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Total synthesis of (±)-lysidicin A

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ABSTRACT

Lysidicin A, which has been isolated from *Lisidicie rhodostegia* possesses complicated structure. A total synthesis of lysidicin A has been achieved and is described herein. The key reaction is single and cascade Claisen rearrangements.

1. Introduction

Lisidicie rhodostegia Hance (Fabaceae) is a Chinese medicinal shrubbery plant, which has been used for the treatment of ache, fractures, and hemorrhage for a long time by local folks in China. Lysidicins A–C (**1**–**3**) have been isolated from the plant by Yu and co-workers in 2006[1] and the isolation of other lysidicins D–H have also been reported by the same group in 2007[2] and 2010.[3] Although lysidicin D–H showed stronger anti-oxidant activity than vitamin E,[2,3] the full details of biological activities of the other lysidicins have not been clarified yet. Meanwhile, among the lysidicin family, lysidicin A (**1**) has the most unique and complicated structure in which two acetals form spiro[furan-furofuran] ring system. Moreover, any other compounds possessing this unique structure have not been isolated. Interest in the construction of this novel structure and the additional contribution to bioassay prompted us to embark on the synthetic study of lysidicin A (**1**). Herein, we report a full detail of the efficient total synthesis of (±)-lysidicin A (**1**) (Fig. 1).

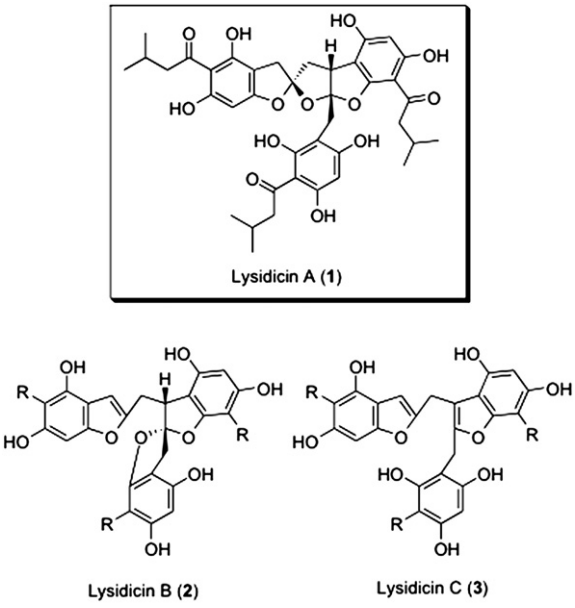

Fig. 1. Structures of lysidicin family: R=isovaleryl.

2. Results and discussion

Our synthetic strategy is shown in Scheme 1. Lysidicin A (**1**) would be synthesized from spiro[furan-furofuran] **4** by three Friedel–Crafts acylations. Spiro[furan-furofuran] **4** would be obtained from diene **5** by oxidative cleavage of two *exo*-olefins and subsequent intramolecular acetalization. The key step is the single and cascade Claisen rearrangements (**6**→**5**), which deliver the three aromatic rings to the correct positions, at the same time installing the two *exo*-methylenes as we have already reported the preliminary results recently.[4] Triether **6** would be readily obtained from phloroglucinol derivative **7** and triol **8**.

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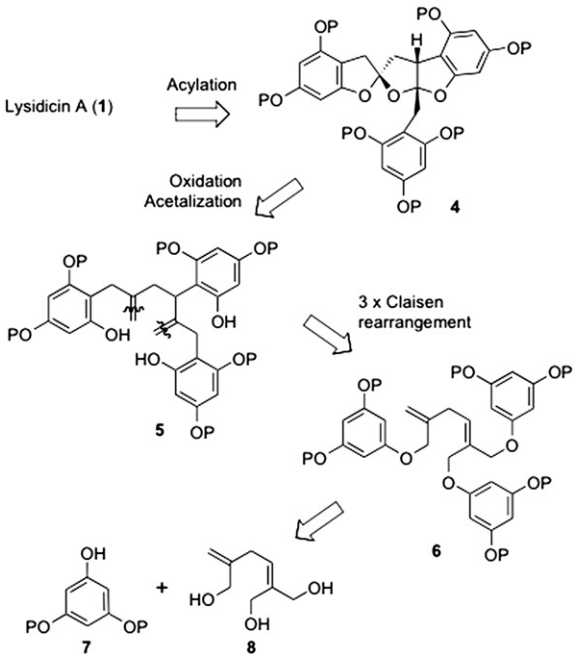
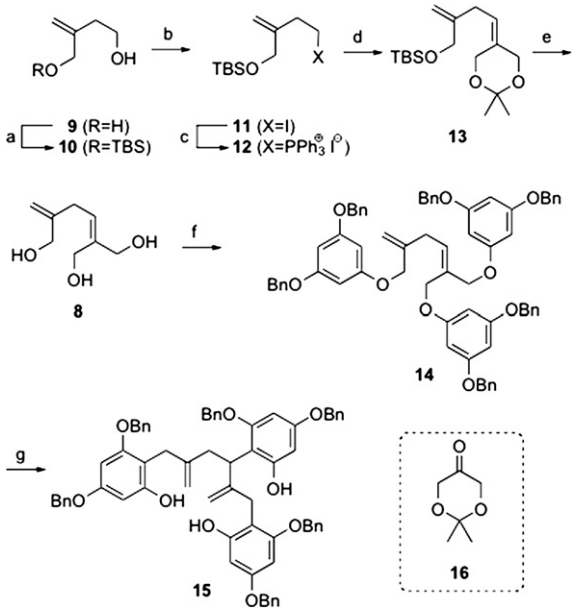


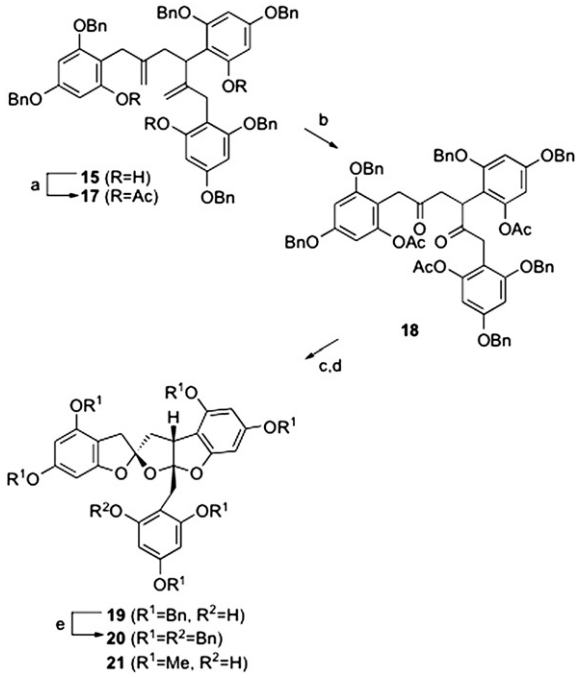
Scheme 1. Retrosynthetic analysis: P=protecting group.

The precursor **6** for the Claisen rearrangement was prepared from known **9**,[5] **16**[6,7] and phlorogulcinol dibenzyl ether [**7** (P=Bn)][8] in six steps almost in the same manner described previously by us except for the protecting groups in **7** (benzyl ethers instead of methyl ethers) as shown in Scheme 2.[4] In the Mitsunobu reaction (**8**–**14**), intramoleculary alkylated by-product, which was similar to the methyl protected compound described in our previous paper,[4] was also obtained (23%). The key step, single and cascade Claisen rearrangements, was then examined. As reported previously,[4] when the phenolic hydroxy groups of the substrate were protected as methyl ethers, the rearrangements were accelerated successfully only by aqueous Me_3Al[9] in refluxing CH_2Cl_2 and other thermal or Lewis acidic conditions resulted in failure. However, the same successful conditions were not fully applicable to benzylated precursor **14** due to the decomposition of the rearranged product, which decreased the yield to 35%. After several investigations, it was found that Me_3Al in the absence of water catalyzed the reaction more effectively even at room temperature and the product **15** was obtained in excellent yield (84%).

After the successful key step, the core framework of lysidicin A (**1**), spiro[furan-furofuran] ring system, was constructed (Scheme 3). Three phenolic hydroxy groups of **7** were temporarily acetylated, and the product **17** was submitted to ozonolysis to give desired diketone **18** in good yield. Removal of acetyl groups of **18** and subsequent acid treatment afforded the spiro[furan-furofuran] **19** successfully. ^{1}H NMR spectral data of the product **19** showed good accordance with those of our previously synthesized compound **21** whose stereostructure has been clarified unambiguously by X-ray crystallographic analysis.[4] The remaining phenolic hydroxy group of **19** was then protected to afford benzyl ether **20**.

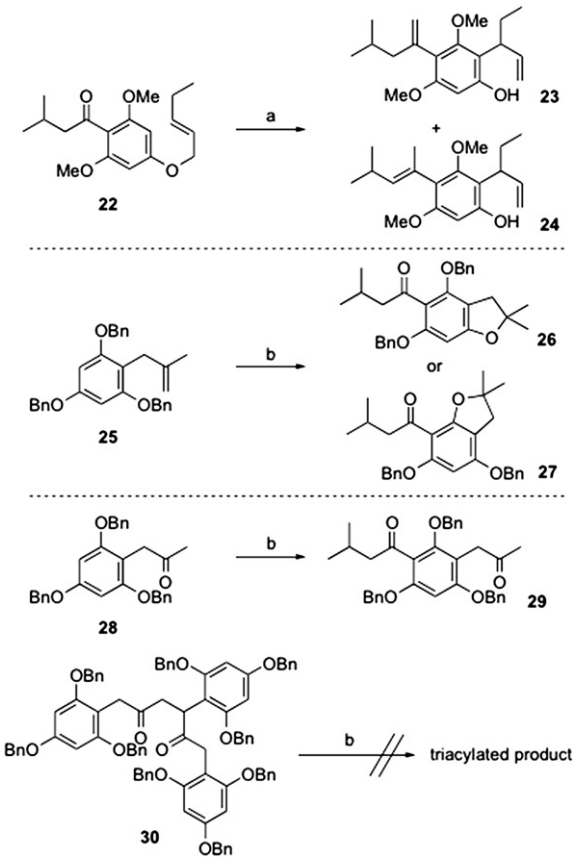


Scheme 2. Preparation of **15**: reagents and conditions; (a) TBSCl, NaH, THF, −10 °C, 43%. (b) I_2, Imid., PPh_3, THF, rt. (c) PPh_3, CH_3CN, reflux. (d) *n*-BuLi, DME, then **16**, −78 to 0 °C, 83% in three steps. (e) AcOH/H_2O/THF=1:1:1, rt, 84%. (f) **7** (P=Bn), DEAD, PPh_3, THF, 0 °C to rt, 50%. (g) Me_3Al, CH_2Cl_2, 0 °C to rt, 84%.

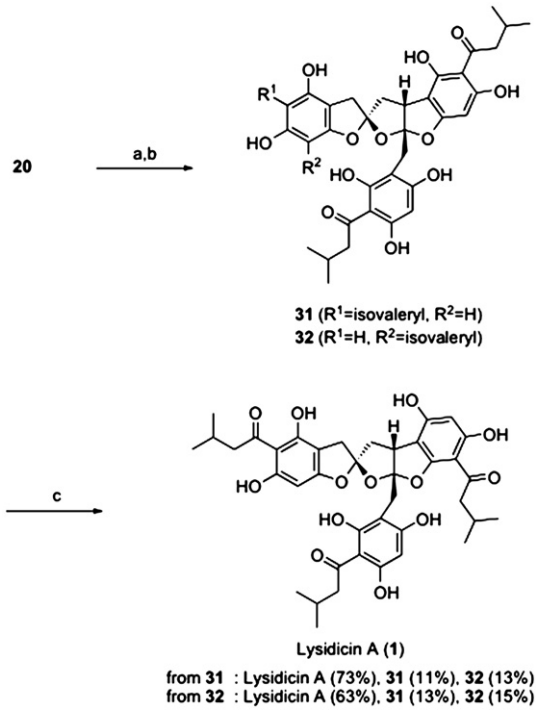


Scheme 3. Preparation of spiro[furan-furofuran] **20**: reagents and conditions; (a) Ac_2O, NaH, THF, 0 °C, 92%. (b) O_3, CH_2Cl_2, −78 °C, then PPh_3, 83%. (c) K_2CO_3, MeOH, 0 °C. (d) TsOH, CH_2Cl_2, 0 °C to rt, 81% in two steps. (e) BnBr, NaH, DMF, 0 °C, 97%.

As described in the retrosynthetic analysis part, we planned to introduce the isovaleryl groups at the final stage of the synthesis. It should be noted that the acylation at the earlier stage gave the unsuccessful results as summarized in Scheme 4. When the model compound **22** with the isovaleryl group was subjected to Claisen rearrangement, the ketone reacted with Me_3Al and dehydrated products **23** and **24** were obtained. Friedel–Crafts acylation of **25** also caused an undesired benzofuran formation as well as the acylation to give **26** or **27** (regiochemistry was not determined). On the other hand, **28** with a partial substructure of **30** afforded the acylated product in good yield. However, **30** itself could not be triacylated probably due to the structural complexity.



Scheme 4. Summary unsuccessful results: reagents and conditions; (a) Me_3Al, H_2O, CH_2Cl_2, reflux, 42%, (**23**/**24**=1:1), (b) isovaleryl chloride, AgOTf, CH_2Cl_2, −78 °C to rt, 38% for **26** or **27**, 90% for **29**.



Scheme 5. Synthesis of lysidicin A: reagents and conditions; (a) isovaleryl chloride, AgOTf, CH_2Cl_2, −78 °C. (b) H_2, $Pd(OH)_2$, EtOH/AcOEt=2:1, 27% of **31**, 35% of **32**. (c) TsOH, CH_2Cl_2/ether=5:1, 73% of lysidicin A (**1**), 11% of **31**, 13% of **32**.

For the completion of the total synthesis of lysidicin A, Friedel–Crafts acylation of **20** was examined (Scheme 5). To our delight, when isovaleryl chloride was activated with AgOTf,[10] the reaction proceeded smoothly to give a mixture of regioisomers, which were difficult to be isolated. The mixture was therefore subjected to hydrogenolysis and the product was separated to afford **31** and **32** in 27% and 35% yields (in two steps), respectively, whose regiochemistries were confirmed by HMBC measurement. Both **31** and **32** were regioisomeric compounds of lysidicin A, they were separately subjected to acid catalyzed isomerization of the acetalic spiro[furan-furofuran] ring system and total synthesis of (±)-lysidicin A (**1**) have been accomplished.

In conclusion, we have achieved the first total synthesis of (±)-lysidicin A effectively via single and cascade Claisen rearrangements and Friedel–Crafts acylation using AgOTf. The overall yield was 3.5% in 15 steps from known diol **9**. This approach would provide an efficient synthetic way for analogous compounds.

3. Experimental

3.1. General

Dry THF and DME were freshly prepared by distillation from benzophenone ketyl and dry CH_2Cl_2 was freshly prepared by distillation from P_2O_5 before use. Melting points were measured with a Yanaco micro-melting point apparatus and are uncorrected values. IR spectra were measured with a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR were recorded on JEOL JNM AL300 or JEOL JNM GSX500. Chemical shifts (δ) were referenced to the residual solvent peaks as the internal standard ($CDCl_3$: δ_H=7.26, δ_C=77.23; DMSO-d_6: δ_H=2.49, δ_C=39.5, benzene-d_6: δ_H=7.15, CD_3CN: δ_H=1.93, δ_C=1.39, CD_3NO_2: δ_C=60.5). Refractive indexes were measured with an Atago 1T refractometer. Mass spectra were recorded on JEOL JMS SX102. Column chromatography was performed using Kanto silica gel 60N (0.060–0.200 mm). TLC was carried out on Merck glass plates precoated with silica gel 60 F_{254} (0.25 mm).

3.2. Synthetic studies

*3.2.1. 4-(tert-Butyldimethylsilyloxy)-3-methylenebutan-1-ol (**10**).* To a suspension of sodium hydride (60% in mineral oil, 2.17 g, 54.3 mmol) in THF (70 ml) was added diol **9** (5.04 g, 49.4 mmol) in THF (20 ml) at −78 °C under argon atmosphere. After the reaction mixture was warmed up to −40 °C over 1 h with stirring, TBSCl (7.81 g, 51.8 mmol) was added. After stirring for 45 min, the reaction mixture was poured into 10% aqueous solution of K_2CO_3, and extracted three times with ether. The organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with hexanes/EtOAc (8:1) gave silyloxy alcohol **10** (4.68 g, 44%) as colorless oil. n_D=1.4505. IR (film): ν=3352, 2931, 2857, 1471, 1254, 1082, 836, 776 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.08 (6H, s), 0.90 (9H, s), 2.32 (2H, t, J=6.0 Hz), 2.39 (1H, br s), 3.70 (2H, t, J=6.0 Hz), 4.09 (2H, s), 4.93 (1H, s), 5.10 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.21, 18.51, 26.06, 37.12, 61.61, 66.66, 113.01, 145.76. ESI-TOFMS m/z calcd for $C_{11}H_{24}NaO_2Si$ $[M+Na]^+$ 239.1438, found 239.1414.

*3.2.2. 2-[(tert-Butyldimethylsilyloxy)methyl]-4-iodo-but-1-ene (**11**).* To a solution of alcohol **10** (5.00 g, 23.1 mmol) in THF (200 ml) were added imidazole (3.93 g, 57.8 mmol), triphenylphosphine (7.27 g, 27.7 mmol), and iodine (7.62 g, 30.0 mmol) at 0 °C under argon atmosphere. After the reaction mixture was warmed up to room temperature over 30 min with stirring, hexanes (200 ml) was added to the reaction mixture and filtered through a pad of Celite. The filtrate was concentrated in vacuo and the residue was filtered

through a short pad of silica gel (hexanes/EtOAc=10:1). Crude iodide **11** was used for the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.07 (6H, s), 0.91 (9H, s), 2.61 (2H, t, J=7.8 Hz), 3.26 (2H, t, J=7.8 Hz), 4.09 (2H, s), 4.89 (1H, s), 5.12 (1H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.17, 3.64, 18.52, 26.09, 37.50, 65.67, 111.40, 147.26.

*3.2.3. 2,2-Dimethyl-5-{3-[(tert-butyldimethylsilyloxy)methyl]but-3-ene-1-ylidene}-1,3-dioxan (**13**).* To a solution of iodide **11** (3.14 g, 9.62 mmol) in acetonitrile (50 ml) was added triphenylphosphine (2.52 g, 9.62 mmol) at room temperature under argon atmosphere. The reaction mixture was refluxed overnight and concentrated in vacuo. After washing with benzene and ether, the residue was pumped up overnight to give a phosphonium salt **12**. Crude phosphonium salt **12** was used for next reaction without further purification. To a suspension of crude phosphonium salt in dry DME (43 ml) was added *n*-BuLi in hexane (1.59 M, 6.1 ml, 9.30 mmol) slowly at −78 °C under argon atmosphere. After the reaction mixture was warmed up to −40 °C over 1 h with stirring, a solution of ketone **16** (1.21 g, 9.30 mmol) in dry DME (10 ml) was added dropwise at −78 °C. The reaction mixture was warmed up to 0 °C and stirred for 1 h at the same temperature and poured into solution of saturated aqueous $NaHCO_3$. The mixture was extracted three times with ether and the organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with hexanes/EtOAc (10:1) gave dioxan **13** (2.52 g, 83%) as a colorless oil. n_D=1.4658. IR (film): ν=2955, 2855, 1471, 1370, 1222, 1088, 835, 776 cm^{-1}. ^{1}H NMR (300 MHz, C_6D_6): δ=0.04 (6H, s), 0.96 (9H, s), 1.38 (6H, s), 2.51 (2H, d, J=4.5 Hz), 3.95 (2H, s), 4.12 (2H, s), 4.32 (2H, s), 4.82 (1H, br s), 5.06 (1H, m), 5.11 (1H, br s). ^{13}C NMR (125 MHz, C_6D_6): δ=−5.29, 18.46, 24.27, 26.03, 30.21, 59.69, 64.24, 65.94, 99.15, 109.83, 119.36, 135.27, 147.12. ESI-TOFMS m/z calcd for $C_{17}H_{32}NaO_3Si$ [M+Na]$^+$ 335.2013, found 335.2017.

*3.2.4. 2-(Hydroxymethyl)-5-methylenehex-2-ene-1,6-diol (**8**).* Dioxan **13** (905 mg, 2.90 mmol) was dissolved in a mixed solvent (THF/H_2O/AcOH=1:1:1, 15 ml) at room temperature and stirred overnight at the same temperature. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with hexanes/EtOAc (1:1) to $CHCl_3$/MeOH (10:1) gave triol **8** (385 mg, 84%) as a colorless oil. n_D=1.5151. IR (film): ν=3319, 2873, 1652, 1429, 1223, 1011, 902 cm^{-1}. ^{1}H NMR (300 MHz, CD_3CN): δ=2.46 (2H, d, J=7.8 Hz), 2.66 (1H, t, J=6.0 Hz), 2.72 (1H, t, J=6.0 Hz), 2.82 (1H, t, J=6.0 Hz), 3.56 (2H, d, J=6.0 Hz), 3.64 (2H, d, J=6.0 Hz), 3.71 (2H, d, J=6.0 Hz), 4.44 (1H, s), 4.58 (1H, s), 5.13 (1H, t, J=7.8 Hz). ^{13}C NMR (125 MHz, CD_3CN): δ=31.94, 58.92, 65.67, 66.06, 110.32, 126.31, 141.60, 149.93. ESI-TOFMS m/z calcd for $C_8H_{14}NaO_3$ [M+Na]$^+$ 181.0835, found 181.0870.

*3.2.5. 6-(3,5-Dibenzyloxyphenoxy)-2,5-bis[(3,5-dibenzyloxyphenoxy)methyl]hexa-1,4-diene (**14**).* To a solution of triol **8** (500 mg, 3.16 mmol), triphenylphosphine (4.15 g, 15.8 mmol), and phloroglucinol dibenzyl ether (**7**) (4.84 g, 15.8 mmol) in dry THF (15 ml) was added diethyl azodicarboxylate in toluene (2.2 M, 7.20 ml, 15.8 mmol) at 0 °C under argon atmosphere and stirred overnight at room temperature. The reaction mixture was poured into water and extracted three times with ether. The organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with benzene/hexanes (1:1) to benzene gave triether **14** (1.62 g, 50%) as a colorless gum. IR (film): ν=3031, 1597, 1452, 1375, 1151, 1058, 736, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.04 (2H, d, J=7.5 Hz), 4.41 (2H, s), 4.60 (4H, s), 4.85–5.00 (12H, m), 5.04 (1H, s), 5.17 (1H, s), 5.93 (1H, t, J=7.5 Hz), 6.18–6.28 (9H, m), 7.22–7.46 (30H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ=31.66, 63.67, 70.24, 70.86, 94.92, 95.14, 114.23, 127.76, 128.16, 128.75, 130.57, 132.98, 137.00, 142.70, 160.62, 160.68, 160.79. ESI-TOFMS m/z calcd for $C_{68}H_{62}NaO_9$ [M+Na]$^+$ 1045.4286, found 1045.4283.

*3.2.6. 3,5-Dibenzyloxy-2-[3-(4,6-dibenzyloxy-2-hydroxyphenyl)-5-{(4,6-dibenzyloxy-2-hydroxyphenyl)methyl}-2-methylenehex-5-enyl]phenol (**15**).* To a solution of trimethylaluminium (1.08 M in hexane, 40.7 ml, 44 mmol) in dry CH_2Cl_2 (270 ml) was added triether **14** (5.45 g, 5.33 mmol) in dry CH_2Cl_2 (20 ml) by cannula at 0 °C under argon atmosphere. After stirring for 3 h, MeOH (50 ml) was added slowly at the same temperature and the reaction mixture was warmed up to room temperature. Saturated aqueous Rochelle salt (500 ml) was added and the reaction mixture was stirred overnight. After extraction three times with CH_2Cl_2, the organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with benzene/ether (20:1) gave rearranged product **15** (4.61 g, 84%) as a colorless gum. IR (film): ν=3432, 3031, 1617, 1498, 1437, 1146, 1074, 736, 696 cm^{-1}. ^{1}H NMR (500 MHz, C_6D_6): δ=2.80 (1H, dd, J=6.0, 13.5 Hz), 2.92 (1H, dd, J=10.0, 13.5 Hz), 3.51 (1H, d, J=17.0 Hz), 3.56 (1H, d, J=17.0 Hz), 3.61 (1H, d, J=17.0 Hz), 3.74 (1H, d, J=17.0 Hz), 4.61–4.73 (11H, m), 4.79 (1H, br s), 4.80 (1H, br s), 4.83 (1H, d, J=11.5 Hz), 5.08 (1H, br s), 5.14 (1H, br s), 5.31 (1H, br s). 5.65 (1H, br s), 6.15 (1H, br), 6.16 (1H, br d, J=1.5 Hz), 6.19 (1H, br d, J=1.5 Hz), 6.27 (1H, d, J=2.0 Hz), 6.29 (1H, d, J=2.0 Hz), 6.33 (1H, d, J=2.5 Hz), 6.38 (1H, d, J=2.5 Hz), 7.01–7.29 (30H, m). ^{13}C NMR (125 MHz, CD_3CN, at 70 °C): δ=30.64, 30.94, 39.53, 40.54, 94.25, 95.41, 97.13, 97.19, 97.81, 109.72, 109.81, 109.95, 111.06, 112.72, 128.90, 129.03, 129.21, 129.31, 129.51, 130.06, 130.18, 139.34, 139.47, 148.97, 152.52, 158.00, 158.71, 160.09, 160.29, 160.38, 160.56. ESI-TOFMS m/z calcd for $C_{68}H_{62}NaO_9$ [M+Na]$^+$ 1045.4286, found 1045.4305.

*3.2.7. 2-[3-(2-Acetoxy-4,6-dibenzyloxy-phenyl)-5-{(2-acetoxy-4,6-dibenzyloxy-phenyl)methyl}-3,5-dibenzyloxy-2-methylenehex-5-enyl]phenyl acetate (**17**).* To a suspension of sodium hydride (55% in mineral oil, 1.04 g, 23.9 mmol) in DMF (150 ml) was added rearranged product **15** (7.40 g, 7.24 mmol) in DMF (30 ml) at 0 °C under argon atmosphere. After stirring for 5 min, Ac_2O (2.33 ml, 24.6 mmol) was added slowly at the same temperature and the reaction mixture was stirred more over 30 min. Saturated aqueous $NaHCO_3$ (10 ml) was added and the reaction mixture was poured into water (1000 ml). After extraction three times with ether, the organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with benzene/ether (20:1) gave triacetate **17** (7.65 g, 92%) as a colorless gum. IR (film): ν=3031, 1763, 1617, 1586, 1497, 1209, 1141, 1071, 735, 696 cm^{-1}. ^{1}H NMR (300 MHz, CD_3CN, at 70 °C): δ=1.98 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 2.66 (1H, br dd, J=7.2, 15.0 Hz), 2.72 (1H, br dd, J=6.9, 15.0 Hz), 3.05 (1H, br d, J=16.5 Hz), 3.09 (1H, br d, J=16.5 Hz), 3.14 (1H, br d, J=15.9 Hz), 3.17 (1H, br d, J=15.9 Hz), 4.22 (1H, br), 4.36 (1H, br s), 4.38 (1H, br s), 4.61 (1H, br s), 4.77 (1H, br s), 4.90–5.03 (12H, m), 6.32 (1H, d, J=2.4 Hz), 6.34 (1H, d, J=2.4 Hz), 6.35 (1H, d, J=2.4 Hz), 6.49 (1H, d, J=2.4 Hz), 6.50 (1H, d, J=2.4 Hz), 6.51 (1H, d, J=2.4 Hz), 7.21–7.42 (30H, m). ^{13}C NMR (125 MHz, CD_3NO_2, at 90 °C): δ=18.82, 18.91, 19.15, 28.97, 29.72, 37.34, 38.59, 69.59, 69.71, 69.81, 69.99, 97.85, 97.94, 97.94, 100.91, 101.08, 101.71, 107.65, 108.93, 113.99, 114.11, 116.44, 126.49, 126.64, 126.91, 127.18, 127.66, 127.74, 136.71, 136.77, 146.00, 147.80, 150.27, 150.37, 150.43, 157.50, 157.59, 157.65, 157.70, 157.81, 158.22, 168.31, 168.50, 168.58. ESI-TOFMS m/z calcd for $C_{74}H_{68}NaO_{12}$ [M+Na]$^+$ 1171.4603, found 1171.4645.

*3.2.8. 1,4,6-Tris(2-acetoxy-4,6-dibenzyloxyphenyl)hexan-2,5-dione (**18**).* Into a solution of triacetate **17** (7.64 g, 6.51 mmol) in CH_2Cl_2 (300 ml) was bubbled O_3 gas at −78 °C until starting material

disappeared on TLC analysis. Triphenylphosphine (4.75 g, 18.1 mmol) was added to the reaction mixture at same temperature and was warmed up to room temperature overnight. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with benzene/ether (20:1) gave diketone **18** (6.35 g, 83%) as a pale yellow amorphous solid. IR (KBr): ν=3031, 1768, 1716, 1617, 1498, 1371, 1206, 1144, 1072, 737, 697 cm^{-1}. ^1H NMR (300 MHz, CD_3CN, at 70 °C): δ=2.04 (3H, s), 2.05 (3H, s), 2.12 (3H, s), 2.22 (1H, dd, J=4.2, 17.4 Hz), 3.30 (1H, d, J=17.4 Hz), 3.36 (1H, dd, J=5.7, 17.4 Hz), 3.49 (1H, d, J=17.4 Hz), 3.51 (1H, d, J=18.0 Hz), 3.58 (1H, d, J=18.0 Hz), 4.54 (1H, br), 4.89–5.08 (12H, m), 6.34 (1H, d, J=2.1 Hz), 6.36 (1H, d, J=2.1 Hz), 6.40 (1H, d, J=2.7 Hz), 6.43 (1H, d, J=2.7 Hz), 6.49 (1H, d, J=2.4 Hz), 6.54 (1H, d, J=2.4 Hz), 7.26–7.42 (30H, m). ^{13}C NMR (125 MHz, CD_3CN, at 70 °C): δ=21.63, 37.36, 39.67, 42.86, 44.94, 71.93, 71.98, 72.16, 72.28, 99.85, 100.22, 100.32, 103.04, 103.38, 103.65, 111.82, 111.94, 115.32, 128.91, 128.97, 129.03, 129.44, 129.68, 129.76, 130.22, 138.74, 138.78, 138.88, 152.38, 152.71, 159.60, 159.78, 159.88, 160.49, 160.59, 160.93, 170.32, 170.49, 170.63, 206.86, 207.02. ESI-TOFMS m/z calcd for $C_{72}H_{64}NaO_{14}$ $[M+Na]^+$ 1175.4188, found 1175.4206.

3.2.9. (2R,3aR*,8aR*)-8a′-{(4,6-Dibenzyloxy-2-hydroxy-phenyl) methyl}-4,4′,6,6′-tetrabenzyloxy-3a′, 8a′-dihydro-3H,3′H-spiro[1-benzofuran-2,2′-furo[2,3-b][1]benzofuran] (**19**).* To a solution of diketone **18** (1.45 g, 1.26 mmol) in a mixed solvent (MeOH/CH_2Cl_2=1:1, 140 ml) was added anhydrous K_2CO_3 (1.74 g, 12.6 mmol) at 0 °C under argon atmosphere. After stirring for 45 min, the reaction mixture was poured into saturated aqueous NH_4Cl (300 ml) and small amount of 3 N HCl was added to adjust the pH at 7. After extraction three times with CH_2Cl_2, the organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. Organic layer was concentrated in vacuo and crude triphenol was used for next reaction without further purification. To a solution of crude triphenol (1.26 g, 1.23 mmol) in dry CH_2Cl_2 (300 ml) was added *p*-touenesulfonic acid monohydrate (235 mg, 1.23 mmol) at 0 °C under argon atmosphere. After stirring for 3 h at same temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (300 ml). After extraction three times with CH_2Cl_2, the organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. Organic layer was concentrated in vacuo, the residue was chromatographed over silica gel. Elution with benzene/hexanes (5:1) gave furofuran **19** (1.03 g, 81%) as colorless amorphous solid. IR (KBr): ν=3420, 3030, 1624, 1500, 1454, 1149, 1098, 1027, 736, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.98 (1H, dd, 9.0, J=13.5 Hz), 2.57 (1H, d, J=13.5 Hz), 3.02 (1H, d, J=16.5 Hz), 3.20 (1H, d, J=16.5 Hz), 3.23 (1H, d, J=14.7 Hz), 3.38 (1H, d, J=14.7 Hz), 4.02 (1H, d, J=9.0 Hz), 4.79–4.98 (12H, m), 5.87 (1H, d, J=2.1 Hz), 6.06 (1H, d, J=2.1 Hz), 6.16 (3H, s), 6.20 (1H, d, J=2.1 Hz), 7.05 (1H, br s), 7.08–7.39 (30H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ=31.32, 37.01, 41.98, 45.45, 69.99, 70.23, 70.28, 70.42, 70.60, 89.98, 90.48, 93.72, 93.95, 94.08, 94.22, 96.22, 102.94, 104.79, 109.00, 120.23, 124.28, 127.41, 127.51, 127.63, 127.81, 127.89, 128.14, 128.23, 128.56,128.75, 137.10, 155.48, 155.57, 157.63, 158.37, 159.37, 159.79, 160.87, 161.16. ESI-TOFMS m/z calcd for $C_{66}H_{56}NaO_{10}$ $[M+Na]^+$ 1031.3766, found 1031.3728.

3.2.10. (2R,3aR*,8aR*)-8a′-[(2,4,6-Tribenzyloxyphenyl)methyl]-4,4′,6,6′-tetrabenzyloxy-3a′, 8a′-dihydro-3H,3′H-spiro[1-benzofuran-2,2′-furo[2,3-b][1]benzofuran] (**20**).* To a suspension of sodium hydride (55% in mineral oil, 38 mg, 0.89 mmol) in DMF (20 ml) was added furofuran **19** (600 mg, 0.59 mmol) in DMF (10 ml) at 0 °C under argon atmosphere. After stirring for 5 min, benzyl bromide (105 ml, 0.89 mmol) was added at same temperature and the reaction mixture was stirred for further 30 min. Saturated aqueous $NaHCO_3$ (10 ml) was added and the reaction mixture was poured into water (300 ml). After extraction three times with ether, the organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with benzene/hexanes (5:1) gave **20** (633 mg, 97%) as a colorless amorphous solid. IR (KBr): ν=3031, 1607, 1504, 1437, 1375, 1150, 736, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.95 (1H, dd, J=8.7, 13.5 Hz), 2.61 (1H, d, J=13.5 Hz), 2.90 (1H, d, J=16.5 Hz), 3.08 (1H, d, J=16.5 Hz), 3.43 (1H, d, J=13.5 Hz), 3.52 (1H, d, J=13.5 Hz), 4.22 (1H, d, J=8.7 Hz), 4.82–5.06 (14H, m), 5.96 (1H, d, J=2.1 Hz), 6.08 (1H, d, J=2.1 Hz), 6.18 (2H, s), 6.26 (2H, s), 7.19–7.46 (35H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ=30.79, 37.20, 41.91, 45.81, 69.86, 70.02, 70.39, 70.51, 70.60, 90.03, 90.17, 90.55, 93.13, 93.26, 93.58, 105.32, 105.79, 109.57, 119.97, 124.46, 127.35, 127.50, 127.56, 127.81, 128.00, 128.09, 128.28, 128.69, 136.98, 137.20, 137.26, 155.37, 155.51, 159.12, 159.37, 160.17, 160.57, 160.85. ESI-TOFMS m/z calcd for $C_{73}H_{62}NaO_{10}$ $[M+Na]^+$ 1121.4235, found 1121.4282.

3.2.11. (2R,3aR*,8aR*)-8a′-[{2,4,6-Trihyroxy-3-(3′-methyl)butanoyl-phenyl}methyl]-5,5′-di-(3′-methyl)butanoyl-3a′,8a′-dihydro-3H,3′H-spiro[1-benzofuran-2,2′-furo[2,3-b][1]benzofuran]-4,4′,6,6′-tetraol (**31**), (2R*,3aR*,8aR*)-8a′-{[2,4,6-trihyroxy-3-(3′-methyl)butanoyl-phenyl]methyl}-7,5′-di-(3′-methyl)butanoyl-3a′,8a′-dihydro-3H,3′H-spiro[1-benzofuran-2,2′-furo[2,3-b][1]benzofuran]-4,4′,6,6′-tetraol (**32**).* To a solution of furofuran **20** (116 mg, 0.10 mmol) and AgOTf (147 mg, 0.57 mmol) in dry CH_2Cl_2 (5.8 ml) was added isovaleryl chloride (39.9 ml, 0.31 mmol) at −78 °C under argon atmosphere. After stirring for 2 h, isovaleryl chloride (26.6 ml, 0.21 mmol) at the same temperature and reaction mixture was stirred further 2 h. After addition of AgOTf (26 mg, 0.10 mmol) and isovaleryl chloride (13.3 ml, 0.10 mmol), the reaction mixture was stirred further 1 h at same temperature and poured into saturated aqueous $NaHCO_3$ (30 ml). After extraction three times with CH_2Cl_2, the organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. Organic layer was concentrated in vacuo and the residue was short chromatographed over silica gel. Elution with benzene/ether (20:1) gave mixture of triacylated compounds (156 mg). The mixture was used for next reaction without further purification. To a solution of mixture of triacylated compounds (156 mg) in mixed solvent (EtOH/AcOEt=2:1, 15 ml) was added $Pd(OH)_2/C$ (50 mg) at room temperature under hydrogen atmosphere. After stirring for 5 h at same temperature, the reaction mixture was filtered through a pad of Celite. After concentration in vacuo, the residue was chromatographed over silica gel. Elution with hexanes/EtOAc (1:1) gave **31** (18 mg, 27%) and the regioisomer **32** (22 mg, 35%) as yellow powder. Compound **31**: IR (KBr): ν=3379, 2924, 1622, 1440, 1369, 1303, 1242, 1159, 1119, 817 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=0.55 (3H, d, J=6.6 Hz), 0.64 (3H, d, J=6.6 Hz), 0.88–0.92 (12H, m), 1.726 (1H, m), 1.85 (1H, dd, J=7.5, 15 Hz), 2.09–2.20(2H, m), 2.21(1H, dd, J=9.3, 13.8 Hz), 2.44 (1H, dd, J=5.4, 15 Hz), 2.60 (1H, d, J=13.8 Hz), 2.76–2.96 (5H, m), 3.01 (1H, d, J=16.2 Hz), 3.05 (1H, d, J=13.8 Hz), 3.17 (1H, d, J=13.8 Hz), 4.20 (1H, d, J=9.3 Hz), 5.83 (1H, s), 5.87 (1H, s), 6.01 (1H, s), 10.49 (1H, s), 10.70 (1H, s), 10.75 (1H, s), 11.32 (1H, s), 12.99 (1H, s), 13.65 (1H, s), 14.34 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ=21.81, 21.94, 22.63, 22.69, 24.42, 24.94, 25.21, 29.63, 35.32, 40.44, 44.50, 49.21, 52.00, 52.14, 89.22, 94.12, 95.78, 99.40, 100.98, 102.71, 103.62, 105.37, 105.73, 120.71, 124.71, 159.93, 160.15, 160.27, 160.94, 163.46, 163.76, 164.01, 164.08, 164.79, 203.76, 205.05, 205.43. ESI-TOFMS m/z calcd for $C_{39}H_{44}NaO_{13}$ $[M+Na]^+$ 743.2674, found 743.2696. Compound **32**: IR (KBr): ν=3353, 2925, 1622, 1436, 1303, 1241, 1211, 1157, 1117, 822 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=0.87–0.97 (18H, m), 2.05–2.20 (4H, m), 2.47 (1H, d, J=9.9 Hz), 2.81–2.92 (7H, m), 3.02 (1H, d, J=16.5 Hz), 3.05 (1H, d, J=13.5 Hz), 3.16 (1H, d, J=13.5 Hz), 4.16 (1H, d, J=9.0 Hz), 5.58 (1H, s), 5.88 (1H, s), 6.01 (1H, s), 10.48 (1H, s), 10.74 (1H, s), 11.34 (1H, s), 11.36 (1H, s), 13.29 (1H, s), 13.48 (1H, s), 14.34 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ=22.64, 24.67,

24.89, 24.93, 29.03, 35.15, 40.62, 44.32, 52.00, 52.14, 89.28, 89.51, 94.10, 94.44, 101.88, 103.59, 104.99, 105.05, 106.05, 120.58, 124.54, 159.17, 159.66, 160.89, 163.32, 163.45, 163.54, 163.81, 164.22, 164.78, 205.04, 205.52, 205.57. ESI-TOFMS *m*/*z* calcd for $C_{39}H_{44}NaO_{13}$ $[M+Na]^+$ 743.2674, found 743.2690.

3.2.12. (2R,3aR*,8aR*)-8a′-{[2,4,6-Trihyroxy-3-(3′-methyl)butanoylphenyl]methyl}-5,7′-di-(3′-methyl)butanoyl-3a′,8a′-dihydro-3H,3′H-spiro[1-benzofuran-2,2′-furo[2,3-b][1]benzofuran]-4,4′,6,6′-tetraol (**1**) (lysidicin A).* To a solution of **31** (8 mg, 11.1 mmol) in mixed solvent (CH_2Cl_2/ether=5:1, 1.2 ml) was added *p*-touenesulfonic acid monohydrate (1 mg, 5.3 mmol) at 0 °C under argon atmosphere. After stirring for 2 h at same temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 ml). After extraction three times with ether, the organic layer was washed with water and brine and dried over anhydrous magnesium sulfate. Organic layer was concentrated in vacuo, the residue was chromatographed over silica gel. Elution with hexanes/EtOAc (1:1) gave lysidicin A (**1**) (5.8 mg, 73%), the regioisomer **31** (0.9 mg, 11%) and **32** (1.0 mg, 13%) as yellow powder. IR (KBr): ν=3262, 2925, 2853, 1707, 1621, 1509, 1433, 1369, 1307, 1165, 1009, 976, 823, 695 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ=0.55 (3H, d, *J*=7.0 Hz), 0.62 (3H, d, *J*=6.0 Hz), 0.79 (3H, d, *J*=6.5 Hz), 0.80 (3H, d, *J*=6.5 Hz), 0.89 (6H, d, *J*=6.5 Hz), 1.68–1.76 (2H, m), 1.96–2.04 (1H, m), 2.08–2.16(1H, m), 2.35–2.48(2H, m), 2.55(1H, dd, *J*=6.5, 15.5 Hz), 2.63 (1H, d, *J*=13.5 Hz), 2.86 (2H, d, *J*=7.0 Hz), 2.92 (1H, dd, *J*=6.5, 15.5 Hz), 2.95 (1H, d, *J*=16.5 Hz), 3.12 (1H, d, *J*=16.5 Hz), 3.15 (1H, d, *J*=13.5 Hz), 3.21 (1H, d, *J*=13.5 Hz), 4.17 (1H, d, *J*=9.5 Hz), 5.84 (1H, s), 5.85 (1H, s), 6.00 (1H, s), 10.49 (1H, s), 10.73 (1H, s), 10.81 (1H, s), 13.05 (1H, s), 13.27 (1H, s), 14.39 (1H, s). ^{13}C NMR (125 MHz, DMSO-d_6): δ=21.82, 22.02, 22.16, 22.61, 24.83, 24.86, 25.16, 29.94, 35.45, 40.70, 44.54, 48.92, 50.42, 51.97, 94.10, 95.76, 96.09, 99.63, 100.37, 100.92, 102.70, 103.62, 106.31, 120.59, 124.10, 159.85, 160.23, 160.34, 160.50, 160.81, 163.29, 164.09, 164.81, 164.96, 203.54, 203.60, 204.99. ESI-TOFMS *m*/*z* calcd for $C_{39}H_{44}NaO_{13}$ $[M+Na]^+$ 743.2674, found 743.2690.

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