Tetrahedron 74 (2018) 2211–2217

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Merging lithium carbenoid homologation and enzymatic reduction: A combinative approach to the HIV-protease inhibitor Nelfinavir

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ARTICLE INFO

Article history:
Received 29 January 2018
Received in revised form
12 March 2018
Accepted 14 March 2018
Available online 15 March 2018

Keywords:
Homologation
Lithium carbenoids
Enzymatic reductions
Drug Synthesis
a-haloketones
Halohydrins
Selectivity

ABSTRACT

An effective stereocontrolled synthesis of the HIV protease inhibitor Nelfinavir is reported. Two transformations were identified crucial for achieving success: the formation of a densely functionalized α-chloroketone *via* the homologation of a Weinreb amide with chloromethyllithium ($LiCH_2Cl$), followed by its *erythro* selective reduction into the corresponding chiral chlorohydrin. A commercially available enzyme P2-C02 was particularly well suited for this purpose, affording the key alcohol (in an excellent 99% *de*), which was then smoothly converted into the active biologically active agent.

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1. Introduction

The pharmaceutical treatment of HIV diseases ranks at the frontier of modern medicine as a consequence of the important and dramatic repercussions it causes within the society (*e.g.* 40 M infected individuals worldwide).[1] As such, the development of active and resistant-free drugs continues to represent an actively pursued research area for medicinal chemistry.[2] The highly structural differentiation among currently employed drugs constitutes a significant task in synthetic methodology for ensuring rapid and straightforward routes to agents active *via* progressively new identified biological targets, as exemplified by 3′-azido-3′-deoxythymidine (AZT, the first approved nucleoside analogue) and HIV protease inhibitors (Fig. 1).[3] Undoubtedly, the introduction of these agents in the mid 1990s[4] benefited considerably the treatment of the pathology *via* the inhibition of the virus replication guaranteed by the not cleavable peptide bioisosteric hydroxyethylene unit.[5] A prominent example of the class is Nelfinavir, whose mesylate salt (Viracept®) conjugates an effective anti-HIV activity with a convenient pharmacokinetic behaviour (oral administration), thus improving patient compliance.[6]

The rational drug design individuates - *inter alia* - the presence of a chiral substituted 1,3-diamino-butan-2-ol (**I**, Scheme 1) featuring an *anti* (*erythro*) configuration for observing optimal therapeutic activity.[5,7] Accordingly, the retrosynthetic analysis depicted in Scheme 1 highlights the fundamental role displayed by the epoxide-synthon **II** (derived from the halohydrin **III**) whose efficient obtainment in terms of both chemical yield and optical purity represents the most intriguing and relevant event within the whole production process.[5,8] The classical approach towards it is paved on a three-steps sequence – involving a suitable α-amino-alkyl-α′-halomethylketone **IV** as the key synthon[7,9] - constituted by: *i*) carboxylic acid derivative homologation, followed by *ii*) stereocontrolled reduction to a chiral halohydrin **III**, direct precursor – under retentive conditions - of the targeted epoxide **II**.[5] Some points merit mention: a) Focusing on the homologation event it is quite interesting how the usual method employed for synthesizing the ketone **IV** still relies on the Arndt-Eistert procedure,[10] involving the use of highly toxic and hazardous

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https://doi.org/10.1016/j.tet.2018.03.034
0040-4020/Published by Elsevier Ltd.

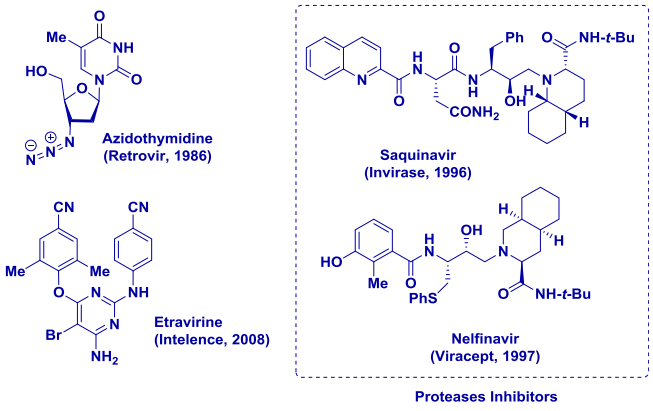


Fig. 1. Commonly used anti-HIV agents.

diazomethane.[11] Since the first preparation by Kaldor in 1997, this formally *direct* homologation requires three different synthetic operations: 1) activation of the carboxylic acid **V** to a more reactive anhydride **VI**; 2) formal CH_2N_2 homologation reaction and, 3) acydolysis[12] to convert the intermediate diazoketone **VII** to the requested α-haloketone **IV**. Notably, a significant excess of CH_2N_2 is required to obtain good yields of diazoketone - [(73% with 4 equiv),[6b] (62% with 2 equiv)[13]] - while the adoption of microfluidic techniques enables to get directly ketone **IV** in 73% yield as elegantly introduced by Kappe.[14] b) Controlling the diastereoselectivity in the reduction to the halohydrin **III** is troublesome and, in the case of Nelfinavir, no available completely stereoselective methods are known.[5,13]

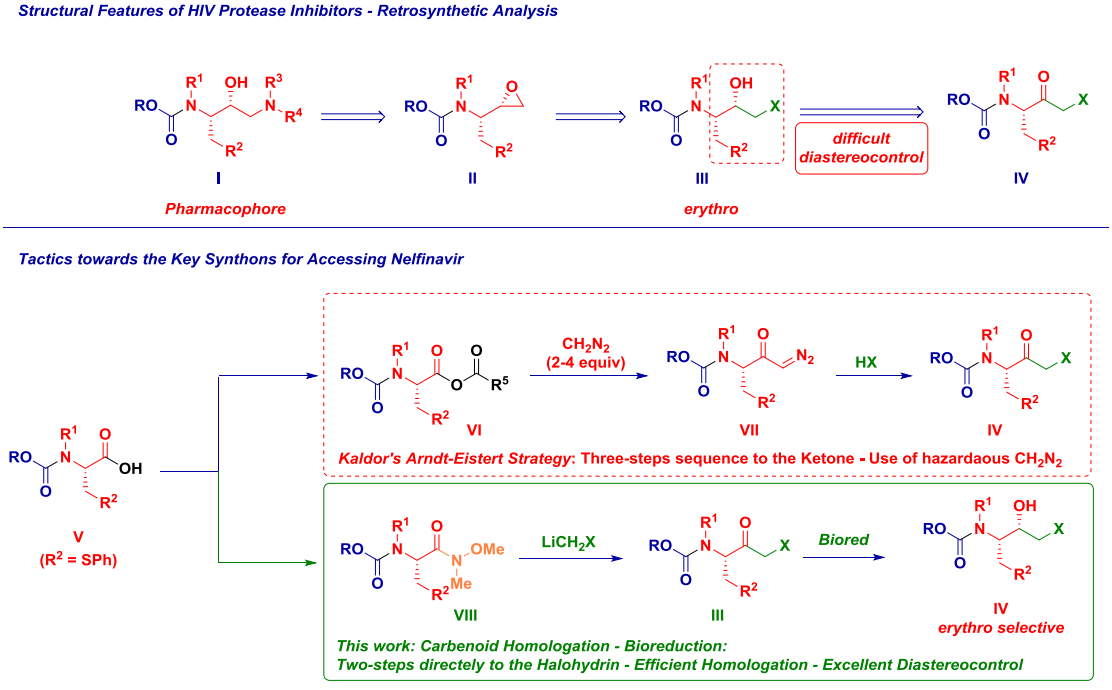
With the aim to design a diazomethane-free homologation strategy and direct carbenoid mediated tactic towards Nelfinavir, herein we detail an effective route in which the key haloketone is in turn reduced to the chiral halohydrine with excellent stereocontrol *via* a straightforward enzymatic reduction finally conducting to this important drug.

In recent years our group reported highly effective and reliable tactics for enabling the formal insertion of a CH_2X fragment into an acyl type electrophile by using lithium carbenoid reagents[15] (*i.e.* $LiCH_2X$, X = Cl, Br, I, F, OR, CN).[16] Such a direct operation presents the intrinsic advantage of installing the nucleophilic unit with the exact degree of functionalization, therefore affording the targeted structure through a single experimental operation. Among the portfolio of electrophiles studied, we introduced Weinreb amides[17] as privileged acylating manifolds for such reagents[18]: the formation of a stable (isolable)[19] tetrahedral intermediate guarantees excellent levels of chemoselectivity and, as a consequence, no undesired over addition processes could be observed.

2. Results and discussion

The commercially available *N*-Carbobenzoxy-*S*-phenyl-L-cysteine **1** activated with carbonyldiimidazole (CDI) provided the corresponding Weinreb amide **2** upon reaction with *N*,*O*-dimethylhydroxylamine hydrochloride (DMHA).[18a,20] Interestingly, the reaction highly benefited from using cyclopentyl methyl ether (CPME)[16f,21]: it proved by far to be the optimal choice compared to other organic solvents (classical dichloromethane or the green solvent 2-MeTHF,[22] 78% and 53% respectively) affording the requested synthon – just after recrystallization - in an excellent 92% yield. With the Weinreb amide **2** in hands, we next focused our attention on the halomethylation procedure. With the goal of rapidly assembling the haloketone **3**, pleasingly we found $LiCH_2Cl$ - generated from ICH_2Cl (3.0 equiv) and MeLi-LiBr (2.8 equiv) – suitable for attacking the Weinreb amide **2** (Scheme 2).

Although ^1H NMR analysis of the reaction crude showed an excellent conversion into **3** (93%), purification through silica gel chromatography provided it pure in a modest 41% isolated yield (Table 1). Analogously troublesome purification was obtained switching to aluminium oxide (neutral, basic or acidic) - Brockmann degree 1, 3 and 4 (entries 2–8).[19] Deactivation of silica gel with triethylamine (2–5%) allowed to increase the isolated yield up to 48% and 55% isolated yields (entries 9–10), respectively. Finally,



Scheme 1. General context of the presented work.