43 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.01 (dd, *J* = 10.5, 11.7 Hz, 1 H), 1.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 141.1, 135.8, 135.7, 133.4, 133.2, 130.2, 129.84, 129.77, 129.75, 127.8, 113.9, 113.7, 102.3, 84.6, 78.5, 72.2, 69.4, 55.4, 35.9, 26.9, 19.4; HRMS (ES) *m/z* (M + Na)$^+$ calcd 555.2537, obsd 555.2516; $[\alpha]^{22}_D$ +59.5 (*c* 0.80, $CHCl_3$).

(−)-(1*S*,2*R*,4*R*)-4-(4-Methoxybenzyloxy)-2-*tert*-butyldiphenylsiloxymethyl)-2-vinylcyclobutanol (21) and (+)-[1*R*,2*R*,4*R*)-4-(4-Methoxybenzyloxy)-2-*tert*-butyldiphenylsiloxymethyl)-2-vinylcyclobutanol (22). A solution of zirconocene dichloride (2.68 g, 9.17 mmol) in THF (150 mL) was treated with a solution of *n*-butyllithium in hexanes (1.45 M, 11.0 mL, 15.9 mmol) at −78 °C. Stirring was maintained at this temperature for 1 h before a solution of **15** (3.25 g, 6.11 mmol) in THF (25 mL) was introduced. The resulting solution was allowed to warm slowly, stirred overnight at rt, and passed through a short silica gel column with ether. The eluate was concentrated and purified by flash chromatography on silica gel (elution with hexanes/ethyl acetate 5:1) to give **21** (1.85 g, 60%) and **22** (0.75 g, 25%) as colorless oils.

For **21**: IR (film, cm^{-1}) 1612, 1514, 1428; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (m, 4 H), 7.47−7.36 (m, 6 H), 7.30−7.25 (m, 2 H), 6.91−6.86 (m, 2 H), 5.95 (dd, *J* = 17.6, 10.9 Hz, 1 H), 5.26 (dd, *J* = 10.9, 1.3 Hz, 1 H), 5.09 (dd, *J* = 17.6, 1.3 Hz, 1 H), 4.46 (s, 2 H), 4.46−4.40 (m, 1 H), 4.20−4.14 (m, 1 H), 3.81 (s, 3 H), 3.64 (d, *J* = 10.1 Hz, 1 H), 3.46 (d, *J* = 10.1 Hz, 1 H), 2.57 (br s, 1 H), 2.27 (ddd, *J* = 12.7, 6.8, 2.3 Hz, 1 H), 2.10 (dd, *J* = 12.7, 4.9 Hz, 1 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 137.6, 135.6 (4 C), 133.3, 133.2, 129.9, 129.7 (2 C), 127.7 (4 C), 116.5, 113.8 (2 C), 71.6, 71.3, 70.8, 67.9, 55.2, 49.9, 31.1, 26.8 (3 C), 19.3; HRMS (ES) *m/z* (M + Na)$^+$ calcd 525.2432, obsd 525.2429; $[\alpha]^{24}_D$ −25.6 (*c* 1.28, $CHCl_3$).

For **22**: IR (film, cm^{-1}) 1613, 1587, 1513, 1428; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4 H), 7.47−7.35 (m, 6 H), 7.32−7.27 (m, 2 H), 6.91−6.86 (m, 2 H), 5.89 (dd, J = 17.7, 11.0 Hz, 1 H), 5.30 (dd, J = 11.0, 1.1 Hz, 1 H), 5.19 (dd, J = 17.7, 1.1 Hz, 1 H), 4.49 (s, 2 H), 4.22 (d, J = 6.4 Hz, 1 H), 3.81 (s, 3 H), 3.77 (dt, J = 8.4, 6.4 Hz, 1 H), 3.65 (d, J = 10.2 Hz, 1 H), 3.50 (d, J = 10.2 Hz, 1 H), 2.13 (dd, J = 11.2, 8.4 Hz, 1 H), 1.79 (dd, J = 11.2, 8.4 Hz, 1 H), 1.72 (br s, 1 H), 1.09 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 137.0, 135.6 (4 C), 133.4 (2 C), 130.4, 129.7 (2 C), 129.4 (2 C), 127.7 (4 C), 117.1, 113.7 (2 C), 78.0, 75.1, 70.5, 67.3, 55.2, 45.4, 27.7, 26.9 (3 C), 19.4; HRMS (ES) m/z $(M + Na)^+$ calcd 525.2432, obsd 525.2423; $[\alpha]^{24}_D$ +10.2 (c 0.66, $CHCl_3$).

(+)-(1*S*,7*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1-((*S*)-4,4-dimethyl-2-oxocyclopentyl)-7-hydroxy-3-oxabicyclo[4.2.0]oct-5-en-4-one (53) and (+)-(1*S*,7*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1-((*R*)-4,4-dimethyl-2-oxocyclopentyl)-7-hydroxy-3-oxabicyclo[4.2.0]oct-5-en-4-one (54). Thionyl chloride (1.08 μL, 0.015 mmol) was added slowly to a solution of **52** (5.1 mg, 0.012 mmol) and triethylamine (5.17 μL, 0.037 mmol) in 0.6 mL of dry CH_2Cl_2 at 0 °C under argon. After 20 min at this temperature, the solution was poured into a mixture of ethyl acetate, water, and a small amount of triethylamine. The organic layer was washed with brine, dried, and concentrated. The solid residue was immediately taken up in 1.0 mL of dry CH_2Cl_2 and cooled to 0 °C. DBU (5.6 μL, 0.037 mmol) was added at 0 °C under argon. After 30 min at 0 °C, the mixture was loaded directly onto a silica gel column, eluted with hexanes/ethyl acetate (3:1, with 1% ethanol) to afford **53** (1.7 mg, 35%) and **54** (1.5 mg, 31%), both as white solids.

For **53**: IR (film, cm^{-1}) 3456, 1725, 1463; ^1H NMR (500 MHz, $CDCl_3$) δ 5.09 (dt, J = 2.4, 6.7 Hz, 1 H), 4.57 (d, J = 14.6 Hz, 1 H), 4.39 (d, J = 14.6 MHz, 1 H), 4.24 (d, J = 10.8 Hz, 1 H), 4.25 (d, J = 10.8 Hz, 1 H), 3.38 (d, J = 7.3 Hz, 1 H), 3.33 (dd, J = 8.3, 13.1 Hz, 1 H), 2.35 (dd, J = 6.6, 13.4 Hz, 1 H), 2.31 (d, J = 20.1 Hz, 1 H), 2.15 (dd, J = 2.7, 13.4 Hz, 1 H), 2.08 (d, J = 19.0 Hz, 1 H), 2.06−2.02 (m, 1 H), 1.71 (t, J = 12.8 Hz, 1 H), 1.22 (s, 3 H), 1.12 (s, 3 H), 0.92 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.1, 163.5, 125.2, 76.0, 70.6, 59.8, 54.4, 53.3, 44.8, 40.1, 38.5, 33.4, 30.1, 27.9, 26.1 (3 C), 18.5, −5.3, −5.4; HRMS (ES) m/z $(M + Na)^+$ calcd 417.2073, obsd 417.2089; $[\alpha]^{22}_D$ +22.4 (c 0.36, $CHCl_3$).

For **54**: IR (film, cm^{-1}) 3410, 1728, 1694; ^1H NMR (500 MHz, $CDCl_3$) δ 5.13 (d, J = 6.3 Hz, 1 H), 4.83 (d, J = 10.5 Hz, 1 H), 4.65 (dd, J = 1.0, 15.8 Hz, 1 H), 4.37 (d, J = 15.8 Hz, 1 H), 4.17 (d, J = 10.5 Hz, 1 H), 3.12 (dd, J = 8.5, 12.6 Hz, 1 H), 2.34 (dd, J = 6.7, 13.5 Hz, 1 H), 2.29 (d, J = 2.2 Hz, 1 H), 2.22−2.15 (m, 2 H), 2.07 (d, J = 18.3 Hz, 1 H), 2.02 (dd, J = 2.6, 13.4 Hz, 1 H), 1.92 (ddd, J = 2.4, 8.4, 12.8 Hz, 1 H), 1.25 (s, 3 H), 1.08 (s, 3 H), 0.93 (s, 9 H), 0.13 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.6, 163.7, 156.9, 125.7, 76.3, 69.9, 61.1, 54.2, 49.1, 44.3, 40.1, 35.8, 33.7, 30.0, 27.8, 26.1 (3 C), 18.5, −5.3, −5.4; HRMS (ES) m/z $(M + Na)^+$ calcd 417.2073, obsd 417.2087; $[\alpha]^{22}_D$ +100.8 (c 0.19, $CHCl_3$).

Equilibration of 53 and 54. A solution of compound **54** (2.6 mg, 6.6 μmol) in dichloromethane (0.6 mL) was treated with DBU (3.0 μL, 19.8 μmol) at rt. After 45 min at rt, the mixture was loaded directly onto a silica gel column and eluted with hexanes/ethyl acetate (3.5:1, with 1% ethanol) to afford **53** (1.4 mg, 54%) and **54** (1.2 mg, 46%).

(*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1-((*S*)-4,4-dimethyl-2-oxocyclopentyl)-3-oxabicyclo[4.2.0]octa-5,7-dien-4-one (55). Triflic anhydride (6.4 μL, 0.038 mmol) was added slowly to a solution of **53** (1.5 mg, 3.80 μmol) and pyridine (6.1 μL, 0.076 mmol) in dry dichloromethane (0.8 mL) at 0 °C under argon. After 15 min at 0 °C, isopropyl alcohol (2.9 μL, 0.038 mmol) was added. After 20 min at 0 °C, DBU (5.7 μL, 0.028 mmol) was introduced dropwise at 0 °C. After another 5 min, the reaction mixture was loaded onto a silica gel column, eluted with hexanes/ethyl acetate/dichloromethane (5:1:1) to afford a slightly yellow solid, which was used directly for the next step.

The above triflate was taken up in 0.2 mL of benzene. DBU (1.7 μL in 30 μL of benzene, 11.4 μmol) was added at rt. After 2 h at rt, the mixture was loaded onto a silica gel column, eluted with hexanes/ethyl acetate/dichloromethane (6:1:1 with 0.5% triethylamine) to afford **55** (less polar, 0.5 mg, 35% over 2steps) and its C-9 epimer (more polar, 0.3 mg, 21%) both as colorless oils;

For **55**: ^1H NMR (500 MHz, C_6D_6) δ 6.71 (d, J = 2.2 Hz, 1 H), 6.16 (d, J = 2.3 Hz, 1 H), 5.02 (d, J = 10.0 Hz, 1 H), 4.86 (d, J = 15.3 Hz, 1 H), 4.59 (d, J = 15.4 Hz, 1 H), 3.97 (d, J = 10.1 Hz, 1 H), 3.18 (dd, J = 9.4, 11.4 Hz, 1 H), 1.93 (d, J = 17.8 Hz, 1 H), 1.68 (d, J = 18.1 Hz, 1H), 1.53−1.49 (m, 2H), 1.03 (s, 9H), 0.83 (s, 3H), 0.63 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H); HRMS (ES) m/z $(M + Na)^+$ calcd 399.1968, obsd 399.1986.

(+)-Fomannosin (1). Tetrabutylammonium fluoride (4.0 μL, 1.0 M in THF, 4.0 μmol) was added dropwise to a solution of **55** (0.5 mg, 1.33 μmol) in tetrahydrofuran (0.5 mL) at 0 °C under argon. After 20 min at 0 °C, the reaction mixture was filtered through a short pad of silica gel, washing with ethyl acetate/dichloromethane (2/1, with 0.5% triethylamine). The filtrate was concentrated. The residue was purified by preparative thin layer chromatography (silica gel, ethyl acetate/dichloromethane 1/1 with 0.5% triethylamine) to afford (+)-**1** (0.3 mg, 86%) as a colorless oil; IR (film, cm^{-1}) 3580, 1724, 1709, 1461, 1408; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, J = 2.4 Hz, *H*-6, 1 H), 6.69 (d, J = 2.4 Hz, *H*-5, 1 H), 4.90 (d, J = 10.2 Hz, *H*-8, 1 H), 4.42 (dd, J = 5.2, 13.8 Hz, *H*-1, 1 H), 4.35 (dd, J = 6.0, 13.8 Hz, *H*-1, 1 H), 4.28 (d, J = 10.2 Hz, *H*-8, 1 H), 3.18 (dd, J = 8.9, 12.4 Hz, *H*-9, 1 H), 2.37−2.35 (m, OH, 1H), 2.22 (d, J = 18.5 Hz, *H*-12, 1 H), 1.95 (d, J = 18.5 Hz, *H*-12, 1 H), 1.73 (ddd, J = 2.4, 8.7, 12.6 Hz, *H*-10, 1 H), 1.57 (*H*-10, 1 H, overlap with H_2O peak), 1.16 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 218.37 (*C*-13), 165.72 (*C*-3), 154.85 (*C*-4), 147.96 (*C*-5), 139.53 (*C*-6), 73.50 (*C*-8), 58.52 (*C*-1), 53.61 (*C*-12), 52.79 (*C*-7), 46.60 (*C*-9), 38.39 (*C*-10), 32.94 (*C*-11), 29.65 (*CH*$_3$), 27.89 (*CH*$_3$); HRMS (ES) m/z $(M + Na)^+$ calcd 285.1103, obsd 285.1119; $[\alpha]^{22}_D$ + 160 (c 0.02, $CHCl_3$). See the Supporting Information for a comparison of ^1H and ^{13}C NMR data for synthetic and natural fomannosin. Due to small quantities of material, ^{13}C data were extrapolated from HSQC and HMBC data.

(−)-*tert*-Butyl(((1*S*,2*R*,3*R*)-2-(*tert*-butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-1-vinylcyclobutyl)methoxy)diphenylsilane (56). To a solution of **22** (1.40 g, 2.78 mmol) and imidazole (0.95 g, 13.9 mmol) in CH_2Cl_2 (10 mL) was added TBSCl (0.63 g, 4.18 mmol) at rt. The mixture was stirred at rt for 3 h before being quenched with MeOH (3 mL). The resulting solution was stirred at rt for 2 h, diluted with CH_2Cl_2 (100 mL), washed with saturated $NaHCO_3$ solution (1×) and brine (1×), dried, and concentrated. The residue was purified by flash chromatography on silica gel (elution with hexanes/ethyl acetate, 30/1) to afford **56** as a pale yellow oil (1.57 g, 91%): IR (film, cm^{-1}) 1613, 1514, 1249; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.63 (m, 4 H), 7.46−7.34 (m, 6 H), 7.27 (d, J = 8.7 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.95 (dd, J = 17.7, 10.9 Hz, 1 H), 5.15 (dd, J = 10.9, 1.4 Hz, 1 H), 5.05 (dd, J = 17.7, 1.4 Hz, 1 H), 4.45 (ABq, J = 11.5 Hz, $\Delta\nu$= 18.6 Hz, 2 H), 4.38 (d, J = 6.6 Hz, 1 H), 3.82 (s, 3 H), 3.82−3.74 (m, 1 H), 3.56 (d, J = 10.3 Hz, 1 H), 3.39 (d, J = 10.3 Hz, 1 H), 2.03 (dd, J = 10.8, 8.1 Hz, 1 H), 1.77 (dd, J = 10.8, 8.6 Hz, 1 H), 1.10 (s, 9 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 138.0, 135.7, 133.6, 133.5, 130.9, 129.6, 129.1, 127.6, 115.2, 113.7, 77.9, 74.2, 70.3, 66.5, 55.3, 45.3, 27.7, 26.9, 25.8, 19.4, 18.0, −4.7; HRMS (ES) m/z $(M + Na)^+$ calcd 639.3296, obsd 639.3247; $[\alpha]^{24}_D$ −18.6 (c 1.7, $CHCl_3$).

(−)-(1*R*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-3-vinylcyclobutanol (57). Trifluoroacetic acid (20 mL) was added quickly to a solution of **56** (21.54 g, 34.91 mmol) in 200 mL of dry CH_2Cl_2 at rt under argon. After 20 min, the reaction mixture was cooled to 0 °C and quenched with an excess amount (50 mL) of triethylamine. The solution was

concentrated. The residue was filtered through a short pad of silica gel, and the pad was washed with hexanes/ethyl acetate (10/1). The filtrate was concentrated, and the residue was purified by flash chromatography (silica gel, elution with hexanes/ethylacetate 15/1) to afford **57** as a colorless oil (15.58 g, 90%): IR (neat, cm^{-1}) 3422, 1472, 1428; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.68 (m, 4 H), 7.48−7.40 (m, 6 H), 5.97 (dd, J = 10.9, 17.7 Hz, 1 H), 5.19 (dd, J = 1.2, 10.9 Hz, 1 H), 5.11 (dd, J = 1.4, 17.7 Hz, 1 H), 4.26 (d, J = 6.3 Hz, 1 H), 3.99−3.94 (m, 1 H), 3.59 (d, J = 10.4 Hz, 1 H), 3.41 (d, J = 10.4 Hz, 1 H), 2.18 (dd, J = 8.5, 10.9 Hz, 1 H), 1.79 (dd, J = 8.7, 10.9 Hz, 2 H), 1.14 (s, 9 H), 0.95 (s, 9 H), 0.14 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 135.8, 133.62, 133.55, 129.8, 127.78, 127.77, 115.4, 76.3, 72.5, 66.2, 44.9, 30.0, 27.1, 26.0, 19.5, 18.2, −4.4, −4.7; HRMS m/z $(M + Na)^+$ calcd 519.2727, obsd 519.2707; $[\alpha]^{22}_D$ −11.6 (c 1.5, $CHCl_3$).

(+)-(2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-3-vinylcyclobutanone (58). A solution of **57** (1.360 g, 2.738 mmol) and IBX (2.300 g, 8.213 mmol) in 30 mL of DMSO was stirred at rt for 4 h. The reaction mixture was diluted with ether and H_2O. The organic layer was washed twice with brine, dried, and filtered. The filtrate was concentrated. The residue was purified by flash chromatography (elution with silica gel, hexanes/ethyl acetate 25/1) to afford **58** (1.265 g, 93%) as colorless oil: IR (neat, cm^{-1}) 1791, 1472, 1428; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.62 (m, 4 H), 7.47−7.38 (m, 6 H), 5.86 (dd, J = 11.0, 17.7 Hz, 1 H), 5.23 (dd, J = 0.5, 11.1 Hz, 1 H), 5.16 (t, J = 2.6 Hz, 1 H), 5.09 (dd, J = 0.8, 17.7 Hz, 1 H), 3.86 (d, J = 10.3 Hz, 1 H), 3.71 (d, J = 10.3 Hz, 1 H), 3.08 (dd, J = 3.0, 16.2 Hz, 1 H), 2.49 (dd, J = 2.2, 16.2 Hz, 1 H), 1.10 (s, 9 H), 0.91 (s, 9 H), 0.13 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.7, 135.74, 135.71, 135.1, 133.1, 133.0, 130.0, 128.0, 127.9, 117.2, 65.1, 43.9, 43.7, 27.1, 25.8, 19.5, 18.3, −4.5, −4.9; HRMS m/z $(M + Na)^+$ calcd 517.2570, obsd 517.2557; $[\alpha]^{22}_D$ +22.2 (c 0.76, $CHCl_3$).

(+)-(1*S*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-3-((*tert*-butyldiphenylsilyloxy)methyl)-3-vinylcyclobutanol (59). Sodium borohydride (8.6 mg, 0.227 mmol) was added to a solution of **58** (56.2 mg, 0.114 mmol) in 5 mL of MeOH at 0 °C. After 15 min, the reaction mixture was quenched with saturated NH_4Cl solution and diluted with ether and H_2O. The organic layer was washed with brine, dried, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, hexanes/ethyl acetate 20/1) to afford **59** as a colorless oil (51.0 mg, 90%): IR (neat, cm^{-1}) 3538, 1471, 1428; ^1H NMR (500 MHz, $CDCl_3$) δ 7.69−7.66 (m, 4 H), 7.48−7.39 (m, 6 H), 6.00 (dd, J = 10.9, 17.7 Hz, 1 H), 5.18 (dd, J = 1.4, 10.9 Hz, 1 H), 5.06 (dd, J = 1.4, 17.7 Hz, 1 H), 4.50 (dd, J = 2.3, 5.7 Hz, 1 H), 4.25−4.20 (m, 1 H), 3.60 (d, J = 10.3 Hz, 1 H), 3.49 (d, J = 10.3 Hz, 1 H), 2.77 (d, J = 8.5 Hz, 1 H), 2.28 (ddd, J = 2.6, 6.7, 10.0 Hz, 1 H), 1.99 (dd, J = 5.0, 12.5 Hz, 1 H), 1.11 (s, 9 H), 0.94 (s, 9 H), 0.095 (s, 3 H), 0.088 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 135.70, 135.65, 133.3, 129.7, 127.73, 127.71, 115.2, 72.6, 67.8, 65.4, 49.1, 35.5, 26.9, 25.9, 19.4, 18.3, −4.6, −4.9; HRMS m/z $(M + Na)^+$ calcd 519.2727, obsd 519.2708; $[\alpha]^{22}_D$ + 14.8 (c 0.54, $CHCl_3$).

(+)-(1*S*,2*R*,3*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-((*tert*-butyldiphenylsilyloxy)methyl)-3-(4-methoxybenzyloxy)cyclobutanecarbaldehyde (*ent*-30b). A solution of TfOH (0.13 μL, 1.45 μmol) in 50 μL of dry ether was added very slowly into a solution of **59** (0.240 g, 0.483 mmol) and PMB imidate (0.341 g, 1.208 mmol) in 10 mL of dry ether at rt under argon. The progress of reaction was closely monitored by TLC. Additional TfOH (0.13 μL, 1.45 μmol) in 50 μL of dry ether was added every 30 min until the starting material had been consumed. The reaction mixture was quenched with excess triethylamine and concentrated. The residue was purified by flash chromatography (silica gel, elution with hexanes/ethyl acetate 25/1) to afford the protected alkene as a colorless oil (0.191 g, 64%): IR (neat, cm^{-1}) 1513, 1428, 1248; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72−7.68 (m, 4 H), 7.49−7.41 (m, 6 H), 7.32 (d, J = 8.6 Hz, 1 H), 6.91 (d, J = 8.6 Hz, 1 H), 6.22 (dd, J = 11.0, 17.8 Hz, 1 H), 5.16 (dd, J = 1.4, 11.0 Hz, 1 H), 4.99 (dd, J = 1.4, 17.8 Hz, 1 H), 4.62 (d, J = 11.6 Hz, 1 H), 4.57 (dd, J = 1.8, 5.3 Hz, 1 H), 4.42 (d, J = 11.6 Hz, 1 H), 4.13−4.09 (m, 1 H), 3.84 (s, 3 H), 3.66 (d, J = 10.3 Hz, 1 H), 3.54 (d, J = 10.3 Hz, 1 H), 2.26 (ddd, J = 2.3, 6.9, 9.9 Hz, 1 H), 2.07 (dd, J = 4.8, 12.1 Hz, 1 H), 1.12 (s, 9 H), 0.96 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 139.3, 135.75, 135.72, 133.47, 133.45, 131.1, 129.7, 129.2, 127.71, 127.70, 114.2, 113.7, 72.9, 72.1, 70.5, 67.1, 55.3, 49.7, 32.0, 31.9, 29.74, 29.70, 29.4, 27.0, 26.0, 22.7, 19.4, 18.4, 14.2, −4.6, −4.7; HRMS m/z $(M + Na)^+$ calcd 639.3302, obsd 639.3310; $[\alpha]^{22}_D$ +0.81 (c 1.1, $CHCl_3$). The spectrometric data are in accordance with those of the precursor of **30b**.

Five drops of a 0.1% solution of Sudan III in dichloromethane were added to a solution of the above product (11.80 g, 19.1 mmol) in dichloromethane (360 mL). The resulting light pink solution was cooled to −78 °C. A stream of O_3 was passed through the solution at −78 °C until the solution turned colorless. Triphenylphospine (7.52 g, 28.7 mmol) was added. The solution was allowed to warm slowly to rt and stirred at rt for 1 h before being concentrated. The residue was filtered through a short pad of silica gel, washing with hexanes/dichloromethane/ethyl acetate (15/15/1). The filtrate containing the product was concentrated. The residue was purified by silica gel chromatography (elution with hexanes/ethyl acetate 20/1) to give *ent*-**30b** (10.98 g, 93%) as a slightly pink oil. The spectrometric data are in accordance with those of **30b**.

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Note Added after ASAP Publication. Due to a production error, the two paragraphs preceding the section "Total Synthesis of (–)-Fomannosin" were missing in the version published ASAP May 20, 2008; the corrected version was published ASAP May 30, 2008.

Supporting Information Available: Full experimental details, high-field ^1H and ^{13}C NMR spectra, and full characterization for all new compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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(49) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Bennani, Y. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2083.