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Total synthesis of the proposed structure of pestalotioprolide A

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ABSTRACT

A chiron approach to the synthesis of the proposed structure of pestalotioprolide A, a 14-membered unsaturated macrolide isolated from the mangrove-derived fungus *Pestalotiopsis* sp. PSU-MA119, starting from D-(+)-gluconic acid δ-lactone is described. The key strategies to assemble the macrolactone include Yamaguchi esterification and ring-closing metathesis.

1. Introduction

The 14-membered macrolides are an important class of fungal polyketide metabolites that possess diverse biological and pharmacological profiles, in particular, antibiotic activity.[1] Pestalotioprolide A **1** is a new 14-membered macrolide isolated along with the previously reported seiricuprolide **2** from the mangrove-derived fungus *Pestalotiopsis* sp. PSU-MA119 by Rukachaisirikul et al. (Fig. 1).[2] Structurally, **1** is an (*E*)-α,β-unsaturated macrolactone containing four contiguous hydroxyl groups and a (*Z*)-double bond, hence a dihydroxy analog of **2**. Based on the ^{1}H NMR coupling constants and the observed specific rotations of its acetate derivatives, the relative and absolute configurations of **1** were assigned to be identical to those of the (5*R*,6*R*)-bromohydrin derivative of **2**. In order to prove the stereochemistry of the natural product and due to the potential biological activities of this group of macrolides, we set out a synthetic program for such compounds. Herein we report the total synthesis of the proposed structure of pestalotioprolide A by a chiron approach.

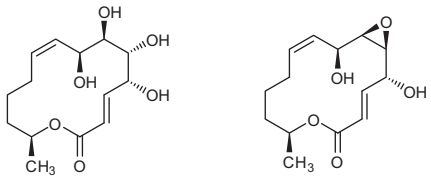

Figure 1. Structures of pestalotioprolide A **1** and seiricuprolide **2**.

The retrosynthetic approach of **1** is outlined in Scheme 1. Ring-closing metathesis (RCM) was envisioned to be the key macrocyclization strategy at C8–C9 (*Z*)-olefin. The RCM diene precursor **3** would be united by esterification of the two key fragments: (*S*)-hept-6-en-2-ol **4** and α,β-unsaturated acid **5**. The α,β-unsaturated acid moiety in **5** would then be constructed via a Wittig olefination of aldehyde **6**. The chiral allylic alcohol moiety of **6** would be accessible from chiral epoxide **7**. All stereogenic centers of **7** could be directly mapped onto D-(+)-gluconic acid δ-lactone **8**, a readily available chiral building block.

2. Results and discussion

The synthesis began with the preparation of chiral epoxide **7** from D-(+)-gluconic acid δ-lactone **8** via four high-yielding steps following the procedures reported by Murphy[3] and Ma.[4] Epoxide **7** was further elaborated into diol **11** via a 3-step sequence reported by Meshram.[5] Regioselective opening of **7** with sulfonium ylide (generated in situ by treatment of trimethylsulfonium iodide with *n*-BuLi) gave enantioenriched homoallylic alcohol **9** in excellent yield, which after protection with *tert*-butyldiphenylsilyl (TBDPS) group gave silyl ether **10** in 70% yield along with unreacted starting material. Selective deprotection of the terminal acetonide using $CuCl_2{\cdot}2H_2O$ in MeCN at 0 °C furnished the desired diol **11** in 61% yield (based on recovered starting bisacetonide). To achieve the requisite aldehyde **6**, diol **11** required selective oxidation of the primary alcohol moiety in the presence of a secondary alcohol. This was accomplished by selective protection of the primary alcohol with benzoyl chloride to give benzoate ester **12** in 73% yield, followed by conversion of the secondary alcohol into the corresponding *t*-butyldimethylsilyl (TBS) ether **13**. Subsequent removal of the benzoate employing DIBALH in CH_2Cl_2 at −78 °C yielded the desired primary alcohol **14** in 77% yield. Oxidation of **14** using (diacetoxy)iodobenzene ($PhI(OAc)_2$) in the presence of catalytic

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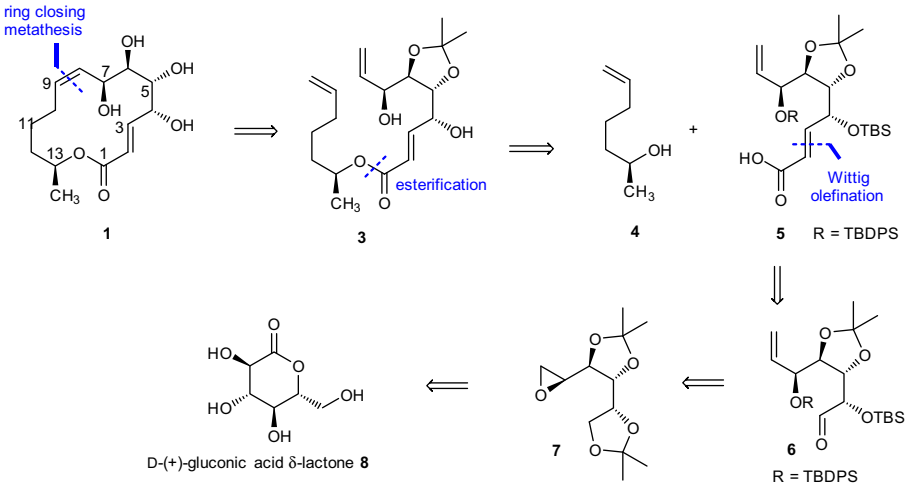
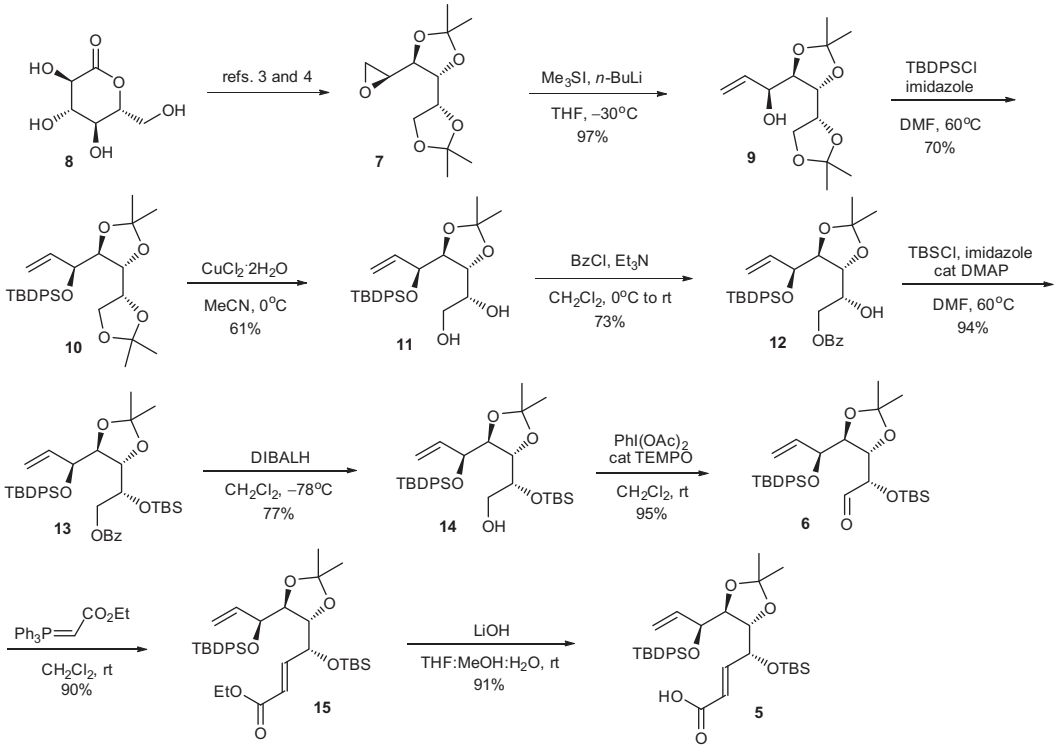
TEMPO in CH_2Cl_2 at room temperature gave aldehyde **6** in 95% yield. Further treatment of **6** with stabilized phosphonium ylide $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 at room temperature furnished (*E*)-α,β-unsaturated ester **15** in 90% yield. Finally, basic hydrolysis of the resultant ester using aqueous LiOH in THF/MeOH afforded the requisite α,β-unsaturated acid **5** in 91% yield (see Scheme 2).

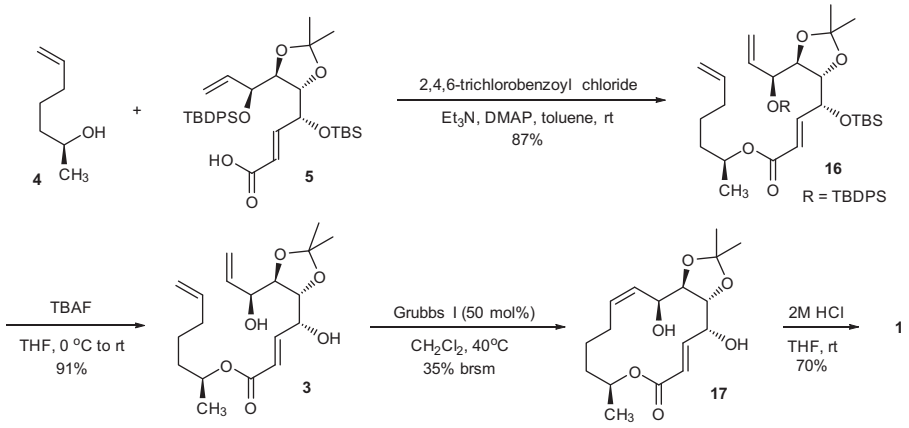
With the key acid **5** in hand, we proceeded to complete the synthesis of RCM diene precursor **3**. Coupling of carboxylic acid **5** and (*S*)-hept-6-en-2-ol **4**[6] was achieved under Yamaguchi conditions[7] to afford diene **16** in 87% yield. The stage was then set for the crucial ring-closing metathesis. RCM reactions to assemble large rings ($\geqslant$10 atoms) are challenging and not always predictable due to decreased ring strain and the probability of end-to-end encounters[8] and the limited number of examples on the synthesis of 14-membered non-aromatic macrolides by RCM are precedented.[9] Direct ring-closing metathesis of **16** using a second generation Grubbs (Grubbs II) catalyst was unsuccessful most likely due to the steric congestion of the TBDPS group.[10] Hence, both silyl protecting groups of **16** were removed with TBAF to give diol **3**. Exposure of **3** to the second generation Grubbs catalyst (10 mol %) in refluxing CH_2Cl_2 at a concentration of 3 mM led to the undesired (*E*)-isomer as the major product in a very low yield along with trace amounts of the (*Z*)-isomer and several other unidentified products. Lowering the reaction temperature or decreasing the reaction concentration did not improve the reaction outcome. Replacing the Grubbs II catalyst with the less reactive first generation Grubbs (Grubbs I) catalyst (20 mol %) in refluxing CH_2Cl_2 provided the macrocycle with the



Scheme 1. Retrosynthesis of pestalotioprolide A **1**.



Scheme 2. Synthesis of α,β-unsaturated acid **5**.



Scheme 3. Completion of the synthesis of **1**.

Table 1
Comparison of ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) data of natural product and synthetic **1**

Position	Natural product		Synthetic **1**	
	δ_H (mult., J in Hz)	δ_C	δ_H (mult., J in Hz)	δ_C
1		165.6		166.3
2	6.26 (d, 15.6)	125.6	6.19 (d, 15.6)	123.8
3	6.86 (dd, 15.6, 7.0)	143.0	6.86 (dd, 15.6, 3.6)	144.6
4	4.73 (m)	71.9	4.63 (m)	72.4
5	4.42 (m)	68.2	3.98 (m)	73.3
6	3.59 (dd, 7.2, 2.0)	73.8	3.40 (d, 7.8)	72.2
7	4.45 (m)	68.6	4.32 (d, 4.5)	69.3
8	5.57 (m)	129.0	5.57 (m)	129.8
9	5.47 (m)	133.0	5.45 (m)	132.1
10	a: 2.20 (m)	29.8	a: 2.16 (m)	29.7
	b: 1.95 (m)		b: 1.92 (m)	
11	a: 1.57 (m)	26.0	a: 1.57 (m)	26.3
	b: 1.11 (m)		b: 1.00 (m)	
12	a: 1.84 (m)	35.0	a: 1.79 (m)	35.5
	b: 1.49 (m)		b: 1.44 (m)	
13	5.02 (m)	73.2	5.01 (m)	72.9
14	1.30 (d, 6.3)	20.6	1.29 (d, 6.3)	20.8

requisite (*Z*)-alkene as the major product with a much cleaner but slower conversion. Increasing the catalyst loading to 50 mol % gave a higher conversion but led to other side products while the desired macrocycle **17** was obtained in a similar yield (35% based on recovered starting diene) to that of the reaction performed with 20 mol % of the catalyst. Removal of the acetonide protecting group with 2 M HCl in THF smoothly gave the desired target **1** in 70% yield (see Scheme 3).

Most of the ^{1}H and ^{13}C NMR data of synthetic **1** were in good agreement with those of the natural product although minor differences were noted (Table 1). One of the noticeable minor differences was the vicinal coupling constants between H-3 and H-4, which appeared to be 3.6 Hz in synthetic **1** and 7.0 Hz in the natural product. Literature precedents have shown that vicinal coupling constants between olefinic and adjacent oxymethine protons in some 14-membered unsaturated macrolactones or synthetic intermediates with similar structural and stereochemical motif can vary significantly (from 3 to 7 Hz) depending upon the stereochemical and conformational framework.[11] The major discrepancy, however, was the chemical shifts of oxymethine protons and carbons at the 5-position. For synthetic **1**, H-5 appeared as a multiplet at δ 4.03–3.93 ppm, whereas H-5 of the natural product was reported at δ 4.42 ppm as a multiplet. The ^{13}C chemical shifts at the 5-position also significantly differed: C-5 of synthetic **1** resonated at δ 73.3 ppm, while the same carbon of the natural products was reported at δ 68.2 ppm. This observation could result from the dissimilarity in the absolute configuration of the stereogenic center at C-5 of the synthetic sample and the natural product. Enhancement of signal intensity of H-5 upon irradiation of H-4 in the NOEDIFF experiment suggested that H-4 and H-5 occupied the same side of the molecule, hence supporting the configurations at C-4 and C-5 of synthetic **1**. Moreover, the *cis*-relationship between H-6 and H-7 was also confirmed by strong NOE correlations between those protons, which further supported the stereochemistry of synthetic **1**. However, NOE data were inadequate to conclusively assign the relative configurations between C-5 and C-6. In addition, the specific rotation of synthetic **1** was observed as −127.6 (*c* 0.15, $CHCl_3$), while $[\alpha]_D^{27}$ of the natural product was reported to be −18.1 (*c* 0.15, $CHCl_3$). Since the absolute stereochemistry of synthetic **1** was derived from D-(+)-gluconic acid δ-lactone and the stereochemical integrity should be retained during the synthesis, the structure of the synthetic sample was assigned as **1**. Further studies may be warranted for the determination of the absolute stereochemistry of the natural product.

3. Conclusion

In conclusion, the total synthesis of the proposed structure of pestalotioprolide A **1** has been accomplished in 13 steps in 3.3% overall yield from chiral epoxide **7** derived from a chiral building block D-(+)-gluconic acid δ-lactone. The key features of the synthesis include Yamaguchi esterification and ring-closing metathesis to construct the 14-membered unsaturated macrolactone. Our synthesis suggested that a stereochemical revision of the natural product would be warranted.

4. Experimental

4.1. General information

Unless otherwise stated, all reactions were performed under an argon atmosphere in an oven- or flamed-dried glassware. Solvents were used as received from suppliers or distilled prior to use using standard procedures. All other reagents were obtained from commercial sources and used without further purification. Column chromatography was performed on SiliaFlash® G60 Silica (60–200 μM, Silicycle). Thin-layer chromatography (TLC) was performed on SiliaPlate™ R10011B-323 (Silicycle). ^{1}H, ^{13}C and 2D NMR spectroscopic data were recorded on a 300 MHz Bruker FTNMR Ultra Shield spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer 783 FTS165 FT-IR spectrometer.

High-resolution mass spectra were obtained on a liquid chromatograph–mass spectrometer (2690, LCT, Waters, Micromass). The optical rotations were recorded on a JASCO P-1020 polarimeter.

4.2. Experimental procedures

4.2.1. (*S*)-1-((4*R*,4′*R*,5*R*)-2,2,2′,2′-Tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)prop-2-en-1-ol 9

To a suspension of trimethylsulfonium iodide (14.2 g, 69.6 mmol) and 74 mL of anhydrous THF at −30 °C was added *n*-BuLi (45.0 mL, ca. 1.5 M solution in hexane, 67.5 mmol) dropwise. The resultant white cloudy suspension was stirred at −30 °C for 50 min before a solution of epoxide **7** (4.47 g, 18.3 mmol) in THF (15 mL) was slowly added. The white cloudy mixture was stirred under Ar at −30 °C for 40 min before it was quenched with saturated aqueous NH_4Cl (120 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo to give a yellow oil. Purification of the crude residue by silica gel column chromatography with 10% EtOAc/hexanes as an eluent yielded the title compound as a light yellow oil (4.62 g, 97%): R_f = 0.26 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ = −25.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 17.1, 10.5, 4.8 Hz, 1H), 5.39 (app d, *J* = 17.1 Hz, 1H), 5.24 (app d, *J* = 10.5 Hz, 1H), 4.36–4.29 (m, 1H), 4.19–3.94 (m, 4H), 3.91–3.82 (m, 1H), 1.42 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 116.0, 110.0, 109.6, 82.5, 77.3, 76.9, 70.8, 67.8, 27.1, 27.0, 26.5, 25.2; IR (neat) 3473, 3080, 2988, 2936, 1373, 1215 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{22}NaO_5$ $(M+Na)^+$ 281.1365, found 281.1359.

4.2.2. *tert*-Butyldiphenyl((*S*)-1-((4*R*,4′*R*,5*S*)-2,2,2′,2′-tetramethyl-4,4′-bi(1,3-dioxolan)-5-yl)allyloxy)silane 10

To a solution of allylic alcohol **9** (300.8 mg, 1.16 mmol) in DMF (2.5 mL) at room temperature was added imidazole (245.2 mg, 3.60 mmol), followed by TBDPSCl (0.45 mL, 475.6 mg, 1.73 mmol). The reaction mixture was heated at 60 °C overnight before being cooled to room temperature and diluted with EtOAc (5 mL). Next, H_2O (5 mL) was added and the organic layer was separated. The aqueous layer was then extracted with EtOAc (5 × 3 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude residue by silica gel column chromatography with 2–5–10% EtOAc/hexanes as an eluent yielded the title compound as a colorless oil (333.9 mg, 70%) and 52.7 mg of recovered **9**: R_f = 0.55 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ = −3.3 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.68 (m, 4H), 7.48–7.33 (m, 6H), 5.92 (ddd, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.93 (d, *J* = 17.4 Hz, 1H), 4.37 (dd, *J* = 7.2, 3.9 Hz, 1H), 4.21–4.12 (m, 2H), 4.06–3.97 (m, 1H), 3.92–3.82 (m, 2H), 1.40 (s, 6H), 1.36 (s, 6H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 136.09, 136.08, 134.0, 133.7, 129.7, 129.6, 127.5, 127.4, 117.4, 109.7, 109.4, 82.9, 77.3, 76.9, 75.1, 66.5, 27.5, 27.3, 27.1, 26.4, 25.4, 19.5; IR (neat) 3073, 2987, 2934, 2859, 1371, 1215 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{40}NaO_5Si$ $(M+Na)^+$ 519.2543, found 519.2540.

4.2.3. (*R*)-1-((4*R*,5*S*)-5-((*S*)-1-(*tert*-Butyldiphenylsilyloxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol 11

To a solution of acetonide **10** (6.89 g, 13.9 mmol) in MeCN (67 mL) at 0 °C was added $CuCl_2{\cdot}2H_2O$ (2.60 g, 15.2 mmol). The reaction mixture was then stirred at 0 °C for 2 h before solid $NaHCO_3$ was added. The brown solution was filtered and concentrated in vacuo. Purification of the crude residue by column chromatography (5% EtOAc/hexanes) yielded the title compound as a colorless oil (3.88 g, 76%): R_f = 0.37 (40% EtOAc/hexanes); $[\alpha]_D^{25}$ = −16.3 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.61 (m, 4H), 7.49–7.32 (m, 6H), 5.86 (ddd, *J* = 17.4, 11.1, 6.0 Hz, 1H), 5.12 (app d, *J* = 11.1 Hz, 1H), 5.07 (app d, *J* = 17.4 Hz, 1H), 4.53–4.46 (m, 1H), 3.92 (app t, *J* = 7.8 Hz, 1H), 3.86–3.74 (m, 2H), 3.71 (app d, *J* = 4.8 Hz, 1H), 3.69–3.62 (m, 1H), 2.80 (br s, 2H), 1.28 (s, 6H), 1.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 136.0, 135.0, 132.6, 132.5, 130.2, 130.1, 127.8, 127.6, 117.9, 109.0, 82.4, 77.1, 73.8, 72.5, 64.0, 27.1, 26.8, 19.3; IR (neat) 3706, 3049, 2933, 2859, 1428, 1380 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{36}NaO_5Si$ $(M+Na)^+$ 479.2230, found 479.2225.

4.2.4. (*R*)-2-((4*R*,5*S*)-5-((*S*)-1-(*tert*-Butyldiphenylsilyloxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyethyl benzoate 12

To a solution of diol **11** (5.82 g, 12.7 mmol) in CH_2Cl_2 (53 mL) at 0 °C was added Et_3N (3.60 mL, 25.5 mmol), followed by benzoyl chloride (2.25 mL, 19.1 mmol). The reaction mixture was stirred under argon from 0 °C to room temperature for 13 h. The mixture was then quenched with saturated aqueous NH_4Cl (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by column chromatography (hexanes–5% EtOAc/hexanes) to give the title compound as a colorless oil (5.22 g, 73%): R_f = 0.35 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ = −8.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10–8.02 (m, 2H), 7.74–7.63 (m, 4H), 7.55 (tt, *J* = 7.5, 1.2 Hz, 1H), 7.48–7.30 (m, 8H), 5.89 (ddd, *J* = 17.4, 10.8, 6.0 Hz, 1H), 5.09 (app d, *J* = 10.8 Hz, 1H), 5.04 (app d, *J* = 17.4 Hz, 1H), 4.61 (dd, *J* = 11.7, 2.7 Hz, 1H), 4.51–4.45 (m, 1H), 4.36 (dd, *J* = 11.7, 6.0 Hz, 1H), 4.06 (app t, *J* = 7.5 Hz, 1H), 3.99–3.91 (m, 2H), 1.32 (s, 6H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 136.1, 136.0, 135.6, 133.0, 132.9, 132.87, 132.82, 130.1, 129.9, 129.7, 128.4, 127.8, 127.6, 117.8, 109.3, 82.6, 76.4, 74.2, 71.5, 66.5, 27.1, 26.9, 19.4; IR (neat) 3698, 2933, 2859, 1724, 1276, 1113 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{40}NaO_6Si$ $(M+Na)^+$ 583.2492, found 583.2498.

4.2.5. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-((4*S*,5*S*)-5-((*S*)-1-(*tert*-butyldiphenylsilyloxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethylbenzoate 13

To a solution of alcohol **12** (2.00 g, 3.57 mmol) in DMF (9 mL) were added DMAP (0.13 g, 1.07 mmol) and imidazole (0.976 g, 14.3 mmol), followed by *tert*-butyldimethylsilyl chloride (1.62 g, 10.7 mmol). The reaction mixture was then stirred at 60 °C for 4 h, after which the mixture was cooled to room temperature before H_2O (30 mL) and EtOAc (30 mL) were added. The organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (50 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude residue was purified by column chromatography (hexanes–3% EtOAc/hexanes) to yield the desired title compound as a colorless oil (2.26 g, 94%): R_f = 0.57 (10% EtOAc/hexanes); $[\alpha]_D^{25}$ = −3.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.74–7.65 (m, 4H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.47–7.27 (m, 8H), 5.89 (ddd, *J* = 17.4, 10.5, 7.5 Hz, 1H), 4.92 (d, *J* = 10.5 Hz, 1H), 4.79 (d, *J* = 17.4 Hz, 1H), 4.52 (dd, *J* = 11.7, 3.6 Hz, 1H), 4.38 (dd, *J* = 11.7, 5.1 Hz, 1H), 4.34–4.24 (m, 2H), 4.15–4.06 (m, 1H), 4.04 (dd, *J* = 6.9, 3.0 Hz, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.07 (s, 9H), 0.84 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 137.1, 136.1, 136.0, 134.0, 133.5, 132.9, 130.2, 129.71, 129.67, 129.5, 128.3, 127.5, 127.3, 117.1, 109.5, 82.2, 77.7, 75.6, 72.0, 66.2, 27.8, 27.2, 27.1, 25.8, 25.7, 19.5, 18.0, −4.4; IR (neat) 3073, 2932, 2858, 1726, 1273, 1113 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{39}H_{54}NaO_6Si_2$ $(M+Na)^+$ 697.3357, found 697.3359.

4.2.6. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-2-((4*S*,5*S*)-5-((*S*)-1-(*tert*-butyldiphenylsilyloxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethanol 14

To a solution of benzoate **13** (2.19 g, 3.24 mmol) in CH_2Cl_2 (28 mL) at −78 °C was slowly added DIBALH (1.0 M in cyclohexane, 10.3 mL, 10.3 mmol). The reaction mixture was then stirred under an atmosphere of argon at the same temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl (40 mL), diluted with 20 mL of CH_2Cl_2, and allowed to warm to room temperature before it was filtered through a pad of Celite. The aqueous phase of the filtrate was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and then concentrated in vacuo. The crude product was purified by column chromatography (2–5% EtOAc/hexanes) to give the title compound as a colorless oil (1.42 g, 77%): R_f = 0.48 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ = +5.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.65 (m, 4H), 7.47–7.30 (m, 6H), 5.92 (ddd, *J* = 17.4, 10.2, 7.8 Hz, 1H), 4.92 (d, *J* = 10.2 Hz, 1H), 4.78 (d, *J* = 17.4 Hz, 1H), 4.29 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.21 (dd, *J* = 6.9, 6.6 Hz, 1H), 3.93 (dd, *J* = 6.9, 3.0 Hz, 1H), 3.83–3.76 (m, 1H), 3.73–3.60 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.09 (s, 9H), 0.86 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 136.1, 134.1, 133.5, 129.8, 129.5, 127.5, 127.3, 116.9, 109.6, 82.8, 78.1, 75.4, 73.7, 64.6, 27.7, 27.2, 27.1, 25.9, 19.5, 18.0, −4.3, −4.4 ; IR (neat) 3706, 3049, 2932, 2859, 1252, 1113 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{32}H_{50}NaO_5Si_2$ $(M+Na)^+$ 593.3094, found 593.3098.

4.2.7. (*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-((4*S*,5*S*)-5-((*S*)-1-(*tert*-butyldiphenylsilyloxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde 6

To a solution of alcohol **14** (979 mg, 1.71 mmol) in CH_2Cl_2 (23 mL) was added (diacetoxyiodo)benzene (586 mg, 1.82 mmol), followed by TEMPO (89.8 mg, 0.566 mmol). The reaction mixture was then stirred under atmosphere of argon at room temperature for 16 h. The mixture was quenched with 20 mL of saturated aqueous NH_4Cl:brine (1:1). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude residue by column chromatography (hexanes–2% EtOAc/hexanes) afforded the title compound as a colorless oil (933 mg, 95%): R_f = 0.50 (10% EtOAc/hexanes); $[\alpha]_D^{25}$ = −3.7 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.77–7.64 (m, 4H), 7.47–7.32 (m, 6H), 5.82 (ddd, *J* = 17.4, 10.5, 6.6 Hz, 1H), 5.01 (d, *J* = 10.5 Hz, 1H), 4.91 (d, *J* = 17.4 Hz, 1H), 4.32 (dd, *J* = 6.6, 3.3 Hz, 1H), 4.29–4.17 (m, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.10 (s, 9H), 0.93 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 136.1, 133.7, 133.2, 129.8, 129.6, 127.5, 127.4, 117.7, 109.2, 79.4, 78.1, 78.0, 74.7, 27.1, 27.0, 25.8, 19.4, 18.3, −4.6, −4.7; IR (thin film) 2932, 2859, 1738, 1254, 1113 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{32}H_{48}NaO_5Si_2$ $(M+Na)^+$ 591.2938, found 591.2940.

4.2.8. (*R*,*E*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-4-((4*S*,5*S*)-5-((*S*)-1-(*tert*-butyldiphenyl-silyloxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate 15

To a solution of aldehyde **6** (913 mg, 1.60 mmol) in CH_2Cl_2 (18 mL) at room temperature was added (carbethoxymethylene) triphenylphosphorane (1.11 g, 3.19 mmol) in one portion. The reaction mixture was then stirred under Ar at room temperature for 4 h, after which the solvent was removed and the crude residue was purified by column chromatography (hexanes–2% EtOAc/hexanes) to give α,β-unsaturated ester **15** as a light yellow oil (916 mg, 90%): R_f = 0.47 (10% EtOAc/hexanes); $[\alpha]_D^{25}$ = −2.7 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.64 (m, 4H), 7.47–7.30 (m, 6H), 6.94 (dd, *J* = 15.6, 5.1 Hz, 1H), 6.01 (dd, *J* = 15.6, 1.5 Hz, 1H), 5.86 (ddd, *J* = 17.4, 10.8, 7.5 Hz, 1H), 4.90 (d, *J* = 10.8 Hz, 1H), 4.74 (d, *J* = 17.4 Hz, 1H), 4.41 (td, *J* = 5.1, 1.5 Hz, 1H), 4.29–4.19 (m, 3H), 4.13 (dd, *J* = 7.5, 4.8 Hz, 1H), 3.92 (dd, *J* = 7.5, 3.3 Hz, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 147.2, 137.1, 136.1, 136.0, 134.1, 133.5, 129.7, 129.5, 127.5, 127.3, 122.3, 117.2, 109.6, 81.6, 79.4, 75.5, 73.0, 60.4, 27.5, 27.3, 27.1, 25.9, 19.5, 18.2, 14.3, −4.4, −4.6; IR (thin film) 3074, 2933, 2859, 1724, 1257 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{36}H_{54}NaO_6Si_2$ $(M+Na)^+$ 661.3357, found 661.3358.

4.2.9. (*R*,*E*)-4-(*tert*-Butyldimethylsilyloxy)-4-((4*S*,5*S*)-5-((*S*)-1-(*tert*-butyldiphenylsilyloxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoic acid 5

To a solution of α,β-unsaturated ester **15** (0.120 g, 0.188 mmol) in 3 mL of THF:MeOH:H_2O (8:1:1) at room temperature was added LiOH·H_2O (80.0 mg, 1.91 mmol) in one portion. The mixture was stirred at ambient temperature for 4.5 h after which it was diluted with 3 mL of H_2O and neutralized with 1 M HCl. The organic layer was separated and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the crude residue by column chromatography (20–40% EtOAc/hexanes) provided the title compound as a colorless oil (105.0 mg, 91%): R_f = 0.50 (60% EtOAc/hexanes); $[\alpha]_D^{25}$ = −1.7 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.64 (m, 4H), 7.47–7.30 (m, 6H), 7.05 (dd, *J* = 15.6, 5.1 Hz, 1H), 6.03 (dd, *J* = 15.6, 1.2 Hz, 1H), 5.86 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H), 4.92 (d, *J* = 10.2 Hz, 1H), 4.77 (d, *J* = 17.4 Hz, 1H), 4.43 (app t, *J* = 4.8 Hz, 1H), 4.24 (dd, *J* = 7.5, 3.0 Hz, 1H), 4.11 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.89 (dd, *J* = 7.2, 3.0 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.07 (s, 9H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 150.0, 137.1, 136.1, 136.0, 134.0, 133.4, 129.8, 129.6, 127.6, 127.4, 121.6, 117.2, 109.7, 81.4, 79.4, 75.3, 72.9, 27.5, 27.2, 27.1, 25.9, 19.5, 18.2, −4.4, −4.6; IR (thin film) 3074, 2957, 2932, 2859, 1701, 1658 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{34}H_{50}NaO_6Si_2$ $(M+Na)^+$ 633.3044, found 633.3047.

4.2.10. (*R*,*E*)-((*S*)-Hept-6-en-2-yl)4-(*tert*-butyldimethylsilyloxy)-4-((4*S*,5*S*)-5-((*S*)-1-(*tert*-butyl-diphenylsilyloxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate 16

To a solution of carboxylic acid **5** (226 mg, 0.370 mmol) in toluene (2.3 mL) was added triethylamine (155 μL, 1.11 mmol), followed by 2,4,6-trichlorobenzoyl chloride (87.0 μL, 0.556 mmol). The solution was stirred under an argon atmosphere at room temperature for 1.5 h before (*S*)-hept-6-en-2-ol **4** (42.5 mg, 0.372 mmol) and DMAP (54.4 mg, 0.445 mmol) were added. The reaction mixture was stirred at room temperature for 3 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL). The aqueous layer was extracted with EtOAc (5 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude residue by column chromatography (5% EtOAc/hexanes) yielded the title compound as a light yellow oil (228 mg, 87%): R_f = 0.74 (20% EtOAc/hexanes); $[\alpha]_D^{25}$ = +2.4 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (app d, *J* = 7.5 Hz, 4H), 7.47–7.30 (m, 6H), 6.89 (dd, *J* = 15.6, 5.4 Hz, 1H), 5.97 (app d, *J* = 15.6 Hz, 1H), 5.92–5.71 (m, 2H), 5.92–5.71 (m, 4H), 4.82–4.71 (m, 1H), 4.36 (app t, *J* = 5.4 Hz, 1H), 4.25 (dd, *J* = 7.5, 3.3 Hz, 1H), 4.09 (dd, *J* = 7.2, 5.1 Hz, 1H), 3.90 (dd, *J* = 7.2, 3.3 Hz, 1H), 2.07 (q, *J* = 6.9 Hz, 2H), 1.70–1.40 (m, 4H), 1.39 (s, 3H), 1.35 (s, 3H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.07 (s, 9H), 0.88 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 146.8, 138.4, 137.1, 136.1, 136.0, 134.1, 133.6, 129.7, 129.5, 127.5, 127.3, 122.9, 117.1, 114.7, 109.7, 81.6, 79.7, 75.6, 73.3, 70.9, 35.4, 33.5, 27.5, 27.3, 27.1, 25.9, 24.6, 20.0, 19.5, 18.2, −4.4, −4.6; IR (thin film) 3074, 2932,

2859, 1721, 1255 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{41}H_{62}NaO_6Si_2$ $(M+Na)^+$ 729.3983, found 729.3986.

4.2.11. (*R*,*E*)-((*S*)-Hept-6-en-2-yl)4-hydroxy-4-((4*R*,5*R*)-5-((*S*)-1-hydroxyallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-2-enoate 3

To a solution of silyl ether **16** (278.7 mg, 0.323 mmol) in THF (4 mL) at 0 °C was slowly added TBAF (1.0 M solution in THF, 1.29 mL, 1.29 mmol). The reaction mixture was stirred under an argon atmosphere from 0 °C to room temperature for 3 h. The solution was quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (15–20% EtOAc/hexanes) to give the title compound as a colorless oil (126.0 mg, 91%): R_f = 0.30 (40% EtOAc/hexanes); $[\alpha]_D^{25}$ = −71.8 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 15.6, 4.5 Hz, 1H), 6.10 (dd, *J* = 15.6, 1.5 Hz, 1H), 5.88 (ddd, *J* = 16.8, 10.5, 5.4 Hz, 1H), 5.75 (ddt, *J* = 16.5, 10.2, 6.3 Hz, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.22 (d, *J* = 10.5 Hz, 1H), 5.07–4.98 (m, 2H), 4.40–4.30 (m, 1H), 4.28–4.19 (m, 1H), 4.01 (dd, *J* = 7.5, 3.6 Hz, 1H), 3.91 (dd, *J* = 7.5, 6.3 Hz, 1H), 3.70 (br s, 1H), 3.21 (br s, 1H), 2.03 (q, *J* = 6.9 Hz, 2H), 1.64–1.40 (m, 4H), 1.39 (s, 6H), 1.21 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 145.7, 138.4, 136.6, 122.2, 116.9, 114.8, 109.8, 80.8, 78.7, 71.4, 35.3, 33.4, 27.1, 24.6, 19.9; IR (thin film) 3376, 3078, 2985, 2936, 1715, 1271 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{30}NaO_6$ $(M+Na)^+$ 377.1940, found 377.1936.

4.2.12. (3a*R*,4*R*,5*E*,9*S*,13*Z*,15*S*,15a*R*)-4,15-Dihydroxy-2,2,9-trimethyl-9,10,11,12,15,15a-hexahydro-3a*H*-[1,3]dioxolo[4,5-*f*][1]oxacyclotetradecin-7(4*H*)-one 17

A solution of diene **3** (30.7 mg, 86.6 μmol) in CH_2Cl_2 (87 mL) was purged with argon over 10 min after which Grubbs 1st generation catalyst (35.7 mg, 43.3 μmol) was added in one portion at room temperature. The reaction mixture was heated at 40 °C for 14 h before being cooled to room temperature and concentrated in vacuo. The crude mixture was purified by column chromatography (20% EtOAc/hexanes) to give the title compound as a light yellow oil (7.1 mg, 35% based on 8.7 mg of recovered **3**): R_f = 0.27 (40% EtOAc/hexanes); $[\alpha]_D^{25}$ = −69.6 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (dd, *J* = 15.6, 2.4 Hz, 1H), 6.27 (dd, *J* = 15.6, 2.4 Hz, 1H), 5.62 (dt, *J* = 10.5, 7.5 Hz, 1H), 5.48 (dd, *J* = 10.5, 9.3 Hz, 1H), 5.18–5.05 (m, 1H), 4.82–4.74 (m, 1H), 4.35–4.23 (m, 2H), 3.80 (d, *J* = 8.4 Hz, 1H), 2.78 (br s, 1H), 2.10–1.97 (m, 2H), 1.93–1.80 (m, 1H), 1.80–1.45 (m, 2H), 1.50 (s, 3H), 1.46 (s, 3H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.20–1.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 141.4, 132.7, 129.9, 122.8, 110.9, 78.2, 78.0, 71.4, 67.4, 65.3, 33.9, 28.8, 27.3, 27.2, 24.9, 20.1; IR (thin film) 3483, 2934, 2936, 1716, 1374, 1262 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{26}NaO_6$ $(M+Na)^+$ 349.1627, found 349.1627.

4.2.13. Macrolactone 1

To a solution of acetonide **17** (24.5 mg) in THF (3.9 mL) was added 2 M HCl (3.8 mL). The reaction mixture was then stirred at room temperature for 5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (8 mL). The aqueous layer was extracted with EtOAc (8 × 10 mL). The combined organic layers were washed with brine and concentrated in vacuo. The crude product was purified by column chromatography (80% EtOAc/hexanes) to give macrolactone **1** as a white solid (15.0 mg, 70%): R_f = 0.57 (20% $MeOH/CH_2Cl_2$); mp 118–120 °C; $[\alpha]_D^{25}$ = −127.6 (*c* 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 15.6, 3.6 Hz, 1H), 6.19 (d, *J* = 15.6 Hz, 1H), 5.63–5.51 (m, 1H), 5.51–5.39 (m, 1H), 5.07–4.04 (m, 1H), 4.69–4.55 (m, 1H), 4.32 (d, *J* = 7.8 Hz, 1H), 4.03–3.93 (m,1H), 3.40 (d, *J* = 4.5 Hz, 1H), 2.25–2.07 (m, 1H), 1.98–1.86 (m, 1H), 1.86–1.72 (m, 1H), 1.62–1.52 (m, 1H), 1.52–1.37 (m, 1H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.09–0.91 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 144.6, 132.1, 129.8, 123.8, 73.3, 72.9, 72.4, 72.2, 69.3, 35.5, 29.7, 26.3, 20.8; IR (thin film) 3392, 3018, 2975, 2930, 1714, 1261 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{22}NaO_6$ $(M+Na)^+$ 309.1314, found 309.1314.

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