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Tandem Semipinacol/Schmidt Reaction Leading to a Versatile and Efficient Approach to Azaquaternary Alkaloid Skeletons

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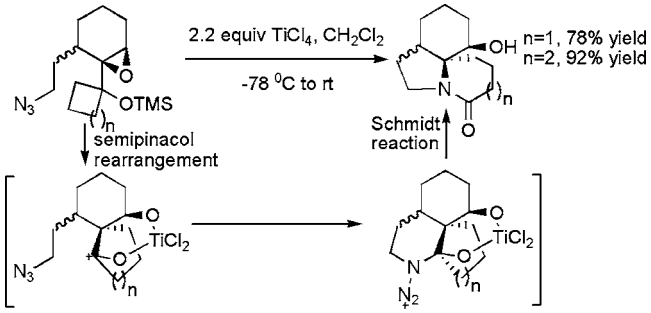
ABSTRACT



A $TiCl_4$-promoted tandem semipinacol/Aubé's type intramolecular Schmidt reaction of α-siloxy-epoxy-azide has been designed and developed to be a general method for efficient construction of azaquaternary carbon units. As applicable examples, some key tricyclic azaquaternary skeletons incorporated in many important alkaloids, such as cephalotaxine, stemonamine, erythrinan, and homoerythrinan alkaloids, have been constructed.

A number of alkaloids possessing the azaquaternary center units are widespread in nature. In particular, those alkaloids (e.g, serratine, stemonamine, cephalotaxine, erythrinan, and homoerythrinan alkaloids, and so on; Figure 1) incorporating the key intriguing tricyclic structure **4**, which has a nitrogen atom located at a highly steric tertiary carbon, exhibit significant biological activities. For example, the esters of cephalotaxine show important antileukemia activity and are currently undergoing advanced clinical trials.[1] Because of their particular structures and important pharmacological values, these alkaloids continue to attract considerable attention from organic chemists.[2−6] Although great efforts have been made toward this subject during the past years, it is still necessary to develop a more efficient and compact method to construct the complex azaquaternary tricyclic structure **4**.

Following our previous studies on tandem semipinacol rearrangement of α-hydroxy epoxide for constructing the quaternary carbon units,[7] recently we have designed and demonstrated a novel tandem semipinacol/Aubé type Schmidt rearrangement of α-siloxy-epoxy-azide. This reaction could be developed to be a general and very efficient synthetic

(1) For a review, see: Kantarjian, H. M.; Talpaz, M.; Santini, V.; Murgo, A.; Cheson, B.; O'Brien, S. M. *Cancer* **2001**, *92*, 1591−1605.

(2) For synthesis of cephalotaxine, see: (a) Eckelbarger, J. D.; Wilmot, J. T.; Gin, D. Y. *J. Am. Chem. Soc.* **2006**, *128*, 10370−10371. (b) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264−10269. (c) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931−2934 and references therein.

(3) Recently, we have developed an efficient strategy for erythrinan and homoerythrinan alkaloids. See: Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; Jiang, Y.; Zhao, Y.; Fan, X.; Zhang, S. *Org. Lett.* **2006**, *8*, 2373−2376 and other strategies cited therein.

(4) Kende, A. S.; Hernando, J. I. M.; Milbank, J. B. *Org. Lett.* **2001**, *3*, 2505−2508.

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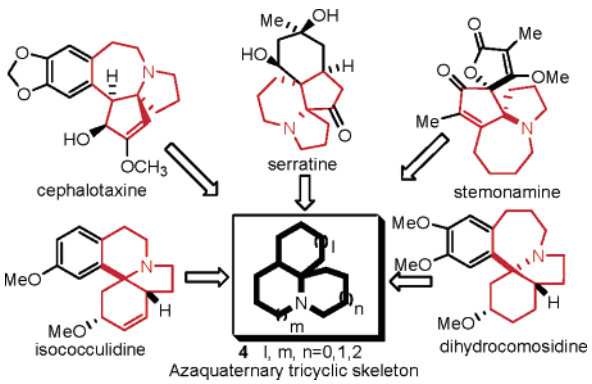
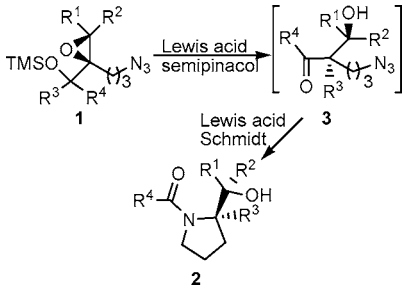


Figure 1. Some representative natural alkaloids incorporating azaquaternary tricyclic structures **4**.

method of azaquaternary carbon units and particularly favors the construction of azaquaternary tricyclic structure **4**. Here, we report our experimental results.

The tandem reaction we designed is outlined in Scheme 1. We envisioned that the α-siloxy-epoxy-azide substrate **1**

Scheme 1. Design of a Tandem Semipinacol/Schmidt Rearrangement



could undergo a Lewis acid promoted semipinacol rearrangement to generate a keto-azide intermediate **3** through a carbon−carbon 1,2-migration.[7,8] Then, **3** was expected to successively undergo a Schmidt rearrangement through a carbon−nitrogen migration under the same conditions[9−11] to give the expected ultimate product **2**.

According to the above idea, initially we started our investigation of this protocol using the simple α-siloxy-epoxy-azide substrate[12] **1a** (Table 1). Thus, **1a** was treated with 2.2 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C for 10 min,

Table 1. $TiCl_4$-Promoted Tandem Reaction of α-Siloxy-epoxy-azide[a]

entry	substrate	product	Time[b]	yield %[d]
1	**1a**[c] R=Me	Ar = Ph **2a**	1.5 h	95
2	**1b**[c] R=H	Ar = Ph **2b**	0.5 h	80
3	**1c**[c] R=Me	Ar=*m*-OMe-Ph **2c**	10 h	77
4	**1d**	n=0 **2d**	3 h	77
5	**1e**	n=1 **2e**	0.5 h	67
6	**1f**	n=2 **2f**	8 h	66
7	**1g**[b]	**2g**	3 h	61
8	**1h**	**2h**	1 h	92
9	**1i**	n=1 **2i**	3 h	78[e]
10	**1j**	n=2 **2j**	0.5 h	92[e]

[a] The tandem reaction experiments were performed by using 2.2 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C for 10 min and then warmed to rt for [b] additional time. [c] Syn/anti mixtures were used. [d] Isolated yield. [e] Mixed isomers (**1i**, β/α 6:1; **2i**, β/α 7:1; **1j**, β/α 8:1; **2j**, β/α 8:1).

and then the reaction mixture was warmed to room temperature and stirred for an additional 1.5 h. After quenching with water and purification on a silica column, we obtained the expected amide **2a** in 95% yield as a white solid. Encouraged by this result, we investigated more examples. Thus, the analogous substrates **1b** and **1c** were prepared and

(5) For syntheses of serratine and related alkaloids, see: Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem.* **2002**, *114*, 1861−1863; *Angew. Chem., Int. Ed.* **2002**, *41*, 1783−1785 and references therein.

(6) For reviews on total synthesis of the cylindricine/fasicularin/lepadiformine family of tricyclic marine alkaloids, see: (a) Weinreb, S. M. *Acc. Chem. Res*. **2003**, *36*, 59−65. (b) Weinreb, S. M. *Chem. Rev.* **2006**, *106*, 2531−2549.

(7) (a) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem*. **1999**, *64*, 629−633. (b) Fan, C.-A.; Wang, B.-M.; Tu, Y. Q.; Song, Z.-L. *Angew. Chem.* **2001**, *113*, 3995−3998; *Angew. Chem., Int. Ed.* **2001**, *40*, 3877−3880. (c) Hu, X.-D.; Fan, C.-A.; Zhang, F.-M.; Tu, Y. Q. *Angew. Chem.* **2004**, *116*, 1734−1737; *Angew. Chem., Int. Ed.* **2004**, *43*, 1702−1705.

(8) For semipinacol rearrangement and related reaction, see: (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimasaki, M.; Usuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827−3829. (b) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431−6432. (c) Nagasawa, T.; Taya, K.; Kitamura, M.; Suzuki, K. *J. Am. Chem. Soc.* **1996**, *118*, 8949−8950. (d) Maruoka, K.; Sato, J.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5449−5450. (e) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208−12209. (f) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379−7388. (g) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150−12158. (h) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944−5951.

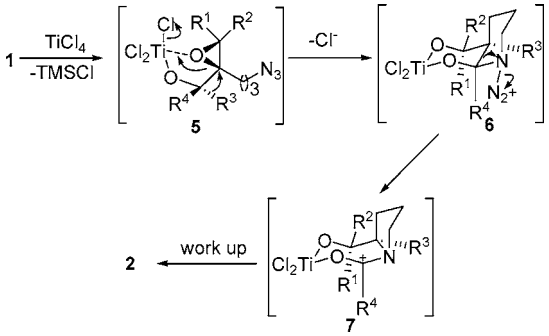
(9) For studies of the intramolecular Schmidt reaction, please see: (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459.

also successfully converted to the corresponding products **2b** and **2c** in 77% and 80% yields (entries 2 and 3) in the above general procedure. Successively, the more complex cyclic substrates **1d**−**h** were examined also, and the corresponding bicyclic lactam products **2d**−**h** were obtained in 61−92% yields (entries 4−8). Similarly, experiments using even more complex bicyclic substrates **1i** and **1j** demonstrated the efficiency of this tandem rearrangement and gave the synthetically valuable tricyclic lactams **2i** and **2j** in 78% and 92% yields (entries 9 and 10).

The main favorable characteristics of this tandem process included the following: it was effective to a wide scope of substrates; the quenched reaction system was clear and easy to purify; and more importantly, the stereochemistry was well controlled. For example, in entry 8, only one diastereoisomer was isolated, and in entries 9 and 10, the major isomers[13] **2i** and **2j** were also furnished. The stereochemistries of **2h** and **2i** were confirmed unambiguously by X-ray crystallography analysis.

According to the above experimental results and the literature reports,[14] a possible sequential mechanism of this tandem reaction was proposed as depicted in Scheme 2. First,

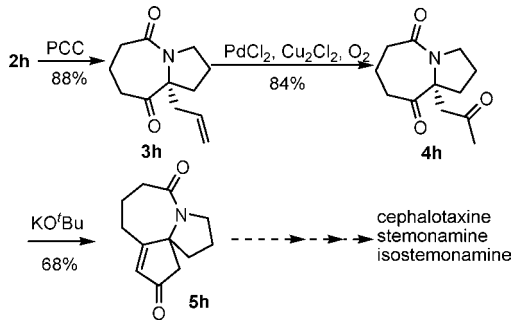
Scheme 2. Possible Reaction Mechanism



it probably proceeded through the chelate transition states **5** and **6** of titanium(IV) with two oxygens, which induced the epoxy ring opening, and the synchronous antiperiplanar migration of R^3 led to the formation of diastereoselective intermediate **6**. Second, the sequent antiperiplanar migration of the quaternary carbon to electron-deficient nitrogen proceeded with retention of the configuration and provided the final product **2**.

Finally, it was most significant that this tandem reaction established a new method for compact synthesis of the azaquaternary tricyclic skeletons **4** of various alkaloids. For example, the product **2h** could be readily converted through three steps (Scheme 3) to a 5-7-5 tricyclic system **5h**, the

Scheme 3. Approach to Stemonamine/Isostemonamine and the Cephalotaxine Alkaloid Skeleton



key skeleton for synthesis of stemonamine/isostemonamine and cephalotaxine.

In addition, the example (entry 9) provided a very efficient and short approach to the 6-5-6 tricyclic skeleton **2i** of isococculidine (Figure 1). Furthermore, another example (entry 10) provided a direct approach to the 6-5-7 tricyclic skeleton **2j** of dihydrocomosidine (Figure 1). The stereochemistries of two skeletons, **2i** and **2j**, were consistent with the natural products. The possibility for absolute stereochemical control of these tricyclic lactams also exists if a certain asymmetric epoxidation procedure was applied to the substrate preparation.[15] We believe that this tandem reaction could be applied to the total synthesis of these and more alkaloids if proper substrates are used.

In summary, we have designed and successfully developed a new Lewis acid promoted tandem semipinacol/Aubé type Schmidt reaction of α-siloxy-epoxy-azide. This tandem process has many advantages combining both semipinacol and Schmidt reactions. The total syntheses of stemonamine/isostemonamine and erythrinan/homoerythrinan alkaloids are underway in our group.

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Supporting Information Available: General experimental procedures, characterization data for all substrates and products, and X-ray crystallographic data for compounds **2h** and **2i** which are deposited at the Cambridge Crystallographic data center with the deposition numbers CCDC 616555 and 616556. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For a domino reaction involving an intramolecular Schmidt reaction, see: (a) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316−4318. (b) Zeng, Y.; Reddy, D. S.; Hirt, E.; Aubé, J. *Org. Lett.* **2004**, *6*, 4993−4995. (c) Zeng, Y. Y.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 15712−15713.

(11) For additional examples involving rearrangement of epoxy-azides, see: (a) Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583−585. (b) Reddy, P. G.; Baskaran, S. *J. Org. Chem.* **2004**, *69*, 3093−3101. (c) Lang, S.; Kennedy, A. R.; Murphy, J. A.; Payne, A. H. *Org. Lett.* **2003**, *5*, 3655−3658.

(12) **CAUTION!** Alkyl azides are potential explosion hazards in substrate synthesis. See the Supporting Information.

(13) The mixtures of **2i** and **2j** were formed from the corresponding mixed substrates **1i** and **1j**, respectively.

(14) For the mechanism of the intramolecular Schmidt reaction, see: Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Reddy, D. S.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914−7922 and ref 9b.

(15) For tandem asymmetric allylation/diastereoselective epoxidation of cyclic enones, see: (a) Jeon, S.-J.; Walsh, P. J. *J Am. Chem. Soc.* **2003**, *125*, 9544−9545. (b) Kim, J. G.; Waltz, K. M.; Garcia, L. F.; Kwiatkowski, D.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 12580−12585. (c) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416−16425.