JOC*Article*

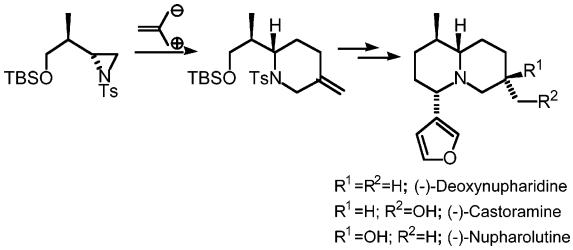
Development of a Flexible Approach to *Nuphar* Alkaloids via Two Enantiospecific Piperidine-Forming Reactions

Katharine M. Goodenough,[†] Wesley J. Moran,[†] Piotr Raubo,[‡] and Joseph P. A. Harrity*,[†]

Department of Chemistry, University of Sheffield, Sheffield S3 7HF, and Neuroscience Research Centre, Merck, Sharp and Dohme, Terlings Park, Harlow, Essex CM20 2QR, U.K.

j.harrity@sheffield.ac.uk

Received September 2, 2004

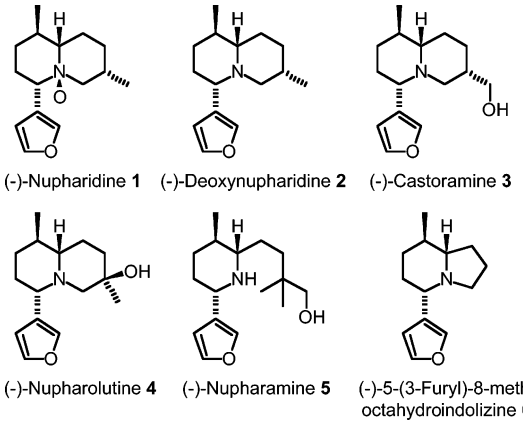


In this paper we describe the stereoselective synthesis of functionalized lactam **7** via two enantiospecific piperidine-forming techniques and its employment in a general synthetic approach to *Nuphar* alkaloids. Specifically, the formation of piperidine **18** by formal [3 + 3] cycloaddition and stepwise annelation processes is described; the latter technique was found to be significantly more efficient than the Pd-catalyzed TMM addition process. Finally, exploitation of the exocyclic alkene installed in the piperidine-forming reaction in the transformation of **18** to (−)-deoxynupharidine ((−)-**2**), (−)-castoramine ((−)-**3**), and (−)-nupharolutine ((−)-**4**) via intermediate lactam **7** is delineated.

Introduction

The asymmetric synthesis of piperidine-based alkaloids is a field of intensive research as these compounds display a broad range of biological activities, and in many cases are available from natural sources in only trace amounts.[1] One such family of sesquiterpenoid and tripernoid alkaloids incorporating piperidine, indolizidine, and quinolizidine rings isolated from aquatic plants of the genus *Nuphar* are known as *Nuphar* alkaloids.[2] The structural motif common to *Nuphar* alkaloids is the presence of a trisubstituted piperidine ring with a methyl group attached at C-3 and a 3-furyl substituent at C-6 (Chart 1). *Nuphar japonicum* DC. is a perennial rhizomatous herb with a wide distribution in the temperate zone of the northern hemisphere. In China and Japan, the dried rhizomes of this plant are used in folk medicine as diuretics and stomach analgesics. Extraction and isolation studies have revealed that sesquiterpene alkaloids such as nupharidine (**1**) and deoxynupharidine (**2**) are present in these rhizomes. Aquatic plants are not the only source of *Nuphar* alkaloids: for example, (−)-5-(3-furyl)-8-methyloctahydroindolizine ((−)-**6**) is a minor compound (0.0002%) detected in castoreum, a perfume extract from the dried scent glands of the Canadian beaver (*Castor fiber* L.).

CHART 1



[†] University of Sheffield.
[‡] Merck, Sharp and Dohme.

(1) (a) Strunzand, G. M.; Finlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1986; Vol. 26, p 89. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.

(2) (a) LaLonde, R. T.; Wong, C.-F.; Das, K. C. *J. Am. Chem. Soc.* **1972**, *94*, 8522. (b) Maurer, B.; Ohloof, G. *Helv. Chim. Acta* **1976**, *59*, 1169.

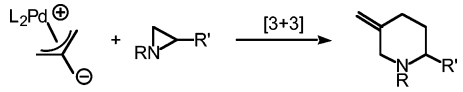
10.1021/jo048455k CCC: $30.25
Published on Web 12/02/2004

In terms of biological activity, Miyazawa and co-workers reported recently their findings on the use of certain *Nuphar* alkaloids as insecticides against *Drosophila melanogaster* Meigen (the common fruit fly).[3] (−)-7-*epi*-Deoxynupharidine and (−)-castoramine ((−)-**3**) revealed themselves as potent insecticides against larvae and adults of this species. In mammals, (−)-deoxynupharidine ((−)-**2**) has been shown to exhibit a central paralysis effect while related dimeric thioalkaloids display potent immunosuppressive and antimetastatic activity.[4]

The total synthesis of *Nuphar* alkaloids has been an active area of research for the past four decades, with the first synthesis of (±)-**3** reported in 1963 by Bohlmann and co-workers, which utilized a reductive amination strategy to assemble the quinolizidine core.[5] **2** has seen considerably more synthetic interest than **3**, as there have been no less than six approaches published.[6] The most recent of these was reported in 1985 by Hwang and Fowler and utilized an intramolecular Diels−Alder reaction to assemble the quinolizidinone core.[6a] (−)-Nupharamine ((−)-**5**) has also been a subject of synthetic interest, with the most recent approach reported in 1999 by Barluenga and co-workers, which utilized a Diels−Alder strategy.[7]

Nuphar alkaloids consist of functionalized piperidine, quinolizidine, and indolizine rings; therefore, a potentially facile route to some of these alkaloids could be envisaged utilizing the palladium-catalyzed [3 + 3] cycloaddition technology recently developed in our laboratories (Scheme 1).[8,9] This technique provides an efficient method for the synthesis of enantiopure 2-substituted piperidines from the corresponding aziridines using Trost's in situ generated Pd−trimethylenemethane (Pd−TMM) reagent.[10]

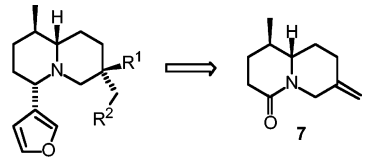
SCHEME 1



Results and Discussion

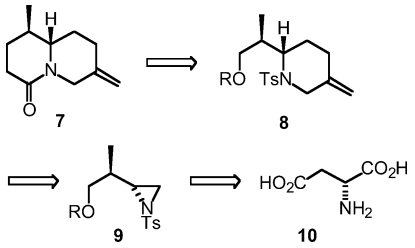
As outlined in Scheme 2, we anticipated that (−)-**2**, (−)-**3**, and (−)-nupharolutine ((−)-**4**) could potentially be accessed from one common late-stage intermediate, **7**, through appropriate functionalization reactions of the exocyclic methylene group and addition of the 3-furyl group using the method of Fowler.[6a,b]

SCHEME 2

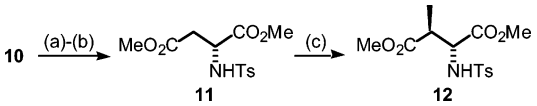


R^1=R^2=H; **2**
R^1=H; R^2=OH; **3**
R^1=OH; R^2=H; **4**

SCHEME 3



SCHEME 4[a]



[a] Reagents and conditions: (a) MeOH, $SOCl_2$, rt, 48 h, 98%; (b) TsCl, Et_3N, THF, rt, 16 h, 79%; (c) LiHMDS, MeI, THF, −78 °C to rt, 16 h, 89%.

Disconnection of quinolizidinone **7** at the lactam suggested the *N*-tosylpiperidine derivative **8**, which in turn was envisaged to originate from aziridine **9** after implementation of the [3 + 3] cycloaddition reaction. Enantiomerically pure aziridines are readily available from the corresponding amino acids; thus, we anticipated that **9** would derive from (*R*)-aspartic acid (**10**) (Scheme 3).

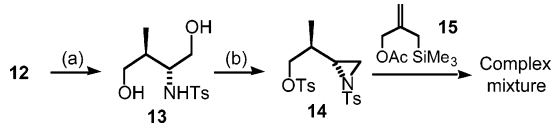
The work of Kim and co-workers, concerning the synthesis of α-amino acid containing aziridines, provided the inspiration for the formation of aziridines of general structure **9**.[11] Accordingly, **10** was converted into the dimethyl ester by treatment with thionyl chloride in methanol for 48 h; subsequent protection of the amine with tosyl chloride provided **11** in high overall yield. With this substrate in hand, the key alkylation reaction was attempted to install the C-3 methyl group in a diastereoselective fashion. In the event, treatment with strong base and quenching of the resulting enolate with iodomethane provided smooth access to the alkylated product **12** in excellent yield as a single diastereomer (Scheme 4).[12]

Our rationale for the observed diastereoselectivity in the formation of **12** is depicted in Chart 2. Initial removal of the sulfonamide proton directs formation of the (*Z*)-enolate[13] that could exist as structure **I** or **II**. Structures

(3) Miyazawa, M.; Yoshio, K.; Ishikawa, Y.; Kameoka, H. *J. Agric. Food Chem.* **1998**, *46*, 1059.
(4) (a) Matsuda, H.; Shimoda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2001**, *9*, 1031. (b) Matsuda, H.; Morikawa, T.; Oda, M.; Asao, Y.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4445.
(5) Bohlmann, F.; Winterfeldt, E.; Laurent, H.; Ude, W. *Tetrahedron* **1963**, *19*, 195.
(6) For recent approaches see: (a) Hwang, Y. C.; Fowler, F. *J. Org. Chem.* **1985**, *50*, 2719. (b) Hwang, Y. C.; Chu, M.; Fowler, F. *J. Org. Chem.* **1985**, *50*, 0, 3885. (c) Yasuda, S.; Hanaoka, M.; Arata, Y. *Chem. Pharm. Bull.* **1980**, *28*, 831. (d) Szychowski, J.; Leniewski, A.; Wrobel, J. T. *Chem. Ind. (London)* **1978**, 273.
(7) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1999**, *64*, 3736.
(8) (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.
(9) For a preliminary report on our studies toward *Nuphar* alkaloids see: Moran, W. J.; Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2003**, *5*, 3427.
(10) For a comprehensive review see: Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.
(11) Park, J.-I.; Tian, G. R.; Kim, D. H. *J. Org. Chem.* **2001**, *66*, 3696.
(12) The relative stereochemistry of **12** was assigned by X-ray crystallography. Crystallographic data for **12** have been deposited with the CCDC as Supplementary Publication Number CCDC 210220.
(13) Humphrey, J. M.; Bridges, R. J.; Hart, J. A.; Chamberlin, A. R. *J. Org. Chem.* **1994**, *59*, 2467.

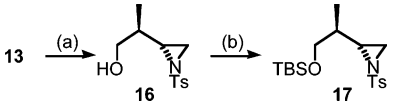
CHART 2

SCHEME 5[a]



[a] Reagents and conditions: (a) LAH, THF, rt, 16 h, 99%; (b) TsCl, Et_3N, cat. DMAP, rt, 16 h, 67%; (c) **15**, 10 mol % $Pd(OAc)_2$, 60 mol % P(OPr-*i*)$_3$, 20 mol % BuLi, THF, 70 °C, 16 h.

SCHEME 6[a]



[a] Reagents and conditions: (a) ADDP, PBu_3, toluene, rt, 16 h; (b) TBSCl, imidazole, THF, rt, 5 h, 90% (over two steps).

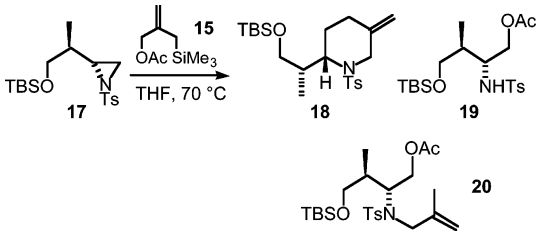
similar to **I** have been put forward by Hanessian and co-workers during their functionalization studies on *N*-tosyl aspartates and glutamates.[14] More recently, Wang and co-workers have reported closely related diastereoselective alkylation reactions via a structure analogous to **II**.[15]

At this stage we wished independently to manipulate one of the two ester groups of **12** but were unable to find conditions for the selective reduction of either ester and therefore undertook exhaustive reduction to furnish diol **13**. Subsequent treatment with *p*-TsCl and base provided smooth access to aziridine **14** in good yield. The stage was now set for the key [3 + 3] cycloaddition reaction. In the event, treatment with 1.5 equiv of conjunctive reagent **15** in the presence of a palladium phosphite catalyst system failed to provide the desired piperidine product; instead an intractable mixture of compounds was produced (Scheme 5).

We next decided to investigate a Mitsunobu cyclization of diol **13** in an attempt to produce an aziridine that would be armed with a hydroxyl moiety that could be appropriately protected. After some initial optimization studies we were pleased to find that smooth and selective formation of aziridine **16** could be achieved using the PBu_3/ADDP system.[16] Some difficulty was encountered in removing residual hydrazide in the purification; therefore, TBS protection of the crude alcohol was effected to furnish aziridine **17** (Scheme 6).

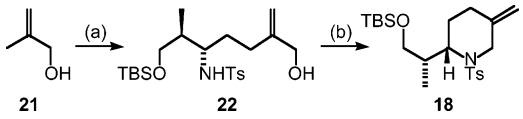
We next turned our attention to the key piperidine-forming cycloaddition reaction, and our results are summarized in Table 1. Employing our established conditions,[8] aziridine **17** was converted to piperidine **18** in a disappointing 20% yield; the remaining mass balance consisted of unreacted aziridine (entry 1). We screened a range of Pd catalyst systems and found triarylphosphine ligands to perform poorly in the reaction; for

TABLE 1



		yield (%)		
entry	conditions	**18**	**19**	**20**
1	10% $Pd(OAc)_2$, 60% P(OPr-*i*)$_3$	20		
2	10% $Pd(PPh_3)_4$	4		
3	10% $Pd(OAc)_2$, 30% P(Bu-*n*)$_3$	28	20	50
4	10% $Pd(OAc)_2$, 25% DPPP	41	20	30

SCHEME 7[a]



[a] Reagents and conditions: (a) (i) BuLi (2.6 equiv), TMEDA (3.0 equiv), Et_2O, 16 h; (ii) $MgBr_2$, THF; (iii) **17**, THF, 70 °C, 18 h, 92%; (b) ADDP, PBu_3, toluene, 16 h, 87%.

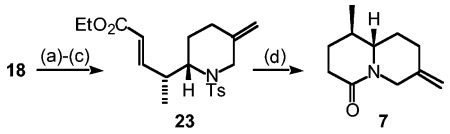
example, $Pd(PPh_3)_4$ furnished **18** in only 4% yield (entry 2). We next examined a series of more electron rich phosphines and were pleased to find a significant improvement in reaction conversion. Indeed, tri-*n*-butylphosphine provided **18** in an improved 28% yield; however, byproducts **19** and **20**[17] arising from acetate ring opening represented the majority of the remaining mass balance. Finally, we examined some bisphosphines and found DPPP to provide the best balance of high reaction conversion while minimizing the formation of byproducts.[18]

Frustrated by the inefficiency of the Pd-catalyzed cycloaddition technique, we decided to investigate an alternative route to **18** from aziridine **17** that would allow a greater quantity of the piperidine to be made available for further elaboration to the target *Nuphar* alkaloids. Accordingly, we established a complementary two-step strategy to **18** as outlined in Scheme 7. Methallyl alcohol **21** was treated with excess butyllithium followed by $MgBr_2$ and the resulting Grignard reagent reacted with **17**[19] to give amino alcohol **22** in excellent yield. Pleasingly, subjection of **22** to the Mitsunobu reaction using ADDP and PBu_3 furnished the piperidine **18** in 87% yield. Thus, the two-step procedure allowed us to prepare the piperidine intermediate in an 80% overall yield from starting aziridine **17**.

With an efficient route to piperidine **18** secured, attention was turned to the remaining steps of the synthesis. Removal of the silyl protecting group with

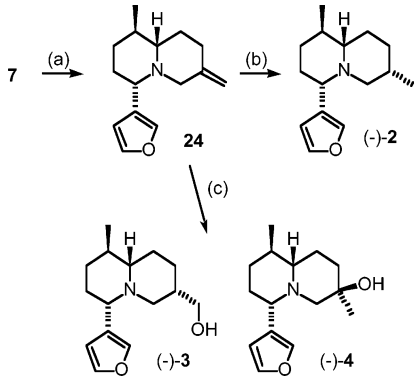
(14) Hanessian, S.; Vanasse, B. *Can. J. Chem.* **1993**, *71*, 1401.
(15) Wang, J.; Hou, Y.; Wu, P.; Qu, Z.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1999**, *10*, 4553.
(16) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639.
(17) Related alkylation products have been observed 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
(18) We investigated various analogues of **17** bearing TBDPS, TES ethers, and acetate, but these showed similar reactivities.
(19) The double deprotonation of **21** is the first step in the preparation of conjunctive reagent **15**: Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58.

SCHEME 8[a]



[a] Reagents and conditions: (a) TBAF, THF, rt, 4 h, 86%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to rt, 2 h; (c) $Ph_3P{=}CHCO_2Et$, THF, rt, 16 h, 78% (over two steps); (d) Mg, MeOH, rt, 3 h, 72%.

SCHEME 9[a]

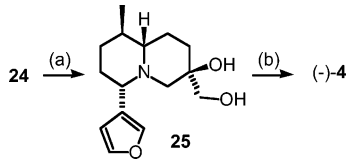


[a] Reagents and conditions: (a) (i) 3-LiC_4H_3O, Et_2O, −78 °C to rt, 2 h; (ii) DIBAL-H, 1 h, 76%; (b) H_2, Rh/Al_2O_3, EtOAc, rt, 3 h, 60%; (c) (i) BH_3·DMS, THF, rt, 2 h; (ii) H_2O_2, NaOH, rt, 52% (**3**:**4** = 1:1).

TBAF followed by Swern oxidation provided an aldehyde that was converted to the α,β-unsaturated ester **23** after a Wittig reaction (Scheme 8). To convert piperidine **23** into key late-stage intermediate quinolizidinone **7**, three transformations were required: (a) chemoselective reduction of the conjugated alkene in the presence of the exocyclic methylene group, (b) removal of the tosyl group, and (c) lactamization. We anticipated that the first two transformations could be achieved in one pot under reductive conditions. An established method of alkene reduction in enoates uses magnesium in methanol,[20] while the same reagents represent a mild method of cleaving sulfonamides.[21] Accordingly, piperidine **23** was stirred in a suspension of Mg turnings in dry methanol, and we were delighted to find that all three transformations took place in one pot to provide **7** in high overall yield.

Our final task was to convert **7** into a series of *Nuphar* alkaloids, and we chose (−)-**2**, (−)-**3**, and (−)-**4** as representative targets; our results are shown in Scheme 9. Installment of the furan moiety was carried out first to leave the exocyclic alkene for further elaboration to (−)-**2**, (−)-**3**, and (−)-**4**. Addition of 3-lithiofuran to the lactam **7** and in situ reduction of the intermediate carbinolamine with borane−dimethyl sulfide (DMS) led to a complex mixture of products. It seemed likely that competing alkene hydroboration was responsible for the observed outcome, and we therefore opted to use DIBAL-H as the reducing agent. In the event, addition of 3-lithiofuran followed by reduction with DIBAL-H resulted in the formation of quinolizidine **24** in good yield and

SCHEME 10[a]



[a] Reagents and conditions: (a) cat. OsO_4, NMO, acetone/H_2O (4:1), rt, 1 h, 71%; (b) (i) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, 48 h; (ii) LAH, THF, reflux, 3 h, 66%.

pleasingly as a single diastereomer. We were now in a position to investigate the functionalization of **24** toward *Nuphar* alkaloids. Indeed, hydrogenation of **24** in the presence of a Rh/Al_2O_3 catalyst furnished (−)-**2**, which showed spectroscopic data identical to those reported by Fowler.[6a,b] Additionally, subjection of **24** to borane−DMS resulted in the formation of an equal mixture of two compounds that were characterized as (−)-**3** and (−)-**4**.[22] We were surprised by the poor regioselectivity observed in the hydroboration and suspect that this arises from competing steric control (to give **3**) and electronic control (to give **4**). The latter pathway is perhaps particularly evident due to complexation of borane to the quinolizidine N-atom.[23]

Finally, we investigated a more selective route to (−)-**4**. Initial studies focused on the oxymercuration of **24**; however, these proceeded in very low conversion. An alternative stepwise procedure was next examined, and this route is outlined in Scheme 10. Dihydroxylation of **24** proceeded with excellent stereocontrol to provide diol **25**. Pleasingly, tosylation of the primary alcohol followed by reduction with LAH furnished (−)-**4** as a single diastereoisomer in good overall yield.

Conclusion

We have developed an efficient strategy to quinolizidinone **7** and found this compound to be a useful late-stage synthetic intermediate for the synthesis of three *Nuphar* alkaloids. Compound **7** was prepared by two complementary and enantiospecific strategies; a Pd−TMM-mediated formal [3 + 3] cycloaddition reaction and a stepwise annelation process. The latter technique may prove to overcome some limitations associated with the [3 + 3] reaction, and work is currently under way in our laboratories to evaluate the scope and potential of this methodology.

Experimental Section

General experimental methods have been reported previously.[8b]

(2*R*,3*S*)-*N*-(*p*-Toluenesulfonyl)-3-methylaspartic Acid Dimethyl Ester (12). A solution of diester **11**[21,24] (1.25 g, 4.0 mmol) in THF (12 mL) was added via cannula to a stirred

(20) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287.

(21) Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *65*, 9455.

(22) The synthetic sample of **4** showed satisfactory spectroscopic data; see: (a) LaLonde, R. T.; Donvito, T. N.; Tsai, A. I. *Can. J. Chem.* **1975**, *53*, 1714. (b) Wróbel, J. T.; Iwanow, A.; Martin, T. I.; MacLean, D. B. *Can. J. Chem.* **1972**, *50*, 1831. However, the ^{13}C spectral data of our synthetic sample of **3** showed some discrepancies with those reported,[3] and further COSY and NOESY experiments were carried out that confirmed the stereochemistry of **3** as that depicted in Chart 1. These data are described in full in the Supporting Information.

(23) Hydroboration of *N*-allylpiperidine provides a 9:1 mixture of primary/secondary alcohols: Baboulène, M.; Torregrosa, J.-L.; Spèziale, V.; Lattes, A. *Bull. Soc. Chim. Fr.* **1980**, 565.

solution of 1.06 M lithium hexamethyldisilazane in THF (LiHMDS, 8.7 mL, 8.7 mmol) precooled to −78 °C under a nitrogen atmosphere. After 2 h, iodomethane (0.3 mL, 4.8 mmol) was added slowly to the reaction mixture, which was warmed to rt, and stirring was continued for a further 15 h. The mixture was quenched by the addition of 3 N HCl to pH ≈ 3, and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure to give an oily residue. Purification by column chromatography (2:1 petroleum ether/EtOAc) gave **12** as a colorless solid (1.17 g, 89%). Mp 73.5−75.5 °C. $[\alpha]^{25}_D$ −24 (c = 1.0, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (3H, d, J = 7.5 Hz), 2.38 (3H, s), 3.11 (1H, dq, J = 4.0, 7.5 Hz), 3.45 (3H, s), 3.62 (3H, s), 4.05 (1H, dd, J = 4.0, J = 9.5 Hz), 5.60 (1H, d, J = 9.5 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.70 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.6, 21.5, 42.3, 52.2, 52.6, 57.8, 127.3, 129.5, 137.0, 143.6, 170.4, 173.5. FTIR (CH_2Cl_2): 3357 (br), 3062 (w), 2956 (m), 1742 (s), 1344 (m), 1166 (s) cm^{-1}. Anal. Calcd for $C_{14}H_{19}NSO_6$: C, 51.05; H, 5.81; N, 4.25; S, 9.74. Found: C, 50.92; H, 5.76; N, 4.20; S, 9.82.

(1*R*,2*S*)-*N*-(3-Hydroxy-1-hydroxymethyl-2-methylpropyl)-4-methylbenzenesulfonamide (13). A solution of the diester **12** (710 mg, 2.2 mmol) in THF (10 mL) was added dropwise via cannula to a solution of lithium aluminum hydride (164 mg, 4.3 mmol) in THF (15 mL) at 0 °C under a nitrogen atmosphere, and the resulting solution was stirred for 16 h at rt. Aqueous HCl solution was added to quench the reaction and the resulting mixture extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to give **13** as a colorless solid (575 mg, 98%). Mp 76.0−78.0 °C. $[\alpha]^{25}_D$ +7 (c = 1.0, $(CH_3)_2CO$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.86 (3H, d, J = 7.0 Hz), 1.76−1.93 (1H, m), 2.42 (3H, s), 3.18−3.25 (1H, m), 3.31 (1H, dd, J = 4.0, 11.5 Hz), 3.45 (1H, dd, J = 6.5, 11.0 Hz), 3.56 (1H, dd, J = 3.0, 11.5 Hz), 3.75 (1H, dd, J = 3.0, 11.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.77 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.8, 21.5, 37.3, 58.0, 63.0, 64.0, 127.1, 129.8, 137.5, 143.6. FTIR (CH_2Cl_2): 3359 (br), 2968 (m), 2935 (m), 1599 (m), 1413 (s), 1332 (s), 1161 (s), 1093 (s) cm^{-1}. HRMS Calcd for $C_{12}H_{20}NSO_4$: 274.1113. Found: 274.1115.

Toluene-4-sulfonic Acid 2-(1-Benzenesulfonylaziridin-2-yl)propyl Ester (14). A solution of the diol **13** (220 mg, 0.8 mmol) in THF (2 mL) was cooled to 0 °C and treated with *p*-toluenesulfonyl chloride (490 mg, 4.8 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred for 16 h at rt and quenched with water and the product extracted with ethyl acetate. Removal of solvent in vacuo and purification by flash chromatography (5:1 petroleum ether/EtOAc) gave **14** as a colorless oil (200 mg, 64%). $[\alpha]^{25}_D$ +10 (c = 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.92 (3H, d, J = 7.0 Hz), 1.58−1.71 (1H, m), 2.12 (1H, d, J = 3.5 Hz), 2.47 (6H, s), 2.53−2.63 (1H, m), 2.58 (1H, d, J = 4.5 Hz), 3.68 (1H, dd, J = 6.5, 9.5 Hz), 3.83 (1H, dd, J = 5.0, 9.5 Hz), 7.35 (4H, d, J = 8.0 Hz), 7.75 (2H, d, J = 8.0 Hz), 7.79 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.6, 21.7 (x2), 32.4, 35.0, 41.9, 71.7, 127.9, 128.0, 129.8, 129.9, 132.8 (×2), 144.9 (×2). FTIR (CH_2Cl_2): 2976 (m), 1598 (m), 1362 (s), 1327 (s), 1178 (s), 1094 (m) cm^{-1}. HRMS: *m/z* calcd for $C_{19}H_{24}NS_2O_5$ 410.1096, found 410.1106.

2(*S*)-[*N*-(*p*-Toluenesulfonyl)aziridin-2(*S*)-yl]propan-1-ol (16). Tributylphosphine (0.56 g, 2.7 mmol, 1.5 equiv) was added to a solution of diol **13** (0.5 g, 1.8 mmol, 1 equiv) in toluene (12 mL) at rt under a nitrogen atmosphere. The temperature was lowered to 0 °C and ADDP (0.69 g, 2.7 mmol, 1.5 equiv) added portionwise. The reaction mixture was stirred for 16 h at rt, and then the solvent was removed in vacuo. Careful chromatography provided a small sample of analytically pure **16**; generally, however, the crude alcohol was used directly in the subsequent reaction. $[\alpha]^{25}_D$ −30 (c = 1.7, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.00 (3H, d, J = 7.0 Hz), 1.41−1.55 (1H, m), 2.14 (1H, d, J = 4.5 Hz), 2.46 (3H, s), 2.61 (1H, d, J = 7.0 Hz), 2.65−2.74 (1H, m), 3.50−3.58 (2H, m), 7.34 (2H, d, J = 8.0 Hz), 7.84 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.8, 21.6, 32.9, 37.6, 42.1, 65.9, 128.0, 129.7, 134.5, 144.8. FTIR (CH_2Cl_2): 3417 (br), 2964 (m), 2935 (m), 1736 (s), 1495 (s), 1220 (s), 1161 (s), 1061 (s) cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_{18}NSO_3$ 256.1007, found 256.0995.

2(*S*)-[2-(*tert*-Butyldimethylsilanyloxy)-1(*S*)-methylethyl]-*N*-(*p*-toluenesulfonyl)aziridine (17). *tert*-Butyldimethylsilyl chloride (0.33 g, 2.2 mmol) and imidazole (0.16 g, 2.3 mmol) were added to a solution of impure aziridine **16** (0.46 g) in dry THF (10 mL) at 0 °C, and the reaction mixture was stirred for 5 h. The solvent was removed in vacuo and the residue purified by flash chromatography (silica gel, 8:1 petroleum ether/EtOAc) to give aziridine **17** (0.61 g, 90% over two steps) as a colorless solid, which was recrystallized from petroleum ether. Mp 81.0−82.0 °C. $[\alpha]^{25}_D$ −4 (c = 1.0, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ −0.05 (6H, s), 0.84 (9H, s), 0.89 (3H, d, J = 6.5 Hz), 1.32−1.42 (1H, m), 2.15 (1H, d, J = 3.0 Hz), 2.43 (3H, s), 2.55−2.70 (2H, m), 3.21 (1H, dd, J = 6.0 Hz, 9.5 Hz), 3.30 (1H, dd, J = 4.5 Hz, 9.5 Hz), 7.32 (2H, d, J = 8.0 Hz), 7.81 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −5.7, 13.5, 18.2, 21.6, 25.8, 32.0, 37.7, 42.3, 65.3, 128.1, 129.6, 135.0, 144.5. FTIR (CH_2Cl_2): 2957 (m), 2950 (m), 2858 (m), 1472 (m), 1323 (m), 1162 (s) cm^{-1}. HRMS: *m/z* calcd for $C_{18}H_{32}NSO_3Si$ 370.1872, found 370.1859. Anal. Calcd for $C_{18}H_{31}NSSiO_3$: C, 58.49; H, 8.45; N, 3.79; S, 8.68. Found: C, 58.52; H, 8.77; N, 3.78; S, 8.76.

Pd-Catalyzed Cycloaddition Approach to 2(*S*)-[2-(*tert*-butyldimethylsilanyloxy)-1(*S*)-methylethyl]-5-methylene-1-(toluene-4-sulfonyl)piperidine (18). Formation of the 0.07 M palladium catalyst batch: A flask was charged with palladium acetate (20 mg, 0.089 mmol, 1 equiv), 1,3-bis-(diphenylphosphino)propane (92 mg, 0.22 mmol, 2.5 equiv), and THF (1.28 mL) to give a yellow solution that was used directly in the cycloaddition processes. To a solution of aziridine **17** (300 mg, 0.81 mmol, 1 equiv) in THF (8 mL) were added 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (227 mg, 1.2 mmol, 1.5 equiv) and an aliquot of 0.07 M palladium catalyst solution (1.14 mL, 0.08 mmol, 0.1 equiv), and the reaction mixture was heated at reflux for 16 h. The solvent was removed in vacuo and the residue purified by flash chromatography (10:1 petroleum ether/EtOAc).

Data for 18. $[\alpha]^{25}_D$ +24 (c = 1.4, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.06 (3H, s), 0.07 (3H, s), 0.91 (9H, s), 0.95 (3H, d, J = 6.5 Hz), 1.11−1.30 (1H, m), 1.56−1.70 (1H, m), 1.81−1.93 (1H, m), 2.09−2.26 (2H, m), 2.41 (3H, s), 3.33 (1H, dd, J = 8.5, 10.0 Hz), 3.58−3.82 (3H, m), 4.33 (1H, d, J = 16.0 Hz), 4.64 (1H, br), 4.76 (1H, br), 7.24 (2H, d, J = 8.0 Hz), 7.69 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −5.4, 14.1, 18.3, 21.5, 24.8, 26.0, 27.3, 34.8, 47.2, 50.0, 65.6, 110.2, 127.5, 129.4, 138.0, 141.0, 142.8. FTIR (CH_2Cl_2): 3075 (m), 2957 (s), 2857 (s), 1806 (w), 1734 (s), 1655 (m), 1598 (s), 1472 (s), 1338 (s), 1251 (s), 1160 (s), 1092 (s), 910 (s) cm^{-1}. HRMS: *m/z* calcd for $C_{22}H_{38}NSO_3Si$: 424.2341, found 424.2377.

Data for 19. $[\alpha]^{25}_D$ +22 (c = 0.5, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.04 (6H, s), 0.78 (3H, d, J = 7.0 Hz), 0.90 (9H, s), 1.73−1.87 (1H, m), 1.91 (3H, s), 2.40 (3H, s), 3.41 (1H, dd, J = 4.5, 10.5 Hz), 3.49 (1H, app q, J = 6.0 Hz), 3.72 (1H, dd, J = 3.0, 10.5 Hz), 4.07 (2H, d, J = 6.0 Hz), 5.84 (1H, d, J = 7.0 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.72 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −5.7, −5.6, 14.4, 18.1, 20.7, 21.5, 25.8, 34.9, 56.1, 64.8, 64.9, 118.8, 127.0, 129.5, 138.4, 143.1, 170.8. FTIR (CH_2Cl_2): 2957 (m), 2931 (m), 1740 (s), 1600 (w), 1472 (m), 1333 (m), 1269 (s), 1094 (s) cm^{-1}. HRMS: *m/z* calcd for $C_{20}H_{35}NSO_5Si$ 430.2083, found 430.2072.

Data for 20. $[\alpha]^{25}_D$ +10 (c = 1.8, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.00 (3H, s), 0.01 (3H, s), 0.88 (9H, s), 0.95 (3H, d, J = 6.5 Hz), 1.67 (3H, s), 1.88 (3H, s), 1.95−2.07 (1H, m), 2.41 (3H, s), 3.26 (1H, dd, J = 7.5, 10.0 Hz), 3.47 (1H, dd, J = 4.0 Hz, 10.0 Hz), 3.77 (2H, s), 3.88 (1H, dt, J = 4.0, 9.0

(24) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapaport, H. *J. Org. Chem.* **1990**, *55*, 3068.

Hz), 4.11 (1H, dd, J = 9.0, 12.0 Hz), 4.26 (1H, dd, J = 4.0, 12.0 Hz), 4.88 (1H, s), 4.93 (1H, s), 7.27 (2H, d, J = 8.0 Hz), 7.71 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −5.5, 14.6, 18.3, 20.0, 20.8, 21.4, 25.9, 36.8, 51.7, 58.9, 63.3, 65.7, 114.8, 127.5, 129.4, 138.3, 142.0, 143.1, 170.7. FTIR (CH_2Cl_2): 2931 (s), 2858 (s), 1739 (s), 1599 (m), 1472 (s), 1337 (s), 1245 (s), 1093 (s) cm^{-1}. HRMS: *m/z* calcd for $C_{24}H_{42}NSO_5Si$ 484.2553, found 484.2559.

***N*-{1-[2-(*tert*-Butyldimethylsilanyloxy)-1-methylethyl]-4-hydroxymethyl-pent-4-enyl}-4-methylbenzenesulfonamide (22).** A 100 mL two-necked flask was charged with 2.5 M *n*-butyllithium (25 mL, 62 mmol, 2.6 equiv). The hexane was removed at reduced pressure with stirring in a warm water bath until a thick yellow oil was obtained. The system was carefully recharged with nitrogen and cooled to 0 °C. Then Et_2O (40 mL) and TMEDA (16 mL, 71 mmol, 3 equiv) were added. 2-Methyl-2-propen-1-ol (**21**; 2 mL, 24 mmol, 1 equiv) was then added dropwise. The reaction was allowed to warm to rt overnight. The formation of the dianion as a dark red gummy solid from the orange solution was observed. The solution was cooled to 0 °C, and $MgBr_2$ (11.4 g, 62 mmol, 2.6 equiv) was added in three portions; the precipitation of lithium salts was observed. **17** (1.0 g, 2.7 mmol) in THF (5 mL) was added to the solution of Grignard reagent (titrated as a 0.1 M solution, 2.5 equiv) and the reaction mixture stirred at rt for 16 h. The reaction was quenched with saturated aqueous NH_4Cl and then extracted with EtOAc. The solution was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by flash chromatography (2:1 petroleum ether/ethyl acetate) to give **22** as a colorless oil, 1.09 g (92%). $[\alpha]^{25}_D$ +20 (c = 1.0, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.0 (6H, s), 0.66 (3H, d, J = 7.0 Hz), 0.87 (9H, s), 1.52−1.72 (4H, m), 1.98 (2H, t, J = 6.0 Hz), 2.37 (3H, s), 3.18−3.29 (1H, m), 3.31 (1H, dd, J = 5.5, 10.5 Hz), 3.61 (1H, dd, J = 3.5, 10.5 Hz), 3.97 (2H, s), 4.75 (1H, s), 4.97 (1H, s), 5.66 (1H, d, J = 7.5 Hz), 7.23 (2H, d, J = 8.0 Hz), 7.69 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ −5.6, 14.0, 18.1, 21.5, 25.8, 28.8, 31.2, 36.9, 57.2, 65.1, 65.9, 109.7, 127.0, 129.4, 138.6, 142.9, 148.3. FTIR (CH_2Cl_2): 3457 (br), 3292 (br), 2929 (m), 2857 (m), 1652 (w) cm^{-1}. HRMS: *m/z* calcd for $C_{22}H_{40}NSO_4Si$ 442.2447, found 442.2455.

2(*S*)-[2-(*tert*-Butyldimethylsilanyloxy)-1(*S*)-methylethyl]-5-methylene-1-(toluene-4-sulfonyl)piperidine (18). To a solution of **22** (1.15 g, 2.6 mmol, 1 equiv) in toluene (10 mL) at 0 °C were added tributylphosphine (0.85 mL, 3.4 mmol, 1.3 equiv) and ADDP (0.79 g, 3.1 mmol, 1.2 equiv). The resulting solution was stirred at rt for 16 h and then concentrated in vacuo. The residue was purified by flash chromatography (12:1 petroleum ether/ethyl acetate) to yield **18** as a colorless oil, 0.95 g (87%).

2(*S*)-[5-Methylene-1-(toluene-4-sulfonyl)piperidin-2(*S*)-yl]propan-1-ol. To a solution of piperidine **18** (0.95 g, 2.3 mmol, 1 equiv) in THF (10 mL) was added 1.0 M TBAF (2.9 mL, 2.9 mmol, 1.3 equiv). Stirring was continued for 4 h, whereupon water was added to the reaction mixture and the product extracted with EtOAc. The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo to provide the crude alcohol, which was purified by flash chromatography (3:1 petroleum ether/ethyl acetate) to give the title compound as a colorless oil (0.61 g, 86%). $[\alpha]^{25}_D$ +68 (c = 0.9, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.04 (3H, d, J = 7.0 Hz), 1.51−1.68 (1H, m), 1.92 (1H, dt, J = 14.0, 4.5 Hz), 1.98−2.23 (2H, m), 2.42 (3H, s), 2.85−2.95 (1H, m), 3.42−3.53 (1H, m), 3.62−3.75 (2H, m), 3.98−4.06 (1H, m), 4.40 (1H, d, J = 16.0 Hz), 4.68 (1H, s), 4.82 (1H, s), 7.26 (2H, d, J = 8.0 Hz), 7.70 (2H, d, J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.4, 21.5, 24.7, 27.1, 33.4, 47.3, 53.9, 60.4, 63.9, 110.7, 127.4, 129.6, 140.6, 143.3. FTIR (CH_2Cl_2): 3527 (s), 2947 (s), 2883 (m), 1655 (m), 1599 (m), 1462 (s), 1447 (s), 1336 (s), 1159 (s), 1090 cm^{-1}. HRMS: *m/z* calcd for $C_{16}H_{24}NSO_3$ 310.1477, found 310.1469.

4(*R*)-[5-Methylene-1-(toluene-4-sulfonyl)piperidin-2(*S*)-yl]pent-2-enoic Acid Ethyl Ester (23). Oxalyl chloride (0.17 mL, 2.0 mmol, 2.25 equiv) in DCM (5 mL) was stirred at −78 °C for 10 min. DMSO (0.28 mL, 3.9 mmol, 4.5 equiv) was added, and stirring was continued for a further 30 min. 2(*S*)-[5-Methylene-1-(toluene-4-sulfonyl)piperidin-2(*S*)-yl]propan-1-ol (270 mg, 0.87 mmol, 1.0 equiv) in DCM (5 mL) was added via cannula and stirring continued for 30 min. Et_3N (0.82 mL, 5.9 mmol, 6.75 equiv) was added and the mixture allowed to warm to rt over 1 h. The reaction was quenched with water and extracted with DCM. The extracts were dried with $MgSO_4$ and solvent removed in vacuo to provide the crude aldehyde, which was used directly in the next step. The crude aldehyde was dissolved in THF (10 mL) and cooled to 0 °C, $Ph_3P{=}CHCO_2Et$ (460 mg, 1.3 mmol, 1.5 equiv) added, and stirring continued at room-temperature overnight. Evaporation of the volatiles and purification of the crude mixture by flash chromatography (8:1 petroleum ether/ethyl acetate) gave **23** as a colorless oil (256 mg, 78%). $[\alpha]^{25}_D$ +20 (c = 1.3, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.10 (3H, d, J = 6.5 Hz), 1.31 (3H, t, J = 7.0 Hz), 1.35−1.48 (1H, m), 1.51−1.79 (1H, m), 1.86 (1H, dt, J = 14.5, 5.0 Hz), 2.11−2.28 (2H, m), 2.41 (3H, s), 2.81−2.99 (1H, m), 3.59 (1H, d, J = 16.0 Hz), 3.78 (1H, q, J = 4.5 Hz), 4.21 (2H, q, J = 7.0 Hz), 4.68 (1H, br), 4.79 (1H, br), 5.83 (1H, d, J = 15.5 Hz), 6.92 (1H, dd, J = 15.5, 8.5 Hz), 7.24 (2H, d, J = 8.0 Hz), 7.69 (2H, d J = 8.0 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.3, 16.5, 21.5, 24.6, 27.1, 37.2, 47.1, 56.8, 60.3, 110.6, 121.3, 127.6, 129.4, 138.5, 140.6, 143.1, 150.7, 166.3. FTIR (CH_2Cl_2): 3063 (w), 2982 (m), 1713 (s), 1656 (m), 1599 (m), 1446 (m), 1340 (s), 1242 (s), 1160 (s), 1092 (s), 1033 (m), 982 (m) cm^{-1}. HRMS: *m/z* calcd for $C_{20}H_{28}NSO_4$ 378.1739, found 378.1722.

1(*R*)-Methyl-7-methylene-9(*S*)-octahydroquinolizin-4-one (7). Piperidine **23** (577 mg, 1.53 mmol, 1 equiv) in MeOH (30 mL) was treated with Mg turnings (1.86 g, 76.4 mmol, 50 equiv) and the slurry stirred at rt for 3 h. The reaction was quenched by addition of 1 M HCl, extracted with EtOAc, and dried over $MgSO_4$. The crude product was purified by flash chromatography (2:1 petroleum ether/ethyl acetate) to give **7** as a colorless solid (199 mg, 72%). Mp 73.0−75.0 °C. $[\alpha]^{25}_D$ +66 (c = 0.5, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.08 (3H, d, J = 6.5 Hz), 1.30−1.82 (4H, m), 2.06−2.52 (5H, m), 2.92 (1H, ddd, J = 11.0, 8.5, 2.5 Hz), 3.06 (1H, d, J = 14.0 Hz), 4.77−4.81 (1H, m), 4.89−4.93 (1H, m), 5.14 (1H, dd, J = 14.0, 1.5 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.1, 27.9, 32.0, 32.5, 33.2, 35.0, 48.0, 63.0, 110.5, 141.9, 169.1. FTIR (CH_2Cl_2): 2949 (m), 2880 (w), 1631 (s), 1466 (m), 1420 (m), 1534 (w), 1307 (m), 1251 (m), 1151 (w), 904 (m) cm^{-1}. HRMS: *m/z* calcd for $C_{11}H_{18}NO$ 180.1388, found 180.1393.

4-Furan-3-yl-1-methyl-7-methyleneoctahydroquinolizine (24). A solution of 3-bromofuran (0.154 mL, 1.71 mmol, 4 equiv) in Et_2O (2.5 mL) was added to a solution of 2.5 M BuLi (0.512 mL, 1.28 mmol, 3 equiv) in Et_2O (2.5 mL) at −78 °C and the reaction mixture stirred for 20 min. Quinolizidinone **7** (0.077 g, 0.43 mmol, 1 equiv) in Et_2O (2.5 mL) was added dropwise and the resulting mixture allowed to warm to rt over 1.5 h. To this solution was added diisobutylaluminum hydride (1.0 M in DCM, 4.3 mL, 10 equiv) and the reaction stirred for a further hour. A 20% aqueous Na_2CO_3 solution was added and the aqueous layer extracted with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to yield **24** as a yellow oil (0.076 g, 76%). $[\alpha]^{25}_D$ −43 (c = 1.1, $CHCl_3$) [lit.[2b] $[\alpha]^{20}_D$ −70 (c = 4.0, $CHCl_3$)]. ^{1}H NMR (250 MHz, $CDCl_3$): 0.86 (3H, d, J = 6.5 Hz), 1.00−2.36 (11H, m), 2.92 (1H, dd, J = 10.5, 3.0 Hz), 3.20 (1H, dd, J = 11.5, 1.0 Hz), 4.52 (1H, s), 4.58 (1H, s), 6.39 (1H, br), 7.26 (1H, br), 7.30 (1H, br). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.3, 31.0, 32.8, 33.9, 34.7, 36.3, 59.4, 61.2, 69.1, 108.5, 109.5, 128.5, 139.5, 143.0, 144.9. FTIR (Film): 2929 (s), 2362 (w), 1659 (br), 1502 (w), 1439 (br), 1159 (m), 1104 (m), 1022 (m), 896 (w) cm^{-1}. HRMS: *m/z* calcd for $C_{15}H_{22}NO$ 232.1702, found 232.1701.

(−)-Deoxynupharidine ((−)-2). To a solution of **24** (5 mg, 0.02 mmol) in EtOAc (1.0 mL) was added a small quantity

(<5 mg) of 5% Rh/Al_2O_3 catalyst under an atmosphere of N_2. The N_2 atmosphere was replaced by a H_2 atmosphere, and the suspension was stirred for 3 h at rt. The reaction mixture was filtered through Celite and the solvent removed in vacuo to yield (−)-**2** as a colorless oil (3 mg, 60%). The sample showed spectroscopic and analytical data identical to those reported previously.[9]

(−)-Castoramine ((−)-3) and (−)-Nupharolutine ((−)-4). To a solution of **25** (0.025 g, 0.11 mmol, 1 equiv) in THF (2.5 mL) at 0 °C was added borane−dimethyl sulfide (0.020 mL, 0.22 mmol), and the temperature was raised to rt over 1 h. An aqueous solution of NaOH (1 M, 0.22 mL, 0.22 mmol, 2 equiv) and hydrogen peroxide (30%, 24 μL, 0.22 mmol, 2 equiv) were added to the reaction mixture, and stirring was continued for a further hour. The product was extracted with EtOAc and purified by flash chromatography (3:1 petroleum ether/ethyl acetate) to yield a 1:1 mixture of (−)-**3** (7 mg, 26%) as a colorless oil and (−)-**4** (7 mg, 26%) as a colorless solid. Mp 101.8−103.5 °C (lit.[2a] mp 101.5−102.5 °C).

Data for 3. $[\alpha]^{25}_D$ −60 (c = 0.5, $CHCl_3$) [lit.[2b] $[\alpha]^{20}_D$ −80 (c = 0.5, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, d, J = 6.5), 1.08−2.10 (12H, m), 2.85−2.98 (1H, m), 3.02−3.14 (1H, m), 3.70−3.87 (2H, m), 6.45 (1H, br), 7.33 (1H, br), 7.39 (1H, br). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 28.2, 28.6, 33.4, 33.8, 35.1, 36.8, 56.7, 60.4, 69.0, 69.1, 108.9, 128.7, 139.4, 143.4. HRMS: m/z calcd for $C_{15}H_{24}NO_2$ 250.1807, found 232.1800.

Data for 4. $[\alpha]^{25}_D$ −65 (c = 0.3, $CHCl_3$) [lit.[3] $[\alpha]^{25}_D$ −100 (c = 0.8, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, d, J = 6.0), 1.21 (3H, s), 1.04−1.99 (11H, m), 2.66 (1H, dd, J = 11.0, 2.0), 2.99−3.09 (1H, m), 6.35 (1H, br), 7.26−7.33 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 25.4, 28.0, 33.6, 34.2, 34.9, 38.3, 59.6, 63.0, 68.2, 69.3, 109.3, 129.1, 139.3, 142.9.

6-Furan-3-yl-3-hydroxymethyl-9-methyloctahydroquinolizin-3-ol (25). A solution of **24** (21 mg, 0.09 mmol) in a 4:1 mixture of acetone/H_2O (10 mL) was treated with NMO (32 mg, 0.27 mmol) and a crystal of OsO_4. The mixture was stirred at rt for 1 h. The reaction was quenched by addition of a saturated aqueous solution of Na_2SO_3 and the reaction mixture evaporated to dryness in vacuo. The residue was extracted with CH_2Cl_2/MeOH (10:1), the organic phase dried over $MgSO_4$, and the crude material purified by column chromatography (20:1:0.2 CH_2Cl_2/MeOH/NH_3) to yield **25** as a colorless solid (17 mg, 71%). Mp 120.5−123.0 °C. $[\alpha]^{25}_D$ −80 (c = 0.6, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): 0.85 (3H, d, J = 6.5 Hz), 1.02−1.71 (9H, m), 1.78−1.95 (2H, m), 2.82 (1H, dd, J = 11.5, 2.0 Hz), 2.94 (1H, dd, J = 10.5, 4.0 Hz), 3.46 (1H, d, J = 11.0 Hz), 3.63 (1H, d, J = 11.0 Hz), 6.30 (1H, br), 7.24 (1H, br), 7.30 (1H, br). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.2, 28.0, 33.3, 34.3, 34.6, 36.0, 59.6, 60.2, 68.2, 68.5, 70.0, 108.7, 128.9, 139.6, 143.4. FTIR (film): 3387 (br), 2929 (s), 1501 (w), 1459 (m), 1159 (m), 1032 (m) cm^{-1}. HRMS: m/z calcd for $C_{15}H_{23}NO_3$ 266.1756, found 266.1754.

(−)-Nupharolutine ((−)-4). To a solution of **25** (17 mg, 0.06 mmol) in CH_2Cl_2 (1.0 mL) were added p-toluenesulfonyl chloride (36 mg, 0.18 mmol), triethylamine (27 μL, 0.18 mmol), and a crystal of DMAP. The reaction mixture was stirred at rt for 48 h and quenched with water. The product was extracted with CH_2Cl_2 and the solvent removed in vacuo. The crude sulfonate ester was dissolved in THF (0.5 mL) and transferred via cannula to a suspension of LAH (10 mg, 0.26 mmol) in THF (0.5 mL) at 0 °C. The mixture was warmed to rt and then refluxed over a period of 3 h. The reaction mixture was quenched by the addition of a few drops of diluted NaOH, the organic layer dried over $MgSO_4$, and the product purified chromatographically as before to provide (−)-**4** as a colorless solid.

Acknowledgment. We are grateful to the EPSRC and the University of Sheffield for financial support and MSD for a studentship award (K.M.G.). We also thank Prof. Miyazawa for providing us with NMR and mass spectroscopy data for compounds **3** and **4**.

Supporting Information Available: ^1H and ^{13}C NMR spectra for selected compounds and $^1H-^1H$ COSY, $^1H-^{13}C$ COSY, and NOESY spectra of compound **(−)-3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO048455K