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SYNTHESIS OF DEISOVALERYLBLASTMYCIN

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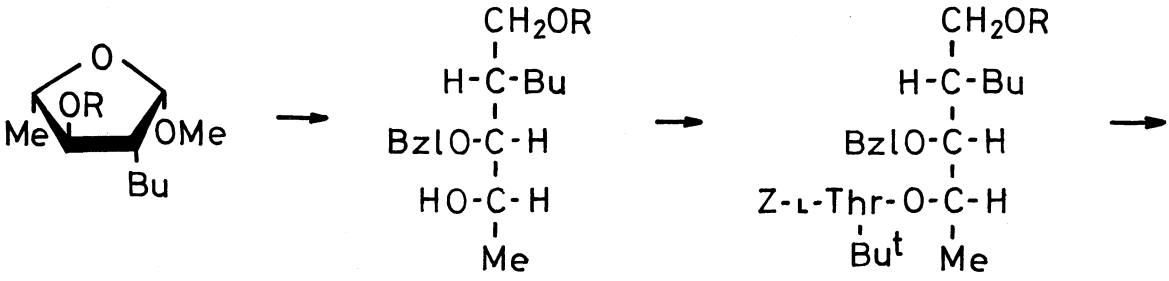
Methyl 3-O-benzoyl-2-C-butyl-2,5-dideoxy-β-L-arabinofuranoside (1) was converted to (2R,3R,4S)-4-(N-benzyloxycarbonyl-L-threonyloxy)-3-benzyloxy-2-butylpentanoic acid (8). Lactonization of 8 was conducted through the 2-pyridylthio ester 9 activated by silver perchlorate to afford the desired dilactone 10 (33% yield), which was transformed to the title compound.

In 1969 Ishiyama et al.[1] announced a new antibiotic, deisovalerylblastmycin from Streptomyces sp. possessing antimicrobial activity against Piricularia oryzae, and based on their structural study it was elucidated that the antibiotic was the de-O-isovalerylated derivative of blastmycin (antimycin A_3), one of the major components of antimycin A complex. Enzymatic transformation of antimycin A(complex) to deacylantimycin A by hog kidney acylase was reported in 1972 by Singh et al.[2] We now wish to describe the synthesis of deisovalerylblastmycin which constitutes a new route for the stereospecific synthesis of antimycin A.

De-O-benzoylation of methyl 3-O-benzoyl-2-C-butyl-2,5-dideoxy-β-L-arabinofuranoside (1)[3] with methanolic sodium methoxide followed by O-benzylation with sodium hydride and benzylbromide in tetrahydrofuran afforded the 3-O-benzyl derivative 2 in 81% yield; $C_{17}H_{26}O_3$*, $[\alpha]_D^{21}$ -98°(c 1.1, $CHCl_3$). Hydrolysis of 2 with 0.2M hydrogen chloride in aqueous dioxane followed by sodium borohydride-reduction gave (2S,3R,4S)-3-O-benzyl-2-butylpentane-1,3,4-triol (3) in 94% yield; $C_{16}H_{26}O_3$*, $[\alpha]_D^{21}$ +1°, $[\alpha]_{365}^{21}$ -18°(c 0.4, $CHCl_3$).

Tritylation of 3 in the usual way afforded quantitatively the 1-O-trityl derivative 4. The remaining secondary hydroxy group in 4 was then acylated with N-benzyloxycarbonyl-O-t-butyl-L-threonine in the presence of N,N'-dicyclohexylcarbodiimide and pyridine in ether to give the ester 5 in 74% yield; $C_{51}H_{61}NO_7$*, $[\alpha]_D^{21}$ +3°, $[\alpha]_{365}^{21}$ +26°(c 0.39, $CHCl_3$). De-tritylation of 5 with 90% aqueous acetic acid afforded the alcohol 6 in 95% yield; $C_{32}H_{47}NO_7$*, $[\alpha]_D^{21}$ +3°, $[\alpha]_{365}^{21}$ +18°(c 0.95,

* Microanalyses support the expected molecular formula shown.

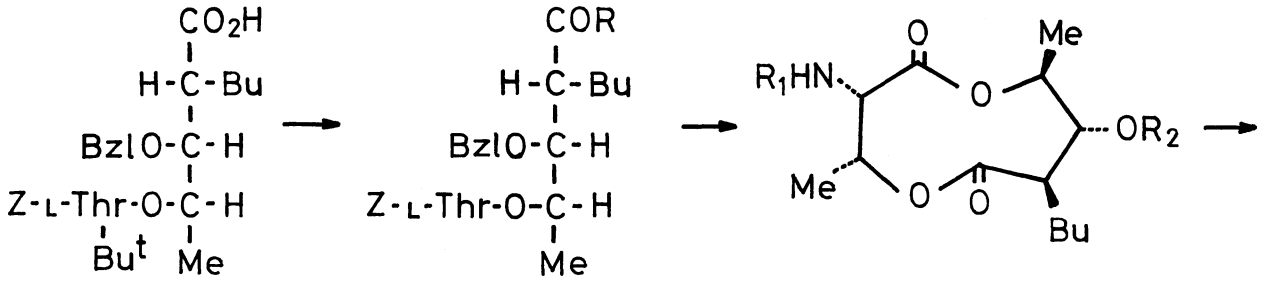


1: R=Bz
2: R=Bzl

3: R=H
4: R=Tr

5: R=Tr
6: R=H

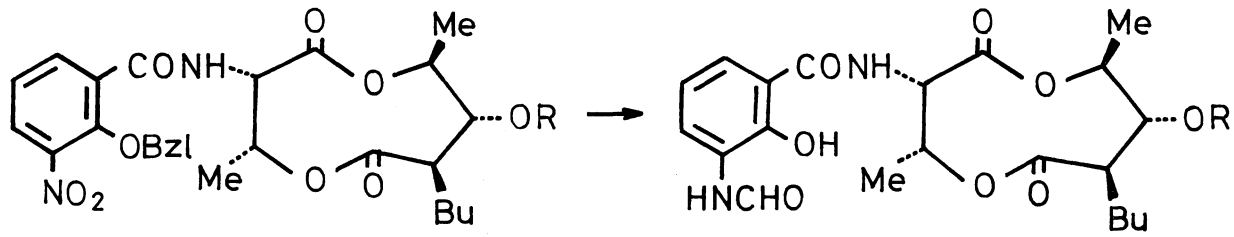
[Bz: C_6H_5CO, Bzl: $C_6H_5CH_2$, Tr: $(C_6H_5)_3C$, Z: $C_6H_5CH_2OCO$]



7

8: R=OH
9: R=S

10: R_1=Z, R_2=Bzl
11: R_1=R_2=H



12: R=H
13: R=Bu^{i}CO

Deisovalerylblastmycin : R=H
Antimycin A_3(Blastmycin): R=Bu^{i}CO

$CHCl_3$). Oxidation of 6 with a solution of chromium trioxide in acetic acid and pyridine[4] gave (2R,3R,4S)-4-(N-benzyloxycarbonyl-O-t-butyl-L-threonyloxy)-3-benzyloxy-2-butylpentanoic acid (7) in 76% yield; $C_{32}H_{45}NO_8$*, $[\alpha]_D^{23}$ +3°, $[\alpha]_{365}^{23}$ +14°(c 2.4, $CHCl_3$).

The t-butyl group of 7 was removed by treatment with trifluoroacetic acid to afford the hydroxyester-acid 8. Lactonization[5] of 8 was effected smoothly by the method of Gerlach et al.[8] through the 2-pyridylthiol ester 9 which was prepared from 8 according to the procedure reported by Mukaiyama et al.[9] using 2,2'-dithiopyridine and triphenylphosphine in benzene and was isolated (85% based on 7) by silica gel column chromatography. To a 0.01M solution[10] of 9 in benzene, was

thus added silver perchlorate[11] under stirring at room temperature. After 30 min the reaction mixture was filtered. The filtrate was evaporated and chromatographed on silica gel to afford (3S,4R,7R,8R,9S)-8-benzyloxy-3-benzyloxycarboxamido-7-butyl-4,9-dimethyl-1,5-dioxacyclononane-2,6-dione (10) (33%) and the hydroxyester-acid 8 (60%) which was again subjected to lactonization via the thiol ester 9 to give an additional amount of 10. The total yield of 10 based on 8 amounted about 33%; $C_{28}H_{35}NO_7$*, mp 118.5-119.5°(needles from ethyl acetate), $[\alpha]_D^{22}$ +53°(c 0.73, $CHCl_3$), m/e 497.2445 (calcd 497.2413), ($CDCl_3$) 1.28(d, 4-CH_3, J=6.8 Hz), 1.43(d, 9-CH_3, J=6.5 Hz), 2.46(m, H-7), 3.46(dd, H-8, $J_{7,8}$=9.5 Hz), 4.65(s, O-$CH_2C_6H_5$), 4.90(dq, H-9, $J_{8,9}$=9.5 Hz), 4.91(dd, H-3, $J_{3,NH}$=9.0 Hz), 5.12(s, $OCH_2C_6H_5$ of Z) and 5.54(dq, H-4, $J_{3,4}$=7.5 Hz), ν_{max}(0.1M in CCl_4) 3432(NH), 1744 cm^{-1} (ester and urethane).

The N,O-protected dilactone 10 was hydrogenolyzed over palladium black in methanol containing a small amount of hydrogen chloride at 3.45×10^5 Nm^{-2} for 1 hr to give the deblocked aminohydroxy-dilactone 11, which was selectively N-acylated with O-benzyl-3-nitrosalicylic acid N-hydroxysuccinimide ester[12] in tetrahydrofuran to afford 12 in 72% yield; $C_{27}H_{32}N_2O_9$*, mp 164.5-165.5°, $[\alpha]_D^{20}$ +35°(c 0.71, $CHCl_3$). O-Acylation of 12 with isovaleric anhydride in pyridine gave the 8-isovalerate (88%). The product was identified by PMR spectroscopy to the intermediate 13[6] which was previously synthesized and converted to the natural antimycin A_3. This fact proved that 10 and 12 have the same configuration as that of the natural antimycin A_3(blastmycin).

Hydrogenolysis of 12 over palladium black in methanol for 20 min followed by N-formylation with p-nitrophenylformate[13] in tetrahydrofuran at room temperature afforded deisovalerylblastmycin in 63% yield; $C_{21}H_{28}N_2O_8$*, mp 188-190°, $[\alpha]_D^{21}$ +37°(c 0.3, MeOH), λ_{max}^{MeOH} nm(ε) 226(27720) and 322(5150), $\lambda_{max}^{0.1MHCl-MeOH}$ 238(9150) and 302(4640), $\lambda_{max}^{0.1MNaOH-MeOH}$ 343(8680), ν_{max}(0.1M in $CHCl_3$) 3412(NH), 1742(lactone), 1694(NHCHO), 1644(ArCONH), 1612(ArH) and 1528 cm^{-1}(ArCONH), δ(acetone-d_6) 1.37(d, 4-CH_3, J=6.5 Hz), 1.40(d, 9-CH_3, J=6.5 Hz), 2.2-2.4(m, H-7), 3.46(dd, H-8, $J_{7,8}$=$J_{8,9}$=9.5 Hz), 4.77(dq, H-9), 5.37(dd, H-3, $J_{3,NH}$=7.8 Hz), 5.64(dq, H-4, $J_{3,4}$=7.3 Hz), 6.92(dd, H-5', $J_{4',5'}$=

Table 1. MIC(mcg/ml) of Synthetic Deisovalerylblastmycin and Antimycin A Complex[15]

Organisms	Deisovaleryl-blastmycin	Antimycin A Complex
Penicillium chrysogenum Q176	> 50	> 50
Candida krusei	> 100	> 100
Trichophyton asteroides 429	> 50	> 50
Piricularia oryzae	1.56	0.05
Pellicularia filamentosa	> 50	6.25

Medium: 1% glucose nutrient agar, 27°C

$J_{5',6'}$=7.8 Hz), 7.78(dd, H-4', $J_{4',6'}$=1.2 Hz), 8.48(dd, H-6') and 8.52(s, ArNHCHO). The synthetic specimen proved to be identical with the natural product[14] in all respects.

Synthetic deisovalerylblastmycin exhibited less antifungal activity against Piricularia oryzae and Pellicularia filamentosa than antimycin A complex (Table 1).

References and Notes

1) T. Ishiyama, T. Endo, N. Otake and H. Yonehara, Abstract Papers, Annual Meeting of the Agricultural and Chemical Society of Japan (Tokyo), p 140, April, 1969.

2) K. Singh, G. Schilling, S. Rakhit and C. Vezina, J. Antibiot. (Tokyo), 25, 141(1972).

3) S. Aburaki, N. Konishi and M. Kinoshita, Bull. Chem. Soc. Japan, 48, 1254(1975).

4) J. C. Sheehan, H. G. Zachan and W. B. Lawson, J. Amer. Chem. Soc., 80, 3349(1958).

5) Lactonization of hydroxyester-acid 8 with trifluoroacetic anhydride in hot benzene[6] was not successful in this case. On the other hand, the cyclization reaction of 8 was attempted by a modification of Corey's method[7]; the crude 2-pyridylthio ester 9 produced from 8 was without isolation diluted with xylene and resulting solution(0.005M) was refluxed for 72 hr under argon atmosphere to afford an intramolecular cyclization product as a homogeneous syrup [13.7%, $C_{28}H_{35}NO_7$*, m/e 497.2405 (calcd 497.2413), $[\alpha]_D^{23}$ 0°(c 1.65, $CHCl_3$)]. The PMR spectrum ($CDCl_3$) of this product was distinguishable in the ring proton coupling constants ($J_{7,8}$=4.0, $J_{8,9}$=9.2 Hz) from that of 10 and this suggested that the product might be the 7-epimer of 10.

6) M. Kinoshita, S. Aburaki, M. Wada and S. Umezawa, Bull. Chem. Soc. Japan, 46, 1279(1973).

7) E. J. Corey and K. C. Nicolaou, J. Amer. Chem. Soc., 96, 5614(1974).

8) H. Gerlach and A. Thalmann, Helv. Chim. Acta , 57, 2661(1974).

9) T. Mukaiyama, M. Araki and H. Takei, J. Amer. Chem. Soc., 95, 4763(1973).

10) Even in higher dilution(0.001M), the yield of the dilactone 10 was not improved.

11) The used silver perchlorate was thoroughly dried over P_2O_5 at 50-60° under reduced pressure (1 Torr) for 10 hr.

12) M. Kinoshita and S. Umezawa, Bull. Chem. Soc. Japan, 43, 897(1970).

13) K. Okawa and S. Hase, ibid., 36, 754(1963).

14) The sample of natural deisovalerylblastmycin was kindly supplied by Prof. Hiroshi Yonehara, Institute of Applied Microbiology, Tokyo University, to whom the authors' thanks are due.

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