CONFIGURATIONAL STUDIES ON THIOMARINOL

Sir:

A new antibiotic, thiomarinol, was isolated from the culture broth of a marine bacterium, Alteromonas rava sp. nov. SANK 733901. The structure of thiomarinol was deduced to be a hybrid of a pseudomonic acid analogue and holothin. In a previous paper, we suggested that the stereochemistry of the six-membered ether ring in the monic acid moiety of thiomarinol was very similar to that of pseudomonic acid C by the coupling constants and acetonide formation. In this paper, we report the absolute configuration of the 4-hydroxymonic acid C moiety of thiomarinol, except at C-12. Hydrolysis of thiomarinol (1) with 0.1N NaOH in 60% MeOH solution afforded a 4-hydroxymonic acid C (2) and its methyl ester (3), as described previously, and a new bicyclic compound (4, C17H28O7; FAB-MS: m/z 345 (M+H)+), as shown in Fig. 1.

The formation of the bicyclic compound (4) proceeded from intramolecular Michael attack of the C-6 hydroxy group on the acrylate ester function in the monic acid. This compound (4), having a rigid structure, is a suggestive one, because the relative configuration at C-4 can be solved by NMR analysis. In the 1H NMR spectrum of 4, the allyl methyl at C-15 disappeared, and a methyl and an isolated methylene signals newly appeared at δ 1.25 and 2.62, both as singlets. Also, comparison of the 13C NMR spectra between 2 and 4 suggested the disappearance of 2,3-double bond. Acetylation of 4 with acetic anhydride in pyridine gave a triacetate (5, C23H34O10; FAB-MS: m/z 471 (M+H)+). In the 1H NMR spectrum of 5, protons at 4-H, 7-H and 13-H were shifted to low field at δ 5.53, 5.26 and 4.82, and all carbinol protons at 4-H, 5-H, 6-H, 7-H, 13-H and 16-H were well separated. The relative configuration of the bicyclic ring of 5 was deduced from the coupling constants of J4,5=8.7Hz, J5,6=10.7Hz, J6,7=2.4Hz, J7,8=2.4Hz, J8,16a=0Hz and J8,16b=2.9Hz, as shown in Fig. 2. The veracity of this conformation was strengthened with the aid of additional information on the NOEs between 2-H and 4-H, 4-H and 6-H, 6-H and 7-H, 6-H and 9-H, and 5-H and 15-H.

The absolute configuration of 4 was elucidated by the modified Mosher's method of 2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid (MTPA) derivatives. The S or R MTPA ester derivatives of thiomarinol were prepared by the reaction with S or R MTPA and dicyclohexylcarbodiimide (DCC) in THF solvent. We isolated mono O- (S and R) MTPA esters of C-4 (6), C-7 (7), and C-13 (8), respectively, by preparative HPLC (Senshu-pak, ODS, H-4251, 10×250mm, 60% CH3CN, 5ml/minute). 1H NMR spectra of all compounds were measured in CDCl3 solution with 400 MHz. The δδ (ppm) values are shown in Fig. 3.

From these results, the absolute configurations of secondary alcohols at C-4, C-6 and C-13 were R, R and S, respectively. In addition, the absolute configurations at C-5, C-7 and C-8 were also deduced as S, R and S, respectively, from the relative configuration of 4. Finally, the geometry of double bonds at C-2~C-3 and C-10~C-11 were assigned as both E, by NMR spectra. Alexander et al. reported the geometry of the C-2~C-3 double bond of...
pseudomonic acid A and its isomer by $^1$H and $^{13}$C NMR spectra. In its $^{13}$C NMR spectra, chemical shifts of the C-15 signal in the E and Z configurations of the C-2~C-3 double bond appeared at $\delta$ 19.1 and 27.4, respectively. On the other hand, obvious NOE between 2-H and 15-H was only observed in the Z-isomer. The C-15 signal of thiomarinol in the $^{13}$C NMR spectrum appeared at $\delta$ 15.7, near the E-configuration of pseudomonic acid A, and the NOE between 2-H and 15-H was not observed. As additional evidence, the NOEs in 2 were not observed between 2-H and 15-H, but between 2-H and 4-H. The coupling constant between 10-H and 11-H in thiomarinol was observed at 15.5 Hz. This value was assigned as signifying a trans double bond. Therefore, the five asymmetric centers except at C-12 of 4-hydroxymonic acid derivative of thiomarinol were established as 4R, 5S, 6R, 1R, 85 and 13S, and the geometry of double bonds at C-2~C-3 and C-10~C-11 were both E, as shown in Fig. 4. These configurations and geometries, except at C-4 and C-12, of thiomarinol are the same as those of pseudomonic acid C.

Recently, two new pseudomonic acid derivatives were isolated from a marine bacterium, Alteromonas sp. The structure of one of them contained the 4-hydroxymonic acid derivative, which was identical with that of thiomarinol. However, the absolute configuration of this compound was not reported.

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References


