Natural Product Synthesis

DOI: 10.1002/anie.201006528

Total Synthesis and Absolute Stereochemistry of Seragakinone A**

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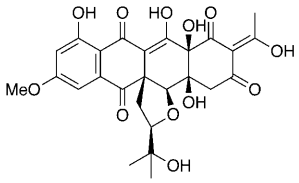
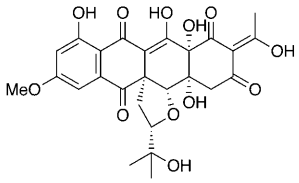
Dedicated to Professors Gilbert Stork, Samuel J. Danishefsky, and Mamoru Ohashi

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



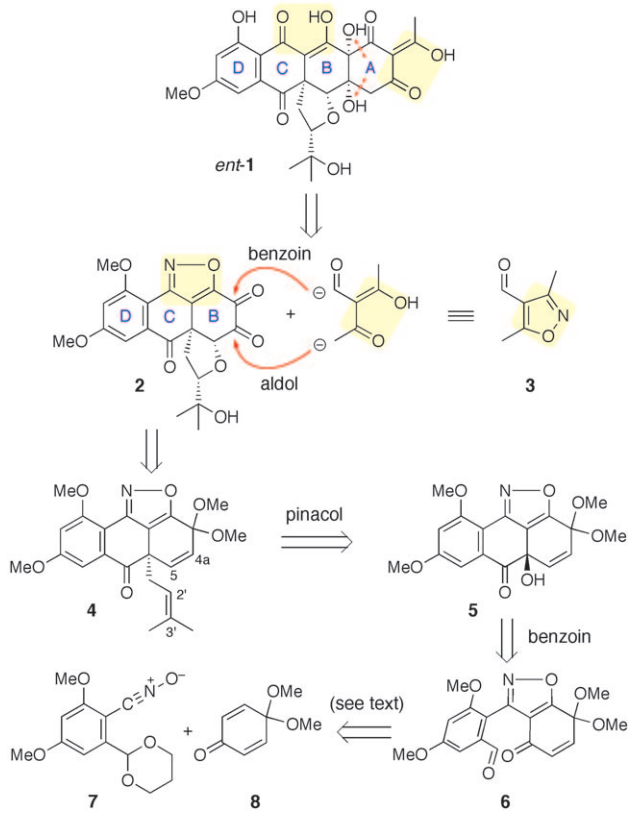
(+)-seragakinone A (**1**)



(−)-seragakinone A (*ent*-**1**)

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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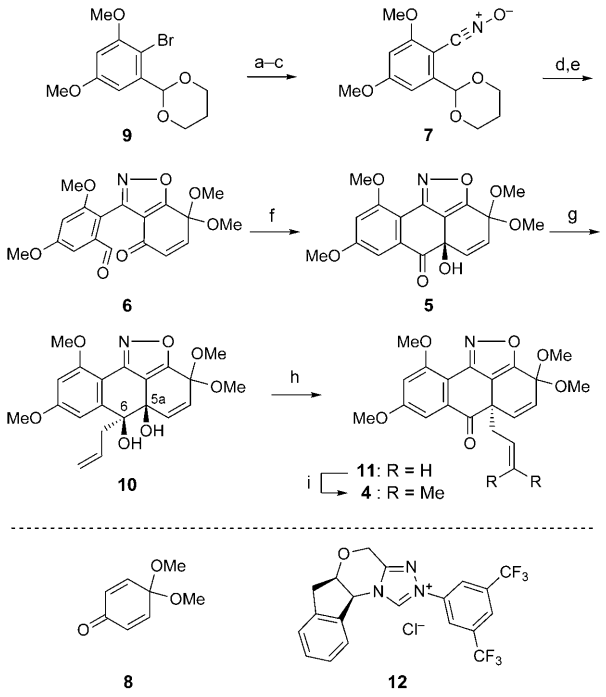
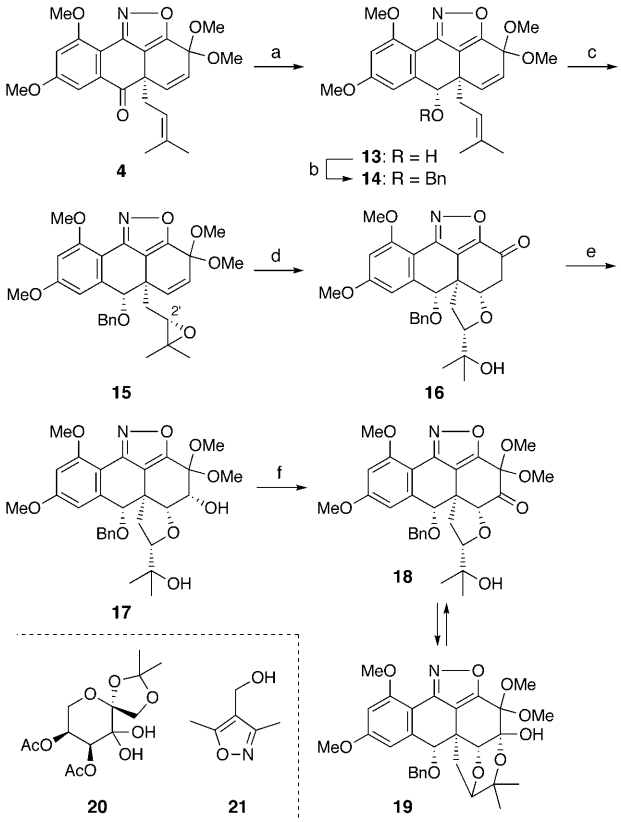
[**] We thank Prof. Dr. Jun'ichi Kobayashi (Hokkaido Univ.) and Prof. Dr. Hideyuki Shigemori (Tsukuba Univ.) for kindly providing a comparison sample of **1**. We are grateful to Sachiyo Kubo for X-ray analysis, and Dr. Haruko Takahashi for HSCCC purification.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201006528.



Scheme 2. Prenyl ketone **4**. Reagents and conditions: a) *n*BuLi, THF, Et_2O, −78 °C, 1 h, then DMF, −78→0 °C, (95%); b) $NH_2OH{\cdot}HCl$, 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) $TsOH{\cdot}H_2O$, 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) CH_3SO_2Cl, 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.

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, nBu_4NI, THF, RT, 2.5 h (94%); c) **20** (20 mol%), Oxone, K_2CO_3, nBu_4NHSO_4, $CH_2(OMe)_2$, 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) $PhI(OAc)_2$, 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.

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. $BF_3{\cdot}OEt_2$, 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 ($CH_2{=}SO_2$).[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]

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] Benzylation 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 (92%, **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.

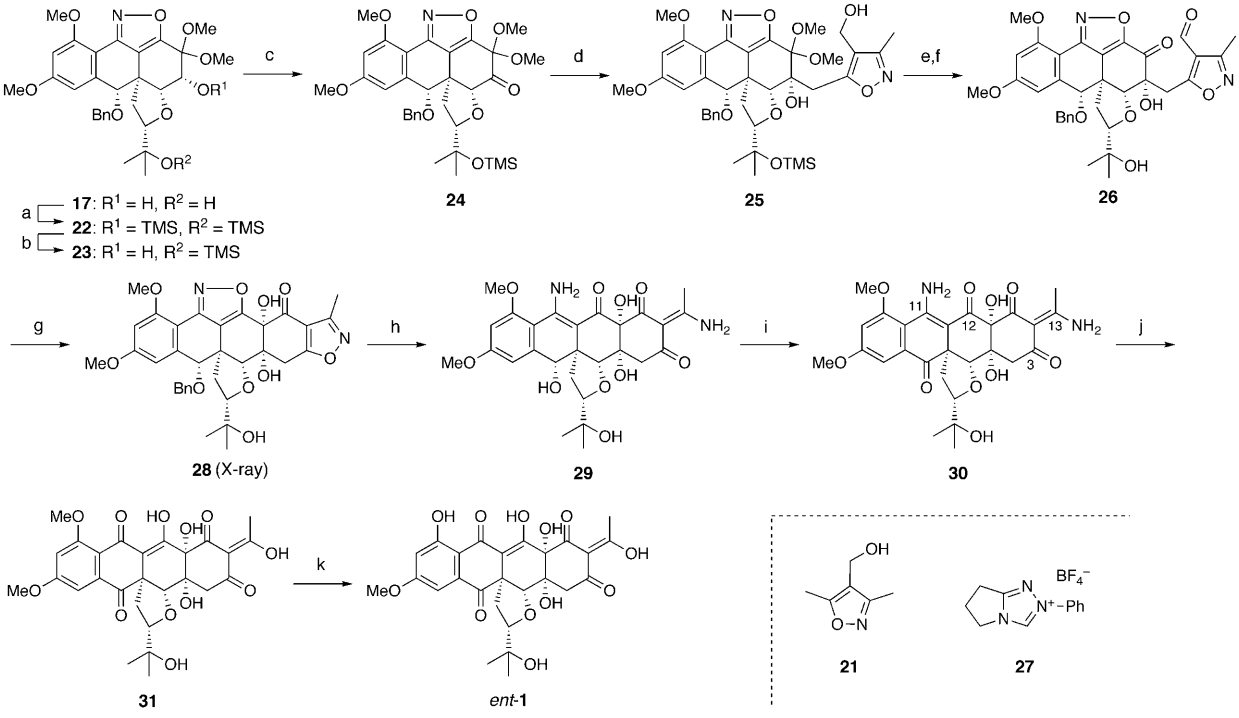
We had planned to react ketone **18** with the dianion, generated from isoxazole **21**,[19] but all attempts failed to give the corresponding adduct. Since ketone **18** did not undergo attack even by simpler nucleophiles (e.g. MeLi, MeMgBr), we assumed that the failure was a result of an equilibrium 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, CH_2Cl_2) 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 $(HF)_x$py 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 $PdCl_2$ effected debenzylation 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 $CeCl_3 \cdot 7H_2O$.[24–26] The synthetic material was identical in all respects (^1H, ^{13}C NMR, IR, HRMS) to the natural sample except for the sign of optical rotation: $[\alpha]_D^{30} = -144$ ($c = 1.00$, MeOH), lit. $[\alpha]_D^{26} = +146$ ($c = 1.0$, 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-



Scheme 4. Endgame. Reagents and conditions: a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 30 min (94%); b) $(HF)_x$py, THF, −78→0°C, 8 h (99%); c) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, RT, 5 h (97%); d) **21** (3 equiv), *n*BuLi (6 equiv), THF, −78°C, 2 h then **24**, THF, −78°C, 30 min (69%); e) $TsOH \cdot H_2O$, H_2O, THF, reflux, 4.5 h (82%); f) Dess–Martin periodinane, CH_2Cl_2, RT, 1 h (90%); g) **27** (20 mol%), DBU (20 mol%), MeOH, RT, 30 min (90%, d.r. 15:1); h) H_2 (balloon), $PdCl_2$, MeOH, H_2O, AcOH, RT, 2 h (96%); i) Dess–Martin periodinane, CH_2Cl_2, RT, 1 h (80%); j) *t*BuONO, CF_3CO_2H, DMSO, RT, 21 h then 1M NaOH aq., RT, 1.5 h; k) NaI, $CeCl_3 \cdot 7H_2O$, CH_3CN, reflux, 33 h (49%, 2 steps). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMSO = dimethyl sulfoxide, py = pyridine, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

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

Received: October 18, 2010
Published online: February 3, 2011

Keywords: antibiotics · cyclization · natural products · organocatalysis · total synthesis

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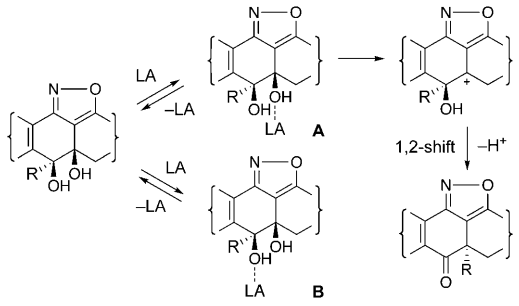
[12] The origin of the regioselectivity of the 1,2-shift is worth discussing. Although it may be accounted for by the steric and/or electronic differences of two hydroxy groups (see text), the regioselectivity holds even without such a difference. An important point is the extremely facile ionization assisted by the neighbouring isoxazole if the leaving group ability of the C5a–OH group is enhanced, for example, by a Lewis acid (LA).[3] Coordination of an LA to the C5a–OH (**A**) induces facile ionization and a 1,2-shift, whereas coordination of an LA to the C6–OH (**B**) does not. Given the microscopic reversibility of this reaction, we are tempted to propose that such a mechanism applies also to a "sulfene" intermediate ($CH_2{=}SO_2$).



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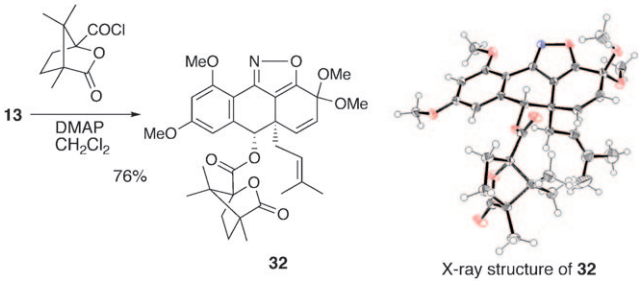
[14] Esterification of **13** with (–)-camphanyl chloride gave camphanate **32**. The recrystallized sample (Et_2O, $CHCl_3$, vapor diffusion) was subjected to X-ray analysis. The thermal ellipsoids are shown at 50 % probability. DMAP = 4-dimethylaminopyridine.



[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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[26] Purification of **1** by preparative TLC methods using a diol-modified silica-gel plate caused tailing, which decreased the yield of isolated product. In contrast, high-speed counter-current chromatography (HSCCC) enabled us to purify **1** without any loss of the material. See the Supporting Information. For a review on HSCCC, see; Y. Ito, *J. Chromatogr. A* **2005**, *1065*, 145 – 168.

