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Synthetic Study on Tetrapetalones: Stereoselective Cyclization of *N*-Acyliminium Ion To Construct Substituted 1-Benzazepines

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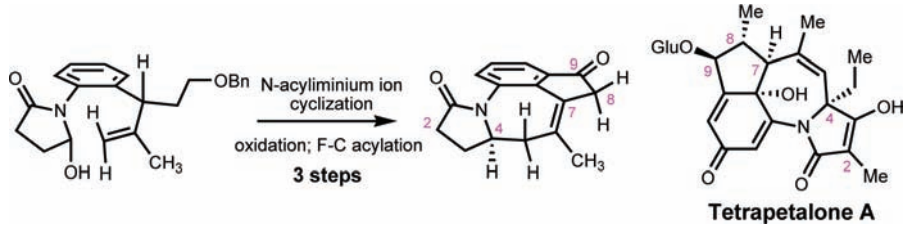
ABSTRACT



The synthesis of the tetracyclic core of complex antibiotic tetrapetalones has been achieved in three steps starting from the simple intermediate γ-hydroxy amide, which can be accessed through a high-yielding six-step sequence. The successful synthesis relies on a novel strategy based on the *N*-acyliminium ion cyclization.

Human lipoxygenase (LOX) and cyclooxygenase (COX) mediate the metabolism of arachidonic acid (AA). The resulting leukotrienes, lipoxins, and prostaglandins are important signaling molecules that may participate in a variety of human diseases, such as inflammation, bronchospasm, and congestion.[1] Searching for potent inhibitors of these oxygenases continues to be a significant topic in medicinal chemistry. Recently, a class of novel soybean lipoxygenase (SBL) inhibitors, tetrapetalones A−D (Scheme 1), was identified by Komoda et al. from the culture filtrate of the *Streptomyces* sp. strain USF-4727.[2] Several groups embarked on the total synthesis of tetrapetalones due to their biological significance and the unprecedented tetracyclic skeleton appending a β-rhodinosyl moiety. The Nazarov cyclization was chosen by Sarpong et al. as a starting point for the construction of the B-ring, although the complete synthesis for the C and D rings has not been reported to date.[3] An ingenious biomimetic approach published by Porco et al. was not successful in constructing the tetracyclic skeleton due to the ease of fully oxidizing the electron-rich arene during the oxidative [4 + 3] annulation.[4] Up to now, the successful construction of the architecture of tetrapetalones has not been reported.

Coupled with our interest in exploiting biomimetic approaches in natural product synthesis, we realized that the formation of the quaternary carbon center (C4) bearing an amide group hampers the previous biomimetic endeavor.[4]

(1) (a) Ghosh, J.; Myers, C. E. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 13182–13187. (b) Samuelsson, B. *Science* **1983**, *220*, 568–575.

(2) (a) Komoda, T.; Sugiyama, Y.; Abe, N.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Tetrahedron Lett.* **2003**, *44*, 7417–7419. (b) Komoda, T.; Yoshida, K.; Abe, N.; Sugiyama, Y.; Imachi, M.; Hirota, H.; Koshino, H.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 104–111. (c) Komoda, T.; Kishi, M.; Abe, N.; Sugiyama, Y.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 903–908.

(3) Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6379–6383.

(4) Wang, X.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2005**, *44*, 3067–3071. See the corrigenda on the quinone form being incorrectly assigned to the tetracyclic structure: Wang, X.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 6607.

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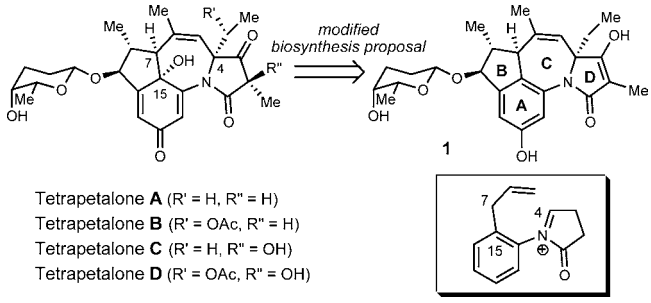
The formation of the cyclohexadienone (A ring) is envisaged here as the possible ending point in the synthetic design which is strategically similar to the biosynthesis of ansamycins.[5,6] Biosynthetically, the C_7-C_{15} bond formation may be introduced prior to the installation of the C(15)-hydroxy group at the A-ring of **1**, which mechanistically resembles the corresponding reactions with singlet oxygen and autoxidations.[7] Moreover, several oxidative dearomatizations have been surveyed in recent literature.[8] Thus, we turned our attention on the formation of the functionalized 1-benzazepine (C-ring) arising from an *N*-acyliminium ion cyclization (inset, Scheme 1) as the primary goal in this investigation.

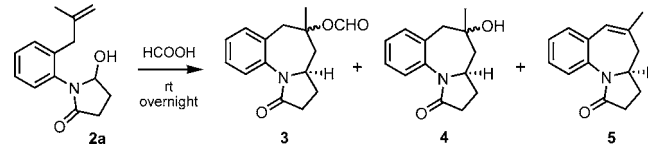
Scheme 1. Modified Biosynthesis Proposal for Tetrapetalones and Strategy for the Construction of 1-Benzazepine through *N*-Acyliminium Ion



With the seminal work contributed by the research groups of Speckamp and Hiemstra, the *N*-acyliminium ion cyclization has evolved into a reaction of significance in many natural product syntheses utilizing its power to install a heteroatom in the carbon chiral center.[9] The reaction has also conventionally been selected to establish the core of 1-benzazepine, which is a basis for drug discovery.[10] However, the detailed stereochemical course of the azepine ring formation has not been established in a valuable way except in a few conformational analyses.[11]

Our initial studies relied on the cyclization of readily generated *N*-acyliminium ions into functionalized benzazepines. Different 1-aryl-γ-hydroxylactams (**2**) were prepared from commercially available 2-nitroaniline derivatives, which were subjected to the Sandmeyer iodonation, Knochel's copper-mediated cross-coupling with 2-methylpropenyl bromide, subsequent reduction of the nitro group, succinimidation, and DIBALH reduction.[12] Formic acid is commonly used in the *N*-acyliminium ion cyclization in the literature;[9] however, in our hands, three products **3**−**5** have been observed with no preference of their stereoisomers (Scheme 2). The cationic character of the intermediate induces different reaction pathways under polar conditions. The complex results prevented us from further optimizing the reaction conditions in the presence of protic acids.

Scheme 2. Formic Acid-Promoted *N*-Acyliminium Ion Cyclization of **2a**



Oxophilic Lewis acids were screened since the formation of the *N*-acyliminium ion requires the extrusion of an OH group (entries 1−5 in Table 1). In the presence of $SnCl_4$, alkene **5** was isolated (15% yield) along with halogenated products **6a** and **7a** (entry 1). The relative configurations of **6a** and **7a** were established with COSY and 2D NOE experiments. The use of the weak Lewis acid $ZnCl_2$ gave full conversion after 24 h with a slightly higher yield of **6a** and **7a** (entry 3, Table 1). $FeCl_3$ resulted in a better diastereoselectivity and isolated yield (entry 4). More importantly, $FeCl_3$ can largely suppress the formation of **5** (<3% yield). A catalytic amount of $FeCl_3$ was observed to complete the cyclization without deterioration of the selectivity and yield (entry 5).[13] TMSCl was found to dramatically improve the efficiency of $FeCl_3$ and gave a higher isolated yield of **6a** (entry 6), while TMSCl alone was not able to catalyze the cyclization even after 24 h (entry 10). Further decreasing the amount of $FeCl_3$ resulted in a comparable distereoselectivity and isolated yield albeit the slower reaction rate (entry 7). Other nonpolar solvent such as benzene lead

(5) (a) Komoda, T.; Sugiyama, Y.; Hirota, A. *Org. Biomol. Chem.* **2007**, *5*, 1615–1620. (b) Komoda, T.; Akasaka, K.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2392–2397.

(6) Funayama, S.; Cordell G. A. In *Bioactive Natural Products (Part D)*; Atta-Ur-Rahman, Ed.; Elsevier: Amsterdam, 2000; Vol. 23, pp 51−106.

(7) From a biomimetic point of view, the C15-hydroxy group can be introduced through mechanisms ranging from free radical to a base-promoted pathway; see the following precedented biomimetic (or enzyme-mimic) studies. (a) Singlet oxygen-mediated dearomatization: Carreño, M. C.; González-López, M.; Urbano, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 2737–2741. (b) The Base-promoted autoxidation: Ham, S. W.; Dowd, P. *J. Am. Chem. Soc.* **1990**, *112*, 1660–1661. Also see an early comprehensive review: Matsuura, T. *Tetrahedron* **1977**, *33*, 2869–2905, and references therein.

(8) For a comprehensive review, see: (a) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383–1430. (b) Copper-mediated oxidative dearomatization: Zhu, J.; Grigoriadis, N. P.; Lee, J. P.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 9342–9343.

(9) Selected reviews: (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352. (c) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (d) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, pp 1047−1082. (e) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 32, p 271. (f) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416.

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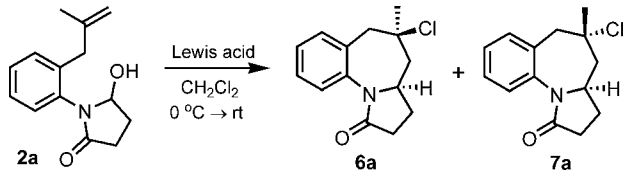
(12) See the Supporting Information for details.

(13) A catalytic system of $Fe(acac)_3$/TMSCl was recently developed for the Prins cyclization leading to hydropyridine rings; see: Miranda, P. O.; Carballo, R. M.; Martiìn, V. S.; Padroìn, J. I. *Org. Lett.* **2009**, *11*, 357–360.

to a slower reaction and lower stereoselectivity (entry 9). A strict reaction condition may not be required since the molecule sieves did not provide any improvement (entry 8). A combination of $FeCl_3$ (0.5 equiv) and TMSCl (2 equiv) was thus selected as an optimized condition for the cyclization of substrates.

Table 1. Screen of Lewis Acids for Iminium Ion Cyclization

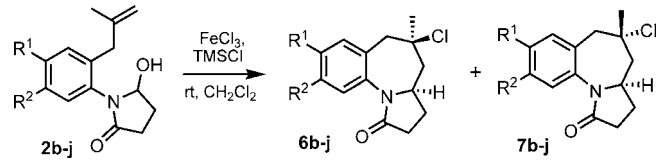


entry	LA (equiv)	additive (equiv)	time (h)	convn[a] (%)	ratio (**6a**/**7a**)	yield[b] (%)
1	$SnCl_4$ (1.5)		1	100	3:1	54
2	$TiCl_4$ (1.5)		1	100	2:1	57
3	$ZnCl_2$ (1.5)		24	95	3:1	60
4	$FeCl_3$ (1.5)		1	100	4:1	62
5	$FeCl_3$ (0.5)		24	>95	4:1	65
6	$FeCl_3$ (0.5)	TMSCl (2)	1	100	4:1	80
7	$FeCl_3$ (0.1) $FeCl_3$ (0.5)	TMSCl (2)	24	>95	4:1	75
8	+ MS 4 Å	TMSCl (2)	1	>95	4:1	76
9[c]	$FeCl_3$ (0.5)	TMSCl (2)	1	80	3:1	56
10	TMSCl (2)		24	<10		*d*

[a] Determined by ^1H NMR. [b] The combined yield of **6a** and **7a**. [c] Benzene was used as the solvent. [d] Not determined.

With the optimized condition in hand, the substrate scope was examined for the generality of the *N*-acyliminium ion cyclization bearing substituents at the 7- or 8-position. As shown in Table 2, for substrates with electron-withdrawing groups (7-F, 7-Cl, 8-CF_3) no selectivity was observed in the formation of the corresponding diastereomeric products. The profound substituent effect encourages us to propose a nonsymmetrically π-bridged carbocation[14] during the cationic cyclization as shown in Scheme 3. After the alkene reacts with the *N*-acyliminium ion, the subsequent tertiary carbon cation may be stabilized by the adjacent aryl group. Such participation leads to the positive charge partially delocalized into the aromatic ring. Although the detailed significance of aryl participation needs to be further measured quantitatively, the experiments in Table 2 indicate that the stereoselectivity of cyclization is correlated with different electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) at C-7 and C-8. In systems with EDGs, the aryl ring constitutes an extra stabilization for the chairlike transition state **TS-1**. Chloride approach from the side opposite to the departing aryl ring generates *cis*-**6**. The pseudoequatorial

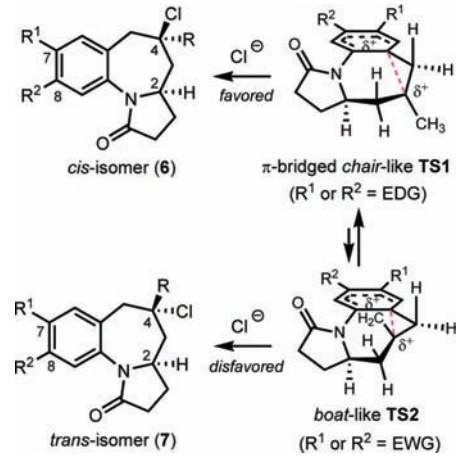
Table 2. Scope of *N*-Acyliminium Ion Cyclization[a]



entry	substrate	R^1	R^2	ratio (**6**/**7**)	yield[b] (%)
1	**2b**	OMe	H	4:1	89
2	**2c**	NMe_2	H	1:1	60[c]
3	**2d**	Cl	H	1:1	84
4	**2e**	H	OMe	>99:1	72
5	**2f**	H	Me	>97:3	97
6	**2g**	H	F	7:1	84
7	**2h**	H	OTBDPS	6:1	80
8	**2i**	H	Cl	4:1	94
9	**2j**	H	CF_3	1:1	85

[a] Reaction condition: substrate (1 equiv), $FeCl_3$ (1.5 equiv), and TMSCl (2 equiv) in CH_2Cl_2 (0.06 M). [b] The combined yield of **6** and **7**. [c] Alkene side products (~25%, regioisomers) were isolated.

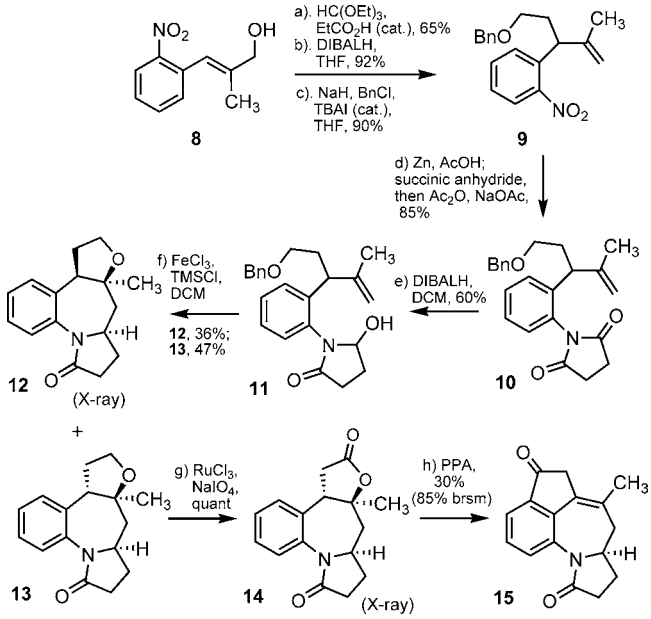
Scheme 3. Mechanistic Proposal for the Stereochemical Course in Benzazepine (the Dashed Line Represents a π-Bridged Delocalization)



nucleophilic attack of the chloride ensures a maximum overlap of the *p*-orbital chloride with the *p*-orbital of the carbocation. The less favorable boatlike conformer **TS-2** gives *trans*-isomer **7** as a minor product via the pseudoequatorial attack of the chloride. The aryl group bearing EWGs in entries 3 and 9 (Table 2) is not able to form the sufficient π-bridged carbocation and the positive charge fully localized on the tertiary carbon C-4. In the absence of EWGs and EDGs, the intrinsic discrimination of **TS-1** and **TS-2** during the cyclization of **2a** can be interpretated as the electron-donating effect of the amide group. The astonishing behavior of 8-fluorine in **2g** may be due to the 2p−2p carbocation−fluorine lone-pair interaction in the carbocation.[15] The aminyl group (−NMe_2, entry 2) exerts an influential electron-withdrawing inductive effect (the ratio of 1/1 of diastereoisomers). It may

(14) For a comprehensive review, see: (a) Lancelot, C. J.; Cram, D. J.; Schleyer, P. v. R. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; John Wiley: New York, 1972; Vol. III, pp 1347−1483. (b) Also see: Masuda, S.; Nakajima, T.; Suga, S. *J. Chem. Soc., Chem. Commun.* **1974**, 954–955. (c) Masuda, S.; Nakajima, T.; Suga, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1089–1094.

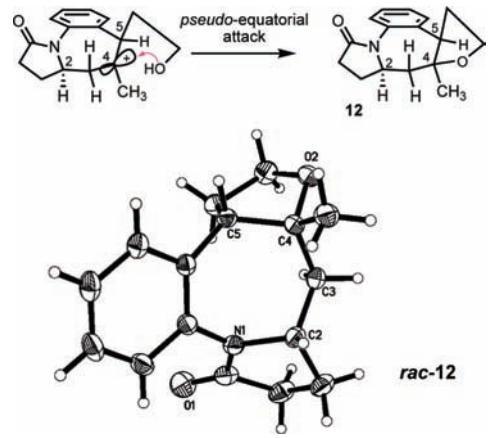
Scheme 4. *N*-Acyliminium Ion Cyclization To Construct Tetracyclic Ring System of Tetrapetalones



be attributed to the strong coordination of the aminyl group with the Lewis acid.

With the consideration of the complex tetracyclic structure of the tetrapetalones, examples with respect to substituents at the 5-position further clarified the power of the iminium ion approach. The introduction of a two-carbon unit at the 5-position as dictated in Scheme 4 would largely benefit the ease of constructing the B ring in tetrapetalones. Starting from the cinnamic alcohol derivative **8**,[16] subsequent transformations gave **9** in 54% over three steps (Scheme 4). With the subsequent reduction and succinimidation, the resulting **10** was subjected to a careful DIBALH monoreduction of the imide giving γ-hydroxylactam **11**. An $FeCl_3$-catalyzed cyclization of **11** afforded structurally complex products **12** and **13**. The *cis*-configuration of H-5 and H-2 in the tetracyclic ring system of **12** was ubiquitously identified by X-ray analysis.[17] The tetrahydrofuran ring was nearly antiperpendicular to the arene due to the steric repulsion (Scheme 5). The pseudoequatorial orientation of the C_4-O bond is also consistent with the mechanistic proposal (Scheme 3). The structural assignment of **13** was further verified by the X-ray diffraction of lactone **14**,[16] which was derived from oxidation with $RuCl_3$ and $NaIO_4$.[18] The stereochemistry

Scheme 5. ORTEP Diagram of the Single-Crystal X-ray Structure of Compound *rac*-**12** and Interpretation of Its Stereochemistry



assignments of **12** and **13** are informative evidence for the preference of the chairlike **TS-1** during the iminium ion cyclization as shown in Scheme 3. The subsequent Friedel−Crafts acylation to complete the B-ring was smoothly realized in an acceptable yield by means of PPA[19] through a dehydration/acylation sequence.

In summary, we have successfully established the *N*-acyliminium ion cyclization in the preparation of 1-benzazepine derivatives. A working model was proposed to illuminate the stereochemical course in the cationic cyclization. The tetracyclic core of the tetrapetalones was constructed using the current approach featuring the Claisen rearrangement, the *N*-acylimnium ion cyclization and the Friedel−Crafts acylation. Further investigations dedicated to the installation of appropriate functionalities in context of the execution of our biosynthetic proposal of tetrapetalones are currently ongoing in this laboratory.

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Supporting Information Available: Complete experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) (a) Rosenthal, J.; Schuster, D. I. *J. Chem. Educ.* **2003**, *80*, 679–690. (b) For a recent review: O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.

(16) The compound **8** can be readily prepared based on the literature precedence: Sundberg, R. J.; Kotchmar, G. S., Jr. *J. Org. Chem.* **1969**, *34*, 2285–2288.

(17) CCDC 731776 (**12**) and CCDC 732094 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre viaww-w.ccdc.cam.ac.uk/ data_request/cif.

(18) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938. (b) Application of the same oxidation conditions for **12** only resulted in a complex mixture.

(19) Gilmore, J. C., Jr. *J. Am. Chem. Soc.* **1951**, *73*, 5879–5880.