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THE TOTAL SYNTHESIS OF OLEANDOMYCIN#

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Summary: The key aglycone, oleandolide, has been synthesized by coupling two segments of C1-C7 and C8-C14 portions, which are enantiospecifically derived from methyl α-L- and D-rhamnosides, respectively.

Oleandomycin (**1**) is a medicinally important 14-membered-ring macrolide antibiotic. Herein we describe the first total synthesis of oleandomycin (**1**), which has been already derived from the key aglycone, oleandolide (**21**), by introduction of the two sugar moieties in our laboratories.[1] The construction of the aglycone **21** is based on coupling of the C1-C7 segment **9** and the C8-C14[2] segment **14**.

In reaching both segments **9** and **14**, we took advantage of our recently developed epoxide-swinging reaction[3] of methyl α-L- and D-rhamnosides, which gave the C-methylated L- and D-idopyranosides (**2** and **2'**) in 40% overall yield in 5 steps.

The synthesis of the segment **9** began with conversion of **2** into the alcohol **3**[4] (60%; $[\alpha]_D$ -6.9°) in 4 steps: benzylation (BnBr/n-Bu_4NI/NaH/THF), hydrolysis (HCl/aq. dioxane) to give an idose derivative, $NaBH_4$ (MeOH) reduction to afford a free diol, and selective O-silylation (TBDPS-Cl/imidazole/DMF). PCC oxidation (MS 3A/CH_2Cl_2) of **3** afforded the methyl ketone **4**[4] (99%; $[\alpha]_D$+11°). This was transformed into the olefin **5**[4] (75%; $[\alpha]_D$+10°) according to a Shapiro's method[5] by reaction with tosylhydrazide (THF, 67h) to give the corresponding hydrazone followed by treatment with n-butyllithium (hexane/THF, 2h). Ozonolysis of **5** with reductive workup (O_3/MeOH, -78°C, 1min; then, $(MeO)_3P$) gave the C-5 aldehyde, which was subjected to Roush's crotylboration with (*R,R*)-tartrate (*E*)-crotylboronate[6] (PhMe, -78°C, 1.5h) to afford exclusively the required "threo aldol" [6] product **6**[4] (90%; $[\alpha]_D$+3°, Rf 0.26 (hexane-EtOAc 15:1)). The stereochemistry was confirmed by ^{1}H-NMR analysis of the diacetate **7**[4], which was derived from **6** in 4 steps.[7] Benzylation (BnBr/NaH/DMF) and desilylation (n-Bu_4NF/THF) of **6** gave the alcohol **8**[4] (70%; $[\alpha]_D$+3°). Swern oxidation[8] followed by further oxidation of the resultant aldehyde ($NaClO_2$/NH_2SO_3H/aq. dioxane) led to the desired acid **9**[4] (80%; $[\alpha]_D$-13°, Rf 0.21 (hexane-EtOAc 3:1)).

Dedicated to Professor Sumio Umezawa on the occasion of his 80th birthday.

The synthesis of the other segment **14** started with transformation of the D-isomer **2'** into the galactoside **11** as follows. Treatment of **2'** with $BF_3 \cdot OEt_2$ in benzyl alcohol (50°C, 2h) afforded exclusively the 2,3-unsaturated benzyl α-D-glycoside **10**[4] (92%; $[\alpha]_D$-79°). Stereoselective hydroboration with dicyclohexylborane (THF, 50°C, 14h; then, H_2O_2, NaOH, 60°C, 2h) followed by benzylation (BnBr/NaH/DMF) gave the galactoside **11**[4] (42%; $[\alpha]_D$+192°). This was hydrolyzed (AcOH/aq. dioxane, 70°C, 9h) to give the galactose **12**, which was not affected by reaction with the lithiated dimethyl methylphosphonate[9]. Then, **12** was oxidized (PDC/MS 3A/CH_2Cl_2) to the lactone **13**[4] (85%; plates, mp 59°C, $[\alpha]_D$+124°), which smoothly reacted with the lithiated dimethyl methylphosphonate (n-BuLi/hexane/THF, -78°C, 1h) to afford, after $LiBH_4$ reduction (THF), the desired alcohol **14**[4] (85%; $[\alpha]_D$+6.3°, Rf 0.37 and 0.32 ($CHCl_3$-MeOH 12:1)).

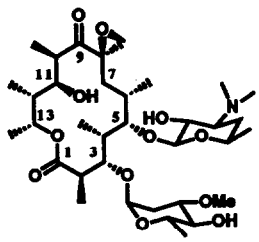
The stage was now set for a combination of the two segments **9** and **14**. The C-13 hydroxyl group of **14** was selectively esterified[10] (DMAP/PhH, 1.5h) by using the mixed anhydride, which was prepared from the acid **9** and 1-naphthoyl chloride (Et_3N/THF), to afford exclusively the ester **15**[4] (59%; Rf 0.43 and 0.27 ($CHCl_3$-Me_2CO 6:1)). PCC oxidation (MS 3A/CH_2Cl_2) followed by ozonolysis of the olefin (O_3/MeOH, -79°C, 4min; then, $(MeO)_3P$) led to the keto phosphonate **16**[4] (80%; $[\alpha]_D$-45°, Rf 0.45 (PhH-EtOAc 1:2)). The intramolecular Horner-Emmons reaction of **16** (18-Crown-6/K_2CO_3/PhMe, 50°C, 3h) provided a macrolactone, which was converted by hydrogenation (H_2/Pd-black/EtOH) and benzylidenation ($BrC_6H_4CH(OMe)_2$/CSA/CH_2Cl_2) into the p-bromobenzylidene **17**[4] (40%; $[\alpha]_D$-40°, Rf 0.31 (hexane-EtOAc 5:2)). Introduction of the C-8 exo-methylene group was accomplished by reaction of the lithiated **17** ($LiN(TMS)_2$/THF, -40°C, 3h) with gaseous formaldehyde followed by mesylation (MsCl/Et_3N/CH_2Cl_2) and elimination (DBU/CH_2Cl_2), yielding the labile compound **18**[4] (45%; Rf 0.25 (hexane-EtOAc 2:1)). As previously reported,[1] $NaBH_4$ reduction (MeOH) of **18** produced the 9β alcohol **19**[4] (90%; cubes, mp 223°C, $[\alpha]_D$+26°), which was submitted to stereoselective epoxidation (MCPBA/CCl_4) and C-9 selective oxidation (PDC/CH_2Cl_2) to afford the desired β-epoxide **20**[1,4] (65%; amorphous, $[\alpha]_D$ -70°). Reductive debenzylidenation (H_2/$Pd(OH)_2$/dioxane) of **20** gave an interconvertible mixture (91%; crystals, mp 122-126°C, $[\alpha]_D$-13°, Rf 0.31 (hexane-EtOAc 1:1)) of oleandolide (**21**) and its 5,9-hemiacetal **21'**.[1] The mixture was acetylated (Ac_2O/Py, 2 days) to afford quantitatively the triacetate **22**[1,4] (plates, mp 231°C, $[\alpha]_D$+43°, Rf 0.28 (PhH-EtOAc 3:1)).

The aforementioned compounds **20**, **21** [with its 5,9-hemiacetal **21'**] and **22** were identical with the previously described samples[1] by comparison of mp, mmp, spectra, $[\alpha]_D$, and TLC behaviors. Since the intact aglycone, oleandolide (**21**; with its 5,9-hemiacetal), has already been transformed into oleandomycin (**1**),[1] the synthesis of **21** constitutes the completion of the task.

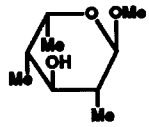
Acknowledgment. We are grateful to the Institute of Microbial Chemistry for the generous support of our program. Financial support by the Ministry of Education, Science and Culture (Grant-in-Aid for Scientific Research) is gratefully acknowledged.

References and Notes:

1) K. Tatsuta, Y. Kobayashi, H. Gunji, and H. Masuda, Tetrahedron Lett., **29**, 3975 (1988).



1: Oleandomycin



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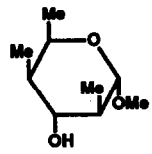
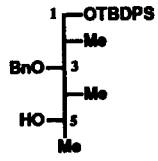
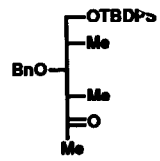


2'



$3^{2)}$



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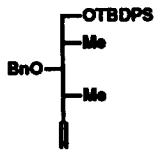

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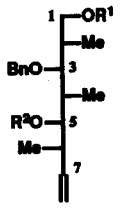
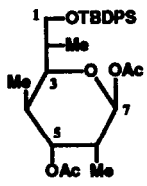


6: R^1=TBDPS, R^2=H

8: R^1=H, R^2=Bn



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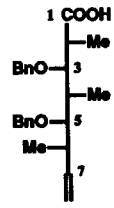

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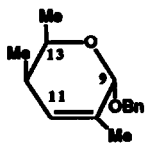
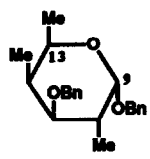


$10^{2)}$



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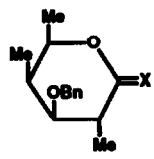
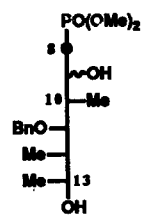


12: X=H, OH

13: X=O



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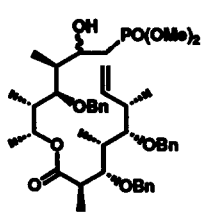

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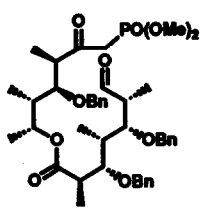

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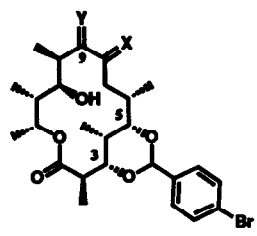
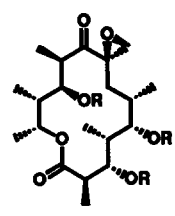


17: $X=H_2$, Y=O

18: $X=CH_2$, Y=O

19: $X=CH_2$, Y= 

20: X=  , Y=O



21: R=H
(Oleandolide)

22: R=Ac

2) This carbon-numbering protocol anticipates the construction of oleandolide (21).

3) K. Tatsuta, Y. Koguchi, and M. Kase, Bull. Chem. Soc. Jpn., **61**, 2525 (1988).

4) All reactions were carried out at room temperature, unless otherwise stated. All compounds were purified by recrystallization (EtOAc-hexane) or silica gel column chromatography, and were fully characterized by spectroscopic means and elemental analyses. Optical rotations were measured in $CHCl_3$ at c 1.0 (23°C). Rf-values were measured on silica gel Merck TLC 60F-254. NMR (270, 400 or 500MHz: δ, ppm from TMS, and J in Hz) spectra were in $CDCl_3$ solution. Significant ^{1}H-NMR spectral data are the following. **3**: 1.08 (s, t-Bu), 3.72 (t, J=5.9, H-3[2]), 3.96 (m, H-5). **4**: 2.17 (s, $COCH_3$), 2.85 (dq, J=6.8 and 6.8, H-4), 4.01 (dd, J=6.8 and 3.7, H-3). **5**: 4.98 (dd, J=10.4 and 2.4, H-6), 5.04 (ddd, J=17, 2.4 and 1.0, H-6'), 5.75 (ddd, J=17, 10.4 and 8.0, H-5). **6**: 0.91, 0.93 and 1.00 (each d, J=7.0, Me-2, 6 and 4), 5.74 (ddd, J=18, 9.2 and 8.3, H-7). **7**: 2.03 and 2.12 (each s, OAc X 2), 3.85 (dd, J=10 and 2.2, H-3), 4.94 (t, J=3.0, H-5), 5.66 (d, J=9.6, H-7). **8**: 3.19 (dd, J=6.2 and 4.5, H-5), 5.94 (ddd, J=17.4, 9.9 and 7.8, H-7). **9**: 2.85 (dq, J=7.0 and 5.0, H-2), 3.89 (t, J=5.0, H-3), 5.88 (ddd, J=17.6, 10 and 8.6, H-7). **10**: 1.70 (s, Me-10), 4.78 (s, H-9), 5.66 (dull d, J=8.0, H-11). **11**: 3.64 (dd, J=11.6 and 4.4, H-11), 4.06 (dq, J=7 and 2.8, H-13), 4.71 (d, J=4.2, H-9). **13**: 2.56 (dq, J=10.1 and 6.8, H-10), 3.51 (dd, J=10.1 and 4.0, H-11). **14**: 3.75, 3.76, 3.76 and 3.77 (each d, J≈11, P-OMe X 2 in total). **15**: Rf 0.43 Substance: 3.69 and 3.73 (each d, J=11, P-OMe X 2), 5.38 (dq, J=6.4 and 2.2, H-13), 5.88 (ddd, J=17, 10.2 and 7.6, H-7); Rf 0.27 Substance: 3.70 (d, J=11.3, P-OMe X 2), 5.25 (dq, J=6.8 and 3.8, H-13), 5.87 (ddd, J=17.2, 10.6 and 7.8, H-7). **16**: 3.12 (dd, J=22.4 and 14.1, H-8), 3.29 (dd, J=22.7 and 14.1, H-8'), 9.73 (d, J=2.8, H-7). **17**: 2.77 (dq, J=6.8 and 1.8, H-10), 2.90 (dq, J=10.6 and 6.7, H-2), 5.60 (s, benzylidene CH), 5.64 (dq, J=6.8 and 1.7, H-13). **18**: 5.39 and 5.99 (each s, exo CH_2-8), 5.57 (s, benzylidene CH), 5.64 (dq, J=6.9 and 1.4, H-13). **19**: 5.14 and 5.50 (each s, exo CH_2-8), 5.48 (q, J=5.9, H-13), 5.58 (s, benzylidene CH). **20**: 3.00 and 3.12 (ABq, J=3.6, CH_2-8), 3.05 (dq, J=6.2 and 1.6, H-10), 5.77 (q, J=6.9, H-13). **21**: 2.79 and 3.07 (ABq, J=5.4, CH_2-8), 5.68 (dq, J=7.2 and 1.2, H-13), and **21'**: 2.71 and 2.98 (ABq, J=5.4, CH_2-8), 5.02 (dq, J=7.2 and 2.2, H-13). **22**: 4.75 (d, J=6.8, H-5), 5.01 (dd, J=6.8 and 1.8, H-11), 5.19 (q, J=7.2, H-13), 5.22 (dd, J=10.4 and 2.1, H-3).

5) R. H. Shapiro and M. J. Heath, J. Am. Chem. Soc., **89**, 5734 (1967).

6) W. R. Roush and R. L. Halterman, J. Am. Chem. Soc., **108**, 294 (1986).

7) **6**→**7** (45% overall yield): i) OsO_4/NMO/aq. Me_2CO; ii) H_2/Pd-black/EtOH; iii) $NaIO_4$/aq. Me_2CO; iv) Ac_2O/Py.

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