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Total synthesis of Angucyclines. Part 18: A short and efficient synthesis of (+)-ochromycinone

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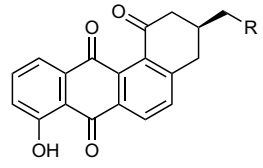
Abstract—A short and highly enantiospecific (seven steps, 99% ee) synthesis of (+)-ochromycinone **2** in 19% overall yield is reported. Key steps are the regioselective Diels–Alder reaction of the juglone derivative **4** with the mixture of dienes **5** and **9** derived from 3-methylcyclohexanone (99% ee) and the photooxidation of 1-deoxyochromycinone **3** to the natural ketone **2**. A pronounced concentration dependence of the specific rotation was observed for (+)-ochromycinone **2** in $CHCl_3$.

1. Introduction

Recently Taniguchi et al.[1] reported on the structure of a new angucycline antibiotic (reviews[2,3]) YM-181741 **1**, bearing a hydroxyl group at the C-3 methyl group of the known[4] angucycline antibiotic ochromycinone **2** (Chart 1). The authors also reported that YM-181741 **1** showed selective activity against *Helicobacter pylori*, the major cause of stomach ulcers,[5,6] with a MIC value of 0.2 μg/mL.[1] In fact, antibiotics with selective activity against *H. pylori* are urgently needed since the treatment of ulcer diseases with the broad-spectrum antibiotics such as amoxicillin and clarithromycin[7] causes diarrhoea by the disturbance of intestinal microbial flora[8] and also increasing antibiotic resistance in *H. pylori* infection is observed.[9] Taniguchi et al. also found that ochromycinone **2** is twice as active as YM-181741 **1** without losing its selectivity against *H. pylori*, for example, the low activity against other common bacteria. This finding stimulated our interest to develop a short and efficient total synthesis of enantiomerically pure (+)-ochromycinone **2**.



R = OH: antibiotic YM-181741 **1**
R = H: ochromycinone **2**

Chart 1. Structures of antibiotic YM-181741 **1** and ochromycinone **2**.

Several syntheses of racemic ochromycinone are known. With the exception of the work of Katsuura and Snieckus,[10,11] who used an aromatic directed metallation strategy, the Diels–Alder reaction with juglone derivatives and appropriate dienes was mostly employed to construct the tetrahydrobenz[*a*]anthraquinone skeleton.[12–14] Larsen et al.[15] achieved a kinetic resolution with respect to a racemic diene in the Diels–Alder reaction using a chiral catalyst in their asymmetric synthesis of (+)-ochromycinone. In the work of Carreño et al.,[16] an enantiomerically pure sulfinylquinone dienophile was the source of asymmetry to affect a kinetic resolution of a racemic diene in their synthesis of enantiomerically enriched (+)-ochromycinone. Very recently, the related (+)-rubiginone B_2 (*O*-methyl ether of **2**) was prepared via an intramolecular [2+2+2] cycloaddition of a chiral triyne precursor, derived from (+)-citronellal.[17]

We now disclose a very short, simple, and efficient enantiospecific synthesis of (+)-ochromycinone, using the Diels–Alder strategy. However, in contrast to the two known procedures, we have incorporated the commercially available and surprisingly cheap enantiomerically pure (*R*)-(+)-3-methylcyclohexanone **6** (99% ee) as the starting material for the enantiomerically pure diene **5** as shown in the retrosynthetic Scheme 1. 5-Acetoxy-2-bromo-1,4-naphthoquinone **4**[18] was used as the dienophile

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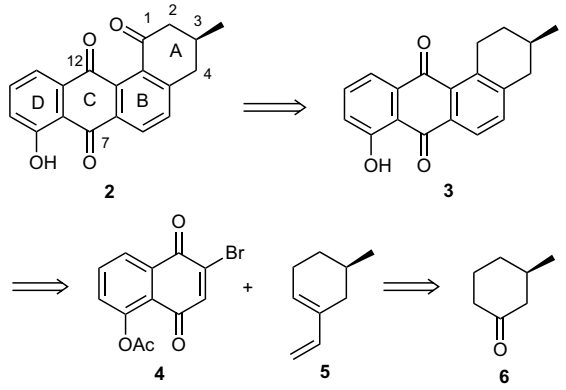
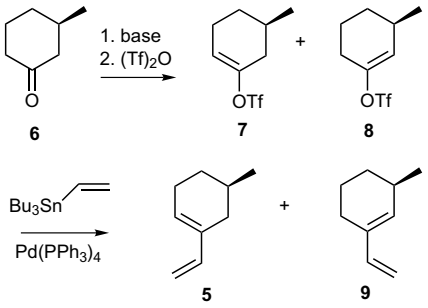


Scheme 1. Retrosynthetic scheme using (*R*)-(+)-3-methylcyclohexanone **6** as the source of chirality in the synthesis of (+)-ochromycinone.

because the bromine atom was known to direct the regiochemistry in the Diels–Alder reaction very efficiently.[19] Thus, the presence of an electron donating substituent such as a methoxy[14] group on the terminal end of the diene can be avoided, reducing the number of synthetic steps. In addition, the presence of the bromine atom in the immediate Diels–Alder adduct facilitates the aromatization of ring B by elimination of hydrogen bromide.[19] Our scheme further envisaged the mild photooxidation at C-1[20] in the final step to convert the precursor **3** into the natural product **2**.

2. Results and discussion

The starting materials for this investigation were readily accessible from known compounds. Thus, 5-acetoxy-2-bromo-1,4-naphthoquinone **4** was prepared following the method of Grunwell and Heinzman[18] by NBS-bromination of 1,5-diacetoxynaphthalene. The synthesis of the required diene **5** started with the deprotonation of enantiomerically pure (*R*)-(+)-3-methylcyclohexanone **6** with different bases followed by trapping of the enolates with triflic anhydride to yield the vinyltriflate **7** and its regioisomer **8** (Scheme 2). We expected that the formation of the desired triflate **7** was favored over the regioisomer **8** due to steric hindrance of the methyl group during kinetically controlled enolate formation. Three different bases were tried to investigate the regioselectivity of the enolate formation. The best result was obtained using lithium tetramethylpiperidide (LTMP, **7**:**8** = 5.4:1), followed by lithium diisopropylamide (LDA, **7**:**8** = 2.4:1) and lithium hexamethyldisilazide (LHMDS, **7**:**8** = 2:1). Antony and Maloney[21] also reported a kinetically controlled reaction with similar results using tritylllithium in monoglyme and (±)-3-methylcyclohexanone. Hsung et al.[22] synthesized vinyl triflate **8** (yield 13%) from 3-methylcyclohex-2-enone, but the synthesis of triflate **7** is reported here for the first time. The isomeric ratio of the enol triflates **7** and **8** was determined by GC. The assignment was possible by analysis of the ^{1}H NMR spectra of the mixtures, showing a broad singlet at δ 5.78 ppm for the olefinic



Scheme 2. Synthesis of dienes **5**/**9** via Stille reaction of enoltriflates **7**/**8** with tributylvinylstannane.

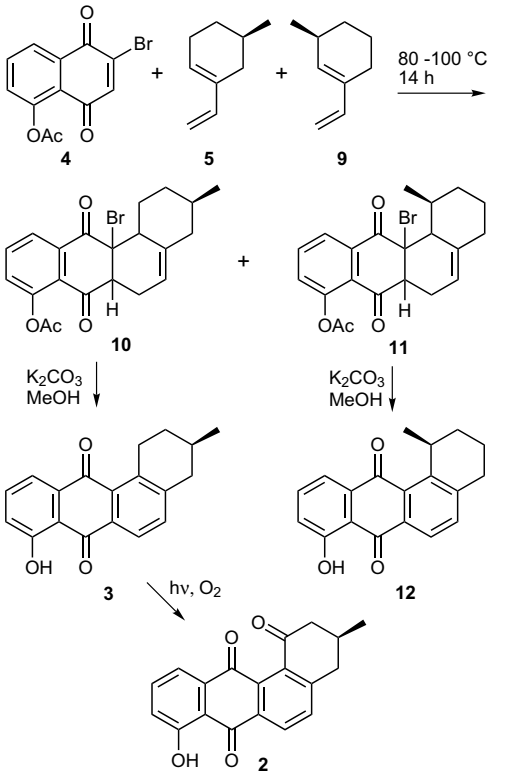
proton (CH_2CH=C) of **7** and a broad singlet at δ 5.66 ppm for olefinic proton ($CH(CH_3)CH$=C) of **8**.

A Stille reaction[23,24] was used to prepare the dienes **5** and **9** by coupling the triflates **7** and **8** and tributylvinylstannane in the presence of $Pd(PPh_3)_4$ (2 mol %) in 88% combined yield, similar to its execution in the deoxybrasiliquinone B synthesis.[25] The use of α-haloalkanesulfonyl bromides by Block et al.[26] for the racemic vinylcyclohexenes was less convenient for our purpose. The ratio of the dienes **5** and **9** reflected that of the respective triflate starting materials. The respective structures were assigned by characteristic signals in the ^{1}H NMR spectra for **5** (triplet at δ 5.78 ppm for CH_2CH=C) or **9** (doublet at δ 5.64 ppm for $CH(CH_3)CH$=C).

The Diels–Alder reaction of the dienes **5** and **9** with juglone **4** afforded mixtures (as evidenced from NMR) of two regioisomeric primary Diels–Alder products **10** and **11** in 79% combined yield (Scheme 3). The ratio of the regioisomers slightly improved with respect to the starting dienes **5** and **9** in favor of the desired isomer **10**, probably due to steric hindrance of the methyl group in **9** and the bromine atom in **4**. Dehydrobromination, saponification and dehydrogenation of **10**/**11** to **3** and **12** was induced in one operation by mild base treatment (K_2CO_3 in methanol) in the presence of air. The major aromatic isomer **3** was isolated in pure form and good yield (48%) after crystallization from the mixture of **3** and **12**.

The minor isomer **12** was present in the mother liquor and could eventually be obtained in crystalline form after repeated column chromatography and preparative TLC (8%). Both the aromatic regioisomers **3** and **12** were optically active {$[\alpha]_D^{25} = +114$, (*c* 0.09, $CHCl_3$) for **3** and $[\alpha]_D^{25} = -173$, (*c* 0.07, $CHCl_3$) for **12**} but the enantiomeric purity of (+)-ochromycinone **2** was determined later by chiral HPLC (see below). The 1D and 2D NMR spectra supported the structures of the respective aromatization products. The structure of the minor product **12** was further confirmed by single crystal X-ray analysis (Fig. 1), thus indirectly also proving the structure of the major product **3**.

In the final step, the precursor **3** was converted to (+)-ochromycinone **2** by photooxygenation with diffuse



Scheme 3. Synthesis of the benzo[*a*]anthraquinones **3** and **12** by Diels–Alder reaction and photooxidation of **3** to (+)-ochromycinone **2**.

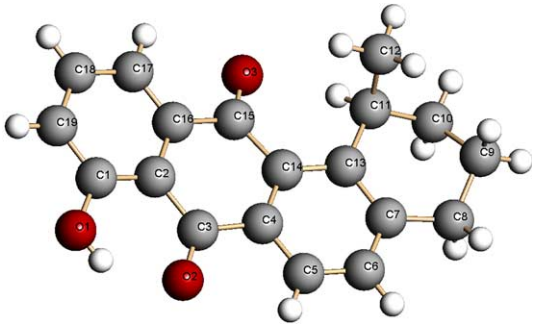


Figure 1. Molecular structure of **12**.

sunlight in 70% yield after chromatographic purification followed by crystallization. This mild oxidation reaction was discovered in our laboratory during the synthesis of a daunomycinone/rabelomycinone hybrid[20] (compare[27]) and is now frequently used as the last reaction step in angucycline synthesis.[16,17,28–30] The relevant anisotropic spectroscopic data of the synthetic material **2** were in agreement with those reported for the natural ochromycinone.[13,31]

To determine the enantiomeric excess (ee), we first determined the specific rotation of **2** in chloroform. To our great surprise, we found a great dependency of the specific optical rotation on the concentration of **2**. To the best of our knowledge, such a pronounced nonlinear

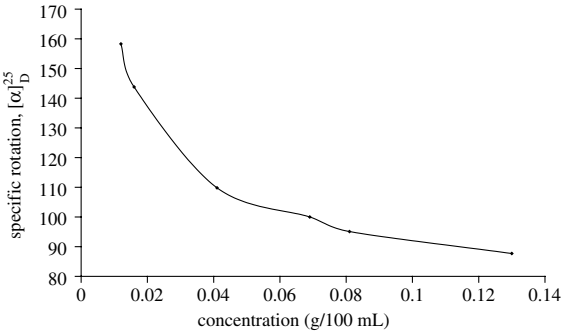


Figure 2. Dependency of the specific rotation on the concentration of (+)-ochromycinone **2** in $CHCl_3$.

effect,[32,33] as shown in Figure 2, has not yet been observed at such low concentrations and may be largely attributed to π-stacking.[34] Interestingly, the effect was not observed in the more polar solvent acetonitrile and is also not seen for the deoxy compound **3**. Evidently, the increase in polarity by the presence of the C-1 carbonyl group contributes to the interaction of the anthracyclinone molecules. In view of these observations, the determination of ee in previous enantioselective syntheses by specific rotation[15,16] have to be revisited. To check the enantioselectivity of our product, we used HPLC chromatographic techniques on an enantioselective stationary phase (Chiralcel OD-H-type column) and a partially racemic product (80% ee) as the reference material (details see Experimental). Not surprisingly, our product showed 99% ee, since the starting material had 99% ee and no racemization-prone step occurred during our synthesis.

In summary, we have reported a very short (seven steps from commercially available material) and highly enantiospecific (99% ee) synthesis of (+)-ochromycinone in 19% (LTMP as the base) or 12% (LDA as the base) overall yield. A large dependency of the specific rotation on the concentration of **2** in $CHCl_3$ was observed for the first time for angucyclinones.

3. Experimental

For general methods and instrumentation see reference.[35] Conditions for the GC analysis: Initial temperature: 50 °C; final temperature: 100 °C; temperature program: 5 °C/min; initial time: 0; end time: 10 min; solvent: CH_2Cl_2; column type: 25 m, 0.25 mm (inner diameter), FS-OV-1-CB- 0.1, CS 32180-72; carrier gas: helium; flow rate: 1 mL/min (carrier gas); detector type: FID.

Conditions for the HPLC analysis: column type: Chiralcel OD-H; detector type: UV (operated at 254 nm); pump A type: L-700; solvent A: hexane 80%; solvent B: isopropanol 20%; volume injected: 20 μL; flow rate: 0.7 mL/min.

3.1. (*R*)-5-Methylcyclohex-1-enyl trifluoromethanesulfonate 7 and (*R*)-3-methylcyclohex-1-enyl trifluoromethanesulfonate 8

A solution of 2,2,6,6-tetramethlypiperidine (TMP) (0.84 mL, 0.7 g, 4.9 mmol) in THF (15 mL) was cooled to −10 °C, and *n*-butyllithium in toluene (2.2 mL of a 2.5 M solution) was added slowly. The mixture was stirred for 30 min at −10 °C and subsequently cooled to −78 °C. A solution of the ketone **6** (Aldridge 0.55 mL, 0.5 g, 4.5 mmol) in THF (10 mL) was added by means of a syringe pump within 1 h with intensive stirring. The mixture was stirred for 2 h at −78 °C, and trifluoromethanesulfonic acid anhydride (0.83 mL, 1.4 g, 4.9 mmol) was added. The mixture was allowed to warm to 20 °C and stirring was continued for an additional 15 h. The reaction mixture was quenched by addition of HCl (0.1 M, 30 mL), neutralized by addition of $NaHCO_3$ (5%, 1.0 mL), dried (Na_2SO_4), filtered, and concentrated at reduced pressure. Flash chromatography of the residue on silica gel (pentane/5% Et_2O) gave a mixture of triflates **7** and **8** as a colorless oil. Similar reactions were performed with LDA and LHMDS; the isomer ratios and the yields were determined by GC. (LTMP: **7**:**8** = 5.4:1, 71% combined isolated yield; LDA: **7**:**8** = 2.4:1, 44% combined isolated yield; LHMDS: **7**:**8** = 2:1, by GC).

3.1.1. Data for (*R*)-5-methylcyclohex-1-enyl trifluoromethanesulfonate 7. *IR (KBr) 2961, 2934, 2874, 2853, 1694, 1460, 1422, 1368, 1352, 1248, 1221, 1145, 1031 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.78 (br s, 1H, 2-H), 2.17–2.58 (m, 3H, 6-H, 3-H_2), 1.83–2.16 (m, 1H, 6-H), 1.65–1.83 (m, 2H, 4-H, 5-H), 1.17–1.34 (m, 1H, 4-H), 1.07 (d, $J = 6.4$ Hz, 3H, 5-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.2 (C-1), 122.1 (*C*F_3), 118.4 (C-2), 35.9 (sec), 29.7 (C-5), 29.5 (sec), 23.8 (sec), 21.3 (*C*H_3); *MS (EI/200 °C) 244 (35) [M^+], 110 (33), 95 (26), 94 (27), 83 (22), 79 (84), 69 (74), 55 (100), 41 (71), 39 (20), 28 (25) (*data for mixed triflates **7** and **8**).

3.1.2. Data for (*R*)-3-methylcyclohex-1-enyl trifluoromethanesulfonate 8. ^1H NMR (200 MHz, $CDCl_3$) δ 5.66 (br s, 1H, 2-H), 2.17–2.58 (m, 3H, 5-H, 6-H_2), 1.83–2.02 (m, 1H, 5-H), 1.65–1.83 (m, 2H, 3-H, 4-H), 1.17–1.34 (m, 1H, 4-H), 1.08 (d, $J = 7.0$ Hz, 3H, 3-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.5 (C-1), 124.4 (*C*-2), 115.8 (*C*F_3), 30.3 (C-3), 30.0 (sec), 27.9 (sec), 21.7 (sec), 21.3 (*C*H_3).

3.2. (*R*)-5-Methyl-1-vinylcyclohex-1-ene 5 and (*R*)-3-methyl-1-vinylcyclohex-1-ene 9

A solution of the mixture of the triflates **7** and **8** (ratio ca. 2.4:1, 2.86 g, 11.7 mmol, from LDA experiment) and vinyltributylstannane (3.8 mL, 4.1 g, 12.89 mmol) was added to a slurry of LiCl (5.2 g, 123 mmol) and $Pd(PPh_3)_4$ (0.3 g, 2.0 mol %) in dry THF (110 mL). The mixture was heated under reflux for 15 h, cooled to room temperature, and diluted with pentane. The resulting solution was washed sequentially with a 10% aqueous ammonium hydroxide (3 × 50 mL) solution and water (3 × 50 mL). This solution was dried (Na_2SO_4), filtered, and concentrated at reduced pressure. Flash chromatography of the residue on silica gel (pentane) gave a mixture of dienes **5** and **9** as colorless oil 1.26 g (88% combined yield, **5**:**9** = 2.4:1 by NMR).

3.2.1. (*R*)-5-Methyl-1-vinylcyclohex-1-ene 5. ^1H NMR (200 MHz, $CDCl_3$) δ 6.41 (dd, $J_{1',2'a} = 10.7$ Hz, $J_{1',2'b} = 17.5$ Hz, 1H, 1′-H), 5.78 (t, 1H, 2-H), 5.12 (d, $J_{1',2'b} = 17.5$ Hz, 1H, 2′b-H); 4.94 (d, $J_{1',2'a} = 10.7$ Hz, 1H, 2′a-H); 2.05–2.43 (m, 3H), 1.62–1.94 (m, 3H), 1.26–1.35 (m, 1H), 1.07 (d, $J = 6.0$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.4 (C-1′), 136.2 (C-1), 129.8 (C-2), 110.0 (C-2′), 32.8 (sec), 31.2 (sec), 28.8 (C-5), 26.3 (sec), 22.4 (*C*H_3).

3.2.2. (*R*)-3-Methyl-1-vinylcyclohex-1-ene 9. ^1H NMR (200 MHz, $CDCl_3$) δ 6.38 (dd, $J_{1',2'a} = 10.7$ Hz, $J_{1',2'b} = 17.5$ Hz, 1H, 1′-H), 5.64 (d, $J = 3.9$ Hz, 1H, 2-H), 5.12 (d, $J_{1',2'b} = 17.5$ Hz, 1H, 2′b-H); 4.96 (d, $J_{1',2'a} = 10.7$ Hz, 1H, 2′a-H); 2.05–2.43 (m, 3H), 1.62–1.94 (m, 3H), 1.26–1.35 (m, 1H), 1.05 (d, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.5 (C-1′), 136.4 (C-2), 135.5 (C-1), 110.5 (C-2′), 31.7 (sec), 31.3 (C-3), 24.2 (sec), 21.9 (*C*H_3), 21.7 (sec).

3.3. (3*R*)-12a-Bromo-1,2,3,4,6,6a,7,12,12a,12b-decahydro-3-methyl-7,12-dioxotetraphen-8-yl acetate 10 and (1*S*)-12a-bromo-1,2,3,4,6,6a,7,12,12a,12b-decahydro-1-methyl-7,12-dioxotetraphen-8-yl acetate 11

A solution of **4** (2.4 g, 8.1 mmol) and the mixture of the dienes **5** and **9** (ratio ca. 2.4:1, 0.9 g, 7.4 mmol) in dry toluene (70 mL) was heated under argon for 12 h at 80 °C followed by 2 h at 100 °C (TLC monitoring). The solvent was removed at reduced pressure and the resulting material was purified by flash chromatography (CH_2Cl_2) to afford a mixture of cycloadducts **10** and **11** (2.42 g, 79% combined yield, ratio **10**:**11** = 2.6:1 by NMR).

3.3.1. Data for (3*R*)-12a-bromo-1,2,3,4,6,6a,7,12,12a,12b-decahydro-3-methyl-7,12-dioxotetraphen-8-yl acetate 10. *IR (KBr) 2956, 2923, 2869, 2847, 1776, 1705, 1667, 1596, 1450, 1368, 1324, 1265, 1237, 1189, 1102, 1015, 911, 868 cm^{-1}; *UV (CH_2Cl_2) λ_{max} (lg ε) 272 nm (3.55), 311 (3.39); ^1H NMR (200 MHz, $CDCl_3$) δ 8.09 (dd, $J_{9,11} = 1.1$ Hz, $J_{10,11} = 7.9$ Hz, 1H, 11-H), 7.77 (t, $J_{9,10} = J_{10,11} = 7.9$ Hz, 1H, 10-H), 7.40 (dd, $J_{9,10} = 7.9$ Hz, $J_{9,11} = 1.1$ Hz, 1H, 9-H), 5.46 (t, $J = 1.9$ Hz, 1H, 5-H), 3.60 (dd, $J = 2.3$ Hz, 6.2 Hz, 1H, 6a-H), 2.77 (m, 1H, 12b-H), 2.45–2.71 (m, 2H), 2.41 (s, 3H, COCH_3), 2.33–2.38 (m, 2H), 2.05 (m, 1H), 1.65–1.81 (m, 2H), 1.42–1.61 (m, 2H), 0.93 (d, $J = 6.6$ Hz, 3H, 3-CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.2 (C-7 or C-12), 191.3 (C-7 or C-12), 169.7 (*C*OCH_3), 149.3 (C-8), 135.8 (quat), 135.3 (C-10), 135.0 (quat), 130.2 (C-9), 126.6 (C-11), 117.7 (C-

5), 115.1 (quat), 69.8 (quat), 57.7 (C-6a), 50.1 (C-12b), 41.9 (sec), 35.7 (sec), 35.5 (sec), 32.4 (sec), 29.0 (C-3), 21.4 ($CO\mathit{C}H_3$), 17.9 ($\mathit{C}H_3$); *MS (EI/200 °C) 337 (45) [M^+−HBr], 296 (23), 295 (100), 294 (62), 293 (21), 292 (34), 278 (13), 277 (48), 263 (22), 149 (16), 121 (23), 98 (42), 85 (16), 84 (17), 82 (32), 81 (12), 80 (33), 79 (12), 60 (31), 45 (38), 43 (70), 28 (7). *Anal. Cald for $C_{21}H_{21}BrO_4$: C, 60.44; H, 5.07. Found: C, 60.27; H, 4.79 (*data for mixed cycloadducts **10** and **11**).

3.3.2. Data for (1*S*)-12a-bromo-1,2,3,4,6,6a,7,12,12a,12b-decahydro-1-methyl-7,12-dioxotetraphen-8-yl acetate 11. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (dd, $J_{9,11} = 1.2$ Hz, $J_{10,11} = 7.9$ Hz, 1H, 11-H), 7.77 (t, $J_{9,10} = J_{10,11} = 7.9$ Hz, 1H, 10-H), 7.38 (dd, $J_{9,10} = 7.9$ Hz, $J_{9,11} = 1.2$ Hz, 1H, 9-H), 5.46 (t, $J = 1.9$ Hz, 1H, 5-H), 3.63 (dd, $J = 2.3$ Hz, 6.1 Hz, 1H, 6a-H), 2.77 (m, 1H, 12b-H), 2.45–2.71 (m, 2H), 2.42 (s, 3H, $COC\mathit{H}_3$), 2.33–2.38 (m, 2H), 2.05 (m, 1H), 1.65–1.81 (m, 2H), 1.42–1.61 (m, 2H), 1.15 (d, $J = 6.6$ Hz, 3H, 1-$C\mathit{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.3 (C-7 or C-12), 190.4 (C-7 or C-12), 169.7 ($\mathit{C}OCH_3$), 149.6 (C-8), 139.5 (quat), 136.2 (quat), 135.3 (C-10.), 130.0 (C-9), 126.5 (C-11), 117.1 (C-5), 115.1 (quat), 69.7 (quat), 56.2 (C-6a), 49.9 (C-12b), 35.3 (sec), 35.0 (C-1), 28.0 (sec), 25.8 (sec), 24.7 (sec), 24.0 ($\mathit{C}H_3$), 21.4 ($CO\mathit{C}H_3$).

3.4. (*R*)-1,2,3,4-tetrahydro-8-hydroxy-3-methyltetraphene-7,12-dione 3 and (*S*)-1,2,3,4-tetrahydro-8-hydroxy-1-methyltetraphene-7,12-dione 12

A solution of the mixture of **10** and **11** (ratio ca. 2.6:1, 1.42 g, 3.4 mmol) in methanol (10 mL) was treated with 1.6 g of K_2CO_3. The suspension was stirred for 16 h (TLC monitoring) at room temperature in the dark. The alkaline reaction mixture was acidified by addition of HCl (2 N, 5 mL), the suspension was filtered and the solvent removed under reduced pressure. The crude material was redissolved in CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), filtered, and the solvent was evaporated at reduced pressure to afford a mixture of **3** and **12**. The major isomer **3** (mp 162 °C) was isolated by flash chromatography of the crude mixture followed by crystallization of the nonpolar fraction to yield 0.48 g (48%) of **3**. The mother liquor was again purified by flash chromatography on silica gel followed by preparative TLC and crystallization to yield 0.08 g (8%) of **12** (combined isolated yield of **3** and **12** 56%).

3.4.1. Data for (*R*)-1,2,3,4-tetrahydro-8-hydroxy-3-methyltetraphene-7,12-dione 3. R_f 0.52 (1:1 pentane–dichloromethane); $[\alpha]_D^{25} = +114$ (*c* 0.09, $CHCl_3$); IR (KBr) 2950, 2923, 2363, 2341, 1667, 1634, 1580, 1553, 1482, 1450, 1417, 1373, 1324, 1276, 1243, 1156 cm^{-1}; UV ($CHCl_3$) λ_{max} (lg ε) 268 nm (4.24), 285 (4.11), 402 (3.89); ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.53 (s, 1H, 8-OH), 8.09 (d, $J_{5,6} = 8.0$ Hz, 1H, 6-H), 7.71 (dd, $J_{9,11} = 1.5$ Hz, $J_{10,11} = 7.7$ Hz, 1H, 11-H), 7.63 (t, $J_{9,10} = J_{10,11} = 7.7$ Hz, 1H, 10-H), 7.43 (d, $J_{5,6} = 8.0$ Hz, 1H, 5-H), 7.23 (dd, $J_{9,11} = 1.5$ Hz, $J_{9,10} = 7.9$ Hz, 1H, 9-H), 3.44–3.65 (m, 1H, 1-H), 3.10–3.34 (m, 1H, 1-H), 2.85–3.05 (m, 1H, 4-H), 2.43–2.63 (m, 1H, 4-H), 1.75–2.13 (m, 2H, 2-H, 3-H), 1.19–1.50 (m, 1H, 2-H), 1.12 (d, $J = 6.5$ Hz, 3H, $C\mathit{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.1 (C-7 or C-12), 185.2 (C-7 or C-12), 162.1 (C-8), 146.8 (quat), 141.9 (quat), 136.9 (C-10), 135.5 (quat), 135.0 (C-5), 133.1 (quat), 131.6 (quat), 125.1 (C-6), 123.4 (C-9), 119.6 (C-11), 115.9 (quat), 40.2 (sec), 31.7 (sec), 29.6 (sec), 28.2 (C-3), 22.0 ($\mathit{C}H_3$). MS (EI/200 °C) 292 (100) [M^+], 278 (33), 277 (71), 264 (15), 263 (69), 152 (7), 151 (27), 150 (58), 84 (12), 57 (17), 49 (10), 44 (9), 43 (18), 41 (10), 28 (9). Anal. Cald for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.24; H, 4.91.

3.4.2. Data for (*S*)-1,2,3,4-tetrahydro-8-hydroxy-1-methyltetraphene-7,12-dione 12. R_f 0.56 (1:1 pentane–dichloromethane); $[\alpha]_D^{25} = -173$ (*c* 0.07, $CHCl_3$); IR (KBr) 2922, 2351, 2194, 1664, 1634, 1617, 1582, 1460, 1367, 1268, 1157, 1082, 1041 cm^{-1}; UV (CH_2Cl_2) λ_{max} (lg ε) 269 nm (4.22), 285 (4.01), 399 (3.76); ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.56 (s, 1H, 8-OH), 8.19 (d, $J_{5,6} = 8.0$ Hz, 1H, 6-H), 7.78 (dd, $J_{9,11} = 1.2$ Hz, $J_{10,11} = 7.6$ Hz, 1H, 11-H), 7.68 (t, $J_{9,10} = J_{10,11} = 7.9$ Hz, 1H, 10-H), 7.51 (d, $J_{5,6} = 8.0$ Hz, 1H, 5-H), 7.28 (dd, $J_{9,11} = 1.2$ Hz, $J_{9,10} = 8.3$ Hz, 1H, 9-H), 4.49 (m, 1H, 1-H), 2.99 (m, 2H), 1.80–2.06 (m, 4H), 1.31 (d, $J = 6.9$ Hz, 3H, $C\mathit{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.3 (C-7 or C-12), 185.2 (C-7 or C-12), 162.1 (C-8), 147.7 (quat), 146.2 (quat), 136.9 (C-10), 135.9 (quat), 135.6 (C-5), 133.6 (quat), 131.1 (quat), 125.3 (C-6), 123.3 (C-9), 119.9 (C-11), 115.9 (quat), 31.4 (sec), 30.1 (sec), 29.8 (C-1), 22.6 ($\mathit{C}H_3$), 17.3 (sec). MS (EI/200 °C) 292 (100) [M^+], 277 (42), 264 (19), 263 (71), 98 (20).

3.4.3. Crystal structure determination of 12.[36] $C_{19}H_{16}O_3$, $M_r = 292.3$, monoclinic, space group P $2_1/c$, $a = 8.0593(10)$, $b = 11.7374(14)$, $c = 14.5045(17)$ Å, $\beta = 90.849(3)°$, $V = 1371.9(3)$ Å^3, $Z = 4$, $D_x = 1.415$ g/cm^3, $F(000) = 616$, $T = 120(2)$ K. Bruker-AXS SMART APEX, graphite monochromator, λ (MoKα) = 0.71073 Å, $\mu = 0.095$ mm^{-1}, yellowish crystal, size $0.20 \times 0.12 \times 0.08$ mm^3, 11541 intensities collected $4.4 < 2\theta < 56.8°$, $-10 < h < 10$, $-15 < k < 15$, $-19 < l < 19$. Structure solved by direct methods, full-matrix least-squares refinement based on F^2 and 201 parameters, all but H atoms refined anisotropically, H atoms refined with riding model on idealized positions with $U = 1.5\ U_{iso}$ (O, C-methyl) and $1.2\ U_{iso}$(C). Refinement converged at $R1(F) = 0.058$, $wR2$ (F^2, all data) = 0.113, $S = 0.72$, $\max(\delta/\sigma) < 0.001$, min/max height in final ΔF map −0.19/0.21 e/Å^3. Figure 1 shows the molecular structure. Programs used: SHELXTL[36].

Full crystallographic data (excluding structure factors) for **12** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-223554. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

3.5. (*S*)-3,4-Dihydro-8-hydroxy-3-methyltetraphene-1,7,12(2*H*)-trione; (+)-ochromycinone 2

A solution of the dione **3** (22 mg, 0.075 mmol) was dissolved in CH_2Cl_2 (15 mL), and exposed to diffuse sunlight for about 40 h in five NMR tubes (TLC and NMR monitoring). The combined solutions were concentrated at reduced pressure. The crude reaction mixture was then subjected to flash chromatography followed by recrystallization to afford **2** (16.2 mg, 70%) as yellow needles, mp 160 °C. All spectral data of synthetic **2** were identical to those of the natural ochromycinone.[13,31] For determination of specific rotations see Figure 2.

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