

Total Synthesis of Leiocarpin C and (+)-Goniodiol via an Olefin Cross-Metathesis Protocol

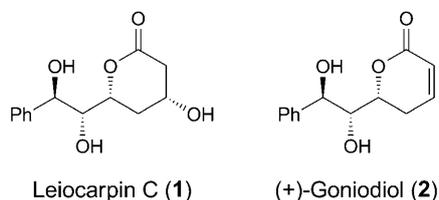
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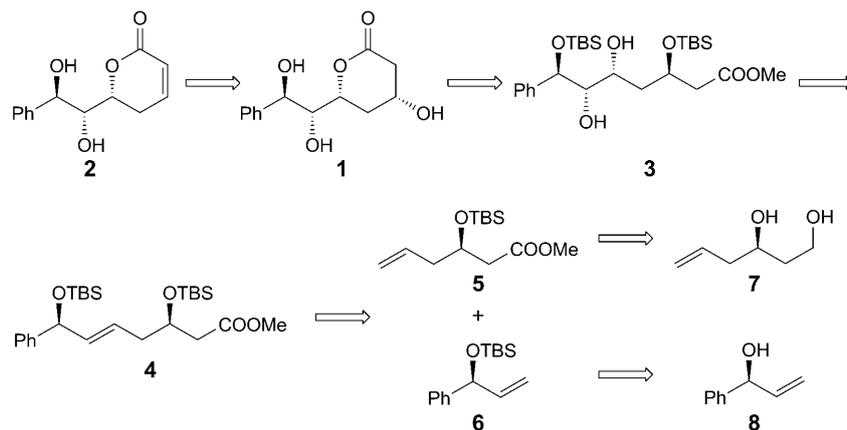
A stereoselective total synthesis of leiocarpin C (**2**) and (+)-Goniodiol (**1**) by applying olefin cross-metathesis and substrate directed dihydroxylation as the key steps is reported (*Scheme 3*).

Introduction. – Leiocarpin C (**1**) is a natural styryl lactone. Styryl lactones are natural products that exhibit significant biological activities such as antitumor, antifungal, and antibiotic properties [1]. Compound **1** was isolated from the stem bark of the tropical plant *Goniothalamus leiocarpus* [2]. Recently, two syntheses of **1** were reported [3]. (+)-Goniodiol (**2**) was isolated from the stem bark of *Goniothalamus gigantus*, and from the leaves and twigs of *Goniothalamus sesquipetalis* [4b], and it has been shown as selectively cytotoxic against human lung carcinoma cells A-549 (ED_{50} $0.12 \mu\text{g/ml}^{-1}$) and p-388 murine leukemia cells (IC_{50} $4.56 \mu\text{g ml}^{-1}$) [4]. Several syntheses of **2** have been already reported [3][5]. Impressed by the bio-profile of these compounds, coupled with our interest in the synthesis of such pyrone containing natural products [6], we embarked on their total synthesis. Here, we report the total synthesis of **1** and **2** by a novel methodology involving olefin cross-metathesis and dihydroxylation as the key steps to access the basic premise of the skeleton and thence its elaboration to the targets.



Retrosynthetically (*Scheme 1*), **2** could be obtained from **1** according to a reported procedure [3b]. The latter could be obtained by the desilylation/concomitant lactonization of acyclic ester **3**, which, in turn, could be prepared by the substrate-controlled dihydroxylation of the cross-metathesis product **4**. Formation of **4** could be realized from the cross-metathesis reaction of two olefinic fragments **5** and **6**. While, fragment **5** could be prepared from the known compound **7** [7a] by protection of the secondary alcohol, oxidation of the primary alcohol, and esterification of the

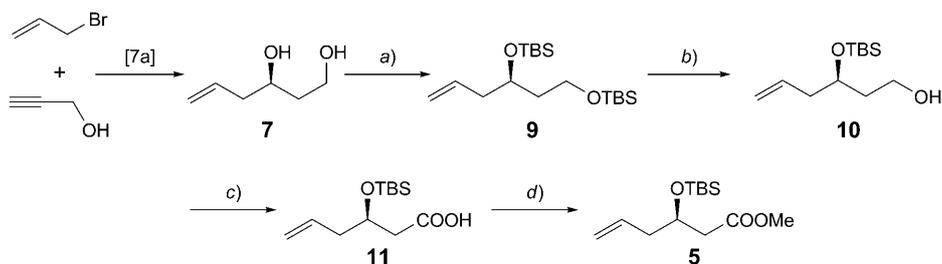
Scheme 1. Retrosynthetic Analysis



corresponding acid as the key steps, the other fragment **6** could be prepared by the (*t*-Bu) Me_2Si (TBS) etherification of the known (*S*)-1-phenylprop-2-en-1-ol ((*S*)-**8**) that has been earlier prepared by us [7b].

Results and Discussion. – The synthesis of **1** commenced by accessing the two fragments **5** and **6** independently. First, olefinic ester **5** was synthesized as depicted in *Scheme 2*. The secondary OH group of diol **7** was protected as its TBS ether. To differentiate between the primary and secondary alcohols, a selective deprotection of the bis-TBS ether in the primary position was employed: the bis-TBS ether **9** was formed, followed by the selective removal of the primary silyl group to afford **10** (74%). The primary alcohol **10** was oxidized to the corresponding aldehyde under *Swern* oxidation conditions, which was further oxidized [8] to the acid **11** (86% over two steps). The latter was subsequently esterified to afford **5** (85%) using CH_2N_2 in Et_2O .

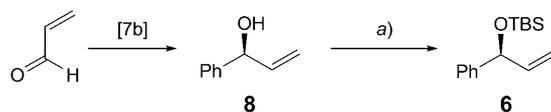
Scheme 2. Synthesis of Fragment 5



a) (*t*-Bu) Me_2SiCl (TBSCl), 1*H*-imidazole, CH_2Cl_2 , 0° , 2 h; 95%. b) TsOH, MeOH, -10° , 0.5 h; 74%. c) 1. DMSO, $(\text{COCl})_2$, Et_3N , CH_2Cl_2 , -78° , 1 h; 2. NaClO_2 , NaH_2PO_4 , 2-methylbut-2-ene, H_2O , 0° , 3 h; 86% (over two steps). d) CH_2N_2 , Et_2O , 0° , 5 min; 85%.

The known methanol derivative **8** was protected (*Scheme 3*) as its silyl ether **6**. Based on our earlier results, this protection was warranted to enable a facile cross-metathesis reaction.

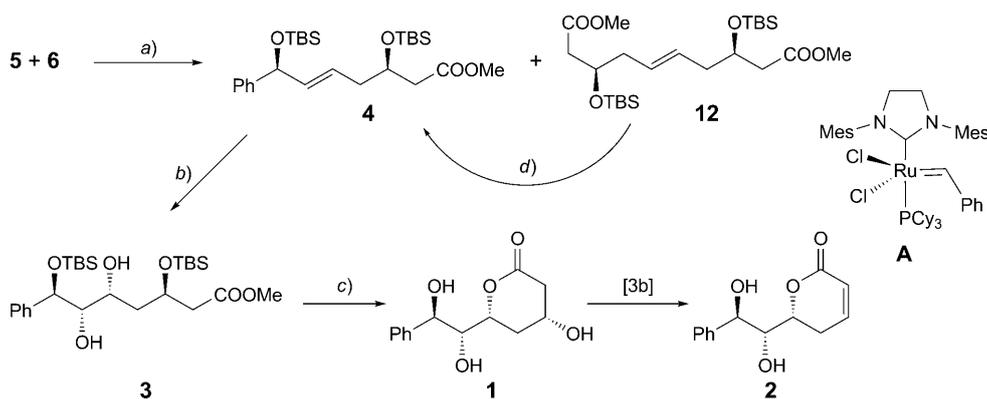
Scheme 3. Synthesis of Fragment 6



a) TBSCl, 1*H*-imidazole, CH₂Cl₂, 0°, 0.5 h, 80%.

As outlined in *Scheme 4*, the crucial olefin cross-metathesis reaction [9] between olefinic ester **5** and **6** (1:1.5 ratio) using *Grubbs-II* catalyst, **A**, resulted in product **4** (60%) as a single stereoisomer and the homo-dimer **12** (5%) of **5**. Compound **12** was effectively converted to the desired olefin **4** (60%) by using a second cross-metathesis reaction with **6** under the same conditions. Subsequently, **4** was dihydroxylated [10] to give the desired diol **3** as the major isomer (75%) after column chromatography. The minor diastereoisomer was obtained in 18% yield. Diol **3** was treated with *Amberlyst 15* resin in MeCN to furnish **1** (93%). The physical and spectroscopic data of **1** were identical to the reported ones of natural leiocarpin C [α]_D²⁵ = –63.1 (c = 0.30, CHCl₃) [2][3]. Finally, **1** was converted to **2** according to the known procedure [3b]. The spectroscopic data of **2** were in agreement with those reported in [3][5].

Scheme 4



a) *Grubbs-II* (**A**, 10 mol-%), CH₂Cl₂, r.t., 24 h, 60%. b) OsO₄, *N*-methylmorpholine *N*-oxide (NMO), acetone/H₂O 4:1, 24 h, 75%. c) *Amberlyst 15*, MeCN, r.t., 2 h, 93%. d) **6**, *Grubbs-II* (**A**, 10 mol-%), CH₂Cl₂, r.t., 24 h, 60%.

In summary, a stereoselective synthesis of **1** was achieved in ten steps and in 24.5% overall yield by cross-metathesis, followed by dihydroxylation as the key steps to access the advanced intermediate **3** that was endowed with all stereogenic centers and functionalities; and **3** was easily converted to the target compound **1**. Further, the synthesis of **2** was also accomplished.

Experimental Part

General. Org. solns. were dried over anh. Na_2SO_4 and concentrated below 40° *in vacuo*. Column chromatography (CC): silica gel (SiO_2 ; *Acme's*, 60–120 mesh). Optical rotations : *JASCO DIP 300* digital polarimeter at 25° . IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics. ^1H - and ^{13}C -NMR: *Bruker Avance-300 MHz*, and *Inova 500 MHz*; 7–10 mm solns. in CDCl_3 ; TMS as internal standard; *J* values in Hz. MS: *Finnigan Mat 1210* double-focusing mass spectrometers operating at a direct inlet system.

(5*R*)-2,2,3,3,9,9,10,10-Octamethyl-5-(*prop*-2-*en*-1-yl)-4,8-dioxa-3,9-disilaundecane (**9**). To a stirred soln. of diol **7** [7a] (0.30 g, 2.5 mmol) in CH_2Cl_2 (3.5 ml), 1*H*-imidazole (0.7 g, 10.3 mmol) was added at 0° , and the mixture was stirred for 5 min, then TBS-Cl (0.85 g, 5.6 mmol) was added, and the stirring was continued for 2 h at r.t. The mixture was diluted with CH_2Cl_2 (4 ml), and the org. layer was washed with H_2O (5 ml), followed by brine (5 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2 ; 1% AcOEt/hexane) to afford **9** (0.84 g, 95%). Colorless oily liquid. $[\alpha]_D^{25} = -60.4$ ($c = 0.8$, CHCl_3). IR (neat): 3454, 2954, 2857, 1742, 1638, 1253, 1088, 834, 776. ^1H -NMR (300 MHz, CDCl_3): 6.03–5.86 (*m*, 1 H); 5.16 (*dd*, $J = 1.5, 12.1$, 2 H); 4.03 (*quint.*, $J = 6.0$, 1 H); 3.81 (*t*, $J = 6.7$, 2 H); 2.47–2.27 (*m*, 2 H); 1.83–1.71 (*m*, 2 H); 1.05 (*s*, 18 H); 0.21 (*s*, 6 H); 0.19 (*s*, 6 H). ^{13}C -NMR (75 MHz, CDCl_3): 135.0; 116.9; 68.7; 59.6; 42.2; 39.7; 26.1 (6 C); 18.1 (2 C); –4.1 (2 C); –5.1 (2 C). ESI-MS: 345 (71, $[M + \text{H}]^+$), 367 (100, $[M + \text{Na}]^+$).

(3*R*)-3-[(*tert*-Butyl)(*dimethyl*)silyloxy]hex-5-*en*-1-ol (**10**). To a stirred soln. of **9** (0.82 g, 2.38 mmol) in dry MeOH (10 ml), TsOH (0.04 g, 0.17 mmol) was added at -10° , and the mixture was stirred for 0.5 h. The reaction was quenched with 1.5 ml of Et_3N , the solvent was evaporated, the residue was dissolved in AcOEt (2 \times 5 ml), and washed with H_2O (6 ml), and brine (6 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (SiO_2 ; 10% AcOEt/hexane) to afford **10** (0.40 g, 74%). Syrupy liquid. $[\alpha]_D^{25} = -64.4$ ($c = 0.85$, CHCl_3). IR (neat): 3380, 2932, 2858, 1740, 1640, 1253, 1068, 835, 774. ^1H -NMR (300 MHz, CDCl_3): 5.82–5.67 (*m*, 1 H); 5.06 (*d*, $J = 4.1$, 1 H); 5.01 (*s*, 1 H); 3.99–3.91 (*m*, 1 H); 3.83–3.72 (*m*, 1 H); 3.70–3.61 (*m*, 1 H); 2.28 (*t*, $J = 6.2$, 2 H); 1.82–1.72 (*m*, 1 H); 1.67–1.56 (*m*, 1 H); 0.89 (*m*, 9 H); 0.09 (*s*, 3 H); 0.08 (*s*, 3 H). ^{13}C -NMR (75 MHz, CDCl_3): 134.4; 117.3; 71.1; 60.0; 41.6; 37.6; 25.7; 17.9; –4.4; –4.8. ESI-MS: 231 (23, $[M + \text{H}]^+$), 253 (100, $[M + \text{Na}]^+$). HR-MS: 253.1601 ($\text{C}_{12}\text{H}_{26}\text{NaO}_2\text{Si}^+$; calc. 253.1599).

(3*R*)-3-[(*tert*-Butyl)(*dimethyl*)silyloxy]hex-5-*enoic* Acid (**11**). To a soln. of oxalyl chloride (0.28 ml, 2.47 mmol) in dry CH_2Cl_2 (3 ml) at -78° , dry DMSO (0.27 ml, 4.95 mmol) was added dropwise and stirred for 10 min. A soln. of **10** (0.38 g, 1.65 mmol) in dry CH_2Cl_2 (2 ml) was added, and the mixture was stirred for 1 h at -78° . The reaction was quenched with Et_3N (1.28 ml, 9.9 mmol), and the mixture was diluted with CH_2Cl_2 (5 ml), washed with H_2O (4 ml) and brine (4 ml), dried (Na_2SO_4), and evaporated to furnish the corresponding aldehyde. To a cooled (0°) soln. of the above aldehyde (0.38 g, 1.65 mmol) in *t*-BuOH (2 ml), 2-methylbut-2-ene (1 ml), followed by a soln. of NaClO_2 (0.3 g, 3.3 mmol) and NaH_2PO_4 (0.51 g, 3.3 mmol) in H_2O (1 ml), was added, and the mixture was stirred at r.t. for 3 h. The solvent was evaporated, the residue was dissolved in AcOEt (5 ml) and washed with H_2O (5 ml) and brine (5 ml), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue by CC (SiO_2 ; 12% AcOEt/hexane) gave **11** (0.34 g, 86% over two steps). Yellow syrup. $[\alpha]_D^{25} = -48.2$ ($c = 0.7$, CHCl_3). IR (neat): 3380, 2932, 2858, 1740, 1640, 1253, 1068, 835, 774. ^1H -NMR (300 MHz, CDCl_3): 5.84–5.67 (*m*, 1 H); 5.09 (*s*, 1 H); 5.05 (*d*, $J = 3.5$, 1 H); 4.18 (*quint.*, $J = 5.6$, 1 H); 2.51–2.37 (*m*, 2 H); 2.27 (*pseudo-t*, $J = 6.2$, 2 H); 0.86 (*s*, 9 H); 0.07 (*s*, 3 H); 0.04 (*s*, 3 H). ^{13}C -NMR (75 MHz, CDCl_3): 177.3; 133.7; 118.0; 68.8; 41.9; 41.7; 25.7; 17.9; –4.5; –4.9. ESI-MS: 245 (26, $[M + \text{H}]^+$), 267 (100, $[M + \text{Na}]^+$). HR-MS: 267.1405 ($\text{C}_{12}\text{H}_{24}\text{NaO}_3\text{Si}^+$; calc. 267.1392).

Methyl (3*R*)-3-[(*tert*-Butyl)(*dimethyl*)silyloxy]hex-5-*enoate* (**5**). To a stirred soln. of **11** (0.32 g, 1.31 mmol) in Et_2O (5 ml), CH_2N_2 in Et_2O was added, until yellow color sustained at 0° , and the mixture was stirred for 5 min. Evaporation of the solvent under reduced pressure and purification of the residue by CC (SiO_2 ; 2% AcOEt/hexane) afforded **5** (0.28 g, 85%). Yellow oil. $[\alpha]_D^{25} = -68.4$ ($c = 0.55$, CHCl_3). IR (neat): 3078, 2932, 2858, 1711, 1644, 1433, 1254, 1090, 834, 776. ^1H -NMR (300 MHz, CDCl_3): 5.84–5.68 (*m*, 1 H); 5.07 (*s*, 1 H); 5.03–4.99 (*m*, 1 H); 4.17 (*quint.*, $J = 6.0$, 1 H); 3.64 (*s*, 3 H); 2.40–2.38 (*m*, 2 H); 2.27–2.23 (*m*, 2 H); 0.85 (*s*, 9 H); 0.06 (*s*, 3 H); 0.02 (*s*, 3 H). ^{13}C -NMR (75 MHz, CDCl_3): 177.3;

(500 MHz, CDCl₃): 7.47–7.25 (m, 5 H); 4.91 (d, *J* = 7.8, 1 H); 4.73 (dd, *J* = 4.4, 9.8, 1 H); 4.28 (quint., *J* = 6.8, 1 H); 3.7 (d, *J* = 8.8, 1 H); 2.86 (dd, *J* = 5.4, 17.2, 1 H); 2.55 (dd, *J* = 7.3, 17.2, 1 H); 2.20–2.14 (m, 1 H); 2.08–1.99 (m, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 172.1; 141.3; 128.5; 127.8; 127.2; 78.0; 68.9; 67.0; 66.8; 41.1; 40.1. ESI-MS: 275 (100, [*M* + Na]⁺). HR-MS: 275.0907 (C₁₃H₁₆NaO₅⁺; calc. 275.0895).

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