ORGANIC LETTERS

2002
Vol. 4, No. 3
331−333

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

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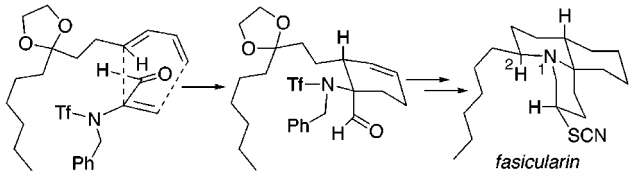
Received October 3, 2001

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. Fasicularin[1] 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 (IC_{50} of 14 μg/mL).[1a] The structure was established primarily by NMR spectroscopy and is quite similar to that of cylindricine B[3] and lepadiformine[4] which have been isolated from the ascidians *Clavelina cylindrica* and *C. lepadiformis*, respectively (Figure 1). We have recently reported a total synthesis

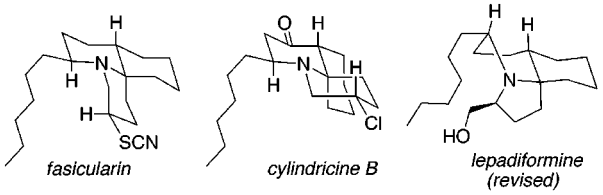


Figure 1.

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.

(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.

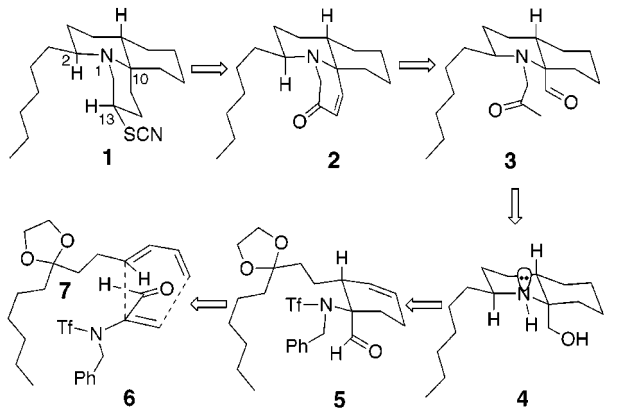
(3) Cylindricine B is in equilibrium (2:3) via an aziridinium ion intermediate with cylindricine A, which possesses a (chloromethyl)-pyrrolidine ring instead of the chloropiperidine ring found in cylindrincine B. For the isolation of these and other cylindricines, see: (a) Blackman, A. J.; Li, C.; Hockless, 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. (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.

10.1021/ol016850g CCC: $22.00
Published on Web 01/09/2002

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

Our retrosynthetic analysis is presented in Scheme 1. We planned to introduce the sensitive thiocyanate[6] functionality

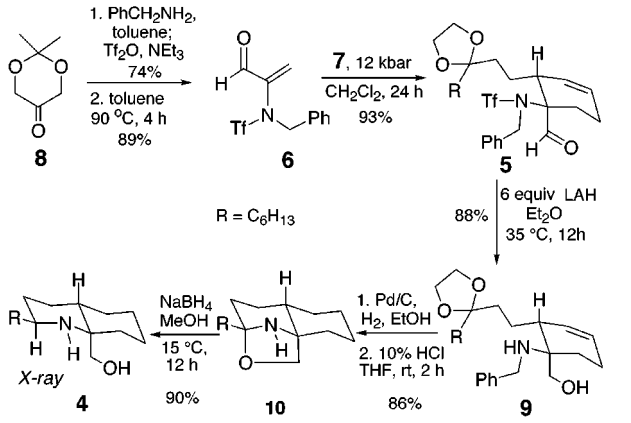
Scheme 1



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. H_2/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 derivative of 1,3-dioxan-5-one (**8**)[9] was converted to the corresponding 5-(triflamido)-1,3-dioxin (Tf_2O, NEt_3), 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 $LiAlH_4$ and concomitant removal of the trifluoromethanesulfonyl group[8] 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 $NaBH_4$ in MeOH[11] 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.

Scheme 2



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.

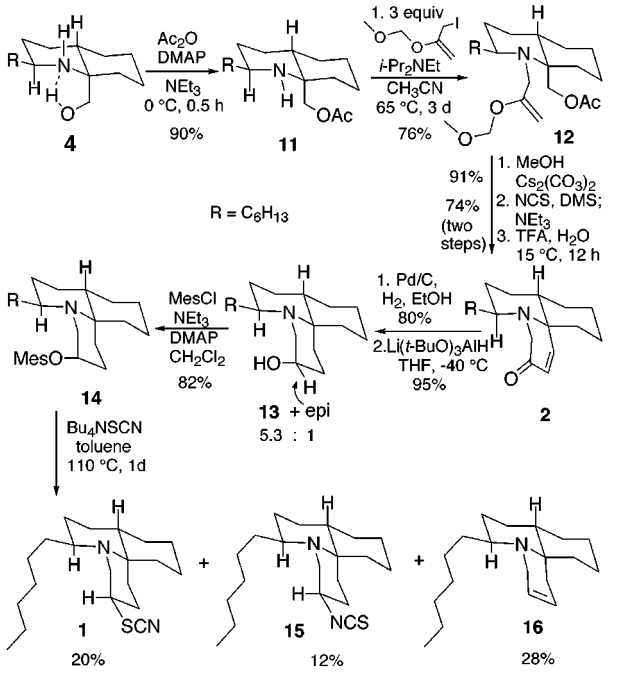
(9) Prepared in two steps from tris(hydroxymethyl)aminomethane hydrochloride. Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 687.

(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-

Scheme 3



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, IBX[13]). Fortunately, the Corey−Kim[14] protocol (NCS, DMS; NEt_3) cleanly gave an unstable aldehyde that was directly subjected to hydrolysis and/or aldol condensation[15] 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-*tert*-butoxyaluminohydride 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,Ph_3P, 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 thiocyanate[16] 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.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (GM28663). We thank Dr. Douglas R. Powell of the University of Wisconsin for the X-ray crystallographic analysis of compound **4**. We thank Dr. Alan J. Freyer of GlaxoSmithKline Pharmaceuticals for providing authentic spectra of fasicularin.

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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(12) (a) Janicki, S. A.; Fairgrieve, J. M.; Petillo, P. A. *J. Org. Chem.* **1998**, *63*, 3694. (b) The corresponding chloride has also been employed as a chloroacetone equivalent, see: Gu, X.-P.; Nishida, N.; Ikeda, I.; Okahara, M. *J. Org. Chem.* **1987**, *52*, 3192.

(13) A variety of amino alcohols have been oxidized with this reagent, see: Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

(14) (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. For another example where this oxidant was the only successful one, see: Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Sitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3438.

(15) A related hydrolysis/aldol condensation using similar conditions to prepare a 2*H*-1,6-dihydro-3-pyridinone substructure in the context of the total synthesis of the 2,2,3-trialkyindoline vallesamidine has been reported, see: Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem.* **1990**, *55*, 798.

(16) Spurlock, L. A.; Cox, G. W. *J. Am. Chem. Soc.* **1971**, *93*, 146.