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A Formal Construction of Fasicularin

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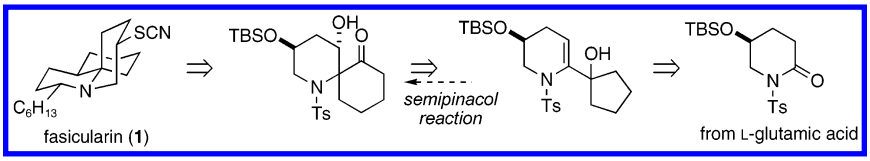
ABSTRACT



Our synthetic approach toward fasicularin is presented. Key steps in this construction are a siloxy-epoxide semipinacol rearrangement, a *B*-alkyl Suzuki reaction and an intramolecular S_N2 reaction.

Fasicularin (**1**) was isolated from the marine invertebrate *Nephteis fascularis* in 1997 by Patil and co-workers (Figure 1).[1] Its interesting tricyclic structure containing a spiro ring junction adjacent to nitrogen, is similar to other recently isolated marine alkaloids such as lepadiformine (**2**) and the cylindricines (e.g., cylindricine A and B, **3** and **4**).[2] The major structural difference between fasicularin and the latter compounds is its *trans*-1-azadecalin A−B ring system. In addition, screening assays had found that **1** could induce DNA damage through a currently unknown process. Fasicularin was also shown to be cytotoxic to Vero cells (IC_{50} of 14 μg/mL).

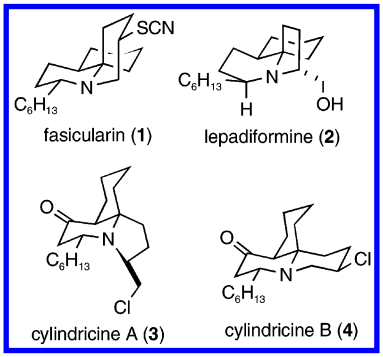


Figure 1. Fasicularin and related marine natural products.

Unsurprisingly, the appealing structure of **1** coupled with its reported biological activities have made it, as well as **2** and **3**, an attractive target for the synthetic organic community.[3,4] Two previous total syntheses that produce **1** in racemic form have been reported. Each used elegant cycloaddition strategies to address the formation of the spiro ring fusion of **1**. The first construction from Kibayashi's laboratory utilized an acylnitroso Diels−Alder process,[5] and the second synthesis by Funk and Maeng produced the precursor to the spiro center using a 2-amidoacrolein Diels−Alder cycloadduct.[6] Our interest in **1** stemmed from its

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(3) (a) The synthetic work on lepadiformine has been nicely summarized: Weinreb, S. M. *Acc. Chem. Res.* **2003**, *36*, 59. See also: (b) Abe, H.; Aoyagi, S.; Kibayashi, C. *Angew. Chem., Int. Ed. Eng.* **2002**, *41*, 3017. (c) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (d) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507. (e) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511. (f) Reference **5**. (g) Abe, H.; Aoyogi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1205. (h) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865. (i) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688. (j) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686. (k) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369.

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(5) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583.

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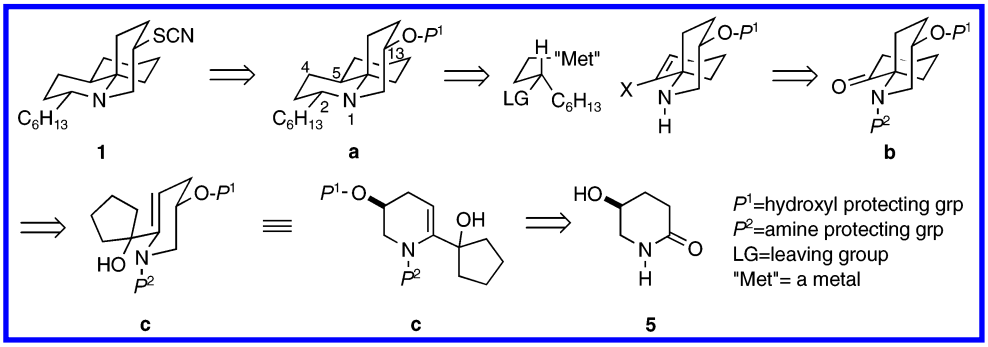
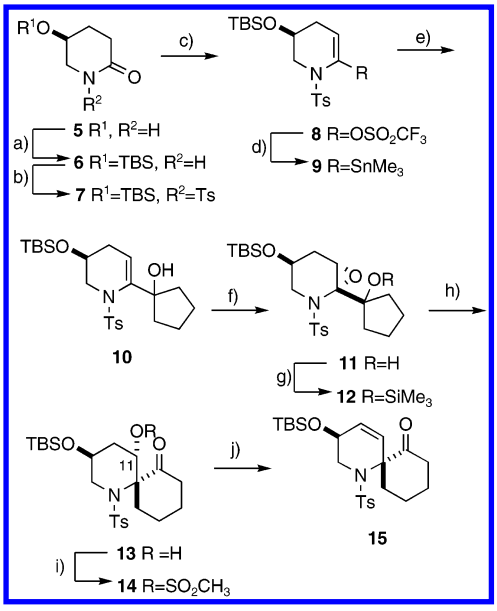
Scheme 1. Analysis of 1



spirocyclic center and the possibility of using a semipinacol rearrangement for its construction.[7,8]

Our analysis of **1** is presented in Scheme 1. Similar to the previous syntheses, we planned late stage introduction of the thiocyanate unit using tricyclic amine **a** as an advanced intermediate. Retro-annulation by cleavage of the N1−C2 bond and the C4−C5 bond produces the key spirocyclic ketone intermediate **b**. Formation of the C4−C5 bond was believed to be possible through a Pd(0)-catalyzed cross-coupling reaction, and *N*-alkylation would serve to form the N1−C2 bond. We planned to use a siloxy-epoxide rearrangement reaction of **c** to build the critical spirocyclic intermediate **b**. Cyclopentanol **c** was thought to be derivable from the known lactam **5**.

Scheme 2. Construction of Azaspirocyclic Ketone **15**[a]



[a] (a) TBSCl, imidazole, DMF, rt, 92%; (b) *n*BuLi, TsCl, THF, −78 °C, 75%; (c) KHMDS, Comins' reagent, THF, −78 °C → rt, 76%; (d) Pd_2dba_3 (10 mol %), $AsPh_3$ (40 mol %), Me_6Sn_2, THF, rt, 7 h, 71%; (e) MeLi, −78 → 0 °C, 10 min, then $MgBr_2$ at −78 °C, 30 min, then cyclopentanone at −100 °C → rt, 89%; (f) DMDO, K_2CO_3, rt; (g) TMSOTf, 2,6-lutidine, THF, rt, 83% (over both steps); (h) $TiCl_4$, CH_2Cl_2, −78 °C, 30 min, 96%; (i) MsCl, DMAP, CH_2Cl_2, rt, 87%; (j) DBU, toluene, reflux, 91%.

Our construction of the critical spirocyclic ketone intermediate is presented in Scheme 2. Lactam **5**, which can be derived from L-glutamic acid (five steps) in multigram scales using a slightly modified literature procedure,[9] was protected as its *tert*-butyldimethylsilyl ether **6** using standard conditions. Sequential treatment of **6** with *n*-butyllithium followed by *p*-toluenesulfonyl chloride in THF produced the *N*-*p*-toluenesulfonyl imide **7** in 75% yield. The conversion of **7** into its enol trifluoromethanesulfonate (triflate) **8** using potassium hexamethyldisilazane and *N*-(5-chloro-2-pyridyl)-triflimide proceeded uneventfully.[10] The vinylstannane reagent **9** was produced using a palladium(0)-catalyzed cross-coupling between **8** and hexamethyldistannane.[11] The organomagnesium species generated from **9** ((a) 2.2 equiv of methyllithium, (b) magnesium bromide etherate) could add to cyclopentanone with a minimum of side reactions at −100 °C. The cyclopentanol **10** was isolated in 89% yield after workup and purification. Multigram batches could be routinely processed through this sequence. Because the attempted semipinacol reaction of **10** using protic acid failed, a siloxy-epoxide rearrangement was used to generate the desired spirocyclic ketone.[7] To that end, the alkene in **10** was epoxidized by the action of dimethyldioxirane (DMDO) in the presence of potassium carbonate to produce **11** as a single diastereomer. This crude mixture was treated with trimethylsilyl triflate and 2,6-lutidine to generate trimethylsilyl ether **12** (83%, over two steps). Treatment of **12** with 1 equiv of titanium tetrachloride in dichloromethane at −78 °C for 30 min resulted in smooth ring expansion to produce cyclohexanone **13** in 96% yield after workup and purification.[7,12] The structure and stereochemistry of **13** was confirmed using X-ray crystallography.[7] At this point, the

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(10) Comins, D. L.; Dehghan, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

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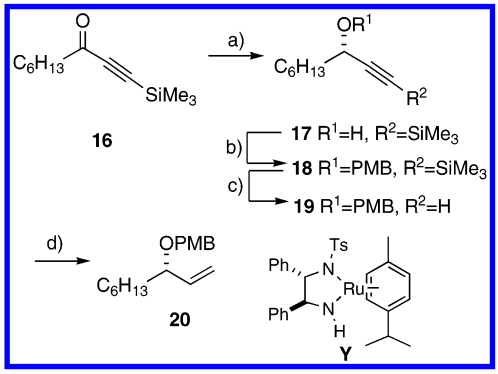
hydroxy group at C11 (fasicularin numbering) was to be removed. Because of difficulties in generating a xanthate ester required for a Barton−McCombie deoxygenation, the pseudoaxial alcohol functionality was ultimately removed by an elimination-hydrogenation sequence. Conversion of **13** to methanesulfonate **14** (MsCl, DMAP, 87%) followed by treatment with DBU in refluxing toluene produced alkene **15** in 91% isolated yield.

The segment used for the annulation of the third ring of **1** was constructed in a straightforward manner as shown in Scheme 3. Reduction of 1-trimethylsilyl-1-nonyne-3-one (**16**)

Scheme 3. Construction of Alkene **20**[a]

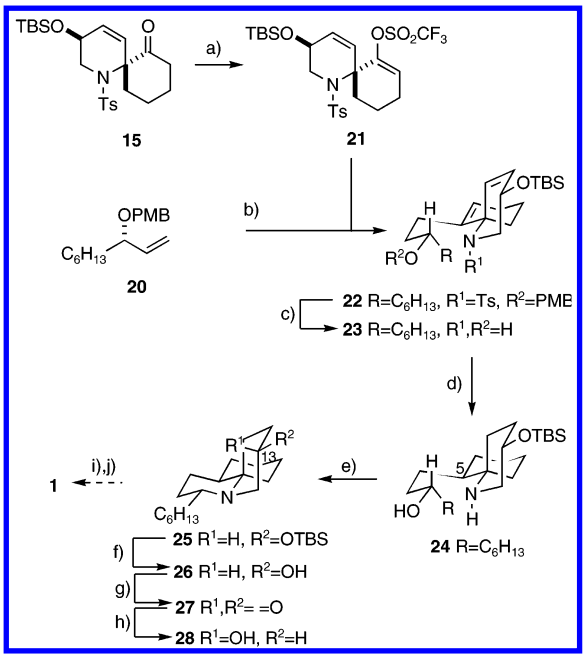


[a] (a) Catalyst **Y** (12 mol %), 2-propanol, rt, 94%, (>99% ee); (b) *p*-methoxybenzyl trichloroacetimidate, PPTS (10 mol %), CH_2Cl_2, 73%, (97% brsm); (c) TBAF, THF, 95%; (d) H_2 (1 atm), $Pd/CaCO_3$ (Pb poisoned), EtOH, −6 °C, 93%.

using transfer hydrogenation conditions developed by Noyori generated (*S*)-propargyl alcohol **17** (94% yield, 99% ee (chiral GC)).[13] The alcohol was protected as its PMB ether (*p*-methoxybenzyl trichloroacetimidate, PPTS, 73%, (97% based on recovered starting material)) and then desilylated using tetrabutylammonium fluoride (TBAF) to give **19** in 95% yield. Hydrogenation of **19** over Lindlar's catalyst produced **20** in 93% yield.

A *B*-alkyl Suzuki cross-coupling reaction was planned to connect fragments **20** and **15**.[14] Ketone **15** was converted to its enol trifluoromethanesulfonate derivative **21** using standard conditions (KHMDS, $PhN(Tf)_2$, 96%). Alkene **20** was subjected to hydroboration conditions using 9-BBN-H followed by addition of water.[15] To this intermediate was added **21** in conjunction with a Pd(0) catalyst system,[16] which resulted in the isolation of **22** in 84% yield. Dissolving metal reduction smoothly deprotected both the toluenesulfonamide and the *p*-methoxybenzyl ether to the corresponding amino-alcohol **23**. Diastereoselective reduction of the alkenes in **23** was best performed using 1 atm of hydrogen over rhodium on carbon in ethanol to give the saturated amine **24** in 76% yield with 10.5:1 diastereoselectivity at C5 favoring the shown epimer. Cyclodehydration of **24** to **25** was effected using Kibayashi's conditions.[17] Deprotection of the TBS ether in **25** took place in 82% yield using TBAF with 4 Å molecular sieves, a crucial additive. Omission of the sieves resulted in decomposition. At this point the alcohol was oxidized using TPAP-NMO to produce ketone **27**, an intermediate that was generated in racemic form by the Funk group.[6] The reduction of **27** using L-Selectride at −78 °C

Scheme 4. Construction of 1[a]



[a] (a) KHMDS, $PhNTf_2$, THF, −78 °C, 96%; (b) 9-BBN, THF, rt, 1 h, then add H_2O, rt, 1 h, then cannulate to a solution of **21**, $PdCl_2dppf{\cdot}CH_2Cl_2$ (10 mol %), Ph_3As (10 mol %), KBr, $CsCO_3$, DMF/THF/H_2O, 60 °C, 14 h, 84%; (c) Li^0, NH_3/THF, −78 °C, 83%; (d) H_2 (1 atm), Rh/C (20 mol %), EtOH, rt, 69%; (e) PPh_3, CBr_4, Et_3N, CH_2Cl_2, 0 °C → rt, 84%; (f) TBAF, 4 Å MS, THF, rt, 82%; (g) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 79%; (h) Li $HB(^sC_4H_9)_3$, THF, −40 °C, 67%; (i) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 84%; Bu_4NSCN, toluene, 110 °C, 1 d.

generated a single desired diastereomeric alcohol **28** resulting from "equatorial" attack of hydride. Conversion of **27** or **28** to **1** has been reported to be capricious and low-yielding,[5,6]

(12) Siloxy-epoxide and related rearrangements: (a) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G.-i. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (b) Shimazaki, M.; Itara, I.; Suzuki, K.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1987**, *28*, 5891. (c) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431. (d) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (e) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944. (f) Tu, Y. Q.; Sun, L. D.; Weng, P. Z. *J. Org. Chem.* **1999**, *64*, 629. (g) Matsubara, S.; Yamamoto, H.; Oshima, K. *Angew. Chem., Int. Ed. Eng.* **2002**, *41*, 2837.

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(16) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014.

(17) Shishido, Y.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 2876.

and there was no exception in our case. Funk and Maeng, after being unable to repeat the sequence of transformations reported by Kibayashi to install the thiocyanate group, disclosed a procedure to convert **28** to **1** in ~20% yield. In our hands, sequential treatment of this alcohol with the conditions reported by Funk and Maeng ((a) MsCl, $N(C_2H_5)_3$; (b) Bu_4NSCN, toluene, reflux) produced, as expected, a mixture of several compounds. Signals attributable to **1** were observed in the ^1H NMR spectrum of the crude reaction mixture. Unfortunately, the low yield for the incorporation of the thiocyanate coupled with difficulties in isolating and purifying **1** from this mixture prevented us from obtaining an analytically pure sample.[18]

In summary, our construction of fasicularin (or at least a very late stage precursor to **1**) has been presented. Our strategy differs markedly from previous approaches as a cycloaddition reaction was not used to install the critical spirocyclic ring system. Rather, key steps in this synthetic route are the use of a siloxy-epoxide rearrangement to construct the spiro ring system and a *B*-alkyl Suzuki reaction within a complex molecular setting. As our starting material is derived from the chiral pool (L-glutamic acid), our construction would produce one enantiomer of **1**, but because of the absence of either natural material or optical rotation data, the absolute configuration of naturally occurring **1** cannot be established. This route does demonstrate the viability of azaspirocycle formation using semipinacol reactions in alkaloid synthesis. We are now extending this methodology to the construction of other alkaloid natural products.

(18) A major difficulty in the final step is the detection and isolation of fasicularin. The deactivation of silica (gel or chromatography plates) using a 1% ammonium hydroxide wash is critical for the detection of the desired compound. Funk, R., Penn State University, personal communication.

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Supporting Information Available: Experimental procedures and characterization data for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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