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Stereoselective total synthesis of (+)-cryptofolione and (+)-goniothalamin ☆

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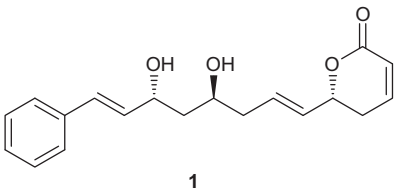
ABSTRACT

The stereoselective total synthesis of two naturally occurring α-pyrone derivatives (+)-cryptofolione and (+)-goniothalamin has been accomplished via a common intermediate. The synthetic sequence involves the asymmetric reduction of a propargyl ketone and olefin cross-metathesis as the key reactions.

1. Introduction

Naturally occurring α-pyrone derivatives exhibit various important biological properties, such as cytotoxic, antiviral, and antibacterial activities.[1] (+)-Cryptofolione **1**, a member of this group, was isolated from different *Cryptocarya* species.[2] The compound was found to be active against the trypomastigots of *Trypanosoma cruzi* reducing their number by 77% at 250 μg/ml.[3] (+)-Goniothalamin **2**, another related α-pyrone derivative, was isolated from the genus *Cryptocarya*[4] and *Goniothalamus*.[5] The compound displayed an in vitro cytotoxic effect by inducing apoptosis on different cancer cell lines, such as breast carcinoma, ovarian carcinoma, and leukemia.[6] The synthesis of both of these compounds (+)-cryptofolione **1**[7] and (+)-goniothalamin **2**[8] has recently become an attractive target to organic chemists. The stereoisomers of cryptofolione *O*-benzyl ethers have also been synthesized.[9] In continuation of our work[10] on the construction of natural α-pyrones we have synthesized **1** and **2** with a convenient approach through a common intermediate.



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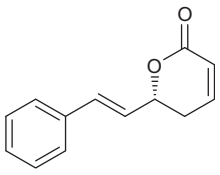

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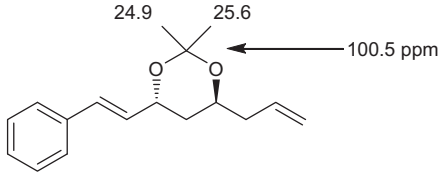
2. Results and discussion

The retrosynthetic analysis (Scheme 1) suggested that (+)-cryptofolione **1** could be prepared from intermediates **3** and **4** by olefin cross-metathesis. Compound **3** can be obtained from the propargyl alcohol **5** which in turn can be prepared from phenyl acetylene **6** and propane 1,3-diol **7**.

The present synthesis of (+)-cryptofolione **1** was initiated (Scheme 2) by protecting one of the hydroxyl groups of propane-1,3-diol **7** by treatment with PMB-Br in THF to yield the PMB ether **8**. Compound **8** was subjected to oxidation with PCC followed by reaction with phenyl acetylene **6** using *n*-BuLi in THF to form the propargyl alcohol **9**. The free hydroxyl group of this alcohol was oxidized with IBX in DMSO to produce the propargyl ketone **10**. The asymmetric reduction[11] of **10** was accomplished with $BH_3{\cdot}Me_2S$ in the presence of (*R*)-2-methyl-CBS-oxazaborolidine as a catalyst to generate the chiral propargyl alcohol **5** (ee 97%) with an α-OH group.

The reduction of alcohol **5** with lithium aluminium hydride in THF afforded the chiral allylic alcohol **11** in high yield. The hydroxyl group of **11** was acetylated and the PMB ether group of the product **12** was deprotected with DDQ in CH_2Cl_2–H_2O (4:1) to furnish compound **13**. This acetate derivative underwent oxidation with IBX in DMSO and the resulting aldehyde was subjected to Maruoka allylation[12] with the Binol complex (*S*,*S*)-**I** and allyl tributyltin. The reaction mixture was purified to give the desired fragment **3** and to remove its minor diastereoisomer (3%). The 1,3-*anti* relationship of the hydroxyl and acetoxy group in **3** was established by analysis of the ^{13}C NMR spectrum[13] of the corresponding acetonide **16** (Scheme 3) prepared via the dihydroxy compound **15**. The spectrum showed that the methyl groups of the acetonide appeared at δ 25.6 and 24.9 and the quaternary carbon at δ 100.5.



Compound **3** was subsequently coupled (Scheme 1) with **4** by olefin cross-metathesis reaction[14] using Grubb's second generation catalyst. Compound **4** was previously prepared by us starting from

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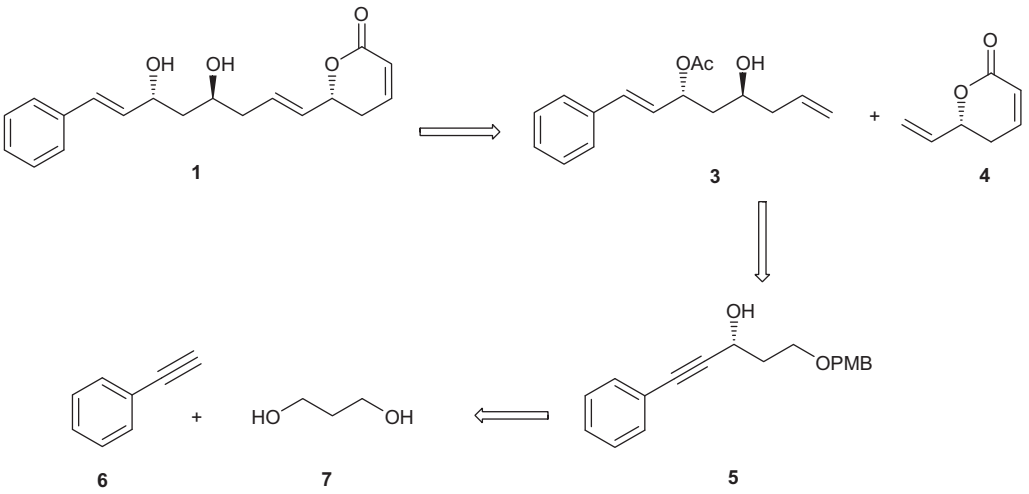
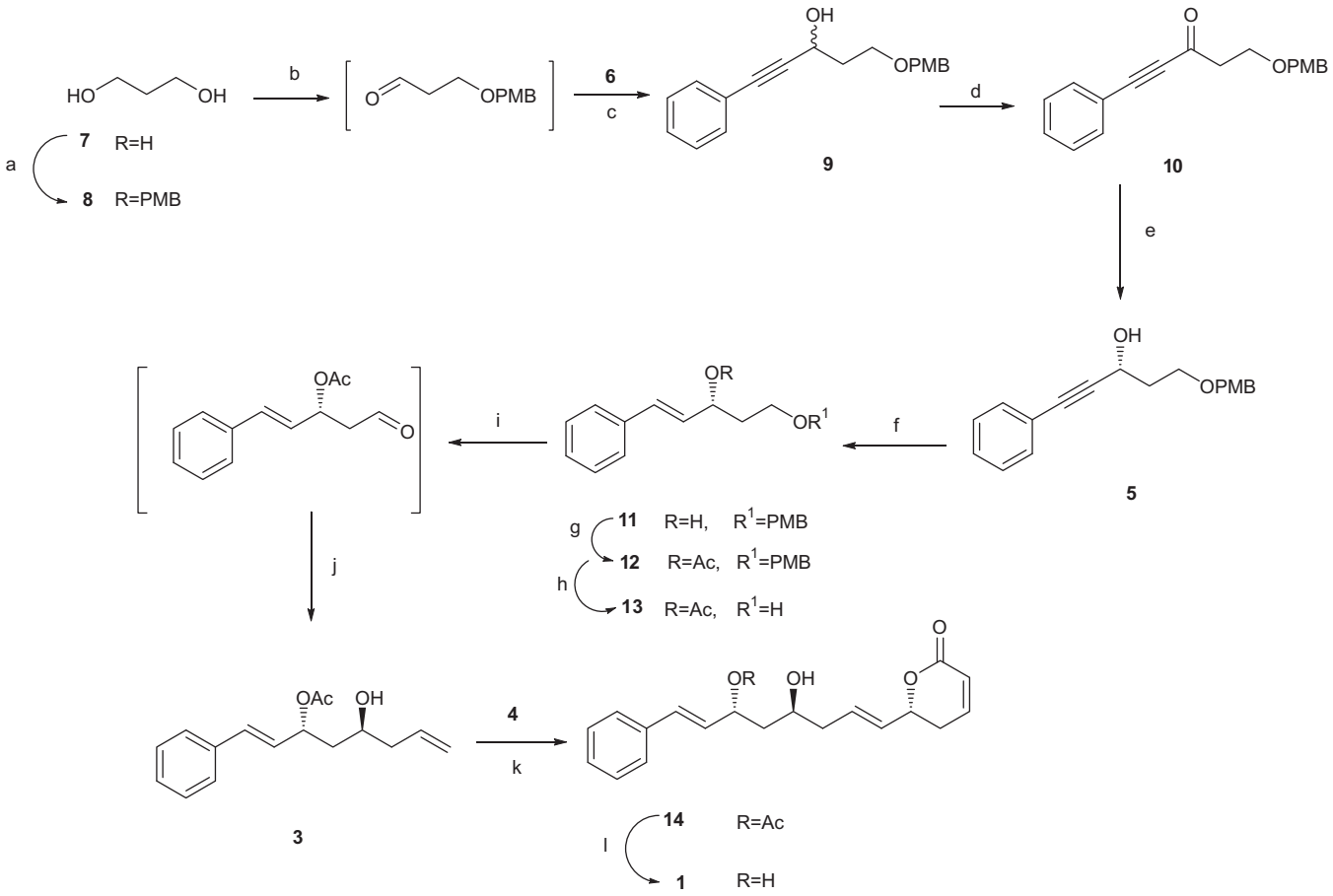
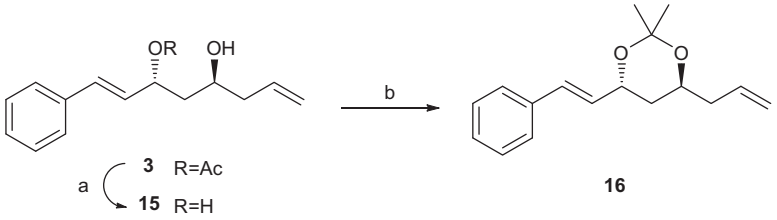


Scheme 1.

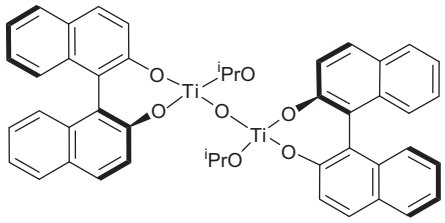


Scheme 2. Reagents and conditions: (a) NaH, PMB-Br, TBAI, THF, 0 °C to rt, 3 h, 90%; (b) PCC, DCM, Celite, rt, 1.5 h, 92%; (c) **6**, *n*-BuLi, THF, 0 °C, 2 h, 89%; (d) IBX, DMSO, DCM, 0 °C to rt, 4 h, 88%; (e) (*R*)-(Me)-CBS (1.0 M in toluene), THF, $BH_3{\cdot}Me_2S$, −20 °C, 2 h, 70%, ee 97%; (f) LAH, THF, 0 °C to rt, 2 h, 89%; (g) Ac_2O, Et_3N, DMAP, DCM, 0 °C to rt, 45 min, 91%; (h) DDQ, DCM/H_2O-8:2, 2.5 h, 83%; (i) IBX, DMSO, DCM, 0 °C to rt, 1.5 h, 92%; (j) (*S,S*)-**I**, allyl tributyl stannane, DCM, 0 °C, 18 h, 74%, (97:3, *anti*/*syn* ratio); (k) Grubb's II catalyst (0.01 mmol), DCM, 50 °C, 3 h, 71%; (l) 10% HCl, CH_3CN–H_2O, 6 h, 72%.

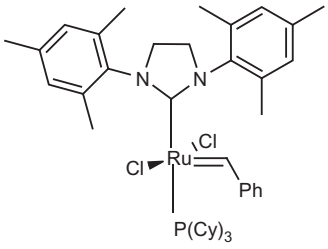


Scheme 3. Reagents and conditions: (a) K_2CO_3, methanol, rt, 30 min, 84%; (b) 2,2-DMP, acetone, *p*-TSA, 3 h, 89%.

L-ascorbic acid.[10c] The coupling reaction afforded the α-pyranone derivative **14** whose acetate group was hydrolyzed to produce the target molecule (+)-cryptofolione **1**. The spectroscopic data of **1** were identical to those reported earlier.[7]



(*S*,*S*)-**I**



Grubbs' Catalyst
(**II** generation)

The Maruoka allylation using a Ti-Binol complex and the ring closing metathesis were used previously in an approach for the synthesis of cryptofolione **1**.[7c] This method involved the addition of a complex silyloxydiene with *trans*-cinnamaldehyde. The yield of the metathesis reaction in this method was 58%. The synthesis of the stereoisomers of cryptofolione-*O*-benzyl ethers also utilized the metathesis reaction, but several attempts to deprotect the benzyl groups of the products were unsuccessful.[9] In our present method, the protecting group (acetate) was easily removed to generate the target molecule **1**.

The intermediate **13** (Scheme 2) was subsequently utilized for the synthesis of another α-pyranone derivative, (+)-goniothalamin **2** (Scheme 4). The former was oxidized with IBX in DMSO to give the corresponding aldehyde, which was subjected to Still–Gennari–Wittig reaction with $(CF_3CH_2O)_2P(O)CH_2COOMe$ to afford the α,β-unsaturated ester **17**. The acetate group of this ester was hydrolyzed with methanolic K_2CO_3 and the resulting product **18** was cyclized with methanol and PPTS to produce (+)-goniothalamin.

Another alternative approach for the synthesis of **2** was the coupling of styrene **19** with **4** (Scheme 5) by olefin cross-metathesis reaction using a Grubb's second generation catalyst. The spectroscopic data of **2** prepared by both methods (Schemes 4 and 5) were in good agreement with those reported earlier.[8]

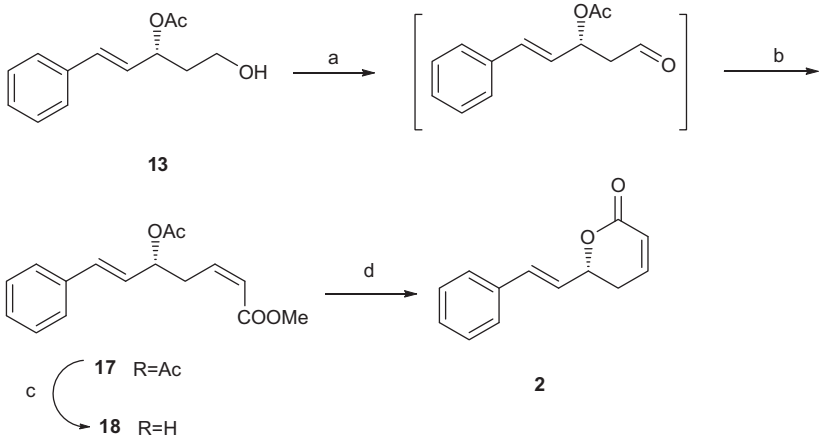
3. Conclusion

In conclusion, the stereoselective total synthesis of (+)-cryptofolione and (+)-goniothalamin has been achieved via a common intermediate. The synthesis employed the reduction of a propargyl ketone and olefin cross-metathesis as the key steps.

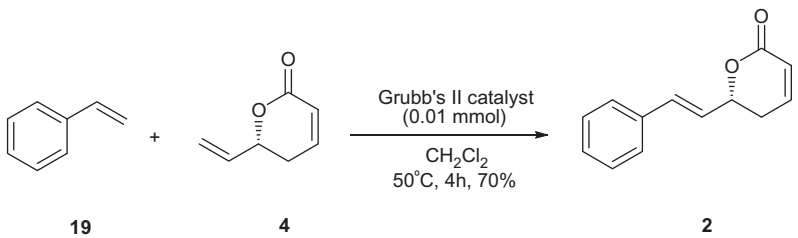
4. Experimental

4.1. General

Silica gel F_{254} plates were used for thin layer chromatography (TLC) in which the spots were examined under UV light and then developed by an iodine vapor. Column chromatography was performed with silica gel (BDH 100–200 mesh). Solvents were purified according to standard procedures. The spectra were recorded with



Scheme 4. Reagents and conditions: (a) IBX, DMSO, DCM, 0 °C to rt, 4 h, 92%; (b) NaH, $(CF_3CH_2O)_2P(O)CH_2COOMe$, THF, 0 °C to −78 °C, 1 h, 84%; (c) K_2CO_3, methanol, rt, 30 min, 70%; (d) MeOH, PPTS, 0 °C to rt, 6 h, 76%.



Scheme 5.

the following instruments; IR: Perkin–Elmer RX FT-IR spectrophotometer; NMR: Varian Gemini 200 MHz (^{1}H) and 50 MHz (^{13}C) spectrometer; ESIMS: VG-Autospec micromass. Organic extracts were dried over anhydrous Na_2SO_4. Optical rotations were measured with a JASCO DIP 300 digital polarimeter at 25 °C.

4.1.1. 3-(4-Methoxybenzyloxy) propan-1-ol 8

Propane-1,3-diol (5.0 g, 65.78 mmol) was taken in 50 mL of dry THF. Next, NaH (60% dispersion in mineral oil, 2.49 g, 65.78 mmol) was added in portions at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Tetrabutylammonium iodide (TBAI) (1.6 g, 0.66 mmol) was added to it followed by the addition of 4-methoxybenzylbromide (13.2 g, 65.78 mmol) in THF (50 mL). The reaction mixture was stirred for a further 2 h at room temperature. Ice water (15 mL) was added carefully to the reaction mixture to quench any excess of NaH. The reaction mixture was extracted with EtOAc (50 mL). The organic layer was washed with water (15 mL) and brine (20 mL). Evaporation and purification by means of silica gel chromatography (EtOAc/hexane = 20:80) afforded compound **8** (11.6 g, 90%) as a colorless liquid. IR: ν 3393, 1613, 1513, 1462, 1248 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): 7.22 (2H, d, J = 8.0 Hz), 6.83 (2H, d, J = 8.0 Hz), 4.41 (2H, s), 3.79 (3H, s), 3.70 (2H, d, J = 7.0 Hz), 3.56 (2H, d, J = 7.0 Hz), 2.52 (1H, br s), 1.86–1.74 (2H, m); ^{13}C NMR (50 MHz): δ; ESIMS: m/z 197 $[M+H]^+$, Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.46; H, 8.11.

4.1.2. 5-(4-Methoxybenzyloxy)-1-phenylpent-1-yn-3-ol 9

To a stirred solution of **8** (8 g, 40.81 mmol) in dry CH_2Cl_2 (70 mL) was added Celite (50 g) and PCC (16.98 g, 61.21 mmol) at 0 °C and the reaction was stirred for 1.5 h at room temperature. The reaction was diluted with ether (45 mL) and then passed through a silica gel column and eluted with ethyl acetate/hexane (10:90) to afford the corresponding aldehyde (7.28 g, 92%) as a colorless liquid.

To a solution (3.39 mL, 30.92 mmol) of phenyl acetylene in 50 ml of dry THF at 0 °C was added (19.3 mL, 30.92 mmol) of *n*-BuLi (1.6 M in hexane). After 30 min, the aldehyde (6 g, 30.92 mmol) was added dropwise. After being stirred for 2 h, the reaction was quenched with 25 mL of saturated NH_4Cl solution and extracted with EtOAc (3 × 35 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue upon purification by column chromatography (ethylacetate/hexane = 15:85) afforded pure 5-(4-methoxybenzyloxy)-1-phenylpent-1-yn-3-ol **9** (8.14 g 89%) as a colorless liquid; IR: ν 3425, 1612, 1513, 1443, 1247 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.16 (7H, m), 6.82, (2H, d, J = 8.0 Hz), 4.78 (1H, m), 4.49 (2H, s), 3.88 (1H, m), 3.75 (3H, s), 3.67 (1H, m), 2.11 (1H, m), 1.99 (1H, m); ^{13}C NMR (50 MHz): δ 159.2, 132.0, 129.9, 129.5, 128.7, 123.0, 113.9, 89.5, 84.8, 73.0, 67.2, 62.0, 55.1, 37.0 ESIMS: m/z 319 $[M+Na]^+$; HRESIMS: Calcd for $C_{19}H_{20}O_3$ m/z 319.1325 $[M+Na]^+$, Found m/z 319.1310 $[M+Na]^+$.

4.1.3. 5-(4-Methoxybenzyloxy)-1-phenylpent-1-yn-3-one 10

To an ice-cold solution of IBX (15.12 g, 54.05 mmol) in DMSO (30 mL), was added a solution of **9** (8 g, 27.02 mmol) in anhydrous CH_2Cl_2 (70 mL) and the reaction mixture was stirred at 25 °C for 4 h. The mixture was diluted with CH_2Cl_2 (20 mL), stirred for 4 h, filtered through a Celite pad, and the pad was washed with CH_2Cl_2 (10 mL) The combined filtrates were washed with H_2O (5 mL), dried over anhydrous Na_2SO_4, and concentrate under reduced pressure and the residue was purified by column chromatography (ethyl acetate/hexane = 2:48) to afford the pure propargyl ketone **10** as a pale yellow liquid (7.1 g, 88%). IR: ν 1670, 1611, 1512, 1248 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55 (2H, d, J = 8.0 Hz), 7.48–7.34 (3H, m), 7.28 (2H, d, J = 8.0 Hz), 6.85 (2H, d, J = 8.0 Hz), 4.49 (2H, S), 3.86 (2H, t, J = 7.0 Hz), 3.78 (3H, s), 2.93 (2H, t, J = 7.0 Hz); ^{13}C NMR (50 MHz): δ 185.9, 159.5, 133.2, 132.1, 130.9, 130.0, 129.1, 128.2, 120.1, 114.0, 91.2, 87.9, 73.0, 64.3, 55.5, 45.2; ESIMS: m/z 295 $[M+H]^+$; HRESIMS: Calcd for $C_{19}H_{18}O_3Na$ m/z 317.1168 $[M+Na]^+$, Found m/z 317.1153 $[M+Na]^+$.

4.1.4. (*R*)-5-(4-Methoxybenzyloxy)-1-phenylpent-1-yn-3-ol 5

A 1 M solution of (*R*)-(Me)-CBS in toluene (4.29 mL, 4.08 mmol) under a static atmosphere of N_2 was dissolved in anhydrous THF. To this solution was added $BH_3{\cdot}SMe_2$ (5.1 mL, 5 M in THF, 20.4 mmol) and the mixture was cooled to −20 °C. Then a solution of propargyl ketone **9** (6 g, 20.4 mmol) in anhydrous THF was added slowly via syringe and the mixture was stirred at −20 °C for 2 h. The reaction was quenched with MeOH (20 mL) at the same temperature and allowed to warm to 25 °C. The solvent was removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate/hexane = 18:82) to afford pure chiral alcohol **5** as a pale brown oil (4.2 g, 70%). $[\alpha]_D^{25} = +50.5$ (c 1.5, $CHCl_3$); IR: ν 3425, 1612, 1513, 1443, 1247 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.40–7.16 (7H, m), 6.82, (2H, d, J = 8.0 Hz), 4.78 (1H, m), 4.49 (2H, s), 3.88 (1H, m), 3.75 (3H, s), 3.67 (1H, m), 2.11 (1H, m), 1.99 (1H, m); ^{13}C NMR (50 MHz): δ 159.2, 132.0, 129.9, 129.5, 128.7, 123.0, 113.9, 89.5, 84.8, 73.0, 67.2, 62.0, 55.1, 37.0; ESIMS: m/z 319 $[M+Na]^+$; HRESIMS: Calcd for $C_{19}H_{20}O_3Na$ m/z 319.1325 $[M+Na]^+$, Found m/z 319.1316 $[M+Na]^+$.

4.1.5. (*R*,*E*)-5-(4-Methoxybenzyloxy)-1-phenylpent-1-en-3-ol 11

To a stirred solution of $LiAlH_4$ (0.535 g, 14.16 mmol) in dry THF (5 mL) under N_2 was added **7** (3.5 g, 11.82 mmol) dissolved in THF (25 mL) at 0 °C. After stirring for 2 h, the reaction mixture was quenched with a saturated Na_2SO_4 solution at 0 °C and filtered. The residue was washed with EtOAc (45 mL) and the EtOAc layer was concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/*n*-hexane—19:81) to obtain **11** (3.115 g, 89%) as a pale yellow oil; $[\alpha]_D^{25} = +4.65$ (c 1.75, $CHCl_3$); IR: ν 3420, 1612, 1511, 1453, 1249 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35–7.11 (7H. m), 6.81 (2H, d, J = 8.0 Hz), 6.54 (1H, d, J = 18.0 Hz), 6.15 (1H, dd, J = 18.0, 6.0 Hz), 4.49–4.37 (3H, m), 3.78 (3H, s), 3.69–3.54 (2H, m), 1.90–1.79 (2H, m); ^{13}C NMR (50 MHz): δ 159.2, 137.0, 132.0, 130.1, 130.0, 129.6, 128.4, 128.2, 127.1, 126.8, 113.9, 73.1, 71.8, 67.9, 55.2, 36.2; ESIMS: m/z 321 $[M+Na]^+$; HRESIMS: Calcd for $C_{19}H_{22}O_3Na$ m/z 321.1466 $[M+Na]^+$, Found m/z 217.0508 $[M+Na]^+$.

4.1.6. (*R*,*E*)-5-(4-Methoxybenzyloxy)-1-phenylpent-1-en-3-yl acetate 12

To a stirred solution of compound **11** (3 g, 10.06 mmol) in dry CH_2Cl_2 (25 mL) was added Et_3N (4.2 mL, 30.2 mmol) followed by acetic anhydride (1.8 mL, 20.13 mmol) and DMAP (0.12 g, 1.06 mmol) at 0 °C. The reaction mixture was continuously stirred for 45 min and then diluted with CH_2Cl_2 (5 mL). The organic layer was washed with brine (25 mL), and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure followed by column chromatography (ethylacetate/hexane = 5:95) afforded acetate **12** (2.7 g, 91%) as a colorless liquid; $[\alpha]_D^{25} = +24.6$ (c 0.8, $CHCl_3$); IR: ν 1735, 1612, 1511, 1453 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38–7.20 (7H, m), 6.86 (2H, d, J = 8.0 Hz), 6.60 (1H, d, J = 18.0 Hz), 6.12 (IH, dd, J = 18.0, 8.0 Hz), 5.59 (1H, m), 4.42 (2H, s), 3.79 (3H, s), 3.49 (2H, t, J = 7.0 Hz), 2.10–1.88 (5H, m); ^{13}C NMR (50 MHz): δ 170.2, 159.1, 132.2, 130.1, 129.0, 128.1, 127.8, 126.9, 126.1, 125.8, 113.9, 72.9, 72.1, 65.3, 55.0, 34.8, 31.2; ESIMS: m/z 363 $[M+Na]^+$; HRESIMS: Calcd for $C_{21}H_{24}O_4Na$ m/z 363.1571 $[M+Na]^+$, Found m/z 363.1572 $[M+Na]^+$.

4.1.7. (*R*,*E*)-5-Hydroxy-1-phenylpent-1-en-3-yl acetate 13

To a stirred solution of compound **12** (2 g, 5.88 mmol) in CH_2Cl_2/H_2O (8:2) was added DDQ at 0 °C (1.44 g, 6.47 mmol) and stirred for 2.5 h. The solution was quenched with solid $NaHCO_3$ (100 mg) at 0 °C, filtered through a Celite pad, and washed with CH_2Cl_2 (10 mL). Concentration of the residue under reduced pressure followed by purification by column chromatography (ethyl acetate/hexane = 25:75) pure compound **13** (1.032 g, 83%) as a pale yellow oil; $[\alpha]_D^{25} = +17.3$ (*c* 1.15, $CHCl_3$); IR: *v* 3430, 1732, 1449, 1372, 1242 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 7.39–7.21 (5H, m), 6.62, (1H, d, *J* = 18.0 Hz), 6.15 (1H, dd, *J* = 18.0, 8.0 Hz), 5.62 (1H, m), 3.72–3.55 (2H, m), 2.11 (3H, s), 1.98–1.85 (2H, m); ^{13}C NMR (50 MHz): 171.2, 136.1, 132.8, 128.5, 128.0, 126.9, 126.1, 72.1, 58.3, 37.8, 21.1; ESIMS: *m/z* 243 $[M+Na]^+$; Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.91; H, 7.27. Found: C, 70.83; H, 7.32.

4.1.8. (3*R*,5*S*,*E*)-5-Hydroxy-1-phenylocta-1,7-dien-3-yl acetate 3

To an ice-cold solution of IBX (2.3 g, 8.26 mmol) in DMSO (8 mL) was added a solution of **13** (1 g, 4.13 mmol) in anhydrous CH_2Cl_2 and the reaction mixture was stirred at 25 °C for 1.5 h. The mixture was diluted with CH_2Cl_2 (5 mL), filtered through a Celite pad, and the pad was washed with CH_2Cl_2. The combined filtrates were washed with H_2O (10 mL), dried over anhydrous Na_2SO_4, and the residue concentrated under reduced pressure to afford the aldehyde, (0.91 g, 92%) which was used directly after flash chromatography for the next reaction.

To a stirred solution of $TiCl_4$ (0.03 g, 0.20 mmol) in CH_2Cl_2 (2 mL) was added dried $Ti(OiPr)_4$ (0.17 g, 0.61 mmol) at 0 °C under a nitrogen atmosphere and the mixture was allowed to warm to room temperature. After 1 h, silver(I) oxide (0.09 g, 0.41 mmol) was added at room temperature, 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 (0.17 g, 0.53 mmol) at room temperature for 2 h to furnish chiral bis-Ti (IV) oxide (*S*,*S*)-**I**. The in situ generated (*S*,*S*)-**I** was cooled to −15 °C, and treated sequentially with the aldehyde (0.9 g, 4.12 mmol) and allyltri-*n*butyltin (1.4 mL, 5.35 mmol) at the same temperature. The mixture was allowed to warm to 0 °C and stirred for 18 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether (3 x 4 mL). The organic extracts were dried over anhydrous Na_2SO_4. Evaporation of the solvents and purification of the residue by column chromatography on silica gel (EtOAc/hexane = 20:80) gave homoallyl alcohol **3** (0.357 g, 74%) as a pale yellow liquid; $[\alpha]_D^{25} = +25.1$ (*c* 0.15, $CHCl_3$); IR: *v* 3450, 1735, 1446, 1373, 1242 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.32–7.04 (5H, m), 6.54 (1H, d, *J* = 18.0 Hz), 5.10 (1H, dd, *J* = 18.0, 8.0 Hz), 5.72 (1H, m), 5.59 (1H, m), 5.10–4.93 (2H, m), 3.61 (1H, m), 2.32–2.15 (2H, m), 2.02 (3H, s), 1.81–1.62 (2H, m); ^{13}C NMR (50 MHz): *δ* 170.3, 137.0, 134.4, 132.2, 129.9, 128.8, 127.5, 126.4, 118.8, 70.3, 68.0, 46.0, 42.1, 21.1; ESIMS: *m/z* 283 $[M+Na]^+$; HRESIMS: calcd for $C_{16}H_{20}O_3Na$ *m/z* 283.1303 $[M+Na]^+$, found *m/z* 283.1310 $[M+Na]^+$.

4.1.9. (1*E*,3*R*,5*S*,7*E*)-5-Hydroxy-8-((*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-1-phenylocta-1,7-dien-3-yl acetate 14

A solution of compound **3** (0.15 g, 0.5769 mmol) and compound **4** (0.031 g, 0.28846 mmol) in dry CH_2Cl_2 (15 mL) was first bubbled with an N_2 flow, after which Grubb's second generation catalyst (5 mg, 0.01 mmol) was added at once and the resulting mixture heated under N_2 at 50 °C for 3 h. After cooling the solvent was evaporated in vacuo. The residue upon purification by column chromatography (ethyl acetate/hexane = 80:20) afforded pure (1*E*,3*R*,5*S*,7*E*)-5-hydroxy-8-((*R*)-6-oxo-3,-dihydro-2*H*-pyran-2-yl)-1-phenylocta-1,7-dien-3-yl acetate **14** (0.1479 g, 71%) as a colorless liquid. $[\alpha]_D^{25} = +7.7$ (*c* 0.4, $CHCl_3$); IR: *v* 3447, 1720, 1378, 1244 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.39–7.20 (5H, m), 6.84 (1H, m), 6.61 (1H, d, *J* = 18.0 Hz), 6.15 (1H, d, 18.0, 8.0 Hz), 6.02 (1H, d, *J* = 8.0 Hz), 5.88 (1H, m), 5.75–5.60 (2H, m), 4.88 (1H, m), 3.62 (1H, m), 2.48–2.32 (3H, m), 2.29–2.20 (2H, m), 2.12 (3H, s), 1.80–1.62 (2H, m); ^{13}C NMR (50 MHz): *δ* 170.2, 164.3, 145.1, 136.8, 132.1, 131.1, 130.2, 130.1, 128.6, 127.7, 126.5, 121.3, 76.7, 70.5, 68.2, 42.2, 40.4, 29.5, 22.3; ESIMS: *m/z* 379 $[M+Na]^+$; Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.79; H, 6.74. Found: C, 70.68; H, 6.77.

4.1.10. 6-[(1*E*,4*R*,6*S*,7*E*)-4,6-Dihydroxy-8-phenylocta-1,7-dien-1-yl]-5,6-dihydro-2*H*-pyran-2-one [(+)-cryptofolione)] 1

An aqueous 10% soln of HCl (2 mL) was added to a stirred solution of **14** (0.12 g, 0.38 mmol) in MeCN (5 mL) at 0 °C, and the mixture was stirred at 0 °C for 6 h. The reaction was quenched with solid $NaHCO_3$ (150 mg) and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (EtOAc/hexane, 60:40) to afford (+)-cryptofolione **1** (74 mg, 72%) as a colorless oil. The spectroscopic properties of the compound were similar to those reported earlier.[7] $[\alpha]_D^{25} = +45.6$ (*c* 0.44, $CHCl_3$) IR: *v* 3442, 1711, 1639, 1384, 1252 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.38–7.14 (2–5H, m), 6.83 (1H, m), 6.60 (1H, d, *J* = 16.0 Hz), 6.23 (1H, dd, *J* = 16.0, 7.0 Hz), 5.99 (1H, d, *J* = 8.0 Hz), 5.87 (1H, m), 5.62 (1H, dd, *J* = 16.0, 7.0 Hz), 4.84 (1H, m), 4.60 (1H, m), 4.01, (1H, m), 3.24 (2H, br s), 2.42–2.33 (2H, m), 2.25 (2H, t, *J* = 7.0 Hz), 1.80–1.62 (2H, m); ^{13}C NMR (50 MHz): *δ* 164.2, 145.0, 136.6, 132.0, 131.1, 130.1, 130.0, 128.9, 127.9, 126.8, 121.5, 76.5, 70.3, 68.0, 42.1, 40.2, 29.7; ESIMS: *m/z* 337; HRESIMS: Calcd for $C_{19}H_{24}O_4Na$ *m/z* 337.1428 $[M+Na]^+$, Found *m/z* 337.1415 $[M+Na]^+$.

4.1.11. (3*R*,5*S*,*E*)-1-Phenylocta-1,7-diene-3,5-diol 15

To a stirred solution of compound **3** (0.15 g, 0.57 mmol) in CH_3OH, was added K_2CO_3 (0.39 g, 2.88 mmol) at 25 °C and stirred for 30 min. Then the solution was filtered and the filtrate concentrated in vacuo and purified by column chromatography (EtOAc/hexane = 40:60) to afford compound **15** (0.105 g, 84%) as a pale yellow oil. $[\alpha]_D^{25} = +36.4$ (*c* 0.5, $CHCl_3$); IR: *v* 3414, 1642, 1446, 1252 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.38–7.15 (5H, m), 6.61 (1H, d, *J* = 18.0 Hz), 6.23 (1H, dd, *J* = 18.0, 8.0 Hz), 5.80 (1H, m), 5.18–5.10 (2H, m), 4.61 (1H, m), 4.01 (1H, m), 2.31–2.20 (2H, m), 1.81–1.72 (2H, m); ^{13}C NMR (50 MHz): *δ* 137.0, 134.2, 131.9, 130.0, 128.8, 127.9, 126.3, 118.5, 70.3, 68.0, 42.0; ESIMS: *m/z* 241 $[M+Na]^+$; Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.06; H, 8.26. Found: C, 77.18; H, 8.21.

4.1.12. (4*S*,6*R*,*E*)-4-Allyl-2,2-dimethyl-6-styryl-1,3-dioxane 16

To a stirred solution of compound **15** (0.07 g, 0.271 mmol) in dry acetone (3 mL) under an N_2 atmosphere at 0 °C was added *p*-TSA (20 mg) followed by 2,2-dimetoxy propane. (0.4 mL, 0.325 mmol). The solution was stirred for 3 h, and then quenched with solid $NaHCO_3$ powder (30 mg) and filtered. The filtrate was concentrated under reduced pressure and subjected to column chromatography (EtOAc/hexane = 10:90) to afford pure compound **16** (67 mg, 89%) as a colorless oil. $[\alpha]_D^{25} = +47.2$ (*c* 1.0, $CHCl_3$); IR: *v* 1643, 1605, 1445, 1271 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.36–7.14 (5H, m), 6.51 (1H, d, *J* = 18.0 Hz), 6.17 (1H, dd, *J* = 18.0, 8.0 Hz), 5.80 (1H, m), 5.12–5.02 (2H, m), 4.48 (1H, m), 3.91 (1H, m), 2.38–2.19 (2H, m), 1.89–1.72 (2H, m), 1.39 (6H, s); ^{13}C NMR (50 MHz): *δ* 136.9, 134.5, 130.5, 129.9, 128.5, 127.4, 126.5, 117.2, 100.5, 68.1, 66.1, 40.2, 37.4, 25.5, 24.9; ESIMS: *m/z* 281 $[M+Na]^+$; Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.07; H, 8.53. Found: C, 79.23; H, 8.47.

4.1.13. (5*R*,2*Z*,6*E*)-Methyl 5-acetoxy-7-phenylhepta-2,6-dienoate 17

To an ice-cold solution of IBX (0.51 g, 0.18 mmol) in DMSO (2 mL), was added a solution of **13** (0.2 g, 0.91 mmol) in anhydrous CH_2Cl_2 and the reaction mixture was stirred at 25 °C for 3 h. The

mixture was diluted with CH_2Cl_2 (2 mL). The solution was stirred for 4 h, filtered through a Celite pad, and the pad was washed with CH_2Cl_2 (3 mL). The combined filtrates were washed with H_2O (4 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford the aldehyde, (0.18 g, 92%) which was used directly after flash chromatography for the next reaction.

To a suspension of NaH (60% dispersion in mineral oil, 0.034 g, 0.90 mmol) under an N_2 atmosphere in dry THF (2 mL) was added bis-(2,2,2-trifluoroehtyl)(methoxy-carbonyl methyl) phosphonate (0.3 mL, 0.99 mmol) at 0 °C. After the mixture was stirred for 30 min at the same temperature, the reaction mixture was cooled to −78 °C, and then a solution of the aldehyde (0.18 g, 0.82 mmol) in dry THF was added dropwise. After stirring for 1 h, the reaction mixture was diluted with 5 mL of ether and quenched by the slow addition of 2 mL of water. The reaction mixture was extracted with ether (2 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue upon purification by column chromatography (ethyl acetate/hexane, 2:8) afforded pure (5*R*,2*Z*,6*E*)-methyl-5-acetoxy-7-phenylhepta-2,6-dienoate **17** (0.16 g, 84%) as a colorless oil; $[\alpha]_D^{25} = +6.1$ (*c* 1.45, $CHCl_3$); IR: *ν* 1720, 1628, 1485, 1260 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.40–7.22 (5H, m), 6.62 (1H, d, *J* = 16.0 Hz), 6.27 (1H, dd, *J* = 16.0, 7.0 Hz), 6.11 (1H, dd, *J* = 8.0, 5 Hz), 5.89 (1H, d, *J* = 8.0 Hz), 5.52 (1H, m), 3.72 (3H, s), 3.11 (2H, t, *J* = 7.0 Hz), 2.08 (3H, s); ^{13}C NMR (50 MHz): *δ* 17.5, 166.8, 144.2, 133.1, 131.9, 129.1, 128.8, 127.9, 126.5, 122.0, 73.7, 51.2, 34.0, 21.1; ESIMS: *m/z* 297 $(M+Na)^+$ Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.07; H, 6.57. Found: C, 70.18; H, 6.62.

4.1.14. (*R*,*E*)-6-Styryl-5,6-dihydropyran-2-one[(+)-goniothalmin] 2

To a stirred solution of compound **17** (0.15 g, 0.57 mmol) in CH_3OH, was added K_2CO_3 (0.302 g, 2.1 mmol) at 25 °C and stirred for 30 min. Then the solution was filtered and the filtrate was concentrated in vacuo and purified by column chromatography (EtOAc/hexane—15:85) to afford compound **18** (0.09 g, 76%) as a colorless oil.

4.1.14.1. Method A. To a stirred solution of compound **18** (0.06 g, 0.25 mmol) in CH_3OH at 0 °C was added pyridinium *p*-toluene sulfonate (25 mg) and stirred for 6 h. The solution was quenched with solid $NaHCO_3$ powder (40 mg), filtered, and concentrated under reduced pressure and subjected to column chromatography (EtOAc/hexane = 5:5) to afford pure (+)-goniothalmin **2** (38 mg, 76%) as a white solid.

4.1.14.2. Method B. A solution of compound **19** (0.039 g, 0.018 mmol) and compound **4** (0.04 g, 0.37 mmol) in dry CH_2Cl_2 (5 mL) was first bubbled with an N_2 flow, after which Grubb's second generation catalyst (5 mg, 0.01 mmol) was added at once and the resulting mixture heated under N_2 at 50 °C for 4 h. After cooling the solvent was evaporated in vacuo. The residue upon purification by column chromatography (ethyl acetate/hexane, 5:5) afforded pure (+)-goniothalamin **2** (51 mg, 70%) as a white solid. The spectroscopic data of **2** prepared by both methods were in good agreement with those reported earlier.[8] $[\alpha]_D^{25} = +167.8$ (*c* 1.34, $CHCl_3$); IR: *ν* 1719, 1651, 1381, 1243 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.40–7.22 (5H, m), 6.91 (1H, m), 6.71 (1H, dd, *J* = 18.0 Hz), 6.23 (1H, dd, *J* = 18.0, 6.0 Hz), 6.08 (1H, d, *J* = 10.0 Hz), 5.09 (1H, m), 2.58–2.51 (2H, m) ^{13}C NMR (50 MHz): *δ* 164.2, 144.8, 136.0, 133.1, 128.3, 126.9, 125.9, 121.9, 78.0, 29.6 ESIMS: *m/z* 223 $(M+Na)^+$ Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.00; H, 6.00. Found: C, 78.21; H, 6.08.

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References

1. (a) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021; (b) Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Planta Med.* **2000**, *66*, 199; (c) Murga, J.; Falomir, E.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447.
2. (a) Schlapelo, B. M.; Drewes, S. E.; Scott-Shaw, R. *Phytochemistry* **1994**, *37*, 847; (b) Cavalheiro, A. J.; Yoshida, M.; Jodynis-Liebert, J.; Murias, M.; Bloszyk, E. *Phytochemistry* **2000**, *53*, 811.
3. Schemda-Hirschmann, G.; Astuddillo, L.; Bastida, J.; Codina, C.; De Arias, A. R.; Ferrira, M. E.; Inchaustti, A.; Yaluff, G. *J. Pharm. Pharmcol.* **2001**, *53*, 563.
4. (a) Hlubucek, J. R.; Robertson, A. V. *Aust. J. Chem.* **1967**, *20*, 2199; (b) Cavalheiro, A. J.; Yoshida, M. *Phytochemistry* **2000**, *53*, 811.
5. (a) El-Zayet, A. E.; Ferrigni, N. R.; Mc Cloud, T. G.; McKenzie, A. T.; Bryn, S. R.; Cassady, J. M.; Chang, C.; McLauglin, J. L. *Tetrahedron Lett.* **1985**, *26*, 955; (b) Ahmad, F. B.; Tukol, W. A.; Omar, S.; Sharif, A. M. *Phytochemistry* **1991**, *30*, 2430; (c) Goh, S. H.; Ee, G. C. L.; Chauh, C. H.; Wei, C. *Aust. J. Chem.* **1995**, *48*, 199.
6. (a) Hengartner, M. O. *Nature* **2000**, *12*, 770; (b) Chien, A. L. T.; Pihie, A. H. L. *J. Biochem. Mol. Biol.* **2003**, *36*, 269.
7. (a) Matsuoka, Y.; Aikawa, K.; Irie, R.; Katsuki, T. *Heterocycles* **2005**, *66*, 187; (b) Sabitha, G.; Reddy, S. S. S.; Reddy, D. V. *Synthesis* **2010**, 3453; (c) Kumar, R. N.; Meshram, H. M. *Tetrahedron Lett.* **2011**, *52*, 1003.
8. (a) de Fatima, A.; Pilli, R. A. *Arkivoc* **2003**, 118; (b) de Fathima, A.; Kohn, L. K.; Antonio, M. A.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2005**, *13*, 2927; (c) Sabitha, G.; Sudhakar, K.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 8599; (d) Pospisil, J.; Marko, I. E. *Tetrahedron Lett.* **2006**, *47*, 5933; (e) Bose, D. S.; Reddy, A. V. N.; Srikanth, B. *Synthesis* **2008**, 2323; (f) Bressy, C.; Bargiggia, F.; Guyonnet, M.; Aroseniyadis, S.; Cossy, J. *Synlett* **2009**, 565; (g) Harsh, P.; O' Doherty, G. A. *Tetrahedron* **2009**, *65*, 5051; (h) Wach, J.-Y.; Guttinger, S.; Kutay, V.; Gdemann, K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 243.
9. Gowravaram, S.; Vangala, B.; Reddy, S. S. S.; Yadav, J. S. *Chin. J. Chem.* **2010**, *28*, 2421.
10. (a) Das, B.; Suneel, K.; Satyalakshmi, G.; Kumar, D. N. *Tetrahedron: Asymmetry* **2009**, *20*, 1536; (b) Das, B.; Laxminarayana, K.; Krishnaiah, M.; Kumar, D. N. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6396; (c) Das, B.; Veeranjaneyulu, B.; Balasubramanyam, P.; Srilatha, M. *Tetrahedron: Asymmetry* **2010**, *21*, 2762.
11. (a) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861; (b) Wendt, K. U.; Schulz, G. E.; Liu, D. R.; Corey, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812; (c) Sabitha, G.; Bhikshapathi, M.; Ranjith, N.; Ashiwini, N.; Yadav, J. S. *Synthesis* **2011**, 821.
12. Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708.
13. (a) Rychnovsky, S. D.; Skalitzsky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945; (b) Evans, D. A.; Reiger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
14. (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, N.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783; (b) Truka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.