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Tandem Conjugate Cyanide Addition–Dieckmann Condensation in the Synthesis of the ABCD-Ring System of Lactonamycin

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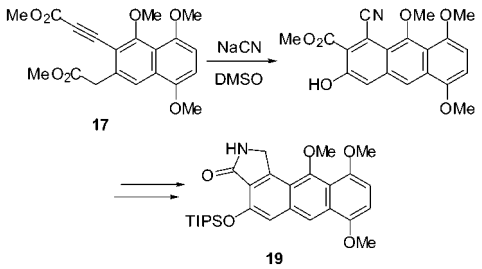
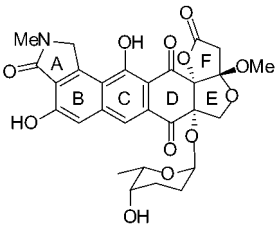
ABSTRACT



An efficient synthesis of the ABCD-ring system of lactonamycin (1) is reported in this Letter. The key step is the tandem cyanide conjugate addition–Dieckmann condensation of alkyne 17 to afford a fully functionalized anthracene. Selective reduction of the cyano group with subsequent lactam formation affords the tetracyclic core of lactonamycin 19.

Lactonamycin (**1**) (Figure 1) was isolated by Matsumoto and co-workers in 1996 from *Streptomyces rishiriensis* in a screen for new antibiotics active against drug resistant bacterial strains.[1] Lactonamycin exhibits potent antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[2]

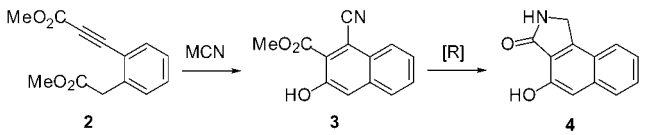


(+)-Lactonamycin (**1**)

Figure 1.

Recent work by Danishefsky's group reported the construction of the densely functionalized DEF-ring system in the context of a model system.[3] Since no work has been reported concerning construction of the ABCD-ring system, we were prompted to report our efforts aimed at this tetracyclic core. The approach we envisioned builds the AB-ring system by construction of a naphthalene nucleus as shown in Scheme 1. Thus, conjugate addition of cyanide into alkynyl ester **2** with concomitant Dieckmann condensation would afford phenol **3** after tautomerization. Selective

Scheme 1



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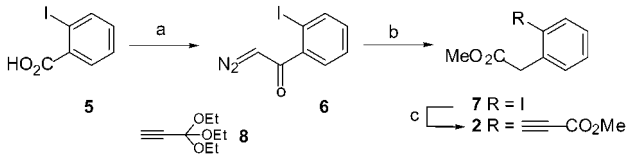
reduction of the cyanide moiety and closure onto the *ortho* ester functionality would provide the A-ring lactam **4**.

Examination of this strategy began with a model system constructed from commercially available *o*-iodobenzoic acid **5** as shown in Scheme 2. Treatment of acid **5** with oxalyl

Scheme 2[a]



[a] (a) $(COCl)_2$, catalytic DMF, THF/PhH, 0 °C; CH_2N_2, Et_2O, 0 °C (79%); (b) AgOBz, NEt_3, MeOH, 0 °C (86%); (c) **8**, $PdCl_2(PPh_3)_2$, CuI, NEt_3, MeCN, 0 °C to rt; TsOH, MeOH (85%).

chloride in the presence of catalytic DMF,[4] followed by treatment with diazomethane,[5] afforded diazoketone **6**. Wolff rearrangement was effected with silver benzoate[6] in the presence of triethylamine in methanol to afford homologated ester **7**. Sonogashira coupling[7] with alkynyl ortho ester **8**[8] under standard conditions followed by unraveling of the ortho ester functionality gave cyclization substrate **2**. The key cyclization reaction was then examined with various sources of cyanide as summarized in Table 1.

Table 1. Tandem Cyanide Addition−Dieckmann Condensation

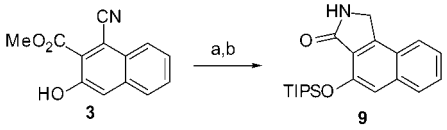
2 **3**

entry	MCN	time (h)	yield (%)
1	NaCN	5	88
2	KCN	7	80
3	Bu_4NCN	3.5	86

Reactions were initially conducted in DMF, though it was found that DMSO gave superior conversions. All reactions were run at room temperature. The effect of changing the countercation was minimal. Cyclizations with sodium cyanide (entry 1) gave consistently higher yields than those conducted with potassium cyanide (entry 2). The reaction time could be significantly reduced by use of the noncoordinating tetrabutylammonium cation (entry 3).

With the successful demonstration of the tandem cyanide conjugate addition−Dieckmann cyclization to form intermediate **3**, we next examined the selective reduction of the resultant aromatic cyano group in the presence of the ortho ester functionality as shown in Scheme 3. Protection of the

Scheme 3[a]



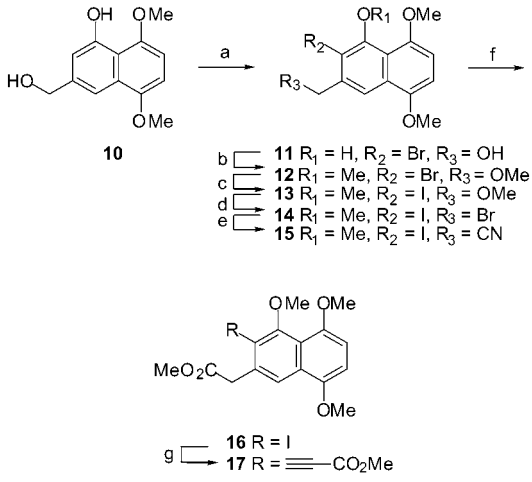
3 **9**

[a] (a) NaH, TIPSCl, DMF (quantitative); (b) $CoCl_2$, $NaBH_4$, MeOH/THF (71%).

phenolic group as its TIPS ether was followed by selective cyanide reduction with the combination of cobalt chloride and sodium borohydride in methanol−THF solvent.[9] The resultant amine group spontaneously cyclized on the ortho ester group to afford lactam **9** in 71% yield over the two steps.

Confident that the model system was complete, our attention turned to application in a system that would be appropriate for the total synthesis of lactonamycin. A convenient starting point was the known naphthalene system **10**[10] as shown in Scheme 4. Regioselective bromination with pyridinium bromide perbromide[11] gave alcohol **11**. The

Scheme 4[a]



[a] (a) $PyrH^+Br_3^-$, THF, 0 °C (99%); (b) NaH, MeI, DMF (84%); (c) n-BuLi, THF; I_2, −78 °C (91%); (d) HBr, HOAc, 50 °C (65−79%); (e) KCN, EtOH−H_2O, reflux (82%); (f) TfOH, MeOH, reflux (86%); (g) **8**, $PdCl_2(PPh_3)_2$, CuI, NEt_3, MeCN, 0 °C to rt; TsOH, MeOH (97%).

(1) Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Sawa, R.; Kinoshita, N.; Homma, Y.; Takahashi, Y.; Iinuma, H.; Naganawa, H.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1996**, *49*, 953.

(2) (a) Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Kinoshita, N.; Homma, Y.; Iinuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1999**, *52*, 269. (b) Matsumoto, N.; Tsuchida, T.; Nakamura, H.; Sawa, R.; Takahashi, Y.; Naganawa, H.; Iinuma, H.; Sawa, T.; Takeuchi, T. *J. Antibiot.* **1999**, *52*, 276.

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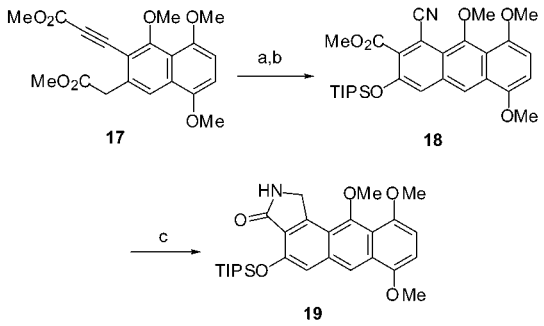
alcohol and phenolic groups were protected as their methyl ethers, which afforded permethylated naphthalene derivative **12**. Bromine was exchanged for iodine through lithium−halogen exchange,[12] giving iodonaphthalene **13**. The benzylic methoxy group of **13** was exchanged for bromine by action of aqueous hydrogen bromide in acetic acid.[13] The resultant benzylic bromide **14** was immediately converted to the corresponding benzylic cyanide **15**. Finally, the cyano group was methanolyzed[14] to ester **16** followed by Sonogashira coupling to ortho ester **8** with subsequent ortho ester hydrolysis to afford the fully elaborated cyclization substrate **17**. It should be noted that attempts to carry out the Sonogashira coupling with the bromide gave poor results, thus requiring the change from bromide **12** to iodide **13**.

Cyclization of **17** under the optimized conditions proceeded smoothly (albeit much slower than in the model **2**) (Scheme 5), and the resultant phenolic group was immediately protected as its TIPS ether **18** in 68% yield over the two steps. The intermediate phenol was found to be somewhat unstable, and protection without prior purification always gave about 10−20% higher yields. Reduction of cyanide **18** also proved to be sluggish relative to the model **3**, and it was necessary to heat the reaction to 50 °C for the reaction to proceed. Reduction followed by lactam formation gave anthracene **19** in 52% yield.

Scheme 5[a]



[a] (a) NaCN, DMSO; (b) NaH, TIPSCl, DMF (68% two steps); (c) $CoCl_2$, $NaBH_4$, MeOH/THF, 50 °C (52%).

With **19** in hand, further elaboration of the EF-ring system of lactonamycin onto this core is under investigation. Finally, tandem conjugate addition−Dieckmann condensations with nucleophiles other than cyanide are being investigated as a means of constructing highly substituted naphthalenes and anthracenes.

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Supporting Information Available: Experimental procedures and full characterization data for compounds **2**, **3**, **6**, **7**, **9**, and **11**−**19**. This information is available free of charge via the Internet at http://pubs.acs.org.

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