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Stereoselective Synthesis of the C-8–C-13 Segment of Oleandonolide

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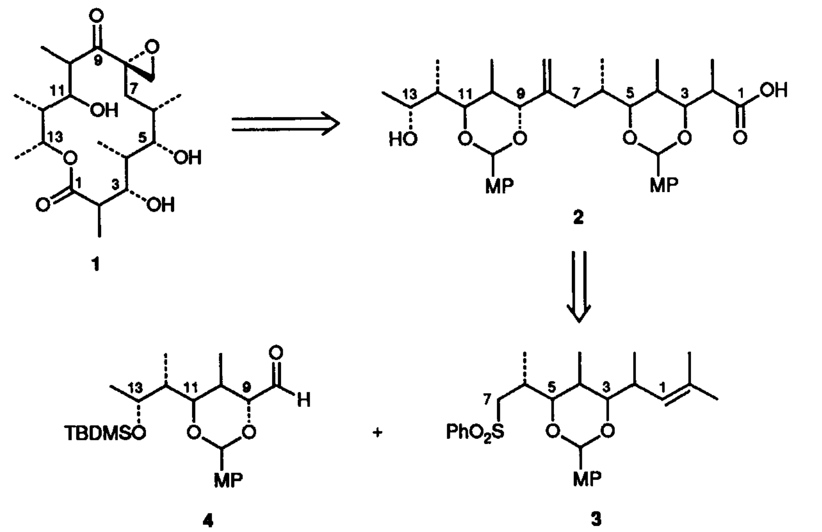
The stereoselective synthesis of C-8–C-13 segment of oleandonolide from a D-glucose derivative has been accomplished.

Clinically important 14-membered macrolide antibiotics[1] represent an attractive target for total synthesis[2]. Many attempts have been made[3–7] to synthesise oleandonolide **1**, the aglycone of the well known antibiotic oleandomycin; quite recently this synthesis was successfully completed.[8]

Our approach, based on the use of sugar synthons containing a number of chiral centres,[9–11] allows the full synthesis of erythronolides A and B to be accomplished.[12] The next step in our programme involves the synthesis of two other antibiotics of this group, lankanolide and oleandonolide. These macro-



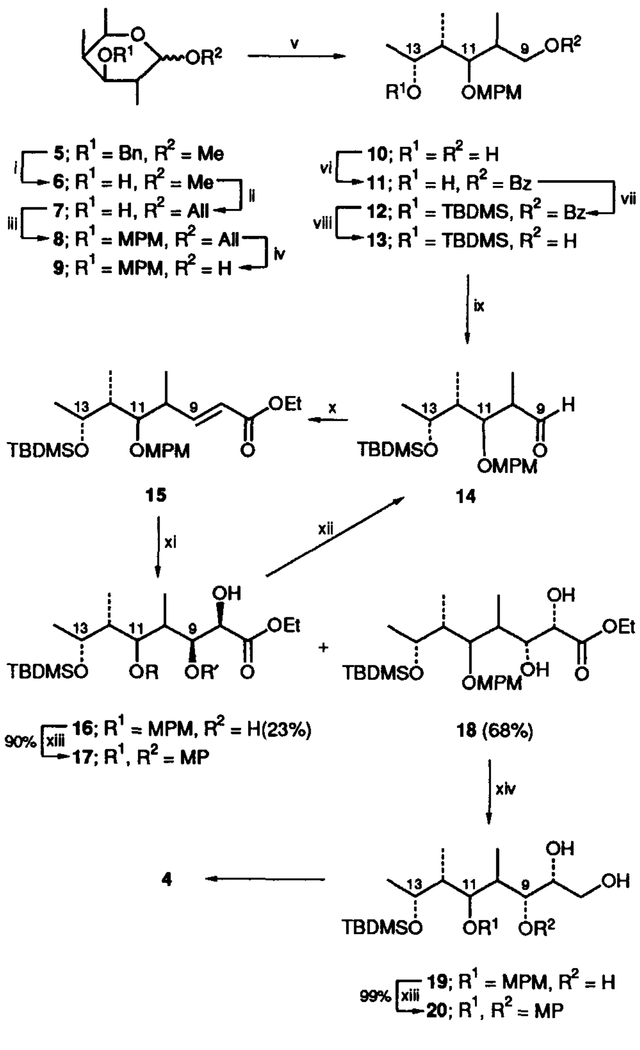
Scheme 1

lides contain an identical C-1–C-7 segment and closely related C-8–C-15 and C-8–C-13 segments, respectively. Recently we discussed a retrosynthetic scheme for the synthesis of lankanolide and reported the synthesis of the C-1–C-7 segment.[13]

The oleandonolide synthesis was planned according to a similar scheme (see retrosynthetic Scheme 1). The carbon backbone of oleandonolide **1** can be obtained by macrolactonization of the appropriate seco-acid derivative **2** which can be derived by coupling of the C-1–C-7[13] and C-8–C-13 segments **3** and **4**, respectively. The synthesis of the C-8–C-13 segment **4** can be accomplished from derivative **5**, which has been obtained previously[14] from 1,6-β-D-anhydroglucose (levoglucosane). We report here the synthesis of **4** (Scheme 2). The stereochemistry of **5** corresponds exactly with that of the C-10–C-13 part of oleandonolide and for the transformation **5**→**4** one has to convert **5** into the acyclic derivative **14** and build up the correct configuration at C-9 during the elongation of the carbon chain.

Debenzylation of **5** and transglycosylation of the anomeric mixture **6** gave rise to the corresponding allylglycosides **7**. Protection of the hydroxy group as the *p*-methoxybenzyl (MPM) derivative **8**, removal of the allyl group and reduction of free monosaccharide **9** led to diol **10** ($[\alpha]_D^{25}$ − 3.8°). Selective benzoylation of the primary and silylation of the secondary hydroxy groups (**11**), ($[\alpha]_D^{25}$ + 24.0°) and removal of the benzoyl protecting group (**12**) ($[\alpha]_D^{25}$ + 44.4°) gave rise to **13** ($[\alpha]_D^{25}$ − 8.7°). After oxidation of **13** aldehyde **14** ($[\alpha]_D^{25}$ − 43.1°) was obtained, which represents the C-9–C-13 segment of oleandonolide.†

After experimentation the optimal route from **14** to **4** was found (Scheme 2). Wittig reaction of **14** with carbethoxymethyltriphenylphosphorane resulted exclusively in (*E*)-alkene **15** {$[\alpha]_D^{28}$ + 14.3°; ^{1}H NMR δ 5.88 (1H, dd, $J_{8,9}$ 16 Hz, 8-H), 7.20 (1H, dd, $J_{9,10}$ 7 Hz, 9-H)}. Hydroxylation of **15** gave rise to a mixture of diols **16** and **18** (1:3) which could be separated easily by chromatography; the stereochemistry of **16** and **18** was established by ^{1}H NMR spectroscopy of the corresponding cyclic acetals **17** and **20**.† Reduction of the major isomer **18** led to triol **19** which was transformed into *p*-methoxybenzylidene (MP) acetal **20** by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Oxidation with lead tetraacetate gave **4**,† the C-8–C-13 segment of oleandonolide, with the correct stereochemistry for coupling with the C-1–C-7 segment **3**. The minor isomer **16** can be recycled into the synthetic sequence by periodate oxidation *via* aldehyde **16**.



Scheme 2 *Reagents and conditions*: i, Raney Ni, MeOH, heat (92%); ii, allyl alcohol, pyridinium toluene *p*-sulphonate (PPTS) (cat.), heat (81%); iii, *p*-methoxybenzyl chloride, NaH–dimethylformamide (DMF) (100%); iv, Bu^{t}OK, dimethyl sulphoxide (DMSO), 100 °C; $Hg(OAc)_2$, Me_2CO–H_2O (8:2) (93%); v, $NaBH_4$–EtOH (70%); vi, BzCl/py (93%); vii, *tert*-butyldimethylsilyl trifluoromethanesulphonate (TBDMSOTf), Et_3N, CH_2Cl_2 (100%); viii, 15% NaOH, EtOH (92%); ix, $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N (100%); x, $Ph_3P{=}CH$-CO_2Et, tetrahydrofuran (THF), heat (78%); xi, OsO_4 (cat.), 4-methylmorpholine *N*-oxide (NMO)·H_2O, Me_2CO–H_2O (8:2) (91%); xii, $NaIO_4$, THF–H_2O (4:1) (87%); xiii, DDQ, 3 Å molecular sieve, CH_2Cl_2 (90%); xiv, $LiAlH_4$, Et_2O, − 35→10 °C (35%); xv, $Pb(OAc)_2$, MeCN, NaOAc, − 20 °C (51%)

† All compounds obtained as chromatographically pure syrups and gave satisfactory ^{1}H NMR spectra. All ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer in $CDCl_3$ (internal standard $SiMe_4$). All optical rotations were measured on a DIP-360 (JASCO, Japan) in $CHCl_3$ (*c* 1.0).

Characterisation data for **17**: $[\alpha]_D^{30}$ − 12.7°; δ_H, − 0.02 (s) and 0.018 [s, 6H, 13-Bu^t(CH_3)$_2$SiO), 0.77 (d, 3H, $J_{Me,12}$ 7 Hz, 12-Me), 0.89 (s, 9H, 13-*Bu*^{t}Me$_2$SiO), 1.10 (d, 3H, $J_{Me,13}$ 6.5 Hz, 13-Me), 1.15 (d, 3H, $J_{Me,10}$ 6.75 Hz, 10-Me), 1.32 (t, 3H, J_{Me,CH_2} 7 Hz, CH_3 CH$_2$O), 1.56 (m, 1H, $J_{12,11}$ 10, $J_{12,13}$ 1.75 Hz, 12-H), 1.73 (m, 1H, $J_{10,11}$ 2, $J_{10,9}$ 9 Hz, 10-H), 3.60 (dd, 1H, 11-H), 3.82 (s, 3H, 9,11-CH_3OC$_6$H$_4$CH), 4.00 (dd, 1H, $J_{9,8}$ 2.25 Hz, 9-H), 4.29 (m, 3H, 13-H, MeCH_2O), 4.34 (m, 1H, 8-H), 5.49 (s, 1H, 9,11-MeOC$_6$H$_4$C*H*), 6.91 and 7.42 (m, 4H, 9,11-MeOC$_6$*H*$_4$CH); NOE: (H acetal) 9-H 8.7%; (H acetal) 11-H 7.8%.

20: $[\alpha]_D^{31}$ − 24.3°; δ_H, 0.01 (s, 6H, 13-Bu^t(CH_3)$_2$SiO), 0.77 (d, 3H, $J_{Me,12}$ 6.5 Hz, 12-Me), 0.89 (s, 9H, 13-*Bu*^{t}Me$_2$SiO), 1.08 (d, 3H, $J_{Me,13}$ 6.25 Hz, 13-Me), 1.25 (d, 3H, $J_{Me,10}$ 6.25 Hz, 10-Me), 1.52 (m, 1H, $J_{12,13}$, 1.75, $J_{12,11}$ 10 Hz, 12-H), 1.68 (m, 1H, $J_{10,11}$ 2, $J_{9,10}$ 10 Hz, 10-H), 3.57 (dd) and 3.65 (dd, 2H, $J_{7,8}$ 4.2, J_{gem} 12 Hz, AB-system, 7,7-H), 3.62 (s, 3H, 9,11-CH_3OC$_6$H$_4$CH), 3.68 (m, 1H, $J_{8,9}$ 2.5 Hz, 9-H), 3.90 (m, 1H, 11-H), 4.27 (m, 1H, 13-H), 4,31 (m, 1H, 8-H), 5.76 (s, 1H, 9,11-MeOC$_6$H$_4$C*H*), 6.92 and 7.45 (m, 4H, 9,11-MeOC$_6$*H*$_4$CH); NOE: (H acetal) 8-H 7%; (H acetal) 11-H 7%.

4: $[\alpha]_D^{30}$ − 67.5°; δ_H, 0.00 (s) and − 0.05 (s, 6H, 13-Bu^t(CH_3)$_2$SiO), 0.80 (d, 3H, $J_{Me,12}$ 6.5 Hz, 12-Me), 0.86 (s, 9H, 13-*Bu*^{t}Me$_2$SiO); 1.08 (d, 3H, $J_{Me,13}$ 6.25 Hz, 13-Me), 1.26 (d, 3H, $J_{Me,10}$ 6.25 Hz, 10-Me), 1.50 (m, 1H, $J_{12,11}$, 10, $J_{12,13}$ 1.75 Hz, 12-H), 2.35 (m, 1H, $J_{10,11}$ 2.25, $J_{10,9}$ 10 Hz, 10-H), 3.60 (dd, 1H, 11-H), 4.23 (dd, 1H, 13-H), 4.28 (d, 1H, 9-H), 5.71 (s, 1H, 9,11-MeOC$_6$H$_4$C*H*), 6.93 and 7.48 (m, 4H, 9,11-MeOC$_6$*H*$_4$CH), 10.05 (s, 1H, 8-H).

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References

1 *Macrolide Antibiotics; Chemistry, Biology, and Practice*, ed. S. Omura, Academic Press, New York, London, 1984.
2 I. Paterson and M. M. Mansuri, *Tetrahedron*, 1985, **41**, 3569.
3 I. Paterson, *Tetrahedron Lett.*, 1983, **24**, 1311.
4 S. S. Costa, A. Olesker, T. T. Thang and G. Lukacs, *J. Org. Chem.*, 1984, **49**, 2338.
5 K. Tatsuta, Y. Kobayashi, K. Akimoto and M. Kinoshita, *Chem. Lett.*, 1987, 187.
6 K. Tatsuta, Y. Kobayashi, H. Gunji and H. Masuda, *Tetrahedron Lett.*, 1988, **29**, 3975.
7 I. Paterson and P. Araya, *Tetrahedron*, 1988, **44**, 253.
8 K. Tatsuta,T. Ishiyama, S. Tajima, Y. Koguchi and H. Gunji, *Tetrahedron Lett.*, 1990, **31**, 709.
9 N. K. Kochetkov, A. F. Sviridov, M. S. Ermolenko, D. V. Yashunsky and O. S. Chizhov, *Yglevody v synteze prirodnykh soedinenii* (Carbohydrates in the synthesis of natural products), Nauka, Moscow, 1985 (in Russian).
10 S. Hanessian, *Total Synthesis of Natural Products; The 'Chiron' Approach*, Pergamon Press, Oxford, 1984.
11 N. K. Kochetkov, A. F. Sviridov, M. S. Ermolenko, D. V. Yashunsky and V. S. Borodkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 151.
12 N. K. Kochetkov, A. F. Sviridov, M. S. Ermolenko, D. V. Yashunsky and V. S. Borodkin, *Tetrahedron*, 1989, **45**, 5109.
13 N. K. Kochetkov, D. V. Yashunsky, A. F. Sviridov and M. S. Ermolenko, *Carbohydr. Res.*, 1990, **200**, 209.
14 A. F. Sviridov, D. V. Yashunsky, M. S. Ermolenko and V. S. Borodkin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 1166.