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A synthesis of FR901464

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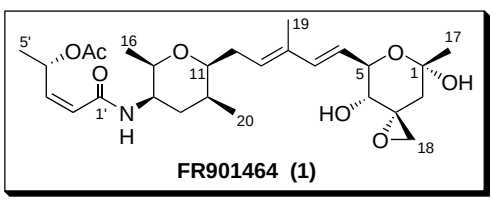
Abstract—FR901464, a potent cell cycle inhibitor, was synthesized in a convergent manner using natural chiral pool, L-threonine, ethyl (*S*)-lactate and 2-deoxy-D-glucose as starting materials.

FR901464 (**1**), which has two highly functionalized tetrahydropyran rings linked by a diene chain (Fig. 1), was isolated from the culture broth of the bacterium *Pseudomonas* sp. No. 2663.[1] This compound shows transcriptional regulating activity and induces characteristic G1 and G2/M phase arrest in the cell cycle. Related to these activities, it also exhibits a potent antitumor effect. The absolute configuration of **1**, which was initially ambiguous, was elucidated by spectroscopic and chemical analysis.[2] Its unique structure as well as the significant biological activities prompted us to undertake the synthesis of this compound. Herein, we describe a stereoselective synthesis of **1**.

Our synthetic strategy is illustrated in Scheme 1. From a synthetic perspective, we sought an efficient and convergent approach to our target, and decided upon disconnections at the diene and amide bonds generating segments **A**, **B** and **C**. Recently, Jacobsen et al. reported a total synthesis of **1** in which every chiral building block was prepared using asymmetric catalysts.[3] In contrast, we decided to synthesize all of the segments taking full advantage of materials from the chiral pool.[4] Segments **A** and **C** would be prepared from commercially available ethyl (*S*)-lactate and 2-deoxy-D-glucose, respectively. Segment **B**, in which all the substituents on the tetrahydropyran ring are *cis*-oriented, would be synthesized by stepwise carbon chain elongation via **D** and **E** starting from Garner's aldehyde[5] derived from L-threonine.



FR901464 (1)

Figure 1.

The synthesis of segment **B** is shown in Scheme 2. Garner's aldehyde[5] was subjected to a Wittig reaction followed by hydrogenation to give an inseparable 2:1 mixture of diastereoisomers. In this hydrogenation step, high stereoselectivity as described in the literature[6] was not observed. This mixture was converted under standard conditions into lactone **3**, which was then treated with Lawesson's reagent[7] affording thiolactone **4**. Although the methyl group at C-2 epimerized completely to the undesired α-orientation during this reaction, its stereochemistry was not important hereafter. The carbon chain was elongated by another Wittig reaction, and deconjugation was performed with DBU to furnish **5**. The double bond of **5** was stereoselectively hydrogenated with platinum oxide to give the desired all *cis*-isomer **6** exclusively. The ester moiety of **6** was reduced to an aldehyde with DIBAL and a three-carbon chain was added by the Wittig reaction. The resultant ethyl ester **7** was then reduced to an alcohol and converted into the desired sulfone **8** in four steps.

The synthesis of segment **A** is displayed in Scheme 3. Known aldehyde **9**,[8] derived from ethyl (*S*)-lactate, was subjected to the (*Z*)-selective Horner–Emmons reaction[9] followed by hydrolysis with LiOH to furnish α,β-unsaturated carboxylic acid **10** quantitatively.

Keywords: FR901464; cell cycle inhibitor; asymmetric synthesis; coupling reactions.

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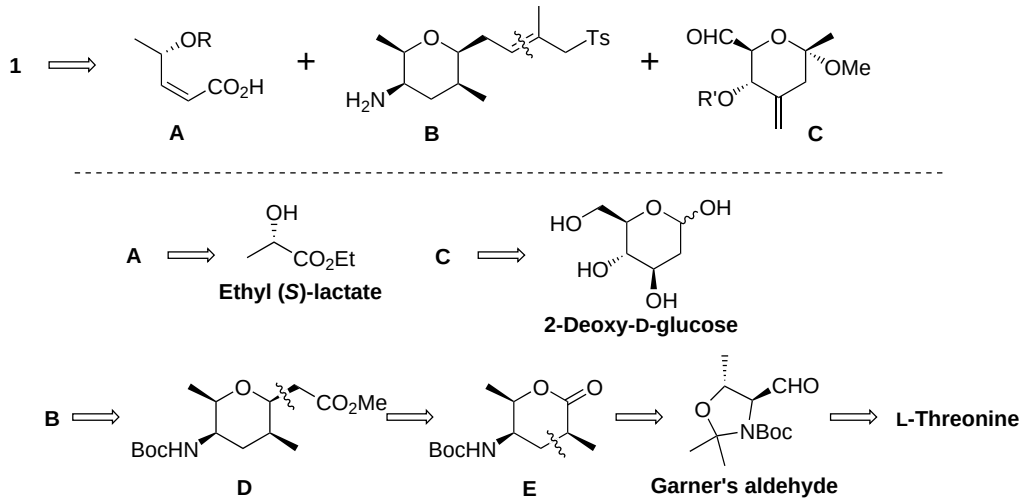
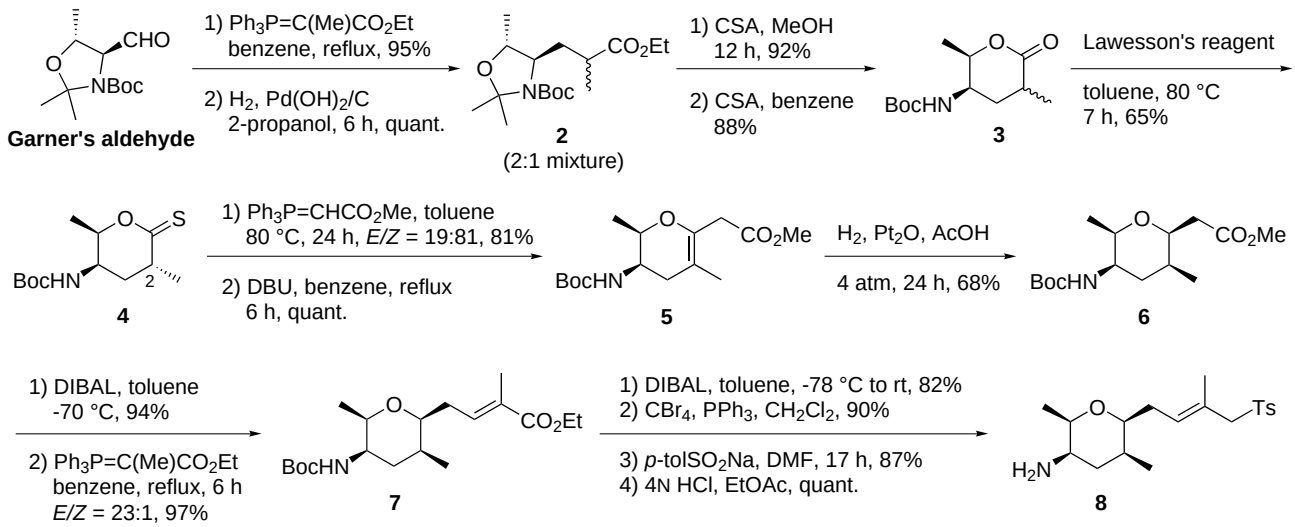
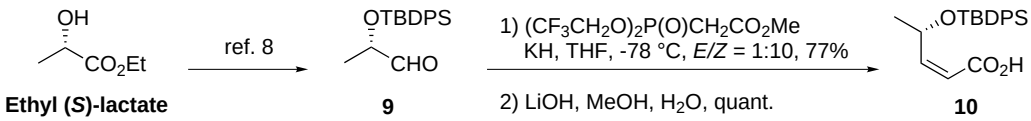


Scheme 1.



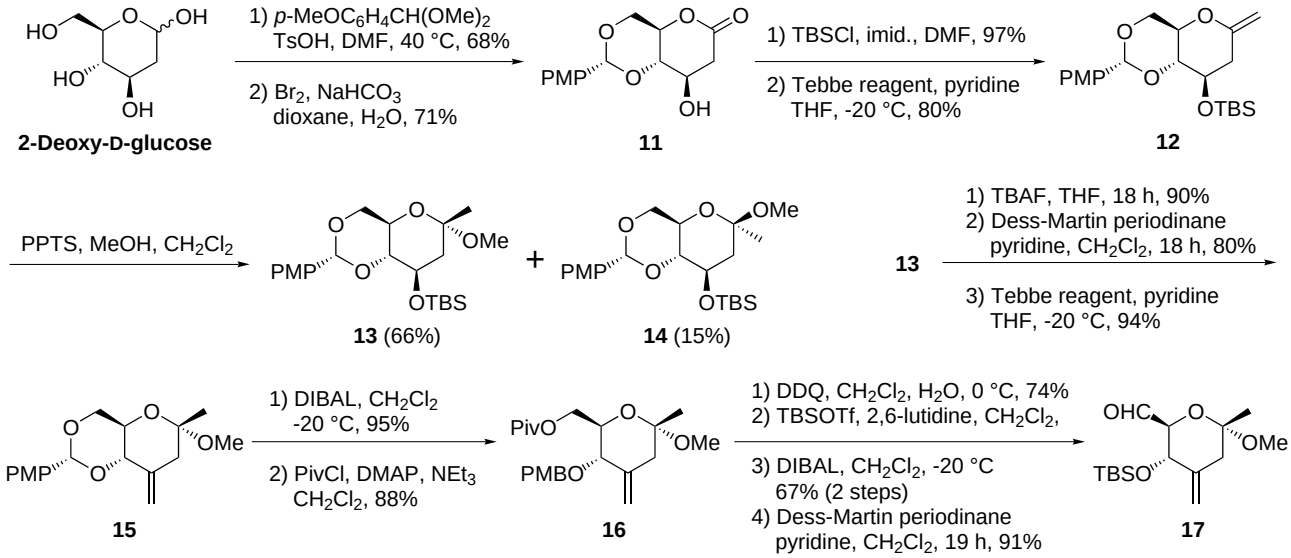
Scheme 2.



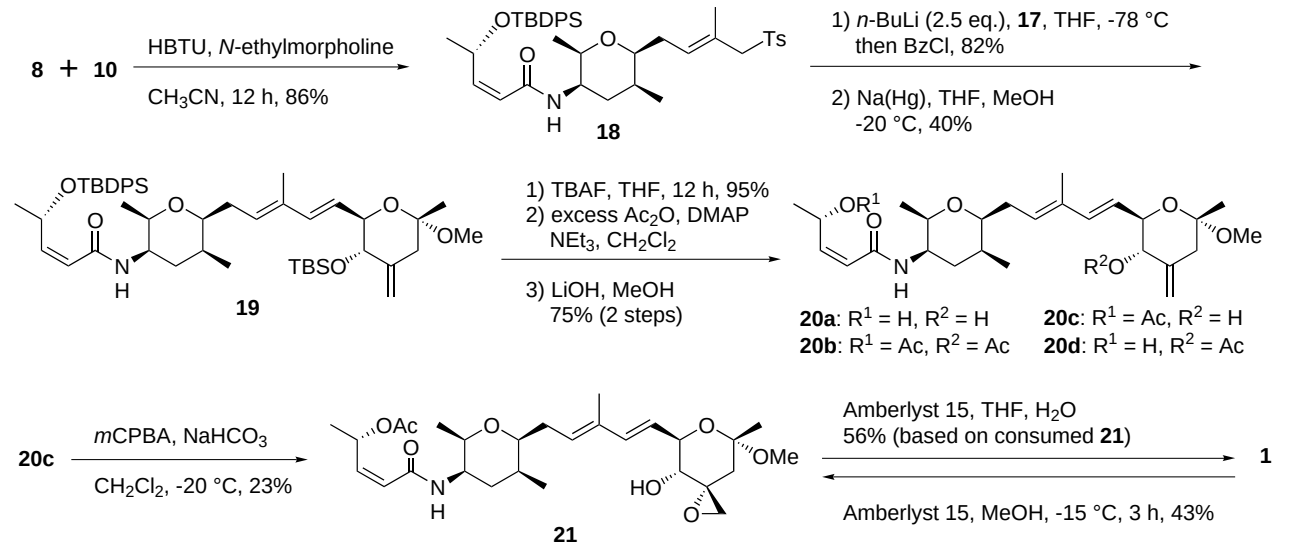
Scheme 3.

To synthesize segment **C**, the two hydroxyl groups of 2-deoxy-D-glucose were first protected as a *p*-methoxybenzylidene acetal and the anomeric hydroxyl group was selectively oxidized with bromine to lactone **11** (Scheme 4). Protection of the remaining hydroxyl group followed by olefination with the Tebbe reagent[10] provided vinyl ether derivative **12**. Treatment of **12** with PPTS and MeOH afforded a separable mixture of **13** and **14**. Removal of the TBS group of **13** and Dess–Martin oxidation[11] of the liberated hydroxyl group, followed by Tebbe methylenation[10] gave *exo*-olefin **15**. DIBAL reduction generated a primary alcohol, which in turn was protected as its pivalate ester. At this stage, the PMB group was replaced with a TBS group because it had proved difficult to remove the PMB group at a later stage of the synthesis in earlier work. Removal of the pivaloyl group and Dess–Martin oxidation[11] furnished aldehyde **17**.

In the final assembly phase, amine **8** and carboxylic acid **10** were first condensed using HBTU to provide **18** (Scheme 5). Sulfone **18** and previously prepared aldehyde **17** were successfully coupled by Julia olefination[12] to afford diene **19**. The TBS group and TBDPS group of **19** were removed with TBAF, and the resultant diol **20a** was acetylated to give **20b**. Diacetate **20b** was then hydrolyzed to furnish the desired **20c** (37%), and the undesired compounds (**20a**, **20b** and **20d**, 60% for three



Scheme 4.



Scheme 5.

compounds). Compounds **20a** and **20d** were acetylated to provide diacetate **20b** again. This acetylation–hydrolysis process was repeated twice to give the desired **20c** in 75% total yield. Epoxidation of **20c** with *m*CPBA (1 equiv.) furnished **21** in 23% yield.[13] ^{1}H NMR spectroscopic data of our synthetic **21** showed complete accordance with those of material derived from natural **1** by acid treatment in MeOH.[14–16] The final deacetalization was examined by using the sample prepared from natural **1**. After many investigations, we found out that Amberlyst 15 in wet THF gave the target molecule **1**[17] as a single isomer in a moderate yield despite the acid-sensitivity of the product.

In conclusion, we have accomplished the relay synthesis of FR901464 using natural chiral pool. Further investigations are under way to refine each step of the synthesis. Results will be reported in a full account in due course.

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13. This reaction condition has not been optimized yet.
14. Yoshimura, S.; Nakajima, H., unpublished results.
15. ^{1}H NMR data of synthetic **21** (300 MHz, $CDCl_3$): δ (ppm) 1.02 (3H, d, $J=7.2$ Hz, H-20), 1.15 (3H, d, $J=6.3$ Hz, H-16), 1.26 (3H, d, $J=1.8$ Hz, H-5′), 1.38 (3H, s, H-17), 1.74 (1H, d, $J=14.7$ Hz, H-2_{ax}), 1.78 (1H, m, H-12), 1.79 (3H, s, H-19), 1.92–1.98 (2H, m, H-13), 2.04 (3H, s, -$COCH_3$), 2.18–2.45 (2H, m, H-10), 2.31 (1H, d, $J=14.7$ Hz, H-2_{eq}), 2.50 (1H, d, $J=4.8$ Hz, H-18_a), 2.99 (1H, d, $J=4.8$ Hz, H-18_b), 3.28 (3H, s, -OMe), 3.52 (1H, m, H-4), 3.66 (1H, m, H-15), 3.95 (1H, m, H-14), 4.05 (1H, m, H-5), 5.51 (1H, t, $J=6.8$ Hz, H-9), 5.65–5.75 (2H, m, H-6, 2′), 5.89 (1H, dd, $J=7.8$, 11.4 Hz, H-3′), 6.00 (1H, d, $J=9.3$ Hz, -NH), 6.26 (1H, m, H-4′), 6.40 (1H, d, $J=15.6$ Hz, H-7).
16. Specific rotation of **21** prepared from natural **1**: $[\alpha]_D^{26}=+13.6$ ($c=0.26$, $CHCl_3$).
17. This deacetalized compound was identical with the natural product in spectroscopic and chemical properties.