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Short Synthesis of the CDEF Ring System of Lactonamycin

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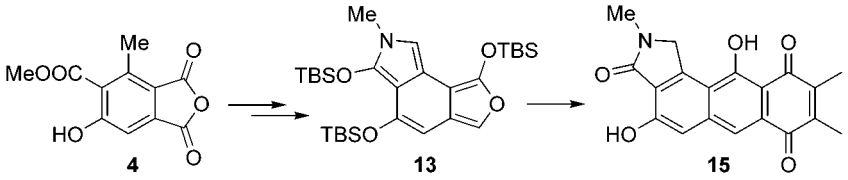
ABSTRACT



A synthesis of the CDEF fragment of lactonamycin is achieved in eight steps (six pots) from the known and readily available anhydride 4 via a Diels–Alder reaction between tricycle 13 and 2,3-dimethylbenzoquinone.

The recently discovered antibiotic lactonamycin (**1**) has a hexacyclic core structure that is unlike that of any other molecule. In addition, lactonamycin exhibits sub-μg/mL activity against a variety of bacteria resistant to most current antibiotics, including methicillin-resistant (MRSA) and vancomycin-resistant (VRE) strains.[1]

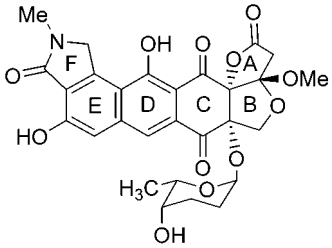


Figure 1. Lactonamycin (**1**).

The remarkable structure and biological activity of lactonamycin have generated considerable interest. However, to date no synthesis of lactonamycin has been recorded, and only the Danishefsky laboratory[2] has described preliminary studies aimed at its construction. We now report the synthesis of **15**, the CDEF ring system of **1**, in six pots from readily available materials (Scheme 1).

The known **4**,[3] prepared in three operations from methyl acetoacetate via the Diels−Alder reaction of **2** and **3**, was reduced to lactone **5** in 87% yield and with ≥95% favorable regioselectivity, using L-Selectride.[4] Benzylic bromination of **5** was initially a quagmire. The first equivalent of NBS, even in the presence of both AIBN and bright light, cleanly ring brominates **5** to **6**. Substitution of **16** for **5** put a stop to ring bromination but afforded the undesired regioisomer **17** in 99% yield (Scheme 2). Reaction of **6** with additional NBS under free radical conditions led to competing benzylic bromination of the methyl and methylene positions to give a mixture of **7** and **8**, but the benzylic bromination reaction stopped, even with excess NBS and AIBN, when **6** was still the major component of the reaction mixture. Eventually, a serendipitous discovery, that addition of partially hydrated P_2O_5 to the bromination reaction causes benzylic bromination

(1) (a) Matsumoto, N.; Tsuchida, T.; Maruyama, M.; Kinoshita, N.; Homma, Y.; Iinuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T.; Heida, N.; Yoshioka, 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.; Shiro, M. *J. Antibiot.* **1999**, *52*, 276. (c) 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. (d) Takeuchi, T.; Tsuchida, T.; Iinuma, H.; Sawa, T.; Osanawa, H.; Hamada, M. *Jpn. Kokai Tokyo Koho* **1997** JP 0948781; *Chem. Abstr.* **1997**, *126*, 250256r.

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(3) Bingham, S. J.; Tyman, J. H. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3637.

(4) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 4810.

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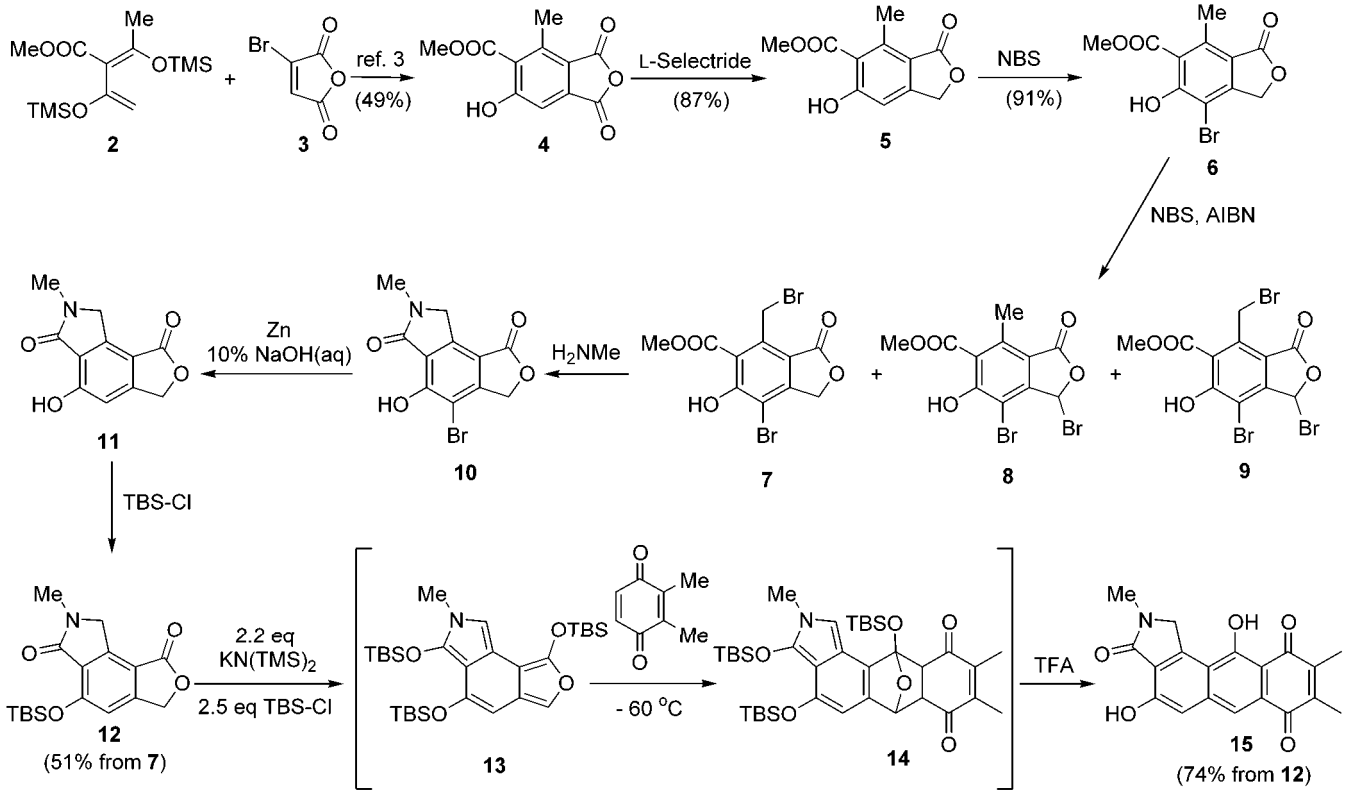
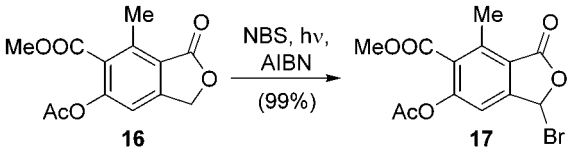
Scheme 1. Synthesis of the CDEF Ring of Lactonamycin



of **6** to go to completion, overcame this difficulty.[5] The result, still a work in progress,[6] is a crude mixture containing 38% of the desired **7**, 26% of recovered **6**, 22% of **9**, and 14% of **8**. Isolation affords **7** in 24% yield (32% based on conversion of **6**). Dibromide **8** can be recycled to **5** in 90% yield by reaction with Zn/10% NaOH(aq).[7]

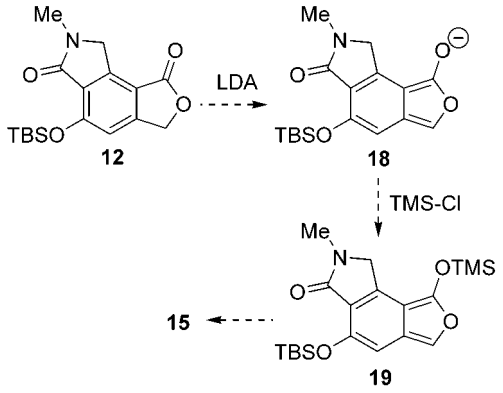
Scheme 2. Lactone Bromination of **16**



Conversion of **7** to **12** was achieved without purification of intermediates. Treatment of **7** with methanolic methylamine affords **10**, presumably by way of initial benzylic displacement followed by cyclization. The ring bromine, having played its role in hindering benzylic bromination at the adjacent lactone methylene, was removed by reduction with Zn/10% NaOH(aq)[7] to give **11**. The phenol **11** was then protected as the *tert*-butyldimethylsilyl (TBS) ether to give **12**, in 51% yield over the three steps.

The original plan had been to deprotonate the benzylic γ-position of lactone **12** to give enolate **18** (Scheme 3) and to trap the latter with TMS-Cl to give isobenzofuran **19**. It was anticipated that Diels−Alder reaction of **19** with an appropiate dienophile would afford the annelated product **15**, after fragmentation of the initially formed oxabicyclo[2.2.1] system.

Scheme 3. Planned Deprotonation/Silylation of **12**



The utility of isobenzofurans as partners in Diels−Alder reactions is well established,[8] but the use of siloxyisoben-

(5) The discovery was made using a reflux condenser that unknowingly (initially) contained some moist P_2O_5 (used for purifying recovered CCl_4). The role of the P_2O_5/H_2O is unclear.

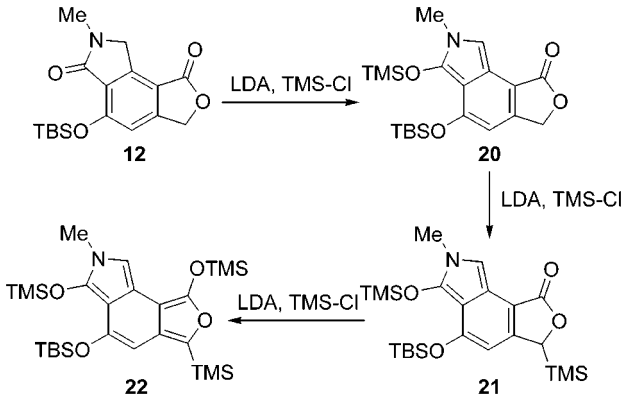
(6) Free radical bromination of the methyl group in **4** was successful, but the product could not be advanced.

(7) Groenewould, P. W. G.; Robinson, R. *J. Chem. Soc.* **1936**, 199.

zofurans derived from deprotonation/silylation of phthalides is relatively rare. The latter strategy was first introduced nearly 20 years ago,[9] but it has been enlisted only infrequently[10] despite its potential to greatly abbreviate synthetic sequences. Perhaps difficulties such as we encountered in the initial examination of this reaction account for the method's underutilization. The results described below, however, demonstrate that once the difficulties have been overcome, a powerful method is at hand.

Treatment of **12** with a wide variety of strong bases (LDA, $KN(TMS)_2$, LiTMP, $(i\text{-Pr})_2NMgBr$[11]) followed by trapping with TMS-Cl gave (Scheme 4) the undesired isoindole **20**

Scheme 4. Synthesis of Isobenzofuran **22** from **12** Using a Sequential Deprotonation/Silylation Protocol



(or recovered **12**) rather than the desired **19** under all conditions examined. Subjection of isoindole **20** to further LDA/TMS-Cl treatment resulted in deprotonation of the lactone, but silylation occurred on carbon, not on oxygen, giving **21** (for related results see ref 10b). A third round of LDA/TMS-Cl finally delivered an isobenzofuran, **22**. Preliminary studies indicated that **22** might serve as a precursor to **15**, but a simpler solution emerged. The key observation was that replacing TMS-Cl with TBS-Cl in the deprotonation/silylation of **12** results in *O*-rather than *C*-silylation. In fact, reaction of **12** (Scheme 1) with 2.2 equiv of $KN(TMS)_2$ and 2.5 equiv of TBS-Cl affords **13** directly.

Compound **13** has two sites of potential Diels−Alder reactivity, an isoindole and an isobenzofuran-type unit. The latter proved much more reactive, so exposure of **13** to 1 equiv of 2,3-dimethylbenzoquinone[12] resulted in reaction at the desired position. The Diels−Alder reaction is exceedingly facile, being complete in 10 min at −60 °C (the reaction is less clean at room temperature). Without isolation, treatment of **14** with CF_3COOH then affords **15**; the overall yield of **15** from **12** is 74%. The NMR spectra of **15** are in excellent agreement with the corresponding parts of the spectra of **1**.

In summary, a short synthesis of the CDEF ring system of lactonamycin has been achieved. Work to extend these efforts to the synthesis of **1** itself is underway.

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Supporting Information Available: Experimental procedures and characterization data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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