THE TOTAL SYNTHESIS OF VERRUCAROL

by

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Submitted to the Department of Chemistry on
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ABSTRACT

The development of a stereoselective chemical synthesis of the trichothecene ring system, culminating in the total synthesis of verrucarol, is described. The key feature of the synthesis focused on the stereospecific annelation of the trichothecene A ring onto a bicyclic precursor.

A series of transformations analogous to the well-k own Robinson annelation were explored on model lactone 2-oxabicyclo [3.2.1]octan-3-one. The key synthetic steps involved the formylation of this model lactone and the stereoselective Michael addition of the resulting hydroxymethylene lactone to methyl vinyl ketone to afford only one of two possible adducts. The stereochemistry of this single adduct was verified by subsequent chemical and spectroscopic evidence. Completion of the study involved aldol closure to form the trichothecene A ring and the biomimetic cyclization to the trichothecene model, 13,14-dinor-15-hydroxy-trichothec-9-ene; the first trichothecene derivative bearing a C.15 hydroxymethyl group to be synthesized.

A [3.2.1] bicyclic lactone corresponding to the B,C-ring system of verrucarol was synthesized from (methylcyclopentadienyl)trimethylsilane. The key steps employed to synthesize this lactone involved (1) the Diels-Alder cyclization of the above disubstituted cyclopentadiene with methyl acrylate; (2) the controlled Wagner-Meerwein rearrangement of the bicyclic Diels-Alder adduct which reorganized the functional group relationships on the bicyclic ring system to correspond to the natural trichothecenes (both the initial Diels-Alder reaction and the Wagner-Meerwein rearrangement were controlled by the trimethylsilyl group); and, (3) the selective reduction of a bicyclic epoxide with Li in ethylenediamine-THF. In practice the crucial formylation and Michael addition to methyl vinyl ketone, comprising the Robinson annelation strategy developed in our model study, proved to be more difficult and lower in chemical yields than anticipated. An alternative and most efficient annelation sequence was then developed which consisted of an initial Diels-Alder spiro-annelation of 1-acetoxy-3-methyl-1,3-butadiene to the [3.2.1] bicyclic α -methylene lactone corresponding to the B,C ring system of verrucarol. The resulting C.11 epimeric mixture of spiro Diels-Alder adducts was then reduced with $LiAlH_4$ and cyclized to the trichothecene

nucleus in biomimetic fashion. The completion of the synthesis of verrucarol then involved the introduction of the 12,13-spiro epoxide. This was accomplished by selective protection of the C.15 and C.4 hydroxyl groups, oxidation of the free C.12 hydroxyl group and Wittig methylenation of the resulting ketone. Final epoxidation of the 12,13-double bond followed by deprotection of the C.15 hydroxyl group (and the 9,10-double bond) with Zn-Ag couple then afforded racemic verrucarol, mp 170-171.5°C.

Two studies on the synthesis of trichothecene analogues are reported. The synthesis of three B,C ring spiro-epoxide analogues corresponding to the bicyclic nucleus of verrucarol are reported. These compounds were tested *in vivo* and found inactive against representative tumor screens. Studies on the synthesis of C.14 desmethyl verrucarol, from prostaglandin precursors, are also reported.

Thesis Supervisor: Dr. William R. Roush

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To Constance

CHAPTER ONE

INTRODUCTION

The trichothecene mycotoxins constitute a family of biologically active fungal metabolites.(1) They are produced by pathogenic fungi (Fusarium, Myrothecium, Trichoderma, Cephalosporium, Verticimonosporium and Stachybotrys species) which infect various agricultural grains and plants.

Disorders of humans, horses, swine, poultry and cattle have been attributed to ingestion of trichothecene contaminated cereal grains. Representative toxicoses include human alimentary toxic aleukia, stachybotrytotoxicosis and dendrodochiotoxicosis reported in the Soviet Union and Central Europe, moldy corn toxicosis reported in the United States and, akakabi (red-mold) poisoning and bean-hulls poisoning reported in Japan. Symptoms of these various mycotoxicoses are similar and cover a range of headaches, chills, nausea, vomiting, diarrhea, skin inflammation, leukopenia, angina, shock, somatitis, dermal necrosis, hemorrhage

(1) Reviews:
(a) Doyle, T.W.; Bradner, W.T. in "Anticancer Agents Based on Natural Product Models"; Cassidy, J.M.; Douros, J., Eds., Academic Press: New York, 1980; Chapter 2;
(b) Ueno. Y. Adv. Nutr. Res. 1980, 3, 301;
(c) "Mycotoxins in Human and Animal Health"; Rodricks, J.V.; Hesseltine, C.W.; Mehlman, M.A., Eds., Pathotox Publishers: 1977; p. 188;
(d) Bamburg, J.R. Adv. Chem. Ser. No.149, 1976, p. 144;
(e) Tamm, Ch. Fortschr. Chem. Org. Naturst. 1974, 31, 63;
(f) Bamburg, J.R.; Strong, F.M. "Microbial Toxins"; Kadis, S.; Ciegler, A.; Ajl, S.J., Eds., Academic Press: New York, 1971; Vol.7, p. 207;

and abortion. Fatalities of humans and animals, documented examples of which were reported as early as 1891[2], have been attributed to ingestion of cereal grains infected with trichothecene producing molds. The above toxicoses, though, have only in retrospect been related to trichothecenes.[3]

The trichothecenes have been isolated and their structures elucidated only within the last thirty five years. Surprisingly, the original stimulus for their isolation were observations of antifungal and phytotoxic effects. The first trichothecenes, the verrucarins (e.g., (17)) in 1946[4] and trichothecin 14 in 1948[5] were isolated in a search for antibiotics. Diacetoxy

(2) Woronin, M. Botanisch. Z. 1891, 49, 81.

(3) For example:
(a) Bamburg, J.R.; Riggs, N.V.; Strong, F.M. Tetrahedron 1968, 24, 3329;
(b) Tatsuno, T.; Saito, M.; Enomoto, M.; Tsunoda, H. Chem. Pharm. Bull. 1968, 16, 2519;
(c) Ueno, Y.; Ueno, I.; Amakai, K.; Ishikawa, Y.; Tsunoda, H.; Okubo, K.; Saito, M.; Enomoto, M. Japan. J. Exp. Med. 1971, 41, 507;
(d) Ueno, Y.; Ishii, K.; Sakai, K.; Kanaeda, S.; Tsunoda, H.; Tanaka, T.; Enomoto, M. Ibid 1972, 42, 187;
(e) Ueno, Y.; Sato, N.; Ishii, K.; Sakai, K.; Enomoto, M. Ibid 1972, 42, 461;
(f) Mirocha, C.J.; Pathre, S. Appl. Microbiol. 1973, 26, 719;
(g) Eppley, R. M.; Bailey, W.J. Science 1973, 181, 758.

(4) Brian, P.W.; McGowan, J.C. Nature 1946, 157, 334.

(5) Freeman, G.G.; Morrison, R.I. Nature 1948, 162, 30.

scirpenol 9, also known as anguidine, was the earliest of the phytotoxins to be discovered (1961).[6] Other trichothecenes possessing cytotoxicity, antiprotozoal, antiviral and antitumor activity were discovered shortly thereafter. Only then, subsequent to these initial discoveries, were trichothecene-producing fungi implicated in animal and human toxicoses.[3] Although the first trichothecene isolation was reported in 1946, almost twenty years elapsed before the molecular structure of this class of compounds was unambiguously deduced. Considerable structural data was accumulated for trichothecolone 15, trichodermol 4 and verrucarol 1 by several reports on chemical structural modifications and spectroscopic studies.[7] It was the publication in 1964 of the X-ray crystal structure of trichodermol,[8] however, which established the stereochemistry of the trichothecene nucleus. The majority of metabolites subsequently isolated were interrelated with these substances.

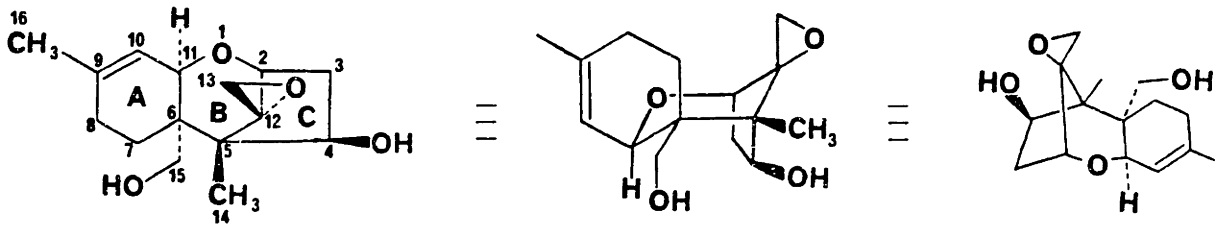
(6) Brian, P.W.; Dawkins, A.W.; Grove, J.E.; Hemming, H.G.; Lowe, D.; Norris, G.L.F. J. Exp. Bot. 1961, 12, 1.

(7) For example:
(a) Gutzwiller, J.; Mauli, R.; Sigg, H.P.; Tamm, Ch. Helv. Chim. Acta 1964, 47, 2234;
(b) Zurcher, W.; Gutzwiller, J.; Tamm, Ch. Ibid 1965, 48, 840;
(c) Sigg, H.P.; Mauli, R.; Flury, E.; Hauser, D. Ibid 1965, 48, 962. Also see reference 1f.

(8) Godtfredsen, W.O.; Vangedal, S. Proc. Chem. Soc. 1964, 188.

The structures of representative trichothecenes are summarized in Figures 1-4. Each of these natural products possesses the same polycyclic carbon nucleus. The designations of rings A, B and C and the trichothecene numbering system are illustrated in Figure 1. Although the predominant conformation of the trichothecene nucleus is best depicted by 1b, the majority of literature citations use structural representations such as 1a. We have also adopted the use of representation 1c which we find useful when discussing trichothecene syntheses. All three designations will be used throughout this thesis.(9)

Figure 1



1a 1b 1c

(9) The structures used throughout this thesis depict intermediates or metabolites using the absolute configuration of the naturally occurring trichothecenes. With the exception of the compounds in Figures 1-4, most structures reported herein represent racemic mixtures. Optically active compounds will be designated as such.

There are essentially two distinct structural differences among the many trichothecenes (See Figure 2, Figure 3 and Figure 4). One difference is the degree of oxidation of the carbon skeleton. For instance, verrucarol 1 has hydroxyl groups at C.4 and at C.15. The simplest metabolite 3 is devoid of functionality at these sites. Other tricothecenes, for example, tricodermol 4 or nivalenol 13, possess hydroxyl or carbonyl functionality at up to five sites: C.3, C.4, C.7, C.8 and C.15.(10) The second variable feature of the trichothecenes is the presence of esters, both simple and macrocyclic. The effects that these structural differences may have on the biological activity and mode of action of the trichothecenes will be discussed in due course.

(10) A naturally occuring epoxide of the 9,10 double bond is known, ie., baccharin 2. See:

(a) Kupchan, S.M.; Jarvis, B.B.; Dailey, R.G.; Bright, W.; Bryan, R.F.; Shizuri, Y. J. Am. Chem. Soc. 1976, 98, 7092;

(b) Kupchan, S.M.; Streelman, D.R.; Jarvis, B.B.; Dailey, R.G.; Sneden, A.T.; J. Org. Chem. 1977, 42, 4221.

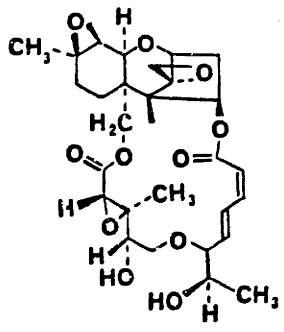


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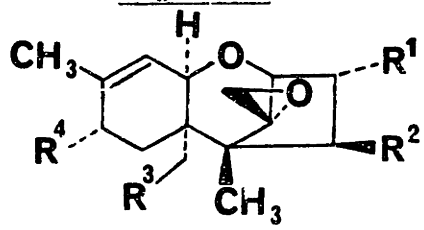
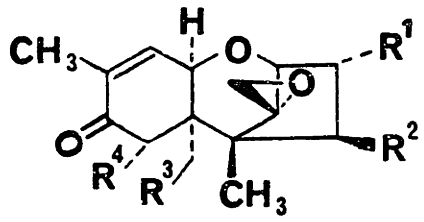
Figure 2

Figure II



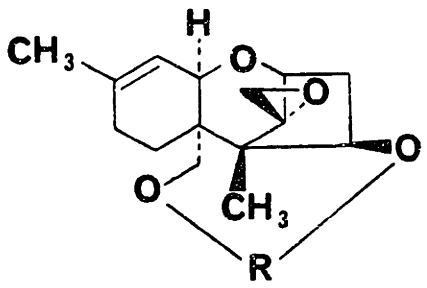
#	Name	R^1	R^2	R^3	R^4
1	Verrucarol	H	OH	OH	H
3	----------	H	H	H	H
4	Trichodermol	H	OH	H	H
5	Trichodermin	H	OAc	H	H
6	T-2 Tetraol	OH	OH	OH	OH
7	T-2 Toxin	OH	OAc	OAc	$OCOCH_2CH(CH_3)_2$
8	Scirpentriol	OH	OH	OH	H
9	Diacetoxy scirpenol	OH	OAc	OAc	H
10	Diacetyl verrucarol	H	OAc	OAc	H
11	Neosolaniol	OH	OAc	OAc	OH
12	Calonectrin	OAc	H	OAc	H

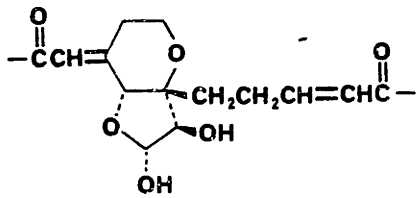
Figure 3



#	Name	R^1	R^2	R^3	R^4
13	Nivalenol	OH	OH	OH	OH
14	Trichothecin	H	$OCOCH=CHCH_3$	H	H
15	Trichothecolone	H	OH	H	H
16	Fusarenone	OH	OAc	OH	OH

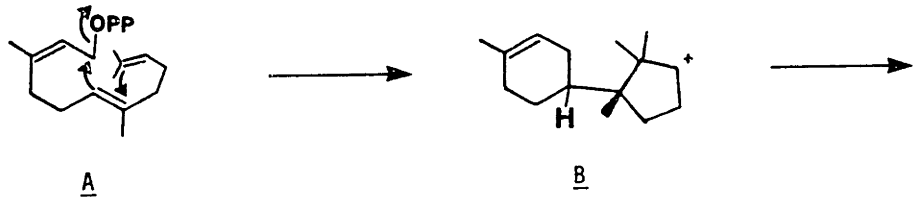
Figure 4



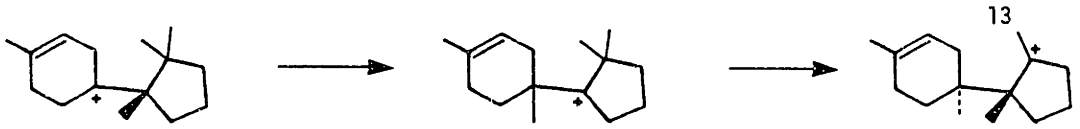
#	Name	R
17	Verrucarin A	-C(O)CH(OH)CH(CH$_3$)CH$_2$CH$_2$OC(O)CH=CHCH=CHC(O)-
18	Roridin A	-C(O)CH(OH)CH(CH$_3$)CH$_2$CH$_2$OC(CH(OH)CH$_3$)CH=CHCH=CHC(O)-
19	Vertisporin	
2	Baccharin (10)	

The biosyntheses of the trichothecenes have been extensively studied.[11] The acyclic precursor of the trichothecene nucleus has been suggested to be cis,trans-farnesyl pyrophosphate A which is believed to cyclize in the manner indicated (A to B). Hydride transfer (B to C) precedes two separate methyl transfers (C to D and D to E). Finally loss of a proton from C.13 of E leads to the isolable intermediate trichodiene 20. Enzymatic epoxidation and hydroxylations of trichodiene to trichodiol 21 are believed to precede a dehydrative cyclization (21 to 3) to the trichothecene nucleus 3. Further nuclear oxidations and esterifications of 3 then lead to the more complex trichothecenes.

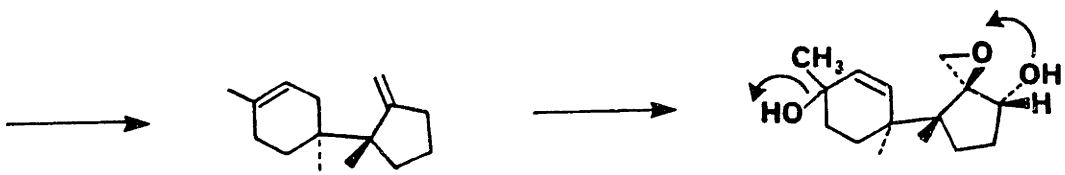
(11) For leading references:
(a) Cane, D.E.; Swanson, S.; Murthy, P.P.N. J. Am. Chem. Soc. 1981, 103, 2136;
(b) Jarvis, B.B.; Pavanasasivam, G.; Holmlund, C.E.; DeSilva, T.; Stahly, G.P.; Mazzola, E.P. J. Am. Chem. Soc. 1981, 103, 472;
(c) Evans, R.; Hanson, J.R. J. Chem. Soc., Perkin I 1976, 326;
(d) Muller, B.; Achini, R.; Tamm, Ch. Helv. Chim. Acta 1975, 58, 453;
(e) Arigoni, D.; Cane, D.E.; Muller, B.; Tamm, Ch. Ibid 1973, 56, 2946;
(f) Machida, Y.; Nozoe, S. Tetrahedron 1972, 28, 5113.



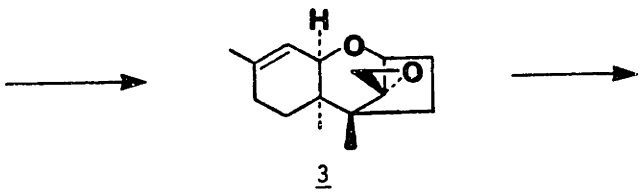
A B



C D E



20 21



3

Various Trichothecenes

It is now known that trichothecenes are toxic to various animal, plant and fungal cells. They are virtually non-toxic to bacteria. Trichothecenes also exhibit antiprotozoal activity and antitumor activity against certain neoplastic diseases. The utilization of trichothecenes as antitumor agents has been considered and will be discussed in a following portion of this chapter.

Allegations have recently been made before the United Nations that the Soviet Union is using or supplying crude trichothecene formulations as offensive weapons of chemical warfare in Afghanistan and Southeast Asia. The chemical attacks have become known as "Yellow Rain".(12) Support for these allegations comes from the isolation of nivalenol 13, T-2 toxin 7 and anguidine 9 from soil samples taken from villages where a chemical attack has occurred. The victims of Yellow Rain attacks display symptoms appallingly similar to those described for the toxicoses which result from ingestion of trichothecene contaminated grains.

On a macroscopic scale the trichothecenes are fearsome because they cause tissue damage, organ damage, hemorrhage and death.(13) The LD_{50} measurements rank the trichothecenes among

(12) (a) Chem. Eng. News 1981, 59(46), 10;
(b) Chem. Eng. News 1982, 60(26), 8;
(c) Marshall, E. Science 1982, 217, 31;
(d) Cullen, D.; Caldwell, R.W. Ibid 1982, 217, 776;
(e) Meisner, H. Ibid 1982, 217, 776;
(f) Mirocha, C.J. Ibid 1982, 217, 776.

(13) Long term studies of several trichothecenes have failed to yield evidence of mutagenicity. See: Ueno, Y.; Kubota, K. Cancer Res. 1976, 36, 445. Also see reference 1c.

the most toxic compounds known. For example the LD_{50} of verrucarin A 17 administered intraperitoneally to mice was 0.5 mg per kilogram body weight. By way of comparison, the LD_{50} of potassium cyanide orally administered to rats is 10 mg/Kg. To understand why these compounds are so toxic, we need to consider the mechanism of action of the trichothecenes at the molecular level.(1)

The trichothecenes are potent inhibitors of protein synthesis in eukaryotic cells.(14) They also inhibit DNA, RNA and polysaccharide synthesis in these cells, but it appears that primary cellular destruction results from trichothecene inhibition of protein synthesis.(15)

The trichothecenes have been subclassified according to the stage at which protein synthesis is interrupted. Specific inhibitors of the initiation, elongation, and termination stages have been identified. Initiation-type inhibitors (I) are generally more active than the elongation (E) or termination (T) types. It has been suggested that a C.15 acyl substituent determines I vs. E or T activity.(16) Others have pointed

(14) For leading references see: Gale, E.F.; Cundliffe, E.; Reynolds, P.E.; Richmond, M.H.; Waring, M.J. "The Molecular Basis of Antibiotic Action", 2nd ed. John Wiley and Sons Ltd.,London, 1981, p. 508. For a recent reference see: Hernandez, F.; Cannon, M. J. Antibiot. 1982, 35, 875.

(15) For instance see:
(a) Ueno, Y.; Fukushima, K. Experientia 1968, 24, 1032;
(b) Also see 1b and references therein.

(16) Cundliffe, E.; Davies, J.E. Antimicrob. Agents Chemother. 1977, 11, 491.

out, however,that C.15 hydroxylated derivatives can be effective initiation inhibitors if C.3 is substituted with an α-hydroxyl group.(14)

The actual inhibition process is not fully understood. The minimum structural features required for biological activity appear to be the presence of the 12,13-epoxytrichothecene skeleton. Reduction of the epoxide leads to inactive derivatives while hydrogenation of the 9,10-double bond leads to a substantial loss of activity. Rearrangement of the trichothecene skeleton to the apotrichothecene ring system or opening of ring C also lead to loss of activity. A β-C.4 hydroxyl or acyloxyl group is required for *in vitro* inhibition of peptidyl transferase.(1) In the macrocyclic series of verrucarol derivatives (Figure 4), the macrocyclic ring must be intact for the roridins and verrucarins to have biological activity.(11b) Epoxidation of the 9,10-double bond or introduction of an allylic hydroxyl group at C.8 leads to an increase in potency.(14),(17)

The cytostatic properties of certain trichothecenes have stimulated hopes that one of the naturally occurring trichothecenes, or a closely related analogue of it, would join the arsenal of chemotherapeutic agents available to combat neoplastic disease in man. This expectation has not yet been

(17) Jarvis, B.B.; Stahly, G.P.; Pavanasasivam, G.; Mazzola, E.P. J. Med. Chem. 1980, 23, 1054.

realized. Initial tests in mice indicated that anguidine, available in large quantities and pure form from fermentation broths (Fusarium equiseti)[6] exhibited strong antitumor activity against several mice leukemias and also in adenocarcinoma of the colon in mice.[1a] These preliminary results prompted the National Cancer Institute to take anguidine into clinical trials.[18],[19]

The results of Phase I and Phase II clinical testing of anguidine in humans have been discouraging. In studies of patients with metastatic colon or rectal cancer and also patients with advanced breast cancer no measurable regression was observed. This, coupled with observed violent toxic side effects, rules out the likelihood that anguidine will proceed to Phase III trials.

(18) (a) Embers, L. Chem. Eng. News 1981, 59(48), 29;
(b) Murphy, W.K.; Livingston, R.B.; Gottlieb, J.A.; Burgess, M.A.; Rawson, R.W. Proc. Assoc. Cancer Res. 1976, 17, 90;
(c) Yap, H.Y.; Murphy, W.K.; DiStefano, A.; Blumenshein, G.R.; Bodey, G.P. Cancer Treat. Rep. 1979, 63, 789.

(19) A potential chemotherapeutic drug goes through three levels of testing to determine its efficacy. The first level, Phase I, is designed to determine the highest dose tolerated and also the toxic side effects. It is performed on patients with significantly advanced disease. Phase II studies examine the therapeutic effects of a drug in a well-defined patient population. Phase III testing compares the antitumor prowess of a particular drug to other existing treatments.

Based on an understanding of the trichothecene interaction with eukaryotic ribosomes, it seems plausible that an antitumor drug possessing some of the structural features of the trichothecenes will eventually be developed. Trichothecenes other than anguidine have not yet been studied in the clinic. It appears, however, that the macrocyclic trichothecenes (Figure 4) now show more promise.(1a),(17)

Research Objective

The interesting structure and potent biological properties of the trichothecenes have stimulated much interest in their chemistry and synthesis. My goal was to develop an efficient chemical synthesis of the trichothecene nucleus; our specific target was verrucarol 1.(20)

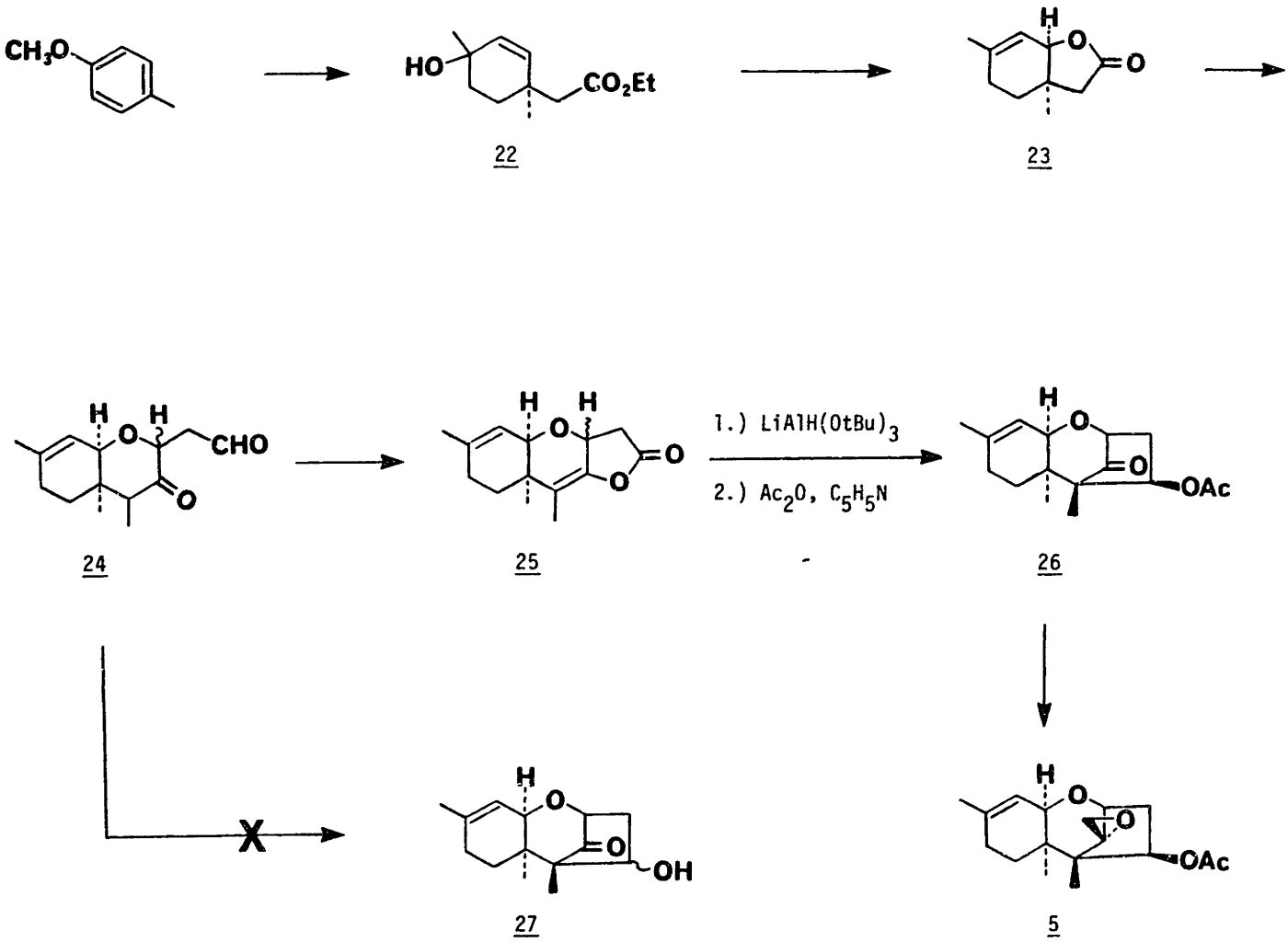
In this section, a brief review of the work published prior to and concurrent with our work on this problem is presented. A discussion of our strategy to solve this problem appears on page 37 and our successful synthesis is described beginning in Chapter 3.

(20) Verrucarol 1 occurs in nature as the diacetate 10 and also as the nucleus of a majority of the macrocyclic di- and triester derivatives. (see Figure 4).

(21) (a) Colvin, E.W.; Raphael, R.A.; Roberts, J.S. J. Chem. Soc., Chem. Commun. 1971, 858;
(b) Colvin, E.W.; Malchencko, S.; Raphael, R.A.; Roberts, J.S. J. Chem. Soc., Perkin I, 1973, 1989;
(c) Colvin, E.W.; Malchenko, S.; Raphael, R.A.; Roberts, J.S. J. Chem. Soc., Perkin I, 1978, 658.

The first trichothecene synthesis was reported by Colvin.[21] The polycyclic ring system was assembled in a left-to-right (A-->AB-->ABC) fashion, the crucial step being the intramolecular aldol closure of 24 to 27 (Scheme II). The intramolecular aldol precursor 24, an epimeric mixture at C.2, was

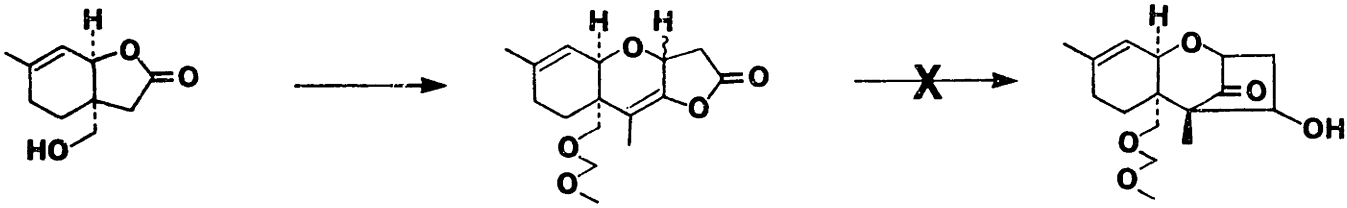
Scheme II



synthesized in straightforward fashion. Thirty seven different attempts with varying conditions were performed in an effort to effect condensation of 24 to 27, none of which were successful. However, 24 could be converted to the epimeric enol lactones 25. Treatment of this mixture with lithium tri-t-butoxy aluminum hydride produced a 53% yield of 24 and only a 7% yield of the desired aldol adduct. This material was then converted to racemic trichodermin 5.

An attempt to synthesize verrucarol from 29 using an analogous approach was not successful (Scheme III).[21c]

Scheme III



28 29 30

The logic of this approach (Scheme II) was certainly well-founded. One could not a priori predict the difficulties which were experienced. An axially oriented acetaldehyde substituent at C.2 (trichothecene numbering) is required in the B ring for successful condensation of 24 to 27. The desired isomer of 24, however, is thermodynamically less stable than its C.2 epimer. Presumably, the facile epimerization at C.2 is the source of problems, for this C.2 epimer cannot directly cyclize to 27.

Several groups have reported syntheses of intermediates very similar to 24 or its precursors. Welch reported a synthesis of 23[22] and later used this compound as an intermediate in a synthesis of racemic trichodiene 20.[23] Goldsmith and his colleagues at Emory University performed considerable synthetic work on trichothecene precursors.[24] Snider and Amin synthesized 28[25] and Trost and Rigby synthesized a precursor similar to 29.[26] Reports from these laboratories on the completion of trichothecene syntheses have not yet appeared.

A second intramolecular aldol strategy which forms the C.2, C.3 bond (i.e., 34 to 35, Scheme IV) was developed by Fujimoto in a synthesis of 3. In this strategy C.5 is stereochemically fixed and not subject to epimerization.

(22) (a) Welch, S.C.; Wong, R.Y. Tetrahedron Lett. 1972, 1853
(b) Welch, S.C.; Wong, R.Y. Synth. Commun. 1972, 2, 291.

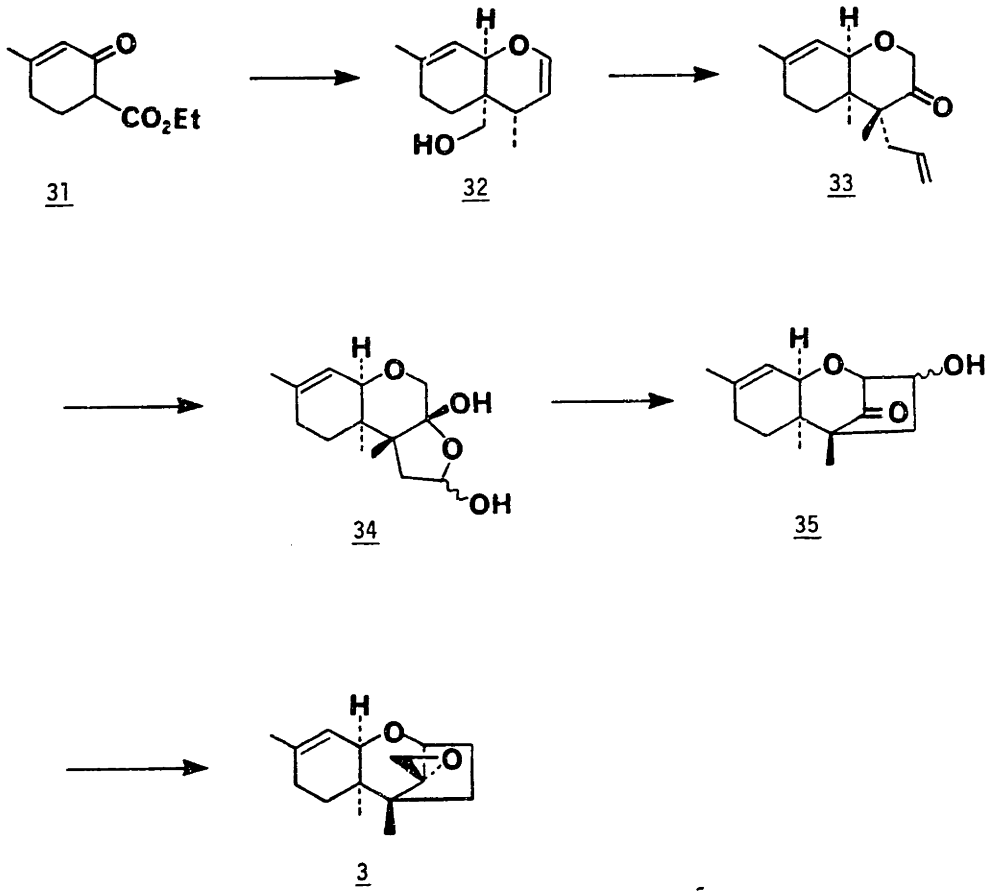
(23) (a) Welch, S.C.; Prakasa Rao, A.S.C,; Wong, R.Y. Synth. Commun. 1976, 6, 443;
(b) Welch, S.C.; Prakasa Rao, A.S.C.; Gibbs, C.G. Synth. Commun. 1976, 6, 485;
(c) Welch, S.C.; Prakasa Rao, A.S.C.; Gibbs, C.G.; Wong, R.Y. J. Org. Chem. 1980, 45, 4077;
(d) For another work on trichodiene see: Yamakawa, K.; Sakaguchi, R.; Nakamura, T.; Watanabe, K. Chem. Lett. 1976, 991.

(24) (a) Still, W.C.; Goldsmith, D.J. J. Org. Chem. 1970, 35, 2282;
(b) Still, W.C.; Lewis, A.J.; Goldsmith, D. Tetrahedron Lett. 1971, 1421;
(c) Goldsmith, D.J. Helmes, C.T. Synth. Commun. 1973, 3, 231;
(d) Goldsmith, D.J.; Lewis, A.J.; Still, W.C. Tetrahedron Lett. 1973, 4807.

(25) Snider, B.B.; Amin, S.G. Synth. Commun. 1978, 8, 117.

(26) Trost, B.M.; Rigby, J.H. J. Org. Chem. 1978, 43, 2938

Scheme IV



31 32 33 34 35 3

Ketone 33 was synthesized by using a Claisen rearrangement to introduce the proper relationship between C.5 and C.6. The vinyl group of 33 served as a latent aldehyde and was unmasked to give the hydrate 34. Treatment of 34 with sodium methoxide in refluxing methanol produced the adduct 35 in 90% yield. Here the

intramolecular aldol condensation was effected without complication. This intermediate was then transformed into the natural product 3.[27]

This strategy was adopted and refined by Kraus in a recent synthesis of calonectrin 12.[28]

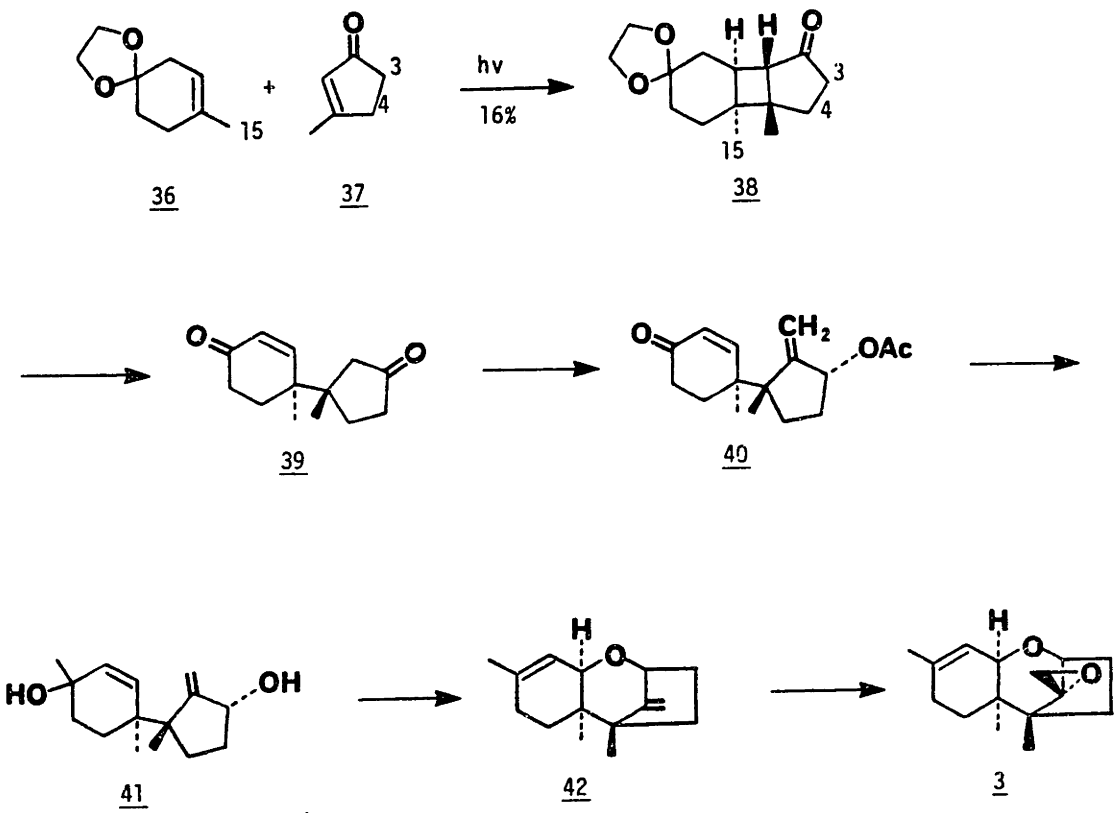
The first chemists to report studies on a synthetic strategy which did not involve an aldol closure of the BC ring system were headed by Professor Kamikawa at Osaka City University in Japan.[29] This group correctly reasoned that once the stereochemical relationship between C.5 and C.6 had been properly established, a biomimetic ring closure (i.e., 41-->42, Scheme V; see also page 18) would produce the desired ring system.

(27) Fujimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsuno, T.; Kenkyusho, R. Tetrahedron Lett. 1974, 2523.

(28) (a) Kraus, G.A.; Frazier, K. J. Org. Chem. 1980, 45, 4820;
(b) Kraus, G.A.; Roth, B. J. Org. Chem. 1980, 45, 4825;
(c) Kraus, G.A.; Roth, B.; Frazier, K.; Shimagaki, M. J. Am. Chem. Soc. 1982, 104, 1114.

(29) (a) Masuoka, N.; Kamikawa, T.; Kubota, T. Chem. Lett. 1974, 751;
(b) Masuoka, N.; Kamikawa, T. Tetrahedron Lett. 1976, 1691;
(c) Also see: Yamakawa, K.; Kurita, J.; Sakaguchi, R. Tetrahedron Lett. 1973, 3877; and reference 13(d).

Scheme V



36 37 38 39 40 41 42 3

The cyclization substrate 41 was synthesized by a route involving the photochemical addition of 36 to enone 37. This reaction produced the desired photo-adduct 38 in only 16% yield.

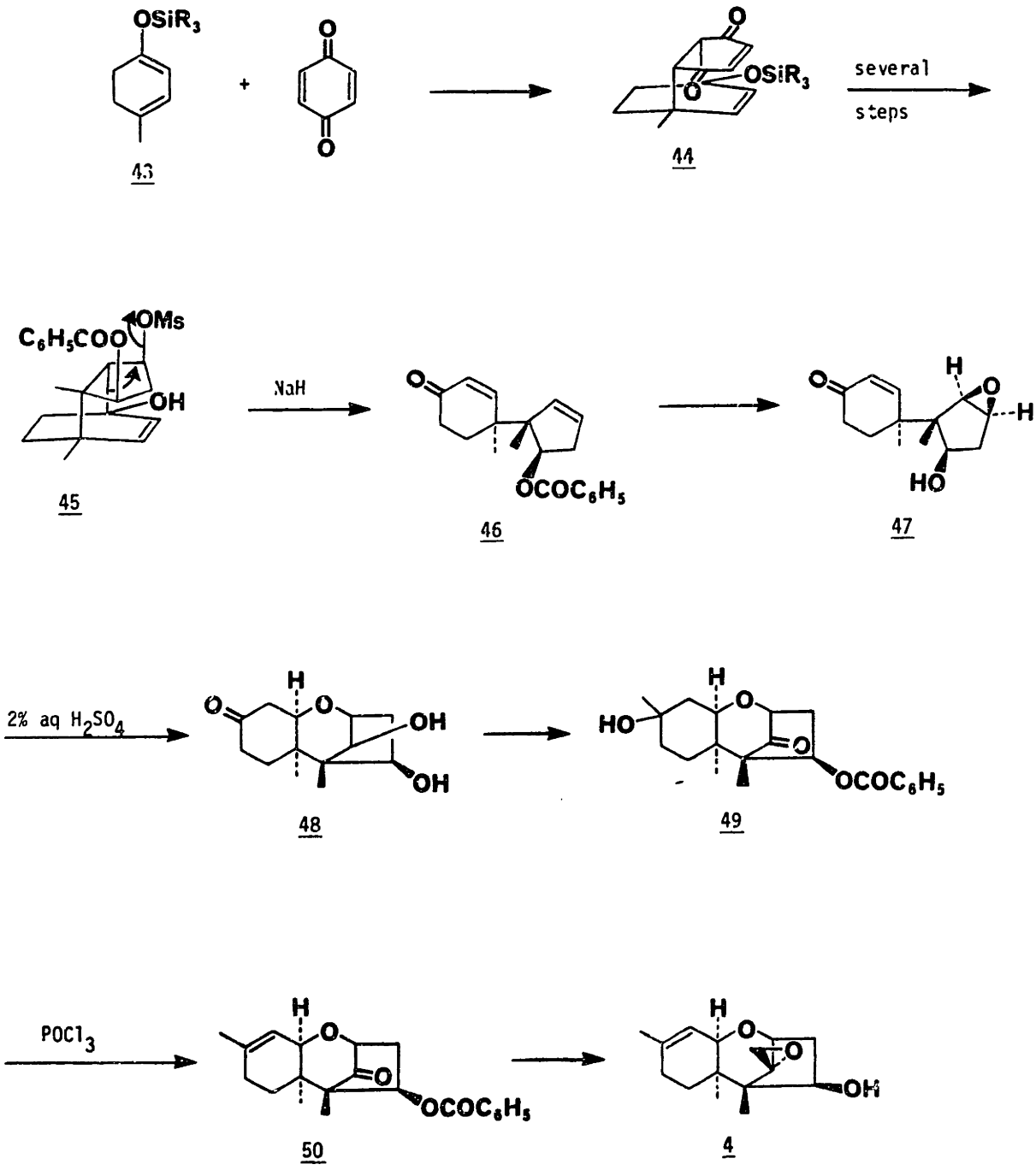
Treatment of 41 with mild acid produced the desired trichothecene nucleus 42, in 40% yield (from 40), in agreement with biogenetic expectations; apparently none of the trans-fused AB product was formed. Epoxidation of 42 then afforded 3.

Although the initial step was nonspecific and appears poorly suited for application to more complicated substrates, Kamikawa's synthesis demonstrated the feasability and power of using a biomimetic sequence for final closure to the polycyclic skeleton. Transformations analogous to 41----->42 have been adopted in a number of recent syntheses, including that which is described in Chapters 2 and 3 of this thesis.

Still, who first became involved with trichothecene synthesis through his work as a graduate student with Professor Goldsmith,[24] has successfully completed a second synthesis of trichodermol 4 (Scheme VI).[30] Still used the rigid polycyclic Diels-Alder adduct 44 to introduce the necessary stereochemical relationships between substituents on C.4, C.5 and C.6 of 4. A crucial step of this synthesis is the hydrolysis of 47 and Michael addition of the resulting triol to directly give 48. This Michael addition which occurred under the hydrolysis

(30) Still, W.C.; Tsai, M.Y. J. Am. Chem. Soc. 1980, 102, 3654.

Scheme VI


OSiR3
O
O
43
44
OSiR3
several
steps
C6H5COO
OMs
OH
45
NaH
OCOC6H5
46
H
O
H
HO
47
2% aq H2SO4
H
O
O
OH
OH
48
HO
OCOC6H5
49
POCl3
OCOC6H5
50
OH
4

conditions, resembles the biosynthetic ring closure previously discussed (see page 18). As was the case in the biomimetic closure performed by Kamikawa, only cis ring fusion at the resulting A,B ring junction was obtained. Selective protection of the C.4 hydroxyl group set the stage for final elaboration to trichodermol 4.

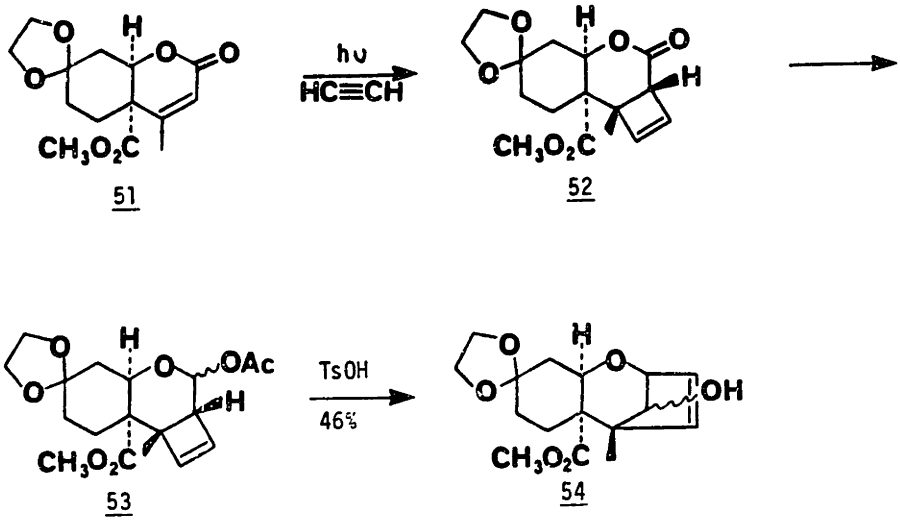
Pearson has developed a novel synthetic route to intermediates similar to 46 utilizing nucleophilic addition to $Fe(CO)_3$ diene complexes.(31)

An interesting construction of the trichothecene ring system has been reported by White.(32) The key steps of this approach (Scheme VII) are the regioselective photochemical addition of acetylene to unsaturated lactone 51 and the acid catalyzed isomerization of 53 to 54. The polycycle 54 possesses functionality sufficient, in principle, to permit the synthesis of a variety of naturally occurring trichothecenes.

(31) (a) Pearson, A.J. J. Chem. Soc., Perkin I 1977, 2069;
(b) Pearson, A.J. J. Chem. Soc., Chem. Commun. 1977, 339;
(c) Pearson, A.J.; Raithby, P.R. J. Chem. Soc., Perkin I 1980, 395;
(d) Pearson, A.J.; Ong, C.W. Tetrahedron Lett. 1980, 21, 4641;
(e) Pearson, A.J.; Ong, C.W. J. Am. Chem. Soc. 1981, 103, 6686;
(f) Pearson, A.J.; Ham, P.; Ong, C.W.; Perrior, T.R.; Rees, D.C. J. Chem. Soc., Perkin I 1982, 1527.

(32) White, J.D.; Matsui, T.; Thomas, J.A. J. Org. Chem. 1981, 46, 3376.

Scheme VII



51 52 53 54

Quite recently a synthesis of verrucarol 1 has been reported[33] by Schlessinger (Scheme VIII). The key steps of

this synthesis include the treatment of the enolate of lactone 57 with gaseous formaldehyde, yielding directly the α - methylene lactone 58, and the regioselective Diels-Alder addition of 1-methoxy-3-trimethylsilyloxybutadiene to 58 to afford, after acidic hydrolysis, a 76% yield of spiro-cyclohexenone 59. Elaboration of 59 to verrucarol 1 involved the biomimetic cyclization of 60 to 61 and the selective epoxidation of the C.12,C.13-double bond by temporarily masking the C.9,C.10-double bond as the bromo-ether 62. The similarity of Schlessinger's synthesis to that developed in our laboratories will become apparent as our work is described (Chapters 2 and 3).

Other studies dealing with trichothecene synthesis have also been published[34],[35],[36] but are not discussed here.[37]

(33) Schlessinger, R.H.; Nugent, R.A. J. Am Chem. Soc. 1982, 104, 1116.

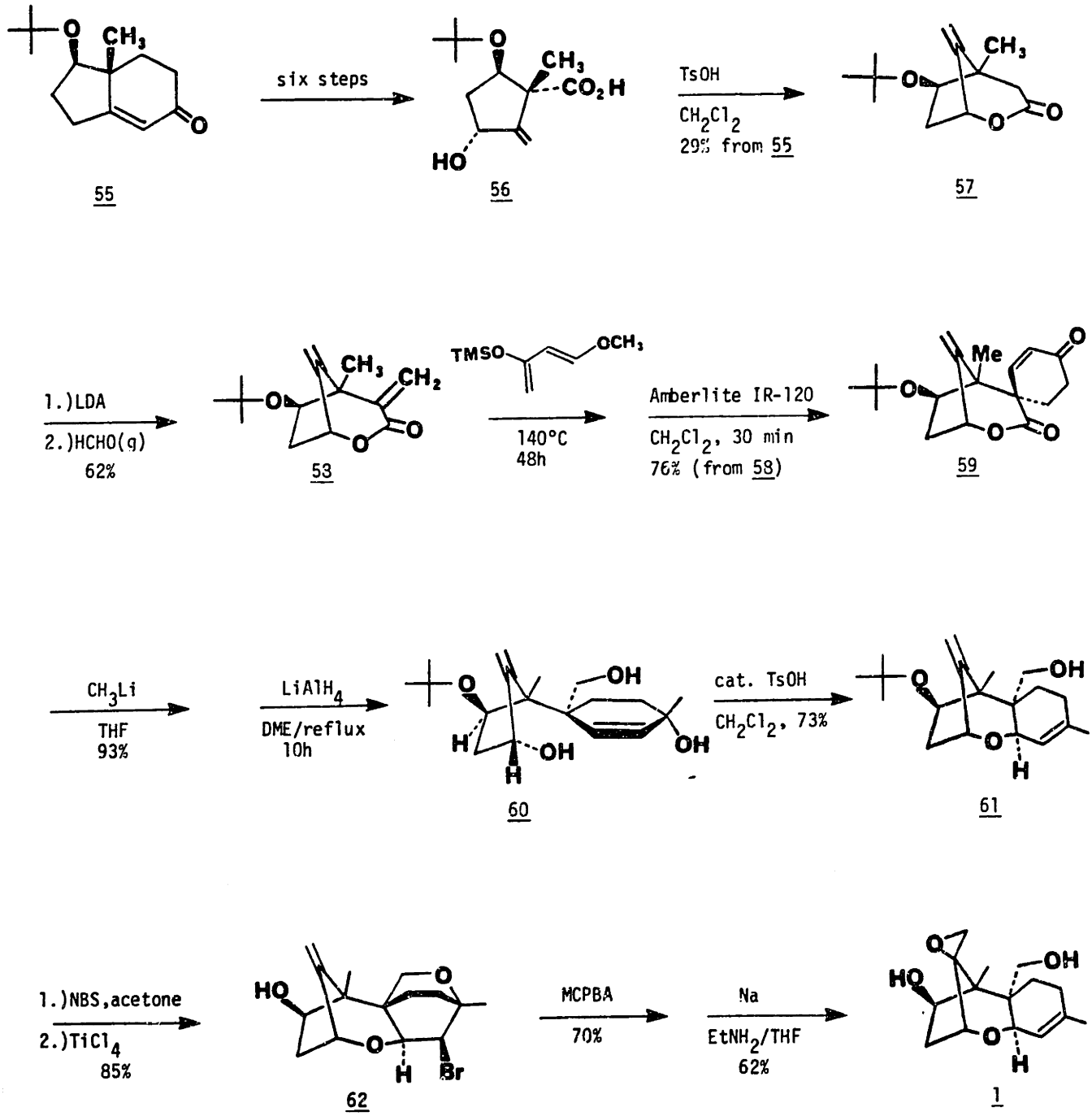
(34) (a) Anderson, W.K.; LaVoie, E.J.; Lee, G.E. J. Org. Chem. 1977, 42, 1045;
(b) Anderson, W.K.; Lee, G.E. J. Org. Chem. 1980, 45, 501;
(c) Anderson, W.K.; Lee, G.E. J. Med. Chem. 1980, 23, 96.

(35) Goldsmith, D.J.; John, T.K.; Kwong, C.D.; Painter, G.R. J. Org. Chem. 1980, 45, 3989.

(36) Tulshian, D.B.; Fraser-Reid, B. Tetrahedron Lett. 1980, 4549.

(37) A recent study on a synthesis of anguidine 9 using our Robinson annelation route (Chapter 2): Brooks, D.W.; Grothaus, P.G.; Palmer, J.T. Tetrahedron Lett. 1982, 23, 4187.

Scheme VIII



55 56 57 53 59 60 61 62 1

Synthetic Considerations

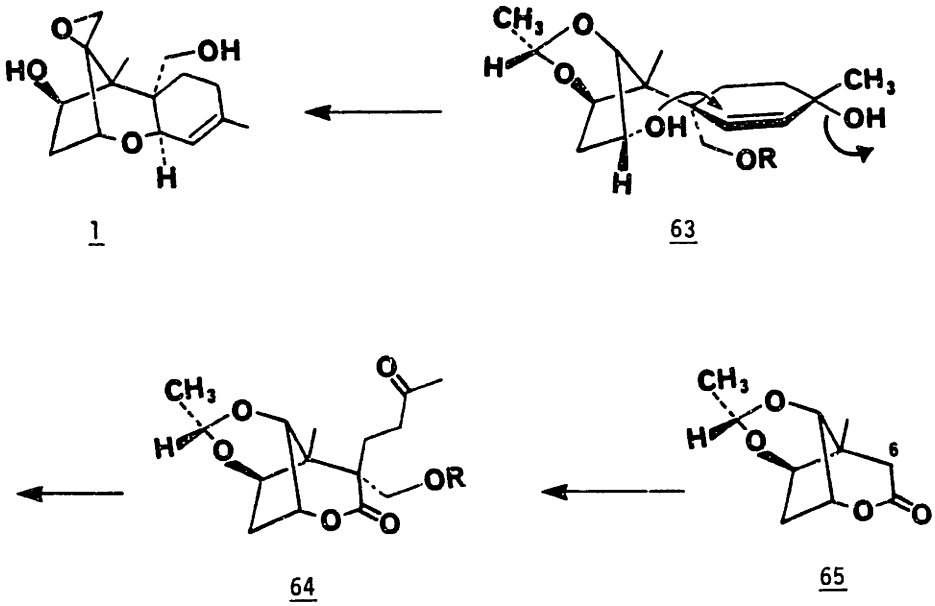
The work described in this thesis was initiated in January, 1979. The approaches recently reported by Still, Pearson, White, Kraus and Schlessinger had not yet been published.

Our retrosynthetic reasoning is depicted in Scheme IX. We recognized that the B,C ring system of verrucarol 1 is a [3.2.1] oxabicyclooctane structure. Ample precedent existed to suggest that the β (or exo) face of such a system is stereochemically less hindered than the corresponding endo face.(38) We therefore reasoned that the A ring might be introduced by a controlled annelation sequence performed on a bicyclic lactone such as 65(39). Final elaboration to the trichothecene ring system from 63 would be biomimetic.

(38) (a) Corey, E.J.; Hartmann, R.; Vatakencherry, P.A. J. Am. Chem. Soc. 1962, 84, 2611;
(b) Zirkle, C.L.; Geissman, T.A.; Bloom, M.; Craig, P.N.; Gerns, F.R.; Indek, Z.K.; Pavloff, A.M. J. Org. Chem. 1962, 27, 1269;
(c) Sauers, R.R.; How, H.M.; Feilich, H. Tetrahedron 1965, 21, 983;
(d) Acharya, S.P.; Brown, H.C. J. Org. Chem. 1970, 35, 196;
(e) Ikoto, B.; Ganem, B. J. Am. Chem. Soc. 1978, 100, 351;
(f) Stork, G.; Logusch, E.W. Tetrahedron Lett. 1979, 3361;
(g) Logusch, E.W. Ibid, 1979, 3365;
(h) Takaishi, N.; Inamoto, Y.; Aigami, K. Chem. Lett. 1979, 803.

(39) Our strategy for the synthesis of 65 is discussed in Chapter 3.

Scheme IX



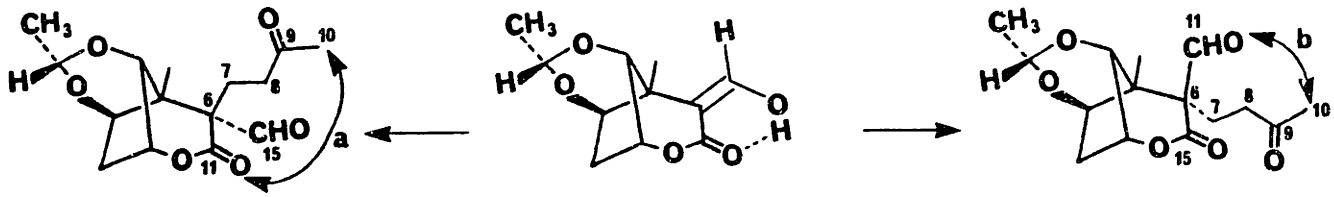
We initially pursued a Robinson-type annelation strategy utilizing lactone 65.[40] We felt that sequential carbon-carbon bond forming reactions at C.6 (trichothecene numbering) could be used to selectively incorporate the correct stereochemistry at this center. Addition of methyl vinyl ketone (MVK) to enol lactone 66 was expected to yield Michael adduct 67. The trichothecene A ring could then be formed from 67 by connecting carbons

(40) An alternative annelation strategy involving an intramolecular Diels-Alder cyclization sequence was also explored in these laboratories: T.A. Blizzard, unpublished results.

C.10 and C.11 as indicated in Scheme X. In the event that this Michael reaction proceeded with reversed (unexpected) stereoselectivity to give 68, a synthesis of verrucarol could still be completed. The carbons functioning as C.11 and C.15 of 68 could be reversed, relative to that in 67, as indicated in Scheme X.(41)

The development of this strategy and the synthesis of racemic verrucarol are the subjects of the remaining chapters. Portions of this work have been published.(42)

Scheme X



67 66 68

(41) A method for this spiro-annelation has been reported. Corey, E.J.; Tius, M.A.; Das, J. J. Am. Chem. Soc. 1980, 102, 7612.

(42) (a) Roush, W.R.; D'Ambra, T.E. J. Org. Chem. 1980, 45, 3927;
(b) Roush, W.R.; D'Ambra, T.E. Ibid 1981, 46, 5045.

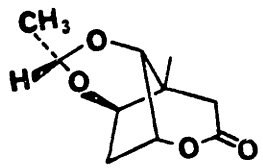
CHAPTER TWO[43]

Model Study:

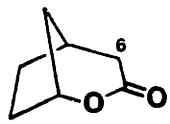
The Total Synthesis of 13,14-Dinor-15-hydroxy-trichothec-9-ene

(43) A preliminary account of this work has been published, see reference 42a.

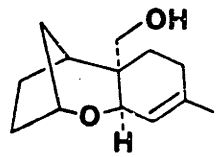
The crucial transformations in our synthetic strategy (Scheme IX, page 38) required the complex bicyclic lactone 65 as the annelation substrate. We decided to explore the viability of these transformations using the readily available lactone 69 as a model system. Our initial target thus became the simple bis nor trichothecene 70.



65



69



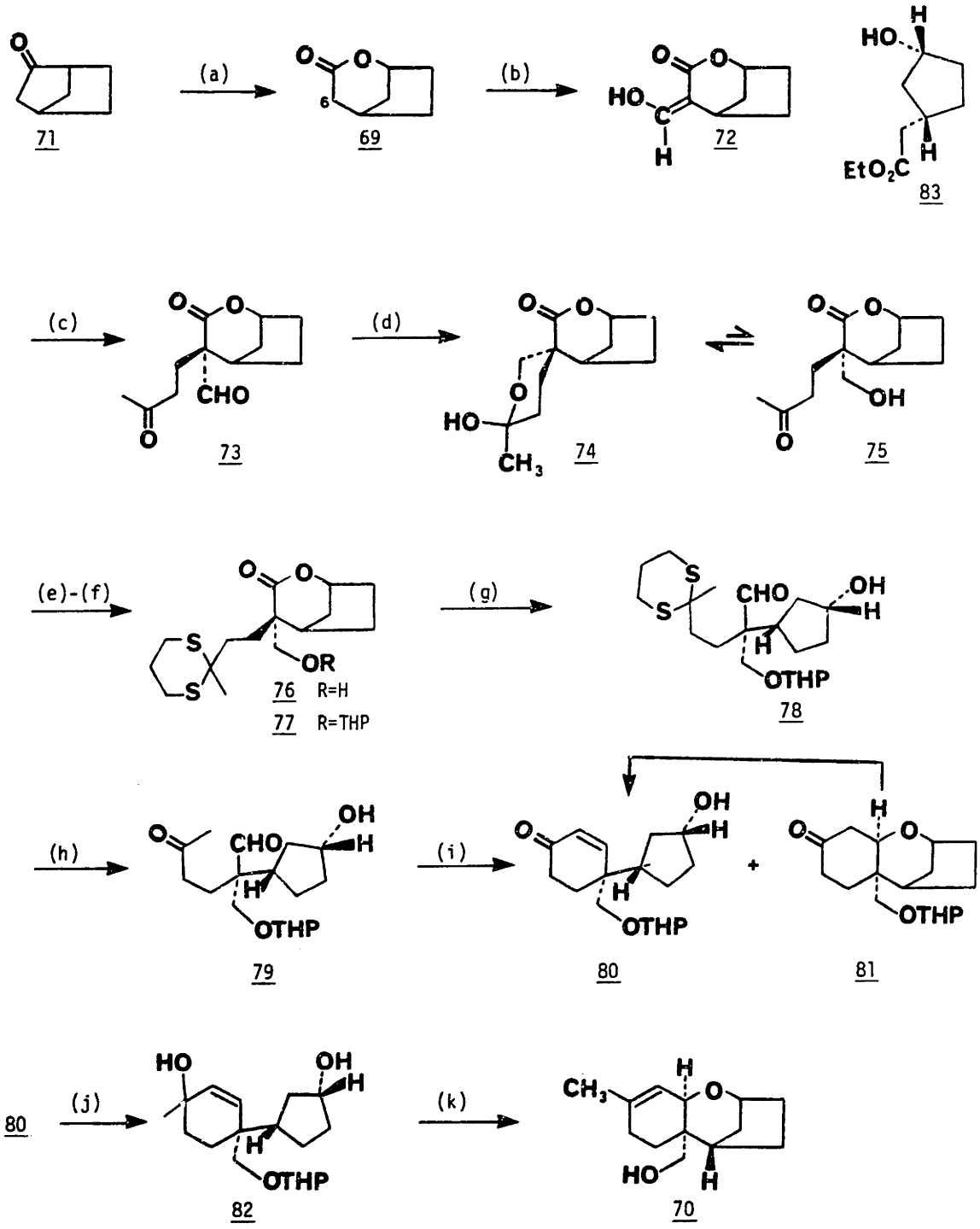
70

The synthesis of 70 is outlined in Scheme XI. Baeyer-Villiger oxidation of commercially available norcamphor 71 afforded lactone 69[44] in 90% yield; formylation of which gave the crystalline vinylogous acid 72, mp 122-123°C, in 85% yield. It proved necessary to use tert-butyl formate [45] in this transformation since with ethyl formate and potassium t-butoxide 72 was obtained in lower yield (50%) together with hydroxy ethyl ester 83 (38%) deriving from 69 by lactone ethanolysis.

(44) (a) Rassat, A.; Ourisson, G. Bull. Soc. Chim. France 1959, 1133;
(b) Meinwald, J.; Frauenglass, E. J. Am. Chem. Soc. 1960, 82, 5235.

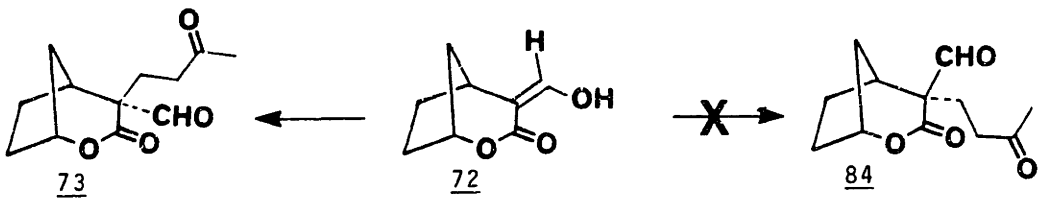
(45) (a) Stevens, W.; Van Es, A. Recl. Trav. Chim. Pays-Bas 1964, 83, 1287;
(b) Ibid, 1965, 84, 704.

Scheme XI



(a) MCPBA, $NaHCO_3$, CH_2Cl_2, 2h (90%);
(b) Tert-butyl formate, KO-t-Bu, THF, RT, 90 min (85%);
(c) Methyl vinyl ketone, THF, t-BuOH, KO-t-Bu (catalytic), 2h (90%);
(d) 0.25 equiv. of $NaBH_4$, EtOH, $-10^{\circ}C$, 2h (96%);
(e) 1,3-propanedithiol, BF_3-OEt_2, 20 min (96%);
(f) Dihydropyran, pTsOH (catalytic), CH_2Cl_2, 1h (95%);
(g) DIBAL, toluene, $-78^{\circ}C$, 3h (80-85%);
(h) NBS, collidine, CH_3CN-H_2O (4:1), $0^{\circ}C$, 20 min (74%);
(i) KOH, CH_3OH, H_2O, 3h (80-89%);
(j) CH_3Li (excess), THF, $-78^{\circ}C$;
(k) 1N HCl, THF, 6-18h (65-75% from 80).

Treatment of 72 with methyl vinyl ketone (KOt-Bu, t-BuOH, THF) afforded Michael adduct 73 in 90-98% yield. The presence of only one aldehyde resonance (δ 9.85) in the 270 MHz ^1H NMR spectrum of 73 implied that only a single isomer of the two possible products, 73 and 84, had been produced.

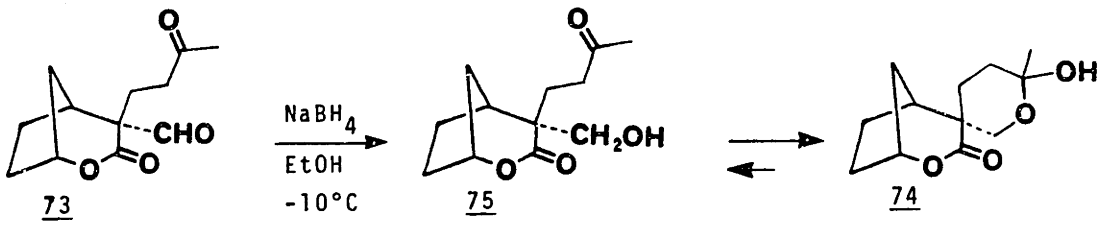


73 72 84

Initially we assigned the stereochemistry of this single Michael adduct, as depicted in 73, by assuming that methyl vinyl ketone approaches the enolate of 72 from the exo face of this bicyclic nucleus.[38] The alternative adduct, 84, could be produced only by Michael addition from the more hindered, endo face of 72.

That 73 was indeed the isomer produced was verified by chemical evidence which is subsequently described.

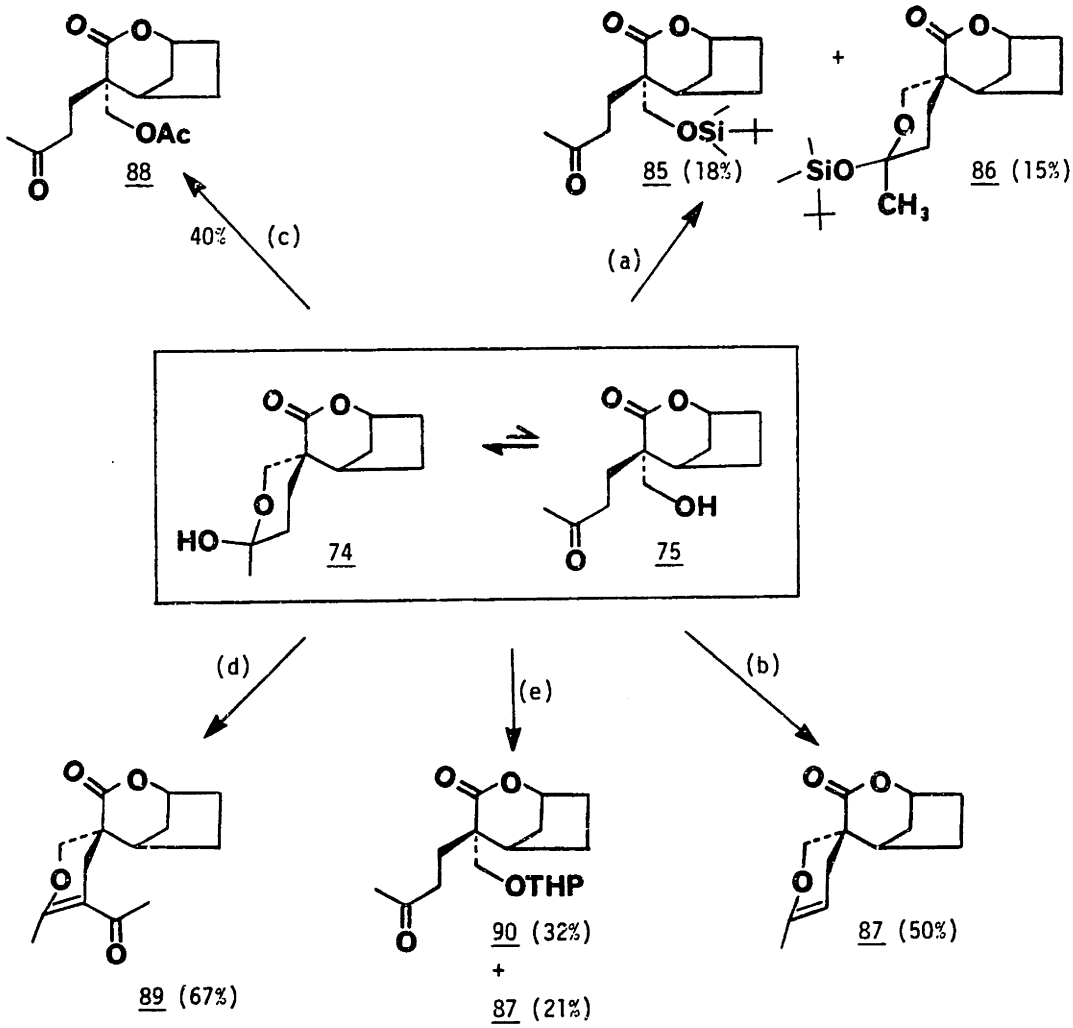
As expected, the differing degrees of reactivity of the lactone, ketone and aldehyde functionalities of 73 could be exploited to effect the transformation of 73 to bis-nor-trichothecene 70. Treatment of 73 with 0.25 equivalents of sodium borohydride (exactly one hydride equivalent)[46] at -10°C afforded 75 (96%), mp 133-134°C, which exists in solution largely as the hemiketal 74. Considerable difficulty was encountered,



however, differentiating the hydroxyl and ketone functionality of this intermediate. A few of our results are summarized in Scheme XII.

(46) (a) Sell, C.S. Aust. J. Chem. 1975, 28, 1383, and references therin.
(b) Gribble, G.W.; Ferguson, D.C. J. Chem. Soc., Chem. Commun. 1975, 535;

Scheme XII



(a) TBDMSCl, imidazole, DMF, RT, 19h;
(b) Triphenylmethyl chloride, C_5H_5N, 3h[47];
(c) Ac_2O, C_5H_5N, RT, 3.75h;
(d) Ac_2O, catalytic $ZnCl_2$, 45°C, 2.5h[48],[49];
(e) Dihydropyran, CH_2Cl_2, catalytic TsOH.

(47) Gardner, T.S.; Wenis, E.; Lee, J. J. Org. Chem. 1950, 15, 841.

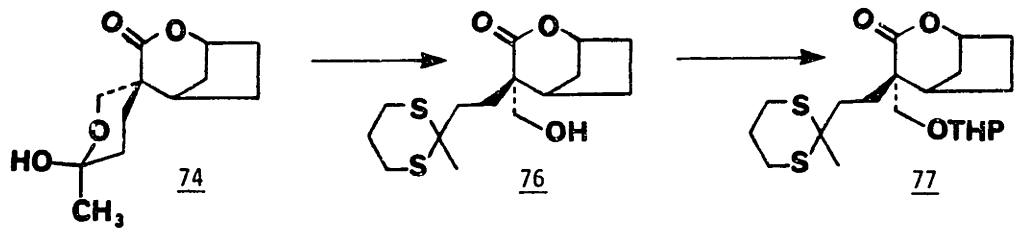
Each of the conversions illustrated in Scheme XII, together with several other attempts not listed[50] were directed towards the selective protection of the hydroxyl group of 75. Unfortunately the best yield of a protected derivative, 88, was only 40%. As evidenced by the results in Scheme XII, the high concentration of cyclic hemiketal 74, in equilibrium with 75, was apparently interfering with the desired hydroxyl protection. Notable products in Scheme XII include enol ether 87 (which arose through dehydration of 74) and vinylogous ester 89.[49] Presumably 89 results from Friedel-Crafts acylation of enol ether 87.

Alternatively, treatment of the equilibrating mixture of 74 and 75 with 1,3-propane-dithiol and BF_3-Et_2O afforded the crystalline alcohol 76 (96%, mp 120-124°C). Related procedures have been long used to unmask the carbonyl functionality of carbohydrates.[51] The free hydroxyl of 76 was then transformed by reaction with dihydropyran to give 77 in 95% yield.[52]

(48) Cramer, F.B.; Pacsu, E. J. Am. Chem. Soc. 1937, 59, 1467.

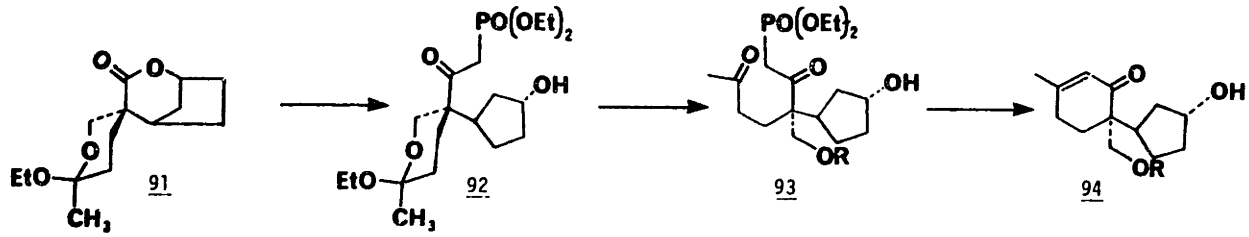
(49) Spectral data for 89: NMR (^1H, 60 MHz) δ 4.86 (br m, $W_{1/2}$ = 7.6 Hz, 1 H), 4.22 (dd, J = 2.2, 11.0 Hz, 1 H), 3.92 (d, J = 11.0 Hz, 1 H), 2.67 (br m, $W_{1/2}$ = 12 Hz, 2 H), 2.08 (S, 6H), 1.6-2.4 (complex multiplet, 7H); IR ($CHCl_3$) 1725, 1678; mass spectrum m/e 250 (parent), 235 (minus CH_3), 207 (minus CH_3CO). Visible to long wave uv light on TLC plates.

(50) Other experiments performed on the mixture 74, 75 ((a) methyl chloroformate, Et_3N, THF, 0°C, 1h; (b) KO-t-Bu (1.1 equiv.), THF, $C_6H_5CH_2Br$ (xs), 0°--->RT, 7h; (c) Ac_2O and either AcOH, $ZnCl_2$, $AlCl_3$ or C_5H_5N at a range of temperature (RT to 50°C)) afforded either complex mixtures or various amounts of 87, 88 and 89.



(51) (a) Fischer, E. Ber. 1894, 27, 673;
(b) Pappas, N.; Nace, H.R. J. Am. Chem. Soc. 1959, 81, 4556.

(52) Before settling on this dithiane/tetrahydropyran protecting-group solution, we examined an approach to transform 91 (available from 74, 75 upon acidic workup of the aforementioned $NaBH_4$ reduction) to 94 utilizing phosphonate ester 92. Although 92 was obtained in high yield (92%) upon the treatment of 91 with $(EtO)_2OPCH_2Li$ (THF, -78°--->$23^{\circ}C$, 2.5h),(53) numerous attempts to transform 92 to 94 were unsuccessful.

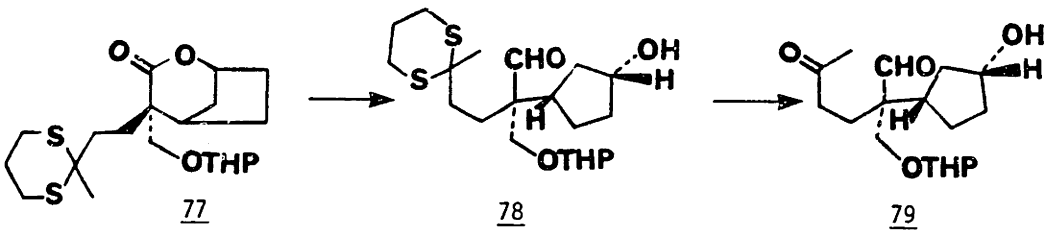


(53) (a) Ford-Moore, A.H.; Williams, J.H. J. Chem. Soc. 1947, 1465;

(b) Corey, E.J.; Kwiatkowski, G.T. J. Am. Chem. Soc. 1966, 88, 5654;

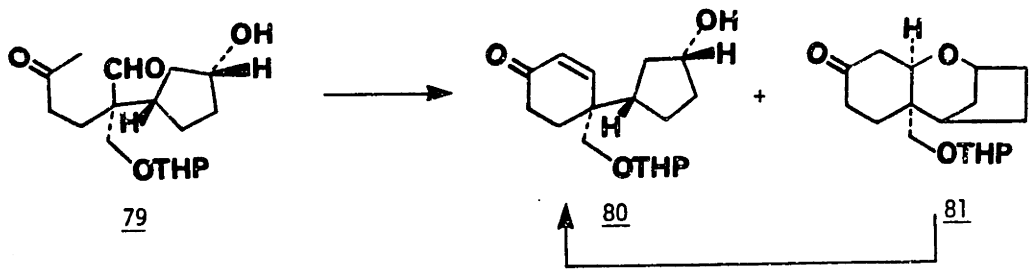
(c) Dauben, W.G.; Beasley, G.H.; Broadhurst, M.D.; Muller, B.; Peppard, D.J.; Pesnelle, P.; Suter, C. J. Am. Chem. Soc. 1975, 97, 4973.

Reduction of 77 with DIBAL (1.2 equiv., toluene, -78°C, 3h, 80-85%) afforded hydroxy aldehyde 78, the dithiane group of which was removed using NBS in aqueous CH_3CN (buffered with collidine)[54] to give keto-aldehyde 79 (74%).



77 78 79

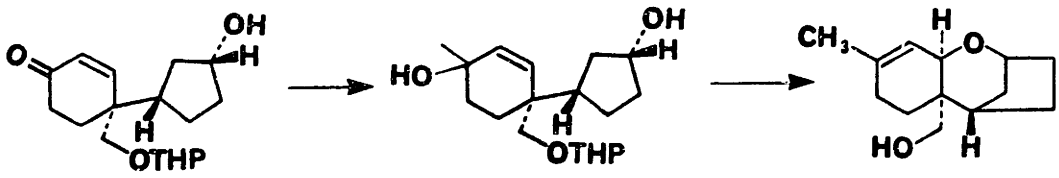
Intramolecular aldol condensation of 79 (KOH, H_2O, CH_3OH) then afforded enone 80 (80%) together with a small amount of Michael adduct 81 (10%). Control experiments established that this mixture is probably the equilibrium mixture; subjection of recovered Michael adduct 81 to the above described conditions effected its conversion to 80 in 73% yield.



79 80 81

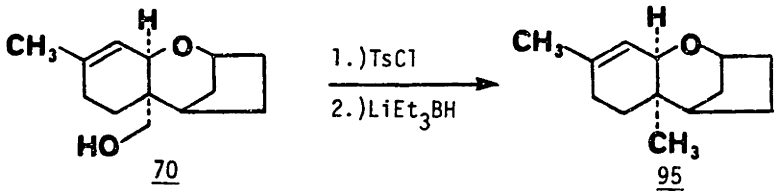
(54) Corey, E.J.; Erickson, B.W. J. Org. Chem. 1971, 36, 3553.

The stage was now set for ring closure of 80 to 70. This was accomplished by treating a THF solution of 80 with excess CH_3Li (at -78°C) followed by addition of 1N aqueous HCl. The resulting two-phase suspension was vigorously stirred at ambient temperature for 6-18 h to afford 70 directly in 65-75% yield. A detailed examination of this cyclization sequence revealed that two isomeric alcohols 82 (3:1 ratio, HPLC analysis) were produced upon CH_3Li treatment of 80. These isomers could be isolated and separated if the reaction was worked up under non acidic conditions. Each cyclized to 70 when treated with 1N aqueous HCl as previously described, supporting our hypothesis that an allylic carbonium ion is an intermediate in the cyclization of 82 to 70 (and perhaps also an intermediate in a similar cyclization in the biosynthesis of the trichothecenes; page 18). Since both isomers cyclized, the mixture of 82 was not separated on a routine basis.



80 82 70

It is noteworthy that 70 was the first trichothecene derivative possessing a C.15 hydroxymethyl group to be synthesized. Alternatively, tosylation of 70 (p-TsCl, C_5H_5N) followed by reduction with lithium triethylborohydride[55] produced the volatile C.15-deoxy derivative 95 (41% yield).



70 95

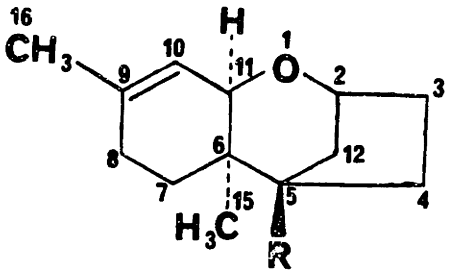
The spectroscopic properties of 70 and 95 are fully consistent with the assigned structures and compare favorably with those of known trichothecene derivatives.[56] For example, it is clear from ^1H NMR data that the A-B ring fusion is cis (70, $J_{10,11}$ = 4.9 Hz; 95, $J_{10,11}$ = 4.8 Hz). If the ring fusion were trans, then the C.9-C.10 dihedral angle would be approximately 90° and $J_{10,11}$ would be approximately 0 Hz. Also, pertinent ^1H NMR data of 95 and synthetic trichothecene 96[29] are similar (Table II).[57]

(55) (a) Krishnamurthy, S.; Schubert, R.M.; Brown, H.C. J. Am. Chem. Soc. 1973, 95, 8486;
(b) Krishnamurthy, S. J. Organomet. Chem. 1978, 156, 171.

(56) For a compendium of physical data and leading references to various trichothecenes see: Cole, R.J.; Cox, R.H. "Handbook of Toxic Fungal Metabolites", Academic Press, New York, 1981, Chapter 5.

(57) We are grateful to Professor Kamikawa for sending us a ^1H NMR spectrum of 96.

Table II



	250 MHz 95 (R=H) δ (ppm)	100 MHz 96 (R=CH_3) δ (ppm)
H_{10}	5.33 (d m, J = 4.8 Hz)	5.19 (d m, J = 5.1 Hz)
H_2	4.27 (br m, $W_{1/2}$ = 9.3 Hz)	4.10 (br m, $W_{1/2}$ = 6.1 Hz)
H_{11}	3.51 (d, J = 4.8 Hz)	3.35 (d, J = 5.1 Hz)
C_{16}	1.67 (s, 3H)	1.66 (s, 3H)
C_{15}	0.74 (s, 3H)	0.72 (s, 3H)

Finally, the relevant ^{13}C NMR data for 70 and 95 correlate well with the published ^{13}C NMR spectra(58) of trichodermin (5), trichodermol (4), verrucarol (1), diacetyl verrucarol (10) and calonectrin (12) (Table III).

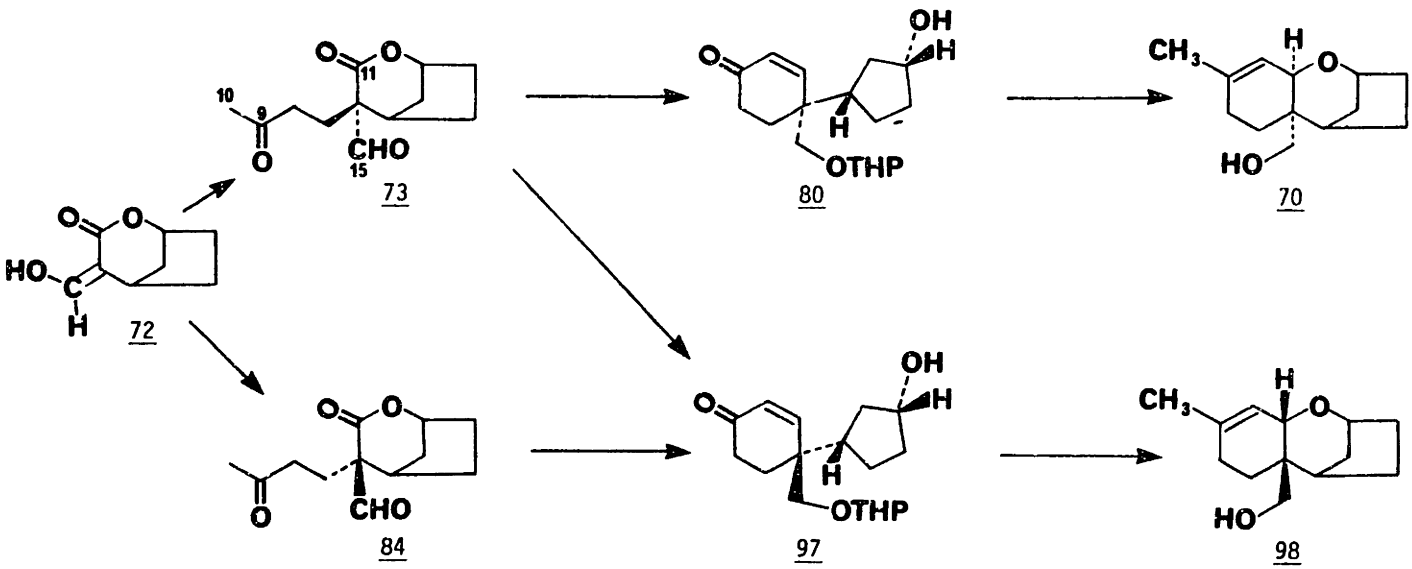
(58) (a) Wehrli, F.W.; Nishida, T. Prog. Chem. Org. Prod. 1979, 36, 37;
(b) Riisom, T.; Jakobsen, H.J.; Rastrup-Anderson, N.; Lorck, H. Acta Chem. Scand. Ser. B 1978, 32, 499;
(c) Breitenstein, W.; Tamm, Ch. Helv. Chim. Acta 1975, 58, 1172;
(d) Hanson, J.R.; Marten, T.; Siverns, M. J. Chem. Soc., Perkin Trans. 1 1974, 1033.

Table III

(ppm)	(5) (57b)	(4) (57b)	(1) (57c)	(10) (57c)	(4) (57d)	(12) (57d)	(70)	(95)
C.2	79.2	78.8	78.5	78.4	70.8	68.2	76.0	76.1
C.9	140.1	140.1	140.4	139.6	140.5	140.3	139.9	139.3
C.10	118.8	118.8	118.7	118.2	119.4	119.0	120.2	120.1
C.11	70.6	70.4	66.4	66.2	79.3	78.1	66.6	70.3
C.15	16.0	15.8	62.1	63.0	16.0	63.7	62.0	—

In spite of these similarities, we could envision a second, AB-cis-fused compound 98 which might possess the spectroscopic

Scheme XIII

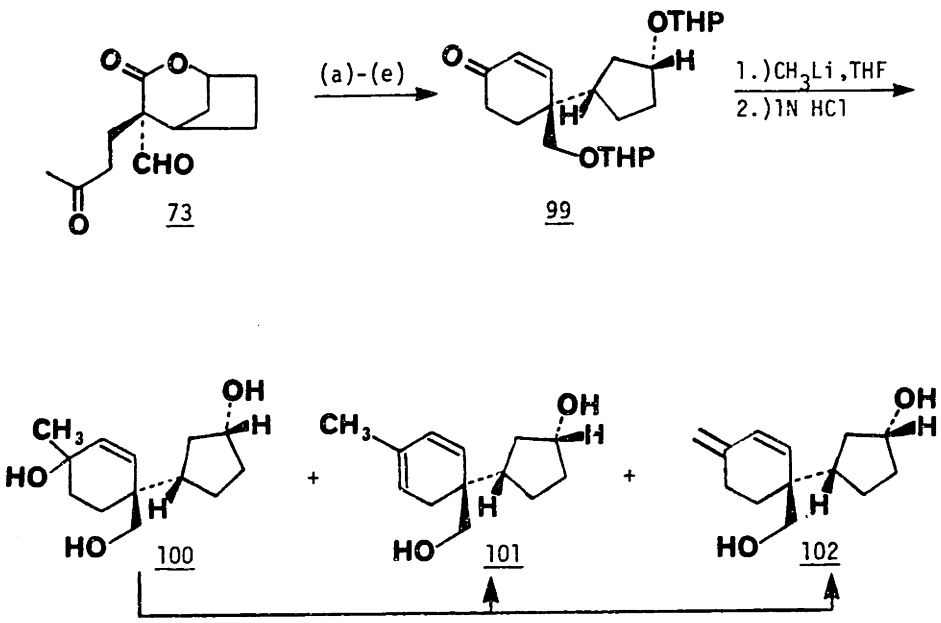


properties which we assigned to 70. The stereochemical assignments for 70 and 95 rest ultimately on the assumed stereochemistry of the Michael addition reaction 72--->73. If this Michael adduct was actually 84, rather than 73, then the annelation sequence previously described would have afforded 98 rather than 70. We could not assume, a priori, that structure 98 was inconsistent with the data presented for 70. We decided, therefore, to attempt to synthesize 98 from 73 in order to make spectroscopic comparison. We recognized that an enone with the relative stereochemistry present in 97 could be obtained from 73 by effecting an intramolecular aldol reaction between C.10 and the C.15 aldehyde (rather than the C.10 - C.11 connection used in our synthesis of 70). The actual sequence, in practice, proceeded as outlined in Scheme XIV.

Cyclohexenone 99, a protected version of 97, was synthesized in 50% overall yield from 73 by (1) protection of the ketone and the aldehyde as dithianes, (2) reduction of the lactone to the corresponding diol, (3) protection of both hydroxyl groups as THP ethers, (4) deprotection of the aldehyde and ketone carbonyl groups, and (5) aldol closure[59]. Attemps to effect closure of 99 to a polycyclic ether by treatment with CH_3Li and then 1N aqueous HCl under the conditions used for the transformation

(59) For an alternative way to effect this transformation see reference 42.

Scheme XIV



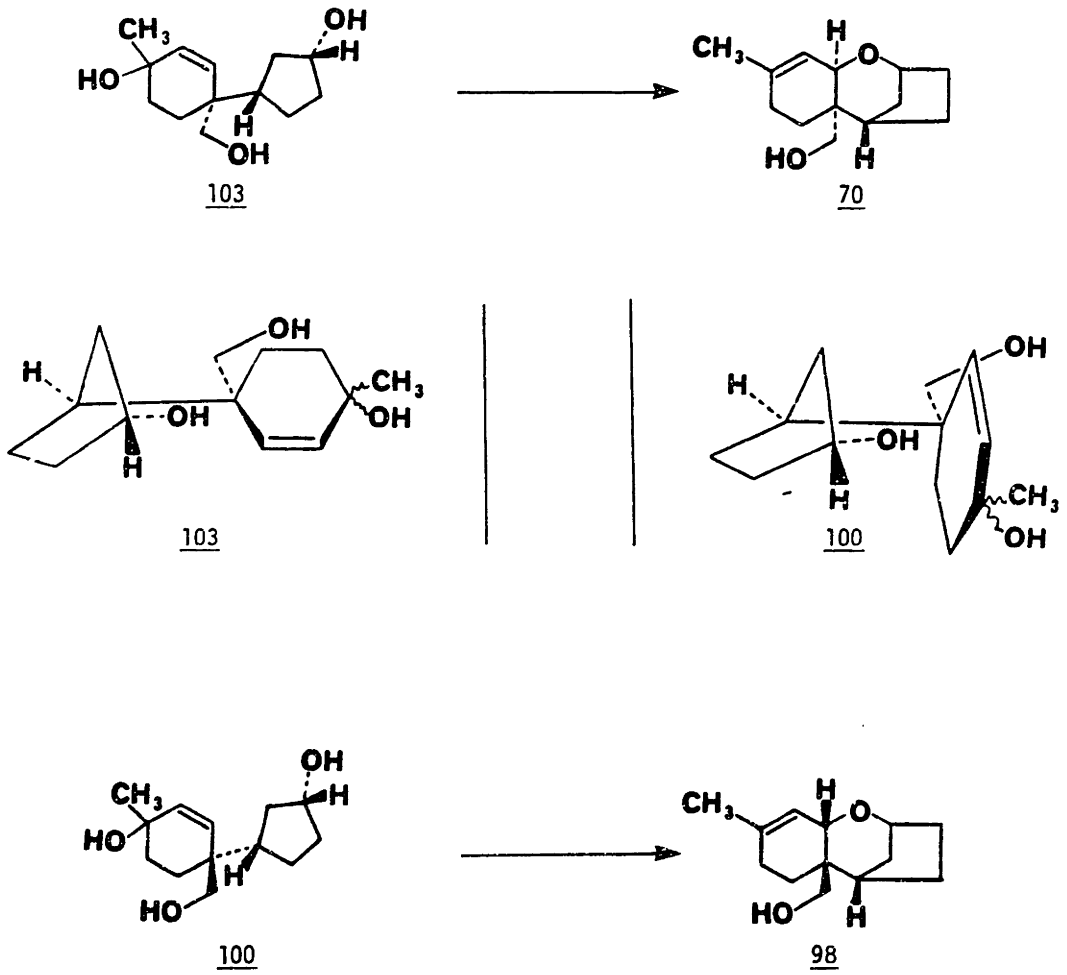
(a) $HS(CH_2)_3SH$, BF_3-Et_2O;
(b) DIBAL (xs), THF;
(c) Dihydropyran, CH_2Cl_2, p-TsOH (catalytic);
(d) NBS, collidine, H_2O-CH_3CN (1:4);
(e) KOH, H_2O, CH_3OH.

80--->70 afforded, however, none of 98. Rather mixtures of 100, 101 and 102 (57% yield of 101 and 102, an inseparable 2:1 mixture, respectively) as well as small amounts of the corresponding mono THP ethers were obtained. Prolonged acid treatment of 100 afforded only 101 and 102 (68%; 2:1 mixture).

Molecular model analysis (Scheme XV) reveals that if the attempted cyclization 100--->98 were to occur, the developing tetrahydropyranyl B ring would be forced to adopt a boat-like

conformation in the transition state. This conformation contains a flagpole interaction between C.11-H and C.12-H and eclipsing interactions between C.4 and C.7.[60] These interactions, which are absent in the cyclization of 103 to 70, (in this case the developing tetrahydropyranyl B ring can adopt a chair-like orientation in the transition state,) are presumably responsible for the failure of the cyclization 100---->98.

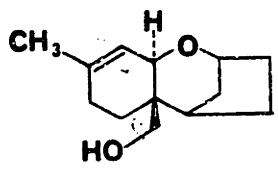
Scheme XV



Since Masuoka and Kamikawa have previously employed a biomimetic cyclization analogous to 103--->70[29], our stereochemical assignment for 70 (in light of the failed cyclization 100--->98) appears well-founded.

This study demonstrated that the trichothecene ring system can be prepared with exceptional stereochemical control by an efficient route involving annelation of the A ring onto a bicyclic precursor (10 steps; 19-25% overall yield). Our adaptation of this strategy to the total synthesis of verrucarol is the subject of the following chapter.

(60) The cyclization of 100 to the trans-fused isomer 104 is precluded on steric grounds, since the C.2 hydroxyl group of 104 cannot easily interact with the C.11 p lobe cis to the adjacent C.15 hydroxymethyl group.



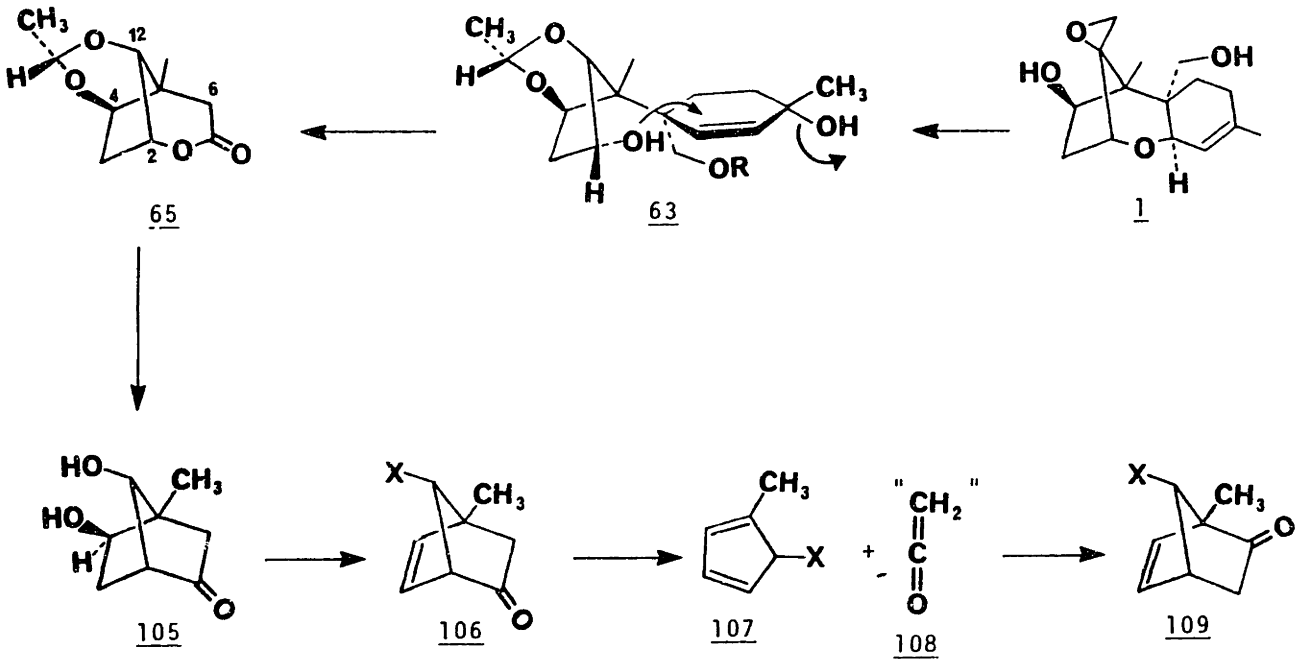
104

CHAPTER THREE

The Total Synthesis of Verrucarol

The preliminary studies outlined in Chapter Two demonstrated that a feasible strategy for the synthesis of verrucarol 1 would involve a stereoselective annelation of the A ring onto bicyclic precursor 65. Our attention now focused on the synthesis of this substrate and its elaboration to verrucarol. Our solution to the synthetic problem posed by 65 was envisaged as in Scheme XVI.

Scheme XVI



Certain structural features of 65, i.e., the lactone and the C.4 and C.12 alkoxyl groups, suggested that bicycloheptenone 106, or a suitable synthetic equivalent, might be an appropriate

precursor. This, in turn, suggested a Diels-Alder construction involving a ketene equivalent 108 and a disubstituted cyclopentadiene 107. We, of course, were aware of a number of obvious pitfalls to this strategy. For instance, disubstituted cyclopentadienes such as 107 are not, in general, readily available. More important, the thermal stability of 107 (e.g., X = OR) relative to other tautomers would be a problem ([1,5] hydrogen shifts), except in cases where 107 could be synthesized and worked with at low temperature.(61) Finally, all known ketene equivalents(62) would be expected to add to 107, preferentially, in the undesired regiochemical sense, leading to the carbonyl-transposed isomer 109. On the assumption that the first two problems could be solved, some means of inverting the orientational preference of 108 with an appropriate cyclopentadiene would be required, or, alternatively, a method for reorganizing the functional group relationships in the Diels-Alder adduct 109 (to 106), would need to be employed. Our synthesis of 65(63) utilizes the latter logic and involves use of

(61) Such is the case with 5-alkylcyclopentadienes. See, for example:
(a) Corey, E.J.; Ravindranathan, T.; Terashima, S. J. Am. Chem. Soc. 1971, 93, 4326;
(b) Heck, J.V. Ph.D. Thesis, Harvard University, Cambridge, Massachusetts, 1976.

(62) Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K. J. Am. Chem. Soc. 1974, 96, 5261. See also reference 61a,b.

(63) A preliminary account of the synthesis of 105 has been published: reference 42b.

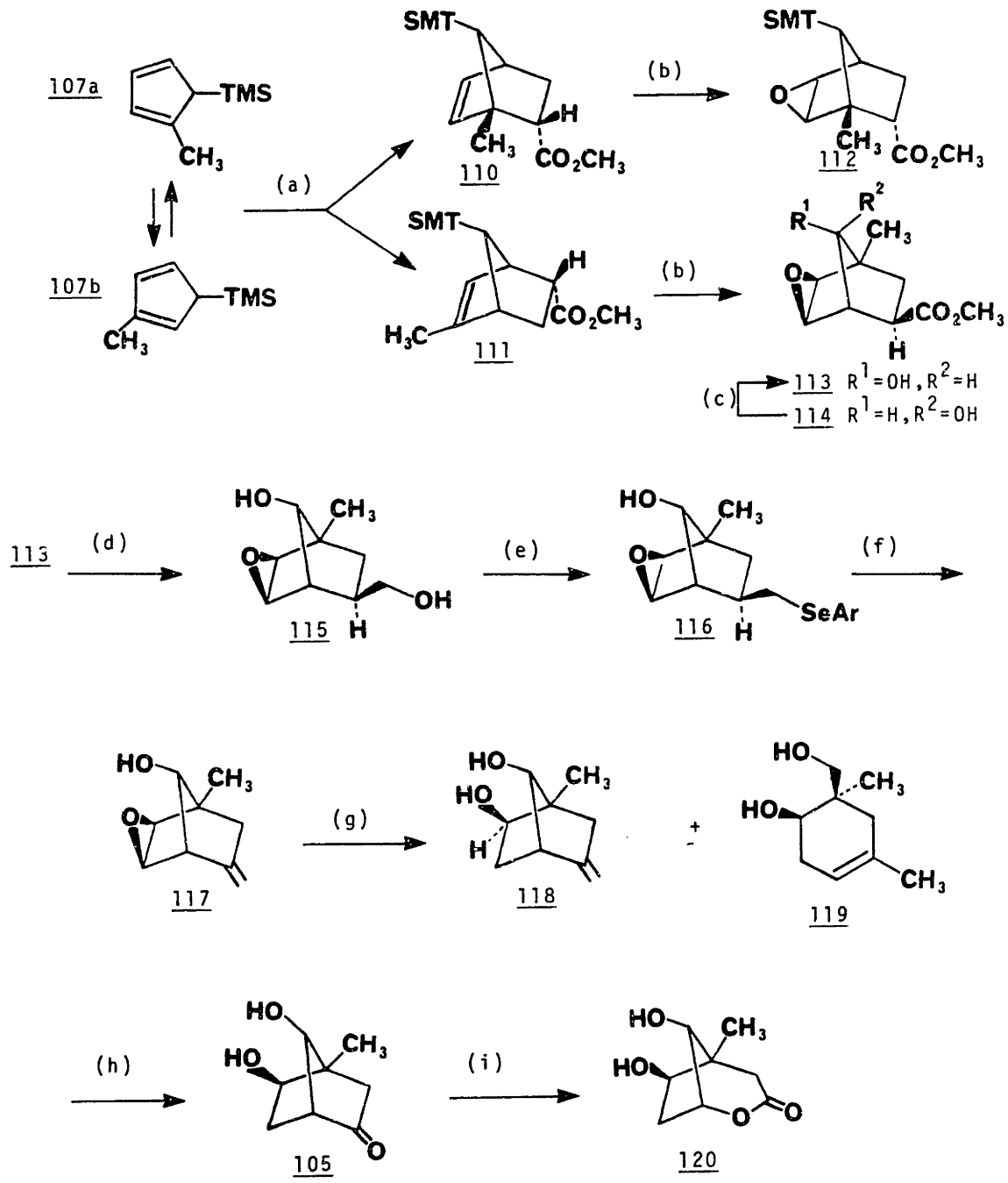
107 (X = $SiMe_3$; Scheme XVII). The choice of a trimethylsilyl group not only simplified the synthesis of 107[64] but also ensured a sufficient steady-state concentration of 107b,[65] the desired regioisomer for use in this synthesis, and ultimately controlled the crucial Wagner-Meerwein rearrangement (123---> 124)[66] which served to reorganize the initial bicycloheptene Diels-Alder adduct.

(64) (a) Davison, A.; Rakita, P.E. Inorg. Chem. 1970, 9, 289;
(b) J. Am. Chem. Soc. 1968, 90, 4479.

(65) The rate of trimethylsilyl [1,5] migrations is 10^6 that of the rate of [1,5] hydrogen migrations in trimethylsilyl cyclopentadiene: Ashe, A.J. J. Am. Chem. Soc. 1970, 92, 1233.

(66) (a) Fleming, I; Michael, J.P. J. Chem. Soc., Perkin I 1981, 1549;
(b) J. Chem. Soc., Chem. Commun. 1978, 245.

Scheme XVII[a]



[a] (a) methyl acrylate (1.1 equiv.), BF_3-OEt_2 (1.2 equiv.), CH_2Cl_2, -78°C, 2h (89%; ratio of 111 : 110 = 82:18); (b) Method A: (1) DNPBA (1.4 equiv.), $NaHCO_3$, CH_2Cl_2, 4d; (2) CH_3OH-1N aqueous HCl (10:1), 40 min; (3) DNPBA (excess), $NaHCO_3$, CH_2Cl_2, 24h (113, 42-52%; 114, 10-14%; 112, 15%); Method B: (1) MCPBA (excess), $NaHCO_3$, CH_2Cl_2, RT, 48h; (2) 1N aqueous HCl-CH_3OH (1:10), RT, 40 min; (3) MCPBA (excess), $NaHCO_3$, CH_2Cl_2, RT, 15h; (113, 59% (from 107); 114, 5-6%); (c) (1) TFAA, DMSO, -60°C, and then Et_3N (90%); (2) $NaBH_4$, EtOH (70%); (d) $LiAlH(OCH_3)_3$ (excess), THF, RT, 1h (93-98%); (e) o-nitrophenyl selenocyanate (1.1 equiv.), n-Bu_3P, THF, RT, 30 min (71-84%); (f) MCPBA (1.1 equiv.), CH_2Cl_2, -10°C, 15 min, and then i-Pr_2NH (2 equiv.), RT, 5-7h (95%); (g) Li (excess), ethylenediamine, THF, RT, 0.5-1h (50-66% of 118); (h) O_3, CH_2Cl_2, -78°C, 1h, and then CH_3SCH_3, RT, 4d (84%); (i) MCPBA, $NaHCO_3$, CH_2Cl_2, RT, 4h (84-93%).

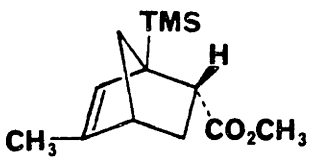
Treatment of readily available (methylcyclopentadienyl) trimethylsilane, a rapidly equilibrating mixture of isomers consisting largely of tautomers 107a and 107b[64] with the BF_3-OEt_2 complex of methyl acrylate in CH_2Cl_2 at -78°C produced an 82:18 mixture (average value of numerous runs varying between 80:20 and 85:15), respectively, of 111 (deriving from 107b) and

110 (from 107a) in 89% combined yield.[67] Pure samples of each isomer (milligram amounts) were obtained by semi-preparative reverse phase HPLC.[68],[69],[70]

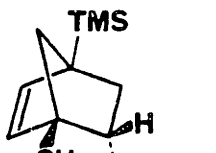
(67) These ratios were determined by integration of the 250 or 270 MHz ^1H NMR spectrum of the crude reaction product. This yield and product ratio were reproducibly obtained on 30 g scale reactions. The ratio was not affected by conducting the reaction at lower temperature (-95°C).

(68) Waters μ-Bondapak C_{18} column (10 μm particle size, 7.8 x 30 cm), 1:1 CH_3CN-H_2O.

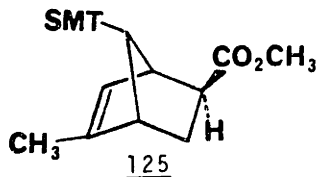
(69) Minor amounts (less than 5% of the total product mixture) of two other Diels-Alder adducts were obtained by this separation. They have tentatively been assigned the stuctures 121 and 122.



121



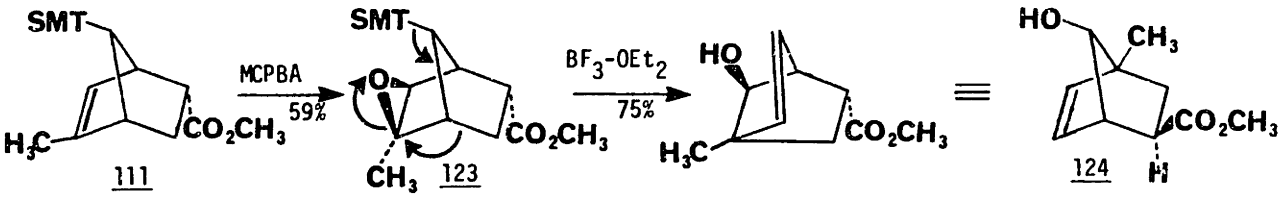
122



125

(70) A more detailed study of this Diels-Alder reaction has recently been performed by John K. Rogowski. Optimum conditions (methyl acrylate, Et_2AlCl, CH_2Cl_2, -78°C, 2h) afforded a 98% yield of a 72:12:11:5 mixture respectively of 111, 122, 125 and an as yet unidentified adduct. We are grateful to Mr. Rogowski for performing these experiments.

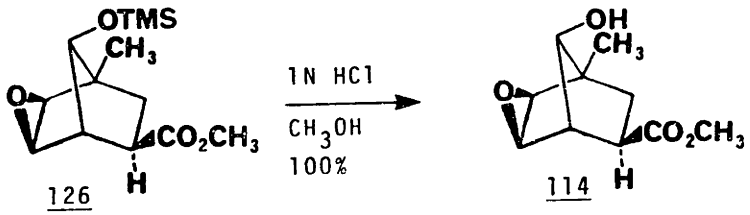
We expected from the outset that epoxidation of 111 would afford 123 which, in turn, would undergo a trimethylsilyl-controlled Wagner-Meerwein rearrangement to 124 on exposure to a Lewis acid.(66) This indeed proved to be the case.



However, oxidation of 111 with $NaHCO_3$-buffered MCPBA proved to be quite sluggish; in one instance, 59% of 123, 19% of 111, and even 15% of 113 were obtained from a two day reaction. Peroxidation of 111 with an excess of the more reactive 3,5-Dinitroperoxybenzoic acid, DNPBA(71) (CH_2Cl_2, buffered with suspended $NaHCO_3$) was comparably slow. In this case, however, a mixture of the highly

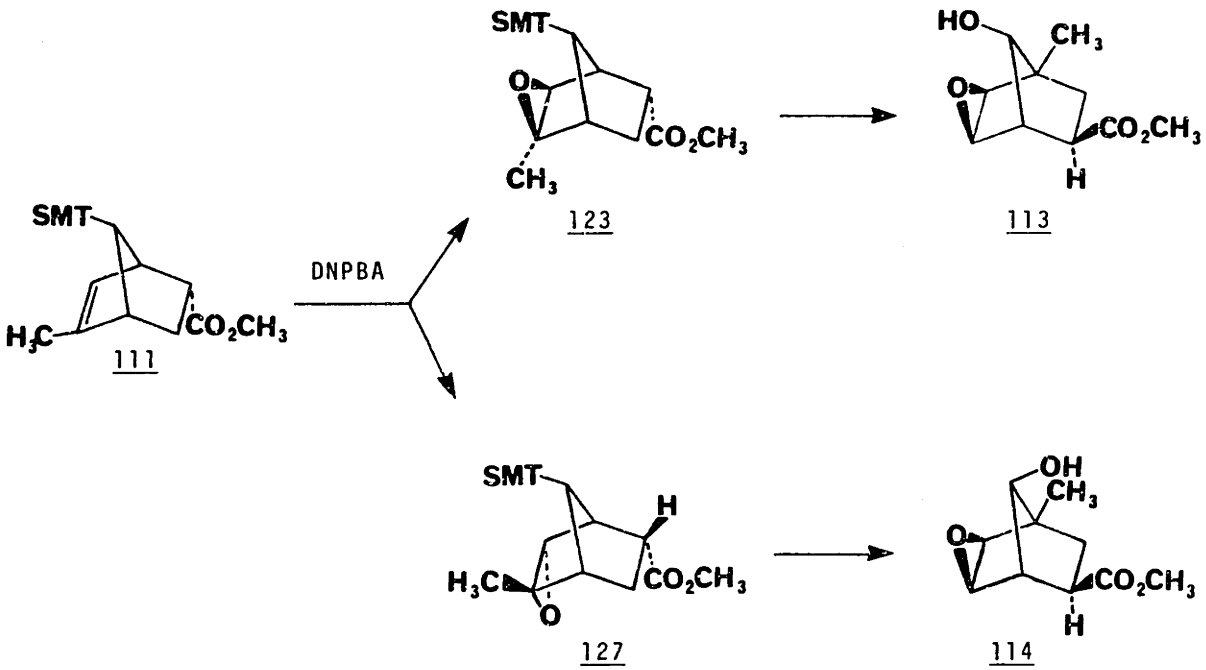
(71) Rastetter, W.H.; Richard, T.J.; Lewis, M.D. J. Org. Chem. 1978, 43, 3163.

oxidized, rearranged, epoxy alcohol 113 (68%), its C.12 hydroxy epimer 114 (mp 93-94°C, 19%) and a small amount of 126 (6%) were obtained. Mild aqueous hydrolysis effected conversion of 126 to 114.



126 114

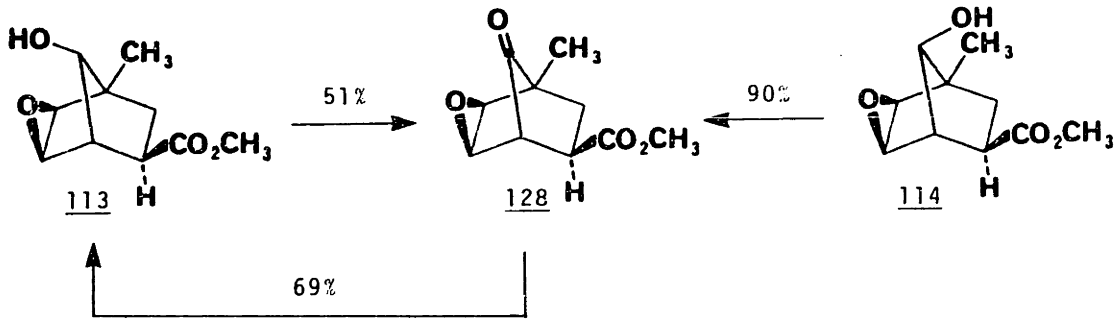
The rearrangement of 123 to 124 and the epoxidation of 124 to 113 thus occur under these reaction conditions. The presence of 114 presumably reflects a low degree of stereoselectivity in the DNPBA oxidation of 111, since subjection of 123 to the aforementioned reaction conditions afforded 113 as the sole epoxy alcohol product.



In no case, however, was any material corresponding to the endo epoxide 127 ever isolated from a DNPBA oxidaton of 111.

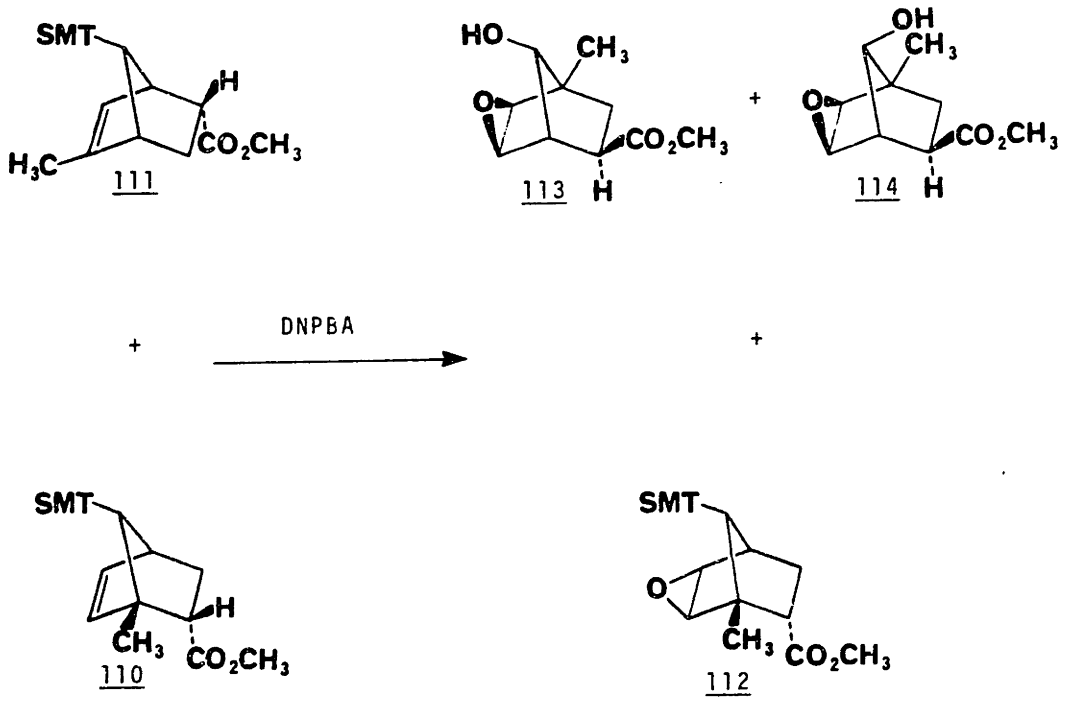
The epimeric relationship of 113 and 114 was by no means clear from spectroscopic data alone. However, oxidation of each under conditions described by Swern[72] [(1) TFAA, DMSO, -60°C; (2) Et_3N] afforded ketone 128, $NaBH_4$ reduction of which

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

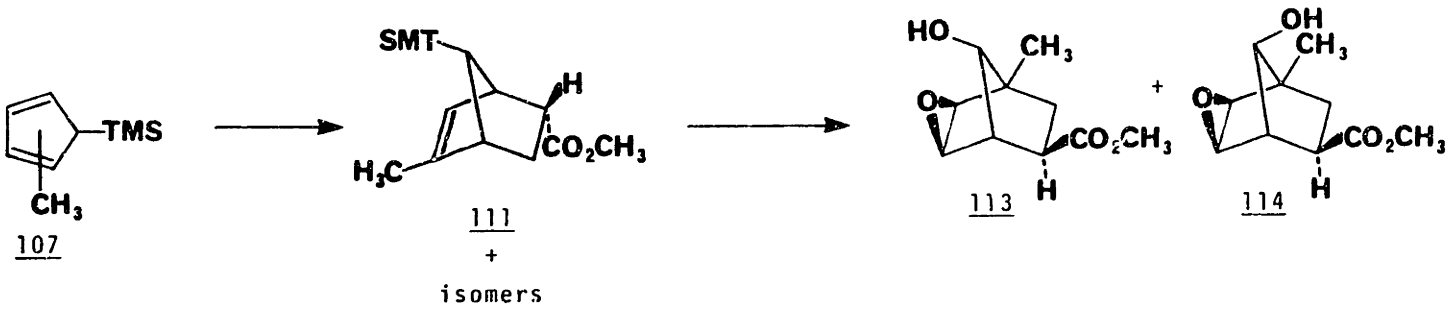


(EtOH, 0°C, 35 min) furnished 113, uncontaminated with 114. In this manner 114 was routinely recycled to 113.

For large-scale work, it proved unnecessary to separate the mixture of Diels-Alder adducts 110 and 111. In initial



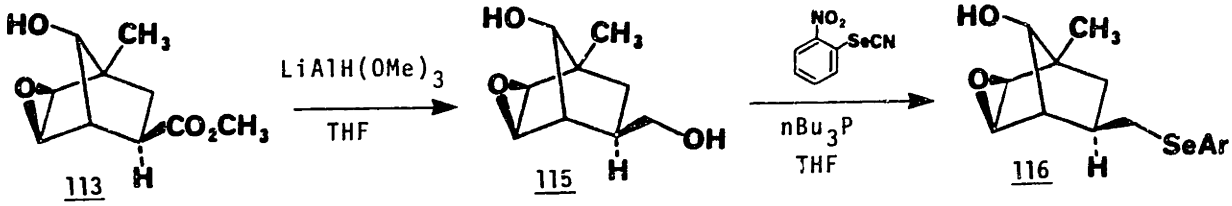
experiments we treated this mixture with DNPBA, as described above, to afford easily separable mixtures of 113, 114 and epoxysilane 112 (which derives from 110 but does not rearrange under these reaction conditions). In some runs, however, we found that significant quantities of 123 remained from incomplete Wagner-Meerwein rearrangement, often regardless of how many days the reaction mixture was stirred with excess DNPBA.(73) In addition to the problem of incomplete reaction, a facile means to transform the small quantities of silyl ether 126, present in the crude reaction product mixtures, directly to 114 was desired. We thus found it more convenient to employ a three-step sequence for the conversion of 110 and 111 to the mixture of 112, 113 and 114: (i) DNPBA (1.4 equiv.), $NaHCO_3$, CH_2Cl_2, 4 days; (ii) CH_3OH, 1N aqueous HCl (10:1), 40 min. (which promoted the rearrangement of 123 to 124 and hydrolyzed any silyl ethers (eg. 126) which might be present); and, (iii) DNPBA (excess), $NaHCO_3$, CH_2Cl_2, 24h). In this manner we routinely obtained 113 in 42-52% yields, 114 in 10-14% yields and epoxysilane 112 in 15-16% yields. Conducting



(73) In retrospect it appears that the variable amounts of rearrangement of 123 might be due to the presence or absence of acidic impurities in the reagent peracid. DNPBA was prepared by the method of Rastetter; Reference 71.

the above three step sequence by substituting the less reactive, and consequently more selective MCPBA in place of DNPBA, we obtained 113 in 59% overall yield from 107 and only 5-6% of its C.12 epimer 114.(70)

The next transformation of our synthesis involved oxidative degradation of the carbomethoxyl group of 113 to a ketone. Reduction of 113 to the crystalline alcohol 115, mp 79-81°C, was accomplished by using $LiAlH(OCH_3)_3$ (93-98% yield).(74)



Treatment of 115 with o-nitrophenyl selenocyanate(75) and $n\text{-}Bu_3P$ in THF(76) afforded the selenide 116, mp 109.5-110.5°C, in 78% from 113. Oxidation of 116 with MCPBA (CH_2Cl_2, -10°C) followed by selenoxide elimination in the presence of diisopropylamine(77)

(74) Brown, H.C.; Weissman, P.M. J. Am. Chem. Soc. 1965, 87, 5614.

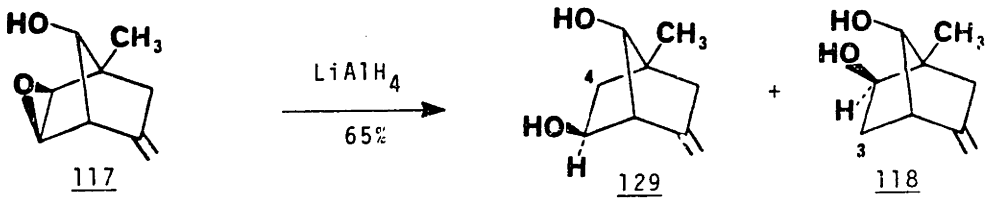
(75) Sharpless, K.B.; Young, M.W. J. Org. Chem. 1975, 40, 947. The reagent was prepared by the method detailed in this paper but with modification as described on page 163.

(76) Grieco, P.A. Gilman, S.; Nishizawa, M. J. Org. Chem. 1976, 41, 1485.

(77) Reich, H.J.; Wollowitz, S.; Trend, J.E.; Chow, F.; Wendelborn, D.F. J. Org. Chem. 1978, 43, 1697.

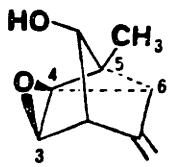
afforded the extremely volatile olefin 117 in up to 95% yield after chromatography.(78)

We anticipated on the basis of steric considerations that reduction of 117 with a hydride reducing reagent would afford alcohol 118. Much to our surprise, however, reduction of the epoxide functionality of 117 with $LiAlH_4$ produced a 63:37



117 129 118

63:37



117

(78) (a) The usual two step (one pot) sequence for conversion of an alcohol 115 to the olefin 117 [(1) o-nitrophenyl selenocyanate, n-Bu_3P, THF; (2) H_2O_2] resulted in diminished yields (33%) of 117. In addition, treatment of purified selenide 116 with H_2O_2 also afforded a poor yield (15%) of 117.

(b) An alternative sequence (p-TsCl, C_5H_5N, reflux) for the transformation 115 ---> 117 was unsuccessful.

mixture, respectively, of 129 and 118 in 65% combined yield. These isomeric diols were separable by careful chromatography. Assignment of structure followed from examination of the 250 MHz ^1H NMR spectrum of each:

(a) The chemical shifts of the olefinic protons in 129 (δ 4.95 and δ 4.70) are deshielded relative to 118 (δ 4.80 and δ 4.56);

(b) The chemical shift of C.4-H in 118 (δ 3.62) is shielded by the methyl group relative to C.3-H in 129 (δ 3.93);[79]

(c) The chemical shift of the C.14 methyl group of 118 (δ 1.20) is deshielded relative to the corresponding C.14 resonance of 129 (δ 1.15).

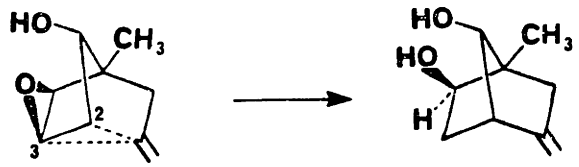
Our subsequent synthesis of verrucarol from 118 supports these assignments. The major product of this reaction, 129, thus resulted from hydride attack at C.4 of 117, which we had perceived to be the more hindered site. Presumably the methyl group at C.5 of 117 must facilitate the neighboring group participation of the C.5 - C.6 bond in weakening the C.4 to oxygen bond (relative to the C.3 to oxygen bond). The steric

(79) Such shielding is well known. For references see Jackman, L.M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, 1975.

hindrance of hydride delivery to C.4 of 117 is thus offset by the anchimeric assistance available to this site(80). Related Wagner-Meerwein rearrangements in the $LiAlH_4$ reduction of norbornyl epoxides are well known.(81)

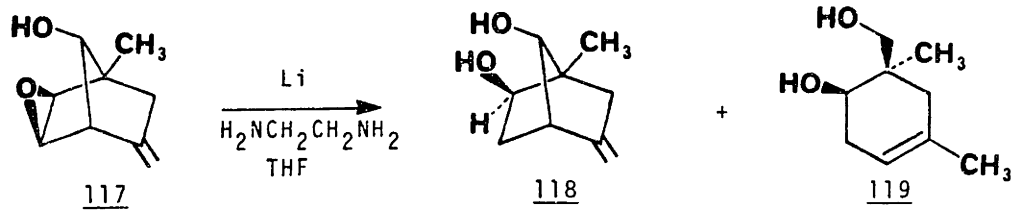
The above problem of regioselectivity was surmounted by treatment of 117 using a modification of Brown's procedure(81) (Li, ethylenediamine-THF(2:1), room temperature). In this manner, we obtained crystalline 118, mp 97-98°C, uncontaminated with its regioisomer 129 in 50-66% yield. Under these conditions, however, 118 was also converted to 119,

(80) This type of bond participation might also occur in the reduction of 117 to 118. In this case hydride attack at either C.2 or C.3 of 117 would still afford 118. It would be interesting to conduct this reduction on optically pure 117 to see whether racemic or partially racemized 118 is obtained.



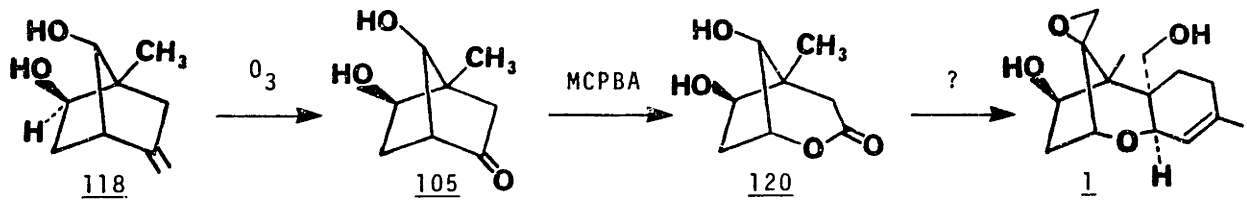
117 118

(81) Brown, H.C.; Ikegami, S.; Kawakami, J.H. J. Org. Chem. 1970, 35, 3243. These conditions were developed specifically to minimize rearrangements or eliminations in the reduction of norbornyl epoxides. The regioselectivity we observed for the reduction of 117 to 118 using these conditions was far better than we would have expected on the basis of some of the examples reported in this paper.

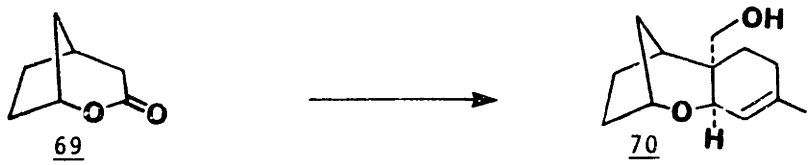


117 118 119

mp 76°C; in 5-8% yield. Ozonolysis of 118 produced ketone 105 (84% yield; mp 100-101°C), which was then oxidized (MCPBA, $NaHCO_3$, 84-93% yield) to lactone 120, mp 180-184°C.



118 105 120 1

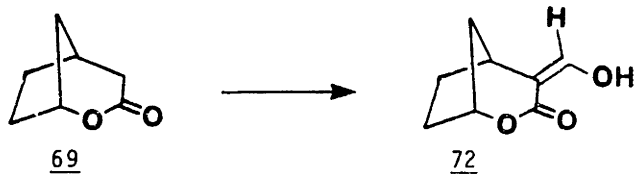


69 70

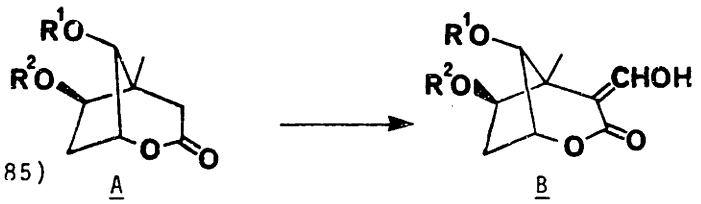
The stage was now set for the transformation of 120 to verrucarol 1 using an annelation sequence analogous to our model study (69--->70, see Chapter Two).[42a] We were aware that model lactone 69 lacked certain key structural features of 120, particularly the methyl group at C.5, and as a consequence we suspected that functionalization of C.6 of 120 might be more difficult than the first steps in our synthesis of 70. The formation of carbon-carbon bonds at a neopentyl center (cf, C.6 of 120), however, has been successfully addressed in a number of similarly hindered substrates.[82] In practice, the functionalization of C.6 of a protected derivative of 120 (i.e., 65, Scheme XVIII) was accomplished, but only with considerable difficulty as subsequently described.

(82) (a) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. J. Am. Chem. Soc. 1978, 100, 6536;
(b) Paquette, L.A.; Schostarez, H.; Annis, G.D. J. Am. Chem. Soc. 1981, 103, 6526;
(c) Smith, A.B.; Wexler, B.A.; Slade, J. Tetrahedron Lett. 1982, 23, 1631;
(d) Reference 38f;
(e) Reference 38g;
(f) Corey, E.J.; Smith, J.G. J. Am. Chem. Soc. 1979, 101, 1038;
(g) Smith, J.G. Ph.D. Thesis, Harvard University, 1979;
(h) Reference 23c;
(i) Reference 41;
(j) Tius, M.A. Ph.D. Thesis, Harvard University, 1980.

Scheme XVIII



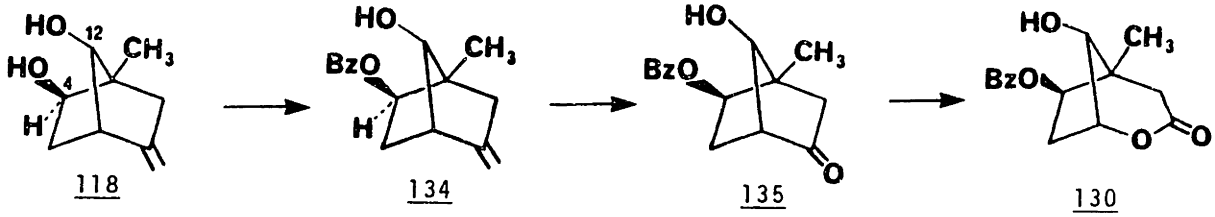
69 72



120 $R^1=R^2=H$
130 $R^1=H, R^2=Bz$ (83)
131 $R^1=R^2=Bz$ (COC_6H_5) (85)
132 $R^1=R^2=CH_3$ (86)
133 $R^1=R^2=TBDMS$ (88)
65 $R^1=R^2=CHCH_3$ (acetal) (89)

A B

(83) Prepared from 118 by (1) C_6H_5COCl (0.9 equiv.), C_5H_5N, 0^oC (87% yield of a 3.6:1 mixture of 134 and its C.12 monobenzoate isomer; see Chapter Four and also reference 30); (2) O_3, CH_2Cl_2, -78^oC and then CH_3SCH_3 (76%); (3) MCPBA



118 134 135 130

(1.5 equiv.), $NaHCO_3$, CH_2Cl_2 (85%). See reference 84.

(84) The spectroscopic properties of these compounds (^1H NMR, IR, MS) were fully consistent with the assigned structures.

It was also clear from the outset that the choice of a suitable protecting group for the C.4 - and C.12 - hydroxyl groups of 120 would have to be addressed. In practice, several variations of protecting groups were evaluated (Scheme XVIII) before we focused on the ethylidene acetal protected lactone 65.

Analogous to the initial transformation in our model study of Chapter Two (the formylation of lactone 69 to hydroxymethylene lactone 72), a variety of reagents and conditions were examined

(85) Prepared from 118 by (1) C_6H_5COCl (3 equiv.), C_5H_5N, RT, 13h; (2) O_3, CH_2Cl_2, -78°C and then CH_3SCH_3 (59% from 118); (3) MCPBA (1.5 equiv.), $NaHCO_3$, CH_2Cl_2, RT, 20h (61%). See reference 84.

(86) Prepared from 118 by (1) KH (excess), CH_3I (5 equiv.), THF-DMF (4:1), 5 min, 0°C; (2) catalytic OsO_4, $NaIO_4$,[87] dioxane - H_2O (3:1), RT, 2h; (3) MCPBA (1.8 equiv.), $NaHCO_3$, CH_2Cl_2, RT, 17h. See reference 84.

(87) Pappo, R.; Allen, D.S.; Lemieux, R.U.; Johnson, W.S. J. Org. Chem. 1956, 21, 478.

(88) Prepared from ketone 105 by (1) t-butyl dimethylsilyl chloride (5 equiv.), imidazole (5 equiv.), DMF, RT, 24.5 h (44%); (2) MCPBA (1.5 equiv.), $NaHCO_3$ (2.6 equiv), CH_2Cl_2, RT, 21h (70%). See reference 84.

(89) Prepared from lactone 120 by treatment with excess $CH_3CH(OCH_3)_2$ (11 equiv.) and catalytic pyridinium p-toluenesulfonate (C_6H_6, reflux, 20h), in 74-79% yield. Only one diastereomer was produced from this reaction. We presume that the stereochemistry is as depicted in 65 since in the other diastereomer a severe 1,3 - diaxial interaction would exist between the acetal-CH_3 and C.3 of the bicyclic nucleus. The corresponding acetonides of either lactone 120 or olefin 118 could not be induced to form, presumably due to this severe diaxial strain.

in attempts to effect the formylation of lactones 65, 120, or 130 - 133. Several of the unsuccessful experiments include the following:

(a) KOtBu, tBuOCHO, THF, 25°-60°C (these conditions, successful with 69, failed to give any formylated product with 65, 120, 130, 131 and 132; other bases (NaH) and formylating reagents (EtOCHO) were also unsuccessful here);[91]

(b) Bis-dimethylamino-t-butoxymethane (Bredereck reagent),[90] DME, 70° (unsuccessful with 120);[91]

(c) Mukaiyama's Lewis acid catalyzed condensation of a ketene silyl acetal with a trialkylorthoformate;[92] thus, (1) LDA, THF, -78°C, then TMSCl; (2) $(CH_3O)_3CH$, $TiCl_4$, -78°C. Although this method failed in attempts with 132 and 133 (the ketene silyl acetals were isolated),[93],[94] the method was successfully applied to lactone 69.[95]

(90) (a) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. Ber. 1968, 101, 41; (b) For a recent application of this reagent, see Danishefsky, S.; Berman, E.; Clizbe, L.A.; Hirama, M. J. Am. Chem. Soc. 1979, 101, 4385.

(91) In retrospect, the undesired formylation of the free hydroxyl groups in either 120 or 130, using the above described reagents and conditions, may have complicated the interpretation of the complex product mixtures.

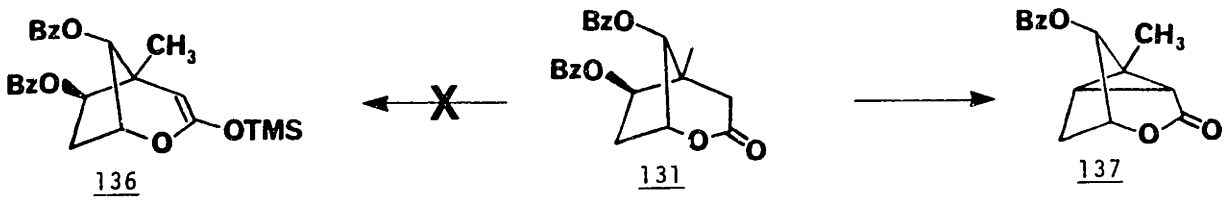
(92) Saigo, K.; Osaki, M.; Mukaiyama, T. Chemistry Lett. 1975, 989; 1976, 769.

(93) Stork, G.; Hudrlik, P.F. J. Am. Chem. Soc. 1968, 90, 4462.

(94) ^1H NMR data (90 MHz, $CDCl_3$) obtained on a 20:80 mixture of 132 and its derived TMS-enolate: δ 4.51 (d, J=5.4 Hz, 0.8H, H_2), 3.64 (s, 0.8H, H_6), 3.41 (s, 2.4H, OCH_3), 3.28 (s, 2.4H, OCH_3), 1.12 (s, 2.4H, CH_3), 0.21 (s, 7.2H, CH_3).

These preliminary results were certainly discouraging, yet we were confident that with the variety of methods available for functionalization of carbonyl containing compounds (96) we would be able to overcome this impasse.(97)

(95) This experiment was first attempted on dibenzoate lactone 131. In this case, none of the expected TMS-enolate 136 was isolated. Rather, we obtained a 50% yield of cyclopropane 137 along with 40% of recovered 131. Data for 137:

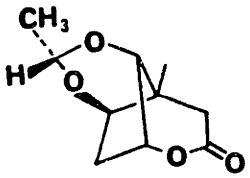


136 131 137

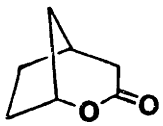
NMR (^{1}H, 250 MHz, $CDCl_3$) δ 5.22 (br s, $W_{1/2}$=3.2 Hz, 1H, H_{12}), 4.54 (br m, $W_{1/2}$= 6.3 Hz, 1H, H_2), 2.36 (dm, J=13.2 Hz, 1H, H_{3B}) 2.06 (dm, J=7.4 Hz, 1H, H_4 or H_6), 1.99 (dd, J=0.7, 7.4 Hz, 1H, H_4 or H_6), 1.91 (d, J=13.2 Hz, 1H, $H_{3\alpha}$), 1.37 (s, 3H, CH_3); IR (CH_2Cl_2) 3045, 2960, 2935, 2870, 1725 (C=0), 1600, 1580; mass spectrum m/e 258 (parent ion), 215, 184, 152, 136, 105.

(96) For example:
- (a) Gutzwiller, J.; Pizzolato, G.; Uskokovic, M. J. Am. Chem. Soc. 1971, 93, 5907;
- (b) Ban, Y.; Taga, N.; Oishi, T. Tetrahedron Lett. 1974, 187;
- (c) Krishnamurty, H.G.; Prasad, J.S. Tetrahedron Lett. 1977, 3071;
- (d) Kahne, D.; Collum, D.B. Tetrahedron Lett. 1981, 22, 5011;
- (e) Mock, W.L.; Tsou, H.-R. J. Org. Chem. 1981, 46, 2557;
- (f) Konen, D.A.; Pfeffer, P.E.; Silbert, L.S. Tetrahedron 1976, 32, 2507;
- (g) Paterson, I.; Fleming, I. Tetrahedron Lett. 1979, 993;
- (h) Grieco, P.A.; Hiroi, K. J. Chem. Soc.,Chem. Commun. 1972, 1317; Tetrahedron Lett. 1973, 1831;

We initially assumed that the greater difficulty in functionalizing lactone 65 (and its other closely related derivatives, Scheme XVIII) relative to 69 was due to the steric hindrance caused by the methyl group at C.5. In a parallel set of studies on the synthesis of trichothecene analogues (see Chapter Five) we synthesized lactones 142 and 143. Although



65



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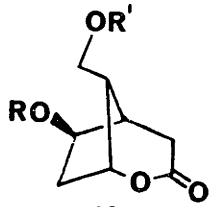
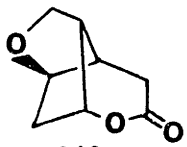
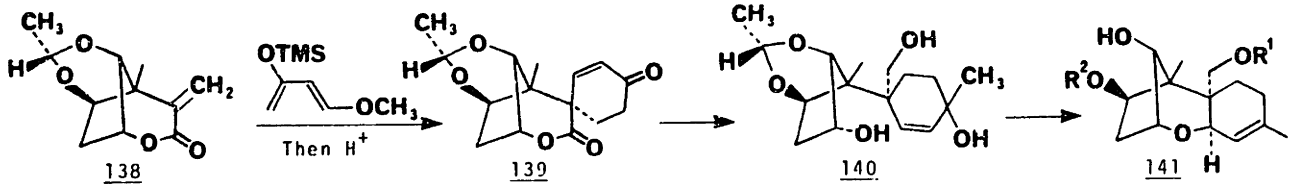


142



143

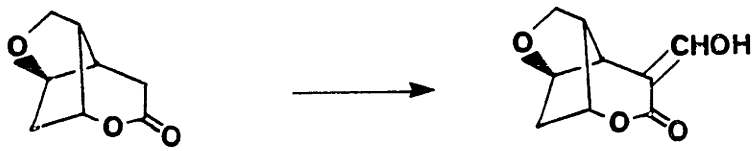
(97) At this stage we began to envision alternative routes which would fulfill our annelation sequence. An attractive idea was envisioned as the Diels-Alder addition of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) to α-methylene lactone 138. Based on our model study (Chapter Two), we were convinced that this diene would approach 138 from the less hindered exo face to afford, after acidic



138 139 140 141

hydrolysis, spiro-cyclohexenone 139. It was apparent that the elaboration of 139 to verrucarol via 141 would be shorter and thus more efficient than our original approach. (To our surprise, this was precisely the annelation sequence which Schlessinger reported for his verrucarol synthesis (Reference 33)).

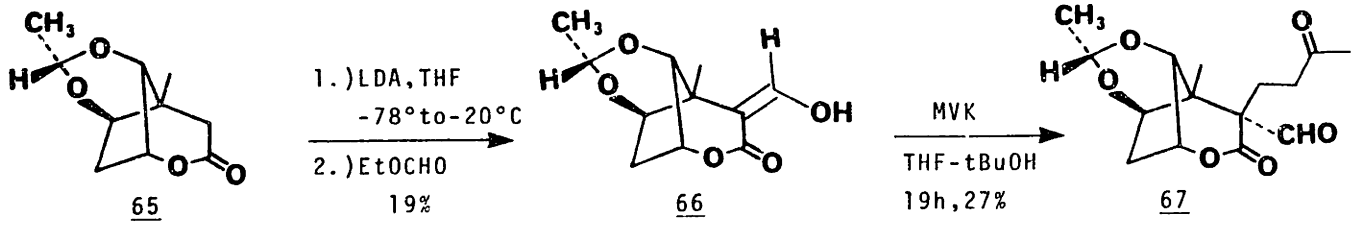
these substrates lack a methyl substituent at C.5, the reactivity of these lactones resembles that experienced with 65 (and derivatives) more closely than 69. Indeed, attempts to formylate 142 and 143 using the conditions developed in Chapter Two for 69 (HCO_2tBu, KOtBu, THF) were unsuccessful, as were a number of other conditions. Thus treatment of 143 with 3-10 equivalents of t-butyl formate in the presence of a variety of different bases ((a) KOtBu, THF; (b) LiOtBu, NaH, THF, HMPT, 50°C; (c) NaH, DME, 65°C; (d) LDA, THF, HMPT, -78°C; (e) NaH, THF, HMPT, 50°C) afforded, at best, only trace amounts (<10%) of 144 along with recovered 143. Best results were realized when the LDA derived



143 144

enolate of 143 was treated with t-butyl formate (4.6 equiv.) over 10 min at -78°C to 23°C. In this instance we obtained 144, mp 139-140°C, in 30% yield.

These results suggested that our experience with 65 was not simply the consequence of steric hindrance. The study of 142 and 143 did, however, provide a set of experimental conditions which were successfully applied to 65. Thus, treatment of the lithium enolate of 65 (LDA, THF, -78 ---> -20°C) with two to five



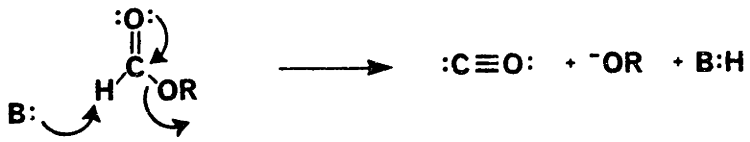
65 66 67

equivalents of EtOCHO(98) afforded hydroxymethylene lactone 66 (19% yield) along with recovered 65 (62%). Many attempts at optimizing the yield of this conversion failed to afford reproducible improvement.(99) Analogous to our model study

(98) These conditions with t-BuOCHO were unsuccessful.

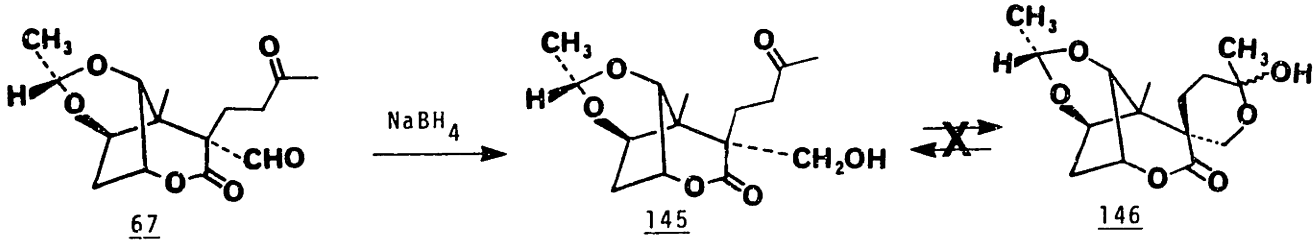
(99) (a) On one attempt, a 40% yield of 66 along with 48% of 65 was obtained. We were unable, however, to duplicate this conversion.

(b) Two significant side reactions complicate this experiment. One is the abstraction of the carbonyl

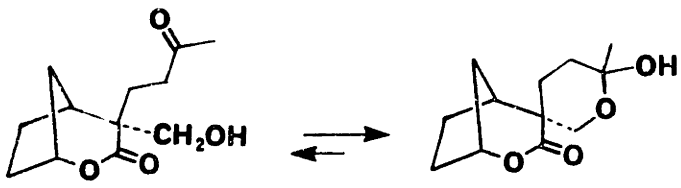


proton of the formate ester, liberating carbon monoxide and the corresponding alkoxide. This side reaction was observed in all reactions with base and formate esters, (even KOt-Bu and tBuOCHO, as described in Chapter Two). This side reaction necessitated the use of excess LDA in the above experiments, in which case significant quantities of N,N-diisopropyl formamide were also formed.

(Chapter Two), Michael adduct 67[100] was then obtained, but in this case required the vapor phase introduction of methyl vinyl ketone into the reaction mixture,[101] using THF and t-BuOH (1:1) as co-solvents. The reaction was sluggish (19h) and afforded 67[102] in poor yield (27%) along with considerable polymeric material.[103] Treatment of 67 with 1.3 hydride equivalents of $NaBH_4$ (THF-EtOH (1:1), -10°C, 60 min) afforded hydroxy ketone 145 (76%). In contrast to the equilibrium observed for 74 and 75 as described in Chapter Two, 145 appears to exist uncontaminated with its hemiketal isomer 146.



67 145 146



75 74

While our attention focused on the optimization of the preparations of 66 and 67, alternative sequences were also being considered. For example, the LDA derived enolate of 65 (-78°---> -20°C) was treated with gaseous carbon dioxide(104) to afford, after treatment of the crude product with excess ethereal diazomethane, carbomethoxylated lactone 147, but again in poor yield (28-33%). The 270 MHz ^{1}H NMR spectrum of 147 indicated it

(100) Michael addition of methyl vinyl ketone to hindered substrates has previously been accomplished:
(a) Buchi, G.; Jeger, O.; Ruzicka, L. Helv. Chim. Acta 1948, 31, 241;
(b) Reference 41.

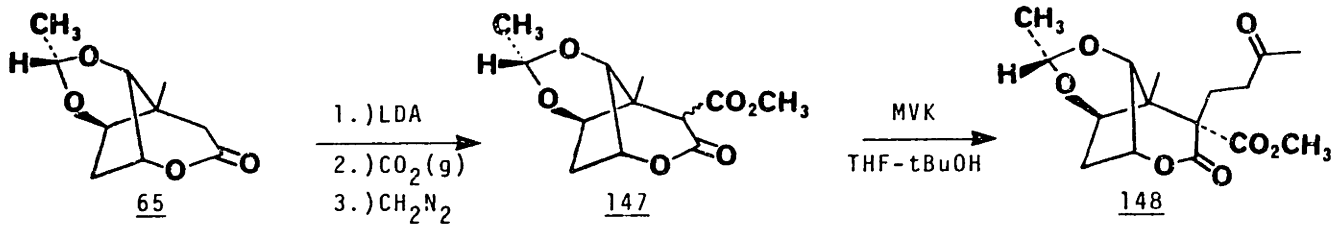
(101) (a) DeBoer, C.D. J. Org. Chem. 1974, 39, 2426;
(b) Reference 41;
(c) Reference 81j.

(102) As in Chapter 2, only one of two possible Michael adducts was obtained. The stereochemistry of this adduct was assigned on the basis of these previous results.

(103) This extensive polymerization we observed might be avoided by resorting to trimethylsilyl substituted methyl vinyl ketone:
(a) Stork, G.; Ganem, B. J. Am. Chem. Soc. 1973, 95, 6152;
(b) Boeckman, R.K. Ibid 1974, 96, 6179;
(c) Stork, G.; Singh, J. Ibid 1974, 96, 6181.

(104) Grieco, P.A.; Hiroi, K. J. Chem. Soc., Chem. Commun. 1973, 500.

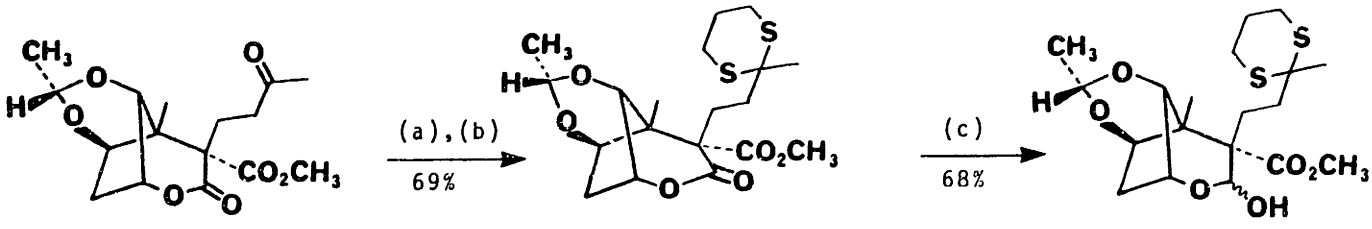
to be a 3:1 mixture, respectively, of the corresponding C.6 α- and β - epimers. In these experiments, 27-43% of unconsumed 65 was routinely recovered.



65 147 148

Condensation of 147 with excess methyl vinyl ketone (KOt-Bu, THF-tBuOH (1:1)) afforded 38% of Michael adduct 148,(102) again along with considerable polymeric material.(103) Further exploratory chemistry with 148 is summarized in Scheme XIX.

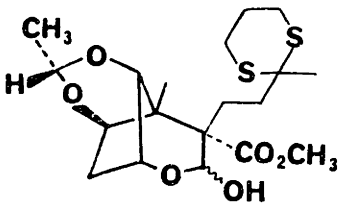
Scheme XIX



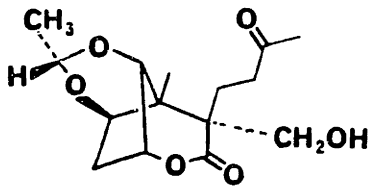
148 149 150

(a) $HSCH_2CH_2CH_2SH$ (1.6 equiv.), BF_3-OEt_2, 15 min;
(b) $CH_3CH(OCH_3)_2$, C_6H_6, cat. TsOH-C_5H_5N, reflux, 19h;
(c) DIBAL (6 equiv.), Toluene, -78°C, 3h.

Protection of the ketone carbonyl of 148 as a dithiane was readily accomplished, although we also observed concomitant loss of the ethylidene acetal protecting group. This group was reintroduced using the conditions previously described[89] to afford 149 (69% yield from 148). Treatment of 149 with excess DIBAL (6 equiv., $C_6H_5CH_3$, -78°C, 3h) produced lactol 150 (68% yield). Thus, we observed selective attack on the lactone carbonyl, even with a large excess of reductant.



150



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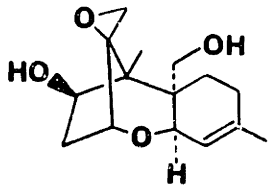
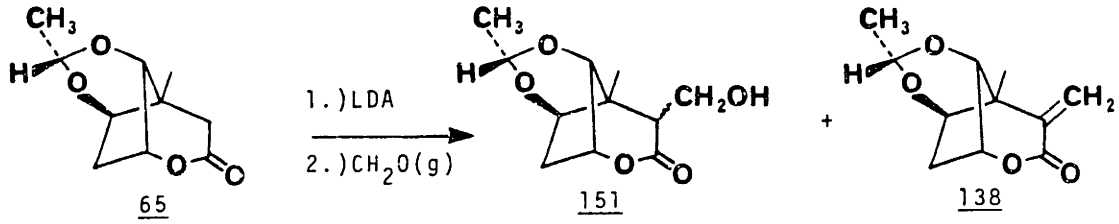


1

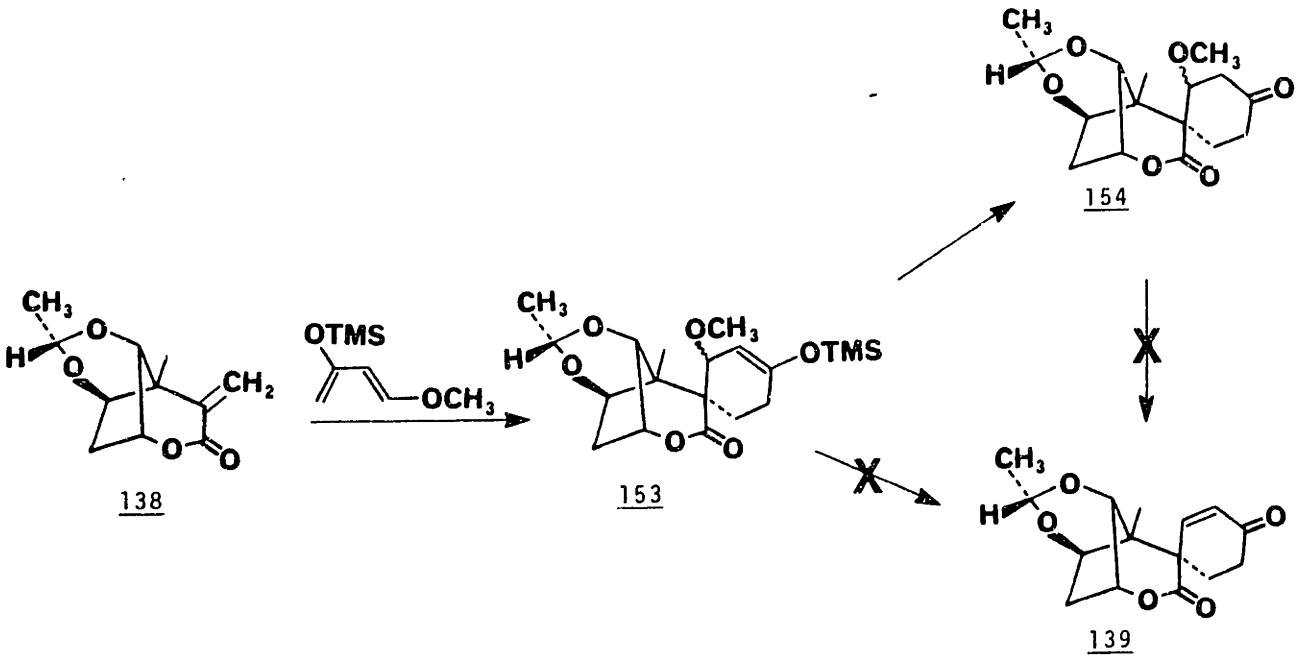
Both intermediates 150 and 145 appeared to be promising precursors of verrucarol, especially considering our results of Chapter Two. In view of the difficulties (especially the poor yields) encountered in the preparation of 147 and 148 (as well as the corresponding preparation of 66 and 67), however, we decided to shift our attention to a more efficient Diels-Alder spiroannelation sequence, which we had previously envisioned.[97]

Treatment of 65 with LDA and gaseous formaldehyde using the method described by Grieco[96h] afforded the expected α-hydroxymethyl lactones 151 (epimeric at C.6) in low yield (21%)



65 151 138

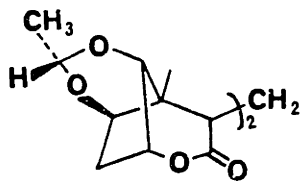
together with 7% of α -methylene lactone 138. Careful optimization of the reaction conditions [1.2 equiv. LDA, 65, THF, -78°C, 30 min; warm to -20°C and add gaseous HCHO (generated from six equiv. of anhydrous paraformaldehyde (P_2O_5)), 160°C, Ar stream, 2h; warm to room temperature and stir for 10 - 24h] afforded 138, mp 157.5 - 159°C, in 69 - 71% yield after chromatography.(105) An analogous alpha-methylenation was discovered by Schlessinger (reference 33 and Chapter One, page 36).



154 138 153 139

With pure 138 available in good yield, we next explored the condensation of this intermediate with 4-methoxy-2-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene).[106] This transformation was very facile in toluene at 100°C (31h), and afforded the expected adduct 153 in good yield.[107] Attempts to hydrolyze 153 to the desired enone 139, however, utilizing either (a) 1N aqueous HCl;[108] (b) Amberlite IR-120, CH_2Cl_2, 3h;[33] or (c) Amberlite IR-120, THF, 20h[109] afforded none of the

(105) If insufficient paraformaldehyde was used, a significant amount of material tentatively identified as dimer 152 was obtained.



152

(106) Danishefsky, S. Accs. Chem. Res. 1981, 14, 400.

(107) The stereochemistry of this adduct was assumed to be that as depicted for approach of the diene to the less hindered exo face of the bicyclic nucleus. Precedent for this assumption derives from the work described in Chapter Two of this thesis as well as that described by Schlessinger (reference 33).

(108) Danishefsky, S.; Kitahara, T.; Yan, C.F.; Morris, J. J. Am. Chem. Soc. 1979, 101, 6996.

(109) Jain, T.C.; McCloskey, J.E. Tetrahedron 1975, 31, 2211.

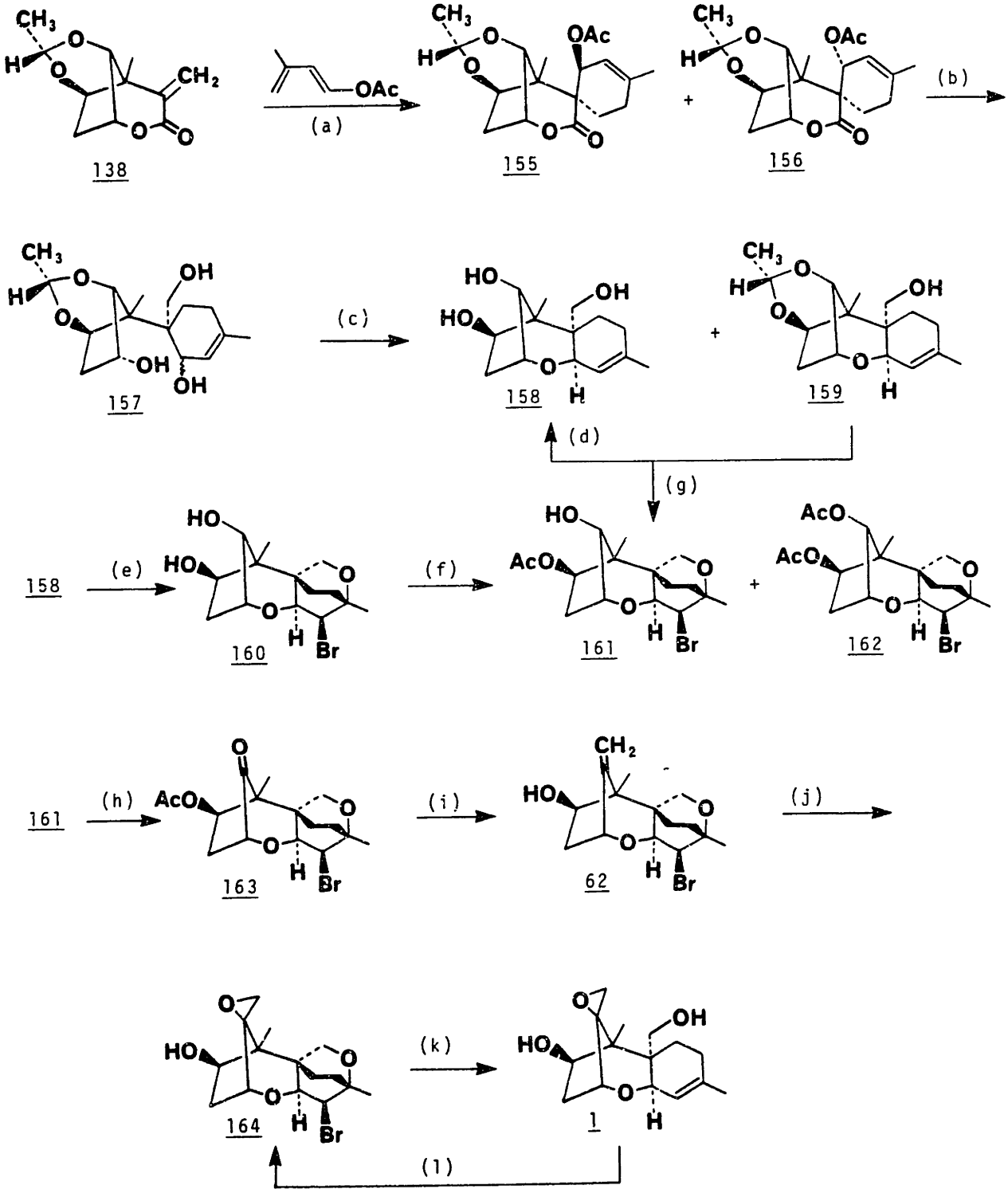
expected cyclohexenone product.(110) Rather we obtained β-methoxy ketone 154. Attempts to promote conversion of 154 to 139 ((a) catalytic pyridinium p-toluenesulphonate, C_6H_6, reflux; or (b) neutral alumina(111)) were also unsuccessful.

Parallel to the above experiments, we were also exploring the Diels-Alder reaction between 138 and 1-acetoxyisoprene which ultimately led to the successful completion of the synthesis of verrucarol, as outlined in Scheme XX.

(110) Harsher conditions (BF_3-OEt_2, -78°C, 20 min) led to complex product mixtures.

(111) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R J. Am. Chem. Soc. 1980, 102, 2838.

Scheme XX


138
(a)
155
156
(b)
157
(c)
158
159
(d)
(g)
158
(e)
160
(f)
161
162
161
(h)
163
(i)
62
(j)
164
(k)
1
(l)

(a) $C_6H_5CH_3$, 140°C, 48 - 52h (53-57% of an approximate 3:1 mixture of 155 and 156);
(b) $LiAlH_4$, DME, 1h, RT; then 20h, reflux;
(c) Catalytic pyridinium p-toluene sulphonate, wet C_6H_6, reflux, 30 - 60 min (55 - 65% (from 155, 156) of varying ratios of 158, 159);
(d) 1N aqueous HCl, acetone (1:10), 5h, RT (100%);
(e) NBS, reagent grade CH_3CN (70 - 84%);
(f) Ac_2O, C_5H_5N, 60h, (161, 29-30%; 162, 12-14%; 160, 25-30% (from 158));
(g) NBS (2.6 equiv.), CH_3CN, 4.25h (31%);
(h) Jones reagent, acetone (88%);
(i) Methylenetriphenylphosphorane (six equiv.), THF, 60°C, 3h (52-60%);
(j) MCPBA, $NaHCO_3$, CH_2Cl_2, RT, 21h (99%);
(k) Zn-Ag (excess), THF-EtOH (5:1), reflux, 12h (81%);
(l) NBS, CH_3CN, quantitative.

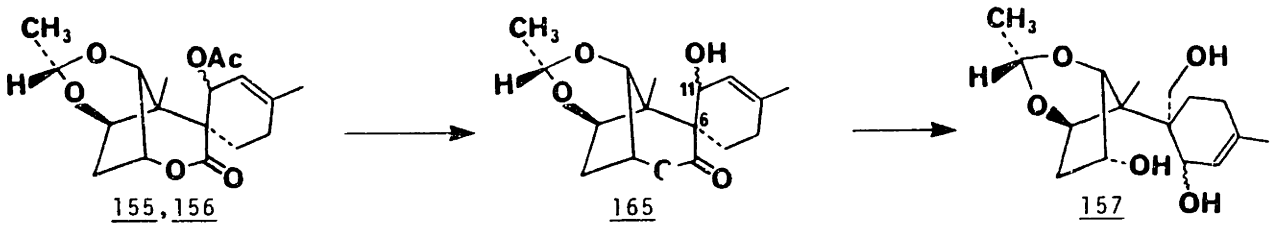
Condensation of lactone 138 with 3-methyl-1-acetoxy-1,3-butadiene[112] ($C_6H_5CH_3$, 140°C, 48-52h) afforded approximately a 3:1 mixture of two Diels-Alder adducts 155, mp 234-236°C, and 156, mp 260.5-262°C, in 53-57% yield together with significant amounts (25-30%) of recovered 138.[113] Although the stereochemistry at C.11 of 155, 156 has not been established

(112) (a) Reference 25; (b) Cookson, R.C.; Cramp, M.C.; Parsons, P.J. J. Chem. Soc., Chem. Commun. 1980, 197.

(113) This ratio of 155 and 156 is temperature dependent. At 140°C, an approximate 3:1 mixture, respectively, of 155 and 156 was obtained. In one experiment at 150°C (48h), an approximate 1:1 ratio was observed. Even in this case however, recovered 138 (25-30%) was still obtained.

unambiguously,(114) it is clear from the following results that both isomers possess identical configurations at C.6. Both products, therefore, derive from a cycloaddition reaction in which the diene approached the [3.2.1]-bicyclic dienophile from the least hindered face.

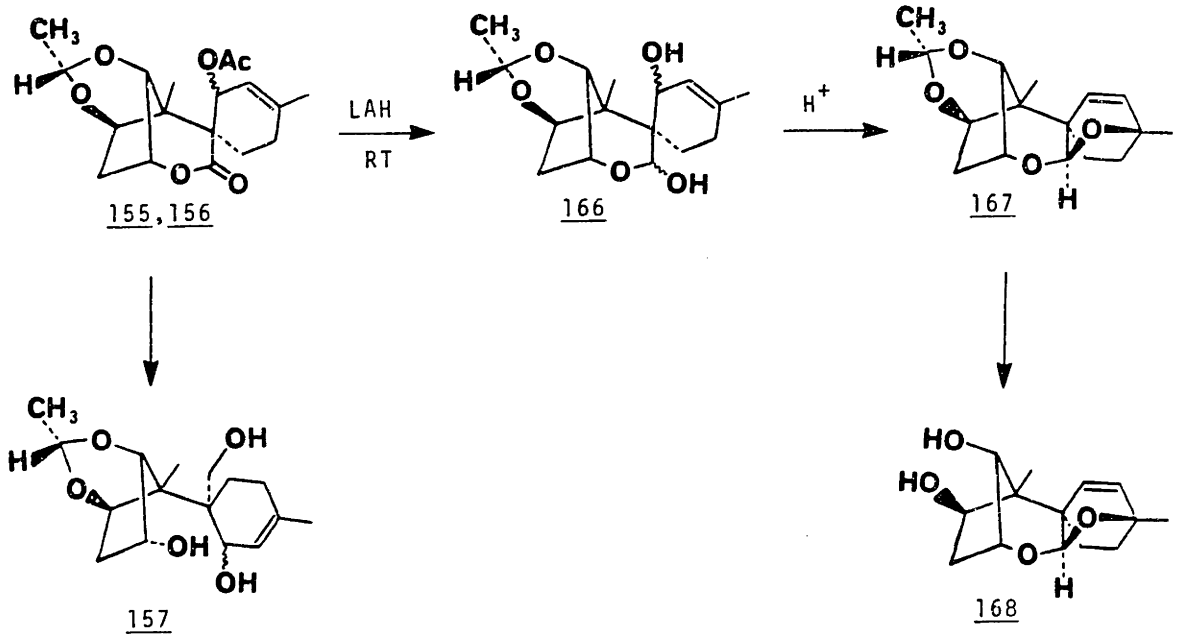
Our next transformation required the reduction of the Diels-Alder adduct mixture (155 and 156) to 157. We were wary of the possibility for significant retro-aldol cleavage of the C.6-C.11



bond of intermediate allylic alcohols 165.(115) In practice treatment of the Diels-Alder adduct mixture with $LiAlH_4$ (6 equiv., RT, 1h) afforded one major product by TLC analysis. Subjection of this crude reduction product to catalytic p-TsOH (benzene, room temperature, 15 min) afforded a rearranged material (50% yield from 155, 156) which lacked the basic spectral features of the trichothecene nucleus. Upon close

(114) The major adduct here has been assigned the structure 155 assuming an endo transition state in the Diels-Alder reaction (approach of diene to dienophile 138 from its exo face).

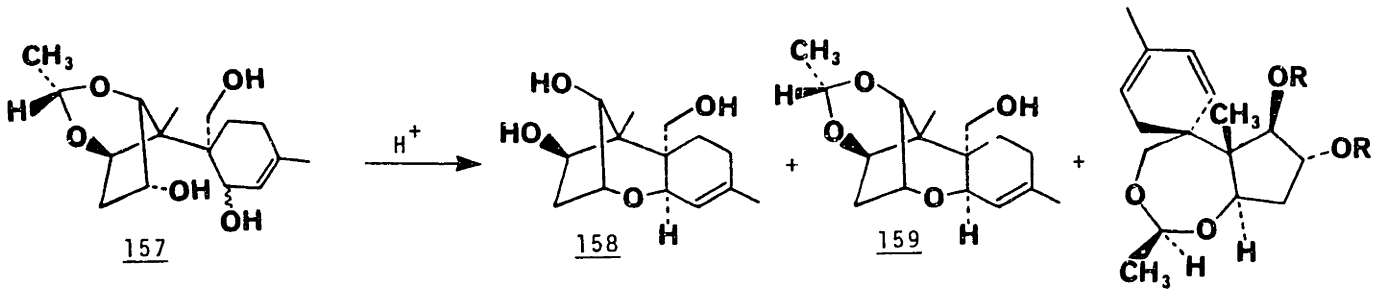
analysis of the spectral data this product was assigned structure 167. Thus $LiAlH_4$ reduction at room temperature had only afforded lactol 166 which upon acid treatment rearranged to cyclic acetal 167 (which was characterized as its deprotected derivative 168).(116) Using harsher reduction conditions ($LiAlH_4$, DME, 1h, room temperature; then 20h, reflux) the mixture of adducts 155, 156 was smoothly converted to triols 157. The stage was now set for dehydration of triols 157 to the trichothecene ring system.



(115) Allylic alcohol 165 (single diastereomer) was obtained in low yield (26%) as the only identifiable product upon the treatment of the mixture 155,156 with one equivalent of $NaOCH_3$ (CH_3OH-THF, 40 min).

(116) Exploratory reactions carried out on samples of isomerically pure 155 and isomerically pure 156 (1N aqueous HCl treatment instead of p-TsOH in C_6H_6) indicated that both adducts were converted to 168 directly.

A variety of conditions were examined in attempts to optimize the cyclization of 157 to either 158 or 159. We found that treatment of 157 with a catalytic amount of pTsOH-C_5H_5N (wet C_6H_6, reflux, 30-60 minutes) afforded 55-65% combined yields of 158 (mp 40-44°C) and 159 (the ratio 158:159 varied from run to run), and also small amounts of 169 (~5%). Attempts to



157 158 159 169 R=H 170 R=Ac

find conditions which produced either 158 or 159 exclusively, (for example, (a) TsOH-C_5H_5N, wet C_6H_6; (b) TsOH, molecular sieves,[117] CH_2Cl_2) were unsuccessful. Nevertheless, 159 was hydrolyzed to 158 (1N aqueous HCl, acetone (1:10), 5h, room temperature) in quantitative yield. Other conditions evaluated for the cyclization of 157 to 158 or 159 were either extremely sluggish

(117) Roelofsen, D.P.; van Bekkum, H. Synthesis 1972, 419.

((a) SiO_2, THF, room temperature; (b) $AgClO_4$,[118] C_6H_6, room temperature; (c) C_5H_5N-TsOH in either CH_2Cl_2 or C_6H_6; (d) BF_3-OEt_2, CH_2Cl_2, -78^oC; (e) Amberlite IR-120, CH_2Cl_2, room temperature) or afforded diminished amounts of 158 and 159 and increased amounts of 169. Some of the results in this latter category are summarized in Table IV. Thus, treatment of triols 157 with 1N aqueous HCl in THF (the conditions which were successful in our model study; Chapter Two) led to a complex product mixture. The use of p-TsOH as the cyclization catalyst was successful in affording cyclized products; but, in these cases, lesser amounts of 158 and 159 and significant amounts of 169 were formed. Most notable among these experiments are the last two, which were performed on the product of $LiAlH_4$ reduction (DME, reflux, 10-20h) of isomerically pure Diels-Alder adduct. In this instance, triol 157 derived from pure 155 was treated with pTsOH (CH_2Cl_2, 5 min, RT) to afford a 20% combined yield of 158 and 159 (plus 16% of diene 169).[119] Treatment of triol 157 derived from pure 156 with pTsOH (DCE, 5h, RT) gave similar results.[119] For preparative scale cyclizations (on the mixture of triols 157) the conditions cited originally (catalytic pTsOH-C_5H_5N, C_6H_6, reflux, 30-60 min) were used.

(118) (a) Mukaiyama, T.; Kobayashi, S.; Kamio, K.; Takei, H. Chemistry Lett. 1972, 237;
(b) Mukaiyama, T.; Kuwahara, M.; Izawa, T.; Ueki, M. Chemistry Lett. 1972, 287;
(c) Wakamatsu, T.; Hashimoto, K.; Ogura, M. Synthetic Commun. 1978, 8, 319.

Table IV

Entry	Conditions	158	159	169
(1)	1N aqueous HCl, THF	trace	---	---
(2)	TsOH, CH_2Cl_2, RT[a] 10-20 min	31%	19%	29%
(3)	TsOH, DCE, 3h, 0°C	49%	---	---
(4)	TsOH, C_6H_6, 30 min, RT	45%	---	---
(5)	From MAJOR Adduct (155) TsOH, CH_2Cl_2, 5min, RT	12%	8%	16%
(6)	From MINOR Adduct (156) TsOH, DCE, 5h, RT	---	18%	19%

(a) These figures represent the optimum yield obtained from several experiments with these conditions.

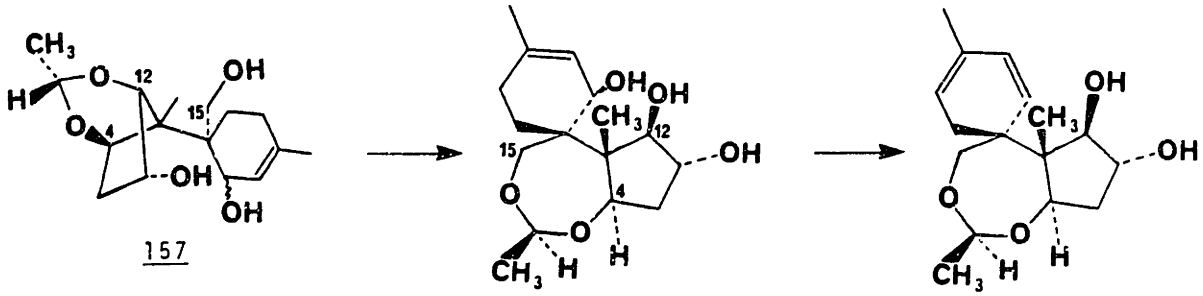
Assignment of structure to the cyclization products 158 and 159 was initially based on the similarity of their spectral data (notably 250 or 270 MHz ^1H NMR) to that of known trichothecenes. The conversion of 158 to verrucarol, which is subsequently

(119) These experiments were performed before optimal conditions had been established.

described, bore out this assignment. This ring closure, 157 ---> 159, resembles the biosynthetic ring closure of the natural trichothecenes (Chapter 1, page 18), first examined in a synthetic context by Kamikawa[29] and later used in our model studies (Chapter Two). In the above case (157--->159), however, the allylic carbonium ion intermediate derives from a secondary allylic alcohol, rather than from a tertiary allylic alcohol as has been suggested for the natural trichothecenes.

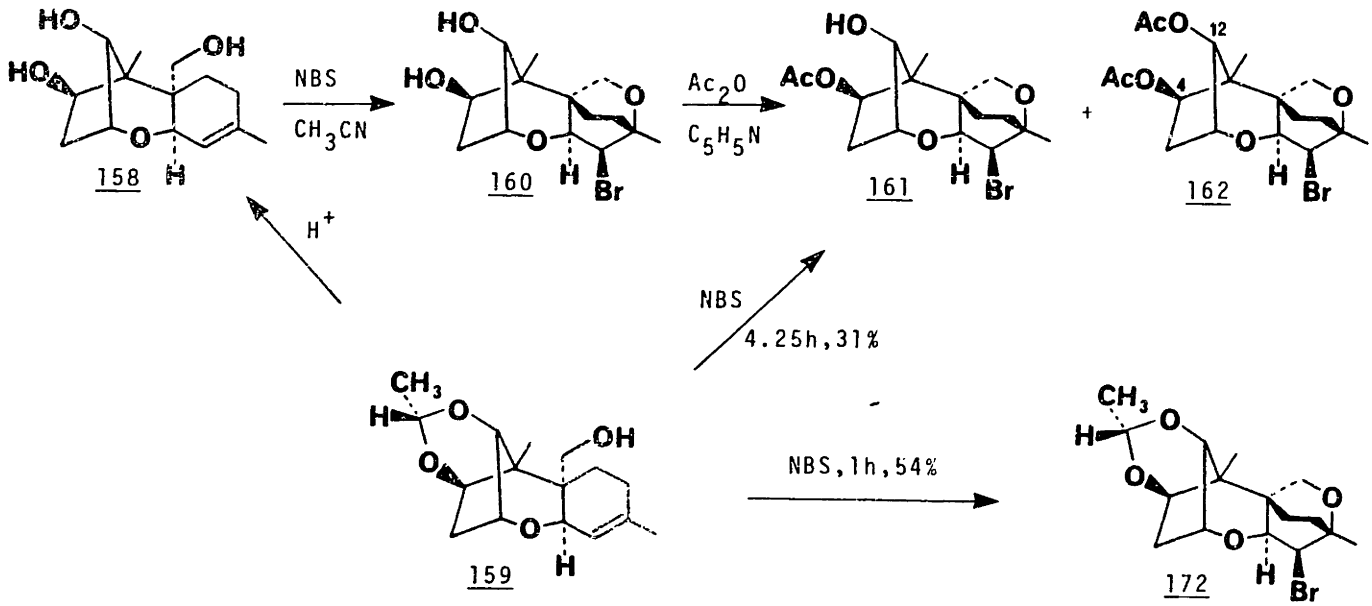
Assignment of structure to diene 169 was less straightforward. The presence of a chromophore in 169 was indicated by the detection of this compound on TLC plates with long wave UV light. Based upon the proton NMR spectrum, this chromophore was attributed to a diene subunit. It was also obvious from the NMR spectrum that 169 still possessed the ethylidene acetal. The presence of coupled resonances at δ 4.07 (ddd, J=3.8, 6.6, 10.5 Hz, H_2) and at δ 3.78 (d, J=6.6 Hz, H_{12}) (confirmed by homonuclear spin decoupling experiments) assigned to H_2 and H_{12}, respectively, suggested that the ethylidene acetal

had migrated from the C.12 hydroxyl to the C.15 hydroxyl group. This was confirmed by acylation of 169 with excess Ac_2O in C_5H_5N. The corresponding resonances for H_2 and H_{12} in 170 were respectively, δ 5.12 and δ 5.33. We speculate that 169 results from initial ethylidene migration in 157 to an intermediate such as 171. As a consequence of the steric constraints imposed by the acetal in 171, cyclization would lead to a very strained species. Dehydration is thus the only recourse left for an allylic carbonium ion which might then form from 171. As evident



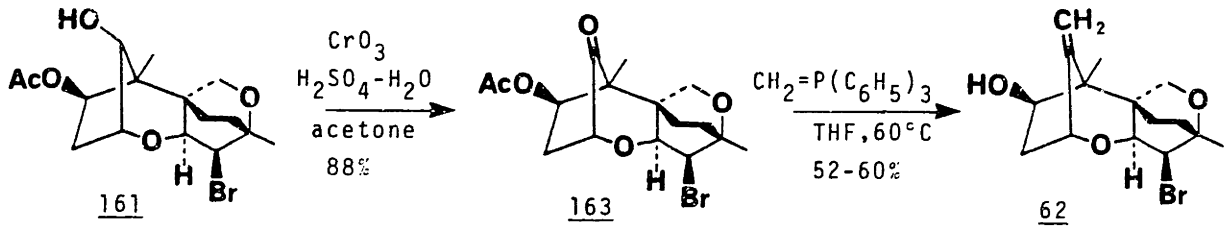
from the results in Table IV, varying amounts of this diene were formed when p-TsOH was used as the cyclization catalyst. Fortunately this pathway was minimized when the cyclization of 157 was performed with pyridinium tosylate in wet benzene, as previously described.

Elaboration of the trichothecene ring system of 158 to verrucarol 1 proceeded as follows. The C.15 hydroxyl group and the 9,10-double bond were protected simultaneously as a bromoether (NBS, reagent grade CH_3CN, 70-84% yield).[120] Acylation of the C.4 hydroxyl group was then accomplished (1.5 equiv. of Ac_2O, C_5H_5N, 60h) to give 29-30% (from 158) of 161 plus 25-30% of recovered 160 and, unfortunately, 12-14% (from 158) of diacetate 162 (which was recycled to 160, mp 189.5-191°C, with saturated K_2CO_3 in CH_3OH, 88%).[121] In no instance was any material corresponding to a C.12 monoacetate ever detected.[122]



(120) Schlessinger (reference 33) and Kraus (reference 28c) have utilized analogous bromo ethers in their trichothecene syntheses in order to achieve a selective epoxidation of the 12,13-double bond. On the basis of their results we chose to simultaneously protect the C.15 hydroxyl group (which needed to be protected for the following acylation and oxidation steps) and the 9,10-double bond in one step.

Our desire to selectively obtain the C.4 monoacetate 161 originated in the prior discovery that prolonged treatment of 159 with excess NBS (CH_3CN, 4.25h) directly afforded monoacetate 161 in a single step (31% yield).[123] Oxidation of the ethylidene acetal of 172 (with excess NBS) thus led directly to the desired C.4 monoacetate. As in the treatment of diol 160 with Ac_2O, none of the isomeric C.12 monoacetate was ever detected. A few attempts to optimize the yield of this conversion (as well as attempts to optimize the conversion of 157 to 159) were unsuccessful. Therefore, as mentioned previously, on a



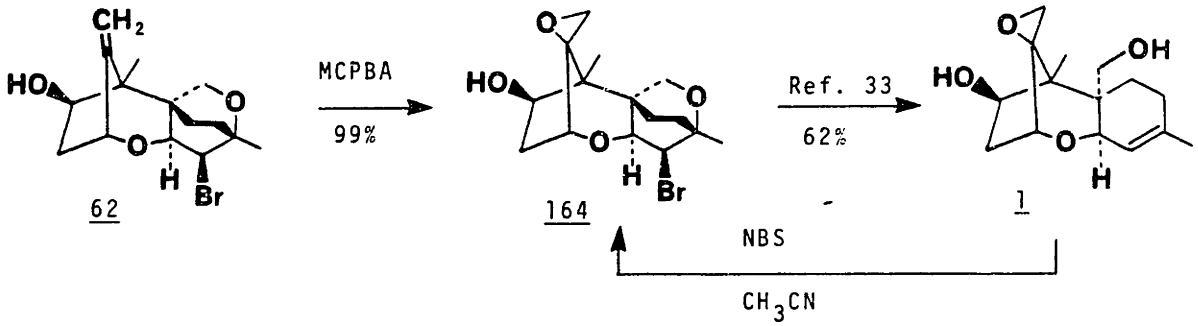
(121) The use of excess Ac_2O or added DMAP (as an acylation catalyst) afforded 1:1 ratios of 161 and 162.

(122) A related monobenzoylation was previously discovered (reference 30). Also see reference 83.

(123) Shorter reaction times afforded the expected bromo ether 172 (in one instance 54% yield).

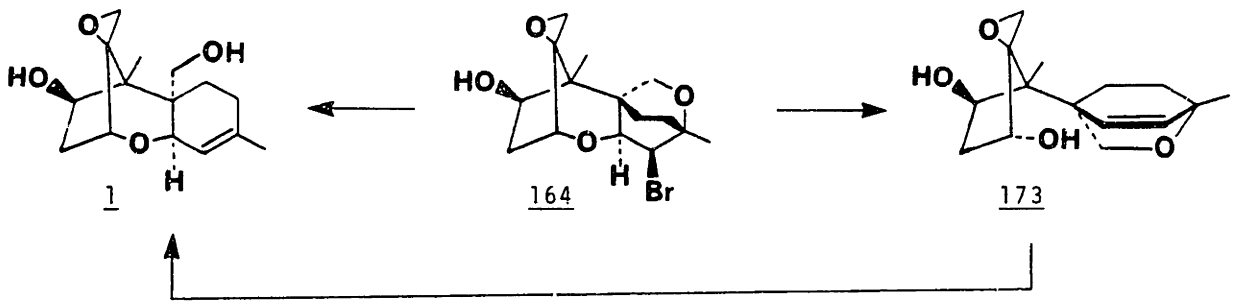
preparative scale acetal 159 was routinely converted to 158 (as opposed to being oxidized with NBS).

Although monoacetate 161 could not be obtained directly in a high yielding step (either from 160 or 159) sufficient quantities were available through the selective C.4 monoacylation of diol 160 with the subsequent recycling of diacetate 162. Oxidation of the C.12 hydroxyl of 161 was then accomplished with Jones reagent (88%). Treatment of the resulting ketone 163 with methylenetriphenylphosphorane (6 equiv., 60°C, 3h) afforded the known hydroxy olefin 62[33] directly in 52-60% yield.[124] Epoxidation of 62 (MCPBA, CH_2Cl_2, 21h, 99%) afforded 164, mp 227-229°C, which was identical in all respects to an authentic sample prepared from natural verrucarol 1 (NBS, CH_3CN).[125], [126]



(124) The introduction of C.13 by a Wittig olefination with methylenetriphenylphosporane on the assembled trichothecene nucleus has been used a number of times; for example: References 27, 28c, 31e, 34c and 35. In previous cases in which the trichothecene ring system possessed a C.4 protected ester function, however, the yields of this Wittig reaction had previously been suspect (references 21b and 30).

At this stage a formal synthesis of verrucarol had been completed since Schlessinger had already reported the epoxidation of 62 and the reductive elimination of 164 to 1 using Na in $EtNH_2$ (62%).[33] Nevertheless, we decided to explore alternative conditions for completing the synthesis. Much to our surprise, treatment of a THF solution of naturally derived 164 with excess n-BuLi[127] for 5 min at room temperature afforded 54% of 173



(125) Natural verrucarol was prepared from natural anguidine by the procedure of Fraser-Reid (reference 36). I am grateful to T.A. Blizzard for a generous supply of verrucarol, obtained as such.

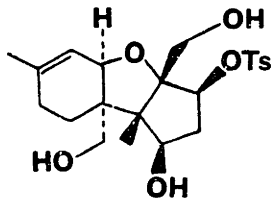
(126) Various attempts to form the 12,13-spiro epoxide of the trichothecene configuration directly by reaction of ketones analogous to 163 with either sulfonium or sulfoxonium methylide reagents have not been successful. Based on those results (references 21a, 27, 34a and 35) we did not explore similar reactions with ketone 163.

(127) Schollkopf, U.; Paust, J.; Patsch, M.R. Org. Syn. 1969, 49, 86.

(10% of 164 was recovered) as the product of syn elimination. Verrucarol was not detected in the crude reaction mixture. Conducting the reaction at lower temperatures (0°C) or with added HMPT (-15°C) did not effect its course. Preliminary efforts to cyclize 173 to verrucarol ((a) catalytic p-TsOH, CH_2Cl_2, 10 min; (b) 1N aqueous HCl, EtOH) led to product mixtures containing only traces of verrucarol.[128]

Treatment of synthetic 164 with Zn-Ag couple[129] (THF-EtOH (5:1), reflux (65°C), 12h) afforded synthetic verrucarol (81%) together with a small amount of 175 (19%).[130] Synthetic verrucarol, mp 170-171.5°C (recrystalized from C_6H_6-hexane)[131] was identical in all respects to a natural sample (mp 160-161°C; C_6H_6-hexane) kindly provided by Professor Ch. Tamm.

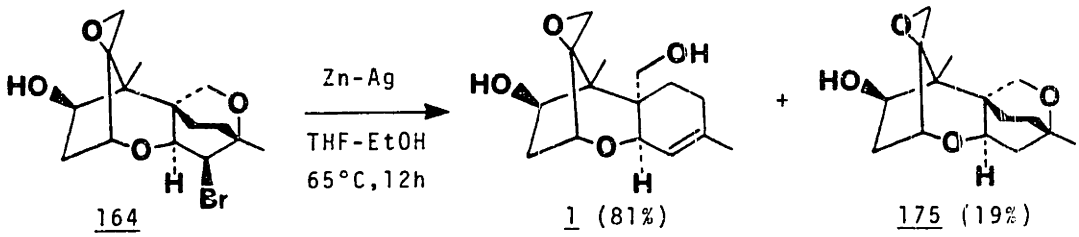
(128) The apotrichothecene 174 was isolated (25%) when 173 was treated with less than the stoichiometric amount of p-TsOH in CH_2Cl_2.



174

(129) (a) Denis, J.M.; Girard, C.; Conia, J.M. Synthesis 1972, 549; (b) See also reference 28c.

(130) Reduction of naturally derived 164 with a different batch of Zn-Ag, as described above, afforded none of 175. In this instance, however, traces (~5%) of 173 were detected.

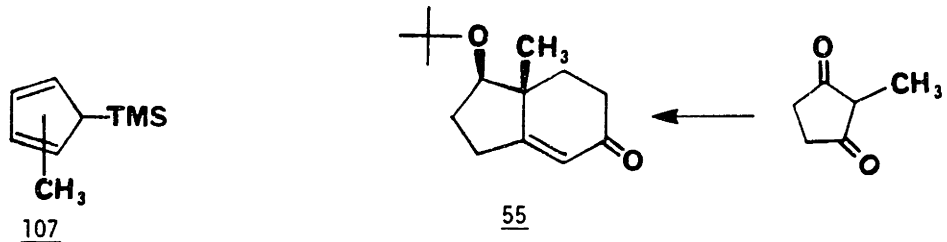


164 → 1 (81%) + 175 (19%)

The total synthesis of racemic verrucarol was thus completed in 21 steps from readily available (methylcyclopentadienyl) trimethylsilane.(132) The key steps of this synthesis, the annelation of the trichothecene A ring onto a suitable bicyclic precursor, should open the way for the preparation of a host of trichothecene analogues.*

(131) The melting point of racemic verrucarol has also been reported to be 159-161°C (Et_2O); reference 33.

(132) Our 21 step synthesis of verrucarol starting from 107 is comparable to Schlessinger's 17 step synthesis from 55.



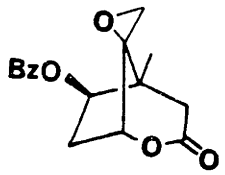
107 ← 55

* Note added in proof. A third synthesis of verrucarol has very recently been published: Trost, B.M.; McDougal, P.G. J. Am. Chem. Soc. 1982, 104, 6110. In this paper the melting point of racemic verrucarol is reported to be 165.5-167°C (ether-chloroform).

CHAPTER FOUR

Trichothecene Analogue Studies

The previous two chapters dealt with our development and elaboration of a synthetic route to the trichothecene nucleus, culminating in the total synthesis of verrucarol 1. The marked cytotoxicity reported for several members of the trichothecene class of compounds coupled with their suspected mechanism of action (reviewed in Chapter One) suggests that an effective antitumor drug based on the trichothecene ring system may eventually be developed. In this chapter we describe our efforts to develop various trichothecene analogues. Specifically discussed are (1) the synthesis and in vivo cancer screens of three B-C ring spiro epoxides (e.g., 176), and (2) our studies on the synthesis of C.14 desmethyl verrucarol, 177.



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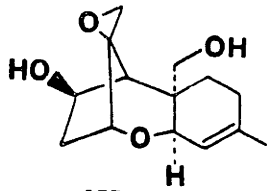
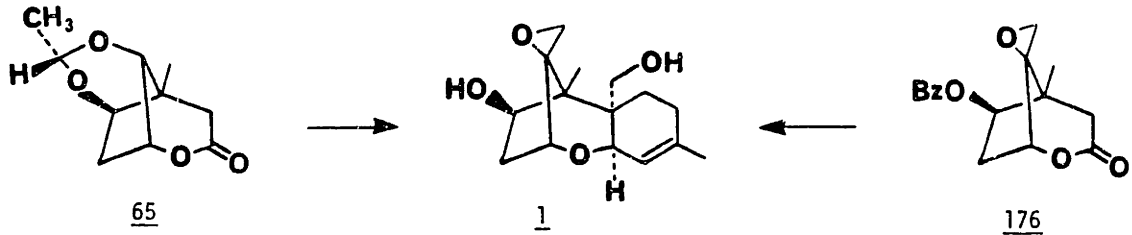


177

B,C-Ring Spiro Epoxide Analogues

At one point we considered the possibility that 176 might be a suitable alternative to 65 for use in our annelation sequence



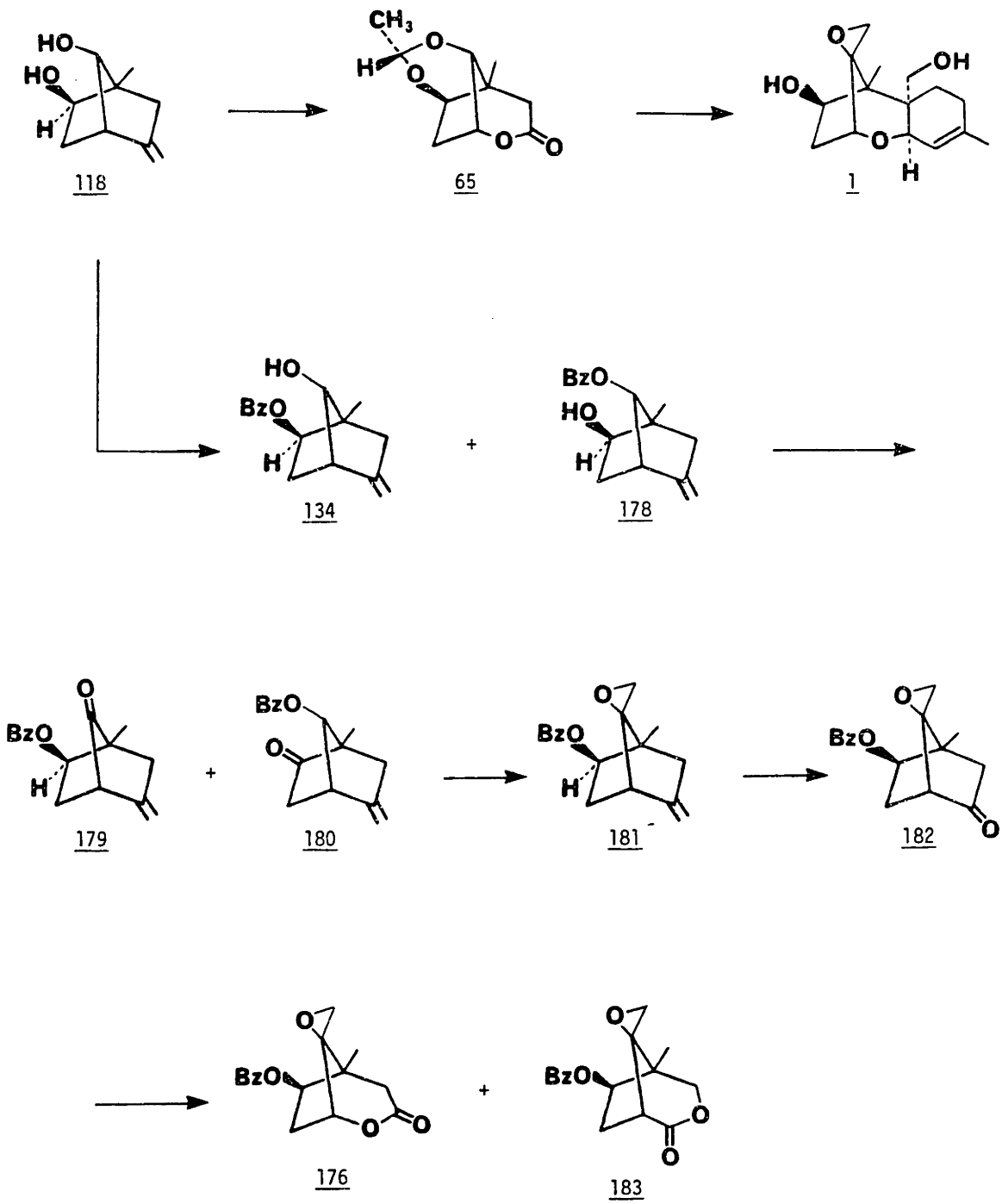
65 1 176

to verrucarol. Introduction of the 12,13-spiro epoxide at this stage of the synthesis would eliminate the necessity of protecting either the C.15 - OH or the 9,10 - double bond late in the synthetic sequence. An additional advantage would be that all synthetic intermediates could then be studied for structure-activity parameters. Further considerations (such as the reactivity of the spiro epoxide) together with the lowered regioselectivity observed in the Baeyer-Villiger oxidation of 182 to 176, as subsequently described, convinced us that the use of 176 in the annelation sequence would probably be impractical. Exploratory experiments, however, verified that epoxides 181, 182 and 176 were available through stereoselective synthesis. We therefore prepared each for *in vivo* cancer screens, with hope that these simple structures would possess significant biological activity.

Our synthesis of these epoxides began with the readily available diol 118 (see Chapter Three). Treatment of 118 (Scheme XXI) with 0.9 equivalents of benzoyl chloride (C_5H_5N, 0°C)[30] produced a 78:22 mixture, respectively, of monobenzoates 134 and 178 (87% yield based on consumed 118).[133]

(133) Treatment of 118 with one equivalent of TBDMSCl and excess imidazole in DMF afforded a 2:1 mixture of C.12 and C.4 monosilyl adducts together with some diprotected material.

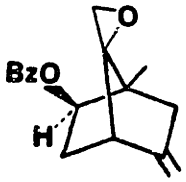
Scheme XXI


HO
HO
H
118
CH3
O
H
O
O
O
65
O
OH
HO
O
H
1
HO
BzO
H
134
+
BzO
HO
H
178
O
BzO
H
179
+
BzO
O
180
O
BzO
H
181
O
BzO
182
O
BzO
O
O
176
+
O
BzO
O
O
183

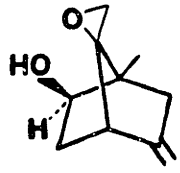
This mixture of 134 and 178 was not readily separable by TLC. Assignment of structure for these monobenzoates was based on the multiplicities observed in the 270 MHz ^{1}H NMR spectrum of the mixture (major isomer: δ 5.05 (ddd, J=1.5, 3.9, 6.8 Hz, 0.78 H, H.4); minor isomer: δ 4.90-4.93 (m, 0.22H, H_{12})).

Oxidation of the mixture with trifluoroacetic anhydride and dimethyl sulfoxide[72] (CH_2Cl_2, -60°C; then Et_3N; 85%) afforded the expected mixture of ketones 179 and 180. Although 179, mp 87-88.5°C, and 180, mp 77.5-78°C, proved separable by HPLC, it was convenient to postpone the separation until after the next transformation.

Treatment of 1.19g of this mixture of 179 and 180 with dimethylsulfonium methylide (2 equiv., 0°C, 105 min) yielded 820 mg of a mixture of epoxide 181 along with recovered 179 and 180, which was separated by using reverse phase HPLC. In this manner 85.3 mg (7%) of 180, 96.2 mg (8%) of 179 and 302.5 mg (25%) of



184

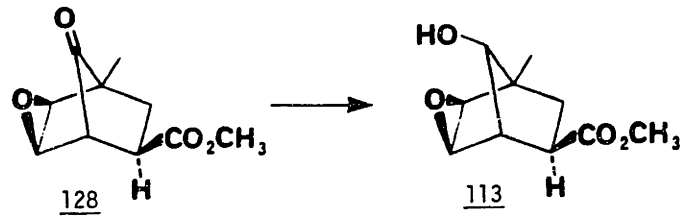


185

epoxide 181, mp 72.5-73.5°C, were obtained. In no instance was any isomeric epoxide 184, or an epoxide deriving from 180 ever obtained.

That a single epoxide was produced in this reaction was clear from high field ^1H NMR experiments. Molecular model analysis clearly indicates that the re face of the ketone carbonyl in 179 is more susceptible to nucleophilic attack.(134) In addition the O-H stretch in the infrared spectrum of the volatile debenzoylated derivative 185 (obtained as a byproduct in the reaction of ketone 179 with dimethyl sulfonium methylide or alternatively, by treatment of epoxide 181 with $NaOCH_3$ in CH_3OH) a sharp singlet at 3560 $cm^{(-1)}$, is consistent with intramolecular hydrogen bonding.(135)

(134) Similar stereoselectivity was observed in the $NaBH_4$ reduction of 128 (Chapter 3, page 67).



128 113

(135) Nakanishi, K.; Solomon, P.H. "Infrared Absorption Spectra", 2nd ed.; Holden-Day, Inc.: San Francisco, 1977; page 25.

Ozonolysis of 181 proceeded without complication to afford ketone 182, mp 120.5-122°C, in 76% yield. Much to our surprise, however, Baeyer-Villiger oxidation (MCPBA, $NaHCO_3$, CH_2Cl_2) of 182 afforded a 3:1 mixture of regioisomeric lactones 176 and 183. This result was surprising in that we had never before witnessed such a low degree of regioselectivity in the Baeyer-Villiger oxidations of a variety of related bicyclic ketones. Pure 176, mp 157.5-158.5°C, was obtained, however, by repeated fractional recrystallization from benzene.

Epoxides 176, 181 and 182 were tested for in vivo antitumor activity by the National Cancer Institute (the NCI preliminary antitumor screen performed under contract with A.D. Little, Inc.) and Bristol Laboratories (epoxides 181 and 182 only; P388 leukemic screen). The results summarized in Table V and Table VI reveal that these compounds do not mimic the in vivo activity of the trichothecenes against these tumor screens. It is unclear, however, whether these results are the consequence of a lack of activity at the molecular level or whether they simply reflect rapid metabolism or cellular transport difficulties. In vitro tests using cell free systems might help to clarify this matter.

Table V

Effect of Trichothecene Analogs on P388 Leukemia (Bristol Laboratories)

Material	Dose, IP mg/kg/inj	MST Days	Effect MST % T/C	Survivors Day 5(30)
Anguidine	3.6	13.5	169	6/6
	1.8	13.0	163	6/6
	0.9	12.0	150	6/6
	0.45	11.5	144	6/6
181	12	8.0	100	4/6
	6	9.0	113	6/6
	3	9.0	113	6/6
	1.5	8.0	100	5/6
182	12	8.0	100	6/6
	6	8.5	106	6/6
	3	8.0	100	5/5
	1.5	8.0	100	6/6
Control	Saline	8.0	-	9/9

Tumor inoculum: 10^6 ascites cells implanted ip.

Host : CDF_1 ♀ mice.

Tox : < 4/6 mice alive on D.5

Evaluation : MST = median survival time.

Effect : % T/C = (MST treated/MST control) x 100.

Criteria : % T/C≥ 125 considered significant antitumor activity.

Table VI

Effect of Trichothecene Analogues in NCI Tumor Screen.

Material	Dose Per Inj	Test Eval	% T/C	Survivors Day 5
181	3200	11.0	100	6/6
	1600	11.3	102	6/6
	800	11.1	100	6/6
	400	11.0	100	6/6
	200	10.9	99	6/6
182	3200	10.9	99	6/6
	1600	11.7	106	6/6
	800	11.0	100	6/6
	400	10.7	97	5/6
	200	11.3	102	6/6
176	1600	11.1	100	6/6
	800	10.4	94	6/6
	400	11.0	100	6/6
	200	11.4	103	6/6
	100	11.3	102	6/6

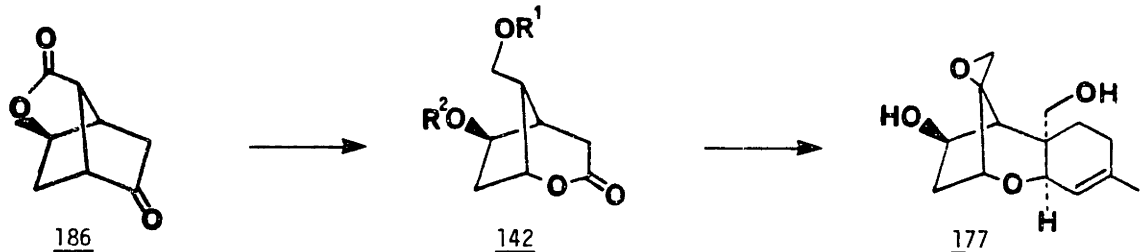
Studies on the Synthesis of 14-Desmethyl Verrucarol

We were also interested in the synthesis of trichothecene analogues which lacked the C.14 methyl group. We reasoned that this functionality might have little effect on the biological properties of the trichothecenes.(136) Moreover, if therapeutic agents based on the trichothecene ring system were to be

(136) We speculate that the C.14 methyl group of verrucarol may be an artifact of its biogenesis (see page 18) and not a necessary factor for the mechanism of action of this compound.

developed, such C.14-desmethyl analogues would be more easily synthesized than members of the natural series. Indeed, the presence of the C.14 methyl group had led to a number of complications in our synthesis of verrucarol.

By analogy to the work described in Chapters Two and Three of this thesis, we recognized that straightforward manipulations of prostaglandin precursor 186[137] would lead to a short synthesis of lactone 142 from which 177 would be prepared.

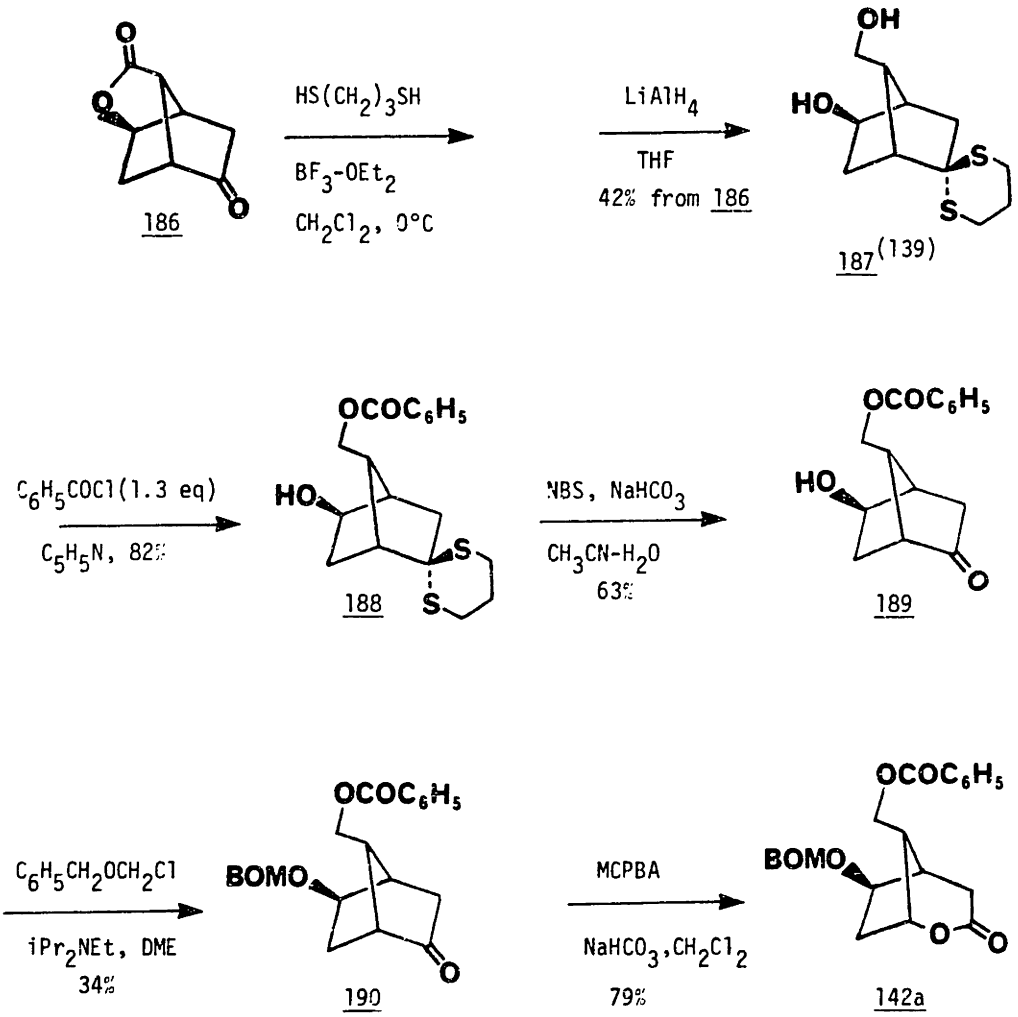


186 142 177

The first of these goals, namely the elaboration of 186 to lactones of general structure 142, was accomplished as outlined in Scheme XXII and Scheme XXIII. Our original plan was to subject 142a or 142b to the annelation sequence outlined in Chapter Two. Attempts to formylate these intermediates, however, by treatment with HCO_2tBu and tBuOK proved unsuccessful. These results in conjunction with the difficulties encountered in functionalizing 65 (Chapter Three) prompted us to concentrate our efforts on tetrahydrofuran 143, the simplest derivative of lactone 142.

(137) (a) Bindra, J.S.; Grodski, A.; Schaaf, T.K.; Corey, E.J. J. Am. Chem. Soc. 1973, 95, 7522;
(b) Peel, R.; Sutherland, J.K. J. Chem. Soc., Chem.Commun. 1974, 151;
(c) Beeley, N.R.A.; Peel, R.; Sutherland, J.K.; Holohan, J.J.; Mallion, K.B.; Sependa, G.J. Tetrahedron Supplement No. 9 1981, 37, 411.

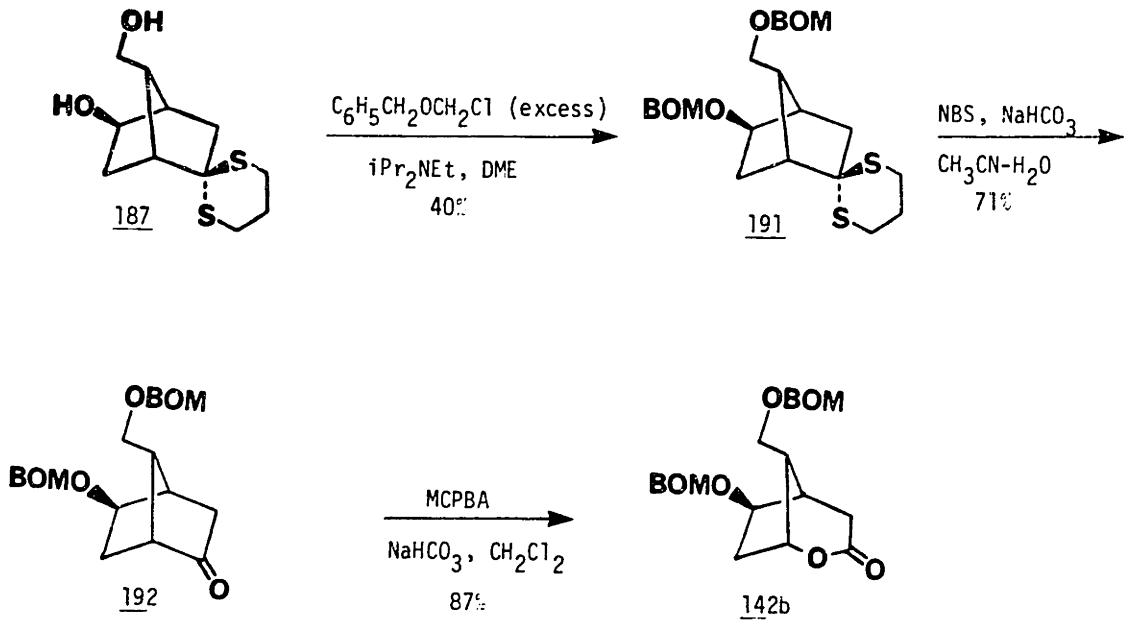
SCHEME XXII (138)



(138) The spectroscopic properties of these compounds (^{1}H NMR, IR, MS) were fully consistent with the assigned structures.

(139) mp 189°C; Anal. Calcd. for $C_{11}H_{18}O_2S_2$: C, 53.62; H, 7.36; S, 26.03. Found: C, 53.38; H, 7.71; S, 26.18

Scheme XXIII[138]



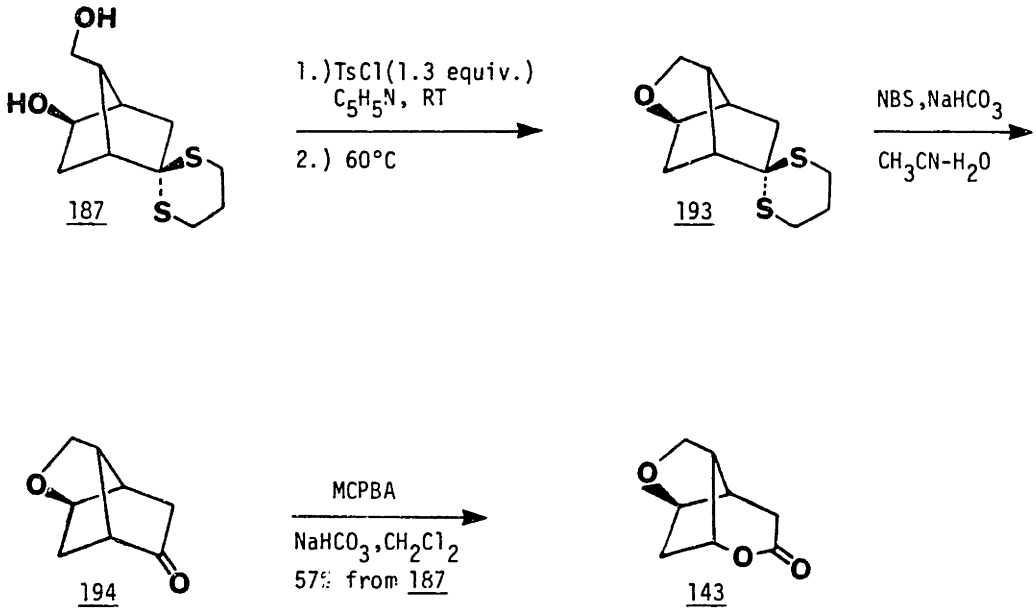
Lactone 143 was prepared from 187 as described in Scheme XXIV. Thus treatment of diol 187 with TsCl (1.3 equiv., room temperature, 1h; then 60°C, 12h) afforded the expected tetrahydrofuran 193, mp 112-113°C,[140] the dithiane group of which was removed with NBS in CH_3CN-H_2O ($NaHCO_3$) to afford ketone 194.[141] Baeyer-Villiger oxidation of this intermediate provided lactone 143,[142] mp 51-58°C, in 57% overall yield from 187.

(140) Anal. Calcd. for $C_{11}H_{16}OS_2$: C, 57.85; H, 7.06; S, 28.08. Found: C, 57.86; H, 7.10; S, 27.89.

(141) 2,4-Dinitrophenyl hydrazone: mp 210-212°C; High resolution mass spectrum. Calcd. for $C_{14}H_{14}N_4O_5$: 318.09642. Found: 318.09518.

(142) Anal. Calcd. for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.37; H, 6.49.

Scheme XXIV[138]



Our efforts to formylate lactone 143 were summarized in Chapter Three (page 80). Here, too, difficulties were encountered under a variety of conditions which afforded, at best, only traces (10% or less) of hydroxymethylene lactone 144.

Finally, however, treatment of the LDA derived enolate of 143 (-78°C) with 4.6 equivalents of t-butyl formate (10 min at -78° to 23°C) did afford hydroxymethylene lactone 144,(143), mp 139-140°C, but still only in 30% yield.

The problems encountered in formylating 142a,b and 143 thus parallel those discussed in Chapter Three for lactone 65. While the reasons for the surprising behavior of these compounds are not fully evident at present, it is clear that alternative functionalization procedures should be explored. The problem of annelation of lactone 65 was successfully addressed in Chapter Three. Application of such a Diels-Alder strategy to 142a or 142b may well provide a suitable solution to the synthesis of 14-desmethylverrucarol and other trichothecene analogues.

(143) Anal. Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.41; H, 5.71.

CHAPTER FIVE

EXPERIMENTAL PROCEDURES

Proton (^1H) NMR spectra were measured at 60 MHz on a Varian T60 instrument; at 90 MHz on a Jeol FXQ instrument; at 250 and 270 MHz on Bruker WM 250 and 270 instruments. Chemical shifts are reported in δ units using added tetramethylsilane or the 7.27 ppm resonance of residual chloroform as internal reference. Carbon (^{13}C) NMR spectra were measured at 22.5 MHz on a Jeol FXQ instrument and at 63.8 MHz on a Bruker instrument. ^{13}C chemical shifts are reported in δ_C units using the 77.0 ppm resonance of $CDCl_3$ as internal reference. NMR spectra were measured either in $CDCl_3$ or CCl_4 (at 60 MHz only). Assignment of proton and carbon resonances for all intermediates, where possible, are given numbers which correspond to the numbering of the trichothecene ring system (see Chapter One, page 13). 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}). Mass spectra were measured on a Varian MAT 44 instrument. High resolution mass spectra were provided by the Facility at MIT supported by NIH Grant RR0317 (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 analyses 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.

Reactions requiring anhydrous or oxygen-free conditions were conducted in oven-dried (120°C) glassware under an atmosphere of dry N_2 or Ar. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Methylene chloride, t-butyl alcohol and pyridine were freshly distilled from CaH_2. Toluene was distilled from sodium metal. Methanol and ethanol were distilled, respectively, from $Mg(OCH_3)_2$ and $Mg(OEt)_2$. Dimethyl sulfoxide was distilled from CaH_2 at reduced pressure.

Paraformaldehyde was dried for several days in a vacuum desiccator (0.3 mm Hg) over P_2O_5 prior to use. Methyl vinyl ketone, acetic anhydride and benzoyl chloride were freshly distilled prior to use. Boron trifluoride etherate, triethyl amine, diisopropyl amine, and ethyl formate were distilled from calcium hydride.

In vacuo refers to the vacuum achieved by a water aspirator attached to a Buchi rotary-evaporator. All non-volatile samples were pumped to constant weight at room temperature (0.3 mm) following the removal of solvent in vacuo.

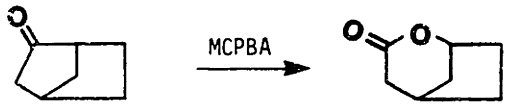
Analytical thin layer chromatography (TLC) was performed using 2.5 x 10 cm plates coated with 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Spots were visualized with long-wave UV light, and by staining with either iodine vapor, vanillin or phosphomolybdic acid. Preparative TLC was performed using 20 x 20 cm plates coated with 0.25-, 0.5-, 1.5- and 2.0-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were eluted from the adsorbents with Et_2O or acetone. Column chromatography was performed using

70-230 mesh SiO_2 (Merck) or by the method of Still[144] using 230-400 mesh SiO_2 (Merck). Chromatography solvents were distilled prior to use.

High pressure liquid chromatography (HPLC) was performed using a Waters 6000A pump with a differential refractometer detector (Model R401) in series with an ultraviolet absorbance detector (Model 440) measuring absorbance at 254 nm. Solvents (HPLC grade) were filtered and degassed prior to use.

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

Experimental Procedures for Chapter Two.

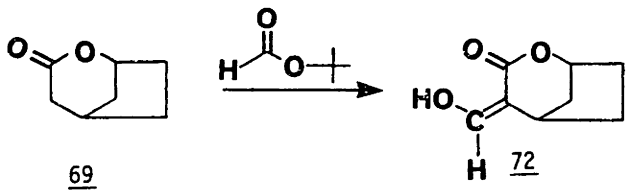


71 69

2-Oxabicyclo[3.2.1]octan-3-one (69)

To a suspension of 6.9 g of norcamphor 71 (62.7 mmol) and 10.4 g of $NaHCO_3$ (123 mmol) in 180 mL of dry CH_2Cl_2 was added 16.8 g of 90% pure MCPBA. Within 20 min the mixture began to reflux and was then cooled to 0°C. After being stirred for 2 additional hr, the reaction mixture was extracted with 150 mL of saturated aqueous NaCl. The organic phase was decanted and washed once with 100 mL of saturated aqueous $NaHCO_3$ and once with 100 mL of saturated aqueous $NaHSO_3$. The solution was filtered to remove insoluble material and washed again with 100 mL of saturated aqueous $NaHCO_3$, 100 mL of saturated $NaHSO_3$ and 100 mL of saturated $NaHCO_3$. The organic solution was filtered twice through cotton and the solvent concentrated in vacuo to give 7.75 g (98% yield) of 69. This material was of sufficient purity for use directly in subsequent transformations. A sample was, however, purified by distillation, bp 75-85°C (0.25 mm Hg); lit. bp 77°C (0.25 mm) [44b]: TLC (1:1 hexane-Et_2O) R_f 0.24; NMR (^1H, 60 MHz) δ 4.78 (br s, $W_{1/2}$ = 6 Hz, 1H, H_2), 1.20-2.95 (m, 9H); NMR

(^{13}C, 22.5 MHz) δ_C 170.4, 80.6, 40.2, 35.3, 32.1, 31.4, 28.8; IR (CCl_4) 2960, 2880, 1735, 1381, 1228, 1202.

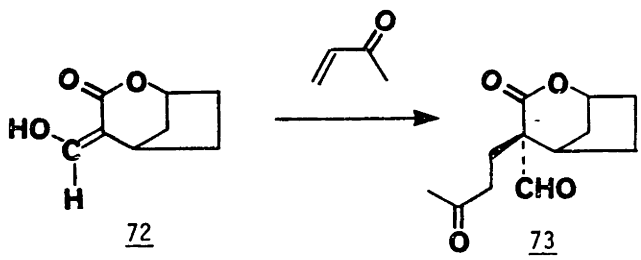


69 72

4(Z)-Hydroxymethylene-2-oxabicyclo[3.2.1]octan-3-one(72)

To a solution of 8.4 g (66.7 mmol) of lactone 69 and 20.5 mL (175 mmol) of t-butyl formate (45) in 20 mL of THF under N_2 at room temperature was added over 40 min 80 mL of a 0.85M solution of KOt-Bu in anhydrous t-butyl alcohol. (Vigorous bubbling was observed which we attribute to the evolution of carbon monoxide. In smaller scale experiments, a precipitate was formed; in this case, the mixture became a sludge.) After being stirred for 90 min, the reaction mixture was diluted with 100 mL of 1N aqueous HCl. The aqueous phase was separated and extracted twice with 50 mL of Et_2O. The combined organic solutions were then extracted five times with 100 mL portions of 1N aqueous NaOH. The combined aqueous extracts were acidified to pH < 3 by the dropwise addition of concentrated HCl and extracted five times with 100 mL portions of $CHCl_3$. The aqueous solution was then saturated with solid NaCl and extracted with 50 - 100 mL portions of $CHCl_3$ (800 mL total) until TLC analysis (Et_2O; R_f 0.42) indicated that the

extraction was complete. The combined organic extracts were filtered through a cotton plug and concentrated *in vacuo* to give 8.92 g (87%) of 72. This material was sufficiently pure for use directly in the next step. An analytical sample was prepared by crystallization from acetone to give white needles, mp 122-123°C: NMR (^{1}H, 60 MHz) δ 11.80 (d, J=12 Hz, 1H, OH), 7.00 (d, J=12 Hz, 1H), 4.90 (br m, $W_{1/2}$ = 6 Hz, 1H, H_2), 2.85 (br m, $W_{1/2}$ = 7 Hz, 1H, H_5), 1.3-2.3 (complex multiplet, 6H); NMR (^{13}C, 22.5 MHz) δ_C 159.3, 107.2, 80.7, 35.7, 35.4, 33.0, 32.1; IR (CH_2Cl_2) 2500 - 3500 (br), 3055, 2955, 2880, 1678 (C=O), 1618; Mass spectrum m/e 154 (parent ion), 125 (M-CHO). *Anal.* Calcd. for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found (average of two determinations): C, 62.62; H, 6.59.

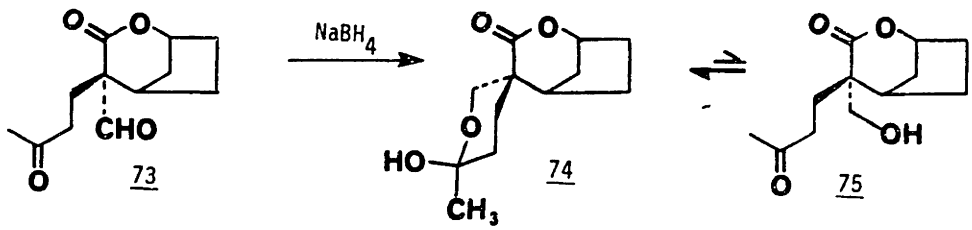


72 73

Michael adduct 73

To a solution of 576 mg of hydroxymethylene lactone 72 (3.74 mmol) and 0.6 mL (7.4 mmol) of freshly distilled methyl vinyl ketone in 15 mL of THF was added 0.4 mL of a 1.0M solution of t-BuOK in t-BuOH. The reaction mixture was stirred at room

temperature for 95 minutes and then was partitioned between 50 mL of Et_2O and 20 mL of saturated aqueous NaCl. The Et_2O extract was washed with 20 mL of saturated aqueous NaCl. The two aqueous washings were each extracted with a 30 mL portion of Et_2O. The combined Et_2O extracts were then concentrated <u>in vacuo</u>. The residue was dissolved in CH_2Cl_2, filtered through cotton and concentrated again <u>in vacuo</u>. In this manner, 824 mg (98%) of <u>73</u> a viscous, colorless liquid, was obtained. This material was used directly in the next step without further purification: TLC (Et_2O) R_f 0.40; NMR (^1H, 60 MHz) δ 9.85 (s, 1H), 4.88 (br m, $W_{1/2}$ = 7 Hz, 1H, H_2), 2.17 (s, 3H); IR (CCl_4) 1750 (C=O), 1722 (C=O), 1377, 1153; Mass spectrum m/e 224 (parent ion), 196 (M-CO). High resolution mass spectrum. Calcd. for $C_{12}H_{16}O_4$: 224.10486. Found: 224.10720.

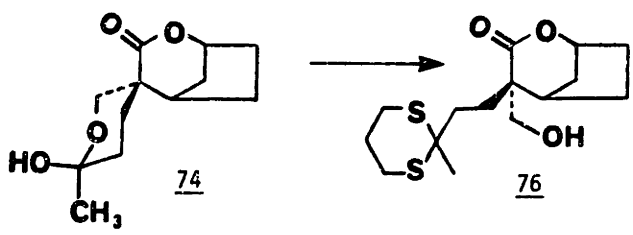


73 74 75

Hemiketal <u>74</u>

A stock solution of 1.18 g (31.2 mmol) of $NaBH_4$ in 70 mL of anhydrous EtOH was prepared. A solution of 3.17 g of Michael adduct <u>73</u> (14.1 mmol) in 40 mL of anhydrous EtOH was cooled in a methanol - ice water bath and maintained below -10°C. To this solution was then added 8.8 mL (1.1 hydride equiv.) of the $NaBH_4$

solution over 5 min. The reaction mixture was then allowed to gradually warm to room temperature, as the cooling bath warmed to ambient conditions. After 105 min, the mixture was partitioned between 100 mL of H_2O and 50 mL of $CHCl_3$. An emulsion formed which was broken by the addition of solid NaCl. The aqueous phase was then extracted two additional times with 50 mL portions of $CHCl_3$. The organic extracts were combined, filtered through cotton and concentrated *in vacuo*. The residue was crystallized by dissolution in and concentration from CCl_4. In this manner, 3.08 g (96%) of white crystals were obtained. A small amount of this material was recrystallized twice from acetone to give analytically pure 74, mp 133-134°C. The remainder was used directly in the next step. TLC (Et_2O) R_f 0.38; NMR (^1H, 60 MHz) δ 4.85 (br m, $W_{1/2}$ = 6 Hz, 1H, H_2), 4.46 (d, A of AB, J_{AB}=12 Hz, 0.6H, (60% hemiketal) H_{15a}), 3.6 - 4.0 (complex multiplet), 1.3 - 3.3 (complex multiplet), 2.18 (s, CH_3, methyl ketone), 1.45 (s, CH_3, hemiketal); IR (CH_2Cl_2) 3585, 3350 - 3650 (br), 2960, 1712 (C=O), 1455, 1378; Mass spectrum m/e 226 (parent ion), 208 (M-H_2O), 198 (M-CO), 196 (M - CHOH). *Anal.* Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.74: H, 8.17.

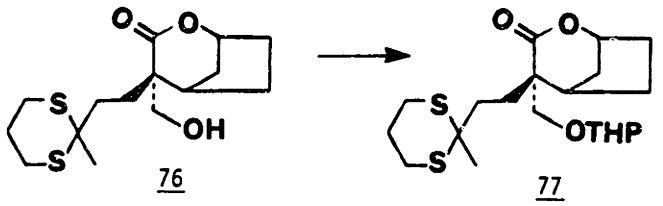


Dithiane 76

A slurry of 3.0 g (13.3 mmol) of hemiketal 74 in 3.0 mL of propane-1,3-dithiol (29.9 mmol) was cooled in an ice bath. Boron trifluoride etherate, 3.0 mL (24.3 mmol), was then added. (In other runs, stoichiometric amounts of dithiol and BF_3-OEt_2 were used with similar results.) The ice bath was removed and the resulting oil was stirred at room temperature for 20 minutes. The reaction mixture was then poured into 100 mL of Et_2O and washed with 50 mL of saturated aqueous NaCl. The Et_2O layer was concentrated in vacuo.

The residue was purified by flash chromatography using a 50 mm column containing 6 inches of silica gel packed with 6:1 hexane-Et_2O. The residue was mixed with 6:1 hexane-Et_2O and applied to the column. One liter of 6:1 hexane-Et_2O was run through the column. The product was then isolated by elution with Et_2O, collecting 50 mL fractions. Fractions 7-20 were combined and concentrated in vacuo to afford 4.0g (95%) of 76, which slowly crystallized. An analytical sample was prepared by recrystallization (two times) from acetone, mp 120-124°C: TLC (Et_2O) R_f 0.67, (1:1 hexane-Et_2O) R_f 0.13; NMR(^1H, 60 MHz) δ 4.84 (br s, $W_{1/2}$ = 6.4 Hz, 1H, H_2), 3.90 (dd, J=4, 12 Hz, 1H, H_{15a}), 3.47 (d, J=12 Hz, 1H, H_{15b}), 2.6 - 3.05 (multiplet, 6H), 1.60 (s, 3H, $-CH_3$); NMR (^{13}C, 22.5 MHz) δ_C 81.1, 64.5, 50.1, 48.9, 38.3, 34.7, 33.4, 31.7, 29.6, 27.6, 26.5, 25.1, 23.8; IR (CCl_4) 3200 - 3700 (br), 2955, 1720 (C=O), 1380, 1165; Mass spectrum m/e 316 (parent ion), 209 (M-$SCH_2CH_2CH_2SH$). Anal. Calcd. for $C_{15}H_{24}O_3S_2$: C, 56.93; H, 7.64; S, 20.26. Found: C,

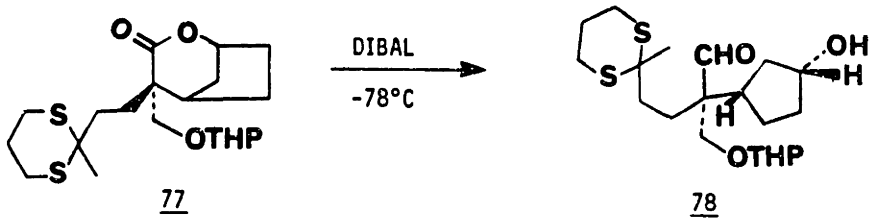
56.97; H, 7.78; S, 20.33 (average for two sulfur determinations on the same sample (21.15, 19.52)).



76 77

THP ether lactone 77

A solution of 400 mg of 76 (1.27 mmol) and 0.18 mL of dihydropyran (1.98 mmol) in 5 mL of CH_2Cl_2 was treated with a catalytic amount of p-toluenesulfonic acid. The mixture was stirred for one hour at room temperature. The product was purified by chromatographing the reaction mixture on two 2-mm preparative TLC plates (one development with 1:1 hexane-Et_2O) to yield 493 mg of 77 as a colorless, viscous liquid (97%): TLC (Et_2O) R_f 0.73, (1:1 hexane-Et_2O) R_f 0.23; NMR (^1H, 60 MHz) δ 4.67 (br m, $W_{1/2}$ = 6 Hz, 1H), 4.48 (br m, $W_{1/2}$ = 8 Hz, 1H), 3.85, 3.40 (AB, J_{AB}=10 Hz, 2H), 1.48 (s, 3H, CH_3); IR (CCl_4) 2945, 2872, 1730 (C=0), 1452, 1442, 1375; Mass spectrum m/e 400 (parent ion), 315 (M-C_5H_9O), 209, 161, 133, 85. High resolution mass spectrum. Calcd. for $C_{20}H_{32}O_4S_2$: 400.17421. Found: 400.17372.



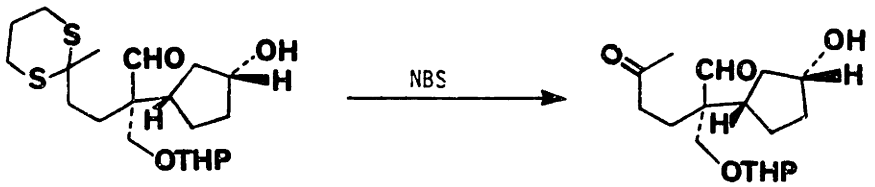
77 78

Dithiane aldehyde 78

A solution of 477 mg (1.19 mmol) of lactone 77 in 10 mL of anhydrous toluene under Ar was cooled to -78°C. Diisobutyl aluminum hydride, 1.6 mL of a 1M solution in hexane, was then dripped into the reaction mixture over ten minutes. The mixture was stirred for an additional 3 h at -78°C. Excess hydride was quenched by the dropwise addition of 1.0 mL of CH_3OH and the mixture stirred at -78°C for an additional 20 minutes. The mixture was then warmed to room temperature and 1-2 mL of H_2O added. The resulting gel was filtered through Celite using 150 mL of Et_2O. The organic washings were concentrated in vacuo.

The residue was purified by flash chromatography, utilizing a 30 mm column, eluting with 1:2 hexane-Et_2O and collecting 20 mL fractions to yield 499 mg ($\leq$87%) of aldehyde 78, a very viscous oil. Pumping under vacuum (0.3 mm Hg) for several days was not successful in removing entrapped solvent. Also obtained was 63 mg of diol (13%) produced by over reduction of aldehyde 78. Data

for 78: TLC (Et_2O) R_f 0.62; NMR (^1H, 60 MHz) δ 9.60 (s, 1H, CHO), 4.53 (br m, $W_{1/2}$ = 6.6 Hz, 1H), 4.17 (m, $W_{1/2}$ = 14 Hz, 1H), 3.23-4.0 (multiplet, 3 H); IR (CCl_4) 3100-3650, 2955, 2730, 1727 (C=O); Mass spectrum m/e 402 (parent ion), 317 (M-C_5H_9O), 211. High resolution mass spectrum. Calcd. for $C_{20}H_{34}O_4S_2$: 402.18986. Found: 402.18714.

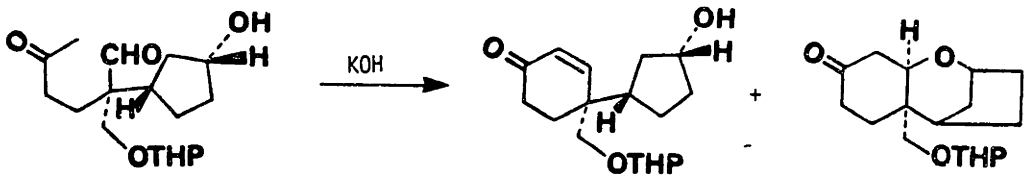


78 79

Ketone aldehyde 79

A solution of 499 mg of 78 (from the previous reaction) in 10 mL of CH_3CN was added over 5 minutes to a 0°C solution of 1.15 g of NBS (6 equiv.) and 1.3 mL of collidine (9.5 equiv.) in 20 mL of a 4:1 mixture of CH_3CN and H_2O. The resulting yellow solution was stirred at 0°C for 20 minutes. The mixture was then shaken with 20 mL of saturated aqueous Na_2SO_3. The organic phase was then sequentially washed with an additional 40 mL portion of saturated aqueous Na_2SO_3, three times with 25 mL portions of 5M aqueous cupric nitrate and two times with 40 mL portions of saturated aqueous NaCl. The resulting organics were filtered through cotton and concentrated in vacuo. A 50 mL portion of 1:1

hexane-CH_2Cl_2 was used to extract each set of aqueous washings. This was filtered through a cotton plug, combined with the initial product residue and concentrated in vacuo. The residue was purified by flash chromatography, utilizing a 30 mm column packed with Et_2O. The product was eluted with Et_2O, collecting 20 mL fractions to give 240 mg (74%) of pure 79: TLC (Et_2O) R_f 0.32; NMR (^1H, 60 MHz) δ 9.62 (s, 1H), 4.54 (br m, $W_{1/2}$ = 6 Hz, 1H), 4.32 (m, 1H), 3.2 - 4.05 (multiplet, 3H), 2.11 (s, 3H, CH_3); IR (CH_2Cl_2) 3120 - 3650, 2950, 2880, 2735, 1722 (C=O); Mass spectrum m/e 313 (M+1), 295 (M-OH). High resolution mass spectrum. Calcd. for $C_{17}H_{27}O_4$ (M-OH): 295.19093. Found: 295.19144.

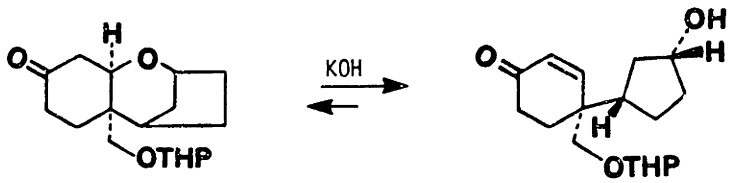


79 80 81

Cyclohexenone 80 and Michael adduct 81

A solution of 66 mg (0.21 mmol) of ketone aldehyde 79 in 5 mL of CH_3OH was purged with N_2. One mL of a 1.0M aqueous KOH solution was added with continuous N_2 purge. The mixture was stirred at room temperature for 200 minutes. The reaction

mixture was then poured into 10 mL of saturated aqueous NaCl and extracted three times with 15 mL portions of CH_2Cl_2. The organic extracts were combined and concentrated in vacuo. The residue was chromatographed on a 0.5-mm preparative TLC plate (one development with Et_2O) to give 55 mg (89%) of cyclohexenone 80 (R_f 0.50) and 7 mg (11%) of Michael adduct 81 (R_f 0.72).



81 80

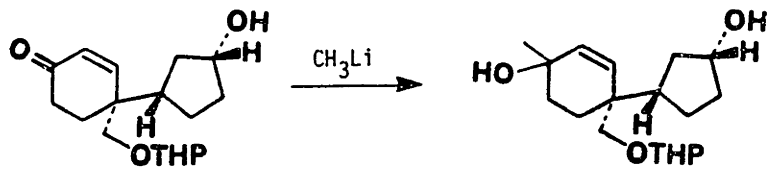
Equilibration of Michael adduct 81

Michael adduct 81, 19.2 mg (0.065 mmol), was dissolved in 3 mL of CH_3OH and the solution degassed with N_2. A 0.5 mL aliquot of a 0.8M aqueous KOH solution was then added and the mixture stirred at room temperature under N_2 for 26.5 h. The reaction mixture was then poured into 10 mL of saturated aqueous NaCl and extracted three times with 10 mL of CH_2Cl_2. The combined extracts were filtered through cotton and concentrated in vacuo. Analysis of the crude product by TLC, using the conditions as described above, revealed that both compounds, 80 and 81, were present. The product residue was chromatographed on a 0.25-mm preparative TLC plate (one development with Et_2O) to give 14 mg

(73%) of 80. Michael adduct 81 was not recovered from this experiment.

Data for 80: NMR (^{1}H, 60 MHz) δ 6.78 (d, J=10 Hz, 1H, H_{11}), 6.04 (d, J=10 Hz, 1H, H_{10}), 4.57 (br m, $W_{1/2}$ = 7.4 Hz, 1H), 4.27 (br m, $W_{1/2}$ = 14 Hz, 1H), 3.82, 3.32 (AB, J_{AB} = 10 Hz, 2H, $H_{15a,15b}$); IR (CH_2Cl_2) 3630, 3200 - 3600, 2955, 2880, 1685 (C=O); Mass spectrum m/e 294 (parent ion). High resolution mass spectrum. Calcd. for $C_{17}H_{26}O_4$: 294.18311. Found: 294.18089.

Data for 81: NMR (^{1}H, 60 MHz) δ 4.53 (br m, $W_{1/2}$ = 6 Hz), 4.30 (br m, $W_{1/2}$ = 6 Hz), 1.0 - 4.0 (complex multiplet); IR (CCl_4) 2955, 2880, 1722 (C=O); Mass spectrum m/e 294 (parent ion), 209 ($M-C_5H_9O$).



80 82

Tertiary allylic alcohols 82

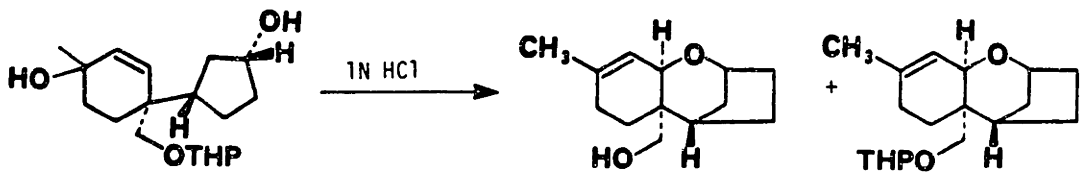
A solution of 170 mg (0.58 mmol) of cyclohexenone 80 in 15 mL of THF under N_2 was treated with 3 mL of a 1.3M ethereal solution of CH_3Li. The resulting mixture was stirred for 15 minutes at room temperature. Saturated aqueous $NaHCO_3$, 7 mL, was then added and the resulting mixture poured into 15 mL of

saturated aqueous NaCl. This was extracted three times with 20 mL portions of CH_2Cl_2. The combined extracts were filtered through cotton and concentrated *in vacuo*. The residue was chromatographed on a 2-mm preparative TLC plate (one development with 1:2 hexane-Et_2O and one development with 1:4 hexane-Et_2O) to give 138 mg (77%) of a mixture of isomeric methyl lithium adducts 82. The ratio of isomers was determined to be 3.2:1 by HPLC analysis (Waters μ Porasil analytical HPLC column (P/N 27477 S/N); 1:4 hexane-Et_2O; flow rate of 9.0 mL/min ($\sim$2300 psi)). The major isomer had a retention time of 3 min, K' = 6.0 and the minor isomer had a retention time of 7 min, K' = 13.4. Samples of each adduct were obtained by careful chromatography. Thus, 50 mg of the above mixture was rechromatographed on a 0.5-mm plate (developed four times with 1:3 hexane-Et_2O) to yield 32.2 mg of the higher R_f component and 9.3 mg of the lower R_f component.

Data for major isomer: NMR (^1H, 60MHz) δ 5.83, 5.43 (AB, J_{AB} = 10 Hz, 2H), 4.57 (br m, $W_{1/2}$ = 5 Hz, 1H), 4.30 (br m, $W_{1/2}$ = 24 Hz, 1H), 3.0-4.0 (complex multiplet, 4H), 1.30 (s, 3H, CH_3); Mass spectrum m/e 207, 178.

Data for minor isomer: NMR (^1H, 90 MHz) δ 5.81, 5.54 (AB, J_{AB} = 10 Hz, 2H), 4.53 (br m, $W_{1/2}$ = 6 Hz, 1H), 4.29 (br m, $W_{1/2}$ = 12 Hz, 1H), 3.2-4.0 (multiplet, 4 H), 1.28 (s, 3H, CH_3); Mass spectrum m/e 207, 178.

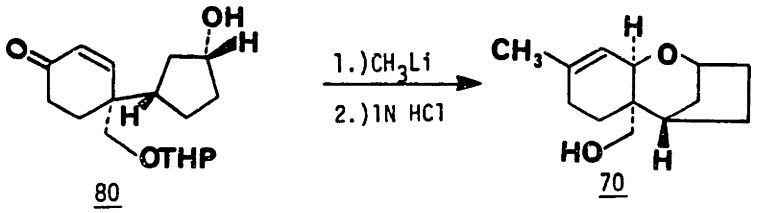
13,14-Dinor-15-hydroxy-trichothec-9-ene 70



82 70 195

Method A-From Isolated 82 (mixture)

A solution of 95 mg (0.31 mmol) of the 3:1 mixture of methyl lithium adducts 82 in 7 mL of THF was treated with three mL of 1N aqueous HCl. The mixture was stirred at ambient temperature for 18 h, then poured into 6 mL of saturated aqueous NaCl and extracted with Et_2O. The combined extracts were concentrated *in vacuo* and the residue chromatographed on a 0.5-mm preparative TLC plate (one development with Et_2O). In this manner, there was obtained 41.5 mg (64%) of 70 (R_f 0.48-0.64) and 11 mg (12%) of the C.15 tetrahydropyranylated derivative 195 (R_f 0.73-0.82).



80 70

Method B-Direct Conversion from Enone 80

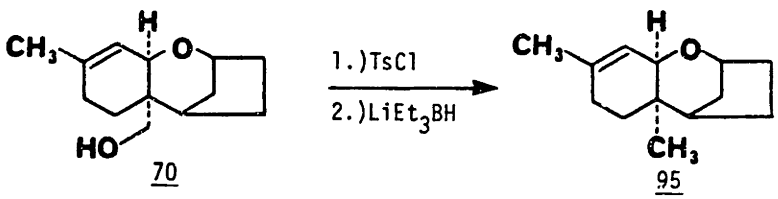
A solution of 30 mg (0.10 mmol) of cyclohexenone 80 in 5 mL of THF under N_2 was treated with 0.6 mL of a 1.3M ethereal solution of CH_3Li (7.8 equiv.) as described above for the preparation of 82. Excess CH_3Li was then quenched by the addition of 15 mL of 1N aqueous HCl; the resulting two phase suspension was then stirred for 280 minutes. This mixture was then poured into 7 mL of saturated aqueous NaCl and extracted three times with 15 mL of CH_2Cl_2. The extracts were combined and concentrated in vacuo. The residue was chromatographed on a 0.25-mm preparative TLC plate (one development with Et_2O) to yield 16 mg (77%) of 70. A significant amount of 195 is obtained if insufficient aqueous acid or short hydrolysis times are employed. Even in the above case, a small amount of this THP ether was detected by analytical TLC.

Method C - From Purified Tertiary Allylic Alcohols 82a and 82b

An isomerically pure sample of the major CH_3Li adduct 82a was treated as described in Method A to afford, after chromatography, 55% of 70 and 34% of 195.

An isomerically pure sample of the minor CH_3Li adduct 82b was treated in a similar fashion to afford both 70 and 195 (analytical TLC determination).

Data for 70: NMR (^1H, 250 MHz) δ 5.32 (br d, J=4.9 Hz, 1H, H_{10}), 4.27 (br m, $W_{1/2}$ = 9 Hz, 1H, H_2), 3.27-3.40 (m, 3H, $H_{15a,15b}$ and H_{11}), 2.27 (t, J=5.25 Hz, 1H), 2.13 (br d, J=12.1 Hz, 1H), 1.66 (s, 3H, CH_3), 1.3-2.03 (multiplet, 8H), 1.10 (ddd, J=2.56, 5.15 and 12.1 Hz, 1H); NMR (^{13}C, 22.5 MHz) δ_C 139.9 (s, C.9), 120.2 (d, C.10), 76.0 (C.2), 66.6 (d, C.11), 62.0 (q, C.15), 38.4, 33.2, 28.1, 24.1, 23.4, 21.7; IR (CH_2Cl_2) 3620, 3300-3600, 2960, 2945, 2878, 1675, 1609; Mass spectrum m/e 208 (parent ion), 193, 177 (M-CH_2OH), 140. High resolution mass spectrum. Calcd. for $C_{13}H_{20}O_2$: 208.14633. Found: 208.14715.



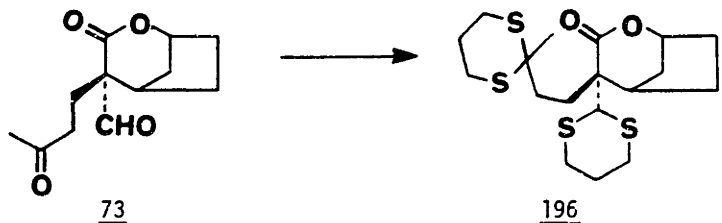
70 95

13,14--Dinor-trichothec-9-ene 95

A solution of 22 mg of 70 (0.106 mmol) in 3 mL of pyridine was cooled to 0°C and 89 mg (0.47 mmol) of p-toluenesulfonyl chloride was added. This mixture was stirred for 6.5 h during which time the reaction mixture was allowed to gradually warm to room temperature. The reaction mixture was then concentrated to a volume of approximately 1.0 mL in vacuo, poured into 10 mL of 1N aqueous HCl and extracted with 15 mL of Et_2O. The Et_2O extract was washed with 10 mL of 1N aqueous HCl. The combined aqueous washings were extracted twice with 15 mL portions of Et_2O. The Et_2O extracts were combined and concentrated in vacuo. The product residue was chromatographed on a 0.25-mm preparative TLC plate (one development with 1:2 hexane-Et_2O) to yield 24.2 mg (63%) of tosylate: NMR (^1H, 60 MHz) δ 7.73, 7.30 (AB, J_{AB} = 8 Hz, 4H), 5.12 (br m, $W_{1/2}$ = 10 Hz, 1H, H_{10}), 4.10 (br m, $W_{1/2}$ = 8 Hz, 1H, H_2), 3.60 (s, 2H, $H_{15a,15b}$) 3.27 (br m, $W_{1/2}$ = 10 Hz, 1H, H_{11}), 2.47 (s, 3H, CH_3), 1.65 (s, 3H, CH_3).

To a 65°C solution of 24.2 mg of the above tosylate (0.067 m mol) in 7 mL of THF, degassed with Ar, was added dropwise 0.7 mL of a 1.0M solution of $LiEt_3BH$ in THF. This mixture was stirred at 65°C for 5 h. The solution was then cooled and 0.5 mL of CH_3OH was added. The resulting mixture was concentrated in vacuo. The residue was chromatographed on a 0.25-mm preparative plate (one development with 1:2 hexane-Et_2O) to give 8.0 mg of 95 (62%): NMR (^1H, 250 MHz) δ 5.33 (dm, J=4.8 Hz, 1H, H_{10}), 4.27 (br m, $W_{1/2}$= 9.3 Hz, 1H, H_2), 3.51 (d, J=4.8 Hz, 1H, H_{11}), 1.67 (s, 3H, CH_3), 1.5-2.25 (complex multiplet, 9H), 1.05 (dd, J=2.2,

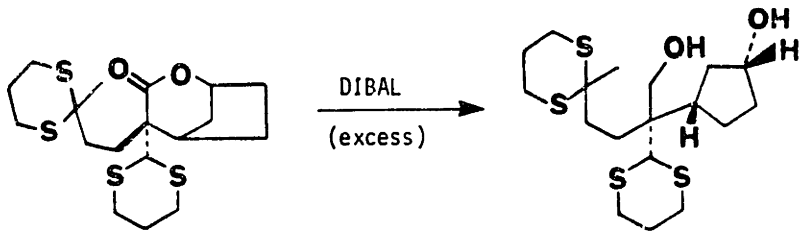
4.8 Hz, 1H), 1.00 (dd, J=2.5, 5.0 Hz, 1H), 0.74 (s, 3H, CH_3, C_{15}); NMR (^{13}C, 63.8 MHz) δ_c 139.3 (C.9), 120.1 (C.10), 76.1 (C.2), 70.3 (C.11), 44.9, 33.7, 33.5, 28.2; IR (neat) 3010, 2960, 2910, 2865, 1675, 1465, 1445, 1378; Mass spectrum m/e 192 (parent ion), 177 ($M-CH_3$), 164, 149, 126, 109. High resolution mass spectrum. Calcd. for $C_{13}H_{20}O$: 192.15141. Found: 192.15029.



73 196

Bis dithiane 196

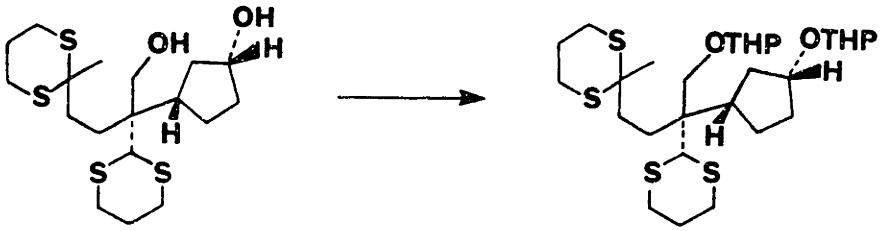
A mixture of Michael adduct 73, 700 mg (3.1 mmol), and 1.5 mL (14.9 mmol) of propane-1,3-dithiol was treated with 1.5 mL (12.1 mmol) of BF_3-OEt_2. The resulting slurry was maintained at ambient temperature with occassional manual mixing. After 45 minutes, this mixture was applied directly to 5" of 230-400 mesh SiO_2 in a 30 mm column. Elution with 1:1 hexane-Et_2O thus afforded 1.26 g (100%) of 196. NMR (^1H, 60 MHz) δ 4.70 (br m, $W_{1/2}$ = 6 Hz, 1H, H_2), 4.40 (s, 1H, H_{15}), 1.40 (s, 3H, CH_3); Mass spectrum m/e 404 (parent ion), 329, 298, 243, 119.



196 197

Diol 197

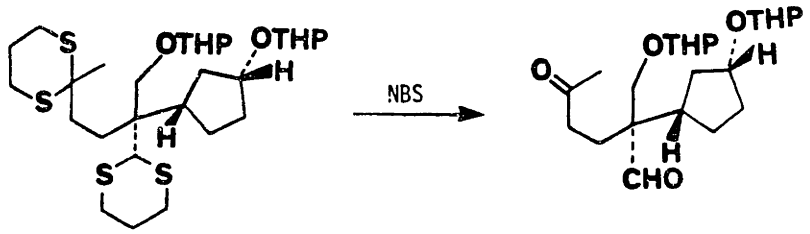
To a 0°C solution of 1.26 g (3.1 mmol) of lactone 196 in 25 mL of dry THF under N_2 was added dropwise 14 mL (9.8 mmol) of a 0.7M DIBAL solution in hexane. The mixture was allowed to warm to room temperature and stirred for 1.0 h. Excess DIBAL was quenched by the dropwise addition of methanol. The resulting sludge was partitioned between 1N aqueous HCl and Et_2O. The Et_2O extract was then washed four times with 1N aqueous HCl; each aqueous wash was back extracted with three 20 mL portions of Et_2O. The combined organic extracts were concentrated in vacuo. The residue was dissolved in CH_2Cl_2, filtered through cotton and again concentrated in vacuo to yield 1.12 g (89%) of 197: NMR (^1H, 60 MHz) δ 4.2 - 4.45 (m, 2H), 3.90 (br s, 2H), 3.72 (br m, $W_{1/2}$ = 6 Hz, 1H), 1.48 (s, 3H, CH_3).



197 198

THP ether 198

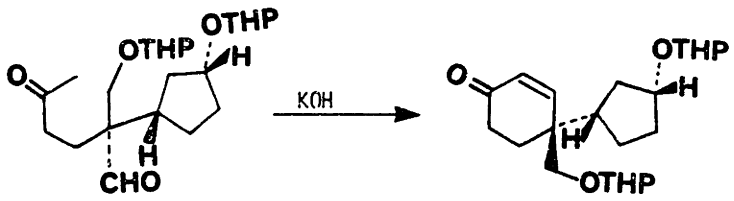
To a solution of 1.0 g (2.45 mmol) of diol 197 in 30 mL of CH_2Cl_2 and 0.7 mL (7.7 mmol) of dihydropyran was added three small crystals of pTsOH. The mixture was stirred at ambient temperature for 45 minutes and then poured into 20 mL of saturated aqueous NaCl. The aqueous layer was then extracted with 25 mL of CH_2Cl_2. The combined organics were filtered through cotton and concentrated in vacuo to give 198 which was used directly in the next step. NMR (^1H, 60 MHz) δ 4.82 (br m, $W_{1/2}$ = 8 Hz, 1H), 4.54 (br m, $W_{1/2}$ = 8 Hz, 2H), 4.33 (s, 1H); IR (neat) 2930, 2860, 1450, 1435, 1418, 1345.



198 199

Keto-aldehyde 199

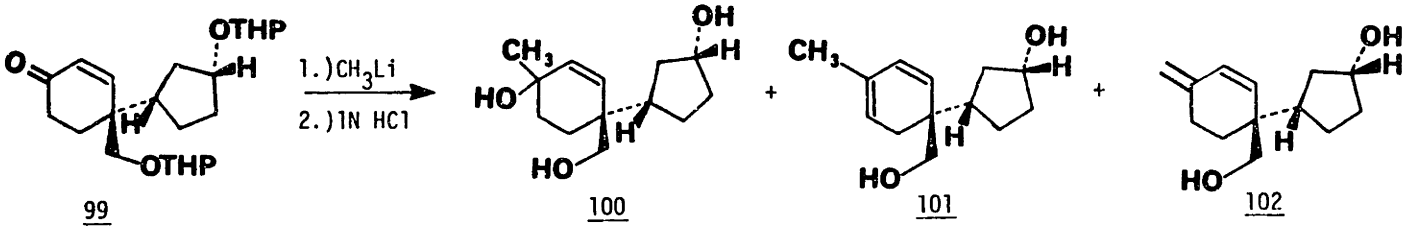
A solution of 198 (all of the material prepared in the previous experiment) in 20 mL of CH_3CN was added to a 0°C solution of 6.0 g of NBS (33.7 mmol) and 5.5 mL (42 mmol) of collidine in 40 mL of 4:1 CH_3CN-H_2O. This mixture was stirred for 20 minutes. Excess NBS was then quenched by the addition of 60 mL of saturated aqueous Na_2SO_3. The resulting mixture was then extracted with 100 mL of 1:1 hexane-CH_2Cl_2. The organic extract was washed twice with 25 mL portions of 5M cupric nitrate and twice with 25 mL of saturated aqueous NaCl. Each of the aqueous washings was extracted with 40 mL of 1:1 hexane-CH_2Cl_2. The combined organics were filtered through cotton and concentrated *in vacuo*. The product was purified by flash chromatography (40 mm column, elution with 1:1 hexane-Et_2O, 35 mL fractions). Fractions 9-20 afforded 510 mg of 199 as a viscous oil (53% from 197): NMR (^1H, 60 MHz) δ 9.50 (s, 1H), 4.50 (br m, $W_{1/2}$ = 8 Hz, 2H), 2.05 (s, 3H, CH_3).



199 99

Cyclohexenone 99

A solution of 500 mg (1.2 mmol) of 199 in 25 mL of CH_3OH was degassed with Ar. A solution of 226 mg of KOH (4.0 mmol) in 4 mL of H_2O was then added with continuous Ar purge. The reaction mixture was stirred at ambient temperature for a total of 10 minutes and then poured into 20 mL of saturated aqueous $NaHCO_3$. This mixture was then extracted three times with 30 mL portions of CH_2Cl_2 and the combined extracts concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, filtered through cotton and again concentrated *in vacuo* to give 430 mg (92%) of 99: NMR (^1H, 60 MHz) δ 6.73 (dd, J=4, 11 Hz, 1H, H_{11}), 5.95 (d, J=11 Hz, 1H, H_{10}), 4.58 (br m, $W_{1/2}$ = 9.5 Hz, 1H), 3.2-4.4 (complex multiplet), 1.2-2.6 (complex multiplet); IR (neat) 3020, 2935, 2860, 1675 (C=O), 1610; Mass spectrum m/e 264, 211, 193, 108.



99 100 101 102

Triol 100 and Cyclohexadienes 101 and 102

A solution of 97 mg (0.26 mmol) of 99 in 10 mL of THF was purged with N_2. Excess methyl lithium in Et_2O (1.3M, 6 equiv.) was then added. The mixture was stirred for 15 minutes at room temperature and then quenched with 4 mL of 1N aqueous HCl. This mixture was stirred for 24 h, then neutralized by the addition of 5 mL of saturated aqueous $NaHCO_3$. The resulting mixture was extracted three times with 10 mL of CH_2Cl_2. The combined extracts were concentrated in vacuo and the residue chromatographed (0.5-mm preparative TLC plate, one development with Et_2O). The major, UV active band (R_f 0.27-0.42) afforded 30.5 mg (57%) of a 2:1 mixture, respectively, of 101 and 102 (ratio determined by NMR integration). This mixture was inseparable by TLC.

Data for the mixture of 101 and 102: NMR (^1H, 250 MHz) 101: δ 5.84 (d, J=9.9 Hz, 0.67H), 5.45 (d, J=9.9 Hz, 0.67H), 4.29 (br m, 0.67H, H_2); 3.42 (br s, 1.33H); 102: δ 6.22 (d, J=9.9 Hz, 0.33H), 5.59 (d, J=9.9 Hz, 0.33H), 4.82 (br m, $W_{1/2}$ = 4 Hz, 0.33H), 4.79 (br m, $W_{1/2}$ = 4 Hz, 0.33H), 4.29 (br m, 0.33H, H_2),

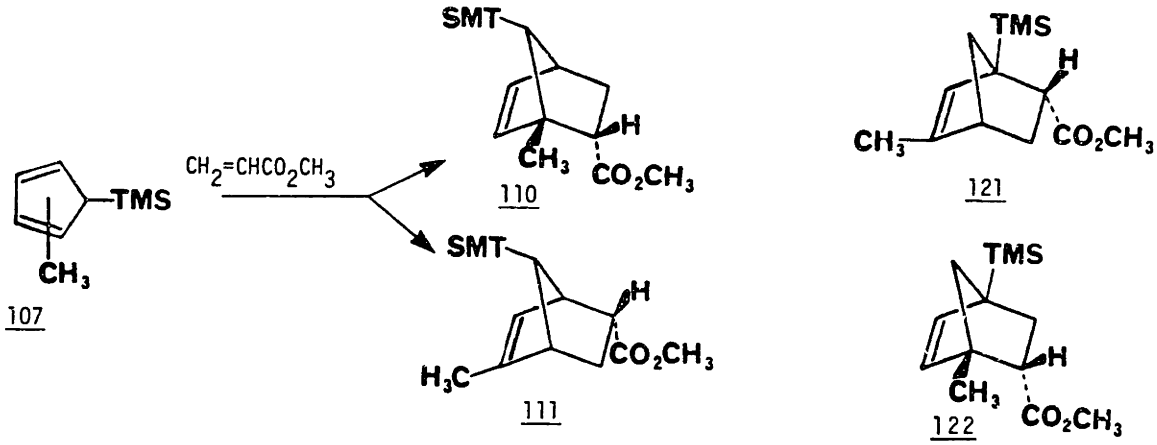
3.53 (br s, 0.67H); IR (neat) 2600-3680, 3010, 2930, 2860, 1705, 1655, 1630, 1590, 1430; Mass spectrum m/e 208 (parent ions), 180, 159, 105.

In a separate experiment, the methyl lithium adduct mixture was treated with 1N aqueous HCl for 190 minutes. In this instance, no diene (101 or 102) was detected. However, 38% of 100 was isolated along with other compounds tentatively identified as mono-THP ethers of 100. Data for 100: NMR (^{1}H, 60 MHz) δ 6.35 (d, J=9 Hz, 1H,), 6.10 (d, J=9 Hz, 1H), 4.22 (br m, $W_{1/2}$ = 9 Hz, 1H), 2.8-3.8 (complex multiplet), 1.28 (s, 3H, CH_3), 1.1-2.2 (complex multiplet).

Dehydration of triol 100 to dienes 101 and 102

To a solution of 17 mg (75 umol) of triol 100 in 3 mL of THF was added one mL of 1N aqueous HCl. The resulting mixture was stirred at room temperature for 22 h, then neutralized with 0.5 mL of saturated aqueous $NaHCO_3$ and concentrated in vacuo. The remaining aqueous solution was extracted with 10 mL of CH_2Cl_2 and this extract concentrated in vacuo. The product residue was chromatographed on 1/2 of a 0.25-mm preparative TLC plate (one development with 1:1 hexane-Et_2O and one development with Et_2O) to afford 10.6 mg (68%) of a 2:1 mixture of 101 and 102.

Experimental Procedures for Chapter Three.



Bicyclo[2.2.1]2-methyl-5(R^*)-carbomethoxy-7(R^*)-trimethylsilyl-hept-2-ene 111 and Bicyclo[2.2.1]1-methyl-6(R^*)-carbomethoxy-7(S^*)-trimethylsily-hept-2-ene 110

To a -78°C solution of 15 mL (0.17 mol) of methyl acrylate in 250 mL of anhydrous CH_2Cl_2 under Ar was added 22 mL (0.18 mol) of BF_3-OEt_2. The mixture was stirred for 15 min and then 22.9 g (0.15 mol) of (methylcyclopentadienyl)trimethyl silane 107[63] was slowly added over 30 min. The reaction mixture was stirred for 2 h at -78°C, the cold bath was then removed and the mixture slowly brought to ambient temperature.

The reaction mixture was poured into 200 mL of H_2O and the mixture neutralized, with stirring, by the careful addition of solid Na_2CO_3. The aqueous portion was then extracted twice with 100 mL portions of CH_2Cl_2. The combined organic extracts were concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, filtered through cotton and again concentrated *in vacuo* to yield

31.7 g (89%) of an 82:18 mixture, respectively, of 111 and 110 (NMR analysis). These adducts were inseparable by conventional SiO_2 chromatography and this mixture was routinely used directly in the next reaction.

Pure samples of each adduct were obtained by HPLC using a Waters semi-preparative reverse phase C_{18} column, P/N 84176 (1:1 H_2O-CH_3CN, 6 mL/min). Fifteen injections of 30-40 mg of the mixture of 110 and 111 were separated. Each sample was loaded onto the column either neat or dissolved in a minimum amount of CH_3CN. One recycle was employed for each chromatographic run. The products were isolated from the eluant by extraction with pentane. In this manner was obtained 178 mg of pure 111 ($t_{retention}$= 41.8 min; K'=40.8) and 46 mg of 110 ($t_{retention}$= 38.7 min; K'=37.7) which was uncontaminated with 111 but contaminated with two other substances. A sample of the fraction containing 110 was rechromatographed using the above HPLC conditions (6 recycles) to afford 6.5 mg of 110, 1.5 mg of a substance tentatively identified as 121 and 1.5 mg of a substance tentatively identified as 122.

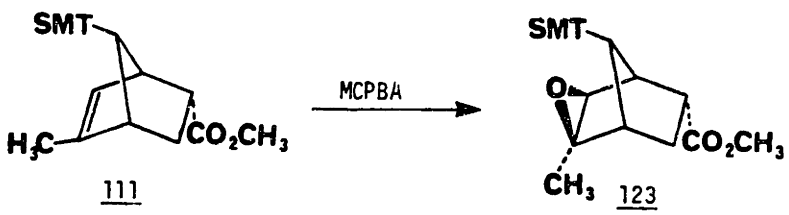
Data for 111: TLC (2% Et_2O in hexane) R_f 0.45; NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 5.35 (br m, $W_{1/2}$ = 6.5 Hz, 1H), 3.62 (S, 3H, OCH_3), 3.16 (br m, $W_{1/2}$ = 6.5 Hz, 1H), 2.98 (m, $W_{1/2}$ = 9.9 Hz [J=4.2, 9.2 Hz], 1H), 2.70 (br d, $W_{1/2}$ = 6.5 Hz [J=3.7 Hz], 1H), 1.90 (ddd, J=3.7, 9.2, 11.6 Hz, 1H), 1.74 (d, J=1.8 Hz, 3H, CH_3), 1.48 (dd, J=4.2, 11.6 Hz, 1H), 0.90 (br s, $W_{1/2}$=3.3 Hz, 1H), -0.08 (s, 9H); IR (CH_2Cl_2) 3045, 2955, 1725, 1432; Mass spectrum m/e 223 ($M-CH_3$), 207 ($M-OCH_3$), 159, 152.

High resolution mass spectrum. Calcd. for $C_{12}H_{19}O_2Si$ ($M-CH_3$): 223.11543. Found: 223.11371.

Data for 110: TLC (2% Et_2O in hexane) R_f 0.45; NMR (^1H, 250 MHz, $CDCl_3$, [spin decoupling]) δ 6.07 (dd, J=2.9, 5.5 Hz, 1H), 5.67 (d, J=5.5 Hz, 1H), 3.63 (s, 3H, OCH_3), 2.90 (m, $W_{1/2}$ = 9.4 Hz [J=2.9, 3.7 Hz], 1H), 2.70 (dd, J=4.4, 9.2 Hz, 1H), 2.05 (ddd, J=3.7, 9.2, 11.7 Hz, 1H), 1.50 (s, 3H, CH_3), 1.49 (dd, J=4.4, 11.7 Hz, 1H), 0.85 (br s, $W_{1/2}$=2.9 Hz, 1H); IR (CH_2Cl_2) 3040, 2950, 2840, 1720 (C=O), 1600, 1415.

Data for 122: NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 6.07 (d, J=5.5 Hz, 1H), 5.85 (d, J=5.5 Hz, 1H), 3.63 (s, 3H, OCH_3), 2.70 (dd, J=4.4, 9.2 Hz, 1H), 2.06 (dd, J=9.2, 11.8 Hz, 1H), 1.46 (s, 3H, CH_3), 1.46 (dd, [J=4.4, 11.8 Hz], 1H), 0.05 (s 9H).

Data for 121: NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 5.35 (br m, $W_{1/2}$=5.1 Hz, 1H), 3.60 (s, 3H, OCH_3), 2.92 (dd, J=4.0, 9.2 Hz, 1H), 2.71 (br m, $W_{1/2}$=7.6 Hz [J=4.0 Hz], 1H), 1.93 (ddd, J=4.0, 8.8, 11.4 Hz, 1H), 1.81 (d, J=1.8 Hz, 3H, CH_3), 0.06 (s, 9H).

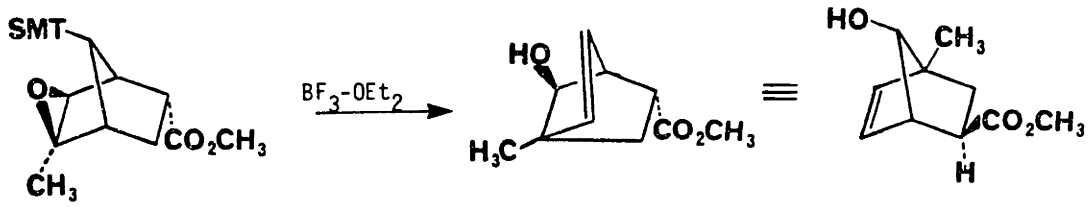


111 123

Bicyclic epoxide 123

A solution of 39 mg (0.16 mmol) of pure 111, 33 mg (0.39 mmol) of $NaHCO_3$ and 47 mg of 70% MCPBA (0.19 mmol) in 2.0 mL of anhydrous CH_2Cl_2 was stirred for 2 d at room temperature. The mixture was then filtered through a glass fritted funnel and the resulting solids washed with CH_2Cl_2. The filtrate was concentrated in vacuo and the residue chromatographed on a 0.25-mm preparative TLC plate (one development with 6:1 hexane-Et_2O) to yield 24.5 mg (59%) of epoxide 123 (R_f 0.75-0.90); 7.5 mg (19%) of 111 (R_f 0.90-0.95) and 41 mg of a white solid (R_f 0.20-0.75). This latter material was dissolved in 7 mL of CH_2Cl_2 and washed with 30 mL of a 5:1 saturated aqueous Na_2SO_3-saturated aqueous NaCl mixture. This aqueous washing was extracted with 10 mL of CH_2Cl_2. The combined organic portions were filtered through cotton and concentrated in vacuo to afford 4.8 mg (15%) of 113.

Data for 123: TLC (6:1 hexane-Et_2O) R_f 0.57; NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 3.68 (s, 3H, OCH_3), 2.92 (br s, $W_{1/2}$ = 2.2 Hz, 1H), 2.88 (m, [J=4.4 Hz], 1H), 2.85 (m, J=4.0, 4.4, 9.6 Hz, 1H), 2.38 (br d, J=4.0 Hz, 1H), 1.91 (dd, J=4.0, 12.9 Hz, 1H), 1.79 (ddd, J=4.0, 9.6, 12.9 Hz, 1H), 1.44 (s, 3H, CH_3), 0.35 (br s, $W_{1/2}$=2.9 Hz, 1H), -0.03 (s, 9H); IR (CH_2Cl_2) 2955, 2885, 1725(C=O), 1415; Mass spectrum m/e 239 ($M-CH_3$), 207, 195, 179. High resolution mass spectrum. Calcd. for $C_{13}H_{22}O_3Si$: 254.13382. Found: 254.13319.



123 124

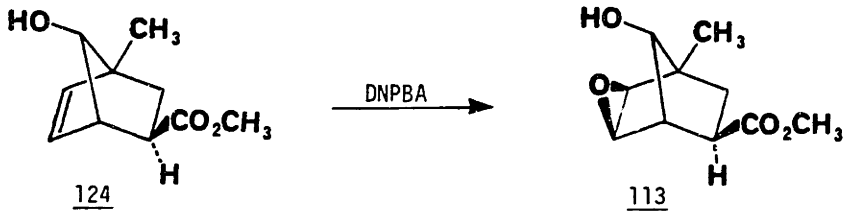
Bicyclo[2.2.1]1-methyl-5(R^*)-carbomethoxy-7(S^*)-hydroxy-hept-2-ene 124(145)

To a 0°C solution of 39 mg (0.15 mmol) of 123 in 1.5 mL of CH_2Cl_2 was added 0.019 mL (0.15 mmol) of BF_3-OEt_2.(66) The resulting mixture was stirred for 45 min, then diluted with 10 mL of saturated aqueous $NaHCO_3$ and extracted twice with 10 mL of CH_2Cl_2. The combined extracts were concentrated in vacuo. The residue was chromatographed on a 0.5-mm preparative TLC plate (1:1 hexane-Et_2O) to afford 21 mg (75%) of 124: NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 6.11 (br m, [J=2.9, 5.5 Hz], 1H, H_3) 5.88 (d, J=5.5 Hz, 1H, H_4), 3.79 (br d, J=11.0 Hz, 1H, H_{12}), 3.71 (s, 3H, OCH_3), 2.99 (br m, $W_{1/2}$=6.5 Hz [J=2.9 Hz], 1H, H_2), 2.22 (dd, J=4.8 and 10.3 Hz, 1H, H_{11}), 1.81 (d, J=11.0 Hz, 1H, OH), 1.80 (dd, J=4.8, 12.1 Hz, 1H, $H_{6\beta}$), 1.48 (dd, J=10.3, 12.1 Hz, 1H, $H_{6\alpha}$), 1.28 (s, 3H, CH_3); IR (CH_2Cl_2) 3675, 3550, 3045,

(145) This experiment was performed by W.R. Roush.

2955, 1726 (C=O), 1602, 1420; Mass spectrum m/e 165 (M-OH), 151 ($M-OCH_3$), 123, 106, 94. High resolution mass spectrum. Calcd. for $C_{10}H_{12}O_2$ ($M-H_2O$): 164.08373. Found: 164.08390.

Epoxy-Alcohol 113

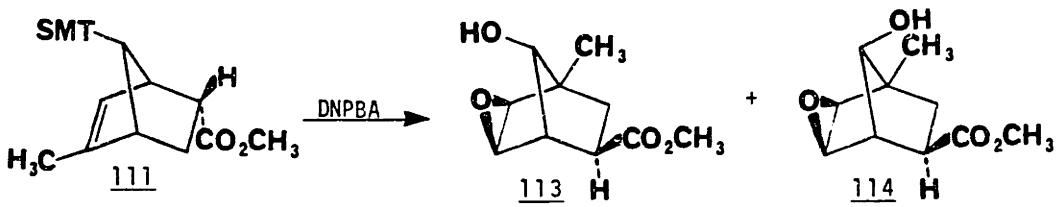


124 113

Method A: Epoxidation of 124

A solution of 4.5 mg (0.25 mmol) of 124, 19 mg (0.23 mmol) of $NaHCO_3$ and 23 mg of 95% 3,5-DNPBA[71] (96 umol) in 2.0 mL of CH_2Cl_2 was stirred for 7 h at room temperature. The mixture was filtered and the solids washed with CH_2Cl_2. The resulting solution was concentrated in vacuo. The residue was chromatographed on one half of a 0.25-mm preparative TLC plate (one development with 1:2 hexane-Et_2O) to yield 5.0 mg (100%) of 113. An analytical sample was prepared by sublimation (62°C, 0.5 mm) to afford crystalline 113: TLC (1:1 hexane-Et_2O) R_f 0.37, (2:1 hexane-EtOAc) R_f 0.53; NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 3.65 (s, 3H, OCH_3), 3.55 (m, [J=1.5, 3.3 Hz], 1H, H_3), 3.40 (d, J=11.8 Hz, 1H, OH), 3.31 (m, J=11.8 Hz, [J= 1.5, 1.5 Hz], 1H, H_{12}), 3.27 (dd, J=1.5, 3.3 Hz, 1H, H_4), 2.80 (br s,

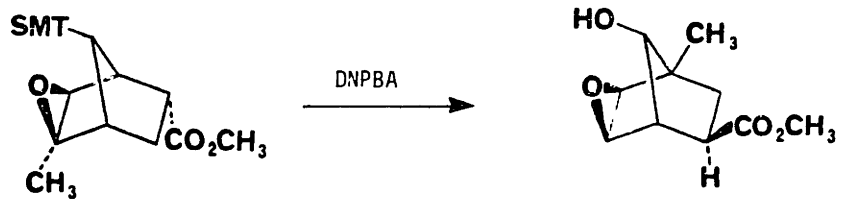
$W_{1/2}$ = 4.0 Hz, 1H, H_2), 2.33 (dd, J= 5.1, 9.9 Hz, 1H, H_{11}), 1.71 (dd, J= 5.1, 13.0 Hz, 1H, $H_{6\beta}$), 1.58 (dd, J= 9.9, 13.0 Hz, 1H, $H_{6\alpha}$), 1.28 (s, 3H, CH_3); IR (CH_2Cl_2) 3500, 3040, 2955, 1729 (C=O); Mass spectrum m/e 167 ($M-OCH_3$). High resolution mass spectrum. Calcd. for $C_{10}H_{12}O_3$ ($M-H_2O$): 180.07864. Found: 180.08061. Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.63, H, 7.37.



Method B: From 111 with 3,5-dinitro-peroxybenzoic acid (DNPBA)

A solution of 48 mg (0.20 mmol) of 111, 125 mg (1.49 mmol) of $NaHCO_3$ and 209 mg of 90% 3,5-DNPBA[71] (0.83 mmol) in 15 mL of dry CH_2Cl_2 was stirred at room temperature for 53 h. The mixture was filtered through a fritted glass funnel and the solids washed with 25 mL of CH_2Cl_2. The resulting solution was concentrated in vacuo and the residue chromatographed on a 0.25-mm preparative TLC plate (one development with 1:1 hexane-Et_2O) to yield 27.4 mg (68%) of 113 (R_f 0.37-0.52), 7.6 mg (19%) of 114 (R_f 0.27-0.37) and 3.3 mg (6%) of 126 (R_f 0.73-0.84). Treatment of 126 with 1.8 mL of 8:1 MeOH-1N aqueous HCl for 30 min afforded 114 quantitatively.

Data for 114: mp 93-94°C (C_6H_6-hexane (1:10)) TLC (1:1 hexane-Et_2O) R_f 0.30, (2:1 hexane-EtOAc) R_f 0.37; NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 3.70 (s, 3H, OCH_3), 3.56 (br d, J= 6.3 Hz, 1H, H_{12}), 3.27 (dd, J= 1.5, 4.0 Hz, 1H, H_3), 3.09 (d, J= 4.0 Hz, 1H, H_4), 2.84 (m, $W_{1/2}$ = 5.2 Hz [J= 1.5 Hz], 1H, H_2), 2.74 (d, J= 6.3 Hz, 1H, OH), 2.51 (dd, J= 5.1, 9.2 Hz, 1H, H_{11}), 1.94 (dd, J= 5.1, 12.9 Hz, 1H, $H_{6\beta}$), 1.68 (dd, J= 9.9, 12.9 Hz, 1H, $H_{6\alpha}$), 1.24 (s, 3H, CH_3); IR (CH_2Cl_2) 3600, 3425, 3040, 2950, 1715 (C=O), 1212; Mass spectrum m/e 199 (parent ion + 1), 167 (M-OCH_3). High resolution mass spectrum. Calcd. for $C_{10}H_{14}O_4$: 198.0892. Found: 198.0882.



123 113

Method C: From 123 with DNPBA

A solution of 15.4 mg (0.061 mmol) of 123, 40 mg (0.48 mmol) of $NaHCO_3$ and 36 mg of 95% 3,5-DNPBA (0.15 mmol) in 10 mL of CH_2Cl_2 was stirred at room temperature for 4 days. The reaction mixture was filtered and the solids washed with CH_2Cl_2. The resulting solution was washed with 15 mL of saturated aqueous Na_2SO_3 and then concentrated in vacuo.

The residue was dissolved in 3 mL of CH_3OH and 0.3 mL of 1N aqueous HCl was added. The resulting mixture was stirred for 30 min at room temperature, then quenched by the addition of 4 mL of saturated aqueous $NaHCO_3$. This mixture was concentrated *in vacuo* and the resulting aqueous residue extracted once with CH_2Cl_2. The combined extracts were filtered through cotton and again concentrated *in vacuo*. The residue was chromatographed on three quarters of a 0.25-mm preparative TLC plate (one development with 1:2 hexane-Et_2O) to yield 10.5 mg (89%; R_f 0.57-0.72) of a 4:1 mixture, respectively, of **113** and **124**.

Method D: From the Mixture of Diels-Alder adducts **110** and **111** with DNPBA

A 2 L, three-neck round bottom flask fitted with a mechanical stirrer was charged with 37.8 g (0.159 mol) of an 82:18 mixture of **111** and **110** and 33 g (0.39 mol) of $NaHCO_3$ in one Liter of reagent grade CH_2Cl_2. To this suspension was added in large portions 51 g of 98% 3,5-DNPBA (0.22 mol). The resulting mixture was stirred at room temperature for 4 days. The reaction mixture was then filtered through a 500 mL medium fritted glass funnel. The solids were washed with 700 mL of CH_2Cl_2 and the filtrate concentrated *in vacuo*.

The residue was dissolved in one Liter of CH_3OH and 100 mL of 1N aqueous HCl was added. The reaction mixture was stirred for 40 min and then was diluted with 200 mL of saturated aqueous $NaHCO_3$. Methanol was removed *in vacuo* and the resulting aqueous solution was extracted with CH_2Cl_2 (4 x 200 mL). The combined extracts were then concentrated *in vacuo*.

The residue was now dissolved in one Liter of CH_2Cl_2 and 40 g (0.48 mol) of solid $NaHCO_3$, 30 g of 70% MCPBA (0.12 mol) and 41 g of 99% 3,5-DNPBA (0.18 mol) were added. The resulting mixture was stirred for 24 h, then filtered through sintered glass with 700 mL of CH_2Cl_2. The solution was concentrated *in vacuo*.

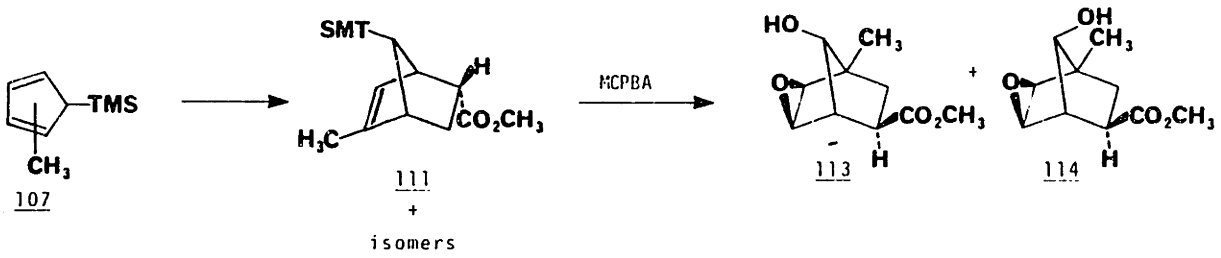
The crude product was dissolved in 500 mL of Et_2O and was extracted with saturated aqueous Na_2SO_3 (3 x 250 mL) and saturated aqueous Na_2CO_3 (3 x 150 mL). The aqueous extracts were back extracted with Et_2O (4 x 200 mL) which, in turn, were washed with aqueous Na_2SO_3 (50 mL) and aqueous Na_2CO_3 (40 mL). The combined extracts were concentrated *in vacuo* to give 38.1 g of a mixture of products.

The products were separated by chromatography (60 mm column filled with a 14 inch pad of SiO_2, packed using 9:1 hexane-EtOAc). The residue was applied as a solution in 50 mL of 2:1 hexane-EtOAc and eluted with 9:1 hexane-EtOAc (seven fractions of 225 mL), 5:1 hexane-EtOAc (seven fractions of 225 mL and seven fractions of 125 mL), 3:1 hexane-EtOAc (ten fractions of 125 mL) and 2:1 hexane-EtOAc (17 fractions of 125 mL).

Fractions 1-10 afforded 7.6 g of *112* (80% purity; therefore, 15% yield). Fractions 15-22 afforded 9.6 g (30%) of *113*.

Fractions 30-42 afforded 3.4 g (11%) of 114. Fractions 11-14 and 23-29 were combined and rechromatographed as above to give an additional 6.9 g (22%; total yield = 16.5 g (52%)) of 113 and 1.1 g (3%; total yield = 4.5 g (14%)) of 114.

Data for 112: TLC (1:1 hexane-Et_2O) R_f 0.63; NMR (^1H, 250 MHz, $CDCl_3$) δ 3.72 (s, 3H, OCH_3), 3.59 (dd, J=3.5, 4.0 Hz, 1H, H_3), 3.39 (d, J=4.0 Hz, 1H, H_4), 2.41 (dd, J=4.4, 12.0 Hz, 1H, H_6), 2.33 (dd, J=3.5, 4.0 Hz, 1H, H_2), 2.02 (dd, J=4.4, 11.8 Hz, 1H, $H_{11\alpha}$), 1.87 (ddd, J=4.0, 11.8, 12.0 Hz, 1H, H_{11}), 1.54 (s, 3H, CH_3), 1.29 (br s, $W_{1/2}$ = 3.2 Hz, 1H, H_{12}); IR (CH_2Cl_2) 3020, 2950, 2890, 2835, 1720 (C=O), 1420; Mass spectrum m/e 239 (M-CH_3), 195, 179, 105. High resolution mass spectrum. Calcd. for $C_{13}H_{22}O_3Si$: 254.13382. Found: 254.13328.



Method E: From the mixture of Diels-Alder adducts with MCPBA(146)

A solution of 3.05 g (12.8 mmol) of purified 111 (obtained from the Diels-Alder reaction of 107 (13.1 mmol), methyl acrylate (14.5 mmol) and Et_2AlCl-hexane (14.4 mmol)) in 80 mL of CH_2Cl_2

under N_2 was treated with 4.30 g (51.2 mmol) of $NaHCO_3$ and 5.53 g (25.6 mmol) of 80% MCPBA. The resulting mixture was stirred at room temperature for 2 days. The mixture was then filtered and the solids washed with 500 mL of CH_2Cl_2. The filtrate was then concentrated in vacuo.

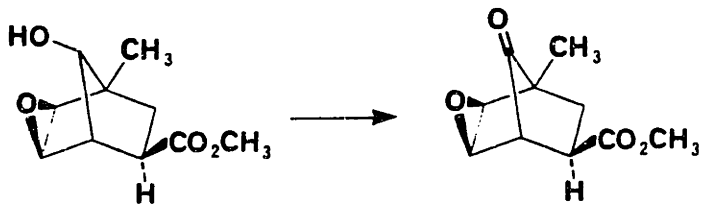
This crude product residue was dissolved in 40 mL of CH_3OH and the resulting solution treated with 4.0 mL of 1N aqueous HCl. The reaction mixture was stirred for 40 min at room temperature. The reaction mixture was then treated with 90 mL of saturated aqueous $NaHCO_3$ and 60 mL of H_2O and then extracted with CH_2Cl_2 (7 x 50 mL). The combined extracts were filtered through cotton and concentrated by distillation at atmospheric pressure.

A solution of the above product residue, 2.15 g (25.6 mmol) of $NaHCO_3$ and 2.76 g (12.8 mmol) of 80% MCPBA in 75 mL of CH_2Cl_2 was then stirred at room temperature under N_2 for 24 h. The reaction mixture was filtered and the solids washed with 425 mL of CH_2Cl_2. The filtrate was concentrated in vacuo. The crude product residue was dissolved in 130 mL of Et_2O and washed with saturated aqueous Na_2SO_3(3 x 40 mL), saturated aqueous Na_2CO_3 (3 x 40 mL) and saturated aqueous NaCl (75 mL). The aqueous washings were each back extracted with Et_2O (3 x 60 mL). The combined extracts were filtered through cotton and concentrated in vacuo. The crude product was purified by flash chromatography (60 mm column filled with a 250 mm pad of SiO_2,

(146) This experiment was performed by J.K. Rogowski.

packed with 1:1 hexane-Et_2O). The column was eluted with 1:1 hexane-Et_2O (25 mL fractions). Fractions 25-53 afforded pure 113. Fractions 54-120 were concentrated in vacuo and then rechromatographed as above. In this manner a total of 1.53 g (7.73 mmol; 59% yield from 107) of 113 and 158 mg (0.80 mmol; 6% yield from 107) of 114 were obtained.

Bicyclic Epoxy-Ketone 128



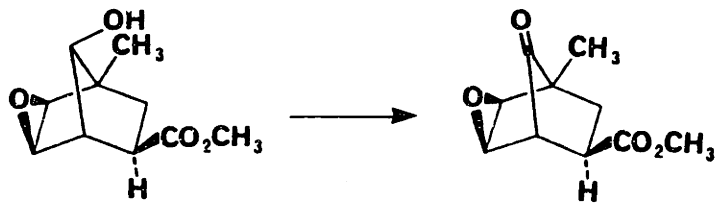
113 128

Method A: From 113

To a -60°C solution of 60 uL (0.85 mmol) of DMSO in 3 mL of anhydrous CH_2Cl_2 was added dropwise 0.10 mL (0.70 mmol) of trifluoroacetic anhydride (TFAA) and the mixture stirred for 10 min.[72] To this mixture was then added dropwise a solution of 135 mg (0.68 mmol) of 113 in 1.5 mL of CH_2Cl_2. The reaction mixture was stirred for 30 min with the temperature being maintained at or below -50°C. Triethylamine, 0.28 mL (2.0 mmol) was then added dropwise. The cooling bath was removed and the reaction mixture allowed to warm gradually to room temperature.

The reaction mixture was concentrated *in vacuo* and the residue chromatographed on a 0.5-mm preparative TLC plate (one development with 1:2 hexane-Et_2O) to yield 68 mg (51%; R_f 0.35-0.48) of 128.

An analytical sample was prepared by two sublimations (85°C, 0.6 mm) to afford soft, white crystals, mp 44.5-45.5°C: NMR (^1H, 250 MHz, $CDCl_3$) δ 3.69 (dd, J=1.5, 4.8 Hz, 1H, H_3), 3.46 (d, J=4.8 Hz, 1H, H_4), 2.90 (dd, J=5.1, 10.7 Hz, 1H, H_{11}), 2.83 (d, J=1.5 Hz, 1H, H_2), 2.15 (dd, J=10.7, 13.2 Hz, 1H, $H_{6\alpha}$), 1.91 (dd, J=5.1, 13.2 Hz, 1H, $H_{6\beta}$), 1.23 (s, 3H, CH_3); IR (CH_2Cl_2 3045, 2955, 1790 (C=O), 1730 (C=O), 1420, 1260; Mass spectrum m/e 165 ($M-OCH_3$), 125. High resolution mass spectrum. Calcd. for $C_9H_9O_3$ ($M-OCH_3$): 165.05517. Found 165.05426. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 60.90; H, 6.16.

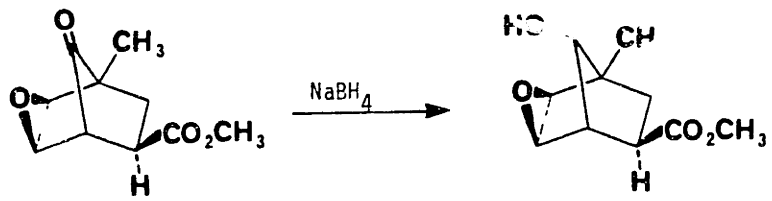


114 128

Method B: From 114

In two batches a total of 8.0 g of 114 (40.4 mmol) was oxidized to 128 using the reagent prepared from 4.0 mL of DMSO (56.4 mmol), 7.4 mL of TFAA (52.1 mmol) and 22.2 mL of Et_3N (160 mmol) in 190 mL of CH_2Cl_2 according to the procedure previously

described for the preparation of 128 from 113 (Method A). On a small scale, the yield of 128 from 114 was 90% (isolated by preparative TLC). In the above experiments, however, the crude product residues were contaminated with approximately 10% of 114 due to incomplete oxidation. Nevertheless, the crude product from these two reactions was used directly in the subsequent transformation ($NaBH_4$ reduction to 113).

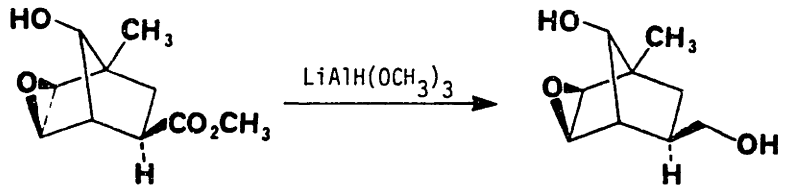


128 113

$NaBH_4$ Reduction of 128

Crude 128 from the oxidation of 5.15 g (26.0 mmol) of 114 as previously described was reduced in two batches using a total of 1.1 g (29 mmol) of $NaBH_4$ in 130 mL of absolute EtOH at 0°C for 30 min. Each reaction mixture was then diluted with saturated aqueous NaCl and extracted with CH_2Cl_2 (3 x 230 mL). The extracts were filtered through a cotton plug and concentrated in vacuo. The samples were combined and chromatographed on a 60 mm column (450 g of SiO_2 packed using 5:1 hexane-EtOAc). The crude product residue was applied to the column in 20 mL of 2:1 hexane-EtOAc and eluted with 5:1 hexane-EtOAc (thirteen fractions of 150

mL and eleven fractions of 125 mL), 3:1 hexane-EtOAc (11 fractions of 125 mL) and 2:1 hexane-EtOAc (14 fractions of 125 mL). Fractions 23-38 afforded 3.06 g of 113 (59% yield from 114). Fractions 40-48 afforded 480 mg of 114 (9% for 2 steps) which is obtained because of incomplete oxidation in the previous step. On a small scale experiment using purified 128 (preparative TLC), 114 was not detected in the crude reaction product after treatment with $NaBH_4$ as described above (NMR analysis).



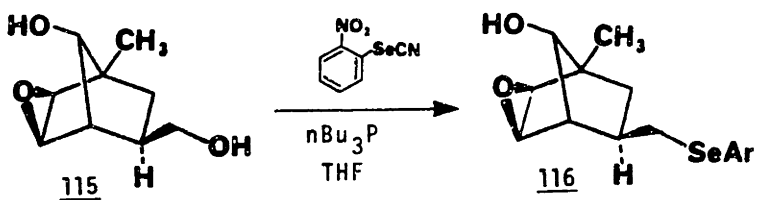
113 115

Diol 115

A two Liter 3-neck round bottom flask equipped with a 125 mL addition funnel, a mechanical stirrer and an Argon purge was charged with 600 mL of a 0.60M solution of $LiAlH_4$ in THF and was diluted with 400 mL of THF. This solution was cooled to 0°C and 44 mL (1.1 mol) of CH_3OH was then slowly added over 30 min.[73] The resulting solution of $LiAlH(OMe)_3$ (360 mmol) was stirred for an additional 10 min, and then a solution of 16.5 g (83 mmol) of 113 in 100 mL of THF was slowly added over 25 min. The cooling

bath was removed and the reaction mixture stirred for 1 h. Excess hydride was then destroyed by the careful addition of 25 mL of CH_3OH. To the resulting jelly was added 30 mL of H_2O and the mixture was stirred for a few minutes. The resulting emulsion was filtered through sintered glass and washed with 800 mL of CH_2Cl_2. The filtrate was then concentrated *in vacuo* to yield 13.8 g (98%) of **115** which was used directly in the next step.

An analytical sample was prepared by sublimation (70-75°C, 0.3-0.6 mm Hg) which yielded a white solid, mp 79-81°C: TLC (Et_2O) R_f 0.47; NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 3.60 (d, J=12.1 Hz, 1H, OH [to C.12]), 3.56 (m, $W_{1/2}$=4.9 Hz, [J=3.3 Hz], 1H, H_3), 3.52 (d, J=7.4 Hz, 2H), 3.31 (dd, J=1.5, 3.3 Hz, 1H, H_4), 3.28 (br d, J=12.1 Hz, $W_{1/2}$=6.5 Hz, 1H, H_{12}), 2.57 (m, $W_{1/2}$=3.6 Hz, 1H, H_2), 2.0-2.2 (br, OH), 1.69-1.81 (m, [J=4.8, 7.4, 9.9 Hz], 1H, H_{11}), 1.55 (dd, J=9.9, 12.9 Hz, 1H, $H_{6\alpha}$), 1.30 (s, 3H, CH_3), 0.97 (dd, J=4.8, 12.9 Hz, 1H, $H_{6\beta}$); IR (CH_2Cl_2) 3670, 3600, 3260-3580, 3040, 2950, 2870, 1460, 1255; Mass spectrum m/e 152 ($M-H_2O$), 139 ($M-CH_2OH$), 109, 93. Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.22; H, 8.40.



115 116

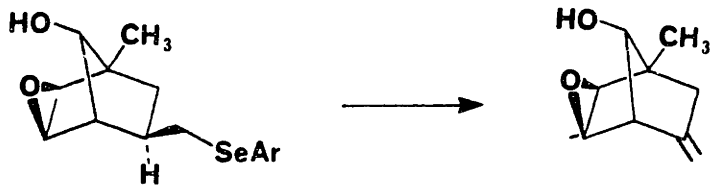
Selenide 116

To a 23°C solution of 13.8 g (81 mmol) of 115 and 21.9 g (96.5 mmol) of o-nitrophenyl selenocyanate(147) in 450 mL of anhydrous THF was added 24 mL (97 mmol) of tri-n-butyl phosphine over one min.(76) The resulting mixture was stirred for 30 min at room temperature, then 5 mL of CH_3OH was added and the reaction mixture concentrated in vacuo.

The product residue was purified by column chromatography, (60 mm column, 450g of SiO_2 packed with 1:1 hexane-Et_2O). The product residue was applied as a solution in 50 mL of Et_2O and eluted sequentially with 1:1 hexane-Et_2O (14 fractions of 225 mL), with 1:2 hexane-Et_2O (three fractions of 225 mL and 14 fractions of 125 mL) and with Et_2O (11 fractions of 125 mL). Fractions 6-16 afforded 18.3 g of 116. Fractions 4,5 and 17-25 were rechromatographed (450 g of SiO_2, 60 mm column, eluted as above) to give an additional 4.6 g of 116 (total yield = 22.9 g; 78% from 113). An analytical sample was prepared by recrystallization twice from 1:2 benzene-hexane, mp 109.5-110.5°C: TLC (1:2 hexane-Et_2O) R_f 0.33, (Et_2O) R_f 0.90; NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 8.29 (dd, J=1.5, 8.1 Hz, 1H), 7.54 (m, J=8.1 Hz, 1H), 7.45 (dd, J=1.5, 8.1 Hz, 1H), 7.34 (m, J=1.5, 8.1 Hz, 1H), 3.55 (m, $W_{1/2}$ = 7.4 Hz [J=3.3 Hz], 1H, H_3), 3.52 (d,

(147) Prepared by the method of Sharpless (reference 75). The crude brown solid described in this procedure was dissolved in Et_2O (1g/100 mL), decolorized with activated charcoal, filtered, concentrated in vacuo and then recrystallized from EtOH, yielding golden needles, mp 144-144.5°C (lit. mp 139-141°C).

J=11.8 Hz, 1H, OH), 3.38 (br d, J= 11.8 Hz, $W_{1/2}$=6.7 Hz, 1H, H_{12}), 3.30 (dd, J=1.5, 3.3 Hz, 1H, H_4), 3.00 (dd, J=7.7, 11.4 Hz, 1H), 2.87 (dd, J=7.7, 11.4 Hz, 1H), 2.60 (br s, $W_{1/2}$=5.1 Hz, 1H, H_2), 1.82-1.93 (m, [J=4.0, 7.7, 9.6 Hz], 1H, H_{11}), 1.77 (dd, J=9.6, 12.1 Hz, 1H, $H_{6\alpha}$), 1.32 (s, 3H, CH_3), 1.16 (dd, J=4.0, 12.1 Hz, 1H, $H_{6\beta}$); IR (CCl_4) 3510, 3030, 2955, 2870, 1588, 1564, 1512, 1455, 1429; Mass spectrum m/e 355 (parent ion (Se^{80})), 353 (parent ion (Se^{78})), 352 (parent ion (Se^{77})), 338 and 336 (M-H_2O). High resolution mass spectrum. Calcd. for $C_{15}H_{17}NO_4Se^{80}$: 355.03228. Found: 355.03108. Calcd. for $C_{15}H_{17}NO_4Se^{78}$: 353.03307. Found: 353.03167. Anal. Calcd. for $C_{15}H_{17}NO_4Se$: C, 50.86; H, 4.84; N, 3.95; Se, 22.29. Found: C, 51.17; H, 4.97; N, 3.96; Se, 21.23 (duplicate Se, 21.35).



116 117

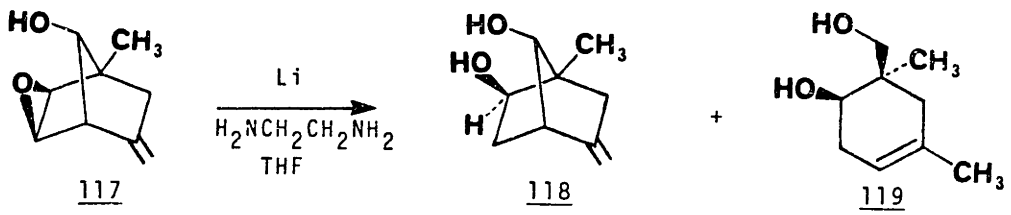
Olefin 117

To a -20°C solution of 7.8 g (22 mmol) of selenide 116 in 250 mL of CH_2Cl_2 was added in one portion, 5.4 g of 85% MCPBA (27 mmol). After the reaction mixture was stirred for 15 min, 7.4 mL (53 mmol) of diisopropyl amine was added.(77) The mixture

was brought to room temperature and stirred for one hour. The mixture was then concentrated *in vacuo*, at 0°C.[148] The crude residue was chromatographed on a 50 mm column (320 g of SiO_2 packed with 4:1 pentane-Et_2O). The residue was applied with 25 mL of CH_2Cl_2 and 15 mL of Et_2O and eluted with 4:1 pentane-Et_2O (16 fractions of 100 mL) and 2:1 pentane-Et_2O (10 fractions of 100 mL). Fractions 8-15 were concentrated *in vacuo at 0°C*.[148] Olefin 117 is extremely volatile. In preparative scale experiments, we found it best therefore to use this material (obtained as above) directly in the next step without attempting to separate the selenium-containing impurities which invariably were also obtained. On a small scale experiment a 95% yield of pure, chromatographed (preparative TLC) 117 was obtained: TLC (2:1 hexane-Et_2O) R_f 0.81; NMR (^1H, 250 MHz, $CDCl_3$) δ 4.97 (t, J=2.6 Hz, 1H), 4.75 (br t, J=2.0 Hz, 1H), 3.65 (d, J=11.8 Hz, 1H, OH), 3.50 (dd, J=1.8, 3.3 Hz, 1H, H_3), 3.34 (dd, J=1.7, 3.3 Hz, 1H, H_4), 3.21 (dq, J=1.8, 11.8 Hz, 1H, H_{12}), 3.06 (br m, $W_{1/2}$=4.3 Hz, 1H, H_2), 2.05 (dt, J=2.2, 16.5 Hz, 1H, $H_{6\alpha}$), 1.95 (dt, J=2.6, 16.5 Hz, 1H, $H_{6\beta}$), 1.32 (s, 3H, CH_3); IR (CCl_4) 3515, 3080, 3045, 3025, 2990, 2960, 2930, 2875, 1668, 1450; Mass spectrum m/e 152 (parent ion), 134 (M-H_2O), 123, 105. High resolution mass spectrum. Calcd. for $C_9H_{12}O_2$: 152.08373. Found: 152.08501.

(148) The vessel was surrounded in a 0°C bath and concentrated on a Buchi rotary-evaporator, at water aspirator pressure.

Bicyclo[2.2.1]1-methyl-2(R^*)-hydroxy-5-methylene-7(S^*)-hydroxy-heptane 118



117 118 119

Method A

To approximately 2 g (4" in 1/8" pieces) of Li wire in 200 mL of ethylene diamine[81] at 0°C was added 70 mL of THF. This mixture was stirred until it turned deep blue and then a solution of 117 from the previous reaction in 30 mL of THF was added. The mixture was stirred at room temperature while an additional 3" (1.5 g) of Li wire, cut as above, was added. The color of the reaction mixture turned from deep blue to black, then gradually cleared and finally became deep blue again. After this last color change, the mixture was stirred for an additional 10 min, then carefully quenched with 20 mL of H_2O. The reaction mixture was carefully poured into one Liter of H_2O and extracted 5 times with 200 mL of Et_2O. The combined extracts were concentrated in vacuo.

The residue was purified by chromatography on a 50 mm column (300 g of SiO_2 packed in 4:1 hexane-Et_2O). The residue was applied with 20 mL of Et_2O and eluted with 4:1 hexane-Et_2O (8 fractions of 225 mL and 1 fraction of 125 mL), 2:1 hexane-Et_2O (15 fractions of 125 mL), 1:1 hexane-Et_2O (10 fractions of 125 mL) and Et_2O (6 fractions of 125 mL).

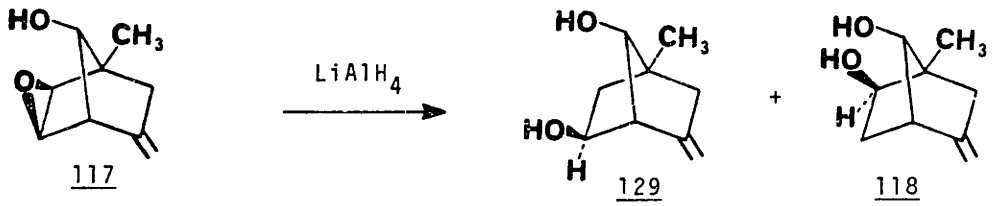
Fractions 19-28 afforded 1.48 g of white crystalline 118 (44% yield from 116). An analytical sample was prepared by recrystallization from 1:1 hexane-Et_2O, mp 97-98°C.

Fractions 35-40 afforded 161 mg of 119 (5% yield from 116), mp 76°C.

On a 50 mg scale experiment, using purified 117, the yield of 118 was 66%. Isomer 129 (see Method B) was not detected in the high field ^1H NMR spectrum of the crude Li-ethylenediamine reduction product mixtures.

Data for 118: NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]) δ 4.80 (br m, $W_{1/2}$=6.5 Hz, 1H), 4.56 (br m, $W_{1/2}$=6.5 Hz, 1H), 3.69 (br m, $W_{1/2}$=10 Hz [J=5.1 Hz], 1H, H_{12}), 3.62 (br m, $W_{1/2}$=15 Hz [J=7.7 Hz], 1H, H_4), 2.64 (br s, $W_{1/2}$=7.5 Hz, 1H, H_2), 2.53 (d, J=5.1 Hz, 1H, OH), 2.42 (d, J=7.7 Hz, 1H, OH), 2.05 (dm, J=17 Hz, 1H, H_{6a}), 2.02 (multiplet, 2H, $H_{3a,3b}$), 1.80 (dm, J=17 Hz, 1H, H_{6b}), 1.20 (s, 3H, CH_3); IR (CH_2Cl_2) 3590, 3400-3620, 3040, 2920, 2860, 1660, 1415; Mass spectrum m/e 154, 136 ($M-H_2O$), 121, 118, 107. High resolution mass spectrum. Calcd. for $C_9H_{14}O_2$: 154.09938. Found: 154.09665. Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.42.

Data for 119: TLC (1:1 hexane-Et_2O) R_f 0.17; NMR (^1H, 250 MHz, $CDCl_3$) δ 5.22 (br m, $W_{1/2}$=9.3 Hz, 1H), 3.73 (br d, $W_{1/2}$=10.5 Hz, J=4.4 Hz, 1H), 3.63 (br d, J=10.5 Hz, 1H), 3.48 (br d, J=10.5 Hz, 1H), 3.08 (br m, $W_{1/2}$=14.5 Hz, 1H, OH), 2.90 (br d, J=4.4 Hz, 1H, OH), 2.32 (dm, J=18.5 Hz, 1H), 2.19 (br d, J=17.6 Hz, 1H), 2.05 (dm, J=18.5 Hz, 1H), 1.65 (br s, $W_{1/2}$=5.8 Hz, 3H, CH_3), 1.54 (br d, J=17.6 Hz, 1H), 0.85 (s, 3H, CH_3); IR (CH_2Cl_2) 3605, 3000-3700, 3020, 2800-3000, 1670, 1602, 1440; Mass spectrum m/e 157 (M+1), 138 (M-H_2O), 121, 107.



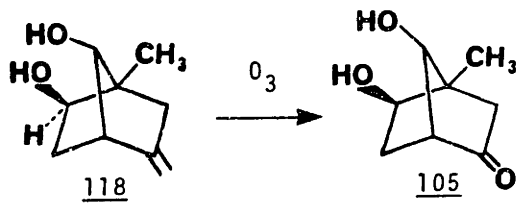
117 129 118

Method B

To a solution of 18 mg (0.12 mmol) of pure 117 in 2 mL of THF under N_2 was added 0.6 mL of a 1M $LiAlH_4$-THF solution. The reaction mixture was stirred for 12 h at room temperature, then carefully quenched with CH_3OH. The resulting solution was poured into 15 mL of H_2O and extracted twice with 10 mL of CH_2Cl_2. The combined extracts were filtered through cotton and concentrated in vacuo. This crude residue was chromatographed on 1/2 of a 0.25-mm preparative TLC plate (one development with 1:1 hexane-

Et_2O) to yield 12 mg (65%; R_f 0.24-0.42) of an oil consisting of a 3:2 mixture, respectively, of 129 and 118 (250 MHz ^1H NMR analysis). These isomers were separated by chromatography on a full 0.25-mm preparative TLC plate (3 developments with 1:2 hexane-Et_2O). In this manner 4.3 mg of 129 (23% yield; R_f 0.72-0.77) and 4.5 mg of 118 (24% yield; R_f 0.64-0.72) were obtained.

Data for 129: NMR (^1H, 250 MHz, $CDCl_3$ [spin decoupling]), δ 4.95 (br m, $W_{1/2}$=5.0 Hz, 1H), 4.70 (br m, $W_{1/2}$=5.5 Hz, 1H), 3.93 (m, [dd, J=7.4, 7.5Hz], 1H, H_3), 3.68 (br m, J=6.3 Hz, 1H, H_{12}), 2.80 (d, J=6.3 Hz, 1H, OH), 2.76 (d, J=7.4 Hz, 1H, OH), 2.71 (br s, $W_{1/2}$=4.3 Hz, 1H, H_2), 1.83-2.0 (multiplet, 3H, $H_{4a,4b}$ and H_{6a}), 1.62 (dm, J=14 Hz, 1H, H_{6b}), 1.15 (s, 3H, CH_3); IR (CH_2Cl_2) 3590, 3150-3650, 3070, 2955, 2925, 2870, 1655, 1425; Mass spectrum m/e 136 ($M-H_2O$), 121, 118, 107. High resolution mass spectrum. Calcd. for $C_9H_{12}O$ ($M-H_2O$): 136.08881. Found: 136.08995.



118 105

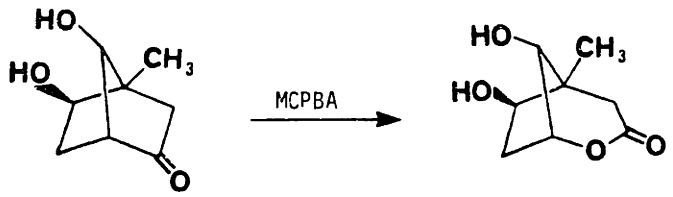
Bicyclo[2.2.1]4-methyl-5(R^*)-hydroxy-7(S^*)-hydroxy-heptan-2-one

105

Ozone (0.9 mmol/min) in a stream of oxygen was bubbled through a -78°C solution of 1.48 g (9.6 mmol) of 118 in 350 mL of CH_2Cl_2 for 40 min. (The color of the solution turned to deep blue after 20 min.) The blue reaction mixture was stirred for an additonal 40 min. Excess O_3 was then quenched slowly and very carefully by the dropwise addition of $(CH_3)_2S$, then an additional 15 mL of $(CH_3)_2S$ was added. The reaction mixture was then brought to room temperature and stirred for 84 h. An additional 6 mL of CH_3SCH_3 was then added (TLC analysis indicated the presence of ozonides) and the mixture was stirred for another 24 h. The solution was then concentrated in vacuo and the residue purified by flash chromatography on a 50 mm column (140 g of SiO_2 packed with 1:1 hexane-Et_2O). The residue was applied with 15 mL of Et_2O and eluted with 1:1 hexane-Et_2O (32 fractions of 50 mL), 1:2 hexane-Et_2O (18 fractions of 50 mL), and Et_2O (5 fractions of 50 mL and 6 fractions of 75 mL). Fractions 46-61 afforded 1.17 g (78%) of 105. Fractions 10-28 afforded 535 mg of a mixture of ozonides and 118 which was dissolved in 60 ml of CH_2Cl_2 and stirred with 8 mL of $(CH_3)_2S$ for 5 days. This mixture was then worked up and purified as above to afford an additional 92 mg (6%) of 105,[149] mp 100-101°C: TLC (2:1 hexane-EtOAc) R_f

(149) A similar experiment performed in CH_3OH led to a complex product mixture containing no readily identifiable products.

0.13; NMR (^{1}H, 250 MHz, $CDCl_3$) δ 3.95 (br m, $W_{1/2}$=6.4 Hz, 1H, H_{12}), 3.76 (br m, $W_{1/2}$=15.0 Hz, 1H, H_4), 3.45 (br m, $W_{1/2}$=9.4 Hz, 1H, OH (to C.12)), 3.10 (br d, J=8.1 Hz, 1H, OH (to C.4)), 2.63 (br m, $W_{1/2}$=7.5 Hz, 1H, H_2), 2.16 (complex multiplet, 2H, $H_{3\alpha,3\beta}$), 1.96 (d, J=18.8 Hz, 1H, H_{6a}), 1.87 (d, J=18.8 Hz, 1H, H_{6b}), 1.30 (s, 3H, CH_3); IR (CH_2Cl_2) 3585, 3060-3680, 2915, 2870, 1740 (C=O), 1415; Mass spectrum m/e 156 (parent ion), 138 (M-H_2O), 120, 109. High resolution mass spectrum. Calcd. for $C_8H_{12}O_3$: 156.07865. Found: 156.07754.



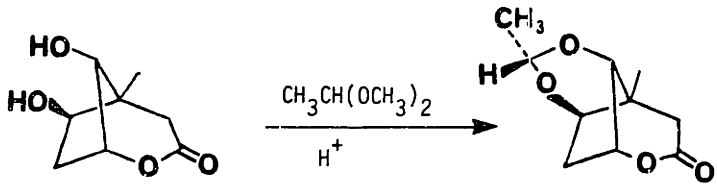
105 120

2-Oxabicyclo[3.2.1]5-methyl-6(R^*)-hydroxy-8(R^*)-hydroxy-octan-3-one 120

A solution of 910 mg (5.8 mmol) of 105, 900 mg (10.7 mmol) of $NaHCO_3$ and 1.26 g of 88% MCPBA (6.4 mmol) in 60mL of CH_2Cl_2 was stirred at room temperature. Reaction progress was monitored by TLC, and, in this particular case, an additional 400 mg of 88% MCPBA (2 mmol) was added after 4 h. After 22 h, the reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (30 mm column, 55 g of SiO_2 packed in 1:2 hexane-Et_2O). The product residue was applied in 15 mL of Et_2O

and eluted with 1:2 hexane-Et_2O (16 fractions of 50 mL) and Et_2O (10 fractions of 50 mL). Fractions 18-24 afforded 851 mg (84% yield) of crystalline 124.

An analytical sample was prepared by recrystallization (2x) from Et_2O to afford pure 120, mp 180-184°C: TLC (Et_2O) R_f 0.31; NMR (^1H, 250 MHz, $CDCl_3$) δ 4.67 (dd, J=1.1, 5.9 Hz, 1H, H_2), 3.9-4.1 (multiplet, 2H, H_4 and H_{12}), 2.70-2.95 (br, OH), 2.66 (dd, J=6.8, 16.9 Hz, 1H, $H_{3\alpha}$), 2.63, 2.48 (AB, J=19.3 Hz, 2H, $H_{6a,6b}$), 2.32 (ddd, J=1.8, 5.9, 16.9 Hz, 1H, $H_{3\beta}$), 1.6-1.8 (br, OH), 1.24 (s, 3H, CH_3); IR (CH_2Cl_2, 3580, 3120-3660, 3040, 2925, 1730 (C=O), 1400, 1360; Mass spectrum m/e 173 (M+1), 154 ($M-H_2O$), 136, 126, 111. Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.36; H, 7.10.



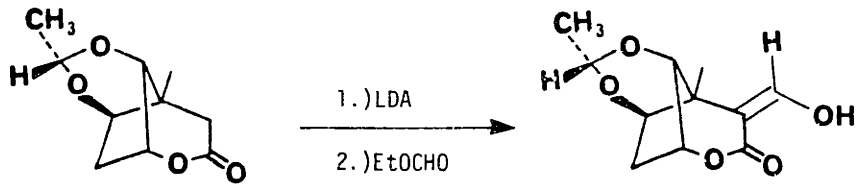
120 65

[3.2.1] Bicyclic lactone 65

To 60 mL of benzene in a 100 mL round bottom flask fitted with a Dean-Stark trap was added 1.0 g (5.8 mmol) of 120 and the solution heated to reflux until all 120 dissolved. The mixture was cooled and 6 mL (57 mmol) of 1,1-dimethoxyethane and 10 mg

(1%) of TsOH-C_5H_5N were added. The resulting mixture was stirred at room temperature for 90 min and then heated at reflux for 14.5 h. TLC analysis of the cooled reaction mixture indicated that the reaction was not quite complete. An additional 1.0 mL of 1,1-DME was added, the mixture stirred for 1 h at room temperature and then refluxed again for 5 h. The mixture was cooled and then concentrated in vacuo to approximately 5 mL.

This solution was purified by flash chromatography (30 mm column, 65 g of SiO_2 packed in 2:1 hexane-EtOAc). The product residue was applied with 15 mL of Et_2O and eluted with 2:1 hexane-EtOAc (8 fractions of 40 mL) and 1:1 hexane-EtOAc (12 fractions of 40 mL). Fractions 5-11 afforded 847 mg (74%) of 65. A small sample was sublimed twice (90°C, 0.3 mm Hg) to afford analytically pure 65, mp 123-124.5°C: TLC (1:3 hexane-EtOAc) R_f 0.75; NMR (^1H, 270 MHz, $CDCl_3$) δ 4.90 (q, J=4.8 Hz, 1H), 4.87 (d, J=6.6 Hz, 1H, H_2), 4.16 (dd, J=2.0, 5.5 Hz, 1H, H_4), 4.06 (br s, $W_{1/2}$=5.4 Hz, 1H, H_{12}), 2.70 (dd, J=6.6, 17.2 Hz, 1H, H_3), 2.64, 2.48 (AB, J=19.8 Hz, 2H, $H_{6a,6b}$), 2.23 (dd, J=5.5, 17.2 Hz, 1H, $H_{3\alpha}$), 1.37 (s, 3H, CH_3), 1.34 (d, J=4.8 Hz, 3H, CH_3); IR (CH_2Cl_2) 3040, 2980, 2950, 2895, 1740 (C=O), 1450, 1400; Mass spectrum m/e 154 (M-CH_3CHO), 126, 111, 97, 82. Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.42; H, 7.36.



65 66

Formylation of lactone 65: representative procedure

To a -78°C solution of 0.14 mL (1.0 mmol) of diisopropyl amine in 3 mL of THF under Ar was added 0.78 mL (1.0 mmol) of a 1.28M solution of n-BuLi in hexane. This mixture was stirred for 15 min, then a solution of 100 mg (0.51 mmol) of lactone 65 in 2.0 mL of THF was slowly added. This solution was stirred for 30 min (at -78°C), then 0.05 mL (0.62 mmol) of ethyl formate was slowly dripped in. (Moderate evolution of carbon monoxide was observed). After being stirred for five minutes at -78°C, the reaction mixture was warmed to 0°C by placing the reaction vessel in an ice bath. The mixture was stirred for an additional five minutes and then an additional 0.02 mL (0.25 mmol) of ethyl formate [150] was added dropwise. After being stirred an additional 2 min,[151] the reaction mixture was warmed to room

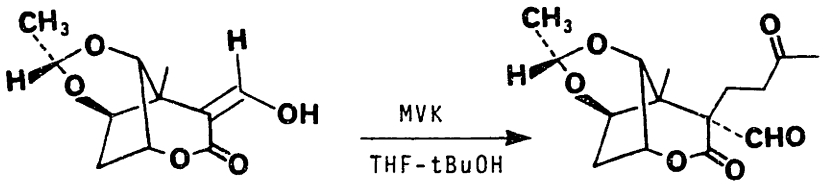
(150) We found it crucial to reflux ethyl formate over CaH_2 for several hours before distilling.

(151) Longer reaction times had no effect.

temperature and poured into 25 mL of 1:1 saturated aqueous NaCl-1N aqueous HCl and extracted five times with 25 mL portions of CH_2Cl_2. The combined extracts were concentrated *in vacuo*. The product residue was partitioned between saturated aqueous Na_2CO_3 and EtOAc.

The organic extracts were concentrated *in vacuo* and the residue chromatographed on a 0.5-mm preparative TLC plate (one development with 1:1 hexane-EtOAc) to afford 62 mg (R_f 0.53-0.66; 62% yield) of recovered **65**.

The aqueous extracts were acidified to pH<1 by the careful dropwise addition of concentrated HCl, and then were extracted six times with 20 mL of CH_2Cl_2. The combined extracts were concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2, filtered through a plug of Kimwipe and again concentrated *in vacuo* to afford 21.8 mg (19%) of crystalline, vinylogous acid **66**: NMR (^1H, 270 MHz, $CDCl_3$) δ 12.48 (d, J=10.2 Hz, 1H, OH), 7.38 (d, J=10.2 Hz, 1H), 4.92 (multiplet, 2H, H_2 and acetal-H), 4.14 (dd, J=5.0, 7.7 Hz, 1H, H_4), 4.01 (br s, $W_{1/2}$=5.8 Hz, 1H, H_{12}), 2.62 (dd, J=6.6, 16.8 Hz, 1H, $H_{3\beta}$), 2.26 (dd, J=5.0, 16.8 Hz, 1H, $H_{3\alpha}$), 1.48 (s, 3H, CH_3), 1.35 (d, J=5.0 Hz, 3H, CH_3); IR ($CHCl_3$) 3600-2300(br), 2985, 2960, 2880, 1665 (C=O), 1608, 1450; Mass spectrum m/e 226 (parent ion), 182 (M-CH_3CHO), 166, 154.

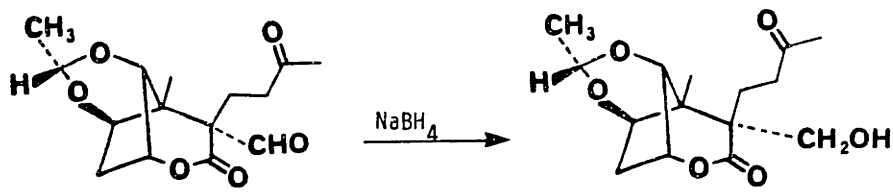


66 67

Michael adduct 67

A solution of 52 mg (0.23 mmol) of hydroxymethylene lactone 66 in 3.0 mL of 1:1 THF-tbutyl alcohol under Ar was treated with 6 mg (0.05 mmol) of KOt-Bu. Excess methyl vinyl ketone in a stream of Ar (generated by bubbling Ar through a solution of MVK) was then passed through a medium glass fritted filter (101) and into the reaction mixture over 3 h. The reaction mixture was stirred at room temperature for an additional 17 h and then was poured into a mixture of 10 mL of 1N aqueous HCl and 10 mL of saturated aqueous NaCl. This mixture was extracted five times with 10 mL of CH_2Cl_2. The combined extracts were concentrated *in vacuo*. The product residue was chromatographed on a 0.5-mm preparative TLC plate (one development with 1:3 hexane-EtOAc) to afford 18.3 mg (27%; R_f 0.76-0.82) of 67: NMR (^1H, 270 MHz, $CDCl_3$) δ 9.57 (s, 1H, CHO), 4.90 (m, 2H, H_2 and acetal-H), 4.32 (dd, J=1.9, 4.9 Hz, 1H, H_4), 4.27 (br s, $W_{1/2}$=4.5 Hz, 1H, H_{12}), 2.73 (dd, J=7.0, 17.3 Hz, 1H, $H_{3\beta}$), 2.15-2.65 (multiplet, 5H),

2.13 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.33 (d, J=4.9 Hz, 3H, CH_3).

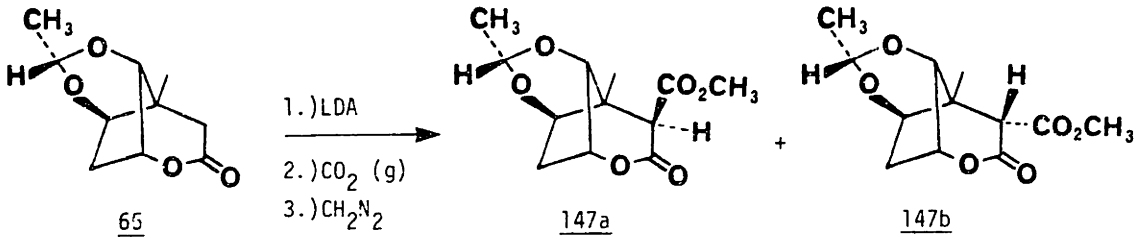


67 145

$NaBH_4$ reduction of 67

To a -10°C solution of 18 mg (0.061 mmol) of Michael adduct 67 in 3.0 mL of 1:1 absolute EtOH-THF was added 0.04 mL (1.3 hydride equiv.) of a 0.49 M solution of $NaBH_4$ in EtOH. The resulting mixture was stirred for 1 h at -10°C, then poured into 10 mL of saturated aqueous NaCl and extracted four times with 15 mL of CH_2Cl_2. The combined extracts were concentrated in vacuo. The residue was dissolved in CH_2Cl_2, filtered through a Kimwipe plug and again concentrated in vacuo. The crude product residue was chromatographed on 1/2 of a 0.25-mm preparative TLC (one development with 1:3 hexane-EtOAc) to afford 13.8 mg (76%; R_f 0.63-0.80) of 145: NMR (^1H, 270 MHz, $CDCl_3$) δ 4.95 (q, J=4.8 Hz, 1H), 4.84 (d, J=6.4 Hz, 1H, H_2), 4.60 (dd, J=2.3, 4.8 Hz, 1H, H_4), 4.37 (br s, $W_{1/2}$ = 6.1 Hz, 1H, H_{12}), 3.73 (br m, $W_{1/2}$ = 14.2 Hz, 2H, $H_{15a,15b}$), 2.3-2.7 (multiplet, 4H), 2.13 (s, 3H, CH_3), 1.98 (dd, J=6.8, 14.8 Hz, 1H, H_{7a}), 1.85 (dd, J=4.8, 8.8 Hz, 1H, $H_{3\alpha}$,

1.48 (dd, J=11.1, 14.8 Hz, 1H, H_{7b}), 1.41 (s, 3H, CH_3), 1.33 (d, J=4.8 Hz, 3H, CH_3); IR (CH_2Cl_2) 3595, 3610-3350, 3060, 2960, 2940, 2890, 1725 (C=O), 1460, 1405; Mass spectrum m/e 268 (M-CH_2O), 210, 181.



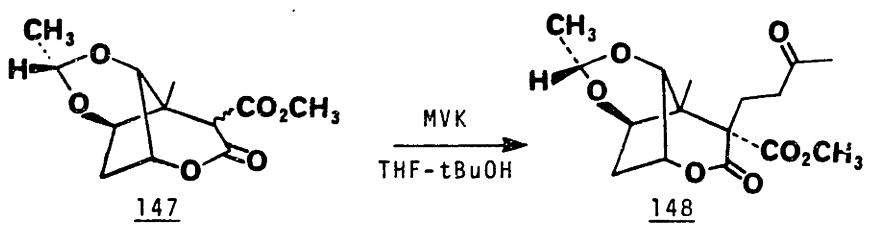
65 147a 147b

Carbomethoxylation of lactone 65

To a -78°C solution of 0.26 mL (1.85 mmol) of diisopropyl amine in 4 mL of THF under Ar was added 1.44 mL (1.84 mmol) of a 1.28M solution of n-BuLi in hexane. This mixture was stirred for 15 min, then a solution of 93 mg (95% purity; 0.47 mmol) of lactone 65 in 1.5 mL of THF was added dropwise. The resulting mixture was stirred for 30 min at -78°C, then warmed to -20°C and stirred for an additional 5 min. Anhydrous CO_2 was then bubbled through the reaction mixture[104] for 10 min. The mixture was then stirred for an additional 10 min at -20°C after which it was allowed to warm to room temperature. The reaction mixture was poured into 25 mL of 1N aqueous HCl and extracted four times with 25 mL of CH_2Cl_2. The combined extracts were concentrated *in vacuo*. The crude product residue was dissolved in 2 mL of Et_2O

and treated with excess ethereal CH_2N_2. The mixture was then concentrated in vacuo and the crude product was chromatographed on a 0.5-mm preparative TLC plate (one development with 1:1 hexane-EtOAc). In this manner 40 mg (33%; R_f 0.58-0.73) of product, a 1:3 inseparable mixture, respectively of 147a and 147b and 24.8 mg (27%; R_f 0.45-0.58) of recovered 65 were obtained.

Data for 147: NMR (^1H, 270 MHz, $CDCl_3$) δ 4.90 (m, 2H, H_2 and acetal-H), 4.48 (br s, $W_{1/2}$=5.7 Hz, 0.24H, H_{12}), 4.26 (dd, J=2.2, 4.8 Hz, 0.76H, H_4), 4.16 (dd, J=2.4, 5.1 Hz, 0.24H, H_4), 4.03 (br s, $W_{1/2}$=6.0 Hz, 0.76H, H_{12}), 3.80 (s, 2.28H, OCH_3), 3.77 (s, 0.72H, OCH_3), 3.64 (s, 0.76H, H_6), 3.31 (s, 0.24H, H_6), 2.72 (dd, J=7.2, 17.0 Hz, 0.24H, $H_{3\beta}$), 2.70 (dd, J=6.4, 17.4 Hz, 0.76H, $H_{3\beta}$), 2.57 (dd, J=5.1, 17.0 Hz, 0.24H, $H_{3\alpha}$), 2.14 (dd, J=4.8, 17.0 Hz, 0.24H, $H_{3\alpha}$), 1.46 (s, 3H, CH_3), 1.33 (d, J=4.5 Hz, 3H, CH_3).

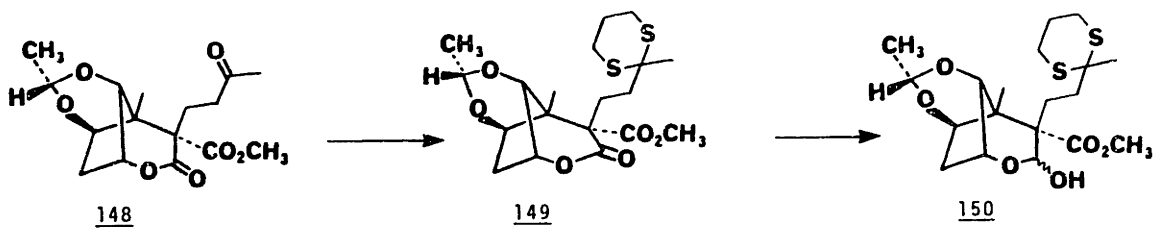


147 148

Michael adduct 148

To a solution of 35 mg (0.14 mmol) of 147 in 3.0 mL of 1:1 THF-tBuOH under Ar was added 0.02 mL (0.25 mmol) of methyl vinyl ketone and 3 mg (0.2 equiv.) of KOt-Bu. The resulting mixture was stirred for 18.5 h, during which the disappearance of 147 was monitored by analytical TLC. The reaction mixture was then poured into 20 mL of half-saturated aqueous NaCl and extracted four times with 20 mL portions of CH_2Cl_2. The combined extracts were concentrated in vacuo. The product residue was chromatographed on a 0.25-mm preparative TLC plate (one development with 1:1 hexane-EtOAc) to afford 17.1 mg (38%; R_f 0.55-0.70) of Michael adduct 148. Other bands at R_f 0.44-0.55 (8.9 mg) and R_f 0.28-0.44 (16.5 mg) were not readily identifiable.

Data for 148: NMR (^1H, 270 MHz, $CDCl_3$) δ 4.91 (q, J=4.8 Hz, 1H, acetal-H), 4.86 (br d, J=4.9 Hz, 1H, H_2), 4.32 (br s, $W_{1/2}$=6.1 Hz, 1H, H_{12}), 4.04 (dd, J=3.1, 6.5 Hz, 1H, H_4), 3.79 (s, 3H, OCH_3), 2.15-2.75 (multiplet, 6H), 2.12 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.33 (d, J=4.9 Hz, 3H, CH_3).

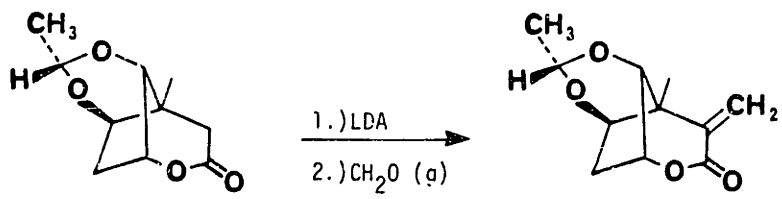


Lactol 150

To a solution of 16 mg (0.05 mmol) of 148 and 8 uL (0.08 mmol) of propane-1,3-dithiol in 0.5 mL of CH_2Cl_2 was added 8 uL (0.07 mmol) of BF_3-OEt_2. The resulting mixture was stirred for 15 min, then chromatographed directly on a 0.25-mm preparative TLC plate (one development with 1:2 hexane-EtOAc) to afford 13.5 mg (69% yield; R_f 0.44-0.61) of diol corresponding to 149: NMR (^1H, 250 MHz, $CDCl_3$) δ 4.76 (dd, J=1.0, 5.9 Hz, 1H, H_2), 4.22 (br m, $W_{1/2}$=10.0 Hz, 1H, H_{12}), 3.91 (t, J=7.4 Hz, 1H, H_4), 3.78 (s, 3H, OCH_3), 3.44 (br d, J=6.3 Hz, 1H), 1.70-3.0 (multiplet, 13H), 1.55 (s, 3H, CH_3), 1.42 (s, 3H, CH_3).

To a solution of 13 mg (0.033 mmol) of the above diol and 0.05 mL (0.47 mmol) of 1,1-dimethoxy ethane in 3 mL of C_6H_6 was added a small crystal of pTsOH-C_5H_5N. The resulting mixture was stirred at room temperature for 1.25 h and then heated to reflux for 17.5 h. The cooled reaction mixture was then concentrated in vacuo and the product residue chromatographed on 3/4 of a 0.25-mm preparative TLC plate (one development with 1:1 hexane-EtOAc) to afford 19.4 mg (R_f 0.52-0.78) of 149 (this material was contaminated with considerable stopcock grease, but was of sufficient purity for use directly in the next experiment): NMR (^1H, 250 MHz, $CDCl_3$) δ 4.90 (multiplet, 2H, H_2 and acetal-H), 4.26 (br s, $W_{1/2}$=5.9 Hz, 1H, H_{12}), 3.94 (br m, $W_{1/2}$=7.1 Hz, 1H, H_4), 3.79 (s, 3H, OCH_3), 1.75-3.0 (multiplet, 11H), 1.54 (s, 6H, $(CH_3)_2$), 1.34 (d, J=4.8 Hz, 3H, CH_3).

The product obtained in the previous step was dissolved in 3 mL of dry toluene and cooled to -78°C. To this solution was added dropwise 0.20 mL of a 1M solution of DIBAL in hexane. The resulting mixture was stirred for 3 h at -78°C, then excess reductant was quenched by the dropwise addition of 0.5 mL of CH_3OH. The reaction mixture was then warmed to room temperature, one mL of H_2O added and the resulting mixture stirred for an additional 5 min. The mixture was then filtered through Celite with Et_2O and the resulting solution concentrated *in vacuo*. The product residue was chromatographed on 1/2 of a 0.25-mm preparative TLC plate (one development with 2:1 hexane-EtOAc) to afford 9.4 mg (68% yield; R_f 0.58-0.74; 46% yield from 148) of lactol 150: NMR (^1H, 270 MHz, $CDCl_3$) δ 5.57 (d, J=3.7 Hz, 1H, H_{11}), 4.95 (q, J=4.8 Hz, 1H, acetal-H), 4.76 (br s, $W_{1/2}$=4.5 Hz, 1H, H_{12}), 4.51 (d, J=5.9 Hz, 1H, H_2), 4.08 (dd, J=1.8, 4.7 Hz, 1H, H_4), 3.76 (s, 3H, OCH_3), 2.7-2.9 (multiplet, 4H), 1.57 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.30 (d, J=4.8 Hz, 3H, CH_3).



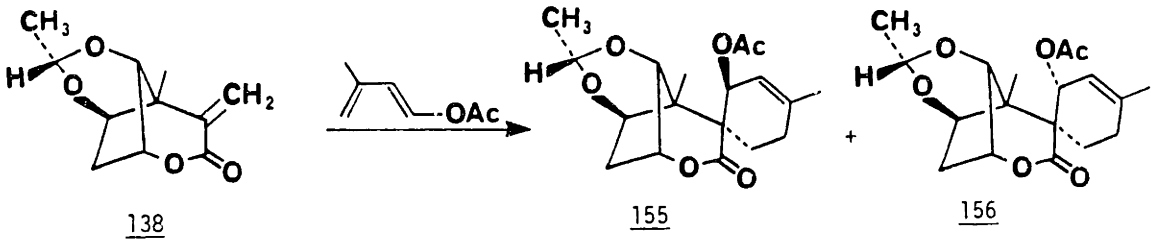
65 138

α-Methylene lactone 138

To 0.51 mL (3.6 mmol) of diisopropyl amine in 25 mL of anhydrous THF under Ar at -78°C was added dropwise 3.0 mL of a 1.20M n-BuLi solution in hexane, and the resulting mixture stirred for 30 min. A solution of 598 mg (3.0 mmol) of lactone 65 in 6 mL of THF was then slowly dripped in. The reaction mixture was stirred for 30 min at -78°C and then warmed to -20°C. The mixture was stirred for an additional 5 min, and then gaseous formaldehyde ($(CH_2O)_x$ dried over P_2O_5; heated to 160°C, Ar stream) was passed over the surface of the mixture over 120 min. The resulting gummy mixture was diluted with 15 mL of THF, warmed to room temperature and stirred for 11.5 h. The mixture was filtered through 1" of Celite in a 60 mL medium fritted glass funnel (aspirator vacuum) and the Celite washed with 400 mL of EtOAc. The solution was concentrated in vacuo to afford 682 mg of a crystalline solid. This material was purified by flash chromatography (30 mm column, 50 g of SiO_2 packed in 3:1 hexane-EtOAc). The crude residue was applied in 9 mL of EtOAc and eluted with 3:1 hexane-EtOAc (17 fractions of 25 mL). Fractions 4-14 afforded 448.5 mg (71%) of crystalline 138.

An analytical sample was prepared by two sublimations (80°C, 0.45 mm); mp 157.5-159°C: TLC (1:3 hexane-Et_2O) R_f 0.92; NMR (^1H, 270 MHz, $CDCl_3$) δ 6.57 (s, 1H), 5.87 (s, 1H), 4.95 (multiplet, 2H, H_2 and acetal-H), 4.07 (multiplet, 2H, H_4 and H_{12}), 2.68 (dd, J=6.8, 16.8 Hz, 1H, $H_{3\beta}$), 2.18 (dd, J=4.8, 16.8 Hz, 1H, $H_{3\alpha}$), 1.55 (s, 3H, CH_3), 1.36 (d, J=4.9 Hz, 3H, CH_3); IR (CH_2Cl_2)3050, 2960, 1730 (C=O), 1620, 1450, 1400. Mass spectrum m/e 167 (M-

CH_3CHO), 138, 124, 109. Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.12; H, 6.68.



138 155 156

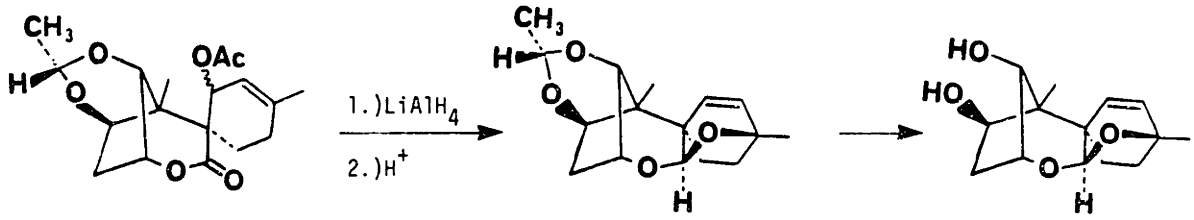
Diels-Alder adducts 155 and 156

A 50 mL Carius tube containing a magnetic stirring bar was charged with 448 mg (2.1 mmol) of α-methylene lactone 138, 1.1 mL (8.4 mmol) of 3-methyl-1-acetoxy-1,3-butadiene[112] and 49 mg (0.22 mmol) of butylated hydroxytoluene (BHT) in 21 mL of toluene. The resulting mixture was purged with Ar for 30 min. The tube was sealed and then heated in a 140°C oil bath for 48 h. The cooled reaction mixture was then concentrated in vacuo and the crude product was purified by column chromatography (40 mm column, 125 g of SiO_2, packed with 4:1 hexane-EtOAc, 50 mL fractions). The residue was applied with 10 mL of EtOAc and eluted with 4:1 hexane-EtOAc (24 fractions) and 2:1 hexane-EtOAc (20 fractions). Fractions 10-24 yielded 226 mg of recovered 138 (approximately 60% pure; hence, 30% yield of recovered 138. This

was suitable for use again without further purification). Fractions 25-41 afforded 400 mg (57%) of a 5:2 mixture, respectively, of crystalline Diels-Alder adducts 155, mp 234-236°C, and 156, mp 260.5-262°C; TLC (2:1 hexane-EtOAc) R_f 0.44. Pure samples of each adduct were obtained by fractional recrystallization from 2:1 hexane-benzene.

Data for major adduct 155:[114] NMR (^{1}H, 270 MHz, $CDCl_3$) δ 5.93 (br m, $W_{1/2}$=7.8 Hz, 1H, H_{10}), 5.22 (br m, $W_{1/2}$=6.8 Hz, 1H, H_{11}), 4.92 (q, J=4.8 Hz, 1H, acetal-H), 4.83 (d, J=6.6 Hz, 1H, H_2), 4.32 (dd, J=2.1, 4.8 Hz, 1H, H_4), 4.28 (br m, $W_{1/2}$=4.1 Hz, 1H, H_{12}), 2.73 (dd, J=6.6, 16.9 Hz, $H_{3\beta}$), 2.45 (m, 1H, H_{8a}), 2.16 (dd, J=4.8, 16.8 Hz, 1H, $H_{3\alpha}$), 2.08 (s, 3H, CH_3), 1.95 (m, 1H, H_{8b}), 1.77 (multiplet, 2H, $H_{7a,7b}$), 1.73 (br s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.33 (d, J=4.8 H, 3Hz, CH_3); IR (CH_2Cl_2) 2970, 2905, 1740, 1600, 1450, 1405; Mass spectrum m/e 336 (parent ion), 293, 277 (M-OAc), 266, 251, 232, 212. Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.32; H, 7.03.

Data for minor adduct 156:[114] NMR (^{1}H, 250 MHz, $CDCl_3$) δ 6.09 (br m, $W_{1/2}$=9.4 Hz, 1H, H_{10}), 5.46 (br m, $W_{1/2}$=6.6 Hz, 1H, H_{11}), 4.95 (q, J=4.7 Hz, 1H, acetal-H), 4.88 (d, J=6.4 Hz, 1H, H_2), 4.47 (dd, J=2.2, 4.8 Hz, 1H, H_4), 4.32 (br m, $W_{1/2}$=5.3 Hz, 1H, H_{12}), 2.76 (dd, J=6.9, 17.1 Hz, 1H, $H_{3\beta}$), 2.08 (s, 3H, CH_3), 1.69 (br s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.37 (d, J=4.7 Hz, 3H, CH_3); IR (CH_2Cl_2) 2980, 2960, 2905, 1740, 1600, 1450, 1405; Mass spectrum m/e 336 (parent ion), 293 (M-CH_3CO), 266, 249, 211. Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.43; H, 7.47.

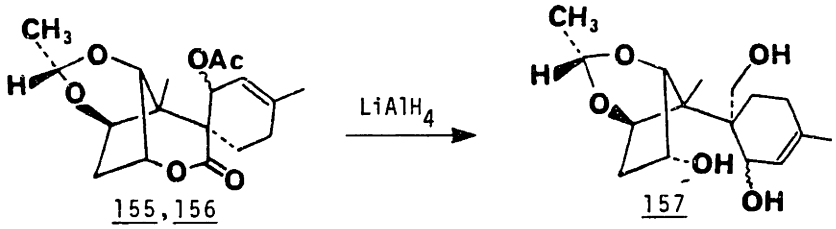


155,156 167 168

Diol-acetal 168

A solution of 31.4 mg (0.093 mmol) of a 3:1 mixture of 155 and 156 in 2.5 mL THF under Ar was treated with 21 mg (0.55 mmol) of $LiAlH_4$ and the resulting solution was stirred for 40 min at room temperature. Excess hydride was quenched by the addition of 4 drops of H_2O and then the reaction mixture was filtered through Celite with 30 mL of EtOAc and 30 mL of acetone. The resulting solution was concentrated in vacuo. The crude product was dissolved in 2.5 mL of C_6H_6 and treated with a catalytic amount of p-TsOH. The solution was stirred at room temperature for 15 min, then quenched with 10 mL of saturated aqueous $NaHCO_3$ and extracted three times with 10 mL of CH_2Cl_2. The combined extracts were concentrated in vacuo. The crude product was chromatographed on a 0.25-mm preparative TLC plate to afford 12.6 mg (48% yield) of 167. This material was fully characterized as the deprotected diol 168. Thus, in this instance, 3.5 mg (0.012 mmol) of 167 in 1 mL of CH_2Cl_2 was treated with 5.3 mg (0.0175 mmol) of N-phenyl selenophthalimide and a crystal of p-TsOH for

40 min. The reaction mixture was directly chromatographed on one half of a 0.25-mm preparative TLC plate (one development with 2:1 hexane-EtOAc) to yield 3.4 mg (100% yield; R_f 0.05-0.15) of 168: NMR (^1H, 270 MHz, $CDCl_3$) δ 6.35, 6.23 (AB, J=8.4 Hz, 2H, H_{10}, H_{11}), 4.69 (br s, $W_{1/2}$=4.7 Hz, 1H, H_{15}), 4.28 (d, J=5.4 Hz, 1H, H_2), 4.21 (br m, $W_{1/2}$=15.9 Hz, 1H, H_4), 4.06 (br s, $W_{1/2}$=5.4 Hz, 1H, H_{12}), 2.64 (dd, J=7.3, 15.9 Hz, 1H, $H_{3\alpha}$), 1.3-2.15 (multiplet, 6H), 1.42 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); IR (CH_2Cl_2) 3670, 3600, 3040, 2940, 2875, 1605, 1445; Mass spectrum m/e 252 (parent ion), 234 (M-H_2O), 206, 188, 145. High resolution mass spectrum. Calcd. for $C_{14}H_{20}O_4$: 252.13616. Found: 252.13944.



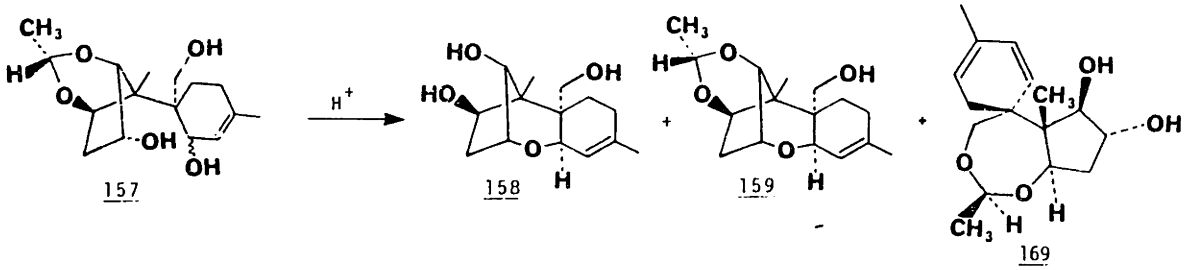
155,156 157

Triols 157

To a 0°C solution of 400 mg (1.2 mmol) of the mixture of 155 and 156 in 65 mL of reagent grade DME under Ar was added 600 mg (15.8 mmol) of $LiAlH_4$. The resulting mixture was stirred for one hour at room temperature and then heated at reflux for 20 h.

Excess hydride in the cooled reaction mixture was quenched by the careful and cautious addition of 24 drops of H_2O. To this mixture was then added sequentially 0.6 mL of H_2O, 0.6 mL of 3N aqueous NaOH and 1.8 mL of H_2O and the resulting mixture stirred for 2 h. The reaction mixture was filtered through Celite with 400 mL of EtOAc. The resulting solution was concentrated in vacuo to yield 363 mg (100%) of a white solid which was used directly in the next step without further purification.

Trichothecene triol 158



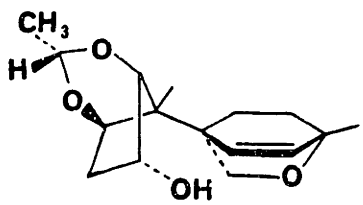
Method A: From triols 157

A suspension of 35 mg (0.12 mmol) of 157 (sparingly soluble) in 20 mL of benzene was treated with 6 drops of H_2O and a catalytic amount of pyridinium tosylate. The solution was heated to reflux for 30 min, at which point 157 had completely dissolved and been consumed (TLC analysis). Solid $NaHCO_3$ was added to the

cooled reaction mixture and then the mixture was concentrated in vacuo. The residue was dissolved in acetone, filtered and again concentrated in vacuo. The resulting product mixture was separated by chromatography on a 0.25-mm preparative TLC plate (one development with 1:1 hexane-EtOAc) to give 12.7 mg (42%) of triol 158 (R_f 0.15) and 7.6 mg (23%) of ethylidene acetal 159 (R_f 0.68).

This cyclization procedure was scaled up to 363 mg (1.2 mmol) of 157 (the preparation of which is described in the previous experimental procedure) in 75 mL of benzene containing 20 drops of H_2O. In this case, the reaction was terminated after 40 min, the point at which all of 157 had dissolved (TLC analysis indicated that all of 157 had been consumed, but also indicated the additional presence of a previously undetected and unidentified component). The reaction was worked up as described above, and the crude product was purified by flash chromatography (20 mm column, 30 g of SiO_2 packed in 1:1 hexane-EtOAc; 10 mL fractions). The product mixture was applied in 10 mL of EtOAc and eluted with 1:1 hexane-EtOAc (9 fractions) and EtOAc (30 fractions). Fractions 3-11 afforded 90.8 mg (27% yield) of acetal 159. Fractions 16-32 afforded 106.6 mg of a mixture of triol 158 and an unidentified product[152] which was separated by chromatography on a 0.5-mm preparative TLC plate (one development with

(152) This substance has tentatively been assigned the structure 200.



200

1:3 hexane-EtCAc) to yield 48.9 mg (16% yield) of triol 158 (R_f 0.25; mp 40-44°C) and 11.1 mg of the unidentified byproduct[152] (R_f 0.53). Fractions 12-15 yielded an additional 125 mg of this byproduct.[152] This material was treated as above (C_6H_6, H_2O, catalytic pyridinium tosylate, reflux, 35 min) to afford after chromatography (0.5-mm preparative TLC plate) an additional 19.8 mg (110.6 mg total, 33% yield) of 159, 20.3 mg (69.2 mg total, 23% yield) of 158 and 12.3 mg (4% yield) of diene 169.

Data for acetal 159: TLC (1:1 hexane-EtOAc) R_f 0.54; NMR (^1H, 250 MHz, $CDCl_3$) δ 5.38 (br d, J=5.1 Hz, 1H, H_{10}), 5.09 (q, J=4.6 Hz, 1H, acetal-H), 4.80 (dd, J=2.2, 5.2 Hz, 1H, H_4), 4.53 (d, J=6.6 Hz, 1H, H_2), 4.15 (d, J=5.1 Hz, 1H, H_{11}), 4.04 (br s, $W_{1/2}$=6.3 Hz, 1H, H_{12}), 3.65, 3.54 (br AB, J=11.1 Hz, 2H, $H_{15a,15b}$) 2.66 (dd, J=5.2, 16.9 Hz, 1H, $H_{3\alpha}$), 2.30 (dd, J=6.6, 16.9 Hz, 1H, $H_{3\beta}$), 1.5-2.0 (multiplet, 4H), 1.71 (br s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.31 (d, J=4.6 Hz, 3H, CH_3); IR (CH_2Cl_2) 3710, 3010, 2960, 2935, 2850, 1605, 1455, 1435, 1400; Mass spectrum m/e 280 (parent ion), 265 (M-CH_3), 236 (M-CH_3CHO), 218, 205, 193, 175, 161.

Data for diol 158: TLC (1:1 hexane-EtOAc) R_f 0.07; NMR (^1H, 270 MHz, $CDCl_3$) δ 5.36 (dm, J=5.4 Hz, 1H, H_{10}), 4.47 (br m, $W_{1/2}$=16.8 Hz, 1H, H_2), 4.29 (dd, J=1.1, 4.9 Hz, 1H, H_4), 4.08 (br s, $W_{1/2}$=6.8 Hz, 1H, H_{12}), 3.63, 3.50 (AB, J=12.0 Hz, 2H, $H_{15a,15b}$), 3.42 (d, J=5.4 Hz, 1H, H_{11}), 2.47 (dd, J=7.4, 16.0 Hz, 1H, $H_{3\beta}$), 1.65-2.1 (multiplet, 5H), 1.70 (br s, 3H, CH_3), 1.26 (s, 3H, CH_3); IR (CH_2Cl_2) 3595, 3680-3140 (br), 2935, 1605, 1445; Mass spectrum m/e 254 (parent ion), 239 (M-CH_3), 218, 205, 193,

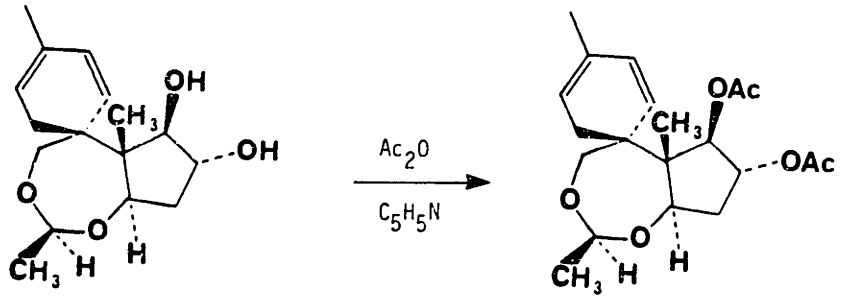
175, 161. High resolution mass spectrum. Calcd. for $C_{14}H_{22}O_4$: 254.15181. Found: 254.15246.

Data for diene 169: TLC (1:1 hexane-EtOAc) R_f 0.23; NMR (^1H, 270 MHz, $CDCl_3$) δ 6.02 (br s, 2H, H_{10}, H_{11}), 5.43 (br m, $W_{1/2}$=10.1 Hz, 1H, H_8), 4.97 (q, J=5.2 Hz, 1H, acetal-H), 4.27 (t, J=9.4 Hz, 1H, H_4), 4.07 (ddd, J=3.8, 6.6, 10.5 Hz, 1H, H_2), 3.85, 3.83 (AB, J=12.2 Hz, 2H, $H_{15a,15b}$), 3.78 (d, J=6.6 Hz, 1H, H_{12}), 1.76 (d, J=1.4 Hz, 3H, CH_3), 1.24 (d, J=5.2 Hz, 3H, CH_3), 0.91 (s, 3H, CH_3); IR (CH_2Cl_2) 3585, 3700-3100 (br), 3008, 2920, 1600, 1440; Mass spectrum m/e 280 (parent ion), 252, 232, 222, 204.

Method B: From Isomerically Pure Cycloadducts 155, 156

Isomerically pure 155 and 156 (less than 5% cross contamination by 250 MHz ^1H NMR analysis) were obtained by fractional crystallization as previously described. Both isomers were transformed to a mixture of 158, 159 and 169 when reduced with $LiAlH_4$ and then treated with an acid catalyst. It should be noted, however, that the cyclizations described below were performed before optimal conditions (pyridinium tosylate, C_6H_6, reflux) had been deduced. Thus, 45 mg of the major Diels-Alder adduct 155 was transformed ((1) $LiAlH_4$, DME, reflux; (2) catalytic pTsOH, CH_2Cl_2, RT, 5 min) to give 3.0 mg (8%) of 159, 4.1 mg (12%) of 158 and 6.0 mg (16%) of 169. Analogous treatment of 41.7 mg of the minor Diels-Alder adduct 156 ((1) $LiAlH_4$, DME, reflux; (2) CH_2Cl_2, p-TsOH (catalytic), 12 min (incomplete cycli-

zation); (3) p-TsOH (catalytic), dichloroethylene, 5h) afforded 5.4 mg (18% yield) of 159 and 4.6 mg (19%) of 169.

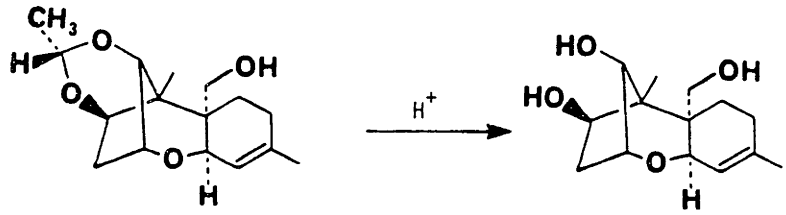


169 170

Diacetate 170

A solution of 2.9 mg (0.01 mmol) of 169 in 0.5 mL of CH_2Cl_2 was treated with 0.03 mL (0.03 mmol) of Ac_2O and a small crystal of N,N-dimethylamino-pyridine. The resulting mixture was stirred for 17.5 h at room temperature. Excess Ac_2O was quenched by the addition of 0.5 mL of CH_3OH and the reaction mixture stirred for an additional hour. The reaction mixture was then concentrated in vacuo and the product residue purified by chromatography on one half of a 0.25-mm preparative TLC plate (one development with 4:1 hexane-EtOAc) to yield 1.3 mg (35% yield; R_f 0.53-0.64) of diacetate 170: NMR (^1H, 250 MHz, $CDCl_3$) δ 5.98, 5.87 (AB, J=9.8 Hz, 2H, H_{10}, H_{11}), 5.33 (d, J=5.6 Hz, 1H, H_{12}), 5.27 (br m, $W_{1/2}$=12.5 Hz, 1H, H_8), 5.12 (m, 1H, H_2), 5.00 (q, J=5.5 Hz, 1H, acetal-H), 4.45 (t, J=9.4 Hz, 1H, H_4), 3.71, 3.57 (AB, J=12.2 Hz, 2H, $H_{15a,15b}$), 2.04 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 1.69 (br s, 3H, CH_3), 1.25 (d, J=5.5 Hz, 3H, CH_3), 1.03 (s, 3H, CH_3); IR

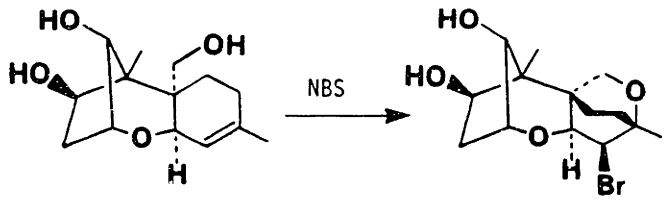
(CH_2Cl_2) 3020, 2955, 2920, 1735, 1605.



159 158

Deprotection of 159

A solution of 110 mg (0.39 mmol) of acetal 159 in 30 mL of reagent grade acetone was treated with 3 mL of 1N aqueous HCl and the resulting solution stirred for 5 h at room temperature. Solid $NaHCO_3$ was added and the mixture then concentrated in vacuo (to 0.3 mm). The product residue was dissolved in acetone, filtered through a plug of Kimwipe and again concentrated in vacuo to yield 100 mg of 158 (100%). This material was used directly in the next reaction without further purification.



158 160

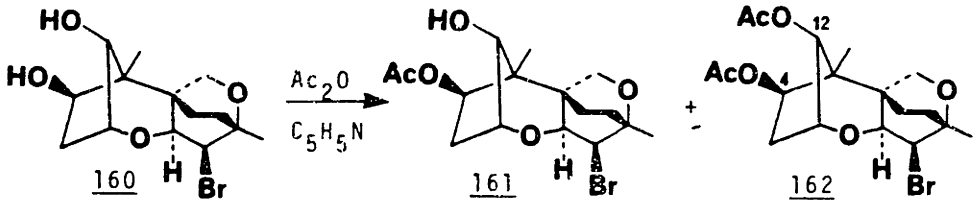
Bromoether 160

A solution of 100 mg (0.39 mmol) of 158 (from the hydrolysis of acetal 159) in 10 mL of reagent grade CH_3CN was treated with 96 mg (0.54 mmol) of NBS. The resulting mixture was stirred at room temperature for 20 min and then concentrated in vacuo to a volume of approximately 4 mL. This solution was then directly chromatographed on two 0.5-mm preparative TLC plates (three developments with 1:1 hexane-EtOAc) to afford 115 mg (70%) of a 1:1 mixture of 160 and succinimide. A parallel experiment using 69 mg (0.27 mmol) of 158 afforded 97 mg (84%) of the mixture of 160 and succinimide. Such mixtures could not be separated by chromatography and routinely were used as such in the next step of the synthesis.

A pure sample of bromoether 160 was obtained by deacylation of diacetate 162. Thus, a solution of 42 mg (0.01 mmol) of 162 in 10 mL of saturated methanolic K_2CO_3 was stirred for 19 h at ambient temperature. The reaction mixture ws then adjusted to pH 5 by the addition of 50 drops of 1N aqueous HCl. The resulting solution was concentrated in vacuo (to 0.3 mm) and the product

residue purified by chromatography on 3/4 of a 0.25-mm preparative TLC plate (one development with 1:3 hexane-EtOAc) to afford 29.4 mg (88%; R_f 0.37-0.52) of bromoether 160: NMR (^1H, 270 MHz, $CDCl_3$) δ 4.46 (dd, J=1.3, 5.3 Hz, 1H, H_2), 4.20 (dd, J=1.7, 8.6 Hz, 1H, H_{11}), 4.14 (m, 1H, H_4), 4.01 (br d, J=4.9 Hz, 1H, H_{12}), 3.79 (d, J=9.5 Hz, 1H, $H_{15\beta}$), 3.68 (dd, J=3.1, 9.5 Hz, 1H, $H_{15\alpha}$), 3.63 (dd, J=2.3, 8.6 Hz, 1H, H_{10}), 2.55 (dd, 7.4, 16.0 Hz, 1H, $H_{3\alpha}$), 1.95-2.3 (multiplet, 5H), 1.6-1.85 (m, 2H), 1.27 (s, 3H, CH_3), 1.04 (s, 3H, CH_3); IR (CH_2Cl_2) 3600, 3575, 3400, 3040, 2960, 2940, 2880, 1485, 1450, 1380; Mass spectrum m/e 332, 334 (parent ions), 314, 316 ($M-H_2O$), 272, 235.

Monoacetate 161



Method A: Acylation of 160

A solution of 115 mg of the mixture of 160 and succinimide (78% of 160 by weight; hence, 0.31 mmol) in 4 mL of dry pyridine was treated with 0.04 mL (0.42 mmol) of reagent grade Ac_2O. The resulting mixture was stirred at room temperature and the progress of the reaction was monitored by analytical TLC (1:1 hexane-EtOAc; visualized with PMA stain). Periodically, 0.01 mL

(0.11 mmol) aliquots of Ac_2O were added; in this case, at 16 h, 22 h and at 34 h. After 60 h, a few drops of H_2O were added and the resulting solution concentrated *in vacuo*. The crude product was separated by chromatography on two 0.5-mm preparative TLC plates (one development with 1:1 hexane-EtOAc) to yield 38.1 mg (30%; R_f 0.45) of monoacetate *161*, 22.6 mg (16%; R_f 0.68) of diacetate *162*, and 55.3 mg of a mixture of recovered *160* and succinimide (which now contained approximately 50% of *160* by weight).(153)

A parallel experiment performed starting with 97 mg of a 1:1 mixture of *160* and succinimide afforded 30.7 mg (30%) of *161*, 15.0 mg (13%) of *162* and 55 mg of recovered *160* and succinimide.

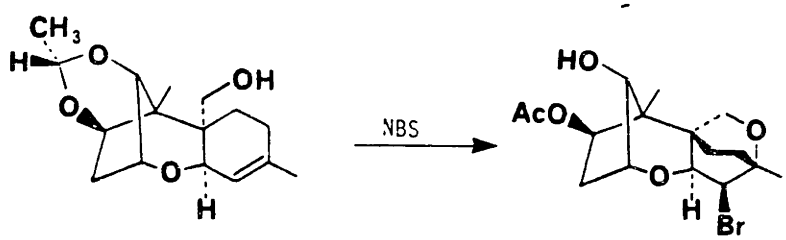
The two samples of recovered *160* and succinimide were combined (110.3 mg) and acylated; this time treated directly with excess Ac_2O (0.1 mL, 1.1 mmol) in 4 mL of dry pyridine for 4 days. This reaction was worked up and chromatographed, as described above, to give 26.5 mg of *161* and 42.2 mg of *162*.

Thus, a *total* of 169 mg (0.66 mmol) of diol *158* was converted to bromoether *160* which was acylated to give a *total* of 95.3 mg (38% overall) of *161* and 79.8 mg (29% overall) of *162*. Diacetate *162* was recycled to pure *160* by the procedure described in the preceding experiment.

(153) (a) None of the isomeric C.12 monoacetate was ever detected in NMR analyses of the crude product.
(b) The amount of recovered *160* was estimated based on the subsequent conversion of this mixture of *160* and succinimide (with excess Ac_2O) to monoacetate *161* and diacetate *162*, as described below.

Data for 161: NMR (^{1}H, 250 MHz, $CDCl_3$) δ 5.46 (dd, J=3.7, 7.9 Hz, 1H, H_4), 4.44 (dd, J=1.3, 6.1 Hz, 1H, H_2), 4.22 (dd, J=1.7, 8.6 Hz, 1H, H_{11}), 3.98 (br s, $W_{1/2}$=6.6 Hz, 1H, H_{12}), 3.89 (dd, J=2.8, 9.8 Hz, 1H, H_{15a}), 3.75 (d, J=9.8 Hz, 1H, H_{15b}), 3.74 (dd, J=2.3, 8.6 Hz, 1H, H_{10}), 2.49 (dd, J=7.9, 15.9 Hz, 1H, $H_{3\alpha}$), 1.6-2.3 (multiplet, 5H), 2.08 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 0.91 (s, 3H, CH_3); IR (CH_2Cl_2) 3580, 2955, 2925, 2875, 1730 (C=O), 1600; Mass spectrum m/e 374, 376 (parent ions), 314, 316, 295, 271, 273, 235.

Data for 162: NMR (^{1}H, 250 MHz, $CDCl_3$) δ 5.43 (dd, J=3.8, 7.6 Hz, 1H, H_4), 5.16 (br s, $W_{1/2}$=5.3 Hz, 1H, H_{12}), 4.42 (d, J=4.0 Hz, 1H, H_2), 4.21 (d, J= 8.6 Hz, 1H, H_{11}), 3.90 (dd, J=2.4, 9.6 Hz, 1H, H_{15a}), 3.70-3.77 (m, 2H, H_{10}, H_{15b}), 2.49 (dd, J=7.6, 15.6 Hz, 1H, $H_{3\alpha}$), 1.5-2.3 (multiplet, 5H), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 0.78 (s, 3H, CH_3).

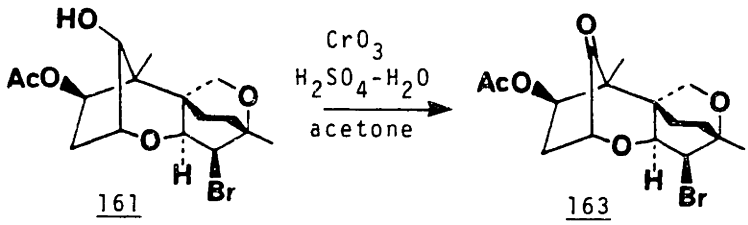


159 161

Method B: From 159

A solution of 3.4 mg (0.0012 mmol) of 159 in 0.5 mL of CH_3CN was treated with 6 mg (0.034 mmol) of NBS and the resulting

solution was stirred for 4.2 h at room temperature. The reaction mixture was concentrated in vacuo and the product residue was chromatographed on 1/2 of a 0.25-mm preparative TLC plate (one development with 1:1 hexane-EtOAc) to afford 1.4 mg of 161 (31% yield; R_f 0.57-0.69). Attempts to improve the yield of 161 from this reaction were unsuccessful.

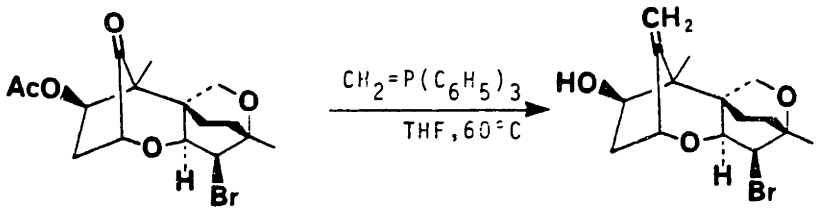


161 163

Ketone 163

A solution of 79.8 mg (0.21 mmol) of monoacetate 161 in 10 mL of reagent grade acetone was treated with a slight excess of Jones reagent (15 drops) and the resulting mixture stirred for 30 min at room temperature. Excess oxidant was then quenched with six drops of isopropanol. A small amount of solid $NaHCO_3$ was added and the resulting mixture was then filtered through Celite (a 0.5 inch pad in a Pasteur pipette) with 20 mL of acetone. The resulting solution was concentrated in vacuo to afford 163, the 250 MHz ^1H NMR spectrum of which was very clean. A small sample was chromatographed on 3/4 of a 0.25-mm preparative TLC plate (one development with 1:1 hexane-EtOAc) to afford 9.0 mg (R_f

0.82-0.92) of pure 163, which was used for characterization purposes. The remaining crude product 59.6 mg (88% total yield) was used directly in the following reaction, without purification: NMR (^{1}H, 250 MHz, $CDCl_3$) δ 5.62 (dd, J=3.9, 8.8 Hz, 1H, H_4), 4.28 (dd, J=1.3, 8.7 Hz, 1H, H_{11}), 4.17 (multiplet, 2H, H_2, H_{10}), 3.95 (dd, J=2.6, 9.7 Hz, 1H, $H_{15\alpha}$), 3.68 (d, J=9.7 Hz, 1H, $H_{15\beta}$), 2.79 (dd, J=8.8, 16.3 Hz, 1H, $H_{3\beta}$), 1.5-2.3 (multiplet, 5H), 2.04 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 0.82 (s, 3H, CH_3); IR (CH_2Cl_2) 3045, 2975, 2940, 2880, 1768 (C=0), 1740 (C=0), 1450, 1420, 1372, 1228; Mass spectrum m/e 372, 374 (parent ions), 330, 332 (M-OAc), 312, 314, 284, 286.



163 62

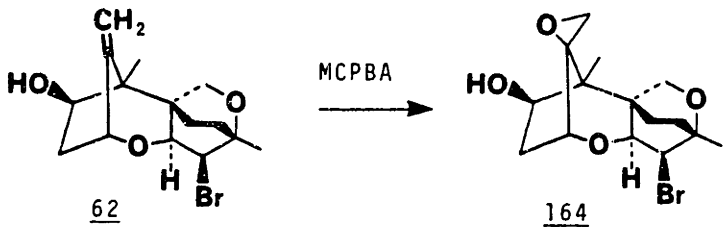
Olefin 62

A solution of 58 mg (0.16 mmol) of ketone 163 in 3 mL of THF was added dropwise to a solution of 1.0 mmol of methylenetriphenylphosphorane in 10 mL of THF under Ar. (The ylid was prepared in the usual fashion from 370 mg (1.0 mmol) of methyl triphenylphosphonium bromide and a slight excess of n-BuLi in hexane). The reaction mixture was heated to reflux for 3 h. To

the cooled reaction mixture was added 7 drops of H_2O, with the immediate formation of a white precipitate. The reaction mixture was then filtered through one inch of Celite with acetone and the resulting solution concentrated *in vacuo*. The crude product residue was filtered through 20 g of SiO_2 with 120 mL of 1:1 hexane-EtOAc (to remove $(C_6H_5)_3PO$ and phosphonium salts) and the solution concentrated again *in vacuo*. The residue was then chromatographed on a 0.5-mm preparative TLC plate (one development with 2:1 hexane-EtOAc) to yield 27.5 mg (52%, R_f 0.12-0.28) of 62. Also isolated was 3.2 mg (R_f 0.92; 1:1 hexane-EtOAc) of a substance presumably derived from retro-aldol cleavage (methyl doublet at δ 0.97, J=6.8 Hz) of deacylated ketone 163. From a small scale experiment (5 mg of chromatographed 163; 6 equiv. of $(C_6H_5)_3P=CH_2$, 60°C, 2.25 h), 2.8 mg (65% yield) of 62 was isolated along with 0.7 mg (15% yield; R_f 0.27-0.40; 4:1 hexane-EtOAc) of the acetate derivative of 62.

Data for 62: NMR (^1H, 270 MHz, $CDCl_3$) δ 5.19 (s, 1H, H_{13a}), 4.72 (s, 1H, H_{13b}), 4.58 (d, J=5.2 Hz, 1H, H_2), 4.33 (br m, $W_{1/2}$=17.2 Hz, 1H, H_4), 4.21 (dd, J=1.5, 8.6 Hz, 1H, H_{11}) 3.82 (dd, J=2.4, 8.6 Hz, 1H, H_{10}), 3.74 (br s, 2H, $H_{15a,15b}$), 2.61 (dd, J=7.3, 15.5 Hz, 1H, $H_{3\alpha}$), 2.1-2.25 (m, 1H), 1.7-1.9 (m, 2H), 1.66 (ddd, J=3.1, 5.2, 15.5 Hz, 1H, $H_{3\beta}$), 1.51 (br d, J=6.1 Hz, 1H), 1.35-1.45 (m, 1H), 1.26 (s, 3H, CH_3), 0.92 (s, 3H, CH_3); IR (CH_2Cl_2) 3605, 3700-3300 (br), 3045, 2965, 2938, 2880, 1680, 1483, 1450; Mass spectrum m/e 328, 330 (parent ions), 313, 315 ($M-CH_3$), 284, 286, 219.

Epoxide 164

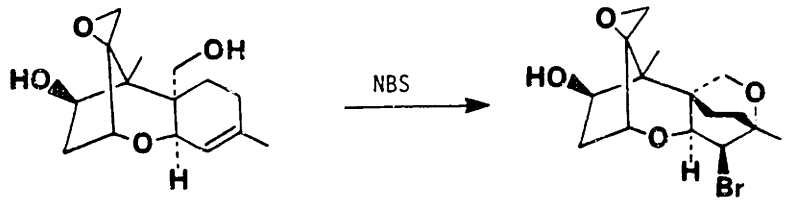


62 164

Method A: From Olefin 62

A solution of 25.5 mg (0.078 mmol) of 62, 40 mg (0.47 mmol) of $NaHCO_3$ and 29 mg (148 umol) of 88% MCPBA in 3 mL of CH_2Cl_2 was stirred at room temperature for 21 h. The reaction mixture was then filtered through a Kimwipe plug with 15 mL of acetone and the resulting solution concentrated in vacuo. The product residue was chromatographed on a 0.25-mm preparative TLC plate (one development with 1:1 hexane-EtOAc) to yield 26.8 mg (99%; R_f 0.39-0.58) of crystalline, synthetic epoxide 164, mp 227-229°C: NMR (^1H, 250 MHz, $CDCl_3$) δ 4.33 (dd, J=3.2, 7.5 Hz, 1H, H_4), 4.23 (dd, J=1.8, 8.6 Hz, 1H, H_{11}), 3.98 (d, J=5.3 Hz, 1H, H_2), 3.76 (multiplet, 3H, H_{10},H_{15a},H_{15b}), 3.14, 2.78 (AB, J=3.8 Hz, 2H,

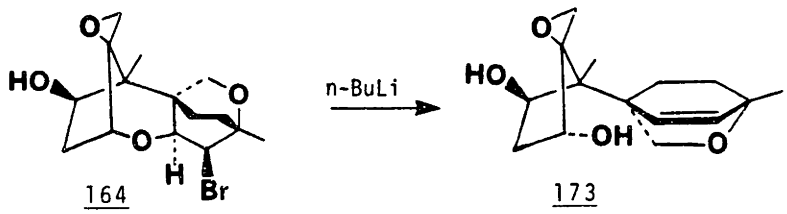
$H_{13a,13b}$), 2.64 (dd, J=7.5, 15.9 Hz, 1H, $H_{3\alpha}$), 2.22 (dd, J=10.1, 13.2 Hz, 1H), 1.5-2.1 (multiplet, 5H), 1.28 (s, 3H, CH_3), 0.72 (s, 3H, CH_3); IR (CH_2Cl_2) 3690, 3045, 2970, 2940, 2880, 1455, 1380; Mass spectrum m/e 326, 328 (M-H_2O), 313, 315 (M-CH_2OH), 303, 301, 300, 298, 271, 236.



1 164

Method B: From natural verrucarol

To a solution of 25 mg (0.94 mmol) of verrucarol (derived from natural anguidine)[125] in 3 mL of CH_3CN was added 25 mg (0.14 mmol) of NBS and the resulting solution stirred at room temperature for 15 min. The reaction mixture was then concentrated in vacuo and the product residue purified by chromatography on a 0.5-mm preparative TLC plate (one development with 1:1 hexane-EtOAc). In this manner 42 mg (100%) of a crystalline 1:1 mixture of naturally derived 164 and succinimide (R_f 0.28) was obtained. A pure sample (1-2 mg) of natural 164 was obtained (as unconsumed reactant) upon workup of the following n-BuLi reductive cleavage reaction. Natural 164 was identical in all respects (250 MHZ ^1H NMR, IR, Mass spectrum and TLC) to synthetic 164 described previously.

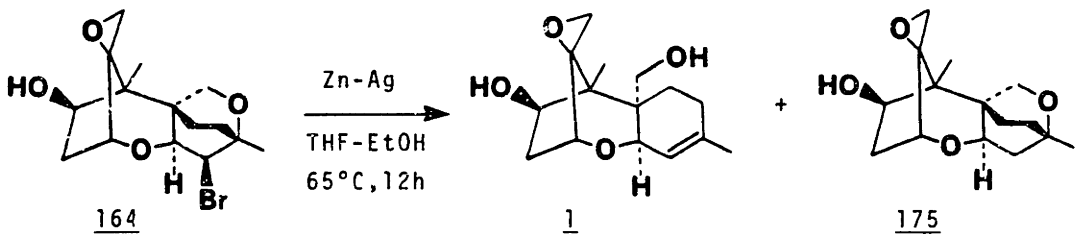


164 173

Syn-elimination product 173

A solution of 10.5 mg (0.030 mmol) of natural 164 in 0.5 mL of THF under Ar at room temperature was treated with 0.04 mL (0.09 mmol) of a 2.2M solution of n-BuLi in hexane. A precipitate formed immediately. This mixture was stirred for 5 min, and then the reaction was quenched by the addition of 4 drops of 1N aqueous HCl. The reaction mixture was directly chromatographed on 1/2 of a 0.25-mm preparative TLC plate (one development with 1:3 hexane-EtOAc) to yield 4.3 mg (54%; R_f 0.40-0.56) of 173 and 1.0 mg (10%; R_f 0.62-0.72) of recovered 164.

Data for 173: NMR (^1H, 250 MHz, $CDCl_3$) δ 6.37, 6.27 (AB, J=8.6 Hz, 2H, H_{10}, H_{11}), 4.60 (br dd, J=9.0, 12.4 Hz, 1H, H_4), 3.89 (d, J=7.7 Hz, 1H, H_{15a}), 3.83 (br m, $W_{1/2}$=12.5 Hz, 1H, H_2), 3.30 (dd, J=3.3, 7.7 Hz, H_{15b}), 3.10, 2.95 (AB, J=4.3 Hz, 2H, $H_{13a,13b}$), 2.1-1.6 (multiplet, 6H), 1.36 (s, 3H, CH_3), 1.4-1.2 (multiplet, 2H), 1.07 (s, 3H, CH_3); IR (CH_2Cl_2) 3595, 3700-3100, 3045, 2960, 2930, 2875, 1605, 1450; Mass spectrum m/e 266 (parent ion), 238, 236, 221, 207.



164 1 175

Synthetic verrucarol 1

A solution of 14 mg (41 umol) of synthetic 164 in 3 mL of THF and 0.6 mL of EtOH under Ar was treated with a large excess of freshly prepared ethereal Zn-Ag couple[129] (approximately 200 mg of Zn-Ag in 1.5 mL of Et_2O). The resulting heterogeneous mixture was maintained at 65°C (mild reflux) for 12h. The cooled reaction mixture was concentrated in vacuo. The crude residue was dissolved in acetone and filtered through a one inch pad of SiO_2 in a Pasteur pipette. The resulting solution was again concentrated in vacuo. The product residue was chromatographed on 3/4 of a 0.25-mm preparative TLC plate (one development with 1:3 hexane-EtOAc) to yield 8.9 mg (81%; R_f 0.30-0.42) of pure synthetic verrucarol 1 and 2.1 mg (19%; R_f 0.42-0.50) of a substance identified as 175. Synthetic verrucarol was recrystallized from benzene-hexane to afford flat crystals, mp 170-171.5°C. In a similar fashion, natural verrucarol (obtained from Tamm) was also recrystallized ($C_6H_6$to afford colorless needles,

mp 160-161°C.

A sample of 9.3 mg (0.027 mmol) of naturally derived 164 was treated in a similar fashion (an excess of freshly prepared Zn-Ag couple, THF-EtOH (5:1), reflux, 8 h) to afford 4.7 mg (65%) of natural verrucarol. (Unconsumed 164 was detected in the crude product by analytical TLC, but was not isolated.) In this instance 175 was not detected. A trace of syn-elimination product 173 (~5%), however, was also formed. The variation in these results (ie., minor amounts of byproducts 173 or 175) is probably related to differences in the activity of the Zn-Ag couple (fresh batches were prepared for each experiment) employed in these experiments.

Data for verrucarol 1 (natural): NMR (^{1}H, 250 MHz, $CDCl_3$) δ 5.44 (dm, J=5.6 Hz, 1H, H_{10}), 4.63 (br m, $W_{1/2}$=18.8 Hz, 1H, H_4), 3.82 (d, J=5.4 Hz, 1H, H_2), 3.77, 3.57 (AB, J=11.9 Hz, 2H, $H_{15a,15b}$), 3.62 (d, J=5.6 Hz, 1H, H_{11}), 3.12, 2.82 (AB, J=3.9 Hz, 2H, $H_{13a,13b}$), 2.58 (dd, J=7.6, 15.7 Hz, 1H, $H_{3\alpha}$), 1.70-2.1 (multiplet, 5H), 1.73 (br s, 3H, CH_3), 0.95 (s, 3H, CH_3); IR (CH_2Cl_2) 3620, 3750-3350 (br), 3040, 2970, 2940, 1680, 1475; Mass spectrum m/e 266 (parent ion), 251 (M-CH_3), 235 (M-CH_2OH), 223, 217, 205.

Data for verrucarol 1 (synthetic): NMR (^{1}H, 250 MHz, $CDCl_3$) δ 5.44 (dm, J=5.6 Hz, 1H, H_{10}), 4.63 (ddd, J=2.7, 7.6, 10.0 Hz, 1H, H_4), 3.83 (d, J=5.3 Hz, 1H, H_2), 3.78 (dd, J=4.6, 11.9 Hz, 1H, H_{15a}), 3.62 (d, J=5.6 Hz, 1H, H_{11}), 3.57 (dd, J=5.6, 11.9 Hz, 1H, H_{15b}), 3.12, 2.82 (AB, J=3.9 Hz, 2H, $H_{13a,13b}$), 2.58 (dd, J=7.6, 15.8 Hz, 1H, $H_{3\alpha}$), 1.65-2.1 (multiplet, 5H), 1.73 (br s, 3H,

CH_3), 1.66 (d, J=10.0 Hz, 1H, OH (to H_4)), 1.36 (t, J=5.3 Hz, 1H, OH (to $H_{15a,15b}$)), 0.95 (s, 3H, CH_3); IR (CH_2Cl_2) 3620, 3750-3350 (br), 3040, 2970, 2940, 1680, 1475; Mass spectrum m/e 266 (parent ion), 251 ($M-CH_3$), 235 ($M-CH_2OH$), 223, 217, 205.

Data for 175: NMR (^1H, 250 MHz, $CDCl_3$) δ 4.32 (m, 1H, H_4), 3.75-3.87 (multiplet, 4H, H_2,H_{11},H_{15a},H_{15b}), 3.08, 2.79 (AB, J=3.9 Hz, 2H, $H_{13a,13b}$), 2.61 (dd, J=7.3, 15.6 Hz, 1H, $H_{3\beta}$), 1.95-2.2 (multiplet, 2H), 1.90 (ddd, J=3.2, 5.3, 15.6 Hz, 1H, $H_{3\alpha}$), 1.5-1.8 (multiplet, 4H), 1.38 (dd, J=5.7, 13.2 Hz, 1H), 1.12 (s, 3H, CH_3), 0.73 (s, 3H, CH_3); IR (CH_2Cl_2) 3600, 3040, 2980, 2940, 2870, 1450, 1380; Mass spectrum m/e 266 (parent ion), 251 ($M-CH_3$), 248 ($M-H_2O$), 235, ($M-CH_2OH$), 223, 220, 204.

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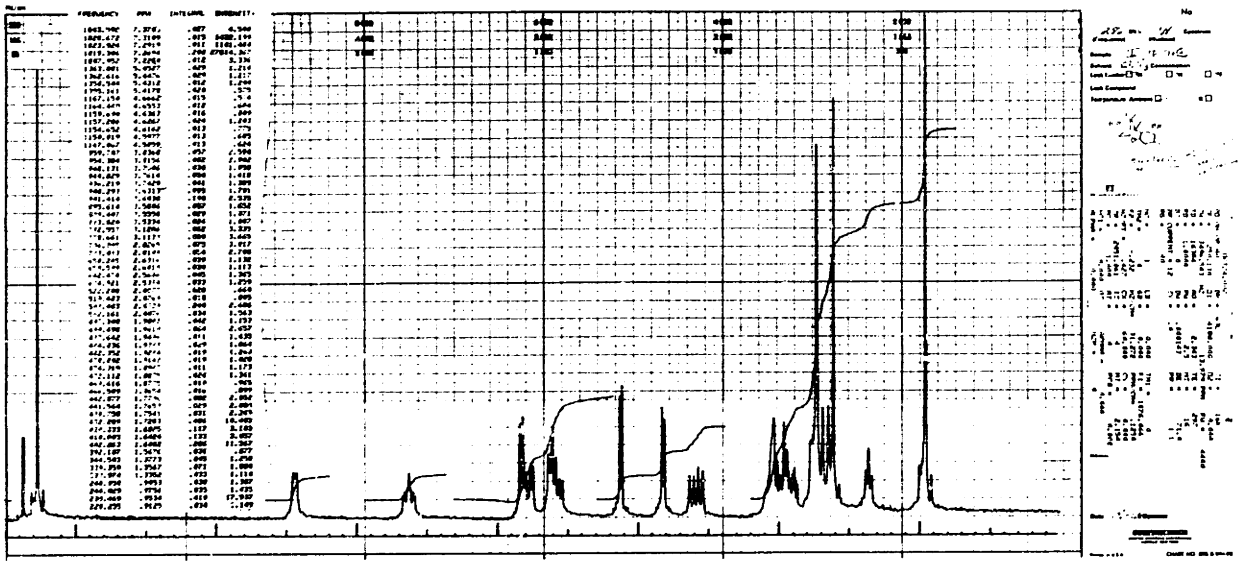
^{1}H (250 MHz) NMR Spectrum

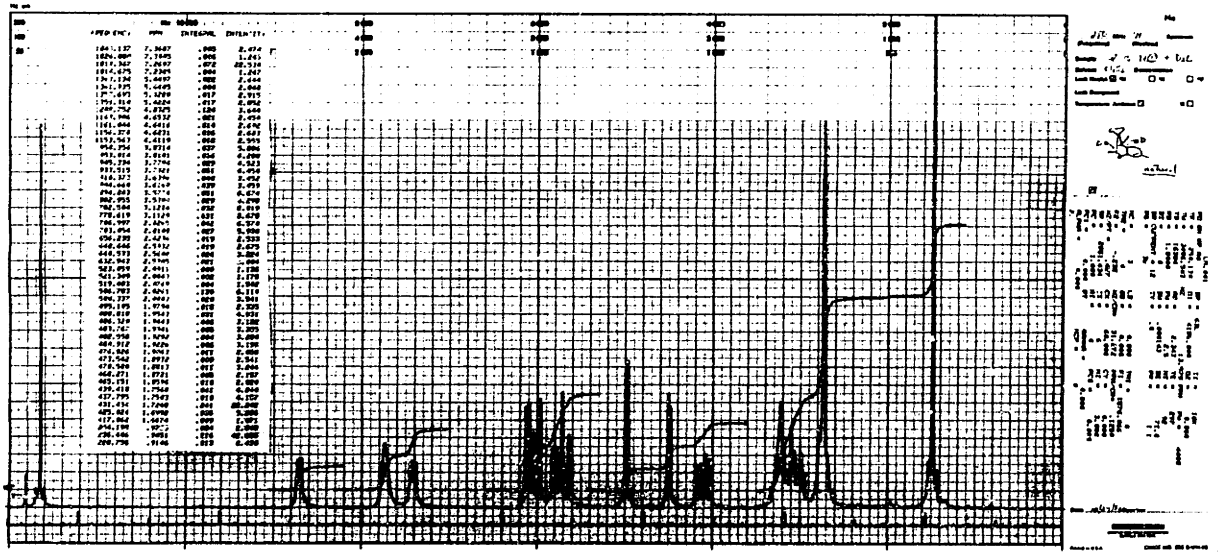


Synthetic verrucarol

Natural verrucarol

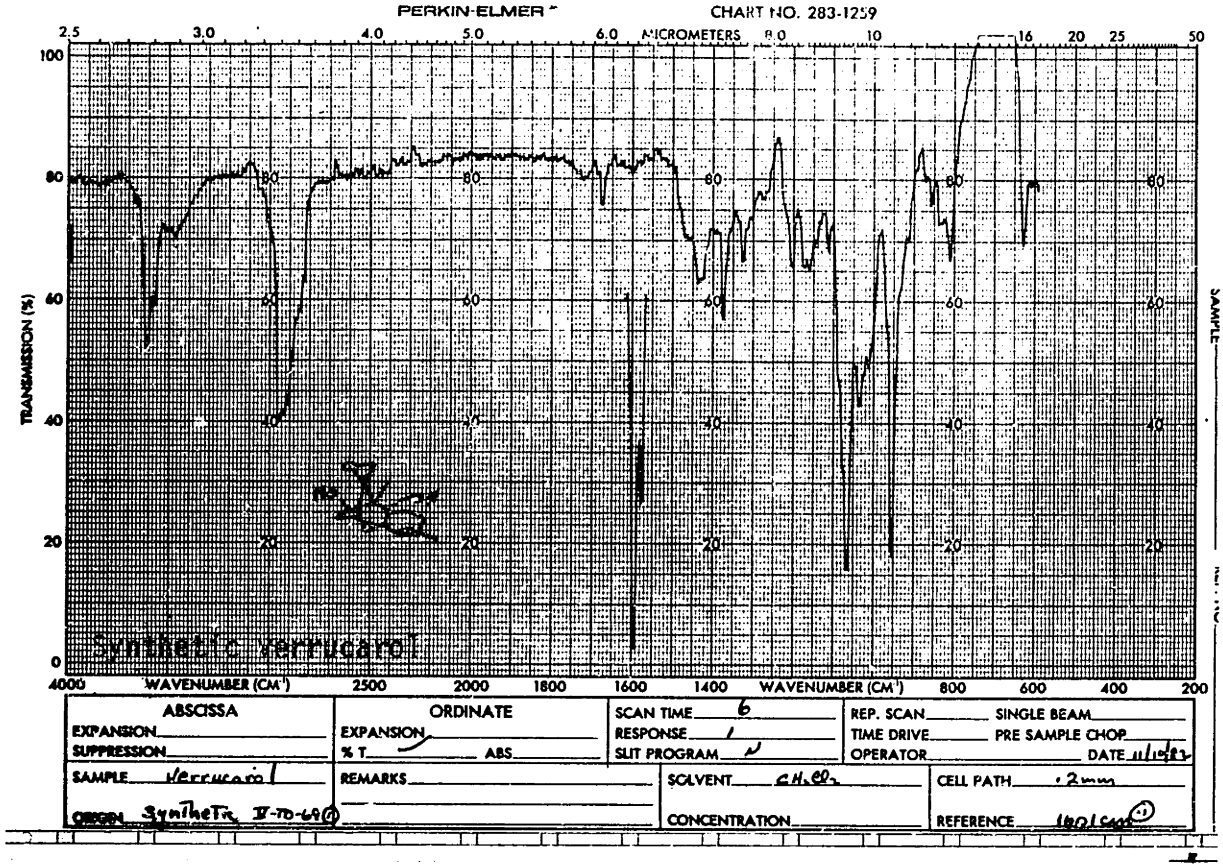
^1H (250 MHz) NMR Spectrum ($+D_2O$)

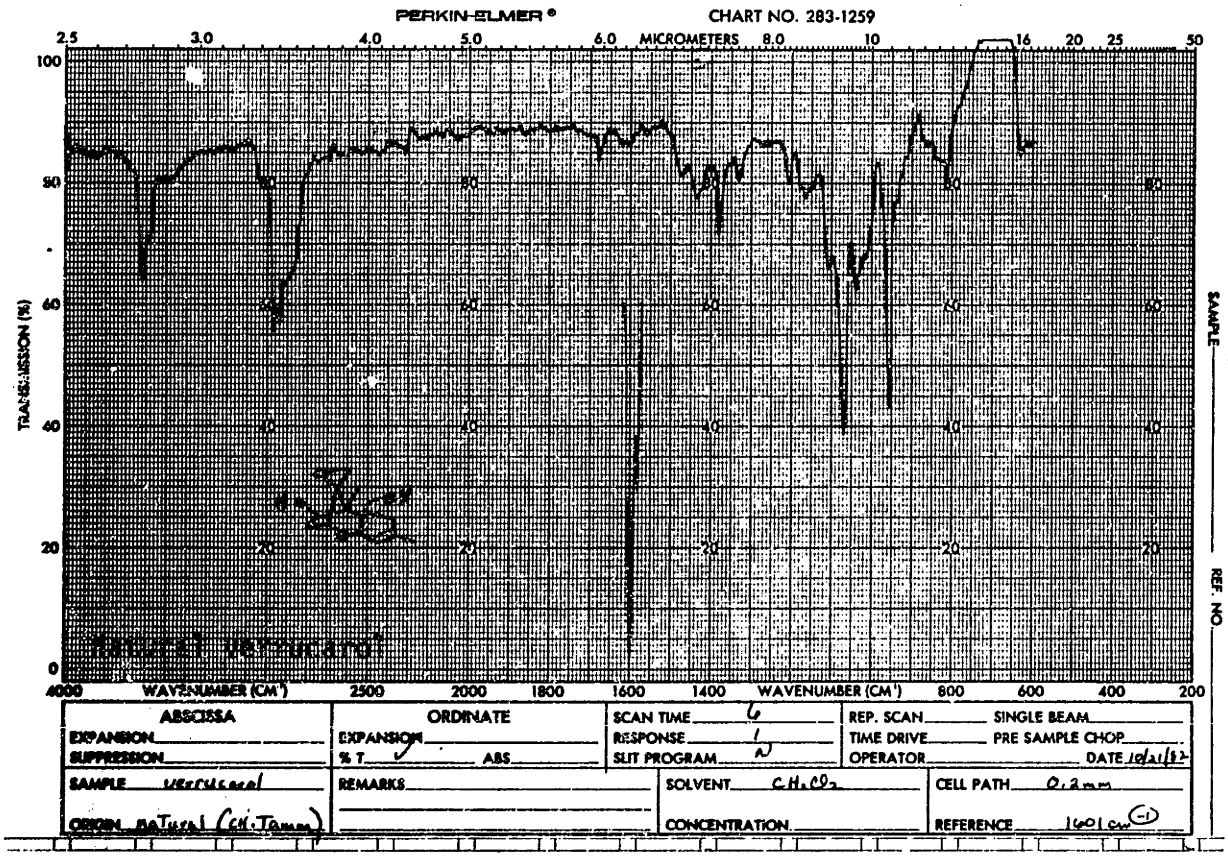
Synthetic verrucarol



Natural verrucarol

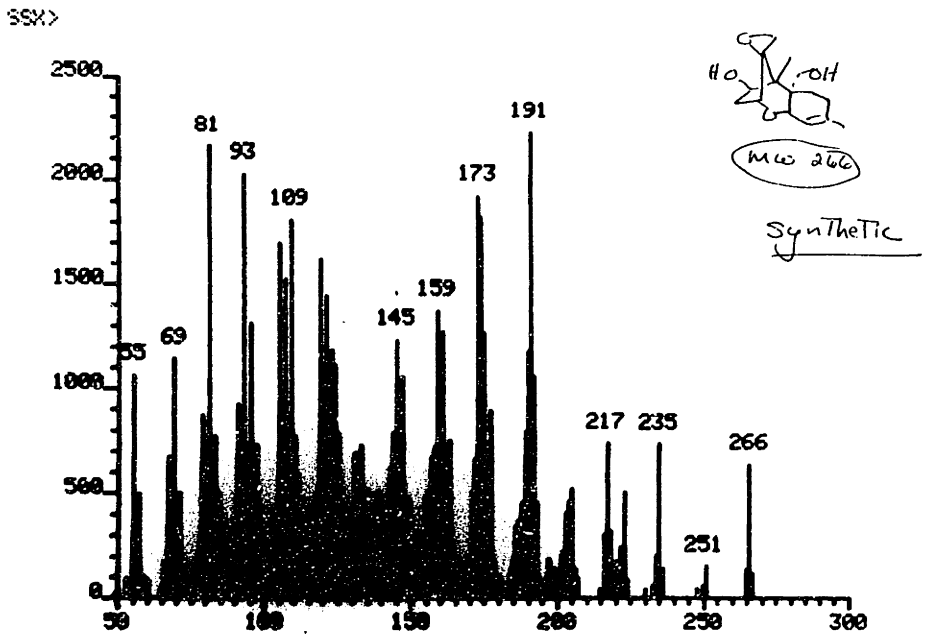
Infrared Spectrum





Mass Spectrum

J - TD-69①



MW 266

Synthetic

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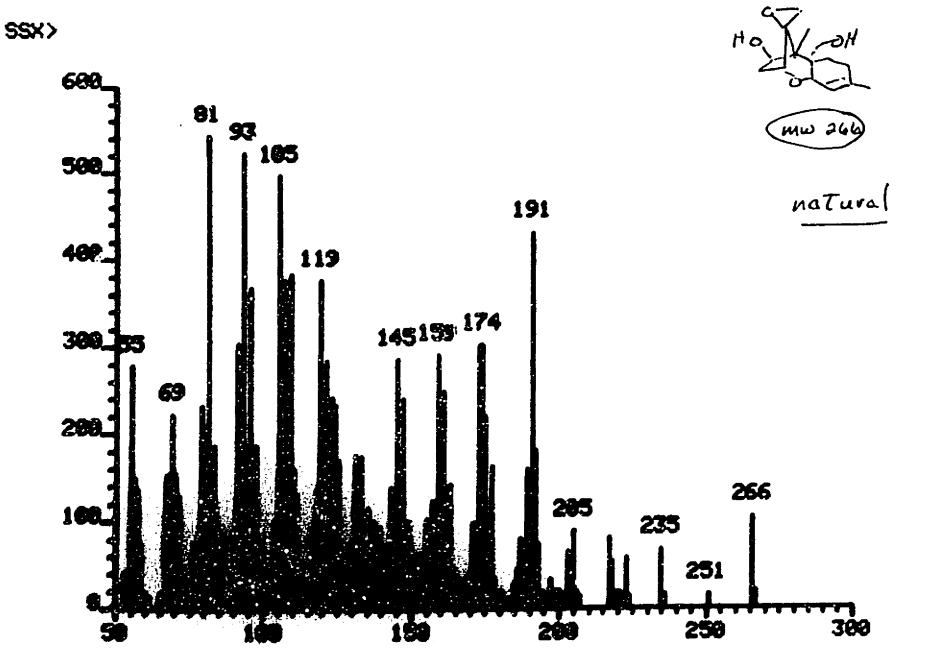
Synthetic verrucarol



MW 266

natural

ANALYSIS NAME: D16001.DAT SPEC# 50 NORM: A /SCALE: 600
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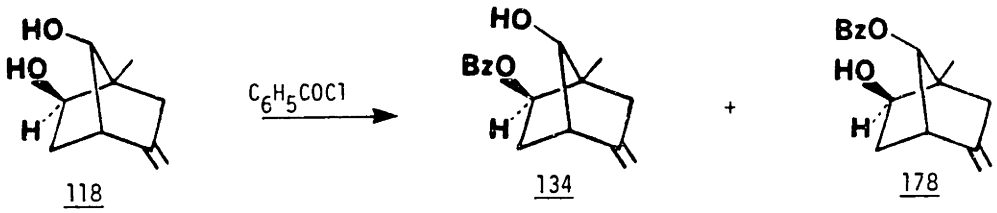
Natural verrucarol

Experimental Procedures for Chapter Four.



Bicyclo[2.2.1]1-methyl-2(R^*)-benzoyloxy-5-methylene-heptan-7(S^*)-ol 134 and Bicyclo[2.2.1]1-methyl-5-methylene-7(S^*)-benzoyloxy-heptan-2(R^*)-ol 178

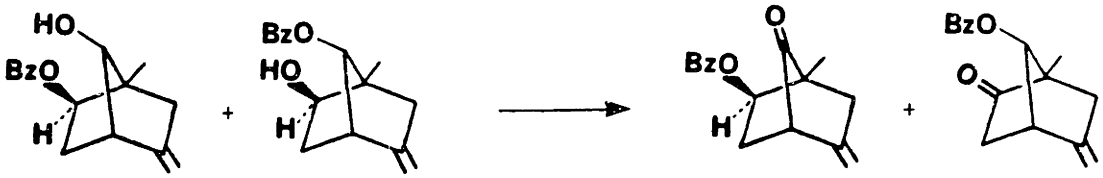
To a 0°C solution of 1.09 g (7.08 mmol) of 118 in 15 mL of pyridine under Ar was added dropwise 0.74 mL (6.37 mmol) of benzoyl chloride. The resulting mixture was stirred at room temperature for 160 min.

The mixture was then poured into 250 mL of 1N aqueous HCl and extracted three times with 100 mL of Et_2O. Each extract was washed with 30 mL of 1N aqueous HCl. The combined extracts were dried over Na_2SO_4, filtered and concentrated in vacuo.

The product residue was purified by flash chromatography (40 mm column, 100 g of SiO_2 packed in 3:1 hexane-Et_2O). The residue was applied in 10 mL of Et_2O and eluted with 3:1 hexane-Et_2O (25 mL fractions). Fractions 4-23 yielded 1.26 g (69%) of a 78:22 mixture, respectively, of 134 and 178. This inseparable mixture was used directly in the next step. Fractions 25-56 yielded 224 mg of recovered 118 (21%).

Data for 134 (measured on the 78:22 mixture): NMR (^{1}H, 270 MHz, $CDCl_3$) δ 5.05 (ddd, J=6.8, 3.9, 1.5 Hz, 0.78H, H_4), 4.92 (br m, $W_{1/2}$=7.3 Hz, 0.78H, vinyl-H), 4.68 (br m, $W_{1/2}$=6.1 Hz, 0.78H, vinyl-H), 3.73 (br m, $W_{1/2}$=11.5 Hz, 0.78H, H_{12}), 2.73 (br m, $W_{1/2}$=8.4 Hz, 0.78H), 1.9-2.3 (m, 3.12H), 1.23 (s, 2.34H, CH_3).

Data for 178: (NMR ^{1}H, 270 MHz, $CDCl_3$) δ 4.90-4.93 (m, 0.22H, H_{12}), 4.89 (br m, $W_{1/2}$=5.4 Hz, 0.22H, vinyl-H), 4.71 (br m, $W_{1/2}$=5.4 Hz, 0.22H, vinyl-H), 3.70 (br m, 0.22H, H_4), 2.96 (br m, $W_{1/2}$=9.6 Hz, 0.22H), 1.90-2.30 (m, 0.88H), 1.26 (s, 0.66H, CH_3).



134 178 179 180

Bicyclo[2.2.1]1-methyl-2(R*)-benzoyloxy-5-methyleneheptan-7-one 179 and Bicyclo[2.2.1]1-methyl-5-methylene-7(S*)-benzoyloxy-heptan-2-one 180

To a -60°C solution of 0.65 mL of dry DMSO (9.17 mmol) in 50 mL of CH_2Cl_2 was added 1.16 mL of trifluoroacetic anhydride[72] (8.18 mmol) and the resulting mixture stirred for 15 min. A solution of 1.41 g (5.47 mmol) of the mixture of alcohols 134 and 178 in 10 mL of CH_2Cl_2 was then added dropwise. This mixture was

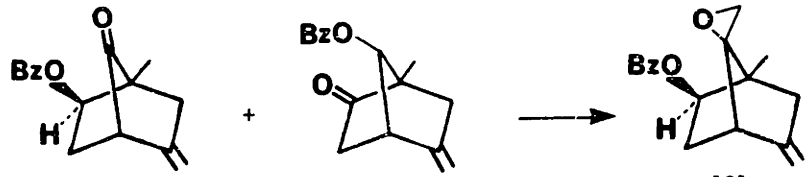
stirred for 30 min, then 3.5 mL (25.3 mmol) of triethylamine was added. The reaction mixture was warmed to ambient temperature and stirred for 40 min.

The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography (40 mm column, 115 g of SiO_2 packed in 5:1 hexane-Et_2O). The product residue was applied in 10 mL of Et_2O and eluted with 5:1 hexane-Et_2O (25 mL fractions). Fractions 5-17 yielded 1.19 g of a mixture of ketones 179 and 180 (85%). As these ketones were not easily separable, this mixture was used directly in the next step without further purification. Analytical samples of each were prepared from samples of 179 and 180 separated by HPLC fractionation of the next reaction product mixture.

Data for 179: mp 87-88.5°C (3-methylpentane); NMR (^1H, 270 MHz, $CDCl_3$) δ 5.22 (dd, J=2.6, 8.5 Hz, 1H, H_4), 5.05 (m, $W_{1/2}$=6.0 Hz, 1H, vinyl-H), 4.85 (m, $W_{1/2}$=6.4 Hz, 1H, vinyl-H), 2.74 (d, J=4.6 Hz, 1H, H_2), 2.50 (br m, $W_{1/2}$=6.4 Hz, 2H, $H_{6a,6b}$), 2.44 (dd, J=8.5, 13.7 Hz, 1H, $H_{3\alpha}$), 2.08 (ddd, J=2.6, 4.6, 13.7 Hz, 1H, $H_{3\beta}$), 1.14 (s, 3H, CH_3); IR (CH_2Cl_2) 3060, 2970, 2940, 2880, 1780, 1718, 1665, 1600, 1585; Mass spectrum m/e 134 (M-C_6H_5COOH), 120, 105, 91, 77. Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H,6.29. Found: C, 75.01; H, 6.29.

Data for 180: mp 77.5-78.0°C (3-methylpentane); NMR (^1H, 270 MHz, $CDCl_3$) δ 5.19 (m, $W_{1/2}$=6.4 Hz, 1H, H_{12}), 5.15 (m, $W_{1/2}$=5.7 Hz, 1H, vinyl-H), 4.89 (m, $W_{1/2}$=7.2 Hz, 1H, vinyl-H), 3.32 (dd, J=2.4, 4.6 Hz, 1H, H_2), 2.64 (ddd, J=1.5, 4.6, 17.6 Hz, 1H, $H_{3\beta}$), 2.46 (dm, J=17.1 Hz, $W_{1/2}$=7.6 Hz, 1H, H_{6a}), 2.27 (dm,

J=17.1 Hz, $W_{1/2}$=6.8 Hz, 1H, H_{6b}), 2.14 (dd, J=2.2, 17.6 Hz, 1H, $H_{3\alpha}$), 1.22 (s, 3H, CH_3); Mass spectrum m/e 151 ($M-C_6H_5CO$), 134 ($M-C_6H_5COOH$), 123, 105, 77. Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.05; H, 6.24.



179 + 180 → 181

Bicyclo[2.2.1]1-methyl-2(R^*)-benzoyloxy-5-methylene-7((S^*)-spiroepoxymethano)-heptane 181

To an ice cold slurry of 3.06 g (15 mmol) of trimethylsulfonium iodide in 143 mL of THF was added 6.5 mL of a 2.3M solution of n-BuLi in hexane (15.0 mmol). This mixture was stirred for 10 min to give a 0.1M stock solution of the sulfonium ylid.

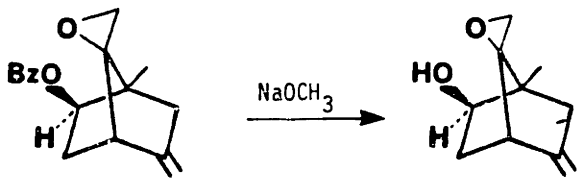
To a 0°C solution of 1.19 g (4.6 mmol) of the mixture of 179 and 180 in 50 mL of THF was slowly added 94 mL (2 equiv.) of the above 0.1M sulfonium methylide solution. The resulting mixture was stirred at 0°C for 105 minutes. The reaction mixture was then poured into a mixture of 200 mL of half saturated aqueous NaCl and 50 mL of CH_2Cl_2 and was extracted twice with 100 mL of CH_2Cl_2. The combined organic extracts were filtered through a glass fritted funnel and concentrated in vacuo.

The product residue was initially purified by flash chromatography (40 mm column, 118 g of SiO_2 packed with 10:1 hexane-Et_2O). The product residue was applied with 10 mL of Et_2O and eluted with 10:1 hexane-Et_2O (25 mL fractions). Fractions 8-26 yielded 817 mg of a mixture of epoxide 181, unreacted ketones 179 and 180, (154) and a small amount of an unidentifiable substance. None of the possible isomeric epoxides were detected here or in other repetitions of this reaction.

This mixture of compounds was separated by HPLC, on a Whatman reverse phase Partisil Magnum 9 (ODS-3) column using 1:1 CH_3CN-H_2O as the eluant at a flow rate of 6 mL/min. The above mixture was dissolved in 1 mL of CH_3CN and then 20 separate 30-40 mg injections of dissolved components were purified. Each chromatographic run required one recycle. Each separated component was recovered by diluting the eluant with 150 mL of H_2O and then extracting with CH_2Cl_2 (3x100 mL). The combined extracts were concentrated in vacuo. The residue was dissolved in CH_2Cl_2, filtered through a plug of cotton and again concentrated in vacuo. In this manner we obtained 85.3 mg (7.2%)

(154) In a separate experiment using 2.5 equivalents of sulfonium methylide, pure 179 and a longer reaction time, all of 179 was consumed to afford only a 34% yield of 181. Now, however, we also observed competitive loss of the benzoate ester of 181, producing the very volatile epoxide 185.

of recovered 180 ($t_{retention}$=32.0 min, K'=8.4), 96.2 mg (8.1%) of recovered 179 ($t_{retention}$=36.4 min, K'=9.7) and 302.5 mg (24%)of epoxide 181 ($t_{retention}$=40.8 min, K'=11.0). An analytical sample of 181 was prepared by recrystallization from 3-methyl pentane: mp 72.5-73.5°C; NMR (^{1}H, 270 MHz, $CDCl_3$) δ 5.14 (dd, J=3.4, 7.3 Hz, 1H, H_4), 4.94 (br m, $W_{1/2}$=5.7 Hz, 1H, vinyl-H), 4.75 (br m, $W_{1/2}$=4.9 Hz, 1H, vinyl-H), 2.87, 2.81 (AB, J=4.4 Hz, 2H, $H_{13a,13b}$), 2.22-2.41 (multiplet, 4H), 2.16 (ddd, J=3.4, 3-4, 13.2 Hz, 1H, $H_{3\alpha}$), 0.95 (s, 3H, CH_3); IR (CH_2Cl_2) 3040, 2960, 2930, 2880, 2855, 1710, 1662, 1598, 1580, 1488, 1445; Mass spectrum m/e 177, 165 (M-C_6H_5CO), 148 (M-C_6H_5COOH), 133, 120, 105. Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.55; H, 6.82.



181 185

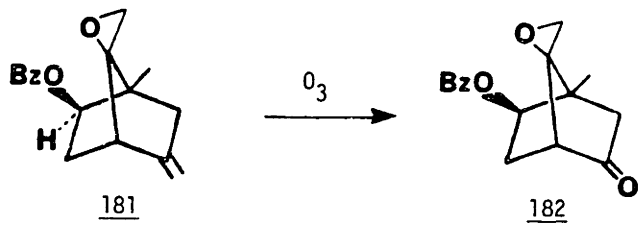
Bicyclo[2.2.1]1-methyl-5-methylene-7((S*)-spiroepoxymethano)-heptan-2(R*)-ol 185

To a solution of 35 mg of 181 (0.13 mmol) in 2 mL of anhydrous CH_3OH was added 5 mg of $NaOCH_3$. This mixture was stirred at ambient temperature, the progress of the reaction

being monitored by TLC. After 45 min, another 5 mg of $NaOCH_3$ was added. The mixture was stirred an additional 2 h at ambient temperature and then maintained at 0°C for 28 h.

The mixture was partitioned between 5 mL of saturated aqueous $NaHCO_3$ and 10 mL of CH_2Cl_2. The aqueous portion was then extracted twice with 5 mL of CH_2Cl_2. The combined organic extracts were concentrated in vacuo. The residue was dissolved in CH_2Cl_2, filtered through a plug of cotton and again concentrated in vacuo.

The product residue was chromatographed on a 0.25-mm preparative TLC plate (one development with 1:1 hexane-Et_2O). A UV active band (R_f 0.85-0.92) yielded 7.2 mg (21%) of recovered 181. A non-UV active band (R_f 0.38-0.48) yielded 1.7 mg (8%) of 185. This product proved to be extremely volatile. NMR (^1H, 250 MHz, $CDCl_3$) δ 4.88 (br m, $W_{1/2}$=6.5 Hz, 1H, vinyl-H), 4.68 (br m, $W_{1/2}$=5.7 Hz, 1H, vinyl-H), 3.75 (ddd, J=2.6, 7.4, 10.5 Hz, 1H, H_4), 2.85, 2.77 (AB, J=4.0 Hz, 2H, $H_{13a,13b}$), 2.31 (br d, J=4.4 Hz, 1H, H_2), 2.27 (dm, J=16.9 Hz, $W_{1/2}$=6.5 Hz, 1H, H_{6a}), 2.18 (dd, J=7.4, 13.2 Hz, 1H, $H_{3\alpha}$), 2.07 (dm, J=16.9 Hz, $W_{1/2}$=7.1 Hz, 1H, H_{6b}), 1.95 (ddd, J=2.6, 4.4, 13.2 Hz, 1H, $H_{3\beta}$), 1.83 (d, J=10.5 Hz, 1H, OH), 0.94 (s, 3H, CH_3); IR (CH_2Cl_2) 3560 (sharp, H-bonded OH group), 3040, 2955, 2925, 1660, 1425, 1245.



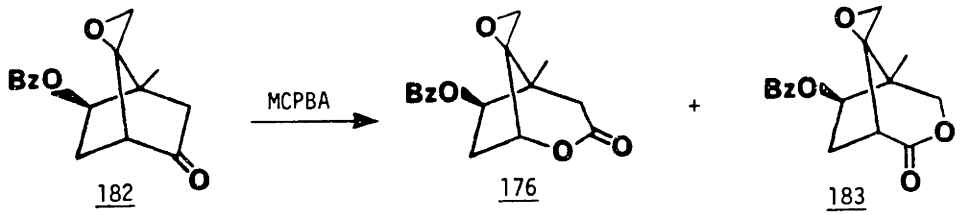
181 182

Bicyclo[2.2.1]4-methyl-5(R^*)-benzoyloxy-7((S^*)-spiroepoxymenthano)-heptan-2-one 182

Ozone (0.9 mmol/min) in a stream of oxygen was bubbled through a -78°C solution of 230 mg (0.85 mmol) of 181 in 10 mL of CH_2Cl_2 for 2 min until a light blue color persisted. The solution was maintained at -78°C for 5 min and then excess ozone was slowly and carefully quenched by the dropwise addition of one mL of CH_3SCH_3. The mixture was warmed to ambient temperature and stirred for 20 h.

The reaction mixture was then concentrated in vacuo, and the product residue purified by flash chromatography (20 mm column, 50 g of SiO_2 packed in 2:1 hexane-Et_2O). The product residue was applied in 8 mL of Et_2O and eluted with 2:1 hexane-Et_2O (10 mL fractions). Fractions 4-13 yielded 110.6 mg of 182 (48%). Fractions 1-3 yielded 114.9 mg of a 1.8:1 mixture of isomeric ozonides. These ozonides were dissolved in CH_2Cl_2 and treated with CH_3SCH_3 as before for 86h. In this manner we obtained, after preparative TLC (0.5-mm plate, one development with 1:1

hexane-Et_2O) an additional 66 mg (R_f 0.27-0.43) of ketone 182 (total yield=76%). An analytical sample was prepared by recrystallization from C_6H_6-3methyl pentane, mp 120.5-122°C; NMR (^1H, 270 MHz, $CDCl_3$) δ 5.27 (dd, J=3.2, 7.1 Hz, 1H, H_4), 2.96, 2.93 (AB, J=3.9 Hz, 2H, $H_{13a,13b}$), 2.27-2.51 (multiplet, 5H), 1.08 (s, 3H, CH_3); IR (CH_2Cl_2) 3035, 2950, 2878, 1750 (C=O), 1708 (C=O), 1655, 1595, 1410; mass spectrum m/e 167 (M-C_6H_5CO), 150 (M-C_6H_5COOH), 135, 122, 105, 77. Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.68; H, 6.08.


BzO
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was washed with 5 mL of saturated NaCl. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. A 270 MHz ^1H NMR spectrum of the reaction product showed it to be a 3:1 mixture, respectively, of 176 and 183. In our hands, this mixture was inseparable to preparative silica gel chromatography and HPLC.

The mixture was recrystallized twice from 2-3 mL of 30% benzene in hexane. In this manner 20 mg of analytically pure 176, mp 157.5-158.5°C, was obtained. The mother liquors were concentrated *in vacuo* to yield 46.8 mg of a 7:3 mixture, respectively, of 176 and 183.

Data for 176: NMR (^1H, 250 MHz, $CDCl_3$) δ 5.49 (dd, J=2.9, 7.4 Hz, 1H, H_4), 4.34 (d, J=5.3 Hz, 1H, H_2), 3.17, 3.01 (AB, J=3.7 Hz, 2H, $H_{13a,13b}$), 2.94 (dd, J=7.4, 16.5 Hz, 1H, $H_{3\alpha}$), 2.96, 2.82 (AB, J=19.1 Hz, 2H, $H_{6a,6b}$), 2.40 (ddd, J=2.9, 5.3, 16.5 Hz, 1H, $H_{3\beta}$), 0.98 (s, 3H, CH_3); IR (CH_2Cl_2) 3040, 2965, 2940, 1743 (C=O), 1715 (C=O), 1600, 1580, 1560, 1475, 1450; Mass spectrum m/e 166 (M-C_6H_5COOH), 122, 105. Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 67.06; H, 5.76.

Data for 183 (measured on a mixture containing 176): NMR (^1H, 250 MHz, $CDCl_3$) δ 5.57 (dd, J=3.6, 7.5 Hz, 0.3H, H_4), 4.34, 4.12 (AB, J=11.2 Hz, 0.6H, $H_{6a,6b}$), 2.3-2.5 (m, 0.3H), 0.93 (s, 0.9H, CH_3).