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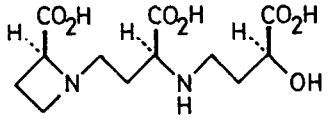
SYNTHESIS OF THE SERINE EQUIVALENT, (2R) AND (2S)-AMINO-3-BUTENOL DERIVATIVES. SYNTHETIC APPROACHES TO THE METAL CHELATING POLY-AMINO ACID, "ASPERGILLOMARASMINE A"

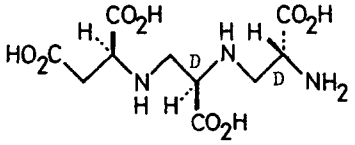
Yasufumi Ohfune* and Natsuko Kurokawa
Suntory Institute for Bioorganic Research,
Shimamoto-cho, Mishima-gun, Osaka 618, Japan

Summary: Chiral synthons, equivalent to the C_3 amino acid serine, were synthesized in both (2R) and (2S) form from D or L-methionine respectively; Utilization of this synthon in the construction of metal chelating poly-amino acid aspergillomarasmine A skeleton is presented.

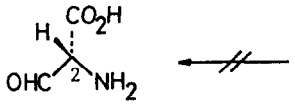
Poly-amino acids, in which amino acid moieties are connected by an N-alkyl bond, have received considerable attention owing to their biological and metal chelating activities.[1] Synthetic studies of mugineic acids(i.e., 2'-deoxymugineic acid(1)) constructed from three C_4 amino acid units have been reported by us[2] and Nozoe[3] independently, using the reductive amination method with sodium cyanoborohydride($NaBH_3CN$).[4] However, poly-amino acids containing a C_3 amino acid (serine) moiety such as aspergillomarasmine A(2),[5] isolated from Aspergillus fluvas oryzae, have not, as yet, been synthesized due to the difficulty of connecting this unit to N-alkyl groups in optically pure form. The synthesis of 2 by employment of the same method as above requires condensation of an amine moiety with 2-amino malonic half aldehyde 3 which is likely to racemize and thus lead to formation of a diastereomeric mixture. Accordingly, a C_3 amino acid equivalent had to be developed for the synthesis of 2. Thus, the (2R) and (2S)-amino-3-butenol derivatives of type 4 were employed as the masked serine moiety for the synthesis of 2. We describe here an efficient synthesis of 4 and approaches to the synthesis of aspergillomarasmine A(2).



2'-Deoxymugineic acid (1)



Aspergillomarasmine A (2)



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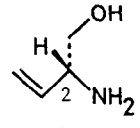
D-Serine



4

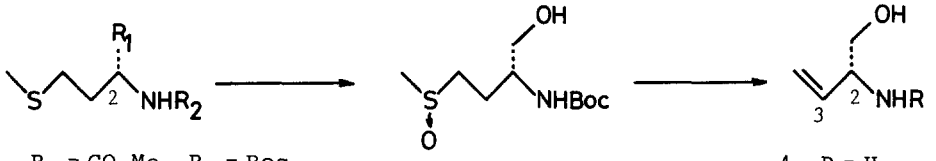
L or D-Methionine was used as starting material because of the availability of both enantiomers and the presence of a functional group which is convertible to a double bond. Esterification(CH_2N_2/ether) of N-t-butoxycarbonyl(t-Boc)-D-methionine to 5[6][oil, $[\alpha]_D$ -25.5°(c 2.0, $CHCl_3$)] followed by reduction($LiAlH_4$/THF, 0°C, 1 h, room temperature, 1 h) afforded the amino alcohol 6[6,7] in 89% yield; mp 47.5~48.5°C, $[\alpha]_D$ +13.7°(c 2.5, $CHCl_3$). No racemization occurred as ascertained by conversion of 6 into the (+)-N,O-diMTPA[α,α-methoxy-trifluoromethyl-phenylacetic acid(MTPA)[8] amide and ester] compound 7b[(i) CF_3CO_2H/CH_2Cl_2, (ii) Dowex 50W x 4/1N NH_3, (iii) (+)-MTPACl/CCl_4/pyridine]; oil, $[\alpha]_D$ +36.4°(c 3.2, $CHCl_3$). Namely, comparison of its 360MHz ^1H NMR with that of the corresponding derivative prepared from dl-methionine clearly showed that two sets of signals were completely separated in the latter, and indicated 7b was a single diastereomer.[9] Oxidation of 6[$NaIO_4$/MeOH-H_2O(2:1), 91%] to the sulfoxide 8[6] was followed by a thermal elimination(o-dichlorobenzene/5 equiv NaOAc[10], 170°C, 20 h) to provide optically pure (2R)-N-t-Boc-amino-3-butenol(4a) in 65% yield; mp 36~37°C, $[\alpha]_D$ +29.0°(c 1.6, $CHCl_3$); ^1H NMR($CDCl_3$) δ1.43(s, t-BuO), 3.66(broad s, 1-CH_2O), 4.22(m, 2-H), 4.84(d, J=7Hz, NH), 5.15~5.36(m, AB part of ABX, 4-CH_2), 5.80(ddd, X part of ABX, J=5, 10, 16Hz, 3-H); MS(CI method), m/z 188$(M+H)^+$. (2S)4b[6] was synthesized in a similar manner; mp 36.5~37.5°C, $[\alpha]_D$ -29.0°(c 2.5, $CHCl_3$). The N-benzyloxycarbonyl(Z) compounds (2R)4c[6] and (2S)4d[6] were prepared from the corresponding N-Z-methionine, respectively; (i) CH_2N_2, (ii) $LiAlH_4$/THF, 91%, (iii) $NaIO_4$, 96%, (iv) o-dichlorobenzene, 170°C, 66%. (2R)4c; mp 51~52.5°C, $[\alpha]_D$ +32.3°(c 2.4, $CHCl_3$); ^1H NMR($CDCl_3$) δ5.05(s, CH_2Ph), 5.17~5.35(m, AB part of ABX, 4-CH_2), 5.80(ddd, X part of ABX, J=5, 8, 14Hz, 3-H), 7.28(s, Ph). (2S)4d; mp 52~53.5°C, $[\alpha]_D$ -32.1°(c 3.1, $CHCl_3$).

The serine equivalent 4a obtained in this manner was converted into aldehyde 3a(oil) by ozonolysis(MeOH, -78°C/dimethylsulfide, -78°C, 3 h, room temperature, 1 h), which upon reductive coupling($NaBH_3CN$/MeOH, 0°C, 3 h, room temperature, 14 h) with 4 provided the desired adduct 9. Protection of the imino group with a t-Boc group(di-t-butyl dicarbonate/0.3 equiv triethylamine/THF, room temperature, 40 h) gave 10[6][oil, $[\alpha]_D$ +2.1(c 1.0, $CHCl_3$); ^1H NMR($CDCl_3$) δ1.40(s, t-BuO), 1.44(s, t-BuO), 5.04~5.32(m, AB part of ABX, 4-CH_2), 5.84(ddd, X part of ABX, J=6, 10, 17Hz, 3-H); MS(CI method), m/z 361$(M+H)^+$], which upon ozonolysis and coupling with L-aspartic acid moiety 11($NaBH_3CN$/MeOH, 0°C, 3 h, room temperature, 14 h)[12] afforded the triamino acid moiety 12[6] in 64% yield(from 10; amorphous solid). It was necessary for the two hydroxyl groups in 12, constructed by two consecutive reductive aminations, to be oxidized for the synthesis of aspergillomarasmine A (2). Several attempts of this oxidation are described. The imino group of 12 was protected(di-t-butyl dicarbonate/0.3 equiv tiethylamine, room temperature, 40 h) and the benzyl group was removed(H_2/Pd-C/EtOH, room temperature, 14 h) to give the tri-N-t-Boc compound 14[6][91% from 12; amorphous solid, $[\alpha]_D$ +11.3(c 0.8, $CHCl_3$)], which was treated with various oxidizing reagents; however, this

resulted in either recovery of starting material or formation of a complex mixture. Finally, oxidation with $KMnO_4$ (4 equiv NaOH/H_2O, room temperature, 3 h) proceeded in good yield to afford a single triacid, whose structure has not been unambiguously determined, but appears to be either 15a or 15b.[13] However, one of hydroxymethyl groups(C-2' or C-2") remained unchanged probably due to steric hindrance.

Conversion of 14 to 2 by changing the N-protecting group and employment of chiral synthons 4a~4d in the synthesis of nitrogen containing natural products are in progress.

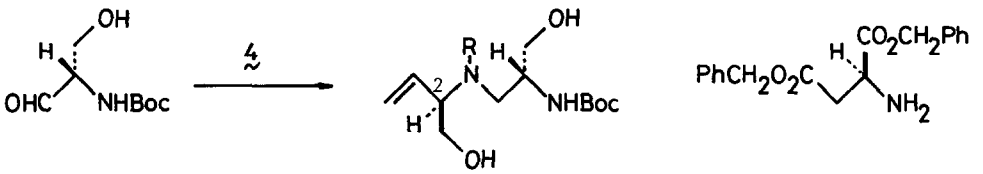
ACKNOWLEDGEMENT: We thank Prof. Koji Nakanishi for generous discussions and encouragement during this work.



5 $R_1 = CO_2Me$, R_2 = Boc
6 $R_1 = CH_2OH$, R_2 = Boc
7a $R_1 = CH_2OH$, R_2 = H
7b $R_1 = CH_2OMTPA$, R_2 = MTPA

8

4 R = H
(2R) 4a R = Boc
(2S) 4b R = Boc
(2R) 4c R = Z
(2S) 4d R = Z



3a

9 R = H
10 R = Boc

11

12 $R_1 = CH_2Ph$, R_2 = H
13 $R_1 = CH_2Ph$, R_2 = Boc
14 R_1 = H, R_2 = Boc

15a $R_1 = CH_2OH$, $R_2 = CO_2H$
15b $R_1 = CO_2H$, $R_2 = CH_2OH$

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6. Satisfactory spectroscopic data as well as elementary analytical data were obtained for this compound.
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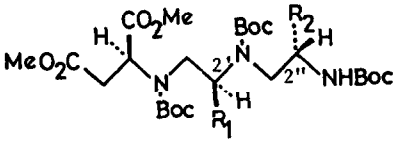
9. 360MHz ^{1}H NMR($CDCl_3$) of the (+)-N,O-diMTPA compound 7b; δ1.99(s, CH_3S), 2.37(t, J=7.2Hz, 4-CH_2S), 3.30(q, J=2.0Hz, CH_3O), 3,53(q, J=1.7Hz, CH_3O). Signals of the diastereomer corresponding to 7b; δ2.07(s, CH_3S), 2.47(dt, J= 7.2, 14.1Hz, 1H of 4-CH_2S), 2.53(dt, J=7.2, 14.1Hz, 1H of 4-CH_2S), 3.27(q, J=2.0Hz, CH_3O), 3.45(q, J=1.7Hz, CH_3O).
10. This reaction required some trapping agent, othewise t-Boc group was cleaved and the yield was poor(~30%).
11. (2R)-N-Z-amino-3-butenol 4c and (2S) 4d were prepared alternatively from their corresponding N-t-Boc-2-amino-3-butenol; (i) CF_3CO_2H/CH_2Cl_2, (ii) Dowex 50W x 4/1N NH_3, (iii) Benzyloxycarbonyl chloride/NaOH-H_2O.
12. Prepared from N-t-Boc-L-aspartic acid in two steps: (i) 2 equiv KOH/$PhCH_2Br$/DMF, 90%, (ii) CF_3CO_2H/CH_2Cl_2.
13. One of the hydroxymethyl groups(C-2' or C-2") was oxidized selectively to 15a or 15b. This was ascertained by converting to the trimethyl 16a or 16b (CH_2N_2); oil; ^{1}H NMR($CDCl_3$) δ1.42(2, 2 x t-BuO), 1.47(s, t-BuO), 3.78(s, CH_3O), 3.80(s, CH_3O), 3.82(s, CH_3O); MS(SIMS), m/z 636$(M+H)^+$. While C-2' position seemed to be more hindered, it was not clear which isomer was obtained.



16a $R_1 = CH_2OH$, $R_2 = CO_2Me$
16b $R_1 = CO_2Me$, $R_2 = CH_2OH$

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