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The Tandem Pummerer-Isomünchnone Route to (±)-Pumiliotoxin C

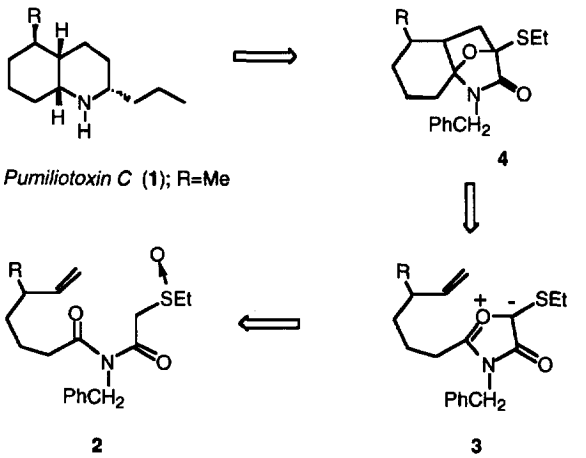
*Jeffrey T. Kuethe and Albert Padwa**
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Abstract: The Pummerer reaction of imidosulfoxides containing tethered π-bonds results in the formation of isomünchnone dipoles which readily undergo intramolecular dipolar cycloaddition to furnish 5-substituted α-pyridones. An application of the method to (±)-pumiliotoxin C was carried out.

The pumiliotoxin alkaloids are a group of decahydroquinolines isolated from strikingly colored neotropical frogs that possess remarkably potent pharmacological activity.[1,2] Several imaginative syntheses of pumiliotoxin C (**1**) have been reported,[3] but none of these have employed a dipolar cycloaddition of a mesoionic betaine[4] as the key step in the synthesis. For the past several years, we have been exploring the synthetic utility of 1,3-oxazolium-4-oxides (isomünchnones) as useful building blocks for the preparation of various classes of alkaloids.[5] In this communication we report a formal synthesis of pumiliotoxin C *via* a novel *tandem Pummerer-induced cyclization-isomünchnone dipolar cycloaddition sequence.*

Recent publications from these laboratories have described the internal trapping of Pummerer thionium ions[6] by adjacent carbonyl groups as a method for generating reactive dienes for subsequent use in Diels-Alder chemistry.[7] In the context of our studies dealing with the tandem chemistry of thionium ions, we discovered that the Pummerer reaction can also be utilized for generating mesoionic dipoles of

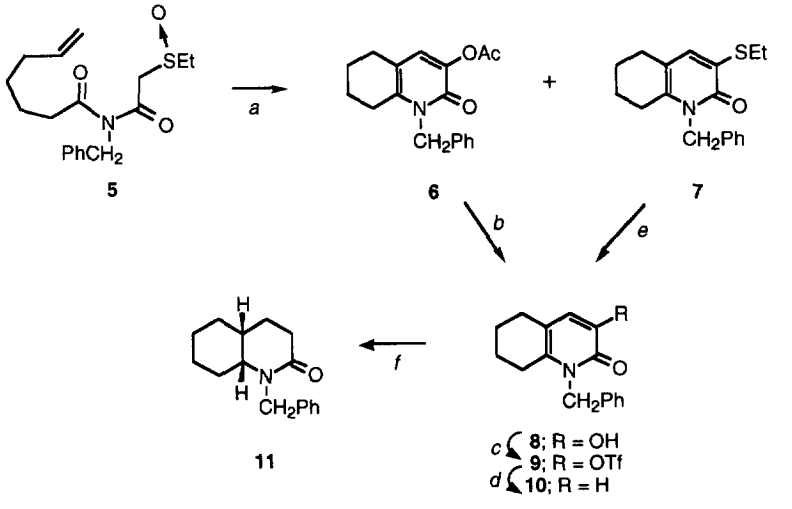
Scheme 1



type **3**.[8] Our approach to the decahydroquinoline skeleton of pumiliotoxin C is shown in antithetic format in Scheme 1 and is centered on the construction of the key oxabicyclic intermediate **4**. We reasoned that isomünchnone **3**, formed by a cyclization-deprotonation sequence should undergo intramolecular dipolar cycloaddition. The resultant cycloadduct is expected to undergo ready ring-opening and our synthetic plan called for a controlled reduction of **4** to generate the *cis*-decahydroquinoline system of **1**.

Our initial goal was to demonstrate that the Pummerer reaction of the model imidosulfoxide system **5** could be used to generate an isomünchnone dipole which would then cycloadd across the pendant olefinic π-bond.[9] Indeed, heating a solution of **5** in Ac_2O at 110 °C afforded a 3:1-mixture of pyridones **6** and **7** in 72% overall yield that were readily separated by silica gel chromatography. The initially formed dipolar cycloadduct (*e.g.*, **4**, R=H) was not isolated as it underwent rapid oxybridge cleavage to give **6** (*via* **8** + excess Ac_2O) and **7**. Hydrolysis of the acetoxy group of **6** with K_2CO_3 followed by reaction of the resulting 5-hydroxypyridone **8** with McMurray's reagent[10] afforded triflate **9** in 96% overall yield. Conversion of **9** into the unsubstituted pyridone was achieved *via* a palladium(0) catalyzed formate reduction[11] to furnish **10** in 71% yield. This same compound was also formed in 80% yield from the Ra(Ni) reduction of **7**. Catalytic hydrogenation (PtO_2) of **10** gave the known[12] *cis*-decahydroquinoline **11** in 98% yield.

Scheme 2

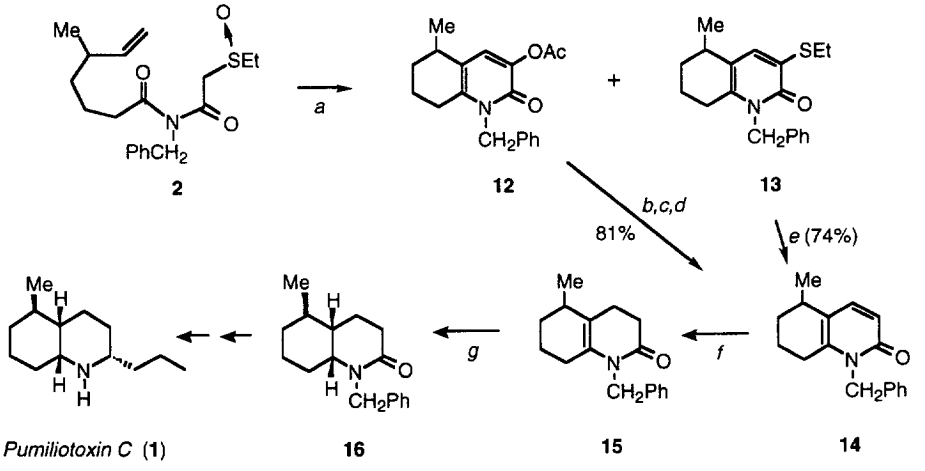


Reagents: (a) Ac_2O, *p*-TsOH (trace), Δ (b) K_2CO_3, MeOH; (c) $(TfO)_2NPh$, NEt_3 (d) $Pd(OAc)_2$, Ph_3P, HCO_2H, Et_3N; (e) Ra-Ni, EtOH (65 °C); (f) H_2, PtO_2

The facility with which α-pyridone **10** could be assembled from imidosulfoxide **5** prompted us to use the above methodology for the preparation of (±)-pumiliotoxin C. While many approaches for the

preparation of this alkaloid have been put forward, there is still a need for general strategies for the construction of *cis*-decahydroquinolines. A short synthesis of pumiliotoxin C was carried out as depicted in Scheme 3. The Pummerer-induced reaction of imidosulfoxide **2** (R=Me) gave mainly 5-acetoxy-pyridone **12** (73%) together with lesser quantities of **13** (13%). Both compounds were independently converted to pyridone **14** *via* the procedure outlined in Scheme 3. Selective reduction of **14** with L-Selectride[13] afforded the ene-lactam **15** in 77% yield. Catalytic hydrogenation of **15** over PtO_2 furnished **16** (86%) with a high degree of diastereoselectivity.[14] The preparation of **16** constitutes a formal synthesis of (±)-pumiliotoxin C, as **16** had previously been converted into the natural product.[15]

Scheme 3



Reagents: (a) Ac_2O, *p*-TsOH (trace), Δ (b) K_2CO_3, MeOH; (c) $(TfO)_2NPh$, NEt_3; (d) $Pd(OAc)_2$, Ph_3P, HCO_2H, Et_3N; (e) Ra-Ni, EtOH (65 °C); (f) $LiB[CH(CH_3)C_2H_5]_3H$; (g) H_2, PtO_2

In conclusion, this study has demonstrated that the Pummerer reaction of imidosulfoxides represents a highly efficient method for the synthesis of azabicyclic ring systems. We have achieved a short, straightforward formal synthesis of pumiliotoxin C and the method should be amenable to the synthesis of other members of the *cis*-decahydroquinoline based natural products.

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References and Notes

1. Witkop, B.; Gossinger, E. In *Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol 21, p 190.

2. Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1986; Vol 4, pp 1-274.
3. Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60,* 204. Bonin, M.; Royer, J.; Grielson, D. S.; Husson, H. P. *Tetrahedron Lett.* **1986**, *27,* 1569. Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *J. Org. Chem.* **1992**, *57,* 2521. Comins, D. L.; Dehghani, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1838. Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35,* 9213. Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493. Toyota, M.; Takanobu, A.; Fukumoto, K. *Tetrahedron Lett.* **1996**, *37,* 4401. Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32,* 5697. Braudi, A.; Cordero, F. M.; Goti, A.; Guarua, A. *Tetrahedron Lett.* **1992**, *33,* 6697. Polniaszek, R. P.; Dillard, L. W. *J. Org. Chem.* **1992**, *57,* 4103. Meyers, A. I.; Milot, G. *J. Am. Chem. Soc.* **1993**, *115*, 6652. Mehta, G.; Praveen, M. *J. Org. Chem.* **1995**, *60,* 279.
4. Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123.
5. Marino, J. P., Jr.; Osterhout, M. H.; Padwa, A. *J. Org. Chem.* **1995**, *60,* 2704.
6. DeLucchi, O.; Miotti, U.; Modena, G. *Organic Reactions;* Paquette, L. A., Ed.; John Wiley: New York, 1991, Chap. 3, pp 157-184. Grierson, D. S.; Husson, H. P. In *Comprehensive Organic Synthesis;* Trost, B. M., Ed.; Pergamon: Oxford, 1991, Vol 6, pp 909-947.
7. Cochran, J. E.; Padwa, A. *Tetrahedron Lett.* **1995**, *36,* 3495. Cochran, J. E.; Padwa, A., *J. Org. Chem.* **1995**, *60,* 3938. Padwa, A.; Cochran, J. E.; Kappe, C. O. *J. Org. Chem.* **1996**, *61,* 3706. Padwa, A.; Kappe, C. O.; Reger, T. S. *J. Org. Chem.* **1996**, *61,* 4888. Kappe, C. O.; Padwa, A. *J. Org. Chem.* **1996**, *61,* 6166.
8. Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1997**, *62,* in press.
9. Imidosulfoxide **5** was prepared in 3 steps from 6-heptenoic acid by conversion to the corresponding *N*-benzylamide followed by reaction with ethylsulfenylacetyl chloride and oxidation using sodium periodate.
10. McMurray, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24,* 979.
11. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25,* 4821.
12. Ibuka, T.; Masaki, N.; Saji, I.; Tanaka, K.; Inubushi, Y. *Chem. Pharm. Bull.* **1975**, *23,* 2779.
13. Mabic, S.; Castagnoli, N., Jr. *J. Org. Chem.* **1996**, *61,* 309.
14. Murahashi, S.; Sasao, S.; Saito, E.; Naota, T. *Tetrahedron* **1993**, *49,* 8805.
15. Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60,* 48. Maruola, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105,* 2831.

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