Total Synthesis of (±)-Fasicularin via a 2-Amidoacrolein Cycloaddition

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ABSTRACT



The total synthesis of the cytotoxin fasicularin is described. The key steps include the following: (1) an intermolecular Diels–Alder cycloaddition of a 2-(triflamido)acrolein with the dioxolane ketal of trideca-1,3-dien-7-one to establish the *trans*-perhydroisoquinoline stereochemistry, (2) a stereoelectronically controlled hydride addition to a N(1)–C(2) iminium ion to introduce the equatorial hexyl substituent, and (3) elaboration of the pyrido ring by an internal aldol reaction.

Improved screening assays continue to uncover structurally unique compounds possessing useful biological activities. Fasicularin¹ was recently isolated from a marine invertebrate, the ascidian *Nephteis fasicularis*. The compound was discovered using a yeast strain in which the RAD 52 gene had been deleted, thus rendering the organism incapable of recombination and repair of DNA double strand breaks.^{1a} Consequently, the yeast is sensitive to agents that produce DNA damage by diverse mechanisms.² Fasicularin was subsequently shown to be cytotoxic to Vero cells (IC₅₀ of 14 μ g/mL).^{1a} The structure was established primarily by

(2) For a related yeast bioassay, see: (a) Zhou, B.-N.; Hoch, J. M.; Johnson, R. K.; Mattern, M. R.; Eng, W.-K.; Ma, J.; Hecht, S. M.; Newman, D. J.; Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 1273. For a review of yeast mutant bioassays, see: Perego, P.; Jimenez, G. S.; Gatti, L.; Howell, S. B.; Zunino, F. *Pharmacol. Rev.* **2000**, *52*, 477.

(3) Cylindricine B is in equilibrium (2:3) via an aziridinium ion intermediate with cylindricine A, which possesses a (chloromethyl)-pyrrolidine ring instead of the chloropiperidine ring found in cylindrincine B. For the isolation of these and other cylindricines, see: (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645. (b) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355.

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NMR spectroscopy and is quite similar to that of cylindricine B^3 and lepadiformine⁴ which have been isolated from the ascidians *Clavelina cylindrica* and *C. lepadiformis*, respectively (Figure 1). We have recently reported a total synthesis



of lepadiformine^{4g} that featured the construction of the *trans*perhydroisoquinoline substructure from a 2-amidoacrolein Diels—Alder cycloadduct.⁵ Fasicularin also contains a *trans*perhydroisoquinoline, although the tricycle is composed of a *pyrido*-quinoline rather than the *pyrrolo*-quinoline found

⁽¹⁾ The absolute configuration of fasicularin is unknown. For the isolation and structural determination, see: (a) 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. For the first total synthesis, see: (b) Abe, H.; Aoyagi, S.; Kibayashi, C. J. Am. Chem. Soc. **2000**, *122*, 4583. For the synthesis of related azaspirocycles, see: (c) Fenster, M. D. B.; Patrick, B. O.; Dake, G. R. Org. Lett. **2001**, *3*, 2109. (d) Bagley, M. C.; Oppolzer, W. *Tetrahedron: Asymmetry* **2000**, *11*, 2625.

⁽c) Li, C.; Blackman, A. J. Aust. J. Chem. 1995, 48, 955. For total syntheses, see:
(d) Snider, B. B.; Liu, T. J. Org. Chem. 1997, 62, 5630. (e) Molander, G. A.; Rönn, M. J. Org. Chem. 1999, 64, 5183. (f) Liu, J. F.; Heathcock, C. H. J. Org. Chem. 1999, 64, 8263.

in lepadiformine. We show herein that our amidoacroleincycloaddition-based methodology can also facilitate the rapid assembly of this novel tricyclic ring system in a total synthesis of (\pm) -fasicularin.

Our retrosynthetic analysis is presented in Scheme 1. We planned to introduce the sensitive thiocyanate⁶ functionality



of fasicularin (1) at the conclusion of the synthesis by displacement of an axial C(13) leaving group, in turn, available by equatorial ketone reduction of the dihydro derivative of enone 2. The pyrido ring of tricycle 2 might arise from an internal aldol reaction of keto aldehyde 3. The amino alcohol 4 is adequately functionalized for elaboration to the keto aldehyde 3 and its C(2) hydrogen atom could be derived from a stereoelectronically controlled hydride addition to the corresponding N(1)-C(2) iminium ion.⁷ The iminium ion precursor, a C(10) primary amine, could be prepared by two-stage reduction (1. LAH;⁸ 2. H₂/Pd) of triflamide 5. Finally, on the basis of previous work in our laboratories,^{4g,5} the 2-(triflamido)acrolein **6** was expected to undergo a regio- and stereoselective (endo) cycloaddition with diene 7 to afford the cycloadduct 5 possessing the requisite stereochemistry for elaboration to the trans-perhydroisoquinoline 4.

The 2-(triflamido)acrolein **6** was prepared using our established protocol (Scheme 2). The *N*-benzylimine deriva-



tive of 1,3-dioxan-5-one $(8)^9$ was converted to the corresponding 5-(triflamido)-1,3-dioxin (Tf₂O, NEt₃), which was then subjected to standard retrocycloaddition conditions to afford the dienophile 6 and acetone. The key cycloaddition reaction of amidoacrolein 6 with diene 7^{10} was best accomplished using high-pressure conditions (12 kbar) and afforded a single cycloadduct, triflamide 5, in excellent yield. Reduction of aldehyde 5 with LiAlH₄ and concomitant removal of the trifluoromethanesulfonyl group⁸ proceeded smoothly to the desired amino alcohol 9. Simultaneous reduction of the cyclohexene double bond of amino alcohol 9 and hydrogenolysis of the N-benzyl substituent (H_2 , Pd/ C) provided an amino alcohol, which was directly subjected to hydrolysis conditions to afford the expected oxazolidine 10. Subjection of oxazolidine 10 to NaBH₄ in MeOH¹¹ gave rise to a single amino alcohol, compound 4, via stereocontrolled α /axial addition of hydride to an iminium ion intermediate through a chair-chair conformer. The stereochemical assignment for 4 was confirmed by X-ray crystallography.

Having established a viable route to the central C(2) equatorially substituted *trans*-perhydroquinoline substructure of fasicularin, we turned our attention to annulating the remaining ring of the tricyclic system by the aforementioned aldol-reaction-based strategy. To that end, we examined the *N*-alkylation of amino alcohol **4** with bromoacetone or equivalents, e.g., 3-iodo-2-methylpropene and 3-iodo-2-

⁽⁴⁾ For isolation, see: (a) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691. For synthetic effort which led to a structural revision, see: (b) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 686. (c) Werner, K. M.; De los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1999**, *64*, 4865. (c) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369. (e) Pearson, W. H.; Ren, Y. *J. Org. Chem.* **1999**, *64*, 688. For total syntheses, see ref 1b and the following: (f) Sun, P.; Sun, C.; Weinreb, S. M. *Org. Lett.* **2001**, *3*, 3507. (g) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511.

⁽⁵⁾ For the total synthesis of another novel tricyclic alkaloid (FR901483) using this methodology, see: Funk, R. L.; Maeng, J. H. *Org. Lett.* **2001**, *3*, 1125.

⁽⁶⁾ The chemistry of thiocyanates has been reviewed, see: Erian, A. W.; Sherif, S. M. *Tetrahedron* **1999**, *55*, 7957.

^{(7) (}a) Stevens, R. V. Acc. Chem. Res. **1984**, *17*, 289. (b) Deslongchamps, P. Stereoelectronic Effects in Organic Chemistry; Pergamon Press: New York, 1983; p 209.

⁽⁸⁾ Tertiary triflamides can be efficiently desulfonylated, see: (a) Hendrickson, J. B.; Bergeron, R.; Giga, A.; Sternbach, D. J. Am. Chem. Soc. **1973**, *95*, 3412. (b) Hendrickson, J. B.; Bergeron, R.; Sternbach, D. D. Tetrahedron **1975**, *31*, 2517.

⁽⁹⁾ Prepared in two steps from tris(hydroxymethyl)aminomethane hydrochloride. Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 687.

⁽¹⁰⁾ Prepared from the known hepta-4,6-dienylnitrile (Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1986**, *42*, 2847) and hexylmagnesium bromide (2.5 equiv, Et_2O , reflux, 1 h, 60%).

⁽¹¹⁾ For selected reductions of oxazolidines, see: (a) McCarthy, J. R.; Wiedeman, P. E.; Schuser, A. J.; Whitten, J. P.; Barbuch, R. J.; Huffman, J. C. J. Org. Chem. **1985**, 50, 3095. (b) Beulshausen, T.; Groth, U.; Schöllkopf, U. Liebigs Ann. Chem. **1992**, 523. (c) Farr, R. A.; Holland, A. K.; Huber, E. W.; Peet, N. P.; Weintraub, P. M. Tetrahedron **1994**, 50, 1033. (d) Hamdani, M.; Scholler, D.; Bouquant, J.; Feigenbaum, A. Tetrahedron **1996**, 52, 605.

(methoxymethoxy)propene,¹² but in all cases recovered only starting material using a variety of solvents and reaction conditions. We speculated that the nucleophilicity of the basic nitrogen was compromised by an internal hydrogen bond as well as the obvious steric factors. Accordingly, we investigated the selective protection of the *hydroxyl* substituent. Thus, acetylation of the amino alcohol **4** gave the desired acetate **11** which underwent a smooth, albeit slow, alkylation with 3-iodo-2-(methoxymethoxy)propene in the presence of Hünig's base to furnish the desired tertiary amine **12** (76%) and recovered starting material (20%) (Scheme 3). Trans-



esterification of acetate **12** gave an alcohol that could not be cleanly oxidized to an aldehyde using many of the standard reagents (PCC, Swern, Dess–Martin, IBX¹³). Fortunately, the Corey–Kim¹⁴ protocol (NCS, DMS; NEt₃) cleanly gave an unstable aldehyde that was directly subjected

to hydrolysis and/or aldol condensation¹⁵ conditions (TFA, H_2O , 1:1) to deliver the desired enone 2 in 74% yield for the two steps. Although hydrogenation of the carbon-carbon double bond of enone 2 was uneventful, the reduction of the resulting ketone was not. Reduction with sodium borohydride afforded a 1:1 mixture of ketone 13 and its C(13) epimer, whereas lithium tri-sec-butylborohydride gave none of the desired product. However, the diastereomeric ratio was improved (5.3:1) upon reduction with lithium tri-tertbutoxyaluminohydride to produce alcohol 13 as the major isomer, whose spectral properties were identical with those reported by Kibayashi.^{1b} Alcohol 13 had been previously converted to fasicularin in low yield [20%, due to competitive formation of isothiocyante 15 (2%) and elimination product 16 (54%)] using a Mitsunobu procedure (HSCN.Ph₃P. DEAD, benzene, 40 °C, 72 h).^{1b} However, in our hands only trace amounts of fasicularin were observed. After considerable experimentation, we discovered that treatment of the mesylate 14 with tetrabutylammonium thiocyanate¹⁶ in toluene furnished fasicularin, albeit in poor yield (20%), accompanied by the isothiocyanate 15 (12%) and the elimination product 16 (28%). The spectral properties of our racemic fasicularin (1) were in agreement with those previously reported.1a,b

In summary, we have documented another example of tricyclic alkaloid ring construction from a 2-(amido)acrolein Diels—Alder cycloadduct by judicious choice of the nitrogen acyl/sulfonyl and alkyl substituents. Additional applications are underway 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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⁽¹⁶⁾ Spurlock, L. A.; Cox, G. W. J. Am. Chem. Soc. 1971, 93, 146.