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First diastereoselective total synthesis of bicyclic styryl lactone: (1*R*,5*R*,7*R*)-7-((*E*)-styryl)-2,6-dioxabicyclo[3.3.1]nonan-3-one

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ABSTRACT

A concise and facile diastereoselective first total synthesis of bicyclic styryl lactone **1** is described in nine steps. This biologically active bicyclic styryl lactone was obtained in 8% overall yield from cinnamaldehyde **2** and (*R*)-3-hydroxyhex-5-enoic acid **3.** Jacobsen resolution, Pinnick oxidation and Prins cyclisation reactions are the key steps involved in the synthesis.

Introduction

2,6-Dioxabicyclo[3.3.1]nonan-3-one (pyranopyrone) skeleton is found in many natural products such as cryptocaryolone, cryptocaryolone diacetate, leiocarpin A and polyrhacitide A & B which were isolated from the bark extract of a South African plant *Cryptocarya latifolia* [1], a Chinese plant *Goniothalamus leiocarpus* [2] and Chinese ant species *Polyrhacis lamellidens* [3] respectively (Fig. 1). These natural products are known to exhibit promising biological activities [4–6]: Cryptocaryolone containing bark extract has been used for the treatment of headaches, morning sickness, cancer, pulmonary diseases, and a variety of other bacterial and fungal infection [4]. Leiocarpin A exhibited excellent anticancer activity against different type of Cancer cells [5]. The ant extract has been used as a folk medicine in the treatment of rheumatoid arthritis and hepatitis in China and the ethanolic extract that contains polyrhacitides A & B was found to display significant analgesic and anti-inflammatory effects [6]. Drewes, *et. al.* have reported the isolation of bicyclic styryl lactone **1** from the bark of South African tree *Cryptocarya wyliei* [1] in the racemic form along with related natural products acetyl and deacetyl-cryptocaryalactones. After three years the same group reported compound **1** prepared from acetyl and deacetyl-cryptocaryalactones by a base induced cyclization [7]. The structure of bicyclic styryl lactone **1** was identified based on exhaustive NMR studies and the absolute configuration was assigned from the X-ray crystal data and correlation of stereogenic centers in the parent cryptocaryalactones to establish the absolute configuration as (*1R,5R,7R*)-pyranopyrone [1,7]. The absolute and relative stereochemistries of pyranopyrone core of leiocarpin A and bicyclic styryl lactone found identical. As these natural products are available in very scarce amounts, total synthesis becomes a viable approach for its availability towards exploring the biological properties. Several synthetic approaches have been developed for the synthesis of natural products having 2,6-dioxabicyclo[3.3.1]nonan-3-one skeleton through oxy-Michael, iodo-lactonization, hetero-Diels-Alder reaction, domino-Aldol reaction, *cis*-Wittig olefination and Baylis-Hillman reaction as key steps [8]. To date no report has been available for the total synthesis of bicyclic styryl lactone **1**.

Results and discussion

Because of the intriguing structural features and inherent biological properties of bicyclic styryl lactone **1**, we were interested in developing an efficient synthetic route to prepare this bicyclic compound. Intermolecular Prins cyclisation is the most effective method for stereoselective synthesis of natural products possessing THP ring, fused/bridged oxacycles and spirocycles [9]. We developed a novel coupling partner **3** that comprises homoallyl alcohol with a carboxylic acid group. This partner is anticipated to undergo Prins cyclization and then intramolecular esterification to produce the complex bicyclic lactone [10]. In this paper, a novel method for the one-step synthesis of bicyclic styryl lactone **1** using tandem Prince cyclization lactonization, involves coupling cinnamaldehyde **2** and (*R*)-3-hydroxyhex-5-enoic acid **3** in the

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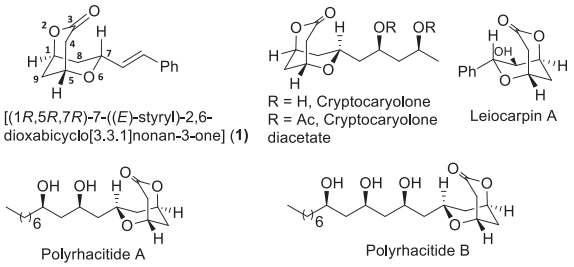


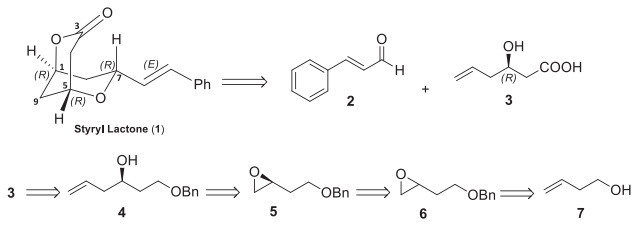
Fig. 1. Natural products harboring a bicyclic lactone (Pyranopyrone) skeleton.

presence of a Lewis acid catalyst, is provided.

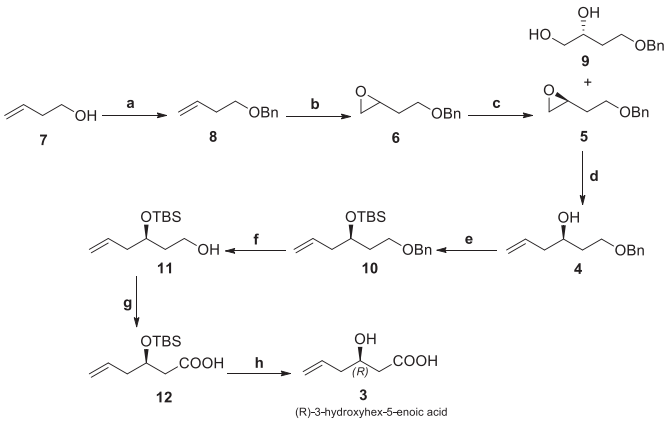
Bicyclic styryl lactone **1** can be synthesized according to the retrosynthetic analysis shown in Scheme 1. Retrosynthetically, it was envisaged that the target compound could be obtained from the key precursor (*R*)-3-hydroxyhex-5-enoic acid **3** which can undergo TMSOTf mediated one-pot Prins cyclisation to give target molecule **1.** The precursor **3** can be synthesized from chiral epoxide **5** following a three-step sequence involving regioselective ring opening of epoxide **5** by vinyl Grignard, secondary hydroxyl group protection, primary hydroxyl group deprotection, Pinnick oxidation and deprotection of secondary hydroxyl group as the key steps. The chiral epoxide **5** in turn can be obtained from Jacobsen resolution of racemate **6**. Racemate **6** can be obtained from homoallylic alcohol **7** following a two-step sequence involving hydroxyl group protection and epoxidation (Scheme 1).

As depicted in Scheme 2 the synthesis of styryl lactone **1** was began from homoallylic alcohol **7**, which was subjected to benzylation using NaH and BnBr in THF to obtain benzyl ether **8** in 90 % yield. The compound **8** was subjected to an epoxidation using MCPBA in CH_2Cl_2 to yield the product **6** as a racemic mixture in 80 % yield. An important element to our synthetic strategy is the utility of asymmetric Jacobsen resolution reaction to establish the initial asymmetry. Thus, Jacobsen hydro kinetic resolution of racemic epoxide **6** using (*S*,*S*)-(Salen) Co (II) complex [11] in AcOH provided chiral epoxide **5** with desired stereogenic center in 46 % yield (96 % ee) along with side product diol **9** in 48 % yield (98 % ee) Scheme 2. Regioselective ring-opening of compound **5** with vinyl magnesium bromide [12] in THF provided corresponding homoallylic alcohol **4** in 90 % yield. The resulting homoallylic alcohol **4** was then reacted with TBSCI, Imidazole, and a catalytic DMAP in CH_2Cl_2 to get silyl ether **10** in 92 % yield [13]. Chemoselective benzyl ether deprotection of compound **10** was achieved using Li, naphthalene, in THF yielded the primary alcohol **11** in 80 % yield [14]. The alcohol was then converted to corresponding aldehyde by reacting with Dess-Martin periodinane [15]. Subsequently it was subjected for Pinnick oxidation [16] employing $NaClO_2$, 2-Methyl-2-butene in *t*-BuOH-H_2O (3:1) to give the desired carboxylic acid **12** in 85 % yield. Deprotection of secondary hydroxyl group of carboxylic acid **12** utilizing TBAF in THF gave the required starting material **3** in 84 % yield [17].

After, having two coupling fragments (*R*)-3-hydroxyhex-5-enoic acid **3** and cinnamaldehyde **2** in hand we went for the tandem one pot coupling–cyclization reaction. A 10 mol % TMSOTf was added to a mixture of compounds **3** and **2** in CH_2Cl_2 at −40 and stirring at 0 °C for 2 h yielded the bicyclic styryl lactone **1** exclusively as a single diastereomer



Scheme 1. Retrosynthetic Analysis of bicyclic styryl lactones.



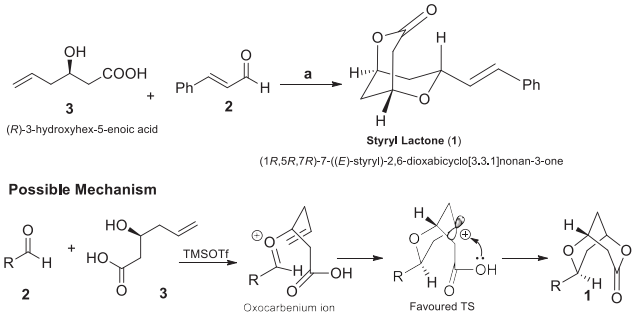
Scheme 2. Reagents and conditions: (a) NaH, BnBr, THF, rt, 1 h, 90 %; (b) MCPBA, CH_2Cl_2, 0 °C-rt, 6 h, 80 %; (c) (S,S) Co-(Salen), AcOH, H_2O, THF, 0 °C-rt, 22 h, 46 %; (d) Vinyl bromide, Mg, THF, 1,2-dibromoethane, CuCN, −78–40 °C, 6 h, 90 %; (e) TBSCI, Imidazole, CH_2Cl_2, DMAP, 0 °C-rt, 1 h, 92 %; (f) Li, Naphthalene, THF, −25 °C, 1 h, 80 %; (g) i) DMP, CH_2Cl_2, 2 h, 80 %; ii) $NaClO_2$, *t*-BuOH-H_2O (3:1), 2-methyl-2-butene, 0 °C-rt, 2 h, 85 %; (h) TBAF, THF, 0 °C-rt, 3 h, 84 %.

in 50 % yield [18,19]. A possible mechanism [20] for the Prins cyclisation and subsequent intramolecular cyclisation was represented in Scheme 3. The structure of bicyclic styryl lactone **1** was derived through NMR experiments such as NOESY, TOCSY, DQFCOSY, HSQC and HMBC. The analytical data was found to be identical and optical rotation was comparable with the reported data of both the natural [1,7] and synthetic product.

The coupling constants $^3J_{H\text{-}1/H\text{-}8a} = 6.0$ Hz, $^3J_{H\text{-}1/H\text{-}8b} = 2.2$ Hz, $^3J_{H\text{-}1/H\text{-}9a} = 4.2$ Hz, $^3J_{H\text{-}1/H\text{-}9b} = 2.0$ Hz indicating that H-1 equitorial to H-9a, H-9b and H-8a, H-8b protons. The large di-axial coupling $^3J_{H\text{-}7/H\text{-}8b} =$ 11.7 Hz and di equitorial coupling $^3J_{H\text{-}7/H\text{-}8a} = 2.6$ Hz and strong NOE correlations, H-4a/H-7, H-4b/h-9b and H-8b/H-9a are consistent with the chair conformation of the six membered ring (Fig. 2). The energy minimized structure adequately supports the proposed structure of bicyclic styryl lactone **1**.

Conclusion

In conclusion, a concise and stereoselective first total synthesis of bicyclic styryl lactone **1** has been accomplished in nine steps with an 8 % overall yield. Jacobsen hydrolytickinetic resolution of epoxide, selective oxidation using Pinnick oxidation and a tandem Prins cyclisation lactonization reactions are the key steps involved in the synthesis of natural bicyclic styryl lactone. This approach may find wide applications in exploring the synthesis of other bioactive molecules containing pyranopyrone skeleton.



Scheme 3. Plausible mechanism; Reagents and conditions: (a) 10 mol %, TMSOTf, CH_2Cl_2, −40 °C, 2 h, 50 %.

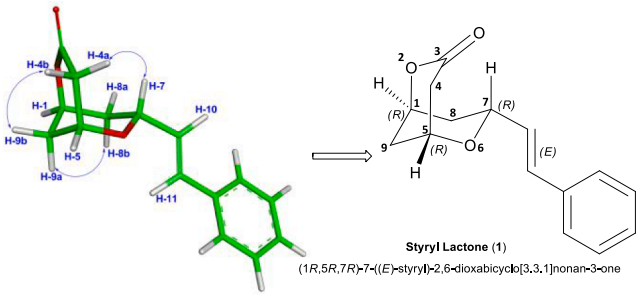


Fig. 2. Energy minimized structure (NOE) of bicyclic styryl lactone **1**.

CRediT authorship contribution statement

Dhanraj O. Biradar: Investigation, Methodology. **Yogesh D. Mane:** Writing – review & editing. **A.V. Narsaiah:** Conceptualization, Supervision. **B.V. Subba Reddy:** Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dhanraj O Biradar reports financial support was provided by CSIR New Delhi.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rechem.2022.100717.

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[17] Spectral data for few selected compounds: (*R*)-2-[2-(Benzyloxy)ethyl]oxirane (**5**): Colorless oil, $[\alpha]_D^{22} = +16.3$ ($c = 1.5$, $CHCl_3$); Lit. + 16.0 ($c = 2$, $CHCl_3$), IR (KBr): ν_{max} 3489, 3031, 2996, 2922, 2860, 1492, 1453, 1260, 1103, 1025, 908, 833, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.40-7.26 (m, 5H), 4.52 (s, 2H), 3.62 (dd, J = 9.6, 3.7 Hz, 2H), 3.12-3.02 (m, 1H), 2.78 (t, J = 4.5 Hz, 1H), 2.52 (dd, J = 5.0, 2.7 Hz, 1H), 1.98-1.70 (m, 2H); ^{13}C NMR (124 MHz, $CDCl_3$): δ 138.1, 128.1, 127.3, 72.8, 66.8, 49.8, 46.8, 32.7; MS-ESIMS: *m/z* 178 $[M+H]^+$; HRMS calcd for $C_{12}H_{14}O_2$: $[M+H]^+$ 178.84442, found 178.84460; (*R*)-1-(Benzyloxy)hex-5-en-3-ol (**4**): Colorless liquid, $[\alpha]_D^{22} = -2.0$ ($c = 1.5$, $CHCl_3$), IR (KBr): ν_{max} 3440, 3069, 3030, 2919, 2862, 1640, 1495, 1364, 1206, 1096, 1026, 914, 738 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 5.88-5.78 (m, 1H), 5.14-5.07 (m, 2H), 4.52 (s, 2H), 3.91-3.84 (m, 1H), 3.75-3.62 (m, 2H), 2.90 (s, 1H), 2.27-2.23 (m, 2H), 1.79-1.71 (m, 2H); ^{13}C NMR (124 MHz, $CDCl_3$): δ 137.7, 134.6, 128.1, 127.3, 117.1, 73.0, 69.5, 68.2, 41.6, 35.6; MS-ESIMS: *m/z* 207 $[M+H]^+$, 229 $[M+Na]^+$; HRMS calcd for $C_{13}H_{19}O_2$: $[M+H]^+$ 207.13796, Found 207.13738; (*R*)-3-Hydroxyhex-5-enoic acid (**3**): Colorless oil, $[\alpha]_D^{22} = -112.2$ ($c = 0.48$, $CHCl_3$), IR (KBr): ν_{max} 3404, 3077, 2926, 2855, 1718, 1644, 1404, 1176, 1054, 995, 920 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.81 (ddd, J = 15.0, 11.8, 6.4 Hz, 1H), 5.15 (dd, J = 9.6, 6.6 Hz, 2H), 4.16-4.09 (m, 1H), 2.61-2.43 (m, 2H), 2.37-2.24 (m, 2H); ^{13}C NMR (124 MHz, $CDCl_3$): δ 176.7, 133.6, 118.4, 67.4, 40.8, 40.5, 18.5; MS-ESIMS: *m/z* 131 $[M+H]^+$, 153 $[M+Na]^+$; HRMS calcd for $C_7H_{14}O_2Na$ $[M+Na]^+$ 153.08860, found 153.08826; (1R,5R,7R)-7-((E)-Styryl)-2,6-dioxabicyclo[3.3.1] nonan-3-one (**1**): White solid, mp= 155-157 °C, $[\alpha]_D^{22} = +4.83$ (*c* 0.40, $CHCl_3$), IR (KBr): ν_{max} 3419, 2924, 2853, 1744, 1462, 1377, 1161, 1112, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.34-7.16 (m, 5H), 6.57 (d, J = 15.9 Hz, 1H), 6.08 (dd, J = 15.9, 6.1 Hz, 1H), 5.00-4.94 (m, 1H), 4.50- 4.44 (m, 2H), 2.92 (d, J = 19.3 Hz, 1H), 2.78 (dd, J = 19.3, 5.3 Hz, 1H), 2.31-2.20 (m, 2H), 2.15-2.08 (m, 1H), 2.02 (ddd, J = 11.2, 6.6, 4.6 Hz, 1H), 1.94-1.88 (m, 1H), 1.71 (ddd, J = 13.9, 11.8, 2.0 Hz, 1H); ^{13}C NMR (124 MHz, $CDCl_3$): δ 169.6, 136.2, 131.7, 128.6, 128.1, 128.0, 126.5, 72.8, 66.8, 66.1, 37.1, 36.5, 31.9; MS-ESIMS: *m/z* 245 $[M+H]^+$, 267 $[M+Na]^+$; HRMS calcd for $C_{15}H_{16}O_3Na$: $[M+Na]^+$ 267.09894, found 267.09917.
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