Chem. Soc. Rev., 1991, **20**, 271–339

Avermectins and Milbemycins Part II *

By H. Geoffrey Davies and Richard H. Green
MEDICINAL CHEMISTRY DEPARTMENT, GLAXO GROUP RESEARCH, GREENFORD, MIDDLESEX, UB6 0HE

7 Total Synthesis

A. Milbemycins.—The first reported synthesis of one of this large family of macrolides was that of Smith and colleagues,[132,1] who described the preparation of racemic milbemycin β_3. Shortly after this synthesis was published, Williams and co-workers in Indiana[133,1] described their synthesis of optically pure milbemycin β_3, which was obtained by the condensation of two asymmetric moieties both derived from the same chiral precursor, (−)-(3*S*)-citronellol. In addition to the pioneering work of Smith and Williams, three other groups have reported total syntheses of milbemycin β_3, one group the synthesis of milbemycin β_1 and one further group the synthesis of milbemycin E. In each case optically active material was obtained. Chronologically, the first of the three milbemycin β_3 syntheses was that described by Baker and co-workers.[68–70,134–136] The chiral spiroacetal diol (279)[68] was transformed into the aldehyde (280), and this was immediately treated with ethoxycarbonylethylidene triphenylphosphorane to give the α,β-unsaturated ester (281) (Scheme 36). This was shown by both ^{1}H and ^{13}C NMR spectroscopy to be a single component possessing, exclusively, the *E*-stereochemistry about the double bond. Reduction of the ester followed by mesylation and iodination gave an unstable iodide which was immediately used to alkylate the oxazolidinone (282), resulting in the introduction of the C-12 methyl group of the milbemycin skeleton. Reductive removal of the oxazolidinone ring from (283), followed by tosylation, nucleophilic substitution, and oxidation, afforded the C-11 to C-25 fragment of the milbemycins (284). In the original report of their total synthesis of milbemycin β_3,[134] Baker and colleagues had used an adaptation of Williams' work[133,1] to introduce the C-14–C-15 double bond. However, an alternative route to this tri-substituted double bond was later established,[136] and it was this route which was utilized in the full paper on the total synthesis in question.[135] This new approach involved treatment of (284)

* Avermectins and Milbemycins Part I (Fermentation and Isolation; Structure Determination; Biosynthesis; Metabolism and Assay; Partial Synthesis) appeared in *Chemical Society Reviews*, 1991, Vol. 20, Issue 2 (June).

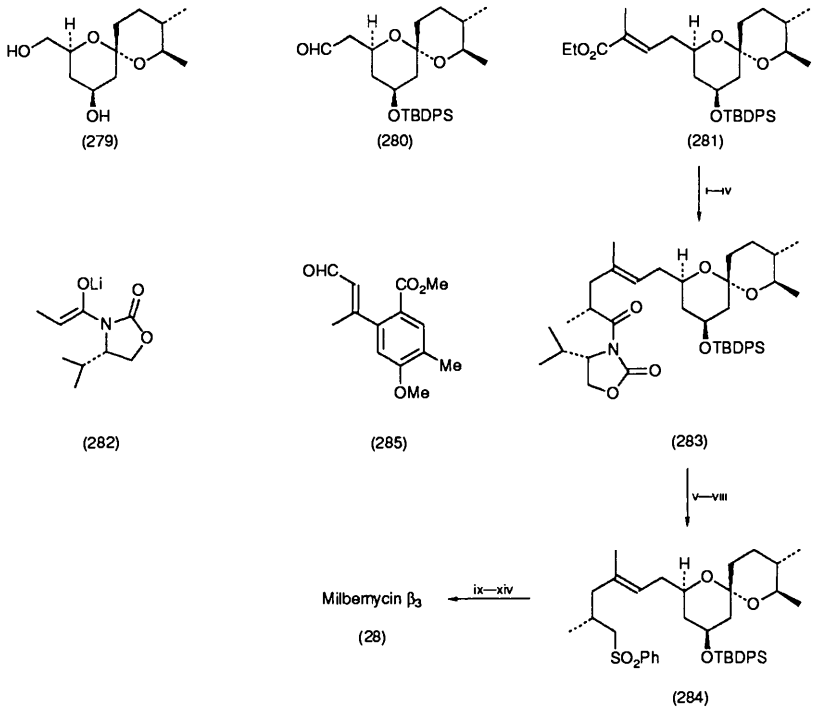
[132] A. B. Smith, S. R. Schow, J. D. Bloom, A. S. Thompson, and K. N. Winzenberg, *J. Am. Chem. Soc.*, 1982, **104**, 4015; S. R. Schow, J. D. Bloom, A. S. Thompson, K. N. Winzenberg, and A. B. Smith, *J. Am. Chem. Soc.*, 1986, **108**, 2662.

[133] D. R. Williams, B. A. Barner, K. Nishitani, and J. G. Phillips, *J. Am. Chem. Soc.*, 1982, **104**, 4708.

[134] R. Baker, M. J. O'Mahony, and C. J. Swain, *J. Chem. Soc., Chem. Commun.*, 1985, 1326.

[135] R. Baker, M. J. O'Mahony, and C. J. Swain, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1623.

[136] R. Baker, M. J. O'Mahony, and C. J. Swain, *Tetrahedron Lett.*, 1986, **27**, 3059.



Reagents: i, Dibal-H, THF, −78 °C; ii, $MeSO_2Cl$, pyr, DMAP; iii, NaI, THF; iv, LDA, THF, (282), −78 °C, then add (281); v, $LiAlH_4$, Et_2O; vi, *p*-TsCl, pyr; vii, Na, PhSH, MeOH; viii, $KHSO_5$, EtOH, H_2O; ix, Bu^{t}Li, THF, −78 °C, then (285); x, PhCOCl; xi, Na/Hg, MeOH, THF; xii, Bu^n_4NF, THF; xiii, KH, THF; xiv, EtSH, Na, DMF

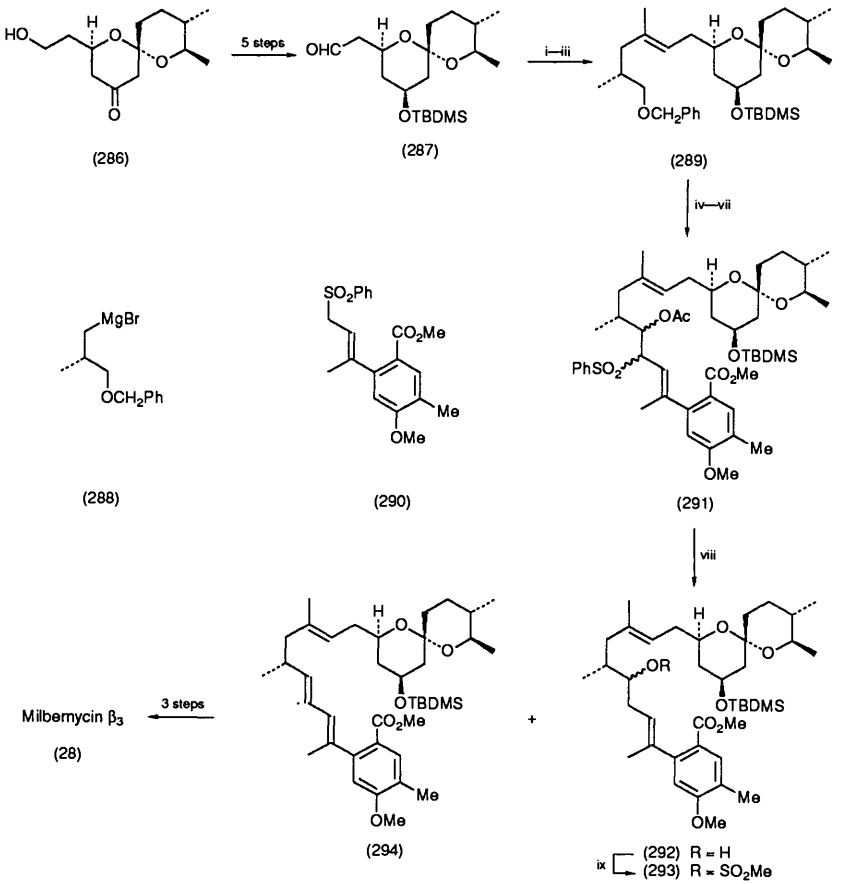
Scheme 36

with t-butyl-lithium followed by addition of the *E*-aldehyde (285), readily available from 4-methoxy-3-methylbenzoic acid. Quenching of the reaction mixture with benzoyl chloride afforded a mixture of diastereoisomeric benzoates which were not separated but treated directly with sodium amalgam. This served to generate the required *trans*-butadienyl system in nearly 80% yield with complete stereocontrol in the formation of the diene system. Protecting group removal followed by macrolactonization and demethoxylation then provided (+)-milbemycin β_3 (28).

Two different approaches to milbemycin β_3 have been described by Kocienski and colleagues. In their earlier synthesis,[74,137] the hydroxy spiroacetal (286), prepared by a Lewis acid catalysed intramolecular aldol reaction,[138] was transformed using routine chemistry into the aldehyde (287) (Scheme 37) in an overall yield of *ca* 41%. Chain extension of this aldehyde and construction of the

[137] S. D. A. Street, C. Yeates, P. Kocienski, and S. F. Campbell, *J. Chem. Soc., Chem. Commun.*, 1985, 1386.

[138] P. Kocienski and S. D. A. Street, *J. Chem. Soc., Chem. Commun.*, 1984, 1381.



Reagents: i, $PhSO_2CH(Li)CH_3$, THF, −78 °C followed by Ac_2O; ii, NaOH, dioxane; iii, $Fe(acac)_3$, (288); iv, Na, NH_3; v, CrO_3·2pyr, CH_2Cl_2; vi, LDA, THF, −78 °C, (290); vii, Ac_2O; viii, Na/Hg, THF, MeOH, −20 °C; ix, $MeSO_2Cl$, Et_3N, CH_2Cl_2, −10 °C

Scheme 37

C-14–C-15 double bond was then achieved using conditions first employed by Julia and colleagues.[139] Condensation of the aldehyde (287) with the lithium salt of phenylethyl sulphone, followed by acetylation, gave a mixture of four diastereoisomeric β-acetoxy sulphones. These were not separated but simply subjected to basic hydrolysis to give exclusively an (*E*)-vinylsulphone. Reaction of this with the Grignard reagent (288) in the presence of a catalytic amount of tris(acetonylacetonato)iron(III) then provided the required olefin (289) with

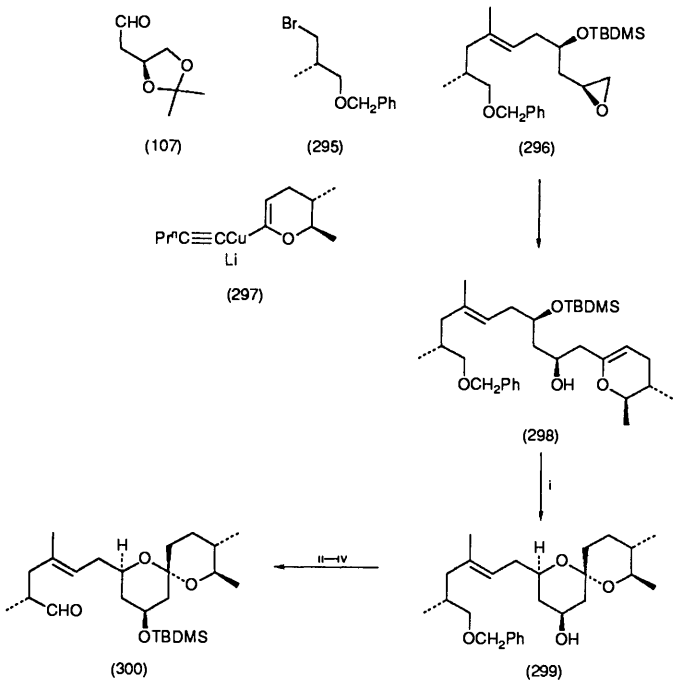
[139] M. Julia, M. Launay, J.-P. Stacino, and J.-N. Verpaux, *Tetrahedron Lett.*, 1982, **24**, 2465; J.-L. Fabre, M. Julia, and J.-N. Verpaux, *ibid.*, p. 2469.

>95% retention of double bond stereochemistry Although this process suffered the disadvantage of a low overall yield (26%), mainly because of the capricious nature of the Grignard reaction, this was offset by the high stereoselectivity observed in the formation of the double bond Further compensation for the low yield was the fact that any unreacted vinyl sulphone could be recovered and recycled Although conversion of this primary alcohol (289) into the corresponding aldehyde, earlier prepared in racemic form by Smith and colleagues,[132] proceeded without event, final conversion of the aldehyde into milbemycin β_3 proved problematic Coupling of the phenylsulphone (290) with the aldehyde proceeded smoothly to afford the β-acetoxysulphone (291) as a mixture of diastereoisomers However, reductive elimination of this material to give the required (*E,E*)-diene did not proceed smoothly, the required compound only being obtained in low yield There were three main reasons for this disappointing result First, the reaction was very sluggish and thus base-catalysed side reactions were a problem In addition the *trans*-stereoselectivity of the process was low, and simple reductive desulphonation and ester methanolysis predominated, resulting in the diastereomeric alcohols (292) being the major products of the reaction However, in spite of these limitations, the required diene (294) could be isolated in 39% yield as a 5 1 mixture of *E Z* isomers Although the alcohols (292) could be dehydrated *via* the mesylate (293) to give the diene (294) using DBN, stereoselectivity was very poor (*E Z* = 3 2)

Interestingly, simply by interconversion of the benzoyl and sulphonyl groups, Baker[134] was able to demonstrate a remarkably facile reduction to occur with none of the inherent problems described above Conversion of the diene (294) into milbemycin β_3 (28) was then achieved employing Smith's conditions giving the required macrocycle in 60% overall yield

Kocienski and his associates[85] have also reported an alternative, more practical, synthesis of the aldehyde (300) and its transformation (as detailed above) into milbemycin β_3 The two chiral synthons (107) and (295), readily available from (*S*)-(−)-malic acid and (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate respectively, were transformed, in ten steps, into the epoxide (296) This was then treated with the mixed organocuprate (297) (Scheme 38), resulting in nucleophilic scission of the epoxide to give the dihydropyran derivative (298) This highly sensitive intermediate was not purified but immediately treated with camphorsulphonic acid in methanol giving the spiroacetal (299) in an overall yield of 55% from the epoxide (296) Conversion of this material into the aldehyde (300) was then smoothly accomplished as shown in the Scheme

The third synthesis of milbemycin β_3 to appear in the literature was that of Barrett and his associates (Scheme 39) Their synthesis involved the preparation of three key intermediates and their coupling and subsequent elaboration to give the required macrocycle The syntheses of these key synthons (301), (302), and (303) were first described at a symposium on the Chemistry of Insect Control,[140] and they have since been successfully utilized[141 142] in a total synthesis of milbemycin β_3 Hydrogenation of the spirodihydropyrone (301) over rhodium on



Reagents: i, Camphorsulphonic acid, MeOH, 20 °C; ii, Bu^{t}Me$_2$SiCl, DMF, Et$_3$N; iii, Na, NH$_3$(L); iv, CrO$_3$·2pyridine, CH$_2$Cl$_2$

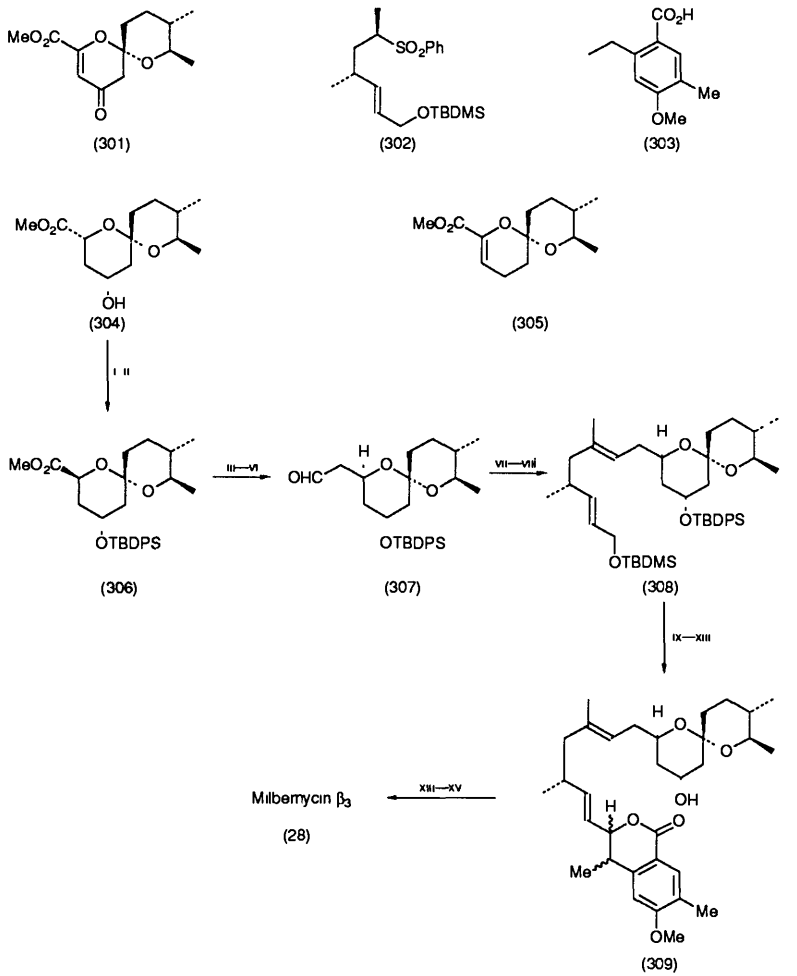
Scheme 38

alumina generated the alcohol (304), although the yield was variable. On the small scale, yields of 90% were reported, but on scale up only 58% of the alcohol (304) was observed along with approximately 6% yield of the epimeric alcohol. In addition, extreme care had to be observed in the hydrogenation process, since a trace of acid totally inhibited the formation of the alcohol (304); the sole observed product (85%) was the α,β-unsaturated ester (305). Protection of the alcohol (304) as its t-butyldiphenylsilyl ether followed by kinetically controlled epimerization of the ester group afforded the spiroacetal (306) in 94% yield. Homologation of this ester in routine fashion provided the aldehyde (307). Condensation of this aldehyde with the lithium anion of the phenylsulphone (302)

[140] S. V. Attwood, A. G. M. Barrett, R. A. Carr, M. A. W. Finch, and G. Richardson, 'The Application of Novel Carbanion Chemistry in Milbemycin–Avermectin Synthesis' in 'Recent Advances in the Chemistry of Insect Control', ed. N. F. Janes, The Royal Society of Chemistry Special Publication No. 53, London, 1985, p. 257.

[141] S. V. Attwood, A. G. M. Barrett, R. A. Carr, and G. Richardson, *J. Chem. Soc., Chem. Commun.*, 1986, 479.

[142] A. G. M. Barrett, R. A. E. Carr, S. V. Attwood, G. Richardson, and N. D. A. Walshe, *J. Org. Chem.*, 1986, **51**, 4840.



Reagents i, Bu^tPh_2SiCl, DMF, imidazole, ii, LDA, THF, −78 °C then AcOH, iii, Dibal-H, toluene, −78 °C, iv, $Ph_3P{=}CH_2$, THF, 0 °C, v, B_2H_6, Et_2O then NaOH, H_2O_2, vi, PCC, CH_2Cl_2, vii, (302), $BuLi$, Et_2O, 0 °C then Ac_2O, viii, Na/Hg, THF, MeOH, −20 °C, ix, AcOH, H_2O, THF, x, PCC, CH_2Cl_2, xi, (303), NaH, Bu^tLi, THF, −50 °C then TFA, xii, TBAF, THF, 45 °C, xiii, KH, 18-crown-6, Et_2O, −5 °C then chromatography, xiv, Ph_3P, DEAD, THF, xv, EtSNa, DMF, heat

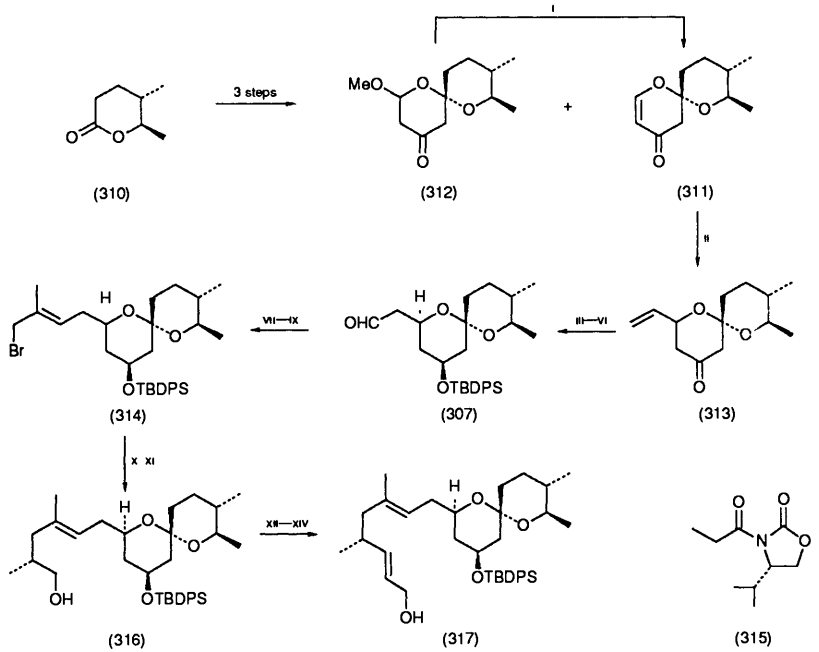
Scheme 39

followed by acetylation gave a complex mixture of diastereoisomers However, reductive elimination afforded the required alkene (308) in high yield, although the geometric selectivity of the process was poor (Δ^{14} *E Z* = 5 3) Although this selectivity could be increased by performing the elimination at reduced temperature, the yield of the process deteriorated dramatically Since

chromatographic separation of the isomers was impractical at this stage, the mixture was processed until separation could be achieved. Selective deprotection of the t-butyldimethylsilyl ether followed by oxidation gave an intermediate aldehyde, which was condensed with the double anion of the benzoic acid (303). Acidic work-up, followed by removal of the t-butyldiphenylsilyl ether, provided the benzopyrone (309) in an overall yield of 73%. Although this was obtained as a complex mixture of diastereoisomers at C-8 and C-9 and geometric isomers at C-14, base-mediated elimination, using a variation of Williams' chemistry,[133] followed by chromatography, gave the required *trans, trans*-diene. The use of 18-crown-6 in this process considerably enhanced the rate of the reaction, thus allowing it to be performed at a lower temperature. Macrolactonization under Mitsunobu conditions[73] followed by Smith's phenol de-O-methylation procedure[132] finally completed the synthesis of milbemycin β_3 (28) in 51% yield. Although the spectroscopic data for this material were in excellent agreement with published data on milbemycin β_3, one minor discrepancy was the value observed for the optical rotation. There is much conflict in the literature over this data since different groups have observed different values. For example, Williams[133] reported a figure of $+26.5°$ (c. 0.2 in methanol) in his original synthesis, and similar values were obtained by both Baker[134] ($+26.1°$) and Kocienski[137] ($+32.8°$, c. 0.3 in methanol). In a later corrigendum,[143] Baker amended his value to $+105°$ but, again, did not report the solvent employed. In addition, Kocienski[74] has reported a value of $+105°$ when the measurement was carried out in chloroform and stressed in his report that it was essential for the solvent to be *alcohol-free* chloroform. Barrett's report,[141,142] on the other hand, claims the value to be $+102°$ (c. 0.2 in methanol) and presents a reasoned argument for the discrepancy. In addition, he also reports that Williams now observes the following values for his synthetic material: $+103°$ (c. 0.28 in methanol), $+125.5°$ (c. 0.27 in chloroform), and $+115.6°$ (c. 0.25 in acetone). Since the Sankyo chemists[65] did not report the optical rotation for natural milbemycin β_3 and the material is now no longer available, no conclusions can safely be drawn as to the correct value, although on the basis of Barrett's argument it would appear that his observed value is correct.

In addition to these total syntheses of milbemycin β_3, Crimmins and colleagues[144] have reported a formal synthesis which culminated in the attainment of the Williams intermediate (317). The lactone (310), an important intermediate in a number of synthetic approaches to milbemycin β_3,[85,132,133,136,137,141,142] was transformed in three steps into a mixture of the spiroenone (311) and the spiroacetal (312) (Scheme 40). The unwanted (312) could be readily converted into the required spiroenone by simple treatment with wet Amberlyst® resin and thus the spiroenone was obtained in an overall yield of 52% from the lactone (310). Addition of vinyl magnesium bromide to the α,β-unsaturated ketone (311) in the presence of a catalytic amount of $[Bu_3PCuI]_4$

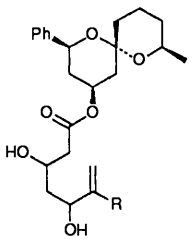
[143] R. Baker, M. J. O'Mahony, and C. J. Swain, *J. Chem. Soc., Chem. Commun.*, 1986, 276.
[144] M. T. Crimmins, D. M. Bankaitis-Davis, and W. G. Hollis, Jr., *J. Org. Chem.*, 1988, **53**, 652.



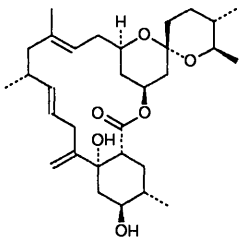
Reagents i, wet amberlyst, CH_2Cl_2, heat, ii, ⟋MgBr, $[Bu_3PCuI]_4$, Et_2O, −55 °C, iii, $NaBH_4$, DME, iv, Bu^tPh_2SiCl, DMF, DMAP, imidazole, v, 9-BBN, THF, ultrasound, vi, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, vii, $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, viii, Dibal-H, THF, ix, Ph_3P, CBr_4, CH_3CN, x, (315), LDA, xi, $LiAlH_4$, Et_2O, xii, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, xiii, $Ph_3P{=}CH{\cdot}CO_2Et$, CH_2Cl_2, heat, xiv, Dibal-H, THF, −78 °C

Scheme 40

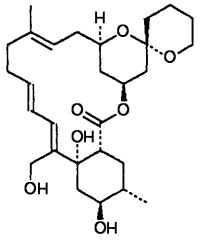
gave a 5 1 mixture of diastereoisomers which were separated to give the olefin (313) in 60% yield, the stereochemistry of the product was verified by 250 MHz ^1H spectroscopy The stereoselectivity of the process is dramatically affected by the size of the substituent at C-25 since earlier work [77] had shown a selectivity of 25 1 when there was an isopropyl group at this position Reduction of the ketone with borohydride gave a 3 1 mixture of epimers which were separated and the minor, unwanted, epimer recycled by Jones oxidation Protection of the required equatorial alcohol, followed by hydroboration and Swern oxidation, then led to the spirocyclic aldehyde (307), an intermediate common to Williams' embryonic synthesis of optically active milbemycin β_3, in excellent yield The C-14–C-15 olefin was then smoothly introduced by Wittig coupling with complete stereocontrol of olefin geometry Reduction and bromination then gave the bromide (314) Addition of this bromide to an excess of the lithium enolate of (315), followed immediately by reduction, gave the alcohol (316) in 50% yield as a single diastereoisomer as observed by 400 MHz proton spectroscopy This alcohol was then routinely



R = H or Me
(318)



(319)

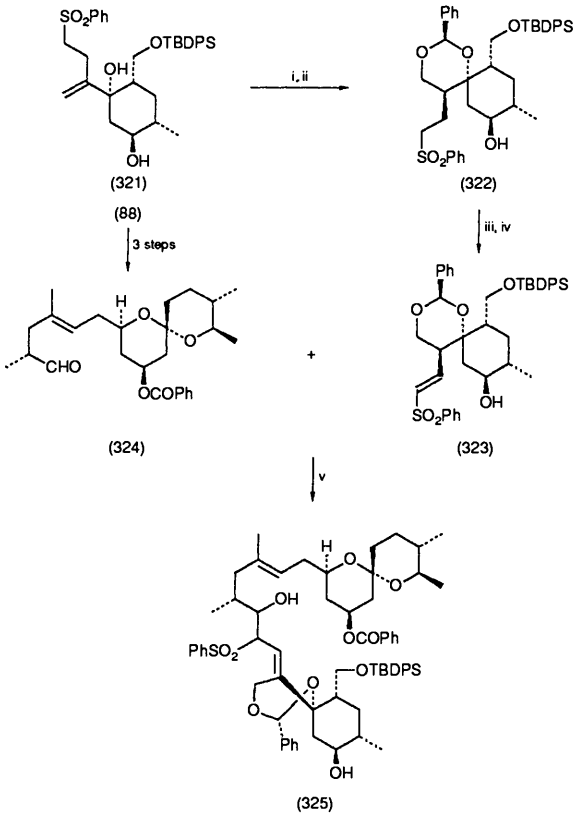


(320)

transformed into the allylic alcohol (317), a late stage synthon in Williams' synthesis[133] of milbemycin β_3.

A number of model studies by Ley and colleagues at Imperial College have recently culminated in the fourth total synthesis of a milbemycin, namely milbemycin β_1.[36,145] In early 1987, these workers had described a synthesis of the seco-analogue (318) which, disappointingly, was reported to be devoid of biological activity.[146] Shortly after this synthesis was published, a series of papers appeared dealing with the syntheses of the two model compounds (319)[147] and (320),[148] and it was this work that provided the basis for the total synthesis of milbemycin β_1. In the earlier paper,[147] the crucial intermediate (321) was obtained in 13 steps from 4-methylanisole. This synthesis involved initial Birch reduction and Prins alkylation followed by trivial protection, resolution using (1*S*)-(−)-camphanic acid chloride, and subsequent elaboration to give the required intermediate (321). Following conditions elucidated in their second paper,[148] these workers were able to modify this molecule further such that a feasible synthesis of milbemycin β_1 was available. Thus, stereoselective hydroboration of (321) (Scheme 41) gave a 4:1 mixture of primary alcohols from which the predominant isomer was separated. Treatment of this with benzaldehyde under Dean–Stark conditions gave a 1:1 mixture of products from which the acetal (322) could be isolated in approximately 30% overall yield. Formation of the α-sulphonyl carbanion followed by quenching with phenylselenyl chloride gave a diastereoisomeric pair of selenides which, upon oxidation, underwent smooth *syn*-elimination providing the key intermediate (323). The intermediate (88) (see references 78 and 80) was then routinely converted into the aldehyde (324) and, on addition of this to the dianion of (323), the olefin (325) was produced in high yield. The exclusive *E*-geometry of this olefin was attributed to the minimization of non-bonded interactions between the bulky phenylsulphonyl and t-butyldiphenylsilyl groups. This material underwent smooth reductive elimination on treatment with sodium amalgam and the resulting *E,E*-diene was converted as shown in Scheme 42 into the carboxylic acid (326). Removal of the benzoyl

[145] N. J. Anthony, A. Armstrong, S V. Ley, and A Madin, *Tetrahedron Lett.*, 1989, **30**, 3209.
[146] T. Clarke and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, 1987, 131
[147] C. Greck, P Grice, A. B. Jones, and S. V. Ley, *Tetrahedron Lett.*, 1987, **28**, 5759.
[148] N. J. Anthony, P Grice, and S. V Ley, *Tetrahedron Lett.*, 1987, **28**, 5763.

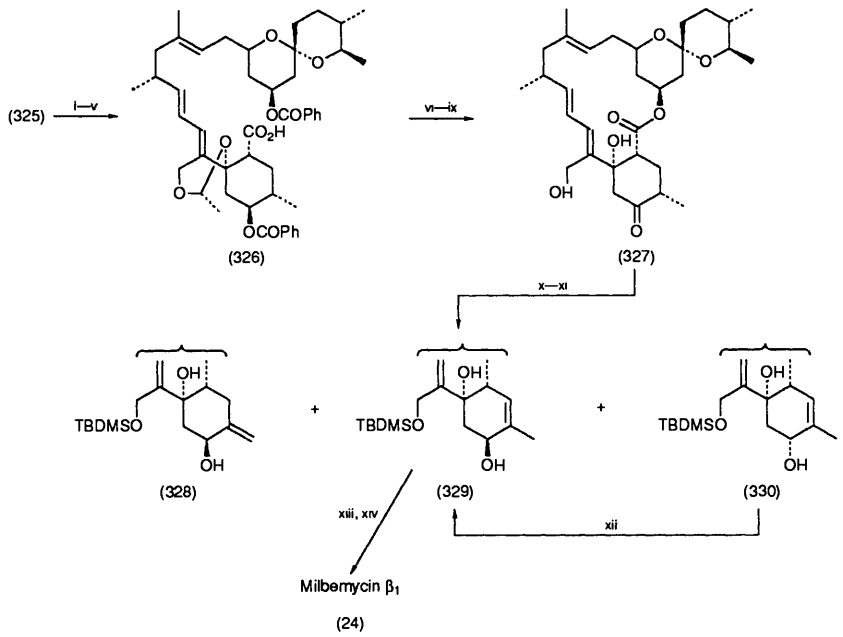


Reagents: i, BH_3·DMS, THF then aq. NaOH, H_2O_2; ii, PhCHO, PPTS, benzene, reflux; iii, 2.2 eq. Bu^{t}Li, THF, −78 °C then PhSeCl; iv, mcpba, CH_2Cl_2, aq. $NaHCO_3$; v, 2.2 eq. Bu^{t}Li, THF, −78 °C

Scheme 41

groups followed by macrolactonization under Mukaiyama conditions[149] gave the desired 16-membered lactone, which was then oxidized at C-5 and the benzylidene acetal cleaved to afford the ketone (327). Treatment of this material with t-butyldimethylsilyl triflate served not only to protect the C-8 alcohol but also provide the thermodynamic silyl enol ether at C-5. Obtention of this enol ether was critical to the successful conclusion of the synthesis. Thus treatment with phenylselenyl chloride followed by oxidation gave the intermediate selenoxides which spontaneously *syn*-eliminated to give a 1:2 mixture of *exo* and *endo* olefin products. In order to prevent aromatization, this mixture was immediately reduced with sodium borohydride to give the mixture of alcohols

[149] T. Mukaiyama, M. Usui, and K. Saigo, *Chem. Lett.*, 1976, 49.



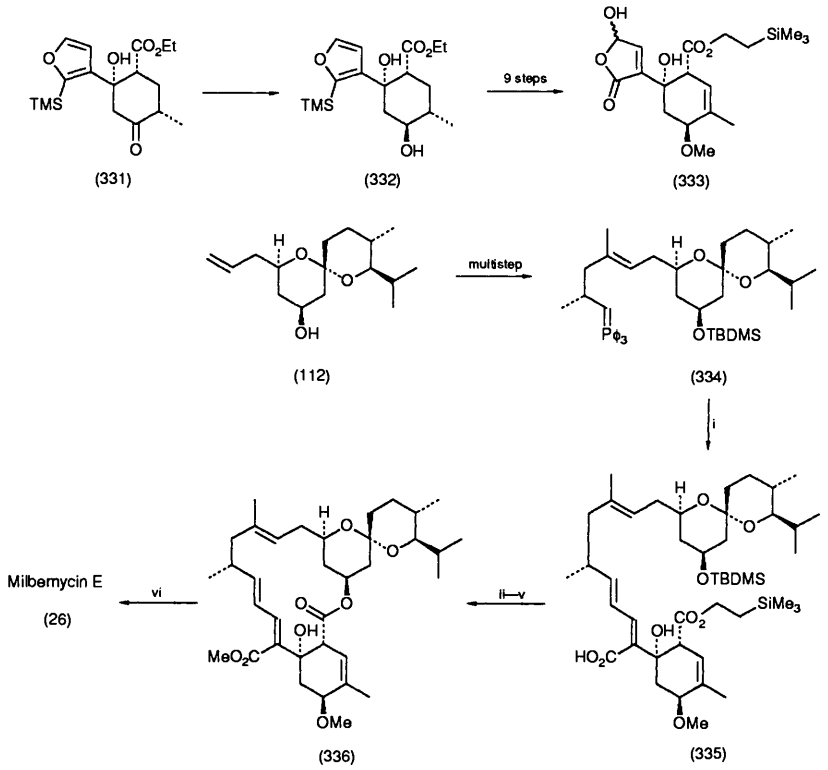
Reagents: i, 6%Na/Hg, Na_2HPO_4, THF, MeOH, −40 °C; ii, PhCOCl, DMAP, pyridine, CH_2Cl_2; iii, Bu^n_4NF, THF, reflux, 15 min; iv, TPAP, NMO, 4 Å ground sieves, CH_2Cl_2; v, $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, Bu^tOH, H_2O; vi, NaOMe, MeOH; vii, 2-chloro-1-methyl pyridinium iodide, Et_3N, CH_3CN, reflux, 9 h; viii, TPAP, NMO, 4 Å ground sieves, CH_2Cl_2; ix, TFA, CH_2Cl_2; x, 4 eq. TBDMS.OTf, 20 eq. Et_3N, CH_2Cl_2, r.t., then PhSeCl, CH_2Cl_2, −78 °C; xi, 2-benzenesulphonyl-3-(*p*-nitrophenyl)oxaziridine, $CDCl_3$, r.t., then $NaBH_4$, $CeCl_3$, MeOH, r.t.; xii, TPAP, 4 Å ground sieves, CH_2Cl_2, then $NaBH_4$, $CeCl_3$, MeOH, r.t.; xiii, MeI, Ag_2O, ultrasound; xiv, HF, pyridine, CH_3CN

Scheme 42

(328), (329), and (330) in a 1:1:1 ratio. These were readily separated by chromatography and the least polar component (330) recycled, to provide further quantities of the equatorial alcohol (329), by the previously successful oxidation–reduction sequence. Finally, methylation of the C-5 alcohol (329) with methyl iodide under ultrasonication followed by deprotection of the t-butyldimethylsilyl ether gave the desired natural product, (+)-milbemycin β_1 (24), in 55% yield from the alcohol (329).

A synthesis of 3,4-dihydromilbemycin E has been reported by Thomas and colleagues and the chemistry involved adapted to a synthesis of milbemycin E (Scheme 43).[150] The racemic Robinson annelation product (331)[116] was resolved, through its derived C-5 alcohol, by the use of (*S*)-(+)-acetoxymandelic acid, to give the dihydroxy ester (332), and this was transformed in nine steps into the hydroxy butenolide (333). Employing similar chemistry to that first described by

[150] E. R. Parmee, P. G. Steel, and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1989, 1250.



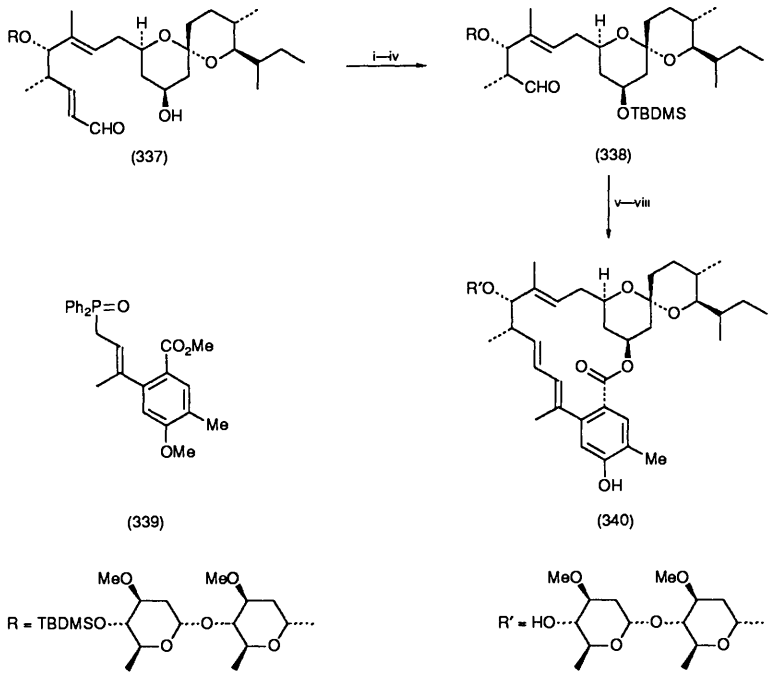
Reagents: i, 2 eq. LiHMDS, add (333), −78 °C to −15 °C, 3 h; ii, CH_2N_2, Et_2O; iii, I_2 benzene; iv, TBAF, THF, 10 h; v, DCC, DMAP, CH_2Cl_2, 0 °C, 16 h; vi, Dibal-H, toluene, −78 °C, 1 h

Scheme 43

Baker and colleagues,[136] the spiroacetal (112)[82,84] was transformed into the phosphorane (334) and reaction of this with the hydroxy butenolide (333) afforded the required diene (335) along with some of its C-10,C-11 geometrical isomer. These were not separated but esterified with diazomethane, and the double bond was isomerized using a catalytic amount of iodine to provide the required (*E*)-isomer in about 37% yield. Removal of the silyl protecting groups followed by macrocylic cyclization using DCC then provided the cyclic structure (336). Reduction of this ester as shown in the Scheme then provided milbemycin E (26) in high yield. A notable feature of the synthesis was that the Δ^3 double bond was not found to migrate into conjugation with the carboxylic acid, a problem which has beset a number of syntheses of the avermectins (*vide infra*).

Finally, Smith and Thompson have reported an efficient synthesis of an

[151] A. B. Smith and A. S. Thompson, *Tetrahedron Lett.*, 1985, **26**, 4283.



Reagents: i, TBDMS.OTf, CH_2Cl_2, 2,6-lutidine, 0 °C, 15 min; ii, $NaBH_4$, MeOH, 0 °C to r.t., ½ h; iii, $Mo(CO)_6$, Bu^tOOH, benzene, Δ, 1.5 h; iv, H_5IO_6, Et_2O, r.t., 40 min; v, NaHMDS, (339), THF, HMPA; vi, Bu^n_4NF, THF, 18 h; vii, KH, KHMDS, THF, r.t., 1 h; viii, EtSNa, DMF, Δ

Scheme 44

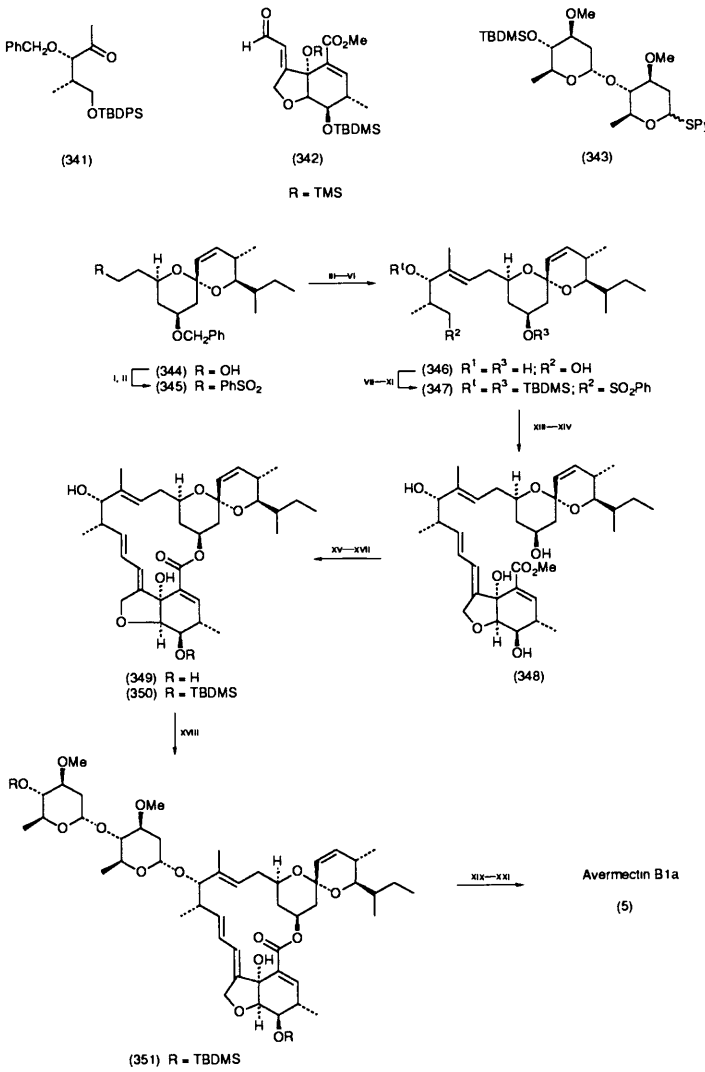
avermectin–milbemycin hybrid.[151] The aldehyde (337), readily available in five steps by degradation of avermectin B_{1a}[152] (*vide infra*), was protected as its t-butyldimethylsilyl ether and the aldehyde functionality reduced to a primary alcohol (Scheme 44). Sharpless epoxidation of the C-10–C-11 olefin, followed by oxidative cleavage, afforded the aldehyde (338) in 13% overall yield. Horner–Emmons condensation of the aldehyde with the phosphine oxide (339)[132] in the presence of sodium hexamethyldisilylazide, followed by desilylation, macrolactonization, and demethylation, led to the formation of the macrocyclic hybrid (340). The amount of base employed was critical to the successful Horner–Emmons condensation. Two equivalents led only to β-elimination, whereas with three equivalents and excess phosphine oxide, a 77% yield of product was observed.

B. Avermectins.—While there has been a wealth of literature on the partial synthesis of the avermectins and milbemycins as well as a number of reports of

[152] A. B. Smith and A. S. Thompson, *Tetrahedron Lett.*, 1985, **26**, 4279.

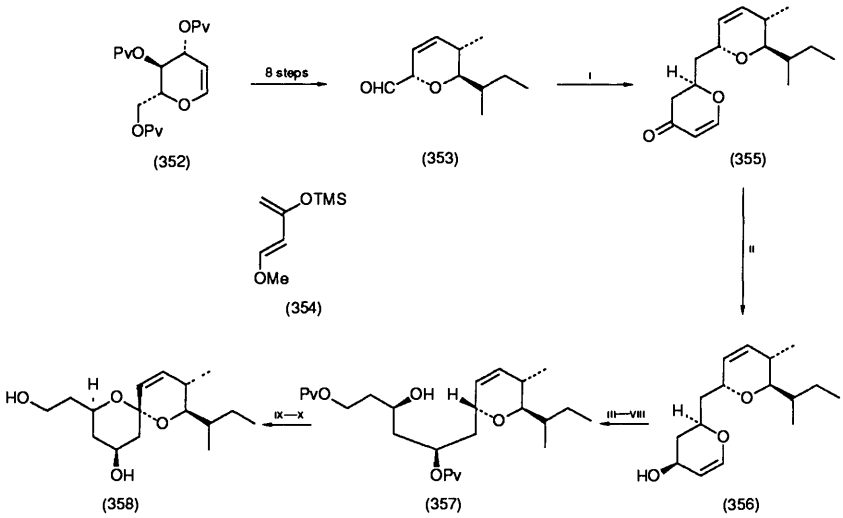
total syntheses of milbemycins, a total synthesis of an avermectin had, until recently, proved elusive. However, in 1986, Hanessian and his co-workers successfully surmounted this obstacle and reported the first total synthesis of a member of this group of macrocycles[94,95] when they described the total synthesis of avermectin $B1_a$ (Scheme 45). These workers had earlier described the synthesis of the spiroacetal (344) from chiral precursors,[153,1] and this was utilized in the total synthesis by conversion into its phenylsulphonyl derivative (345) in routine fashion. Condensation of the anion of this with the chiral ketone (341), obtained in nine steps from (*S*)-malic acid, followed by reductive elimination and protecting group removal, resulted in the formation of the triol (346). Chemical differentiation between the primary and secondary alcohol moieties then served to generate the phenylsulphonyl derivative (347) as shown in the Scheme. Condensation of this with the aldehyde (342), reportedly obtained by a controlled oxidative degradation of avermectin $B1_a$[154] (*vide infra*), followed by reductive elimination and desilylation, provided the *trans*-diene (348) as the only dienic product. Removal of the ester protection and macrolactonization then gave the cyclic compound (349), which was protected at C-5 as a t-butyldimethylsilyl ether (350). All that now remained to complete the total synthesis was the coupling of the disaccharide unit at C-13 and deconjugation of the C-2 olefin. The first problem was achieved by resort to a procedure developed by Hanessian,[155] whereby the protected ether (350) was treated with the 2-pyridylthioglycoside derivative of the disaccharide (343) in the presence of silver triflate. This process provided a mixture of glycosides from which the desired product (351) could be isolated after chromatography. The final stage of the synthesis relied upon a pivotal deconjugation of the C-2 olefin. This was successfully achieved by initial protection of the C-7 hydroxyl group, to preclude its participation in the subsequent acid quench, followed by treatment with strong base in the presence of trimethylsilyl chloride. Acid hydrolysis of the so formed keteneacetal then served to deliver its proton from the requisite face of the intermediate, resulting in the formation of the elusive avermectin (5) after desilylation. In spite of this prodigious achievement, later work by Hanessian and colleagues,[156] in an attempt to optimize the deconjugation process, showed the reaction to be extremely capricious. They noted 'an unpredictable variation in the nature of the products, even with only the slightest change in experimental procedure'. In relation to this work, Fraser-Reid and colleagues also investigated the deconjugation stage[157] but were unable to duplicate the work of Hanessian, who concludes[156] that 'the material produced in the original deconjugation was not the primary product of deconjugation, but possibly the result of a subsequent epimerization of an initially formed 2-*epi* isomer'. In spite of the mutable nature of the final deconjugation step of the synthesis, this work nevertheless constitutes

[153] S. Hanessian, A. Ugolini, and M. Therien, *J. Org. Chem.*, 1983, **48**, 4427.
[154] S. Hanessian, A. Ugolini, P. J. Hodges, and D. Dube, *Tetrahedron Lett.*, 1986, **27**, 2699.
[155] S. Hanessian, C. Bacquet, and N. LeHong, *Carbohydr. Res.*, 1980, **80**, C17.
[156] S. Hanessian, D. Dube, and P. J. Hodges, *J. Am. Chem. Soc.*, 1987, **109**, 7063.
[157] B. Fraser-Reid, H. Wolleb, R. Faghih, and J. Barchi, Jr., *J. Am. Chem. Soc.*, 1987, **109**, 933.



Reagents: i, PhSSPh, Ph_3P, THF; ii, *m*-CPBA, CH_2Cl_2, $-10\,^{\circ}C$; iii, Bu^nLi, THF, $-78\,^{\circ}C$ then add (341); iv, Na/Hg, MeOH, THF, KH_2PO_4; v, Bu^n_4NF, THF; vi, Li/NH_3; vii, Bu^tOCl, Et_3N, CH_2Cl_2; viii, Bu^tMe_2SiCl, imidazole, DMAP, DMF; ix, NaOMe, MeOH, CH_2Cl_2; x, PhSSPh, Bu^n_3P, THF; xi, *m*-CPBA, CH_2Cl_2; xii, Bu^nLi, THF, $-78\,^{\circ}C$ then add (342); xiii, $SOCl_2$, pyr then Na/Hg, MeOH; xiv, Bu^n_4NF, THF; xv, aqueous KOH, THF, then Dowex 50 (H^+); xvi, DCC, DMAP, CH_2Cl_2; xvii, Bu^tMe_2SiCl, imidazole, DMF; xviii, (343), CH_2Cl_2, AgOTf, toluene; xix, Me_3SiCl, Et_3N, DMAP, CH_2Cl_2; xx, LDA, Me_3SiCl, THF, $-78\,^{\circ}C$ then AcOH, THF, $-78\,^{\circ}C$ to r.t.; xxi, Bu^n_4NF, THF

Scheme 45



Reagents I, (354), $MgBr_2$, CH_2Cl_2, II, $NaBH_4$, $CeCl_3$, CH_2Cl_2, EtOH, −78 °C, III, TBDMS OTf, CH_2Cl_2, lutidine, −78 °C, 30 min, IV, NBS, $NaHCO_3$, aq THF, V, Bu_3SnH, AIBN, toluene, VI, $LiBH_4$, THF, VII, PrCl, CH_2Cl_2, Et_3N, DMAP, VIII, 5% HF in CH_3CN, IX, HgO, I_2, CCl_4, *hv*, 1 5 h, X, LiOH, MeOH, THF, H_2O

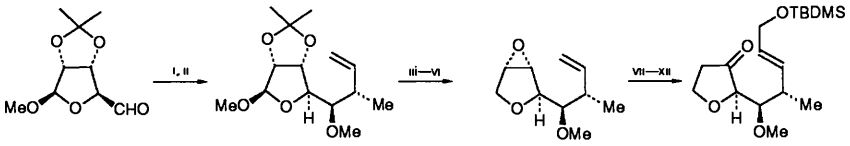
Scheme 46

an immense scientific achievement due to the high degree of stereoselectivity that is realised A fuller explanation of the results of the deconjugation/epimerization experiments of Hanessian and Fraser-Reid is presented in a later Section of this review

More recently, Danishefsky and his associates have reported their investigations, which culminated in the total synthesis of another member of the avermectin family, namely avermectin $A1_a$ [96 97 158] In order to obtain their goal, they identified two chiral intermediates, (358) and (362), as being the keys to the synthesis Thus the D-glucal derivative (352) was transformed, in eight high yielding steps (30% overall yield), into the chiral aldehyde (353) (Scheme 46) which, on treatment with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (354), afforded a diastereoisomeric pair containing the isomer (355) as the major constituent This mixture was reduced and the product purified by chromatography to give the homogeneous unsaturated alcohol (356) Progression of this, as shown in the Scheme, furnished the alcohol (357), in 49% overall yield, and oxidative cyclization followed by depivaloylation gave the target spiroacetal (358) This material was identical to an authentic sample obtained by osmium tetroxide degradation of Δ^2 avermectin $A1_a$ aglycon [159] (*vide infra*) The second

[158] S Danishefsky H G Selnick D M Armistead and F E Wincott, *J Am Chem Soc* 1987 **109** 8119

[159] H G Selnick and S J Danishefsky *Tetrahedron Lett*, 1987 **28** 4955



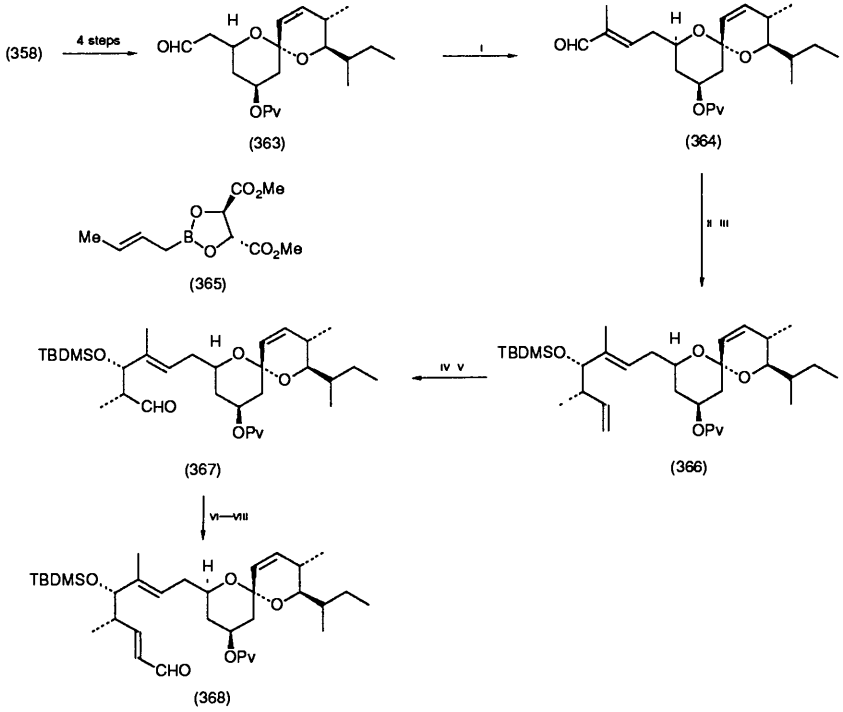
(359) (360) (361) (362)

Reagents: i, (*E*)-trimethylcrotylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C; ii, NaH, THF, MeI; iii, HCl, MeOH; iv, Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2; v, $Me_2C(OAc)CO{\cdot}Br$, CH_2Cl_2, 1 h; vi, Amberlite IRA-400, MeOH; vii, $LiEt_3BH$, THF, 0 °C, 6 h; viii, O_3, CH_2Cl_2, −78 °C, 5 min then Zn, AcOH; ix, $Ph_3P{=}CH{\cdot}CO_2Me$, CH_2Cl_2, 12 h; x, Dibal-H, Et_2O, 0 °C, 2 h; xi, Bu^tMe_2SiCl, Et_3N, DMAP, CH_2Cl_2; xii, PCC, NaOAc, CH_2Cl_2

Scheme 47

target intermediate (362) was obtained by an adaptation of some earlier model studies.[110] Thus the aldehyde (359), readily obtainable from D-ribose, was reacted with (*E*)-trimethylcrotylsilane followed by methylation, yielding the olefin (360) (Scheme 47). Conversion of this acetonide to the epoxide (361) was successfully achieved by resort to a well established process, and this epoxide was regioselectively reduced with lithium triethylborohydride to provide the potential C-7 hydroxyl group of the final product. Ozonolysis, with reductive work-up, of the terminal olefin, followed by Wittig coupling, reduction and protection, served to generate an alcohol, which was oxidized to afford the second target intermediate (362). The next stage of the synthesis involved the stereoselective introduction of the C-12 methyl and C-13 hydroxyl substituents. Protecting group manipulation of the spiroacetal (358) gave the aldehyde (363), and this was homologated, as shown in Scheme 48, which served to introduce the required *E*-olefin and afforded the α,β-unsaturated aldehyde (364) in excellent yield. Utilization of the elegant crotonyl borate chemistry of Roush and colleagues[160] provided access to the stereocontrolled introduction of the C-12 and C-13 substituents, resulting in the formation of the vital C-11 to C-25 fragment of the avermectins. The product was obtained as a 4:1 mixture of diastereoisomers which proved difficult to separate. However, protection of the secondary alcohol to give (366), followed by selective dihydroxylation of the monosubstituted olefin and cleavage of the resulting diol with lead tetraacetate, provided a mixture of aldehydes from which the major diastereoisomer (367) was obtained by chromatography. Simple homologation as shown in the Scheme then gave the α,β-unsaturated aldehyde (368). The total synthesis was then completed by the process depicted in Scheme 49. The lithium enolate of (362) was condensed with the α,β-unsaturated aldehyde (368) and the product dehydrated with methanesulphonyl chloride to afford the (*E,E*)-diene system, which was selectively deprotected and oxidized to afford the aldehyde (369). Cyclization to the hexahydrobenzofuran system (370) was accomplished as shown and the product oxidized and deprotected to give the hydroxy acid (371) in high yield.

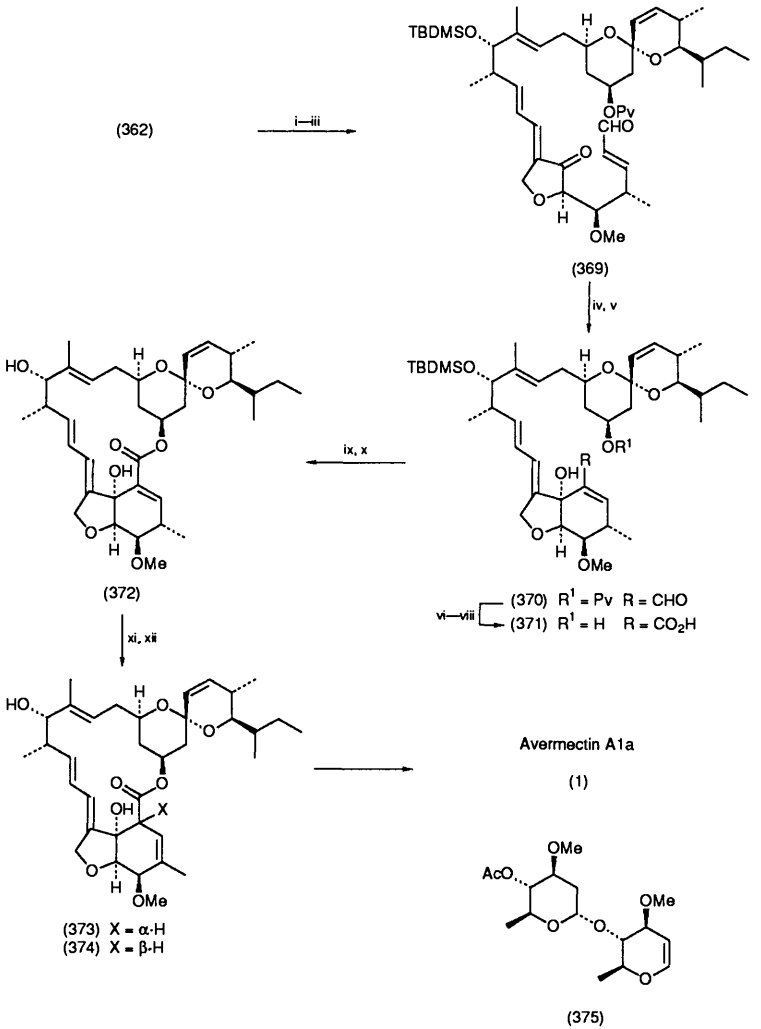
[160] W. R. Roush and A. D. Palkowitz, *J. Am. Chem. Soc.*, 1987, **109**, 953.



Reagents i, $Ph_3P{=}C(CHO)CH_3$, benzene, reflux, 36 h, ii, (365), toluene, −78 °C, 1 5 h, iii, Bu^tMe_2SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 0 5 h, iv, OsO_4, THF, pyridine, v, $Pb(OAc)_4$, CH_2Cl_2, 0 °C, 5 min then chromatography, vi, $Ph_3P{=}CH{\cdot}CO_2Me$, CH_2Cl_2, r t, 24 h, vii, Dibal-H, THF, −78 °C, 2 h, viii, $(COCl)_2$, CH_2Cl_2, DMSO, −78 °C, 1 5 h

Scheme 48

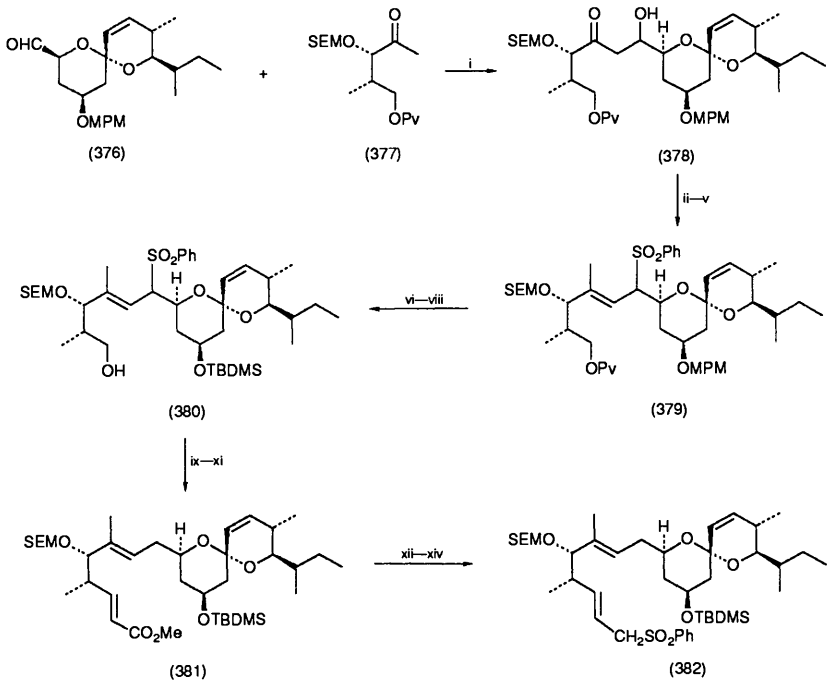
Macrolactonization using the Mukaiyama procedure[149] followed by desilylation, then produced the Δ^2 isomer of avermectin $A1_a$ aglycon (372) The final stage of the synthesis was achieved by employment of Hanessian's modified deconjugation methodology[156] Thus action of lithiumdiisopropylamide on (372) followed by quenching with aqueous hydrochloric acid gave a 75% yield of C-2 *epi*-avermectin $A1_a$ aglycon (373) along with a 21% yield of recovered starting material These were readily separated by chromatography and the C-2 *epi*-compound (373) heated with a concentrated solution of imidazole in benzene for 1 5 hours This resulted in a mixture of 33% recovered starting material (373), 21% of Δ^2 avermectin $A1_a$ aglycon (372), and a 32% yield of the elusive aglycon of avermectin $A1_a$ (374), all of these compounds were readily separated by chromatography To complete the synthesis of the natural product, Danishefsky has developed a new protocol[158] for the formation of the disaccharide portion and its coupling with the aglycon (374) Thus the unsaturated disaccharide (375) was coupled to the aglycon (374) through the use of *N*-iodosuccinimide, followed



Reagents: i, LiHMDS, (368), THF, −78 °C then $MeSO_2Cl$, Et_3N; ii, HF, CH_3CN, −20 °C; iii, PCC, NaOAc, CH_2Cl_2; iv, Me_3Al, PhSLi, THF, 0 °C, 10 min then *m*-CPBA, CH_2Cl_2, −20 °C, 2 h; v, toluene, heat, 30 min; vi, Bu^{t}OH, 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4; vii, CH_2N_2, Et_2O; viii, LiOH, MeOH, H_2O; ix, 2-chloro-*N*-methylpyridinium iodide, Et_3N, CH_2Cl_2, CH_3CN, heat; x, Bu^n_4NF, THF, r.t., 2 h; xi, LDA, THF, −78 °C, 15 min then 1N-HCl; xii, imidazole, benzene, reflux, 1.5 h; xiii, *N*-iodosuccinimide, CH_3CN, (375), r.t., 1 h; xiv, Bu^n_3SnH, AIBN, toluene, reflux, 10 min; xv, $LiEt_3BH$, THF, −78 °C, 3 h

Scheme 49

by reductive dehalogenation and deacylation, which resulted in the completion of the total synthesis of avermectin $A1_a$ (1).



Reagents: i, LDA, THF, −78 °C, 0.5 h; ii, Ac_2O, Et_3N, DMAP, CH_2Cl_2 then DBU; iii, MeMgCl, THF, 0 °C, 1 h; iv, PhSCl, Et_3N, CH_2Cl_2, −78 °C to 25 °C; v, oxone, MeOH, H_2O; vi, $(NH_4)_2Ce(NO_3)_6$, H_2O, CH_3CN; vii, Bu^tMe_2SiOTf, 2,6-lutidine, CH_2Cl_2; viii, $LiAlH_4$, THF; ix, Na(Hg), Na_2HPO_4, MeOH, 25 °C, 2 h; x, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 25 °C; xi, $Ph_3PCH{\cdot}CO_2Me$, toluene; xii, Dibal-H, toluene, −75 °C; xiii, NCS, Me_2S, CH_2Cl_2, 0 °C to 25 °C; xiv, $PhSO_2Na$, DMF, 25 °C, 48 h

Scheme 50

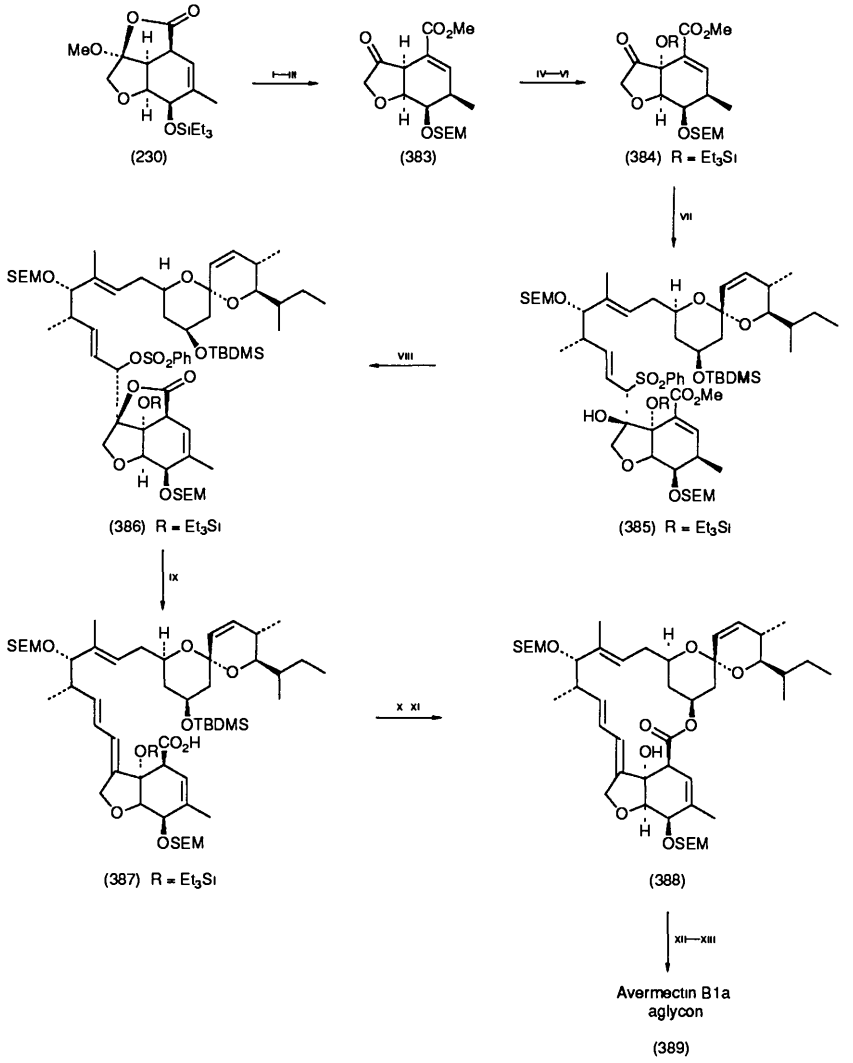
To date, two other total syntheses of an avermectin have been described; the first of these was reported by White and colleagues.[98] These workers had previously published routes to both the spiroacetal[87] (Scheme 11) and oxahydrindene[121] (Scheme 28) moieties of avermectin $B1_a$, and they have now succeeded in linking these two portions to provide the third total synthesis of an avermectin, namely avermectin $B1_a$ aglycon. The linear segment (377) required for the completion of the synthesis was obtained in routine fashion from ethyl levulinate in ten steps. The lithium anion of this molecule (377) was condensed with the aldehyde (376) [readily obtainable by Swern oxidation of the primary alcohol (124)[87]] giving the crossed aldol product (378) (Scheme 50) in high yield. β-Elimination of this hydroxy ketone and reaction with methyl Grignard, followed by elaboration as shown in the Scheme, afforded the sulphone (379). Protecting group adjustment followed by reductive removal of the pivalate protection then provided the primary alcohol (380). Reductive removal of the phenyl sulphonyl group was accomplished in reasonable yield and the product

oxidized and subjected to Wittig coupling, giving the α,β-unsaturated ester (381) in high yield. Standard chemistry then served to provide the sulphone (382) as shown in Scheme 50. In order to complete the synthesis of avermectin $B1_a$, some minor modifications had to be made to the previously described oxahydrindene[121] synthesis in order to introduce the C-7 hydroxyl function (avermectin numbering) of the final product. Thus the previously described silyl ether (230) was converted to a SEM ether and the lactone opened with methoxide ion; accompanying migration of the double bond then occurred, providing the bicyclic ketone (383) (Scheme 51). That the double bond had migrated into conjugation with the ester moiety proved advantageous, in that conversion of the ketone into its silyl ether followed by epoxidation provided the required C-7 hydroxylated oxahydrindene. Routine protection then gave the silyl ether (384). Julia coupling[161] of this ketone (384) with the previously described sulphone (382) (Scheme 50) gave the hydroxy sulphone (385) in 50% yield, but all attempts to effect elimination failed and in each case the major product was the lactone (386). Fortunately these workers were able to take advantage of this unexpected occurrence and thus by sodium amalgam reduction were able to produce the requisite diene (387). Deprotection of the t-butyldimethylsilyl ether followed by macrolactonization under Mukaiyama conditions[149] afforded the lactone (388) of inverse stereochemistry at C-2 to that present in the naturally occurring avermectins. In order to overcome this problem, resort to Hanessians epimerization conditions[156] provided a 34:50 ratio of C-2 epimers, along with 16% of a Δ^2 isomer which was removed by chromatography. Finally, cleavage of the remaining protecting groups followed by chromatographic purification provided the target avermectin aglycon (389), whose spectroscopic properties were identical to those of an authentic sample derived from hydrolysis of the naturally occurring macrocycle.[162]

Very recently, Ley and his colleagues at Imperial College have published a series of papers[99–102] describing their success in achieving a total synthesis of avermectin $B1_a$. The optically active cyclohexanone (390), a precursor in Ley's total synthesis of milbemycin β_1,[36] was dehydrated and the resulting α,β-unsaturated ketone epoxidized with dimethyldioxirane (Scheme 52).[99] This provided a 5:1 mixture of α and β epoxides which were readily separated by chromatography. Addition of 2-lithio-4-phenylthiobut-1-ene to the major epoxide then provided the sulphide (391) as the only detectable isomer. Confirmation of the absolute stereochemistry of this product was obtained by *X*-ray crystallography of a derivative of the corresponding sulphone. Oxidation of the sulphide (391) followed by epoxide ring opening gave the tetraol (392). Unfortunately, the vigorous conditions required for epoxide opening also removed the protecting group at C-1. Protecting group adjustment followed by inversion of the alcohol at C-6, utilizing an oxidation–reduction sequence, gave a 6:1 mixture of alcohol diastereoisomers from which the major one (393) was

[161] M Julia, *Pure Appl Chem*, 1985, **57**, 763

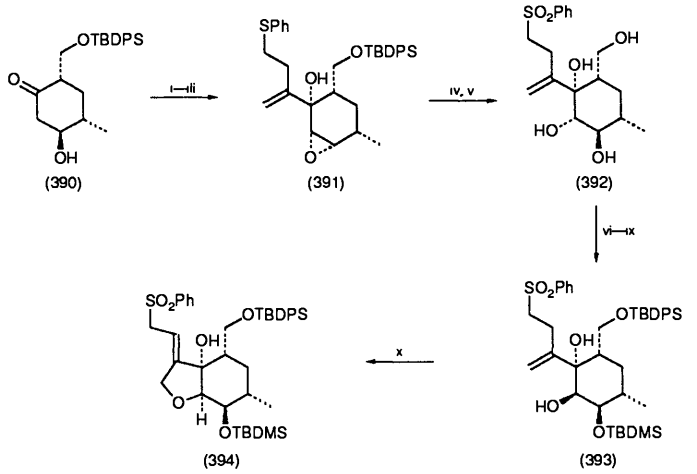
[162] H Mrozik, P Eskola, B H Arison, G Albers-Schonberg, and M Fisher, *J Org Chem*, 1982, **47**, 489



Reagents I, TFA, THF, H_2O, II, $Me_3SiCH_2CH_2OCH_2Cl$, Pr^i_2NEt, CH_2Cl_2, III, K_2CO_3, MeOH, IV, Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, V, *m*-CPBA, CH_2Cl_2, VI, Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, VII, Bu^nLi, THF, (382), −78 °C, VIII, NaOMe, Na_2HPO_4, MeOH, 0 °C, 0 5 h, IX, Na(Hg), Na_2HPO_4, MeOH, 0 °C, 3 h, X, TBAF, THF, XI, 2-chloro-1-methylpyridinium iodide, Et_3N, CH_3CN, reflux, 2 5 h, XII, imidazole, benzene, reflux, 1 5 h, XIII, HF, MeCN

Scheme 51

obtained pure by chromatography Conversion of this material into the important intermediate (394) was then achieved by utilization of similar chemistry to that employed in the total synthesis of milbemycin β_1 [36]



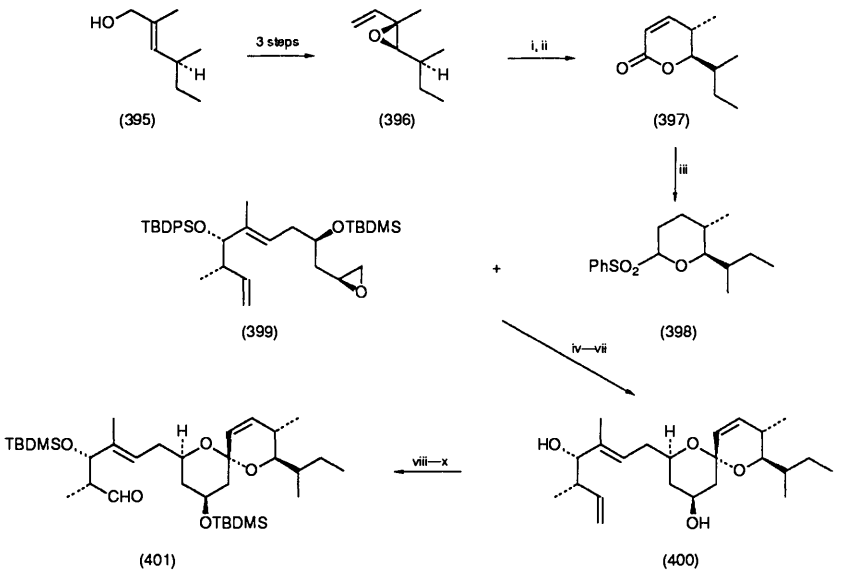
Reagents: i, MsCl, Et_3N, CH_2Cl_2; ii, dimethyldioxirane, Me_2CO, CH_2Cl_2; iii, $PhS(CH_2)_2C(=CH_2)Li$, THF, −78 °C; iv, oxone; v, 15% H_2SO_4, THF, 60 °C; vi, Bu^tPh_2SiCl, imidazole, DMF; vii, Bu^tMe_2SiOTf, Et_3N, CH_2Cl_2; viii, $(COCl)_2$, DMSO then Et_3N; ix, $NaBH_4$, MeOH; x, ref. 36

Scheme 52

The next stage of the synthesis involved preparation of the C-11–C-25 spiroacetal portion, and this was achieved by resorting to the use of π-allyl iron complexes.[100] The readily available allylic alcohol (395) was converted, in three steps, into the epoxide (396) (Scheme 53); this, on treatment with di-iron nonacarbonyl, gave a mixture of diastereoisomeric π-allyltricarbonyliron lactone complexes. Interestingly, although these products are diastereoisomeric, the key homochiral asymmetric carbon atom is common to both isomers and thus on exhaustive carbonylation only one enantiomer (397) was obtained. Conversion of this lactone into the sulphone (398) was then achieved using previously reported chemistry.[163] Condensation of the sulphone (398) with the epoxide (399), readily obtained from 2-propynyl-1-ol, gave an unstable enol ether which was immediately transformed using standard methodology into the spiroacetal diol (400). Protection of the two alcohol moieties followed by oxidative cleavage of the double bond and oxidation of the resulting diol gave the required intermediate (401).

With these two important precursors (401) and (394) in hand, the total synthesis of avermectin $B1_a$ was now within reach. Thus sulphone-stabilized anion coupling of (401) and (394) gave the diastereoisomeric hydroxy sulphones (402) (Scheme 54).[101] This unstable mixture was immediately subjected to reductive elimination and the resulting diene fully deprotected. The so formed penta-hydroxy derivative was then selectively oxidized at C-1, in two steps, to

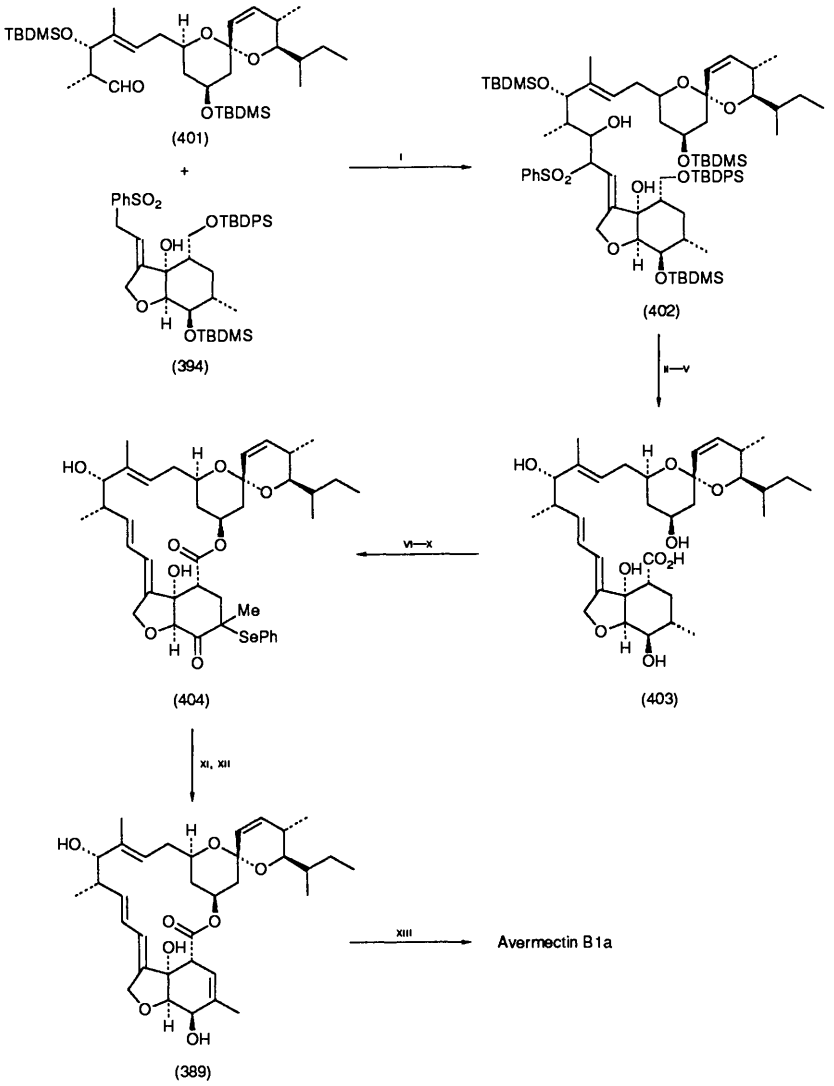
[163] D. S. Brown, M. Bruno, R. J. Davenport, and S. V. Ley, *Tetrahedron*, 1989, **46**, 4293.



Reagents: i, $Fe_2(CO)_9$, THF; ii, CO, 250 atm, benzene, Δ; iii, ref. 167; iv, $BF_3{\cdot}Et_2O$, BuLi, −78 °C, THF; v, PhSeCl, MeOH, Et_2N, CH_2Cl_2 then CSA, MeOH, CH_2Cl_2; vi, *p*-nitrophenyl-*N*-sulphonyl oxaziridine, $CHCl_3$, 50 °C; vii, TBAF, THF, Δ; viii, Bu^tMe_2SiCl, imidazole, DMF; ix, OsO_4, NMNO, Bu^tOH, THF, H_2O; x, $NaIO_4$, KH_2PO_4, H_2O, MeOH

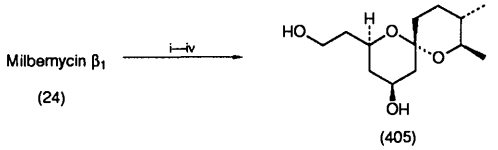
Scheme 53

afford the carboxylic acid (403). Cyclization under Mukaiyama conditions[149] provided the 16-membered ring macrocycle and this was subsequently oxidized at C-5. Treatment of the resulting ketone with trimethylsilyl triflate provided the silylenol ether at C-5 along with simultaneous protection of the C-7 and C-13 alcohols. Conversion of the enol ether to the intermediate selenide followed by removal of the unwanted silyl protecting groups then provided the ketone (404) as a 1:1 mixture of diastereoisomers. Selenoxide formation followed by *syn*-elimination and reduction then provided the elusive avermectin aglycon (389) in reasonable yield. The C-4-exomethylene isomer was also obtained from the selenoxide elimination but was readily removed by chromatography. An intriguing feature of the synthesis is the lack of protecting groups employed in the final stages; this was achieved by the innovative exploitation of the differential chemical reactivity of the individual hydroxyl groups. With the aglycon in hand, all that now remained to complete the synthesis of avermectin $B1_a$ was to introduce the disaccharide moiety at C-13. In order to achieve this final stage, Ley and colleagues have developed a new synthesis of the bis-oleandrose fragment involving π-allyl tricarbonyliron lactone complexes as synthetic intermediates.[102] Thus, by utilization of this type of chemistry, the fourth total synthesis of an avermectin was successfully completed.



Reagents: i, 2.2M Bu^{t}Li, THF, −78 °C; ii, 6% Na/Hg, THF, MeOH, −30 °C; iii, TBAF, THF, Δ; iv, $RuCl_2(PPh_3)_3$, C_6H_6; v, $NaOCl_2$, KH_2PO_4, 2-methyl-2-butene, Bu^{t}OH; vi, 2-chloro-1-methylpyridinium iodide, Et_3N, MeCN, Δ; vii, TPAP, CH_2Cl_2, 0 °C; viii, TMSOTf, Et_3N, CH_2Cl_2, 0 °C; ix, PhSeCl, CH_2Cl_2, −78 °C; x, TBAF, THF, 0 °C to r.t.; xi, *p*-nitrophenyl-*N*-sulphonyloxaziridine, $CHCl_3$, r.t.; xii, $NaBH_4$, $CeCl_3$, MeOH, 0 °C; xiii, ref. 166

Scheme 54



Reagents: i, O_3, CH_2Cl_2, $-78\,^{\circ}C$; ii, Me_2S; iii, $NaBH_4$; iv, OH^-

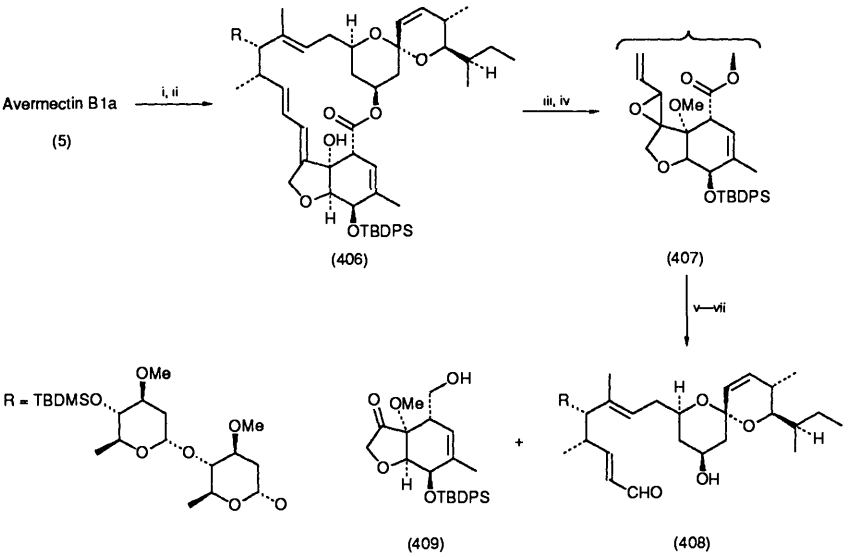
Scheme 55

In view of the vast amount of excellent work that has been published on the synthesis of a variety of fragments of the avermectins, it is to be expected that a number of other total syntheses will be reported in the near future. It is also to be hoped that the content of these will be as chemically stimulating as the four syntheses already published.

8 General Chemistry

A. Degradation of Natural Avermectins and Milbemycins.—Avermectin and milbemycin fragments derived from degradation of the natural products are necessary both to confirm the structures of synthetic intermediates and to act as relay compounds in the course of a total synthesis. This problem was first addressed by Smith and his co-workers, who degraded milbemycin β_1 (24) to provide the spiroacetal fragment (405) in 28% overall yield (Scheme 55).[132] A more difficult problem was to degrade one of these macrolides in such a way as to provide intact C-9 to C-28 and C-1 to C-8 fragments. For avermectin $B1_a$ (5), the solution lay in recognizing the C-8–C-9 double bond as part of an allylic alcohol system and thus susceptible to chemoselective functionalization.[152] Protection of the C-5 and C-4″ hydroxyl groups, as t-butyldiphenylsilyl and t-butyldimethylsilyl ethers respectively (or as a bis-acetate), gave the allylic alcohol (406), which was subjected to Sharpless epoxidation (Scheme 56). It was then necessary to protect the C-7 hydroxyl group as a methyl ether (407) before opening the epoxide with aqueous fluoroboric acid. Reduction of the macrolide ester group with lithium aluminium hydride and oxidative cleavage of the 8,9-diol with lead tetra-acetate gave the required fragments (408) and (409) in good overall yield [a protected form of the aldehyde (408) was later used in a synthesis of a milbemycin–avermectin hybrid].

Degradation of avermectin $B1_a$ (5) into C-1–C-10 and C-11–C-28 segments has been reported by Hanessian and his co-workers (Scheme 57).[154] In this approach the Δ^3 double bond was deliberately moved into conjugation with the ester group to minimize the risk of aromatization of the oxahydrindene group during subsequent manipulations. The macrolide ester was simultaneously hydrolysed during the isomerization to give the seco-ester (410) after esterification with diazomethane; the seco-ester lacking the disaccharide unit was obtained from the aglycon. After silylation of (410) the C-10–C-11 double bond was selectively ozonized in the presence of Sudan 7B as an indicator, and the resulting ozonides were reduced with sodium borohydride to give the fragments (411) and (412).



Reagents: i, Bu^{t}Ph$_2$SiCl, imidazole; ii, Bu^{t}Me$_2$SiCl, imidazole; iii, Bu^{t}OOH, VO(acac)$_2$; iv, CH_2N_2; v, HBF_4, H_2O, Et_2O; vi, $LiAlH_4$; vii, $Pb(OAc)_4$

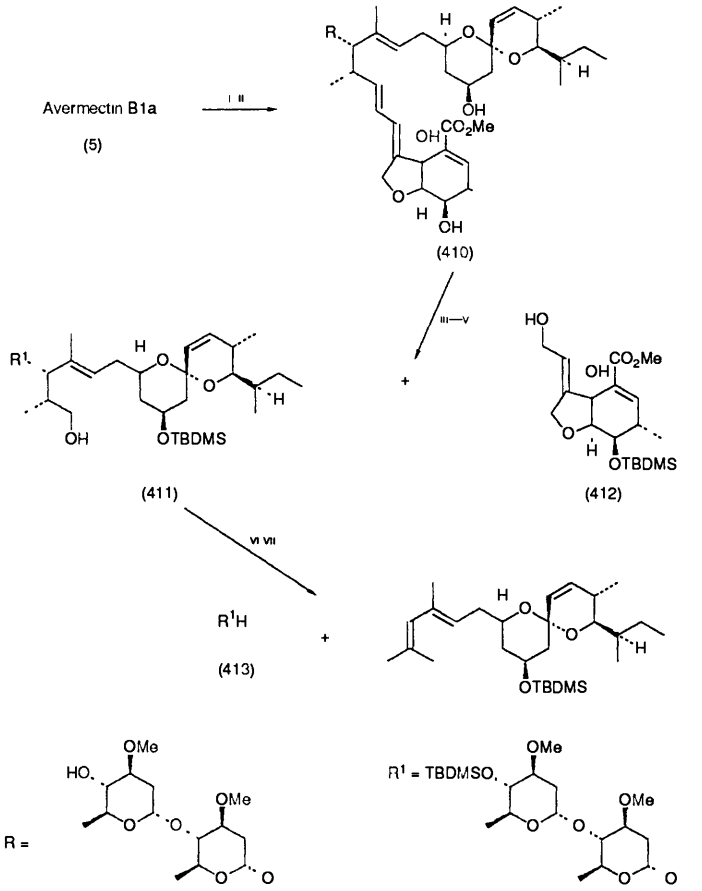
Scheme 56

The intact disaccharide moiety (413) could be obtained from (411) by pyridinium chlorochromate oxidation and base-catalysed elimination.

This degradative procedure to obtain the disaccharide unit has been improved by workers at Merck, who eliminated the conjugation/hydrolysis and esterification steps and ozonized 4″,5-bis-O-t-butyldimethylsilyl avermectin B1 directly.[164] The resulting ozonide was decomposed with methyl sulphide, and DBU was then added to eliminate the disaccharide unit (413). Thus, at the expense of the loss of the aglycon sub-unit, the disaccharide unit could readily be obtained in 57% overall yield with a single day's work.

A method for cleaving avermectin A1$_a$ (1) at C-14–C-15/C-13–C-14 and the macrolide ester has been provided by Selnick and Danishefsky (Scheme 58).[159] The aglycon of avermectin A1$_a$ was converted into the conjugated isomer (414) with DBU in benzene, and this was treated with osmium tetroxide to provide the tetra-ol (415) as a single isomer. This was assigned the 14α,15α-*cis*-hydroxyl structure, as osmylation on the β face of the avermectin would be sterically hindered. When treated with lead tetra-acetate the tetra-ol was cleaved into an ester-dial which was reduced and hydrolysed to give the two fragments (416) and (417). A corresponding osmylation on the non-conjugated avermectin A1$_a$ aglycon gave a mixture of products corresponding to osmylation at C-3–C-4 as well as C-14–C-15.

[164] T. A. Blizzard, G. Marino, H. Mrozik, and M. H. Fisher, *J. Org. Chem.*, 1989, **54**, 1756.



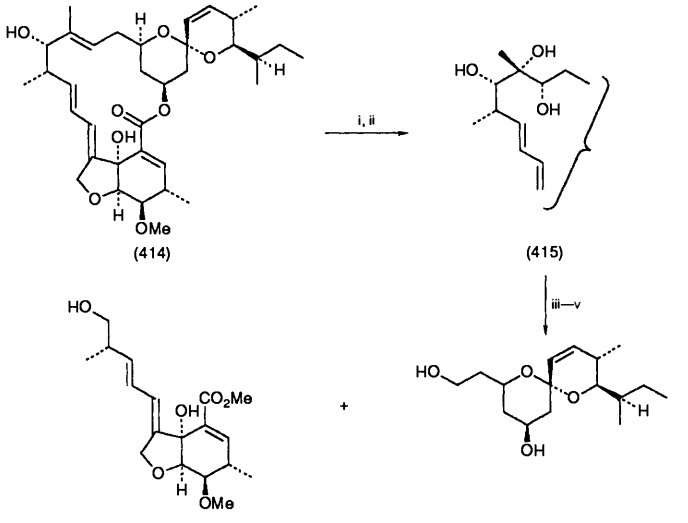
Reagents i, KOH, H_2O, DME, ii, CH_2N_2, iii, Bu^tMe_2SiCl, imidazole, iv, O_3, Sudan Red, v, $NaBH_4$, vi, PCC, vii, KHMDS, THF

Scheme 57

Upon treatment of avermectin B1 with DBU in methanol at 55 °C, the seco-ester (410), previously obtained by Hanessian, was formed in 25–30% yield [165] An interesting minor by-product (418) was also obtained, presumably formed by a series of retro-aldol reactions When the DBU reaction was repeated using diethylamine as solvent, the sole product, obtained in 90% yield, was the Δ^2-isomer of avermectin B1

Ozonolysis of the milbemycin S541 factor B (now called nemadectin B), followed by reductive work-up with dimethyl sulphide, gave an approximately

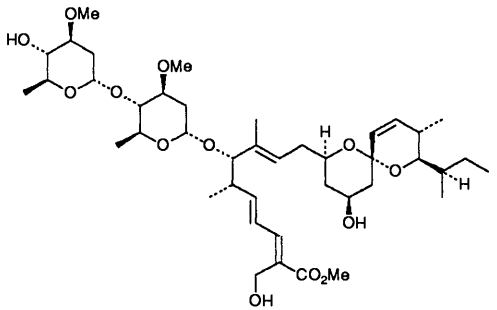
[165] T A Blizzard, H Mrozik, and M H Fisher *Tetrahedron Lett* 1988, **29** 3163



(414) (415) (416) (417)

Reagents: i, OsO_4; ii, $NaHSO_3$; iii, $Pb(OAc)_2$, MeOH, C_6H_6; iv, $NaBH_4$; v, K_2CO_3, MeOH

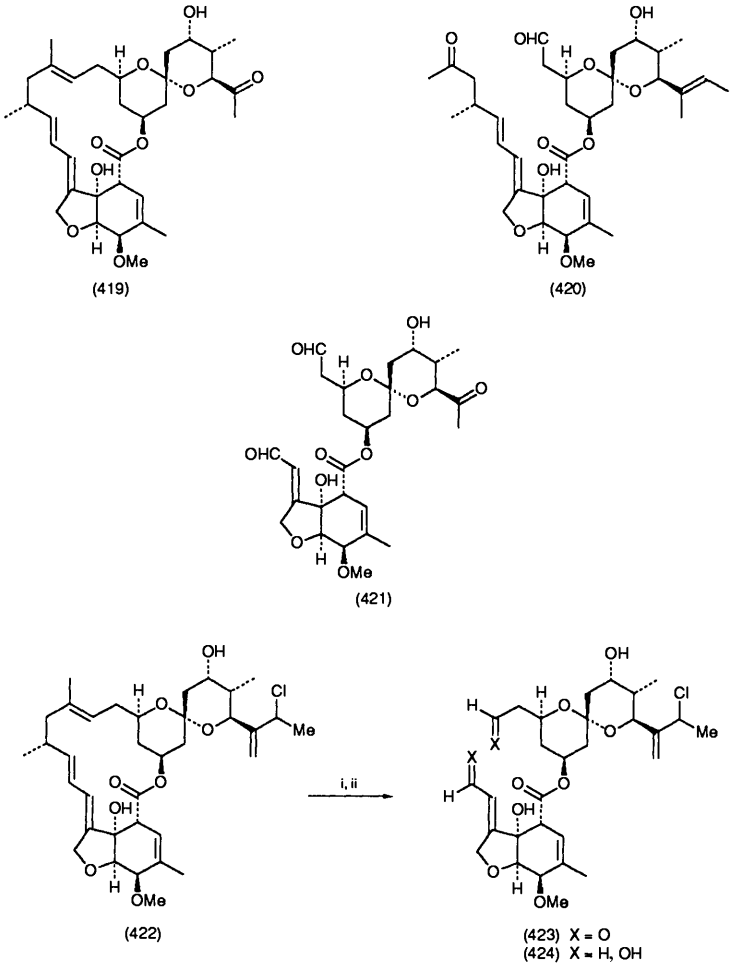
Scheme 58



(418)

equal mixture of three components (419)—(421) corresponding to non-specific cleavage of the macrolide and C-25 side-chain.[166] However, when the side-chain was protected by conversion into the chloro-compound (422) (see Section 8H), the ozonolysis was more selective and excised the C-11—C-14 fragment to give the dial (423) in 59% yield (Scheme 59). When the chlorination and ozonolysis were performed concurrently with no intermediate purification and the ozonide was reduced with sodium borohydride, the corresponding diol (424) could be obtained in 28% overall yield. The C-25 side-chain could then be resurrected by reduction with tributyltin hydride with only 20% contamination by the isomeric

[166] C. E. Mowbray, M. J. V. Ramsay, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1813.

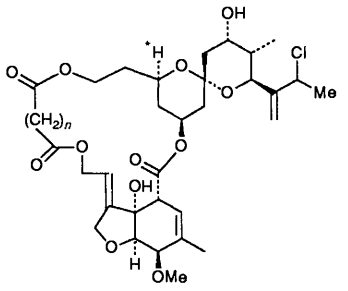


Reagents: i, O_3; ii, $NaBH_4$

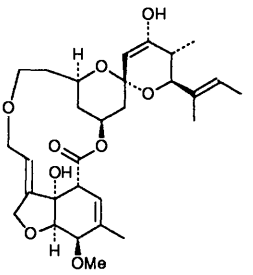
Scheme 59

1-isopropylethene analogue. Various 'semi'-milbemycins (425) were prepared from the diol (424) by cyclization with dicarboxylic acid chlorides, and the dechlorinated material was also converted into lactones by treatment with malonyl and glutaryl chlorides. The macrocyclic ether (426) was prepared in 18% yield by tosylation of the diol (424).

The specific cleavage of the outer spiroacetal ring of avermectins and



(425) n = 0 to 3

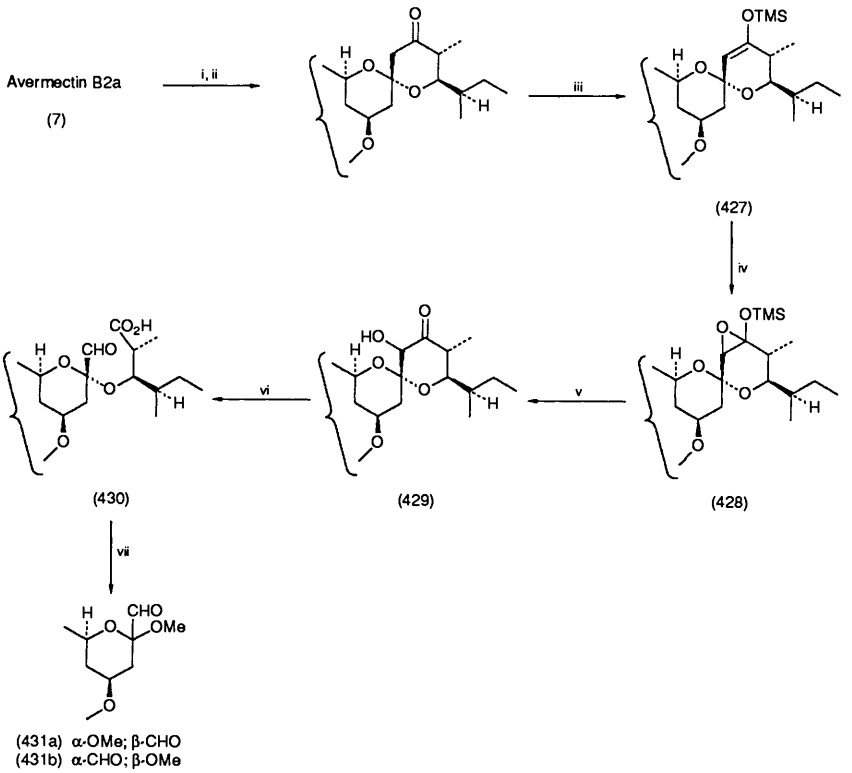


(426)

milbemycins is a desirable goal as it offers a means of preparing these compounds with totally novel spiroacetal substituents. This goal has been achieved by workers at Merck and at Beecham by very different methods. The Merck group formed the enolate of 23-oxo avermectin $B2_a$ (silyl protected at C-4″ and C-5 and trapped this with trimethylsilyl chloride to produce the TMS-enol ether (427) (Scheme 60).[167] The choice of base for the enolization was critical in view of the labile proton at C-2 of the avermectin (see Section 8F), but it was found that lithium bis(trimethylsilyl)amide regioselectively gave the required enolate in 75% yield. As the silyl enol ether is electron rich, it was preferentially epoxidized with *m*-chloroperoxybenzoic acid, only a little reaction being observed at the 14,15-double bond. Dilute acid treatment of the silyloxy-epoxide (428) gave the α-hydroxy-ketone (429), which was readily oxidized with lead tetra-acetate to the aldehydo-acid (430). Transacetalization then gave a 1:1 mixture of the methoxy-aldehydes in high yield, which could be isomerized to the thermodynamically most stable diastereoisomer (431a) by extending the reaction time for the transacetalization.

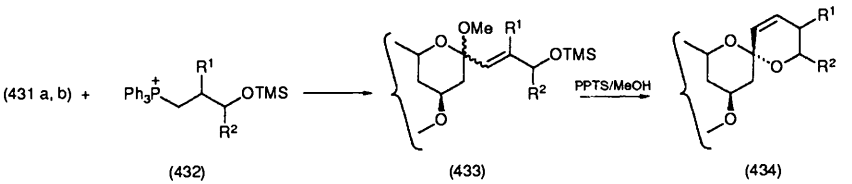
These methoxy-aldehydes were ideal precursors to avermectin analogues, as described in the subsequent paper.[168] Reaction of either isomer of the aldehyde (431) with unstabilized Wittig reagents (432) (Scheme 61) gave the expected *cis*-alkene (433), which was spiroacetalized with pyridinium *p*-toluenesulphonate in methanol to give the required avermectin analogue (434) in 33—49% overall yield. A range of avermectin analogues were readily prepared in this manner. It should be noted that the use of TMS protection for the primary alcohol is critical; replacement with a TBDMS group gives complex mixtures as the methoxyacetal then undergoes hydrolysis and fragmentation before the primary alcohol is free to trap the incipient carbocation. Whichever diastereoisomer of the Wittig product was used for the spiroacetalization, a single isomer at the spiroacetal centre was isolated. Ultimate confirmation that this was the case was provided by reconstituting avermectin $B1_a$ (5) from the methoxy-aldehyde (431), the resulting product being identical to the natural material.

[167] T. L. Shih, H. Mrozik, M. A. Holmes, and M. H. Fisher, *Tetrahedron Lett.*, 1990, **31**, 3525.
[168] T. L. Shih, H. Mrozik, M. A. Holmes, and M. H. Fisher, *Tetrahedron Lett.*, 1990, **31**, 3529.



Reagents: i, Bu^tMe_2SiCl, Et_3N; ii, $(COCl)_2$, DMSO; iii, LiHMDS, TMSCl; iv, mcpba; v, AcOH, MeOH; vi, $Pb(OAc)_4$; viii, H^+, MeOH

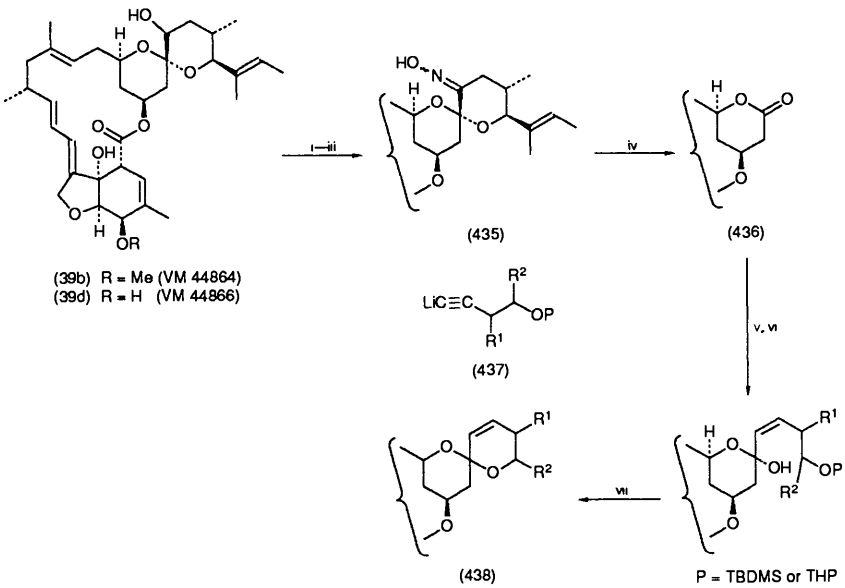
Scheme 60



Scheme 61

The Beecham milbemycins VM44864 and VM44866, (39b) and (39d) respectively, possessing a C-22 hydroxyl group, were degraded by a Beckmann degradation of the derived oxime (435) (Scheme 62).[169] By this process, low to

[169] G. H. Baker, R. J. Dorgan, D. O. Morgan, R. M. Banks, S. E. Blanchflower, M. E. Poulton, and P. R. Shelley (Beecham Group plc), European Patent, EP 319 142 (1989).



Reagents: i, Bu^tMe_2SiCl (for 39d); ii, $(COCl)_2$, DMSO; iii, $NH_2OH{\cdot}HCl$, H_2O, MeOH; iv, $(CF_3SO_2)_2O$ or p-$O_2N{\cdot}C_6H_4{\cdot}SO_2Cl$, p-TsOH; v, (437); vi, H_2, Lindlar catalyst; vii, H^+

Scheme 62

medium yields of the lactone (436) were obtained which were reacted with lithium acetylides (437).[169,170] The resulting alkynes were semi-hydrogenated and cyclized to give novel milbemycins (438), a huge range of which are claimed in these patents. The stereochemistry of the C-24 and C-25 substituents clearly depends upon the alkyne used as starting material; the stereochemistry at the spiroacetal junction is not described in these patents although, from the Merck paper,[168] it could be assumed that this corresponds to that found in the natural material. This approach is conceptually related to the synthesis of the spiroacetal fragment recently reported by Takano, Sekiguchi, and Ogasawara (see Scheme 5).[76]

Treatment of 4″-oxo-5-O-t-butyldimethylsilyl avermectin B1 with samarium di-iodide at low temperature selectively removed the 3″-methoxy group.[171] Borohydride reduction of the product gave access to the 4″-epi-3″-desmethoxy avermectin. Other examples are provided in this patent.

A final example of milbemycin interconversion is provided by the hydrolysis of the 13-iso-butanoate group of N787-182-9 (42i). This was achieved with lithium aluminium hydride in ether at $-23\,°C$.[23]

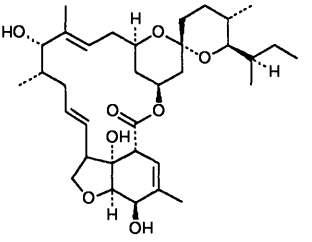
[170] R. J. Dorgan, D. O. Morgan, R. M. Banks, S. E. Blanchflower, and P. R. Shelley (Beecham Group plc), European Patent, EP 353 959 (1990).
[171] P. J. Sinclair (Merck and Co. Inc.), US Patent, US 4 897 393 (1989).

B. Reduction and Photo-isomerization.—Wilkinson's catalyst, [tris-(triphenylphosphine)-rhodium(I) chloride has been frequently used in avermectin and milbemycin chemistry to selectively reduce the Δ^{22} double bonds [1] A further example can be found in the reduction of 5-acetoxy-Δ^{22}-S541 Factor A, only the C-22–C-23 double bond is reduced, with the unsaturated double bond being unaffected [172] This method has also been used to prepare [22,23-$^3H_2$]dihydroavermectin $B1_a$ of high specific activity [173]

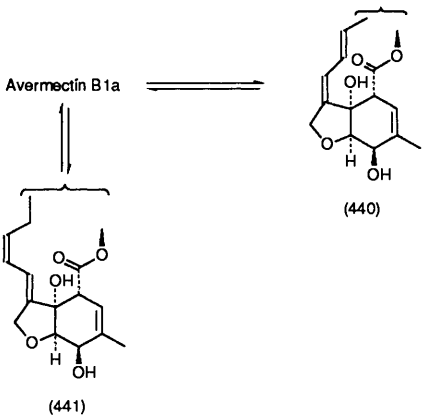
A patent and a paper concerning the hydrogenation of avermectins and milbemycins over a supported palladium catalyst have been published by Mrozik and his co-workers [174a,b] Reduction of 5-O-t-butyldiphenylsilyl avermectin B1 in ethanol over 5% palladium on charcoal at 90 pounds pressure was stopped when one molar equivalent of hydrogen had been absorbed The major component at this stage was the 22,23-dihydroavermectin After the absorption of a further mole of hydrogen the major product became 10,11,22,23-tetrahydroavermectin The patent reported that a similar reduction of 22,23-dihydroavermectin B1 at 90 p s i, when stopped after the uptake of one molar equivalent of hydrogen, gave a mixture which was estimated by HPLC to contain 23% of starting material and 46% of 10,11,22,23-tetrahydroavermectin B1, small amounts of 3,4,10,11,22,23-hexahydroavermectin B1 were also isolated The paper, however, reports that this reduction, when performed at 20 p s i with one equivalent of hydrogen, yields a 2 1 ratio of the 10,11,22,23-tetrahydro and 3,4,10,11,22,23-hexahydroavermectins B1 The reduction of avermectin B2 over 5% palladium on charcoal in ethanol with 1 5 equivalents of hydrogen at atmospheric pressure gave a mixture containing 50% of 10,11-dihydroavermectin B2 3,4-Dihydroavermectin B2 (30%) and 3,4,10,11-tetrahydroavermectin B2 (10%) were also present Reduction of avermectin B1 with half an equivalent of hydrogen at 20 p s i pressure gives, in addition to starting material, a mixture of 10,11-dihydro (20%) and 22,23-dihydroavermectins (10%) In contrast, when 13-deoxy-22,23-dihydroavermectin B1 aglycon was reduced with 5% palladium on charcoal in ethanol at 'slightly elevated pressure' and the reduction was stopped at an intermediate stage, the major product was 10,11,22,23-tetrahydroavermectin $B1_a$ aglycon (28%) A considerable amount (17%) of a further product was also isolated This was assigned the structure (439), corresponding to reduction of the Δ^{22}-double bond and a 1,4-reduction of the diene unit between C-8 and C-11 (small amounts of the corresponding $B2_a$ products were also isolated) Analogues of this curious reduction product were also produced from 5-O-t-butyldimethylsilyl avermectin B1 itself, and milbemycins α_1 and α_3

Similar reductions of 22,23-dihydroavermectin B1 aglycon or its 5-O-t-butyldimethylsilyl derivative are described as only giving the 10,11,22,23-tetrahydroavermectin The reductions of avermectin A2 aglycon or LL-F28249β

[172] O Z Pereira and M V J Ramsay (American Cyanamid Co) European Patent EP 346 133 (1988)
[173] G Toth J Kardos A Fodor and F Sirokman *J Labelled Compds Radiopharm* 1986 **24** 683
[174] (*a*) H Mrozik and T L Smith (Merck and Co Inc) European Patent EP 266 131 (1988) (*b*) T L Shih H Mrozik J Ruis-Sanchez and M H Fisher *J Org Chem* 1989 **54** 1459 (*c*) T A Blizzard H Mrozik F A Preiser and M H Fisher *Tetrahedron Lett* 1990 **31** 4965



(439)



(440)

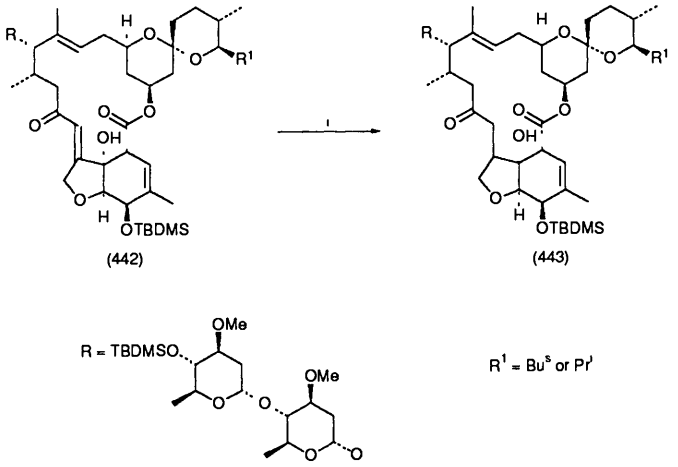
(441)

Scheme 63

are similarly unexceptional and yield the 10,11-dihydro derivatives.[174a] When 22,23-dihydroavermectin B1 was reduced at 60 p.s.i. pressure until four equivalents of hydrogen were absorbed, a 2:1 mixture of 3,4,10,11,22,23-hexahydroavermectin B1 and the fully reduced avermectin was produced. The conclusion that the Merck workers derived from these studies was that, for palladium/carbon catalyst, the relative ease of hydrogenation for each double bond was Δ^{10} and $\Delta^{22} > \Delta^{3} > \Delta^{8} \gg \Delta^{14}$.

The interest in semi-reduced avermectins and milbemycins is not solely a result of chemical interest. Such systems should have greater photo-stability which would lead to a prolonged shelf life for commercial products, and a greater half-life in applications which involve their exposure to sunlight. Studies of the photo-stability of avermectins and semi-reduced avermectins have been performed by workers at Merck, Sharp, and Dohme who photolysed avermectin $B1_a$ (containing 6% $B1_b$).[175] The major photo-product (41%) was (8,9-*Z*)-avermectin $B1_a$ (440) (Scheme 63), a small amount of the (10,11-*Z*) isomer (441) (8%) was also

[175] H. Mrozik, P. Eskola, G. F. Reynolds, B. H. Arison, G. M. Smith, and M. H. Fisher, *J Org. Chem.*, 1988, **53**, 1820.



Reagents i, $Li(OMe)_3AlH$, CuBr, THF

Scheme 64

isolated Similar results were obtained for 22,23-dihydroavermectin $B1_a$ aglycon Time-course experiments have shown that after 20 h of ultraviolet irradiation (maximum at 300 nm) only 5% of 22,23-dihydroavermectin B1 remains [174a] For 10,11,22,23-tetrahydroavermectin B_1, under similar conditions, 75% remains after 20 h irradiation, and 40 h irradiation still leaves 36% undecomposed [174a]

Previous work has demonstrated that conjugate reduction of the Δ^3 double bond of 5-oxo milbemycin D can be performed with triethylsilane in the presence of catalytic amounts of rhodium or ruthenium,[1] but a more spectacular example of conjugate reduction is provided by the reduction of the 10-oxo-10,11-dihydroavermectin (442) with cuprous bromide/lithium trimethoxyaluminiumhydride [174a] This gave a 50% yield of the 8,9,10,11-tetrahydro-10-oxo product (443) (Scheme 64)

Further examples of the reduction of the carbonyl group of various 5-oxo milbemycins with sodium borohydride have been reported [176a b] An alternative method, however, is to use the inherent reductase activity of various milbemycin-producing strains and their mutants [177] While hydride reduction of 5-oxo-milbemycins regenerates the natural configuration, this is not true for the 22-oxo Beecham compounds which, with lithium tri-s-butylborohydride, give the *epi* isomer [178] Epimerization at C-23 of the Glaxo S-541 compounds was achieved

[176] For example (*a*) O Z Pereira M V J Ramsay and S Freeman (American Cyanamid Co) European Patent, EP 307219 (1987) (*b*) K Sato and T Otsu (Sankyo Co Ltd) Japanese Patent JP62/70379 (1987)

[177] B A M Rudd and M V J Ramsay (American Cyanamid Co) European Patent EP 333404 (1988)

[178] G H Baker R J Dorgan, R M Banks, and M E Poulton (Beecham Group plc) European Patent EP 288205 (1988)

by sodium borohydride reduction of the 23-ketones, which yielded a 2:1 mixture of the natural product and its epimer.[179]

C. Dehydration, Dehydroxylation, and Halogenation.—The previously described[180] pyrolytic elimination of a 23-thiocarbonate group has been used to prepare Δ^{22} analogues of the Glaxo and Cyanamid S-541 and LL-F compounds.[181] Dehydration of the 23-hydroxy group of 5-acetoxy S541 Factor A, or its 5-oxo analogue,[182] with diethylaminosulphur trifluoride, however, gave exclusively the Δ^{23} analogues.[181a] Δ^{23}-Avermectins $A2_a$, $A2_b$, $B2_a$, and $B2_b$ were also prepared by DAST-induced dehydration of 23-hydroxy avermectins.[183] Burgess' reagent has also been used to prepare Δ^{23}-5-acetoxy S541 Factor A.[181a]

Reductive removal of the 23-hydroxy group of Cyanamid's LL-F milbemycins in two steps has been described.[184a,b] Conversion of the 23-hydroxy group into the corresponding bromide with triphenylphosphine dibromide was followed by radical debromination with tributyltin hydride to provide the required derivatives. A similar dehydrobromination was used to prepare 10,11-dihydro-10-hydroxy avermectins and 10,11-dihydro-10,13-dihydroxy milbemycins from the corresponding 11-bromo compounds.[174a] Dehydrochlorination by this procedure was used to prepare 5-O-t-butyldimethylsilyl-13-deoxy-10,11-dihydro-10-fluoro avermectin B1 aglycon from the 13-chloro-10-fluoro compound.[174a] 23-Bromo S541 Factor A has also been dehydrobrominated by treatment with zinc in an acetic acid and isopropanol mixture.[185]

The reaction of the previously described 23-thiocarbonate avermectins and milbemycins with tributyltin hydride provided a ready means of preparing 23-deoxy analogues which has been widely applied.[23,186] An alternative one-pot method to prepare 23-deoxy-5-acetoxy S541 Factor A was to react the milbemycin with oxalyl chloride and then add the resulting reaction mixture to a refluxing solution of 2-mercaptopyridine-*N*-oxide and trityl thiol in toluene in the presence of a catalytic quantity of 4,4-dimethylaminopyridine.[187]

Avermectin and milbemycin analogues dehydroxylated at C-5 have also been prepared by the reaction of tributyltin hydride with 5-halo or 5-thiocarbonate

[179] N. E. Beddall, P. D. Howes, M. V. J. Ramsay, S. M. Roberts, A. M. Z. Slawin, D. R. Sutherland, E. P. Tiley, and D. J. Williams, *Tetrahedron Lett.*, 1988, **29**, 2595.

[180] H. H. Mrozik (Merck and Co. Inc.), US Patent, US 4 550 160 (1979).

[181] (*a*) J. B. Ward, H. M. Noble, N. Porter, R. A. Fletton, D. Noble, D. R. Sutherland, and M. V. J. Ramsay (Glaxo Group Ltd.), European Patent, EP 215 654 (1986); (*b*) G. Asato and S. Y. Tamura (American Cyanamid Co.), European Patent, EP 259 688 (1988).

[182] G. Asato and Z. Ahmed (American Cyanamid Co.), European Patent, EP 264 576 (1986).

[183] H. H. Mrozik and F. S. Waksmunski (Merck and Co. Inc.), European Patent, EP 326 357 (1988).

[184] (*a*) G. Asato and S. Y. Tamura (American Cyanamid Co.), European Patent, EP 262 384 (1988); (*b*) *ibid.*, European Patent EP 280 928 (1988).

[185] M. V. J. Ramsay, S. Freeman, A. H. Shingler, O. Z. Pereira, and S. C. Dolan (American Cyanamid Co.), European Patent, EP 307 221 (1987).

[186] (*a*) B. G. Christensen, M. H. Fisher, and H. H. Mrozik (Merck and Co. Inc.), European Patent, EP 284 255 (1987); (*b*) M. V. J. Ramsay, P. D. Howes, R. Bell, E. P. Tiley, and D. R. Sutherland (Glaxo Group Ltd.), European Patent, EP 307 220 (1989); (*c*) G. Asato and S. Y. Tamura (American Cyanamid Co.), European Patent, EP 280 929 (1988).

[187] M. V. J. Ramsay and S. C. Dolan (American Cyanamid Co.), European Patent, EP 307 226 (1989).

analogues Examples may be found in the reaction of tin hydride with 5-chloro-23-(*E*)-methoxyimino S541 Factor A,[188] or with 5-bromo-23-deoxyavermectin $B2_a$ [189] No isomerization of the double bond is reported in these reactions The 5-halo compounds used in these dehydroxylations were prepared from the corresponding alcohols by treatment with triphenylphosphine/carbon tetrachloride[188] or from the corresponding mesylates or tosylates [189]

The hydroxylation at C-13 of milbemycin derivatives by allylic bromination,[1] rearrangement of 15-hydroxy-Δ^{13}-analogues (see Section 8H), or the use of avermectin aglycons, offers the possibility of introducing 13-halo substituents on to the macrocyclic skeleton by direct halogenation Both 13α- and 13β-fluoro milbemycins have been prepared by the use of diethylaminosulphur trifluoride, while the chloro analogues were prepared with thionyl chloride, bromo analogues with phosphorus tribromide, and iodo analogues with trimethylsilyl iodide [190]

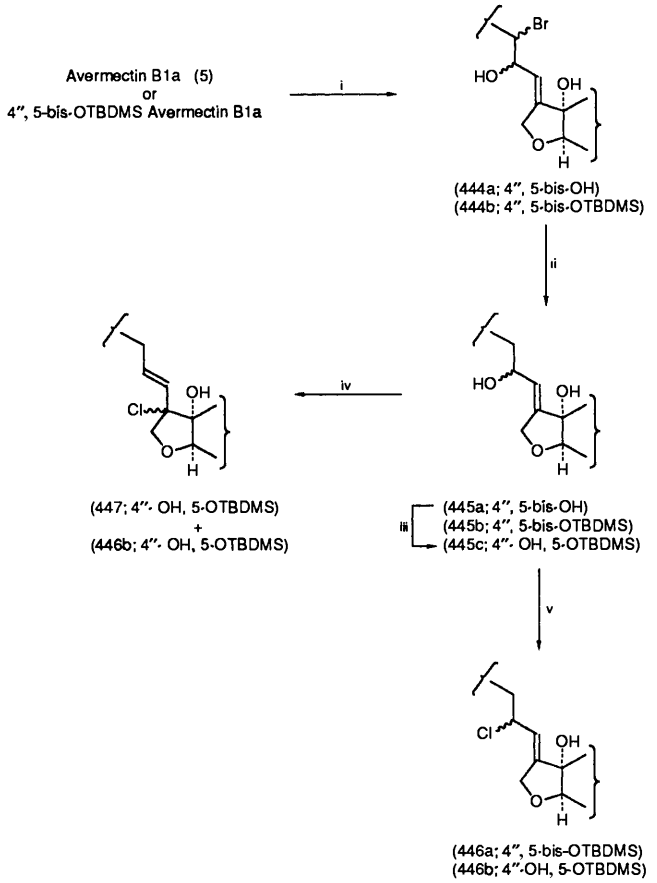
In the search for a selective method of saturating the Δ^{10} double bond of avermectin $B1_a$ (5), Shih and his co-workers found that treatment with hypobromous acid (from *N*-bromoacetamide in aqueous acetone) regioselectively gives the unstable 11-bromo-10,11-dihydro-10-hydroxy avermectin $B1_a$ (444a) (Scheme 65) as the only bromohydrin [174*b*] When the avermectin is protected at the 5- and/or 4″-positions the reaction is equally successful and similar reactions were observed for 22,23-dihydroavermectin B1 and 5-O-t-butyldimethylsilyl-13-hydroxy milbemycins α_1 and α_3 [174*a*] Reductive removal of the bromine from (444a) or (444b) with tributyltin hydride gave 10,11-dihydro-10-hydroxy derivatives (445a and b), a starting point for the preparation of further derivatives Oxidation by a Swern procedure gave 10-oxo derivatives,[174*a*] while 10-fluoro derivatives were prepared using diethylaminosulphur trifluoride [174*b*] Reaction of 4′,5-diprotected 10,11-dihydro-10-hydroxy avermectin B1 (445b) with triphenylphosphine/hexachloroacetone at 0 °C in THF gave the corresponding 10-chloro analogue (446a),[174*a*] but the use of triethylamine/dichlorotriphenylphosphine in methylene chloride on the 5-*O*-TBDMS protected avermectin (445c) gave a mixture of the expected 10-chloro compound (446b) and the allylically rearranged 8-chloro-8,11-dihydro compound (447) [174*a*] Hydrodechlorination of this mixture gave a 2 1 mixture of 10,11- and 8,11- dihydroavermectins [174]

Mixed halo derivatives of these reduced milbemycins have been prepared from the avermectins by preparing the 10-halo aglycons and halogenating further 13-Chloro-10-fluoro and 10,13-difluoro analogues have been prepared in this way, and 13-deoxy-10,11-dihydro-10-fluoro avermectin B1 aglycon was prepared by tin hydride dehydrochlorination of the 13-chloro-10-fluoro analogue [174]

[188] M V J Ramsay, D N Evans, D R Sutherland, E P Tiley, J B Ward, N Porter R A Fletton, and D Noble (American Cyanamid Co), European Patent, EP 327 270 (1988)

[189] W Roben, W Stendel, and P Andrews (Bayer AG) European Patent EP 303 933 (1987)

[190] (*a*) B Frei, A C O Sullivan, and P Maienfisch (Ciba-Geigy AG), European Patent, EP 180 539 (1985), (*b*) K Sato, T Yanai, N Kitang, A Nishida, B Frei, and A C O'Sullivan (Sankyo Co Ltd) European Patent, EP 203 832 (1986)



Reagents: i, HOBr; ii, Bu^n_3SnH; iii, Bu^tMe_2SiCl, DMAP, CH_2Cl_2; iv, Ph_3PCl_2, Et_3N, CH_2Cl_2; v, Ph_3P, CCl_3COCCl_3, THF

Scheme 65

D. Acylation and Protection.—Methods of selectively protecting and revealing the separate hydroxyl groups in avermectins and milbemycins were carefully detailed by early workers in this field,[1] and no radically new methods of protection have been reported. Further examples exemplifying extant knowledge are, however, available. Thus the easiest site to protect is the allylic C-5 hydroxyl group, which can be selectively silylated in the presence of all other hydroxyl groups. Examples can be found in the 5-silylation of avermectin $B1_a$ monosaccharide,[152] 10-hydroxy-10,11,22,23-tetrahydroavermectin B1 aglycon,[174a] and the Glaxo/Cyanamid milbemycins, which can be selectively silylated at C-5 with t-butyldimethylsilyl chloride or trimethylsilyl chloride under mild conditions.[17b,191]

Many different acyl groups have been introduced to the avermectins and milbemycins in a search for more active analogues or to improve bio-dynamic parameters An exhaustive catalogue of these would take many pages, and thus this review will only detail selected examples to illustrate any new chemistry

Further examples of selective acetylation at C-5 in the presence of a free C-23 hydroxyl group are available from work on the Glaxo/Cyanamid milbemycins [17b 191 192] The acetylation of both the 5- and 23-hydroxyl groups of S541 Factor A requires excess acetic anhydride, pyridine as solvent, and 4,4-dimethylamino pyridine as catalyst for extended periods [17b] 23-acetoxy Factor A can then be prepared by mild hydrolysis of the 5,23-diacetate [17b] An alternative method is to acetylate the 5-O-TBDMS milbemycin and then remove the silyl group [193]

Acylation of milbemycin D with *N*-(trichloroethoxycarbonyl)-glycine and dicyclohexylcarbodiimide, unsurprisingly, is also selective in acylating at C-5 [194] DCC has also been used to prepare other 5-O-acetyl substituted milbemycins such as 5-O-(1,2,4-triazol-1-yl)acetyl-13-methyl and 13-vinyl milbemycin α_3 [195] Milbemycins and avermectins have been acetylated at C-4a with a range of acid chlorides, using pyridine as a catalyst [25] Among the compounds thus prepared from 4a-hydroxylated 5-O-TBDMS milbemycin α_3 were milbemycins α_{11}, α_{13}, and α_{14}, which had previously been isolated as fermentation products (see Section 2)

Aryloxy and alkyloxy-acetate analogues at C-5 of milbemycins were prepared by simple acylation at 0 °C, using the acid chloride with 4,4-dimethylaminopyridine and di-isopropylethylamine or pyridine as catalyst [191 193 195b] Thus LL-F28249α gives 5-methoxyacetoxy-LL-F28249α at 0 °C, whereas repetition of the reaction at 80 °C for 20 h gives the 5,23-bis-acetylated compound [193] Mono-acyloxy derivatives at C-23 of LL-F compounds were prepared by acylation at 80 °C of C-5 protected derivatives with an acyl halide in the presence of di-isopropylethylamine [193]

Acetylation with chloroacetyl chloride provides active analogues and also gives a further handle for manipulation Thus, 5-O-(chloromethoxycarbonyl) milbemycin D has been shown to be active as an anthelmintic agent against *Ascaris suum* larvae 5-Iodoacetyl milbemycin D was prepared from the chloro derivative by a Finkelstein reaction, and the iodide was displaced by azide, 1,2,4-triazole, and imidazole to give the corresponding 5-azoacetyloxy milbemycins [196] A similar displacement with 4-methyl-imidazole gave a separable mixture of 5-O-(4- and 5′-methylimidazol-1′-yl)-acetyl milbemycins D, but it could not be

[191] J B Ward H M Noble N Porter R A Fletton D Noble D R Sutherland and M V J Ramsay (Glaxo Group Ltd) British Patent GB 2 176 182 (1986)
[192] G Asato (American Cyanamid Co) European Patent EP 259 668 (1986)
[193] G Asato (American Cyanamid Co) European Patent EP 259 686 (1986)
[194] A Terada S Naruto R Matsueda H Rei K Susumu and K Kitano (Sankyo KK) Japanese Patent JP 60/184 085 (1985)
[195] (*a*) P Maienfisch and A C O Sullivan (Ciba Geigy AG) British Patent GB 2 187 453 (1986) (*b*) P Maienfisch (Ciba Geigy AG) European Patent EP 282 456 (1988)
[196] E Sturm and P Maienfisch (Ciba Geigy AG) European Patent EP 184 989 (1985)

ascertained with certainty which isomer was which. An extensive list of such aza-heterocyclic milbemycin D, α_1 and α_3 analogues prepared in this way is described in this patent. 5-O-Chloroacetyl milbemycins have also been converted into other analogues such as 5-O-(fluoroacetoxyacetyl)- and 5-O-[(*S*)-2- hydroxypropionyloxy]acetyl milbemycins α_3 by simple displacement reactions in DMF solution.[197]

The C-23-chloroacetate of S541 Factor D has also been prepared and similarly transformed into the iodoacetyl analogue.[17b] This was used as a precursor for the 23-azidoacetate and the 23-glycylester.[17b] This paper also describes the preparation of the 23-trichloroethylcarbonates of S541 Factor D and 5-acetoxy Factor A which were converted into the corresponding urethanes (O·CONH·Me).

Now that 13-hydroxy milbemycins are available (see Section 8H), their reaction to give 13-acyloxy milbemycins,[198] substituted alkyl and aryloxyacetyl milbemycins,[199] and 13-carbonate esters[200] by previously detailed methods has been described. The well-known reaction of isocyanates with alcohols has been applied to 13-hydroxy milbemycins D, α_1 and α_3 to provide a range of 13-carbamoyloxy milbemycins for testing.[201]

5-Phosphate esters of avermectins, and their corresponding acids, have been described previously by workers at Merck,[1] and similar analogues of the S541 compounds have been prepared by Glaxo workers.[202]

E. Oxidation and Derivatives of Oxidized Products.—S541 Factor A, its 5-acetate and its TBDMS ether, have been converted into their 4a-hydroxy analogues by the previously described method[1] utilizing selenium dioxide and t-butyl hydroperoxide as oxidant at room temperature.[203]

Acylation of such 4a-hydroxy milbemycins with the appropriate acid chloride was used by workers at Sankyo to prepare synthetic samples of the milbemycins α_{11}, α_{13}, and α_{14} [(43a), (43g), and (43c) respectively][25] which had been obtained by fermentation (see Section 2). Some selectivity could be obtained in the acetylation of the new hydroxy group at C-4a in the presence of a free 5-hydroxy group by the use of triphenyl phosphine/diethyl azodicarboxylate/acetic acid.[203]

Several further examples of milbemycins being selectively oxidized at the allylic C-5 hydroxyl group with manganese dioxide to give the corresponding α,β-unsaturated ketones have been described.[178,204] This has an important

[197] P Maienfisch and E Sturm (Ciba-Geigy AG), European Patent, EP 217 742 (1985)

[198] (*a*) B Frei, H B Merevala, A C O'Sullivan, K Sato, and T Yanai (Ciba-Geigy AG), British Patent, GB 2 168 345 (1986), (*b*) B Frei (Ciba-Geigy AG), European Patent, EP 253 767 (1988)

[199] K Sato, T Yanai, T Kinoto, T Toyama, K Tanaka, A Nishida, B Frei, and A C O'Sullivan (Sankyo Co Ltd), European Patent, EP 246 739 (1987)

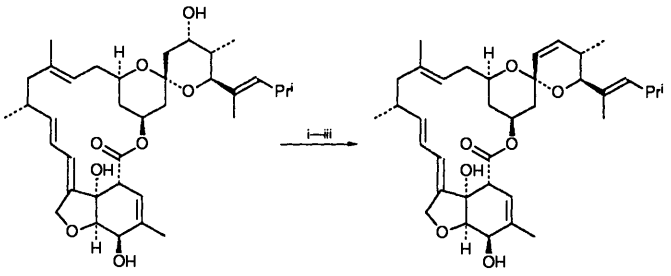
[200] P Maienfisch (Ciba-Geigy AG), European Patent, EP 245 209 (1987)

[201] P Maienfisch (Ciba-Geigy AG), European Patent, EP 239 528 (1987)

[202] M V J Ramsay, E P Tiley, O Z Pereira, J B Ward, N Porter, H M Noble, R A Fletton, D Noble, and D R Sutherland (Glaxo Group Ltd), European Patent, EP 238 259 (1986)

[203] J B Ward, N Porter, H M Noble, R A Fletton, D Noble, and D R Sutherland (Glaxo Group Ltd), European Patent, 237 341 (1987)

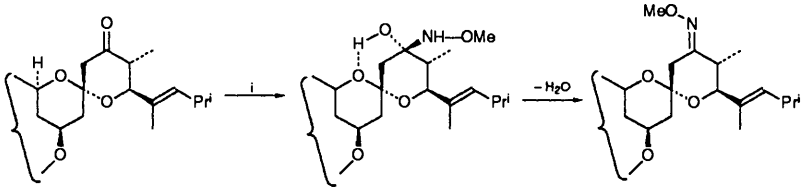
[204] D R Sutherland, N Porter, B M Bain, M V J Ramsay, H M Noble, E P Tiley, R A Fletton, J B Ward and D Noble (Glaxo Group Ltd), European Patent, EP 238 258 (1987)



(34a)

Reagents: MnO_2, Et_2O; ii, Me_2NSF_3, $(MeOCH_2)_2$; iii, $NaBH_4$

Scheme 66



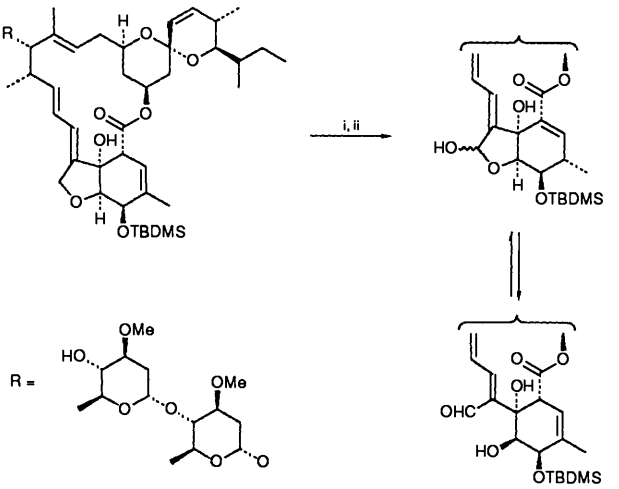
Reagent: i, $MeONH_2$

Scheme 67

consequence for the Glaxo S541 Factor A as the resulting ketone is readily crystallized and purified, an important consideration in a series which is generally non-crystalline and hence more difficult to handle on an industrial scale. Many oxime, hydroxylamine, semicarbazide, and hydrazone derivatives of the 5-ketones have been prepared.[199,204,205] As the C-5 alcohol is the easiest position to oxidize, this can also be used as a means of protecting this alcohol in order to carry out a conversion elsewhere in the molecule; reduction with sodium borohydride then regenerates the correct stereochemistry at C-5. An example of this strategy can be seen in the synthesis of Δ^{23}-LL-F28249α (Scheme 66).[182]

Both hydroxyl groups at C-5 and C-23 of the milbemycin analogue S541 Factor A have been oxidized with Jones reagent in a two-phase mixture of ethyl acetate and water using tetra-n-butylammonium sulphate as phase-transfer catalyst.[206] When the resulting 5,23-diketone was treated with one equivalent of methoxylamine hydrochloride, the 23-*E*-methoxyimine was by far the major product. This accelerated reaction at C-23 was considered to be a consequence of intramolecular hydrogen bonding between the intermediate hemi-aminal hydroxy group and the oxygen atom at C-17 (Scheme 67), the exclusive formation of the *E* isomer of the oxime was thought to be due to control of the loss of water by

[205] (*a*) Sankyo KK, Japanese Patent, J6 3045281 (1987); (*b*) B. Frei and A. C. O'Sullivan (Ciba-Geigy AG), European Patent, EP 279783 (1987).
[206] S. Freeman (American Cyanamid Co.), European Patent, EP 307222 (1989).



Reagents: i, $PhCOO_2Bu^t$, CuCl; ii, AcOH, H_2O

Scheme 68

the adjacent C-24 group.[179] A range of 5-oxo-23-alkoximes have also been prepared.[17a]

Avermectins hydroxylated at C-8a have been isolated as metabolites from soil [1] and can be prepared in the laboratory by oxidation with t-butyl peroxybenzoate/cuprous chloride[207] (Scheme 68). 8a-Oxo avermectins (448) are now synthetically available by treating the suitably protected natural compounds with an excess of pyridinium dichromate in DMF at room temperature.[207] Reduction of the 8a-oxo or 8a-hydroxy avermectins with sodium borohydride/cerium chloride gives the diol (449) (Scheme 69).

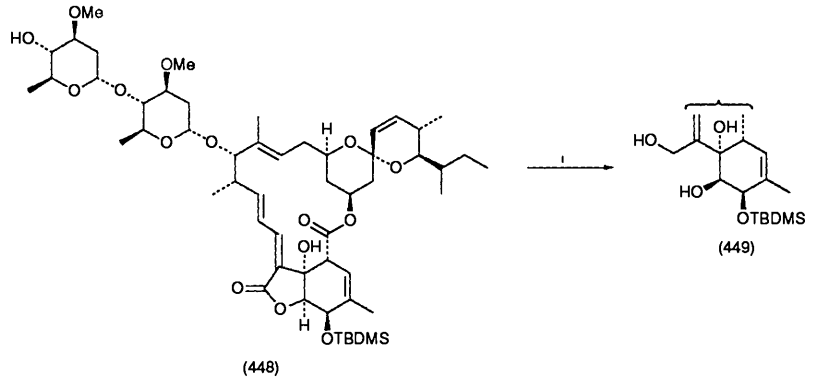
Oxidation of 4″,5-di-O-t-butyldimethylsilyl-10-hydroxy avermectin B1 to the corresponding 10-ketone by a Swern procedure has been described.[174a]

In contrast to the above described hydroxylations at C-4a, reaction of selenium dioxide with 5-oxo-milbemycins α_2, α_4, and D, or 5-oxo-LL-F28249α, in formic or acetic acid gave milbemycins which were acetoxylated at C-13.[208] Hydrolysis of these crude products gave 13-hydroxy milbemycins in yields greater than 40%. This oxidation can equally well be performed on the 5-oximes.[209] A curious result has been reported for the selenium dioxide/t-butyl hydroperoxide oxidation of 23-desoxy-S541 Factor A 5-acetate; by analogy with

[207] (*a*) H. H. Mrozik and F. S. Waksmunski (Merck and Co. Inc.), US Patent, US 4 547 491 (1985); (*b*) M. H. Fisher, M. J. Wyvratt, and H. Mrozik (Merck and Co. Inc.), European Patent, EP 343 715 (1989).

[208] (*a*) K. Sato, T. Yanai, T. Kinoto, and S. Mio (Sankyo Co. Ltd.), European Patent, EP 184 308 (1986); (*b*) Y. Tsukamoto, K. Sato, and T. Yanai (Sankyo KK Ltd.), Japanese Patent, J87-210 805 (1987).

[209] T. Yanai, K. Sato, and T. Otsu (Sankyo KK Ltd.), Japanese Patent, JP 860 425 (1986).



Reagents i, $NaBH_4$, $CeCl_3$

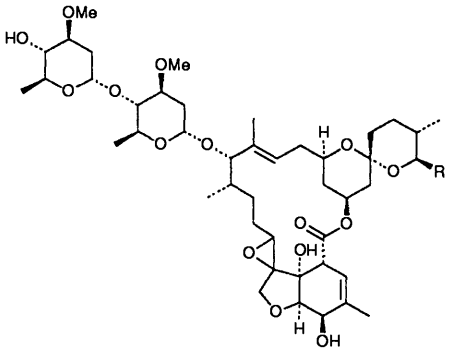
Scheme 69

previous work this would be expected to produce a 4a-hydroxylated milbemycin, yet the patent claims the product to be (13*R*)-hydroxy-23-desoxy Factor A 5-acetate, albeit obtained in low yield (*ca.* 12%).[186b]

The oxidation of avermectin B aglycones (*i.e.* 13-hydroxy-milbemycin type structures) with chromium trioxide in the presence of 3,5-dimethyl-pyrazole, or under Swern conditions, to give 13-oxo-derivatives, and their conversion into 13-imino and 13-amino derivatives, has been described.[210,211] These 13-oxo derivatives have been converted into the 13-methylene compounds on treatment with Tebbe's reagent in toluene at $-40\,^{\circ}C$.[212]

The initial step in the Beecham degradation of the outer spiroacetal ring (see Section 8A) utilizes the oxidation of the hydroxyl group at C-22 by a Swern procedure.[178] Various oximes were thus prepared of VM44864 and 5-O-TBDMS VM44866. Swern-type oxidation has also been used to prepare 23-oxo analogues of suitably protected 13-deoxy avermectin aglycones[213] and S541 type milbemycins; pyridinium dichromate and chlorochromate have also been used.[179,214] The formation of methoxyimines of these 23-oxo milbemycins was highly stereospecific providing only the *E* isomer in 80% yield. The same product was obtained from the corresponding 5,23-diketone in 54% yield, only trace amounts of the isomeric 5-methoxyimine being formed. As previously described, hydrogen bonding in the transition state between the 17-oxygen atom and the transient 23-hydroxy group was postulated to explain the preferential functionalization at C-23. The preferential formation of the *E* imine was thought to be due to the equatorial C-24 methyl group controlling the direction of

[210] M V J Ramsay, P D Howes, R Bell, E P Tiley, and D R Sutherland (American Cyanamid Co), European Patent, EP 307 220 (1987)
[211] B O Linn and H H Mrozik (Merck and Co Inc), European Patent, EP 165 029 (1985)
[212] P Maienfisch and M Riediker (Ciba-Geigy AG), German Patent, DE 3 631 387 (1986)
[213] G Asato and D J France (American Cyanamid Co), European Patent, EP 260 537 (1988)
[214] G Asato and D J France (American Cyanamid Co), European Patent, EP 259 779 (1988)



(450) R = Pr^{i} or Bu^{s}

elimination of water from the aminal intermediate. Many other oximes, imines, and semicarbazones of 23-oxo milbemycins and avermectins have been prepared as the resulting compounds are frequently very active.[214,215]

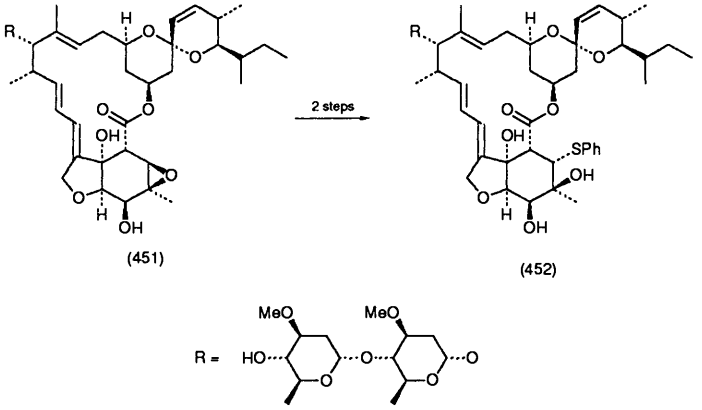
Few medicinal chemists, when presented with a double bond, can resist the temptation of preparing an epoxide! There are many reasons for this: preservation of overall molecular shape, change in electronic characteristics, and as a synthetic handle. Avermectin and milbemycin chemists have not been immune to this temptation.

Earlier work has shown that epoxidation of milbemycins or avermectins under Sharpless conditions selectively provides 8,9-epoxy derivatives, directed by the 7-hydroxy group;[1] this was the basis of the degradative procedure utilized by Smith and Thompson[152] (see Section 8A). A further example of this reaction can be found in the epoxidation of 10,11,22,23-tetrahydroavermectin B1 with slightly over one equivalent of t-butyl hydroperoxide to give the 8,9-epoxide (450).[174a]

When the 7-hydroxy group is blocked by silylation, Sharpless epoxidation gives the 3,4-oxide (451) in moderate yield.[174c] As the free 5-hydroxy group was presumed to direct the epoxidation, the stereochemistry of the epoxide group was assigned as β; this was confirmed by NMR analysis of the product obtained by thiophenol opening of the epoxide (452) (Scheme 70). Reaction of the epoxide (453) with anisylethylamine in methanol, however, did not yield products derived by ring opening of the epoxide (Scheme 71). The major product was the conjugated allyl alcohol (454) while the minor product was the corresponding seco-ester (455). Replacement of the secondary amine with DBU in this reaction resulted in a reversal of the yields of the two products.

An interesting acid-catalysed rearrangement of 4″,5,7-tris-O-trimethylsilyl avermectin B1 8,9-oxide (456) has been reported by Blizzard and his co-workers (Scheme 72).[165] Upon treatment with *p*-toluene sulphonic acid in wet

[215] (*a*) D. R. Sutherland, M. V. J. Ramsay, E. P. Tiley, O. Z. Pereira, J. B. Ward, N. Porter, H. M Noble, R. A. Fletton, and D. Noble (Glaxo Group Ltd.), British Patent, GB 2 192 630 (1987); (*b*) G. Asato and D J. France (American Cyanamid Co.), European Patent, EP 250 536 (1988).

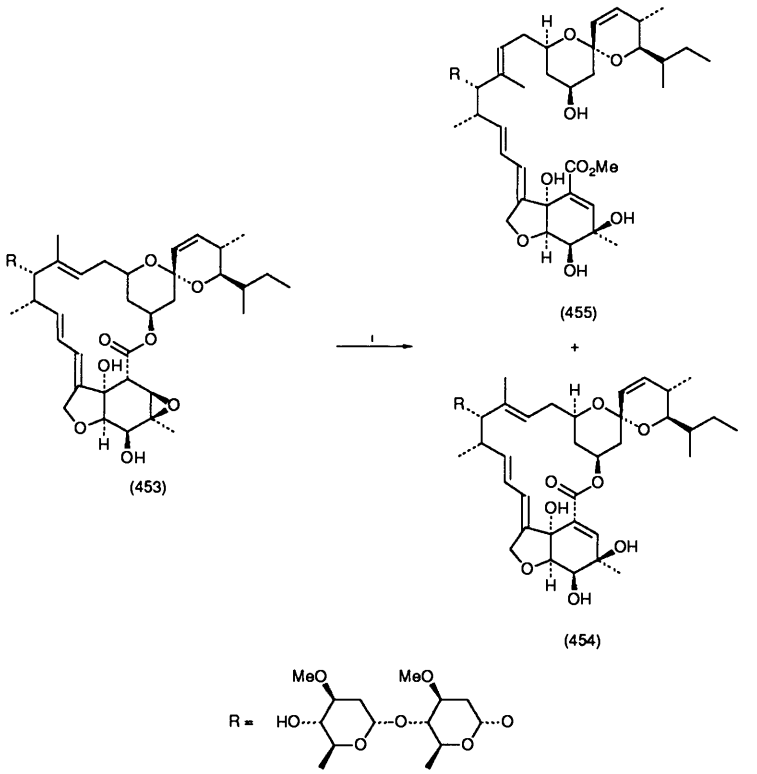


Scheme 70

tetrahydrofuran this epoxide gave 60—70% of the novel tricycle (457). The presence of the 7-O-trimethylsilyl group was indicated as necessary to the success of the reaction, as a similar reaction on the non-silylated epoxide only gave the expected 8,9-diol. 4″,5,7-Tris-O-trimethylsilyl avermectin B1 itself only gave desilylated avermectin B1 under these conditions.

Preparation of 14,15-epoxides of the milbemycins by reaction with one equivalent of *m*-chloroperoxybenzoic acid at ambient temperature is a well established procedure for milbemycins,[1] and the resulting epoxides have proved of great utility in the preparation of novel avermectins and milbemycins (see Section 8H). The Glaxo S-541/Cyanamid LL-F milbemycins, however, contain an additional exocyclic, double bond with approximately the same reactivity as the 14,15-double bond. This is shown by treatment of S541 Factor B (34d) with one equivalent of *m*-chloroperoxybenzoic acid at 0 °C—r.t., which gave an (approximately) equal amount of 14,15- and 26,27-epoxides [(458a) and (458b) respectively, R = Me, R′ = H].[216] Similar treatment of S541 Factor A gave a mixture of 14,15- (458a) and 26,27-epoxides (458b), and 14,15,26,27-bis-epoxide (458c).[216,217] Some selectivity for the epoxidation can be obtained by reducing the reaction temperature; epoxidation of 5,23-di-O-TBDMS LL-F28249α, initially at −70 °C and warming by stages to −20 °C, gives a 4:1 mixture of the 26-epoxide [(458b) R = R′ = TBDMS] and bis-epoxide [(458c) R = R′ = TBDMS].[186c] Deprotection of the 26-epoxide and re-protection with one equivalent of t-butyldimethylsilyl chloride gave the 5-O-TBDMS epoxide [(458b) R = TBDMS, R′ = H] which was oxidized with pyridinium chlorochromate to the 23-oxo analogue, from which a range of oximes and imines were prepared.[218]

[216] J B Ward, N Porter, H M Noble, R A Fletton, and D Noble (Glaxo Group Ltd), European Patent, EP 241 146 (1987)
[217] G Asato and S Y Tamura (American Cyanamid Co), European Patent, EP 280 929 (1988)
[218] G Asato and S Y Tamura (American Cyanamid Co), European Patent, EP 293 549 (1987)



Reagents: i, DBU, MeOH or *p*-Et·NH·CH_2·C_6H_4·OMe

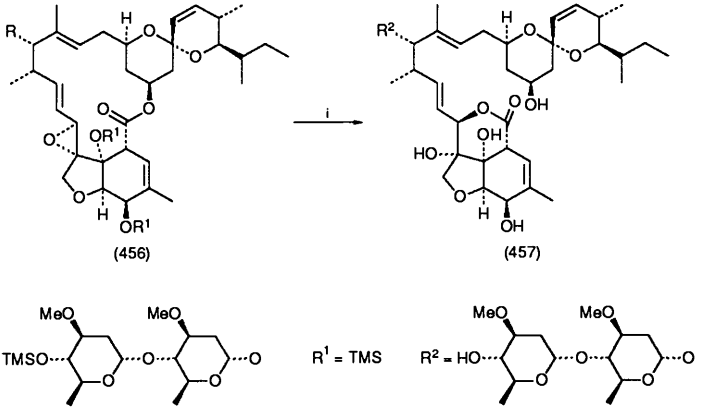
Scheme 71

Oxidation of S541 Factor B with two equivalents of *m*-chloroperoxybenzoic acid at room temperature, predictably, gave the bis-epoxide [(458c) R = Me, R′ = H].[216]

The exocyclic 13-epoxide (459) has been prepared by reaction of 13-oxo milbemycins with dimethylsulphonium methylide.[195b] 13-Formyl milbemycins were obtained from this epoxide by acid-catalysed rearrangement with dilute hydrofluoric acid or camphor-sulphonic acid.[195b]

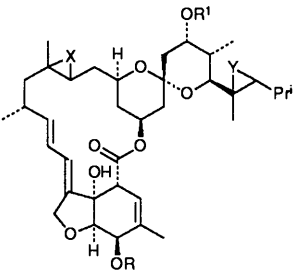
25-(1-Methylthioethyl) avermectins, prepared by directed biosynthesis (see Section 2), have been converted into 25-ethenyl avermectins (460) by *m*-chloroperoxybenzoic acid oxidation to the sulphoxide and thermal elimination at high temperature,[219] and these have been subjected to Wacker oxidation (Scheme 73). 25-Ethenyl avermectin A2 [(460) R = Me, X = CH_2, Y = CHOH], when treated with palladium chloride and cupric chloride and stirred vigorously

[219] B. J. Banks and M. J. Witty (Pfizer Ltd.), European Patent, EP 335 541 (1989)

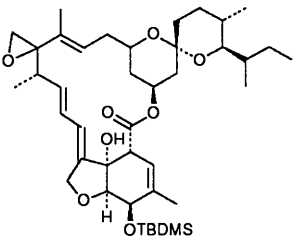


Reagents: i, TsOH, H_2O, THF

Scheme 72



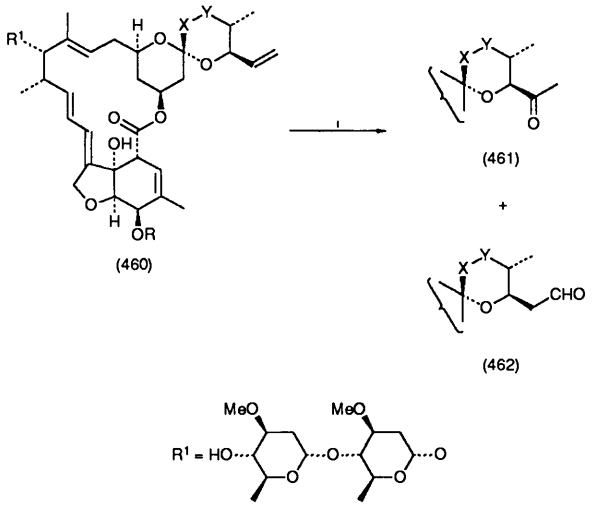
(458) (a) X = O, Y = bond
(b) X = bond, Y = O
(c) X = Y = O



(459)

in the air, gave a 50% yield of 25-acetyl avermectin A2 [(461) R = Me, X = CH_2, Y = CHOH].[220] A similar reaction of 25-ethenyl avermectin B1 [(460) R = H,

[220] B. J. Banks and M. J. Witty (Pfizer Ltd.), European Patent, EP 340932 (1989).



Reagents: i, H_2O, DMF, $CuCl_2$, $PdCl_2$, O_2

Scheme 73

Table 1

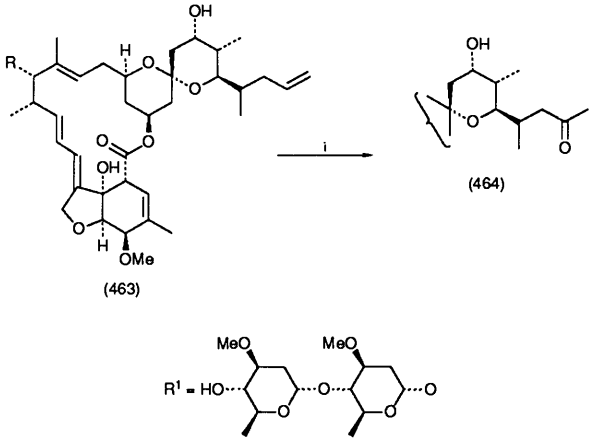
	Avermectin produced					
Avermectin fed	$A1_a$	$A2_a$	$B1_a$	$B2_a$	$B2_a$ AG	$B2_a$ MS
$A1_a$	100					
$A2_a$		93				
$B1_a$	2.7		93.6			
$B2_a$		29.7		68.3		
$B2_a$ AG		9.3		31.6	46.3	5.6
$B2_a$ MS		18.6		45.2		32.2

AG = Aglycon. MS = Monosaccharide

XY = CH=CH), quenched with methanol, gave a mixture of 25-acetyl avermectin B1 [(461) R = H, XY = CH=CH], 25-formylmethyl avermectin B1 [(462) R = H, XY = CH=CH], and their corresponding acetals. When the Wacker procedure was applied to 25-(1-methylbut-3-enyl) avermectin A2 (463) (also prepared by directed biosynthesis) the ketone (464) was obtained (Scheme 74).

The 25-ethenyl avermectin B1 [(460) R = H, XY = CH=CH] was also converted into the 1,2-diol (465) (Scheme 75) and thence the 25-epoxide (466), while Lemieux–Johnson oxidation of 25-ethenyl avermectin B1 gave the 25-formyl avermectin (467) and, by further oxidation with pyridinium dichromate in the presence of methanol, the 25-methoxycarbonyl avermectin (468).[220]

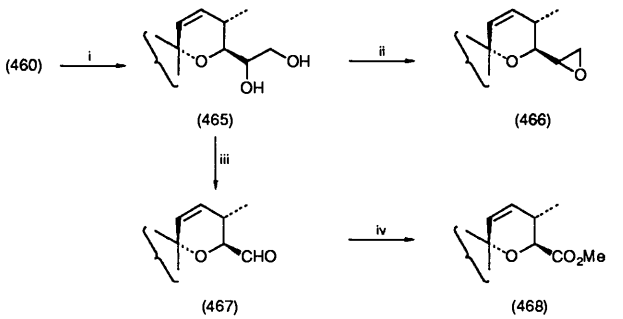
Microbiological hydroxylation of 22,23-dihydroavermectin $B1_a$ aglycon with *Cunninghamella Blakesleeana* gave avermectins mono-hydroxylated at C-12a and



(463) (464)

Reagents: i, H_2O, DMF, $CuCl_2$, $PdCl_2$, O_2

Scheme 74



(465) (466) (467) (468)

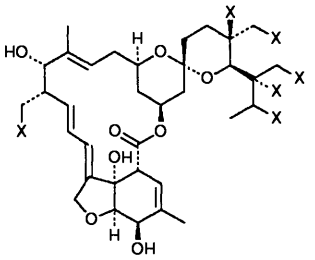
Reagents: i, OsO_4; ii, TsCl; iii, $NaIO_4$; iv, PDC, DMF, MeOH

Scheme 75

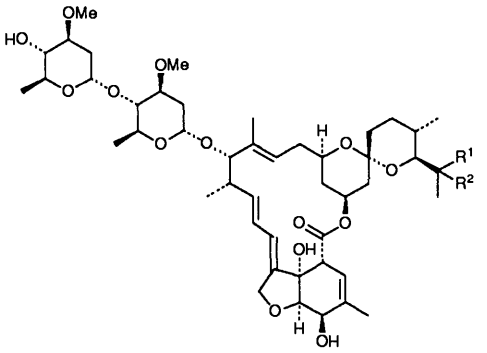
C-24, or in the C-24 and C-25 side-chains (Scheme 76).[221] Hydroxylations of milbemycin analogues with *Cunninghamella Blakesleeana* (ATCC 8688a) gave a similar spectrum of products, but additional dihydroxylated products were formed with a hydroxyl group at C-14a and with a β-hydroxy group introduced into the C-13 position to produce a 13-epi-avermectin. Hydroxylations of avermectin $B1_a$ and 22,23-dihydroavermectin $B1_a$ with *Nocardia autotrophica* (ATCC 35203) were more specific, producing compounds mono-hydroxylated only in the C-27 position, *e.g.* (469).[222] Avermectin $B1_b$ gave a 26-hydroxy

[221] R. T. Goegelman, E. S. Inamine, and R. F. White (Merck and Co. Inc.), European Patent, EP 194125 (1986); US Patent 4666937 (1987).

[222] R. T. Goegelman, E. S. Inamine, and R. F. White (Merck and Co. Inc.), European Patent, EP 212867 (1985).



X = positions of hydroxylation by *C. Blakesleeana*



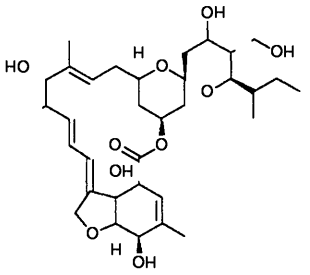
(469) R^1 = Me•CH(OH); R^2 = H
(470) R^1 = Me; R^2 = OH

Scheme 76

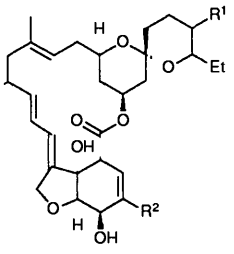
avermectin (470) under these conditions. Different specificity was shown by *Streptomyces bikiniensis* MA 5853 which hydroxylated 22,23-dihydroavermectin $B1_a$ aglycon at C-13, C-23, and C-24a to give (471).[223]

Milbemycins can be hydroxylated at C-14a with *S. nigricans* NRRL12479, *S. racemosum* IFO4287, 4814 or 4828 and *Rhizopur circinans* ATCC 1225224 while *Amycolata autotrophica* FERM P-6182 converts the C-12 methyl group of milbemycins into a hydroxymethyl group.[224,225] When cultured with *Amycolata autotrophica* FERM P-6183, milbemycin α_3 gave the three compounds (472a–c)[226] while a P450 enzyme isolated from *S. carbophilus* SAND 62585 gave 13-hydroxy milbemycin α_3.[227] As such a one-step method of production of 13-

[223] Merck and Co. Inc., Japanese Patent, JP 62 029 589 (1987).
[224] K. Nakagawa, Y. Tsukamoto, K. Sato, and A. Torigata (Sankyo KK), Japanese Patent, JO 1 199 591 (1988).
[225] I. Yamamoto and Y. Sugino (Sugiyo KK), Japanese Patent, JO 1 243 966 (1988).
[226] S. Nakagawa, A. Torigata, K. Sato and H. Kajino (Sankyo KK) Japanese Patent J 63 264 484 (1987).
[227] T. Matsuoka and S. Miyakoshi (Sankyo KK), European Patent, EP 281 245 (1988).



(471)



(472)

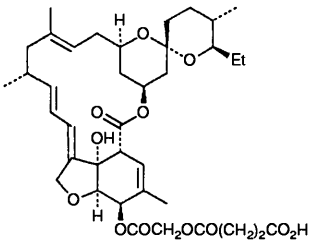
(a) $R^1 = CH_2OH$, $R^2 = Me$
(b) $R^1 = CH_2OH$, $R^2 = CH_2OH$
(c) $R^1 = CO_2H$, $R^2 = Me$

Table 2

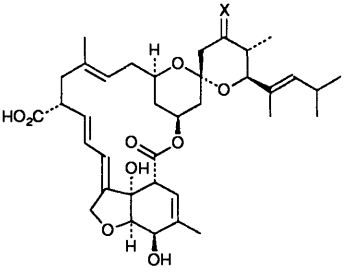
Added solvent	% *Conversion*	% 13β-OH	% 14,15-*Epoxide*
nil	37	70	30
Acetone	98	77	23
Acetonitrile	57	60	40
t-Butyl alcohol	71	63	37
DMF	98	64	36
DMSO	97	74	26
Ethyl alcohol	100	59	41

hydroxy milbemycins would be preferred to the multi-step chemical route, workers at Ciba-Geigy have studied this bio-transformation in some depth [228] From initial screening of eleven micro-organisms *S violascens* ATCC 31560 was chosen and shown to produce, at 37% conversion, a 7 3 mixture of 13-hydroxy milbemycin α_4 and the 14,15-epoxide of milbemycin α_4 from milbemycin α_4 Separate fermentations of *S violascens* with 14,15-epoxy milbemycin α_4 and 15-hydroxy milbemycin α_4 (see Section 8H for preparations) produced no 13-hydroxy milbemycins, implying that the epoxide is not an intermediate in the formation of the 13-alcohol and that it may be possible to adjust the conditions of the fermentation to maximize the production of the alcohol Adding 5% v/v organic solvents to the fermentation had a marked effect on the ratio of products (see Table 2), with optimization of the fermentation medium seven days incubation gave 92% of 13-hydroxy milbemycin and 8% of 14,15-epoxide at 91% conversion Lipophilic analogues of milbemycin α_4 such as the 5-acetate, 5-O-silyl ether or 5-oxime were not hydroxylated under the original conditions and the 5-ester (473) was only hydroxylated after the ester group had been hydrolysed off Addition of 5% DMSO to the fermentation medium of 5 oximino milbemycin α_4 resulted in a 35% yield of the 13-hydroxy compound but had no effect on the fermentations of the 5-acetoxy or 5-O-TBDMS analogues

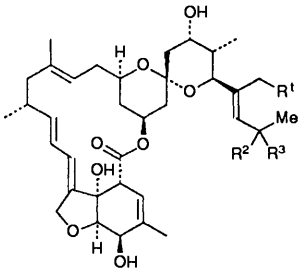
[228] (*a*) G M R Tombo O Ghisalba H P Schar B Frei P Maienfisch and A C O Sullivan *Agric Biol Chem* 1989 **53** 1531 (*b*) G Ramos O Ghisalba H P Schar B Frei P Maienfisch and A C O Sullivan (Ciba Geigy AG) European Patent EP 277 916 (1988)



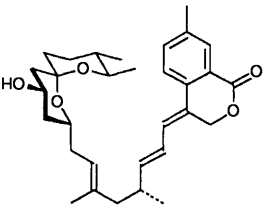
(473)



X = H, OH or O
(474)



(475) R^1 = H; R^2 = H; R^3 = CH_2OH
(476) R^1 = OH; R^2 = H; R^3 = CH_2OH
(477) R^1 = H; R^2 = OH; R^3 = Me
(478) R^1 = H; R^2 = H; R^3 = CO_2H

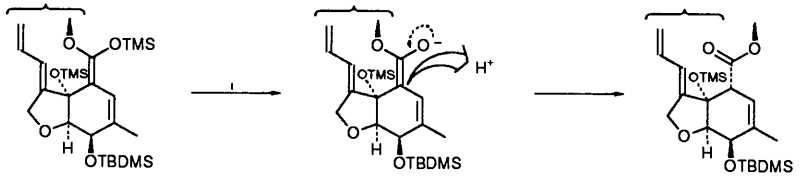


(479)
Lacrimin A

Milbemycins α_3 and D were also converted into mixtures of 13-hydroxy and 14,15-epoxides, but in these cases the epoxides were the major product.

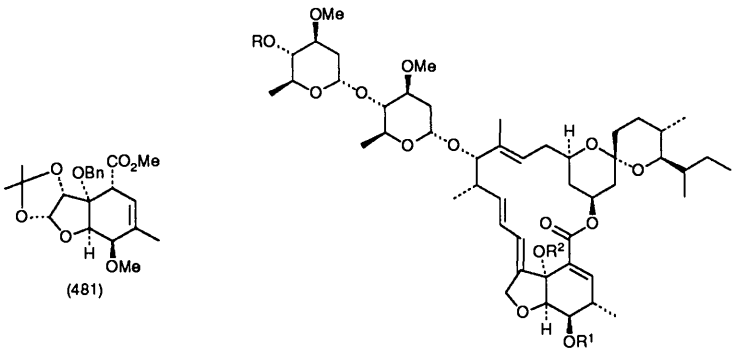
S541 Factor A or its 5-oxo analogue, when incubated with *S. platensis ssp. malvinus* NRRL 3761, gave the corresponding milbemycin 12-carboxylic acid (474). The 12a-hydroxymethyl milbemycin could also be isolated, leading to the supposition that this must be an intermediate in the oxidation process.[229] Other Streptomyces strains, *S. mashuensis* ISP 5221 and *S. rimosus* NRRL 2455, hydroxylated S-541 Factor A to give a 12-hydroxymethyl analogue; the latter strain also produced 4a,12a-dihydroxy Factor A while *Absidia cylindrospora* NRRL 2796 produced the tertiary alcohol 12-hydroxy S541 Factor A.[229] When a different fermentation medium was used with this micro-organism two metabolites from S541 Factor A were isolated which were mono- and di-hydroxylated in the C-25 side-chain, (475) and (476).[230] *S. eurythermus* ISP5014 also gave the mono-hydroxylated product (475) in addition to the tertiary alcohol (477), while *S. avermitilis* ATCC 31272 gave the carboxylic acid (478) in addition to (475) and the 5-methoxylated analogue of (475).[230]

[229] M. J. Dawson, D. Noble, G. C. Lawrence, R. A. Fletton, S. J. Lane, M V. J. Ramsay, O. Z. Pereira, D. R. Sutherland, and E. P. Tiley (American Cyanamid Co.), European Patent, EP 341 974 (1989).
[230] G. C. Lawrence, M. J. Dawson, D. Noble, R. A. Fletton, and S. J. Lane (American Cyanamid Co.), European Patent, EP 345 078 (1989).



Reagent i, AcOH

Scheme 77



(482) (a) R^1 = TBDMS; R^2 = TMS
(b) R^1 = TBDMS; R^2 = H

F. Conjugation and Deconjugation at C-2.—Previous work has shown that avermectins and milbemycins are inherently unstable to strong base.[1] Sankyo, however, have serendipitously found that the aqueous base-induced decomposition of milbemycin β_1 (24) at a pH > 12 gives a compound which is an antihypotensive agent.[231] This compound, given the name Lacrimin A (479), has recently been synthesized.[232]

Avermectins react with hydroxide ion in aqueous methanol to give two major products.[1] Initially, epimerization at C-2 occurs followed by movement of the Δ^3 double bond into conjugation to give a Δ^2 avermectin. This facile conjugation of the hydrindene double bond has recently been a cause of some discussion. In Hanessian's synthesis of avermectin $B1_a$ (5), the last step involves a deconjugation of the double bond to give, reportedly, the correct isomer of the required product in good yield. This was rationalized as a topside proton delivery to the ketene acetal derivative (480) under carefully controlled conditions (Scheme 77).[94,95] As Fraser-Reid had experienced difficulties with trying to prevent double bonds

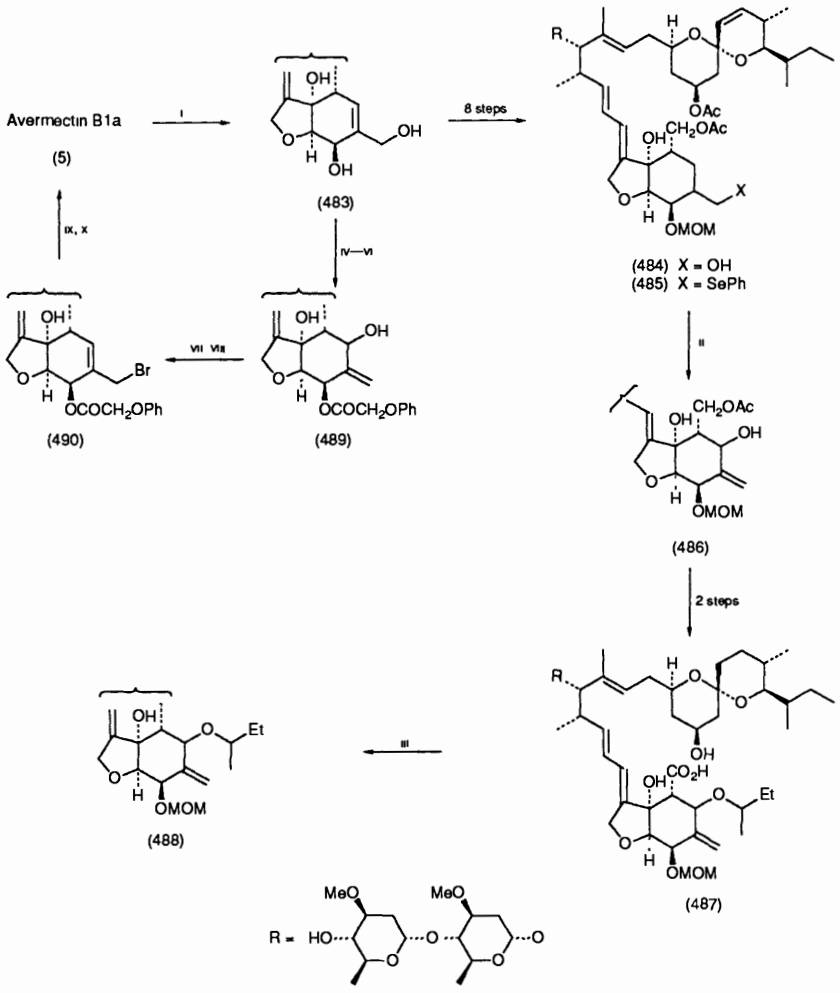
[231] H Takiguchi, J Ide, H Koike, and M Terao (Sankyo Co Ltd), Japanese Patent, JP 58-69 886 (1983)
[232] A Takle and P Kocienski, *Tetrahedron Lett*, 1989, **30**, 1675

moving into conjugation in intermediates such as (481), he determined to study this facile deconjugation.[157] Thus he prepared trisilylated Δ^2 Ivermectin (482a) and attempted the deconjugation under a variety of conditions. The only products isolated, however, were deconjugated 2-epi Ivermectin and the 7-hydroxy avermectin (482b). These experiments were then repeated with silylated Δ^2 avermectin $B1_a$ in case the additional C-22–C-23 double bond in avermectin $B1_a$ provided a subtle conformational change which favoured the deconjugation reaction. Yet again, however, a wide range of conditions only sufficed to produce 2-epi avermectin where deconjugation had taken place. As this appears to be the kinetic product an attempt was made to epimerize at C-2 under protic conditions ($NaOH/MeOH/H_2O$). For the trislylated 2-epi avermectin $B1_a$, this gave none of the required natural product. Significantly, however, unprotected 2-epi avermectin $B1_a$ did give 25% of the natural avermectin $B1_a$ under these conditions. Fraser-Reid attributes this to the polarity of the reaction medium and the substrate. An additional factor may be that hydrogen bonding between the macrolide and the solvent encourages the formation of the correct isomer. Such a hydrogen bonding network has been shown to be important in the crystal structure.[1]

Later in the same year, Hanessian, Dube, and Hodges published a further paper[156] on the last stages of their avermectin $B1_a$ synthesis. Subsequent work had revealed that the deconjugation step was 'prone to unpredictable variation in the nature of the products, even with the slightest change in reaction conditions, scale of operation, or mode of work-up' and that 'the material produced in our original deconjugation was not the primary product of deconjugation, but possibly the result of a subsequent epimerization of an initially formed 2-epi isomer'. They thus determined to produce the 2-epi isomer deliberately and then epimerize at the 2-position in a subsequent step. Addition of 4″,5,7-tris[O-(trimethylsilyl]-Δ^2-4(*R*)-avermectin $B1_a$ to lithium diethylamide and trimethylsilyl chloride followed by rapid quenching with aqueous acid gave a high yield of the 2-epi derivative which was subjected to various conditions in order to epimerize the C-2 position. While a variety of conditions, both protic and non-protic, were successful, the best conditions were found to be with imidazole in benzene under reflux. This gave a 40% yield of the required natural avermectin, 8% of the Δ^2 isomer and 34% of the starting material which could be recycled through the process to enhance the overall yield. A similar experiment on unprotected 2-epi avermectin $B1_a$ gave 40% of avermectin $B1_a$ along with 34% recovery of the 2-epi starting material. That this process was a true equilibrium was shown by subjecting avermectin $B1_a$ to the same process when an identical ratio of products was observed.

The final stage of Danishefsky's synthesis of avermectin $A1_a$ aglycon also involved a deconjugation of the Δ^2 double bond.[97] Conversion of the synthetic, conjugated, aglycon (372) into the C-2 epi-isomer was followed by epimerization with imidazole in benzene to yield 32% of the correct isomer of avermectin $A1_a$ aglycon admixed with 33% of the 2-epi avermectin and 31% of the Δ^2 isomer.

The facile conjugation of the Δ^3 double bond and consequent loss of stereochemical integrity at C-2 poses problems at a late stage of synthesis which



Reagents i, SeO_2, Bu^tOOH, ii, H_2O_2, pyridine, iii, DCC, DMAP, iv, *N*-(phenylselenophthalimide), Bu^n_3P, CH_2Cl_2, v, $PhOCH_2COCl$, vi, H_2O_2, pyridine, vii, CH_3SO_2Cl, viii, LiBr, ix, $NaBH_4$, DMF, x, MeOH, NH_3

Scheme 78

are best avoided The solution to this problem lies in 'parking' the double bond in an exocyclic position at C-4, as has been described by Fraser-Reid and his co-workers in a carefully considered, and well written paper (Scheme 78) [233] Two possible problems in this approach needed to be assessed (i) can seco-acid

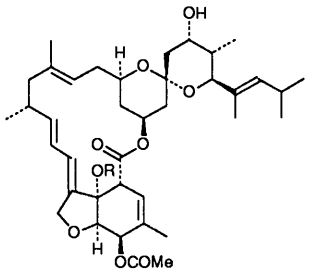
[233] B Fraser-Reid, J Barchi, and R Faghih, *J Org Chem*, 1988, **53**, 923

intermediates still be macro-lactonized, and (ii) can the double bond be moved between the $\Delta^{3,4}$ and ^{4,4a} positions without any problems of C-2 epimerization or conjugation. Answers to these questions were sought by transformations of avermectin $B1_a$ (5). Allylic oxidation of (5) at C-4a followed by cleavage of the macrocyclic lactone with lithium aluminium hydride and protection gave the alcohol (484). This was converted into the selenide (485), which was oxidized and allylically rearranged to the model C-3 alcohol (486). Deprotection and oxidation of the primary alcohol at C-1 gave a 3-hydroxy-$\Delta^{4,4a}$-seco-acid (487) which was successfully lactonized to reform the macrolide ring (488). The exocyclic double bond was then readily isomerized to the Δ^3 position by a sequence of sulphonation and brominolysis. Debromination with sodium borohydride in dimethylformamide and deprotection then gave back avermectin $B1_a$.

Selenylation of unprotected 4a-hydroxy avermectin $B1_a$ (483) with the Nicolau reagent specifically gave the required 4a-selenide, which was oxidatively rearranged and protected to give the exocyclic olefin (489). This was proved to have the same skeleton as (487) by conversion into a common triol. As this alcohol (489) had been converted back into avermectin $B1_a$ with no loss of stereochemical integrity or problems with conjugation, it can be seen that this strategy represents an exceptionally useful method of circumventing the problems which have bedevilled the synthesis of these macrolides.

G. Alkylation and Alkyl Derivatives.—Previous work has shown that avermectins and milbemycins can be O-alkylated by treatment with an alkyl halide in the presence of silver oxide;[1] later work has shown that other silver salts; the carbonate, salicylate, and perchlorate, can be used in this type of reaction.[191,204] For S541 Factors A and C, treatment with methyl iodide/silver oxide in ether gives methylation almost exclusively at the allylic C-5 oxygen; prolonged reaction times, or a change of solvent to HMPA, are necessary for methylation to occur at the C-23 hydroxyl group.[17b] On occasions, even methylation of the hindered C-7 group has been observed.[178] An extreme example of this can be seen in the alkylation of 5-O-TBDMS-22,23-dihydroavermectin $B1_a$ aglycon with methyl iodide/silver oxide which gave exclusively the 7-O-methyl ether.[234] In contrast, alkylation of this aglycon with 2-methoxyethoxymethyl chloride and *N,N*-diisopropylethylamine gave only the 13-O-ether.[234] Similarly surprising results have been reported, indicating that the C-7-hydroxyl group of S-541 milbemycin analogues is not always the least favourable position for reaction.[17b] Reaction of 5-methoxy S-541 Factor D with an excess of methyl isocyanate, catalysed by 4,4-dimethylaminopyridine, gave the 7-*N*-methylcarbamate as the major product, while 5-acetoxy S541 Factor A (491a), when alkylated with t-butyl bromoacetate and a sterically demanding base (KF/alumina or thallium oxide), gave the 7-substituted milbemycin (491b) as the only significant product in quite reasonable yield; very little reaction at C-23 was observed in either case. The isocyanate

[234] H. Mrozik, B. O. Linn, P. Eskola, A. Lusi, A. Matzuk, F. A. Preiser, D. A. Ostlind, J. M. Schaeffer, and M. H. Fisher, *J. Med. Chem.*, 1989, **32**, 375.



(491) (a) R = H
(b) R = $CH_2CO_2Bu^t$

result was explained as a consequence of the compact and fairly rigid spiroacetal structure blocking approach of the isocyanate to the C-23 oxygen atom after the base had associated with the hydroxyl group. A similar situation could arise with the alkylation by bromoacetate.

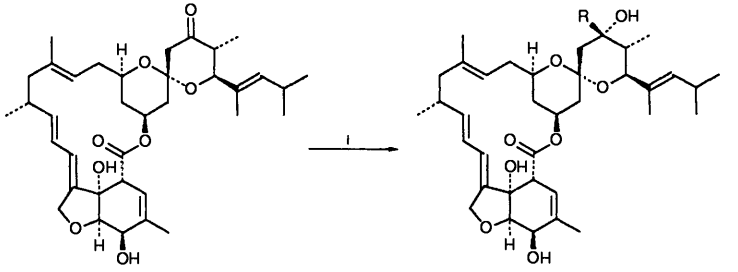
Preparation of a range of 13-alkoxymethoxy avermectins from 5-O-silylated avermectin B aglycons by *N,N*-di-isopropylethylamine catalysed etherification has been described;[235] 13-epi alkoxymethoxy avermectins were also prepared from the corresponding aglycons.[236]

Methylation and ethylation at the C-23 group of 5-protected S541 analogues was achieved with the appropriate trialkyloxonium tetrafluoroborate.[237] Analogous reactions were performed on the epimeric 23-hydroxy compounds (prepared by a Mitsunobu acylation/hydrolysis inversion sequence)[238] and on 13*R*-hydroxy--23-desoxy S541 (prepared by selenium dioxide oxidation, see Section 8E).[239]

Reaction of 5-O-TBDMS-13-hydroxy milbemycin α_4 with dihydropyran under acid catalysis gave the two diastereoisomers of the 2-tetrahydropyranyl analogue which were active anthelmintics.[240]

C-Substituted milbemycins have been prepared by addition of alkyl-lithium or Grignard reagents to the 23-ketone group of the S541 analogue (492) (Scheme 79).[179,241] These additions are highly stereoselective. For example, methyl magnesium iodide gave a 19:1 mixture of β:α isomers while trimethylsilylmethyl magnesium iodide gave only the β isomer. The Peterson product was converted into the 23-methylene derivative by acid treatment; the use of methylenetriphenylphosphorane or zinc/di-iodomethane with titanium tetrachloride to prepare this compound was markedly inferior.[242]

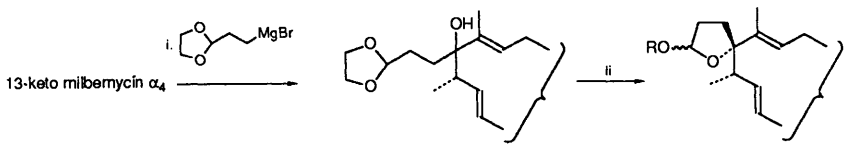
[235] Y Morisawa, A Saito, T Toyama, and S Kaneko (Sankyo KK), European Patent, EP 357460 (1988)
[236] B O Linn and H H Mrozik (Merck and Co Inc), US Patent, US 4 587 247 (1986)
[237] E P Tiley and M V J Ramsay (American Cyanamid Co), European Patent, EP 307 223 (1989)
[238] R Bell, M V J Ramsay, H M Noble, D Noble, N Porter, J B Ward, and R A Fletton (American Cyanamid Co), European Patent, EP 307 224 (1989)
[239] M V J Ramsay, R Bell, P D Howes, E P Tiley, and D R Sutherland (American Cyanamid Co), European Patent, EP 341 972 (1988)
[240] B Frei, A C O'Sullivan, and E Sturm (Ciba-Geigy AG), Swiss Patent, CH 669 382 (1989)
[241] M V J Ramsay, R A Fletton, J B Ward, D Noble, and N Porter (Glaxo Group Ltd), European Patent, EP 241 145 (1986)



(492) (493) R = Me or CH_2SiMe_3

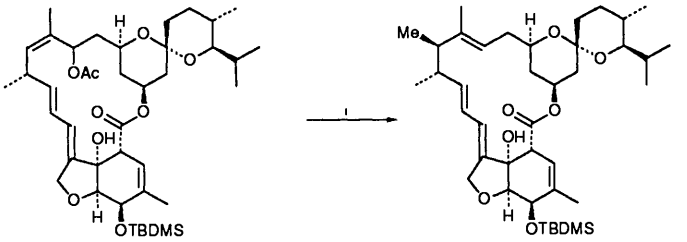
Reagents: i, MeMgI or Me_3SiCH_2MgI

Scheme 79



Reagents: ii, *p*-TsOH, ROH

Scheme 80



(494) (495)

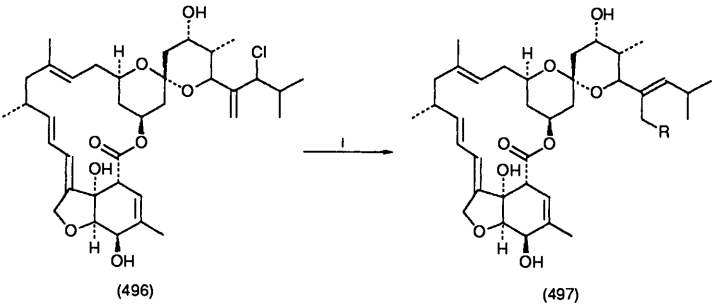
Reagents: i, Me_3Al, CH_2Cl_2

Scheme 81

Similar Grignard additions to 23-oxo avermectins have been reported although the stereochemistry of the newly created centre was not reported.[243] Grignard reactions at C-5 of 5-oxo S541 compounds,[179] and at C-5, C-10, C-13, C-4′, and C-4″ of 5-oxo avermectins have also been described.[244] A Grignard reaction was also used to append a 5′-alkoxy-tetrahydrofuran group onto the C-13 position of milbemycins; in this case the stereochemistry was as shown in the diagram with a 3:1 ratio of isomers at C-5′ on the tetrahydrofuran ring (Scheme 80).[244]

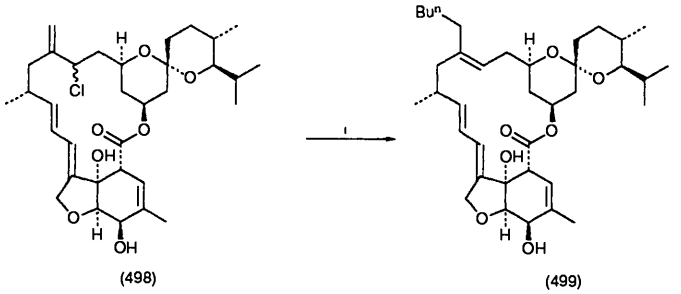
Reaction of the allylic 15-acetoxy compound (494) (Scheme 81) (see Section

[242] M. V. J. Ramsay, B. M. Bain, J. B. Ward, H. M. Noble, N. Porter, R. A. Fletton, D. Noble, D. R. Sutherland, and P. D. Howes (Glaxo Group Ltd.), European Patent, EP 231 104 (1987).
[243] P. Eskola, T. L. Shih, and H. Mrozik (Merck and Co. Inc.), European Patent, EP 351 923 (1990).
[244] P. Maienfisch (Cib-Geigy AG), European Patent, EP 284 563 (1988).



Reagents i, RMgBr, CuX

Scheme 82



Reagents i, Bu^{n}Li, CuCN

Scheme 83

8H for preparation) with trimethylaluminium gave the 13-methyl substituted milbemycin (495),[195a] which could also be obtained from the reaction of trimethylaluminium with 5-O-t-butyldimethylsilyl-13-ethoxycarbonyl milbemycin D.[245] Other 13-alkyl milbemycins were also obtained from (494) by reaction with trialkylaluminiums.[245]

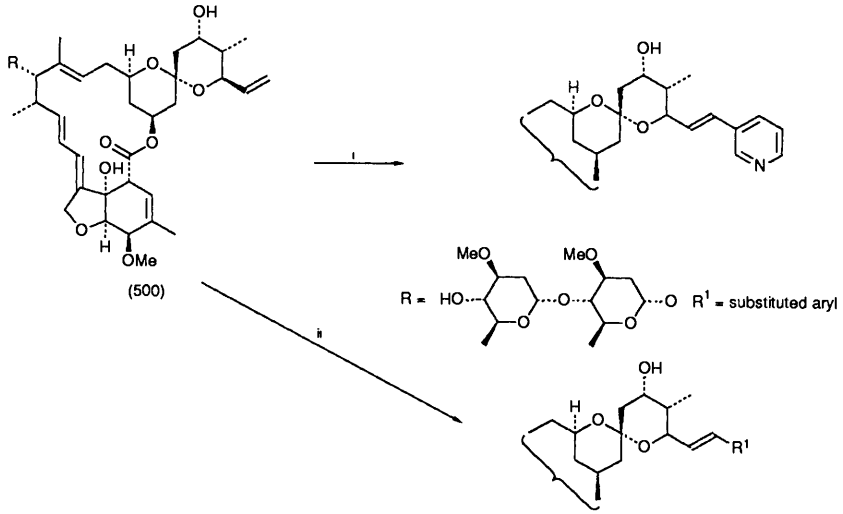
The S-541 halides (496), deriving from hypohalous acid addition (see Section 8H), were used to prepare a range of differently substituted C-25 analogues (497) by conjugate addition of alkyl or arylcopper lithiums, or alkyl vanadates (Scheme 82).[246] The chloride (498) (for preparation see Section 8H) could similarly be reacted with n-butyl-lithium/cuprous cyanide to give the 14-pentyl milbemycin analogue (499) (Scheme 83).[247]

25-Methylene avermectin A2, *e.g.* (500) (see Section 8E for preparation) has

[245] K Gubler, Y Tsukamoto, K Sato, and T Tanai (Ciba-Geigy AG), European Patent, EP 253 378 (1986)

[246] B M Bain, N Porter, P F Lambeth, H M Noble, A C Rosemeyer, R A Fletton, J B Ward, D Noble, D R Sutherland, M V J Ramsay, and E P Tiley (Glaxo Group Ltd), European Patent, EP 237 339 (1987), Australian Patent AU 307 050 (1987)

[247] U Burckhardt (Ciba-Geigy AG), European Patent, EP 165 900 (1985)



Reagents: i, (*o*-Me-C_6H_4)$_3$P, Et_3N, MeCN, 3-bromopyridine; ii, Pd/C, Et_3N, RI, MeCN

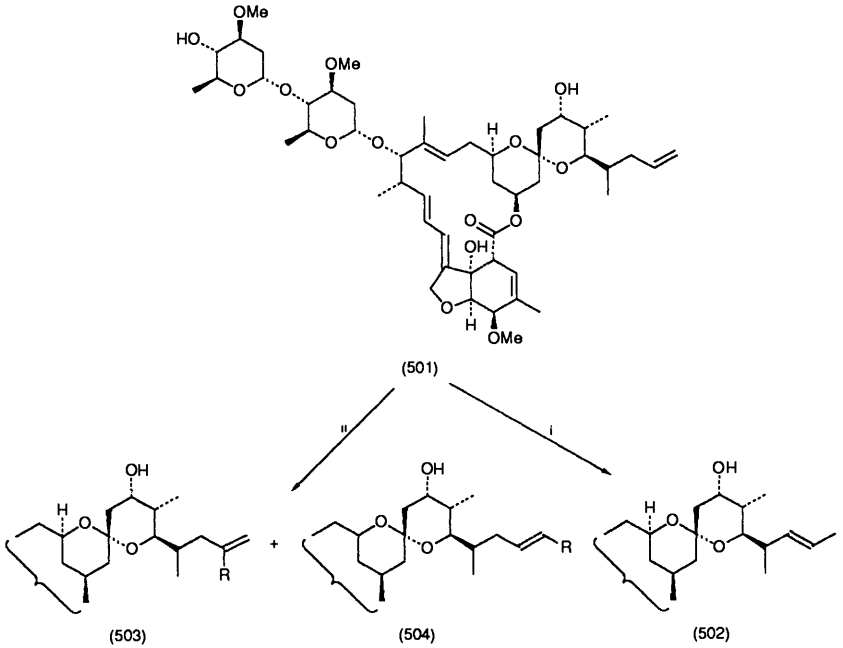
Scheme 84

been utilized to prepare a range of 25-arylethylene substituted avermectins by palladium-catalysed Heck reaction; a 2-carbomethoxyethylene derivative was also prepared (Scheme 84) as were several B2 analogues.[219] This combination of directed biosynthesis and Heck alkylation is a very powerful method of preparing new analogues; a further example can be found in the but-3-enyl analogue (501). Isomerization of the double bond into the chain is simply achieved (502) (Scheme 85), and Heck alkylations on (501) have been reported to give mixtures of 3- and 4-substituted butyl analogues (503) and (504) (Scheme 85).[219] For two of these alkylations, only physical data for the 4-substituted butyl analogue were reported, implying this to be the sole product. This is not explicitly stated in the patent.

Exocyclic methylene groups, both substituted and unsubstituted, have been added to the 13-position of milbemycins by reaction of the 13-oxo compound with Tebbe type titanocene–diolefin complexes, *e.g.* (505).[212,248] 13-Formyl milbemycins, prepared from the epoxide (459) by acid-catalysed rearrangement, were reacted with titanium-aluminium complexes, *e.g.* (506), to give a separable 2:1 mixture of β:α 13-vinyl milbemycins in good yields.[195b]

Treatment of 5-O-t-butyldimethylsilyl Ivermectin with zinc/copper couple and di-iodomethane gave a mixture of 3,4- and 8,9-methano and 3,4-8,9-dimethano Ivermectins in the ratio 8:2:3.[249] All of the introduced cyclopropanes were on the α-face of the molecule. Presumably the direction of addition is controlled by

[248] P. Maienfisch and K. Oertle (Ciba-Geigy AG), German Patent, DE 3 808 634 (1988)
[249] M. J. Wyvratt (Merck and Co. Inc.), US Patent, US 4 581 345 (1985).



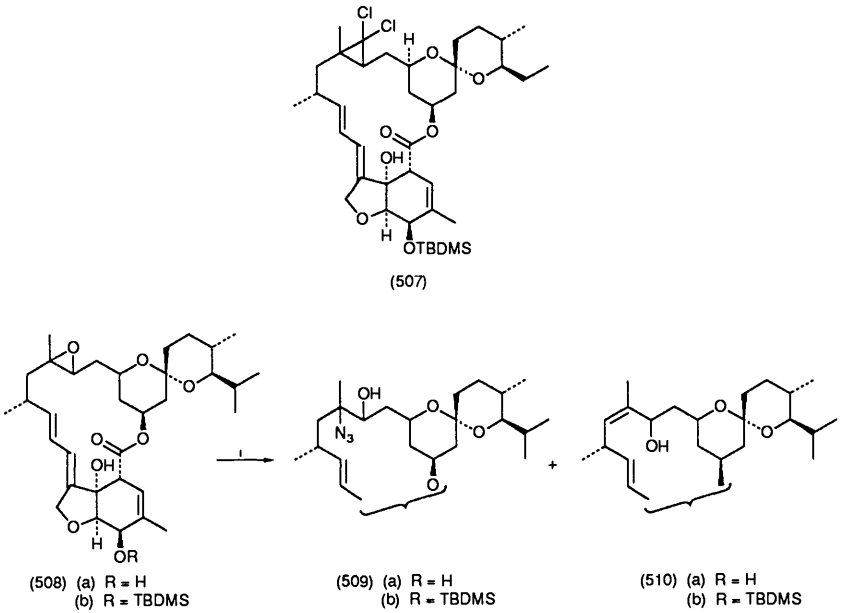
Reagents I, $COD(MePh_2P)_2Ir^+ PF_6^-$, H_2, II, $Pd(OAc)_2$, Et_3N, RI, MeCN

Scheme 85

the 7-hydroxy group.[250] The major product, however, from the addition of dichlorocarbene to 5-O-t-butyldimethylsilyl milbemycin α_3, is the 14,15-dichloromethylene adduct (507), a small amount of the 3,4-14,15 bis-adduct was also isolated.[251] A similar reaction on milbemycin α_1, with dichlorocarbene (again generated from chloroform and aqueous sodium hydroxide) with the phase-transfer agent tetra-butylammonium chloride added, gave only the 14,15-adduct. Similarly, dichlorocarbene generated from n-butyl-lithium and chloroform reacted with 5-O-t-butyldimethylsilyl milbemycin α_3 to give similar specificity. Dibromocarbene addition (from magnesium turnings and bromoform) to milbemycin α_3 gave only the 14,15-dibromomethylene adduct, which could be

[250] Unpublished work reported in 'Recent Advances in the Chemistry of Insect Control', ed N F Janes, Royal Society of Chemistry Special Publication No 53, London, 1985, p 70

[251] J C Gehret (Ciba-Geigy AG), European Patent, EP 285 561 (1988)



Reagents: i, Et_3Al, HN_3

Scheme 86

reduced with zinc in acetic acid to give a mixture of monobromo-cyclopropane and the unsubstituted cyclopropane. This patent claims dihalocarbene adducts with all conceivable combinations of halides, but no experimental details are given apart from those detailed above.

H. Reactions of the C-13–C-15 Sub-unit.—The allylic grouping between C-13 and C-15 of the avermectins and milbemycins merits special attention, as a range of reactions occur in this region which can be modulated allylically by the Δ^{13} double bond, or homo-allylically by the Δ^{10} double bond.

Reaction of the 14,15-epoxide of milbemycin D (508a) with a 1:1 molar mixture of hydrazoic acid and triethylaluminium in toluene solution gave a 61% yield of 14-azido-15-hydroxy-milbemycin D (509a), no other product being reported.[252] The use of a 3:2 (approximately) mixture of triethylamine and hydrazoic acid in diethyl ether solution, however, gave only 10% of the azido-alcohol (509a); the major product (45%) was the allylic alcohol (510a).[196] When this reaction was repeated on 5-O-t-butyldimethylsilyl milbemycin D (508b), using THF as solvent, the major product (47%) was, again, the allylic alcohol (510b) along with a very small amount (2%) of 13-β-azido milbemycin D

[252] H. B. Merevala and B. Frei, *Helv. Chim. Acta*, 1986, **69**, 415.

(511) [196] Derivatives of the allylic alcohol (510a) were also obtained from 5-O-methyldiphenylsilyl milbemycin α_3, milbemycin α_4, and 5-O-t-butyldimethylsilyl-13-deoxy-22,23-dihydroavermectin $B1_a$

Reaction of the 15-hydroxy milbemycins (510b) with diethylaminosulphur trifluoride gave the allylic rearrangement products, 13-β-fluoro milbemycins (512, X = F) in good yield 13-β-Fluoro milbemycins have also been prepared from 13-hydroxy milbemycins by reaction with diethylaminosulphur trifluoride [190b]

The susceptibility of Δ^{13} 15-hydroxy milbemycins to allylic rearrangement can be seen by the wide range of 13-substituted compounds prepared therefrom 13-Chloro, bromo, and iodo compounds,[196] and 13-alkoxy, thioalkyl,[253] thioacyl,[254] and 13-acyloxy [198a b] milbemycins have all been reported, as has the rearrangement of 5-O-t-butyldimethylsilyl-15-hydroxy Δ^{13} milbemycin D to the corresponding 13-hydroxy milbemycin with pyridinium dichromate in DMF [253]

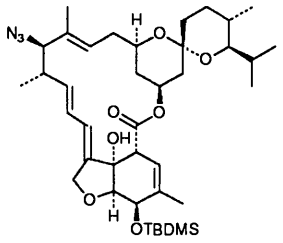
Swern oxidation of this 13-hydroxy milbemycin and reduction of the 13-oxo product with sodium borohydride gave 13-hydroxy milbemycin D, an analogue of an avermectin aglycon [190a]

There is very little conformational flexibility in the macrolide ring of avermectins and milbemycins, and because of this the atoms O-13, C-13, C-14, C-14a, and C-15 lie in almost the same plane [234] Thus the σ bond of a 13β leaving group lies in the plane of the C-14–C-15 π orbitals, and any reactions of a 13β-substituted compound should show considerable allylic character In contrast the σ orbitals of a 13α leaving group are orthogonal to the plane of the C-14–C-15 π orbitals, and thus there should be no allylic interactions in reactions observed at this centre Homoallylic interactions with the C-10–C-11 double bond are, however, possible A further facet of the chemistry at C-13 is provided by apparent steric hindrance in the reactions of the natural 13α-substituted aglycon This can be clearly observed in the reaction of 22,23-dihydroavermectin $B1_a$ aglycon with t-butyldimethylsilyl chloride to give only the 5-O-silylated product, no silylation at C-13 is seen under normal conditions [234]

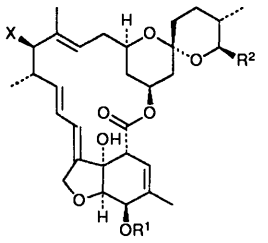
Displacements at C-13 of the avermectin aglycon have been studied extensively using the readily available 5-O-t-butyldimethylsilyl-22,23-dihydroavermectin $B1_a$ aglycon (513, R = H) (see above) [234 250] Solvolysis of the derived tosylate in methanol gave the 13-methoxy compound (514, R = MeO) with retention of configuraion, probably by participation of the Δ^{10} double bond forming a homoallylic cation (Scheme 87) When the solvolysis was conducted in the presence of HCl the 13α-chloro derivative (514, R = Cl) was obtained, while solvolysis in a mixture of HF/THF/pyridine gave the 13α fluoride (514, R = F) as a major product along with some of the 13β fluoride (515d) as a minor product (Scheme 87) Other similar solvolyses have been reported [236]

In an intermediate step in the previously described correlation of the avermectins and milbemycins, the mono-protected aglycon (513, R = H) was reacted with 2-nitrobenzenesulphonyl chloride to give the inverted 13β-

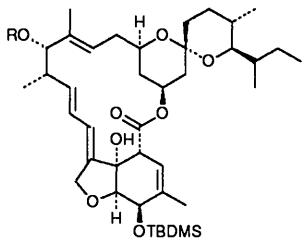
[253] B Frei and A C O Sullivan (Ciba-Geigy plc) British Patent GB 2 167 751 (1986)
[254] A C O Sullivan and B Frei (Ciba Geigy AG) European Patent FP 252 879 (1986)



(511)



(512) R^1 = Me, TBDMS, TBDPS
R^2 = Me, Et, Pr^i, Bu^s
X = F, Cl, Br, I, OR, SR, SCOR, OCOR



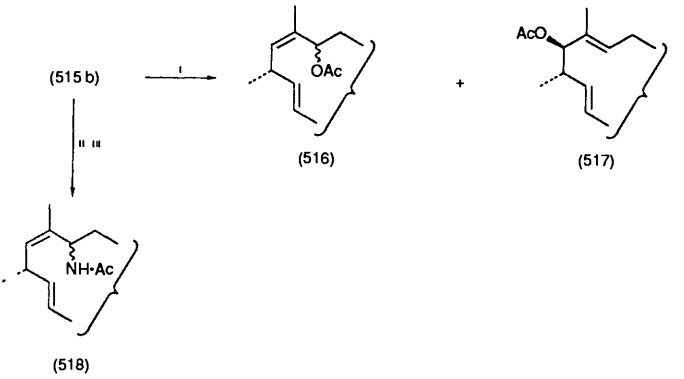
(513)

(514) R = OH, OMe, OEt, OAc, Cl, F

(515) (a) R = Cl
(b) R = I
(c) R = Br
(d) R = F

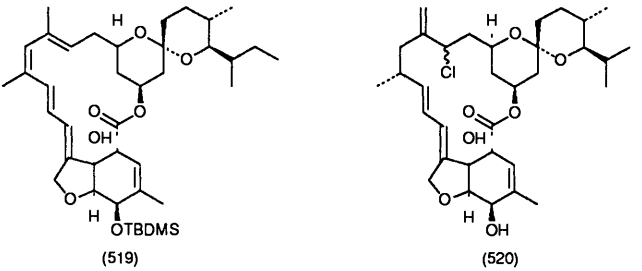
Scheme 87

chloro derivative (515a).[1,4] This was obviously formed by displacement of the 2-nitrobenzenesulphonate intermediate with chloride ions in solution, a supposition supported by the observation that addition of an excess of tetrabutylammonium iodide gives the 13β-iodo analogue (515b) in good yield.[234] The expected allylic reactivity of this iodide is demonstrated by its reaction with silver acetate in glacial acetic acid, in that the allylically rearranged 15-acetate (516) was obtained in addition to the 13-acetate (517) (Scheme 88).[234,236] A further illustration of the allylic character of the 13β-iodide (515b) can be found in its reaction with methylamine, followed by acetylation, to give the Δ^{13} 15-amide (518) (Scheme 88).[234] The reaction of 13-β-iodo-5-oxo milbemycin α_3 with substituted phenethyl alcohols to give 13-β-phenylethoxy milbemycins has been described in a Sankyo



Reagents I, AgOAc, II, $MeNH_2$, III, Ac_2O, pyridine

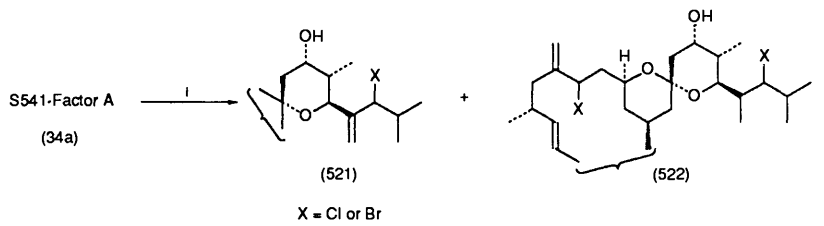
Scheme 88



patent [235] No allylically rearranged products were described but as experimental details in patents are rarely complete this does not necessarily mean they were not formed The retention of stereochemistry observed, however, argues for the intervention of a homoallylic cation Dehydroiodination of (515b) with collidine at 100 °C gave a mixture of the tetra-ene (519) (of undetermined stereochemistry about the C-12–C-13 double bond),[234] whereas the use of DBU gave the tetra-ene with a concomitant shift of the Δ^3 double bond into the Δ^2 position [250] A by-product obtained from the collidine reaction was the 13β isomer of the initial aglycon (515 R = OH), this *epi* aglycon could be obtained in good yield if the reaction was repeated in aqueous collidine [234]

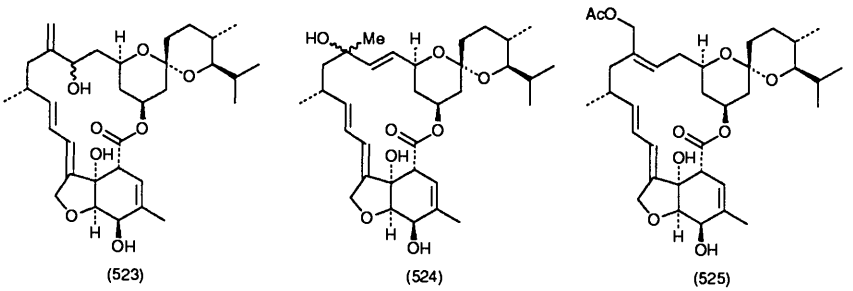
Reaction of milbemycin D with hypochlorous acid or sulphuryl chloride gives a 'surprisingly high yield' of Δ^{14} 15H-15-chloro milbemycin D (520) [255] Similar reactions have been reported for milbemycins α_1 and α_3, and 13-deoxy-22,23-dihydroavermectin $B1_a$ aglycon [255] S-541 Factor A, which possesses an additional double bond in the 25-alkyl substituent, has also been reacted with hypochlorous

[255] (*a*) U Burckhardt (Ciba-Geigy Corp), US Patent, US 4 584 314 (1986) (*b*) European Patent EP 143 747 (1984)



Reagents: i, HOCl or HOBr

Scheme 89



acid.[256] Two products were isolated, a monochloride substituted in the C-25 side chain (521, X = Cl), and a dichloride (522, X = Cl) analogous to the milbemycin D product but also substituted in the side chain (Scheme 89). Hypobromous acid reacted in a similar way, while phenylselenyl bromide gave only the side-chain substituted compound (521, X = Br). Cyanamid have reported that the use of *N*-bromoacetamide in aqueous acetone or *N*-chlorosuccinimide in methanol give the side-chain halogenated products (521, Hal = Cl or Br).[184b,257]

Oxidation of milbemycin D with singlet oxygen followed by reduction with triphenylphosphine generates the 15-hydroxy $\Delta^{14,14a}$ milbemycin (523) in good yield; a small quantity of the tertiary alcohol (524) was also isolated.[257] This reaction was also carried out on 5-oxo milbemycin D and various 5-protected milbemycins with similar results. Solvolysis of the mesylate of the allylic alcohol (523) in glacial acetic acid gave the 14a-acetoxy milbemycin analogue (525);[258] the allylic aldehyde was also prepared and converted into various oximes.[257]

The preparation of 5-oxo milbemycins and avermectins by mercuric acetate induced isomerization of the 3,4-double bond of a 5-methoxy derivative followed by acid hydrolysis of the resulting enol ether has been reported.[1,178,259] This process, however, has been reported to be unsatisfactory on an industrial scale

[256] S. Y. Tamura and G. Asato (American Cyanamid Co.), European Patent, EP 297 205 (1988).
[257] (*a*) J. C. Gehret (Ciba-Geigy AG), European Patent, EP 144 285 (1985); (*b*) B. Frei, H. B. Merevala, U. Burckhardt, and J. C. Gehret (Ciba-Geigy AG), Swiss Patent, CH 656 129 (1986).
[258] J. C. Gehret (Ciba-Geigy AG), European Patent, EP 281 522 (1987).
[259] H. Mrozik, P. Eskola, and M. H. Fisher, *J. Org. Chem.*, 1986, **51**, 3058.

for several reasons, not the least of which is the ecological problem induced by using large quantities of mercury salts [208a] In the course of circumventing this problem, these workers oxidized 5-oxo milbemycins with selenium dioxide in formic or acetic acids and, after hydrolysis of the total crude products, obtained good yields of 13-hydroxy milbemycins by allylic oxidation

I. Unnatural Sugar Derivatives of Avermectins and Milbemycins.—Treatment of 5-O-t-butyldimethylsilyl avermectins with sulphur trioxide/pyridine complex gives the 4′-O-sulphate derivatives [260] and several simple derivatives, such as semicarbazones and hydrazones, of 4″-oxo avermectins have been described [174a 261] Reformatsky reactions have been performed on these 4″-oxo avermectins (and also on the 4-monosaccharide) to give, for example, 4′-[(ethoxycarbonyl)methyl] avermectin B1 [262]

More fundamental changes in the saccharide groups at C-13 are provided by the alkylation of 13-hydroxy milbemycins (avermectin aglycons) The standard Koenigs–Knorr procedure used previously [1] has been largely supplanted by the coupling of 1-fluoro and 1-phenylthio sugars, which gives better yields [263] An example can be found in the coupling of 1-S-(2-pyridyl)-sugars to 5-protected 13-hydroxy milbemycin D with silver perchlorate followed by mild acid treatment, compounds such as 13-O-(3,4-di-O-acetyl-2-deoxy-L-rhamnosyl) and 13-O-(4-O-acetyl-L-oleandrosyl) milbemycin D and 13-O-[4′-O-(L-oleandrosyl)-L-oleandrosyl] milbemycin α_3 were prepared in this way [264] 1-Fluoro sugars were used to prepare C-2″β and C-2″α-fluoro avermectins $B1_a$ [265] An avermectin with a third oleandrose group at the C-4″ position has been prepared which is equipotent with avermectin B1 [266]

The preparation of 13-β-(α-L-oleandrosyl-α-L-oleandrosyloxy) milbemycin derivatives, and thus the mono-oleandrosyl analogues, by the incubation of 13β-hydroxy milbemycins with *S avermitilis* ATCC 31272 or ATCC 31780 has been described [267] This should present a very effective method for many milbemycin derivatives as such bio-organic approaches frequently require little in the way of protection of the substrate [268]

5-O-sugar derivatives of milbemycin D have been prepared by coupling acetohalo-sugars or S-pyridylaceto-sugars in the presence of di-isopropylethylamine and a silver salt [269]

[260] M J Wyvratt (Merck and Co Inc), US Patent, US 4 622 313 (1986)
[261] B O Linn and H H Mrozik (Merck and Co Inc), European Patent, EP 343 708 (1989)
[262] M J Wyvratt (Merck and Co Inc), US Patent, US 4 833 168 (1989)
[263] K C Nicolaou R E Dolle, D P Papahatjis, and J L Randall, *J Am Chem Soc*, 1984, **106**, 4189
[264] B Frei and H B Merevala (Ciba-Geigy AG), European Patent, EP 235 085 (1987)
[265] C Bliard F C Escribano G Lukacs A Oleskar and P Sarda *J Chem Soc Chem Commun* 1987, 368
[266] M J Wyvratt *et al*, unpublished work reported in Topics in Medicinal Chemistry 4th SCI RSC Medicinal Chemistry Symposium, ed P R Leeming, Royal Society of Chemistry Special Publication No 65, 1988
[267] G T Lawrence, M J Dawson, D Noble M V J Ramsay R Bell D R Sutherland, and E P Tiley (American Cyanamid Co), European Patent, EP 341 973 (1989)
[268] H G Davies, R H Green, D R Kelly, and S M Roberts, 'Biotransformations in Organic Chemistry' Academic Press, London, 1989

9 Conclusion

The commercial success of Ivermectin has stimulated many other companies to produce their own macrolide antiparasitics. Scientifically, however, the greatest advance must be the stimulus given to synthetic chemistry, methods of structure determination, and fermentation techniques.

The complex nature of the avermectins and milbemycins has caused many problems. Perusal of any of the avermectin and milbemycin total syntheses proves this point. Is there any point in further tempting fate by devising other avermectin and milbemycin syntheses? The answer, surely, is a resounding yes. The successful total synthesis of such a macrocycle with multiple stereogenic centres represents a formidable proof of a particular synthetic concept and needs all the power of modern organic chemistry. The present syntheses detailed in this review are outstanding examples of the synthetic art but there may well be shorter, more efficient, methods to the natural avermectins and milbemycins which can be devised in the future. For the medicinal chemist future synthetic work will be aimed at producing analogues with improved pharmacological properties, either by total synthesis or semi-synthetic methods. Such is the potential market for improved endectocides that there is sure to be much more work to be done in the coming years.

In the introduction to our first review,[1] we noted that parasitic infections of livestock in America have been estimated to cost more than $3 billion annually. If this is the cost borne by one of the richest nations in the world, how much greater must be the cost in both economic and human terms in those third world countries where parasites take such a terrible toll of both animal and human health. If avermectins and milbemycins can reduce this toll in any way then the scientific work put into them will have reaped a rich harvest.

Acknowledgements. The authors gratefully acknowledge the assistance of Miss J. Bradshaw of Glaxo's Information Science and Services Department, Glaxo Library (Greenford) and also the staff of Glaxo's Intellectual Property Department.

[269] J C Gehret, E. Sturm, and B. Frei (Ciba-Geigy AG), European Patent, EP 185 623 (1985)