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The contiguous five asymmetric carbon centers in the monomer counterpart 21 were constructed in a highly stereoselective manner by using different epoxide-opening reactions of α,β-unsaturated γ,δ-epoxy esters and epoxy alcohol derivatives as the key steps. The monomer 23 was successfully transformed into the MOM protected diolide 27 by Yamaguchi macro lactonization.

Key words lepranthin; regioselective epoxide-opening reaction; Yamaguchi macro lactonization; dimeric macroide

Macrolide antibiotics have provided us with great opportunities discovering drugs that exhibit a wide range of biological activities. Bacteria, fungi and algae produce a large number of macrolides, which are classified as polyketide macrolides in their biosynthetic pathways. Interestingly, a number of macrolides, which are classified as polyketide macro lactones, are active against a wide range of organisms. Bacteria, fungi and algae have been isolated from lichens, which may represent a symbiotic relationship between fungi and algae.1) Lepranthin (1) was isolated from the crustaceous lichen Arthonia impolita (Ehrh.) Borrer by Zopf in 1904.2) Almost a century later, Huneck and colleagues determined the structure of 1 using NMR techniques and finally X-ray crystallographic analysis, which disclosed the unique 16-membered dimeric macro line structure containing two secondary hydroxyl groups and four secondary acetates.3) In spite of its characteristic macro line structure, biological activity and synthetic studies of 1 have not been reported so far. We thought that a sufficient supply of 1 by total synthesis should advance the study of biological properties and set about synthetic studies. We report herein the stereoselective synthesis of methoxymethyl group (MOM) protected diolide 27, a fully functionalized congener of lepranthin (1), based on regioselective epoxide-ring opening strategies and subsequent Yamaguchi macro lactonization.

Our synthesis started with allyl alcohol 24 which was derived from commercially available methyl (R)-3-hydroxybutylate in four steps. First, 2 was converted to α,β-unsaturated γ,δ-epoxy ester 6 by a four-step reaction sequence: (1) Katsuki–Sharpless epoxidation5 with 1-((+)-diethyl tartrate (DET), Ti(OPr)4, and tert-butyl hydroperoxide (TBHP) in CH2Cl2 at −30 °C, leading to epoxy alcohol 3 (87%); (2) Dess–Martin oxidation6 followed by a Wittig reaction (91% yield); (3) desilylation (97%); (4) protection of the resulting alcohol with a MOM group (95%). Reductive cleavage of the epoxide 6 with HCOOH and tris(dibenzylideneaceto)-dipalladium(o)-chloroform adduct (Pd(dba)2·CHCl3)7 smoothly occurred to give alcohol 7 regioselectively in 91% yield, which was transformed into epoxy alcohol 10 through the sequence of protection of the secondary alcohol with a silyl group, diisobutylaluminum hydride (DIBAH) reduction, and the Katsuki–Sharpless epoxidation. The substitution reaction of 10 with Me2CuCNLi2−∧10 in Et2O furnished a mixture of 11 and its regioisomer in a ratio of ca. 3 : 1, which was treated with NaOEt in aqueous tetrahydrofuran (THF) to afford the pure 1,3-diol 11 in 62% isolated yield. The diol 11 was then converted to α,β-unsaturated ester 14 in three steps: (1) selective oxidation of the primary alcohol to aldehyde with 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) (91%); (2) Horner–Emmons olefination (84%); (3) protection of the secondary alcohol with a MOM group (95%). Reduction of the ester 14 with DIBAH followed by the Katsuki–Sharpless epoxidation produced epoxy alcohol 16 in 91% yield. Upon treatment of 16 with Me2CuCNLi2 in Et2O, the regioselective substitution reaction smoothly occurred to give diol 17 as a single product in 97% yield, which was then converted to benzyl ester 20 by a three-step reaction sequence: (1) TEMPO oxidation11; (2) sodium chlorite oxidation12−13; (3) esterification with benzyl bromide in the presence of Cs2CO3 and TBAI in Me2SO (92%, three steps). The resulting secondary alcohol 20 was protected with a MOM group to provide 21 in 97% yield.

Thus, the contiguous five asymmetric carbon centers in the monomer counterpart 21 were constructed in a highly stereoselective manner by using different epoxide-opening reactions of the γ,δ-epoxy unsaturated ester 6 and two epoxy alcohols 10 and 16. The remaining task for the synthesis of lepranthin (1) is construction of dimeric structure by macro lactonization. For this end, when 21 was treated with DDQ in aqueous THF, the silyl group was successfully removed to give rise to alcohol 22 in 91% yield.19 On the other hand, hydrogenolysis of 21 over a Pd/C catalyst in AcOEt provided carboxylic acid 23, which was immediately subjected to esterification with 22 using the Yamaguchi reagent17 in the presence of N,N-diisopropylethylamine (DPEA) and 4-(dimethylamino)pyridine (DMAP) leading to dimeric ester 24(18) (78%). The diester 24 was transformed into seco-acid 26 via the same reaction sequence for 21, that is, removal of the silyl group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by removal of the benzyl ester under catalytic hydrogenation. Finally, the seco-acid 26 was transformed into the targeted diolide 27(19) by macro lactonization17 with 2,4,6-trichlorobenzoyl chloride in the presence of DPEA and DMAP in 52% yield.
Reagents and Conditions: (a) L-(+)-DET, Ti(OiPr)4, TBHP, CH2Cl2, 30 °C; (b) Dess–Martin periodinane, CH2Cl2, then Ph3P, CH2CO2Me; (c) tert-butylammonium fluoride (TBAF), THF; (d) MOMCl, DIPEA, CH2Cl2; (e) Pd2(dba)3· CHCl3, HCOOH, Et3N, Bu3P; (f) tert-butyldimethylsilyl chloride (TBSCl), imidazole, DMF; (g) DIBAH, THF, 25 °C; (h) L-(+)-dissopropyl tartrate (DIPT), Ti(OiPr)4, TBHP, CH2Cl2, 40 °C; (i) MeLi, CuCN, Et2O, then NaIO4, THF, 55 °C; (j) TEMPO, NaOCl, tetrabutylammonium bromide (TBAB), CH2Cl2, NaHCO3 aq., 0 °C; (k) (MeO)2P(O)CH2CO2Me, NaH, THF, 0 °C; (l) MOMCl, DIPEA, tetrabutylammonium iodide (TBAI), (CH2Cl)2, 50 °C; (m) DIBAH, THF, −30 °C; (n) L-(+)-DIPT, Ti(OiPr)4, TBHP, CH2Cl2, −40 °C; (o) MeLi, CuCN, Et2O, −50 to −10 °C, then NaIO4, THF, H2O; (p) TEMPO, NaOCl, TBAB, CH2Cl2, NaHCO3 aq., 0 °C; (q) NaClO2, NaH2PO4·2H2O, 2-methyl-2-butene, THF, H2O, 0 °C; (r) benzyl bromide (BnBr), C6H5CO2H, TBAI, DMF; (s) MOMCl, DIPEA, TBAI, (CH2Cl)2, 50 °C.

Reagents and Conditions: (a) DDQ, THF, H2O, 60 °C; (b) Pd/C, H2, AcOEt; (c) 22, 2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, THF; (d) 2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, THF.
Next, we carried out preliminary experiments for removal of the MOM groups in 27. However, surprisingly, treatment of 27 with a catalytic amount of TsOH·H2O in BuOH/H2O at 80 °C or HCl in THF at 0 °C produced a mixture of two fragment lactones 28 and 29. On the other hand, upon treatment of 27 with CF3SO3H in CH2Cl2 at −20 °C, symmetric 16-membered diolide 30 containing two dioxane rings was formed.

In summary, we succeeded in the stereoselective synthesis of the diolide congener 27 of lepranthon (1) based on regio- and stereospecific epoxide-opening reactions. Namely, reductive cleavage of the epoxide and stereospecific epoxide-opening reactions. Crucial intermediate successfully performed using the Yamaguchi reagent. Further centers at the C2—C5 positions were constructed by the ter. On the other hand, four contiguous asymmetric carbon centers at the C2—C5 positions were constructed by the epoxide-opening reactions with the Lipshutz reagent (10→11 and/or 16→17). The subsequent key macro lactonization was successfully performed using the Yamaguchi reagent. Further studies toward the total synthesis of lepranthon (1) from the crucial intermediate 27 is now in progress in our laboratory.

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References and Notes
16) For data of [α]D25 −25.11 (c=1.02, CHCl3); HR-ESI-MS m/z 1001.5831 (Calcd for C36H68O16Na: 1001.5845); IR (ATR) 1731 cm−1.
17) For data of [α]D25 −25.11 (c=1.02, CHCl3); HR-ESI-MS m/z 354.11 (c=1.02, CHCl3); HR-ESI-MS c/z 25.11 (c=1.02, CHCl3); HR-ESI-MS c/z 25.11 (c=1.02, CHCl3); IR (ATR) 1728 cm−1.
19) For data of [α]D25 −25.11 (c=1.02, CHCl3); HR-ESI-MS m/z 1001.5831 (Calcd for C36H68O16Na: 1001.5845); IR (ATR) 1731 cm−1.