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STUDIES IN MACROLIDE SYNTHESIS: A HIGHLY STEREOSELECTIVE SYNTHESIS OF (+)-(9*S*)-DIHYDROERYTHRONOLIDE A USING MACROCYCLIC STEREOCONTROL.

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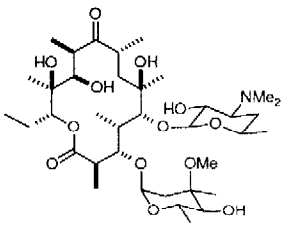
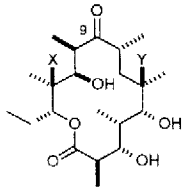
Summary: (+)-(9*S*)-Dihydroerythronolide A, **1**, is prepared in 8 steps from macrolide **3** by exploiting the conformational preferences of the (5*E*,11*E*)-diene intermediate **2**. The stereocontrolled introduction of the hydroxyl groups at C_6, C_{11}, and C_{12} is achieved by osmylation, **2** → **13** and **15** → **1**, while that at C_5 is obtained by a $Zn(BH_4)_2$ reduction, **13** → **14**.

Erythromycin A (from *S. erythraeus*) is one of the most important members of the macrolide class of polyketide antibiotics in clinical and veterinary practice.[1,2] Its medical importance and complex structure have stimulated the efforts of many synthetic chemists over the last 10-15 years. While the total synthesis of erythromycin A,[3] together with the aglycones erythronolides A[4] and B[5] and 6-deoxyerythronolide B[6], have all been accomplished, more efficient routes continue to be sought — particularly with regard to improvements in stereochemical control.[7,8]

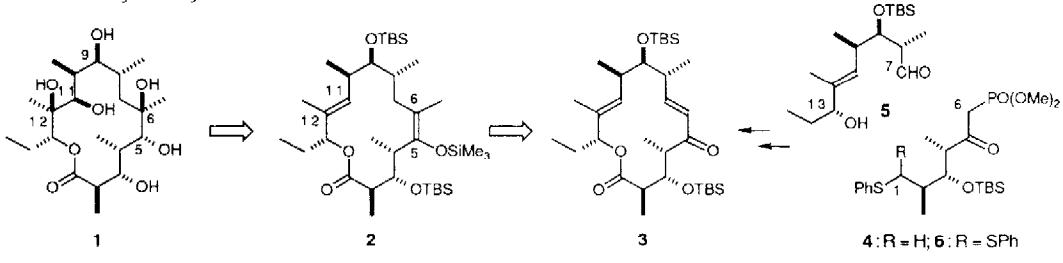


erythromycin A



erythronolide A: X = Y = OH;
erythronolide B: X = H, Y = OH;
6-deoxyerythronolide B: X = Y = H

At Cambridge, we have adopted a unified synthetic approach to all of the erythronolides based on a combination of acyclic and macrocyclic stereocontrol. From molecular modelling, the macrolide diene **2** in Scheme 1 was proposed as a suitable intermediate for the synthesis of (9*S*)-dihydroerythronolide A, **1**, and hence erythronolide A (as well as erythronolide B, 6-deoxyerythronolide B, and various structural analogues). A short asymmetric synthesis of the macrolide intermediate **3** has already been described.[8] We now report (*i*) some improvements in the synthesis of **3**, (*ii*) its efficient elaboration into the required (5*E*,11*E*)-diene intermediate **2**, and (*iii*) a stereocontrolled synthesis of (+)-(9*S*)-dihydroerythronolide A from **2** using two osmylation reactions to introduce the hydroxyl groups at C_6, C_{11}, and C_{12} and a ketone reduction for that at C_5. This work also represents a formal total synthesis of both erythronolide A[4c] and the antibiotic erythromycin A.[3]

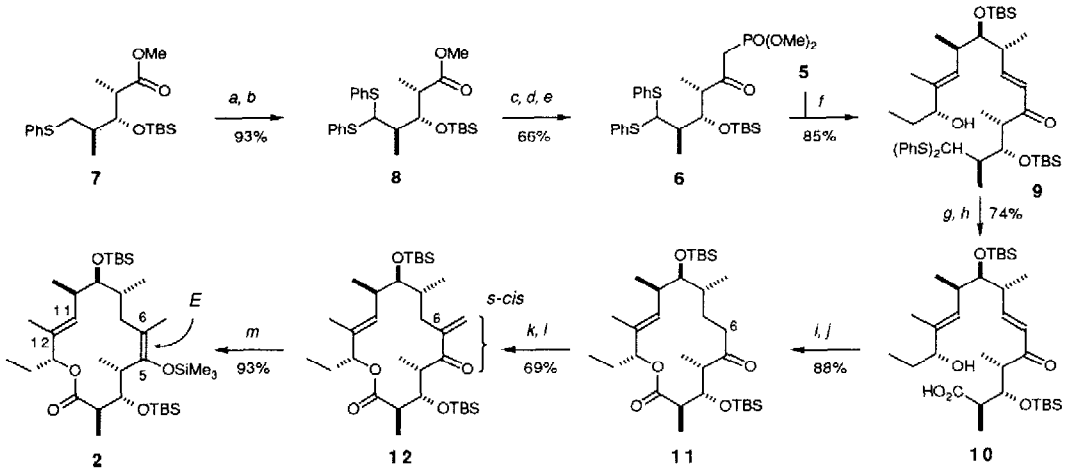


1 **2** **3** **4**: R = H; **6**: R = SPh

Scheme 1

In our earlier work,[8] the seco-acid precursor of **3** was prepared by manipulation of the C_1 functionality after coupling of the C_1-C_6 and C_7-C_{13} segments, **4** and **5**, respectively. This entailed protection of the 13-hydroxyl and a troublesome chlorination/hydrolysis of the phenylthiomethyl group to give an aldehyde, which was oxidised to the required C_1 carboxylic acid, with deprotection giving the seco-acid derivative. The synthesis of **3** is improved by replacing $PhSCH_2$ with $(PhS)_2CH$, as a protected aldehyde, to give the new C_1-C_6 segment **6**, which is then efficiently coupled with the C_7-C_{13} segment **5**.

A mild procedure was first developed for **7** → **8** based on NCS α-chlorination of the phenylsulphide (**Scheme 2**)[8] followed by a novel high yielding reaction with $PhSSiMe_3$, under $ZnBr_2$ catalysis (~0.05 equiv.), to give the bisphenylthioacetal (93% overall).[9] Direct addition of the lithiated derivative of methyl dimethylphosphonate to the methyl ester in **8**, which was possible for the synthesis of **4**,[8] now only gave the required β-ketophosphonate **6** in low yield (~30%) due to unavoidable competing elimination. Elaboration of **8** into **9** could, however, be achieved in 66% overall yield by DIBAL reduction to the aldehyde at -98 °C, addition of the lithiated methylphosphonate in THF, and PDC oxidation in DMF. Using the previously developed conditions for the Horner-Emmons reaction,[8] coupling of **5** and **6** provided the *E*-enone **9** in 85% yield. The conversion of **9** into **10** was now possible without protection of the 13-hydroxyl group by dithioacetal hydrolysis[10] to the aldehyde using HgO/HBF_4 (89%), and selective oxidation using buffered sodium chlorite[11] (83%). Macrolactonisation by the Yamaguchi method[12] then gives the macrolide **3** in 91-96% yield.[8]



Scheme 2. (a) NCS, CCl_4, 50 °C, 1.5 h; (b) $PhSSiMe_3$, cat. $ZnBr_2$, Et_2O, 20 °C, 0.5 h; (c) DIBAL, Et_2O, -98 °C, 0.5 h; (d) ^nBuLi, $(MeO)_2P(O)Me$, THF, -78 °C, 10 min (→ 3:1 mixture of epimers); (e) PDC, DMF, 3A sieves, 30 °C, 4 h; (f) 10 eq $^iPr_2NEt$, 10 eq LiCl, 3A sieves, CH_3CN, 20 °C, 30 h; (g) HgO, aq HBF_4, THF, 20 °C, 0.5 h; (h) $NaOCl_2$, 2-methyl-2-butene, NaH_2PO_4, aq ^tBuOH, 20 °C, 0.5 h; (i) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 20 °C, 2 h; then add to DMAP, PhMe, 80 °C over 4 h (→ **3**); (j) H_2, 5% Rh/Al_2O_3, THF, 20 °C, 1 h; (k) LDA, THF; CH_2O, -43 °C, 1.5 h; (l) MsCl, Et_3N, CH_2Cl_2, 20 °C, 12 h; DBU, 20 h; (m) L-Selectride, THF, -78 °C, 2 h; Me_3SiCl, Et_3N.

An efficient 4 step sequence was then developed for transformation of **3** into the required silyl enol ether **2**. Firstly, selective hydrogenation of the enone double bond in **3** was carried out to give the ketone **11**, $[\alpha]_D^{20}$ = +38.3° (c 2.4, $CHCl_3$), using 5% Rh/Al_2O_3 (92%). Deprotonation of **11** by LDA in THF at -43 °C took place exclusively at C_6 to give a single enolate stereoisomer (by Me_3SiCl quench), which underwent aldol addition with formaldehyde (CH_2O gas was blown over the stirred enolate solution in a stream of Ar) to give a 57:43 mixture of hydroxymethylated isomers. The aldol adducts were then together subjected to mesylation and *in situ* elimination with DBU to give the α-methylene ketone **12**, $[\alpha]_D^{20}$ = +8.5° (*c* 1.0, $CHCl_3$). This enone is calculated (MM2)[13] to prefer the *s-cis* conformation over the *s-trans* form by >4 kcal mol^{-1} and so was predicted[14] to give only the required *E*-enolate on 1,4-addition of a suitable metal hydride reducing agent. Experimentally, reaction of **12** with L-Selectride in THF at -78 °C followed by quenching with Me_3SiCl gave a 93% yield of a single silyl enol ether, which must have the *E*-geometry as shown in **2** (the corresponding *Z*-isomer is highly strained and is calculated by MM2 to be >8 kcal mol^{-1} higher in energy[13]). This key intermediate[15] for erythronolide synthesis is, therefore, available in 13 steps from **7** in 22% overall yield.

Transformation of the (5*E*,11*E*)-diene **2** into the erythronolides requires high π-face selectivities in addition of suitable reagents to the two double bonds. Modelling studies on ground-state conformations,[13,16] and some precedent,[17,18] indicated that we could have some confidence in obtaining the required stereochemistry at C_{11} and C_{12} by attack of the reagent on the peripheral face of the $C_{11,12}$ trisubstituted double bond, as shown in **Fig. 1**. However, reagent attack on the silyl enol ether from the top face was a riskier prediction as greater conformational flexibility is possible about the C_2-C_9 side of the ring (*e.g.* the aldol with formaldehyde and methylation reactions at C_6 in **11** showed low selectivity).

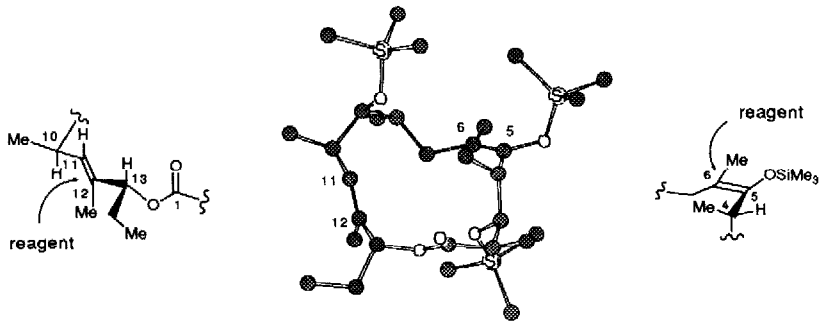
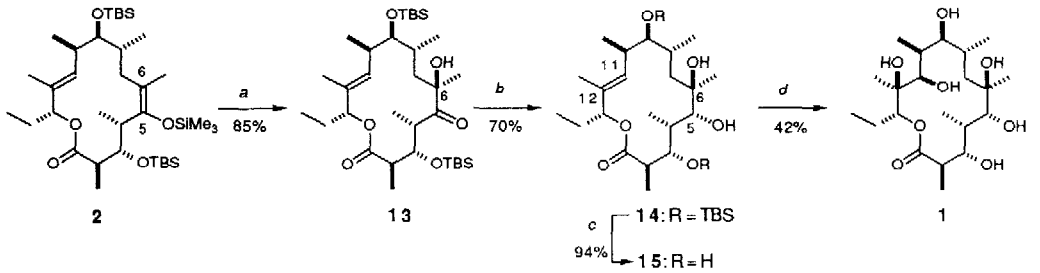


Fig. 1. Minimum energy conformation calculated for **2** (TMS for TBS).[13]

In practice (**Scheme 3**), osmylation of the silyl enol ether in **2** proceeded cleanly to give a single α-hydroxyketone **13** in 85% yield (the correct C_5 stereochemistry was subsequently established by completion of the synthesis). The optimum conditions required the use of catalytic osmium tetroxide (NMO as reoxidant) with quinuclidine, acting both as a ligand for osmium and as an acid scavenger, in aqueous acetone. Here the substrate π-face selectivity is essentially 100%, as the corresponding Sharpless asymmetric osmylation[19] of **2** using dihydroquinine and dihydroquinidine chiral ligands (which give opposite enantioface selectivity with achiral alkenes and enol ethers) gave in both cases only **13** (77 and 92%, respectively). Longer reaction times did not lead to any dihydroxylation of the $C_{11,12}$ double bond with any of these conditions.



Scheme 3. (a) OsO_4, NMO, quinuclidine, aq acetone, 20 °C, 1 h; $Na_2S_2O_5$; (b) $Zn(BH_4)_2$, Et_2O, 20 °C, 0.5 h; (c) 40% aq HF, CH_3CN, 20 °C, 2 h; (d) OsO_4, aq THF, 20 °C, 5 days; NMO; $Na_2S_2O_5$.

We anticipated that the sense of macrocyclic stereocontrol in hydride addition to the C_5 ketone in **13** might also involve top face attack, particularly if this was reinforced by chelation control using the C_6 hydroxyl. Reduction of the C_5 ketone **13** with zinc borohydride[20] (Et_2O, 20 °C, 0.5 h; 70%) gave a single diol product (^1H and ^{13}C NMR), which was found to have the desired configuration, *i.e.* **14**. At this stage, the TBS groups in **14** were removed together on treatment with HF/MeCN to give the tetraol **15** in 94% yield (*N.B.* these are the only hydroxyl protecting groups used in the whole synthesis). Finally, dihydroxylation of the alkene in **15** was highly selective, although sluggish (42% at 34% conversion; yield based on consumed **15**), using excess OsO_4 and gave (+)-(9*S*)-dihydroerythronolide, **1**, which was identical (400 MHz ^1H NMR, ^{13}C NMR, FAB-MS, IR, TLC) to an authentic sample (kindly provided by Prof. G. Stork) obtained by degradation of erythromycin A. This constitutes a formal total synthesis of erythromycin A based on the work of the Woodward group.[3]

By postponing the introduction of the stereochemistry and hydroxylation pattern at C_5, C_6, C_{11}, and C_{12} until after macrocycle formation, the synthesis has the following advantages: (*i*) flexibility in the manipulation of the silyl enol ether and (less reactive) $C_{11,12}$ double bonds in **2**; (*ii*) brevity due to the limited use of protecting groups (~20 steps = 2 steps/chiral centre); (*iii*) a high yielding macrolactonisation (91-96%), as there are fewer transannular and vicinal interactions and the sp^2 carbon skeleton imparts extra conformational rigidity, thus favouring cyclisation; (*iv*) highly stereoselective reactions are obtained due to the conformational preferences of the macrolide intermediates.

In summary, the present synthesis is noteworthy for its brevity (20 steps from (±)-2-methyl-3-phenylthiopropanal[8]), respectable overall yield (~4.4% from each aldol adduct), and versatility (the other erythronolides and

analogues should also be accessible). Moreover, it is highly stereoselective (95% overall diastereoselectivity) by taking advantage of both acyclic and macrocyclic stereocontrol; the only step found to give any *undesired* stereoisomer (5%) is on setting up the C_{13} stereocentre in **5** by an asymmetric ketone reduction.

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(15) Diene **2** had: ^{1}H NMR δ (250 MHz, $CDCl_3$) 5.28 (1H, dd, *J* = 9.1, 1.1Hz), 5.04 (1H, dd, *J* = 8.1, 6.2 Hz), 4.23 (1H, dd, *J* = 12.8, 3.0 Hz), 3.60 (1H, dd, *J* = 4.3, 0.9 Hz), 2.7-2.5 (3H, m), 2.44 (1H, qd, *J* = 7.4, 3.0 Hz), 2.12 (1H, dd, *J* = 13.5, 2.4 Hz), 1.8-1.5 (3H, m), 1.64 (3H, s), 1.60 (3H, d, *J* = 1.1 Hz), 1.15 (3H, d, *J* = 7.4 Hz), 1.00 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.3 Hz), 0.92 (9H, s), 0.91 (3H, d, *J* = 5.5 Hz), 0.89 (9H, s), 0.87 (3H, t, *J* = 7.5 Hz), 0.23 (9H, s), 0.09 (6H, s), 0.08 (3H, s), 0.00 (3H, s); ^{13}C NMR δ (100.6 MHz, CD_2Cl_2) 175.7, 148.8, 133.7, 133.1, 114.7, 82.4, 75.4, 72.3, 53.6, 46.6, 41.4, 40.0, 39.6, 35.7, 29.9, 26.1, 26.0, 24.9, 18.5, 18.4, 17.9, 15.7, 11.7, 10.1, 1.8, -3.8, -4.1; HRMS (CI, NH_3) found M+H$^+$ 669.4766, $C_{36}H_{73}O_5Si_3$ requires 669.4766.

(16) A similar C_{10}-C_1 conformation is shown in the X-ray crystal structure of macrolide **3** to the lowest energy conformation calculated for the diene **2** (cf. left-hand diagram in **Fig. 1**): Paterson, I.; Rawson, D. R.; Raithby, P. *unpublished results.*

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