AN ABSTRACT OF THE THESIS OF

Ulhas S. Warrier for the degree of Master of Science in Chemistry presented on May 28, 1987.

Title: Synthesis of a Model of the Spiroketal Portion of Avermectin B_{1a}

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Avermectin B_{1a} is a member of a class of medicinally important natural products known for its potent antiparasitic activity and interesting structural features. In this thesis, synthesis of a model for the spiroketal portion of the avermectins is presented.

Oxidation of (S)-2-methylbutanol, followed by a stereoselective chromium mediated reaction with crotyl bromide, gave (3S,4R,5S)-3,5-dimethyl-1-hepten-4-ol as the major isomer. After investigating a variety of protecting groups, the alcohol was masked as a t-butyldimethylsilyl ether and subsequent ozonolytic cleavage of the vinyl group afforded the corresponding aldehyde. Reaction of this aldehyde with carbon tetrabromide and triphenylphosphine resulted in its homologation to a dibromoolefin, which underwent elimination with butyllithium to yield (3S,4R,5S)-4-t-butyldimethylsiloxy-3,5-dimethyl-1-heptyne.

Selective protection of the primary alcohol of R-(-)-1,3-butanediol as its 2,4,6-triisopropylbenzenesulfonate, followed by the acetylation of the secondary alcohol, provided (2R)-4-(2,4,6-triisopropylbenzenesulfonyloxy)-2-acetoxybutane. The latter was

converted to the corresponding iodide which, when treated with lithium diisopropylamide, cyclized to (R)-δ-caprolactone.

Alkylation of the δ-lactone with either the dibromoolefin or the alkyne after treatment with butyllithium, followed by reaction with methanol on Amberlite ion exchange resin, gave (2RS,6R)-2-[(3S,4R,5S)-4-t-butyldimethylsiloxy-3,5-dimethyl-1-heptynyl]-2-methoxy-6-methyltetrahydropyran. Deprotection, and then Lindlar hydrogenation of this compound with an acidic workup led to the formation of the target compound (2R,3S,6R,8R)-3,8-dimethyl-2[(1S)-1-methylpropyl]-1,7-dioxaspiro[5.5]undec-4-ene.

Synthesis of a Model of the Spiroketal Portion of Avermectin B_{1a}

by

Ulhas S. Warrier

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SYNTHESIS OF A MODEL OF THE SPIROKETAL PORTION OF AVERMECTIN B_{1a}

INTRODUCTION

The discovery of avermectin B_{1a} and other members of its class stems from the search for effective drugs against parasitic diseases in animals and man.[1,2] These diseases constitute serious problems in many countries of the world and cause proportionately large economic losses wherever livestock is raised. Parasitic worms (nematodes and helminths) and arthropods are responsible for most of the losses which continue to occur despite the development of many effective antiparasitic drugs in the past few years. Chemotherapeutic control of parasites requires the use of different drugs for different kinds of parasites. However, the emergence of drug resistance in parasites mandates a continuing search for new and effective agents to treat these infections.[3,4]

Many of the antihelmintic compounds studied in the past three decades belong to the aminoglycoside family of antibiotics. These include destomycin,[5] paramomycin,[6] hygromycin B,[7] the antibiotic G418,[8] and the antibiotic compound S115-1.[9] Antihelmintic activity is also exhibited in antibiotics and other structural classes, such as anthelvenicin which is related to netropsin,[10] and the glycine-containing antibiotics that include aspiculamycin and anthelmycin.[12]

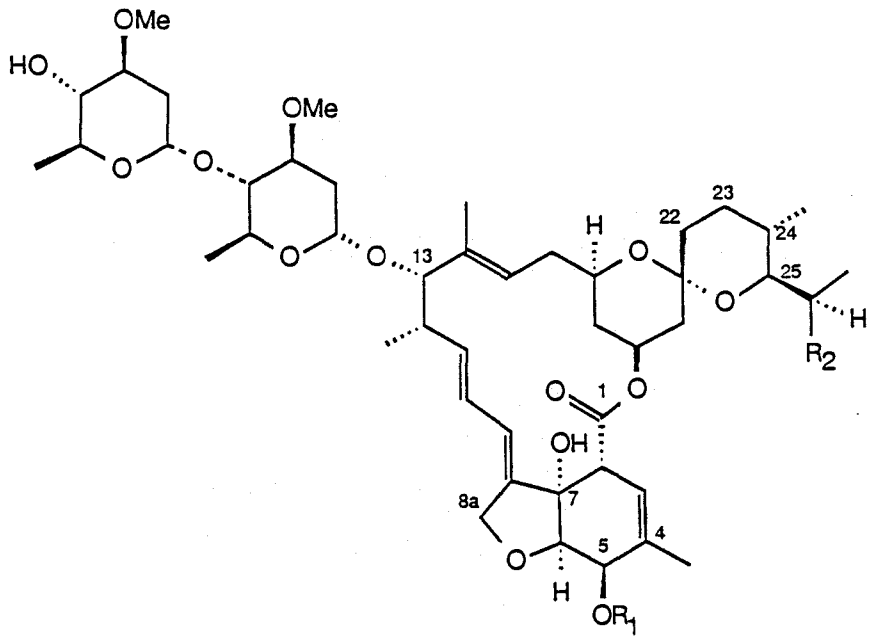
Screening efforts for less toxic compounds with more potent antihelmintic properties uncovered the avermectins which exhibit highly

potent, broad-spectrum antiparasitic properties. Using a screen with mice infected by the helminth Nematodirus dubius, researchers at Merck found antihelmintic activity in a broth produced by a culture of Streptomyces avermitilis. This culture originated from an actinomycete isolated at the Katasato Institute from a soil sample collected at Kawana, Ito City, Japan.[1] A concentrate of the broth, in which the actinomycete had been cultured, showed remarkable activity against this helminth which is typically difficult to eradicate with common antihelmintics such as benzimidazoles. The concentrate had no apparent toxic effect to the host over an eight-fold dosage range.

The avermectins are best known for their potent activity against two major classes of parasites, the nematodes and the arthropods (insects, ticks, lice and mites).[13] Since their toxicity in mammals is very low, they have emerged as commercially valuable antihelmintic and ectoparasiticidal agents and a derivative, known as Ivermectin (9), has been developed and marketed as a broad-spectrum antihelmintic drug by Merck.

Structurally, the naturally produced avermectins 1 - 8 fall into two main groups, designated A and B (Figure 1). The former has a methoxy substituent and the latter a hydroxy substituent at C-5. These two groups are further subdivided into a 1- series, with a C-22 - C-23 double bond, and a 2- series, having a hydroxyl group at C-23. A final subdivision into a and b series designates the presence of a sec-butyl or an isopropyl substituent at C-25, respectively.

The history of avermectins parallels closely that of a structurally similar series of compounds, the milbemycins, which were



		R_1	R_2	C_{22}-C_{23}
1	Avermectin A_{1a}	Me	Et	CH = CH
2	Avermectin A_{1b}	Me	Me	CH = CH
3	Avermectin A_{2a}	Me	Et	CH_2- CH(OH)
4	Avermectin A_{2b}	Me	Me	CH2 -CH(OH)
5	Avermectin B_{1a}	H	Et	CH = CH
6	Avermectin B_{1b}	H	Me	CH = CH
7	Avermectin B_{2a}	H	Et	CH_2 - CH(OH)
8	Avermectin B_{2b}	H	Me	CH_2 - CH(OH)
9	Ivermectin (22,23-dihydro-avermectin B_{1a})	H	>80% Et <20% Me	CH_2-CH(OH) CH_2-CH_2

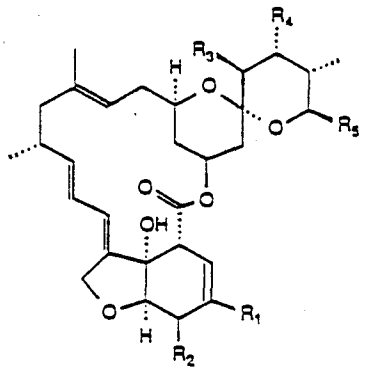
Figure 1. Structures of Avermectins

isolated in 1975. Subsequent screening showed that the milbemycins possess remarkably potent pesticidal activity against a host of agricultural pests, including aphids, larval forms of insects of the order Lepidoptera, mites, rice-leaf beetles, and tent caterpillars. There was little or no associated phytotoxicity. Milbemycins, like avermectins, are members of a class of sixteen-membered macrolides and, although they possess a simpler structure, they have a greater diversity of functionalization which gives them a less ordered nomenclature (Figure 2,3).

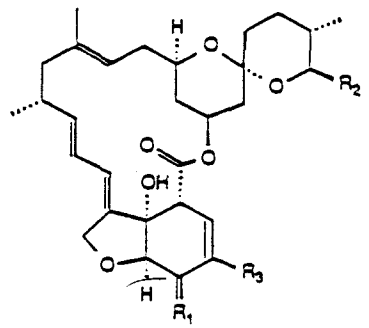
The only real subdivision which has been made of milbemycins is into the α series (10 - 24) and the β series (25 - 29). The α series has a tetrahydrofuran ring fused to the cyclohexene ring and are true analogues of the avermectins, while the β series has no tetrahydrofuran ring. The aromatic ring of milbemycin β_3 (29) is a feature unique to this compound.

The major structural difference between the avermectins and the milbemycins is the absence of a disaccharide moiety at C-13 in the milbemycin series. Further, the avermectins have sec-butyl or isopropyl side chains attached to C-25, while the milbemycins have methyl or ethyl substituents at this position.

The relative configuration of milbemycins was established by means of spectroscopic and x-ray studies. The chemical correlation of an avermectin aglycon with milbemycin D and the identification of structural subunits in the avermectins by ^{13}C and ^{1}H NMR and mass spectroscopy revealed their close similarity to the milbemycins. The point of attachment of the disaccharide substituent in the avermectins was determined by chemical degradation of avermectin A_{2a} into



	Milbemycin	R_1	R_2	R_3	R_4	R_5
10	α_1	Me	OH	H	H	Me
11	α_2	Me	OMe	H	H	Me
12	α_3	Me	OH	H	H	Et
13	α_4	Me	OMe	H	H	Et
14	α_5	Me	OH	OH	OCOCHMeBu^n	Me
15	α_6	Me	OMe	OH	OCOCHMeBu^n	Me
16	α_7	Me	OH	OH	OCOCHMeBu^n	Et
17	α_8	Me	OMe	OH	OCOCHMeBu^n	Et
18	α_9	pyrr	OH	H	H	Me
19	α_{10}	pyrr	OH	H	H	Et



		R_1	R_2	R_3
20	D	H, β - OH	iPr	Me
21	F	H, β - OH	iPr	pyrr
22	G	H, β - OH	iPr	Me
23	J	O	Me	Me
24	K	O	Et	Me

pyrr =

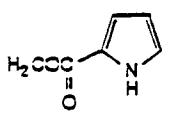
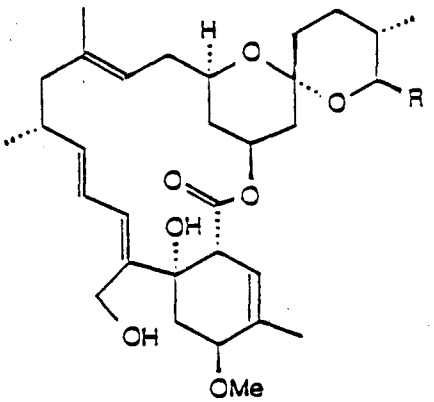
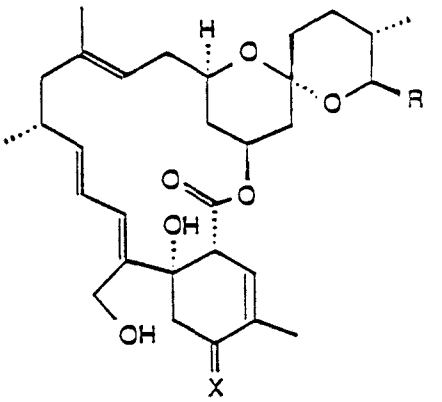


Figure 2. Structures of α Milbemycins.



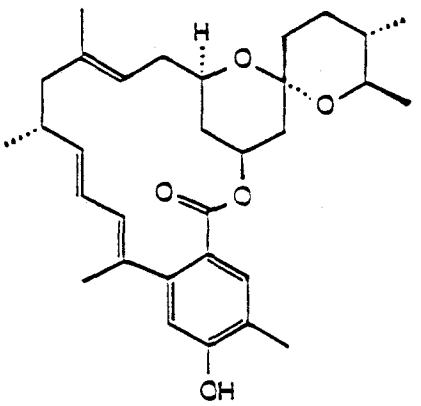
(25) β_1 R_{25} = Me

(26) β_2 R_{25} = Et



(27) β_1 R = CH_2OH, X = H, OMe

(28) β_2 R = CH_3 , X = O



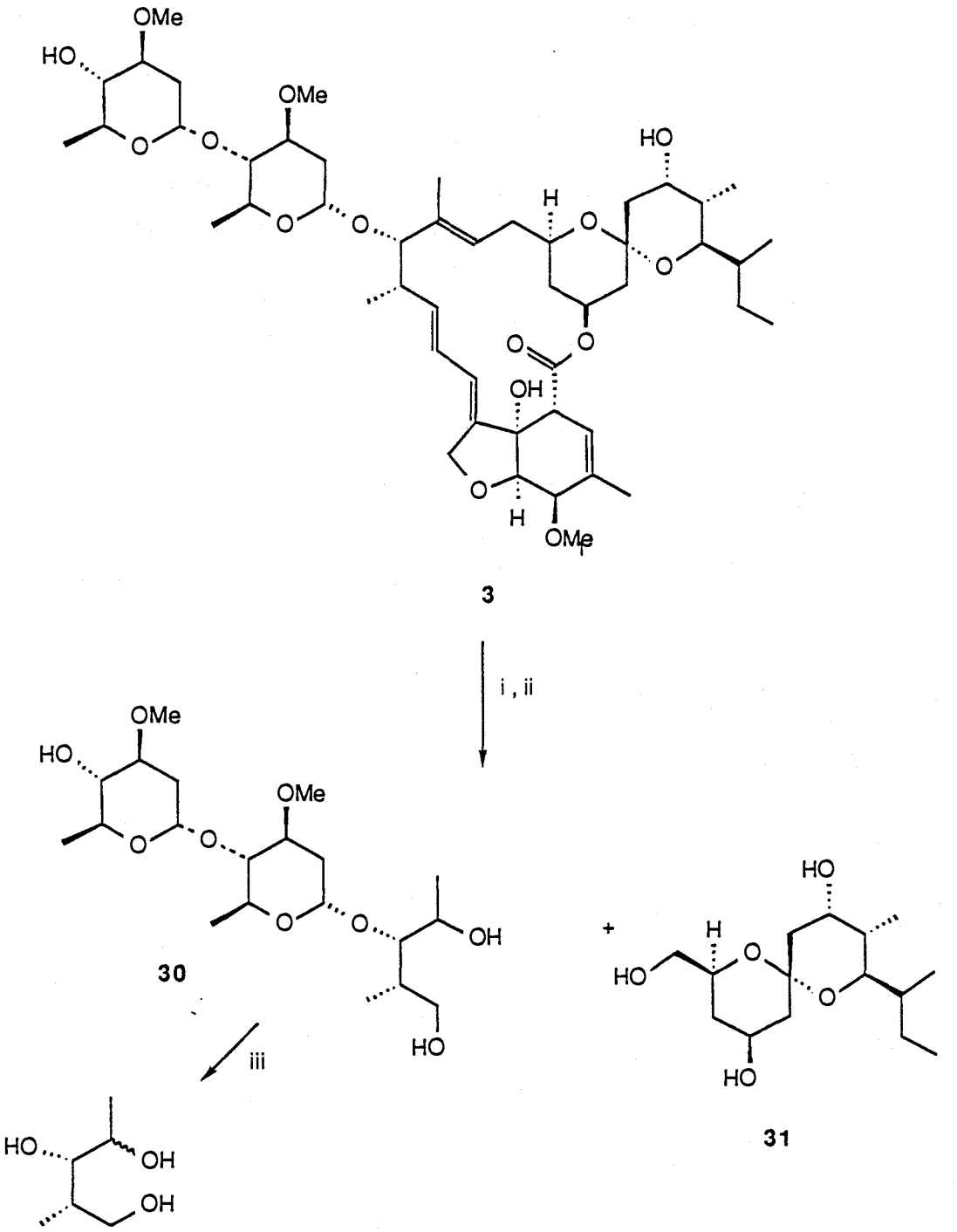
(29) β_3

Figure 3 : Structures of ß Milbemycins

the disaccharide and spiroketal fragments, 30 and 31, respectively, by ozonolysis and reduction with sodium borohydride (Scheme 1).[15] X-ray crystallographic analysis of avermectin B_{1a} and the aglycon of avermectin B_{2a} permitted the assignment of absolute configuration to the macrocyclic ring.[16] The x-ray structure of avermectin B_{1a} shows that the saturated ring of the spiroketal exists as a chair conformer, with the unsaturated ring adopting a half-chair conformation.

Most of the research aimed at determining the biological mode of action of these macrolides was carried out with avermectin B_1. Early studies on free living nematodes suggested that avermectin B_1 does not act as a nicotinic antagonist or a blocking agent for cholinergic nerve transmission.[17] In electrophysiological studies on Ascaris Suum, in which the response of the dorsal excitatory motoneuron to indirect stimulation by way of the ventral nerve cord was recorded, it was found that concentrations of 5 μg/mL of avermectin B_1 caused this response to be completely absent. When the neurons were washed with picrotoxin, which is an antagonist of gamma aminobutyric acid (GABA), the response was restored. These findings indicate that GABA is the neurotransmitter that is inhibited and that avermectin B_1 acts by blocking signal transmission from interneurons to excitatory motoneurons.

Studies conducted on nerve transmission to muscle using the stretcher muscle in the leg of lobster further showed that avermectin B_1 inhibited both the excitatory and inhibitory postsynaptic potentials by reducing muscle membrane resistance.[18] Since the chloride ion conductance stimulated by avermectin B_1 is GABA-mediated, this



Reagents : i. O_3 , CH_2Cl_2 ; ii. $NaBH_4$; iii. 1% H_2SO_4 , MeOH.

Scheme 1. Chemical Degradation of Avermectin A_{2a}.

inhibition also involves the GABA receptor. The overall antiparasitic effect of avermectin B_1 might be due to its acting as a GABA antagonist, to stimulation of presynaptic GABA release, or to potentiation of GABA binding to its receptor. Studies on rat and dog brains, which have a high density of GABA nerves, indicate that avermectin B_1 does not compete with GABA for binding sites.[19] Further studies are needed to clarify these GABA-related effects and to evaluate their importance in the antiparasitic activity of the avermectins.

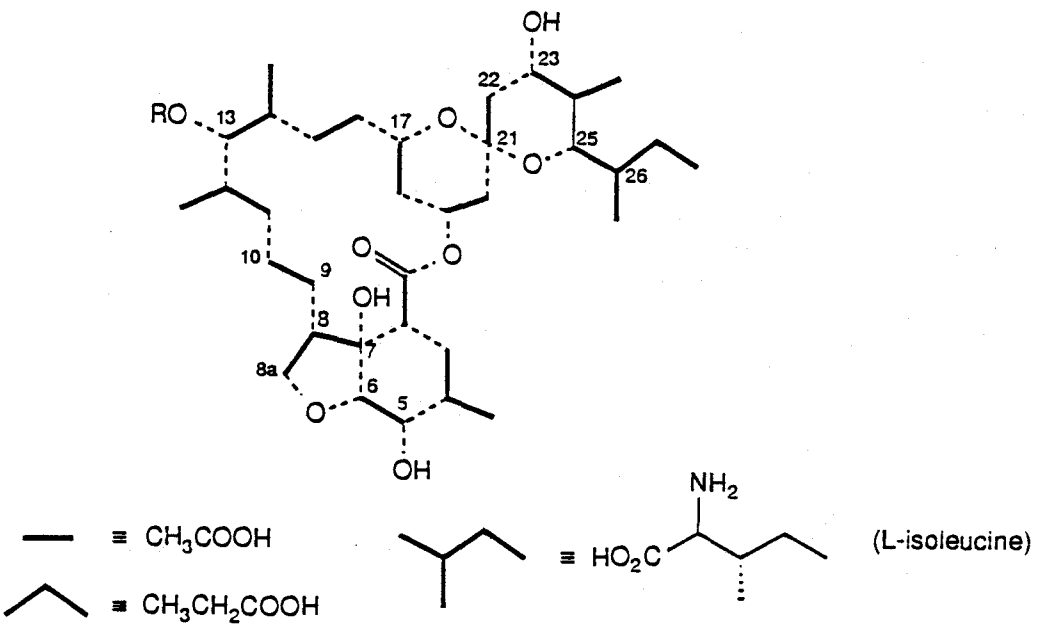


Figure 4 : Biosynthetic Scheme for Avermectins

Isotope enrichment studies have demonstrated the incorporation of propionate into milbemycins and suggest that milbemycin α_2 is derived from eight acetate and five propionate units. Methionine provides the methoxy group at C-5 and acetate provides C-25 and the attached methyl group. An analogous set of feeding experiments

demonstrated that the skeleton of the avermectins is biosynthesized in a similar fashion to the milbemycins with the exception that the isobutyl group at C-25 is derived from L-isoleucine (Figure 4). Incorporation studies with labelled oxygen suggest that the spiroketal is generated by ketalization of a carbonyl group (C-21) with a pair of secondary hydroxyl groups at C-17 and C-25 (Figure 5).[20] These studies also strongly imply that the milbemycins are derived from the avermectins by dehydration and reduction prior to condensation with the acetate unit that corresponds to C-9 and C-10.

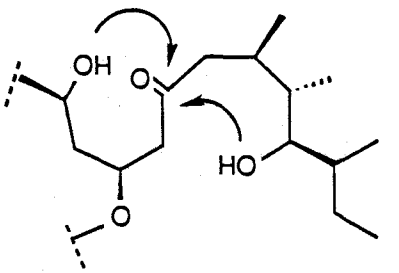
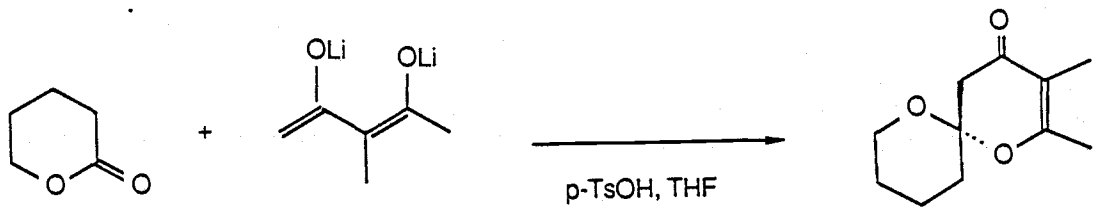


Figure 5. Hypothetical Precursor to the Spiroketal Segment of Avermectin B_{1a}.

The biological activity of avermectins and milbemycins has stimulated widespread interest in the chemistry of these agents. Because of their unique structural, functional and topological features, these 16-membered macrocyclic lactones also present interesting objectives for total synthesis. Although the structures of these natural products are diverse, x-ray crystallographic studies have confirmed that the spiroketal subunits in these molecules generally adopt a common conformation that can be explained by the anomeric effect and the semi-rigid structure of the spiroketal system. It is likely that

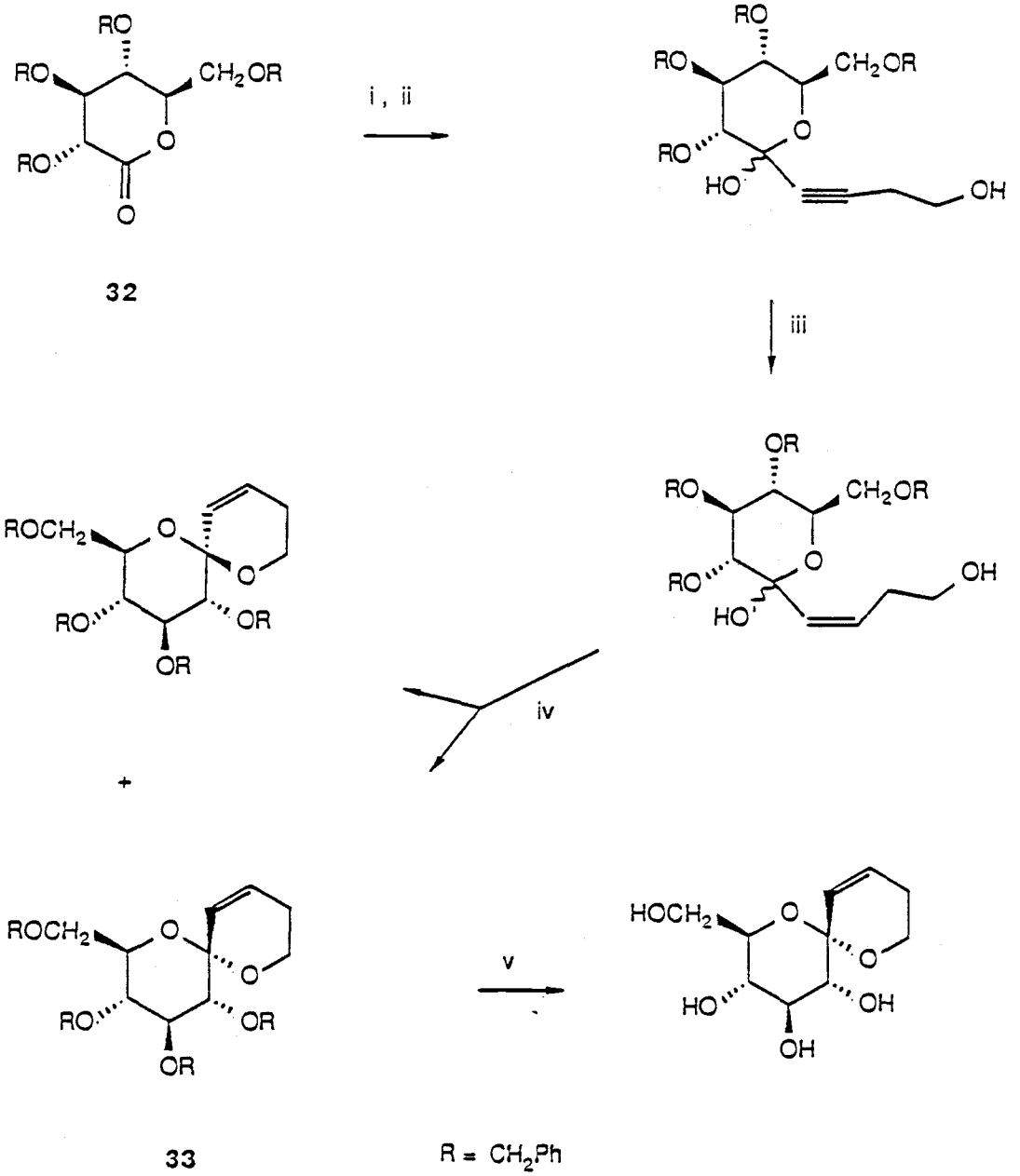
the spiroketal subunit, a major structural feature present in both the avermectins and the milbemycins, will constitute an important building block in the synthesis of these compounds. The purpose of the research described in this thesis was to devise a stereocontrolled synthetic route to the spiroketal moiety of the avermectins.

In addition to the avermectins and milbemycins, the spiroketal unit is found in many other biologically important natural products as an integral part of their molecular architecture. Chalcogran and various aggregation substances contain the 1,6-dioxaspiro-[4,4]-nonane and [4,5]-undecane systems with and without substituents in either ring.[21,22] Related structures are found in the ionophore antibiotics.[23]



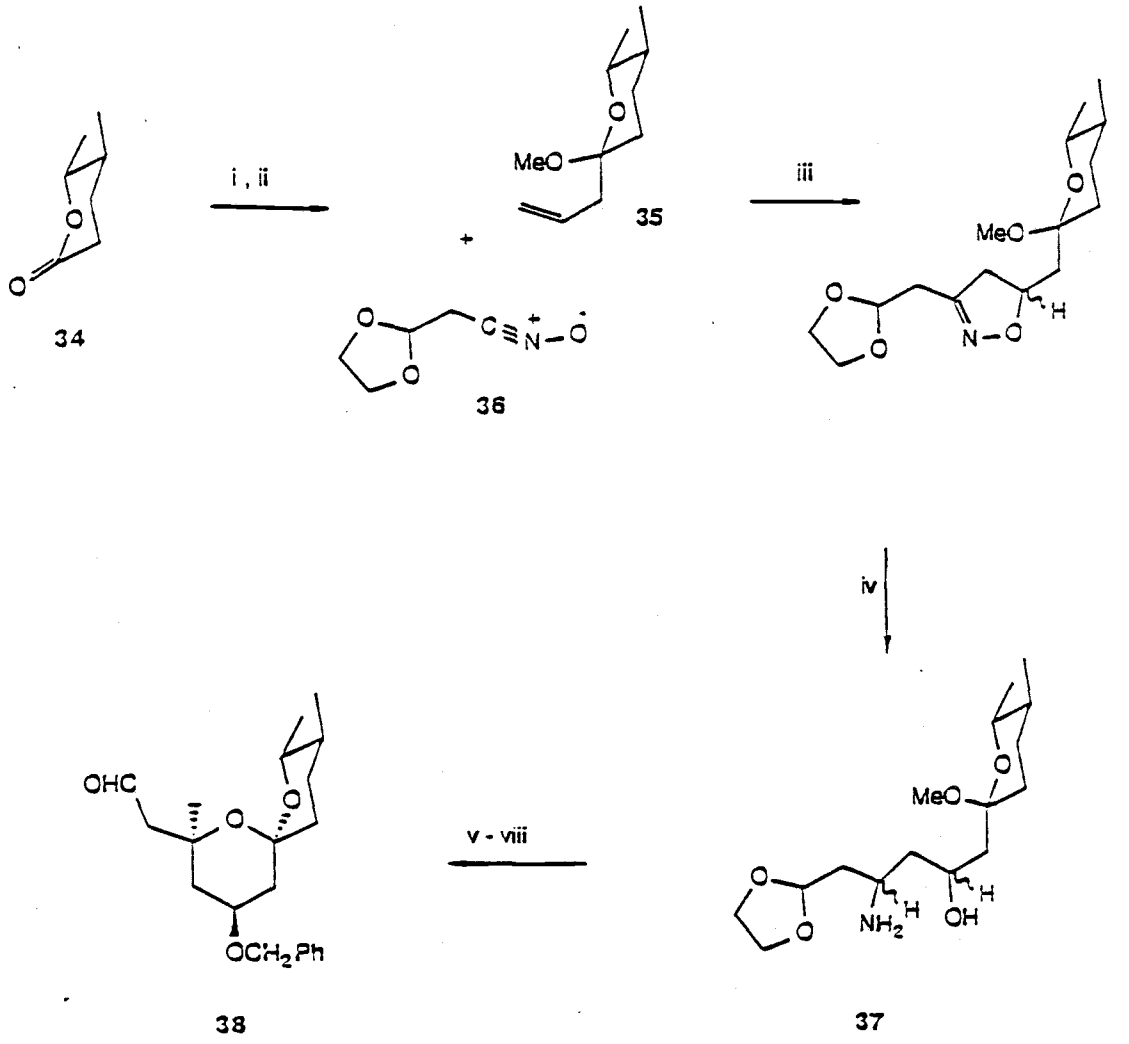
Scheme 2. Barrett's Synthesis of a Model Spiroketal.

Not surprisingly, a large number of synthetic schemes have been reported that focus on the spiroketal subunits of the avermectins and milbemycins. In their model studies, Barrett et al obtained spiroketals by treating tetrahydropyran-2-ones with dianions of β-diones and quenching with p-toluenesulfonic acid (Scheme 2).[24] A model for the spiroketal unit 33 of avermectin B_{1a}, prepared in chiral form from 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone (32), has been described by Hanessian (Scheme 3).[25]



Reagents : i. LiC ≡C[CH_2]$_2$OSiMe_3 ii. H^+, MeOH iii. H_2, Pd/ $BaSO_4$
iv. Camphorsulfonic acid v. Li, liq NH_3

Scheme 3. Hanessian's Synthesis of a Model Spiroketal.



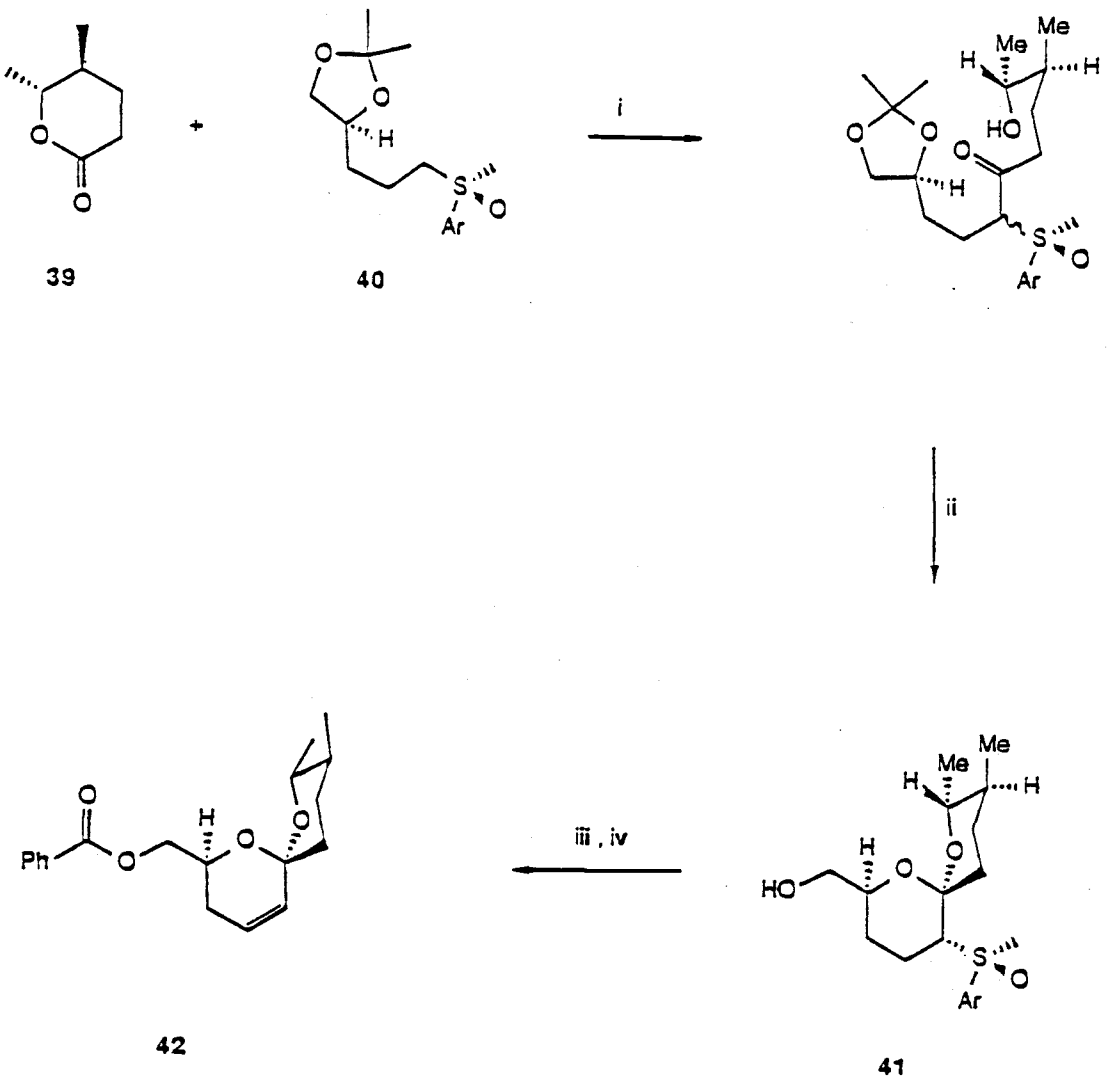
Reagents : i. CH_2 =$CHCH_2MgCl$, THF, -78°C ii. $CH(OMe)_3$, $CeCl_3.7H_2O$, 18°C iii. C_6H_6, Δ_x. iv. $LiAlH_4$ v. KH, 0°C vi. $PhCH_2I$, 0°C vii. CH_3I, 25°C viii. TsOH - H_2O, 25°C.

Scheme 4. Smith's Synthesis of Milbemycin Spiroketal.

As part of their synthetic plan for avermectins and milbemycins, Smith and co-workers at the University of Pennsylvania have described the synthesis of the spiroketal **38** (Scheme 4).[26] Racemic trans-4,5-dimethylvalerolactone (**34**) was treated with allylmagnesium bromide and the product was subjected to O-methylation to provide **35**. Cycloaddition of nitrone **36** with **35**, followed by reduction with lithium aluminum hydride, gave **37** which was cyclized to the spiroketal **38**. A similar intermediate **42** was prepared by an Indiana University group as part of their synthesis of milbemycin β_3 (Scheme 5).[27] Thus, condensation of the homochiral lactone **39**, prepared from (-)-(S)-citronellol, with sulfone **40**, followed by treatment with an acid catalyst, afforded **41**.

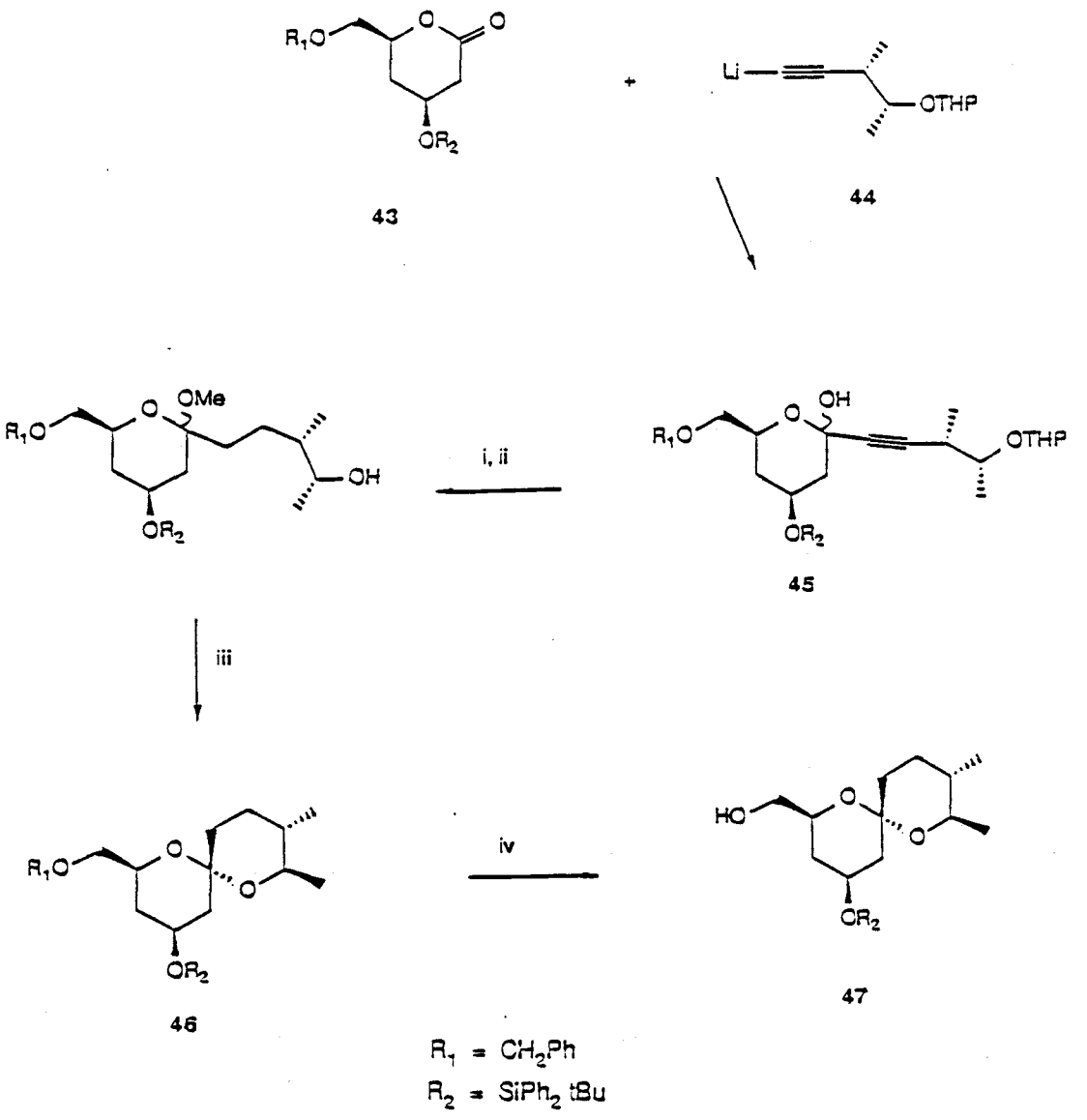
A synthesis of the enantiomerically pure spiroketal portion **47** of milbemycins β_1 and β_3 from the lactone **43** has been reported by Baker (Scheme 6).[28] Reaction of **43**, which was prepared from laevoglucosan in twelve steps, with the lithium acetylide **44** afforded the alkyne **45**. Methanolysis, followed by reduction of the alkyne and treatment with a catalytic amount of camphorsulfonic acid, furnished the spiroketal **46**. Debenzylation then gave the alcohol **47**.

Kocienski has described a synthesis of the spiroketal portion of milbemycin β_3 that is elegant in spite of its low yield (Scheme 7).[29] Acid catalyzed reaction of the ortholactone **48** with the diol **49** gave spirocyclic ortholactones **50** and **51**. After their conversion into the silyl enol ethers **52** and **53**, treatment of **52** with boron trifluoride afforded the spiroketal **55**. This



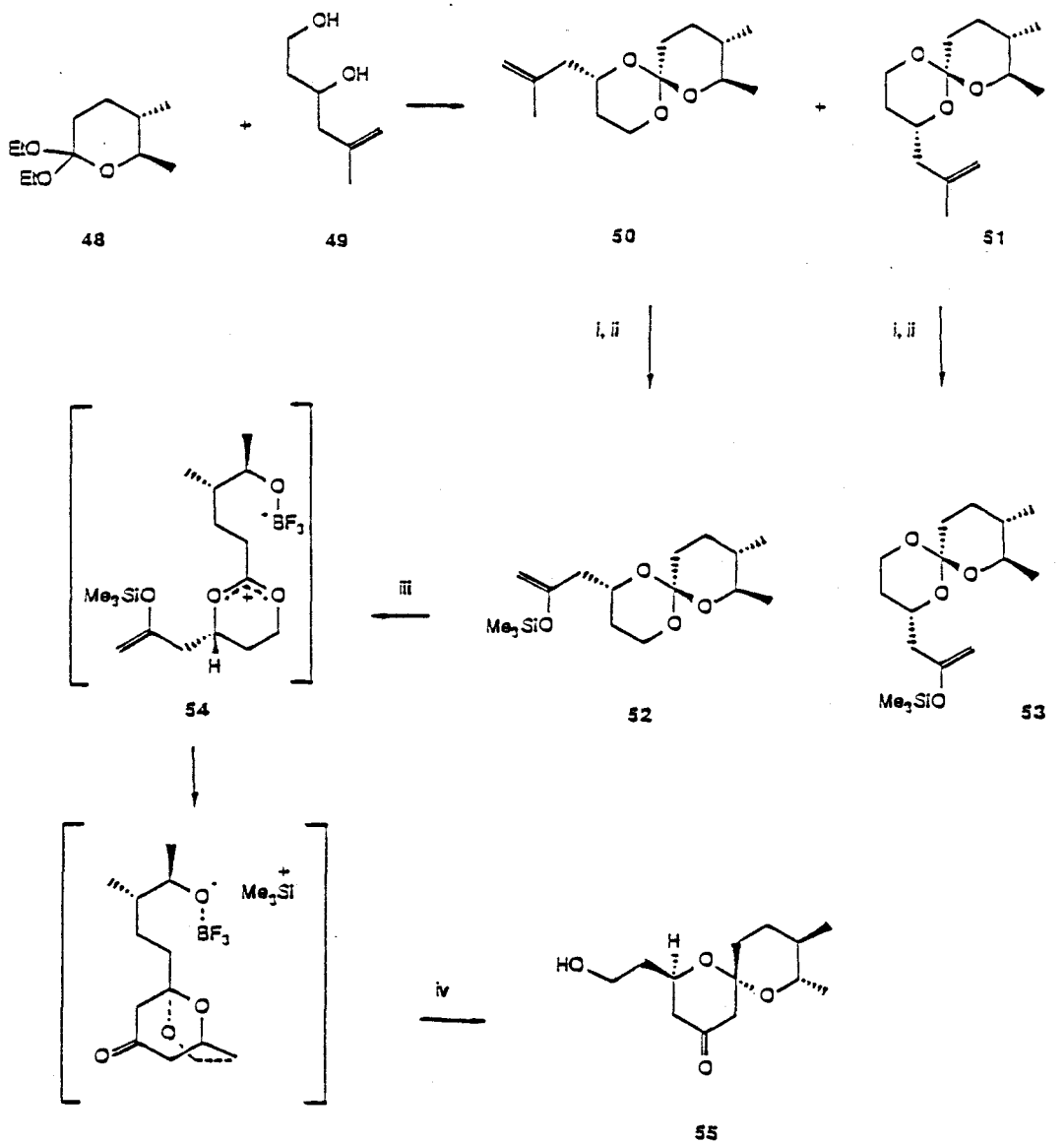
Reagents : i. LDA, THF, -78°C ii. cat. MsCH, H_2O-C_6H_6, 5°C iii. BzCl iv. $P(OMe)_3$, toluene, Δ_x.

Scheme 5. Williams' Synthesis of Milbemycin Spiroketal.



Reagents : i. MeOH, Amberlite resin IR -118 ii. H_2, Pd/C, 1 h iii. Camphorsulphonic acid
iv. H_2, Pd/C, 24 h.

Scheme 6. Baker's Synthesis of Milbemycin Spiroketal.



Reagents : i. O_3 ii. LDA,THF, -78°C, Me_3SiCl iii. $BF_3.Et_2O,CH_2Cl_2$ iv. H_2O .

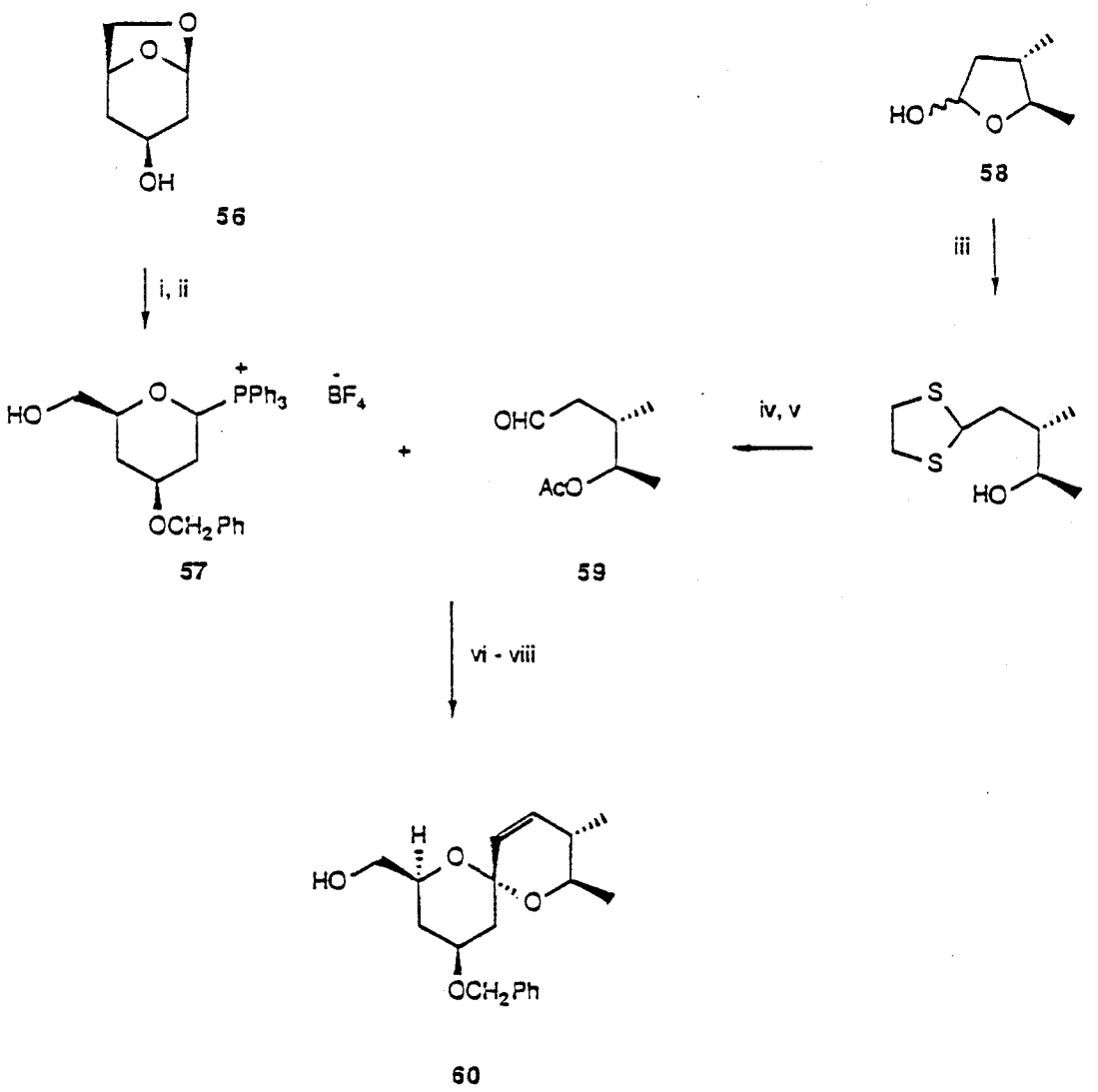
Scheme 7. Kocienski's Synthesis of Milbemycin Spiroketal.

reaction is thought to involve an intramolecular attack of the silyl enol ether on the dioxonium ion **54**.

The spiroketal **60**, has been prepared in optically pure form by Ley and co-workers (Scheme 8).[30] The phosphonium salt **57**, derived from the readily available alcohol **56**, was converted to the corresponding phosphorane and reacted with aldehyde **59**, obtained from the lactol **58**. Deprotection and acid catalyzed cyclization led to the optically pure spiroketal **60**.

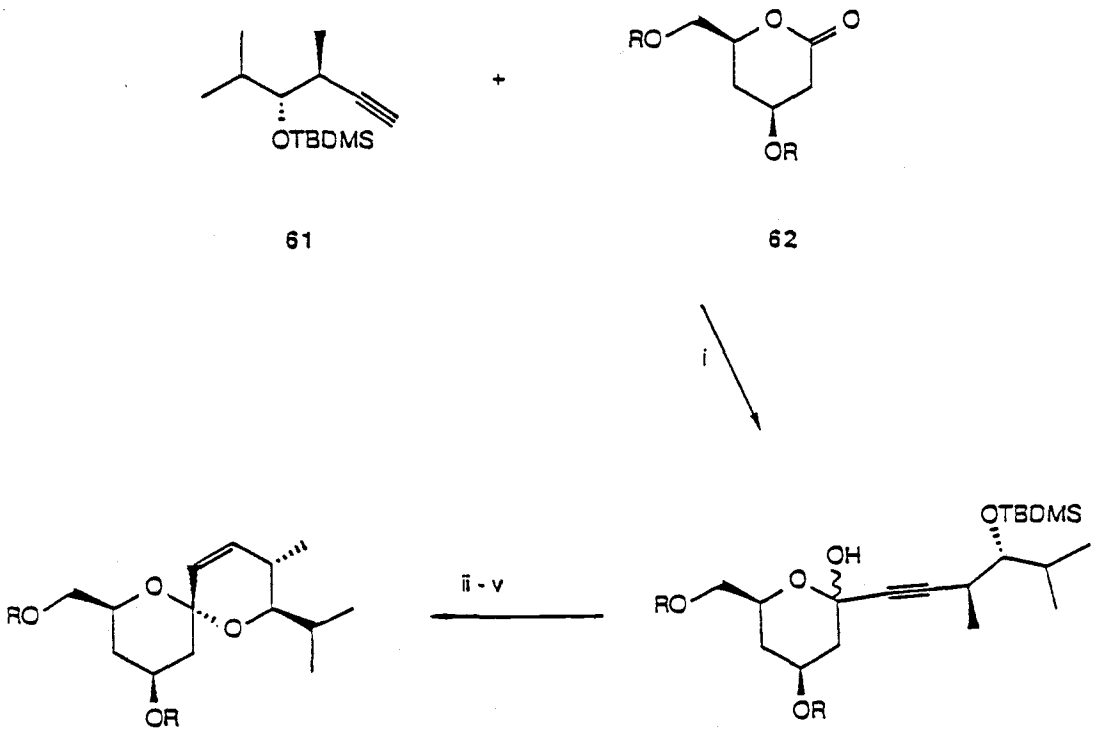
Baker *et al* described the synthesis of spiroketal segments of avermectins B_{1b} and B_{2b}, containing an isopropyl group at C-25 of the macrolide (Scheme 9).[31] Isobutyraldehyde was converted to the optically pure alkyne **61** in a nine-stage sequence and the derived lithium acetylide was reacted with lactone **62**, prepared from laevoglucosan, to give the hemiacetal **63**. Methanolysis of **63**, followed by desilylation and semi-hydrogenation gave a Z-olefin. Treatment of this substance with a catalytic amount of camphor-sulfonic acid afforded the spiroketal portion of avermectin B_{1b} (**64**).

Hanessian and co-workers at the University of Montreal have described a synthesis of the spiroketal portion of avermectin B_{1a}, containing a sec-butyl group at C-15, in optically active form (Scheme 10).[32] This sequence involves condensation of lactone **65** with alkyne **66**, both derived from D-glucose, to obtain the hemi-ketal **67**. Lactone **65** was also synthesized from (-)-(S)-malic acid. Partial reduction of the alkyne functionality in **67** to a Z-olefin **68**, followed by treatment with boron trifluoride, led to the enantiomerically pure spiroketal **69** as the only isomer. More



Reagents : i. $PhCH_2Br$, nBu_4NI ii. $Ph_3HP^+ BF_4^-$ iii. $HS(CH_2)_2SH$, $TiCl_4$ iv. MeCOCl, pyridine v. $Tl(OCOCF_3)_3$ vi. nBuLi vii. NaOMe viii. aq. HCl.

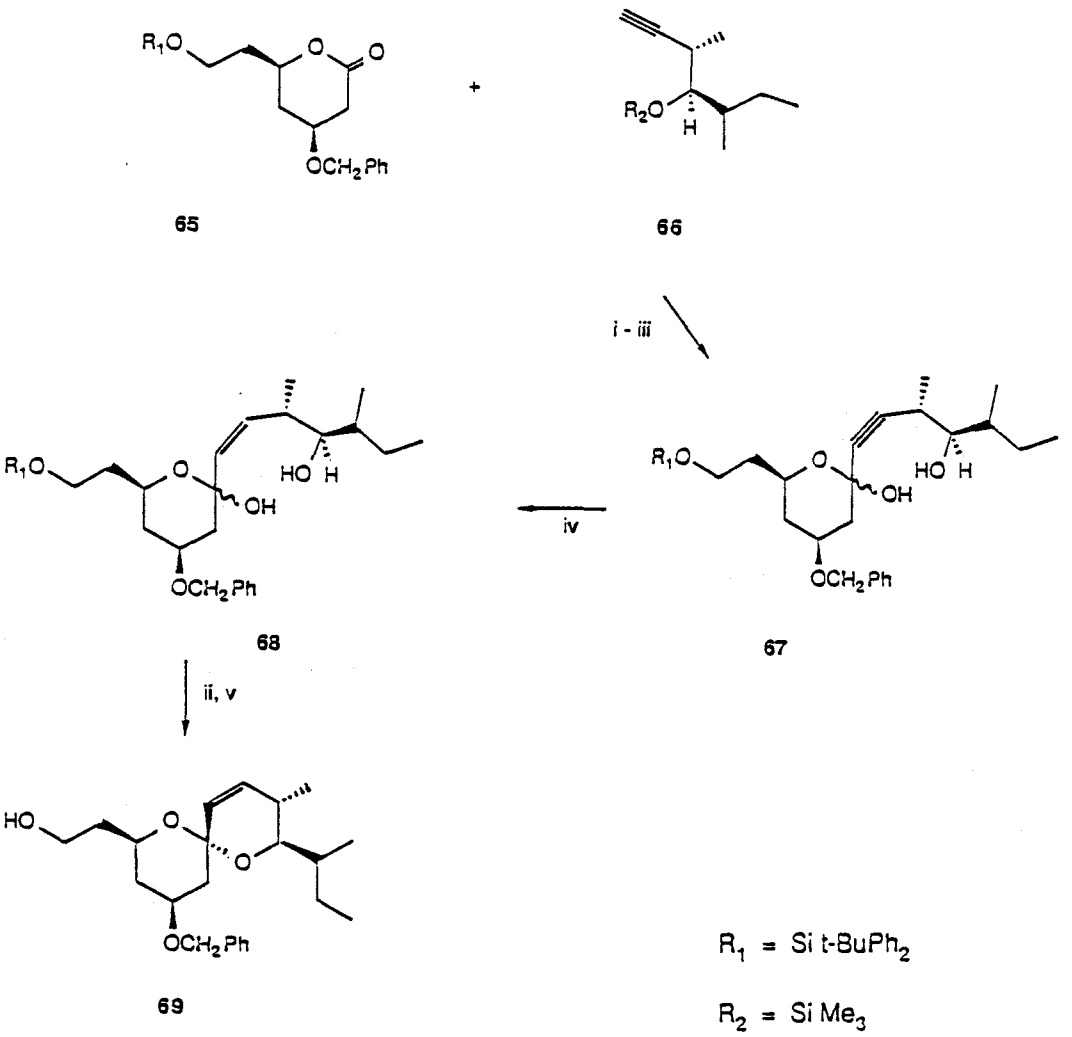
Scheme 8. Ley's Synthesis of Milbemycin Spiroketal.



R = CH_2Ph

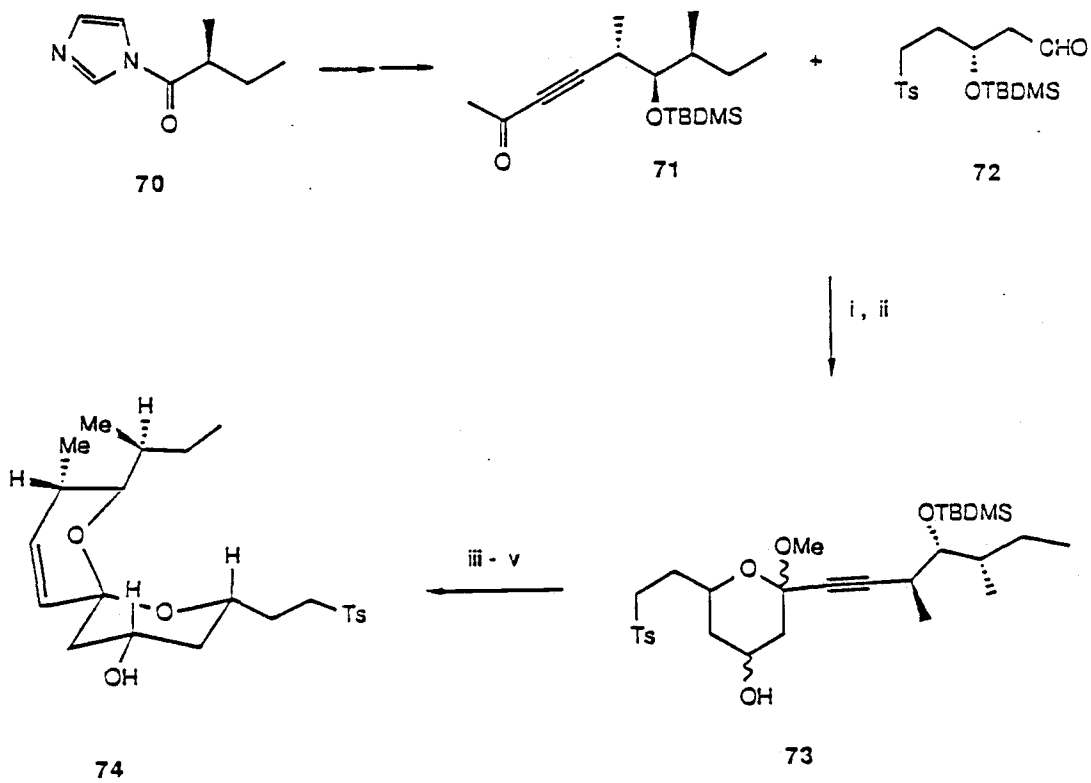
Reagents : i. nBuLi ii. Amberlyst H^+, MeOH iii. nBu_4NF iv. H_2, Lindlar catalyst
v. Camphorsulfonic acid.

Scheme 9. Baker's Synthesis of Avermectin Spiroketal.



Reagents : i. *n*BuLi, THF, -70°C ii. $BF_3.Et_2O.$, THF iii. H^+, H_2O iv. H_2, Pd/ $BaSO_4$, EtOAc, pyridine v. nBu_4NF, THF.

Scheme 10. Hanessian's Synthesis of Avermectin Spiroketal.



Reagents : i. LDA, -78°C, THF ii. MeOH, $CH(OMe)_3$, p-TsOH (cat.), 5 h iii. nBu_4NF, THF iv. H_2, Lindlar cat., toluene v. Camphorsulfonic acid (cat.), CH_2Cl_2.

Scheme 11. Hirama's Synthesis of Avermectin Spiroketal.

recently, Hanessian has reported a synthesis of spiroketal 69 which involves an alternate route to the alkyne 66 starting from L-isoleucine.[33]

An enantiospecific synthesis of the spiroketal unit 74 of avermectin B_{1a} has also been described by Hirama and co-workers (Scheme 11).[34] Aldol condensation of the alkyne 71, prepared from the imidazolide 70 in eight steps, with the homochiral aldehyde 72, followed by regioselective deprotection in the presence of an acid catalyst, afforded the ketal 73. Removal of the silyl group, Lindlar hydrogenation of the triple bond, and treatment with a catalytic amount of camphorsulfonic acid furnished spiroketal 74 as the major product.

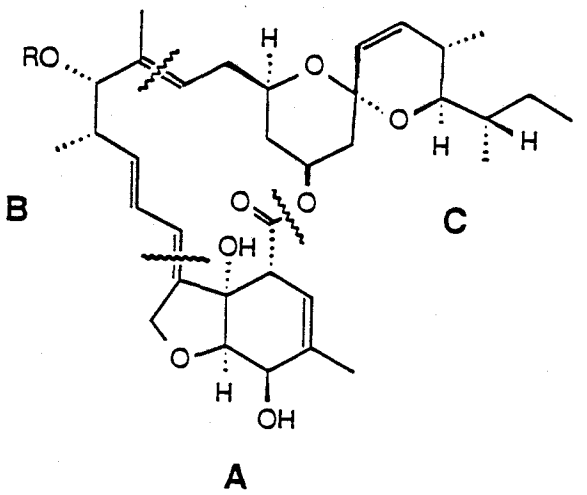
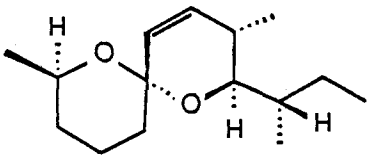


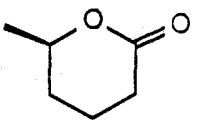
Figure 6. Retrosynthetic Analysis of Avermectin B_{1a}

Our approach to the synthesis of avermectin B_{1a} is planned around the construction of the three segments A, B and C (Figure 6). These would be connected in a final, convergent assembly of the

macrolide. Before beginning a synthesis of segment C it was recognized that construction of a model system would be desirable for testing the feasibility of our synthetic scheme. The spiroketal 75 was chosen as our target, in part because the optically active lactone



75

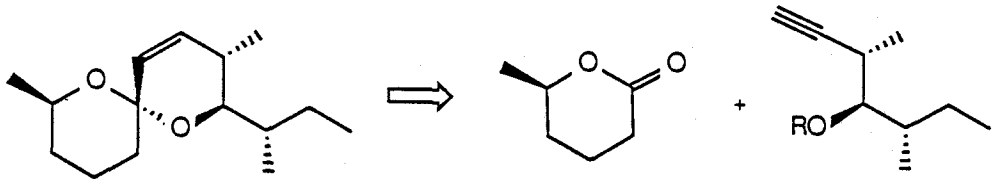


76

76, had already been synthesized by our research group for another project. It was also surmised that the methyl group in the saturated ring would enhance the anomeric stereoselection in the final cyclization. In the discussion that follows, the synthesis of spiroketal 75 in optically pure form is described.

DISCUSSION

Our approach towards synthesis of a spiroketal unit **75**, to be used as a model for synthesis of the analogous segment in avermectin B_{1a}, is outlined in Figure 7 in retrosynthetic form.



75 **76** **77**

Figure 7. Retrosynthetic Scheme for Synthesis of Spiroketal **75**.

The key element in this strategy involves attack by an acetylide anion on the 5-hexanolide **76**. The choice of acetylene **77** as nucleophile was determined by the need to incorporate the three contiguous asymmetric centers found in the corresponding subunit of avermectin B_{1a} as well as the latent alcohol required for spiroketalization. After addition of **77** to **76**, a partial reduction of the acetylenic group to a cis olefin was envisioned by Lindlar hydrogenation. The hydroxyl group, after deprotection, could then be employed in a cyclization of the resulting hemiketal to generate the desired spiroketal. It was assumed that this cyclization would give, as the major product, the thermodynamically favored isomer **75** as a result of anomeric stereoselection.

Synthesis of Alkyne 86

The acetylenic group in alkyne 77 can be derived, in principle, from either an aldehyde or an alkene to which an appropriate carbon chain is attached. The major concern in the synthesis of this portion then becomes the construction of the three contiguous chiral centers. A retrosynthetic analysis of one possible approach to this problem is given in Figure 8. This analysis postulates that olefin 78 can be obtained with all three stereogenic centers in the required absolute configuration by making use of a highly stereoselective reaction of (S)-aldehyde 80 with crotyl bromide (79), as reported by Hiyama and co-workers.[35]

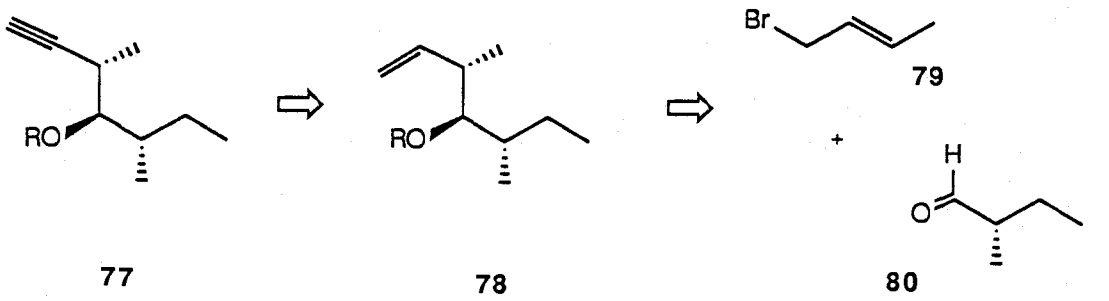
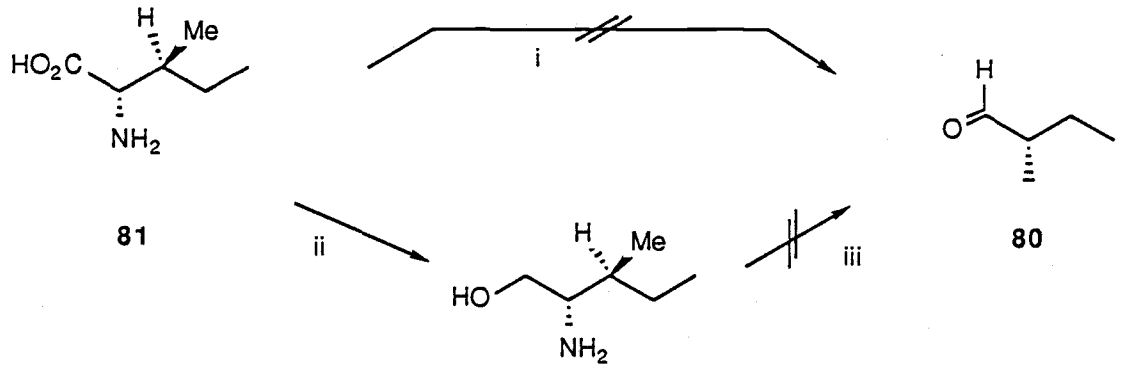


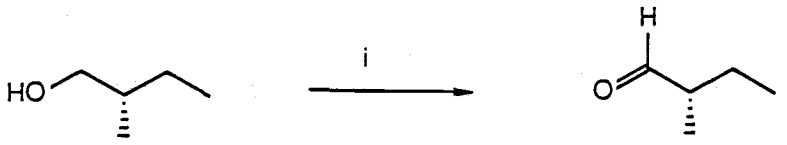
Figure 8. Retrosynthetic Scheme for Synthesis of **77**.

The adoption of this plan requires a suitable preparation of (2S)-2-methylbutanal (80). The first starting material considered was isoleucine (81), which is the biogenetic precursor of the corresponding portion of the avermectins,[36] and which thus possesses the desired (S) configuration at the methyl-bearing carbon. Unfortunately neither of the two methods[37] explored for the conversion of 81 to 80 proved satisfactory and an alternative route, starting from commercially available (2S)-2-methylbutanol (82), was



Reagents : i. Silver [II] picolinate, H_2O. ii. BH_3, THF , $BF_3.Et_2O$ iii. $NaIO_4$, H_2O, MeOH.

therefore attempted. It was recognized that in the oxidation of 82 to 80, racemization could pose a threat to the stereochemical

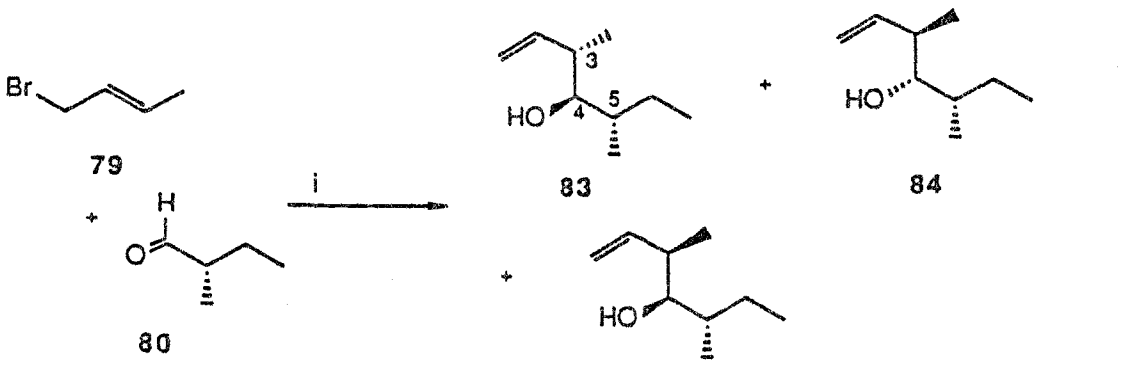


82 **80**

Reagents : i. $(COCl)_2$, DMSO, CH_2Cl_2, -78° C.

integrity of the product and, indeed, treatment of 82 with pyridinium dichromate[38] gave aldehyde 80 whose optical rotation was much lower than that reported in the literature.[39] However, when a Swern oxidation[40] with dimethyl sulfoxide and oxalyl chloride was carried out on 82, 80 was obtained in optically pure form. This favorable outcome is due to the very low temperature and the non-acidic conditions of the Swern oxidation.

Elaboration of 80 to alkene 83 was carried out by a Barbier-Grignard reaction with trans crotyl bromide mediated by a chromium(II) reagent.[35] Although 83 was obtained as the major



Reagents : i. $CrCl_3$, $LiAlH_4$, THF, rT, 3h.

product in this reaction, two minor isomers, 84 and 85, were also produced. The composition of the mixture of homoallylic alcohols from this reaction indicates that there is selectivity (91:9) for the threo over the erythro configuration at C3 and C4. This can be rationalized by the chair transition state shown in Figure 9, where the steric interactions of the methyl and the R groups are minimized. It is also seen that Cram selectivity is obeyed in the stereochemical relationship of C4 and C5, but here the selectivity is lower (70:30). This selectivity is in accord with the Cram model which predicts that, in the favored orientation shown in Figure 10, attack on the

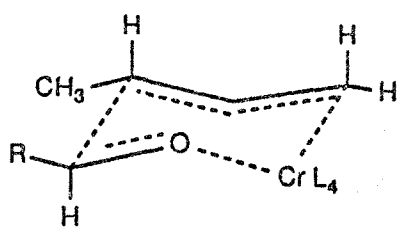


Figure 9. Chair Transition State for the Reaction of **80** with **79**.

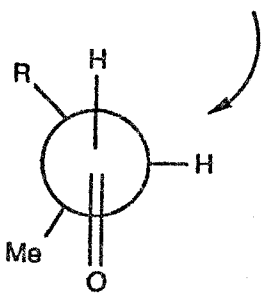
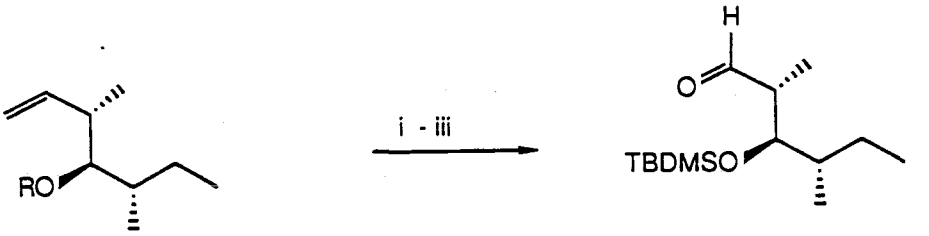


Figure 10. Cram Model for the Reaction of **80** with **79**.

carbonyl group of **80** takes place from the direction indicated by the arrow. The nature of the substituent(s) α to the aldehyde plays a dominant role in this stereoselection. In their studies of this reaction, Kishi *et al* have shown[41] that, if the α substituent is a saturated cyclic ring, there is a marked improvement in stereoselectivity at C3 and C4. The enhanced selectivity obtained by this means makes this reaction quite practical for a multi-step synthesis.

The chromium(II) reagent employed in the reaction of **79** with **80** was generated *in situ* by reduction of anhydrous chromium(III) chloride with lithium aluminum hydride. Flash chromatography of the product mixture containing the three isomers **83**, **84** and **85** separated **85** from isomers **83** and **84**. The desired diastereomer **83** was then separated from this mixture by high performance liquid chromatography (HPLC). Since alcohol **83** was fairly volatile, it was characterized as its 2,4-dinitrobenzoyl derivative.

The plan beyond this point envisioned conversion of the olefinic group in **83** to a dihalide followed by elimination to give alkyne **77**. Unfortunately, attempts at directly transforming the alkene to the vicinal dibromide by addition of bromine and subsequent elimination with various bases were unproductive. Therefore a different approach based on elimination of a terminal vinyl dihalide was considered. Before pursuing this sequence, however, it was decided to first mask the free seconday alcohol in **83** to avoid possible complications arising from its deprotonation in the presence of strong bases. A variety of protecting groups, including the methoxymethyl,[38] tetrahydropyranyl,[42] trimethylsilylethoxymethyl[43] and tert-butyldimethylsilyl groups, were investigated for this purpose.

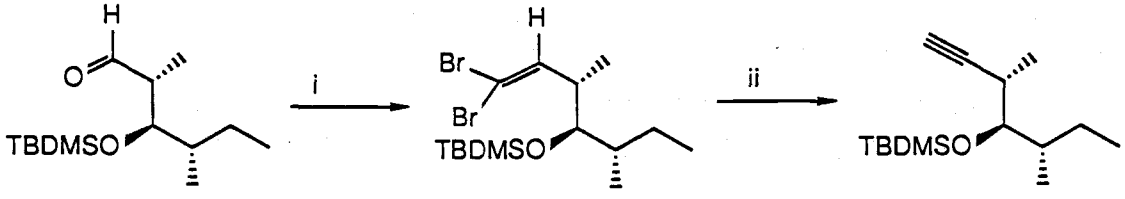


83 R = H
86 R = TBDMS

Reagents : i. t-$BuMe_2SiOTf$, 2,6 - lutidine, CH_2Cl_2 ii. O_3, MeOH iii Me_2S

Among these, the tert-butyldimethylsilyl (TBDMS) ether proved to be the most promising in terms of the ease of synthesis and the yields in subsequent reactions. Thus protection of **83** with tert-butyldimethylsilyl triflate[44] gave **86**, which then became the focus of our efforts to prepare the alkyne **77**.

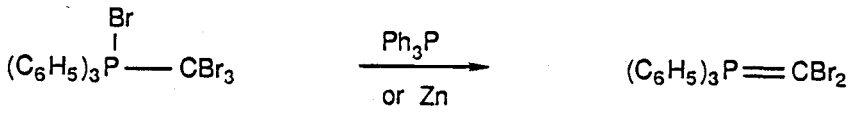
Ozonolysis of **86**, followed by reductive work-up with dimethylsulfide, provided aldehyde **87**. Homologation of **87** to the dibromoolefin **88** was accomplished by the reaction of **87** with carbon tetrabromide and triphenylphosphine, according to the procedure of Corey et al.[46] In conformity with results reported by Corey, the yield of this reaction was improved considerably by addition of activated zinc to the medium. Isolation of the product was easily



87 **88** **90**

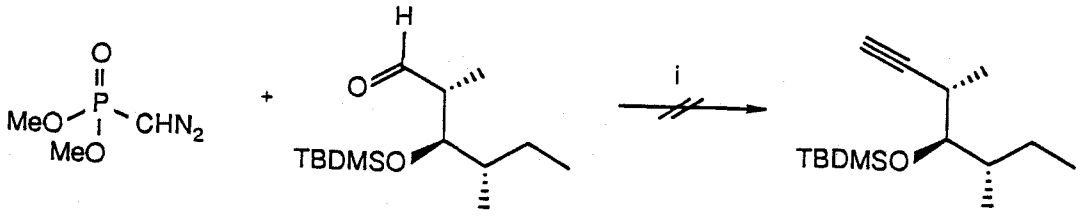
Reagents : i. CBr_4, PPh_3, Zn, CH_2Cl_2 ii. BuLi, THF.

accomplished by extraction with pentane since the excess triphenylphosphine precipitated from this solvent. The presence of zinc further simplified the isolation procedure since the amount of phosphine required for the reaction was reduced. It was observed that best results were obtained when the reactants were introduced in a certain order. Thus, carbon tetrabromide was first added to a solution of **87** in dry tetrahydrofuran and to this was added zinc dust, followed by slow addition of tryphenylphosphine.



89

The reaction of triphenylphosphine with carbon tetrabromide involves an attack by phosphorus on bromide[47] and leads directly to an intermediate **89** with pentavalent phosphorus. Reaction of **89** with a second molecule of triphenylphosphine (or zinc) generates the dibromomethylenephosphorane and this ylide reacts with aldehyde **87** to give **88** and triphenylphosphine oxide. The dibromide **88** underwent a rapid elimination when treated with two equivalents of butyllithium to form the lithium acetylide which, upon quenching with water, afforded **90**.



87 **90**

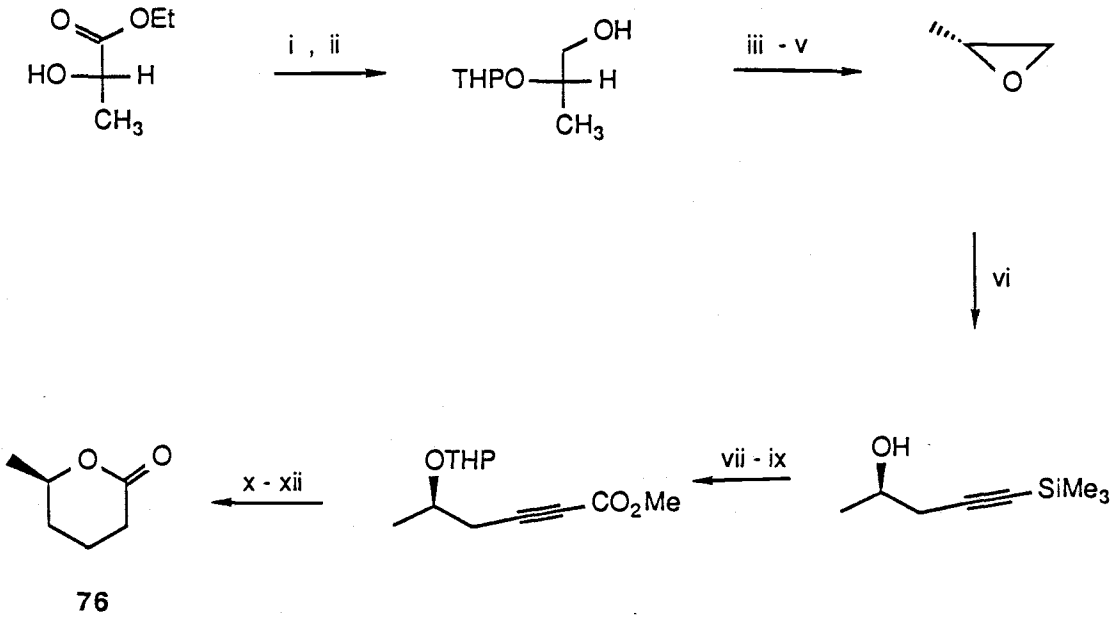
Reagents : i. t-BuOK, THF, -78°C, 12h.

A third route for converting **87** directly to alkyne **90** via a Horner-Emmons modification of the Wittig reaction was also investigated. In this process **87** was reacted with the anion of dimethyl diazomethylphosphonate along lines described by Colvin and Hamill.[48] However, there was no indication of the formation of the desired acetylenic product from this process.

Synthesis of δ-Lactone **76**

Lactone **76** was selected as a model for the reaction with **78** since it is a reasonably close facsimile of the corresponding portion in the avermectins and is easily available in optically pure form. Figure 11 shows one route, employed in our research group[49] previously, to optically active **76** and several other syntheses of this material have been described in the literature.[50] Before embarking on the synthesis of **76** using the chemistry shown in Figure 11, however, the possibility of a shorter route was considered. The fact the (R)-**91** is commercially available suggested the plan depicted retrosynthetically in Figure 12.

The first step in this approach from **91** to **76** required masking the primary alcohol with an appropriate protecting group. This group must not only be selective in its reaction with the primary over the secondary alcohol but is subsequently required to serve the function of a leaving group. When the reaction of **91** was carried out with p-toluenesulfonyl chloride, selectivity was poor. However, this was improved when the bulkier 2,4,6-triisopropylbenzenesulfonyl chloride was employed, and a solution of diol **91** in pyridine, when



Reagents : i. DHP, H^+ ii. $LiAlH_4$ iii. pTsCl, pyridine iv. H_2SO_4, MeOH v. KOH
vi. Li C = C $SiMe_3$ vii. DHP, H^+ viii. $Bu_4N^+ F^-$ ix. BuLi , $ClCO_2Me$
x. H_2 , Pd - C xi. pTsOH xii. pTsOH, C_6H_6 , Δ_x

Figure 11. A Previous Synthesis of (R)δ -Caprolactone (**76**).

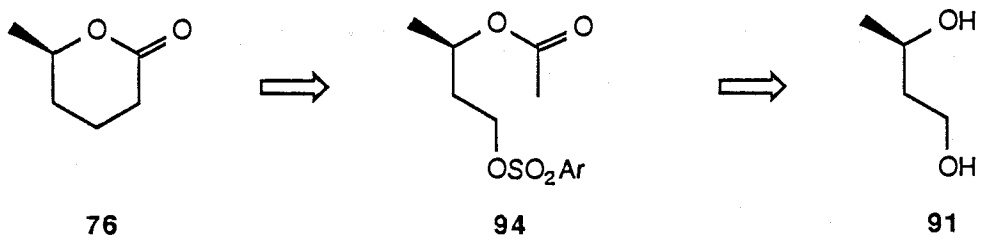
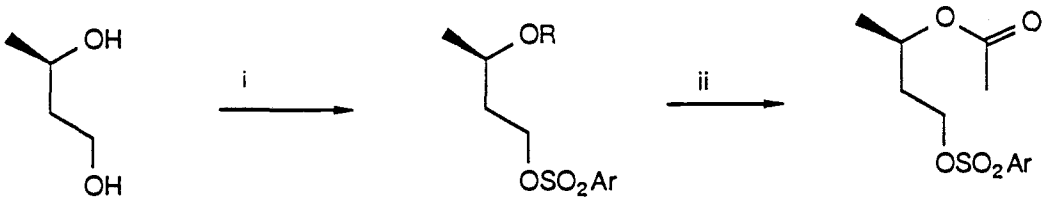


Figure 12. Retrosynthetic Scheme for Lactone **76** .



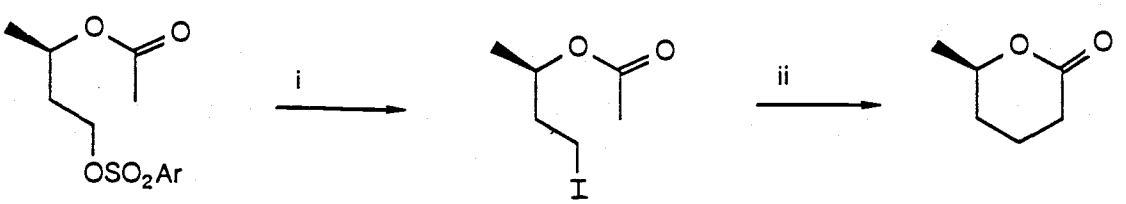
91 **92** R = H **93** R = SO_2Ar **94**

Ar = 2,4,6 - $[(Me)_2CH]_3C_6H_2$

Reagents : i. 2,4,6 - $[(Me)_2CH]_3C_6H_2SO_2Cl$, pyridine. ii. Ac_2O, pyridine.

sulfonated with this reagent, produced 92 as a white crystalline solid along with only a small amount (4%) of the disulfonate 93.

With 92 in hand, its conversion to 94 by acetylation of the free secondary alcohol with acetic anhydride in pyridine was straightforward. Although this reaction could be done on 92 without isolation, the overall yield of 94 was considerably improved if 92 was first purified.



94 **95** **76**

Reagents : i. NaI, 2- butanone, Δ_x. ii. LDA, -78°C.

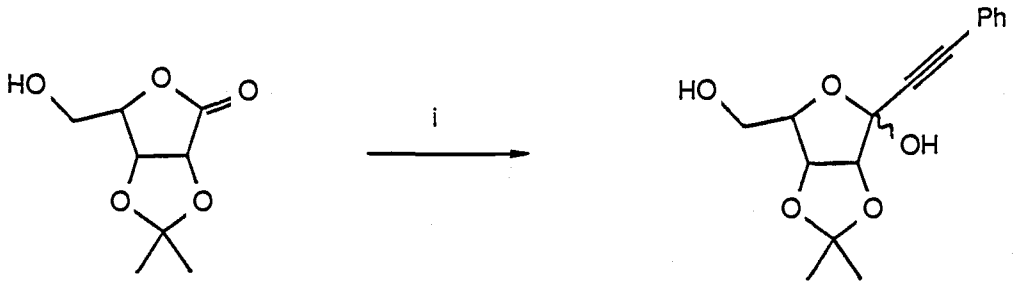
Our initial plan was to effect cyclization of 94 through intramolecular displacement of the sulfonate by the enolate anion generated from the acetate. However this gave unsatisfactory results and replacement of the sulfonate by an iodide was therefore considered in

the expectation that the latter would provide a more responsive leaving group. Displacement of the sulfonate was achieved by refluxing 93 with sodium iodide in 2-butanone to form 95 and, pleasingly, cyclization to the lactone occurred without difficulty when 95 was treated with lithium diisopropylamide (LDA).

This route to 76 is short and efficient and provides a product of high optical purity. Moreover, since the S enantiomer of 91 is commercially available, this method could also be employed for preparation of the optical antipode of 76.

Synthesis of Spiroketal 75

With synthesis of the requisite enantiomers of 76 and 90 accomplished, the next step entailed coupling of these components and elaboration of the resulting adduct to the spiroketal 75. Encouraging precedent for the plan set forth in Figure 1 is found in the reaction of carbohydrate lactones with metal acetylides to form acetylenic lactols[51] (e.g., Figure 13). Furthermore, this strategy was successfully demonstrated in both the Baker and Hanessian schemes for synthesis of the avermectin spiroketal. Thus, whereas the



Reagents : i. HC≡CPh, BuLi, Et_2O.

Figure 13. Ogura's Preparation of Acetylenic Lactol.

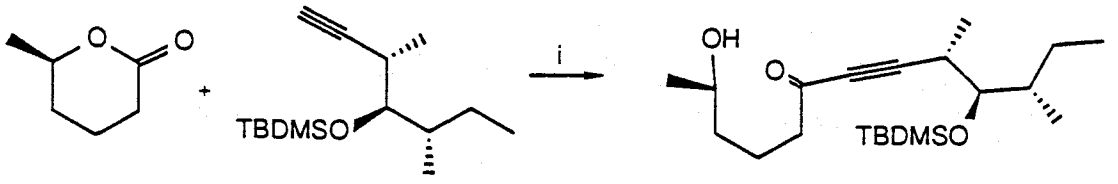
addition of organolithium compounds to esters leads to tertiary alcohols, acetylenic lactols generally result from lactones and acetylides. That these lactols readily revert to the acyclic isomer was demonstrated by Chabala and Vincent,[52] who reported that 5-pentanolide, 4-butanolide and, to a lesser extent, 6-hexanolide reacted with lithium acetylides to give α,β-ynones. Other studies aimed at the preparation of spirocyclic ketals have also utilized the condensation of lactones with lithium acetylides,[53,54] suggesting that the proposed route to **75** from **76** and **90** is eminently sound.

In spite of these favorable antecedents, the addition of lactone **76** to the acetylide derived from **90** with butyllithium gave acetylenic ketone **96** in only low yield. Numerous attempts to improve the yield, for example, by the introduction of boron trifluoride etherate into the medium were unsuccessful. A variation using the cerium acetylide derived from **90**, following the procedure employed by Imamoto and coworkers[55] for addition to easily enolizable ketones, was also unrewarded. It was found, however, that if the dibromoolefin **88** was treated with two equivalents of butyllithium and then reacted immediately with **76**, the yield of **96** was improved (44% based on **88**). Moreover, nearly 50% of unreacted acetylene **90** could be recovered. In spite of considerable experimentation, these conditions proved to be optimal for the preparation of **96**.

A closer scrutiny of the literature revealed that our experiences with the reaction leading to **95** were not unique. In several cases, reactions of lactones with acetylides were carried to only partial completion and, even in those instances, yields were some

times low. Two possible complications can be recognized in the reaction of 76 with the lithium derivative of 90. First, the reaction is easily reversed and, second, the acetylide can function as a base to remove a proton α to the lactone carbonyl of 76 in competition with nucleophilic attack.

The rationale for preparing the lithium acetylide from its precursor 88 *in situ* was based on the supposition that the acetylide could be obtained more rapidly and cleanly by this means than by the reaction of 90 with butyllithium, a conjecture that was borne out experimentally. This implies that the reaction of 88 with two equivalents of butyllithium may not pass through 90 on the way to the acetylide and the improved yield of 96 with *in situ* preparation of the acetylide could simply be a consequence of this mechanistic detour. However, there are other possible explanations, including one that takes account of the presence of lithium bromide in the reaction medium. Another view might hold that the true reactant with 76 is a species different from the acetylide of 90. Present evidence does not permit distinction to be drawn among these mechanistic hypotheses.

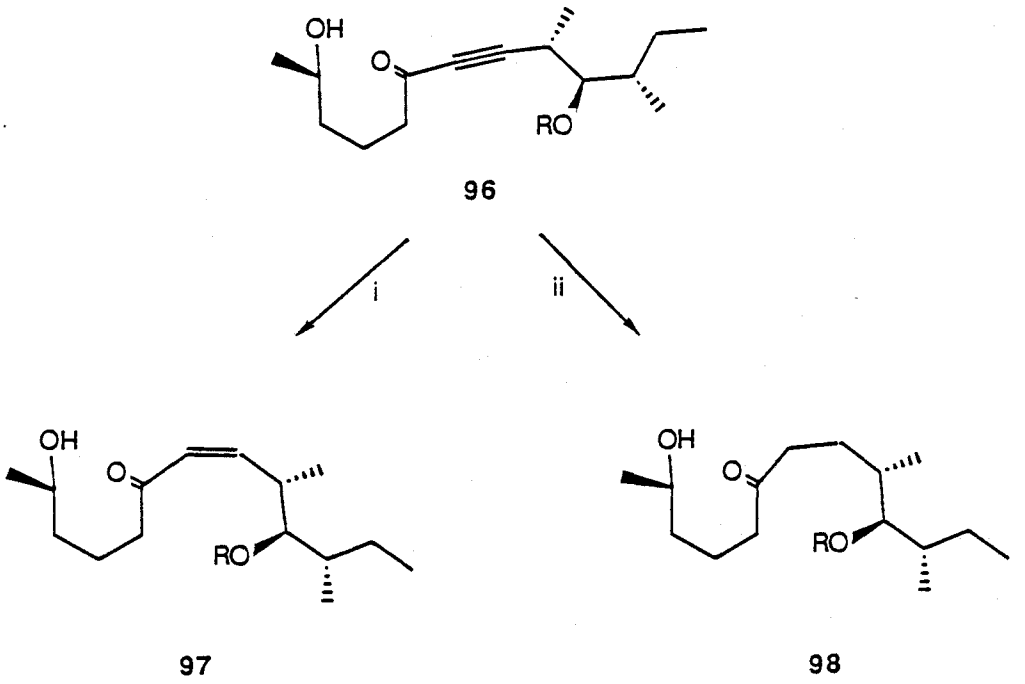


76 90 96

Reagents : i. BuLi, THF.

Partial hydrogenation of the acetylenic linkage in 96 was accomplished over palladium on barium sulfate in the presence of

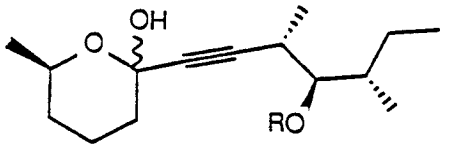
quinoline and provided the cis alkene **97** in excellent yield. The fully saturated derivative **98** was obtained when hydrogenation of **96** was carried out with palladium on carbon as the catalyst. Under acidic conditions, ketones **96** and **97** underwent cyclization to form hemiketals **99** and **100**, accompanied by their dehydrated derivatives **101** and **102**, respectively.



96 **97** **98**

Reagents : i. H_2, Pd / $BaSO_4$, quinoline, MeOH ii. H_2, Pd / C, EtOAc.

Removal of the silyl ether from **97** with tetra-n-butylammonium fluoride proved to be difficult and, as an alternative, treatment of **97** with hydrofluoric acid in acetonitrile was carried out in an attempt to obtain spiroketal **75** directly. This protocol, however, produced a very low yield of the desired product. In a modification of this sequence, suggested by the work of Baker et al, **96** was first exposed to the resin Amberlite H^+ in methanol to obtain the



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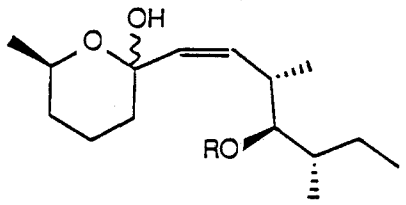

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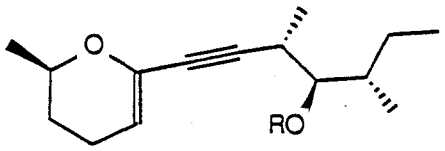

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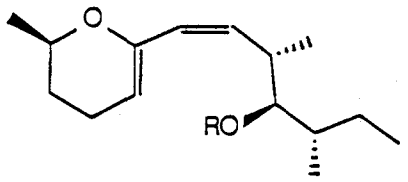
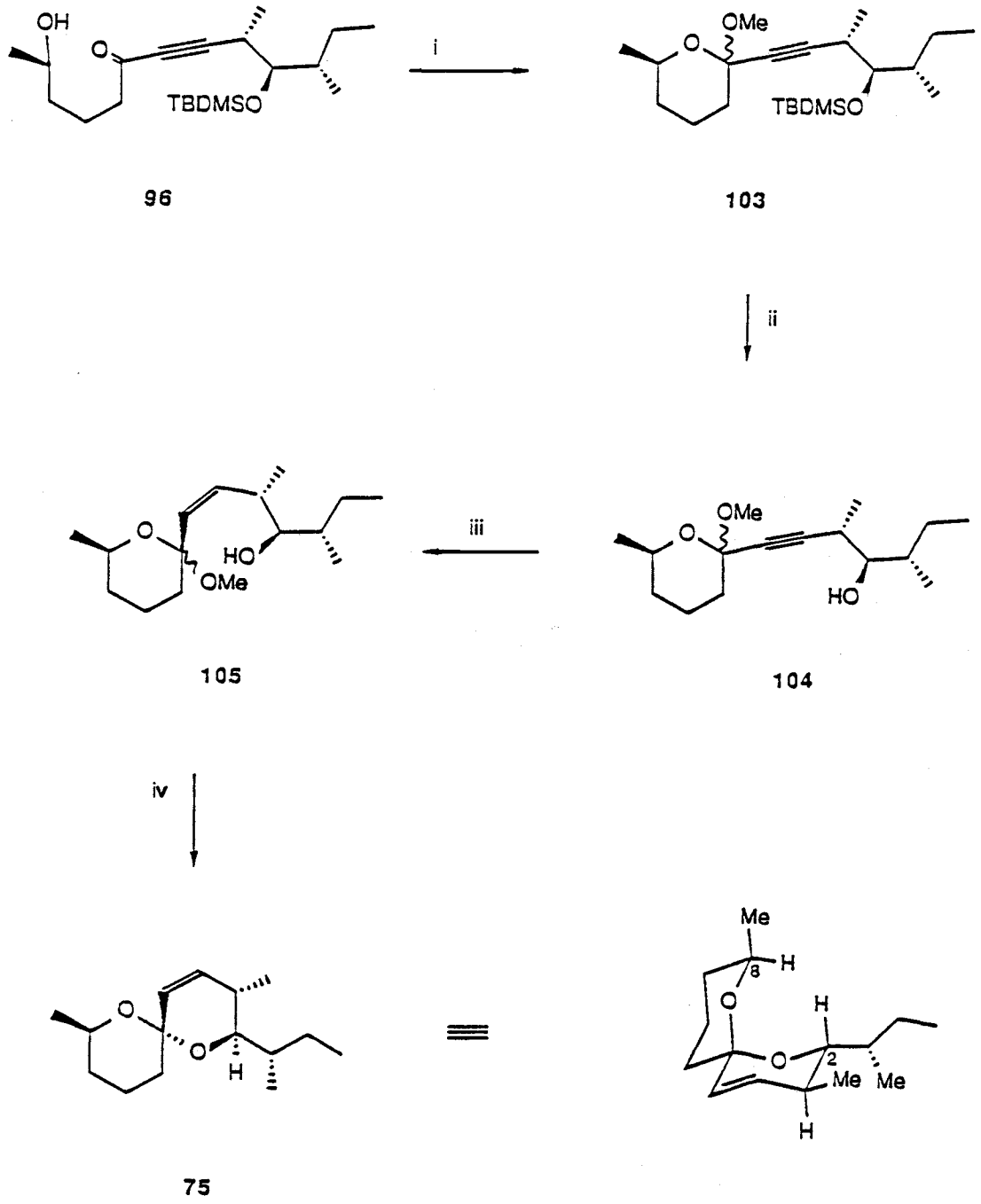


102

R = TBDMS

methoxyacetal 103. When deprotection of the silyl ether was carried out on this substance with tetra-n-butylammonium fluoride, alcohol 104 was obtained in very good yield. The latter was semi-hydrogenated as for 96 to give the cis alkene 105. Not surprisingly, 105 showed a high propensity for cyclization to the spiroketal 75 and it was therefore treated, without isolation, with a catalytic quantity of camphorsulphonic acid in ether to drive cyclization to completion. Examination of the 400 MHz spectrum of 75 along with COSY data indicated that this substance was a single stereoisomer.

Thus, although the cyclization of 105 can lead, in principle, to two diastereomers, each of which could exist in two conformations, a single isomer prevails. It was anticipated that the favored configuration at the spiro carbon of this product would be that which bears



Reagents : i. Amberlite H^+, MeOH. ii. TBAF, THF. iii. H_2 , Pd / $BaSO_4$, quinoline, MeOH.
iv. cat. CSA

each ring oxygen in an axial orientation on the ring to which it is attached, since this provides maximum stabilization from the anomeric effect. Additional stability is achieved in the conformer shown for **75** because all substituents are in the equatorial or pseudo-equatorial positions. The conformation and spiro configuration depicted for **75** is supported by the observation that the protons at C-2 and C-8 (δ 3.48 and δ 3.90, respectively) show characteristic deshielding due to their 1,3 diaxial interaction with the oxygen atoms of the adjacent ring.

With the synthesis of **75** achieved, an appropriate model system has been constructed for the corresponding spiroketal fragment of avermectin B_{1a}. Future work will focus on the preparation of a δ-lactone analogous to **76** that bears functionality suitable for elaboration of the complete segment C of the avermectin structure.

EXPERIMENTAL

Solvents used for reactions were reagent grade and were distilled before use. Ether and tetrahydrofuran were distilled from sodium and benzophenone under nitrogen. Acetonitrile, methylene chloride and amines were distilled from calcium hydride under nitrogen. Starting materials were procured from commercial sources and used without further purification. 'Brine' refers to a saturated solution of sodium chloride. 'Ether' used in workups refers to anhydrous ethyl ether. For isolation of reaction products, the solvent was removed by rotary evaporation at water aspirator pressure and, unless otherwise mentioned, the residual solvent was removed under high vacuum (less than 1 mm). Reaction flasks and syringes were dried in an oven at 160°C and allowed to cool in a dessicator over anhydrous calcium sulfate prior to use. In certain instances, flasks were flame-dried under a stream of nitrogen. Reactions were routinely carried out under an inert atmosphere of nitrogen or argon. Analytical thin-layer chromatography (TLC) was performed on silica precoated aluminum foil plates (silica gel 60 F-254, 0.2 mm thick) manufactured by E. Merck. For flash column chromatography silica gel (230-400 mesh ASTM) from E. Merck was used. High pressure liquid chromatography (HPLC) was performed using a Waters solvent delivery system (Model 510) with a Waters U6K injector, two Waters μ-Porasil columns in series and a Micromeretics 771 refractive index detector. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Infrared spectra were obtained on a Nicolet Model 5DXB FT-IR spectrometer. ^{13}C and ^{1}H nuclear magnetic resonance

(NMR) spectra were obtained on either Varian FT-80 or Bruker AM-400 spectrometers. Chemical shifts are expressed in ppm downfield from the internal standard tetramethylsilane (TMS). Proton NMR data are given in the following sequence: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constants in Hertz. Optical rotations were measured in 1 dm cells of 1 mL capacity using a Perkin-Elmer Model 243 polarimeter. Low resolution mass spectra were obtained on either Varian MAT CH-7 or Finnigan Model 4500 spectrometers. Elemental analyses were performed by MicAnal (now Desert Analytics), Tucson, Arizona.

(S)-(-)-2-Methylbutanal (80). A solution of oxalyl chloride (5.40 mL, 62.4 mmol) in dry dichloromethane (142 mL) was placed in a 500 mL three-necked round-bottom flask equipped with a mechanical stirrer and two pressure equalizing dropping funnels containing dimethylsulfoxide (8.90 mL, 125.0 mmol) in dichloromethane (30 mL) and (S)-(-)-2-Methyl-1-butanol (5.0 g, 57.0 mmol) in dichloromethane (60 mL). The dimethylsulfoxide solution was added dropwise to the oxalyl chloride solution at -65°C and the mixture was stirred for 15 min. Triethylamine (39.70 mL, 283.5 mmol) was added and the mixture was stirred for a further 10 min before warming to room temperature. Water (300 mL) was added to the reaction mixture and the aqueous layer was separated and extracted twice with dichloromethane (150 mL). The organic layers were combined and washed with 2% aqueous hydrochloric acid until the aqueous layer was slightly acidic (pH ~ 3). The organic phase was then washed with a 20 mL portion of 5%

aqueous sodium carbonate solution. The hydrochloric acid and sodium carbonate washings were reextracted with dichloromethane, and the organic layers were combined, washed three times with saturated sodium chloride solution, and then dried over sodium sulfate.

The aldehyde **80** was isolated from this solution by distillation at atmospheric pressure. After carefully distilling off most of the dichloromethane and dimethylsulfide using a long Vigreaux column, the residue was transferred to a short path still to give 3.98 g (82%) of **81** (bp 80-85°C); (82%); $[\alpha]_D^{25}$ = +32.61° (c = 2.73, acetone); IR (neat) 2725, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=7.4), 1.09 (d, 3H, J=7.2), 1.44 (m, 1H), 1.75 (m, 1H), 2.28 (m, 1H), 9.63 (d, 1H, J=2.1); ^{13}C NMR ($CDCl_3$) δ 10.53, 12.17, 23.08, 47.22, 203.91; MS m/z (relative intensity) 86 (38.6), 57 (68.2), 29 (44.7).

(3S,4R,5S)-4-Hydroxy-3,5-dimethyl-1-heptene (83). A dry 500 mL three-neck flask equipped with a magnetic stirrer and a pressure equalizing funnel was charged with 13.1 g (83.1 mmol) of chromium trichloride and 80 mL of dry tetrahydrofuran. The mixture was stirred for 10 min under nitrogen and cooled to 0°C. To this was added 1.5 g (41.8 mmol) of lithium aluminum hydride in small portions over a period of 30 min, during which the mixture changed color from bright purple to blackish green. The mixture was stirred for 10 min and to this, a solution of 1.5 g (16.6 mmol) of **80** and 5.6 g (41.1 mmol) of crotyl bromide in 55 mL of dry tetrahydrofuran was added through the dropping funnel. The resulting mixture was stirred for 3 h at room temperature, during which its color changed to dark brown. Water

(150 mL) was added to the reaction mixture followed by the addition of 75 mL of ether. The aqueous layer was separated and reextracted with ether (2x20 mL) and the organic layers were combined, washed with brine (2x25 mL) and dried over sodium sulfate. The solvents were removed by distillation using a long Vigreaux column and the residue was partially purified by flash column chromatography on silica 60 (pentane/ether 10:1). The solvents were again removed by distillation and the mixture of alcohols was separated by HPLC (hexane/ethyl acetate 20:1) to yield 1.30 g (53%) of 83: $[\alpha]_D^{25}$ = +1.427° (c = 0.815, chloroform); IR (neat) 3410, 1640, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, 3H, J=5.7), 0.92 (t, 3H, J=5.3), 0.98 (d, 3H, J=6.7), 1.43 (m, 1H), 1.5 (m, 3H), 2.29 (m, 1H), 3.23 (dd, 1H, J=4.1,2.1), 5.13 (m, 2H), 5.75 (m, 1H); MS m/z (relative intensity) 125 (M^+-17,1.2), 87 (68.8), 85 (25.3), 69 (43.2), 57 (50.7), 55 (27.9). Alcohol 83 was further characterized as its 3,5-dinitrobenzoate: $[\alpha]_D^{25}$ = -3.98 (c = 0.44, $CHCl_3$); Anal. calcd for $C_{16}H_{20}N_2O_6$: C, 57.17; H, 5.99; N, 8.33. Found: C, 57.19; H, 5.92; N, 8.11.

(3S,4R,5S)-4-t-Butyldimethylsiloxy-3,5-dimethyl-1-heptene (86). A dry 100 mL flask equipped with a magnetic stirrer was charged with a solution of 1.0 g (7.0 mmol) of 83 in 60 mL of dry dichloromethane under an atmosphere of nitrogen. To this was added, with stirring, 2.1 mL (9.1 mmol) of t-butyldimethylsilyl triflate and the mixture was stirred for 3 h and then poured into 70 mL of a saturated solution of sodium bicarbonate. The aqueous layer was separated and washed with dichloromethane (3x50 mL). The organic layers were combined, dried over sodium sulfate and concentrated. The crude product was purified

by flash column chromatography on silica gel 60 (hexane/ethyl acetate 15:1) to give 1.5 g (86%) of **86**: $[\alpha]_D^{25}$ = -2.06° (c = 2.77, chloroform); IR (neat) 1640, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.84 (t, 3H, J=5.3), 0.85 (d, 3H, J=5.7), 0.89 (s, 9H), 0.99 (d, 3H, J=6.8), 0.98-1.15 (m, 1H), 1.38-1.47 (m, 2H), 2.33 (m, 1H), 3.38 (t, 2H, J=4.2), 4.90-4.96 (m, 2H), 5.80-5.89 (m, 1H); ^{13}C NMR ($CDCl_3$) δ -3.82, -2.94, 12.18, 14.65, 17.92, 25.71, 26.16, 38.94, 42.44, 79.32, 113.62, 142.35; MS m/z (relative intensity) 256 (M^+, 2.5), 241 (1.3), 201 (49.5), 199 (32.5), 57 (14.1).

(2S,3R,4S)-3-t-Butyldimethylsiloxy-2,4-dimethyl-hexanal (87). A dry 200 mL three neck flask equipped with a magnetic stirrer was fitted with an inlet tube from an OREC ozonator and outlet tube to a potassium iodide indicator solution. The flask was charged with a solution of 1.2 g (4.7 mmol) of **86** in 50 mL of absolute methanol and cooled to -78°C. Ozone gas was then bubbled through the solution for about 10 min giving the solution a slight blue color. The reaction mixture was then flushed with argon and 20 mL of dimethyl sulfide was added slowly via syringe. The mixture was slowly warmed to room temperature and stirred for 12 hours. After testing the reaction mixture with starch paper for the absence of ozonide, 30 mL of water was added followed by 30 mL of pentane. The aqueous layer was separated and extracted with pentane (2x30 mL), and the organic layers were combined and dried over sodium sulfate. The sodium was then concentrated to give 1.2 g (92%) of **87**: $[\alpha]_D^{25}$ = -38.83° (c = 1.025, chloroform); IR (neat) 1730, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (m, 15H), 1.08 (m, 4H), 1.52 (m, 2H), 2.54 (m, 1H), 3.77

(t, 1H, J=4.1), 9.73 (d, 1H, J=2.7); ^{13}C NMR ($CDCl_3$) δ -4.31, -4.02, 12.22, 12.41, 14.43, 18.28, 25.66, 25.95, 39.97, 49.91, 78.13, 205.7; MS m/z (relative intensity) 258 (M^++1,1.6), 201 (12.1), 131 (17.1), 115 (13.8), 57 (20.9).

Aldehyde **87** was further characterized as its 2,4-dinitrophenylhydrazone: $[\alpha]_D^{25}$ = +7.04° (c = 0.49, chloroform); Anal. calcd for $C_{20}H_{34}N_4O_5Si$: C, 54.80; H, 7.76; N, 12.79. Found C, 55.40; H, 7.99, N, 12.93.

(3S,4R,5S)-1,1-Dibromo-4-t-butyldimethylsiloxy-3,5-dimethyl-1-heptene (**88**). A dry 250 mL flask equipped with a magnetic stirrer was charged with a solution of 0.90 g (3.3 mmol) of **87** in 60 mL of dry dichloromethane under an atmosphere of nitrogen. To this solution was added 2.20 g (7.0 mmol) of freshly sublimed carbon tetrabromide and the mixture was stirred for 15 min. Activated zinc dust (0.4 g, 7.0 mmol) was then added and the solution was stirred for a further 15 min. To this mixture a solution of 1.6 g (7.0 mmol) of triphenylphosphine in 30 mL of dry dichloromethane was added dropwise over a period of 20 min and the resulting brown mixture was stirred for 4 h. Solvent was removed by evaporator leaving a thick brown liquid which was dissolved in 50 mL of acetonitrile. This solution was extracted with pentane (3x30 mL), and the pentane layers were combined and concentrated. To the residue was added 10 mL of hexane and the solution was allowed to stand for 4 h. The white precipitate that formed was filtered off and the filtrate was then purified by flash column chromatography on silica 60 (hexane/ethyl acetate 20:1) to give 1.1 g (83%) of **88**: $[\alpha]_D^{25}$ = -2.27° (c = 1.145, chloroform); IR (neat) 1650,

1125 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (t, 3H, J=7.3), 0.87 (d, 3H, J=6.7), 0.92 (s, 9H), 1.00 (d, 3H, J=7.2), 1.06 (m, 1H), 1.48 (m, 2H), 2.64 (m, 1H), 3.46 (t, 1H, J=3.9), 6.45 (d, 1H, J=9.5); ^{13}C NMR ($CDCl_3$) δ -4.07, -3.87, 12.43, 14.89, 17.66, 18.32, 25.34, 26.06, 40.34, 41.60, 78.97, 87.14, 141.87; MS m/z (relative intensity) 357 (M^+-57,26.4), 271 (90.6), 201 (100.0), 115 (27.6), 57 (29.7).

(3S,4R,5S)-4-t-Butyldimethylsiloxy-3,5-dimethyl-1-heptyne (90). A dry 25 mL flask equipped with a magnetic stirrer was charged with a solution of 0.2 g (0.5 mmol) of **88** in 10 ml of dry tetrahydrofuran cooled to -78°C and 0.8 mL of a 1.5M solution of butyllithium (1.25 mmol) in hexane was added slowly with stirring. The stirring was continued for 30 min while the mixture warmed slowly to room temperature. A saturated aqueous solution of ammonium chloride (7 mL) was added to the solution and the resulting mixture was extracted with ether (3x15 mL). The organic layers were dried over sodium sulfate and concentrated. The crude product was purified by flash column chromatography on silica 60 (hexane/ethyl acetate 15:1) to give 0.1 g (86%) of 90: $[\alpha]_D^{25}$ = +3.36° (c = 0.565, chloroform); IR 2114, 1125 cm^{-1}; ^1H NMR δ 0.06 (s, 3H), 0.09 (s, 3H), 0.88 (t, 3H, J=7.3), 0.88 (d, 2H, J=6.8), 0.91 (s, 9H), 1.18 (d, 1H, J=6.9), 1.25 (m, 1H), 1.52 (m, 2H), 2.03 (d, 1H, 2.8 Hz), 2.63 (m, 1H), 3.53 (dd, 1H, 3.8 Hz); ^{13}C NMR ($CDCl_3$) δ -4.01, -3.94, 12.03, 14.42, 17.48, 18.40, 26.08, 27.11, 31.48, 38.41, 69.77, 77.62, 87.68; MS m/z (relative intensity) 255 (M^++1, 2.1) 201 (100.0), 197 (16.1), 57 (27.2); Anal. calcd for $C_{15}H_{30}OSi$: C, 70.87; H, 11.81. Found C, 71.35; H, 12.28.

(3R)-1-(2,4,6-Triisopropylbenzenesulfonyloxy)-butan-3-ol (92). A flame dried, 250 mL flask equipped with nitrogen inlet and magnetic stirrer was charged with 2.5 g (0.03 mol) of R-(-)-1,3-butanediol and 100 mL of distilled pyridine. The solution was cooled to 0°C and 11.7 g (0.04 mol) of 2,4,6-triisopropylbenzenesulfonyl chloride was added in several portions. The reaction mixture was warmed to room temperature, stirred for 5 h, and then poured into 320 mL of 3N hydrochloric acid over ice. The aqueous solution was extracted with 3x100 mL of ether and the organic fractions were combined and dried over sodium sulfate. The solvent was removed in vacuo and the crude product was flash chromatographed on silica 60 (hexane/ethyl acetate 20:1) to give 6.0 g (62%) of **92**: Mp 73-75°C (recrystallized from hexane); $[\alpha]_D^{25}$ = -6.25° (c = 1.37, chloroform); IR (KBr) 3300, 1351, 1176 cm^{-1}; ^1H NMR $CDCl_3$ δ 1.22 (d, 3H, J=6.0), 1.26 (d, 18H, J=6.6), 1.76 (m, 2H), 1.88 (m, 1H), 2.91 (septet, 1H, J=6.9), 4.00 (m, 1H), 4.14 (m, 3H), 4.27 (m, 1H), 7.19 (s, 2H); ^{13}C NMR ($CDCl_3$) 23.55, 23.66, 24.73, 29.60, 34.25, 38.07, 64.24, 66.63, 123.79, 129.33, 150.79, 153.72; MS m/z (relative intensity) 356 (M^+, 1.8), 283 (6.6), 267 (32.1), 202 (65.4), 187 (100.0); Anal. calcd for $C_{19}H_{32}O_4$: S: C, 64.01; H, 9.04. Found C, 63.74; H, 9.31.

(3R)-3-Acetoxy-1-(2,4,6-Triisopropylbenzenesulfonyloxy)-butane (94). A flame dried 250 mL flask equipped with nitrogen inlet and magnetic stirrer was charged with 1.9 g (5.33 mmol) of **92** and 55 mL of distilled pyridine. The solution was cooled to 0°C and 3.01 mL (31.97 mmol) of acetic anhydride was added dropwise. The reaction mixture was warmed to room temperature, stirred for 10 h, and then

poured into 180 mL of 3N hydrochloric acid over ice. This aqueous solution was extracted with 3x60 mL of ether and the combined organic layers were washed with 2x50 mL of a saturated aqueous solution of sodium bicarbonate and then with 50 mL of brine. The organic phase was dried over sodium sulfate, the solvent was removed in vacuo, and the crude product was flash chromatographed on silica 60 (hexane/ethyl acetate 8:2) to give 1.8 g (85%) of **94**. $[\alpha]_D^{25}$ = -8.23° (c = 1.92, chloroform); IR (neat) 1735, 1240, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3H, J=6.1), 1.26 (d, 18H, J=6.5), 1.97 (m, 2H), 2.00 (s, 3H), 2.93 (septet, 1H, J=6.7), 4.12 (t, 2H, J=6.5), 4.14 (septet, 2H, J=6.6), 4.98 (m, 1H), 7.18 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 20.00, 21.12, 23.55, 24.71, 29.58, 34.25, 35.18, 65.63, 67.53, 123.78, 129.37, 150.78, 153.74, 170.36; MS m/z (relative intensity) 398 (M^+, 1.7), 283 (20.5), 202 (59.8), 187 (52.4), 159 (28.6), 115 (100.0), 55 (47.3); Anal. calcd for $C_{21}H_{34}O_5S$: C, 63.29; H, 8.59. Found: C, 63.09; H, 8.40.

(3R)-3-Acetoxy-1-iodobutane (**95**). A flame dried 500 mL flask equipped with a magnetic stirrer was charged with 5 g (12.5 mmol) of **94** and 200 mL of distilled 2-butanone and 5.63 g (37.5 mmol) of sodium iodide was added. The resulting yellow solution was gently refluxed for 1 h, the solvent was removed in vacuo, and the residue was treated with 150 mL of distilled water. A small amount of sodium thiosulfate was added, resulting in decolorization, and the solution was extracted with 3x100 mL of dichloromethane. The organic phase was dried over sodium sulfate and the solvent was removed in vacuo. The crude residue was flash chromatographed on silica 60 (hexane/ethyl acetate 15:2) to give 2.86 g (95%) of **95**: $[\alpha]_D^{25}$ = -7.09° (c = 1.65,

chloroform); IR (neat) 1737, 1241 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H, J=6.5), 2.05 (s, 3H), 2.14 (m, 2H), 3.14 (m, 2H), 4.94 (m, 1H); ^{13}C NMR ($CDCl_3$) δ -0.15, 19.40, 21.09, 39.52, 70.83, 170.35; MS m/z (relative intensity) 243 (M^++1, 2.1), 199 (2.9), 183 (2.4), 127 (3.1), 115 (100.0).

R-δ-Caprolactone (76). To a dry 250 mL three-neck flask was added a solution of 8.1 mL (58.1 mmol) of diisopropylamine in 70 mL of dry tetrahydrofuran under an atmosphere of nitrogen. After cooling the solution to -78°C, 23.2 mL of a 1.5M solution of butyllithium (34.9 mmol) in hexane was added slowly. The mixture was stirred at -78°C for 1 h, after which a solution of 2.8 g (11.62 mmol) of 95 in 50 mL of dry tetrahydrofuran was added. The reaction mixture was stirred at -78°C for 1 h and 40 mL of a saturated aqueous solution of ammonium chloride was introduced. The resulting mixture was extracted with ether (3x50 mL) and the separated aqueous layer was subjected to continuous extraction with ether. The organic layers were combined, dried over sodium sulfate, and the solvent removed in vacuo. The residue was purified by flash column chromatography on silica 60 (hexane/ethyl acetate 3:1) to give 780 mg (60%) of 76: $[\alpha]_D^{25}$ = +31.6° (c = 1.22, Ethanol); IR (neat) 1730, 1240, 1060 am^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (d, 3H), 1.48-1.58 (m, 1H), 1.82-1.90 (m, 3H), 2.40-2.62 (m, 2H), 4.42-4.50 (m, 1H); ^{13}C NMR δ 18.52, 21.69, 29.21, 29.56, 76.94, 171.88.

(2R,9S,10R,11S)-10-t-Butyldimethylsiloxy-2-hydroxy-9,11-dimethyl-6-oxo-tridec-7-yne (96). A dry 100 mL flask was charged

with a solution of 400 mg (1.0 mmol) of **88** in 30 mL of dry tetrahydrofuran. After cooling the solution to -78°C, 1.5 mL of a 1.5M solution of butyllithium (2.2 mmol) in hexane was added slowly under an atmosphere of nitrogen and the mixture was stirred for 30 min. This solution was added slowly via a cannula to a 100 mL flask containing a stirred solution of 111 mg (1.0 mmol) of **76** in 20 mL of dry tetrahydrofuran at -78°C. The mixture was allowed to warm to room temperature and stirred for 8 h. A saturated aqueous solution of ammonium chloride (20 mL) was added to the mixture which was then extracted with ether (3x20 mL). The organic layers were dried over sodium sulfate, the solvent was evaporated and the residue was subjected to flash column chromatography on silica 60 (hexane/ethyl acetate 10:1) to give 156 mg (44%) of **96**: $[\alpha]^{25}$ = 1.20° (c=1.250, chloroform); IR 3601, 2213, 1669, 1130; ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.89 (d, 3H, J=6.8), 0.91 (t, 3H, J=3.7), 0.92 (s, 9H), 1.20 (d, 3H, J=6.5), 1.23 (d, 3H, J=6.8), 1.34-1.73 (m, 7H) 2.56 (t, 2H, J=7.3), 2.78 (m, 1H), 3.54 (t, 1H, J=3.8), 3.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ -4.18, -3.95, 12.08, 14.60, 17.45, 18.30, 20.06, 23.45, 25.95, 26.33, 31.47, 38.37, 39.38, 45.24, 67.54, 77.69, 82.40, 97.18, 188.04; MS m/z (relative intensity) 368 (M^+, 2.3), 351 (2.4), 311 (4.6), 201 (100.0), 115 (13.3), 57.

(2RS,6R)-2-[(3S,4R,5S)-4-t-Butyldimethylsiloxy-3,5-dimethyl-1-heptynyl]-2-methoxy-6-methyltetrahydropyran (**103**). To a solution of 32.6 mg (0.09 mmol) of **96** in 3 mL of methanol was added Amberlite IR118 ion-exchange resin and the suspension was stirred at

room temperature for 2 h. The mixture was filtered into a base-washed flask and the resin was washed thoroughly with methanol. Removal of the solvent, followed by flash chromatography of the residual oil on silica 60 (hexane/ether 8:2), gave 24.5 g (72%) of a ~2:1 mixture of diastereomers of **103**: IR (neat) 2231, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) of major isomer δ 0.04 (s, 3H), 0.06 (s, 3H), 0.87 (d, 3H, J=6.5), 0.88 (t, 3H, J=6.5), 0.90 (s, 9H), 1.16 (d, 3H, J=6.1), 1.18 (d, 3H, J=6.9), 1.22 (m, 2H), 1.56 (m, 4H), 1.85 (m, 3H), 2.67 (m, 1H), 3.35 (s, 3H), 3.53 (t, 1H, J=4.0), 3.70 (m, 1H); MS m/z (relative intensity) 351 (M^+-OMe, 5.5), 325 (13.1), 201 (100.0), 115 (15.6), 57 (7.5); MS (high resolution, M^+-OMe) caluclated for $C_{21}H_{39}O_2Si$, 351.2721; found 351.2719.

(2RS,6R)-2-[(3S,4R,5S)-3,5-dimethyl-4-hydroxy-1-heptynyl]-2-methoxy-6-methyltetrahydropyran (104). To a solution of 24.5 mg (0.06 mmol) of **103** in 3 mL of tetrahydrofuran was added 128 µL of a 1M solution of tetra-n-butylammonium fluoride (0.13 mmol) in tetrahydrofuran at room temperature. The resulting pale yellow solution was stirred at 50°C for 3 h, then cooled to room temperature and partitioned between ether and a saturated aqueous solution of sodium bicarbonate. The aqueous phase was separated and extracted with ether, and the organic layers were combined, washed with brine and dried over magnesium sulfate. After removing the solvent flash chromatography on silica 60 (hexane/ether 1:1) gave 15.8 mg (92%) of **104** as a colorless oil: IR (neat) 3410, 2240 cm^{-1}; ^1H NMR ($CDCl_3$) of major isomer 0.91 (d, 3H, J=6.6), 0.93 (t, 3H, J=6.7), 1.19 (d, 3H, J=6.0), 1.22 (d, 3H, J=6.7), 1.23 (m, 2H), 1.54 (m, 4H),

1.88 (m, 3H), 2.75 (m, 1H), 3.26 (t, 1H), 3.35 (s, 3H), 3.71 (m, 1H); MS m/z (relative intensity) 237 (M^+-OMe, 30.6), 211 (3.9), 182 (45.8), 150 (100.0), 135 (20.8), 121 (83.7), 87 (18.3), 57 (32.2); MS (high resolution, M^+ -OMe) calculated for $C_{15}H_{26}O_2$, 237.186; found 237.1854.

(2R,3S,6R,8R)-3,8-Dimethyl-2-[(1S)-1-methylpropyl]-1,7-dioxaspiro-[5.5]undec-4-ene (75). To a solution of 12.9 mg (0.048 mmol) of 105 in 2 mL of methanol was added 3.2 mg of quinoline followed by 4.2 mg of palladium on barium sulfate. The suspension was stirred under hydrogen for 20 min and filtered through a Celite pad. The filtrate was evaporated in vacuo and the residue taken up into 3 mL of ether. The solution was acidified with camphorsulphonic acid and the mixture was stirred at room temperature for 1.5 h. The quinolinium camphorsulfonate was removed by filtration and washed three times with ether. The organic phase was washed with a saturated aqueous solution of sodium bicarbonate, water and brine and dried over magnesium sulfate. Removal of the solvent, followed by flash chromatography of the residue on silica 60 (hexane/ether 9:1), gave 5.6 mg (49%) of 76 as a colorless oil: $[\alpha]_D^{25}$ = +63.3° (c = 0.260, chloroform); IR 1640, 1450 cm^{-1}; ^1H NMR δ 0.89 (d, 3H, J=6.2), 0.90 (d, 3H, J=6.8), 0.93 (t, 3H, J=7.4), 1.13 (d, 3H, J=6.4), 1.25 (m, 2H), 1.38-1.62 (m, 7H), 2.23 (m, 1H), 3.48 (dd, 1H, J=9.6,1.4), 3.90 (m, 1H), 5.55 (dd, 1H, J=9.8, 2.5), 5.69 (dd, 1H, J=9.7,1.3); ^{13}C NMR δ 12.13, 12.84, 16.51, 19.01, 22.12, 27.58, 30.84, 32.64, 34.69, 35.41, 66.13, 74.56, 93.99, 129.67, 135.13; MS m/z 238 (M^+, 6.2), 181 (9.3) 152 (100.0); MS (high resolution, (M^+) calculated for $C_{15}H_{25}O_2$, 238.1934; found, 238.1933.

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