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Tetrahedron Letters 45 (2004) 677–680
Tetrahedron Letters

Asymmetric synthesis of macrolactin analogue

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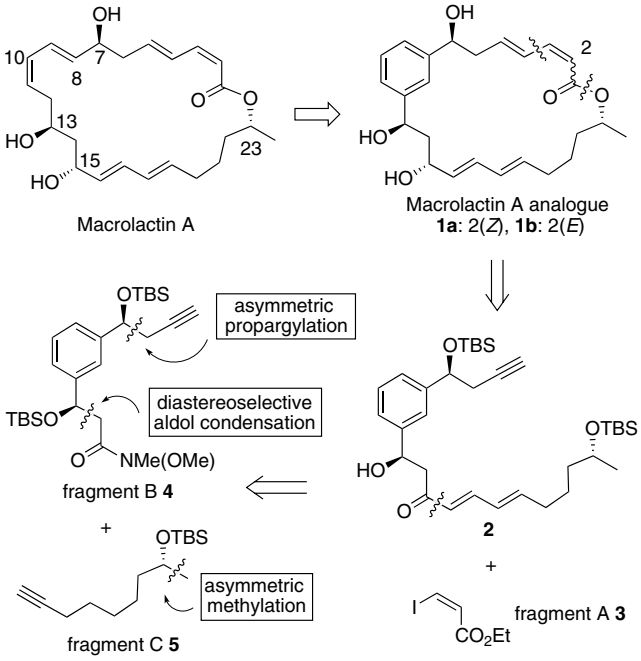
Received 14 October 2003; revised 8 November 2003; accepted 14 November 2003

Abstract—Total asymmetric synthesis of macrolactin A analogue was accomplished by the convergent strategy. Rapid access to advanced intermediate **16** through isomerization of ynone to (*E*,*E*)-conjugated dienone is a key step of this synthesis. Overall, control of all of the four stereocenters was achieved by means of asymmetric and diastereoselective reactions without using any chiral natural sources.

Macrolactin A was isolated from a deep sea marine bacterium in 1989 as a 24-membered polyene macrolide antibiotic.[1] This compound possesses three sets of conjugated dienes and four stereogenic centers in the molecule, and exhibits a broad spectrum of activity with significant antiviral and cancer cell cytotoxic properties including inhibition of B16-F10 murine melanoma cell replication.[2] Because of its unreliable supply from cell culture as well as its structural uniqueness and broad therapeutic potential, macrolactin A has been an attractive target for asymmetric synthesis. Although, thus far, three total syntheses[3] and novel synthetic studies[4] have been developed, there are still problems to be solved for therapeutic applications. With the expectation of increasing the stability and activity of macrolactin A, we designed new structural analogues of macrolactin A **1a**–**b**, bearing a more rigid aromatic ring instead of the (*E*,*Z*)-dienic moiety (C8–C12).[5] We report herein an asymmetric total synthesis of a macrolactin analogue that utilized three types of asymmetric C–C bond formation and phosphine-catalyzed isomerization from ynone to (*E*,*E*)-conjugated dienone.

The synthetic plan involves assembly of three fragments **3**–**5** as shown in Scheme 1. Alkyne **5** bearing a stereogenic center (C23), plays a central role in our strategy, serving not only as an ideal nucleophile for joining with the amide **4**, but also as a latent functional group of the (*E*,*E*)-conjugated dienone moiety of **2**. We anticipated that these compounds **4** and **5** could be prepared from **6** and **11** by asymmetric propargylation[6] and subsequent diastereoselective aldol condensation of Nagao's



Scheme 1.

Keywords: Macrolactin A; Antibiotics; Antivirus; Asymmetric synthesis; Ynone; Isomerization; (*E*,*E*)-Conjugated dienone.
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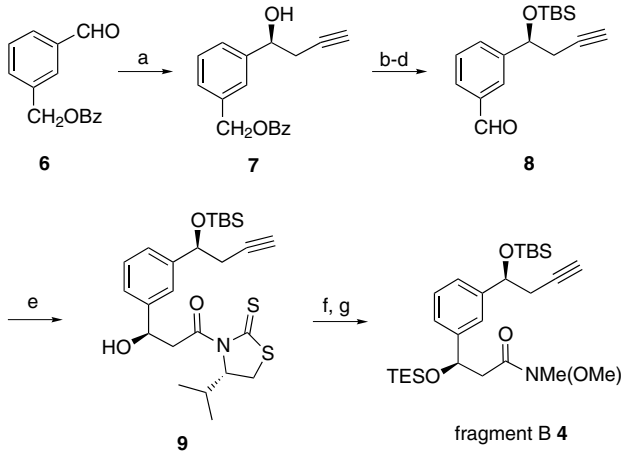
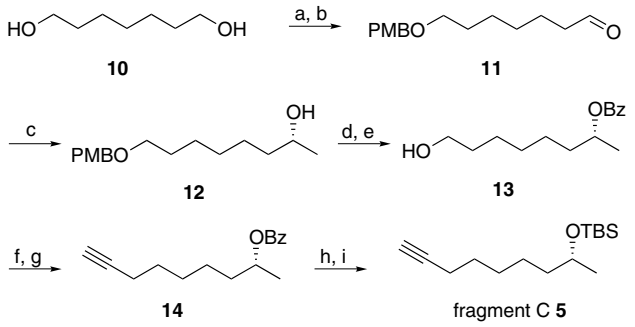
doi:10.1016/j.tetlet.2003.11.055



Scheme 2. Reagents and conditions: (a) $CH_2{=}C{=}CHB(OH)_2$, (+)-diisopropyl tartrate, MS 4A, toluene, −78 °C, 85%, 80% ee; (b) TBSCI, imidazole, DMF, quant; (c) K_2CO_3, MeOH, 95%; (d) IBX, DMSO, THF, 90%; (e) 3-acetyl-(4*S*)-IPTT, $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 80%, 92% de; (f) MeONHMe·HCl, Et_3N, CH_2Cl_2 91%; (g) TESCl, pyridine, quant.

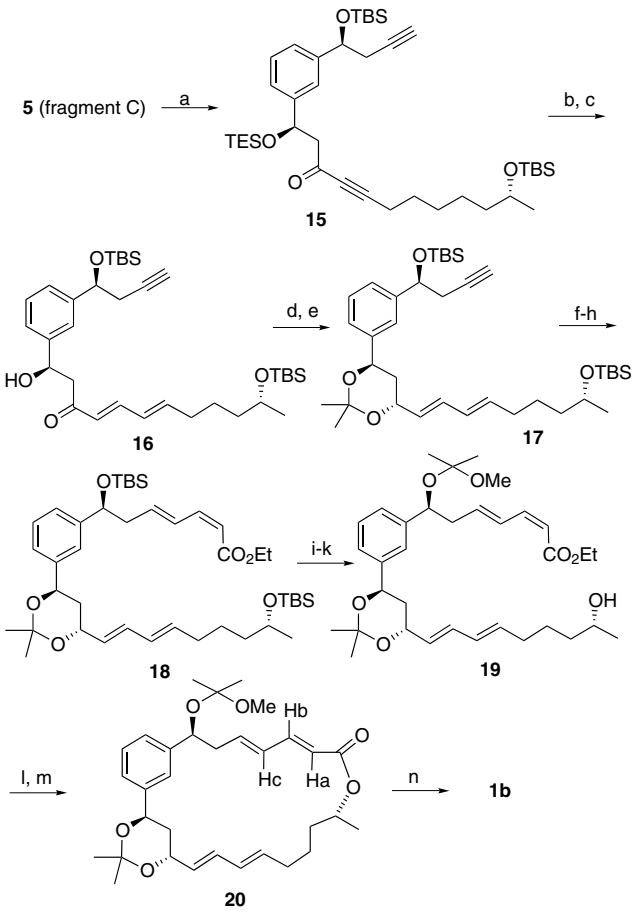


Scheme 3. Reagents and conditions: (a) PMBCl, NaH, THF, 0 °C; (b) IBX, DMSO, THF, 48% (two steps); (c) Me_2Zn, (+)-TADDOL, Ti(O-*i*-Pr)$_4$, toluene, −25 °C, 90%, 95% ee; (d) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, quant; (e) DDQ, CH_2Cl_2, H_2O, 80%; (f) IBX, DMSO, THF, 95%; (g) $(MeO)_2P(O)CHN_2$, *t*-BuOK, THF, −78 °C → rt, 85%; (h) 3 N KOH/MeOH (1:1), 87%; (i) TBSCl, imidazole, DMF, quant.

acetate[7] [(*S*)-3-acetyl-4-isopropyl-1,3-thiazolidine-2-thione], and asymmetric methylation with Me_2Zn, respectively. Construction of the fragment **4** commenced from aldehyde **6**. Propargylation of **6** with allenylboronic acid and diisopropyl(L)-tartrate was carried out under Yamamoto conditions[6] and gave chiral alcohol **7** as the single product, but with moderate enantioselectivity (85% yield, 80% ee) (Scheme 2). Fortunately, the optically pure alcohol **7** (>95% ee) was easily obtained by recrystallization of **7** (80% ee) from a mixture of AcOEt and hexane. The enantioselectivity and absolute configuration were determined by a modified method of the Mosher protocol.[8] After protection of the alcohol **7**, hydrolysis of the benzoate afforded the primary alcohol (K_2CO_3, MeOH), which was oxidized with IBX[9] (2-iodoxybenzoic acid) to provide the desired aldehyde **8**. Condensation of **8** with (*S*)-3-acetyl-4-isopropyl-1,3-thiazolidine-2-thione in the presence of $TiCl_4$ (1.1 equiv) and *i*-Pr_2NEt (1.1 equiv) afforded aldol product **9**[10] along with a small amount of its diastereomer (80% yield, 92% de). These were separated by column chromatography, and major product **10** was treated with *N*-methoxymethylamine, followed by TESCl to yield Weinreb amide **4** in good yield.[11]

Having established the synthesis of the C4–C15 fragment, we next sought an efficient enantioselective method for the preparation of alkynyl fragment C **5** (Scheme 3). Synthesis of **5** began with PMB aldehyde **11** derived from 1,7-heptanediol **10** in two steps. This aldehyde **11** was first subjected to asymmetric methylation using Me_2Zn and Ti(O-*i*-Pr)$_4$ in the presence of (+)-TADDOL[12] (20 mol%) as a chiral ligand, and the desired secondary alcohol **12**[10] was obtained in 90% yield with high enantioselectivity (95% ee). The resulting alcohol was protected as a benzoate before removal of the terminal PMB ether to furnish primary alcohol **13**. Oxidation of **13** to an aldehyde, followed by exposure to the Seyferth–Gilbert reagent,[13] produced alkyne **14**, which finally replaced the protecting group from benzoate to *tert*-butyldimethysilyl (TBS) ether to give the desired product **5**.

With the two chiral building blocks now accessible, we investigated the key steps of this strategy, that is, their coupling reaction and stereoselective construction of the (*E*,*E*)-conjugated dienone unit (Scheme 4). The coupling reaction of **4** and **5** proceeded smoothly using ethylmagnesium bromide as a base[11] to afford the desired ynone **15** in good yield. Although the triphenylphosphine-catalyzed isomerization of ynone to conjugated dienone has been reported,[14] the desired product could not be obtained in reasonable yield under the standard conditions (toluene, 120 °C). After many experiments, use of bis(diphenylphosphino)butane (dppb) in a mixture of toluene and THF (1:1) at room temperature led to the best result to give **16** in 40% overall yield, after removal of the TES protecting group. Subsequent construction of the fourth stereogenic center was carried out by hydroxyl-directed reduction.[15] Reduction of **16** with $Me_4NBH(OAc)_3$ provided the corresponding 1,3-*anti*-diol in 89% yield and 93:7 diastereoselectivity.[16] This 1,3-*anti*-diol was protected as acetonide **17** under the standard conditions. We next examined the final coupling of acetonide **17** and iodide **3** using Cu-catalyzed reaction. Under carefully optimized conditions, bromination/Pd-mediated hydrostannation[17] of **17** was followed by reaction with (*Z*)-3-iodopropenoate **3** in the presence of copper(I) 2-thiophenecarboxylate[18] (CuTC) to afford the desired addition product **18** in 58% yield from **17**. When this coupling reaction was performed under Stille cross-coupling conditions [19] [$Pd_2(dba)_2$, *i*-Pr_2NEt, DMF], **18** was obtained in poor yield due to serious production of a destannation adduct. At this stage, it was revealed that regioselective deprotection of two TBS groups (C7 and C23) was problematic. Although the reaction of **18** under acidic conditions gave a mixture of mono-TBS adducts, the C7 TBS group of **18** could be removed regioselectively with TBAF, which was followed by protection/deprotection manipulation to furnish the desired alcohol **19** as the single isomer. After hydrolysis of **19**, lactonization of the resulting



Scheme 4. Reagents and conditions: (a) EtMgBr, **4** (fragment B), THF, 70%; (b) dppb, toluene, THF; (c) AcOH/THF/H_2O (8:8:1), 40% (two steps); (d) $Me_4NBH(OAc)_3$, AcOH, MeCN, 89%; (e) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 83%; (f) BrCN, *n*-BuLi, THF, −78 °C → −40 °C, 90%; (g) $PdCl_2(PPh_3)_2$, Bu_3SnH, benzene; (h) CuTC, ethyl (*Z*)-3-iodopropenoate **3**, NMP, 64% (two steps); (i) TBAF, THF, 0 °C, 92%; (j) CH_2=CMe(OMe), PPTS, CH_2Cl_2, −40 °C, 82%; (k) TBAF, AcOH (1:1), THF, 89%; (l) 3 N KOH, THF, EtOH, 60 °C; (m) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, toluene, 40% (three steps); (n) PPTS, MeOH, 61%.

(2*Z*,4*E*)-carboxylic acid ($J_{Ha–Hb} = 11.3$ Hz) by a modified Yamaguchi's method[20] did not provide the desired (2*Z*,4*E*)-lactone at all, and gave unexpected (2*E*,4*E*)-lactone **20** as the single isomer ($J_{Ha–Hb} = 15.3$ Hz).[21] From the fact that McClure and co-workers[3c] succeeded in a total synthesis of macrolactin A by the same procedure, the replacement of the (8*E*,10*Z*)-dienic moiety to the aromatic ring seems to prohibit the macrocyclization into the (2*Z*,4*E*)-lactone. Finally, global deprotection of the methoxyisopropylidene acetal and acetonide of **20** afforded the macrolactin A analogue **1b** in 61% yield.

The synthesis of **1b** was thus completed in 23 steps in the longest linear sequence. The use of **5** allowed rapid access to advanced intermediate **16** through isomerization of ynone to (*E*,*E*)-conjugated dienone. Overall, control of all of the four stereocenters was achieved by means of asymmetric and diastereoselective reactions without using any chiral natural sources. Unfortunately, the desired product **1a** could not be synthesized. However, these methods would be a versatile synthetic tool for other macrolactin analogues. The synthetic derivatives in these studies will be used in order to establish structure–activity relationship, in particular the effects of the (2*Z*,4*E*)- and (8*E*,10*Z*)-moieties of macrolactin A, and to design compounds with better biological properties.

Acknowledgements

This research was supported by grants from 21st Century COE Program 'Knowledge Information Infrastructure for Genome Science' and the Japan Health Sciences.

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