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An Aza-Wittig/π-Furan Cyclization Approach Toward the Homoerythrina Alkaloid (±)-Selaginoidine

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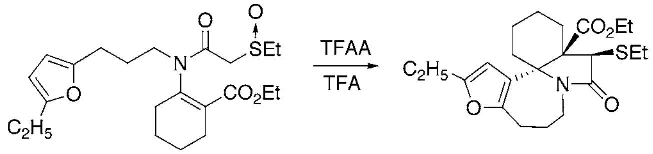
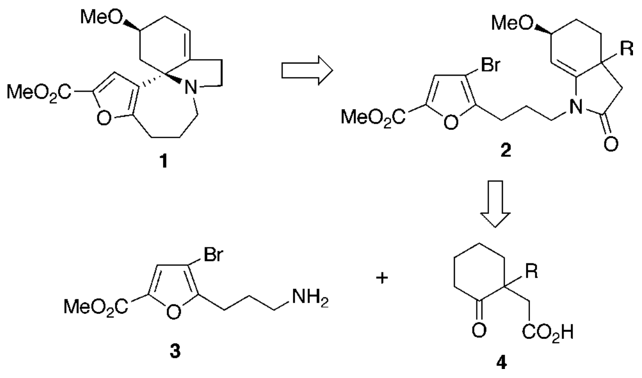
ABSTRACT



A one-pot procedure was developed to efficiently prepare hexahydroindolinones containing a tethered furan ring. Reaction of a furanyl azide with Bu_3P delivered the iminophosphorane, which was allowed to react with 1-methyl-(2-oxocyclohexyl)acetic acid to give the desired hexahydroindolinone ring system. Further treatment with trifluoroacetic acid afforded the tetracyclic lactam skeleton found in the alkaloid (±)-selaginoidine.

The taxodeaceous plant *Athrotaxis selaginoides* is well-known in Tasmania under the name of King Billy Pine and is highly valued as a source of softwood timber.[1,2] Some specimens of the tree attain a height of 40 m and are over 1000 years old. A number of alkaloids are present in all of its plant materials, including the bark and leaves.[3] One of the compounds isolated was assigned the structure of (±)-selaginoidine (**1**), which corresponds to a unique nonbenzenoid member of the homoerythrina alkaloid family.[4] On the basis of our earlier work using hexahydroindolinone derivatives for the synthesis of various erythrina alkaloids,[5] we felt that a suitably substituted hexahydroindolinone precursor might allow for a facile entry to the tetracyclic core of selaginoidine (**1**). The formation of the homoerythrina skeleton of **1** was envisioned to come about from either a Heck or radical-induced cyclization of the bromo-furanyl hexahydroindolinone **2** (Scheme 1). A convenient way to construct **2** would involve condensation of furanylamine **3** with a (1-substituted-2-oxo-cyclohexyl)acetic acid derivative (i.e., **4**) under Dean−Stark conditions.[6]

Scheme 1



Accordingly, 2,3-dibromo-5-carbomethoxyfuran (**5**)[7] was subjected to a Pd(0)-catalyzed coupling with allyl alcohol.[8] This resulted in exclusive reaction at the 2-bromo position

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[1] Curtis, W. M. *The Student's Flora of Tasmania, Part I*; Tasmanian Government Printer: Hobart, 1956; p 6.

[2] Bick, I. R. C.; Bremner, J. B.; Razak, A.; Thuc, L. V. *Experientia* **1980**, *36*, 1135.

[3] Panichanun, S.; Bick, I. R. C. *Tetrahedron* **1984**, *40*, 2685.

[4] Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1996; Vol. 48, pp 249−337.

[5] Lee, H. I.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 5067.

[6] (a) Ragan, J. A.; Claffey, M. C. *Heterocycles* **1995**, *41*, 57. (b) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D, W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813.

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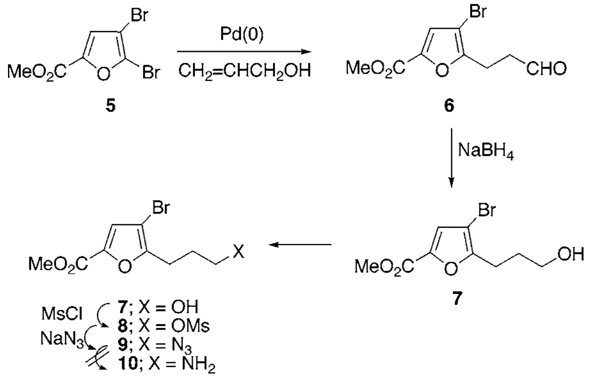
and delivered aldehyde **6** in 70% yield.[9] A subsequent reduction of **6** with sodium borohydride afforded the expected alcohol **7**, which in turn was converted into the corresponding mesylate **8**. Treatment of **8** with NaN_3 in DMF furnished furanyl azide **9** in 93% yield (Scheme 2).

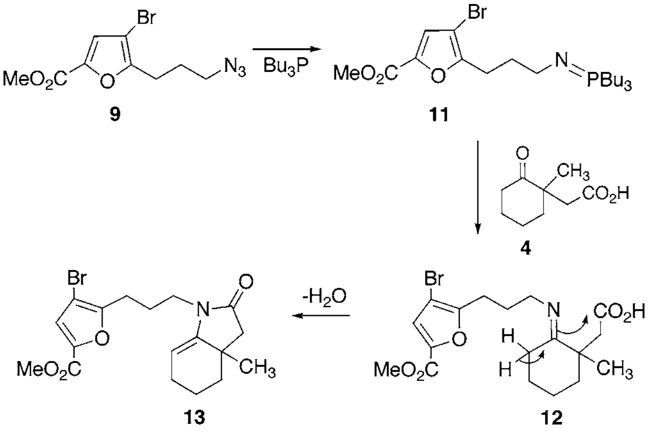
Scheme 2



The reduction of azides to amines is a reaction of paramount importance in organic synthesis; therefore, a great many reagents have been reported to effect this transformation.[10] Indeed, there has always been a considerable interest in searching for more efficient and chemoselective azide reducing agents.[11] In our hands, however, the reduction of azide **9** to amine **10** proved somewhat problematic due to the presence of both the ester and bromo groups. Our attempts to hydrogenate the azide group were complicated as a result of the simultaneous reduction of the bromo group. The Staudinger reaction[12] using the iminophosphorane derived from **9** also proved troublesome, as we could only obtain amine **10** as an impure oil in low yield.

Iminophosphoranes were first prepared at the beginning of the last century by Staudinger and have become extremely useful reagents for the construction of nitrogen containing heterocycles.[12] The aza-Wittig reaction corresponds to the nitrogen analogue of the Wittig olefination process and involves the reaction of an iminophosphorane with a carbonyl group. The reaction has been used to prepare various cyclic imines and its synthetic relevance has been summarized in several review articles.[13] The intramolecular version of this reaction has drawn considerable attention in recent years because of its high potential for heterocyclic synthesis.[14] Since we were having a great deal of difficulty in converting azide **9** into amine **10** for subsequent condensation with ketoacid **4** (R = Me), we wondered whether it might be possible to use azide **9** directly without the intervention of **10**. Thus, an aza-Wittig type reaction of **11** with ketoacid **4** should generate imine **12**, which we expected to rapidly cyclize and furnish the desired hexahydroindolinone system **13** (Scheme 3).[15] Indeed, this proved to be the case, especially when microwave technology was applied to the condensation reaction.

Scheme 3



The advent of single mode microwave reactors, which enable precise control of reaction conditions, has opened the way for the exploration of microwave-assisted methods for organic synthesis.[16] With this in mind, we used microwave irradiation employing several different azides to rapidly access a number of heterocyclic frameworks with abbreviated reaction times and yields far exceeding those of conventional thermal methods. In a typical example, the reaction of azide **9** with tributylphosphine (Bu3P) was carried out at 25 °C using xylene as a solvent. Preformation of the iminophosphorane intermediate was necessary. Addition of ketoacid **4** followed by microwave irradiation in a sealed 10-mL vial

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[7] Chadwick, D. J.; Chambers, J.; Meakins, G. D.; Snowden, R. L. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1766.

[8] Diederich, F., Stang, P. J., Eds.; *Metal-Catalyzed Cross-Coupling Reactions;* Wiley-VCH; Weinheim, Germany, 1998.

[9] Bach, T.; Krüger, L. *Synlett* **1998**, 1185.

[10] (a) Marson, C. M.; Hobson, A. D. In *Comprehensive Organic Functional Group Transformations*; Ley, S. V., Ed.; Pergamon-Elsevier: Oxford, U.K., 1995; Vol. 2, pp 297−332. (b) Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 8, pp 381−402. (c) Hassner, A. In *Houben-Weyl Methods of Organic Chemistry*, 4th ed.; Georg-Thieme Verlag: Stuttgart, Germany, 1990; Vol. E16a, Part 2, pp 1243−1290. (d) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 298.

[11] For some recent methods, see: (a) Rao, H. S. P.; Siva, P. *Synth. Commun.* **1994**, *24*, 549. (b) Ranu, B. C.; Sarkar, A.; Chakraborty, R. *J. Org. Chem.* **1994**, *59*, 4114. (c) Alvarez, S. G.; Fisher, G. B.; Singaram, B. *Tetrahedron Lett.* **1995**, *36*, 2567. (d) Salunkhe, A. M.; Brown, H. C. *Tetrahedron Lett.* **1995**, *36*, 7987. (e) Capperucci, A.; Degl'Innocenti, A.; Funicello, M.; Mauriello, G.; Scafato, P.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 2254. (f) Goulaouic-Dubois, G.; Hesse, M. *Tetrahedron Lett.* **1995**, *36*, 7427. (h) Ramesha, A. R.; Bhat, S.; Chandrasekaran, S. *J. Org. Chem.* **1995**, *60*, 7682. (i) Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J. S.; Ghosh, A. C. *Tetrahedron Lett.* **1996**, *37*, 4559. (j) Peters, R. G.; Warner, B. P.; Burns, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 5585.

[12] Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.

[13] (a) Wamhoff, H.; Richardt, G.; Stölben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 159. (b) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209. (c) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.* **1991**, *23*, 1. (d) Fresneda, P. M.; Molina, P. *Synlett* **2004**, 1.

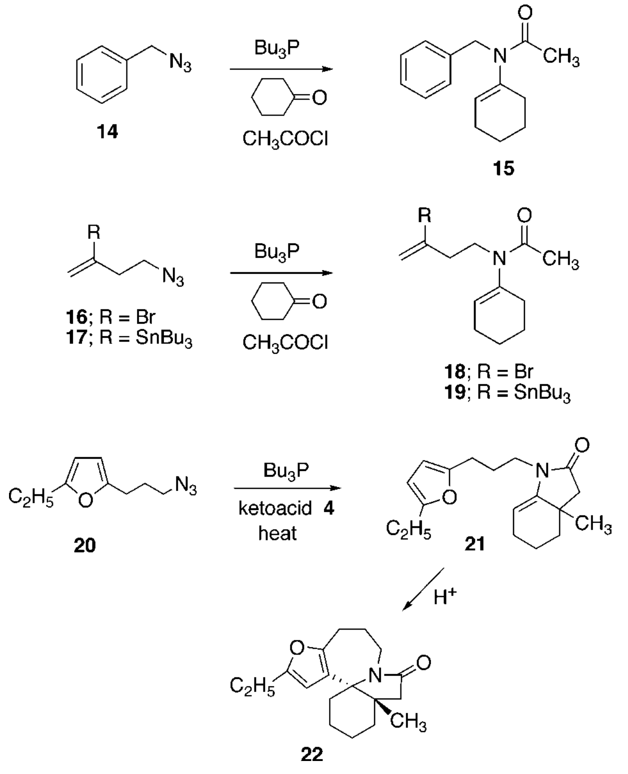
[14] (a) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1917. (b) Gusari, N. I. *Russ. Chem. Rev. (Engl. Transl.)* **1991**, *60*, 146.

[15] Unfortunately, all of our attempts to induce a Heck or radical cyclization of **13** failed. We are currently investigating a Lewis acid induced cyclization of the debrominated furan derived from **13**.

[16] Loupy, A., Ed.; *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.

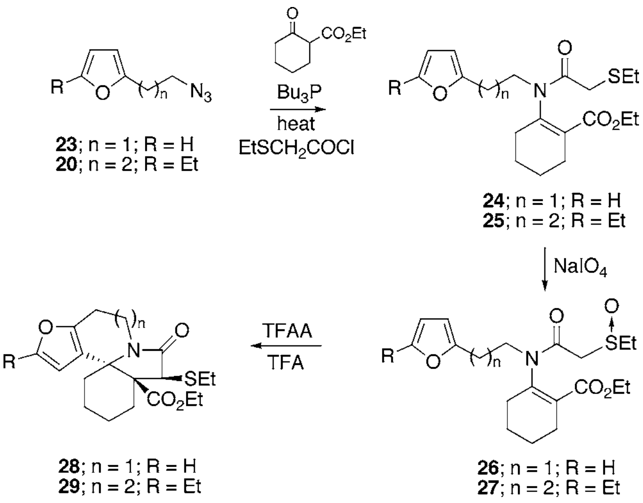
(200 W, 150 °C, 30 min) gave the best results, producing hexahydroindolinone **13** in 63% yield. This optimized method was then applied to a number of related condensation reactions where the azide, ketone, and acid chloride were varied (Scheme 4). Heating a 1:1 mixture of furanyl azide **20** with ketoacid **4** in a microwave reactor at 180 °C for 30 min delivered not only the desired hexahydroindolinone **21** (80%) but also the tetracyclic furan **22** (15%) derived from a *N*-acyliminium ion promoted cyclization of **21** under the reaction conditions.[17] Further experimentation showed that treating **21** with either trifluoroacetic acid or trifluoromethane sulfonic acid gave lactam **22** in >90% yield.

Scheme 4



Earlier work in our laboratory has shown that the Pummerer reaction followed by a π-cyclization represents an effective and general method for the preparation of many diverse azapolycyclic skeletons.[18] Since the combination of a Pummerer/Mannich cyclization sequence offers unique opportunities for the assemblage of complex target molecules,[19] we decided to study the acid-induced cyclization of enamides **27** ($n = 1$) and **28** ($n = 2$) to determine whether these systems could also be used to assemble the core skeleton of the erythrina/homoerythrina family of alkaloids. Furanyl azide **23** was easily converted into the desired enamide sulfide (i.e., **24**) following the azide/iminophosphorane/ethylthioacetyl chloride protocol already established (Scheme 5). A subsequent sodium periodate oxidation afforded sulfoxide **26**, which on treatment with trifluoroacetic acid furnished the tetracyclic lactam **28** in 76% yield as the exclusive product. The preferential formation of **28** is consistent with our earlier stereochemical observations, suggesting that a 4π-Nazarov type electrocyclization controls the direction of closure from the α-acylthionium ion intermediate.[21] The Pictet–Spengler step involves attack of the proximal furanyl ring from the less hindered side of the iminium ion.

Scheme 5



To demonstrate that this methodology could also be used for assembling the homoerythrina skeleton, the homologous enamido furanyl sulfoxide **27** was subjected to the acid-catalyzed cyclization conditions (Scheme 5). The major product isolated (40%) corresponded to the cyclized lactam **29**. Presumably, the lower yield of product is related to the entropically more demanding seven-membered ring cyclization onto the resulting *N*-acyliminium ion formed from the initial Pummerer reaction. Further studies need to be carried out in order to maximize the yield of **29**.

In summary, we have shown that a variety of vinylogous amides and hexahydroindolinones can be prepared using an aza-Wittig reaction of iminophosphoranes derived from furanyl azides and 1-methyl-(2-oxo-cyclohexyl)acetic acid. Intramolecular electrophilic substitution on the furan ring occurs when the hexahydroindolinone is treated with acid. Further studies on the synthesis of selaginoidine (**1**) and

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(17) (a) Ito, K.; Suzuki, F.; Haruna, M. *J. Chem. Soc., Chem. Commun.* **1978**, 733. (b) Tsuda, Y.; Hosoi, S.; Katagiri, N.; Kaneko, C.; Sano, T. *Chem. Pharm. Bull.* **1993**, *41*, 2087. (c) Hosoi, S.; Nagao, M.; Tsuda, Y.; Isobe, K.; Sano, T.; Ohta, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1505.

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related homoerythrinane alkaloids are in progress and will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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