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Pd-Catalyzed Carbonylative Lactamization: A Novel Synthetic Approach to FR900482

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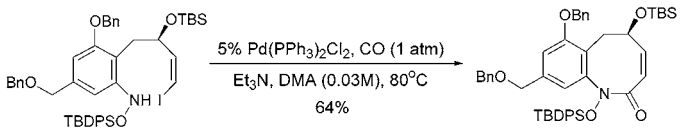
ABSTRACT



An asymmetric synthesis of the benzazocine core of FR900482 has been achieved in 15 steps from 3,5-dinitro-*p*-toluic acid. Key features of the synthesis include an enantioselective *N*-methylephedrine-mediated zinc acetylide addition to a highly enolizable arylacetaldehyde and a novel Pd-catalyzed carbonylative lactamization to form an eight-membered ring.

The anticancer drug mitomycin C (**1**) has been in widespread clinical use for over 30 years and remains an important component of combination cancer therapy and radiotherapy for solid tumors.[1] However, due to its high hematotoxicity, mitomycin C may soon be replaced by the structurally related mitomycinoid FK317 (**2**), which is currently undergoing advanced clinical trials in Japan.[2] FK317 is a semisynthetic derivative of FR900482 (**3**), an alkaloid isolated from the fermentation broth of *Streptomyces sandaensis* by the Fujisawa Pharmaceutical Co.[3] Analogous to the mitomycins, the cytotoxicity of both FK317 and FR900482 can be attributed to covalent cross-linking of duplex DNA in the minor groove following reductive activation in cells.[4] Thus, due to their potent antitumor activity, intriguing mode of action, and densely functionalized molecular architecture, FR900482 and related congeners (i.e., FR66979 **4**)[5] have attracted considerable attention from the synthetic community.[6]

In addition to comprising the core of several natural products, the benzazocine ring system has been utilized as a late-stage intermediate in synthetic routes to both the mitomycins and the Fujisawa mitomycinoids. Varying the oxidation state of the arylamine in the benzazocine allows either the pyrrolo[1,2-*a*]indole framework of the mitomycins or the bicyclo[3.3.1] hemiketal of the FR900482 alkaloids to be accessed (Scheme 1).[7]

Although the direct formation of medium-sized rings from acyclic precursors is disfavored by entropic and enthalpic

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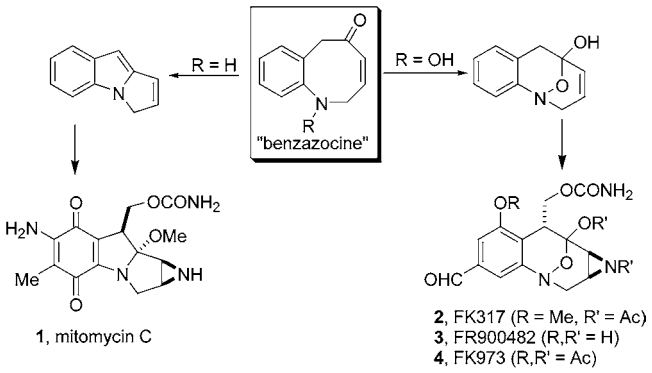
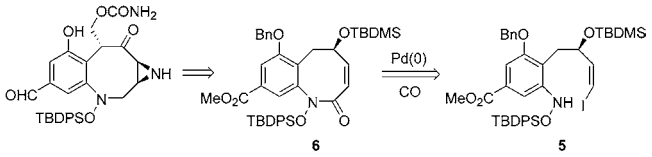
Scheme 1. Benzazocines as Mitomycin/FR900482 Intermediates



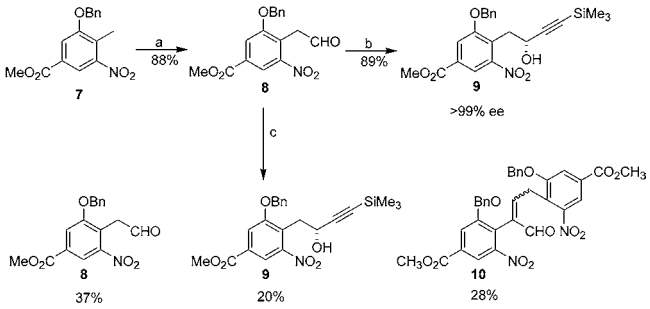
constraints, the presence of sp^2-hybridized atoms can facilitate the cyclization by minimizing transannular interactions. Thus, transition-metal-catalyzed carbonylative cyclizations of vinyl halides represent a promising method for assembling medium-sized rings because three contiguous sp^2-hybridized atoms are introduced in a single step.[8] Herein we disclose an enantioselective synthesis of the benzazocine core of FR900482 utilizing a Pd-catalyzed carbonylative cyclization of an arylhydroxylamine with a tethered vinyl iodide **5** to form the eight-membered ring **6** (Scheme 2).

Scheme 2. Retrosynthesis of FR900482 Benzazocine



In their elegant total synthesis of FR900482, Fukuyama and co-workers demonstrated that a chiral allylic alcohol could direct the epoxidation of a proximal olefin in a functionalized benzazocine.[6a] In hopes of employing a similar strategy, we required an asymmetric synthesis of cyclization precursor **5**. To this end, commercially available 3,5-dinitro-*p*-toluic acid was converted to aryl ether **7** in four steps as described by Ziegler and Belema.[9] Subsequent condensation with *N*,*N*-dimethylformamidedimethyl acetal afforded a mixture of E/Z enamines, which were not isolated but immediately hydrolyzed under acidic conditions to provide arylacetaldehyde **8** (Scheme 3). Upon addition of this aldehyde to a toluene solution of the zinc acetylide generated in situ from $Zn(OTf)_2$, Et_3N, (+)-*N*-methylephedrine, and trimethylsilylacetylene according to the procedure of Carreira et al.,[10] propargylic alcohol **9** was isolated in 89% yield and greater than 99% ee. The enantiopurity of the product was determined by chiral HPLC comparison with a racemic standard prepared by adding trimethylsilylethynyl Grignard to aldehyde **8**, and the absolute stereochemistry was tentatively assigned by analogy to similar chiral propargylic alcohols reported by Carreira and co-workers.

Scheme 3. Carreira Asymmetric Alkynylation[a]



[a] Conditions: (a) *N*,*N*-Dimethylformamide dimethylacetal, DMF, 140 °C; then AcOH, THF/H_2O. (b) $Zn(OTf)_2$ (1.5 equiv), (+)-*N*-methylephedrine (1.6 equiv), Et_3N, TMS−acetylene, toluene, rt. (c) $Zn(OTf)_2$ (0.2 equiv),(+)-*N*-methylephedrine (0.22 equiv), TMS−acetylene, toluene, 60 °C.

Although Carreira has developed catalytic conditions for the asymmetric acetylide addition,[11] the higher temperature required for catalytic turnover promoted a dimerization of the starting material to afford aldehyde **10**. Given the general tendency for aldehydes without α-branching to undergo some degree of aldol self-condensation under the basic reaction conditions, it is surprising that the highly enolizable arylacetaldehyde **8** is a good substrate for the stoichiometric asymmetric acetylide addition. In fact, it is possible that a reversible deprotonation of the benzylic hydrogen does occur, but the two ortho substituents on the aromatic ring provide enough steric hindrance to inhibit the aldol side-reaction at room temperature. However, at higher temperatures the aldol reaction becomes a competing process, leading to undesired consumption of the starting aldehyde.

The product of the Carreira asymmetric alkynylation **9** could be smoothly transformed to the (Z)-vinyl iodide substrate **5** for the Pd-catalyzed carbonylative cyclization in 70% yield over five steps (Scheme 4). Following protection of secondary alcohol **9** as its *tert*-butyldimethylsilyl ether, the silylacetylene was converted to (*Z*)-vinyl iodide **12** by a two-step procedure involving iododesilylation and diimide reduction.[12] The presence of the bulky *tert*-butyldimethylsilyl group prevented overreduction during the diimide reaction, as a significant amount of alkyl iodide formed when the free alcohol was used. Subsequent reduction of nitroarene **12** with samarium diiodide[13] at low temperature cleanly afforded a

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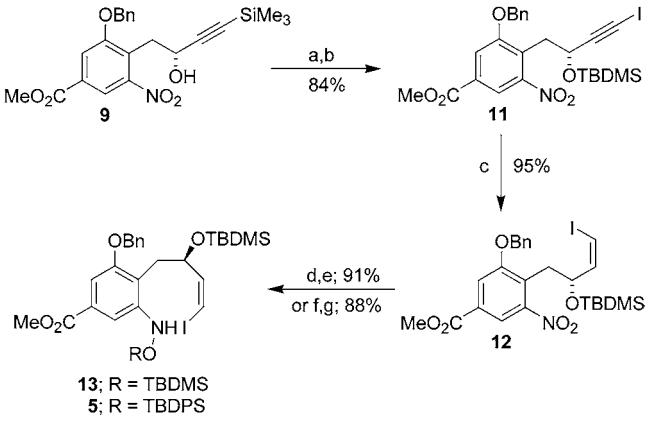
(13) Kende, A. S.; Mendoza, J. S. *Tetrahedron Lett.* **1991**, *32*, 1699.

Scheme 4. Synthesis of Cyclization Precursor[a]

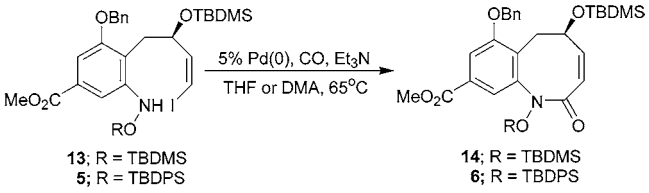


[a] Conditions: (a) TBSCl, imid, CH_2Cl_2, rt. (b) 10% $AgNO_3$, NIS, acetone, rt. (c) Dipotassium azodicarboxylate, pyridine, AcOH, MeOH, rt. (d) SmI_2 (4 equiv), THF/MeOH, −78 °C. (e) TBSCl, imid, CH_2Cl_2, rt. (f) Zn, NH_4Cl, THF/MeOH/H_2O, rt. (g) TBDPSCl, imid, CH_2Cl_2, rt.

sensitive hydroxylamine, which was immediately converted to the *O-tert*-butyldimethylsilyl derivative **13** in 91% yield over two steps. Due to the low solubility of samarium diiodide in THF, a mild dissolving metal reduction with zinc dust and aqueous ammonium chloride was employed for large-scale reductions of the nitro group. As in the samarium diiodide reduction, the crude hydroxylamine could be directly silylated under standard conditions to afford the *O-tert*-butyldiphenylsilyl derivative **5** in 88% yield over two steps.[14]

With enantiopure hydroxylamines **5** and **13** in hand, a thorough investigation of the Pd-catalyzed carbonylative lactamization was initiated (Table 1).[15] Upon refluxing a dilute solution of hydroxylamine **13**, triethylamine, and 5% $Pd(PPh_3)_4$ in THF (0.03M) under an atmosphere of carbon monoxide, a 36% yield of the desired lactam **14** was obtained, along with some recovered starting material (49% brsm; Table 1, entry 1). Formation of the lactam was confirmed by a new carbonyl stretch at 1700 cm^{-1} in the IR spectrum. Furthermore, the allylic methine hydrogen shifted downfield in the ^1H NMR spectrum from 4.58 to 5.56 ppm, and the observed coupling constant of 11.8 Hz between the two vinyl protons at 6.25 and 5.66 ppm is diagnostic for a cis olefin in an eight-membered ring. Additional experimentation revealed that the choice of catalyst and solvent both dramatically influenced the success of the cyclization. When $Pd(PPh_3)_2Cl_2$ was used as the precatalyst, no reaction was observed in refluxing THF or benzene, and an intractable mixture of compounds formed in DMF, acetonitrile, and *N*-methylpyrrolidinone.

Table 1. Pd-Catalyzed Carbonylative Lactamization[a]



entry	substrate	catalyst	solvent[b]	CO pressure	% yield[c]
1	13	$Pd(PPh_3)_4$	THF	1 atm	36(49)
2	13	$Pd(PPh_3)_2Cl_2$	DMA (0.03 M)	1 atm	78
3	13	$Pd(PPh_3)_2Cl_2$	DMA (0.01 M)	1 atm	41
4	13	$Pd(dppf)Cl_2$	DMA	1 atm	20(47)
5	5	$Pd(PPh_3)_2Cl_2$	DMA	1 atm	66
6	5	$Pd(PPh_3)_2Cl_2$	DMA	4 atm	35

[a] See Supporting Information for experimental details. [b] All reactions performed at 65 °C and 0.03 M, except entry 3 (0.01 M). [c] Number in parentheses refers to yield based on recovered starting material.

However, when the cyclization was conducted at 65 °C in *N*,*N*-dimethylacetamide, the desired lactam **14** was produced as the only product in 78% isolated yield (entry 2). Since the incomplete mass balance may be due to competing oligomerization, more dilute cyclization conditions were explored. However, decreasing the concentration from 0.03 to 0.01 M lowered the yield of the desired eight-membered ring from 78 to 41% (entry 3). Switching catalysts from $Pd(PPh_3)_2Cl_2$ to $Pd(dppf)Cl_2$ resulted in low conversion and lactam **14** was isolated in only 20% yield (47% brsm, entry 4).

To differentiate the silyl protecting groups on the hydroxylamine and the allylic alcohol, we also investigated the Pd-catalyzed carbonylative cyclization of *O-tert*-butyldiphenylsilyl hydroxylamine **5**. Under the identical reaction conditions optimized for the cyclization of the *tert*-butyldimethylsilyl derivative **13**, hydroxylamine **5** cleanly produced the desired lactam **6** in 66% isolated yield (Table 1, entry 5). The product possessed ^1H NMR, ^{13}C NMR, and IR data analogous to that of lactam **14**.

It was anticipated that the methyl ester in the lactam product would present problems during the late-stage aldol reaction, which introduces the hydroxymethyl side chain in the benzylic position of FR900482. By activating the benzylic hydrogen toward deprotonation, the ester increases the probability of epimerization or dehydration of the aldol product.[6a] To avoid these issues and obviate potential chemoselectivity problems during the reduction of the α,β-unsaturated lactam, ester **15** was reduced to a primary alcohol with diisobutylaluminum hydride prior to lactam formation (Scheme 5). Following desilylation of the acetylene with basic methanol and protection of the primary alcohol as a benzyl ether, the hydroxylamine substrate **16** for the Pd-catalyzed carbonylative lactamization could be assembled in 69% yield over four steps following the same procedure described previously. When *O-tert*-butyldiphenylsilyl hy-

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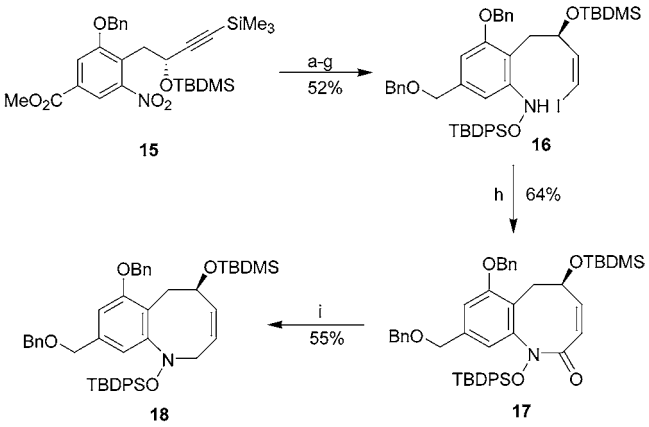
Scheme 5. Synthesis of FR900482 Benzazocine[a]



[a] Conditions: (a) DIBAL-H, THF, −78→0 °C, 99%. (b) K_2CO_3, MeOH, 97%. (c) NaH, BnBr, cat Bu_4NI, THF, 96%. (d) NIS, 10% $AgNO_3$, acetone, 94%. (e) Dipotassium azodicarboxylate, pyridine, AcOH, MeOH, rt, 97%. (f) SmI_2 (4 equiv), THF/MeOH, −78 °C, 98%. (g) TBDPSCl, imid, CH_2Cl_2, 77%. (h) 5% $Pd(PPh_3)_2Cl_2$, CO (1 atm), Et_3N, DMA (0.03 M), 80 °C, 64%. (i) BH_3−SMe_2,THF, 0 °C, 55%.

droxylamine **16** was subjected to the same Pd-catalyzed cyclization conditions optimized for hydroxylamine **5**, only recovered starting material was obtained. Fortunately, simply increasing the temperature from 65 to 80 °C promoted the cyclization and afforded the desired eight-membered ring **17** in 64% yield. To complete the synthesis of the FR900482 benzazocine core, lactam **17** was reduced with borane−methyl sulfide complex to provide hydroxylamine **18** in 55% yield without competing 1,4-reduction or cleavage of the N−O bond.[16]

In summary, we have reported an asymmetric route to the benzazocine core of FR900482. The eight-membered ring was assembled using a palladium-catalyzed carbonylative lactamization, and this procedure should prove to be useful for the synthesis of other alkaloids containing azocines and benzazocines. Current efforts are directed at fully elaborating the benzazocine core to provide FR900482 and related mitomycinoids and will be reported in due course.

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

OL049583Y

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