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THE ASYMMETRIC SYNTHESIS OF (-)-CAPTOPRIL UTILISING THE IRON CHIRAL AUXILIARY $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$

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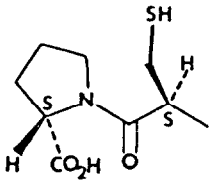
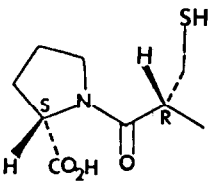
Summary: Stereoselective alkylation of (R)-$[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2CH_3]$ with bromomethyl-t-butyl sulphide, followed by oxidative decomplexation in the presence of L-proline t-butyl ester gave, after deprotection, (-)-Captopril enantiomerically and diastereomerically pure in an overall yield of 59%.

(-)-Captopril, 1-(3-mercapto-2-methyl-1-oxopropyl)-L-proline (S,S)-1, the amide derived from (S)-3-mercapto-2-methylpropionic acid and L-proline has been designed[1,2] to specifically bind to the active site of angiotensin converting enzyme (ACE) thus inhibiting its action[2] with the effect of lowering blood pressure. Captopril is being used successfully in the treatment of hypertension and causes few side-effects.[3] The epimer (S,R)-2 of Captopril, i.e., the amide derived from (R)-3-mercapto-2-methylpropionic acid and L-proline is 100 times less active than Captopril itself.[2] In general, synthetic routes to Captopril generate mixtures of epimers (S,S)-1 and (S,R)-2 which require separation.[4,2]



(-)-Captopril 1

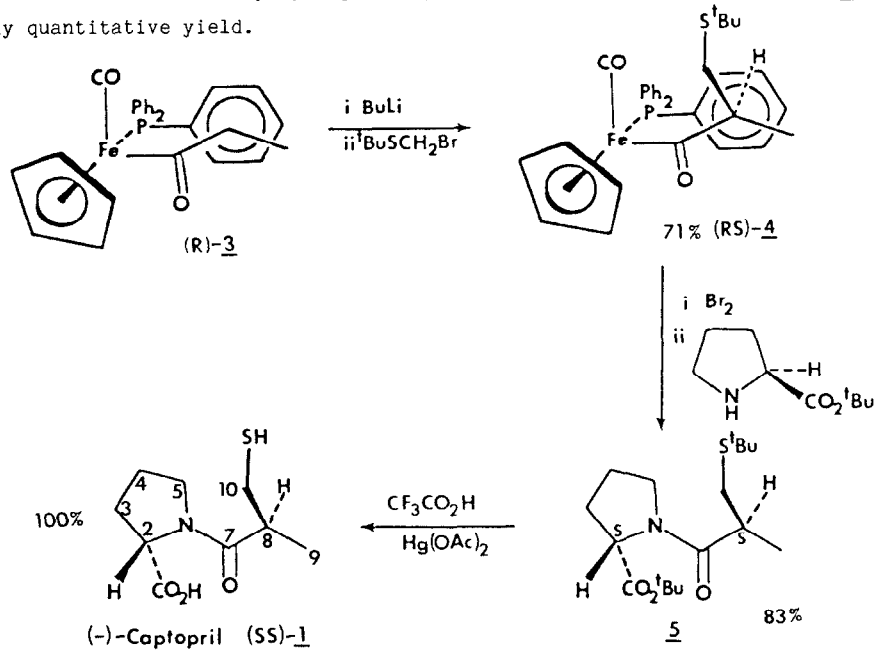


(-)-epiCaptopril 2

We describe herein the use of the chiral iron auxiliary $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)]$ to achieve the asymmetric synthesis of the S-t-butyl protected fragment of Captopril and its direct coupling with L-proline t-butyl ester to generate after deprotection (-)-Captopril 1.

We have previously demonstrated the highly stereoselective alkylations of the racemic propanoyl complex 3 via stereoselective formation of the E-enolate with n-butyllithium and subsequent electrophilic addition exclusively to its unhindered face.[5] In this case enantiomerically pure propanoyl complex[6] (R)-3 was deprotonated with n-butyllithium at -78°C in tetrahydrofuran to generate the corresponding E-enolate which on addition of bromomethyl-t-butyl sulphide[7] generated the (R,S)-complex 4 as a single diastereoisomer (> 200:1) in 71% yield. No trace of the R,R-diastereoisomer could be detected by 300 MHz ^{1}H n.m.r. spectroscopy. The relative and hence absolute stereochemistry of the new α-chiral centre in 4 was assigned from the chemical shift of the α-methyl group at δ 3.11[8], and confirmed by the subsequent conversion of (R,S)-4 into (-)-Captopril. Decomplexation was achieved by addition of bromine; addition of L-proline t-butyl ester[9] generated the di-t-butyl derivative of Captopril 5 in 83% yield. Compound 5 was also diastereoisomerically pure by 300 MHz ^{1}H n.m.r.

spectroscopy confirming the stereoselectivity observed in the previous alkylation reaction. Finally, deprotection of both t-butyl groups was achieved on addition of trifluoroacetic acid and mercuric acetate followed by hydrogen sulphide gas[10] to yield (-)-Captopril 1 in essentially quantitative yield.



Starting from (R)-3 the above sequence has resulted in the synthesis of (-)-Captopril in 59% yield identical in all respects[11] including ^{1}H n.m.r., m.pt., mixed m.pt., optical rotation, etc., to an authentic sample.

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11. (-)-Captopril: ^{1}H n.m.r. (300 MHz, $CDCl_3$) δ, ppm: 9.18 1H, b, CO_2H; 4.6-4.62 1H, m, H-2; 3.59-3.68 2H, m, 2H-5; 2.77-2.95 2H, m, H-8, H-10; 2.43-2.52 1H, m, H-10'; 2.26-2.32 1H, m, H-3; 2.00-2.15 3H, m, H-3', 2H-4; 1.56 1H, t, SH ^{2}J= 8.6Hz; 1.20 3H, d, CH_3, ^{2}J= 6.6Hz; I.R. (CH_2Cl_2): 3200, 2680, 1740, 1580 cm^{-1}; Melting point: 103-105°C; Mixed melting point: 103-105°C, Lit.[2] m.p. : 104-105°C; $[\alpha]_D^{22}$ = -129.4° (EtOH, c=1.35), Lit.[2] : $[\alpha]_D^{22}$ = -131.0°.

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