^{13}C NMR SPECTRA OF STREPTOLYDIGIN, TIRANDAMYCIN, AND RELATED DEGRADATION PRODUCTS

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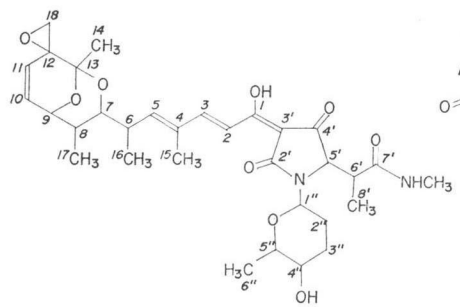
Absorptions of the 32 carbon atoms of streptolydigin, a 3-acyltetramic acid, have been assigned in its ^{13}C NMR spectrum, as have the adsorptions of tirandamycin and related degradation products. Methods employed in assigning the individual carbons include off-resonance decoupling, single frequency decoupling, and comparison studies with appropriate model compounds.

We have recently renewed our long-standing interest in 3-acyl tetramic acids[1] due in view of their reported selective inhibition of terminal deoxynucleotidyl transferase from leukemic cells,[2] and we have found it necessary to assign the individual carbon absoprtions in their ^{13}C NMR spectra, both for studying their biosynthesis and for characterizing new, related compounds. In the present paper we report the ^{13}C NMR assignments of streptolydigin (**1**) and tirandamycin (**2**), as well as those of streptolic acid (**3**) and tirandamycic acid (**4**), degradation products obtained *via* periodate oxidation of the respective sodium salts of **1** and **2**, and of streptal (**5**) and tirandamycal (**6**), compounds obtained by ozonolysis of **1** and **2**.

^{13}C NMR Spectra of Degradation Products (**3**, **4**, **5** and **6**)

Chemical shifts for the carbon atoms of **1**~**6** were determined on proton decoupled spectra and



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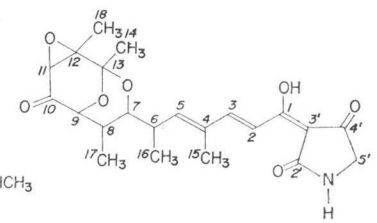

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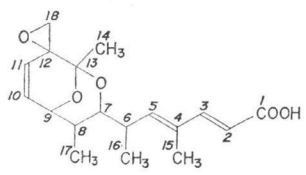

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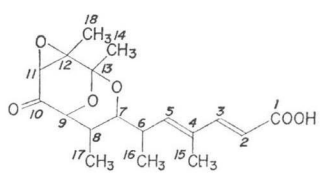

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Table 1. ^{13}C NMR assignments for streptolydigin, tirandamycin and their degradation products.

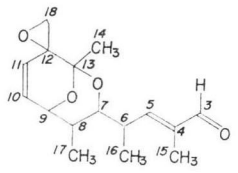
Carbon		δ, ppm[a,b,c,d]					
Type	No.	Strepto-lydigin **1**	Tiranda-mycin **2**	Streptolic acid **3**	Tiranda-mycic acid **4**	Streptal **5**	Tiranda-mycal **6**
CH_3–	C-14	22.2#	22.6	22.2	22.6	22.1	22.6
	C-15	12.2	12.5#	12.2#	12.2#	9.1	—
	C-16	17.1**	17.1	17.1	17.0	16.5	11.2*
	C-17	12.5	11.4	12.5	11.4	12.4	11.5*
	C-18	—	15.6	—	15.6	—	15.6
	C-8′	10.3	—	—	—	—	—
	C-6″	17.0**	—	—	—	—	—
CH_3–N–		26.7#	—	—	—	—	—
–CH_2–	C-2″	30.2	—	—	—	—	—
	C-3″	21.3	—	—	—	—	—
–CH_2–NH–	C-5′	—	51.6	—	—	—	—
–CH_2–O–	C-18	50.5#	—	50.5	—	50.4	—
–CH–	C-6	34.1#	34.5*	33.8	34.2*	33.9	46.9
	C-8	35.2	34.7*	35.1#	34.7*	35.2	34.5
	C-6′	42.1#	—	—	—	—	—
–CH–N	C-5′	63.0	—	—	—	—	—
–CH–O–	C-7	75.9	76.8	76.1	77.0	75.9	76.4
	C-9	71.3#	78.7	71.4	78.3	71.3	78.7#
	C-11	—	61.2	—	61.2	—	61.2
	C-4″	66.2#	—	—	—	—	—
	C-5″	76.1	—	—	—	—	—
–C–O–	C-12	55.0	57.0	55.0	57.1	54.9	56.8
–N–CH–O–	C-1″	78.8	—	—	—	—	—
–O–C–O–	C-13	98.8	96.7	98.8	96.8	98.9	97.1
=CH–	C-2	116.0	116.6	115.1	115.7	—	—
	C-3	150.3	149.3	151.7	151.5	—	—
	C-5	145.9	143.2	143.1	141.4	153.9	—
	C-10	133.6#	—	133.6	—	133.5	—
	C-11	130.4#	—	130.5	—	130.6	—
=C–	C-4	133.9	134.7	132.4	133.5	139.1	—
	C-3′	99.7	100.0	—	—	—	—
–C=O	C-4′	193.5	192.4	—	—	—	—
–COOH	C-1	—	—	172.6	172.6	—	—
=C–OH	C-1	173.4***	176.4**	—	—	—	—
–CH=O	C-3	—	—	—	—	195.2	—
	C-5	—	—	—	—	—	203.0
–C=O	C-10	—	202.1	—	202.5	—	202.2
–N–C=O	C-2′	174.7***	174.7**	—	—	—	—
	C-7′	174.9***	—	—	—	—	—

[a] Ppm downfield from TMS. [b]# Confirmed by single frequency decoupling (SFD). [c] Signals marked. *, **, *** may be interchanged in the column where they appear. [d] Proton off-resonance spectra were obtained on all compounds.

are tabulated in Table 1. Assignments were made by comparison of the fully decoupled spectra with proton off-resonance decoupled spectra, by single frequency proton decoupling experiments, from standard chemical shift data,[3] and by comparison with chemical shifts of model compounds (*vide infra*). Considerable assistance was provided by the previously interpreted ^{1}H NMR spectra,[4] since unequivocal assignments could usually be obtained by single frequency proton decoupling if the proton signals differed by more than 0.1 ppm.

Initial studies were performed with streptolic acid (**3**) and tirandamycic acid (**4**) because of their identical structure in the region from the carboxyl group through the dioxane ring (C-1 through C-9 and C-13 through C-17) and the lack of interfering resonances from the tetramic acid and L-rhodinose units. Carbon resonances were divided initially into the groups shown in Table 1 according to the multiplicity of the carbons' resonances in the off-resonance spectrum (*i.e.*, into methyl, methylene, methine, and quaternary carbons).

This immediately assigned C-18 in streptolic acid (the only methylene carbon), C-12 (55.0 ppm in streptolic acid, 57.1 ppm in tirandamycic acid), and C-13 (98.8 ppm in **3**, 96.8 ppm in **4**) in both acids (quaternary carbons bearing one and two oxygens, respectively), C-10 in tirandamycic acid (202.5 ppm, ketone carbonyl carbon), C-1 in both acids (172.6 ppm, carboxyl carbons), and C-4 (132.4 in **3**, 133.5 in **4**) in both acids (quaternary olefin carbons). These assignments were repeated for streptal (**5**) and tirandamycal (**6**) in which all the carbons noted (where present) appeared within 0.3 ppm of the corresponding carbons of **3** and **4**, except C-4 of **5** which was downfield of C-4 in streptolic acid but as the only quaternary olefin carbon was unmistakable.



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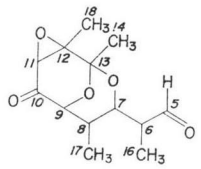

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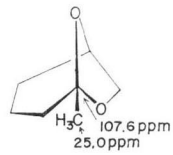

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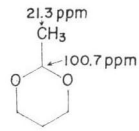

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CH_3 Carbons

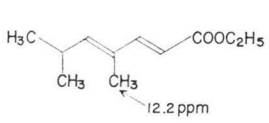
Comparison of the spectra of tirandamycic acid (**4**) which has five methyl carbons, and streptolic acid (**3**), which has four methyl carbons, readily assigned the 15.6 ppm resonance to C-18 of **4**. The identical chemical shift is observed for C-18 in tirandamycal (**6**). Of the remaining four methyl carbons in **3** and **4**, C-14 should be at lowest field due to the double β-deshielding effect[3b] of the oxygen atoms in the 2,9-dioxabicyclo[3.3.1]nonane ring. Thus, C-14 in **3**~**6** appears in the range 22.1~22.6 ppm, while *exo*-brevicomin (**7**)[3b] and 2-methyl-1,3-dioxane (**8**)[3b] display methyl resonances at 25.0 and 21.3 ppm, respectively.

Of the remaining three methyl carbons (C-15, C-16, and C-17) in acids **3** and **4**, C-17 and C-15 should, *a priori*, be upfield from C-16, since C-17 experiences a double γ-shielding effect due to the two oxygen atoms in the bicyclic system,[3b] while C-15 is on an olefinic carbon.[3a,b] Although chemical shifts for C-15 and C-17 differed by less than one ppm, they were distinguished by single frequency decoupling. Irradiation of the C-15 methyl protons at 1.91 ppm in streptolic acid (**3**) caused a quartet→singlet transformation of the 12.2 ppm resonance; thus, by difference, the C-17 resonance is at 12.5

ppm. For tirandamycic acid (**4**) single frequency decoupling at 1.83 ppm assigned the C-15 and C-17 carbons at 12.2 ppm and 11.4 ppm, respectively. Additional arguments for the C-17 *vs.* C-15 assignments are the different position of C-17 for **3** and **4** (near the C-10 through C-18 region where **3** and **4** differ) while C-15 is unchanged and the fact that C-17 remains the same in **3** and **5** as well as in **4** and **6**, while C-15 is shifted upfield for **5** *vs.* **3** and is missing in **6**. A model for C-15, ethyl 4,6-dimethyl-(*E*,*E*)-2,4-heptadienoate (**9**),[1d] displays the γ-methyl resonance at 12.2 ppm, while in the (*E*,*Z*)-isomer, **10**, it is at 20.0 ppm.[1d,5] The other methyl carbon in compound **3**~**4**, C-16, appeared at 17.0~17.1 ppm, but is slightly shifted in **5** and shifted upfield to 11.2 ppm in **6**. The lower field value for this carbon is attributable to its allylic position (partially offset by its gamma position to a heteroatom).

–CH– Carbons

There are only two aliphatic methine carbons (C-6 and C-8) attached only to carbons in **3**, **4**, **5**, and **6**, but they were distinguishable only by single frequency decoupling studies. In streptolic acid (**3**), when H-8 at 2.03 ppm was irradiated the signal at 35.1 ppm underwent a doublet→singlet transformation. Thus, C-8 and C-6 appear at 35.1 and 33.8 ppm, respectively. The same carbons in aldehyde **5** appear undisplaced at 35.2 and 33.9 ppm, respectively, while in tirandamycic acid (**4**) they appear at 34.7 and 34.2 ppm and in tirandamycal (**6**) at 34.5 ppm (C-8) and 46.9 ppm (C-6).



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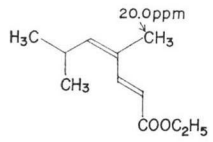

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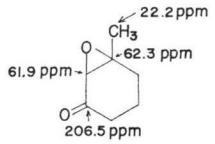


11

–CHO– Carbons

Comparison of the spectra of **3**~**6** showed that C-11 appeared at 61.2 ppm for both of the tirandamycin degradation products. The shift is similar to that of the methine carbon (61.9 ppm) in the model compound, 6-methyl-7-oxabicyclo[4.1.0]heptan-2-one (**11**). Of the remaining two –CHO– carbons, C-7 and C-9 in streptolic acid and streptal were assigned as those at 76.1 and 75.9 ppm (C-7) and 71.4 and 71.3 ppm (C-9), respectively, by single frequency decoupling studies on streptolydigin (**1**, *vide infra*). In tirandamycic acid (**4**), C-9 and C-7 appear at 78.3 ppm and 77.0 ppm and in the aldehyde **6** at 78.7 ppm and 76.4 ppm, respectively. Single frequency decoupling by irradiation of H-9 in **6** (at 4.10 ppm) caused a doublet→singlet transformation for the 78.7 ppm resonance; thus, this is due to C-9 and the 76.4 ppm resonance is due to C-7.

=CH– Carbons

Comparison of the spectra of acids **3** and **4** and of aldehydes **5** and **6** showed two additional olefinic resonances, in streptolic acid (**3**) at 133.6 and 130.5 ppm and at 133.5 and 130.6 ppm in streptal (**5**), for C-10 and C-11, respectively. Assignments were made by single frequency decoupling studies on streptolydigin (**1**, *vide infra*). The remaining three olefinic carbons (C-2, C-3, C-5), common to both acids **3** and **4**, were assigned from electronic considerations. *A priori*, C-3 should be the furthest downfield, followed by C-5 and C-2, on the basis that electronic release from the olefinic system to

the carbonyl group results in the lowest electron density on the β-carbon (C-3), and next lowest on the δ-carbon (C-5),[3] with the α-carbon (C-2) far upfield. Thus, in streptolic acid, the 151.7, 143.1, and 115.1 ppm resonances are attributed to C-3, C-5, and C-2, respectively, while in tirandamycic acid (**4**) the same carbons are at 151.5, 141.4, and 115.7 ppm, respectively. Confirming this is the relatively different environments of C-5 in **3** and **5**. The single –CH= carbon (a β-carbon) in streptal (**5**) is at 153.9 ppm. The same chemical shift trend is observed with the streptovaricins.[5]

^{13}C NMR Spectra of Streptolydigin and Tirandamycin (1 and 2)

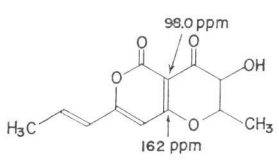
When the ^{13}C NMR spectra of tirandamycic acid (**4**) and tirandamycin (**2**) are compared, the major differences can be attributed to the four carbon atoms (C-2′ to C-5′) on the tetramic acid ring. In addition, C-1 is shifted downfield (to 176.4 ppm or 174.7 ppm) on going from a carbonyl to an enol. The off-resonance spectra showed four singlets at 192.4, 176.4, 174.7 and 100.0 ppm and a triplet at 51.6 ppm. The latter two resonances must be due to C-3′ and C-5′, respectively, while the 192.4 ppm resonance is due to C-4′. A carbon similar to C-3′ in radicinin (**12**) appeared at 98.0 ppm.[3b] The two singlets at 176.4 and 174.7 ppm were attributed to C-1 and C-2′; but they were too similar to be distinguishable.

Recently, tirandamycin B was reported by HAGENMAIER, *et al.*,[6] reportedly differing from tirandamycin by the replacement of the 15.6 ppm (C-18 methyl) resonance by that due to a hydroxymethyl (–CH_2OH) group found at 57.65 ppm (triplet in the off-resonance spectrum).

Subtraction of the ^{13}C NMR contribution of carbons C-2 through C-18 for the streptolyl unit from streptolydigin leaves fifteen additional resonances for the remaining carbons of C-1 and the N-1-rhodinosyl-2,4-pyrrolidione unit. These signals were divided into the expected multiplicity groups: (a) C-8′, C-6″, and the NCH_3 methyl carbons, (b) C-2″ and C-3″ methylene carbons, (c) C-5′, C-6′, C-1″, C-4″, and C-5″ methine carbons, (d) C-1, C-2′, C-3′, C-4′, and C-7′ quaternary and carbonyl carbons.

CH_3 Carbons

A priori, the NCH_3 should be the methyl carbon furthest downfield due to the heteroatom effect, and confirmation of the CH_3N assignment was effected by irradiation at NCH_3 proton frequency (3.0 ppm), which resulted in a quartet→singlet transformation of the 26.7 ppm resonance. Assignment of the C-6″ methyl carbon to the 16~18 ppm region was effected by comparison to β-L-rhamnose (**13**), which has a methyl carbon (at 17.0 ppm) in a similar environment.[3a] Expansion of the off-resonance spectrum of **1** in the 15~21 ppm region showed two quartets, at 17.0 and 17.1 ppm, with one due to C-16 (*vide supra*) and the other, therefore, due to C-6″. By difference, the absorption at 10.3 ppm must be due to C-8′.



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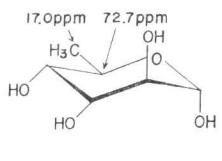

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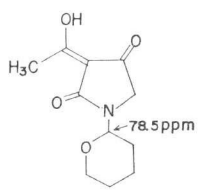

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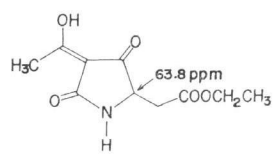


15

$-CH_2-$ Carbons

The methylene carbon signals at 30.2 and 21.3 ppm are assigned to C-2″ and C-3″, respectively, in the basis that C-2″ is deshielded by the β-effect of two heteroatoms (N and O), while C-3″ experiences a minimal β-effect from the C-4″ equatorial hydroxyl group.

-CH- Carbons

The five methine resonances for C-5′, C-6′, C-1″, C-4″, and C-5″ can be separated into two groups, with those bonded to an oxygen (C-1″, C-4″ and C-5″) expected to be deshielded more than the others (C-5′, and C-6′). The anomeric carbon (C-1″) is bonded to two heteroatoms and should give the signal at 78.8 ppm, furthest downfield, while C-5″ is α to the ring oxygen, β to the C-4″ hydroxyl, and γ to the anomeric nitrogen is next furthest downfield (76.1 ppm). These assignments were confirmed by comparison to the model compounds **13** and **14**. The anomeric carbon in 3-acetyl-1-(2-tetrahydropyranyl)-2,4-pyrrolidione (**14**) appears at 78.5 ppm, while the C-5 carbon of β-L-rhamnose (**13**) appears at 72.7 ppm. By difference, the 66.2 ppm resonance should be due to C-4″, and single frequency proton decoupling of H-4″ (2.67 ppm) afforded a doublet→singlet conversion of the 66.2 ppm resonance. Of the remaining two methine carbons, C-5′ is deshielded by bonding to nitrogen and should be that at 63.0 ppm, and the methine carbon in **15** (analogous to C-5′) appears at 63.8 ppm. The remaining carbon, C-6′, must be that at 42.1 ppm, and irradiation of H-6′ (2.5 ppm) caused a doublet→singlet transformation of the 42.1 ppm resonance.

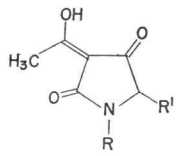
Quaternary Carbons

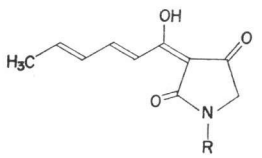
Of the quaternary and carbonyl carbons, C-3′ and C-4′ were assigned at 99.7 and 193.5 ppm by analogy to other 3-acyltetramic acids (natural and synthetic, *vide supra*). The remaining carbons (C-1, C-2′, and C-7′) at 173.4, 174.7 and 174.9 ppm could not be assigned due to the similarity in their chemical shifts.

Single Frequency Proton Decoupling

Additional single frequency decoupling studies performed on streptolydigin (**1**) confirmed the assignments of carbons similar to those in the degradation products, as noted above. Differentiation of C-10 and C-11 of **1**, by decoupling the H-10 olefinic proton at 6.24 ppm resulted in a doublet→singlet transformation of the 133.6 ppm resonance, while irradiation of the H-11 olefinic proton at 5.86 ppm collapsed the 130.4 ppm doublet. Irradiation of the H-6 methine proton at 3.0 ppm resulted in a change in the shape of the 34.1 ppm carbon resonance; thus, the 35.2 ppm resonance must be due to C-8. Irradiation of the H-14 methyl protons at 1.28 ppm caused a change in the shape of the 22.2 ppm carbon resonance, thus confirming the C-14 assignment in **1**~**6**.

The similar chemical shifts for the C-1 and C-2′ carbons in antibiotics **1** and **2** was not unexpected based on our model studies. It was observed in the 3-acetyltetramic acids **14**~**18** that C-2′ (172.5~175.0 ppm) was well separated from C-1 (184.2~185.7 ppm), but that in the





16 R=CH_3; R^1=$CH_2CONHCH_3$ **19** R=cyclohexyl
17 R=cyclohexyl; R^1=H **20** R=$CH_2C_6H_5$
18 R=R^1=H

3-dienoyltetramic acids **19** and **20** the two signals differed by less than 1 ppm.[1b,1d]

Experimental Section

^{13}C NMR spectra were recorded by the FOURIER transform technique on a Varian XL-100 spectrometer interfaced to a Digilab computer. Single frequency decoupling studies involved irradiation of the appropriate proton signal, as assigned earlier,[4] measured in Hz from tetramethylsilane on a Varian HA-100 or XL-100 spectrometer. The solvent, deuteriochloroform, was used as the deuterium lock. Chemical shifts (δ) are reported as ppm from tetramethylsilane as internal standard. Mass spectra were obtained on a Varian MAT CH-5DF (low resolution) and Varian MAT 731 (high resolution) spectrometers by Mr. J. C. COOK, Jr., and his associates.

Microanalyses were obtained at the University of Illinois by Mr. J. NEMETH and associates. Partition chromatography was performed on acid-washed Celite that was washed to neutrality and dried at 105°C overnight. In preparation of a partition chromatography column, the stationary phase (9.0 ml per 10.0 g of Celite) was thoroughly mixed with the solid support before packing in the mobile phase with external pressure. The sample was dissolved in a minimal amount of stationary phase and applied to the packing.

Streptolydigin (1)

A sample of crude streptolydigin (6.0 g, The Upjohn Co., 2677-DEV-137) was equilibrated in 200 ml of the biphasic system ether - acetone - water (2: 1: 2). The organic phase was separated, filtered, and concentrated *in vacuo*. The semicrystalline material was crystallized thrice by dissolving it in warm ethyl acetate and allowing it to crystallize in the cold to afford 620 mg of light yellow microcrystals, mp 149~151°C (lit.[7] 143~144°C)

Tirandamycin (2)

A sample of crude tirandamycin (2.0 g, The Upjohn Co., 9177-DEG-51-2) was suspended in 100 ml of 0.2 N sodium hydroxide in dimethylformamide for 15 minutes and filtered. The filtrate was acidified with glacial acetic acid and exhaustively extracted with methylene chloride to afford a light yellow oil which was triturated with benzene. The resultant benzene solvate was obtained as yellow crystals (525 mg), mp 125~127°C (lit.[4a] mp 124~127°C). Solution of the solvate in chloroform and concentration *in vacuo* (twice) afforded yellow crystals of tirandamycin free of all traces of benzene, as indicated by the ^1H NMR spectrum.

Streptolic Acid (3)

A solution of streptolydigin (**1**, 3.86 g) in 600 ml of *tert*-butyl alcohol and 400 ml of deionized water was cooled to 0~5°C in an ice bath. Sodium bicarbonate (540 mg) in 20 ml of water was added, followed by a solution of 24.0 g of sodium periodate in 1,100 ml of water. The reaction was protected from light and maintained at 5°C for 27 hours, then quenched with 16 ml of ethylene glycol. The reaction mixture was extracted with ether and the solvent was removed *in vacuo* to afford 3.95 g of orange oil, which was purified by partition chromatography over Celite (8: 2 methanol - water as stationary phase, 9: 1 heptane - chloroform as mobile phase) to give 710 mg (35%) of crystalline **3**, mp 164~165°C (lit.[8] 168~170°C).

Tirandamycic Acid (4)

A mixture of 1.2 g of sodium tirandamycin in 2.0 liters of distilled water and 750 ml of *tert*-butyl alcohol was stirred at ambient temperature for several hours until most of the material was dissolved. A solution of 20.0 g of sodium periodate in 1.0 liter of water was added and the reaction was protected from light for 3 days. The reaction was quenched with 16 ml of ethylene glycol and extracted with ether. Workup followed by partition chromatography on Celite (as in the preparation of **3** above) afforded a white solid, mp 70~74°C. Recrystallization from benzene-petroleum ether afforded 590 mg (57%) of tirandamycic acid (**4**), mp 91~92°C (lit.[4a] 89~92°C); $[\alpha]_D^{28}+63°$ (c 0.950, in $CHCl_3$).

Streptal (5)

A cold solution (−78°C) of 6.0 g of streptolydigin in 200 ml of 0.05 M methanolic sodium hydro-

xide was treated with ozone until an aliquot gave a negative ferric chloride test. Residual ozone was purged with a stream of nitrogen and 5.0 ml of dimethyl sulfide added. The reaction mixture was concentrated *in vacuo* and the residue taken up in methylene chloride. Workup followed by partition chromatography over Celite (40 mm×500 mm, 8: 2 methanol - water as stationary phase, 9:1 heptane - chloroform as mobile phase) afforded streptal (**5**) as a yellow viscous oil (764 mg). The TLC and ^1H NMR data showed it to be *ca.* 95% pure.

Tirandamycal (**6**)

A solution of 2.09 g of tirandamycin in 200 ml of 0.027 M methanolic sodium hydroxide was ozonized in the same manner as **5** above. The resultant crude aldehyde was chromatographed over a Bio-Sil A column (Bio-Rad Laboratories, 12 mm×275 mm), with chloroform elution. The product was recrystallized from ether-pentane, affording 510 mg (40%) of aldehyde **6**, mp 129~131°C.

Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14; mol wt, 254.
Found: C, 61.10; H, 6.94; mol wt, 254 (mass spec.).

6-Methyl-7-oxabicyclo[4.1.0]heptan-2-one (**11**)

A solution of 10.0 g of 3-methyl-2-cyclohexenone; 32 ml of 30% hydrogen peroxide and 75 ml of methanol was cooled to 5°C and treated dropwise with 17 ml of 3 N sodium hydroxide. After it had been stirred for 3 hours at 25°C, the reaction mixture was extracted with ether and the combined extracts were dried and distilled to afford 7.0 g (65%) of epoxyketone **11**, bp 105~106°C (32 mm) [lit.[9] 86° (15 mm)].

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