Natural Products Synthesis

Highly Efficient Total Synthesis of (+)-Citreoviral

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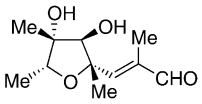
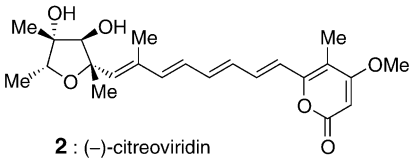
(−)-Citreoviridin (**2**) was isolated by Hirata and co-workers from *Penicillium citreoviride*[1] as a potent inhibitor of the



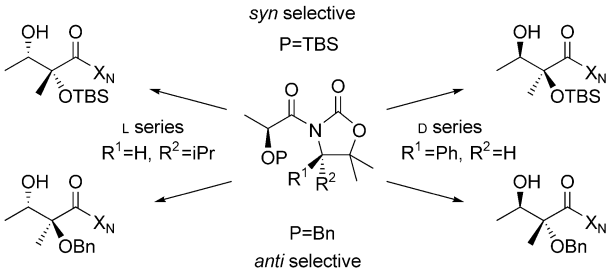
1 : (+)-citreoviral



2 : (−)-citreoviridin

mitochondrial ATPase and oxidative phosphorylation[2] and was recently reported to exhibit anti-HIV activity.[3] Structurally related (+)-citreoviral (**1**) was also isolated from the same microorganism.[4] These compounds have a highly substituted and oxygenated tetrahydrofuran moiety as a common subunit. Owing to the structural complexity as well as significant biological activities, these compounds have attracted a great deal of attention from a synthetic point of view. Indeed, total syntheses of citreoviral and citreoviridin have already been reported by several groups.[5]

We recently reported a general methodology for the stereoselective construction of 1,2-diols including a stereogenic quaternary carbon center by a titanium-mediated aldol reaction of lactate-bearing chiral oxazolidin-2-one.[6] Control of all the stereogenic centers is possible by the correct choice of chiral oxazolidin-2-one and the protecting group for the hydroxy function of the lactate unit (benzyl or TBS) (Scheme 1). In the tetrahydrofuran moiety of citreoviral and



Scheme 1. Stereoselective construction of 1,2-diols that include a stereogenic quaternary carbon center.

citreoviridin, we can recognize several 1,2-diol units and we expected that our methodology could be effectively utilized for the synthesis of citreoviral and related compounds. Since the transformation of citreoviral into citreoviridin has already been established, we focused on the synthesis of citreoviral.

The tetrahydrofuran moiety of citreoviral includes two sets of adjacent secondary and tertiary alcohol groups. Our retrosynthetic analysis for the synthesis of **1** is shown in Scheme 2. Although the structure of **1** presents many opportunities for the use of our 1,2-diol-forming reaction, we decided to employ the strategy starting from an *anti* aldol product, as the stereoselectivity of *anti* aldol reactions is generally higher (> 50:1) than that of *syn* aldol reactions (≈ 10:1). Our first analysis of the oxygenated furan **3**, the core structure of **1**, is shown as route A in which **4** would be synthesized by coupling of **5** and **6**. Although our *anti* aldol reaction should be effective in this route, there are two problems: 1) stereoselective construction of aldehyde **5** and 2) possible intramolecular S_N2 reaction of the tertiary alcohol group at the carbon center bearing the halide function. To avoid the long sequence required for the synthesis of **5** and the potentially problematic (albeit unprecedented) S_N2 reaction, we chose route B via the bicyclic intermediate **7** (Scheme 2). This route also involves an intramolecular S_N2 reaction with the tertiary alcohol function, but the iodide **8** has the preferred conformation **8′**[7] in which the tertiary alcohol group interacts strongly with the C–I* bond; thus the desired S_N2 reaction should proceed smoothly. The iodide **8** can be obtained by stereospecific iodolactonization of **9**. There have been a number of precedents for the iodolactonization of γ,δ-unsaturated β-hydroxycarboxylic acids,[8] and theoretical calculations of the transition states were investigated in

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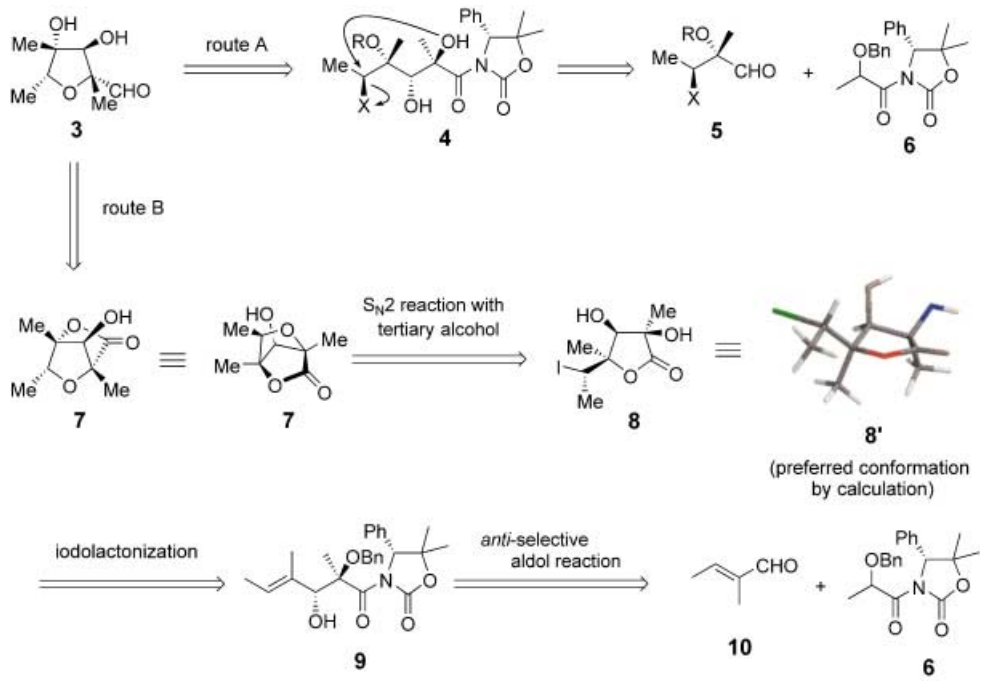


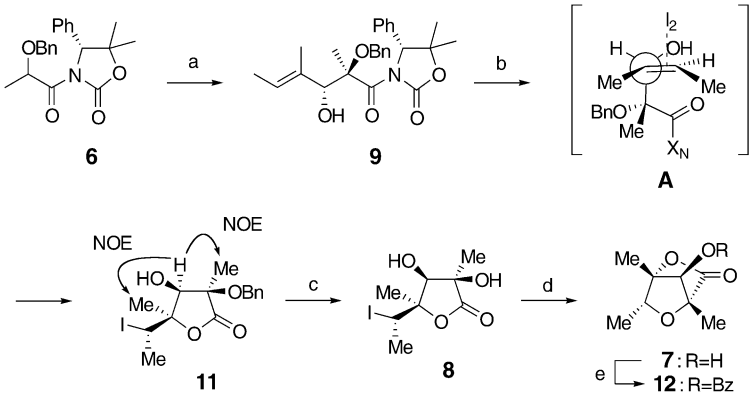
Scheme 2. Retrosynthetic analysis.

detail by Houk et al.[9] Imide **9** would be obtained by our *anti*-selective aldol reaction between tiglic aldehyde (**10**) and lactate derivative **6**.

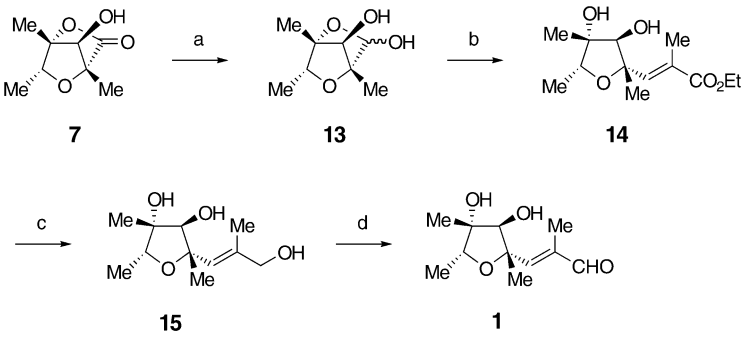
The actual synthesis of the (+)-citreoviral core **3** is shown in Scheme 3. According to the established protocol, **6** was treated with LDA followed by Ti(O*i*Pr)$_3$Cl; the reaction of the resulting titanium enolate with **10** afforded the *anti* aldol **9** in 71% yield. The stereoselectivity of this reaction is excellent (*anti*/*syn* > 99:1), and we could not detect the formation of any other isomers. Iodolactonization of the resulting aldol adduct **9** was next attempted. Unsaturated imide **9**, which includes a chiral auxiliary, was treated directly with I_2 and $NaHCO_3$ in CH_3CN/H_2O (4:1) at room temperature. As expected, iodolactonization proceeded smoothly to afford iodolactone **11** in 92% yield as a single isomer. The employment of an imide[10] as the substrate for iodolactonization accompanied by removal of the chiral auxiliary as well as the high selectivity were quite important from a practical point of view. The stereochemistry of γ-lactone **11** was confirmed by NOE studies, as shown in Scheme 3. The stereochemical course of the present iodolactonization could be explained by considering the "inside alkoxy effect",[9] as depicted in the transition state **A**.

The benzyl group in γ-lactone **11** was cleanly removed by exposure to BCl_3 in CH_2Cl_2 to obtain the free tertiary alcohol **8** in 79% yield (Scheme 3). Next, we attempted the critical intramolecular S$_N$2 reaction of tertiary alcohol **8**. After a number of attempts with various bases and additives, we finally obtained the desired bicyclic lactone **7** in 92% yield by treatment of **8** with $AgNO_3$ in DMF. The structure of **7** was confirmed unambiguously by conversion into the known benzoate **12**.[5c] The spectral data of **12** were in good agreement with reported data. Thus, the tetrahydrofuran moiety of **1** was constructed in four steps in a completely stereoselective manner from chiral imide **6**.

The bicyclic lactone **7** was transformed into **1** by employing a sequence of reactions similar to those reported by Overman and co-workers[5c] (Scheme 4). Reduction of **7** with DIBAL at −78 °C in CH_2Cl_2 generated the lactol **13** in 94% yield. Wittig reaction of **13** with (carboethoxyethylidene)triphenylphosphorane in refluxing benzene yielded a mixture of α,β-unsaturated esters (*E*/*Z* = 6:1), from which the desired isomer (*E*)-**14** was isolated in 82% yield by chromatographic separation. The α,β-unsaturated δ,ε-dihydroxyester **14** was treated directly with DIBAL to afford triol **15** in 82% yield. Finally, selective oxidation of allylic alcohol **15** with $BaMnO_4$ completed the total synthesis of (+)-citreoviral (**1**). The data for synthetic **1** were identical in all respects with reported



Scheme 3. Reagents and conditions: a) LDA, Ti(O*i*Pr)$_3$Cl; then **10**, THF, −78 → −40 °C, 71%; b) I_2, $NaHCO_3$, MeCN/H_2O (4:1), room temperature, 92%; c) BCl_3, CH_2Cl_2, −78 → 0 °C, 79%; d) $AgNO_3$, DMF, room temperature, 92%; e) BzCl, NEt_3, DMAP, CH_2Cl_2, room temperature, 79%. LDA = lithium diisopropylamide, DMF = *N*,*N*-dimethylformamide, DMAP = 4-dimethylaminopyridine.



Scheme 4. Reagents and conditions: a) DIBAL, CH_2Cl_2, −78 °C, 94 %; b) (carboethoxyethylidene)triphenylphosphorane, benzene, reflux, 82 %; c) DIBAL, CH_2Cl_2, 0 °C, 82 %; d) $BaMnO_4$, benzene, reflux, 58 %. DIBAL = diisobutylaluminum hydride.

data. The eight-step sequence from **6** gave enantiomerically pure **1** in 18 % overall yield.

In conclusion, we have completed a highly efficient total synthesis of (+)-citreoviral through a route involving an *anti*-selective aldol reaction, the iodolactonization of an unsaturated imide, and the intramolecular S_N2 reaction of a tertiary alcohol. This short and highly stereoselective route can be applied to a variety of highly oxygenated bioactive compounds.

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