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Synthesis of the Louisianin Alkaloid Family via a 1,2,4-Triazine Inverse-Electron-Demand Diels−Alder Approach

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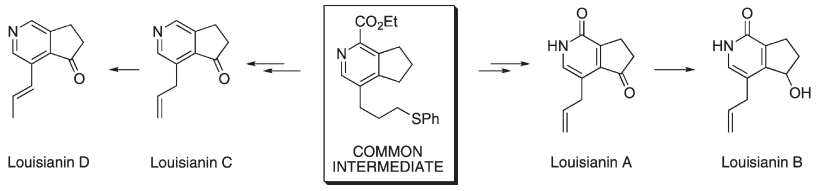

Isolated in 1995, the four members of the louisianin family (A, B, C and D) are simple pyridine and 2-pyridone alkaloids that display both antibacterial and anticancer activity. Herein we describe the synthesis of all four members of the louisianin family, from a conveniently prepared 1,2,4-triazine and via a common tetrasubstituted pyridine intermediate. This study includes the synthesis of louisianin B in both racemic form and as the (−)-enantiomer.

Introduction

Pyridines and pyridones are ubiquitous compounds in nature and privileged structures in medicinal chemistry and agrochemistry. For example, the common drugs Atazanavir (Bristol-Myers-Squibb, antiretroviral HIV)[1] and Esomeprazole (AstraZeneca, proton pump inhibitor)[2] and the pesticide Imidacloprid (Baeyer)[3] all feature pyridine cores in various forms. Pyridine alkaloids also represent a huge class of natural products encompassing many structures, from the relatively simple epibatidine[4] to the complex cyclothiazamycin B1.[5] Moreover, the utility of pyridines as building blocks for supramolecular chemistry[6] and as ligands for organometallic chemistry has been amply demonstrated.[7]

The importance of the pyridine core has led to the development of many synthetic approaches to pyridines (and dihydropyridines).[8] Classically, pyridines have been prepared via condensation reactions as exemplified by the well-known Hantzsch synthesis of dihydropyridines from 1,5-dicarbonyl compounds and ammonia.[9] Other important condensation approaches to pyridines include the Bohlmann−Rahtz reaction[10] (recently expanded by Bagley and co-workers[11]) and the Kröhnke reaction.[12] More contemporary approaches to pyridines have also been described. The [2 + 2 + 2]-cobalt-catalyzed cycloaddition of 2 equiv of alkyne with a nitrile developed by Bönnenmann and Vollhardt has proved useful,[13] especially when used in an intramolecular context.[14]

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(9) Phillips, A. P. *J. Am. Chem. Soc.* **1949**, *71*, 4003.

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(11) See, for example: (a) Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459. (b) Bagley, M. C.; Chapaneri, K.; Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.* **2005**, *70*, 1389.

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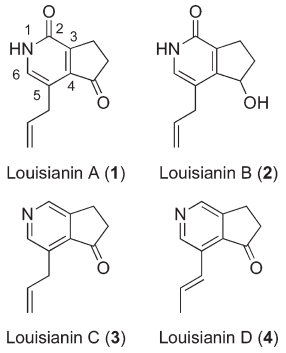
Recently, [4 + 2]-cycloadditions have also been popularized for the synthesis of pyridines. For example, Ghosez and co-workers[15] and Moody and co-workers[16] have demonstrated the use of an inverse-electron-demand hetero-Diels−Alder sequence involving aza-dienes and alkynes to afford either pyridines or pyridones depending upon the constitution of the aza-diene. Furthermore, the use of triazines as masked aza-dienes in [4 + 2]-inverse-electron-demand Diels−Alder (IED-DA) reaction sequences has been successfully exploited (vide infra).

CHART 1



Isolated in 1995 by Omura and co-workers[17,18] from the cultured broth of *Streptomyces* sp. WK-4028 obtained from a soil sample collected in Louisiana, the louisianins A−D (Chart 1, **1**−**4**) are a family of simple pyridine and pyridone alkaloids. A common core structure with a cyclopentane ring fused to a pyridine in the C3−C4 position is present in all of the family members. The most notable difference between the family members is the oxidation level at the C-2 position. Whereas louisianins C and D are pyridines, louisianins A and B are 2-pyridones. Other differences can be found in either the C-5 substituent [louisianin D (**4**) contains a 1-propenyl group rather than the allyl group present in the other three members] or the oxidation level of the C-4 benzylic position [louisianin B (**2**) contains a secondary alcohol whereas the other three members exist as ketones]. It is noteworthy that the stereochemistry of the secondary alcohol center in louisianin B was not reported by Omura and co-workers and thus remains undefined. Though the biological properties of the louisianins have been explored only in an initial screening, some interesting biological properties have been identified. For instance, louisianin A proved to be a potent inhibitor of testosterone-responsive carcinoma SC115, while louisianins C and D were potent suppressors of cultured vascular endothelial cells.[17]

To date, there have been five reports on the synthesis of members of the louisianin family, including our own previous communication on the synthesis of louisianins C and D.[19] Prior to any total syntheses, as part of the structural elucidation studies in 1997, Omura and co-workers[20] described the chemical interconversion of natural louisianin A to louisianin C (and then subsequently into louisianin D). A reaction sequence involving formation of the chloropyridine from the pyridone (with phosphorus oxychloride) and chloride reduction (with zinc/hydrochloric acid) afforded louisianin C, and then isomerization of the allyl group in louisianin C to the 1-propenyl group of louisianin D was accomplished with DBU. However, it was not until 2003 that Kelly and co-workers described the first total synthesis of one of the family members, louisianin C (**3**).[21] Their nine-step (11% overall yield) synthesis featured a key intramolecular, fluoride-induced silylpyridine to aldehyde cyclization to form the cyclopentane ring. Subsequently, in 2006, Chang and co-workers reported the first total synthesis of louisianin A (**1**) in seven steps (24% overall yield).[22] In a manner similar to that for the Kelly route, annulation of the cyclopentane ring was achieved at a late stage of the synthesis via a Dieckmann−Thorpe cyclization. A recent publication from Chang and co-workers extended this Dieckmann−Thorpe cyclization approach to the synthesis of louisianins C and D[23] and utilized an orthogonal cross-coupling strategy to install either the C-5 allyl or 1-propenyl group of louisianins C and D, respectively, without recourse to an isomerization step; this enabled both louisianins C and D to be prepared in 22% and 20% yield, respectively, for the seven overall steps. These first three approaches, from different commercially available pyridines, are characterized by a stepwise synthesis featuring a late-stage annulation. An alternative approach was conceived by Chen and co-workers in which an early stage [3 + 3]-annulation of ethyl cyclopentene-1-carboxylate was used to construct an aza-bicyclic system which ultimately gave louisianin D in 10 steps (20% overall yield).[24] It is noteworthy that, to date, louisianins A, C, and D have all been prepared, but there are no literature reports concerning the synthesis of louisianin B.

In contrast to the other reported approaches, our synthetic route to the louisianins is based upon the use of 1,2,4-triazines as suitable aza-dienes for construction of the pyridine core via [4 + 2]-cycloaddition chemistry. 1,2,4-Triazines[25,26] have been known since the initial report of Bischler in 1889,[27] and although some natural products featuring this template are known,[25] such compounds generally represented chemical curiosities until the realization that they were capable electron-deficient dienes in Diels−Alder chemistry (with electron-rich olefins). Though the first report of

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(17) Isolation and biological properties: Komiyama, K.; Takamatsu, S.; Kim, Y. P.; Matsumoto, A.; Takahashi, Y.; Hayashi, M.; Woodruff, H. B.; Omura, S. *J. Antibiot*. **1995**, *48*, 1086.
(18) Physiochemical properties and characterization data: Takamatsu, S.; Kim, Y. P.; Hayashi, M.; Furuhata, K.; Takayanagi, H.; Komiyama, K.; Woodruff, H. B.; Omura, S. *J. Antibiot*. **1995**, *48*, 1090.
(19) Catozzi, N.; Wasnaire, P.; Taylor, R. J. K. *Tetrahedron Lett*. **2008**, *49*, 2865.
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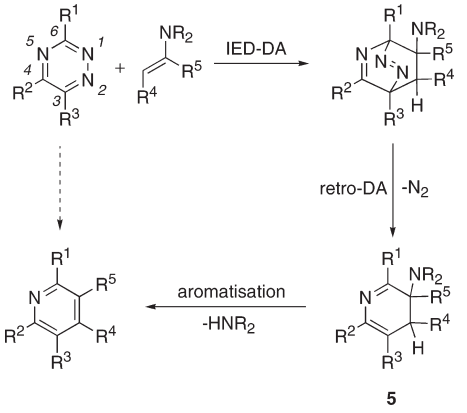
an IED-DA with a 1,2,4-triazine, to afford pyridines and dihydropyridines, was described by Neunhöffer and Frühauf in 1969,[28] this chemistry was plagued by dubious regioselectivity and modest yields. However, the rigorous study of Boger and Panek established that the reaction of pyrrolidine enamines with triazines provides an efficient and regioselective route to pyridines and dihydropyridines via reaction across the C3−C6 diene (Scheme 1).[29] Boger and co-workers also showed that the enamines required can be conveniently prepared in situ from the desired amine and ketone substrate. Further work established robust procedures for the synthesis of 1,2,4-triazines and utilized these IED-DA reactions with electron-rich olefins in natural product synthesis.[30,31]

SCHEME 1



We investigated the use of the triazine IED-DA chemistry methodology to prepare highly substituted pyridines but noticed a reluctance of the elimination/aromatization to proceed, and aminodihydropyridines **5** were obtained. A tethered imine−enamine approach was therefore developed in which a secondary amine linked to a primary amine via a two-carbon spacer provides an imine−enamine **6** when treated with the requisite ketone. Upon completion of the IED-DA/retro-DA sequence, the resulting dihydropyran contains a second basic center which facilitates the required elimination/aromatization (Scheme 2, eq a).[32] Further studies into the development of a one-pot pyridine synthesis resulted in the identification of a rapid, solvent-free, microwave-mediated variant of the Boger reaction (Scheme 2, eq b).[33] More recently, we have also disclosed a more practical procedure which utilizes a silica-mediated aromatization/elimination protocol (Scheme 2, eq c).[34] These studies prompted our interest in the application of this triazine methodology to natural product targets. First, it was realized that the dihydropyridine **5** produced from the initial IED-DA reaction could function as an aza-diene for a second IED-DA reaction producing complex tetracycles.[35] Second, we became

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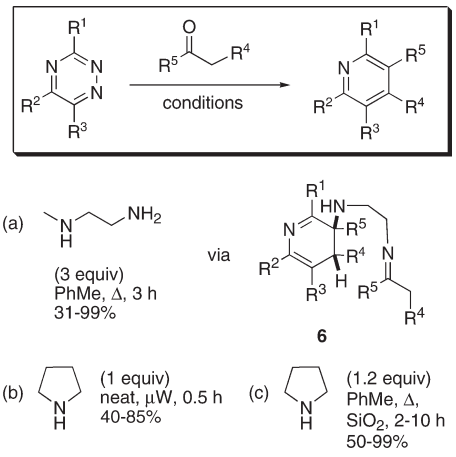
SCHEME 2



interested in the preparation of the louisianin family of alkaloids. The synthesis of louisianins C and D was reported in a prior communication.[19] Herein we present our full findings on the preparation of all four members of the louisianin family by a unified synthetic approach.

Results and Discussion

Retrosynthesis. We envisaged that the preparation of all four of the louisianin family members could be achieved from a single suitably functionalized intermediate; this led us to the retrosynthetic analysis illustrated in Scheme 3. The key intermediate in such a plan would be the tetrasubstituted pyridine ester **9**. Ester **9** has the potential to undergo both reductive transformation (toward louisianins C and D) and oxidative transformation (toward louisianins A and B). Thus, it was postulated that the ester group of pyridine **9** could undergo hydrolysis and subsequent decarboxylation to afford the reduced pyridine **8**, the intermediate necessary to synthesize louisianins A and B. Conversely, it seemed likely that oxidative transformation of the ester group via one of several potential methods (Dakin oxidation,[36] Baeyer−Villiger oxidation,[36] or carboxy inversion[37]) would give rise to the pyridone oxidation level necessary to prepare louisianins A and B via pyridone **7**. A series of common steps would then lead to the natural products. First, the key oxygenation in the C-4 benzylic position was to be achieved via the anionic oxidation method of Chen,[24] and then the allyl group was to be revealed via sulfide oxidation/elimination. The final steps would then be standard oxidation and/or isomerization steps. We anticipated that the required tetrasubstituted pyridine **9** could be prepared via the IED-DA/retro-Diels−Alder/elimination reaction between 3,6-substituted-1,2,4-triazine **10** and the enamine derived from cyclopentanone and pyrrolidine; this required the preparation of 1,2,4-triazine **10**, which we anticipated should arise via the oxidative cyclocondensation of the novel α-hydroxyketone **12** and amidrazone **11**.[31]

Preparation of 1,2,4-Triazine 10 and Tetrasubstituted Pyridine 9. In order to construct triazine **10**, the α-hydroxy ketone **12** was required; the two-step preparation of this fragment is illustrated in Scheme 4. Ultimately, the preparation of **12**

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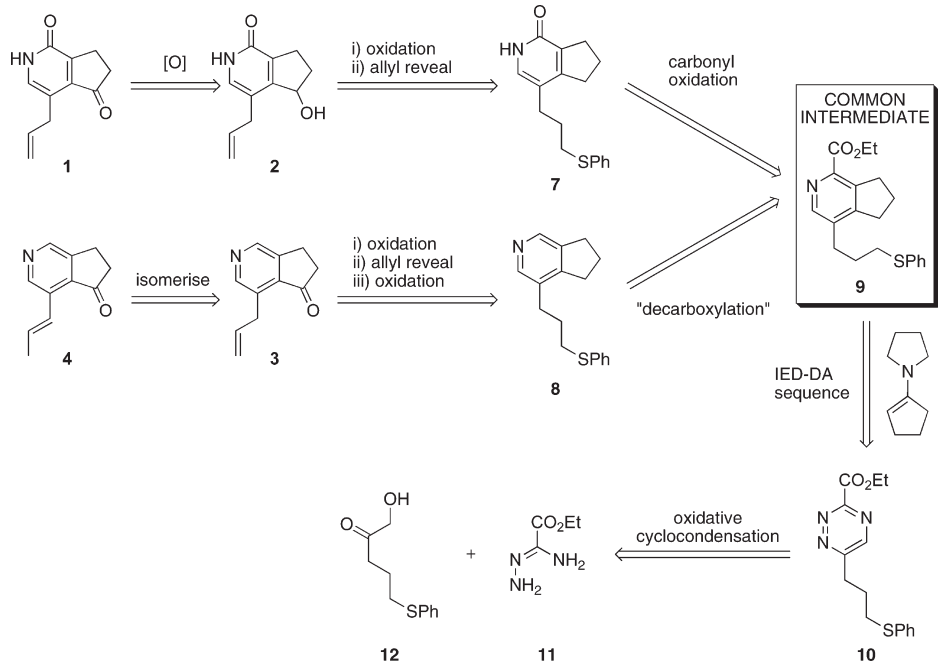
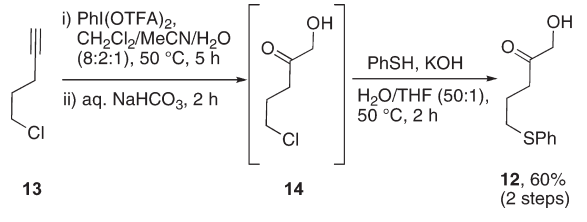
(37) Denney, D. B.; Sherman, N. *J. Org. Chem.* **1965**, *30*, 3760.

SCHEME 3



was achieved via an alkyne oxidation and subsequent substitution reaction; however, the preparation of the desired α-hydroxy-γ′-haloketone proved to be nontrivial. Although many methods are known for the preparation of α-hydroxyketones, including the bis(trifluoroacetoxy)iodobenzene (PIFA) oxidation of methyl ketones[38] and the Rubottom oxidation of silyl enol ethers,[39] the ready availability of 5-bromopentene and 5-chloropentyne suggested the oxidation of either of these precursors. Both the RuO_4-[40] and $KMnO_4$-promoted[41] oxidations of alkenes have been reported in the literature for the convenient preparation of α-hydroxy ketones. Unfortunately, application of either method to the oxidation of 5-bromopentene proved unsuccessful, and the rapid formation of considerable amounts of polymeric material was observed. In contrast, the hypervalent iodine (PIFA)-promoted oxidation of 5-chloropentyne **13** under the conditions reported by Tamura and co-workers[42] afforded α-hydroxy-γ′-chloroketone **14**. It is noteworthy that an aqueous bicarbonate quench was required to hydrolyze the large proportion of the trifluoroacetate ester formed during the reaction; the method described by the authors of passing the material through silica gel had no effect. Chloride **14** proved somewhat unstable, and any attempts at purification resulted in a substantial loss of material. Given the presence of an electrophile and nucleophile in the same molecule, this is, perhaps, unsurprising! However, chloride **14**, without purification, could be readily subjected to an S_N2 displacement with potassium thiophenolate. This reaction readily proceeded in a straightforward fashion in aqueous solution to afford the desired α-hydroxyketone **12** in a 60% yield over the two steps.

SCHEME 4



With α-hydroxyketone **12** in hand, we were then able to examine the preparation of the 3,6-disubstituted 1,2,4-triazine **10**. In order to obtain the required triazine regioisomer (i.e., the desired 3,6-regioisomer vs the alternative 3,5-regioisomer), the triazine construction had to be carried out sequentially with the initial formation of amidrazone hydrazone **15** followed by oxidative cyclocondensation (Scheme 5).[43] Thus, amidrazone **11** (prepared according to the procedure of Boger and Panek)[31] and α-hydroxyketone **12** were condensed in ethanolic solution to afford the desired hydrazone **15**. Compound **15** could be isolated and purified, in 62% yield, as a 3:2 mixture of isomers (presumably isomeric around the N−N bond), which rapidly interconvert in solution. However, the polarity of this compound made it more convenient to telescope the condensation with the subsequent oxidative cyclocondensation. Toward this goal, hydrazone **15** was heated in toluene solution in the presence of 10 equiv of MnO_2 to afford the desired triazine **10** in 75% optimal yield over the two steps. The regioselective nature of this two-step process is noteworthy; none of the

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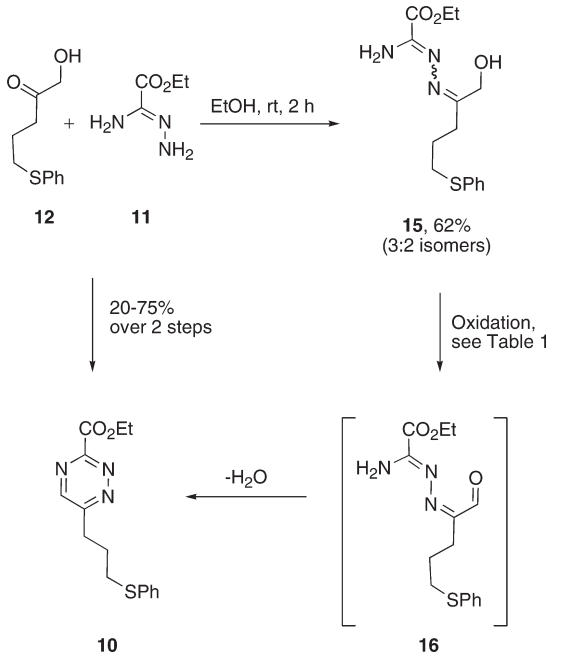
(43) Laphookhieo, S.; Jones, S.; Raw, S. A.; Sainz, Y. F.; Taylor, R. J. K. *Tetrahedron Lett.* **2006**, *47*, 3865.

SCHEME 5



alternative 3,5-disubstituted 1,2,4-triazine regioisomer was obtained. To our disappointment, however, the MnO_2 reaction proved to be capricious, and considerable variability was observed in the yields obtained (20−75% yield). One possible explanation for this is that MnO_2 may oxidatively decompose hydrazone **15** (or amidrazone **11** present in equilibrium).[44]

Thus, we turned our attention to the development of a more robust tandem oxidation−cyclization procedure and examined the use of other oxidants (Table 1). Somewhat surprisingly, common oxidants such as PDC and TPAP led only to decomposition of the starting material (entries 2 and 3). Alternatively, the metal-catalyzed aerobic oxidations, e.g., $RuCl_2(PPh_3)_3$, that we have previously used in tandem oxidation/heterocycle formation chemistry[45] returned only starting material (entry 4). Although both the Dess−Martin periodinane and Parikh−Doering oxidation cleanly afforded triazine **10** (entries 5 and 6), Parikh−Doering oxidation proved to be the method of choice because of the superior yields obtained (reproducibly > 50%). Of interest was the identification of some of the intermediate aldehyde **16** in the reaction mixture; from the unpurified reaction mixture, a ratio of 4:1 triazine/aldehyde was observed. However, although a small amount of the aldehyde (4%) could be isolated from the reaction mixture, the majority of the product was the cyclized triazine **10**. This presumably indicates that a mild source of acid is sufficient to catalyze cyclocondensation; indeed standing aldehyde **16** in $CDCl_3$ led to the formation of triazine **10**. With this in mind, the Pfitzner−Moffat oxidation[46] of hydrazone **15** was examined, with the view that the acidic reaction conditions would favor the complete formation of

(44) We have previously observed that this is a problem in tandem triazine-forming reactions under microwave heating (ref 43).
(45) Robinson, R. S.; Taylor, R. J. K. *Synlett* **2005**, 1003.
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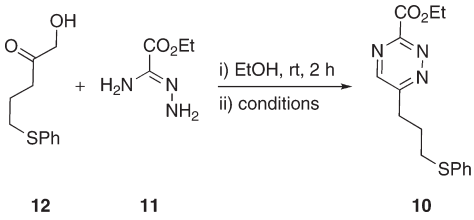
TABLE 1. Oxidative Cyclocondensation



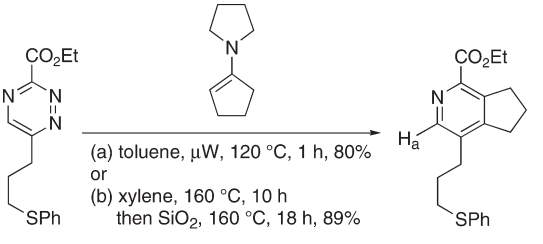
entry	conditions	yield, %[a]
1	MnO_2, PhMe, Δ	20−75
2	PDC, CH_2Cl_2, rt	0[b]
3	TPAP, NMO, CH_2Cl_2, rt	0[b]
4	$RuCl_2(Ph_3P)_3$, TEMPO, 4 Å ms, MeCN, O_2, Δ	0[c]
5	DMP, CH_2Cl_2, rt	35
6	SO_3·Py, Et_3N, DMSO/CH_2Cl_2, rt	60[d]
7	DCC, TFA, DMSO/CH_2Cl_2, rt	0[b]

[a]Yield of chromatographically homogeneous material. [b]Starting material decomposed. [c]No reaction occurred. [d]4% of aldehyde **16** was also obtained.

triazine **10** (entry 7); unfortunately, only decomposition was observed.

With a reliable route to triazine **10** established, the IEDDA/retro-DA/elimination sequence between the enamine derived from cyclopentanone and pyrrolidine was investigated (Scheme 6). We were delighted to obtain the required pyridine **9** in excellent yield (80−89%) using both the microwave and silica variants of the Boger procedure. The "one-pot" microwave variant of this reaction[33] proceeded smoothly and efficiently on a 250 mg scale (80% yield, 1 h), although the yield diminished with larger scale reactions. In contrast, the thermal SiO_2 procedure[34] could be conducted on a multigram scale with no loss in yield (89%). It should be noted, however, that optimal yields were obtained by adding the silica gel after the successful formation of the dihydropyridine and then subsequently reheating the reaction mixture. As expected, pyridine **9** was obtained as a single regioisomer as evidenced by the observation of only one singlet (H_a, 1 H, 8.34 ppm) in the aromatic region. With pyridine **9** in hand, the common intermediate necessary for the preparation of all four louisianin family members was available.

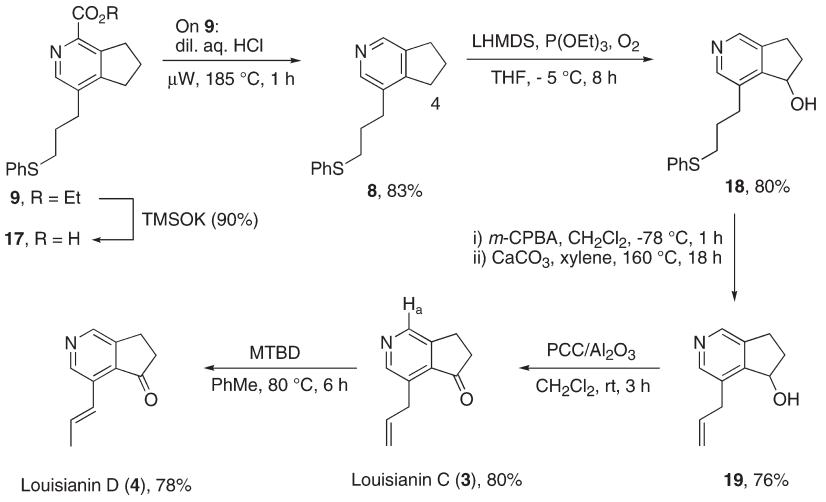
SCHEME 6



Louisianins C and D. In order to complete the synthesis of louisianins C and D it was necessary to achieve the decarboxyethylation of pyridine ester **9**. The literature contains few examples of the direct ethoxydecarbonylation of quinolines or indoles bearing an ester adjacent to the nitrogen heteroatom and only a single example for pyridines.[47] Normally,

(47) Messinger, P.; Meyer-Barrientos, H. *Liebigs. Ann. Chem.* **1981**, 2087.

SCHEME 7



decarboxylation is accomplished via a two-step saponification/decarboxylation protocol. To this end, saponification of ethyl ester **9** was readily accomplished by treatment with potassium trimethylsilanolate giving acid **17** in 90% yield (vide infra). The decarboxylation step is classically accomplished by strong heating either neat[48] or in the presence of copper powder[49] or copper/quinoline.[50] Unfortunately, none of these decarboxylation methods proved successful and returned only the carboxylic acid **17**. In contrast, we were delighted to discover that dilute aqueous hydrochloric acid was able to effect the desired decarboxyethylation of ester **9** directly in 83% yield (Scheme 7). The conditions for this transformation were crucial to ensure that the decarboxyalkylation proceeded efficiently. In this regard, microwave irradiation of ester **9** in 0.74% hydrochloric acid (1:50 37% HCl/H_2O) at 185 °C/50 W for 1 h were identified as the optimum reaction conditions; in the presence of more concentrated acid the reaction product was 2-pyridinecarboxylic acid **17**. To the best of our knowledge, this conversion also represents the first example of the microwave acceleration of a direct pyridine decarboxylation.[51]

Benzylic oxidation was attempted next, and this was potentially one of the most difficult steps because of the paucity of available methods. However, Chen and co-workers in their synthesis of louisianin D[24] demonstrated that oxidation of the cyclopentapyridine proceeded exclusively in the C-4 position (para position) upon exposure to 6 equiv of LHMDS followed by oxygenation. Despite the close similarity of pyridine **8** to Chen's substrate, we were disappointed to find that, although oxidation did occur to afford a 2:1 mixture of isomeric alcohols, we could neither drive the reaction to completion nor identify the nature of the isomeric byproduct. However, application of Corey and Ensley's[52] in situ hydroperoxide quench procedure, that is carrying out the same reaction in the presence of triethyl phosphite, was entirely successful. Under these conditions, a completely regioselective oxidation was observed affording the desired benzylic alcohol **18** in 80% yield (Scheme 7). The finely balanced nature of this oxidation reaction was further illustrated in the completion of the louisianin A and B synthesis (vide infra).

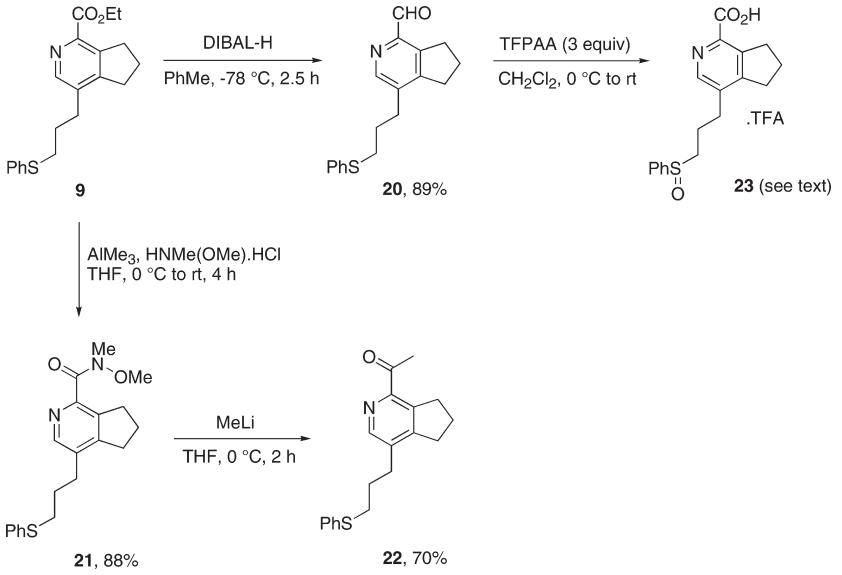
Having successfully achieved decarboxylation and oxidation, the only functionality awaiting installation was the allyl group in the C-5 position. This was readily revealed by chemoselective oxidation of sulfide **18** to the corresponding sulfoxide (*m*-CPBA, −78 °C, 1 h) and then subjection of the "crude" sulfoxide to thermolysis (xylene, 150 °C) in the presence of calcium carbonate to trap the extruded benzenesulfenic acid. This reaction cleanly afforded the desired alkene **19** in a 76% yield over the two steps (Scheme 7). Furthermore, no evidence for any isomerization of the allyl group was observed under these conditions.

With the allyl group in place, we then undertook the final oxidation necessary to obtain louisianin C (**3**). Omura's work on the interconversion of the louisianin family successfully utilized the Jones oxidation for this transformation.[20] Unfortunately, in our hands, this reaction proved to be low yielding. Equally surprising was the observation that manganese dioxide oxidation led only to decomposition of the substrate. Ultimately, we were able to successfully use PCC supported on alumina to achieve this oxidation in 80% yield (Scheme 7). The product obtained displayed data identical to those reported for louisianin C (**3**) [e.g., δ_C ($CDCl_3$) 208.0; δ_H ($CDCl_3$) 8.76 (1 H, s, Ha) [lit.[18] δ_C ($CDCl_3$) 207.3; δ_H ($CDCl_3$) 8.75 (1 H, s, Ha)]].

Next, louisianin D (**4**) was prepared from louisianin C (**3**) via isomerization of the allyl to the required 1-propenyl substituent. Omura's group had shown that this could be accomplished by treatment of louisianin C with DBU in benzene at reflux.[20] In order to expedite the workup procedure we attempted the use of polymer-supported methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) but were surprised to observe extensive decomposition and only obtained a 10% yield of louisianin C (**4**). However, when heated with MTBD in toluene (80 °C, 6 h), lousianin D (**4**) was obtained

(48) Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron* **2004**, *60*, 8893.
(49) Kenyon, J.; Thaker, K. *J. Chem. Soc.* **1957**, 2531.
(50) Schultz, C.; Link, A.; Kunick, C. *Arch. Pharm.* (*Weinheim*) **2001**, *334*, 163.
(51) Subsequent to our initial communication on the synthesis of lousianins C and D (ref 19), a report on the copper-catalyzed microwave-promoted decarboxylation of arylcarboxylic acids was disclosed: Goossen, L. J.; Manjolinho, F.; Khan, B. A.; Rodriguez, N. *J. Org. Chem.* **2009**, *74*, 2620.
(52) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

SCHEME 8



in 78% yield (Scheme 7). Once again, the characterization data obtained showed that the synthetic product was identical to the natural product [mp 83−85 °C (lit.[20] mp 83−86 °C)].

Louisianins A and B. In contrast to the route employed to access louisianins C and D, the pyridone core structure of louisianins A and B requires an oxidative transformation of the ethyl ester group present in pyridine **9**. The most direct route to achieve this aim appeared to be either a Dakin or Baeyer−Villiger oxidation of the corresponding aldehyde or methyl ketone, respectively (Scheme 8). In this regard, pyridine ester **9** was successfully transformed into aldehyde **20** via a standard DIBAL-H reduction in 89% yield. Furthermore, conversion of the ester **9** into Weinreb amide **21** via the aluminum amide method[53] followed by treatment with methyllithium gave the methyl ketone **22** in 62% yield over the two steps.

With the required substrates in hand, attention was turned to the oxidation of aldehyde **20** (Scheme 8). Acknowledging the absence of precedent in the literature for the Dakin oxidation of 2-formylpyridines, and the potential for over-oxidation, a range of oxidants were examined for this transformation. Unfortunately, none of the conditions examined produced any of the required formate. The use of 2 equiv of oxidant led to a 3:1 sulfoxide/sulfone mixture (*m*-CPBA) or sulfoxide alone (monoperoxymaleic acid) with no reaction at the formyl group. The strongest oxidant known for the Dakin oxidation, trifluoroperacetic acid (TFPAA),[36] promoted oxidation of the aldehyde to the corresponding carboxylic acid and concomitant oxidation of the sulfide; the resulting product, obtained in essentially quantitative but unpurified yield, was identified as the carboxylate salt **23** (Scheme 8).[54] More nucleophilic peroxide sources such as NaOOH or $PhSeO_3H$[55] were also investigated, but unfortunately, only decomposition was observed.

Attention was therefore switched to the attempted Baeyer−Villiger oxidation of methyl ketone **22**, but these studies were equally frustrating. The acetyl group proved remarkably inert under any conditions, even with TFPAA. Consequently, only oxidation to the sulfoxide was observed. Perhaps this is not surprising given that the only literature precedent for the Baeyer−Villiger oxidation of 2-acetylpyridine[56] required forcing conditions and pyridine **22** is appreciably more electron-rich. These results discouraged examination of the carboxy inversion reaction[37,57] and rapidly curtailed the direct oxidation approach to the required pyridones.

Next, an alternative approach to the introduction of the required oxidation at the C-2 position via a hydroxy-Sandmeyer reaction on the 2-pyridyldiazonium salt was explored.[58] Thus, pyridine ester **9** was converted into the 2-aminopyridine **24**, the required diazonium precursor, via a series of straightforward reaction steps; saponification to the potassium carboxylate with potassium trimethylsilanolate,[59] acyl azide formation with diphenylphosphoryl azide, and subsequent Curtius rearrangement[60] followed by acidic deprotection and decarboxylation afforded the desired 2-aminopyridine **24** in a 63% overall yield for this telescoped three-step sequence (Scheme 9).

The literature scope for the hydroxy-Sandmeyer reaction with 2-aminopyridine substrates is limited, and moderate yields are observed.[61] Such reactions are usually conducted

(53) Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **2001**, *12*, 1185.

(54) Compound **23** was characterized by ^{1}H NMR, ^{13}C NMR, and IR and the structure assigned on the basis of these data. HRMS could not be obtained because MS analysis of the crude salt provided no sensible information. Furthermore, the free base of the salt could not be isolated because of the extremely polar nature of the corresponding acid sulfoxide that evaded aqueous extraction and could not be purified by chromatography.

(55) Syper, L. *Synthesis* **1989**, 167.

(56) Llamas, R.; Jimenez-Sanchidrian, C.; Ruiz, J. R. *Tetrahedron* **2007**, *63*, 1435.

(57) For elegant examples of this reaction in synthesis, see, for example: (a) Danishefsky, S.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 6889. (b) Breder, A.; Chinigo, G. M.; Waltman, A. W.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8514.

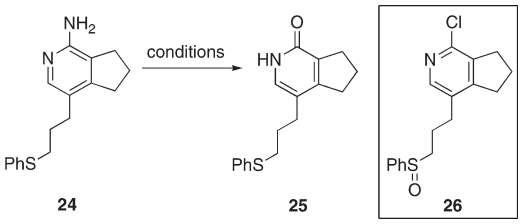
(58) (a) Cohen, T.; Dietz, A. G.; Miser, J. R. *J. Org. Chem.* **1977**, *42*, 2053. (b) Hanson, P.; Rowell, S. C.; Walton, P. H.; Timms, A. W. *Org. Biomol. Chem.* **2004**, *2*, 1838.

(59) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831.

(60) Donald, J. R.; Edwards, M. G.; Taylor, R. J. K. *Tetrahedron Lett.* **2007**, *48*, 5201.

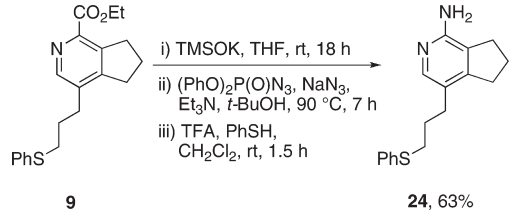
(61) See, for example: (a) Van de Poel, H.; Guillaumet, G.; Viaud-Massuard, M. C. *Heterocycles* **2002**, *57*, 55. (b) Manera, C.; Benetti, V.; Castelli, M. P.; Cavallini, T.; Lazzarotti, S.; Pibiri, F.; Saccomanni, G.; Tuccinardi, T.; Vannacci, A.; Martinelli, A.; Ferrarini, P. L. *J. Med. Chem.* **2006**, *49*, 5947.

TABLE 2. Hydroxy-Sandmeyer Reactions of Aminopyridine 24



entry	conditions	product	yield, %
1	$NaNO_2$, HCl/H_2O (1:10), 0 °C; then NaOH, 100 °C		0
2	$NaNO_2$, HCl/AcOH (1:10), 0 °C; then $CuSO_4$, 100 °C		0
3	$NaNO_2$, $HCl/H_2O/CH_2Cl_2$ (1:10:11), 0 °C; then $CuSO_4$, 100 °C		0
4	$NaNO_2$, HCl/H_2O (1:10), 0 °C; then $CuSO_4$, 100 °C	**26**	32
5	*t*-BuONO, $BF_3 \cdot OEt_2$, THF, 0 °C; then CuCl, aq NaOH		0
6	$NaNO_2$, H_3PO_2, H_2O, 0 °C to rt	**25**	22

SCHEME 9



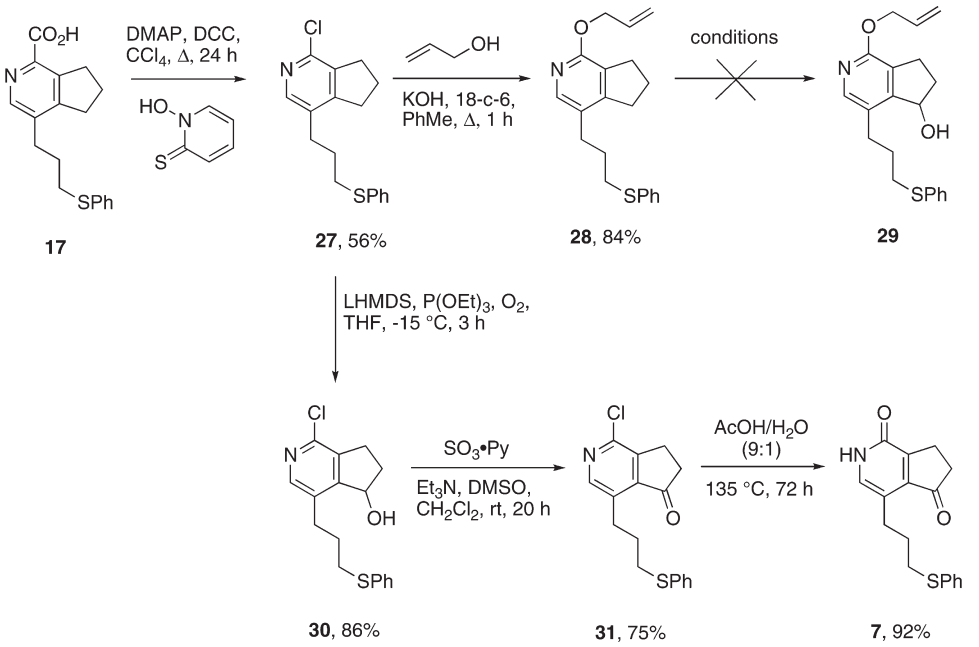
with either $CuSO_4$ or NaOH as the "hydroxide" source. Several conditions for the hydroxy substitution reaction using amine **24** were examined, and the results are compiled in Table 2. Generation of the arene diazonium salt under standard reaction conditions with $NaNO_2$ and HCl followed by application of either aqueous $CuSO_4$ or NaOH and heating led only to decomposition and the formation of a multitude of products (entries 1−3). These reactions were hindered by the poor solubility of the diazonium salt in the reaction media, and attempts to use a variety of solvent combinations to alleviate this problem met with no success. Nevertheless, when the reaction was conducted in solely aqueous solution with hydrochloric acid/water (entry 4), chloride substitution of the diazonium salt and concomitant sulfide oxidation were observed producing adduct **26** in 32% yield. Alternative methods for the generation of the diazonium salt were therefore explored. Though *tert*-butyl nitrite has been successfully used for 2-aminopyridines,[62] again only decomposition was observed (entry 5). Hypophosphorus acid (H_3PO_2) is generally used for reduction of diazonium salts to the corresponding pyridine. However, as Porter and co-workers[63] reported that hypophosphorus acid can effect the hydroxy-Sandmeyer reaction, the same reaction with pyridine **24** was studied. Initially, an encouraging 22% yield of the desired pyridone **25** was obtained, but further investigation failed to give higher yields. In search of a more robust and successful method of pyridone formation, other approaches were therefore explored.

Success was eventually achieved using the halodecarboxylation of carboxylic acid **17** and a subsequent S_NAr reaction with a suitable "hydroxide" source (Scheme 10). Classically, halodecarboxylation via the Hunsdiecker reaction was promoted by either silver or mercury salts.[64] Although there have been many successful advances in Hunsdiecker technology, particularly the Kochi variants,[65] success has never been demonstrated with 2-pyridinecarboxylic acids.[66] In contrast, the report of Inouye and co-workers[67] on the double bromodecarboxylation of 4-*n*-butoxypyridine-2,6-dicarboxylic acid demonstrated that Barton halodecarboxylation[68] was a viable method for 2-pyridinecarboxylic acids. Accordingly, when carboxylic acid **17** was combined with Barton's alcohol, DMAP, and DCC and thermolysis in carbon tetrachloride, the corresponding 2-chloropyridine **27** was obtained in 56% yield. The Barton ester formed in situ proved to be highly unstable and could be neither isolated nor detected in the reaction mixture. Despite this, the reaction, although somewhat slow (24 h reflux in CCl_4 was required), was robust, reliable, and scalable. Since the original disclosure of Barton halodecarboxylation, improved conditions have been reported to provide higher yields using either photolytic conditions[69] or xanthate esters;[70] we found that these methods offered no improvement in yield over the original protocol.

With chloropyridine **27** in hand, treatment with a range of alcohols was explored. Initial results confirmed the literature view that S_NAr reaction on 2-chloropyridines are difficult to effect in the absence of electron-withdrawing substituents.[71]

(62) Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Ma, W.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2002**, *45*, 4755.
(63) Wijtmans, M.; Pratt, D. A.; Brinkhorst, J.; Serwa, R.; Valgimigli, L.; Pedulli, G. F.; Porter, N. A. *J. Org. Chem.* **2004**, *69*, 9215.
(64) Crich, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 717−734.
(65) Kochi, J. K.; Sheldon, R. A. *Org. React.* **1972**, *19*, 279.
(66) Uemura, S.; Tanaka, S.; Okano, M.; Hamana, M. *J. Org. Chem.* **1983**, *48*, 3297.
(67) Inouye, M.; Miyake, T.; Furusyo, M.; Nakazumi, H. *J. Am. Chem. Soc.* **1995**, *117*, 12416.
(68) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
(69) Dauben, W. G.; Kowalczyk, B. A.; Bridon, D. P. *Tetrahedron Lett.* **1989**, *30*, 2461.
(70) Nyfeler, E.; Renaud, P. *Org. Lett.* **2008**, *10*, 985.
(71) There are very few examples of such reactions with 2-chloropyridines. Typically, those reported contain one or more electron-withdrawing groups to facilitate the reaction. See, for example: (a) Uray, G.; Kriessmann, I. *Synthesis* **1984**, 679. (b) Sycheva, T. V.; Rubtsov, N. M.; Sheinker, Y. N.; Yakhontov, L. N. *Chem. Heterocycl. Compd.* **1987**, *23*, 82.

SCHEME 10



Thus, the use of 2-trimethylsilylethanol,[72] potassium *tert*-butoxide[73] and potassium trimethylsilanolate gave no reaction under any of the reaction conditions applied. In contrast, reactive alcohol nucleophiles such as allyl alcohol and benzyl alcohols successfully underwent the desired S_NAr reaction. For example, when 5 equiv of allyl alcohol, chloropyridine **27**, potassium hydroxide, and 18-crown-6 were combined in toluene under Dean−Stark conditions,[74] the desired allyloxypyridine **28** was obtained in 84% yield (Scheme 10). Given the plethora of methods available to remove allyl protecting groups[75] we anticipated that the pyridone could be revealed by deallylation at a later stage.

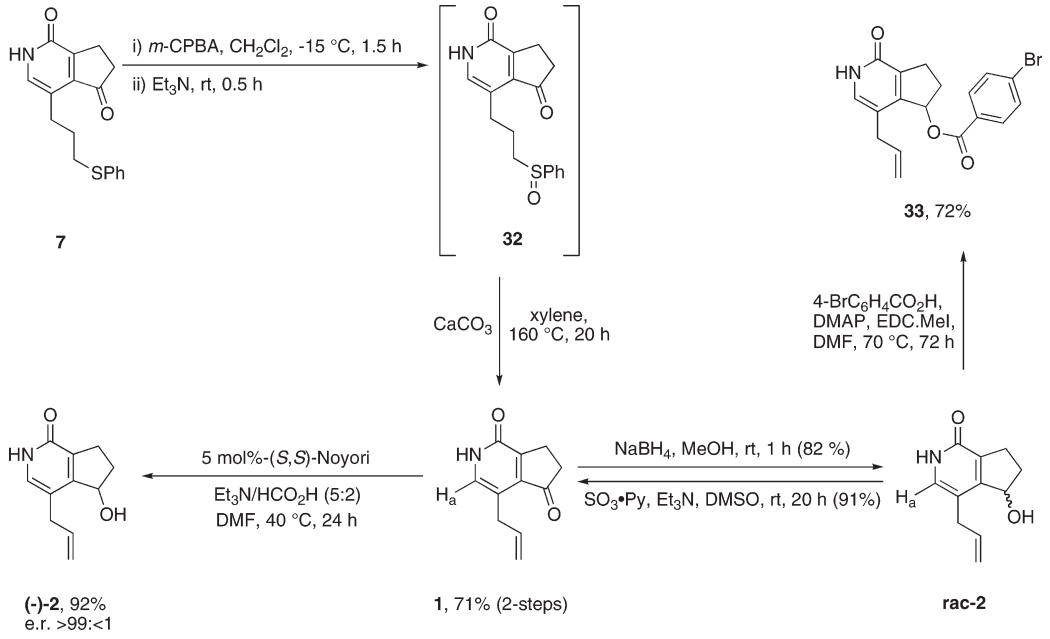
We next planned to carry out the C-4 oxidation via the procedure successfully used in the route to louisianins C and D. However, it was soon established that allyloxypyridine **28** was inert to any of the oxidation conditions examined. A range of bases (including NaH,[76] KO-*t*-Bu[77] and LHMDS) and conditions failed to return anything other than starting material. Analysis of the oxidation results suggests that the reaction is finely balanced by the requirement for deprotonation to occur at the benzylic position. The regioselective nature of the reaction with pyridine **8** occurs with deprotonation only in the most acidic position (i.e., 4-picoline vs 3-picoline). Given the relative pK_a of the benzylic position (~35, γ-picoline, DMSO)[78] and LHMDS (30, DMSO) and the excess of base required (10 equiv) for the reaction to occur, it is clear that the other benzylic positions are not sufficiently acidic for oxygenation to occur. Moreover, the increased electron density of in the pyridine ring in pyridine **28** would appear to render the substrate insufficiently acidic to deprotonate.

This revelation required a revision of the planned strategy. A reversal of the steps so that oxidation preceded S_NAr appeared to be a possible solution. Thus, we were delighted to find that application of the same oxidation conditions used on pyridine **8** proceeded smoothly on chloropyridine **27** to afford the desired benzylic alcohol **30** in 86% yield (Scheme 10). Apparently, the electron-withdrawing chlorine substituent permits the desired deprotonation to occur without acidifying the other benzylic positions sufficiently to promote alternative oxidation products. Unfortunately, any attempts to perform S_NAr on pyridine **30** to generate the corresponding pyridone led only to destruction of material whether the conditions were basic, neutral or acidic; presumably, via elimination pathways. We rationalized that oxidation of the benzylic alcohol to the corresponding ketone **31** would render the pyridine more activated to any subsequent S_NAr reaction. To this end, Parikh−Doering oxidation of alcohol **30** proceeded under standard conditions to provide ketone **31** in 75% yield. Although attempts to conduct S_NAr reactions on compound **31** under basic conditions were unsuccessful, the use of "non-anhydrous"[79] acetic acid gave a slow, yet clean, hydrolysis to the corresponding pyridone **7** (92%). Once more we were pleased to discover that this reaction could be scaled up without any lowering of the yield. This key transformation was supported by the characteristic shift of the C-6 proton (**31**, 8.14 ppm; **7**, 7.15 ppm) and the appearance of the pyridone signal in the IR spectrum (υ 1660 cm^{-1}).

With the pyridone oxidation level established, all that remained was to reveal the allyl group from its masked precursor (Scheme 11). The low solubility of pyridone **7** at

(72) Lluis, J.; Matheu, M. I.; Castillon, S. *Tetrahedron Lett.* **1998**, *39*, 1807.
(73) Birkholz, M. N.; Dubrovina, N. V.; Jiao, H. J.; Michalik, D.; Holz, J.; Paciello, R.; Breit, B.; Borner, A. *Chem. Eur. J.* **2007**, *13*, 5896.
(74) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923.
(75) Greene, T. W.; Wuyts, P. G. M. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2006.
(76) Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239.
(77) Sanz, R.; Castroviejo, M. P.; Guilarte, V.; Perez, A.; Fananas, F. J. *J. Org. Chem.* **2007**, *72*, 5113.
(78) Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 463.
(79) Lavecchia, G.; Berteina-Raboin, S.; Guillaumet, G. *Tetrahedron Lett.* **2004**, *45*, 6633.

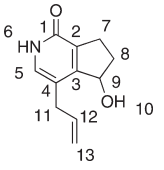
SCHEME 11



−78 °C and the high-water solubility of sulfoxide **32** predicated the use of slightly unusual conditions for the oxidation−elimination sequence. Thus, oxidation of sulfide **7** at −15 °C was followed by the addition of excess triethylamine and filtration through silica gel to afforded unpurified sulfoxide **32** that was then immediately thermolysis in the presence of $CaCO_3$ to afford louisianin A (**1**) in 71% yield over the two steps. Pleasingly, there was again no evidence for isomerization of the allyl group. The characterization data obtained compares favorably with the isolation data[18] and also with that reported by Chang and co-workers[22] [e.g., mp 185−188 °C (lit.[18] mp 189−191 °C, lit.[22] mp 187−188 °C); δ_C ($CDCl_3$) 207.5; δ_H ($CDCl_3$) 7.16 (1 H, s, H_a) [lit. δ_C ($CDCl_3$) 208.6,[18] 207.7;[22] lit. δ_H ($CDCl_3$) 7.18 (1 H, s, Ha),[22] 7.20 (1 H, s, Ha)[18]]].

All that remained was to complete the synthesis of louisianin B (**2**) via reduction of the ketone; treatment of louisianin A (**1**) with $NaBH_4$ in methanol afforded louisianin B (**2**), in 82% yield. The ^{13}C NMR data (Table 3) and mp obtained were in good agreement with the isolation data reported by Omura and co-workers [e.g., mp 163−165 °C, lit.[18] mp 168−170 °C], but the ^1H NMR data were found to vary consistently from those reported. We believe that this is due to misassignment of the residual solvent (CD_2HOH) peak in the original spectra.[80] Thus, when reported proton data are recalibrated (+0.36 ppm), the data are comparable (Table 3). All attempts to prepare crystals of louisianin A (**1**), or of the derived *p*-bromobenzoate derivative **33**, that were suitable for X-ray analysis were unsuccessful. However, in

TABLE 3. NMR Comparison for Natural and Synthetic Louisianin B (2)



	recorded ^{13}C NMR 100 MHz[a]	reported[18] ^{13}C NMR 68 MHz[b]	recorded ^1H NMR 400 MHz[c]	reported[18] ^1H NMR 270 MHz[d]	adjusted ^1H NMR 270 MHz[e]
1	164.1	163.9			
2	133.8	133.8			
3	158.6	158.5			
4	119.6	119.7			
5	133.2	133.2	7.09	6.73	7.09
7	28.0	28.5	2.65, 2.92	2.30, 2.56	2.66, 2.92
8	34.7	35.2	1.95, 2.40	1.59, 2.05	1.95, 2.41
9	76.8	77.1	5.24	4.89	5.25
11	33.6	34.0	3.33, 3.46	2.95, 3.10	3.31, 3.46
12	138.0	137.9	5.97	5.62	5.98
13	117.2	117.3	5.10, 5.10	4.73, 4.73	5.09, 5.09

[a] ^{13}C NMR (100 MHz) for compound **2** in CD_3OD. [b] ^{13}C NMR data (68 MHz) for reported by Omura and co-workers for louisianin B in CD_3OD. [c] ^1H NMR data (400 MHz) for compound **2** in CD_3OD. [d] ^1H NMR data (270 MHz) reported by Omura and co-workers for louisianin B in CD_3OD. [e] ^1H NMR isolation data adjusted by applying a correction factor of + 0.36 ppm (see text).

order to provide further confirmation for the structural assignment, louisianin B (**2**) was reoxidized using the Parikh−Doering procedure ($SO_3 \cdot Py$, Et_3N, DMSO) to give louisianin A (**1**) in 91% yield, and this sample displayed spectral data entirely consistent with those reported.[18]

Finally we examined the asymmetric reduction of louisianin A (**1**) in order to prepare enantioenriched louisianin B (**2**). It should be noted that an optical rotation was not recorded in the original isolation papers.[17,18,80] Both Corey−Baskshi−Shibata (CBS) reduction[81] and Noyori transfer hydrogenation[82] have proven to be excellent methods for the enantioselective reduction of ketones. Although neither method is precedented for the reduction of pyridone ketones, the Noyori protocol appeared more suited to our purposes because of its compatibility with alkenes. Accordingly, when louisianin A (**1**) was subjected to Noyori reduction with 5 mol % of the [Ru(*S*,*S*)-TsDPEN)] complex in the presence of formic acid/triethylamine (5:2),[83] enantioenriched louisianin B (**2**) was obtained in 92% yield and $>99:<1$ er as determined by chiral HPLC (3 μM AD-3 column, 90:5:5 isohexane/EtOH/MeOH, flow rate 1.00 mL/min, $\lambda = 254$ nm). We sought to use Mosher's ester analysis[84] to determine the absolute configuration of the carbinol center but found that the MTPA derivative could not be prepared, even under the forcing conditions used to prepare *p*-bromobenzoate derivative **33**. The reluctance of Mosher's esters to form with hindered alcohols has been noted previously (and new reagents developed to attenuate the problems);[85] presumably, this is the reason for the failure of alcohol **2** to react. There are also limited examples of using sterically more accessible enantiopure isocyanates to form diastereomeric carbamate derivatives to assign the absolute configuration;[86] unfortunately, this technique also proved to be unsuccessful. Therefore, we are currently unable to assign the absolute configuration of the enantioenriched (−)-louisianin B (**2**). According to the rationale for enantioselectivity reported by Noyori and co-workers,[87] the product obtained (using the (*S*,*S*)-TsDPEN ligand) might be expected to have the (*S*)-configuration, but in the absence of reduction of alternative pyridone ketones, there is no evidence to corroborate this.

Conclusion

In conclusion, we have described the preparation of all four members of the louisianin family (A−D) from the common tetrasubstituted pyridine intermediate **9**. The pyridine intermediate was itself assembled from triazine **10** via the inverse-electron-demand Diels−Alder/retro-Diels−Alder chemistry we have previously developed for the preparation of highly functionalized pyridines. Louisianins A and B were prepared via transformation of the 2-ethoxycarbonylpyridine into a 2-chloropyridine and subsequent hydrolysis to the pyridone with an acid-catalyzed S_NAr reaction. In contrast, louisianins C and D were prepared through a key decarboxyethylation of the 2-ethoxycarbonylpyridine intermediate. In both series, oxidation in the C-4 position was accomplished via an oxidation reaction and the allyl group obtained from a masked sulfide precursor. This appears to be the first reported total synthesis of louisianin B. We have also reported the preparation of (−)-louisianin B in enantio-enriched form via a Noyori asymmetric transfer hydrogenation of the ketone in louisianin B.

Experimental Section

General Experimental Procedures. See the Supporting Information for complete experimental details including full characterization data and general experimental detail.

4-Allyl-6,7-dihydro-1*H*-cyclopenta[*c*]pyridine-1,5(2*H*)-dione, Louisianin A (1). A solution of sulfide **7** (205 mg, 0.685 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (12 mL) under argon was cooled to −15 °C, and then purified *m*-CPBA[2] (124 mg, 0.718 mmol, 1.05 equiv) was added in a single portion. The reaction mixture was stirred at −15 °C until disappearance of starting material (TLC, 1 h). Triethylamine (83 mg, 0.822 mmol, 115 μL, 1.20 equiv) was added via microsyringe and the reaction warmed to rt and stirred for 1 h. The mixture was then preadsorbed onto SiO_2 and passed through a pad of SiO_2 with 4:1 EtOAc/EtOH to afford the intermediate sulfoxide pyridone **32**. This material was sufficiently pure for the following step. The sulfoxide was dispersed onto the side of a large pressure tube (20 cm × 2.5 cm) by evaporation from CH_2Cl_2, and then xylene (14 mL) and $CaCO_3$ (257 mg, 2.569 mmol, 3.75 equiv) were charged to the tube. The tube was sealed, placed in a 160 °C oil bath, and heated for 18 h. The sulfoxide gradually dissolved upon heating, and the resultant brown suspension was cooled to rt, transferred to a round-bottom flask, and preadsorbed onto SiO_2. Column chromatography (SiO_2, 19:1 EtOAc/EtOH) afforded the title compound, louisianin A (**1**), as a cream solid (91.5 mg, 0.484 mmol, 71% for the two steps). Recrystallization from acetonitrile afforded **1** as fine, colorless needles. Data for **1**: R_f 0.30 (19:1 EtOAc/EtOH, det: $KMnO_4$); mp 185−188 °C (MeCN) (lit.[18] mp 189−191 °C); ^{1}H NMR (400 MHz, $CDCl_3$) 12.73 (br s, 1 H, NH(6)), 7.16 (s, 1 H, CH(5)), 5.93 (ddt, $J = 16.9$, 10.3, 6.6 Hz, 1 H, CH(11)), 5.11−5.03 (m, 2 H, CH_2(12a and 12b)), 3.52 (dd, $J =$ 6.6, 1.1 Hz, 2 H, CH_2(10)), 3.01−2.97 (m, 2 H, CH_2(7)), 2.72−2.68 (m, 2 H, CH_2(8)); ^{13}C NMR (100 MHz, $CDCl_3$) 207.5 (C(9)), 163.9 (C(1)), 149.3 (C(2)), 144.6 (C(3)), 135.6 (C(11)), 132.1 (C(5)), 116.9 (C(12)), 116.0 (C(4)), 36.3 (C(8)), 31.4 (C(10)), 22.8 (C(7)); IR ν_{max} (CH_2Cl_2)/cm^{-1} 3143, 2918, 2848, 1716, 1663, 1612, 1471, 1448, 1424, 1292, 1240, 1198, 1079, 942, 906, 878, 772, 737; MS (ESI, *m*/*z*) 212 (MNa^+); HMRS (ESI) found 212.0689, calcd for $C_{11}H_{11}NNaO_2$ [MNa^+] 212.0682 (3.3 ppm error).

(±)-4-Allyl-5-hydroxy-2,5,6,7-tetrahydro-1*H*-cyclopenta[*c*]-pyridin-1-one, Louisianin B (2). Sodium borohydride (8 mg, 0.203 mmol, 1.0 equiv) was added in a single portion to a 0 °C solution of louisianin A (**1**) (38.5 mg, 0.203 mmol, 1.0 equiv) in MeOH (5 mL). The reaction was then stirred for 1 h at 0 °C. Upon completion of the reduction, the reaction was quenched by the addition of one drop of glacial acetic acid. The reaction mixture was then preadsorbed onto SiO_2 and purified by column

(80) Professor Omura confirmed that an α-D value had not been recorded and that no sample remained. Private communication (email dated Aug 12, 2008).

(81) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(82) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

(83) Noyori's initial report (ref 83a) uses the isolated complex [RuCl(*S*,*S*)-TsDPEN] to catalyze the reaction. We found it more convenient to use the procedure reported by Tanis and co-workers (ref 83b) to generate the catalyst in situ: (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (b) Tanis, S. P.; Evans, B. R.; Nieman, J. A.; Parker, T. T.; Taylor, W. D.; Heasley, S. E.; Herrinton, P. M.; Perrault, W. R.; Hohler, R. A.; Dolak, L. A.; Hester, M. R.; Seest, E. P. *Tetrahedron: Asymmetry* **2006**, *17*, 2154.

(84) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451.

(85) See for example: (a) Takeuchi, Y.; Itoh, N.; Koizumi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1514. (b) Williamson, R. T.; Sosa, A. C. B.; Mitra, A.; Seaton, P. J.; Weibel, D. B.; Schroeder, F. C.; Meinwald, J.; Koehn, F. E. *Org. Lett.* **2003**, *5*, 1745 and references cited therein.

(86) Vodicka, P.; Streinz, L.; Koutek, B.; Budesinsky, M.; Ondracek, J.; Cisarova, I. *Chirality* **2003**, *15*, 472.

(87) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818.

chromatography (SiO_2, 9:1 EtOAc/EtOH) to give louisianin B (**2**) (32 mg, 0.167 mmol, 82%) as a colorless solid. Recrystallization from acetonitrile afforded **2** as a colorless microcrystalline solid. Data for **2**: R_f 0.25 (9:1 EtOAc/EtOH, det: $KMnO_4$); mp 163−165 °C (MeCN) (lit.[18] mp 168−170 °C); ^{1}H NMR (400 MHz, $CDCl_3$, limited solubility) 12.64 (br s, 1 H, NH(6)), 7.09 (s, 1 H, CH(5)), 5.93 (dddd, J = 16.6, 10.2, 6.4, 6.4 Hz, CH(12)), 5.26 (dd, J = 7.2, 3.6 Hz, CH(9)), 5.14−5.06 (m, 2 H, CH_2(13a and 13b)), 3.37 (dddd, J = 16.3, 6.4, 2.3, 1.4 Hz, 1 H, CH_2(11a)), 3.27 (dddd, J = 16.3, 6.4, 2.2, 1.5 Hz, 1 H, CH_2(11b)), 2.97 (ddd, J = 16.9, 8.5, 5.8 Hz, 1 H, CH_2(7a)), 2.72 (ddd, J = 16.9, 9.0, 4.2 Hz, 1 H, CH_2(7b)), 2.42 (dddd, J = 13.3, 9.0, 7.4, 5.8 Hz, 1 H, CH_2(8a)), 1.98 (dddd, J = 13.3, 8.5, 4.2, 3.6 Hz, 1 H, CH_2(8b)), 1.67 (br s, 1 H, OH(10)); ^{1}H NMR (400 MHz, CD_3OD) 7.09 (s, 1 H, CH(5)), 5.97 (dddd, J = 17.5, 9.6, 7.0, 5.9 Hz, 1 H, CH(12)), 5.24 (dd, J = 7.4, 3.8 Hz, 1 H, CH(9)), 5.13−5.07 (m, 2 H, CH_2(13a and 13b)), 3.46 (dd, J = 15.9, 7.1 Hz, 1 H, CH_2(11a)), 3.33 (m, 1 H, CH_2(11b, obscured by CD_3 quintet), 2.92 (ddd, J = 16.6, 8.6, 5.8 Hz, 1 H, CH_2(7a)), 2.65 (ddd, J = 16.6, 9.0, 4.6 Hz, 1 H, CH_2(7b)), 2.40 (dddd, J = 13.9, 9.0, 7.4, 5.8 Hz, 1 H, CH_2(8a)), 1.95 (dddd, J = 13.9, 8.6, 4.6, 3.8 Hz, 1 H, CH_2(8b)); ^{13}C NMR (100 MHz, CD_3OD) 164.1 (C(1)), 158.6 (C(3)), 138.0 (C(12)), 133.8 (C(2)), 133.2 (C(5)), 119.6 (C(4)), 117.2 (C(13)), 76.8 (C(9)), 34.7 (C(8)), 33.6 (C(11)), 28.0 (C(7)); IR ν_{max} (CH_2Cl_2)/cm^{-1} 3386, 2927, 2884, 1658, 1618, 1561, 1461, 1434, 1322, 1281, 1112, 992, 915; MS (ESI, m/z) 214 (MNa^+); HMRS (ESI) found 214.0830, calcd for $C_{11}H_{13}NNaO_2$ [MNa^+] 214.0838 (4.1 ppm error).

Asymmetric Noyori Transfer Hydrogenation of Louisianin A: Preparation of Enantioenriched Louisianin B (2). A stock solution of Noyori catalyst was prepared according to the general precedent of Tanis and co-workers:[5] $[RuCl_2(p\text{-cymene})]_2$ (50 mg, 0.0818 mmol) and (*S*,*S*)-TsDPEN (60 mg, 0.163 mmol) were charged to a 5 mL round-bottom flask fitted with a reflux condenser and three-way tap connected to argon and vacuum. The flask was purged under argon, and then argon-sparged *i*-PrOH (0.65 mL) and triethylamine (33 mg, 0.327 mmol, 46 μL) were added. The mixture was heated to reflux for 1 h and the resultant red-brown solution cooled to rt. The volatiles were removed, and the residual solid was dissolved in 2 mL of anhydrous DMF to afford a 0.0813 M catalyst solution. A flame-dried round-bottom flask under argon was charged with louisianin A (**1**) (10 mg, 0.0523 mmol, 1.0 equiv). Anhydrous DMF (0.8 mL) and then argon-sparged Et_3N/HCO_2H (5:2, 0.2 mL) were added via syringe followed by the catalyst stock solution (0.00262 mmol, 5 mol %, 32 μL of a 0.0813 M stock solution in DMF). The resultant orange solution was then stirred under argon for 24 h at 40 °C. The orange-brown solution was then transferred to a round-bottom flask and concentrated in vacuo (high vacuum pump, 40 °C). The crude brown oil was preadsorbed on SiO_2 and purified by column chromatography (SiO_2, 6:1 EtOAc/EtOH) to give louisianin B (**2**) (9.2 mg, 0.048 mmol, 92%) as a pale yellow amorphous solid. Data for (−)-**2**: $[\alpha]_D^{25}$ −33.6 (c 0.42, MeOH); HPLC analysis (3 μM AD-3 column, 90:5:5 isohexane/EtOH/MeOH, flow rate 1.00 mL/min, λ = 254 nm), t_R = 5.10 min (major, 99.4%), 6.60 min (minor, 0.6%), er > 99: < 1.

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