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Direct Access to Marine Pyrrole-2-aminoimidazoles, Oroidin, and Derivatives, via New Acyl-1,2-dihydropyridin Intermediates

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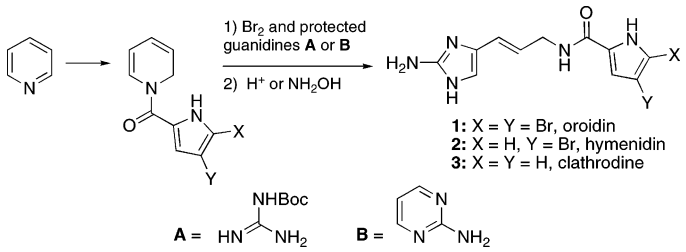
ABSTRACT



A short synthesis of the $C_{11}N_5$ oroidin derivatives is reported. The key step of the strategy is a one-pot oxidative bromine-mediated addition of protected guanidines to the *N*-acyl-1,2-dihydropyridines 9a–c. The new *N*-acyl-1,2-dihydropyridines were prepared directly from pyridine and pyrrole-2-carbonyl chloride by reduction with borohydride reagent in one step.

Current interest in the group of pyrrole-2-aminoimidazole marine metabolites, which includes the important putative biogenetic intermediates oroidin (**1**),[1] hymenidin (**2**),[2] and clathrodine (**3**)[3] (Figure 1), has been concerned not only with

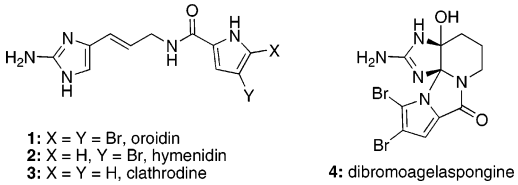
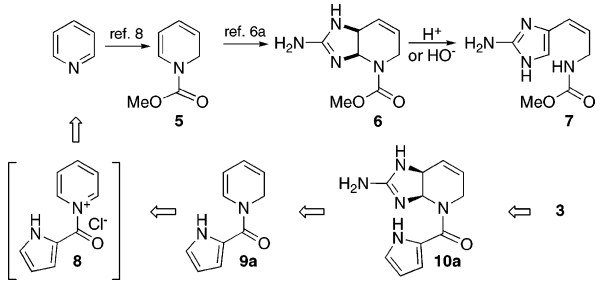


Figure 1. Structures of the marine metabolites oroidin, hymenidin, clathrodine, and dibromoagelaspongine.

preparative synthesis and biological activities[4] but also with their biomimetic chemical reactivity.[5]

We have recently described a new preparation of the 2-aminoimidazole derivative **7** (Scheme 1) bearing the allylic amine substituent on the C4(5) position, using a bromine

Scheme 1. Targeted 2-Aminoimidazole Derivatives from 1,2-Dihydropyridine



oxidative addition of Boc-guanidine to the *N*-carbomethoxy-dihydropyridine **5**.[6]

On the basis of our studies on the synthesis of various N-substituted 1,2-dihydropyridines and their reactivity with

(1) (a) Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *Chem. Commun.* **1971**, 1129−1130. (b) Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Chem. Soc., Chem. Commun.* **1973**, 78−79.

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guanidine, we planned to use this procedure for a rapid and straightforward preparation of the natural products **1**−**3** and their derivatives.[7] Our synthetic strategies are inspired from a global analysis of the structures and reactivities of the natural metabolites. The structure of dibromoagelaspongine (**4**), isolated from the sponge *Agelas* sp.,[8] exhibits a structural proximity with oroidin (**1**) suggesting a common chemical approach via a dihydropyridine intermediate.

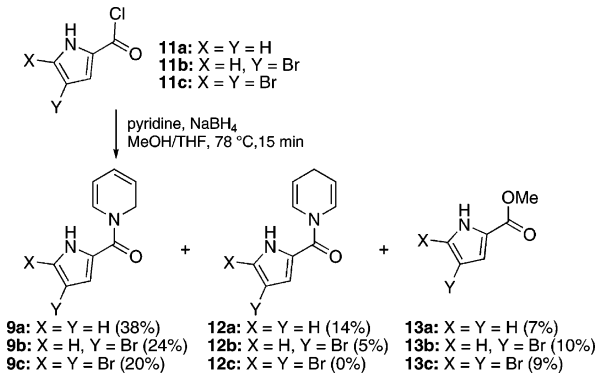
It then appears clearly that the cyclic clathrodine derivative **10a** was the relevant target via the dihydropyridine intermediate **9a** (Scheme 1). However, it is of special interest to note that in contrast with *N*-carbomethoxydihydropyridine **5**, described by Fowler,[9] the *N*-acyl-1,2-dihydropyridines such as **9a** were not readily available from pyridine via the reduction of the corresponding pyridinium salts.[10] Moreover, the preparation of N-substituted 1,2-dihydropyridines is hampered by a regioselectivity problem leading to formation of the 1,4-dihydropyridine regioisomer.[11]

This article expands to the first report of the acyldihydropyridine **9a** synthesis based on the reduction of the pyrrolic *N*-acyl-pyridinium **8** and further short synthesis of the $C_{11}N_5$ clathrodine (**3**) and derivatives.

Our retrosynthetic approach is depicted in Scheme 1. Extension of Fowler's methodology to the reduction of *N*-acylpyridinium **8** should afford dihydropyridine intermediate **9a**. Subsequent nucleophilic addition of a protected guanidine in oxidative conditions would lead to the formation of the bicyclic compound **10a**. We anticipated that **10a** might have reactivity similar to that of **6** to undergo aminal opening, affording the natural 2-aminoimidazolic clathrodine (**3**).

To prepare the requisite pyrrolic dihydropyridines **9a**−**c**, we investigated the reaction conditions for the reduction, starting from pyridine and pyrrole-2-carbonyl chloride (**11a**)-(Scheme 2). After preliminary assays, it appeared that the

Scheme 2. Reduction of *N*-Acyl-dihydropyridinium Salts into *N*-Acyl-dihydropyridines

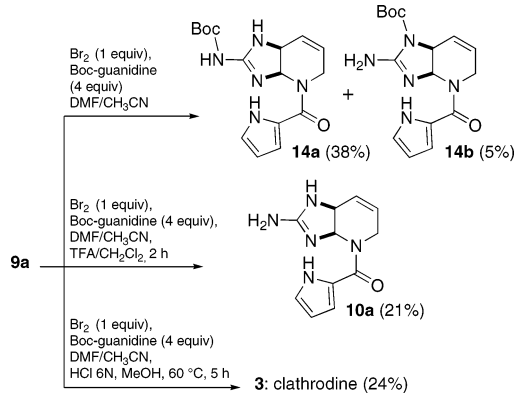


desired major product 1,2-dihydropyridine **9a** was formed along with the contaminants 1,4-dihydropyridine **12a** and methyl-2-pyrrole carboxylate (**13a**). The presence of MeOH is determinant for the reduction of the *N*-acyl pyridinium salt intermediate; thus, the optimization to minimize side products was conducted by varying the quantities of MeOH, pyridine, and $NaBH_4$. It was found that the use of 0.15 mL of MeOH per millimole of **11a**, 2 equiv of pyridine, and 0.5 equiv of $NaBH_4$ was optimal for obtaining the best yield (38% of isolated **9a**). Although the yield of *N*-acyl-dihydropyridine is apparently low, we can say that this is the first and shortest preparation of **9a**.

With the optimized reaction conditions in hand, we next examined the formation of the brominated derivatives **9b**,**c**. We observed that the yield of the major product decreases with the bromination degree of the pyrrole ring (Scheme 2).

N-Acyl-1,2-dihydropyridine **9a** smoothly underwent reaction with 4 equiv of Boc-guanidine in the presence of 1 equiv of bromine, affording the bicyclic product **14a** (38%) and its regioisomer **14b** (5%) (Scheme 3). It is noteworthy that

Scheme 3. Clathrodine (**3**) Synthesis from **9a**.



the use of 2 or 3 equiv of bromine led to a mixture of pyrrole brominated derivatives of **14a**,**b**. Deprotection of **14a**,**b** in the presence of TFA gave **10a** in 21% isolated yield. Clathrodine (**3**) was obtained directly from **9a** using the same conditions followed by 6 N HCl treatment in methanol for 6 h. Deprotection, cleavage of the aminal, and $Z \rightarrow E$ isomerization of the double bond were conducted without any purification of the intermediates. Despite the low yields of the reactions, clathrodine (**3**) was quickly obtained in 9% overall yield.

(2) Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Experientia* **1986**, *42*, 1176−1177.

(3) Morales, J. J.; Rodriguez, A. D. *J. Nat. Prod.* **1991**, *54*, 629−631.

(4) For recent reviews of synthetic efforts, see: (a) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753−1783. (b) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551−1565 and references therein.

(5) (a) Al-Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237−243. (b) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674−2677.

(6) (a) Abou-Jneid, R.; Ghoulami, S.; Martin, M.-T.; Tran Huu Dau, E.; Travert, N.; Al-Mourabit, A. *Org. Lett.* **2004**, *6*, 3933−3936. (b) Sanchez Salvatory, M. del R.; Abou-Jneid, R.; Ghoulami, S.; Martin, M.-T.; Zaparucha, A.; Al-mourabit, A. *J. Org. Chem.* **2005**, *70*, 8208−8211.

(7) Al-Mourabit, A.; Travert, N.; Abou-Jneid, R.; Ghoulami, S. WO 2004/101573 A1, 25.11.2004, Demande PCT/Fr2004/001059 30.04.2004.

(8) Fedoreyev, S. A.; Il'yin, S. G.; Utkina, N. K.; Maximov, O. B.; Reshetnyak, M. V.; Antipin, Mu. Y.; Struchkov, Yu. T. *Tetrahedron* **1989**, *45*, 3487−3492.

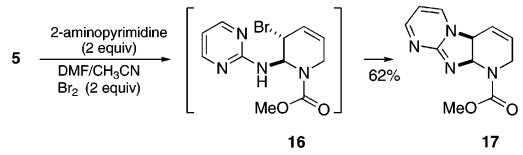
(9) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321−1323.

(10) Whyle, M. J.; Fowler, F. W. *J. Org. Chem.* **1984**, *49*, 4025−4029.

(11) (a) Ref 8. (b) Knaus, E. E.; Redda, K. *Can. J. Chem.* **1977**, *55*, 1788−1791.

Surprisingly, treatment of the dibromodihydropyridine **9c** (Scheme 2) under the same oxidative conditions did not provide the desired bicyclic adduct, but a mixture of unstable compounds from which tricyclic dihydropyridine **15**[12] was the only identifiable product in 14% yield. The dibromopyrrole moiety appeared to promote intramolecular nucleophilic attack of the bromonium intermediate by the nitrogen of the pyrrole ring, instead of the intermolecular addition of the protected guanidine. To circumvent this problem, we needed a more nucleophilic guanidine derivative than *N*-Boc-guanidine. For this purpose, we selected 2-aminopyrimidine (2-AP) as a readily available protected guanidine. Initially, the reactivity of 2-AP in the coupling reaction in the presence of bromine was examined using the Fowler dihydropyridine **5** (Scheme 4). Indeed, with 2 equiv of bromine,

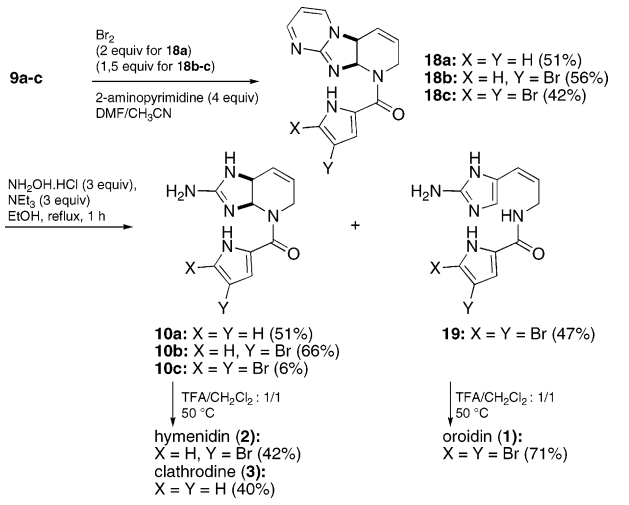
Scheme 4



tricyclic ring system **17** was obtained via the intermediate **16** in 62% yield.

Running the reaction on the pyrrolic dihydropyridines **9a**−**c** afforded condensation products **18a**−**c** in acceptable isolated yields without any trace of the tricyclic compounds related to **15** (Scheme 5).[13]

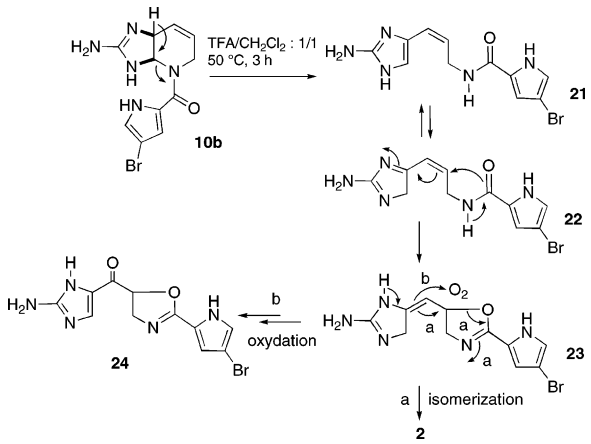
Scheme 5. Targeted 2-Aminoimidazole Derivatives from 1,2-Dihydropyridine



The guanidine motif was revealed by treatment of the tricyclic **18a** and the monobrominated **18b** with hydroxylamine[14] to give **10a**,**b** in 51% and 66% yield, respectively. The dibrominated derivative **18c** afforded **10c** in only 6% yield along with the *Z*-oroidin (**1**) in 47% yield. The electronic influence of the bromine atoms destabilizes **10c** which undergoes aminal opening immediately after the deprotection of **18c**. The ratio of these two products was found to be time dependent. $Z \rightarrow E$ isomerization of **19** using TFA/CH_2Cl_2 provided oroidin (**1**) in 71% yield.[15] Applying the same treatment to the bicyclic compounds **10a**,**b** resulted in the formation of clathrodine (**3**) and hymenidin (**2**) in 40% and 42% yields, respectively.

Pyrrole-2-aminoimidazole (P-2-AI) derivatives are very sensitive to variations in pH and atmospheric oxygen. Thus, the yields of the reactions were closely dependent on the reaction time and purification processes. For example, when compound **10b** was heated at 50 °C for 3 h, the oxidized side product **24** was isolated in 13% yield (Scheme 6). The

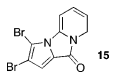
Scheme 6



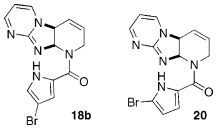
latter compound was not observed when running the reaction under argon.

Compound **24** was the result of an unexpected competitive air oxidation, as the consequence of the isomerization of the *Z*-hymenidin **21** into the natural *E* stereoisomer **2**. The important intermediate **23**, pointed out in our earlier paper,[6a] could also be oxidized by atmospheric oxygen to give **24**. The tautomerism relating **10a**, **21**, and **22** is created by the ambivalent reactivity of the 2-aminoimidazole part of these metabolites.[5] Regarding the sensitivity of oroidin derivatives to atmospheric oxygen, Lindel and co-workers have recently

(12) Structure of compound **15**.



(13) In the case of **9a**, small amounts of two brominated compounds **18b** (6%) and **20** (5%) were isolated and identified.



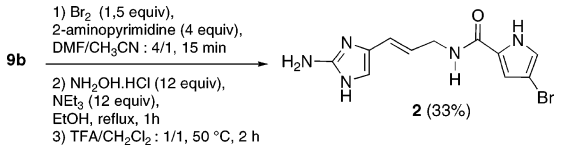
(14) Fajgelj, S.; Stanovnik, B.; Tister, M. *Heterocycles* **1986**, *24*, 379−386.

(15) For an alternative synthesis of *Z*-oroidin, see: Lindel, T.; Hochgürtel, M. *J. Org. Chem.* **2000**, *65*, 2806−2809.

reported similar oxidation by treatment of sventrine with TFA/$CHCl_3$.[16]

To avoid the formation of the side products by repetitive manipulations, preparation of hymenidin (**2**) from **9b** was tested without any purification of the intermediates. This revealed an interesting economy of time. Thus, hymenidin (**2**) was prepared from **9b**, in 1 day, in 33% overall yield (Scheme 7). Although the yield of **9b** is low, we can say that the global yield is favorable. This is obvious if we take into account the overall yield and the overall time required for the synthesis.

Scheme 7



In summary, a short and original method for the preparation of P-2-AI marine metabolites from the new *N*-acyl-1,2-dihydropyridines has been developed. Our current studies are directed toward extension of the preparative scope, development of analogues of P-2-AI synthesis for further biomimetic synthesis of more challenging congeners, and biological testing.

Supporting Information Available: Detailed experimental procedures and compound characterization data, including ^1H and ^{13}C NMR spectra for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0608451

(16) Lindel, T.; Breckle, G.; Hochgürtel, M.; Volk, C.; Köck, M. *Tetrahedron Lett.* **2004**, *45*, 8149−8152.