Catalytic Asymmetric Synthesis of Halenaquinone and Halenaquinol

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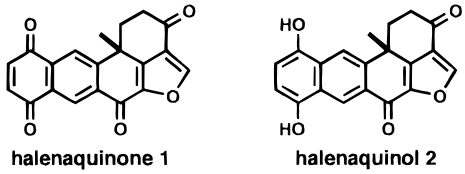
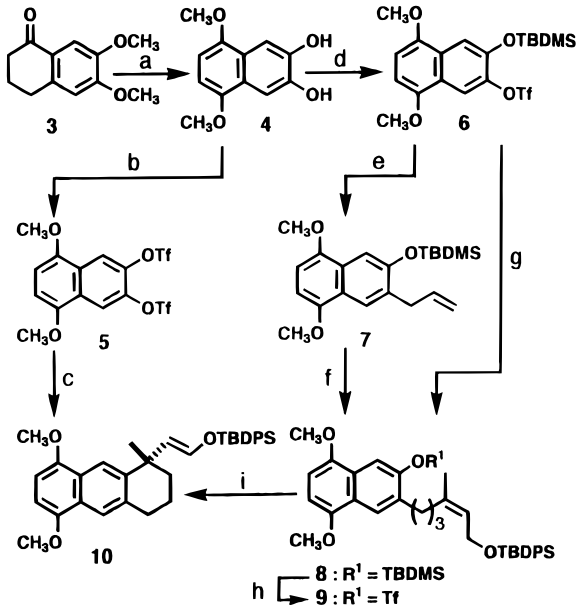
Halenaquinone (**1**) and halenaquinol (**2**), which have a benzylic quaternary carbon center, have been isolated from a variety of sea sponges (Chart 1).[1] These marine natural products have been shown to possess antibiotic, cardiotonic, and protein tyrosine kinase inhibitory activity.[2] To date, only Harada and co-workers have succeeded in the total synthesis of **1** and **2** starting from optically pure Wieland−Miescher ketone.[3] We report here the catalytic asymmetric synthesis of **1** and **2** starting from commercially available 6,7-dimethoxy-1-tetralone (**3**).[4,5] This synthesis features the first use of a cascade Suzuki cross-coupling and an asymmetric Heck reaction as well as the one-pot construction of a pentacyclic ring system from a tricyclic ring system.

The catalytic asymmetric synthesis of the tricyclic key intermediate **10**, which has a benzylic quaternary carbon center, was achieved through three different routes (Scheme 1). The dihydroxynaphthalene derivative **4** was synthesized from **3** in 58% overall yield (five steps) as shown in Scheme 1, and was first converted to the ditriflate **5** (99%). To the best of our knowledge, there has been no previous example of a cascade Suzuki cross-coupling[6] and an asymmetric Heck reaction.[7] However, we considered that this quite challenging process could be possible under suitable reaction conditions to give optically active **10** in a single step. Therefore, alkylborane **12** was prepared,[8] and after many attempts, we were very pleased to find that treatment of **5** with **12**[9] (1.1 equiv), $Pd(OAc)_2$ (20 mol %), (*S*)-BINAP[10] (40 mol %), and K_2CO_3 (6 equiv) in THF (0.063 M) at 60 °C for 42 h gave **10** with 85% ee in 20% yield.[11] The enantiomeric excess of **10** was determined by DAICEL CHIRALCEL OD (hexane:2-propanol, 9:1) using **15** readily derived from **10**. The absolute configuration of **10** was unequivocally determined from the successful conversion of **10** to natural halenaquinone and halenaquinol. Although the chemical yield is still unsatisfactory, this is the first example of a cascade Suzuki cross-coupling and

Chart 1. Structure of 1 and 2



Scheme 1. Catalytic Asymmetric Synthesis of 10[a]



[a] Reaction conditions: (a) (1) BBr_3 (2.1 equiv), CH_2Cl_2, −78 °C to rt, (2) BnBr (2.0 equiv), K_2CO_3, *n*-Bu_4NI, DMF, 60 °C, (3) CrO_3 (5 equiv), AcOH−H_2O, 0 °C to rt, (4) KHMDS (3 equiv), THF, −78 °C, then MeI (6 equiv), −78 °C to rt, (5) H_2 (1 atm), Pd−C, AcOEt, rt (five steps, 58%); (b) Tf_2O (3 equiv), pyridine, CH_2Cl_2, −78 °C to rt (99%); (c) **12** (1.1 equiv), $Pd(OAc)_2$ (20 mol %), (*S*)-BINAP (40 mol %), K_2CO_3, THF, 60 °C (85% ee, 20%); (d) (1) TBDMSCl (1.1 equiv), Et_3N, CH_2Cl_2, 0 °C, (2) Tf_2O (1.3 equiv), Et_3N, CH_2Cl_2, −78 °C to rt (two steps, 85%); (e) $CH_2{=}CHCH_2MgBr$ (5 equiv), $PdCl_2(dppf){\cdot}CH_2Cl_2$ (9 mol %), Et_2O, −78 °C to rt (quant); (f) (1) 9-BBN (2.1 equiv), THF, 0 °C to rt, (2) **11** (1.5 equiv), $PdCl_2(dppf){\cdot}CH_2Cl_2$ (5 mol %), $K_3PO_4{\cdot}nH_2O$, THF, 50 °C (90%); (g) **12** (1.3 equiv), $PdCl_2(dppf){\cdot}CH_2Cl_2$ (10 mol %), K_2CO_3, THF, 50 °C (61%); (h) (1) *n*-Bu_4NF (1.0 equiv), THF, 0 °C, (2) Tf_2O (1.3 equiv), Et_3N, CH_2Cl_2, −78 °C to rt (two steps, 69%); (i) $Pd(OAc)_2$ (10 mol %), (*S*)-BINAP (20 mol %), K_2CO_3, THF, 60 °C (87% ee, 78%).

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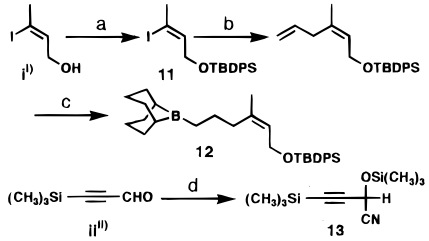
(8) Compounds **11**−**13** were prepared as follows ((I) Cochrane, J. S.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1972**, *3*, 361. (II) Kruithof, K. J. H.; Schmits, R. F.; Klumpp, G. W. *Tetrahedron* **1983**, *39*, 3073).



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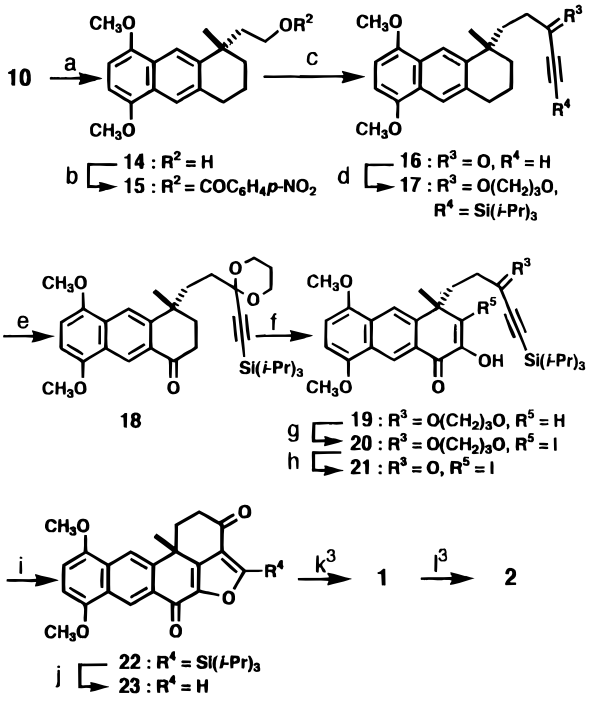
an asymmetric Heck reaction. Alternatively, the benzylic quaternary carbon **10** was also constructed through a multistep sequence of reactions. **4** was converted to the silyl ether, which underwent trifluoromethanesulfonylation to give **6** in 85% overall yield. The Pd(0)-catalyzed cross-coupling reaction gave **7** in a quantitative yield, which underwent hydroboration followed by a Suzuki cross-coupling reaction using **11**[8] to give **8** (90%). Silyl ether **8** was also constructed by a Suzuki cross-coupling reaction using **6** and trialkylborane **12** (61%). **8** was then converted to the requisite triflate **9** (69%) for an asymmetric Heck reaction in a two-step sequence of reactions. Treatment of **9** with $Pd(OAc)_2$ (10 mol %), (*S*)-BINAP (20 mol %), and K_2CO_3 (3 equiv) in THF at 60 °C for 22 h gave **10** with 87% ee in 78% yield.

Having developed a catalytic asymmetric synthesis for the key intermediate **10**, which has a benzylic quaternary carbon center, we then examined the conversion of **10** to natural halenaquinone and halenaquinol (Scheme 2). We expected that the alkenyl iodide **21** would be a reasonable synthetic intermediate for constructing the pentacyclic ring system in a one-pot reaction.[12] Therefore, **10** was first converted to alcohol **14** in a two-step sequence of reactions (93%). Transformation of **14** to the triflate followed by reaction with the acyl anion equivalent **13**[8] and then 2% NaF gave ketone **16** (68% yield). After protection of the carbonyl functionality as an acetal (98%), and of the ethynyl functionality with a triisopropylsilyl group (98%), **17** underwent benzylic oxidation to give **18** (96%). Exposure of **18** to O_2 (1 atm) in the presence of KO-*t*-Bu (5 equiv) in *tert*-butyl alcohol gave enol **19** (79%). Treatment of **19** with NaI (10 equiv) and $CuSO_4 \cdot 5H_2O$ (10 equiv) in aqueous methanol gave the requisite alkenyl iodide **20** quite efficiently (97%),[13] and exposure of **20** to *p*-toluenesulfonic acid in aqueous acetone furnished **21** (98%). We were very pleased to find that reaction of **21** with $Pd_2(dba)_3 \cdot CHCl_3$ (0.28 molar equiv) and K_2CO_3 (5 equiv) in DMF at room temperature for 8 h gave the desired pentacycle **22** in a single step (72%). The pentacyclic intermediate **22** was subjected to desilylation, which gave **23** in 83% yield: $[\alpha]^{23}_D$ +123.7 (*c* 0.335, CH_2Cl_2, 87% ee). Finally, Harada's synthetic intermediate **23**[3] was readily converted to halenaquinone (**1**) and halenaquinol (**2**).

Scheme 2. Synthesis of 1 and 2 from 10[a]



[a] Reaction conditions: (a) (1) *n*-Bu_4NF (2 equiv), AcOH (3 equiv), THF, 0 °C to rt, (2) $NaBH_4$ (5 equiv), MeOH, 0 °C to rt (two steps, 93%); (b) 4-nitrobenzoyl chloride (1.1 equiv), Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2, 0 °C to rt (96%); (c) (1) Tf_2O (1.2 equiv), pyridine, CH_2Cl_2, −78 °C to rt, (2) LDA/**13** (1.5 equiv), THF, −78 °C, then 2% NaF (two steps, 68%); (d) (1) $HO(CH_2)_3OH$ (10 equiv), $TsOH \cdot H_2O$, benzene, reflux (98%), (2) *n*-BuLi (2 equiv), THF, −78 to −50 °C, then TIPSCl (2 equiv), −78 °C to rt (98%); (e) DDQ (3 equiv), CH_2Cl_2, H_2O, rt (96%); (f) O_2 (1 atm), KO-*t*-Bu (5 equiv), *t*-BuOH, 35 °C (79%); (g) NaI (10 equiv), $CuSO_4 \cdot 5H_2O$ (10 equiv), MeOH, H_2O, rt (97%); (h) $TsOH \cdot H_2O$, acetone, H_2O, 60 °C (98%); (i) $Pd_2(dba)_3 \cdot CHCl_3$ (0.28 equiv), K_2CO_3, DMF (0.003 M), rt (72%); (j) *n*-Bu_4NF (16 equiv), AcOH (24 equiv), THF, MeCN, 60 °C (83%); (k) CAN (5 equiv), MeOH, H_2O, 0 °C (45%); (l) $Na_2S_2O_4$ (20 equiv), acetone, H_2O, 0 °C (quant).

In conclusion, we have developed a catalytic asymmetric synthesis of **1** and **2** (87% ee) that incorporates the first example of a cascade Suzuki cross-coupling–asymmetric Heck reaction as well as a single-step process promoted by Pd(0) for constructing a pentacyclic ring system from a tricyclic ring system.

Supporting Information Available: Details of the preparation and characterization of **1**, **2**, **5**, **6**, **8**–**10**, **14**, **16**, and **18**–**23** (29 pages).

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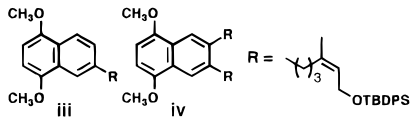
(11) The byproducts are **iii** and **iv**.



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