of Pharmacy, University of Wisconsin, for spectral determinations, Luigi Garlaschelli for preparation of **1** labeled by [1-^{14}C,2-^{3}H]-acetate, and Professor J. W. Cornforth (Sussex, England) for critical reading of the manuscript.

Biosynthesis of Macrolide Antibiotics. 4.[1] Stereochemistry of Hydrogen Labeling of Brefeldin A by [2-$^{2}H_3$]Acetate†

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Macrolide antibiotics are some of the structurally and stereochemically most diverse natural products known to science. Apart from the knowledge that these antibiotics are assembled from simple two-to-four carbon compounds, little is known about their biosynthetic pathways.[2,3] Nevertheless, it is usually presumed that macrolides are assembled in a manner analogous to the well-understood biosynthesis of fatty acids.[3]

We are testing the above assumption by examining the biosynthesis of selected macrolides. In the preceding paper,[1] we have summarized our observations on the regiochemistry of isotopic hydrogen labeling of the C_{16} macrolide antibiotic, brefeldin A (**1**), by acetate in vivo. In the present paper we describe the stereochemistry of this labeling process and consider the comparative biochemistry of fatty acids and macrolide antibiotics.

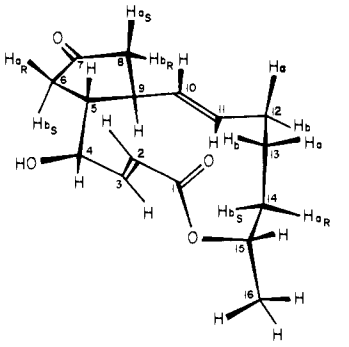

Figure 1. Conformation of 7-oxobrefeldin A (**3**), 7 mg, dissolved in degassed pyridine-d_5, 0.3 mL, that is consistent with qualitative intramolecular proton relationships deduced from ^{1}H:^{1}H nuclear Overhauser enhancement difference spectroscopy experiments.

Examination of the regiochemical distribution of isotopic labels in brefeldin A enriched with [2-^{3}H]- and [2-$^{2}H_3$]acetate[1] has revealed that C-6 and C-8 are the only methylene groups isotopically substituted in the same way as the corresponding groups in fatty acids. Configurational assignments at these positions therefore permit the stereochemistry of labeling of **1** to be compared directly with that observed for fatty acids. If introduction of labels has proceeded by the stereospecific reduction of enoyl-enzyme intermediates, as occurs in the biosynthesis of fatty acids (vide infra), either the pro-*R* or pro-*S* diastereotopic hydrogens attached to C-6 and C-8 will be isotopically substituted.

The labeling stereochemistry was determined by first assigning the ^{1}H NMR spectrum of a suitable derivative of **1** and then analyzing the ^{2}H NMR spectrum of the same derivative prepared from **1** enriched with [2-$^{2}H_3$]acetate. 4,7-Diacetylbrefeldin A (**2**) was used for some preliminary experiments; however, 7-oxobrefeldin A (**3**) proved to be the only derivative with a large enough chemical shift dispersion in the ^{2}H NMR spectrum for the easy identification of resonances due to diastereotopic deuteriums at C-6 and C-8.

^{1}H NMR assignments for **3** were checked by two independent techniques. Proton double irradiation experiments at 270 MHz in $C_5{}^{2}H_5N$, and at 360 MHz in $C^{2}HCl_3$ and $C_5{}^{2}H_5N$, combined

Table I. ^{1}H NMR Spectral Data for 7-Oxobrefeldin A (**3**)[a]

b	H-2	H-3	H-4	H-5	H-6a	H-6b
c	6.56	7.71	4.48	2.33	3.13	2.52
d	dd	dd	ddd	dddd	ddd	ddd
e	$J_{2,3}$ = 15.5 $J_{2,4}$ = 2.0	$J_{3,4}$ = 3.3	$J_{4,5}$ = 9.4	$J_{5,6a}$ = 7.9 $J_{5,6b}$ = 10.4 $J_{5,9}$ = 9.7	$J_{6a,6b}$ = 18.1 $J_{6a,8a}$ = 1.4	$J_{6b,8b}$ = 1.4
b	H-8a	H-8b	H-9	H-10	H-11	H-12a
c	2.25	2.62	2.81	2.25	5.84	1.98
d	ddd	ddd	dddd	dd	ddd	dddd
e	$J_{8a,8b}$ = 18.1 $J_{8a,9}$ = 11.1	$J_{8b,9}$ = 8.1	$J_{9,10}$ = 9.1	$J_{10,11}$ = 15.3	$J_{11,12a}$ = 10.1 $J_{11,12b}$ = 5.1	$J_{12a,12b}$ = 12.5 $J_{12a,13a}$ = 2.6 $J_{12a,13b}$ = 5.1
b	H-12b	H-13a	H-13b	H-14a	H-14b	H-15	H-16
c	1.81	1.06	1.70	1.61	1.50	4.98	1.24
d	dddd	ddddd	dddd	ddd	dddd	m	d
e	$J_{12b,13a}$ = 12.2 $J_{12b,13b}$ = 2.6	$J_{13a,13b}$ = 14.3 $J_{13a,14a}$ = 7.3 $J_{13a,14b}$ = 1.3	$J_{13b,14a}$ < 0.1 $J_{13b,14b}$ = 6.1	$J_{14a,14b}$ = 14.3 $J_{14a,15}$ = 2.4	$J_{14b,15}$ = 8.3	$J_{15,16}$ = 6.25	

[a] Determined at 270 MHz on a Bruker WH-270 NMR spectrometer. SW = 2400 Hz, T = 28 °C, resolution = ±0.08 Hz. Compound (5 mg) was dissolved in pyridine-d_5 (0.3 mL). [b] Numbering corresponds to numbering shown in Figure 1. [c] Chemical shifts are in ppm relative to internal Me_4Si as standard. [d] Signal multiplicity. [e] Coupling constants, $J_{p,q}$, are in Hz. All spin-spin coupling systems were analyzed with the Nicolet spin simulation program on ITRCAL 1 and 2 data systems.

† NRCC No. 19056.

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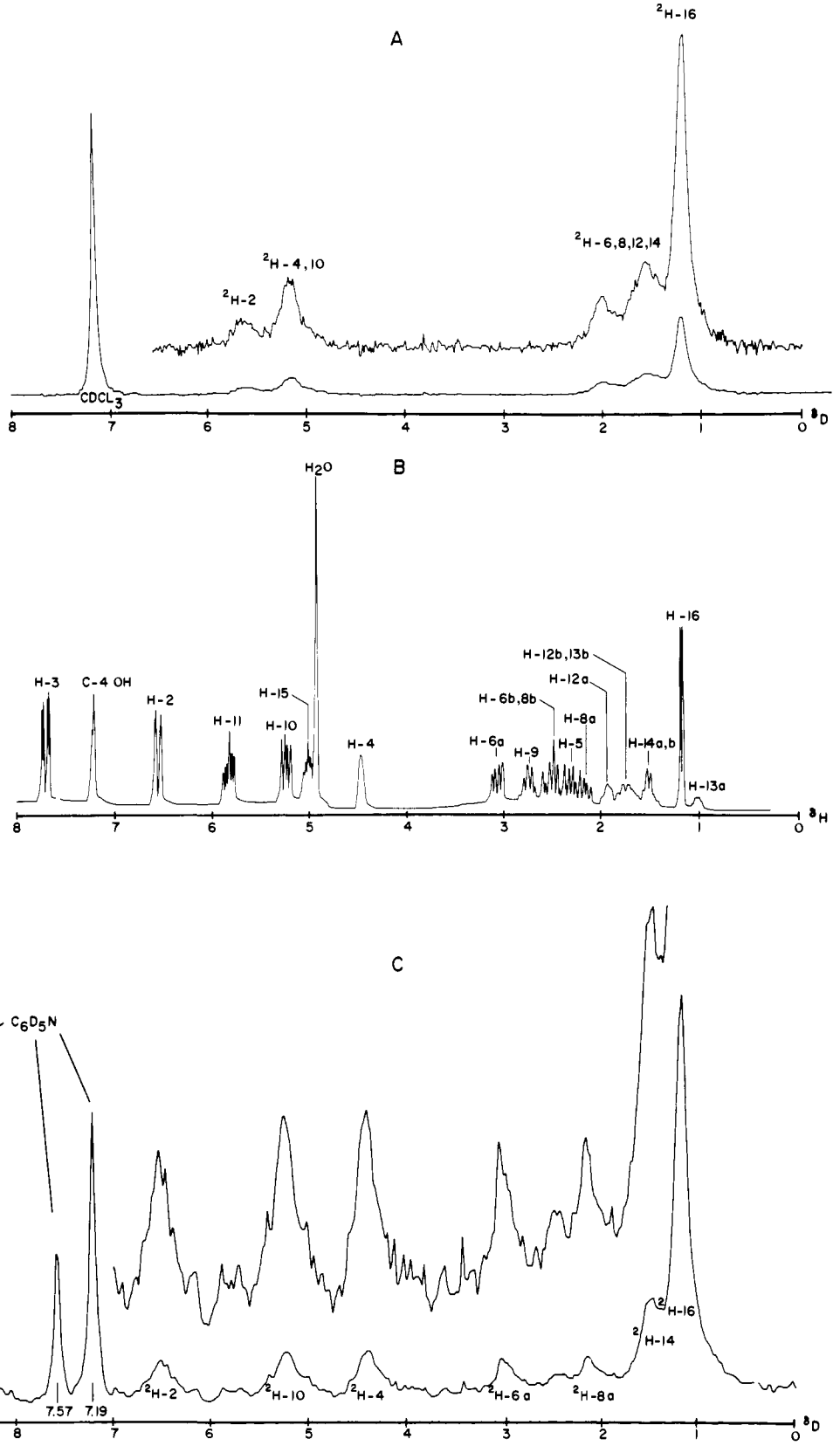
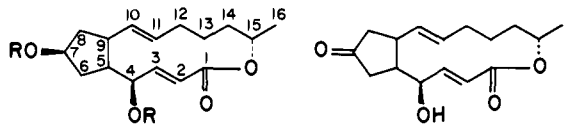


Figure 2. High-field NMR spectra of brefeldin A derivatives. (A) 41.44-MHz ^{2}H{^{1}H} NMR spectrum of 4,7-diacetylbrefeldin A (**2**) labeled by [2-^{2}H$_3$]acetate. Compound (36 mg) was dissolved in C*H*Cl$_3$ (0.5 mL) containing C^{2}HCl$_3$ as internal standard to which the δ_D are referred (C^{2}HCl$_3$ = 7.27 ppm). The spectrum was collected over 4K data points/1000 Hz, acquisition time 2.05 s at 28 °C, and transformed into 8K data points with 0.5-Hz line broadening. Total spectral acquisitions = 6171. (B) 270-MHz ^{1}H NMR spectrum of 7-oxobrefeldin A (**3**), 7 mg, in degassed C$_5^2$H$_5$N (0.3 mL). (C) 41.44-MHz ^{2}H{^{1}H} NMR spectrum of 7-oxobrefeldin A (**3**), 17.5 mg in C$_5$H$_5$N (0.5 mL), derived from brefeldin A (**1**) and labeled by [2-^{2}H$_3$]acetate. Compound (17.5 mg) was dissolved in C$_5$H$_5$N (0.3 mL) containing 0.01 mmol C^{2}HCl$_3$ as an internal standard. The δ_D are referred to the upfield signal of residual C$_5^2$H$_5$N (δ_D 7.19). The spectrum was determined as for (A) but with 1.0-Hz line broadening and a spectral width of 2000 Hz. Total spectral acquisitions = 22 120.



1, R = H
2, R = $COCH_3$

3

with spectral simulation and other data[4-6] gave the parameters listed in Table I. As the crucial assignments for H-6a, H-6b, H-8a, and H-8b depended solely on magnitudes of coupling constants in five-membered carbocyclic rings, which are not as well understood[7] as those for six-membered rings,[8] the assignments were confirmed by nuclear Overhauser enhancement (NOE)[9] difference spectroscopy[10] measurements on $C_5{}^2H_5N$ solutions of **3**. It is noteworthy that the NOE data (Table II) indicate that **3** has a conformation in $C_5{}^2H_5N$ identical with that in the solid state as determined by X-ray crystallographic analysis[4] (Figure 1).

Cultures of *Penicillium brefeldianum* Dodge (Sandoz 464) to which 5 mM [2-$^2H_3$]acetate was added on days 1 and 2 of the 3-day metabolic period resulted in a sample of brefeldin A containing adequate overall ^2H enrichment for ^2H NMR analysis. Part of the labeled antibiotic was converted to [^2H]**2** and the remainder to [^2H]**3** by the same conditions used to oxidize [^3H]**1** to [^3H]**3**[1] without loss of ^3H from the molecule.[11] Subsequent $^2H\{^1H\}$ NMR spectral analysis at 41.44 MHz of [^2H]**2** and [^2H]**3** established that significant ^2H labeling was present only at the H-2, H-4, H-6a (pro-*R*, L configuration), H-8a (pro-*S*; L configuration), H-10, H-14, and H-16 positions as shown by Figure 2a,c. There is also the possibility that a small amount of ^2H also is present at the H-6 pro-*S* and H-8 pro-*R* positions,[11] but H-12 clearly does not contain significant ^2H enrichment. Finally, the ^2H chemical shift dispersion for labeled **2** and **3** was insufficient to ascertain if the diastereotopic hydrogens attached to C-14 were stereoselectively labeled.

It is important to compare polyketide and fatty acid biosynthesis in order to determine whether they have common mechanistic features. If they do, the wealth of knowledge available on fatty acid biosynthesis may help to rationalize how intricate polyketides such as the macrolides are assembled.

The regiochemical distributions of ^{13}C and ^2H labels in brefeldin A and fatty acids strongly suggest a common basic anabolic biochemistry;[1] any difference, such as that observed at C-14 of the former, reflects mechanistic details unique to the biosynthesis of the macrolide.

Hydrogen isotopic labeling of butyric acid by yeast fatty acid synthetase[12] and of palmitoleic acid by yeast[14] has shown unequivocally that even-numbered carbons bear a hydrogen derived from malonate at the pro-*R* (D configuration) and a hydrogen from the environment at the pro-*S* (L configuration) position. However, labeling by yeast fatty acid synthetase may be atypical as its enoyl reductase component is the only one known to have an absolute requirement for flavin mononucleotide.[13] This was suggested by studies on palmitic, palmitoleic, and linolenic acids from two algae,[14,15] and palmitic acid from *E. coli*,[16] which established that malonate labeled the pro-*S*, and the environment the pro-*R*, hydrogen at even-numbered positions because the enoyl reductase in these organisms had the reverse stereospecificity. These stereochemical features are also present at C-6 and C-8 of ^2H-enriched brefeldin A, and this combined with the similar retention of ^2H at C-2 through C-10[1] strongly supports the hypothesis that the steps of brefeldin A biosynthesis proceed by stereospecific reactions similar to those involved at each stage of fatty acid formation in algae[14] and *E. coli*.[16]

The configuration of ^2H attached to C-4 of brefeldin A is more consistent with oxidation of a double bond at C-4, C-5 than a C-4 methylene group.[17] The latter should possess a pro-*S* label, by analogy with C-6 and C-8, which would be lost on biological hydroxylation by known pathways.[18] Hydroxylation with inversion of configuration is less likely, although examples where this is claimed to occur have been reported.[19] Stereospecific olefin oxidation, on the other hand, followed by formation of the cyclopentanol ring as previously suggested[5] would result in retention of ^2H at C-4.

Finally, the chiral center at C-15 of **1** has an *S* configuration in contrast to the hydroxymethylene groups of fatty acid intermediates which have an *R* configuration,[20] and the absolute

Table II. $\{^1H:^1H\}$ Nuclear Overhauser Enhancement Data for 7-Oxobrefeldin A (**3**)[a]

proton irradiated[b]	observed NOE[c] (proton)[b]
4	2, 3, 6b, 9
5	4, 6a, 10
6a	5, 6b
8a	8b, 10
9	3, 4, 8b, 11
10	5, 8a, 11
11	3, 9, 10, 12a, 14b
12a	10, 11, 12b, 13a
12b + 13b	11, 12a, 13a
13a	12a, 13b, 14a, 15
15	2, 13a, 14a
16	15

[a] Spectra were determined on a Bruker WH-270 NMR spectrometer in the HG operating mode (cf. ref 10b, p 6279, for a detailed explanation of this operating procedure). Compound **3** (7 mg) was dissolved in 0.3 mL of pyridine-d_5 and the solution degassed by four freeze–thaw cycles in vacuo. The spectra were collected in alternating blocks of 50 off-resonance and then 50 on-resonance spectra using a SW of 1000 Hz with 8K data points for 200 spectral acquisitions each, transformed, and then subtracted after matching the upfield pyridine line to identical data addresses. [b] Numbered as shown in Figure 1. [c] All observed NOE's had a S/N ratio of >2 in the difference spectra and ranged in area between 2 and 23% of the area of a nonenhanced proton resonance.

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configuration of the ω2 position of all other fungal macrolides. Thus either the reductase involved in the production of this chiral center has a different stereospecificity than the corresponding component of fatty acid synthetase, or acetoacetyl-enzyme is first reduced to (3*R*)-3-hydroxybutyryl-enzyme and then converted to the 3*S* enantiomer by an enzyme similar to 3-hydroxybutyryl-CoA racemase.[21]

The information presented in this paper and the preceding one[1] substantiates the supposition that fatty acids and brefeldin A are assembled by enzymes that exhibit similar or identical stereoselectivities in the reactions which they catalyze. It now remains to be seen how these similarities in comparative biochemistry produce the fascinating stereochemical relationships found among the macrolide antibiotics.

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Naked-Metal Clusters in Solution.[1] 4. Indications of the Variety of Cluster Species Obtainable by Extraction of Zintl Phases: Sn_4^{2-}, $TlSn_8^{5-}$, $Sn_{9-x}Ge_x^{4-}$ (x = 0-9), and $SnTe_4^{4-}$

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We recently reported a multinuclear NMR study which gave prima facie evidence for the fluxional nature of naked-metal clusters such as Sn_9^{4-} in solution, established for the first time the existence of heteroatomic naked-metal cluster anions such as $Sn_{9-x}Pb_x^{4-}$ (x = 0-9),[2,3] and showed that they can be generated electrochemically.[4] Here, we present evidence which demonstrates the rich *variety* of homo- and heteroatomic anions obtainable in solution from Zintl phases.[5] This report includes a new naked cluster in solution,[3] Sn_4^{2-}, the new heteroatomic naked cluster $TlSn_8^{5-}$, the $Sn_{9-x}Ge_x^{4-}$ (x = 0-9) series, and a "conventional" $SnTe_4^{4-}$ which is proposed to be tetrahedral. Parameters which correlate with chemical shift and lead to the assignment of naked-metal clusters are discussed, also.

If alloys of composition $Na_{1-2}Sn$ are maintained in contact with ethylenediamine (en), the resulting red solution gives a signal 665 ppm upfield from Sn_9^{4-} in the ^{119}Sn NMR in both the presence and absence of 2,2,2-crypt. The solution never becomes as intensely colored as those for Sn_9^{4-}, but with prolonged accumulation a triplet with 0.12/1.00/0.12 relative intensities and a ^{119}Sn-^{117}Sn coupling of 1224 Hz can be observed. Our calculations of relative intensity as a function of cluster size[3] suggest that this is a four-atom cluster, since patterns of 0.16/1.00/0.16, 0.12/1.00/0.12, and 0.08/1.00/0.08 are expected for five, four, and three tin atoms, respectively. A rough analysis of Na/Sn by ^{23}Na and ^{119}Sn NMR indicated a Na_2Sn_4 stoichiometry. Empirical deduction would also suggest a Sn_4^{2-} rather than Sn_4^{4-}, since no known naked clusters in solution bear anything approaching a unit negative charge per Sn atom. Only in a solid phase such as β-NaSn could a Sn_4^{4-} be construed.[6]

If the Allred-Rochow electronegativity scale[7] (χ_{Pb}/χ_{Sn} = 0.910) is used to assign a charge per Sn atom (Z_{Sn}) in the series of clusters $Sn_{9-x}Pb_x^{4-}$ (x = 0-9) by maintaining the total charge of the cluster at -4 and the charge is plotted vs. the chemical shift, the equation δ(Sn-119) = [8991(Z_{Sn}) + 2760] ppm is found [where δ(Sn-119) is the shift relative to external Me_4Sn = 0]. This relationship gives calculated chemical shifts of -836 and -1735 ppm for Sn_5^{2-}(Z_{Sn} = -0.4) and Sn_4^{2-}(Z_{Sn} = -0.5), respectively. Since tin chemical shifts have been shown in certain instances to follow electronegativity,[8] the observed -1895 value corroborates the rough analytical data metioned above. We have not yet observed a Sn_5^{2-} in solution, although its crystal structure has been reported.[9] We also find such charge considerations nicely fit the chemical shifts of the previously reported Te_6^{4+}, Te_4^{2+}, Te_3Se^{2+}, $Te_2Se_2^{2+}$, $TeSe_3^{2+}$ series,[10] among others. However, such correlations do not appear to be general as indicated by the $Sn_{9-x}Ge_x^{4-}$ discussed later.

The intensity of the Sn_4^{2-} NMR signal in solutions over the alloy increases and peaks after about 2 weeks at 298-303 K. After that time new species which include Sn_9^{4-} are apparent by ^{119}Sn NMR spectroscopy; their complete characterization will require additional work with sensitive instrumentation. The solution structure of Sn_4^{2-} has been examined theoretically.[11] Subsequent to our discovery of Sn_4^{2-} in solution, it also has been isolated and investigated by X-ray.[12]

Alloys of composition NaSnGe and KSnGe give deep red solutions when treated with en. These solutions give a rich ^{119}Sn NMR spectrum which suggests the existence of a *nido*-$Sn_{9-x}Ge_x^{4-}$[13] (x = 0-9) series to parallel the well established *nido*-$Sn_{9-x}Pb_x^{4-}$ series of fluxional clusters. However, unlike the situation with ^{207}Pb, the signals due to the $Sn_{9-x}Ge_x^{4-}$ series show no discernable spin-spin coupling to ^{73}Ge (7.7%, I = $^9/_2$) which can be attributed to its quadrupolar nature and rapid relaxation. With the absence of ^{119}Sn-^{73}Ge coupling the cluster stoichiometry must be inferred by analogy to the $Sn_{9-x}Pb_x^{4-}$ series. Still, a series

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