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Asymmetric Total Synthesis and Revision of the Absolute Configuration of 4-Keto-Clonostachydiol

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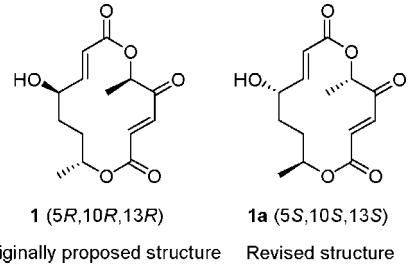


The first total synthesis of the 14-membered natural macrocyclic bislactone 4-keto-clonostachydiol, along with its enantiomer, has been accomplished in 13 steps with overall yields of 8.4% and 8.0%, respectively. The absolute configuration of 4-keto-clonostachydiol **1** has been revised as (5*S*,10*S*,13*S*).

4-Keto-clonostachydiol **1**, a 14-membered nonsymmetric macrocyclic bislactone, was first isolated from New Zealand marine alga-derived fungus *Gliocladium* sp.[1] 4-Keto-clonostachydiol **1** exhibits various biological properties, such as strong cytotoxicity against P388 cells (IC_{50} 0.55 μM) and significant activities against *Bacillus subtilis*, the fungi *trichophyton mentagrophytes*, and *cladosporium resinae*. The originally proposed stereochemistry of **1** was assigned as (5*R*,10*R*,13*R*) based on the comparison of NMR spectra and optical rotation of a known compound clonostachydiol **2**, which was the Luche reduction product of **1** (Figure 1).[3,4] The structure of **1** has recently been patented for its excellent cytotoxic and antibacterial activities.[2] Syntheses toward clonostachydiol **2** have been reported by two individual groups.[5,6] Herein we describe the first asymmetric total synthesis of 4-keto-clonostachydiol from commercially available chiral methyloxirane along with the revision of the absolute configuration of **1** as (5*S*,10*S*,13*S*).

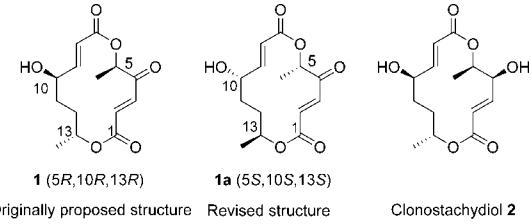
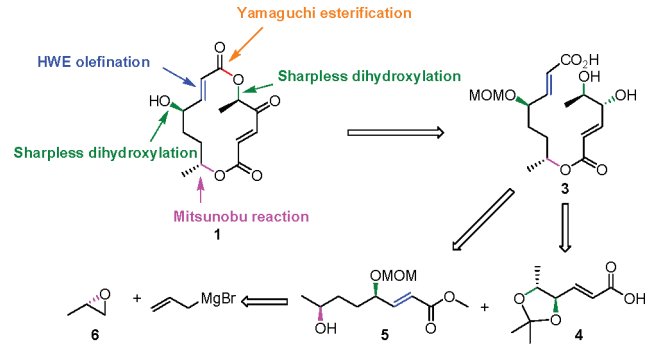
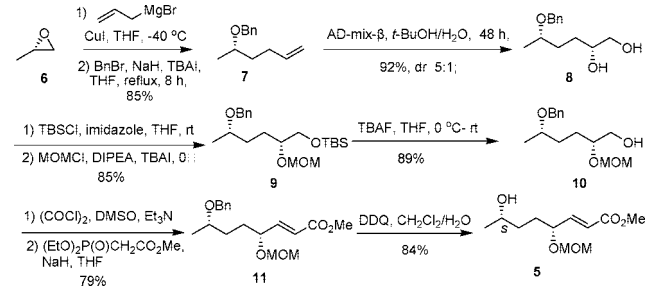


FIGURE 1. Structure of 4-Keto-Clonostachydiol (**1**) and Clonostachydiol (**2**).

SCHEME 1. Retrosythetic Analysis of 4-Keto-Clonostachydiol 1



SCHEME 2. Synthesis of Enoate Alcohol 5



As outlined in Scheme 1, we envisioned that the lactone ring of 4-keto-clonostachydiol **1** could be closed by an intramolecular Yamaguchi lactonization reaction of dihydroxy acid **3**, which was assembled of carboxylic acid **4** and enoate alcohol **5** via Mitsunobu reaction. The two stereocenters in acid **4** could easily be established by Sharpless asymmetric dihydroxylation of the corresponding diene while fragment **5** was prepared from (*S*)-(+)-methyloxirane **6** and allyl magnesium bromide.

Synthesis of alcohol **5** began with commercially available (*S*)-methyloxirane **6** (Scheme 2). Regioselective ring-opening of epoxide **6** by allyl magnesium bromide in the presence of

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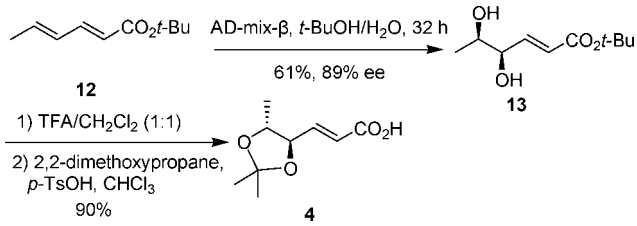
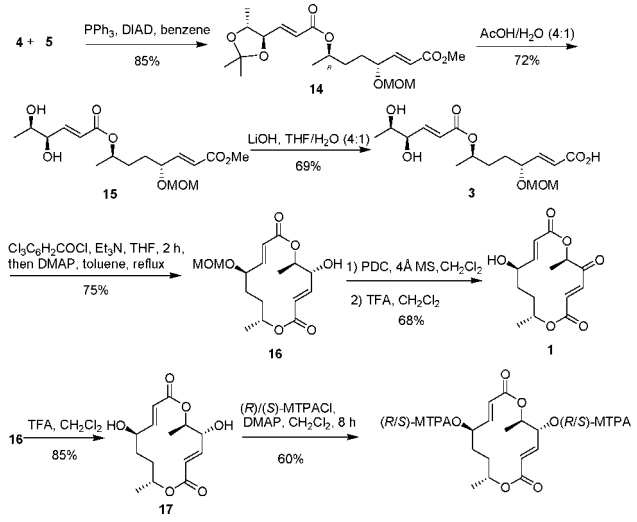
SCHEME 3. Synthesis of Acid 4



SCHEME 4. Synthesis of 4-Keto-Colonstachydiol 1



CuI yielded the alcohol, which was protected as benzyl ether **7** (85% yield for two steps). Asymmetric dihydroxylation of the terminal olefin with AD-mix-β afforded diol **8** (dr 5:1).[8] protection of the primary and secondary hydroxyl group as TBS ether and MOM ether, respectively, resulted in compound **9**. Desilylation of **9** with treatment with TBAF generated primary alcohol **10**. After sequential Swern oxidation[9] and Horner−Wadsworth−Emmons olefination,[10] enoate **11** was obtained. Subsequently, enoate **11** was subjected to oxidative debenzylation with DDQ[11] in aqueous CH_2Cl_2 to yield enoate alcohol **5**.

Synthesis of acid **4** started from (2*E*,4*E*)-*tert*-butyl hexa-2,4-dienoate **12**. Regioselective Sharpless asymmetric dihydroxylation of ester **12** with AD-mix-β (89% ee)[12,13] afforded the corresponding *syn* diol **13**, which was converted to key fragment **4** through acidic hydrolysis and acetonide protection (Scheme 3).[14]

With fragments **4** and **5**in hand (Scheme 4), the Mitsunobu reaction[15] was employed to construct dienoate **14** with the inversion of the C-13 configuration. Deprotection of **14**,[16] followed by

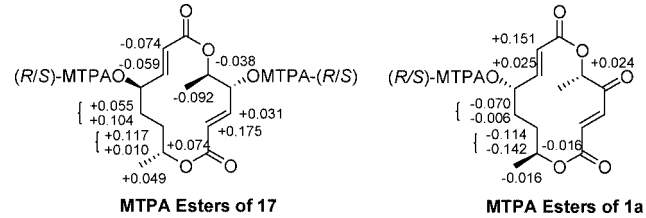
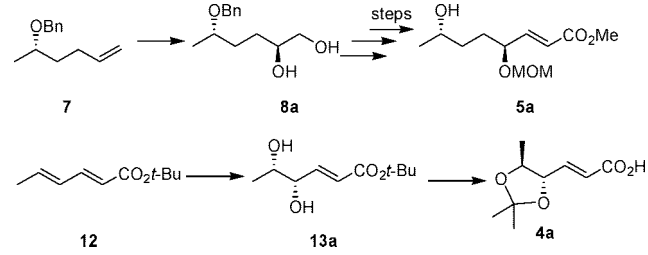


FIGURE 2. $\Delta\delta$ values for the MTPA esters of **17** and **1a** ($\Delta\delta = \delta_S - \delta_R$).

SCHEME 5. Synthesis of Fragments 5a and 4a



hydrolysis of the methyl ester group with LiOH in THF/H_2O gave dihydroxy acid **3**, which underwent intramolecular ring closure by using Yamaguchi's protocol[17] to afford 14-membered macrolide **16**. Then PDC oxidation of **16**, followed by deprotection of MOM ether with TFA,[18] gave the 4-keto-clonostachydiol **1**, whose spectral data (^{1}H and ^{13}C NMR) were in good agreement with the literature (see the Supporting Information). The specific optical rotation of synthetic 4-keto-clonostachydiol ($[\alpha]^{20}_D$ −76 (*c* 0.1, CH_3OH)) is quite different from that of the natural one ($[\alpha]^{20}_D$ +49 (*c* 0.33, CH_3OH)). To confirm our result and further determine the absolute configuration, the modified Mosher's method[19] was adopted. Removal of the MOM group in **16** with TFA afforded 4-*epi*-clonostachydiol **17**. Upon treatment of **17** with (*R*)- and (*S*)-MTPACl [α-methoxy-α-(trifluoromethyl)phenylacetyl chloride], (*S*)- and (*R*)-MTPA esters were obtained, respectively. ^{1}H−^{1}H COSY data enabled assignment of the proton signals for MTPA ester. Analysis of the $\Delta\delta_{S-R}$ values (Figure 2) for the two diastereomeric esters confirmed the absolute configuration of **17** at C-4 as *R* and that at C-10 as *R*, but the optical rotation symbols of synthetic product and natural product were opposite, indicating that our synthetic 4-keto-clonostachydiol **1** was actually the enantiomer of the natural product, which prompted our further synthesis toward its antipode.

The antipode of **1** was then prepared from precursors **7** and **12** through similar routes. Treatment of benzyl ether **7** with AD-mix-α produced diol **8a**, which was converted into **5a** according to the above procedures (see the Supporting Information). Fragment **4a** was prepared from dienoate **12** following the same pathway of **4** except the AD-mix-β reagent was replaced by AD-mix-α (Scheme 5).

Condensation of fragments **4a** and **5a** under Yamaguchi condition provided enoate **14a** in a yield of 76%, while Keck protocol only yielded 35%.[20] Consecutive manipulation, including deprotection, hydrolysis, esterification, oxidation, and deprotection, finally led to (+)-4-keto-clonostachydiol **1a** (Scheme 6) (see the Supporting Information). The spectral data (^{1}H and ^{13}C NMR) and optical rotation of synthetic (+)-4-keto-clonostachydiol **1a** were both in accord with the reported ones

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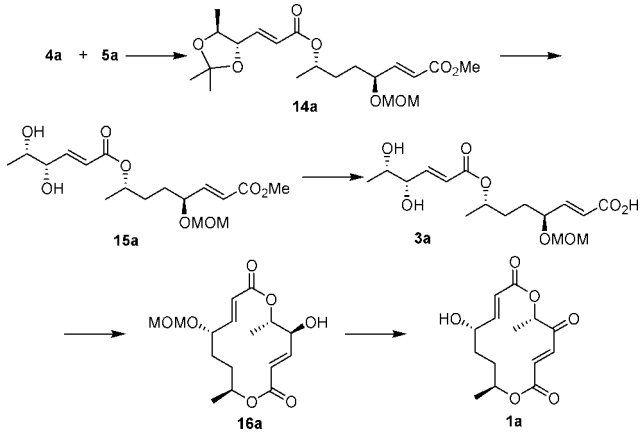
SCHEME 6. Synthesis of (+)-4-Keto-Colonstachydiol 1a



of the natural product. Upon treatment of **1a** with (*R*)- and (*S*)-MTPACl, (*S*)- and (*R*)-MTPA esters were obtained, respectively. Analysis of the $\Delta\delta_{S-R}$ values for the two diastereomeric esters demonstrated that the absolute configuration of **1a** at C-10 was *S* (Figure 2). Therefore, we corrected the absolute configuration of the natural product 4-keto-clonostachydiol **1** as (5*S*,10*S*,13*S*).

In summary, we have finished the total synthesis of both (+)- and (−)-4-keto-clonostachydiol through a highly stereoselective route, and the result was further confirmed by Mosher's method. The absolute configuration of 4-keto-clonostachydiol was revised as (5*S*,10*S*,13*S*) on the basis of our current synthesis.

Experimental Section

(2*R*,5*S*)-5-(Benzyloxy)hexane-1,2-diol (8). A mixture of AD-mix-β (7.0 g, 5 mmol) in 50 mL of *t*-BuOH/H_2O (1:1 v:v) was stirred at rt for 15 min, and then cooled to 0 °C. To this solution was added benzyl ether **7** (0.95 g, 5 mmol). The reaction mixture was stirred at 0 °C for 48 h and then quenched with Na_2SO_3 (7.5 g) at 0 °C within 0.5 h. EtOAc was added to the reaction mixture, and the aqueous layer was further extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 1:1) to give 1.03 g of the corresponding diol **8** (92%) as a colorless oil: $[\alpha]^{20}_D$ +29 (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26−7.34 (m, 5 H), 4.59 (d, J = 11.4 Hz, 1 H), 4.20 (d, J = 11.4 Hz, 1 H), 3.52−3.62 (m, 3 H), 3.52−3.62 (m, 2 H), 2.79 (s, 1 H), 1.59−1.70 (m, 2 H), 1.47−1.58 (m, 2 H), 1.21 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.4, 127.8, 127.6, 74.8, 72.1, 70.3, 66.7, 32.7, 29.0, 19.3; IR (film) υ_{max} 3384, 2930, 1066, 738, 698 cm^{-1}; HRMS (ESIMS) calcd for $C_{13}H_{21}O_3$ $[M + H]^+$ 225.1485, found 225.1492.

Dienoate 14. To a solution of **4** (400 mg, 1.6 mmol) and triphenylphosphine (852 mg, 3.2 mmol) in benzene (20 mL) was added a solution of DIAD (657 mg, 3.2 mmol) and acid **5** (358 mg, 1.9 mmol) in benzene (20 mL) over 30 min at rt. The reaction mixture was stirred overnight, and then quenched with H_2O (40 mL). This mixture was extracted with $CHCl_3$, washed with brine, and dried by Na_2SO_4, then the solvents were evaporated. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 10:1) to give 572 mg of **15** (85%) as a colorless oil: $[\alpha]^{20}_D$ +19 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (m, 2 H), 6.09 (d, J = 15.3 Hz, 1 H), 5.98 (d, J = 15.9 Hz, 1 H), 4.97 (m, 1 H), 4.58 (dd, J = 14.7, 6.3 Hz, 2 H), 4.18 (m, 1 H), 4.05 (m, 1 H), 3.83 (m, 1 H), 3.73 (s, 3 H), 3.35 (s, 3 H), 1.64 (br, 4 H), 1.46 (s, 4 H), 1.30 (d, J = 6 Hz, 3 H), 1,23 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 165.4, 147.5, 143.3, 123.1, 121.7, 109.2, 94.6, 81.6, 76.4, 74.8, 70.9, 55.6, 51.6, 31.4, 30.7, 27.2, 26.6, 19.9, 16.6; IR (film) υ_{max} 3365, 2983, 1721, 1272, 1095, 1036, 984, 919 cm^{-1}; HRMS (ESIMS) calcd for $C_{20}H_{36}NO_8$ $[M + NH_4]^+$ 418.2435, found 418.2426.

Macrolide 16. To a solution of *seco*-acid **3** (40 mg, 0.12 mmol) in anhydrous THF (1 mL) under argon was added Et_3N (63 μL, 0.46 mmol), after 30 min, followed by trichlorobenzoyl chloride (20 μL, 0.47 mmol). The resulting heterogeneous mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with dry toluene (100 mL) and the supernatant solution was transferred to a flask. The resulting solution was slowly added (5 mL/h) to a refluxing solution of DMAP (107 mg, 0.88 mmol) in toluene (50 mL) over 20 h. The mixture was refluxed for a further 11 h, and then diluted with diethyl ether. The organic layer was washed with brine and dried by $MgSO_4$, then the solvents were evaporated. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 2:1) to give 28 mg of **17** (75%) as a colorless oil: $[\alpha]^{20}_D$ +22 (*c* 2.7, CH Cl_3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (m, 2 H), 6.15 (d, J = 15.6 Hz, 1 H), 5.89 (d, J = 15.6 Hz, 1 H), 5.32 (m, 1 H), 5.19 (m, 1 H), 4.60 (m, 2 H), 4.50 (m, 1 H), 4.45 (m, 1 H), 3.36 (m, 1 H), 2.03−2.09 (m, 1H), 1.53−1.76 (m, 3 H), 1.44 (d, J = 6.3 Hz, 3 H), 1.20 (d, J = 6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.7, 150.0, 146.8, 122.2, 121.5, 94.6, 74.0, 73.2, 71.1, 69.4, 55.5, 27.1, 26.1, 17.4, 15.9; IR (film) υ_{max} 3502, 2984, 1713, 1361, 1223, 1043, 513 cm^{-1}; HRMS (ESIMS) calcd for $C_{16}H_{28}NO_7$ $[M + NH_4]^+$ 346.1860, found 346.1870.

4-Keto-Clonostachydiol 1. Under Ar atmosphere, pyridinium dichromate (PDC) (515 mg, 2.88 mmol) was added in portions to a stirred solution of the alcohol **17** (75 mg, 0.23 mmol) and molecular sieves 4Å (450 mg) in CH_2Cl_2 (10 mL) at 0 °C. After continuous stirring for 1 h at rt, the reaction mixture was diluted with ether (50 mL) and filtered through Celite. The solvents were evaporated. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 5:1) to give 59 mg of the corresponding ketone (80%) as a colorless oil: $[\alpha]^{20}_D$ −44 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 16 Hz, 1 H), 7.02 (dd, J = 15.6, 4 Hz, 1 H), 6.48 (d, J = 16 Hz, 1 H), 6.14 (dd, J = 15.6, 1.2 Hz, 1 H), 5.31 (q, J = 7.2 Hz, 1 H), 5.05 (m, 1 H), 4.64 (m, 2 H), 4.44 (m, 1 H), 3.38 (s, 3 H), 1.81−1.92 (m, 3 H), 1.60 (m, 1 H), 1.56 (d, J = 6.4 Hz, 3 H), 1.28 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 165.7, 164.1, 150.1, 135.3, 131.1, 120.6, 94.7, 75.6, 74.0, 72.0, 55.7, 28.3, 28.1, 18.5, 16.4; IR (film) υ_{max} 3420, 2935, 1722, 1263, 1042, 981 cm^{-1}; HRMS (ESIMS) calcd for $C_{16}H_{26}NO_7$ $[M + NH_4]^+$ 344.1704, found 344.1710.

Trifluoroacetic acid (1.5 mL) was added to a solution of the ketone (13 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C under Ar atmosphere. After continuous stirring for 2 h at rt the solvents were evaporated. The crude product was purified by column chromatography on silica gel (hexanes/EtOAc 2:1) to give 8 mg of 4-keto-clonostachydiol **1** (85%) as a colorless oil: $[\alpha]^{20}_D$ −76 (*c* 0.1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (d, J = 16 Hz, 1 H), 7.20 (dd, J = 15.6, 3.2 Hz, 1 H), 6.39 (d, J = 16 Hz, 1 H), 5.93 (dd, J = 15.6, 2 Hz, 1 H), 5.21 (d, J = 4.4 Hz, 1 H), 5.16 (q, J = 7.2 Hz, 1 H), 4.92 (m, 1 H), 4.36 (br, 1 H), 1.89 (m, 1 H), 1.68 (m, 1 H), 1.56 (m, 1 H), 1.49 (d, J = 7.2 Hz, 4 H), 1.20 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 200.3, 165.8, 164.0, 154.5, 136.8, 129.9, 118.1, 75.4, 72.0, 68.6, 30.4, 27.6, 18.6, 15.9; IR (film) υ_{max} 3375, 2990, 1764, 1243, 1058 cm^{-1}; HRMS (ESIMS) calcd for $C_{14}H_{22}NO_6$ $[M + NH_4]^+$ 300.1442, found 300.1444.

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Supporting Information Available: General experimental details and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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