Natural Product Synthesis

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Total Synthesis of Thuggacin B**

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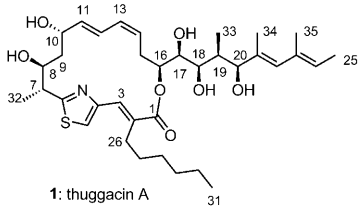
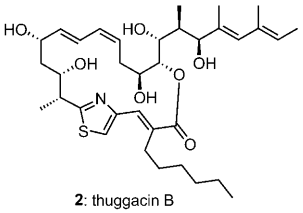
Dedicated to Ernst Schaumann on the occasion of his 65th birthday

After AIDS, tuberculosis (TB) is the infectious disease with the highest mortality worldwide.[1] TB and HIV epidemics fuel one another in co-infected people, and at least 11 million adults are infected with both pathogens.[2] The efficacy of first-line anti-TB drug regiments is often reduced owing to drug resistance.[3] Additionally, the ability of *Mycobacterium tuberculosis* to persist in latent infections necessitates the development of alternative antibiotics, preferably with novel modes of action.[1]

Recently, Jansen et al.[4] and we[5] disclosed the complete structures of the polyketide natural products thuggacin A (**1**), B (**2**), and C (**3**) which had been isolated from the myxobacterium *Sorangium cellulosum* (Figure 1). These compounds show strong antibiotic activity against various organisms including *Mycobacterium tuberculosis* by targeting the bacterial respiratory chain.[6]





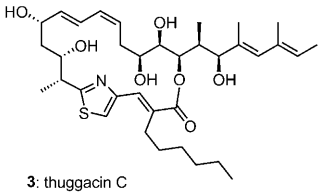
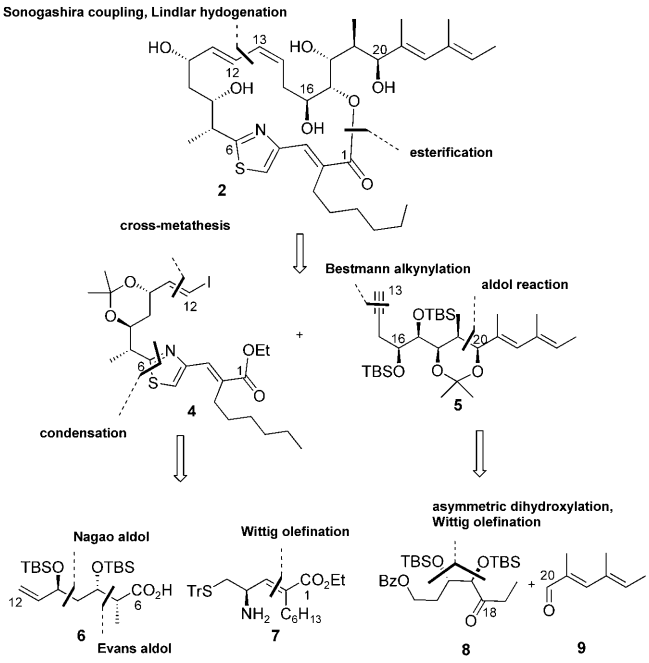


Figure 1. Thuggacins A, B, and C.

Thuggacin A (**1**) features a 17-membered α,β-unsaturated macrolactone with a thiazole ring, a diene (11*E*,13*Z*), and an *n*-hexyl side chain at C2. A side chain at C16 bearing three hydroxy groups and a diene unit complements the structure. Thuggacin B (**2**) shares these structural features except for the ring size: the lactone is closed at O17 instead of at O16 in thuggacin A. Thuggacin C (**3**) is macrocyclized at O18. Importantly, the thuggacins slowly equilibrate in methanol within five days at room temperature by transacylation (**1**/**2**/**3** = 1:2.1:2.7).[4] The rate of interconversion can be slowed by acidifying the methanolic solution or by switching to an aprotic solvent.

To further evaluate the biological properties of the thuggacins we planned a total synthesis which should also pave the way for accessing analogues. Therefore, we developed a highly convergent approach that could be used later to prepare simplified macrocycles.

Our retrosynthetic analysis (Scheme 1) of the thuggacins **1**–**3** relies on a macrolactonization and a Pd-mediated cross-coupling reaction to form the bond linking C12 and C13, such that major fragments **4** and **5** should serve as key building blocks in this project. Precursor **4** was further disconnected to carboxylic acid **6**, which can be obtained from acrolein and cysteine-derived amine **7**. The vinyl iodide moiety at C11/C12



Scheme 1. Retrosynthetic analysis of thuggacin B (**2**). TBS = *tert*-butyldimethylsilyl, Bz = benzoyl, Tr = triphenylmethyl.

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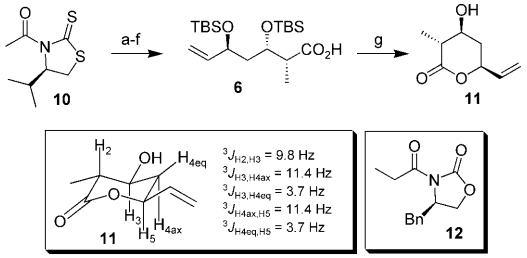
could be installed by a cross-metathesis strategy. Major fragment **5** was planned to be prepared by the substrate-controlled aldol reaction of aldehyde **9**[7] and ketone **8**, which in turn should be generated from benzoic acid 3-oxo-propyl ester **19**.[8]

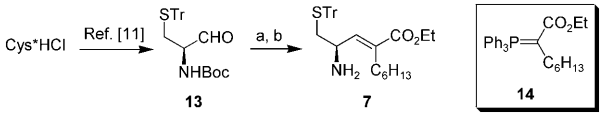
Our synthesis commenced with carboxylic acid **6**, which was prepared by a standard sequence that involved the known Nagao aldol reaction[9] with acrolein followed by an Evans aldol reaction[10,11] with the intermediate aldehyde (Scheme 2). After protection of the alcohol, the auxiliary



Scheme 2. Synthesis of **6**. a) $TiCl_4$, DIEA, CH_2Cl_2, −40 °C; then acrolein, −78 °C, quant. d.r 5:1; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 93%; c) DIBAL, toluene, −78 °C, 94%; d) Bu_2BOTf, DIEA, **12**, CH_2Cl_2, 0 °C; then −78 °C, quant.; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 96%; f) LiOH, H_2O_2, THF/H_2O, 0 °C, 74%; g) 40% HF in H_2O, MeCN, RT, 59%. DIEA = diisopropylethyl amine; Tf = trifluoromethanesulfonyl; DIBAL = diisobutylaluminum hydride; Bn = benzyl.

was removed under basic conditions to liberate the carboxylic acid **6**. Since the analytical data of this compound does not entirely correspond to reported values,[11] we unequivocally confirmed the relative stereochemistry of acid **6** after formation of lactone **11** and characterization by NMR spectroscopy.

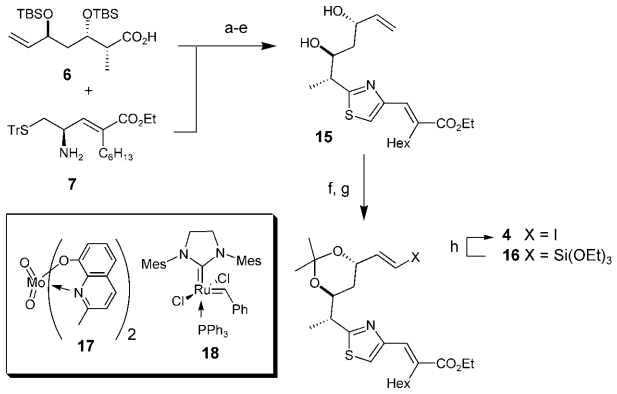
The α,β-unsaturated ethyl ester **7** was prepared from L-cysteine via the known aldehyde **13**[12] (Scheme 3). Olefina-



Scheme 3. Preparation of amine **7**. a) **14**, $CHCl_3$, reflux, 94%; b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 79%. Cys = cysteine, Boc = *tert*-butyloxycarbonyl, TMS = trimethylsilyl.

tion with ylide **14**[13] had to be optimized with respect to the desired *E* selectivity and complete conversion of aldehyde **13**. We found that a high excess of ylide **14** and low concentration of aldehyde are required to prevent decomposition of aldehyde **13**. The Boc group was then efficiently removed using TMSOTf/2,6-lutidine.[12]

Formation of the amide bond between fragments **6** and **7** was achieved using TBTU as the coupling reagent (Scheme 4). Removal of the trityl protecting group liberated the thiol group which was cyclized to give the thiazoline using Mo complex **17**, which was disclosed by Sakakura et al. very recently.[14] Other Lewis acids including the related [MoO_2-(acac)$_2$][15] did not effect ring closure in sufficient yields.

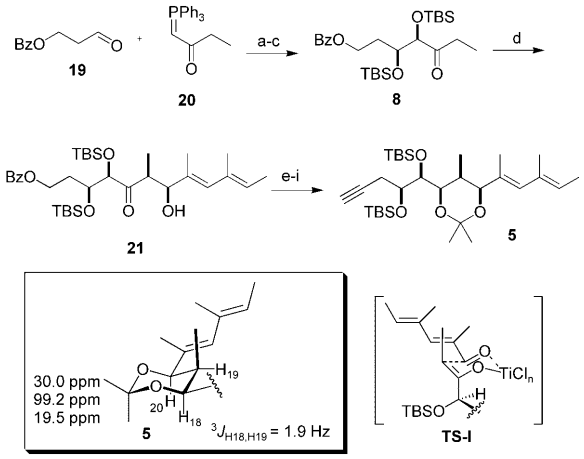


Scheme 4. Preparation of vinyl iodide **4**. a) TBTU, HOBt, DIEA, CH_2Cl_2, RT, quant.; b) $Hg(OAc)_2$, EtOH/ethyl acetate, $NaBH_4$, RT, 82%; c) **17**, Dean–Stark conditions, benzene, 95%; d) NiO_2, CH_2Cl_2, RT, 74%; e) TBAF, THF, RT, 74%; f) $(EtO)_3SiCH{=}CH_2$, cat. Grubbs II **18**, CH_2Cl_2, reflux, 61%; g) 2,2-DMP, cat. PPTS, RT, 2 h, 72%; h) MeOH, KHF_2, RT, 12 h, then I_2, RT, 4 h, 94%. TBTU = 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, HOBt = hydroxybenzotriazole, TBAF = tetra-*n*-butylammonium fluoride, 2,2-DMP = 2,2-dimethoxypropane, CSA = camphorsulfonic acid.

Aromatization was best achieved with freshly prepared NiO_2 as the oxidant.[16]

Conversion of the terminal olefinic double bond into the *E*-configured vinyl iodide was achieved via vinylsilane **16**, which was prepared by cross-metathesis with vinyl triethyoxysilane in the presence of the Grubbs II complex **18**.[17] Removal of the two TBS protecting groups was necessary to allow cross-metathesis to occur in satisfactory yields. Most likely the size of the protecting groups hampered addition of the catalyst to the olefinic double bond. Prior to formation of the vinyl iodide moiety the diol had to be protected as acetonide. Based on the Kumada protocol, synthesis of the intermediate fluoro silicate was achieved with KHF_2 and subsequent addition of molecular iodine yielded vinyl iodide **4**.[18]

The synthesis of the northern fragment started with the Wittig olefination of aldehyde **19**[8] with ylide **20**[19] (Scheme 5). Treatment of the resulting α,β-unsaturated ketone with ADmix-α[20] followed by TBSOTf/2,6-lutidine gave ketone **8**. The aldol reaction between ketone **8** and aldehyde **9**[7] served as a key reaction in the construction of the northern fragment. Two aspects make this step a challenge. Firstly, dienal **9** proved to be rather unreactive towards nucleophilic attack because of the extended conjugation. Secondly, there is no precedence in the literature for the stereochemical outcome of this type of aldol reaction. In fact, no systematic studies exist on the influence of 1,4 versus 1,5 induction in aldol reactions of α,β-bis-siloxy ketones like **8**. Initial experiments with the boron enolate afforded the aldol product in only moderate yield and selectivity.[21] After switching from boron to titanium ($TiCl_4$)[22] and substantially optimizing the reaction time and temperature, we could significantly improve the outcome of the reaction (Table 1). To our delight, the desired hydroxyketone **21** was formed in 88% yield with good selectivity for the desired diastereoisomer under the optimized conditions.



Scheme 5. Preparation of alkyne **5**. a) $CHCl_3$, 40 °C, 70 %; b) AD-mix α, water/*t*BuOH, 0 °C, 78 %; > 96 % *ee* (recryst.); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C→RT, 79 %; d) aldehyde **9** (see Scheme 1), $TiCl_4$, DIEA, CH_2Cl_2, −78 °C→−40 °C, (88 %; d.r. > 20:1); e) Et_2BOMe, $NaBH_4$, THF/MeOH, −30 °C→−15 °C, 89 %, (*syn*/*anti* = 8:1); f) 2,2-DMP, CSA, DMF, RT, 92 %; g) K_2CO_3, MeOH,RT, 95 %; h) cat. TPAP, NMO, MS 3 Å, CH_2Cl_2, RT, 90 %; i) Bestmann's reagent, K_2CO_3, MeOH, 0 °C, 89 %. TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide; Bestmann's reagent = $CH_3(CO)C(N_2)P(O)(OCH_3)_2$.

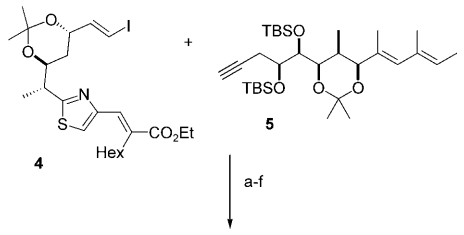
Table 1: Conditions for the aldol reaction of **8** and **9**.

Lewis acid	Conditions (enolate formation/reaction)	Yield (d.r.)
Bu_2BOTf[a]	1 h, −78 °C/16 h, −78 °C→0 °C	51 % (4:1)
$TiCl_4$[b]	3.5 h, −78 °C/4.5 h −78 °C→−45 °C	65 % (> 20:1)
$TiCl_4$[b]	3.5 h, −78 °C/16 h, −78 °C→−35 °C	88 % (> 20:1)

[a] 1.2 equiv Bu_2BOTf, 1.3 equiv DIEA, 4 equiv **9**. [b] 1.2 equiv $TiCl_4$, 1.4 equiv DIEA, 4 equiv **9**.

This complex substrate-controlled titanium aldol reaction presumably proceeds via transition state TS-I.[22] Facial selectivity is governed by electrostatic repulsion between the enolate and the α-OTBS group. The correct 1,4-stereoinduction was confirmed by analysis of the Mosher esters prepared from hydroxyketone **21**. The formation of the *syn*-aldol product was confirmed after preparation of the 1,3-*syn*-diol using $NaBH_4$ in the presence of Et_2BOMe[23] and formation of the acetonide. The acetonide showed the expected coupling constants (*J*) and ^{13}C NMR chemical shifts[24] of the acetonide carbon atoms (Scheme 5). After saponification and oxidation alkyne **5** was generated by action of Bestmann's reagent.[25]

The complete carbon backbone of the thuggacins was assembled by a Sonogashira cross-coupling reaction in excellent yield; the reaction conditions described by Wipf et al. in their synthesis of disorazole C were applied (Scheme 6).[26] After desilylation and ester hydrolysis, the enyne was reduced to the *E*,*Z*-diene by Lindlar hydrogenation. The hydrogenation proceeded with moderate selectivity for monoreduction of the alkyne.[27] The inseparable mixture was subjected to the macrocyclization, which was carried out according to the protocol of Shiina et al.[28] Ring closure



Scheme 6. Completion of the total synthesis of thuggacin B (**2**). a) $[PdCl_2(PPh_3)_2]$, CuI, Et_3N, MeCN, −20 °C→RT, 74 %; b) TBAF, THF, 99 %; c) KOH (3 M), 90 %; d) Lindlar catalyst, py, 56 %; e) MS 4 Å, MNBA, DMAP, toluene, 70 °C; 54 %; f) CSA, MeOH; 38 % **2**, and < 7 % **1**. DMAP = *N*,*N*-dimethylaminopyridine), MNBA = 2-methyl-6-nitrobenzoic anhydride;

occurred selectively with the 17-hydroxy group. This unexpected selectivity for lactonization in favor of the thuggacin B derivative is most likely a result of structural and conformational changes caused by the two acetonides. It should be noted that we had isolated the same compound as a by-product after Mosher ester formation during our studies on the structure elucidation of the thuggacins.[5]

Removal of the acetonides could be accomplished by repeated action of CSA in methanol. After a reaction time of 30 minutes thuggacin B (**2**) was isolated and the residue was again treated with CSA (three times). This procedure provided thuggacin B (**2**) in 38 % yield and thuggacin A (**1**) in < 7 % yield. Since the presence of acids is known to hamper acyl migration of the thuggacins, thuggacin B (**2**) was isolated as major product after acetal cleavage. Extending the reaction time without removing the freshly formed thuggacin B led to decomposition (presumably elimination of water at C7/C8 as well as methanolysis). The spectroscopic data (^1H NMR, ^{13}C NMR, HRMS, CD) of the synthetic thuggacin B (**2**) are identical to those of an authentic sample of **2**. Moreover, we observed slow rearrangement of thuggacin B into the thuggacins A (**1**) and C (**3**) in the NMR tube.[4,29] The interconversion was judged from analysis of diagnostic signals (3-H and 5-H), thus, confirming that the three thuggacins interconvert by a transacylation mechanism.

In summary, we have achieved the first total synthesis of the thuggacins A–C (**1**–**3**) by a highly stereoselective and modular route which should be amenable to the preparation of analogues. Thuggacin B (**2**) was synthesized in 23 linear steps (longest linear sequence) from acrolein in 0.6 % overall yield. Notable features include a substrate-controlled, titanium-mediated aldol reaction, a cross-metathesis approach for converting terminal alkenes into the corresponding *E*-vinyl iodides, and the cross-coupling reaction of a complex vinyl iodide and terminal alkyne by the Sonogashira reaction. The synthesis gives final proof of the reported structures and paves the way for detailed studies on structure–activity relationships.

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[24] S. Rychnovsky, D. J. Skalitzky, *Tetrahedron Lett.* **1990**, *31*, 945 – 948. Diagnostic ^{13}C NMR data (δ) for 1,3-*syn*: $Me_{ax} \approx 20$ ppm, $Me_{eq} \approx 30$ ppm; for 1,3-*anti*: both Me ≈ 25 ppm. Occasionally, also the ^{13}C δ values for the quatenary C are analyzed: $\delta <$ 100 ppm (for 1,3-*syn*) and $\delta > 100$ ppm (for 1,3-*anti*). Diagnostic ^{13}C δ values for 1,2-*anti*: $Me_{\beta} \approx 25$ ppm, $Me_{\gamma} \approx 28$ ppm; for 1,2-*syn* both Me ≈ 27 ppm.
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[29] As acyl migration requires a protic solvent to occur, the rather slow rearrangement in DMSO is probably a result of traces of water in the solvent. This also explains the different ratios of the thuggacins observed in DMSO and methanol (**1**/**2**/**3** = 2.5:8.3:1) (see the Supporting Information).

