Total Synthesis of FR901464. Convergent Assembly of Chiral Components Prepared by Asymmetric Catalysis

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · OCTOBER 2000

Impact Factor: 12.11 · DOI: 10.1021/ja0055357

Total Synthesis of FR901464. Convergent Assembly of Chiral Components Prepared by Asymmetric Catalysis

Christopher F. Thompson, Timothy F. Jamison, and Eric N. Jacobsen*

Department of Chemistry and Chemical Biology Harvard University, Cambridge, Massachusetts 02138

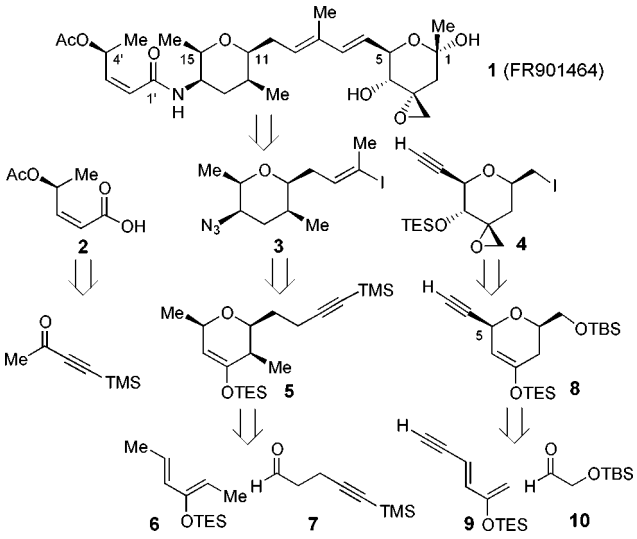
Received August 18, 2000

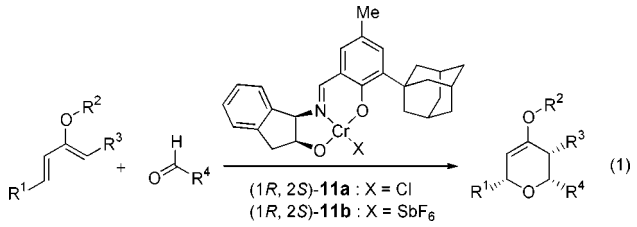
FR901464 (**1**, Scheme 1) is the most potent member of a new series of bacterially produced antitumor antibiotics identified by the Fujisawa pharmaceutical company using a transcriptional regulation assay.[1] This natural product displays pronounced activity against human solid tumors, and although its precise target and mechanism of action have not been identified, it has been shown to induce G_1 and G_2/M phase arrest in treated cells, cause changes in chromatin structure, and display strongly differentiated transcriptional regulatory activity.[2] In the latter context, its regulatory profile is substantially different from those of chromatin remodeling agents that are known inhibitors of histone deacetylase,[3] suggesting clearly that FR901464 has a fundamentally different mode of action. In addition to these intriguing biological properties, only a tentative stereochemical assignment of FR901464 was made, as the absolute configuration of the C4′ position in the amide side chain has been established unambiguously, but only the relative stereochemistry within each of the tetrahydropyran units has been elucidated.[4] These issues render FR901464 a most interesting target for biological and chemical study, and we sought to develop a versatile, stereoselective synthetic route that would provide ready access to **1** and its diastereomers.

From both a structural and retrosynthetic standpoint, **1** can be divided into three fragments of differing complexity: two highly functionalized pyran rings connected through a diene system, and an acyclic side chain joined to the rest of the molecule via an amide bond. As part of our general effort to effect natural product synthesis via convergent assembly of chiral building blocks prepared by asymmetric catalysis,[5] we envisioned joining the fragments by highly reliable and general reactions—in the present case acylation and Pd-catalyzed cross coupling—and focusing on the development of efficient methods for the enantioselective preparation of the requisite chiral components. This strategy would not only enable the preparation of **1**, but would also be readily adaptable to the synthesis of stereochemical and structural analogues.

The *Z*-allylic acetate side chain **2** is the simplest of the fragments, but its likely sensitivity toward low-valent metal complexes suggested that it would best be incorporated after the Pd-catalyzed introduction of the dienyl linkage between the pyran rings. While identification of efficient routes to pyran units **3** and **4** clearly presented the greatest methodological challenge to this synthetic exercise, we were encouraged by our group's recent discovery of highly enantio- and diastereoselective chromium-catalyzed hetero-Diels−Alder (HDA) reactions employing dienes with a single oxygen substituent (eq 1).[6] Application of the new catalysts to the HDA reaction between diene **6** and ynal **7** could serve to establish all three stereocenters in **5**, with further elaboration to **3** expected to be relatively straightforward. Similarly, the HDA reaction between dienyne **9** and aldehyde **10** could provide **8**, thereby establishing the complete carbon framework of the right-hand fragment and the key stereocenter at C5, from which the other three could be derived. To the extent that the HDA had never been investigated in the context of reacting partners as complex as **7** or **9**, this approach would also serve to test the scope of this new catalytic methodology.

Scheme 1. Retrosynthetic Analysis





The synthesis of chiral fragments required for the assembly of **1** is outlined in Scheme 2. The lone stereocenter in the acyclic left-hand fragment **2** was established with excellent enantioselectivity using Noyori's Ru-catalyzed asymmetric transfer hydrogenation of commercially available 4-(trimethylsilyl)-3-butyn-2-one.[7] The optically enriched alcohol **12** was then elaborated by a deprotection/carboxylation[8]/acetylation sequence to give carboxylic acid **13**. Lindlar reduction afforded the desired cis alkene **2**.

The synthesis of the central fragment began with a HDA reaction between diene **6**[6] and aldehyde **7**,[9] each accessible in one or two steps from commercially available materials. Although the cycloaddition was catalyzed in excellent yield with either the Cl or the SbF_6 complex **11a** or **11b**, superior enantioselectivity

(1) Nakajima, H.; Sato, B.; Fujita, T.; Takase, S.; Terano, H.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 1196−1203.

(2) Nakajima, H.; Hori, Y.; Terano, H.; Okuhara, M.; Manda, T.; Matsumoto, S.; Shimomura, K. *J. Antibiot.* **1996**, *49*, 1204−1211.

(3) (a) Nakajima, H.; Kim, Y. B.; Terano, H.; Yoshida, M.; Horinouchi, S. *Exp. Cell Res.* **1998**, *241*, 126−133. (b) Taunton, J.; Hassig, C. A.; Schreiber, S. L. *Science* **1996**, *272*, 408−411.

(4) (a) Nakajima, H.; Takase, S.; Terano, H.; Tanaka, H. *J. Antibiot.* **1997**, *50*, 96−99. (b) Nakajima, H., private communication. (c) For previous synthetic efforts toward the synthesis of FR901464, see: Horigome, M.; Watanabe, K.; Kitahara, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1999**, *41*, 73−78; *Chem. Abstr.* **2000**, *132*, 676.

(5) (a) Schaus, S. E.; Brånalt, J. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876−4877. (b) Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624−9625.

(6) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400.

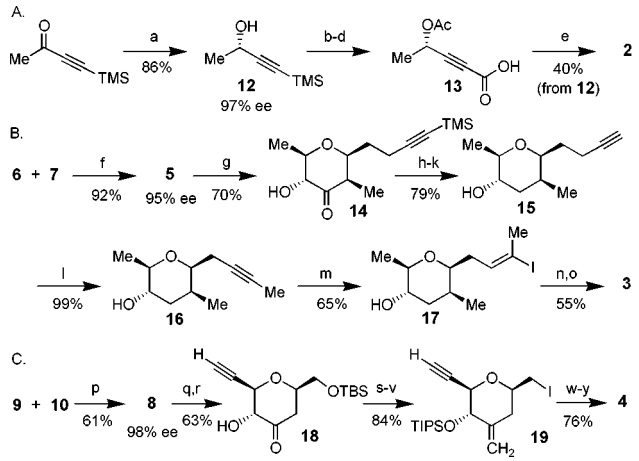
(7) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8378−8379.

(8) Getty, S.; Berson, J. *J. Am. Chem. Soc.* **1991**, *113*, 4607−4621.

(9) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699−2708.

10.1021/ja0055357 CCC: $19.00
Published on Web 10/06/2000

Scheme 2. Fragment Synthesis[a]

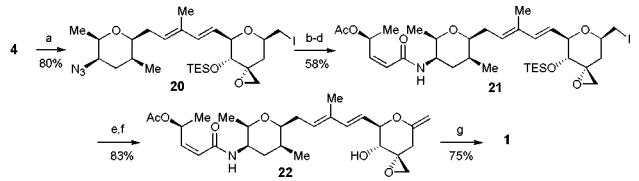


[a] Conditions: (a) Reference 7. (b) TBAF. (c) *n*-BuLi; CO_2. (d) AcCl; H_2O (pH 9). (e) H_2, Pd/$CaCO_3$, quinoline, EtOH. (f) (1*R*,2*S*)-**11b** (5 mol %). (g) *m*-CPBA, $NaHCO_3$, toluene, 0 °C. (h) $TsNHNH_2$. (i) $Na(CN)BH_3$, pH 4. (j) NaOAc, EtOH. (k) TBAF. (l) *t*-BuOK (3 equiv) DMSO (degassed), 1 min, rt. (m) (1) $Cp_2Zr(H)Cl$ (3 equiv); (2) I_2. (n) $ClCH_2SO_2Cl$, DMAP, pyridine. (o) LiN_3, DMPU. (p) (1*R*,2*S*)-**11b** (5 mol %). (q) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C. (r) K_2CO_3 (cat.), MeOH. (s) TIPSOTf. (t) $Ph_3P{=}CH_2$. (u) HOAc/THF/H_2O. (v) I_2, PPh_3, imidazole. (w) TBAF/HOAc. (x) $VO(acac)_2$, TBHP. (y) TESOTf, Et_3N.

was achieved using the SbF_6 counterion (95 vs 86% ee).[10] Rubottom oxidation of the silyl enol ether afforded the desired α-hydroxy ketone **14**. The ketone functionality was then reduced via the tosylhydrazone by a three-step sequence.[11] The terminal acetylene **15** obtained upon desilylation underwent rapid and quantitative isomerization to the thermodynamically more stable internal alkyne **16** in the presence of KO*t*-Bu in DMSO.[12,13] Treatment of **16** with Schwartz's reagent under equilibrating conditions followed by quenching of the vinylzirconium intermediate with I_2 gave the desired vinyl iodide **17**.[14] Installation of the azide by S_N2 displacement proved difficult, as might be anticipated given the steric and conformational properties of this ring system. After careful optimization, it was found that conversion of the alcohol to the monochloromethanesulfonate leaving group[15] followed by displacement with LiN_3 in DMPU gave an acceptable yield of **4**, thereby completing the synthesis of the central fragment.[16]

The synthesis of the right-hand fragment began with the cycloaddition of commercially available **10** with the novel dienyne **9**,[17] catalyzed by **11b** in 98% ee.[18] Rubottom oxidation of **8** gave a mixture of epimeric α-hydroxy ketones which could be equilibrated to the desired stereoisomer **18** in good yield using catalytic K_2CO_3 in MeOH.[19] Elaboration to the primary iodide **19** was then effected in excellent yield by a straightforward four-step sequence. Deprotection of the secondary alcohol permitted efficient directed epoxidation of the exo alkene to produce **4** as a single isomer.

Scheme 3. Fragment Coupling and Completion[a]



[a] Conditions: (a) (1) $Cp_2Zr(H)Cl$, THF, 0 °C; (2) $ZnCl_2$, THF, 0 °C; (3) **3**, $Pd(PPh_3)_4$ (6.5 mol %). (b) PMe_3, THF, rt. (c) H_2O. (d) **2**, HBTU, DIPEA, CH_3CN/CH_2Cl_2 (5:1). (e) DBU, DMF, rt, 60 h. (f) TBAF/HOAc, THF, 0 °C. (g) TsOH, THF/H_2O.

Hindered diene systems of the type found in FR901464 can be accessed under mild conditions and in good yield by hydrozirconation/Negishi coupling sequences,[14] and given the high reactivity of Schwartz's reagent toward terminal alkynes, we anticipated that the epoxide functionality in **4** might withstand hydrozirconation.[20] Indeed, the coupling of **4** with **3** proceeded in excellent yield to afford **20** (Scheme 3). Completion of the synthesis required azide reduction and acylation with side chain **2**, as well as installation of the hemiketal group by an elimination/hydration sequence. Experimentally, it proved preferable to effect azide reduction prior to elimination. Thus, Staudinger reaction[21] of **20** followed by coupling of the resulting amine to carboxylic acid **2** afforded **21**. The epoxide and primary alkyl iodide moieties withstood reaction with trimethyl phosphine as well as the acylation reaction without detectable decomposition. Elimination of the iodide with DBU, although slow, proceeded to give the desired enol in good yield. The product of the elimination reaction was found to be quite unstable and was immediately desilated to give alcohol **22**. Finally, hydration of the enol with *p*-toluenesulfonic acid in THF/H_2O afforded **1** with NMR, mass spectral, and optical rotatory data matching those reported for FR901464.[22]

The synthesis of the antitumor antibiotic FR901464 highlights the successful application of asymmetric catalytic reactions to access building blocks of varying complexity, along with the use of powerful established coupling strategies for the convergent assembly of the target structure. This strategy is readily adapted to the preparation of analogues, and the synthesis of such compounds and their evaluation along with FR901464 in biological systems are now underway.

Acknowledgment. We are grateful to Prof. Stuart L. Schreiber for stimulating discussions. This work was supported by the NIH (GM-59316) and by a postdoctoral fellowship to T.F.J. from the Cancer Research Fund of the Damon Runyon-Walter Winchell Foundation (DRG-1431). We thank Dr. H. Nakajima (Fujisawa) for providing spectra of **1**, and D. Lehsten for experimental contributions.

Supporting Information Available: Experimental section and NMR spectra of synthetic and natural FR901464 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA0055357

(10) The protiodesilylated analogue of aldehyde **7** underwent cycloaddition with similar ee's, but its reactivity was greatly diminished. The absolute stereochemistry of HDA adducts was assigned by analogy to assignments made in ref 6.

(11) Nair, V.; Sinhababu, A. *J. Org. Chem.* **1978**, *43*, 5013−5017.

(12) Takano, S.; Shimazaki, Y.; Iwabuchi, Y.; Ogasawara, K. *Tetrahedron Lett.* **1990**, *31*, 3619−3622.

(13) Although 3-pentyn-1-al would have provided a cycloaddition adduct with proper placement of the alkyne functionality, this aldehyde was found to be quite unstable and was not compatible with the conditions for HDA reactions.

(14) (a) Hu, T.; Panek, J. S. *J. Org. Chem.* **1997**, *62*, 4912−4913. (b) Drouet, K. E.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 456−457. None of the undesired vinyl iodide regioisomer was obtained.

(15) Shimizu, T.; Ohzeki, T.; Hiramoto, K.; Hori, N.; Nakata, T. *Synthesis* **1999**, 1373−1385.

(16) Approximately 35% of the corresponding elimination product was also obtained. Standard displacement conditions such as NaN_3 in DMF or DMSO gave much lower yields of the desired product.

(17) Diene **9** is available from trimethylsilyl propynal in three steps with an overall yield of 50%. See Supporting Information.

(18) With the chloride catalyst **11a**, the HDA adduct **8** was obtained in >99% ee. However, product yields did not exceed 30−40%.

(19) On preparative scale (5−10 mmol), the best results were obtained by subjecting the HDA reaction mixture to quick filtration through a pad of silica gel to remove sieves and catalyst. The crude HDA adduct was then subjected to Rubottom oxidation and equilibration with K_2CO_3. Using this procedure, a 30% yield for the three-step sequence could be obtained reproducibly.

(20) Epoxides are generally considered to be incompatible with Schwartz's reagent: Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853−12909.

(21) Knapp, S.; Jaramillo, C.; Freeman, B. *J. Org. Chem.* **1994**, *59*, 4800−4804.

(22) We are currently undertaking the synthesis of diastereomers of **1** derived from *ent*-**2** and *ent*-**3**. While this is required for the unambiguous confirmation of the relative stereochemistry of FR901464, the fact that all physical data of **1** match those of the natural product provides compelling support for the original, tentative stereochemical assignment (ref 4b).