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Asymmetric Synthesis of (-)-Leiocarpin A via (-)-(*S*)-Goniothalamin Employing Julia-Kocienski Olefination

Suresh Babu Meruva[1,2], Raghavendra Rao Kamaraju[1], Aaseef Mohammed[1], Vilas H. Dahanukar[1], U. K. Syam Kumar[1], P. K. Dubey[2]

[1]Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd., Hyderabad, India, [2]Department of Chemistry, College of Engineering, JNTUH, Hyderabad, India

Corresponding author. Suresh Babu Meruva and U. K. Syam Kumar, Email: sureshbabum@drreddys.com, syam_kmr@yahoo.com

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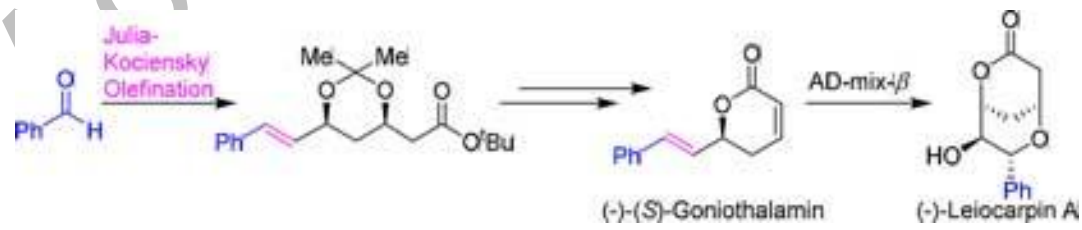
Abstract

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 synthesized (-)-(S)-goniothalamin. Then Sharpless asymmetric dihydroxylation-intramolecular Michael addition on (-)-(S)-goniothalamin provided (-)-leiocarpin A.

Graphical Abstract:



KEYWORDS: Julia-Kocienski olefination, Acetonide deprotection, Lactonization, Saturated and unsaturated pyranone, Sharpless asymmetric dihydroxylation and Michael addition

INTRODUCTION

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

RESULTS & DISCUSSION

The core dihydro-2-pyranone frame work in (+)-(*R*)-goniothalamin (**1**), and its non-natural enantiomer (-)-(*S*)-goniothalamin (**2**)[21-29, 32] is synthesized either by Grubs metathesis, [30-31] enantioselective hetero Diels–Alder or Wittig-Horner reaction.[25] The dihydroxylation of the exocyclic olefinic double bond, intramolecular Michael addition-heteroannulation protocol is reportedly adapted for the synthesis of (+)-9-deoxygoniopypyrone (**3a**) starting from (+)-(*R*)-goniothalamin (**1**).[33-34] For the synthesis of **2** there are various approaches in the literature, out of which majorly utilized Grubs metathesis as key step. However there are several straight forward and short synthesis 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 began to aim for the synthesis of **3a** from **2** and optimized the reaction conditions and the isolated compound subjected for characterization considering that obtained compound might be 3a. Latter based on the single cell X-ray crystallographic data it was confirmed as (-)-Leiocarpin A (**3b**). The **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 sulphone **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**) is begin with Julia-Kocienski olefination of sulphone **10,** and benzaldehyde (**11**). The Sulphone **10** was prepared as per the literature procedure with minor modifications.[41] We have been 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 employed pre-metallic conditions with other bases such as NaH, KO^{t}Bu, 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 -65 °C the sulfone **10** was undergone self-degradation. Whereas in the case of sodium or potassium enolates of sulfone it was observed more stable enolates. This might be concluding that when employed the Barbier conditions with lithium, observed higher *E* isomer over *Z* isomer. The Julia-Kocienski olefination reaction when carried out with NaHMDS, the olefin was formed in good yield (80%); however with diminished *E*:*Z* ratio. The use of bases like LDA and NaH in the olefination reaction resulted in low conversion as well as deteriorated *E*/*Z* ratios. Though the use of KO^{t}Bu,

KHMDS were provided the olefinic ester **9** with improved yields, 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**[43-45] *via* step wise process involving acetonide deprotection (**12a**), hydrolysis of ester and intramolecular lactonization. The acetonide deprotection of **9** when carried out using TFA in acetonitrile-water 10:2 ratios, due to the extended conjugation epimerization [41-42] of C5-OH group was observed. The epimerization is found 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 0.05 N HCl in solvents like acetonitrile, THF, and toluene, higher content (range 4 to 10%) of epimer was observed. However the acetonide deprotection when attempted with oxalic acid, though the epimerization was able to control well below 3% (by HPLC); the rate of reaction is very slow and about 20% of **9** was remained unreacted (Scheme 3).

To circumvent afore mentioned issues, altered the reactions and performed hydrolysis of olefinic ester **9** first under basic conditions, followed by acetonide deprotection subsequently lactonization. Thus **9** was subjected for ester hydrolysis using aqueous NaOH solution in MeOH at reflux temperature followed by pH adjustment afforded 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 co-workers (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 [mp 82 °C; Reported 81-82 °C. specific optical rotation, $[\alpha]_D^{25}$ = -111.6 (c, 0.3 w/v, $CHCl_3$); Reported $[\alpha]_D^{25}$= -112.7 (c, 0.3 w/v, $CHCl_3$)].[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 co-workers[11b] reported the synthesis of (+)-9-deoxygoniopypyrone (**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, the required product (-)-leiocarpin A (**3b**) was obtained in about 5% after maintaining the reaction mixture over a period of 24h 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 mole ratio of substrate to reagents as described above, the required product **3b** was obtained in 25% yield. When this reaction was conducted with higher Eqv. 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 of 20 h at 30 °C and the isolated product in 65% yield (scheme 5) and it was 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); and further the structural elucidation was carried out with 2D-spectroscopic experiments such as NOESY, COSY, and HSQC. Finally the single crystal of (-)-leiocarpin (**3b**) was generated from $CHCl_3$ and single cell X-ray crystallography was recorded. The ORTEP diagram [47] of the product thus obtained is conclusively proved the stereo chemical

orientation of the product, with configuration 1*S*,5*S*,7*R*,8*S* and confirmed the structure of **3b** as (-)-leiocarpin A (Fig. 2).

EXPERIMENTAL

General methods: All reactions were carried out in oven dried glassware under an atmosphere of N_2. ^1H & ^{13}C NMR spectra were recorded in $CDCl_3$ & DMSO-d_6 on *Varian Gemini 400 MHz FT* spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants (*J*) are given in Hertz. 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-((4*R*, 6*S*)-2,2-dimethyl-6-((*E*)-styryl)-1,3-dioxan-4-yl)acetate (9).[42] To a stirred solution of *tert*-butyl 2-((4*R*,6*S*)-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) was added benzaldehyde **13** (14.0 g, 0.13 mol).The reaction mixture was cooled to -75 °C. To the reaction mixture was added LiHMDS 22% THF solution (100 mL, 0.13mol) in 60 minutes. The reaction mixture maintained at that temperature for about 1 h and it was 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% aq. $KHCO_3$ solution and separated the THF layer. The organic layer was washed with saturated brine solution and dried over anhydrous sodium sulphate and concentrated to dryness. The

crude residue purified by column chromatography (eluent: ethyl acetate/hexanes = 0.5/9.5) to yield 31 g (85%) of **9** as pale yellow liquid and upon holding in refrigerator at 0-10 °C an off-white solid was obtained. Yield = 85%; mp 53.2-55.4 °C. $[\alpha]_D^{25}$ = -2.5 (c, 1 w/v, CHCl3). ^{1}H NMR: (400 MHz, $CDCl_3$) 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* = 5.6Hz, 2H), 7.38 (d, *J* = 1.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) δ: 170.1, 136.5, 132.5, 130.7, 128.6, 128.2, 127.3, 126.4, 98.9, 80.2, 69.9, 65.7, 42.5, 36.6, 30.1, and 19.7. Mass (ESI) *m/z* $[M+]^+$ 355.2. HPLC purity: 91.9 *E* isomer, 8.1 *Z* Isomer; Column: Kinetex, C18, diameter: 100 x 4.6, 2.5 µ. Mobile phase B: Acetonitrile: methanol 40:60; Mobile phase A: 20 mm Ammonium acetate: methanol 60:40.

Synthesis of (4*R*, 6*S*)-4-hydroxy-6-((*E*)-styryl)tetrahydro-2*H*-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 washed with AcOEt (25 mL) and layers were separated. Adjusted the aqueous layer pH to 1.5 - 2.5 using aqueous sodium bisulphate solution. Extracted the product 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), water (12 mL) was added to it. Reaction mixture was stirred for 30-60 minutes at 25-35 °C and then based on TLC indication for starting material content approximately 5% it was diluted with saturated brine solution. Layers

were separated and the acetonitrile layer was dried over anhydrous sodium sulphate and concentrated to dryness. Toluene (60mL) was added to the residue and it was refluxed for 5h. Cooled the reaction mass to room temperature and toluene layer 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 obtained the 3.8g of **7** as white color solid (over all yield for 3 steps is 58%); White solid; mp 112-112.9 °C. $[\alpha]_D^{27}$ = 10.8 (c, 0.8 w/v, $CHCl_3$); Reported $[\alpha]_D^{27}$= 9.8 (c, 0.8 w/v, $CHCl_3$).[28] ^{1}H NMR: (400 MHz, $CDCl_3$) 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). ^{13}C 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-((2*R*, 3*R*)-3-phenyloxiran-2-yl)-5,6-dihydro-2H-(1.05 gm, 9 mmol) was added to a solution of **7** (1.0 gm, 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 by TLC indication for absent of starting material the reaction mixture washed with brine solution and the organic layer dried over anhydrous Na_2SO_4. 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 color solid. Yield: 80%; mp 82 °C. $[\alpha]_D^{25}$ = -111.6 (c, 0.3 w/v, $CHCl_3$); Reported $[\alpha]_D^{25}$= -112.7 (c, 0.3 w/v, $CHCl_3$). ^{1}HNMR: (400 MHz, $CDCl_3$) δ: 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 (1*S*,5*S*,7*R*,8*S*)-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, AD-mix-*β* (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 2h and then allowed to room temperature and it was stirred at that temperature for 20h, 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 (230-400 mesh silica gel) and eluted with 40% EtOAc/hexanes and afforded **3b.** Yield: 65%; white crystalline solid, mp 214-219 °C. $[\alpha]_D^{25}$ = -9.8 (c, 0.2 w/v, EtOH); Reported $[\alpha]_D^{25}$ -94.9 (c 0.4, $CHCl_3$).[3] ^{1}HNMR: (500 MHz, DMSO d^6) δ: 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 & 13.5 Hz), 2.77 (d, 1H, *J* = 19 Hz), 2.40 (dd, 1H, *J* =

4.5 & 9.5 Hz), 1.85 (dd, 1H, *J* = 4.0 & 10.0 Hz). ^{13}CNMR (100 MHz, DMSO d^6) δ: 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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Table 1. Base screening for Julia-Olefination

S. No.	Base/ Eqv.	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	KO^{t}Bu (1.2)	88	75/25	78

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.

Figure 1. Natural products related to goniothalamins.

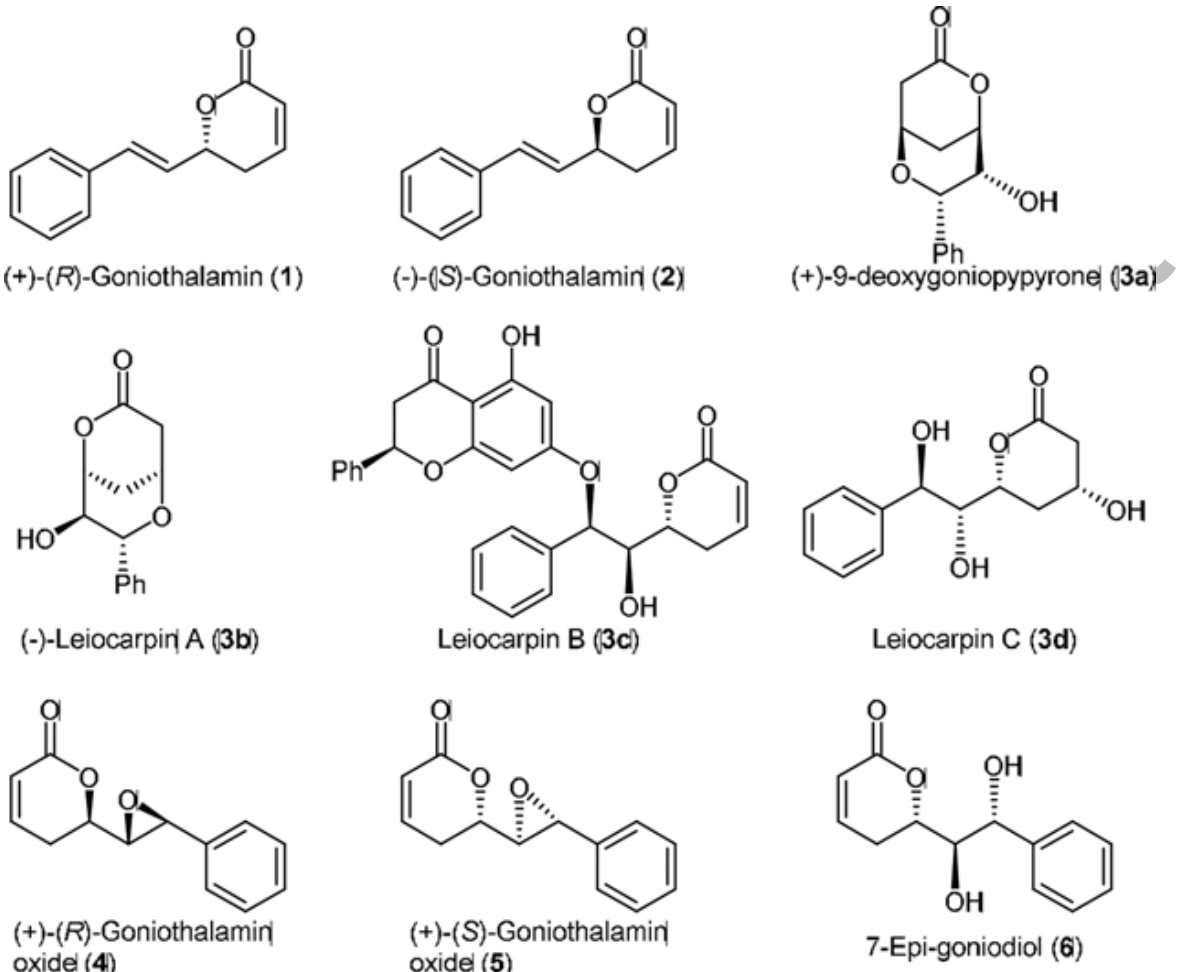
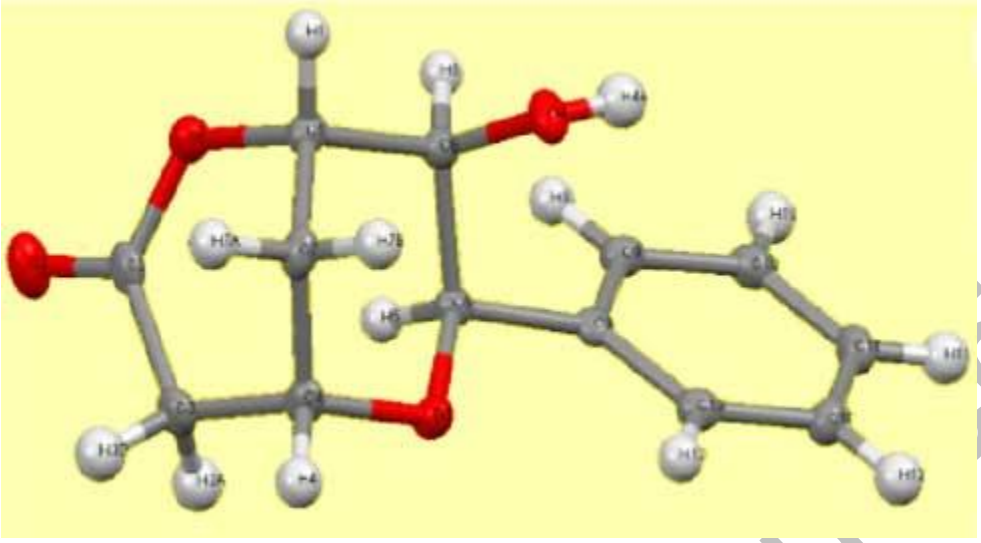
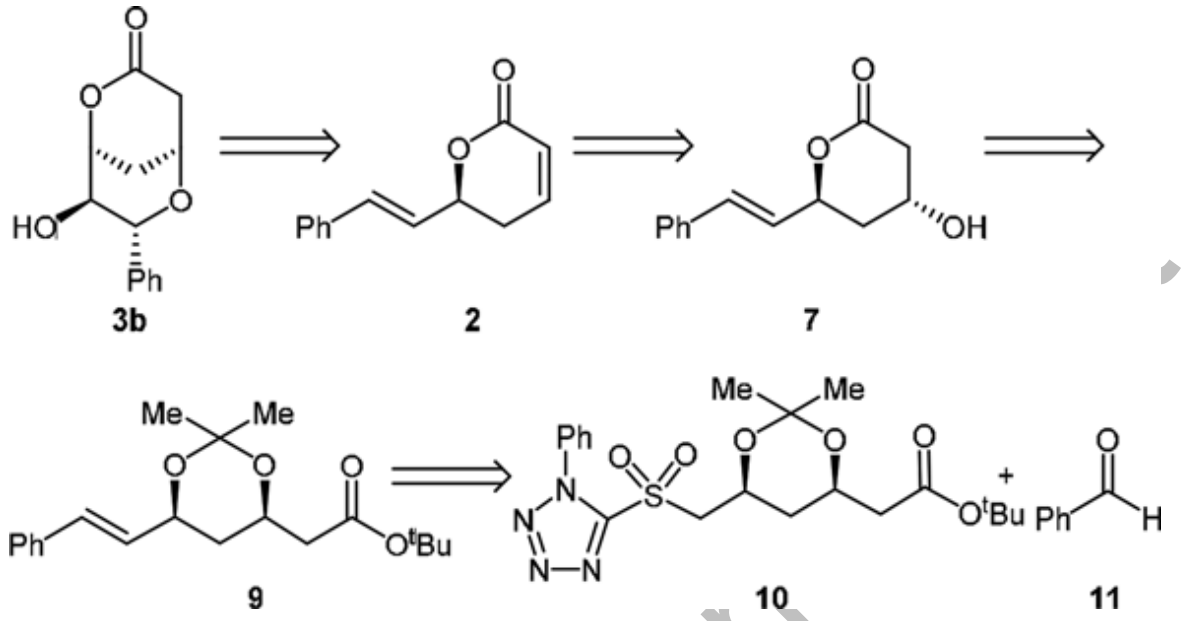


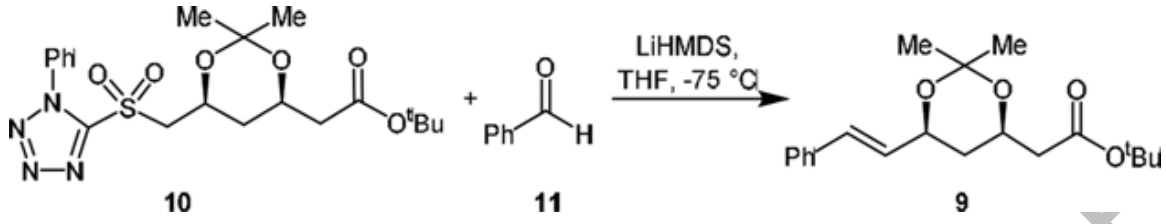
Figure 2 ORTEP diagram of (-)-leiocarpin A (**3b**).



Scheme 1. Retro synthetic scheme for (-)-leiocarpin A (3b).

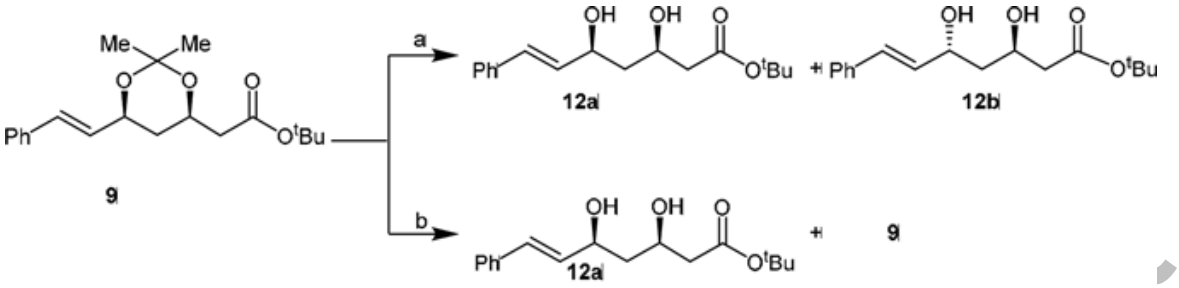


Scheme 2. Synthesis of 9.



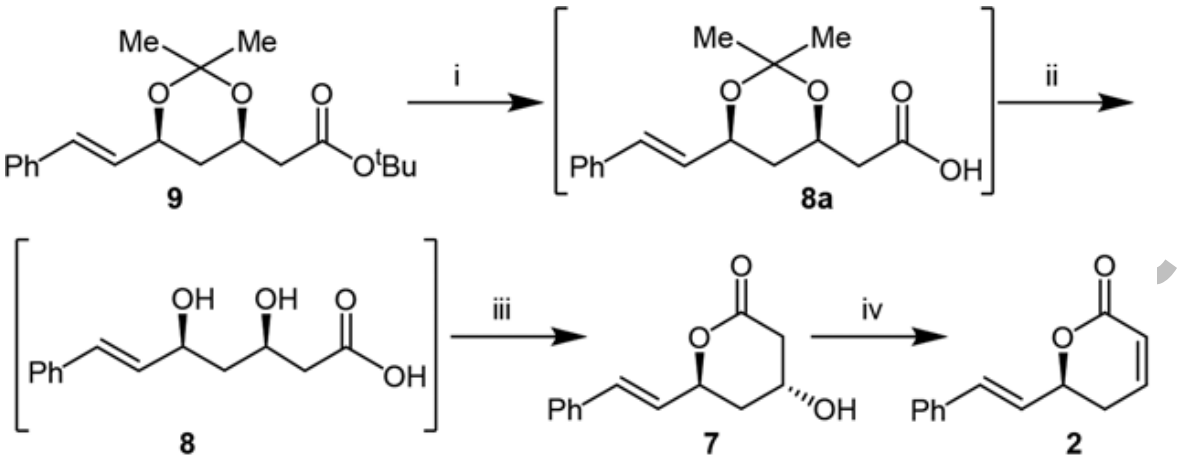
10 11 9

Scheme 3.



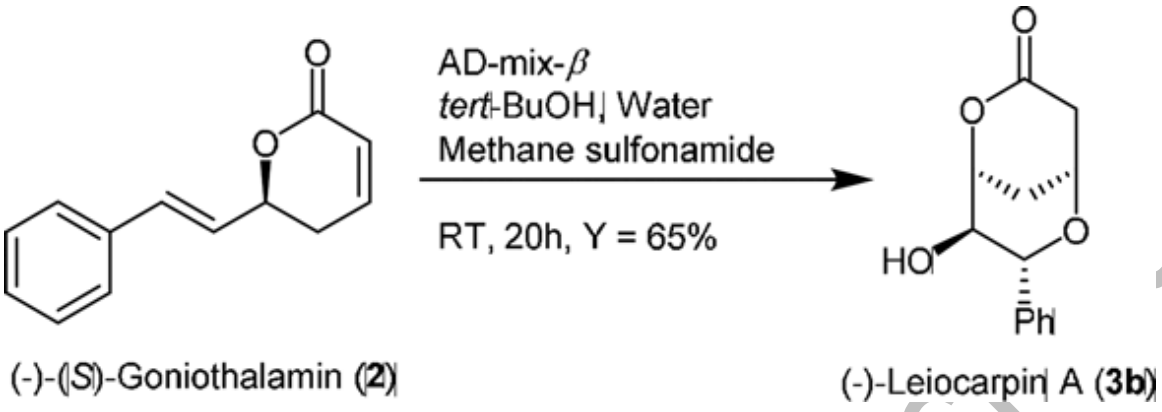
a = TFA (1.0 eqv.) (or) Aqueous HCl, acetonitrile (10 vol.), H_2O (2 vol.), R.T. b = oxalic acid (2 eqv.), acetonitrile (10vol), H_2O (2 vol), R.T.

Scheme 4. Synthesis of **2**



i = aq. NaOH, MeOH, RT, $NaHSO_4$. ii = Oxalic acid, acetonitrile, H_2O, RT. iii = Toluene reflux (58% yield, over 3 steps). iv. MsCl, TEA, -35 °C, 4h, Y = 80%

Scheme 5 Synthesis of **3b.**



(-)-(*S*)-Goniothalamin (**2**)

(-)-Leiocarpin A (**3b**)