Tetrahedron Letters, Vol.22, No.35, pp 3431 - 3432, 1981
Printed in Great Britain

0040-4039/81/353431-02$02.00/0

SYNTHESIS AND ABSOLUTE CONFIGURATION OF A-FACTOR, THE INDUCER OF STREPTOMYCIN BIOSYNTHESIS IN INACTIVE MUTANTS OF *STREPTOMYCES GRISEUS*

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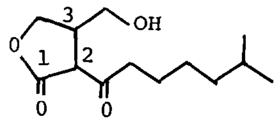
Abstract: The absolute configuration at C-3 of A-factor, 2-(6-methylheptanoyl)-3-hydroxymethyl-4-butanolide 1a, was determined to be S by synthesizing (3S)-(+)-A-factor.

A-factor is known to be the inducer of the biosynthesis of streptomycin in inactive mutants of *Streptomyces griseus*.[1] It also induces the formation of spores in asporophological modifications of *S. griseus*.[1] In 1976,Khokhlov and his co-workers proposed the structure of A-factor to be (2S, 3R)-1 by chemical and spectroscopic studies.[2] The proposed gross structure was confirmed by a synthesis of (±)-1.[3] As a β-keto lactone, A-factor can exist either as a keto-form 1a or as an enol-form 1b. This makes it difficult to apply directly the Klyne lactone sector rule[4] for the clarification of the absolute stereochemistry.[5] We have now synthesized (3S)-(+)-A-factor, establishing the (3S)-stereochemistry of the natural product.

(-)-Paraconic acid 2 was chosen as the starting material, since its absolute configuration was known to be R by its conversion to (S)-(-)-methylsuccinic acid.[6] Reduction of (R)-(-)-1, mp 57-58° ; $[\alpha]_D^{23}$ - 59.6° (MeOH) (lit.[6] mp 48° ; $[\alpha]_D^{30}$ + 49° (MeOH) for (S)-(+)-1), with $H_3B{\cdot}SMe_2$ in THF at 0-5° afforded (S)-(-)-3-hydroxymethyl-4-butanolide 3a, $[\alpha]_D^{22}$ - 46.3° ($CHCl_3$).[7] This was converted to the corresponding TMS ether 3b, bp 140-144°/26mm ; n_D^{23} 1.4368 ; $[\alpha]_D^{23}$ -34.8° (ether), by treatment with $(Me_3Si)_2NH$ and Me_3SiCl in C_5H_5N. The lactone enolate generated by treating 3b with 2.5 eq of $LiNPr^i_2$ in THF at -78° was acylated with 1.05 eq of 6-methylheptanoyl chloride at -78° to give 1c. This was dissolved in EtOH-H_2O (4 : 1) and the solution was heated under reflux for 10min. Subsequent work-up followed by silica gel chromatography afforded (3S)-(+)-A-factor 1a as a waxy solid, $[\alpha]_D^{23}$ - 13.1° ($CHCl_3$) ; CD(MeOH): 283.5 nm ($\Delta\varepsilon$ + 0.699), 221 nm ($\Delta\varepsilon$ + 0.420) [cf. natural A-factor[2] : 285 nm ($\Delta\varepsilon$ + 0.349), 225 nm ($\Delta\varepsilon$ + 0.215)].[8] The CD spectral comparison proved the stereochemical identity of (3S)-(+)-A-factor 1a with the natural product.[9] The CD data also suggested the higher optical purity (ca. x 2) of the synthetic A-factor than that of the natural one. Synthesis of the antipode as well as analogs of A-factor will be reported in due course.



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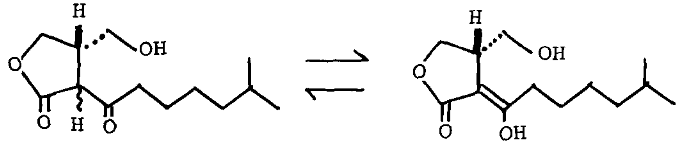
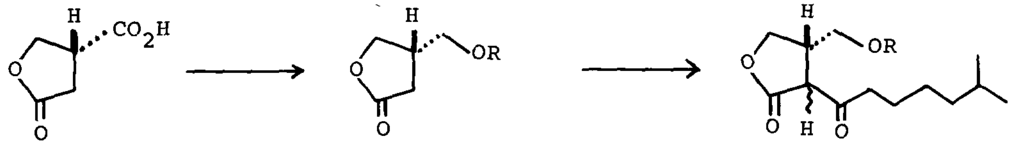


1a 1b



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3a R=H
b R=$SiMe_3$

1a R=H
c R=$SiMe_3$

Acknowledgements - I am grateful to Prof. T. Beppu and Mr. O. Hara, this Department, for bioassay. Thanks are due to Drs. A. Matsuo and M. Horiba, Sumitomo Chemical Co., for CD measurements. I also thank Prof. H. Meguro, Tohoku University, for discussions on the CD data.

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5. The previous stereochemical assignment was based on this rule.[2]
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7. Unfortunately determination of the optical purity of 3a by analyzing itself or its (S)-(-)-MTPA ester (α-methoxy-α-trifluoromethylphenylacetate) was unsuccessful. The hydroxylactone 3a as well as A-factor 1a itself was highly susceptible to racemization in the presence of a base or an acid due to intramolecular transesterification. Careless work-up of 3a or 1a led tc partial or complete racemization.
8. IR (film) ν_{max} 3460 (m), 1765 (s), 1720 (s), 1640 (w), 1170 (s), 1025 (s) cm^{-1} ; UV λ_{max} 283.5 (ε 250), 255 (ε 855) nm ; ^1H-NMR (60 MHz, $CDCl_3$) δ 0.82 (6H, d, J=6Hz), 1.0-2.0 (9H, br), 2.5-3.3 (3H, m), 3.5-3.8 (2H, m), 3.7-4.2 (2H, m); ^{13}C-NMR (25 MHz, $CDCl_3$) δ22.260, 23.167, 26.443, 27.466, 38.348, 39.225, 42.297, 54.758, 61.310, 69.120, 172.728, 203.062; MS : m/z 242.1604 ($M^+ = C_{13}H_{22}O_4$).
9. Since the C-2 position of 1a is readily epimerizable via keto-enol tautomerization, the configuration at that position is uncertain. (2S, 3S)-1a may be more thermodynamically stable than (2R, 3S)-1. Our synthetic (3S)-1a was bioactive at 0.01 μg/disc as the inducer of streptomycin biosynthesis in inactive mutants of Streptomyces griseus.

(Received in Japan 27 May 1981)