ORGANIC LETTERS

2011
Vol. 13, No. 17
4592–4595

Accessing the Structural Diversity of Pyridone Alkaloids: Concise Total Synthesis of *Rac*-Citridone A

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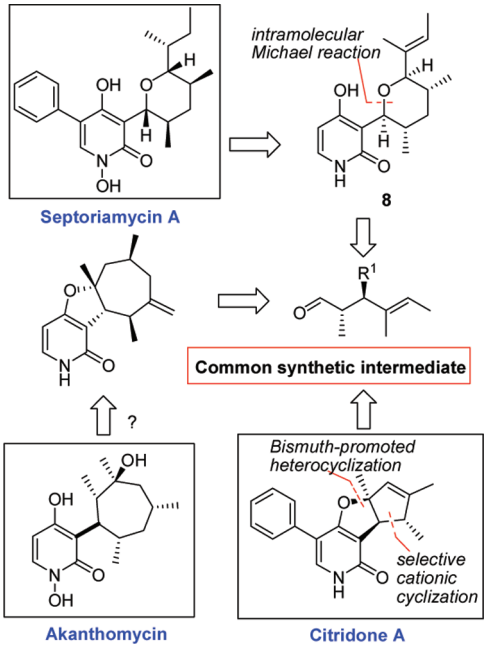
Received July 4, 2011

ABSTRACT



A unique route to the structural diversity of pyridone alkaloids is described based on the concept of a common synthetic strategy. Three different core structure analogues corresponding to akanthomycin, septoriamycin A, and citridone A have been prepared by using a highly selective and novel carbocyclization reaction.

4-Hydroxy-2-pyridone alkaloids constitute a family of natural products that is extremely wealthy in diverse biological activity and pharmaceutical applications.[1] Despite the increasing knowledge provided by the large number of isolated compounds of their family, numerous unanswered questions remain concerning their biosynthesis, unknown congeners, and most importantly their biological targets.

Seeking to uncover missing biosynthetic links between apparently unrelated natural compounds, our interest focused on three pyridone alkaloids, namely akanthomycin, citridone A, and septoriamycin A.[2]

Akanthomycin (**1**) was isolated from the entomopathogenic fungus *Akanthomyces gracilis* ARS 2910 as a mixture of atropoisomers with restricted rotation around the C-6−C-7 bond.[3] Biosynthetic akanthomycin is believed to derive from cordypyridone A−B atropoisomers (**2**)

(1) Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010**, *27*, 1168–1185.

(2) Since there is no name assigned in the literature until now, compound **4** was named septoriamycin A for purpose of clarity: Kumarihamy, M.; Fronczek, F. R.; Ferreira, D.; Jacob, M.; Khan, S. I.; Nanayakkara, N. P. D. *J. Nat. Prod.* **2010**, *73*, 1250–1253.

(3) Wagenaar, M. M.; Gibson, D. M.; Clardy, J. *Org. Lett.* **2002**, *4*, 671–673.

10.1021/ol2017802
Published on Web 08/05/2011

through a cationic ring expansion, which along with cordypyridone C (**3**) represents its hexacyclic congener, isolated from pathogenic fungus *Cordyceps nipponica* BCC 1389.[3,4]

Septoriamycin A (**4**) was isolated from a culture medium of *Septoria pistaciarum*.[2] It possesses moderate activity against both methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureous*, antimalarial activity against chloroquine-sensitive, and chloroquine resistant strains of *Plasmodium falciparum* as well as cytotoxic activity against *Vero* cells.

Interestingly, the structurally unrelated compound citridone A (**5**) can also be envisioned to derive from a potential synthetic precursor of akanthomycin or septoriamycin prior to its carbocyclization. Citridone A is produced by *Penicillium sp*. FKI-1938 and was found to possess miconazole activity against *Candida albicans*.[5]

The rich biological profile of **1**, **4**, and **5** along with their highly functionalized carbocyclic structures led us to investigate a potentially unified strategy to access the presented molecular diversity. Thus, compounds **1**, **4**, and **5** were envisioned to derive from common synthetic intermediates **6** and **7** as shown in retrosynthetic Figure 1.

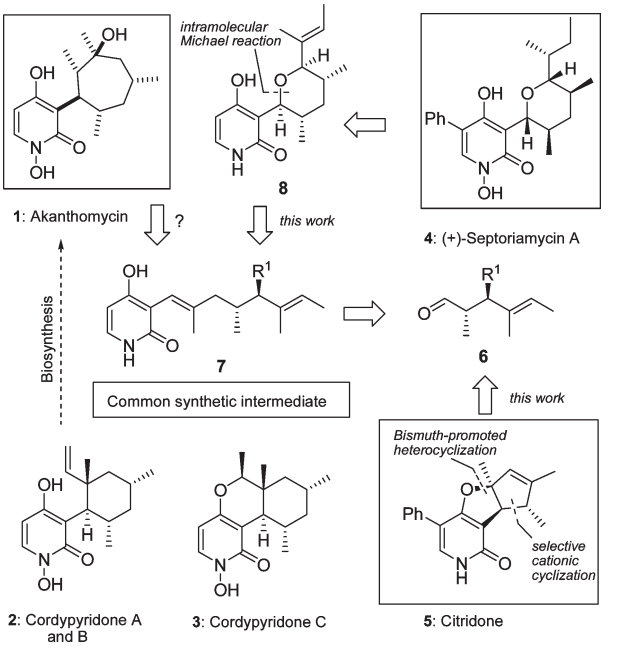


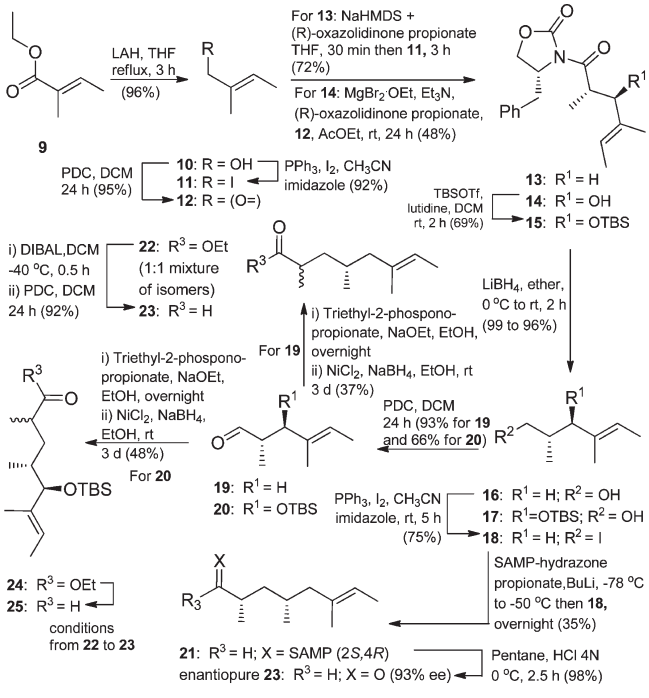
Figure 1. Selected pyridone natural products and disconnection of their molecular complexity to common synthetic intermediate **7**.

In this communication, we report the convergent route to three highly substituted pyridone-2 structures, representing the cores for akanthomycin, citridone A, and septoriamycin A natural compounds, from a common synthetic strategy.

Despite the interesting biological profiles of these alkaloids, only the synthesis of citridone A has been recently reported. This total synthesis consists of 24 steps and has an overall yield of 3.2%, indicating the difficulty of the synthetic task.[6] Meanwhile, in an elegant study by Snider, a biomimetic approach of Knoevenagel-Diels–Alder sequence was used to construct several members of pyridone alkaloids, including pyridoxatin, leporin, and analogues.[7] Although his strategy surely follows our logic of disconnection, it fails to give any result in the case of the cordypyridones and akanthomycin cores. On the other hand a different strategy was used by the Williams group to approach 3-alkoxy pyridones, funicolosin and sambutoxin, based on the late formation of the pyridone core.[8] Recently, Jones et al. also reported a well-designed synthesis of cordypyridones A and B and their epimers, but yet without answering if the biosynthetic hypothesis correlating cordypyridones and akanthomycin is correct.[9]

Our synthetic plan commenced with the construction of the requisite advance intermediate **26** (Scheme 2), starting from ethyl tiglate **9**. As shown in Scheme 1, reduction of **9** with LAH provided us with alcohol **10**, which was either iodinated following a known protocol[10] or oxidized with PDC to give compounds **11** and **12** respectively. Reaction of **11** was achieved using the Evans reaction[11] with (*R*)-4-benzyl-3-propionyloxazolidin-2-one[12] under standard basic

Scheme 1. Synthesis of Polypropionate Intermediates **23** and **25**



(4) Isaka, M.; Tanticharoen, M. *J. Org. Chem.* **2001**, *66*, 4803–4808.
(5) Fukuda, T.; Tomoda, H.; Omura, S. *J. Antibiot.* **2005**, *58*, 315–321.
(6) Miyagaya, T.; Nagai, K.; Yamada, A.; Sugihara, Y.; Fukuda, T.; Fukuda, T.; Uchida, R.; Tomoda, H.; Omura, S.; Nagamitsu, T. *Org. Lett.* **2011**, *13*, 1158–1161.
(7) (a) Snider, B. B.; Lu, Q. *J. Org. Chem.* **1994**, *59*, 8065–8070. (b) Snider, B. B. *Synth. Commun.* **2001**, *31*, 2667–2679. (c) Snider, B. B.; Lu, Q. *Tetrahedron Lett.* **1994**, *35*, 531–534. (d) Snider, B. B.; Lu, Q. *J. Org. Chem.* **1996**, *61*, 2839–2844.
(8) (a) Williams, D. R.; Lowder, P. D.; Gu, Y. –G. *Tetrahedron Lett.* **1997**, *38*, 327–330. (b) Williams, D. R.; Turske, R. A. *Org. Lett.* **2000**, *2*, 3217–3220.
(9) Jones, I. L.; Moore, F. K.; Chai, C. L. L. *Org. Lett.* **2009**, *11*, 5526–5529.

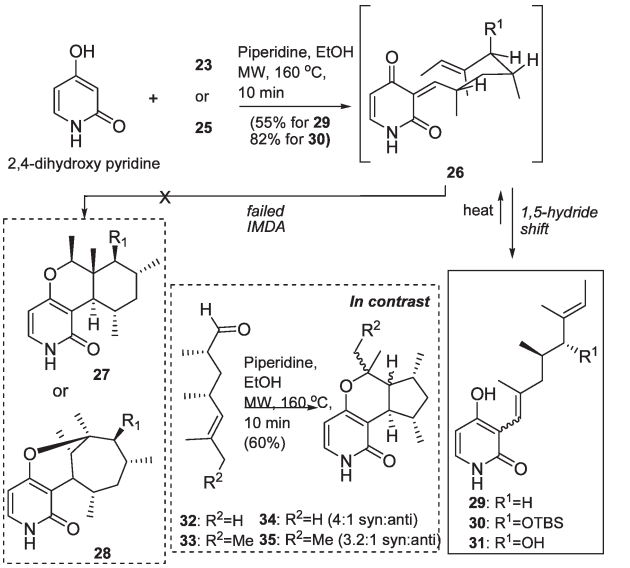
conditions providing the enantiopure compound **13** in 72% yield. An alternative procedure utilizing of $MgBr_2 \cdot OEt$ was used to synthesize *anti*-compound **14** in excellent diastereoselectivity (dr = 28:1).[13] Compound **14** was protected with TBS-group and then both **13** and **15** were reduced to **16** and **17** respectively using lithium borohydride. Iodination of alcohol **16** followed by SAMP-hydrazone[14] alkylation and subsequent acid catalyzed hydrolysis led to the enantioselective construction of (2*S*,4*R*) aldehyde **23** in moderate yield but in high enantioselectivity (93% ee).

Several conditions were tried to couple (2*S*,4*R*) aldehyde **23** to 2,4-dihydroxy pyridine, without any success, due to the epimerization of the sensitive α-positioned methyl group. This setback led us to modify our strategy to target the more easily accessible α-methyl diasteromeric mixture of **23** as the coupling partner of the 2,4-dihydroxy pyridine compound. As a result, oxidation of **16** and **17** to **19** and **20**, respectively, followed by Horner–Emmons reaction with triethyl-2-phosphonopropionate afforded the desired alkenes,[15] which were selectively reduced to **22** and **24** by using nickel chloride and sodium borohydride.[16] Further reduction using DIBAL gave the monounsaturated alcohols, which were directly oxidized to the desired diastereomeric aldehydes **23** and **25** by PDC oxidation.

The best conditions found for the coupling reaction between 2,4-dihydroxy pyridine and **23** or **25** involved heating both components using microwave irradiation in the presence of piperidine as a base at 160 °C for 10 min as shown in Scheme 2. Under these conditions none of the cyclized products **27** and **28** were obtained, as reported for the total synthesis of pyridoxatin and leporin.[7] Instead, the only isolable products were diasteroisomeric mixtures of compounds **29** and **30** along with unreacted 2,4-dihydroxy pyridine and dimerized products.[17]

In an effort to explain the inability of aldehyde **23** to undergo an intramolecular Diels–Alder reaction, we prepared aldehydes **32** and **33**.[18] Interestingly, these compounds reacted cleanly to give cyclized products **34** and **35** in a 4:1 and 3.2:1 *syn:anti* mixture of diastereoisomers. On the basis of these results, we assumed that the steric constraints imposed by intermediate **26** play the most important role in its inability to undergo an intramolecular Diels–Alder reaction.

Scheme 2. Synthesis of Advanced Intermediates **29**–**31** and Failed Plan to Synthesize Key Products **27** and **28**



With compounds **29** and **30** in hand, the stage was set for developing appropriate selective C–C reactions in order to access the structural diversity of the pyridone family. In the beginning, we tested the possibility of an inverse 1,5-hydride shift that would lead to the key intermediate quinone **26** which, probably under different reaction conditions, may lead to **27** or **28**. Interestingly, when compound **29** was heated at 160 °C for several hours in the presence or absence of base, only a dimeric pyridone compound[19] was isolated along with extented decomposed byproducts.

Our explanation for the latter was a retro-Knoevenagel reaction leading to an excess of 2,4-dihydroxy pyridine in the reaction solution. A closer look reveals a retro-1,5-hydride shift to form intermediate **26**, which then reacted with the formed 2,4-dihydroxy pyridine.

We hypothesized that this process could be advantageous if an internal nucleophile was used to capture the formed intermediate. Thus, when compound **31** was heated to 110 °C for 2 days in benzene, compound **37** was isolated as a sole product in 66% yield (Scheme 3). Compound **37** represents the core structure of septoriamycin A.

After extended experimentation it was found that compound **30**, bearing the protected hydroxy group can also be

(10) Boeckman, K., Jr.; Pero, J. E.; Boehmler, D. J. *J. Am. Chem. Soc.* **2006**, *128*, 11032–11033.

(11) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313.

(12) Cage, J. R.; Evans, D. A. *Org. Syn.* **1990**, *68*, 83–85.

(13) (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393. (b) Diastereomeric ratio determined by GLC. (c) For reason of comparison, *syn*-aldol products have also been obtained by reacting aldehyde **12** with (*R*)-oxazolidinone propionate and dibutylborontriflate. See Supporting Information for spectral data.

(14) SAMP (*S*-1-amino-2(methoxymethyl)pyrrolidine: Enders, D.; Nübling, C.; Schubert, H. *Liebigs Ann.* **1997**, 1089–1100.

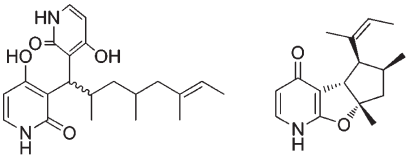
(15) A 1.5:1 *E*,*Z* mixture of alkenes was obtained from compound **19** in contrast with the *E*-selective formation when compound **20** was used. See Supporting Information for more details.

(16) Several other conditions were tried leading either to isomerization of the remaining double bond or to unreacted starting material. Nickel chloride and sodium borohydride reduction according to: Hanessian, S.; Grillo, A. T. *J. Org. Chem.* **1998**, *63*, 1049–1057.

(17) Several conditions concerning different bases or acids were examined under various temperatures. The same products were always obtained varying from 30 to 55% yield. Heating under regular conditions provided extented decomposition.

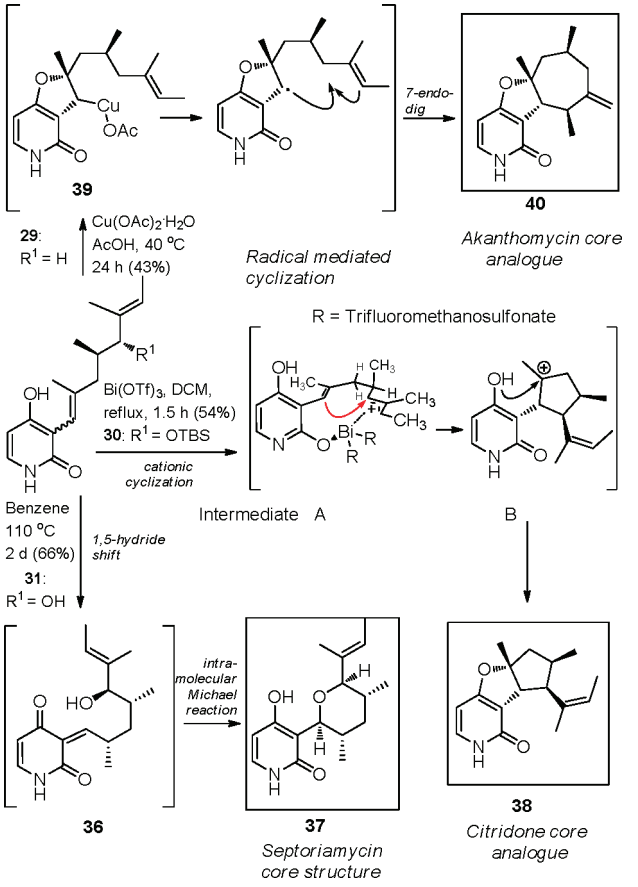
(18) For more experimental details, please see the Supporting Information provided.

(19) The isolation of dimeric product **44** was persistent in every conditions used in the coupling reaction.



44 **45**

Scheme 3. Core Structure Synthesis of Septoriamycin and Analogues of Citridone and Akanthomycin



cyclized to the different carbocyclic core **38** when treated with the appropriate Lewis acids. Bismuth triflate was the reagent of choice to avoid decomposition, providing **38** in 54% yield.[20] The mechanism is believed to incorporate a cycloisomerization reaction triggered by the formation of a bismuth−amide complex (intermediate A), which activates the distal allylic acetate position. Internal etherification quenches the formed cation to produce compound **38**.[21]

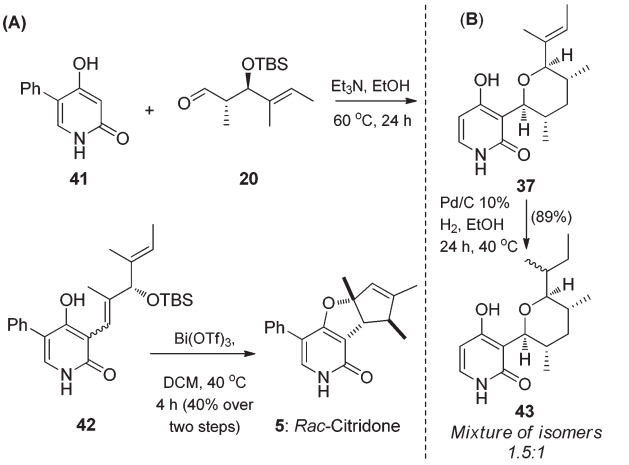
Meanwhile, when compound **29**, bearing no substituent (R^1 = H), was reacted with bismuth triflate, no reaction was observed. The use of copper(II) acetate instead, however, promoted a completely different pathway leading this time to what we believe to be a radical 7-*endo-dig* reaction forming compound **40**, which represents a close related analogue of akanthomycin natural product.

Consequently, by modifying the reaction conditions, advanced intermediate compounds **29**−**31** can generate highly diversified building blocks that are closely related to natural substances. These building blocks can be easily transformed either to a plethora of "privileged structures" or to the corresponding natural compounds. As an example of such modification, the dephenyl analogue of septoriamycin A and the total synthesis citridone A are presented (Scheme 4).

Compound **37** was hydrogenated with 10% Pd/C to provide compound **43** as a 1.5:1 mixture of isomers with the major component being the one possessing the wrong stereochemistry with respect to the natural compound.

Finally, the developed methodology using bismuth triflate can easily be modified leading to citridone A. The use of aldehyde **20** in coupling with 4-hydroxy-5-phenyl pyridone-2[22] provides a complex mixture of isomers **42**. Subsequent treatment with bismuth triflate promotes the carbocyclization providing citridone A in 40% yield.

Scheme 4. (A) Completion of the Total Synthesis for rac-Citridone A (**5**) and (B) Core Structure Synthesis of Septoriamycin A **43**



In summary, we have described a unique route to the structural diversity presented in pyridone alkaloids by using the concept of common synthetic intermediates. The success of this process depended on the development of (a) a highly selective C−C bond formation using a novel bismuth promoted cationic etherocarbocyclization reaction, (b) a copper mediated etherocarbocyclization, and (c) a unique intramolecular Michael reaction to tetrahydro-pyrane core of septoriamycin. The total synthesis of citridone A was also presented as evidence of the practicality of the described method in providing readily biologically active scaffolds.

A large array of natural and synthetic compounds were prepared using these concepts and are currently being tested for their biological profile. These results will be published in due course.

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

(20) Isomeric compound **45** (aprox. 12%) was isolated from the reaction mixture. Lewis-acid is crucial on the amound of **38** formed. When indium (III) chloride is used, **45** was isolated as the major product in 42% yield.

(21) The described reaction is highly stereoselective. A test reaction using an eight compound diastereomeric mixture led only to the described compound.

(22) 5-Phenyl-4-hydroxy pyridone-2 was prepared according to previously described method, see ref 7d.