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The first total synthesis and establishment of absolute structure of luminacins C_1 and C_2

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Abstract—Luminacins C_1 and C_2 (**1** and **2**), novel angiogenesis inhibitors, have been synthesized from a carbohydrate. The correlation of **1** and **2** confirms their structures to be different only at C1″ and establishes the relative and absolute configurations.

Luminacins C_1 and C_2 (**1** and **2**) were isolated from *Streptomyces* sp. as novel angiogenesis inhibitors. Their structures, including the relative configuration of the carbohydrate portion, were determined mainly by NMR studies.[1] As a result, they were found to have the same planar structure as SI-4228 and UCS15A, which were reported to be microbial products showing antimicrobial, immunosuppressive,[2] antitumor and bone resorption inhibitory activities.[3] However, the absolute structure of luminacins C_1 and C_2 remained undetermined. The significant clinical potential of luminacins has stimulated considerable interest in the synthesis and structure–function studies.

Herein, we report the first total synthesis of luminacins C1 and C2 (UCS15A) to disclose their absolute structures unambiguously.

From both structural and retrosynthetic standpoints, luminacins C_1 and C_2 (**1** and **2**) are reasonably expected to be constructed from the aromatic segment **3** and the carbohydrate segment **4** as outlined in Fig. 1. The sensitive epoxide at C6′-8′ is selectively introduced at the latter stage of the synthesis by S_N2 displacement. The enantiopure segment **3** having the lone stereocenter may be prepared from Grignard reaction of the benzaldehyde **5** with isopropylmagnesium bromide followed by kinetic resolution. The segment **4** is prepared from the *exo*-olefin **6** by ozonolysis followed by epimerization at C5′.[4] The olefin **6** can be synthesized from the primary alcohol **7**, which is derived from L-glucal **10** through successive Wittig olefinations.

Although we have synthesized all possible isomers, especially at C1″, C2′ and the carbohydrate portion of

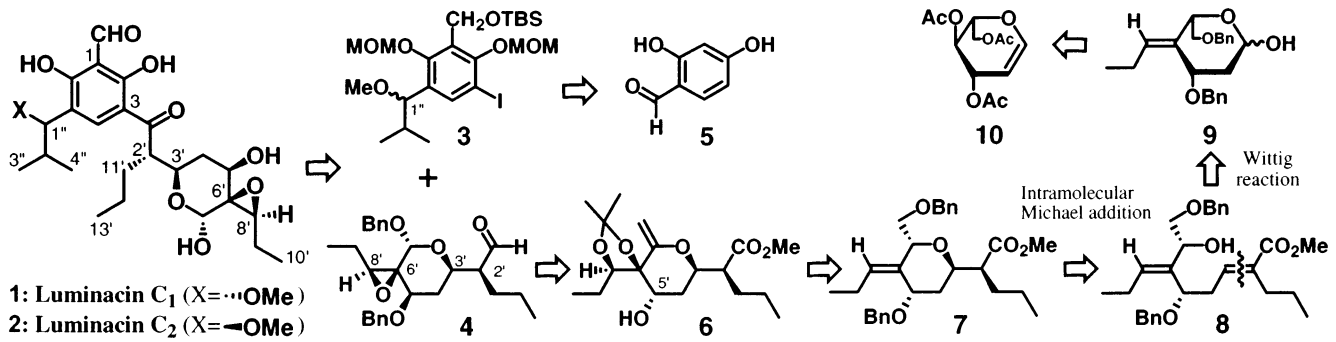

Figure 1.

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luminacins C_1 and C_2 (**1** and **2**) to determine the absolute structures, the synthesis of enantiomers (**1′** and **2′**) of the natural products is conveniently described from (*R*)- and (*S*)-**3** (**3R** and **3S**) and D-glucal **10′** in detail. The latter **10′** is an inexpensive material. The natural products could be synthesized by using L-glucal **10**.

The synthesis of the chiral fragments required for the assembly of **1′** and **2′** is outlined in Schemes 1 and 2.

On one hand, the aromatic segments **3R** and **3S** were synthesized from the benzaldehyde **5**. Methoxymethylation of **5** was followed by Grignard reaction to give the racemic alcohol **11**.[5] The kinetic resolution of **11** was effectively carried out by acylation with 0.8 equiv. of (−)-camphanic chloride in THF at −78°C for 30 min to give, after recrystallization from ether–hexane, the diastereomerically pure (*R*)-isomer **12R** in 45% yield (the theoretical yield is 50%). The absolute structure was determined by the X-ray analysis.[6] The unreacted **11** having the (*S*)-enantiomer as the major component was acylated with enantiomeric (+)-camphanic chloride to give **12S** in 41% yield. The enantiomerically pure **11R** ($[\alpha]_D^{26}$+26° (*c* 0.99, MeOH)) and **11S** ($[\alpha]_D^{26}$−25° (*c* 1.1, MeOH)) were obtained from **12R** and **12S** by methanolysis, respectively. The *O*-methyl derivative **13R** was regioselectively lithiated to react with formaldehyde, followed by *O*-silylation to give **14R**. This was iodinated to the desired (*R*)-iodide **3R**.

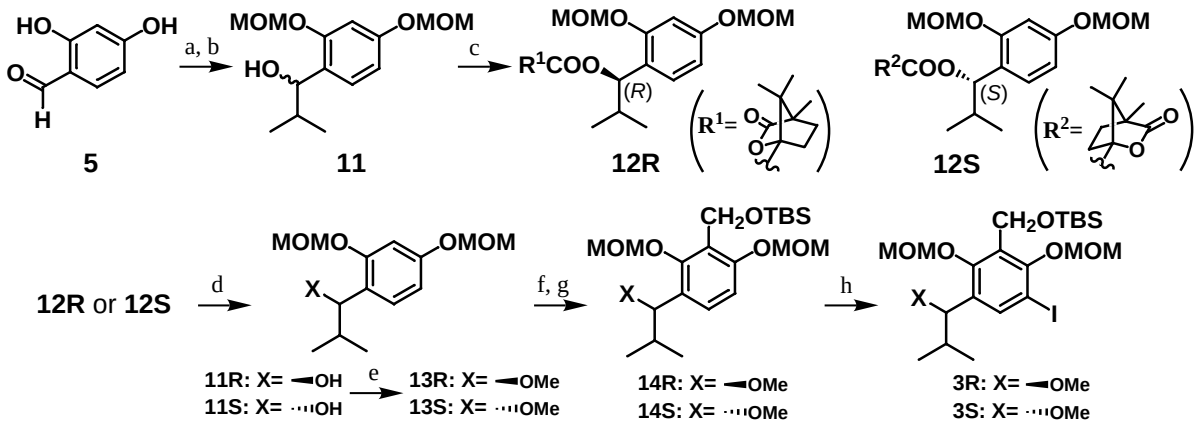
On the other hand, the carbohydrate segment **4′** was prepared from the D-glucal **10′**. We found that de-*O*-acetylation of **10′** proceeded regioselectively by KOH in DMF at 0°C to give **15**. This was successively methoxymethylated, de-*O*-acetylated and benzylated to afford **16** in high yield. Methanolysis of **16** was followed by Swern oxidation to the ketone **17**, which was submitted to Wittig olefination using *n*-$PrPPh_3Br$ and *n*-BuLi. The resulting unsaturated methyl glycoside was hydrolyzed to the anomeric mixture **9′**. Wittig reaction of **9′** with **18** gave, after purification on silica-gel column chromatography, the α,β-unsaturated ester **8′**. This was stereoselectively cyclized by intramolecular Michael reaction to give **19** as a single product. We anticipated that the cyclization would give the (3′*S*)-isomer having the equatorial substituent at C3′, because of the presence of the diaxial substituents at C5′ and C7′ due to strong repulsion with an *exo*-olefin. In fact, the absolute structure was confirmed to have the 3′*S*-configuration by the X-ray analysis of the derivative **29**.[7]

As **19** could not be converted to the desired products **1′** and **2′**, the configuration at C2′ was epimerized for the total synthesis by treatment with MeONa to give a 1:1 mixture of **7′** and **19**. The mixture was separated by silica-gel column chromatography to afford **7′** in 45% yield. The absolute structure was also confirmed by the X-ray analysis.[7]

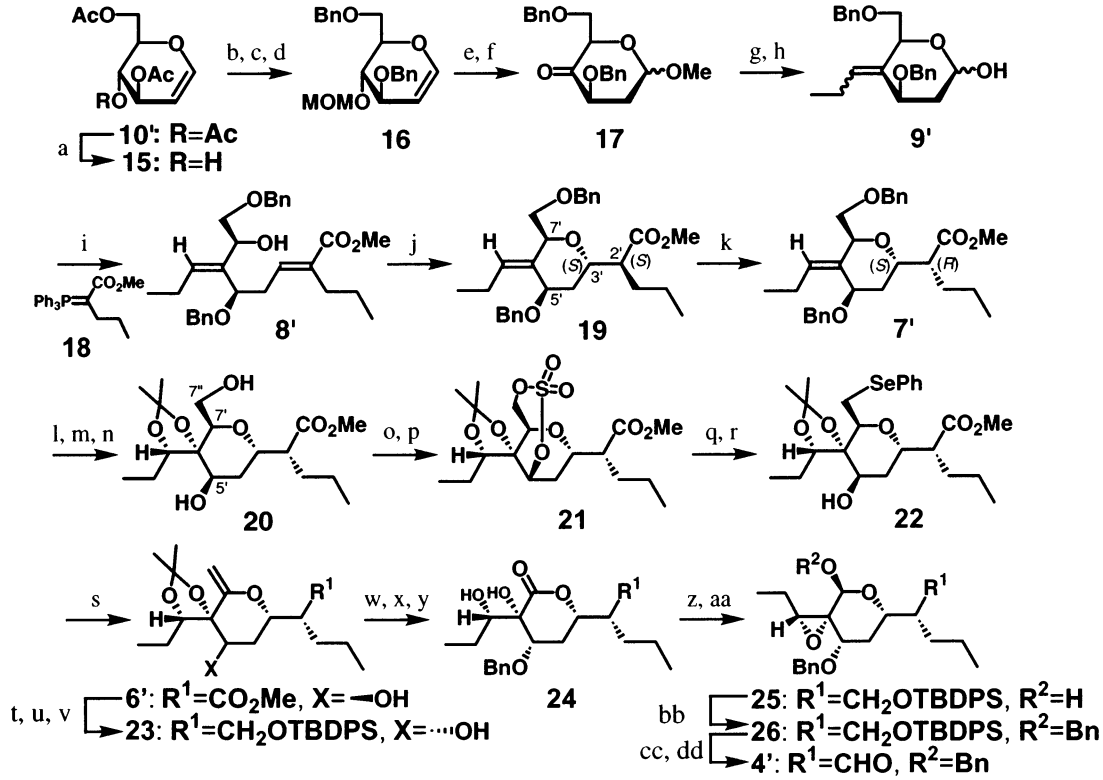
Dihydroxylation of the olefin **7′** with OsO_4 was expected to occur at the less hindered site. Acetonation of the resulting *cis*-diol was followed by hydrogenolysis to give **20**.

We examined the displacement of the primary alcohol of **20** with the phenylselenide group in order to obtain an *exo*-olefin, but the desired displacement failed to occur. As the C5′ and C7′ substituents were present in the diaxial positions and, moreover, the *O*-leaving group of C7″ was outside of the tetrahydropyran ring, the C5′ hydroxyl group could readily attack the C7″ position to form a furan ring. After extensive experimentation, we were able to displace the primary alcohol under more forcing conditions by preparation of the cyclic sulfate **21**, where the nucleophile could approach from outside of the pyran ring. Compound **20** was first treated with $SOCl_2$ followed by oxidation to give **21**.[8] The latter reacted smoothly with the phenylselenide anion to give, after removal of the sulfate by acidic hydrolysis,[9] the desired **22** in 93% yield. This phenylselenide was exposed to H_2O_2 to afford the *exo*-olefin **6′** by elimination.

At this stage, the configuration of the hydroxyl group in **6′** was changed to the desired one by oxidation and

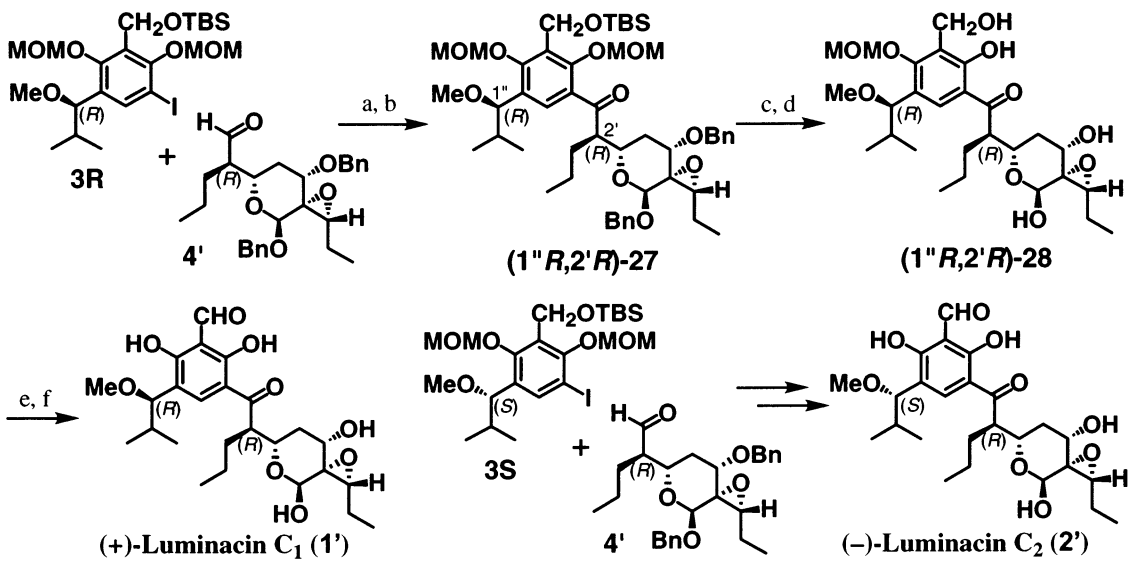


Scheme 1. (a) MOMCl, *i*-Pr_2NEt/DMF, rt; (b) *i*-PrMgBr/THF, 0°C, 83% two steps; (c) (−)-camphanic chloride, Py/THF, −78°C, 45%; (d) KOH/MeOH, rt, 92%; (e) MeI, NaH/DMF, rt, 96%; (f) $(HCHO)_n$, *s*-BuLi, TMEDA/THF, −78°C; (g) TBSCl, imidazole/DMF, rt, 67% two steps; (h) NIS, *s*-BuLi/THF, −78°C, 80%.



Scheme 2. (a) KOH/DMF, 0°C, 69%; (b) MOMCl, *i*-Pr_2NEt/PhMe, rt; (c) NH_3/MeOH, 40°C; (d) BnCl, *t*-BuOK/DMF, rt, 95% three steps; (e) $Ph_3P{\cdot}HBr$, MeOH/PhMe, rt, 89%; (f) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, −78 to 0°C, 96%; (g) *n*-$PrPPh_3Br$, *n*-BuLi/THF, −78°C to rt, 84%; (h) aq. AcOH, 50°C, 80%; (i) PhMe, 100°C, 76%; (j) MeONa (cat.)/PhMe, 70°C, 80%; (k) MeONa/MeOH, 60°C, 45%; (l) OsO_4, NMO/aq. MeCN, rt, quant.; (m) 2-methoxypropene, PPTS/$CHCl_3$, rt, quant.; (n) H_2, $Pd(OH)_2$-C/EtOH, rt, quant.; (o) $SOCl_2$, Et_3N/CH_2Cl_2, −78°C; (p) $RuCl_3{\cdot}nH_2O$, $NaIO_4/CCl_4$–MeCN–H_2O, rt; (q) PhSeNa/THF, 0°C; (r) aq. H_2SO_4/THF, rt; (s) aq. H_2O_2, $NaHCO_3$/THF, rt to 50°C, 67% five steps; (t) TPAP, NMO, MS4A/CH_2Cl_2, rt; (u) $LiAlH_4$/THF, 0°C to rt; (v) TBDPSCl, imidazole/DMF, rt, 77% three steps; (w) BnBr, NaH/DMF, rt, 95%; (x) O_3/CH_2Cl_2, −78°C then Ph_3P, 80%; (y) TFA/CH_2Cl_2, rt, 80%; (z) Tf_2O, Py/CH_2Cl_2, −78°C; (aa) DIBAL-H/PhMe, −78°C; (bb) BnBr, NaH/DMF, rt; (cc) TBAF/THF, rt; (dd) $(COCl)_2$, DMSO, Et_3N/CH_2Cl_2, −78°C to 0°C, 88% five steps.

hydride reduction. Simultaneously, the ester group of **6′** was reduced to a primary alcohol, which was selectively silylated to **23**. *O*-Benzylation of **23** was followed by ozonolysis and de-acetonation to give the lactone **24**. This was converted by S_N2 displacement to the epoxide and reduced with DIBAL to the lactol **25**. *O*-Benzyla-



Scheme 3. (a) *n*-BuLi/THF, −78 to 0°C; (b) TPAP, NMO, MS4A/CH_2Cl_2, rt, 70% two steps; (c) H_2, $Pd(OH)_2$-C/EtOH, rt, 45%; (d) THF–AcOH–H_2O, 60°C, 65%; (e) $MnO_2/CHCl_3$, rt; (f) THF–AcOH–H_2O, 60°C, 61% two steps.

tion of **25** to give exclusively the benzyl β-glycoside **26** was followed by de-*O*-silylation and oxidation of the resulting alcohol to the aldehyde **4′**.

With sufficient quantities of enantio-pure segments **3R**, **3S** and **4′** in hand, we turned to their combination as shown in Scheme 3. Lithiation of **3R** followed by addition of **4′** yielded the alcohol, which was oxidized to the ketone (1″*R*,2′*R*)-**27**. Deprotection by hydrogenolysis and hydrolysis gave the mono-*O*-MOM derivative **28**. The primary alcohol was oxidized to the aldehyde, followed by removal of the *O*-MOM group to give (+)-luminacin C_1 (**1′**) ($[\alpha]_D^{26}$+97° (*c* 0.47, $CHCl_3$)). When treated with the enantiomer **3S**, compound **4′** gave similarly (1″*S*,2′*R*)-**27**. This was converted into (−)-luminacin C_2 (**2′**) ($[\alpha]_D^{26}$−54° (*c* 0.17, $CHCl_3$)) by similar procedures through (1″*S*,2′*R*)-**28** as described above.

Both synthetic products **1′** and **2′** were identical in NMR, IR and mass spectral analyses with natural luminacins C_1 and C_2 (**1** and **2**), although the signs of their optical rotations were completely opposite to those of the natural products.[10] Finally, luminacins C_1 and C_2 (**1** and **2**) could be synthesized from L-glucal **10** with **3S** and **3R**, respectively, by the same procedures described above. Thus, the correlation of **1** and **2** confirmed their structures to be different only at C1″ and established the relative and absolute configurations to be as shown in Fig. 1.

Acknowledgements

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References

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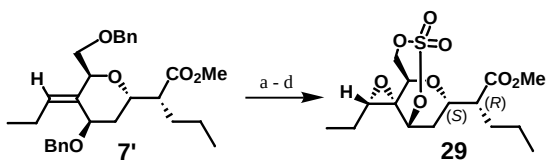
4. The carbon-numbering protocol parallels conveniently that of the natural product **1**.
5. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. ^{1}H NMR (600 MHz: δ, ppm from TMS, and *J* in Hz) spectra were in $CDCl_3$ solution, unless otherwise stated. Significant ^{1}H NMR spectral data are the following. **1′**: 3.27 (1H, dd, *J*=7.0 and 5.5, H-8′), 3.60 (1H, m, H-2′), 4.18 (1H, ddd, *J*=12.0, 12.0 and 5.0, H-5′), 4.39 (1H, ddd, *J*=11.5, 7.0 and 1.5, H-3′), 4.96 (1H, d, *J*=2.5, H-7′), 8.08 (1H, s, H-4), 10.41 (1H, s, CHO-1), 12.97 (1H, s, OH-6), 14.16 (1H, s, OH-2). **2′**: 3.27 (1H, dd, *J*=7.0 and 6.0, H-8′), 3.65 (1H, ddd, *J*=10.0, 7.5 and 4.0, H-2′), 4.18 (1H, br dd, 12.0 and 4.5, H-5′), 4.40 (1H, ddd, *J*=11.5, 7.5 and 1.5, H-3′), 4.95 (1H, s, H-7′), 8.04 (1H, s, H-4), 10.42 (1H, s, CHO-1), 12.97 (1H, s, OH-6), 14.18 (1H, s, OH-2). **3R** and **3S**: 4.33 (1H, d, *J*=6.5, H-1″), 4.69 (1H, d, *J*=10.5, CH_2-1), 4.73 (1H, d, *J*=10.5, CH_2-1), 7.76 (1H, s, H-4). **4′**: 3.30 (1H, t, *J*=6.5, H-8′), 4.12 (1H, dd, *J*=11.5 and 4.5, H-5′), 4.29 (1H, ddd, *J*=12.0, 5.0 and 2.0, H-3′), 4.55 (1H, s, H-7′), 9.76 (1H, d, *J*=2.0, H-1′). **6′** [in $(CD_3)_2CO$]: 3.64 (3H, s, CO_2Me), 4.02 (1H, ddd, *J*=4.0, 4.0 and 2.0, H-5′), 4.14 (1H, ddd, *J*=11.0, 8.5 and 3.0, H-3′), 4.22 (1H, dd, *J*=10.5 and 3.0, H-8′), 4.59 (1H, d, *J*=1.0, H-7″), 4.61 (1H, d, *J*=1.0, H-7″). **7′**: 3.67 (3H, s, CO_2Me), 4.15 (1H, ddd, *J*=11.5, 7.5 and 2.0, H-3′), 4.43 (1H, dd, *J*=3.5 and 3.0, H-5′), 5.60 (1H, t, *J*=7.5, H-8′). **12R** and **12S**: 0.90, 1.05, 1.10 (3H, each s, camphanyl Me), 6.06 (1H, d, *J*=7.0, H-1″), 6.66 (1H, dd, *J*=8.0 and 2.0, H-3), 6.79 (1H, d, *J*=2.0, H-1), 7.16 (1H, d, *J*=8.0, H-4). **14R** and **14S**: 4.35 (1H, d, *J*=6.5, H-1″), 4.68 (1H, d, *J*=10.5, CH_2-1), 4.76 (1H, d, *J*=10.5, CH_2-1), 6.95 (1H, d, *J*=9.0, H-3), 7.24 (1H, d, *J*=9.0, H-4). **21**: 3.70 (3H, s, CO_2Me), 4.27 (1H, dd, *J*=12.0 and 2.5, H-8′), 4.58 (1H, ddd, *J*=12.0, 6.5 and 3.5, H-3′), 4.63 (1H, dd, *J*=13.5 and 2.5, H-7″), 4.70 (1H, dd, *J*=13.5 and 1.5, H-7″), 4.80 (1H, dd, *J*=3.5 and 2.5, H-5′). **24**: 3.70 (1H, dd, *J*=10.5 and 4.5, H-1′), 3.73 (1H, dd, *J*=10.5 and 6.5, H-1′), 3.83 (1H, dd, *J*=10.0 and 2.5, H-8′), 3.92 (1H, dd, *J*=6.5 and 6.5, H-5′), 4.69 (1H, ddd, *J*=8.0, 8.0 and 4.5, H-3′). (1″*R*,2′*R*)-**27**: 3.29 (1H, t, *J*=6.5, H-8′), 3.62 (1H, ddd, *J*=8.5, 8.0 and 4.0, H-2′), 4.12 (1H, dd, *J*=12.0 and 4.5, H-5′), 4.29 (1H, ddd, *J*=11.5, 8.0 and 1.5, H-3′), 4.54 (1H, s, H-7′), 4.69 (1H, d, *J*=10.5, CH_2-1), 4.76 (1H, d, *J*=10.5, CH_2-1), 7.61 (1H, s, H-4). (1″*S*,2′*R*)-**27**: 3.28 (1H, t, *J*=6.5, H-8′), 3.62 (1H, ddd, *J*=8.0, 8.0 and 4.0, H-2′), 4.12 (1H, dd, *J*=12.0 and 4.5, H-5′), 4.28 (1H, ddd, *J*=11.5, 8.0 and 1.5, H-3′), 4.54 (1H, s, H-7′), 4.71 (1H, d, *J*=10.5, CH_2-1), 4.78 (1H, d, *J*=10.5, CH_2-1), 7.62 (1H, s, H-4).
6. The X-ray data of **12R** has been deposited with CCDC (CCDC 165798).
7. The derivative **29** was prepared from **7′** as shown in Scheme 4. The X-ray data of **29** has been deposited with CCDC (CCDC 167727).



Scheme 4. (a) *m*CPBA/$CHCl_3$, rt, 95%; (b) H_2, $Pd(OH)_2$–C/EtOH, rt, quant.; (c) $SOCl_2$, Et_3N/CH_2Cl_2, rt; (d) $RuCl_3 \cdot nH_2O$, $NaIO_4/CCl_4$–MeCN–H_2O, rt, 80% two steps.

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10. Authentic samples of luminacins C_1 (**1**: ($[\alpha]_D^{26}$−98° (*c* 0.28, $CHCl_3$)) and C_2 (**2**: UCS15A; ($[\alpha]_D^{26}$+54° (*c* 0.13, $CHCl_3$)) were kindly provided by K. Dobashi, Mercian Corp. and Y. Kanda, Kyowa Hakko Kogyo Co., Ltd.