

Concise Synthesis of a Lactonamycin Model System by Diastereoselective Dihydroxylation of a Highly Functionalized Naphthoquinone

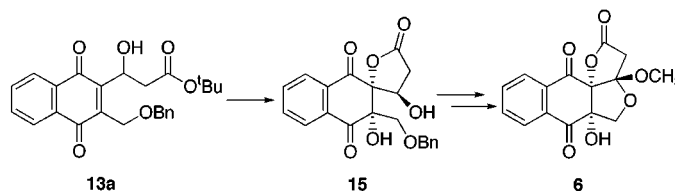
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ABSTRACT



In this Letter, we describe an approach to the highly functionalized tetracycle **6**, a model compound corresponding to the CDEF ring system contained in the recently discovered antibiotic lactonamycin. Our approach features an unprecedented, highly stereoselective dihydroxylation of quinone **13a**, which leads directly to spirocyclic lactone **15**, following acid-promoted deprotection/cyclization. The methodology described herein paves the way for a concise, highly diastereo- and enantioselective synthesis of the natural product.

Lactonamycin (**1**, Figure 1), recently isolated from *Streptomycies rishiriensis*, was shown to exhibit cytotoxicity against

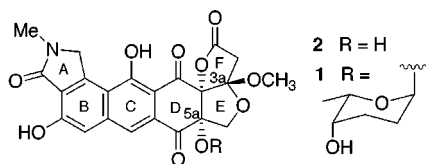


Figure 1. Structures of (+)-lactonamycin (**1**) and the aglycon, lactonamycinone (**2**).

a number of cell lines.¹ Of potentially greater significance is its potent antimicrobial activity against both methacilin-

and vancomycin-resistant organisms. The goal of assembling lactonamycin in the laboratory constitutes a significant challenge. The dual prospects of stimulating chemistry and the opportunity to evaluate new agents of potential value to the vital mission of circumventing antibiotic resistance served to identify lactonamycin as an appropriate orienting target for a total synthesis program.

It seems likely that the introduction of the required 2,3-dideoxyfucose residue at the tertiary C-5a hydroxy center will constitute a problem at the frontier of difficult glycosylations.² Notwithstanding this concern, we focused on

(1) (a) Isolation and biological evaluation: Matsumoto, Y.; Tsuchida, T.; Maruyama, M.; Kinoshita, N.; Homma, Y.; Inuma, H.; Sawa, T.; Hamada, M.; Takeuchi, T.; Heida, N.; Yoshioka, T. *J. Antibiot.* **1999**, *52*, 269. (b) Structure determination: Matsumoto, Y.; Tsuchida, T.; Nakamura, H.; Sawa, R.; Takahashi, Y.; Naganawa, H.; Inuma, H.; Sawa, T.; Takeuchi, T.; Shiro, M. *J. Antibiot.* **1999**, *52*, 276.

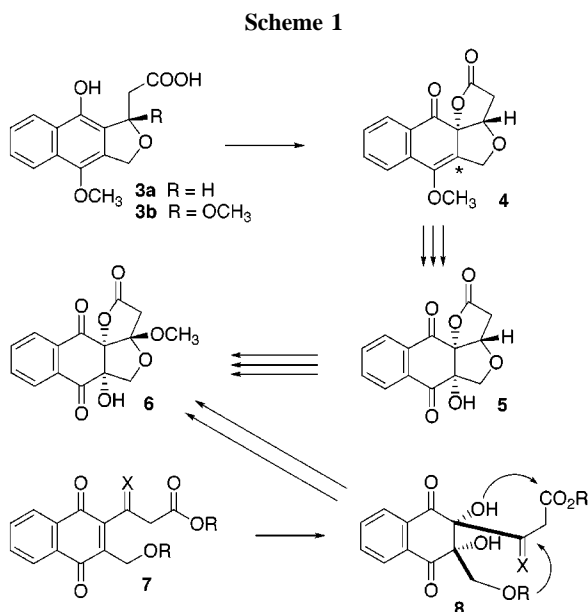
(2) For a review of the difficulty in coupling 2-deoxy sugars, see: Veyrières, A. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: New York, 2000; Vol. 1, Chapter 15.

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lactonamycinone (**2**) as our subgoal. Clearly, the densely functionalized DEF sector in **2** emerges, even on cursory inspection, as an important battleground in this venture. It goes without saying that for a solution to the DEF problem to be of maximal value in the projected total synthesis of lactonamycin itself, this substructure must be assembled with strict control over all issues of relative and absolute stereochemistry.

In a recent Letter,³ we described an approach to the model tetracyclic system **6** (Scheme 1). Our route featured a key

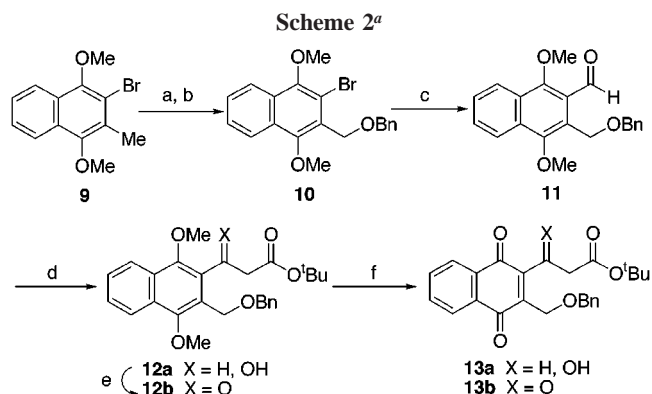


intramolecular Wessely oxidative cyclization (**3a** → **4**). Though we were able to reduce our ideas to practice, some significant trouble spots were revealed. For instance, we were unable to generate the desired Wessely precursor **3b** containing the angular methoxy group. Late stage introduction of this C-3a methoxy group (lactonamycin numbering) was achieved only after significant retrofitting. Furthermore, stereoselective hydroxylation at C-5a (see asterisk in **4**) from the desired α -face proved problematic and was only accomplished after a three-step sequence. Finally, the prospects for control over the absolute stereochemistry by this route did not seem to be particularly promising.

In this Letter, we provide an alternative synthesis of the core structure **6**. The pathway detailed below is more direct than the previous Wessely route in terms of conciseness and stereocontrol, and also reveals a direct solution to the problem of enantioselective construction of the natural product. We describe a rare instance of a highly diastereoselective osmylation of a tetrasubstituted allylic alcohol, while demonstrating the potential value of osmium-mediated dihydroxylation of quinones in complex synthetic settings. The proposed sequence of **7** → **8** → **6**, though unspecified in detail, reveals the underlying logic of our new plan.

(3) Cox, C.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 3493.

We began our endeavor with the readily available bromide **9**,⁴ synthesized in two steps from 2-methyl-1,4-naphthoquinone (Scheme 2). Conversion to the protected benzyl



^a (a) NBS, benzoyl peroxide, CCl₄, reflux (100%); (b) NaH, BnOH, TBAI, THF (81%); (c) *n*-BuLi, then EtOCHO, -95 °C, THF (80%); (d) LDA, *t*-BuOAc, -78 °C, THF (100%); (e) DMP, CH₂Cl₂ (76%); (f) CAN, CH₃CN/H₂O (97% of **13a** from **12a**, ~20% of **13b** from **12b**). Abbreviations: TBAI = tetrabutylammonium iodide; DMP = Dess–Martin periodinane; CAN = ceric ammonium nitrate.

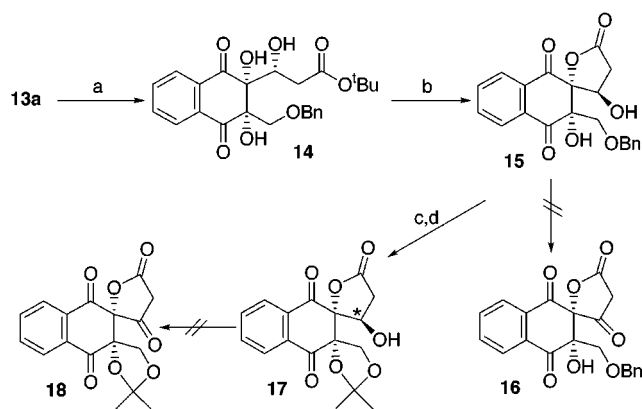
alcohol **10**, followed by halogen–metal exchange at low temperature and a rapid quench with ethyl formate, provided aldehyde **11**. Addition of the lithium enolate of *tert*-butyl acetate to **11** afforded **12a**, which, upon ceric ammonium nitrate (CAN)-mediated oxidative demethylation, provided α -hydroxyquinone **13a**. The α -ketoquinone **13b** was obtained via Dess–Martin oxidation of **12a**, followed by CAN oxidation. The CAN oxidation of **12b** (with the ketone in place) occurred rather poorly (~20%) but did provide a suitable quantity of **13b**.

A survey of the literature indicated that the dihydroxylation of quinones has been carried out in several simple cases⁵ but does not appear to have been successfully applied to extensively elaborated synthetic intermediates. Our initial attempts focused on the dihydroxylation of α -ketoquinone **13b**, as such a reaction would lead to an equivalent of intermediate **8** (X = O), corresponding to the desired level of oxidation at the future C-3a. However, not surprisingly, attempts to dihydroxylate the highly electron-deficient quinone double bond in **13b** were unsuccessful.

Fortunately, alcohol **13a** did, indeed, serve as a viable substrate for the dihydroxylation. Classic dihydroxylation conditions (catalytic OsO₄ and a stoichiometric amount of the oxidant *N*-methylmorpholine *N*-oxide) furnished a triol in 71% yield (Scheme 3). *Significantly, this product was*

(4) Aldersley, M. F.; Dean, F. M.; Mann, B. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2217.

(5) For examples of OsO₄-promoted dihydroxylations on simple quinones, see: (a) Savoie, J. Y.; Brassard, P. *Can. J. Chem.* **1971**, *49*, 3515. (b) Krohn, K.; Mondon, A. *Chem. Ber.* **1976**, *109*, 855. Adam has recently noted that several hydroquinones, upon treatment with dimethyldioxirane, can provide varying yields of the formal dihydroxylation product of the parent quinone, see: (c) Adam, W.; Schönberger, A. *Tetrahedron Lett.* **1992**, 53.

Scheme 3^a

^a (a) OsO₄, NMO, acetone/H₂O (71%); (b) 90% TFA/H₂O, CH₂Cl₂ (83%); (c) BBr₃, CH₂Cl₂, -78 °C (85%); (d) AlCl₃, Et₂O/acetone, 0 °C (79%). Abbreviations: NMO *N*-methylmorpholine *N*-oxide; TFA = trifluoroacetic acid.

found to be a single diastereomer, subsequently shown to be **14** (*vide infra*).

The high stereoselectivity of the osmylation, providing the triol with a syn arrangement between the “directing” secondary alcohol moiety and the newly installed 1,2-diol unit, deserves some comment. Although it is generally believed that osmylations can be directed by certain proximal functional groups,⁶ seminal work by Kishi in acyclic systems demonstrated that OsO₄ is not “directed” per se by alcohols but in fact approaches from the face of the alkene opposite to that of the hydroxyl group.^{7,8} Although there appears to be scant literature on the dihydroxylation of tetrasubstituted allylic alcohols, the examples we identified all proceed with high stereochemical fidelity on the face opposite to that of the hydroxyl group.⁹

We hypothesize that minimization of the steric interactions felt by the ortho side chains of the C=C double bond favors a reactive conformer in which entry of OsO₄ anti to the -OH group provides the observed product (Figure 2).¹⁰ We note

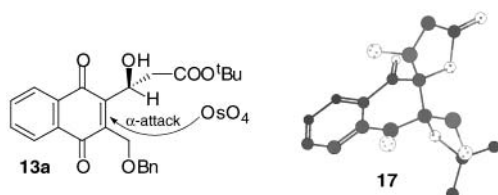


Figure 2. Proposed reactive conformer of **13a** and Chem-3D representation of the X-ray structure of **17**.

that this highly stereoselective dihydroxylation reaction provides a practical solution to the enantioselective construction of lactonamycinone, provided that an aldol reaction of

11 can be conducted with high stereocontrol.¹¹ Treatment of triol **14** with trifluoroacetic acid in CH₂Cl₂ served to accomplish deprotection and concomitant cyclization to provide spirocyclic lactone **15**.

At this stage, it appeared that model system **6** was easily within our grasp by (1) oxidation of the secondary alcohol in **15** to the ketone level (cf. **16**), (2) removal of the benzyl ether with spontaneous cyclization to form a hemiacetal, and (3) acid-catalyzed methanolysis to provide **6**. Unfortunately, all attempts to oxidize diol **15** to ketone **16** were fruitless. Compound **15** was amazingly unreactive to many protocols, including Dess–Martin, Jones, PCC, TPAP-NMO, TEMPO, and chromyl chloride. For instance, heating **15** at 150 °C in DMSO for 24 h in the presence of 5 equiv of IBX resulted in quantitative recovery of starting material. In contrast, Swern oxidation conditions led to destruction of the ring system. Prior protection of the tertiary alcohol in **15** also led to a substrate that was completely resistant to oxidation. Similarly, the product arising from deprotection of the benzyl ether followed by protection of the 1,2-diol as an acetonide (cf. **17**) was totally resistant to oxidation as well.

While **17** was a noncompetent substrate for oxidation to **18**, it is a crystalline compound, mp = 228 °C. This crystallinity was used to advantage in that an X-ray structure of **17** served to corroborate its structure, and thus the structures of **14** and **15** (Figure 2).¹² Examination of the crystallographically derived structure of **17** reveals that the crucial methine proton (see asterisk in **17**), whose abstraction is required for oxidation, is in a hindered environment. Efforts to reach the desired ketone level of oxidation at the stage of triol **14** were also unsuccessful.¹³

(6) For reports on the directing abilities of specific functional groups, see: (a) Sulfoxide: Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458. (b) Sulfoximine: Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 2459. (c) Nitro: Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621.

(7) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, 3947. (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

(8) A recent report has convincingly shown that an OsO₄·TMEDA complex in *nonpolar* solvents can be efficiently directed by hydrogen bonding to allylic alcohols, see: Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, 5027.

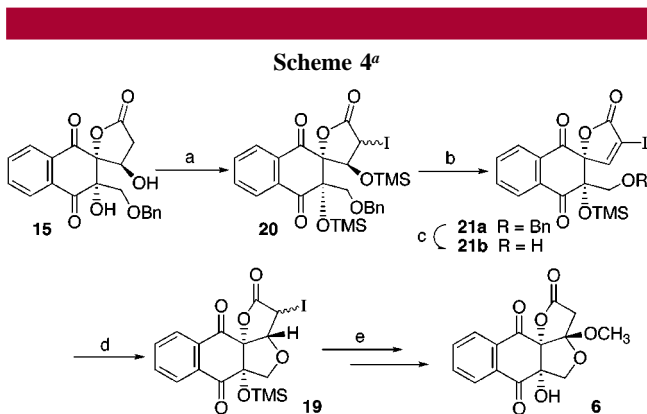
(9) (a) Shibasaki, M.; Mase, T.; Ikegami, S. *Chem Lett.* **1983**, 1737. (b) Honda, T.; Tomitsuka, K.; Tsubuki, M. *J. Org. Chem.* **1993**, *58*, 4274. (c) Kita, Y.; Yoshida, Y.; Mihara, S.; Furukawa, A.; Higuchi, K.; Fang, D.-F.; Fujioka, H. *Tetrahedron* **1998**, *54*, 14689.

(10) Also deserving of consideration is a conformer featuring a planar hydrogen bond between the secondary alcohol and the adjacent quinone carbonyl group. In such a reacting ensemble, the phenyl group of the benzyl ether side chain can fold over and engage in a π -stacking interaction with the quinone, successfully explaining the observed stereochemistry. However, two additional considerations do not support this explanation: (1) the proposed hydrogen bond is expected to deactivate the C=C bond toward dihydroxylation and (2) when the hydroxyl group in **13a** is protected as a TBS ether, **14a** is again obtained with very high stereochemical fidelity (between 8:1 and >20:1, depending on conditions). A full discussion of the stereochemistry observed in this dihydroxylation will be provided in a forthcoming full paper on the subject.

(11) We have recently shown that a titanium-carbohydrate complex, first introduced by Duthaler,^{12a} is capable of introducing >95% ee for the aldol reaction on an equivalent of **11** that is projected to be useful for our total synthesis of lactonamycinone. (a) Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 495.

(12) Crystallographic data for **17** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC-165580.

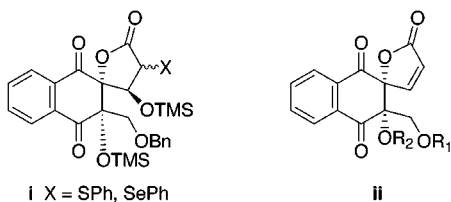
In time, we were able to find a solution to our dilemma (Scheme 4). We recalled an anomalous characteristic of



^a (a) TMSCl, THF, then LiHMDS, then NIS, $-78\text{ }^{\circ}\text{C}$ (85%); (b) DBU, THF (82%); (c) BBr_3 , CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$; (d) **21b**, SiO_2 , CHCl_3 (84% for 2 steps); (e) 4 steps, see ref 3. Abbreviations: NIS = *N*-iodosuccinimide.

α -iodolactone **19**, a key intermediate from our previous model study.³ Though obtained crude as a mixture of epimers (at the α -position) significantly enriched in one form, it was isolated as a nearly 1:1 mixture following chromatography on silica gel. We considered the possibility that this equilibration may be the result of a retrograde Michael ring-opening process, followed by a ring-closing Michael reaction.

(13) Other methods to advance the C-3a center to the correct oxidation state, such as a sulfoxide or selenoxide elimination of **i**, Tsuji^{15a,b} or Wacker-type^{15c} oxidations on α,β -unsaturated lactone **ii**, or Saegusa oxidation^{15d,e} of the silyl ketene acetal derived from **15**, were also unsuccessful. (a) Tsuji, J.; Nagashima, H.; Hori, K. *Chem. Lett.* **1980**, 257. (b) Ueda, Y.; Damas, C. E.; Belleau, B. *Can. J. Chem.* **1983**, *61*, 1996. (c) Auclair, S. X.; Morris, M.; Sturgess, M. A. *Tetrahedron Lett.* **1992**, 7739, and references therein. (d) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (e) Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfuné, Y. *J. Org. Chem.* **1991**, *56*, 4167.



We thus reasoned that interception of the retro-Michael product (cf. **21b**) in a synthetic sequence would provide a viable substrate for ring-closure to **19**.

To this end, the required α -iodo substituent was introduced via trapping of the in situ generated silylketene acetal with NIS, followed by elimination of the β -OTMS group with DBU, to provide vinyl iodide **21a**. Deprotection of the benzyl ether, followed by stirring the resultant primary alcohol in chloroform in the presence of silica gel, indeed provided lactone **19** as a 1.5:1 mixture of diastereomers in 84% yield from **21a**. We have previously shown that the mixture of diastereomers of **19** could be converted to the target system **6** in four steps.³

In conclusion, a viable method for the construction of the key DEF tricyclic ring system of lactonamycin has been demonstrated. It features an unprecedented, exceedingly stereoselective dihydroxylation of highly functionalized naphthoquinone **13a**. This new work overcomes the most serious shortcomings of the original Wessely oxidation route, such as adaptability to an asymmetric variant (made possible by the stereospecificity of the dihydroxylation), as well as the ability to readily adapt the dihydroxylation strategy to a fully elaborated hexacyclic construct necessary for the total synthesis of lactonamycinone. For the moment, one of the major drawbacks of the Wessely route, the inability to gain smooth and early access to the required oxidation level at C-3a, has not been solved in this route due to our surprising inability to oxidize the secondary alcohol moiety of **14**, **15**, or **17**. Application of this dihydroxylation strategy to an enantioselective total synthesis of lactonamycinone is currently ongoing and will be reported shortly.

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Supporting Information Available: Experimental procedures and full characterization data for **10–15**, **17**, and **19–21**. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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