APPLICATION OF CARBON-13 IN BIOSYNTHETIC STUDIES; FT-^{13}C NUCLEAR MAGNETIC RESONANCE SPECTRA OF DIHYDROLATUMCIDIN

Sir:

The advantage of biosynthetic studies conducted on microbial metabolites, which utilize carbon-13 precursors in combination with FT cmr *versus* those with carbon-14 tracers have been previously noted[1].

The antibiotic latumcidin[2] (abikoviromycin)[3] produced by *Streptomyces reticuli* var. *latumcidicus* would be a metabolite of choice to be studied with carbon-13 precursors, since it seems to be biosynthesized from acetate *via* a polyketide as shown in Fig. 1.

Latumcidin separately labeled with either $CH_3{}^{13}COONa$ or $^{13}CH_3COONa$ was reduced with $NaBH_4$[3] to a relatively stable derivative, dihydrolatumcidin in order to overcome the difficulty caused by the decomposition of latumcidin during isolation. The reduction product, consisting of only one isomer, was proven to be identical with naturally occurring dihydrolatumcidin, the intermediacy of which had been verified by its enzymatic conversion to latumcidin[4].

The cmr spectrum of dihydrolatumcidin labeld with $CH_3{}^{13}COONa$ (see Fig. 2) exhibited five enhanced peaks assignable[5] to C-2, 4, 6, 7a and 8 while peaks C-3, 4a, 5, 7 and 9 were considerably weaker. On the other hand, the reversal of the signal intensity is evident in the spectrum (Fig. 3) obtained from $^{13}CH_3COONa$ labeling experiment. The following peaks were assigned unambiguously by the aid of off-resonance and selective proton decoupling experiments; δc^{TMS} 14.0(C-9), 25.9(C-3), 39.6(C-2), 59.2(C-4), 63.1(C-7a), 64.1(C-4a), 114.9(C-8), 131.7(C-6), 133.8(C-7) and 140.0(C-5). It should be noted that the C-C coupling (J=57 Hz) between 4a and 5 observed is in agreement with the previous assignments.

These results clearly indicate that latumcidin is biosynthesized from five acetate units as shown in Fig. 1.

The incorporation ratio was determined by the direct comparison of the signal intensities

Fig. 1. Biogenetic pathway of latumcidin

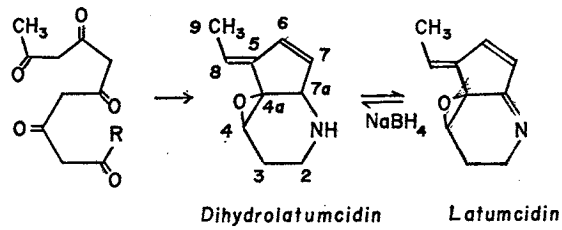


Fig. 2. Proton noise decoupled FT-cmr spectrum of dihydrolatumcidin in $CDCl_3$ from $CH_3{}^{13}COONa$ (56 atom %), 112 mg. The spectrum was taken at 25.5 MHz on a Varian XL-100 spectrometer. pulse width =25 μsec; acquisition time =0.8 sec; 1,000 transients.

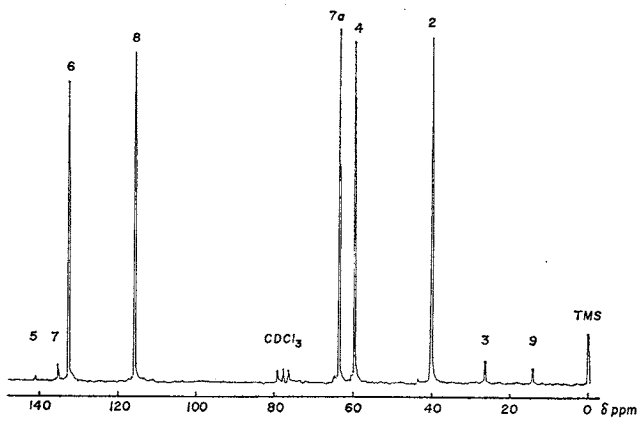


Fig. 3. Proton noise decoupled FT-cmr spectrum of dihydrolatumcidin in $CDCl_3$ from $^{13}CH_3COONa$ (61 atom %), 79 mg. Other data are same as in Fig. 2.

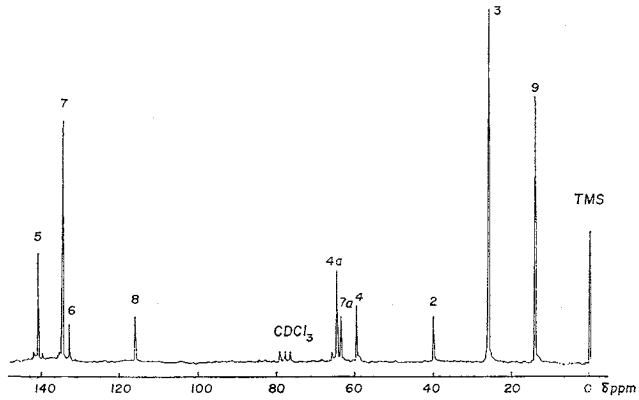
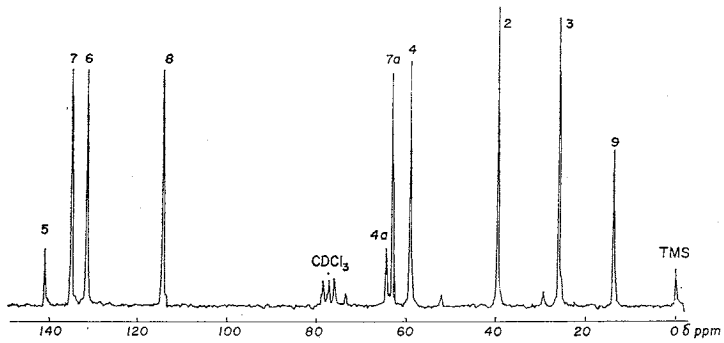


Fig. 4. Proton noise decoupled FT-cmr spectrum of unlabeled dihydrolatumcidin. 34,000 transients.



of C_6 and C_7 in the cmr spectra of the labeled samples, since the intensities of these two peaks in the spectrum of the unlabeled sample are completely same (Fig. 4). The values obtained are 17.3% for the sample labeled with $CH_3{}^{13}COONa$ and 6.6% for the sample labeled with $^{13}CH_3COONa$.

Although the cyclization mechanism remains to be studied, it seems likely that latumcidin can be formed through a mechanism similar to that involved in the biosynthesis of brefeldin A[6].

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