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STUDIES IN MACROLIDE SYNTHESIS: A CONCISE ASYMMETRIC SYNTHESIS OF A MACROLIDE INTERMEDIATE FOR THE ERYTHRONOLIDES.

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Summary: The enantiomerically-pure 14-membered ring macrolide **1** is prepared in 14 steps from the racemic aldehyde **4**, Z=SPh. The C_2-C_4 and C_8-C_{10} stereorelationships in **1** are controlled in a single step by an Evans aldol condensation with (±)-**4**. Macrolactonisation, **23** → **1**, takes place in high yield (91%).

The macrolide antibiotics, with their multiple asymmetric centres and complex array of substituents and functional groups, have been the focus of intense synthetic interest.[1,2] While much has already been achieved, there is still considerable scope for improvements both in methods[2] and strategy directed towards the more efficient synthesis[1] of these testing targets and their structural analogues. We have adopted a unified approach to the synthesis of erythronolides A and B, together with 6-deoxyerythronolide B,[3] based on a combination of acyclic and macrocyclic stereocontrol strategies (see **Scheme 1**). In our approach, the chiral sequences spanning C_1-C_5 and C_7-C_{11} in the unsaturated (9*S*)-dihydro derivative **1** are set up in a single asymmetric aldol condensation,[4] which fully exploits the stereochemical relationship between **2** and **3**. The remaining stereochemistry and hydroxylation pattern at C_5, C_6, C_{11}, and C_{12} in the erythronolides may then be controlled by the conformational bias of the large-ring lactone.[5] We now report a short and efficient asymmetric synthesis of the simplified erythronolide derivative **1** (R=TBS), which marks the completion of the initial stage of this work.

Scheme 1

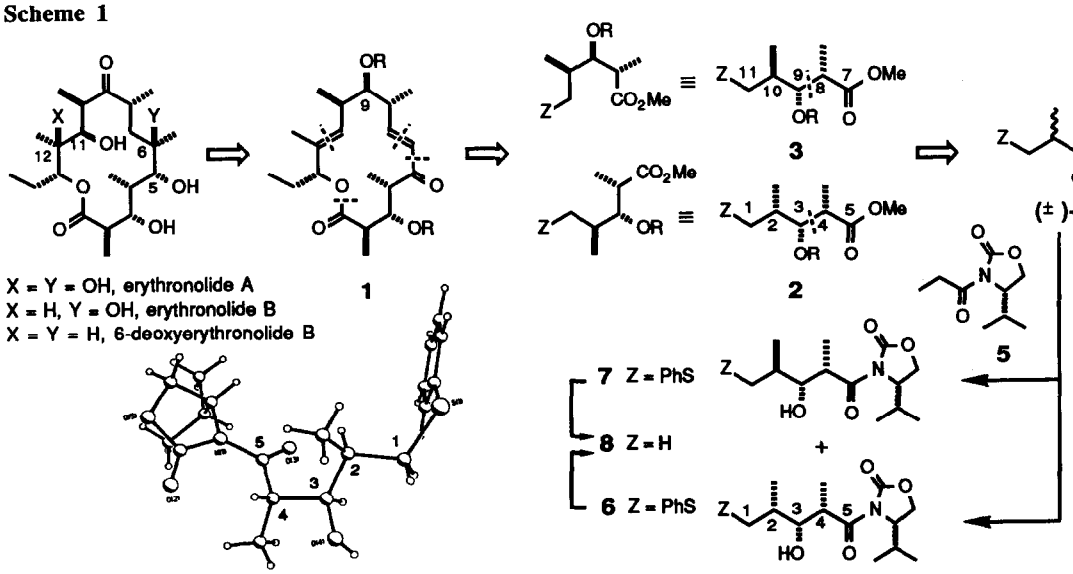
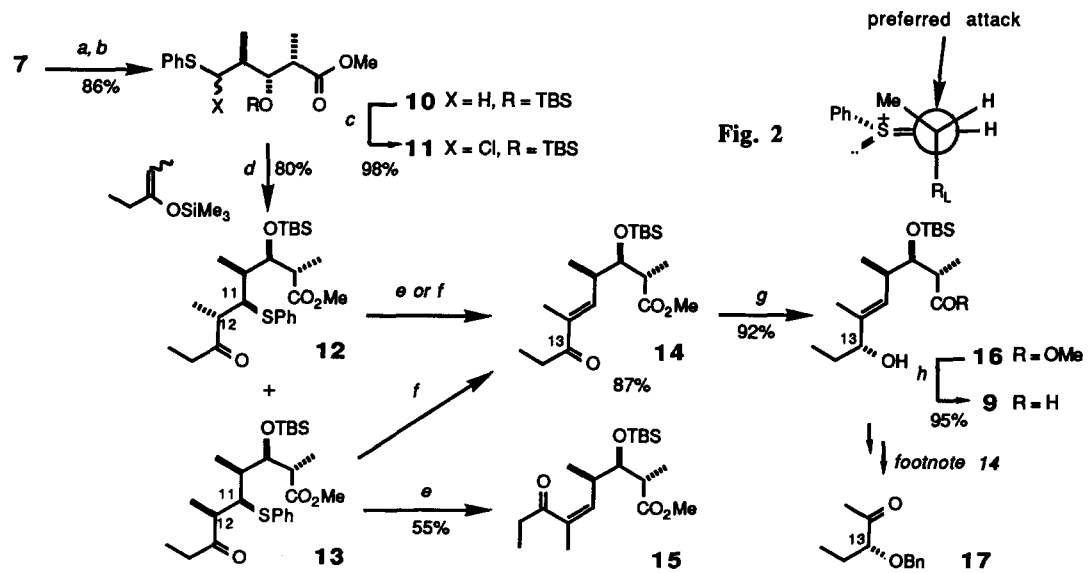


Fig. 1 Crystal structure of low R_f aldol adduct **6**

The direct synthesis of C_1-C_5 and C_7-C_{11} erythronolide fragments is possible by resolution of a racemic aldehyde **4** by aldol condensation with a suitable chiral propionate enolate. In our earlier work,[4] this was accomplished for (±)-**4**, Z=OBn, by Evans asymmetric aldol methodology[6] using the *L*-valine derived propionimide **5**. We have now improved on this key aldol step by adding the di-*n*-butylboron enolate ($^nBu_2BOTf$, $^iPr_2NEt$, CH_2Cl_2) of **5** to (±)-**4**, Z=SPh,[7] which leads to a 1:1 mixture of the two diastereomeric adducts **6** and **7** in 70% yield on a 10 g scale. The replacement of OBn by SPh in this reaction allows easier separation of the aldol adducts **6** and **7**; both by flash chromatography (R_f=0.37, 0.48 in 5% Et_2O/CH_2Cl_2) and by fractional crystallisation of **6** (m.p. 43-44°C) from an ether/hexane solution of the mixture. The stereochemistry of **6** was established as shown by X-ray crystallography, *cf.* **Fig. 1**, while that of **7** was deduced to be epimeric at a single chiral centre by Raney nickel desulphurisation giving the

same β-hydroxyimide **8** as that obtained from **6**. *This single reaction, therefore, sets up five out of the ten chiral centres of the erythronolides.*

The less polar adduct **7**, which corresponds to a C_7-C_{11} erythronolide fragment, was then elaborated into the aldehyde **9** (**Scheme 2**) in preparation for coupling with a suitable C_1-C_6 fragment. Removal of the Evans auxiliary by methanolysis of **7** was followed by TBS protection to give the ester **10** in 86% yield. We decided to build in C_{12}-C_{13} by extending off the PhS substituted end of **10**. This was readily achieved by use of our silyl enol ether phenylthio-alkylation reaction.[8] NCS chlorination of **10** cleanly gave the α-chlorosulphide **11**, which was reacted directly with the trimethylsilyl enol ether of diethylketone (2:1 ***E/Z*** mixture[9]) under mild $ZnBr_2$ catalysis (CH_2Cl_2, 20°C, 2 h). We unexpectedly obtained only two out of the four possible diastereomeric alkylation products in a 1:1 ratio (80%). After separation, these were shown to be epimeric at C_{12} as reductive desulphurisation (W-2 Raney Ni, Me_2CO, 20°C) gave two different ketones, while sulphoxide *syn* elimination gave different enone isomers, *i.e.* **14** and **15** (see below). The common stereocentre at C_{11} presumably arises from a high degree of 1,2-asymmetric induction in attack of the silyl enol ether on the intermediate sulphonium ion formed from **11**. By analogy with the Felkin-Anh model for nucleophilic addition to α-chiral aldehydes,[10] we *tentatively* assign the C_{11} configuration in **12** and **13** as ***R*** arising from preferred attack as shown in **Fig. 2**. Similar diastereofacial selectivity for the addition of silyl enol ethers to α-chiral sulphonium ions (from diphenylthioacetals) has also recently been observed by Bartlett and Heathcock,[11] although highest selectivity required the use of bulky mesitylthio derivatives. In comparison, the very high face selectivity in our reaction is probably due to use of a more substituted silyl enol ether combined with a more sterically biased substrate. This unforeseen result allowed us to stereoconvergently form the C_{11}-C_{12} double bond with ***E*** geometry in a novel manner by either of two methods. The separated isomers were each converted into **14** by a *syn* sulphoxide elimination (90%) from **12** and an *anti* sulphone β-elimination (86%) from **13** (sulphoxide elimination on **13** gave the isomeric ***Z***-enone **15**). This could be simplified to a one-pot operation by *m*CPBA oxidation of the isomer mixture, **12** + **13**, to the sulphones and addition of DBU, which effected epimerisation at C_{12} and clean elimination of $PhSO_2H$ to give only the desired ***E***-enone **14** (87%).

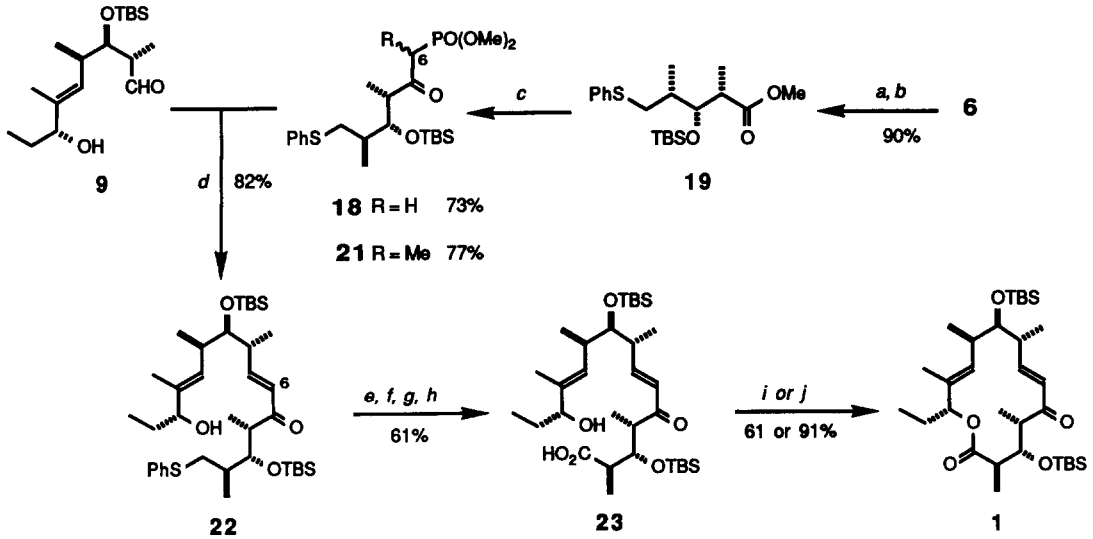


Scheme 2. (*a*) NaOMe, MeOH, -23°C, 20 min; (*b*) TBSOTf, lutidine, CH_2Cl_2, -23°C, 0.5 h; (*c*) NCS, CCl_4, 50°C, 1 h; (*d*) $ZnBr_2$, 0.05 eq., 4A mol. sieves, CH_2Cl_2, 20°C, 2 h; (*e*) $NaIO_4$, 10:1 MeOH/H_2O, 20°C, 6 d; (*f*) *m*CPBA, CH_2Cl_2, 0°C, 15 min; DBU, 20°C, 2.5 h; (*g*) (+)-*N*-methylephedrine, *N*-ethylaniline, $LiAlH_4$, Et_2O, -78°C, 30 min; (*h*) DIBAL, Et_2O, -98°C, 10 min.

Fig. 2

Reduction at C_{13} by $NaBH_4/CeCl_3$[12] (MeOH, -78°C; 98%) gave moderate stereoselectivity (67:33) in favour of the required 13-(***R***) alcohol, **14** → **16**. This represents a rare example of 1,4-asymmetric induction in nucleophilic addition to the carbonyl group of an acyclic enone.[13] The sense of asymmetric induction was established by conversion of the major isomer **16** to the chiral ketone **17**, $[\alpha]_D^{20}$=+105° (*c* 0.6, $CHCl_3$), which has been previously reported[14] in its enantiomeric form with $[\alpha]_D^{20}$=-113° (*c* 2.6, $CHCl_3$). The level of stereocontrol could be improved to

94:6 in favour of **16** (92% yield) by use of Terashima's (+)-*N*-methylephedrine/*N*-ethylaniline chirally-modified $LiAlH_4$ reagent[15] at -78°C. In contrast, use of (*S*)-Alpine-Borane®[16] failed to give any detectable allylalcohol, while (*R*)-(+)-binaphthol-modified[17] $LiAlH_4$ at -104°C gave only 80% stereoselectivity towards **16** (88% yield). Reduction of the methyl ester of **16** by DIBAL (Et_2O, -98°C) then gave the aldehyde **9** in 95% yield, completing the synthesis of the C_7-C_{13} fragment.



Scheme 3. (*a*) NaOMe, MeOH, -23°C, 20 min; (*b*) TBSOTf, lutidine, CH_2Cl_2, -23°C, 0.5 h; (*c*) ^tBuLi, $(MeO)_2POCH_2R$, 2% HMPA-THF, R=H -78°C, R=Me -42°C, 0.5 h; (*d*) LiCl, 10 eq., $^iPr_2NEt$, 10 eq., MeCN, 4A mol. sieves, 30°C, 72 h; (*e*) TFAA, Et_3N, DMAP, CH_2Cl_2, 0°C, 5 min; (*f*) NCS, CCl_4, 50°C, 1 h; $HgCl_2$, $MeCN/H_2O$, 20°C, 1 min; (*g*) Jones reagent, Me_2CO, 0°C, 20 min; (*h*) $NaHCO_3$, 20°C, 3 h; (*h*) DCC, DMAP, DMAP.HCl, 4A mol. sieves, $CHCl_3$, 70°C, 21 h (syringe pump); (*j*) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF; DMAP, PhMe, 80°C, 3h.

For the C_1-C_6 fragment (**Scheme 3**), the more polar crystalline adduct **6** was converted into the β-ketophosphonate **18** in preparation for Horner-Emmons coupling with **9**. Removal of the auxiliary and silylation by $^tBuMe_2SiOTf$ to give **19** was carried out as in **7** → **10**. This was followed by the addition of **19** to the lithiated derivative of methyl dimethylphosphonate in THF-HMPA to give **18** (63% overall yield from **7**). We also prepared the C_6-methylated analogue **21** by use of ethyl dimethylphosphonate. After extensive screening of reagents and conditions, we found that the two fragments **9** and **18** could be coupled in 82% yield to give only the *E*-enone **22** by modification of the method developed by Masamune and Roush (LiCl, 10 eq., $^iPr_2NEt$, 10 eq., MeCN, 4A mol. sieves, 30°C, 72 h).[18] However, under these same conditions, no trisubstituted enone[19] could be obtained from reaction of **9** with **21**. This finding necessitates the introduction of the C_6 methyl group of the erythronolides after macrolactonisation.

Transformation of **22** to the secoacid **23**[20] was performed by the following sequence of reactions: trifluoroacetylation of the 13-OH (99%); α-chlorination[8] of the phenylsulphide at C_1 (NCS, CCl_4) followed by direct hydrolysis to the aldehyde ($HgCl_2$, $MeCN/H_2O$; 74%); Jones oxidation and $NaHCO_3$ hydrolysis of the trifluoroacetate (83%). We were delighted to find that the critical macrolactonisation reaction, **23** → **1**,[20] proceeded in 61% yield under the method of Keck[21] (DCC, DMAP, DMAP.HCl, 4A mol. sieves, $CHCl_3$, 70°C, 21 h). If the Yamaguchi[22] procedure (2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF; followed by dilution with PhMe and syringe pump addition over 3h to DMAP in PhMe at 80°C) was used, *macrolactonisation proceeded in a remarkable 91% yield.* The extra conformational rigidity imparted by the sp^2 carbon skeleton is probably beneficial in promoting this macrocyclisation.

This route provides the enantiomerically-pure unsaturated macrolide **1**, $[\alpha]_D^{20}$= -50.6° (*c* 0.9, $CHCl_3$), in 14 steps from the starting aldehyde (±)-**4** and 23% overall yield from the aldol adduct **7**. Studies towards the elaboration of this macrolide intermediate into the erythronolides are underway.

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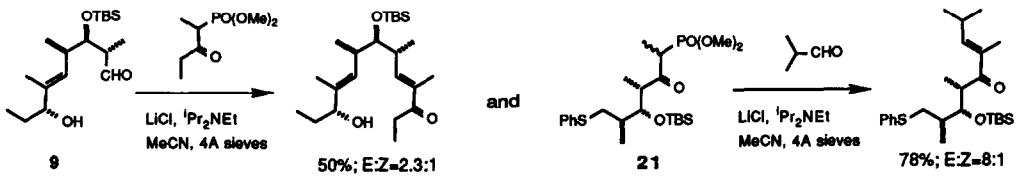
(19) Under more vigorous conditions (*e.g.* warming above 40°C or using DBU as the base), β-elimination of TBSOH from **9** to give the enal occurred. However, model Horner-Emmons coupling reactions did succeed in giving trisubstituted enones, albeit with poorer stereoselectivity:



(20) Secoacid **23** had ^{1}H-NMR (250 MHz, $CDCl_3$) 6.81 (1H, dd, *J* = 8.4, 15.5 Hz), 6.25 (1H, d, *J* = 15.5 Hz), 5.43 (1H, dd, *J* = 1.0, 9.6 Hz), 4.30 (1H, dd, *J* = 4.4, 6.5 Hz), 3.89 (1H, t, *J* = 7.2 Hz), 3.49 (1H, dd, *J* = 1.8, 7.0 Hz), 2.7-2.4 (4H, m), 1.6-1.5 (2H, m), 1.44 (3H, d, *J* = 1.0 Hz), 1.14 (3H, d, *J* = 7.1 Hz), 1.07 (3H, d, *J* = 6.8 Hz), 1.06 (3H, d, *J* = 6.8 Hz), 0.91 (9H, s), 0.89 (3H, d, *J* = 6.9 Hz), 0.87 (9H, s), 0.78 (3H, t, *J* = 7.4 Hz), 0.07, 0.05, 0.02, -0.04 (12H, 4x s); ^{13}C-NMR (100.6 MHz, $CDCl_3$) 201.8, 178.1, 150.5, 135.5, 129.5, 126.9, 80.5, 79.7, 73.3, 50.1, 45.1, 43.0, 35.4, 29.7, 27.0, 26.0, 25.9, 18.8, 18.3, 18.2, 17.1, 13.2, 11.0, 10.2, -3.7, -4.0, -4.1, -4.4. Lactone **1** had ^{1}H-NMR (250 MHz, $CDCl_3$) 6.77 (1H, dd, *J* = 7.5, 16.1 Hz), 5.86 (1H, dd, *J* = 1.3, 16.1 Hz), 5.58 (1H, dd, *J* = 1.3, 10.0 Hz), 5.06 (1H, t, J = 7.0 Hz), 4.10 (1H, dd, J = 5.6, 8.7 Hz), 3.57 (1H, dd, J = 1.4, 5.2 Hz), 2.99 (1H, qd, *J* = 5.6, 7.2 Hz), 2.6-2.4 (3H, m), 1.7-1.5 (2H, m), 1.58 (3H, d, *J* = 1.3 Hz), 1.13 (3H, d, *J* = 7.0 Hz), 1.07 (3H, d, *J* = 7.3 Hz), 1.05 (3H, d, *J* = 6.9 Hz), 0.93 (3H, d, *J* = 6.9 Hz), 0.91 (9H, s), 0.89 (9H, s), 0.76 (3H, t, *J* = 7.5 Hz), 0.11, 0.07, 0.06, 0.04 (12H, 4x s); ^{13}C-NMR (100.6 MHz, $CDCl_3$) 201.6, 174.0, 149.1, 133.7, 129.8, 128.4, 81.1, 79.9, 73.2, 48.1, 47.7, 43.3, 33.9, 29.7, 26.1, 25.9, 24.6, 19.3, 18.2, 16.8, 15.8, 14.3, 11.4, 9.5, -3.8, -4.0, -4.7.

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