Tetrahedron Letters,Vol.24,No.44,pp 4805-4808,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

(2S,3S,4R)-4-AMINO-3-HYDROXY-2-METHYLPENTANOIC ACID. ENANTIOSELECTIVE SYNTHESIS OF AN AMINO ACID CONSTITUENT OF BLEOMYCIN.

Robert M. DiPardo and Mark G. Bock*
Merck Sharp & Dohme Research Laboratories
West Point, Pennsylvania 19486

SUMMARY: (2S,3S,4R)-4-Amino-3-hydroxy-2-methylpentanoic acid has been synthesized through acylation of a chiral enolate and subsequent stereoselective reduction.

The antitumor antibiotic bleomycin A_2, consisting of a linear hexapeptide and disaccharide (Fig.1), has been the focus of intense chemical efforts culminating in a total synthesis recently achieved by Umezawa and coworkers.[1] Despite the formidable array of attendant functionality, antithetic analysis of bleomycin A_2 reveals several strategic bond cleavages which yield more readily accessible fragments (cf. Fig. 1). Of these, (2S,3S,4R)-4-amino-3-hydroxy-2-methylpentanoic acid (AHMPA) 1 emerges as the linchpin in a convergent synthetic strategy which makes its availability in high enantiomeric purity desirable. The recent stereoselective synthesis of 1 by Ohno, et al.,[2] requiring separation of diasteriomeric aldol products, prompts disclosure of our own work in this area.[3]

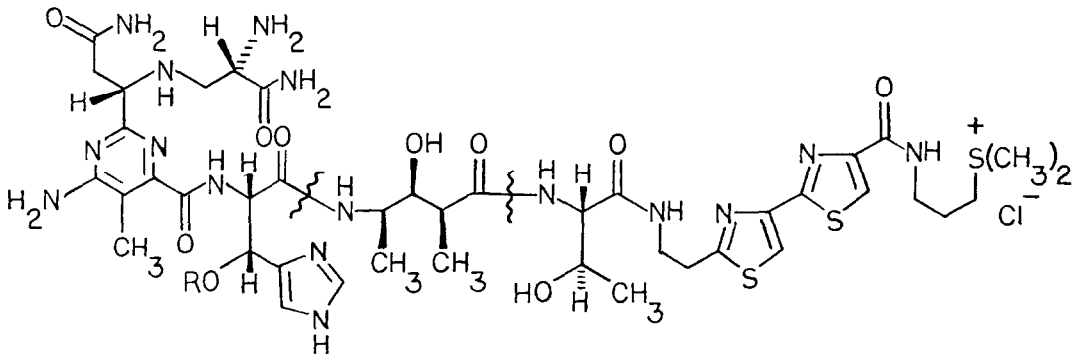
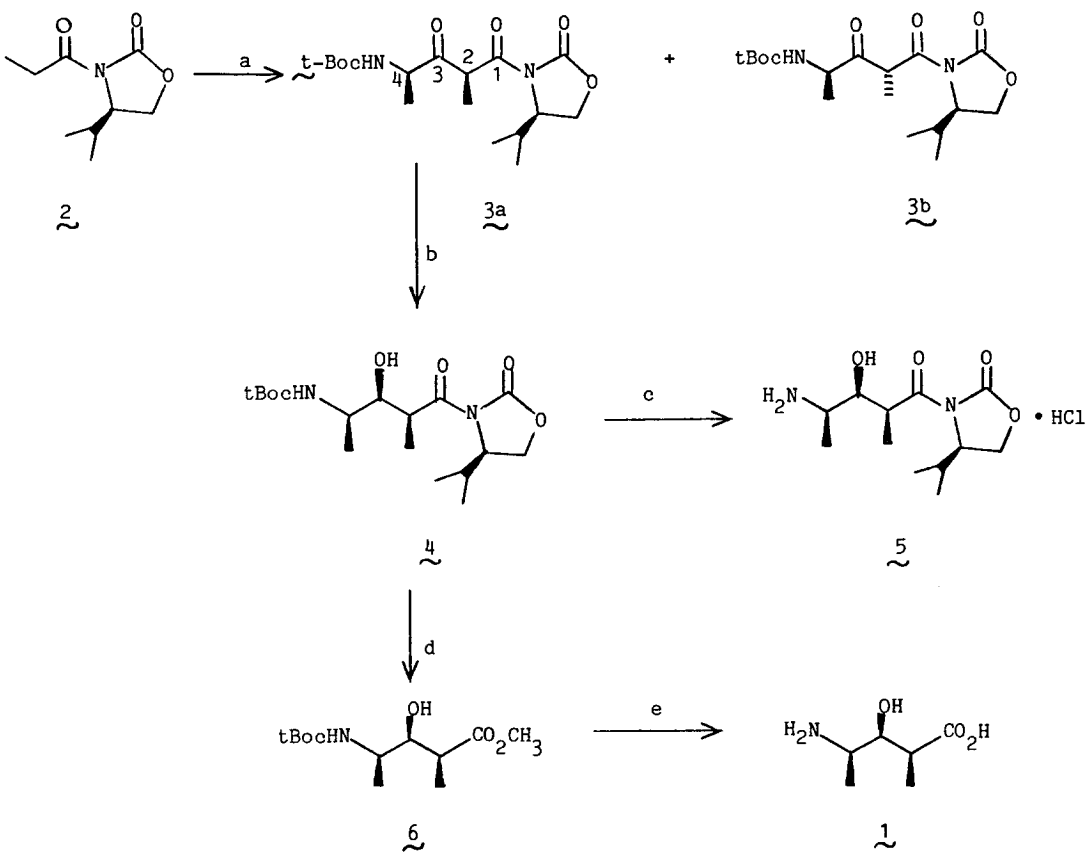


Figure 1. Bleomycin A_2: R = 2-O-(3-O-carbamoyl-α-D-mannopyranosyl)-β-L-gulopyranosyl; Deglycobleomycin A_2: R = H.

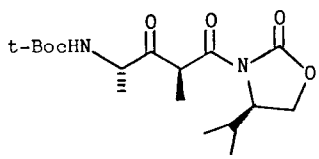
The present method derives from a consideration of the practical methodology currently available for assembling a carbon framework with three adjacent asymmetric centers. In this context, the development by Evans of a series of remarkably stereo-regulated reactions via chiral enolates guided our

Scheme I

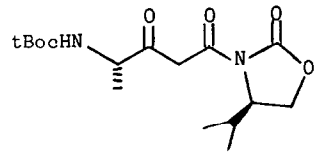


a) LDA, THF, -78 °C, 2 hr, (tBoc-D-Ala)$_2$O; b) Zn(BH$_4$)$_2$, Et$_2$O, -25 °C, 0.5 hr; c) 2N HCl, dioxane or HCl (g), EtOAc; d) 1N NaOMe, MeOH, 0 °C, 5 min; e) 2N HCl, 55 °C, 5 hr.

approach (Scheme I).[4] Metallation of the N-acyloxazolidinone 2[5] with lithium diisopropylamide (THF, -78 °C, 2 hr) afforded the corresponding lithium enolate which when reacted with t-Boc-D-alanine anhydride (inverse addition) yielded crystalline ketone 3a in 78% yield (70% conversion).[6] HPLC analysis[7] of the crude product mixture revealed 3a to be the predominant diasteriomer formed (<1% of 3b).[8] This result is consistent with the alignment of the chelated (Z)-lithium enolate of 2 with the acylating agent such that the latter is situated trans to the isopropyl group. As anticipated, the resident chirality of the enolate overrides that of the anhydride and accordingly determines the sense of diastereoface selection.[9] Ketone 3a was then reduced diastereoselectively with freshly prepared zinc borohydride (Et_2O, -25 °C) to give the erythro-2S,3S,4R-alcohol 4 (95%).[6,10] The stereoselectivity in this process was again exceedingly high as less than 1% of the corresponding threo-2S,3R,4R-isomer could be detected.[7] That it is the 2-position in 3a (not the 4-position or chiral center on the oxazolidinone ring) which predetermines the configuration of the 3-hydroxyl group in 4 was demonstrated by subjecting ketones 7[11] and 8[11] to identical reduction conditions (vide supra) (Fig. 2). Reduction of 7 yielded the corresponding 2S,3S,4S-alcohol[6] in



7



8

Figure 2

diasteriomeric purity comparable to 4, whereas reduction of 8 afforded a mixture of 3S and 3R-alcohols. Alcohol 4 can be elaborated at both termini in either order. Thus, brief exposure of 4 to HCl (gas, EtOAc or 2N aq., dioxane) gave the amine salt 5[6] (>90%); alternatively, treatment of 4 with sodium methoxide (dry CH_3OH, 0 °C, 5 min) afforded the protected amino acid ester 6 (60-72%).[6] Pmr analysis of 6 confirmed the syn relationship between the 2-methyl and 3-hydroxyl groups ($J_{2,3}$ 5.15 Hz).[12] Conversion of 6 with hydrochloric acid gave the title compound 1 (>95%) as its salt whose structure and purity were rigorously established.[6]

Acknowledgments

We thank Messrs. J. P. Moreau and C. F. Homnick for elemental and chromatographic analyses and Drs. D. W. Cochran and B. E. Evans for useful discussions. We extend our appreciation to Prof. S. Danishefsky for his suggestions and to Drs. D. F. Veber and P. S. Anderson for their guidance and encouragement throughout the course of these studies.

References and Notes

(1) T. Takita, Y. Umezawa, S. Saito, H. Morishima, H. Naganawa, H. Umezawa, T. Tsuchiya, T. Miyake, S. Kageyama, S. Umezawa, M. Otsuka, M. Narita, S. Kobayashi, and M. Ohno, Tetrahedron Lett., (1982) 23, 521. For some outstanding contributions to this area by the Hecht group, see; W. K. Hagmann, F. Z. Basha, M. Hashimoto, R. B. Frye, S. Kojo, and S. M. Hecht, J. Org. Chem., (1981) 46, 1413 and references cited therein.

(2) M. Narita, M. Otsuka, S. Kobayashi, M. Ohno, Y. Umezawa, H. Morishima, and S. Saito, ibid., (1982) 23, 525.

(3) For other syntheses of AHMPA see: (a) T. Ohgi and S. M. Hecht, J. Org. Chem., (1981) 46, 1232. (b) M. D. Levin, K. Subrahamanian, H. Katz, M. B. Smith, D. J. Burlett, and S. M. Hecht, J. Amer. Chem. Soc., (1980) 102, 1452. (c) T. Takita and H. Umezawa, J. Antibiot. (Tokyo), (1974) 27, 356.

(4) (a) D. A. Evans, 183rd Amer. Chem. Soc. National Meeting, Las Vegas, Nevada, March 30, 1982. (b) D. A. Evans, Aldrichimica Acta, (1982) 15, 21. (c) D. A. Evans, M. D. Ennis, and D. J. Mathre, J. Amer. Chem. Soc., (1982) 104, 1737; and references cited therein.

(5) Prepared from D-valine in three steps according to D. A. Evans, J. Bartroli, and T. L. Shih, J. Amer. Chem. Soc., (1981) 103, 2127.

(6) All compounds prepared during the course of this study were fully characterized spectroscopically and had acceptable combustion analyses (± 0.25%). Reaction conditions were not optimized and yields refer to isolated products. Selected PMR data: 3a, (MeOH-d_4): 0.90 and 0.93 (6H, 2d, J = 7), 1.27 and 1.30 (6H, 2d, J = 8), 1.45 (9H, s), 2.38 (1H, m), 4.32 (2H, m), 4.36 (1H, q, J = 7), 4.43 (1H, m), 4.89 (1H, q, J = 7). 4, (MeOH-d_4): 0.89 and 0.93 (6H, 2d, J = 7), 1.14 and 1.17 (6H, 2d, J = 7), 1.43 (9H, s), 2.31 (1H, m), 3.62 (1H, m), 3.75 (1H, dd, J = 5,7), 3.96 (1H, p, J = 7), 4.31 (2 H, m), 4.49 (1 H, m), 6.1 (1H, d, J = 8). 5, (MeOH-d_4): 0.87 and 0.94 (6H, 2d, J = 7), 1.24 and 1.29 (6H, 2d, J = 7), 2.29 (1 H, m), 3.3 (1H, obs. by solvent), 3.38 (2 H, m), 4.34 (2H, m), 4.47 (1H, m). 6, ($CDCl_3$): 1.18 and 1.27 (6H, 2d, J = 7), 1.44 (9H, s), 2.67 (1H, dq, J = 5, 7), 3.0 (1H, brs), 3.71 (3 H, s), 3.74 (2H, m), 4.6 (1H, brd, J = 9). 1, (D_2O): 1.26 and 1.29 (6H, 2d, J = 7), 2.59 (1H, dq, J = 9.5, 7), 3.53 (1H, dq, J = 3, 7), 3.90 (1H, dd, J = 3, 9.5).

(7) Waters C-18 column, acetonitrile-trimethylaminephosphate buffer (pH 3.2).

(8) Compound 3a does not racemize on brief exposure to base (e.g. diisopropylethyl amine). However, we have detected traces of another diasteriomer (TLC) after prolonged standing of 3a at room temperature (>4 weeks).

(9) Reference 4b; note that the 2S,3S-configuration of 4 is opposite that observed for aldol condensations using chiral boron enolates (reference 5).

(10) T. Nakata and T. Oishi, Tetrahedron Lett., (1980) 21, 1641.

(11) Prepared in a manner similar to 3a.

(12) See reference 2 and references cited therein.

(Received in USA 18 July 1983)