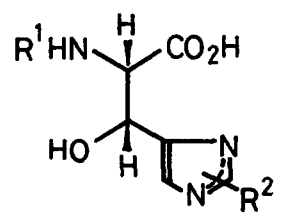
Tetrahedron Letters,Vol.23,No.5,pp 529-532,1982 0040-4039/82/050529-04$03.00/0
Printed in Great Britain

A NEW SYNTHESIS OF DEGLYCO-BLEOMYCIN A2 AIMING AT THE TOTAL SYNTHESIS OF BLEOMYCIN

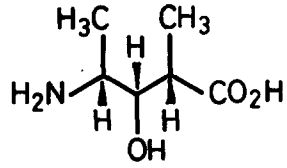
Sei-ichi Saito, Yoji Umezawa, Hajime Morishima,
Tomohisa Takita, Hamao Umezawa*
Institute of Microbial Chemistry
Shinagawa-ku, Tokyo 141, Japan
Masatoshi Narita, Masami Otsuka, Susumu Kobayashi and Masaji Ohno
Faculty of Pharmaceutical Sciences, University of Tokyo
Bunkyo-ku, Tokyo 113, Japan

Summary: An improved route to synthesize deglyco-bleomycin A2, the aglycon of bleomycin A2, aiming at the total synthesis of bleomycin is described. The new route is characterized by the stepwise elongation of the amino acid constituents and the use of a thiol ester obtained by aldol condensation.

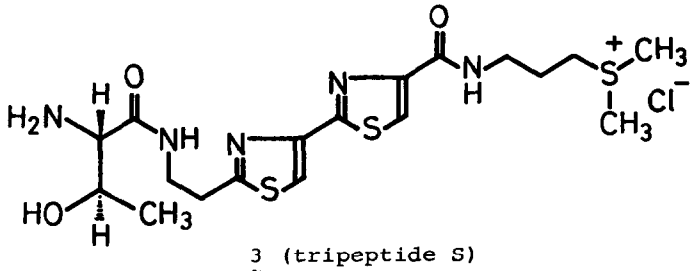
Deglyco-bleomycin A2, the aglycon of bleomycin (BLM) A2, is a hexapeptide consisting of five amino acids and a terminal amine[1]. Deglyco-BLM was found in the culture broth in a trace amount and also isolated from the mild acid hydrolyzate of BLM[2]. The first total synthesis of deglyco-BLM A2[3], achieved by us, was based on the fragment condensation of the dipeptide (1-2) and tripeptide S[3] (3) followed by coupling with pyrimidoblamic acid (4).



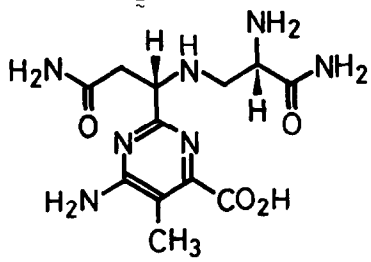
1 R^1 = H, R^2 = H
7 R^1 = Boc, R^2 = Dnp



2



3 (tripeptide S)

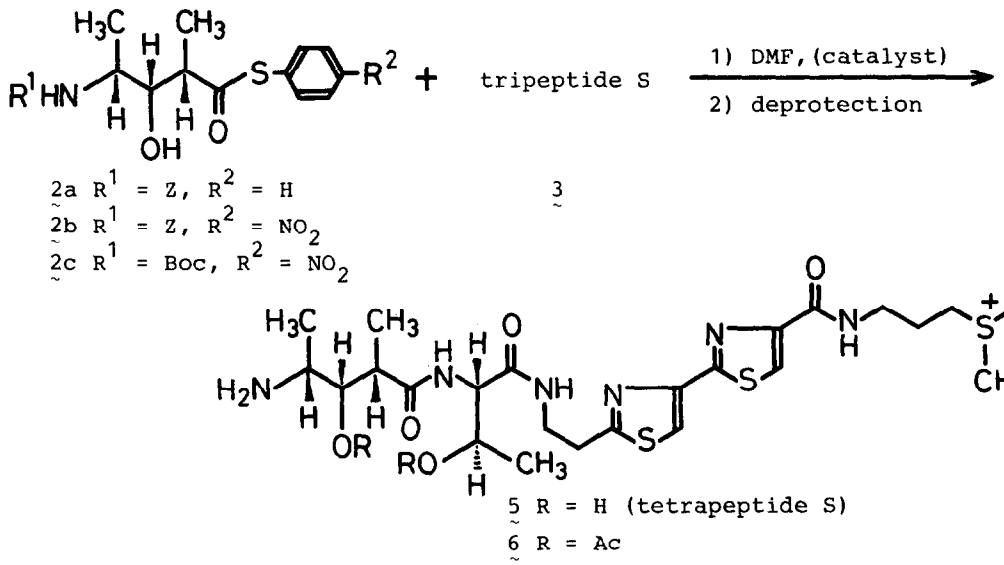


4 (pyrimidoblamic acid)

Although deglyco-BLM A2 thus synthesized was fully characterized and optically pure, the yield in the final condensation was not satisfactory (30% after deprotection and purification) and, moreover, it is hard to prepare a derivative suitable for further elaboration leading to the total synthesis of BLM. We report herein an improved route to deglyco-BLM A2 via the stepwise elongation utilizing a thiol ester of 2 as a key intermediate.

As described in the preceding paper[4], optically pure thiol esters 2a-c were directly obtained by stereoselective aldol condensation using E-vinyloxyboranes. Compounds 2a-c are N-protected active esters of 2 suitable for the peptide synthesis. Thus, these thiol esters were tried to react with tripeptide S. The results are shown in Scheme 1 and Table 1. In the case of (p-nitrophenyl)thio esters 2b and c, the condensation took place smoothly at room temperature without any catalyst, while an elevated temperature and catalytic

Scheme 1



2a R^1 = Z, R^2 = H
2b R^1 = Z, R^2 = NO_2
2c R^1 = Boc, R^2 = NO_2

3

5 R = H (tetrapeptide S)
6 R = Ac

Table 1 Condensation of thiol esters 2a-c and tripeptide S 3.

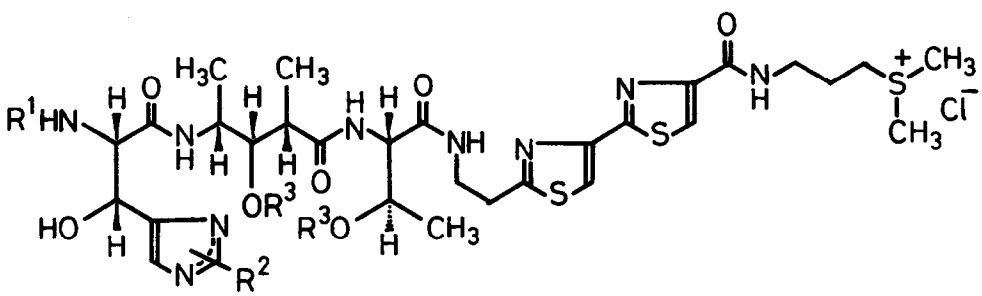
R^1	R^2	catalyst	temp.	time	yield(%)*
Z	H	$Cu(OAc)_2$	40°C	2 days	28
Z	NO_2	—	r.t.	4 hrs.	47
Boc	NO_2	—	r.t.	4 hrs.	53

* Yields after removal of the amino protective group, R^1.

amount of $Cu(OAc)_2$ were needed for the condensation of the phenylthio ester 2a. The resulting Boc- and Z-derivatives of tetrapeptide S were deprotected with 25% HBr-AcOH and CF_3CO_2H, respectively, and were chromatographed on CM-Sephadex C-25, pretreated with 0.05 M pH 7.1 sodium phosphate buffer, developed with a linear gradient of NaCl to give tetrapeptide S (5). The synthetic tetrapeptide S was identical with the natural sample[5] in all respects (TLC, ^{1}H-NMR, and optical rotation[6]).

Treatment of 5 with CH_3COCl in 6N HCl-AcOH (1:1) at room temperature afforded the di-O-acetyl derivative (6) (O-Ac: δ2.74 and 2.49 in D_2O, external TMS reference) in 98% yield. Next, 6 was allowed to react with Boc- and Dnp-masked β-hydroxyhistidine (7)[3] by DCC-HOBt in DMF to give a pentapeptide masked with Boc, Dnp and Ac(X2), (8)[7], in 65% yield after purification by Sephadex LH-20 (developed with MeOH) and Amberlite XT-2 (developed with 50-80% MeOH) chromatographies. The Boc-group of 8 was removed by TFA (almost quantitative) and then allowed to react with Boc-masked pyrimidoblamic acid[8] by DCC-HOBt in DMF to give deglyco-BLM A2 masked with Boc, Dnp and Ac(X2), (10)[7], in 96% yield after purification by the Sephadex and Amberlite chromatographies. To confirm the structure of 10, the protecting groups were removed by two steps: the Dnp- and Ac-groups were first removed by treatment with 0.5N NaOH-MeOH (1:1), followed with TFA to remove the Boc-group. The resulting deglyco-BLM A2 (11) was purified by CM-Sephadex C-25 chromatography as described previously[3]. The synthetic deglyco-BLM A2 thus obtained in 56% yield was identical with the natural sample[2] in all respects (TLC, ^{1}H-NMR, and optical rotation[9]).

This new route to deglyco-BLM A2 not only gave a better overall yield than the previous one[3], but also gave a starting material for the total synthesis of BLM A2 as described in the other paper[10].



8 R^1 = Boc, R^2 = Dnp, R^3 = Ac
9 R^1 = H, R^2 = Dnp, R^3 = Ac
10 R^1 = Boc-pyrimidoblamyl, R^2 = Dnp, R^3 = Ac
11 R^1 = pyrimidoblamyl, R^2 = R^3 = H (deglyco-BLM A2)

References and Notes

1) The terminal amine was counted as one amino acid unit, since it is the decarboxylation derivative of amino acid.

2) Y. Muraoka, M. Suzuki, A. Fujii, Y. Umezawa, H. Naganawa, T. Takita, and H. Umezawa, J. Antibiot., 34, 353 (1981).

3) T. Takita, Y. Umezawa, S. Saito, H. Morishima, H. Umezawa, Y. Muraoka, M. Suzuki, M. Otsuka, S. Kobayashi, and M. Ohno, Tetrahedron Lett., 22, 671 (1981).

4) M. Narita, M. Otsuka, S. Kobayashi, M. Ohno, Y. Umezawa, H. Morishima, S. Saito, T. Takita, and H. Umezawa, Tetrahedron Lett., preceding paper in this issue.

5) Y. Muraoka, T. Takita, K. Maeda, and H. Umezawa, J. Antibiot., 25, 185 (1972).

6) Data for optical rotations, $[\alpha]_{365\ nm}^{20-21°}$ (c 0.5-0.75, 0.1N HCl) of tetrapeptide S are as follows. Natural sample, -52°; sample from 2a, -54°; sample from 2b, -53°; sample from 2c, -51°.

7) The compound is only stable under acidic and dark conditions. Therefore, the structure and purity were ensured only by ^{1}H-NMR in AcOH-d_4.

8) Y. Umezawa, H. Morishima, S. Saito, T. Takita, H. Umezawa, S. Kobayashi, M. Otsuka, M. Narita, and M. Ohno, J. Am. Chem. Soc., 102, 6630 (1980).

9) Natural sample, $[\alpha]_D^{24}$ (c=0.5, 0.1N HCl) -15°; synthetic sample, $[\alpha]_D^{22}$ (c=0.5, 0.1N HCl) -15°.

10) T. Takita, Y. Umezawa, S. Saito, H. Morishima, H. Naganawa, H. Umezawa, T. Tsuchiya, T. Miyake, S. Kageyama, S. Umezawa, Y. Muraoka, M. Suzuki, M. Otsuka, M. Narita, S. Kobayashi, and M. Ohno, Tetrahedron Lett., preceding paper in this issue.

(Received in Japan 17 October 1981)