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# Stereoselective nitrenium ion cyclizations: asymmetric synthesis of the (+)-Kishi lactam and an intermediate for the preparation of fasicularin

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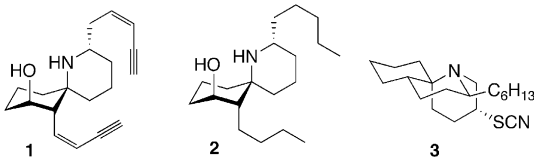
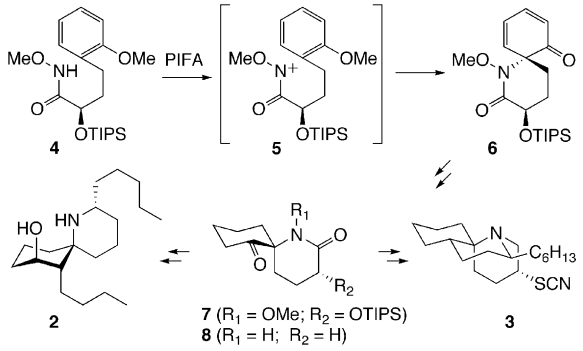
**Abstract**—The asymmetric synthesis of the (+)-Kishi lactam and an intermediate for the preparation of the marine natural product fasicularin is reported. The keystone of this divergent synthesis is the diastereoselective azaspirocyclization of an *N*-methoxy γ-arylbutanoamide, which is believed to proceed through the intermediacy of an *N*-acylnitrenium ion.


The 1-azaspiro[5.5]undecane ring system forms the substructure of a select number of biologically active natural products. Histrionicotoxin (**1**), isolated from the South American frog, *Dendrobates histrionicus*, is a potent noncompetitive blocker of neuromuscular nicotinic receptor-gated channels which, together with its perhydro derivative **2**, have been used extensively as a biochemical probe.[1] Fasicularin (**3**), on the other hand, was isolated from the Micronesian ascidian *Nephteis fasicularis*[2] by Patil et al. In addition to displaying selective activity against strains of yeast, which lack the double-strand DNA repair gene RAD-52, this tricyclic alkaloid is cytotoxic toward Vero cells. The biological activity and novel structures of these natural products have stimulated extensive investigation.[3,4] Total syntheses of racemic **3** have been reported by Kibayashi and co-workers[5] and Funk and co-workers,[6] while Dake[7] recently reported the asymmetric synthesis of a late stage intermediate common to both of these routes. The absolute configuration of fasicularin remains to be established.




As part of an on-going study of the chemistry of nitrenium ions,[8] we recently developed a novel strategy for the stereocontrolled preparation of 1-azaspiranes, based on the π-face selective spirocyclization of *N*-acylnitrenium ions.[9] Herein we report the successful application of this methodology to the asymmetric synthesis of **8**, an intermediate in Kishi's pioneering synthesis of (±)-perhydrohistrionicotoxin (**2**),[4a,10] and compound **7**, which represents a usefully functionalized platform from which to launch an asymmetric synthesis of fasicularin (**3**).

As outlined in Scheme 1, we initially envisioned that azaspirocyclization of *N*-acyl-*N*-methoxynitrenium ion




**Scheme 1.**

*Keywords*: Nitrenium ions; Dearomatization; Fasicularin; Polyvalent iodine; Histrionicotoxin.
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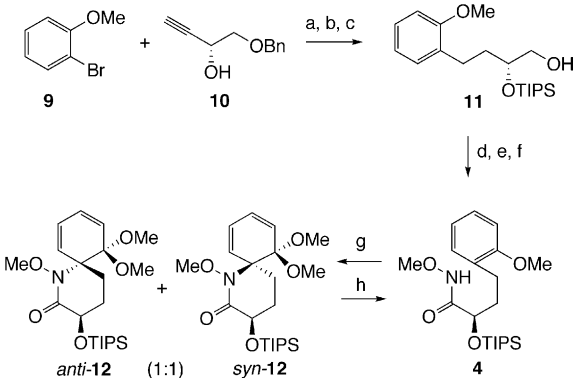
**5**, generated through oxidation of amide **4** with phenyliodine(III) bistrifluoroacetate (PIFA), would provide 2,4-dienone **6**.[11] Given the findings of our previous study,[9] we anticipated that nonbonding interactions between the triisopropylsilyloxy substituent on the side chain and the *ortho* position of the aromatic ring would favor the formation of *anti*-**6** during the spirocyclization of **5**. Reduction of **6** would then offer an ingress to both (−)-perhydrohistrionicotoxin (**2**) and fasicularin (**3**), by way of common intermediate **7**.

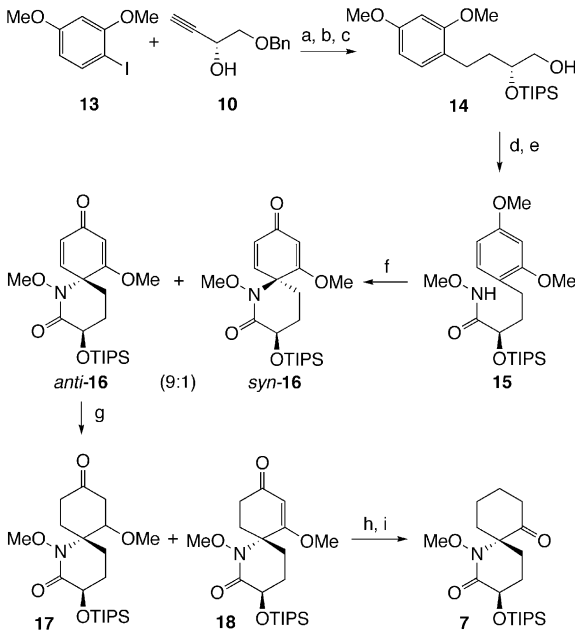
Our route to **4** commenced from 2-bromoanisole (**9**) and (*R*)-4-benzyloxy-3-hydroxy-1-butyne (**10**),[12] which underwent Sonogashira cross-coupling to provide the corresponding alkynylarene in high yield (Scheme 2). Protection of this secondary alcohol, as the triisopropylsilyl ether, then concomitant de-*O*-benzylation and reduction of the acetylene gave **11** in high overall yield. Not withstanding the apparently trivial nature of this task, conversion of **11** to amide **4**, through two oxidations and an amine coupling, proved to be quite problematic. The low overall yield of this transformation is a reflection of the proclivity with which the intermediate carboxylic acid underwent rearrangement to the corresponding triisopropylsilyl ester.

Treatment of **4** with PIFA in a mixture of $CH_2Cl_2$ and MeOH[9] generated an intractable mixture of products. Suspecting that the trifluoroacetic acid generated in this reaction might trigger dienone–phenol rearrangement of the desired product,[13] triethylamine was added to the reaction mixture prior to workup. This modification failed to provide **6**, but instead generated a chromatographically inseparable mixture of acetals **12**, which presumably arise through interception of the Wheland intermediate generated upon attack of the acylnitrenium ion on the arene ring.[14] Disappointingly, attempts to convert **12** to dienone **6**, through acidic hydrolysis lead only to decomposition. In an attempt to access **7** from **12**, without the necessity of proceeding through **6**, we attempted to reduce the diene system. However, submission of **12** to catalytic hydrogenation over a range of heterogeneous catalysts, including Adams catalyst ($PtO_2$),[15] served only to trigger rearomatization and formation of amide **4**.




**Scheme 2.** Reagents and conditions: (a) $PdCl_2$ (6 mol%), $Ph_3P$ (6 mol%), CuI (4 mol%), $Et_3N$, ultrasonication, 40 °C, 17 h (83%); (b) TIPSCl, Im, DMAP, DMF, rt, 16 h; (c) $H_2$ (1 atm), Pd(C) (10%), EtOAc, rt, 3 h (92%, two steps); (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −60 °C, then $Et_3N$, −60 °C → rt, 2 h; (e) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*-BuOH, 2-methyl-2-butene, 5 h (39%, two steps); (f) $NH_2OMe{\cdot}HCl$, EDC·HCl, $Et_3N$, rt, 14 h (55%); (g) $PhI(OCOCF_3)_2$, $CH_2Cl_2$–MeOH (1:1), −78 → −10 °C, then $Et_3N$, −10 → 0 °C, 10 min (76%); (h) $H_2$ (1 atm), 10% Pd(C), EtOAc, 20 min, rt (99%).

Given our inability to access 2,4-dienone **6**, we now shifted our attention to the preparation of 2,5-dienone **16** in the expectation that this cross-conjugated system would be more stable. As shown in Scheme 3, the requisite precursor **15** was prepared from iodoarene **13** in a similar fashion to **4**, with the exception that the conversion of **14** to the corresponding carboxylic acid was accomplished in one step, using Jones reagent. Gratifyingly, spirocyclization of **15** now proceeded smoothly to generate **16** as a 9:1 mixture of diastereomers. That the major product was the *anti* diastereomer was established through a combination of COSY, HMQC, and homonuclear $^1H$ NOE experiments; the salient NOE enhancements for *anti*-**16** are illustrated in Figure 1. This




**Scheme 3.** Reagents and conditions: (a) $PdCl_2$ (3 mol%), $Ph_3P$ (3 mol%), CuI (2 mol%), $Et_3N$, ultrasonication, 40 °C, 4 h (81%); (b) TIPSCl, Im, DMAP, DMF, rt, 24 h; (c) $H_2$ (1 atm), Pd(C) (10%), EtOAc, rt, 28 h (86%, two steps); (d) $CrO_3$, $H_2SO_4$, acetone, 25 °C, 30 min; (e) *i*-BuOCOCl, $Et_3N$, −20 °C, 1 h, then $NH_2OMe{\cdot}HCl$, $Et_3N$, −20 °C → rt, 18 h (67%, two steps); (f) $PhI(OCOCF_3)_2$, $CH_2Cl_2$, MeOH, −78 → 20 °C, 1 h (90%, dr 9:1); (g) $H_2$ (1 atm), $PtO_2$, EtOAc, 7 min, rt (**17**, 20%; **18**, 67%); (h) (i) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 15 min, 0 °C; (ii) 1 M HCl, THF, rt, 30 min (87%); (i) $H_2$ (1 atm), 10% Pd(C), EtOAc, rt, 30 min (99%).

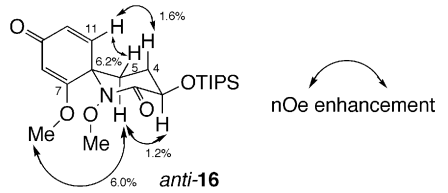
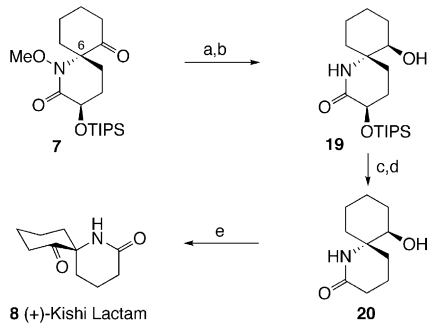



**Figure 1.** NOE enhancements observed for compound *anti*-**16**.




**Scheme 4.** Reagents and conditions: (a) $NaBH_4$, MeOH, $CH_2Cl_2$, 0 °C, 15 min (99%); (b) $SmI_2$, THF–HMPA (25:1), rt, 30 min; (c) TBAF, THF, rt, 20 min; (d) $SmI_2$, $EtCO_2H$, THF, ultrasonication, rt, 28 h (80%, three steps); (e) $(COCl)_2$, DMSO, $CH_2Cl_2$, −60 °C, then $Et_3N$, −60 °C → rt, 2 h (81%).

mixture of spirodienones was then hydrogenated over $PtO_2$ to provide vinylogous ester **18**, again, as a mixture of diastereomers. Cyclohexanone **17** was also generated in this reaction and found to be a single diastereomer by $^1H$ NMR spectroscopy. In order to prevent formation of this undesired product, it was necessary to strictly limit the duration of this reaction. Luche reduction of **18** and exposure of the resulting allylic alcohol to aqueous HCl then provided the transposed enone, which was hydrogenated to provide ketone **7** as a single diastereomer. This ketone is suitably functionalized to allow introduction of the second piperidine ring and the C-2 *n*-hexyl side chain of fasicularin (**3**) and as such represents a useful platform from which to complete the asymmetric synthesis of this natural product.

In order to access the (+)-Kishi lactam (**8**), it was now necessary to expunge the *N*-methoxy and α-triisopropylsilyloxy groups from compound **7** (Scheme 4). To avoid the reductive cleavage of the N–C6 bond, the ketone group of **7** was reduced with sodium borohydride to provide the corresponding alcohol as a 3:1 mixture of *anti* and *syn* diastereomers. While a priori, we envisioned that cleavage of the N–O bond and the α-triisopropylsilyloxy group could be accomplished in one pot, using samarium diiodide, treatment of the alcohol mixture derived from **7** with $SmI_2$ mediated only N–O bond cleavage and provided **19** in high yield. Nevertheless, after removal of the TIPS protecting group, treatment with $SmI_2$ in the presence of propionic acid now furnished **20** as a single diastereomer in excellent overall yield. Finally, Swern oxidation of **20** provided crystalline (+)-**8** in good yield. A comparison of the spectroscopic and physical data collected for this material with that previously reported confirmed its identity. Significantly, the optical rotation of **8** $\{[\alpha]_D^{25}$ +60.4 (*c* 0.48, $CHCl_3)\}$ was close to the value reported by Luzzio and Fitch $\{[\alpha]_D^{25}$ +60.3 (*c* 0.54, $CHCl_3)\}$.[4a] This observation therefore confirms that the spirocyclization of amide **14** proceeded with *anti* selectivity, as anticipated.

In summary, we report the application of a stereoselective nitrenium ion cyclization to the asymmetric preparation of a useful intermediate for the synthesis of the marine natural product fasicularin. The (+)-Kishi lactam (**8**) has also been prepared in 14 steps with an overall yield of 16%, which compares favorably with Luzzio's synthesis of this target molecule (15 steps, 9% yield).[4a] Since the transformation of **8** into (±)-perhydrohistrionicotoxin (**2**) has previously been reported,[10] our synthesis of (+)-**8** also constitutes a formal synthesis of (−)-perhydrohistrionicotoxin.

## Acknowledgements

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## References and notes

1. Daly, J. W. *J. Nat. Prod.* **1998**, *61*, 162.
2. Patil, A. D.; Freyer, A. J.; Reichwein, R.; Carte, B.; Killmer, L. B.; Faucette, L.; Johnson, R. K.; Faulkner, D. J. *Tetrahedron Lett.* **1997**, *38*, 363.
3. For recent approaches to the 1-azaspiro[5.5]undecane ring system, see: (a) Davison, E. C.; Fox, M. E.; Holmes, A. B.; Roughley, S. D.; Smith, C. J.; Williams, G. R. M.; Davies, J. E.; Raithby, P. R.; Adams, J. P.; Forbes, I. T.; Press, N. J.; Thompson, M. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1494; (b) Jachak, S. M.; Karche, N. P.; Dhavale, D. D. *Tetrahedron Lett.* **2001**, *42*, 4925; (c) David, M.; Dhimane, H.; Vanucci-Bacque, C.; Lhommet, G. *Heterocycles* **2001**, *55*, 941; (d) Ciblat, S.; Canet, J. L.; Troin, Y. *Tetrahedron Lett.* **2001**, *42*, 4815; (e) Stockman, R. A. *Tetrahedron Lett.* **2000**, *41*, 9163.
4. For recent synthetic work and leading references on the histrionicotoxins, see: (a) Luzzio, F. A.; Fitch, R. W. *J. Org. Chem.* **1999**, *64*, 5485; (b) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4900; (c) Comins, D. L.; Zhang, Y. M.; Zheng, X. L. *J. Chem. Soc., Chem. Commun.* **1998**, 2509; (d) Tanner, D.; Hagberg, L. *Tetrahedron* **1998**, *54*, 7907.
5. Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583.
6. Maeng, M.-H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331.
7. Fenster, M. D. B.; Dake, G. R. *Org. Lett.* **2003**, *5*, 4313.
8. (a) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053; (b) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353; (c) Wardrop, D. J.; Landrie, C.; Ortz, J. A. *Synlett* **2003**, *9*, 1352.
9. Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortz, J. A. *Tetrahedron Lett.* **2003**, *43*, 2587.
10. Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009.
11. Kikugawa, Y. *Rev. Heteroatom Chem.* **1996**, *15*, 263.
12. Kanger, T.; Niidas, P.; Mrisepp, A.-M.; Pehk, T.; Lopp, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2499.
13. Whiting, D. A. In *Comprehensive Organic Synthesis: Selectivity, Strategy, and Efficiency in Modern Organic Chemistry*; Trost, B. A.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 803–820.
14. For examples of the trapping of arenium intermediates, generated upon *ipso* nitration, see: Fischer, A.; Henderson, G. N.; Iyer, L. M. *Can. J. Chem.* **1985**, *63*, 2390.
15. Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E. M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397.