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A highly enantioselective synthesis of (−)- and (+)-juglomycin A through Dötz annulation and asymmetric dihydroxylation

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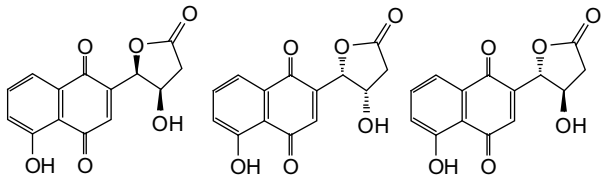
Abstract

A highly enantioselective synthesis of (−)- and (+)-juglomycin A, a quinone antibiotic is described. The synthesis is completed in eight steps, and 19% overall yield and in a high enantioselectivity of 99.5% [for (−)-juglomycin A] and 98.5% [for (+)-juglomycin A]. The synthetic strategy features an efficient combination of the Dötz annulation reaction and asymmetric dihydroxylation as the keys steps.

Keywords: Juglomycins; Asymmetric synthesis; Dötz annulation; Modified Knoevenagel reaction; Asymmetric dihydroxylation

Juglomycins A **1** and B **2** (Fig. 1) isolated from the culture filtrate of the fungus *Streptomyces* sp. 190–2[1] show antitumor activity as well as antibacterial activity against both Gram-negative and Gram-positive bacteria.[1] A few syntheses of racemic juglomycins have been reported.[2] The formal syntheses of **1** and its analogs are also known.[3] There is only one report on the asymmetric synthesis of **1** (in 15% overall yield) by Kraus and Maeda.[4] Herein, a highly enantioselective synthesis of both (−)-juglomycin A **1** and its unnatural isomer (+)-*ent*-**1** is described. The synthetic strategy features an efficient combination of the Dötz annulation and asymmetric dihydroxylation as the key steps.

The retrosynthesis of (−)-juglomycin A **1** and (+)-*ent*-**1** is shown in Scheme 1. The target compounds can be envisioned to be derived from a β,γ-unsaturated ester **3** through asymmetric dihydroxylation. Ester **3** can be obtained from alcohol **4** through oxidation and a decarboxylative deconjugative Knoevenagel condensation.[5] The alcohol **4** with required aryl functionalization could be prepared by Dötz annulation[6] from Fischer carbene **6**.



1 (-)-juglomycin A *ent*-**1** (+)-juglomycin A (unnatural) **2** juglomycin B

Fig. 1. Juglomycins A **1**, *ent*-**1** (unnatural), and B **2**.

The detailed synthesis of β,γ-unsaturated ester **3** is shown in Scheme 2. To begin with, the Fischer carbene complex **6**[7] was prepared from 2-bromoanisole **7** in 83% yield. Condensation of **6** with alkyne **5**[8] afforded the Dötz annulated product **8** in a good yield of 78%. Methylation of the phenolic hydroxyl with MeI gave **9** in 81% yield. Deprotection of the TBDMS group in **9** was effected with TBAF to afford alcohol **4** in quantitative yield. Further, Swern oxidation of **4** gave the corresponding aldehyde which when condensed with the half ester of malonic acid under decarboxylative deconjugative Knoevenagel conditions[5] afforded the β,γ-unsaturated ester **3** in a good yield of 72% (over two steps).

The synthesis of (−)-juglomycin A **1** from **3** was completed as shown in Scheme 3. Sharpless asymmetric

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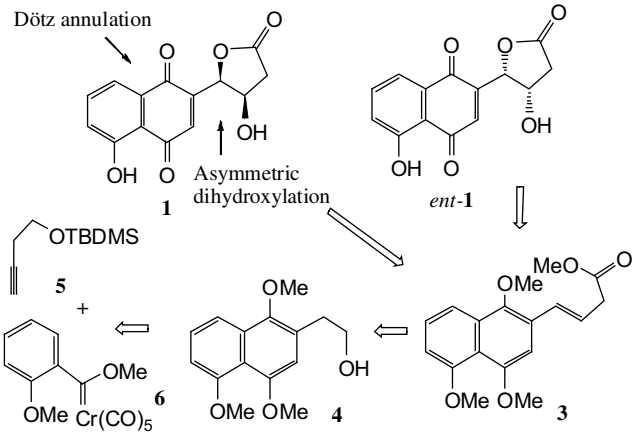
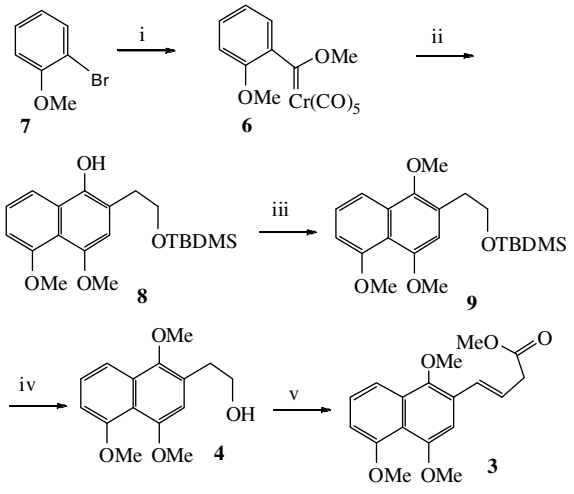
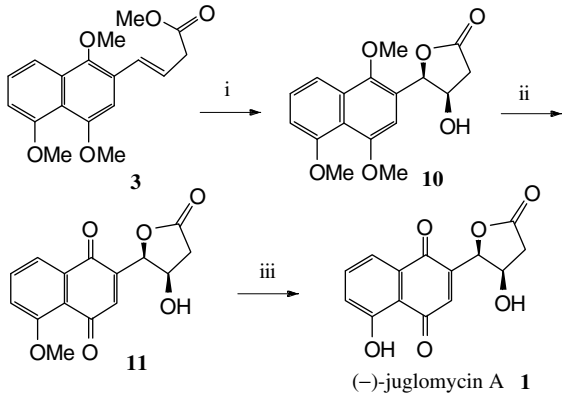


Scheme 1. Retrosynthesis of (−)-juglomycin A **1** and *ent*-**1**.

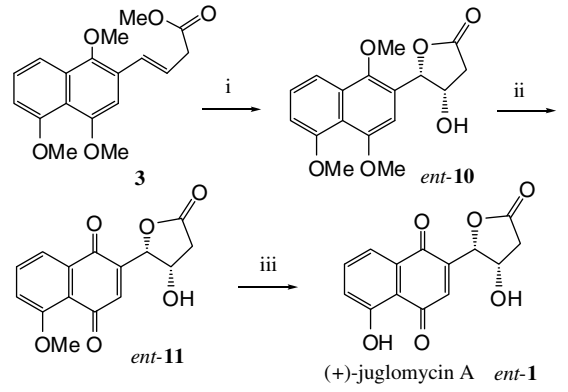
dihydroxylation[9] of **3** with the $(DHQD)_2$-PHAL ligand afforded the β-hydroxy-γ-lactone **10**[10] in a good yield of 84% and with an excellent enantioselectivity of 99.5% ee.[11] Further treatment of **10** with CAN afforded quinone **11** in a very good yield of 94%. Demethylation of **11** with $AlCl_3$ gave (−)-juglomycin **1** in 92% yield as a yellow solid, $[\alpha]_D^{25}$ −51.6 (*c* 0.25, $CHCl_3$) [lit.[1] −51.9 (*c* 0.42, DMSO)], mp 171–173 °C (decomp. at 170 °C) [lit.[4] 175–177 °C (decomp.)]. The spectroscopic and analytical data of **1** were in full agreement with that reported.[4] The overall yield for this eight step strategy was 19%. Similarly, the unnatural isomer *ent*-**1** (Scheme 4) was synthesized from **3** through asymmetric dihydroxylation using the $(DHQ)_2$-PHAL ligand to give *ent*-**10**[10] in 83% yield and 98.5% ee.[11] Further, quinone formation (*ent*-**11**) and demethylation afforded the unnatural isomer (+)-juglomycin A, *ent*-**1** as a yellow solid, $[\alpha]_D^{25}$ +49.2 (*c* 0.2, $CHCl_3$), mp 168–171 °C



Scheme 2. Synthesis of β,γ-unsaturated ester **3**. Reagents and conditions: (i) *n*-BuLi (1.04 equiv), THF, −78 °C, 5 min, $Cr(CO)_6$ (1.0 equiv), −78 °C to 0 °C, 3 h, then Me_3OBF_4 (1.5 equiv), CH_2Cl_2, 0 °C to rt, 3 h, 83%; (ii) **5** (1.5 equiv), THF, 45 °C, 12 h, 78%; (iii) NaH (3.0 equiv), MeI (3.1 equiv), DMF, 0 °C to rt, 3 h, 81%; (iv) TBAF (1.2 equiv), THF, rt, 2 h, quant.; (v) (a) $(COCl)_2$ (1.4 equiv), DMSO (2.0 equiv), −78 °C, 20 min, **4**, 45 min, Et_3N (4 equiv), −60 °C, 30 min, to room temperature, 1 h; (b) $MeO_2CCH_2CO_2H$ (2.0 equiv), Et_3N, reflux, 12 h, 72% over two steps.



Scheme 3. Synthesis of (−)-juglomycin A **1** from **3**. Reagents and conditions: (i) $(DHQD)_2$-PHAL (1.0 mol %), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $NaHCO_3$ (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), $K_2OsO_4{\cdot}2H_2O$ (0.4 mol %), *t*-BuOH–H_2O (1:1), 0 °C, 24 h, then rt, 12 h, 84%; (ii) $(NH_4)_2Ce(NO_3)_6$ (2.0 equiv), MeCN–H_2O (1:1), rt, 15 min, 94%; (iii) $AlCl_3$ (2.0 equiv), CH_2Cl_2, 0 °C, 10 min, then rt, 45 min, 92%.



Scheme 4. Synthesis of (+)-juglomycin A *ent*-**1** from **3**. Reagents and conditions: (i) $(DHQ)_2$-PHAL (1.0 mol %), $K_3Fe(CN)_6$ (3.0 equiv), K_2CO_3 (3.0 equiv), $NaHCO_3$ (3.0 equiv), $MeSO_2NH_2$ (1.0 equiv), $K_2OsO_4{\cdot}2H_2O$ (0.4 mol %), *t*-BuOH–H_2O (1:1), 0 °C, 24 h, then rt, 12 h, 83%; (ii) $(NH_4)_2Ce(NO_3)_6$ (2.0 equiv), MeCN–H_2O (1:1), rt, 15 min, 94%; (iii) $AlCl_3$ (2.0 equiv), CH_2Cl_2, 0 °C, 10 min, then rt, 45 min, 93%.

(decomp. at 168 °C). The spectroscopic and analytical data of *ent*-**1** were similar to **1**.

In summary, a highly enantioselective synthesis of both (−)- and (+)-juglomycin A has been achieved in eight steps, 19% overall yield (for both), and 99.5% ee and 98.5% ee respectively. The synthetic strategy features an efficient combination of Dötz annulation and asymmetric dihydroxylation as the key steps. Thus, the above strategy with high enantiocontrol and versatility to target both enantiomers represents an alternative to the known methods. Application of this strategy to other related compounds is in progress.

Acknowledgments

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10. *(4R,5R)-4-Hydroxy-5-(1,4,5-trimethoxynaphth-2-yl)dihydrofuran-2(3H)-one* (**10**). To a mixture of $K_3Fe(CN)_6$ (4.22 g, 12.81, 3 equiv), K_2CO_3 (1.77 g, 12.81 mmol, 3 equiv), $MeSO_2NH_2$ (406 mg, 4.27 mmol, 1 equiv), $NaHCO_3$ (1.08 g, 12.81 mmol, 3 equiv), $(DHQD)_2$-PHAL (33.3 mg, 0.427 mmol, 1 mol %), $K_2OsO_4{\cdot}2H_2O$ (6.3 mg, 17.1 μmol, 0.4 mol %), *t*-BuOH (10 mL) and water (25 mL) were added. The mixture was stirred for 5 min and cooled to 0 °C in a ice bath. To the cooled mixture, a solution of the β,γ-unsaturated ester **3** (1.35 g, 4.27 mmol) in *t*-BuOH (15 mL) was added. The reaction mixture was stirred at 0 °C for 24 h and at room temperature for 12 h. It was then quenched with solid Na_2SO_3 (3 g) and stirred for 30 min. The solution was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with 1 M KOH (15 mL), water (50 mL), brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash-chromatography using petroleum ether/EtOAc (3:2–1:1) as eluent to afford **10** (1.14 g, 84%) as a white solid (mp 134–136 °C). The enantiomeric excess was determined to be 99.5% ee by chiral HPLC as reported.[11] $[\alpha]_D^{25}$ −11.2 (*c* 0.6, $CHCl_3$). IR ($CHCl_3$):ν = 3289, 3004, 2966, 2945, 2843, 1782, 1731, 1622, 1603, 1588, 1513, 1466, 1355, 1340, 1323, 1261, 1232, 1159, 1123, 1081, 1044, 984, 915 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.05$ (s, 1H, OH), AB signal ($\delta_A = 2.73$, $\delta_B = 2.91$, $J_{AB} = 17.4$ Hz, A-part shows no additional splitting by $J_{A,4}$, B-part in addition is split by $J_{B,4} = 5.5$ Hz, 2H, 3-H_2), 3.86, 3.95 and 3.96 (3s, 3 × 3H, 3 × MeO), 4.83 (m, 1H, 4-H), 5.84 (d, 1H, $J_{5,4} = 3.6$ Hz, 5-H), 6.88 (d, 1H, $J_{6',7'} = 8.1$ Hz, 6′-H), 6.89 (s, 1H, 3′-H), 7.42 (dd, 1H, $J_{7',6'} = J_{7',8'} = 8.1$ Hz, 7′-H), 7.58 (dd, 1H, $J_{8',7'} = 8.4$ Hz, $^4J_{8',6'} = 1.2$ Hz, 8′-H). ^{13}C NMR (100 MHz, $CDCl_3$/$CHCl_3$): $\delta = 38.22$ (C-3), 56.53, 56.66 and 61.89 (3 × MeO), 69.70 (C-4), 81.77 (C-5), 103.98 (C-3′), 107.20 (C-6′), 114.36 (C-8′), 127.1 (C-7′), 118.44, 122.33 and 130.61 (C-2′, C-4′a, C-8′a), 145.90, 153.82 and 157.45 (C-1′, C-4′, C-5′), 175.57 (C-2). EIMS: $m/e = 318$ [M^+] (100), 304 (72), 233 (54), 205 (20), 83 (39). $C_{17}H_{18}O_6$ (318.3) Calcd: C, 64.14; H, 5.70. Found: C, 63.97; H, 5.86. Similarly, the asymmetric dihydroxylation of β,γ-unsaturated ester **3** (1.0 g, 3.17 mmol) with $(DHQ)_2$-PHAL ligand following the above procedure afforded *ent*-**10** (0.835 g, 83%) as a white solid (mp 131–133 °C), $[\alpha]_D^{25}$ +11.0 (*c* 0.4, $CHCl_3$). The enantiomeric excess was determined to be 98.5% ee by chiral HPLC as reported.[11] The spectroscopic and analytical data of *ent*-**10** were similar to **10**.
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