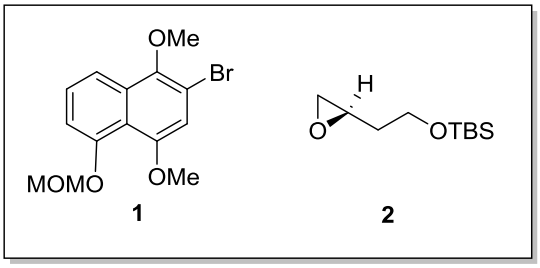
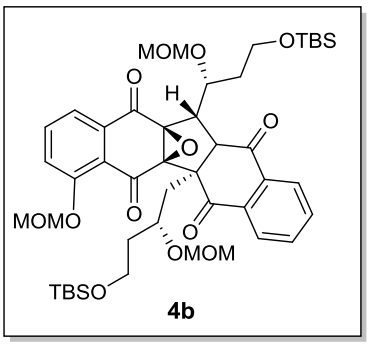
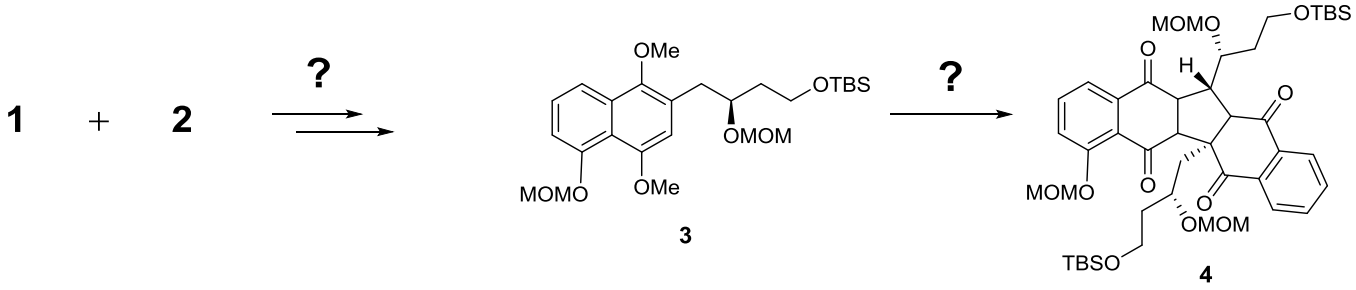
Exercise meeting **07.10.2016**

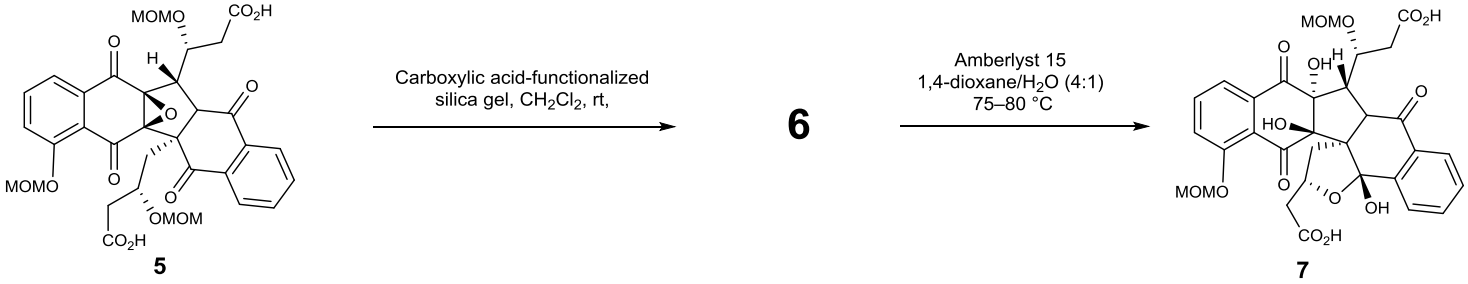
Syntheses of *Juglorescein* and *Juglocombins* A and B

Submitted by Camilo M.









1. How would you prepare the epoxide **2** from aspartic acid? *Hint:* Diazotisation.

2. The heavily substituted naphthalene derivative **3** can be prepared from **1** and **2** in two steps. Propose the needed reagents and the corresponding mechanism leading to the target molecule.

3. Propose the step(s), reagent(s) and the mechanism(s) involved in the dimerization reaction whose product is the compound **4**.

4. Which additive would you include to obtain compound **4a** instead? (Under the same condition reactions for the preparation of **4**) Discuss a method to prepare **4a** directly from **4**. Would be this transformation suitable?

5. Give the structure of the missing compound **6** and the mechanism involved in the transformation taking place from it to **7**.

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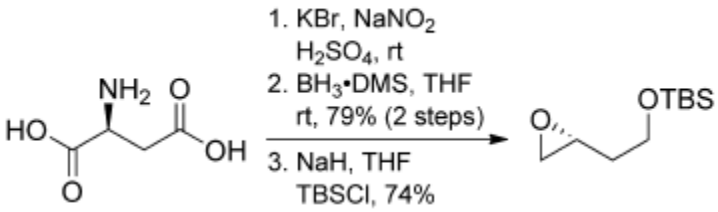
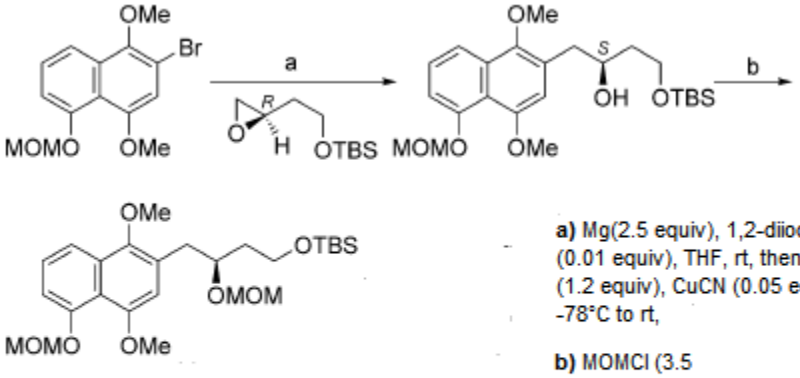
- *How would you prepare the epoxide **2** from aspartic acid? Hint: Diazotisation.*



- *The heavily substituted naphthalene derivative **3** can be prepared from **1** and **2** in two steps. Propose the needed reagents and the corresponding mechanism leading to the target molecule.*



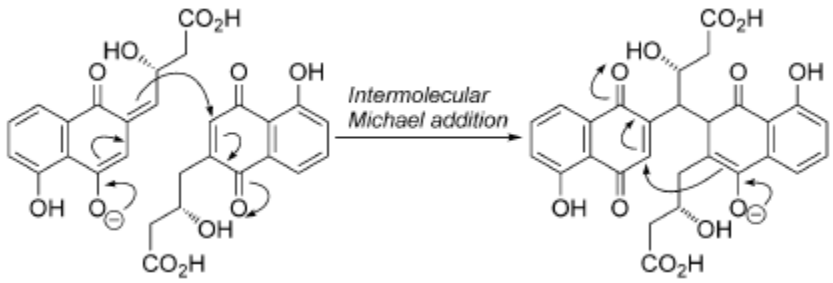
a) Mg(2.5 equiv), 1,2-diiodoethane (0.01 equiv), THF, rt, then epoxide (1.2 equiv), CuCN (0.05 equiv), THF, -78°C to rt,

b) MOMCl (3.5 equiv), DIPEA (3.6 equiv), TBAI (0.1 equiv), CH_2Cl_2, reflux.

- *Propose the step(s), reagent(s) and the mechanism(s) involved in the dimerization reaction whose product is the compound **4**.*

Reaction conditions: DBU (3.0 equiv), O2, CH2Cl2, -25 °C, 5 d,

Mechanism:

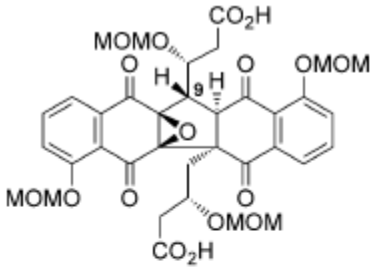


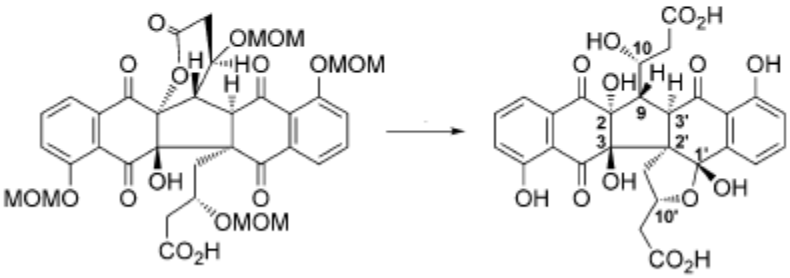
- *Which additive would you include to obtain compound **4a** instead? (Under the same condition reactions for the preparation of **4**) Discuss a method to prepare **4a** directly from **4**. Would be this transformation suitable?*

The addition of oxygen to the reaction yields the corresponding epoxide **4a.**

The epoxidation could be performed by employing N-bromosuccinmide in tetrachloromethane (hv) then dihydrogen peroxide; sodium carbonate in water; acetone T=0 - 20°C. The main disadvantage of this reaction is that would be hard to control the mono-epoxidation.

- *Give the structure of the missing compound **6** and the mechanism involved in the transformation taking place from it to **7**.*





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Fused-Ring Systems

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Total Syntheses of Juglorescein and Juglocombins A and B

Shogo Kamo, Kai Yoshioka, Kouji Kuramochi, and Kazunori Tsubaki*

Abstract: *Total syntheses of juglorescein and juglocombins A and B are reported. The highly oxygenated 6/6/5/6/6-fused pentacyclic ring system of these natural products was constructed through a bioinspired dimerization of 1,4-naphthoquinone. Notably, five new stereogenic centers were constructed in a single step by the dimerization reaction. The epoxide intermediate obtained from the dimerization was successfully converted into juglocombins A and B through photoinduced reduction of the epoxide, dehydration, and conversion of the resultant quinone into a hydroquinone derivative. The same epoxide intermediate was also converted into a dicarboxylic acid, which was transformed into juglorescein through intramolecular lactonization, hydrolysis of the resulting lactone, and removal of the protecting groups. Furthermore, the relative and absolute configurations of juglorescein and juglocombins A and B were determined.*

Juglorescein (**1**), and juglocombins A (**2**) and B (**3**) have been isolated from *Streptomyces* sp. 815 and GW4184 (Figure 1 a).[1] Because **2** and **3** are unstable and highly polar, they were converted into dimethyl esters (**2′** and **3′**) and 1′-*O*-methyljuglocombin B dimethyl ester (**4**) to confirm their structures. Although the structures were confirmed by detailed NMR studies, the relative and absolute configurations of the compounds remained undetermined. These compounds have a highly oxygenated, 6/6/5/6/6-fused A/B/C/D/E ring system. The related naphthoquinone dimers zeylanone,[2a,b] zeylanone epoxide,[2c] and two shikometabolins,[2d] are shown in Figure 1 b. Zeylanone shows antibacterial and antifungal activity.[2b] This compound also exhibits cytotoxic activity against cancer cell lines.[2b] Shikometabolins E and F show significant neuraminidase inhibitory activity.[2d,e] Total synthesis of racemic zeylanone and zeylanone epoxide was achieved by our group.[3] However, no total synthesis of **1**–**3** has been reported to date, because construction of this carbon framework with multiple contiguous stereogenic centers has proven challenging. Herein, we report the first total syntheses and determination of the absolute configurations of **1**–**3**. Construction of the ring system, including the five stereogenic centers, was achieved through a bioinspired dimerization of a naphthoquinone monomer.

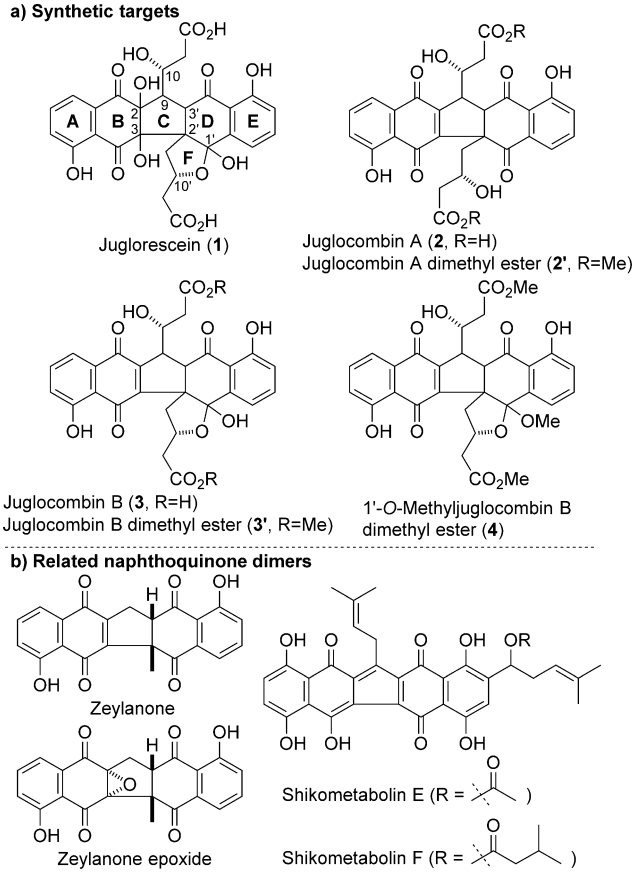

Figure 1. a) Structures of juglorescein (**1**), juglocombins A (**2**), and B (**3**), and their derivatives (**2′**, **3′**, and **4**). b) Related naphthoquinone dimers zeylanone, zeylanone epoxide, and shikometabolins E and F.

The proposed biosynthetic pathway to **1**–**3** involves the dimerization of juglomycin C (**5**; Scheme 1).[1,4] Sequential intermolecular and intramolecular Michael addition of **5**, followed by oxidation of the resulting hydroquinone, gives **2** and **3**. Compound **3** is then enzymatically oxidized to yield **1**.

Our retrosynthetic analysis of **1**–**3** is illustrated in Scheme 2. We propose that these compounds can be synthesized from common intermediate **6**, which in turn can be prepared through a bioinspired dimerization reaction of the juglomycin C derivative **7**.[1] We envisioned that this dimerization would proceed in a highly regio- and stereoselective manner via a five-membered cyclic transition state (**I**). Epoxidation of the resultant hydroquinine monoanion with oxygen[5] would occur preferentially from the opposite side of the side chain at C-2′.[3] Compound **7** can readily be prepared

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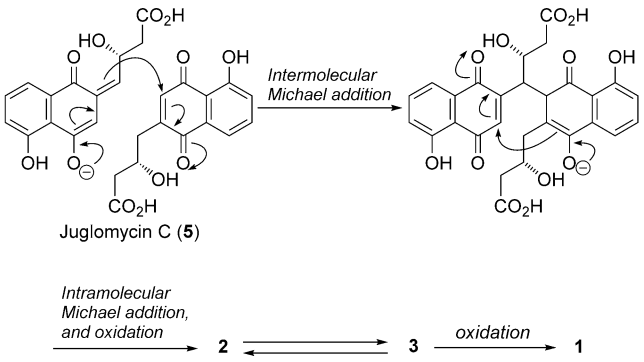
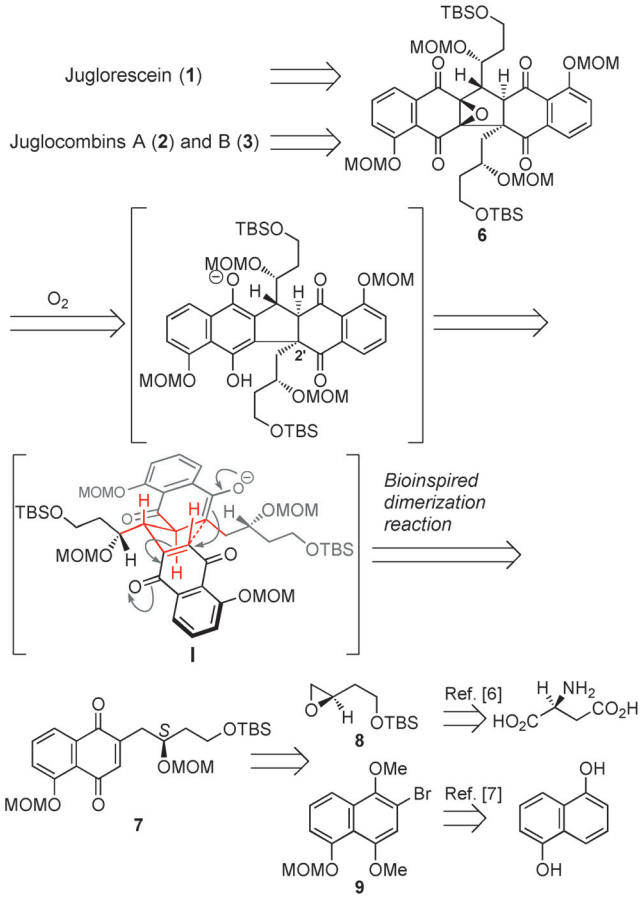
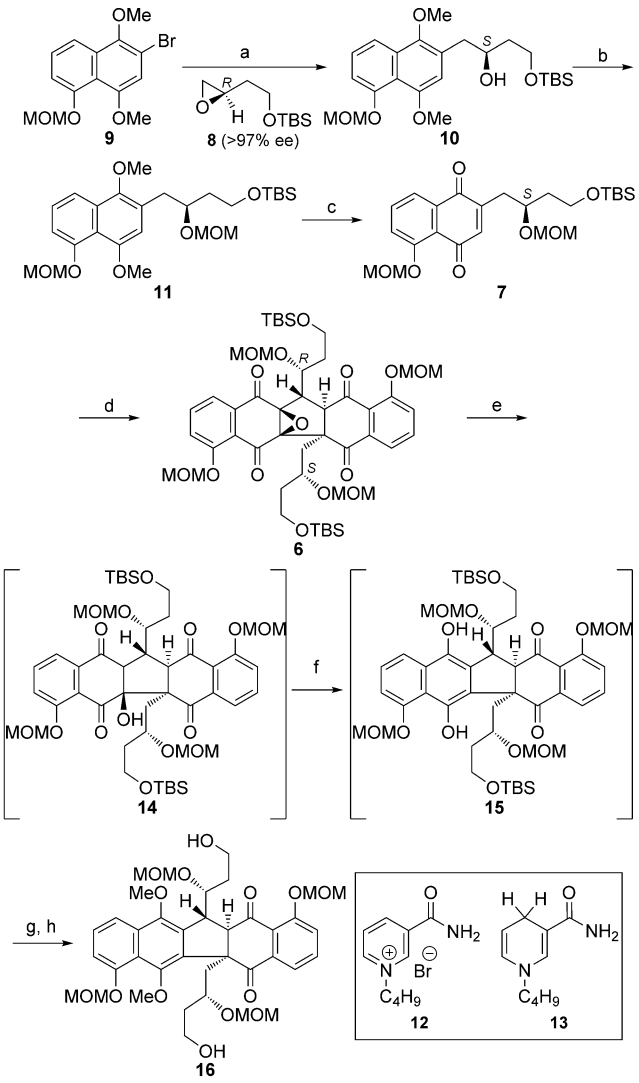


Scheme 1. Proposed biosynthesis of **1**–**3**.



Scheme 2. Retrosynthetic analysis of **1**–**3**. TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl.



Scheme 3. Reaction conditions for the synthesis of **16**: a) **9**, Mg (2.5 equiv), 1,2-diiodoethane (0.01 equiv), THF, RT, 35 min, then **8** (1.2 equiv), CuCN (0.05 equiv), THF, −78 °C to RT, 1.5 h, 57% yield; b) MOMCl (3.5 equiv), DIPEA (3.6 equiv), TBAI (0.1 equiv), CH_2Cl_2, reflux, 2 d, 74% yield; c) PIDA (1.5 equiv), TFE/H_2O (5:3), RT, 15 min, 90%; d) DBU (3.0 equiv), O_2, CH_2Cl_2, −25 °C, 5 d, 73% yield; e) **12** (7.1 equiv), Na_2CO_3 (75.4 equiv), $Na_2S_2O_4$ (60.3 equiv), EtOAc/H_2O (1:1), white light, RT, 3 days; f) **13** (7.1 equiv), 4 Å molecular sieves, toluene, 50 °C, 35 min; g) Me_2SO_4 (15.3 equiv), K_2CO_3 (15.2 equiv), acetone, reflux, 22 h; h) TBAF (5.1 equiv), AcOH (3.8 equiv), THF, 30 °C, 2 d, 30% yield over four steps. THF = tetrahydrofuran, DIPEA = *N*,*N*-diisopropylethylamine, TBAI = tetra-*n*-butylammonium iodide, PIDA = iodobenzene diacetate, TFE = 2,2,2-trifluoroethanol, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBAF = tetra-*n*-butylammonium fluoride.

from the known optically active epoxide (**8**)[6] and 2-bromonaphthalene (**9**).[7]

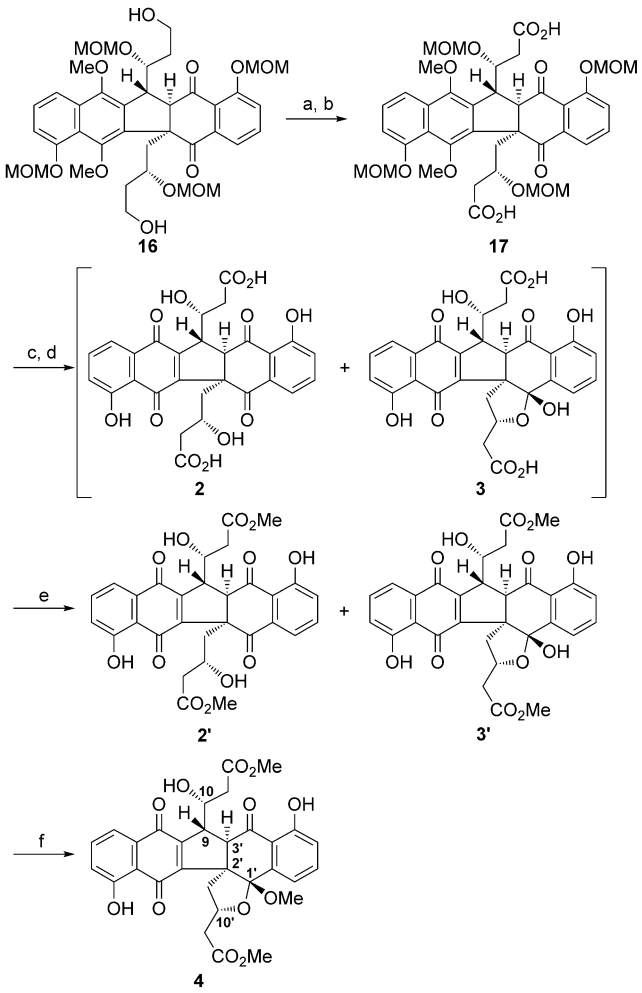
Our synthesis began with the generation of a Grignard reagent from aryl bromide **9**, which was treated with optically active epoxide **8** to give **10** in 57% yield (Scheme 3). The hydroxy group in **10** was protected as a methoxymethyl (MOM) ether to give **11** in 74% yield. Oxidation of **11** with iodobenzene diacetate (PIDA) gave juglomycin C derivative **7** in 90% yield.[8] The key dimerization reaction of **7** under basic conditions using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in an oxygen atmosphere proceeded to produce the desired dimer **6** in 73% yield.[9] Notably, five new stereogenic centers were generated in a single step. With dimer **6** in hand, reduction of the epoxide in **6** was examined. Traditional sets of conditions, including molybdenum hexacarbonyl in toluene,[10a] zinc powder in AcOH,[10b] and titanocene dichloride in THF,[10c] were examined, yet neither the desired alcohol nor the naphthoquinone compound was obtained. However,

a solution of **6**, sodium carbonate, sodium hydrosulfite, and **12**[11] was irradiated under white light to give alcohol **14**.[12] Thermal dehydration of alcohol **14** proceeded easily, but the resultant naphthoquinone was too unstable to isolate. Therefore, **14** was treated with dihydronicotinamide **13** under heating at 50 °C to give hydroquinone **15**. Without purification, methylation of the two phenolic hydroxy groups in **15**, followed by removal of the *tert*-butyldimethylsilyl (TBS) protecting groups with tetra-*n*-butylammonium fluoride (TBAF)/AcOH gave **16** in 30% yield over the four steps from **6**. The relative and absolute configurations of **16** were determined by rotating frame nuclear Overhauser effect spectroscopy (ROESY) correlations and comparison of the calculated and experimental circular dichroism (CD) spectra (see Figure S1 in the Supporting Information).

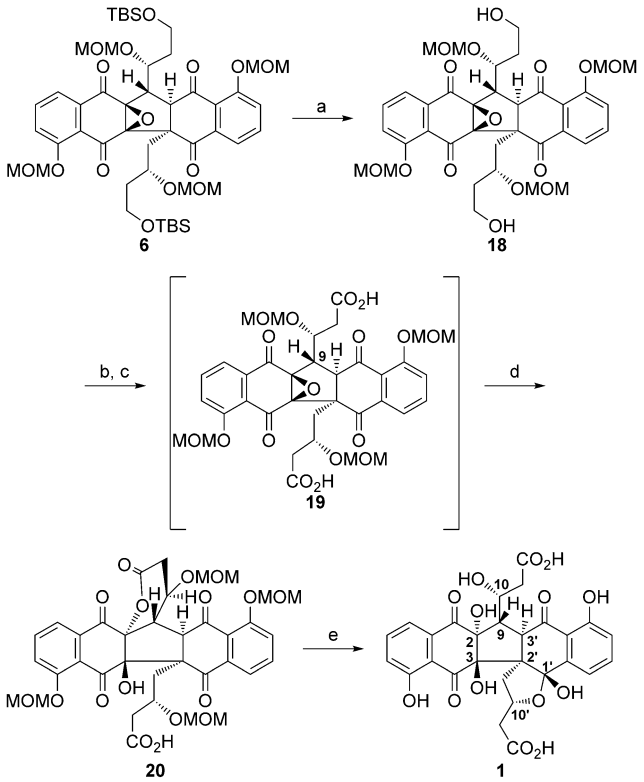
The synthesis of juglocombins A and B is shown in Scheme 4. Oxidation of the primary alcohols in **16** through Dess–Martin oxidation[13] and Pinnick oxidation[14] gave dicarboxylic acid **17** in 94% yield over two steps. Oxidation of the 1,4-dihydroxynaphthalene moiety in **17** with [bis(trifluoroacetoxy)iodo]benzene (PIFA),[8] followed by removal of the four MOM protecting groups with trifluoroacetic acid (TFA) in CH_2Cl_2 gave juglocombins A (**2**) and B (**3**) as an unstable tautomeric equilibrium mixture. Therefore, **2** and **3** were converted into dimethyl esters **2′** and **3′** through methylation with trimethylsilyldiazomethane. The ^1H and ^{13}C NMR spectroscopic data for synthetic **2′** and **3′** were in agreement with those reported for the same compounds derived from natural **2** and **3**. Furthermore, treatment of dimethyl esters **2′** and **3′** with *p*-toluenesulfonic acid in methanol gave 1′-*O*-methyljuglocombin B dimethyl ester (**4**) in 68% yield ($[\alpha]_D^{24}$ −133.0 (*c* 0.20, acetone); lit. $[\alpha]_D^{20}$ −133.3 (*c* 0.2, acetone)). The spectroscopic data and optical rotation of synthetic **4** were identical to those of the same compound derived from natural juglocombins A and B, thus indicating that their absolute configurations were 1′*R*,2′*R*,3′*R*,9*R*,10*R*,10′*S*.

The synthesis of juglorescein (**1**) is shown in Scheme 5. Removal of the two TBS protecting groups in epoxide intermediate **6** gave diol **18** in 78% yield. Oxidation of the primary alcohols in **18** through Dess–Martin oxidation and Pinnick oxidation gave dicarboxylic acid **19**. Intramolecular lactonization of **19** using a carboxylic acid functionalized silica gel (Chromatorex-COOH) easily afforded six-membered lactone **20** in 81% yield over the three steps.[15] Because the carboxylic acid attacks from the opposite side of the epoxide, the *anti* relationship between the epoxide and the side chain at C-9 in **6** was validated. Finally, removal of the MOM protecting groups and hydrolysis of the lactone under acidic conditions gave juglorescein (**1**) in 62% yield ($[\alpha]_D^{24}$ −99.1 (*c* 0.58, MeOH); lit. $[\alpha]_D^{20}$ −107.4 (*c* 0.29, MeOH)). Because the spectroscopic data and optical rotation of synthetic **1** agreed with those reported for natural **1**, the absolute configuration of natural **1** was determined to be 1′*S*,2*R*,3*R*,2′*R*,3′*R*,9*R*,10*R*,10′*S*.

In conclusion, the first total syntheses of juglorescein (**1**) and juglocombins A (**2**) and B (**3**) have been accomplished. Juglorescein (**1**) was synthesized in nine steps and in 11% overall yield from known compounds **8** and **9**. 1′-*O*-Methyljuglocombin B dimethyl ester (**4**), a common derivative of juglocombins A and B, was synthesized in 14 steps and 3% overall yield from compounds **8** and **9**. The key feature of this synthesis is a bioinspired dimerization of a juglomycin C derivative, which efficiently provides access to the 6/6/5/6/6-fused core skeleton. A photoinduced reduction of the epoxide in dimer **6**, followed by further transformations, gave juglocombins A and B. Conversion of dimer **6** into dicarboxylic acid **19**, and an acid-promoted intramolecular lactonization followed by hydrolysis of the resultant lactone, afforded juglorescein. Notably, our total syntheses of **1**–**4** establish the relative and absolute configurations of these compounds. The synthetic route reported herein will support synthetic and biological studies of these natural products and their derivatives.



Scheme 4. Reaction conditions for the synthesis of 1′-*O*-methyljuglocombin B dimethyl ester (**4**): a) Dess–Martin periodinane (4.0 equiv), CH_2Cl_2, RT, 25 min; b) $NaClO_2$ (5.8 equiv), 2-methyl-2-butene (21.6 equiv), $NaH_2PO_4 \cdot 2H_2O$ (10.0 equiv), *tert*-BuOH/THF/H_2O (1:1:1), 0 °C, 15 min, 94% yield over two steps; c) PIFA (1.2 equiv), TFE/H_2O (5:3), 0 °C to RT, 1 h; d) TFA/CH_2Cl_2 (4:1), 0 °C to reflux, 30 min; e) trimethylsilyldiazomethane (8.1 equiv), CH_2Cl_2/MeOH (1:2), RT, 15 min, 56% over three steps; f) TsOH·H_2O (2.5 equiv), MeOH, RT, 24 h, 68%. PIFA = [bis(trifluoroacetoxy)iodo]benzene, TFA = trifluoroacetic acid, TsOH = *p*-toluenesulfonic acid.



Scheme 5. Reaction conditions for the synthesis of juglorescein (**1**): a) TBAF (3.0 equiv), AcOH (2.6 equiv), THF, RT, 2 d, 78%; b) Dess–Martin periodinane (3.9 equiv), CH_2Cl_2, RT, 30 min; c) $NaClO_2$ (5.9 equiv), 2-methyl-2-butene (19.4 equiv), $NaH_2PO_4 \cdot 2H_2O$ (9.8 equiv), *tert*-BuOH/THF/H_2O (1:1:1), 0 °C, 10 min; d) carboxylic acid functionalized silica gel, CH_2Cl_2, RT, 3 h, 81% yield over three steps; e) Amberlyst 15, 1,4-dioxane/H_2O (4:1), 75–80 °C, 4 d, 62% yield.

Acknowledgements

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Keywords: 1,4-naphthoquinone · biomimetic synthesis · dimerization · fused-ring systems · total synthesis

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