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Synthesis of Ovalicin Starting from D-Mannose

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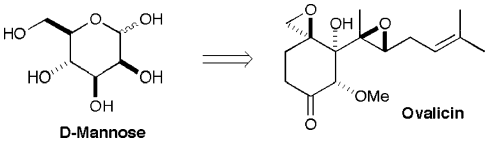
Received August 10, 2005



A new synthesis of epoxyketone **22** is described that is a key intermediate in Barton's synthesis of ovalicin (**2**), a powerful anti-angiogenetic 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-angiogenetic 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 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 studies[12] on heterocyclic natural products based on the "Chiron" approach,[13] we describe herein an efficient synthesis of **2** starting from D-mannose.

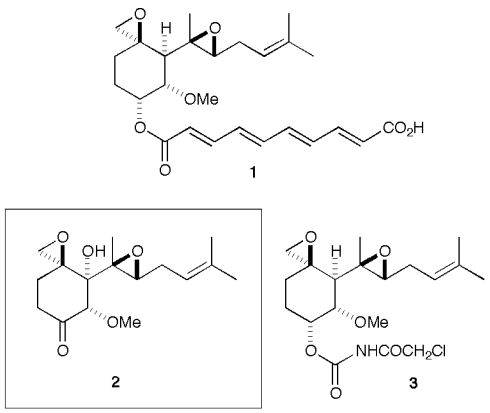


FIGURE 1. Structures of Anti-Angiogenesis Inhibitors.

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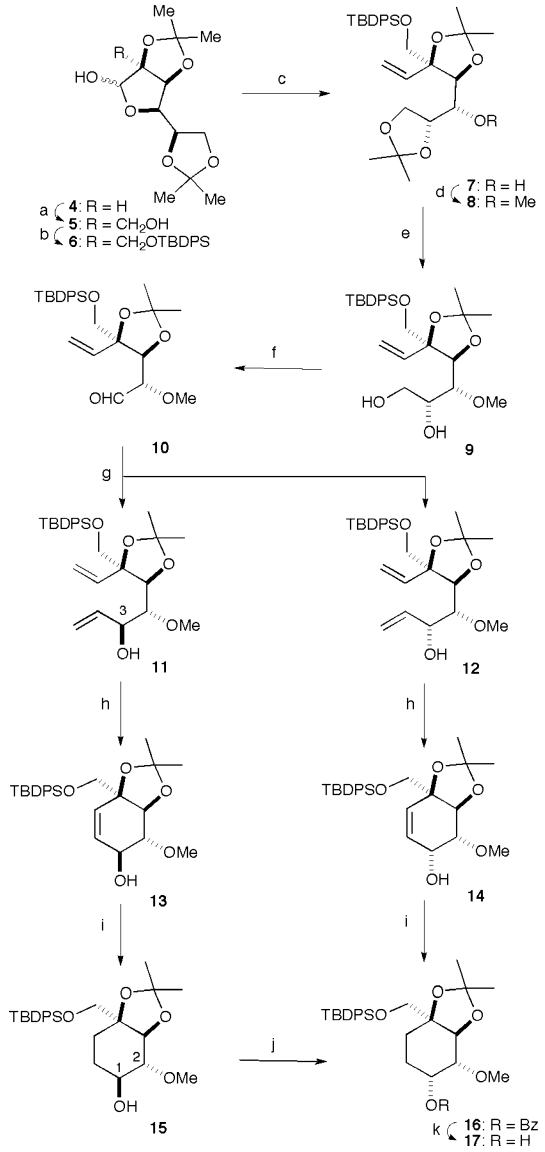
10.1021/jo051686m CCC: $30.25
Published on Web 10/20/2005

To construct the carbon backbone of **2**, we adopted Barton's strategy[9] that uses a stereoselective coupling reaction between cyclohexane **22** and vinyllithium 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-mannnofuranose (**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 conditions[16] 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 deisopropylidenation to afford diol **9**. For the construction of another olefin unit in **9**, selective oxidation[17] 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 ^{1}H 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 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**.

SCHEME 1. Synthesis of Cyclohexanol 17[a]



[a] Reagents and conditions: (a) ref 15; (b) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt, 85%; (c) $Ph_3P^+CH_3Br^-$, KO*t*-Bu, toluene, 105 °C, 97%; (d) NaH, MeI, THF, 0 °C, 97%; (e) aq. AcOH, 50 °C, 72%; (f) $NaIO_4$, THF/H_2O, rt, and then $(CH_2OH)_2$, 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, H_2, EtOAc, rt, 99% for **15**, 95% for **17**; (j) DEAD, Ph_3P, benzoic acid, THF, 0 °C to rt; (k) NaOMe, MeOH, rt, 95% from **15** (two steps).

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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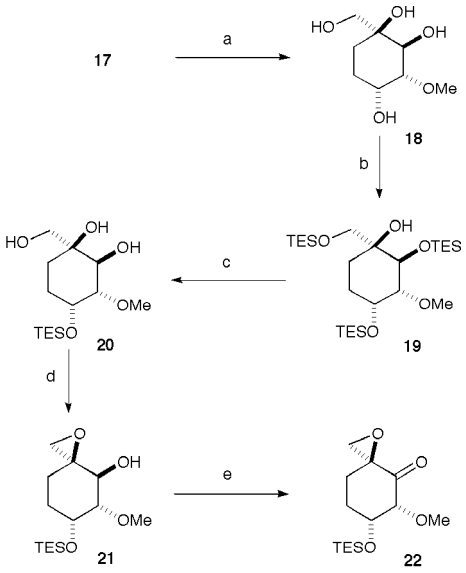
TABLE 1. Vinylation of Aldehyde 10

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 ^{1}H NMR analysis. [c] Prepared from MeLi and $(vinyl)_4Sn$ at 0 °C.

SCHEME 2. Synthesis of Epoxyketone 22[a]



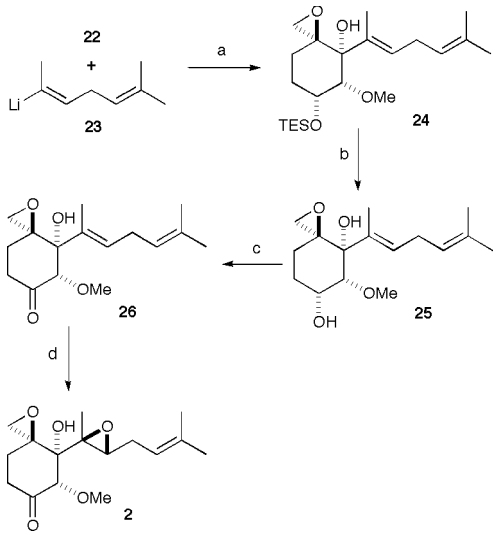
[a] Reagents and conditions: (a) HCl/MeOH, 0 °C to rt, 97%; (b) TESCl, imidazole, DMF, 0 °C, 95%; (c) TBAF, THF, −78 °C, 87%; (d) (i) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt; (ii) K_2CO_3, MeOH, 0 °C, 93%; (e) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C, 98%.

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 regioselecivity 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 periodinane[19] in the presence of $NaHCO_3$, **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 procedure[9] (Scheme 3). Thus, ketone **22** was treated at −78 °C with vinyllithium 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

(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

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, CH_2Cl_2, 0 °C to rt; 79%; (d) $VO(acac)_2$, *t*-BuO_2H, benzene/decane, 0 °C to rt, 64%.

reaction. Epoxidation of **24** under Sharpless's condition[20] resulted in a stereoisomeric mixture (ca. 2−3:1) of diepoxides 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 oxide[21] to produce ketone **26** in good yield. Finally, epoxidation[8] 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*-Butyldiphenylsilanyloxymethyl)-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 florisil, 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: $[\alpha]^{28}_D$ +66.6 (*c* 1.04, $CHCl_3$); IR (neat) 3480, 3073, 2986, 2828, 1589, 1473, 1429, 1412, 1381, 1375, 1250, 1120 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): 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 $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74.

(1*R*,4*S*,5*S*,6*R*)-4-(*tert*-Butyldiphenylsilanyloxymethyl)-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: $[\alpha]^{28}_D$ +11.7 (*c* 0.41, $CHCl_3$); IR (neat) 3480, 3073, 2986, 2830, 1589, 1471, 1429, 1410, 1375, 1252, 1220, 1080 cm^{-1}; ^{1}H 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 $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74.

(1*S*,2*S*,3*R*,4*R*)-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: $[\alpha]^{28}_D$ −66.7 (*c* 1.18, $CHCl_3$); IR (neat) 3460, 2953, 2878, 1458, 1414, 1238, 1120, 1078, 1037 cm^{-1}; ^{1}H 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 $C_{12}H_{25}O_5Si$ (M − Et): 277.1552. Found: 277.1462. Anal. Found: C, 54.42; H, 9.99. Calcd for $C_{14}H_{30}O_5Si\cdot0.2H_2O$: C, 54.23; H, 9.88.

Acknowledgment. We are grateful to Dr. T. Chihara and his collaborators in RIKEN for the elemental analyses. We also thank Drs. T. Nakamura and Y. Hongo (RIKEN) for mass spectral measurements. This work was supported by the Chemical Biology Project (RIKEN).

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.

JO051686M