Tetrahedron Letters,Vol.24,No.32,pp 3395-3396,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

STUDIES IN MACROLIDE SYNTHESIS:
AN EFFICIENT SYNTHESIS OF TWO CHIRAL FRAGMENTS OF ERYTHRONOLIDE A

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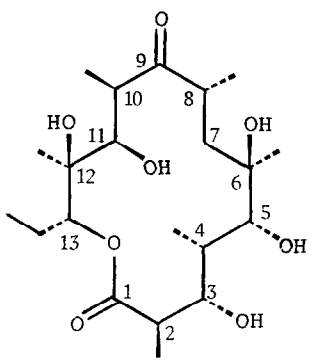
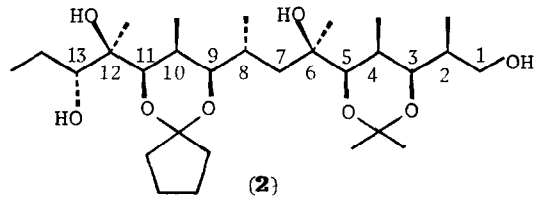
Summary: An efficient asymmetric synthesis of the C_1-C_5 fragment (**3**) together with the epimeric C_7-C_{11} fragment (**4**) used in the Stork approach to the synthesis of erythronolide A is described.

The wealth of stereochemistry and functionality present in the structures of the macrolide antibiotics demands well-planned strategy and efficient stereocontrol in efforts directed towards their total synthesis. In the Stork approach to the synthesis of erythronolide A (**1**),[1] the protected polyol intermediate (**2**) - containing all 10 chiral centres of the macrolide aglycone in the proper absolute configuration - was simply and efficiently constructed from two related fragments. These were the (+)-δ-lactone (**3**), a C_1-C_5 fragment, and the epimeric (-)-lactone (**4**), which is a C_7-C_{11} fragment. Although **3** could be prepared stereospecifically in good overall yield, the corresponding synthesis of fragment (**4**) from a common precursor was less satisfactory involving an expensive configuration inversion sequence using Pd(II) acetate. We now describe a highly efficient common route to **3** and **4**, which makes use of the recently introduced chiral imide aldol condensation of Evans.[2]



(**1**)



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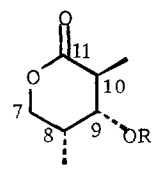
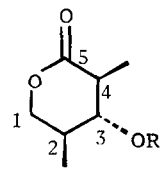


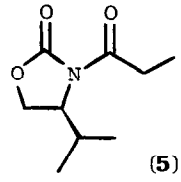
(**4**) R = $SiMe_2Bu^t$
(**13**) R = H



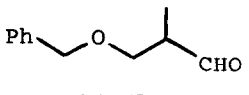
(**3**) R = $SiMe_2Bu^t$
(**12**) R = H

The overall objective was to set up the desired absolute stereochemistry at the two configurationally identical centres in **3** and **4**, while obtaining a roughly 1:1 *RS* mixture at the other chiral carbon. This was easily realised by condensing the (Z)-boron enolate obtained from the *enantiomerically pure (S)*-oxazolidone (**5**)[2] (Bu^n_2BOTf, Pr^i_2NEt, CH_2Cl_2, -78→0°C) with the readily prepared *racemic* aldehyde (**6**)[3] (1 equiv., -78→20°C, 1.5h) to give, after oxidative workup (H_2O_2, MeOH, 0°C), a 54:46 mixture[4] of two erythro (2,3-syn) adducts (**7**) in 85% yield. Removal of the recyclable chiral auxiliary[2] (96% recovery) was then achieved by NaOMe (1.1 equiv., MeOH, 0°C,

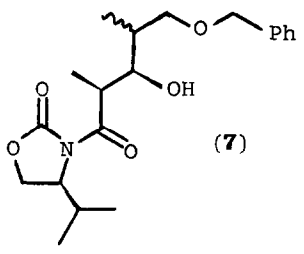
20 min) cleavage of the adduct mixture (**7**) to give the (separable) epimeric methyl esters (**8**) and (**9**), which were conveniently silylated together by titration with Bu^tMe_2SiOTf[5] (2-6-lutidine, CH_2Cl_2, -23°C, 87% overall) to give the esters (**10**) and (**11**). Hydrogenolysis of the benzyl group (H_2, 10% Pd-C, Et_2O) followed by addition of a catalytic amount of acid (1*M* HCl in THF) then gave the separable[1] δ-lactones (+)-(**3**)[6] and (-)-(**4**)[6] in high yield (95%), with some enrichment (45:55)[4] *in favour of the more valuable* **4**. *Both compounds had physical* ($[\alpha]_D$, *m.p.*) and spectroscopic data[6] in agreement with those obtained in the earlier synthesis.[1]



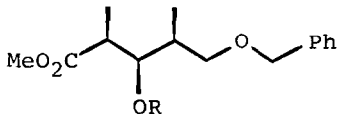
(**5**)



(±)-(**6**)

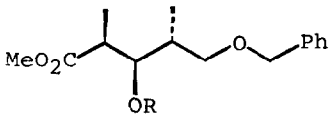


(**7**)



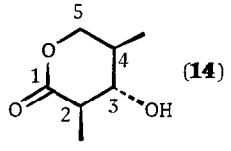
(**8**) R=H

(**10**) R=$SiMe_2Bu^t$



(**9**) R=H

(**11**) R=$SiMe_2Bu^t$



(**14**)

We have also prepared the corresponding unprotected lactones (**12**) and (**13**) by hydrogenolysis (H_2, 10% Pd-C, Et_2O) of the chromatographically separated methyl esters (**8**) (SiO_2, 5% Et_2O/CH_2Cl_2; R_f 0.25) and (**9**) (R_f 0.32). The lactone (**12**, 92%), m.p. 89-90°C (hex/Et_2O), had $[\alpha]_D$=+5.5° (c 1.1, MeOH) and is the enantiomer of lactone (**14**), m.p. 87-8°C, $[\alpha]_D$=-5.0°(MeOH), obtained from C_1-C_5 in the degradation of (9*S*)-dihydroerythromycin A by Gerson.[7,8]

NOTES[9] AND REFERENCES

[1] G. Stork, I. Paterson, and F. K. C. Lee, *J. Amer. Chem. Soc.*, *104*, 4686 (1982).

[2] D. A. Evans, J. Bartroli, and T. L. Shih, *ibid.*, *103*, 2127 (1981); D. A. Evans, J. V. Nelson, and T. R. Taber, *Topics in Stereochemistry*, *13*, 1 (1982); D. A. Evans, *Aldrichimica Acta*, *15*, 23 (1982).

[3] Aldehyde (**6**) was prepared in 3 steps from methallyl alcohol in 60-70% yield: (i) NaH, $PhCH_2Br$, THF; (ii) BH_3-SMe_2, THF; NaOH, H_2O_2; (iii) PCC, CH_2Cl_2 or DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2.

[4] One enantiomer of **6** presumably reacts slightly faster than the other with the boron enolate of **5**. Although selective loss of one diastereomeric product may also take place.

[5] E. J. Corey, H. Cho, C. Rücker, and D. H. Hua, *Tetrahedron Letters*, *22*, 3455 (1981).

[6] **3**, $[\alpha]_D$=+20° (c 1.8, $CHCl_3$), m.p. 30°C (hex), had ^{1}H-NMR ($CDCl_3$, 200 MHz); δ4.38 (dd, *J* 11.4, 4, OC*H*Heq), 3.89 (dd, *J* 11.4, 6.4 OC*H*axH), 3.27 (dd, *J* 7.9, 5, CHOSi), 2.47 (dq, *J* 7.9, 7.1, CHCO), 1.95 (m, C*H*Me), 1.28 (d, *J* 7.1, *Me*CHCO), 0.98 (d, *J* 7.1, CH*Me*), 0.88 (s, Bu^t), 0.05 (s, Me_2Si); ^{13}C-NMR ($CDCl_3$) δ174.2, 77.4, 69.7, 44.3, 38.1., 25.8, 18.0, 15.5, and 14.6. **4**, $[\alpha]_D$=-23.1° (c 1.3, $CHCl_3$), m.p. 59.5-60°C (hex), had ^{1}H-NMR ($CDCl_3$, 200 MHz), δ4.07-4.33 (2H, m, CH_2O), 3.66 (t, *J* 3.7, CHOSi), 2.68 (dq, *J* 7.9, 3.7, COC*H*Me), 2.14 (m, C*H*Me), 1.25 (d, *J* 7.9, COCH*Me*), 0.93 (d, *J* 7.5, CH*Me*), 0.85 (s, Bu^t), 0.04 and 0.02 (s, MeSi); ^{13}C-NMR ($CDCl_3$): δ 173.7, 73.5, 70.1, 43.6, 30.3, 25.7, 17.9, 16.2, and 12.0.

[7] K. Gerzon, E. H. Flynn, M. V. Sigel, P. F. Wiley, R. Monohan, and U. C. Quarck, *J. Amer. Chem. Soc.*, *78*, 6396 (1956).

[8] Lactone (**13**, 81%), $[\alpha]_D$=-20.4° (c 1.7, MeOH), is the C-9 epimer of the other Gerzon δ-lactone[7] obtained from C_7-C_{11} of (9*S*)-dihydroerythromycin A.

[9] We thank the SERC for support.

(Received in UK 25 May 1983)