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Tetrahedron Letters 49 (2008) 463–466
Tetrahedron Letters

Stereoconvergent synthesis of the C1–C11 and C12–C24 fragments of (−)-macrolactin-A

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Received 11 July 2007; revised 14 November 2007; accepted 20 November 2007
Available online 23 November 2007

Abstract

Stereoconvergent syntheses of the C1–C11 and C12–C24 fragments of (−)-macrolactin-A are reported.
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Keywords: Macrolactin-A; Macrolide; Fragments; Sharpless asymmetric epoxidation; Sonogashira coupling

Macrolactin-A (**1**), a 24-membered polyene macrolide, which was isolated in 1989 by Fenical and co-workers[1] from a deep-sea marine bacterium, belongs to the class of macrolactins whose other members have recently been isolated.[2] This compound possesses three 1,3-diene units (*Z*,*E*-; *E*,*Z*-; *E*,*E*) and four stereogenic centres. It exhibits a broad spectrum of activity with significant antiviral and cancer cell cytotoxic properties including inhibition of B16-F10 murine melanoma cell replication ($IC_{50} = 3.5\ \mu g/mL$). Because of its unreliable supply from cell cultures, as well its structural uniqueness and broad therapeutic potential, macrolactin-A has been the subject of synthetic studies by several research groups.[3–5]

By retrosynthetic analysis, macrolactin-A was disconnected into C1–C11 and C12–C24 fragments **2** and **3**. In the forward sense they can be connected by epoxide opening using the Yamaguchi protocol followed by reduction using Lindlar's catalyst and macrolactonization. Herein we report the syntheses of the C1–C11 and C12–C24 fragments using epoxide opening for the introduction of the stereogenic centres at C7, C13 and C23 (Scheme 1).

The primary hydroxyl group of 3-butyn-1-ol **4** was protected as its PMB ether **7** using PMB–Br and NaH in 92% yield. Treatment of ether **7** with EtMgBr and paraformaldehyde afforded alcohol **8** in 75% yield. Compound **8** was converted to the allyl alcohol **9** using $LiAlH_4$ in refluxing THF in 79% yield. Sharpless asymmetric epoxidation[6] of **9** afforded epoxyalcohol **10** in 83% yield (95% ee).[7] A Swern oxidation of compound **10** followed by Wittig olefination gave the α,β-unsaturated ester **12**. Reduction of the ester group of compound **12** using DIBAL-H at −100 °C afforded the epoxy allylic alcohol **13** in 65% yield. Compound **13** was converted to the epoxy allylic chloride **14** by treatment with triphenylphosphine, $NaHCO_3$ and CCl_4 at reflux in 77% yield. Treatment of **14** with $LiNH_2$ at −33 °C or LDA at −78 °C gave the hydroxy-enyne **15** in 80% yield.[8] The secondary hydroxyl group of **15** was protected as its silyl ether **16** using TBDMS–Cl and imidazole. Deprotection of the PMB group of **16** was achieved in the presence of DDQ[9] followed by IBX oxidation to give aldehyde **18**. A two-carbon extension of **18** using triphenylphosphoranylideneacetaldehyde afforded **19** in 73% yield. Applying the Stille–Gennari[10] reaction to compound **19** completed the synthesis of the C1–C11 fragment **2** using methyl *P*,*P*′-bis(2,2,2-trifluoroethyl)phosphonoacetate in the presence of NaH at −78 °C with excellent stereoselectivity (*Z*,*E*/*E*,*E* 95:5) in 80% yield (Scheme 2).

The synthesis of fragment C12–C17 started from the 1,2-protected (*R*)-1,2,4 butanetriol **20** (synthesized from (*R*)-malic acid).[11] A one-pot Swern oxidation and Wittig

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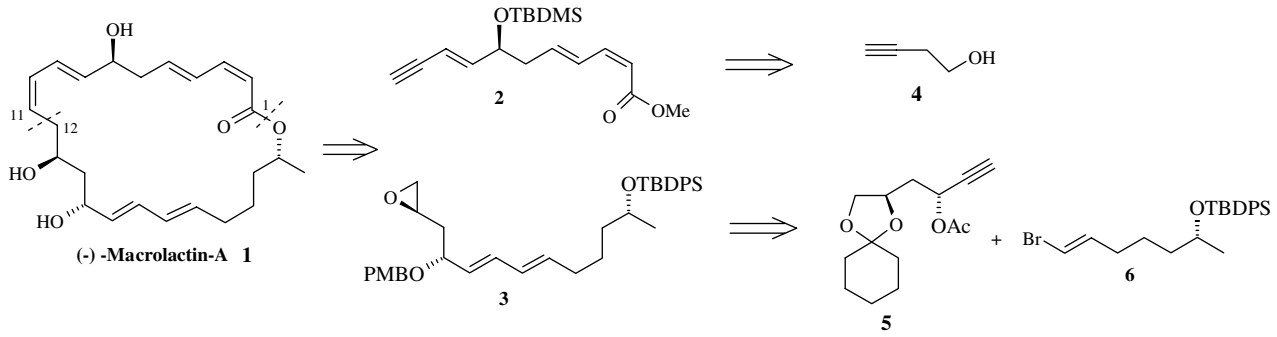
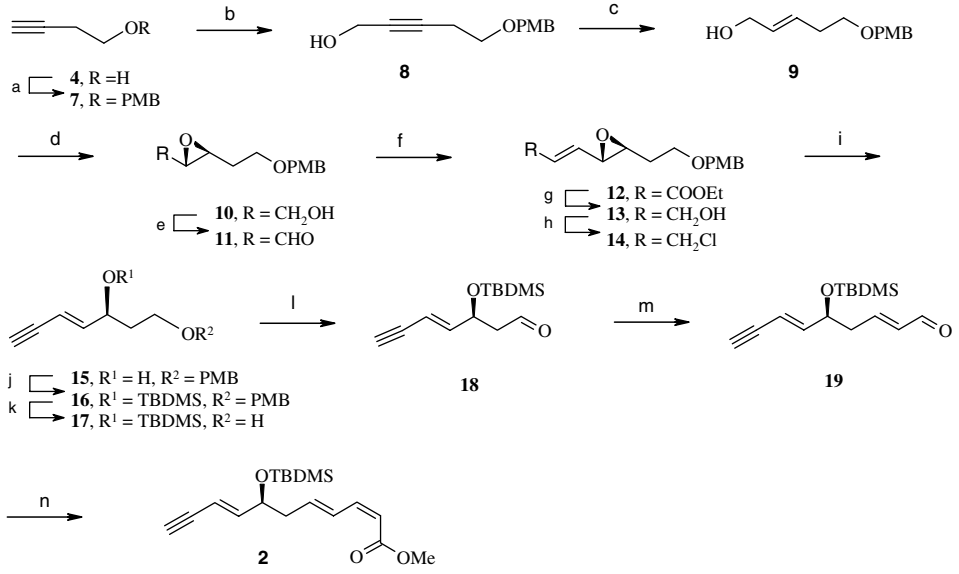
0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.11.107



Scheme 1. Retrosynthetic approach to the total synthesis of macrolactin-A.

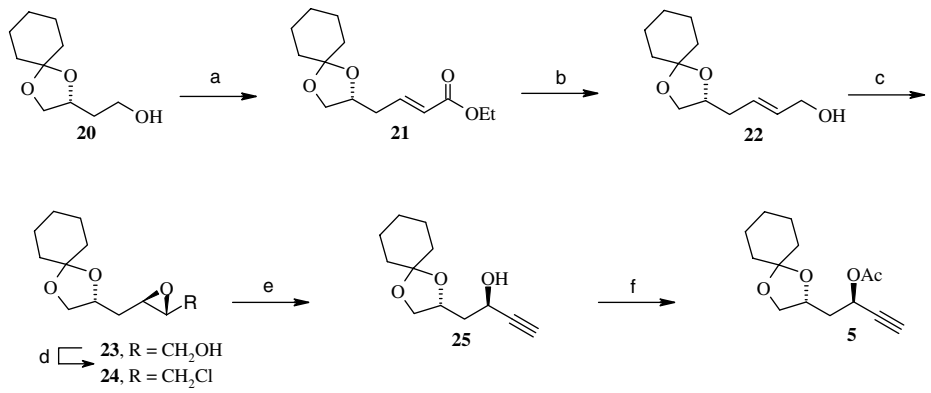


Scheme 2. Reagents and conditions: (a) NaH, PMB–Br, THF, 0 °C, 6 h, 92%; (b) EtMgBr, $(CH_2O)_n$, THF, 3 h, 75%; (c) $LiAlH_4$, THF, reflux, 4 h, 79%; (d) L-(+)-DET, $Ti(O^iPr)_4$, TBHP, DCM, −20 °C, 6 h, 83%; (e) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 86%; (f) $Ph_3P{=}CHCO_2Et$, C_6H_6, rt, 12 h, 83%; (g) DIBAL-H, DCM, −100 °C, 2 h, 65%; (h) Ph_3P, $NaHCO_3$, CCl_4, reflux, 4 h, 77%; (i) $LiNH_2$, −33 °C, 3 h, 80%; (j) TBDMSCl, imidazole, DCM, 0 °C, 2 h, 87%; (k) DDQ, DCM/H_2O (9:1), 3 h, 75%; (l) IBX, DCM, 2 h, 73%; (m) $Ph_3P{=}CHCHO$, DCM, rt, 12 h, 73%; (n) $(CF_3CH_2O)P(O)CH_2CO_2Me$, NaH, −78 °C, 2 h, 80%.

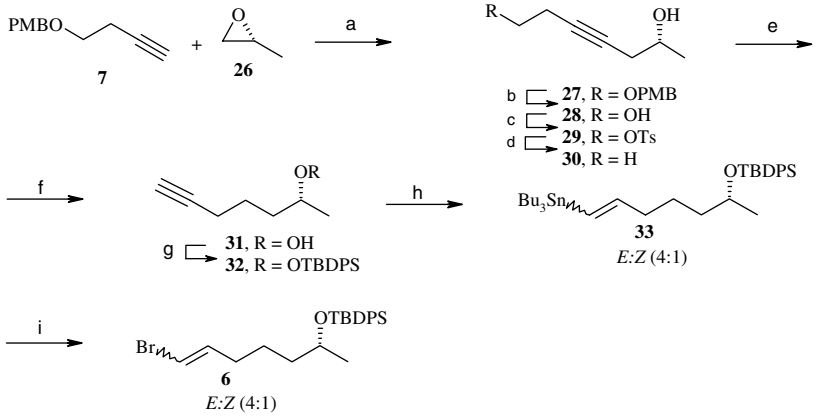
olefination of this alcohol gave the α,β-unsaturated ester **21** in 89% yield. DIBAL-H reduction of ester **21** followed by a Sharpless asymmetric epoxidation gave epoxyalcohol **23** (96% de).[12] This was converted to the corresponding chloride **24** by treatment with triphenylphosphine, $NaHCO_3$ and CCl_4 under reflux. Treatment of chloride **24** with $LiNH_2$ at −33 °C or with LDA at −78 °C afforded the chiral propargyl alcohol **25**,[13] which upon acetylation using Ac_2O and Et_3N gave the desired acetate **5** (Scheme 3).

The synthesis of the C18–C24 fragment started by opening of (*R*)-propyleneoxide[14] **26** using alkyne **7** to afford the secondary alcohol **27** in 76% yield.[15] Alcohol **27** was deprotected using DDQ followed by selective tosylation in the presence of TsCl and Et_3N at 0 °C to afford tosylate **29** in 88% yield. The tosyl group was then converted to a methyl group by treatment with LAH at 40 °C. Zipper isomerization of alkyne **30** in the presence of $NaNH_2$ and 1,3-diaminopropane at 80 °C gave the terminal alkyne **31** in 73% yield.[16] Protection of alcohol **31** as its TBDPS ether **32** was achieved using TBDPSCl and imidazole. Stannylation[17] of alkyne **32** using *n*-Bu_3SnH and AIBN at 120 °C followed by treatment with NBS afforded bromide **6** as an inseparable mixture of *E* and *Z* isomers in a 4:1 ratio (Scheme 4).[18]

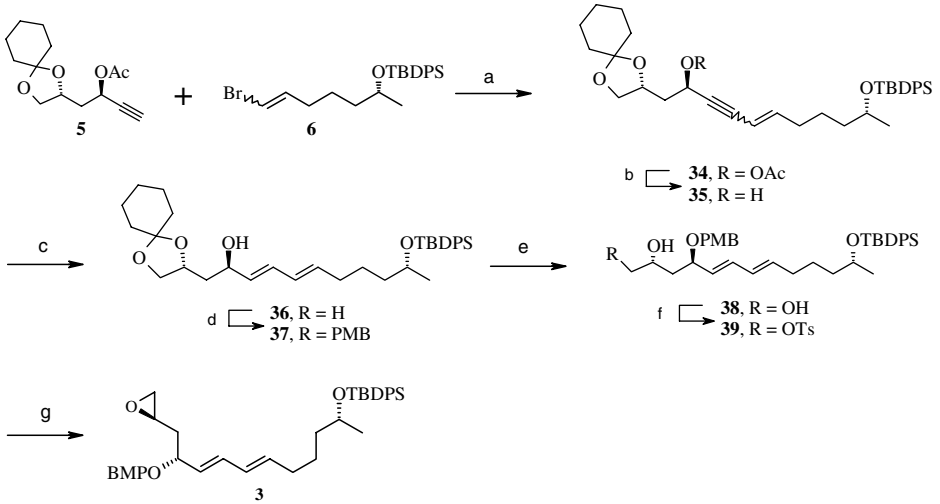
Vinyl bromide **6** was coupled with alkyne **5** in the presence of a catalytic amount of $Pd(PPh_3)_4$, CuI and diethylamine at rt, to afford enyne **34** as an inseparable mixture of *E* and *Z* isomers (9:1) in 60% yield.[19] Methanolysis of acetate **35** using K_2CO_3 in MeOH at room temperature, followed by LAH reduction gave the *E* isomer **36** (after separation from its *Z* isomer). The hydroxyl group of **36** was protected as the PMB ether **37** using PMB–Br and NaH under reflux. Removal of cyclohexylidene acetal in **37** was achieved with PTSA in MeOH to afford diol **38**, which on tosylation using TsCl, Et_3N gave tosylate **39**.



Scheme 3. Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 1 h followed by $Ph_3P{=}CHCO_2Et$, 6 h, 82%; (b) DIBAL-H, DCM, 0 °C, 2 h, 79%; (c) D-(−)-DET, $Ti(O^iPr)_4$, TBHP, DCM, −20 °C, 82%; (d) Ph_3P, $NaHCO_3$, CCl_4, reflux, 4 h, 79%; (e) $LiNH_2$, −33 °C or LDA, −78 °C, 3 h, 82%; (f) Ac_2O, Et_3N, cat DMAP, DCM, 0 °C, 1 h, 91%.



Scheme 4. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, *n*-BuLi, THF, −78 °C, 2 h, 76%; (b) DDQ, DCM/H_2O (9:1), 3 h, 91%; (c) TsCl, Et_3N, cat DMAP, DCM, 0 °C, 4 h, 88%; (d) $LiAlH_4$, THF, 40 °C, 3 h, 66%; (e) $NaNH_2$, $H_2N(CH_2)_3NH_2$, 80 °C, 4–6 h, 73%; (f) TBDPSCl, imidazole, DCM, 0 °C, 1 h, 96%; (g) *n*-Bu_3SnH, AIBN, 120 °C, 3 h, 65%; (i) NBS, CH_3CN, 0 °C, 2 h, 90%.



Scheme 5. Reagents and conditions: (a) $(Ph_3P)_4Pd$, Et_2NH, CuI, toluene, rt, 2 h, 60%; (b) K_2CO_3, MeOH, rt, 1 h, 81%; (c) $LiAlH_4$, THF, 0 °C, 3 h, 79%; (d) NaH, PMB–Br, THF, reflux, 12 h, 82%; (e) PTSA, MeOH, rt, 2 h, 74%; (f) TsCl, Et_3N, cat DMAP, DCM, 0 °C, 4 h, 75%; (g) K_2CO_3, MeOH, rt, 2 h, 84%.

Finally tosylate **39** was converted to the corresponding epoxide in the presence of K_2CO_3 in MeOH at room temperature to afford the C12–C24 fragment of macrolactin-A **3** (Scheme 5).[20]

In conclusion, the C1–C11 and C12–C24 fragments of macrolactin-A have been synthesized employing Sharpless asymmetric epoxidation, Wittig, Stille–Gennari and Sonogashira reactions as key steps. Efforts to complete the total synthesis are in progress.

Acknowledgement

M.R.K. thanks CSIR, New Delhi for the award of a fellowship.

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20. The spectral data of selected compounds. Compound **2**: $[\alpha]_D^{25}$ −2.5 (*c* 0.8, $CHCl_3$): ^1H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.90 (s, 9H), 2.39–2.45 (m, 2H), 2.90 (d, $J = 1.5$ Hz, 1H), 3.72 (s, 3H), 4.21–4.28 (m, 1H), 5.58 (d, $J = 11.1$ Hz, 1H), 5.64 (dd, $J = 5.6$, 16.3 Hz, 1H), 6.00 (dt, $J = 5.3$, 15.2 Hz, 1H), 6.22 (dd, $J = 5.2$, 15.6 Hz, 1H), 6.54 (t, $J = 11.1$ Hz, 1H), 7.40 (dd, $J = 11.1$, 15.5 Hz, 1H); IR (neat): 2924, 2354, 1686, 1636, 1098 cm^{-1}; FABMS: 320 (M^+); Anal. Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.51; H, 8.87. Compound **5**: $[\alpha]_D^{25}$ +57.4, (*c* 3, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 1.40–1.62 (m, 10H), 1.91–2.14 (m, 2H), 2.10 (s, 3H), 2.42 (d, $J = 2.6$ Hz, 1H), 3.52 (dd, $J = 4.1$, 8.1 Hz, 1H), 4.10 (dd, $J = 2.6$, 8.1 Hz, 1H), 4.10–4.20 (m, 1H), 5.34–5.44 (m, 1H); IR (neat): 3283, 2937, 1745, 1106 cm^{-1}; EIMS: *m*/*z* 253 (M^++H); Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.69; H, 7.92. Compound **6**: ^1H NMR (300 MHz, $CDCl_3$, *E* isomer): δ 1.04 (s, 9H), 1.06 (d, $J = 6.2$ Hz, 3H), 1.33–1.55 (m, 4H), 1.91 (q, $J = 6.7$ Hz, 1H), 2.20 (q, $J = 6.7$ Hz, 1H), 3.76–3.82 (m, 1H), 5.89 (d, $J = 13.9$ Hz, 1H), 6.09 (dt, $J = 3.0$, 15.1 Hz, 1H), 7.35–7.80 (m, 6H), 7.61–7.70 (m, 4H); IR (neat): 2932, 2858, 1108, 704 cm^{-1}; FABMS: 431 (M^+); Anal. Calcd for $C_{23}H_{31}BrOSi$: C, 64.02; H, 7.24; Br, 18.52. Found: C, 64.08; H, 7.21; Br, 18.50. Compound **34**: ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (d, $J = 6.2$ Hz, 3H), 1.20 (s, 9H), 1.30–1.40 (m, 4H), 1.41–1.65 (m, 10H), 1.88–2.02 (m, 4H), 2.22 (s, 3H), 3.62 (dd, $J = 4.4$, 12.6 Hz, 1H), 3.80–4.10 (m, 1H), 4.20 (dd, $J = 2.9$, 12.6 Hz, 1H), 4.30–4.22 (m, 1H), 5.45–5.52 (m, 1H), 6.00 (dt, $J = 9.1$, 16.2 Hz, 1H), 6.42 (d, $J = 16.2$ Hz, 1H,), 7.30–7.80 (m, 6H), 7.60–7.70 (m, 4H); IR (neat): 2935, 2220, 1747, 1590, 1108 cm^{-1}; LCMS: 625 (M^++Na); Anal. Calcd for $C_{37}H_{50}O_5Si$: C, 73.71; H, 8.36. Found: C, 73.74; H, 8.33. Compound **3**: $[\alpha]_D^{25}$ −46.5 (*c* 0.3, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (s, 9H), 1.20 (d, $J = 6.0$ Hz, 3H), 1.28–1.58 (m, 4H), 1.79–2.00 (m, 4H), 2.45–2.50 (m, 1H), 2.68–2.77 (m, 1H) 2.98–3.10 (m, 1H) 3.69–3.84 (m, 4H), 3.90–4.06 (m, 1H), 4.25–4.46 (m, 2H), 5.44 (dd, $J = 6.3$, 15.1 Hz, 1H), 5.58 (dd, $J = 6.9$, 15.2 Hz, 1H) 5.84–6.15 (m, 2H), 6.80 (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 8.1$ Hz, 2H), 7.25–7.40 (m, 6H), 7.54–7.69 (m, 4H); IR (neat): 2927, 1734,1513, 1108, 910, 737, 703 cm^{-1}; LCMS: 607 (M^++Na); Anal. Calcd for $C_{37}H_{48}O_4Si$: C, 75.98; H, 8.27. Found: C, 75.92; H, 8.30.