Tetrahedron Letters,Vol.25,No.45,pp 5155-5156,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVE SYNTHESIS OF (+)-BLASTMYCINONE

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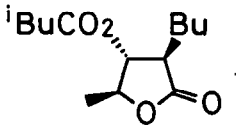
Summary: *(+)-Blastmycinone has been synthesized based on diastereoselective synthesis of (2R,3S)-2-hydroxy-3-(1-propenyl)heptanoic acid by the ester enolate Claisen rearrangement of (R)-(E)-1-methyl-2-heptenyl glycolate and stereoselective reduction of α-hydroxy ketone with $Zn(BH_4)_2$.*

Antimycin A_3 (Blastmycin) (2)[1] is an antibiotic effective against fungi and yeasts. (+)-Blastmycinone (1)[1a,b] obtained by saponification of antimycin A_3 under mild conditions has been synthesized both racemic and optically active forms by several groups.[2] There is, however, no report to synthesize optically active (+)-blastmycinone by a method of the stereocontrolled construction of acyclic systems. In the previous paper[3] from our laboratory, the ester enolate Claisen rearrangement of (*E*)-2-butenyl glycolate has been reported to afford the corresponding *erythro*-2-hydroxy-3-methyl-4-pentenoic acid in high diastereoselectivity. We now report here that the stereoselective synthesis of optically active (+)-blastmycinone (1) was achieved by the rearrangement of (*R*)-(*E*)-1-methyl-2-heptenyl glycolate (5), and followed by the stereoselective reduction of α-hydroxy ketone (8) with zinc borohydride.[4]

The starting material (*R*)-(*E*)-1-methyl-2-heptenyl glycolate (5, $[\alpha]_D^{24}$ +78.8° (c 0.99, $CHCl_3$)) was derived from 2-methyl-1,3-dioxolane-4-one and (*R*)-(*E*)-3-octen-2-ol (4, $[\alpha]_D^{24}$ +1.56° (c 1.02, 1,4-dioxan), 100%E) in 45% yield,[5] which was obtained by reduction of (*R*)-3-octyn-2-ol (3, $[\alpha]_D^{24}$ +35.2° (c 0.93, 1,4-dioxan)) with $NaAlH_2(O\frown\!\!\smile O)_2$ in 94% yield.[6] The alcohol 3 was prepared from optically active 1-methyl-2-heptynyl hydrogen phthalate resolved with D-(+)-α-phenylethylamine. NMR analysis using chiral shift reagent, $Eu(hfc)_3$, indicated that 3 is optically pure.

The ester enolate Claisen rearrangement[3] of 5 gave (2*R*,3*S*)-2-hydroxy-3-(1-propenyl)heptanoic acid (7) (*erythro* : *threo* = 98:2) in 88% yield; $[\alpha]_D^{24}$ -3.82° (c 0.942, $CHCl_3$). This rearrangement proceeds through a chair-like six membered



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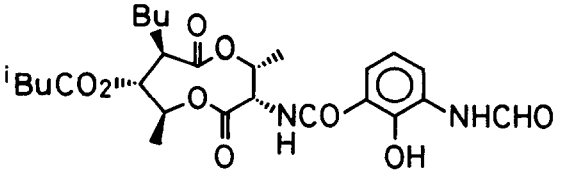

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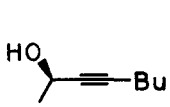
transition state 6 in which methyl group of the asymmetric center occupies more favorable equatorial position than the axial one by a 1,3-diaxial interaction. When carboxylic acid (7) was treated with methyl lithium in ether at -30 °C for 12 h, (3*R*,4*S*)-3-hydroxy-4-(1-propenyl)-2-octanone (8) was obtained in 72% yield; $[\alpha]_D^{24}$ -110° (c 1.06, $CHCl_3$). Reduction of 8 with zinc borohydride ($Zn(BH_4)_2$) in ether at -50 °C for 20 min gave (2*S*,3*R*,4*S*)-4-(1-propenyl)octane-2,3-diol (9) with 97% diastereoselectivity in 90% yield; $[\alpha]_D^{24}$ -16.8° (c 0.98, $CHCl_3$). Protection of diol 9 with 2-methoxypropene and catalytic amount of picric acid at room temperature for 20 h gave (2*S*,3*R*,4*S*)-2,3-isopropylidene-dioxy-4-(1-propenyl)octane (10) in 93% yield; $[\alpha]_D^{24}$ -16.8° (c 0.98, $CHCl_3$). Ozonolysis of 10 followed by dimethyl sulfide work up afforded (2*S*,3*R*,4*S*)-2,3-isopropylidenedioxy-4-formyloctane (11) in 76% yield; $[\alpha]_D^{24}$ +63.3° (c 1.04, $CHCl_3$). Oxidation of aldehyde 11 with the Jones reagent gave carboxylic acid, and successive treatment of carboxylic acid with 2N HCl afforded (-)-blastmycinolactol (12) in 38% yield; $[\alpha]_D^{24}$ -14.2° (c 0.97, MeOH). Finally, treatment of 12 with isovaleric anhydride in pyridine gave (+)-blastmycinone (1) in 75% yield; $[\alpha]_D^{24}$ +11.1° (c 0.97, $CHCl_3$). This value of the optical rotation is almost same as the highest value (+11.5°)[1a] reported for 1, which shows that the ester enolate Claisen rearrangement of 5 proceeds with a high degree of asymmetric transfer, along with a high *erythro*-selectivity.



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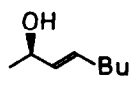

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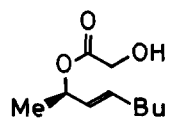

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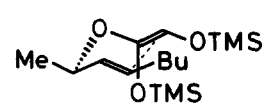

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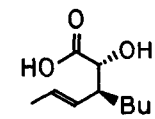

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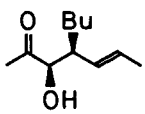

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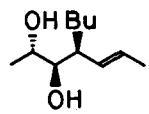

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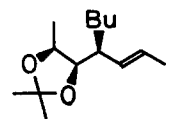

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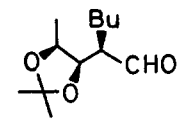

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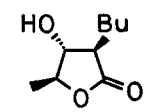

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As mentioned above, total synthesis of natural (+)-blastmycinone with high optical purity was achieved by the ester enolate Claisen rearrangement and the stereoselective reduction with zinc borohydride.

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(Received in Japan 19 July 1984)