# Asymmetric Syntheses and Absolute Stereochemistry of 5,6-Dihydro-α-pyrones, A New Class of Potent HIV Protease Inhibitors

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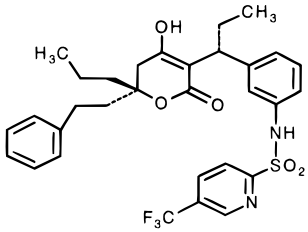
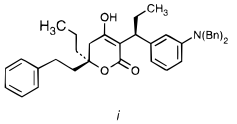
Inhibition of the HIV protease enzyme, which plays a key role in viral maturation, represents a promising therapeutic strategy for treatment of the escalating problem of HIV infection.[1−4] At Pharmacia & Upjohn we have developed two classes of low molecular weight HIV protease inhibitors, α-pyrones (PNU-96988[5] and PNU-103017[6]) and 5,6-dihydro-α-pyrones (PNU-140690). The latter class of compounds represents the first nonpeptide HIV protease inhibitors which possess the antiviral potency of their peptide counterparts and importantly have therapeutically useful pharmaceutical properties.[7] Moreover, HIV-1 isolates highly resistant to ritonavir and broadly cross-resistant to a number of other protease inhibitors, including saquinavir and indinavir, remain sensitive to PNU-140690.[7] In this communication we describe the first asymmetric synthesis of the unique non-peptidic HIV protease inhibitor PNU-140690.



**1 (PNU-140690 (3αR,6R))**

The synthetic challenge presented by **1** (PNU-140690) was clearly to devise a means of firmly controlling the two remote asymmetric centers present in the molecule. In an earlier synthesis of α-pyrones, we successfully used the addition of an organocuprate to a chiral unsaturated acylimide to establish the C3α center.[8] That strategy resulted in high chemical and enantiomeric yields and thus provided a logical starting point for the current campaign. The successful extension of that strategy would ultimately depend on conversion of the readily available Michael adduct to a 3,6-disubstituted 4,5-dihydro-α-pyrone in a stereocontrolled manner to yield the necessary chirality at C6 in the final product.

Addition of the lithium salt of (*R*)-4-phenyl-2,5-oxazolidinone (**2**) to pentenoyl chloride afforded the unsaturated imide **3** in 95% yield as a crystalline solid (Scheme 1). Addition of the aryl cuprate derived from [3-[bis(trimethylsilyl)amino]phenyl]-magnesium bromide (**4**)[9] to **3** afforded the Michael adduct as a single diastereomer.[10] The trimethylsilyl protecting groups could be removed under mildly acidic conditions to yield an aniline intermediate, which was subsequently bisbenzylated to afford crystalline **5** in 78% overall yield. Introduction of an acetyl group to **5** required a two step protocol[11] involving first generation of the titanium enolate, followed by the addition of 2-methyl-2-methoxy-1,3-dioxolane (**6**). Subsequent acid hydrolysis of the resulting ketal provided methyl ketone **7** as a single diastereomer in 95% yield over the two steps. We first investigated the aldol chemistry of **7** using $Ti(O^iPr)Cl_3$ as the Lewis acid and Hunig's base to generate the enolate species.[14] Treatment of the resultant enolate with 4-heptanone (**8**) cleanly afforded aldol adduct **10** in 91% isolated yield. Treatment of that same enolate with the 1-phenylhexan-3-one (**9**) afforded a 3/2 mixture of diastereomeric aldol adducts **11** and **12** in 73% yield.[12] Aldol adduct **10** and the major diastereomer **11** from the reaction with unsymmetrical ketone **9** were independently lactonized to yield dihydro-α-pyrones **13** and **14**, respectively. Debenzylation and subsequent sulfonylation of **13** and **14**



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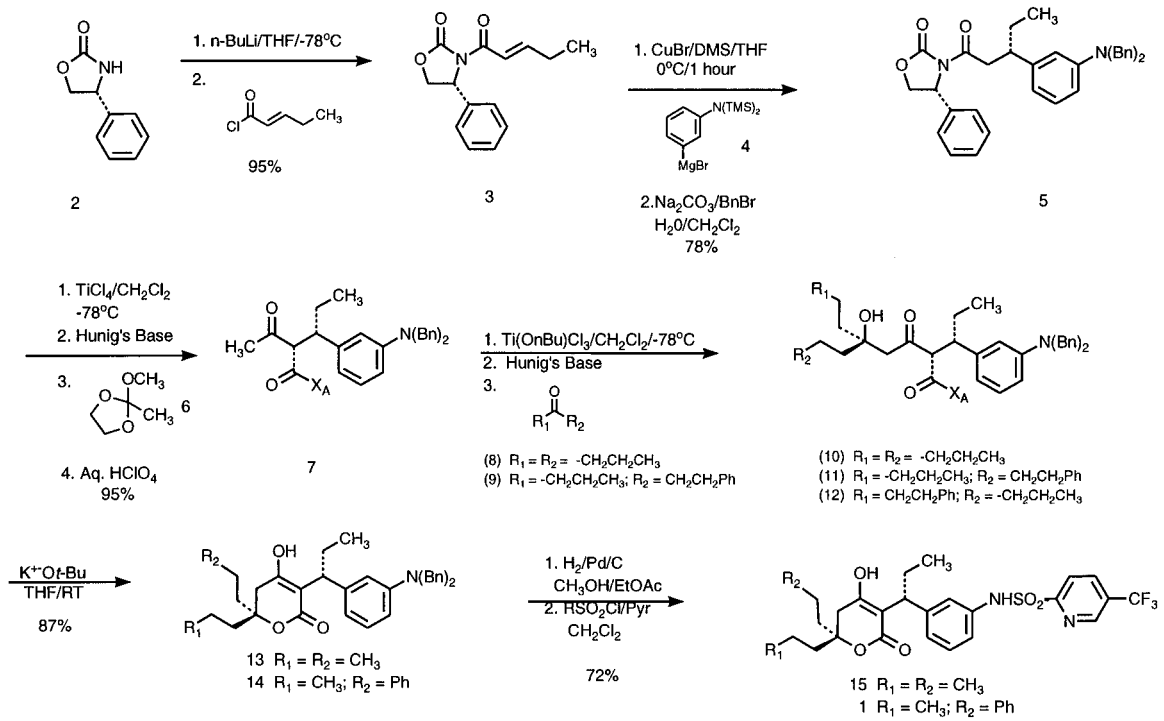
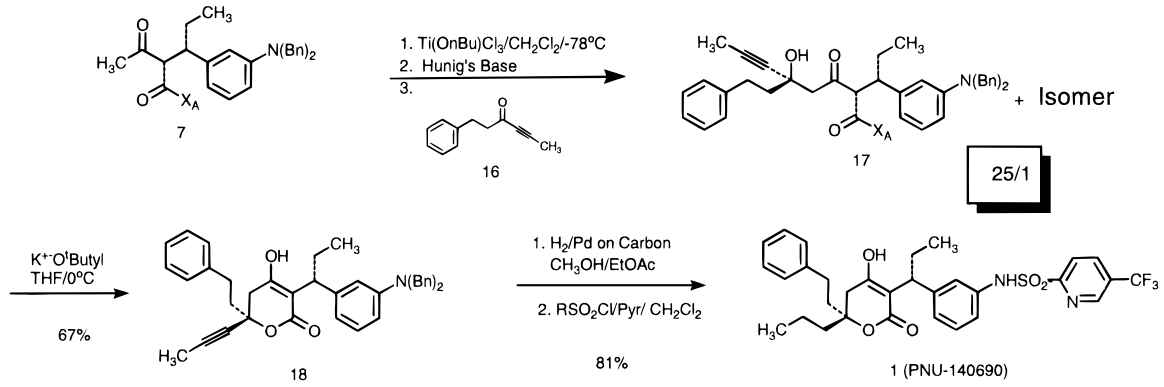
(12) The assignment of the absolute stereochemistry in **11** and **12** was established using an X-ray crystal structure of lactone intermediate in the diastereomeric C3*S* series.

S0002-7863(96)03434-8 CCC: $14.00 

**Scheme 1**




**Scheme 2**




afforded the (3α*R*)-dihydro-α-pyrone **15** and the desired 3α*R*,6*R* stereoisomer of dihydro-α-pyrone **1**, respectively.

The modest selectivity observed with unsymmetrical ketone **9** prompted examination of the reaction of the acetylenic ketone **16**[13] with the enolate derived from **7** (Scheme 2). The acetylenic aldol adduct **17** was isolated in 55% yield from an 8/1 mixture of diastereomers when Ti(O$^i$Pr)Cl$_3$ was used as the Lewis acid. Using Ti(O$^n$Bu)Cl$_3$ as the Lewis acid, **17** was isolated in 62% yield from a 25/1 mixture of diastereomers. Aldol adduct **17** was treated with potassium *tert*-butoxide in THF to smoothly effect lactonization to yield **18** (67%). Subsequent hydrogenation and sulfonylation of **18** then afforded the clinical candidate **1** (PNU-140690) in excellent yield.

In summary, we have developed a short efficient asymmetric synthesis and established the absolute stereochemistry of the potent nonpeptidic HIV protease inhibitor **1** (PNU-140690). (*R*)-4-Phenyl-2,5-oxazolidinone played a critical role in establishing the C3α stereocenter via organocuprate chemistry and the C6 stereocenter via a unique "titanium mediated" aldol condensation using an unsymmetrical acetylenic ketone.

**Supporting Information Available:** Experimental details and characterization data for **1**, **3**, **5**, **7**, **17**, and **18** (9 pages). See any current mastheadpage for ordering and Internet access instruction.

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