The First Total Synthesis of a Macrocyclic Anti-protozoan, LL-Z1640-2

Kuniaki Tatsuta,* Satoko Takano, Toshimitsu Sato, and Satoshi Nakano
Department of Applied Chemistry, School of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555

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Anti-protozoan, LL-Z1640-2 has been stereoselectively synthesized from D-ribose through Sonogashira coupling, Tsuji hydrogenolysis, and Mukaiyama lactonization.

A macrocyclic nonaketide, LL-Z1640-2 (**1**) was isolated as an anti-protozoan from fungi, and the structure was determined by X-ray studies to be a zearalenone-like macrocyclic compound (Figure 1).[1] Recently, LL-Z1640-2 (**1**) was also found to inhibit the JNK/p38 pathways in signal-specific manner.[2]

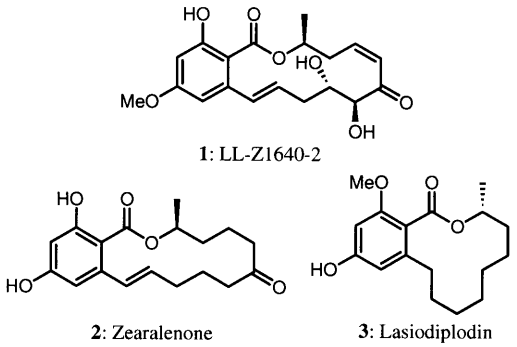


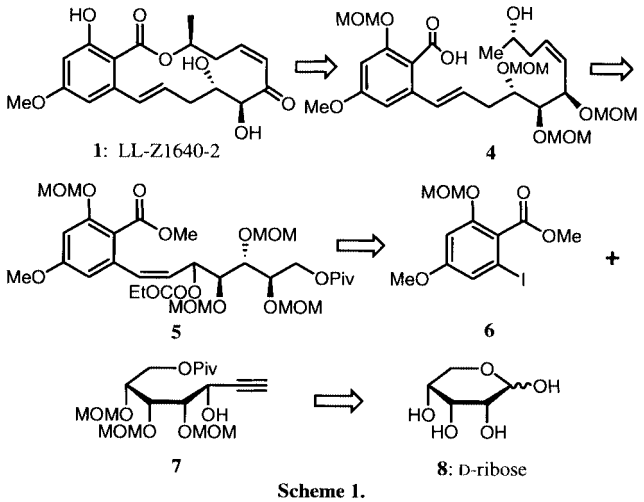
Figure 1.

It is well-known that the synthesis of simple zearalenone analogs such as **2** and **3** is effected by various methodologies, for example: 1) Wittig reaction with poly-substituted benzaldehydes; 2) Dieckmann or aldol-type reaction;[3] 3) reaction of phenylsulfonyl- or thiomethylbenzenes with alkyl iodides;[4] 4) reaction of trialkylstannyl olefins with iodobenzenes;[5,6] 5) ring-forming olefin methathesis.[7] However, the more complex and labile structure **1** can limit the scope of the above-mentioned methods. The total synthesis of LL-Z1640-2 (**1**) has not been accomplished by these earlier routes.

Herein, we describe the first total synthesis of LL-Z1640-2 (**1**) from a carbohydrate by a straightforward strategy.

Retrosynthetically, we envisioned the Mukaiyama cyclization[8] of the hydroxy acid **4** to be a means potentially well suited to the assembly of the lactone **1** (Scheme 1). Access to this advanced intermediate was to be gained by Tsuji hydrogenolysis[9] of **5** followed by reaction with the optically active epoxide **15**. The key compound **5** would be prepared through Sonogashira coupling[10] of **6** with **7**, the latter of which could be derived from D-ribose (**8**).

D-Ribose (**8**) was converted into the properly protected ribopyranose **9** in 3 steps (Scheme 2). Reaction of **9** with the lithiated acetylide was followed by selective pivaloylation to



Scheme 1.

give **10**[11] as a single product with a trace of its diastereomer. Without determination of the configuration, **10** was used for the following reactions, because the hydroxy group would be removed in a later step (**5**→**13**). After removal of the TMS group, the resulting **7** was coupled with the iodobenzene **6**, which was prepared according to Hegedus' procedures,[5] in the presence of $Pd(OAc)_2$, CuI and Ph_3P to afford **11**.[12] This was protected to the ethoxycarbonate **12** which, upon reduction with Lindlar catalyst, gave the *Z*-olefin **5**. Hydrogenolysis of **5** proceeded smoothly under Tsuji's conditions[9] to give the desired *E*-olefin **13**. After de-*O*-acylation of **13**, the produced primary alcohol was oxidized to the aldehyde, which was treated with CBr_4 and Ph_3P to give the dibromo-olefin **14**. Exposure of **14** with *n*-BuLi produced the intermediary lithiated acetylide, which reacted with the optically active (*S*)-propylene oxide **15** to afford the alcohol **16**. This was also hydrogenated over Lindlar catalyst to the *Z*-olefin **17**. Saponification of **17** to the hydroxy acid **4** was followed by cyclization under Mukaiyama conditions[8] to afford the lactone **18**. After removal of all *O*-MOM groups, oxidation of the resulting allyl alcohol was examined under various conditions. Only Dess–Martin reagent and DDQ effected selective oxidation of the allyl alcohol to give the α,β-unsaturated ketone **1** in 62% and 20% yields, respectively. This ketone was identical in all respects with the natural product **1**,[13] completing the total synthesis.

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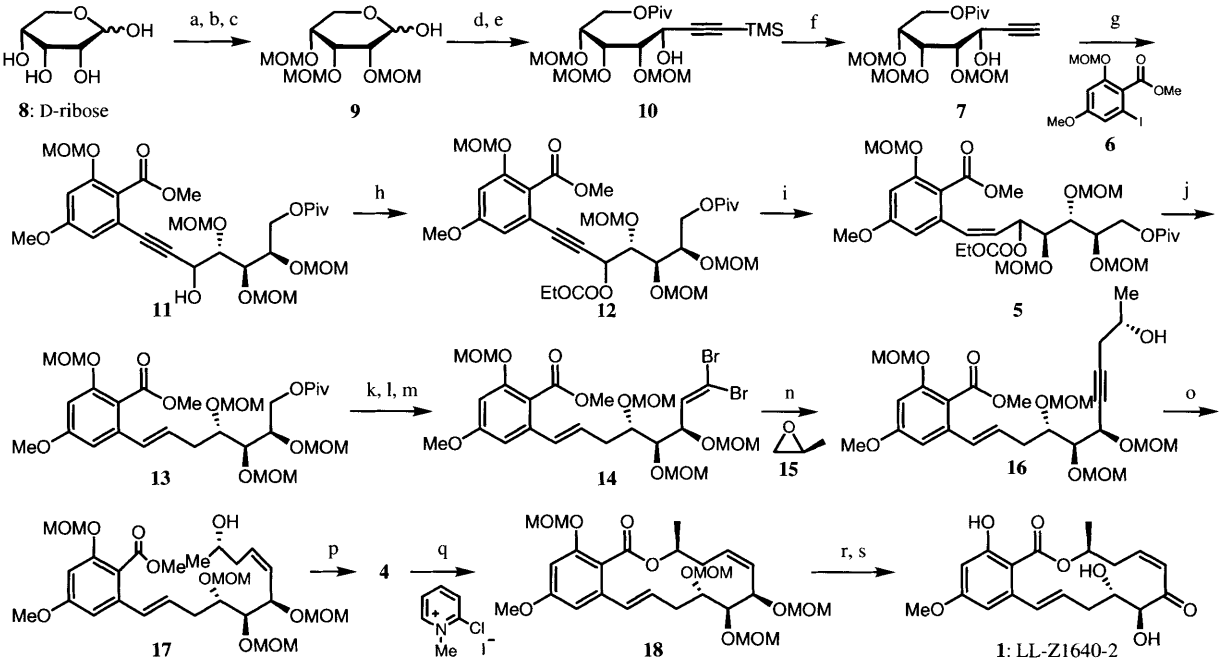

Scheme 2. a) CSA/BnOH, 80 °C, 89%. b) MOMCl, *i*-Pr_2NEt/MeCN, 50 °C, 4 h, 85%. c) H_2, $Pd(OH)_2$/EtOH, 3 h, quant. d) TMS-acetylene, *n*-BuLi, BF_3•Et_2O/THF, -78 °C– rt. e) PivCl/Py, 0 °C, 1 h, 2 steps 48%. f) TBAF, AcOH/THF, 2 h, quant. g) $Pd(OAc)_2$, CuI, Ph_3P/Et_3N, 2 h, 85%. h) $ClCO_2Et$/Py, 0 °C, 1 h, 98%. i) H_2, Pd/$BaCO_3$, quinoline/EtOH, 30 min. j) $Pd_2(dba)_3CHCl_3$, *n*-Bu_3P, $HCOONH_4$/1,4-dioxane, 95 °C, 1 h, 2 steps 96%. k) NaOMe/MeOH, 50 °C, 3 h, 95%. l) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2 , -78 °C– rt. m) Ph_3P, CBr_4/CH_2Cl_2, 0 °C, 15 min, 2 steps 85%. n) *n*-BuLi, BF_3•Et_2O/THF, -78 °C - rt, 45%. o) H_2, Pd/$BaCO_3$, quinoline/AcOEt, 30 min. p) 2M NaOH/MeOH–1,4-dioxane, 90 °C. q) Et_3N/MeCN, 50 °C, 1 h, 3 steps 47%. r) 5%HCl-MeOH, 50 °C, 2 h, 76%. s) Dess–Martin periodinane/CH_2Cl_2, 15 min, 62%.

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11 Selected data for key compounds: Optical rotations (22 °C) and ^{1}H NMR spectra (*J* in Hz; 400 and 500 MHz) were measured in MeOH and $CDCl_3$. **1**: mp 166–168 °C; $[\alpha]_D$ –73° (*c* 0.33, MeOH) [lit.,[1] mp 172 °C; $[\alpha]_D$ –75° (MeOH)]; ^{1}H NMR δ 1.47 (3H, d, *J* = 6.0), 2.14 (1H, ddd, *J* = 16.0, 10.5, and 3.0), 2.21 (1H, m) 2.42 (1H, br d, *J* = 9.0), 2.51 (1H, dddd, *J*=17.0, 3.0, 2.0, and 2.0), 3.58 (1H, ddd, *J* = 17.0, 12.0, and 12.0), 3.75 (1H, d, *J* = 5.5), 3.81 (3H, s), 3.99 (1H, br s), 4.51 (1H, m), 5.25 (1H, ddq, *J* = 12.0, 6.0, and 2.0), 5.99 (1H, ddd, *J* = 16.0, 10.5, and 4.0), 6.21 (1H, ddd, *J* = 12.0, 12.0, and 2.0), 6.33 (1H, dd, *J* = 12.0 and 3.0), 6.38 (1H, d, *J* = 3.0), 6.40 (1H, d, *J* = 3.0), 6.88 (1H, dd, *J* = 16.0 and 2.0), 12.15 (1H, s), **5**: ^{1}H NMR δ 1.20 (9H, s), 1.38, (3H, t, *J* = 7.0), 3.84 (1H, m), 4.00 (2H, m), 4.16 (3H, m), 4.35 (1H, dd, *J* = 12.5 and 3.0), 5.76 (1H, dd, *J* = 10.0 and 5.0), 5.81 (1H, dd, *J* = 11.5 and 10.0), 6.65 (1H, d, *J* = 2.0), 6.75 (1H, d, *J* = 11.5), 6.91 (1H, d, *J* = 2.0), **6**: ^{1}H-NMR δ 3.56 (3H, s), 3.78 (3H, s), 3.92 (3H, s), 5.14 (3H, s), 6.70 (1H, d, *J* = 1.5), 6.98 (1H, d, *J* = 1.5), **7**: ^{1}H NMR δ 1.22 (9H, s), 2.49 (1H, d, *J* = 2.0), 3.86 (1H, dd, *J* = 8.5 and 2.0), 3.94 (1H, dd, *J* = 8.5 and 2.0), 4.10–4.16 (2H, m), 4.34 (1H, dd, *J* = 10.0 and 2.0), 4.63 (1H, dd, *J* = 2.0 and 2.0), 4.64 (1H, s), **10**: ^{1}H NMR δ 0.01 (9H, s), 1.05 (9H, s), 3.68 (1H, dd, *J* = 8.0 and 1.0), 3.79 (1H, dd, *J*=8.0 and 2.0), 3.94–4.00 (2H, m), 4.16 (1H, d, *J* = 8.0), 4.43 (1H, d, *J* = 1.0), **11**: ^{1}H NMR δ 1.21 (9H, s), 3.41 (3H, s), 3.42 (3H, s), 3.46 (3H, s), 3.51 (3H, s), 3.79 (3H, s), 3.89 (1H, dd, *J* = 8.0 and 2.0), 3.91 (3H, s), 3.99 (1H, dd, *J* = 8.0 and 2.0), 4.14 (1H, dd, *J* = 11.0 and 8.0), 4.17 (1H, ddd, *J* = 8.0, 2.0, and 2.0), 4.38 (1H, dd, *J* = 11.0 and 2.0), 4.74 (1H, d, *J* = 8.0), 4.75 (1H, d, *J* = 8.0), 4.77 (2H, s), 4.80 (1H, d, *J* = 8.0), 4.81 (1H, d, *J* = 8.0), 4.82 (1H, d, *J* = 2.0), 5.15 (2H, s), 6.66 (1H, d, *J* = 2.5), 6.71 (1H, d, *J* = 2.5), **12**: ^{1}H NMR δ 1.21 (9H, s), 1.32 (3H, dd, *J* = 7.0 and 7.0), 4.05 (1H, dd, *J* = 6.0 and 4.0), 4.14 (2H, m), 4.20 (1H, dd, *J* = 12.0 and 6.0), 4.23 (1H, q, *J* = 7.0), 4.24 (1H, q, *J* = 7.0), 4.42 (1H, dd, *J* = 12.0 and 3.0), 5.79 (1H, d, *J* = 4.0), 6.67 (1H, d, *J* = 2.5), 6.72 (1H, d, *J* = 2.5), **13**: $[\alpha]_D$ +19° (*c* 0.62, MeOH); ^{1}H NMR δ 1.22 (9H, s), 2.56 (2H, m), 3.88 (1H, m), 3.94 (1H, m), 3.96 (1H, m), 4.16 (1H, dd, *J* = 12.0 and 6.0), 4.47 (1H, dd, *J* = 12.0 and 3.0), 6.26 (1H, dt, *J* = 16.0 and 6.5), 6.46 (1H, d, *J*=16.0), 6.61 (1H, d, *J* = 2.0), 6.69 (1H, d, *J* = 2.0), **14**: $[\alpha]_D$ –15° (*c* 0.69, MeOH); ^{1}H NMR δ 2.59 (2H, m), 3.84 (1H,m), 3.85 (1H, m), 4.51 (1H, dd, *J* = 9.0 and 4.0), 6.29 (1H, dt, *J* = 16.0 and 7.0), 6.47 (1H, d, *J* = 16.0), 6.55 (1H, d, *J* = 9.0), 6.60 (1H, d, *J* = 2.5), 6.70 (1H, d, *J* = 2.5), **16**: $[\alpha]_D$ –77° (*c* 0.71, MeOH); ^{1}H NMR δ 1.24 (3H, d, *J* = 6.0), 2.34 (1H, ddd, *J* = 16.0, 7.0, and 2.0), 2.45 (1H, ddd, *J* = 16.0, 4.0, and 2.0), 2.56 (1H, dddd, *J* = 15.0, 8.0, 8.0, and 1.0), 2.68 (1H, dddd, *J* = 15.0, 7.0, 4.0, and 1.0), 3.89 (1H, m), 3.94 (1H, ddd, *J* = 7.0, 6.0, and 4.0), 3.98 (1H, ddd, *J* = 8.0, 6.0, and 4.0), 4.64 (1H, m), 6.28 (1H, ddd, *J* = 18.0, 8.0, and 7.0), 6.46 (1H, ddd, *J*=18.0, 1.0, and 1.0), 6.60 (1H, d, *J* = 2.5), 6.70 (1H, d, *J* = 2.5), **17**: ^{1}H NMR δ 5.54 (1H, dd, *J* = 11.0 and 9.0), 5.84 (1H, dt, *J* = 11.0 and 8.0), 6.30 (1H, dt, *J* = 16.0 and 7.0), 6.45 (1H, d, *J* = 16.0), **18**: $[\alpha]_D$ +22° (*c* 0.88, MeOH), ^{1}H NMR δ 1.39 (3H, d, *J* = 6.0), 2.31 (1H, br s), 2.39 (1H, dddd, *J* = 16.0, 8.0, 4.5, and 1.0), 2.71 (1H, m), 3.04 (1H, br s), 3.36 (3H, br s), 3.37 (3H, s), 3.39 (3H, s), 3.45 (3H, s), 3.79 (3H, s), 3.85 (1H, m), 3.97 (1H, br s), 4.53 (1H, d, *J* = 6.0), 4.54 (1H, d, *J* = 6.0), 4.64 (1H, d, *J* = 5.5), 4.65 (1H, d, *J* = 5.5), 4.71 (1H, d, *J* = 6.0), 4.75 (1H, d, *J* = 6.0), 4.77 (1H, d, *J* = 6.0), 5.11 (1H, d, *J* = 6.0), 5.17 (1H, d, *J* = 6.0), 5.42 (1H, br s), 5.57 (1H, dd, *J*=10.0 and 10.0), 5.85 (1H, br s), 6.12 (1H, br s), 6.51 (1H, d, *J*=2.0), 6.57 (1H, d, *J* = 2.0), 6.60 (1H, br s).
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13 An authentic sample of natural LL-Z1640-2 was kindly provided by Dr. Y. Iino, Ajinomoto Co., Inc.