Tetrahedron Letters,Vol.29,No.49,pp 6509-6512,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE ASYMMETRIC SYTHESIS OF (-)-ACTINONIN USING THE IRON CHIRAL AUXILIARY [(η^5-C_5H_5)Fe(CO)(PPh_3)]

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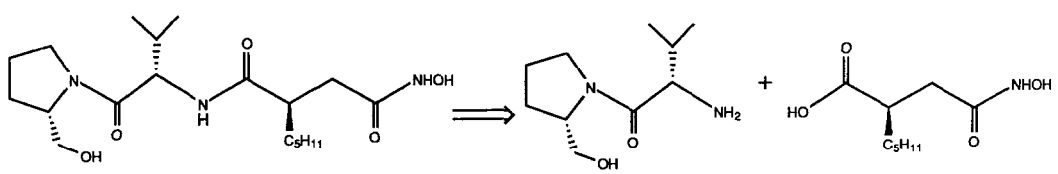
Abstract: The asymmetric synthesis of the α-pentyl succinate fragment of (-)-Actinonin is achieved using the chiral iron acetyl S-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$] and subsequently converted to (-)-Actinonin in an overall yield of 41%.

Hydroxamic acid derivatives of amino acids and pseudopeptides have been shown to be effective enzyme inhibitors[1,2]. Their activity is thought to involve chelation of the hydroxamic acid moiety onto the zinc sites of the enzyme, forming stable tetrahedral intermediates [3]. The remaining structural units of these hydroxamates are also of importance through their assistance in site recognition and specific binding interactions to other subunits of the enzyme.

Actinonin **1** is one such hydroxamic acid, which exhibits very high anticollagenase activity [4], comparable to other known low-molecular-weight inhibitors. Since several pathological conditions in humans[5] are associated with the degradation of collagen by the metallo-peptidase, collagenase[6], the potential clinical use of Actinonin as a collagenase inhibitor can be envisaged. Tests both *in vitro*[3,4], and *in vivo*[7] have proven the effective inhibitory activity of Actinonin and have shown its low acute-toxicity. Actinonin **1** was first isolated from *Actinomycete*[8], and subsequently from *Streptomycete* strains, and was shown to have antibiotic activity *in vitro* against Gram-positive and Gram-negative bacteria[3]. To date Actinonin has been obtainable generally from cultures of *Streptomycese*. The synthesis of Actinonin has been reported by Ollis *et al*, however, it involved the inefficient separation of a mixture of diastereoisomers in order to obtain enantiomerically pure (-)-Actinonin[9].

Our approach to Actinonin **1** involves the preparation, in suitably protected form, of the amino acid-derived fragment **2** and the asymmetric synthesis of the (R)-α-pentyl succinate fragment **3** to give, after coupling and deprotection, **1**.

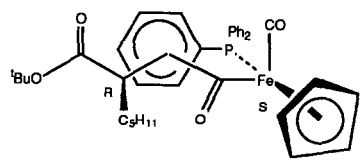


(S,S,R)- (-)- Actinonin **1** (S,S)-**2** (R)-**3**

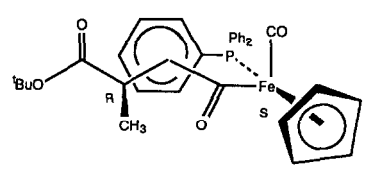
Fragment **2** is derived in homochiral form from L-prolinol **4** and L-valine. The asymmetric synthesis of fragment **3** involves the conversion of the commercially available chiral iron acetyl (S)-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)-$COCH_3$][10] **10** to (S)-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_2CH_2CO_2$tBu] **11** and the latters' use as a novel chiral, differentially protected, succinate enolate equivalent.

N,N'-Dicyclohexylcarbodi-imide (DCC) coupling of N-Boc-L-valine **5** and *ortho*-nitrophenol gave the activated ester **6**. Addition of L-prolinol to **6** gave the amide **7** in 85% yield. Compound **7** was then O-protected by benzylation to give **8** in 92% yield. This sequence proved more effective than the coupling of O-benzyl-L-prolinol with **6** to provide **8** directly. Treatment of **8** with trifluoroacetic acid removed the N-Boc protecting group in quantitative yield to give **9**, the required protected form of fragment **2**.

The(R)-α-pentyl succinate unit was synthesised as a single enantiomer starting from homochiral acetyl complex (S)-(+)-[(η^5-C_5H_5)Fe(CO)(PPh_3)$COCH_3$] **10**. This was deprotonated at -78°C with n-butyllithium (BuLi) then alkylated using t-butyl bromoacetate to provide the succinoyl complex **11** in practically quantitative yield. This complex **11** was deprotonated at -78°C with BuLi and the enolate thus formed treated with 1-iodopentane. This alkylation reaction was completely regioselective giving **12**, consistent with expected[11] selective deprotonation α to the ester rather than α to the iron acyl. Furthermore the alkylation reaction was highly stereoselective giving **12** as a 22:1 (d.e.>91%) mixture of diastereoisomers (SR:SS) as observed by ^{1}H nmr spectroscopy of the crude reaction mixture. The relative configurations within the major diastereoisomer were assigned as (S,R) by analogy with the corresponding racemic β-methyl succinoyl complex **14** whose structure has been unambiguously established by a single crystal X-ray structure analysis[12]. Purification of the crude reaction mixture by column chromatography on alumina gave (S,R)-(+)-**12** as a single diastereoisomer (>100:1 by ^{1}H nmr spectroscopy).



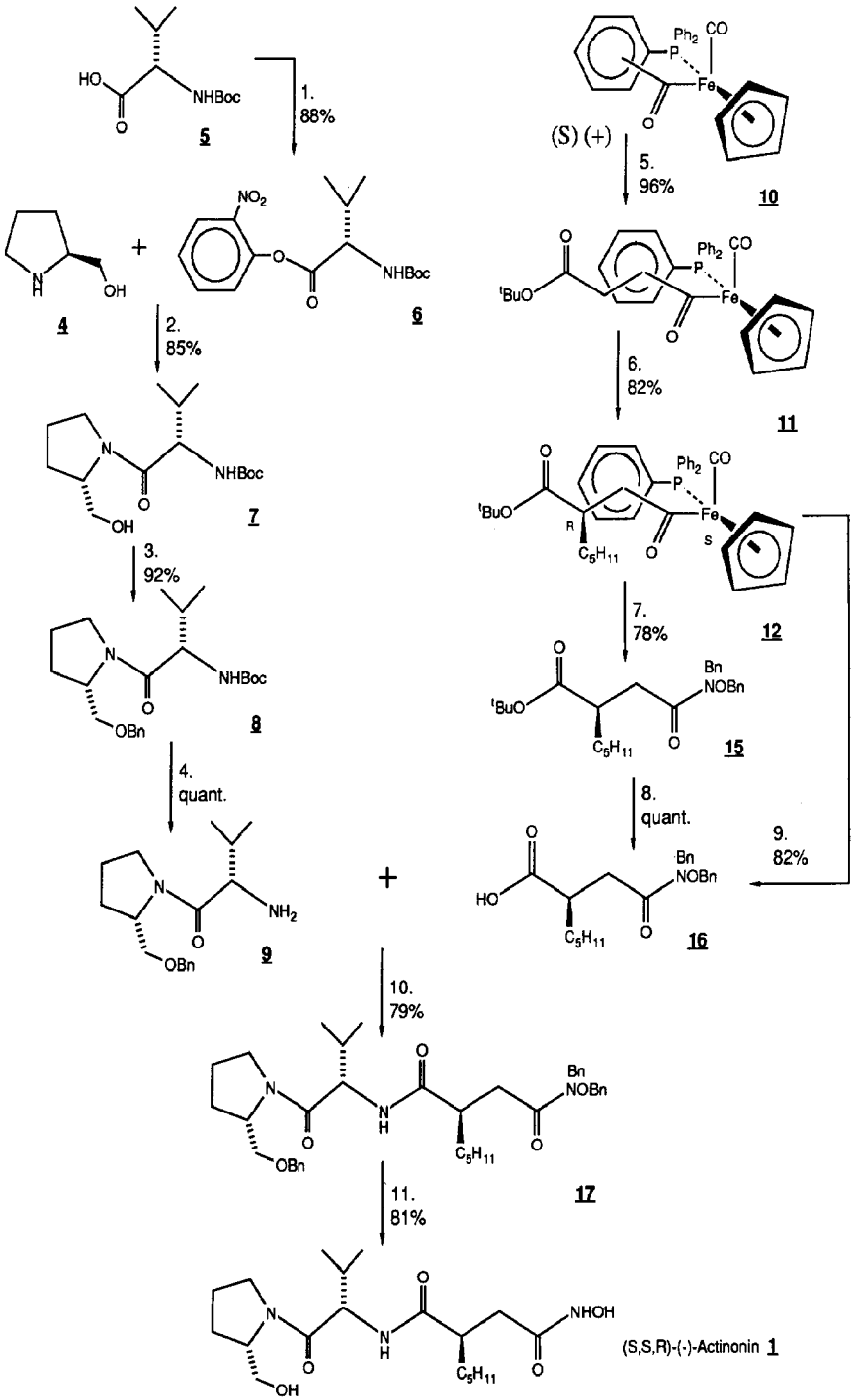
(S,R)-**12**



(S,R)-**14**

Oxidative decomplexation of (S,R)-(+)-**12** by N-bromosuccinimide in the presence of N,O-dibenzyl-hydroxylamine[13] led to the formation of the protected hydroxamic acid **15**. Selective deprotection of the t-butyl ester function in **15** with trifluoroacetic acid provided the required protected form of fragment **3**, the acid **16**[14] in 78% yield from **12**. Alternatively **12** undergoes decomplexation with bromine in the presence of N,O-dibenzyl-hydroxylamine to give the acid **16** directly in 82% yield. In the latter reaction the deprotection occurs *in situ* due to the equivalent of hydrogen bromide released during the decomplexation.

Coupling of the two protected fragments, the amine (S,S)-(+)-**9** and the acid (R)-(+)-**16** was achieved *via* the mixed anhydride derived from **16** and i-butyl chloroformate. In this manner, tribenzyl-Actinonin (S,S,R)-(-)-**17** was obtained in 79% yield as a single diastereoisomer. The stereochemical integrity of (S,S,R)-(-)-**17** verifies the homochirality of the succinate fragment (R)-(+)-**16** and confirms that no epimerisation occurs during the coupling step. Deprotection was readily achieved by hydrogenation under two atmospheres of pressure over palladium hydroxide on carbon at 20°C to provide (S,S,R)-(-)-Actinonin **1** in 81% yield.



1. THF, DCC, o-NO_2-phenol, 3hr; **2.** CH_2Cl_2, 3hr; **3.** THF, NaH, BnBr, 10hr; **4.** CH_2Cl_2, TFA, 10min.;
5. THF, BuLi, $BrCH_2CO_2{}^tBu$, -78°C, 5min.; **6.** i) THF, BuLi, $C_5H_{11}I$, -78°C- 0°C, 5hr., ii) chromatography;
7. CH_2Cl_2, NBS, BnON(Bn)H, -40°C- 25°C, 3hr.; **8.** CH_2Cl_2, TFA, 10min.; **9.** CH_2Cl_2, Br_2, BnON(Bn)H, -40°C- 20°C, 3hr.;
10. i) THF, N-Me-morpholine, $^tBuOCOCl$, 0°C, 15min, ii) compound **9**, 20°C, 1hr.; **11.** MeOH, H_2-$Pd(OH)_2$, 2atm, 20°C, 4hr.

Synthetic (-)-Actinonin was identical in all respects including ^{1}H nmr., mixed ^{1}H nmr., mpt., mixed mpt., and optical rotation to an authentic sample of (-)-Actinonin. This synthetic sequence provides (-)-Actinonin in 41% overall yield from the (S)-(+) chiral iron acetyl **10**.

Acknowledgements: We thank the S.E.R.C. for support (to G.B.) and gratefully acknowledge Professor W.D.Ollis, University of Sheffield, for the generous gift of (-)-Actinonin.

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(Received in UK 16 September 1988)