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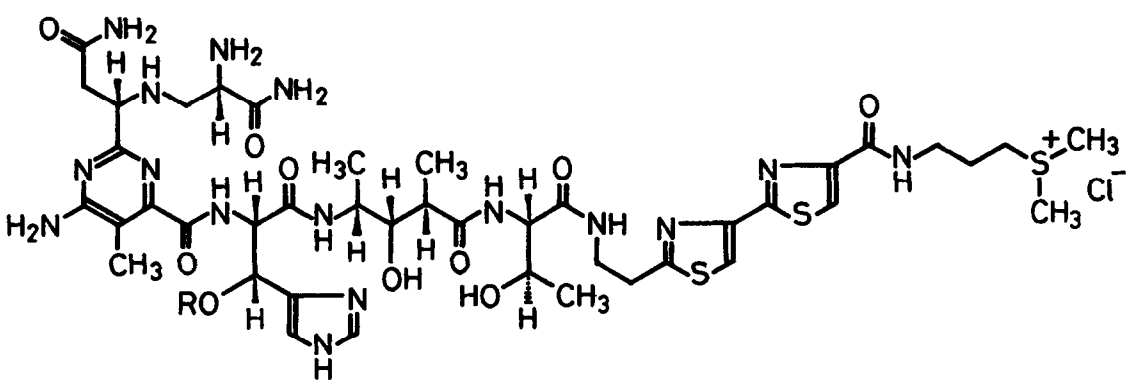
STEREOSELECTIVE SYNTHESIS OF (2S,3S,4R)-4-AMINO-3-HYDROXY-2-METHYL-PENTANOIC ACID, AN AMINO ACID CONSTITUENT OF BLEOMYCIN, BY ALDOL CONDENSATION[1)]

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

Summary: (2S,3S,4R)-4-Amino-3-hydroxy-2-methylpentanoic acid, a novel amino acid constituent of bleomycin, has been synthesized stereoselectively through aldol condensation of (R)-2-aminopropionaldehyde derivatives and E-vinyloxy-boranes.

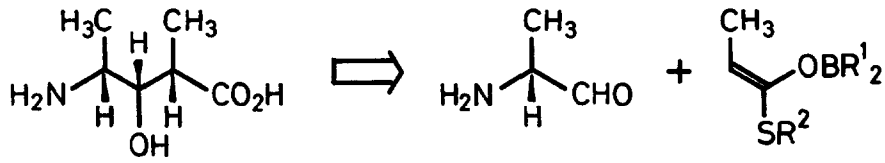
Bleomycin (BLM) is an antitumor antibiotic clinically used in the treatment of squamous cell carcinoma, malignant lymphoma and testis tumors. BLM consists of a linear hexapeptide and disaccharide (Fig. 1)[2)]. Although the syntheses of the aglycon[3)] and disaccharide[4)] moieties have already been achieved, the successful achievement of the total synthesis of BLM was largely dependent upon the availability of each fragment in proper configurations and suitable forms. (2S,3S,4R)-4-Amino-3-hydroxy-2-methylpentanoic acid (1)

Figure 1



Bleomycin A2: R = 2-O-(3-O-carbamoyl-α-D-mannopyranosyl)-α-L-gulopyranosyl
Deglyco-bleomycin A2: R = H

Scheme 1



1 2 3

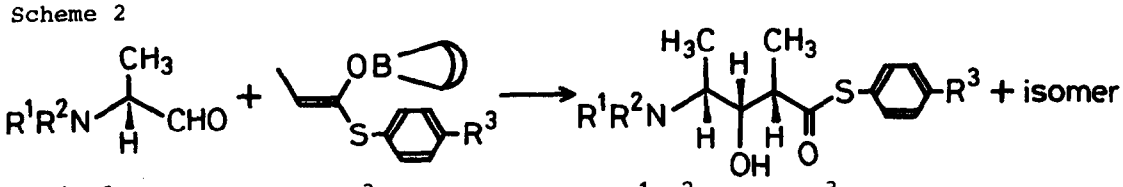
having three consecutive asymmetric centers was not easily prepared in the optically pure form by the routes reported previously. The first synthesis of 1[5], in which the corresponding 3-keto derivative was reduced by sodium borohydride, was not stereoselective, and afforded a mixture of the stereoisomers. An alternate synthesis was carried out by the transformation from L-rhamnose[6] via conventional multi-step reactions, yielding 1 in about 10% overall yield. Thus, a new facile and stereoselective synthesis of 1 was requested.

The most straightforward construction of 1 can be achieved by aldol condensation of chiral aldehyde 2 and boron enolates 3 as depicted in Scheme 1. Two new chiral centers at C-2 and C-3 can be created in a stereoselective manner[7]. Another advantage of this synthesis is: if a boron enolate derived from a thiol ester is used in the aldol condensation, the product will be used directly as an active ester in the bleomycin synthesis. We will report here a facile and stereoselective synthesis of 1 by aldol condensation of a chiral aldehyde and vinyloxyborane derived from thiol ester.

(R)-2-Aminopropionaldehyde derivatives 2a~c were prepared from D-alanine as follows. The amino group was protected according to the usual procedure[8] (Pht, 85%; Z, 88%; Boc, 85% yields), and then, the carboxyl group was transformed into aldehyde by following procedures. Pht-D-alanine was converted into the acyl chloride ($SOCl_2$; quantitative yield), which was subjected to Rosenmund reduction (H_2, Pd-C; 60% yield) to give 2a[9] (mp, 98°C, $[\alpha]_D^{20}$ +38.4° (c 2.2, C_6H_6)). Z- and Boc-D-alanine were converted into the corresponding 3,5-dimethylpyrazolides[10] (3,5-dimethylpyrazole, DCC; Z, 79%; Boc, 95% yields), which were subjected to mild reduction ($LiAlH_4$, THF, -20°C) to give 2b[9] and 2c[9,11] (2b: 95% yield; oily; $[\alpha]_D^{20}$ -46.6°, c 1.76, $CHCl_3$) (2c: 85% yield; mp, 88°C; $[\alpha]_D^{20}$ -43.2°, c 1.05, $CHCl_3$). E-Vinyloxyboranes 3a and 3b were prepared from S-phenyl propanethioate (for 3a) or S-p-nitrophenyl propanethioate (for 3b), 9-BBN triflate, and diisopropylethylamine according to Masamune's procedure[7a].

Aldol condensation are illustrated in Scheme 2 and the results are summarized in Table 1. The combined yield of the aldol product 4a, 4b, 4c, 4d or 4e[9,12] and their corresponding isomer was generally good. By using phenylthio E-vinyloxyborane 3a, the synthesis of 4 with the excellent yield was achieved under a kinetically controlled condition (0°C, 30 min). The high stereoselection can be rationalized by the commonly accepted six-membered ring transition state[7b,13]. Stereochemistry of the aldol products 4a-e was shown to be the

Scheme 2



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

3a R^3 = H
3b R^3 = NO_2

4a R^1,R^2 = Pht; R^3 = H
4b R^1,R^2 = Z,H; R^3 = H
4c R^1,R^2 = Boc,H; R^3 = H
4d R^1,R^2 = Z,H; R^3 = NO_2
4e R^1,R^2 = Boc,H; R^3 = NO_2

5

Table 1. Aldol condensation of (R)-aldehydes (2a-c) with vinyloxyboranes (3a,b)

R^1,R^2	R^3	Temp.	Time	Combined yield (%)	Ratio* 4:5
Pht	H	r.t.	ovn.	60	7:1
Pht	H	0°C	30 min.	70	8:1
Z,H	H	r.t.	ovn.	77	20:1
Z,H	H	0°C	30 min.	60	35:1
Boc,H	H	0°C	30 min.	62	>20:1
Z,H	NO_2	0°C	30 min.	60	10:1
Boc,H	NO_2	0°C	60 min	64	8:1

*Isolated by chromatography on silica gel (eluted with n-hexane:AcOEt=5:1)

desired (2S,3S,4R) configuration by following evidences. Compounds 4a-e showed coupling constants $J_{2,3}$= 5Hz, indicating 2,3-syn relationships[14]. Thiol esters, 4b and 4e, were hydrolyzed by treatment with $Hg(CF_3CO_2)_2$ in CH_3CN (r.t., overnight) to give the corresponding free carboxylic acids, which exhibited $J_{2,3}$=2∿3Hz[14]. These aldol products were treated with 2N HCl (reflux, 7 hr) to give 1, identical with the natural authentic sample on HPTLC (Rf 0.33, Merck HPTLC plates, Art 5628, developed with BuOH:AcOH:H_2O=4:1:2). Finally, the configuration of the main aldol products was confirmed by successful synthesis of tetrapeptide S[15] as described in the following paper[16].

The result described here contributed to the improved synthesis of deglyco-BLM A2 (Fig. 1)[16] and the first total synthesis of BLM A2[17] as reported in other papers.

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References and Notes

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