Stereoselective Synthesis of the Non-Lactonic Portion of (*Z*)-Cryptofolione and Approaches towards Its Conversion to (*Z*)-Cryptofolione[1])

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The stereoselective synthesis of the non-lactonic part of the natural G_2 checkpoint inhibitor, (*Z*)-cryptofolione, has been accomplished. Butane-1,4-diol was used as the starting material, and the stereogenic centers were generated through L-proline-catalyzed α-aminoxylation and *Maruoka* asymmetric allylation. We attempted to convert this non-lactonic moiety to (*Z*)-cryptofolione *via* olefin cross-metathesis reaction, but by this approach another naturally occurring lactonic compound, goniothalamin, was obtained.

Introduction. – (*Z*)-Cryptofolione (**1**) was isolated from the crude extract of *Cryptocarya conncina*, a plant of the laurel family [1]. The molecule contains an α,β-unsaturated δ-lactone ring, along with two more olefinic C=C bonds (one with (*E*)- and the other with (*Z*)-configuration), as well as two OH groups of opposite configuration (one at C(4′) in β- and the other at C(6′) in α-orientation). Compound **1** possesses G_2 checkpoint inhibition capacity in human breast carcinoma MCF-7 cells and is more active than its (*E*)-isomer [1]. However, in spite of its interesting structural features and significant biological properties, the total synthesis of (*Z*)-cryptofolione **1** has not yet been accomplished. In recent years, several natural products containing the δ-lactone moiety such as (+)-goniothalamin [2a][2b], (+)-cryptocaryalactone [2c], (+)-cryptofolione [2d], and (+)-strictifolione [2e] (*Fig. 1*) have been synthesized. In a common approach of their synthesis, two olefinic fragments of the compounds are prepared, and these two fragments are coupled by olefin cross-metathesis reaction using *Grubbs*' catalyst [2d][2e]. Continuing our work [3] on the construction of natural bioactive compounds, we attempted to synthesize (*Z*)-cryptofolione (**1**) by this approach. We prepared the olefinic fragment **2** of the target molecule **1**. However, the attempted cross-metathesis reaction of **2** with the known ethenyl compound **3** occurred with the (*Z*)-configured C=C bond of the former but not with the terminal $CH{=}CH_2$ group, leading to the formation of another natural lactonic compound. Herein, we report the stereoselective synthesis of the non-lactonic moiety **2** of (*Z*)-cryptofolione (**1**), and our attempts to convert it to the natural compound **1** (*Scheme 1*).

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[1]) Part 84 in the series, 'Synthetic Studies on Natural Products'.

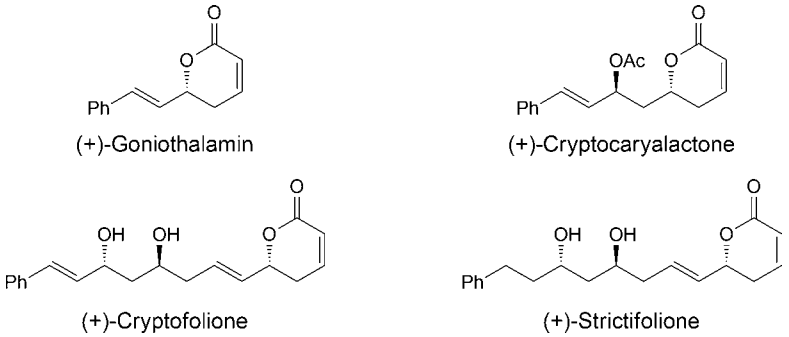
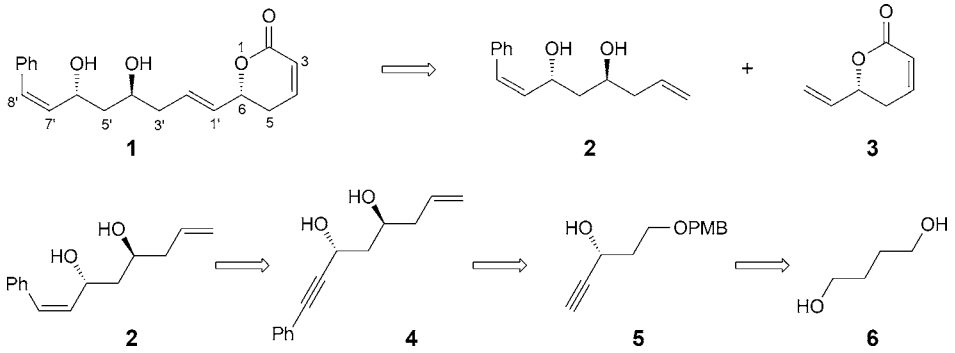


Figure. *Structures of natural products containing δ-lactone moieties*

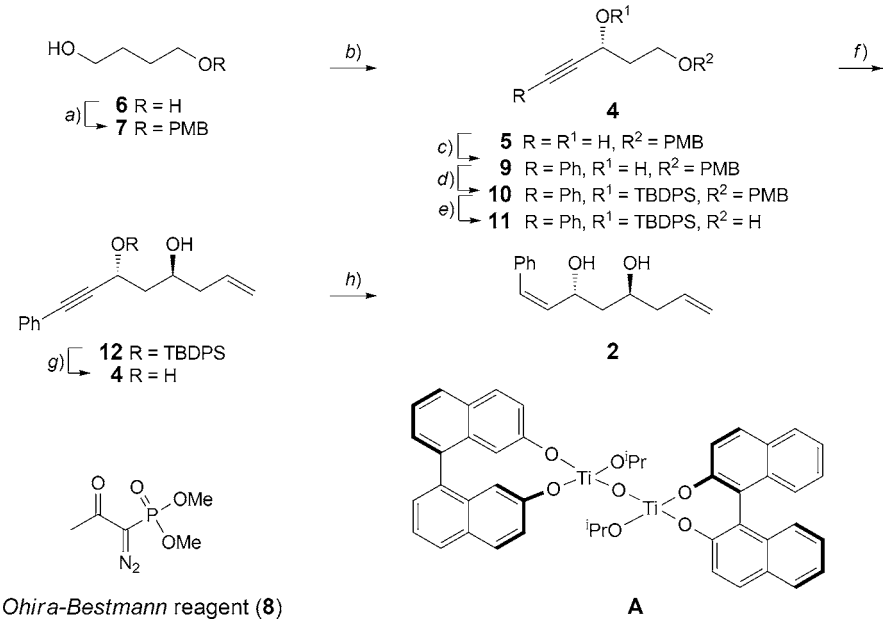
Scheme 1. *Retrosynthetic Analysis of* **1** *and* **2**



Results and Discussion. – The retrosynthetic analysis (*Scheme 1*) of **2** indicates that it can be synthesized from the alkyne **4**, which in turn can be prepared from the propargyl alcohol **5** derived from butane-1,4-diol (**6**).

Our synthesis was initiated by protection of one OH group of butane-1,4-diol (**6**) by treatment with 4-methoxybenzyl bromide (PMB-Br) and NaH to form the PMB ether **7** (*Scheme 2*). The latter was oxidized with pyridinium chlorochromate (PCC), and the aldehyde obtained was subjected to asymmetric aminoxylation [4] using L-proline and PhNO, followed by addition of the *Ohira-Bestmann* reagent **8** and K_2CO_3 to furnish the chiral propargyl alcohol **5** (ee 96%, determined by chiral HPLC) [5]. The alcohol **5** was treated with PhI in the presence of CuI, Ph_3P, and Pd/C to form the alkyne **9** [6]. The free OH group of **9** was protected as (^{t}Bu)Ph_2Si (TBDPS) ether (**10**), and the PMB-ether group of the latter was deprotected to afford the alcohol **11**. The latter was oxidized with 2-iodoxybenzoic acid (IBX), and the corresponding aldehyde was subjected to asymmetric *Maruoka* allylation [7] with allyl(tributyl)tin and the bis{[(*S*)-binaphthoxy](isopropoxy)titanium} oxide complex **A** to afford the chiral homoallylic alcohol **12** (de 97%). Thus, both stereogenic centers present in **2** have been created. Next, the TBDPS-ether group of **12** was deprotected to furnish the diol **4**. Finally, the selective hydrogenation [8] of the C≡C bond of **4** with $(AcO)_2Ni$, $NaBH_4$, and ethane-1,2-amine under H_2 yielded the non-lactonic part **2** of (*Z*)-cryptofolione **1**.

Scheme 2. *Stereoselective Synthesis of the Non-Lactonic Moiety* **2** *of* **1**

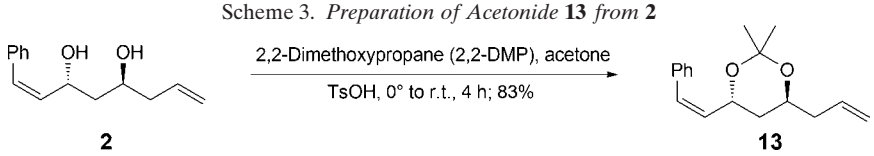


a) NaH, 4-Methoxybenzyl bromide (PMB-Br), THF, 0° to r.t., 3 h; 87%. *b*) 1) Pyridium chlorochromate (PCC), CH_2Cl_2, r.t., 1.5 h. 2) L-proline, nitrosobenzene (PhNO), −20°, 24 h. 3) K_2CO_3, **8**, 67% (over three steps); *ee* 96%. *c*) 10% Pd/C, Ph_3P, CuI, K_2CO_3, PhI, 1,2-dimethoxyethane (DME)/H_2O 3:1, 85°, 5 h; 89%. *d*) 1*H*-Imidazole, (^{t}Bu)Ph_2SiCl (TBDPS-Cl), 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0° to r.t., 6 h; 88%. *e*) 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O 8:2, 0° to r.t., 3 h; 85%. *f*) 1) 2-Iodoxybenzoic acid (IBX), DMSO, CH_2Cl_2, 0° to r.t., 1.5 h; 92%. 2) (*S*,*S*)-**I**, Allyl(tributyl)stannane, CH_2Cl_2, 0°, 18 h; 74% (de 97%). *g*) Bu_4NF, THF, 0° to r.t., 5 h; 78%. h) $(AcO)_2Ni$, $NaBH_4$, $NH_2(CH_2)_2NH_2$, H_2, EtOH, r.t.; 76%.

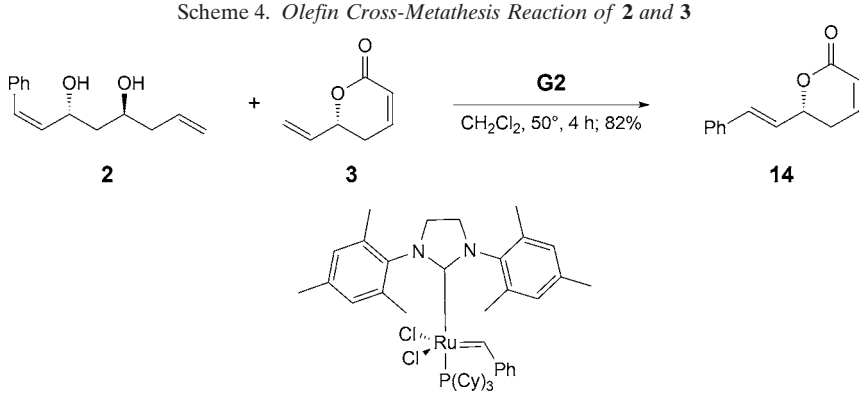
The 1,3-*anti*-relationship of the two OH groups of **2** was established by analysis of the ^{13}C-NMR spectrum [9] of the corresponding acetonide **13** prepared from **2** (*Scheme 3*). The spectrum exhibited the Me signals of the acetonide at 25.8 and 25.2, and that of the quaternary C-atom at 100.2 ppm.

Next, we attempted to convert the fragment **2** to the natural (*Z*)-cryptofolione **1** by olefin cross-metathesis reaction [10] with the olefinic lactone **3** [11] using *Grubbs*' 2nd-generation catalyst, **G2**, under different conditions. However, we did not obtain compound **1**. Interestingly, the cross-metathesis reaction occurred with the internal (*Z*)-configured C=C bond of **2** (*Scheme 4*) to generate another naturally occurring lactonic compound, goniothalamin **14** [12].

Scheme 3. *Preparation of Acetonide* **13** *from* **2**



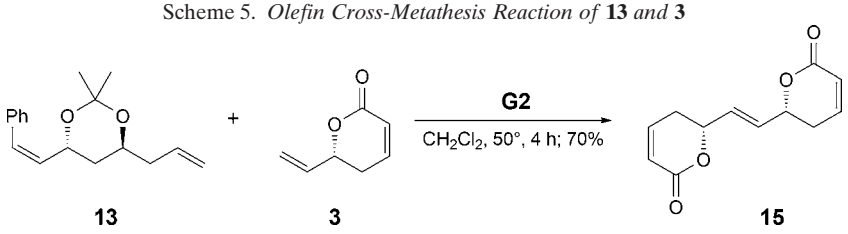
Scheme 4. *Olefin Cross-Metathesis Reaction of* **2** *and* **3**



Grubbs' 2nd-generation catalyst (G2)

We also tried to carry out the olefinic cross-metathesis reaction with the acetonide **13**, derived from **2**, and the olefinic lactone **3** using **G2**. However, in this case the lactonic dimer **15** was the only product obtained (*Scheme 5*).

Scheme 5. *Olefin Cross-Metathesis Reaction of* **13** *and* **3**



In conclusion, we have developed a stereoselective synthesis of the non-lactonic moiety of the natural (*Z*)-cryptofolione (**1**) and attempted, unsuccessfully, to convert it to **1**. One of the approaches afforded another natural compound, goniothalamin **14**.

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Experimental Part

General. The solvents used were all of AR grade. TLC: *Merck* silica-gel *60* F_{254} plates. Column chromatography (CC): silica gel (SiO_2, 60–120 mesh; *Qingdao Marine Chemical*, P. R. China). Optical rotations: *JASCO DIP 360* digital polarimeter. NMR Spectra: *Gemini* 200-MHz spectrometer; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ESI-MS: *VG-Autospec* micromass instrument; in *m*/*z*.

4-[(4-Methoxyphenyl)methoxy]butan-1-ol (**7**). *Butane-1,4-diol* (**6**; 5.0 g, 55.55 mmol) was taken in 50 ml of dry THF. NaH (60% dispersion in mineral oil; 2.49 g, 55.55 mmol) was added to it portionwise at 0°. The mixture was stirred at 0° for 30 min. Bu_4NI (1.6 g, 0.55 mmol) was added, followed by the addition of 4-methoxybenzyl bromide (11.16 g, 55.55 mmol) in THF (50 ml). The mixture was stirred for a further 2 h at r.t. Ice-water (15 ml) was added carefully to the mixture to remove any excess of NaH. The mixture was extracted with AcOEt (50 ml), and the org. layer was washed with H_2O (15 ml) and brine (20 ml). Evaporation of the solvent and purification of the residue by CC (AcOEt/hexane 20:80) afforded **7**

(10.17 g, 87%). Colorless liquid. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.28 (*d*, *J* = 8.0, 2 H); 6.89 (*d*, *J* = 8.0, 2 H); 4.47 (*s*, 2 H); 3.81 (*s*, 3 H); 3.67 (*t*, *J* = 7.0, 2 H); 3.49 (*t*, *J* = 7.0, 2 H); 1.73–1.62 (*m*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 159.0; 130.1; 129.2; 113.6; 72.5; 69.9; 62.3; 55.1; 29.8; 26.3. ESI-MS: 211 ($[M+H]^+$). Anal. calc. for $C_{12}H_{18}O_3$ (210.28): C 68.54, H 8.63; found: C 68.63, H 8.67.

*(3*R*)-5-[(4-Methoxyphenyl)methoxy]pent-1-yn-3-ol* (**5**). To a stirred soln. of **7** (8.0 g, 37.91 mmol) in dry CH_2Cl_2 (70 ml) were added *Celite* (50 g) and PCC (16.07 g, 56.85 mmol) at 0°, and the mixture was stirred for 1.5 h at r.t. The mixture was diluted with Et_2O (45 ml) and subjected to CC (SiO_2; AcOEt/hexane 10:90) to afford the corresponding aldehyde (7.04 g, 89%) as a colorless liquid, which was used directly after flash chromatography (FC) for the next reaction.

The aldehyde (7.0 g, 33.49 mmol) was dissolved in MeCN (55 ml) and cooled to −20°. To this mixture, L-proline (0.768 g, 6.68 mmol) was added, followed by addition of PhNO (3.47 g, 33.49 mmol). The resulting mixture was stirred for 24 h, and, the solvent was evaporated. The residue was redissolved in MeOH (60 ml). Next, the *Ohira-Bestmann* reagent (**8**; 236 mg, 1.23 mmol) in MeOH (8 ml) and K_2CO_3 (3.46 g, 18.07 mmol) were added sequentially. The mixture was stirred for 8 h at 0°. The reaction was quenched by sat. NH_4Cl (1 × 10 ml), and the mixture was stirred for an additional 24 h at r.t. The org. solvent was removed under reduced pressure, and the aq. layer was extracted with AcOEt (3 × 10 ml). The combined org. layers were washed with brine (10 ml), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified by CC (hexane/AcOEt 7:1) to give **5** (2.2 g, 67% for three conversions). Pale-yellow oil. $[\alpha]_D^{25} = -8.9$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.22 (*d*, *J* = 8.0, 2 H); 6.88 (*d*, *J* = 8.0, 2 H); 4.63–4.61 (*m*, 1 H); 4.49 (*d*, *J* = 12.0, 1 H); 4.42 (*d*, *J* = 12.0, 1 H); 3.83–3.81 (*m*, 1 H); 3.81 (*s*, 3 H); 3.67–3.65 (*m*, 1 H); 3.11–3.09 (*m*, 1 H); 2.09–2.07 (*m*, 1 H); 1.93–1.91 (*m*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 159.4; 130.0; 129.8; 113.9; 85.5; 73.1; 73.0; 67.7; 61.2; 55.1; 36.6. ESI-MS: 221 ($[M+H]^+$). Anal. calc. for $C_{13}H_{16}O_3$ (220.26): C 70.89, H 7.32; found: C 70.98, H 7.36.

*(3*R*)-5-[(4-Methoxyphenyl)methoxy]-1-phenylpent-1-yn-3-ol* (**9**). To a soln. of **5** (2.0 g, 9.09 mmol) in DME (60 ml) were added H_2O (20 ml), K_2CO_3 (3.10 g, 22.5 mmol), CuI (0.068 g, 0.36 mmol), Ph_3P (0.21 g, 0.92 mmol), and a cat. amount of 10% Pd/C. The resulting mixture was stirred at r.t. for 30 min, then PhI was added, and the mixture warmed at 85° for 5 h. The mixture was cooled to r.t., filtered through a *Celite* pad, washed with hot AcOEt (2 × 25 ml). The soln. was diluted with H_2O (50 ml) and extracted with AcOEt (2 × 50 ml). The org. phase was washed with brine (50 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC to afford **9** (2.3 g, 89%). Pale-yellow liquid. $[\alpha]_D^{25} = +49.2$ (*c* = 0.5, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.40–7.18 (*m*, 7 H); 6.81 (*d*, *J* = 8.0, 2 H); 4.79–4.77 (*m*, 1 H); 4.48 (*s*, 2 H); 3.89–3.87 (*m*, 1 H); 3.78 (*s*, 3 H); 3.66–3.64 (*m*, 1 H); 2.98 (*d*, *J* = 7.0, 1 H); 2.17–2.15 (*m*, 1 H); 1.99–1.97 (*m*, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 159.2; 132.0; 130.1; 129.8; 128.3; 128.1; 122.9; 114.1; 89.9; 85.0; 72.9; 67.1; 61.9; 55.2; 37.1. ESI-MS: 297 ($[M+H]^+$). Anal. calc. for $C_{19}H_{20}O_3$ (296.36): C 77.0, H 6.80; found: C 77.14, H 6.91.

*(tert-Butyl)({(3*R*)-5-[(4-methoxyphenyl)methoxy]-1-phenylpent-1-yn-3-yl}oxy)diphenylsilane* (**10**). 1*H*-Imidazole (0.78 g, 11.4 mmol), DMAP (cat.), and TBDPSCl (2.5 g, 9.12 mmol) were added to a stirred soln. of **9** (2.25 g, 7.6 mmol) in anh. CH_2Cl_2 (25 ml) at 0°. Stirring was continued for 3 h, and then the mixture was diluted with CH_2Cl_2 (15 ml). The org. layer was washed with brine (25 ml) and then dried (Na_2SO_4). Evaporation of the solvent under reduced pressure, followed by CC (SiO_2; AcOEt/hexane 10:90) afforded **10** (3.57 g, 88%). Colorless liquid. $[\alpha]_D^{25} = +66.6$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.74 (*d*, *J* = 8.0, 2 H); 7.69 (*d*, *J* = 8.0, 2 H); 7.40–7.23 (*m*, 7 H); 7.20–7.04 (*m*, 6 H); 6.72 (*d*, *J* = 8.0, 2 H); 5.75 (*t*, *J* = 7.0, 1 H); 4.31 (*s*, 2 H); 3.73 (*s*, 3 H); 3.68–3.54 (*m*, 2 H); 2.14–1.98 (*m*, 2 H); 1.09 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 159.2; 144.1; 136.1; 136.0; 131.2; 129.9; 129.4; 128.1; 127.8; 127.7; 123.0; 113.1; 90.5; 85.3; 72.6; 66.2; 62.0; 55.4; 38.7; 27.2; 19.1. ESI-MS: 535 ($[M+H]^+$). Anal. calc. for $C_{35}H_{38}O_3Si$ (534.26): C 78.61, H 7.16; found: C 78.51, H 7.20.

*(3*R*)-3-{[(*tert*-Butyl)(diphenyl)silyl]oxy}-5-phenylpent-4-yn-1-ol* (**11**). To a stirred soln. of **10** (3.3 g, 6.17 mmol) in CH_2Cl_2/H_2O 8:2, DDQ was added at 0° (1.54 g, 6.79 mmol), and the mixture was stirred for 2.5 h. The reaction was quenched with solid $NaHCO_3$ at 0°, and the mixture was filtered through *Celite* pad and washed with CH_2Cl_2. Concentration of the mixture under reduced pressure, followed by purification by CC (AcOEt/hexane 25:75), afforded pure **11** (2.8 g, 85%). Pale-yellow oil. $[\alpha]_D^{25} = +84.3$ (*c* = 1.5, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.80 (*d*, *J* = 8.0, 2 H); 7.75 (*d*, *J* = 8.0, 2 H); 7.48–7.32 (*m*,

6 H); 7.29–7.12 (*m*, 5 H); 4.80 (*t*, *J* = 7.0, 1 H); 4.04–4.02 (*m* , 1 H); 3.88–3.86 (*m*, 1 H); 2.23–1.92 (*m*, 3 H); 1.10 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 136.1; 135.9; 131.5; 130.1; 130.1; 128.1; 127.9; 127.8; 89.8; 86.0; 63.3; 60.0; 40.1; 27.0; 19.4. ESI-MS: 415 ($[M+H]^+$). Anal. calc. for $C_{27}H_{30}O_2Si$ (414.61): C 78.22, H 7.29; found: C 78.26, H 7.31.

*(4*R*,6*R*)-6-{[(1,1-Dimethylethyl)diphenylsilyl]oxy}-8-phenyloct-1-en-7-yn-4-ol* (**12**). To an ice-cold soln. of IBX (3.92 g, 14.5 mmol) in DMSO (5 ml) was added a soln. of **11** (2.71 g, 6.56 mmol) in anh. CH_2Cl_2, and the mixture was stirred at 25° for 1.5 h. The mixture was diluted with CH_2Cl_2 (15 ml), filtered through *Celite* pad, and the pad was washed with CH_2Cl_2. The combined filtrates were washed with H_2O (10 ml), dried (Na_2SO_4), and the residue was concentrated under reduced pressure to afford the aldehyde (2.74 g, 92%), which was used directly after FC for the next reaction.

To a stirred soln. of $TiCl_4$ (0.04 g, 0.33 mmol) in CH_2Cl_2 (5 ml) was added dried (^{i}PrO)$_4$Ti (0.281 g, 0.99 mmol) at 0° under N_2, and the mixture was allowed to warm to r.t. After 1 h, Ag_2O (0.152 g, 0.66 mmol) was added at r.t., and the mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with CH_2Cl_2 (3 ml) and treated with (*S*)-BINOL (0.377 g, 1.32 mmol) at r.t. for 2 h to furnish **A**. The *in situ* generated **A** was cooled to −15°, and treated sequentially with aldehyde (2.74 g, 6.6 mmol) and (allyl)(tributyl)tin (2.7 ml, 8.5 mmol) at the same temp. The mixture was allowed to warm to 0° and stirred for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$, and the mixture was extracted with Et_2O (3 × 10 ml). The org. extracts were dried (Na_2SO_4). Evaporation of solvents and purification of the residue by CC (SiO_2; AcOEt/hexane 20:80) gave **12** (2.2 g, 74%). Pale-yellow liquid. $[\alpha]_D^{25} = -12.4$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.79 (*d*, *J* = 8.0, 2 H); 7.48–7.32 (*m*, 7 H); 7.28–7.19 (*m*, 2 H); 7.06 (*d*, *J* = 8.0, 2 H); 5.84–5.82 (*m*, 1 H); 5.19–5.10 (*m*, 2 H); 4.80 (*t*, *J* = 7.0, 1 H); 4.05–4.03 (*m*, 1 H); 2.34–2.25 (*m*, 3 H); 2.02–1.94 (*m*, 2 H); 1.10 (*s*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 136.4; 136.2; 134.2; 129.7; 129.2; 127.7; 127.3; 127.1; 118.1; 89.9; 86.1; 68.8; 63.2; 44.5; 42.0; 26.9; 19.5. ESI-MS: 455 ($[M+H]^+$). Anal. calc. for $C_{30}H_{34}O_2Si$ (454.23): C 79.24, H 7.54; found: C 79.36, H 7.51.

*(3*R*,5*R*)-1-Phenyloct-7-en-1-yne-3,5-diol* (**4**). To a stirred soln. of **12** (2.2 g, 4.43 mmol) in dry THF (10 ml) at 0° was added Bu_4NF (6.34 g, 5.76 mmol) dropwise. After completion of addition, the mixture was kept at r.t. and stirred for 5 h. After completion (TLC), the reaction was quenched with sat. $(NH_4)_2CO_3$ soln. (3 ml), and the mixture was extracted into CH_2Cl_2 (2 × 15 ml) and dried (Na_2SO_4). The combined org. layer was concentrated *in vacuo* and subjected to CC (SiO_2; hexane/AcOEt 6:4) to afford **4** (0.81 g, 78%). Colorless liquid. $[\alpha]_D^{25} = +31.9$ (*c* = 1.5, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.45–7.36 (*m*, 2 H); 7.31–7.22 (*m*, 3 H); 5.83–5.81 (*m*, 1 H); 5.18–5.07 (*m*, 2 H); 4.85 (*t*, *J* = 7.0, 1 H); 4.23–4.21 (m, 1 H); 3.80 (br. *s*, 1 H); 2.92 (br. *s*, 1 H); 2.31–2.21 (*m*, 2 H); 1.91–1.82 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 134.1; 131.2; 128.7; 128.6; 122.8; 118.9; 89.9; 85.1; 68.3; 61.1; 42.2; 42.0. ESI-MS: 217 ($[M+H]^+$). Anal. calc. for $C_{14}H_{16}O_2$ (216.28): C 77.75, H 7.46; found: C 77.86, H 7.49.

*(1*Z*,3*R*,5*S*)-1-Phenylocta-1,7-diene-3,5-diol* (**2**). To a stirred soln. of $(AcO)_2Ni$ (40 mg, 1.98 mmol) in dry EtOH was added under H_2 at r.t. $NaBH_4$ (75 mg, 1.98 mmol) in EtOH and 3 drops of ethane-1,2-diamine. To the resulting black mixture, **4** (0.65 g, 3.03 mmol) was added, and the mixture was stirred under H_2 until the reduction of the C≡C group was completed (TLC). The reaction was quenched by addition of active coal, and the mixture was filtered through *Celite*. Concentration of the filtrates *in vacuo* and FC (SiO_2) afforded **2** (0.498 g, 76%). Pale-yellow liquid. $[\alpha]_D^{25} = +38.2$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.32–7.12 (*m*, 5 H); 6.41 (*d*, *J* = 10.0, 1 H); 5.81–5.63 (*m*, 2 H); 5.10–5.00 (*m*, 2 H); 4.88–4.86 (*m*, 1 H); 3.93–3.91 (*m*, 1 H); 3.58–3.22 (br. *s*, 2 H); 2.22–2.14 (*m*, 2 H); 1.80–1.61 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 136.4; 134.5; 134.1; 130.1; 128.8; 128.2; 127.2; 118.0; 68.1; 65.8; 42.1; 42.0. ESI-MS: 219 ($[M+H]^+$). Anal. calc. for $C_{14}H_{18}O_2$ (218.29): C 77.03, H 8.31; found: C 77.18, H 8.29.

*(4*R*,6*S*)-2,2-Dimethyl-4-[(*Z*)-2-phenylethenyl]-6-(prop-2-en-1-yl)-1,3-dioxane* (**13**). To a stirred soln. of **2** (0.25 g, 1.157 mmol) in dry acetone (3 ml) under N_2 at 0° was added TsOH (20 mg) and 2,2-dimethoxypropane (0.4 ml, 1.38 mmol). The soln. was stirred for 3 h, and the reaction was quenched with solid $NaHCO_3$ powder (30 mg). After filtration, the filtrate was concentrated under reduced pressure and subjected to CC (AcOEt/hexane 10:90) to afford pure **13** (0.245 mg, 83%). Colorless oil. $[\alpha]_D^{25} = +54.6$ (*c* = 1.0, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.48–7.22 (*m*, 5 H); 6.59 (*d*, *J* = 10.0, 1 H); 5.88–5.64 (*m*, 2 H); 5.15–5.02 (*m*, 2 H); 4.77 (*q*, *J* = 7.0, 1 H); 3.98–3.96 (*m*, 1 H); 2.39–2.15 (*m*, 2 H); 1.76 (*t*, *J* = 7.0, 2 H); 1.42 (*s*, 3 H); 1.38 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 134.2; 132.1; 131.8; 128.8;

128.2; 127.3; 116.9; 100.2; 64.0; 63.7; 40.2; 37.9; 25.8; 25.2. ESI-MS: 259 ($[M+H]^+$). Anal. calc. for $C_{17}H_{22}O_2$ (258.36): C 74.97, H 7.40; found: C 74.89, H 7.43.

Goniothalamin (=*(6*R*)-5,6-Dihydro-6-[(*E*)-2-phenylethenyl]-2*H*-pyran-2-one*; **14**) [2a][2b][12]. A soln. of **2** (0.10 g, 0.46 mmol) and **3** (0.025 g, 0.23 mmol) in dry CH_2Cl_2 (10 ml) was first bubbled with N_2 flow, after which *Grubbs*' 2nd-generation catalyst **G2** (5 mg, 0.01 mmol) was added at once, and the resulting mixture was heated under N_2 at 50° for 3 h. After cooling, the solvent was evaporated *in vacuo*. The residue on purification by CC (AcOEt/hexane 80:20) afforded pure **14** (0.075 g, 82%). White solid. $[\alpha]_D^{25} = +167.4$ ($c = 1.3$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 7.41–7.22 (*m*, 5 H); 6.92–6.90 (*m*, 1 H); 6.71 (*d*, $J = 10.0$, 1 H); 6.23 (*dd*, $J = 15.0, 6.0$, 1 H); 6.09 (*d*, $J = 10.0$, 1 H); 5.08 (*q*, $J = 7.0$, 1 H); 2.58–2.50 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 164.2; 144.8; 136.0; 133.1; 128.3; 126.9; 125.9; 121.9; 78.0; 29.6. ESI-MS: 201 ($[M+H]^+$). Anal. calc. for $C_{17}H_{22}O_2$ (200.23): C 74.97, H 7.40; found: C 74.85, H 7.43.

*(6*R*,6′*R*)-6,6′-[(*E*)-Ethene-1,2-diyl]bis(5,6-dihydro-2*H*-pyran-2-one)* (**15**). Through a soln. of **13** (0.015 g, 0.585 mmol) and **3** (0.026 g, 0.234 mmol) in dry CH_2Cl_2 (10 ml) was first bubbled N_2, then **G2** (5 mg, 0.01 mmol) was added at once, and the resulting mixture was heated under N_2 at 50° for 4 h. After cooling, the solvent was evaporated *in vacuo*. The residue on purification by CC (AcOEt/hexane, 5:5) afforded pure **15** (0.090 g, 70%). Colorless liquid. $[\alpha]_D^{25} = -8.9$ ($c = 0.5$, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): 6.92–6.83 (*m*, 2 H); 6.08–5.98 (*m*, 4 H); 5.01–4.90 (*m*, 2 H); 2.57–2.22 (*m*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 165.6; 143.3; 131.7; 129.0; 75.8; 19.3. ESI-MS: 221 ($[M+H]^+$). Anal. calc. for $C_{12}H_{22}O_4$ (220.23): C 65.45, H 5.49; found: C 65.33, H 5.47.

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