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Efficient Method for Synthesis of Angucyclinone Antibiotics via Gold-Catalyzed Intramolecular [4 + 2] Benzannulation: Enantioselective Total Synthesis of (+)-Ochromycinone and (+)-Rubiginone B_2

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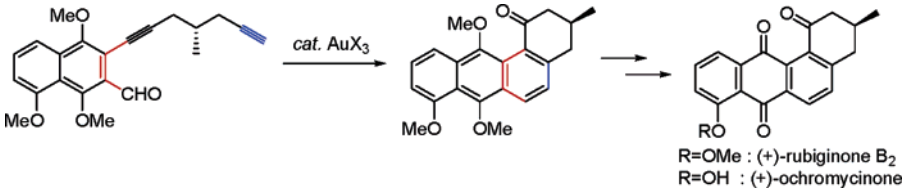
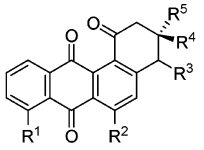


An efficient synthetic approach to angucyclinone antibiotics, (+)-ochromycinone and (+)-rubiginone B_2, is reported. The key step involves the facile formation of 2,3-dihydrophenantren-4(1*H*)-one skeleton, an important framework of angucyclinone natural products, by using gold-catalyzed intramolecular [4 + 2] benzannulation reaction.

Introduction

The family of angucyclinone exhibits a wide range of remarkable antibiotic properties (Scheme 1).[1,2] Ochromycinone and rubiginones B_2, first isolated by Bowie[3] and Oka[4] from the strain of *Streptomyces,* are one of the simple and useful angucyclinones. A group of rubiginones has been shown to potentiate the cytotoxicity of the chemotherapeutic agent vincristine-resistant P388 leukemia and human Moser cells in vitro and in vivo.[5] Ochromycinone was recently reported to have selective anti-*Helicobacter pylori* activity, the major cause of stomach ulcers and duodenal ulcer, with low activity against other common bacteria.[6] The Diels−Alder reaction between juglone derivatives and the corresponding dienes is one of the most convenient methods for the preparation of angucyclinone frameworks.[7,8] However, a

SCHEME 1. Anitibiotics Angucyclinone



R^1	R^2	R^3	R^4	R^5	
OH	H	H	Me	H	(+)-ochromycinone (**1**)
OH	OH	H	Me	OH	tetrangulol (**2**)
OH	OH	H	Me	H	rabelomycin (**3**)
OH	H	H	CH_2OH	H	YM-181741 (**4**)
OMe	H	H	Me	H	rubiginone B_2 (**5**)
OMe	H	OH	Me	H	rubiginone A_2 (**6**)

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† E-mail: yoshi@yamamoto1.chem.tohoku.ac.jp.

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(8) For other examples for total synthesis of ochromycinone and (+)-rubiginone B_2, see: (a) Katsuura, K.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 9−12. (b) Katsuura, K.; Snieckus, V. *Can. J. Chem.* **1987**, *65*, 124−130. (c) Kalogerakis, A.; Groth, U. *Synlett* **2003**, 1886−1888.

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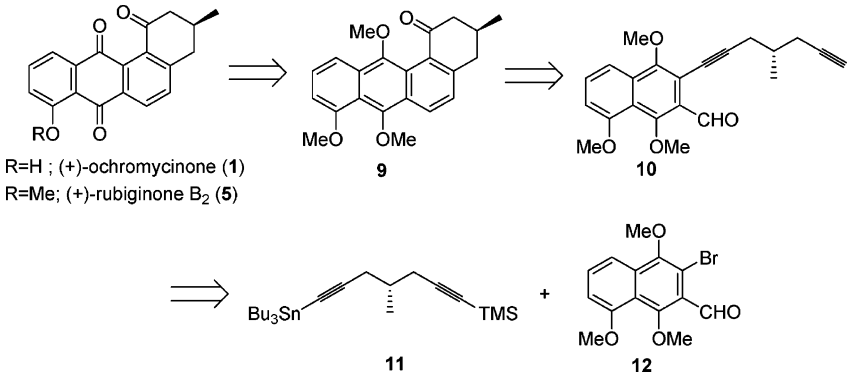
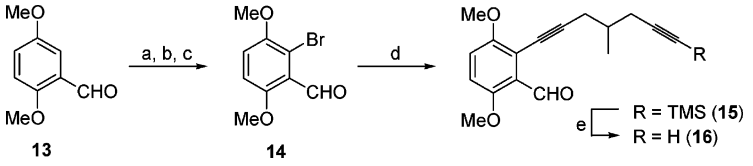
SCHEME 2. Synthetic Plan of (+)-Ochromycinone and (+)-Rubiginone B_2

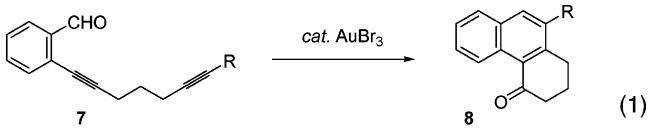


SCHEME 3. Synthesis of 16 for a Model Experiment[a]



[a] Reagents and conditions: (a) *p*-TsOH, $HO(CH_2)_3OH$, benzene, reflux, quant. (b) BuLi, $(BrCF_2)_2$, hexane/benzene, −25 °C, 10 h, 70%. (c) 11 N HCl, 0 °C, 30 min, quant. (d) (*rac*)-**11**, $Pd_2(dba)_3{\cdot}CHCl_3$, P(*t*-Bu)$_3$, toluene, 50 °C, 4 h, 70%. (e) TBAF, AcOH, THF, rt, 30 min, quant.

drawback of this methodology lies in the difficulty in preparation of the diene parts. Recently we developed the Lewis acid catalyzed intramolecular [4 + 2] benzannulation using the tethered alkynyl enynals **7** to give the 2,3-dihydrophenanthren-4(1*H*)-one derivatives **8** in moderate to high yields (eq 1).[9] Herein, we report a new approach to the synthesis of (+)-ochromycinone and (+)-rubiginone B_2 through the gold-catalyzed intramolecular [4 + 2] benzannulation, in which a key step for the total synthesis exists in the construction of 2,3-dihydrophenanthren-4(1*H*)-one skeleton.[10]

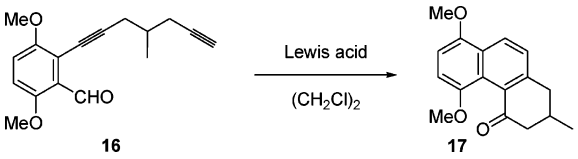


(1)

Results and Discussion

Our synthetic plan of (+)-ochromycinone and (+)-rubiginone B_2 is described in Scheme 2. The previous study suggested that the framework of 3,4-dihydrotetraphen-1(2*H*)-one skeleton of **9** would be constructed by gold-catalyzed intramolecular benzannulation of **10**, which would be prepared by the Pd-catalyzed coupling reaction between **11** and **12**. It was thought that the chiral diyne **11** would be synthesized by the combination of known reactions; the asymmetric conjugate addition of an organocopper reagent by using Evans's chiral oxazolizinone, the reduction of the resulting amide, the transformation of the resulting aldehyde to alkyne by Cory−Fuchs method, and the conversion of terminal alkyne to the corresponding Bu_3Sn−alkyne should afford **11**.

TABLE 1. Lewis Acid Catalyzed Intramolecular Benzannulation of 16[a]



(eq 2)

entry	Lewis acid	conditions	yield[b] (%)
1[c]	$AuBr_3$	rt, 1 h	70
2	$AuBr_3$	50 °C, 1 h	77
3	$AuCl_3$	50 °C, 1 h	90
4	$PtCl_2$	50 °C, 1 h	83

[a] The reaction of **16** (0.5 mmol) was carried out in the presence of 2 mol % Lewis acid in $(CH_2Cl)_2$ (0.13 M) unless otherwise noted. [b] Chemical yield was determined by ^{1}H NMR using dibromomethane as an internal standard. [c] The reaction concentration was 0.33 M.

Before starting the total synthetic study of angucyclinone antibiotics, we first performed the intramolecular benzannulation of the tethered alkynyl enynal **16**, having two methoxy groups on the benzene ring, as a model experiment. The substrate **16** was prepared from a commercially available aldehyde **13** by known procedures, as shown in Scheme 3.[11] The selected results of the Lewis acid catalyzed benzannulation of **16** were summarized in Table 1. When the reaction of **16** was carried out in the presence of 2 mol % $AuBr_3$ at room temperature for 1 h, the starting material was consumed completely, and the desired product **17** was obtained in 70% yield together with small amounts of unknown byproducts (entry 1). When the concentration of the reaction mixture was diluted from 0.33 to 0.13 M, the

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(10) Recently, applications to synthesis of natural products via Au-catalyzed cycloisomerization of *o*-alkynylbenzaldehyde and *o*-alkynylaryl ketone were reported; see: (a) Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239−1243. (b) Dyker, G.; Hildebrandt, D. *J. Org. Chem.* **2005**, *70*, 6093−6096.

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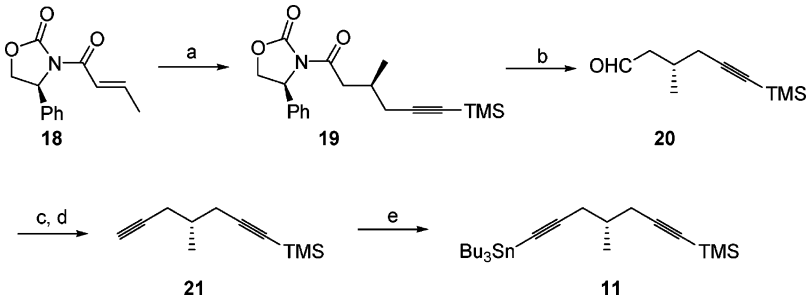
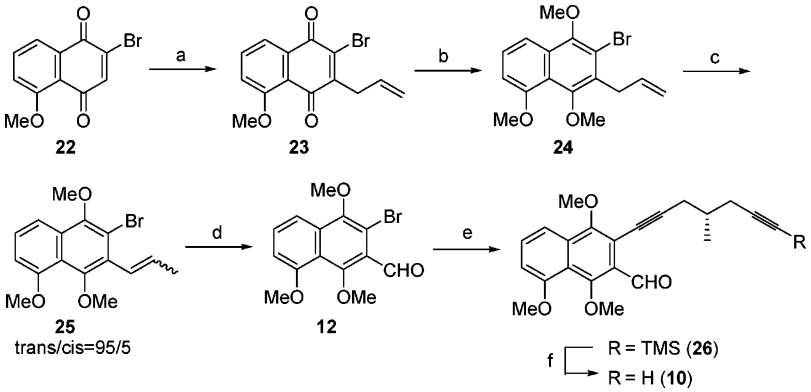
SCHEME 4. Synthesis of the Diyne Derivative 11[a]



[a] Reagents and conditions: (a) CuBr·DMS, BF_3·OEt_2, TMSC≡CCH_2MgCl, THF, −40 °C, 20 h, 90%. (b) DIBALH, CH_2Cl_2, −78 °C, 1 h, 96%. (c) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 2 h. (d) BuLi, −78 °C, 1 h, and then aq NH_4Cl, rt, 1 h, 71% in two steps. (e) BuLi, −78 °C, 30 min, and then Bu_3SnCl,1 h, quant.

SCHEME 5. Synthesis of the Naphthalene Derivative 10[a]



[a] Reagents and conditions: (a) vinyl acetic acid, $AgNO_3$, $(NH_4)_2S_2O_8$, CH_3CN/H_2O, 65 °C, 10 h, 65%. (b) $SnCl_2$, conc HCl, EtOH, 50 °C, 30 min, and then Me_2SO_4, 50% aq KOH, 65 °C, 3 h, 97%. (c) KO*t*-Bu, THF, 4 °C, 1 h, 92%. (d) O_3, MeOH, −78 °C, 20 min, and then PPh_3 in CH_2Cl_2, rt, 1 h, 79%. (e) diyne derivative **11**, $Pd_2(dba)_3$·$CHCl_3$, P(*t*-Bu)$_3$, toluene, rt, 9 h, 97%. (f) TBAF, AcOH, THF, rt, 30 min, quant.

yield was increased to 77% yield, although it was necessary to raise the temperature from room temperature to 50 °C to complete the reaction within 1 h (entry 2). Finally we found that the chemical yield was increased up to 90% by using $AuCl_3$ as a catalyst. This result is interesting because we have already reported that $AuBr_3$ was a more effective catalyst than $AuCl_3$ for both of the inter- and intramolecular [4 + 2] benzannulation reaction of *o*-alkynylaryl aldehydes having no methoxy group on the benzene ring.[12] In the previous papers, we proposed that the benzannulation proceeded through the formation of a benzopyrylium-type intermediate. Probably, in the present case, the two methoxy groups of the aromatic ring make the formation of the intermediate easier and therefore less Lewis acidic $AuCl_3$ enables induction of the benzannulation efficiently. $PtCl_2$ was also suitable catalyst for the present reaction (entry 4).

Since the model experiments showed that the intramolecular benzannulation proceeded well even with the methoxy-substituted starting material **16**, the synthetic study of angucyclinone antibiotics was started along the line shown in Scheme 2. First, we performed the synthesis of the diyne segment as shown in Scheme 4. According to the reported procedure, the reaction of the organocopper reagent, derived from trimethylsilyl-substituted propargylmagnesium chloride[13] and CuBr, with the α,β-unsaturated carbonyl compound **18**, having (*S*)-4-phenyl oxazolidinone as a chiral auxiliary, was carried out.[14] The reaction proceeded smoothly and the conjugate addition product **19** was obtained in 90% yield. The diastereomeric ratio, 96% dr, was determined by GC/MS, and it was increased up to 99% by recrystallization of **19** from EtOH. The cleavage of chiral auxiliary of **19** by reduction with diisobutylaluminum hydride (DIBALH) afforded the alkynyl aldehyde **20** in 96% yield,[15] which was converted to the 1,6-heptadiyne derivative **21** in 71% yield using the Corey−Fuchs method. Treatment of **21** with BuLi, followed by addition of Bu_3SnCl, gave **11** quantitatively.[16]

Next, we examined the preparation of the naphthalene derivative **12** and the coupling reaction between **11** and **12** as depicted in Scheme 5. The bromonaphthoquinone **22** was prepared from 1,5-dihydronaphthalene in four steps in 74% yield by the known procedure.[17] The introduction of the allyl group to the quinone part of **22** was carried out using vinyl acetic acid in the presence of

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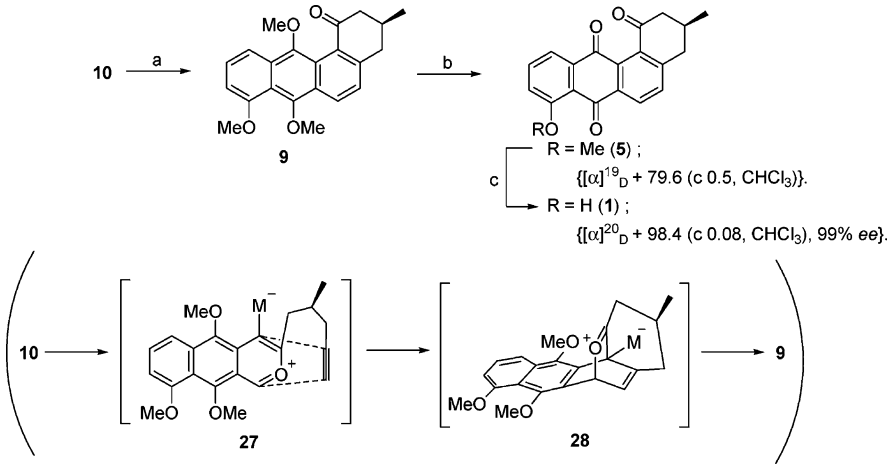
SCHEME 6. Total Synthesis of (+)-Ochromycinone (1) and (+)-Rubiginone B_2 (5)[a]



[a] Reagents and conditions: (a) 2 mol % $AuCl_3$, $(CH_2Cl)_2$, 50 °C, 1 h, 84%. (b) CAN, CH_3CN/H_2O, rt, 1 h, 97%. (c) BCl_3, CH_2Cl_2, −78 °C, 1 h, 89%.

silver nitrate, ammonium persulfate, and **23** was obtained in 65% yield.[18,19] Reduction to the hydroquinone of **23** using $SnCl_2$ and concentrated HCl in EtOH, followed by treatment of the resulting 1,4-dihydroxynaphthalene with Me_2SO_4 under basic conditions gave **24** in 97% yield. The terminal olefin on the allyl group of **24** was isomerized to the internal one by KO*t*-Bu in tetrahydrofuran (THF) and **25** was obtained in 92% yield as a 95:5 mixture of trans and cis isomers.[19] Interestingly, while the oxidative cleavage of olefin group of **25** by ozonolysis in CH_2Cl_2 gave only a trace amount of **12**, the chemical yield was dramatically improved by using MeOH as a solvent and **12** was obtained in 79% yield. We next examined the coupling reaction between **12** and the diyne part. Unfortunately, the desired compound **26** was not obtained under the Sonogashira coupling conditions using **21** as a diyne part, and most of the starting material was recovered.[20] However, we found that the reaction of **12** with the alkynyl stannane **11**, instead of **21**, proceeded well under the Stille coupling conditions and the coupling product **26** was obtained in 97% yield.[21] The trimethylsilyl (TMS) group at the terminus of the acetylene group of **26** was removed by tetrabutylammonium fluoride (TBAF) in the presence of AcOH in THF and **10** was obtained almost quantitatively.

On the basis of the results shown in Table 1, we examined the intramolecular benzannulation reaction of **10** in the presence of 2 mol % $AuCl_3$ in $(CH_2Cl)_2$ at 50 °C for 1 h as shown in Scheme 6. As expected, the reaction proceeded smoothly and the dihydrotetraphenone derivative **9** was obtained in 84% yield. Rubiginone B_2 (**5**) was produced in 97% yield by oxidation of **9** using ceric ammonium nitrate (CAN).[22] Finally, (+)-ochromycinone (**1**) was prepared in 89% yield from **5** by demethylation using BCl_3. The synthetic (+)-rubiginone B_2 **5** and (+)-ochromycinone **1** exhibited physical and spectroscopic data identical to those reported previously.[23]

Conclusion

The total synthesis of (+)-ochromycinone and (+)-rubiginone B_2 was accomplished via the $AuCl_3$-catalyzed intramolecular [4 + 2] benzannulation reaction as the key step. This result indicates that the intramolecular benzannulation is useful for construction of 2,3-dihydrophenanthren-4(1*H*)-one skeleton, an important structural framework in a wide rage of bioactive compounds, such as tanshinone family containing the activity to ischemia disease.[24] Further study to apply the present methodology for the synthesis of other natural products is in progress in our laboratory.

Experimental Section

(*S*)-7,8,12-Trimethoxy-3-methyl-3,4-dihydrotetraphen-1(2*H*)-one (9). To $AuCl_3$ (12 mg, 0.04 mmol) was added a solution of **10** (0.70 g, 2.0 mmol) in $(ClCH_2)_2$ (20 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred for 1 h at 50 °C and then transferred to a silica gel column. The solvent was removed under reduced pressure to give a crude product, which was purified by silica gel column chromatography using hexane/ethyl acetate = 3/1 as eluent to give **9** as a yellow solid (0.59 g, 1.68 mmol) in 84% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.41 (dd, J = 7.6, 8.6 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 4.07 (s, 3H), 3.99 (s, 3H), 3.73 (s, 3H), 3.09−2.97 (m, 2H), 2.81−2.74 (m, 1H), 2.62−2.50 (m, 2H), 1.25 (d, J = 5.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.2, 156.1, 149.1, 148.3, 145.1, 129.9, 129.4, 128.1, 125.9, 125.6, 119.9, 118.5, 115.7, 104.2, 104.2, 63.8, 61.2, 56.1, 47.6, 39.0, 30.9, 21.3; IR (KBr) 2835, 1676, 1599, 1553, 1452, 1256, 1221, 1090, 1003, 812, 565 cm^{-1}; MS (EI) *m/z* 350 (M^+, 54). HRMS (ESI). Calcd for $C_{22}H_{22}O_4Na$ (M^+ + Na): 373.1410. Found: 373.1410. mp = 204−208 °C. $[\alpha]^{31}_D$ + 172.9 (*c* 0.05, $CHCl_3$).

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(21) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc*. **2002**, *124*, 6343−6348.

(22) The α_D value of synthetic **5** {$[\alpha]^{19}_D$ + 79.6 (*c* 0.5, $CHCl_3$)} was identical to that of natural (+)-rubiginone B_2 {$[\alpha]^{20}_D$ + 78 (*c* 0.5, $CHCl_3$)}.[4]

(23) The α_D value of synthetic **1** {$[\alpha]^{20}_D$ + 98.4 (*c* 0.08, $CHCl_3$), 99% *ee*} was identical to that of (+)- ochromycinone {$[\alpha]^{25}_D$ + 96 (*c* 0.08, $CHCl_3$), 99% *ee*} synthesized by Krohn and co-workers.[7f]

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(*S*)-8-Methoxy-3-methyl-3,4-dihydrotetraphene-1,7,12-(2*H*)-trione [(+)-Rubiginone B_2 (5)]. To a solution of **9** (0.35 g, 1.0 mmol) in acetonitrile (8 mL) at 0 °C was added a solution of CAN (1.64 g, 3.0 mmol) in H_2O (20 mL), and the reaction mixture was allowed to warm to room temperature over 30 min and stirred for 1 h additionally. The resulting mixture was extracted with CH_2Cl_2 twice and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a crude product, which was purified by recrystallization from EtOH to give **5** as a yellow solid (0.31 g, 0.97 mmol) in 97% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, J = 8.2 Hz, 1H), 7.77 (dd, J = 1.0, 7.6 Hz, 1H), 7.70 (dd, J = 7.6, 8.5 Hz, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.29 (dd, J = 1.0, 8.5 Hz, 1H), 4.04 (s, 3H), 3.03−2.95 (m, 2H), 2.68 (dd, J = 10.8, 16.6 Hz, 1H), 2.56 (dd, J = 11.2, 15.9 Hz, 1H), 2.47 (m, 1H), 1.20 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.7, 184.3, 181.4, 159.7, 149.0, 137.6, 135.2, 135.0, 134.9, 132.9, 132.9, 129.5, 120.6, 119.6, 117.1, 56.5, 47.6, 38.4, 30.9, 21.5; IR (KBr) 2957, 1707, 1676, 1560, 1508, 1267, 1040, 1015, 968, 826 cm^{-1}; MS (EI) *m/z* 320 (M^+, 100). HRMS (ESI). Calcd for $C_{20}H_{16}O_4Na$ (M^+ + Na): 343.0941. Found: 343.0941. $[\alpha]^{19}_D$ + 79.6 (*c* 0.5, $CHCl_3$).

(*S*)-8-Hydroxy-3-methyl-3,4-dihydrotetraphene-1,7,12-(2*H*)-trione [(+)-Ochromycinone (1)]. To a solution of **5** (96 mg, 0.3 mmol) in CH_2Cl_2 (15 mL) at −78 °C under an argon atmosphere was added dropwise a solution of BCl_3 in heptane (1.80 mL, 1.80 mmol, 1 M), and the mixture was stirred for 1 h. Methanol (3 mL) was added, the resulting mixture was allowed to warm to room temperature over 1 h, and then a solution of aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with CH_2Cl_2 twice and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a crude product, which was purified by recrystallization from EtOH to give (**1**) as a yellow solid (82 mg, 0.27 mmol) in 89% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.29 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.70−7.64 (m, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.27 (m, 1H), 3.06−2.99 (m, 2H), 2.69 (dd, J = 11.0, 16.6 Hz, 1H), 2.58 (dd, J = 11.0, 15.2 Hz, 1H), 2.52−2.44 (m, 1H), 1.22 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.8, 187.3, 182.7, 161.9, 150.2, 136.9, 136.4, 135.7, 134.9, 133.3, 132.9, 128.8, 123.5, 119.4, 115.3, 47.5, 38.4, 30.8, 21.5; IR (KBr) 2974, 1705, 1668, 1636, 1454, 1364, 1281, 1157, 829, 600 cm^{-1}; MS (EI) *m/z* 306 (M^+, 43). HRMS (ESI). Calcd for $C_{19}H_{14}O_4Na$ (M^+ + Na): 329.0784. Found: 329.0786. mp = 166−167 °C. $[\alpha]^{20}_D$ + 98.4 (*c* 0.08, $CHCl_3$), 99% *ee*.

Supporting Information Available: Preparation methods of **19**−**21**, **11**, **23**−**25**, **12**, **26**, and **10** and spectroscopic and analytical data for **16**, **17**, **19**−**21**, **11**, **23**−**25**, **12**, **26**, **10**, **9**, **5**, and **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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