Synthetic Studies of the Lichen Macrolide Lepranthin. Stereoselective Synthesis of the Diolide Framework Based on Regioselective Epoxide-Opening Reactions

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Received December 9, 2010; accepted January 14, 2011; published online January 24, 2011

Stereoselective synthesis of the 16-membered diolide 27, a fully functionalized congener of lepranthin (1), is described. The requisite five asymmetric carbon centers in monomer 23 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 macrolactonization.

Key words lepranthin; regioselective epoxide-opening reaction; Yamaguchi macrolactonization; dimeric macrolide

Macrolide antibiotics have provided us with good 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 few polyketide macrolides 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 macrolide structure containing two secondary hydroxyl groups and four secondary acetates.[3] In spite of its characteristic macrolide 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 macrolactonization.

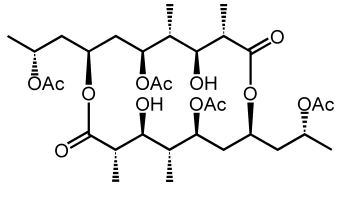

Fig 1. Lepranthin (**1**)

Our synthesis started with allyl alcohol **2**[4] 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 epoxidation[5] with L-(+)-diethyl tartrate (DET), $Ti(O^iPr)_4$, and *tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2 at $-30\,^\circ C$, leading to epoxy alcohol **3** (87%); (2) Dess–Martin oxidation[6] 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(dibenzylideneacetone)-dipalladium(*o*)-chloroform adduct ($Pd_2(dba)_3 \cdot CHCl_3$)[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 $Me_2CuCNLi_2$[8—10] in Et_2O furnished a mixture of **11** and its regioisomer in a ratio of *ca.* 3 : 1, which was treated with $NaIO_4$ 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%)[11]; (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 $Me_2CuCNLi_2$[8] in Et_2O, 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 oxidation[11]; (2) sodium chlorite oxidation[12—15]; (3) esterification with benzyl bromide in the presence of Cs_2CO_3 and TBAI in *N*,*N*-dimethylformamide (DMF) (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 macrolactonization. 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.[16] 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 reagent[17] in the presence of *N*,*N*-diisopropylethylamine (DIPEA) 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 macrolactonization[17] with 2,4,6-trichlorobenzoyl chloride in the presence of DIPEA and DMAP in 52% yield.

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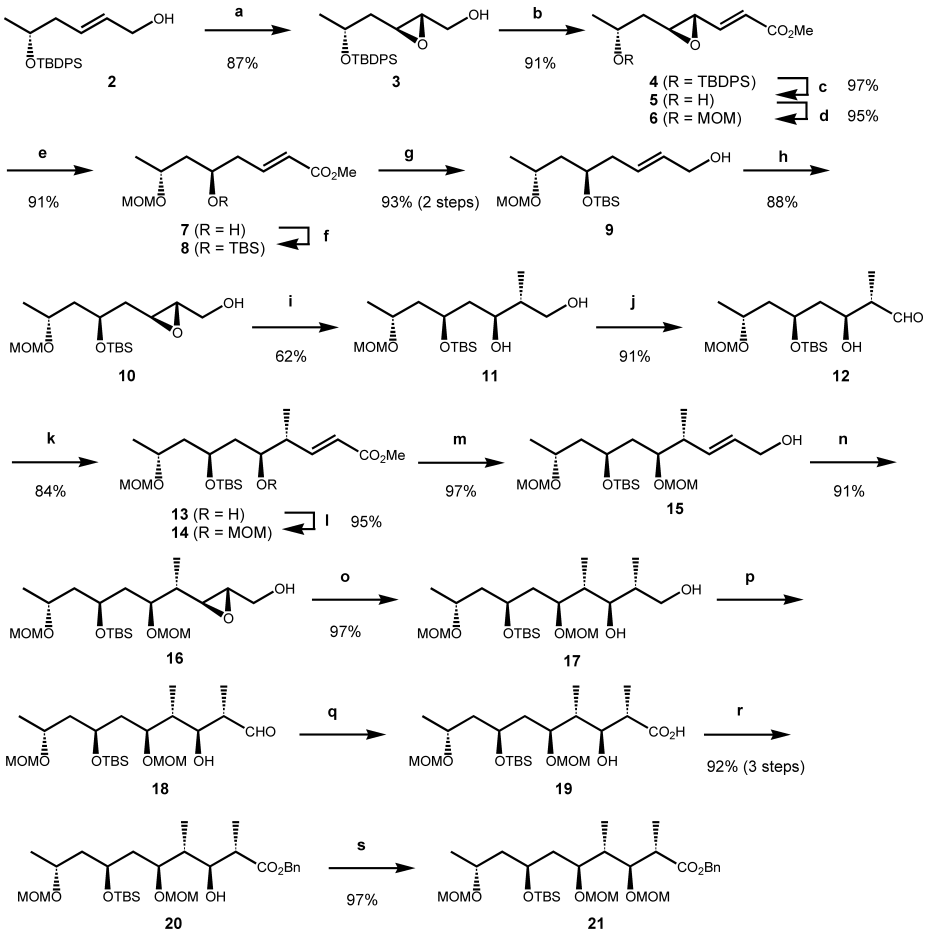
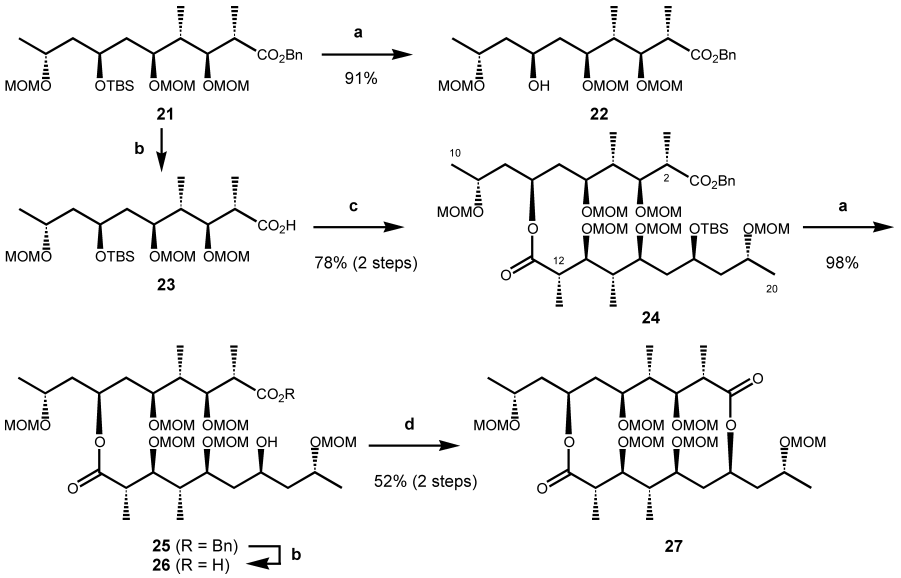


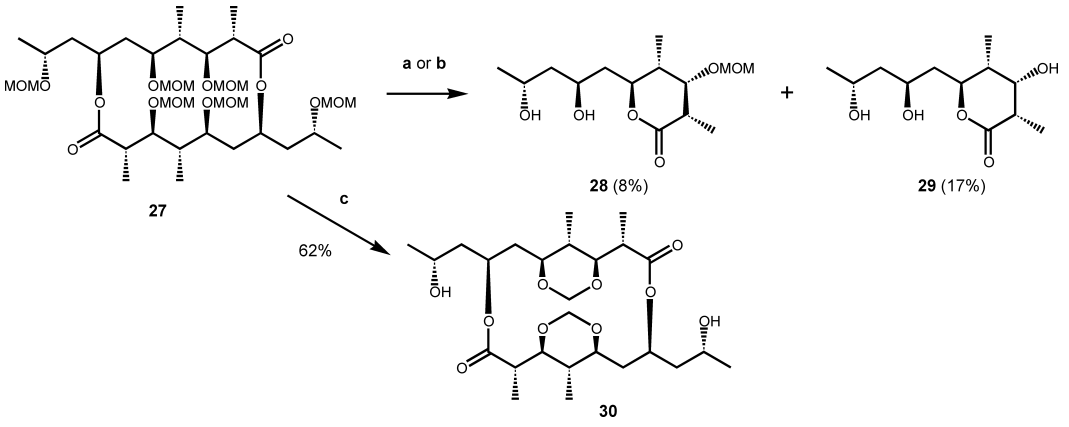
Reagents and Conditions: (a) L-(+)-DET, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −30 °C; (b) Dess–Martin periodinane, CH_2Cl_2, then $Ph_3P{=}CHCO_2Me$; (c) *tert*-*n*-butylammonium fluoride (TBAF), THF; (d) MOMCl, DIPEA, CH_2Cl_2; (e) $Pd_2(dba)_3 \cdot CHCl_3$, HCOOH, Et_3N, Bu_3P; (f) *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, DMF; (g) DIBAH, THF, −25 °C; (h) L-(+)-diisopropyl tartrate (DIPT), $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −40 °C; (i) MeLi, CuCN, Et_2O, −55 °C, then $NaIO_4$, THF, H_2O; (j) TEMPO, NaOCl, tetra-*n*-butylammonium bromide (TBAB), CH_2Cl_2, $NaHCO_3$ aq., 0 °C; (k) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C; (l) MOMCl, DIPEA, tetra-*n*-butylammonium iodide (TBAI), $(CH_2Cl)_2$, 50 °C; (m) DIBAH, THF, −30 °C, (n) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −40 °C; (o) MeLi, CuCN, Et_2O, −50 to −10 °C, then $NaIO_4$, THF, H_2O; (p) TEMPO, NaOCl, TBAB, CH_2Cl_2, $NaHCO_3$ aq., 0 °C; (q) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, THF, H_2O, 0 °C; (r) benzyl bromide (BnBr), Cs_2CO_3, TBAI, DMF; (s) MOMCl, DIPEA, TBAI, $(CH_2Cl)_2$, 50 °C.

Chart 1



Reagents and Conditions: (a) DDQ, THF, H_2O, 60 °C; (b) Pd/C, H_2, AcOEt; (c) **22**, 2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, THF; (d) 2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, THF, benzene.

Chart 2



Reagents and Conditions: (a) $TsOH \cdot H_2O$, ^tBuOH, H_2O, 80 °C; (b) HCl, THF, 0 °C; (c) CF_3SO_3H, CH_2Cl_2, −20 °C.

Chart 3

Next, we carried out preliminary experiments for removal of the MOM groups in **27**. However, surprisingly, treatment of **27** with a catalytic amount of $TsOH \cdot H_2O$ in $^tBuOH/H_2O$ 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 CF_3SO_3H in CH_2Cl_2 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 lepranthin (**1**) based on regio- and stereospecific epoxide-opening reactions. Namely, reductive cleavage of the epoxide **6** with HCOOH and $Pd_2(dba)_3 \cdot CHCl_3$ was used for construction of the C7 asymmetric center. 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 macrolactonization was successfully performed using the Yamaguchi reagent. Further studies toward the total synthesis of lepranthin (**1**) from the crucial intermediate **27** is now in progress in our laboratory.

Acknowledgement Financial support from the Ministry of Education, Culture, Sports, Science and Technology, Japan (a Grant-in-Aid for Scientific Research (B) (No. 19350027) and Advanced Promotion Research Program for Education of Graduate School) is gratefully acknowledged.

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18) For data of **24**: $[\alpha]_D^{27}$ −25.11 (c=1.02, $CHCl_3$); HR-ESI-MS m/z 1001.5831 (Calcd for $C_{49}H_{90}O_{17}Na$: 1001.5845); IR (ATR) 1731 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36—7.29 (5H, m), 5.25—5.19 (1H, br m), 5.12 (2H, s), 4.66—4.54 (12H, m), 4.04 (1H, tt, J=9.6, 2.8 Hz), 3.86—3.81 (1H, m), 3.80—3.74 (2H, br m), 3.73—3.65 (3H, m), 3.38 (6H, s), 3.36 (3H, s), 3.35 (3H, s), 3.34 (3H, s), 3.32 (3H, s), 2.96 (1H, qd, J=6.8, 6.0 Hz), 2.87 (1H, qd, J=7.2, 5.6 Hz), 2.17—2.11 (2H, m), 1.94—1.53 (7H, m), 1.41—1.33 (1H, m), 1.22—1.18 (12H, m), 0.89 (3H, d, J=7.2 Hz), 0.89 (9H, s), 0.83 (3H, d, J=7.2 Hz), 0.09 (3H, s), 0.07 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 174.03 (C), 173.66 (C), 135.88 (C), 128.46 (2C, CH), 128.22 (2C, CH), 128.14 (CH), 98.35 (CH_2), 98.13 (CH_2), 98.87 (CH_2), 95.81 (CH_2), 95.73 (CH_2), 95.51 (CH_2), 83.44 (CH), 83.34 (CH), 74.97 (CH), 74.92 (CH), 71.69 (CH), 70.15 (CH), 69.72 (CH), 67.15 (CH), 66.21 (CH_2), 56.04 (2C, CH_3), 55.88 (CH_3), 55.74 (CH_3), 55.40 (CH_3), 55.22 (CH_3), 45.04 (CH_2), 43.07 (2C, CH), 41.65 (CH_2), 38.86 (CH_2), 38.01 (CH), 37.98 (CH), 35.52 (CH_2), 25.92 (3C, CH_3), 21.83 (CH_3), 21.20 (CH_3), 17.99 (C), 12.27 (2C, CH_3), 10.94 (CH_3), 10.74 (CH_3), −3.80 (CH_3), −4.62 (CH_3).
19) For data of **27**: $[\alpha]_D^{30}$ −40.87 (c=1.01, $CHCl_3$); HR-ESI-MS m/z 779.4412 (Calcd for $C_{36}H_{68}O_{16}Na$: 779.4405); IR (ATR) 1728 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.21 (2H, m), 4.70—4.53 (12H, m), 3.79 (2H, br d, J=5.6 Hz), 3.75—3.66 (4H, m), 3.40 (6H, s), 3.35 (6H, s), 3.32 (6H, s), 2.84 (2H, quintet, J=6.7 Hz), 2.15 (2H, m), 1.96—1.75 (4H, m), 1.75—1.57 (4H, m), 1.21 (6H, d, J=6.4 Hz), 1.20 (6H, d, J=6.4 Hz), 0.86 (6H, d, J=6.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 173.77 (C), 98.23 (CH_2), 95.76 (CH_2), 95.47 (CH_2), 82.98 (CH), 74.42 (CH), 70.13 (CH), 70.03 (CH), 56.09 (CH_3), 55.92 (CH_3), 55.46 (CH_3), 43.11 (CH), 41.37 (CH_2), 37.58 (CH), 35.06 (CH_2), 21.21 (CH_3), 12.11 (CH_3), 10.67 (CH_3).