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A FAVOURABLE DIASTEREOSELECTIVE SYNTHESIS OF N-(1-S-ETHOXYCARBONYL-3-PHENYLPROPYL)-S-ALANINE

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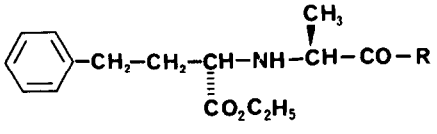
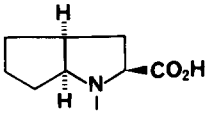
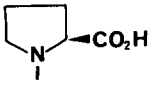
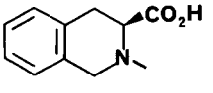
Summary: N-(1-S-Ethoxycarbonyl-3-phenylpropyl)-S-alanine is prepared by Michael addition of S-alaninebenzylester to ethyl-4-oxo-4-phenyl-2-butenoate in a regio- and diastereoselective fashion and subsequent catalytic hydrogenolysis.

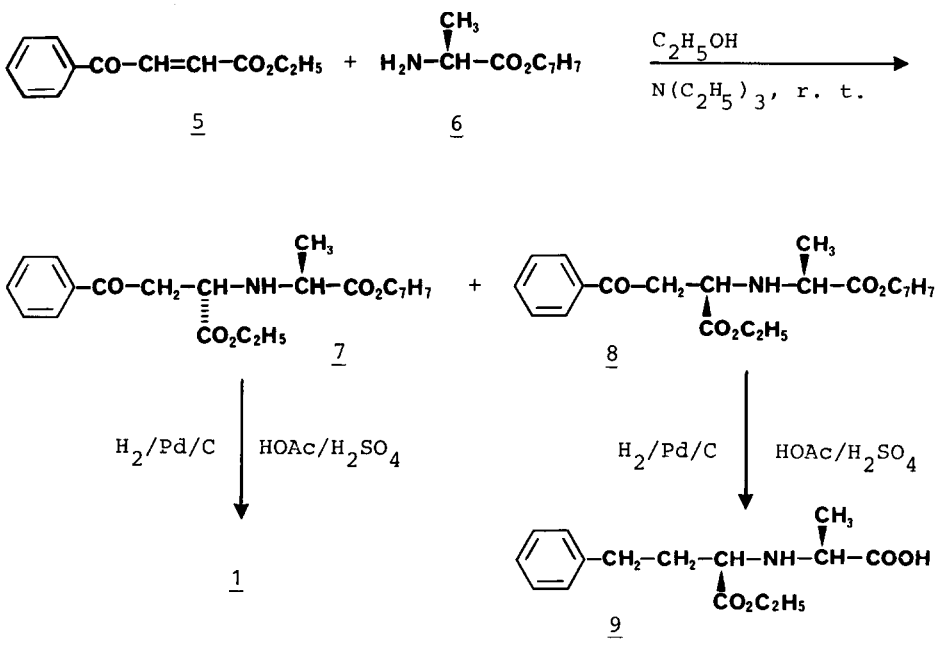
N-(1-S-Ethoxycarbonyl-3-phenylpropyl)-S-alanine 1 is a portion of the molecule of the angiotensin-converting-enzyme (ACE)-inhibitors Hoe 498 2[1], MK 421 3[2], CI 906 4[3] and others, which have attracted great therapeutic interest in the cardiovascular field.



	R		
1	OH		1
Hoe 498			2
MK 421			3
CI 906			4

In view of studying structure-activity relationships of ACE-inhibitors we looked for a favourable synthesis of 1.
Treatment of trans-ethyl-4-oxo-4-phenyl-2-butenoate 5[4] with S-alaninebenzylester 6 in ethanol at room temperature in the presence of $N(C_2H_5)_3$ gives rise to a diastereomeric mixture of 7 and 8 exclusively in a Michael type addition in 97 % yield (Scheme I).

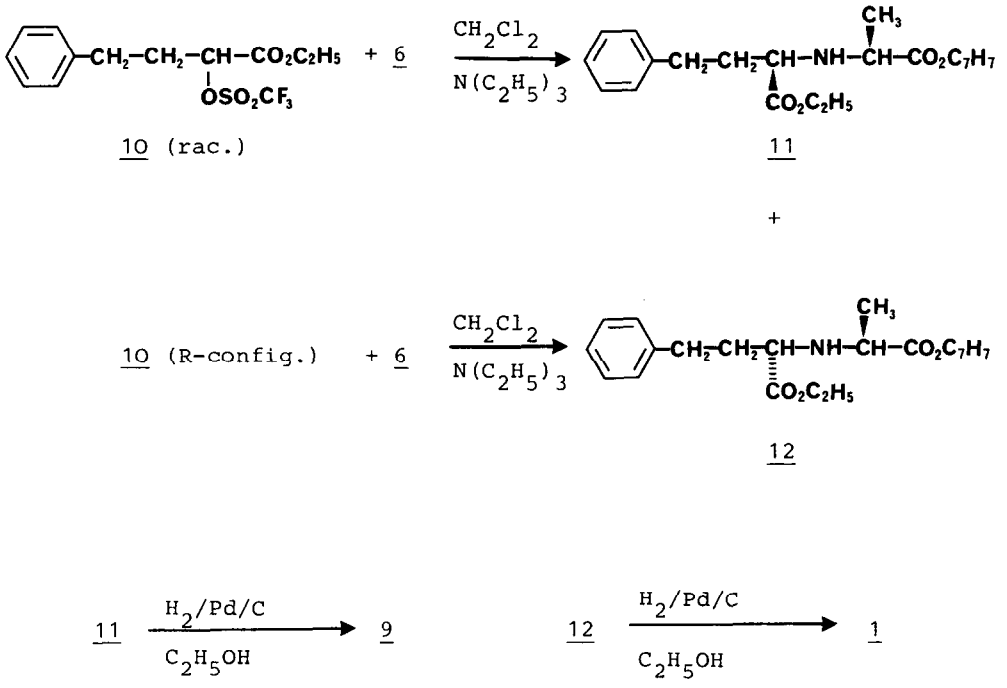
Scheme I



The diastereomer 7 with (S,S)-configuration is only slightly soluble in ethanol and precipitates out of solution in 55 - 65 % yield (mp.: 73 - 74 °C, $[\alpha]_D^{20}$: -17.8° (c = 1, CH_3OH)). After cooling of the mother liquor another portion of 7 precipitates out (total yield 77 %). 7 is subjected to catalytic hydrogenolysis (Pd/C, H_2, glacial acetic acid containing 1.6 % conc. H_2SO_4 (v/v), 25 - 30 °C, 1 atm) to give 1 in 91 % yield (mp.: 148 - 150 °C, $[\alpha]_D^{20}$: + 28,2° (c = 1, CH_3OH)). The (R,S)-diastereomer 8, which has to be used immediately after filtration of 7[5], is hydrogenated in the same manner to give 9 in 74 % yield (mp.: 128 - 130 °C, $[\alpha]_D^{20}$: = -25° (c = 1, CH_3OH)).

To confirm the configuration of 1 and 9 we carried out the following reaction sequence (Scheme II):

Scheme II



The racemic triflate 10 (rac. hydroxyester, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, 0°C, 84 % yield) reacts with S-alaninebenzylester and $N(C_2H_5)_3$ in CH_2Cl_2 at room temperature to give the diastereomeric mixture of 11 and 12, which can be separated easily by column chromatography (SiO_2, cyclohexane/diisopropylether 8 : 2). 11 is eluted as the less polar compound ($[\alpha]_D^{20}$: -0.4° (c = 1, CH_3OH); 12:$[\alpha]_D^{20}$: -11.4° (c = 1, CH_3OH)). 11 and 12 were debenzylated (Pd/C/H_2,C_2H_5OH, r. t., 1 atm) to give 9 (mp.: 136 - 137 °C;$[\alpha]_D^{20}$: -27,9° (c = 1, CH_3OH)) and 1 (mp.: 148 - 149 °C,$[\alpha]_D^{20}$: +28,0° (c = 1, CH_3OH)). To decide whether 1 or 9 possessthe (S,S)-configuration, the triflate 10 (R-config.)[6] was subjected to the reaction with S-alaninebenzylester 6. Under inversion 12 was obtained exclusively[8] which was debenzylated to give 1, which has the (S,S)-configuration. Accordingly, 9 possesses the (R,S)-configuration.

Acknowledgement: We are grateful to Dr. H.-W. Fehlhaber for analytical support

References and Notes:

1) P.U. Witte, M. Metzger, R. Irmisch, Naunyn-Schmiedeberg's Arch. Pharmacol. 324 (Suppl.): R 75 (1983).
R.H.A. Becker,B.A. Schoelkens, Th. Unger, W. Linz, Naunyn-Schmiedeberg's Arch. Pharmacol. 324 (Suppl.): R 42 (1983).

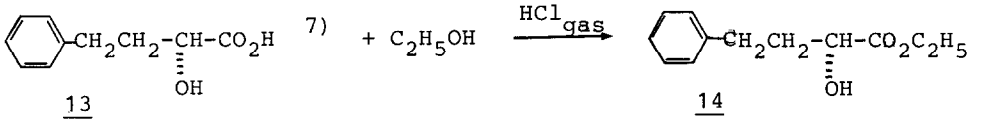
2) Drugs Fut. 8, 731 (1983).

3) Pharmacologist 24, Abs. 446 (1982).

4) G. P. Rice, J. Amer. Chem.Soc. 45, 233 (1923).

5) 7 is the thermodynamically more stable product in comparison to 8. 8 (oil) is converted into crystalline (7) after standing at room temperature for several days. ^{1}H-NMR (270 MHz) of 8 ($CDCl_3$) : δ = 1.23 (t, 3H); 1.32 (d,3H); 3.37 (m, 2H); 3,54 (q, 1H); 3.91 (t, 1H); 4.13 (m, 2H); 5.13 (m, 2H); 7.25 - 8.0 (m, 10H) ppm ^{1}H-NMR (270 MHz) of 7 ($CDCl_3$): δ = 1.23 (t, 3H); 1.35 (d, 3H); 3.43 (m, 2H); 3.65 (q, 1H); 3.81 (t, 1H); 4.18 (q, 2H); 5.14 (m, 2H); 7.25 - 7.95 (m, 10H) ppm.

6) 10 (R-config.) is obtained by the following reaction:



13 14

$[\alpha]_D^{20}$: -22.1° (c = 1, $CHCl_3$)

bp.: 96 - 98 °C/0.04

$\xrightarrow[CH_2Cl_2,\ r.\ t.]{(CF_3SO_2)_2O/Pyr}$ 10; 10 was used as a crude product

(tl c: one spot; SiO_2, cyclohexane/ethylacetate 9 : 1, R_f: 0.36).

7) D. Biquard, Ann. de Chimie 20, 146 (1933).

8) F. Effenberger could show that triflates of optically pure α-hydroxycarboxylic esters react with amines under inversion to yield the corresponding amine derivatives[9].

9) F. Effenberger, U. Burkhard, J. Willfahrt, Angew. Chem. 95, 50 (1983).

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