A Stereoselective Approach for the Total Synthesis of Clonostachydiol

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Abstract: A stereoselective synthesis of clonostachydiol is accomplished using readily available (±)-epichlorohydrin as a precursor. The synthesis involves direct and straightforward reactions such as Sharpless asymmetric epoxidation, iodination, stereoselective opening of epoxide with allylmagnesium chloride and Sharpless asymmetric dihydroxylation.

Key words: Sharpless asymmetric epoxidation, allylmagnesium chloride, Sharpless asymmetric dihydroxylation

The cytotoxic clonostachydiol, a 14-membered bismacrolactone was isolated from a marine algae derived fungus.[1] Fungi derived from the marine source are well-known producers of novel and pharmacologically active secondary metabolites.[2,3] Clonostachydiol (**1**) is cytotoxic, active against *Bacillus subtilis* and the fungi *Trichophyton mentagrophytes* and *Cladosporium resine*. The promising biological activity and fascinating structure of this family of macrolactones make them attractive synthetic targets. The absolute and relative stereochemistry of clonostachydiol (**1**) was established by Rao et al.[4] Clonostachydiol (**1**) is structurally similar to the colletol family (Figure 1).[5]

The extreme scarcity of the natural material together with its novel structure prompted us to attempt the total synthesis of clonostachydiol (**1**). Herein, we wish to report an efficient stereoselective approach for the total synthesis of clonostachydiol (**1**) from commercially available (±)-epichlorohydrin (**6**) employing the Jacobsen's hydrolytic kinetic resolution, Sharpless asymmetric oxidations and macrolactonization as the key steps. Retrosynthetic analysis of clonostachydiol (**1**) is depicted in Scheme 1.

The retrosynthetic analysis reveals that the target molecule could be synthesized from two independent fragments **4** and **5** using Yamaguchi coupling reaction followed by Shiine's conditions.

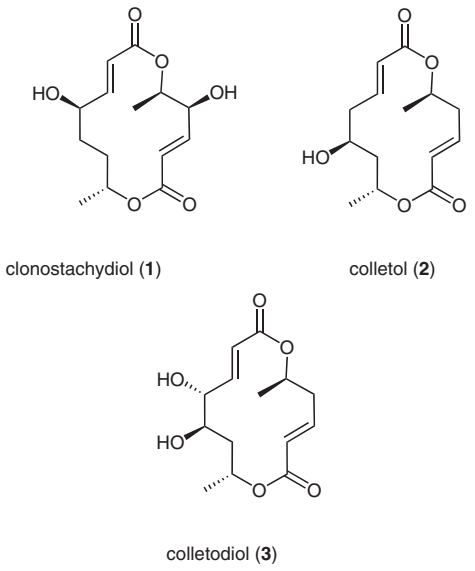
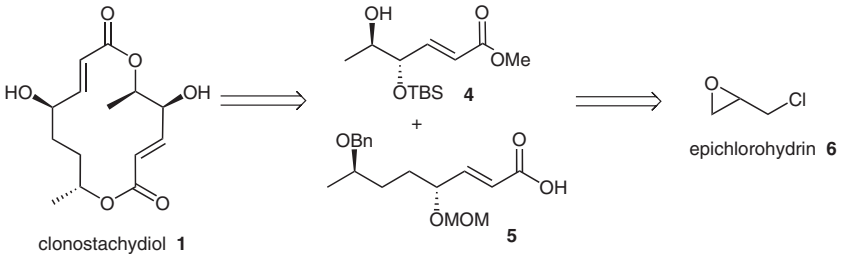


Figure 1

The synthesis of clonostachydiol (**1**) began with (±)-epichlorohydrin (**6**), which was converted into *p*-methoxybenzyl-protected glycidol (±)-**7**[6] by treating with NaH and *p*-methoxybenzyl alcohol in THF at 0 °C in 82% yield. The hydrolytic kinetic resolution[7] of the racemic epoxide (±)-**7** (1 equiv) with 0.55 equivalent of H_2O in the presence of 0.003 mol% of (salen)Co(III)OAc complex {(*S*,*S*)-[*N*,*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diamino]cobalt(III) acetate} gave chiral epoxide **8** in 43% yield with 98% enantiomeric excess and diol **9** in 50% yield with 92% enantiomeric excess (Scheme 2).

The chiral epoxide **8** was converted into secondary alcohol **9** using LAH in THF at room temperature.[8] The secondary alcohol was protected as its benzyl ether **10** using



Scheme 1

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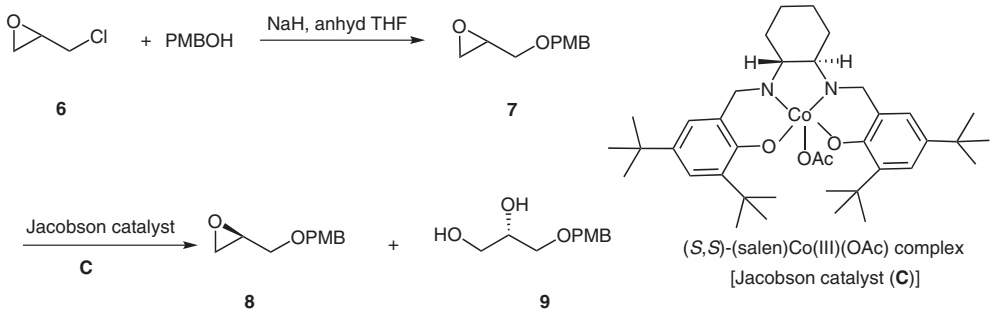
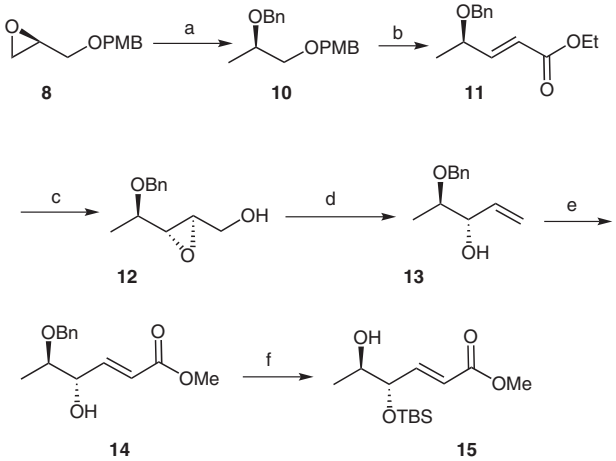


Scheme 2

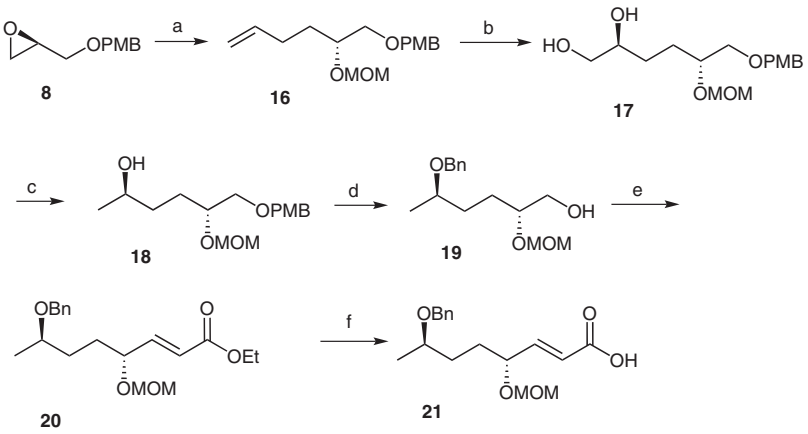
sodium hydride and benzyl bromide in THF. Selective removal of the *p*-methoxybenzyl group from compound **10** using ceric ammonium nitrate in acetonitrile–water (1:1) gave the primary alcohol. Oxidation of alcohol under Swern oxidation[9] conditions afforded the aldehyde, that was subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in benzene at reflux to furnish *E*-α,β-unsaturated ester **11** in 94% yield. The ester **11** was reduced to allylic alcohol[10] using DIBAL-H in THF at –25 °C. Sharpless asymmetric epoxidation afforded the epoxy alcohol **12** in 80% yield[11] and this was converted into the corresponding epoxy iodide by treating with iodine, triphenylphosphine and imidazole in a mixture of diethyl ether and acetonitrile (3:1) at 0 °C. The iodo compound was converted into secondary allylic alcohol **13** by treating with activated zinc and sodium iodide in refluxing methanol[12] and **13** was coupled with methyl acrylate in the presence of 5 mol% of the second-generation Grubbs catalyst in dichloromethane to afford the desired *trans* product **14** in 92% yield.[13] The secondary alcohol **14** was protected as its TBS ether using *tert*-butyldimethylsilyl chloride and imidazole in dichloromethane at 0 °C. Finally, the removal of benzyl group with DDQ in aqueous dichloromethane gave fragment **15** in 85% yield[14] (Scheme 3).

The regioselective ring opening of epoxide **8** with Grignard reagent, derived from magnesium metal and allyl chloride gave a secondary alcohol that was protected with MOMCl and DIPEA in the presence of a catalytic amount of TBAI to afford MOM ether **16** in 92% yield. Sharpless asymmetric dihydroxylation with AD-mix-α gave diol **17** in 88% yield with 89% diastereomeric excess[15] and this was treated with one equivalent of *p*-TsCl and Et_3N in dichloromethane to give the *mono*-tosylate in 89% yield. This was converted into secondary alcohol **18** using LAH in THF and **18** was protected as its benzyl ether with benzyl bromide and sodium hydride in THF. Selective removal of the *p*-methoxybenzyl group using ceric ammonium nitrate in acetonitrile–water (1:1) gave primary alcohol **19**, which was oxidized under Swern oxidation[9] and Wittig olefination of the resulting aldehyde with (ethoxycarbonylmethylene)triphenylphosphorane in refluxing benzene gave olefin **20** with *E* geometry in 91% yield. Hydrolysis of ethyl ester **20** using LiOH in aqueous THF gave the carboxylic acid **21** in 86% yield[16] (Scheme 4).

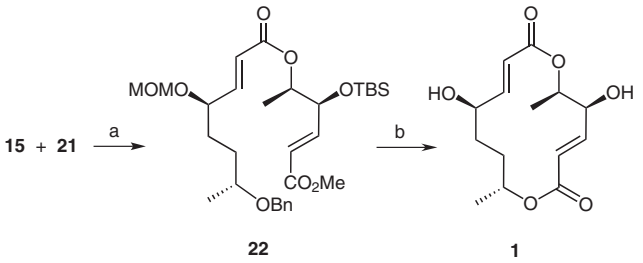
Coupling of fragments **15** and **21** was achieved by the Yamaguchi esterification using 2,4,6-trichlorobenzoyl chloride and triethylamine in dichloromethane at room temperature to furnish **22** in 70% yield.[17] Deprotection of the benzyl ether from compound **22** with DDQ in CH_2Cl_2–H_2O gave the corresponding alcohol in 90% yield and selective hydrolysis of the methyl ester with LiOH in THF–H_2O gave the *seco* acid in 70% yield. This *seco* acid was eventually cyclized via a mixed anhydride formed in situ from 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) to give the 14-membered ring lactone in 60% yield.[18] Removal of the TBS and MOM groups from the bicyclic lactone using concentrated HCl in MeOH gave the target clonostachydiol (**1**)[19] in 85% yield (Scheme 5).



Scheme 3 *Reagents and conditions*: (a) (i) LAH, THF, 85%; (ii) NaH, BnBr, THF, 93%; (b) (i) ceric ammonium nitrate, MeCN–H_2O (9:1), 90%; (ii) $(COCl)_2$, DMSO, Et_3N, –78 °C, 92%; (iii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 94%; (c) (i) DIBAL-H, THF, –40 to 0 °C, 85%; (ii) D-(–)-DET, Ti(O*i*-Pr)$_4$, TBHP (*tert*-butyl hydroperoxide), CH_2Cl_2, –20 °C, 80%; (d) (i) TPP (tetraphenylporphyrin), I_2, imidazole, CH_2Cl_2, 92%; (ii) Zn, NaI, MeOH, 85%; (e) methyl acrylate, Grubbs II catalyst, CH_2Cl_2, 92%; (f) (i) TBDMSCl, imidazole, CH_2Cl_2, 92%; (ii) DDQ, CH_2Cl_2–H_2O (18:2), r.t., 85%.



Scheme 4 *Reagents and conditions*: (a) (i) allyl chloride, Mg, Et_2O, 90%; (ii) MOMCl, DIPEA, CH_2Cl_2, 92%; (b) AD-mix-α, *t*-BuOH–H_2O, 0 °C, 88%; (c) (i) *p*-TsCl, Et_3N, CH_2Cl_2, 92%; (ii) LAH, THF, 85%; (d) (i) NaH, BnBr, THF, 93%; (ii) ceric ammonium nitrate, MeCN–H_2O (9:1), 90%; (e) (i) $(COCl)_2$, DMSO, Et_3N, –78 °C, 92%; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 91%; (f) LiOH, THF–H_2O (3:1), 86%.



Scheme 5 *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, 70%; (b) (i) DDQ, CH_2Cl_2–H_2O (18:2), r.t., 90%; (ii) LiOH, THF–H_2O (3:1), 70%; (iii) 2-methyl-6-nitrobenzoyl anhydride, 4-(*N*,*N*-dimethylamino)pyridine, CH_2Cl_2, 60%; (iv) concd HCl, MeOH, r.t., 85%.

The structure of the clonostachydiol (**1**) was confirmed by comparing its spectroscopic and physical data with the natural product and also with those in a previous synthetic report.[4] These data and specific rotation were in agreement with the data reported.

In summary, we have described a highly stereoselective synthetic route for the synthesis of clonostachydiol (**1**) using readily available (±)-epichlorohydrin (**6**) as a starting material. The synthesis involves a sequence of reactions including Sharpless asymmetric epoxidation, iodination, stereoselective opening of epoxide with allylmagnesium chloride and Sharpless asymmetric dihydroxylation which makes for convenient scale-up. This approach is also useful for the synthesis of other stereoisomers and for the design of analogues.

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(19) **Compound 15**: $[\alpha]_D$ +7.5 (*c* = 1, $CDCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.95 (dd, *J* = 15.8, 4.5 Hz, 1 H), 6.00 (d, *J* = 15.8 Hz, 1 H), 4.25 (dd, *J* = 6.7, 4.5 Hz, 1 H), 3.75–3.85 (m, 1 H), 3.72 (s, 3 H), 1.15 (d, *J* = 6.7 Hz, 3 H), 0.95 (s,

9 H), 0.10 (s, 3 H), 0.06 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.4, 147.4, 121.6, 75.6, 70.2, 51.3, 25.6, 18.0, –4.6. IR (Neat): 3452, 2928, 2885, 1714, 1642, 1412, 1225, 915 cm^{-1}. MS (ESI): *m*/*z* = 297 [M + Na$^+$]. HRMS: *m*/*z* calcd for $C_{13}H_{26}O_4SiNa$: 297.1498; found: 297.1491.

Compound 21: $[\alpha]_D$ +7.5 (*c* = 0.6, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.35 (m, 5 H), 6.90 (dd, *J* = 15.6, 6.2 Hz, 1 H), 5.95 (d, *J* = 15.6 Hz, 1 H), 4.50–4.62 (m, 2 H), 4.45 (d, *J* = 6.6 Hz, 2 H), 4.06–4.15 (m, 1 H), 3.45–3.55 (m, 1 H), 3.35 (s, 3 H), 1.50–1.75 (m, 4 H), 1.20 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.4, 152.2, 130.0, 129.6, 129.4, 123.5, 97.2, 77.0, 76.1, 72.5, 55.0, 34.5, 32.2, 23.6. MS (ESI): *m*/*z* = 309 [M$^+$ + 1], 331 [M$^+$ + Na]. HRMS: *m*/*z* calcd for $C_{17}H_{24}O_5Na$: 331.1521; found: 331.1519.

Compound 1: $[\alpha]_D$ +101 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.85 (dd, *J* = 14.3, 4.3 Hz, 1 H), 6.78 (dd, *J* = 15.1, 6.1 Hz, 1 H), 6.08 (d, *J* = 14.3 Hz, 1 H), 5.95 (d, *J* = 15.1 Hz, 1 H), 4.90–4.98 (m, 1 H), 4.15–4.25 (m, 2 H), 3.85–3.95 (m, 1 H), 1.55–1.68 (m, 4 H), 1.25 (d, *J* = 6.0 Hz, 3 H, Me), 1.25 (d, *J* = 6.0 Hz, 3 H, Me). IR (Neat): 3350, 2984, 2918, 1709, 1643, 1252, 1175 cm^{-1}. LCMS: *m*/*z* = 307 [M$^+$ + Na].