**$N^2$-[4-(2,2,6,6-Tetramethyl-1-piperidinyloxy)]actinomycin D (3). A General Method.** To 200 mg of the 2-deamino-2-chloroactinomycin D (**2**) [prepared according to the published methods,[12,13] $R_f$ 0.46 (B)] dissolved in 20 mL of dry benzene, 150 mg (5 equiv) of 4-amino-2,2,6,6-tetramethyl-1-piperdinyloxy (**6**) in 10 mL of benzene was added. The reaction mixture was stirred at room temperature for 84 h (at this time all of **2** had reacted). The organic solvent was removed under reduced pressure and the residue crystallized from benzene–hexane. Further purification was achieved by LH-20 column chromatography using 95% methanol as eluant, affording 100 mg (40%) of a red solid: mp 240–244 °C dec; TLC (solvent system) $R_f$ 0.84, and homogeneous; UV $\lambda_{max}$ ($CH_3OH$) 245 nm ($\epsilon$ 37 250), 435 (15 950), 455 (15 550); UV $\lambda_{max}$ (5 mM phosphate, pH 7.4), 198 nm ($\epsilon$ 72 430), 248 (32 170), 433–434 (17 470). Anal. ($C_{71}H_{102}N_{13}O_{17}\cdot 5CH_3OH$) C, N; H: calcd, 7.78; found, 7.21.

**$N^2$-[2-[[4-(2,2,6,6-Tetramethyl-1-piperidinyloxy)]-amino]ethyl]actinomycin D (4).** This compound was prepared from **2** and the diamine spin-label **7** in 27% yield: mp 232–235 °C dec, TLC (solvent system B) $R_f$ 0.54; UV $\lambda_{max}$ ($CH_3OH$) 245 nm ($\epsilon$ 23 818), 435 (10 890); UV $\lambda_{max}$ (5 mM phosphate, pH 7.7) 199 nm ($\epsilon$ 67 230), 240 (24 050), 442 (11 820). Anal. ($C_{73}H_{107}N_{14}O_{17}\cdot 6H_2O$) C, N; H: calcd, 7.68; found, 7.00.

**$N^2$-[3-[[4-(2,2,6,6-Tetramethyl-1-piperidinyloxy)]-amino]propyl]actinomycin D (5).** This was similarly prepared from the intermediate **2** and the diamine spin-label **8** in 31% yield: mp 211–213 °C dec; TLC (solvent system B) $R_f$ 0.51; UV $\lambda_{max}$ ($CH_3OH$) 245 nm ($\epsilon$ 28 750), 358–359 (18 430), 430–432 (10 350); UV $\lambda_{max}$ (5 mM phosphate, 7.4) 199 nm ($\epsilon$ 57 810), 243 (27 850), 360–362 (17 670), 443 (10 450). Anal. ($C_{74}H_{109}N_{14}O_{17}\cdot 6H_2O$) C, H, N.

**Acknowledgment.** The authors thankfully acknowledge the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute, for a supply of actinomycin D. The authors thank Miss Paula Parisius of the Microanalytical Laboratory, National Institute of Arthritis, Metabolism, and Digestive Disease, National Institute of Health, for performing the microanalyses. The technical assistance of Ms. Ovella Ayers in performing cytotoxicity studies is gratefully acknowledged.

## References and Notes

(1) W. Kersten, H. Kersten, and W. Szybalski, *Biochemistry*, **5**, 236 (1966).
(2) I. H. Goldberg, M. Rabinowitz, and E. Reich, *Science*, **136**, 315 (1962).
(3) J. E. Kay and H. L. Cooper, *Biochem. Biophys. Res. Commun.*, **35**, 526 (1969).
(4) E. J. Modest and S. K. Sengupta in "Chromosome Identification Technique and Application in Biology and Medicine", T. Casperson and L. Zech, Eds., Academic Press, New York, 1973, pp 327–333.
(5) S. Farber, *J. Am. Med. Assoc.*, **198**, 826 (1966).
(6) J. L. Lewis, Jr., *Cancer*, **30**, 1517 (1972).
(7) H. M. Sobell, *Cancer Chemother. Rep.*, **58**, 101 (1974).
(8) T. R. Krugh, *Proc. Natl. Acad. Sci. U.S.A.*, **69**, 1911 (1972).
(9) I. H. Goldberg, M. Rabinowitz, and E. Reich, *Proc. Natl. Acad. Sci. U.S.A.*, **48**, 2094 (1962).
(10) I. H. Goldberg, M. Rabinowitz, and E. Reich, *Proc. Natl. Acad. Sci. U.S.A.*, **49**, 226 (1963).
(11) H. Brockmann and H. Lackner, *Naturwissenschaften*, **57**, 384 (1964).
(12) S. Moore, M. Kondo, M. Copeland, J. Meinhofer, and R. K. Johnson, *J. Med. Chem.*, **18**, 1098 (1975).
(13) C. W. Mosher, K. F. Kuhlmann, D. G. Kleid, and D. W. Henry, *J. Med. Chem.*, **20**, 1055 (1977).
(14) M. S. Madhavarao, M. Chaykovsky, and S. K. Sengupta, *J. Med. Chem.*, **21**, 958 (1978).
(15) B. K. Sinha and C. F. Chignell, *J. Med. Chem.*, **18**, 669 (1975).
(16) C. F. Chignell, D. K. Starkweather, and B. K. Sinha, *J. Biol. Chem.*, **250**, 5622 (1975).
(17) B. K. Sinha, R. L. Cysyk, D. B. Millar, and C. F. Chignell, *J. Med. Chem.*, **19**, 994 (1976).
(18) B. K. Sinha and C. F. Chignell, *Life Sci.*, **17**, 1829 (1975).
(19) B. K. Sinha and C. F. Chignell, unpublished results.
(20) M. Klimek, *Nature (London)*, **209**, 1256 (1966).
(21) N. M. Emanuel, N. P. Konovola, and R. F. Djachkovskaya, *Cancer Treat. Rep.*, **60**, 1605 (1976).
(22) C. W. Mosher and L. Goodman, *J. Org. Chem.*, **37**, 2928 (1972).
(23) H. Ziffer, K. Yamaoka, and A. B. Mauger, *Biochemistry*, **7**, 996 (1968).
(24) J. A. Allison, R. L. O'Brien, and F. E. Hahn, *Science*, **149**, 1111 (1965).
(25) F. E. Hahn, R. L. O'Brien, J. Ciak, J. A. Allison, and J. G. Olenick, *Mil. Med. Suppl.*, **131**, 1071 (1966).
(26) E. Marquez, J. Cranston, R. W. Rudon, and J. H. Burckhalter, *J. Med. Chem.*, **17**, 856 (1974).
(27) F. J. Bollum, *Proced. Nucleic Acid Res.*, 1, 296 (1966).
(28) B. K. Sinha, R. Sato, R. P. Phillen, and R. L. Cysyk, *J. Med. Chem.*, **20**, 1528 (1977).
(29) B. K. Sinha and R. Sato, *J. Pharm. Sci.*, **67**, 407 (1978).
(30) G. E. Moore, A. A. Sandberge, and K. Vlrich, *J. Natl. Cancer Inst.*, **36**, (1966).
(31) R. I. Green, N. H. Greenberg, M. M. MacDonald, A. M. Schumaker, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3**(2) 1 (1972).
(32) N. R. Bachur, M. V. Gee, and S. L. Gordon, *Proc. Am. Assoc. Cancer Res.*, **19**, 75 (1978).

# Antifungal Agents. 5.[1] Chemical Modification of Antibiotics from *Polyangium cellulosum* var. *fulvum*. Alcohol, Ketone, Aldehyde, and Oxime Analogues of Ambruticin

David T. Connor* and Maximillian von Strandtmann[2]

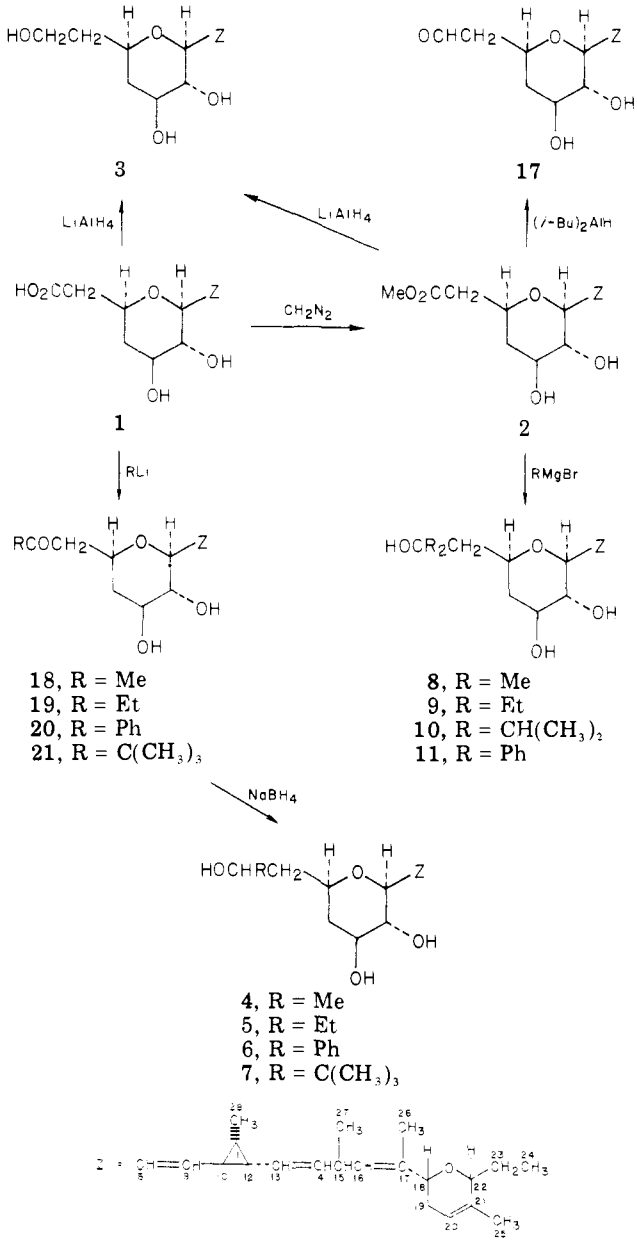
*Warner-Lambert/Parke-Davis, Pharmaceutical Research Division, Ann Arbor, Michigan 48106.* *Received January 12, 1979*

Alcohol, ketone, aldehyde, and oxime analogues of ambruticin (1) were prepared. The analogues were tested against *Histoplasma capsulatum*, *Microsporum fulvum*, *Candida albicans*, and *Streptococcus pyogenes*. Structure–activity relationships are described. Increasing the bulk of substituent at $C_1$ and $C_5$ reduces antifungal activity.

In part 4 of this series,[1] we described the structure–activity relationship of esters and amides derived from the potent antifungal antibiotic ambruticin (1).[3] Ambruticin was isolated from the fermentation broth of *Polyangium cellulosum* var. *fulvum*. The present paper describes the synthesis and biological activity of alcohols, ketones, al-

0022-2623/79/1822-1055$01.00/0 

Scheme I




3 17 1 2

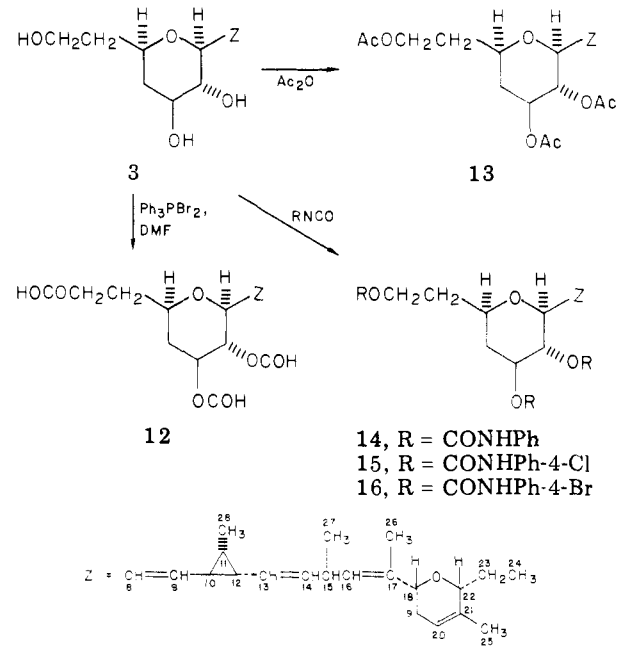
18, R = Me
19, R = Et
20, R = Ph
21, R = $C(CH_3)_3$

8, R = Me
9, R = Et
10, R = $CH(CH_3)_2$
11, R = Ph

4, R = Me
5, R = Et
6, R = Ph
7, R = $C(CH_3)_3$



Scheme II

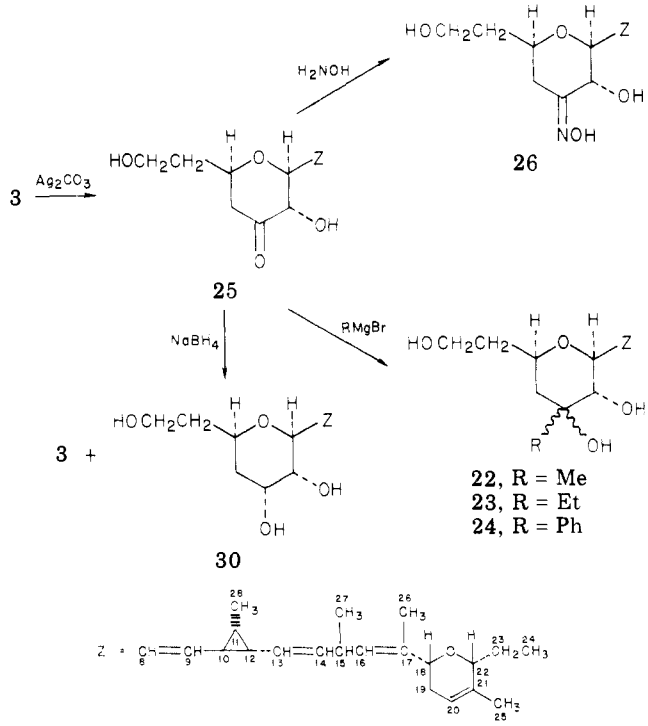



3 13 12

14, R = CONHPh
15, R = CONHPh-4-Cl
16, R = CONHPh-4-Br



Scheme III




3 26 25 30

22, R = Me
23, R = Et
24, R = Ph



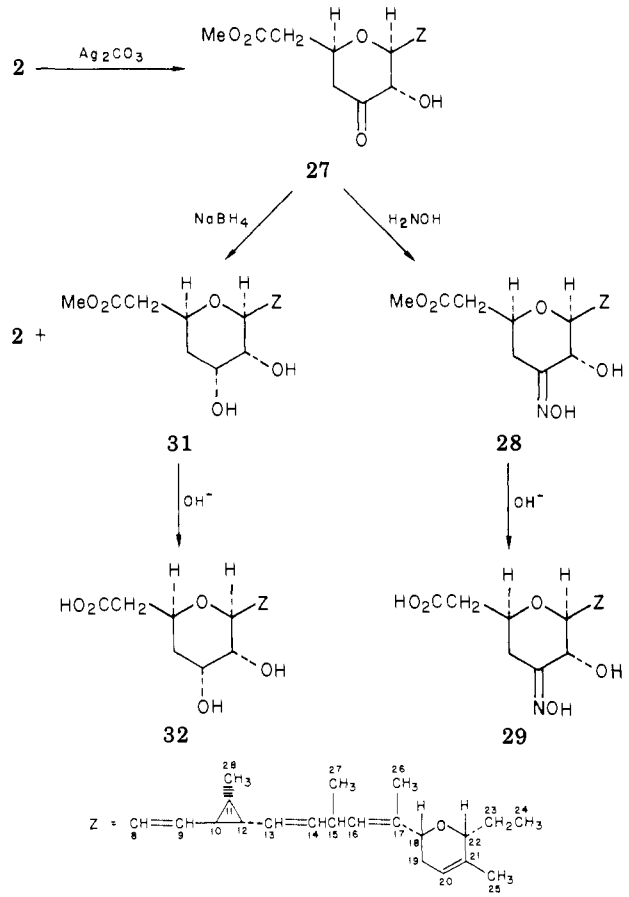
dehydes, and oximes derived from 1. The effect of epimerization at $C_5$ on antifungal activity is also discussed.

The compounds were synthesized by the routes shown in Schemes I–IV. Reduction of ester 2 with lithium aluminum hydride gave triol 3 and with diisobutylaluminum hydride gave aldehyde 17. Reaction of 2 with Grignard reagents gave alcohols 8–11. Treatment of acid 1 with alkyllithiums gave ketones 18–21, which were reduced to the corresponding alcohols 4–7 with sodium borohydride. Triol 3 was converted to ketodiol 25 by oxidation with silver carbonate. Ketone 25 was transformed to alcohols 22–24 with Grignard reagents and to oxime 26 with hydroxylamine hydrochloride. Reduction of 25 with sodium borohydride gave a mixture of epimeric alcohols 3 and 30. Oxidation of ester 2 with silver carbonate gave ketoester 27, which was converted to oxime 28 on treatment with hydroxylamine hydrochloride. Reduction of 27 with sodium borohydride gave a mixture of epimeric ester diols 2 and 31. Hydrolysis of 31 with aqueous sodium hydroxide solution gave acid 32. Antifungal antibiotic acid 32 is also a naturally occurring compound and was isolated[4] previously from the fermentation broth of *Polyangium cellulosum* var. *fulvum*.

The analogues were tested against Gram-positive bacteria, including *Streptococcus pyogenes*, and fungi, including *Histoplasma capsulatum*, *Microsporum fulvum*, and *Candida albicans*. Antimicrobial testing was carried out by a standard broth-dilution procedure. The results are summarized in Table I.

**Biological Activity.** None of the analogues showed any antibacterial activity. The analogues were also inactive against *C. albicans*. The triols were all highly active antifungal agents (Table I) unless bulky substituents were present (10 and 11). Antifungal activity decreased with increasing bulk at $C_1$. This effect is illustrated by the series 3–7 and the series 8–11. The series 3 and 22–24 illustrates declining antifungal activity with increasing bulk at $C_5$.

Scheme IV



Compounds in which $C_1$ is a carbonyl carbon are active, and once again increasing the bulk of the substituent at $C_1$ decreases antifungal activity, as illustrated by the series **17–21**. Compounds in which $C_5$ is part of a ketone or oxime group were also highly active antifungal agents. The antifungal activity exhibited by analogues **30–32** indicated that epimerization at $C_5$ has little effect on activity.

**Conclusions.** Molecules with unhindered polar substituents on carbons 1, 5, and 6 are antifungal agents. Antifungal activity is retained when $C_1$ is part of an acid, ester, amide, aldehyde, ketone, or alcohol group. Antifungal activity is displayed by compounds in which the oxygen function at $C_5$ is part of an alcohol, ketone, or oxime.

## Experimental Section[5]

Infrared spectra were recorded on a Perkin-Elmer 700 spectrometer. Mass spectra were obtained with an AEI MS-902 instrument. TLC was performed on silica gel plates (Quantum) using iodine vapor for visualization.

**General Procedure for the Preparation of Ketones 18–21.** A solution of acid 1 (1 equiv) and alkyllithium (20 equiv) in ether was stirred at room temperature under nitrogen for 4 h. The reaction mixture was poured onto ice–water and extracted with ether. The extracts were dried over $MgSO_4$ and evaporated to give a yellow oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a yellow oil (homogeneous by TLC).

**1-Methyl-1-oxopolyangi-5,6-diol (18):** yield 93 mg (47%); IR (film) 1710 $cm^{-1}$ (CO); MS *m/e* (relative intensity) 472 (2), 454 (2), 443 (2), 377 (2), 359 (1), 277 (3), 259 (2), 193 (100). Found: $M^+$ 472.3213; $C_{29}H_{44}O_5$ requires 472.3190.

**1-Ethyl-1-oxopolyangi-5,6-diol (19):** yield 35 mg (36%); IR (film) 1710 $cm^{-1}$ (CO); MS *m/e* (relative intensity) 486 (2), 468 (2), 457 (4), 439 (1), 391 (1), 373 (2), 355 (1), 291 (2), 273 (3), 273 (3), 257 (2), 193 (100). Found: $M^+$ 486.3312; $C_{30}H_{46}O_5$ requires 486.3345.

Table I. Antifungal Activity (in Vitro)[a]

| | MIC, μg/mL | |
|---|---|---|
| no. | *H. capsulatum* | *M. fulvum* |
| 1[b] | 0.39 | 0.098 |
| 2[b] | 0.39 | 0.39 |
| 3[b] | 0.098 | 0.098 |
| 4 | 0.098 | 0.195 |
| 5 | 0.78 | |
| 6 | 1.56 | 1.56 |
| 7 | 6.25 | >50 |
| 8 | 0.78 | 0.195 |
| 9 | 1.56 | 3.12 |
| 10 | 50 | >50 |
| 11 | 50 | >50 |
| 12[b] | 0.049 | 0.39 |
| 13[b] | 50 | >50 |
| 14[b] | 12.5 | >50 |
| 15 | 25 | >50 |
| 16[b] | 50 | >50 |
| 17 | 0.78 | 0.098 |
| 18 | 0.39 | 0.195 |
| 19 | 0.78 | 0.78 |
| 20 | 6.25 | 25 |
| 21 | 12.5 | >50 |
| 22 | 0.78 | 0.78 |
| 23 | 1.56 | 1.56 |
| 24 | 3.12 | 6.25 |
| 25 | 6.25 | 0.78 |
| 26 | 0.098 | 0.195 |
| 27[b] | 0.39 | 0.195 |
| 28 | 0.78 | |
| 29 | 3.12 | 1.56 |
| 30 | 0.39 | 0.39 |
| 31 | 0.39 | 0.39 |
| 32 | 0.78 | 0.195 |

[a] The microbiological testing procedures are described by S. M. Ringel, *Antimicrob. Agents Chemother.*, **13**, 762 (1978). [b] See ref 3.

**1-Phenyl-1-oxopolyangi-5,6-diol (20):** yield 20 mg (18%); IR (film) 1680 $cm^{-1}$ (CO); MS *m/e* (relative intensity) 534 (5), 516 (8), 505 (7), 498 (3), 487 (2), 439 (6), 421 (6), 348 (9), 347 (14), 323 (11), 287 (40), 235 (16), 193 (100). Found: $M^+$ 534.3232; $C_{34}H_{46}O_5$ requires 534.3446.

**1-(1,1-Dimethylethyl)-1-oxopolyangi-5,6-diol (21):** yield 9 mg (9%); IR (film) 1710 $cm^{-1}$ (CO); MS *m/e* (relative intensity) 514 (44), 496 (40), 485 (100). Found: $M^+$ 514.3671; $C_{32}H_{50}O_5$ requires 514.3658.

**General Procedure for the Preparation of Triols 4–7.** Sodium borohydride (10 equiv) was added to a solution of ketone (1 equiv) in methanol. The reaction mixture was stirred under nitrogen at room temperature for 4 h. The methanol was removed under reduced pressure to give a white solid. The solid was dissolved in water and extracted with ether. The extracts were dried over $MgSO_4$ and evaporated to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (TLC indicates a mixture of diastereomers).

**1-Methylpolyangi-1,5,6-triol (4):** yield 28 mg (59%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 474 (18), 456 (10), 445 (14), 379 (10), 279 (61), 193 (100). Found: $M^+$ 474.3303; $C_{29}H_{46}O_5$ requires 474.3346.

**1-Ethylpolyangi-1,5,6-triol (5):** yield 10 mg (40%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 488 (36), 470 (25), 459 (45), 293 (66), 193 (100). Found: $M^+$ 488.3402; $C_{30}H_{48}O_5$ requires 488.3502.

**1-Phenylpolyangi-1,5,6-triol (6):** yield 7 mg (70%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 536 (8), 518 (8), 507 (7), 474 (4), 445 (4), 423 (4), 347 (14), 341 (28), 193 (100). Found: $M^+$ 536.3511; $C_{34}H_{48}O_5$ requires 536.3498.

**1-(1,1-Dimethylethyl)polyangi-1,5,6-triol (7):** yield 2 mg (33%); IR (film) 3600–3100 $cm^{-1}$ (OH).

**General Procedure for the Preparation of Triols 8–11.** A solution of ester **2** (1 equiv) and alkylmagnesium bromide (10 equiv) in ether was refluxed under nitrogen for 4 h. The reaction mixture was cooled and poured onto ice and ammonium chloride.

The resulting mixture was extracted with ether. The extracts were dried over $MgSO_4$ and evaporated to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil (homogeneous by TLC).

**1,1-Dimethylpolyangi-1,5,6-triol (8)**: yield 36 mg (74%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 488 (20), 470 (19), 459 (40), 452 (25), 493 (12), 475 (16), 293 (60), 193 (100). Found: $M^+$ 488.3605; $C_{30}H_{48}O_5$ requires 488.3502.

**1,1-Diethylpolyangi-1,5,6-triol (9)**: yield 11 mg (19%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 516 (20), 498 (20), 487 (16), 480 (18), 469 (13), 421 (6), 403 (9), 383 (10), 321 (50), 193 (100).

**1,1-Bis(1-methylethyl)polyangi-1,5,6-triol (10)**: yield 10 mg (18%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 526 (19), 508 (15), 497 (16), 479 (8), 431 (10), 413 (5), 387 (7), 341 (7), 329 (19), 311 (25), 197 (100), 193 (100). Found: $M^+ - 18$, 526.4025; $C_{34}H_{54}O_4$ requires 526.4022.

**1,1-Diphenylpolyangi-1,5,6-triol (11)**: yield 30 mg (49%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 612 (1), 594 (2), 576 (2), 572 (3), 543 (6), 207 (12), 197 (24), 180 (100), 165 (55). Found: $M^+$ 612.3849; $C_{40}H_{52}O_5$ requires 612.3815.

**Polyangi-1,5,6-triol Tris(4-Chlorophenylcarbamate) (15).** A solution of polyangi-1,5,6-triol (25 mg) and 4-chlorophenyl isocyanate (40 mg) in toluene (2 mL) was refluxed under nitrogen for 3 h. The solvent was removed under reduced pressure to give an oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless gum: homogeneous by TLC; yield 23 mg (46%); IR (film) 3400–3200 (NH), 1705 $cm^{-1}$ (CO).

**Preparation of Aldehyde 17.** A solution of diisobutylaluminum hydride (142 mg) in hexane (0.7 mL) was added to a solution of ester **2** (195.2 mg) in toluene (5 mL) at −78 °C under nitrogen with stirring. The reaction mixture was stirred at −78 °C for 5 min and then partitioned between ether and 2 N hydrochloric acid. The ether extracts were dried over $MgSO_4$ and evaporated to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil: homogeneous by TLC; yield 104 mg (56%); IR (film) 3600–3200 (OH), 1730 $cm^{-1}$ (CO); MS *m/e* (relative intensity) 458 (6), 440 (4), 429 (33), 411 (3), 393 (3), 363 (5), 345 (12), 327 (8), 299 (7), 263 (17), 193 (100). Found: $M^+$ 458.2941; $C_{28}H_{42}O_5$ requires 458.3032.

**5-Oxopolyangi-1,6-diol (25).** Silver carbonate on Celite (2 g) was added to triol **3** (144 mg) in toluene (50 mL). The reaction mixture was refluxed under nitrogen with vigorous stirring for 1 h. During this time, a further 2 g of silver carbonate on Celite was added in 1-g portions. The inorganic solids were filtered off and washed with ethyl acetate. The filtrate and washings were evaporated under reduced pressure to give a brown oil. Purification by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) gave a yellow oil: homogeneous by TLC; yield 80 mg (55%); IR (film) 3600–3200 (OH), 1720 $cm^{-1}$ (CO).

**5-Oxpolyangi-1,6-diol Diacetate (25a).** Acetic anhydride (1 mL) was added to a solution of **25** (3 mg) in pyridine (2 mL). The reaction mixture was allowed to stand at room temperature overnight. Methanol was added to decompose the excess acetic anhydride, and the solvents were removed at reduced pressure to give a yellow oil: homogeneous by TLC; yield 2 mg; IR (film) 1740 (CO), 1735 $cm^{-1}$ (CO); MS *m/e* (relative intensity) 542 (6), 513 (18), 482 (4), 447 (8), 289 (11), 276 (9), 193 (100). Found: $M^+ - 29$ 513.2805; $C_{30}H_{41}O_7$ requires 513.2852.

**Preparation of Oxime 26.** A solution of diol **25** (5 mg), hydroxylamine hydrochloride (1 mg), and sodium acetate (1 mg) in absolute ethanol (7 mL) and water (1 mL) was refluxed for 2 h under nitrogen. The solvents were removed under reduced pressure. The product was isolated by preparative TLC with the solvent system ethyl acetate–2-propanol–water (85:10:5) to give a white amorphous solid: homogeneous by TLC; yield 3 mg (58%); IR (film) 3600–3000 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 473 (17), 456 (70), 193 (80), 165 (100).

**General Procedure for the Preparation of Triols 22–24.** A solution of ketodiol **25** (1 equiv) and alkylmagnesium bromide (10 equiv) in ether was refluxed under nitrogen for 3 h. The reaction mixture was cooled and poured onto ice and ammonium chloride. The resulting mixture was extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated to give a colorless oil. The product was purified by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) to give a colorless oil: homogeneous by TLC.

**5-Methylpolyangi-1,5,6-triol (22)**: yield 13 mg (63%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 474 (8), 456 (8), 445 (10), 438 (4), 379 (2), 361 (6), 279 (100), 193 (50), 165 (52). Found: $M^+$ 474.3290; $C_{29}H_{46}O_5$ requires 474.3345.

**5-Ethylpolyangi-1,5,6-triol (23)**: yield 2 mg (12%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 488 (22), 470 (18), 459 (54), 393 (13), 293 (54), 193 (100). Found: $M^+$ 488.3499; $C_{30}H_{48}O_5$ requires 488.3502.

**5-Phenylpolyangi-1,5,6-triol (24)**: yield 8 mg (15%); IR (film) 3600–3100 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 536 (23), 518 (19), 507 (10), 500 (8), 341 (83), 323 (16), 244 (26), 236 (43), 195 (77), 193 (77), 177 (100). Found: $M^+$ 536.3585; $C_{34}H_{48}O_5$ requires 536.3502.

**Polyangi-1,5,6-triol (3) and 5-*epi*-Polyangi-1,5,6-triol (30).** A mixture of ketone **25** (50 mg) and sodium borohydride (40 mg) in methanol (5 mL) was stirred at room temperature for 3 h. The methanol was removed at reduced pressure. The residue was dissolved in water and the resulting solution was extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to give a yellow gum. The gum was fractionated by preparative TLC with the solvent system ethyl acetate–cyclohexane (4:1) into two compounds. Triol **3**: homogeneous by TLC; yield 20 mg (40%); IR (film) 3500–3200 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 460 (4), 442 (3), 431 (8), 365 (7), 265 (25), 247 (11), 241 (5), 195 (75), 193 (100). Triol 30: yield 9 mg (18%); IR (film) 3500–3200 $cm^{-1}$ (OH); MS *m/e* (relative intensity) 460 (11), 442 (12), 431 (23), 365 (6), 347 (12), 265 (100), 247 (11), 231 (18), 193 (77). Found: $M^+$ 460.3142; $C_{28}H_{44}O_5$ requires 460.3189.

**5-*epi*-Polyangi-1,5,6-triol (30) from Methyl 5-*epi*-5,6-Dihydroxypolyangioate (31).** Lithium aluminum hydride (20 mg) was added to a solution of 5-*epi*-5,6-dihydroxypolyangioate (70 mg) in THF (3 mL). The reaction mixture was refluxed under nitrogen for 3 h. The mixture was cooled in an ice bath and a few drops of water were added, followed by $MgSO_4$ (50 mg). The inorganic solids were filtered off and washed with ethyl acetate. The filtrate and washings were evaporated to give a colorless gum. The product was purified by preparative TLC with the solvent system ethyl acetate–2-propanol–water (85:10:5) to give a colorless oil: homogeneous by TLC; yield 30 mg (45%); IR (film) 3500–3200 $cm^{-1}$ (OH). Found: $M^+$ 460.3247; $C_{28}H_{44}O_5$ requires 460.3189.

**Preparation of Oxime 28.** A solution of ketone **27** (40 mg), hydroxylamine hydrochloride (8 mg), and sodium acetate (8 mg) in absolute ethanol (15 mL) and water (4 mL) was refluxed for 30 min under nitrogen. The solvents were removed under reduced pressure to give a brown oil. The product was purified by preparative TLC to give a colorless oil: homogeneous by TLC; yield 29 mg (73%); IR (film) 3600–3200 (OH), 1740 $cm^{-1}$ (CO); MS *m/e* (relative intensity) 501 (9), 484 (29), 193 (100), 165 (71).

**Preparation of Oxime 29.** A solution of 5% aqueous sodium hydroxide (6 mL) was added to a solution of **28** (18 mg) in methanol (2 mL). The reaction mixture was stirred and refluxed under nitrogen for 30 min. The methanol was removed at reduced pressure. The aqueous residue was acidified and extracted with chloroform. The extracts were dried ($MgSO_4$) and evaporated to give a white amorphous solid: homogeneous by TLC; yield 10 mg (57%); IR (film) 3600–3200 (OH), 2800–2400 (OH), 1720 $cm^{-1}$ (CO).

**Acknowledgment.** The authors are grateful to Dr. S. M. Ringel and Mr. S. Roemer for antimicrobial screening.

## References and Notes

(1) For part 4, see D. T. Connor and M. von Strandtmann, *J. Med. Chem.*, **22** (1979), in the notes section of this issue.
(2) Corresponding address: ICI North America, Wilmington, Del.
(3) D. T. Connor, R. C. Greenough, and M. von Strandtmann, *J. Org. Chem.*, **42**, 3664 (1977).
(4) D. T. Connor and M. von Strandtmann, *J. Org. Chem.*, **43**, 4606 (1978).
(5) The compounds described in this paper were either oils or gums. The homogeneity of each compound was checked

by TLC in two solvent systems, ethyl acetate–cyclohexane (4:1) and ethyl acetate–2-propanol–water (85:10:5). Molecular formulas were determined by high-resolution mass spectroscopy. In cases where high-resolution spectra were not obtained, the molecular composition of the low-resolution molecular ion was obvious from either the composition of the starting material or from a subsequent transformation product.

# Fluorinated Retinoic Acids and Their Analogues. 1. Synthesis and Biological Activity of (4-Methoxy-2,3,6-trimethylphenyl)nonatetraenoic Acid Analogues

Beverly A. Pawson,* Ka-Kong Chan, James DeNoble, Ru-Jen L. Han, Virginia Piermattie, Anthony C. Specian, Srisamorn Srisethnil,

*Chemical Research Department*

Patrick W. Trown, Oksana Bohoslawec,

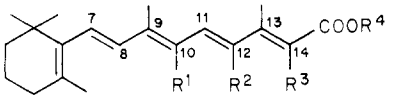
*Chemotherapy Department*

L. J. Machlin, and Edda Gabriel

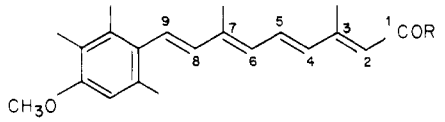
*Department of Biochemical Nutrition, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.* *Received January 22, 1979*

(4-Methoxy-2,3,6-trimethylphenyl)nonatetraenoic acids, esters, and amides (analogues of retinoic acid) bearing a fluorine atom(s) or a trifluoromethyl group on the polyene side chain were synthesized. The biological activities of these compounds and of 10-, 12-, and 14-fluororetinoic acid esters were evaluated in vivo in a chemically induced mouse papilloma test; the toxicities were assessed in an in vivo mouse hypervitaminosis A test. Antipapilloma activity greater than the parent nonfluorinated ester was found for **1c** (ethyl 12-fluororetinoate) and **23** and **39** (aromatic 4- and 6-fluororetinoid esters, respectively). A similar increase in antipapilloma activity was observed for **71** and **72**, the aromatic 4- and 6-fluororetinoic acids, respectively, relative to **2** and for **73** (aromatic 4-fluororetinoid amide) relative to **4**.

Recent studies[1-3] have demonstrated that retinoic acid (**1a**) and the aromatic analogues **2**–**4** (retinoids) can inhibit



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| 1a | -H | -H | -H | -H |
| b | -F | -H | -H | $-C_2H_5$ |
| c | -H | -F | -H | $-C_2H_5$ |
| d | -H | -H | -F | $-C_2H_5$ |
| e | -H | -H | -H | $-C_2H_5$ |



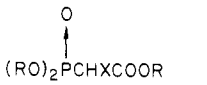
2, R = -OH
3, R = $-OC_2H_5$
4, R = $-NHC_2H_5$

the growth of and cause marked regression of chemically induced papillomas and carcinomas in mice. Retinoids have also been shown to inhibit the growth of and cause the regression of a transplantable chondrosarcoma.[4] Furthermore, topical or systemic administration of retinoic acid (**1a**) was found to have some effect on precancerous conditions in humans.[5] Numerous reports concerning the effectiveness of natural and synthetic retinoids for the prevention or reversal of a number of precancerous conditions in animals have also appeared.[1,6]

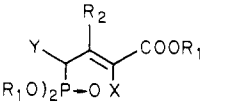
Although these findings are encouraging, experimental and clinical results have also demonstrated that systemic application of large doses of natural and synthetic retinoids can induce a series of toxic side effects, known as hypervitaminosis A.[1-3] While the synthetic retinoids **3** and **4** were shown to be more potent and less toxic[2,3] than retinoic acid, they still have toxic effects. As a result, the research described below was undertaken to synthesize new retinoids which might be more effective and less toxic for the prophylaxis and therapy of precancerous conditions.

Since many fluorine-containing compounds are known to be useful therapeutic agents,[7] it was of interest to introduce a fluorine atom or a trifluoromethyl group at different positions on the side chain of the aromatic retinoids. Recently, 10- and 14-fluororetinal were synthesized and shown to form fluorinated rhodopsin analogues.[8] Although the 10-, 12- and 14-fluororetinoic acid derivatives **1b–d**, respectively, were synthesized in 1964[9b,c]

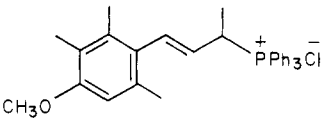
Chart I. Synthons for Fluorinated Retinoids



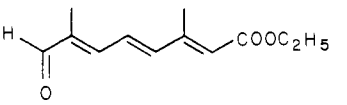
| | R | X | ref |
|---|---|---|---|
| 5 | $-CH_3$ | -H | 11 |
| 6 | $-C_2H_5$ | -H | 11 |
| 7 | $-C_2H_5$ | -F | 9a |



| | $R_1$ | $R_2$ | X | Y | ref |
|---|---|---|---|---|---|
| 8 | $-C_2H_5$ | $-CH_3$ | -F | -H | 9b |
| 9 | $-C_2H_5$ | $-CH_3$ | -H | -F | 9c |
| 10 | $-CH_3$ | $-CH_3$ | -H | -H | 12 |
| 11 | $-C_2H_5$ | $-CF_3$ | -H | -H | 13 |



32, ref 10



55, ref 10

0022-2623/79/1822-1059$01.00/0 