Journal of Fluorine Chemistry 132 (2011) 327–338

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

Copper mediated defluorinative allylic alkylation of difluorohomoallyl alcohol derivatives directed to an efficient synthetic method for (*Z*)-fluoroalkene dipeptide isosteres

Daisuke Watanabe [a], Minoru Koura [a], Akio Saito [a,1], Hikaru Yanai [a,*], Yuko Nakamura [b], Midori Okada [b], Azusa Sato [b], Takeo Taguchi [a,*]

[a] School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan
[b] Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

ARTICLE INFO

Article history:
Received 5 March 2011
Received in revised form 9 March 2011
Accepted 9 March 2011
Available online 13 April 2011

Keywords:
Fluoroalkene
Difluorohomoallyl alcohol
Alkylaluminium
Grignard reagent
Overman rearrangement
Dipeptide isostere

ABSTRACT

Difluoroallylation of optically pure *O*-silylated (*S*)-2-methyl-3-hydroxypropanal **10a** with bromodifluoropropene mediated by indium provided the corresponding difluorohomoallyl alcohol **11a** with low diastereoselectivity, but without a decrease in optical purity. Defluorinative allylic alkylation of each diastereomer of the difluorohomoallyl alcohol efficiently proceeded by the reaction with trialkylaluminium and Cu(I) system or Grignard reagent and a catalytic amount of CuI system in THF to give the fluorine-substituted allylic alcohol **12** in an high yield and in an excellent *Z* selective manner. Subsequent imidate Claisen rearrangement of the allylic alcohol **12** proceeded with a complete 1,3-chirality transfer to give the fluoroalkene dipeptide isostere structure **14** after the final conversion of the primary alcohol **20** into the carboxylic acid form.

1. Introduction

It has been widely accepted that a fluoroalkene moiety (–CF = CH–) would be an ideal mimic for an amide bond (–CO–NH–) due to the similarity of both steric and electronic properties. Contrary to such similarities, fluoroalkene moiety would be a nonhydrolyzable bond both chemically and enzymatically, and the lack of rotational freedom of this bond is also a different property from that of an amide bond [1]. Due to these unique properties, utilization of fluoroalkene dipeptide isosteres as nonhydrolyzable and/or conformationally restricted replacements for the parent amide bonds has attracted much attention in the field of medicinal chemistry [2,3]. Not only such an application of fluoroalkene compounds in medicinal chemistry [2–4], but also functionalized fluoroalkene compounds are important in synthetic chemistry as a building block for a variety type of organofluorine compounds [5].

For the synthesis of such fluoroalkene dipeptide isosteres, stereo-control of the C–C double bond configuration (either *Z* or *E*) and the relative stereochemistry of the two chiral centers at C2 and C5 (either *syn* or *anti*) is a major issue to be solved (see, Fig. 1). In addition to these, final product should be prepared in optically pure form. Although, so far, a number of reports dealing with the preparative methods for such compounds have been appeared [2,6–13], till now development of more convenient methods is a current subject.

We have reported a highly regio- and stereoselective route involving defluorinative allylic alkylation of 5-hydroxy-4,4-difluoro-2-alken-1-ol **1** with a trialkylaluminium-Cu(I) system to introduce an alkyl group into 2 position in an excellent 2,5-*syn* and *Z* selective manner giving rise to the fluoro-olefin compound **2**. Subsequent conversion of the hydroxy group into the amino group via S_N2 azidation step of **3** with NaN_3 via unstable mesylate followed by immediate $LiAlH_4$ reduction of the azide **4** gave the *N*-protected amino alcohol **5** (Scheme 1) [13a,b].

Although our method proceeds in a highly stereo-controlled manner, it has some disadvantages to be solved. (1) Firstly, availability of trialkylalminium is quite limited. (2) In this reaction, due to relatively low reactivity, an excess amount of trialkyaluminium (5 molar equivalent under optimized conditions) and copper salt (2.5 equivalent) as well as long reaction time are required. In particular, compared to the *E* isomer, the *Z* isomer of the starting material (***Z***) – **1** showed much lower reactivity to give the desired product ***anti*-2** in low yield. (3) Although in a laboratory

* Corresponding author. Tel.: +81 426 76 3257; fax: +81 426 76 3257.
E-mail addresses: yanai@toyaku.ac.jp (H. Yanai), taguchi@toyaku.ac.jp (T. Taguchi).
[1] Present <fn0005>address: Showa Pharmaceutical University, 3-3165 Higashi-Tamagawagakuen, Machida, Tokyo 194-8543, Japan.

0022-1139/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2011.03.007

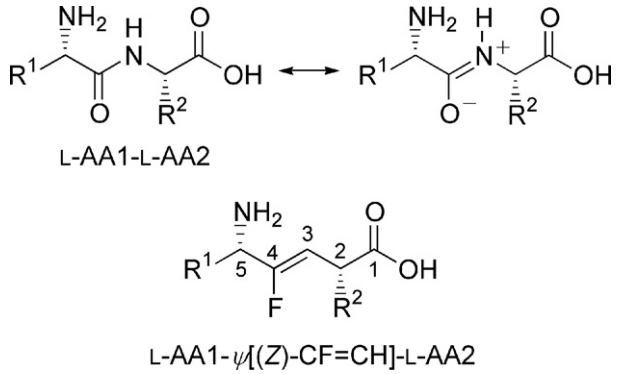


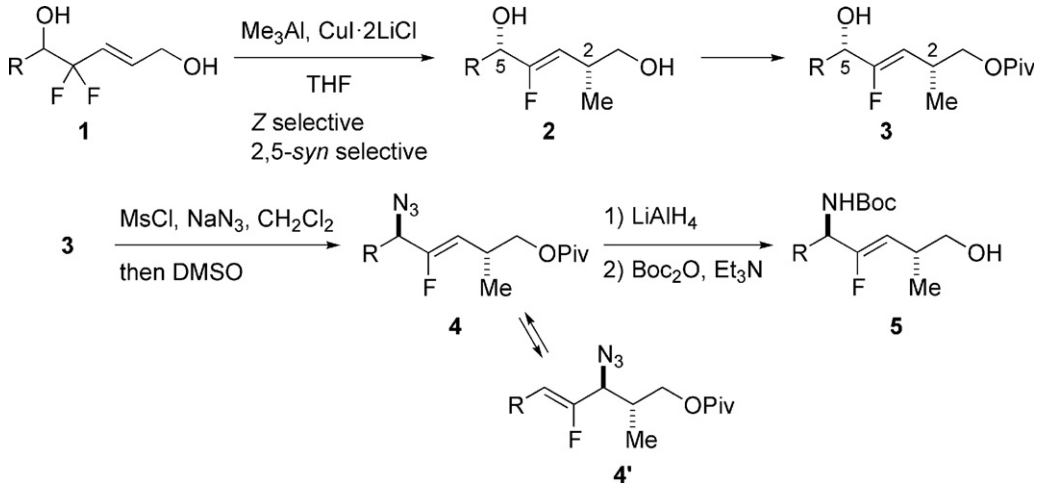
Fig. 1. Natural dipeptide and its fluoroalkene isostere.

experimental work a variety of Grignard reagents can be available or can be easily prepared, Grignard reagent did not work well with this starting material **1** having a vicinally disubstituted olefin structure, instead giving rise to a complex mixture. (4) Conversion of the allylic hydroxy group in the alkylated product **2** into the amino group via the azide intermediate **4** is somewhat problematic, since [3,3]-sigmatropic rearrangement of the allylic azide **4** easily proceeds to give a mixture of the regio isomers (**4** + **4**′) (Scheme 1) [13b,14]. (5) *Syn* selective conversion of **(*E*)** – **1** into **2** and S_N2 type azidation provides a fluoroalkene dipeptide isostere corresponding to the L-AA1-D-AA2 or D-AA1-L-AA2 dipeptide form containing unnatural D form amino acid. (6) Improvement for the preparation of the starting material **1** is also a remaining subject. That is, multiple steps are required for the preparation of **1** [13]. Furthermore, we need convenient procedures to obtain both enantiomers of **1** in optically pure form.

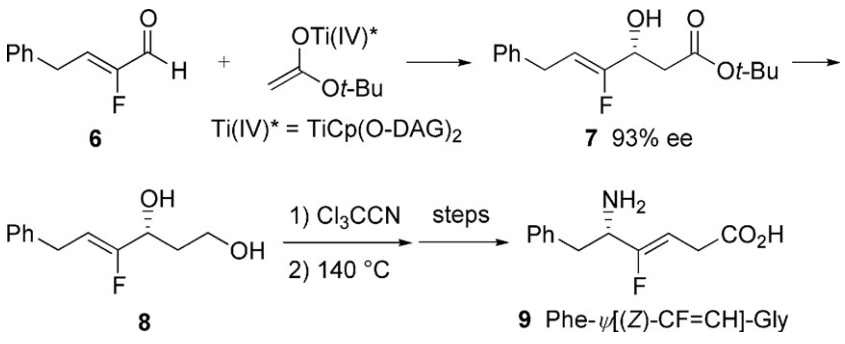
Considering above mentioned issues, an alternative starting material should be chosen mainly on the basis of its reactivity in the reaction with readily available organometallics such as Grignard reagent and its easy availability in optically pure form. Furthermore, the use of problematic allylic azide intermediate should be avoided.

In Allemendinger's pioneering synthetic work for the preparation of fluoroalkene dipeptide isosteres such as Phe–ψ[(*Z*)–CF = CH]–Gly **9**, *Z* configuration of the C–C double bond was derived by the use of a *Z* isomer of α-fluoro-α,β-unsaturated aldehyde **6** as a starting material and the stereo-control of the configuration of the amino functionality was achieved by chirality transfer through the imidate Claisen rearrangement (Overman rearrangement) of the chiral fluorinated allylic alcohol **8** obtained by enantioselective aldol reaction of the aldehyde **6** with chiral titanium enolate (Scheme 2) [6]. Later similar strategies were also reported by other groups [7]. Although the enatioselective or diastereoselective aldol reaction is not always a facile route to obtain the product such as **7** in completely optically pure form, an excellent chirality transfer and operational simplicity of the latter rearrangement attracted our interest.

In Scheme 3 is depicted our second route for the preparation of AA1–ψ[(*Z*)–CF = CH]–AA2 **14**, where the corresponding dipeptide is consisting of two amino acids AA1 and AA2. In this scheme difluoroallylation of the chiral aldehyde **10** (P = protective group) with bromodifluoropropene provided a diastereomer mixture of the alcohol **11** easily separated by column chromatography. Subsequently, copper mediated defluorinative allylic alkylation of diastereomerically pure **11** with organometallics (trialkylalu-



Scheme 1.



Scheme 2.