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STUDIES IN MACROLIDE SYNTHESIS:
A SYNTHESIS OF TWO CHIRAL FRAGMENTS OF OLEANDOMYCIN AND LANKAMYCIN.

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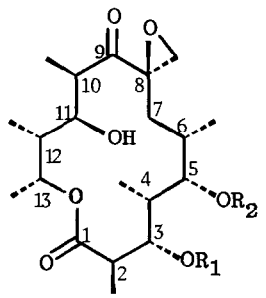
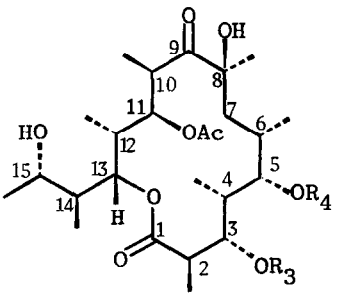
Summary: A synthesis of the two structurally-related chiral fragments, C_1-C_7 and C_8-C_{13}, of oleandomycin and lankamycin is described.

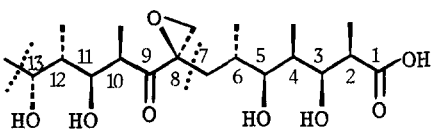
The macrolide antibiotics,[1,2] as a large class of structurally-complex natural products, contain many interesting targets for total synthesis. The stereochemical similarities, both between different macrolides[2] and different segments of the same structure (i.e. the presence of molecular symmetry), provide useful guidance in designing potential synthetic routes. This 'symmetry consideration' is well-illustrated in the Stork approach[3] to the synthesis of erythronolide A, the aglycone of erythromycin.



(**1**) R_1 = L-oleandrosyl; R_2 = D-desosaminyl.



(**2**) R_3 = *O*-acetyl-L-arcanosyl; R_4 = D-chalcosyl.



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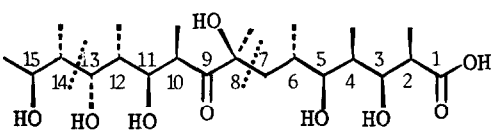

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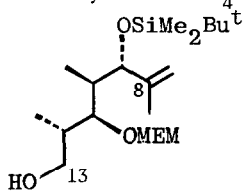

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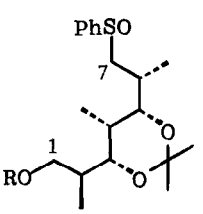


(**5**)

The aglycones of the medically-important oleandomycin (**1**)[4] and the related 14-membered macrolide lankamycin (**2**)[5,6] are configurationally identical at all 10 chiral centres between C_1 and C_{13}. In addition, the chiral sequence between C_4 and C_6 is the same as that found at C_{10} to C_{12}. This can be clearly seen from their respective seco-acid structures (**3**) and (**4**). Based on bond disconnections at C_7-C_8 and C_{13}-C_{14}, we describe here a synthesis of two fragments common to oleandomycin (**1**) and lankamycin (**2**) — a C_1-C_7 right-hand fragment (**5**) and a C_8-C_{13} left-hand fragment (**6**) — both of which can be obtained from a single advanced intermediate (**7**).

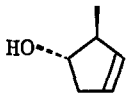
The silyl enol ether (+)-(**8**)[3] is readily available in 4 steps from **9** (63% overall yield), which is obtained in high enantiomeric purity (>95% ee) from cyclopentadiene using asymmetric hydroboration.[7] This chiral synthon (**8**) was intended as the source of the asymmetric carbons at C_2, C_3, and C_4 (right-hand fragment), as well as at C_9 and C_{10} (left-hand fragment). Its conversion to the δ-hydroxyester (**10**) was possible using a modified[3] sequence of ozonolysis (MeOH-CH_2Cl_2, 2:1, -78°C), addition of $NaBH_4$ (-78°C, 2h; 20°C, 2h), solvent evaporation and mild acidification (1*M* HCl, 0°C), then finally esterification (CH_2N_2,Et_2O). Hydroxyl protection was immediately carried out on **10** ($PhCH_2OCH_2Cl$, Pr^i_2NEt, CH_2Cl_2) to give the benzyloxymethyl ether (**11**) (70% from **8**). Reduction of **11** with DIBAL (2.5 equiv., CH_2Cl_2, -78°C), followed by PCC oxidation of the derived alcohol (3 equiv., propylene oxide, CH_2Cl_2; 95%) then gave the aldehyde (**12**).

Introduction of the next 2 chiral centres was possible with high stereoselectivity using the aryl ester aldol condensation of Heathcock.[8] Addition of the aldehyde (**12**) to a solution of the Li enolate (**14**) at -100°C (THF, 10 min) gave two aldol diastereomers in ratio of 13:1[8] (92% combined yield), which were easily separated chromatographically (SiO_2, Pr^i_2O-pentane, 1:3). The major aldol (**7**)[9], R_f 0.14, had $J_{a,b}$ 9.4 Hz supporting the expected[8] *threo*-stereochemistry, while the indicated stereo-relationship between the ester β- and γ-carbon atoms (b and c) was confirmed by correlation[10] with the known acetonide (**15**, R=$SiPh_2Bu^t$).[3] The aryl ester (-)-(**7**) now contains all of the chirality needed in the prospective left- and right-hand fragments (**5** and **6**).

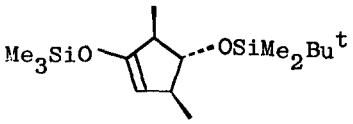
The synthesis of the (nucleophilic) right-hand fragment, the phenylsulphoxide derivatives (**5**, R=H or $PhCH_2OCH_2$) were initially chosen, from **7** required only minor structural changes. Reduction with $LiAlH_4$ (Et_2O, 0°C) followed by desilylation (TBAF, THF) gave the triol (**16**), which was first mono-tosylated (TsCl, Et_3N-DMAP, CH_2Cl_2) then converted into the acetonide (**17**) ($(MeO)_2CMe_2$-CH_2Cl_2, pyridinium tosylate) in 70% yield from **7**. Tosylate (**17**) could be easily converted into **5**, R=$PhCH_2OCH_2$, by displacement with NaSPh (EtOH) followed by sulphur oxidation ($NaIO_4$, aq. MeOH; 93% overall). Alternatively, the free alcohol (**5**, R=H) could be prepared by hydrogenolysis of the benzyloxymethyl ether (**17**) (H_2, 10% Pd-C, Pr^i_2O) to give **18**, followed by these same 2 steps (89% overall).

The synthesis of the left-hand fragment (**6**) common to both oleandomycin and lankamycin requires the loss of one redundant chiral centre from **7**.[11] This sequence was initiated by protection of the secondary hydroxyl in **7** as its MEM ether (MEM-$\overset{+}{N}Et_3$ Cl^-,[12] MeCN, reflux, 32h), which on hydrogenolysis (H_2, 10% Pd-C, Pr^i_2O) gave ester (**19**) (96% overall). Treatment of (**19**) with *o*-$NO_2(C_6H_4)SeCN$ (Bu^n_3P, THF, 0°C)[13] was followed by addition of 30% H_2O_2 to give the alkene (**20**)[11], which was finally reduced (DIBAL, CH_2Cl_2, -78°C) to give (-)-(**6**)[14] in 80% overall yield. The C_8 alkene is intended eventually, in each synthetic scheme, to become a suitable carbonyl derivative for coupling with the anion of **5**.

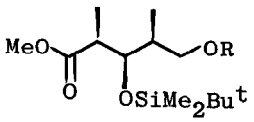
Finally, for our approach to the synthesis of oleandomycin (**1**), we have briefly examined the question of controlling the stereochemistry at C_{13}. Addition of MeMgCl to the aldehyde, obtained by oxidation of **6** (PCC, propylene oxide, CH_2Cl_2), in THF at -100°C gave an 8:1 ratio of C_{13}-epimers (93% combined yield). On the basis of chelation-controlled addition to this β-alkoxy-aldehyde,[15] we tentatively assign structure (**21**) to the major adduct (^{1}H-NMR:H_{13}, dq at δ 4.25; Me doublet at δ 1.23). If this is correct, a configuration inversion step (perhaps on cyclisa-



(**9**)

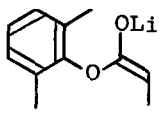


(**8**)



(**10**) R = H

(**11**) R = $PhCH_2OCH_2$



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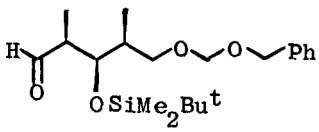

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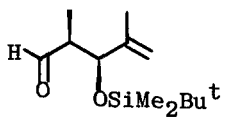

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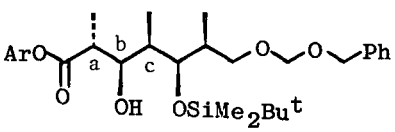
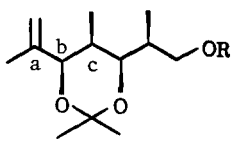
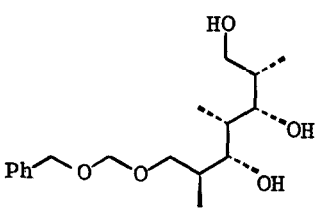


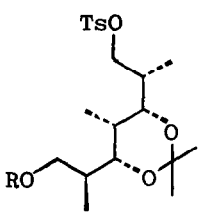
(**7**)



(**15**)

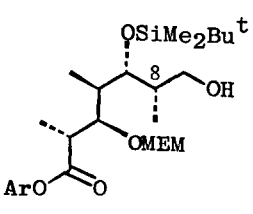


(**16**)



(**17**) R = $PhCH_2OCH_2$

(**18**) R = H



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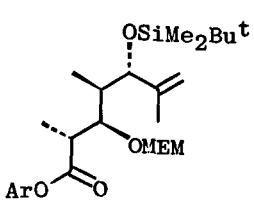
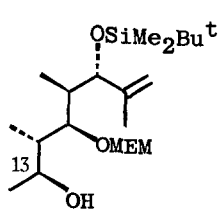


(**20**)



(**21**)

tion[16]) would be needed to gain the natural C_{13} stereochemistry of oleandomycin (**1**).

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Notes and References:

[1]Reviews: S. Masumune, G. S. Bates, and J. W. Corcoran, *Angew. Chem. Internat. Ed.*, *16*, 585 (1977); K. C. Nicolaou, *Tetrahedron*, *33*, 683 (1977).

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[8]M. C. Pirrung and C. H. Heathcock, *J. Org. Chem.*, *45*, 1727 (1980). Condensation of **14** with 2-phenylpropanal at -78°C was reported to give a 4:1 "Cram/anti-Cram" ratio of the two *threo*-adducts.

[9]Major aldol diastereomer (**7**), $[\alpha]_D$ = -6.2° (c 2.58, $CHCl_3$), had ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 7.24 - 7.38 (5H, m, Ph), 7.04 (3H, m, Ar), 4.70 - 4.80 (2H, m, OCH_2O), 4.61 (2H, s, CH_2Ph), 4.02 (1H, dd, *J* 9.4, 2.3, H_b), 3.88 (1H, dd, *J* 6.4, 2.3, CHOSi), 3.57 (1H, dd, *J* 9.5, 6.7, C*H*HO), 3.45 (1H, dd, *J* 7.0, 9.5, CH*H*O), 2.92 (1H, dq, *J* 9.4, 7.0, H_a), 2.16 (6H, s, Me), 2.02 - 2.16 (1H, m), 1.78 - 1.89 (1H, m), 1.33 (3H, d, *J* 7.0, *Me*CH_a), 0.97 (3H, d, *J* 7.0, Me), 0.94 (3H, d, Me), 0.92 (9H, s, Bu^t), 0.11 and 0.09 (3H, s, MeSi); ^{13}C-NMR ($CDCl_3$) δ 174.01, 148.08, 137.95, 130.27, 128.68, 128.48, 127.91, 127.74, 125.94, 94.84, 75.10, 73.99, 71.29, 69.55, 44.34, 37.88, 37.17, 26.25, 18.53, 16.53, 14.47, 11.79, 8.97.

[10]The major aldol adduct (**7**) was converted into acetonide (**15**, R = $PhCH_2OCH_2$) by the sequence: (i) $LiAlH_4$, Et_2O; (ii) TBAF, THF; (iii) Bu^tPh_2SiCl, Et_3N (DMAP), CH_2Cl_2; (iv) $(MeO)_2CMe_2$, TsOH.py; repeat (ii); (v) *o*-$NO_2(C_6H_4)$SeCN, Bu^n_3P, THF, followed by 30% H_2O_2. **15** (R = Bu^tPh_2Si) and its epimer at C_b, as well as their respective methyl ketone derivatives,[3] have markedly different ^{1}H-NMR spectra. In particular, the axial H_b in **15** occurs at δ 4.22, while its epimer has H_b at higher field in the region of δ 3.3 - 3.8.

[11]The ester (**20**) could be prepared in fewer steps, but with lower overall yield, by aldol addition of **14**[8] to the olefinic aldehyde (**13**) (prepared from **10**), followed by formation of the MEM ether. The aldol diastereoselectivity now obtained was reduced to 8:1 at -100°C.

[12]E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Letters*, 809 (1976).

[13]P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, *41*, 1485 (1976).

[14]**6**, $[\alpha]_D$ = -15.5° (c 1.16, $CHCl_3$), had ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 4.92 (2H, bs, C=CH_2), 4.70 - 4.82 (2H, m, OCH_2O), 3.92 (1H, d, *J* 9.0, CHOSi), 3.30 - 3.84 (6H, m), 3.36 (3H, s, OMe), 2.62 (1H, bs, OH), 1.64 - 1.88 (2H, m, C*H*Me), 1.62 (3H, s, MeC=C), 0.97 (3H, d, *J* 7.0, Me), 0.94 (3H, d, *J* 7.0, Me), 0.89 (9H, s, Bu^t), 0.05 and 0.00 (3H, s, MeSi); ^{13}C-NMR ($CDCl_3$) δ 114.90, 97.80, 83.26, 79.42, 71.66, 67.89, 65.17, 59.05, 39.61, 38.28, 25.85, 18.25, 16.61, 15.04, 10.32, 0.2.

[15]W. C. Still and J. A. Schneider, *Tetrahedron Letters*, 1035 (1980).

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