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SYNTHETIC STUDIES OF LEPRANTHIN, A LICHEN-PRODUCED DIMERIC MACROLIDE. STEREOSELECTIVE SYNTHESIS OF A SECO-ACID BASED ON STEREOSPECIFIC EPOXIDE-OPENING REACTIONS

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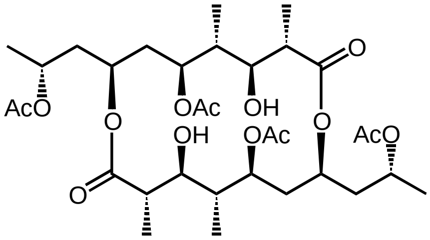
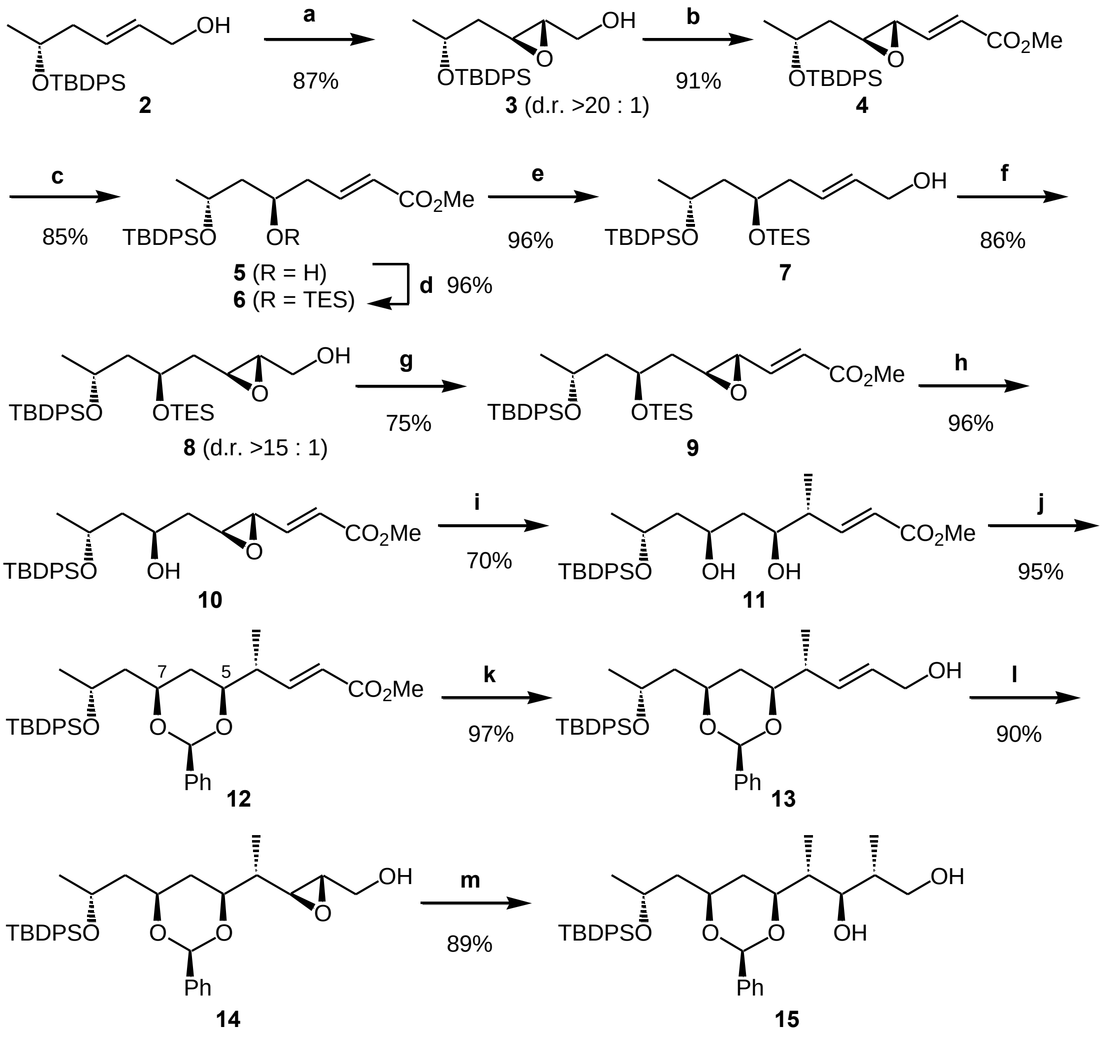
Abstract – The stereoselective synthesis of a seco-acid derivative of lepranthin (**1**), a lichen-produced unique 16-membered dimeric macrolide, is described wherein all asymmetric carbon centers were constructed in a highly stereoselective manner, respectively, by using different epoxide-opening reactions of the α,β-unsaturated γ,δ-epoxy ester system and an epoxy alcohol derivative as the key steps.



lepranthin (**1**)

Figure 1

Bacteria, fungi and algae produce a large number of macrolides which are classified as polyketide-derived macrolides in their biosynthetic pathways. These compounds often provided us with good opportunities discovering new drugs. Interestingly, a few macrolides have been isolated from lichens too, which may imply 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] Nearly century later, a NMR investigation and X-ray analysis by Huneck *et al*. revealed **1** to be a 16-membered homo-macrodiolide which contains two secondary hydroxyl groups and four secondary acetates.[3] Although biological properties and synthetic studies of **1** have not been reported so far, its unique diolide structure would attract attention of synthetic chemists. We report herein the stereoselective synthesis of a seco-acid derivative **28**, the key monomer segment of **1**, based on stereospecific epoxide-ring opening strategies.

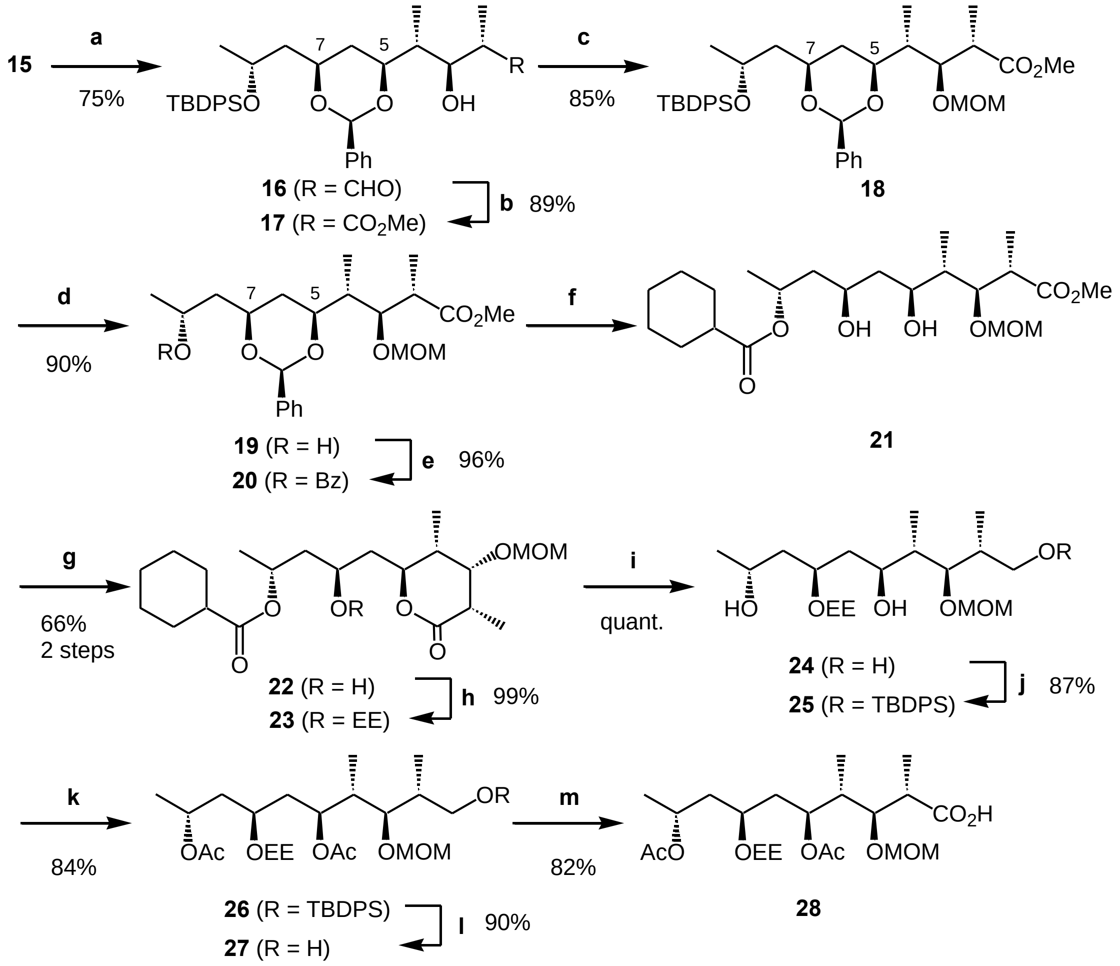


Scheme 1. (a) L-(+)-DET, Ti(O^{i}Pr)$_4$, TBHP, CH_2Cl_2, -30 °C; (b) Dess-Martin periodinane, CH_2Cl_2, then $Ph_3P{=}CHCO_2Me$; (c) $Pd_2(dba)_3 \cdot CHCl_3$, HCO_2H, Et_3N, Ph_3P; (d) TESCl, imidazole, CH_2Cl_2; (e) DIBAH, THF, 0 °C; (f) L-(+)-DET, Ti(O^{i}Pr)$_4$, TBHP, CH_2Cl_2, -30 °C; (g) Dess-Martin periodinane, CH_2Cl_2, then $Ph_3P{=}CHCO_2Me$; (h) DDQ, THF, H_2O; (i) Me_3Al, H_2O, CH_2Cl_2, -50 °C; (j) PhCHO, $TsOH \cdot H_2O$, benzene, reflux; (k) DIBAH, THF, 0 °C; (l) L-(+)-DET, Ti(O^{i}Pr)$_4$, TBHP, CH_2Cl_2, -30 °C; (m) CuCN, MeLi, Et_2O, -50 to -30 °C.

Our synthesis started with allyl alcohol **2** which was prepared from commercially available methyl (*R*)-3-hydroxybutylate in five steps.[4] First, **2** was converted to α,β-unsaturated γ,δ-epoxy ester **4** by a two-step reaction sequence: (1) Katsuki-Sharpless epoxidation[5] with L-(+)-DET, Ti(O^{i}Pr)$_4$, and TBHP in

CH_2Cl_2 at -30 °C, leading to epoxy alcohol **3**[6] (87%); (2) Dess-Martin oxidation[7] followed by Wittig olefination (91% yield). Reductive cleavage of the epoxide **4** with HCO_2H and $Pd_2(dba)_3 \cdot CHCl_3$[8] smoothly occurred to give alcohol **5** in 85% yield, which was then transformed into allyl alcohol **7** through the sequence of protection of the secondary alcohol with a silyl group and subsequent DIBAH reduction. The allyl alcohol **7** thus obtained was again transformed into α,β-unsaturated γ,δ-epoxy ester **9** by the same reaction sequence as that for **2**: (1) Katsuki-Sharpless epoxidation leading to **8**[6] (86%); (2) Dess-Martin oxidation; (3) a Wittig olefination (75%, two steps). After removal of the TES group in **9** with DDQ,[9] treatment of the resulting epoxy alcohol **10** with Me_3Al-H_2O in CH_2Cl_2 at -50 °C afforded the desired product **11** in 70% yield.[10] Protection of *syn*-1,3-diol **11** with a benzylidene acetal group furnished **12**[11] in high yield, which was further converted to epoxy alcohol **14**[12] in two steps: (1) reduction with DIBAH in THF (97%); (2) Katsuki-Sharpless epoxidation with L-(+)-DET, $Ti(O^iPr)_4$, and TBHP in CH_2Cl_2 at -30 °C (90%). Upon treatment of **14** with $Me_2CuCNLi_2$[13] in Et_2O at -50 to -30 °C, the regioselective methyl substitution reaction smoothly occurred to give **15** as a single product in 89% yield. Thus, the requisite five stereogenic centers in the targeted molecule were stereoselectively constructed by using different epoxide-opening reactions of the two γ,δ-epoxy unsaturated esters, **4** and **10**, and the epoxy alcohol **14**.

The remaining task for the synthesis of a seco-acid was discrimination of the five hydroxyl groups in **15**. To this end, sequential oxidations of **15** with TEMPO[14] and then with $NaClO_2$[15] followed by esterification with CH_2N_2 produced ester **17** in 67% overall yield. Next, the hydroxyl group in **17** was protected with a MOM group by treatment with MOMCl, DIPEA, and NaI in 1,2-DME, giving rise to **18** in 85% yield. Among discrimination of the five hydroxyl groups, the most difficult task was that between C5 and C7 hydroxyl groups protected by benzylidene acetal. All attempts aiming at a regioselective reductive cleavage of the benzylidene acetal moiety in **18** failed unfortunately. Eventually, distinction between these hydroxyl groups was performed as follows. Removal of the silyl group in **18** with TBAF/AcOH in DMF (90%) followed by treatment of the resulting alcohol with BzCl and pyridine in CH_2Cl_2 furnished **20** (96%), which was converted to diol **21** by catalytic hydrogenolysis with PtO_2 in EtOH. Unexpectedly, the benzene ring in **20** was smoothly hydrogenated concomitantly to produce **21**. Further treatment of **21** with PPTS[16] in refluxing 1,2-dichloroethane in the presence of pyridine resulted in facile lactonization to give lactone **22**, whose hydroxyl group was then protected with ethyl vinyl ether and PPTS[16] in CH_2Cl_2 to afford ethoxyethyl ether **23** quantitatively. Unfortunately, however, subsequent hydrolysis of **23** under alkaline conditions underwent elimination of the MOM group to give unsaturated lactone exclusively. To overcome this difficulty, the lactone **23** was reduced with $LiAlH_4$ in THF and subsequent regioselective protection of the primary alcohol with a TBDPS group produced diol **25** (87%). After protection of the diol with acetyl groups (84%), removal of the TBDPS group with TBAF in THF gave the primary alcohol (90%), which was successfully converted to seco-acid **28**[17] for the total synthesis of lepranthin (**1**), in two steps: (1) TEMPO oxidation; (2) sodium chlorite oxidation (82%).



Scheme 2. (a) TEMPO, $PhI(OAc)_2$, CH_2Cl_2; (b) (1) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, THF, ^{t}BuOH, H_2O, (2) CH_2N_2, Et_2O, 0 °C; (c) MOMCl, DIPEA, NaI, 1,2-DME, reflux; (d) TBAF, AcOH, DMF; (e) BzCl, pyridine, CH_2Cl_2; (f) PtO_2, H_2, EtOH; (g) PPTS, pyridine, $(CH_2Cl)_2$, reflux; (h) Ethyl vinyl ether, PPTS, CH_2Cl_2; (i) $LiAlH_4$, THF; (j) TBDPSCl, imidazole, CH_2Cl_2, -25 °C; (k) AcCl, pyridine, CH_2Cl_2; (l) TBAF, THF; (m) (1) TEMPO, TBAB, NaOCl, CH_2Cl_2, $NaHCO_3$ aq., 0 °C, (2) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4 \cdot 2H_2O$, THF, H_2O.

In summary, we completed the asymmetric synthesis of the seco-acid **28**, the key monomer of lepranthin (**1**), based on stereospecific epoxide-opening reactions including the stereospecific methylation reaction of the γ,δ-epoxy unsaturated ester **10** with Me_3Al-H_2O system. Further studies of the crucial macrolactonization of the seco-acid **28** toward total synthesis of lepranthin (**1**) are now in progress in our laboratory.

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11. Benzyl proton peak in ^{1}H NMR spectrum of compound **12** showed the NOE correlations with peaks at the C5 and C7 positions (each ca. 10%).
12. The peaks for a diastereomer were not observed in the ^{1}H NMR spectrum of compound **14**.
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17. Seco-acid **28** was obtained as a diastereomeric mixture (ca. 0.55 : 0.45) concerning the ethoxyethyl group. $[\alpha]_D^{27}$ -19.21 (c 1.38, $CHCl_3$); FAB-MS (POSI) m/z 465 (MH^+), 433, 386; HR-FABMS m/z 465.2722 (calcd for $C_{22}H_{41}O_{10}$: 465.2700); IR (ATR) 2978, 1732, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16-5.11 (1H, m), 5.09-5.00 (1H, m), 4.72 (1H×0.55, q, J = 5.6 Hz), 4.69-4.65 (2H, m), 4.60 (1H×0.45, q, J = 5.2 Hz), 3.70-3.43 (5H, m), 3.39 (3H, s), 2.98-2.90 (1H, m), 2.15-1.98 (2H, m), 2.06 (3H×0.55, s), 2.05 (3H×0.45, s), 2.02 (3H×0.45, s), 2.01 (3H×0.55, s), 1.95-1.73 (3H,

m), 1.60-1.49 (1H, m), 1.284 (3H×0.45, d, J = 5.2 Hz), 1.283 (3H×0.55, d, J = 5.6 Hz), 1.26-1.22 (6 H, m), 1.21 (3H×0.45, t, J = 6.8 Hz), 1.16 (3H×0.55, t, J = 7.2 Hz), 0.97 (3H×0.55, d, J = 7.6 Hz), 0.96 (3H×0.45, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.39 (C), 179.14 (C), 170.69 (C), 170.67 (C), 170.22 (C), 170.19 (C), 101.23 (CH), 98.26 (CH_2), 98.23 (CH_2), 97.55 (CH), 83.25 (CH), 83.10 (CH), 72.25 (CH), 71.27 (CH), 71.07 (CH), 68.84 (CH), 68.32 (CH), 67.84 (CH), 60.49 (CH_2), 60.07 (CH_2), 56.28 (CH_3), 56.26 (CH_3), 43.05 (CH), 43.01 (CH), 41.33 (CH_2), 41.05 (CH_2), 38.51 (CH for both isomers), 35.83 (CH_2), 34.42 (CH_2), 21.27 (CH_3), 21.25 (CH_3), 21.13 (CH_3), 21.10 (CH_3), 20.75 (CH_3), 20.63 (CH_3), 20.36 (CH_3), 20.34 (CH_3), 15.27 (CH_3), 15.25 (CH_3), 12.83 (CH_3), 12.77 (CH_3), 11.36 (CH_3), 11.22 (CH_3).