*Bioorganic & Medicinal Chemistry Letters*, Vol.2, No.6, pp. 579-582, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00


# ACID-CATALYZED O-ALLYLATION OF β-HYDROXY-α-AMINO ACIDS: AN ENTRY INTO CONFORMATIONALLY CONSTRAINED DIPEPTIDE SURROGATES

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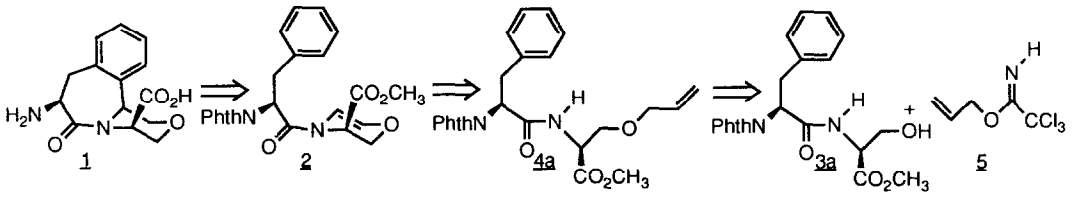
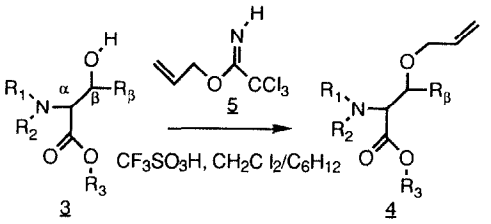
(*Received* 23 *March* 1992)

**Abstract:** O-Allylation using allyl trichloroimidate 5 was found to be an effective method for the introduction of an acetaldehyde equivalent onto the hydroxyl group of β-hydroxy-α-amino acid derivatives. Rigid oxygen containing tricyclic anti-phenylalanyl-leucine mimic 1 was efficiently synthesized using this method. This mimetic was further elaborated to provide 7c, a potent inhibitor of angiotensin-1 converting enzyme (ACE).

Conformationally restricted molecules which mimic energetically favored and hence highly populated orientations of amino acid side chains have proven useful as active-site probes for metalloproteinases. The rigid oxygen containing tricyclic anti-phenylalanyl-leucine mimic 1 was thought to provide an attractive complement to the carbocyclic and thiomorpholine analogs previously reported.[1] This communication describes a versatile method for appending an acetaldehyde equivalent onto β-hydroxy-α-amino acid derivatives using allyl trichloroimidate 5. Allyl ether 4a was efficiently converted to constrained peptide mimetic 1.

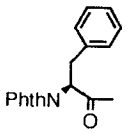



We report that allyl trichloroacetimidate 5[2] is a convenient reagent for the O-allylation of β-hydroxy-α-amino acid derivatives under mildly acidic conditions. This method is compatible with imide or amide amino-protecting groups and methyl or benzyl ester carboxyl-protecting groups. The protected β-hydroxy-α-amino acids[4] were dissolved in dichloromethane/cyclohexane (1:1, 0.1M) and allyl trichloroacetimidate (2.0 eq) and trifluoromethanesulfonic acid (0.9 eq) were added. The reactions were allowed to stir at 20°C until the alcohols (3) were completely converted to the corresponding allyl ethers (4); 4 h for serine derivative (3a → 4a), 6-12 h for threonine derivatives (3b → 4b and 3c → 4c) and 18-24 h for β-phenylserine derivatives (3d → 4d and 3e → 4e) (see Table 1). Aqueous workup and flash chromatographic purification afforded the allyl ethers in 60-74% yield.




3 5 4

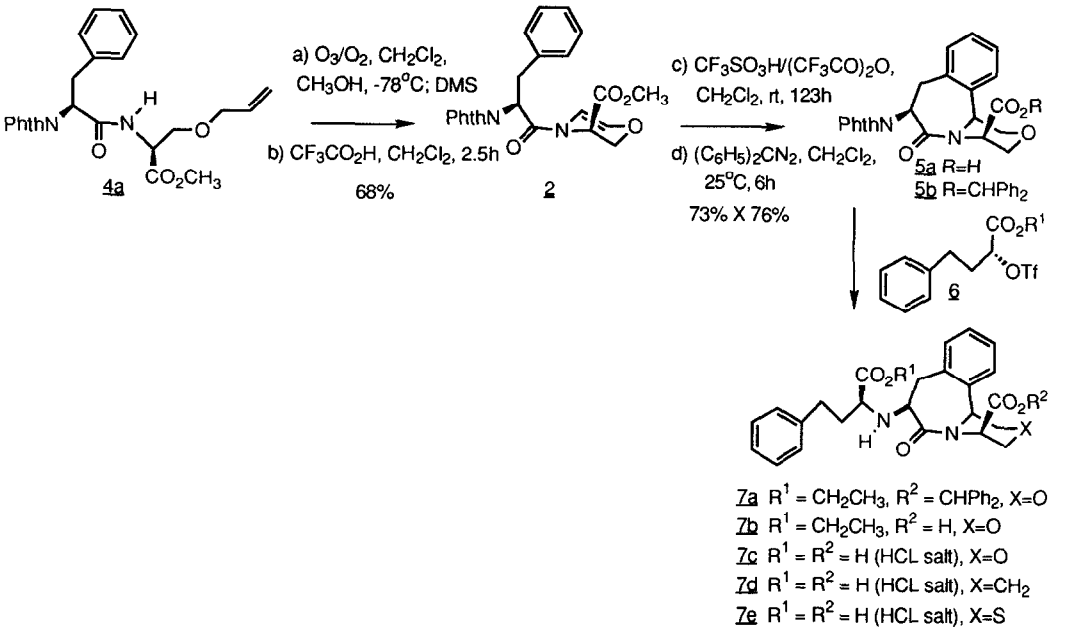
**Table 1.** Allylation of β-hydroxy-α-amino acid derivatives with allyl trichloroacetimidate 5

| Alcohol | Allyl Ether | $R_1, R_2$ | $R_3$ | $R_\beta$ | Configuration α | Configuration β | Time (hr) | % Yield |
|---|---|---|---|---|---|---|---|---|
| 3a | 4a |  | $CH_3$ | H | S | - | 4 | 60 |
| 3b | 4b | Phth | $CH_2C_6H_5$ | $CH_3$ | S | R | 6 | 69 |
| 3c | 4c | Phth | $CH_2C_6H_5$ | $CH_3$ | S | S | 12 | 70 |
| 3d | 4d | Phth | $CH_3$ | $C_6H_5$ | S | S | 18 | 70 |
| 3e | 4e | Phth | $CH_3$ | $C_6H_5$ | R | R | 22 | 74 |

The O-allyl ether of N-phthaloyl-L-phenylalanyl-L-serine **4a** was efficiently converted to conformationally constrained *anti*-Phe-Leu mimetic **1** using the following sequence. Ozonolysis of the O-allyl ether **4a** ($O_3$, $CH_2Cl_2$, $CH_3OH$, -78°C; $(CH_3)S$ 78°C → 20°C) followed by acid catalyzed cyclization ($CH_2Cl_2/CF_3CO_2H$ (10:1), 20°C, 2.5 h) and purification afforded morpholinoenamine **2** (68%, mp = 70-72°C, $[\alpha]_D^{20}$ = -368° (c=1, $CHCl_3$)). Intramolecular acyliminium ion cyclization of **2** under rigorously anhydrous conditions ($CF_3SO_3H$ (7.7 eq), $(CF_3CO)_2O$ (1.2 eq), $CH_2Cl_2$, 20°C, 123 h) gave carboxylic acid **5a** (73%) which was esterified ($Ph_2CN_2$, $CH_2Cl_2$, 20°C, 6 h) and purified by plug filtration on silica gel to afford **5b** in 76% yield (mp = 178-181°C, $[\alpha]_D^{20}$ = -116° (c=1, $CHCl_3$)).

The anti-Phe-Leu mimetic 1 was elaborated to diacid 7c for evaluation as an inhibitor of angiotensin-1 converting enzyme (ACE). The phthalimide protecting group was removed ($H_2NNH_2$, $CH_3OH$), Δ) and the free amine was treated with (R)-triflate[5] 6 ($CH_2Cl_2$, 1,8-bis-dimethylaminonaphthalene, 20°C, $CH_2Cl_2$) to give coupled diester 7a in 94% yield. Cleavage of the benzhydryl ester ($H_2$, 5% Pd/C, $CH_3CH_2OH$, TFA, 99%) provided ethyl ester 7b which was hydrolyzed with lithium hydroxide in methanol and purified by ion exchange chromatography to give diacid 7c in 73% yield.

Diacid 7c was evaluated biochemically using rabbit lung ACE by methodology described previously.[6] Morpholino derivative 7c was a potent inhibitor of ACE ($IC_{50}$ = 0.09 nM) similar to that determined for carbocyclic analog (7d) and thiomorpholine analog (7e).




**Acknowledgment:** We would like to thank Dr. F. Mark Laskovics for synthesizing additional quantities of L and D-β-phenylserine.

**References and Notes**

1. a) Flynn, G.A.; Giroux, E.L.; Dage, R.C. *J. Am. Chem. Soc.*, **1987**, *109*, 7914. b) Flynn, G.A.; Giroux, E.L.; Beight, D.W. in Peptide Chemistry; Shiba, T.; Sakakibara, S., Eds.; Protein Research Foundation, Osaka, **1987**, 631.
2. Wessel, H.P.; Iversen, T.; Bundle, D.R. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2247.
3. See Sham, H.L.; Bolis, G.; Stein, H.H.; Fesik, S.W.; Marcotte, P.A.; Plattner, J.J.; Rempel, C.A.; Greer, J. *J. Med. Chem.*, **1988**, *31*, 284, for the allylation of sodium carboxylate of N-Boc-Serine. Attempted allylation of β-hydroxy-phenylalanine methyl ester derivatives under base catalyzed conditions (NaH, allyl bromide, THF or LDA, allyl bromide, THF) led to undesired products resulting from retro-aldol condensation and β-elimination of the O-allyl ether.
4. The acid chloride of N-phthalimido-L-phenylalanine was acylated with L-serine methyl ester hydrochloride in $CH_2Cl_2$ in the presence of 4-methylmorpholine to afford **3a** in 67% yield. L-Threonine and L-allo-threonine were allowed to react with phthalic anhydride in refluxing dioxane followed by esterification (benzylbromide and diisopropylethylamine in $CH_2Cl_2$) to afford **3b** and **3c**, respectively (59% and 85%). L and D-β-Phenylserine were prepared using the method of Evans (Evans, D.A.; Sjogren, E.B.; Weber, A.E.; Conn, R.E. *Tetrahedron Lett.*, **1987**, *28*, 39). Treatment with N-carboethoxyphthalimide followed by esterification ($CH_2N_2$) afforded **3d** and **3e** (68% and 62%), respectively.
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