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SYNTHESIS OF THE $C_{1'}$-$C_{11'}$ PORTION OF PAMAMYCIN-607 VIA A STEREOSELECTIVE OXYMERCURATION OF A GAMMA-SILYLOXYALLENE AND A STEREOSPECIFIC MAGNESIUM-METHANOL REDUCTION

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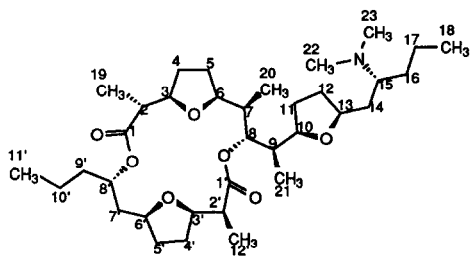
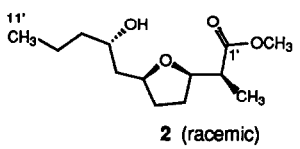
Abstract: The $C_{1'}$-$C_{11'}$ portion of the antibiotic pamamycin-607, a novel homologue and C_2-epimer of nonactic acid, was synthesized in six steps from 4,5-hexadien-1-ol via a novel cis-selective oxymercuration/transpalladation/methoxycarboxylation of a γ-silyloxyallene and a syn-selective reduction of a 2-(2-tetrahydrofuranyl)acrylate using magnesium in methanol. Spectroscopic properties of a derivative of the synthetic $C_{1'}$-$C_{11'}$ portion match those of material derived from the natural product.

In 1979, a structurally unique class of autoregulatory and antibiotic substances, the pamamycins, were discovered in Streptomyces alboniger.[1] Mass spectrometric analysis indicated that the pamamycins were a series of homologous alicyclic amines. No further structural information about the pamamycins was revealed until 1987, when Marumo and coworkers reported the structure of the molecular weight 607 homologue, pamamycin-607 (1).[2] The relative stereochemistry of 1 was assigned on the basis of NMR studies. The absolute configuration of pamamycin-607 has yet to be determined. The presence of three cis-2,5-disubstituted tetrahydrofuran rings in pamamycin-607 has inspired us to apply our recently-reported cyclization of γ-silyloxyallenes to form cis-2-(5-alkyltetrahydrofuran-2-yl)acrylates[3] to the synthesis of this antibiotic. This report describes a synthesis of the $C_{1'}$-$C_{11'}$ moiety of pamamycin-607, as the methyl ester 2, which utilizes this methodology plus a novel syn-selective reduction of 2-(2-tetrahydrofuranyl)-acrylates.



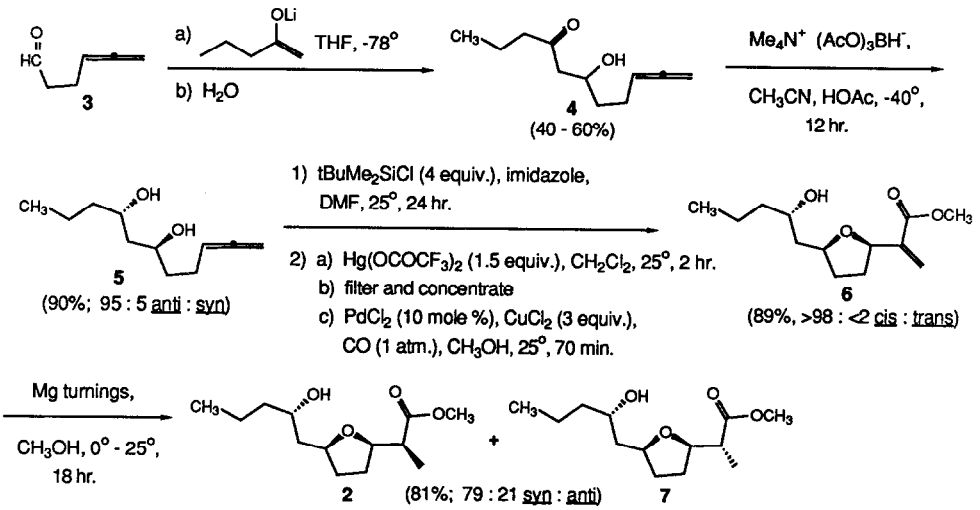
1 ***(Pamamycin-607)***



2 (racemic)

Our results are indicated in Scheme 1. Addition of the lithium enolate derived from 2-pentanone to the aldehyde 3 yielded the β-hydroxyketone 4. Reduction of 4 using Evans'

Scheme 1 (all compounds indicated are racemic)

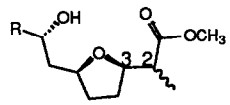


triacetoxyborohydride reagent[4] yielded the diol 5 as a 95:5 anti:syn mixture. The anti versus syn relationships of the hydroxyl groups in the two diastereomers of 5 were verified by the relative ^{13}C-NMR chemical shifts of their carbinol carbons (syn downfield from anti), in agreement with observations in the literature.[4,5,6]

Formation of the bis(tert-butyldimethylsilyl) ether derivative of the anti diol 5, then intramolecular oxymercuration followed by transpalladation/methoxycarbonylation[3] resulted in the formation of the cis-2,5-disubstituted tetrahydrofuran 6 accompanied by less than 2% of the trans isomer according to HPLC analysis. (In contrast, the direct oxypalladation/methoxycarbonylation of the diol 5 yielded a 50:50 cis:trans mixture). The downfield chemical shifts of the NMR signals from the acyclic portions of the major isomer of 6, relative to the corresponding NMR signals in the minor (trans) isomer, argue for the indicated cis geometry.[7]

Catalytic hydrogenations of 2(10)-dehydrononactates like 6 yield 50:50 mixtures of 2,3-syn and 2,3-anti products.[8] However, 6 could be reduced using magnesium metal in methanol[9] to give moderate (78:21 syn(2):anti(7)) stereoselectivity. The assignment of the 2,3-syn geometry to the major product from this reduction is based on an apparent consistency in the variation of the chemical shifts for the methoxy and 2-methyl protons with the C_2-configuration of such methyl nonactate homologues, as indicated in Table 1.[10,11]

The reduction of acrylates using magnesium has recently been noted for its selectivity and efficiency.[9] Our 2,3-syn-selective stereospecific reduction of 6 (and other 2(10)-dehydrononactates[8]) implies that stereoselectivity might be expected in general from magnesium reductions of polyoxygenated systems. We contend that the 2,3-syn selectivity observed in this case is due to the formal delivery of hydrogen to the less hindered face of a cyclic complex between the substrate and Mg(II). Further studies of this potentially general "chelation-controlled" stereoselective reduction are necessary.

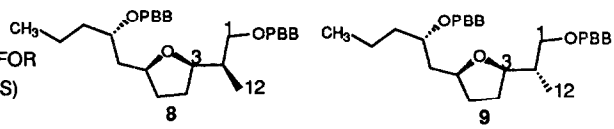
Table 1  ^{1}H-NMR CHEMICAL SHIFTS OF METHYL NONACTATE HOMOLOGUES[a]

R	C_2-C_3 Configuration	δ CH_3O	δ 2-Methyl	Reference
CH_3	syn ("2-epi-nonactate")	3.683	1.222	10[b]
CH_3	anti (nonactate)	3.696	1.132	10[b]
CH_3CH_2	syn ("2-epi-homononactate")	3.684	1.226	8[c]
CH_3CH_2	anti (homononactate)	3.698	1.131	8[c]
$CH_3CH_2CH_2$	syn (compound 2)	3.682	1.223	This work[c]
$CH_3CH_2CH_2$	anti (compound 7)	3.696	1.130	This work[c]

([a]Chemical shifts relative to TMS, measured in $CDCl_3$. [b]250 MHz. [c]200 MHz.)

The methyl ester 2 is an important subunit of pamamycin-607, and represents a homologue of nonactic acid which is unique for having the 2,3-syn geometry. To verify this remarkable structural feature of pamamycin-607, the bis(para-bromobenzoate) derivatives 8 and 9 were prepared from 2 and 7 respectively,[12] and their ^{1}H-NMR spectra were compared with a spectrum of 8 derived from pamamycin-607.[13] Table 2 indicates those signals for which significant differences between the spectra of 8 and 9 could be discerned. A closer correspondence between

Table 2
^{1}H-NMR CHEMICAL SHIFTS FOR BIS(para-BROMOBENZOATES) 8 AND 9[a]



Compound	Source	C_1	C_3	C_{12}
8	Pamamycin-607[13b]	4.29, 4.20	3.81	1.04
8	Compound 2[c]	4.29, 4.18	3.81	1.04
9	Compound 7[c]	4.42, 4.20	3.72	0.98

([a]Chemical shifts relative to TMS, measured in $CDCl_3$. [b]500 MHz. [c]200MHz.)

the spectra of the bis ester derived from 2 and that derived from pamamycin-607 was observed than for the bis ester derived from 7. Thus our studies support the 2',3'-syn geometry of pamamycin-607.

A synthesis of the C_1-C_{18} moiety of pamamycin-607 which will utilize some of the same stereoselective synthetic methodology as described above is currently underway.[14]

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2) Kondo, S., Yasui, K., Katayama, M., Marumo, S., Kondo, T., Hattori, H. Tetrahedron Lett. 1987, 28, 5861.

3) Walkup, R. D., Park, G. Tetrahedron Lett. 1987, 28, 1023.

4) Evans, D. A., Chapman, K. T., Carreira, E. M. J. Am. Chem. Soc. 1988, 110, 3560.

5) ^{13}C NMR chemical shifts for carbinol carbons: δ 68.93 and 68.50 for the major (anti) isomer; δ 72.76 and 72.30 for the minor (syn) isomer. The general upfield shifts for anti-diols relative to syn-diols have been noted: Kathawala, F. G., Prager, B., Prasad, K., Repic, O., Shapiro, M. J., Stabler, R. S., Widler, L. Helv. Chim. Acta 1986, 69, 803; Kiyooka, S.-I., Kuroda, H., Shimasaki, Y. Tetrahedron Lett. 1986, 27, 3009.

6) ^{1}H-NMR for anti-5: δ 5.14 (1H, pentet, J = 6.6 cps); 4.67 (2H, m); 3.97 (2H, m); 3.28 (variable, 1H); 3.12 (variable, 1H); 2.12 (2H, m); 1.43-1.59 (8H, br m); 0.93 (3H, t, J = 7.0 cps). ^{13}C: δ 208.38; 89.56; 75.10; 68.93; 68.50; 42.31; 39.52; 36.38; 24.42; 18.91; 14.01. ^{1}H-NMR for syn-5: identical to that for anti-5. ^{13}C-NMR for syn-5: δ 208.38; 89.56; 75.10; 72.76; 72.30; 42.61; 40.27; 37.05; 23.95; 18.46; 14.01.

7) Cis product: ^{1}H-NMR: δ 6.23 (1H, dd, J = 1.3, 1.3 cps); 5.90 (1H, dd, J = 1.3, 1.3 cps); 4.72 (1H, dd, J = 7.4, 6.1 cps); 4.21 (1H, m); 3.90 (1H, m) 3.76 (3H, s); 2.56 (variable, 1H); 2.28 (1H, m); 2.00 (1H, m); 1.48-1.76 (8H, br m); 0.94 (3H, t, J = 6.7 cps). ^{13}C-NMR: δ 166.33; 141.73; 123.78; 77.27; 77.14; 69.00; 51.71; 41.72; 39.61; 32.00; 30.87; 18.94; 14.05.
Trans product: ^{1}H-NMR: δ 6.20 (1H, dd, J = 1.4, 1.4 cps); 5.90 (1H, dd, J = 1.4, 1.4 cps); 4.83 (1H, br t, J = 7.1 cps) 4.37 (1H, m); 3.88 (1H, m); 3.76 (3H, s); 2.55 (variable, 1H); 2.37 (1H, m); 2.07 (1H, m); 1.45-1.70 (8H, br m); 0.94 (3H, t, J = 6.7 cps). ^{13}C-NMR: 166.33; 141.73; 123.18; 80.82; 77.15; 69.10; 51.70; 41.24; 39.61; 32.60; 31.85; 18.96; 14.10.

8) Walkup, R. D., Park, G., full paper in preparation.

9) See Hudlicky, T., Sinai-Zingde, G., Natchus, M. G. Tetrahedron Lett. 1987, 28, 5287, and references therein.

10) Bartlett, P. A., Meadows, J. D., Ottow, E. J. Am. Chem. Soc. 1984, 106, 5304.

11) 2,3-Syn isomer (2): ^{1}H-NMR: δ 4.13 (1H, m); 3.99 (1H, q, J = 7.1 cps); 3.83 (1H, br m); 3.68 (3H, s); 2.80 (variable, 1H); 2.59 (1H, pentet, J = 7.1 cps); 1.97 (2H, m); 1.39-1.69 (8H, br m); 1.22 (3H, d, J = 7.0 cps); 0.93 (3H, t, J = 7.2 cps). ^{13}C-NMR: δ 174.86; 80.47; 77.25; 68.76; 51.62; 44.70; 41.05; 39.44; 30.70; 28.79; 18.96; 14.09; 13.92.
2,3-Anti isomer (7): ^{1}H-NMR: δ 4.15 (1H, m); 3.99 (1H, m); 3.83 (1H, m); 3.70 (3H, s); 2.83 (variable, 1H); 2.54 (1H, br pentet, J ∿ 7 cps); 1.99 (2H, m); 1.39-1.69 (8H, br m); 1.13 (3H, d, J = 7.0 cps); 0.93 (3H, t, J = 7.1 cps). ^{13}C-NMR: δ 175.29; 81.06; 77.22; 68.79; 51.72; 45.30; 40.97; 39.38; 30.57; 28.84; 19.01; 14.13; 13.54.

12) Preparation: a) excess $LiAlH_4$, Et_2O, 25 °C, 30 minutes; aqueous workup; b) p-bromobenzoyl chloride (4 equiv.); 4-DMAP, CH_2Cl_2, 25° overnight. Compound 8: 'H-NMR: 7.90 (2H, d, J = 8.6 cps); 7.89 (2H, d, J = 8.6 cps); 7.58 (2H, d, J = 8.6 cps); 7.57 (2H, d, J = 8.6 cps); 5.27 (1H, p, J = 6.2 cps); 4.29 (1H, dd, J = 10.9, 5.9 cps); 4.18 (1H, dd, J = 10.9, 6.6 cps); 3.91 (1H, p, J = 6.5 cps); 3.81 (1H, q, J = 6.2 cps); 1.92-2.10 (4H, m); 1.30-1.50 (8H, m); 1.04 (3H, d, J = 6.8 cps); 0.93 (3H, t, J = 7.2 cps). ^{13}C-NMR: δ 165.82; 185.40; 131.88; 131.62; 131.06; 129.58; 129.22; 127.80; 80.06; 76.00; 73.28; 67.83; 40.44; 37.57; 36.90; 31.75; 28.62; 18.40; 13.96; 13.00.
Compound 9: ^{1}H-NMR: δ 7.89 (4H, d, J = 8.5 cps); 7.57 (2H, d, J = 8.6 cps); 7.56 (2H, d, J = 8.6 cps); 5.27 (1H, p, J = 6.1 cps); 4.42 (1H, dd, J = 10.9, 4.6 cps); 4.20 (1H, dd, J = 10.9, 6.8 cps); 3.91 (1H, p, J = 6.4 cps); 3.72 (1H, q, J = 6.7 cps); 1.92-2.10 (4H, m); 1.30-1.50 (8H, m); 0.98 (3H, d, J = 6.9 cps); 0.92 (3H, t, J = 7.2 cps). ^{13}C-NMR: δ 165.85; 165.40; 131.65; 131.09; 129.60; 129.39; 127.85; 80.42; 76.37; 73.25; 67.64; 40.61; 38.26; 36.94; 31.46; 28.88; 18.44; 13.99; 13.59.

13) A copy of this spectrum was kindly provided to us by Professor Marumo.

14) This research was made possible by grants from the Robert A. Welch Foundation (#D-1147) and the Donors of the Petroleum Research Fund administered by the American Chemical Society (#16702-G1, #19870-AC1). The NMR spectrometers employed during this research were purchased using funds provided by the National Science Foundation (#CHE-851404). We are grateful to Professor Shingo Marumo of Nagoya University for unpublished information concerning pamamycin-607.

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