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A Stereoselective Synthesis of N-[(S)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanine Derivatives by Means of Reductive Amination

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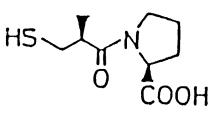
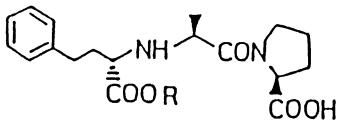
A stereoselective synthesis of N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanine, a portion of the molecule of angiotensin converting-enzyme(ACE) inhibitors, by reductive amination utilizing catecholborane and further applications of the reaction to the synthesis of ACE inhibitors are described.

In the field of hypertension drugs, much attention has been focused on the inhibitors of angiotensin converting enzyme (ACE), which converts the precursor decapeptide angiotensin I to the powerful vasoconstrictor substance angiotensin II. Based on rational drug design, captpril (SQ 14225) was developed by Ondetti et al., as the first orally active inhibitor.[1] More recently, Pacthett and his co-workers have demonstrated a new class of potent inhibitors, such as enalapril (MK 421), enalaprilat (MK 422) and its lysine analogue (lisinopril, MK 521).[2-4]

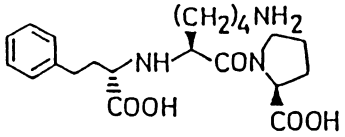


Captopril (SQ 14225)



Enalapril (MK 421) R=Et

Enalaprilat (MK 422) R=H



Lisinopril (MK 521)

Scheme 1.

It has also been confirmed that in these novel ACE inhibitors which contain three asymmetric carbons, the (S,S,S) diastereoisomer is the most biologically active one. Hitherto, these novel inhibitors, enalapril, lisinopril, have been synthesized by the reductive amination of 2-oxo-4-phenylbutyric acid or its ester [5] with dipeptide units using sodium cyanoborohydride or by catalytic

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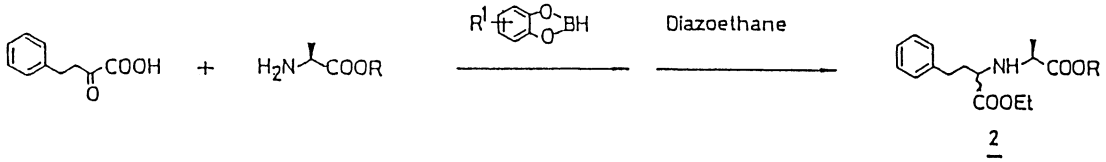
hydrogenation. Under these conditions, however, excess α-keto acid is required and, furthermore, these reactions usually result in the formation of a diastereomeric mixture (i.e. S,S,S and R,S,S) with a ratio of ca. 1:1.

We now wish to describe a stereoselective synthesis of the generally usable component for the above representative ACE inhibitors, i.e. N-[(S)-1-ethoxycarbonyl-3-phenylpropyl]-L-alanine (1),[6] and further applications of the procedure to the synthesis of ACE inhibitors themselves. Reductive amination coupling of 2-oxo-4-phenylbutyric acid or its ester with L-alanine derivatieves was thoroughly investigated using various type of reducing reagents under several conditions. When an equimolar mixture of 2-oxo-4-phenylbutanoate and L-alanine t-butylester was treated with BH_3.THF complex (in CH_2Cl_2) or BH_3.N-diethylaniline complex (in EtOH), selective reduction of carbonyl function proceeded and then the corresponding α-hydroxy ester was obtained exclusively. However, when catecholborane was used in CH_2Cl_2, the reaction proceeded smoothly to give the corresponding N-substituted amino acid derivative (2, R= t-Bu) in 64%, as a diastereomeric mixture with a ratio of 1:1. Finally, the reductive condensation of 2-oxo-4-phenylbutyric acid instead of its ester with L-alanine t-butylester in the presence of catecholborane was examined. The reaction proceeded efficiently in CH_2Cl_2 and desired diastereoisomer was formed selectively.[7] As further confirmations of this selectivity, various reaction conditions were investigated and results were summarized in Table 1.

Table 1. Reductive amination reaction of 2-oxo-4-phenylbutyric acid with L-alanine derivatives



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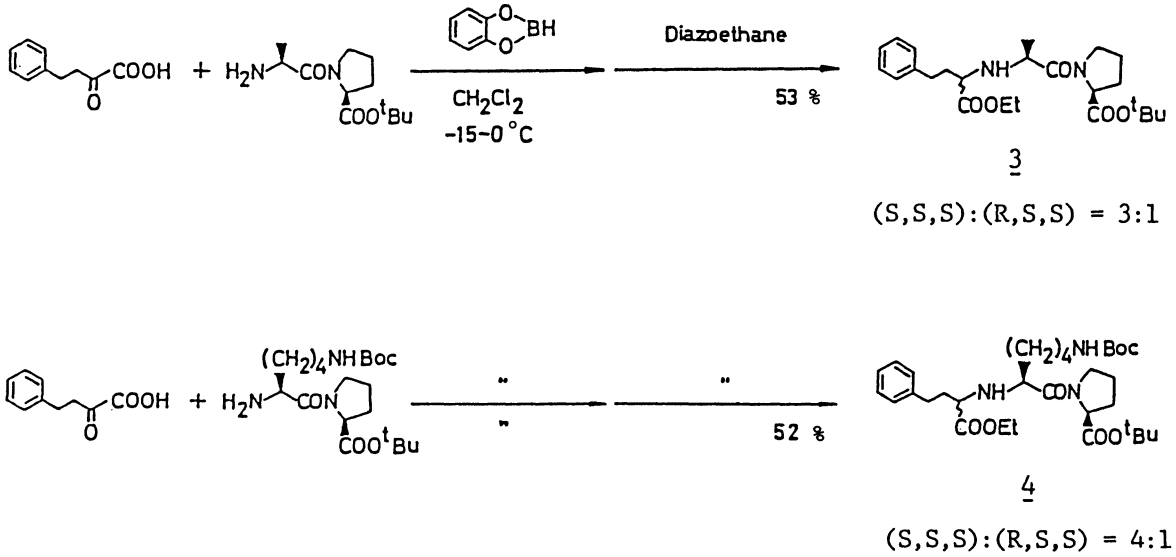
R	R^1	Solvent	Temp /°C	Time / h	Yield of 2 / %	Ratio (SS : RS)
t-Bu	H	THF	-15 — 0	2	62	2.1 : 1
〃	〃	1,4-Dioxane	25	〃	73	2.9 : 1
〃	〃	Benzene	〃	〃	48	1.7 : 1
〃	〃	Toluene	-15 — 0	〃	57	2.0 : 1
〃	〃	CH_2Cl_2	〃	〃	64	5.5 : 1
〃	3-Me	〃	〃	〃	65	6.8 : 1
Benzyl	H	〃	〃	〃	62	2.9 : 1
〃	3-Me	〃	〃	〃	60	4.0 : 1

As shown in Table 1, excellent selectivity was achieved especially in the case of 3-methyl-catecholborane [8]-CH_2Cl_2 system. It seems likely that steric interaction between chiral imine, which was fixed by carboxy group, and bulky catecholborane raises the selectivity. A typical procedure is as follows. To a solution of 2-oxo-4-phenylbutyric acid (200 mg, 1.1 mmol) and L-alanine t-butylester hydrochloride (245 mg,1.35 mmol) in 10 ml of CH_2Cl_2 were added 1g of 4 Å molecular sieves and sodium acetate (184 mg, 2.24 mmol). After the mixture was stirred for 1 h, a solutuion of catecholborane (202 mg, 1.69 mmol) in 5 ml of CH_2Cl_2 was added slowly to the mixture for 1 h at -15 – -10 °C, and then additional stirring was continued for 1 h at -10 – 0 °C. The reaction mixture was filtered through celite and washed with CH_2Cl_2 and MeOH. To the filtrate was added 5 ml of 30% of H_2O_2 and the mixture was stirred for 3 – 4 h at room temperature. The mixture was extracted with CH_2Cl_2 several times and the extracts were esterified with diazoethane, washed with brine, dried over anhydrous sodium sulfate, and then concentrated in vacuo. Purification of the residue by silica gel chromatography (25% ethyl acetate / hexane) afforded 206.5 mg of (S,S)-2 and 37.5 mg of (R,S)-2(R= t-Bu).

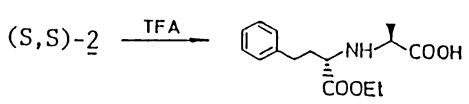
As a further extension of this reaction, we examined the reaction of 2-oxo-4-phenylbutyric acid with L-alanyl-L-proline t-butylester and N-(N^6-t-butoxycarbonyl-L-lysyl)-L-proline t-butylester under the same conditions using catecholborane. In the former case, corresponding adduct was obtained in 53% yield with a ratio of 3:1 (S,S,S / R,S,S), and , in the latter case, in 52% yield with a ratio of 4:1 (S,S,S / R,S,S). These (S,S,S) diastereoisomers were easily converted to enalapril and lisinopril, respectively by stepwise removal of the protecting groups.[9] (Scheme 2.)



Scheme 2.

References

1) M. A. Ondetti and D. W. Cushman, Science, 196, 441 (1977).
2) A. A. Patchett, E. Harris, E. W. Tristram, M.J. Wyvratt, M. T. Wu, D. Taub, E. R. Peterson, T.J. Ikeler, J. ten Broeke, L. G. Payne, D. L. Ondeyka, E. D. Thorsett, W. J. Greenlee, N.S. Lohr, R. D. Hoffsommer, H. Joshua, W. V. Ruyle, J. W. Rothrock, S. D. Aster, A. L. Maycock, F. M. Robinson, R. Hirschmann, C. S. Sweet, E. H. Ulm, D. M. Gross, T. C. Vassil, and C. A. Stone, Nature, 288, 280 (1984).
3) M. J. Wyvratt, E. W. Tristran, T. J. Ikeler, N. S. Lohr, H. Joshua, J. P. Spring, B. H. Arison, and A. A. Patchett, J. Org. Chem., 49, 2816 (1980).
4) M. T. Wu, A. W. Douglas, D. L. Ondeyka, L. G. Payne, T. J. Ikeler, H. Joshua, and A. A. Patchett, J. Pharm. Sci., 74, 352 (1985).
5) L. M. Weinstock, R. B. Currie, and A. V. Lovell, Synth. Commun., 11, 943(1981). The carboxylic acid is obtained by acid hydrolysis (concd HCl-AcOH) of its ester.
6) H. Urbach and R. Henning, Tetrahedron Lett., 25, 1143 (1984).
7) The desired (S,S) diastereoisomer of 2(R= t-Bu) was converted to 1 by following treatment,

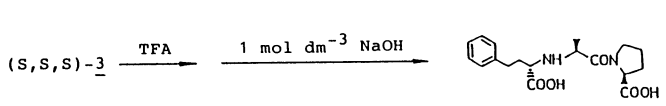


(1)

5) $[\alpha]_D^{20}$ +30° (c 1, MeOH)
mp 153-154 °C

rf. $[\alpha]_D^{20}$ +28.2° (c 1, MeOH)
mp 148-150 °C

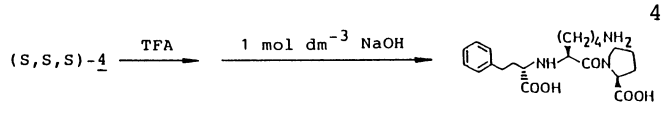
8) For the synthesis of 3-methyl-catecholborane, see: H. C. Brown, S. K. Gupta, J. Am. Chem. Soc., 93, 1816 (1971).
9) The desired (S,S,S) diastereoisomer of 3 or 4 was converted to enalapril, or lisinopril, respectively by following treatments,



Enalaprilat

3) $[\alpha]_D^{25}$ -52° (c 1, MeOH)
mp 147-148 °C

rf. $[\alpha]_D^{25}$ -53.5° (c 1, MeOH)
mp 149-151 °C



Lisinopril

4) $[\alpha]_D^{25}$ -23.5° (c 0.596, MeOH)

rf. $[\alpha]_D^{25}$ -23.3° (c 1, MeOH)

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