

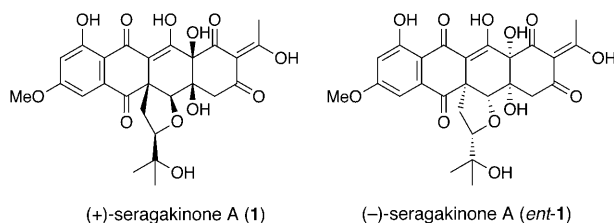
Natural Product Synthesis

Total Synthesis and Absolute Stereochemistry of Seragakinone A**

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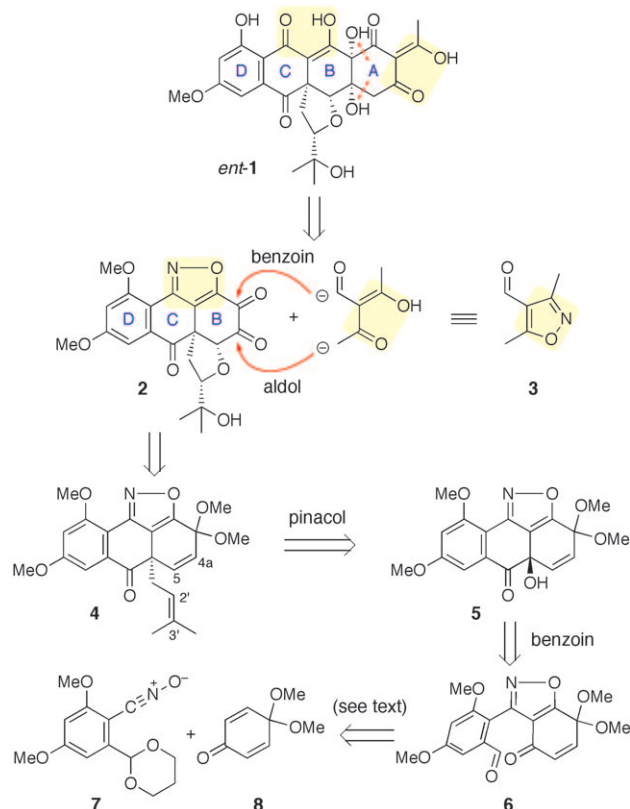
Dedicated to Professors Gilbert Stork, Samuel J. Danishefsky, and Mamoru Ohashi

Seragakinone A (**1**), an antifungal and antibacterial compound, is produced by an unidentified marine fungus that is in symbiosis with rhodophyta *Ceratodictyon spongiosum* and was collected at Seragaki beach, Okinawa.^[1] The intriguing



structure of **1** features a densely oxygenated pentacyclic core having an angular prenyl substituent, and it was determined by using extensive spectroscopic studies and single-crystal X-ray analysis; however the absolute configuration was unassigned. The three major challenges in this synthesis are: 1) the construction of the pentacyclic framework, 2) the stereoselective introduction of a prenyl unit into the sterically hindered angular position, and 3) the regio- and stereocontrolled installation of multiple oxygen functionalities. Herein, we describe the first total synthesis of *ent*-**1**, which proved to be enantiomeric to the natural product and thus allowed assignment of the absolute structure of seragakinone A.

Retrosynthetic analysis of *ent*-**1** (Scheme 1) started with a disconnection of the A ring, which could be constructed using a benzoin-forming reaction and an aldol reaction as a key annulation. A key feature of our approach is the use of an isoxazole as a 1,3-diketone equivalent.^[2] This allowed a disconnection of *ent*-**1** into two isoxazole-containing fragments, **2** and **3**. Dione **2** could be formed from diene **4** by the regio- and stereoselective oxygenation of the two C=C bonds



Scheme 1. Retrosynthetic analysis of (–)-seragakinone A (*ent*-**1**).

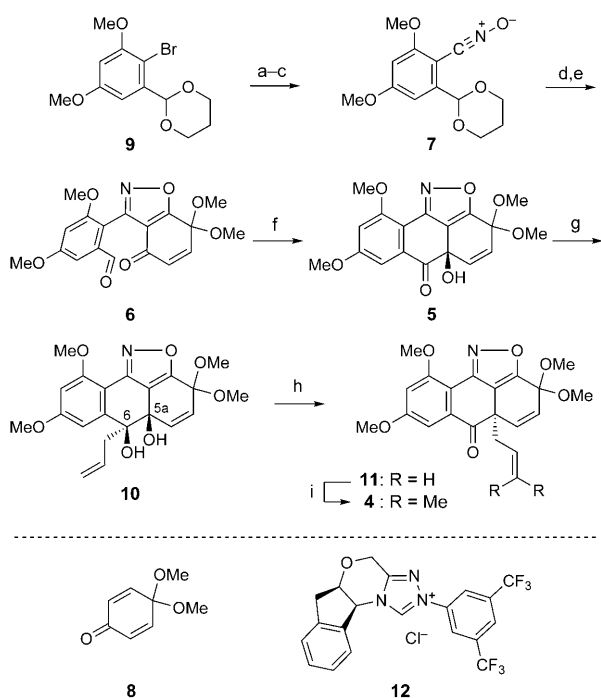
at C4a–C5 and C2'–C3'. Based on our previous study,^[3] we planned to install the angular prenyl group in **4** through an isoxazole-assisted, stereospecific pinacol-type 1,2-shift, which allowed a further disconnection to give the stereogenic ketol **5**. This ketol could be formed by an asymmetric benzoin cyclization^[4] of ketoaldehyde **6**, and a final disconnection suggested nitrile oxide **7**^[5] and quinone monoacetal **8** as starting materials.

Scheme 2 shows the preparation of prenyl ketone **4**, beginning with the conversion of the known bromide **9**^[6] into nitrile oxide **7**. Bromide **9** was treated with *n*-butyllithium, and the resulting lithium species was trapped with DMF to afford the corresponding aldehyde. This aldehyde was converted into nitrile oxide **7** by treatment with hydroxylamine and subsequent exposure to NCS in the presence of triethylamine.^[5] The regioselective 1,3-dipolar cycloaddition of nitrile oxide **7** with quinone monoacetal **8**, with subsequent

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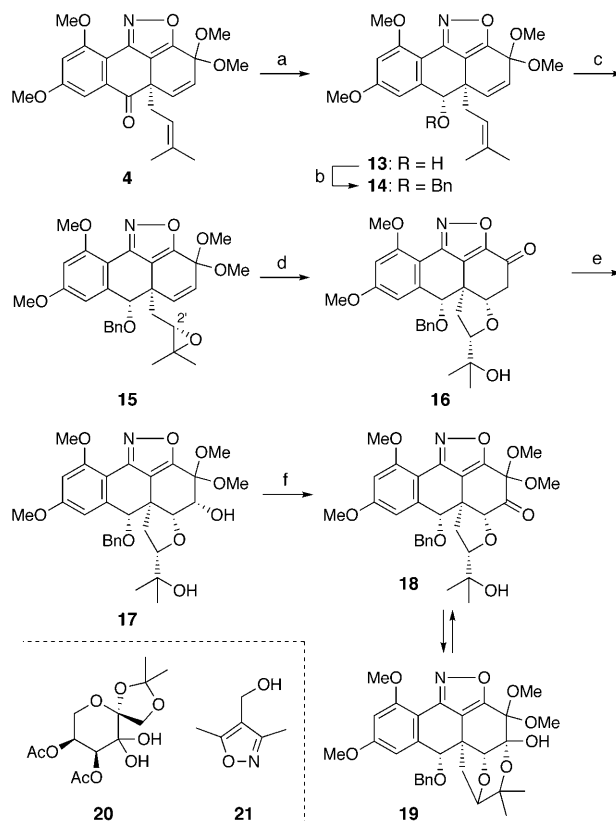


Scheme 2. Prenyl ketone **4**. Reagents and conditions: a) $n\text{BuLi}$, THF, Et_2O , -78°C , 1 h, then DMF, $-78 \rightarrow 0^\circ\text{C}$, (95%); b) $\text{NH}_2\text{OH}\cdot\text{HCl}$, K_2CO_3 , MeOH, H_2O , 0°C , 1 h (98%); c) NCS, Et_3N , CHCl_3 , 0°C , 30 min (90%); d) **8**, toluene, RT, 11 h then MnO_2 , 80°C , 10 min (75%); e) $\text{TsOH}\cdot\text{H}_2\text{O}$, MeOH, RT, 2 h, then 2 M H_2SO_4 aq., THF, RT, 10 h (91%); f) **12** (10 mol%), Et_3N (10 mol%), THF, RT, 4 h (86%, 99% ee); g) allylmagnesium bromide, THF, -78°C , 20 min (92%); h) $\text{CH}_3\text{SO}_2\text{Cl}$, Et_3N , CH_2Cl_2 , 0°C , 10 min (83%); i) 2-methyl-2-butene, Grubbs II catalyst (8 mol%), CH_2Cl_2 , 40°C , 14 h (89%). DMF = N,N' -dimethylformamide, NCS = N -chlorosuccinimide, Ts = 4-toluenesulfonyl.

dehydrogenation (MnO_2)^[7] and hydrolysis of the resulting cyclic acetal gave ketoaldehyde **6**, which was then ready for the key benzoin cyclization. Pleasingly, when using the modified Rovis triazolium salt **12**^[4d,8] (10 mol%) in the presence of triethylamine (10 mol%), the proposed reaction of **6** proceeded with excellent enantioselectivity to give the cyclic ketol (*R*)-**5** in high yield (86%, 99% ee).^[9]

Nucleophilic addition of allylmagnesium bromide to ketone **5** selectively afforded *cis*-diol **10** as a single diastereomer,^[10] ready for the key pinacol rearrangement. In contrast to the model system reported previously,^[3a] the attempted 1,2-shift failed under a variety of acidic conditions (e.g. $\text{BF}_3\cdot\text{OEt}_2$, TfOH), because of the decomposition of the acetal moiety. Hoping to achieve the key regioselective activation of the angular hydroxy group, we examined the conditions required for methanesulfonylation mediated by sulfene ($\text{CH}_2=\text{SO}_2$).^[11] Pleasingly, a rapid 1,2-shift occurred upon treatment of diol **10** with triethylamine and methanesulfonyl chloride (0°C , 10 min), thereby giving the desired ketone **11** in 83% yield.^[3a,9] Although the intermediate mesylate was not detected, this outcome is consistent with the selective sulfonylation of the C5a-OH and then an isoxazole-assisted ionization followed by a 1,2-shift of the allyl group.^[12]

Notably the stereochemical integrity was preserved during the migration. The HPLC analysis using a chiral stationary phase confirmed the enantiopurity (99% ee) of **11**. The key prenyl ketone **4** was then synthesized by cross-metathesis (excess 2-methyl-2-butene and Grubbs II catalyst).^[13] Reduction of ketone **4** with NaBH_4 afforded alcohol **13** as a single isomer (Scheme 3), and the unambiguous



Scheme 3. Ketone **18**. Reagents and conditions: a) NaBH_4 , THF, MeOH, 0°C , 10 min (92%); b) BnBr , NaH, $n\text{Bu}_4\text{NI}$, THF, RT, 2.5 h (94%); c) **20** (20 mol%), Oxone, K_2CO_3 , $n\text{Bu}_4\text{NH}_2\text{SO}_4$, $\text{CH}_2(\text{OMe})_2$, MeCN, H_2O (pH 6), 0°C , 24 h (92%, d.r. 8.2:1); d) PPTS, 1,4-dioxane, H_2O , 70°C , 12 h (78%); e) $\text{PhI}(\text{OAc})_2$, KOH, MeOH, 0°C , 2 h (64%); f) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2 , RT, 3 h (86%). NMO = 4-methylmorpholine N -oxide, PPTS = pyridinium *p*-toluenesulfonate, TPAP = tetra-*n*-propylammonium perruthenate.

assignment of the absolute configuration was made by derivatization of **13** into the corresponding camphanate ester, which was then used in X-ray analysis.^[14,15] Benzylolation of alcohol **13** produced ether **14**, thus setting the stage for the stereocontrolled tetrahydrofuran ring construction. Since simple oxidation of the prenyl side chain failed to give a significant level of diastereoselection (e.g. **15/2'-epi-15** = 1:1.4, with *m*-chloroperoxybenzoic acid), we opted instead for reagent control. Shi epoxidation^[16] catalyzed by ketone hydrate **20** (20 mol%) proved effective, thereby furnishing the desired epoxide **15** in high selectivity (**15/2'-epi-15** = 8.2:1). After separation, epoxide **15** was treated with PPTS in aqueous 1,4-dioxane, which induced hydration of the epoxide

and tetrahydrofuran ring formation with subsequent hydrolysis to give ketone **16**. The Moriarty α -hydroxylation^[17] of ketone **16** proceeded stereoselectively when using diacetoxyiodobenzene (KOH, methanol) to afford α -hydroxy dimethylacetal **17** as a single diastereomer. The stereochemistry of **17** was verified by X-ray analysis.^[15] TPAP oxidation^[18] of **17** provided ketone **18**, which was then ready for the A ring formation.

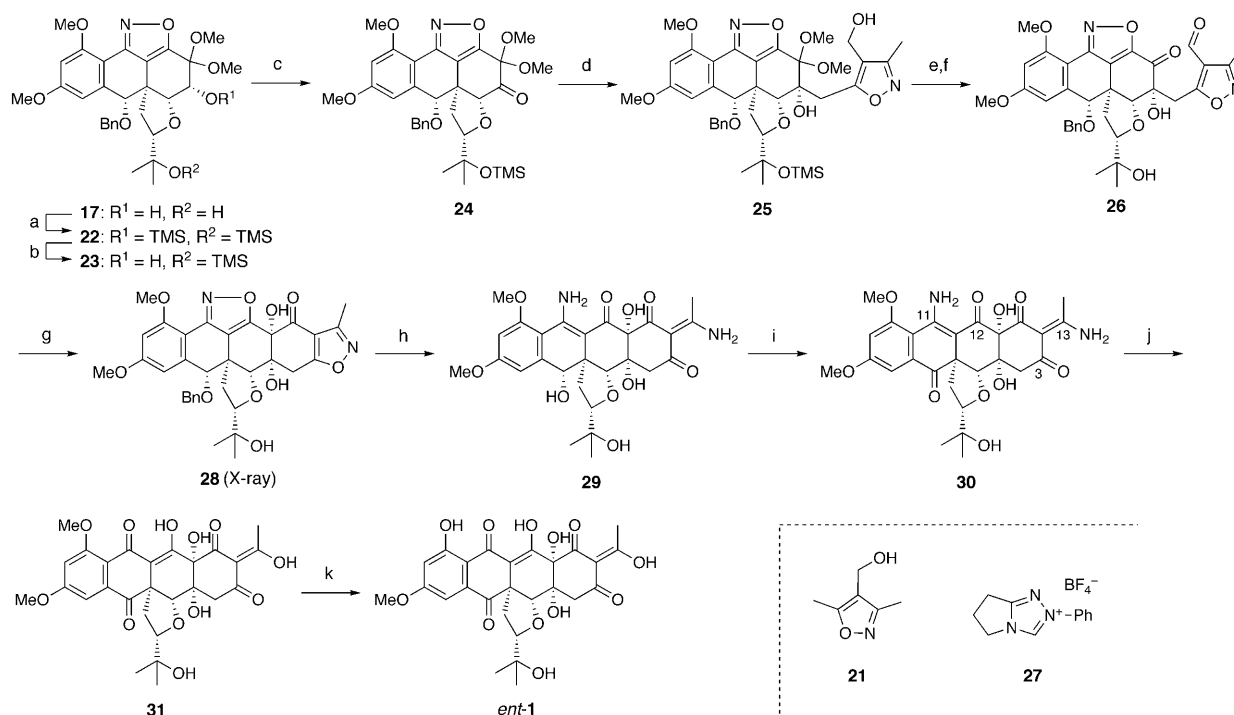
We had planned to react ketone **18** with the dianion, generated from isoxazole **21**,^[19] but all attempts failed to give the corresponding adduct. Since ketone **18** did not undergo attack even by simpler nucleophiles (e.g. MeLi, MeMgBr), we assumed that the failure was a result of an equilibrium between **18** and hemiacetal **19**. Attempted protection of the tertiary alcohol in **18** was not possible, for example, treatment of ketone **18** with TMSOTf (2,6-lutidine, CH₂Cl₂) only effected the silylation of the hemiacetal **19**.

At this juncture, an indirect protocol was devised (Scheme 4). After bis-silylation of diol **17**, exposure of bis-silyl ether **22** to (HF)₃py allowed selective desilylation of the secondary silyl ether to give mono-alcohol **23**, which was oxidized to furnish ketone **24**. Pleasingly, ketone **24** underwent nucleophilic attack by the dianion generated from **21**, thus affording alcohol **25** in 69% yield. Desilylation of **25** and then hydrolysis of the resulting acetal gave a ketone. Dess–Martin oxidation^[20] of the primary alcohol afforded ketoaldehyde **26**.

Benzoin cyclization of **26** proceeded nicely using triazolium salt **27**^[21] (20 mol%) and DBU (20 mol%) in MeOH (RT, 30 min), to give ketol **28** in 90% yield with excellent diastereoselectivity (d.r. 15:1). The stereochemistry of **28** was verified by single-crystal X-ray analysis.^[15]

Hydrogenation of **28** in the presence of PdCl₂ effected debenzoylation and reductive cleavage of two isoxazoles to give enaminone **29**, and Dess–Martin oxidation^[20] of the secondary alcohol gave ketone **30**. Conventional acidic conditions proved ineffective for the hydrolysis of the two enaminones in **30** to yield the corresponding 1,3-diketones. After a series of trials the hydrolysis of the C11–C12 enaminone was realized by diazotization using *t*BuONO,^[22] and a basic workup (1M NaOH) hydrolyzed the C13–C3 enaminone to give 1,3-diketone **31**.^[23] The final step was the selective demethylation, which was achieved by using NaI and CeCl₃·7H₂O.^[24–26] The synthetic material was identical in all respects (¹H, ¹³C NMR, IR, HRMS) to the natural sample except for the sign of optical rotation: [α]_D³⁰ = –144 (*c* = 1.00, MeOH), lit. [α]_D²⁶ = +146 (*c* = 1.0, MeOH), thereby allowing assignment of the synthetic material as the antipode of the natural product.

In summary, we have achieved the first asymmetric total synthesis of (–)-seragakinone A. Noteworthy features of the synthesis include: 1) the benzoin-forming reactions, which worked well to effect two separate cyclizations, including one catalytic enantioselective reaction, 2) the pinacol-type rear-



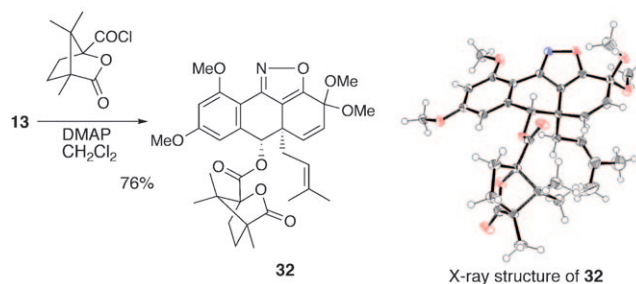
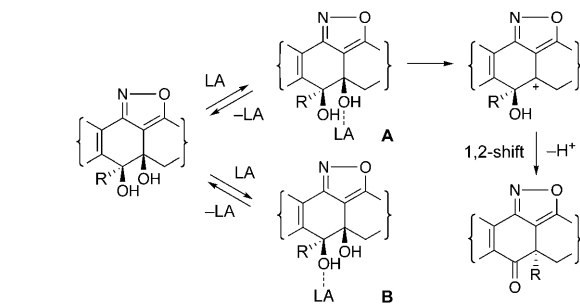
rangement that was effective for installing the angular prenyl substituent and, 3) determination of the absolute configuration of the natural product.

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- [15] CCDC 783964 (**17**), 783965 (**32**), and 783966 (**28**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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