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Synthesis of P1 Aspartate-Based Peptide Acyloxymethyl and Fluoromethyl Ketones as Inhibitors of Interleukin-1β-Converting Enzyme

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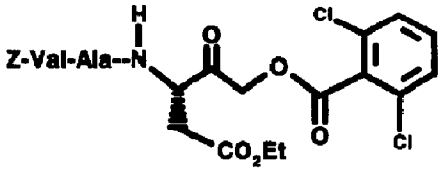
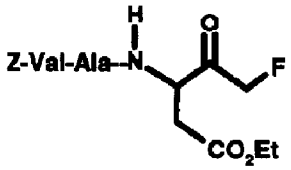
Abstract: Improved procedures have been developed for the synthesis of P1 aspartate-based 2,6-dichlorobenzoyloxymethyl ketone **1** and fluoromethyl ketone **2**, the prodrugs of two potent ICE-inhibitors. **1** was prepared from *(R)-trans*-4,5-O-isopropylidene-4,5-dihydroxy-2-pentenecarboxylic acid ethyl ester; **2** was obtained via a nitro-aldol condensation as key step from *in situ* generated fluoroacetaldehyde.

ICE (Interleukin-1β-converting enzyme) is a recently discovered atypical cysteine protease, which processes an inactive precursor to the proinflammatory cytokine IL-1β and may regulate programmed cell death in neuronal cells [1, 2]. Since specific inhibitors of ICE may be of benefit in inflammatory and degenerative neuronal diseases such as Rheumatoid Arthritis, Alzheimer's and Parkinson's diseases, we wanted to test their in vivo potential in animal models and needed large amounts of **1** and **2**, the ethyl ester prodrugs of two potent ICE-inhibitors [3,4].



1

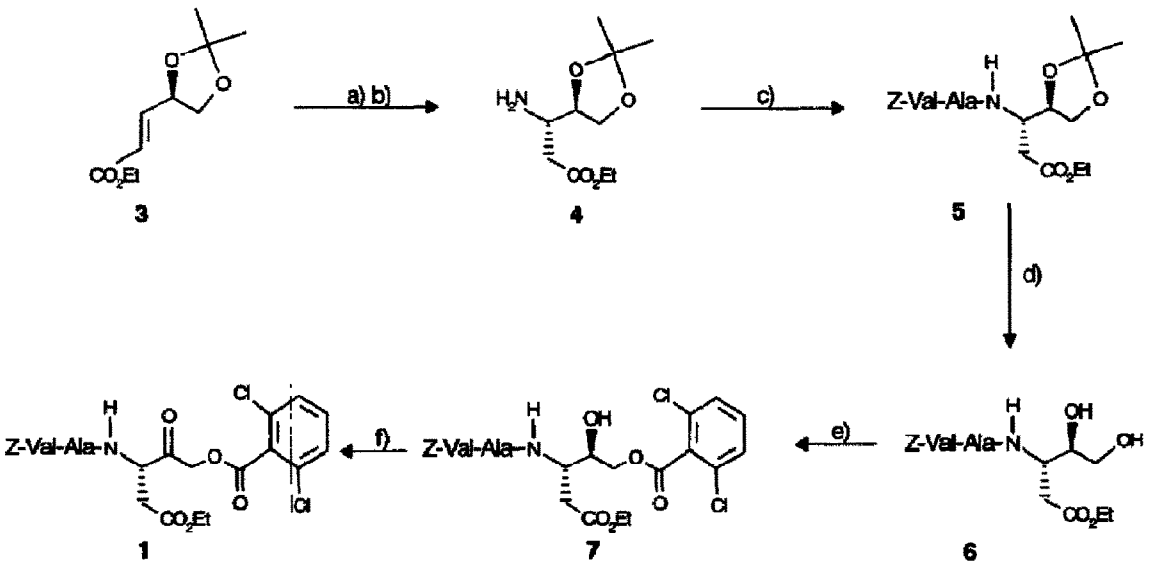


2

Current methods for preparing acyloxymethyl ketones as thiol protease inhibitors use diazomethane [5] for the homologation of a conveniently protected amino acid, where the resulting diazomethyl ketone is converted to the corresponding bromide and then reacted with an acid to provide the desired product. We have developed a method suitable for the large scale preparation of aspartate-based acyloxymethyl ketones of type

1, avoiding the use of diazomethane *(Scheme 1)*. Commercially available *(R)-trans*-4,5-O-isopropylidene-4,5-dihydroxy - 2 - pentenecarboxylic acid ethyl ester **3** was treated with benzylamine at -20° C for 40 h according to [6] and rendered the desired addition product in 75% yield, which was hydrogenated to the amine **4** and isolated as crystalline oxalate.

Scheme 1



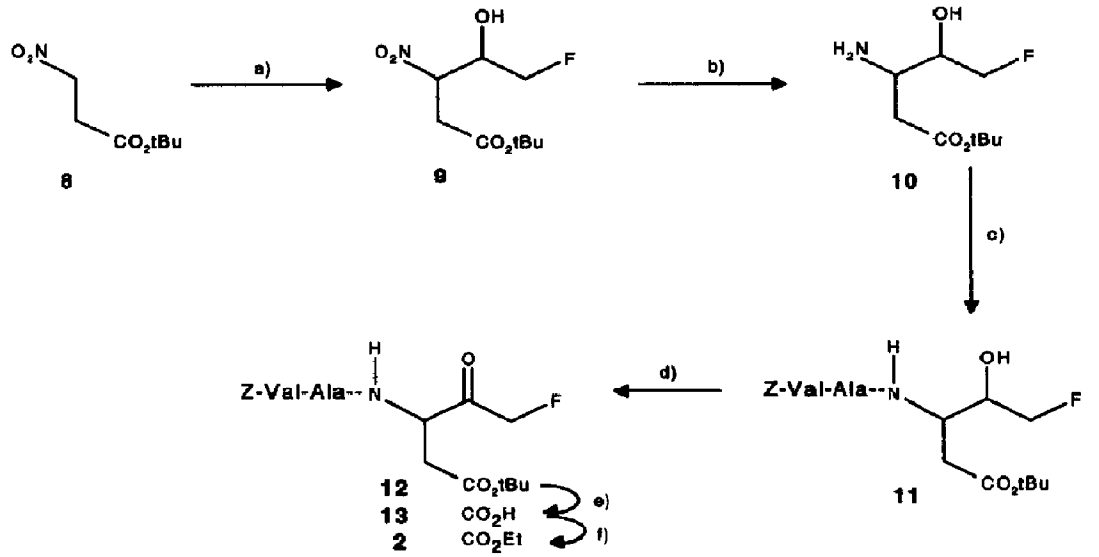
a) Benzylamine, -20°C, 40hrs. Chromatography, 75% b) H_2, Pd/C, EtOH. Oxalate crystallized from EtOAc/Ether, 95%. c) Z-Val-Ala-OH, EDCI, HOBt, THF, 0° C to r.t., 12 hrs., 66%. d) EtOH/H2O (5:1) K10 Montmorillonite, 2.75hrs, 75°C, 73%. e) 2,6-Dichlorobenzoylchloride, pyridine, DMAP (2eq.), DMPU (2eq.), 2 days, 93%. f) Dess-Martin, 0°C to r.t. 3.5hrs, 90%.

The free base of **4** was coupled to Z-Val-Ala-OH under standard conditions (HOBt, EDCI, THF) to yield ketal **5**, which was selectively hydrolyzed to diol **6** with Montmorillonite K10 in EtOH/water. The latter was esterified with 2,6-dichlorobenzoyl chloride in pyridine/DMAP using DMPU as cosolvent. Several methods were elaborated for the final oxidation step, since ketone **1** [7] was sensitive to epimerization under basic conditions. Swern oxidation e.g. gave a ~1:1 mixture of epimers, while the procedures of Dess-Martin and Pfitzner-Moffatt

[8] gave pure **1**.

Fluoromethyl ketones are generally prepared with limited success according to a modified Dakin West procedure [9], which has been used by R. Black in [4b] for the synthesis of BOC-Asp-CH_2-F. We decided to synthesize **2** via nitro-aldol condensation [10] as a key step *(Scheme 2)*. For this purpose, fluoroethanol was submitted to a Swern oxidation, which was followed by the addition of the nitro derivative **8** without isolation of the intermediate fluoroacetaldehyde. The yield of nitroalcohol **9** resulting from this one-pot oxidation/condensation reaction amounted to 89% after purification by chromatography. Hydrogenation over Raney-Nickel gave amino alcohol **10** in 85% yield, which was converted to **11** by coupling with Z-Val-Ala-OH under standard conditions. Dess-Martin oxidation proceeded in 62% yield to the keto ester **12** as a crystalline solid. Deprotection of the *tert*.butyl ester with TFA provided the acid **13**, which was esterified in HCl/EtOH over night at r.t. to generate **2**, obtained as a crystalline solid and according to NMR as a ~1:1 mixture of epimers [7]. No attempt was made to separate the epimers.

Scheme 2



a) 2-Fluoroethanol, $(COCl)_2$, DMSO, NEt_3, -60°C to r.t., 1.5 hrs, then add **8**, r.t. 1hr. 89%. b) Raney-Nickel, MeOH, H_2, r.t. 12 hrs. 85%. c) Z-Val-Ala-OH, EDCI, HOBT, DMAP, THF, 12 hrs. 97% white solid. d) Dess-Martin reagent (7eq.), CH_2Cl_2, 30min. 62% white solid. e) TFA, CH_2Cl_2, 30 min. r.t. 91% white solid. f) EtOH saturated with HCl, 14 hrs. r.t. 86% white solid.

In models of acute inflammation, such as the LPS-pyrexia and Carrageenan oedema, **1** and **2** showed potent effects upon oral administration with the ED_{50}'s less than 0.1 mg/kg p.o. Whether these activities are mediated by inhibition of IL-1β, is under current investigation.

Acknowledgements:

The authors express their appreciation to the Analytical Department of Sandoz Preclinical Research Basel for NMR and MS data.

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[7] Diagnostic physical data for **1**: M.p.: 193° C; $[\alpha]_D^{20}$= -52.0° C [c=1.05 in acetone]. ^{13}C NMR (360MHz; DMSO) δ 13.98; 17.71; 18.07; 19.21; 30.33; 34.25; 48.10; 52.88; 59.86; 60.34; 65.40; 67.72; 127.58; 127.69; 128.26; 128.44; 130.79; 132.51; 137.00; 156.10; 163.20; 170.09; 170.98; 172.90; 199.44.

For **2**: ^{1}H NMR (360MHz, DMSO-d_6, 120°C) δ 0.84-0.92(m,6H); 1.18 (t, 3H, J=8Hz); 1.22 and 1.25 (two d, 3H, J=8Hz, Me of Ala); 1.96-2.09 (m, 1H); 2.58-2.67 (dd, 1H); 2.80-2.88 (m, 1H); 3.88-3.93 (m, 1H); 4.08(q, 2H, J=8Hz); 4.23-4.35(m, 1H); 4.60-4.72(m, 1H); 4.95-5.23(m, 2H, CH2F); 5.05 (d, 2H, PhCH2O); 6.62(bd, 1H, J=9Hz); 7.25-7.33(m, 5H); 7.60-7.70(bq, 1H); 7.98-8.05(bt, 1H)

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