THE PARTIAL SYNTHESIS OF ANTIBIOTIC X-14547A

by

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B.A., Dartmouth College

(1978)

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

AUGUST 1983

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August 29, 1983

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ABSTRACT

The intramolecular Diels-Alder cyclization of pentaene 98, the methyl ester of a potential biosynthetic precursor to ionophore antibiotic X-14547A (1) resulted in the diastereoselective formation of X-14547A methyl ester (11). The hydrolysis of 11 to give the natural product has been described previously by two different research groups. A key feature of our synthesis of 11 was the use of diisopropylphosphonate alcohol reagent 178 in the coupling with naturally derived tetrahydropyran aldehyde (E)-7 which allowed the selective construction of the requisite all (E)- tetraene functionality and the introduction of a suitable aldehydic precursor at C.19 in the same step. The final stages of this synthesis are marked by a high degree of convergence with respect to the left hand half component (E)-7 (four manipulations to X-14547A) and of functional group compatibility at each stage.

An evaluation of suitable aldehydic precursors for C.19 and of olefination methods to generate all (E)- tetraene systems was performed in preliminary studies which culminated in the synthesis of X-14547A model compound 101. The all (E)- tetraene 119 was prepared with greatest facility either by coupling of diene phosphonate 154 with aldehyde 109 or by Na-Hg reduction of β-benzoyloxy sulfone 148. The former method affords the best yields and requires the fewest manipulations of the aldehydic component and, therefore, was deemed best suited for our synthesis. Unmasking of the C.19 aldehyde functionality was accomplished by a highly selective 9-BBN oxidation sequence (cf, 119→107), a sequence which required the manipulation of a vinyl group in the presence of a conjugated tetraene. Aldehyde 107 was then treated with phosphorane 96 in 2:1 CH_2Cl_2-MeOH at 23°C for several days to give model compound 101 directly in 53% yield as the only trans-fused cycloadduct.

A new synthesis of α-chiral aldehydes from optically active epoxyalcohols was examined in connection with our approach to X-14547A. Although treatment of optically active 2,3 disubstituted epoxyalcohols with Me_3Al followed by $NaIO_4$ cleavage provided α-methyl chiral aldehydes with optical activity identical to that of the starting epoxides, the use of Et_3Al with 195 resulted in α-ethyl aldehyde 180 with optical purity

significantly less than that of 195. The use of Et_4AlNa-$NiCl_2$ or Et_2Mg with 195 produced 180 with high optical activity but in only modest yield (32-38%). The reduction of chiral 3,3-disubstituted 2,3-epoxy-alcohols 207 and 208 with BH_3-$LiBH_4$ followed by periodate cleavage afforded 180 in better yield (56%) but in lower optical purity than that prepared from 195. Thus, compound 180 prepared via the Et_4AlNa or Et_2Mg opening of 195 was elaborated to dienephosphonate alcohol 178 and thence to antibiotic X-14547A.

Thesis Supervisor: Dr. William R. Roush

Title: Rodger and Georges Firmenich Career Development Associate Professor of Natural Products Chemistry; Fellow of the Alfred P. Sloan Foundation, 1982-1984

To my loving wife

Marian

(μέ όλη μου τήν αγάπη)

ACKNOWLEDGEMENTS

I extend my sincere gratitude to Professor William R. Roush whose professional excellence was a source of continual benefit to me during my years at MIT. His high standards and enthusiasm will be forever benchmarks of quality when making evaluations in my professional life.

I thank Professor David M. Lemal of Dartmouth College for the opportunities and guidance he provided in my undergraduate chemistry years. I am grateful to all the professors at Dartmouth who make chemistry such a dynamic and fascinating course of study.

I appreciate greatly the efforts of Jim Simms, Jeanne Owens, Deborah Western, and others whose efforts maintained the all important MIT "Spec Lab" in the best possible operating condition.

The past and present members of the Roush Group are fondly remembered for the many informative and enjoyable moments that we shared. I deeply appreciate the assistance provided by the present group members in proofreading this thesis.

Always cherished and never forgotten are my mother and late father who, undeniably, supplied the requisite basis for everything I may do in life. Their love and values provided the support and encouragement necessary for me to achieve that which I have. My brother and sister-in-law are likewise appreciated for their love and support.

Finally, but most important, I am grateful for the love, support, and understanding of my wife, Marian.

ABBREVIATIONS

Bn	-	benzyl
9-BBN	-	9-borabicyclononane
DCC	-	dicyclhexylcarbodiimide
DIBAL	-	diisobutylaluminum hydride
DIPEA	-	diisopropylethylamine
DIPT	-	diisopropyltartrate
DME	-	dimethoxyethane
DMF	-	dimethylformamide
DMSO	-	dimethylsulfoxide
HMPA	-	hexamethylphosphorictriamide
LDA	-	lithium diisopropylamine
MEM	-	β-methoxyethoxymethyl
PCC	-	pyridinium chlorochromate
PDC	-	pyridinium dichromate
Ph or ϕ	-	phenyl
SEM	-	trimethylsilylethoxymethyl
p-TsOH	-	p-toluenesulfonic acid
TsO	-	p-toluenesulfonate
TBDMS	-	tert-butyldimethylsilyl
TBDPS	-	tert-butyldiphenylsilyl
TBHP	-	tert-butylhydroperoxide
TFAA	-	trifluroacetic anhydride
THF	-	tetrahydrofuran

FORWARD

This thesis describes research performed February, 1981, through June, 1983, in connection with the partial synthesis of antibiotic X-14547A. Two publications (see references 21 and 56) resulting from these studies have appeared. Research performed between January, 1979, and January, 1981, involved studies on the utility of intramolecular Diels-Alder reactions for the construction of angularly methylated trans-perhydroindene ring systems. These studies have been published (see: Roush, W.R.; Peseckis, S.M. J. Am. Chem. Soc. 1981, 103, 6696.) and are not discussed in this thesis.

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CHAPTER I

INTRODUCTION

The isolation of X-14547A (1), an intriguing ionophore antibiotic of the polyether class, from Streptomyces antibioticus (NRRL 8167) was reported in 1978 by Westley and coworkers at Hoffman-La Roche Inc.[1-4] X-14547A (1) is a potent antibiotic which is active in vitro against gram positive bacteria[1,2] such as Staphylococcus aureus, Sarcina lutea, Bacillus megaterium, Mycobacterium phlei, and Streptomyces cellulosae. It possesses a spectrum of activity similar to the ionophore antibiotics lasalocid A (2) and calcimycin (also known as A23187, 3). It is essentially inactive, however, in tests against gram negative bacteria such as Escherichia coli, Proteus vulgaris, Pseudomonas aeruginose, Klebsiella pneumoniae, and Serratia marcescens. The fungi imperfectii Penicillium digitatum, the yeast Candida abicans, and the common yeast Saccharomyces cerevisiae likewise appear unaffected by 1 even though growth of the former pair is inhibited by calcimycin (3).

X-14547A (1) also has the ability to increase the efficiency of feed utilization by ruminants and thereby to promote growth.[2,4] This property is displayed by other polyether antibiotics such as monensin (4), lasalocid (2), and nigericin (5).[5]

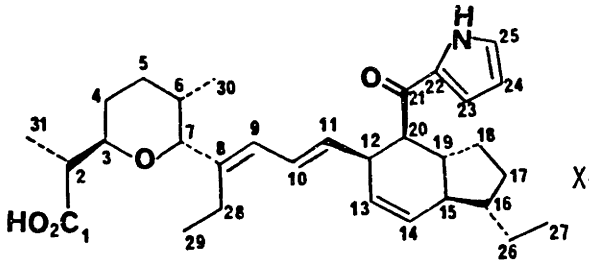
1. Westley, J.W.; Evans, R.H., Jr.; Liu, C.-M.; Hermann, T.E.; Blount, J.F. J. Am. Chem. Soc. 1978, 100, 6784.

2. Liu, C.-M.; Hermann, T.E.; Liu, M.; Bull, D.N.; Palleroni, N.J.; Prosser, B.L.T.; Westley, J.W.; Miller, P.A. J. Antibiotics 1979, 32, 95.

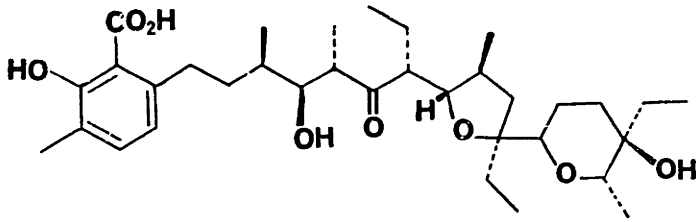
3. Westley, J.W.; Evans, R.H., Jr.; Sello, L.H.; Troupe, N.; Liu, C. -M.; Blount, J.F. J. Antibiotics 1979, 32, 100.

4. Westley, J.W.; Liu, C.-M. U.S. Patent 4 100 171, 1978.

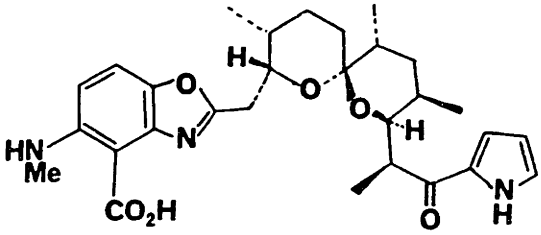
5. Westley, J.W. Adv. Appl. Microbiol. 1977, 22, 177.



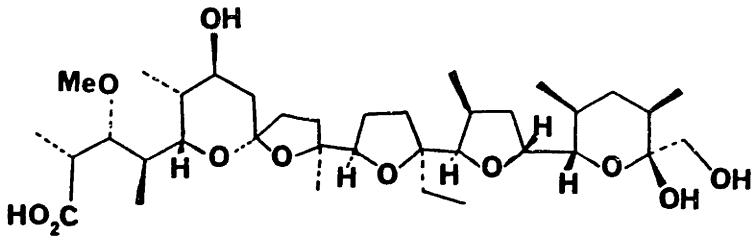
X-14547A (1)



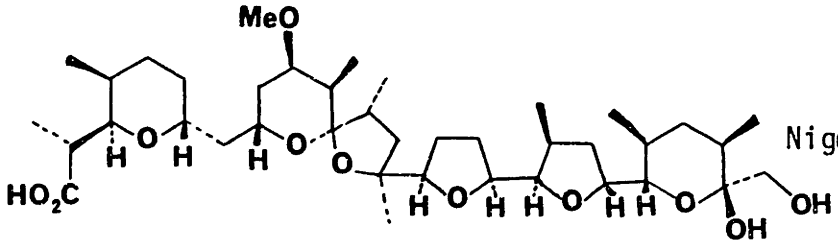
Lasalocid A (2)



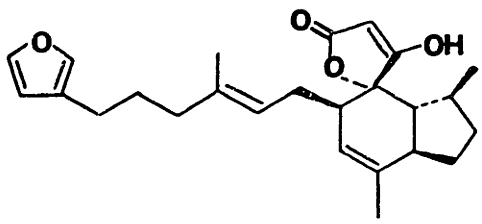
Calcimycin (3)
(A23187)



Monensin (4)



Nigericin (5)



Iracianin (6)

In addition to the foregoing biological properties, antibiotic X-14547A (1) is also characterized as an ionophore.[1,3,6] For example, radioactive $^{45}Ca^{2+}$ and $^{86}Rb^{+}$ cations are transported by 1 through a chloroform phase from one aqueous solution to another in a typical U-tube system. An X-ray structure determination of the bromophenethylamine salt of X-14547A exhibited a two-to-one ratio of X-14547A (1) to amine even though the antibiotic is a monocarboxylic acid and the amine is monobasic.[1,3] This observation is consistent with the ability of 1 to transport both monovalent and divalent inorganic cations as demonstrated by the U-tube experiments.

The group at Hoffman La-Roche has also reported that antibiotic X-14547A possesses antitumor activity.[7] A full report on these properties has not been published to date, however.

Antibiotic X-14547A (1) contains several unique structural features distinct from that of other polyether compounds.[6] It is the first ionophore to contain a 1,3 butadiene functionality and only the second example of this class, the other being calcimycin (3),[8] to contain a

6. (a) Westley, J.W. "Polyether Antibiotics, Naturally Occuring Acid Ionophores, Volume 1: Biology" 1st ed., Marcel Dekker Inc., New York, 1982; pp. 315, and references therein. X-14547A is referred to as "Polyether A".

   (b) Westley, J.W. "Polyether Antibiotics, Naturally Occuring Acid Ionophores, Volume 2: Chemistry" 1st ed., Marcel Dekker Inc., New York, 1983; pp. 186, and references therein.

7. Westley, J.W. personal communication.

8. (a) Chaney, M.O.;Demarco, P.V.; Jones, N.D.; Occolowitz, J.L. J. Am. Chem. Soc. 1974, 96, 1932.

   (b) Chaney, M.O.; Jones, N.D.; Debono, M. J. Antibiotics 1976, 29, 424.

pyrrole ring. With iracianin (6)[9] it shares the distinction of being only one of the few natural products which possess a trans-fused hexahydroindene ring system. As a consequence, Westley speculated that the biosynthesis of X-14547A (1) may be different from that of other well characterized polyether antibiotics such as monensin (4) and lasalocid (2).[6] Roush and Myers later postulated that its biosynthesis may involve an intramolecular Diels-Alder cyclization.[10,11]

The unique structural features of 1 has prompted a number of research groups to undertake its total synthesis. One synthetic strategy is based on the initial division of X-14547A into two halves, a left hand half containing the tetrahydropyranyl ring system and a right hand half consisting of the perhydroindene nucleus (Pathway A, Scheme 1). The dislocation of the two halves is made at the

9. Hofheinz, W.; Schönholzer, P. Helv. Chim. Acta 1977, 60, 1397.

10. Roush, W.R.; Myers, A.G. J. Org. Chem. 1981, 46, 1510.

11. Reviews: (a) Brieger, G.; Bennett, J.N. Chem. Rev. 1980, 80, 63.

(b) Oppolzer, W. Synthesis 1978, 793.

(c) Oppolzer, W. Angew. Chem., Int. Ed. Engl. 1977, 16, 10.

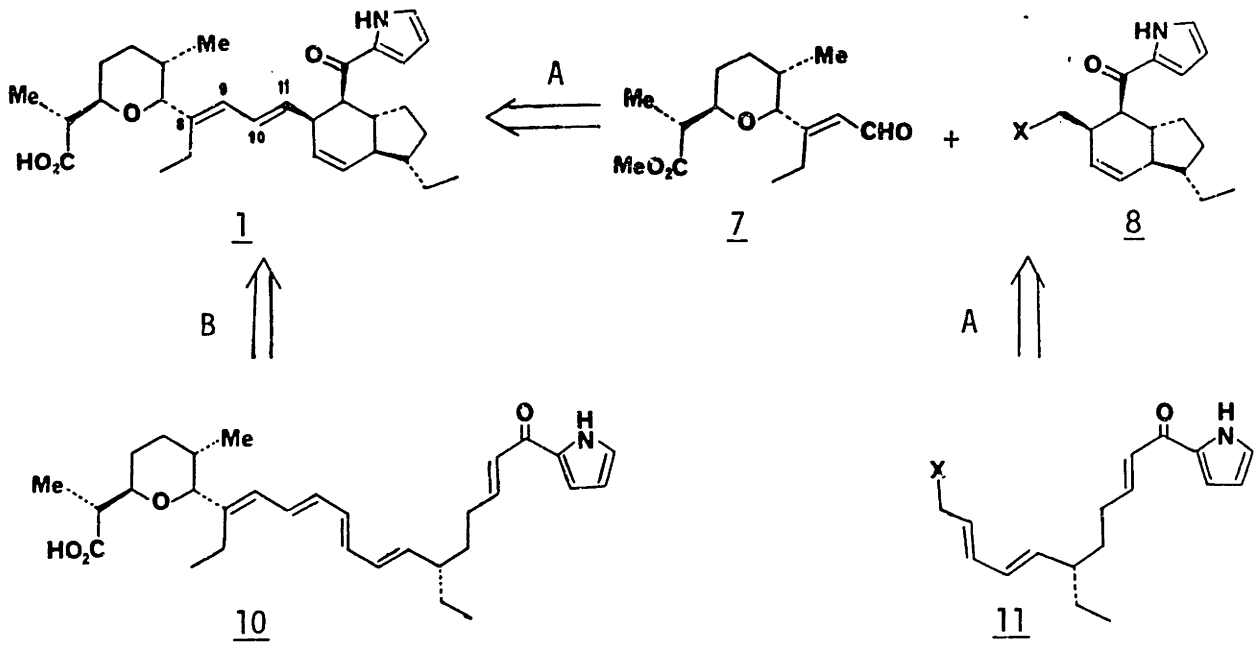
(d) Funk, R.L.; Vollhardt, K.P.C. Chem. Soc. Rev. 1980, 9, 41.

(e) Carlson, R.G. Annu. Rep. Med. Chem. 1974, 9, 270.

(f) Ciganek, E. Organic Reactions, in press.

(g) Fallis, A.G. Can. J. Chem., in press.

Scheme 1



1 7 8 10 11

disubstituted double bond at C.10,11 (see numbering, Scheme 1) rather than at the trisubstituted double bond at C.8,9 in deference to the ease and variety of methods available for the stereoselective construction of disubstituted double bonds. This approach should permit a convergent synthesis with the independent synthesis of the two halves which can be coupled at an advanced stage in the synthesis to provide the natural product. This approach has been pursued by Nicolaou,[12] Ley,[13] and

12. (a) Nicolaou, K.C.; Magolda, R.L. J. Org. Chem. 1981, 46, 1506.

(b) Nicolaou, K.C.; Papahatjis, D.P.; Claremon, D.A.; Dolle, R.E., III. J. Am. Chem. Soc. 1981, 103, 6967.

(c) Nicolaou, K.C.; Claremon, D.A.; Papahatjis, D.P.; Magolda, R.L. J. Am. Chem. Soc. 1981, 103, 6969.

13. (a) Edwards, M.P.; Ley, S.V.; Lister, S.G. Tetrahedron Lett. 1981, 22, 361.

(b) Edwards, M.P.; Ley, S.V.; Lister, S.G.; Palmer, B.D. J. Chem. Soc., Chem. Commun. 1983, 630.

Ho,[14] and is central to the successful total synthesis of X-14547A reported in 1981 by Nicolaou[12b,c] and in 1983 by Ley.[13b] An alternative retrosynthesis is based on the hypothesis that the biosynthesis of X-14547A may involve an intramolecular Diels-Alder reaction of 10 (see retrosynthesis B, Scheme 1). The latter approach is the subject of this thesis.

Utilization of an intramolecular Diels-Alder reaction to prepare the perhydroindane nucleus and introduce the four stereocenters of the cyclohexenyl ring in X-14547A (1) has precedence in the early work by House[15] and recent extensive studies by Roush.[16] Examination of the molecular models of the two diastereomeric endo transition states available to 10 also suggested that transition state A (shown next page), leading to 1, should be preferred over B, leading to the enantiomer of the ethyl epimer of 1, as a consequence of a destabilizing steric interaction between H_a and the C.16 ethyl group in the transition state B. This differentiation of the transition states A and B would

14. Ho, P.-T. Can. J. Chem. 1982, 60, 90.

15. House, H.O.; Cronin, T.H. J. Org. Chem. 1965, 30, 1061.

16. (a) Roush, W.R. J. Am. Chem. Soc. 1978, 100, 3599.

(b) Roush, W.R. J. Org. Chem. 1979, 44, 4008.

(c) Roush, W.R. J. Am. Chem. Soc. 1980, 102, 1390.

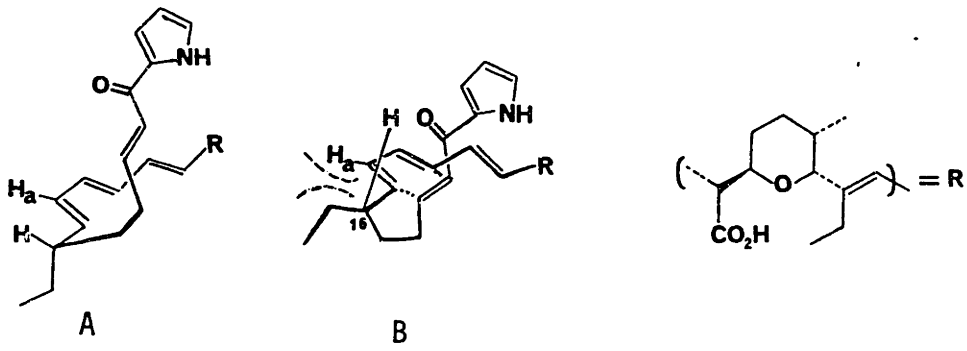
(d) Roush, W.R.; Ko, A.I.; Gillis, H.R. J. Org. Chem. 1980, 45, 4264.

(e) Roush, W.R.; Gillis, H.R. J. Org. Chem. 1980, 45, 4267.

(f) Roush, W.R.; Gillis, H.R. J. Org. Chem. 1980, 45, 4283.

(g) Roush, W.R.; Gillis, H.R., Ko, A.I. J. Am. Chem. Soc. 1982, 26, 2269, and references therein.

(f) Roush, W.R.; Gillis, H.R. J. Org. Chem. 1982, 47, 4825.



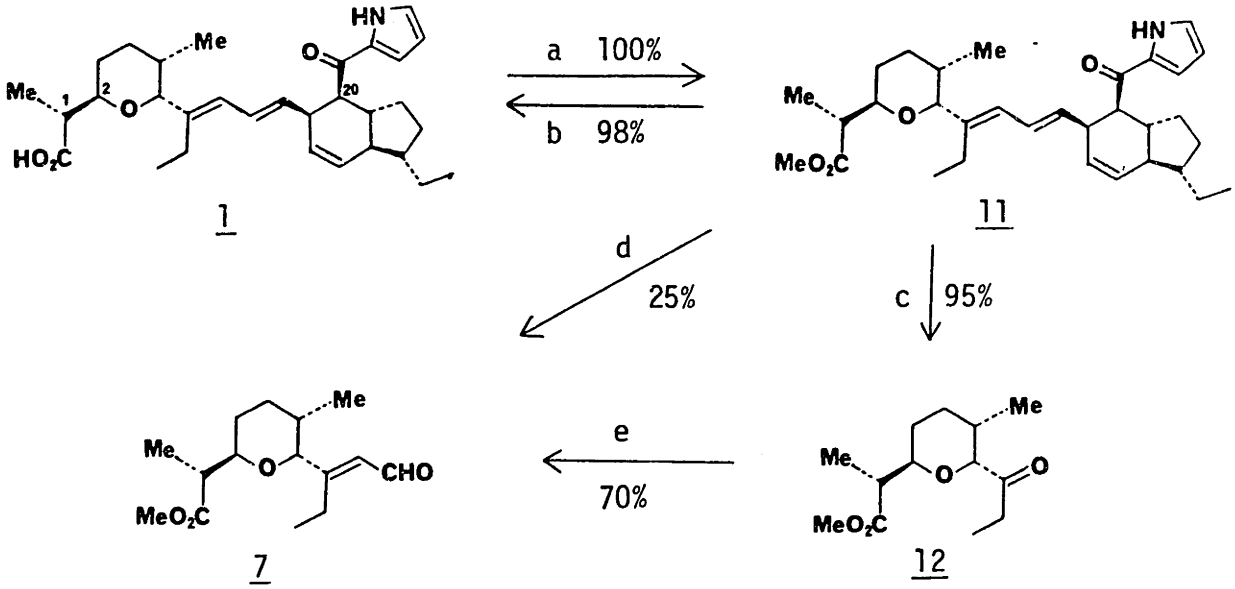
be expected to be more pronounced than was observed in Roush's total synthesis of dendrobine[16a-c] in which a benzyloxy group was allylic to the diene, since an ethyl group is sterically larger than a protected hydroxyl group.[17] This analysis suggested that all of the stereochemistry of the right hand half of 1 could be induced from an acyclic triene precursor containing a single stereocenter at C.16. Such Diels-Alder approaches have been pursued independently by the Roush, Nicolaou, and Ley research groups.

Degradation studies by Nicolaou and Magolda[12a] identified several important potential synthetic intermediates (Scheme 2). They observed that the carboxylic acid functionality could be esterified

17. (a) Hirsch, J.A. In "Topics in Stereochemistry"; Allinger, N.L.; Eliel, E.L. Eds.; John Wiley & Sons: New York, 1967; Vol. 1, p 199.

(b) Several examples which show the pronounced effect of an alkyl substituent allylic to the diene have been reported for trienes which cyclize to give octalin ring systems. See for example: Vig, O.P.; Trehan, I.R.; Kumar, R. Indian J. Chem. 1977, 15B, 319; Vig, O.P.; Trehan, I.R.; Malik, N.; Kumar, R. Indian J. Chem. 1978, 16B, 449; Taber, D.F.; Gunn, B.P. J. Am. Chem. Soc. 1979, 101, 3992.

Scheme 2

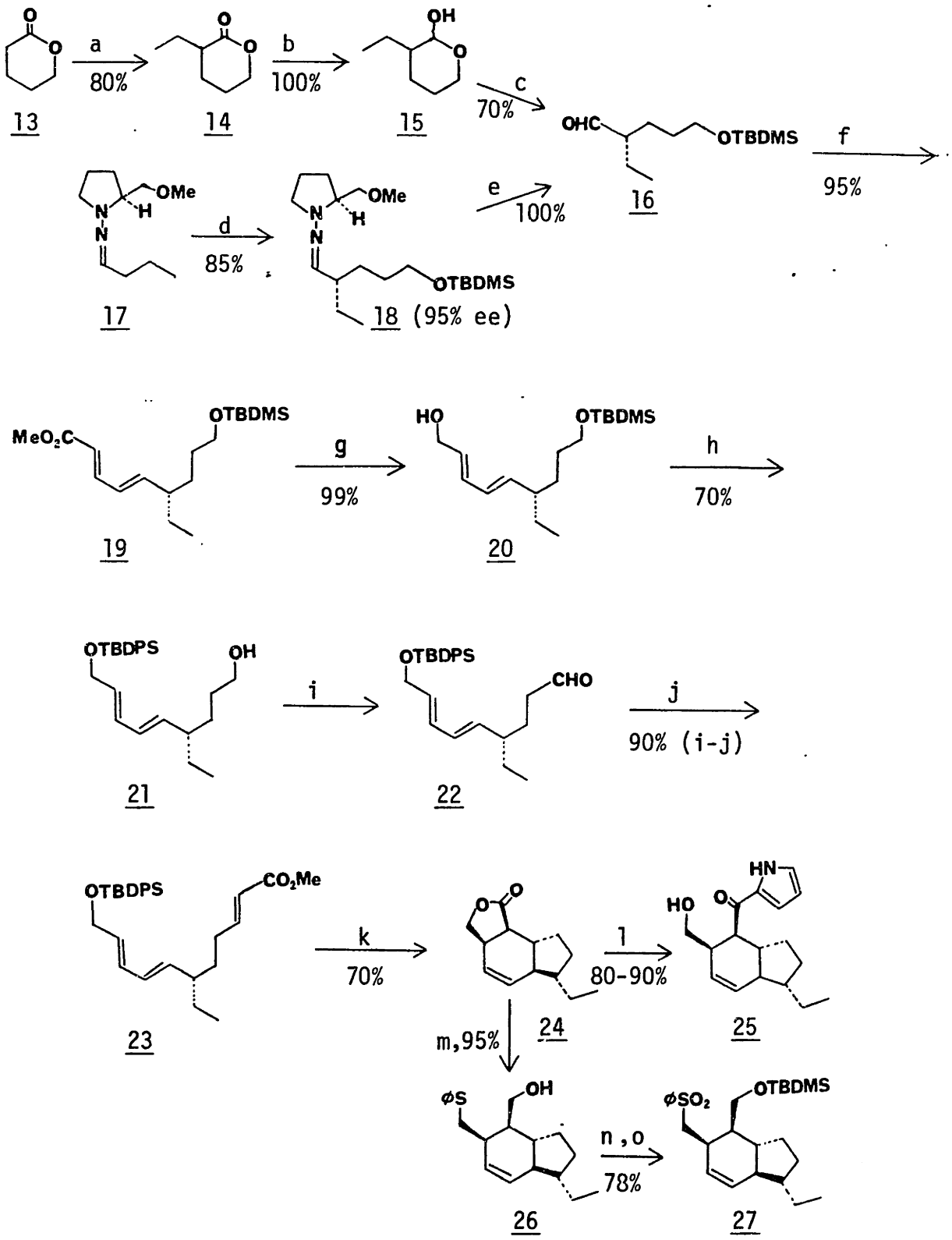


Scheme 2; Key: (a) CH_2N_2, Et_2O; (b) LiOH, THF-H_2O; (c) O_3, AcOH, CH_2Cl_2, then Me_2S; (d) OsO_4, $NaIO_4$, tBuOH-THF; (e) CH_2:CHMgBr, THF, then PCC, CH_2Cl_2.

with diazomethane to 11 and, most notably, that 11 could be saponified to 1 by using excess lithium hydroxide in aqueous THF without epimerization of C.2, C.3, or C.20. Ozonolysis of 11 afforded ketone 12 (95%) while treatment of 11 with catalytic OsO_4 and $NaIO_4$ (2.4 equiv.) afforded the α,β unsaturated aldehyde 7 (25%). The latter compound was also prepared by treatment of 12 with vinyl magnesium bromide followed by oxidation with PCC (70%, E:Z= 6:1). No fragments derived from the right hand half of 1 could be identified from these degradation studies.

Ketopyrrole 25, which corresponds to the right hand half of X-14547A (1) has been synthesized independently by Nicolaou[12a] and Ley.[13a] As seen in Scheme 3, Nicolaou synthesized racemic 25 from δ-valerolactone (13) by a ten step sequence in 23% overall

Scheme 3


a
80%
b
100%
c
70%
f
95%
d
85%
e
100%
g
99%
h
70%
i
j
90% (i-j)
k
70%
l
80-90%
m,95%
n,o
78%
13
14
15
16
17
18 (95% ee)
19
20
21
22
23
24
25
26
27
OTBDMS
OTBDPS
OMe
CO2Me
CHO
OH
HO
HN
φS
φSO2

Scheme 3; Key: (a) LDA, EtI, THF-HMPA; (b) DIBAL, CH_2Cl_2; (c) TBDMSCl, imidazole, DMF; (d) LDA, Et_2O, then $ICH_2CH_2CH_2OTBDMS$; (e) O_3, CH_2Cl_2; (f) $(MeO)_2OPCHLiCH{=}CHCO_2Me$, THF; (g) DIBAL, CH_2Cl_2; (h) TBDPSCl, imidazole, DMF, then AcOH-THF-H_2O; (i) PCC, CH_2Cl_2; (j) $Ph_3P{=}CHCO_2Me$, toluene; (k) toluene, 130°C, then n-Bu_4NF, THF; (l) MeMgCl, pyrrole, toluene; (m) LiSPh, DMF, then CH_2N_2, Et_2N, then $LiAlH_4$, Et_2O; (n) $(PhS)_2$, 30% H_2O_2, Et_2O-CH_2Cl_2; (o) TBDMSCl, Et_3N, DMAP, CH_2Cl_2.

yield. The stereochemistry of these intermediates was confirmed by an X-ray crystallographic analysis of 24. This intermediate was then converted to racemic 25 by treatment at elevated temperature with pyrrole magnesium bromide.

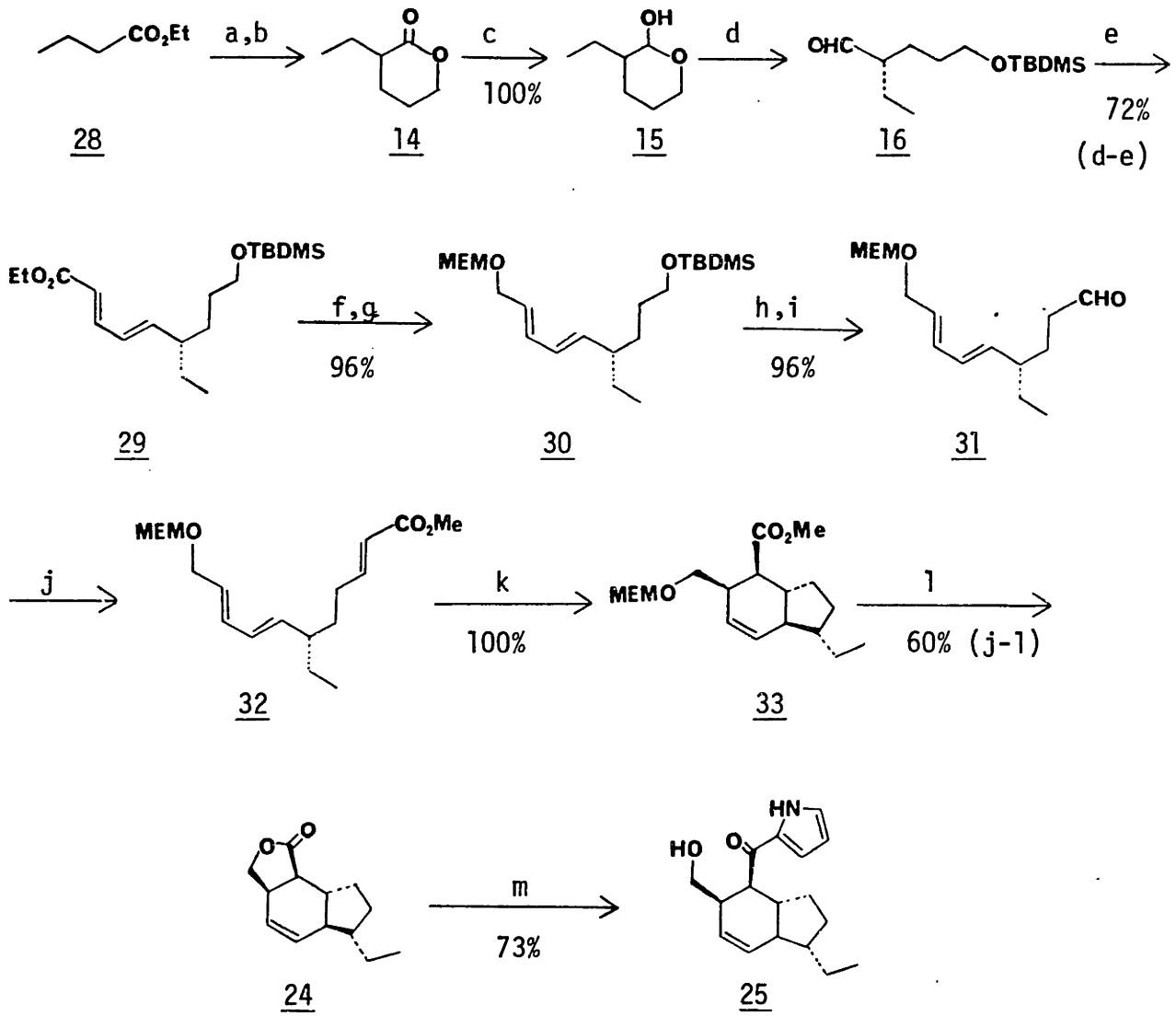
Ley[13a] synthesized 25 by a route which was very similar to Nicolaou's route. As seen in Scheme 4, Ley's synthesis of racemic 25 differs from Nicolaou's only in the use of a β-methoxyethoxy methyl (MEM) alcohol protecting group for the allylic hydroxyl group in intermediates 30-33. The cyclization of 32 afforded 33 with less than 10% of other stereoisomers being produced, whereas Nicolaou reported the isolation of 70% of 24 plus 15% of other cycloadducts from the cyclization of 23 (see Scheme 3). The reasons for this slight difference in product selectivity are not obvious at present.

In Nicolaou's total synthesis of X-14547A,[12b,c] tricyclic lactone 24 was again used as an intermediate. Ender's method[18] for the asymmetric alkylation of optically active S-1-amino-2-methoxy-methyl-pyrrolidine (SAMP) hydrazones (17→18, Scheme 3) was used to synthesize 18, which was greater than 98% diastereomerically pure as determined by ^{1}HNMR-Eu(fod)$_3$ techniques. This hydrozone was ozonized to give chiral aldehyde 16 which was then converted to chiral lactone 24 by the same sequence used to synthesize the racemate. Introduction of the ketopyrrole unit, however, was postponed until after the two halves had been joined. Silyl ether 27 served as the substrate for the coupling sequence, and was prepared from chiral 24 by the three step sequence summarized in Scheme 3.

18. (a) Enders, D.; Eichenauer, H. Tetrahedron Lett. 1977, 191.

(b) Enders, D.; Eichenauer, H. Chem. Ber. 1979, 112, 2933.

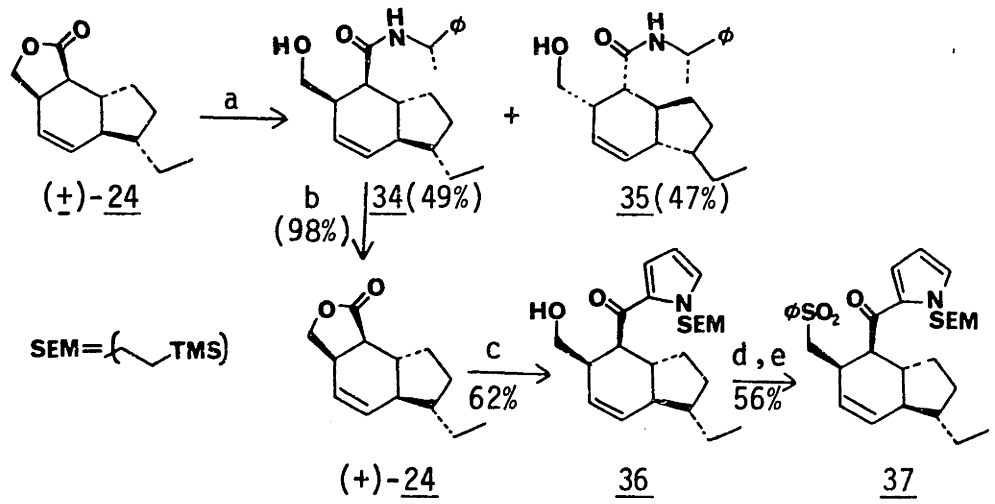
Scheme 4



Scheme 4; Key: (a) base, $TMSOCH_2CH_2CH_2I$; (b) H^+ then warm $PhCH_3$/PTSA; (c) DIBAL, $PhCH_3$; (d) TBDMSCl, imidazole; (e) $(EtO)_2POCHLiCH{=}CHCO_2Et$; (f) DIBAL, $PhCH_3$; (g) MEMCl, $(iPr)_2NEt$, CH_2Cl_2; (h) n-Bu_4NF, THF; (i) CrO_3/pyr, CH_2Cl_2; (j) $Ph_3P{=}CHCO_2Me$; (k) $PhCH_3$, reflux; (l) $ZnBr_2$, CH_2Cl_2; (m) pyrrole-MgBr, $PhCH_3$.

Tricyclic lactone 24 was resolved in Ley's total synthesis of X-14547A.[13b] Racemic 24 was treated with S-(-)-α-phenylethylamine to give an equal mixture of diastereomers 34 and 35 (Scheme 5). After chromatographic separation of the mixture over silica gel, the desired 34 was hydrolyzed to optically pure (+)- 24. This optically pure lactone was then treated with 2-lithio-N-β-trimethylsilylethoxymethyl pyrrole (2-lithio-N-SEM-pyrrole) to give protected ketopyrrole 36. This intermediate was then converted into sulfone 37, which served as Ley's right hand half equivalent.

Scheme 5

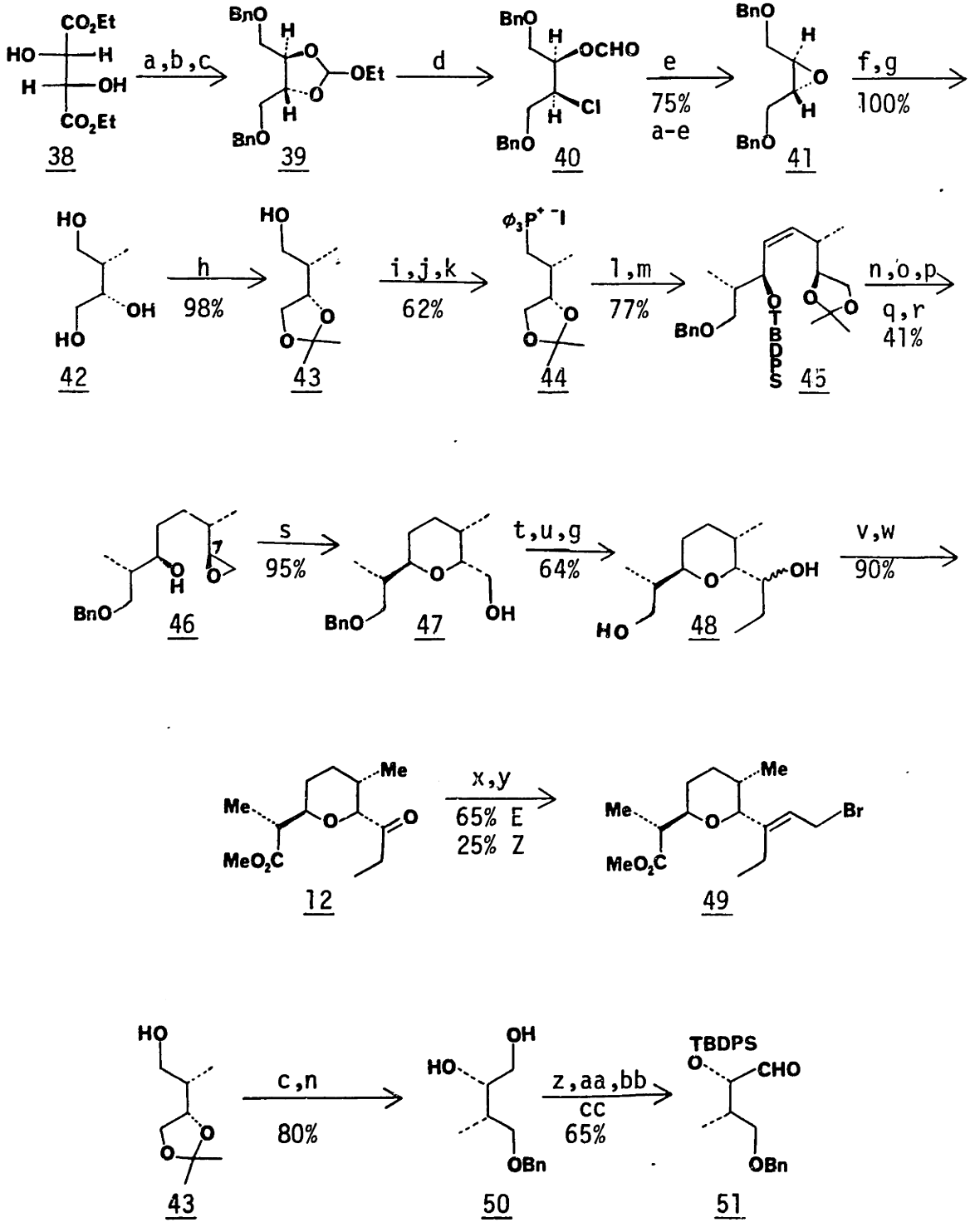


Scheme 5; Key: (a) $PhCHMeNH_2$, 2-hydroxypyridine, $PhCH_3$; (b) 0.5M H_2SO_4, dioxane-H_2O; (c) 2-lithio-N-SEM-pyrrole, DME; (d) NPSS (N-phenylsulphenylsuccinimide), n-Bu_3P, C_6H_6; (e) H_2O_2, $(PhSe)_2$, CH_2Cl_2-Et_2O.

Allylic bromide 49 served as the electrophilic left hand synthon in Nicolaou's total synthesis (Scheme 6). The preparation of 49 proceeded in twenty-six steps with a maximum overall yield of 5.5% from (-)-diethyl-D-tartrate (38). Important transformations include the opening of symmetrical epoxide 41 with dimethyl cuprate, deprotection to give triol 42, and then selective acetonide formation to give the key intermediate 43. Alcohol 43 served as a precursor of both the Wittig reagent 44 and aldehyde 51. Coupling of 44 and 51 afforded 45 which was transformed into 47 via epoxide 46 with inversion of stereochemistry at C.7. Standard transformations were used to elaborate 47 to X-14547A degradation product 12, and thence to allylic bromide 49.

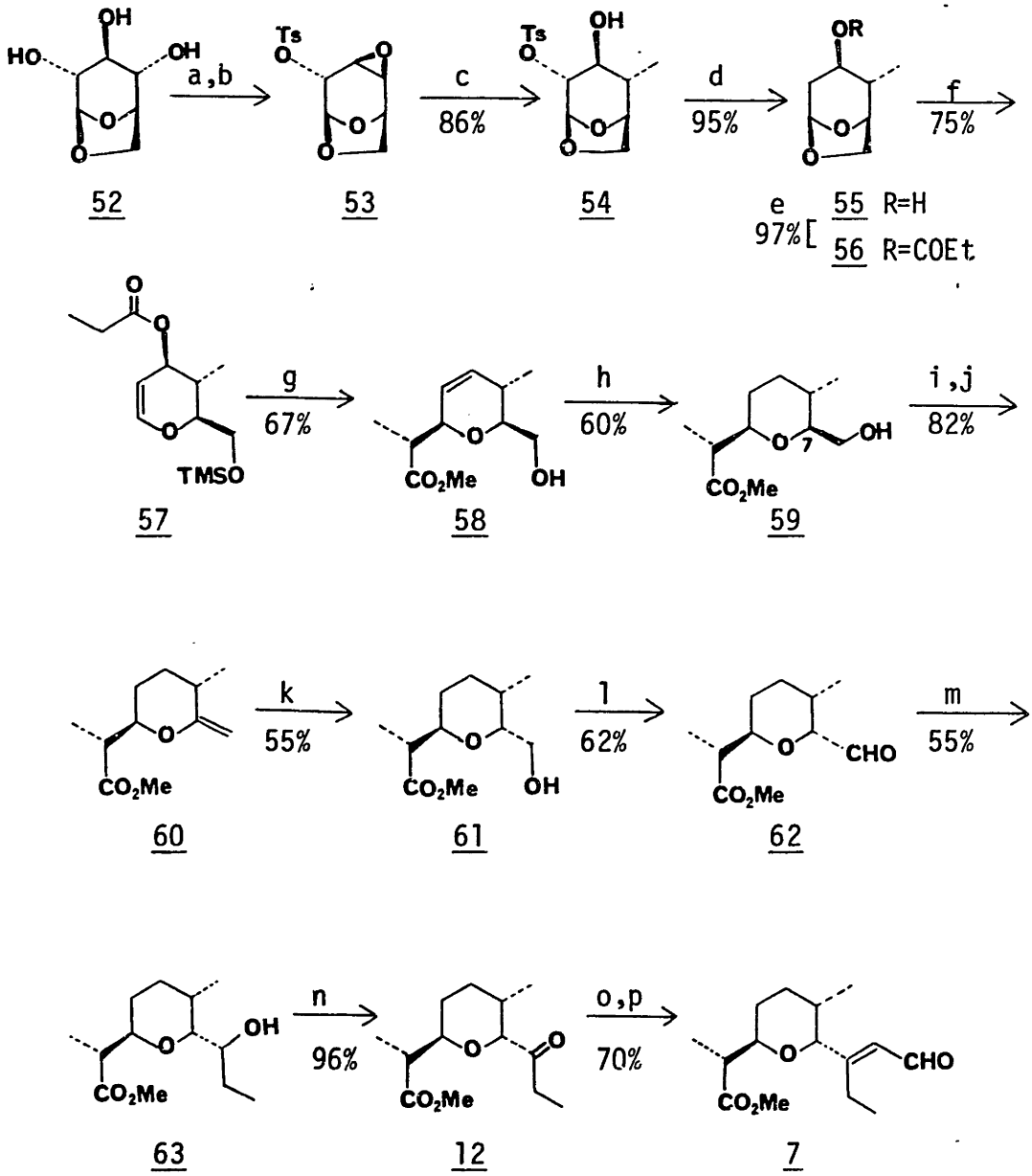
The electrophilic left hand half in Ley's total synthesis was α,β unsaturated aldehyde 7, a known degradation product of X-14547A. Ley's synthesis of 7 utilized 1,6-anhydro-β-D-glucose 52 (laevoglucosan) as a starting material. As seen in Scheme 7, 52 was converted by standard procedures into epoxide 53, which was then opened with methylmagnesium chloride with copper (I) catalysis to give alcohol 54. Elaboration of 54 to ester 57 then allowed use of a Claisen ester-enolate rearrangement to transfer chirality from C.5 to C.3 in the preparation of 58. Reduction of the C.4,5 double bond of 58 gave 59. Since 59 possessed the undesired configuration at C.7, this chiral center was epimerized by elimination of the C.8 alcohol to give olefin 60 followed by hydroboration (BH_3-THF) to give 61. Standard transformations were then used to effect conversion of 61 to 12, which was elaborated to unsaturated aldehyde 7 by Nicolaou's procedure.[12a]

Scheme 6


a,b,c
d
e
75%
a-e
f,g
100%
h
98%
i,j,k
62%
l,m
77%
n,o,p
q,r
41%
s
95%
t,u,g
64%
v,w
90%
x,y
65% E
25% Z
c,n
80%
z,aa,bb
cc
65%
38
39
40
41
42
43
44
45
46
47
48
12
49
43
50
51

Scheme 6; Key: (a) $(EtO)_3CH$, CSA, $PhCH_3$; (b) $LiAlH_4$, THF; (c) BnBr, NaH, DME; (d) PCl_5, CH_2Cl_2; (e) K_2CO_3, CH_3OH; (f) Me_2CuLi, Et_2O; (g) 10% Pd/C, H_2, EtOH; (h) $CH_3C(OMe)_2CH_3$, C_6H_6, CSA: (i) TsCl, pyr.; (j) NaI, acetone; (K) Ph_3P, CH_3CN-$(EtO)_3CH$; (l) Dimsyl sodium, DMSO; (m) C_6H_6, 51; (n) Amberlite IR-120, EG-DME; (o) TsCl, pyr.; (p) NaOMe, MeOH; (q) nBu_4NF, THF; (r) 5% Pd/C, H_2, EtOAc; (s) CSA; (t) PCC, NaOAc; CH_2Cl_2; (u) EtMgBr, C_6H_6; (v) Jones' reagent, acetone; (w) CH_2N_2, Et_2O; (x) CH_2=$CHMgBr$, THF; (y) PBr_3, Et_2O; (z) tBuOCl, pyr.; (aa) TBDPSCl, imidazole, DMF; (bb) DIBAL, CH_2Cl_2; (cc) CrO_3-HCl-pyr, 4Å molecular sieves, CH_2Cl_2.

Scheme 7



Scheme 7; Key: (a) TsCl, pyr.; (b) NaOMe, MeOH; (c) MeMgCl, CuBr-Me_2S, THF; (d) $LiBHEt_3$, THF; (e) nBuLi, THF, then CH_3CH_2COCl; (f) TMSI, $PhCH_3$ then DBU; (g) LDA, THF, then TMSCl, Et_3N, then nBu_4NF and CH_2CN_2; (h) PtO_2, H_2, EtOAc; (i) Ph_3P, imidazole, I_2, C_6H_6; (j) AgF, pyr.; (k) BH_3-THF, THF then NaOH, H_2O_2; (l) PCC, CH_2Cl_2; (m) EtMgBr, THF; (n) H_2CrO_4, acetone; (o) CH_2=CHMgBr, THF; (p) PCC, CH_2Cl_2.

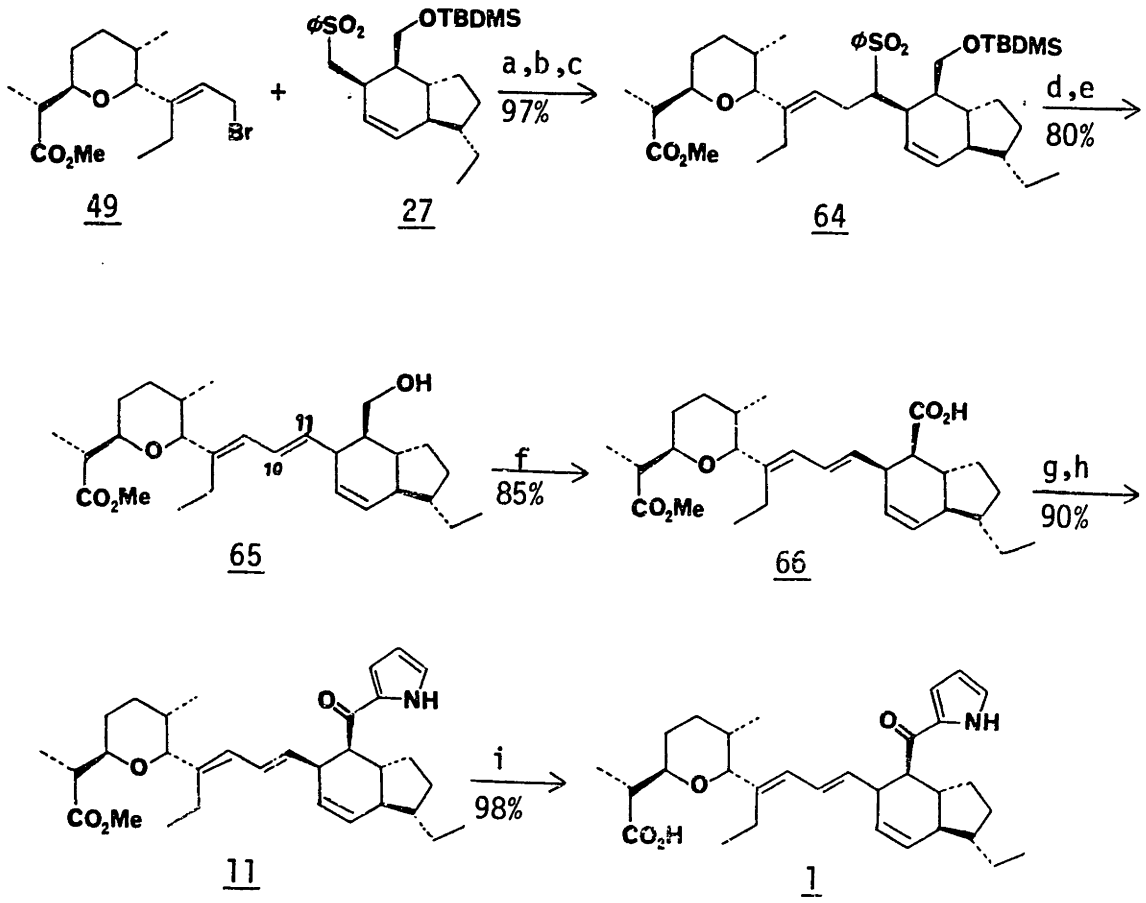
Interestingly, Nicolaou reported a 6:1 E:Z isomer ratio in the preparation of 7 whereas Ley realized a 3:1 E:Z mixture.

Nicolaou completed the total synthesis of X-14547A by first coupling the lithium anion of 27 with allylic bromide 49 to obtain adduct 64 in high yield (see Scheme 8). Adduct 64 was then converted in six steps to X-14547A. The (E)- double bond at C.10,11 was generated by elimination of arylsulfinate by treatment with 40% Triton B (benzyltrimethylammonium hydroxide) in methanol. These conditions also resulted in saponification of the methyl ester (which was reesterified in a subsequent step with diazomethane) and desilylation of the C.21 alcohol. Diene alcohol 65 was obtained in 80% overall yield at 40% conversion. The C.21 hydroxyl group was oxidized to the acid with excess Jones' reagent to give 66. This acid was then activated as the 2-pyridinethiol ester[19] as a prelude to introduction of the pyrrole unit by treatment with pyrrole magnesium chloride. Alkaline hydrolysis of the resulting X-14547A methyl ester (11) afforded the natural product.

The final stage of Ley's synthesis began by coupling the lithium anion of 37 with unsaturated aldehyde 7 and trapping the intermediate alkoxide with benzoyl chloride to afford 67 (see Scheme 9). Sodium-amalgam treatment of 67 in methanol-THF at -20°C effected stereoselective reduction to give (E,E)-diene 68. This coupling sequence has been previously investigated by Julia and

19. Nicolaou, K.C.; Claremon, D.A.: Papahatjis, D.P. Tetrahedron Lett. 1981, 22, 4647.

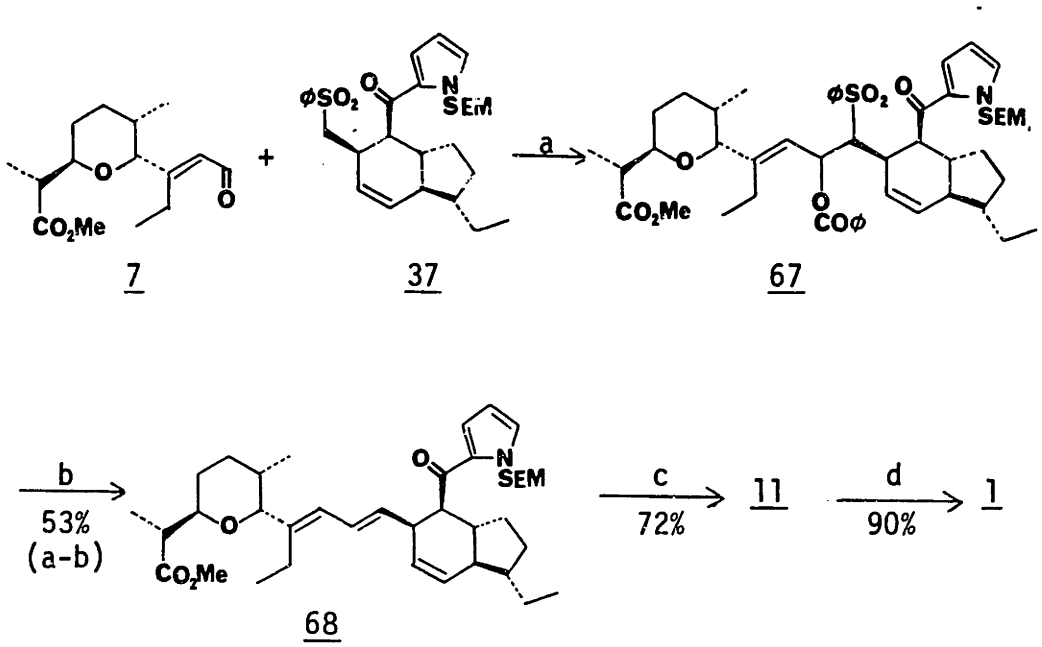
Scheme 8



49 27 64 65 66 11 1

Scheme 8; Key: (a) LDA, THF; (b) HMPA; (c) 46, THF; (d) 40% Triton B, MeOH; (e) CH_2CN_2, Et_2O; (f) Jones' reagent (CrO_3, H_2SO_4), acetone; (g) 2-pyridinedisulfide, Ph_3P, C_6H_6; (h) pyrrole-MgCl, $PhCH_3$, THF; (i) LiOH, THF-H_2O.

Scheme 9



7 37 67 68 11 1

Scheme 9; Key: (a) nBuLi, 37, THF, HMPA, then PhCOCl; (b) Na-Hg, THF-MeOH; (c) nBu_4NF, THF; (d) NaOH, MeOH-H_2O.

Lythgoe.[20] Reaction of 68 with tetra-n-butylammonium fluoride in THF removed the SEM protecting group to afford X-14547A methyl ester (11). Hydrolysis of 11 with sodium hydroxide in methanol-water at 60°C for 3h converted 11 into X-14547A in 90% yield, thereby completing the second total synthesis of this natural product.

Ho[14] has synthesized left hand half intermediates by using methodology very similar to that reported by Nicolaou. Ho's synthesis of the racemic tetrahydropyranyl left hand synthon 47 is presented in Schemes 10 and 11. Important features include the use of racemic 71, a diastereomer of Nicolaou's optically active intermediate 43, as a precursor of iodide 72 as well as of the two diastereomeric epoxides 74 and 76. Each epoxide diastereomer was used in a synthesis of racemic 47 (see Scheme 11). Conversion of 72 to the cuprate reagent 77 followed by treatment with 74 or 76 gave the adducts 78 and 81, respectively. Adduct 78 was transformed into 47 via C.7 alkoxide displacement of the C.3 tosylate in intermediate 79. This route proceeds with inversion of configuration at C.3. Adduct 81 was converted into 47 via the acid catalyzed opening of the C.7,8 epoxide by the C.3 hydroxyl group in 46 with inversion at C.7.

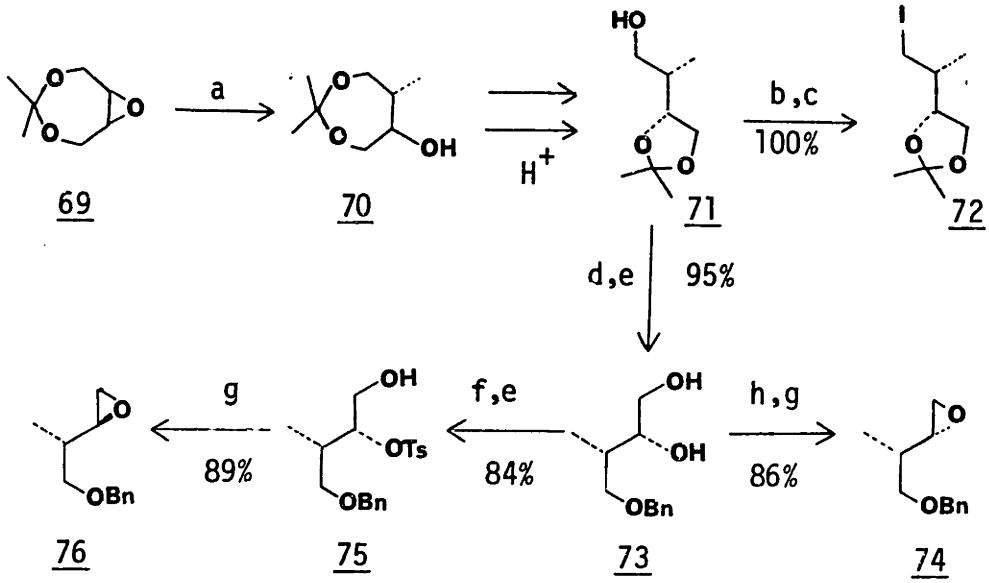
20. (a) Julia, M.; Paris, J.-M. Tetrahedron Lett. 1973, 4833.

(b) Kocienski, P.J.; Lythgoe, B.; Ruston, S. J. Chem. Soc., Perkin Trans. I 1978, 829.

(c) Kocienski, P.J.: Lythgoe, B.; Ruston, S. J. Chem. Soc., Perkin Trans. I 1978, 834.

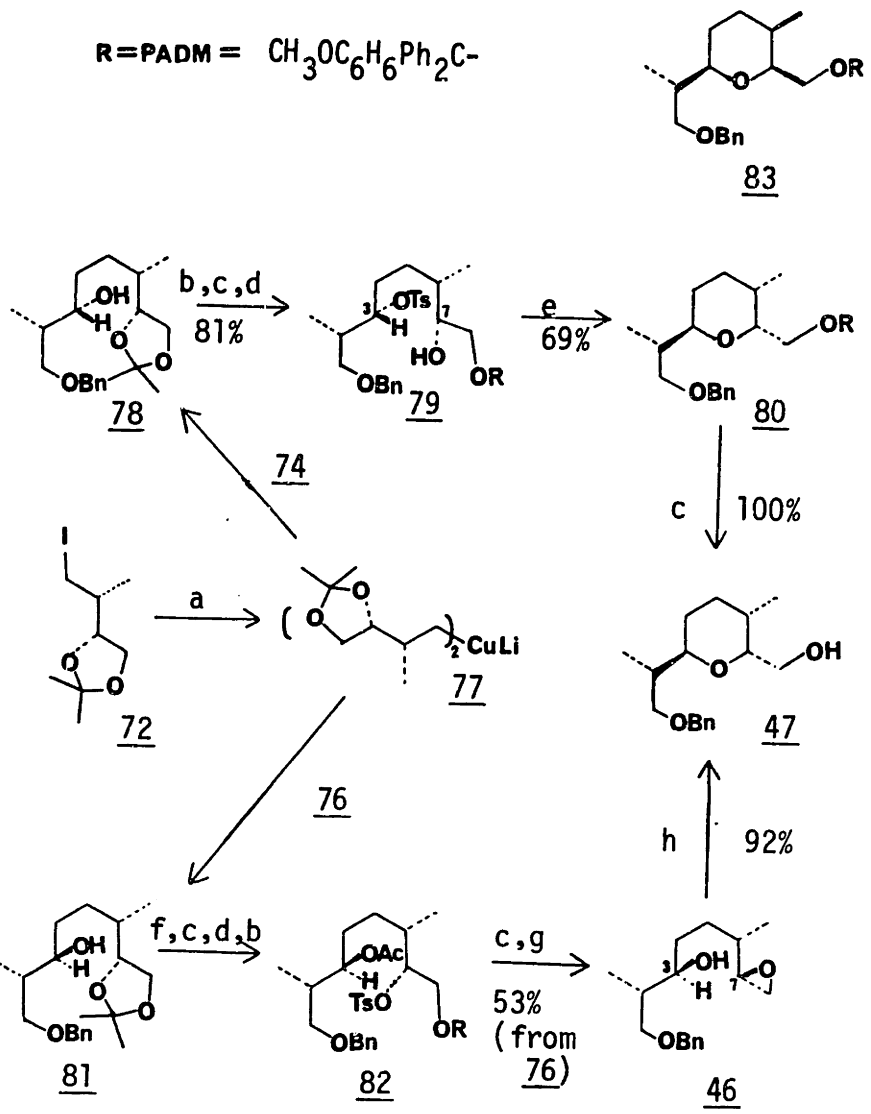
(d) Kocienski, P.J.; Lythgoe, B.; Waterhouse, I. J. Chem. Soc., Perkin Trans. I 1980, 1045.

Scheme 10



Scheme 10; Key: (a) Me_2CuLi; (b) TsCl, pyridine; (c) NaI, acetone; (d) NaH, BnBr, THF; (e) 80% aqueous HOAc; (f) p-anisyldiphenylmethyl-chloride, pyridine, 12h; then TsCl; (g) KOH, MeOH; (h) TsCl (1 equiv.), pyridine, CH_2Cl_2.

Scheme 11

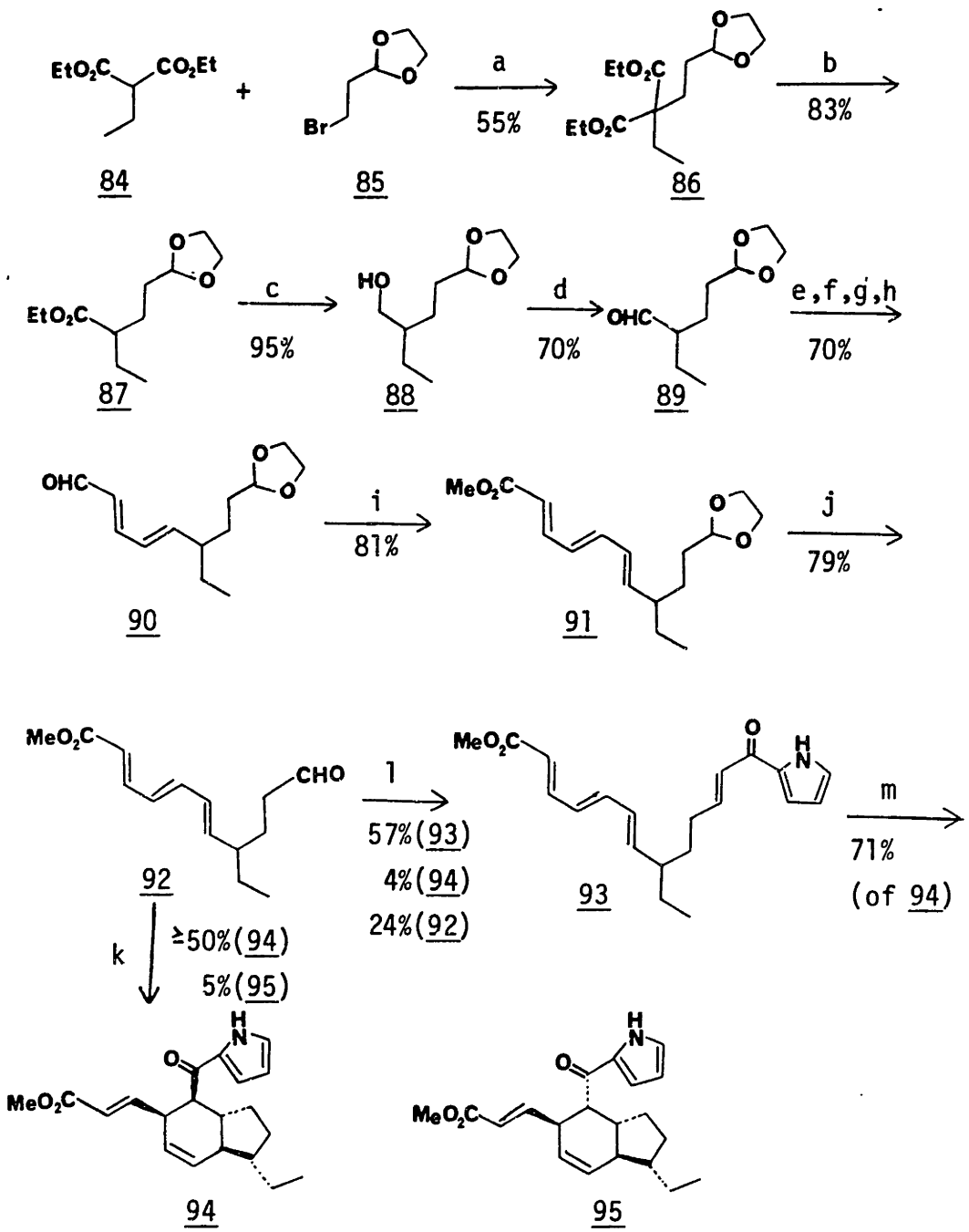


Scheme 11; Key: (a) n-BuLi, THF, -78°C; then CuI; (b) TsCl, pyridine; (c) 80% aqueous HOAc; (d) p-anisyldiphenylmethyl chloride, pyridine; (e) NaH, C_6H_6; (f) Ac_2O, pyridine; (g) KOH, MeOH; (h) HOAc.

Comparison of the two routes reveals that the sequence involving epoxide 76 (49% overall yield for conversion of 76 to 47) is more efficient than that involving 74 (39% overall yield). Both routes, however, suffer from a number of problems. Because iodide 72 and epoxides 74/76 are racemic, the coupling of 72 to the racemic epoxides leads to diastereomeric mixtures in adducts 78 and 81. These mixtures could not be separated, even by high pressure liquid chromatography (HPLC). Consequently, these diastereomeric pairs were carried through to the cyclized products. In the preparation of 47 from 74, tetrahydropyran 80 can be separated from its diastereomer 83 by column chromatography. Whereas this diastereomer problem can be avoided by use of optically pure substrates, the cuprate coupling employed is inherently inefficient since two equivalents of iodide 72 are consumed per adduct formed.

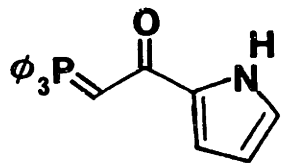
A third intramolecular Diels-Alder approach to the right hand half of X-14547A has been reported by Roush and Myers,[10] who studied the use of α, β unsaturated ketopyrrole dienophiles in their synthesis of 94 (see Scheme 12). This work serves as background to the chemistry discussed in this thesis. Diethyl malonate (84) was condensed with bromide 85 to give diester 86 which was then decarboalkoxylated to give ester 87. Reduction of 87 followed by oxidation of the resulting alcohol 88 with pyridinium dichromate (PDC) afforded aldehyde 89 in good overall yield. Condensation of 89 with the lithium anion of 1-methoxybut-1-en-3-yne followed by *in situ* lithium aluminum hydride ($LiAlH_4$) reduction of the intermediate propargyl alcohol afforded dienal 90 in 70% yield. This intermediate was then treated with [(carbomethoxy)methylene] triphenylphosphorane to give the triene

Scheme 12



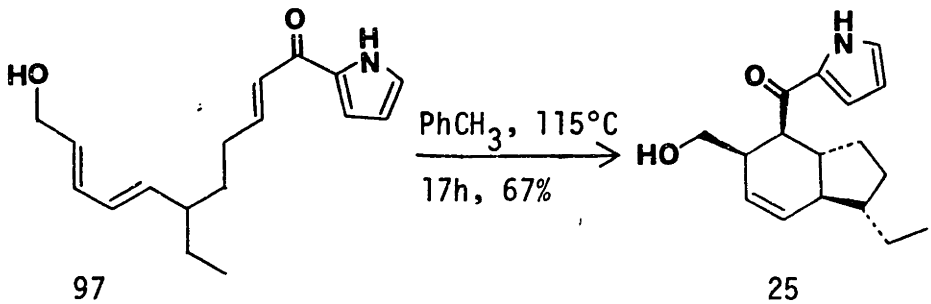
Scheme 12; Key: (a) NaOEt, EtOH; (b) LiCl, H_2O, Me_2SO; (c) $LiAlH_4$; (d) PDC, CH_2Cl_2; (e) $CH_3OCH{=}CHC{\equiv}CH$, n-BuLi, THF; (f) 89; (g) $LiAlH_4$; (h) 1N HCl; (i) $Ph_3P{=}CHCO_2Me$; (j) H_3O^+; (k) 96, $PhCH_3$, reflux, 25h; (l) 96, CH_2Cl_2, 25°C; (m) $EtAlCl_2$, CH_2Cl_2, 0°C, 1.5h.

ester 91. The acetal protecting group of this intermediate was removed by acid catalyzed hydrolysis. The resulting aldehyde 92 when treated with phosphorane 96 in CH_2Cl_2 at 23°C (4 days) afforded tetraene intermediate

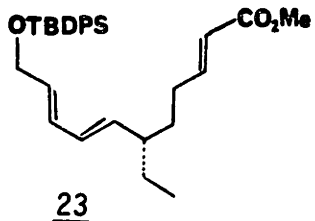


96

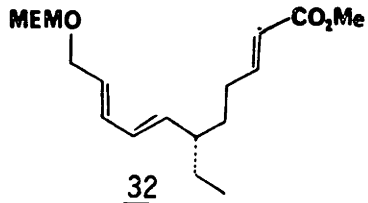
93 in 57% yield along with 4% of cycloadduct 94 and 24% of recovered 92. Tetraene 93 cyclized to give 94 in good yield (70%) and high selectivity when treated with diethylaluminum chloride (Et_2AlCl) in CH_2Cl_2 at 0°C. No other stereoisomers were isolated under these conditions. In contrast, when an inhomogeneous mixture of aldehyde 92 and phosphorane 96 in toluene were heated to reflux for 25h, a mixture of 50% of 94, 5% of acylpyrrole epimer 95, and 10% of cis fused products were obtained. Roush and Myers also demonstrated that ketopyrrole triene 97 cyclized in toluene at 115°C (17h) in good yield (67%) to give cycloadduct 25, which was previously described in the work of Nicolaou[12a] and Ley.[13a] This latter observation when compared to the cyclization conditions for 23 and 32



97 25



23



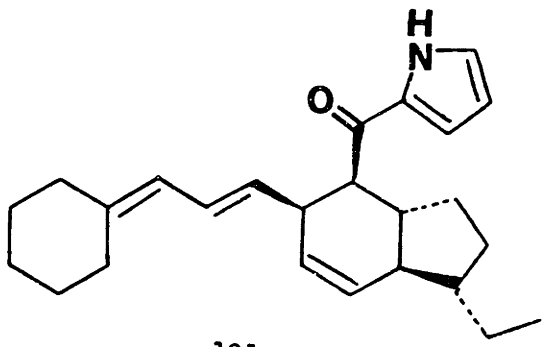
32

(toluene, 130°C, 36-70h) demonstrated the greater dienophile activating ability of a ketopyrrole group as compared to a methyl ester.

With the work of Roush and Myers completed, our study on the synthesis of X-14547A (1) via proposed biosynthetic intermediate 10 was initiated. In the following chapter, we describe studies which resulted in the synthesis of X-14547A model system 101. In Chapter 3 we describe the improvement and application of our pentaene approach to a partial synthesis of X-14547A. In this connection we also describe explorations into new chemistry useful for the construction of chiral intermediates needed in this work.

CHAPTER II

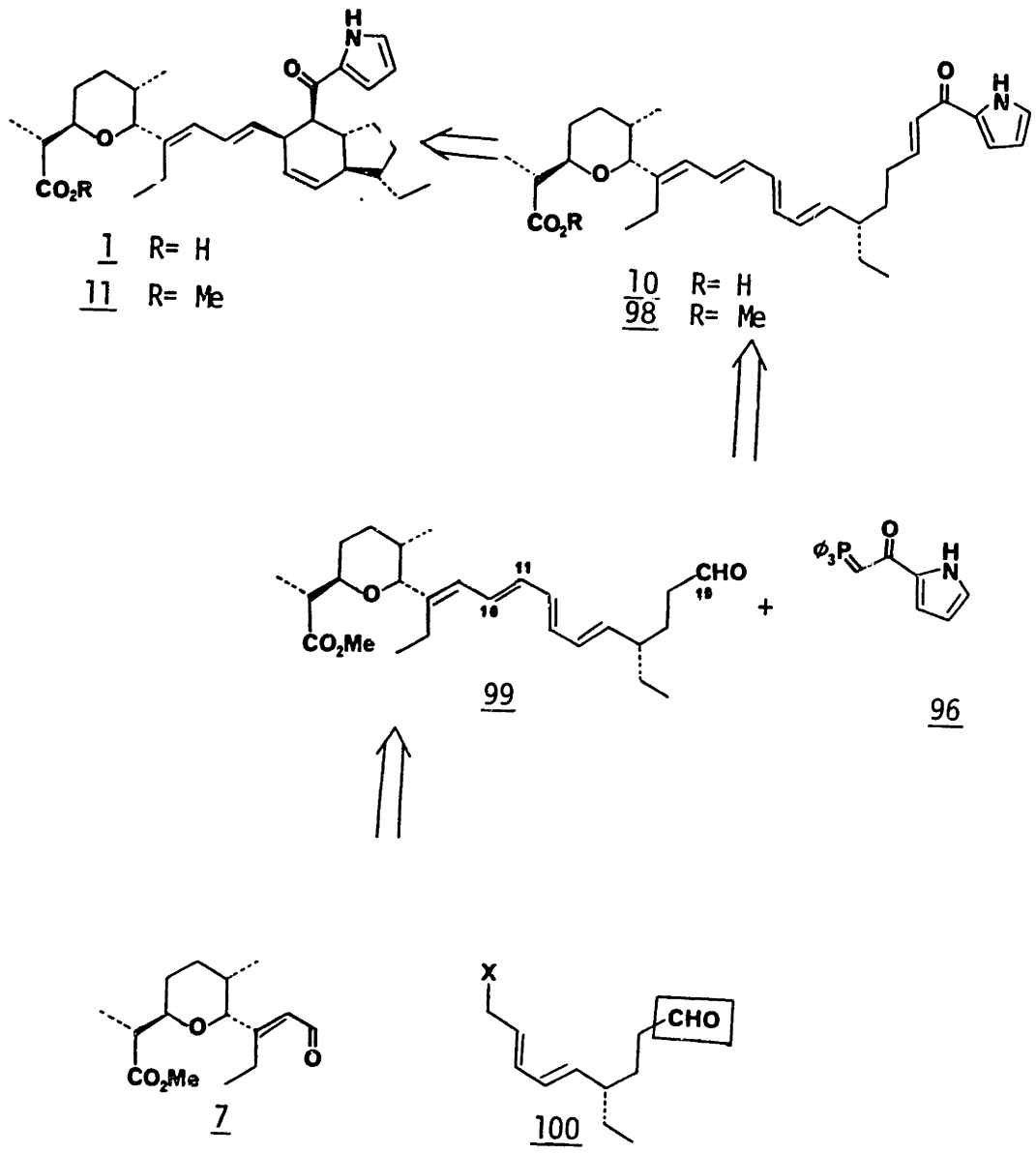
Our approach to X-14547A (1) is based on the hypothesis that the biosynthesis of the natural product may proceed via the internal cyclization of a pentaene intermediate such as 10 (Scheme 13). Not only did we imagine that 10, or the corresponding methyl ester 98, would be suitable synthetic precusors to 1, we also recognized that such intermediates could be assembled from precursors 7, 96, and 100 by a sequence in which all of the functionality of 10 (and hence 1) would be fully differentiated and mutually compatible at every stage of the synthesis. In this chapter, we describe the development of this strategy culminating in the synthesis of X-14547A model compound 101.[21] In the following chapter we apply these results towards a partial synthesis of the natural product.



101

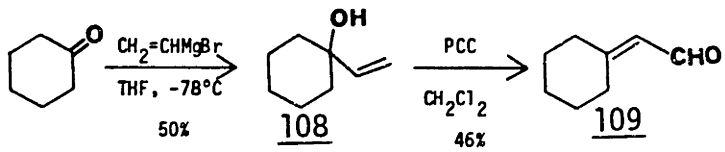
21. An account of portions of this study has been published: Roush, W.R.; Peseckis, S.M. Tetrahedron Lett. 1982, 23, 4879.

Scheme 13



The first problem addressed in the synthesis of 101 was the selection of a protecting group for the aldehydic subunit 100. In initial studies we continued working with intermediates used in Myer's synthesis of 94 (see Scheme 12, Chapter 1). Thus, aldehyde 89 was treated with the lithium anion of ethyl 4-diethylphosphonocrotonate to give unsaturated ester 102 (78-89%, see Scheme 14). Reduction of 102 with lithium aluminum hydride ($LiAlH_4$) afforded alcohol 103 (85%) which when treated with triphenylphospine-bromine complex in acetonitrile afforded the unstable diene allylic bromide 104. Exposure of 104 to triphenylphosphine in benzene afforded phosphonium salt 105 in 72% yield from 103. Treatment of 105 with n-butyllithium in THF at -78°C generated a deep red solution of the corresponding phosphorane, which condensed smoothly with aldehyde 109[22] to give tetraene 106 in 75% yield as a 3:1 mixture of (E)- and (Z)- isomers at the newly formed double bond.

22. Aldehyde 109 was prepared from cyclohexanone by treatment with vinylmagnesium bromide followed by pyridinium chlorochromate (PCC) oxidation of the intermediate allylic alcohol 108.



(a) Babler, J.H.; Coghlan, M.J. Synthetic Comm. 1976, 6, 469.

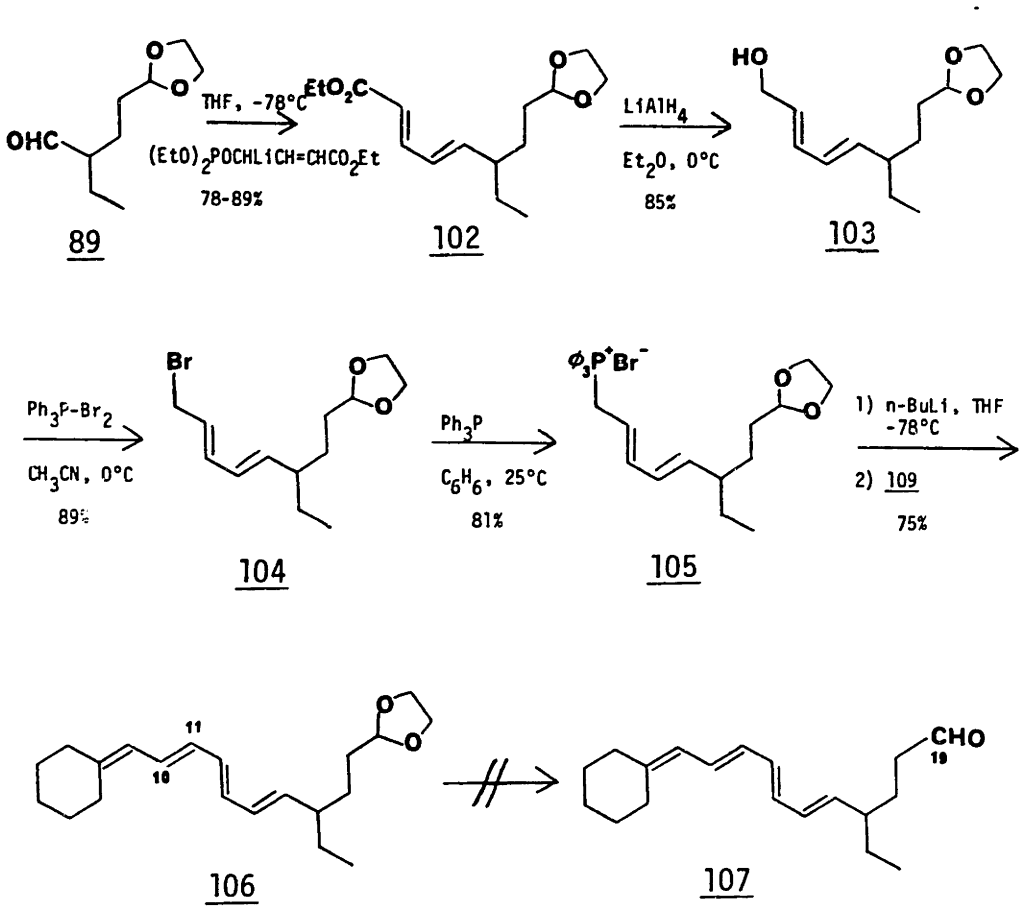
(b) Dauben, W.G.; Michno, D.M. J. Org. Chem. 1977, 42, 682.

For other syntheses of 109 see:

(c) Chaco, M.C.; Iyer, B.H. J. Org. Chem. 1960, 25, 186.

(d) Babler, J.H.; Olson, D.O. Tetrahedron Lett. 1974, 351.

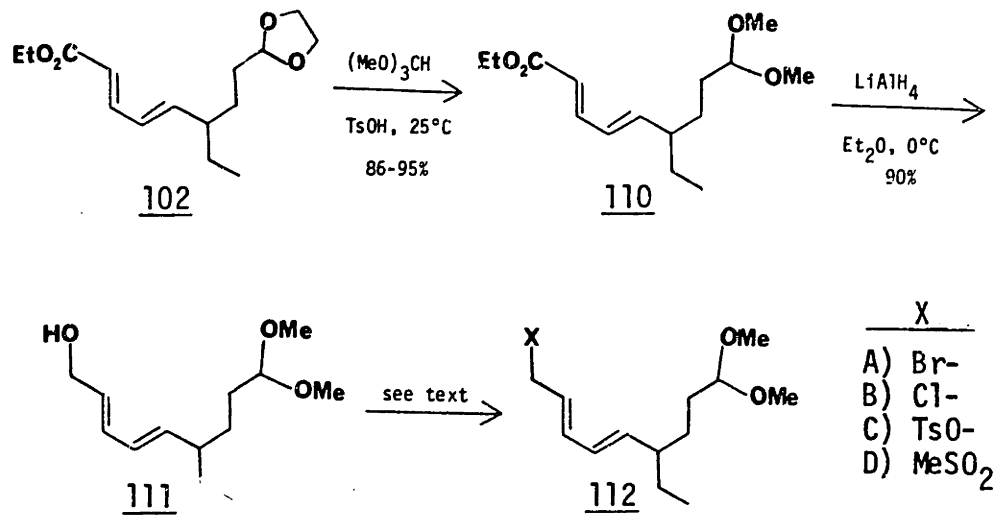
Scheme 14



With 106 in hand, we decided to explore its conversion to 107 before examining methods for increasing the stereoselectivity of the olefination-coupling step. Unfortunately, however, all attempts to remove the ethylene glycol acetal of 106 were unsuccessful. Thus, heating 106 at 95°C for 25 h with and without 2,6-di-tert-butyl-4-methylphenol (BHT, an antioxidant) in a 5.7:4:1 THF:H_2O glacial acetic acid mixture as used by Roush and Myers[10] to convert 91 into 92 (Scheme 12) resulted in a mixture of products exhibiting tetraene decomposition. Likewise, treatment of 106 with p-toluenesulfonic acid (pTsOH) and BHT (0.3 equiv. w/w) in a 4:1 acetone:

H_2O mixture[23] for 8 to 22 h gave a similar mixture of decomposition products.

Having discovered that the conditions for cyclic acetal hydrolysis were too acidic for the tetraene functionality to survive, we considered the use of more acid labile acyclic acetals. As shown below, the ethylene glycol acetal of 102 was exchanged for a dimethyl acetal in 86-89% yield. Lithium aluminum hydride reduction of 110, as before, afforded alcohol 111. Unfortunately, all attempts to convert 111 to the bromide (112A), chloride (112B), tosylate (112C), or mesylate (112D) gave unsatisfactory results. Most efforts to generate the bromide 112A by use of the triphenylphosphine-bromine complex (Ph_3P-Br_2)[24] in acetonitrile or ether (with or without s-collidine as



23. (a) Vig. O.P.; Matta, K.L.; Anand, R.; Raj, I. Indian J. Chem. 1965, 42, 841.

(b) See also the literature cited in reference 17b.

24. (a) Wiley, G.A.; Hershkowitz, R.L.; Rein, B.M. J. Am. Chem. Soc. 1964, 86, 964.

(b) Wiley, G.A.; Hershkowitz, R.L.; Rein, B.M. Tetrahedron Lett. 1964, 2509.

(c) Machinek, R.; Lüttke, W. Synthesis 1975, 4, 255.

an acid scavenger), triphenylphosphine-carbon tetrabromide complex (Ph_3P-CBr_4)[25] in acetonitrile (with or without s-collidine), or dimethylsulfide-N-bromosuccinimide complex (Me_2S-NBS)[26] in CH_2Cl_2 resulted in some loss of the dimethyl acetal or in elimination of hydrogen bromide. Attempts to reintroduce the acetal after bromination by treatment of product mixtures in methanol with excess trimethyl-orthoformate and p-TsOH resulted in diene decomposition. Experiments designed to prepare chloride 112B,[27] tosylate 112C,[28] or mesylate 112D[29] derivatives usually gave poor yields of desired products as a mixture with unreacted starting material and products of elimination reactions.

These results can be rationalized as follows. Hydrogen bromide liberated during the bromination step leading to 112A, or during reaction workup, catalyzed hydrolysis of the acid labile dimethoxy acetal. On the other hand, the bases used in the formation of the chloride, tosylate, and mesylate derivatives assisted in the elimination of hydrogen chloride, toluenesulfonic acid or methanesulfonic acid from

25. Axelrod, E.H.; Milne, G.M.; von Tamelen, E.E. J. Am. Chem. Soc. 1970, 92, 2139.

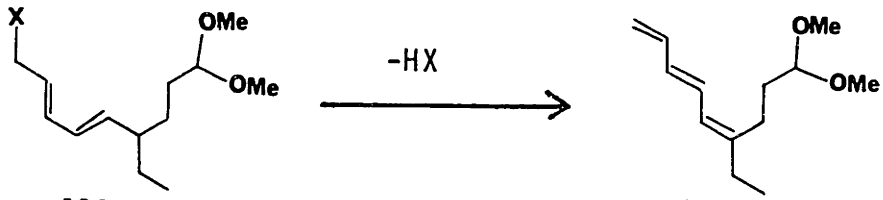
26. Corey, E.J.; Kim, C.U.; Takeda, M. Tetrahedron Lett. 1972, 42, 4339.

27. n-BuLi then TsCl and LiCl in Et_2O-HMPT was tried:
Collington, E.W.; Meyers, A.I. J. Org. Chem. 1971, 36, 3044; Tetrahedron 1971, 27, 5979.

28. TsCl, pyridine, CH_2Cl_2; tosyl-imidazole, CH_2Cl_2; n-BuLi then TsCl were investigated.

29. $MeSO_2Cl$, Et_3N, CH_2Cl_2; $MeSO_2Cl$, LiBr, s-collidine, DMF were tried.
(a) Stork, G.; Grieco, P.A.; Gregson, M. Tetrahedron Lett. 1969, 1393.
(b) Stork, G.; Grieco, P.A.; Gregson, M. Org. Syn. 1974, 54, 68.

the reaction products to give, for example, a stable triene system 113. This elimination also occurs very readily if bromides such as 104 are chromatographed over Florisil or alumina supports. Thus, regardless of the methods employed, diene allylic systems containing a dimethyl acetal 112 could not be formed cleanly and efficiently.



112 b-d 113

After determination that acetals were inappropriate protecting groups in intermediates leading to 107, we turned to the possibility that a terminal olefin could serve as a latent aldehyde precursor. This reasoning proved justified when pentaene 119, synthesized initially as described in Scheme 15, was selectively hydroborated by treatment with 9-BBN[30] (THF, 0°C, 3h; workup with NaOH, H_2O_2, 25°C, 3h) to give alcohol 120 in 80% yield. No products of hydroboration of the internal conjugated olefins were detected. Swern oxidation of 120

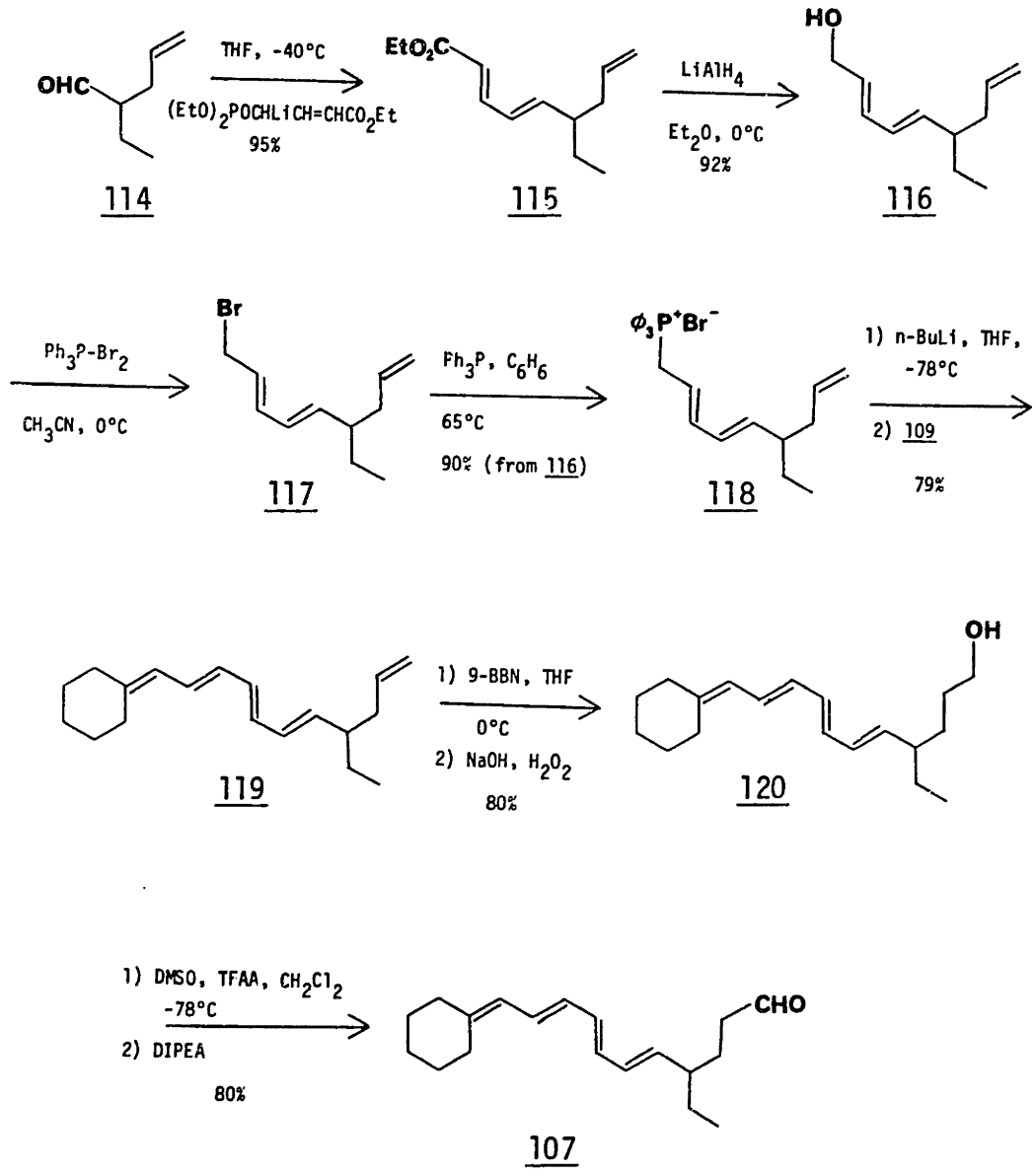
30. For general review , see:
(a) Brown, H.C. "Organic Synthesis Via Boranes" John Wiley and Sons, Inc., New York, NY, 1975.

For specific information, see:
(b) Brown, H.C.; Knights, E.F.; Scouten, C.G. J. Am. Chem. Soc. 1974, 96, 7765.

(c) Brown, H.C.; Krishnamurthy, S.; Yoon, N.M. J. Org. Chem. 1977, 42, 2702.

(d) Brown, H.C.; Liotta, R.; Kramer, G.W. J. Org. Chem. 1978, 43, 1058.

Scheme 15


OHC
THF, -40°C
(EtO)2POCHLiCH=CHCO2Et
95%
EtO2C
LiAlH4
Et2O, 0°C
92%
HO
114
115
116
Ph3P-Br2
CH3CN, 0°C
Br
Ph3P, C6H6
65°C
90% (from 116)
φ3P+Br-
1) n-BuLi, THF,
-78°C
2) 109
79%
117
118
1) 9-BBN, THF
0°C
2) NaOH, H2O2
80%
OH
119
120
1) DMSO, TFAA, CH2Cl2
-78°C
2) DIPEA
80%
CHO
107

(DMSO, TFAA; then diisopropylethylamine)[31] gave the desired aldehyde 107 in 80% yield. It is interesting to note that chromium based reagents such as PDC[32] or PCC[33] were less useful for this conversion since they promoted tetraene decomposition, presumably due to the one electron transfer characteristics of the chromium reagents.[34] The oxidant prepared from oxalyl chloride and DMSO[35] also effected rapid tetraene decomposition, in this case possibly a consequence of HCl liberated in the oxidation process.

Satisfied that a terminal olefin constituted one means of masking the C.19 aldehyde functionality,[36] our attention next focussed upon the construction of the all (E)- tetraene system. This problem is important since (E)- (Z)- olefin isomers at C.8,9 and C.10,11 produced in the coupling sequence would be carried through to products of the intra-

31. (a) Omura, K.; Sharma, A.K.; Swern, D. J. Org. Chem. 1976, 41, 957.

    (b) Huang, S.L.; Omura, K.; Swern, D. Synthesis 1978, 297.

    (c) Omura, K.; Swern, D. Tetrahedron 1978, 34, 1651.

    (d) Mancuso, A.J.; Brownfain, D.S.; Swern, D. J. Org. Chem. 1979, 44, 4148.

    (e) Pfitzner, K.E.; Moffat, J.G. J. Am. Chem. Soc. 1965, 87, 5670.

32. Corey, E.J.; Schmidt, G. Tetrahedron Lett. 1979, 399.

33. (a) Corey, E.J.; Suggs, J.W. Tetrahedron Lett. 1975, 2647.

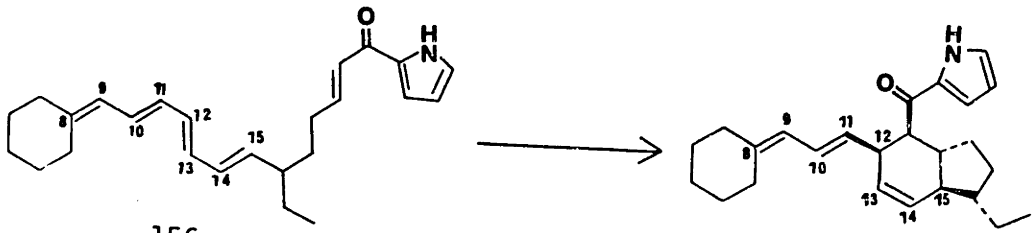
    (b) Corey, E.J.; Boger, D.C. Tetrahedron Lett. 1978, 2461, and references cited therein.

34. House, H.O. "Modern Synthetic Reactions" 2nd ed., W.A. Benjamin, Inc., Reading, MA, 1972; p. 261, and references cited therein.

35. Mancuso, A.J.; Huang, S.L.; Swern, D. J. Org. Chem. 1978, 43, 2480.

36. In Chapter 3 we describe the synthesis of an alternative series of tetraene precursors in which C.19 is introduced in the alcohol oxidation state. Such species were not prepared for use in this model study.

molecular Diels-Alder (IDA) reaction. Olefin mixtures at the C.12,13 and C.14,15 are less critical, however, since the (Z)- isomers will not cyclize in the Diels-Alder step. They are, nonetheless, undesirable since they will contribute to diminished overall yields of cyclization products.



156 101

Our initial work on the synthesis of (E,E,E)- 119 concentrated on the coupling of diene system 117 with aldehyde 109 (see Scheme 15). From the outset we imagined that this coupling could be accomplished by using Wittig,[37] Horner,[38] or phosphonate anion chemistry.[39]

37. (a) Harrison, I.T.; Lythgoe, B. J. Chem. Soc. 1958, 843.

(b) Truseheit, E.; Eiter, K. Justus Liebigs Ann. Chem. 1962, 658, 65.

(c) Barlow, L.; Pattenden, G. J. Chem. Soc., Perkin Trans. I 1976, 1029.

(d) Hendrick, C.A. Tetrahedron 1977, 33, 1845.

(e) Henrick, C.A.; Anderson, R.J. J. Am. Chem. Soc. 1975, 97, 4327.

(f) Näf, F.; Decorzant, R.; Thommen, W.; Willholm, B.; Ohloff, O. Helv. Chim. Acta 1975, 58, 1016.

(g) Schwieter, U.; Planta, C. v.; Rüegg, R.; Isler, O. Helv. Chim. Acta 1962, 45, 541.

Stereochemical studies of olefination reactions involving allylic and diene allylic phosphoranes,[37a,b,c,f] allylic and diene allylic phosphine oxides,[38a-c] and diene allylic phosphonate anions[39b] have shown that these reactions proceed with retention of stereochemistry of the original double bonds. These reactions differ, however, with respect to the stereochemical control realized in the newly formed olefin. Allylic phosphoranes generally afford (E)- (Z)- mixtures with a slight preference for the (E)-olefin.[37] On the other hand, allylic phosphonate anions -although restricted in scope -generally show high selectivity for the (E)-olefin.[39] In addition, several literature reports were available which suggested that allylic phosphine oxides would also be highly (E)- selective in olefination sequences.[38] Although this literature survey suggested that allylic phosphoranes (e.g. 118) would be only slightly

38. (a) Lythgoe, B.; Moran, T.A.; Namdudiry, M.E.N.; Ruston, S.; Tideswell, J.; Wright, P.W. Tetrahedron Lett. 1975, 3863; J. Chem. Soc., Perkin Trans. I 1976, 2386.

(b) Clough, J.M.; Pattendon, G. Tetrahedron Lett. 1978, 4159.

(c) Clough, J.M.; Pattendon, G. Tetrahedron 1981, 37, 3911.

(d) Buss, A.D.; Warren, S. J. Chem. Soc., Chem. Commun. 1981, 100.

(e) Schlosser, M.; Tuong, H.B. Chimia 1976, 30, 197.

(f) Savage, M.P.; Trippett, S. J. Chem. Soc. C. 1966, 1842.

(g) Vedejs, E.; Campbell, J.B.Jr.; Gadwood, R.C.; Rodgers, J.D.; Spear, K.L.; Watanabe, Y. J. Org. Chem. 1982, 47, 1534.

(h) Baggiolin, E.G. J. Am. Chem. Soc. 1982, 104, 2945.

39. (a) Review: Wadsworth, W.S., Jr. Organic Reactions 1977, 25, 73.

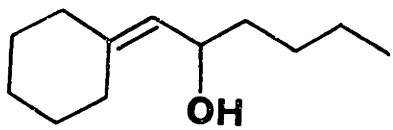
(b) Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W.J. J. Am. Chem. Soc. 1978, 100, 7775.

(c) Piechucki, C. Synthesis 1976, 187.

(d) Corey, E.J.; Cane, D.E. J. Org. Chem. 1969, 34, 3053.

selective in the preparation of (E,E,E)- 119, we were optimistic that use of modified experimental conditions (e.g. Schlosser-type procedures)[40] would lead to the development of a highly selective olefination sequence. Consequently, we examined the coupling of 109 and 118 in some detail (see Table I).

Under optimal conditions [118, n-BuLi, THF, -78°C, LiBr (4 equiv.); addition of 109, -78°C with warming to -25°C, quench with MeOH], a 78:22 mixture of (E,E,E)- 119 and its 9,10-(Z)- olefin isomer was obtained in 86% yield (Table I, entry 2). All attempts to improve this ratio by using conditions known to increase (E)- selectivity with alkylphosphoranes (Table I, entries 3,10),[37e] or conditions under which equilibration of the intermediate betaines should occur (entries 8,9), were unsuccessful. It is interesting to note that under the conditions of entry 10, butyllithium adduct 121 was isolated in 90% yield. This result suggested that the rate of addition of the dieneallylic phosphorane to 109 is slow, and that the rate of elimination of the betaine



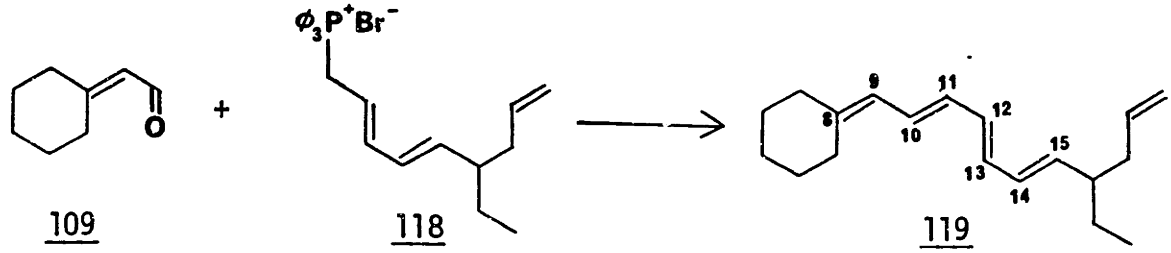
121

40. (a) For a review see reference 37e, and literature cited therein.

See also:
(b) Schlosser, M.; Christmann, K.F. Angew. Chem., Int.Ed.Eng. 1966, 5, 126.

(c) Schlosser, M.; Christmann, K.F. Justus Liebigs Ann. Chem. 1967, 708, 1.

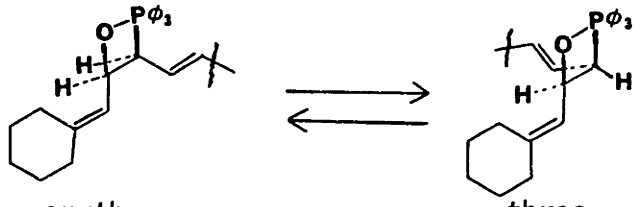
Table I



109 118 119

Entry	Conditions	Yield	Product Ratio C.10,11 E:Z
1	a) 118, 1.05 equiv. n-BuLi, THF, -78°C b) add 109, -78°to 0°C	70-79%	67:33
2	a) 118, 4 equiv. LiBr, THF, -78°C b) n-BuLi c) 109, -78°to 0°C	86%	78:22
3	a) 118, 8 equiv. LiBr, THF, -78°C; then n-BuLi, -50°C b) 109, 20 min, -50°C c) LiOMe/MeOH then NaOMe/MeOH	17%	75:25
4	a) 118, n-BuLi, Et_2O, 0 to -78°C b) 109, -78°to 25°C	15%	46:54
5	a) 118, n-BuLi, Et_2O, 0 to -78°C b) 109, 45 min. c) -78°C, MeOH	45%	30:70
6	a) 118, n-BuLi, tBuOH, THF, -30°C b) -30°C, 109	48%	58:42
7	a) 118, n-BuLi, MeOH, THF, -78°C b) 109, -78°C, 4h c) -78°C to 25°C	54%	66:44
8	a) 118, 109, THF, -78°C, 1.4 eqiv., KOtBu/ 0.12 N in tBuOH, 1h b) -78°C to 25°C	73%	64:46
9	a) 118, 109, THF, -78°C 1.4 equiv., NaOMe/ 0.2 N in MeOH, 1h b) -78°C to 25°C	24%	66:44
10	a) 118, n-BuLi, THF, -78°C b) 109, -78°C, 30 min c) n-BuLi, -78°C d) KOtBu/tBuOH, -78° to 0°C	11%	58:42

intermediate to olefinic products is fast at -78°C. That a maximum (E):(Z) ratio of 78:22 was obtained, which is comparable to the maximum selectivity realized with other allylic phosphoranes,[37] may be the consequence of the smaller steric size of alkenyl substituents as compared with alkyl groups.[17a] That is, this maximum product ratio may in fact reflect the equilibrium distribution of the threo and erythro betaines, respectively, assuming that the two adducts decompose to olefins at comparable rates.



erythro
122

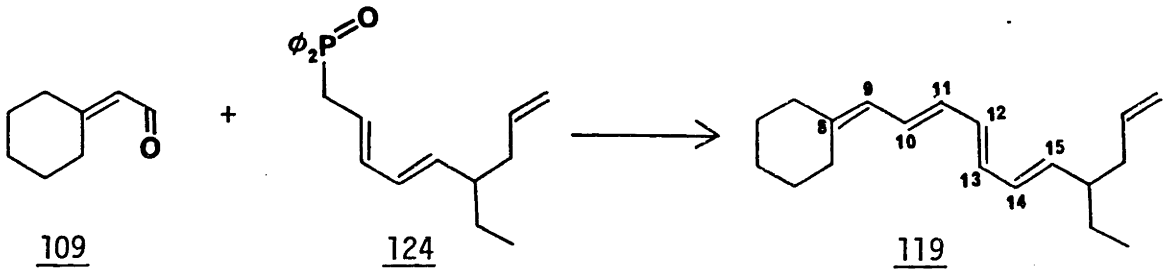
threo
123

During the course of these studies we briefly explored the possibility that these olefin mixtures could be isomerized to (E,E,E)- 119. Unfortunately, all attempts to increase the percentage of (E,E,E)- 119 in these mixtures by iodine catalyzed isomerization[41] were unsuccessful, presumably a consequence of the sensitivity of 119 to tetraene decomposition.

Improved product ratios (up to 95:5) were obtained in the coupling sequence (see Table II) by using phosphine oxide 124, prepared as shown in Scheme 16, as the nucleophilic component.

41. Schneider, D.F.; Garbers, C.F. J. Chem. Soc. C 1964, 2465.

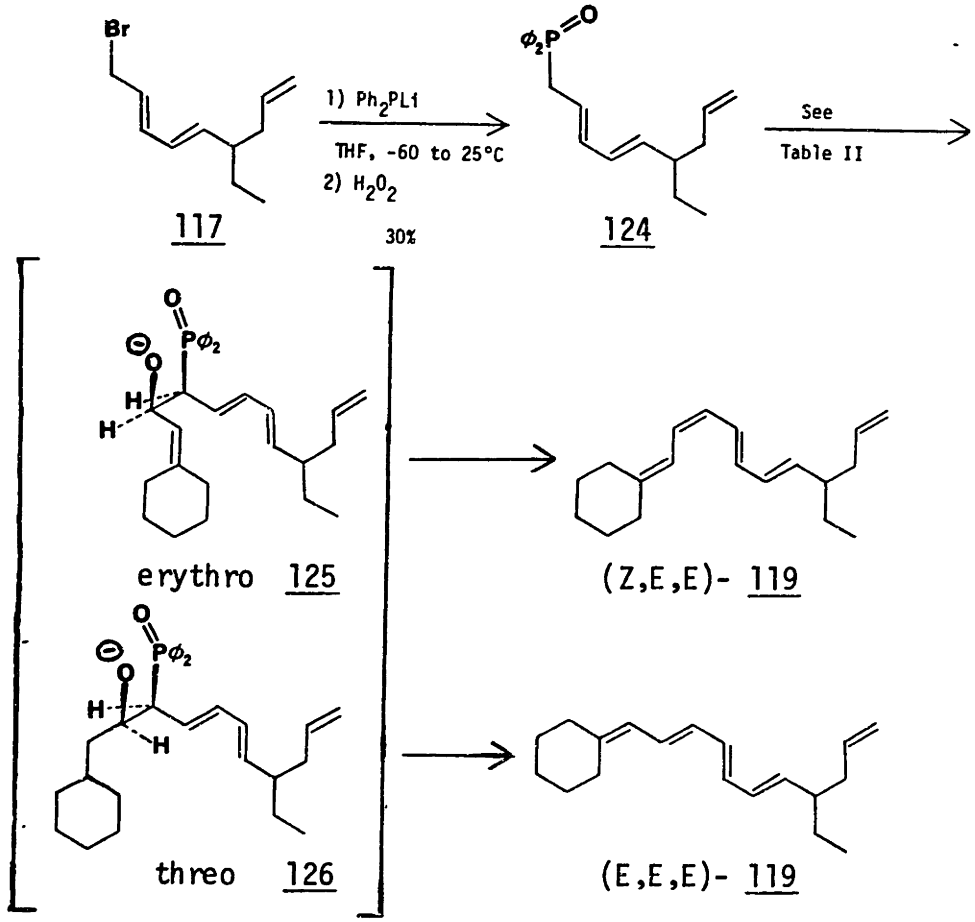
Table II



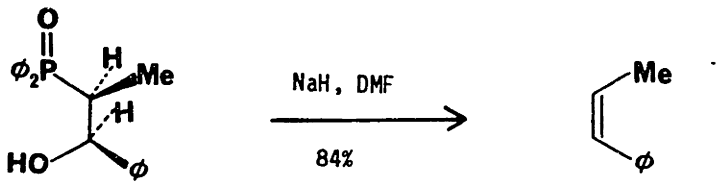
109 + 124 → 119

Entry	Conditions	Yield	Product Ratio C.10,11 E:Z
1	a) 124, n-BuLi, THF, -78°C b) 109, -78°C	56%	83:17
2	a) 124, n-BuLi, LiBr, THF, -78°C b) 109	Poor	91:9
3	a) 124, NaH, DME, 25 to -40°C b) 109, -40 to 25°C	37%	95:5
4	124, 109, KOtBu/tBuOH, THF, -78 to 0°C	18%	90:10
5	a) 124, 2.5 equiv. LiOMe, THF, -78°C b) 109	0	---
6	a) 124, n-BuLi, Et_2O, -78°C b) 109, -78 to 25°C	0	---

Scheme 16



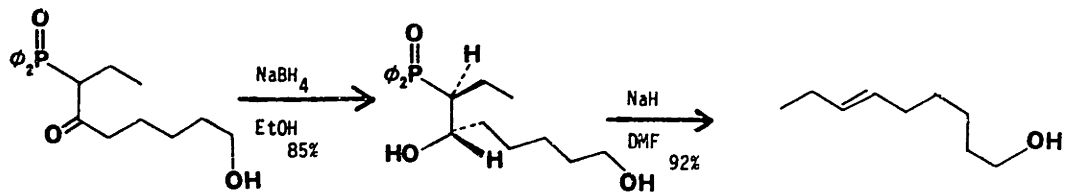
This increase in selectivity, however, was accompanied with substantially diminished product yields (18-56%). These observations are consistent with the selective decomposition[38b,c,d] of the threo betaine adduct 126 to (E,E,E)- 119 in the presence of the more difficultly decomposed erythro adduct 125. Although we have not isolated any intermediates in the conversion of 124 to 119, other workers have isolated and characterized intermediates in the Wittig-Horner reactions. Thus, Buss and Warren[38d] isolated erythro adduct 127, confirmed the assignment of erythro configuration by X-ray crystallographic analysis, and demonstrated that it eliminated exclusively to (Z)- olefin 128. They



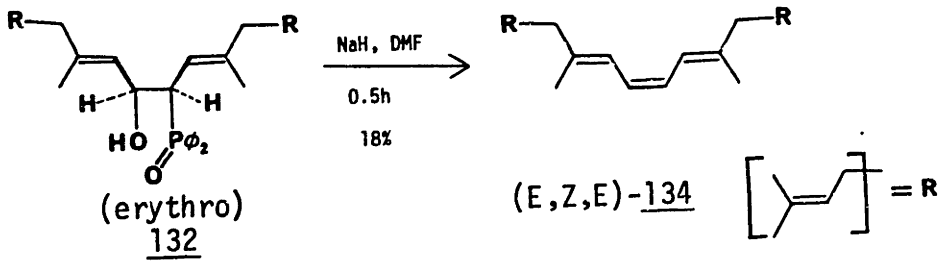
(erythro)
127

128

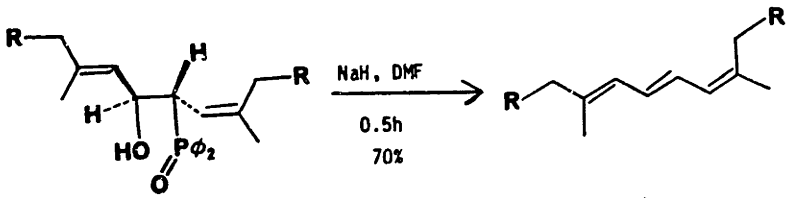
also prepared threo adduct 130 by reduction of ketophosphine oxide 129. This isomer eliminated cleanly to give pure (E)- olefin 131 when treated with sodium hydride in DMF. Clough and Pattendon[38c] prepared and separated a mixture of erythro and threo adducts, 132 and 133.



129 (threo) 130 131



(erythro)
132

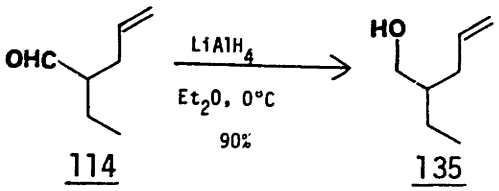


(threo)
133

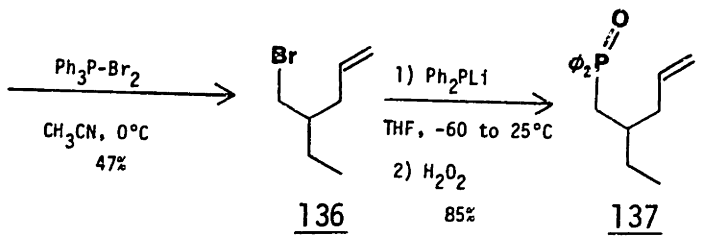
(E,E,E)-134

They established that these isomers eliminated very selectively to the (Z)- and (E)- olefins, respectively, and also determined that elimination of 132 to (E,Z,E)- 134 occurred at a much slower rate than that of 133 to (E,E,E)- 134. Evidently, steric deceleration occurs in the decomposition of the erythro intermediates as the alkyl groups move closer together along the reaction coordinate leading to the product (Z)- olefin. These steric interactions do not develop as the threo intermediates decompose to (E)- olefins, so a lower activation energy is required for the decomposition of adducts in this series.

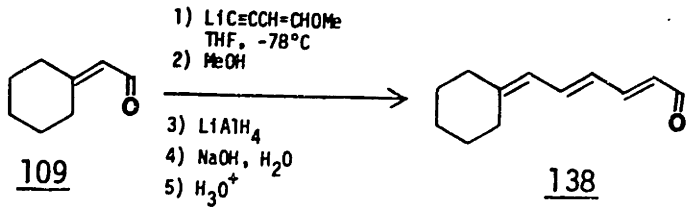
While the above studies were in progress we were also exploring routes to 119 via coupling at the C.14,15 olefinic linkage. Diphenylphosphine oxide 137 was prepared as shown from aldehyde 114 and coupled with triene aldehyde 138 to give a mixture of adducts 139



114 135

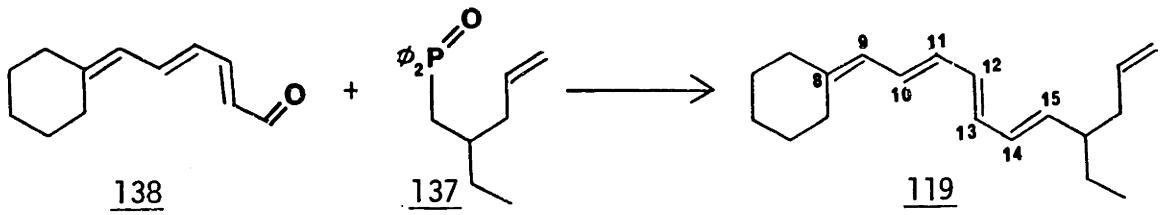


136 137



109 138

Table III



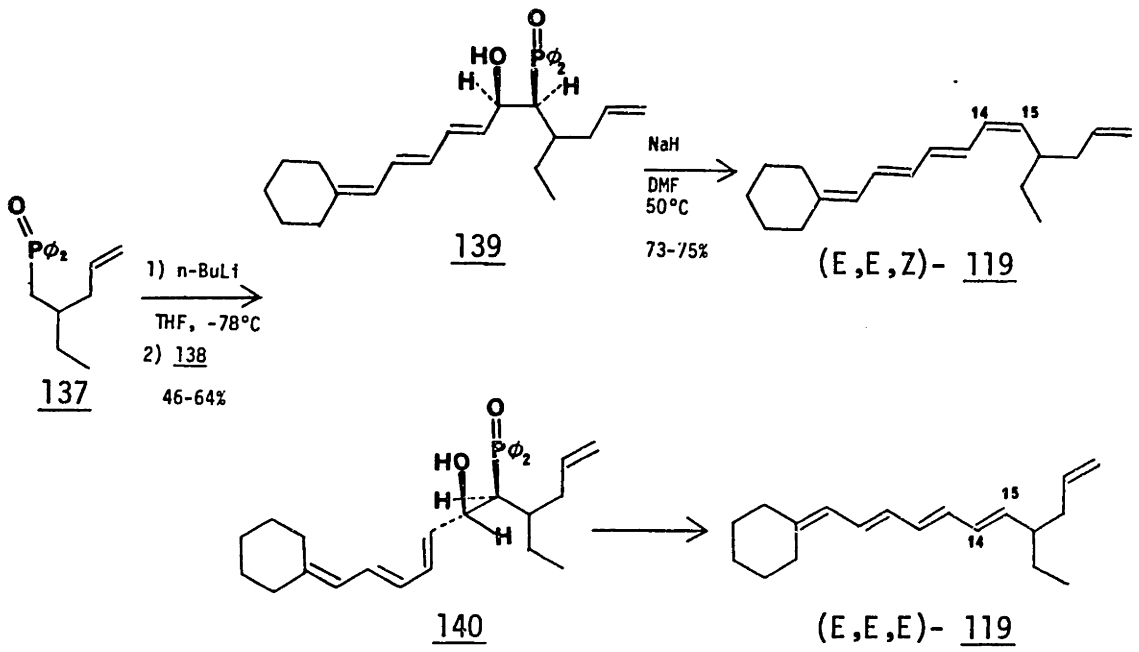
138 137 119

Entry	Conditions	Yield[a] 139/140	Yield[a] 119[b]	Product[c] Ratio (E:Z)
1	a) 137, n-BuLi, THF, -78°C b) 138, Isolate adducts 139/140 c) NaH, DMF, 50°C	56%	75%	44:56
2	a) 137, n-BuLi, THF, -78°C b) 138, -78°C, c) n-BuLi, -78°C; Isolate adducts d) NaH, DMF, 50°C	64%	73%	17:83
3	a) 139/140, n-BuLi, THF, -78°C b) MeOH, -78 to 25°C; Isolate adducts c) NaH, DMF, 50°C	67%	74%	30:70
4	a) 137, n-BuLi, THF, -78°C b) 138, -60 to 25°C c) LiH, THF, 60°C, 5h	---	18%	90:10

(a) All yields are for chromatographically purified samples.

(b) Yield of 119 from adducts 139/140.

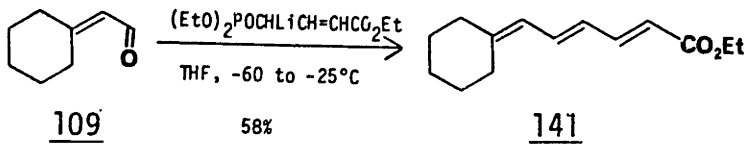
(c) Ratio of olefin isomers at the C.14-C.15 double bond.



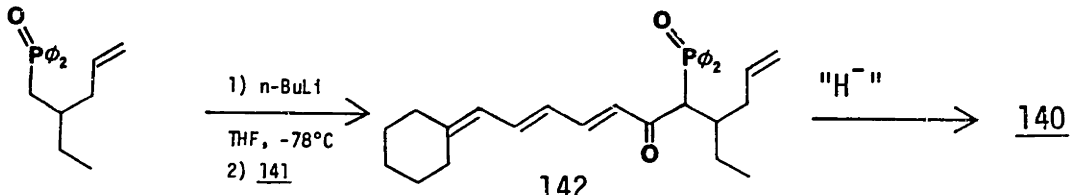
and 140 in 46-64% yield. These inseparable adducts were converted to pentaene 119 in 73-75% yield when treated with sodium hydride in DMF at 50°C. Again, however, mixtures of olefin isomers were produced. Thus, coupling of the lithium anion of 137 with aldehyde 138 followed by treatment of the adducts 139-140 with NaH as described above afforded a 44:56 mixture of (E,E,E)- 119 and (E,E,Z)- 119 (Table III, entry 1). All attempts to improve this ratio by using Schlosser-type modifications (entry 2) or equilibrating (139⇄140) conditions (entry 3) before the adduct decomposition step led to increased selectivity for (E,E,Z)-119. Only when lithium hydride was used in the elimination step was good selectivity (90%) for (E,E,E)-119 realized. The overall yield in this case, however, was only 18% (entry 4). This result was again interpreted in terms of selective decomposition of the threo adduct 140.

Buss and Warren[38d] have reported that reduction of saturated

α-keto diphenylphosphine oxides with sodium borohydride in ethanol is a highly selective route to threo β-hydroxyphosphine oxides (see 129 to 130), which can be converted to (E)- olefins in a subsequent elimination step. Thus, adduct 142 was prepared from 137 and triene ester 141 in 58% yield. Unfortunately, ketone 142 was recovered unchanged when subjected to sodium borohydride in ethanol, while



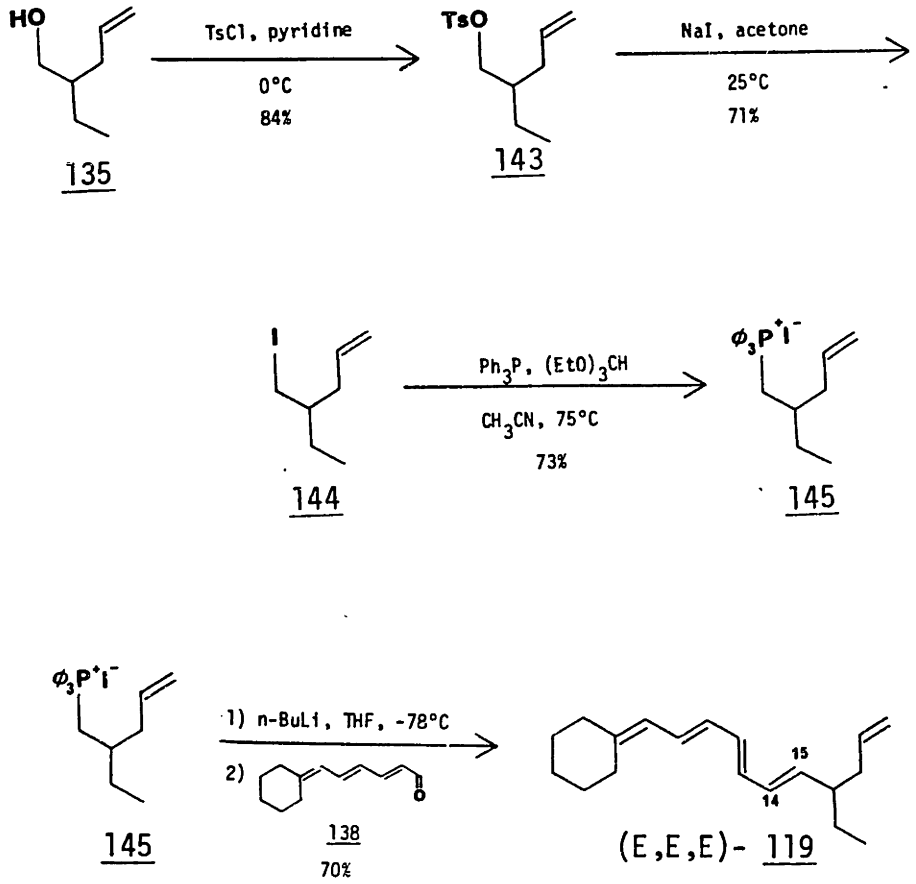
109 58% 141



137 142 140

treatment of 142 with lithium aluminum hydride in ether, with or without peroxide workup (in the event of phosphine oxide reduction), or diisobutylaluminum hydride (DIBAL) in hexane gave complex product mixtures from which no 119 was obtained after the subsequent elimination step (NaH, DMF, 50°C). Overreduction of 142 under these conditions was suspected.

Attempts to prepare 119 by using phosphonium salt 145 also were disappointing. Reagent 145 was initially difficult to prepare since heating of bromide 136 with triphenylphosphine resulted in a phosphonium salt in which hydrogen bromide had added to the terminal olefin. Use of iodide 144 and triethylorthoformate[12b] as an acid scavenger, however, led to an uneventful formation of the desired



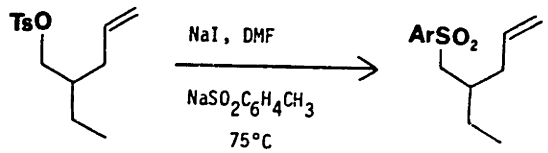
phosphonium salt 145. Standard coupling of 145 and 138 (145 in THF at -78°C treated with n-BuLi followed by addition of 138) afforded a 1:4 mixture of (E,E,E)- 119 and (E,E,Z)- 119, respectively, in 60-70% yield. An attempt to improve the (E)- selectivity of this conversion by use of Schlosser-type or equilibrating conditions (e.g. n-BuLi or tBuOH/KOtBu treatment of the intermediate betaine) led to an insignificant increase in the relative amount of (E,E,E)- 119, at the expense of decreased overall yield (36-39%).[42] These results led us to suspect that

42. Predominant formation of (Z)- olefination products is well known for non-stabilized primary phosphoroanylids. See:
(a) Gosney, I.; Rowley, A.G. In "Organophosphorous Reagents in Organic Synthesis"; Cadogan, J.I.G. Ed.; Academic Press: New York, 1979; p 17, and references cited therein.

(b) Schlosser, M. In "Topics in Stereochemistry"; Allinger, N.L.; Eliel, E.L. Eds.; John Wiley & Sons: New York, 1970; Vol. 5, p 1.

betaine decomposition in this case was fast even at -78°C, and prompted us to lower the temperature even further. Indeed, the phosphorane prepared from 145 in Trap solvent (4:1:1 THF-Et_2O-pentane) at -120°C was treated with aldehyde 138 in THF to form the betaine, which was then treated at this temperature with an additional equivalent of n-butyllithium. The mixture was quenched with methanol and warmed to 23°C, whereupon a 19:1 mixture of (E,E,Z)-119 and the desired (E,E,E)- isomer was obtained (30% yield)! This method, quite clearly, was unsuited for use in a synthesis of (E,E,E)- 119.

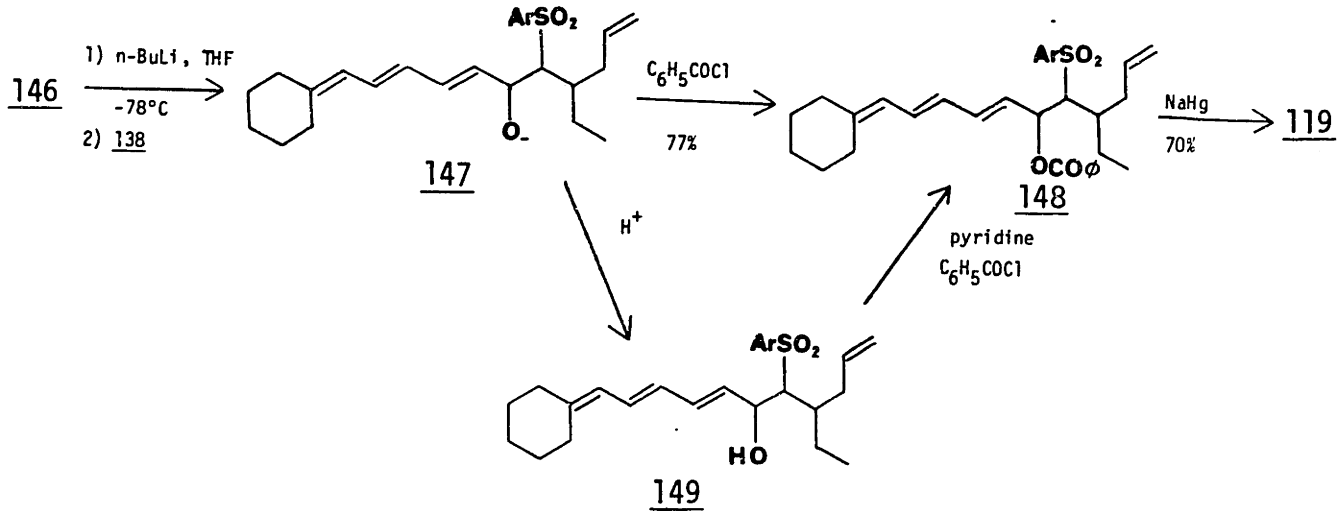
Our first successful synthesis of (E,E,E)- 119 was realized by adaptation of methodology investigated by Lythgoe and coworkers for synthesis of olefins from β-benzoyloxy sulfones.[20b-d,43] Thus, a THF solution of the lithium anion of sulfone 146 was treated at -78°C with



143 88% 146

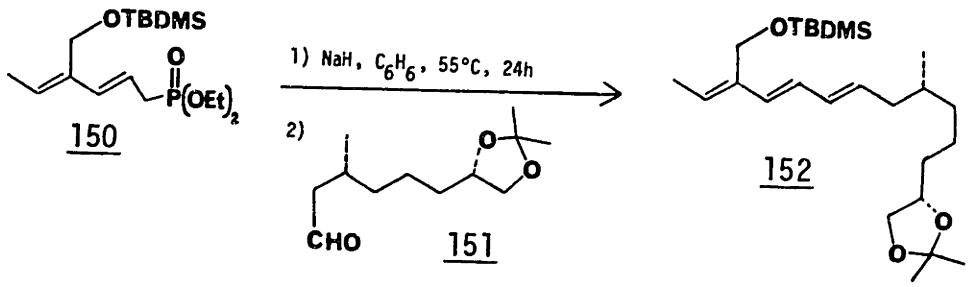
triene aldehyde 138. The resulting alkoxide 147 was then quenched with benzoyl chloride to give adduct 148 in 70-77% yield. Treatment of adduct 148 with 5% sodium amalgam in a 3:1 THF-MeOH at -20°C gave a 70% yield of 119 as a 91:9 mixture of (E)- and (Z)- olefin isomers at the newly formed double bond. Efforts to optimize the yield of this sequence both by isolation of sulfone alcohol adduct 149 and then careful benzoylation,

43. β - hydroxysulfoximes can also be reductively eliminated to olefins by using Al-Hg;
Johnson, C.R.; Kirchoff, R.A. J. Am. Chem. Soc. 1979, 101, 3062.

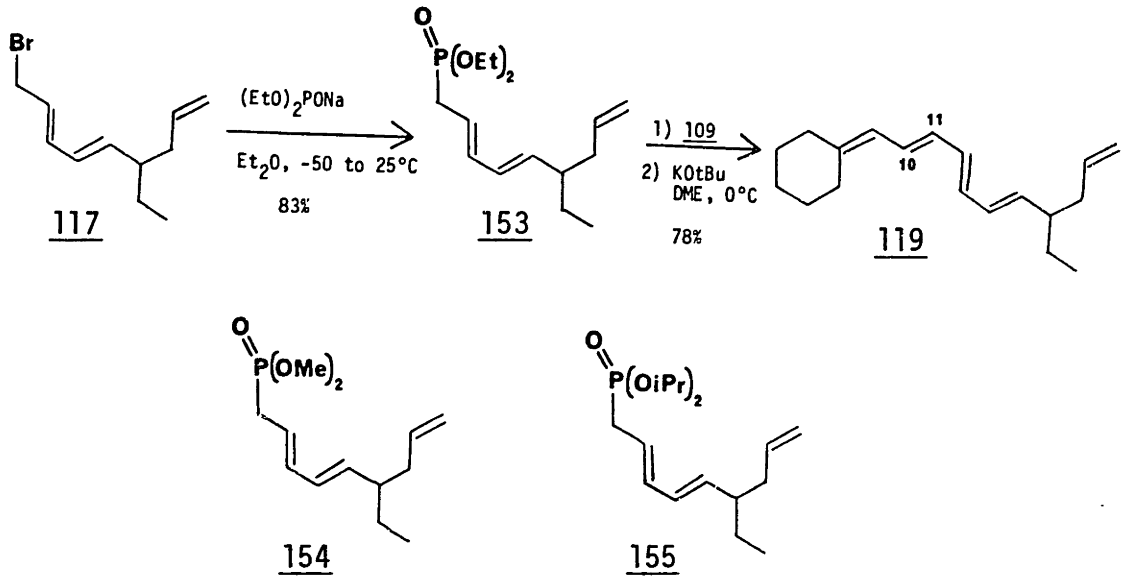


or by modification of the elimination conditions gave no noticeable improvements. Although this procedure provided a selective method for constructing (E,E,E)- 119 in 49% overall yield from sulfone 146, application of this method to the eventual synthesis of 1 would require more manipulations of the left hand component (i.e. would be less convergent) than routes involving coupling at the C.10,11 olefin. We thus returned to the unsolved problem of the coupling of aldehyde 109 with diene allylic anion equivalents.

In Stork's synthesis of cytochalasin B,[39b] diene phosphonate 150 was coupled (NaH, C_6H_6, 55°C, 24h then 151) with aldehyde 151



to give intermediate 152 in 50% overall yield. We thus began an examination of the utility of diene allylic phosphonates for the synthesis of (E,E,E)- 119. Diethyl phosphonate 153, synthesized from bromide 117 and the sodium salt of diethylphosphite via Michaelis-Becker reaction,[44] was allowed to react with unsaturated aldehyde 109 under the conditions cited by Stork. The desired pentaene 119 was not observed, however. Additional experiments were performed by using dimethylphosphonate 154, which was prepared in good yield (78%) by



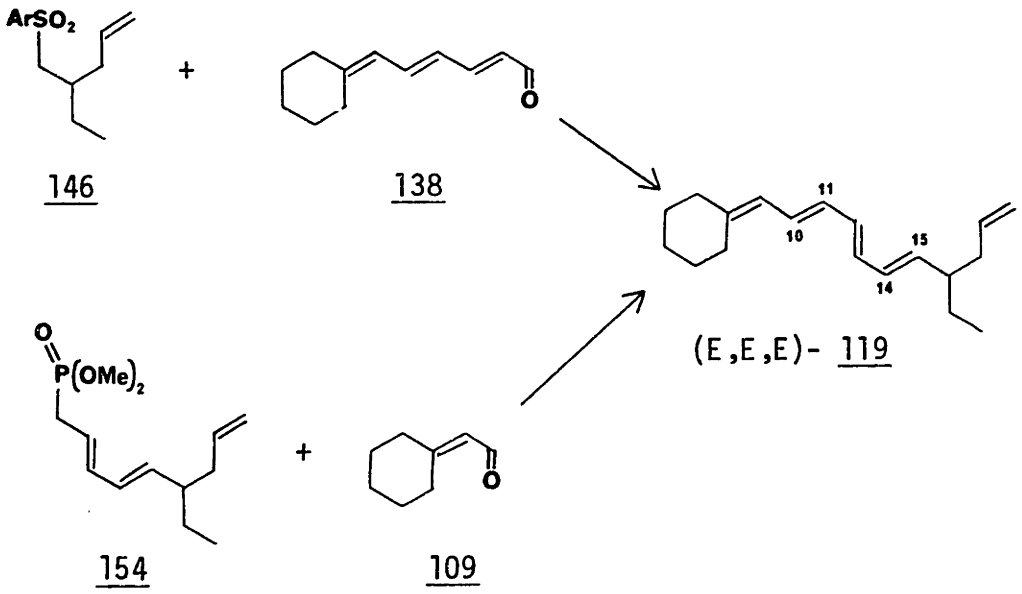
treatment of 117 with trimethylphosphite at 120°C (Arbusov reaction). Treatment of 154 with lithium diisopropylamide (LDA) at -78°C followed by addition at -40°C of aldehyde 109 with subsequent warming to 25°C gave poor yields (23%) of 119 as a 80:20 mixture of (E,E,E)- 119 and its C.10,11 (Z)- olefin isomer. Optimum conditions were achieved when a

44. (a) Sassa, K. in E. Müller, ed., Methoden der Organischen Chemie (Houben-Weyl), Vol 12, Part 1, Georg Thieme Verlag, Stuttgart, Germany, 1963, p 446.

(b) De Roos, A.M.; Toet, H.J. Rec. Trav. Chim. Pays-Bas. 1959, 78, 59.

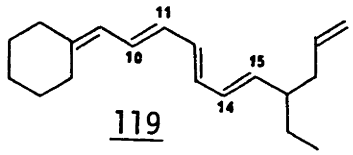
mixture of phosphonate 154 and aldehyde 109 in DME was added to a solution of potassium tert-butoxide in DME at 0°C. Under these conditions, a 95% yield of 119 was obtained as a 19:1 (E)- to (Z)- olefin isomer ratio at C.10,11. Use of bulkier phosphonate ligands (e.g. diethyl phosphonate 153 or diisopropyl phosphonate 155) gave lower yields of 119 (78-85%) with no noticable improvement in (E)- to (Z)- selectivity.[45]

The assignment of stereoselectivity to the various isomers produced in these studies was facilitated by detailed high field ^1H NMR analysis of samples purified by reverse phase HPLC (Waters μ-Bondapak C-18 column, 4:1 CH_3CN-H_2O, 3 recycles), and by comparison of samples prepared by couplings at different olefinic linkages. For example, the major products prepared via the sulfone (146 + 138) and phosphonate routes (154 + 109), which were identical, must be (E,E,E)- 119 since 138 and



45. Improvement of (E)- olefin selectivity with greater bulk in the phosphonate unit would be expected. This phenomenum will be discussed further in Chapter III.

154, respectively, possess (E)- configurations at each of the disubstituted double bonds. Examination of olefin mixtures before and after purification indicated that no change in isomer ratios occurred during chromatography. Isomer ratios in the product mixtures were determined by integration of the characteristic ^1H NMR signals summarized below (these assignments were confirmed by double irradiation experiments).



119

Isomer of 119	H_{10} (δ)	H_{15} (δ)
(E,E,E)	6.45 (m)	5.47 (dd,J=14.3,8.3 Hz)
(E,E,Z)	6.45 (m)	5.14 (t,J=10.7 Hz)
(Z,E,E)	6.63 (t,J=11.0 Hz)	5.47 (dd,J=14.3,8.3 Hz)

It is interesting to note that the UV spectra of the 119 isomers were not useful in determining the olefin geometries. The bathochromic shifts predicted for the LC- purified (Z)- isomers were not observed. Similar results with a series of trienes were observed by Ohloff, et al.[46]

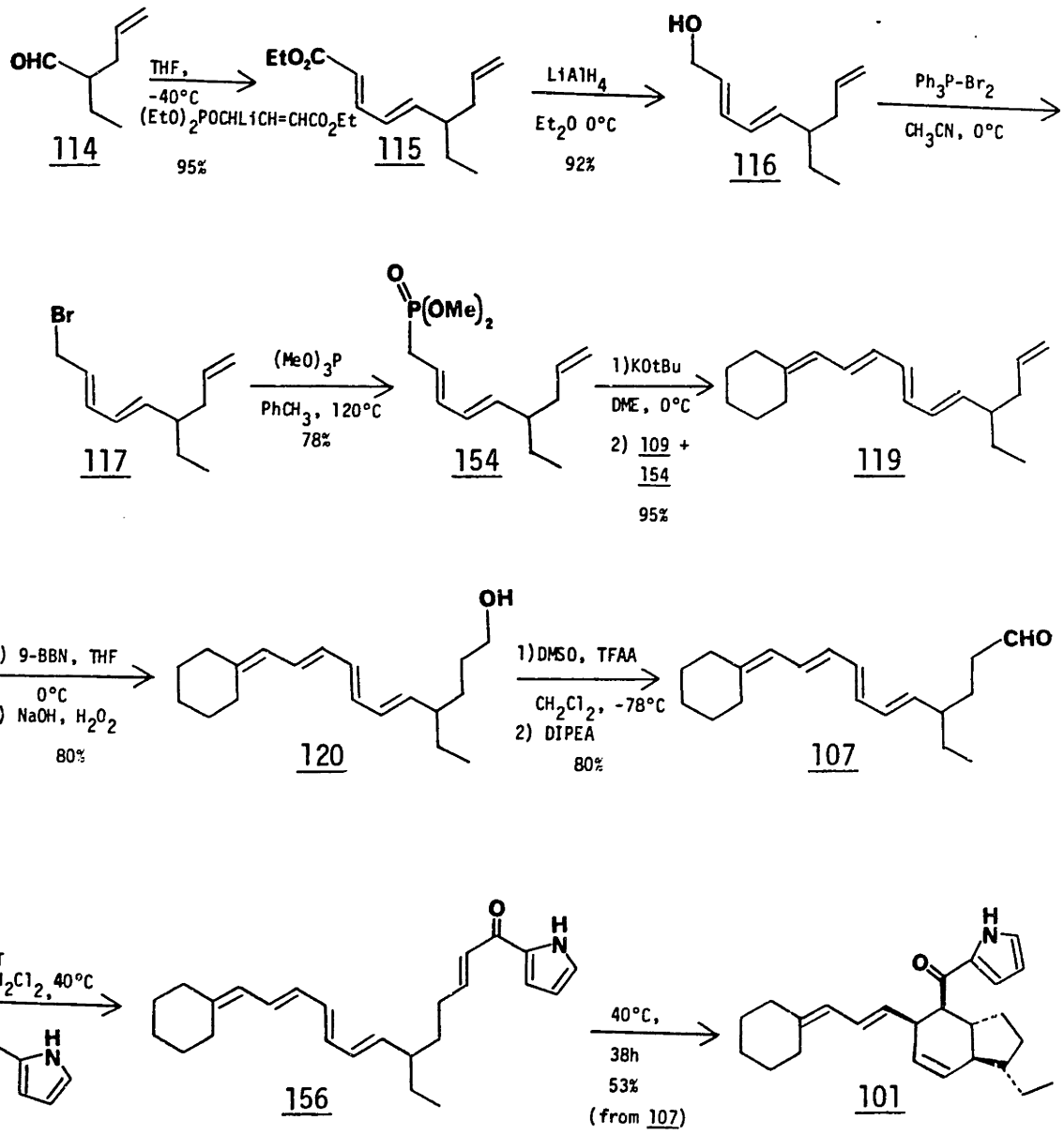
The use of diene phosphonate 154 for preparation of 119 satisfied all of our criteria for eventual use in a synthesis of X-14547A. With this efficient and selective method in hand, we turned to completion of the synthesis of X-14547A model compound 101. The optimized sequence is summarized below (Scheme 17).

Treatment of aldehyde 114 with the lithium anion of ethyl 4-diethylphosphonocrotonate in THF at -40°C with warming to 25°C afforded diene ester 115 in 95% yield. Reduction of 115 ($LiAlH_4$, Et_2O, 0°C, 92%) afforded

46. (a) See references 37f and 42.

(b) For tetraene UV data, see:
Ziegenbein, W. Chem. Ber. 1965, 98, 1427.

Scheme 17

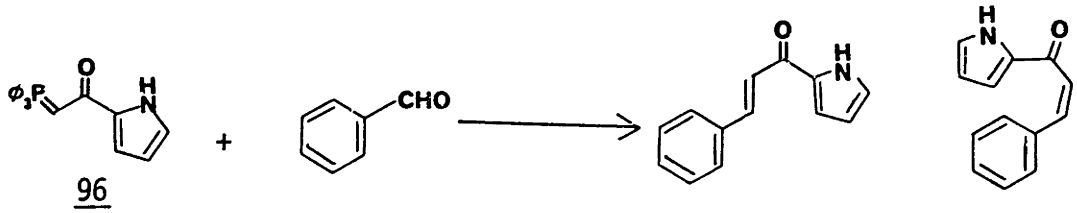

OHC
THF, -40°C
(EtO)2POCHLiCH=CHCO2Et
95%
EtO2C
114
115
LiAlH4
Et2O 0°C
92%
HO
116
Ph3P-Br2
CH3CN, 0°C
Br
117
(MeO)3P
PhCH3, 120°C
78%
O
P(OMe)2
154
1)KOtBu
DME, 0°C
2) 109 + 154
95%
119
1) 9-BBN, THF
0°C
2) NaOH, H2O2
80%
OH
120
1)DMSO, TFAA
CH2Cl2, -78°C
2) DIPEA
80%
CHO
107
BHT
MeOH, CH2Cl2, 40°C
O
Φ3P
H
N
96
156
40°C,
38h
53%
(from 107)
101

alcohol 116, bromination (Ph_3P-Br_2, CH_3CN, 0°C) of which provided the expected bromide 117 in excellent yield. The latter compound was then treated with trimethylphosphite in hot toluene (120°C) to give phosphonate 154 in 78% yield from 117. A mixture of 154 (1.0 equiv.) and aldehyde 109 (1.0 equiv.) in DME was added dropwise to a solution of KOtBu (2.0 equiv.) in DME at 0°C to give pentaene 119 in 95% yield as a 95:5 mixture of isomers at the newly formed double bond. Due to the sensitive nature of the tetraene functionality of 119 towards radical induced polymerization reactions, a small amount of BHT was added during all subsequent reactions and manipulations. All tetraene intermediates were purified by column chromatography over ether-prewashed neutral alumina under nitrogen (significantly lower yields were obtained when silica gel was used). The sensitive nature of these intermediates also required that the following reaction sequence be performed as rapidly as possible after tetraene construction in order to minimize material loss due to decomposition reactions. Hydroboration of 119 with 9-BBN in THF at 0°C (alkaline H_2O_2 workup) afforded alcohol 120 (80% yield after chromatography) which was oxidized to aldehyde 107 (80% yield) by using the Swern reagent previously described.

The stage was now set for completion of the synthesis of model compound 101 by condensation of aldehyde 107 with ylid 96 followed by cyclization of pentaene 156. Myers, however, had noted the extreme insolubility of 96 in a number of organic solvents, which had presented problems in the efficient preparation of his cyclization substrate 93 (see Scheme 12, Chapter I).[10] Since we wished to prepare and isolate pentaene 156, which we suspected would cyclize under very mild conditions,

we searched for a solvent in which 96 would be soluble. Surprisingly, the reagent dissolves readily in a 1:2 methanol-methylene chloride solvent mixture at 40°C to give a homogeneous solution (0.1M) but not in either solvent alone.

This solvent mixture was selected by screening the reagent's solubility in a variety of solvents (DMSO, DMF, pyridine, acetonitrile, acetone, methanol, formamide, ether, ethyl acetate) and its reactivity in these solvents with benzaldehyde. Unfortunately, protic solvents such as methanol which gave the fastest rate of reaction (complete by



96 + → 157 : 158

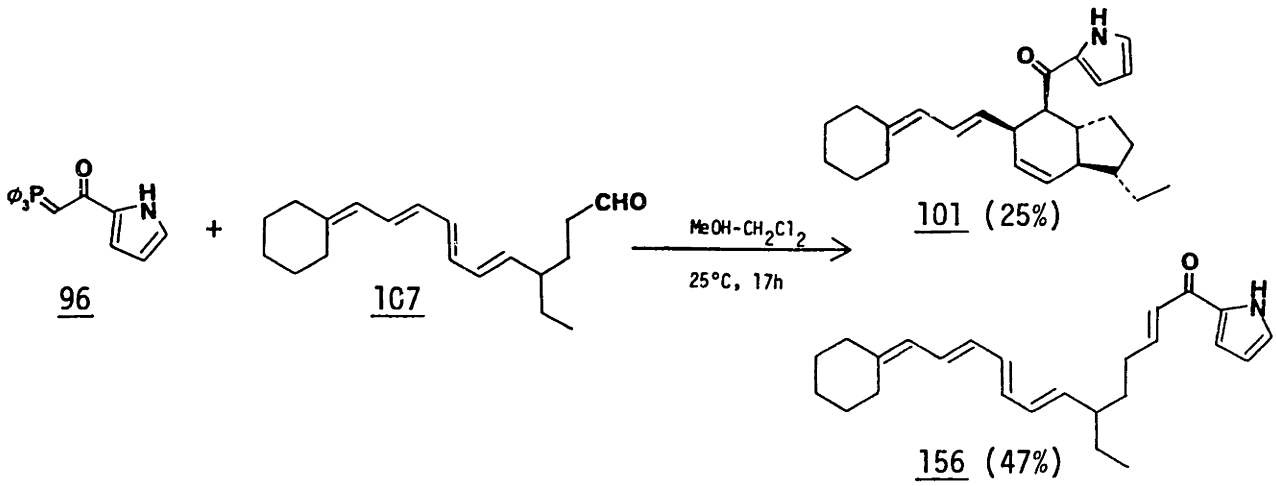
MeOH	60°C,12h,66%	82	:	18
DMSO	60°C,17h,84%	97	:	3

12h, 60°C) afforded greater amounts of (Z)- olefin 158 than observed with polar aprotic solvents (DMSO, formamide).[47] For example, 96 with benzaldehyde in methanol at 60°C for 17h afforded a 82:18 mixture of 157:158 in 66% overall yield while use of DMSO afforded a 97:3 ratio in 84% overall yield.

Treatment of 107 with phosphorane 96 in a 2:1 CH_2Cl_2-MeOH solvent mixture (39h, 40°C) afforded X-14547A model compound 101 directly in 53% yield together with 17% of a mixture of cis fused products. Alternatively, the Wittig reaction of soluble 96 (CH_2Cl_2-MeOH) with

47. No reaction appeared to take place in acetonitrile, acetone, ether, or ethyl acetate in the course of 36 h at 25°C, presumably due to the extreme insolubility of 96 in these solvents. As will be seen in Chapter III, 1,2-dichloroethane was also found to be a suitable solvent for use of 96.

107 at 25°C for 17h afforded 47% of pentaene 156 together with 25% of cycloadducts and 10% of recovered 107. The longer reaction times and higher

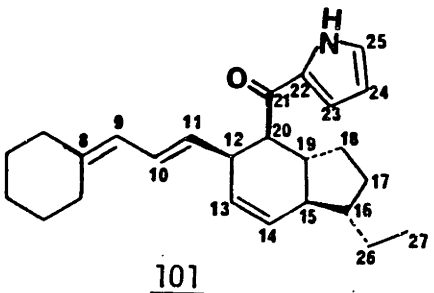


reaction temperature cited in Scheme 17 were used to insure complete reaction of 107 and complete cyclization of 156. Unfortunately, however, attempts to suppress the formation of the cis fused byproducts by use of Lewis acids ($EtAlCl_2$, CH_2Cl_2, 0°C; $MgCl_2$ or $CaCl_2$ in aqueous methanol) in the cyclization step using purified pentaene 156 proved unsuccessful.

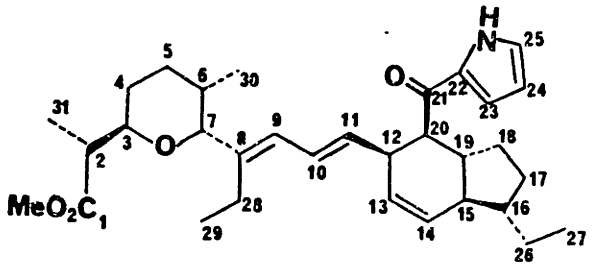
Only one trans fused cycloadduct was isolated from this Diels-Alder reaction. The stereochemistry of this compound, 101, was assigned by comparison of its ^1H and ^{13}C NMR data to that of X-14547A methyl ester 11 and the perhydroindene fragments 25 and 94 synthesized in these laboratories by Myers.[10] As seen in Tables IV and V, comparison of the ^1H and ^{13}C NMR data for 101 and 11 revealed many similarities. Characteristic of 101 is the diastereoselectivity of the thermal cyclization of 156 that results in the formation of only one trans fused cycloadduct, which, therefore, appears to parallel the simpler cases previously reported.[10,12a,13a]

It is noteworthy that cyclization of 156 to 101 occurs to the extent of 25% in 17h at 25°C. This is probably the consequence of the combined activating influence of the ketopyrrole and diene substituents.

Table IV



101

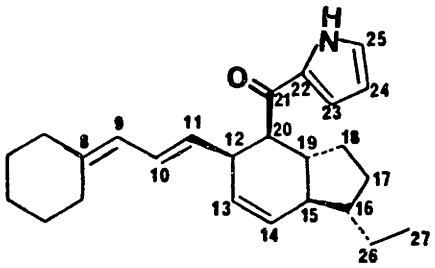


11

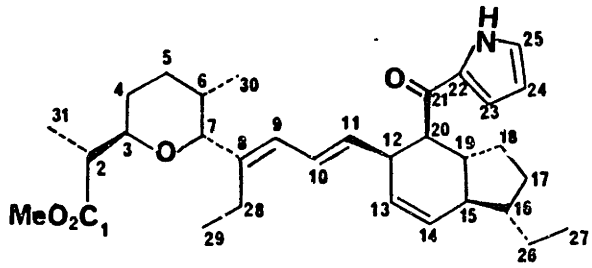
Summary of ^{1}H NMR (δ) data for 101 and 11

H	101	11
N-H	9.33 (s)	9.68 (s)
H.23,24,25 (pyrrole)	7.00 (m)	7.02 (m)
	6.92 (m)	6.89 (m)
	6.29 (m)	6.28 (m)
	5.93-6.03 (m, 2H)	5.72-5.88 (m, 2H)
H.9	5.65 (d, J= 10.4 Hz)	5.98 (d, J= 9.8 Hz)
	5.51 (dt, J= 9.9, 2.8 Hz)	5.52 (dt, J= 9.8, 3.0 Hz)
H.11	5.40 (dd, J= 8.3, 7.2 Hz)	5.42 (dd, J= 13.7, 8.7 Hz)
H.12;H.20	3.41 (m, 2H)	3.40 (m, 2H)
H.27	0.94 (t, J= 7.2 Hz, 3H)	0.94 (t, J= 7.3 Hz, 3H)

Table V



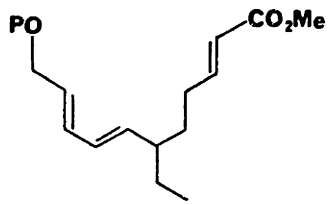
101



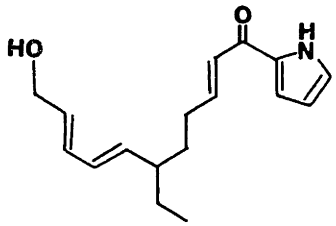
11

^{13}C NMR (δ) data for 101 and 11

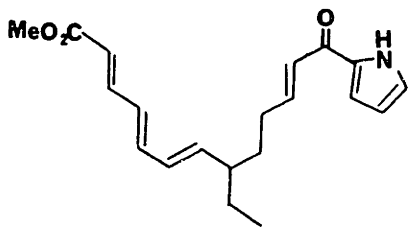
C	101	11
C.21	191.1	191.6
C.8	142.0	140.8
C.22	132.6	132.4
C.9	130.5	132.3
C.11	129.6	129.4
C.13,14	129.1	129.1
	127.1	127.3
C.10	124.0	125.3
C.23,24,25 (pyrrole)	121.9	123.9
	115.2	116.4
	110.3	110.3
C.12,15,16,19,20	52.5	52.5
	50.2	50.1
	44.8	45.0
	43.7	44.0
	40.5	41.2
C.27	12.4	12.5



23 P= OTBDPS
32 P= MEM



97



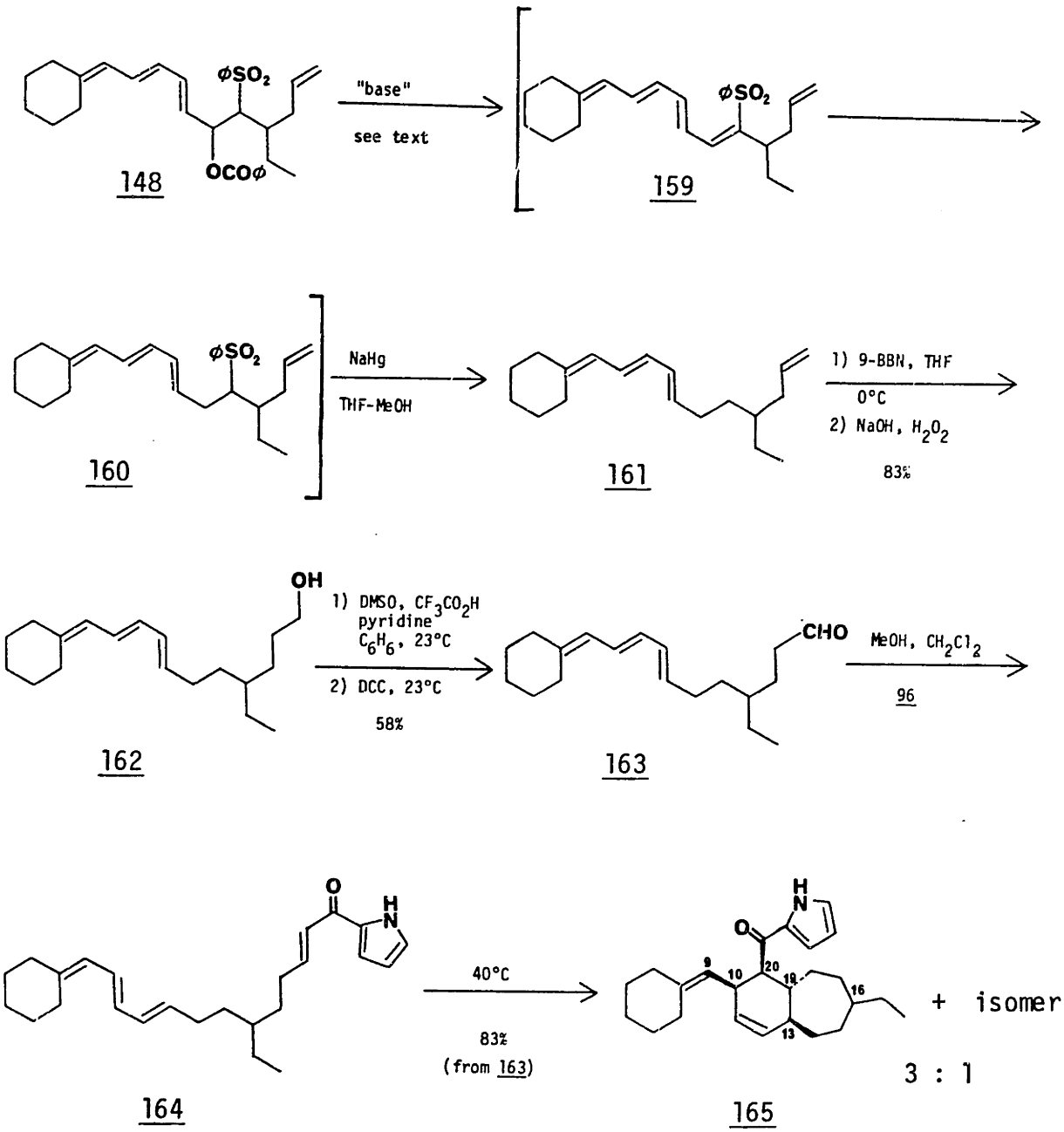
93

Note that triene ester 23 (used by Nicolaou) required 48h at 130°C for complete cyclization.[12a] Triene 32 used by Ley required 36 to 70h for this conversion.[13a] Systems 97 and 93 prepared by Myers required 17h at 115°C and 25h at 110°C, respectively, for cyclization.[10] In addition, 93 cyclized only to the extent of about 6% in four days at 25°C.

Another example which illustrates the activating influence of a ketopyrrole dienophile was discovered in the course of our investigations. A minor amount (21%) of tetraene 161 (Scheme 18) was observed in some initial experiments involving the conversion of sulfone adduct 148 to pentaene 119. This product (161) was presumably formed by elimination of benzoic acid from adduct 148 to give α,β unsaturated sulfone 159 (probably during the preparation of 148), which was reduced by 5% sodium amalgam via 160 to give tetraene 161. Reasonable care to protect 148 from strong bases corresponded to the absence of tetraene 161 in subsequent elimination mixtures. That pentaene 119 is not the precursor to 161 was verified by subjecting 119 to the reduction conditions from which it was recovered unchanged.

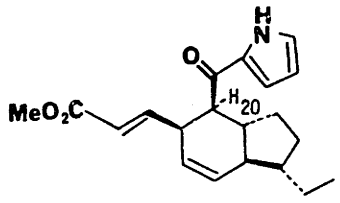
Mixtures of 119 and 161, when obtained, were easily separated by

Scheme 18


φSO2
OCOφ
"base"
see text
148
159
NaHg
THF-MeOH
160
161
1) 9-BBN, THF
0°C
2) NaOH, H2O2
83%
OH
1) DMSO, CF3CO2H
pyridine
C6H6, 23°C
2) DCC, 23°C
58%
162
163
CHO
MeOH, CH2Cl2
96
O
H
N
40°C
83%
(from 163)
9
10
20
18
16
13
+ isomer
3 : 1
164
165

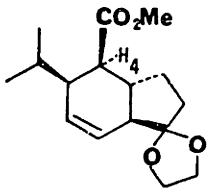
reverse phase HPLC (Waters μ-Bondapak column, 30 cm length X 3.9 mm I.D., 1:4 H_2O-CH_3CN). Tetraene 161 when treated with 9-BBN in THF at 0°C (alkaline H_2O_2 workup) afforded primary alcohol 162 as the sole reaction product (83% yield after chromatography). Moffat oxidation[31e] of 162 gave aldehyde 163 in 58% yield which upon treatment with ketopyrrole phosphorane 96 in 2:1 CH_2Cl_2-MeOH at 40°C for 31 h provided a 76:24 mixture of two cycloadducts in 83% yield. The major product, 165, was isolated in isomerically pure form by careful chromatography. Examination of the UV spectrum of 165 in ethanol clearly indicated the presence of the ketopyrrole group (λ max 291, ε = 16,100) and the absence of conjugated olefins. The IR spectrum showed the ketopyrrole carbonyl group at 1640 cm^{-1}. Although no parent ion was observed in the low resolution mass spectrum, ions at m/e 337 (loss of C_2H_5) and 270 (loss of ketopyrrole) were observed. The 250 MHz ^1H NMR data were consistent with the assigment of stereochemistry indicated for 165 in Scheme 18. In particular, the signal for H_{20} appeared at δ 3.39 as a doublet of doublets, J = 11.0, 6.4 Hz. These data are very similar to tne characteristic resonances for the protons α to the carbomethoxyl groups of trans-fused cycloadducts in the perhydroindene (e.g. 94, 166) and decalin (e.g. 167) series.[16g,48] If this stereochemical assignment is correct, then 165 is the product of an endo cyclization pathway. The stereochemistry of the C.16 ethyl substituent, or of the minor Diels-Alder adduct, however, were not assigned.

48. Roush, W.R.; Hall, S.E. J. Am. Chem. Soc. 1981, 103, 5200.



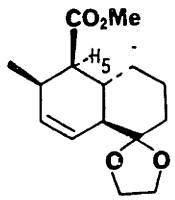
H_{20}: δ 3.45(dd, J=10.7,6.2Hz)

94



H_4: δ 2.75(dd, J=10.5,7.2Hz)

166



H_5: δ 2.56(dd, J=11.3,5.9Hz)

167

This preparation of 165 is the first example of facile formation of a 6-7 fused ring system by an intramolecular Diels-Alder reaction.[11,49] Other examples of intramolecular Diels-Alder reactions in this series require much more vigorous conditions. Oppolzer, for example, reported that triene 168 cyclized at 80°C in 18 h to give cis fused 169 in 90% yield.[49a] Earlier work by Wenkert had indicated that treatment of 170 with aluminum (III) chloride at 110°C provided 171 in 70% yield.[49b]

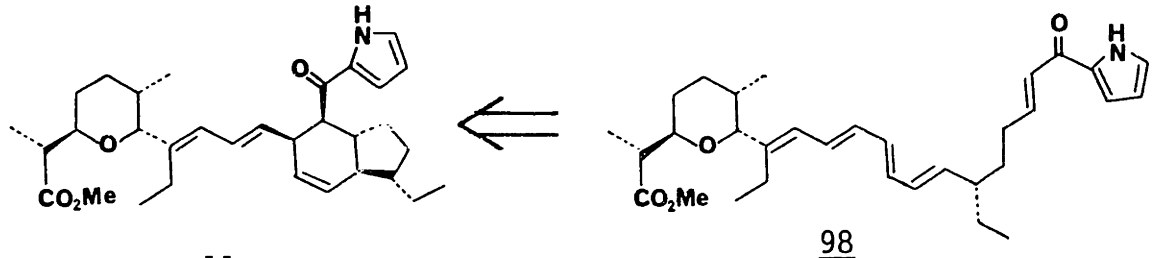
168 R= $-OP(OEt)_2$ C_6H_6, 80°C, 18h, 90% 169 R= $-OP(OEt)_2$

170 R= H $AlCl_3$, 110°C 70% 171 R= H

49. (a) Oppolzer, W.; Snowden, R.L. Helv. Chim. Acta 1981, 64, 2592.

(b) Wenkert, E.; Naemura, K. Synth. Commun. 1973, 45.

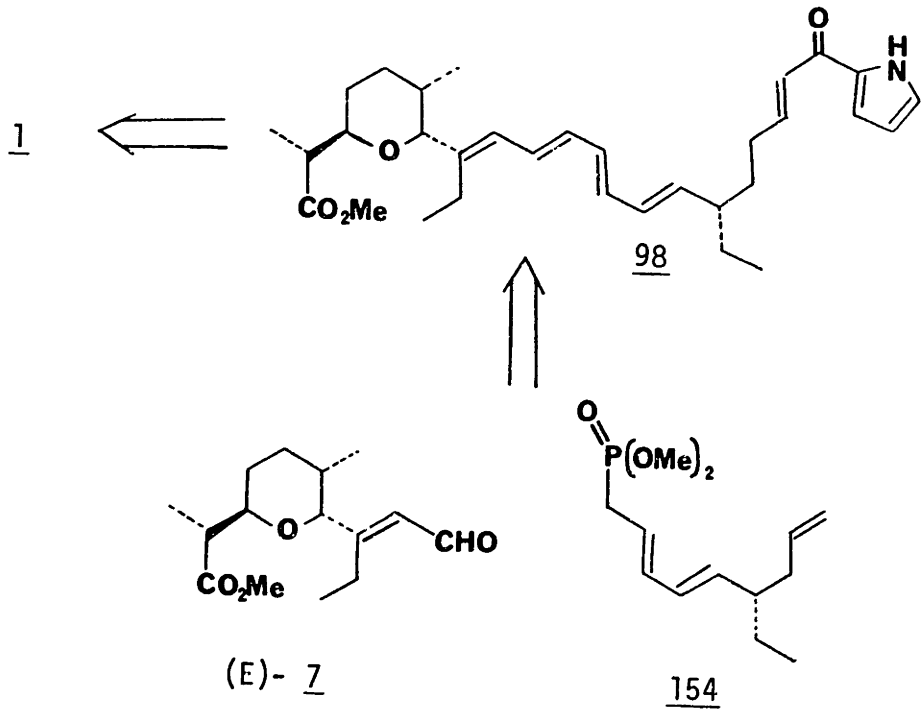
In summary, these preliminary studies indicated that pentaene 98 was a reasonable synthetic target which would be expected to cyclize under mild conditions to give X-14547A methyl ester (11). Our synthesis of 98 and its conversion to 11 is the subject of the following chapter.



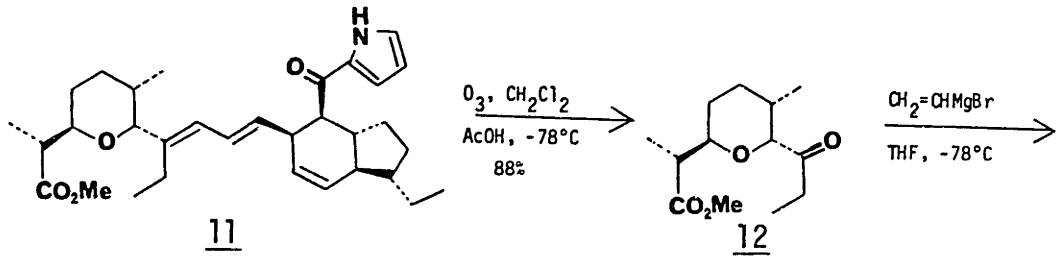
11 98

CHAPTER III

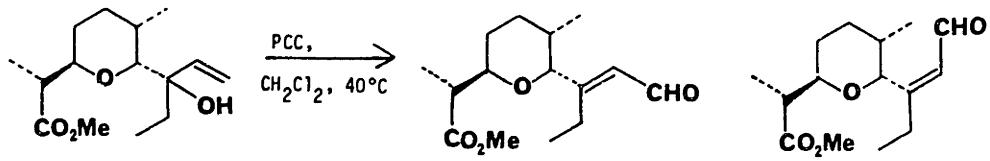
An approach to the sythesis of antibiotic X-14547A utilizing the intramolecular Diels-Alder reaction of 98 as a key step seemed feasible following the successful completion of the model study described in the previous chapter of this thesis.[21] Unsaturated aldehyde 7 and chiral phosphonate 154, in turn, appeared to be the logical precursors to 98. Our attention therefore focused immediately on the synthesis of these subunits.



An approach to the synthesis of 7 was initiated shortly after completion of the work described in Chapter 2. This line of research was abandoned, however, after the appearance of very similar approaches by Nicolaou[12b] and Ho[14]. We decided that our efforts would best be directed towards the synthesis of optically active 154 and its coupling with 7. Accordingly, aldehyde 7 used throughout this work was prepared by degradation[12a] of natural X-14547A which was generously provided by Dr. J. Westley of Hoffman-LaRoche. Thus, ozonolysis of X-14547A methyl ester (11) according to Nicolaou's procedure[12a] afforded ketone 12 in 88% yield. Sequential treatment of 12 with vinylmagnesium bromide (THF, -78°C) followed by PCC oxidation (CH_2Cl_2, 40°C) of the resulting allylic alcohol 172 afforded a 4-5:1 mixture of (E)-7 and its (Z)- isomer. These isomers were separated by reverse phase HPLC (Waters C-18 μ-Bondapak, 60:40 H_2O-CH_3CN). It is interesting to note that although Nicolaou[12a] and Ley[13b] have reported the conversion of 12 to 7, neither group has described a method for separating the two olefin isomers.

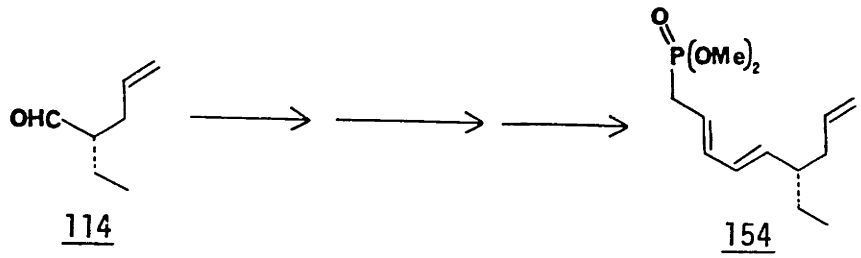


11 12



172 (E)- 7 (31% from 12) (Z)- 7 (4% from 12)

Our efforts next focused on the synthesis of optically active phosphonate 154. Needed for this work was a source of optically active 114, the racemic version of which had already been transformed into racemic 154 (see Scheme 17, Chapter 2). We selected Evan's



114 154

enantioselective alkylation methodology[50] for use in the synthesis of (S)- 114. Thus, the sodium anion of 173 was treated with butyryl chloride to give oxazoline 174 in 88% yield (see Scheme 19). While alkylation of the lithium anion of 174 with allyl bromide gave 175 in 48-55% yield, use of allyl iodide as the alkylating agent gave an improved yield of 62-71%. Reduction of 175 with lithium aluminum hydride followed by bulb-to-bulb distillation of the product mixture provided optically active alcohol 135 in 75% yield. Alcohol 135 was then oxidized by the Parikh reagent (DMSO, pyridine-SO_3) [50c, 51] to give

50. (a) Evans, D.A.; Ennis, M.D.; Mathre, D.J. J. Am. Chem. Soc. 1982, 104, 1737.

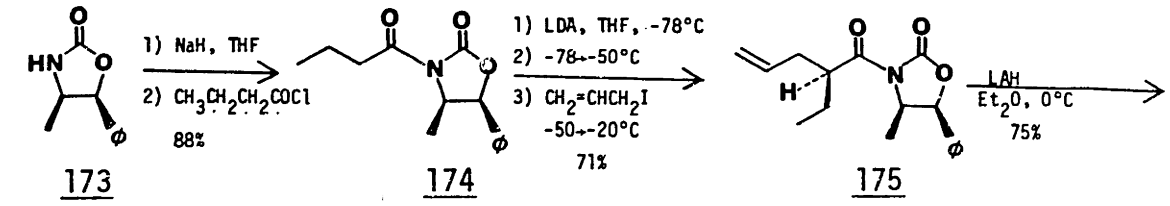
(b) Evans, D.A. Aldrichimica Acta 1982, 15, 23.

(c) Evans, D.A.; Bartoli, J. Tetrahedron Lett. 1982, 23, 807.

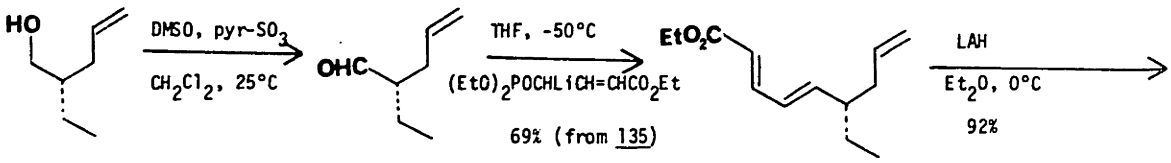
(d) Evans, D.A.; Nelson, J.V.; Taber, T.R. In "Topics in Stereochemistry"; Allinger, N.L.; Eliel, E.L.; Wilen, S.H. Eds.; John Wiley & Sons: New York, 1982; Vol. 13, p 1.

51. Parikh, J.R.; Doering, W. von E. J. Am. Chem. Soc. 1967, 89, 5505.

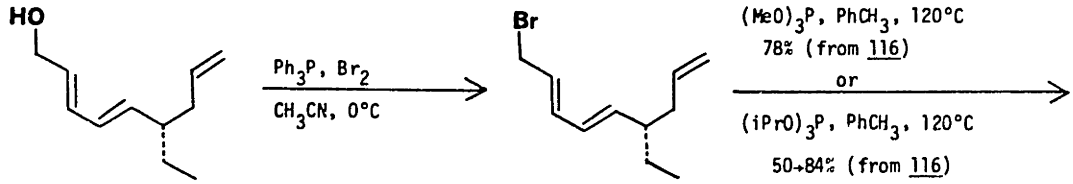
Scheme 19



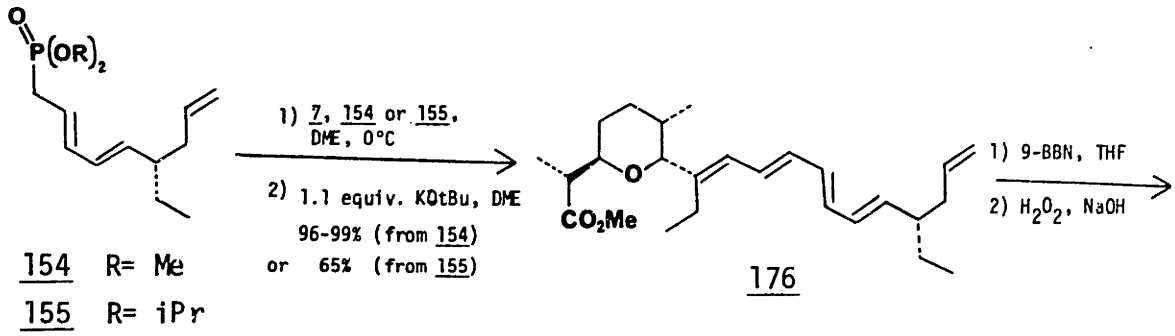
173 174 175



135 114 115

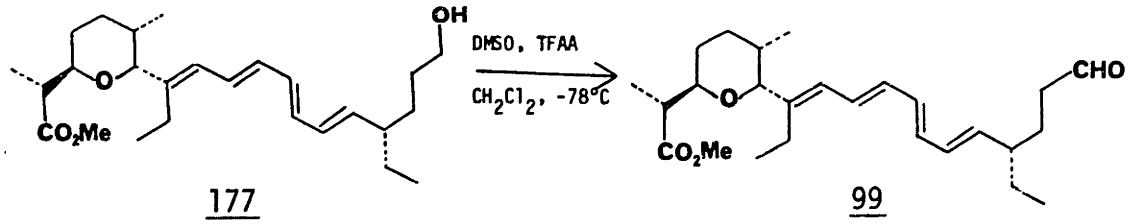


116 117



154 R= Me
155 R= iPr

176



177 99

the desired aldehyde 114 which upon treatment with the lithium anion of ethyl-4-diethylphosphonocrotonate afforded unsaturated ester 115 in 69% yield from 135. Elaboration of 115 to 154 was then performed as previously described.

The determination of the optical purity of 175, 135, 114, and other intermediates in this series was very difficult. Oxazoline 175 was greater than 95% diastereomerically pure by ^{1}H NMR analysis (only one isomer observed). Efforts to determine the enantiomeric excess of alcohol 135, however, were less successful. Esterification of racemic and optically active 135 with (-)-α-methoxy-α-trifluoromethylphenylacetyl chloride gave the corresponding Mosher ester.[52] Well resolved proton resonances unique to either diastereomeric ester were not observed in the high field NMR spectra of these derivatives. Application of chiral or achiral shift reagents with these Mosher esters were ineffective in improving resolution of overlapping diastereomeric proton resonances. Chiral shift experiments performed on samples of racemic and optically active alcohol 135, ester 115, or diene alcohol 116 were also unsuccessful in producing well-resolved proton NMR resonances unique to each enantiomer. Assuming no loss of optical purity in the conversion of 175 to 154, 154 was at least 95% of one diastereomer (90% ee) based on the diastereomeric analysis of 175. This assumption could not, however, be verified experimentally.

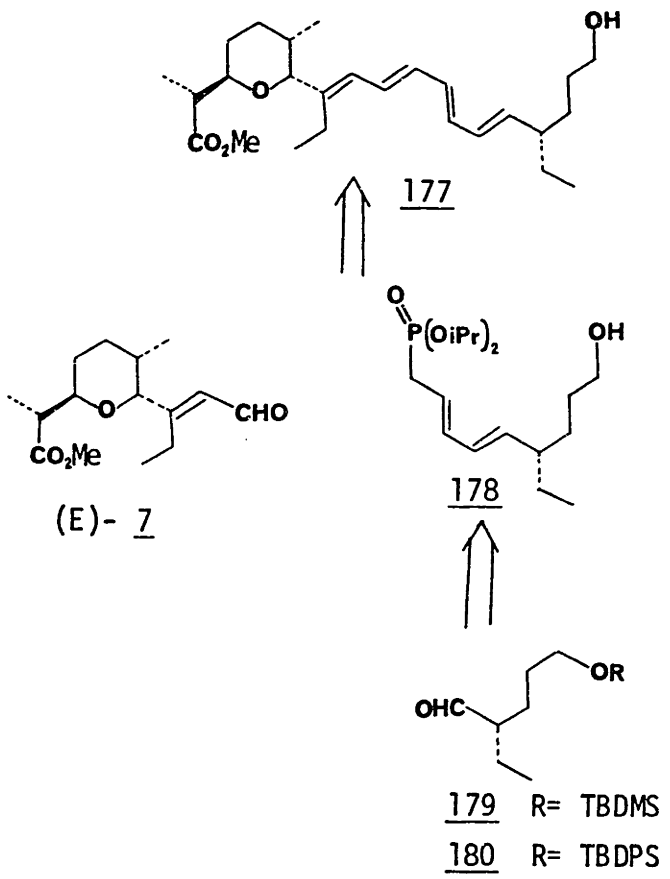
Phosphonate 154 and aldehyde 7 were coupled by using the optimized conditions determined from the model study. Thus, a mixture of 7 and 154 in DME at 0°C was added to a solution of 2.0 equivalents of potassium tert-butoxide in DME. In this manner a 48% yield of the

52. Dale, J.A.; Dull, D.L.; Mosher, H.S. J. Org. Chem. 1969, 34, 2543.

pentaene 176 was obtained as a 4:1 E:Z isomer mixture at the newly formed double bond. When the order of addition was reversed and the amount of potassium tert-butoxide reduced to 1.1 equivalents, the yield of 176 was increased to 96-99%, but 176 was again obtained as a 3.2:1 E:Z isomer mixture. Because the stereoselectivity of this reaction was unexpectedly poor, diisopropylphosphonate 155[53] was synthesized and then condensed with aldehyde 7 under the improved reaction conditions. Pentaene 176 was isolated from this reaction in up to 68% yield as a 9-10:1 E:Z olefin isomer mixture. The increased selectivity of this conversion more than compensated for the somewhat diminished yields.

The hydroboration of 176 with 9-BBN appeared to proceed without complication until the point of attempted purification of the alcohol product 177. In spite of considerable efforts, 177 could not be separated readily from cis-1,5-cyclooctanediol derived from the 9-BBN reagent. The manipulations of 177 necessitated by these attempts to obtain a pure product contributed to substantial product decomposition. Thus, attempts to transform crude 177 to aldehyde 99 were made. Unfortunately, the cyclooctanediol also interfered with the oxidation of 177. In light of these problems, we decided to modify the synthetic scheme in order to circumvent the hydroboration step. As it turns out, the modifications adopted resulted in a more convergent synthesis with respect to the left hand half component 7.

53. Suprisingly, the effect of increased bulk of phosphonate ligands on trans olefin selectivity was reported for the first time only recently in connection with synthetic studies on the rifamycins: Nagaoka, H.; Kishi, Y. Tetrahedron 1981, 37, 3873.



179 R= TBDMS

180 R= TBDPS

We envisioned that coupling of phosphonate 178 with aldehyde 7 would lead directly to tetraene alcohol 177.[54] Phosphonate 178 would be synthesized from an optically active aldehyde precursor such as 179 or 180. Nicolaou had already prepared 179 by using Enders' alkylation chemistry.[12c,18] We hoped, however, to apply new methodology involving the synthesis of α-chiral aldehydes from 2,3-epoxyalcohols which we had studied in connection with our aborted attempt to synthesize left-hand component 7. We selected a tert-butyldiphenylsilyl (TBDPS) ether protecting group for 180 due to its great acid stability[55] - a desirable property when considering the chemistry under consideration for the synthesis of 178. In addition, the ease of removal of silyl ether

54. Although no examples of olefin syntheses involving hydroxy phosphonates have been reported, uses of oxido phosphonium ylids are well known. For a brief review, see: Maryanoff, B.E.; Reitz, A.B.; Duhl-Emswiler, B.A. Tetrahedron Lett. 1983, 24, 2477, and references cited therein.

55. Hanessian, S.; Lavallee, P. Can. J. Chem. 1975, 53, 2975.

protecting groups with fluoride ion was another feature which led to the selection of the TBDPS ether over other potential protecting groups. We describe below some of the preliminary studies which provided the basis for our work on the synthesis of 180.[56]

We had hoped to use either 1,2-diol 182 or 1,3-diol 183 in our synthesis of 7. Accordingly, we studied reactions of epoxyalcohol 181[57] with lithium dimethylcuprate[58] and trimethylaluminum[59] with hope that a selective ring opening reaction could be achieved. Indeed, treatment of (R,R)-epoxide 181[57a] (>95% ee) with Me_2CuLi (1.2 equiv.) in ether at -20°C

56. Roush, W.R.; Adam, M.A.; Peseckis, S.M. Tetrahedron Lett. 1983, 24, 1377.

57. (a) Katsuki, T.; Lee, A.W.M.; Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Tuddenham, D.; Walker, F.J. J. Org. Chem. 1982, 47, 1373.

(b) Danishefsky, S.; Regan, J. Tetrahedron Lett. 1981, 22, 3919.

58. (a) Johnson, M.R.; Nakata, T.; Kishi, Y. Tetrahedron Lett. 1979, 4343.

For general reviews of organocopper reagents in synthesis, see:
(b) Posner, G.H. Organic Reactions 1972, 19, 1.

(c) Posner, G.H. Organic Reactions 1975, 22, 253.

(d) Posner, G.H. "An Introduction to Synthesis Using Organocopper Reagents" John Wiley and Sons, Inc., New York, N.Y., 1980.

59. (a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. Tetrahedron Lett. 1982, 23, 3597.

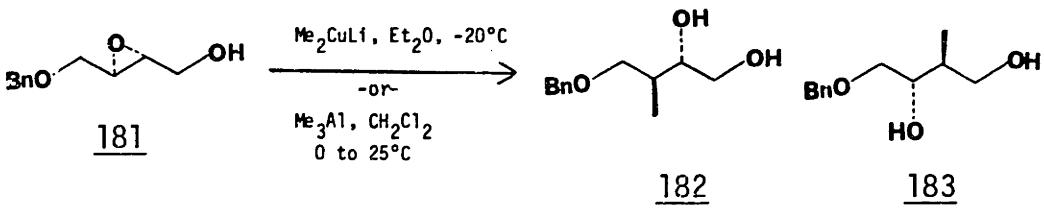
(b) Pfaltz, A.; Mattenberger, A. Angew. Chem., Int. Ed. Engl. 1982, 21, 71.

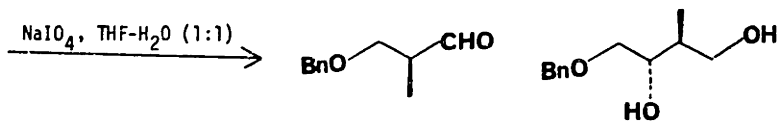
(c) Bruno, G. "The Use of Aluminum Alkyls in Organic Synthesis" Second printing, Ethyl Corporation, Baton Rouge, Louisiana, 1977.

(d) Bruno, G. "The Use of Aluminum Alkyls in Organic Synthesis, 1969-1972 Supplement" Ethyl Corporation, Baton Rouge, LA, 1973.

(e) Honeycutt, J.B. "The Use of Aluminum Alkyls in Organic Synthesis, 1972-1978 Supplement" Ethyl Corporation, Baton Rouge, LA, 1979.

for 1h afforded a mixture of 182 and 183 (ca. 1:6 by NMR analysis), whereas complementary regioselectivity was realized when 181 was treated with Me_3Al (3 equiv.) in methylene chloride (0°C to 25°C over 10h; ca. 5:1 mixture of 182:183). These mixtures were inseparable by conventional chromatographic techniques. Purification of 1,3-diol 183, however, was accomplished after treating these mixtures with sodium periodate ($NaIO_4$) in aqueous THF, which transformed 1,2 diol-182 to aldehyde 184. In this manner diol 183 ($[\alpha]_D^{30}$+16.5°,c=1.18, $CHCl_3$) was obtained in 74-79% yield via the cuprate sequence.





Me_2CuLi	experiment	10-12%	74-79%
Me_3Al	experiment	69-73%	13-14%

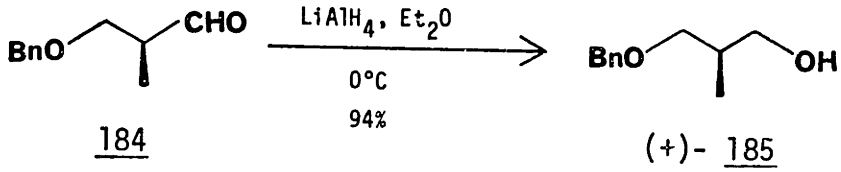
We recognized, however, that the sequence involving the Me_3Al reaction could also prove useful in synthesis. Aldehyde 184 and its enantiomer are well-known intermediates usually prepared from (S)-ß-hydroxyisobutyric acid,[60] and have been used in a number of recent

60. (a) Goodhue, C.T.; Schaeffer, J.R. Biotechnol. Bioeng. 1971, 13, 203.

(b) Cohen, N.; Eichel, W.F.; Lopresti, R.J.; Neukom, C.; Saucy, G. J. Org. Chem. 1976, 41, 3505.

(c) Choy, W.; Ma, P.; Masamune, S. Tetrahedron Lett. 1981, 22, 3555.

natural product synthese.[61] Indeed, aldehyde 184 ($[\alpha]_D^{21}$ +28.4°, c=1.56, $CHCl_3$) prepared as outlined above was shown to be at least 95% optically pure by conversion to the known alcohol 185[62] ($[\alpha]_D^{21}$ +16.5°, c=1.05, $CHCl_3$; lit.[53] $[\alpha]_D$ +17.2°,c=3.24, $CHCl_3$; $[\alpha]_D^{21}$ +5.2°, c=1.46, EtOH; lit.[50a] $[\alpha]_D$ +5.3°, c=2.2, EtOH).



184 (+)- 185

These results encouraged us to study the reactions of a number of 2,3-epoxyalcohols with trialkylaluminum reagents, and to consider the applicability of these reactions in sythese of α-chiral aldehydes. Results obtained in collaboration with M. A. Adam of this laboratory are summarized in Table VI. Each of the substrates examined underwent substitution preferentially at the position furthest removed from the hydroxyl substituent. No product of attack at the α position (C.2) was realized with substrates 191, 193, and 195.[63] With 181 and 189, however,

61. (a) Meyers, A.I.; Hudspeth, J.P. Tetrahedron Lett. 1981, 22, 3925.

(b) See also reference 53.

(c) McWhorter, W.W., Jr.; Kang, S.A.; Kishi, Y. Tetrahedron Lett. 1983, 24, 2243.

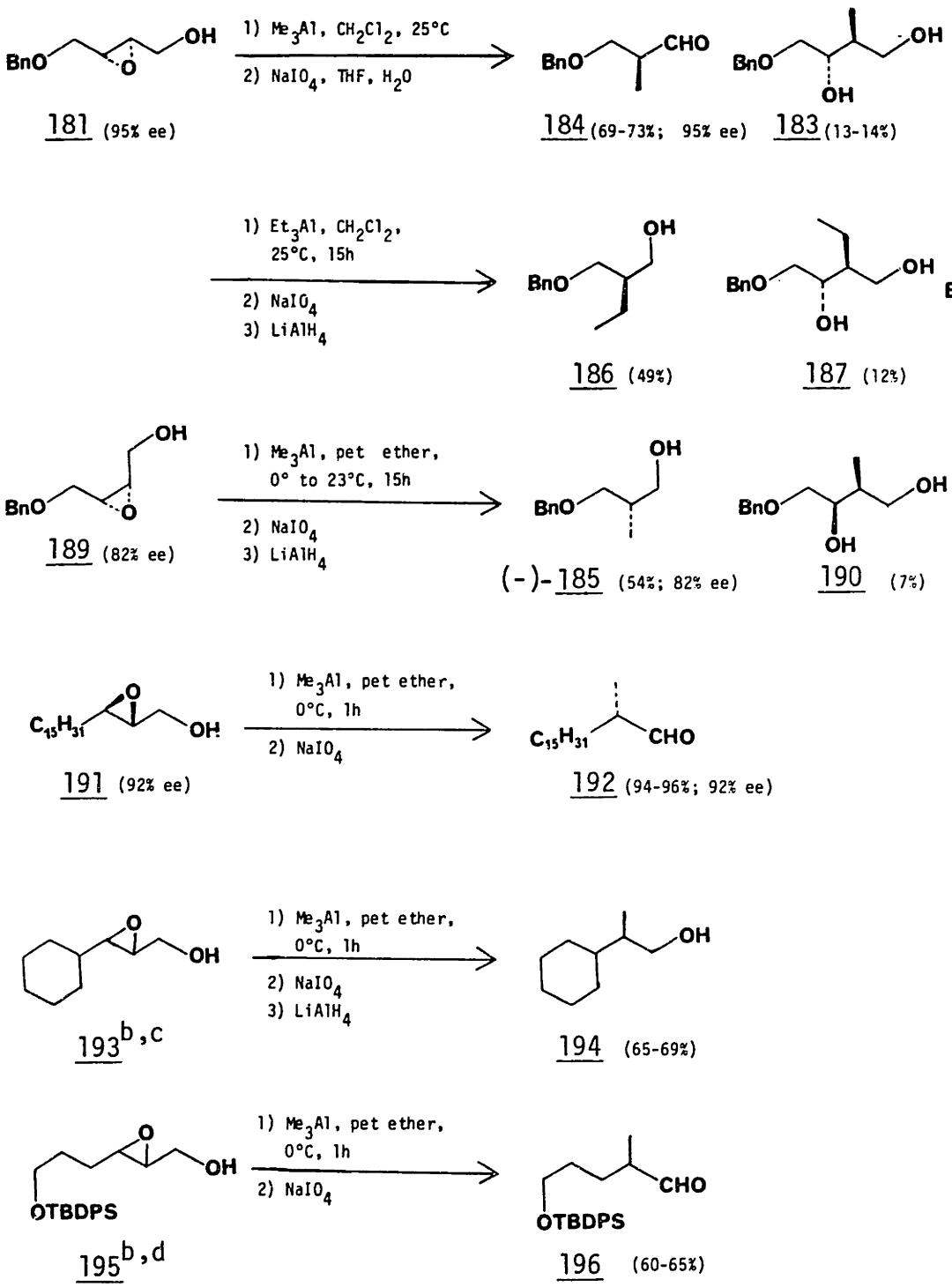
(d) Collum, D.B.; McDonald, J.H., III.; Still, W.C. J. Am. Chem. Soc. 1980, 102, 2118 (see reference 13 therein).

(e) McGuirk, P.R.; Collum, D.B. J. Am. Chem. Soc. 1982, 104, 4496.

62. An enantioselective synthesis of 184 has been reported, see reference 50a.

63. Authentic samples of the unobserved 1,3-diols were prepared by treating 191, 193, and 195 with Me_2CuLi and then $NaIO_4$. In none of these cases was the regioselectivity as high as observed with 181. The 1,3-diol was favored from 193, but only by a ratio of 70:30. The ratios for the other substrates ranged from 60:40 (1,3: 1,2) for 189 to 40:60 for 191.

Table VI



(a) This compound was separated by chromatography before the periodate cleavage step.
(b) Racemic epoxide was used.
(c) An unidentified mixture of by-products (12-13%) was isolated from this sequence.
(d) An unidentified mixture of by-products (ca. 25%) was also obtained.

a lesser degree of regioselectivity was realized owing to the benzyloxy substituent at C.4 which inductively deactivates C.3 towards nucleophilic attack.

With respect to the applicability of this chemistry towards the synthesis of α-chiral aldehydes, it is noteworthy that optically active epoxides 181 (>95% ee), 189[56] (82% ee), and 191[64] (92% ee) were transformed to 184 (>95% ee), (-)- 185 (82% ee), and 192 (92% ee; determined after $LiAlH_4$ reduction to the corresponding alcohol), respectively, with no detectable racemization. Thus, at least in these examples, the optical purity of the α-chiral aldehydes produced was determined by the optical purity of the starting epoxyalcohols, each of which was prepared by the Sharpless enantioselective epoxidation procedure.[65]

One problem which became apparent during the course of this work was the proclivity of alkylaluminum reagents to serve as hydride donors[59,66] and promote epoxide reduction[59a,67] reactions (see second entry of Table VI).

64. Mori, K.; Umemura, T. Tetrahedron Lett. 1981, 22, 4433.

65. (a) Katsuki, T.; Sharpless, K.B. J. Am. Chem. Soc. 1980, 102, 5974.

(b) Rossiter, B.E.; Katsuki, T.; Sharpless, K.B. J. Am. Chem. Soc. 1981, 103, 464.

66. For a discussion of trialkylaluminum reagents as hydride donors, see: House, H.O. "Modern Synthetic Reactions" Second ed., W.A. Benjamin, Inc., Reading, MA, 1972; pp 67, and references cited therein.

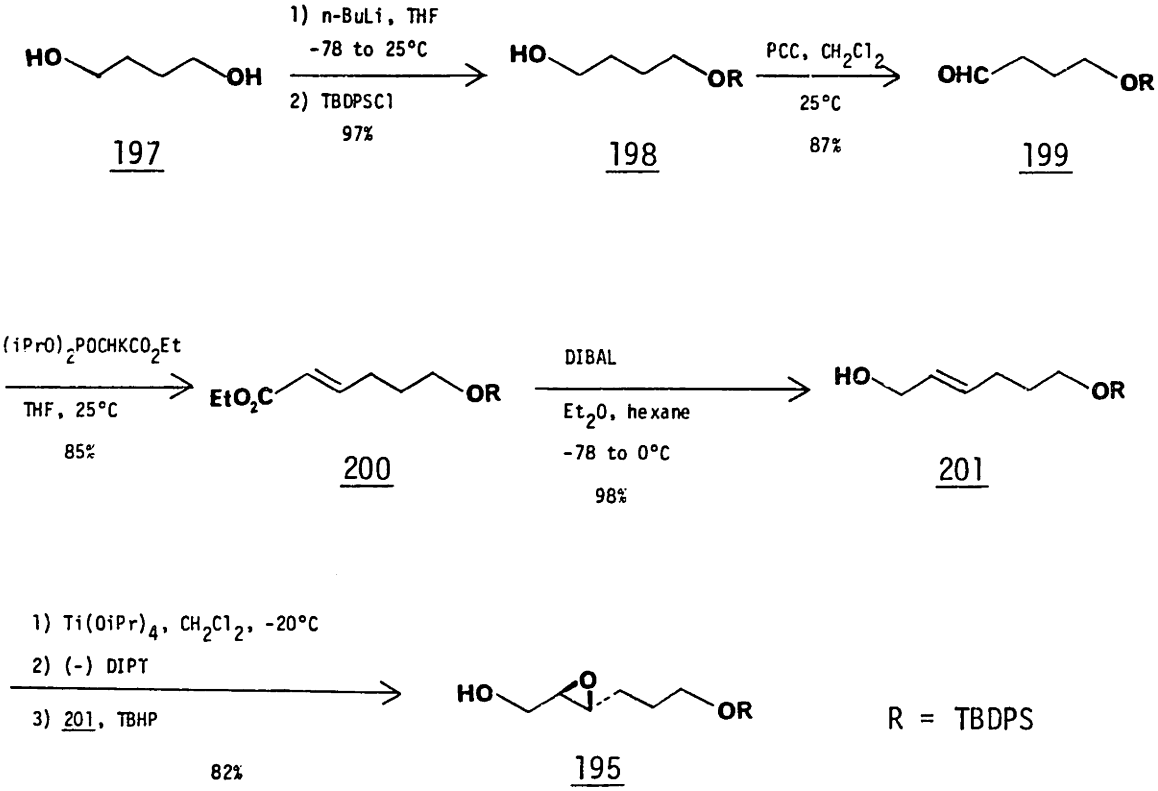
67. Reductions of disubstituted 2,3 epoxyalcohols are well known:
(a) Viti, S.M. Tetrahedron Lett. 1982, 23, 4541.

(b) Finan, J.M.; Kishi, Y. Tetrahedron Lett. 1982, 23, 2719.

(c) Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Viti, S.M. J. Org. Chem. 1982, 47, 1378.

(d) See also reference 59a.

Nonetheless, we were optimistic that a solution to this problem could be found, and proceeded, therefore, to synthesize optically active epoxide 195[68] as outlined below and study its reaction with a variety of ethyl organometallic reagents.



Unfortunately, our expectation that a highly selective conversion of 195 to 1,2-diol 202 could be developed was not realized (see Table VII). A mixture of at least two, and sometimes three, products was obtained with each of the reagents examined. For example, treatment of 195 with Et_3Al in petroleum ether under a variety of conditions (0°C, 3h; -78°C, 15h) afforded a mixture (ca. 3:1) of the

68. Epoxide 195 was at least 90% optically pure (90% ee) by Mosher ester analysis. On the basis of subsequent chemical conversions, however, this epoxide appeared to be more optically pure than implied by this conservative lower limit.

Table VII

Entry	Conditions[a]	Yields[b] 202	(180)[c]	203	204	206, $[\alpha]_D$ [d]
1	Et_3Al (3 equiv.), pet. ether, 0°C, 3h	---	(32%)	12%	16%	+4.5°
2	Et_4AlNa (3 equiv.), $NiCl_2$ (3 equiv.), pet. ether, 25°C, 63h	37%	---	25%	---	+7.2°
3[e]	Et_4AlNa (3 equiv.), $NiCl_2$ (3 equiv.), pet. ether, 40°C, 48h	---	(31%)	18%	28%	+7.2°
4	Et_2Mg (3 equiv.), Et_2O, 25°C, 46h	38%	---	39%	---	+7.4°
5	EtMgBr, CuI, THF, -60 to 25°C, 16h	---	(18%)	61%	---	+7.8°

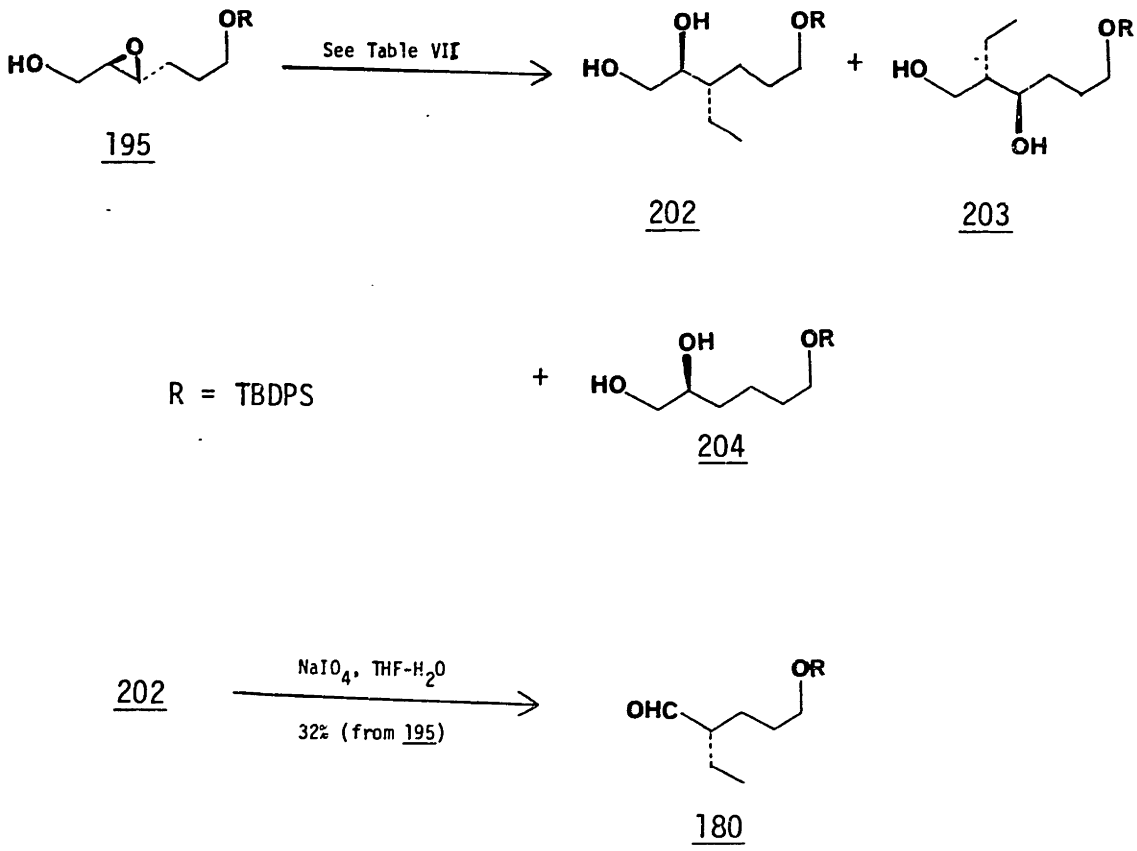
(a) Epoxide 195 used in these experiments had $[\alpha]_D^{21}$ +19.3° (c=1.30, $CHCl_3$).

(b) All yields are for isolated compounds.

(c) The yields in parentheses are for aldehyde 180 prepared by periodate cleavage of unseparated 202/203 mixtures obtained from the epoxide opening reactions.

(d) Optical rotation of diene ester 206 prepared from 180.

(e) The Et_4AlNa used in this experiment had been aged for three weeks before use. In contrast, the reagent used in entry 2 was freshly prepared.



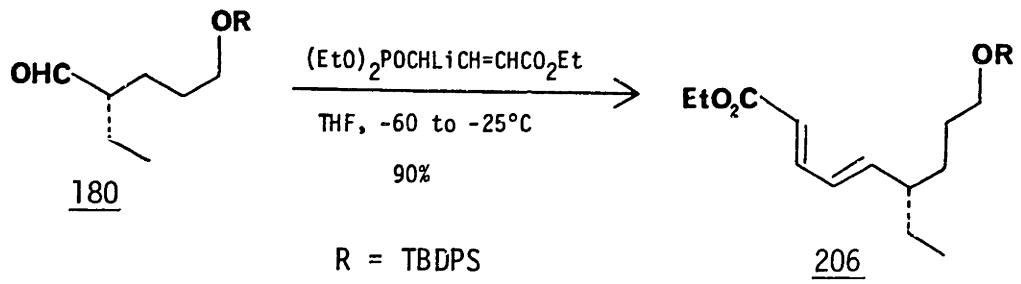
two isomeric ethyl opened products (202 and 203) along with diol 204 produced by hydride reduction of the epoxide.[69] Hydride reduction was not observed, however, in experiments involving Et_2Mg,[70] EtMgBr/CuI, or

69. Compound 203 was not detected in our initial studies of the reactions of racemic 195 with Et_3Al. This erroneous result was, unfortunately published in our preliminary account of this work (reference 56). The existence of 1,3-diol 205, the product of hydride reduction of 195 at C.2, was not verified in these experiments although it may have been present with 203.

70. Diethylmagnesium was prepared from diethylmercury, magnesium, and catalytic mercury(II) chloride in ether at 100°C. Preparation of diethylmagnesium by dioxane precipitation of magnesium bromide from ethylmagnesium bromide solutions produced a reagent containing unacceptable amounts of magnesium bromide, which added to 195 in competition with Et_2Mg. For further details, see reference 91.

freshly prepared Et_4AlNa.[71] These reagents, however, afforded substantially greater amounts of 1,3-diol 203 relative to the desired 1,2-diol 202 (see entries 2-5, Table VII). No reaction was observed when 195 was treated with Et_2Zn, and a complex mixture resulted from attempts to open 195 with Et_4AlNa in the presence of $TiCl_4$.

The behavior of 195 with Et_3Al was very surprising in light of the results summarized in Table VI. Not only was some 1,3-diol 203 produced when none was expected, the opening of the epoxide at C.3 also appeared to proceed with partial stereochemical scrambling. The latter result was inferred on the basis of the following evidence. First, the mixture of 202 and 203 produced in entry 1 of Table VII was not separable by silica gel chromatography (indicating the presence of a complex mixture of diastereomers), whereas the 202/203 diol mixtures obtained from the Et_4Al, Et_2Mg, and EtMgBr/CuI experiments were easily separated. Second, and more significant, was the observation that the optical rotation of

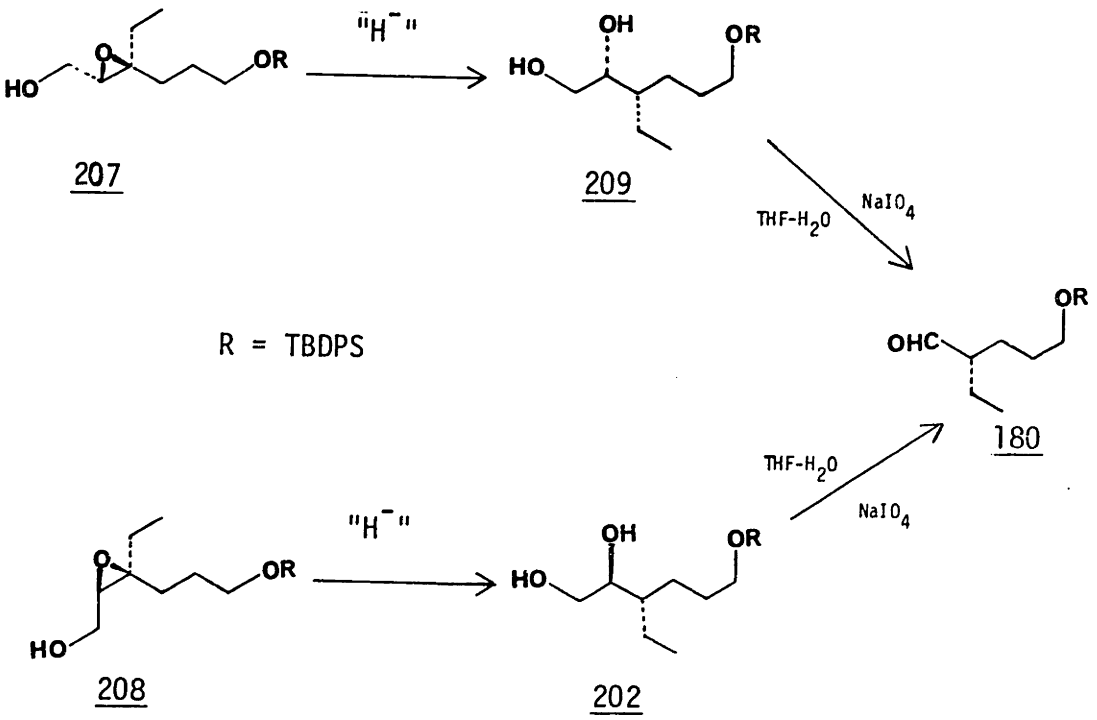


71. Some hydride opening was observed with Et_4AlNa which had been aged for three weeks prior to use. Hydride opening was also observed using Et_4AlLi prepared *in situ* from Et_3Al and EtLi. The reactivity and stereoselectivity of aluminate treatment of epoxides with and without catalysts has been investigated:
(a) Boireau, G.; Abenhaim, D.; Henry-Basch, E. Tetrahedron 1980, 36, 3061.

(b) Boireau, G.; Abenhaim, D.; Bernardon, C.; Henry-Basch, E.; Sabouratt, B. Tetrahedron Lett. 1975, 30, 2521.

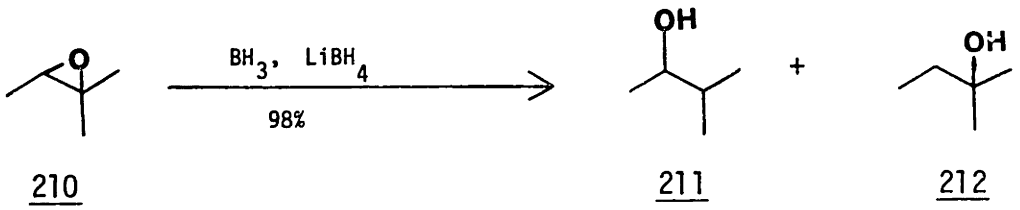
diene 206 prepared from aldehyde 180 brought through the Et_3Al sequence was only approximately 60% of that for 206 prepared from 195 via the Et_4AlNa, Et_2Mg, or EtMgBr/CuI sequences (see last column of Table VII).[72] Quite clearly, the Et_3Al sequence was not suitable for use in our approach to X-14547A.

While these studies were in progress we considered the possibility that a hydride reduction could be used to advantage in the synthesis of aldehyde 180 from a trisubstituted epoxyalcohol such as 207 or



72. That 206 prepared from intermediates brought through the Et_3Al sequence was less optically pure than samples prepared via the other organometallic sequences was also apparent at later stages of the synthesis. Intermediates 177, 99, and X-14547A methyl ester (11) prepared by the coupling of aldehyde 7 and Et_3Al-derived samples of 178 were clearly diastereomeric mixtures (^1H NMR analysis). These same intermediates prepared from 206 with $[\alpha]_D > 7.2°$ (see Table VI), however, appeared to be diastereomerically pure (> 95% one isomer).

208.[67,73] Brown and Yoon had noted that treatment of epoxide 210 with borane in the presence of lithium borohydride ($LiBH_4$) afforded a 75:25 mixture of 211:212.[73a] We anticipated that the hydroxyl substituent in

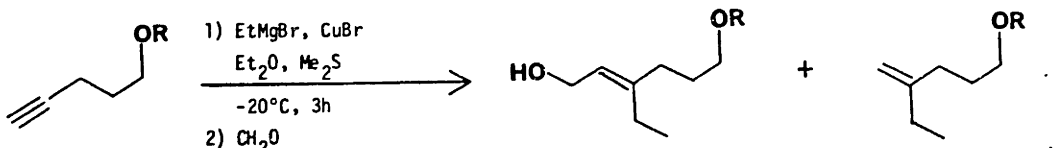


210 211 212

75 : 25

207 or 208 would deactivate C.2 towards nucleophilic (reductive) attack, and were optimistic that a careful choice of hydride reagent would result in good yields of the desired 1,2-diols 209 and 202.

A direct synthesis of the allylic alcohol (214) precusor to 207 was investigated first. Treatment of acetylene 213 with EtMgBr and



213 R = TBDPS 214 (15-19%) 215 (22-80%)

73. Studies on the selective reduction of trisubstituted epoxides at the more highly substituted position have been reported:
(a) Brown, H.C.; Yoon, N.M. J. Am. Chem. Soc. 1968, 90, 2686.

(b) Murphy, D.K.; Alumbaugh, R.L.; Rickborn, B. J. Am. Chem. Soc. 1969, 91, 2649.

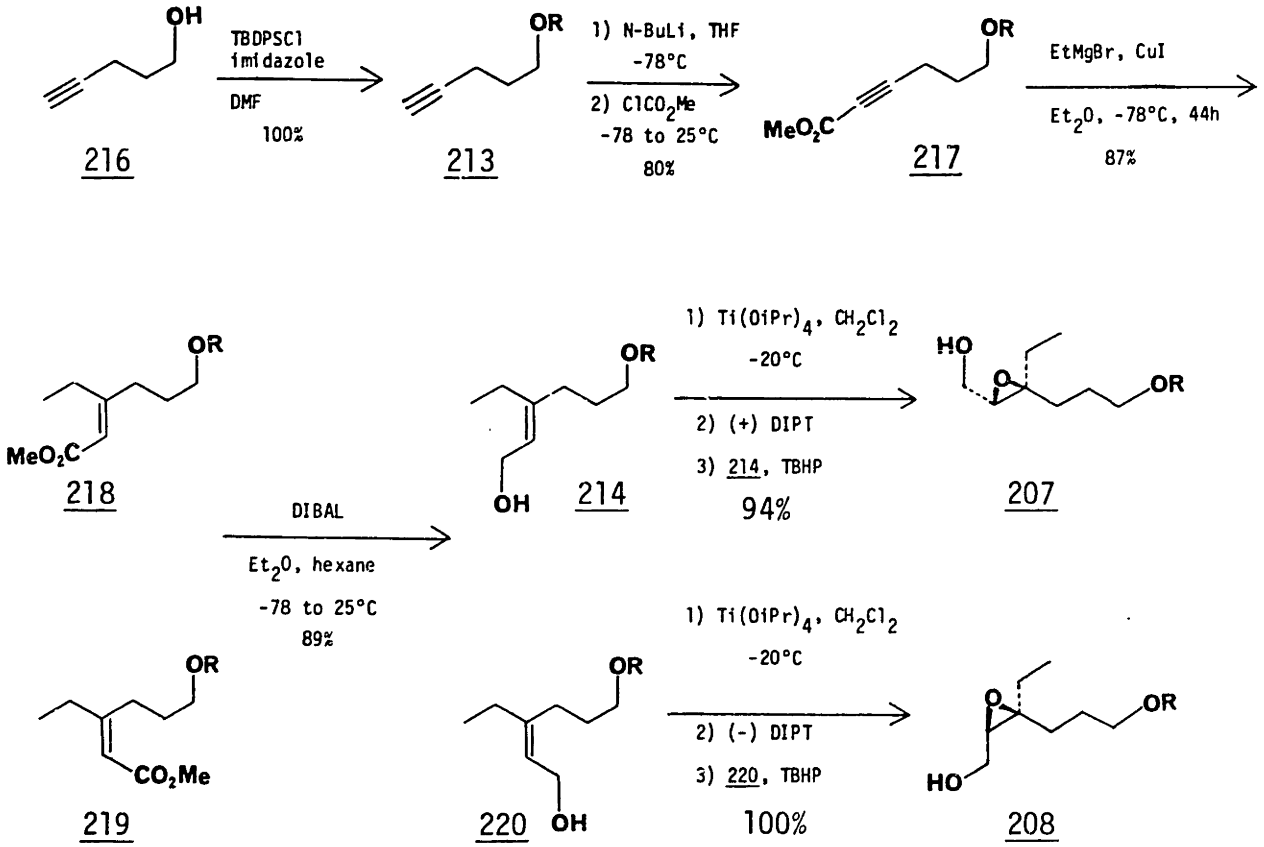
(c) Rerick, M.N.; Eliel, E.L. J. Am. Chem. Soc. 1962, 84, 2356.

(d) Ashby, E.C.; Prather, J. J. Am. Chem. Soc. 1966, 88, 729.

(e) Buchanan, J.G.; Sable, H.Z. "Selective Organic Transformations" John Wiley and Sons, Inc., New York, NY, Vol. 2, 1972; p. 37.

(f) Kishi, Y. Aldrichimica Acta 1980, 13, 23.

stoichiometric CuBr-Me_2S in 1:1 ether-dimethylsulfide[74] at -20°C for 3h followed by treatment with gaseous formaldehyde afforded isomerically pure 214 but only in 15-19% yield. In spite of considerable effort, the yield of this conversion could not be improved. The major product under all circumstances was olefin 215 (22-80%). Alternatively, acetylene 213 was carbomethoxylated to give 217. This acetylenic ester was then treated



R = TBDPS

74. (a) Marfat, A.; McGuirk, P.R.; Helquist, P. J. Org. Chem. 1979, 44, 1345; 3888, and references cited therein.

(b) Normant, J.F.; Cahiez, G.; Chait, C.; Alexakis, A.; Villieras, J. Bull. Soc. Chim. Fr. 1974, 1656.

(c) Normant, J.F.; Bourgain, M. Tetrahedron Lett. 1971, 2583.

(d) Alexakis, A.; Normant, J.F.; Villieras, J. Tetrahedron Lett. 1976, 3461.

with the reagent prepared from ethylmagnesium bromide (2 equiv.)/ copper(I) iodide (1 equiv.)[75] in THF at -78°C for 44h to give an inseparable mixture of 218 and 219 in 87% yield. Reduction of this mixture with diisobutylaluminum hydride afforded a 42:58 mixture of alcohols 214 and 220, which could be separated, albeit with great difficulty. Careful, laborious, chromatography of these mixtures afforded isomerically pure 214 and 220. With quantities of 214 and 220 available, epoxides 207 and 208 were synthesized by application of the Sharpless enantioselective epoxidation procedure.[76] Importantly, epoxidation of 214 by using (+)-diisopropyltartrate (DIPT) and 220 by using (-)-diisopropyltartrate as the chiral auxiliaries should, according to the Sharpless paradigm,[65a] give diastereomeric epoxides with the same absolute configuration at C.3.

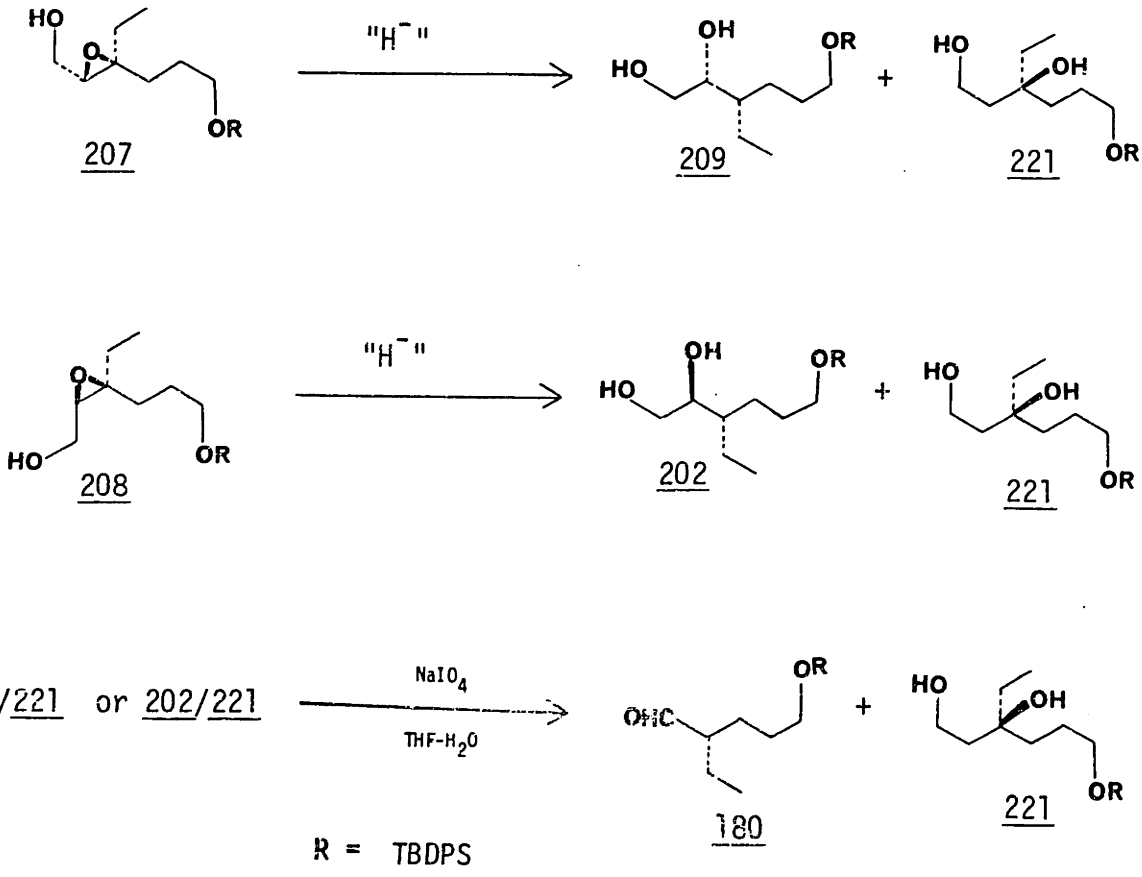
Preliminary reduction experiments with 207 showed that both diisobutylaluminum hydride in benzene and aluminum hydride ($LiAlH_4$, $AlCl_3$) in ether (each at 23°C for 41 h) completely removed the silyl protecting group. No reduction of 207 was observed by using BH_3-THF complex in

75. (a) Corey, E.J.; Katzenellenbogen, J.A. J. Am. Chem. Soc. 1969, 91, 1851.

(b) Siddall, J.B.; Biskop, J.H. J. Am. Chem. Soc. 1969, 91, 1853.

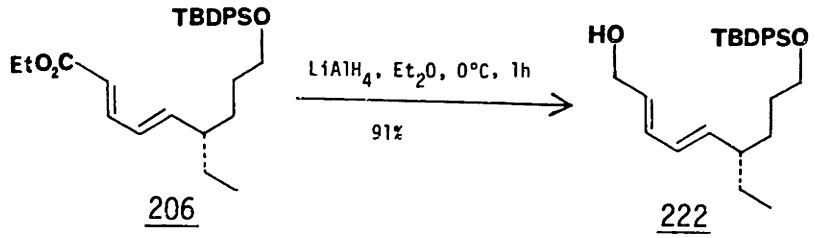
76. The optical purities of epoxides 207 and 208, as judged qualitatively by optical rotation measurements, were much higher when 5 equiv. of tartrate was employed as compared to the usual recipe involving 1.5 equiv. of the chiral ligand. This higher loading ratio is recommended in footnote 8 of the following paper:
Reed, L.A.; Ito, Y.; Masamune, S.; Sharpless, K.B. J. Am. Chem. Soc. 1982, 104, 6468.
A discussion of problems encountered in determining the absolute optical purities of 207 and 208 appears in a subsequent section of this chapter.

petroleum ether at 0°C or with BH_3-Me_2S/$(MeO)_3B$ reagent in THF at 25°C. Success was realized finally when 207 was treated with BH_3-THF complex in THF at 0°C for 32h. Under these conditions, however, a mixture of 1,2- and 1,3- diols (209 and 221) was produced. This problem, in fact, plagued all of our attempts to achieve the selective reductions of 207 and 208, and presented a number of technical difficulties in analyzing



the product mixtures. The mixture of 209 and 221 (as well as the mixture of diols 202 and 221 produced from 208) were not easily separated by silica gel chromatography. Product ratios (ca. 60:40 209 or 202 to 221) were determined, therefore, by isolation of 221 and aldehyde 180 following a

subsequent periodate cleavage step. That 209 or 202 could not be readily purified from the reduction mixture also made it difficult to determine the stereospecificity of the reduction step, since one of the stereocenters of 202/209 was destroyed in the periodate cleavage. Some insight as to the selectivity of the reduction process, however, was gained by comparing the optical rotations of dienes 206 or 222 derived from aldehyde 180. Those reducing reagents which proceeded with more complete inversion



206 222

of configuration at C.3 would lead to intermediates exhibiting higher optical activity at the stage of 206/222 than those reagents which induced partial stereochemical scrambling upon reduction, presumably via partial carbonium ion formation at C.3.

The rate of reduction of 207 by BH_3-THF was improved (18h) when $LiBH_4$ was added to the reaction mixtures. This modification also led to an increase in the overall yield of 180 (56%) following the periodate cleavage step. Substitution of BH_3-Me_2S for BH_3-THF gave no noticable improvements in the yield of 180. These preliminary studies indicated that the best reagent for reduction of epoxides 207 and 208 was the BH_3-THF complex in THF in the presence of $LiBH_4$. This system, therefore, was studied in some detail (see Table VIII).

Table VIII

Entry	Substrate	$[\alpha]_D$ [a]	Conditions	180 [b] Yield	180 [b] $[\alpha]_D$	221 Yield	206 [c] $[\alpha]_D$	222 [d] $[\alpha]_D$
1	207	+4.0°	BH_3-THF, THF, 0 to 25°C, 16h	42%	+1.2°	e	+3.1°	-0.4°
2	207	+4.2°	BH_3-THF/$LiBH_4$, THF, 0°C, 41h	56%	+1.5°	40%	+5.4°	-1.2°
3	208	-5.1°	BH_3-THF/$LiBH_4$, THF, 0°C, 41h	56%	+1.6°	37%	+6.0°	-1.2°
4	208	-5.9°	BH_3-THF/$LiBH_4$, DME, 0°C, 25h	35%	---	29%	+6.1°	-1.2°
5	208	-5.9°	BH_3-THF/$LiBH_4$/BF_3-Et_2O, DME, 0°C, 14h	66%	---	c	---	+0.4°

(a) All rotations for 207 and 208 were measured at concentrations in the range of 1.4-2.2 g/100 mL.

(b) The yields recorded for 180 and 221 are for the chromatographically homogeneous samples isolated after the periodate cleavage step. All rotations for 180 were measured at concentrations in the range of 1.2-1.6 g/100 mL.

(c) All rotations for 206 were measured at concentrations in the range of 1.0-1.8 g/100 mL.

(d) All rotations for 222 were measured at concentrations in the range of 1.1-2.0 g/100 mL.

(e) Compound present but not isolated.

As seen in Table VIII, hydride opening of chiral 207 with BH_3-THF at 25°C followed by periodate cleavage gave a 42% yield of 180 (entry 1). Use of BH_3-THF complex with $LiBH_4$ in THF at 0°C afforded a 56% yield of 180 (entry 2). Comparison of optical rotation values for diene ester 206 and diene alcohol 222 suggested that the BH_3-THF reduction was less stereoselective than experiments in which $LiBH_4$ was present. Use of the BH_3-THF/$LiBH_4$ reagent with epoxide 208 also gave 180 in 56% yield (entry 3). Substitution, however, of DME for THF in this experiment afforded 180 in somewhat lower yield (entry 4). In an effort to increase the amount of hydride attack at the more substituted position, BF_3-Et_2O was added to a reduction mixture containing 208 and BH_3-THF/$LiBH_4$ in DME (entry 5). A good yield (60%) of aldehyde 180 was obtained after periodate cleavage. Considerable epimerization of C.3 occurred under these conditions, however, as suggested by the optical rotation of the derived diene alcohol 222 prepared from 180 (see last entry of Table VIII). Other attempts to direct hydride attack to C.3 relied on steric shielding of attack at C.2. Unfortunately, when 207 was treated first with 9-borabicyclononane (9-BBN) at 25°C for 4h, in an attempt to complex the bulky reagent with the primary alcohol, followed by treatment with the BH_3-THF/$LiBH_4$ reagent, only loss of the silyl protecting group was observed.

By this time a number of routes for the synthesis of aldehyde 180 from a chiral 2,3- epoxyalcohol intermediate had been explored. The most efficient route, in terms of the key manipulations of the epoxyalcohol intermediates, was that involving reduction of trisubstituted epoxides 207 or 208 (56% yield of 180). In contrast, the best yield of 180 from

the organometallic reactions of disubstituted epoxide 195 was 38%. On the other hand, samples of 180 prepared from 195 possessed higher optical purity than those prepared from 207-208, as judged by the optical rotations of the derived diene esters 206 (see Tables VII and VIII). This factor, coupled with the inefficient synthesis of the allylic alcohol precursors to 207-208, clearly suggested that intermediates prepared via the organometallic openings of 195 were the best suited for use in completion of the partial synthesis of X-14547A.[77]

There are two possible explanations for the lower optical purities observed for intermediates prepared via the sequence involving epoxides 207 or 208. One possibility is that the $BH_3/LiBH_4$ reduction proceeds with some retention of configuration at C.3; the second is that the Sharpless enantioselective epoxidation of the trisubstituted allylic alcohols 214 and 220 is not as enantioselective as is the epoxidation of (E)- disubstituted olefin 201. In order to evaluate which factor is at fault, it would be necessary to quantify the enantiomeric purity of epoxides 207 and 208, and intermediates derived therefrom. Regrettably, ^1H NMR analysis of the Mosher esters[52] prepared from racemic and optically active 207-208 was ineffective in quantifying the relative amounts of diastereomers present (qualitatively, however, it was clear that one diastereomer greatly predominated). Nonetheless, we suspect that the

77. Here again, independent verification that samples 206 with $[\alpha]_D$ 6.0°-6.1° prepared from epoxides 207 and 208 were less optically pure than 206 ($[\alpha]_D$ >7.2°) prepared from 195 was provided by conversion of the former to phosphonate 178 which was coupled with aldehyde 7 as subsequently described. Tetraene 177 so obtained was clearly a diastereomeric mixture (^1H NMR analysis). For comparison, see also reference 72.

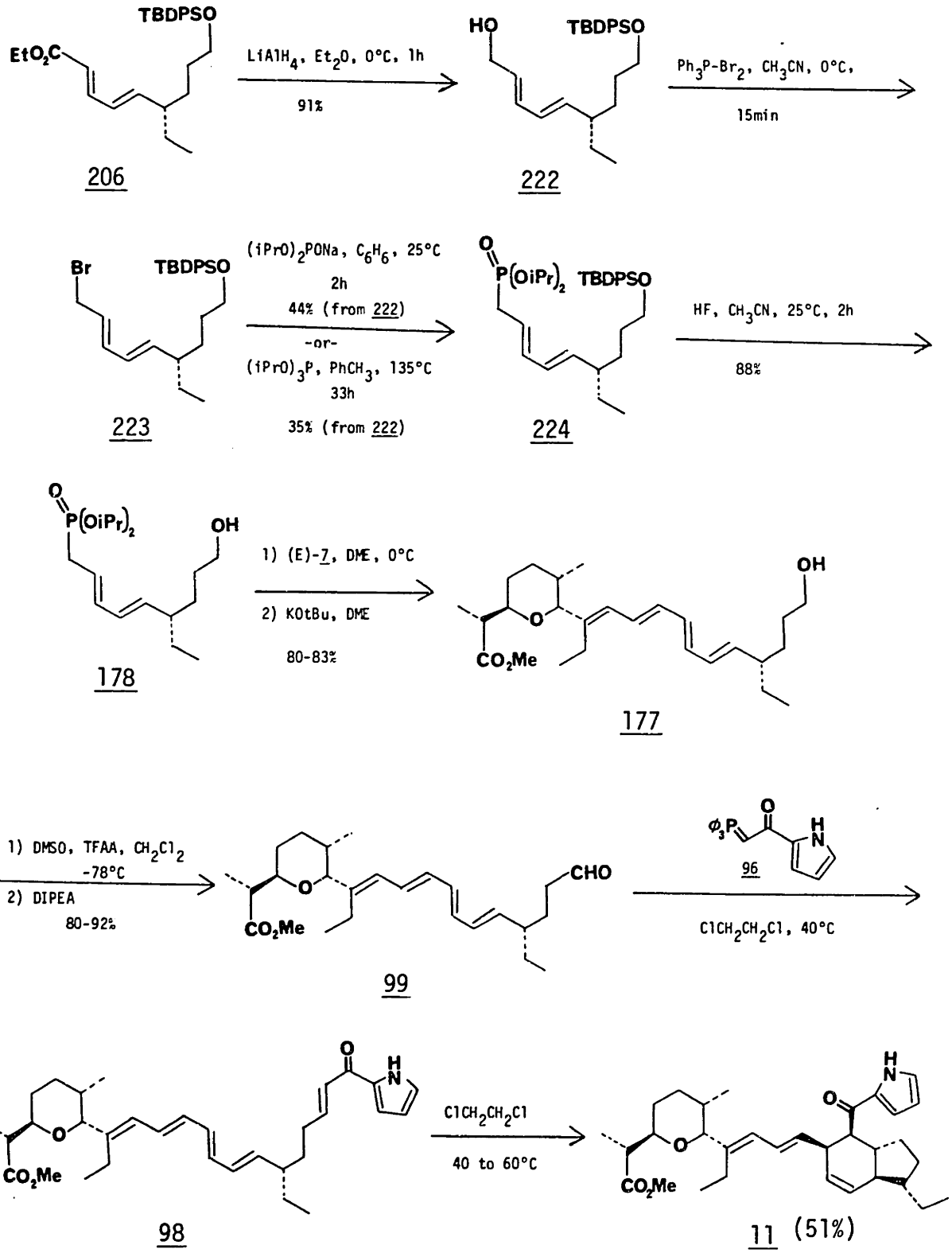
Sharpless epoxidation is, at least in part, at fault. Examination of reports involving the Sharpless enantioselective epoxidation[65] of (Z)-disubstituted and trisubstituted allylic alcohols indicates that increasing steric size of the C.3 substituent cis to the primary alcohol often corresponds to decreases in the optical purity of the epoxide product.[56,65,78]

Although a satisfactory synthesis of aldehyde 180 had not been achieved, sufficient quantities of material were available from the Et_4AlNa or Et_2Mg reactions of 195 to complete our essential studies on the synthesis of X-14547A. Thus, unsaturated ester 206, obtained in high yield (84-92%) by treatment of aldehyde 180 with the lithium anion of ethyl 4-diethylphosphonocrotonate, was uneventfully reduced to allylic alcohol 222 (see Scheme 20). Alcohol 222 when treated with one equivalent of triphenylphosphine-bromine complex[24] in acetonitrile at 0°C for 15 minutes afforded bromide 223 in good yield without loss of the tert-butyldiphenylsilyl protecting group. Treatment of 223 with sodium diisopropylphosphite in benzene at 25°C afforded phosphonate 224 in 44% yield from 222. Alternatively, bromide 223 when heated with triisopropylphosphite in toluene at 135°C for 33h produced 224 in 35% overall yield. It is important to note that some bromination of C.19 occurred when 1.5 equivalents of triphenylphosphine-bromine complex was used in the conversion of 222 to 223. Thus, treatment of the crude product mixture obtained from

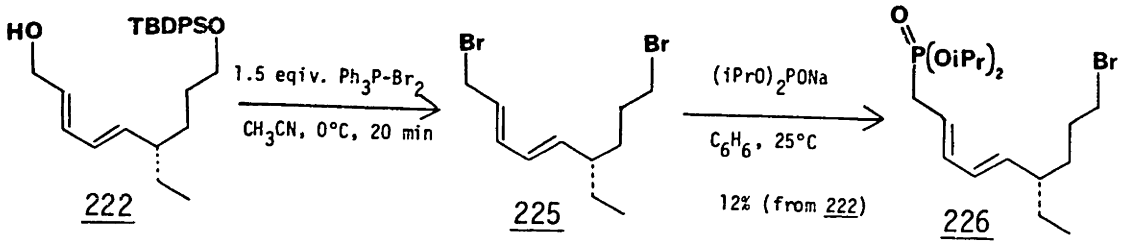
78. (a) Sharpless, K.B.; Behrens, C.H.; Katsuki, T.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; Walker, F.J.; Woodard, S.S. Pure and Appl. Chem. 1983, 55, 589 (see footnote #2).

(b) Wood, R.D.; Ganem, B. Tetrahedron Lett. 1982, 23, 707.

Scheme 20


TBDPSO
EtO2C
LiAlH4, Et2O, 0°C, 1h
91%
206
HO
TBDPSO
222
Ph3P-Br2, CH3CN, 0°C,
15min
Br
TBDPSO
223
(iPrO)2PONa, C6H6, 25°C
2h
44% (from 222)
-or-
(iPrO)3P, PhCH3, 135°C
33h
35% (from 222)
O
P(OiPr)2
TBDPSO
224
HF, CH3CN, 25°C, 2h
88%
O
P(OiPr)2
OH
178
1) (E)-7, DME, 0°C
2) KOtBu, DME
80-83%
OH
CO2Me
177
1) DMSO, TFAA, CH2Cl2
-78°C
2) DIPEA
80-92%
CHO
CO2Me
99
Φ3P
O
H
N
96
ClCH2CH2Cl, 40°C
O
H
N
CO2Me
98
ClCH2CH2Cl
40 to 60°C
H
N
O
CO2Me
11 (51%)

such an experiment with sodium diisopropylphosphite afforded 12% of 226 along with 23% of 224. Phosphonate 226 was not observed, however, when one equivalent of triphenylphosphine-bromine complex was used in the



222 225 226

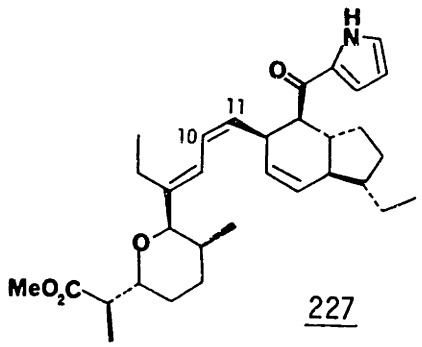
bromination step. Phosphonate 224 was efficiently deprotected upon treatment with dilute hydrogen fluoride[79] in acetonitrile which afforded alcohol 178 in 88% yield. Use of tetra-N-butylammonium fluoride gave inferior results.

With phosphonate 178 in hand, we were in a position to complete our synthesis of X-14547A. Thus, to a mixture of phosphonate 178 and aldehyde 7 in DME at 0°C was added one equivalent of potassium tert-butoxide. This procedure provided tetraene 177 as a 10-15:1 E:Z olefin isomer mixture at the newly formed double bond in 80-83% yield. Oxidation of 177 with Swern's reagent[35] (DMSO, TFAA) afforded aldehyde 99 in 80-92% yield. When this aldehyde was allowed to react

79. Although aqueous HF in acetonitrile has not been previously reported for deprotection of TBDPS ethers, it is a standard method for cleavage of TBDMS ethers.
(a) Newton, R.F.; Reynolds, D.P.; Finch, M.A.W.; Kelly, D.R.; Robert, S.M. Tetrahedron Lett. 1979, 3981.

(b) Greene, T.W. "Protecting Groups in Organic Synthesis" 1st. ed., John Wiley and Sons, Inc., New York, NY, 1981; pp 45,47.

with Wittig reagent 96 in 1,2 dichloroethane for three days at 40°C and for a fourth day at 60°C, a mixture of cycloadducts was obtained from which isomerically pure X-14547A methyl ester 11 was isolated in 51% yield by careful chromatography (a combination of reverse phase HPLC and silica gel chromatography). This semi-synthetic 11 was identical in all respects to a sample prepared from natural X-14547A. Also isolated from this cyclization was 5% of C.10,11 (Z)- olefin isomer 227 and 5-10% of a mixture of cis-fused and uncyclized pentaene.



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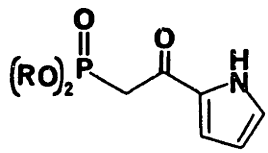
Efforts to prepare and isolate pentaene 98 for cyclization studies under "biological-like" or Lewis acid assisted conditions have not been successful. In order to form 98 at a reasonable rate, aldehyde 99 was treated with phosphorane 96 in 1,2 dichloroethane at 40°C. Unfortunately, under these conditions, 98 cyclizes very readily to 11. Attempts to separate 98 from partially cyclized mixtures by chromatography on Florisil or silica gel led either to significant decomposition or cyclization of 98. The failure to isolate 98 free of 11 precluded further studies on the cyclization of 98 or the corresponding carboxylic acid 10, the proposed biological precusor to X-14547A (1).

Future Studies

The facile cyclization of 98 to 11 does not prove that 10 is the biological precursor to 1, but is consistent with the hypothesis that 10 might cyclize very readily under biological conditions. Recent studies by Breslow[80a,b] and Grieco[80c] on the rate acceleration of Diels-Alder reactions in aqueous media lend further support to this hypothesis. These studies lead to the prediction that 98 should cyclize to 11 in water at a rate much faster than that observed for the cyclization of 98 in organic media. In addition, the acid 10, or the corresponding sodium salt, with its greater water solubility might cyclize even faster, perhaps by a factor of one hundred.[80] However, in order to verify these hypotheses, it is first necessary to obtain quantities of 98 and 10. This may be possible by use of reverse phase HPLC separation of a mixture of 98 and 11. A more efficient approach, however, would be to synthesize ketopyrrole phosphonate 228 and to use this reagent to prepare 98 from tetraene aldehyde 99 at reduced temperature (-78 to -60°C), conditions under which the cyclization of 98 to 11 would be precluded. With pure 98 in hand, mild alkaline hydrolysis of 98 should afford 10 without complication.



228

80. (a) Rideout, D.C.; Breslow, R. J. Am. Chem. Soc. 1980, 102, 7816.

(b) Breslow, R,; Maitra, U.; Rideout, D. Tetrahedron Lett. 1983, 24, 1901.

(c) Grieco, P.A.; Garner, P.; He, Z. Tetrahedron Lett. 1983, 24, 1897.

CHAPTER IV

EXPERIMENTAL PROCEDURES

Proton (^1H) NMR spectra were measured at 60 MHz on a Varian T60 or a Perkin-Elmer R-24B instrument, at 90 MHz on a Jeol FX90Q instrument, and at 250 or 270 MHz on Bruker WM 250 and 270 instruments. Chemical shifts are reported in δ units using tetramethylsilane or the 7.27 ppm resonance of residual chloroform as internal reference. Carbon (^{13}C) NMR spectra were measured at 63.8 or 67.9 MHz on the above Bruker instruments. Carbon chemical shifts are reported in δ_c units using the 77.0 ppm resonance of $CDCl_3$ as internal reference. NMR spectra were measured in $CDCl_3$ or CCl_4 (at 60 MHz only). Infrared spectra were measured on a Perkin-Elmer Model 283B Infrared Spectrophotometer calibrated with the 1601 cm^{-1} absorption of polystyrene. IR spectra are reported in wave numbers (cm^{-1}). Ultraviolet spectra were measured on a Perkin-Elmer 330 UV-Visible Spectrophotometer. Wavelengths are reported in nanometers (nm). Optical rotations were measured on a Perkin-Elmer 144 Polarimeter or on a Rudolph Autopol® III Automatic Polarimeter using a 1 cm^3 capacity quartz cell (10 cm path length). Mass spectra were measured at 70 eV on a Varian MAT 44 instrument. High resolution mass spectra were provided by the facility at MIT supported by NIH Grant RR 0317 (principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources, and were obtained on a CEC 21-110B high resolution mass spectrometer equipped with a PDP-1145 computer system to process data recorded on photographic plates. Elemental analysis were performed by Robertson Laboratories of Florham Park, New Jersey. Melting points were obtained on a Fisher-Johns hot stage melting point apparatus and

are uncorrected.

All reactions were conducted in oven dried (125°C) or flame dried glassware with magnetic stirring under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, and DME were distilled from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2), acetonitrile, 2,4,6-collidine, triethylamine, diisopropylamine, diisopropylethylamine, and DMSO (reduced pressure) were distilled from CaH_2. Hexane, petroleum ether, benzene, toluene, and xylene were distilled from sodium metal. Pyridine was distilled from sodium hydroxide. Dimethyl sulfide (Me_2S) and DMF (reduced pressure) were dried with activated 3 Å molecular sieves prior to distillation. Methanol was distilled from $Mg(OCH_3)_2$.

All extracts were dried with anhydrous Na_2SO_4, filtered through a cotton or Kimwipe plug, and then concentrated *in vacuo*. "*In vacuo*" refers to the vacuum achieved by a water aspirator attached to a Büchi rotary evaporator. All non-volatile samples were pumped (< 0.5 mm Hg) to constant weight at ambient temperature following removal of solvent *in vacuo*.

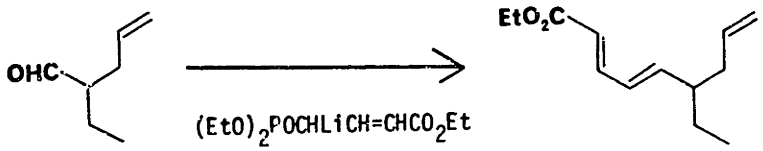
Analytical thin layer chromatography (TLC) was performed by using 2.5 cm X 10 cm plates coated with 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin layer chromatography (PTLC) was performed by using 20 cm X 20 cm plates coated with 0.25-, 0.5-, and 1.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were visualized with shortwave UV light, or by staining with either iodine vapor or vanillin/H_2SO_4. Unless indicated otherwise, compounds were eluted

from the adsorbents with ether. Flash column chromatography[81] was performed over activity I Woelm 70-230 mesh silica gel (Merck), activity I Woelm 230-400 mesh silica gel (Merck), 100-200 mesh Florisil® (Floridin Company, Fisher, Aldrich), or activity I Woelm alumina (Woelm, Baker) packed to a height of 15 cm in columns of specified diameter. Compounds were eluted from the columns with eluants of either constant or increasing polarity (controlled solvent polarity allowed use of 70-230 mesh silica gel except in those rare instances indicated as "flash silica gel" in the experimental section when 230-400 mesh silica gel was essential) under positive nitrogen pressure. All solvents used for chromatography were distilled prior to use.

High pressure liquid chromatography (HPLC) was performed by using a Waters 600A pump with a differential refractometer detector (Model R401) in series with an ultraviolet absorbance detector (Model 440) set at 254 nm. All reverse phase separations were performed by using a Waters C-18 μ-Bondapak column (30 cm length X 3.9 mm I.D.) with mixtures of CH_3CN-H_2O at a flow rate of 6.0 mL/min. HPLC grade solvents were filtered through a micropore filter (Millipore HA 0.45 μm membrane for water; Fluoropore® 0.5 μm membrane for organic solvent), mixed, and degassed prior to use.

81. Still, W.C.; Kahn, M.; Mitra, A. J. Org. Chem. 1978, 43, 2923.

Experimental Procedures for Chapter II



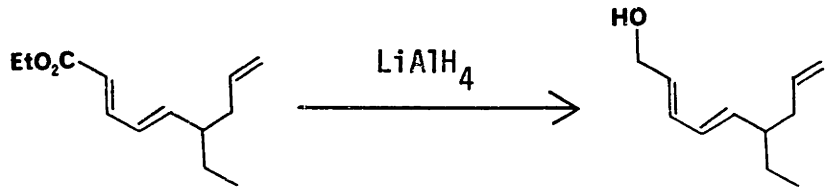
114 115

Diene ester 115

To a stirred solution of 21.4 mL (153 mmol) of diisopropylamine in 50 mL of THF at -78°C was added dropwise 63.0 mL (153 mmol) of 2.43M n-BuLi in hexane. This solution was stirred for 20 min at -78°C before 33.7 mL (143 mmol) of ethyl 4-diethylphosphonocrotonate was added dropwise over a 20 min period. This mixture was allowed to warm to -40°C and was stirred vigorously for 30 min. To the resulting deep red-brown solution was added dropwise 10.7 g (95.6 mmol) of aldehyde 114[82] in 11 mL of THF. This mixture was then allowed to warm to 23°C. After being stirred at 23°C for 1 h, the reaction mixture was extracted with aqueous 1N HCl (4 X 75 mL). The combined aqueous extracts were extracted with hexane (2 X 50 mL). The organic extracts were combined, dried, filtered, and concentrated in vacuo. The resulting crude product was purified by flash chromatography (silica gel, 40-mm column, 7:1 hexane-ether as eluant) to afford 18.9 g (95%) of pure ester 115: R_f 0.72 (3:1 hexane-ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.26 (dd, J = 15.6, 10.7 Hz,

82. Brannock, K.C. J. Am. Chem. Soc. 1959, 81, 3379.

1H), 6.15 (dd, J = 15.1, 10.7 Hz, 1H), 5.91 (dd, J = 15.1, 7.8 Hz, 1H), 5.80 (d, J = 15.6 Hz, 1H), 5.73 (m, 1H), 5.01 (m, 1H), 4.20 (q, J = 6.8 Hz, 2H), 2.13 (m, 3H), 1.51 (m, 1H), 1.33 (m, 1H), 1.29(t, J = 7.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); IR (neat) 3075, 2965, 2930, 2875, 1715, 1640, 1615 cm^{-1}; mass spectrum m/e 208 (parent ion). Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.10; H, 9.33.

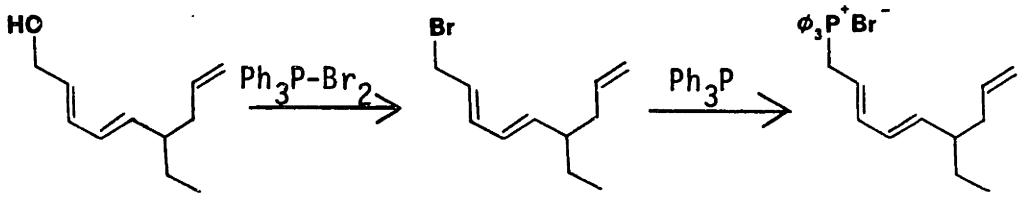


115 116

Diene alcohol 116

To a solution of 1.93 g (50.8 mmol) of lithium aluminum hydride in 50 mL of ether was added dropwise over 30 min a solution of 7.55 g (36.3 mmol) of ester 115 in 50 mL of ether. This mixture was stirred at 23°C for 2 h before being cooled to 0°C, at which point 2.0 mL of H_2O and then 6.0 mL of aqueous 1N NaOH were added cautiously. The mixture was then filtered, and the white precipitate rinsed with 60 mL of ether. The combined organic filtrates were concentrated in vacuo. The crude product was bulb-to-bulb distilled (128-134°C, 0.9-1.1 mm Hg) to give 5.64 g (92%) of 116: R_f 0.44 (1:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.22 (dd, J = 15.1, 10.7 Hz, 1H), 6.02 (dd, J = 15.1, 10.2 Hz, 1H), 5.72 (m, 2H), 5.48 (dd, J = 15.1, 8.3 Hz, 1H), 5.0 (m, 2H), 4.15 (br s, 2H), 2.18-1.93 (m, 4H), 1.46 (m, 1H), 1.26 (m, 1H), 0.85 (t, J = 7.3 Hz,

3H); IR (neat) 3320, 3080, 3020, 3000, 2960, 2920. 2870. 1655, 1649 cm^{-1}; mass spectrum m/e 166 (parent ion). Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.92; H, 11.14.

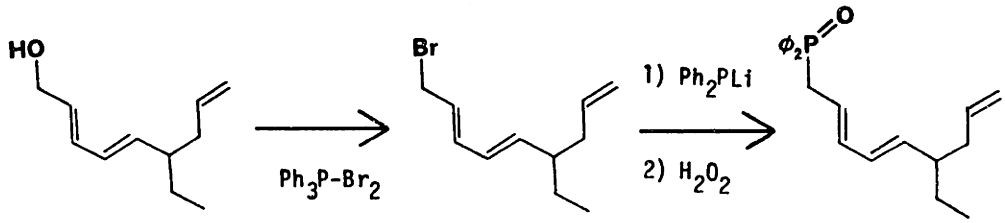


116 117 118

Diene bromide 117 and diene phosphonium salt 118

A stirred solution of 3.46 g (13.2 mmol) of triphenylphosphine (Ph_3P) in 20 mL of CH_3CN at 0°C was treated with 0.68 mL (13.2 mmol) of Br_2. The pale yellow solution was stirred for 20 min and then 1.41 g (8.50 mmol) of alcohol 116 was added. After being stirred for 40 min at 0°C, this mixture was treated with 0.7 mL of methanol and then with 2.4 g of anhydrous K_2CO_3. Solvent was removed in vacuo and the resulting residue was rinsed with 10-15 mL portions of 10% CH_2Cl_2 in hexane (100 mL total). The combined extracts were filtered and concentrated in vacuo. The crude bromide 117 thus obtained (R_f 0.78, 3:1 hexane-ether) was dissolved in 15 mL of benzene and treated with 2.2 g of Ph_3P. The mixture was heated to reflux for 2.5 h and then cooled to 23°C. Solvent was removed in vacuo and the yellow oily residue triturated with ether-CH_2Cl_2 to give 3.47 g (71 mmol, 84%) of 118 as a yellow powder: mp 147°C (dec); ^1H NMR (250 MHz, $CDCl_3$) δ 7.64-7.88 (m, 15H), 6.38 (m, 1H), 5.87 (dd,

J = 15.4, 10.7 Hz, 1H), 5.66 (m, 1H), 5.38 (m, 2H), 4.95 (m, 2H), 4.74 (dd, J = 15.1, 7.4 Hz, 2H), 2.00 (m, 2H), 1.15-1.27 (m, 3H), 0.78 (t, J = 7.4 Hz, 3H); IR (CH_2Cl_2) 3030, 2960, 2870, 1640, 1605, 1590 cm^{-1}.



116 117 124

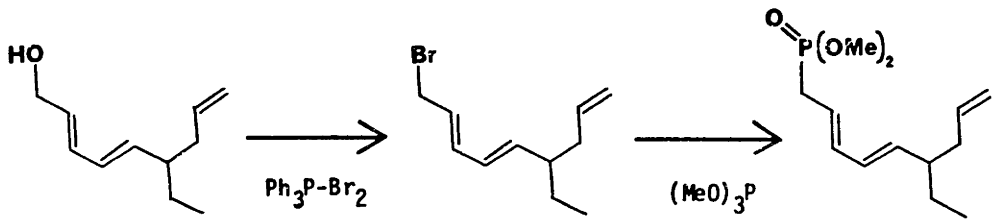
Diene diphenylphosphine oxide 124

The crude bromide 117, prepared as previously described from 224 mg (1.35 mmol) of alcohol 116, was dissolved in 5 mL of THF, cooled to -60°C, and then was treated with an excess of a deep red solution of lithium diphenylphosphide (prepared by treatment of Ph_2PCl in 2 mL of THF at 23°C with 50 mg of lithium wire for 4 h).[38a-c,83] The red reaction mixture was allowed to warm to 23°C over 30 min and, after 15 min at 23°C, was treated with 0.5 mL of H_2O. Following removal of the solvents in vacuo, the residue was dissolved in 20 mL of CH_2Cl_2 (analytical TLC: one spot, R_f 0.79, 3:1 hexane-ether). This solution was then treated with 30 mL of aqueous 5% H_2O_2 solution for 15 min with vigorous stirring. The organic layer was washed with 30 mL each of saturated aqueous Na_2SO_4, aqueous 0.3N HCl, and half saturated aqueous Na_2HCO_3, and

83. (a) Clark, P.W. J. Organometal. Chem. 1977, 139, 385.

(b) Vedejs, E.; Fuchs, P.L. J. Am. Chem. Soc. 1972, 94, 822.

was then concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 30 mm column, ethyl acetate as eluant) to afford 143 mg (0.41 mmol, 30% from 116) of 124: R_f 0.35 (ethyl acetate); ^1H NMR (270 MHz, $CDCl_3$) δ 7.67-7.77 (m, 4H), 7.40-7.54 (m, 6H), 5.83-6.14 (m, 2H), 5.66 (m, 1H), 5.50 (m, 1H), 5.30 (m, 1H), 4.93 (m, 2H), 3.15 (dd, J = 14.6, 7.3 Hz, 2H), 1.78-2.07 (m, 3H), 1.39 (m, 1H), 1.18 (m, 1H), 0.77 (t, J = 7.4 Hz, 3H); mass spectrum m/e 149 (M - Ph_2PO).

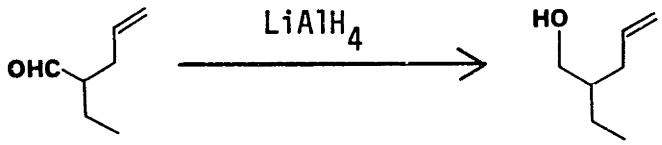


116 117 154

Diene phosphonate 154

The crude bromide 117 prepared in the usual manner from 1.95 g (11.7 mmol) of 116 and 18.2 mmol of the Ph_3P-Br_2 complex in CH_3CN at 0°C was combined with 2.76 mL (23.4 mmol) of trimethylphosphite [$(MeO)_3P$] in 80 mL of toluene. The mixture was heated to 120°C for 22 h, and then all volatile components were removed by distillation at atmospheric pressure. The residue was bulb-to-bulb distilled (160°C, 0.5 mm Hg) to give 2.36 g (78%) of 154: R_f 0.40 (1:1 ether-CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 6.16 (m, 1H), 5.99 (dd, J = 15.0, 10.5 Hz, 1H), 5.72 (m, 1H), 5.46 (m, 2H), 5.0 (m, 2H), 3.76 (d, J = 10.7 Hz, 6H), 2.64 (dd, J = 22.3, 7.5 Hz, 2H), 1.95-2.15 (m, 3H), 1.43 (m, 1H), 1.23 (m, 1H), 0.84 (t, J = 7.3 Hz, 3H); IR (neat) 3070, 2960, 2920,2875, 2860, 1640; mass spectrum

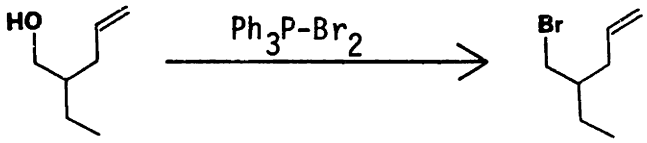
m/e 258 (parent ion). Anal. Calcd. for $C_{13}H_{23}O_3P$: C, 60.45; H, 8.98; P, 11.99. Found: C, 60.24; H, 9.28; P, 12.10.



114 135

Alcohol 135

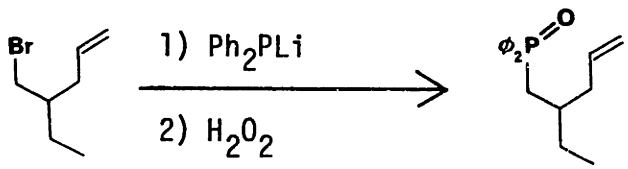
A solution of 7.98 g (7.12 mmol) of aldehyde 114[82] in 20 mL of ether was added dropwise over a 45 min period to a stirred solution of $LiAlH_4$ (1.5 g, 30 mmol) in 20 mL of ether at 0°C. The mixture was allowed to warm to 23°C, stirred for 2 h, and then cooled to 0°C. To the resulting vigorously stirred mixture was added cautiously 1.5 mL of H_2O and then 5.0 mL of aqueous 1N NaOH. The mixture was filtered and the white precipitate rinsed with portions of ether (75 mL total). The combined organic filtrates were concentrated in vacuo and the residue bulb-to-bulb distilled (140-150°C, 100 mm Hg) to give 7.28 g (90%) of alcohol 135: R_f 0.26 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 5.77 (m, 1H), 4.98 (m, 2H), 3.49 (d, J = 5.9 Hz, 2H), 2.06 (m, 2H), 1.98 (br s, 1H), 1.47 (m, 1H), 1.31 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H); IR (neat) 3325, 3080, 2970, 2930, 2880, 1640 cm^{-1}; mass spectrum m/e 96 (M - H_2O). Anal. Calcd. for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.88; H, 12.66.



135 136

Bromide 136

To 15.5 g (59.0 mmol) of Ph_3P in 60 mL of CH_3CN was added 3.0 mL of Br_2. This light yellow solution was stirred for 10 min and then 5.19 g (45.5 mmol) of alcohol 135 in 10 mL of CH_3CN was added slowly. Fifteen minutes later, the reaction mixture was diluted with 3.6 mL of methanol followed by 40 mL of water. The aqueous layer was extracted with hexane (4 X 60 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was bulb-to-bulb distilled (120-130°C, 100 mm Hg) to give 3.82 g (20.9 mmol, 47%) of bromide 136: R_f 0.77 (3:1 hexane-ether, $KMnO_4$ visualization); ^1H NMR (250 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.08 (m, 2H), 3.44 (d, J = 4.5 Hz, 2H), 2.14 (m, 2H), 1.62 (m, 1H), 1.27-1.49 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); IR (neat) 3085, 2960, 2930, 2870, 1640; mass spectrum m/e 179, 177 (parent ions).

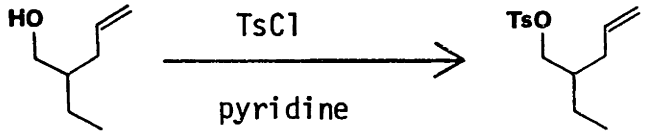


136 137

Diphenylphosphine oxide 137

To a suspension of 232 mg (33.3 mmol) of freshly cut lithium wire in 2 mL of THF at 23°C was added 1.64 mL (9.15 mmol) of chlorodiphenylphosphine (Pn_2PCl).[83] This mixture was then stirred for 3.5 h to give a deep red solution which was cooled to -60°C. To this mixture was then added 1.47 g (8.32 mmol) of bromide 136 in 3 mL of THF over a 15 min interval. The reaction mixture was then allowed to warm to 23°C over 30 min. Fifteen minutes later, 0.5 mL of water was added. Solvent was then removed in vacuo and the resulting residue was diluted with 25 mL of CH_2Cl_2. This solution was treated with 25 mL of aqueous 5% H_2O_2 in a separatory funnel for 15 min with vigorous mixing. The organic layer was washed sequentially with 25 mL each of saturated aqueous Na_2SO_4, aqueous 0.3N HCl, and half saturated aqueous $NaHCO_3$. The combined organic layers were dried, filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (silica gel, 40 mm column, ethyl acetate as eluant) to afford 2.11 g (85%) of 137, a white solid: mp 60.5-61.0°C, R_f 0.11 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.67-7.80 (m, 4H), 7.42-7.55 (m, 6H), 5.65 (m, 1H), 4.98 (m, 2H), 2.10-2.35 (m, 4H), 1.92 (m, 1H), 1.53 (m, 1H), 1.38 (m, 1H), 0.82 (t,

J = 7.3 Hz, 3H); IR (CH_2Cl_2) 3040, 2970, 2930, 1640 cm^{-1}; mass spectrum m/e 298 (parent ion). Anal. Calcd. for $C_{19}H_{23}OP$: C, 76.49; H, 7.77; P, 10.38. Found: C, 76.24; H, 7.64; P, 10.21.

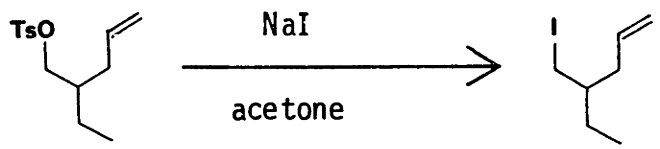


135 143

Tosylate 143

To a stirred solution of 6.19 g (54.3 mmol) of alcohol 135 in 50 mL of pyridine at 0°C was added 15.5 g (81.0 mmol) of p-toluenesulfonyl chloride. This mixture was allowed to warm to 23°C, stirred for 12 h, and then diluted with 20 mL of H_2O and 100 mL of ether. The organic layer was extracted sequentially with aqueous 1N HCL (3 X 75 mL), H_2O (1 X 75 mL), and half saturated aqueous $NaHCO_3$ (1 X 75 mL). Each aqueous extract was extracted with ether (1 X 100 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 50 mL column, 4:1 hexane-ether as eluant) to afford 12.3 g (84%) of tosylate 143: R_f 0.41 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.76 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 5.60 (m, 1H), 4.91 (m, 2H), 3.90 (m, 2H), 2.42 (s, 3H), 2.02 (t, J = 6.8 Hz, 2H), 1.62 (m, 1H), 1.30 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H); IR (neat) 3370, 2960, 2925,

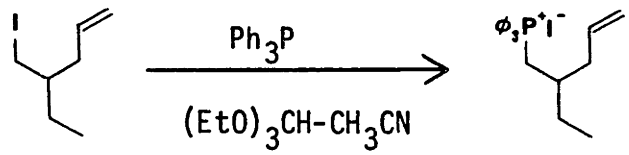
2875, 1640, 1600 cm^{-1}; mass spectrum m/e 95 (M - OTs). Anal. Calcd. for $C_{14}H_{20}O_3S$: C, 62.64; H, 7.52; S, 11.95. Found: C, 62.52; H, 7.84; S, 11.93.



143 144

Iodide 144

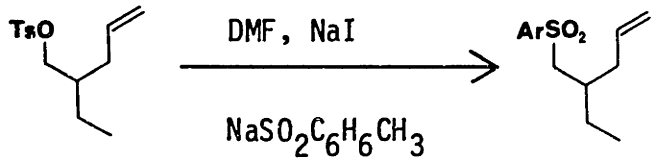
A solution of 1.24 g (4.6 mmol) of tosylate 143 in 15 mL of acetone at 23°C was treated with 1.9 g (9.3 mmol) of NaI. The mixture was stirred for 57 h and then solvent was removed in vacuo. The residue was dissolved in 50 mL of aqueous 0.5M sodium thiosulfate ($Na_2S_2O_3$) and extracted with CH_2Cl_2 (3 X 40 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, 30 mm column, 9:1 hexane-ether as eluant) to provide 738 mg (71%) of iodide 144: R_f 0.78 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 5.68 (m, 2H) 5.12 (m, 2H), 3.24 (d, J = 4.4 Hz, 2H), 2.07 (m, 2H), 1.34 (m, 2H), 1.18 (m, 1H), 0.87 (t, J = 7.3 Hz, 3H); IR (neat) 3080, 2970, 2930, 2880, 2840, 1640 cm^{-1}; mass spectrum m/e 224 (parent ion). Anal. Calcd. for $C_7H_{13}I$: C, 37.52; H, 5.85. Found: C, 37.87; H, 5.96.



144 145

Phosphonium salt 145

To 1.03 g (4.63 mmol) of iodide 144 in 10 mL of 4:1 CH_3CN-triethylorthoformate was added 1.21 g (4.63 mmol) of Ph_3P. This mixture was heated at 75°C for 60 h, cooled to 23°C, and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and then 145 precipitated (oil) upon addition of Et_2O. This procedure repeated three times provided 1.64 g (3.37 mmol, 73%) of pure gummy 145: ^1H NMR (270 MHz, $CDCl_3$) δ 7.71-7.89 (m, 15H), 5.61 (m, 1H), 5.05 (m, 2H), 3.38-3.67 (m, 2H), 1.78-2.24 (m, 3H), 1.28-1.53 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H).

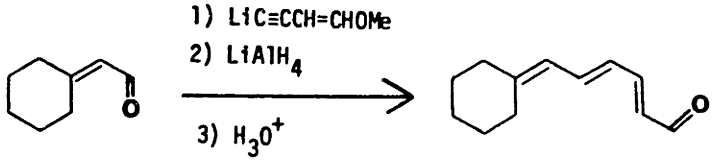


143 146

Sulfone 146

To a stirred solution of 3.88 g (14.5 mmol) of tosylate 143 in 20 mL

of DMF at 23°C was added 2.18 g (14.5 mmol) of NaI and 4.34 g (20.3 mmol) of sodium p-toluenesulfinate dihydrate ($C_7H_7SO_2Na$-2 H_2O). The stirred mixture was heated at 75°C for 12 h and then cooled to 23°C. It was diluted with 60 mL of half saturated aqueous NaCl and extracted with 1:1 hexane-ether (3 X 60 mL). Each organic extract was washed with 50 mL of half saturated aqueous NaCl. The combined organic extracts were dried, filtered, and concentrated <u>in vacuo</u>. The crude product was purified by flash chromatography (silica gel, 40 mm column, 9:1 hexane-ether as eluant) to afford 3.23 g (88%) of <u>146</u>: R_f 0.39 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 5.60 (m, 1H), 4.98 (m, 2H), 2.98 (ddd, J = 33.1, 14.6, 5.9 Hz, 2H), 2.43 (s, 3H), 2.14 (m, 2H), 1.98 (m, 1H), 1.43 (m, 2H), 0.81 (t, J = 7.3 Hz, 2H); IR (CH_2Cl_2) 3040, 2960, 2920, 2870, 1640, 1600 cm^{-1}; mass spectrum m/e 97 (M - OTs). <u>Anal.</u> Calcd. for $C_{14}H_{20}O_2S$: C, 66.63; H, 7.99; S, 12.70. Found: C, 66.35; H, 8.20; S, 12.92.



<u>109</u> <u>138</u>

<u>Triene aldehyde 138</u>

To a stirred solution of 1.91 g (22.9 mmol) of 1-methoxy-1-butene-3-

yne[84] in 10 mL of THF at -78°C was added over 10 min 18.0 mL (22.9 mmol) of 1.28M n-BuLi in hexane.[85] Ten minutes later, the black mixture was allowed to warm to 0°C, at which point 2.19 g (17.6 mmol) of 109[86] in 10 mL of THF was added dropwise (1 mL/min). The resulting solution was stirred at 0°C for 10 min and then was allowed to warm to 23°C. Three hours later the solution was cooled to 0°C and quenched with 0.3 mL of methanol. The reaction mixture was then treated cautiously with a slurry of 1.34 g (35.0 mmol) of $LiAlH_4$ in 10 mL of THF. The green-brown mixture was allowed to warm to 23°C, stirred for 3 h, and then cooled to 0°C. To the vigorously stirred mixture was then added cautiously, dropwise, 2.0 mL of H_2O and 6.0 mL of aqueous 1N NaOH. The mixture was filtered and the precipitate rinsed with 5-10 mL portions of THF (40 mL total). The combined organic filtrates were diluted with 60 mL of aqueous 0.5M HCl and then vigorously stirred at 23°C for 1 h. The aqueous layer was separated and extracted with ether (3 X 80 mL). The combined organic phases were dried, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, 40 mm column, 4:1 hexane-ether as eluant) to afford 2.48 g (80%) of 138 : R_f 0.36 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 9.54 (d, J = 8.3 Hz, 1H),

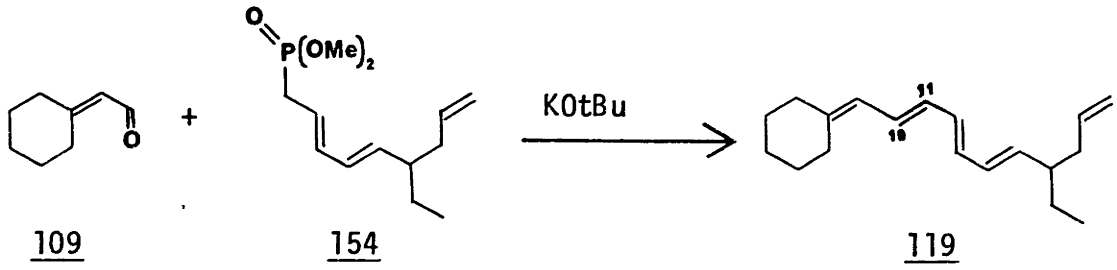
84. The following procedure was used to prepare 1-methoxy-1-butene-3-yne. A commercially available sample (Aldrich) of 1-methoxy-1-butene-3-yne (20 mL) as a 50% w/w mixture in a solution of 4:1 methanol-water was diluted with water (20 mL). The mixture was extracted with CH_2Cl_2 (1 X 30 mL). The organic extract was extracted with water (25mL) and then dried, filtered, and concentrated in vacuo. The dark residue was buld-to-bulb distilled (100-110°C, 100 mm Hg) to afford 6.24 g of clear 1-methoxy-1-butene-3-yne. The compound rapidly yellowed and was stored with a small amount of BHT at -20°C .

85. Marshal, D.; Whitney, M.C. J. Chem. Soc. 1956, 4082.

86. Cyclohexylidene acetaldehyde (109) was prepared according to the procedure of Babler and Dauben (see reference 22) and was bulb-to-bulb distilled (135-145°C, 50 mm Hg) prior to use.

7.17 (dd, J = 15.1, 11.2 Hz, 1H), 6.98 (dd, J = 14.6, 11.7 Hz), 6.36 (dd, J = 14.6, 11.2 Hz, 1H), 6.12 (dd, J = 15.1, 8.0 Hz, 1H), 5.95 (d, J = 11.7 Hz, 1H), 2.37 (br s, 2H), 2.22 (br s, 2H), 1.61 (br s, 6H); IR (neat) 3030, 2930, 2860, 1680, 1605 cm^{-1}; mass spectrum m/e 176 (parent ion).

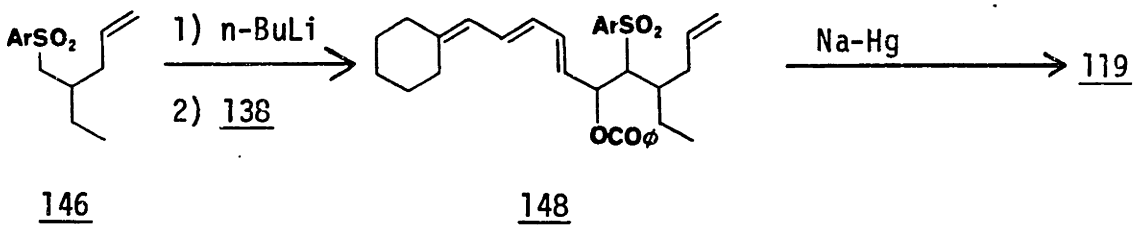
Preparation of pentaene 119



109 154 119

Method A

A solution of 478 mg (1.85 mmol) of phosphonate 154 and 230 mg (1.85 mmol) of aldehyde 109 in 4 mL of DME was added over the course of 5 min to a stirred solution of 416 mg (3.7 mmol) of potassium tert-butoxide (KOtBu) in 2 mL of DME at 0°C. The blood red mixture was stirred for 1 h at 0°C and then for 0.5 h at 23°C prior to removal of solvent in vacuo. The crude product was purified by flash chromatography (neutral alumina, 30 mm column, hexane as eluant) to afford 425 mg (95%) of 119 as a 95:5 E:Z isomer mixture at the newly formed C.10-C.11 double bond: R_f 0.80 (3:1 hexane-ether).

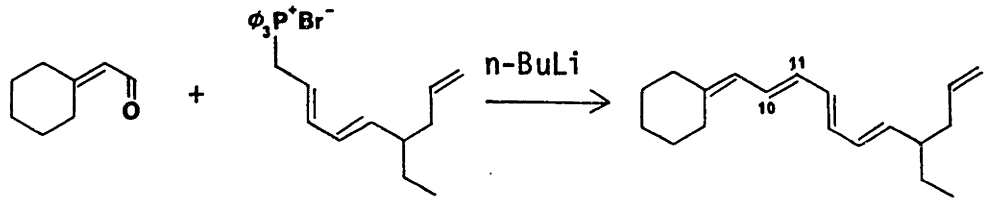


146 148

Method B

To a stirred solution of 162 mg (0.63 mmol) of sulfone 146 in 3 mL of THF at -78°C was added 0.51 mL (0.82 mmol) of 1.6M n-BuLi in hexane. The mixture was stirred for 20 min at -78°C and then 155 mg (0.88 mmol) of aldehyde 138 in 2 mL of THF was added. One hour later 0.18 mL (1.5 mmol) of benzoyl chloride was added. The reaction mixture was allowed to warm slowly to 23°C, stirred for 25 h, and then diluted with 13 mL of half saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 X 15 mL). The combined organic extracts were dried, filtered, and concentrated *in vacuo* to give crude 148 which was purified by flash chromatography (silica gel, 30 mm column, 300 mL 9:1 then 700 mL 3:1 hexane-ether as eluant). In this manner 235 mg (70%) of 148 as a mixture of diastereomers was obtained: R_f 0.28 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.09-7.92 (m, 9H), 5.92-6.55 (m, 4H), 5.45-5.78 (m, 2H), 4.96-5.20 (m, 2H), 3.57-3.73 (m, 1H), 1.30-2.85 (m, 13H), 1.53 (br s, 6H), 0.81-1.00 (m, 3H); IR (CH_2Cl_2) 3060, 3020, 2930, 2880, 2850, 1720, 1630, 1600 cm^{-1}; mass spectrum m/e (no parent ion), 122 ($C_7H_6O_2$), 105 (C_5H_5O), 91 (C_7H_7), 77 (C_6H_6), 64 (SO_2).

A stirred solution of 39 mg (0.61 mmol) of β-benzoyloxy sulfone 148 in 4 mL of 3:1 THF-MeOH at -20°C was treated with 96 mg of powdered 5% sodium amalgam. The reaction mixture was stirred for 2 h at -20°C and then filtered through a Kimwipe plugged pipette. The mixture was washed with 10 mL of H_2O and the aqueous layer extracted with hexane (4 X 10 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (neutral alumina, 10 mm column, 19:1 hexane-ether as eluant) to afford 11 mg (70%) of 119 as a 91:9 E:Z isomer mixture at the newly formed C.14-C.15 double bond: R_f 0.80 (3:1 hexane-ether).

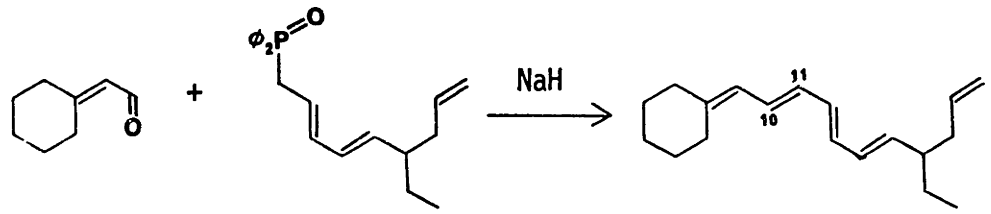


109 118 119

Method C (see entry 2, Table I)

A solution of 137 mg (0.280 mmol) of phosphonium salt 118 and 97 mg (1.1 mmol) of anhydrous LiBr in 5 mL of THF at -78°C was treated with 0.20 mL (0.49 mmol) of 2.43M n-BuLi in hexane. The resulting deep red solution was stirred for 20 min at -78°C prior to addition of 84 mg (0.68 mmol) of aldehyde 109. This reaction mixture was allowed to warm to 23°C over the course of 1.5 h and then stirred at 23°C for 1 h. Methanol (20 mL) was added and the mixture was stirred for an additional 12 h at 23°C.

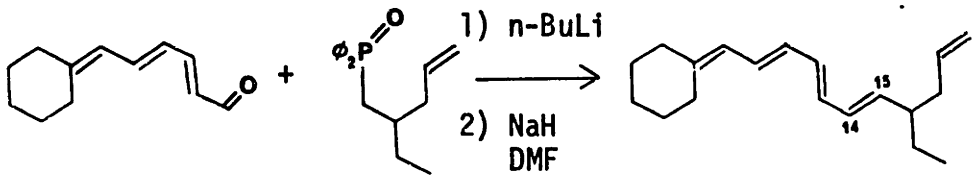
Concentration of the mixture in vacuo afforded a red syrup, which was dissolved in CH_2Cl_2. This material was then purified by flash chromatography (neutral alumina, 10 mm column, 15:1 hexane-ether as eluant) to afford 61 mg (86%) of 119 as a 77:23 E:Z isomer mixture at the newly formed C.10-C.11 double bond.



109 124 119

Method D (see entry 3, Table II)

To a solution of 47 mg (0.14 mmol) of 124 in 1 mL of DME at 23°C was added 22 mg (0.46 mmol) of 50% w/w NaH as an oil dispersion. The yellow reaction mixture was stirred for 15 min at 23°C, cooled to -40°C, and then treated with 17 mg (0.14 mmol) of aldehyde 109. The mixture turned light red as it was allowed to warm to 23°C over a 30 min period. The mixture turned dark red while being stirred for an additional hour at 23°C, at which point it was concentrated in vacuo. The crude product was purified by flash chromatography (neutral alumina, 10 mm column, hexane as eluant) to afford 13 mg (0.05 mmol, 37%) of 119 as a 97:3 E:Z isomer mixture at the newly formed C.10-C.11 double bond.



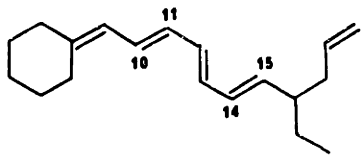
138 137 119

Method E (see entry 2, Table III)

To a stirred solution of 134 mg (0.45 mmol) of diphenylphosphine oxide 137 in 2 mL of THF at -78°C was added 0.22 mL (0.53 mmol) of 2.43M n-BuLi in hexane. The red reaction mixture was allowed to warm to -60°C over the course of 20 min and then was treated with 94 mg (0.53 mmol) of aldehyde 138. Twenty minutes later the light yellow-red mixture was treated with 0.22 mL (0.53 mmol) of 2.43M n-BuLi in hexane. The resulting black reaction mixture was stirred for 45 min at -40°C and then was treated with 0.5 mL of methanol to produce a light yellow solution. The mixture was allowed to warm to 23°C and then the solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, 10 mm column, 1:1 hexane-ether as eluant) to give 139 mg (0.29 mmol, 64%) of a mixture of adducts [139/140; R_f 0.53 (3:1 ether-CH_2Cl_2), 0.14 (3:1 ether-hexane)].

Without further purification 54 mg (0.11 mmol) of 139-140 adduct mixture as a white foam was dissolved in 1 mL of DMF and treated with 30 mg of NaH (50% w/w oil dispersion; prewashed with ether). The resulting mixture was heated to 60°C with stirring for 40 min during which time it turned red and became viscous. The reaction mixture was then diluted

carefully with 10 mL of H_2O. The aqueous layer was extracted with hexane (3 X 10 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (neutral alumina, 10 mm column, 15:1 hexane-ether as eluant) to afford 21 mg (73%) of 119 as a 17:83 E:Z isomer mixture at the newly formed C.14-C.15 double bond.



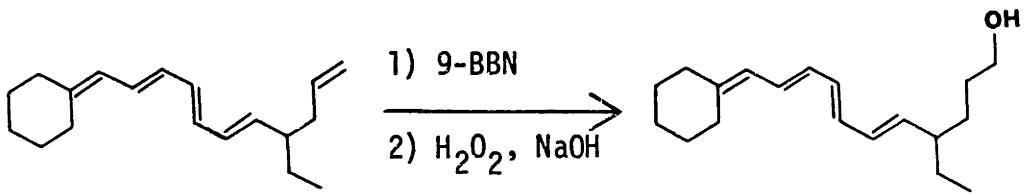
119

Pure samples of each of the olefin isomers of 119 were obtained by separation of the previously described mixtures by HPLC (Waters C-18 μ-Bondapak column, 30 cm length X 3.9 mm I.D., 20:80 H_2O-CH_3CN, flow rate 6.0 mL/min, 3 recycles). The (E,E,Z)- isomer elutes first followed by the (Z,E,E)- and (E,E,E)- isomers. The isomers are not separable by TLC on silica gel or alumina.

Data for (E,E,E)-119: R_f 0.80 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.45 (m, 1H), 6.00-6.23 (m, 4H), 5.82 (d, J = 11.7 Hz, 1H), 5.74 (m, 1H), 5.47 (dd, J = 14.6, 8.1 Hz, 1H), 4.99 (m, 2H), 2.29 (br s, 2H), 2.00-2.15 (m, 5H), 1.56 (br s, 6H), 1.25 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 144.0, 138.1, 137.1, 131.8, 131.6, 130.8, 128.3, 126.0, 122.6, 115.6, 44.4, 39.4, 37.5, 29.4, 28.6, 27.8, 27.4, 26.8, 11.6; IR (CH_2Cl_2) 3005, 2920, 2855, 1638, 1605 cm^{-1}; UV (EtOH) λ 325 (ε = 60,600), 309 (ε = 67,200), 295, 283, 271; mass spectrum m/e 256 (parent ion).

Data for (Z,E,E)-119: R_f 0.80 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.63 (t, J = 11.0 Hz, 1H), 6.06-6.23 (m, 4H), 5.93 (t, J = 10.3 Hz, 1H), 5.74 (m, 1H), 5.50 (dd, J = 14.2, 7.8 Hz, 1H), 4.99 (m, 2H), 2.29 (br s, 2H), 2.05-2.20 (m, 5H), 1.22-1.86 (m, 8H), 0.85 (t, J = 7.5 Hz, 3H); UV (EtOH) λ 323 (ε = 32,000), 308 (ε = 39,300), 294, 284, 270.

Data for (E,E,Z)-119: R_f 0.80 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.37-6.54 (m, 2H), 6.05-6.30 (m, 3H), 5.67-5.85 (m, 2H), 5.14 (t, J = 10.7 Hz, 1H), 4.97 (m, 2H), 2.49 (m, 1H), 2.15 (br s, 2H), 1.07-2.13 (m, 4H), 1.08-1.56 (m, 8H), 0.85 (t, J = 7.3 Hz, 3H); UV (EtOH) λ 323 (ε = 14,900), 308 (ε = 18,700), 295, 282, 271.

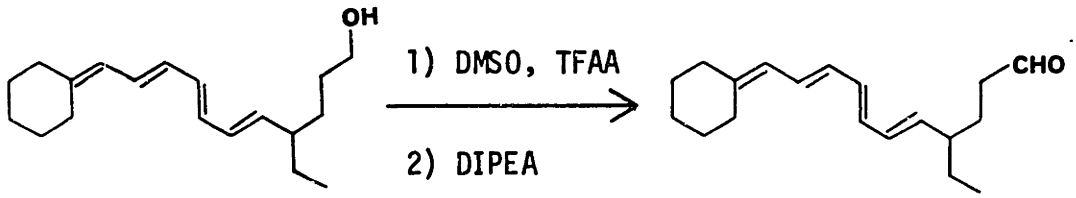


119 120

Tetraene alcohol 120

To 452 mg (1.76 mmol) of 119 (neat) at 0°C was added 8.0 mL (3.5 mmol) of 0.44M 9-BBN in THF. After the mixture was stirred for 3 h at 0°C, 1 mL of methanol was added. Ten minutes later, 5 mL of aqueous 6N NaOH and 10 mL of aqueous 30% H_2O_2 were added and then the mixture was allowed to warm to 23°C. After 3 h, the mixture was diluted with 50 mL of aqueous 3% sodium thiosulfate. The aqueous layer was then extracted with CH_2Cl_2 (4 X 40 mL). The combined organic extracts were

dried, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (neutral alumina, 30 mm column, 3:1 hexane-ether as eluant). The appropriate fractions were concentrated *in vacuo*, diluted with 20 mL of ethanol, and concentrated *in vacuo* to afford 413 mg (86%) of pure alcohol 120: R_f 0.20 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.46 (m, 1H), 6.00-6.27 (m, 4H), 5.83 (d, J = 11.2 Hz, 1H), 5.41 (dd, J = 14.2, 8.8 Hz, 1H), 3.62 (m, 2H), 2.30 (br s, 2H), 2.16 (br s, 2H), 1.93 (m, 1H), 1.22-1.63 (m, 5H), 1.56 (br s, 6H), 1.27 (m, 2H), 0.85 (t, J = 7.3 Hz, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 144.4, 138.5, 131.7, 131.5, 131.0, 130.7, 128.3, 122.6, 63.1, 44.7, 37.5, 34.9, 31.1, 28.6, 28.2, 27.8, 27.5, 26.8, 11.7; IR (CH_2Cl_2) 3600, 3010, 2930, 2860, 1640 cm^{-1}; UV (EtOH) λ 324 (ϵ = 54,600), 309 (ϵ = 60,900), 295, 284, 272; mass spectrum m/e 274 (parent ion).

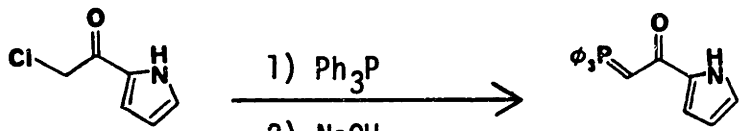


120 107

Tetraene aldehyde 107

To a solution of 50 µL (0.70 mmol) of DMSO at -78°C in 1 mL of CH_2Cl_2 was added 60 µL (0.42 mmol) of trifluoroacetic anhydride. This mixture was stirred for 10 min and then 41 mg (0.15 mmol) of alcohol 120 in 2 mL of CH_2Cl_2 was added. The mixture was then allowed to warm to 23°C over

a 40 min period. It was stirred 20 min at 23°C before 150 μL of diisopropylethylamine (DIPEA) was added. The clear mixture was diluted with 15 mL of water and then the aqueous layer was extracted with CH_2Cl_2 (4 X 15 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (neutral alumina, 20 mm column, 9:1 hexane-ether as eluant) to afford 34 mg (80%) of aldehyde 107: R_f 0.57 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 9.76 (t, J = 1.5 Hz, 1H), 6.48 (m, 1H), 6.00-6.25 (m, 4H), 5.83 (d, J = 11.2 Hz, 1H), 5.34 (dd, J = 14.7, 9.3 Hz, 1H), 2.41 (m, 2H), 2.30 (br s, 2H), 2.16 (br s, 2H), 1.92 (m, 1H), 1.78 (m,1H), 1.57 (br s, 6H), 1.26-1.51 (m, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 202.3, 144.4, 137.1, 132.1, 131.8, 130.5, 128.7, 122.5, 44.4, 42.0, 37.5, 29.4, 28.6, 28.0, 27.8, 27.2, 26.8, 11.6; IR (CH_2Cl_2) 3030, 2935, 2860, 1725, 1640 cm^{-1}; UV (EtOH) λ 324 (ε = 61,400), 309 (ε = 68,000), 295, 284, 272; mass spectrum m/e 272 (parent ion).



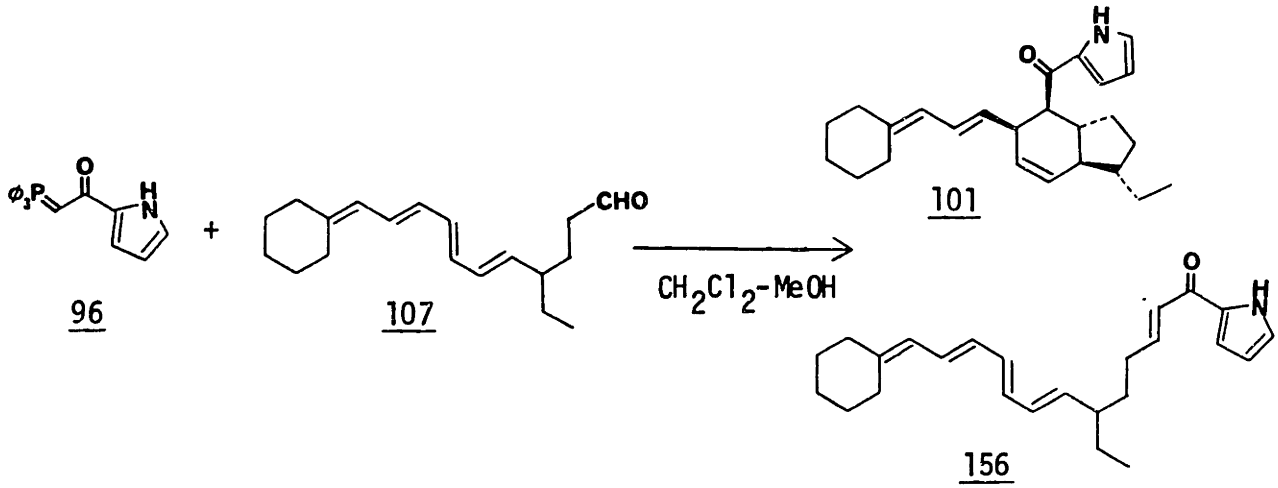
96

Phosphorane 96[87]

A solution of 18.6 g (71 mmol) of triphenylphosphine (Ph_3P) in 50 mL of toluene was added, over the course of 0.5 h, to a refluxing

87. This experiment was performed by A. G. Myers; see reference 10.

solution of 10.1 g (70.4 mmol) of 2-pyrrylchloromethyl ketone.[88] Four hours later it was cooled to 23°C. The solids which precipitated upon cooling were isolated by filtration, washed with toluene, and then dissolved in acidic (pH 3) methanol. The methanolic solution was filtered and then basified with 1M NaOH to pH 13. The resulting precipitate was collected on a Büchner funnel, washed consecutively with methanol and ether, and then dried for several days in vacuo to give 12.7 g (34.5 mmol, 49%) of 96; mp: 250°C (dec).
Data for 96: ^{1}H NMR (60 MHz, CD_3CO_2D + 2 drops D_2O) δ 7.8 (m, 15H), 7.3 (d, J = 3 Hz, 2H), 6.4 (m, 1H), 2.8 (s, 1H); IR (nujol) 3120, 1420 cm^{-1}; mass spectrum m/e 369 (parent ion).



Pentaene 156

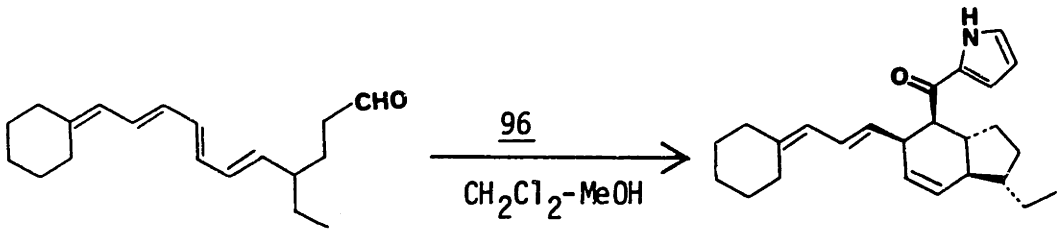
A stirred solution of aldehyde 107 (44 mg, 0.16 mmol) in 3 mL of 2:1 CH_2Cl_2-MeOH at 23°C was treated with phosphorane 96 (200 mg, 0.54 mmol) and a small crystal (3 mg) of BHT. This mixture was stirred

88. (a) Ermili, A.; Castro, A.J.; Westfall, P.A. J. Org. Chem. 1965 30, 339.

(b) Harbuck, J.W.; Rapaport, H. J. Org. Chem. 1972, 37, 3618.

for 17 h at 23°C and then concentrated in vacuo. The crude product was purified by flash chromatography (neutral alumina, 20 mm column, 7:1 hexane-ether as eluant) to afford 7 mg (16%) of aldehyde 107, 15 mg (0.041 mmol, 25%) of cycloadduct 101, and 27 mg (0.075 mg, 47%) of pentaene 156.

Data for 156: R_f 0.16 (3:1 hexane-ether); ^1H NMR (250 MHz, $CDCl_3$) δ 9.76 (br s, 1H), 6.95-7.10 (m, 3H), 6.72 (m, 1H), 6.45 (m, 1H), 6.32 (m, 1H), 6.0-6.2 (m, 4H), 5.84 (d, J = 11.2 Hz, 1H), 5.40 (dd, J = 14.4, 9.1 Hz, 1H), 2.30 (m, 4H), 2.15 (br s, 2H), 1.25-1.62 (m, 4H), 1.57 (br s, 6H), 0.86 (t, J = 7.3 Hz, 3H).



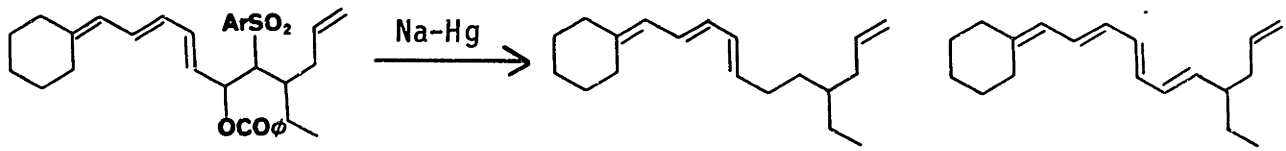
107 101

Cycloadduct 101 (X-14547A model compound)

To a stirred solution of 34 mg (0.12 mmol) of aldehyde 107 and 4 mg (0.02 mmol) of BHT in 3 mL of 2:1 CH_2Cl_2-MeOH at 23°C was added 110 mg (0.31 mmol) of phosphorane 96. This mixture was heated to 40°C for 38 h and then cooled to 23°C. The mixture was filtered through a 0.5 g plug of Florisil and concentrated in vacuo. The residue was purified by chromatography on one 0.5-mm silica gel plate (3:1 hexane-ether, one development) to give 23 mg (0.064 mmol, 53%) of 101, 7 mg

(0.02 mmol, 17%) of cis fused cycloadducts (R_f 0.28, 3:1 hexane-ether), and 10 mg (0.028 mmol, 24%) of non-cyclized material (R_f 0.16; 3:1 hexane-ether) apparently containing (Z)- olefin isomers.

Data for 101: R_f 0.46 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 9.33 (br s, 1H), 7.00 (s, 1H), 6.92 (m, 1H), 6.29 (m, 1H), 5.97 (m, 2H), 5.65 (d, J = 10.4 Hz, 1H), 5.51 (dt, J = 9.9, 2.8 Hz, 1H), 5.40 (dd, J = 8.3, 7.2 Hz, 1H), 3.41 (m, 2H), 1.00-2.28 (m, 19H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 191.1, 142.0, 132.6, 130.5, 129.6, 129.1, 127.1, 124.1, 121.9, 115.2, 110.3, 52.5, 50.2, 44.8, 43.7, 40.7, 37.1, 29.7, 29.1, 28.3, 27.6, 27.3, 27.0, 26.8, 12.4; IR (CH_2Cl_2) 3425, 3010, 2925, 2850, 1640 (br), 1540 cm^{-1}; UV (EtOH) λ 291 (ε = 15,300), 244 (ε = 30,500); mass spectrum m/e 363 (parent ion). High resolution mass spectrum; Calcd. for $C_{25}H_{33}NO$: 363.25621. Found: 363.25815.



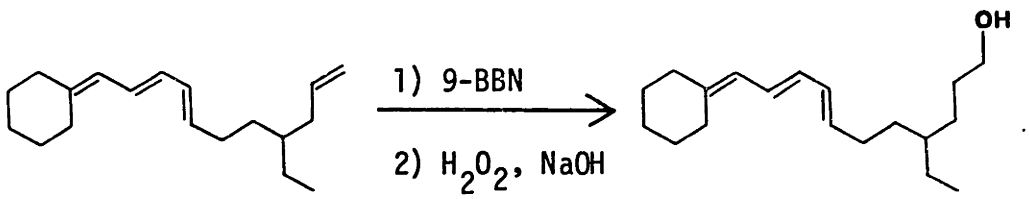
148 161 119

Tetraene 161

When samples of β-benzoyloxy sulfone 148 which had been exposed to strongly basic conditions during preparation were subjected to sodium amalgam reduction, mixtures of 161 and 119 were obtained. Such mixtures were not obtained, however, when 148 was prepared according

to the procedure previously described. Nevertheless, when mixtures of 161 and 119 were obtained, they were easily separated by reverse phase HPLC (Waters C-18 μ-Bondapak, 30 cm length X 3.9 mm ID, 20:80 H_2O-CH_3CN as eluant, flow rate: 6.0 mL/min). Under these conditions, 161 eluted between 31 to 35 min while 119 eluted at 41 to 47 min.

Data for 161: R_f 0.78 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.40 (m, 1H), 6.02-6.18 (m, 2H), 5.80 (d, J = 11.6 Hz, 1H), 5.74 (m, 1H), 5.44 (dd, J = 14.3, 8.2 Hz, 1H), 4.99 (m, 2H), 2.28 (m, 2H), 1.95-2.20 (m, 6H), 1.40-1.56 (m, 9H), 1.18-1.38 (m, 2H), 0.85 (t, J = 7.4 Hz, 1H); IR (CH_2Cl_2) 2920, 2850, 1630 cm^{-1}; UV (EtOH) λ 289 (ε = 39,400), 277 (ε = 52,300), 267 (ε = 37,400).

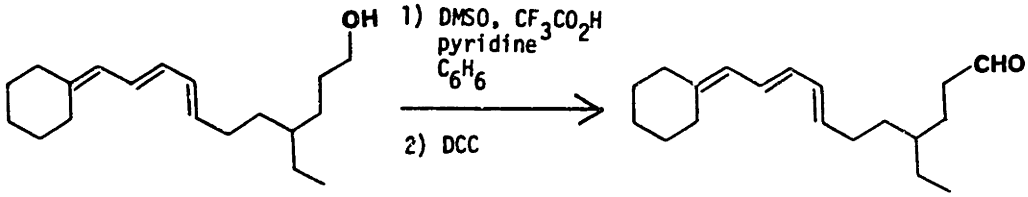


161 162

Triene alcohol 162

A solution of 9-BBN in THF (0.44M, 1.01 mL, 0.46 mmol) was added to 59 mg (0.23 mmol) of tetraene 161 at 0°C. The resulting solution was stirred for 3 h at 0°C and then was treated sequentially with 0.4 mL of MeOH, 0.2 mL of aqueous 6N NaOH, and 0.35 mL of aqueous 30% H_2O_2. This solution was stirred for 3 h at 0°C and then anhydrous K_2CO_3 was

added until a granular solid was obtained. The resulting mixture was filtered and the solid residue rinsed with ether (8 X 2 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash chromatography (neutral alumina, 10mm column, 30 mL hexane and then 400 mL 3:1 hexane-ether as eluant) to afford 53 mg (0.19 mmol, 83%) of alcohol 162: R_f 0.14 (3:1 hexane-ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.40 (m, 1H), 6.01-6.17 (m, 2H), 5.79 (d, J = 11.0 Hz, 1H), 5.37 (dd, J = 14.1, 9.0 Hz, 1H), 3.61 (t, J = 6.3 Hz, 2H), 2.28 (br s, 2H), 2.14 (br s, 2H), 1.82-1.98 (m, 1H), 1.70 (s, 1H), 1.18-1.67 (m, 16H), 0.84 (t, J = 7.4 Hz, 3H); IR (CH_2Cl_2) 3600, 2930, 2850, 1640 cm^{-1}.

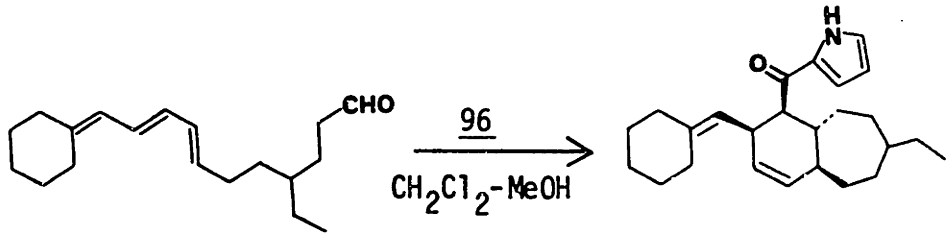


162 163

Triene aldehyde 163

A solution of 50 μL of pyridine, 25 μL of trifluoroacetic acid, and 1 mL of DMSO in 1.5 mL of benzene was added to 44 mg (0.16 mmol) of alcohol 162 at 23°C. To this mixture was added 200 mg (0.97 mmol) of DCC. The resulting mixture was stirred for 14 h at 23°C. It was then treated with 100 mg of oxalic acid in 1.5 mL of methanol and 5 mL of ether. This mixture was stirred for 45 min, and then filtered to remove precipitated dicyclohexylurea. The organic layer was washed

with half saturated aqueous NaCl (2 X 15 mL). Following back extraction of the aqueous washings with 7:1 hexane-ether (2 X 15 mL each), the combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (neutral alumina, 10 mm column, 15:1 hexane-ether as eluant) to afford 25 mg (0.093 mmol, 58%) of aldehyde 163: R_f 0.53 (3:1 hexane-ether), 0.42 (0.3% EtOH in CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 9.75 (t, J = 1.5 Hz, 1H), 6.40 (m, 1H), 6.00-6.12 (m, 2H), 5.93 (d, J = 11.1 Hz, 1H), 5.36 (dd, J = 14.1, 9.1 Hz, 1H), 2.44 (m, 2H), 2.29 (br s, 2H), 2.15 (br s, 2H), 1.64-1.99 (m, 2H), 1.20-1.56 (m, 11H), 0.85 (t, J = 7.4 Hz, 3H); IR (CH_2Cl_2) 2930, 2850, 1720, 1630 cm^{-1}; UV (EtOH) λ 288 (ϵ = 42,900), 275 (ϵ = 55,800), 265 (ϵ = 41,000).



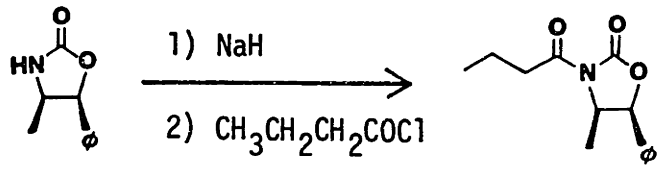
163 165

Cycloadduct 165

To a stirred solution of 25 mg (0.092 mmol) of 163 in 3 mL of 2:1 CH_2Cl_2-MeOH at 23°C was added 100 mg of phosphorane 96. This mixture was stirred for 31 h at 23°C, at which point solvent was removed in vacuo. The residue was purified by chromatography on one 0.5-mm silica gel plate (1:1 hexane-ether, one development) to afford 28 mg (0.076 mmol, 83%)

of a 3:1 mixture of 165 and a cis fused isomer (R_f 0.21, 3:1 hexane-ether). The non-cyclized material (R_f 0.12, 3:1 hexane-ether) was not isolated. The cycloadduct mixture was separated by chromatography on one 0.5 mm silica gel plate (3:1 hexane-ether, two developments) to afford 14 mg (39%) of isomerically pure 165: R_f 0.28 (3:1 hexane-ether), ^1H NMR (250 MHz, $CDCl_3$) δ 9.33 (br s, 1H), 6.97 (m, 1H), 6.89 (m, 1H), 6.27 (m, 1H), 5.91 (d, J = 9.7 Hz, 1H), 5.39 (m, 1H), 4.96 (d, J = 10.4 Hz, 1H), 3.63 (m, 1H), 3.39 (dd, J = 11.0, 6.4 Hz, 1H), 1.01-2.08 (m, 22H), 0.94 (t, J = 7.3 Hz, 3H), 0.88 (m, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 191.0, 12.4; IR (CH_2Cl_2) 3430 (s), 3260 (w), 1920 (s), 1850, 1720 (vw), 1640 (s) cm^{-1}; UV (EtOH) λ 291 (ϵ = 16,100), 234 (ϵ = 5,200); mass spectrum m/e 337 (M - C_2H_5).

Experimental Procedures for Chapter III

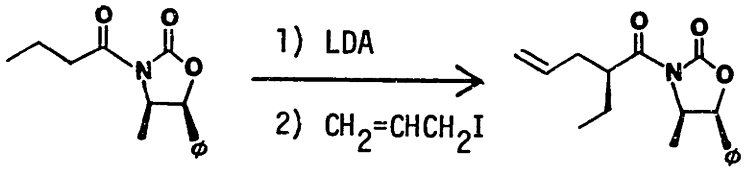


173 174

Imide 174

To a stirred solution of 13.0 g (73.6 mmol) of carbamate 173[50] in 150 mL of THF was added 5.30 g (110 mmol) of sodium hydride (NaH) as a 50% oil dispersion. This mixture was stirred for 1 h at 23°C and then 11.4 mL (110 mmol) of butyryl chloride was added. The reaction mixture was stirred for 3 h, cooled to 0°C, and then diluted carefully with 70 mL of distilled water. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 70 mL). The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 40 mm column, 1 liter of 9:1 then 1 liter of 3:1 hexane-ether as eluant) to afford 16.0 g (88%) of imide 174; mp: 56.5-57.5°C.

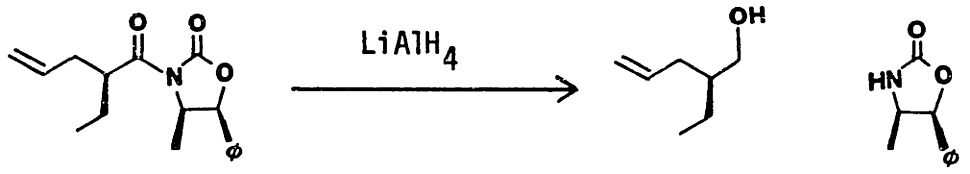
Data for 174: R_f 0.36 (3:1 hexane-ether); $[\alpha]_D^{21}$ +52.9 (c = 1.22, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.28-7.47 (m, 5H), 5.70 (d, J = 7.3 Hz, 1H), 4.78 (m, 1H), 2.82-3.05 (m, 2H), 1.62-1.80 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); 0.90 (d, J = 6.7 Hz, 3H); IR (CH_2Cl_2) 3050, 2970, 2940, 2880, 1785 (vs), 1705 (vs); mass spectrum m/e 247 (parent ion).



174 175

Imide 175

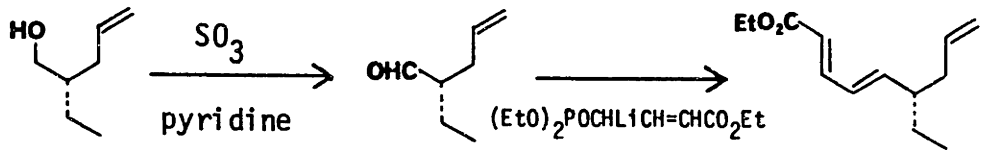
To a solution of 11.0 mmol of lithium diisopropylamine (LDA) in 20 mL of THF at -78°C was added 2.46 g (9.96 mmol) of imide 174 in 10 mL of THF. After one hour at -78°C, the mixture was allowed to warm to -20°C during the course of one hour. The mixture was stirred for 3 h at -20°C and then diluted with 40 mL of aqueous 1N HCl. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 X 50 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 40 mm column, 9:1 hexane-ether as eluant) to afford 2.02 g (71%) of 175: R_f 0.46 (3:1 hexane-ether); $[\alpha]_D^{21}$ +27.0° (c = 1.39, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.28-7.45 (m, 5H), 5.81 (m, 1H), 5.03 (m, 2H), 4.81 (m, 1H), 3.87 (m, 1H), 2.25-2.50 (m, 2H), 1.50-1.81 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); IR (neat) 3070, 2970, 2935, 2880, 1780 (vs), 1700 (vs), 1640 cm^{-1}; mass spectrum m/e 287 (parent ion).



175 135 173

Alcohol 135 (optically active)

To a suspension of 560 mg (14.8 mmol) of lithium aluminum hydride ($LiAlH_4$) in 50 mL of ether at 0°C was added 3.15 g (11.0 mmol) of imide 175 in 20 mL of ether. The mixture was stirred for 2 h and then was quenched by the sequential addition of 0.25 mL of water followed by 0.75 mL of aqueous 1N NaOH. This suspension was stirred at 23°C for 15 min and then the white precipitate was removed by filtration through a sintered glass funnel. The filtrate was concentrated in vacuo and the residue bulb-to-bulb distilled (50-150°C, 40-60 mm Hg, dry ice trap) to afford 940 mg (75%) of optically active alcohol 135 ($[\alpha]_D^{21}$ +1.5° (c = 1.40, $CHCl_3$)), the spectroscopic properties of which were identical to that previously reported for racemic 135.

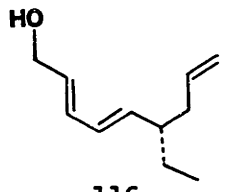


135 114 115

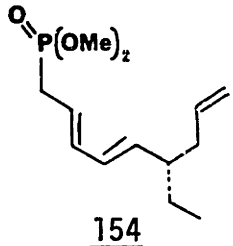
Diene ester 115 (optically active)

To a suspension of 806 mg (5.07 mmol) of sulfur trioxide-pyridine complex and 0.40 mL (5.2 mmol) of DMSO in 3 mL of CH_2Cl_2 at 23°C was added 1.41 mL (10.1 mmol) of triethylamine. All solids dissolved to give a deep red-brown solution. To this mixture was added 193 mg (1.69 mmol) of optically active 135 in 2 mL of CH_2Cl_2. The reaction mixture was stirred for 1 h and then was diluted with 9.0 mL of aqueous 1N HCl (until pH 3) followed by 9.0 mL of saturated aqueous NaCl. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 15 mL). The combined organic extracts were dried, filtered through 0.5 g of Florisil, and concentrated by removal of solvent at atmospheric pressure through a short path still (bath temperature kept below 70°C) until a final volume of approximately 2 mL was obtained. This solution containing optically active 114 was diluted with 3.0 mL of THF and then added to 2.55 mmol of the lithium anion of ethyl 4-diethylphosphonocrotonate in 3.7 mL of THF at -50°C. The mixture was allowed to warm to 23°C over a 2 h period. After being stirred for 4 h at 23°C, the mixture was diluted with 25 mL of aqueous 1N HCl and the aqueous layer was extracted with CH_2Cl_2 (5 X

20 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 20 mm column, 4:1 hexane-ether as eluant) to give 243 mg (69%) of optically active 115 ($[\alpha]_D^{20}$ -14.7° (c = 1.06, $CHCl_3$)).



116



154

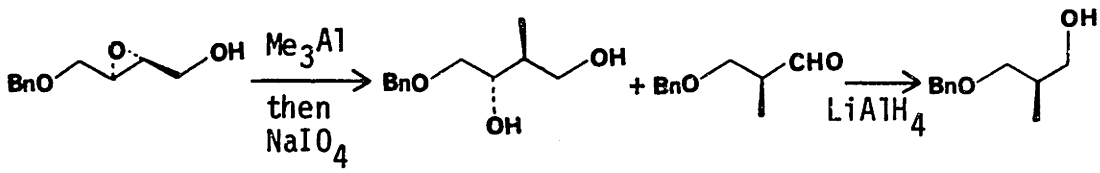
Diene alcohol 116 (optically active)

Reduction of optically active 115 with $LiAlH_4$ as previously described provided optically active alcohol 116 ($[\alpha]_D^{20}$ -24.9° (c = 1.47, $CHCl_3$).

Diene phosphonate 154 (optically active)

The transformation of optically active 116 via bromide 117 to phosphonate 154 as previously described afforded optically active 154 ($[\alpha]_D^{20}$ -22.3° (c = 1.60, $CHCl_3$)

1,3-diol 183, aldehyde 184, and alcohol 185



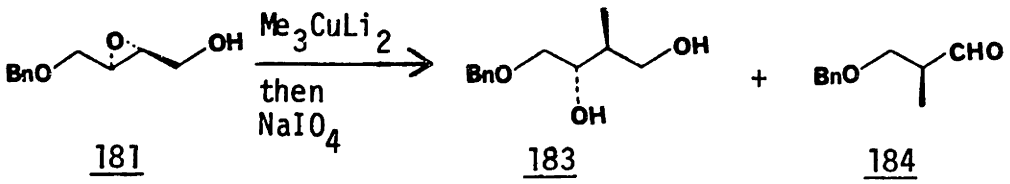
181 183 184 185

Method A

To a 0°C solution of 2.63 g (13.6 mmol) of 181 ($[\alpha]_D^{21}$ +21.4°, c = 1.40, $CHCl_3$; >95% ee)[57] in 20 mL of CH_2Cl_2 was added dropwise 17.2 mL (40.6 mmol, 3 equiv.) of 2.36M Me_3Al in hexane. The reaction mixture was stirred at 23°C for 10 h, cooled to 0°C, and then quenched with 40 mL of aqueous 3N HCl. This solution was stirred for 0.5 h at 23°C and then was extracted with CH_2Cl_2 (4 X 40 mL). The combined extracts were dried, filtered, and concentrated in vacuo. The residue (a 83:17 ratio of 182:183 by 270 MHz ^1H NMR analysis) was dissolved in 70 mL of 1:1 THF-H_2O and treated with 4.35 g (20.3 mmol) of $NaIO_4$. The reaction mixture was stirred for 2 h at 23°C, then diluted with 20 mL of saturated aqueous NaCl and 20 mL of ether. The aqueous layer was separated and extracted with CH_2Cl_2 (4 X 40 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 40 mm column, 3 liter 19:1 and then 1 liter 1:1 hexane-ether as eluant) to give 408 mg

(1.95 mmol, 14%) of 183 (R_f 0.27, 3:1 ether-hexane) and 1.76 g (9.91 mmol, 73%) of 184 (R_f 0.79, 3:1 ether-hexane).

Reduction of 184 in ether at 0°C with $LiAlH_4$ afforded (+)-185 in 93% isolated yield.



181 183 184

Method B

To a stirred suspension of 816 mg (4.30 mmol, 1.2 equiv.) of CuI in 15 mL of Et_2O at 0°C was added 12.9 mL (12.9 mmol, 3 equiv. to CuI) of 1M MeLi in ether. This cloudy white solution was stirred for 20 min at 0°C, cooled to -20°C, and then treated dropwise with 695 mg (3.58 mmol) of optically active epoxide 181 (>95% ee) in 6 mL of Et_2O. This reaction mixture was stirred for 1 h at -20°C prior to careful addition of 15 mL of saturated aqueous NH_4Cl. This suspension was then stirred vigorously for 1.5 h at 23°C. The clear ether layer was removed and the deep blue aqueous layer extracted with CH_2Cl_2 (3 X 30 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The crude product (a 86:14 ratio of 183:182 by 270 MHz

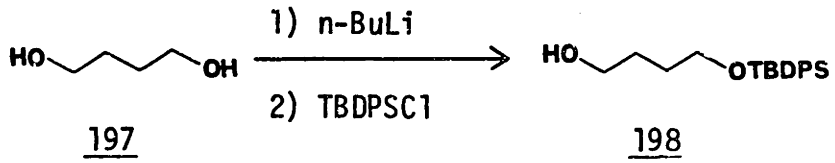
^{1}H NMR analysis) was dissolved in 50 mL of 1:1 H_2O-THF and treated with 300 mg of $NaIO_4$. This mixture was stirred for 12 h at 23°C and then diluted with 50 mL of saturated aqueous NaCl. The aqueous layer was separated and extracted with CH_2Cl_2 (4 X 50 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 30 mm column, 300 mL of 3:1 hexane-ether and then 600 mL ether-hexane as eluant) to afford 81 mg (0.46 mmol, 13%) of aldehyde 184 and 596 mg (2.84 mmol, 79%) of 1,3-diol 183.

Data for 183: R_f 0.27 (3:1 hexane-ether); $[\alpha]_D^{30}$ +16.5° (c = 1.18, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.57 (AB, J = 13.5 Hz, 2H), 3.59-3.79 (m, 4H), 3.46 (dd, J = 9.5, 7.4 Hz, 1H), 3.07 (br s, 1H), 3.02 (br s, 1H), 1.83 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H); IR (neat) 3400, 3090, 3060, 3030, 2960, 2880 cm^{-1}; mass spectrum m/e 210 (parent ion). Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.29; H, 8.87.

Data for 184: R_f 0.79 (3:1 ether-hexane); $[\alpha]_D^{21}$ +28.4° (c = 1.56, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.74 (d, J = 1.6 Hz, 1H), 7.34 (m, 5H), 4.54 (s, 2H), 2.69 (m, 1H), 1.15 (d, J = 6.9 Hz, 3H); IR (neat) 3090, 3070, 3040, 2980, 2870, 2720, 1725 cm^{-1}.

Data for 185: R_f 0.59 (3:1 ether-hexane); $[\alpha]_D^{21}$ +16.5° (c = 1.05, $CHCl_3$) [lit.[53] $[\alpha]_D$ +17.2° (c = 3.24, $CHCl_3$)]; $[\alpha]_D^{21}$ +5.2° (c = 1.46, EtOH) [lit.[50a] $[\alpha]_D$ +5.3° (c = 2.2, EtOH)]; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.53 (s, 2H), 3.40-3.63 (m, 4H), 2.63 (br s, 1H), 2.10 (m, 1H),

0.90 (d, J = 7.0 Hz, 3H); IR (neat) 3380, 3080, 3060, 3020, 2960, 2860 cm^{-1}.

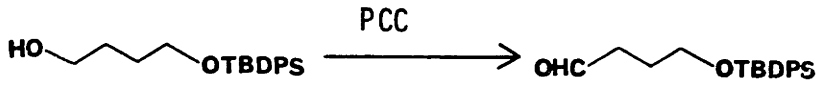


197 198

Alcohol 198

To a solution of 6.96 g (77.3 mmol) of 1,4-butanediol (197) in 80 mL of THF at -60°C was added dropwise 32.8 mL of 2.2M n-BuLi in hexane. This mixture was allowed to warm to 10°C over 30 min and then stirred at this temperature for 1 h. A solution of 15.2 g (55.4 mmol) of tert-butyldiphenylsilylchloride (TBDPSCl) in 5.0 mL of THF was then added dropwise. The reaction mixture was allowed to warm to 23°C, stirred for 22 h, and then diluted with 50 mL of aqueous 1N HCl. The aqueous layer was separated and extracted with CH_2Cl_2 (4 X 40 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 40 mm column, 1 liter of 4:1 hexane-ether and then 1 liter of 1:1 hexane-ether as eluant) to afford 17.6 g (97%) of 198: R_f 0.19 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.70-7.73 (m, 4H), 7.39-7.47 (m, 6H), 3.73 (t, J = 5.7 Hz, 2H), 3.68 (br s, 2H), 2.37 (br s, 1H), 1.68-1.72 (m, 4H), 1.09 (s, 9H); IR (neat) 3340, 3070, 3040, 2930, 2850,

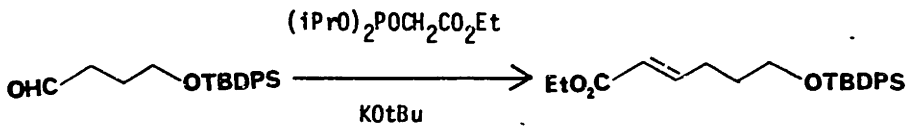
1960 (w), 1880 (w), 1820 (w), 1590 cm^{-1}; Anal. Calcd. for $C_{20}H_{28}O_2Si$: C, 73.12; H, 8.59. Found: C, 73.13; H, 8.77.



198 199

Aldehyde 199

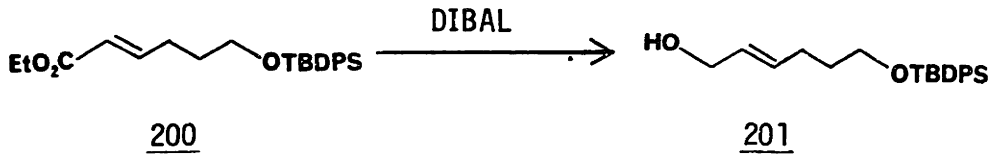
To a solution of 3.18 g (9.69 mmol) of 198 in 60 mL of CH_2Cl_2 at 23°C was added 2.82 g (12.6 mmol, 1.3 equiv.) of PCC. This mixture was stirred for 90 min at 23°C and then 40 mL of ether was added. The organic solution was removed and the black residue washed with ether (4 X 25 mL). The combined organic phases were filtered through 10 g of Florisil and then concentrated in vacuo to afford 2.76 g (8.45 mmol, 87%) of aldehyde 199: R_f 0.49 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 9.81 (t, J = 1.6 Hz, 1H), 7.66-7.69 (m, 4H), 7.37-7.46 (m, 6H), 3.71 (t, J = 6.0 Hz, 2H), 2.55-2.61 (m, 2H), 1.86-1.96 (m, 2H), 1.07 (s, 9H); IR (neat) 3070, 3040, 2950, 2930, 2710, 1960 (w), 1890 (w), 1820 (w), 1725 (vs), 1590 cm^{-1}.



199 200

Unsaturated ester 200

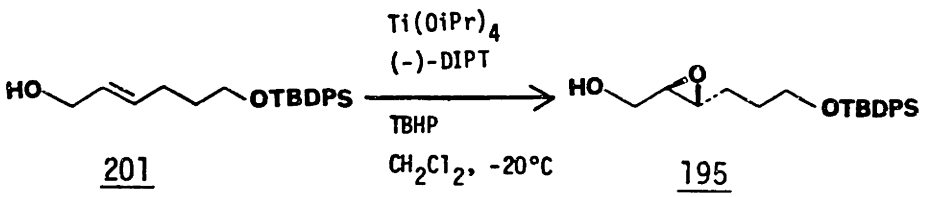
To a 0°C suspension of 3.49 g (31.2 mmol) of potassium tert-butoxide in 40 mL of THF was added 7.30 mL (31.2 mmol) of ethyl diisopropylphosphonoacetate.[53] The reaction mixture was allowed to warm to 23°C, stirred for 2 h, and then cooled to -78°C. To this mixture was added 5.09 g (15.6 mmol) of 199 in 15 mL of THF. Thirty minutes later, the mixture was allowed to warm to 23°C and then stirred for 10 h. The reaction mixture was poured into 80 mL of aqueous NH_4Cl and extracted with CH_2Cl_2 (4 X 50 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 40 mm column, 3:1 hexane-ether as eluant) to afford 5.25 g (13.3 mmol, 85%) of 200: R_f 0.55 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.66-7.69 (m, 4H), 7.37-7.47 (m, 6H), 6.99 (dt, J = 14.9, 7.3 Hz, 1H), 5.84 (dd, J = 14.8, 1.1 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.70 (t, J = 5.9 Hz, 2H), 2.34 (q, J = 7.3 Hz, 2H), 1.73 (quintet, J = 7.3 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H), 1.07 (s, 9H); IR (neat) 3070, 3050, 1960 (w), 1890 (w), 1840 (w), 1720 (s), 1655 (s), 1590 cm^{-1}; mass spectrum m/e 396 (M - C_4H_9); Anal. Calcd. for $C_{24}H_{32}O_3Si$: C, 72.68; H, 8.13. Found: 72.65; H, 8.19.



200 201

Allylic alcohol 201

To 4.16 g (10.5 mmol) of ester 200 in 100 mL of ether at -78°C was added 26.2 mL (26.2 mmol, 2.5 equiv.) of 1.0M diisobutylaluminum hydride (DIBAL) in hexane. The mixture was allowed to warm to 23°C. After being stirred for 2 h at 23°C, the mixture was cooled to 0°C and then 100 mL of aqueous 1N HCl was added carefully. The mixture was stirred for 15 min at 23°C, then the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (4 X 60 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 40 mm column, 1 liter each of 4:1, 3:1, and then 1:1 hexane-ether as eluant) to afford 3.65 g (10.3 mmol, 98%) of 201: R_f 0.18 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.70-7.73 (m, 4H), 7.38-7.49 (m, 6H), 5.59-5.76 (m, 2H), 4.08 (br s, 2H), 3.71 (t, J = 6.4 Hz, 2H), 2.19 (m, 2H), 1.69 (m, 2H), 1.57 (br s, 1H), 1.10 (s, 9H); IR (neat) 3320, 3070, 3050, 3930, 2850, 1960 (w), 1890 (w), 1820 (w), 1590 cm^{-1}; Anal. Calcd. for $C_{22}H_{30}O_2Si$: C, 74.52; H, 8.53. Found: C, 74.51; H, 8.64.



201 195

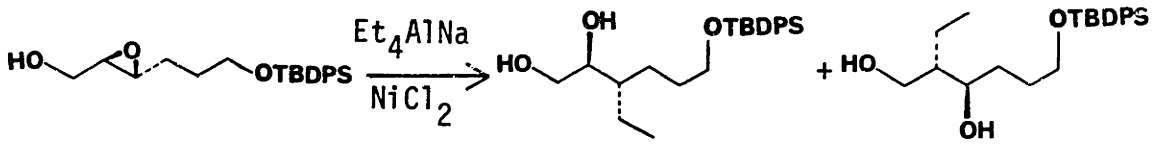
2,3-epoxy alcohol 195

To a solution of 11.6 mL (39.1 mmol, 3.6 equiv.) of titanium(IV) isopropoxide in 80 mL of CH_2Cl_2 at -20°C was added over 20 min 11.4 mL (54.3 mmol, 5.0 equiv.) of (-)-diisopropyltartrate. This solution was stirred for 30 min at -20°C and then 3.84 g (10.9 mmol) of allylic alcohol 201 in 20 mL of CH_2Cl_2 and 3.90 mL (21.7 mmol, 2 equiv.) of 5.57M tert-butylhydroperoxide (TBHP)[89] in CH_2Cl_2 were added. After 23 h at -20°C, the mixture was diluted with 60 mL of ether and 12 mL of saturated aqueous Na_2SO_4. This mixture was stirred vigorously at 23°C for 2 h, and the resulting white precipitate was removed by filtration through powdered molecular sieves (rinsed with ether). The filtrate was concentrated *in vacuo*, diluted with 60 mL of ether and treated with 80 mL of aqueous 1N NaOH saturated with NaCl. This two phase mixture was stirred vigorously at 23°C for 1.5 h. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 80 mL). The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 40 mm column, 1:1 hexane-ether as eluant) to afford 3.30 g (8.90 mmol, 82%) of 195: R_f 0.43 (3:1

89. Sharpless, K.B.; Verhoeven, T.R. Aldrichimica Acta 1979, 12, 63.

hexane-ether); $[\alpha]_D^{21}$ +19.3° (c = 1.30, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.39 (m, 6H), 3.90 (m, 1H), 3.71 (br s, 2H), 3.59 (m, 1H), 2.94 (m, 2H), 1.62-1.74 (m, 5H), 1.06 (s, 9H); IR (CH_2Cl_2) 3600, 3070, 3050, 2940, 2865, 1590 cm^{-1}. Anal. Calcd. for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16. Found: C, 71.21; H, 8.30.

Preparation of 1,2-diol 202 and 1,3-diol 203



195 202 203

Method A (see entry 2, Table VII)

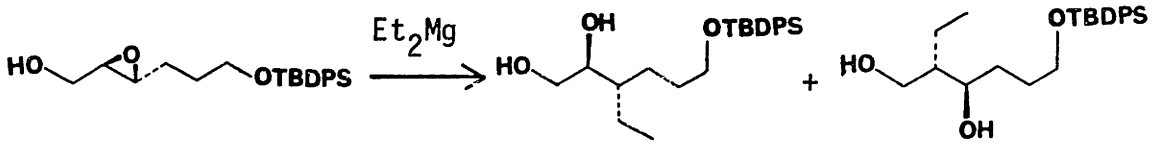
To a stirred solution of 131 mg (0.35 mmol) of 2,3-epoxyalcohol 195 in 5 mL of petroleum ether at 23°C was added 174 mg (1.05 mmol) of freshly prepared Et_4AlNa.[90] After gas evolution from the mixture had ceased, 61 mg

90. The sodium tetraethylaluminate (Et_4AlNa) used in this experiment was prepared by heating 11.1 mL (0.097 mmol) of Et_3Al and 2.0 g (0.087 mmol) of sodium sand in toluene at 115°C for 3 h. The white precipitate was isolated under an inert atmosphere, rinsed with anhydrous petroleum ether, and dried in vacuo (1 mm Hg) for 24 h to give 9.51 g (57.3 mmol, 66%) of Et_4AlNa. See:

(a) Frey, N.F., Jr.; Kobetz, P.; Robinson, G.C.; Sistrunk, T.O. J. Org. Chem. 1961, 26, 2950.

(b) See also reference 71.

(0.47 mmol) of anhydrous $NiCl_2$ was added. THe white solids which had been present prior to the introduction of the $NiCl_2$ immediately dissolved and a second fine dark solid then separated from solution. The otherwise clear reaction mixture was stirred for 63 h at 23°C. This solution was carefully diluted with 12 mL of aqueous 1N HCl and then stirred for 1.5 h at 23°C. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 14 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by chromatography over two 0.5-mm silica gel plates (3:1 ether-hexane, one development) to afford 18 mg (14%) of 195 (R_f 0.39, 3:1 ether-hexane), 36 mg (25%) of 1,3-diol 203, and 52 mg (37%) of 1,2-diol 202.



195 202 203

Method B (see entry 4, Table VII)

To a solution of 175 mg (0.47 mmol) of 195 in 1 mL of ether at 23°C was added an excess (at least 3 equiv.) of Et_2Mg as a solution in ether.[91]

91. The Et_2Mg used in this experiment was prepared by heating Mg (activated before use by consecutive rinses with aqueous 1N HCl, H_2O, EtOH, and ether prior to drying in an argon stream), Et_2Hg, and $HgCl_2$ (catalytic) in ether at 100°C for 4 days in a sealed tube; see:

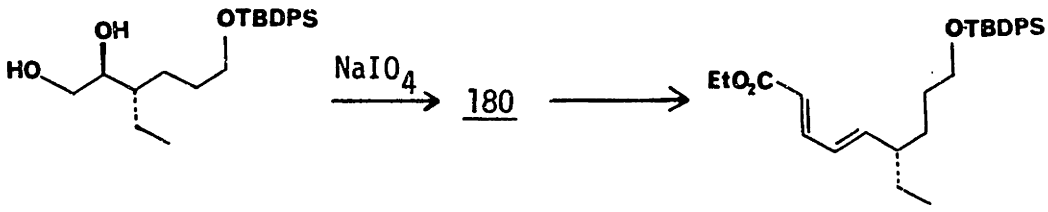
(a) Cowan, D.O.; Mosher, H.S. J. Org. Chem. 1962, 27, 1.

(b) Gilman, H.; Schulze, F. J. Am. Chem. Soc. 1927, 49, 2328.

The resulting mixture was stirred for 46 h at 23°C. To this clear solution was then introduced carefully 6 mL of saturated aqueous NH_4Cl followed by 6 mL of aqueous 1N HCl. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 14 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by chromatography on two 0.5-mm silica gel plates (3:1 ether-hexane, one development) to afford 74 mg (0.19 mmol, 39%) of 1,3-diol 203 and 73 mg (0.018 mmol, 38%) of 1,2-diol 202.

Data for 202: R_f 0.24 (3:1 ether-hexane); $[\alpha]_D^{22}$ +3.3° (c = 1.66, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.39 (m, 6H), 3.67 (m, 4H), 3.54 (m, 1H), 2.18 (br s, 1H), 2.03 (br s, 1H), 1.25-1.65 (m, 7H), 1.06 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H); IR (neat) 3400, 3080, 3050, 2960, 2930, 2860, 1960 (w), 1890 (w), 1830 (w), 1590 cm^{-1}.

Data for 203: R_f 0.31 (3:1 ether-hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.43 (m, 6H), 3.90 (m, 1H), 3.72 (m, 4H), 3.58 (m, 1H), 3.18 (br s, 1H), 1.65-1.82 (m, 5H), 1.44 (m, 2H), 1.06 (s, 9H), 0.96 (t, J = 7.3 Hz, 3H).

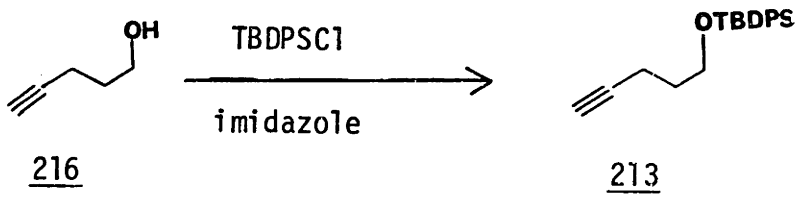


202 206

Diene ester 206

A solution of 52 mg (0.13 mmol) of 1,2-diol 202 in 12 mL of 1:1 THF-H_2O at 23°C was treated with 28 mg (0.13 mmol) of $NaIO_4$. This mixture was stirred for 1.5 h at 23°C and then diluted with 4 mL of saturated aqueous NaCl. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 15 mL). The combined organic extracts were dried, filtered, and then concentrated in vacuo. The crude aldehyde 180 so obtained was dissolved in 2 mL of THF and added to 0.21 mmol of the lithium anion of ethyl 4-diethylphosphonocrotonate in 2 mL of THF at -65°C (prepared as described in the preparation of diene ester 115). This mixture was stirred for 30 min at -50 °C, allowed to warm to 23°C, and then stirred for 10 h at 23°C. The resulting red solution was diluted with 12 mL of aqueous 1N HCl. The aqueous phase was separated and extracted with CH_2Cl_2 (5 X 15 mL). The combined organic extracts were dried, filtered, and then concentrated in vacuo. The residue was purified by chromatography on one 0.5-mm silica gel plate (3:1 hexane-ether, one development) to afford 42 mg (0.090 mmol, 70%) of ester 206.

Data for 206: R_f 0.50 (3:1 hexane-ether); $[\alpha]_D^{22}$ +7.2° (c = 1.55, $CHCl_3$);[92] ^1H NMR (270 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.40 (m, 6H), 7.27 (m, 1H), 6.10 (dd, J = 15.3, 11.0 Hz, 1H), 5.31-5.89 (m, 2H), 4.22 (q, J = 7.0 Hz, 2H), 3.66 (t, J = 5.3 Hz, 2H), 1.98 (m, 1H), 1.28-1.55 (m, 6H), 1.31 (t, J = 7.0 Hz, 3H), 1.06 (s, 9H), 0.84 (t, J = 7.3 Hz, 3H); IR (neat) 3065, 3040, 2950, 2925, 2850, 1955 (w), 1880 (w), 1830 (w), 1710 (s), 1640, 1630, 1585 cm^{-1}; mass spectrum m/e 464 (parent ion); Anal. Calcd. for $C_{29}H_{40}O_3Si$: C, 74.95; H, 8.68. Found: C, 75.03; H, 8.67.



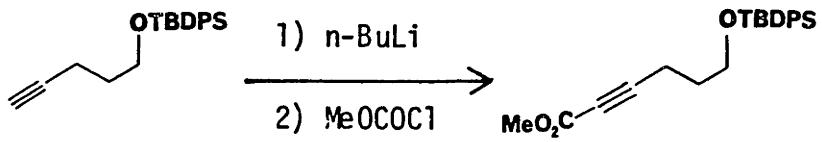
216 213

Acetylene 213

To 18.7 g (68.1 mmol) of tert-butylchlorodiphenylsilane in 50 mL of dry DMF at 23°C was added 10.2 g (150 mmol, 2.2 equiv.) of imidazole and 6.35 mL (71.5 mmol, 1.05 equiv.) of 4-pentyn-1-ol (216). This mixture was stirred for 41 h and then the pale yellow mixture was diluted with 100 mL of half saturated aqueous NaCl. The aqueous phase was extracted with 1:1 hexane-ether (5 X 100 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 40 mm column, 2 liters

92. See Tables VII and VIII in text. The rotation data for 206 showed a dependence on the mode of preparation of aldehyde 180.

of hexane and then 1 liter of 3:1 hexane-ether as eluant) to give 21.9 g (100%) of 213: R_f 0.73 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.44 (m, 6H), 3.78 (t, J = 5.9 Hz, 2H), 2.39 (dt, J = 2.6, 7.2 Hz, 2H), 1.95 (t, J = 2.6 Hz, 1H), 1.76-1.86 (m, 2H), 1.09 (s, 9H); IR (neat) 3310, 3070, 3050, 2960, 2930, 2860, 2120 (w), 1960 (w), 1890 (w), 1820 (w), 1590 cm^{-1}; Anal. Calcd. for $C_{21}H_{26}OSi$: C, 78.20; H, 8.12. Found: C, 78.53; H, 8.02.

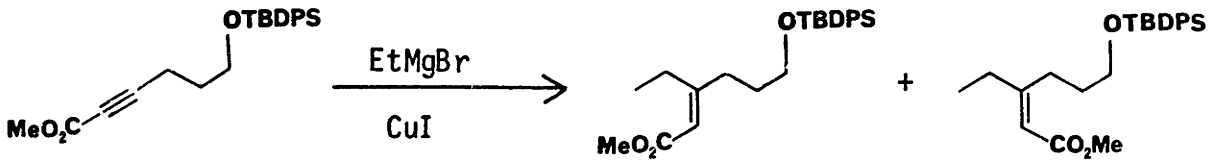


213 217

Acetylenic ester 217

To 7.66 g (23.8 mmol) of acetylene 213 in 20 mL of THF at -78°C was added 16.2 mL (35.7 mmol) of 2.2M n-BuLi in hexane. The red-brown mixture was stirred for 30 min at -78°C and then 2.8 mL of methyl-chloroformate was added. The mixture was then allowed to warm to 23°C, stirred for 3 h, and diluted with 30 mL of half saturated aqueous NaCl. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 30 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 40 mm column, 1 liter each of 19:1 hexane-ether and 9:1 hexane-ether as eluant) to afford 7.27 g (80%) of 217: R_f 0.57 (3:1 hexane-ether);

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.43 (m, 6H), 3.77 (s, 3H), 3.75 (t, J = 5.8 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 1.83 (m, 2H), 1.07 (s, 9H); IR (neat) 3060, 3040, 2950, 2930, 2850, 2220, 1740, 1715, 1590 cm^{-1}; mass spectrum m/e 349 (M - CH_3O), 323 (M - C_4H_9). Anal. Calcd. for $C_{23}H_{28}O_3Si$: C, 72.59; H, 7.42. Found: C, 72.48; H, 7.44.



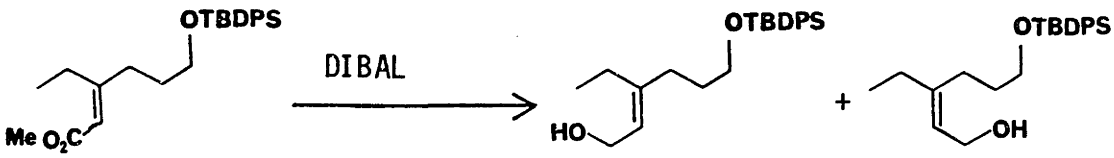
217 218 219

Unsaturated esters 218 and 219

To a mechanically stirred suspension of 3.23 g (16.9 mmol) of copper(I) iodide in 150 mL of THF and 30 mL of Me_2S at -78°C was added 17.6 mL (51.2 mmol) of 2.9M EtMgBr in ether. This mixture was stirred for 2 h at -78°C and then 6.44 g (16.9 mmol) of 217 in 20 mL of THF was added. The resulting mixture was stirred for 44 h at -78°C before being quenched with 20 mL of ethanol. The mixture was allowed to warm to 0°C, at which point it was diluted with 150 mL of saturated aqueous NH_4Cl. The mixture was stirred for 2 h at 23°C and then the deep purple aqueous layer was separated and extracted with CH_2Cl_2 (5 X 150 mL). The combined organic layers were purified by flash chromatography (silica gel, 40 mm column, 19:1 hexane-ether as eluant) to give 6.02 g (87%) of

an inseparable mixture of 218 and 219.

Data for 218/219: R_f 0.56 (3:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.42 (m, 6H), 5.66 (s, 1H), 3,68-3,77 (m, 5H), 2.60-2.74 (m, 2H), 2.15-2.32 (m, 2H), 1.67-1.80 (m, 2H), 1.05-1.12 (m, 12 H); IR (neat) 3070, 3045, 2940, 2860, 1960, 1890, 1820, 1720 (vs), 1640 (s), 1590 cm^{-1}.



218-219 214 220

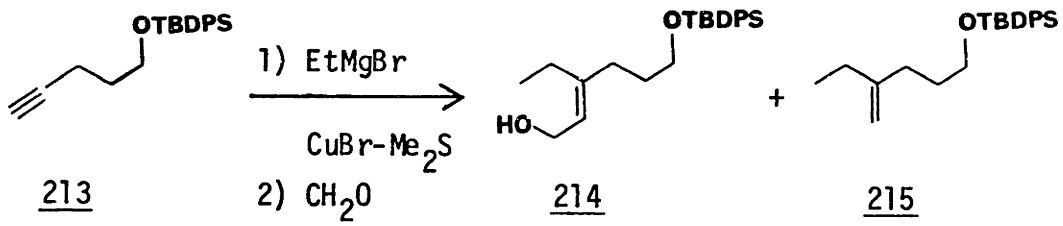
Allylic alcohols 214 and 220

To 5.33 g (13.0 mmol) of a mixture of esters 218 and 219 in 100 mL of ether at -78°C was added 32.5 mL (32.5 mmol) of 1M DIBAL in hexane. The mixture was stirred for 45 min at -78°C, allowed to warm to 23°C over 30 min, and then stirred for 30 min at 23°C. The clear solution was cooled to 0°C and carefully diluted with 100 mL of aqueous 1N HCl. The organic layer was removed and the aqueous layer extracted with CH_2Cl_2 (4 X 100 mL). The combined organic layers were dried, filtered, and concentrated in vacuo to give a mixture (58:42, respectively) of crude 214 and 220. Purification of this mixture by flash chromatography (silica

gel, 40 mm column, 9:1 hexane-ether as eluant) provided 4.42 g (11.5 mmol, 89%) of 214-220. This mixture was separated by careful flash chromatogrphy using "flash" silica gel (40 mm column, 6:1 hexane-ether as eluant); mixed fractions were resubjected to the above chromatographic conditions to give, ultimately, 1.54 g (4.0 mmol, 31%) of isomerically pure 220, 1.70 g (4.4 mmol, 34%) of isomerically pure 214, along with an additional 1.01 g (2.6 mmol, 20%) of mixed fractions.

Data for 214: R_f 0.15 (3:1 hexane-ether), 0.42 (1:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.41 (m, 6H), 5.35 (t, J = 7.3 Hz, 1H), 4.14 (d, J = 7.3 Hz, 2H), 3.68 (t, J = 6.4 Hz, 2H), 2.03-2.16 (m, 5H), 1.64-1.74 (m,2H), 1.04 (3, 9H), 0.98 (t, J = 7.6 Hz, 3H); IR (neat) 3320, 3070, 3040, 2960, 2925, 2855, 1960 (w), 1890 (w), 1820 (w), 1660, 1590 cm^{-1}; mass spectrum m/e 326 (parent ion). Anal. Calcd. for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.15; H, 9.13.

Data for 220: R_f 0.46 (1:1 hexane-ether); ^1H NMR (270 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.44 (m, 6H), 5.46 (t, J = 7.0 Hz, 1H), 4.17 (d, J = 7.0 Hz, 2H), 3.68 (t, J = 5.8 Hz, 2H), 2.21 (t, J = 7.7 Hz, 2H), 2.04 (q, J = 7.4 Hz, 2H), 1.54-1.62 (m, 3H), 1.09 (s, 9H), 1.03 (t, J = 7.4 Hz, 3H); IR (neat) 3350, 3070, 2960, 2925, 2855, 1960 (w), 1890 (w), 1820 (w), 1660, 1590 cm^{-1}; mass spectrum m/e 326 (parent ion). Anal. Calcd. for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.60; H, 9.04.



213 214 215

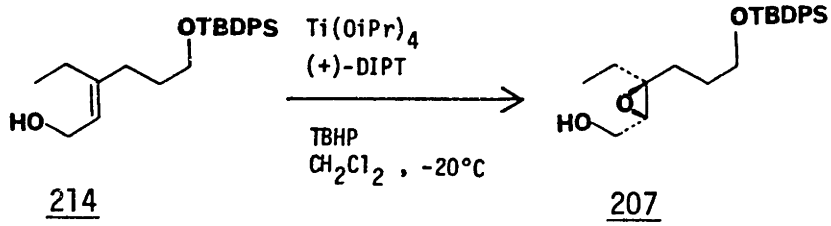
Allylic alcohol 414 and alkene 215

To a mechanically stirred suspension of 1.41 g (6.86 mmol) of copper(I) bromide-dimethylsulfide complex ($CuBr\text{-}Me_2S$) in 30 mL of 1:1 ether-dimethylsulfide at -45°C was added 6.4 mmol of ethylmagnesium bromide (EtMgBr) in 10 mL of ether. The resulting yellow-orange solution was stirred for 2 h before 1.38 g (4.29 mmol) of acetylene 213 in 15 mL of ether was added. The reaction mixture was allowed to warm to -25°C during which time it turned dark green-brown. After being stirred for 2.5 h at -25°C, the mixture was cooled to -70°C. Excess dry gaseous formaldehyde[93] in an argon stream was introduced over a 2 h period. The reaction mixture was then allowed to warm to -20°C. Ninety minutes later the mixture was allowed to warm to 0°C and then stirred at this temperature for 12 h. It was then diluted with 40 mL of saturated aqueous NH_4Cl. The organic layer was separated and the deep blue aqueous phase extracted with CH_2Cl_2 (5 X 40 mL). The combined organic layers were dried, filtered through 2 g of Florisil,

93. Dry gaseous formaldehyde was generated by heating dry paraformaldehyde (dried for 24 h with P_2O_5 at 0.3 mm Hg in a vacuum desiccator) to 140°C in a dry argon stream. This argon stream was passed through a -40°C trap prior to its introduction into the reaction vessel.

and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel, 40 mm column, 1.5 liters each of 3:1 hexane-ether and of 1:1 hexane-ether as eluant) to afford 974 mg of a 78:22 mixture of acetylene 213 and ethyl addition compound 215, and 317 mg (19%) of (E)- allylic alcohol 214. The (Z)- olefin 220 was not present.

Data for 215: R_f 0.75 (3:1 hexane-ether); ^1H NMR (250 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.41 (m, 6H), 4.67 (br s, 2H), 3.68 (m, 2H), 1.73-2.20 (m, 6H), 1.06 (s, 9H), 0.98 (t, J = 7.4 Hz, 3H); IR (neat) 3070, 3050, 2960, 2930, 1960 (w), 1890 (w), 1820 (w), 1645, 1590 cm^{-1}.

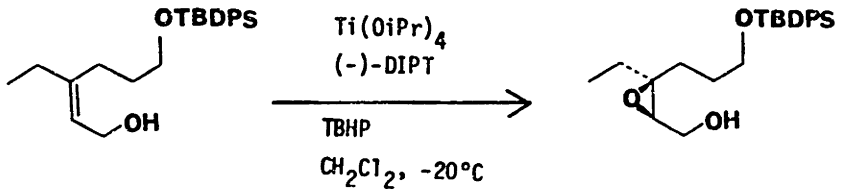


214 207

2,3-epoxyalcohol 207

A colorless solution of 2.57 mL (8.64 mmol, 3.6 equiv.) of titanium(IV) isopropoxide [$Ti(OiPr)_4$] in 20 mL of CH_2Cl_2 at -20°C was treated with 2.52 mL (12.0 mmol, 5 equiv.) of (+)-diisopropyl-tartrate (DIPT). The mixture was stirred for 20 min at -20°C prior to addition of 912 mg (2.40 mmol) of 214 in 10 mL of CH_2Cl_2 and 0.86 mL (2 equiv.) of 5.57M tert-butylhydroperoxide (TBHP)[89] in CH_2Cl_2.

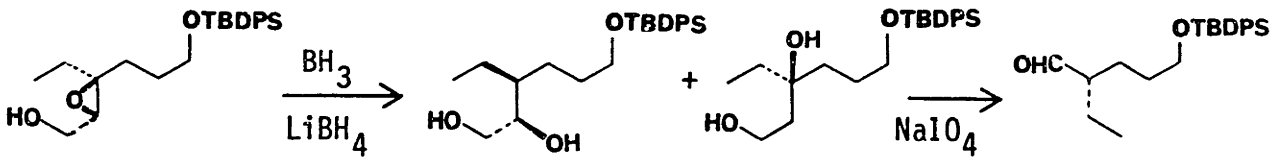
The homogeneous light yellow mixture was maintained at -20°C for 36 h before being diluted with 30 mL of ether and allowed to warm to 0°C. The mixture was treated with 3 mL of saturated aqueous Na_2SO_4, allowed to warm to 23°C, and then stirred for 2 h. The white precipitate which formed was removed by filtration through powdered molecular sieves in a sintered glass funnel, and was washed with 150 mL of ether. The filtrate was concentrated in vacuo, the residue dissolved in 40 mL of ether, and then treated with 40 mL of aqueous 1N NaOH saturated with NaCl. This mixture was vigorously stirred at 23°C for 45 min to hydrolyze the tartrate ester. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 40 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography ("flash" silica gel, 40 mm column, 500 mL of 4:1 hexane-ether and 1000 mL of 3:1 ether-hexane as eluant) to afford 898 mg (94%) of 207: R_f 0.55 (3:1 ether-hexane); $[\alpha]_D^{21}$ -5.9° (c = 1.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.42 (m, 6H), 3.84 (m, 1H), 3.49-3.72 (m, 3H), 2.98 (dd, J = 6.8, 4.2 Hz, 1H), 2.11 (br s, 1H), 1.41-1.74 (m, 6H), 1.07 (s, 9H), 0.99 (t, J = 7.6 Hz, 3H); IR (neat) 3410, 3070, 3040, 2940, 2850, 1960 (w), 1890 (w), 1820 (w), 1590 cm^{-1}; Anal. Calcd. for $C_{24}H_{34}O_3Si$: C, 72.31; H, 8.60. Found: C, 72.23; H, 8.60.



220 208

2,3-epoxyalcohol 208

Allylic alcohol 220 (1.30 g, 3.39 mmol) was epoxidized by treatment with 3.63 mL (12.2 mmol, 3.6 equiv.) of $Ti(OiPr)_4$, 3.55 mL (17.0 mmol, 5 equiv.) of (-)-DIPT, and 1.22 mL (5.57M in CH_2Cl_2, 2 equiv.) of TBHP in 40 mL of dry CH_2Cl_2 at -20°C according to the procedure described for the conversion of 214 to 207. In this manner 1.40 g (100%) of 208 was obtained after chromatographic purification. Data for 208: R_f 0.55 (3:1 ether-hexane); $[\alpha]_D^{21}$ +4.2 (c = 2.05, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.44 (m, 6H), 3.65-3.85 (m, 4H), 3.00 (dd, J = 7.4, 4.9 Hz, 1H), 1.55-1.74 (m, 7H), 1.06 (s, 9H), 0.93 (t, J = 7.6 Hz, 3H); IR (neat) 3430, 3060, 3040, 2955, 2930, 2855, 1960 (w), 1890 (w), 1840 (w), 1740 (w). 1590 cm^{-1}; mass spectrum m/e 368 (M - CH_3O), 342 (M - C_4H_9); Anal. Calcd. for $C_{24}H_{34}OSi$: C, 72.31; H, 8.60. Found: C, 72.23; H, 8.44.



207 209 221 180

Aldehyde 180 and 1,3-diol 221

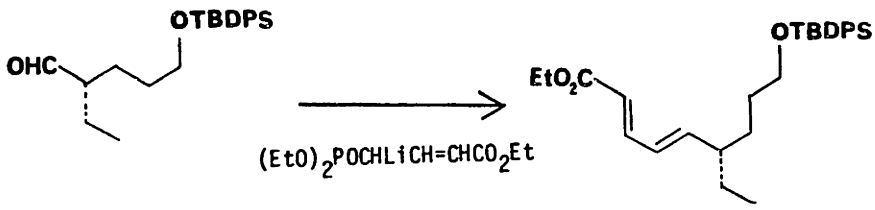
A solution of 747 mg (1.87 mmol) of 207 in 7 mL of THF at 0°C was treated with 1.70 mL (1.87 mmol) of 1.1M BH_3 in THF and 0.19 mL (0.37 mmol) of 2.0M $LiBH_4$ in THF. This clear reaction mixture was stirred for 41 h at 0°C prior to careful addition of 3 drops of H_2O and dilution with 30 mL of aqueous 1N HCl. The aqueous layer was separated and extracted with CH_2Cl_2 (6 X 30 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue (a mixture of 209 and 221) was dissolved in 24 mL of 1:1 THF-H_2O at 23°C and then treated with 800 mg (3.74 mmol) of $NaIO_4$. This mixture was stirred for 3 h at 23°C and then was diluted with 15 mL of saturated aqueous NaCl. The aqueous layer was extracted with CH_2Cl_2 (6 X 30 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, 20 mm column, 4:1 hexane-ether as eluant) to afford 384 mg (1.04 mmol, 56%) of 180 and 280 mg (0.70 mmol, 37%) of 1,3-diol 221.

The treatment of epoxide 208 (1.16 g, 2.90 mmol) in an identical

manner afforded 598 mg (1.62 mmol, 56%) of aldehyde 180 and 467 mg (1.16 mmol, 40%) of 221.

Data for 180: R_f 0.85 (3:1 ether-hexane), 0.63 (3:1 hexane-ether); $[\alpha]_D^{21}$ +1.6°(c = 1.44, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 9.57 (d, J = 2.6 Hz, 1H), 7.67 (m, 4H), 7.40 (m, 6H), 3.67 (t, J = 5.9 Hz, 2H), 2.20 (m, 1H), 1.49-1.73 (m, 6H), 1.06 (s, 9H), 0.92 (t, J = 7.6 Hz, 3H); IR (CH_2Cl_2) 3005, 2930, 2860, 2715, 1960 (w), 1890 (w), 1840 (w), 1720 (s), 1590 cm^{-1}.

Data for 221: R_f 0.22 (3:1 ether-hexane); $[\alpha]_D^{21}$ +26.8 (c = 1.42, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.72 (m, 4H), 7.37 (m, 6H), 4.00 (m, 1H), 3.86 (br s, 1H), 3.67-3.77 (m, 4H), 2.96 (br s, 1H), 1.70-1.75 (m, 2H), 1.46-1.63 (m, 5H), 1.06 (s, 9H), 0.87 (t, J = 7.6 Hz, 3H); IR (CH_2Cl_2) 3600, 3500, 2940, 2855, 1590 cm^{-1}.

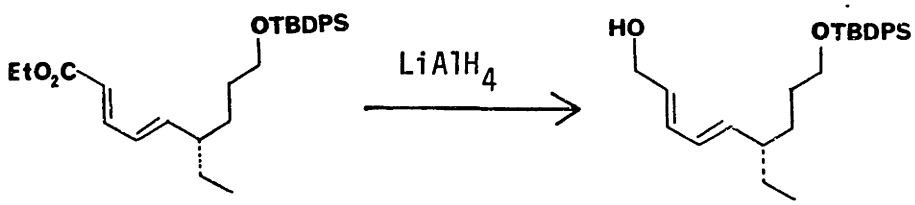


180 206

Diene ester 206

To a solution of 1.28 mmol of lithium diisopropylamine in 5 mL of THF at -78°C was added slowly 0.30 mL (320 mg, 1.3 mmol) of ethyl 4-diethylphosphonocrotonate. The resulting yellow mixture was stirred for 30 min at -78°C, allowed to warm to -60°C, and then treated with 189 mg (0.51 mmol) of 180[94] in 4 mL of THF. This mixture was stirred for 30 min at -60°C, and then allowed to warm to 23°C over a 1 h period and stirred for an additional 2 h. The reaction mixture was then diluted with 12 mL of aqueous 1N HCl. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 15 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 20 mm column, 3:1 hexane-ether as eluant) to afford 212 mg (0.42 mmol, 90%) of pure diene ester 206 ($[\alpha]_D^{22}$ +6.1°, c = 0.99, $CHCl_3$)[92] which was identical to diene ester prepared as previously described from 1,2-diol 202.

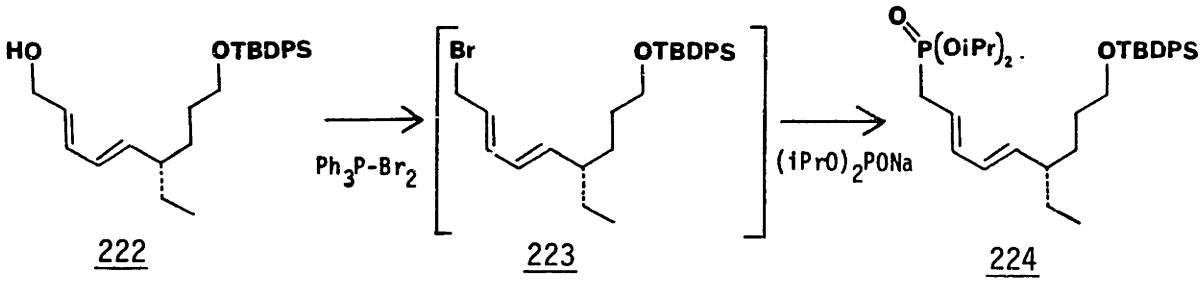
94. Aldehyde 180 was prepared by BH_3-$LiBH_4$ reduction of epoxide 207 followed by periodate cleavage as previously desribed.



206 222

Diene alcohol 222

To a solution of 260 mg (0.56 mmol) of 206 ($[\alpha]_D^{22}$ +7.2°C, c = 1.55, $CHCl_3$) in 8 mL of ether at 0°C was added 21 mg (0.56 mmol) of lithium aluminum hydride. The reaction mixture was stirred for 1 h at 0°C and then 4 drops of water (considerable gas evolution) and 12 drops of aqueous 1N NaOH were added. This mixture was then stirred for 15 min. The resulting white precipitate was removed by filtration through a sintered glass funnel and washed with CH_2Cl_2. The organic filtrates were combined and concentrated in vacuo. The residue was purified by chromatography on two 0.5-mm silica gel plates (1:1 hexane-ether, one development) to afford 217 mg (0.51, 91%) of pure 222: R_f 0.20 (3:1 hexane-ether); $[\alpha]_D^{22}$ -1.6° (c = 2.07, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.42 (m, 6H), 6.24 (dd, J = 15.3, 10.4 Hz, 1H), 6.00 (dd, J = 15.3, 10.4 Hz, 1H), 5.74 (dt, J = 15.3, 6.2 Hz, 1H), 5.44 (dd, J = 15.3, 9.2 Hz, 1H), 4.18 (br s, 2H), 3.66 (t, J = 5.9 Hz, 2H), 1.90 (m, 1H), 1.21-1.61 (m, 6H), 1.07 (s, 9H), 0.85 (t, J = 7.4 Hz, 3H); IR (neat) 3330, 3065, 3045, 3015, 2995, 2960, 2930, 2855, 1955 (w), 1890 (w), 1840 (w), 1660, 1590 cm^{-1}; mass spectrum m/e 422 (parent ion). Anal. Calcd. for $C_{27}H_{38}O_2Si$: C, 76.72; H, 9.06. Found: C, 76.70; H, 9.10.



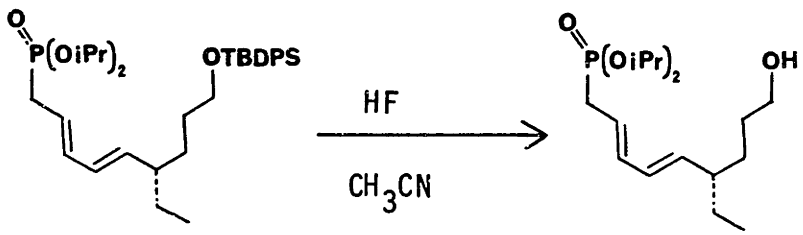
222 223 224

Diene diisopropylphosphonate 224

A 0°C solution of 113 mg (0.43 mmol) of Ph_3P in 2 mL of CH_3CN was treated with 22 μL (0.43 mmol) of Br_2. The resulting light yellow solution was stirred for 15 min at 0°C and then 182 mg (0.43 mmol) of 222 in 3 mL of CH_3CN was added. The reaction mixture was stirred for 10 min at 0°C and then was quenched by addition of 0.5 mL of methanol. Solvent was then removed in vacuo until a volume of approximately 0.5 mL was realized. This material was diluted with ether (3 mL) and then filtered through 1 g of ether-prewashed Florisil by using ether (15 mL) as eluant. The combined organic filtrates were concentrated in vacuo to provide crude bromide 223 which was used directly in the next step (R_f 0.68, 3:1 hexane-ether).

Bromide 223 so obtained was added to an excess of sodium diisopropylphosphite [$(iPrO)_2PONa$] in benzene at 23°C. This mixture was stirred for 45 min at 23°C and then was filtered through 1 g of Florisil by using ether (18 mL) as eluant, The combined organic filtrates were concentrated in vacuo. The residue was purified by chromatography over two 0.5-mm silica gel plates (1:1 CH_2Cl_2-Et_2O, one development) to afford 106 mg (0.19 mmol, 44%) of 224: R_f 0.30 (3:1 ether-hexane),

0.51 (1:1 CH_2Cl_2-Et_2O); $[\alpha]_D^{22}$ -1.1° (c = 1.45, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.37 (m, 6H), 6.12 (m, 1H), 5.95 (m, 1H), 5.51 (m, 1H), 5.34 (m, 1H), 4.61-4.75 (m, 2H), 3.63 (t, J = 5.6 Hz, 2H), 2.59 (dd, J = 22.7, 7.2 Hz, 2H), 1.86 (m, 1H), 1.17-1.56 (m, 6H), 1.32 (d, J = 6.1 Hz, 6H), 1.30 (d, J = 6.1 Hz, 6H), 1.04 (s, 9H), 0.81 (t, J = 7.3 Hz, 3H); IR (CH_2Cl_2) 3082, 3008, 2960, 2930, 2860, 1590 cm^{-1}; mass spectrum m/e 571 (parent ion); Anal. Calcd. for $C_{33}H_{51}O_4PSi$: C, 69.44; H, 9.00; P, 5.43. Found: C, 69.10; H, 9.05; P, 5.16.

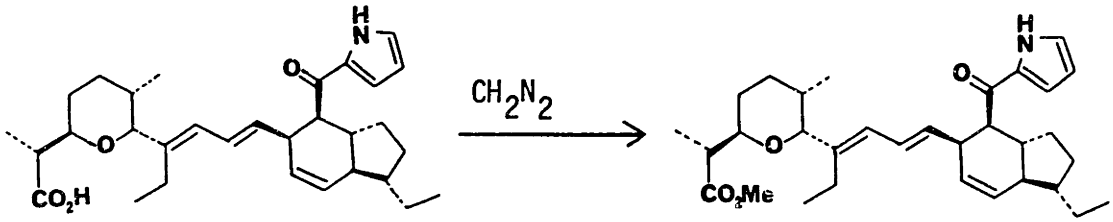


224 178

Diene diisopropylphosphonate alcohol 178

To 99 mg (0.17 mmol) of 224 in 2 mL of CH_3CN at 23°C was added 0.5 mL of 1.45M HF in CH_3CN. The reaction mixture was stirred for 2 h at 23°C and then solvent was removed in vacuo. The residue was purified by chromatography on one 0.5-mm silica gel plate (ethyl acetate, one development) to afford 48 mg (0.15 mmol, 88%) of 178: R_f 0.20 (1:1 CH_2Cl_2-Et_2O); $[\alpha]_D^{22}$ -2.1° (c = 1.40, $CHCl_3$); ^1H NMR

(250 MHz, $CDCl_3$) δ 5.94-6.18 (m, 2H), 5.44-5.58 (m, 1H), 5.35 (m, 1H), 4.62-4.75 (m, 2H), 3.61 (br s, 2H), 2.57 (dd, J = 22.4, 7.4 Hz, 2H), 1.89 (m, 1H), 1.80 (s, 1H), 1.07-1.60 (m, 6H), 1.32 (d, J = 5.9 Hz, 6H), 1.29 (d, J = 5.9 Hz, 6H), 0.83 (t, J = 7.4 Hz, 3H); Ir (neat) 3405, 3015, 2980, 2940, 2880 cm^{-1}; mass spectrum m/e 332 (parent ion). Anal. Calcd. for $C_{17}H_{33}OP$: C, 61.42; H, 10.00. Found: C, 61.13; H, 10.04.



X-14547A (1) 11

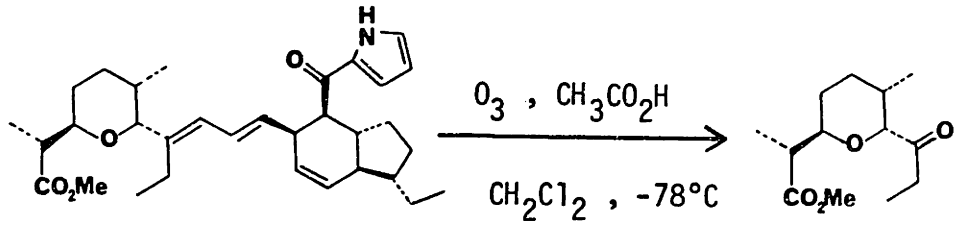
X-14547A methyl ester 11 (from natural X-14547A)[12a]

To 64 mg (0.13 mmol) of natural X-14547A (1)[95] in 2 mL of ether at 0°C was added an ethereal diazomethane solution until no solid was present. The mixture was kept for 1 h at 23°C in the dark and then was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 10 mm column, 2:1 hexane-ether as eluant) to afford 59 mg (0.12 mmol, 89%) of natural 11: R_f 0.68 (1:1 ether-hexane); $[\alpha]_D^{20}$ -308.2° (c = 1.24, $CHCl_3$);[96] ^1H NMR (250 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.02 (m, 1H),

95. A sample of natural X-14547A was generously provided by J. Westley of Hoffman-La Roche, Inc.

96. Nicolaou reported "$[\alpha]_D^{25}$ -170.6 (c = 1.4, $CHCl_3$)" for synthetic 11 which "exhibited identical properties with naturally derived methyl ester of X-14547A (reference 12c)."

6.89 (br s, 1H), 6.28 (m, 1H), 5.98 (d, J = 9.8 Hz, 1H), 5.84 (m, 2H), 5.52 (dt, J = 9.8, 3.0 Hz, 1H), 5.42 (dd, J = 13.7, 8.7 Hz, 1H), 4.12 (d, J = 4.2 Hz, 1H), 3.74 (m, 1H), 3.66 (s, 3H), 3.40 (m, 2H), 2.79 (m, 1H), 1.14-2.03 (m, 16H), 1.10 (d, J = 6.8 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H), 0.78 (t, J = 7.6 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 190.9, 176.0, 140.2, 132.6, 129.5, 129.4, 127.2, 125.1, 124.2, 114.8, 110.1, 77.2, 75.6, 74.0, 52.8, 51.6, 49.9, 45.4, 43.8, 42.4, 40.7, 31.5, 29.7, 27.3, 26.9, 24.0, 22.3, 14.7, 13.9, 13.4, 12.4; IR (CH_2Cl_2) 3440, 3020, 2960, 2930, 2880, 1730, 1645, 1540 cm^{-1}; mass spectrum m/e 507 (parent ion).

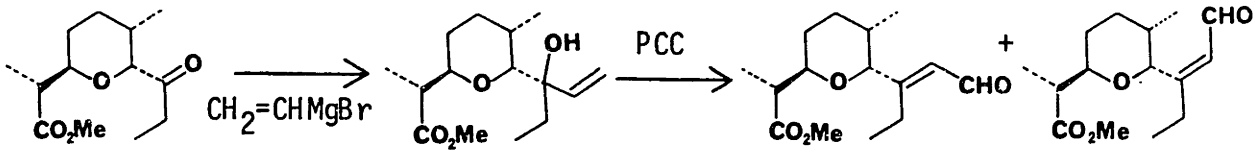


11 12

Ketone 12[12a]

A solution of 123 mg (0.24 mmol) of X-14547A methyl ester (11) in 10 mL of CH_2Cl_2 and 100 μL of acetic acid at -78°C was treated with a stream of O_3 in O_2 until a deep blue-purple color persisted. The addition of ozone was then terminated and the system was flushed with O_2 for 15 min. Dimethylsulfide (1 mL) was then added. The mixture was

allowed to warm to 23°C and stirred for 12 h, at which point all volatile components were removed *in vacuo*. The crude product was purified by flash chromatography (silica gel, 20 mm column, 2:1 hexane-ether as eluant) to afford 52 mg (0.21 mmol, 88%) of 12: R_f 0.57 (1:1 hexane-ether); $[\alpha]_D^{20}$ -29.6° (c = 1.50, $CHCl_3$);[97] ^1H NMR (250 MHz, $CDCl_3$) δ 4.15 (d, J = 4.2 Hz, 1H), 3.65-3.74 (m, 1H), 3.68 (s, 3H), 2.30-2.78 (m, 3H), 1.96-2.06 (m, 1H), 1.78-1.87 (m, 1H), 1.64-1.72 (m, 2H), 1.24-1.40 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 211.3 (C.8), 175.3 (C.1), 79.5 (C.7), 75.3 (OCH_3), 51.5, 43.4, 33.6, 31.5, 26.2, 25.3, 15.1, 13.6, 7.2; IR (CH_2Cl_2) 2950, 2880, 1735, 1715 cm^{-1}.



12 172 (E)-7 (Z)-7

Unsaturated aldehyde 7[12,13]

To a solution of 52 mg (0.21 mmol) of ketone 12 in 2 mL of THF at -78°C was added 0.49 mL of 1.7M vinylmagnesium bromide in THF. This mixture was stirred for 24 h at -78°C and then 0.5 mL of methanol was added followed by 10 mL of saturated aqueous ammonium chloride (NH_4Cl).

97. Nicolaou reported "$[\alpha]_D^{25}$ -21.96° (c = 0.85, $CHCl_3$)" for synthetic 12 which "was identical with material derived from natural X-14547A (see reference 12b)."

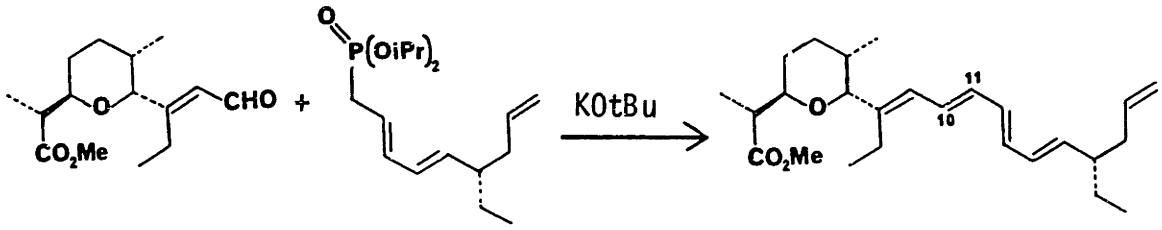
The reaction mixture was allowed to warm to 23°C and diluted with water. The aqueous phase was separated and extracted with CH_2Cl_2 (5 X 15 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo* to give 52 mg (92%) of 172: R_f 0.49 (1:1 hexane-ether); ^1H NMR (250 MHz, $CDCl_3$) δ 5.67 (dd, J = 17.1, 10.6 Hz, 1H), 5.23 (dd, J = 17.1, 1.8 Hz, 1H), 5.09 (dd, J = 10.6, 1.8 Hz, 1H), 4.04 (dd, J = 11.1, 6.0 Hz, 1H), 3.67 (s, 3H), 3.56 (d, J = 2.4 Hz, 1H); 3.05-3.15 (m, 1H), 2.15 (br s, 1H), 1.15-2.03 (m, 7H), 1.12 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H); IR (CH_2Cl_2) 3550, 3075, 2940, 2870, 1732, 1640 cm^{-1}.

Without further purification, a solution of 52 mg of 172 in 12 mL of CH_2Cl_2 was treated with 274 mg of PCC at 40°C. After being heated for 18 h at 40°C, the mixture was cooled to 23°C, diluted with 10 mL of ether, and filtered through 2 g of Florisil with ether as eluant. The combined organic eluants were concentrated *in vacuo*. The residue was purified by chromatography on one 0.5-mm silica gel plate (1:1 hexane-ether, one development) to give 30 mg (55%) of recovered 172 (R_f 0.49, 1:1 hexane-ether) and 32 mg of a mixture of (E)- and (Z)- 7 (R_f 0.34, 1:1 hexane-ether). This mixture was separated by reverse phase HPLC (Waters μ-Bondapak C-18 column, 30 cm length X 3.9 mm I.D., 60:40 H_2O-CH_3CN as eluant, flow rate = 6.0 mL/min). The appropriate fractions were extracted with CH_2Cl_2, and the extracts dried, filtered, and concentrated *in vacuo* to give 17.6 mg (0.066 mmol, 31%) of (E)- 7 (retention time 13-16 min) and 2.5 mg (0.009 mmol, 4%) of (Z)- 7 (retention time 17-21 min).

Data for (E)- 7: white crystalline solid, mp 68.0-69.0°C; $[\alpha]_D^{22}$ -32.1° (c = 0.60, $CHCl_3$);[98] ^1H NMR (250 MHz, $CDCl_3$) δ 10.04 (d, J = 8.2 Hz, 1H), 6.02 (dd, J = 8.2, 1.3 Hz, 1H), 4.42 (br s, 1H), 3.99 (dd, J = 10.7, 3.5 Hz, 1H), 3.60 (s, 3H), 3.06-3.19 (m, 1H), 2.69-2.84 (m, 1H), 2.14-2.28 (m, 1H), 1.84-2.06 (m, 3H), 1.42-1.65 (m, 2H), 1.18 (t, J = 7.6 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 191.8 (C.10), 175.9 (C.1), 126.1 (C.7); IR (CH_2Cl_2) 3060, 2980, 2960, 2880, 1740, 1672/cm^{-1}.

Data for (Z)- 7: $[\alpha]_D^{22}$ -82.8° (c = 0.44, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 10.21 (d, J = 7.6 Hz, 1H), 5.82 (dd, J = 7.6, 1.1 Hz, 1H), 4.91 (br s, 1H), 4.04 (dd, J = 11.0, 4.6 Hz, 1H), 3.61 (s, 3H), 3.14-3.26 (m, 1H), 1.14-2.75 (m, 7H), 1.05-1.12 (m, 6H), 0.94 (d, J = 7.0 Hz, 3H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 194.3 (C.10), 167.6 (C.1); IR (CH_2Cl_2) 3020, 2950, 2880, 1740, 1668 cm^{-1}.

98. Ley reported "m.p. 75-78°C, $[\alpha]_D^{22}$ -44.5° (c = 0.85, $CHCl_3$)" for a 3:1 E:Z mixture of synthetic 7 which "was identical in all respects to a sample prepared from methylated X-14547A by ozonolysis at -78°C (see reference 13b)."



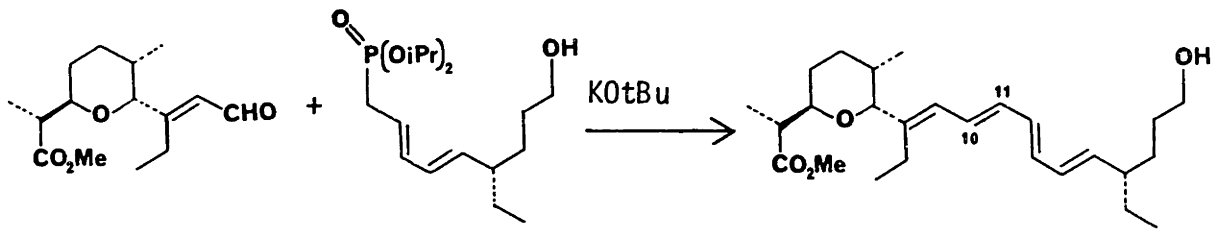
(E)-7 155 176

Pentaene 176

To a mixture of 10.1 mg (0.038 mmol) of (E)- 7 and 15.7 mg (0.05 mmol) of phosphonate 155 in 1 mL of DME at 0°C was added 80 μL of 0.6M potassium tert-butoxide in DME. The light red-yellow solution was stirred for 30 min at 0°C and then was diluted with 10 mL of saturated aqueous NaCl. The aqueous layer was separated and extracted with CH_2Cl_2 (5 X 15 mL). The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (ether-prewashed Florisil, 10 mm column, 10:1 hexane-ether as eluant) to afford 10.2 mg (0.026 mmol, 68%) of 176 as a 89:11 E:Z mixture at the newly formed C.10-C.11 double bond.

Data for 176 (as mixture): R_f 0.75 (3:1 hexane-ether); $[\alpha]_D^{20}$ -38.7° (c = 0.30, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 6.38-6.52 (m, 1H), 5.93-6.29 (m, 5H), 5.67-5.84 (m, 1H), 5.49 (dd, J = 14.6, 8.0 Hz, 1H), 5.02 (m, 2H), 4.30 (br s, 1H), 3.89-4.00 (m, 1H), 3.03-3.11 (m, 1H), 1.80-2.33 (m, 6H), 1.26-1.66 (m, 6H), 1.08 (d, J = 6.3 Hz, 3H), 1.01

(t, J = 7.3 Hz, 3H), 0.86 (t, J = 5.9 Hz, 6H); IR (CH_2Cl_2) 3010, 2960, 2920, 2870, 1735, 1640, 1605 cm^{-1}; UV (EtOH) λ 325 (ε = 54,300), 310 (ε = 63,000), 297 (ε = 42,100), 286 (ε = 22,800).



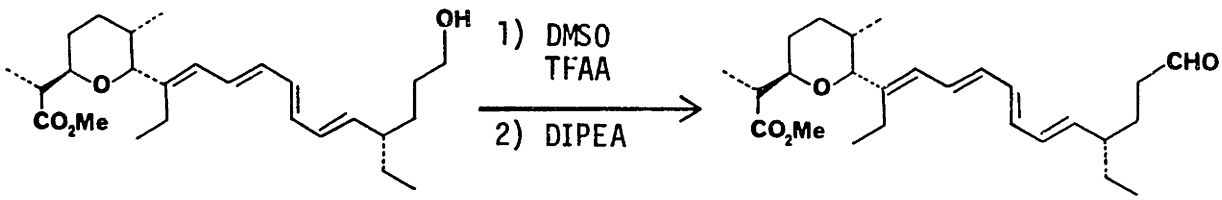
(E)-7 178 177

Tetraene alcohol 177

To a stirred solution of aldehyde (E)- 7 (9.4 mg, 0.035 mmol) and phosphonate 178 (13.9 mg, 0.042 mmol) in 1 mL of DME at 0°C was added 0.5 mL of a solution of 0.085M KOtBu in DME. This yellow solution was stirred for 30 min at 0°C and then diluted with 10 mL of half saturated aqueous NaCl. The aqueous layer was extracted with CH_2Cl_2 (5 X 15 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (ether-prerinsed Florisil, 10 mm column, 1:1 hexane-ether as eluant) to give 12.2 mg (0.029 mmol, 83%) of 177 as a 91:9 E:Z isomer mixture at the newly formed C.10-C.11 double bond.

Data for 177 (as mixture): R_f 0.40 (1:1 hexane-ether); $[\alpha]_D^{23}$ -0.7°

(c = 1.22, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 6.43 (m, 1H), 6.20 (m, 3H), 6.03 (m, 2H), 5.43 (dd, J = 14.6, 9.1 Hz, 1H), 4.30 (br s, 1H), 3.94 (m, 1H), 3.62 (m, 2H), 3.60 (s, 3H), 3.07 (m, 1H), 2.30 (m, 2H), 1.14-2.00 (m, 13H), 1.08 (d, J = 6.8 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H), 0.85 (m, 6H); IR (CH_2Cl_2) 3610, 3020, 2970, 2940, 2870, 1735 cm^{-1}; UV (EtOH) λ 325 (ε = 28,300), 309 (ε = 32,200), 296 (ε = 21,100), 285 (ε = 11,100).

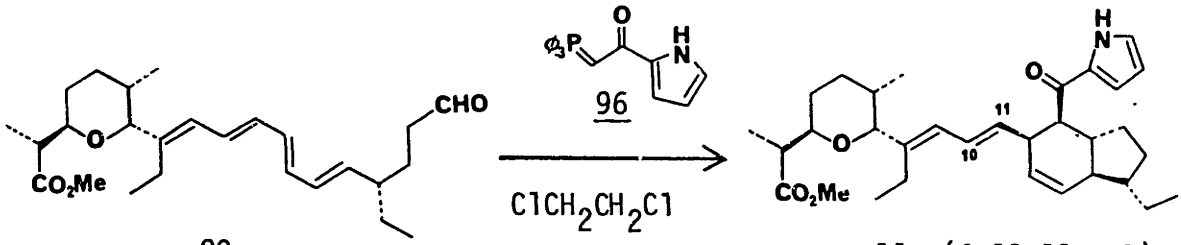


177 99

Tetraene aldehyde 99

To a stirred solution of 0.4 mL of DMSO (6 mmol) in 2 mL of CH_2Cl_2 at -78°C was added 100 μL of trifluoroacetic anhydride (0.7 mmol). The resulting cloudy solution was stirred for 20 min and then treated with 12.2 mg (0.029 mmol) of alcohol 177 in 2 mL of CH_2Cl_2. This mixture was stirred for 1.5 h at -78°C and then 0.5 mL of diisopropylethylamine was added. The reaction mixture was allowed to warm to 10°C over a 1 h interval and then was diluted with 10 mL of half saturated aqueous NaCl. The aqueous layer was separated and extracted with hexane (5 X 15 mL).

The combined organic extracts were dried, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (ether-prerinsed Florisil, 10 mm column, 150 mL of 3:1 and 150 mL of 1:1 hexane-ether as eluant) to afford 9.6 mg (0.023 mmol, 80%) of aldehyde 99: R_f 0.58 (1:1 hexane-ether); $[\alpha]_D^{23}$ -1.1 (c = 0.96, $CHCl_3$), ^1H NMR (250 MHz, $CDCl_3$) δ 9.76 (t, J = 1.5 Hz, 1H), 6.45 (m, 1H), 6.21 (m, 3H), 6.06 (m, 2H), 5.36 (dd, J = 14.5, 9.2 Hz, 1H), 4.31 (br s, 1H), 3.92 (m, 1H), 3.60 (s, 3H), 3.08 (m, 1H), 2.18-2.46 (m, 3H), 1.10-2.07 (m, 11H), 1.08 (d, J = 6.7 Hz, 3H), 1.01 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H); IR (CH_2Cl_2) 2930, 2870, 1730 (br) cm^{-1}; UV (EtOH) λ 327 (ε = 33,500), 312 (ε = 37,700), 298 (ε = 24,800), 286 (ε = 12,900).



99 → 11 (C.10,11 = E)

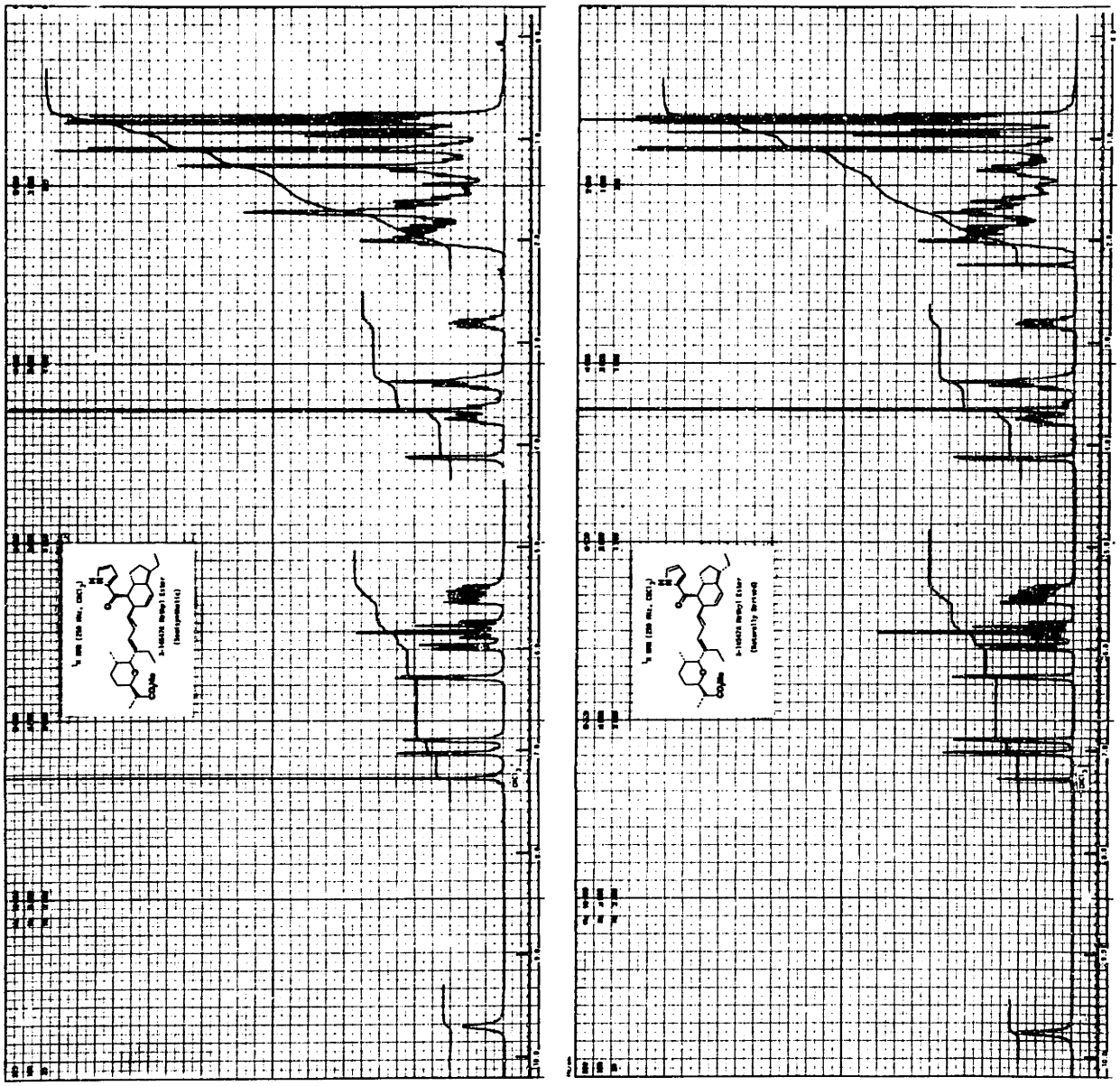
227 (C.10,11 = Z)

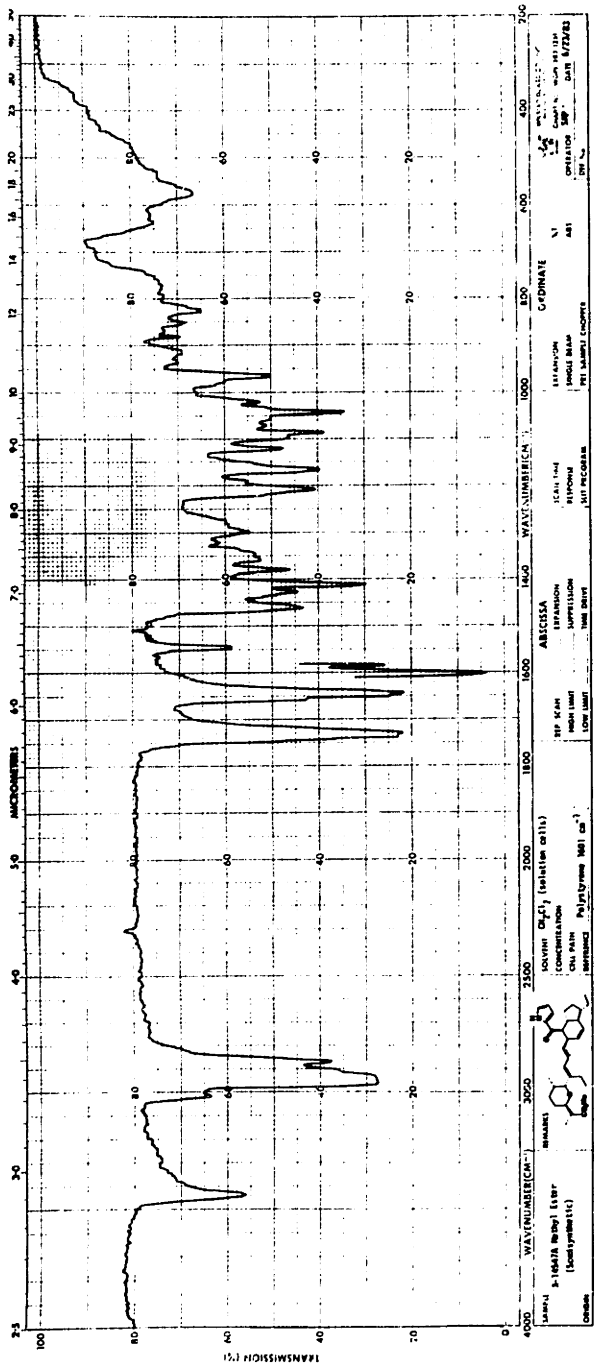
X-14547A methyl ester 11 (semisynthetic) and isomer 227

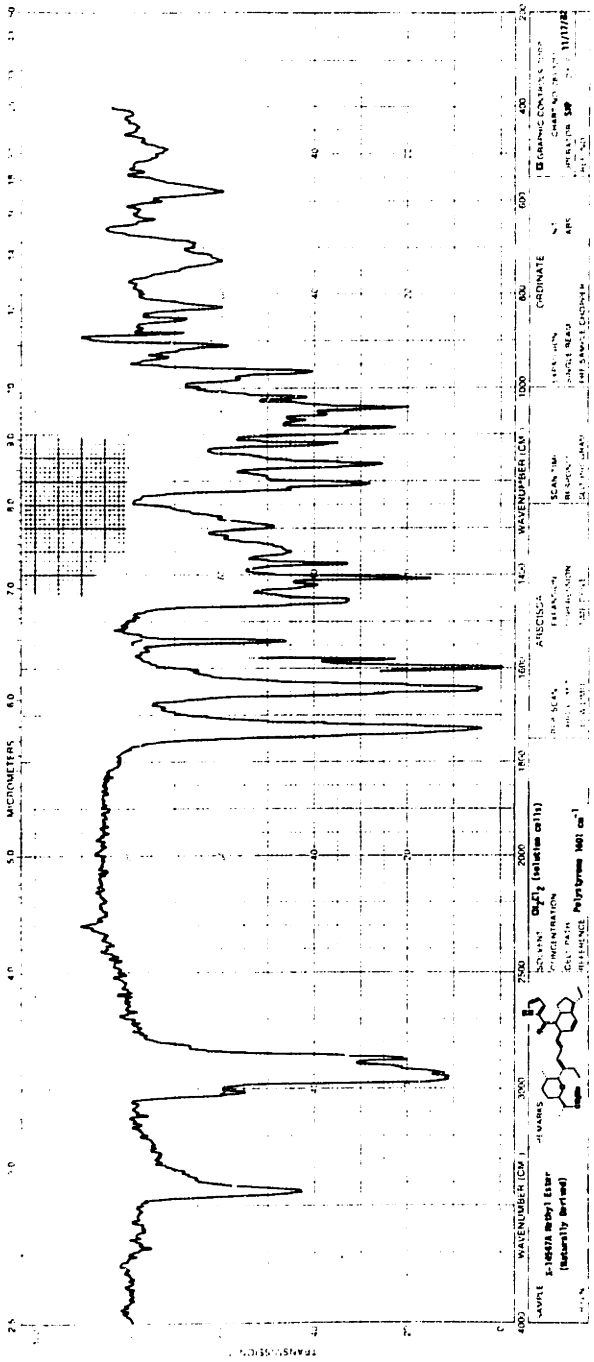
A stirred solution of aldehyde 99 (9.6 mg, 0.023 mmol) in 2 mL of 1,2 dichloroethane was treated with phosphorane 96 (60 mg, 0.16 mmol). This mixture was heated at 40°C for 3 days and at 60°C for one day.

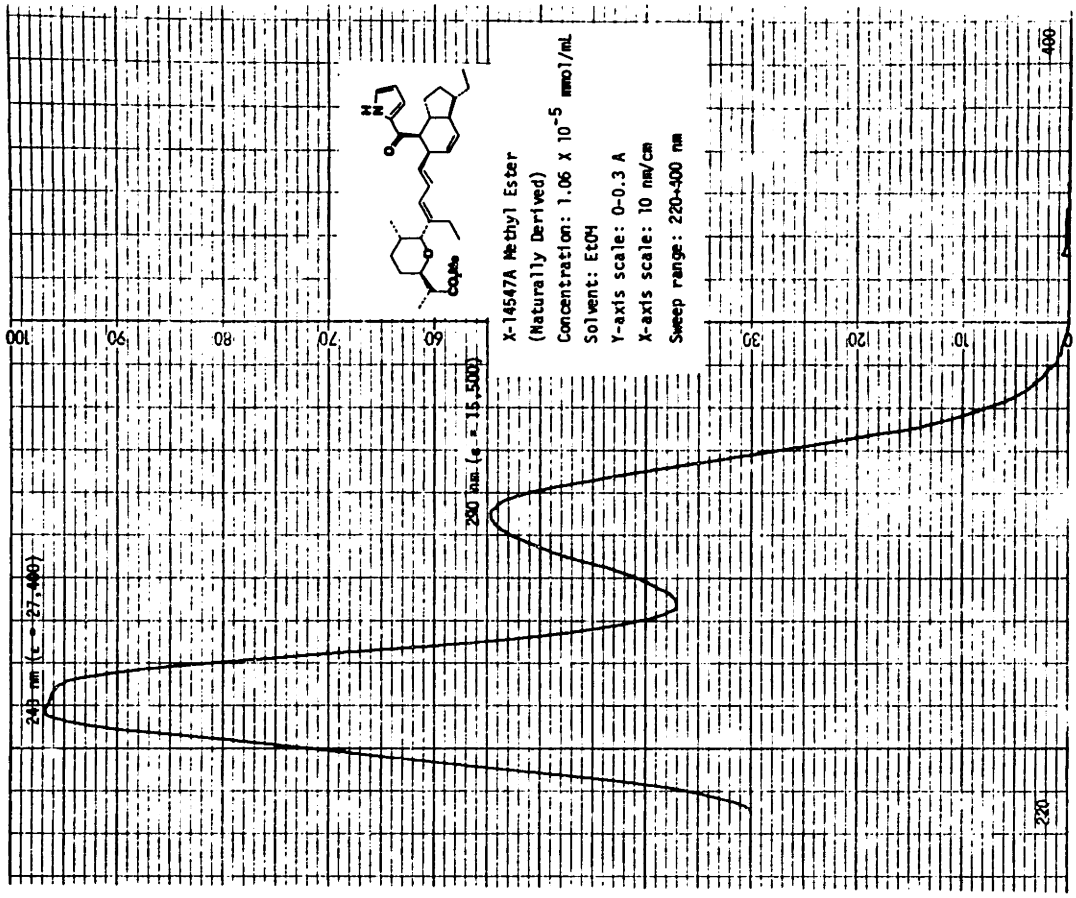
Solvent was removed *in vacuo* and the residue rinsed with ether (8 X 2 mL). The extracts were filtered through 0.5 g of Florisil and then concentrated *in vacuo*.This crude reaction mixture was separated by reverse phase HPLC (Waters μ-Bondapak C-18 column, 30 cm length X 3.9 mm I.D., 3:1 CH_3CN-H_2O, flow rate 0.6 mL/min) to give three fractions consisting of product mixtures (retention times 11.4-13.4 min, 13.4-17.4 min, 17.4-21.6 min). Each fraction was purified by chromatography on a 0.25-mm silica gel plate (1:1 hexane-ether, one development). The first fraction (11.4-13.4 min) afforded 0.55 mg (0.0011 mmol, 5%) of C.10-C.11 (Z)- olefin isomer 227 (R_f 0.49, 1:1 hexane-ether), the second fraction (13.4-17.4 min) gave 0.55mg (0.0011 mmol, 5%) of a mixture of two *cis* fused cycloadducts (tentative assignment; R_f 0.40, 1:1 hexane-ether), and 0.55 mg (0.0011 mmol, 5%) of non-cyclized pentaene (R_f 0.31, 1:1 hexane-ether), while the third fraction afforded 6.0 mg (0.012 mmol, 51%) of pure semisynthetic 11 (R_f 0.046, 1:1 hexane-ether). Methyl ester 11 so obtained ($[\alpha]_D^{22}$ -303.2° , c = 0.60, $CHCl_3$) was identical in all respects (TLC, ^1H NMR, IR, UV, and mass spectrum) to 11 prepared as previously described from natural X-14547A.

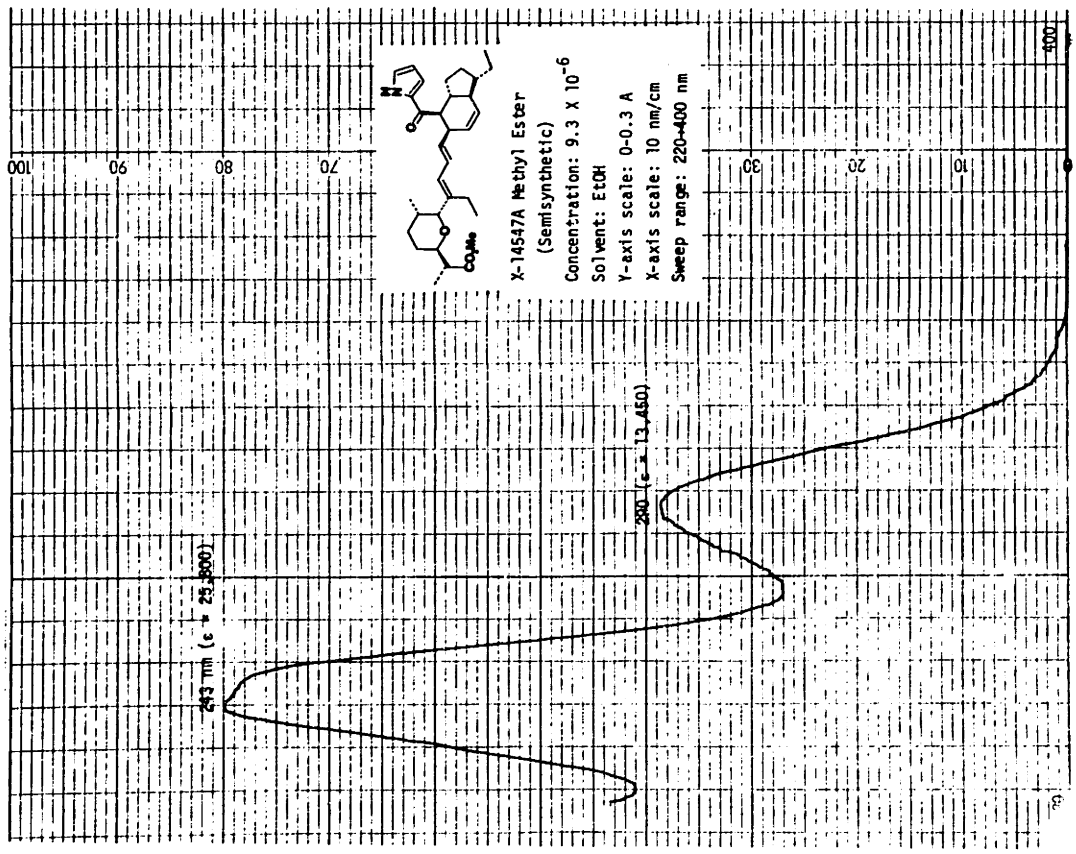
Data for 227: R_f 0.49 (1:1 hexane-ether); ^1H NMR (250 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 6.93 (br s, 2H), 6.23 (m, 1H), 6.07 (t, J = 10.9 Hz, 1H), 5.93 (m, 2H), 5.43 (m, 1H), 5.33 (t, J = 10.5 Hz, 1H), 4.13 (s, 1H), 3.88 (m, 2H), 3.59 (s, 3H), 3.44 (m, 1H), 3.00 (m, 1H), 1.12-2.12 (m, 16 H), 1.07 (d, J = 6.8 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H), 0.55 (d, J = 6.9 Hz, 3H).








X-14547A Methyl Ester
(Naturally Derived)
Concentration: 1.06 X 10⁻⁵ mmol/mL
Solvent: EtOH
Y-axis scale: 0-0.3 A
X-axis scale: 10 nm/cm
Sweep range: 220-400 nm
240 nm (ε = 27,400)
290 nm (ε = 15,500)


X-14547A Methyl Ester
(Semisynthetic)
Concentration: 9.3 X 10⁻⁶
Solvent: EtOH
Y-axis scale: 0-0.3 A
X-axis scale: 10 nm/cm
Sweep range: 220-400 nm
243 nm (ε = 25,300)
280 (ε = 13,450)