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The first stereoselective total synthesis of lankanolide. Part 2☆

Tatsuo Hamada* and Yukinari Kobayashi

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

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Abstract—The *seco*-acid derivative designed by conformation calculation and lactonization experiment of model *seco*-acids was synthesized, and subjected to macrolactonization to afford the lactone derivative. The lankanolide was synthesized via several steps after the lactonization, and the synthetic lankanolide was confirmed to have the same physical data (NMR, mass, IR and αD) as the lankanolide prepared from lankamycin according to the reported method. © 2003 Published by Elsevier Science Ltd.

In the preceding letter,[1] we designed a model *seco*-acid derivative, which is predicted to be easily lactonized, by a conformational analysis and lactonization experiments of model *seco*-acids. According to this design of model *seco*-acid derivatives, we planned to synthesize lankanolide (**2**) (Fig. 1) by the route shown in Scheme 1. The designed *seco*-acid (**3**) was divided into two segments (**4** and **5**) and the two segments were planned to be coupled by the Negishi method.[2]

The synthesis of segment **5** is shown in Scheme 2. Methyl (*S*)-(+)-hydroxypropionate was benzylated by the imidate method, and reduced to alcohol **7** with LAH. The primary alcohol was oxidized to form an aldehyde, and then subjected to chelation-controlled crotylation with $MgBr_2$ and crotylstannane to give anti-Cram *syn* adduct **8**.[3] After DMPM[4] (3,4-dimethoxybenzyl) ether protection of the secondary alcohol, olefin was converted to an aldehyde by two-step oxidation.

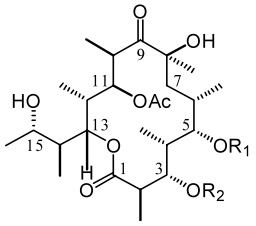
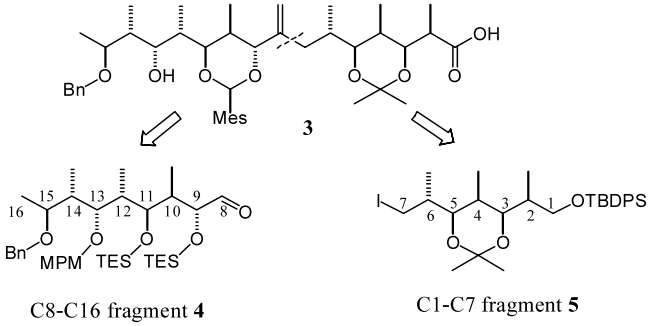


Figure 1. Structures of lankamysin and lankanolide. Lankamysin (**1**): R_1 = D-chalcose, R_2 = acetylarcanose. Lankanolide (**2**): R_1 = H, R_2 = H.

The aldehyde was again crotylated with crotylstannane and BF_3OEt_2 to afford Cram *syn* adduct,[5] and in this case, simultaneous deprotection of DMPM ether occurred to give a diol. The resultant diol was protected with 2,2-dimethoxypropane to form acetonide **10**. Olefin of **10** was degraded oxidatively to give an aldehyde, and the aldehyde was reduced with LAH to form an alcohol and the alcohol was protected with TBDMSCl followed by debenzylation to give **11**. The alcohol was converted to iodide **5** (C1–C7 fragment) via tosylate.

Synthesis of C8–C16 fragment **4**, outlined in Scheme 3, was initiated by benzyloxymethylation of **12** with BOMCl (benzyloxymethyl chloride), followed by LAH reduction to form primary alcohol **13**. After conversion of **13** to an aldehyde by Swern oxidation, the aldehyde was treated with Gilmann reagent to give chelation-controlled adduct **14** as a single isomer.[6] Benzylation of **14**, followed by debenzyloxymethylation, gave alcohol **15**. Swern oxidation and Cram-type crotyl addition catalyzed by borontrifluoride gave **16** (the ratio of **16** to



C8-C16 fragment **4**

C1-C7 fragment **5**

Scheme 1. Retrosynthetic analysis of *seco*-acid derivative **1**.

☆ For Part 1, see Ref. 1.

* Corresponding author.

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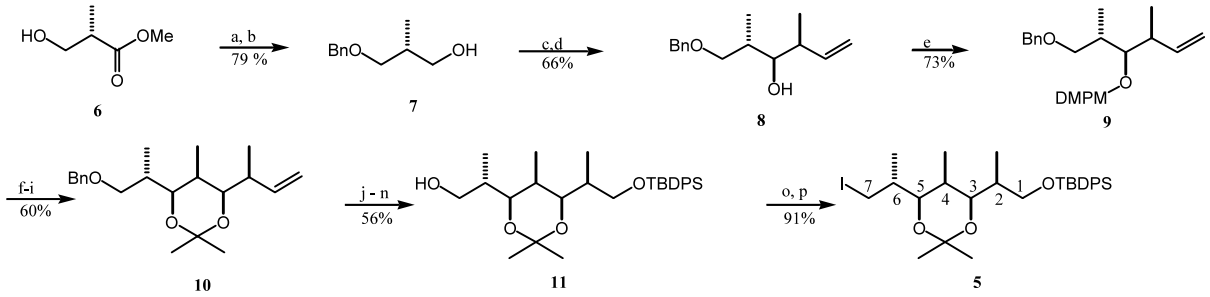
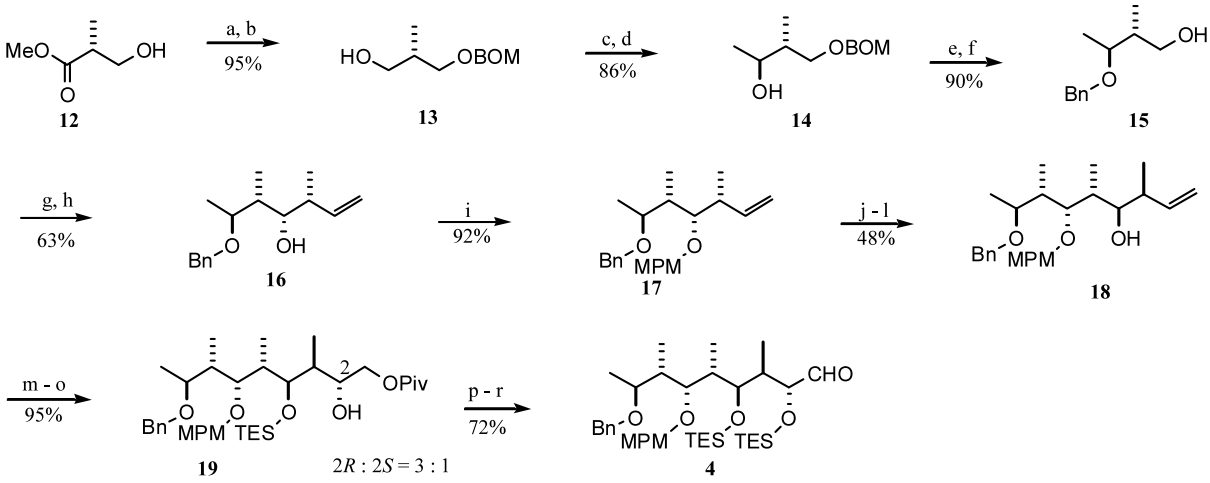


Scheme 2. Synthesis of C1–C7 segment **5**. *Reagents and conditions*: (a) Benzyl trichloroacetimidate, hexane–CH_2Cl_2 (2:1), 0–20°C, 3 h; (b) $LiAlH_4$, Et_2O, 0°C, 1.5 h; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −70 to −60°C, 1 h; (d) crotyltri-*n*-butylstannane, $MgBr_2OEt_2$, CH_2Cl_2, −30°C, 4 h; (e) DMPMCl, KH, 18-crown-6, 25°C, 3 h; (f) OsO_4, NMO, acetone–H_2O (10:1), 25°C, 20 h; (g) $NaIO_4$, acetone–H_2O (4:1), 25°C, 20 h; (h) crotyltri-*n*-butylstannane, BF_3OEt_2, CH_2Cl_2, −90 to −30°C, 6 h; (i) 2,2-dimethoxypropane, TsOH, benzene, 25°C, 14 h; (j) OsO_4, NMO, acetone–H_2O (10:1), 25°C, 20 h; (k) $NaIO_4$, acetone–H_2O (4:1), rt, 1 h; (l) $LiAlH_4$, Et_2O, 0°C, 15 min; (m) TBDPSCl, imidazole, CH_2Cl_2, 25°C, 1 h; (n) Raney Ni (W-2), H_2, EtOH, 25°C, 120 h; (o) TsCl, pyridine, DMAP, CH_2Cl_2, 20°C, 20 h; (p) NaI, $NaHCO_3$, 2-butanone, 60°C, 20 h.

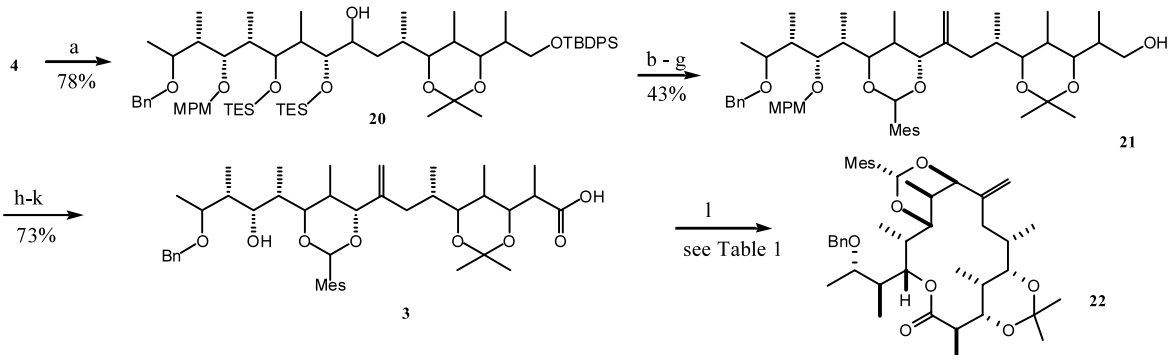


Scheme 3. Synthesis of C8–C16 fragment. *Reagents and conditions*: (a) BOMCl (benzyloxymethyl chloride), *i*-Pr_2NEt, CH_2Cl_2, 0°C to rt, 4 h; (b) $LiAlH_4$, Et_2O, 0°C, 15 min; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −50°C, 4 h; (d) Me_2CuLi, Et_2O, −78°C, 3 h; (e) BnBr, NaH, THF–DMSO (1:1), 20°C, 15 h; (f) 4N HCl, THF, reflux, 18 h; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −50°C, 1 h; (h) crotyltri-*n*-butylstannane, BF_3OEt_2, CH_2Cl_2, −85°C, 1 h; (i) MPMCl, NaH, THF–DMSO (1:1), rt, 15 h; (j) OsO_4, NMO, acetone–H_2O (10:1), rt, 12 h; (k) $NaIO_4$, acetone–H_2O (4:1), rt, 1.5 h; (l) crotyltri-*n*-butylstannane, $MgBr_2OEt_2$, CH_2Cl_2, −30°C to rt, 8 h; (m) TESCl, imidazole, CH_2CH_2, rt, 4 h; (n) OsO_4, NMO, acetone–H_2O (10:1), rt, 20 h; (o) PivCl, pyridine, DMAP, CH_2CH_2, rt, 3.5 h; (p) TESCl, imidazole, CH_2CH_2, rt, 1 h; (q) DIBAH, CH_2Cl_2, −78°C, 0.5 h; (r) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 0.5 h.

undesired products was 3:1). MPM (4-methoxybenzyl) protection of the primary alcohol of **16** formed **17**. Oxidative degradation of **17** to form an aldehyde, followed by chelation-controlled crotyl addition, afforded **18** (the ratio of desired **18** to undesired products was 6:1). TES protection and dihydroxylation and pivaroyl (Piv) protection of the resulting primary alcohol gave **19**, although the face selectivity of osmylation was not so high (2*R*:3*S*=3:1). TES protection, followed by deprotection of the pivaroyl group and Swern oxidation gave C8–C16 fragment **4**.

Synthesis of lactone **22** via *seco*-acid **3** is shown in Scheme 4. Aldehyde **4** was added to a solution of methylene lithium prepared by lithium halogen exchange[2] of iodide **5** with *t*-butyl lithium to afford **20**. Oxidation of the secondary alcohol to ketone followed by Wittig reaction and deprotection of TBDPS and TES to give triol. TBDMS protection of the primary alcohol of the triol followed by acetalization of the resultant diol with mesytaldehyde dimethyl acetal and deprotection of TBDPS afforded **21**. Jones oxidation of the primary alcohol and deprotection of MPM[7] by DDQ formed *seco*-acid **3**.

The cyclization of the *seco*-acid **3** is summarized in Table 1. Because of the crowded surroundings of the alcohol reaction site,[8] cyclization proceeded sluggishly to give lactone **22** in low yield. The best result (22% based on recovered **3**) by the improved Yamaguchi method was obtained under the high dilution condition and xylene reflux (Table 1), and in other solvents

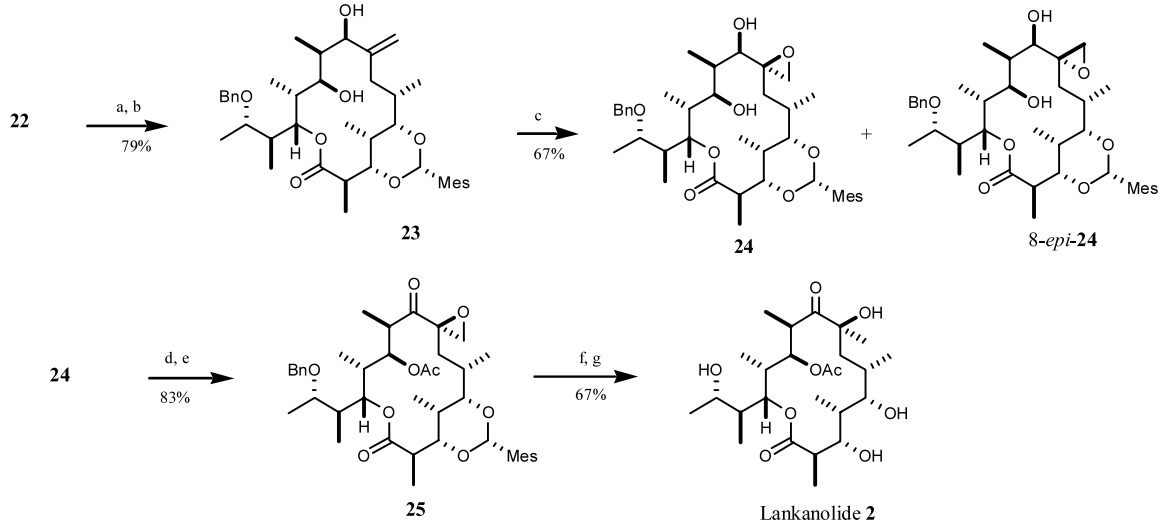


Scheme 4. Synthesis of *seco*-acid derivative **3** and lactone **22**. *Reagents and conditions*: (a) *t*-BuLi, pentane–Et_2O (3:2), −78°C to rt, 1 h, then, **4** was added to the solution, −78°C, 1.5 h; (b) Dess–Martin periodinate, CH_2Cl_2, rt, 2 h; (c) $MePPh_3Br$, *t*-BuOK, toluene, 95°C, 1.5 h; (d) TBAF, THF, rt, 10 h; (e) TBDPSCl, imidazole, CH_2Cl_2, rt, 15 min; (f) $MesCH(OMe)_2$, CSA, CH_2Cl_2, 15°C, 1 h; (g) TBAF, THF, rt, 3 h; (h) Jones reagent, acetone, −30°C, 1.5 h; (i) CH_2N_2, Et_2O, 0°C, 0.5 h; (j) DDQ, CH_2Cl_2–H_2O (20:1), 0°C, 15 min; (k) 3N NaOH, MeOH, rt, 90 h; (l) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, rt, 20 h, then the resulting solution was added to DMAP solution in toluene, toluene, reflux, 20 h.

Table 1. Effect of temperature and solvent on macrocyclization of **3**

Temp. (°C)	Solvent	Reaction time (h)	Addition time (h)[a,b]	Yield (%)	Recovery of **3** (%)
80	Toluene	14	8.5	0	50
Reflux	Toluene	20	19	11	30
Reflux	Xylene	16.5	8.5	13	40
Reflux	EtCN	15	8.5	0	80
Reflux	$CHCl_3$	14	8.5	0	30
Reflux	1,4-Dioxane	16.5	8.5	0	0
Reflux	CCl_4	14.5	8.5	0	0

[a] A dilute solution (2 mM) of the mixed anhydride of **3** was used.
[b] Reaction time includes addition time.



Scheme 5. *Reagents and conditions*: (a) aqueous 3N HCl, THF, 20°C, 140 h; (b) $MesCH(OMe)_2$, CSA, CH_2Cl_2, 20°C, 0.5 h; (c) *m*-CPBA, toluene, 80°C, 1.5 h; (d) Dess–Martin periodinane, CH_2Cl_2, 20°C, 48 h; (e) Ac_2O, pyridine, DMAP, CH_2Cl_2, 20°C, 1 h; (f) LiI, AcOH, THF, 20°C, 0.5 h; (g) $Pd(OH)_2$, H_2, AcOEt, 20°C, 12 h.

(EtCN, $CHCl_3$, dioxane, and CCl_4), lactone **22** was not formed at all.

The conversion of **22** to the final target lankanolide **2** is outlined in Scheme 5. Hydrolysis of **22** afforded a tetraol, and *syn*-1,3-diol (C3 and C5) of the tetraol was protected selectively with mesitaldehyde dimethyl acetal to give **23**.[9] *exo*-Methylene of **23** was epoxidized with *m*-CPBA[10] to give **24** as an epimeric mixture at C8 (**24**:8-*epi*-**24** = 1.5:1). After separating the epimer by

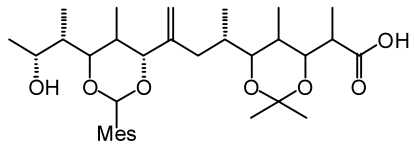


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Figure 2. Model *seco*-acid **26**.

silica gel chromatography, **24** was selectively oxidized to ketone[9] with Dess–Martin periodate,[11] followed by acetylation of C11-alcohol to afford **25**. The epoxide ring-opening of **25**[10] with lithium iodide gave iodohydrin and Pd-catalyzed reduction effected simultaneous deiodation and deprotections of the mesitilidene acetal and benzyl group with $Pd(OH)_2$ and H_2 to afford the final target lankanolide **2**.

The synthesized lankanolide was identical in all respects (proton and carbon NMR, IR, mass, and $[\alpha]_D$) to the lankanolide derived from the natural product lankamycin.[12] From a comparison of $[\alpha]_D$,[13] we were able to conclude that the absolute stereochemistry is the structure as shown in Figure 1.

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