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RECENT DEVELOPMENTS IN THE TOTAL SYNTHESIS OF MACROLIDE ANTIBIOTICS†

I. PATERSON*
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

M. M. MANSURI
Shell Research Ltd., Sittingbourne, Kent ME9 8AG, U.K.

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1. INTRODUCTION

Comprehensive reviews of macrolide synthesis were first published in 1977.[1] Since then, many principal investigators in the field have provided more specialized reviews highlighting their own contributions to the subject.[2] In addition, Masamune and McCarthy[3] have expertly reviewed the synthesis of some selected macrolides (erythromycin, tylosin, and rifamycin S) and have compiled an updated list of synthetic efforts in the general macrolide area.

This Report concentrates on the many recent developments (*ca* 1977–mid-1984) in the total synthesis of the polyoxo-macrolides and the ansamycins. These groups of macrocyclic lactone and lactam natural products with their multiple asymmetric centres and array of substituents and functional groups, together with their important biological activities, have been the centre of much recent synthetic interest. Their total synthesis relies on many new methods both for the construction of the characteristic macrocycle and for controlling the sp^2 and sp^3 stereochemistry of the carbon skeleton. Much of this new methodology, although designed for macrolide synthesis, has general application in organic synthesis and accordingly should find wider use. A clearer understanding of the

† We dedicate this Report to Professor Gilbert Stork.

factors effecting the stereochemical outcome of many established reactions, particularly the aldol condensation,[4] has also emerged from this work.

Four general approaches to controlling the critical sp^3 stereochemistry of macrolides have been developed:

(i) *ring-cleavage*, where the appropriate (*cis/trans*) relationship of asymmetric centres is first secured using the conformational bias of a small or medium ring, which is then opened to give an acyclic fragment with the stereocentres correctly related;

(ii) *carbohydrate*,[2d] where the existing asymmetric centres and functionality of an enantiomerically-pure sugar are manipulated, often on a pyranoside or furanoside ring, which can then be easily opened (related then to (i));

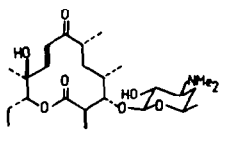
(iii) *acyclic*,[5] where new asymmetric centres are stereoselectively introduced on an acyclic precursor;

(iv) *macrocyclic*,[6] where new asymmetric centres are stereoselectively introduced on to an intact macrolide, or other large ring, using the conformational bias of the large ring.

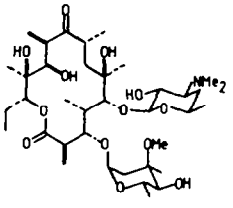
These conceptually different approaches all feature in the various macrolide syntheses which have so far been accomplished. The rough popularity of these approaches to date has been (i) $\simeq$ (ii) > (iii) > (iv); although combinations of these approaches are often adopted. Where possible, the (approximate) overall yield† and number of steps (for the longest linear sequence in a convergent route) are noted at comparable stages in each synthesis together with stereoselectivities obtained for the creation of new asymmetric centres. The critical macrocyclization and glycosidation yields are also given, as appropriate. In many cases the use of innovative strategies is worthy of special note. As well as covering complete total syntheses, partial syntheses and the preparation of recognizable macrolide fragments are also described to a limited extent.

2. THE POLYOXO-MACROLIDES

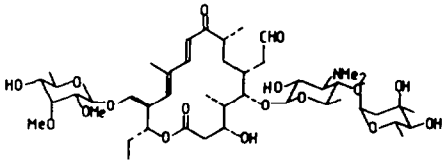
The polyoxo-macrolides, produced by *streptomyces* microorganisms, are a clinically important group of polyketide antibiotics. They are characterized structurally by a 12- (e.g. methymycin), 14- (e.g. erythromycin A), or 16-membered (e.g. tylosin) lactone ring with one or more deoxy-sugars attached and with up to 12 asymmetric centres systematically incorporated into the aglycone.



methymycin



erythromycin A



tylosin

Synthetic efforts directed towards the polyoxo-macrolides began in the mid-1970s with the discovery and development of new methods for constructing large-ring lactones.[1,7,8] In particular, the introduction of efficient methods for the macrolactonization[1,7] of long-chain hydroxyacids, i.e. seco-acids, by the internal esterification of a secondary hydroxyl group with a suitably activated carboxyl group meant that the synthetic problem was reduced to one of stereochemical control. Note, however, that the effectiveness of this standard seco-acid approach to polyoxo-macrolide synthesis is critically dependent on having a seco-acid derivative which can adopt a low-energy conformation, resembling the preferred diamond-lattice of the macrolide ring, in order to facilitate efficient cyclization by one of these methods.[9] As a result macrolactonization yields are generally a function of seco-acid substitution pattern, stereochemistry, and protecting groups. In comparison, there are only a few examples of macrolide total synthesis where macrocyclization is carried out by carbon–carbon bond formation, and these are mainly in the 16-membered ring series. Further developments in this area, therefore, are anticipated.

† When yields for certain synthetic steps are not reported, they are generally calculated as 100%.

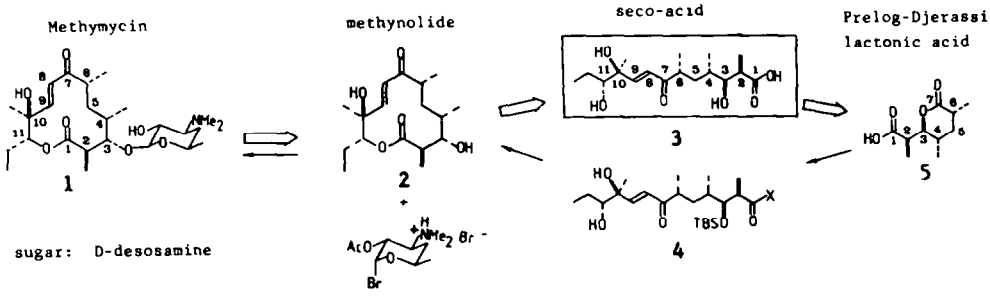
As discussed in the Introduction, several general approaches have been developed for the stereocontrolled synthesis of the unique chiral sequences of the macrolide antibiotics and these have all been applied to the synthesis of individual polyoxo-macrolide structures. Several new purpose-designed reagents and reactions for the control of acyclic stereochemistry have been effectively demonstrated in this context; the aldol condensation reactions of chiral boron enolates are especially noteworthy. The stereochemical similarities, both between different polyoxo-macrolides (based on the Celmer configurational model[10]) and different segments of the same structure, have also provided useful guidance in designing simplified and potentially general routes to these stimulating synthetic targets.

One final problem associated with the total synthesis of the polyoxo-macrolides is the stereo- and regiocontrolled attachment of the appropriate basic or neutral deoxy-sugars onto the macrolide aglycones. Invariably, this task is left right to the end of the synthesis, and often involves the use of relay compounds obtained from degradation of the natural material. Indeed, the critical glycosidation steps have only been worked out so far for a handful of examples (methymycin, erythromycin A, carbomycin B and tylosin). With only a few exceptions,[11a] these use conventional Koenigs–Knorr methodology and proceed at best in moderate yield. The efficiencies of the glycosidation steps so far employed for carbomycin B and tylosin, in particular, are very poor. It is also worth noting that the deoxy-sugars used generally originate from hydrolysis of the natural macrolides themselves. A clear need for the introduction of new purpose-designed methods for efficient sugar attachment[11b–e] and synthesis is, therefore, evident.

2.1. 12-*Membered Macrolides*

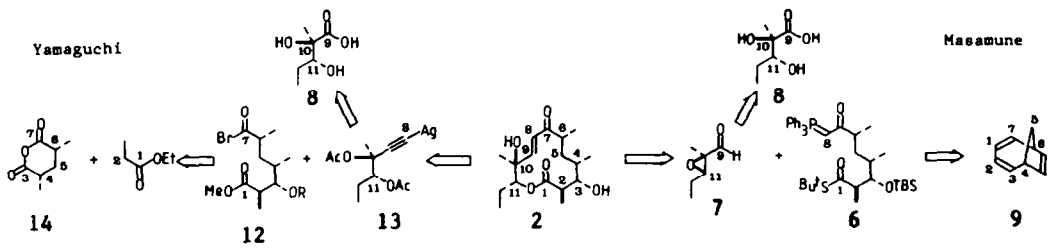
2.1.1. *Methymycin*

The first, and so far the only complete, total synthesis of methymycin (**1**), reported by Masamune *et al.*[12] in 1975, served to demonstrate the effectiveness of the now familiar seco-acid retrosynthetic analysis, **1** ⇒ **2** ⇒ **3**. The 12-membered ring of methynolide was successfully obtained in the synthesis by macrolactonization of a suitable seco-acid derivative, **4** → **2**, followed by a glycosidation step to give the complete macrolide.

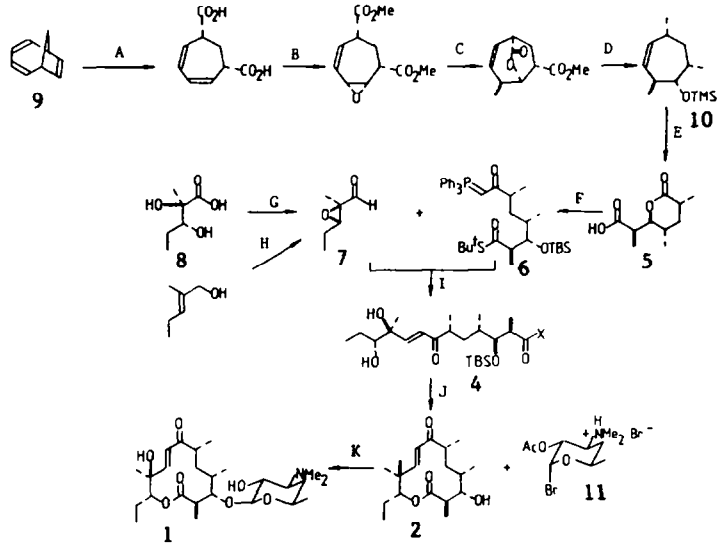


This early work also highlighted the need for efficient methods for controlling the stereochemistry at the six asymmetric carbons of the aglycone **2** both in a relative and an absolute sense. Formal syntheses of methymycin, based on convergence with intermediate **4** (X = OH), have subsequently been completed by the groups of Grieco,[13] Ireland,[14] and White,[15] while Yamaguchi *et al.*[16] have recorded a different synthesis of methynolide. The Prelog–Djerassi lactonic acid (**5**), the key C_1–C_7 fragment in the synthesis of methymycin which is also a degradation product from it[17] and several other polyoxo-macrolides,[18] has also emerged as a popular target for stereocontrolled synthesis.[19]

2.1.1.1. *Masamune synthesis* (Scheme 1).[12] The Masamune synthesis of methynolide is based on the coupling of the racemic nucleophilic C_1–C_8 fragment **6** with the enantiomerically-correct C_9–C_{11} fragment **7**. The epoxide **7** was initially prepared from the resolved acid **8**,[20] but can now be more efficiently made using the Sharpless asymmetric epoxidation reaction.[21] In this classical ring-cleavage approach, the stereocentres at C_2 and C_3 were introduced with 70% stereoselectivity on to the bicyclic triene **9**, which has C_4 and C_6 already controlled. The ylid **6** came from racemic Prelog–Djerassi



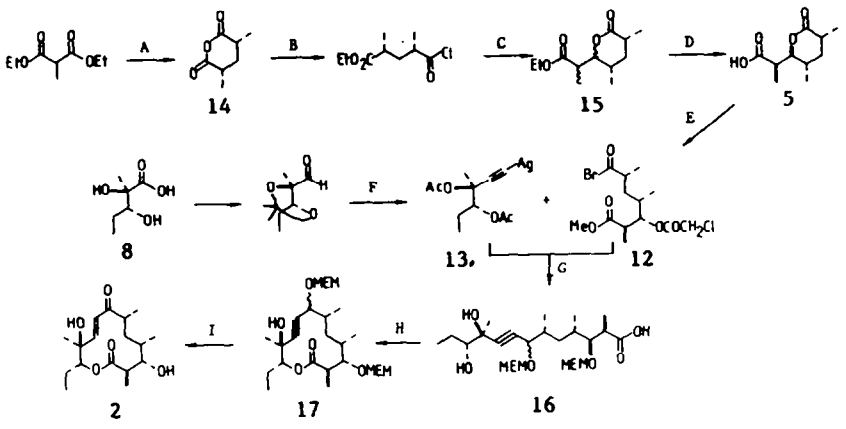
lactonic acid (**5**), which was made by oxidative cleavage of the cycloheptene **10** containing the sequence of four chiral centres already set up with the correct relative stereochemistry. The product of the Wittig coupling after epoxide opening, **4** (X = SBu^t), was macrolactonized to give **2** by either (i) hydrolysis to the acid **4** (X = OH) and formation of the mixed anhydride with $(CF_3CO)_2O$, or (ii) more reproducibly by direct treatment with $Hg(OCOCF_3)_2$ in acetonitrile at high dilution. Under these latter conditions for thioester activation the aglycone **2** was obtained after desilylation in 20–30% overall yield (the uncyclized unnatural diastereomer was removed at this stage). Attachment of D-desosamine at the C_3-hydroxyl of **2** using **11** (83% stereoselectivity for the natural β-glycoside), followed by acetate hydrolysis, completed the total synthesis of methymycin (24 steps from **9**; 0.6% overall yield).



Masamune Methymycin Synthesis[12]: A (i) Sia_2BH; HOO^-; (ii) $Al(OBu^t)_3$, p-benzoquinone; (iii) formylation; (iv) $NaIO_4$; B (i) MCPBA; (ii) CH_2N_2; C Me_2CuLi; D (i) LAH; (ii) TsCl; (iii) Me_3SiCl; (iv) $LiCuH_2$; E $KMnO_4$, $NaIO_4$; F (i) acid chloride formation; (ii) $TlSBu^t$; (iii) KOH; (iv) TBSCl, imidazole; (v) KOH; (vi) N,N'-carbonyldiimidazole; (vii) $Ph_3P{=}CH_2$; G (i) resolution of acid; (ii) CH_2N_2; (iii) TsCl; (vi) Et_3N; (v) DIBAL; H (i) (+)-dimethyltartrate, Bu^tOOH, $Ti(OPr^i)_4$; (ii) oxidation; I (i) Wittig coupling; (ii) H_3O^+; J (X=SBu^t) (i) $Hg(CF_3CO_2)_2$; (ii) TFA; K (i) glycosidation, lutidine; (ii) Et_3N, MeOH.

Scheme 1.

2.1.1.2. *Yamaguchi synthesis* (Scheme 2).[16] In the Yamaguchi synthesis of methynolide (1979), an enantiomerically-correct electrophilic C_1–C_7 fragment **12** was coupled with an enantiomerically-correct C_8–C_{11} fragment **13**. This approach relied on the resolution of the two fragments before coupling and attained only a very modest degree of stereocontrol over C_2 and C_3. Fragment **13** came from elaboration of the resolved Bergel'son[20] acid **8**, while **12** was prepared from the Prelog–Djerassi lactonic acid (**5**). The synthesis of **5** was based on an earlier abortive approach to methynolide by Bergel'son and Batrakov,[22] whereby the *meso*-anhydride **14**, with the C_4 and C_6 stereocentres in position, was converted to the diastereomeric mixture **15**. The required isomer **5** was isolated by selective hydrolysis and could be successfully resolved. Coupling of these fragments gave an acetylenic ketone, which was first reduced at C_7 and then converted into the seco-acid derivative **16** after adjustment of protecting groups and ester hydrolysis. Macrolactonization, **16** → **17**, occurred *via* the

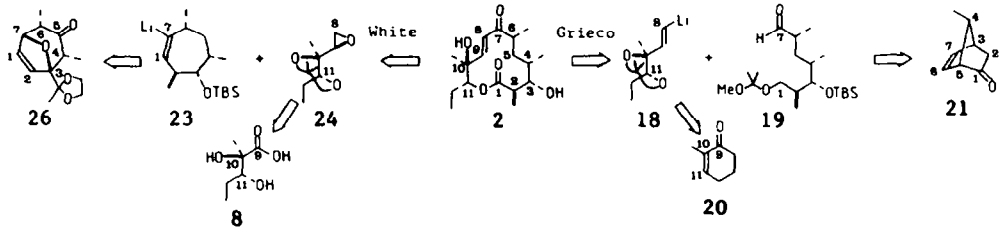


Yamaguchi Methynolide Synthesis[16]: A (i) NaOEt, $BrCH_2CHMeCO_2Et$; H^+; (ii) Ac_2O; B (i) EtOH; (ii) $SOCl_2$; C (i) base, $HO_2CCH(Me)CO_2Et$; H^+; (ii) LAH; D (i) NaOH; (ii) H_3O^+; (iii) CH_2N_2; (iv) hydrolysis to acid and resolution with (-)-D-threo-2-amino-1-(4-methylthiophenyl)-1,3-propanediol; E (i) CH_2N_2; (ii) δ-lactone saponification; (iii) BnBr; (iv) $(ClCH_2CO)_2O$, DMAP; (v) H_2, Pd/C; (v) $(COBr)_2$; F (i) $Ph_3P{=}CHBr$; (ii) NaOH; (iii) H_3O^+; (iv) Ac_2O, DMAP; (v) formation of Ag salt; G (i) coupling; (ii) $NaBH_4$; (iii) Na_2CO_3, MeOH; (iv) MEMCl, $(C_6H_{11})_2NEt$; (v) KOH; H (i) 2,4,6-$Cl_3C_6H_2COCl$; (ii) DMAP, PhH, reflux; I (i) TFA; (ii) MnO_2; (iii) $CrSO_4$.

Scheme 2.

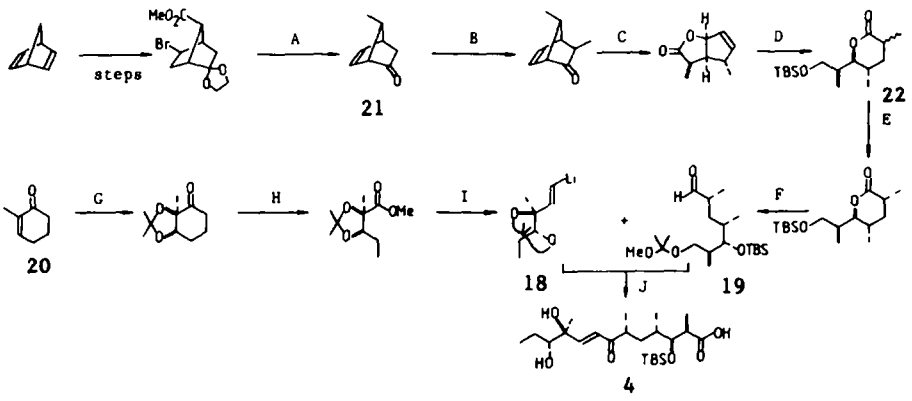
mixed anhydride (2,4,6-$Cl_3(C_6H_2)$COCl, DMAP) in a very respectable 42% yield. Note that the conformational rigidity asserted by the triple bond might be beneficial here in formation of the 12-membered ring. Deprotection, oxidation at C_7, and reduction of the acetylene then gave (+)-**2** (24 steps from **14**; 0.03% overall yield).

2.1.1.3. *Grieco synthesis* (Scheme 3).[13] The Grieco synthesis (1979) of the Masamune seco-acid **4** (X = OH) is based on the coupling of the racemic nucleophilic C_8–C_{11} fragment **18** with the racemic C_1–C_7 fragment **19**. A ring-cleavage approach was used to control the six stereocentres.



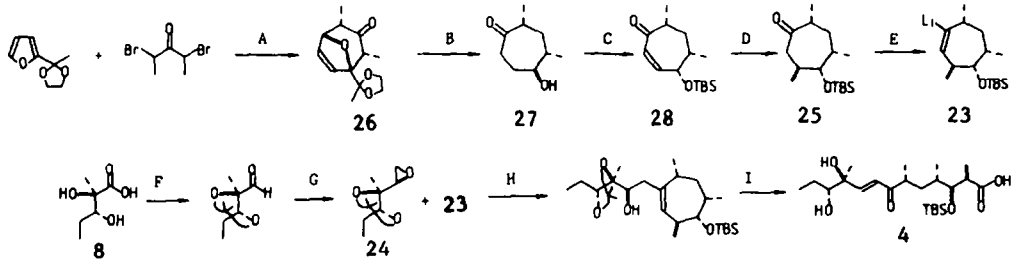
Fragment **18** was prepared from the cyclohexenone **20**, with osmylation controlling the vicinal diol stereochemistry. Fragment **19** was constructed from **21**, which already has the C_3 and C_4 centres in position, with the asymmetric centres at C_2 and C_6 introduced by enolate methylation. The stereoselectivity at C_6 could be improved to 76% by kinetic protonation of the lithium enolate of lactone **22**. Coupling of the two fragments, followed by a further three steps, gave a 1 : 1 mixture of racemic **4** and an unwanted diastereomer (32 steps from norbornadiene; 0.07% overall yield from **21**).

2.1.1.4. *White synthesis* (Scheme 4).[15] The White synthesis of **4** (X = OH) again follows a ring-cleavage approach. The racemic nucleophilic C_1–C_7 fragment **23** was coupled with the enantiomerically-correct C_8–C_{11} fragment **24**, which was once again prepared from the resolved acid **8**. The vinyllithium **23** was prepared from the cycloheptanone **25**, which had earlier been used in the synthesis of Prelog–Djerassi lactonic acid (**5**).[15a] Its synthesis involved manipulation of **26** (obtained by an oxyallyl cation addition to a furan derivative), which again has the C_4 and C_6 stereocentres present. Note that the C_3 stereocentre in **27**, however, first required inversion before the final methyl-bearing asymmetric centre at C_2 was correctly introduced by conjugate addition, **28** → **25**. The same cycloheptanone **25**, but with a MOM protecting group on the C_3-hydroxyl, has also been prepared by Stork and Nair[19a] following a different route and was also transformed into **5**. Ozonolysis of the



Grieco Methynolide Synthesis[13]: A (i) LAH; (ii) DBU; (iii) TsCl, py; (iv) NaI; (v) LAH; (vi) HCl; B LDA; MeI; C (i) MCPBA, $NaHCO_3$; (ii) $BF_3.OEt_2$; D (i) LAH; (ii) H_2, PtO_2; (iii) TBSCl, imidazole; (iv) $CrO_3.2py$; (v) MCPBA, $NaHCO_3$; (vi) LDA; MeI; E LDA; citric acid; F (i) TsOH, MeOH; (ii) 2-methoxypropene, PPTS; (iii) LAH; (iv) BzCl, py; (v) TBSCl, imidazole; (vi) KOH; (vii) $CrO_3.2py$; G (i) OsO_4, $Ba(ClO_3)_2$; (ii) Me_2CO, $CuSO_4$, TsOH; H (i) LDA; Ac_2O; (ii) O_3; Me_2S; (iii) CH_2N_2; (iv) $(Ph_3P)_3RhCl$; I (i) DIBAL; (ii) CBr_4, Ph_3P; (iii) Bu^nLi; (iv) $Cp_2Zr(H)Cl$; (v) I_2; (vi) Bu^nLi; J (i) coupling; (ii) MnO_2; (iii) TsOH; (vi) Jones; (v) H_3O^+.

Scheme 3.

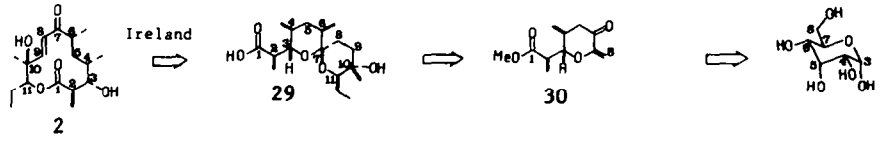


White Methynolide Synthesis[15]: A Zn-Cu; B (i) DIBAL; (ii) H_2, Pd/C; (iii) MsCl, py; (iv) AcOH; (v) H_2Pd/C; (vi) MCPBA; (vii) K_2CO_3, MeOH; C (i) MsCl, py; (ii) $PhCO_2K$, 18-crown-6; (iii) K_2CO_3, MeOH; (iv) TBSCl, imidazole; (v) Li-2,2,6,6-tetramethylpiperidide; PhSeCl; (vi) H_2O_2; D (i) Me_2CuLi; E (i) 2,4,6-$Pr^i_3C_6H_2SO_2NHNH_2$; (ii) Bu^nLi; F (i) resolution with brucine; (ii) $(MeO)_2CMe_2$, TsOH; (iii) LAH; (iv) PCC; G $Me_2S{=}CH_2$; H epoxide opening; I (i) Ac_2O, py; (ii) O_3; $NaBH_4$; (iii) Al_2O_3; (iv) Jones; (v) H_3O^+.

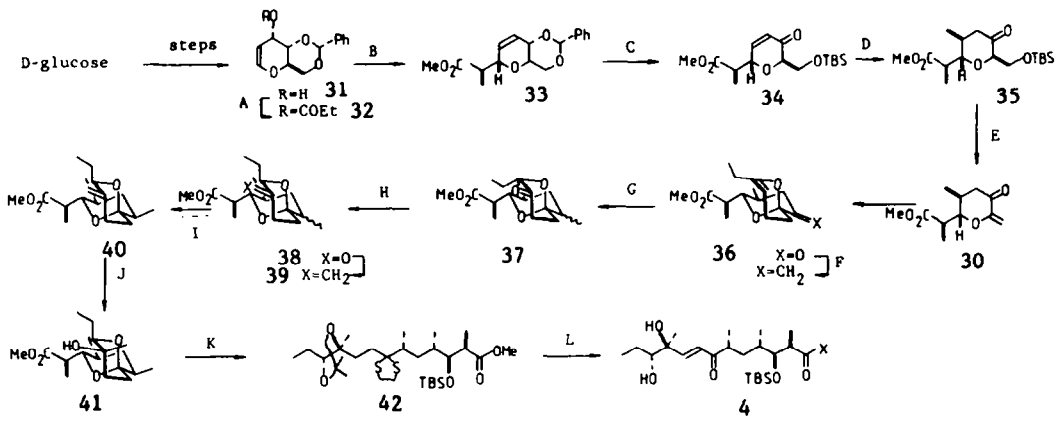
Scheme 4.

coupled material, followed by reductive work up and β-elimination of AcOH, Jones' oxidation, and deprotection, then gave the enantiomerically-pure seco-acid **4** and an unwanted diastereomer (22 steps from 2-acetylfuran; 0.8% overall yield).

2.1.1.5. *Ireland synthesis* (Scheme 5).[14] A different approach to enantiomerically-pure **4**, described by Ireland *et al.* (1983), uses carbohydrate precursors so removing the need for resolutions. Carbohydrates have been widely used by several groups for the total synthesis of macrolide antibiotics. Ireland's novel ring-cleavage strategy (cf. Deslongchamps strategy for the synthesis of erythronolide A, Section 2.2.1.8) is based on the construction of a spiroketal equivalent **29** of the methynolide seco-acid.



The enone **30**, which was the key C_1–C_8 fragment in this linear synthesis, was prepared from the protected D-allopyranose derivative **31** obtained from D-glucose. The chirality of the allyl alcohol was transferred to C_3 using the silyl enolate Claisen rearrangement, **32** → **33**, which also served to set up correctly the C_2 centre with 90% stereoselectivity. Conjugate addition to the derived enone, **34** → **35**, introduced the C_4-stereocentre with 94% stereoselectivity. Intermediate **35** has also been



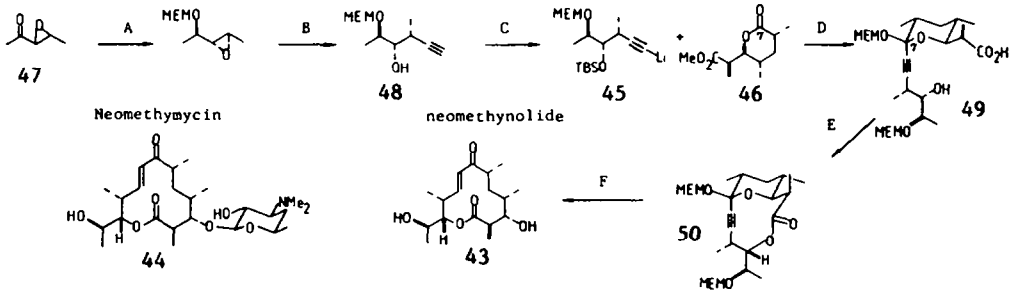
Ireland Methynolide Synthesis[14]: A $(EtCO)_2O$, DMAP, py; B (i) $LiN(SiMe_3)_2$; TBSCl; (ii) PhH, 80°C; H_3O^+; (iii) CH_2N_2; C (i) H_3O^+; (ii) TBSCl, py; (iii) PDC; D Me_2CuLi; E (i) CSA; (ii) AcCl, py; (iii) Et_3N, CH_2=CHCOEt; F Ph_3P=CH_2; G (i) H_2, PtO_2; (ii) H_3B-THF; ^-OOH; (iii) $(COCl)_2$, DMSO; Et_3N; H (i) DBU; (ii) Ph_3P=CH_2; I $BF_3.OEt_2$; J $Hg(OAc)_2$; $NaBH_4$; K (i) $(HSCH_2)_2$, $BF_3.OEt_2$; (ii) TsOH, Me_2CO; (iii) TBSCl, imidazole; L (i) $HgCl_2$, $CaCO_3$; (ii) LDA, Me_3SiCl; (iii) $Pd(OAc)_2$; (iv) DIBAL; (v) Jones; (vi) H_3O^+.

Scheme 5.

converted into (+)-**5**,[14a] as well as into enone **30**. Hetero-Diels–Alder addition of ethyl vinyl ketone to the enantiomerically-correct enone **30** gave the spiroketal **36** with 74% regioselectivity. The configurational and conformational bias of the spiroketal framework, in conjunction with the anomeric effect, was then used to control the required chiral centres at C_6, C_{10} and C_{11}. Note that the C_6 centre was initially introduced stereorandomly by hydrogenation, while C_{11} was introduced with the wrong configuration. However, base-epimerization at C_{11} put the ethyl group into the thermodynamically-favoured equatorial position, **37** → **38**, while acid-equilibration of the spiroketals **39** favoured the desired equatorial epimer **40** (70:30 equilibrium ratio). Oxymercuration of **40** then introduced the C_{10} tertiary alcohol by sterically-controlled equatorial attack (86% stereoselectivity). The spiroketal was opened to the dithioketal, **41** → **42** (note that only a modest yield was obtained for this key step), and standard chemistry was then used to reach the Masamune intermediate **4**[12] (34 steps from D-glucose; 1.7% overall yield from **31**).

2.1.2. *Neomethymycin*

In 1981 Yamaguchi *et al.*[23] reported a convergent synthesis of (+)-neomethynolide (**43**), the aglycone of the closely related antibiotic neomethymycin (**44**), following a similar approach to that used in the earlier methynolide synthesis. In this synthesis (Scheme 6) the nucleophilic enantiomerically-correct C_8–C_{12} fragment **45** (which has the additional 12*R* chiral centre compared with **13**) was added to C_7 of **46**. The new fragment **45** was prepared with high stereoselectivity from **47** by a sequence



Yamaguchi Neomethynolide Synthesis[23]: A (i) $NaBH_4$, $Zn(ClO_4)_2$; (ii) MEMCl, Pr^i_2NEt; B (i) Li-acetylide-ethylenediamine; (ii) resolution as O-methylmandelate ester; (iii) KOH; C (i) TBSCl, imidazole; (ii) Bu^nLi; D (i) coupling; (ii) MEMCl, Pr^i_2NEt; (iii) TBAF; (iv) NaOH; E (i) 2,4,6-$Cl_3C_6H_2COCl$; (ii) DMAP; F (i) TFA; (ii) $ZnBr_2$; (iii) $CrSO_4$.

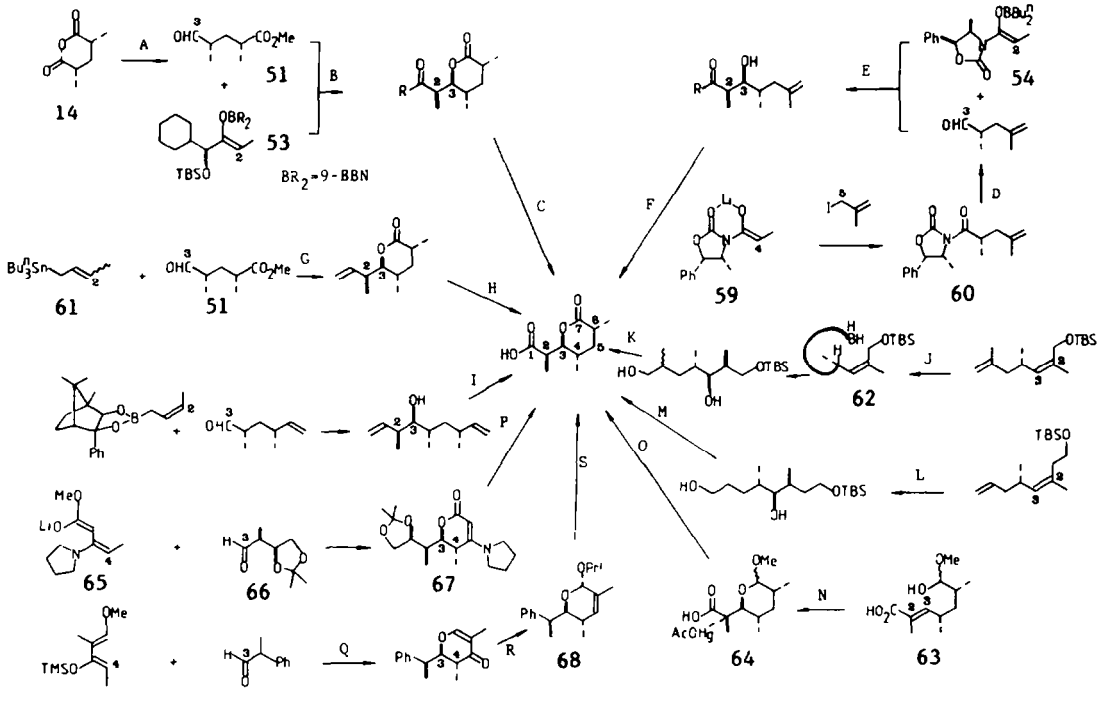
Scheme 6.

involving reduction, protection, epoxide-opening, and resolution of **48**. Further protection and lithiation gave **45**. The mixture of acetals produced on coupling was converted into the seco-acid derivative **49** after adjustment of the protecting groups and separation of the C_7-epimers. The same mixed-anhydride method for macrolactonization, as used earlier, gave the 10-membered ring bicyclic lactone **50** in 33% yield. Deprotection and reduction gave the aglycone of neomethymycin (**43**), establishing the stereochemistry at C_{10}, C_{11} and C_{12} of the macrolide (18 steps from **14**; 0.3% overall yield).

2.1.3. *The Prelog–Djerassi lactonic acid*

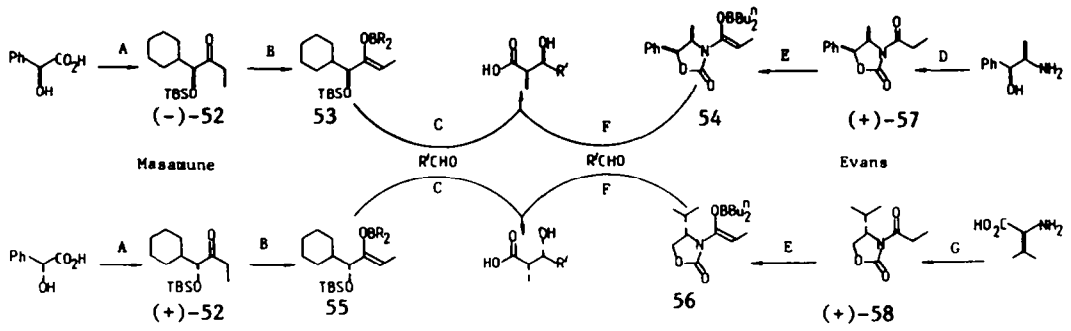
As already mentioned, many other syntheses of the Prelog–Djerassi lactonic acid (**5**) have been completed in recent years.[19] A selection of syntheses which demonstrate potentially general acyclic methods for efficiently controlling relative stereochemistry in macrolides is presented here (Scheme 7).

The evolution of the aldol reaction[2a–c,4] to its current level of sophistication and selectivity is demonstrated by its application to the control of the chiral sequence at C_2–C_4 in **5**. An aldol approach to this sequence requires addition of an *erythro*(*syn*)-selective[4e] enolate to an appropriate aldehyde, e.g. **51**, with α-induction by C_4 opposite to that expected from Cram's rule. This has been best accomplished, in the non-racemic series, by using an enantiomerically-pure chiral enolate **53**[19d] or **54**[19e] (Scheme 8), whose diastereoface selectivity is much greater than the more modest Cram-type diastereoface selectivity of the aldehyde partner. The Masamune (**53** and **55**)[24] and Evans (**54** and **56**)[25] boron enolates have since found general application in the enantioselective synthesis of macrolide antibiotics. The lithium enolate of **57** (and also of **58**) also shows high diastereoface selectivity, but in the opposite sense of induction, in alkylation with reactive alkyl halides, e.g. **59** → **60**.[19e,25b]



Masamune Synthesis[19c,d]: A (i) MeOH; (ii) resolution; (iii) $(COCl)_2$; (iv) H_2, $Pd/BaSO_4$; B aldol; C (i) HF; (ii) $NaIO_4$. Evans Synthesis[19e]: D (i) LAH; (ii) py.SO_3, DMSO, Et_3N; E aldol; F (i) Me_3SiNEt_2, DMAP; (ii) thexylborane; ^-OOH; (iii) $(COOH)_2$; (iv) $(Ph_3P)_3RuCl_2$, N-methylmorpholine-N-oxide; (v) LiOH; Maruyama-Yamamoto Synthesis[19f]: G $BF_3.OEt_2$; H_3O^+; H O_3; H_2O_2; NaOH; Hoffmann Synthesis[19g]: I (i) AcCl, py; (ii) O_3; H_2O_2 (iii) ^-OH; H_3O^+; Still Synthesis[19h]: J $H_3B.THF$; ^-OOH; K (i) Ag_2CO_3-celite; (ii) LDA; H^+; (iii) TsOH, MeOH; (iv) Jones; Morgans Synthesis[19i]: L thexylborane, ^-OOH; M (i) Ag_2CO_3-celite; (ii) LDA; MeI; (iii) H_3O^+; (iv) o-$NO_2C_6H_4SeCN$, Bu^n_3P; (v) H_2O_2; (vi) $RuCl_3$, $NaIO_4$; Bartlett Synthesis[19j]: N $Hg(OAc)_2$; O (i) $Na_2CS_3.2H_2O$, NaOH; (ii) HCl; (iii) Jones; Schlessinger Synthesis[19k]: P (i) Li, NH_3, Bu^tOH; MeI; (ii) MCPBA; Et_3N; (iii) DIBAL; (iv) Pr^iOH, PPTS; (v) H_2, Rh/Al_2O_3; (vi) AcOH; (vii) $NaIO_4$; (viii) CrO_3; Danishefsky Synthesis[19l]: Q $BF_3.OEt_2$; TFA; R (i) DIBAL; (ii) Pr^iOH, TsOH; S (i) H_2, Pd/Al_2O_3; (ii) O_3, TFA, AcOH; H_2O_2.

Scheme 7.



Masamune method[24]: A (i) H_2, Rh/Al_2O_3; (ii) EtLi; (iii) TBSCl, imidazole, DMAP; B (i) R_2BOTf, Pr^i_2NEt; C (i) aldol; oxidative workup; (ii) HF; (iii) $NaIO_4$. Evans method[25]: D (i) $(EtO)_2CO$, K_2CO_3; (ii) Bu^nLi; EtCOCl; E Bu^n_2BOTf, Pr^i_2NEt; F (i) aldol; oxidative workup; (ii) ^-OH; G (i) BH_3, $BF_3 \cdot OEt_2$; (ii) $(EtO)_2CO$, K_2CO_3; (iii) Bu^nLi; EtCOCl.

Scheme 8.

Other efficient methods of controlling the C_2–C_4 chiral sequence of **5** include the $BF_3 \cdot OEt_2$-promoted addition of the crotylstannane **61** to **51**, which proceeds with not only 2,3-*syn* diastereoselectivity, but with impressively high 3,4-*anti* diastereoface selectivity[19f] contrary to Cram's open chain model. The use of an enantiomerically-correct chiral crotylboronate gives the same stereochemical result.[19g] Still and Shaw[19h] and Morgans[19i] have independently reported on the use of cyclic hydroboration, where intramolecular hydroboration in a preferred conformation, such as **62**, leads to a useful degree of α-asymmetric induction by C_4. The Bartlett and Adams[19j] mercuricyclization approach to this problem succeeds in efficiently controlling the 3,4-*anti* relationship, **63** → **64**, but is partly thwarted by the non-stereospecific nature of the demercuration step, which at best gives 75% stereoselectivity at C_2.

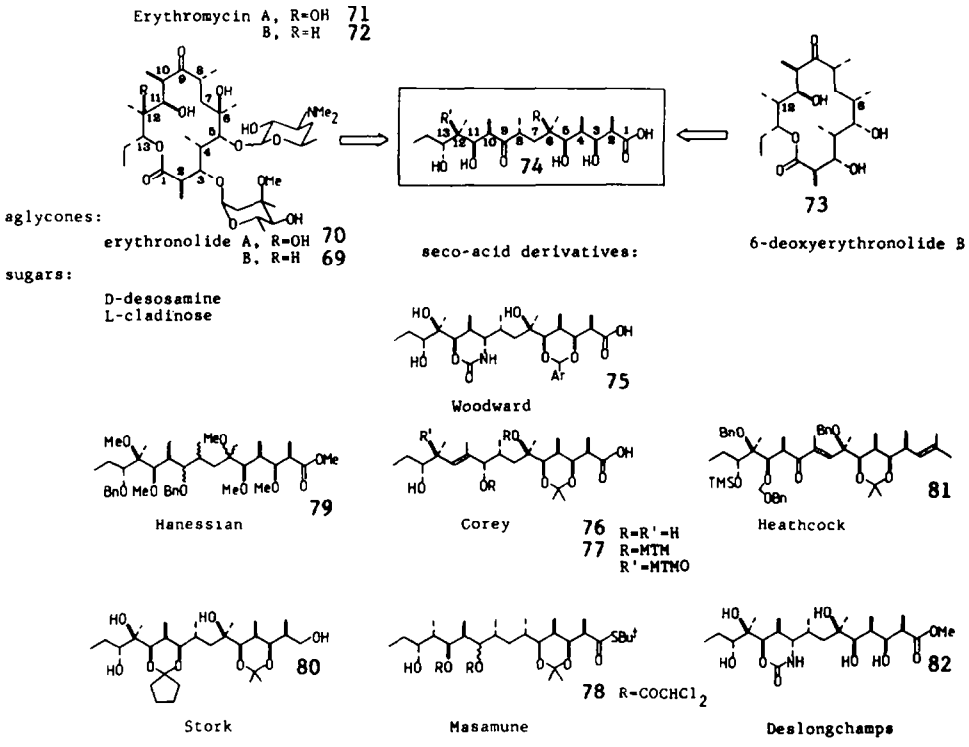
An alternative strategy for controlling the chiral sequence in **5** is based on a C_3–C_4 disconnection, where Cram-type α-induction by C_2 is required (2,3-*syn*) and the new bond must be constructed with *anti*-diastereoselectivity. Schlessinger *et al.*[19k] have reported that the lithium dienolate **65** adds to aldehyde **66** to give **67** with 90% stereoselectivity. Danishefsky *et al.* have reported an alternative procedure, using a cyclocondensation reaction, which proceeds with 81% stereoselectivity.[19l] Note that in both of these syntheses the remaining centre at C_6 was set up by ring-stereocontrol, whereby hydrogenation of **68** occurred from the more accessible β-face.

Finally, other Prelog–Djerassi lactonic acid syntheses have been accomplished by manipulation of carbohydrates,[19m,n] by an ene reaction,[19o] and by a route based on macrocyclic stereocontrol.[19p] A novel approach to a C_1–C_7 methynolide fragment has also been described, where the key step involves a sulfur ylid [2,3]-sigmatropic ring enlargement.[19q]

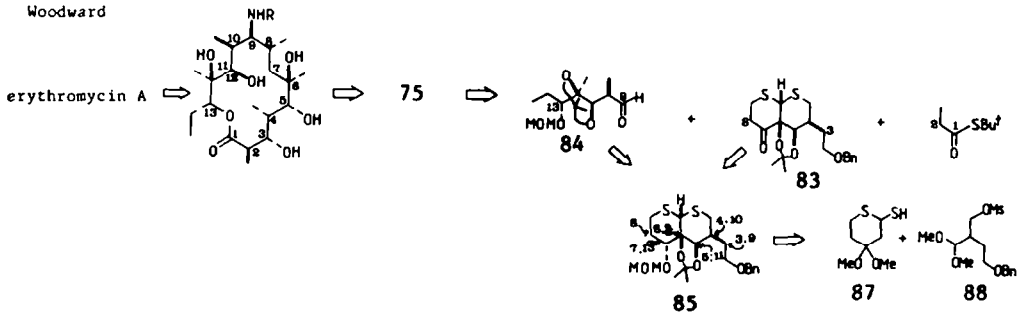
2.2. 14-*Membered Macrolides*

2.2.1. *Erythromycins*

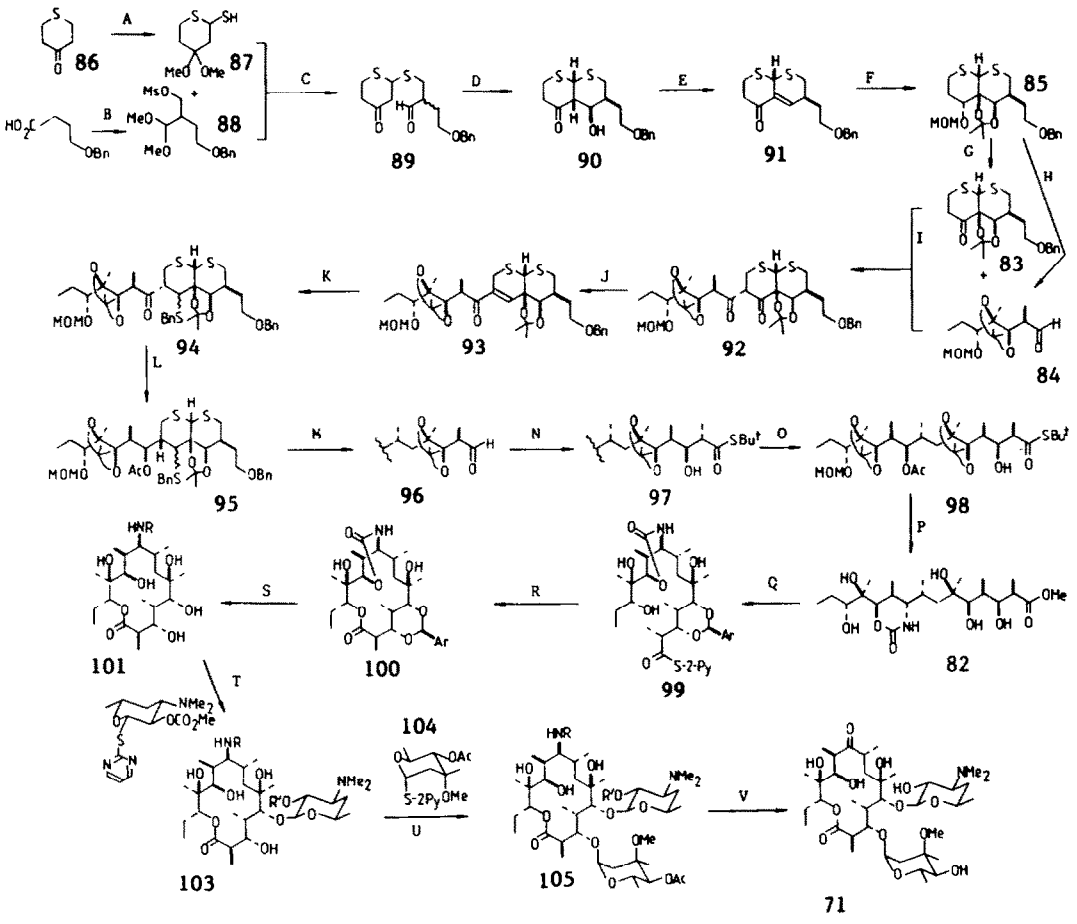
In 1978 Corey *et al.* reported the first total synthesis of erythronolide B (**69**)[26] followed a year later by the synthesis of erythronolide A (**70**),[27] the aglycone of the medicinally most important member of the erythromycin family of antibiotics. In 1981 the Woodward total synthesis[28] of erythromycin A (**71**) itself, with the sugars properly attached, was completed and published posthumously. In the same year a synthesis of 6-deoxyerythronolide B (**73**), the (inactive) biogenetic precursor of all of the erythromycins, was accomplished by the Masamune group at M.I.T. using a highly stereocontrolled aldol construction.[19d] The synthesis of the chiral sequence contained in the erythronolide A seco-acid **74** (R = R′ = OH) has also been more-or-less completed, with varying degrees of stereocontrol, in the laboratories of Hanessian (**79**),[29] Stork (**80**),[30] and Heathcock (**81**),[2b,31] while the Deslongchamps group[32] have almost completed a formal total synthesis of erythromycin A by the independent synthesis of Woodward's intermediate **82**.



2.2.1.1. *Woodward synthesis of erythromycin A* (Scheme 9).[28] The Woodward synthesis of the seco-acid derivative **75** is based on the aldol coupling of enantiomerically-correct C_3–C_8 and C_9–C_{13} fragments, **83** and **84**, respectively, followed by the later introduction of C_1 and C_2 using a thiopropionate derivative in an aldol condensation. The stereochemical equivalence between the C_4–C_6 and C_{10}–C_{12} segments of erythronolide A was exploited by preparing the key fragments **83** and **84** from a common precursor **85**, which was in turn constructed from the racemates **87** and **88**. A ring-cleavage approach was used to control most of the chiral centres in **75** (C_2 and C_3, however, were secured by acyclic stereocontrol).



In the synthesis of intermediate **85**, fragments **87** and **88** were first coupled together to give the mixture of racemic ketoaldehydes **89**. Asymmetric induction in the aldol cyclization of **89** was possible using D-proline as the catalyst, which gave the correct enantiomer **90** (and an equal amount of an unwanted diastereomer) in 36% ee. Dehydration of the enriched **90** and recrystallization gave optically-pure **91**, which was reduced ($NaBH_4$) and osmylated to give, after protection, the key dithiadecalin **85** with complete control of the three new chiral centres. Deprotection and oxidation gave the C_3–C_8 fragment, **85** → **83**, while in a parallel sequence, Raney nickel desulfurization followed by a further two steps gave the acyclic C_9–C_{13} fragment, **85** → **84**. Aldol addition of the lithium enolate of **83** to aldehyde **84**, followed by oxidation at C_9, gave the β-diketone **92**. Reduction of the now redundant ketone group



Woodward Erythromycin A Synthesis[28]: A (i) TsOH, $(CH_2OH)_2$; (ii) NCS; (iii) $(H_2N)_2C{=}S$; (iv) NaOH; (v) H_3O^+; (vi) $(MeO)_3CH$, MeOH, TsOH; B (i) MeOH, H^+; (ii) LDA; HCO_2Me; (iii) $(MeO)_3CH$, MeOH, H^+; (iv) LAH; (v) MsCl, py; C (i) NaH; (ii) AcOH; D D-proline, MeCN; E (i) MsCl, py; (ii) Al_2O_3; (iii) crystallize (+)-enantiomer; F (i) $NaBH_4$; (ii) KH, $MeOCH_2I$; (iii) OsO_4; $NaHSO_3$; (iv) $Me_2C(OMe)_2$, TsOH; G (i) TFA; (ii) TFAA, DMSO; Pr^i_2NEt; H (i) Ra-Ni; (ii) o-$NO_2C_6H_4SeCN$, Bu^n_3P; H_2O_2; (iii) O_3; Me_2S; I (i) mesityllithium; (ii) TFAA, DMSO; Pr^i_2NEt; J (i) KH; AcCl; (ii) $NaBH_4$; (iii) MsCl, py, MeOH; K (i) $PhCH_2SLi$; L (i) LAH; (ii) Ac_2O; M (i) Ra-Ni; (ii) o-$NO_2C_6H_4SeCN$, Bu^n_3P; H_2O_2; (iii) O_3; Me_2S; N EtCOSBu^t, LDA; O (i) Bu^{t}Li, TMEDA; AcOH; P (i) Na_2CO_3, MeOH; (ii) $(PhOCH_2CO)_2O$, py, DMAP; (iii) MsCl, py; (iv) LiOH, H_2O_2; (v) LiN_3; (vi) H_2PtO_2; (vii) p-$NO_2C_6H_4OCOCl$; (viii) $HONH_2.HCl$, KH_2PO_4; (ix) Et_3N; Q (i) mesitaldehyde dimethylacetal, TFA; (ii) EtSLi, HMPA; (iii) ClCOS-2-py, NEt_3; R PhMe, 110°C; S (i) BPCOCl, Et_3N, DMAP; (ii) NaOH; (iii) SiO_2, TFA; T (i) AgOTf; (ii) MeOH; (iii) $ClCO_2Me$; U (i) $Pb(ClO_4)_2$, MeCN; (ii) MeOH; V (i) Na-Hg; (ii) NCS; (iii) AgF; (iv) H_2O.

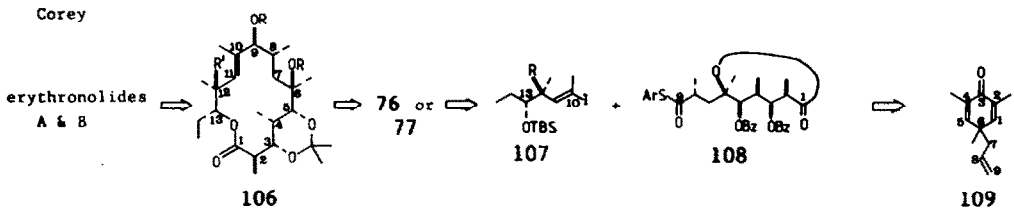
Scheme 9.

at C_7 to a methylene, and the C_9 ketone to a secondary alcohol was then required. In practice, this necessitated conversion to the enone, **92** → **93**, followed by 1,4-addition of benzylthiol to give a single ketone **94** (kinetic protonation from the convex face gives the required stereochemistry at C_8), which was then reduced by $LiAlH_4$ (chelation by the C_{11} ether is presumably responsible for controlling the C_9 stereochemistry on hydride addition) and protected to give **95**. Treatment with Raney nickel caused complete desulfurization as well as debenzylation; the derived aldehyde **96** was then chain-extended by aldol addition of the lithium enolate of EtCOSBu^t to give the Cram addition product **97**, which has the wrong stereochemistry at C_2. The correct C_2 configuration could be obtained, however, by kinetic protonation of the trianion derived from **97** (α-induction by C_3 in a cyclic chelated β-hydroxy ester dianion presumably controls the C_2 stereochemistry) to give **98**, which contains the entire chiral sequence of erythronolide A. Complete failure or low yields were obtained on attempted macrolactonization of various seco-acid derivatives prepared from **98**, as well as on a range of relay

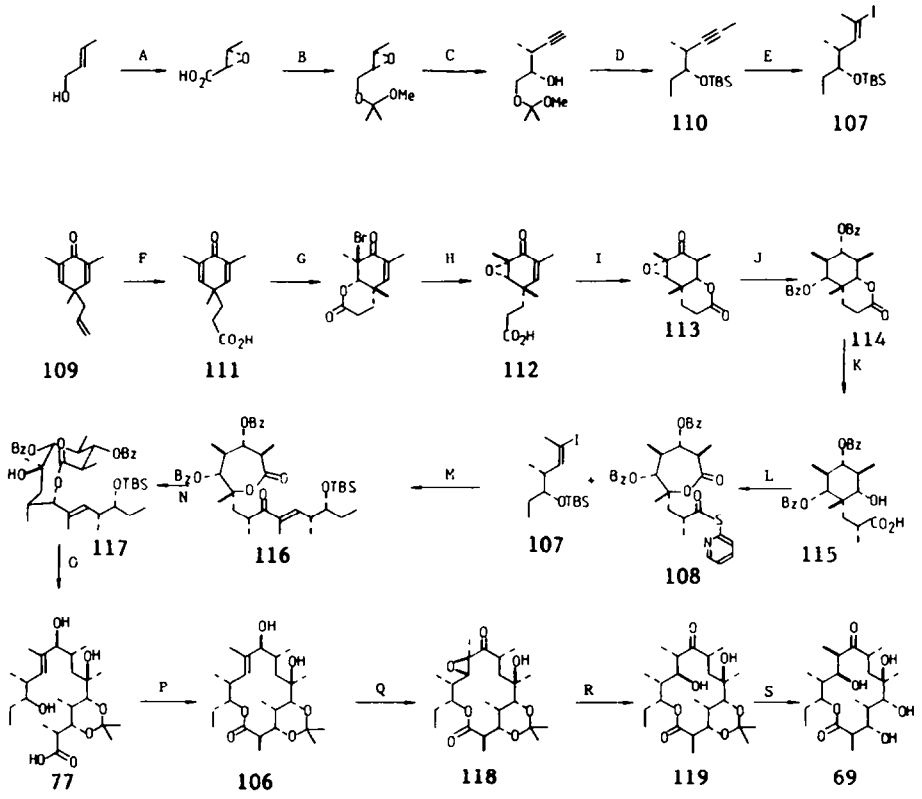
substrates obtained from erythromycin. Efficient cyclization using the Corey–Nicolaou method[7b] could best be obtained using a 9*S*-substrate with cyclic hydroxyl protecting groups linking C_3/C_5 and C_9/C_{11}. This dictated inversion at C_9 of the synthetic material **98**, together with extensive rearrangement of protecting groups, to give the new thioester **99**. This unfortunate detour, **98** → **99**, added 12 more steps to the synthesis. Seco-acid **82** (cf. Section 2.2.1.8) was prepared in 40 steps from **86** in 0.5% yield. Some consolation was obtained, however, by the remarkably efficient cyclization of **99** to the 14-membered lactone **100** in 70% yield, which was then deprotected to give the pentaol **101**.

Completion of the synthesis of erythromycin A required site-selective β-glycosidation at the C_5 hydroxyl with a D-desosamine derivative and α-glycosidation at C_3 with an L-cladinose derivative. Glycosidation of **101** using **102** and AgOTf gave the C_5 β-glycoside **103** (R′ = H) as the major product after methanolysis (36% yield of **103**; 29% combined yield of three minor undesired glycosides). Furthermore, glycosidation of **103** (R′ = CO_2Me) with **104** and $Pb(ClO_4)_2$ in acetonitrile gave the α-glycoside **105** as the major product after methanolysis (55% yield of **105**; 14% yield of an undesired glycoside). Deprotection of **105**, followed by N-chlorination, elimination of HCl, and aqueous hydrolysis finally gave erythromycin A (56 steps from **86**; 0.01% overall yield).

2.2.1.2. *Corey synthesis of erythronolide B* (Scheme 10).[26] The latter part of the Corey erythronolide B synthesis dates from 1975, when it was shown that seco-acid derivative **76** (obtained from degradation of erythromycin B) could be successfully macrolactonized by the double-activation method and converted back via **106** (R = R′ = H) into the aglycone.[33] Macrocyclic stereocontrol was used to secure the chiral centres at C_{10} and C_{11} (note that C_{10} is controlled thermodynamically by base-equilibration). The subsequent non-relay synthesis of erythronolide B is based on the coupling of a Grignard reagent prepared from the enantiomerically-correct C_{10}–C_{13} fragment **107** (R = H) with the racemic C_1–C_9 fragment **108**. A ring-cleavage approach was used to obtain the correct stereochemistry in **108** starting from dienone **109**.



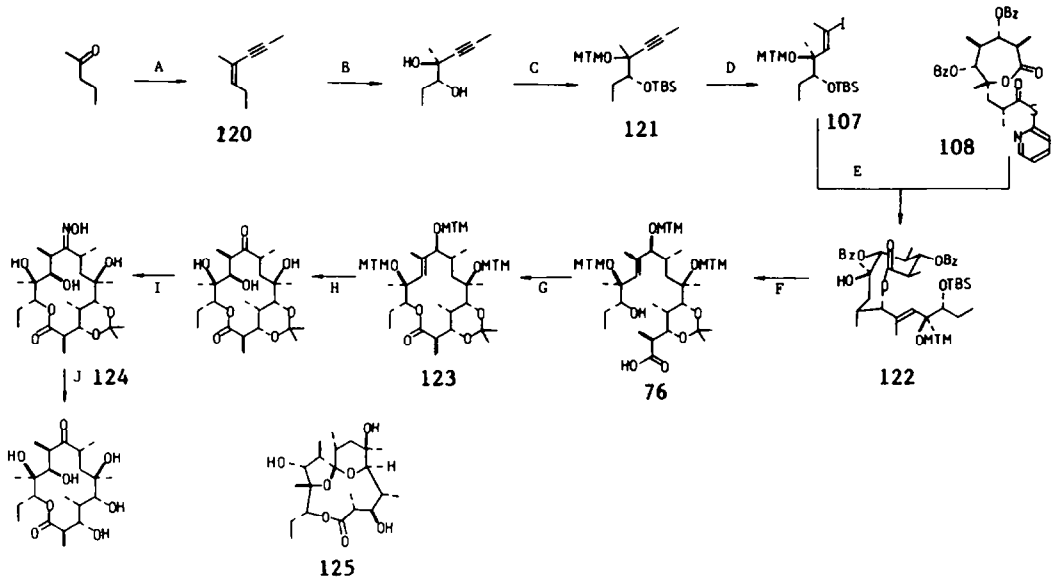
Fragment **107** was prepared (Scheme 10) starting from *trans*-crotyl alcohol by a sequence of oxidation, resolution, reduction, protection, and epoxide-opening (90% regioselectivity). Note that this intermediate is now also available by Sharpless asymmetric epoxidation.[21] A further five steps then gave acetylene **110**, which was hydrozirconated then iodinated to give the vinyl iodide **107**. The synthesis of the racemic C_1–C_9 fragment **108**, which was also used in its enantiomerically-correct form in the later erythronolide A synthesis, started with **109**, which was hydroborated and oxidized to give **111**. Bromolactonization and saponification gave epoxy acid **112**, which was again bromolactonized, then reduced to **113** by Bu^n_3SnH with 87% stereoselectivity. Reductive epoxide-opening followed by hydrogenation and protection gave the dibenzoate **114**, completing the stereocontrolled construction of the C_2–C_6 chiral sequence. The C_8 stereocentre was introduced by methylation of the derived lithium enolate followed by saponification, **114** → **115** (the unwanted C_8-isomer was epimerized in this step). Oxidation of **115** followed by Baeyer–Villiger reaction and formation of the 2-pyridylthioester gave the completed C_1–C_9 fragment **108**. The Grignard reagent prepared from **107** was then efficiently coupled (90% yield) with **108** to give the enone **116** and an unwanted diastereomer. Reduction of **116** at the C_9-ketone using $Zn(BH_4)_2$ was accompanied by translactonization to give a single stereoisomer **117**, which was then converted in five further steps to the seco-acid **77**. Macrocyclization of the thioester derived from **77** under high-dilution conditions gave the 14-membered lactone **106** in 50% yield. Completion of the synthesis of erythronolide B followed the earlier relay route of oxidation at C_9, epoxidation of the C_{10}/C_{11} double bond then hydrogenolysis to give **119**, which was base-epimerized at C_{10} and deprotected to give erythronolide B (29 steps from **109**; 1.3% overall yield).



Corey Erythronolide B Synthesis[26]: A (i) H_2O_2, Na_2WO_4 (ii) resolution with (-)-1-α-naphthylethylamine; B (i) EtOCOCl, Et_3N; (ii) $NaBH_4$; (iii) 2-methoxypropene, H^+; C Li acetylide; D (i) Amberlite IRC-50; (ii) MsCl, py; (iii) Me_2CuLi; (vi) TBSCl, imidazole; (v) LDA; MeI; E Cp_2HZrCl; I_2; F (i) B_2H_6; ^-OOH; (ii) Jones; G Br_2, KBr; H KOH; I (i) Br_2, KBr; (ii) Bu^n_3SnH, AIBN; J (i) Al-Hg; (ii) Ra-Ni, H_2; (iii) BzCl, py; K (i) LDA; MeI; (ii) LiOH; L (i) Jones; (ii) $MeCO_3H$; (iii) 2,2'-dipyridyldisulphide, Ph_3P; M (i) Bu^tLi; $MgBr_2$; addition of thioester; N $ZnBH_4$; O (i) AcOH, H_2O;(ii) LiOH, H_2O_2; (iii) KOH; (iv) CH_2N_2; (v) separation from unwanted diastereomer; (vi) 2-methoxypropene, HBr; (vii) Amberlite IRC-50, MeOH; (viii) KOH; P (i) 4-t-butyl-N-isopropyl-2-mercaptoimidazole; PhMe, reflux; Q (i) MnO_2; (ii) H_2O_2, ^-OH; R (i) H_2, Pd/C; S (i) K_2CO_3; (ii)H_3O^+.

Scheme 10.

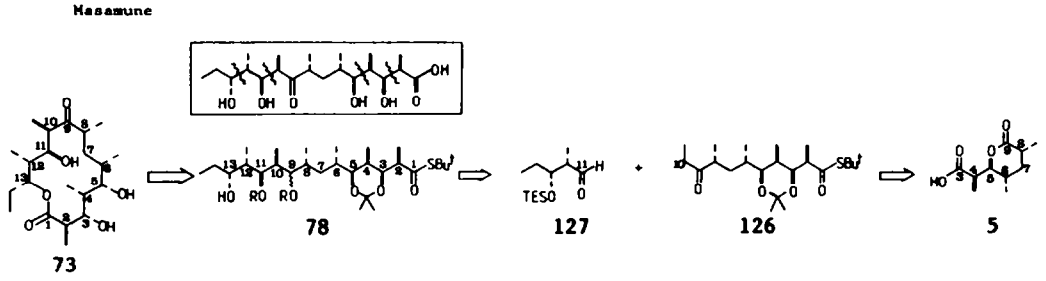
2.2.1.3. *Corey synthesis of erythronolide A* (Scheme 11).[27] Although erythronolides A and B differ structurally by a single hydroxyl function (at C_{12}), Corey's synthesis of erythronolide A patterned after the earlier synthesis of erythronolide B encountered a number of "formidable and unique difficulties", which required extensive experimentation to resolve. In the erythronolide A synthesis the new C_{10}–C_{13} fragment (+)-**107** (R = MTMO) was coupled with the same C_1–C_9 fragment (+)-**108** (prepared by a slightly modified route involving a resolution step). The new fragment was prepared from enyne **120** by osmylation, resolution, and protection to give **121** which could be converted to vinyl iodide **107** via the corresponding borane and chloromercuri derivatives. A mixed cuprate derived from **107** was coupled with thioester **108** to give, after $Zn(BH_4)_2$ reduction, the 9*S*-alcohol **122** with 82% stereoselectivity, which was then transformed into seco-acid **76**. Macrolactonization, **76** → **123**, was accomplished by the Corey–Nicolaou[7b] double-activation method in 30% yield; hydroxyl-protection was now required at C_6, C_9 and C_{12} (cf. erythronolide B synthesis). Subsequent base-epimerization at C_{10} also now required protection of the C_{11} hydroxyl group and proceeded in only modest yield (25%). Completion of the synthesis of the aglycone of erythromycin A necessitated conversion into the C_9-oxime **124**, from which the acetonide protecting group could be successfully removed (38 steps from **109**; 0.04% overall yield). This indirect procedure was necessary as erythronolide A is converted into the spiroketal derivative **125** under acidic conditions.[34]



Corey Erythronolide A Synthesis[27]: A (i) MeC≡CLi; (ii) TsOH; B (i) OsO_4, N-methyl-morpholine-N-oxide; (ii) resolution as O-methylmandelate ester; (iii) Ac_2O, DMSO, AcOH; (iv) KOH; (v) TBSCl, DMAP: D (i) $(C_6H_{11})_2BH$; Me_3N^+-O^-; $Hg(OAc)_2$; NaCl; (ii) I_2; E (i) Bu^tLi; $Me_2C(OMe)C{\equiv}CCu$; addition of thioester; F (i) $Zn(BH_4)_2$; (ii) LiOH, H_2O_2; (iii) KOH; (iv) CH_2N_2; (v) 2-methoxypropene, H^+; (vi) Ac_2O, DMAP; (vii) Ac_2O, DMSO, NaOAc (viii) K_2CO_3, MeOH; (ix) Ac_2O, DMSO, NaOAc; (x) NaOH; (xi) TBAF; G (i) 4-t-butyl-N-isopropyl-2-imidazolyl disulphide, Ph_3P (ii) PhMe, reflux; H (i)K_2CO_3,MeI;(ii) MCPBA, K_2CO_3; (iii) PDC; (iv) H_2, Pd/C; (v) 2-methoxypropene, $POCl_3$; (vi) Triton B methoxide; (vii) PPTS, MeOH; I $HONH_2$.HCl, py; J (i)HCl; (ii) $NaNO_2$, HCl.

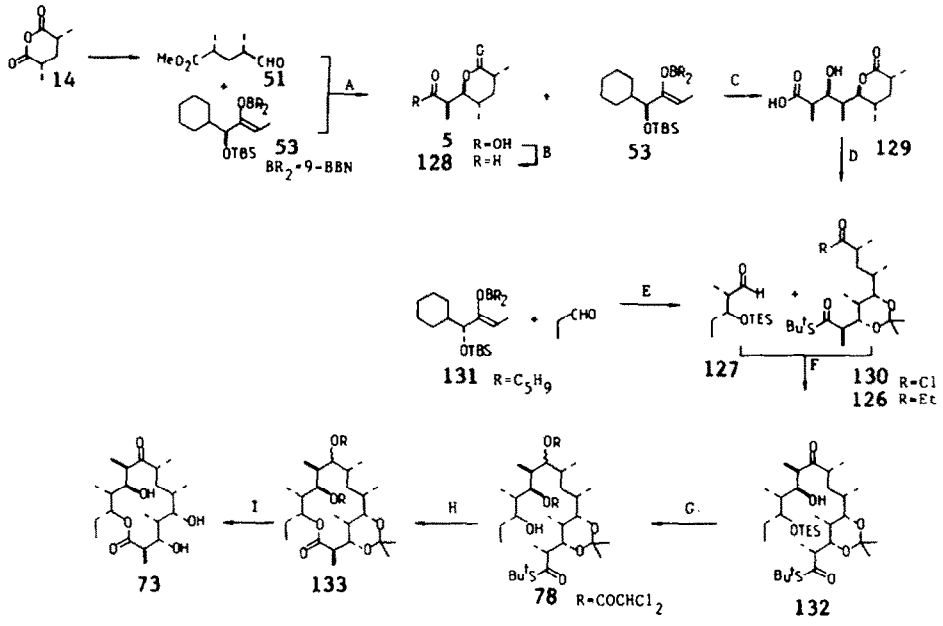
Scheme 11.

2.2.1.4. *Masamune synthesis of 6-deoxyerythronolide B* (Scheme 12).[19d] The Masamune synthesis of 6-deoxyerythronolide B (**73**) is based on the use of a sequence of four *syn*-type aldol condensations to build up the C_1–C_{13} carbon skeleton with the simultaneous control of eight new chiral centres (i.e. two new chiral centres set up for each aldol step). The use of stereocontrolled aldol reactions to construct the characteristic segments of alternating methyl and hydroxyl groups of the polyoxo-macrolides has also been very successfully developed by Heathcock[2b] and Evans.[2c] However, Masamune's synthesis represents the first example, which uses only acyclic stereocontrol by the aldol reaction (using chiral enolates), to construct a complete macrolide seco-acid.



The synthesis of seco-acid derivative **78** is based on the aldol coupling of the enantiomerically correct C_1–C_{10} and C_{11}–C_{13} fragments, **126** and **127**, respectively. Fragment **126** was made from the Prelog–Djerassi lactonic acid (+)-**5**, which acts here as a C_3–C_9 segment, whose stereocontrolled synthesis using the *S*-enolate **53** and optically pure aldehyde **51** was described in Section 2.1.3 (Scheme 7).

The same boron enolate **53** with *S*-configuration was condensed with the derived aldehyde **128** to give, after removal of the chiral auxiliary, the acid **129** with the correct stereochemistry at C_2 and C_3 (93% stereoselectivity). This was then converted in six steps to **130**, which gave fragment **126** on coupling with ethyl cuprate. Fragment **127** containing the C_{12} and C_{13} asymmetric carbons was prepared with 99% stereoselectivity by the enantioselective aldol addition of *R*-enolate **131** to propanal, followed by a series of six steps. The final, and most remarkable, aldol condensation was the addition of the lithium *Z*-enolate of ketone **126** to aldehyde **127**, which gave the desired adduct stereoisomer **132** with control of the C_{10} and C_{11} chiral centres in 94% stereoselectivity (the chelating effect of the C_{13}-ethereal oxygen to the lithium is presumably responsible for this outcome). A suitable seco-acid derivative, **78**, was then prepared by reduction of the C_9-ketone, followed by protection and desilylation. Macrolactonization of **78** by the Masamune activated thioester method[7a] using CuOTf gave **133** which, after deprotection and site-selective oxidation at C_9, gave 6-deoxyerythronolide B (27 steps from **14**; 4.5% overall yield from **51**). A noticeable difference in the cyclization yield was found for the C_9 epimers: 41% for 9*S* vs 23% for 9*R*. Note that this configurational effect at C_9 was also highlighted in the Woodward synthesis.



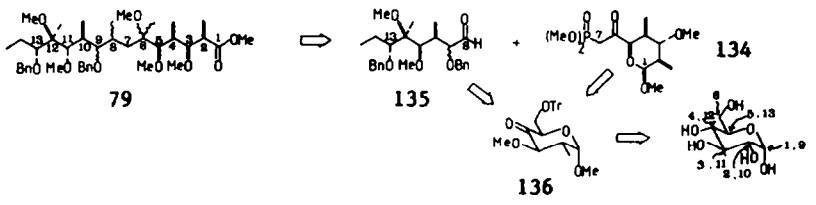
Masamune 6-deoxyerythronolide B Synthesis[19d]: A aldol; B (i) HF; (ii) $NaIO_4$; (iii) $(COCl)_2$; (iv) H_2, Pd/$BaSO_4$, $(Me_2N)_2C{=}S$; C (i) aldol; (ii) TBAF; (iii) $NaIO_4$; D (i) $ClCO_2Et$, py; $TlSBu^t$; (ii) KOH; (iii) Bu^tPh_2SiCl; (iv) 2-methoxypropene, TFA; (v) TBAF; (vi) $(COCl)_2$; (vii) Et_2CuLi; E (i) aldol; (ii) HF; (iii) $NaIO_4$; (iv) CH_2N_2; (v) Et_3SiCl; (vi) DIBAL; (vii) Collins; F $LiN(SiMe_3)_2$; addition of aldehyde; G (i) $NaBH_4$; (ii) $(Cl_2CHCO)_2O$, py; (iii) AcOH; H CuOTf, Pr^i_2NEt; I (i) KOH; (ii) PCC (iii) TFA.

Scheme 12.

Approaches to the Synthesis of Erythronolides

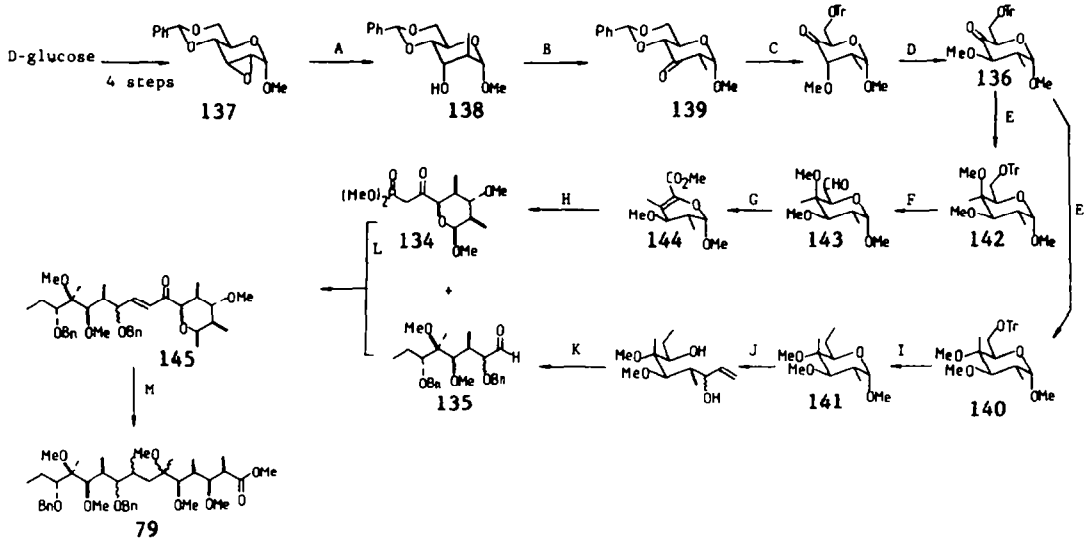
2.2.1.5. *Hanessian approach* (Scheme 13).[29] The carbohydrate approach to the synthesis of the erythromycins, as first proposed by Miljković *et al.*[35] in 1974, has been elegantly and extensively developed by Hanessian and his co-workers. The Hanessian synthesis of erythronolide A seco-acid derivative **79** (the stereocentres at C_6 and C_8 are undefined and are most likely epimeric mixtures), reported in 1978, is based on the coupling of carbohydrate-derived C_1–C_7 and C_8–C_{13} fragments **134** and **135**, respectively. These two enantiomerically-correct fragments were prepared from a common precursor, **136**, with the correct C_2–C_3 (and C_{10}–C_{11}) stereochemistry obtained from manipulation of D-glucose using the conformational bias of the pyranose ring system.

Hanessian



The stereocontrolled synthesis of **136** started with the introduction of the methyl-bearing chiral centre at C_2 by epoxide-opening, **137** → **138**, oxidation of the derived alcohol and base-epimerization to give **139**. Reduction, followed by adjustment of protecting groups, oxidation, and another base-epimerization then secured the C_3-stereocentre in **136**. Treatment with methyllithium then gave **140** as the major adduct after protection, which was converted in four further steps to the C_9–C_{13} segment, **141**. Hydrolysis to the hemiacetal and addition of vinylmagnesium bromide, followed by protection and ozonolysis then gave the electrophilic C_8–C_{13} fragment, **135**. The other fragment, **134**, was prepared from epimeric ether **142** (as well as **140**) by first conversion to aldehyde **143** then base-elimination and oxidation to give **144**. Homologation and catalytic hydrogenation then gave the β-ketophosphonate **134**, where the C_4 and C_5 stereocentres were secured by the α-anomeric substituent directing hydrogen addition to the opposite face of the double bond. The two fragments were then combined by a Horner–Emmons reaction to give **145**. Introduction of the C_6 and C_8 methyl-bearing chiral centres was then carried out without significant stereocontrol, and the mixture of diastereomers produced was converted into the seco-acid derivative **79** (31 steps from D-glucose; *ca* 2% overall yield from **137**). This carbohydrate approach efficiently controls eight out of ten of the chiral centres of erythronolide A; however, the remaining centres at C_6 and C_8 require further study.

2.2.1.6. *Stork approach* (Scheme 14).[30] In 1982 Stork *et al.* outlined a simplified approach to the synthesis of erythronolide A making full use of the stereochemical and structural similarities between

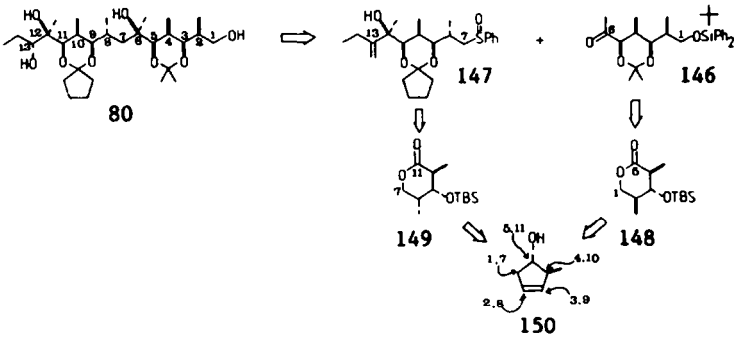


Hanessian Erythronolide A Approach[29]: A Me_2CuLi; B DMSO, Ac_2O; C (i) NaOMe; (ii) $NaBH_4$; (iii) NaH, MeI; (iv) H_2, $Pd(OH)_2/C$; (v) TrCl, py; (vi) DMSO, Ac_2O; D NaOMe; E (i) MeLi; (ii) NaH, MeI; F (i) H_2, $Pd(OH)_2/C$; (ii) $CrO_3.2py$; G (i) $Ca(OH)_2$; (ii) NaCN, MnO_2, MeOH; H (i) H_2, Pd/C; (ii) $(MeO)_2P(O)CH_2Li$; I (i) H_2, $Pd(OH)_2/C$; (ii) $CrO_3.2py$; J (i) AcOH; (ii) CH_2=$CHMgBr$; K (i) NaH, BnBr; (ii) O_3; L NaH; M (i) MeLi; (ii) NaH, MeI; (iii) AcOH; (iv) PCC; (v) KOH; (vi) NaH, MeI; (vii) CH_2N_2.

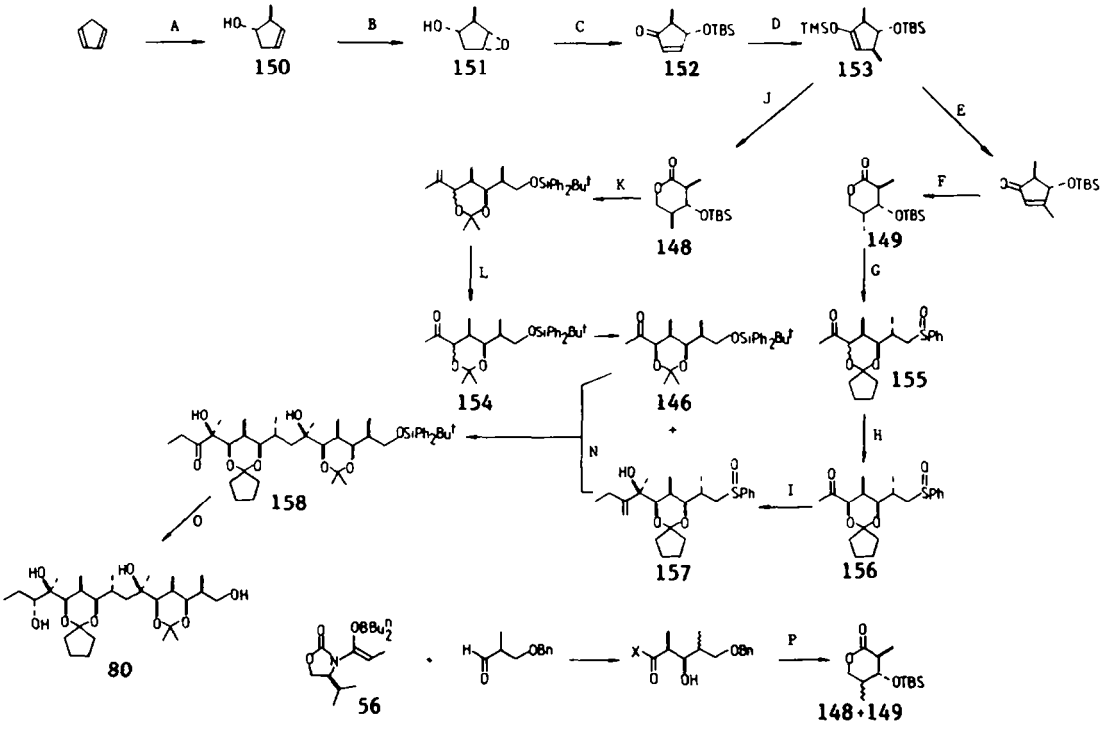
Scheme 13.

different segments of the aglycone. A protected polyol intermediate **80**, containing all ten chiral centres of the seco-acid in the proper absolute configuration, was prepared by the stereoselective coupling of enantiomerically-correct C_1–C_6 and C_7–C_{13} fragments, **146** and **147**, respectively. Note that the chiral sequences at C_2–C_5 and C_8–C_{11} in these fragments are the same except that C_2 and C_8 are antipodal.

Stork



The two fragments were prepared from the appropriate δ-lactones **148** and **149** which were initially obtained by a stereospecific ring-cleavage approach starting with **150**. Cyclopentenol **150** was prepared in high enantiomeric purity from 5-methylcyclopentadiene by asymmetric hydroboration. Hydroxyl-directed epoxidation, **150** → **151**, controlled the C_3–C_4 and C_9–C_{10} relative stereochemistry in the two



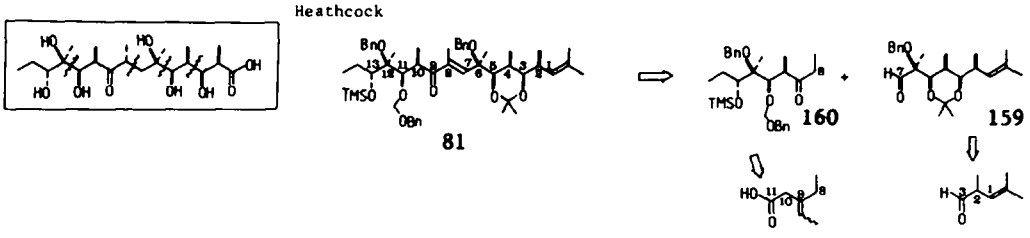
Stork Erythronolide Approach[30]: A Na; MeI; (-)-IPC_2BH; ^-OOH; B Bu^tOOH, $Vo(acac)_2$; C (i) Jones; (ii) Et_3N, TBSCl, DMAP; D Me_2CuLi; Me_3SiCl; E $Pd(OAc)_2$; F (i) H_2, Pd/C; (ii) LDA; Me_3SiCl; (iii) O_3; $NaBH_4$; H^+; G (i) DIBAL; (ii) CH_2=C(Me)Li; (iii) TBAF; (iv) TsCl, DMAP; (v) 1,1-dimethoxycyclopentane, PPTS; (vi) NaSPh; (vii) $NaIO_4$; (vii) $NaIO_4$; (viii) O_3; Me_2S; H K_2CO_3, MeOH; I CH_2=C(Et)MgBr; J O_3; $NaBH_4$; H^+; K (i) DIBAL; (ii) CH_2=C(Me)Li; (iii) TBAF; (iv) Bu^tPh_2SiCl, DMAP; (v) $(MeO)_2CMe_2$, PPTS, L O_3; Me_2S; M (i) K_2CO_3, MeOH; N (i) LDA; (ii) O_3; Me_2S; (iii) Ra-Ni; O (i) LAH; (ii) TBAF; P (i) NaOMe; (ii) TBSOTf; (iii) H_2, Pd/C; H_3O^+.

Scheme 14.

fragments. Conversion to the enone **152** and methyl cuprate 1,4-addition then set in place the C_2-centre to give, after O-silylation, the silyl enol ether derivative **153**, which was cleaved by ozone to give δ-lactone **148** after reduction and acidification. The formation of epimeric lactone **149**, however, required inversion of configuration in **153**, which was carried out by $Pd(OAc)_2$ oxidation followed by catalytic hydrogenation (hydrogen addition occurs selectively from the more accessible β-face) and then another two steps. Lactone **148** was elaborated to the C_1–C_6 fragment **146** firstly by reduction, isopropenyllithium addition, adjustment of protecting groups, and ozonolysis to give the C_5-epimeric methylketones **154**. Base-equilibration then gave the more stable epimer **146** (the equatorial acetyl group relieves an unfavourable 1,3-diaxial interaction) with effectively complete control of the C_5-centre by the resident chirality at C_3. The other δ-lactone **149** was converted by a very similar series of steps into the ketones **155**, which were base-equilibrated to give **156**, with the desired configuration at C_{11} (cf. control of C_5 centre). Addition of a vinylic Grignard reagent then gave the complete C_7–C_{13} fragment **147**, where chelation by the C_{11}-ether oxygen served to control the new chiral centre at C_{12}. Coupling of the fragments took place on addition of the sulfur-stabilized dianion (LDA) of **147** to **146** to give, after ozonolysis and reductive desulfurization, ketone **158** with 83% stereoselectivity for the desired 6*R*-configuration. Finally, chelation-controlled hydride addition using $LiAlH_4$ served to set in place the last remaining chiral centre at C_{13} to give **80** after deprotection (24 steps from cyclopentadiene; 4.6% overall yield).

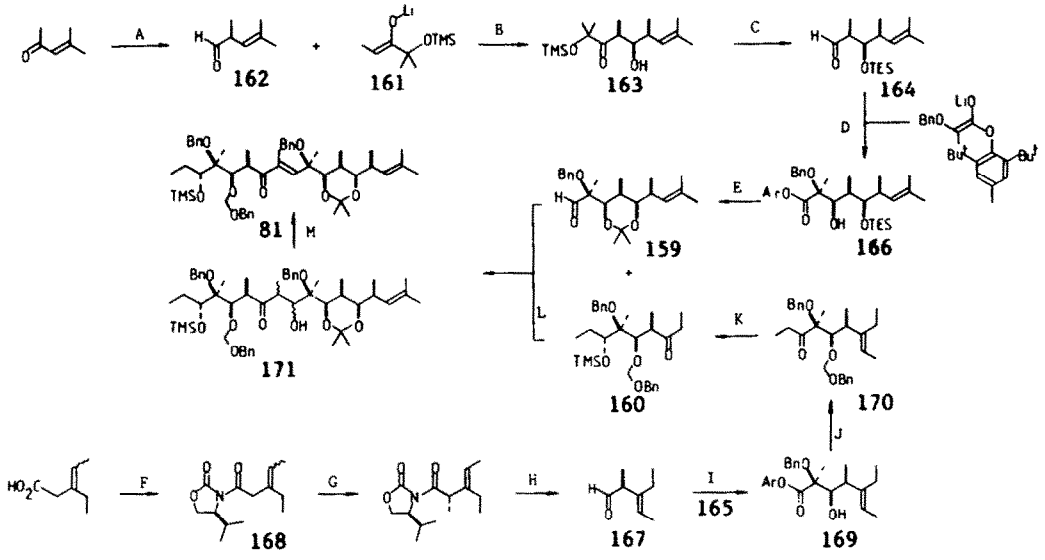
An alternative acyclic approach to the two key δ-lactones **148** and **149**, which has been subsequently developed by Paterson *et al.*[36] uses an aldol condensation between the enantiomerically-pure imide enolate **56**[25a] and a simple racemic aldehyde to secure all of the required stereochemistry.

2.2.1.7. *Heathcock approach* (Scheme 15).[2b,31] Heathcock *et al.* have adopted an acyclic approach to the construction of a seco-acid derivative of erythronolide A using a sequence of four aldol condensations. The critical aldol connections are made at different bonds to that of the Masamune synthesis of the structurally simpler 6-deoxyerythronolide B, which lacks the characteristic tertiary hydroxyl groups at C_6 and C_{12}. The Heathcock group have specifically designed a suitable enolate reagent to introduce these oxygen-bearing C_6 and C_{12} chiral centres.[37a] Note also that chiral enolates are not used in this approach, which depends only on the Cram-type diastereoface selectivity of the aldehyde partner. The synthesis of **81** is based on an aldol coupling of the enantiomerically-correct C_1–C_7 and C_8–C_{13} fragments, **159** and **160**, respectively.[2b]



Fragment **159** was prepared by a pair of stereocontrolled aldol condensations. Addition of the Heathcock *erythro*(syn)-selective enolate **161**[37b] to racemic aldehyde **162** set up the C_2–C_4 chiral sequence. Aldol adduct **163** was then converted in three steps to a new aldehyde **164**, which was condensed with the enolate **165** to give the Cram addition product **166** with 85% stereoselectivity. Reduction followed by resolution and oxidation then gave the enantiomerically-correct aldehyde **159**. The other fragment, **160**, was constructed from aldehyde **167**, which was prepared by enantioselective methylation of the enolate derived from **168** making use of the Evans chiral auxiliary. Aldol condensation of *threo*-selective **165** with **167** then gave the Cram adduct **169**, which was then converted into the ethyl ketone **170**. Chelation-controlled hydride addition to **170** then secured the 13*S* chiral centre (cf. **158** → **80** in Scheme 14), followed by protection and ozonolysis to give the C_7–C_{13} fragment **160**.

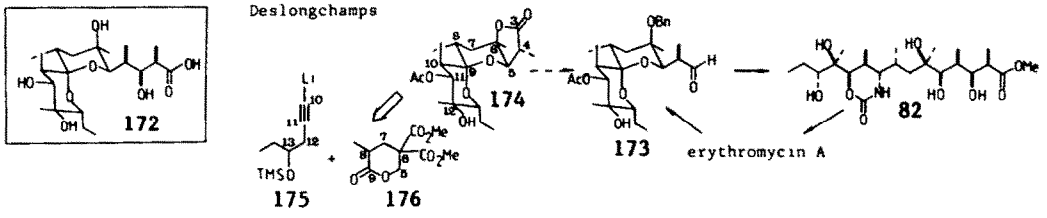
The coupling[31] of the two fragments was performed by addition of the magnesium enolate of **160** to **159**, which gave a mixture of diastereomeric aldols **171** that could be dehydrated to give **81** (19 steps from valine; overall yield not available).



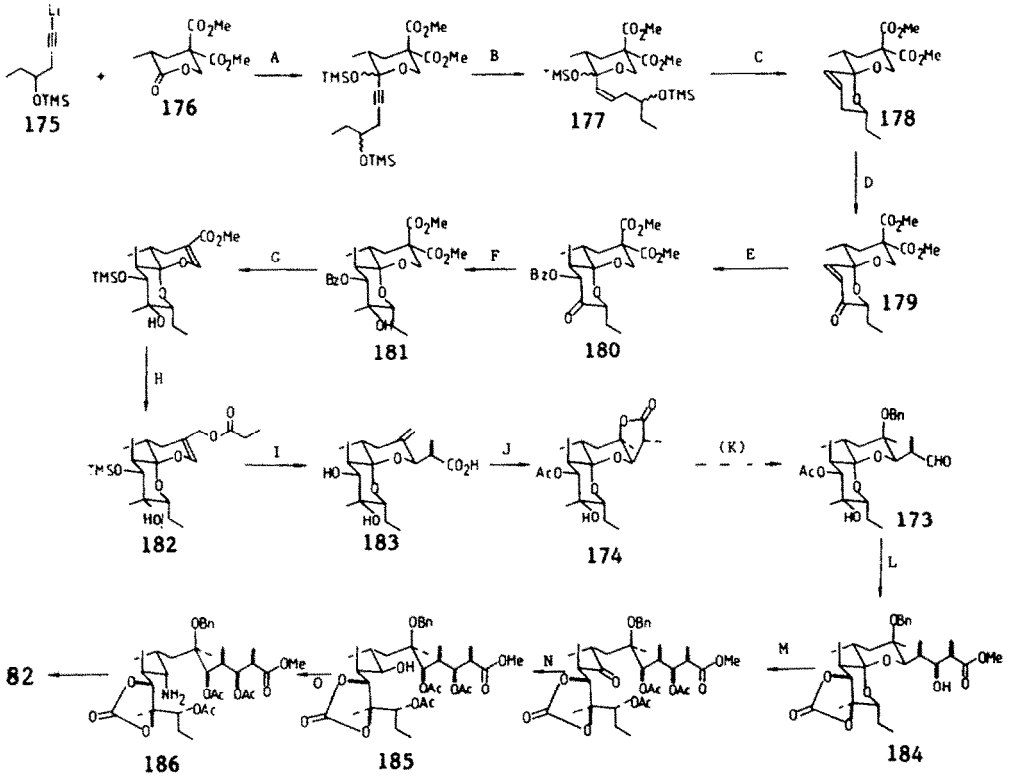
Heathcock Erythronolide Approach[2b,31]: A (i) $(EtO)_2P(O)CHLiOTHP$;(ii) H_3O^+; B aldol coupling; C (i) LAH; (ii) $NaIO_4$; (iii) Et_3SiOTf; D aldol coupling; E (i) Me_2CO, HCl; (ii) LAH; (iii) resolution as O-methylmandelate ester; (iv) PCC; F (i) $SOCl_2$; G $NaN(SiMe_3)_2$; MeI; H (i) LAH; (ii) py.SO_3, DMSO; Et_3N; I cf D; J (i) LAH; (ii) Ac_2O; (iii) $BnOCH_2Cl$; (vi) ^-OH; (v) PCC; K (i) EtLi; (ii) $(COCl)_2$, DMSO; Et_3N; (iii) DIBAL; (iv) Me_3Si-imidazole; (v) O_3; L $(C_6H_{11})_2MgBr$; addition to aldehyde; M $Ph_2S(OC(CF_3)_2\text{-Tol})_2$.

Scheme 15.

2.2.1.8. *Deslongchamps approach* (Scheme 16).[32] The Deslongchamps strategy for the synthesis of erythronolide A is based on the construction of a suitably protected form of the spiroketal derivative **172** of the macrolide seco-acid (cf. Ireland's synthesis of methynolide in Section 2.1.1). The conformational rigidity of the spiroketal framework was cleverly used to set up eight out of the ten chiral centres (C_2 and C_3 were introduced by acyclic stereocontrol). In this route the relay compound **173**, prepared from erythromycin A, was converted into Woodward's intermediate **82**.[28] Deslongchamps and his co-workers will have achieved a formal total synthesis of erythromycin A once intermediate **174**, obtained by synthesis in racemic form, is converted into **173**.



Coupling of acetylide anion **175** and lactone **176** gave the C_5–C_{13} segment **177** after silylation and catalytic hydrogenation. Spiroketal formation and equilibration with mild acid then gave a single compound **178** (the ethyl group at C_{13} adopts the lower energy equatorial orientation and the spirocentre at C_9 is controlled by double anomeric stabilization, while the epimerizable C_8 centre has the methyl substituent in the equatorial orientation to avoid a 1,3-diaxial interaction with the CO_2Me group). Conversion to the enone **179** and conjugate addition of methyl cuprate followed by oxygenation of the enolate correctly set up the C_{10} and C_{11} stereocentres in **180**, while axial-addition of MeMgI selectively gave **181** with the desired stereochemistry at C_{12}. The C_4, C_5 and C_6 centres were then set up on the other ring by first converting **181** through to propionate **182**. Enolate Claisen rearrangement then gave acid **183** with 80% stereoselectivity, which was transformed into **174** by iodolactonization, reduction and acetylation (23 steps from **176**).

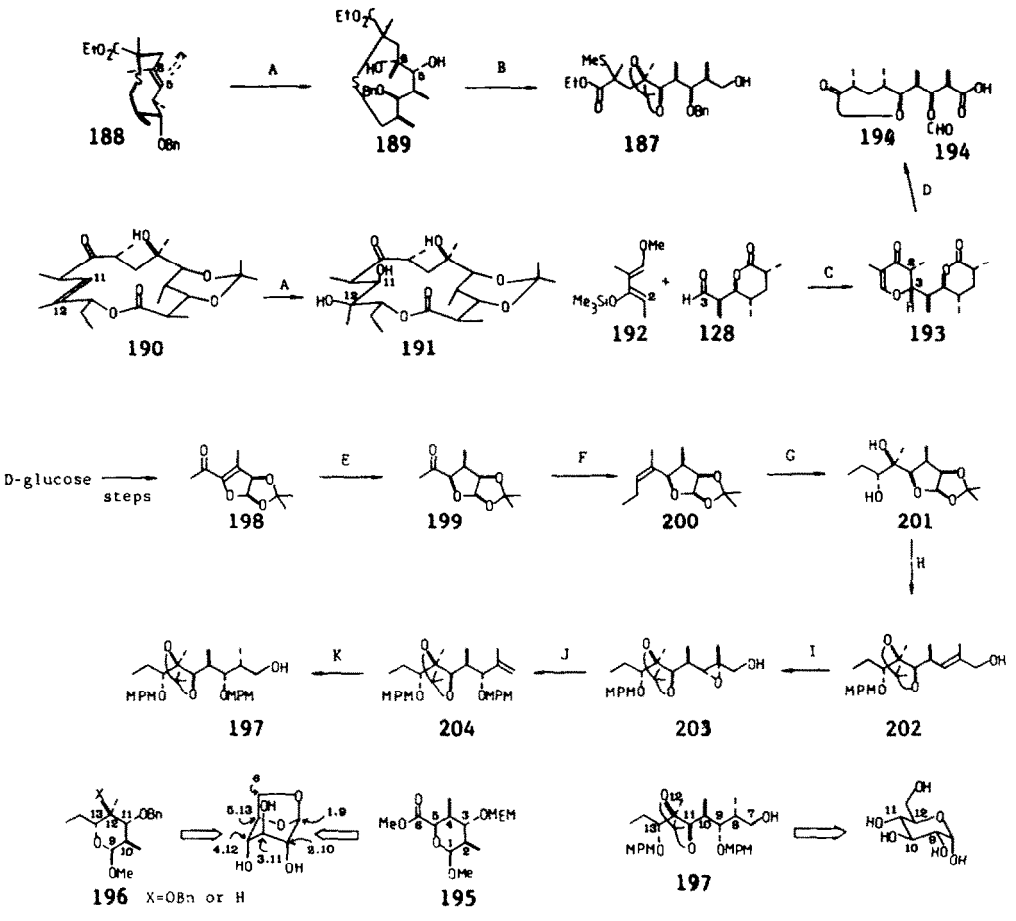


Deslongchamps Erythronolide A Approach[32]: A (i) addition; (ii) Me_3SiCl; B H_2, $Pd/CaCO_3$; C (i) Me_3SiOTf; (ii) PPTS; D (i) SeO_2; (ii) PCC or PDC; E (i) Me_2CuLi; $(PhCO_2)_2$; F MeMgI; G (i) K_2CO_3, MeOH; (ii) LiCl, DMSO; (iii) LDA; PhSeBr; (iv) Me_3SiCl, imidazole; (v) $NaIO_4$; (vi) Pd/C; H (i) LAH; (ii) $(EtCO)_2O$, DMAP, Et_3N; I (i) LDA, TBSCl; (ii) TBAF; J (i) KOH; (ii) I_2, KI, $KHCO_3$; (iii) $Bu^n{}_3SnH$, AIBN; (iv) Ac_2O, DMAP, Et_3N; L (i) $MeCO_2Me$, LDA; $(Cp)_2ZrCl_2$; (ii) X_2CO; M (i) TsOH, AcOH, Ac_2O; (ii) HCl; (iii) Ac_2O, DMAP, Et_3N; N (i) $NaBH_4$; O (i) MsCl, py; (ii) LiN_3; (iii)H_2,PtO_2; P (i) PhH, reflux; (ii) LiI, py; (iii) NaOH; (iv) CH_2N_2; (v) H_2, Pd/C.

Scheme 16.

In the relay section of the synthesis, aldehyde **173** was homologated to **184** by an *erythro*(syn)-selective aldol condensation (10:1 ratio at C_2) followed by formation of the carbonate derivative. Hydrolysis of the spiroketal, acetylation and reduction at C_9 gave a 3:2 mixture of **185** and its C_9-epimer. Compound **185** was then converted into the inverted amine **186**, which could be taken on to the Woodward intermediate **82** (14 steps from **173**). Only the transformation **174** → **173** remains at this time to be solved.

2.2.1.9. *Other approaches* (Scheme 17). A novel construction of a racemic C_1–C_9 fragment, **187**, for the synthesis of erythronolide A has been reported by Vedejs *et al.*,[38] which is based on the stereocontrolled osmylation of an *E*-olefin in a 9-membered ring, **188** → **189**. Osmium tetroxide attacks the peripheral face of the double bond in the preferred crown-like conformation adopted by **188** (where the methyl substitutent at C_4 takes up a pseudoequatorial orientation) to give the desired stereochemistry at the C_5 and C_6 chiral centres. In contrast, an analogous acyclic alkene was found to show essentially no diastereoface selectivity on osmylation.[38] Vicinal diol **189** was converted into acyclic fragment **187** by acetonide formation, followed by solvolysis of an α-chlorosulfide derivative, reduction and *S*-methylation. Trost[39] has independently described an approach to the synthesis of the erythronolides relying on similar macrocyclic stereocontrol, which features a novel macrocyclization using Pd chemistry. Note also that Corey and Hopkins[40] have already shown that the C_{11}–C_{12} vicinal diol relationship of erythronolide A can be correctly introduced by osmylation of the corresponding *E*-olefin, **190** → **191**.



Other Approaches to Erythronolides: A OsO_4; $NaHSO_3$; B (i) acetonide formation, (ii) NCS; (iii) H_2O, $CaCO_3$; (iv) $NaBH_4$; (v) S-methylation; C (i) $ZnCl_2$; (ii) TFA; D O_3; H_2O_2; E H_2, Pd/C; F $Ph_3P{=}CHEt$; G OsO_4, N-methylmorpholine-N-oxide; H (i) p-$MeOC_6H_4CH_2Cl$, NaH; (ii) HCl; (iii) $Pb(OAc)_4$; (vi) LAH; (v) BzCl, py; (vi) $Me_2C(OMe)_2$, TsOH; (vii) KOH; (viii) PCC; (ix) $Ph_3P{=}CMeCO_2Et$; (x) LAH; I MCPBA; J MsCl, Et_3N; (ii) NaI; (iii) Zn-Cu; (iv) p-$MeOC_6H_4CH_2Cl$, NaH; K $Bu^n_4NBH_4$, MeI.

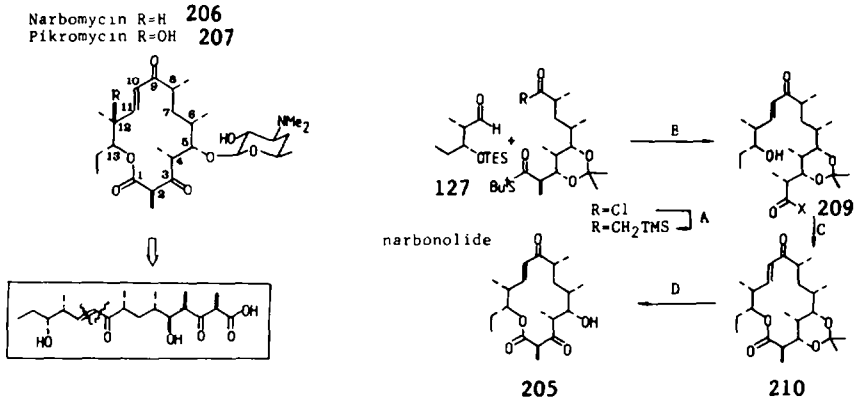
Scheme 17.

Danishefsky *et al.*[41] have described a different procedure for homologating **128** to a C_1–C_9 fragment of 6-deoxyerythronolide B (cf. Scheme 12), which is based on a cyclocondensation with siloxydiene **192** to give predominantly the Cram-adduct **193** (60% stereoselectivity). Ozonolysis and treatment with H_2O_2 then gave the acid **194**.

Other carbohydrate-derived fragments of the erythronolides have also been reported.[42–44] Kochetkov and his co-workers[43] have prepared the C_1–C_6 and C_9–C_{13} fragments, **195** and **196**, respectively, from levoglucosan using a similar approach to Hanessian. Note that these same intermediates, albeit with different hydroxyl protecting groups, have already been used in Hanessian's route to erythronolide A (Section 2.2.1.5).[29] Oikawa *et al.* have reported a synthesis of the C_7–C_{13} fragment **197** from D-glucose, which incorporates the sugar carbons in a different manner to that used previously.[44] D-Glucose was first converted into the furanoside **198**, which was hydrogenated from the α-face to give the ketone **199** with the required stereochemistry at C_{10} and C_{11}. Acyclic stereocontrol was then used to set up the remaining chiral centres. Osmylation of the derived *Z*-olefin **200** controlled the C_{12}–C_{13} vicinal diol relationship to give **201** with 95% stereoselectivity. This product was then elaborated to the allyl alcohol **202**, which gave a single epoxide **203** on reaction with MCPBA. Conversion to the allyl alcohol **204** was then followed by hydroboration to give **197** (28 steps from D-glucose) and its C_8-epimer as a 40:60 mixture.

2.2.2. *Narbomycin*

A synthesis of narbonolide (**205**), the biosynthetic precursor of the 14-membered macrolide antibiotics narbomycin (**206**) and pikromycin (**207**), has been completed by the Masamune group.[9c] The enantiomerically-correct fragments **127** and **130** used in the earlier synthesis of 6-deoxyerythronolide B (Section 2.2.1.4)[19d] were incorporated into this new macrolide aglycone (Scheme 18). Fragment **130** was first converted into the α-(trimethylsilyl)methyl ketone **208**, which was then coupled in a Peterson reaction with aldehyde **127** to give enone **209** (X = SBu^t) after deprotection. Note that a new mixed-anhydride method of carbonyl activation was developed for the macrolactonization of **209** (X = OH), since the activated thioester method failed in this case. Cyclization of the phosphoric acid anhydride **209** (X = $OPO(OPh)_2$) proceeded in the presence of DMAP under high-dilution conditions to give a 32% yield of the desired lactone **210**. Deprotection was followed by oxidation of the C_3-hydroxyl to give narbonolide (25 steps from **14**; 5% overall yield from **51**); the undesired C_5-keto compound also formed in the oxidation could be recycled.

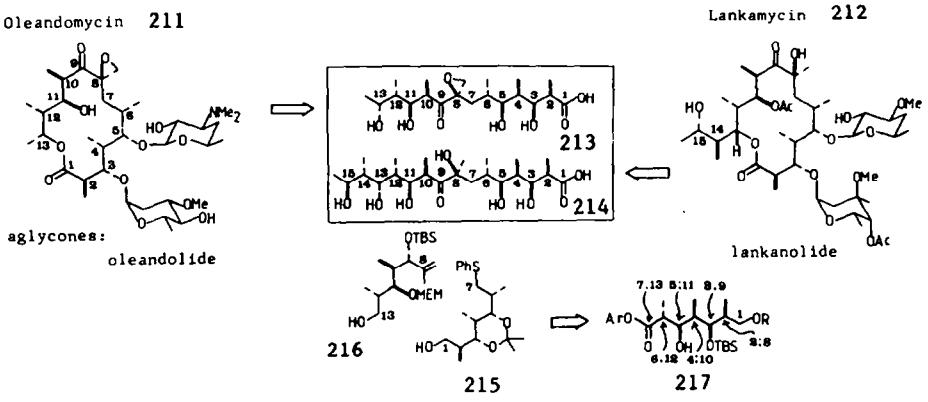


Masamune Narbonolide Synthesis[9c]: A $(Me_3SiCH_2)_2CuLi$; B (i) $(Me_3Si)_2NLi$, addition of aldehyde; (ii) AcOH; (iii) $Hg(CF_3CO_2)_2$; $NaHCO_3$, H_2O; C $(PhO)_2POCl$, Et_3N; DMAP; D (i) TFA; (ii) $RuCl_2(PPh_3)_3$.

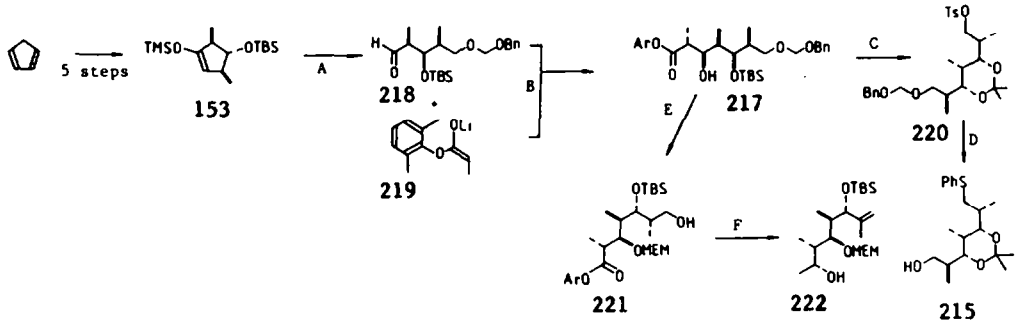
Scheme 18.

2.2.3. *Oleandomycin and lankamycin*

The aglycones of the medicinally-important oleandomycin (**211**) and the related 14-membered macrolide lankamycin (**212**) are configurationally identical at all ten chiral centres between C_1 and C_{13}. In addition, the three chiral centre sequence between C_4 and C_6 is the same as found at C_{10} to C_{12} (cf. seco-acid structures **213** and **214**). Paterson[45] has described a synthesis of two structurally-related and enantiomerically-correct C_1–C_7 and C_8–C_{13} fragments, **215** and **216**, respectively, for use in a projected synthesis of oleandomycin and lankamycin. These fragments were prepared from the common precursor **217**.



Silyl enol ether (+)-**153** (cf. Scheme 14) was used as the source of the asymmetric carbons at C_2, C_3 and C_4, as well as at C_9 and C_{10}. It was first converted to **218** by a sequence of ozonolysis, $NaBH_4$ reduction, and esterification, followed by protection and net reduction to the aldehyde (Scheme 19). An aldol condensation using the *threo*(anti)-selective aryl ester enolate **219**, developed by Heathcock, gave predominantly the desired Cram-adduct **217** with 93% stereoselectivity. Reduction and desilylation gave the triol which was monotosylated and converted into the acetonide **220**. Hydrogenolysis and displacement with LiSPh then gave the C_1–C_7 fragment **215** (16 steps from cyclopentadiene; 11% overall yield), which can be converted into a C_7 carbanion by either deprotonation adjacent to the PhS group using Bu^{t}Li–HMPA, or by reductive metallation with lithium dispersion to give the simple organolithium.[46] The synthesis of the other fragment **216** involves protecting group adjustment to give **221**, followed by net dehydration and reduction. Note that MeMgCl addition to the derived aldehyde gives mainly the Cram-adduct **222** with the correct configuration at C_{13} for oleandolide.[46]



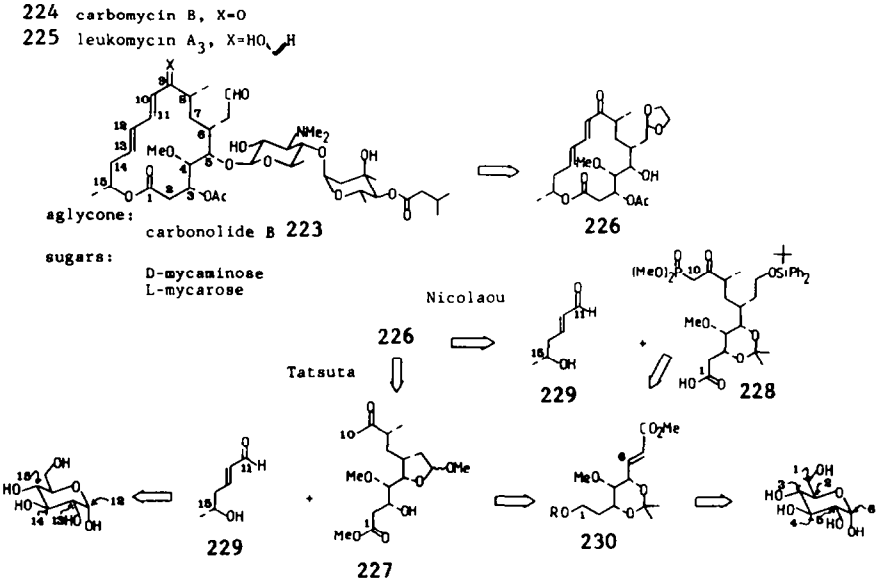
Paterson Oleandolide Approach[45]: A (i) O_3; $NaBH_4$; HCl; CH_2N_2; (ii) $BnOCH_2Cl$, Pr^i_2NEt; (iii) DIBAL; (iv) PCC; B aldol; C (i) LAH; (ii) TBAF; (iii) TsCl, DMAP, Et_3N; (iv) $(MeO)_2CMe_2$, PPTS; D (i) H_2Pd/C; (ii) LiSPh; E (i) MEM-$NEt_3^+Cl^-$; (ii) H_2, Pd/C; F (i) o-$NO_2C_6H_4SeCN$, Bu^n_3P; H_2O_2; (ii) DIBAL; (iii) $(COCl)_2$, DMSO; Et_3N; (iv) MeMgCl.

Scheme 19.

2.3. 16-*Membered Macrolides*

2.3.1. *Carbomycin B and leukomycin A_3 (josamycin)*

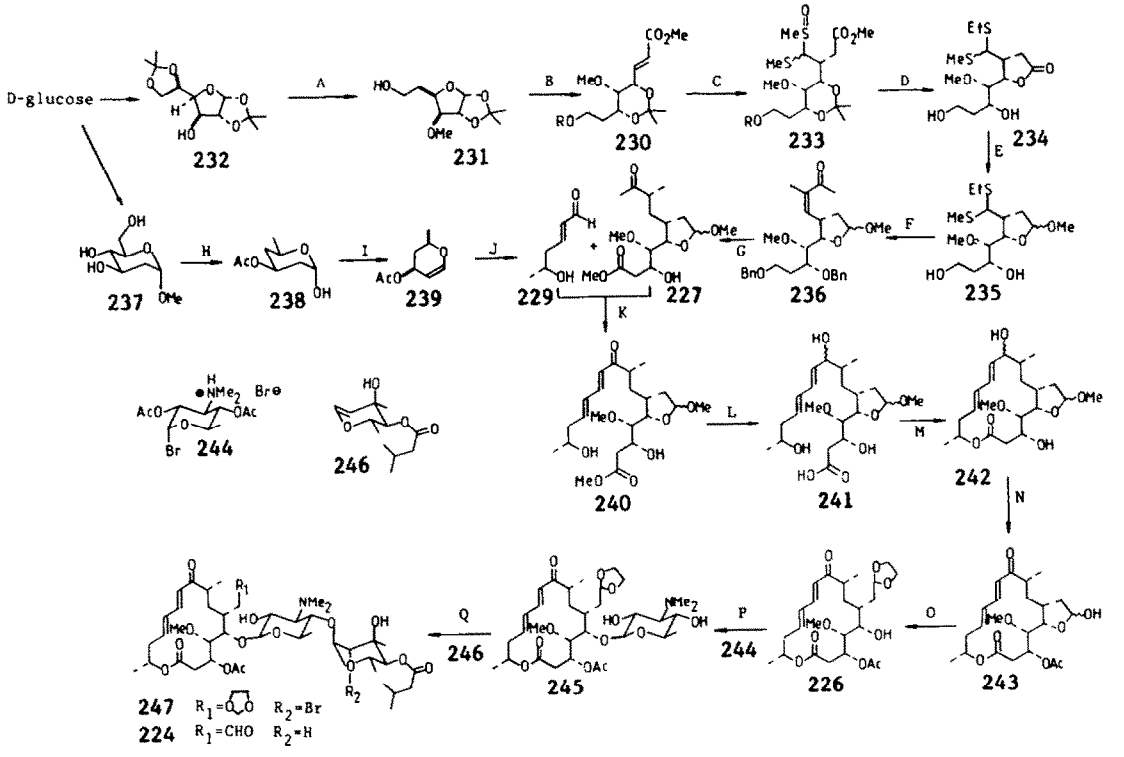
Carbomycin B (**224**) was the first 16-membered polyoxo-macrolide to yield to synthesis. It can also be converted into its close relative leukomycin A_3 (**225**).[47] In 1977 Tatsuta *et al.* reported a partial synthesis of carbomycin B based on the glycosidation of a derivative of carbonolide B obtained by degradation, i.e. **226** → **224**.[48] This was subsequently followed by the independent synthesis of this key intermediate **226** by the groups of Tatsuta[49] and Nicolaou.[50]



The two approaches used are very similar in that they are both based on coupling a nucleophilic C_1–C_{10} fragment, **227** and **228**, respectively, which is prepared from D-glucose, with the enantiomerically-correct C_{11}–C_{15} aldehyde **229**. Note that the chirality of the C_3–C_5 segment in the target macrolide correlates exactly with the C_2–C_4 sequence of glucose. This makes the carbohydrate approach uniquely suited to the synthesis of carbomycin B, as no elaborate modification of the sugar starting material is necessary. A similar carbohydrate strategy for the synthesis of a C_1–C_6 segment of carbomycin B has also been described by Zeigler *et al.*,[51a] who have examined the possibilities of controlling the configuration at C_6 by conjugate addition to oxazolines[51b] and carrying out a novel macrocyclization by a Pd-catalyzed C_{11}–C_{12} coupling process.[51c]

2.3.1.1. *Tatsuta synthesis* (Scheme 20).[49] The key C_1–C_6 segment **230** (containing the chiral centres at C_3, C_4, and C_5) was obtained from D-glucose in both the Tatsuta and Nicolaou syntheses. Tatsuta and co-workers prepared the acetonide **231** from the D-glucose derivative **232** in five steps followed by hydrolysis, Wittig homologation and protection to give **230** (R = MOM). Michael addition of a formyl anion equivalent to **230** gave the adduct **233** with the natural configuration at the new C_6 centre. The chelated delivery of the organometallic nucleophile by the C_5-ethereal oxygen might be responsible for this diastereoface selectivity; however, it is likely that more subtle effects are also operating in these conjugate additions.[51b] Acid-catalyzed reaction with EtSH converted **233** into **234** by deprotection, lactonization, and dithioacetal exchange. This was then transformed by reduction and acetal-formation to give **235**, which was first protected and hydrolyzed to a C_6-aldehyde and then homologated by a Wittig reaction to give the enone **236**, with abnormal *Z*-stereoselectivity.

Catalytic reduction, followed by oxidation of the resulting C_1-alcohol and esterification gave the correct C_1–C_{10} fragment **227** with 62% stereoselectivity. Note that the C_8 chiral centre was not controlled to any useful extent in either of the two syntheses. The C_{11}–C_{15} fragment, optically-pure



Tatsuta Carbomycin B Synthesis[49]: A (i) NaH, MeI; (ii) AcOH; (iii) BzCl, py; (iv) TsCl, py (v) LAH; B (i) H_2SO_4; (ii) $Ph_3P{=}CHCO_2Me$; (iii) $MeOCH_2Cl$, Pr^i_2NEt; (iv) 2,2-dimethoxypropane, TsOH; C $MeSCH_2S(O)Me$, Bu^nLi; D EtSH, $BF_3{\cdot}OEt_2$; E (i) DIBAL; (ii) MeOH, H^+; F (i) NaH, BnBr; (ii) $HgCl_2$, $CdCO_3$, H_2O; (iii) $Ph_3P{=}CMeCOMe$; G (i) H_2,Pd; (ii) O_2, Pt, $NaHCO_3$; (iii) CH_2N_2; H (i) SO_2Cl_2, py; (ii) NaI; (iii) Ac_2O; (iv) Bu^n_3SnH, AIBN; (v) H_3O^+; I TsCl, Et_3N; J $Hg(OAc)_2$; H_3O^+; K LDA; addition of aldehyde; L (i) $NaBH_4$; (ii) KOH; M (i) $(EtO)_2POCl$, Et_3N; TlSPh; (ii) CF_3CO_2Ag, Na_2HPO_4; N (i) CrO_3; (ii) Ac_2O, py; (iii) H_3O^+; O $(HOCH)_2$, TsOH; P (i) $Hg(CN)_2$; (ii) MeOH; Q 1,3-dibromo-5,5-dimethylhydantoin; R (i) TFA; (ii) Bu^n_3SnH, AIBN.

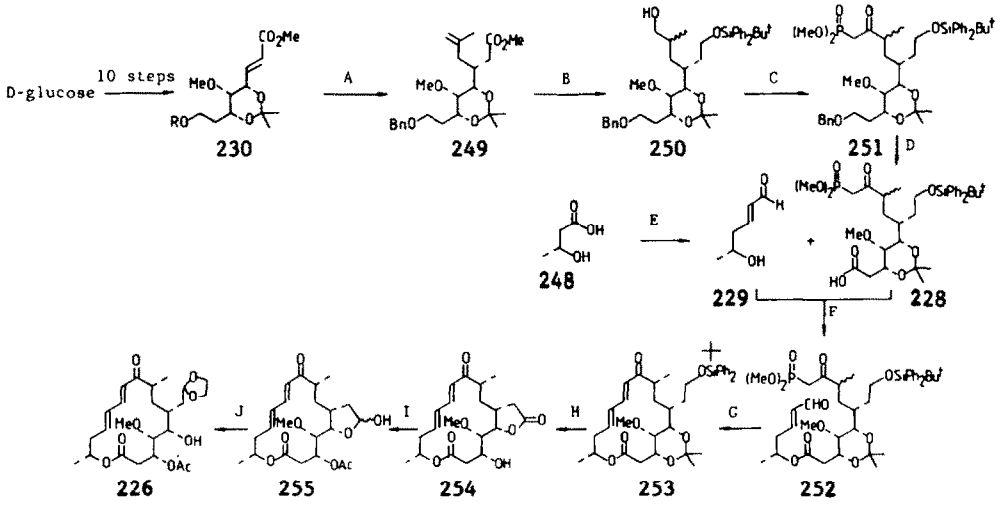
Scheme 20.

aldehyde **229**, was also derived from D-glucose but this time only a single chiral centre was retained. The 2-deoxy derivative **237** was converted in four steps to pyranose **238**, which was dehydrated to the dihydropyran **239** and subsequently transformed into the desired enal **229** using mercuric acetate. Ketone **227** gave the *E,E*-diene **240** in 67% yield on sequential treatment with LDA (3.2 equiv) and aldol condensation with **229** (2 equiv). Reduction of **240** with $NaBH_4$ followed by hydrolysis then gave the seco-acid **241**. Macrolactonization, **241** → **242**, took place in a modest 17% yield using Masamune's[7a] activated thioester procedure. Note that the C_3 and C_9 hydroxyl groups did not require protection. Selective oxidation at C_9, followed by acetylation and hydrolysis gave carbonolide B (**243**), which was converted into the key intermediate **226** (28 steps from D-glucose; 0.03% overall yield).

The final conversion of **226** into carbomycin B was carried out on relay material.[48] Reaction of **226** with the D-mycaminose derivative **244**, in the presence of mercuric cyanide, gave the β-aminoglycoside **245** in a modest 16% yield after methanolysis. Treatment of **245** with 4-O-isovaleryl-L-mycarose glycal (**246**) together with a brominating agent (1,3-dibromo-5,5-dimethylhydantoin) gave a single disaccharide **247** in 11% yield. Hydrolysis of the acetal and radical debromination then completed the synthesis of carbomycin B (33 steps from D-glucose; < 0.01% overall yield).

2.3.1.2. *Nicolaou synthesis* (Scheme 21).[50] The main differences in the Nicolaou synthesis of **226** are that the order of joining the ends of the two key fragments is inverted and the C_{11}–C_{15} aldehyde is prepared from *R*-β-hydroxybutyric acid (**248**). The 16-membered ring of carbonolide B was now formed by an intramolecular ketophosphonate Horner–Emmons coupling[52] at C_{10} and C_{11}.

Conjugate addition of a 3-carbon unit to **230** (R = Bn) using methallyl cuprate gave adduct **249** with the correct C_6-configuration in 93% stereoselectivity. Reduction, protection and hydroboration of **249** gave the mixture of C_8-epimeric alcohols **250**, which was elaborated via the aldehyde to the ketophosphonate **251**. Deprotection of the C_1-hydroxyl group and Jones' oxidation then gave the complete C_1–C_{10} fragment **228**, which was connected to the C_{15}-alcohol **229** by mild esterification to give **252** in 70% yield. Macrocyclization gave the correct C_8-epimer **253** in 20% yield. Compound **253**, which was also prepared by degradation, could be converted into **226** by suitable manipulation of protecting groups and oxidation of the side-chain. Desilylation, oxidation, acid-catalysed removal of the acetonide and lactonization gave **254**, which was then acetylated and selectively reduced and re-oxidized at C_9 to give lactol **255**. Acetal-formation then finally gave the Tatsuta intermediate **226** (30 steps from D-glucose; 0.3% overall yield).



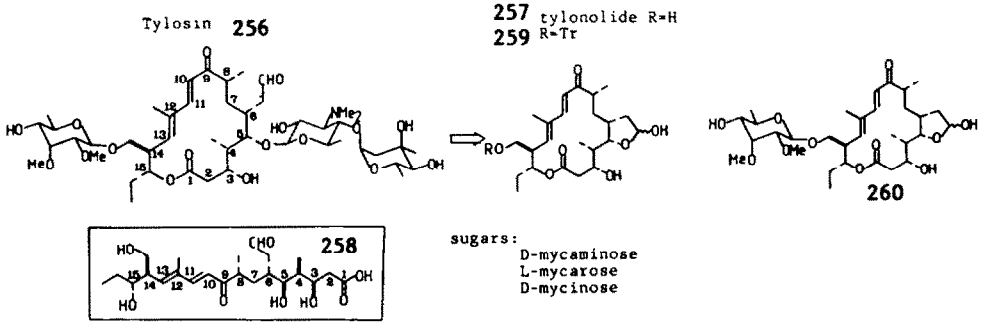
Nicolaou Carbonolide B Synthesis[50]: A methallyllithium, CuI; B (i) HCl; (ii) LAH; (iii) Bu^tPh_2SiCl, imidazole; (iv) $(MeO)_2CMe_2$, CSA; (v) BH_3-THF; ^-OOH; C (i) PCC; (ii) $(MeO)_2P(O)CH_2Li$; (iii) PCC; D (i) H_2, Pd/C; (ii) Jones; E (i) CH_2N_2; (ii) dihydropyran, TsOH; (iii) DIBAL; (iv) PCC; (v) $Ph_3P{=}CHCO_2Et$; (vi) DIBAL; (vii) PCC; (viii) AcOH; F (i) DCC, DMAP; G Na, high dilution; H (i) HF-py; (ii) Jones; (iii) HCl; I (i) Ac_2O, DMAP, py; (ii) $LiAl(OBu^t)_3H$; (iii) DDQ; J $(HOCH_2)_2$, CSA.

Scheme 21.

2.3.2. *Tylosin*

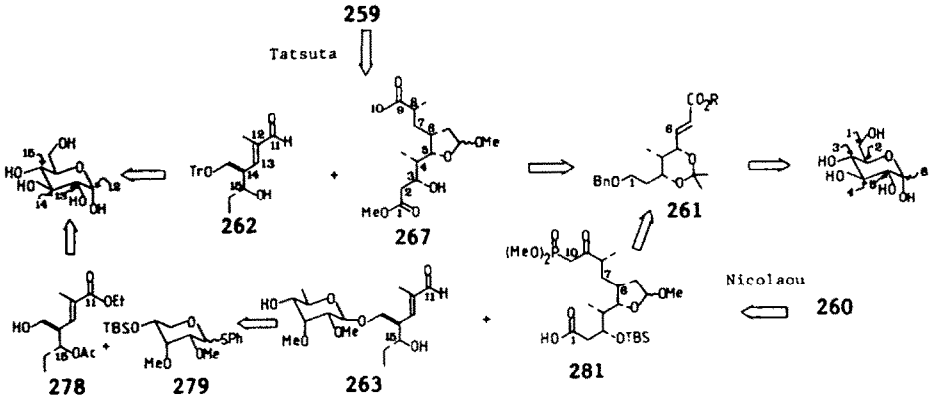
Out of all the 16-membered polyoxo-macrolides, the commercially-important antibiotic and nutrient tylosin (**256**) has attracted by far the greatest synthetic effort to date. Masamune and his co-workers first reported in 1976 a partial synthesis of tylonolide (**257**),[53] the aglycone of tylosin, by macrolactonization of a protected derivative of the seco-acid **258**. In 1982 the Tatsuta group[54a] completed the first total synthesis of tylosin by the stepwise glycosidation of a previously synthesized[54b] tylonolide derivative **259**.

In the same year Nicolaou *et al.*[55] reported the synthesis of O-mycinosyltylonolide **260** (tylosin without the aminodisaccharide), while the groups of Grieco[56] and Masamune[57] each completed a synthesis of tylonolide (**257**). More recently Evans and his co-workers[58] have also completed a synthesis of tylonolide. Assuming the selective protection in **257** → **259** can be performed, a synthesis of tylonolide aglycone now constitutes a formal synthesis of tylosin itself.

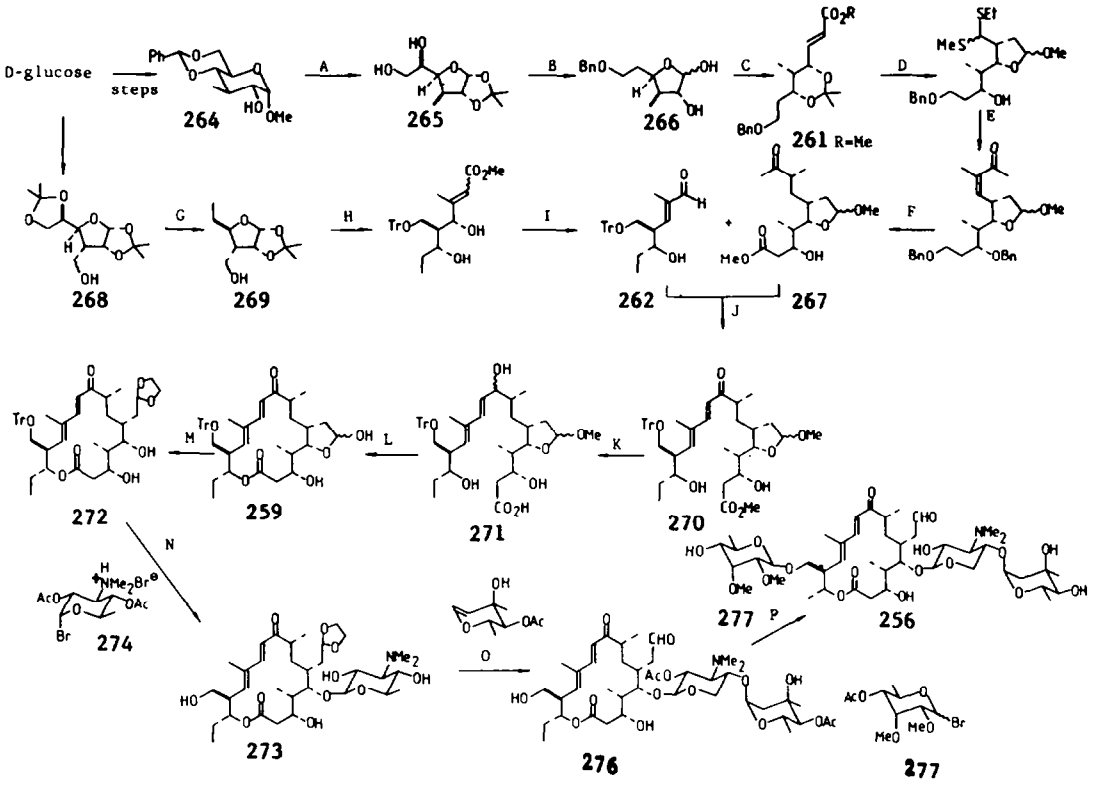


All seven asymmetric carbons of tylonolide are quickly assembled with very high stereocontrol in both the Masamune[57] and Evans[58] (chiral enolate) aldol-based syntheses. Furthermore, macrocyclization to the 16-membered ring of tylonolide by formation of the C_{10}–C_{11} bond in an internal Horner–Emmons reaction, as used by Nicolaou[55] and later by Evans,[58] is found to be superior to the use of the standard activated carboxyl macrolactonization methods.

2.3.2.1. *Tatsuta synthesis* (Scheme 22).[54] Both the Tatsuta and Nicolaou syntheses of the tylonolide skeleton are based on the general carbohydrate-approach developed in their earlier carbomycin B work (Section 2.3.1). Indeed, the same key bond disconnections at C_6–C_7 and C_{10}–C_{11} are again used and many of the reactions are duplicated. The key C_1–C_6 Michael acceptor fragment **261** (cf. compound **230**) in the two routes was prepared from D-glucose, as were also the C_{11}–C_{15} fragments **262** and **263**.



In the Tatsuta synthesis[54] the 3-C-methyl-D-glucoside **264** (available from D-glucose in eight steps) was converted into **265** by first rearrangement to the furanoside and then selective transformation to the monoacetonide. Periodate cleavage of **265** to the aldehyde and a Wittig reaction then gave a homologated aldehyde, which was converted to the 5-deoxyfuranose **266** by reduction and manipulation of protecting groups. Essentially the same reactions were then used for the sequence



Tatsuta Tylosin Synthesis[54]: A (i) Ac_2O, H_2SO_4; (ii) NaOMe, MeOH; (iii) Me_2CO, $CuSO_4$; (iv) AcOH; B (i) $NaIO_4$; (ii) Ph_3P=CHOMe; (iii) AcOH; (iv) $NaBH_4$; (v) NaH, BnBr; (vi) H_2SO_4; C (i) Ph_3P=$CHCO_2Me$; (ii) $(MeO)_2CMe_2$, TsOH; D (i) $MeSCH_2S(O)Me$, Bu^nLi; (ii) EtSH, $BF_3.OEt_2$; (iii) DIBAL; (iv) MeOH, H^+; E (i) NaH, BnBr; (ii) $HgCl_2$, $CdCO_3$, H_2O; (iii) Ph_3P=CMeCOMe; F (i) H_2, Pd; (ii) O_2, Pt, $NaHCO_3$; (iii) CH_2N_2; G (i) Ac_2O, py; (ii) AcOH; (iii) $NaIO_4$; (iv) $Zn(BH_4)_2$; (v) TsCl, py; (vi) MeMgBr, Li_2CuCl_4; H (i) H_2SC_4; (ii) Br_2; (iii) TrCl, py; (iv) MeLi; (v) Ph_3P=$CHCO_2Me$; I (i) TBSCl, imidazole; (ii) LAH; (iii) H_3B-SMe_2; ^-OOH; (iv) $NaIO_4$; (v) NaOMe; (vi) TBAF; J LDA; addition of aldehyde; K (i) $NaBH_4$; (ii) KOH; L (i) 2,2'-dipyridyl disulphide, Ph_3P; (ii) PhMe, 110°C; (iii) CrO_3; (iv) H_3O^+; M $(CH_2OH)_2$, TsOH; N (i) HgO, $HgBr_2$; (ii) MeOH; (iii) Ac_2O; O (i) 1,3-dibromo-5,5-dimethylhydantoin; (ii) TFA; (iii) Bu^n_3SnH, AIBN; P (i) $Hg(CN)_2$; (ii) MeOH; (iii) K_2CO_3, MeOH.

Scheme 22.

266 → **261** → **267** as had been applied to the earlier carbonolide B synthesis. The C_6-stereochemistry was controlled by a Michael addition to **261**, while the correct configuration at C_8 was set up with a modest 66% stereoselectivity by catalytic hydrogenation of a *Z*-enone intermediate.

The C_{11}–C_{15} fragment **262** was prepared from the branched D-allofuranose **268**, which has the correct configuration for the C_{14} and C_{15} centres. This was converted in six steps to **269**, which was then further manipulated to give first an acyclic intermediate and finally the desired aldehyde **262**. A directed aldol condensation between fragments **267** and **262** then gave the adduct **270**, which was converted to seco-acid **271** and cyclized by the Corey–Nicolaou double-activation method[7b] to give the O-trityl derivative of tylonolide **259** after selective oxidation and acid-hydrolysis (37 steps from D-glucose; 0.1% overall yield). Note that the cyclization yields obtained (41 and 28%) again were dependent on the configuration at the C_9 centre (cf. the 14-membered polyoxo-macrolides).

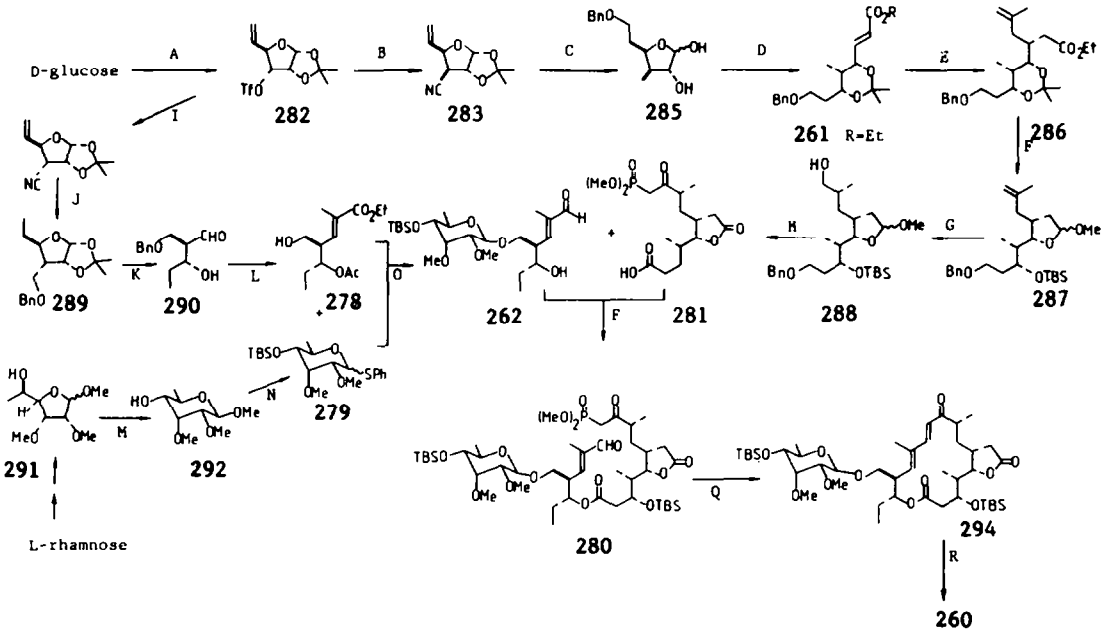
The glycosidation scheme employed was an extension of that used in the earlier synthesis of carbomycin B. Aglycone **259** was converted into the ethylene acetal **272**, which selectively gave the C_5 *β*-aminoglycoside **273** in 22% yield on treatment with the D-mycaminose derivative **274** and mercuric ion, followed by methanolysis. Note the greater reactivity of the C_5-hydroxyl group towards glycosidation compared to that at C_3, which was previously made use of in the Woodward erythromycin synthesis (Section 2.2.1.1). Selective acylation of the $C_{2'}$ hydroxyl group was followed by reaction with the glycal **275** in the presence of 1,3-dibromo-5,5-dimethylhydantoin to give the $C_{4'}$-*α*-glycoside **276** in 26% yield after deprotection and debromination. The third glycosidation was achieved

less selectively by reaction of **276** with the D-mycinose derivative **277**, in the presence of mercuric cyanide, to give a 22% yield of the major β-glycoside. Final deacetylation completed the total synthesis of tylosin (47 steps from D-glucose; < 0.01% overall yield).

2.3.2.2. *Nicolaou synthesis* (Scheme 23).[55] The most significant innovations in the Nicolaou synthesis of O-mycinosyltylonolide (**260**) from D-glucose and L-rhamnose are (i) the attachment of the β-D-mycinosyl group on to a C_{11}–C_{15} segment **278** in good yield (50%) using the phenylthioglycoside **279** and (ii) the remarkably efficient macrocyclization (80% yield) between C_{10} and C_{11} in **280** using an improved ketophosphonate Horner–Emmons reaction.

Both fragments **278** and **281** were prepared by manipulation of D-glucose using the common intermediate **282**, which can be converted kinetically into nitrile **283** and under thermodynamic control (longer reaction time) into the epimeric nitrile **284**. For the synthesis of the C_1–C_{10} fragment **281**, the nitrile group in **283** was first reduced to a methyl group then the vinyl substituent was hydroborated and the alcohol produced was converted into furanose **285**. Wittig homologation and acetonide formation then gave the key Michael acceptor **261**, which underwent conjugate addition with methallyl cuprate to give predominantly the required C_6-epimer **286** with 83% stereoselectivity. This was then converted into **287** in four steps, followed by hydroboration to give a mixture of primary alcohols in which the correct C_8-epimer **288** predominated (stereoselectivity unspecified), which was then further elaborated to the ketophosphonate **281**.

The synthesis of the C_{11}–C_{15} fragment **278** starts from the epimeric nitrile **284** in which the nitrile and vinyl substituents are first reduced to give **289** after benzylation. Acetonide hydrolysis, followed by reduction and periodate cleavage gave the β-hydroxyaldehyde **290**, which was converted into **278** by a Wittig reaction followed by adjustment of protecting groups. The D-mycinose derivative **279** was prepared from L-rhamnose, via furanoside **291**, by rearrangement to the pyranoside **292** followed by thioglycoside formation and silylation. Treatment of **278** with the thioglycoside **279** in the presence of NBS[11b] in acetonitrile gave a *ca* 2:3 mixture of α- and β-glycosides. The major β-glycoside, isolated in *ca* 50% yield, was then converted in two further steps into the complete C_{11}–C_{15} fragment **262**.

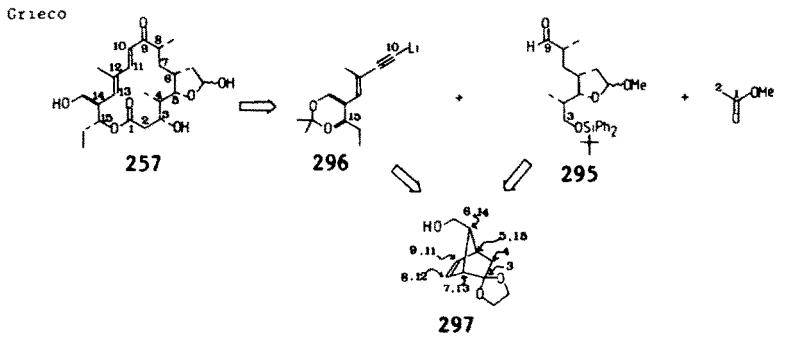


Nicolaou O-Mycinosyltylonolide Synthesis[55]: A (i) Me_2CO, H^+; (ii) RuO_2, $NaIO_4$; (iii) $NaBH_4$; (iv) BzCl, py; (v) H_3O^+; (vi) $(EtO)_3CH$, H^+; (vii) K_2CO_3, MeOH; (viii) $(CF_3SO_2)_2O$, py; B KCN; C (i) DIBAL; H_3O^+; (ii) LAH; (iii) MsCl, Et_3N; (iv) LAH; (v) Sia_2BH, ^-OOH; (vi) KH, BnBr; (vii) Amberlite IR-120; D (i) $Ph_3P{=}CHCO_2Et$; (ii) $(MeO)_2CMe_2$, CSA; E methallyllithium, CuI; F (i) $(HOCH_2)_2$, HCl; (ii) DIBAL; (iii) MeOH, HCl; (iv) TBSCl, imidazole; G BH_3-THF; HOO^-; H (i) PCC, NaOAc; (ii) $(MeO)_2P(O)CH_2Li$; (iii) PCC; (iv) H_2, Pd/C; (v) Jones; I KCN, 48 hrs; J (i) DIBAL; H_3O^+; (ii) LAH; (iii) H_2, Pd/C; (iv) KH, BnBr; K (i) Amberlite IR-120; (ii) $NaBH_4$; (iii) $NaIO_4$; L (i) $Ph_3P{=}CMeCO_2Et$; (ii) Ac_2O, DMAP, py; (iii) $PhSSiMe_3$, Bu^n_4NI, ZnI_2; M HCl, MeOH; N (i) $PhSSiMe_3$, TMSOTf; (ii) TBSCl, imidazole; O (i) NBS, MeCN; (ii) DIBAL; (iii) MnO_2; P DCC, DMAP; Q K_2CO_3, 18-crown-6; R (i) HF,py; (ii) DIBAL; (iii) DDQ.

Scheme 23.

Coupling of the fragments **281** and **262** by formation of an ester linkage gave the ketophosphonate aldehyde **280**, which on treatment with K_2CO_3/18-crown-6 under high-dilution conditions cyclized to the 16-membered lactone **294**. The high overall yield (70%) for the double-coupling sequence, **281** + **262** → **280** → **294**, is particularly impressive. To complete the synthesis of O-mycinosyl tylonolide, **294** was desilylated then selectively reduced (reduction of dienone and γ-lactone) and re-oxidized at C_9 (34 steps from D-glucose; 1.1% overall yield). Completion of the synthesis of tylosin from **294** awaits the development of a new glycosidation method for the introduction of the amino-disaccharide group.

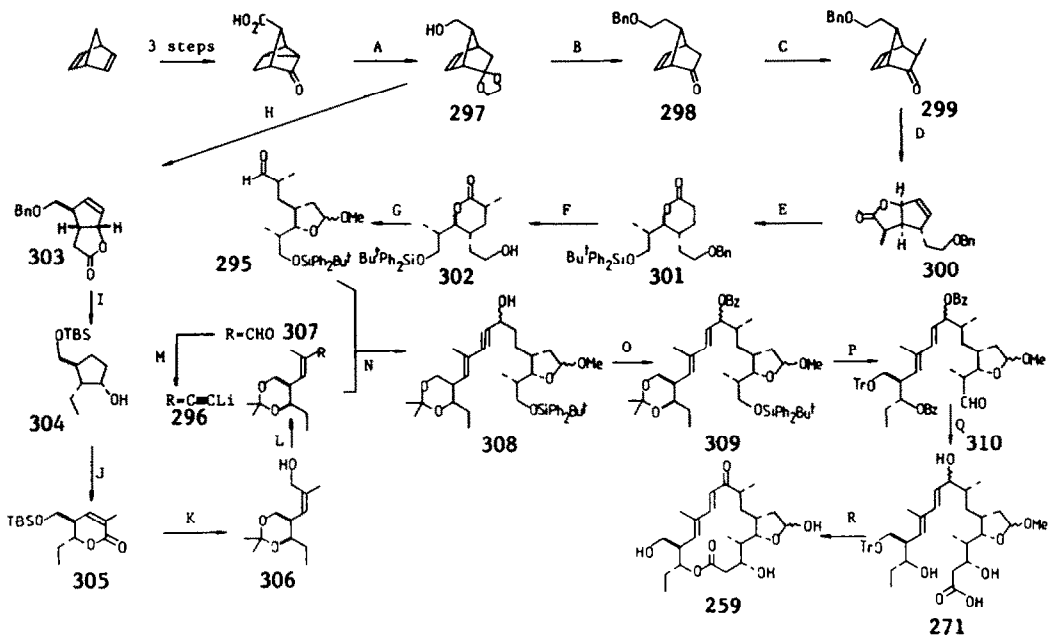
2.3.2.3. *Grieco synthesis* (Scheme 24).[56] The Grieco synthesis of tylonolide follows essentially the same ring-cleavage approach as was used in the earlier methynolide work (Section 2.1.1.3). A C_3–C_{15} carbon chain was constructed by coupling enantiomerically-correct C_3–C_9 and C_{10}–C_{15} fragments, **295** and **296**, respectively, followed by the introduction of C_1–C_2 by an aldol condensation with the enolate of methyl acetate. The two key fragments, **295** and **296**, were prepared by manipulation of the enantiomerically-correct bicyclo[2.2.1]heptenol **297** (available from norbornadiene with resolution of an intermediate), which already has embedded in its carbon skeleton the chiral centres for C_5, C_6, C_{14} and C_{15} of the target.



The synthesis of fragment **295** involved homologation of **297** followed by hydroxyl protection and acetal-hydrolysis to give the ketone **298**. Methylation of the derived lithium enolate occurred exclusively from the more accessible *exo*-face to set up the C_4-stereocentre in **299**. Baeyer–Villiger reaction followed by an acid-catalysed allylic rearrangement then gave γ-lactone **300**, which was converted in five steps to δ-lactone **301**. The C_8-centre was introduced without stereocontrol by methylation of the derived enolate of **301** (cf. C_6 of methynolide in the earlier work) followed by debenzylation to give **302** after isomer separation. Completion of the synthesis of **295** involved oxidation and ring-rearrangement followed by protection and net reduction to the C_9-aldehyde.

For the synthesis of fragment **296**, the common precursor **297** was first protected, hydrolyzed to the ketone, then exposed to Baeyer–Villiger oxidation and acid-catalysed allylic rearrangement to give the γ-lactone **303**. Reduction of the lactone and double bond, followed by net reduction of the primary hydroxyl and protecting group exchange gave cyclopentanol **304**, which was transformed into **305** in a five step sequence. Hydride reduction gave a triol, which was converted into the acetonide **306**, followed by inversion of the olefin geometry to give the *E*-enal **307** after oxidation. The lithium acetylide **296**, prepared in three steps from **307**, was then condensed with the aldehyde **295** to give a mixture of C_9-epimeric alcohols **308** (both epimers could be converted into tylonolide), which gave the *E*,*E*-diene **309** after reduction of the acetylene and benzoylation. Adjustment of protecting groups and oxidation of the C_3-hydroxyl then gave the aldehyde **310**, which was condensed with the lithium enolate of methyl acetate to give a 1:1 mixture of epimers, from which seco-acid **271** could be separated after debenzoylation.

Note that **271** corresponds exactly to the Tatsuta seco-acid intermediate (Section 2.3.2.1), such that a formal synthesis of tylosin itself has actually been achieved at this stage. The Grieco synthesis of tylonolide was completed using the same double-activation methodology for macrolactonization (19% yield), followed by selective oxidation and acid treatment (41 steps from norbornadiene; 0.07% overall yield).

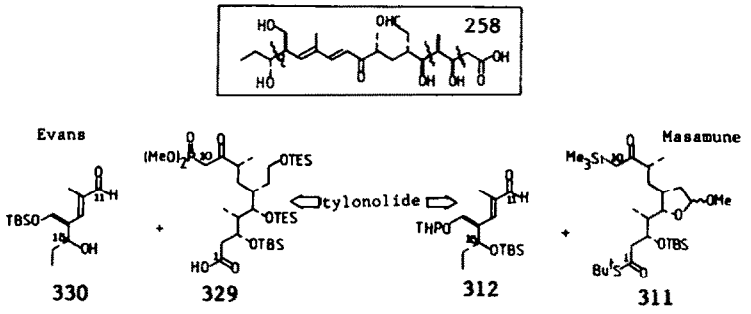


Grieco Tylonolide Synthesis[56]: A (i) AcOH, HBr; (ii) CH_2N_2; (iii) 2-ethyl-2-methyldioxalane, TsOH; (iv) LAH; (v) DBU; B (i) TsCl,py;(ii)NaC ;(iii) KOH; (iv) LAH; (v) NaH, BnCl; (vi) H_3O^+; C LDA; MeI; D (i) H_2O_2, NaOH; (ii) $BF_3.OEt_2$; E (i) LAH; (ii) $NaBH_4$, $NiCl_2$; (iii) Bu^tPh_2SiCl, DMAP, Et_3N; (iv) $CrO_3.2py$; (v) MCPBA; F (i) LDA; MeI; (ii) H_2Pd/C; G (i) $CrO_3.2py$; (ii) TsOH, MeOH; H (i) NaH, BnBr; (ii) H_3O^+ ; (iii) H_2O_2, NaOH; (iv) $BF_3.OEt_2$; I (i) LAH; (ii) $NaBH_4$, $NiCl_2$; (iii) PhSeCN, Ph_3P; (iv) Bu^n_3SnH, AIBN; (v) H_2, Pd/C; (vi) TBSCl, imidazole; J (i) $CrO_3.2py$; (ii) MCPBA; (iii) LDA; MeI; (iv) LDA; PhSeCl; (v) H_2O_2; K (i) $LiAlH(OMe)_3$; (ii) Me_2CO, $CuSO_4$, CSA; L (i) Bu^nLi; p-MeC_6H_4SCl; SiO_2; (ii) $CrO_3.py$; M (i) CBr_4, Ph_3P; (ii) Me_2CO, $CuSO_4$, CSA; N Bu^nLi; addition of aldehyde; O (i) LAH; (ii) BzCl, DMAP, py; P (i) MeOH, PPTS; (ii) TrCl, DMAP, Et_3N; (iii) BzCl, DMAP, py; (iv) TBAF; (v) $CrO_3.2py$; Q (i) CH_2=C(OLi)OMe; (ii) NaOMe; (iii) NaOH; R (i) 2,2'-dipyridyl disulphide, Ph_3P; (ii) PhMe, reflux; (iii) MnO_2; (iv) aq. AcOH.

Scheme 24.

2.3.2.4. *Masamune synthesis* (Scheme 25).[57] The Masamune synthesis of tylonolide features a chiral enolate aldol construction of most of the stereocentres (i.e. three key aldol bond disconnections in the seco-acid **258**), while C_8 is controlled by an asymmetric hydroboration reaction. The present synthesis uses the methodology previously applied to the synthesis of 6-deoxyerythronolide B (Section 2.2.1.4) and narbonolide (Section 2.2.2), supplemented by the introduction of two new chiral enolate reagents for controlling the 14,15-*anti*-stereochemistry and the C_3-configuration. The synthesis of the full carbon skeleton is based on the Peterson-type coupling of the enantiomerically-correct C_1–C_{10} and C_{11}–C_{15} fragments, **311** and **312**, respectively. Note that the coupling of a carbanion at C_{10} with a C_{11}-aldehyde is, with the exception of the Grieco synthesis, a common feature of all the tylonolide syntheses.

The synthesis of the C_1–C_{10} fragment **311** starts with the preparation of aldehyde **313** by alkylation

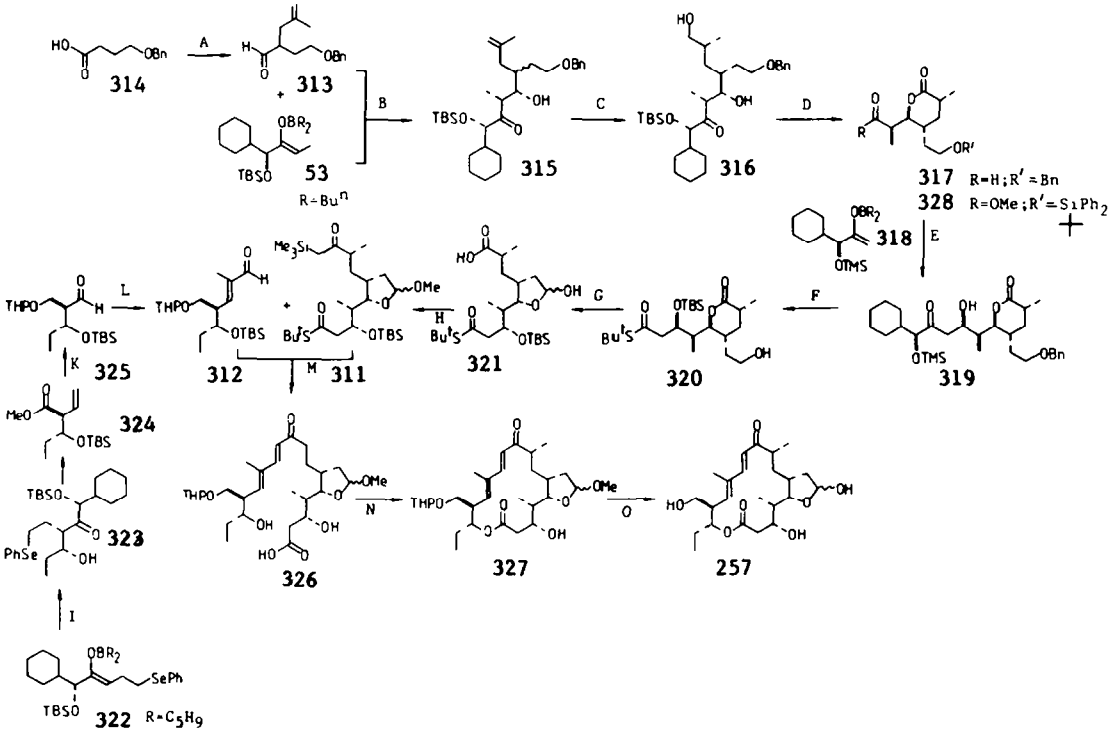


of the dianion derivative of acid **314**, followed by oxidation state adjustment. Aldol condensation of the *S*-chiral enolate **53** (R = Bu^n) with racemic **313** then gave a mixture of adducts **315**, epimeric at C_6, with control of the C_4 and C_5 chiral centres. The required 6*S*-diastereomer was separated, silylated and then

submitted to an asymmetric hydroboration reaction with (−)-bis(isopinocamphenyl)borane to give the primary alcohol **316**, after oxidative work-up, with better than 98% stereoselectivity at the new C_8-centre. This remarkable hydroboration result represents a marked improvement over the lower stereoselectivities achieved at C_8 using achiral boranes on similar substrates (cf. the Nicolaou, Grieco, and Evans syntheses). Selective deprotection and oxidation gave a δ-lactone, which was followed by three further steps to give aldehyde **317**. The second aldol condensation of the synthesis used the chiral acetate enolate **318**. Addition of **318** to **317** gave the required aldol product **319** with 80% stereoselectivity (cf. **310** → **271** in the Grieco synthesis). Chiral auxiliary removal, protecting group changes and thioester formation gave **320**, which on oxidation and acid-treatment gave γ-lactol **321**. Acetal-formation and conversion to the 2-pyridylthioester, followed by a cuprate reaction then gave **311**.

The C_{14} and C_{15} asymmetric carbons of fragment **312** were set up indirectly in a third aldol condensation. The phenylseleno-substituted *R*-chiral enolate **322** was added to propanal to give the 14,15-*syn*-adduct **323**, which was converted to the ester **324**. Reduction, protection and ozonolysis gave the required 14,15-*anti*-β-alkoxy aldehyde **325**, which was homologated to the C_{11}–C_{15} fragment **312**. Coupling of the two fragments, **311** and **312**, gave rise to the seco-acid **326** after hydrolysis and desilylation. Macrolactonization, **326** → **327**, by the phosphoric acid mixed-anhydride method occurred in 34% yield, and finally acid-treatment gave tylonolide (30 steps from **314**; 0.3% overall yield). This new macrolactonization procedure gave double the yield of that attained by the thioester protocol used in the earlier relay synthesis.[53]

An alternative ring-cleavage approach to the right-hand fragment of tylonolide, which was subsequently abandoned in favour of the acyclic approach detailed above, has been reported by Lu.[59] In this work, the racemic lactone **328** was prepared by an adaptation of the first Masamune synthesis of Prelog–Djerassi lactonic acid (Section 2.1.1.1).[12a]



Masamune Tylonolide Synthesis[57]: A (i) LDA; CH_2=$CMeCH_2Cl$; (ii) LAH; (iii) CrO_3.2py; B aldol; C (i) Et_3SiOTf, 2,6-lutidine; (ii) (-)-$(IPC)_2BH$; MCPBA; (iii) AcOH; D (i) Ag_2CO_3-celite; (ii) HF; (iii) H_3B-NH_3; (iv) $NaIO_4$; E aldol; F (i) TBAF; (ii) $NaIO_4$; (iii) H_2, Pd/C; (iv) TBSCl, imidazole, THF; (v) TBSCl, imidazole, DMF; (vi) Et_3N, MeOH; (vii) $ClCO_2Et$; $TlSBu^t$; (viii) AcOH; G (i) CrO_3.2py; (ii) AcOH; H (i) $(MeO)_3CH$, MeOH, TsOH; (ii) 2,2'-dipyridyl disulphide, Ph_3P; (iii) $(Me_3SiCH_2)_2CuLi$; I EtCHO; J (i) HF; (ii) O_3; py; (iii) $NaIO_4$; (iv) CH_2N_2; (v) TBSOTf, 2,6-lutidine; K (i) DIBAL; (ii) dihydropyran, PPTS; (iii) O_3; Me_2S; L (i) Ph_3P=$CMeCO_2Et$; (ii) DIBAL; (iii) CrO_3.2py; M (i) $LiN(SiMe_3)_2$; (ii) $Hg(CF_3CO_2)_2$, Na_2HPO_4; (iii) HF.py; N (i) $(PhO)_2POCl$; Et_3N; (ii) DMAP, 80°C; O aq. AcOH.

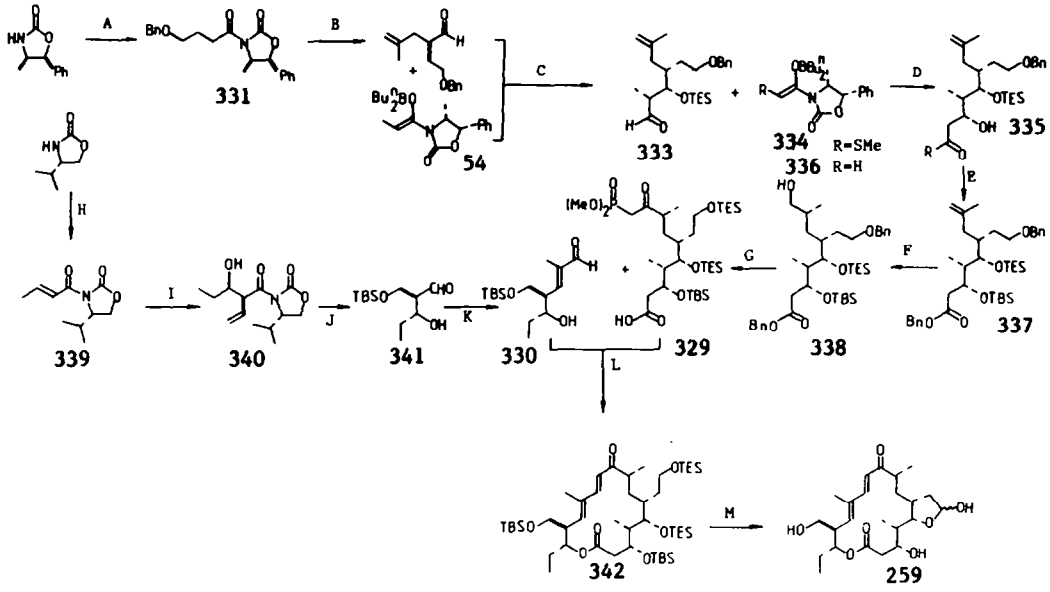
Scheme 25.

2.3.2.5. *Evans synthesis* (Scheme 26).[58] A conceptually similar aldol approach to the synthesis of tylonolide has been independently developed by Evans and co-workers, based on the chiral enolate methodology used in their earlier Prelog–Djerassi lactonic acid synthesis (Section 2.1.3). Again two new chiral enolate reagents were developed to control the stereochemistry at C_{14}, C_{15} and C_3. In contrast to the Masamune synthesis, the absolute configuration at C_6 was controlled by the enantioselective alkylation of a chiral enolate. The Nicolaou double-coupling procedure was used to form the 16-membered ring of tylonolide from the C_1–C_{10} and C_{11}–C_{15} fragments, **329** and **330**, respectively.

Alkylation of the lithium enolate derivative of the enantiomerically-pure imide **331** (available from norephedrine and 1,4-butanediol) gave 95% stereoselectivity at C_6. Conversion to the aldehyde **332** was followed by an aldol condensation with the chiral enolate **54** to give the corresponding adduct with 99% stereoselectivity. This was then elaborated to the new aldehyde **333**, which was condensed with the novel methylthio-substituted chiral enolate **334** to give the desired C_3-epimer **335** after desulfurization. Note that this chiral acetate equivalent gave superior control of the C_3 configuration compared to the earlier syntheses. In contrast, use of the unsubstituted enolate **336** gave only 75% stereoselectivity for the formation of **335** (cf. **317** + **318** → **319** in Scheme 25). Chiral auxiliary removal from **335**, followed by silylation gave **337**, which was hydroborated using thexylborane to give alcohol **338** with 82% stereoselectivity. This was then elaborated in three steps to the *β*-ketophosphonate **329**.

The left-hand C_{11}–C_{15} aldehyde **330**, which apart from differences in protecting groups (or glycosidation) is the same as fragments **262**, **263** and **312** used in earlier syntheses, was very efficiently prepared using the aldol reaction of crotonate imide **339** with propanal. This gave the adduct **340** with 98.6% stereoselectivity, which was then manipulated by reduction, protection and ozonolysis to give the required 14,15-*anti*-*β*-hydroxyaldehyde **341**.

Wittig homologation and subsequent adjustment of oxidation state at C_{11} then provided **330**. Double-coupling of the fragments **329** and **330** by first ester formation and then an intramolecular Horner–Emmons reaction gave the 16-membered lactone **342**. Finally, selective deprotection of the primary hydroxyl group followed by oxidation and complete desilylation gave tylonolide (26 steps from norephedrine; 2.3% overall yield).



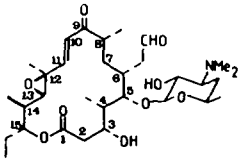
Evans Tylonolide Synthesis[58]: A Bu^nLi; $BnO(CH_2)_3CO_2COBu^t$; B (i) LDA; CH_2=CMeCH$_2$I; (ii) LAH; (iii) py.SO_3, DMSO, Et_3N; C (i) aldol; (ii) Et_3SiOTf, Et_3N; (iii) BnOLi; (iv) RED-Al; (v) py.SO_3, DMSO, Et_3N; D (i) aldol; (ii) Ra-Ni, E (i) BnOLi; (ii) TBSOTf, Et_3N; F thexylborane; ^-OOH; G (i) py.SO_3, DMSO, Et_3N; (ii) $(MeO)_2P(O)CH_2MgBr$; (iii) CrO_3.2py; (iv) H_2, Pd/C; (v) Et_3SiOTf, Et_3N; (vi) H_2O; H Bu^nLi; MeCH=CHCOCl; I Bu^n_2BOTf, Et_3N; EtCHO; J (i) Bu^n_2BOAc; $LiBH_4$; (ii) TBSCl, Et_3N; (iii) O_3; MeS; K (i) Ph_3P=CMeCO$_2$Et; (ii) DIBAL; (iii) MnO_2; L (i) DCC, DMAP; (ii) K_2CO_3, 18-crown-6; M (i) HCl; (ii) CrO_3.2py; (iii) HF.

Scheme 26.

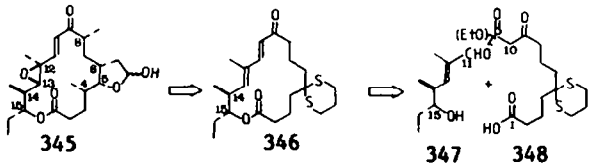
2.3.3. *Rosaramicin*

The 16-membered polyoxo-macrolide rosaramicin (**343**) apparently has superior antibiotic activity to erythromycin. Its aglycone rosaranolide (**344**) is structurally very similar to tylonolide, except that it has an epoxide at C_{12}–C_{13} and a simple methyl group at C_{14}. As an illustration of the potential effectiveness of macrocyclic stereocontrol in macrolide synthesis, Still and Novack[60] have recently completed a synthesis of racemic 3-deoxyrosaranolide (**345**). In this innovative approach, the conformational bias of the large ring provides a medium through which existing chiral centres control kinetically the stereochemical outcome of remote chemical reactions. In the synthesis of **345** the C_{14} and C_{15} centres present in the simple macrocycle **346** were used to efficiently control the configurations of the six new chiral centres spanning C_4–C_{13}.

Rosaramicin **343**

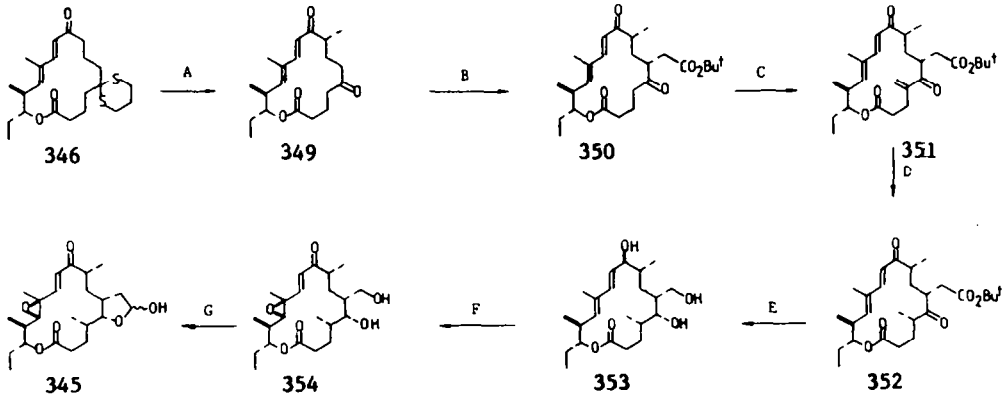


aglycone:
rosaranolide **344**



345 **346** **347** **348**

The 16-membered ring of the target structure was first prepared (Scheme 27) by the now standard Horner–Emmons procedure, **347** + **348** → **346**. Deprotonation of **346** gave an enolate at C_8, which was methylated with better than 95% stereoselectivity to give **349** after deprotection. Regio- and stereoselective introduction of a C_6 side-chain was then carried out by alkylation of the kinetically-generated lithium enolate of **349**. This gave **350** with better than 95% regioselectivity and 85% stereoselectivity. The methyl-bearing chiral centre at C_4 was then controlled by first hydroxymethylation of the C_4 lithium enolate of **350**, followed by elimination to the methylene ketone **351**. Conjugate addition of thiophenol and desulfurization with Raney nickel then gave the 4-methyl derivative **352** with better than 95% stereoselectivity. Note that direct methylation of the enolate of **350** gave the C_3-epimer of **352**. Ester-hydrolysis and $NaBH_4$ reduction of the derived mixed-anhydride then gave the required C_5-alcohol **353** with 83% stereoselectivity. Oxidation at C_9 and epoxidation then gave **354** with better than 93% selectivity, which on selective oxidation of the primary hydroxyl group gave 3-deoxyrosaranolide (16 steps from **347**; 0.9% overall yield).



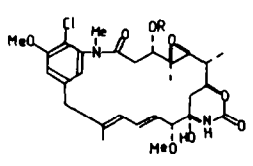
346 **349** **350** **351** **352** **353** **354** **345**

Still 3-deoxyrosaranolide Synthesis[60]: A (i) $KN(SiMe_3)_2$; MeI; (ii) HgO, HBF_4; B (i) $LiN(SiMe_3)_2$; $BrCH_2CO_2Bu^t$; C (i) $LiN(SiMe_3)_2$; HCHO; (ii) MsCl; (iii) base elimination; D (i) PhSH, Et_3N; (ii) Ra-Ni; E (i) TFA; (ii) $ClCO_2Et$, Et_3N; (iii) $NaBH_4$; F (i) MnO_2; (ii) MCPBA, Na_2CO_3; G $(Ph_3P)_3RuCl_2$.

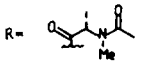
Scheme 27.

3. THE ANSAMYCINS

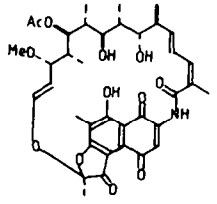
The ansamycins are a class of macrocyclic lactams characterized structurally by a polyketide-derived aliphatic (or ansa) chain linked to non-adjacent positions on an aromatic nucleus. In the rifamycin and streptovaricin series of antibiotics the ansa chain is connected to a naphthoquinone or naphthalene nucleus,[61,62] while in the maytansenoids[63] the aliphatic chain is joined to a benzene ring.



R=H Maytansinol



Maytansine



Rifamycin S

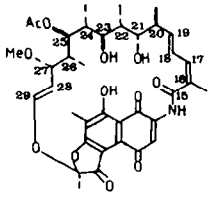
The problems associated with the total synthesis of these stereochemically complex macrocycles are very similar to that of the polyoxo-macrolides. Efficient methods for macrocyclization and stereochemical control are required, together with effective syntheses of the appropriate aromatic fragment. In the case of the maytansenoids, the 19-membered ring has been constructed by macrolactamization of an activated amino acid as well as by carbon–carbon bond formation. In the rifamycin S series, the construction of the 24-membered ring involves intermolecular enol ether formation followed by macrolactamization. Ring-cleavage, carbohydrate and acyclic approaches for stereochemical control all feature in the ansamycin syntheses so far accomplished. Note, however, that efforts to use macrocyclic stereocontrol in these larger rings have been very limited.

3.1. *Rifamycin S*

The first, and still only complete, synthesis of rifamycin S (**355**) was reported by Kishi and his co-workers in 1980.[64] Their approach involved disconnection at the carbon–heteroatom bonds to give an aromatic moiety and the ansa bridge, containing all eight asymmetric centres, which has on its own been the focus of considerable synthetic effort. Since the original racemic synthesis, Kishi has subsequently reported three new asymmetric syntheses of the ansa bridge.[65] Other syntheses of the rifamycin chiral sequence using various acyclic approaches have also been described by the groups of Masamune,[66] Still[67] and Corey;[68] while Hanessian,[69] Kinoshita,[70] and Fraser-Reid[71] and their respective co-workers have reported enantioselective approaches from carbohydrate precursors.

3.1.1. *Kishi synthesis of rifamycin S* (Scheme 28).[64] The Kishi synthesis (1980) of rifamycin S (**355**) is based on the C_{29}–O coupling of the ansa bridge derivative **356** with the aromatic derivative **357** followed by macrocyclization at C_{15}–N to give the 24-membered macrolide. Acyclic stereocontrol was used to set up the chiral sequence of the C_{15}–C_{29} aliphatic chain by a linear sequence of four separate two-carbon extensions starting from the aldehyde **359**. In the first route the Wittig reaction followed by

Kishi



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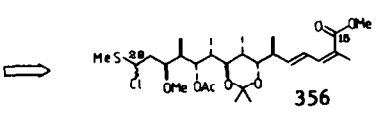

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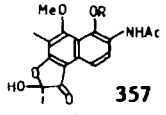

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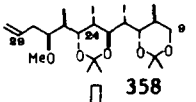

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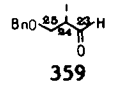


359

372

either hydroboration or epoxidation and then epoxide ring-opening was used to control the relative stereochemistry of the alternating methyl and hydroxyl groups in the growing carbon chain.[72]

The racemic aldehyde **359**, which became C_{23}–C_{25} in the final product, was first converted into the allylic alcohol **361**. The two faces of the double bond are highly differentiated by the bulky TMS group in the preferred conformation shown of **361** and epoxidation gave only one epoxide. The TMS group was removed with retention of stereochemistry and the epoxide opened, regio- and stereospecifically, with methyl cuprate to give the diol **362**, which was then chain-extended to give **363**. Hydroboration of **363** gave the tetraol monobenzyl ether **364** with 82% stereoselectivity, which was subsequently transformed into **366** by using essentially the same homologation and hydroboration sequence (82% stereoselectivity). Addition of diallylzinc to the aldehyde obtained by oxidation of **366** introduced the final C_{27} asymmetric centre with 82% stereoselectivity for the Cram-type adduct **367** (29 steps from **359**; 1.4% overall yield).

Following reorganization of the protecting groups in **367**, the C_{29} aldehyde was liberated and protected as the hemithioacetal **368**. The *E,Z*-diene system was introduced by two Wittig reactions. Oxidation of **368** to the aldehyde and reaction with $Ph_3P{=}CHCO_2Et$ gave the *E*-olefin, followed by further reduction and reoxidation to give the aldehyde **369**. The best selectivity for the second Wittig was obtained by using $(MeO)_2P(O)CH(Me)CN$, which gave the *Z*-olefin **371** with 91% stereoselectivity. The synthesis of the aromatic moiety began with 2-methyl-resorcinolmonomethyl ether (**372**), which was treated first with $Pb(OAc)_4$ and then with pentenyl magnesium bromide to give **373**. Oxidative cleavage of the olefin and then two sequential Friedel–Crafts reactions afforded **374**, which was converted to **375** in five steps. Protecting group manipulation, oxidation at C_{12} and further protections and deprotections gave **376** (R = *p*-$MeOC_6H_4CH_2$).

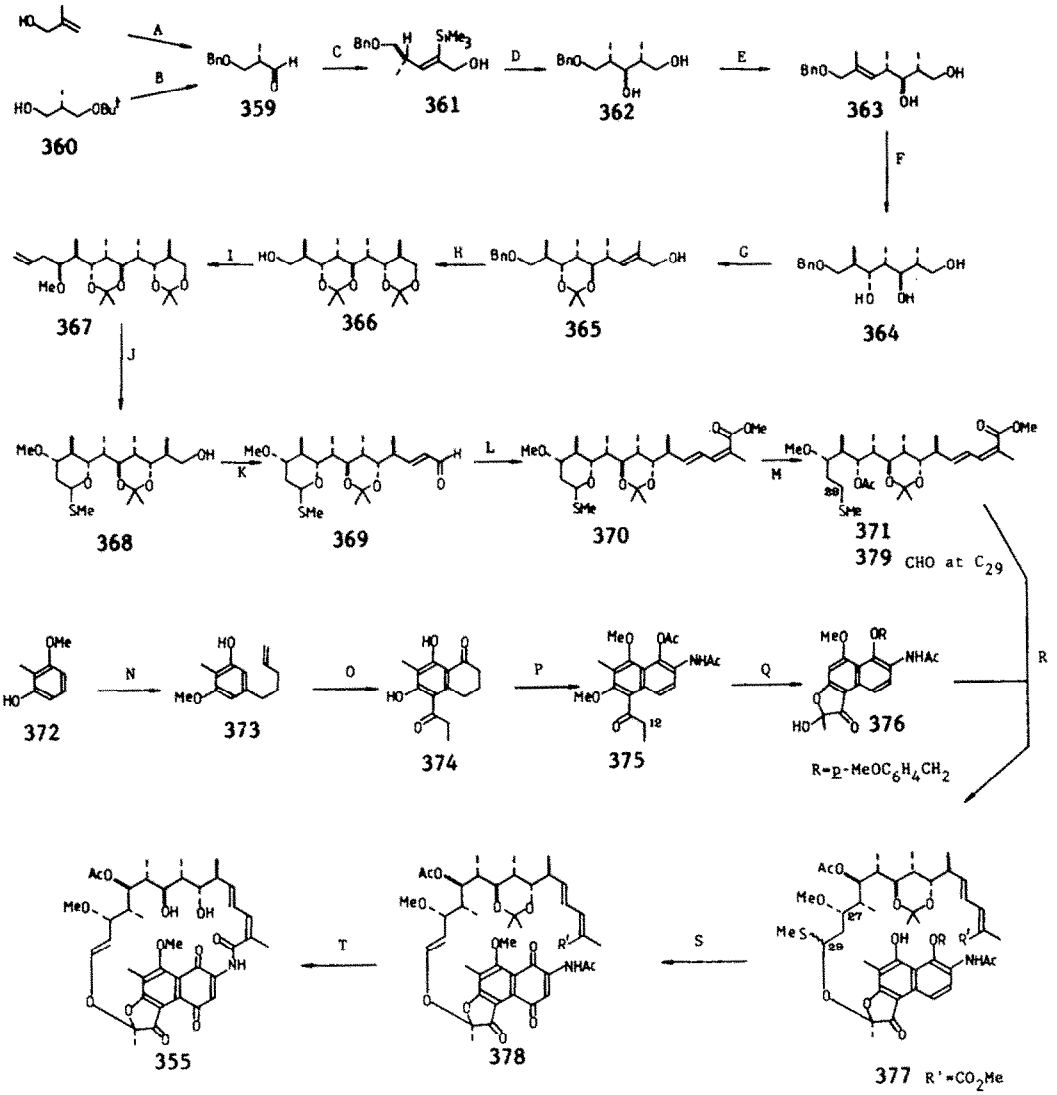
To couple the ansa bridge to the aromatic moiety, the racemic **371** was treated with NCS to give a diastereomeric mixture of α-chlorosulfides, which was then reacted with the racemic aromatic segment **376** (R = *p*-$MeOC_6H_4CH_2$). A mixture of four diastereomers with respect to C_{12}, C_{27} and C_{29} resulted from this displacement reaction (86% yield based on **376** or 31% yield based on **371**), from which the diastereomers **377** with the correct stereochemistry at C_{12} with respect to the ansa bridge were separated. Sulphoxide elimination and oxidation to the quinone gave a 1 : 1 mixture of **378** and its C_{28}–C_{29} double bond isomer. The correct isomer was isolated and taken through to racemic rifamycin S by macrocyclization of the appropriately activated amino acid (62 steps from **359**; < 0.01% overall yield). Note that the critical cyclization step only occurred after conversion of the quinone system to the aminohydroquinone form.

Ansa Bridge Syntheses

3.1.2. *Kishi syntheses* (Schemes 28 and 29).[65] Since their original total synthesis, Kishi and his coworkers have reported three further syntheses of the ansa chain in enantiomerically-correct form. In the first of these new syntheses, optically-pure β-benzyloxyisobutyraldehyde (**359**) was converted to the enantiomerically-correct aliphatic fragment **379** using the previously established route (Scheme 28).

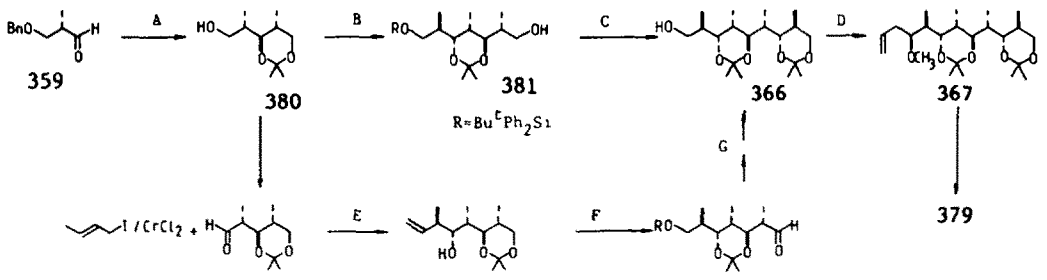
In the second synthesis, greater overall stereoselectivity was achieved mainly due to the use of a sequence of three Sharpless asymmetric epoxidation reactions[73] for controlling the six asymmetric centres at C_{20}–C_{23}, C_{25} and C_{26}. The stereoselectivity at C_{27} was also now substantially improved by using an allyltin(II) reagent instead of the allylzinc reagent. The optically active aldehyde **359** (Scheme 29) was homologated by a Wittig reaction and the product reduced to the *E*-allylic alcohol. Sharpless epoxidation using (+)-diethyl tartrate gave the *anti*-epoxide with 95% stereoselectivity, which was then regioselectively opened to give **380** after some protecting group manipulation. The process of homologation, reduction, epoxidation and epoxide ring-opening was essentially repeated two further times to give **366**. Both the asymmetric epoxidations gave 20 : 1 stereoselectivity. Swern oxidation of **366** to the corresponding aldehyde and addition of diallyltin gave **367** after methylation with 95% stereoselectivity. This unusually high Cram-type stereoselectivity was explained by invoking a chelated *trans*-decalin-like transition state. The olefin **367** was then taken on to **379** as before; the overall yield for this second enantioselective sequence was 2.1% for the 45 steps from **359**.

In the final and most efficient route (Scheme 29), the construction of the C_{19}–C_{27} fragment was further simplified by conducting two of the two-carbon chain-extensions with a crotylchromium reagent.[74] This served to set up correctly the two new asymmetric centres at the same time as chain-extension (cf. aldol approaches).



Kishi Rifamycin S Synthesis[64]: A (i) KH, BnBr; (ii) B_2H_6;HOO^-; (iii) $(COCl)_2$, DMSO; Et_3N; B (i) NaH, BnBr; (ii) TFA; (iii) $(COCl)_2$, DMSO; Et_3N; C (i) CBr_4, PPh_3; (ii) Bu^nLi; Me_3SiCl; (iii) DIBAL; I_2; (iv) Bu^nLi; $ClCO_2Me$; (v) DIBAL; D (i) MCPBA; (ii) Bu^n_4NF; (ii) Me_2CuLi; E (i) Me_2CO, CSA; (ii) Li/NH_3; (iii) $(COCl)_2$, DMSO; Et_3N; (iv) $Ph_3P{=}C(Me)CO_2Et$; (v) LAH; (vi) KH, BnBr; (vii) H_3O^+; F B_2H_6; HOO^-; G (i) Me_3CCOCl, py; (ii) Me_2CO, CSA; (iii) LAH; (iv) $(COCl)_2$, DMSO; Et_3N; (v) $Ph_3P{=}C(Me)CO_2Et$; (vi) LAH; H (i) H_3O^+; (ii) B_2H_6; HOO^-; (iii) 2,2-dimethoxypropane, CSA; (iv) Li/NH_3; I (i) $(COCl)_2$DMSO; Et_3N; (ii) $(CH_2{=}CHCH_2)_2Zn$; (iii) KH, MeI; J (i) H_3O^+; (ii) Me_3CCOCl, py; (iii) OsO_4, KIO_4; (iv) MeSH, $BF_3.OEt_2$; (v) 2,2-dimethoxypropane, CSA; (vi) LAH; K (i) PDC; (ii) $Ph_3P{=}CHCO_2Et$; (iii) DIBAL; (iv) PDC; L (i) $(MeO)_2P(O)CH(Me)CN$, $KOBu^t$; (ii) DIBAL; (iii) NaCN, MnO_2, AcOH; M (i) $HgCl_2$, $CaCO_3$; (ii) $NaBH_4$; (iii) TBSCl, imidazole; (iv) Ac_2O, py; (v) Bu^n_4NF; (vi) MsCl, Et_3N; (vii) MeSNa (for 371); or (vi) $(COCl)_2$, DMSO; Et_3N (for 379); N (i) $Pb(OAc)_4$, AcOH; (ii) $CH_2{=}CH(CH_2)_3MgBr$; O (i) OsO_4, $NaIO_4$; (ii) Jones; (iii) AcCl, $AlCl_3$; (iv) pyridinium hydrochloride; (v) $EtCO_2H$, BF_3; P (i) K_2CO_3, MeI; (ii) SeO_2, AcOH; (iii) $NH_2OH.HCl$; (iv) H_2, Pd/C; (v) AcCl, Et_3N; Q (i) BCl_3; (ii) AcCl, Et_3N; (iii) SeO_2; Na_2CO_3; (iv) p-$MeOC_6H_4CH_2Br$, Pr^i_2NEt; R (i) NCS on 371 (ii) addition of 376, K_2CO_3; (iii) separation of isomers; S (i) MCPBA; (ii) 2,2-dimethoxypropane, CSA; (iii) Pr^i_2NH, 160°C; (iv) Fremy's salt, buffer; (v) separate isomers; T (i) MgI_2; (ii) sodium ascorbate; NaOH; $K_3Fe(CN)_6$; (iii) NaOH; (iv) $ClCO_2Et$, Et_3N; (v) H_2, Lindlar; (vi) THF,50°C, $K_3Fe(CN)_6$; (vii) aq. HCl.

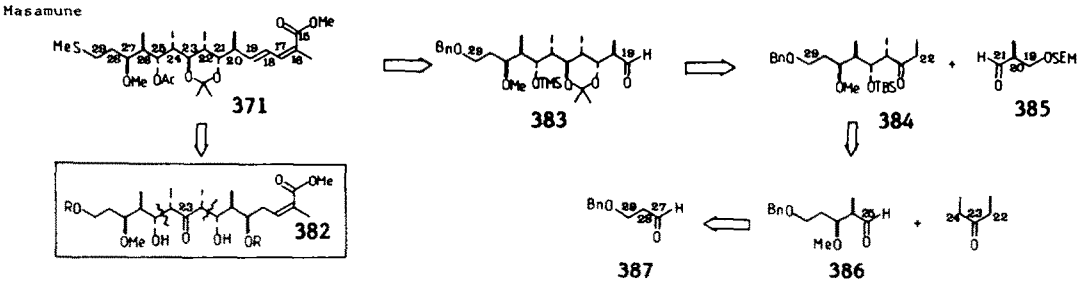
Scheme 28.



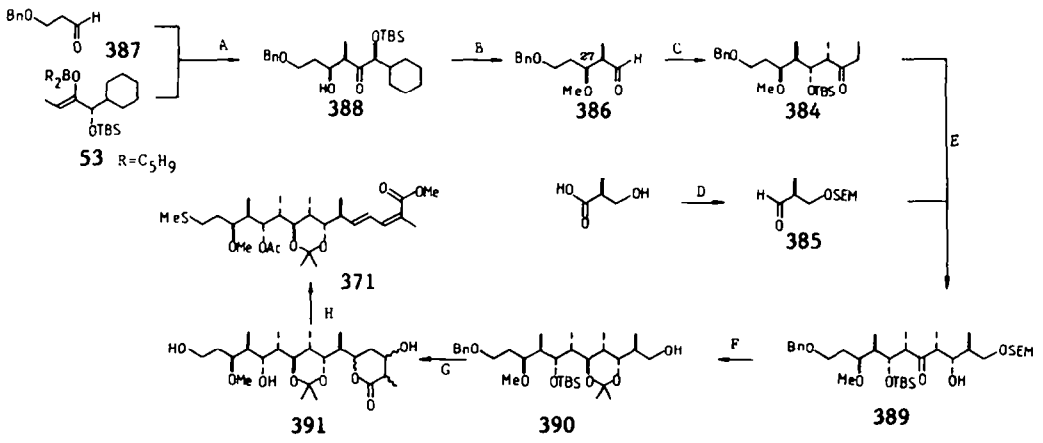
Kishi Ansa Bridge Synthesis[65]: A (i) $(Pr^iO)_2P(O)CH_2CO_2Et$, $KOBu^t$; (ii) DIBAL; (iii) (+)-diethyl tartrate, $Ti(OPr^i)_4$, Bu^tOOH; (iv) Me_2CuLi; (v) Me_2CO, CSA; (vi) Li/NH_3; B (i) $(COCl)_2$, DMSO; Et_3N; (ii) $(Pr^iO)_2P(O)CH_2CO_2Et$, $KOBu^t$; (iii) DIBAL; (iv) (+)-diethyl tartrate, $Ti(OPr^i)_4$, Bu^tOOH; (v) Me_2CuLi; (vi) Bu^tPh_2SiCl, imidazole; (vii) AcOH; (viii) Me_3COCl, py; (ix) 2,2-dimethoxypropane, CSA; (x) LAH; C (i) $(COCl)_2$, DMSO; Et_3N; (ii) $(Pr^iO)_2P(O)CH_2CO_2Et$, $KOBu^t$; (iii) DIBAL; (vi) (-)-diethyl tartrate, $Ti(OPr^i)_4$, Bu^tOOH; (v) Me_2CuLi; (vi) 2,2-dimethoxypropane, CSA; (vii) Bu^n_4NOH D (i) $(COCl)_2$, DMSO; Et_3N; (ii) $CH_2=CHCH_2I$, $SnCl_2$; (iii) KH, MeI; E addition; F (i) O_3; Me_2S; (ii) $NaBH_4$; (iii) Bu^tPh_2SiCl, imidazole; (iv) aq. AcOH; (v) Me_3CCOCl, py; (vi) 2,2-dimethoxypropane, CSA; (vii) LAH; (viii) $(COCl)_2$, DMSO; Et_3N; G (i) $MeCH=CHCH_2I/CrCl_2$; (ii) O_3; Me_2S; (iii) $NaBH_4$; (iv) 2,2-dimethoxypropane, CSA; (v) Bu^n_4NF.

Scheme 29.

3.1.3. *Masamune synthesis* (Scheme 30).[66] Masamune's asymmetric synthesis (1982) of the complete C_{15}–C_{29} chain **371** is highly convergent and significantly shorter than the Kishi synthesis. It cleverly exploits the symmetry within the ansa bridge (i.e. oxidation at C_{23} and hydration at C_{18}–C_{19} gives the C_{18}–C_{28} chain a centre of symmetry at C_{23}, cf. **382**). Masamune and his co-workers rapidly assembled seven of the eight asymmetric centres by four directed aldol condensation reactions; the eighth centre, C_{23}, was controlled by a stereoselective reduction.



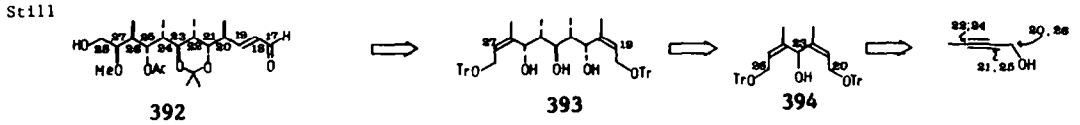
Aldol condensation of the aldehyde **387** with the *S*-chiral boron enolate **53** gave the adduct **388** with 99% stereoselectivity using the methodology successfully applied earlier to the synthesis of 6-deoxyerythronolide B. Removal of the chiral auxiliary from the aldol product, methylation and oxidation afforded **386**. A second aldol between **386** and the *Z*-enolate of 3-pentanone[75] gave **384** after silylation. The stereoselectivity for this second aldol was an impressive 20:1 due to the chelating effect of the β-methoxy group at C_{27}. The *Z*-enolate of **384** then underwent a zirconium-mediated aldol condensation[76] with **385** to give **389** with 89% stereoselectivity (note that with Li or Mg the stereoselectivity is reduced). DIBAL reduction of the C_{23}-carbonyl group in **389** then gave the remaining chiral centre with 16:1 stereoselectivity (α-induction in the Cram acyclic model) and manipulation of the protecting groups gave **390**. The final aldol condensation between the dianion from benzyl-2-methylacetoacetate and the aldehyde derived from oxidation of **390** gave an adduct which was converted to **391**. The lactones **391** were efficiently transformed into the Kishi intermediate **371** (24 steps from **387**; 17% overall yield).



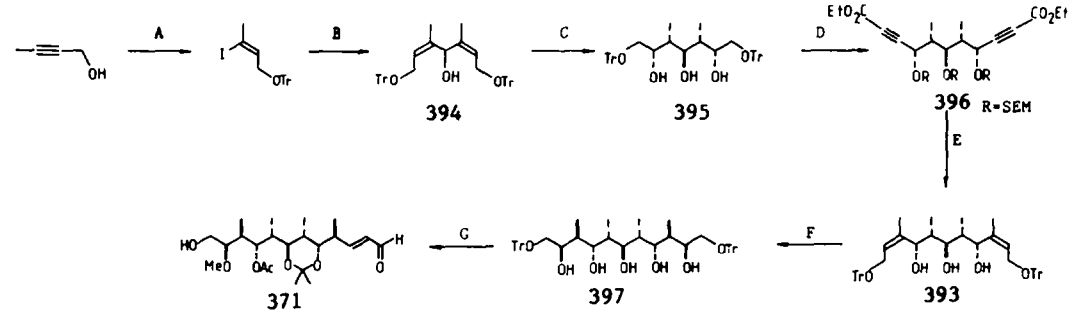
Masamune Ansa Bridge Synthesis[66]: A aldol; B (i) HF; (ii) $NaIO_4$; (iii) CH_2N_2, HBF_4; (iv) LAH; (v) PCC; C (i) Et_2CO, $(Me_2PhSi)_2NLi$; (ii) TBSOTf, 2,6-lutidine; D (i) SEMCl; (ii) LAH; (iii) $CrO_3.2py$; E $(Me_2PhSi)_2NLi$; Cp_2ZrCl_2; 385; F (i) DIBAL; (ii) 2,2-dimethoxypropane, CSA; (iii) Bu^n_4NF; (iv) Me_3SiCl, imidazole; G (i) $CrO_3.2py$; (ii) $CH_3COCH(Me)CO_2Bn$, LDA; iii) $NaBH_4$; (iv) H_2, Pd/C; (v) $PhCH_3$, reflux; H (i) TFAA, Et_3N; (ii) hydrolysis; (iii) TsCl, py; (iv) MeSNa; (v) CH_2N_2; (vi) Ac_2O, py.

Scheme 30.

3.1.4. *Still synthesis* (Scheme 31).[67] Still and Barrish (1983) have exploited the symmetry of the ansa chain by setting up the *anti*-1,3-diol relative stereochemistry by the stereoselective hydroboration of secondary allylic alcohols. In this simple linear approach a prochiral centre at C_{23} is used to set up a chain of five, and then nine, asymmetric centres, which is then converted into the racemic C_{17}–C_{28} segment, **392**.



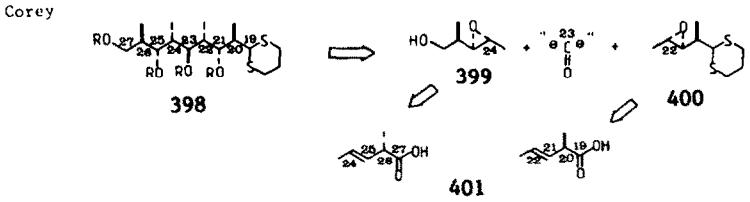
The 1,4-diene **394**, which was prepared from 2-butynol in three steps, was reacted first with thexylborane and then borane itself to give a 5 : 1 ratio of *meso*- and *dl*-triols. The major *meso*-isomer **395** was then converted to **396** in nine steps, followed by manipulation of the oxidation state and protecting groups to give **393**. Hydroboration as before gave **397** with 80% stereoselectivity. The *meso*-product **397** was finally taken through to the C_{17}–C_{28} segment **371** in ten steps (26 steps from 2-butynol; 0.8% overall yield).



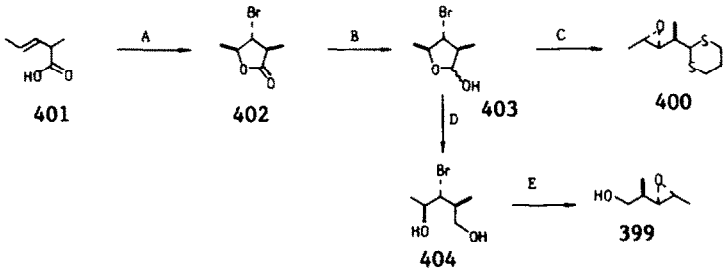
Still Ansa Bridge Synthesis[67]: A (i) LAH, NaOMe; I_2; (ii) TrCl; B Bu^tLi; HCO_2Et; C thexylborane; BH_3; HOO^-; D (i) $Me_3Si(CH_2)_2OCH_2Cl$, Pr^i_2NEt; (ii) H_2, Pd/C; (iii) $(COCl)_2$, DMSO; Et_3N; (iv) CBr_4, Ph_3P; (v) Bu^nLi; $ClCO_2Et$; E (i) Me_2CuLi; (ii) LAH; (iii) TrCl, Et_3N, DMAP; (iv) Bu^n_4NF; F thexylborane; BH_3; HOO^-; G (i) MeI, Ag_2O; (ii) H_2, Pd/C; (iii) ten further steps.

Scheme 31.

3.1.5. *Corey approach* (Scheme 32).[68,77,78] Corey and his co-workers recognized that except for terminal group differentiation the chiral centres of the ansa chain fragment **398** are antipodal around



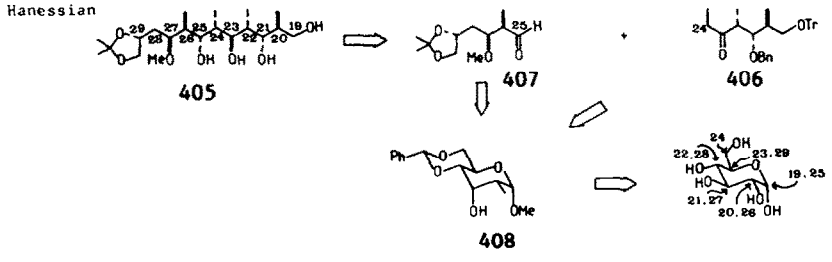
the central C_{23} atom. In this acyclic approach,[68] the acid **401** was halolactonized to give **402** thereby setting up two new vicinal stereocentres. Reduction to the lactol **403** was followed by conversion to the dithiane and then epoxide formation to give racemic **400**. Further reduction of **403** with $LiBH_4$ gave the diol **404**, which was taken through to racemic **399**. Fragments related to **399** and **400** have been joined using deprotonated acetonitrile as the C_{23} nucleophilic carbonyl equivalent, although no details are available. Note that these fragments are also available in enantiomerically-correct form.[68] Corey has also developed a method for the preparation of the *E,Z*-diene unit for C_{15}–C_{18} in the aliphatic chain,[77] although this has only been described for model systems. Finally, the macrolactam ring has been closed on a relay substrate[78] under very similar conditions to those used by Kishi.[64b]



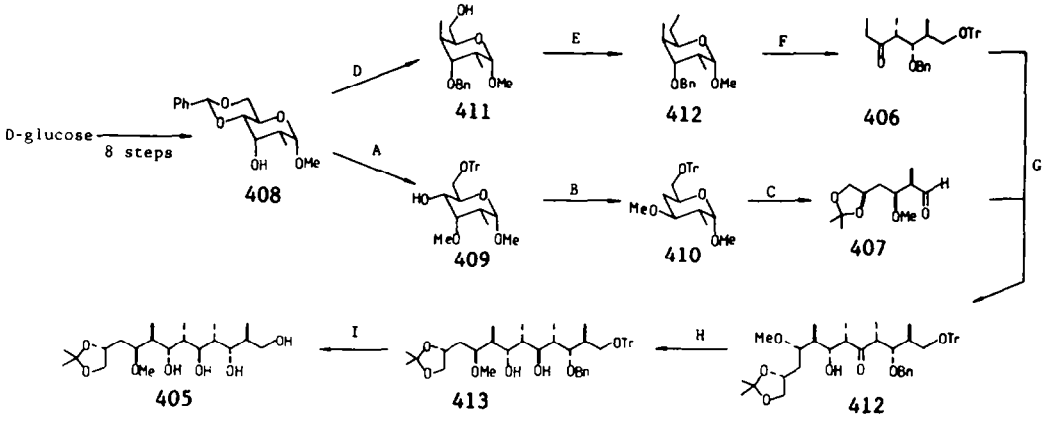
Corey Ansa Bridge Approach[68]: A (i) Thallium salt formation; (ii) Br_2; B DIBAL; C (i) $HS(CH_2)_3SH$, $BF_3.OEt_2$; (ii) $KOBu^t$; D $LiBH_4$; E $KOBu^t$.

Scheme 32.

3.1.6. *Hanessian synthesis* (Scheme 33).[69] Hanessian's carbohydrate approach (1982) to the construction of the C_{19}–C_{29} aliphatic chain **405** is based on the coupling of enantiomerically pure C_{19}–C_{24} and C_{25}–C_{29} fragments, **406** and **407**, respectively, which are derived from the common intermediate **408** used in the earlier erythronolide work (cf. Section 2.2.1.4).[29]



The pyranoside **408** was first converted to **409** followed by inversion at C_3 and a deoxygenation at C_4 (C_{27} and C_{28} in rifamycin, respectively). This first transformation was achieved by an oxidation/epimerization sequence on **409** to set up the C_{27}-centre, followed by reduction of the



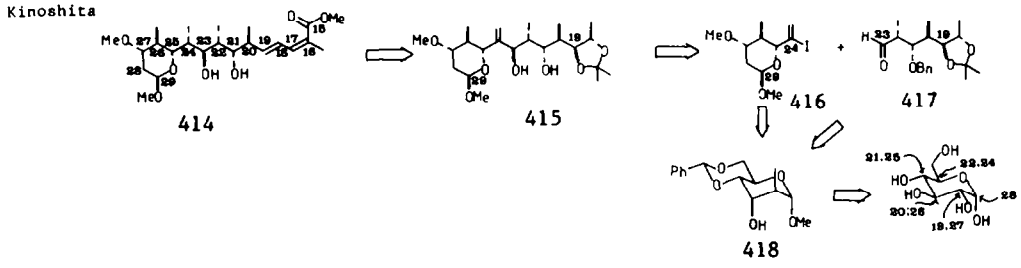
Hanessian Ansa Bridge Synthesis[69]: A (i) NaH, MeI; (ii) H_2, $Pd(OH)_2/C$; (iii) TrCl, py; B (i) $Me_2N(CH_2)_3N{=}C{=}NEt$, HCl, DMSO; (ii) NaOMe; (iii) $NaBH_4$; (iv) SO_2Cl_2, py; (v) Bu^n_3SnH, AIBN; C (i) aq. AcOH; (ii) $NaBH_4$; (iii) 2,2-dimethoxypropane, TsOH; (iv) PCC; D (i) Ac_2O, DMAP; (ii) aq. AcOH; (iii) Bu^tPh_2SiCl, py; (iv) $(COCl)_2$, DMSO; Et_3N; (v) $Ph_3P{=}CH_2$; (vi) KCN, MeOH; (vii) H_2, $Pd(OH)_2/C$; (viii) KH, BnBr; (ix) Bu^n_4NF; E (i) $(COCl)_2$, DMSO; Et_3N; (ii) $Ph_3P{=}CH_2$; (iii) H_2, Rh/Al_2O_3; F (i) aq. AcOH; (ii) $NaBH_4$; (iii) TrCl, py; (iv) PCC; G LDA; 407; H DIBAL; I (i) H_2, Pd/C; (ii) aq. AcOH.

Scheme 33.

adjacent carbonyl group to a methylene to give **410**. Hydrolytic ring-opening of **410** and further functional group manipulation then gave the aldehyde **407**, which has the C_{26} and C_{27} asymmetric centres of the target molecule. Reorganization of the protecting groups in **408**, oxidation of the C_4 hydroxyl group, olefination and hydrogenation afforded **411** with 80% stereoselectivity. The two methyl-bearing centres at C_2 and C_4 (glycoside numbering) become C_{20} and C_{22} in the final product. Conversion of the hydroxymethyl group in **411** to the ethyl group of **412** was followed by pyranoside ring-opening to give ketone **406**, after reorganization of the protecting groups.

The two fragments were coupled by a directed aldol condensation between the lithium enolate of **406** with **407** to give the desired adduct **412** as the major isomer with 70% stereoselectivity. The C_{23} ketone of **412** was reduced using DIBAL with greater than 91% stereoselectivity to give **413** followed by deprotection to give the C_{19}–C_{29} segment **405** (28 steps from D-glucose; 7.5% overall yield from **408**). Note that an aldol coupling at C_{24}–C_{25} and a later reduction are also features of the Masamune route (Section 3.1.3), which proceeds however with higher stereoselectivity.

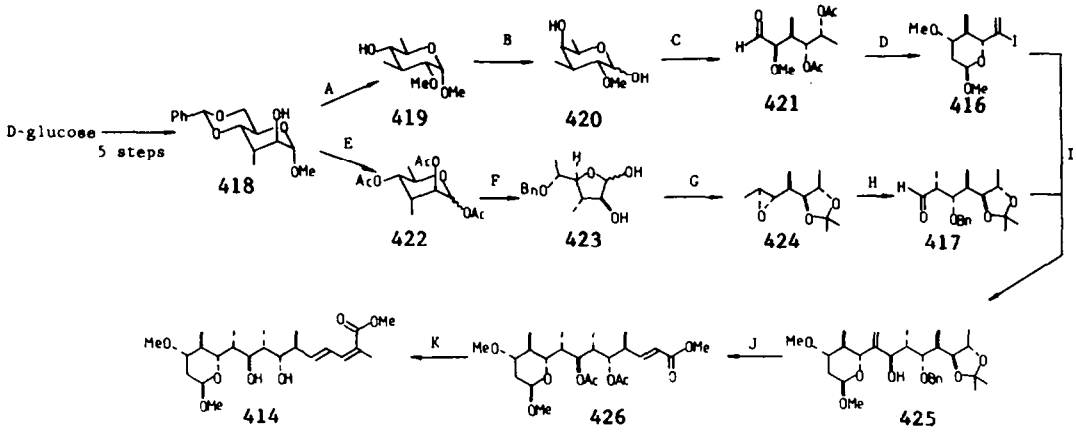
3.1.7. *Kinoshita synthesis* (Scheme 34).[70] This carbohydrate approach (1981) differs from that used by Hanessian[69] in that disconnection of the ansa chain segment **415** is now at C_{23}–C_{24} to leave **416** and **417** as the two fragments, which are derived from the epimeric pyranoside **418** (cf. **408**). Note that the fates of the specific glucose carbon atoms in the two routes are totally different.



For the C_{24}–C_{29} fragment **416**, the stereochemistries at C_2 and C_3 in **418** were inverted by an oxidation/epimerization/reduction sequence, followed by methylation and deoxygenation at C_5 to give **419**. A second inversion, this time at C_4, by an S_N2 displacement and hydrolysis gave **420**, which was converted to the aldehyde **421**. Homologation of **421** by a Wittig reaction introduced the final

carbon (C_{29} in the final product), followed by functional group manipulation to give iodide **416**. In the synthesis of the C_{19}–C_{23} fragment **417** deoxygenation of C_6 in **418** gave **422** as an anomeric mixture. Ring contraction afforded furanose **423** and subsequent treatment with excess MeMgI gave a 6.5 : 1 mixture favouring the desired triol, which was then converted into the epoxide **424**. Addition of dithiane anion to C_{22} introduced the final carbon atom with 75% regioselectivity, which was followed by reorganization of the protecting groups to give the aldehyde **417**.

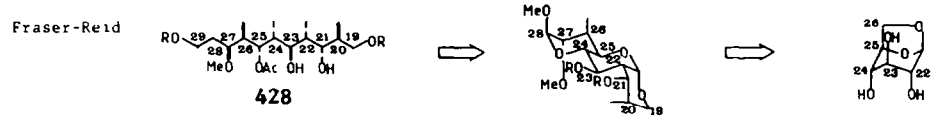
The fragments were coupled by metallation of **416** to give the vinyllithium derivative, followed by addition to **417** to give a 1 : 1.9 ratio of stereoisomers at C_{23}, where the desired isomer **425** was the minor product. Debenzylation and reduction of the olefin in **425** introduced the C_{24} methyl with 94% stereoselectivity, followed by periodate cleavage of the vicinal diol and a Wittig reaction to give **426**. The unsaturated ester **426** was next converted to the corresponding C_{17} ylid in five steps and condensed with methyl pyruvate to give a 1 : 1.25 mixture of geometric isomers with the desired *E,Z*-isomer **414** as the minor component (38 steps from D-glucose; < 0.01% overall yield).



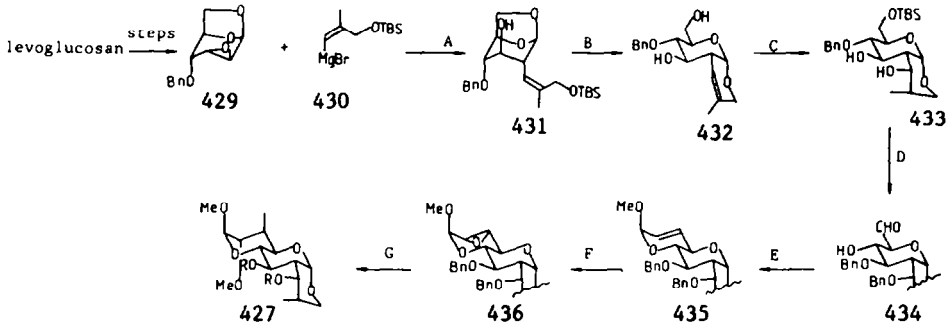
Kinoshita Ansa Bridge Synthesis[70]: A (i) DCC, DMSO, TFAA, py; (ii) Et_3N; (iii) LAH; (iv) NaH; MeI; (v) LAH; B (i) MsCl, py (ii) $PhCO_2Na$; (iii) Ac_2O, H_2SO_4; (iv) NaOH; C (i) $(HSCH_2)_2$, HCl; (ii) Ac_2O, DMAP; (iii) $HgCl_2$, HgO; D (i) Ph_3P=CHOMe; (ii) NBS, MeOH, $NaHCO_3$; (iii) Bu^n_3SnH, AIBN; (iv) NaOH (v) H^+, MeOH; (vi) Jones; (vii) NH_2NH_2, Et_3N; (viii) I_2; Et_3N; E (i) NBS; (ii) LAH; (ii) Ac_2O, H_2SO_4; F (i) NaOH; (ii) Me_2CO, $FeCl_3$; (iii) NaH, BnBr; (iv) AcOH; G (i) MeMgI; (ii) 2,2-dimethoxypropane, TsOH; (iii) Ac_2O, DMAP; (iv) H_2, Pd; (v) MsCl, py; (vi) NaOMe; H (i) 2-lithio-1,3-dithiane; (ii) NaH, BnBr; (iii) $HgCl_2$, HgO; I (i) Bu^nLi then add 417; J (i) H_2, Pd; (ii) H_2, $(Ph_3P)_3RhCl$; (iii) Ac_2O, DMAP; (iv) CHF_2CO_2H; (v) $NaIO_4$; (vi) Ph_3P=$CHCO_2Me$; K (i) DIBAL; (ii) 2,2-dimethoxypropane, TsOH; (iii) MsCl, Et_3N, LiBr; (iv) Ph_3P; (v) Bu^nLi; $MeCOCO_2Me$; (vi) CHF_2CO_2H.

Scheme 34.

3.1.8. *Fraser-Reid approach* (Scheme 35).[71] Since most synthetically useful monosaccharides have only five or six carbons, two or more subunits have to be combined in carbohydrate approaches to the synthesis of stereochemically-complex targets like the macrolide antibiotics. For example, the two approaches just described have both coupled two glucose-derived units to form the ansa bridge of rifamycin. In the case of such molecules containing contiguous chiral centres, however, the coupling reaction may give as many as four diastereomers when acyclic stereocontrol is poor. This can, therefore, detract from any stereochemical advantage gained by using carbohydrate precursors in a convergent synthesis. Fraser-Reid and his co-workers[71] have described one potential solution to this problem based on a novel ring-cleavage approach. In this approach, the anomeric carbon of levoglucosan is intended as a latent methyl group at C_{22} and other "satellite" pyranosides are attached to give **427**, which should generate the C_{19}–C_{28} chain of rifamycin on ring-opening.



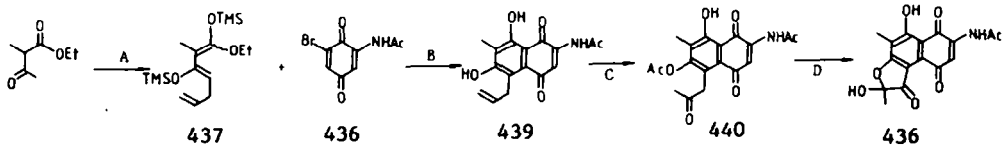
The epoxide **429** was ring-opened with the Grignard reagent **430** to give adduct **431**, which was solvolysed to give mainly the α-anomer **432** with 80% stereoselectivity. Hydroboration and epimerization then gave the C_{21}–OH compound **433**, which was converted to the aldehyde **434**. Elaboration of the "upper satellite" was achieved by homologation of **434** with a Wittig reagent to give a 4:1 mixture of olefins, both of which on acid treatment cyclized to **435**. Epoxidation of **435** with aqueous NBS followed by base-treatment, and subsequent ring-opening with Me_2Mg then gave **427** after methylation. The tricyclic structure **427** still lacks the necessary C_{24} methyl group. However, if it can be successfully ring-opened and this final methyl group introduced, it will give an acyclic segment containing all the eight asymmetric centres of the rifamycin S aliphatic bridge.



Fraser-Reid Ansa Bridge Approach[71]: A epoxide-opening; B HCl; C (i) TBSCl, DMAP, Et_3N; (ii) BH_3.THF; HOO^-; (iii) PCC; (iv) LAH; D (i) H_2, Pd, TFA; (ii) $(MeO)_2CMe_2$, PPTS; (iii) MeOH, PPTS; (iv) NaH, BnBr, Bu^n_4NI; (v) MeOH, PPTS; (vi) PhSMe, NCS, Et_3N; E (i) $\ce{O=C(O)CHCH=PPh3}$; (ii) MeOH, PPTS; F (i) NBS, H_2O; (ii) NaH; G (i) MeLi, MeMgCl; (ii) NaH, MeI.

Scheme 35.

3.1.9. *Aromatic moiety of rifamycin S.* In addition to the Kishi synthesis[644] of the aromatic fragment of rifamycin S, two other groups have described work in this area. Parker and Petraitis[79] have reported the synthesis of a model compound, while Kelly[80] has prepared the intact chromophore **436** (Scheme 36). In this latter work, the diene **437** reacted regiospecifically with **438** to give an adduct, which was transformed directly into **439**. Acetylation and oxidation gave **440**, which on a second oxidation with SeO_2 and hydrolysis afforded the desired compound **436** in eight steps and 37% overall yield based on the dienophile.

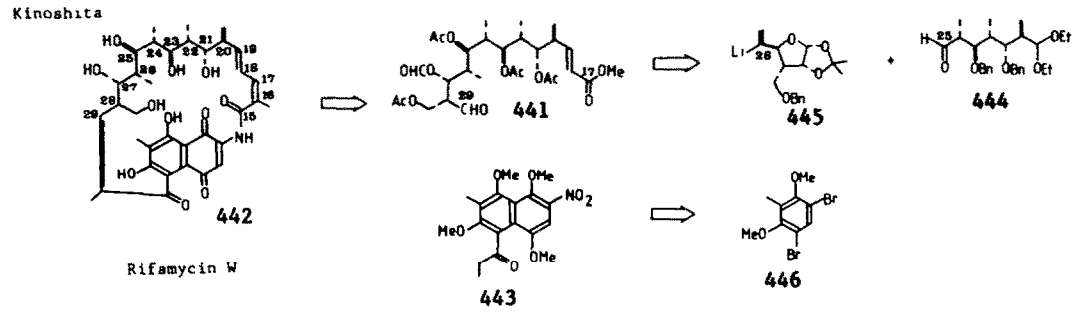


Kelly Aromatic Moiety Synthesis[80]: A (i) NaH; Bu^nLi; CH_2=$CHCH_2Br$; (ii) LDA; Me_3SiCl; B (i) 437 + 438; (ii) HCl; C (i) Ac_2O, py; (ii) $PdCl_2$, H_2O; D (i) SeO_2; (ii) Na_2CO_3, MeOH.

Scheme 36.

3.2. *Rifamycin W*

In addition to the synthesis of the ansa chain of rifamycin S, Kinoshita and his co-workers have reported the enantioselective preparation of the ansa bridge segment **441** of rifamycin W (**442**),[81a] the progenitor of all the rifamycins. They have also described the preparation of the aromatic moiety **443** of rifamycin W and have carried out an aldol coupling reaction between the two pieces.[81b] Only the final steps of the total synthesis now need to be completed. The ansa bridge synthesis is based on the combination of the C_{19}–C_{25} fragment **444** with the C_{26}–C_{29} fragment **445**, both of which are derived from D-glucose.



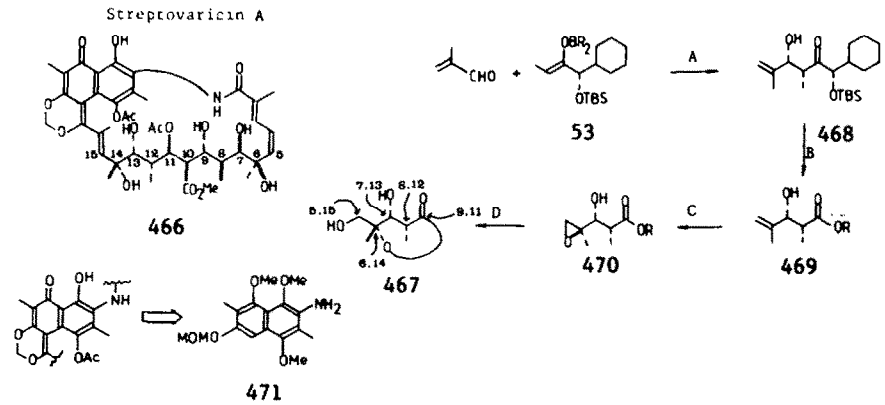
The pyranoside **418** (see Section 3.1.7) was first converted to **447**, which was then taken on to lactol **448** in five steps (Scheme 37). Treatment with MeMgI gave **449** as the major chelation-controlled adduct with 95% stereoselectivity, after protection as the acetonide. Conversion of **449** to the mesylate **450** was followed by intramolecular epoxide formation to give **451**. Epoxide ring-opening with 1,3-dithiane anion gave only adduct **452**. Note that the regiochemical control in this *cis*-epoxide ring-opening was better than that using the corresponding *trans*-isomer. Protection and dithioacetal hydrolysis gave the aldehyde **453**, which was followed by addition of the vinyllithium **454** to give the Cram addition product **455** with 60% stereoselectivity. Desilylation and homogeneous hydrogenation using $(Ph_3P)_3RhCl$ then gave **456** as the sole product, which was converted through to **444** after a periodate cleavage step.

The C_{26}–C_{29} fragment **445** was prepared from the D-glucose-derived compound **457** in eight steps. The condensation of **444** with **445** afforded a 4:1 ratio of adducts in 80% yield, where the major C_{25}-epimer **458** was the desired Cram-adduct. The epimeric mixture was hydrogenated and debenzylated to afford **459** as the major product. Acetylation and selective hydrolysis of **459** followed by a Wittig condensation of the derived aldehyde then gave **460**. Final deacetonation and periodate cleavage of **460** then gave the C_{29} aldehyde **441** (48 steps from D-glucose; < 0.01% overall yield).

For the synthesis of the aromatic piece, the pentasubstituted benzene **446** was converted to the benzyne in the presence of furan to give the cycloadduct **461**, which was transformed to **462** in two steps. Ring-opening gave the naphthol **463**, followed by oxidation with NBS to give the bromonaphthoquinone **464**, which was further converted into **443**. Addition of **441** to the tin(II) enolate of **443** then gave the aldol product **465** as a mixture of diastereomers in 87% yield.

3.3. *Streptovaricins*

In an approach to the ansa portion of the ansamycin streptovaricin A (**466**), McCarthy (1982)[82] recognized that the C_5–C_9 unit was repeated as the C_{15}–C_{11} unit. Using an aldol construction McCarthy has accomplished a synthesis of the γ-lactone **467**, which is equivalent to the C_5–C_9 unit and can potentially be used twice in the ansa chain synthesis.

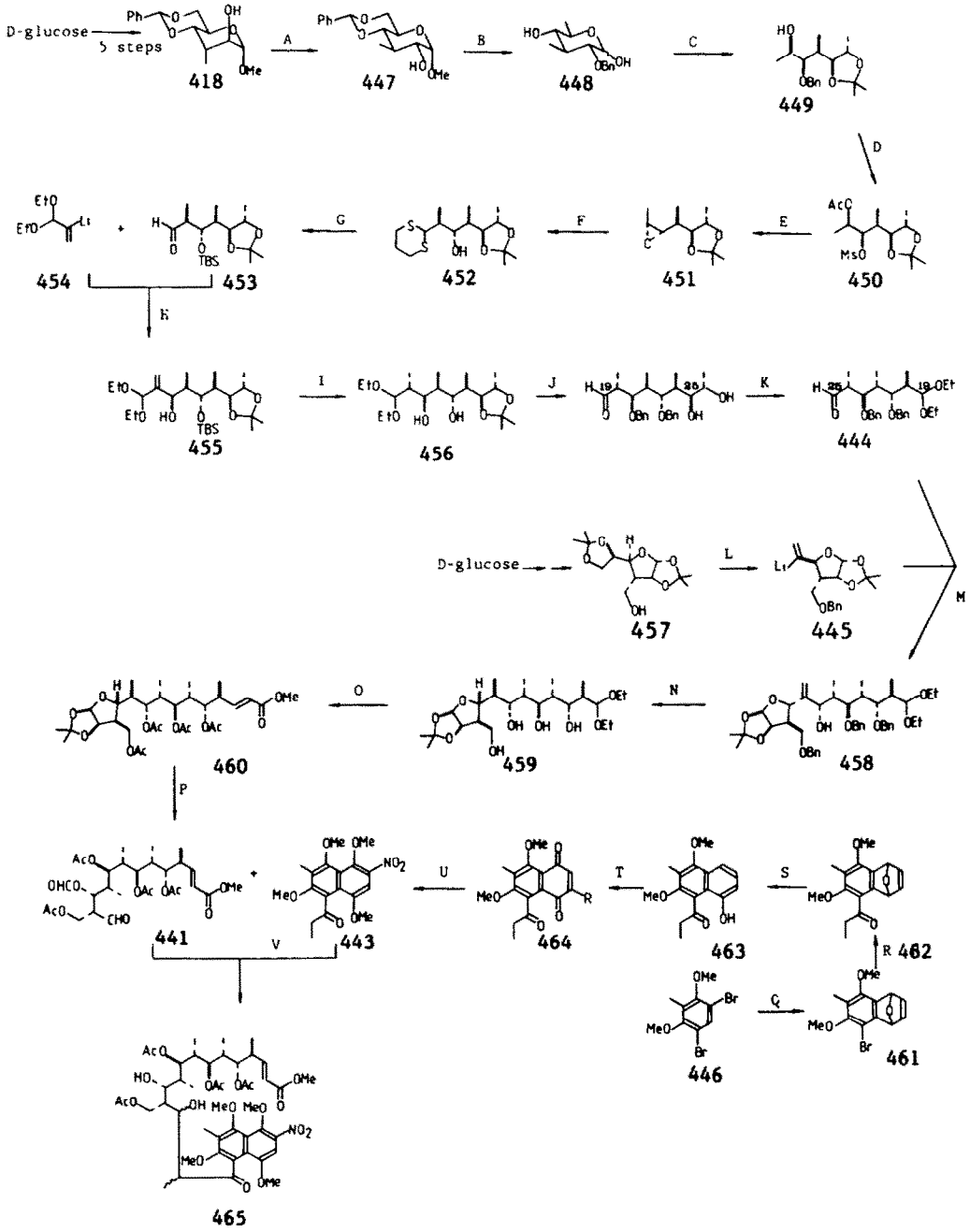


McCarthy Streptovaricin A Approach[82]: A aldol, R=Bu^n; B (i) HF; (ii) $NaIO_4$; (iii) Bu^{t}Ph$_2$SiCl, imidazole; C $VO(OEt)_3$, Bu^{t}OOH, NaOAc; D HF.

Scheme 38.

Aldol condensation of the Masamune *S*-chiral boron enolate **53** with methacrolein gave adduct **468** with 28 : 1 stereoselectivity, which was then converted to **469** (Scheme 38). Stereospecific epoxidation then gave **470**, which was taken on to **467** by an intramolecular epoxide ring-opening reaction (six steps from methacrolein; 57% overall yield).

Trost and Pearson[83] have described a synthesis of **471**, the naphthalene core of stretovaricin D, based on the use of a Diels–Alder reaction to form the carbon skeleton.

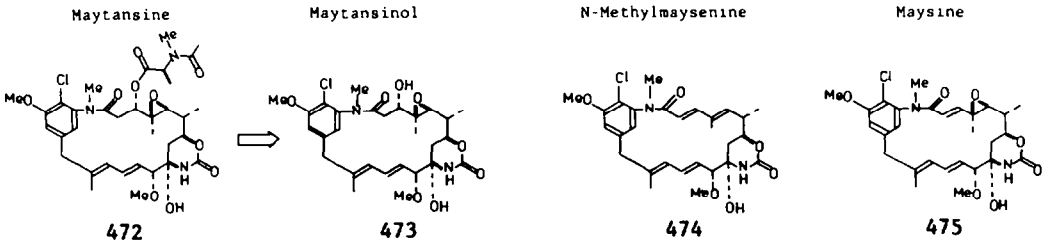


Kinoshita Rifamycin W Approach[81]: A (i) DCC, DMSO, TFA, py; (ii) Et_3N; (iii) LAH; B (i) NaH, BnBr; (ii) HCl; (iii) MsCl, py; (iv) LAH; (v) Ac_2O, H_2SO_4; (vi) NaOH; C (i) MeMgI; (ii) 2,2-dimethoxypropane, Me_2CO, H_2SO_4; D (i) Ac_2O, DMAP; (ii) H_2, Pd; (iii) MsCl, py; E NaOMe; F 2-lithio-1,3-dithiane; G (i) TBSCl, imidazole; (ii) HgO, $HgCl_2$; H addition of 454 to 453; I (i) Bu^n_4NF; (ii) H_2, $(Ph_3P)_3RhCl$; J (i) NaH, BnBr; (ii) $Cl_2CHCOOH$; K (i) TsOH, EtOH; (ii) $NaIO_4$; L (i) NaH, BnBr; (ii) AcOH; (iii) TsCl, py; (iv) LAH; (v) PCC; (vi) Et_3N, $NH_2.NH_2.H_2O$, I_2; (vii) Bu^nLi; M addition; N (i) H_2, $(Ph_3P)_3RhCl$; (ii) Li, NH_3; O (i) Ac_2O, DMAP; (ii) Cl_2CHCO_2H; (iii) $Ph_3P{=}CHCO_2Me$; P (i) TFA; (ii) $NaIO_4$; Q $NaNH_2$; furan; R (i) Bu^nLi; EtCHO; (ii) Jones; S $HClO_4$; T NBS, AcOH; U (i) H_2, Pd/C; (ii) Me_2SO_4, K_2CO_3; (iii) Zn, NaOH; (iv) $Cu(NO_3)_2$, Ac_2O; V (i) (i) $Sn(OTf)_2$, 1-ethylpiperidine; 441.

Scheme 37.

3.4. *Maytansenoids*

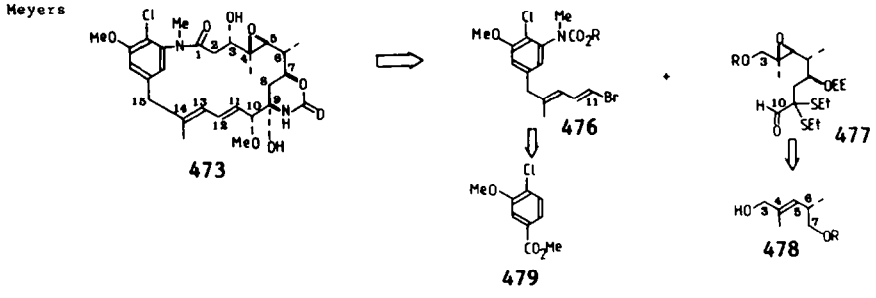
Since 1979 the total synthesis of various members of the maytansenoids, **472–475**, have been reported by the groups of Corey, Meyers and Isobe. In 1980 Corey's group completed the total synthesis of(−)-maytansine (**472**), the key member of this unique and rare class of ansamycin antitumor agents. Meyers and Isobe, and their respective co-workers, have also accomplished formal syntheses of **472** by independently preparing its precursor, maytansinol (**473**).



472 **473** **474** **475**

The Corey and Isobe syntheses are all based on the macrocyclization of an aromatic amine with an activated carboxylic acid at C_1, while that of Meyers interestingly relies on a macrocyclic ring closure between C_1 and C_2. The seven asymmetric centres spanning C_3–C_{10} of the ansa bridge in **473** are controlled to varying extents in the different syntheses, where absolute stereocontrol usually relies on the incorporation of carbohydrate precursors. Note that the C_9 centre, part of the cyclic urethane of the maytansenoids, is epimerizable and adopts the natural configuration. However, control of the effectively remote C_{10} chiral centre is more problematical.

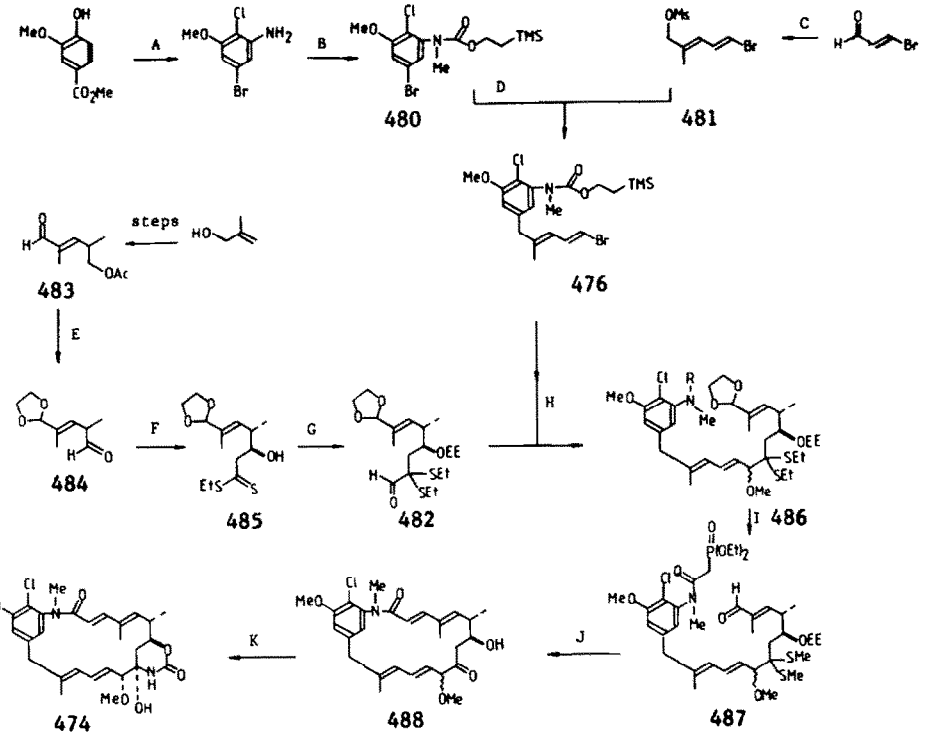
3.4.1. *Meyers synthesis* (Schemes 39 and 40).[84–87] Meyers' approach which is essentially the same for N-methylmaysenine (1979),[84] maysine (1979, 1983)[85] and maytansinol (1980)[86] is based on the coupling of a common C_{11}–N organolithium, prepared from **476**, to the appropriate C_3–C_{10} fragment. Introduction of C_1 and C_2 then gives the full carbon skeleton. The common C_3–C_{10} fragment **477**, containing the C_4–C_7 chiral sequence, is used in both the maytansinol and maysine syntheses and is available in enantiomerically-correct form starting from non-racemic **478**. Note that the C_{10} stereocentre (obtained on coupling) was not controlled in any of the Meyers syntheses; however the critical C_3 centre of **473** was correctly set up in the last step by a stereoselective reduction of the corresponding C_3 ketone.



473 **476** **477** **478** **479**

The key aromatic diene **476** was prepared from the bromide **480** by metallation and formation of a mixed cuprate followed by coupling with the mesylate **481** (Scheme 39). For the synthesis of racemic N-methylmaysenine (**474**),[84] the preparation of the key C_3–C_{10} fragment **482** began with the unsaturated aldehyde **483** (prepared in seven steps from methallyl alcohol), which firstly was converted to **484**. Lithioethyldithioacetate addition to **484** gave the Cram-adduct **485** with 82% stereoselectivity. Protection and reaction with EtMgI then gave an acyl anion equivalent which, on treatment with 2-(N-methyl-N-formyl)-aminopyridine, gave **482**. For the key coupling reaction, metallation of **476** and addition to **482** gave the adduct **486** after methylation as a 1 : 1 epimeric mixture at C_{10}, which lacked only the C_1–C_2 unit to complete the carbon skeleton. Deprotection of **486** gave the corresponding secondary amine, which was transformed to the phosphonate **487** by acylation and acetal-hydrolysis. An intramolecular Horner–Emmons reaction gave the 19-membered lactam **488** after removal of the

protecting groups (74% for the macrocyclization). Finally, cyclic urethane formation via the mixed carbonate and separation of the C_{10}-epimers gave (±)-N-methylmaysenine (16 steps from **483**; 3.6% overall yield).



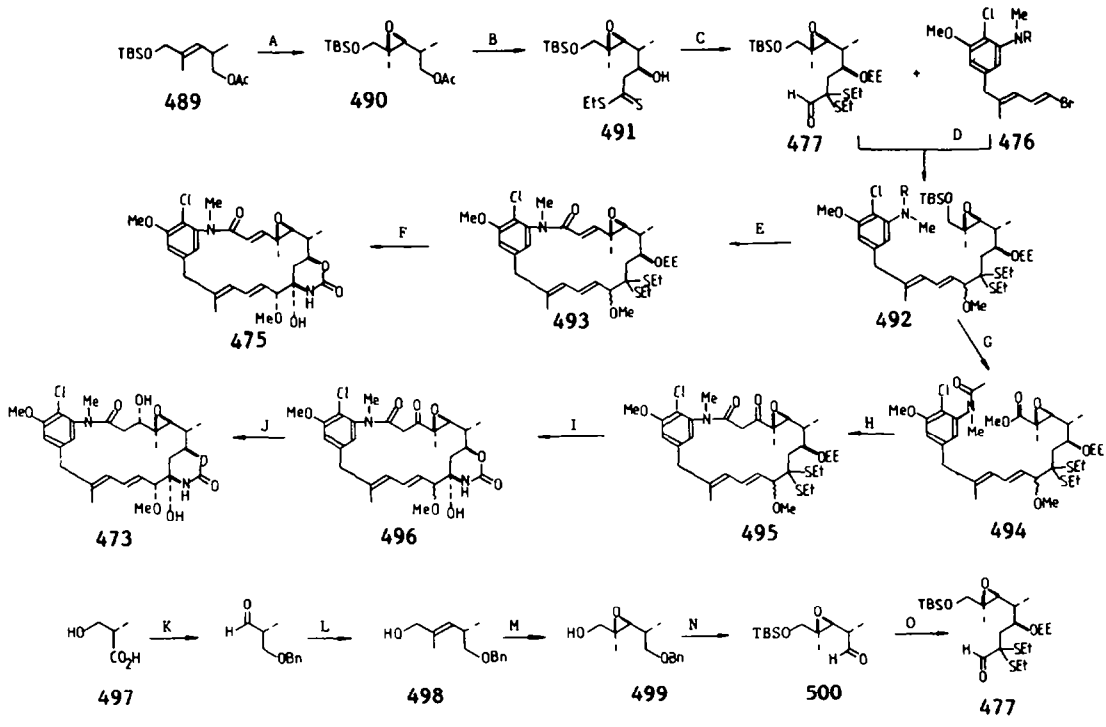
Meyers (±)-N-methylmaysenine Synthesis[84]: A (i) AcOH, HNO_3; (ii) $SOCl_2$; (iii) KOH; (iv) HgO, Br_2; (v) $SnCl_2$, AcOH; B (i) PhOCOCl, py; (ii) $HOCH_2CH_2SiMe_3$, $KOBu^t$; (iii) Bu^tOK, MeI; C (i) $(EtO)_2P(O)CH(Me)CO_2Et$, Bu^tOK; (ii) DIBAL; (iii) MsCl, Et_3N; D (i) Bu^nLi; $C_3H_7C\equiv CCu.((Me_2N)_3P)_2$; 481; E (i) 1,2-ethanediol, PPTs; (ii) K_2CO_3, MeOH; (iii) CrO_3.2py; F $EtSC(CH_2)SLi$; AcOH; G (i) $EtOCH{=}CH_2$, TsOH; (ii) EtMgI; 2-(N-methyl-N-formyl)aminopyridine; H (i) Bu^tLi; 482; (ii) Bu^tOK, MeI; (iii) Bu^n_4NF; I (i) $(EtO)_2P(O)CH_2COCl$, py; (ii) $(CO_2H)_2$; J (i) Bu^tOK; (ii) $HgCl_2$, $CaCO_3$; (iii) HCl; K (i) PhOCOCl, py; (ii) NH_3; (iii) separate C_{10} isomers.

Scheme 39.

For the synthesis of racemic maysine (**475**)[85a] (Scheme 40), the starting enal **483** was first converted to **489**, followed by epoxidation with MCPBA to give the epoxyacetate **490** together with an equal amount of the isomeric α-epoxide. Acetate cleavage followed by oxidation and addition of lithioethyldithioacetate now gave the correct C_7-epimer **491** with 75% stereoselectivity. With the four contiguous asymmetric centres established, **491** was taken through to the C_3–C_{10} aldehyde **477**, which was coupled with the same vinyllithium derived from **476** to give **492** after O-methylation, again as a 1 : 1 mixture of C_{10} epimers. Removal of the protecting groups and cyclization, as discussed earlier, gave **493**, which was then taken through to (±)-maysine by cyclic urethane formation and separation of the C_{10} epimers (18 steps from **483**; 0.7% overall yield).

Meyers' synthesis of racemic maytansinol (**473**)[86] again uses the key intermediate **492** (Scheme 40). In this instance, **492** was converted to amidoester **494** followed by a remarkable cyclization to give **495** in 58% yield. This was converted to **496**, which was still a 1 : 1 mixture of epimers at C_{10}. Sodium borohydride reduction of the C_3 ketone in **496** gave four diastereomers in 94% yield. The major isomer (*ca* 45% yield) was isolated and shown to be (±)-maytansinol (**473**) (22 steps from **483**; 0.1% overall yield).

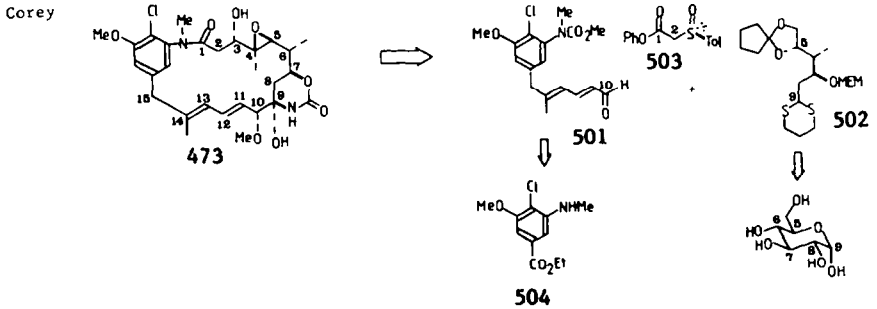
Meyers has subsequently reported an efficient asymmetric synthesis of the enantiomerically-correct C_3–C_8 fragment **477** (Scheme 40),[87] which has allowed the existing route to be adapted to give (−)-maytansine.[85b] The *S*-hydroxy acid **497** was converted to the allylic alcohol **498**, which underwent asymmetric epoxidation to give **499**. Addition of lithiodithioacetate to the derived aldehyde **500** at −120° gave the Cram addition product with improved stereoselectivity (91%), which was finally converted to the enantiomerically-correct **477** (15 steps from **497**; 30% overall yield).



Meyers Synthesis of Maysine[85] and Maytansinol[86]: A (i) MCPBA; (ii) MeMgCl; (iii) separate; B (i) CrO_3.2py; (ii) $EtSC(CH_2)SLi$; AcOH; C (i) $EtOCH{=}CH_2$, TsOH; (ii) EtMgI; 2-(N-methyl-N-formyl)-aminopyridine; D (i) Bu^tLi; addition of 477; (ii) NaH, MeI; E (i) Bu_4^nNF; (ii) Bu^tOMgBr, $C_5H_{10}NCON{=}NCONC_5H_{10}$; (iii) $ClCOCH_2P(O)(OEt)_2$, py; (iv) Bu^tOK; F (i) $HgCl_2$, $CaCO_3$; (ii) HCl; $ClCO_2Ph$, py; (iii) NH_3; (iv) separate; G (i) Bu_4^nNF; (ii) Bu^tOMgBr, $C_5H_{10}NCON{=}NCONC_5H_{10}$; (iii) AcCl, py; (iv) $AgNO_3$, NaOH; (v) CH_2N_2; H $(Me_3Si)_2NLi$; I (i) $HgCl_2$, $CaCO_3$; (ii) HCl; (iii) $ClCO_2Ph$, py; (iv) NH_3; J (i) $NaBH_4$; (ii) separate isomers; K (i) $EtOCH{=}CH_2$, TsOH; (ii) LAH; (iii) Bu^tOK, BnBr; (iv) HCl; (v) $(COCl)_2$, DMSO; Et_3N; L (i) $EtCH{=}NC_6H_{11}$, LDA; (ii) H^+; (iii) $NaBH_4$; M (+)-diethyl tartrate, $Ti(OPr^i)_4$, Bu^tOOH; N (i) TBSCl, imidazole; (ii) Na/NH_3; (iii) CrO_3.2py; O (i) $EtSC(CH_2)SLi$; (ii) $EtOCH{=}CH_2$, TsOH; (iii) EtMgI; 2(N-methyl-N-formyl)-aminopyridine.

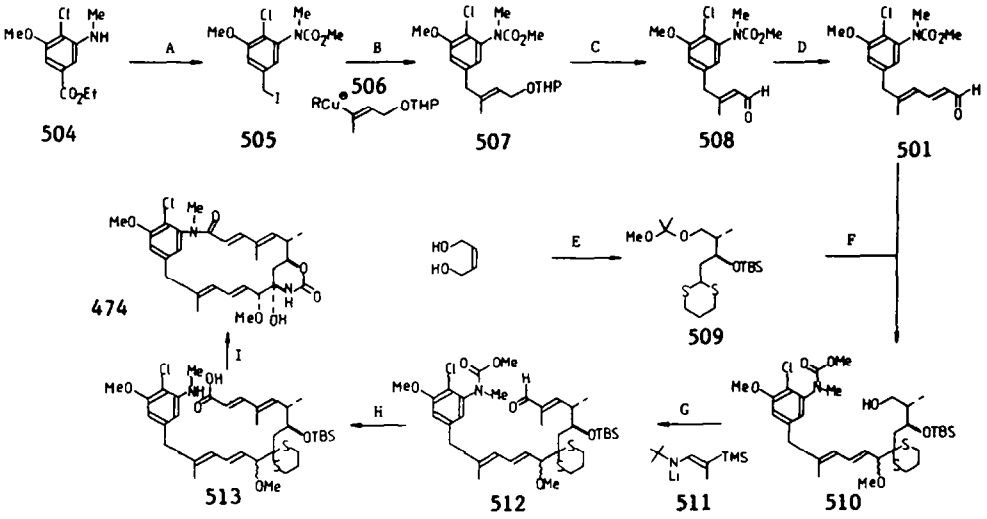
Scheme 40.

3.4.2. *Corey synthesis* (Schemes 41 and 42).[88–91] Corey's synthesis of maytansine (1980),[88] as well as its structurally simpler relative N-methylmaysenine (1978, 1980),[89] is based on the C_9–C_{10} coupling of an aliphatic C_5–C_9 fragment (containing the key C_6 and C_7 asymmetric centres) with the common aromatic C_{10}–N fragment **501**. In the enantiomerically-correct series, this C_5–C_9 unit **502** was prepared from carbohydrate precursors. All seven asymmetric centres of maytansinol were controlled with high stereoselectivity in Corey's synthesis; the C_3 centre was set up by an aldol condensation using the chiral acetate derivative **503**, while C_{10} was secured by reduction of the corresponding ketone with 1,4-asymmetric induction.



For the preparation of the common aromatic intermediate **501** (Scheme 41),[90b] the amino ester **504** (prepared in seven steps from gallic acid)[90a] was first converted to the benzylic iodide **505**. Coupling of

505 with the cuprate **506** then gave the trisubstituted *E*-olefin **507**, which was homologated via the enal **508** to give **501**. The key C_3–C_9 intermediate **509** for the racemic synthesis of N-methylmaysenine was prepared in 12 steps from *cis*-2-buten-1,4-diol.[91] Deprotonation of **509** and addition to the dienal **501** gave the coupled product **510** as a 55 : 45 mixture of C_{10} epimers after O-methylation and deprotection. The introduction of the *E,E*-dienal unit (C_2–C_6) was achieved by two sequential homologations. Addition of the lithioimine **511** to the aldehyde derived from **510** gave the enal **512**, mainly as the *E*-isomer (the small amount of the *Z*-isomer that was formed could be isomerized). A Horner–Emmons reaction with **512** then gave the *E,E*-unsaturated ester, which was converted to the acid **513**. The mixed-anhydride with mesitylenesulfonyl chloride was used to activate the carboxyl group in **513** to macrocyclization to give the corresponding macrolactam in 65% yield; separation of the two C_{10}-epimers and formation of the cyclic urethane gave (±)-N-methylmaysenine (26 steps from *cis*-2-buten-1,4-diol; 3.7% overall yield).

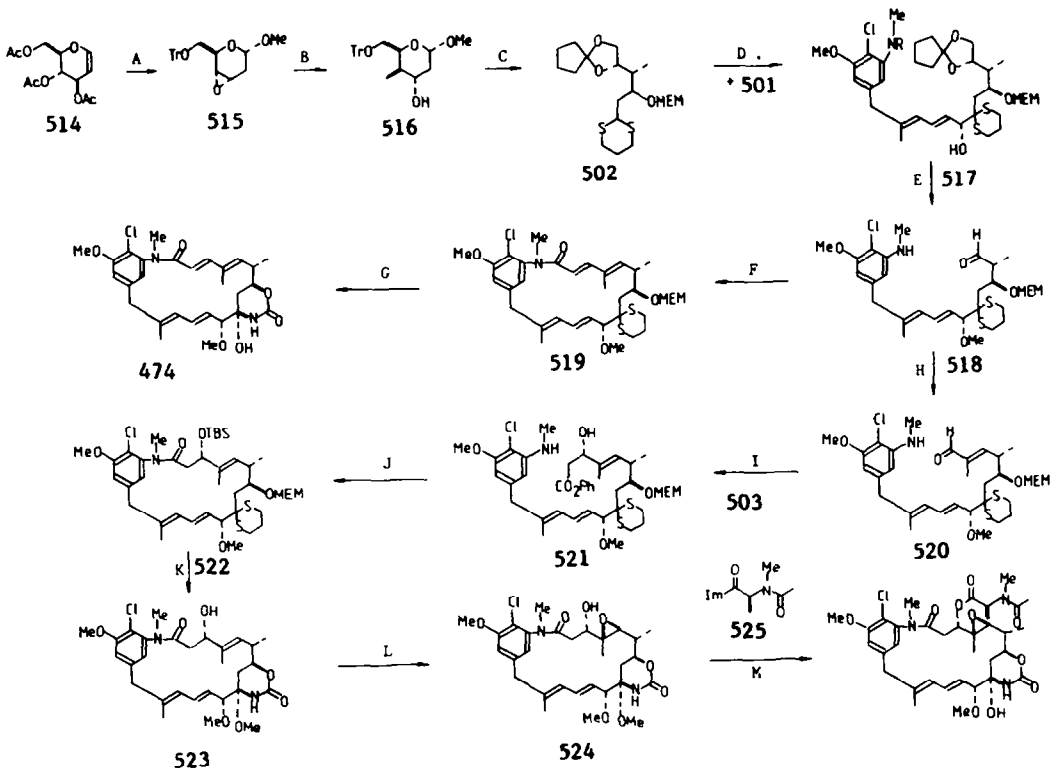


Corey (±)-N-methylmaysenine Synthesis[89a]: A (i) LAH; (ii) $ClCO_2Me$, K_2CO_3; (iii) NaOH; (iv) MsCl, py; (v) NaI; B cuprate displacement; C (i) TsOH; (ii) MnO_2; D (i) $Me_3SiCH_2CH{=}NBu^t$, Bu^sLi; (ii) AcOH, NaOAc; E (i) 12 steps; F (i) Bu^nLi, TMEDA; 501; (ii) NaH, HMPA, MeI; (iii) H_3O^+; G (i) DMSO, diethylcarbodiimide, TFA, py (ii) 511; (iii) AcOH, NaOAc; H (i) $(MeO)_2P(O)CHLiCO_2Me$; (ii) NaOH; (iii) $LiSPr^n$, HMPA; I (i) Bu_4^nNOH; (ii) 2,4,6-$Me_3C_6H_2SO_2Cl$, Pr_2^iNEt; (iii) separate C_{10} epimers; (iv) Bu_4^nNF; (v) $ClCO_2C_6H_4NO_2(p)$, py; NH_4OH; (vi) $HgCl_2$, $CaCO_3$.

Scheme 41.

Corey has also prepared (−)-N-methylmaysenine in enantiomerically-pure form.[89b] In this instance, the construction of the C_3–C_9 fragment began with tri-O-acetyl-D-glucal (**514**), which was transformed into the epoxide **515** (Scheme 42). Regiospecific ring-opening with methyl cuprate gave **516**, which was followed by thioketalization and protection to give **502**. The coupling reaction between the lithiated derivative of **502** and **501** gave a 1 : 1 mixture of epimers about C_{10}. Separation and oxidation of the unnatural C_{10} β-epimer followed by reduction with excess lithium n-butylborohydride gave predominantly the desired 10α-epimer **517** with 90% stereoselectivity. O-Methylation and reorganization of the protecting groups followed by cleavage of the vicinal diol then gave the aldehyde **518**, which was homologated and cyclized to **519** as before. Formation of the cyclic urethane as for the racemic series gave (−)-N-methylmaysenine (24 steps from **514**; 8.4% overall yield).

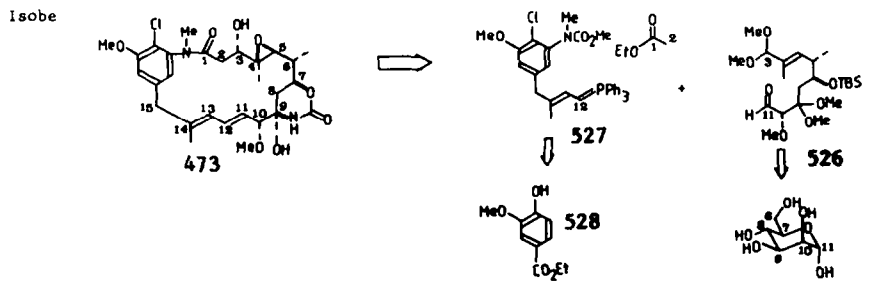
For the synthesis of (+)-maytansine itself (Scheme 42),[88] the aldehyde **520** was condensed with the magnesium derivative of the enantiomerically-pure sulfinyl ester **503** to give, after desulfurization, the desired C_3-epimer **521** with 93% stereoselectivity. Silylation and ester hydrolysis was then followed by efficient macrocyclization (83% yield) using the mixed-anhydride method to give macrolactam **522**, which was further converted into **523**. Epoxidation with $VO(acac)_2$ and t-butylhydroperoxide gave maytansinol 9-O-methyl ether (**524**) with greater than 200 : 1 stereoselectivity (due to the directing effect of the C_3 α-OH together with macrocyclic conformational control). Addition of the required side-chain to the C_3 hydroxyl group using the imidazolide **525** and hydrolysis of the C_9-ether completed the total synthesis of (+)-maytansine (34 steps from **514**; 2.7% overall yield).



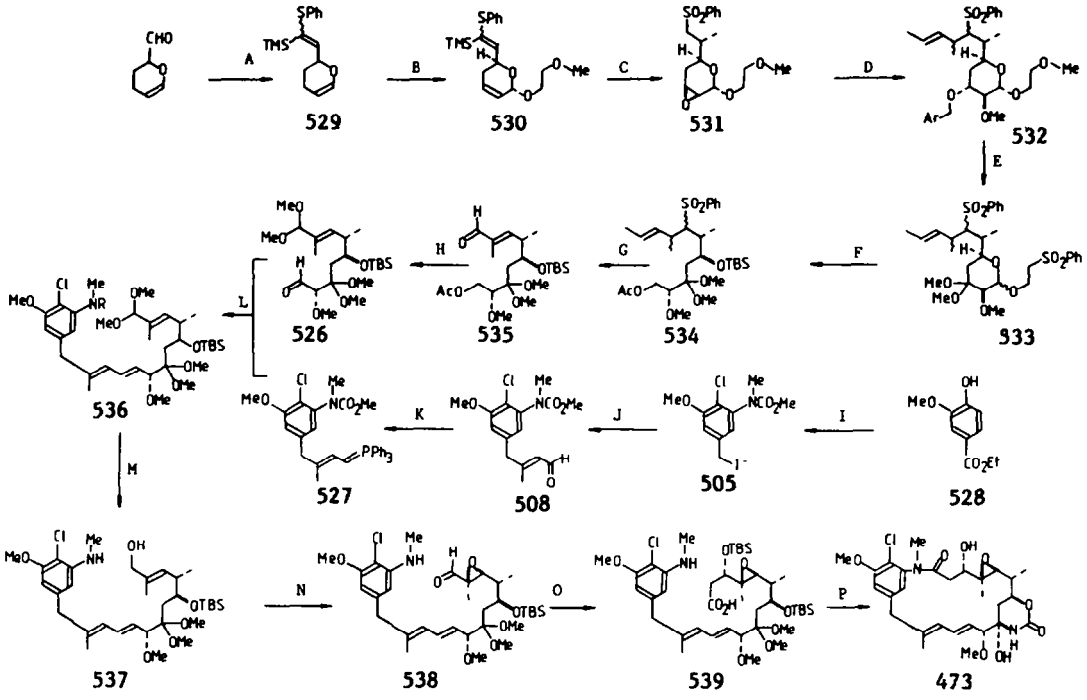
Corey Synthesis of (-)-N-Methylmaysenine[89b] and (+)-Maytansine[88]: A (i) NaOMe; (ii) $Hg(OAc)_2$, MeOH; (iii) NaCl; $NaBH_4$; (iv) TrCl, py; (v) NaH, HMPA; triisopropylbenzenesulphonylimidazole; B MeLi, CuLi; C (i) $HS(CH_2)_3SH$, HCl; (ii) 1-ethoxycyclopentene, $BF_3.OEt_2$; (iii) MEMCl, Pr^i_2NEt; D (i) Bu^nLi, TMEDA; 501; (ii) separate; (iii) MnO_2 oxidation of undesired C_{10} epimer; (vi) $LiBu^nBH_3$ reduction of C_{10} ketone; E (i) NaH, MeI; (ii) MeSLi; (iii) $HClO_4$; (iv) $Pb(OAc)_4$KOAc; F (i) $Me_3SiCH(Me)CH{=}NBu^t$, Bu^sLi; (ii) SiO_2, H_2O; py-HCl; (iii) $(MeO)_2P(O)$-$CHLiCO_2Me$; (iv) Bu^n_4NOH; (v) 2,4,6-$Me_3C_6H_2SO_2Cl$, Pr^i_2NEt; G (i) aq. H_2SO_4; (ii) $ClCO_2C_6H_4NO_2$, py; NH_4OH; (iii) $HgCl_2$, $CaCO_3$; H (i) $Me_3SiCH(Me)CH{=}NBu^t$, Bu^sLi; (ii) H_2O, SiO_2; py.HCl; I (i) R-(+)-p-tolylphenoxycarbonylmethylsuphoxide-Bu^tMgCl; (ii) Al/Hg; (iii) TBSCl, imidazole; (iv) LiOH; J (i) Bu^n_4NOH; (ii) 2,4,6-$Me_3C_6H_2SO_2Cl$, Pr^iNEt; K (i) Pr^iSH, $BF_3.OEt_2$; Pr^iSH, Bu^n_4NOH; (ii) $AgNO_3$,2,6-lutidine; (iii) p-$NO_2C_6H_4OCOCl$, py; NH_4OH; (v) HgCl, $CaCO_3$, Pr^i_2NEt; (vi) HF; (vii) MeOH, TsOH; L (i) $VO(acac)_2$, Bu^tOOH, 2,6-lutidine; (ii) $NaBH_4$; M (i) 525; (ii) py.HCl, H_2O

Scheme 42.

3.4.3. *Isobe synthesis* (Schemes 43 and 44).[92–95] Isobe *et al.* have completed the synthesis of maytansinol (**473**) in both racemic[92] and optically active form.[93] Their approach is based on the C_{11}–C_{12} Wittig coupling of the aliphatic C_3–C_{11} fragment **526** with the aromatic C_{12}–N fragment **527**, followed by introduction of the C_1–C_2 unit using the enolate of ethyl acetate. Macrolactamization was then carried out using Corey's mixed-anhydride protocol. Efficient stereocontrol was achieved at all seven asymmetric centres of (−)-maytansinol by constructing **526** from D-mannose. Note, however, that the C_{10}–C_{11} olefin geometry was not controlled to any useful degree in this route. The C_4–C_5 epoxide function was introduced by hydroxyl-directed epoxidation of an acyclic allylic alcohol, which was followed by a stereocontrolled aldol condensation to secure the natural C_3-configuration. The C_6-centre was controlled in a novel fashion by "heteroconjugate addition".[94]



The ylid **527** was prepared in four steps from the enal **508** (Scheme 43), which was also used in the Corey route (cf. Scheme 41). In the racemic synthesis, the C_3–C_{11} aliphatic fragment **526** was constructed from acrolein dimer by initial addition of $LiC(TMS)_2SPh$ to give the alkenes **529**, followed by conversion to the acetal **530** with 93% stereoselectivity. Epoxidation of **530** proceeded smoothly with **82%** stereoselectivity and conjugate addition of methyl lithium gave the sulfone **531** as the only



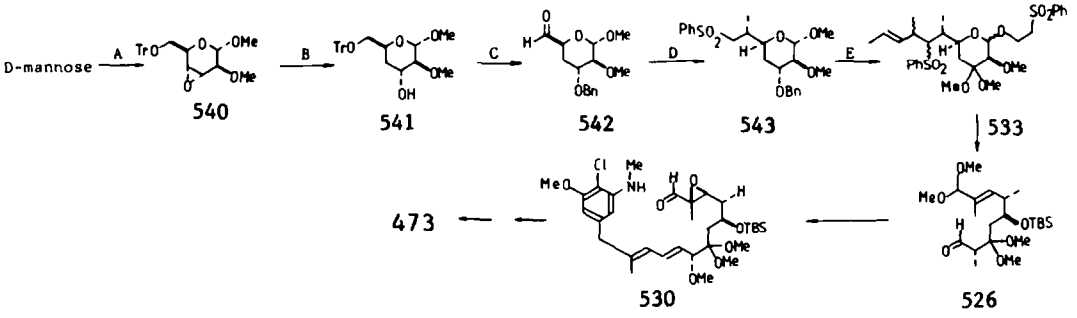
Isobe (±)-Maytansinol Synthesis[92]: A $LiC(SiMe_3)_2SPh$; B PhSeCl; $HOCH_2CH_2OMe$; (ii) MCPBA; (iii) CSA; C (i) MCPBA; (ii) MeLi; (iii) KF; D (i) Bu^nLi; $MeCH{=}CHCH(Br)Me$; (ii) p-$MeOC_6H_4CH_2ONa$; MeI; E (i) $HOCH_2CH_2Cl$, CSA, $(MeO)_3CH$; (ii) $CrO_3.2py$; (iii) $(MeO)_3CH$, MeOH, CSA; (iv) PhSNa; (v) MCPBA; F (i) $NaBH_4$; (ii) AcCl, py; (iii) TBSCl, imidazole; G O_3; Et_3N; H (i) PPTS, $(MeO)_3CH$, MeOH; (ii) NaOMe; (iii) $CrO_3.2py$; I (i) AcOH; HNO_3; (ii) LiCl, $POCl_3$; (iii) H_2, Pd/C, HCl; (iv) PhOCHO; (v) LAH; (vi) iodide formation; J (i) 4-lithio-4-(phenylsulphonyl)-1-pentene; (ii) O_3; Et_3N; K (i) $NaBH_4$; (ii) PBr_3, LiBr, collidine; (iii) PPh_3; (iv) Bu^tLi; L addition; M (i) aq. AcOH; (ii) $NaBH_4$; (iii) KOH; N (i) $Ti(OPr^i)_4$, Bu^tOOH; (ii) $SO_3.py$; O (i) $CH_2{=}C(OLi)OEt$; (ii) TBSCl, imidazole; (iii) KOH; P (i) 2,4,6-$Me_3C_6H_2SO_2Cl$, Pr^i_2NEt; (ii) Bu^n_4NF; (iii) aq. AcOH; (iv) p-$NO_2C_6H_4OCOCl$, py; (v) NH_3.

Scheme 43.

product after removal of the silyl group. This exclusive attack from one face was explained by invoking chelation of the lithium atom to the three ethereal oxygen atoms of the pyranoside. The adduct **531** was next transformed to **532** by epoxide-opening and alkylation followed by conversion via **533** to the acyclic intermediate **534**. Ozonolysis of **534** followed by β-elimination then gave the enal **535**, which was finally converted to the aldehyde **526** by routine operations.

The ylid **527** was then coupled with **526** to give diene **536** as a 55:45 $E:Z$ mixture at C_{11}–C_{12}. Epoxidation of the derived allyl alcohol **537** with $Ti(OiPr)_4$ and t-butylhydroperoxide gave only a single epoxide which, on oxidation, gave **538**. The C_1–C_2 unit was next introduced using the lithium enolate of ethyl acetate to give "almost all one isomer", followed by protection and ester hydrolysis to give **539**. The remarkably high diastereoselectivity in this aldol condensation was rationalized in part by the chelating effect of the remote C_7 ether oxygen. Note that the presence of the C_3–C_4 epoxide function is also critical, as Corey found that an analogous condensation with **520** was not stereoselective. This amino acid **539**, except for protecting group differences, was the same as that employed by Corey. Macrocyclic ring closure and urethane formation, essentially using the Corey procedure, then gave (±)-maytansinol (**472**) (35 steps from acrolein dimer; 0.4% overall yield).

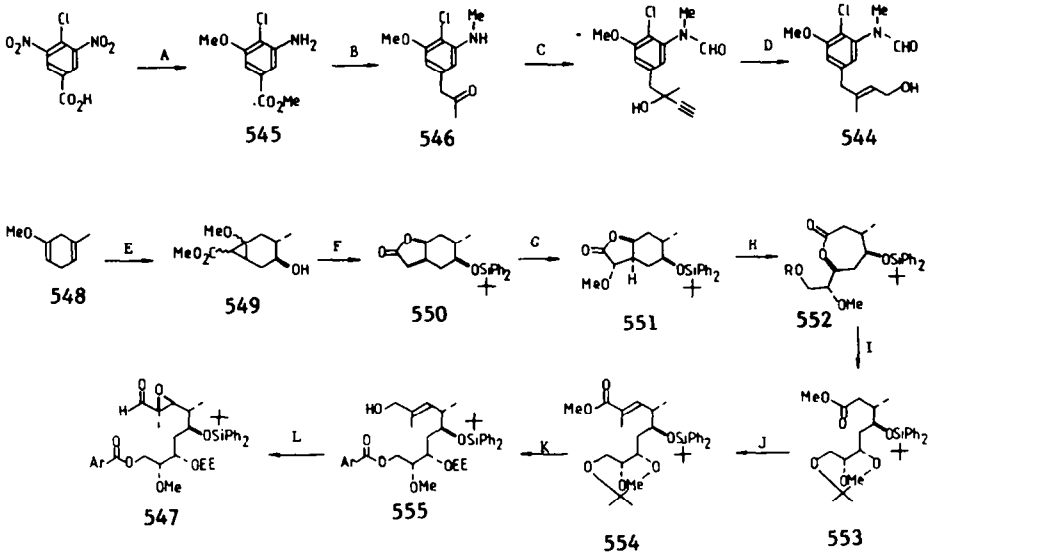
In their enantioselective synthesis,[93] the Nagoya group prepared **526** from D-mannose (Scheme 44). The epoxide **540** was reductively opened with $LiBH_4$ to give **541** with 87% regioselectivity. Addition of $LiC(TMS)_2SPh$ to the derived aldehyde **542**, followed by oxidation to the sulfone and addition of CH_3Li then gave **543** with a high degree of diastereoface selectivity. The pyranoside **543** was then converted via **533** to **526** using essentially the same sequence as before. Completion of this synthesis closely paralleled that of the racemic series to give (−)-maytansinol (43 steps from D-mannose; 3.5% overall yield). Isobe *et al.* have also prepared racemic N-methylmaysenine and maysine using essentially the same approach.[95]



Isobe (-)-Maytansinol Synthesis[93]: A (i) $Me_2C(OMe)_2$, PPTS; (ii) TsCl, py; (iii) NaH, MeI; (iv) H^+; (v) TrCl, py; (vi) Bu^tOK; B (i) $LiBEt_3H$; C (i) NaH, BnBr; (ii) HCl; (iii) $(COCl)_2$, DMSO; Et_3N; D (i) $PhS(Me_3Si)_2CLi$; (ii) MCPBA; (iii) MeLi; (iv) KF; E (i) H_2, Pd; (ii) DHP, PPTS; (iii) Bu^nLi; MeCH=CHCH(Me)Br; (iv) CSA, $HOCH_2CH_2Cl$; (v) $CrO_3.2py$; (vi) CSA, $HC(OMe)_3$, MeOH; (vii) PhSNa; (viii) MCPBA.

Scheme 44.

3.4.4. *Stork approach* (Scheme 45).[96] A similar overall strategy to Isobe is adopted in this approach with key disconnections at N–C_1, C_2–C_3 and C_{11}–C_{12}. The four asymmetric centres spanning the C_6–C_{10} of the ansa chain were controlled by a ring-cleavage approach, while the C_4–C_5 epoxide was



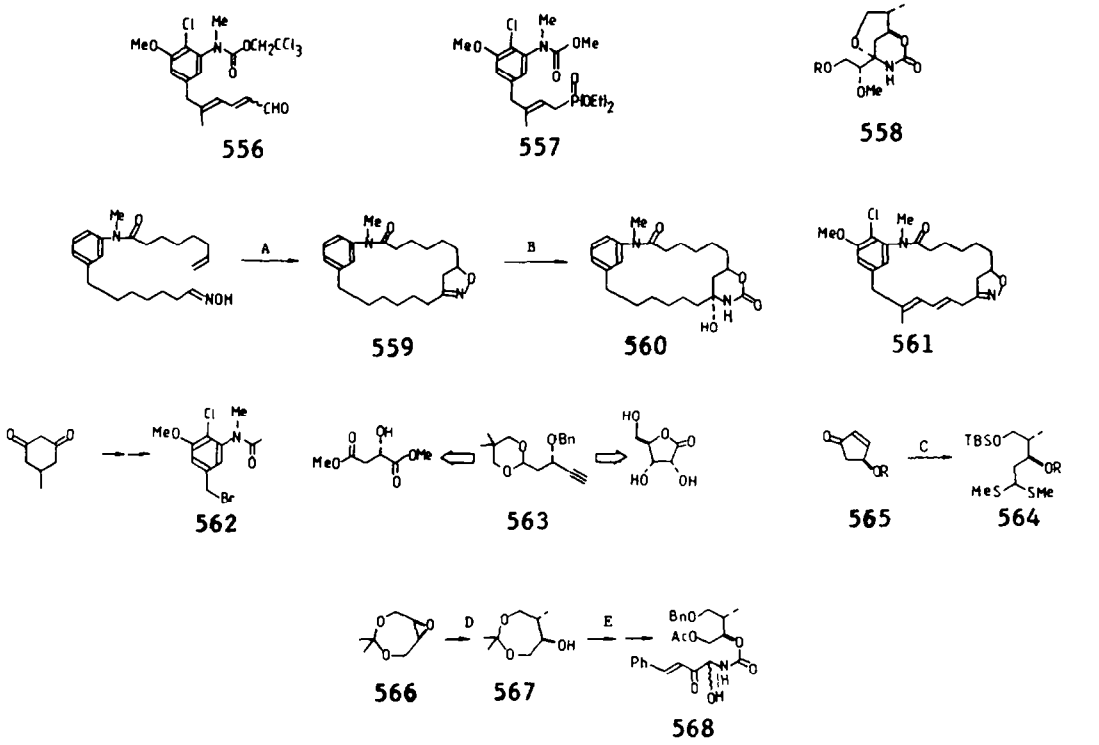
Stork Maytansine Approach[96]: A (i) CH_2N_2; (ii) $TiCl_3$; (iii) Ac_2O; (iv) H_2, Pd/C; (v) $HOSO_2NO_2$, AcOH; (vi) AcOH, H_2SO_4, H_2O; (vii) CH_2N_2; (viii) MeI, K_2CO_3; B (i) HCO_2H, Ac_2O; (ii) RED-AL; (iii) CrO_3, py, H_2O; (iv) $EtNO_2$, NH_4OAc; (v) EtOH, HCl, Fe(III), $FeCl_3$; C (i) $CH{\equiv}CMgBr$; (ii) HCOOH, Ac_2O; D (i) $(Ph_3SiO)_3VO$; (ii) $NaBH_4$; E (i) $CuSO_4$, CHN_2CO_2Me; (ii) BH_3; HOO^-; F (i) H^+(ii) L-selectride; (iii) Ph_2Bu^tSiCl; G (i) LDA; MoOPH; (ii) MeI, Ag_2O; H (i) LAH; (ii) p-MeC_6H_4COCl; (iii) PCC; (iv) MCPBA; I (i) K_2CO_3, MeOH; (ii) 2,2-dimethoxypropane, PPTS; J (i) LAH; (ii) o-$NO_2C_6H_4SeCN$, Bu^n_3P; (iii) H_2O_2; (iv) O_3; Me_2S; (v) $Ph_3P{=}C(Me)CO_2Me$; K (i) RED-AL; (ii) Ac_2O, py; (iii) PPTS; (iv) o-MeC_6H_4COCl; (v) $CH_2{=}CHOEt$, $POCl_3$; (vi) NaOH; L (i) $VO(acac)_2$, Bu^tOOH; (ii) PCC.

Scheme 45.

introduced correctly by diastereoface-selective epoxidation of an acyclic allylic alcohol. For the synthesis of the aromatic segment **544**, 4-chloro-3,5-dinitrobenzoic acid was first converted to **545** and then taken through to the ketone **546**. Formylation and addition of acetylide anion was followed by rearrangement to the enal, which was then reduced to give the alcohol **544**.

The synthesis of the key C_3–C_{11} fragment **547** started with cyclopropanation of the cyclohexadiene **548** followed by hydroboration to give **549**. Ring-opening, reduction and silylation then gave the lactone **550**. Hydroxylation of the enolate derivative of **550** with MoOPH was followed by methylation to give **551**, which was further transformed to the lactone **552**. Ring-opening of **552** was followed by conversion of C_5 to an aldehyde, and a Wittig reaction then led to the homologated product **554**, which was then taken on to the allylic alcohol **555**. Epoxidation of **555** with $VO(acac)_2$ and t-butyl hydroperoxide gave only one epoxyalcohol and oxidation gave **547**. It still remains to couple at C_{11}–C_{12} with the correct stereochemistry and also to control the stereochemistry at C_3 before macrocyclization and cyclic carbamate formation.

3.4.5. *Other approaches* (Scheme 46). In 1977 Götschi *et al.* proposed a similar strategy to Corey, although they have only reported the synthesis of the aromatic diene **556**.[97] Ho has reported the synthesis of the phosphonate **557**,[98] where the overall strategy was similar to that of Isobe and Stork involving disconnection at C_{11}–C_{12}. Ho has also published an enantioselective[100] synthesis of the C_5–C_{11} carbamate **558**. In a recently described model study Confalone has reported a novel approach to maytansenoids.[101] The key reaction was an intramolecular (3 + 2) cycloaddition to give the isoxazoline **559**, which was then converted into the cyclic urethane **560**. A second model compound **561** was also prepared. Ganem and his co-workers have reported model studies for the preparation of the cyclic carbamate system,[102] together with a synthesis of the tetrasubstituted compound **562** from 5-



Other Maytansine Approaches: A chlorox, Bu^n_4NOH; B (i) Ra/Ni, AcOH, MeOH, H_2O; (ii) p-$NO_2C_6H_4OCOCl$; (iii) NH_3; C (i) Me_2CuLi; Me_3SiCl; (ii) O_3; $NaBH_4$; (iii) CH_2N_2; (iv) TBSCl, imidazole; (v) DIBAL; (vi) $(MeS)_3B$; D (i) Me_2CuLi; (ii) resolution; E (i) HCl; (ii) NaH; BnCl; (iii) HCl; (iv) Ac_2O, py; (v) NaOCN, CF_3CO_2H; (vi) $PhCH{=}CH_2COCHO$.

Scheme 46.

methylcyclohexan-1,3-dione.[103] Barton *et al.* have reported two enantioselective routes to a C_1–C_5 fragment **563**[104] of the ansa bridge of bis-nor-4,6-maytansenoids starting with *S*-(−)-dimethyl malate or D-(+)-ribonolactone as well as a synthesis of a C_6–C_{11} portion. Two preliminary studies leading to fragments containing the C_6 and C_7 chiral centres have been reported. Vandewalle's approach[105] gave **564** from the substituted cyclopentenone **565**. Finally, the Fried approach[106] initially involved ring-opening of the epoxide **566** to generate the C_6–C_7 relationship in **567**, which was then elaborated to the carbinolamide **568** as a model for a novel C_9–N macrocyclization step.

4. CONCLUDING REMARKS

Macrolide total synthesis has very rapidly grown into a mature and established area of natural products synthesis. The stereocontrolled construction of the multiple asymmetric centres of these complex targets has provided effective demonstrations of the power and relative efficiencies of the various ring-cleavage, carbohydrate, acyclic and macrocyclic strategies available. Carbohydrate approaches have been widely adopted for controlling the absolute stereochemistry in both the polyoxo-macrolide and ansamycin series. The recent introduction of reliable asymmetric reactions, which proceed with close to 100% ee, however, has provided a viable alternative for enantioselective synthesis. Moreover, the many new methods for attaining high levels of acyclic stereocontrol have made a dramatic impact in rapidly building up the elaborate chiral sequences of the macrolide skeletons. The aldol condensation, in particular, has played the leading role in this area. The advantages of using macrocyclic stereocontrol over a more traditional ring-cleavage approach are also obvious in simplifying and shortening the synthetic route. Indeed it is now possible to design short and efficient enantioselective syntheses of most macrolides by suitable combinations of acyclic and macrocyclic strategies. The development of further new methods for high-yielding macrocycle construction, particularly by carbon–carbon bond formation, together with the introduction of more efficient glycosidation procedures are also considered to be key areas remaining for future research. Important developments in the synthesis of other macrolide classes have also been made recently.[3] Most significantly, these include the boron-containing ionophores (aplasmomycin and boromycin), the cytochalasins, the avermectins and the polyene macrolides (amphotericin and nystatin).

Clearly the many problems associated with macrolide total synthesis have now been largely successfully resolved. It is anticipated that future work will, therefore, be primarily concerned with further improvements in concepts and methods directed towards increasingly more efficient synthesis of these testing targets.

Acknowledgements—We wish to thank the many researchers who have provided us with reprints and/or preprints of their work. We are especially grateful to those who have been kind enough to send us details of unpublished results. We also wish to thank Dr P. Kirby (Shell) for support in this venture. Thanks are also due to N. Paterson for assistance with the diagrams.

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[7] See *inter alia*, [a]S. Masamune, S. Kamata and W. Schilling, *J. Am. Chem. Soc.* **97**, 3515 (1975); [b]E. J. Corey and K. C. Nicolaou, *Ibid.* **96**, 5614 (1974); [c]H. Gerlach and A. Thalmann, *Helv. Chim. Acta* **57**, 2661 (1974); [d]J. Inanaga, K. Hirata, H. Sakai, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Japan* **52**, 1989 (1979).

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