ORGANIC LETTERS

2003
Vol. 5, No. 19
3427−3429

A Concise Asymmetric Route to *Nuphar* Alkaloids. A Formal Synthesis of (–)-Deoxynupharidine

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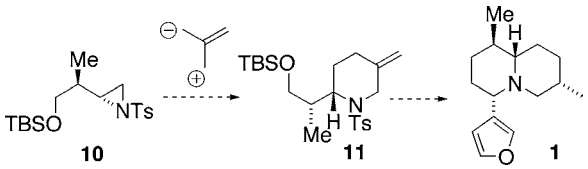
Received June 23, 2003

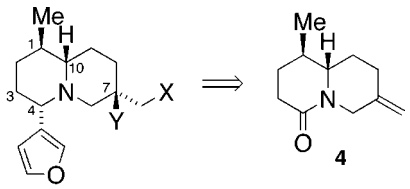
ABSTRACT



A stereocontrolled route to *Nuphar* alkaloids is described that employs a formal [3 + 3] cycloaddition strategy to assemble the piperidine nucleus. The addition of Pd–TMM complexes to aziridine 10 was found to be sluggish; however, the addition of a functionalized allyl Grignard reagent followed by a Mitsunobu condensation reaction provided 11 in high yield. The employment of this route in the formal synthesis of (–)-deoxynupharidine 1 is described.

(−)-Deoxynupharidine **1** is a member of a large class of terpenoid alkaloids isolated from plants of the genus *Nuphar*.[1] All *Nuphar* alkaloids are characterized by the presence of one or more furan rings and almost all display a quinolizidine core. We have been investigating a short and convergent strategy for the stereocontrolled synthesis of **1**[2] and related compounds (−)-castoramine **2**[3] and (−)-nupharolutine **3**.[4] Specifically and as outlined in Figure 1, we envisaged that compounds **1**−**3** could all be prepared from intermediate **4** after appropriate stereoselective oxidative or reductive alkene functionalization reactions. Therefore, quinolizidinone **4** would represent a late-stage intermediate which could be transformed into a variety of *Nuphar* alkaloids after only a few steps. We wish to disclose herein a short stereoselective synthesis of **4** and its employment in a formal total synthesis of (−)-**1**.

We have recently reported a stereoselective technique for the preparation of functionalized piperidines through a formal



X=Y=H; (-)-Deoxynupharidine **1**
X=OH, Y=H; (-)-Castoramine **2**
X=H, Y=OH; (-)-Nupharolutine **3**

Figure 1. Retrosynthesis of alkaloids **1**−**3** to key lactam **4**.

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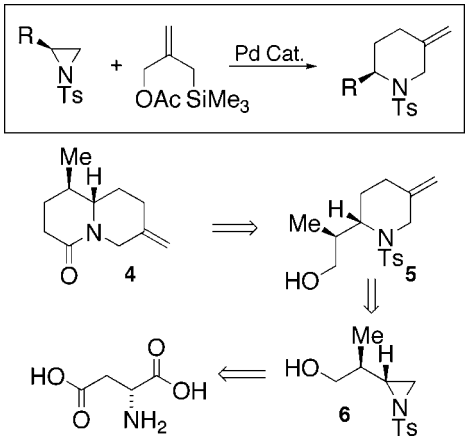
(1) For leading references on isolation studies and bioactivities see: (a) Miyazawa, M.; Yoshio, K.; Ishikawa, Y.; Kameoka, H. *J. Agric. Food Chem.* **1998**, *46*, 1059. (b) Matsuda, M.; Shimoda, H.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 1031.
(2) (a) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719. (b) Hwang, Y. C.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 3885.
(3) Bohlmann, F.; Winterfeldt, E.; Laurent, H.; Ude, W. *Tetrahedron* **1963**, *19*, 195.
(4) (a) Natsume, M.; Ogawa, M. *Heterocycles* **1981**, *15*, 237. (b) LaLonde, R. T.; Muhammad, N.; Wong, C. F.; Sturiale, E. R. *J. Org. Chem.* **1980**, *45*, 3664.

10.1021/ol035156t CCC: $25.00
Published on Web 08/28/2003

[3 + 3] cycloaddition reaction of *N*-tosylaziridines with Pd−trimethylenemethane (Pd−TMM) complexes.[5,6]

This reaction proved to be an effective and expeditious method for the synthesis of 2-substituted piperidines in enantiomerically pure form (Scheme 1, see box). A notable

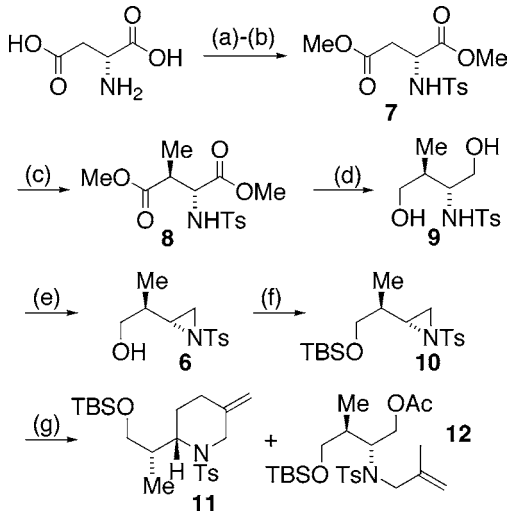
Scheme 1



characteristic of this process is that the products are armed with a readily functionalizable exocyclic alkene moiety. This latter feature made the cycloaddition reaction particularly suitable for the synthesis of **4** since it offered a potentially facile route for piperidine assembly with installment of stereochemistry at C-1 and C-10, as well as introducing the pivotal alkene moiety at C-7. The retrosynthetic analysis for our approach to **4** is described in Scheme 1. We anticipated that the lactam unit could be prepared by suitable elaboration of alcohol **5**, which would in turn be assembled through the key cycloaddition reaction of aziridine **6**. Enantiomerically pure 2-substituted aziridines are readily derived from the corresponding amino acids;[7] therefore, we anticipated that **6** would derive from (*R*)-aspartic acid.

The first goal in our synthetic sequence was to elaborate aspartic acid to a β-methylaspartic acid derivative that would install the Me-group present at the C-1 position of the natural product with correct stereochemistry. A survey of the literature revealed that similar alkylation reactions of β-amino esters proceeded with high levels of stereoselectivity, particularly when *N*-tosyl protecting groups were employed.[8] In view of this fact, coupled with the need for sulfonamide protection of the aziridine nitrogen in the key cycloaddition step,[5a,b] we opted to examine the diastereoselectivity of a *p*-toluenesulfonamide derived aspartate **7**. As outlined in Scheme 2, esterification of (*R*)-aspartic acid followed by

Scheme 2[a]



[a] Key: (a) MeOH, $SOCl_2$, 25 °C, 48 h, 98%; (b) TsCl, Et_3N, 25 °C, 16 h, 79%; (c) LiHMDS, −78 °C; MeI, −78 to +25 °C 16 h, 89%; (d) $LiAlH_4$, 25 °C, 16 h, 98%; (e) PBu_3, ADDP, Tol, 16 h; (f) TBSCl, imidazole, THF 5 h, 90% over two steps; (g) $AcOCH_2C(=CH_2)CH_2SiMe_3$, 10 mol % $Pd(OAc)_2$, 25 mol % DPPP, THF, 65 °C, **11** (41%), **12** (30%).

amine protection with tosyl chloride furnished **7** in high yield. Subsequent deprotonation with LiHMDS at −78 °C followed by quenching of the ester enolate with methyl iodide provided the desired product **8** which was isolated as a single diastereomer in excellent yield. Literature precedent suggested that the requisite (2*R*,3*S*)-stereochemistry would be generated in this process, and this was confirmed by X-ray crystallographic analysis.[9]

At this stage, we were unable to find conditions for the selective reduction of either ester moiety of **8** and therefore undertook exhaustive reduction to furnish diol **9**. Our final steps required the selective functionalization of the α-amino alcohol motif for ring closure to the aziridine; however, we were unable to carry out selective functionalization reactions on either alcohol moiety. We therefore decided to exploit the well-established preference for three-membered ring closure over four-membered ring cyclization to perform the necessary differentiation of the alcohol units. Indeed, we were pleased to find that subjecting **9** to a Mitsunobu condensation reaction resulted in smooth and selective formation of aziridine **6**. We encountered some difficulties in removing residual hydrazide in the purification of **6** and therefore carried out TBS-protection of the crude alcohol to furnish aziridine **10** in excellent yield over the two steps. Unfortu-

(5) (a) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett* **2001**, 1596. (b) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286. (c) Recently, a complementary [3 + 3] cycloaddition approach to piperidines has been reported: Slkenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.-I.; Gerasyuto, A. I.; Brennessel, W. B. *J. Am. Chem. Soc.* **2002**, *124*, 10435.

(6) Trost and co-workers have pioneered the use of Pd-TMM complexes in cycloaddition reactions: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1 and references therein.

(7) Berry, M. B.; Craig, D. *Synlett* **1992**, 41.

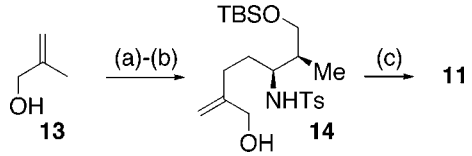
(8) (a) Hanessian, S.; Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401. (b) Humphrey, J. M.; Bridges, R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem.* **1994**, *59*, 2467. (c) Wang, J.; Hou, Y.; Wu, P.; Qu, Z.; Chan, A. S. C. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4553.

(9) Crystallographic data for **8** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 210220. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

nately, **10** proved to be remarkably sluggish toward Pd-catalyzed [3 + 3] cycloaddition in the presence of phosphite ligands. In the event, recourse to more electron-rich DPPP ligand was found to be essential to achieve reasonable levels of aziridine conversion, albeit furnishing piperidine **11** in a modest 41% yield. The remainder of the mass balance from this reaction largely consisted of starting aziridine and acetate-opened product **12**.[10,11]

The low yields afforded by the Pd-catalyzed [3 + 3] cycloaddition process prompted us to investigate alternative, and more nucleophilic, conjunctive reagents for the preparation of **11**. Indeed, we were pleased to find that subjection of aziridine **10** to the allyl Grignard reagent derived from inexpensive **13** furnished **11** in a much improved yield after a Mitsunobu ring-closure reaction of **14** (Scheme 3). Notably,

Scheme 3[a]

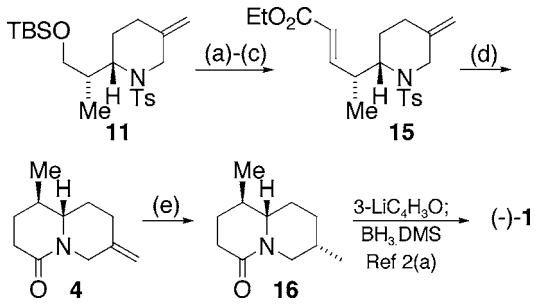


[a] Key: (a) (i) *n*-BuLi (2.6 equiv), TMEDA (3.0 equiv), Et_2O, 0 °C, 16 h, (ii) $MgBr_2$, 0 °C, 4 h; (b) **10**, 25 °C, 48 h, 80%; (c) *n*-Bu_3P, ADDP, Tol, 25 °C, 87%.

the requisite conjunctive reagent for the Pd-catalyzed process (2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate) is prepared from **13** by a two-step procedure.[12] Therefore, this stepwise process represents a complementary technique to the [3 + 3] cycloaddition chemistry and promises to furnish piperidines which are currently inaccessible by the Pd-catalyzed methods.

The final steps toward quinolizidine **4** through homologation of the protected alcohol unit were carried out as shown

Scheme 4[a]



[a] Key: (a) TBAF, THF, 25 °C, 86%; (b) Swern; (c) $Ph_3P{=}C(H)$-CO_2Et, THF, 25 °C, 16 h, 76% over two steps; (d) Mg, MeOH, 25 °C, 56%; (e) H_2, 10% Pd/C, 100% (6.5:1).

in Scheme 4. Desilylation of **11** proceeded without incident and the resulting alcohol was subjected to Swern oxidation followed by Wittig olefination to provide ester **15**. The final steps in the reaction sequence to lactam **4** required chemoselective reduction of the electron deficient alkene and cleavage of the sulfonamide group, both of which could potentially be achieved in a single pot under reductive conditions. We therefore subjected piperidine **15** to excess Mg metal in MeOH and were pleased to find that both alkene reduction and sulfonamide cleavage proceeded smoothly, moreover, the intermediate amine cyclized spontaneously under the reaction conditions to furnish key lactam **4** in 56% yield. Subsequent hydrogenation of **4** over Pd/C provided quinolizidinone **16** as an inseparable 6.5:1 mixture of diastereoisomers favoring the 7-(*S*) isomer. Installment of the furan moiety using Fowler's procedure allowed a pure sample of (−)-**1** to be obtained that gave spectral data in accord with that reported.[2] The employment of this strategy in the preparation of other members of the *Nuphar* family of alkaloids is underway and will be reported in due course.

Acknowledgment. We thank the EPSRC and The University of Sheffield for financial support and MSD for a studentship award (K.M.G.).

Supporting Information Available: Full experimental details for the syntheses reported are provided. This material is available free of charge via the Internet at http://pubs.acs.org

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(10) We have investigated a number of phosphine and phosphite ligands in an attempt to promote this transformation and DPPP has been optimum thus far. For example the use of triisopropyl phosphite resulted in very low conversion (furnishing **11** in 10−15% yield) whereas tributylphosphine generated **12** in >70% yield. A full account of our efforts to promote the Pd-catalysed [3 + 3] cycloaddition reaction will be presented elsewhere.

(11) Related alkylation products have been observed in [3 + 2] cycloaddition reactions: (a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1983**, *105*, 2315. (b) Naz, N.; Al-Tel, T. H.; Al-Abed, Y.; Voelter, W.; Ficker, R.; Hiller, W. *J. Org. Chem.* **1996**, *61*, 3250.

(12) Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.