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Highly Stereoselective *7-Endo-Trig*/Ring Contraction Cascade To Construct Pyrrolo[1,2-*a*]quinoline Derivatives

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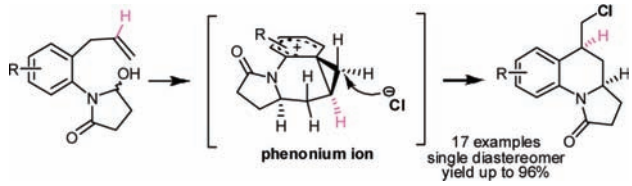
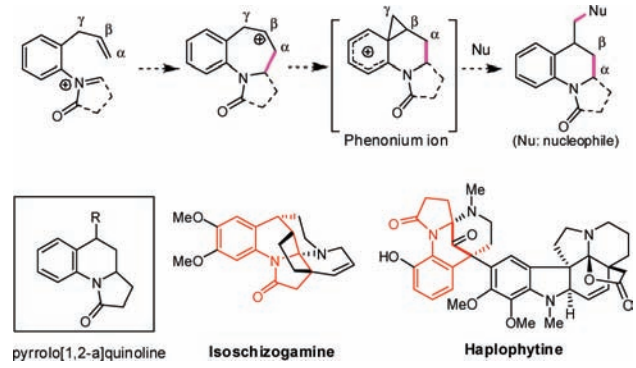
ABSTRACT



With the cooperation of Cram's phenonium ion, a novel cascade reaction was illustrated to construct pyrrolo[1,2-*a*]quinolines as a sole diastereoisomer in good to excellent yields. Preliminary mechanistic studies revealed that the γ-lactam ring and electron-rich arene are important driving forces for ring contraction.

Substituted hydroquinolines are widely embedded in numerous natural products and medicinal compounds. These hetereocycles have been an interesting topic in synthetic chemistry. A plethora of methods have been dedicated to construct functionalized hydroquinolines.[1] During our endeavor in total synthesis of tetrapetalones, a cationic cyclization of the *N*-acyliminium ion with terminal alkene indicated a π-bridged interaction which may be crucial for the stereochemistry outcome of the corresponding substituted benzazepines.[2] We envisaged that the potential phenonium ion intermediate can be formed if the carbocation at C-β is not tertiary. In this way, a ring-contraction would thus be promoted to give pyrroloqinolines (Scheme 1). As highlighted in the represented complex natural products, isoschizogamine and haplophytine, the resulting hydroquinoline or pyrroloquinoline skeleton renders this 7-*endo-trig*/ring contraction cascades approach rather intriguing.[3,4]

Scheme 1. Construction of Pyrroloquinoline via Phenonium Ion and Represented Natural Products



With these considerations in mind, the model cation precursor 1-aryl-γ-hydroxylactam (**2a**) was prepared in two steps from readily available 2-allylaniline.[5] As shown in Table 1, although hydroxyamide **2a** can be successfully

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(1) (a) For a recent review on the synthesis of hydroquinolines, see: Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721–2750, and references therein. (b) Pigeon, P.; Othman, M.; Netchitailo, P.; Decroix, B. *J. Heterocycl. Chem.* **1999**, *36*, 691–695. (c) Santos, L. S.; Pilli, R. A. *Synthesis* **2002**, 87–93. (d) Zhang, W.; Huang, L.; Wang, J. *Synthesis* **2006**, 2053–2063. (e) Wan, C.; Tunge, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 8118–8119. (f) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598–4599. (g) Zhou, Y.; Qian, L.; Zhang, W. *Synlett* **2009**, 843–847.

(2) Li, C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036–4039.

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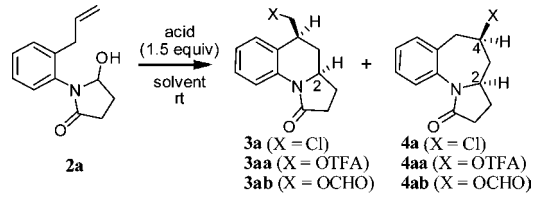
Table 1. Screen of Lewis Acids for *N*-Acyliminium Ion Cyclization[a]



2a

entry	acid	solvent	X	time (h)	convn (%)	**3/4**[b]	yield[c] (%)
1	TFA	CH_2Cl_2	$OCOCF_3$	12	>98	**3aa** only	65[d]
2	HCOOH	HCOOH	OCHO	24	10[e]	n.d.[f]	n.d.
3	$SnCl_4$	CH_2Cl_2	Cl	1	>98	89:11	85
4	$TiCl_4$	CH_2Cl_2	Cl	1	>98	84:16	89
5	$ZnCl_2$	CH_2Cl_2	Cl	24	20	n.d.	n.d.
6	$AlCl_3$	CH_2Cl_2	Cl	24	79	77:23	60
7	$FeCl_3$	CH_2Cl_2	Cl	24	>98	83:17	75
8	$SnCl_4$	$ClCH_2CH_2Cl$	Cl	1	>98	89:11	85
9	$SnCl_4$	$CHCl_3$	Cl	24	30[e]	*g*	n.d.
10	$SnCl_4$	c-hexane	Cl	24	30[e]	*g*	n.d.
11[h]	$SnCl_4$	CH_2Cl_2	Cl	24	95	84:16	80

[a] Reaction conditions: **2a** (0.25 mmol), TFA (0.5 mL), CH_2Cl_2 (5 mL), rt; **2a** (0.25 mmol), Lewis acid (1.5 equiv), CH_2Cl_2 (5 mL), rt. [b] Ratios were determined by ^{1}H NMR (300 MHz) of unpurified mixtures. [c] The combined yields of isolated **3** and **4**. [d] The combined isolated yield of ester and alcohol, see ref 7. [e] The conversion was determined based on recovered starting material. [f] Not determined. [g] Unidentified products were observed. [h] A catalytic amount of $SnCl_4$ (10 mol %) and TMSCl (2 equiv) was used.

consumed within 12 h in the presence of TFA (entry 1),[6] it was found that the instability of the corresponding product to silica gel and complex results after treatment with base retarded further characterization.[7] Substrate **2a** was almost fully recovered when weaker Brönsted acids such as HCOOH were used (entry 2). An excellent diastereoselectivity and overall isolated yield was achieved when $SnCl_4$ was used as the promoter for the cyclization (entry 3). The stereochemistry of the corresponding pyrroloquinonline **3a** and pyrrolobenzazepine **4a** were determined by 2D NOE experiments and unambiguously confirmed with X-ray diffraction (Figure 1).[8] Several oxophilic Lewis acids were screened

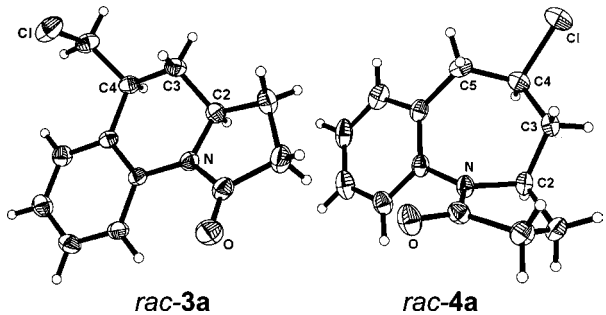


Figure 1. X-ray structure of *rac*-**3a** and *rac*-**4a**.

(entries 3−9). $TiCl_4$ gave a slightly higher yield, albeit lower selectivity (entry 4). It is not surprising that a low conversion was obtained with the use of $ZnCl_2$, due to its weaker oxophilicity (entry 5).[9] A similar ratio of the final products was found when 1,2-dichloroethane was used as a solvent (entry 8), whereas $CHCl_3$ and cyclohexane dramatically retarded the reaction rate and resulted in complex product mixtures (entries 9 and 10). In the presence of TMSCl, a catalytic amount of $SnCl_4$ was still able to promote this novel rearrangement to give products in slightly decreased selectivity and isolated yield (entry 11).

The substrate scope was then examined for the generality of the arene with substituents at the *meta*-, *para*-, or *ortho*-

(3) Several approaches to synthesize lactones via the phenonium ion intermediate were reported, however, application of phenonium ion in synthetic chemistry is rather unexplored. See: (a) Nagumo, S.; Furukawa, T.; Ono, M.; Akita, H. *Tetrahedron Lett.* **1997**, *38*, 2849–2852. (b) Nagumo, S.; Ishii, Y.; Kakimoto, Y.; Kawahara, N. *Tetrahedron Lett.* **2002**, *43*, 5333–5337. (c) Nagumo, S.; Ono, M.; Kakimoto, Y.; Furukawa, T.; Hisano, T.; Mizukami, M.; Kawahara, N.; Akita, H. *J. Org. Chem.* **2002**, *67*, 6618–6622. (d) Boye, A. C.; Meyer, D.; Ingison, C. K.; French, A. N.; Wirth, T. *Org. Lett.* **2003**, *5*, 2157–2159. (e) Ehara, T.; Tanikawa, S.; Ono, M.; Akita, H. *Chem. Pharm. Bull.* **2007**, *55*, 1361–1364. (f) Protti, S.; Fagnoni, M.; Albini, A. *J. Am. Chem. Soc.* **2006**, *128*, 10670–10671.

(4) For methods to construct 4-substituted pyrrolo[1,2-*a*]quinolines, see: (a) Speckamp, W. N.; De Boer, J. J. J. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 410–414. (b) Pearson, W. H.; Fang, W.-k. *J. Org. Chem.* **2000**, *65*, 7158–7174. (c) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129–132, and references therein.

(5) See the Supporting Information for details.

(6) For a comprehensive review dedicated to the *N*-acyliminium ion cyclization, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.

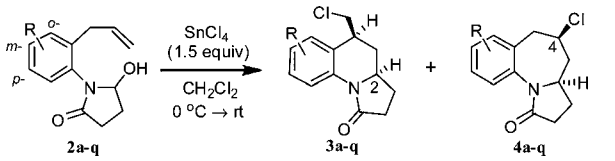
(7) Based on the ^{1}H NMR and ^{19}F NMR spectrum of the unpurified mixtures, **3aa** (X = OTFA) was observed as the major product. The relative configuration was deduced from the hydrolyzed product (X = OH).

(8) For the convenience of discussion, the nomenclature of cyclized products **3** and **4** is based on the core structures such as the quinoline ring and 1-benzazepine ring, respectively.

(9) A free *N*-acyliminium ion intermediate should result in identical rate and product distribution; however, experimental results in Table 1 may imply a tight ion pair with the counterion or a complex with the Lewis acid used. This scenario was widely recognized in the Friedel−Crafts reaction; see: Nelson, K. L. *J. Org. Chem.* **1956**, *21*, 145–155.

position with respect to the allyl group. As shown in Table 2, all substrates bearing different R substituents underwent

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

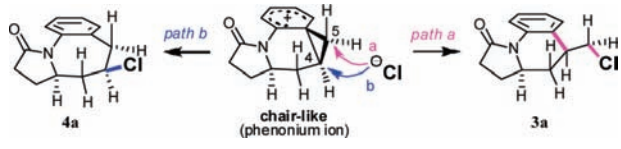


entry	substrate	R	ratio (**3**:**4**)[c]	yield% **3** (**4**)[d]
1	**2a**	H	89:11	78(7)
2	**2b**	*m*-CH_3	91:9	80(6)
3	**2c**	*m*-OCH_3	80:20	70(15)
4	**2d**	*m*-Cl	80:20	66(19)
5	**2e**	*m*-Br	78:22	68(19)
6	**2f**	*p*-OCH_3	98:2	96(0)
7	**2g**	*p*-OTBDPS	>99:1	88(0)
8	**2h**	*p*-F	90:10	88[e]
9	**2i**	*p*-Cl	89:11	79(7)
10	**2j**	*p*-CH_3	86:14	69(9)
11	**2k**	*p*-CF_3	86:14	77(12)
12	**2l**	*p*-CH_2OTBS	97:3	85(0)[f]
13	**2m**	*o*-CH_3	97:3	78(0)
14	**2n**	*o*-OCH_3	>99:1	86(0)
15	**2o**	*m*-F	50:50	99[e]
16	**2p**	*p*-CO_2Et	75:25	80[e,g,h]
17	**2q**	*p*-CH=CH_2	91:9	22(2)[i]

[a] Reaction condition: substrate (0.25 mmol), $SnCl_4$ (0.375 mmol), CH_2Cl_2 (5 mL), rt, 2 h. [b] The stereochemistry assignments of **3b**−**q** and **4b**−**q** were assigned by the similarity of their NMR spectra with those of **3a** and **4a**, see Supporting Information for details. [c] Ratios were determined by ^{1}H NMR (300 MHz) of unpurified mixtures. [d] Yield of isolated products (the isolated yield of 4 was in parentheses). [e] Two products were not separable on silica gel column. [f] The product **3l** was deprotected. [g] Isolated yield was based on recovered starting material. [h] A white precipitate was observed during the reaction; however, the substance **2p** can be recovered in 50% yield after workup. [i] Umoptimized yield; side products were not identified.

cyclization to give exclusively *cis*-products **3a**−**p** and **4a**−**p** with good to excellent yields. The product distribution favoring **3a**−**p** implies the ring contraction was the major pathway (path *a*, Scheme 2). For most of the cases in Table

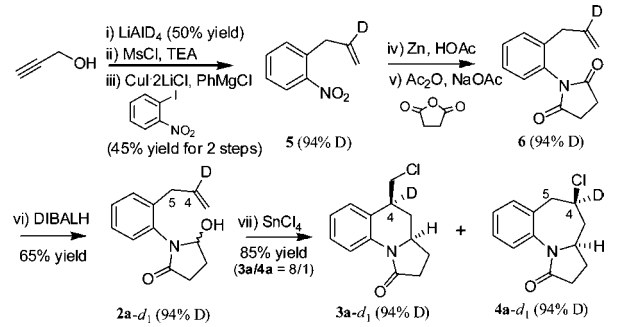
Scheme 2. Proposed Pathway of Cationic Rearrangement



2, after the reaction of iminium ion with alkene, the positive charge developed at C(4) can be further stabilized by the aryl group through the phenonium ion. The fluorinated substrate **2o** (entry 15) can partially overcome the intrinsic tendency (entry 1) due to the strong electron-withdrawing inductive effect of fluorine at the *meta*-position. Nevertheless, the astonishing behavior of **2h** (entry 8), bearing a *p*-fluorine substituent, may be attributed to the carbocation−fluorine lone pair interaction in the σ-bridged carbocation.[10] The most *para*-electron-rich substituents facilitated the exceedingly high selectivity of the ring contraction to give **3f**, **3g**, and **3l** (entries 6, 7, and 12). It is particularly noteworthy when the sterically demanding *o*-methyl- or methoxyl-substituted substrates **2m** and **2n** (entries 13 and 14) were used, formation of rearranged products proceeded with excellent selectivity. The exclusive rearrangement of **2n** bearing the *o*-methoxyl group may be interpreted by a possible oxonium ion intermediate.[11] Even for the reactive vinyl group in **2q** (entry 17), the corresponding product **3q** was still isolated in 22% yield. However, the reactive vinyl group also led to several byproducts, requiring further optimization to extend the functionality tolerence.

For insights into the cyclization/rearrangement cascade and the stereochemistry outcome, a deuterium labeling experiment was conducted (Scheme 3). The synthesis of amide

Scheme 3. Isotopic Labeling Experiment



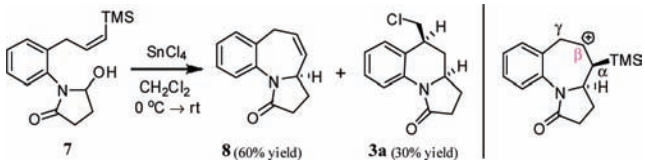
2a-d_1 began with the regioselecitive hydroalumination of 2-propyn-1-ol by $LiAlD_4$, followed by mesylation and the copper-mediated coupling with 2-nitroiodobenzene to give **5** in 23% overall yield with 94% deuterium incorporation at the C(2) of the alkene. The key $SnCl_4$-promoted cationic cyclization gave only two products **3a**-d_1 and **4a**-d_1 (both retains 94% D incorporation at C(4)). There was no deuterium scrambling at other positions of the products. Interconversion between **3a**-d_1 and **4a**-d_1 was not observed when they were individually resubjected to the reaction conditions. These results indicate that the phenonium ion is best invoked as intermediate in the ring contraction. The stereochemical outcome relies on a chairlike cationic intermediate, which may adopt a pseudoequatorial attack at C(4) and C(5) by the incoming chloride to give **3a** and **4a**,

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

(11) (a) Oxonium ion: Manner, J. A. M.; Cook, J. A., Jr.; Ramsey, B. G. *J. Org. Chem.* **1974**, *39*, 1199–1203. (b) The neighboring effect of the methyl group is not clear. One proposed explanation is that the *o*-methyl group may participate in the stabilization of phenonium ion through a C−H hyperconjugation.

respectively.[12] Furthermore, when *Z*-vinylsilane **7** was exposed to the cyclization condition, alkene **8** was identified as the major product due to loss of the silyl group through an $S_{E'}$ pathway (Scheme 4).[13] It was determined that the

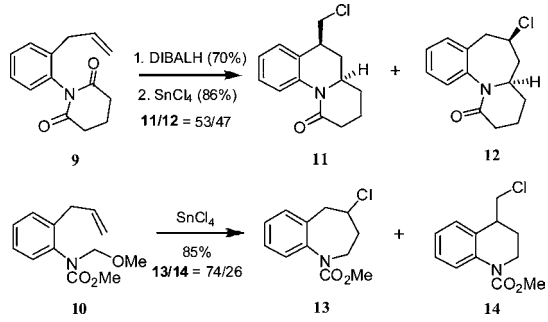
Scheme 4. *N*-Acyliminium Ion Cyclization of Allylsilane **7**



cation at C-β in Scheme 1c is indeed an intermediate, which completes the cation relay process as the proof of concept.

To explore the ring size on the efficiency and understand the origin of rearrangement, the cyclizations of **9** and **10** were compared to **2a** (Scheme 5). The low selectivity 53/47 of

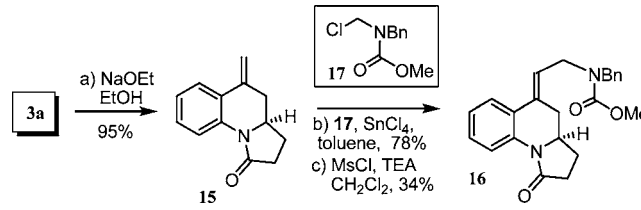
Scheme 5. *N*-Acyliminium Ion Cyclization of **9** and **10**



11 to **12** observed stands in contrast to the cyclization of **2a** to **3a** (ratio: 89/11, 78% of **3a**). Moreover, the cyclization of acyclic substrate **10** afforded benzazepine **13** preferentially to the corresponding rearranged tetrahydroquinoline **14**. These preliminary results clearly indicate that the dominance in compound **3**, as shown in Table 2, may not be solely controlled by substituent on arene, and instead, a compensating steric effect arising from the rigidity of γ-lactam plays a critical role in promoting the rearrangement.

Finally, to further demonstrate the synthetic utility of the current approach,[14] the corresponding **3a** was converted into structurally versatile compounds (Scheme 6). With the

Scheme 6. Synthetic Transformations of **3a**



treatment of NaOEt, the homobenzylic chloride underwent the facile elimination to give a terminal alkene **15**. The multifunctionalities in **15** and **16** allow a variety of transformations for the access to important synthetic motifs as in syntheses of isoschizogamine and the left domain of haplophytine (Scheme 1).[15] The current rearrangement complements published routes to these structures along with greater structural diversity for future biological evaluation.

In conclusion, the *N*-acyliminium ion, in cooperation with a novel rearrangement, has been designed to initiate the highly stereoselective 7-*endo*-*trig*/ring contraction cascade as exemplified in the broad substrate scope on the construction of 4-substituted pyrrolo[1,2-*a*]quinolines. The mechanistic study utilizing isotopic labeling and profound substituent effects shed light on the development of other cationic cyclization/ring contraction cascade. Structurally distinct substrates for exploiting the current approach in the context of asymmetric synthesis 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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(12) However, the origin of exceedingly high stereoselectivity needs to be further investigated with the assistance of computational calculation.

(13) (a) It is tentatively assumed that the chlorinated product **3a** was generated from the cyclization of **2a** derived from the desilylation of **7** in the presence of $SnCl_4$. (b) For the β-effect of the silyl group, see: Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496–1500. (c) Fleming, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, pp 563−593.

(14) For a recent catalytic cyclization of alkene with hydroxyamide by $Fe(OTf)_3$ in 1,4-dioxane, however, this protocol resulted in inseparable alkene isomers; see: Komeyama, K.; Igawa, R.; Morimoto, T.; Takaki, K. *Chem. Lett.* **2009**, *38*, 724–725.

(15) For selected complex natural products bearing pyrroloquinoline, see: (a) Haplophytine: Ueda, H.; Satoh, H.; Matsumoto, K.; Sugimoto, K.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 7600–7603. (b) Nicolaou, K. C.; Dalby, S. M.; Li, S.; Suzuki, T.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7616–7620. (c) Isoschizogamine: Hubbs, J. L.; Heathcock, C. H. *Org. Lett.* **1999**, *1*, 1315–1317. (d) For an advance intermediate in the total synthesis of gephyrotoxin: Ito, Y.; Nakajo, E.; Nakatsuka, M.; Saegusa, T. *Tetrahedron Lett.* **1983**, *24*, 2881–2884.