ORGANIC LETTERS

2000
Vol. 2, No. 22
3493−3496

Synthesis of the Functionalized Tricyclic Core of Lactonamycin by Oxidative Dearomatization

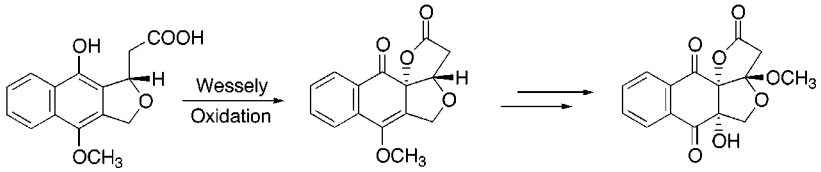
Christopher Cox[†] and Samuel J. Danishefsky*[,†,‡]

Department of Chemistry, Columbia University, Havemeyer Hall, New York, New York 10027, and Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10024

s-danishefsky@ski.mskcc.org

Received August 31, 2000

ABSTRACT



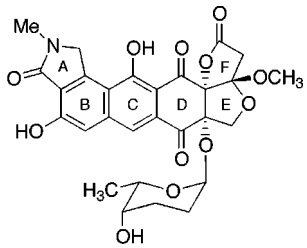
18 19 27

We report in this Letter a synthesis of the densely oxygenated CDEF ring system (27) corresponding to that found in the recently discovered antibiotic lactonamycin. The key steps in the synthesis consist of an intramolecular Wessely oxidative lactonization of acid 18, followed by a hydroxyl-directed epoxidation of enol ether 21.

The isolation of lactonamycin (Figure 1) from *Streptomycies rishirienes* was recently described by Mastumoto and colleagues.[1] Of primary interest at the biological level is its powerful antimicrobial activity against both methacilin- and vancomycin-resistant organisms.

Viewed from the perspective of chemical synthesis, the structure of lactonamycin inherently poses issues of some scope. The stereospecific attachment of a 2-deoxy sugar to a deactivated tertiary acceptor constitutes a challenge at the frontier of difficult glycosylations. Moreover, formation of the hexacyclic aglycone ensemble, even in a gross sense, is far from a simple matter. Particularly challenging is the densely oxygenated DEF substructure. In this Letter, we report a solution to this problem in the context of the synthesis of a tetracyclic construct.

Given the potential importance of lactonamycin as a prospective matrix for a new class of antibiotics, we were particularly desirous of a concise strategy which would gain rapid access to the most functionality-laden section of the



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

Figure 1.

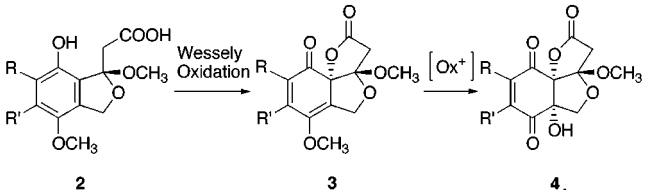
[†] Columbia University.
[‡] Sloan-Kettering Institute for Cancer Research.

(1) (a) Isolation and biological evaluation: Matsumoto, Y.; 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) 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.

10.1021/ol006531+ CCC: $19.00
Published on Web 10/04/2000

molecule. An approach to this domain, which suggested itself in idealized form, is summarized in the progression of **2** → **3** → **4** (Scheme 1). A dihydroisobenzofuran system, properly

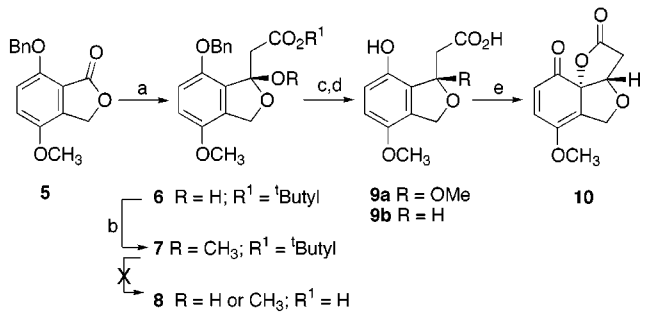
Scheme 1



substituted with geminal methoxy and acetic acid substituents (cf. **2**), was expected to undergo intramolecular Wessely oxidation[2,3] to produce **3** with the desired cis-fused EF assembly. This step might, in turn, set the stage for oxidation of the enol ether linkage by attack of an oxidizing agent (Ox^+) anti to the angular methoxy group, to give rise to the cis-fused DE system with ring D presented as the 1,4 diketone. Such a scenario would be in keeping with a growing theme in our laboratory, which seeks to exploit oxidative dearomatizations toward various synthetic ends.

In our earliest attempts at reduction to practice, we identified a system of type **9a** as a subgoal (Scheme 2).

Scheme 2[a]



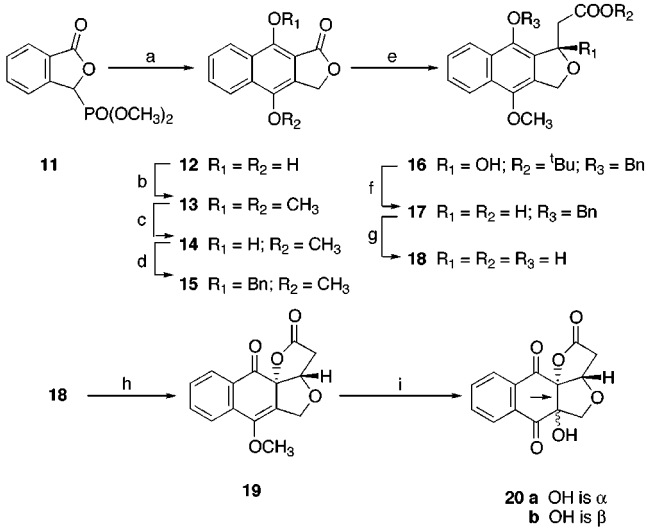
[a] (a) LDA, ^{t}BuOAc, then **5** (85%); (b) Amberlite IR 120(plus), MeOH, 5 min (88%); (c) **6**, TES, TFA, CH_2Cl_2 (95%); (d) H_2, 5% Pd/C, MeOH (99%); (e) **9b**, $Pb(OAc)_4$, CH_2Cl_2 (see ref 5); TES = triethylsilane; TFA = trifluoroacetic acid.

Unfortunately, we were unable to reach this system via esters corresponding to **6** or **7**, due to the very high lability of the benzylic, anomeric-like hydroxy and methoxy functions.[4] Accordingly, we forfeited, for the moment, the incorporation of the angular methoxy functionality prior to the establishment of the DEF substructure, hoping that it could be introduced after assembly of the ring system was complete.

In this vein, treatment of **6** with triethylsilane−trifluoracetic acid led to reduction of the hemiacetal and deprotection of the ester moiety. Following debenzylation, the Wessely precursor **9b** was in hand. Indeed, treatment of this compound with $Pb(OAc)_4$ afforded **10**, albeit in low yield. The poor outcome of this reaction can be attributed to the vulnerability of the product, which was not stable to purification on silica, Florisil or even basic alumina.[5]

Having gained some small measure of confidence as to the feasibility of our route, we pursued a more advanced model comprising the CDEF sector. We hoped that the benzo equivalent of ring C would help confer greater stability to the otherwise labile pre-DEF intermediates. Starting with the known[6] phosphonate **11**, phthalide **12** was constructed by a tandem Michael addition−cyclization sequence (Scheme 3).[7]

Scheme 3[a]



[a] (a) LiOtBu, THF, then **11**, then 2(5*H*)-furanone (80%); (b) Me_2SO_4, K_2CO_3, acetone, reflux (91%); (c) *B*-iodo-9-BBN, CH_2Cl_2, reflux (79%); (d) BnBr, K_2CO_3, acetone, reflux (97%); (e) LDA, ^{t}BuOAc, then **15**; (f) TES, TFA, CH_2Cl_2 (70% for two steps); (g) 1,4-cyclohexadiene, 10% Pd/C, EtOH (97%); (h) $Pb(OAc)_4$, CH_2Cl_2 (74%); (i) DMDO, CH_2Cl_2 (80% of **20b**); TES = triethylsilane; TFA = trifluoroacetic acid.

After differentiation of the phenolic ethers, the general theme of Scheme 2 was followed to reach Wessely precursor **18**.

(2) The Wessely oxidation was introduced originally as a way to access α-acetoxy ketones by the oxidative dearomatization of phenols in acetic acid with $Pb(OAc)_4$, see: (a) Wessely, F.; Sinwell, F. *Montasch. Chem.* **1950**, *81*, 1055. This venerable reaction was advanced by the pioneering work of Yates to include intermolecular trapping by various carboxylic acids in inert solvents, see: (b) Yates, P.; Auksi, H. *J. Chem. Soc., Chem. Commun.* **1976**, 1016. (c) Yates, P. Auksi, H. *Can. J. Chem.* **1979**, *57*, 2853.

(3) Although oxidative dearomatizations of advanced intermediates with $Pb(OAc)_4$ are scarce in the chemical literature, the analogous use of hypervalent iodine reagents is well studied. For the use of I(III) reagents in synthesis, see: (a) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179. (b) Kitamura, T.; Fujiwara, Y. *Org. Prep. Proc. Int.* **1997**, *29*, 409. (c) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271.

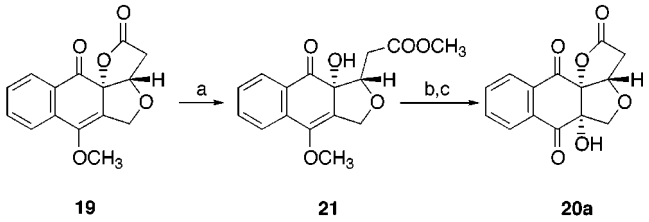
(4) The esters **6** and **7** were extremely sensitive to both acid and base due to facile formation of the corresponding α,*β*-unsaturated ester, which also comes into conjugation with the aromatic ring. Acetal **7** was prepared with a number of other ester protecting groups, including allyl, benzyl, 2-(trimethylsilyl)ethyl, and *tert*-butyldiphenylsilyl. However, these too could not be removed without concurrent destruction of the acetal. Direct addition of the dianion of acetic acid also failed due to competing deprotonation of the highly acidic benzylic protons in **5**.

Upon exposure to $Pb(OAc)_4$ in CH_2Cl_2, **18** underwent smooth, stereospecific oxidative cyclization to provide the stable lactone **19** in 74% yield. Not surprisingly, treatment of **19** with DMDO cleanly led to a hydroxyketone (80% yield). The diastereofacial selectivity of this reaction was in excess of 95% as judged by proton NMR analysis.

Various arguments and counter arguments could be posited in anticipation of the likely course of facial preference in this epoxidation.[8] In fact, X-ray analysis revealed the major isomer to be the undesired **20b**, wherein the DMDO oxidant had approached the enol ether from its β-face.[9] While we could improve the ratio of **20a** to **20b** by altering epoxidation reagents, we could not render it the major product in satisfactory yield.[10]

We were not unmindful that, in principle, diasteromers **20a** and **20b** could be interconverted through a retroaldol−realdol sequence (see arrow).[11] In practice, however, attempts to realize this possibility were not successful. At this juncture, we sought to exploit the directing ability of the free hydroxyl moiety[12] which would be unveiled if the γ-lactone could be opened. Accordingly, compound **19** was treated with lithium methoxide, thereby affording the allylic alcohol **21** (Scheme 4). The success of this reaction under such mild conditions

Scheme 4[a]

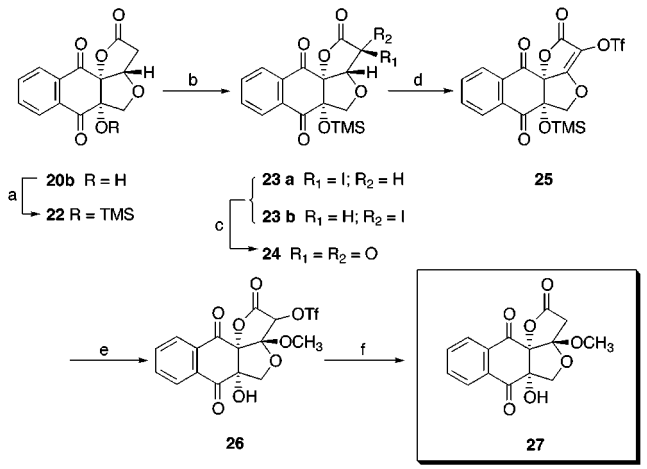


[a] (a) LiHMDS, MeOH, CH_2Cl_2, −35 °C (51% + 40% recovered **19**); (b) TFPAA, Na_2CO_3, CH_2CL_2, 0 °C; (c) TsOH, benzene, reflux (51% for two steps). LiHMDS = lithium bis(trimethylsilyl)amide; TFPAA = trifluoroperacetic acid.

probably reflects significant strain associated with the γ-lactone in the context of this tetracyclic construct. In the event, treatment of **21** with mCPBA in CH_2Cl_2, followed by acid-catalyzed ring closure, provided ketols **20** as a 3:1 mixture favoring the desired α-diastereomer.[13] By performing the epoxidation in benzene, the ratio was increased to 7:1. However, the greatest success was realized through the use of trifluoroperacetic acid (TFPAA), which provided a 20:1 mixture of **20a**:**20b**. In this fashion, **20a** became available as a single isomer in 51% yield from **21**, following recrystallization (mp = 173 °C).

Ultimately, it would be our goal to incorporate and maintain the angular methoxy group prior to construction of the CDEF system. However, for the present, we undertook its installation *post facto*. *Given the strain of the γ-lactone discussed above, it was anticipated that installation of α,β-unsaturation would enable smooth Michael-type addition of MeOH*. In pursuing this conjecture, we attempted to generate the discrete enolate of TMS-protected lactone **22** (Scheme 5). Such efforts, instead, resulted in opening of the E ring

Scheme 5[a]



[a] (a) HMDS, imidazole, cat. TMSCl, CH_2Cl_2 (84%); (b) **20b**, TMSCl, THF, then LiHMDS, then NIS (86%; see ref 15); (c) DMDO, CH_2Cl_2 (71% + 17% recovered **23**); (d) Tf_2O, Hünig's base, CH_2Cl_2 (60%); (e) CSA, MeOH (88%); (f) LiI, THF, HOAc, reflux (55%). HMDS = 1,1,1,3,3,3-hexamethyldisilazane; Tf_2O = trifluoromethanesulfonic anhydride; CSA = camphorsulfonic acid.

via β-elimination. However, upon addition of LiHMDS to lactone **20** in the presence of TMSCl,[14] the corresponding silyl ketene acetal could be generated, as evidenced by its reaction with a number of trapping agents.

Among the electrophiles that reacted successfully with the presumed silyl ketene acetal was *N*-iodosuccinimide, which

(5) We could obtain analytically pure **10** in 10−20% yield after *quickly* passing the crude material through Florisil, or in up to 50−60% of less pure material by an aqueous wash of the crude reaction mixture. Disappointingly, attempted epoxidation led predominately to decomposition, providing only a trace of material with NMR and LRMS signals consistent with those of the desired α-hydroxyketone.

(6) Napolitano, E.; Spinelli, G.; Fiaschi, R.; Marsili, A. *Synthesis* **1985**, 38.

(7) Watanabe, M.; Morimoto, H.; Nogami, K.; Ijichi, S.; Furukawa, S. *Chem. Pharm. Bull.* **1993**, *41*, 968.

(8) While approach from the bottom face is significantly hindered by the lactone ring, epoxidation from the top face would provide the highly strained trans-fused 6:5 ring system. Additionally, π-overlap between the double bond and the proximal β-disposed ketone might have favored attack from the α-face: cf. Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1.

(9) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC-149057 (**20b**) and CCDC-149058 (**27**).

(10) For instance, epoxidation with trifluoroperacetic acid provided an approximately 1:1 ratio of **20a**:**20b**; however, the yield was low, presumably due to competing processes such as protonation of the enol ether and/or Baeyer−Villiger oxidation.

(11) As expected, density functional calculations (pBP/DN*) confirm that the desired **20a** is favored thermodynamically with respect to **20b** (3.1 kcal/mol). We thank Professor James Leighton for access to his SGI O2 running Spartan 5.1.2 to perform this analysis.

(12) For an excellent review of substrate-directed reactions in organic synthesis, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. Some years ago we made use of the sequence of ring opening of a lactone, hydroxyl-directed epoxidation, and re-lactonization in the total synthesis of vernolepin, see: (b) Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etheredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3028.

provided α-iodolactones **23** as a 2:1 mixture favoring **23a**.[15] The halogen had thus been preferentially introduced syn to the bridgehead proton by approach from the convex face of the lactone ring. This mixture of diastereomers was then treated with DMDO in an effort to initiate the syn elimination of a putative alkyl iodoso intermediate.[16] In the event, a single product identified as α-ketolactone **24** was isolated in 71% yield (along with 17% of recovered starting material). The formation of **24** can be viewed from the perspective of an iodoso Pummerer-like transformation.[17] Though not our intended target, the fortuitous generation of the α-keto lactone was used to advantage, commencing with its conversion to enol triflate **25**. As predicted (vide supra), in the presence of a catalytic amount of camphorsulfonic acid, **25** suffered smooth conjugate addition of methanol, giving rise to **26** as a single diastereomer (88% yield).[18] Finally, reductive removal of the α-triflate with lithium iodide under Fleet's conditions[19] provided the target system **27** in 55% yield. Assignment of the relative stereochemistry implied in structure **27** was subsequently corroborated by X-ray crystallography.[9]

In summary, we have reported herein the synthesis of the tricyclic DEF ring system of lactonamycin in the setting of a CDEF construct. The melding of this dense arrangement of functionality is surely a major issue in any projected total synthesis of lactonamycin. Central to the strategy followed here was the use of an intramolecular Wessely oxidation and subsequent hydroxyl-directed epoxidation of enol ether **21**. The application of these lessons to the larger total synthesis problem is a matter of continuing interest.

Acknowledgment. This work was supported by the National Institutes of Health (HL25848). C.C. gratefully acknowledges the NIH for support in the form of a Postdoctoral Fellowship (F32 CA84758). The authors thank Mr. David Churchill and Prof. Ged Parkin of Columbia University for solving the X-ray structures of **20b** and **27** and Ms. Sachiyo Nomura for high-resolution mass spectral analyses.

Supporting Information Available: Experimental procedures and full characterization data for **13**−**27**. This information is available free of charge via the Internet at http://pubs.acs.org.

OL006531+

(13) Lactones **20a**,**b** were isolated as their *m*-chlorobenzoate esters when formed through the action of mCPBA. This is most likely a result of the highly nucleophilic benzoic acid byproduct adding to the carbon containing the methoxy ether with simultaneous opening of the epoxide, followed by intramolecular acyl transfer. An analogous acyl transfer, albeit under acidic conditions, is seen in Kishi's synthesis of tetrodotoxin; see: (a) Kishi, Y.; Aratani, M.; Fukuyama, T.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9217. For acyl transfer from the epoxidation of silyl enol ethers, see: (b) Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K., Jr.; Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1978**, 4603. (c) Jefford, C. W.; Rimbault, C. G. *J. Am. Chem. Soc.* **1978**, *100*, 6437.

(14) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, 495.

(15) Although analysis of the crude reaction indicated that the product initially contained a > 5:1 mixture favoring the syn diastereomer (**23a**), equilibration occurred upon chromatography such that the isolated product was a 2:1 mixture favoring the syn isomer. The assignment of the major isomer as the syn compound was based on the lack of *J*-coupling between the adjacent protons on the lactone ring, whereas the minor component exhibited $J = 6.5$ Hz.

(16) (a) Reich, H. J.; Peake, S. L. *J. Am. Chem. Soc.* **1978**, *100*, 4888. Fuchs has recently re-awakened interest in this seldom used transformation: (b) Kim, S.; Fuchs, P. L. *Tetrahedron Lett.* **1994**, 7163. (c) Mahadevan, A.; Fuchs, P. L. *J. Am. Chem. Soc.* **1995**, *117*, 3272.

(17) A number of other mechanisms can be envisioned for this transformation, including one which proceeds by an initial syn-elimination, followed by epoxidation of the highly strained double bond with subsequent rearrangement (see, for example, Murray, R. W.; Shiang, D. L.; Singh, M. *J. Org. Chem.* **1991**, *56*, 3677). Alternatively, a more simplistic explanation would include tautomerization of the proposed iodoso intermediate (to form the iodo-analogue of an oxime), followed by hydrolysis.

(18) The stereochemistry at the lactone α-carbon was not determined.

(19) Elliott, R. P.; Fleet, G. W. J.; Gyoung, Y. S.; Ramsden, N. G.; Smith, C. *Tetrahedron Lett.* **1990**, 3785.