Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2249-2252, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00267-5

Total Synthesis of Optically Active Deoxyaspergillic Acid from Dipeptidyl Aldehyde

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Abstract: Optically active deoxyaspergillic acid was easily synthesized by a newly developed procedure for preparation of 2(1*H*)-pyrazinone derivatives from L-leucyl-L-isoleucine aldehyde hydrochloride (H-L-Leu-L-Ile-H·HCl).

Deoxyaspergillic acid is a naturally occurring secondary metabolite produced by certain species of aspergillis[1] and streptomyces.[2,3] Because of its structural relationship to aspergillic acid, which exhibits antibacterial activity, deoxyaspergillic acid has been of interest to both organic chemists and biochemists.[4] Deoxyaspergillic acid was also derived from aspergillic acid by reduction with hydrazine or hydroiodic acid[4-6] and its structure was finally determined as 2-hydroxy-3-isobutyl-6-*sec*-butylpyrazine(Figure 1).[7]

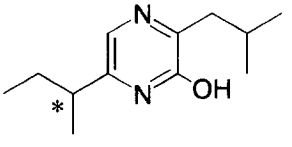


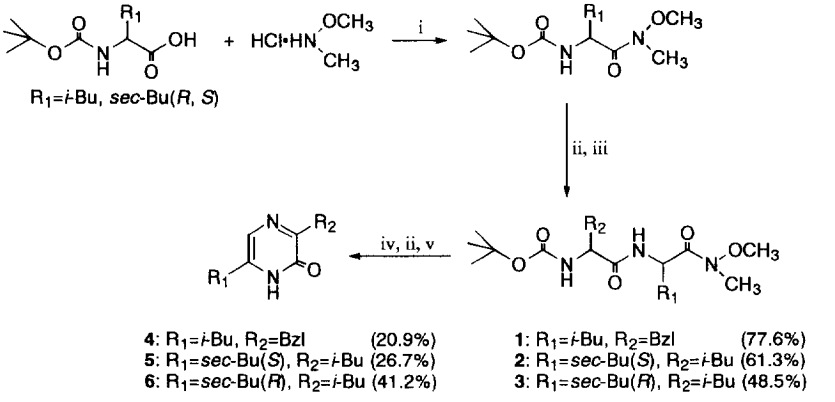
Figure 1 Structure of deoxyaspergillic acid.
*: asymmetric carbon atom.

Several attempts to synthesize deoxyaspergillic acid have been made.[8-11] However, the respective methods were complicated, and only racemic deoxyaspergillic acid was synthesized. Therefore, the absolute configuration of natural deoxyaspergillic acid had still not been confirmed synthetically.

This paper deals with synthesis of optically active deoxyaspergillic acid by a newly developed, convenient synthetic method and determination of the absolute configuration of natural deoxyaspergillic acid.

Previously, we reported a simple and convenient synthetic procedure for 2(1*H*)-pyrazinone derivatives from dipeptidyl chloromethyl ketones.[12-14] Various kinds of dipeptidyl chloromethyl ketones were prepared and converted in good yields to the corresponding 2(1*H*)-pyrazinone derivatives by short-time reflux in MeOH. It was revealed that the corresponding dipeptidyl methyl ketone was also easily converted to the 2(1*H*)-pyrazinone derivatives through a different cyclization mechanism from that of chloromethyl ketones. The above novel method can afford 2(1*H*)-pyrazinone derivatives in which the desired substituent(s) is introduced at position(s) 3 and/or 6. However, position 5 of 2(1*H*)-pyrazinone derivative is substituted with a methyl group . These results provided us with an idea that dipeptidyl aldehydes could also

afford 2(1*H*)-pyrazinone derivatives without a substituent at position 5 by a similar cyclization mechanism to that of dipeptidyl methyl ketones. Therefore, we undertook to prepare 2(1*H*)-pyrazinone derivatives from



Scheme 1 *Reagents and conditions: i, DCC, DMAP; ii, HCl-dioxane; iii, isobutyl chloroformate, Et_3N, Boc-AA-OH(AA: Phe, Leu); iv, $LiAlH_4$, THF, -15°C; v, MeCN, room temp. 13h. Yields are described in parenthesis.*

dipeptidyl aldehyde. According to Scheme 1, Boc-Leu-DMA was prepared from Boc-Leu-OH and *N,O*-dimethylhydroxyamine(DMA) using the DCC/DMAP procedure.[15] After removal of the Boc group, the resultant amine was coupled with Boc-Phe-OH by a mixed anhydride procedure to give Boc-Phe-Leu-DMA **1**. This amide was treated with LiAlH4 to afford Boc-Phe-Leu-H. After removal of the Boc group of this aldehyde by 5.0 N HCl-dioxane, the resultant amine hydrochloride was cyclized to 3-benzyl-6-isobutyl-2(1*H*)-pyrazinone **4**[16] by stirring at room temperature in CH3CN for 13 h. These results showed that, as expected, 2(1*H*)-pyrazinone derivatives could be easily formed from dipeptidyl aldehyde.

This method was applied to the synthesis of naturally occurring deoxyaspergillic acid, because our novel method can easily afford 2(1*H*)-pyrazinone derivatives under slightly acidic conditions. A deoxyaspergillic acid possesses one asymmetric carbon atom (Fig. 1) and this position is easily racemized when heated with alkali.[8] Therefore, up to now, the total synthesis of optically active deoxyaspergillic acid had not been achieved.

According to Scheme 1, Boc-Leu-Ile-DMA **2** and Boc-Leu-allo-Ile-DMA **3** were prepared. These amides were converted to **5**[17] and **6**[18] (*S* and *R* at the asymmetric center of the *sec*-butyl group, respectively)[m. p. : **5** (*S*-configuration), 80-81°C; **6** (*R*-configuration), 80-80.5°C; natural deoxyaspergillic acid,[1] 83°C, $[\alpha]_D^{21}$(*c*=0.7, CHCl3): **5** (*S*), +11.3°; **6** (*R*), -11.2°; natural deoxyaspergillic acid, +11.8°]. From these results, the absolute configuration of the natural deoxyaspergillic acid could be confirmed as *S*-configuration synthetically. Retention times on analytical HPLC of natural deoxyaspergillic acid and **5** were identical as shown in Figure 2. From the NMR data for the compounds **5** and **6**, we can deduce that deoxyaspergillic acid might exist as a pyrazinone, rather than pyrazinol, type.[12]

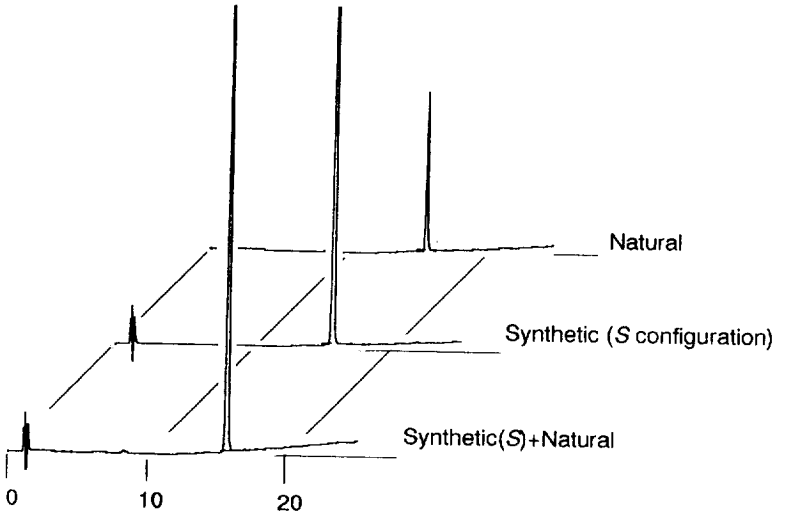


Figure 2 *HPLC Profiles of Natural and Synthetic Deoxyaspergillic Acid.* Column: Nova-PAK C18(3.9 mm x 150 mm), eluent; a = H_2O (0.05 % TFA), b = MeCN (0.05 % TFA); gradient (a:b) 80:20 to 20:80 for 40 min.

Thus, we were able to develop a facile and racemization-free synthetic procedure for 2(1*H*)-pyrazinone derivatives from dipeptidyl aldehydes and have succeeded in the first total synthesis of optically active deoxyaspergillic acid and determination of the absolute configuration of natural deoxyaspergillic acid as *S*-configuration. Our convenient synthetic procedure can contribute to studies on the structure-antibacterial activity relationship.

Acknowledgements

The authors are grateful to Dr. M. Sasaki of the Central Research Institute of Kikkoman Shoyu Co., Ltd., for the supply of natural deoxyaspergillic acid. This work was supported in part by a grant from The Science Research Promotion Fund of the Japan Private School Promotion Foundation.

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16. *Physical and spectroscopic data for* **4**: mp 105-107°C, ^{1}H-NMR ($CDCl_3$ 400MHz) δ:ppm 13.1 (1H, br, NH), 7.39-7.17 (6H, m, 3-CH_2Ph+5-H), 4.09 (2H, s, 3-CH_2Ph), 2.37 (2H, d, J=7.3 Hz, 6-$CH_2CH(CH_3)_2$), 2.06 (1H, m, J=6.8 Hz, 6-$CH_2CH(CH_3)_2$), 0.98 (6H, d, J=6.6 Hz, 6-$CH_2CH(CH_3)_2$), ^{13}C-NMR ($CDCl_3$ 400MHz) δ:ppm 158.2 (q, C-2), 155.5 (q, C-3), 138.5 (q, C-1'), 137.9 (q, C-6), 129.4 (t, C-2', 6'), 128.3 (t, C-3', 5'), 126.4 (t, C-4'), 123.4 (t, C-5), 39.6 (s, 6-$CH_2CH(CH_3)_2$), 39.4 (s, 3-CH_2Ph), 28.1 (t, 6-$CH_2CH(CH_3)_2$), 22.2 (p, 6-$CH_2CH(CH_3)_2$).
17. *Physical and spectroscopic data for* **5**: mp 80-81°C, $[\alpha]_D^{25}$ +11.3°(*c*=0.7, $CHCl_3$), t_R 15.46 min. MS *m/z*: 208 M^+. ^{1}H-NMR ($CDCl_3$ 400MHz) δ:ppm 12.8 (1H, brs, NH), 7.19 (1H, s, 5-H), 2.65 (2H, d, J=6.8 Hz, 3-CH_2-$CH(CH_3)_2$), 2.56 (1H, m, 6-$CH(CH_3)CH_2CH_3$), 2.21 (1H, m, 3-$CH_2CH(CH_3)_2$), 1.82-1.6 (2H, m, 6-$CH(CH_3)CH_2CH_3$), 1.33 (3H, d, J=7.0 Hz, 6-$CH(CH_3)CH_2CH_3$), 0.97 (6H, d, J=6.7 Hz, 3-$CH_2CH(CH_3)_2$), 0.91 (3H, d, J=7.4 Hz, 6-$CH(CH_3)CH_2CH_3$). ^{13}C-NMR ($CDCl_3$ 400MHz) δ:ppm 158.4 (q, C-2), 157.0 (q, C-3), 142.6 (q, C-6), 121.2 (t, C-5), 41.6 (s, 3-$CH_2CH(CH_3)_2$), 37.3 (t, 6-$CH(CH_3)CH_2CH_3$), 28.5 (s, 6-$CH(CH_3)CH_2CH_3$), 27.0 (t, 3-$CH_2CH(CH_3)_2$), 22.7 (p, 3-$CH_2CH(CH_3)_2$), 18.7 (p, 6-$CH(CH_3)CH_2CH_3$), 11.8 (p, 6-$CH(CH_3)CH_2CH_3$).
18. *Physical and spectroscopic data for* **6**: mp 80-80.5°C, $[\alpha]_D^{25}$ -11.2°(*c*=1.0, $CHCl_3$), t_R 15.46 min. MS *m/z*: 208 M^+. ^{1}H-NMR ($CDCl_3$ 400MHz) δ:ppm 12.8 (1H, brs, NH), 7.19 (1H, s, 5-H), 2.65 (2H, d, J=6.8 Hz, 3-CH_2-$CH(CH_3)_2$), 2.56 (1H, m, 6-$CH(CH_3)CH_2CH_3$), 2.21 (1H, m, 3-$CH_2CH(CH_3)_2$), 1.82-1.6 (2H, m, 6-$CH(CH_3)CH_2CH_3$), 1.33 (3H, d, J=7.0 Hz, 6-$CH(CH_3)CH_2CH_3$), 0.97 (6H, d, J=6.7 Hz, 3-$CH_2CH(CH_3)_2$), 0.91 (3H, d, J=7.4 Hz, 6-$CH(CH_3)CH_2CH_3$) ^{13}C-NMR ($CDCl_3$ 400MHz) δ:ppm 158.3 (q, C-2), 157.1 (q, C-3), 142.6 (q, C-6), 121.2 (t, C-5), 41.6 (s, 3-$CH_2CH(CH_3)_2$), 37.3 (t, 6-$CH(CH_3)CH_2CH_3$), 28.4 (s, 6-$CH(CH_3)CH_2CH_3$), 26.9 (t, 3-$CH_2CH(CH_3)_2$), 22.6 (p, 3-$CH_2CH(CH_3)_2$), 18.6 (p, 6-$CH(CH_3)CH_2CH_3$), 11.7 (p, 6-$CH(CH_3)CH_2CH_3$).

(*Received in Japan* 22 *December* 1995; *revised* 1 *February* 1996; *accepted* 8 *February* 1996)