Macrolide Neutral Sugar Chemistry. Chemical Conversion of Oleandomycin Y to 3-(2,6-Dideoxy-L-α-allosyl)oleandomycin Y and 3-(2,6-Dideoxy-L-α-galactosyl)oleandomycin Y

Arthur A. Nagel* and Lawrence A. Vincent

Pfizer Central Research, Groton, Connecticut 06340

Received May 6, 1982

Oleandomycin Y (1) is a 14-membered-ring macrolide antibiotic produced as a byproduct in the fermentation of oleandomycin (2).[1] The structural difference between the two antibiotics resides in the neutral sugar; oleandomycin Y possesses an equatorial 3″-hydroxyl group (L-olivose) as compared to oleandomycin having an equatorial 3″-methoxyl group (L-oleandrose). This relatively minor structural difference confers quite different physical/biological properties on the two macrolides. In particular, oleandomycin Y has significantly greater water solubility but is less potent in vitro as compared to oleandomycin. Realizing that the increased water solubility of oleandomycin Y may offer pharmacokinetic and/or formulation advantages over oleandomycin,[2] an investigation designed to increase the in vitro potency of oleandomycin Y was initiated. It was postulated that the in vitro activity of oleandomycin Y might be increased by inverting the 3″-equatorial alcohol in the olivose sugar to the 3″-axial position. The chemical sequence which accomplishes this transformation (i.e., the conversion of 3-α-L-olivose to 2,6-dideoxy-3-α-L-allose in oleandomycin Y) is outlined below.[3]

Initial attempts at the direct inversion of the 3″-alcohol were first considered. Of the variety of methods available for inverting secondary alcohols,[4] many use basic conditions and/or nucleophiles that would be incompatible with the rest of the macrolide functionality. Also, the fact that oleandomycin Y possesses four different secondary alcohols meant that specific inversion at 3″ would require the design of a complicated blocking sequence. Indeed, oleandomycin Y can be acylated (acetic anhydride, CH_2Cl_2, room temperature, 12 h) in the absence of base to give 2′-acetyloleandomycin Y (3).[5] Further acylation in the presence of base gave various mixtures of *di*- and *tri*acylated oleandomycin Y derivatives, which required tedious separations to provide pure materials. Therefore, this inversion approach was discontinued.

The successful completion of the desired transformation utilized chemistry which focused on the 3″,4″-*trans*-diequatorial alcohol system, as outlined in Scheme I. Successive treatment of 2-acetyloleandomycin Y (3) with (a) triiodoimidazole/triphenylphosphine/imidazole (toluene, reflux, 4 h),[6] (b) saturated $NaHCO_3$, and (c) OsO_4/*N*-methylmorpholine *N*-oxide (*t*-BuOH/acetone/H_2O, room temperature, 3 h)[7] gave a 60:40 mixture of *cis*-diols 6 and 7 in an overall 54% yield. Intermediates 4 and 5 could be isolated but were very unstable compounds. Iodohydrin 4 in the presence of base regenerated the C_8 epoxide with the same stereochemistry as found in oleandomycin Y.[8] Also, the glycosidic linkage in both intermediates 4 and 5 was very susceptible to acid; silica gel chromatography resulted in extensive C_3 glycoside cleavage. As expected, the C_3 glycosidic linkage in *cis*-diols 6 and 7 had similar acid stability to that of a oleandomycin Y (1). Separation of *cis*-diols 6 and 7 could be accomplished by using silica gel chromatography.

Two points of interest deserve comment. First, the iodohydrin formed at C_8 does not further react in the presence of triphenylphosphine/triiodoimidazole to produce C_8 deoxy (double bond) derivatives.[10] Second, attempted osmilation of 4 or 5 by using traditional conditions (1 equiv of OsO_4 in pyridine) gave substantial quantities of macrolide derivatives arising from 3′-(dimethylamino) oxidation. The use of phase-transfer[7] catalysis essentially eliminated the formation of these byproducts.

The relative stereochemistry of *cis*-diol derivatives 6 and 7 was assigned by using NMR analysis.[11] In order to facilitate the NMR analysis both 6 and 7 were first converted to carbonate derivatives 10 and 11 (carbonyldiimidazole, CH_2Cl_2, room temperature, 3 h). Methanolysis of derivatives 10 and 11 (methanol, room temperature, 48 h) afforded the 2′-hydroxy carbonates 12 and 13. Analysis of the 250-MHz NMR spectrum of carbonate 12 revealed a coupling constant of 8.3 Hz for the 4″- and 5″-hydrogens (see Experimental Section). This is indicative of a *trans*-diaxial relationship of the two hydrogens,[12] fixing the 4″-oxygen in the equatorial orientation. This neccesitates that the *cis*-3″-oxygen functionality be axial. The NMR analysis of carbonate 13 was not straightforward since the chemical shift of key neutral sugar protons overlapped with aglycon hydrogens. However, since it is impossible to form the carbonate of oleandomycin Y by using the above conditions (*trans*-1,2-diequatorial diols) the stereochemistry of the diol system of carbonate 13 appears logical.

Methanolysis of derivatives 6 and 7 (methanol, room temperature, 48 h) afforded *cis*-diols 8 and 9. Compound 8 (having the 3″-alcohol oriented in the axial position) was more potent in vitro against gram-positive organisms than either *cis*-diol 9 or oleandomycin Y (1).[13] A more detailed report of the biological activity of compounds 8, 9, and 1 as well as carbonates 12 and 13 will be reported elsewhere.

(1) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413.

(2) Oleandomycin is currently marketed as its triacetyl derivative (trademark TAO) by Pfizer Inc.

(3) LeMahieu and co-workers isolated a novel erythromycin derivative from fermentation which contained oleandrose as the neutral sugar. This compound was biologically less active than the corresponding erythromycin derivative containing the usual cladinose neutral sugar. LeMahieu, R. A.; Ax, H. A.; Blount, J. F.; Carson, M.; Despreaux, C. W.; Pruess, D. L.; Scannell, J. P.; Weiss, F.; Kierstead, R. W. *J. Antibiot.* **1976**, *29*, 728.

(4) Bose, A. K.; Lal, B.; Hoffman, W. A.; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619. Kirby, G. W.; Massey, S. R. *J. Chem. Soc. C* **1971**, 4047. Baker, R.; Hudec, J.; Rabone, K. L. *J. Chem. Soc. C* **1969**, 1605. Harnik, M. *Steroids* **1964**, *3*, 359.

(5) Celmer, W. D.; "Antibiotics Annual 1958–1959"; Medical Encyclopedia, Inc.: New York, 1959; pp 277.

(6) (a) Garegg, P. J.; Samuelsson, B. *Synthesis* **1979**, 469. (b) *Ibid.* **1979**, 813.

(7) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett* **1976**, 1973.

(8) The epoxides in compounds 6 and 7 have ^{13}C and ^1H NMR chemical shifts identical with those of the starting oleandomycin Y. Furthermore, formation of the iodohydrin of 2′,4″,11-triacetyloleandomycin by using the described experimental conditions, followed by epoxide regeneration under basic conditions, gave a compound identical in every respect (^{13}C NMR, ^1H NMR, TLC, rotation, biological activity with 2′,4″,11-triacetyloleandomycin. An unambiguous synthesis of 2′,4″,11-triaceyl-8β-epoxyoleandomycin has been completed[9] and shown to have different physical and biological properties from that of the natural triacetyloleandomycin.

(9) Sciavolino, F. C., Pfizer Central Research, unpublished results.

(10) Garegg and Samuelsson[6a] report that the presence of zinc is needed to obtain dehydration of epoxides under similar conditions.

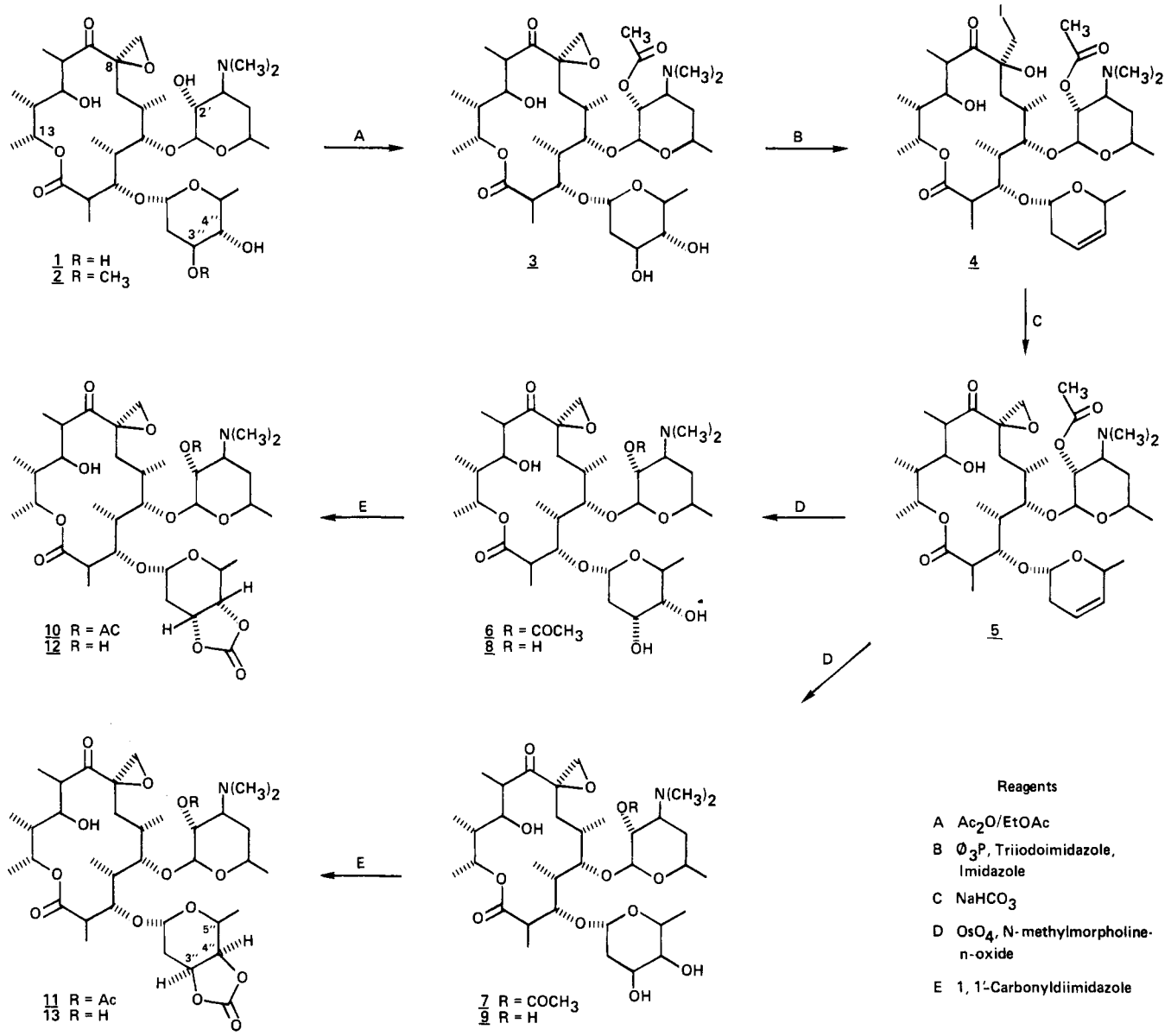
(11) We gratefully acknowledged the help of Drs. E. Whipple, G. Chmurney, Mr. G. DeRose, and Mr. R. Ware for accumulation of ^{13}C and ^1H NMR and mass spectral data.

(12) Lemieux, R. U.; Kullnig, R. K.; Bernstein, H. J.; Schneider, W. J. *J. Am. Chem. Soc.* **1958**, *80*, 6098.

(13) The in vitro results were determined by Dr. James Retsema and coworkers, Pfizer Central Research.

0022-3263/82/1947-4796$01.25/0

Scheme I



In summary, the transformation of the olivose neutral sugar in oleandomycin Y to a 3,6-dideoxy-L-allose derivative (i.e., inversion of the 3''-equatorial alcohol to the 3''-axial position) was accomplished via a dehydration/oxidation transformation. The applicability of new synthetic methodology to a complex natural product has been demonstrated.

Experimental Section

NMR spectra were recorded with a Varian T-60, Varian 270, or Bruker 250-MHz spectrometer with tetramethylsilane (Me_4Si) as an internal standard. Only chemical shifts relevant to structural assignment have been reported. ^{13}C NMR spectra were obtained in the FFT mode on a Varian XL-100-15 (25 MHz) spectrometer equipped with a Nicolet Technology 1080 data system. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. Mass spectra were recorded with an AEI MS-30 spectrometer equipped with a D5-50 data system. TLC was performed by using precoated 0.25-mm-thick silica gel 60 plates (Merck), and column chromatography (unless otherwise noted) was done with 70–230-mesh silica gel (Merck).

2'-Acetyloleandomycin Y (3). A mixture of 1.2 g (0.0018 mol) of oleandomycin Y and 0.19 mL (0.002 mol) of acetic anhydride was stirred in 20 mL of ethyl acetate at room temperature for 4 h. To this solution was added 50 mL of water and the pH adjusted to 9.5. The ethyl acetate was separated from the aqueous layer, dried (Na_2SO_4), and evaporated to yield 1.0 g of 2'-acetyloleandomycin (77% yield) as a white amorphous foam: NMR ($CDCl_3$) δ 5.55 (q, 1 H), 2.26 (s, 6 H), 2.05 (s, 3 H); mass spectrum, m/e 716.3717 (±5.04 ppm; P + H, $C_{36}H_{62}NO_{13}$), 216.1222 (±1.4 ppm; $C_{10}H_{18}O_3N$), 200.1271 (±1.6 ppm; $C_{10}H_{18}O_3N$, base peak), 140.1048 (±2.4 ppm; $C_8H_{16}O_2N$, desosamine sugar), 113.0574 (±2.8 ppm; $C_6H_9O_2$), 95.0541 (±4.4 ppm; C_5H_7O, olivose sugar); TLC (3:1 $CHCl_3/CH_3OH$) R_f 0.60. Anal. Calcd for $C_{36}H_{61}O_{13}N\cdot H_2O$: C, 58.91; H, 8.65; N, 1.91. Found: C, 59.00; H, 8.46; N, 2.07.

2'-Acetyl-3'',4''-dehydrooleandomycin Y Iodohydrin (4). A mixture of 0.25 g (0.000 35 mol) of 2'-acetyloleandomycin Y, 0.25 g (0.000 56 mol) of triiodoimidazole, 0.048 g (0.0007 mol) of imidazole, and 0.37 g (0.0014 mol) of triphenylphosphine was refluxed in 10 mL of toluene for 1.5 h. The solution was added to 500 mL of H_2O. The toluene layer was separated from the aqueous layer and dried ($NaSO_4$). Evaporation of the toluene afforded a white amorphous solid. This solid was dissolved in $CHCl_3$ and placed on a 7-g column of silica gel. After elution with 1:1 $CHCl_3$/acetone as the eluant, the appropriate fractions were combined and evaporated to yield 0.06 g (22%) of 3'',4''-dehydrooleandomycin Y iodohydrin (4) as an amorphous solid: NMR ($CDCl_3$) δ 5.60 (m, 2 H, olefininc H), 5.55 (q, 1 H, C_{13} H), 3.46 (s, 2 H, CH_2I), 2.30 (s, 6 H, $N(CH_3)_2$), 2.01 (s, 3 H, $COCH_3$); mass spectrum, m/e 497.1401 (±0.0 ppm; P - 312, $C_{20}H_{34}O_I$,

aglycon; 200.1270 (±1.6 ppm; $C_{10}H_{18}O_3N$, base peak), 140.1046 (±2.4 ppm; $C_8H_{16}O_2N$, desosamine sugar), 97.0702 (±4.8 ppm; C_6H_9O, 3″,4″-dehydroolivose); TLC (1:1 $CHCl_3$/acetone) R_f 0.50.

2′-Acetyl-3″,4″-dehydrooleandomycin Y (5). A mixture of 0.50 g (0.007 mol) of 2′-acetyloleandomycin Y, 0.37 g (0.0054 mol) of imidazole, 0.64 g (0.0014 mol) of triiodoimidazole and 0.15 g (0.0006 mol) of triphenylphosphene was refluxed for 1 h in 15 mL of toluene. The solution was cooled to room temperature and the solvent evaporated. The residue was dissolved in $CHCl_3$ and chromatographed on 15 g of Woelm basic alumina (activity 1) with 1:1 $CHCl_3$/hexane as the eluant. Appropriate fractions were combined to yield 0.1 g (21%) of 3″,4″-dehydrooleandomycin Y as an amorphous white foam: NMR ($CDCl_3$) δ 5.63 (m, 2 H, olefinic H), 5.55 (q, 1 H, $C_{13}H$), 2.86, 2.80 (2 H, C_8 epoxide methylene), 2.25 (s, 6 H, $N(CH_3)_2$), 2.05 (s, 3 H, $COCH_3$); mass spectrum, *m/e* 585.3492 (±2.1 ppm; P − 97, $C_{30}H_{51}O_{10}N$), 465.2823 (±2.9 ppm; P − 216, $C_{26}H_{41}O_7$), 369.2370 (±5.1 ppm; P − 330, $C_{20}H_{33}O_6$, aglycon), 200.1278 (±0.9 ppm; $C_{10}H_{13}O_3N$, base peak), 140.1070 (±0.6 ppm; $C_8H_{16}O_2N$, desosamine sugar), 97.0685 (±3.1 ppm; C_6H_9O, dehydrated olivose); TLC (1:1 ethyl acetate/acetone) R_f 0.37.

2′-Acetyl-3-(2,6-dideoxy-L-α-allosyl)oleandomycin Y (6) and 2′-Acetyl-3-(2,6-dideoxy-L-α-galactosyl)oleandomycin Y (7). A mixture of 4.0 g (0.0056 mol) of 2′-acetyloleandomycin Y, 4.0 g (0.009 mol) of triiodoimidazole, 0.76 g (0.0112 mol) of imidazole, and 4.4 g (0.0168 mol) of triphenylphosphine was refluxed in 400 mL of toluene for 4 h. The solution was cooled to ambient temperature and washed with saturated $NaHCO_3$, 5% sodium thiosulfate, and saturated brine. The organic layer was dried and the toluene evaporated to yield a yellow amorphous foam. This residue was dissolved in 50 mL of acetone, and to the solution were added successively 3.4 g (0.029 mol) of *N*-methylmorpholine *N*-oxide, 0.125 g (0.000 492 mol) of OsO_4 dissolved in 25 mL of *tert*-butyl alcohol, and 50 mL of water. The solution was stirred 3 h at room temperature after which 1.5 g (0.014 mol) of sodium bisulfite was added. Stirring was continued for 15 min, and the mixture was filtered. The filtrate was diluted with 100 mL of H_2O and the pH adjusted to 8.5. The filtrate was extracted with ethyl acetate. The ethyl acetate layer was recombined with 100 mL of H_2O. The resulting aqueous layer was successively extracted with ethyl acetate at pH 2.5, 4.0, and 9.0. The ethyl acetate layer resulting from the pH 9.0 extraction was dried and evaporated to yield 2.1 g (54%) of a mixture. The mixture was chromatographed on 100 g of silica gel (230–400 mesh) with $CHCl_3/CH_3OH$ (20:1) as the eluant. Appropriate fractions were combined to yield 1.1 g (28%) of **6** as a white amorphous foam, TLC (5:1 $CHCl_3/CH_3OH$) R_f 0.45. Further elution yielded 0.6 g of **7** as a white amorphous foam, TLC (5:1 $CHCl_3/CH_3OH$) R_f 0.38. Further characterization of these compounds was completed as their biologically active 2′-hydroxyl derivatives **8** and **9** (see below).

3-(2,6-Dideoxy-L-α-allosyl)oleandomycin Y (8). A solution of 0.7 g of **6** (0.104 mmol) in 50 mL of CH_3OH was stirred at room temperature for 36 h. The solvent was evaporated under reduced pressure to yield 623 mg (95%) of diol **8** as an amorphous solid: NMR ($CDCl_3$) δ 5.56 (q, 1 H, $C_{13}H$), 4.96 (m, 1 H, $C_{1''}$ H), 2.25 (s, 6 H, $N(CH_3)_2$), 1.32 (d, J = 6 Hz, 3 H, $C_{5''}$ CH_3); ^{13}C NMR, Table I; TLC (5:1 $CHCl_3/CH_3OH$) R_f 0.18.

3-(2,6-Dideoxy-L-α-galactosyl)oleandomycin Y (9). A solution of 0.5 g of **7** (0.743 mmol) in 50 mL of CH_3OH was stirred at room temperature for 36 h. The solvent was evaporated under reduced pressure to yield 0.450 g (96%) of diol **9** as an amorphous solid: NMR ($CDCl_3$) δ 5.59 (q, 1 H, $C_{13}H$), 4.99 (m, 1 H, $C_{1''}$ H), 2.28 (s, 6 H, $N(CH_3)_2$), 1.30 (d, J = 6 Hz, 3 H, $C_{5''}$ CH_3); ^{13}C NMR, Table I; TLC (5:1 $CHCl_3/CH_3OH$) R_f 0.12.

2′-Acetyl-3-(2,6-dideoxy-L-α-allosyl)oleandomycin Y Carbonate (10). To a solution of 100 mg (0.149 mol) of diol **6** dissolved in 10 mL of CH_3CN was added 0.21 mL (0.149 mmol) triethylamine and 0.26 g (0.163 mmol) of 1,1′-carbonyldiimidazole. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was added to an equal volume of water, the pH adjusted to 5.0, and the mixture extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated $NaHCO_3$, dried, and evaporated to yield 0.46 g (45%) of carbonate **10** as an amorphous solid: NMR ($CDCl_3$) δ 2.25 (s, 6 H, $N(CH_3)_2$), 2.03 (s, 3 H, $COCH_3$); TLC (9:1 $CHCl_3/CH_3OH$) R_f 0.65. Further characterization of carbonate **10** was completed on the biologically active 2′-hydroxy compound **12** (see below).

Table I. ^{13}C NMR Chemical Shifts[a] of Oleandomycin Y (1),[b] *cis*-Diol 8 and *cis*-Diol 9

atom	compd 1	8	9
C_1	176.0	175.8	176.4
C_2	44.7	44.7	44.8
C_3	80.6	82.5	80.8
C_4	41.6	41.6	41.6
C_5	84.4	84.3	84.4
C_6	30.5	30.3	31.5
C_7	31.3	30.5	30.6
C_8	62.4	62.4	62.5
C_9	207.6	208.0	208.1
C_{10}	44.7	44.7	44.6
C_{11}	68.9	69.1	69.1
C_{12}	42.9	42.6	43.0
C_{13}	70.5	70.4	70.4
C_2CH_3	19.5	20.0	19.7
C_4CH_3	6.9	6.7	6.8
C_6CH_3	14.3	14.6	14.2
C_8CH_3O	48.6	48.8	48.7
$C_{10}CH_3$	9.4	9.7	9.5
$C_{12}CH_3$	8.8	8.7	8.8
$C_{13}CH_3$	18.3	18.3	18.2
$C_{1'}$	104.4	104.8	104.6
$C_{2'}$	70.1	70.3	70.2
$C_{3'}$	65.2	65.4	65.5
$C_{4'}$	28.3	28.2	28.7
$C_{5'}$	68.9	69.4	69.3
$C_{6'}$	21.0	21.0	21.0
$C_{3'}N(CH_3)_2$	40.1	40.1	40.1
$C_{1''}$	99.0	99.5	97.7
$C_{2''}$	37.4	34.7	32.4
$C_{3''}$	68.4	66.8	66.7
$C_{4''}$	77.8	72.4	71.1
$C_{5''}$	68.3	65.6	65.6
$C_{6''}$	17.7	17.6	16.6

[a] $CDCl_3$ solutions in parts per million from Me_4Si. [b] For the ^{13}C NMR assignment of oleandomycin, see: Nourse, J. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1975**, *97*, 4584.

2′-Acetyl-3-(2,6-dideoxy-L-α-galactosyl)oleandomycin Y Carbonate (11). By use of the above reaction conditions, 100 mg (0.149 mmol) of diol **7** yielded 56 mg (54%) of carbonate **11** as an amorphous solid: TLC (9:1 $CHCl_3/CHCl_3$) R_f 0.63. Carbonate **13** was further characterized as its 2′-hdyroxyl derivative **13** (see below).

3-(2,6-Dideoxy-L-α-allosyl)oleandomycin Y Carbonate (12). A solution of 250 mg (0.34 mmol) of carbonate **10** was stirred in 50 mL of CH_3OH at room temperature for 36 h. The solvent was evaporated under reduced pressure to yield 230 mg (96%) of carbonate **12** as a white amorphous solid: NMR ($CDCl_3$) δ 5.55 (q, 1 H, $C_{13}H$), 5.00 (dd, J = 5.5, 7.9 Hz, 1 H, $C_{1''}$ H), 4.79 (ddd, J = 6, 8.5, 10.4 Hz, 1 H, $C_{3''}$ H), 4.31 (dd, J = 8.2, 8.4 Hz, 1 H, $C_{4''}$ H), 4.02 (dq, J = 8.4, 6.1 Hz, 1 H, $C_{5''}$ H), 2.50 (m, 1 H, $C_{2''}$ H), 2.28 (s, 6 H, $N(CH_3)_2$), 2.07 (m, 1 H, $C_{2''}$ H), 1.38 (d, J = 6.1 Hz, 3 H, $C_{5''}$ CH_3); mass spectrum, *m/e* 369.2373 (±5.3 ppm; P − 330, $C_{20}H_{33}O_6$), 351.2157 (±1.4 ppm; P − 348, $C_{20}H_{31}O_5$, aglycon); 158.1181 (±0.0 ppm; $C_8H_{16}NO_2$, base peak, desosamine sugar), 157.0576 (±7.5 ppm; $C_7H_9O_4$, neutral sugar); TLC (9:1 $CHCl_3/CH_3OH$) R_f 0.35. Anal. Calcd for $C_{35}H_{57}O_{13}N$: C, 60.07; H, 8.21; N, 2.00. Found: C, 59.82; H, 8.27; N, 2.04.

3-(2,6-Dideoxy-L-α-galactosyl)oleandomycin Y Carbonate (13). A solution of 250 mg (0.34 mmol) of carbonate **11** in 50 mL of CH_3OH was stirred at room temperature for 36 h, followed by evaporation of the solvent, to yield 225 mg (94%) of carbonate **13** as an amorphous solid: NMR ($CDCl_3$) δ 5.6 (q, 1 H, C_{13} H) 2.30 (s, 6 H, $N(CH_3)_2$); mass spectrum, *m/e* 369.2403 (±1.0 ppm; P − 330, $C_{20}H_{33}O_6$), 351.2308 (±1.0 ppm; P − 348, $C_{20}H_{31}O_5$, aglycon); 158.1175 (±0.6 ppm; $C_8H_{16}NO_2$, desosamine sugar); 157.0560 (±5.9 ppm; $C_7H_9O_4$, neutral sugar); TLC (9:1 $CHCl_3/CH_3OH$) R_f 0.28. Anal. Calcd for $C_{35}H_{57}O_{13}N$: C, 60.07; H, 8.21;

N, 2.00. Found: C, 60.03; H, 8.22; N, 1.98.

Registry No. 1, 64743-16-4; 3, 81692-79-7; 4, 81686-47-7; 5, 81686-48-8; 6, 81738-68-3; 7, 81738-69-4; 8, 83349-69-3; 9, 83349-70-6; 10, 81767-43-3; 11, 81686-49-9; 12, 81767-44-4; 13, 81686-50-2.

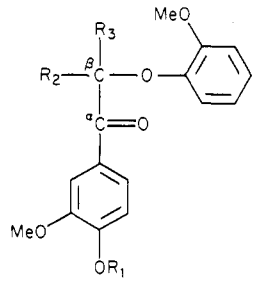
Selective Alkylations of Phenolic Ketones

Donald R. Dimmel* and Donaline Shepard

The Institute of Paper Chemistry, Appleton, Wisconsin 54912

Received April 27, 1982

Lignin models are often used in mechanistic studies in an attempt to understand the chemistry of native lignin, a complex, random, cross-linked polymeric component of wood.[1] We describe a new synthesis of lignin models, one which allows the introduction of β-substituents (1) without having to protect[2] the phenolic hydroxyl group. The method takes advantage of a selective alkylation of a dianion.



1a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_2 = Li$; $R_3 = H$
c, $R_1 = R_2 = H$; $R_3 = Me$
d, $R_1 = R_2 = Li$; $R_3 = Me$
e, $R_1 = H$; $R_2 = R_3 = Me$
f, $R_1 = R_2 = H$; $R_3 = CH_2OH$

A sample of **1a**[3] was treated with an excess of lithium diisopropylamine (LDA), followed by addition of excess methyl iodide (MeI) and then acid, to afford a mixture of starting ketone (**1a**) and monomethylated ketone **1c**. The two ketones were easily separated by column chromatography. The presumed intermediate formed by LDA treatment was the dilithiospecies **1b**, which apparently only alkylated at the β-carbon. The low reactivity of the lithium phenolate group was surprising; both phenol and guaiacol (*o*-methoxyphenol) were also not alkylated with this LDA/MeI treatment. These results suggest that phenols do not have to be protected (i.e., a benzyl ether) prior to base-induced alkylations involving LDA.

The monomethylated ketone **1c** could be converted via **1d** to a mixture of **1c** and dimethylated ketone **1e** by LDA/MeI treatment. Again, the two ketones were easily separated by chromatography.

In an attempt to define the scope of these alkylations, we treated the dilithio species **1b** with a variety of alkylating agents, including ethyl, propyl, and benzyl halides and formaldehyde. Only the latter reaction was successful, producing **1f**. Although extensive variations of reaction conditions were not examined, it appears that the alkylation of **1b** is restricted to some simple, unhindered electrophiles. Two variations which were examined, employing *n*-butyllithium alone as the base and LDA/MeI treatment of the acetate of **1a**, gave methylated product but in lower conversion than the typical procedure.

Experimental Section

The instrumentation used has been described previously.[4] All melting and boiling points are uncorrected.

General Alkylation Procedures. All alkylations employed dried glassware, anhydrous solvents, distilled reagents, and a nitrogen atmosphere. To 100 mL of ice-cooled, stirred tetrahydrofuran (THF) was added 4 equiv of *n*-butyllithium in hexane, followed by 4 equiv of diisopropylamine. After being stirred 15 min, the solution was cooled to −70 °C, and 1 equiv of ketone (about 50 mmol) dissolved in THF was added dropwise. The stirred mixture was then allowed to warm to room temperature for 1 h, followed by cooling again to −70 °C. The alkylating agent (4 equiv), generally an alkyl halide, was dissolved in THF and added dropwise. In the case of formaldehyde, a separate vessel containing dry paraformaldehyde was pyrolyzed at 200 °C and an excess amount of the gaseous reactant swept into the reaction flask with a stream of nitrogen. After addition of the alkylating agent, the mixture was stirred for several hours at room temperature.

The reaction mixture was quenched by the addition of aqueous NH_4Cl. The organic layer was separated and the aqueous layer extracted several times with fresh ether. (If emulsions developed, dilute HCl was added.) The combined organic extracts were washed with 3 M HCl and then twice extracted with 1 M NaOH. The alkaline extracts were acidified and extracted three times with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to afford the crude product, which by ^1H NMR analysis was generally a simple mixture of starting and product ketones.

The crude product was purified by chromatography on a silica gel column with first 600 mL of toluene and then successive 400-mL increments of 10%, 20%, 30%, and 40% ether–toluene over about a 6-h period. The order of elution was β,β-dimethyl ketone **1e**, β-methyl ketone **1c**, unsubstituted ketone **1a**, and β-hydroxymethyl ketone **1f**. Fractions of desired ketone were combined and recrystallized.

1-(4-Hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-1-propanone (1c). The methylation to produce this compound was done several times with varying reactant levels. As an example of a somewhat large scale run, 217 mL of 1.6 M *n*-butyllithium in hexane, 48.7 mL of diisopropylamine, 25 g of **1a**, 21.6 mL of methyl iodide, and roughly 300 mL of THF afforded 27.6 g of crude product which by NMR was roughly a 2:1 mixture of **1c**/**1a** containing small amounts of solvent. Chromatography gave pure **1c**: mp 131–133 °C (benzene–petroleum ether); ^1H NMR and mass spectral data agreed with literature values.[2a,b] In general, the conversion of **1a** to **1c** was 50–65%.

1-(4-Hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-2-methylpropanone (1e). The conversion for **1c** to **1e** was roughly 33%. Consequently, the product of one methylation was used as the starting material for another until the product mixture was rich in the **1e** component. Chromatography afforded pure **1e**: mp 98–100 °C (benzene–petroleum ether); IR (mull) 2900–3500 (OH), 1760 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.65 (s, 6, Me), 3.76 (s, 3, OMe), 3.89 (s, 3, OMe), 6.09 (s, 1, OH), 6.7–6.9 (m, 5, aryl), 7.8–8.2 (m, 2, aryl); ^{13}C NMR ($CDCl_3$) 26.1 (q, Me), 55.4 (q, OMe), 56.0 (q, OMe), 86.0 (s, C_2), 112.2 (d), 112.4 (d), 113.8 (d), 120.3 (d), 120.6 (d), 123.0 (d), 125.8 (d), 127.5 (s), 144.5 (s), 146.0 (s), 149.9 (s) and 151.6 (s) (aryl), 200.1 ppm (s, C_1); MS, *m/e* (relative intensity) 316 (9, M^+), 165 (100), 151 (16), 125 (16), 124 (28), 123 (13).

3-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-1-propanone (1f). This reaction was only per-

(1) Sarkanen, K. V.; Ludwig, C. H., Eds. "Lignins"; Wiley-Interscience: New York, 1971.
(2) The following are examples: (a) Adler, E.; Delin, S.; Miksche, G. E. *Acta Chem. Scand.* **1966**, *20*, 1035. (b) Omori, S.; Dence, C. W. *Wood Sci. Technol.* **1980**, *15*, 67.
(3) Hosoya, S.; Kanazawa, K.; Kaneko, H.; Nakano, J. *Mokuza Gakkaishi* **1980**, *26*, 118.
(4) Dimmel, D. R.; Shepard, D.; Brown, T. A. *J. Wood Chem. Technol.* **1981**, *1*, 123.

0022-3263/82/1947-4799$01.25/0