with dimethyl sulfoxide–acetic anhydride afforded the chromatographically separable methylthiomethyl ethers **2b** and **6b** in 98% yield. Conversion to the crystalline sulfones **3b** (mp 152–153 °C, 60% yield) and **7b** (mp 105–106 °C, 85% yield) was effected with *m*-chloroperoxybenzoic acid. Reduction of these sulfones with sodium naphthalenide in HMPA afforded pure *cis*-1,2-dimethylcyclododecene (**8b**, 74% yield) and *trans*-1,2-dimethylcyclododecene (**9b**, 83% yield). We were unable to rigorously establish the stereochemistry of cyanohydrins **1b** and **5b**, or derivatives thereof, owing to the extreme steric hindrance of the cyano grouping. Attempts at hydrolysis or conversion to the known vicinal glycol derivatives[6] were unsuccessful. However, the findings outlined in Chart I together with the high degree of stereoselectivity observed in the reduction–elimination leading to olefins **8b** and **9b** tend to support the stereochemistry assignments.

In an experiment performed after submission of our original manuscript, we found that the crystalline cyanohydrin methylthiomethyl ether **2b** (mp 51.5–52.5 °C) afforded *cis*-1,2-dimethylcyclododecene directly in 75% yield upon treatment with sodium naphthalenide in HMPA. Thus, conversion to the sulfone derivatives may be unnecessary for the synthesis of olefins by this route. We are exploring the use of methylthiomethyl ethers and their sulfone derivatives as leaving groups in other contexts.

Mechanistic interpretations for the stereochemical findings must await further studies in other cyclic as well as acyclic systems. It should be noted, however, that reduction–eliminations of cyclic phosphate derivatives under similar conditions likewise proceed by a preferred syn pathway.[7,8]

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References and Notes

(1) J. A. Marshall and L. J. Karas, *Synth. Commun.*, **8**, 65 (1978).
(2) See also J. A. Marshall, C. P. Hagan, and G. A. Flynn, *J. Org. Chem.*, **40**, 1162 (1975), for reduction–eliminations of cyano epoxides.
(3) Prepared from cyclododecanone using the method of P. Beak and T. L. Chaffin, *J. Org. Chem.*, **35**, 2275 (1970).
(4) P. M. Pojer and S. Angyal, *Tetrahedron Lett.*, 3067 (1976).
(5) W. Adam, J. Baeza, and J.-C. Liu, *J. Am. Chem. Soc.*, **94**, 2000 (1972); D. S. Noyce and E. H. Baniff, *J. Org. Chem.*, **31**, 4043 (1966); M. Tanabe and R. H. Peters, *ibid.*, **36**, 2403 (1971).
(6) J. Casanova and B. Waegell, *Bull. Soc. Chim. Fr.*, 1295 (1971). The cis and trans olefins were further characterized through conversion to their crystalline diol derivatives with osmium tetroxide. Cf. T. C. Flood, Ph.D. Thesis, M.I.T., 1972.
(7) J. A. Marshall and M. E. Lewellyn, *J. Org. Chem.*, **42**, 1311 (1977).
(8) Satisfactory combustion analyses and spectral data have been secured for all new substances reported herein.

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Biosynthetic Studies with Carbon-13. Lankacidin Group of Antibiotics

Sir:

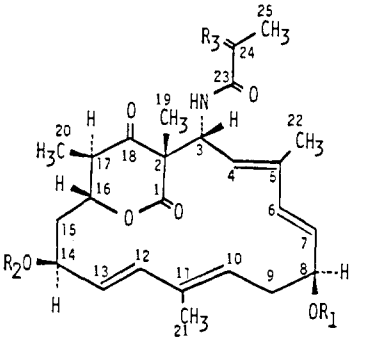
The lankacidins are a unique group of antibiotics that exhibit a broad spectrum of antibacterial activity.[1] Unlike other antibacterial substances, the lankacidins also possess antitumor activity.[2]

Their structures, which incorporate a δ lactone function imbedded into a unique 17-membered carbocyclic ring, have been firmly established by chemical and spectroscopic methods including x-ray crystallographic analyses. The lankacidins **1**, **2**, **3**, **4**, and **5** are interrelated by the presence or absence of an acetyl function at C-14 as well as by a variable oxidation level at C-24.

Table I. ^{13}C NMR Data for Lankacidin C Diacetate (**4**)

Carbon no.	δ_c[a]	Multiplicity[b]	Relative enrichments	J_{C-C}, Hz	
1[c]	169.8	s	6.4	52.2	1–2
2	56.7	s		52.2	
3	51.8	d			
4[d]	124.9	*e*	2.1		
5	139.1	s		53.3	5–6
6[c]	135.9	d	8.3	53.6	
7	126.7	*e*		50.4	7–8
8[c]	75.7	d	5.8	50.3	
9	33.7	t		44.8	9–10
10[c]	128.4	d	8.4	44.8	
11	136.9	s		53.6	11–12
12[c]	140.7	d	7.6	53.9	
13	124.9	*e*		49.2	13–14
14[c]	71.4	d	6.7	49.3	
15	34.2	t		39.7	15–16
16[c]	75.5	d	8.3	40.4	
17	46.4	d		37.8	17–18
18[c]	210.4	s	7.5	37.8	
19[f]	9.4	q	22.9		
20[f]	12.5	q	27.1		
21[f]	12.7	q	32.2		
22[f]	20.9	q	18.1		
23	159.8	s			
24	196.4	s			
25	24.4	q			
26	170.1	s			
27	21.2	q			
28	170.1	s			
29	21.2	q			

[a] Chemical shifts are given in parts per million downfield from internal Me_4Si in $CDCl_3$ and enrichments were measured by relative signal enhancements. [b] Multiplicities in the off-resonance decoupled spectrum: s, singlet; d, doublet; t, triplet; q, quartet. [c] These carbon atoms were enriched by sodium [1-^{13}C]acetate and enrichments are relative to C-25 as 1.0. [d] This carbon atom was enriched by [1-^{13}C]glycine and the enrichment is relative to C-25 as 1.0. [e] Multiplicities of these signals could not be recognized because of the overlapping with other peaks. [f] These carbon atoms were enriched by [$^{13}CH_3$]methionine and enrichments are relative to C-1 as 1.0.



No.	R_1	R_2	R_3	Compd
1	H	H	O	lankacidin C (bundlin A, T-2636 C)
2	$COCH_3$	$COCH_3$	O	lankacidin C diacetate
3	H	$COCH_3$	O	lankacidin A (bundlin B, T-2636 A)
4	H	H	H,OH	lankacidinol (T-2636 F)
5	H	$COCH_3$	H,OH	lankacidinol A (T-2636 D)

In this communication, we present our ^{13}C NMR results, which reveal a novel biosynthetic route to these biologically significant and structurally distinct macrolide substances. The ^{13}C-labeled antibiotics were prepared in feeding experiments

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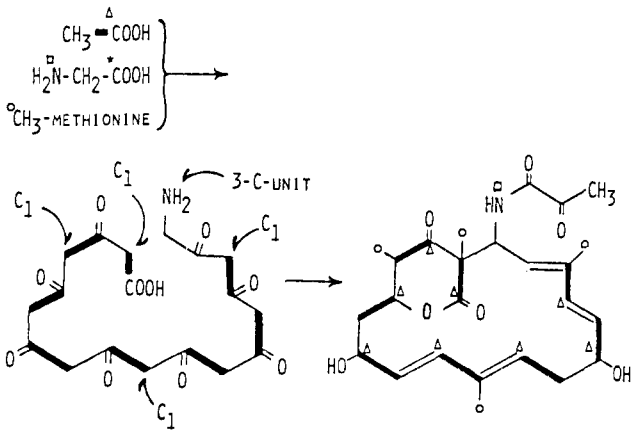
Scheme I



conducted with 90% enriched sodium [1-^{13}C]- and [1,2-^{13}C]acetate, [1-^{13}C]glycine, and [$^{13}CH_3$]methionine as well as with 90% enriched [^{15}N]glycine. These labeled precursors were added to shaking cultures of *Streptomyces sp.*[3] After fermentation, the labeled antibiotics were extracted into methylene chloride, acetylated with acetic anhydride in pyridine (48 h at 10 °C), and purified by preparative TLC using benzene–ethyl acetate (4:1). The lankacidin C diacetate (**2**) provided by this procedure was used for the ^{13}C NMR measurements.

The ^{13}C chemical shift assignments of natural-abundance lankacidin C diacetate shown in Table I were determined by off-resonance decoupling and by comparison with known carbon shift values of model compounds.[4] In addition, many of the previously established ^{1}H NMR shift assignments of the lankacidins[1] were used to determine many of the corresponding carbon shifts in selective proton decoupling experiments.

The labeling results summarized in Table I clearly establish that sodium [1-^{13}C]acetate enriches eight carbons—C-1, C-6, C-8, C-10, C-12, C-14, C-16, and C-18—of the macrolide ring. Incorporation of eight acetate units into the macrolide ring of **2** was corroborated by the antibiotic enriched with sodium [1,2-^{13}C]acetate, which showed eight pairs of carbon–carbon coupling signals as characteristic satellite signals flanking the center signal. Table I also lists the respective J values found.

Glycine was identified as the source of the C-3 amino group, since the ^{13}C NMR spectrum of **2** labeled by incorporation [1-^{13}C]glycine showed strong signal enhancement at only a single peak corresponding to the C-4 signal. A ^{15}N-enriched sample of lankacidin C diacetate prepared from feeding of [^{15}N]glycine indicated by mass spectrometry that a 20% excess ^{15}N was incorporated.[5] This result confirms that the N–C_3–C_4 grouping of the lankacidins is derived from glycine.

Use of [$^{13}CH_3$]methionine confirmed that the branching methyl groups C-19, C-20, C-21, and C-22 are derived through the acetate + C_1 pathway, since strong signal enhancement for only these four methyl carbons was observed. The absence of propionate participation in lankacidin biosynthesis was evident from the lack of any signal enhancement from a [1-^{13}C]propionate feeding experiment.

In contrast, the branching methyl groups of several other classes of macrolide antibiotics such as the 14-membered lactones in erythromycin[6] and picromycin[7] and the ansa macrolides rifamycin S,[8] streptrovaricin D,[9] and geldanamycin[10] have been established as coming from propionic acid units.

Scheme I shows the ^{13}C-label distribution established in our feeding studies. The formation of a linear polyketide chain is initiated by glycine incorporating eight acetic acid units, with methionine accounting for the four branching methyl groups in the positions indicated. A reasonable biogenetic route for the formation of the 17-membered carbocycle from the linear polyketide is through attack by the C-2 nucleophilic center on an electrophilic C-3 imine derivative of the glycine starter unit.

Only the origin of the three-carbon unit attached to the nitrogen remains unidentified in lankacidin biosynthesis; propionate and pyruvate are not incorporated. Further feeding experiments are required to establish its source.

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References and Notes

(1) (a) M. Uramoto, N. Otake, and H. Yonehara, *Agr. Biol. Chem.*, **35**, 27 (1971); (b) S. Harada, T. Kishi, and K. Mizuno, *J. Antibiot.*, **24**, 13 (1971); (c) S. Harada and T. Kishi, *Chem. Pharm. Bull.*, **22**, 99 (1974); (d) M. Uramoto, N. Otake, Y. Ogawa, H. Yonehara, F. Marumo, and Y. Saito, *Acta Crystallogr., Sect. B*, **27**, 236 (1971).
(2) (a) K. Ootsu and T. Matsumoto, *Gann*, **64**, 481 (1973); (b) K. Ootsu, T. Matsumoto, S. Harada, and T. Kishi, *Cancer Chemother. Rep., Part 1*, **59**, 919 (1975).
(3) The culture medium contained soluble starch (2%), pharmamedia (2%), corn steep liquor (1%), $CaCO_3$ (0.3%), KH_2PO_4 (2.18%), and $Na_2HPO_4 \cdot 12H_2O$ (1.43%). Each precursor was added to 100 mL of medium in a 500-mL triple-baffled flask in two pulses 10 and 12 h after inoculation with the organism. The medium was cultivated for 45 h. The pulses were sodium [1-^{13}C]acetate (40 mg), sodium [1,2-^{13}C]acetate (40 mg), [1-^{13}C]glycine (30 mg), [^{15}N]glycine (30 mg), and [$^{13}CH_3$]methionine (30 mg).
(4) (a) L. F. Johnson and W. C. Jankowski, "Carbon-13 nmr Spectra", Wiley, New York, N.Y., 1972; (b) J. B. Stothers, "Carbon-13 nmr Spectroscopy", Academic Press, New York, N.Y. 1972; (c) G. C. Levy and G. L. Nelson, "Carbon-13 nmr for Organic Chemists", Wiley, New York, N.Y., 1972; (d) F. W. Wehrli and T. Wirthlin, "Interpretation of C-13 nmr Spectra", Heydon & Sons, Ltd., London, 1976.
(5) The mass spectral characteristics of lankacidin C are known [M. Uramoto and N. Otake, *Agr. Biol. Chem.*, **38**, 855 (1974)]. Since the molecular ion is not formed, the two nitrogen-containing fragment ions *m/e* 194 ($C_{10}H_{12}NO_3$) and *m/e* 124 (C_7H_9NO) afforded the ^{15}N enrichment of ~20%.
(6) T. Kaneda. J. C. Butte, S. B. Taubman, and J. W. Corcoran, *J. Biol. Chem.*, **237**, 322 (1962).
(7) S. Omura, H. Takeshima, A. Nakagawa, and J. Miyazawa, *J. Antibiot.*, **29**, 316 (1976).
(8) (a) R. J. White, E. Martinelli, G. G. Gallo, G. Lancini, and P. Beynon, *Nature*, **243**, 273 (1973); (b) E. Martinelli, R. J. White, and G. G. Gallo, *Tetrahedron Lett.*, 1367 (1974).
(9) B. Milavetz, K. Kakinuma, K. L. Rinehart, Jr., J. P. Rolls, and W. J. Haak, *J. Am. Chem. Soc.*, **95**, 5793 (1973).
(10) R. D. Johnson, A. Haber, and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **96**, 3316 (1974).

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Lanthanide Effects on the Proton and Carbon-13 Relaxation Rates of Sarcosine. Evidence for Isostructural Amino Acid Complexes along the Lanthanide Series[1]

Sir:

Chemical shifts induced by lanthanide shift reagents should be useful in the determination of molecular structure and conformation in solution.[2,3] The trivalent lanthanide cations[4] or their EDTA chelates[5] can serve as shift reagents in aqueous solution and are applicable to the study of systems of biological

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