Asymmetric synthesis of (–)-leiocarpin A via (–)-(S)-goniothalamin employing Julia–Kocienski olefination

Suresh Babu Meruvaa,b, Raghavendra Rao K.a, Aaseef Mohammeda, Vilas H. Dahanukara, U. K. Syam Kumar a, and P. K. Dubeyb

a Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy’s Laboratories Ltd., Miyapur, Hyderabad, India; b Department of Chemistry, College of Engineering, JNTUH, Kukatpally, Hyderabad, India

ABSTRACT
A concise and enantioselective syntheses of antileukemic natural products such as (–)-(S)-goniothalamin and (–)-leiocarpin A has been accomplished in excellent yields. By employing reported conditions on suitable substrates via Julia–Kocienski olefination, intramolecular lactonization, and subsequently dehydroxylative olefination, (–)-(S)-goniothalamin was synthesized. Then Sharpless asymmetric dihydroxylation–intramolecular Michael addition on (–)-(S)-goniothalamin provided (–)-leiocarpin A.

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Introduction
Chiral unsaturated lactones are one of the core skeletal fragments found in a variety of biologically active natural products. The nuclear export signal inhibiting agents such as ratjadone and callystatin-A possess unsaturated dihydro-2-pyranone with conjugated diene in their structural frameworks.[1] (+)-(R)-Goniothalamin (1) and its variants such as (+)-9-deoxygonioopyrone (3a), (R)-(−)-goniothalamin oxide (4), (−)-dehydroxygoniotriol (5), and (−)-4-dehydroxygoniotriol (6) are also interesting dihydro-2-pyranone-based natural products.[2–9] (+)-(R)-Goniothalamin (1) was isolated from the dried bark of Cryptocarya caloneura in 1967[10–12] and it exhibits antifungal[13] and anti-inflammatory activities along with potential antitumor properties.[14] The structural variants of 1 have demonstrated significant bioactivity towards human tumor cell lines and act as selective cytotoxic agents against human lung cancer cells (A-549).[15–17] The natural products such as leiocarpin A (3b), leiocarpin B (3c), and leiocarpin C (3d) (Figure 1) are styryl lactones isolated from the bark of Goniothalamus leiocarpus (Annonaceae). These compounds exhibit cytotoxic activity against several human tumor cell lines.[18,19] Leiocarpin A (3b) is structurally
related to 9-deoxygoniopyrone (3a) and differs in the stereochemical configuration. Despite the interesting cytotoxic properties of leiocarpin A (3b), the total synthesis of this compound has been reported only by a few research groups.[20]

**Results and discussion**

The core dihydro-2-pyranone framework in (±)-(R)-goniothalamin (1) and its non-natural enantiomer (−)-(S)-goniothalamin (2)[21–29,32] is synthesized either by Grubsmetathesis,[30,31] enantioselective hetero-Diels–Alder reaction, or Wittig–Horner reaction.[25] The dihydroxylation of the exocyclic olefinic double bond and intramolecular Michael addition–heteroannulation protocol are reportedly adapted for the synthesis of (±)-9-deoxygoniopyrone (3a) starting from (±)-(R)-goniothalamin (1).[33,34] For the synthesis of 2 there are various approaches in the literature, which usually utilize Grubs metathesis as a key step. However, there are several straightforward and short syntheses reported in the literature to assemble the styryl lactones and related compounds but we have attempted with the available suitable synthons which enhances the scalability of 2. Therefore as part of our continued efforts to develop new methodologies for the synthesis of biologically active natural and unnatural products,[35–38] herein we describe a concise and highly enantioselective total synthesis of (−)-leiocarpin A (3b). Our strategy for the synthesis of (−)-leiocarpin A (3b) via (−)-(S)-goniothalamin (2) is illustrated (Scheme 1).

However, we aim for the synthesis of 3a from 2 and optimize the reaction conditions and the isolated compound subjected for characterization considering that the obtained compound might be 3a. Based on the single-cell x-ray crystallographic data, it was confirmed...
as (-)-leiocarpin A (3b). Compound 3b could be obtained by the in situ enantioselective dihydroxylation–intramolecular Michael addition methodology with 2 under the Sharpless asymmetric dihydroxylation conditions.[39] The key precursor (-)-(S)-goniothalamin (2) required for the synthesis could be obtained from β-hydroxy lactone 7. The stereo-controlled Julia–Kocienski olefination[40] of the aldehyde 11 with sulfone 10[41–42] followed by a series of transformations involving ester hydrolysis, acetonide deprotection, and intramolecular lactonization would afford the β-hydroxy lactone 7.

The synthesis of (-)-(S)-goniothalamin (2) begins with Julia–Kocienski olefination of sulfone 10 and benzaldehyde (11). The sulfone 10 was prepared as per the literature procedure with minor modifications.[41] We have reported the synthesis 9 using Julia–Kocienski olefination[42] and it was studied in detail to get high E/Z selectivity under various conditions (Scheme 2). The Julia–Kocienski reaction was performed at various conditions: Barbier conditions[40] using LiHMDS and LDA and premetallic conditions with other bases such as NaH, KOtBu, NaHMDS, and KHMDS (Table 1).

During the optimization of the suitable conditions for Julia–Kocienski olefination reaction we have concluded that the lithium enolate of sulfone 10 is stable at –70°C. If the temperature is above −5°C the sulfone 10 was undergone self-degradation. In the case of sodium or potassium enolates of sulfone were more stable. This might lead us to conclude that when the Barbier conditions with lithium are used, there is more E isomer than Z isomer. The Julia–Kocienski olefination reaction, when carried out with NaHMDS, causes the olefin to be formed in good yield (80%) but with diminished E/Z ratio. The use of bases such as LDA and NaH in the olefination reaction resulted in low conversion as well as deteriorated E/Z ratios. Though the use of KOtBu, KHMDS provided the olefinic ester 9 with improved yields and diminished E/Z ratio were observed. However, when the olefination reaction was carried out with LiHMDS in THF, the product was formed in 90% (by HPLC) with 11.5:1 E/Z ratios. The crude olefinic ester 9 thus obtained was then purified by column chromatography and the required E olefin was isolated in 85% yield.
After the synthesis of olefin in good yield, we have converted 9 to lactone 7 via stepwise process involving acetonide deprotection (12a), hydrolysis of ester and intramolecular lactonization. When the reaction was carried out using TFA in acetonitrile/water 10:2 ratios, due to the extended conjugation epimerization of C5-OH group, the acetonide deprotection of 9 was observed. The epimerization is inconsistent and always resulted in a mixture of 12a and 12b. The acetonide deprotection of 9, when attempted with other acids such as pyridine para-toluenesulfonate, trichloroacetic acid, PTSA, and 0.05N HCl in solvents such as acetonitrile, THF, and toluene, gave greater content (range 4 to 10%) of epimer. However, when the acetonide deprotection is attempted with oxalic acid, the rate of reaction is very slow and about 20% of 9 was remained unreacted (Scheme 3) although the epimerization was well below 3% (by HPLC).

To circumvent the aforementioned issues, we altered the reactions and performed hydrolysis of olefinic ester 9 first under basic conditions, followed by acetonide deprotection and subsequent lactonization. Thus 9 was subjected for ester hydrolysis using aqueous NaOH solution in MeOH at reflux temperature followed by pH adjustment to afford the crude acid 8a. The crude acid 8a thus obtained was taken for acetonide deprotection using oxalic acid in aqueous acetonitrile to yield the dihydroxy olefinic acid 8. The 6-exo-trig cyclization of the crude dihydroxy olefinic acid 8 to lactone 7 is carried out in toluene at its boiling temperature, and the lactone 7 was isolated in overall 58% yield starting from 9. Our efforts to isolate pure 8a and 8 were not successful, as these products always contaminated with some percentages of lactone 7. Finally the elimination of hydroxyl group in 7 was done smoothly to yield (–)-(S)-goniothalamin (2) as per the reaction conditions reported by Kaneko and coworkers (Scheme 4).[46]

The (–)-(S)-goniothalamin (2) thus obtained was purified by column chromatography, and the product was obtained in 80% yield. The spectral and analytical data of (–)-(S)-goniothalamin (2) thus synthesized was found to be in accordance with the reported values.

| No. | Base (equiv.) | HPLC purity (9) | E/Z ratio | Yield% |
|-----|--------------|----------------|-----------|--------|
| 1   | LiHMDS (1.2) | 90             | 92/08     | 85     |
| 2   | LDA (1.5)    | 40             | 60/40     | 20     |
| 3   | NaHMDS (1.2) | 90             | 67/33     | 80     |
| 4   | NaH (1.2)    | 60             | 55/45     | 35     |
| 5   | KHMDs (1.2)  | 90             | 74/26     | 75     |
| 6   | KOtBu (1.2)  | 88             | 75/25     | 78     |

Note. 1.2 eq. of benzaldehyde (11) was used for the reaction, conversion, and E/Z ratios of 9 are determined by HPLC method. *Isolated yields.

Scheme 3. CCDC number 999384.
[mp 82 °C; reported 81–82 °C; specific optical rotation, \([\alpha]_{D}^{25} = -111.6\) (c, 0.3 w/v, CHCl₃); reported \([\alpha]_{D}^{25} = -112.7\) (c, 0.3 w/v, CHCl₃)].[2h]

After the successful completion of \((-\)-(S)-goniothalamin (2) synthesis in overall good yield, we have directed our effort towards the conversion of 2 to \((-\)-leiocarpin A (3b). As described in our retrosynthetic strategy, the Sharpless asymmetric dihydroxylation on \((-\)-(S)-goniothalamin (2) followed by intramolecular hydroxylative Michael addition and heteroannulation reaction yielded \((-\)-leiocarpin A (3b)) in a single-pot operation. Lin and coworkers[11b] reported the synthesis of \((+\)-9-deoxygonioppyrone (3a) by employing the dihydroxylation conditions on \((+\)-(R)-goniothalamin (1) with AD-mix-α and obtained enantiomer of 6 and subsequently obtained the 3a. Similarly when employed the AD-mix-β on \((+\)-(R)-goniothalamin (1) obtained the 6-Epi-goniodiol (6) under the Sharpless conditions. Intrigued by this literature report, we have attempted the Sharpless dihydroxylation of \((S\)-goniothalamin (2) with AD-mix-β under various conditions for the synthesis of \((-\)-leiocarpin A (3b).

The in situ Sharpless dihydroxylation–intramolecular hydroxylative Michael addition–heteroannulation reaction initially was carried out using 1 mmol of olefin, 0.86 mmol of AD-mix-β, and 1 mmol of methane sulfonamide, and the required product \((-\)-leiocarpin A (3b) was obtained in about 5% after maintaining the reaction mixture over a period of 24 h at 0 °C in a mixture of tert-butanol and water. However, when the reaction was carried out at 30 °C for 24 h, by keeping the same molar ratio of substrate to reagents as described previously, the required product 3b was obtained in 25% yield. When this reaction was conducted with greater equivalents of AD-mix-β (1.24 mmol) and 1.25 mmol of methane sulfonamide, the complete consumption of the starting material was observed over a period,

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{Bu} \\
i & = \text{aq. NaOH, MeOH, RT, NaHSO₄} \\
\text{ii} & = \text{Oxalic acid, acetonitrile, H₂O, RT.} \\
\text{iii} & = \text{Toluene reflux (58% yield, over 3 steps).} \\
\text{iv} & = \text{MsCl, TEA, -35 °C, 4h, Y = 80%}
\end{align*}
\]

Scheme 4. Synthesis of 2.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{Bu} \\
i & = \text{aq. NaOH, MeOH, RT, NaHSO₄} \\
\text{ii} & = \text{Oxalic acid, acetonitrile, H₂O, RT.} \\
\text{iii} & = \text{Toluene reflux (58% yield, over 3 steps).} \\
\text{iv} & = \text{MsCl, TEA, -35 °C, 4h, Y = 80%}
\end{align*}
\]

Scheme 5. Synthesis of 3b.
of 20 h at 30°C and the isolated product was 65% yield (Scheme 5), characterized by spectral and analytical methods.

Then structure of (−)-leiocarpin (3b) is confirmed by spectral and analytical methods and compared with literature reported data. The specific optical rotation of 3b was recorded using ethanol and specific optical rotation is $[\alpha]_{D}^{25} = -9.8$ (c, 0.2 w/v, EtOH); further the structural elucidation was carried out with 2D-spectroscopic experiments such as nuclear Overhauser effect spectroscopy (NOESY), correlation spectrometry (COSY), and heteronuclear single quantum coherence (HSQC). Finally the single crystal of (−)-leiocarpin (3b) was generated from CHCl₃ and single-cell x-ray crystallography was recorded. The ORTEP diagram[47] of the product thus obtained conclusively proved the stereochemical orientation of the product, with configuration 1S,5S,7R,8S and confirmed the structure of 3b as (−)-leiocarpin A (Figure 2).

**Experimental**

All reactions were carried out in oven-dried glassware under an atmosphere of N₂. ¹H and ¹³C NMR spectra were recorded in CDCl₃ and dimethylsulfoxide (DMSO-δ₆) on Varian Gemini 400-MHz FT spectrometers. Proton chemical shifts ($\delta$) are relative to tetramethylsilane (TMS, $\delta$ 0.00) as internal standard and expressed in parts per million (ppm). Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants ($J$) are given in hertz (Hz). Mass spectra were obtained on a HP-5989A mass spectrometer. Thin-layer chromatography was performed on silica-gel plates (SRL 230–400 mesh). All solvents used are commercially available and were distilled before use.

**Synthesis of tert-butyl 2-((4R,6S)-2,2-dimethyl-6-((E)-styril)-1,3-dioxan-4-yl)acetate (9)[42]**

Benzaldehyde 13 (14.0 g, 0.13 mol) was added to a stirred solution of tert-butyl 2-((4R,6S)-2,2-dimethyl-6-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)methyl)-1,3-dioxan-4-yl)acetate 10 (50.0 g, 0.11 mol) in dry THF (500 mL). The reaction mixture was cooled to −75°C. LiHMDS 22% THF solution (100 mL, 0.13 mol) was added to the reaction mixture in
60 min. The reaction mixture was maintained at that temperature for about 1 h, allowed to room temperature, and stirred for 1–2 h. Then based on TLC indication for absence of starting material it was quenched with 5% aqueous KHCO₃ solution and the THF layer was separated. The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulfate, and concentrated to dryness. The crude residue was purified by column chromatography (eluent: ethyl acetate / hexanes = 0.5/9.5) to yield 31 g (85%) of 9 as pale yellow liquid, and after refrigeration at 0–10°C an off-white solid was obtained. Yield = 85%; mp 53.2–55.4°C. \[\alpha\]D = −2.5 (c, 1 w/v, CHCl₃). ¹H NMR: (400 MHz, CDCl₃) δ: 1.41 (s, 12H), 1.45 (m, 1H,), 1.48 (s, 3H), 1.73–1.69 (td, \(J = 2.4, 7.6\) Hz, 1H), 2.27 (dd, \(J = 6.8, 8.4\) Hz, 1H), 2.48 (dd, \(J = 6.8, 8.4\) Hz, 1H), 4.56 (m, 1H), 4.36 (m, 1H), 6.17 (dd, \(J = 6.4, 16\) Hz, 1H), 6.62 (d, \(J = 16\) Hz, 1H), 7.24 (d, \(J = 4.8\) Hz, 1H), 7.31 (t, \(J = 5.6\) Hz, 2H), 7.38 (d, \(J = 1.8\) Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ: 170.1, 136.5, 132.5, 130.7, 128.6, 128.2, 126.4, 76.4, 62.3, 38.5, and 30.0. Mass: \([M + 1]^+ = 355.2\). HPLC purity: 91.9 E isomer, 8.1 Z isomer; column: Kinetex, C18, diameter: 100 × 4.6, 2.5 μ. Mobile phase B: acetonitrile/methanol 40:60; mobile phase A: 20mm ammonium acetate/methanol 60:40.

**Synthesis of (4R,6S)-4-hydroxy-6-((E)-styryl)tetrahydro-2H-pyran-2-one (7)**

Aqueous NaOH solution (3.6 g, 0.09 mol) was added to a solution of 9 (10 g, 0.03 mol) in MeOH (80 mL) and the reaction mixture was refluxed for 2–4 h. MeOH was removed under reduced pressure; the residue was diluted with water (30 mL). Aqueous layer was washed with AcOEt (25 mL) and layers were separated. The aqueous layer pH was adjusted to 1.5–2.5 using aqueous sodium bisulfate solution. The product was extracted into MTBE (50 mL) and evaporated under reduced pressure. Residue was diluted with acetonitrile (100 mL) and oxalic acid (4.0 g, 0.045 mol), and water (12 mL) was added to it. Reaction mixture was stirred for 30–60 min at 25–35°C and then based on thin-layer chromatography (TLC) indication for starting material content of approximately 5% it was diluted with saturated brine solution. Layers were separated and the acetonitrile layer was dried over anhydrous sodium sulfate and concentrated to dryness. Toluene (60 mL) was added to the residue and it was refluxed for 5 h. The reaction mass was cooled to room temperature and the toluene layer was washed with 2% sodium bicarbonate solution and concentrated to dryness under reduced pressure. The crude residue was purified by column chromatography using AcOEt/hexane (60:40) and gave 3.8 g of 7 as white solid (overall yield for three steps is 58%); mp 112–112.9°C. \[\alpha\]D = 10.8 (c, 0.8 w/v, CHCl₃); reported \[\alpha\]D = 9.8 (c, 0.8 w/v, CHCl₃).\(^{[28]}\) ¹H NMR (400 MHz, CDCl₃) δ: 7.38 (d, \(J = 6.8\) Hz, 2H), 7.33 (t, \(J = 7.2\) Hz, 2H), 7.26 (d, \(J = 6.8\) Hz, 1H), 6.68 (d, \(J = 16\) Hz, 1H), 6.17 (dd, \(J = 6.4, 16\) Hz, 1H), 5.38 (m, 1H), 4.45 (m, 1H), 2.82 (dd, \(J = 4.8, 12.8\) Hz, 2H), 2.70–2.65 (td, \(J = 2.4, 15.2\) Hz, 2H) and 1.98 (t, 1H). ¹³C NMR (125 MHz, CDCl₃) δ: 170.7, 135.7, 132.4, 128.5, 128.1, 126.5, 126.4, 76.4, 62.3, 38.5, and 30.0. Mass: \([M + 1] = 219.2, [M + 23] = 241.0\).

(S)-6-((2R,3R)-3-Phenylxiran-2-yl)-5,6-dihydro-2H-(1.05 gm, 9 mmol) was added to a solution of 7 (1.0 g, 4.5 mmol) and TEA (1.85 gm, 18.3 mmol) in DCM (25 mL) at –35°C. Stirring was continued for 4 h and after TLC indicated no starting material remained, the reaction mixture was washed with brine solution and the organic layer was dried over anhydrous Na₂SO₄. The organic layer was concentrated to dryness under reduced pressure and the obtained residue was purified by column chromatography (hexane and ethyl
acetate 60:40) to yield 2 as white solid. Yield: 80%; mp 82 °C. \( \delta^{25} \text{D} = -111.6 \) (c, 0.3 w/v, CHCl\(_3\)). reported \( \delta^{25} \text{D} = -112.7 \) (c, 0.3 w/v, CHCl\(_3\)). \( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta: 7.38 \) (d, \( J = 8.8 \) Hz, 2H), 7.35 (t, \( J = 7.0 \) Hz, 2H), 7.28 (t, \( J = 5.2 \) Hz, 1H), 6.93 (m, 1H), 6.75 (d, \( J = 15.6 \) Hz, 1H), 6.29 (dd, \( J = 5.6 \), 10 Hz, 1H), 6.10 (td, \( J = 1.6 \), 6.4 Hz, 1H), 5.09 (q, \( J = 7.0 \) Hz, 1H), 2.54 (m, 2H). Mass: \( [M + 1] = 201.0 \).

**Synthesis of (1S,5S,7R,8S)-8-hydroxy-7-phenyl-2,6-dioxabicyclo[3.3.1]nonan-3-one [(–)-leiocarpine A] (3b)**

A 25-mL round-bottomed flask, equipped with a magnetic stirrer, was charged with 5 mL of tert-butyl alcohol, 5 mL of water, and AD-mix-\( \beta \) (2.0 g, 1.23 mmol), and methane sulfonamide (125 mg, 1.25 equiv based on 1 mmol of olefin) was added. The mixture was cooled to 0 °C whereupon some of the dissolved salts precipitated. Goniothalamin (0.2 g, 1 mmol) was added at once, and the heterogeneous slurry was stirred vigorously at 0 °C for 2 h and then allowed to reach room temperature, and it was stirred at that temperature for 20 h. Progress was monitored by TLC. Solid sodium sulfite (1.5 g) was added at room temperature and stirred for 30–60 min. Ethyl acetate (10 mL) was added to the reaction mixture, and after separation of the layers, the aqueous phase was further extracted with ethyl acetate (5 mL). The combined organic layers were washed with 2 N KOH. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to give the crude product. This crude product purified by flash column chromatography (230- to 400-mesh silica gel) and eluted with 40% EtOAc/hexanes to afford 3b. Yield: 65%; white crystalline solid, mp 214–219 °C. \( \delta^{25} \text{D} = -9.8 \) (c, 0.2 w/v, EtOH); reported \( \delta^{25} \text{D} = -94.9 \) (c 0.4, CHCl\(_3\)). \(^1 \text{H} \) NMR: (500 MHz, DMSO-d\(_6\)) \( \delta: 7.36 \) (d, 2H, \( J = 7.5 \) Hz), 7.30 (t, 2H, \( J = 7.5 \) Hz), 7.23 (t, 1H, \( J = 7.0 \) Hz), 5.13 (d, 1H, \( J = 6.5 \) Hz, OH), 4.73 (s, 1H) 4.66–4.63 (m, 1H), 4.37 (brs, 1H), 3.74 (s, 1H), 3.01 (dd, 1H, \( J = 5.5 \) and 13.5 Hz), 2.77 (d, 1H, \( J = 19 \) Hz), 2.40 (dd, 1H, \( J = 4.5 \) and 9.5 Hz), 1.85 (dd, 1H, \( J = 4.0 \) and 10.0 Hz). \(^{13} \text{C} \)NMR (100 MHz, DMSO-d\(_6\)) \( \delta: 169.2, 138.9, 127.5, 126.9, 126.8, 75.4, 70.2, 67.0, 65.5, 35.8, \) and 23.2. Mass: \( [M + 1]^+ = 235.0 \). HRMS (EI): calcd. \( m/z \) for C\(_{13}\)H\(_{15}\)O\(_4\) \([M + 1]^+\) 235.0970, found 235.0964.

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**References**

[1] Quitschalle, M.; Christmann, M.; Bhatt, U.; Kalesse, M. Synthesis of unsaturated lactone moieties by asymmetric hetero-Diels–Alder reactions with binaphthol-titanium complexes. *Tetrahedron Lett.* 2001, 42, 1263.

[2] Pospisil, J.; Marko, I. E. Total synthesis of (R)-(+)-goniothalamin and (R)-(−)-goniothalamin oxide: First application of the sulfoxide-modified Julia olefination in total synthesis. *Tetrahedron Lett.* 2006, 47, 5933.

[3] Nagaiah, K.; Sreenu, D.; Purnima, K. V.; Rao, R. S.; Yadav, J. S. Stereoselective total syntheses of leiocarpin A and (−)-galantalinic acid starting from D-mannitol. *Synthesis* 2009, 8, 1386.

[4] Sam, T. W.; Chew, S. Y.; Sabirin, M.; Gan, E. K.; Dzulkifli, R.; Abdul, L. M. Goniothalamin oxide: An embryotoxic compound from *Goniothalamus macrophyllaus* (Annonaceae). *Tetrahedron Lett.* 1987, 28, 2541.
[5] Cilene, M.; Pilli, R. A.; Fatima, A.; Kohn, L. K.; Ruiz, A. T. G.; Carvalho, J. E. Asymmetric total synthesis and antiproliferative activity of goniotothalamin oxide isomers. Bioorg. Chem. 2009, 37, 52.

[6] Surivet, J. P.; Vatèle, J. M. First total synthesis of (−)-8-epi-9-deoxygoniopypryne. Tetrahedron Lett. 1998, 39, 9681.

[7] Surivet, J. P.; Vatèle, J. M. Total synthesis of antitumor Goniothalamus styrylactones. Tetrahedron 1999, 55, 13011.

[8] Dhaware, G. M.; Prasad, R. K. Stereoselective total synthesis of (−)-9-deoxygoniopypryne. Synlett 2007, 7, 1112.

[9] Aneta, K.; Lucie, D.; Jana, R.; Martin, K.; Irena, V. Lewis base–catalyzed enantioselective allylation of α, β-unsaturated aldehydes. Chem. A. Eur. J. 2010, 16, 9442.

[10] Hlubucek, J. R.; Robertson, A. V. (+)-(5S)-δ-Lactone of 5-hydroxy-7-phenylhepta-2,6-dienoic acid, a natural product from Cryptocarya caloneurea (Scheff.) Kostermans. Aust. J. Chem. 1967, 20, 2199.

[11] Meyer, H. H. Synthesen von (−)-(S)- und (−)-(R)-Goniothalamin; absolute Konfiguration des natürlichen (+)-Goniothalamins. Liebigs Ann. Chem. 1979, 484.

[12] Davies-Coleman, M. T.; Rivett, D. E. Naturally occurring 6-substituted 5,6-dihydro-α-pyrones. Progr. Chem. Org. Nat. Prod. 1989, 55, 1.

[13] Jewers, J. R.; Davies, J. B.; Dougan, J.; Manchanda, A. H.; Blunden, G.; Kyi, A.; Wetchainan, S. Synthesis of (−)-(5S)-Goniothalamin; absolute Konfiguration des natürlichen (+)-Goniothalamins. Tetrahedron: Asymmetry 1999, 10, 2969.

[14] Mu, Q.; Tang, W.; Li, C.; Lu, Y.; Sun, H.; Zheng, X.; Wu, N.; Lou, B.; Xu, B. Four new styryllactones from Goniothalamus leiocarpus. Heterocycles 1999, 12, 2699.

[15] Mu, Q.; Li, C. M.; He, Y. N.; Sun, H. D.; Zheng, H. H.; Lu, Y.; Zheng, Q. T.; Jiang, W. Three new styryl pyrones from Goniothalamus leiocarpus. Chin. Chem. Lett. 1999, 10, 135.

[16] Chen, J.; Lin, G. Q.; Liu, H. Q. Stereoselective synthesis of the styryllactones, 7-epi-goniodiol and leiocarpin A, isolated from Goniothalamus leiocarpus. Tetrahedron Lett. 2004, 45, 8111.

[17] O’Connor, B.; Just, G. Syntheses of argentilactone and goniotothalamin. Tetrahedron Lett. 1986, 27, 5201.

[18] Bennett, F.; Knight, D. W. An alternative approach to mevinic acid analogues from methyl-(3R)-3-hydroxy-5-hexenoate and an extension to rational syntheses of (−)-6R)-goniotothalamin and its non-natural (−)-(6S)-enantiomer. Tetrahedron Lett. 1988, 29, 4625.

[19] Rahman, S. S.; Wakefield, B. J.; Roberts, S. M.; Dowle, M. D. Intramolecular nucleophilic addition to photochemically generated ketenes as a versatile route to lactones and lactams: Synthesis of a mosquito pheromone, goniotothalamin, argentilactone, and the Streptomyces L-factor. J. Chem. Soc. Chem. Commun. 1989, 303.

[20] Honda, T.; Kametani, T.; Kanai, K.; Tatsuzaki, Y.; Tsubuki, M. Enantioselective syntheses of (−)-acetylphomalactone and (6R)-(−)-goniotohalamin from 2-furylmethanols. J. Chem. Soc. Perkin Trans. 1990, 1733.

[21] Tsubuki, M.; Kanai, K.; Honda, T. Enantioselective synthesis of 6-substituted 5,6-dihydro-α-pyranones, (−)-goniotohalamin, and (−)-argentilactone. Heterocycles 1993, 35, 281.

[22] Fuganti, C.; Pedrocce-Fantoni, G.; Sarra, A.; Servi, S. Stereochemistry of Baker’s yeast–mediated reduction of α, β-unsaturated δ-lactones in the goniotohalamin series. Tetrahedron: Asymmetry 1994, 5, 1135.

[23] Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. Asymmetric synthesis of goniotohalamin, hexadecanolide, massoia lactone, and parasorbic acid via sequential allylboration–esterification ring-closing metathesis reactions. Tetrahedron Lett. 2000, 41, 583.
[28] Takano, S.; Kamikubo, T.; Sugihara, T.; Ogasawara, K. Stereocontrolled route to the δ-benzylidenemethyl-β-hydroxy-δ-lactone system utilizing a new chiral epoxycetylene building block. *Tetrahedron: Asymmetry* 1992, 3, 853.

[29] Henkel, B.; Kunath, A.; Schick, H. Enantioselective lactonization of methyl 3,5-dihydroxalkanoates: An access to (3R,5S,6E)-3-hydroxy-7-phenyl-6-hepten-5-olide by enzyme-catalyzed kinetic resolution in organic solvents. *Liebig's Ann. Chem.* 1992, 809.

[30] Sundby, E.; Perk, L.; Anthonsen, T.; Aasen, A. J.; Hansen, T. V. Synthesis of (+)-goniothalamin and its enantiomer by combination of lipase-catalyzed resolution and alkene metathesis. *Tetrahedron* 2004, 60, 521.

[31] Barcelos, R. C.; Pastre, J. C.; Caixeta, V.; Vendramini-Costa, D. B.; de Carvalho, J. E.; Pilli, R. A. Synthesis of methoxylated goniothalamin, aza-goniothalamin, and γ-pyrones and their in vitro evaluation against human cancer cells. *Bioorg. Med. Chem.* 2012, 20, 3635.

[32] Job, A.; Wolberg, M.; Muller, M.; Enders, D. Asymmetric Synthesis of S-(+)-argentinolactone and S-(−)-goniothalamin. *Synlett* 2001, 1796.

[33] Liu, Z.-Y.; Ji, J.-X.; Li, B.-G. Efficient synthesis of the styryllactones, (+)-goniothalamin, (+)-7-epi-goniodiol, and (+)-9-deoxygoniopyrone. *J. Chem. Res.* 2004, 1, 61.

[34] Jian, C.; Lin, G. Q.; Wang, Z. M.; Liu, H. Q. A short and general approach to the synthesis of styryllactones: (+)-Goniodiol, its acetates, and β-trifluoromethyl derivative, (+)-7-epi-goniodiol, and (+)-9-deoxygoniopyrone. *Synlett* 2002, 8, 1265.

[35] Shankar, R.; More, S. S.; Madhubabu, M. V.; Vembu, N.; Syam Kumar, U. K. Synthesis of isoquinoline alkaloids via oxidative amidation–Bischler–Napieralski reaction. *Synlett* 2012, 7, 1013.

[36] Shankar, R.; B. Wagh, M. B.; Madhubabu, M. V.; Vembu, N.; Syam Kumar, U. K. A concise and cascade synthesis of batracyn and substituted isoindolo[1,2-b]quinazolin-12(10H)-ones. *Synlett* 2011, 6, 844.

[37] Wagh, M. B.; Shankar, R.; Syam Kumar, U. K.; Gill, C. H. A concise and convergent synthesis of luotonin B and E. *Synlett* 2011, 1, 84.

[38] Meruva, S. B.; Raghunath, A.; Anil Kumar, N.; Vasudev, R.; Syam Kumar, U. K.; Dubey, P. K. Synthesis of 5-aryl and 5-amidocamptothecins. *J. Heterocycl. Chem.* 2010, 48, 540.

[39] Amberg, W.; Bennani, L. Y.; Crispino, A. G.; Hartung, J.; Kyu-Sung Jeong, K.; Kwong, H.; Zhi-Min Wang, M. K.; Xu, D.; Zhang, X.; Sharpless, B. K. The osmium-catalyzed asymmetric dihydroxylation: A new ligand class and a process improvement. *J. Org. Chem.* 1992, 57, 2768.

[40] Blakemore, P. R. The modified Julia olefination: Alkene synthesis via the condensation of metallated heteroarylalkylsulfones with carbonyl compounds. *J. Chem. Soc., Perkin Trans.* 2002, 1, 2563.

[41] Hobson, L. A.; Akiti, O.; Deshmukh, S. S.; Harper, S.; Katipally, K.; Lai, C. J.; Livingston, R. C.; Lo, E.; Miller, M. M.; Ramakrishnan, S.; Shen, L.; Spink, J.; Tummala, S.; Wei, C.; Yamamoto, K.; Young, J.; Parsons, R. L. Development of a scalable process for the synthesis of a next-generation statin. *Org. Proc. Res. Dev.* 2010, 14, 441.

[42] Meruva, S. B.; Ramamohan, M.; Raghunadh, A.; Raghavendra, R. K.; Pratap, T. V.; Vilas, H. D.; Kumar, U. K. S.; Dubey, P. K. Synthesis of tetrahedral diarylheptanoid ent-diospongin A and epimer-diospongin B by employing Julia–Kocienski olefination. *Tetrahedron Lett.* 2014, 55, 4739.

[43] Birgitta, H.; Annemarie, K.; Hans, S. Enzyme-catalyzed lactonization of methyl (±)-(E)-3,5-dihydroxy-7-phenyl-6-heptenoates: A comparison of the behaviour of syn- and anti-compounds. *Tetrahedron: Asymmetry* 1993, 4, 153.

[44] Hirokazu, U.; Tetsuji, M.; Fumie, S. New chiral blocks for introducing the side chain of HMG-CoA reductase inhibitors. *Tetrahedron Lett.* 1992, 33, 4183.

[45] Bhaskar, R. G.; Minami, T.; Hanomoto, T.; Hiyama, T. Enantioselective synthesis of beta-hydroxy delta-lactones: A new approach to the synthetic congeners of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *J. Org. Chem.* 1991, 56, 5752.

[46] Sato, M.; Sunami, S.; Sugita, Y.; Kaneko, C. Use of 1,3-dioxin-4-ones and related compounds in synthesis, XLIV: Asymmetric aldol reaction of 4-trimethylsiloxy-6-methylene-1,3-dioxines: Use of tartaric acid–derived (acyloxy)borane complex as the catalyst. *Chem. Pharm. Bull.* 1994, 42, 839.