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Stereochemistry of Butyrolactone Autoregulators from Streptomyces

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Abstract: Stereochemistry of virginiae butanolide A 3 was elucidated by its chemical conversion to the acetal 14, establishing also the structures of other related compounds.

In Streptomyces, some butyrolactone autoregulators which control cytodifferentiation and secondary metabolites production are known, such as A-factor 1[1], factor 1 2[2], Gräfe's factors 3, 4 and 5[3], virginiae butanolides A~E 3, 6, 7, 8 and 9[4], and IM-2 10[5]. They have a characteristic 2,3-disubstituted butanolide skeletone in common with a little difference about the C-2 side chain. Regarding the stereochemistry of autoregulators with a C-6 hydroxyl group, Gräfe et al. first proposed 2,3-trans configuration to 2 and 2,3-cis to 3, 4 and 5 from their $J_{2,3}$ values without stereochemical assignment at C-6[2]. Next, we assigned 2,3-cis configuration to 3, 6, 7, 8 and 9, and 2,3-trans to 10, following his assignment and on the basis of synthetic feasibility of two isomers, namely alleged cis and trans configuration[4] without any information about C-6 stereochemistry. Totally, hitherto known autoregulators with a C-6 hydroxyl group were stereochemically classified into two groups, "cis" and "trans" type as shown in Fig. 1-a. Recently, during the course of our biosynthetic study of 3[6], we realized that NOE experiments to confirm the relative stereochemistry of ring protons suggested that 3 might have a 2,3-trans configuration, and this fact prompted us to investigate its stereochemistry in detail. In this paper, we describe the stereochemical elucidation of 3 and its isomer 3' and the revision of the formerly reported stereochemistry of all 6-hydroxy autoregulators.

As a final step of chemical synthesis of 3, reduction of β-keto lactone 11 with sodium borohydride affords only two products, 3 and 3'[4], which have the same stereochemistry as "cis" and "trans" type, respectively. NOE experiments indicated that 3' has a 2,3-trans stereochemistry similarly in the case of 3, which suggested that 3 and 3' were only stereoisomers at C-6. To prove it, dibenzoates of 3 and 3' were prepared by two ways, one was by Mitsunobu reaction[7] accompanying an inversion of a secondary hydroxyl group at C-6 and the other was by usual method with benzoyl cyanide. The dibenzoate of 3 obtained by Mitsunobu reaction was completely identical with that of 3' normally prepared, and vice versa.

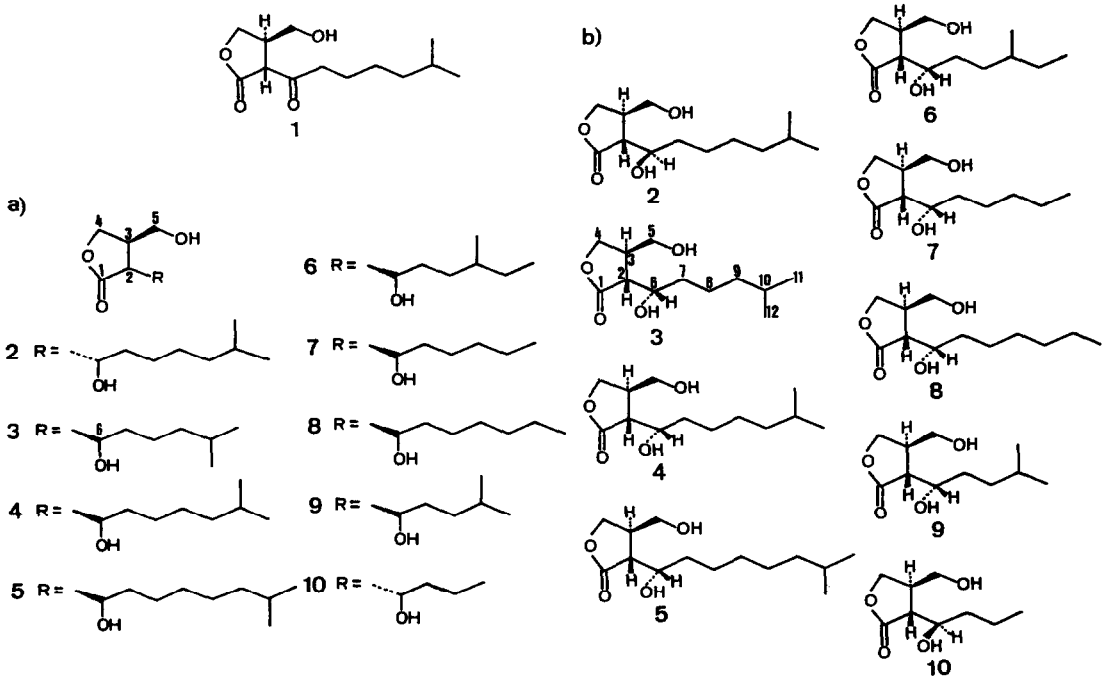
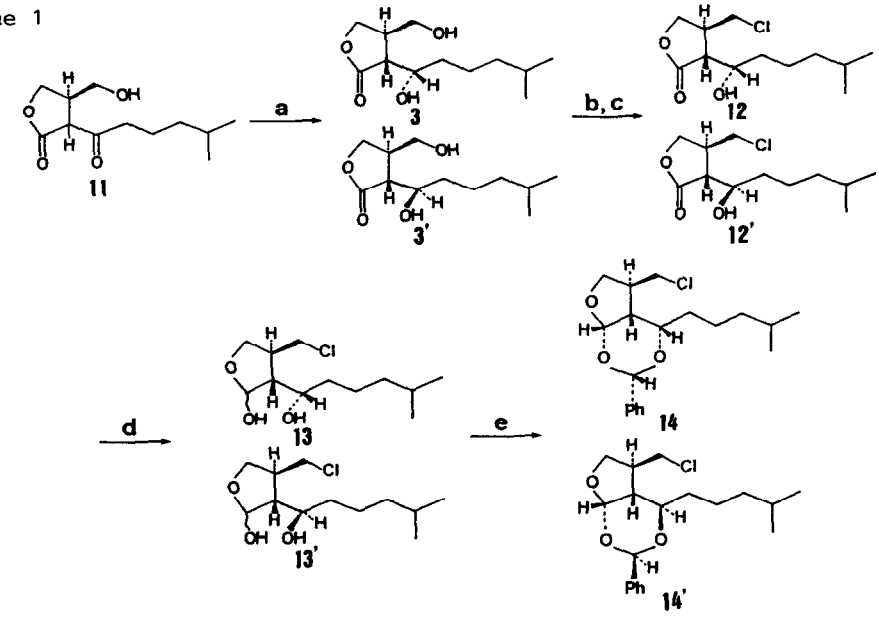


Fig. 1 Structures of butyrolactone autoregulators from Streptomyces.
a)Formerly proposed stereochemistry.
b)Revised stereochemistry.

Since all crystalline derivatives we prepared from natural (-)-3, synthetic (±)-3 and -3' were not suitable for X-ray analysis unfortunately, we tried to determine the stereochemistry of C-6 by converting 3 to 14 (Scheme 1), in which it may become possible to confirm the relative stereochemistry between H-2 and H-6 by the formation of six membered ring. First, hydroxyl group at C-5 was replaced by chlorine to retain the stereochemistry between H-2 and H-3 during transformation reactions. Lactone of the obtained 12 was next reduced by diisobutylaluminum hydride to lactol 13, which easily formed its benzylidene derivative with benzaldehyde dimethylacetal and p-toluenesulfonic acid. 14 was obtained as a main product in 45% yield from 13[8]. In the same manner, 3' was derivatized to 14' in 27% yield from 13'[8]. The J values ($J_{1,2}$=4Hz, $J_{2,6}$=4Hz) and NOE enhancement (13%) of H-6 on irradiation of benzylidene methine proton indicated that the benzylidene ring of 14 existed in the chair form as shown in Fig. 2. The large coupling constant (9Hz) between H-2 and H-3 and NOE enhancement (3.7%) of H-5 on irradiation of H-2 clearly supported a 2,3-trans orientation in 14 before mentioned. On the other hand, the conformation of the benzylidene ring of 14' was confirmed as shown in Fig. 2 by the J values ($J_{1,2}$=4Hz, $J_{2,6}$=10Hz) and NOE enhancement (11%) of H-6 on irradiation of

benzylidene methine proton. A 2,3-trans configuration in 14' was supported by the small $J_{2,3}$ value (<3Hz). Since the C-6 stereochemistry of 3 and 3' could unequivocally be deduced from the cis orientation between H-2 and H-6 of 14 and the trans of 14', the stereochemistry of 3 and other related compounds were determined as shown in Fig. 1-b.

Scheme 1



a) $NaBH_4$, MeOH. b)p-bromobenzenesulfonyl chloride, pyridine, 0 °C.
c) KCl, 18-crown-6, CH_3CN. d)diisobutylaluminum hydride, toluene, -78 °C.
e)benzaldehyde dimethylacetal, TsOH, CH_2Cl_2, 0 °C.

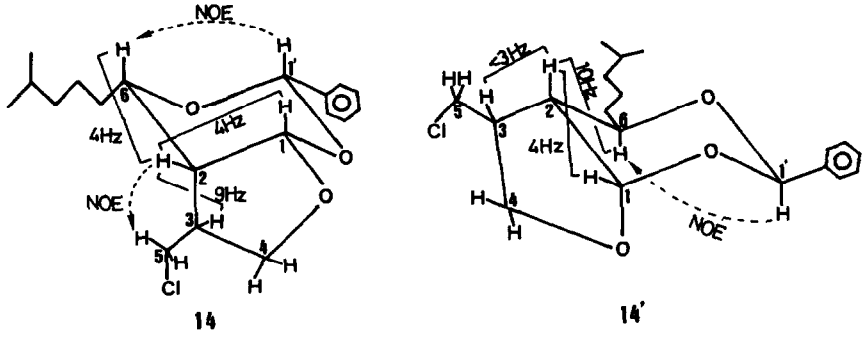


Fig. 2 Relative stereochemistry of 14 and 14'.

Recently, Mori et al. synthesized optically active (3R)-3, 6 and 7 from (S)-paraconic acid, and showed that their CD spectra and biological activitiy were identical with natural ones[9]. Adding our stereochemistry to their result, it was established that virginiae butanolide A, B and C have (2R,3R,6S) absolute configuration. There are no chiroptical data about other compounds with a C-6 hydroxyl group as yet, but if the formerly called "trans" type compounds also have (3R) configuration like A-factor[10] and virginiae butanolides, (2R,3R,6R) configuration is assigned to them.

References and note

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8) Spectral data of 14 and 14', 14; CI-MS m/z 339, 341 $(M+H)^+$, ^{1}H-NMR δ ($CDCl_3$, 600MHz, Brucker AM-600, Faculty of Engineering, Osaka University) : 7.49(2H,m,ph), 7.35(3H,m,ph), 5.53(1H,s,H-1'), 5.46(1H,d,$J_{1,2}$=4Hz,H-1), 4.40(1H,t,$J_{4a,3}$=9Hz,$J_{4a,4b}$=9Hz,H-4a), 4.07(1H,m,H-6), 4.02(1H,dd, $J_{4b,3}$=6Hz,$J_{4a,4b}$=9Hz,H-4b), 3.74(1H,dd,$J_{5a,3}$=3Hz,$J_{5a,5b}$=11Hz,H-5a), 3.56(1H,dd,$J_{5b,3}$=8Hz,$J_{5b,5a}$=11Hz,H-5b), 3.01(1H,m,H-3), 2.10(1H,dt, $J_{2,3}$=9Hz,$J_{2,6}$=4Hz,$J_{2,1}$=4Hz,H-2), 1.20-1.77(7H,H-7,8,9,10), 0.88(6H,d, J=7Hz,11-CH_3,12-CH_3). 14'; CI-MS m/z 339, 341 $(M+H)^+$, ^{1}H-NMR δ ($CDCl_3$, 600MHz) : 7.50(2H,m,ph), 7.35(3H,m,ph), 5.88(1H,s,H-1'), 5.53(1H,d, $J_{1,2}$=4Hz,H-1), 4.30(1H,dd,$J_{4a,3}$=8Hz,$J_{4a,4b}$=10Hz,H-4a), 3.75(1H,dd, $J_{4b,3}$=6Hz,$J_{4b,4a}$=10Hz,H-4b), 3.61(1H,m,H-6), 3.51(2H,d,$J_{5,3}$=7Hz,H-5), 2.31(1H,m,H-3), 2.05(1H,br.dd,$J_{2,1}$=4Hz,$J_{2,6}$=10Hz,H-2), 1.17-1.67(7H, H-7,8,9,10), 0.88(6H,d,J=7Hz,11-CH_3,12-CH_3).

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