A Concise Enantioselective Strategy to (+)-(R)-Goniothalamin and (+)-(R)-Goniothalamin Oxide by Employing Hydrolytic Kinetic Resolution and Ring-Closing Metathesis as Key Steps

D. Subhas Bose,* A. V. Narsimha Reddy, Bingi Srikanth

Organic Chemistry Division III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax +91(40)27160387; E-mail: dsb@iict.res.in; E-mail: bose_iict@yahoo.co.in
Received 10 April 2008; revised 30 April 2008

Abstract: An efficient and general strategy to (R)-goniothalamin and (R)-goniothalamin oxide is described by using Jacobsen’s hydrolytic kinetic resolution of racemic epoxide and ring-closing metathesis (RCM) as key steps, which provided a rapid access to these natural products that display a fascinating array of biological activity. (R)-Goniothalamin oxide was prepared in high yield and diastereomeric excess under various epoxidation conditions.

Key words: Jacobsen’s epoxidation, goniothalamin, styryl lactones, metathesis, natural products

α,β-Unsaturated δ-lactones are structural elements generally found in a diverse array of biologically interesting natural and synthetic products, because such a structural unit is an excellent potential Michael acceptor for nucleophilic amino acid residues of the natural receptors interacting with these compounds. These small exogenous molecules possess interesting biological activities on cell functions, making them useful tools for understanding life processes and for treating life-threatening diseases, such as anti-HIV, antifungal, antibacterial, and antitumor properties.1 α-Pyrones have been utilized as intermediates for synthetic transformations2 and much attention has been paid to their synthesis.

Styryl lactones are a group of secondary metabolites isolated from the genus Goniothalamus.3 (+)-(R)-Goniothalamin (1) belongs to this class of lactones and it was isolated in 1967 from the dried bark of Cryptocarya caloneura4 and given the S configuration. A decade later, the configuration of the stereocenter was revised and established as R.5 Later it was isolated from Cryptocarya moschata,6 Bryonopsis lactiosa,7 and various other species of Goniothalamus8 (115 species9 distributed through the tropics and subtropics). Some of the isolated goniothalamin-based derivatives are illustrated in Figure 1.

Goniothalamin is a potent mosquito larvicide and shows weak antibacterial and significant antifungal activity against a wide variety of gram-positive and gram-negative bacteria and fungi.10 It is one of a new class of compounds with potential anticancer properties displaying cytotoxic and antitumor properties.11

(+)-(R)-Goniothalamin (1) has shown in vitro cytotoxic effects on different cell lines, including MCF-7, T47D, and MDA-MB-231 (breast carcinoma), HeLa cells (human cervical carcinoma), gastric carcinoma (HGC-27), leukemia carcinoma (HL-60), and ovarian carcinoma (Caov-3).3a,12,13b This cytotoxic activity, which results from the selective induction of apoptosis13 on the cancer cell lines, was shown to be surprisingly low on nonmalignant cells. In vivo studies revealed that I possessed tumoricidal and tumorstatic properties on Sprague–Dawley rats with 7,12-dimethylbenzanthracene-induced mammary tumors.14 More recent studies have started to relate the trypanocidal activity of goniothalamin 1 and goniothalamin oxide 2 against free trypanostigotes forms of Trypanosoma cruzi to their biological activity.15

Owing to their biological activity and limited availability from natural sources, these compounds have attracted attention and have become the targets for total synthesis by a number of research groups.16 The majority of publications to date have focused on the antithetic approach to 1 and are based on C2–C3 and/or C6–C7 double bond disconnects (Scheme 1), other methods, such as asymmetric hetero-Diels–Alder cycloadditions and intramolecular nucleophilic additions to ketenes, have been employed. Furthermore, all the previous syntheses that relied upon various olefination methods to establish the C6–C7 double bond, provided the styryl lactone either with low selectivity or in poor yields. It was surmised that Jacobsen’s recently reported hydrolytic kinetic resolution of terminal epoxide technique17 and Grubbs’ catalyst18 for the formation of C–C bond formation methods might
serve as ideal methods to accomplish the desired absolute configuration in the pyran-2-one moiety and olefination in high yields and selectivity. The successful exploitation of this approach will also enable us to prepare a library of goniothalamin I analogues, starting from a common precursor, trans-cinnamaldehyde (7) (Scheme 2), in order to study the structure–activity relationship.

Scheme 1  Retrosynthesis of (+)-(R)-goniothalamin (1)

The substrate for HKR, racemic epoxide 2-[(E)-2-phenylvinyl]oxirane (6)\(^1\) was prepared from 7 with trimethylsulfonium iodide (1.0 equiv), tetrabutylammonium iodide (catalytic amount) in the presence of 50\% aqueous sodium hydroxide in dichloromethane. The resulting epoxide (±)-6 was subjected to Jacobsen’s HKR resolution technique using \((R,R)\)-salen–Co(III)OAc \((R,R)\)-8 (0.5 mol\%) and water (0.55 equiv) at ambient temperature to afford a mixture of epoxide \((R)\)-6 \([\alpha]_D^0 +15.6\) (c 3.0, acetone); Lit.\(^2\) \([\alpha]_D^0 +11.0\) (c 3.56, acetone) in 48\% yield (99\% ee) and the diol \((S)\)-9 in 46\% yield (Scheme 2).

The diol \((S)\)-9 \([\alpha]_D^0 +34.1\) (c 1.0, CHCl\(_3\)); Lit.\(^3\) \([\alpha]_D^0 +34.9\) (c 0.87, CHCl\(_3\)) could be recycled, via the Mitsunobu reaction\(^2\) with diisopropyl azodicarboxylate and triphenylphosphine in refluxing benzene to afford the corresponding epoxide \((S)\)-6 in 86\% yield with 97\% ee. Both epoxides are expected to serve as good precursors for the synthesis of biologically interesting natural products. Copper-catalyzed regioselective opening of epoxide \((S)\)-6 with vinylmagnesium bromide furnished the optically enriched homoallylic alcohol 5 in high yield and purity. The configuration was established by comparing the measured optical rotation which was \([\alpha]_D \)–14.5 (c 2.0, Et\(_2\)O), with the rotation of previously reported value\(^4\) of an \(R\)-enriched sample \([\alpha]_D =-14.5\) (c 2.0, Et\(_2\)O). Acylation of alcohol in 5 using acryloyl chloride or acrylic acid (1.8 equiv), triethylamine (3.6 equiv), 4-(dimethylamino)pyridine (cat.) in dichloromethane at 0 \(^\circ\)C afforded smoothly the metathesis precursor 4 in 78\% yield. Finally, ring-closing metathesis of 4 with the Grubbs 1\(^\text{st}\)-generation catalyst (10 mol\%) in refluxing dichloromethane for ten hours (98\% yield) furnished (+)-(R)-goniothalamin (1)\(^2\) in 65\% overall yield from trans-cinnamaldehyde (7).

Since it is known that (+)-(R)-goniothalamin (1) is a precursor to related natural products,\(^5\) its stereoselective conversion into (+)-(R)-goniothalamin oxide (2) was attempted under various epoxidation conditions. Initial optimization of the reaction with 3-chloroperoxybenzoic acid\(^6\) gave (+)-(R)-goniothalamin oxide (2) in 98\% yield in a satisfactory 93:7 diastereomeric ratio (Table 1).

Table 1  Total Synthesis of (+)-(R)-Goniothalamin Oxide (2)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield</th>
<th>dr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MCPBA(^a) (4.0 equiv), CH(_2)Cl(_2), reflux, 5 h</td>
<td>69</td>
<td>3:2</td>
</tr>
<tr>
<td>2</td>
<td>MCPBA(^b) (4.0 equiv), CH(_2)Cl(_2), r.t., 20 h</td>
<td>98</td>
<td>93:7</td>
</tr>
<tr>
<td>3</td>
<td>(S,S)-salen–Mn(III),(^c) hexafluoroacetone, Oxone, 5 h</td>
<td>90</td>
<td>98:2</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-salen–Mn(III),(^c) trifluoroacetone, Oxone, 5 h</td>
<td>83</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>(S,S)-salen–Mn(III),(^c) acetone, Oxone, 5 h</td>
<td>80</td>
<td>95:5</td>
</tr>
</tbody>
</table>

\(^a\) Commercial grade 70\% MCPBA was used.

\(^b\) Recrystallized acid and H\(_2\)O-free MCPBA were used.

\(^c\) Jacobsen’s catalyst, Bu\(_3\)NHSO\(_4\), buffered solution, MeCN, NaHCO\(_3\), 0 \(^\circ\)C.

Scheme 2  Reagents and conditions: (a) Me\(_3\)SI, 50\% aq NaOH, Bu\(_4\)NI (cat.), CH\(_2\)Cl\(_2\), 50 \(^\circ\)C, 48 h, 85\%; (b) \{Co(OAc)((R,R)-salen)\} \((R,R)\)-8 (0.5 mol\%), H\(_2\)O (0.55 equiv), r.t., 72 h; (c) DIAD, Ph\(_3\)P, benzene, reflux, 24 h, 80\%.

However, the desired chiral epoxide 2 was obtained as the sole product in 90% yield (98:2 dr) by using (+)-(R,R)-salen–Mn(III) catalyst with Oxone using the procedure developed by Han,27 whose analytical data were in good agreement with the reported data.28

In summary, we have carried out the total synthesis of goniothalamin 1 and goniothalamin oxide 2 in high yields from commercially available trans-cinnamaldehyde. This concise and efficient approach compares favorably with the more efficient approaches so far reported in the literature for these natural products and illustrates the utility of the HKR and RCM in providing rapid access to chiral 6-substituted pyran-2-ones. The extension of this synthetic methodology to the synthesis of other chiral natural products with an α, β-unsaturated δ-lactone moiety is being investigated in our laboratory.

Acknowledgement

One of the authors B.S. thanks UGC, New Delhi, for the award of a research fellowship. The authors are also thankful to Director, IICT for his support and encouragement.

References

(3) (c) Segre, A. L.; Logrieco, A. Nature Toxins 1999, 7, 133.
(26) (a) (+)-(R)-Goniothalamin: White crystalline solid; mp 82–83 °C (Lit.16l 81–82 °C). [D +170.3 (CHCl3) [Lit.6 [D +169.4 adjusted to 81–82 °C). [D +169.4 adjusted to 81–82 °C). [D +169.4 adjusted to 81–82 °C). [D +169.4 adjusted to 81–82 °C). [D +169.4 adjusted to 81–82 °C). [D +169.4 adjusted to 81–82 °C). [D +169.4 adjusted to 81–82 °C).
$J_{6,7} = 16.1 \text{ Hz}, J_{6,5} = 6.5 \text{ Hz}, \text{ 1 H}), 6.74 (\text{d, } J_{1,2} = 9.7 \text{ Hz}, J_{1,3} = 4.4 \text{ Hz}, \text{ 1 H}), 7.30-7.42 (\text{m, 5 H}).$ $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 30.1, 77.9, 121.8, 125.5, 126.7, 128.4, 133.3, 135.2, 144.8, 164.1$. MS (APCI): $m/z$ (%): 201.0 (39) [M$^+$ + H], 183.1 (100), 155.2 (66), 130.1 (41).


(26) Work on a similar line has been reported: Pospisil, J.; Marko, I. E. $Tetrahedron Lett.$ 2006, 47, 5933.


(28) ($\pm$)-($R$)-Goniothalamin Oxide (2): Mp 90–92 °C (Lit. ($^{25}$b 90–94 °C). $[\alpha]_D^{25} +100.1$ (c 0.88, CHCl$_3$) [Lit. ($^{25}$b) $[\alpha]_D^{25} +100.7$ (c 0.70, CHCl$_3$)]. $\text{IR (KBr): } 3055, 3025, 2928, 1720, 1605, 1245, 1035, 808 \text{ cm}^{-1}. \text{H NMR (300 MHz, CDCl$_3$): } \delta = 2.59$ (m, 2 H), 3.28 (dd, $J_{6,5} = 5.6 \text{ Hz}, J_{6,7} = 2.0 \text{ Hz}, \text{ 1 H}), 3.91 (\text{d, } J_{2,3} = 9.4 \text{ Hz, } J_{3,5} = 0.6, J_{5,6} = 5.5 \text{ Hz, } \text{ 1 H}), 6.07 (\text{dt, } J_{1,2} = 9.7 \text{ Hz, } J_{2,4} = 2.0 \text{ Hz, } \text{ 1 H}), 6.95 (\text{m, 1 H}), 7.32-7.39 (\text{m, 5 H}). ^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 26.3, 57.5, 61.9, 77.2, 121.6, 125.5, 128.7, 135.5, 144.4, 164.0$. MS (APCI): $m/z$ (%): 217.0 (100) [M$^+$ + H], 199.0 (45), 171.1 (83), 143.1 (45), 139.0 (32), 105.0 (31), 91.0 (31). HRMS: $m/z$ [M + Na$^+$] calcd for C$_{13}$H$_{12}$NaO$_3$: 239.0684; found: 239.0682.