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Two simple and alternative approaches for the synthesis of anticancer active goniothalamin

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This article is dedicated to the fond memory of Dr. Yenamandra Venkateswarlu for his support, encouragement and his contribution to synthetic and natural products chemistry

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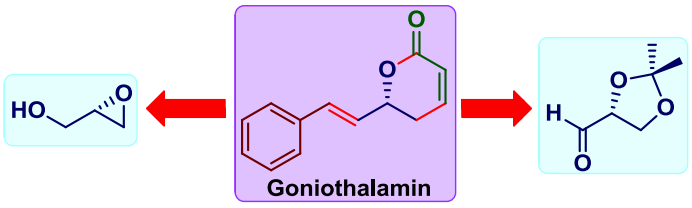
Abstract

Two alternative and straightforward routes were developed for the construction of (*R*)-goniothalamin, a natural anticancer agent. The first method starts with (*R*)-glycidol involving stereoselective (partial) reduction of alkyne and sulfoxide Julia-Lythgoe olefination as key steps. Second method deals with the synthesis of (*R*)-goniothalamin from 2,3-*O*-isopropylidene-D-glyceraldehyde with partial reduction of nitrile and Still-Gennari stereoselective olefination as critical steps. These two methods with simple sequence of standard organic reactions may be adopted for the sophomore or junior's courses in organic chemistry.



Keywords: (*R*)-Goniothalamin, anti-cancer active, two strategies, (*R*)-glycidol, 2,3-*O*-isopropylidene-D-glyceraldehyde

Introduction

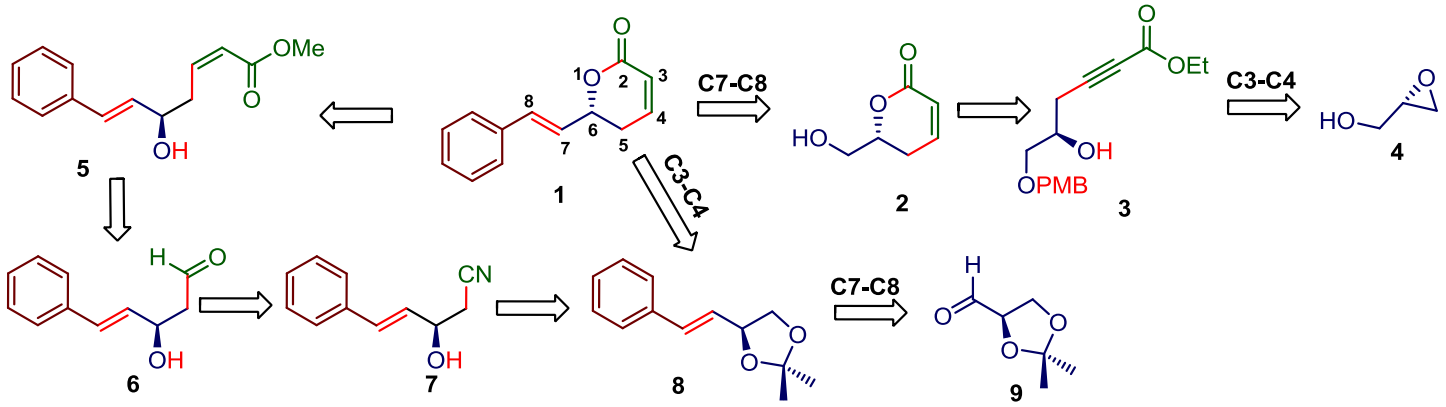
Nature is the source for several bio-potent natural products and are the base for the development of numerous medicinally or pharmaceutically active compounds.[1] Natural products with styryl δ-lactones possess interesting biological activities such as anticancer, antimicrobial, antimalarial, antilarvicidal and etc.[5,6] The genus *Goniothalamus* is a rich source of styryl 5- or 6-membered lactones.[6,7] Goniothalamin (**1**) is prototypical example of styryl δ-lactones, was initially isolated in 1967 from dried bark of *Cryptocarya caloneura* (Scheff.).[8] Later it was found in several plants, for example in *Goniothalamus velutinus*,[9] *Cryptocarya moschata*,[10] *Bryonopsis laciniosa*,[11] and *Alyxia schlechteri*.[12] Goniothalamin was assigned initially (*S*)-configuration,[8] but, revised as (*R*)-configuration after the synthesis of both the enantiomers.[13] Goniothalamin shows a variety of biological activities such as anti-cancer,[14,15,16] anti-microbial,[17,18] anti-inflammatory and antinociceptive,[19,20] antiproliferative,[20,21] plant growth inhibition activity,[22] larvae antifeedant or larvicidal,[23] etc. activities. The activity studies of **1** and its related compounds was revealed by the presence of their side chain.[7,21]

Since it was reported the synthesis of **1** in 1979 by Meyer[13] several reports appeared[16,21,24-32] because of its significant biological properties. Some of the reported syntheses suffers from the requirement of large quantity of hazardous reagents[24,25] or expensive catalysts/auxiliaries[26] or with low overall yields[31,32] etc. Although, some efficient protocols were developed, it is still in demand to develop new/improved synthetic protocols to enhance the scope and possibility of starting materials with simple reactions. In this process we report here, two alternative routes for the synthesis of **1**, involving simple reaction sequences.

Results and Discussion

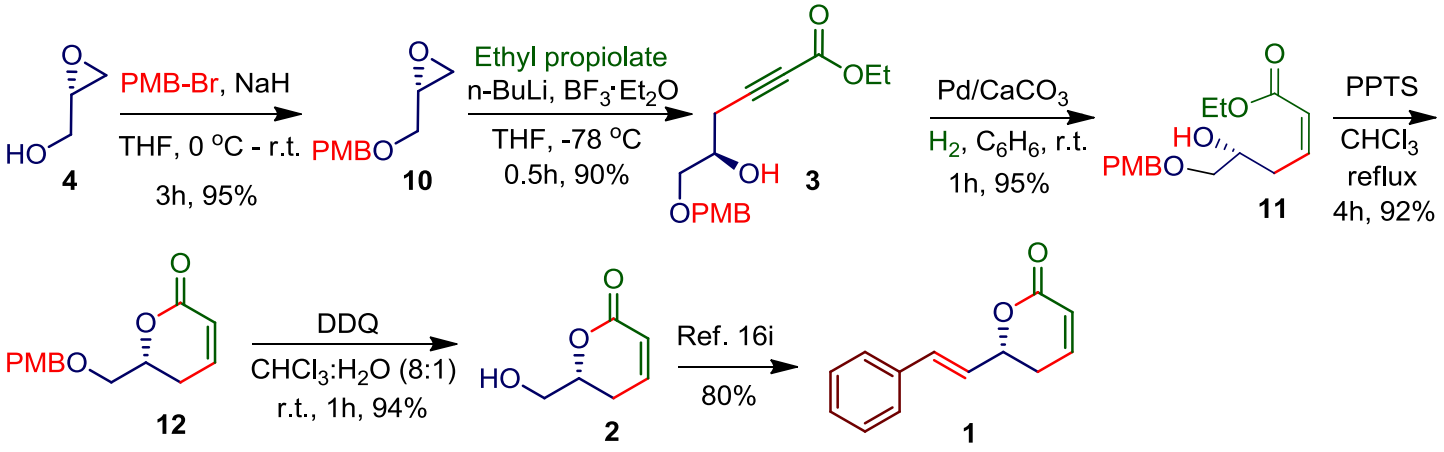
Most of the literature approaches were appeared by C3-C4 disconnection and/or C7-C8 disconnection[24-29] or some of them by hetero Diels-Alder[30] or nucleophilic intramolecular cyclization.[31] The synthetic strategy that we adopted for the synthesis of **1** is represented in the following Scheme (Scheme 1) and is based on the disconnection of both the C3-C4 and C7-C8 double bonds to simple and commercially available chiral precursor, (*R*)-glycidol (**4**) or 2,3-*O*-isopropylidene-D-glyceraldehyde (**9**).

The retrosynthetic approach (Scheme 1) revealed that the target compound **1** may be achieved in two different ways. In the first route lactone **2** is the key intermediate to furnish goniothalamin (**1**). The lactone **2** could be obtained from ester **3**, and is possible to derive from the commercially available (*R*)-glycidol, **4**. In another route, **1** may be obtained from the aldehyde **6**, which in turn obtained from the 2,3-*O*-isopropylidine-D-glyceraldehyde **9**.



Scheme 1. Retrosynthetic analysis of (*R*)-goniothalamin (**1**).

At the beginning of the first route (Scheme 2) we have conducted the protection reaction of (*R*)-glycidol (**4**) with *p*-methoxybenzyl bromide (PMB-Br) in the presence of NaH[33] and obtained PMB ether, **10** in 95% yield. Then the compound **10** was subjected for nucleophilic ring opening of epoxide with ethyl propiolate in the presence of n-BuLi and $BF_3{\cdot}Et_2O$,[34] to give homopropargilic alcohol, **3** in an yield of 90%.



Scheme 2. Synthesis of **1** from (*R*)-glycidol (**4**).

The alkyne function of **3** was then partially and stereoselectively reduced to (*Z*)-olefin, **11** in 95% yield under Lindlar's hydrogenation condition ($Pd/CaCO_3$, H_2).[35] The (*Z*)-olefin (**11**) obtained on treatment with pyridinium *p*-toluenesulfonate (PPTS)[36] under reflux in $CHCl_3$ was provided cyclized product (lactone), **12** in 92% yield. The PMB ether group of **12** was then uninstalled successfully with DDQ in $CHCl_3$:H_2O (8:1) at room temperature[37] and the deprotected alcohol **2** was obtained in 94% yield.

Compound **2** was converted into **1** by Swern oxidation followed by olefin synthesis in one-pot. In this connection several attempts were made for the preparation of **1**. In one attempt, we have oxidized **2** under Swern oxidation conditions [$(COCl)_2$, CH_2Cl_2, DMSO, Et_3N, −78 °C, 30 min)] into its corresponding aldehyde **A** (Figure 1), and added a solution of **B** (Figure 1) in THF and KHMDS at −78 °C to afford **1** with only 20% yield (Julia-Kocienski olefination).[28,38] In another attempt we have used sulfoxide modified Julia-Lythgoe procedure[39] to react Swern oxidation product (**A**) with benzyl phenyl sulfone (**C**) (Figure 1) to give goniothalamin (**1**) in 80% yield. This step revealed that the final step of the reported procedure for the construction of **1**, by Pospíšil and Markó.[28]

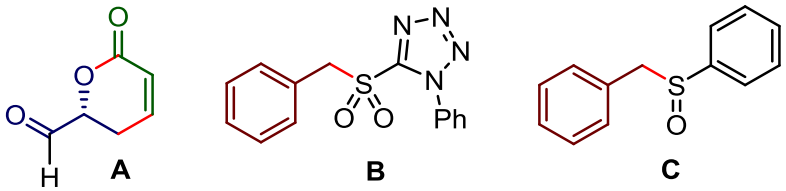
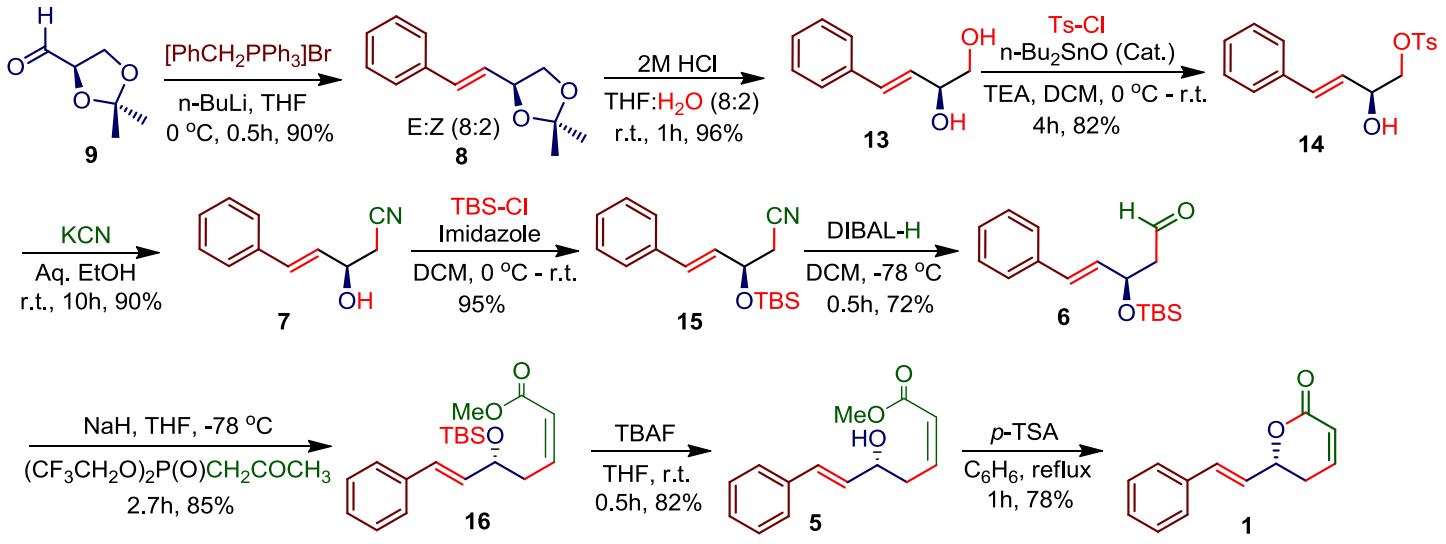


Figure 1. Structures of compounds **A**, **B** and **C**.

We have started the second route (Scheme 3) by a Wittig olefination[40] reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde (**9**) with benzyltriphenylphosphonium bromide in the presence of n-BuLi to obtain olefin, **8** in 90% yield as 8:2 ratio of *E*:*Z* isomers and the *E*-isomer has been separated by column chromatography was used for further step. The acetonide function of *E*-isomer (**8**) was uninstalled to 1,2-diol,

13 (96% yield) with 2M HCl in a mixture of H_2O and THF (2:8) was subjected for selective protection (tosylation) of primary alcoholic function using (*n*-butyl)$_2$SnO (catalytic amount), tosyl chloride and triethylamine (TEA)[41] to furnish compound **14** in 82% yield. Tosylate, **14** was used for nucleophilic substitution reaction with KCN in aq. ethanol[42] to furnish β-cyanohydrin, **7** (90% yield), was used to react with *tert*-butyldimethylsilyl chloride (TBS-Cl) in the presence of imidazole[40] to give TBS protected cyanohydrin, **15** in 95% yield.



Scheme 3. Synthesis of **1** from 2,3-O-isopropylidene-D-glyceraldehyde (**9**).

Compound **15** was partially reduced to aldehyde, **6** (72% yield) by using diisobutylaluminium hydride (DIBAL-H) in CH_2Cl_2 at −78 °C.[43] Aldehyde, **6** was subjected for stereoselective olefination under Still-Gennari conditions[44,45] to provided *cis*-olefin **16** in 85% yield. The TBS function of **16** was uninstalled with tetra-n-butylammonium fluoride (TBAF)[46] to give compound **5** (82% yield), which was on reflux in benzene with *p*-toluenesulfonic acid (*p*-TSA)[47] yielded the target compound (lactone) goniothalamin (**1**) in 78% yield.

The first method has been developed with the reaction sequence; etherification (protection), epoxide ring opening, partial and stereoselective reduction (Lindlar's alkyne hydrogenation), lactonization (ester formation), deprotection, oxidation and stereoselective (sulfone) olefin synthesis. The second method involves the Wittig olefination, ketal hydrolysis, tosylation (protection), nucleophilic replacement, silyl ether formation (protection), nitrile partial reduction, stereoselective (Still-Gennari) olefination and cyclic ester formation (lactonization). These straightforward sequences may be used as the teaching exercise for sophomore or junior's courses in organic chemistry to educate on anti-cancer agents.

Conclusions

In summary, we have developed two independent routes for the synthesis of goniothalamin, a significant anti-cancer agent. Simple reactions with high yields in each step, use of commercially available chiral starting materials and inexpensive reagents are the notable advantages of the present methods. These methods with simple sequence of a variety of organic transformations may be adopted for the sophomore or junior's courses in organic chemistry.

Experimental Section

General. Solvents were dried over standard drying agents and distilled prior to their use. The reagents and starting materials were purchased from Aldrich and Acros were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under nitrogen. Organic portion after workup was dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. All column chromatographic separations were performed using silica gel (Acme's 60-120 mesh). ^{1}H NMR (200 MHz & 300 MHz) and ^{13}C NMR (50 MHz and 75 MHz) spectra were measured with a Varian Gemini FT-200 MHz & Bruker Avance 300 MHz with tetramethylsilane (TMS) as an internal standard in $CDCl_3$. Coupling constant (*J*) values were given in Hz. IR spectra were recorded on a Perkin-Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with Horiba high sensitive polarimeter SEPA-300 at 25^o. Mass spectra were recorded on Agilent Technologies 1100 Series (Agilent Chemistation Software).

(*R*)-2-[(4-Methoxybenzyloxy)methyl]oxirane (10). To a stirred solution of NaH (1.24 g, 54 mmol) in THF (50 ml) at 0 ^{o}C was added (*R*)-glycidol **4** (2 g, 27 mmol) in dry THF (10 ml). After 20 min, *p*-methoxybenzyl bromide (PMB-Br) (5.94 g, 29.7 mmol) was added drop wise and stirred for 3h at room temperature (r.t.). After completion, the reaction was quenched with water and extracted into AcOEt (3 x 30 ml). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated in vacuo to give crude product, which was purified over silica gel column chromatography (CC) by using AcOEt:PE (1:9) as eluent to afford the epoxide **10** (4.98 g, 95% yield) as a viscous liquid. $[\alpha]_D^{25}$ = +3.2° (*c* = 1.5, $CHCl_3$); IR (neat): 3028, 2954, 1597, 1490, 1092, 762; ^{1}H NMR (300 MHz, $CDCl_3$): 7.21 (*d*, *J* 8.0 Hz, 2 H), 6.81 (*d*, *J* 8.0 Hz, 2 H), 4.51−4.41 (*m*, 2 H), 3.76 (*s*, 3 H), 3.64 (*dd*, *J* 3.0, 11.3 Hz, 1 H,), 3.35 (*dd*, *J* 5.2, 11.3 Hz, 1 H), 3.10−3.05 (*m*, 1 H), 2.72 (*t*, *J* 4.5, 9.0 Hz, 1 H), 2.54−2.51 (*m*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.2, 129.8, 129.3, 113.7, 72.8, 70.4, 55.1, 50.7, 44.1; LC-MS: 217 ([M + Na] $^+$).

Ethyl (*R*)-6-(4-methoxybenzyloxy)-5-hydroxyhex-2-ynoate (3). To a cooled (-78 °C) solution of ethyl propiolate (2.02 g, 20.6 mmol) in dry THF (25 ml) was added *n*-BuLi (1.6M, 12.9 ml, 20.6 mmol) drop wise and stirred for 15 min, then added $BF_3{\cdot}Et_2O$ (2.61 ml, 20.6 mmol) and continued stirring for an additional 15 min. Once the formation of dark brown alkyneborane was observed, a solution of epoxide **10** (2 g, 10.3 mmol) in THF (10 ml) was added and stirred for 30 min at -78 °C. After completion, the reaction was quenched at −78 ^{o}C by the addition of saturated Na_2SO_4 (20 ml) and the reaction mixture was extracted with AcOEt (3 x 30 ml). The combined organic phase was washed with brine and dried over anhyd. Na_2SO_4 and concentrated to give crude mass, which was purified by CC (silica gel) using AcOEt:PE (1:9) as an eluent to give the compound **3** (2.71 g, 90% yield) as an oily compound. $[\alpha]_D^{25}$ = +18.2^o (*c* = 1, $CHCl_3$); IR (neat): 3451, 2912, 2865, 2238, 1709, 1612, 1513, 1254, 1076, 823; ^{1}H NMR (300 MHz, $CDCl_3$): 7.25 (*d*, *J* 8.0 Hz, 2 H), 6.85 (*d*, *J* 8.0 Hz, 2 H), 4.45 (*s*, 2 H), 4.15 (*q*, 2 H), 3.98−3.90 (*m*, 1 H), 3.82 (*s*, 3 H), 3.55−3.42 (*m*, 2 H), 3.10 (*brs*, 1 H), 2.58 (*d*, 2 H), 1.28 (*t*, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): 171.2, 159.4, 153.6, 129.8, 129.5, 113.9, 85.4, 74.8, 73.1, 72.4, 68.3, 55.3, 23.8, 14.06; LC-MS: 315 ([M + Na] $^+$).

Ethyl (*R,Z*)-6-(4-methoxybenzyloxy)-5-hydroxyhex-2-enoate (11). To a solution of compound **3** (2.6 g, 8.9 mmol) and quinoline (200 µl) in benzene (20 ml) was added Pd/$CaCO_3$ (200 mg) and flushed with hydrogen gas and stirred for 1h under hydrogen atmosphere and the progress of reaction was ensured by thin layer chromatography (TLC). After completion of the reaction, catalyst was filtered, concentrated and purified on CC (silica gel) using AcOEt:PE (2:8) as an eluent to afford the (*Z*)-acrylate **11** (2.49 g, 95% yield) as a liquid. $[\alpha]_D^{25}$ = +5.6^o (*c* = 0.5, $CHCl_3$); IR (neat): 3448, 2958, 1716, 1632, 1512, 1458, 1076, 823; ^{1}H NMR (300 MHz, $CDCl_3$): 7.19 (*d*, *J* 7.8 Hz, 2 H), 6.81 (*d*, *J* 7.9 Hz, 2 H), 6.42−6.33 (*m*, 1 H); 5.86 (*d*, *J* 11.3, 1 H), 4.43 (*s*, 2 H), 4.15 (*q*, 2 H),

3.89−3.78 (*m*, 1 H), 3.72 (*s*, 3 H), 3.58−3.45 (*m*, 2 H), 2.64−2.38 (*m*, 2 H), 1.42 (*t*, *J* 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): 167.6, 158.4, 146.9, 129.9, 129.6, 122.9, 113.8, 74.3, 73.6, 68.9, 60.1, 54.7, 32.4, 14.0; HRMS: calcd. for $C_{16}H_{22}O_5$ $[M + H]^+$ 295.1523, found 295.1498.

(*R*)-6-[(Benzyloxy)methyl]-5,6-dihydropyran-2-one (12). Compound **11** (1 g, 3.65 mmol) was dissolved in $CHCl_3$ (20 ml) and added pyridinium *p*-toluenesulfonate (PPTS) (0.73 g, 3.65 mmol) and refluxed for 4h. After completion of the reaction as ensured by TLC, water was added and extracted with $CHCl_3$ (3 x 30 ml). The combined organic layer was washed with brine, dried over anhyd. Na_2SO_4 and concentrated. The resulted crude product was purified over silica gel CC using AcOEt:PE (2:8) as an eluent to afford the α-pyrone, **12** (776 mg, 92% yield) as a liquid. $[\alpha]_D^{25}$ = −8.2° (*c* = 1, $CHCl_3$); IR (neat): 2928, 1716, 1390, 1264, 1083; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (*d*, *J* 8.1 Hz, 2 H); 6.93−6.80 (*m*, 3 H), 5.99 (*d*, *J* 11.0 Hz, 1 H), 4.64−4.54 (*m*, 1 H), 4.52 (*s*, 2 H), 3.79 (*s*, 3 H), 3.65 (*d*, *J* 5.1 Hz, 2 H), 2.55−2.32 (*m*, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): 163.6, 159.3, 144.8, 129.3, 121.1, 113.8, 73.2, 70.4, 55.2, 26.1; HRMS: calcd. for $C_{14}H_{16}O_4$ $[M + Na]^+$ 271.2738, found 271.2725.

(*R*)-5,6-Dihydro-6-(hydroxymethyl)pyran-2-one (2). To a stirred solution of α-pyrone, **12** (720 mg, 2.9 mmol) in CH_2Cl_2/H_2O (8:2) was added DDQ (1.31 g, 5.8 mmol) and stirred for 1h at r.t. After the completion as ensured by TLC, the reaction mixture was quenched with saturated aq. $NaHCO_3$, added CH_2Cl_2 and extracted into CH_2Cl_2 (2 x 100 ml). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated to give crude product, was purified over silica gel CC using AcOEt:PE (1:1) to afford pure compound **2** (352 mg, 94% yield) as an oily substance. $[\alpha]_D^{25}$ = +22.8° (*c* = 1, $CHCl_3$); IR (neat): 3415, 2927, 1715, 1390, 1262, 1083, 1039; ^{1}H NMR (300 MHz, $CDCl_3$): 6.96−6.88 (*m*, 1 H), 5.98 (*d*, *J* 11.0 Hz, 1 H), 4.56−4.48 (*m*, 1 H), 3.82−3.68 (*m*, 2 H), 3.35 (*brs*, 1 H), 2.68−2.53 (*m*, 1 H), 1.38−2.24 (*m*, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.3, 145.7, 120.5, 78.4, 63.3, 25.1; LC-MS: 129 ($[M + H]^+$).

Goniothalamin [(*R*)-5,6-dihydro-6-styrylpyran-2-one] (1). Compound **1** was synthesized from **2** by the reported procedure[28] as follows.

To a stirred solution of oxalyl chloride (93 µl, 1.25 mmol) in CH_2Cl_2 (5 ml) was added a solution of dimethylsulfoxide (132 µl, 1.87 mmol) in CH_2Cl_2 (2 ml) at −78 °C under nitrogen atmosphere. After 15 min, (*R*)-5,6-dihydro-6-(hydroxymethyl)pyran-2-one (**2**) (80 mg, 0.63 mmol) was added and the reaction mixture was stirred for further 30 min at the same temperature.

In another flask a solution of sulfoxide (benzyl phenyl sulfone) (110 mg, 0.62 mmol) in dry THF (6.2 ml, 0.1M solution) was cooled to −78 °C and lithium diisopropylamide (LDA) (340 µl, 2M solution in THF, 0.672 mmol) was added drop wise. The color of the reaction mixture changed from light yellow to orange red. After stirring the mixture at −78 °C for 30 min, aldehyde (**A**) obtained in Swern oxidation in THF was added drop wise and the mixture was stirred for an additional 2h at −78 °C. Benzoyl chloride (78 µl, 0.672 mmol) in dry THF (0.5 mL) was added. The resultant mixture was stirred for 30 min at −78 °C and then allowed to warm to r.t. over 1h and stirred for additional 30 min at r.t. $Me_2N(CH_2)_3NH_2$ (119 µl, 0.672 mmol) was added to this and the resultant suspension was stirred for 10 min at r.t. The mixture was diluted with 6 ml of Et_2O/H_2O (1:1) and the layers formed were separated. The aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic layer was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give the crude product, which was used without purification for the next step (reductive elimination). To a solution of SmI_2 (24.5 ml, 0.1M THF solution, 4 eq.) was added HMPA (425 µl, 2.48 mmol) and the mixture was cooled to −78 °C. The crude product (246 mg, 0.612 mmol) in dry THF (0.5 mL) was added drop wise and the resulting mixture was stirred at −78 °C for additional 30 min. Then, saturated aq. NH_4Cl (15 ml) was added and the whole mixture was allowed to warm to r.t. The layers were separated and the aqueous phase was extracted with Et_2O (3 x 20 ml). The combined organic layers were washed with 10% aq. $Na_2S_2O_3$ (15 ml), water (15 ml) and brine (15 ml), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was then

purified by silica gel CC using AcOEt:PE (2:8) as eluent to afford compound **1** as white solid with 80% yield in two sequential steps (Swern oxidation followed by sulfoxide Julia-Lythgoe olefination reaction). $[\alpha]_D^{25}$ = +168.2^o (*c* = 1.5, $CHCl_3$) [lit.[48] $[\alpha]_D^{25}$ = +170.3^o (*c* = 1.38, $CHCl_3$)]; m.p. 80-83 ^{o}C [lit.[48] m.p. 81-82 ^{o}C]; IR (neat): 3052, 3027, 2924, 1725, 1242, 814, 693; ^{1}H NMR (300 MHz, $CDCl_3$): 7.36−7.27 (*m*, 5 H), 6.88 (*dt*, *J* 4.3, 9.6 Hz, 1 H), 6.68 (*d*, *J* 15.8 Hz, 1 H), 6.23 (*dd*, *J* 6.2, 15.8 Hz, 1 H), 6.05 (*d*, *J* 9.8 Hz, 1 H), 2.54−2.48 (*m*, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): 164.1, 144.9, 135.2, 133.2, 128.6, 128.1, 126.7, 125.4, 121.2, 77.9, 30.07; LC-MS: 223 ([M + Na]$^+$).

(*S*)-2,2-Dimethyl-4-styryl-1,3-dioxolane (8). To a suspension of $[PPh_3CH_2Ph]Br$ (6.64 g, 15.4 mmol) in dry THF (50 ml) was added *n*-BuLi (1.6M in hexane, 9.6 ml, 15.4 mmol) at 0 ^{o}C and stirred for 15 min. Then a solution of ketal, **9** (2 g, 15.4 mmol) in THF (10 ml) was added drop wise and the mixture was allowed to stir for an additional 0.5 h at 0 ^{o}C. The reaction was quenched with saturated NH_4Cl (40 ml) and extracted with diethyl ether (3 x 50 ml). The ether solution was washed with brine and dried over anhyd. Na_2SO_4. After removal of solvent, the crude product obtained was purified on a silica gel CC with AcOEt:PE (2:98) (eluent) to afford pure compound **8** (2.82 g, 90% yield) as a liquid as 8:2 mixture of geometric isomers (both are separated and 2.25 g, of *E*-isomer obtained in 72% yield). $[\alpha]_D^{25}$ = +30.2^o (*c* = 1.5, $CHCl_3$); IR (neat): 3062, 3024, 2986, 2929, 2860, 1610, 1498, 1296, 1060; ^{1}H NMR (300 MHz, $CDCl_3$): 7.35−7.17 (*m*, 5 H), 6.61 (*d*, *J* 15.8 Hz, 1 H), 6.10 (*dd*, *J* 7.5, 15.8 Hz, 1 H), 4.65−4.57 (*m*, 1 H), 4.12−4.08 (*m*, 1 H), 3.63 (*t*, *J* 7.5 Hz, 1 H), 1.44 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): 136.1, 133.2, 128.4, 127.8, 126.5, 126.4, 109.3, 77.0, 69.3, 26.6, 25.7; LC-MS: 205 ([M + H]$^+$).

(2*S*,*E*)-4-Phenylbut-3-ene-1,2-diol (13). To a stirred solution of compound **8** (2.1 g, 10.3 mmol) in 15 mL of THF/H_2O (8:2), was added 2N HCl (4 mL) drop wise and stirred the solution at r.t. for 2h. After completion, the reaction was quenched with saturated $NaHCO_3$ and extracted with AcOEt (3 x 25 mL). The combined organic layer was dried over anhyd. Na_2SO_4 and concentrated to a give a crude mass, which was purified over silica gel CC eluting with AcOEt:PE (1:1) to afford the pure diol **13** as a white solid (1.62 g, 96% yield); m.p. 62-64 ^{o}C; $[\alpha]_D^{25}$ = +6.2^o (*c* = 1.5, $CHCl_3$); IR (neat): 3469, 3260, 3080, 2936, 1639, 1598, 1490, 1079, 776; ^{1}H NMR (300 MHz, $CDCl_3$): 7.26−7.15 (*m*, 5 H), 6.55 (*d*, *J* 15.8 Hz, 1 H), 6.09 (*dd*, *J* 6.0, 15.8 Hz, 1 H), 4.38−4.32 (*m*, 1 H), 4.14 (*brs*, 2 H), 3.66 (*dd*, *J* 3.0, 11.3 Hz, 1 H), 3.51 (*dd*, *J* 8.3, 11.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): 136.2, 133.2, 129.6, 128.6, 128.3, 127.5, 68.6, 66.1; LC-MS: 187 ([M + Na]$^+$).

(*S*,*E*)-2-Hydroxy-4-phenylbut-3-enyl 4-methylbenzenesulfonate (14). To a stirred solution of diol **13** (1.5 g, 9.14 mmol), catalytic amount of dibutyltin oxide (15 mg) and triethylamine (2.88 ml, 22.8 mmol) in dichloromethane (30 ml) was added at 0 ^{o}C. After 15 min tosyl chloride (1.74 g, 9.14 mmol) in CH_2Cl_2 (10 ml) was added drop wise and stirred the reaction mixture for 4h at r.t. After completion, the reaction mixture was diluted with water (50 ml) and extracted into CH_2Cl_2 (3 x 50 ml). The combined organic portion was washed with brine solution and dried over anhyd. Na_2SO_4. After the evaporation of solvent under reduced pressure the crude residue was purified on a silica gel CC by eluting with AcOEt:PE (3:7) to afford the compound **14** as a white solid (2.38 g, 82% yield); m.p. 138-141 ^{o}C; $[\alpha]_D^{25}$ = +1.6^o (*c* = 1, $CHCl_3$). IR (neat): 3449, 2924, 1640, 1494, 1359, 1176, 1096; ^{1}H NMR (300 MHz, $CDCl_3$): 7.77 (*d*, *J* 7.5 Hz, 2 H), 7.28−7.18 (*m*, 7 H); 6.62 (*d*, *J* 15.8 Hz, 1 H), 6.00 (*dd*, *J* 6.0, 15.8 Hz, 1 H), 4.54−4.49 (*m*, 1 H), 4.10−4.05 (*m*, 1 H), 3.96−3.90 (*m*, 1 H), 2.95 (*brs*, 1 H), 2.41 (*s*, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): 144.8, 135.6, 135.3, 132.9, 129.7, 128.6, 128.3, 127.9, 126.7, 123.5, 75.3, 71.4, 21.6; LC-MS: 319.2 ([M + H]$^+$); elemental anal calcd. for $C_{17}H_{18}O_4S$ (218.23) C 64.13, H 5.71, S 10.07; found C 64.38, H 5.64, S 10.18.

(*R*,*E*)-3-Hydroxy-5-phenylpent-4-enenitrile (7). To a cooled (0 ^{o}C) solution of tosylate, **14** (2.3 g, 7.23 mmol) in 60% aqueous ethanol (30 ml) was added KCN (0.71 g, 10.84 mmol) and was stirred at r.t. for 10h. After completion of the reaction, ethanol was evaporated under vacuum and diluted with water (20 ml), extracted with AcOEt (3 x 30 ml) and the combined organic phase was washed with brine and dried over anhyd. Na_2SO_4 and the solvent was removed under reduced pressure to get crude residue. The crude product was subjected

silica gel CC using AcOEt:PE (3:7) as an eluent to afford the compound **7** (1.12 g, 90% yield) as colorless oil. $[\alpha]_D^{25}$ = −8.25° (*c* = 1, $CHCl_3$); IR (neat): 3447, 3028, 2252, 1653, 1494, 752; ^{1}H NMR (300 MHz, $CDCl_3$): 7.32−7.20 (*m*, 5 H), 6.61 (*d*, *J* 15.8 Hz, 1 H), 5.68 (*dd*, *J* 6.0, 15.8 Hz, 1 H), 4.82−4.68 (*m*, 1 H), 3.39 (*brs*, 1 H), 2.54−2.51 (*m*, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): 135.5, 132.4, 128.5, 128.2, 128.1, 126.6, 117.3, 68.3, 26.1; LC-MS: 174.18 ([M + H]$^+$); elemental anal calcd. for $C_{11}H_{11}NO$ (173.28) C 76.28, H 6.40, N 8.09; found C 76.14, H 6.47, N 8.19.

(3*R*,4*E*)-3-(*tert*-Butyldimethylsilanyloxy)-5-phenylpent-4-enenitrile (15). To a cooled solution (0 °C) of cyano compound **7** (1.1 g, 6.35 mmol) and imidazole (1.08 g, 15.89 mmol) in CH_2Cl_2 (20 ml) was added drop wise, *tert*-butyldimethylsilyl chloride (TBS-Cl) (0.96 g, 6.35 mmol). After completion, the reaction mixture was diluted with water (15 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layer was washed with brine (10 ml), dried over anhyd. Na_2SO_4 and concentrated under vacuum to furnish the crude residue. The obtained crude residue was purified by flash CC on silica using AcOEt:PE (1:9) as an eluent to afford pure compound **15** (1.73 g, 95% yield) as a colourless oil. $[\alpha]_D^{25}$ = +5.6° (*c* = 1.5, $CHCl_3$); IR (neat): 3068, 3027, 2932, 2856, 2254, 1632, 1470, 1172; ^{1}H NMR (300 MHz, $CDCl_3$): 7.39−7.25 (*m*, 5 H), 6.63 (*d*, *J* 15.6 Hz, 1 H), 6.17 (*dd*, *J* 6.6, 15.8 Hz, 1 H), 4.61−4.54 (*m*, 1 H), 2.57 (*d*, *J* 6.4 Hz, 2 H), 0.93 (*s*, 9 H), 0.15 (*s*, 3 H), 0.09 (*s*, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): 135.8, 131.6, 129.2, 128.5, 128.06, 126.5, 117.2, 69.5, 27.5, 25.6, 18.0, −4.4, −5.0; LC-MS: 326.2 ([M + K]$^+$), elemental anal calcd. for $C_{17}H_{25}NOSi$ (287.17) C 71.03, H 8.77, N 4.87; found C 71.16, H 8.68, N 4.89.

(3*R*,4*E*)-3-(*tert*-Butyldimethylsilanyloxy)-5-phenylpent-4-enal (6). To a stirred solution of compound **15** (1.7 g, 5.92 mmol) in CH_2Cl_2 (20 ml) was added DIBAL-H (4.21 ml, 20 wt.% in sol.) slowly for 15 min at −78 °C and the reaction mixture was stirred for 30 min at −78 °C. After completion, the reaction mixture was quenched with saturated sodium potassium tartrate solution (15 ml). The reaction mixture was stirred vigorously at r.t. for additional 1h and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layer was washed with brine, dried over anhyd. Na_2SO_4 and solvent was removed under vacuum to give a crude product, which was purified by silica gel CC using AcOEt:PE (2:50) as eluent to afford pure aldehyde, **6** (1.24 g, 72% yield) as a colorless oil. $[\alpha]_D^{25}$ = +5.3° (*c* = 0.5, $CHCl_3$); IR (neat): 3047, 2928, 2842, 1733, 1590, 1476, 1370, 1188, 1043, 823; ^{1}H NMR (300 MHz, $CDCl_3$): 9.83 (*s*, 1 H), 7.38−7.16 (*m*, 5 H), 6.49 (*d*, *J* 15.8 Hz, 1 H), 5.70 (*dd*, *J* =6.2, 15.8 Hz, 1 H), 5.22−5.12 (*m*, 1 H), 2.80−2.54 (*m*, 2 H), 0.81 (*s*, 9 H), −0.06 (*s*, 3 H), −0.13 (*s*, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): 201.5, 136.6, 134.5, 129.5, 128.7, 128.6, 127.5, 65.1, 51.4, 25.8, 18.1; LC-MS: 291 ([M + H]$^+$).

(5*R*,2*Z*,6*E*)-5-(*tert*-Butyldimethylsilanyloxy)-7-phenylhepta-2,6-dienoate (16). To a cooled (0 °C) suspension of NaH (0.19 g, 8.27 mmol) in dry THF (5 ml) under N_2 atmosphere was added bis(2,2,2-trifluoromethyl) (methoxy carbonylmethyl)phosphonate (0.87 ml, 4.13 mmol) in dry THF (3 ml) and was allowed to stirring for 30 min. Reaction temperature was adjusted to −78 °C, then the aldehyde, **6** (1.2 g, 4.13 mmol) was added in dry THF (5 ml) drop wise over a period of 10 min. The resulting mixture was stirred for 2h at −78 °C. After completion of the reaction, the reaction mixture was quenched with saturated NH_4Cl and extracted into Et_2O (3 x 15 ml). The combined organic phase was dried over anhyd. Na_2SO_4 and solvent was evaporated under vacuum to obtain crude product, which was purified by flash CC (silica gel) by eluting with AcOEt:PE (1:9) to afford the (*Z*)-acrylate **16** (1.21 g, 85% yield) as light yellow oil. $[\alpha]_D^{25}$ = +16.2° (*c* = 0.5, $CHCl_3$); IR (neat): 3047, 2928, 2842, 1733, 1590, 1476, 1370, 1188, 1043, 823; ^{1}H NMR (300 MHz, $CDCl_3$): 7.34−7.16 (m, 5 H), 6.46−6.31 (*m*, 2 H), 5.85 (*d*, *J* 11.7 Hz, 1 H), 5.65 (*dd*, *J* 6.0, 15.8 Hz, 1 H), 4.76−4.64 (*m*, 1 H), 3.70 (*s*, 3 H), 3.14−2.84 (*m*, 2 H), 0.81 (*s*, 9 H), −0.11 (*s*, 3 H), −0.17 (*s*, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): 166.7, 146.3, 136.7, 135.3, 128.8, 128.1, 127.0, 120.5, 68.0, 51.0, 37.3, 25.7, 18.0, −4.3, −5.01; HRMS: calcd for $C_{20}H_{30}O_3Si$ [M + Na]$^+$ 369.2728, found 369.3167.

(*R*,2*Z*,6*E*)-5-Hydroxy-7-phenylhepta-2,6-dienoate (5). To a cooled (0 °C) solution of compound **16** (1 g, 2.89 mmol) in dry THF (10 ml) was added drop wise, TBAF (2.89 ml, 2.89 mmol, 1M solution in THF) and the mixture was stirred for 30 min at r.t.. After completion of the reaction, water (5 ml) was added to the reaction mixture and extracted with AcOEt (3 x 15 ml). The combined organic phase was washed with brine, dried over anhyd. Na_2SO_4 and concentrated to give the crude mass, which was purified by silica gel CC eluting with AcOEt:PE (2:8) to afford the pure compound **5** (0.551 g, 82% yield) as a liquid. $[\alpha]_D^{25}$ = +11.50^o (*c* = 1, $CHCl_3$); IR (neat): 3445, 2928, 1715, 1636, 1452, 1014, 756; ^{1}H NMR (300 MHz, $CDCl_3$): 7.37−7.26 (*m*, 5 H), 6.57 (*d*, *J* 15.8 Hz, 1 H), 6.41−6.32 (*m*, 1 H), 5.95 (*d*, *J* 11.5 Hz, 1 H), 5.74 (*dd*, *J* 6.0, 15.8 Hz, 1 H), 4.75−4.67 (*m*, 1 H), 3.72 (*s*, 3 H), 3.10−2.87 (*m*, 2 H); LC-MS: 233 ([M + H]$^+$).

Goniothalamin [(R)-5,6-dihydro-6-styrylpyran-2-one] (1). To a stirred solution of compound **5** (0.2 g, 0.86 mmol) in benzene (15 ml) was added a catalytic amount of *p*-toluenesulfonic acid (0.014 mg, 0.08 mmol) under nitrogen atmosphere and reaction mixture was refluxed at 90 ^{o}C for 1h. Then the reaction mixture was cooled to r.t., quenched by an addition of solid $NaHCO_3$, the mixture was filtered and the solvent was evaporated under vacuum to obtain the crude residue, which was purified by flash CC on silica gel by eluting with AcOEt:PE (4:6) to afford goniothalamin **(1)** (0.134g, 78% yield) as a white solid. The spectroscopic data were identical with the data given at Section **2.6**.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra were given at Supplementary Material.

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