Total Synthesis of (+)-Leinamycin

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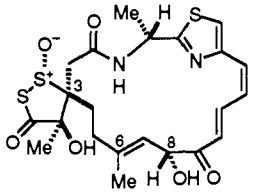
Leinamycin (**1**) has recently been isolated from a culture broth of *Streptomyces* sp. at Kyowa Hakko and has been shown to exhibit potent antitumor activities against experimental tumors.[1,2] The relative configuration of leinamycin was determined by an X-ray crystallographic analysis,[3] and the absolute stereochemistry was deduced as shown on the basis of the degradation studies.[4] The unique structural features of leinamycin include the 1-oxo-1,2-dithiolan-3-one moiety fused in a spiro fashion to an 18-membered lactam with an extensively conjugated thiazole ring. These challenging structural features prompted us[5] and others[6] to undertake the total synthesis of this fascinating molecule. We report herein the first total synthesis of (+)-leinamycin (**1**).



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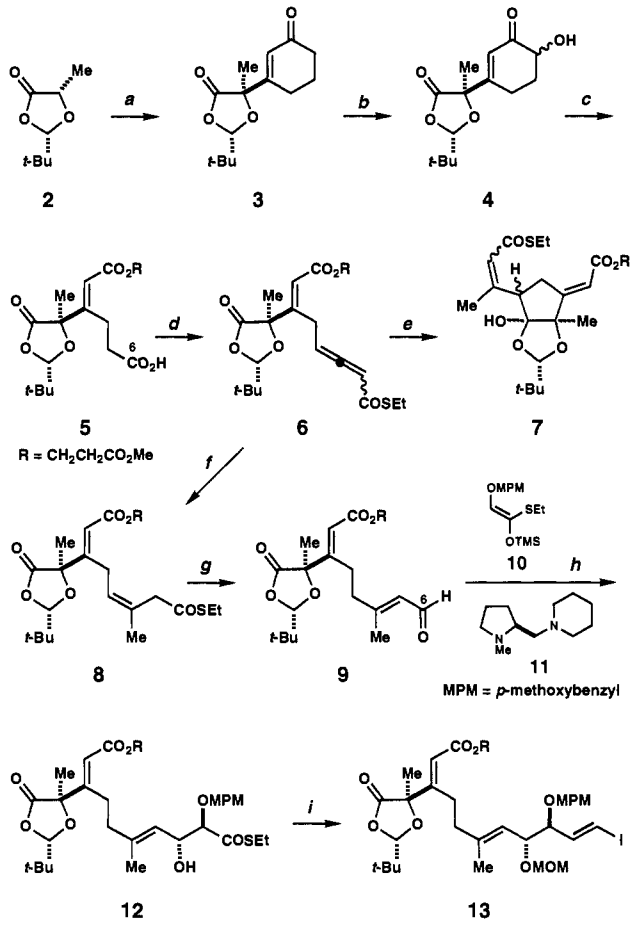
Leinamycin

Treatment of the dioxolanone **2**[7] with LDA followed by addition of 3-ethoxy-2-cyclohexen-1-one furnished, after acidic workup, the cyclohexenone **3** as a single isomer (Scheme I). The ketone **3** was converted to an epimeric mixture of α-ketol **4**, which was cleaved with periodic acid. Esterification[8] of the resultant acid with methyl 3-hydroxypropionate, and Jones oxidation afforded acid **5**. Extension of a C_2 unit with concomitant introduction of a methyl group at the C-6 position (leinamycin numbering) of **5** proved to be an immensely difficult task. To this end, the acid **5** was first converted to a 1:1 diastereomeric mixture of allenic thiol ester **6** by means of the Wittig reaction[9] of the corresponding acid chloride and $Ph_3P{=}CHCOSEt$.[10] While addition of Me_2CuLi to **6** under conventional conditions[11] gave exclusively the undesired product **7**, we found that this side reaction could be completely suppressed by performing the addition *in the presence of phenol*[12] to give predominantly the desired adduct **8**. Upon treatment with Et_3SiH and 10% Pd/C,[13] the thiol ester **8** underwent smooth reduction to give the aldehyde, which was subsequently isomerized to the conjugated (*E*)-enal **9** in the presence of DABCO. The asymmetric aldol reaction developed by Mukaiyama and Kobayashi[14] was employed to control the stereochemistry at the C-8 position, giving the desired *anti*-aldol product **12** in 92% yield. After protection of the hydroxy group, the thiol ester was once again subjected to our reduction conditions[13] to afford the corresponding aldehyde, which was immediately converted to the (*E*)-vinyl iodide **13** according to Takai's procedure.[15]

The hydroxy thiazole **14**[16] prepared from L-lactic acid was converted to the dibromo olefin **15** in a four-step sequence involving protection of the alcohol, $LiAlH_4$ reduction, Swern oxidation, and dibromomethylenation[17] of the aldehyde (Scheme II).

Scheme I[a]



[a] Reagents and conditions: (a) LDA, THF, 3-ethoxy-2-cyclohexen-1-one, −78 °C, then 3 N HCl, 23 °C, 1 h (69%); (b) TMSOTf, Et_3N, Et_2O, 0 °C, 10 min; *m*-CPBA, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C, 20 min; 3 N HCl, THF, 23 °C, 15 min (91%, 3 steps); (c) H_5IO_6, THF, 23 °C, 1.5 h; 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 23 °C, 2 h, then $HO(CH_2)_2CO_2Me$, DMAP, 23 °C, 1 h (59%, 2 steps); Jones reagent, acetone, 0 °C, 10 min (99%); (d) $(COCl)_2$, CH_2Cl_2, 23 °C, 1 h; $Ph_3P{=}CHCOSEt$, Et_3N, CH_2Cl_2, 23 °C, 20 min (73%, 2 steps); (e) Me_2CuLi, Et_2O, −78 °C; (f) Me_2CuLi (4 equiv), PhOH (6 equiv), Et_2O, −78 °C, 20 min (87%); (g) Et_3SiH, 10% Pd/C, acetone, 23 °C, 1 h; DABCO, CH_2Cl_2, 23 °C, 2 h (92%, 2 steps); (h) $Sn(OTf)_2$, **11**, *n*-$Bu_2Sn(OAc)_2$, CH_2Cl_2, 23 °C, 30 min, then **10**, **9**, −78 °C, 18 h (92%); (i) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, reflux, 5 h (91%); Et_3SiH, 10% Pd/C, acetone, 23 °C, 1 h (99%); CHI_3, $CrCl_2$, THF, 23 °C, 40 min (66%).

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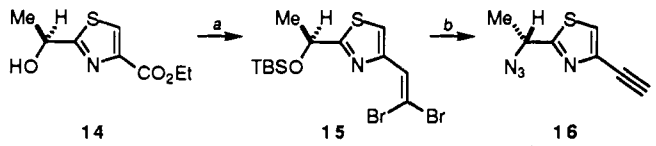
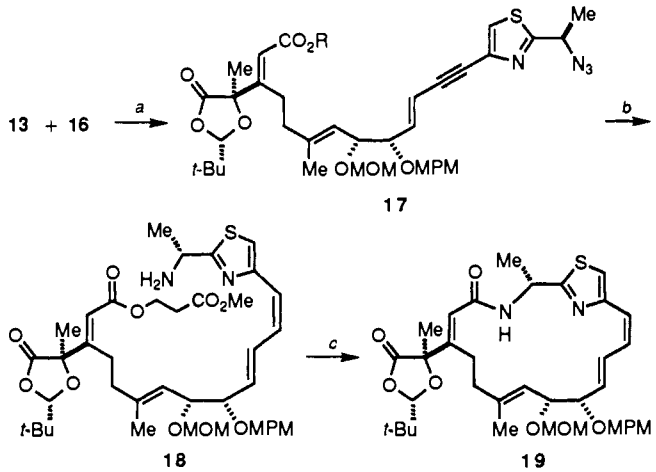
Scheme II[a]



14 15 16

[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, 23 °C, 24 h; $LiAlH_4$, THF, 0 °C, 10 min; DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, 15 min, then Et_3N, −78 → 23 °C, 15 min; CBr_4, PPh_3, CH_2Cl_2, 0 °C, 10 min (86%, 4 steps); (b) *n*-BuLi, THF, −78 °C, 20 min; *n*-Bu_4NF, THF, 0 °C, 2 h (86%, 2 steps); HN_3, PPh_3, DEAD, toluene, 0 °C, 20 min (99%).

Scheme III[a]



17 18 19

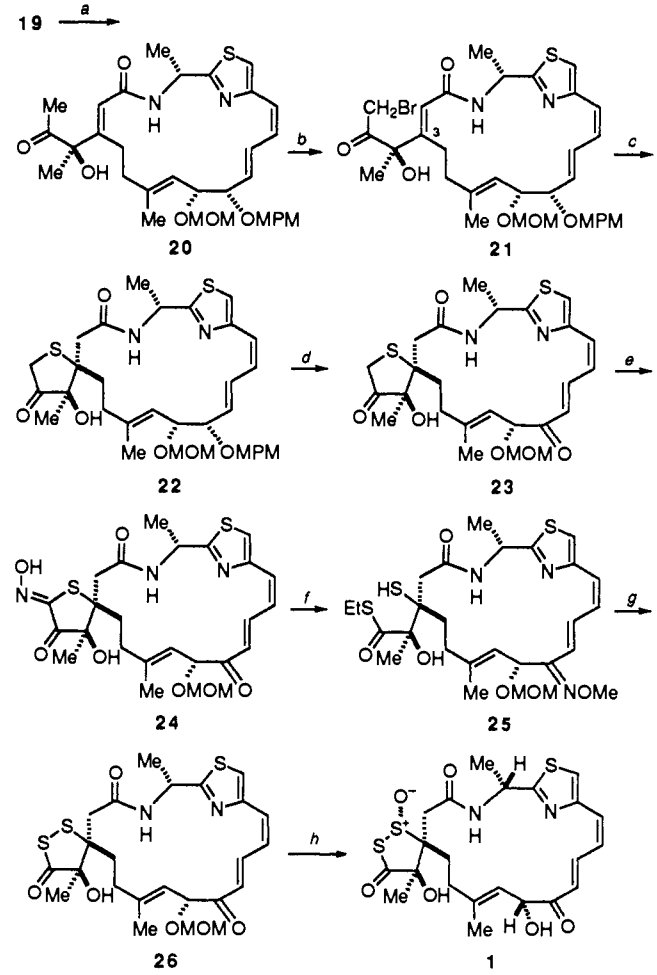
[a] Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, CuBr, Et_3N, THF, 23 °C, 30 min (88%); (b) Zn, AcOH, EtOH, 23 °C, 30 min (99%); H_2, Lindlar catalyst, quinoline, MeOH, 23 °C, 2 h (74%); (c) DBU, CH_3CN, 23 °C, 1.5 h (99%); BOP-Cl, *i*-Pr_2NEt, toluene, 60 °C, 20 min (91%).

Sequential treatment of **15** with *n*-BuLi[17] and *n*-Bu_4NF followed by Mitsunobu reaction using HN_3[18] provided the acetylene azide **16** in 73% overall yield from **14**.

A palladium-mediated coupling reaction[19] between **13** and **16** proceeded smoothly to give the desired ene-yne product **17**, which, after reduction of the azide to amine, was hydrogenated over Lindlar catalyst to afford the (*E*,*Z*)-diene **18** (Scheme III). Upon exposure to DBU, the highly functionalized ester **18** gave the amino acid, which was subjected to macrolactamization by means of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) and *i*-Pr_2NEt[20] to form cleanly the 18-membered lactam **19**.

After numerous attempts to deliver a sulfur atom to the C-3 position of our intermediates, a novel intramolecular protocol has been successfully developed.[5] To apply the protocol to the leinamycin synthesis, the dioxolanone of **19** was first converted to the α-bromo ketone **21** in a four-step sequence (Scheme IV). The intramolecular delivery of a sulfur atom to the C-3 position of **21** was achieved stereoselectively by treatment with H_2S in the presence of Et_3N, giving the desired spiro sulfide **22** in 80% yield along with its C-3 epimer (8% yield). Since nitrosation of the α-thioketone **22** met with complete failure due to the irreversible addition of the lactam nitrogen to the ketone, **22** was converted directly to the more conformationally restricted dienone **23** by oxidation with DDQ.[21] As expected, **23** underwent smooth nitrosation to give the desired oxime **24**. For the crucial Beckmann fragmentation reaction, however, protection of the dienone moiety of **24** was necessary to prevent the undesired Michael addition

Scheme IV[a]



20 21 22 23 24 25 26 1

[a] Reagents and conditions: (a) *p*-$TolSO_2Me$, *n*-BuLi, −78 → 0 °C, 30 min (94%); Al(Hg), THF/H_2O, 23 °C, 40 min (95%); (b) TMSCl, DBU, CH_2Cl_2, reflux, 11 h; NBS, CH_3CN/H_2O, 0 °C, 5 min; 10% $HClO_4$, THF, 23 °C, 8 h (77%, 3 steps); (c) H_2S, Et_3N, THF, 23 °C, 2 h (80%); (d) DDQ, CH_2Cl_2/H_2O, 23 °C, 45 min (95%); (e) *i*-AmONO, NaOMe, 23 °C, 1.5 h (74%); (f) $MeONH_2$-HCl, pyridine, MeOH, 23 °C, 30 min (94%); 2,6-dimethylbenzoyl chloride, pyridine, CH_2Cl_2, 23 °C, 10 min; EtSH, KH, THF, 23 °C, 30 min (52%, 2 steps); (g) NaSH, THF, 23 °C, 20 min, then I_2, 23 °C (82%); 35% HCHO, 3 N HCl, acetone, 23 °C, 77 h (64%); (h) 3 N HCl, AcOH, 0 °C, 45 min (61%); *m*-CPBA, THF, 0 °C, 45 min (84%).

of the thiolate anion. To this end, the ketone **24** was protected as a less electrophilic methoxime (2:1 mixture). Subsequent activation of the oxime as a 2,6-dimethylbenzoate followed by addition of KSEt gave the desired thiol ester **25**. Sequential treatment of **25** with NaSH and I_2 followed by deprotection of the methoxime afforded the 1,2-dithiolanone **26**. Acid-catalyzed hydrolysis of the MOM ether **26** gave (*S*)-deoxyleinamycin, which was oxidized stereoselectively with *m*-CPBA to give (+)-leinamycin (**1**) in 82% yield. The synthetic leinamycin was identical to natural leinamycin by physicochemical comparison (TLC, HPLC, ^1H NMR, IR, MS).

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Supplementary Material Available: Spectroscopic and physical data for key intermediates and synthetic leinamycin (**1**) (7 pages). Ordering information is given on any current masthead page.

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