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Natural Product Synthesis

Direct Aldol Strategy in Enantioselective Total Synthesis of Thuggacin B

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Abstract: An enantioselective total synthesis of thuggacin B, a natural product exhibiting antibiotic activity against Mycobacterium tuberculosis, is described. Asymmetric direct aldol reactions promoted by Cu and Zn catalysts play a pivotal role in constructing four stereogenic centers. The use of direct aldol reactions as the initial steps for the synthesis of two key fragments allowed the construction of the other stereogenic centers through chirality transfer.

Thuggacins A–C are polyketide antibiotics identified in extracts from the myxobacterium *Sorangium cellulosum* So ce895 in bioactivity-guided isolation by Jansen et al. in 2007 (Figure 1).[1] Key structural characteristics are five consecutive stereogenic centers at C16–C20, a macrolide embedded by a thiazole ring, an *E*,*Z*-conjugated diene, and an *E*-unsaturated ester, which are all shared in thuggacins A–C. They differ in macrolactone ring size and interconvert by transacylation in methanol.[1a] A pendant hexyl group at C2 is unusual among the secondary metabolites and its biosynthetic origin was addressed by gene cluster analysis.[2] Particular interest in these novel antibiotics arises from their promising potency against *Mycobacterium tuberculosis* (TB). TB is a life-threatening airborne infectious disease and the second highest cause of death among infectious diseases.[2] The recent emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB strains has stimulated extensive research in seeking novel medications to combat the disease.[3–5] Thuggacins proved effective against TB via a different mode of action from that of antibiotics in current first- and second-line treatments.[1,2] Together with the intriguing potential for TB treatment, the structural features of the polyol system have attracted our particular attention for enantioselective synthesis utilizing our asymmetric catalysts. Just one example of the total synthesis of thuggacin B as well as its stereochemical determination by extensive NMR studies has been completed by Kirschning et al.[6] Synthetic studies were reported based on a chiral auxiliary approach.[7,8] Herein, we report a convergent synthesis of thuggacin B utilizing two distinct direct aldol reactions promoted by Zn and Cu catalysts developed in our group. These catalysts were deployed in the initial stage of the synthesis of two key fragments, allowing the construction of the other stereogenic centers through chirality transfer.

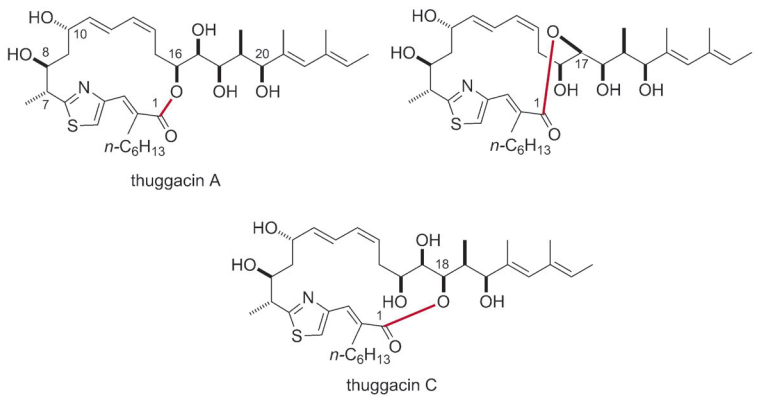

Figure 1. Structure of thuggacins A–C.

Our retrosynthesis of thuggacin B is delineated in Scheme 1. Two C–C bonds at C7–C8 and C16–C17 are to be constructed with concomitant generation of four stereogenic centers by direct catalytic asymmetric aldol reactions that were developed by our group. The macrocycle was disconnected by Sonogashira coupling and macrolactonization to give known key frag-

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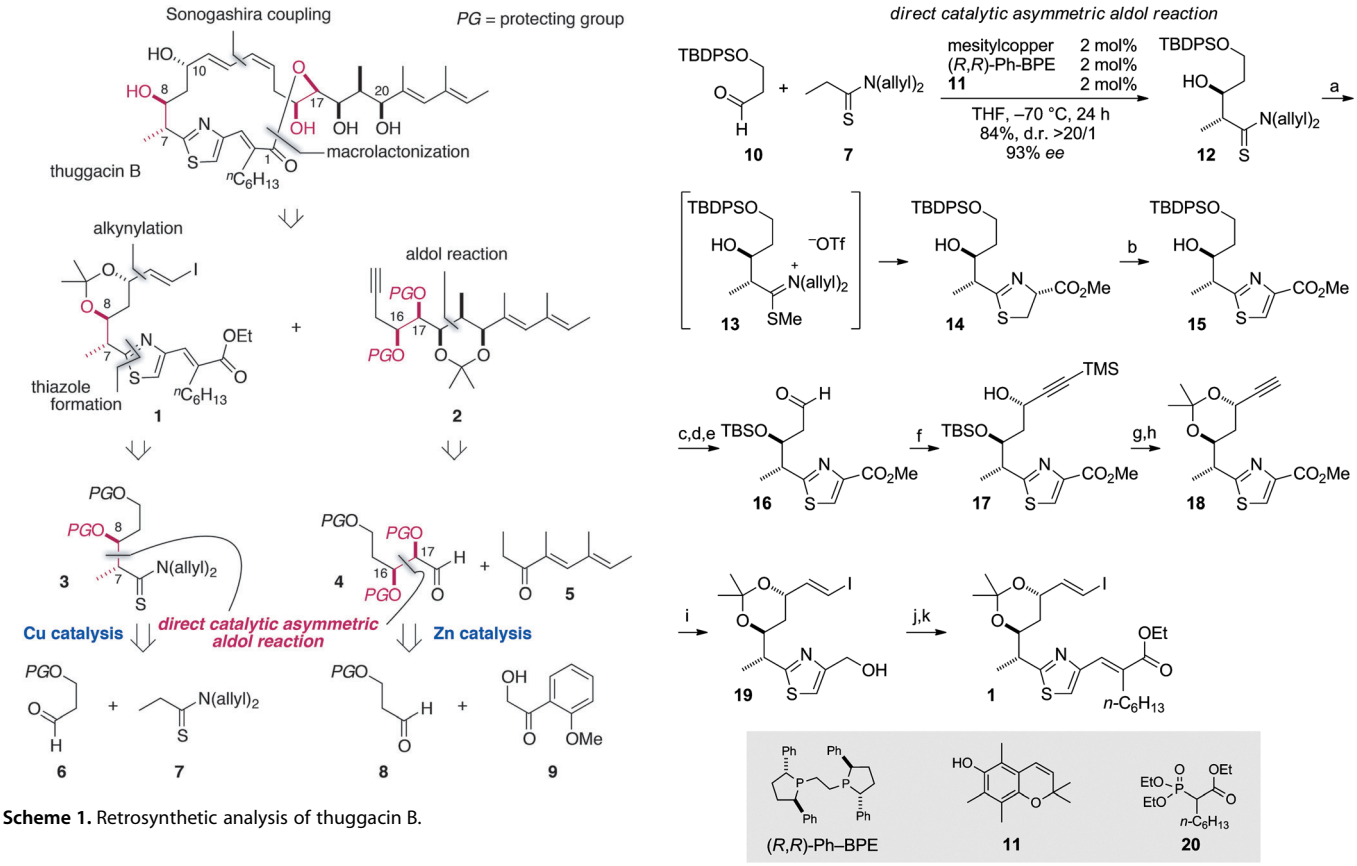


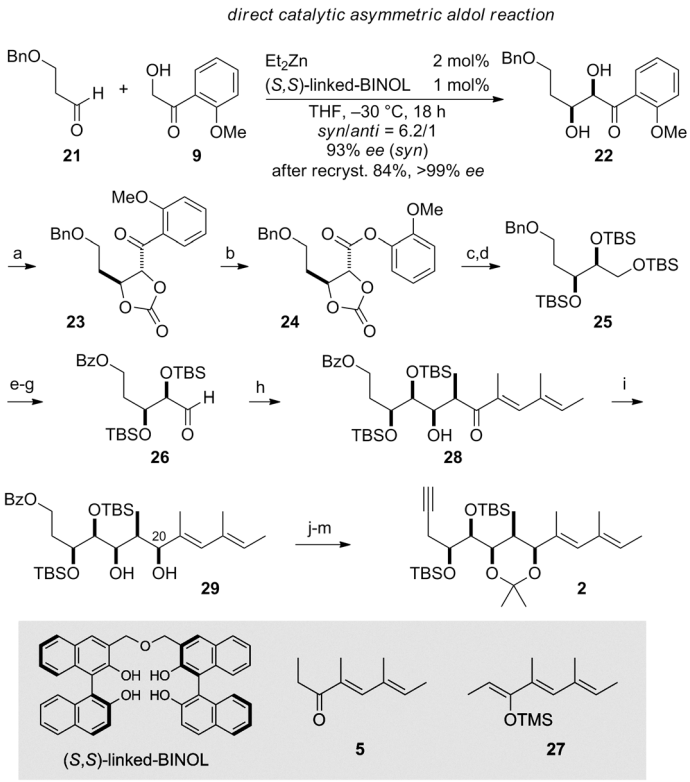
Scheme 1. Retrosynthetic analysis of thuggacin B.

Scheme 2. Synthesis of fragment **1**. Reagents and conditions: a) MeOTf, $NaHCO_3$, CH_2Cl_2, RT; then H–L–Cys–OMe, EtOH, RT, 80%; b) $BrCCl_3$, DBU, CH_2Cl_2, 0 °C, 90%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT; d) NH_4F, MeOH, 50 °C, 87% (2 steps); e) Dess–Martin periodinane, CH_2Cl_2, RT, 96%; f) Li–C≡C(TMS), ether, −78 °C, *anti*/*syn* = 6/1, 74%; g) TBAF, THF, RT, 84%; h) 2,2-dimethoxypropane, PPTS, THF, RT, 63% (after separation of the undesired diastereomer); i) $[Cp_2Zr(H)Cl]$, THF, RT; then I_2, RT, 56%; j) Dess–Martin periodinane, CH_2Cl_2, RT, 95%; k) phosphonate 20, LHMDS, THF, −78 °C, *E*/*Z* = 6/1, 93%. PPTS = pyridinium *p*-toluenesulfonate; LHMDS = lithium bis(trimethylsilyl)-amide.

ments **1** and **2**. The thiazole ring of fragment **1** would be furnished from thioamide **3**, which we expected would be produced by the direct catalytic asymmetric aldol reaction of thioamide **7** in enantio- and diastereoselective fashion by a Cu-based soft Lewis acid/hard Brønsted base cooperative catalyst. Fragment **2** was further disconnected to form aldehyde **4** and ketone **5** by a diastereoselective aldol reaction. The direct catalytic asymmetric aldol reaction of hydroxyketone **9** promoted by a trinuclear Zn catalyst was planned to be applied for enantio- and diastereoselective access of the chiral aldehyde **4**.

Synthesis of fragment **1** commenced with the *syn*-selective direct aldol reaction of *O*-functionalized aldehyde **10** and thiopropanamide **7**, promoted by 2 mol% of the cooperative catalyst composed of mesitylcopper/(*R*,*R*)-Ph-BPE/**11** (Scheme 2).[9–11] The thioamide functionality was particularly advantageous for the rapid construction of the requisite thiazole ring. Desired diastereomer **12** was obtained almost exclusively in 84% yield with 93% *ee*. *S*-selective methylation by MeOTf followed by the addition of L-cysteine methyl ester furnished the thiazoline ring of **14** through the intermediacy of **13**.[12,13] Oxidative aromatization by bromotrichloromethane and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave thiazole **15** in 90% yield.[14] Treatment with NH_4F after the protection of the secondary alcohol of **15** by a *tert*-butyldimethylsilyl ether (TBS) group liberated the primary alcohol,[15] which was oxidized by Dess–Martin periodinane to afford aldehyde **16**.[16] Alkynylation by Li-acetylide in diethyl ether proceeded in a diastereoselective fashion to give the desired propargylic alcohol **17** preferentially.[17] Compound **17** and its minor diastereomer were inseparable, and the mixture was treated with TBAF to remove two silyl groups. After protecting the 1,3-diol unit as an acetonide, **18** was isolated chromatographically as a single diastereomer.[18] The requisite *E*-alkenyl iodide of **19** for Sonogashira coupling with fragment **2** was furnished by hydrozirconation/iodination. The ester at the thiazole ring was simultaneously reduced to a primary alcohol by Schwartz's reagent,[19] and the alcohol was elongated by oxidation followed by a Horner–Wadsworth–Emmons reaction with phosphonate **20** to afford fragment **1**.[20]

The direct aldol reaction of hydroxyketone **9** and *O*-functionalized aldehyde **21** under proton transfer conditions initiated the synthesis of fragment **2** (Scheme 3).[21] The catalytically active trinuclear Zn complex prepared from 2 and 1 mol% of Et_2Zn and linked-BINOL, respectively, promoted the reaction leading to the preferential formation of the *syn*-diol unit in 93% *ee*. Facile chromatographic separation of the undesired *anti*-diastereomer followed by a single recrystallization provided enantiopure *syn*-**22** in 84% yield. After protection of 1,2-



Scheme 3. Synthesis of fragment **2**. Reagents and conditions: a) triphosgene, pyridine, CH_2Cl_2, 0 °C, quant.; b) *m*CPBA, NaH_2PO_4, CH_2Cl_2, 40 °C, 94%; c) Red-Al, THF, 0 °C, 91%; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, quant.; e) $RuCl_3$ (10 mol%), $NaIO_4$, $CH_3CN/CCl_4/H_2O$, RT, 82%; f) CSA, EtOH, 0 °C, 76%; g) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT, 88%; h) enol silyl ether **27**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −40 °C, 49% (desired stereoisomer); i) Et_2BOMe, $NaBH_4$, THF/MeOH, −40 °C, 84%; j) 2,2-dimethoxypropane, CSA, DMF, RT; k) K_2CO_3, MeOH, RT, 85% (2 steps); l) TPAP (10 mol%), NMO, MS 3 Å, CH_2Cl_2, RT, 77%; m) Ohira–Bestmann's reagent, K_2CO_3, MeOH, RT, 73%. NMO = 4-methylmorpholine *N*-oxide.

diol **22** as a cyclic carbonate, Baeyer–Villiger oxidation was effected by *meta*-chloroperoxybenzoic acid (*m*CPBA) to give guaiacol ester **24** exclusively, due to the predominant rearrangement of the electron-rich *o*-anisolyl group.[22] Carbonyl functionalities were reduced by Red-Al and the triol thus obtained was protected by TBS groups. Benzylic oxidation of **25** followed by treatment with camphorsulfonic acid (CSA) resulted in selective removal of the terminal TBS group to generate the primary alcohol, which was oxidized by (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO)/$PhI(OAc)_2$ to afford aldehyde **26**. Subsequent diastereoselective Mukaiyama aldol reaction with enol silyl ether **27** generated from dienone **5** produced the aldol product **28** with the desired stereochemistry in 49% yield.[23] *syn*-Selective reduction of the β-hydroxyketone moiety was attempted with $Et_2BOMe/NaBH_4$ to construct the requisite 5-contiguous stereogenic centers of **29**,[24] the known intermediate for fragment **2** reported by Kirschning et al.[6b] Whereas the desired diastereomer with all-*syn* orientation was obtained as the major product,[25] the inseparable diastereomixture containing the C20 epimer was forwarded to fragment **2** bearing a terminal alkyne by using the reported procedure.[6b] After protecting the free 1,3-diol as an acetonide, methanolysis of the benzoate generated a primary alcohol, which was oxidized to the aldehyde with tetrapropylammonium perruthenate (TPAP). Subsequent treatment with Ohira–Bestmann's reagent furnished fragment **2**.[26]

Completion of the total synthesis of thuggacin B was conducted by using a modification of the reported procedure (Scheme 4).[6b] The two fragments **1** and **2** were assembled by Sonogashira coupling in 72% yield and two TBS groups were removed with TBAF to give free diol **30**. C20 epimer was separated by HPLC at this stage. The ester was hydrolyzed and subsequent partial reduction of alkyne by Lindlar catalyst with quinoline produced cyclization precursor **31** with the *E,Z*-1,3-diene at C10–C13. Macrolactonization under Shiina's conditions using 2-methyl-6-nitrobenzoic anhydride (MNBA) gave rise to the requisite carbon framework with its 18-membered ring core;[27] the two acetonide moieties were hydrolyzed with CSA to afford thuggacin B. All the spectroscopic data of the synthetic thuggacin B matched the reported data.

In summary, enantioselective total synthesis of thuggacin B was achieved by harnessing enantio- and diastereoselective direct aldol methodologies. Two distinct catalysts were used in the initial steps for each key fragment and the other stereogenic centers were constructed through efficient chirality transfer, highlighting the particular utility in stereoselective synthesis of the polyketide framework.

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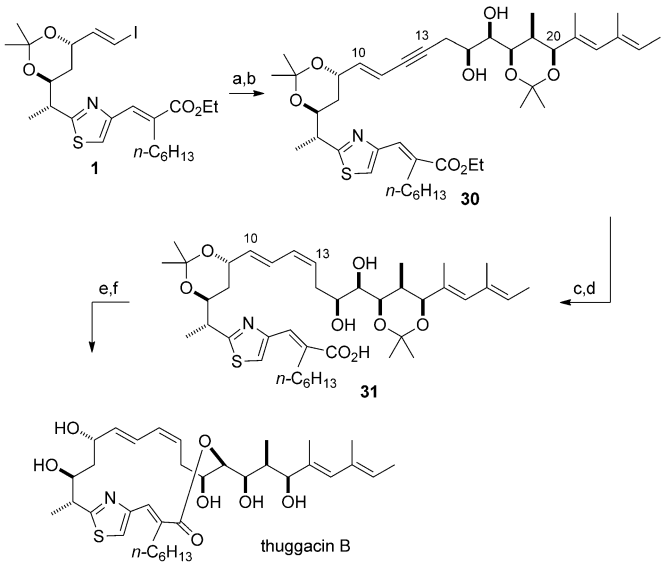

Scheme 4. Completion of total synthesis of thuggacin B. Reagents and conditions: a) **2**, $[PdCl_2(PPh_3)_2]$ (10 mol%), CuI, Et_3N, CH_3CN, −20 °C to RT, 72%; b) TBAF, THF, RT, 97%; after HPLC separation, 50%; c) KOH, EtOH, H_2O, RT, quant.; d) Lindlar catalyst, H_2, quinoline, AcOEt, RT; e) MNBA, DMAP, MS 3 Å, toluene, 70 °C, 38% (2 steps); f) CSA, MeOH, RT, 39%. MNBA = 2-methyl-6-nitrobenzoic anhydride.

Keywords: direct aldol reactions · thioamides · thuggacins · total synthesis · tuberculosis

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[17] The solvent of choice was critical to give the desired alkynylated product.
[18] The stereochemistry of the propargylic position was determined at this stage from the coupling constant in the ^{1}H NMR spectrum. See Supporting Information for details.
[19] The reduction of the ester occurred unexpectedly.
[20] Reaction with other alkali metal hexamethyldisilazides under otherwise identical conditions produced **1** with inferior *E*/*Z* selectivity; NaHMDS: >99% yield, *E*/*Z*=4.7/1; KHMDS: 93% yield *E*/*Z*=4/1.
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[22] The cyclic carbonate was an essential temporary protecting group of the diol for regioselective rearrangement.
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[25] The C20 epimer was inseparable by chromatography and almost all peaks in ^{1}H NMR were superimposed even though several subsequent steps. At the stage of **30**, the C20 epimer was separable by HPLC and ^{1}H NMR of the diastereomixture indicated that approximately 25% of C20 epimer was generated at the reduction.
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