Synthesis of the C1–C9, C11–C19 Pyran Core and C19–C24 Fragments of Macrolactin 3

A. Maheshwar Reddy\textsuperscript{a,b} 
Gowravaram Sabitha\textsuperscript{a,b}

\textsuperscript{a} Natural Products Chemistry Division and CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India  
\textsuperscript{b} Academy of Scientific and Innovative Research (AcSIR), New Delhi 110020, India  
gowravaramsr@yahoo.com

Received: 17.10.2017  
Accepted after revision: 07.11.2017  
Published online: 29.11.2017  
DOI: 10.1055/s-0036-1591844; Art ID: so-2017-d0041-op

License terms: 

Abstract We describe herein an efficient synthesis of the C1–C9, C11–C19 pyran moiety and C18–C24 core fragments of macrolactin 3. The prominent features of this work include construction of the Z-double bond of the 1,3-(Z,E)-diene system utilizing Horner–Wadsworth–Emmons reaction under Still–Gennari conditions. A Sharpless asymmetric epoxidation and subsequent epoxide opening under BF\textsubscript{3}·OEt\textsubscript{2} conditions were applied to generate the stereogenic centers at C15 and C16, oxa-Michael addition and Jacobsen resolution facilitate the synthesis of the fragments.

Key words macrolactin 3, tetrahydropyran, BF\textsubscript{3}·OEt\textsubscript{2}, epoxide opening, Jacobsen, oxa-Michael, D-ribose

Introduction

Marine microorganisms have proven to be excellent sources of novel, bioactive secondary metabolites, and they attract much attention from chemists, pharmacologists, and molecular biologists. Three novel bioactive 24-membered macrolactones 1–3 (Figure 1) were isolated in 2011 from fermentation of a marine microorganism \textit{Bacillus} sp. 09ID194 by Shin and co-workers, and subsequent bio-assay-guided fractionation showed antimicrobial activities against both Gram-positive and Gram-negative pathogens.\textsuperscript{1}

ROESY data analysis,\textsuperscript{2} coupling constants, and application of the modified Mosher’s method\textsuperscript{3–5} were used to establish the structures and absolute stereochemistry of macrolactins 1–3. Compounds 1–3 exhibit a minimum inhibitory concentration (MIC) of 0.16 μM against \textit{Bacillus subtilis} and \textit{Escherichia coli} in a standard in vitro broth dilution assay.\textsuperscript{6} Their MICs against \textit{Saccharomyces cerevisiae} were 0.16, 0.02, and 0.16 μM, respectively. As a continuation of our group’s interest in the synthesis of tetrahydropyran-containing molecules of complex architecture, the bioactivity of macrolactin 3 prompted us to undertake its synthesis.\textsuperscript{7}

Macrolactin 3 is a cyclic ester containing ene diene, tetrahydropyran ring moieties and three -OH groups attached to C7, C15, and C16. The retrosynthetic analysis of macrolactin is summarized in Scheme 1. Macrolactin can be envisaged to be assembled from three segments, (\textit{E}),(\textit{Z})-dien-yn-ol ester 4, vinyl pyran 5, and hydroxyalkene 6.
Synthesis of C1–C9 Fragment 4 (Macrolactins A, C, E, F, N, S and 1–3)

The key building block C1–C9 fragment 4 of macrolactin 3, also present in macrolactins A, C, E, F, N, S and macrolactins 1 and 2, was derived from commercially available 3-butyln-1-ol (homopropargylic alcohol). The known benzyl protected (S)-alcohol 7 was prepared by following a procedure similar to that used for the PMB and THP protected alcohols. The free secondary hydroxyl group was protected as its TBS ether 14, followed by removal of the benzyl group using Li/naphthalene in THF at –30 °C to furnish alcohol 15 (Scheme 2).

Oxidation of alcohol 15 with 2-(iodooxy)benzoic acid (IBX) furnished the corresponding aldehyde, which was subjected to a two-carbon extension using triphenyl-phosphoranylideneacetaldehyde (Ph$_3$P=CHCHO) to afford 16 in 85% yield (Scheme 2). Applying Stille–Gennari conditions to compound 16 provided (E),(Z)-yn-ol ester 4 (C1–C9 fragment) using methyl P,P′-bis(2,2,2-trifluoroethyl)phosphonooacetate in the presence of NaH in THF at –78 °C with excellent stereoselectivity (Z: E 95:5) in 89% yield.

Synthesis of C11–C19 Pyran Core 5

To allow for flexibility in our synthetic plan, we envisaged two pathways to access intermediate 8. Pathway a (Scheme 3) was based on epoxide opening with BF$_3$·OEt$_2$. Accordingly, 3-butyln-1-ol (homopropargyl alcohol) was converted into known benzyl protected 2,3-epoxy alcohol 10 in four steps as reported.$^{10}$ Epoxide 10 was treated with anhydrous acetone in the presence of BF$_3$·OEt$_2$ at 0 °C to furnish acetonide 9 in 85% yield.$^{11}$ Alcohol 9 was converted into the corresponding aldehyde by Swern oxidation and was used for further reaction without isolation or characterization. To create a third stereoengenic center, a Grignard reaction was performed using vinylmagnesium bromide generated in situ, which provided allyl alcohol 17a as a 1:1 mixture of diastereomers. Without separation, the latter was converted into ketone 17. Stereoselective reduction of the ketone was carried out with diisobutylaluminum hydride (DIBAL-H)$^{12}$ in anhydrous CH$_2$Cl$_2$ at –78 °C, affording the required (S)-alcohol 18 in 90% yield. Alcohol 18, on treatment with TBSCl and imidazole, provided the corresponding silyl ether 19, which, on debenzylation with Li/naphthalene in THF at –30 °C, gave...
alcohol 20. Oxidation of 20 to its corresponding aldehyde with 2-iodoxybenzoic acid (IBX), followed by Wittig olefination using the stabilized ylide, Ph₃P=CHCOOEt gave α,β-unsaturated ester 8a.

While our manuscript was under preparation, a report appeared in which a similar synthetic scheme was presented for accessing the pyran core. Therefore, we adopted another pathway from D-ribose to access intermediate 8 (Scheme 4).

The synthesis of fragment 8 began with known alcohol 13, obtained from D-ribose as reported. The hydroxyl group in 13 was protected as its TBDMS ether, followed by hydroboration/oxidation of the terminal alkene with alkaline hydrogen peroxide to produce the corresponding alcohol 12 in 80% yield (over two steps). Swern oxidation of the primary alcohol gave the corresponding aldehyde, which was subjected to Wittig olefination with Ph₃P=CHCOOEt to furnish α,β-unsaturated ester 22 in 90% yield. This was followed by removal of the TBS group with tetrabutylammonium fluoride (TBAF) in THF to obtain alcohol 11 in 90% yield.

Formation of the (S)-vinyl alcohol 8 was envisaged by oxidation of alcohol 11 to the aldehyde, followed by Grignard reaction with vinylmagnesium bromide employing an oxidation/selective reduction protocol. Thus, alcohol 11 was treated with IBX to afford the corresponding aldehyde, which, on reaction with vinylmagnesium bromide, furnished both diastereomers of vinyl alcohol 23. Oxidation of the mixture using Dess–Martin periodinane (DMP) gave
Aketone 24 in 82% yield and the ketone functionality in 24 was reduced with (S)-Me-CBS, BH3·SMe2 in THF, affording 8 in 88% yield.

At this stage, intramolecular oxa-Michael addition reactions were studied using substrates 8 and 8a. Initially, treatment of 8a either with TBAF or Triton B in THF at 0 °C afforded a mixture of 2,6-cis-tetrahydropyran (cis-5) and 2,6-trans-tetrahydropyran (trans-5) in 82% and 80% yields, respectively in a ratio of 7.5:2.5 (Scheme 5).

The stereochemistry of cis-5 was established by TOCSY and ROESY experiments and that of trans-5 by comparison with literature data. Since macrolactin 3 contains a 2,6-trans tetrahydropyran core, we changed the reaction conditions. Thus, intramolecular oxa-Michael cyclization of 8 with KOr-Bu15 (0.05 or 1 equiv) in THF at –78 °C for 30 min gave the required 2,6-trans-tetrahydropyran (trans-5) in 91% yield with excellent diastereoselectivity (dr 19:1). Thus, by simply switching the reaction conditions, either syn or anti pyran rings could be synthesized from 8 or 8a in a stereoselective manner.

Synthesis of the C19–C24 Fragment 6

Synthesis of the C19–C24 fragment, hydroxy alkene 6, began with commercially available hexen-1-ol, which was converted into its corresponding racemic epoxide 26 by reacting with m-CPBA after protecting the alcohol as its benzyl ether (Scheme 6). Chiral S-epoxide 27 was obtained from 26 by Jacobsen resolution with S,S-Jacobsen catalyst. Epoxide 27, on reduction with LAH, furnished R-alcohol 28.
which, on silylation with TBSCI and imidazole in \( \text{CH}_2\text{Cl}_2 \), gave 29. Debenzylation followed by oxidation to the aldehyde and one-carbon Wittig reaction produced alkene 6.

Conclusion

We have accomplished the asymmetric synthesis of the C1–C9, C11–C19 pyran core, and C19–C24 fragments of macrolatin 3. Key features of this approach include epoxide opening, TEMPO-BAIB oxidation, and oxa-Michael cyclization. Work towards the total synthesis of macrolatin 3 is under way.

Unless otherwise mentioned, all reactions were carried out using standard syringe, septa and cannula techniques. All glassware was flame- or oven-dried and cooled under an atmosphere of nitrogen unless otherwise stated. Column chromatography was performed using silica gel (60–120 mesh) and the column was usually eluted with EtoAc–hexanes. The diastereomeric excess of the products were measured with a chiral-phase HPLC using Chiralpak AS column. Acetylation of the C3–C9 aldehydes was achieved either by exposure to iodine vapor or UV light or by dipping the plates in sulfuric acid-

\( \text{H}_2\text{SO}_4 \) for 4 h at reflux condition. After completion of the reaction, the compound was used directly for the next step without purification.

Ethyl (5Z,6E)-7-(2-Methylbutylamino)pentanoate (4)

A solution of ethyl bis(2,2,2-trifluoroethoxy)phosphonoacetate (0.5 g, 1.0 mmol) and anhydrous THF (5 mL) was added slowly to a stirred solution of NaH (0.1 g, 4.1 mmol) in anhydrous THF (10 mL) at 0 °C under N\(_2\). The mixture was stirred at 0 °C for 30 min, then cooled to –78 °C, aldehyde 16 in anhydrous THF was added dropwise over 5 min and the resulting mixture was stirred at –78 °C for 30 min. The reaction was quenched with sat. NH\(_4\)Cl (2 mL), the product was extracted with EtOAc (3 × 20 mL), and the combined extracts were dried over Na\(_2\)SO\(_4\). After filtration, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc, 8:2) to afford (Z)-olefin ester 4.

Yield: 0.5 g (89%); colorless liquid; \( [\alpha]_D^{25} +9.4 \) (c = 0.4, CHCl\(_3\)).

\(^{13}\text{C} \text{NMR (125 MHz, CDCl}_3\)): \( \delta = 166.7, 144.8, 139.5, 129.4, 116.0, 72.7, 71.0, 62.2, 51.0, 41.9, 25.6, 18.0, –4.7, –5.1. \)

IR (neat): 3423, 2954, 2930, 2857, 1732, 1468, 1367, 1248, 1070, 837 cm\(^{-1}\).

ESIMS: \( m/z = 331 \) [M + Na]+.

**(2R,3R)-5-Benzoxyl-2,5-(2,2-dimethyl-1,3-dioxolanyl)pentanol (9)**

To a solution of compound 30 (13.63 g, 66.16 mmol) in acetone was added BF\(_3\).Et\(_2\)O (8.31 mL, 66.16 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 3 h. After completion of reaction, the reaction was quenched by the addition of solid NaHCO\(_3\) at 0 °C and the solvent was evaporated under reduced pressure to yield a residue which was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed once with brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure to afford the crude product, which, upon column chromatography (EtOAc/hexane, 10%) gave pure 31.

Yield: 14.84 g (85%); pale-yellow oil; \( [\alpha]_D^{25} +9.4 \) (c = 0.6, CHCl\(_3\)).

\(^{1}H \text{ NMR (CDCl}_3\)): \( \delta = 7.39–7.28 \) (m, 5 H), 4.53 (s, 2 H), 4.37–4.29 (m, 1 H), 4.21–4.13 (m, 1 H), 3.70–3.53 (m, 4 H), 1.94–1.84 (m, 2 H), 1.71–1.59 (brs, 1 H, OH), 1.45 (s, 3 H), 1.37 (s, 3 H).

\(^{13}\text{C} \text{ NMR (CDCl}_3\)): \( \delta = 138.5, 128.3, 127.5, 127.4, 107.7, 77.7, 74.3, 72.9, 67.5, 61.9, 29.5, 28.1, 25.5; IR (KBr): 3448, 2938, 2856, 1451, 1347, 1253, 1067, 834, 790 cm\(^{-1}\).

ESIMS: \( m/z = 299 \) [M + Na]+.

**Ethyl (E)-5R,6S,7S)-5,6-(2,2-Dimethyl-1,3-dioxolanyl)-7-(1-tet- butylbutyldimethylsilyloxy)non-2-enoate (8a)**

To an ice-cooled solution of 2-iodoxybenzoic acid (0.5 g, 1.9 mmol) in anhydrous MeCN (50 mL) was added a solution of alcohol 20 (0.5 g, 1.6 mmol). The mixture was heated at reflux for 1 h and then allowed to cool to r.t. The solvent was removed under reduced pressure and the compound was used directly for the next step without purification by column chromatography.

To a solution of the above aldehyde in C\(_6\)H\(_6\) (30 mL) was added Ph\(_3\)P=CHCOOEt (0.6 g, 1.7 mmol) and the reaction mixture was stirred at 0 °C for 3 h. After completion of reaction, the reaction was quenched with sat. Na\(_2\)CO\(_3\) solution and the resulting mixture was stirred at 0 °C for 30 min. The reaction was quenched with sat. NH\(_4\)Cl (2 mL), the product was extracted with EtOAc (3 × 20 mL), and the combined extracts were dried over Na\(_2\)SO\(_4\). After filtration, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc, 8:2) to afford the pure \( \Delta^\beta \)-unsaturated ester 8a.

Yield: 0.5 g (85%); colorless oil; \( [\alpha]_D^{25} +9.4 \) (c = 0.4, CHCl\(_3\)).

\(^{1}H \text{ NMR (CDCl}_3\)): \( \delta = 7.0–6.89 \) (m, 1 H), 5.88 (dt, \( J = 15.6, 1.3 \text{ Hz} \)), 5.70 (dd, \( J = 17.3, 10.7 \text{ Hz} \)), 5.36 (dd, \( J = 17.3, 1.5 \text{ Hz} \)), 5.25 (dd, \( J = 10.9, 1.5 \text{ Hz} \)), 4.18 (q, \( J = 7.1 \text{ Hz} \)), 3.99 (l, \( J = 6.7 \text{ Hz} \)), 3.93–3.83 (m, 2 H), 2.68–2.56 (m, 1 H), 2.52–2.55 (m, 1 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.29 (l, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H).

\(^{13}\text{C} \text{ NMR (CDCl}_3\)): \( \delta = 166.4, 145.8, 138.4, 123.1, 117.6, 108.3, 80.1, 76.5, 73.1, 61.0, 32.7, 28.1, 25.7, 18.1, 14.1, –4.5 \text{ (C)}. \)

IR (neat): 2927, 2856, 1739, 1383, 1256, 1046, 759 cm\(^{-1}\).

ESIMS: \( m/z = 407 \) [M + Na]+.
Ethyl (E)-(5R,6S,7S)-5,6-(2,2-Dimethyl-1,3-dioxolanoyl)-7-hydroxyhept-2-enoate (11)
A 1 M solution of TBAF in THF (1.3 mL) was added to a solution of compound 22 (0.5 g, 1.4 mmol) in anhydrous THF (10 mL) at 0 °C. The mixture was stirred at r.t. for 2 h. After completion of the reaction, the mixture was diluted with H2O (5 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na2SO4). Filtration and evaporation of the solvent under reduced pressure, followed by column chromatography (hexane/EtOAc, 6:4) afforded pure 11.
Yield: 0.3 g (90%); colorless liquid; [α]25 +9.8 (c = 0.3, CHCl3).

1H NMR (CDCl3, 500 MHz): δ = 7.03–6.98 (m, 1 H), 5.92 (dt, J = 15.7, 1.5 Hz, 1 H), 4.29–4.26 (m, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 4.18–4.11 (m, 1 H), 3.60 (dd, J = 10.3, 4.6 Hz, 2 H), 2.60–2.55 (m, 1 H), 2.51–2.43 (m, 1 H), 1.42 (s, 3 H), 1.35 (s, 3 H), 1.29 (t, J = 7.1 Hz, 3 H).

13C NMR (CDCl3, 75 MHz): δ = 166.2, 144.7, 108.1, 77.5, 76.8, 60.5, 29.5, 28.1, 25.5.

IR (neat): 2930, 2857, 1738, 1256, 1154, 1047, 836, 775.

ESIMS: m/z = 267 [M + Na]+.

Ethyl (E)-(5R,6S,7S)-5,6-(2,2-Dimethyl-1,3-dioxolanoyl)-7-hydroxy-2,8-dienoate (8)
To a stirred solution of (S)-Me-CBS-oxazaborolidine catalyst (1 M in toluene, 0.1 mL) in anhydrous toluene (1 mL), BH3·DMS (2 M in THF, 0.2 mL) was added at 0 °C and the mixture was stirred for 0.5 h. A 1 M solution of compound 24 (0.1 g, 0.34 mmol) in anhydrous toluene (15 mL) was added and the mixture was stirred for 0.5 h at 0 °C. After reaction was complete, monitored by TLC, the reaction was quenched with MeOH (2 mL) and the mixture was warmed to rt. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 7:3) to afford 8.
Yield: 85 mg (88%); viscous liquid; [α]25 +21.7 (c = 0.45, CHCl3).

1H NMR (CDCl3, 500 MHz): δ = 7.01–6.88 (m, 1 H), 5.88 (dt, J = 15.6 Hz, 1 H), 5.70 (dd, J = 17.1, 10.7 Hz, 1 H), 5.41 (dd, J = 17.3, 1.5 Hz, 1 H), 5.25 (dd, J = 10.9, 1.5 Hz, 1 H), 3.92–3.81 (m, 2 H), 2.67–2.58 (m, 1 H), 2.52–2.44 (m, 1 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H).

13C NMR (CDCl3, 75 MHz): δ = 166.5, 145.7, 138.5, 123.1, 117.1, 108.1, 79.8, 76.3, 71.0, 63.0, 32.7, 27.9, 25.6, 14.1.

IR (neat): 3447, 2983, 2854, 1736, 1374, 1152, 1083, 898 cm−1.

ESIMS: m/z = 293 [M + Na]+.

(E)-6-tert-Butyldimethylsiloxymethylsiloxoxypent-1-ene (6)
To an ice-cooled solution of 2-iodoxybenzoic acid (1.17 g, 4.20 mmol) in DMSO (2 mL) and CH2Cl2 (6 mL) was added a solution of 30 (0.65 g 2.80 mmol) in anhydrous CH2Cl2 (5 mL). The mixture was stirred at rt. for 5 h and then filtered through a Celite® pad and washed with CH2Cl2 (2 × 20 mL). The combined organic filtrates were washed with H2O (2 × 6 mL), brine (2 × 6 mL), dried (Na2SO4), filtered and concentrated in vacuo to afford crude aldehyde. This was used for the next step without further purification. In a reaction flask, n-BuLi (2.5 M in hexane, 3.36 mL, 8.40 mmol) was added under N2 atmosphere to a stirred suspension of methyltriphenylphosphonium iodide (0.5 g, 1.4 mmol) in anhydrous THF (50 mL) at −78 °C. The mixture was allowed to warm to rt, stirred for 1 h, and cooled to −78 °C again. To this mixture, a solution of above crude aldehyde in anhydrous THF (3 mL) was added dropwise, and the resulting mixture was stirred at rt. for 2 h. The reaction was quenched with aqueous NH4Cl and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The residue was purified by column chromatography (98:2 hexane/EtOAc) to give compound 6.
Yield: 0.456 g (72%); liquid.

1H NMR (CDCl3, 300 MHz): δ = 5.89–5.73 (m, 1 H), 5.06–4.90 (m, 2 H), 3.85–3.73 (m, 1 H), 2.09–1.99 (m, 2 H), 1.52–1.31 (m, 4 H), 1.12 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

13C NMR (CDCl3, 75 MHz): δ = 138.9, 114.2, 68.4, 39.1, 33.7, 25.8, 25.0, 23.8, 18.1, −4.4, −4.7.

ESIMS: m/z = 251 [M + Na]+.

Supporting Information
Experimental procedures, spectral data, copies of 1H NMR and 13C NMR spectra are available. Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591844.

References and Notes


