

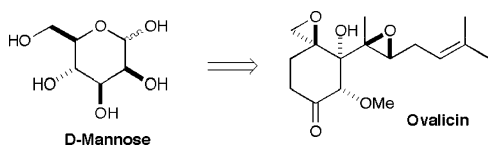
Synthesis of Ovalicin Starting from D-Mannose

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A new synthesis of epoxyketone **22** is described that is a key intermediate in Barton's synthesis of ovalicin (**2**), a powerful anti-angiogenic inhibitor. The key process for the construction of **22** was ring-closing metathesis of olefins **11** and **12** obtained from 2,3:5,6-di-*O*-isopropylidene- α -D-mannofuranose (**4**) and regioselective desilylation of tri-TES ether **19**. Furthermore, an alternative stereoselective route from **22** into **2** has also been developed, and the overall yield of **2** from **4** was 10.0%.

Angiogenesis, the growth and development of new capillary blood vessels, is a process that takes place normally during wound healing. Abnormal angiogenesis is now recognized as a feature of many proliferative diseases.¹ For example, the growth and metastatic spread of solid tumors is known to be dependent on angiogenesis. This suggests that inhibition of angiogenesis is a promising approach for the treatment of cancer.² In 1990, an antibiotic, fumagillin (**1**),^{3,4} was reported to have potent anti-angiogenic activity (Figure 1),⁵ but its high toxicity and instability made the application of **1** to an anti-cancer drug difficult. As a result of further extensive studies, ovalicin (**2**), which was first isolated from cultures of *Pseudorotium ovalis* Stolk,⁶ was found to be nontoxic, noninflammatory, and more potent than **1**; the potency was the same as that of the most active analogue, AGM-1470 (**3**),⁵ which is being evaluated in phase III clinical trials as a potential cancer drug.⁷ These positive observations have stimulated synthetic chemists, and Corey et

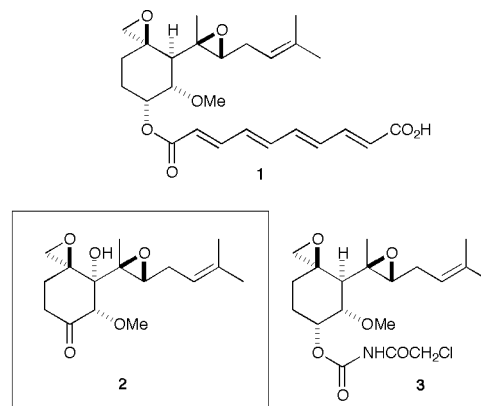


FIGURE 1. Structures of Anti-Angiogenesis Inhibitors.

al. modified the original total synthesis^{8a} of racemic **2** to develop an elegant asymmetric synthesis of **2**,^{8b} while Bath, Barton, and co-workers reported the total synthesis of **2** using L-quebrachitol as a chiral pool.⁹ In addition, a formal total synthesis of **2** was also disclosed.¹⁰ However, more efficient syntheses of **2** and its derivatives are still required for further studies on detailed examination of its biological activity with significant therapeutic potential.¹¹ In connection with our synthetic studies¹² on heterocyclic natural products based on the "Chiron" approach,¹³ we describe herein an efficient synthesis of **2** starting from D-mannose.

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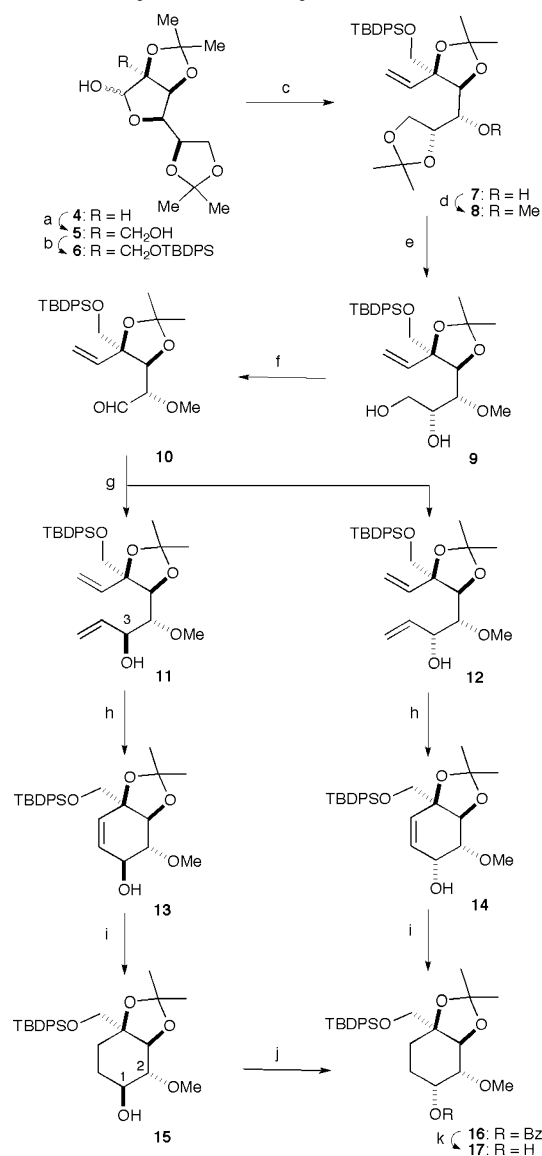
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To construct the carbon backbone of **2**, we adopted Barton's strategy⁹ that uses a stereoselective coupling reaction between cyclohexane **22** and vinyl lithium reagent **23** developed by Corey et al.^{8a} Key features in our synthesis of **22** involve an efficient preparation of cyclohexanol **17** utilizing a ring-closing olefin metathesis (RCM)¹⁴ of olefins **11** and **12** and multifunctionalization on the cyclic ring system through a regioselective desilylation of tri-TES ether **19**. Furthermore, a new efficient route from the coupling product **24** into **2** was also developed.

Synthesis of **2** started with regioselective silylation of acetal **5**¹⁵ obtained from 2,3:5,6-di-*O*-isopropylidene- α -D-mannofuranose (**4**) in 76% yield (Scheme 1). Wittig reaction of the resulting silyl ether **6** under mild conditions using a base such as *n*-BuLi and SHMDS in THF at 0 °C to room temperature (rt) resulted in a low yield of olefin **7**. However, methylenation under the forcing conditions¹⁶ gave the desired olefin **7** in 97% yield. After *O*-methylation of **7**, exposure of the resulting methyl ether **8** to mildly acidic conditions led to selective deisopropylideneation to afford diol **9**. For the construction of another olefin unit in **9**, selective oxidation¹⁷ of the primary hydroxyl group was attempted but failed. DIBAL reduction of the corresponding monobenzylidene derivative also gave unsatisfactory results. Consequently, aldehyde **10** was prepared by sodium periodate oxidation of **9**, and reaction of **10** with several vinylating reagents was examined. The results are shown in Table 1. Under all conditions tried, a low polar substance was obtained as a major product. We estimated that the major isomer was 3*S*-alcohol **11** because this reaction would occur through an α -chelation-controlled mode. The estimation was confirmed at the later stage (vide infra). RCM of **11** with Grubbs's second generation catalyst proceeded nicely to give the desired cyclohexene **13** in good yield. Similarly, the epimer **12** afforded cyclohexenol **14**; the yield slightly decreased because of low recovery of the reaction products. Both compounds **13** and **14** were hydrogenated to afford cyclohexanes **15** and **17**, respectively. In the ¹H NMR spectra of **15**, H-2 was observed at 3.56 ppm as doublets of a doublet ($J_{1,2} = 6.0$ Hz and $J_{2,3} = 4.4$ Hz), while the coupling constant between H-1 and -2 of **17** was 3.8 Hz. The large coupling constant (6.0 Hz) of **15** shows the 1,2-*trans* relationship of two hydroxyl groups, thus establishing the stereochemistry of alcohols **11** and **12**. To invert the stereochemistry at the C-1

SCHEME 1. Synthesis of Cyclohexanol **17**^a



^a Reagents and conditions: (a) ref 15; (b) TBDPSCl, DMAP, Et₃N, CH₂Cl₂, 0 °C to rt, 85%; (c) Ph₃P⁺CH₃Br⁻, KO^t-Bu, toluene, 105 °C, 97%; (d) NaH, MeI, THF, 0 °C, 97%; (e) aq. AcOH, 50 °C, 72%; (f) NaIO₄, THF/H₂O, rt, and then (CH₂OH)₂, quant.; (g) vinylmagnesium chloride, THF, -20 °C, 68% for **11**, 28% for **12**; (h) Grubbs's second generation catalyst, toluene, 80 °C, 94% for **13**, 84% for **14**; (i) 10% Pd/C, H₂, EtOAc, rt, 99% for **15**, 95% for **17**; (j) DEAD, Ph₃P, benzoic acid, THF, 0 °C to rt; (k) NaOMe, MeOH, rt, 95% from **15** (two steps).

position of **15**, this was subjected to the Mitsunobu reaction (diethyl azodicarboxylate, triphenylphosphine, benzoic acid)¹⁸ to afford benzoate **16**, whose benzoyl group was removed by sodium methoxide in methanol to give **17** in 95% overall yield from **15**.

After several attempts to prepare **20** from **17**, a simple method was developed as follows (Scheme 2). Initially, all protecting groups in **17** were removed by the action of hydrogen chloride in methanol, and the resulting tetraol **18** was silylated to give tri-TES ether **19** quantitatively. When this was treated with TBAF (0.75 mol

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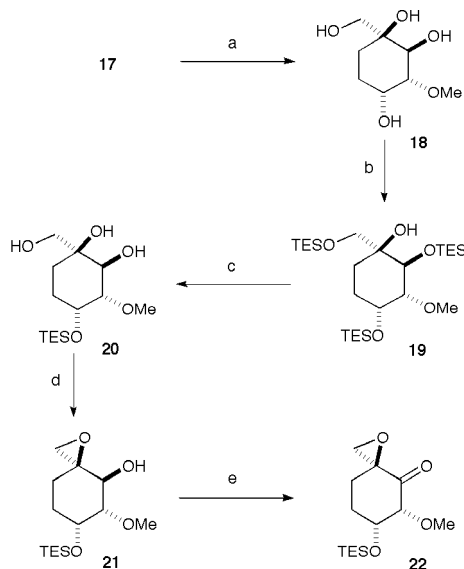
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TABLE 1. Vinylation of Aldehyde 10

entry	reagents ^a	solvent	temp (°C)	ratio ^b (11/12)	yield (%)
1	vinylMgBr	THF	-20	78:22	95
2	vinylMgBr	THF/HMPA	-20	81:19	69
3	vinylMgCl	THF	-20	71:29	96
4	vinylMgCl	THF/HMPA	-20	85:15	78
5	vinylLi ^c	ether	0	59:41	82
6	vinylLi ^c	ether/HMPA	-20	54:46	63

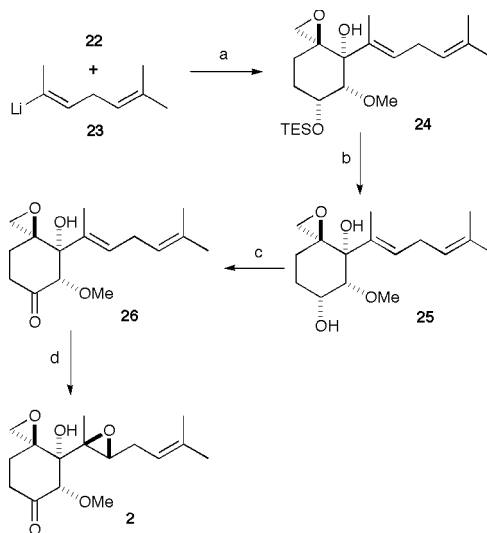
^a A quantity of 2.0–4.0 mol equiv of reagent was employed.
^b Determined by ¹H NMR analysis. ^c Prepared from MeLi and (vinyl)₄Sn at 0 °C.

SCHEME 2. Synthesis of Epoxyketone 22^a

^a Reagents and conditions: (a) HCl/MeOH, 0 °C to rt, 97%; (b) TESOCl, imidazole, DMF, 0 °C, 95%; (c) TBAF, THF, -78 °C, 87%; (d) (i) *p*-TsCl, DMAP, Et₃N, CH₂Cl₂, 0 °C to rt; (ii) K₂CO₃, MeOH, 0 °C, 93%; (e) Dess–Martin periodinane, NaHCO₃, CH₂Cl₂, 0 °C, 98%.

equiv) in tetrahydrofuran at -78 °C, regioselective desilylation occurred to afford the desired mono-TES ether **20** in 87% yield. The use of 1.5–2.0 mol equiv of TBAF decreased the yield of **20** due to the production of a considerable amount of **18**. In contrast, reaction with a catalytic amount of TBAF (0.1 mol equiv) was sluggish. This regioselectivity would be explained by silyl migration derived from the neighboring group participation of the *tert*-hydroxyl group. The triol **20** was transformed into monoepoxide **21** via the corresponding tosylate.¹⁰ Upon treatment with Dess–Martin periodinane¹⁹ in the presence of NaHCO₃, **21** gave Barton's key intermediate **22** (98%). The overall yield of **22** from 2,3:5,6-di-*O*-isopropylidene mannofuranose (**4**) was 26.0% (total 18 steps).

Introduction of the side chain into **22** was performed according to Barton's procedure⁹ (Scheme 3). Thus, ketone **22** was treated at -78 °C with vinylolithium reagent **23**⁸ prepared from acetone 2,4,6-triisopropylbenzenesulfonyl hydrazone to afford the coupling product **24** as a single stereoisomer in 85% yield. We found that the use of a small excess (1.3–1.4 mol equiv) of base was necessary for high yield and the reproducibility of the

SCHEME 3. Coupling Reaction of 22 with 23 and Total Synthesis^a

^a Reagents and conditions: (a) THF, -78 °C, 85%; (b) TBAF, THF, 0 °C, 90%; (c) TPAP, NMO, MS4A, CH₂Cl₂, 0 °C to rt; 79%; (d) VO(acac)₂, *t*-BuO₂H, benzene/decane, 0 °C to rt, 64%.

reaction. Epoxidation of **24** under Sharpless's condition²⁰ resulted in a stereoisomeric mixture (ca. 2–3:1) of di-epoxides as previously reported.⁹ We estimated that the bulky silyl group may interfere with the stereoselective epoxidation. Consequently, the silyl group was removed with TBAF at 0 °C quickly, giving diol **25** in high yield. The prolonged reaction time and higher reaction temperature decreased the yield. Oxidation of the unstable diol **25** was performed by the action of *n*-tetrapropylammonium perruthenate (TPAP)–*N*-methylmorpholine oxide²¹ to produce ketone **26** in good yield. Finally, epoxidation⁸ of **26** afforded ovalicin **2** stereoselectively. The spectral and physical data of synthetic **2** were identical to those of natural **2**.

This "Chiron" approach enabled us to synthesize **2** as an optically pure form in 10.0% overall yield from a commercially available 2,3:5,6-di-*O*-isopropylidene- α -D-mannofuranose (**4**) (total 23 steps). The strategy described herein should be applicable to the preparation of pharmacologically important analogues of **2**.

Experimental Section

(1*S*,4*S*,5*S*,6*R*)-4-(*tert*-Butyldiphenylsilyloxy)methyl)-4,5-*O*-isopropylidenedioxy-6-methoxy-2-cyclohexene-1-ol (**13**). A mixture of **11** (5.46 g, 11.0 mmol) and Grubbs' second generation catalyst (110 mg, 0.13 mmol) in toluene (86 mL) was heated at 80 °C for 1.5 h with stirring and then cooled. After addition of florasil, the resulting mixture was stirred at room temperature for 1 h, filtered through a pad of Celite, and then concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc = 8:1) to give **13** (4.87 g, 94%) as a light yellow oil: [α]_D²⁵ +66.6 (*c* 1.04, CHCl₃); IR (neat) 3480, 3073, 2986, 2828, 1589, 1473, 1429, 1412, 1381, 1375, 1250, 1120 cm⁻¹; ¹H NMR (270 MHz, CDCl₃): δ 7.74–7.69 (m, 4H), 7.42–7.38 (m, 6H), 5.91 (dd, *J* = 10.4, 4.6 Hz, 1H), 5.56 (d, *J* = 10.4 Hz, 1H),

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4.68 (d, $J = 4.9$ Hz, 1H), 4.09 (m, 1H), 3.77 (t, $J = 4.6$ Hz, 1H), 3.74, 3.58 (each d, $J = 10.6$ Hz, 2H), 3.51 (s, 3H), 2.89 (d, $J = 9.0$ Hz, 1H), 1.49 (s, 3H), 1.46 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 135.6, 135.5, 132.9, 132.8, 129.6, 129.5, 128.6, 128.3, 127.5, 127.5, 109.8, 81.3, 80.2, 74.9, 66.0, 65.7, 58.7, 28.5, 27.7, 26.8, 19.3. Anal. Found: C, 69.26; H, 7.70. Calcd for $\text{C}_{27}\text{H}_{36}\text{O}_5\text{Si}$: C, 69.20; H, 7.74.

(1R,4S,5S,6R)-4-(tert-Butyldiphenylsilyloxymethyl)-4,5-O-isopropylidenedioxy-6-methoxy-2-cyclohexene-1-ol (14). Treatment of **12** (1.28 g, 2.57 mmol) with Grubbs' second generation catalyst (39.0 mg, 0.05 mmol) in toluene (30 mL) as described above gave **14** (1.01 g, 84%) as a light yellow oil: $[\alpha]_{\text{D}}^{28} +11.7$ (c 0.41, CHCl_3); IR (neat) 3480, 3073, 2986, 2830, 1589, 1471, 1429, 1410, 1375, 1252, 1220, 1080 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3): δ 7.77–7.71 (m, 4H), 7.43–7.36 (m, 6H), 5.68 (brd, $J = 10.1$ Hz, 1H), 5.44 (brd, $J = 10.1$ Hz, 1H), 4.82 (d, $J = 4.0$ Hz, 1H), 4.40 (m, 1H), 3.91 (t, $J = 4.1$ Hz, 1H), 3.78, 3.53 (each d, $J = 10.6$ Hz, 2H), 3.49 (s, 3H), 2.57 (d, $J = 11.2$ Hz, 1H), 1.50 (s, 3H), 1.40 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 135.6, 135.5, 133.0, 132.8, 130.0, 129.6, 129.5, 127.6, 127.5, 108.6, 80.2, 79.0, 71.3, 65.5, 65.2, 59.0, 28.0, 27.5, 26.9, 19.3. Anal. Found: C, 69.29; H, 7.54. Calcd for $\text{C}_{27}\text{H}_{36}\text{O}_5\text{Si}$: C, 69.20; H, 7.74.

(1S,2S,3R,4R)-1-Hydroxymethyl-4-triethylsilyloxy-3-methoxycyclohexane-1,2-diol (20). To a stirred solution of **19** (1.00 g, 1.87 mmol) in tetrahydrofuran (17 mL) was added dropwise a 1.0 M solution of *n*-tetrabutylammonium fluoride (1.4 mL, 1.4 mmol) in tetrahydrofuran at -78 °C, and the mixture was stirred

at -78 °C for 3 h and at 0 °C for 1 h. After addition of NaCl brine, the resulting mixture was extracted with EtOAc. The extracts were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc = 2:1) to give **20** (498 mg, 87%) as a colorless liquid: $[\alpha]_{\text{D}}^{28} -66.7$ (c 1.18, CHCl_3); IR (neat) 3460, 2953, 2878, 1458, 1414, 1238, 1120, 1078, 1037 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3): δ 4.25 (m, 1H), 3.91 (d, $J = 10.2$ Hz, 1H), 3.77, 3.42 (each d, $J = 10.2$ Hz, 2H), 3.40 (s, 3H), 3.22 (dd, $J = 9.3, 2.1$ Hz, 1H), 3.10–2.70 (brs, 3H), 1.80–1.55 (m, 3H), 1.48–1.43 (m, 1H), 0.96 (t, $J = 7.9$ Hz, 9H), 0.59 (q, $J = 7.9$ Hz, 6H); ^{13}C NMR (67.5 MHz, CDCl_3): δ 82.7, 73.2, 72.6, 69.8, 65.6, 57.0, 27.0, 26.0, 6.8, 4.9; HRMS calcd $\text{C}_{12}\text{H}_{25}\text{O}_5\text{Si}$ (M – Et): 277.1552. Found: 277.1462. Anal. Found: C, 54.42; H, 9.99. Calcd for $\text{C}_{14}\text{H}_{30}\text{O}_5\text{Si} \cdot 0.2\text{H}_2\text{O}$: C, 54.23; H, 9.88.

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Supporting Information Available: Experimental procedures and NMR spectra of **24–26** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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