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FORMAL TOTAL SYNTHESES OF
(±)- AND (+)-APHIDICOLIN

presented by

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of the requirements for

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doctoral degree in Chemistry

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FORMAL TOTAL SYNTHESES OF
(±)- AND (+)-APHIDICOLIN

By

Yu-hwey Chuang

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ABSTRACT

FORMAL TOTAL SYNTHESES OF (±)- AND (+)-APHIDICOLIN

by

Yu-hwey Chuang

Formal total syntheses of (±)- and (+)-aphidicolin **1**, an antiviral substance which is used in the study of DNA replication, have been accomplished (Scheme XVI). The syntheses employ a furan terminated cationic cyclization of (±)- or (+)-**107**, which were prepared by coupling (Li_2CuCl_4) the Grignard reagent derived from 3-chloromethylfuran with (±)-(79%) or (+)-6,7-epoxy-8-benzyloxygeranyl chloride (75%). Exposure of compound **107** to BF_3-OEt_2 yields (±)-**108** (66-72%) and (+)-**108** (66-72%). Oxidation and selective reduction of the 3-one followed by debenzylation provides (±)-**85** (78%) and (+)-**85** (74%). Alkylation, furan oxidation and double-bond reduction affords (±)-**18** (67%) and (+)-**18** (61%); an advanced intermediate in McMurry's total synthesis of (±)-**1**.

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TABLE OF CONTENTS

LIST OF TABLES

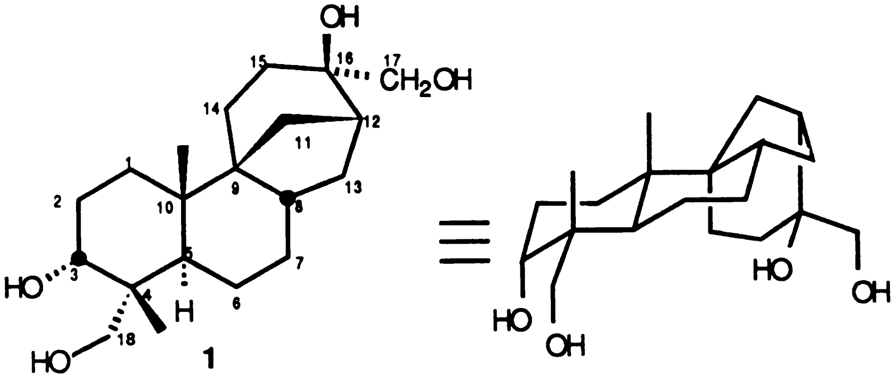
LIST OF FIGURES

LIST OF SCHEMES

Formal total syntheses of (+/-)- and (+)-Aphidicolin

I. INTRODUCTION

Aphidicolin 1, a diterpenoid tetrol produced by the mold *Cephalosporium aphidicola* Petch[1], has provoked wide interest in recent years owing to its striking biological activity; more than 100 publications have appeared in the last 7 years reporting its use in biochemical studies. For example, aphidicolin shows marked activity against herpes virus, both in vitro and in the rabbit eye[2,3]. In addition, aphidicolin possesses considerable antitumor activity in the C6 mouse colon and B16 mouse melanosarcoma screens[4] and has been shown to inhibit the growth of leukemic T- and B-lymphocytes[5].



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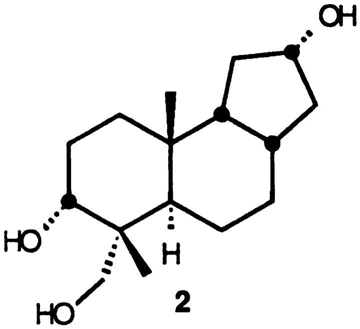
Aphidicolin appears to act as a specific reversible inhibitor of DNA α-polymerase[6-8]. Although the reasons for this activity are not clear, molecular models reveal the striking fact that all four of aphidicolin's hydroxyls can very nearly touch the same flat surface, an observation that may well be connected with the biological activity of the molecule. It appears, however, that not all of the hydroxyl groups are required for activity. Preliminary structure-activity studies have indicated that the nonrigidly held hydroxyl groups at C-17 and C-18 are less important than the rigidly held hydroxyls at C-3 and C-16. Thus, acetylation of the C-17 hydroxyl group causes only a 20% diminution of activity against herpes simplex type 1 virus in human lung cultures, but oxidation of the C-3 hydroxyl to a ketone causes a 97% loss of activity.

On the basis of these data and on measurements made from molecular models, McMurry[9] has hypothesized that aphidicolin's actvity requires the presence of two hydroxyl groups rigidly held on a flat carbon framework at a distance of approximately 6.0 Å. Other hydroxyl groups nearby may also aid in binding but may not be required.



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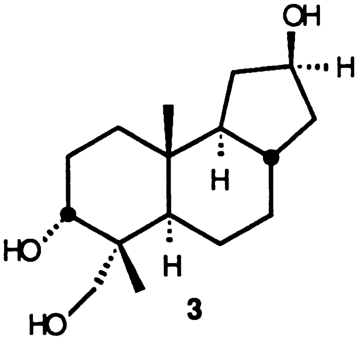

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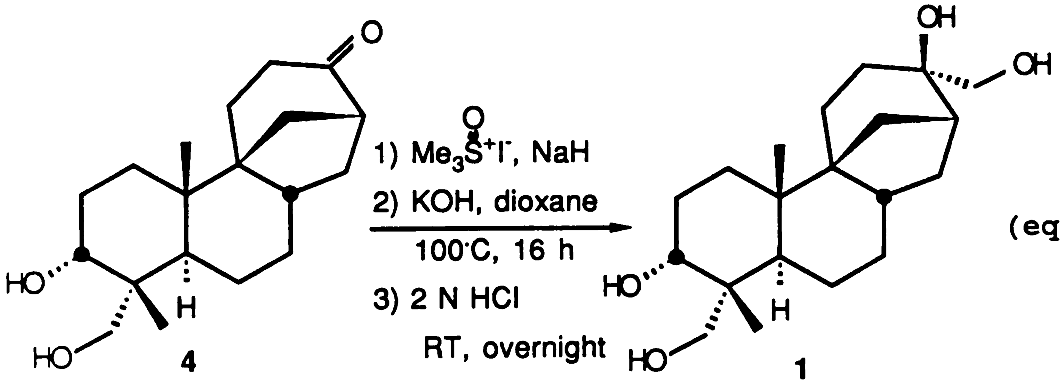
Triol 2 appears from molecular models to be an almost exact duplicate of aphidicolin 1 with respect to the disposition of its three hydroxyl groups. The intramolecular distance between the hydroxyls at C-3 and C-12 in 2 is identical with the distance between C-3 and C-16 hydroxyls in aphidicolin (6.0 Å), and the extension of hydroxyls below the plane of the carbocyclic skeleton is also similar. McMurry[9] prepared (±)-2 and (±)-3 and found that triol 2 showed 45% of the activity of aphidicolin in inhibiting in vitro DNA synthesis at a concentration of 0.33 μg / ml and 3 was found to be inactive as expected. Since the material is racemic, it is possible that the enantiomer of 2 whose absolute stereochemistry corresponds to aphidicolin would exhibit 90% of the activity of 1. This point would have to be verified by synthesis and individual testing of the two enantiomers.

The challenges to synthesis offered by aphidicolin are several. There is, for example, the stereochemical problem presented by the A ring. Although the 3α-hydroxy-4α-hydroxymethyl-4β-methyl substitution pattern seems familiar at first glance, it is in fact unique. No other terpenoid natural product possesses this stereochemistry. Another and more severe stereochemical problem is that posed by the spiro center, C-9. In addition this spiro center, is also adjacent to another quaternary carbon, C-10. The presence of these two adjacent quaternary centers makes this region of aphidicolin quite crowded and thus a likely source of trouble during any projected synthesis.

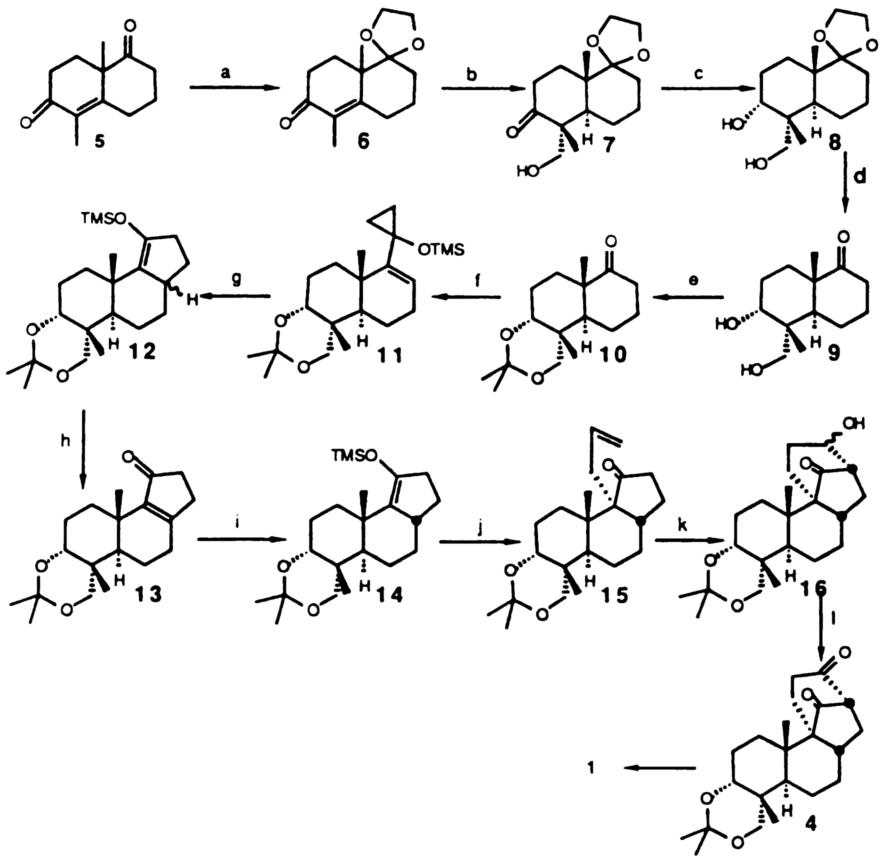
The biological properties mentioned above, together with the unusual structure of aphidicolin, have occasioned much activity among synthetic organic chemists. As a result, several total and formal total syntheses of (+/-)-aphidicolin **1** have been reported[10, 11].



(eq. 1)

For a synthesis of (±)-**1**, some simplification in the target can be accomplished since the ketone **4**, which is obtained by degradation of **1**, had previously been converted into aphidicolin[1] (eq. 1). Trost[10a] has reported a synthesis of (±)-**4** (Scheme I) from the Wieland-Miescher type ketone **8**. Selective ketalization of **5** (79%) followed by a reductive formylation gave a single aldol **7** (68%). Reduction of 3-keto group of the fragile **7** to the 3α alcohol proved troublesome until Trost discovered that the ate complex generated from t-BuLi and $(i\text{-bu})_2AlH$ gave the desired **8**(99%) nearly quantitatively. Hydrolysis afforded **9** (100%) which led to acetonide **10** (92%) after exposure to acetone and p-TsOH. Condensation of the ketone **10** with diphenylsulfonium cyclopropylide[12] under reversible ylide generation conditions followed by silylation gave **11** (56%). Thermal rearrangement of **11** _via_ flash vacuum pyrolysis provided a 2:1 (97%) mixture of epimers of **12** at C-8. To circumvent this unacceptable

Scheme I Trost's synthesis of (±)-1

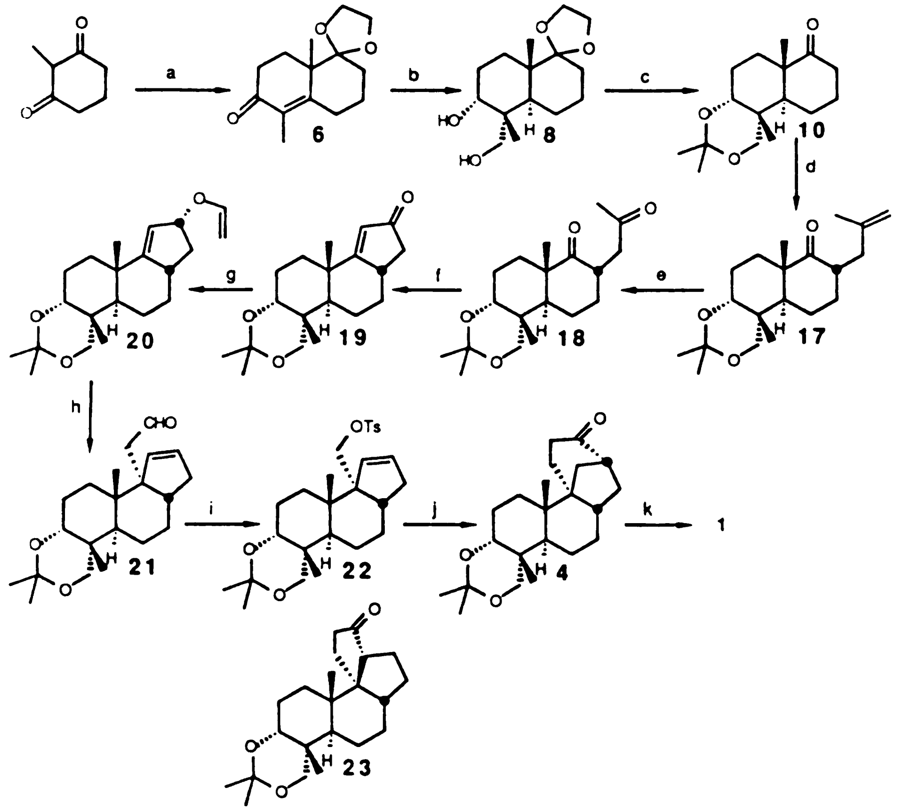


(a) $HOCH_2CH_2OH$, TsOH, PhH, reflux, Dean-Stark, 79%. (b) i. Li, NH_3, THF, 0.8 eq. of t-BuOH, -78°C, quench with isoprene and then Et_3N, Me_3SiCl; ii. CH_3Li, ether, RT, and then -78°C, HCHO, 68%. (c) $(iBu)_2(tBu)AlHLi$, hexane, heptane, ether, -78°C, 99%. (d) 3N HCl, THF, RT, 100%. (e) acetone, TsOH, reflux, 92%. (f) i. $c\text{-}C_3H_5S^+Ph_2BF_4^-$, KOH, Me_2SO; ii. PhSeSePh, $NaBH_4$, DME, 60°C; iii. $CH_3C[OSiMe_3]=NSiMe_3$, Et_3N, PhH, 60°C, 56%. (g) Flash vacuum pyrolysis at 610°C, 97%. (h) $Pd(OAc)_2$, CH_3CN, RT, 73%. (i) i. Li, NH_3, THF, 0.8 eq. of t-BuOH; ii. Me_3SiCl, 82%. (j) n-BuLi, HMPA, THF; inverse addition to allyl iodide, 85°C, 35%. (k) i. $(CH_3)_2CHC(CH_3)_2BH_2$, diglyme, 0°C, and then NaOH, H_2O_2, 45°C, 57%; ii. PCC, NaOAc, CH_2Cl_2, RT and then 2% KOH, CH_3OH, RT, 54%. (l) i. DHP, TsOH, $CHCl_3$, RT; ii. 95% NH_2NH_2, KOH, $HO(CH_2CH_2O)_3H$, 140°-220°C, 91%; iii. 0.5% acetone, TsOH, RT, 78%; iv. see (k)ii., 87%.

outcome, the mixture was directly oxidized ($Pd(OAc)_2$, 73%) to the enone **13**. Dissolving metal reduction then gave a single enol silyl ether (i. Li, NH_3; ii. Me_3SiCl, 82%) **13** corresponding to the minor product of the initial rearrangement. The correct stereochemistry at C-8 presumably resulting from protonation of the anion to afford an axial C-H bond[13]. Inverse quenching of the generated enolate solution into hot (85°C) excess allyl iodide gave **15** (29%) which was converted to **4** (19%) as outlined in Scheme I. This synthesis demonstrates the successful application of the cyclopentanone annulation using the cyclopropylide reagent for creating complex molecular architecture; however the overall yield of the 20 step sequence is only 1.06% from the ene-dione **5**.

McMurry[10b] has reported a concise stereospecific total synthesis of (±)-aphidicolin from **6** (Scheme II). Alkylation of **10** with methallyl iodide generated, as expected, **17** (89%) with the desired stereocenter at C-8. Oxidative cleavage afforded dione **18** (OsO_4, $NaIO_4$, 86%) and aldol cyclization gave McMurry's crucial intermediate **19** (95%). The original plan for the introduction of the elements of the D-ring called for a conjugate addition to enone **19**. However the great degree of steric crowding at the enone β-carbon (C-9) precluded all chances for success. An intramolecular process was much more likely to succeed and was examined as outlined in Scheme II. Reduction of **19** (LAH, 95%) and vinyl ether exchange (CH_2=CHOEt, Hg^{+2}, 90%) provided **20**. The Claisen

Scheme II McMurry's synthesis of (±)-1

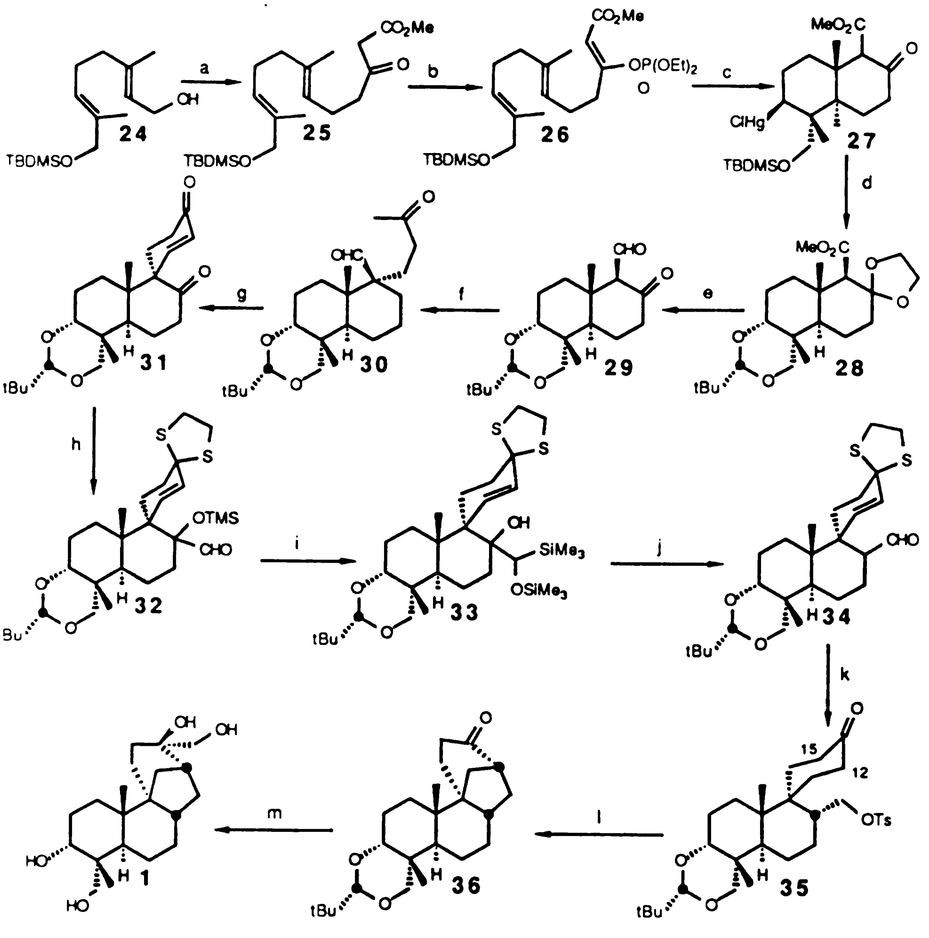


(a) i. CH_2=$CHCOCH_2CH_3$, pyrrolidine, PhH, 75%; ii. $HOCH_2CH_2OH$, p-TsOH, benzeze, 80%. (b) i. Li, NH_3, THF and then Me_3SiCl, Et_3N, 97%; ii. Ch_3Li, THF and then CH_2O, 100%; iii. Li(sec-Bu)$_3$BH, THF. (c) CH_3COCH_3, p-TsOH, CH_2Cl_2, 85%. (d) 1.2 eq. of LICA, THF and then methallyl iodide, 89%. (e) Trace of OsO_4, $NaIO_4$, H_2O, dioxane, 86%. (f) NaH, Trace of t-amyl alcohol, benzene, reflux, 95%. (g) i. LAH, ether, 95%; ii. CH_3CH_2OCH=CH_2, $Hg(OAc)_2$, 90%. (h) 0.03% NaO-t-pentyl, toluene, 220°C, 60%. (i) i. LAH, THF, 93%; ii. p-TsCl, pyr., 95%. (j) $Na_2Fe(CO)_4$, N-methylpiperidone, 30%. (k) i. CH_2=PPh_3; ii. OsO_4, pyr., then $NaHSO_3$; iii. H_3O^+, 36%.

rearrangement of 20 was carried out initially in the presence of strong base to yield 21 (60%). Aldehyde 21 was then further elaborated to tosylate 22 (i. LAH, 93%; ii. p-TsOH, 95%). Tosylate 22 was cyclized by Collman's reagent to provide a 55% yield of 1:1 mixture of 4 and 23. The McMurry synthesis concisely constructs the troublesome D-ring, albeit with some regiochemical problems. The sequence described above gives 4 in 15 steps and 4.89% overall yield.

Corey[10c] utilized a polyene cyclization to establish the A and B rings of aphidicolin with the appropriate stereochemistry (Scheme III). This strategy very efficiently affords access to the basic carbocyclic skeleton upon which the sterically congested spirocyclic D-ring as well as the C-ring must be appended. Condensation of 8-TBDMSO-geranyl bromide with the dianion of methyl acetoacetate afforded β-keto ester 25 (90%). Formation of enol phosphate 26 (NaH, $(C_2H_5O)_2P(O)Cl$, no yield reported), followed by mercury II induced cyclization gave 27 after treatment with aqueous NaCl (60%). Ring A and B were thus established in a single step with the proper relative stereochemistry at C-4, C-5, and C-10. The requisite C-3-oxygen was introduced by free radical oxygenation ($NaBH_4$, O_2); and the streochemistry was corrected by oxidation PDC, deprotection (Bu_4NF) and L-selectride reduction, giving acetal 28 (52%) after protection (tBuCHO, H^+). The addition of the spiro D-ring to keto aldehyde 29 was accomplished by the Michael addition to gaseous methyl vinyl ketone (no yield reported) followed by a Robinson

Scheme III Corey's synthesis of (±)-1

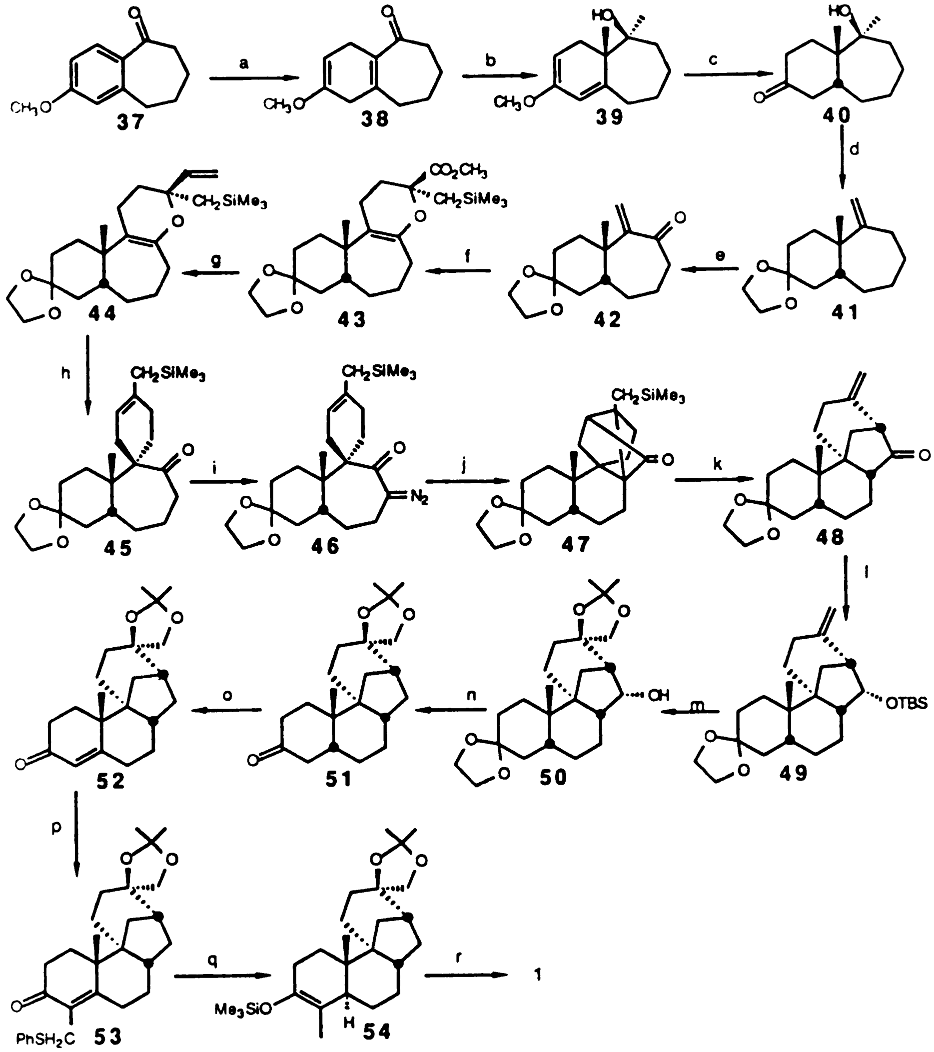


(a) i. MsCl, Et_3N, -20°C; LiBr; ii. MeLi, Na, methyl acetoacetate, THF, 0°C, 90%. (b) NaH, $(C_2H_5O)_2P(O)Cl$, 0°C. (c) $Hg(OTFA)_2$, CH_3NO_2, 0°C; aq. NaCl, 60%. (d) i. $(HOCH_2)_2$, p-TsOH, 90%; ii. $NaBH_4$, O_2, DMF; iii. PDC; iv. $n\text{-}Bu_4NF$ v. L-selectride; vi. $(CH_3)_3CHO$, TsOH, 58%. (e) i. LAH; ii. PCC; iii. acetone-H_2O-$HClO_4$, 90%. (f) THF-tBuOH, DBU, K_2CO_3, MVK(gas). (g) pyrrolidinium acetate. (h) i. $(Me_3SiSCH_2)_2CH_2$, ZnI_2, 88%; ii. Me_3SiCN, ZnI_2, 97%; iii. DIBAL, 75%. (i) Me_3SiLi, HMPA, -35°C, 80%. (j) LDA (3 eq.), HMPA; H^+, 80%. (k) i. Na_2BH_4, ethanol, THF, -20°C; ii. $tBuMe_2SiCl$, DMAP, Et_3N, 90%; iii. 1,3-diiodo-5,5-dimethyl hydantoin, 86%; iv. H_2, Pd/C; v. Bu_4NF; vi. p-TsCl, DMAP, Et_3N. (l) $LiN(tBu)_2$, 90%. (m) 1-ethoxyethoxymethyllithium.

spiroannulation to give **31** (no yield reported). Selective thioketalization of conjugated ketone ($((Me_3SiSCH_2-)_2$, ZnI_2, 88%) [14] followed by the conversion of remaining ketone to the corresponding trimetylsilyl cyanohydrin (Me_3SiCN, ZnI_2, 97%)[15] and reduction of the cyano with diisobutylaluminum hydride gave aldehyde **32** (75%). Reaction of **32** with trimethylsilyllithium in HMPA afforded **33** (80%) which was treated with lithium diisopropylamide and HMPA followed by quenching with aqueous acid giving **34** (80%). This method which is a variant of the Peterson olefination technique might be useful as a one carbon homologation protocol for those hindered systems plagued by enolization. Reduction of the aldehyde **34** ($NaBH_4$), tosylation of the primary alcohol, dithioketalization; and hydrogenation afforded keto-tosylate **35** (70%). Intramolecular alkylation of **35** to form the aphidicolin ring system completely dependant upon reaction conditions; in the event the use of kinetically controlled enolate formation with highly hindered bases at low temperatures favored the desired alkylation at C-12. Sodium methoxide in methanol gave exclusively alkylation at C-15. Reaction of **36** with 1-ethoxyethoxymethyllithium afforded a 1 : 1 mixture of (±)- **1** and epimer at C-16 with no yield reported. The Corey sequence, although effeciently constructing the basic A-, B-ring system, suffers from excessive length in the introduction of rings C and D. The sequence described above gives **1** in 27 steps from **24** in an overall yield of 6.5%, which does not take into account a number of crucial steps for which yields are not reported.

Ireland[10d] reported a stereoselective total synthesis of (±)-aphidicolin from **37** (Scheme IV). Birch reduction of **37** gave **38** (52%). Methylation of **38** led exclusively to the desired angularly methylated ketone which was converted to **41** as outlined in Scheme IV. Photooxygenation of **41** gave **42** (sens., AcOEt, O_2, hν, 81%). The hetero-Diels-Alder reaction of **42** with the methyl(trimethylsilyl)methyl acrylate provided **43** (69%) which was further elaborated to **44** (95%). The Claisen rearrangement of **44** gave **45** (84%) thus constructing the 6 membered D-ring. The diazo ketone **46**, formed through the oximino ketone, was photolyzed in the absence of added nucleophiles, and in an inert solvent medium to afford **48** (51%) as the sole product after cyclobutanone rearrangement on silica gel. Direct removal of the unwanted C-13 carbonyl was not successful because of the epimerization of C-8 center. Therefore, carbonyl group was reduced (99%) and protected by the bulky t-butyldimethylsilyl group (95%) which also blocked the α-face of the molecule. Osmium tetroxide hydroxylation of the olefin **49** was now quite efficient and gave a single diol, and then acetonide **50** (92%), as the only product. Removal of the C-13 hydroxyl function through reduction of its derived phosphorodiamidate was not complicated by overreduction; then ketal exchange provided **51** (82%). Enolization and then trimethylsilyl chloride trapping led virtually exclusively to the C-3,C-4-silyl enol ether which was converted to **52** (90%) by procedure of Saegusa and

Scheme IV Ireland's synthesis of (±)-1

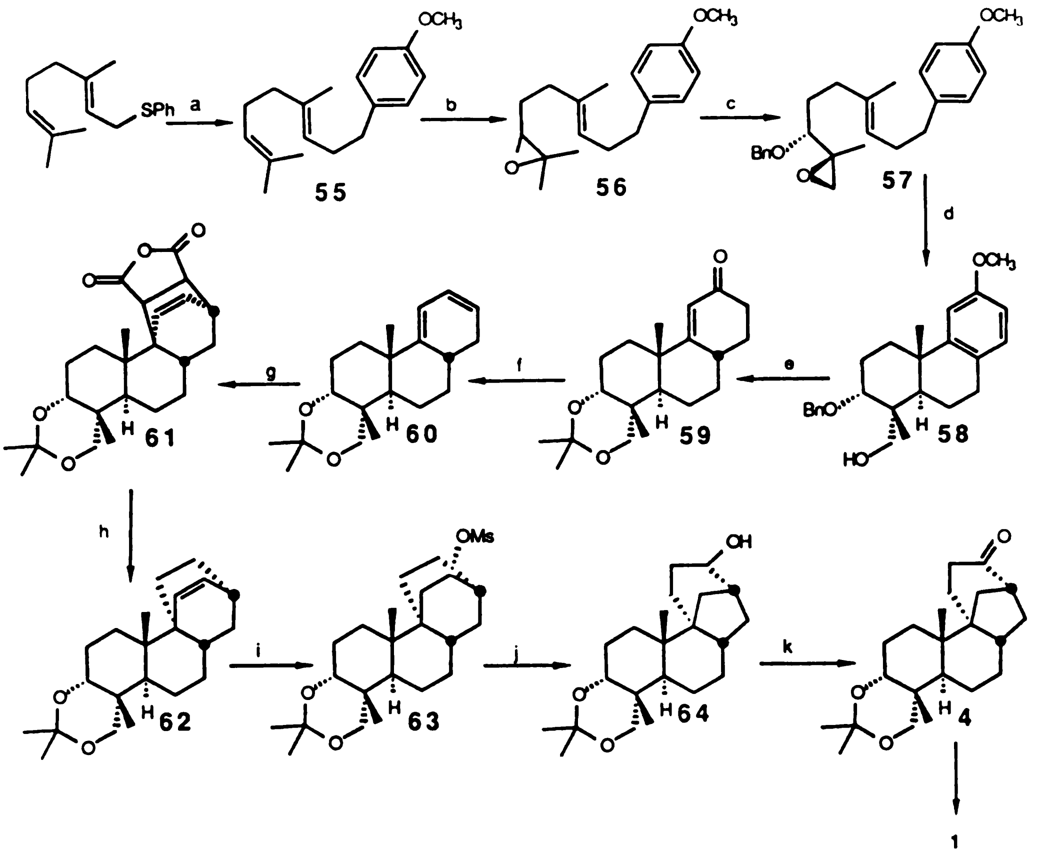


(a) i. Na, EtOH, NH_3-Et_2O, 52%; ii. $Al(OiPr)_3$, CH_3COCH_3, toluene. (b) i. KNH_2, NH_3-Et_2O, MeI; ii. CH_3Li, Et_2O. (c) i. oxalic acid, H_2O-MeOH, 90%; ii. Li, NH_3, Et_2O, 85%. (d) i. Li, NH_3, Et_2O, 66%; ii. $(CH_2CH_2OH)_2$, p-TsOH, benzene, reflux, 85%. (e) hematoporphrin dichloride, AcOEt, O_2, hv, 81%. (f) $CH_2=C(CO_2CH_3)CH_2SiMe_3$, 125°C, sealed tube, hydroquinone, 69%. (g) i. DIBAL, Et_2O, -78°C; ii. $Ph_3P=CH_2$, THF, 95%. (h) 150°C, 7.5 h, 84%. (i) i. n-BuLi, i-AmONO, THF, 85%; ii. NH_4Cl, THF. (j) hv, Et_2O, -73°-0°C. (k) SiO_2, gel, pet. ether/ether, 60%. (l) i. DIBAL, THF, -78°C, 99%; ii. TBSCl, imidazole, DMF, 95%. (m) i. OsO_4, pyr.; $NaHSO_3$; ii. $CH_3C(OCH_3)_2CH_3$, p-TsOH-H_2O; iii. TBAF, THF, 92%. (n) i. n-BuLi, DME/TMEDA, Me_2NPOCl_2; Me_2NH; ii. $MeNH_2$, THF, t-BuOH, Li, NH_4Cl, 86%; iii. pyr.H^+OTs^-, acetone, 95%. (o) i. KH, THF; TMSCl, Et_3N; ii. $Pd(OAc)_2$, CH_3CN, 90%. (p) $(CH_2O)_x$, PhSH, Et_3N, EtOH, 78%. (q) Li, NH_3, t-BuOH-THF; Et_3N, TMSCl-THF, 90%. (r) i. CH_3Li, THF; HCHO; AcOH; ii. L-selectride, THF, aq. NaOH, 30% H_2O_2; 10% HCl-MeOH, 60%.

Ito[16]. Thus, application of the Petrow reaction[17] led to the phenyl thiomethyl enone **53** (78%), which on lithium / ammonia reduction and then trimethylsilyl chloride trapping produced **54** (90%). Compound **54** was converted to (±)-**1** (60%) as outlined in Scheme IV. This synthesis used the spiroannelation of related 2-methylene ketone through first hetero-Diels-Alder condensation and then Claisen rearrangement of the derived allyl vinyl ethers. The central feature of this synthesis is the rearrangement of the intermediate ((trimethylsilyl) methyl)cyclobutanone **47** to the aphidicolin bicyclo[3,2,1] octane ring system. The sequence described above gives (±)-**1** in 31 steps from **37** and 1.36% overall yield.

van Tamelen[10e] adapted his elegant biomimetic cationic cyclizations to the synthesis of (±)-**1**; providing the correct relative stereochemistry at C-3, -4, -5, and 10 (Scheme V). Alkylation of the anion of geranyl phenyl thioether with p-MeO-benzyl chloride provided **55** (86%); reductive cleavage of the C-S bond (Li / NH_3, 47%) and selective functionalization of the terminal double bond by the van Tamelen procedure (i. NBS, aq. tBuOH; ii. K_2CO_3) gave epoxide **55** (33%). Epoxide opening ($LiNEt_2$, 57%); Sharpless epoxidation (tBuOOH, $VO(acac)_2$) gave an (±)-erythro glycidol which was protected as the corresponding benzyl ether **57** (72%). Cyclization ($FeCl_3$, toluene) afforded but 12% of the requisite diol-mono benzyl ether **58** which was subjected to Birch type conditions (Li, THF, EtOH), hydrolysis, and acetonide formation to yield

<u>Scheme V</u> van Tamelen's synthesis of (±)-1



(a) i. base, p-methoxybenzyl chloride, 86%; ii. Li, NH_3, -78°C, 47%. (b) i. NBS, THF-H_2O; ii. K_2CO_3; MeOH, 33%. (c) i. $LiNEt_2$, 57%; ii. TBHP, vo(acac)$_2$, 80%; iii. NaH, $PhCH_2I$, 90%. (d) $FeCl_3$, toluene, 12%. (e) i. Li, EtOH-THF, -78°C; ii. 0.5M HCl, EtOH; iii. CH_3COCH_3, TsOH, 55%. (f) i. trisylhydrazone, TsOH, 70%; ii. BuLi, TMEDA, hexane, -78°C, 82%. (g) maleic anhydride, benzene, 80°C, 86%. (h) i. Pd-C, H_2O-EtOH, 90%; ii. Pb(OAc)$_4$, O_2-sat'd. pyr., 28%. (i) i. MCPBA, 100%; ii. Na, PhH, reflux; iii. MsCl. (j) acetone-H_2O, reflux, $CaCO_3$, 60%. (k) CrO_3-pyr. 90%.

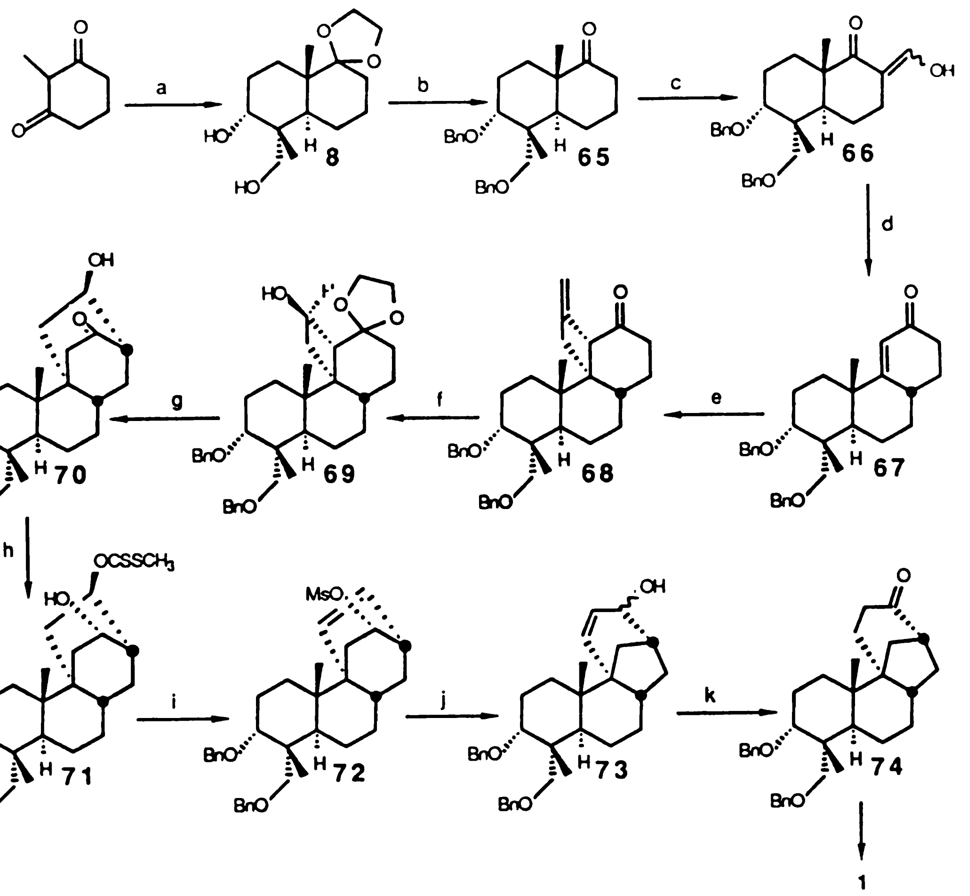
59 (55%).

Construction of the final ring was acomplished by a Diels-Alder cycloaddition to diene **60** which resulted from the Bond modification of the Shaprio reaction (i. 2,4,6-iPrPhSO$_2$NHNH$_2$; ii. nBuLi, 82%). Addition of maleic anhydride to **60** gave adduct **61** (86%). Hydrolysis, and hydrogenation of the diacid (90%) followed by Pb(OAc)$_4$ decarboxylation of the vicinal diacid yielded olefin **62** (28%). Epoxidation (100%) of **62** and reduction with Na (20%) yielded an alcohol which was converted to mesylate **63**. Solvolytic rearrangement led to alcohol **64** (60%) which upon oxidation (Collins, 90%) gave ketone **4**; thus completing a formal total synthesis of (±)-**1**.

The van Tamelen synthesis is the only one thus far reported which controls the stereochemistry at C-3. Unfortunately the extremely low yield obtained in the cyclization coupled with a number of additional low yield reactions and the poorly functionalized C-ring results in a long and very low yield synthesis of ketone **4** (21 steps, 0.007%).

Marini Bettolo[10f] has also reported employing a solvolytic rearrangement for a formal total synthesis of aphidicolin (Scheme VI). The synthesis begins with known diol **8** prepared by McMurry in 49% yield over 6 steps. Diol **8** was converted to the related bis-protected ketone (90%), which was formylated (**66**; NaH, HCO$_2$Et) and treated with methyl vinyl ketone; the Michael adduct was deformylated (NaOMe) and cyclized to provide **67** (75%). Photocycloaddition

Scheme VI Marini Bettolo's synthesis of (±)-1



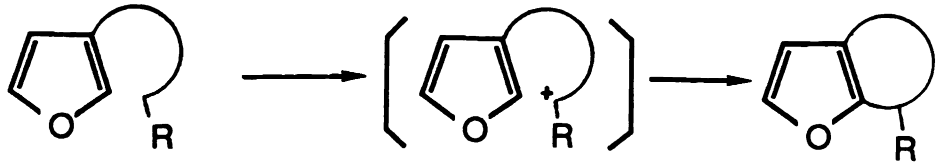
(a) see Scheme II, a and b, 6 steps, 58%. (b) i. NaH, $PhCh_2Br$, reflux, 3 h; 6N HCl, 90%. (c) HCO_2Et, MeONa, PhH; 2N H_2SO_4. (d) 3-buten-2-one, Et_3N, 0°C; MeONa, 75%. (e) allene, hν, THF, -78°C, 86%. (f) i. p-TsOH, PhH, ethylene glycol, reflux, 3 h, 80%. ii. O_3, $EtOH-CH_2Cl_2$, -78°C; $NaBH_4$, -78°C, 4 h. (g) 1N HCl, THF; 1N NaOH, 76%. (h) i. NaH; CS_2, THF, reflux, 2.5 h; MeI, reflux, 1.5 h, 72%; ii. $NaBH_4$, Et_2O/MeOH. -20°C, 91%; (h) i. o-xylene, reflux, 2.5 h, 90%; ii. Et_3N, CH_2Cl_2, 0°C; MsCl. (j) acetone-H_2O, 70°C, 5 h, 97%. (k) i. PDC, 81%; ii. Li, NH_3, -78°C, 69%.

of **67** with allene at -78°C gave only **68** (86%) which led to protected aldol adduct **69** (61%) as outlined in Scheme VI. Ketal hydrolysis and rearrangement provided **70** (76%); which was converted to the corresponding dithio carbonate (72%); and the ketone was reduced ($NaBH_4$) to yield **71** (91%). Dithio carbonate elemination (Δ, 90%); followed by mesylation gave **72**, which suffered smooth solvolytic rearrangement to give **73** (97%). Oxidation (PDC, 81%) followed by Li / NH_3 treatment provided diol **74** (69%) which can be protected as the corresponding acetonide to give **4** (85%).

The Marini Bettolo sequence borrows from the routes of Trost, McMurry and van Tamelen to create the sequence. This formal total synthesis leads to **4** in 5% yield from 2-methyl 1,3-cyclohexane dione.

II. An Approach to the Syntheses of (±)- and (+)-Aphidicolin 1 *via* Furan Terminated Cation Cyclization

We have demonstrated the use of furans as terminators in a variety cationic cyclizations[18]. As illustrated in eq. 2, the generation of an electron deficient center (R) in the side chain of a 3-substituted furan, should lead to **76** after an electrophilic attack and rearomatization. The products of



75 **76** (eq. 2)

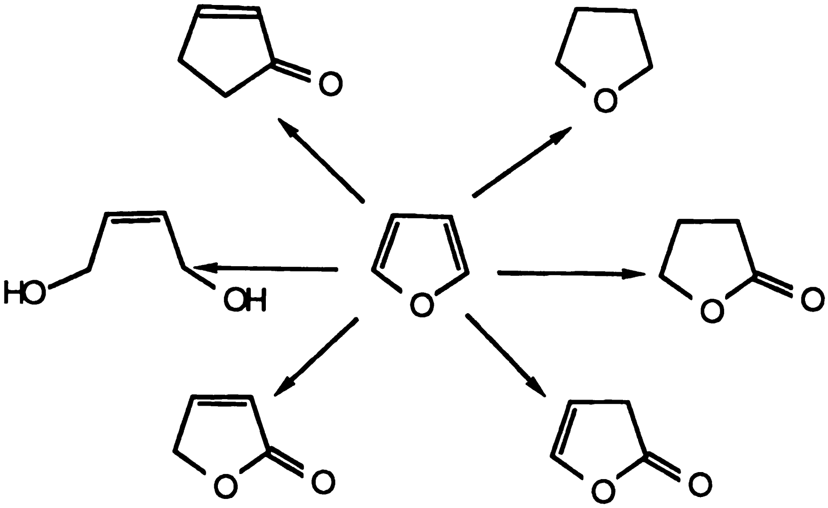
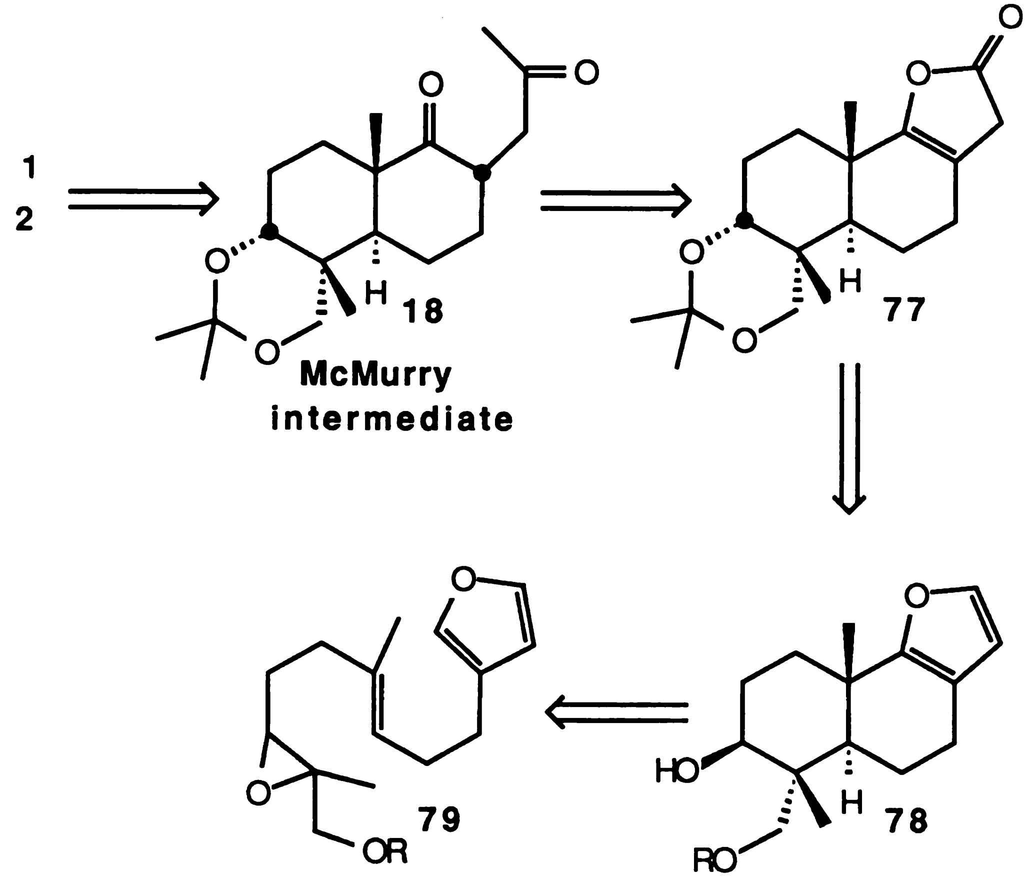


Figure 1 Furan Equivalencies

these cyclization sequences can serve as precursors to a plethora of functional groups such as those illustrated in Figure 1. Therefore, as part of a general program in furan chemistry and an interest in furans as dianion equivalents in annulation processes[19] we were interested in accomplishing formal total syntheses of (+/-)- and (+)-1 as outlined in Scheme VII. This study would exploit; (1) a furan-terminated polyolefin cyclization to rapidly establish the carbocyclic nucleus of aphidicolin 1, followed by (2) a furan to butenolide or dione conversion ultimately yielding McMurry's intermediate dione **18**. Cyclization of **79** would afford **78** in which the A and B rings of the target have been established. With a furyl moiety integrated into the cyclization product, an efficient transformation to the McMurry intermediate **18**

Scheme VII Proposed Retrosynthetic Scheme to Aphidicolin 1 and its analog 2



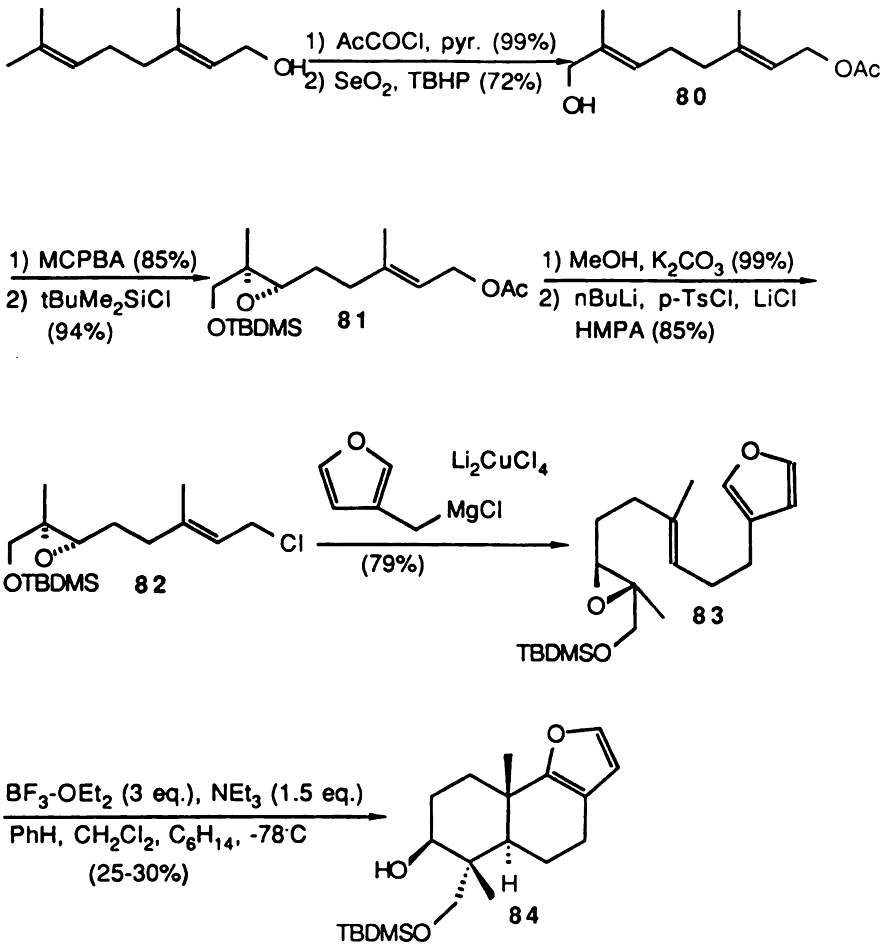
should be possible. The advantages of the sequence are rapid construction of the carbocyclic nucleus with the correct relative configuration at C-4, C-5, and C-10 resulting directly from the cyclization. In addition the possibility of an asymmetric synthesis will be investigated, utilizing optically pure 79, a product of an asymmetric Sharpless epoxidation[20].

III. Results and Discussion

An analysis of the substituents located at C-3 and C-4 of aphidicolin suggests, as in the Corey synthesis[10c], that an ω-oxygenated geranyl halide, after alkylation and cyclization would yield the proper relative stereochemistry at C-4. In addition, should the cyclization substrate possess a 6,7-epoxide, then the cyclized product would have an oxygen at C-3, however opposite in stereochemistry to that desired. We viewed this route as being extremely flexible as one could readily incorporate an optically pure side chain into furan **79**, utilizing (-)-6,7-epoxy-8-TBDMS*O*-geranyl acetate **81** previously prepared by Sharpless[20] as the starting material.

Our original route to (±)-**18**[21] is described in Scheme VIII. In the planning stage, we considered the nature of the protecting group for the C-8-OH incorporated into geranyl acetate **81**. This group must survive conversion to the chloride **82**, coupling[22] with 3-ClMgCH_2furan, cyclization and hydroxyl inversion. We anticipated utilizing the 3-one related to **84** as the vehicle for OH inversion. However, as has been demonstrated by many other groups exploring the construction of **1** with the exception of van Tamelen, the C-4-CH_2OR must be deprotected to obtain good selectivity in the reduction of 3-one. This consideration and the expected fragility of the derived aldol caused us to employ the TBDMS group to protect at C-4.

Scheme VIII Preparation of 84

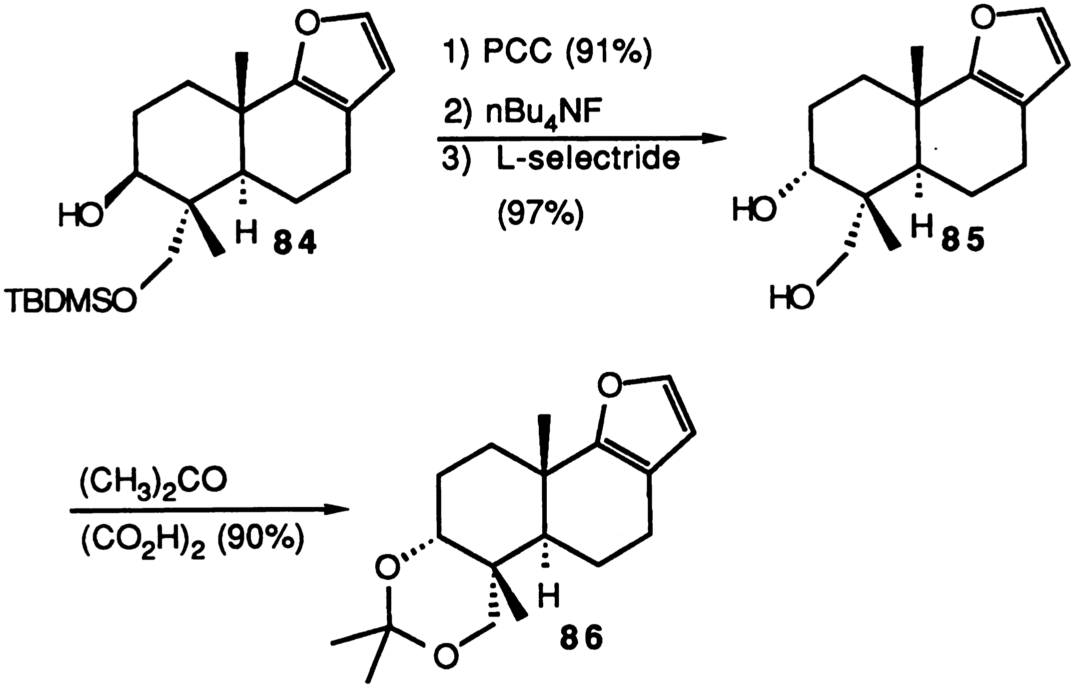


In the event, allylic hydroxylation of geranyl acetate using the catalytic SeO_2 protocol of Sharpless[20], afforded the monoprotected diol **80** (72%). Henbest epoxidation (85%) and protection ($tBuMe_2SiCl$) afforded silyl ether **81** in 94% yield. Acetate cleavage (K_2CO_3, MeOH, 99%) and chlorination by the procedure of Stork[23] gave the highly oxidized geranyl chloride **82** in 85% distilled yield. Chloride **82** was smoothly coupled with 3-$ClMgCH_2$furan in the presence of Li_2CuCl_4[22,24] to yield **83** (79%). With **83** in hand, we next examined the crucial cyclization reaction.

Our first cyclization attempts employed ZnI_2 and $Ti(OiPr)_3Cl$ as Lewis acids. These catalysts performed admirably in our earlier furan terminated epoxide initiated cyclizations, and in fact these Lewis acids gave 62% and 65% yields of 3β-OH pallescensin A, the 4α-CH_3 analog of **84**, from epoxydendrolasin. In this case, exposure of **83** to ZnI_2 and $Ti(OiPr)_3Cl$ provided wildly variable yields (0-49%) of **84**. These results are unacceptable in the racemic route described and are considered useless for a projected optically pure synthesis of (+)- **4**. After considerable experimentation we discovered that consistent 25-35% yields of **84** could be realized after exposure of **83** to BF_3-OEt_2 (3 eq.), Et_3N (1.5 eq.) in CH_2Cl_2-hexane-PhH (1:1:1) at -78°C. Under these conditions the bulk of the reaction mixture consisted of acyclic ketones. With tricyclic **84** available we next examined the inversion of the C-3-O̲ bond.

As is described in Scheme IX, treatment of alcohol **84**

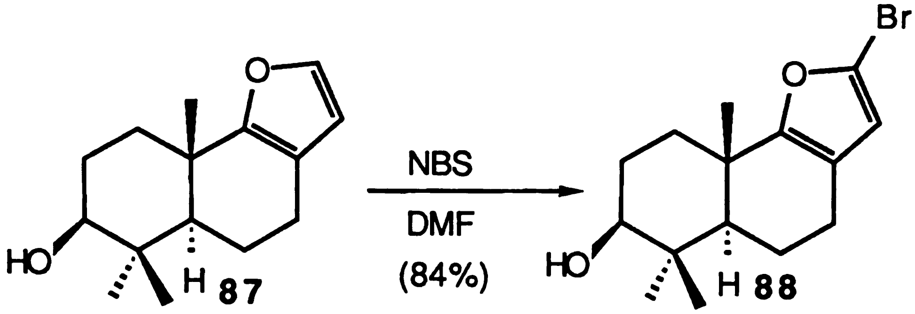
Scheme IX Preparation of **86**



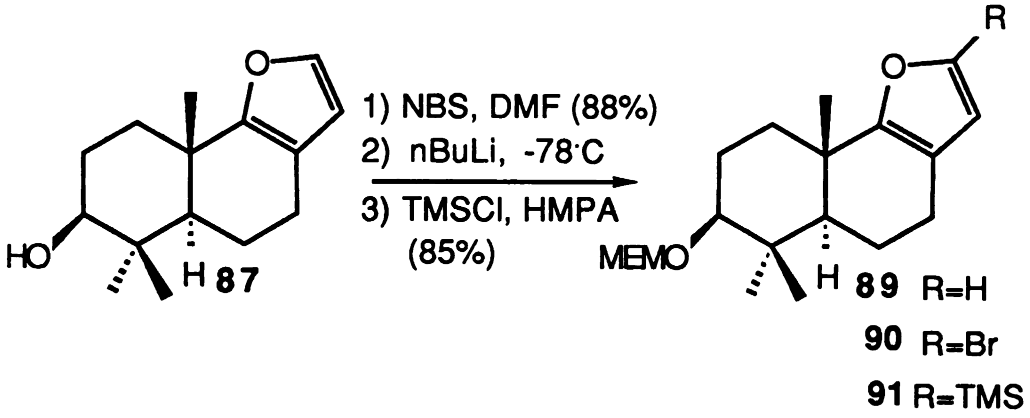
with PCC^{10c} provided the 3-one in 91% yield. Deprotection (Bu$_4$NF) and reduction with L-selectride^{10b,c} gave diol **85** (97%). Exposure of **85** to acetone and oxalic acid in CH$_2$Cl$_2$ afforded the requisite acetonide **86** in excellent yield (90%).

With **86** in hand we examined the conversion of the furyl moiety to more useful functionality. Initially we attempted to introduce the necessary methyl at the unsubstituted furyl α-position by direct metallation and quenching with CH$_3$I. Unfortunately all attempts^{25} to deprotonate furan **86** and capture with CH$_3$I or D$_2$O afforded no products of electrophile capture. Application of more forcing conditions led to destruction of the acetonide moiety. Changing protecting groups for the 3α-OH and 4α-CH$_2$OH to MEM, Me$_3$Si, or tBuMe$_2$Si did not improve the situation. These observations are in good agreement with the similar difficulties in the thiophene series noted by Heathcock[26] during an approach to the Securinega alkaloids.

A potential solution to this problem might lie in a selective and careful bromination of the furyl nucleus, followed by metal-halogen exchange and capture with an electrophile. In the model compound **87** (eq. 3)[27], application of the mild bromination conditions of Mitchell[28] (NBS, DMF) provided **88** in 84% yield. Repetition of this sequence (eq. 4) with the MEM ether **89** gave bromide **90** (88%) which suffered smooth metal-halogen exchange (n-BuLi, -78°C) and capture with Me_3SiCl to provide silylfuran **91** (85%).



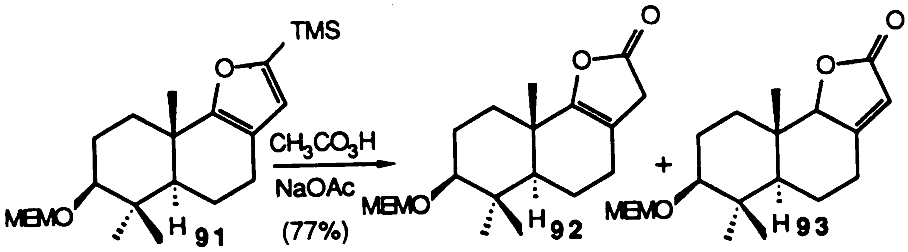
(eq. 3)



(eq. 4)

Oxidation of **91** (eq. 5) utilizing the procedure reported by Kuwajma[29] (CH_3CO_3H) led to a mixture of butenolides **92** and

93 (4:1, 77%). Enol lactone **92** was readily isomerized to **93** upon attempted purification. Compound **92** is potentially quite useful in the formal total synthesis of aphidicolin; as the addition of CH_3-M would afford the desired dione directly[30]. Unfortunately, **92** was readily and easily converted to butenolide **93** rendering this approach useless.

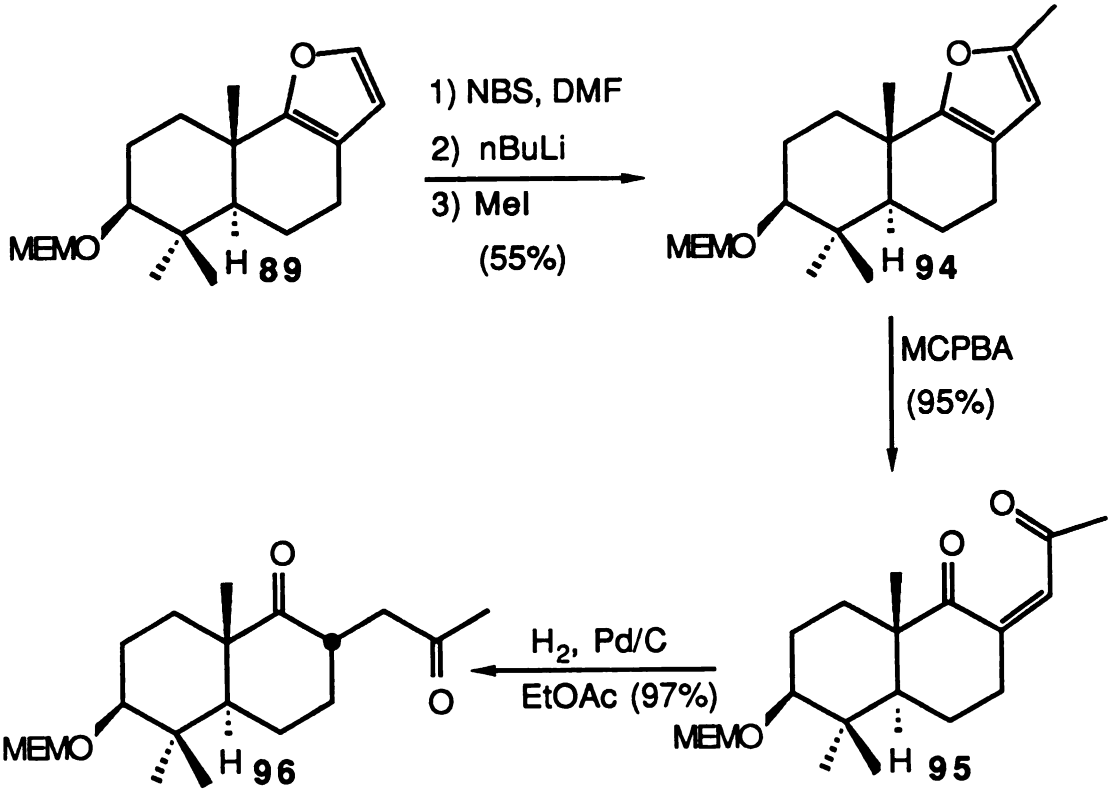


(eq. 5)

As a result of the double-bond isomerization of **92**, we examined the introduction of methyl group onto furan in the alkylation step (Scheme X). In the event, the crude brominated furan **90** was treated with BuLi and quenched with MeI (-78°C) to provide the desired methylated furan **94** in 55% yield accompanied with 14% of starting material **88**. The mixture of **94** and **89** is not separable at this stage. However, exposure of **94** to MCPBA[31] gave ene-dione **94** in excellent yield (95%); the unmethylated **89** survived the MCPBA oxidation quantitatively. These compounds are now readily separated by silica gel chromatography.

Ene-dione **95** was hydrogenated smoothly to the target compound of the model system, **96**, with the correct stereochemistry at C-8 after the epimerization on a column of silica gel. Dione **96** has a strong resemblance to the McMurry

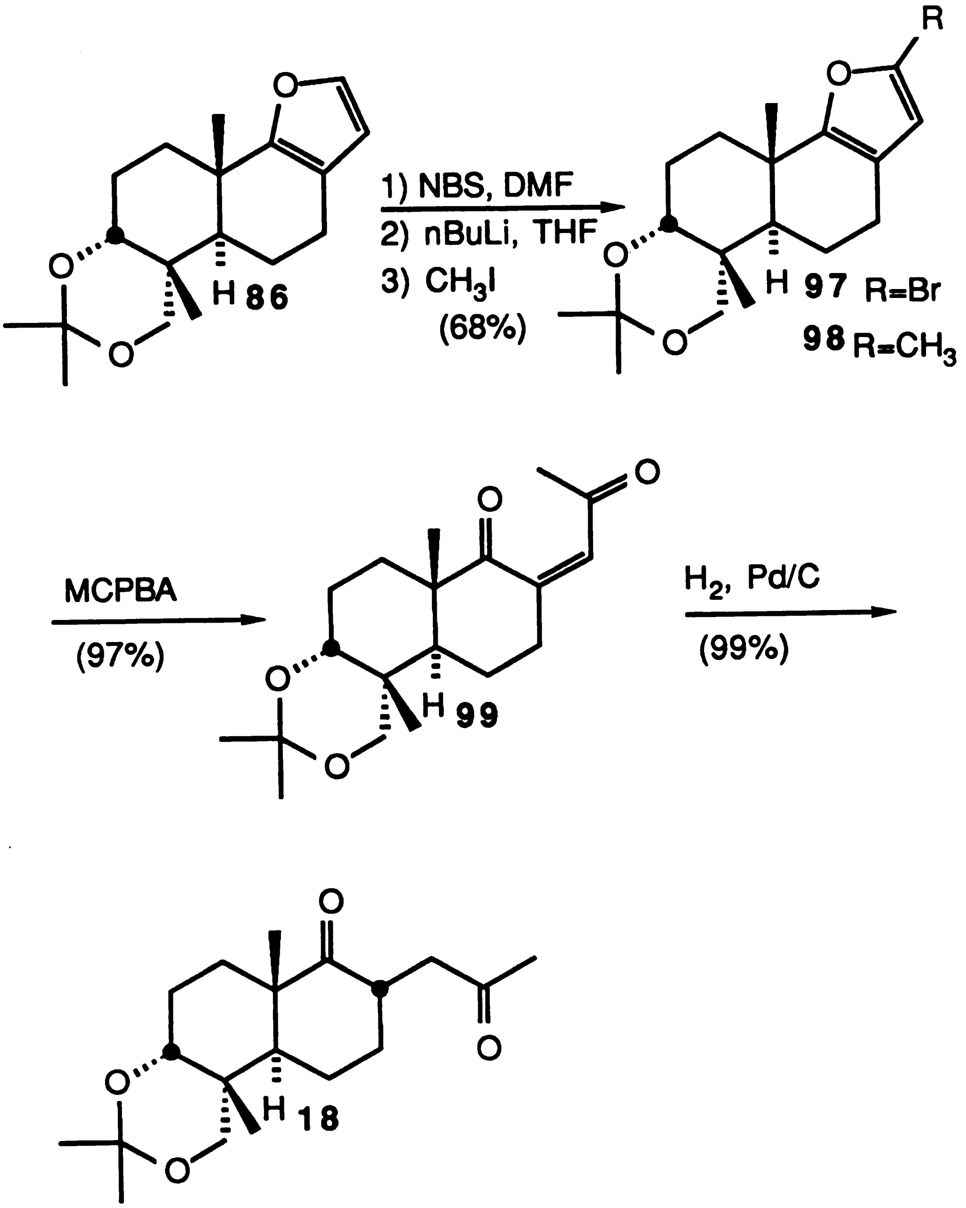
Scheme X Preparation of **96**



intermediate **18** in his total synthesis of (+/-)-aphidicolin. Therefore the likelihood of success in the actual system is high.

Careful bromination (NBS, DMF) of acetonide **86** afforded the unstable bromide **97**. Bromofuran **97** was not purified, but was immediately subjected to metal-halogen exchange (nBuLi, -78°C) and alkylation with CH_3I to provide 68% of the desired methyl furan **98** and 8% of unreacted starting furan **86**. The mixture of **98** and **86** was submitted to the oxidation conditions in the usual way to give ene-dione **99** in 97% yield (based upon **98**) and recovered **86** (8%). Compound **99** was hydrogenated to provide the McMurry intermediate **18**, which was identical in all respects to material prepared by

Scheme XI Preparation of (±)-18

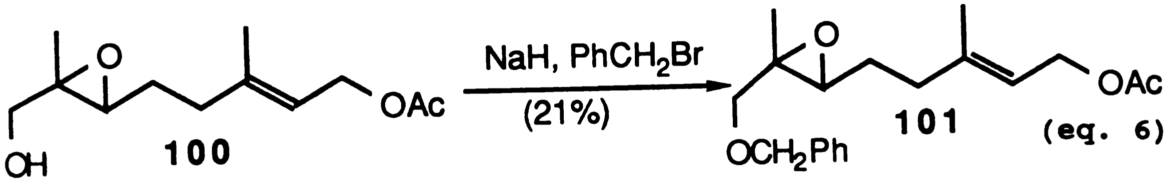


McMurry[10b]; thus accomplishing the formal total synthesis of (±)-aphidicolin 1.

This sequence was undertaken as a prelude to an anticipated formal total synthesis of (+)-1 and to demonstrate the utility of highly oxygenated, complex substrates as initiators in furan terminated cationic cyclizations. Although the route outlined did indeed provide (±)-**18**, thus constituting a formal total synthesis of (±)-**1**, the problems encountered in the cyclization affording **84** were still unresolved. We viewed the 25-35% yield for cyclization as unacceptable in chiral approach to (+)-**1**.

We assumed that the size and the fragility of the silyl ether in **83** were responsible for the low and variable yields of **84** which were obtained. This assumption was based upon a poor mass balance and the observation of a sizeable amount of acyclic ketone in the crude reaction mixture. We reasoned that the bulk of the t-butyldimethylsilylether was preventing the starting epoxide from reaching assuming a productive conformation for cyclization; thus diverting sizable quantities of material to unproductive epoxide opening. The reasons for choosing of t-butyldimethylsilyl ether as the protecting group of choice are (1) silyl groups can be removed under mild conditions (Bu_4NF) without inducing retroaldol reaction; and (2) t-Butyldimethylsilyl group had been employed in the cyclization approach to (±)-**1** by Corey[10c]. Therefore, an alternate protecting function must be carefully chosen to allow an inversion of the C-3-O̲H w̲i̲t̲h̲o̲u̲t̲ the loss of the C-4-CH_2OH, v̲i̲a̲ retro-aldol of the presumed intermediate 3-one. Of the seven total and formal-total syntheses reported in the literature only the elegant **erythro**-glycidol initiated cationic cyclization approach of van Tamelen[10e] constructed the C-3 and C-4 stereocenters differently; hence our concern.

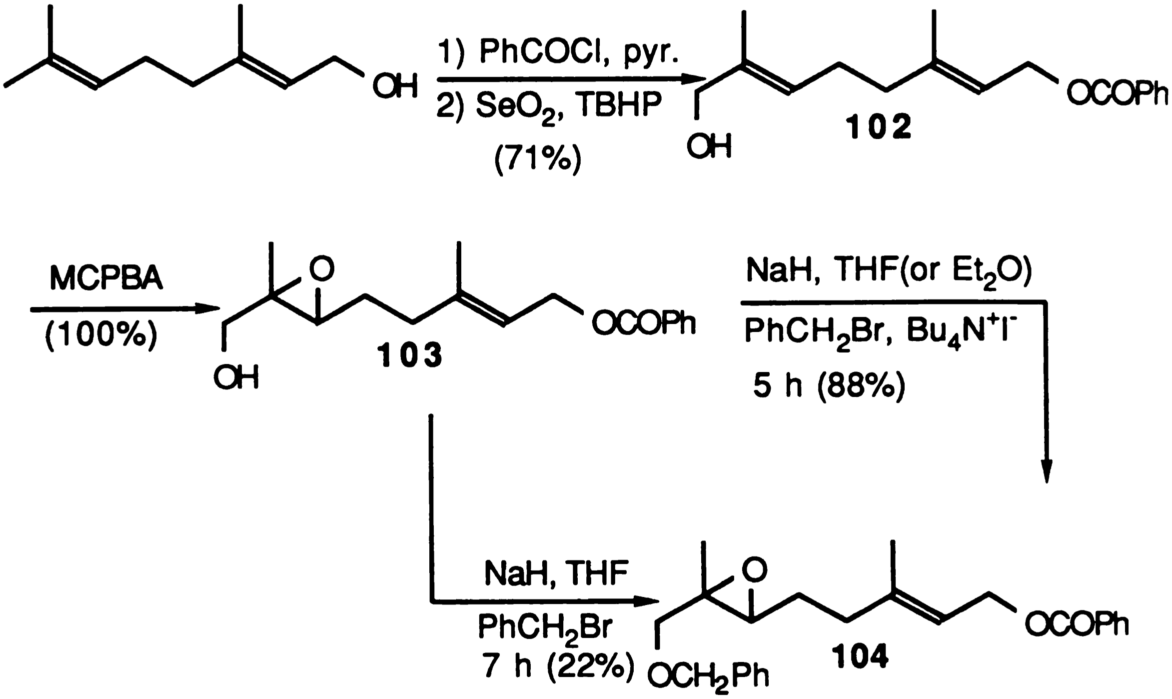
A benzyl ether is relatively small and stable compared to an R_3Si- group. Also, benzyl ethers are known to be removed relatively easily by hydrogenolysis which might not cause the retro-aldol decomposition. Therefore, a benzyl ether was selected as the protecting group of choice for a second generation synthesis.



100 **101** (eq. 6)

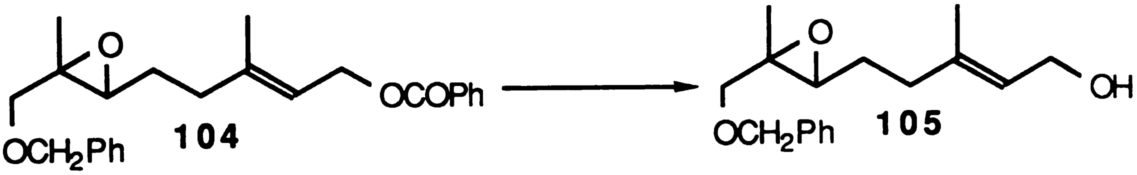
Benzylation of 6,7-epoxy-8-hydroxygeranyl-acetate **100**[25] with benzylbromide and sodium hydride gave **101** albeit in 21% yield (eq. 6). However as a result of scrambling of acetyl group by NaH; and low mass balance we searched for other alternatives. One obvious solution is the utilization of a more robust C-1-<u>O</u>H protecting group. Benzoates are usually stable to such conditions and can be removed without touching the benzyl protecting group. Therefore, a benzoate was selected as the protecting group of choice. Benzoylation of geraniol (PhCOCl, pyridine, DMAP, CH_2Cl_2, 99%) followed by application of the Sharpless catalytic allylic oxidation (SeO_2, TBHP, 71%) gave **102**. Compound **102** was then submitted to Henbest epoxidation (m-chloroperoxybenzoic acid, CH_2Cl_2) to afford the 6,7-epoxy-8-hydroxygeranyl-benzoate, **103**, in 100% crude yield. Without further purification compound **103** was submitted to standard benzylation conditions (NaH, $PhCH_2Br$, THF, 7h, room temperature) giving **104** in 22% yield

Scheme XII Preparation of **104**



with 50% recovered starting material. This reaction did indeed provide the desired **104**; however, the reaction rate is very slow and mass balance is low. We found that the addition of the phase transfer catalyst ($Bu_4N^+I^-$, NaH, THF(or Et_2O), 5h, RT) resulted in smooth benzyl ether formation to give **104** in 88% yield. With **104** in hand, several standard benzoate saponification methods (entry 1-6 in Table 1)[32] were examined, but none of them gave completely satisfactory results (Table 1). Although LiOH in THF-H_2O (entry 6) did provide the desired **105** in 91% yield, the extraordinary long reaction time required rendered these deprotection conditions less than useful. As we learned from the benzylation of **103**, a phase transfer catalyst can be a very important addend to the reaction medium. Therefore, 2.2 equivalents of $Bu_4N^+I^-$

Table 1 Saponification of **104**



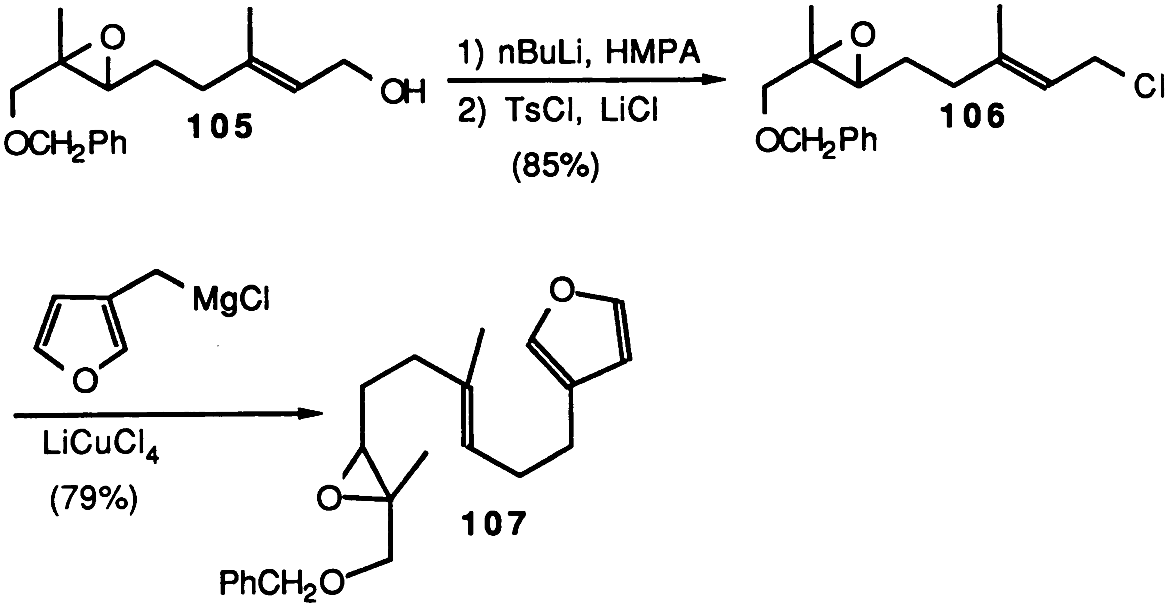
	Conditions	Results
1	1% NaOH / MeOH, 5 days	no reaction
2	MeONa / MeOH, 2 days	10% conversion by GC
3	NaOH / MeOH, reflux, 4 h	decomposed
4	LiOH / THF, reflux, 4 h	decomposed
5	MeONa / MeOH, reflux, 4 h	decomposed
6	LiOH, THF-H_2O (5:1) 14 days	91%
7	LiOH / THF, $Bu_4N^+I^-$(2.2 eq.) 12 h	no reaction
8	MeONa / MeOH $Bu_4N^+I^-$(2.2 eq), 12 h	(99%)

was added to the LiOH and NaOMe mixture (entry 7 and 8). As is shown in Table 1, $Bu_4N^+I^-$ did not significantly accelerate benzoate hydrolysis in the LiOH-THF system, but it did assist the saponification of **104** to **105** by MeONa in methanol giving **105** in 99% distilled yield. With a supply of **105** insured we examined **105** in the chlorination and coupling reactions.

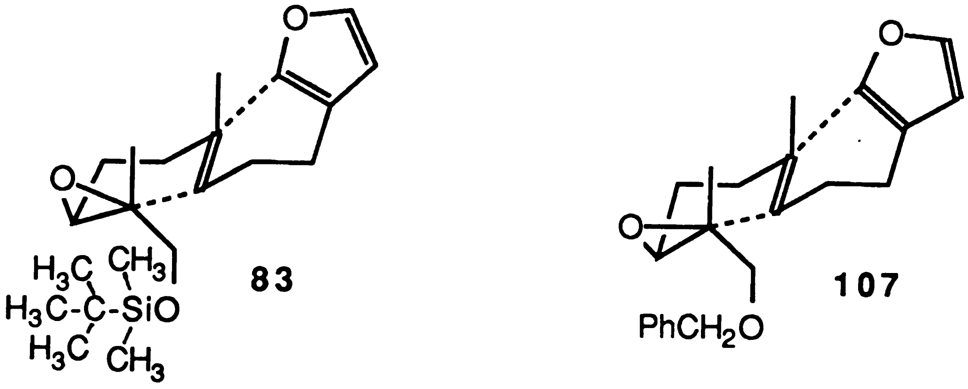
Utilizing Stork's procedure[23] (1. BuLi, HMPA 2. p-TsCl, LiCl), **105** was converted to chloride **106** in 85% yield (Scheme

XIII). This modified epoxygeranyl chloride **106** was then coupled with the Grignard reagent produced from 3-furylmethyl chloride in the usual way (Li_2CuCl_4)[21,22] to afford a 79% yield of coupled product **107**.

Scheme XIII Preparation of **107**



As was disscussed previously, the benzyl group is more stable and smaller than the t-Butyl dimethyl silyl protecting group. Therefore, we expected that the cyclization intermediate **107** would experience less steric crowding and it might more readily assume a fruitful cyclization conformation (Figure 2). When **107** was submitted to the usual cyclization conditions (Table 2) we obtained 30% of desired cyclized product **108** and recovered 60% of starting material **107**. The cyclization process was pushed to completion with slight modification of the Lewis acid-Lewis base solvent brew

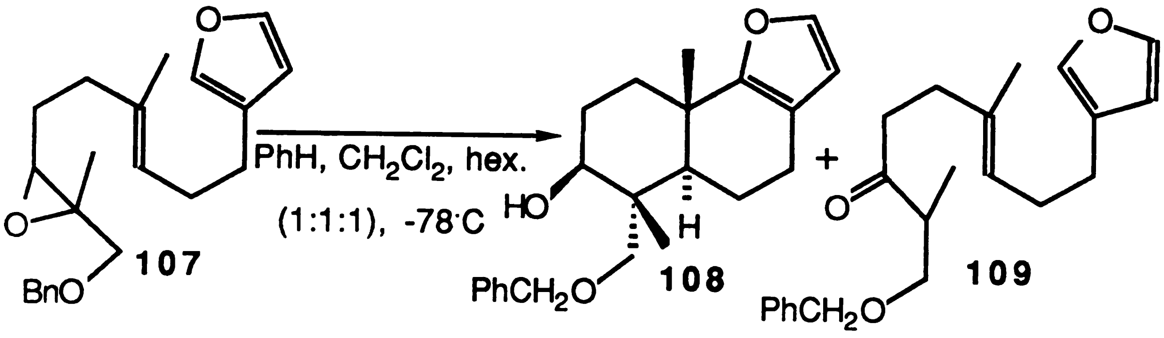


83

107

Figure 2 Cationic Cyclization Intermediates of 83 and 107

Table 2 Cationic Cyclization of 107



107

108

109

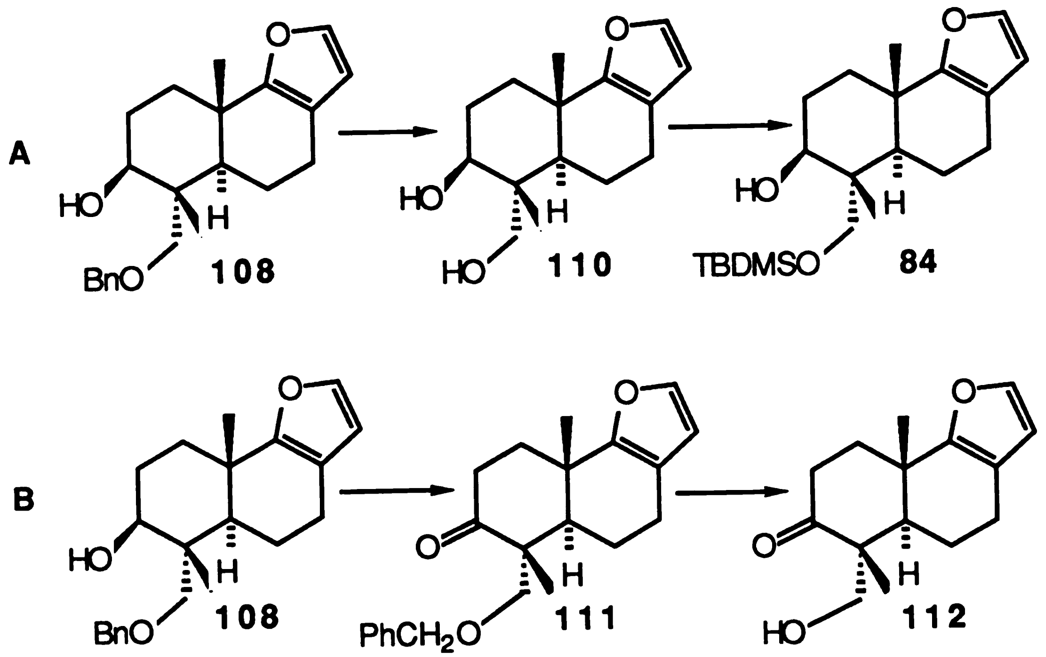
Conditions	108	109	starting material
BF_3-OEt_2(3 eq.) Et_3N(1.5 eq.)	30%	0%	60%
BF_3-OET_2(6 eq.) ET_3N(3 eq.)	72%	5%	0%

(BF_3OEt_2(6 eq.), Et_3N(3 eq.) in hexane, benzene, methylene chloride (1:1:1), -78°C) to afford 72% of cyclized **108** and 5% of acyclic ketone **109** (Table 2). This result suggested that the rationale for the selection of the benzyl protecting group might be correct and that the nature of the protecting group plays a major role in the partitioning of **107** between desired and undesired pathways. We also examined the cyclization of **107** with $Ti(OiPr)_3Cl$; which led to a mixture consisting mostly of a monocyclic compound. The vast improvement in the yield of the crucial cyclization raised our hopes of successfully completing a formal total synthesis of (+)-aphidicolin **1** via a chiral epoxide initiated closure; however we must demonstrate that the C-3-OH stereochemistry can be adjusted.

Compound **108** is the 4-CH_2-O-benzyl equivalent of silyl ether **84**; the conversion of the **108** to furan acetonide **86** requires the inversion of configuration at C-3, a deprotection of the 4-CH_2-O-CH_2Ph; although not necessarily in that order; followed by acetonide formation. However as was mentioned previously we were concerned that a protected (benzyl ether) aldol intermediate would suffer a retroaldol reaction when we attempted to deprotect. Therefore we examined the direct inversion of the C-3-OH via a Mitsunobu reaction[33] of **108**, and nitrite displacement[34] of the mesylate of **108**. Unfortunately, the highly hindered nature of C-3 hydroxyl of **108** precluded any success with these measures.

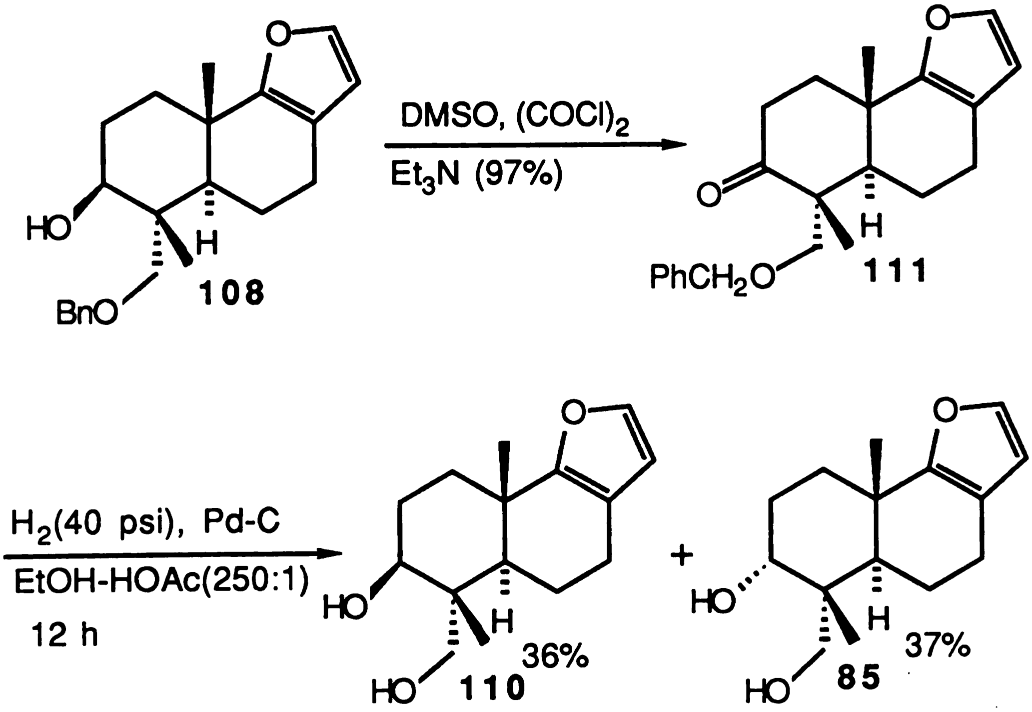
We planned then to accomplish the inversion of C-3 hydroxyl in a manner identical to that utilized in the Corey[10c] and McMurry[10b] syntheses of (±)-1; that is reduction of the C-3-one with the C-4-CH_2-OH unprotected. A number of possibilities exist to accomplish this transformation; for example (Scheme XIV) path A shows a debenzylation of the C-4-CH_2-O-function to give **110**, and in selective silylation of the produced diol would give silyl ether **84** employed in our first generation (Scheme VIII) synthesis. A second possibility (path B) would proceed from ketone **111**. Deprotection of **111** would afford the aldol adduct encountered in the first generation (Scheme IX) approach.

<u>Scheme XIV</u> Possible Routes to Accomplish Synthesis of **18** from **108**



We examined hydrogenolysis and dissolving metal cleavage of the benzyl linkage of **108** under a variety of conditions to no avail. We observed either no cleavage or furan reduction along with cleavage. Therefore path A (Scheme XIV) could not be employed and we examined path B. The cyclized **108** was submitted to the Swern oxidation[35] (DMSO, $(COCl)_2$, Et_3N, THF) to afford **111** in 97% yield. Exposure of **108** to PCC provided wildly variable yields (60-90%) of **111** (Scheme XV).

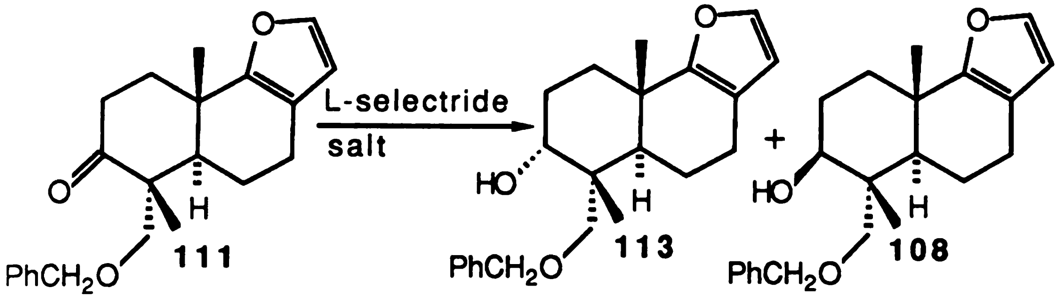
Scheme XV Preparation of **85**



Attempted hydrogenolysis of the benzyl ether **111** under a variety of reaction conditions was uniformly unsuccessful. As shown in Scheme XV, our most successful benzyl cleavage was plagued with concomitant reduction of C-3 ketone. Diol **85** is useful to us; however **110** is of no direct utility. Milder nucleophilic thiol cleavage conditions such as those of Fujita[36] (BF_3OEt_2, CH_3CH_2SH, CH_2Cl_2) destroyed the starting benzyl ether **111**.

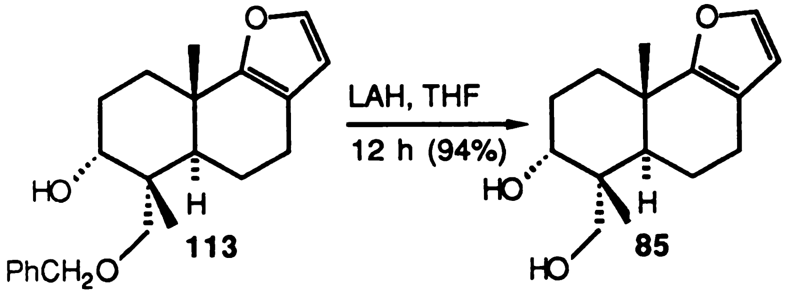
Since we were unable to generate the aldol adduct presumed to be essential for the reported selectivity of L-selectride reduction, we began to exam the reduction of **111** with L-selectride in the absence and in the presence of a

Table 3 L-Selectride Reduction of **111** in the presence of metal salts



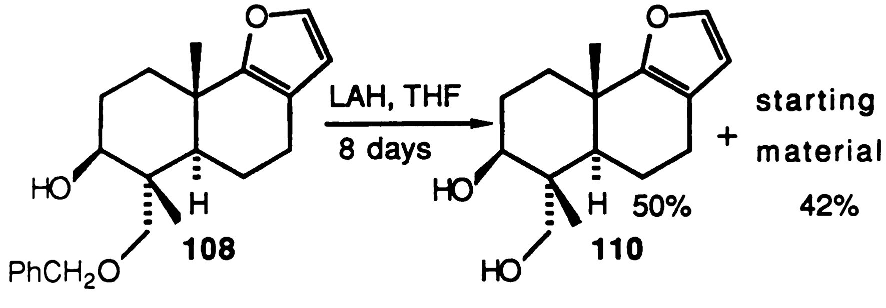
Entry	Salts	113	108	% Yield
1	no salt	2.8	1	99
2	ZnI_2 (1.5 eq.)	1.2	1	93
3	$MgBr_2$-OEt_2 (1.5 eq.)	7.0	1	95
4	$MgBr_2$-OEt_2 (2 eq.)	8.5	1	95
5	$Ti(OiPr)_3Cl$ (1.5 eq.)	4.0	1	96
6	$Ti(OiPr)_4$ (1.5 eq.)	5.7	1	93

variety of metal salts. We assumed that the proper combination of metal salt and solvent would conspire to provide a chelated intermediate which might be selectively reduced[37]. Pre-complexation of **111** with ZnI_2; $MgBr_2$-OEt_2; $Ti(OiPr)_3Cl$ or $Ti(OiPr)_4$ followed by reduction with L-selectride (Table 3) afforded ca. 1.2:1 to 8.5:1 ratios of 3α / 3β alcohols. The best conditions (entry 4) 2 equivalents $MgBr_2$-OEt_2 and L-selectride (CH_2Cl_2, -78°C) afforded a respectable 8.5:1 mixture of **113** and **111** in 95% combined yield.



113 **85**

(eq. 7)



108 **110**

(eq.8)

Our interest in the selective production of mono-protected diol **113** was based on our assumption that the axial 3α-OH would be able to assist in the cleavage of the neighboring 4-CH_2-O-benzyl ether by analogy to the precedent of Kutney[38]. In the event (eq. 7) treatment of **113** with LAH in THF for 12 hours provided exclusively diol **85** in 94% isolated yield. The mono-protected 3β-OH diol **108** when exposed to the Kutney conditions (eq. 8) for 8 days afforded a ca. 1:1 mixture of diol **110** and starting material. This result indicates the importance of neighboring group participation in reductive debenzylation with $LiAlH_4$. Diol **85** was converted to acetonide **86** ($(CH_3)_2CO$, $(CO_2H)_2$, $CaSO_4$, CH_2Cl_2) in a slightly better yield (93%); and the remainder of the sequence follows our previous described route (Scheme XI).

IV. THE FORMAL TOTAL SYNTHESIS OF (+)-APHIDICOLIN

Having successfully overcome the cyclization and protecting group difficulties in the racemic series we examined the route to (+)-**1** outlined in Scheme XVI. Our sole concern in this sequence was the transmission of chirality from the starting epoxy-furan to the product tricyclic aphidicolin precursor. Given the accepted chair-chair type folding of acyclic substrates in cationic cyclizations leading to the formation of six-membered rings[39] and our construction of the proper relative stereochemistry in the racemic routes described above we were confident of a successful outcome provided the C-3-O̲ bond is not compromised in the process.

In the event, epoxidation of 8-HO-geranyl benzoate under the conditions of Sharpless[20] afforded the corresponding epoxide in 71% yield (≥95% ee). The optical purity of (-)-**103** was determined by chiral shift reagent, Eu(HFPC)$_3$, and HPLC studies of its acetate **114** and Mosher ester[40] (MTPA) **115** (Figure 3,4). We have been unable to detect the presence of the enantiomer of (-)-**103**. Benzoate cleavage and chlorination as previously described (Scheme XIII) afforded the requisite allylic chloride (84%) which was coupled with 3-ClMgCH$_2$-furan (Li$_2$CuCl$_4$) to provide the desired cyclization substrate ($[\alpha]_D$-2.168°; c 0.764, CH$_2$Cl$_2$) in 75% yield. Exposure to BF$_3$-OEt$_2$ and Et$_3$N in the benzene, hexane, methylene chloride mixture; at -78°C gave (+)-**108** in 66-72% yield ($[\alpha]_D$+46.813°; c 0.455, MeOH).

Swern oxidation led to (+)-**111** (95%) which was reduced (L-selectride, MgBr$_2$-OEt$_2$) to provide the mono-protected diol (+)-**113** (83%). Treatment of (+)-**113** with LiAlH$_4$ gave (+)-**85** (94%) which was converted to the desired acetonide as described in Scheme XVI. Chiral shift reagent studies of **85** (Eu(hfpc)$_3$, Figure 5), demonstrated that, within our limits of detection, compound **85** was optically pure. However at this point we cannot yet demonstrate that **85** possesses the absolute configuration depicted.

Bromination, metallation, methylation and oxidation as outlined previously yielded a chiral ene-dione which provided (-)-**18** after reduction; thus completing the formal total synthesis of (+)-aphidicolin **1**.

In order to prove that the observed transmission of chirality was in the desired and anticipated sense, we needed

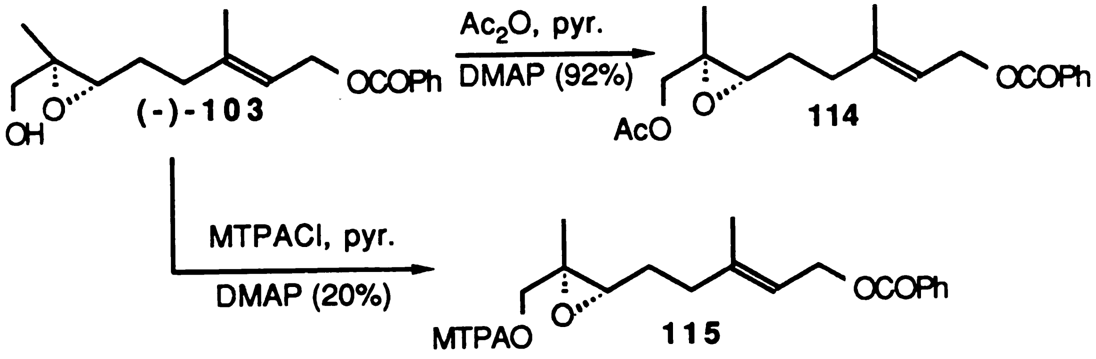
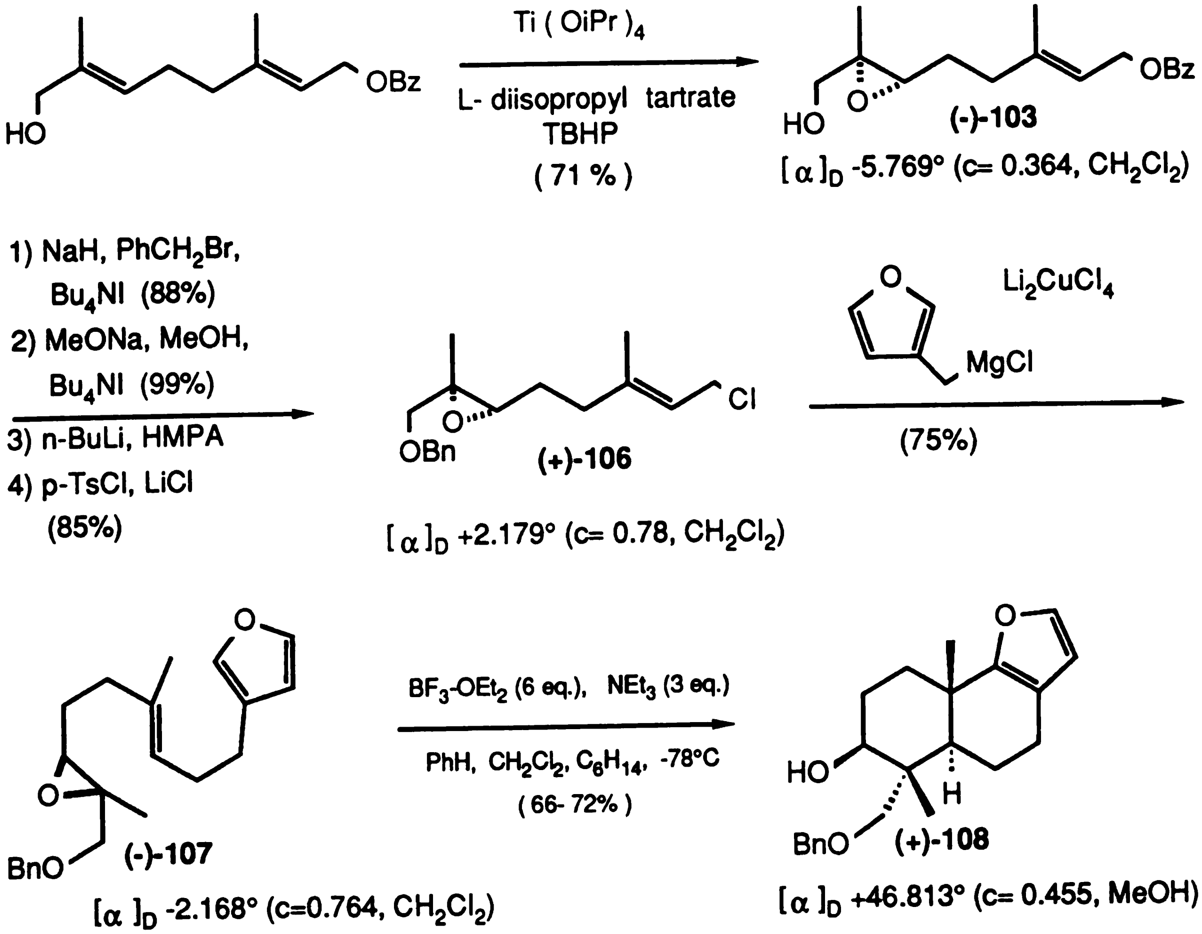
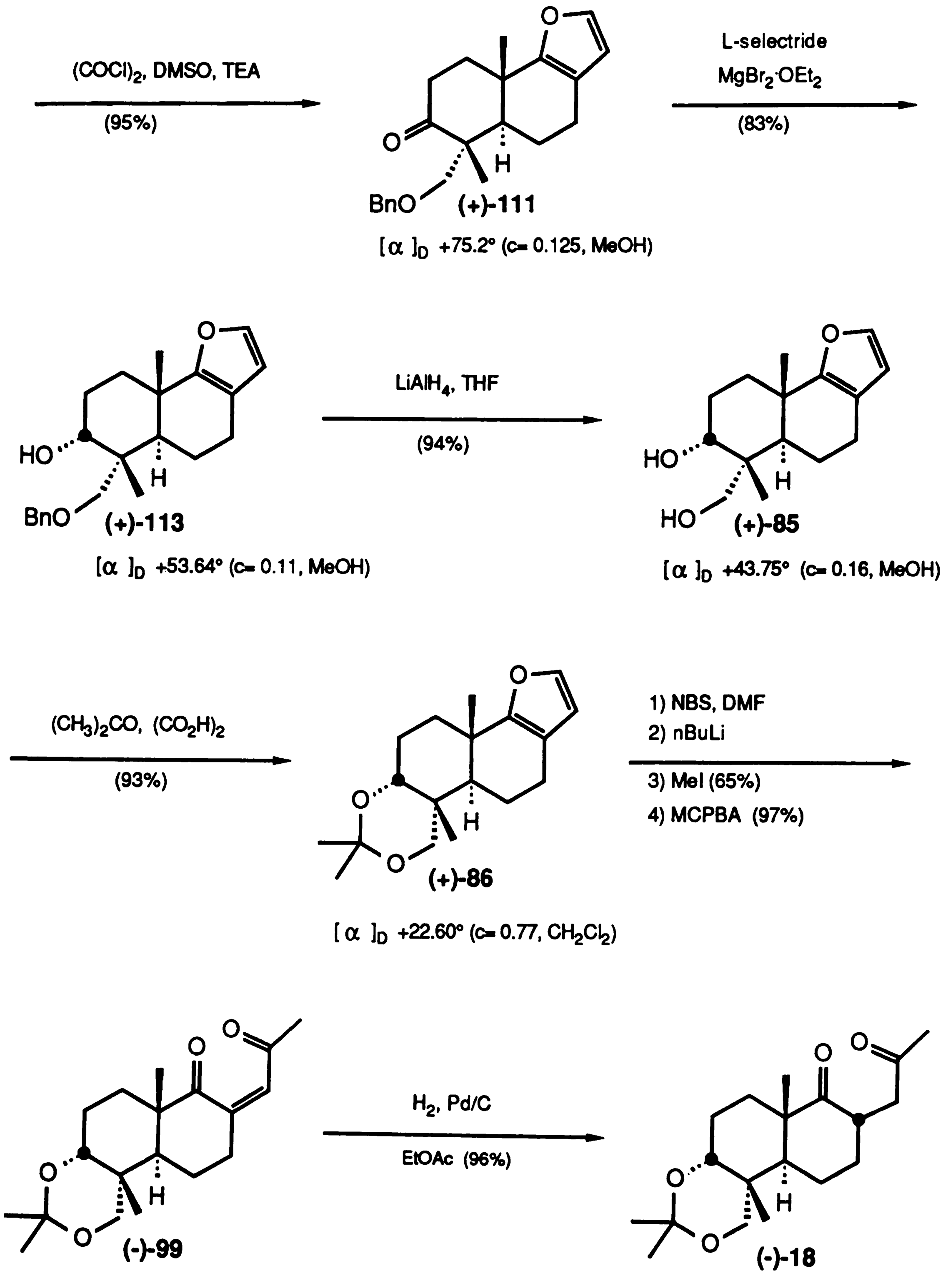


Figure 3 Preparation of 114 and 115

Scheme XVI Formal Total Synthesis of (-)-18





(+)-111

[α]$_D$ +75.2° (c= 0.125, MeOH)

(+)-113

[α]$_D$ +53.64° (c= 0.11, MeOH)

(+)-85

[α]$_D$ +43.75° (c= 0.16, MeOH)

(+)-86

[α]$_D$ +22.60° (c= 0.77, CH_2Cl_2)

(-)-99

[α]$_D$ -95.08° (c= 0.061, MeOH)

(-)-18

[α]$_D$ -44.0° (c= 0.025, MeOH)

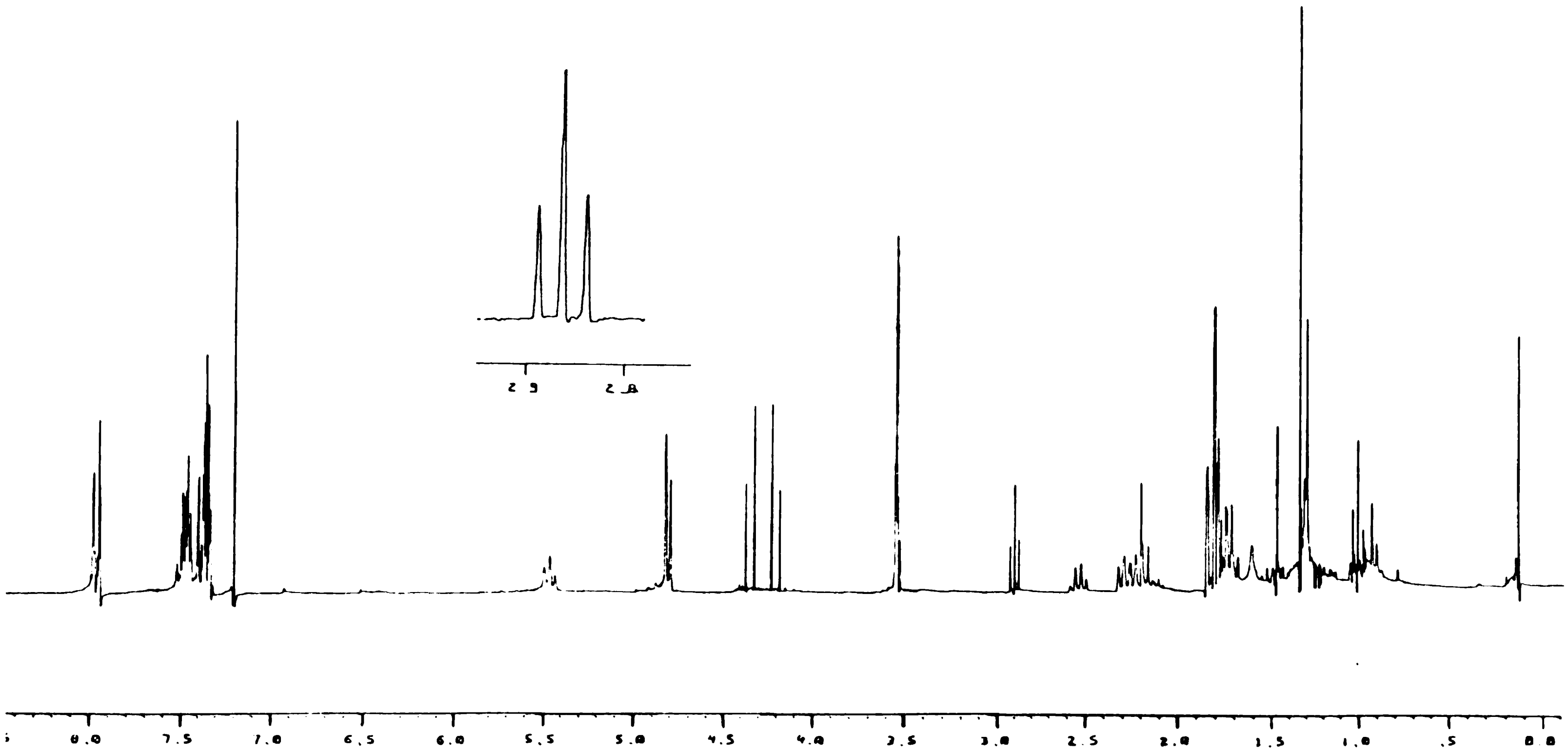


Figure 4 ^{1}H-NMR (250 MHz, $CDCl_3$) Spectrum of 115

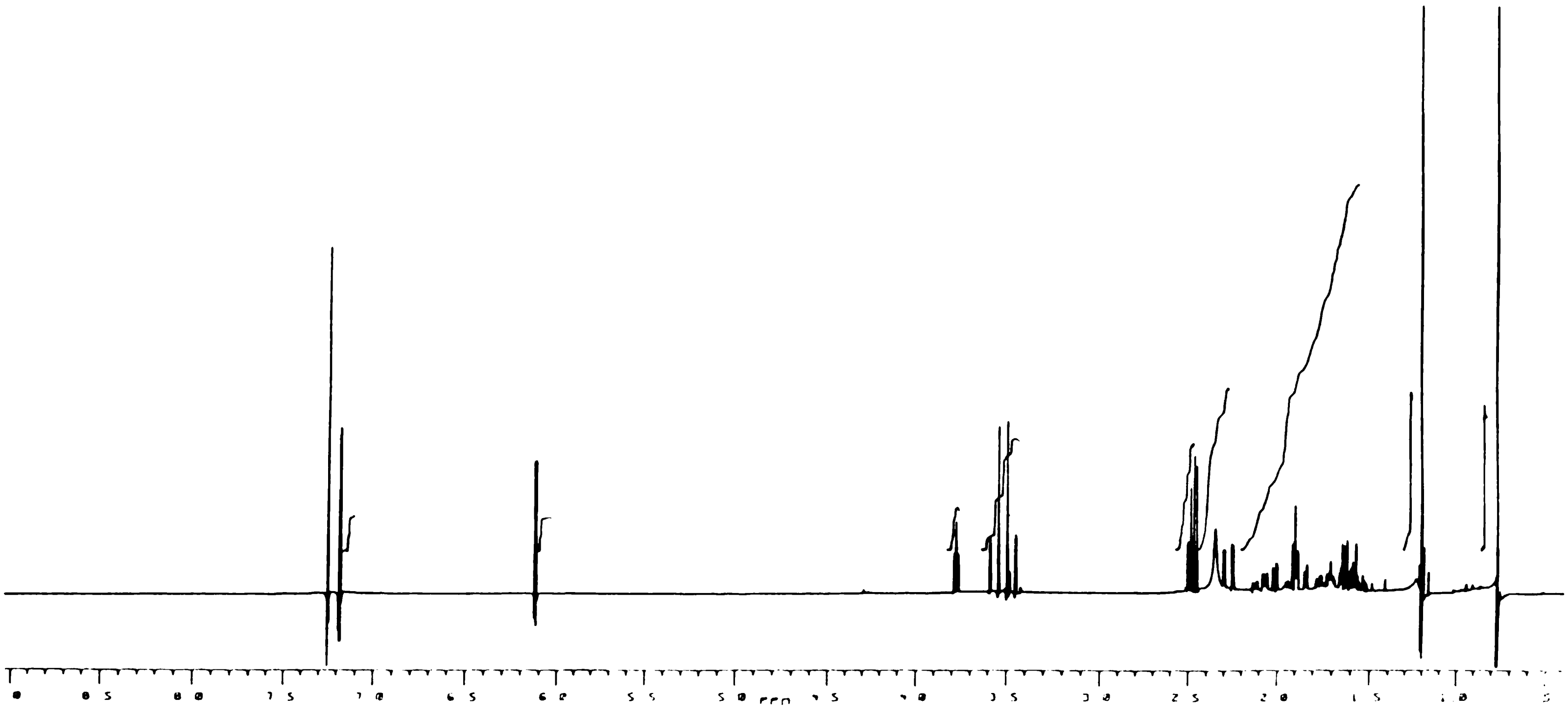


Figure 5a ^{1}H-NMR (250 MHz, $CDCl_3$) Spectrum of (±)-85

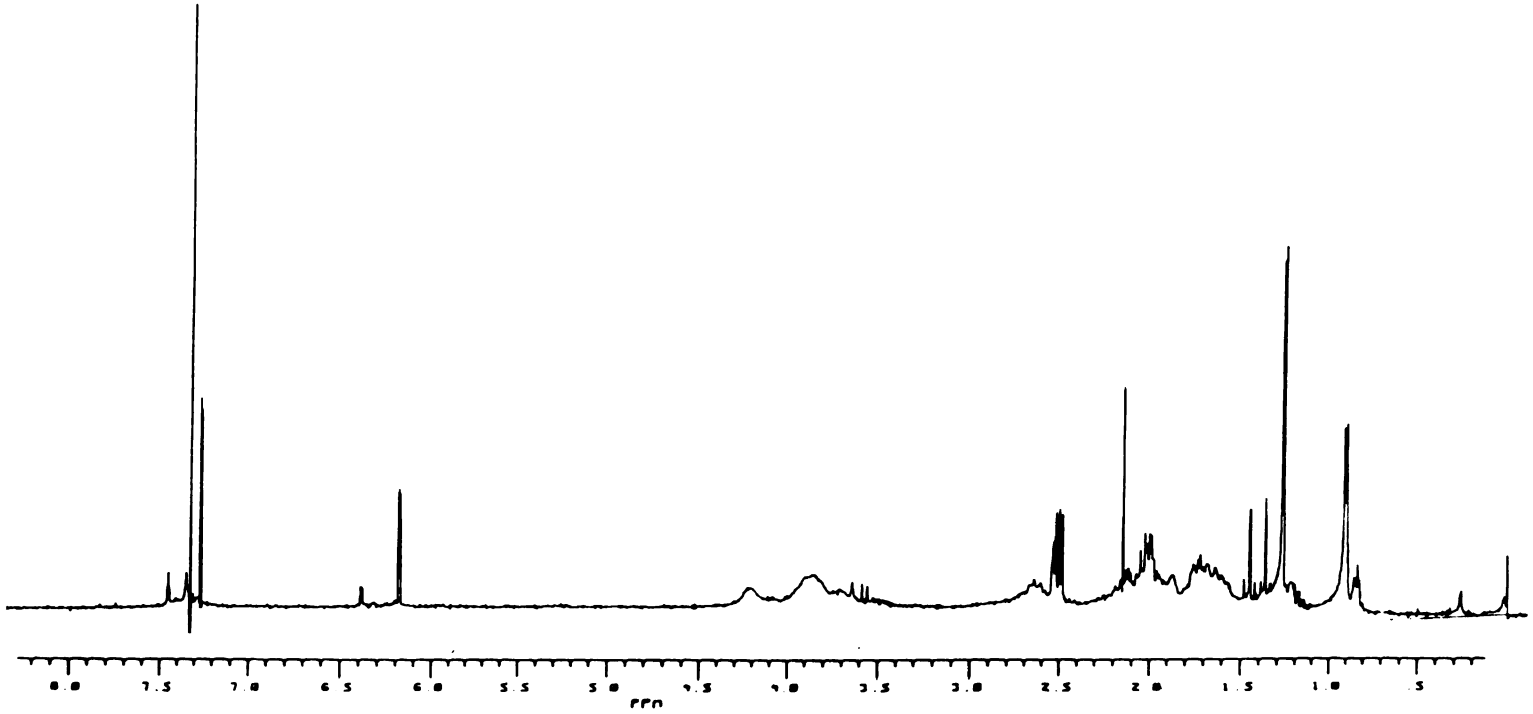


Figure 5b ^{1}H-NMR (250 MHz, $CDCl_3$) Spectrum of (±)-85 with First Addition of $Eu(hfpc)_3$

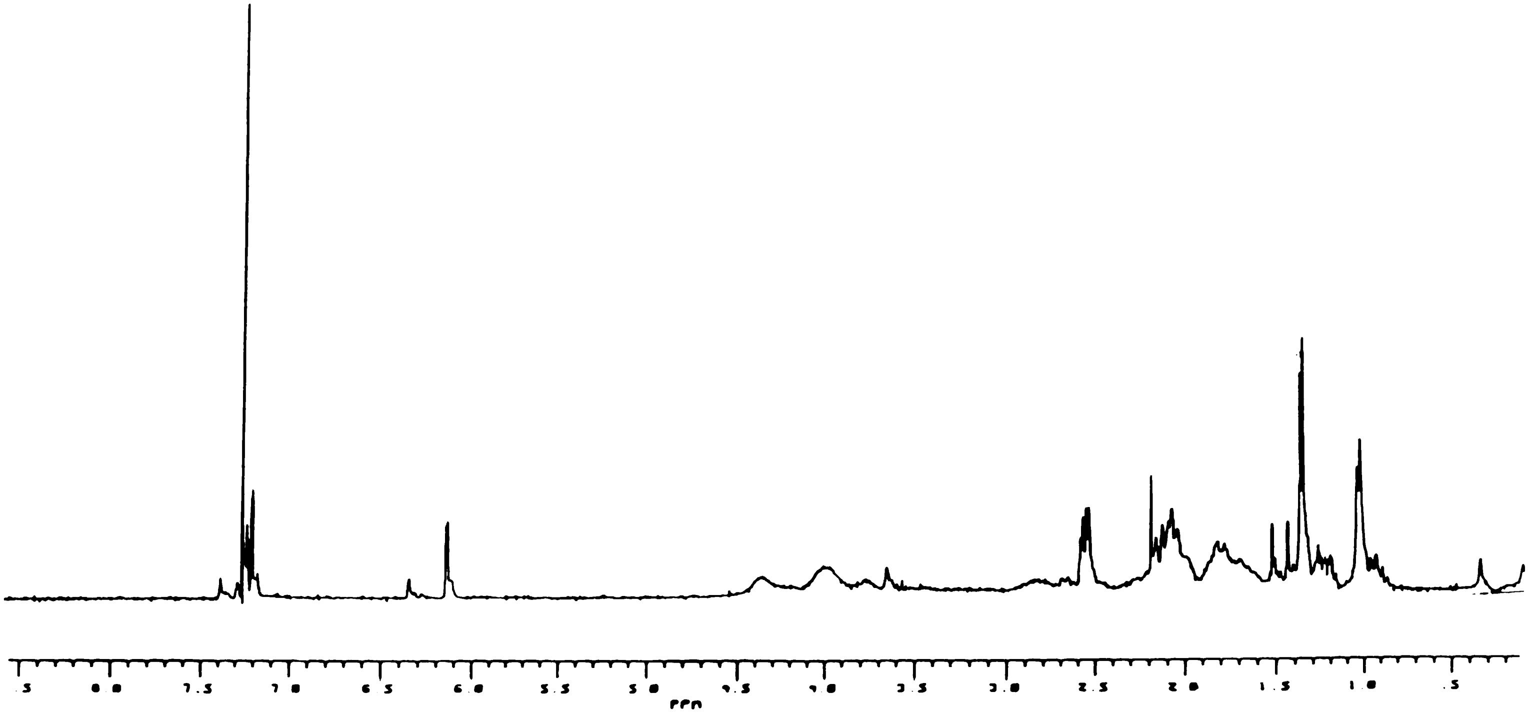


Figure 5c ^{1}H-NMR (250 MHz, $CDCl_3$) Spectrum of (±)-85 with Second Addition of $Eu(hfpc)_3$

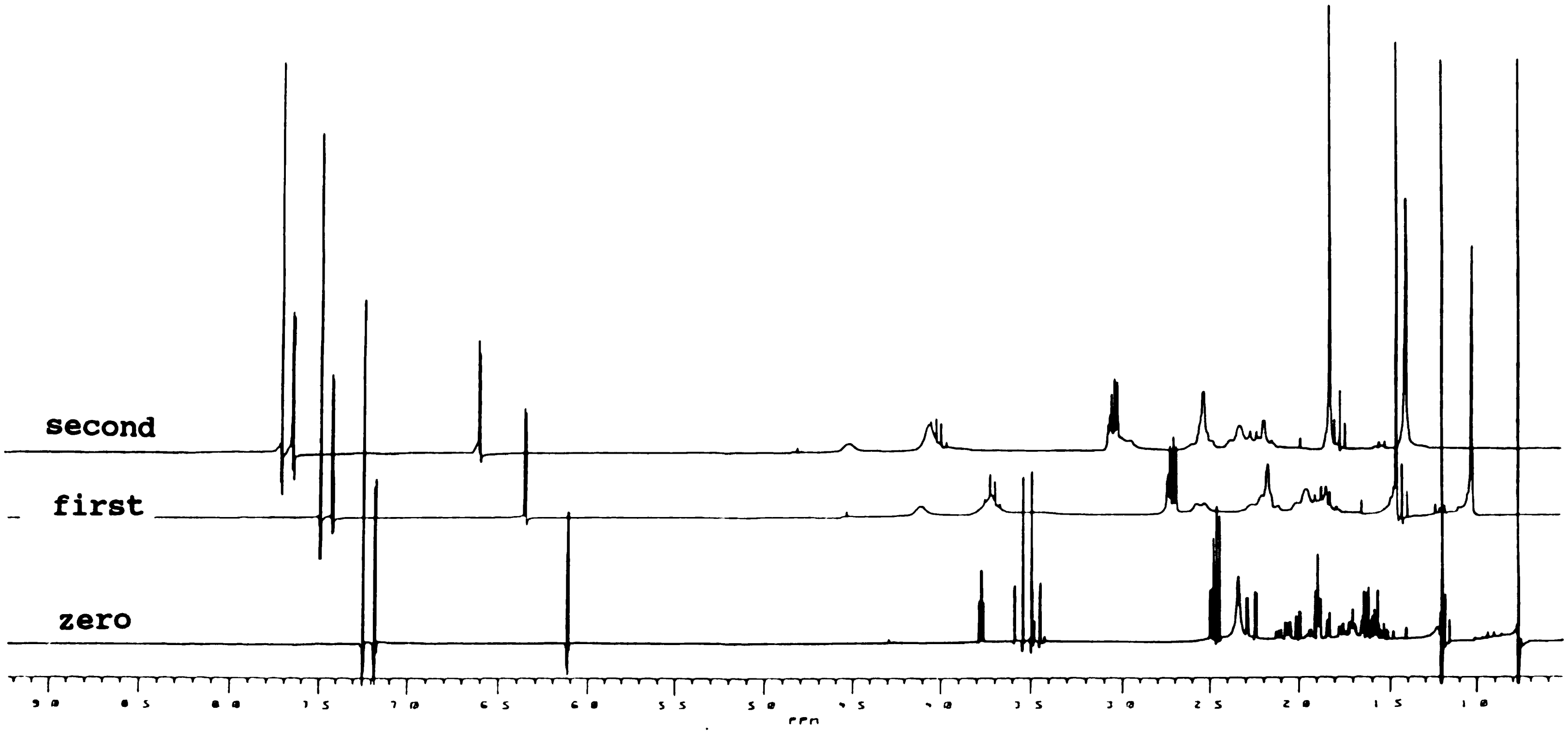


Figure 5d ^{1}H-NMR (250 MHz, $CDCl_3$) Spectrum of (+)-85 with Zero to Second Addition of $Eu(hfpc)_3$

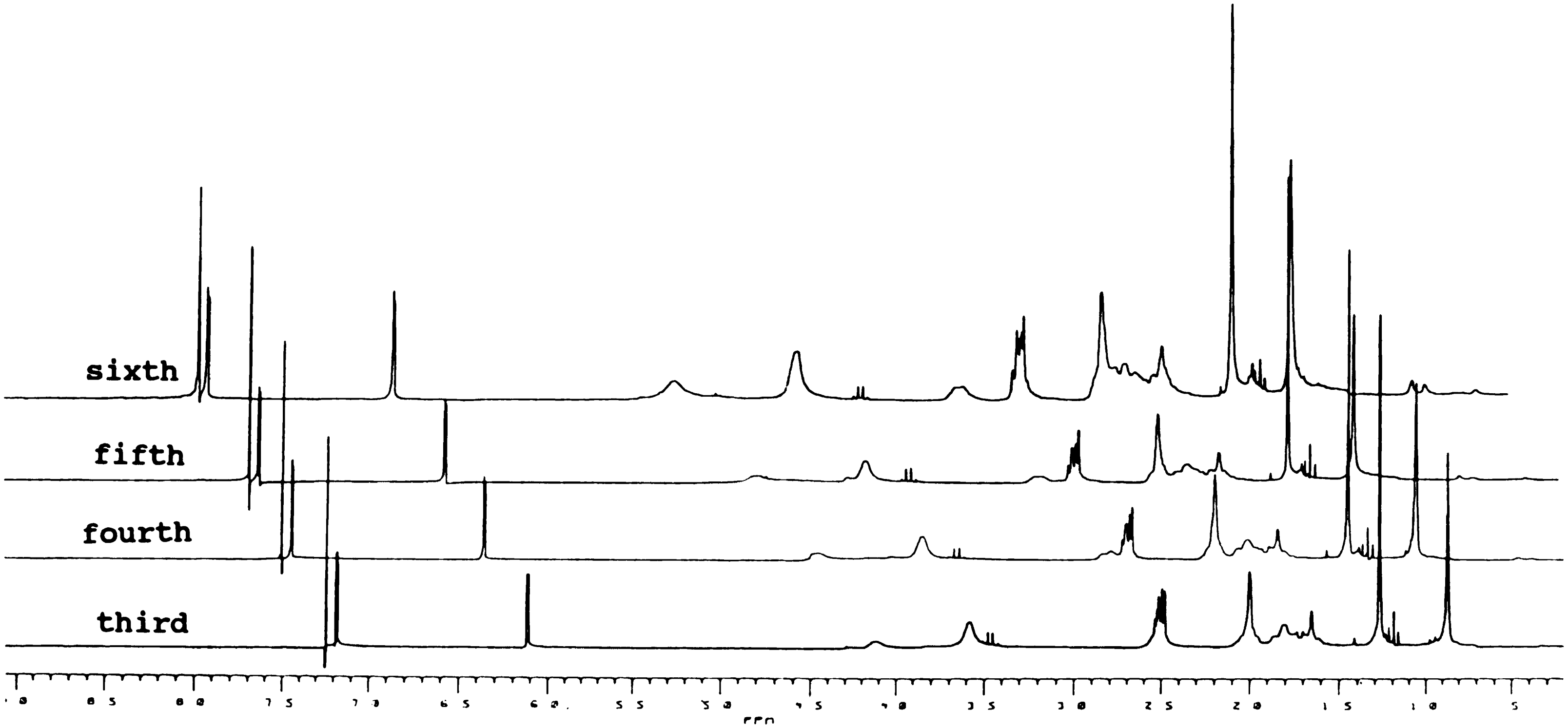
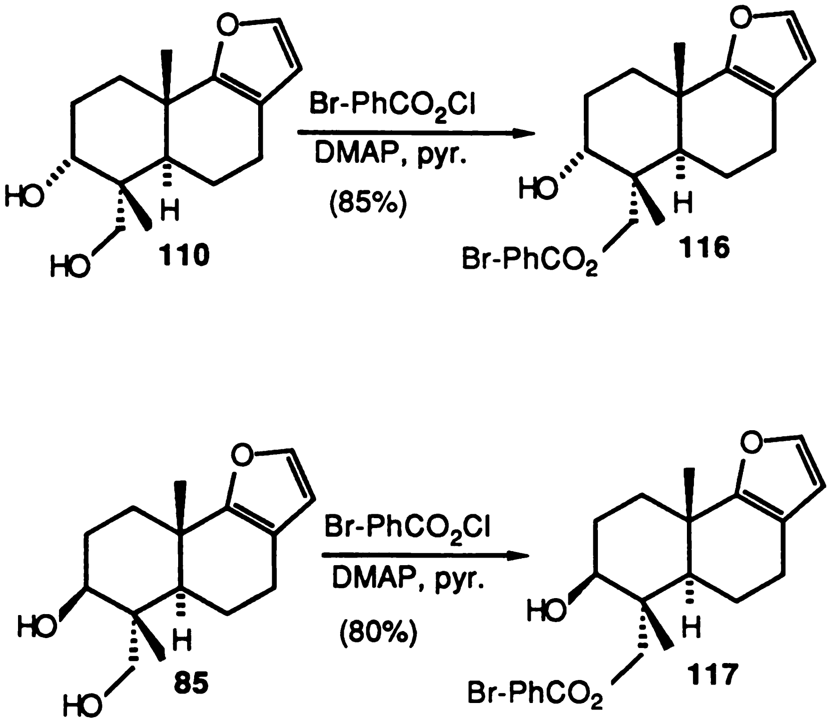


Figure 5e ^{1}H-NMR (250 MHz, $CDCl_3$) Spectrum of (+)-85 with third to Sixth Addition of $Eu(hfpc)_3$

to determine the absolute configurations of the cyclized products. Attempts to prepare bis-bromobenzoate of (+)-**110** and (+)-**85**, in order to utilize the exciton chirality technique of absolute configuration determination[41], were not successful. After numerous attempts we obtained only mono-bromobenzoates **116** and **117** (Figure 6). Therefore, we decided to use the O-methyl mandelate ester for establishment of absolute configuration[42] recently elaborated upon by Trost.



<u>Figure 6</u> Preparation of **116** and **117**

The technique recently described by Trost for establishing the absolute stereochemistry of 2°-alcohol requires that a racemate and optically pure compound be available. One converts both the optically pure series and racemate to the corresponding O-methyl mandelate esters and correlate the ^{1}H-NMR spectra of the esters utilizing the following model. One views the ester via an " extended Newman projection " in which the intervening ester linkage is omitted. That substitutent which eclipses the phenyl ring in such an extended Newman projection is then always shifted upfield, presumably as a result of the shielding it experiences by the phenyl ring. These suggestions were verified by Trost with an extensive series of examples, and has been confirmed by X-ray.

Therefore (±)-**108** was converted to a mixture of diasteriomers **118** and **119** with (S)-O-methyl mandelic acid, DCC and DMAP in CH_2Cl_2 (84%) (Figure 7). According to the Trost model (Figure 8) one would predict that the diasteriomer corresponding to the coupling of (S)-O-methyl mandelic acid with the undesired enantiomer of **108** (ie. **118**) would possess a C-4-CH_3 which should not experience an upfield shift; however then in the desired diasteriomer **119** the 4β-CH_3 should be shielded. We observed 2-methyl signals for the mixture of **118** and **119** δ=0.88 and 0.62 ppm respectively. Therefore, according to the precedent established by Trost we anticipate observing a methyl signal for **119** prepared (eq. 9) from (+)-**108** at δ=0.62 ppm. Reaction of (+)-**108** with (S)-O-methyl mandelic acid, DCC, and DMAP in CH_2Cl_2 afforded an 83% yield of the corresponding mandelate ester, which exhibits a C-4β-CH_3 signal at δ=0.62 ppm (Figure 9) thus confirming the absolute configuration of

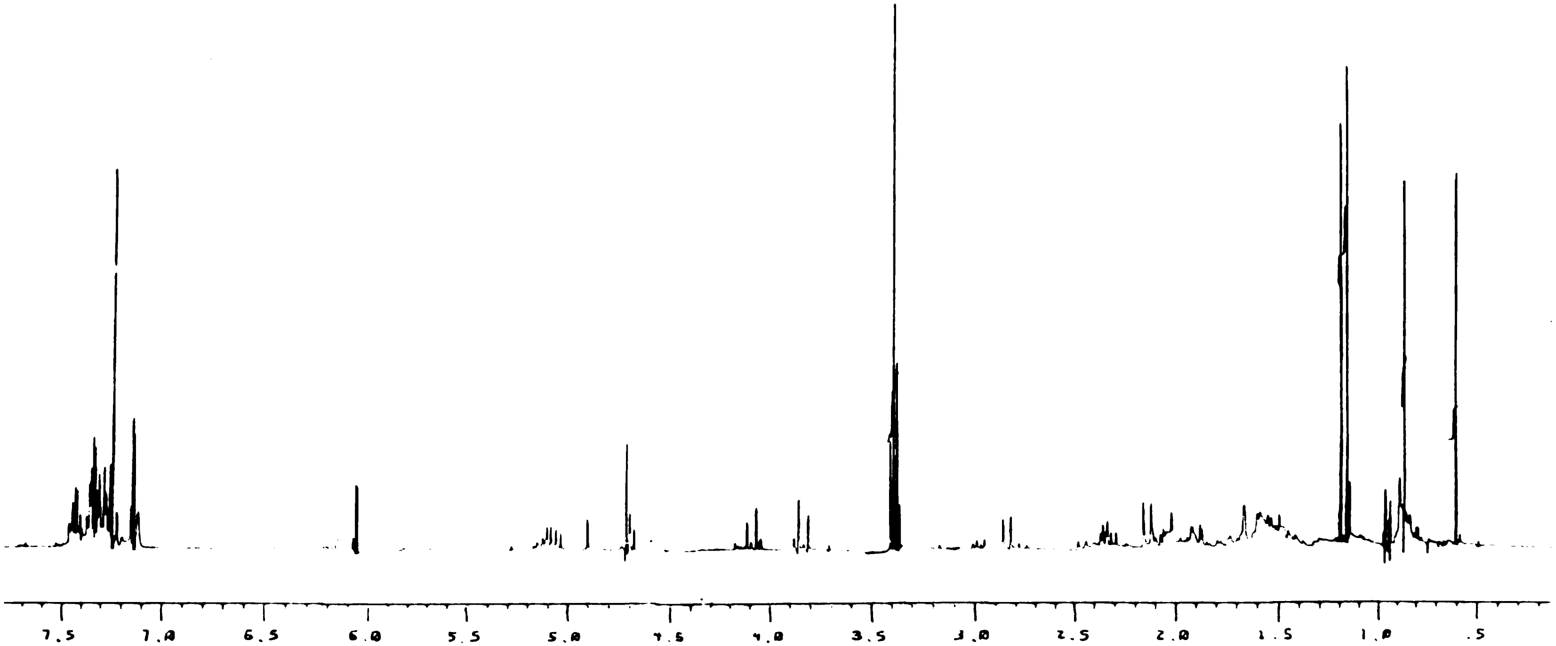


Figure 7 ^{1}H-NMR (250 MHz, $CDCl_3$) Spectrum of a mixture of **118** and **119**

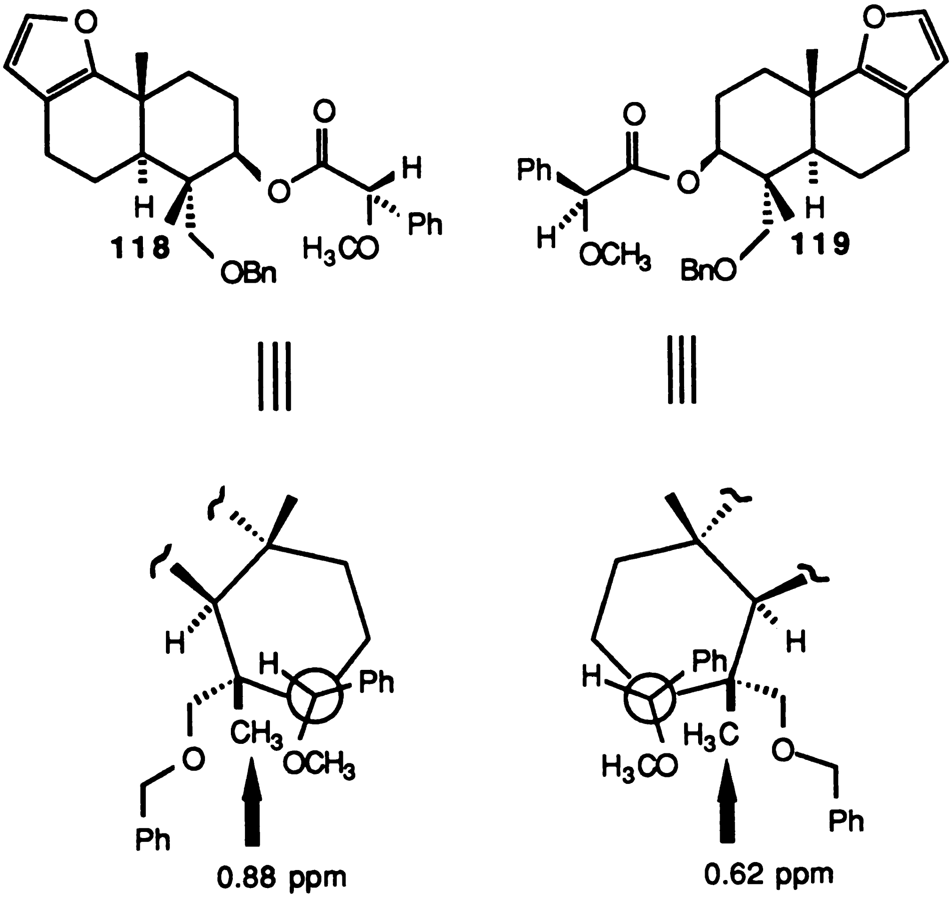


Figure 8 Extended Newman Projection of 118 and 119

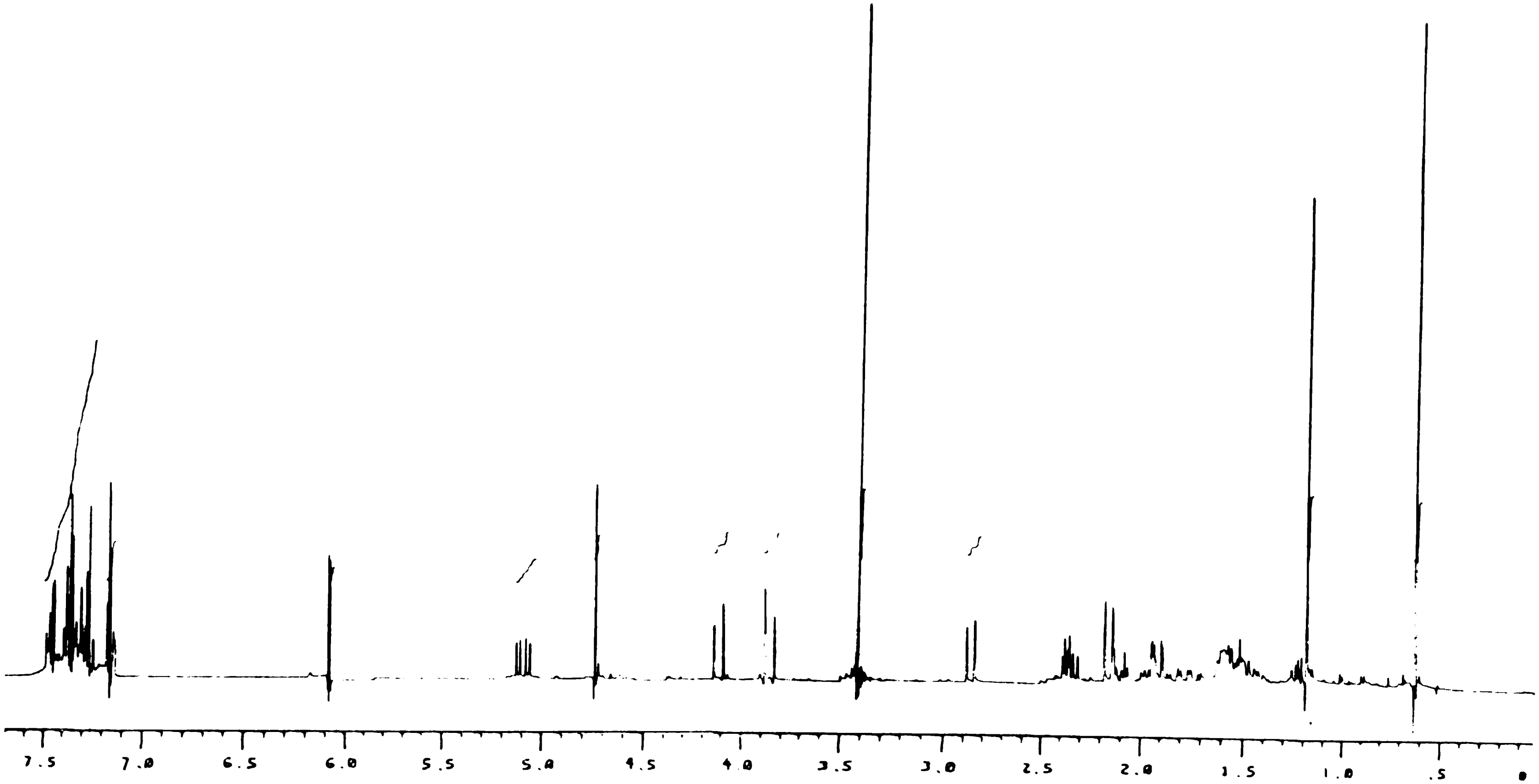
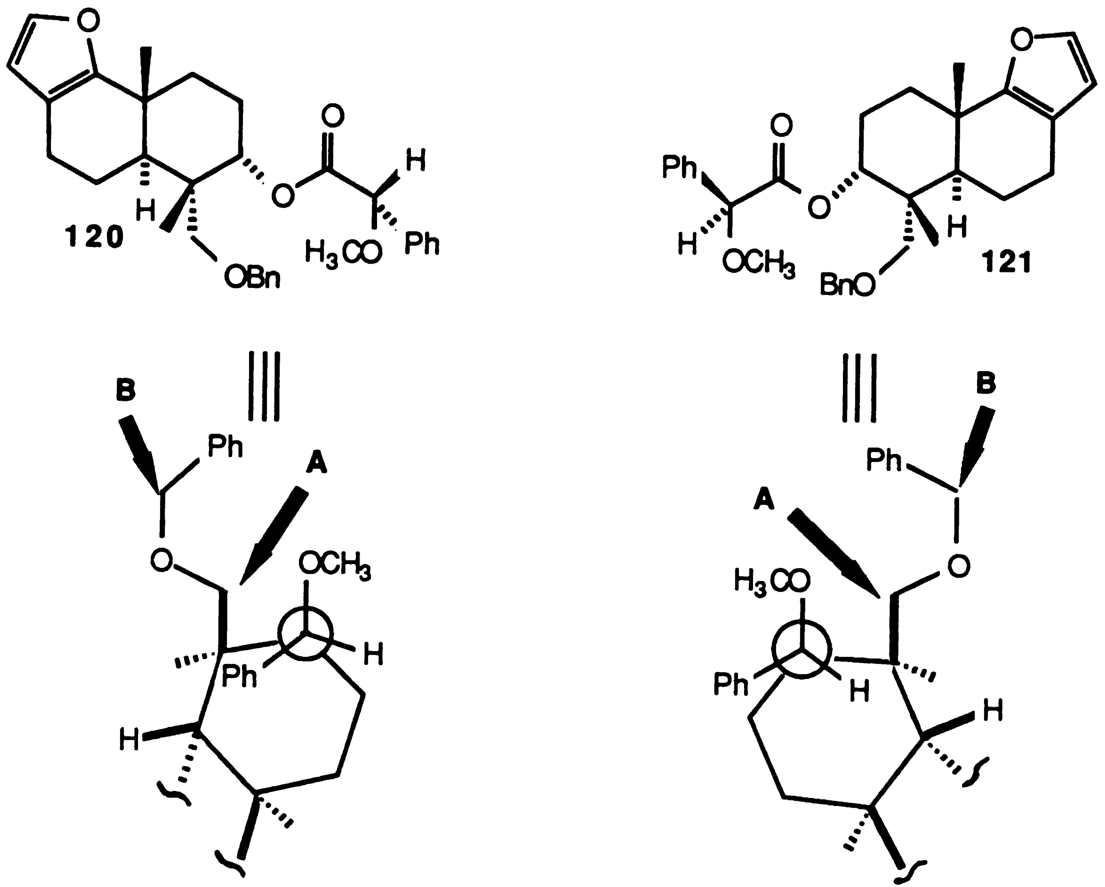


Figure 9 ^{1}H-NMR (250 MHz, $CDCl_3$) Spectrum of **119**



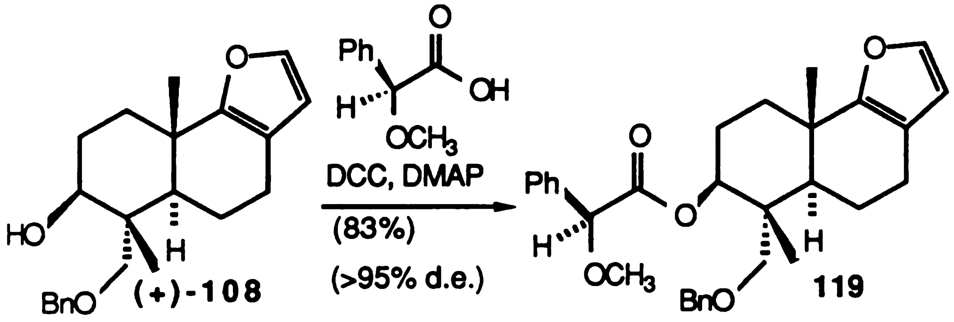
A: 2.97; 2.68
(AB, J=7.9 Hz, 2H)

B: 3.65 (s, 2H)

A: 3.26; 3.16
(AB, J=8.6 Hz, 2H)

B: 4.26; 4.19
(AB, J=12.2 Hz, 2H)

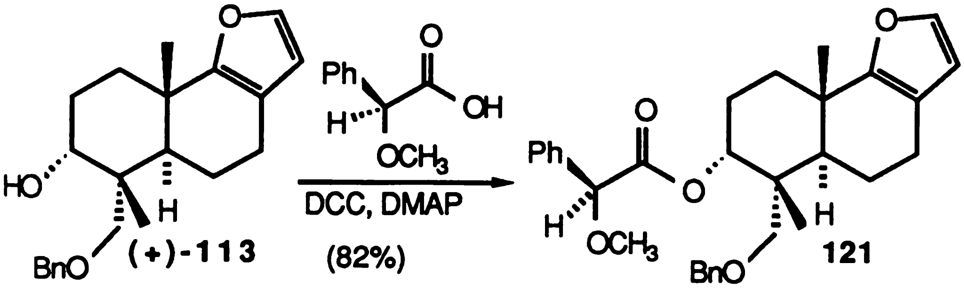
Figure 10 Extended Newman Projection of 120 and 121



(eq. 9)

the material in hand as that depicted in **119**.

Further confirmation of the absolute configuration in this study was obtained from a similar study employing coupling (±)- and (+)-**113** with (S)-O-methyl mandelic acid (DCC, DMAP, CH_2Cl_2) gave **120** and **121**. Figure 10 illustrates the Trost prediction for the NMR shifts associated with the diasteriomers **120** and **121**. We expect to observe an upfield shift of the 4α-CH_2-OBn protons of **120** relative to diasteriomer **121**. In this case we observe an AB pattern assigned to **120** at δ=2.97 (d, J=7.9 Hz); 2.68 ppm (d, J=7.9 Hz) and signal assigned to **121** were observed at δ=3.26 (d, J=8.6 Hz) and 3.16 ppm (d, J=8.6 Hz). The benzyl ether signals should also be effected, and we assigned a resonance



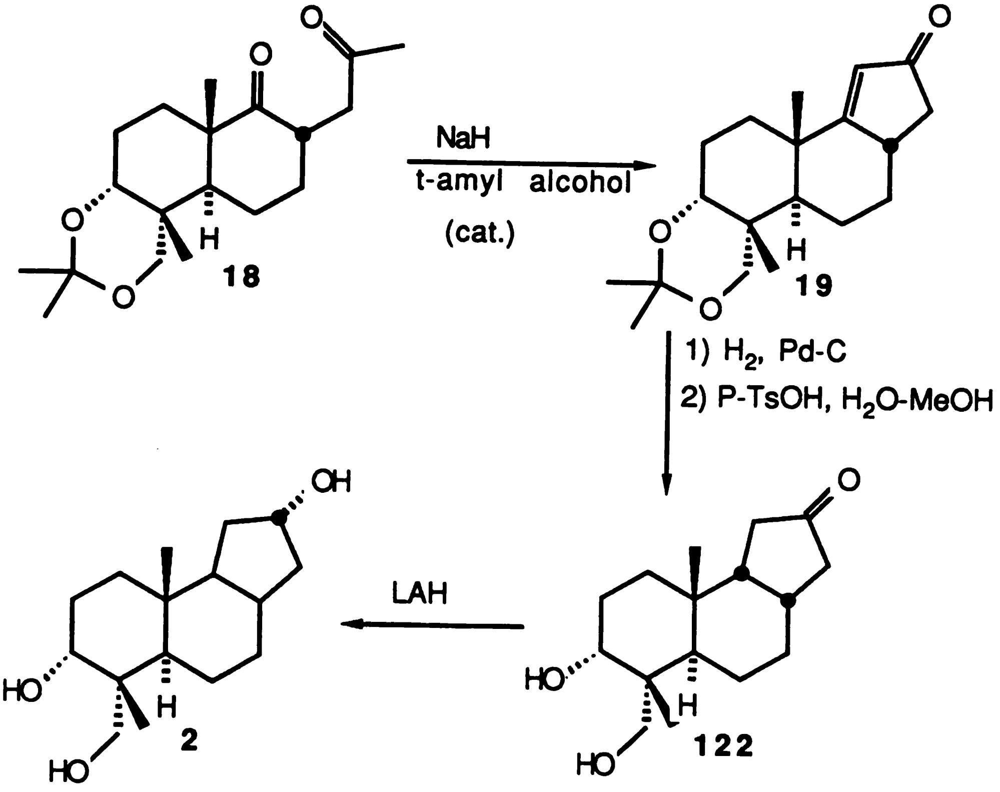
(eq. 10)

at δ=3.65 (s, 2H) to diasteriomer **120**; and signals at δ=4.26 (J=12.2 Hz) and 4.19 ppm (J=12.2 Hz) to diasteriomer **121**. When (+)-**113** was coupled to (S)-O-methyl mandelic acid it provided diasteriomer **121** as predicted (eq. 10).

We have described formal total syntheses of (±)- and (+)-aphidicolin **1**. The second generation approach affords (±)- and (-)-**18** in 16 steps and 13.9% and 8.4% yields respectively from geraniol. This represents a considerable improvement over the first generation synthesis of (±)-**18** (16 steps, 5.9%). The completion of the preparation of (-)-**18** was accomplished with ≥95% ee; demonstrating the utility of the epoxide initiated-furan terminated cyclization sequence for the transmission of chirality in a predictable fashion.

An application of this chemistry to the synthesis of optically pure **2** (Scheme XVII) is under way and will be reported in due course. McMurry[9] has reported that (±)-**2** possessed 45% of the DNA synthesis inhibitory activity of (+)-**1** at a concentration of 0.33μg/ml; should we be able extrapolate to the correct enantiomer of **2** we would predict that we would observe 90% of the DNA inhibitory activity of (+)-**1**. Such activity in a much simplified structure might provide routine access to a valuable biochemical tool.

Scheme XVII Conversion of 18 to 2



EXPERIMENTAL

General Tetrahydrofuran (THF) was dried by distillation under nitrogen from sodium benzophenone ketyl; methylene chloride was dried by distillation under nitrogen from calcium hydride; N,N-dimethylformamide (DMF) was dried by distillation at reduced pressure from phosphorous pentoxide; hexamethylphosphoramide (HMPA) was dried by distillation at reduced presure from calcium hydride; pyridine was dried by distillation under nitrogen from calcium hydride; diisopropylamine was dried by distillation under nitrogen from calcium hydride. Petroleum ether refers to the 30-60°C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Mallinkrodt, Inc., St. Louis, Missouri, and used as received. n-Butyl lithium in hexane was purchased from Aldrich Chemical Company, Milwaukee, Wisconsin and titrated by the method of Watson and Eastham[43]. N-bromosuccinimide was crystallized from hot water and dried _in vacuo_ over P_2O_5. All other reagents were used as recieved unless otherwise stated. All reactions were performed in oven (150°C) dried glassware under argon with the rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP-1000 infrared spectrometer or a Perkin-Elmer Model 167 spectrometer with polystyrene as standard. Proton magnetic resonance spectra (^{1}H-NMR) were recorded on a Varian T-60 at 60 MHz, or a Bruker WM-250 spectrometer at 250 MHz as indicated, as solutions in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million of the δ scale relative to a tetramethylsilane internal standard. Data are reported as follows: Chemical shift (multiplicity (s = single, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration). ^{13}C magnetic resonance spectra were recorded on a Bruker WM-250 spectrometer (68.9 MHz) and are reported in parts per million from tetramethylsilane on the scale. Electron impact (EI/MS) and chemical ionization (CI/MS) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system. High resolution mass spectra were performed by the MSU Regional Mass Spectroscopy Facility; Department of Biochemistry, East Lansing, MI. 48824. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Flash chromatography was performed according to the procedure of Still, et al[44] using 230-400 mesh Merck silica gel and eluted with the solvents mentioned. Analytical thin-layer chromatography was run on either Macherey-Nagel polygram SIL G/UV$_{254}$ pre-coated plastic sheets or Merck SIL G/UV$_{254}$ pre-coated glass plates. Spots were visualized by either dipping into a solution of Vanillin (1.5 g) in absolute ethanol (100 ml) and concentrated sulfuric acid (0.5 ml) and heating with a heat gun or spraying with a 5% solution of molybdophosphoric acid in absolute ethanol and heating to 120°C.

2-Bromo-4,5,5a,6,7,8,9,9a-octahydro-6,6,9a-trimethyl-(5aα,7β,9aβ)-(±)-naphtho[1,2-b]furan-7-ol 88

To a solution of 3β-hydroxypallescensin A 87 (0.12 g, 0.5 mmole) in dry DMF (5 ml) chilled in an ice-water bath was added a solution of NBS (0.1 g, 0.5 mmole) in dry DMF (2 ml) over a period of 5 minutes. Stirring was continued at 0°C for 40 minutes and then quenched with ice-water (50 ml), ether (50 ml) and pentane (50 ml). The organic phase was separated; washed with brine (100 ml); dried ($MgSO_4$); and concentrated <u>in</u> <u>vacuo</u> to provide a brown solid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30 g, 25 mm o.d., 1:5 ether:pet. ether) using the flash technique. Fractions 16 to 19 afforded 1.35 g, 84%, of (±)-**88** as a white solid. TLC (Merck, UV-vanillin, ether:hexane 1:5) R_f=0.06.

<u>^{1}H NMR</u> (250 MHz, $CDCl_3$): δ= 6.02 (s, 1), 3.28 (dd, J=5.1, 11.2 Hz, 1), 2.53-2.25 (m, 2), 2.12 (dt, J=3.0, 12.2 Hz, 1), 1.90-1.25 (m, 7), 1.19 (s, 3), 1.05 (s, 3), 0.86 (s, 3).

<u>EI-MS</u> (70 eV): 314, 312 (M^+, 12.9, 10.9), 281, 279 (23.2, 24.8), 119, 117 (96.7, 100.0), 91 (42.5).

4,5,5a,6,7,8,9,9a-Octahydro-7-methoxyethoxymethoxyl-6,6,9a-trimethyl-(5aα,7β,9aβ)-(±)-naphtho[1,2-b]furan 89

To a solution of diisopropylethyl amine (0.22 ml, 1.2

mmole) in dry methylene chloride (5 ml) chilled in an ice-water bath was added methoxyethoxymethyl chloride (0.14 ml, 1.2 mmole) followed by a solution of (±)-3β-hydroxypallescensin A, **87**, (0.14 g, 0.6 mmole) in methylene chloride (10 ml) over 15 minutes. The reaction mixture was stirred at room temperature for 24 hours; then quenched with ice-water (100 ml) and cast into ether (200 ml). The organic phase was separated; washed with saturated aqueous NH_4Cl (200 ml), brine (200 ml); dried ($MgSO_4$) and concentrated in vacuo to afford crude **89**. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30 g, 25 mm o.d., 1:5 ether:pet. ether) using flash technique. Fractions 15 to 17 afforded 0.183 g, 95%, of **89** as a colorless viscous liquid. TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.39.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 7.17 (d, J=2.0 Hz, 1), 6.12 (d, J=2.0 Hz, 1), 4.88 (d, J=8.3 Hz, 1), 4.73 (d, J=8.3 Hz, 1), 3.88-3.64 (m, 2), 3.57 (t, J=4.2 Hz, 2), 3.40 (s, 3), 3.21 (dd, J=4.2, 12.5 Hz, 1), 2.53-2.24 (m, 2), 2.10 (dt, J=3.0, 12.2 Hz, 1), 1.92-1.26 (m, 6), 1.20 (s, 3), 1.02 (s, 3), 0.88 (s, 3)

EI-MS: (33 eV) 322 (M^+, 10.2), 231 (19.6), 201 (22.6), 177 (15.9), 89 (58.9), 59 (base)

2-Bromo-4,5,5a,6,7,8,9,9a-octahydro-7-methoxyethoxymethoxyl-6,6,9a-trimethyl-(5aα,7β,9aβ)-(±)-naphtho[1,2-b]furan 90

According to the general procedure outlined for the bromination of **87**, on an identical scale, MEM-ether **89** was brominated to give **90** in 88% yield after purification by chromatography on silica gel using the flash technique. TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.42.

<u>^{1}H NMR</u> (60 MHz, $CDCl_3$): δ= 6.00 (s, 1), 4.87 (d, J=7.5 Hz, 1), 4.70 (d, J=7.5 Hz, 1), 3.87-3.40 (m, 4), 3.40 (s, 3), 2.54-2.13 (m, 3), 2.03-1.26 (m, 6), 1.20 (s, 3), 1.02 (s, 3), 0.87 (s, 3)

<u>EI-MS</u>: (70 eV) 402, 400 (M^+, 0.5, 0.5), 149 (2.5), 131 (2.2), 117 (2.1), 89 (37.0), 59 (base)

4,5,5a,6,7,8,9,9a-Octahydro-7-methoxyethoxymethoxyl-6,6,9a-trimethyl-2-trimethylsilyl-(5aα,7β,9aβ)-(±)-naphtho[1,2-b] furan 91

To a solution of **90** (0.1 g, 0.25 mmole) in dry Et_2O (5 ml) cooled in a dry ice-acetone bath was added nBuLi (2.48 M in hexane, 0.11 ml, 0.27 mmole) and the resulting gelatin-like solution was stirred for 30 minutes at -78°C. To the reaction mixture was added trimethylsilyl chloride (0.038 ml, 0.3 mmole), followed by HMPA (0.6 ml). The cooling bath was removed and the reaction mixture was stirred for 1 hour at room temperature; then stored in a refrigerator for 10 hours. The reaction was quenched with water (30 ml) and then cast into ether (50 ml). The organic phase was separated; washed with brine (50 ml); dried ($MgSO_4$); and concentrated <u>in vacuo</u> to provide a pale yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 20 g, 20 mm o.d., 1:5 ether:pet. ether) using the flash technique. Fractions 14 to 17 afforded 0.084 g, 85%, of **91** as white crystals, TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.44.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 6.37 (s, 1), 4.86 (d, J=8.1 Hz, 1), 4.72 (d, J=8.1 Hz, 1), 3.87-3.65 (m, 2), 3.56 (t, J=8.2 Hz, 2), 3.39 (s, 3), 3.21 (dd, J=5.4, 10.3 Hz, 1), 2.59-2.17 (m, 3), 2.00-1.26 (m, 6), 1.19 (s, 3), 1.02(s, 3), 0.88(s, 3), 0.21(s, 9)

EI-MS: (70 eV) 394 (M^+, 3.7), 303 (5.8), 273 (9.6), 231 (6.0), 89 (70.3), 59 (base)

4,5,5a,6,7,8,9,9a-Octahydro-7-methoxyethoxymethoxyl-6,6,9a-trimethyl-(5aα,7β,9aβ)-($\pm$)-naphtho[1,2-b]furan-2(3H)-one 92 and **4,5,5a,6,7,8,9,9a-octahydro-7-methoxyethoxymethoxyl-6,6,9a-trimethyl-(5aα,7β,9aβ)-($\pm$)-naphtho[1,2-b]furan-2(9bH)-one 93**

To a solution of **91** (0.15 g, 0.38 mmole) in dry methylene chloride (4 ml) chilled in an ice-water bath was added NaOAc (0.09 g, 1.1 mmole) in one portion, followed by peracetic acid (0.4 ml, 6 mmole) over 2 minutes. The reaction mixture was stirred at 5°C for 3.5 hours then diluted with ether (50 ml) and washed with water (50 ml), saturated aqueous $NaHCO_3$ (2x25 ml), saturated aqueous sodium thiosulfate (2x25 ml) and saturated aqueous $NaHCO_3$ (25 ml) followed by drying (Na_2SO_4). Removal of solvent *in vacuo* afford 0.085 g, of crude product. The crude ^{1}H-NMR showed

80% of desired deconjugated butenolide **92**. This crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30 g, 20 mm o.d., 1:4 ether:pet. ether) to afford 0.026 g, 20%, of **92**, TLC (Merck, UV-iodine, ether:hexane 1:1) R_f=0.2 and 0.045 g, 35%, Of **93**, R_f=0.02.

Spectral data of **92**: ^{1}H NMR (250 MHz, $CDCl_3$): δ= 4.86 (d, J=8.4 Hz, 1), 4.72 (d, J=8.4 Hz, 1), 3.79-3.70(m, 2), 3.56 (t, J=4.2 Hz, 2), 3.39 (s, 3), 3.18 (dd, J=4.2, 11.2 Hz, 1), 3.10-3.05 (m, 2), 2.15-1.25 (m, 9), 1.67 (s, 3), 1.01 (s, 3), 0.86 (s, 3)

Spectral data of **93**: ^{1}H NMR (250 MHz, D_6-acetone): δ= 5.69 (t, J=1.2 Hz, 1), 4.80 (d, J=6.8 Hz, 1), 4.69 (d, J=6.8 Hz, 1), 4.48 (bds, 1), 3.72-3.66 (m, 2), 3.50 (t, J=4.2 Hz, 2), 3.30 (s, 3), 3.22 (dd, J=4.2, 10.4 Hz, 1), 2.92-2.77 (m, 1), 2.49-2.30 (m, 1), 2.10-1.83 (m, 2), 1.68-1.22 (m, 5), 1.08 (s, 3), 0.85 (s, 3), 0.70 (s, 3)

4,5,5a,6,7,8,9,9a-Octahydro-7-methoxyethoxymethoxyl-2,6,6,9a-tetramethyl-(5aα,7β,9aβ)-(±)-naphtho[1,2-b]furan 94

According to the general procedure for preparation of **98**, **89** (0.38 g, 1.18 mmole, in 15 ml DMF) was brominated by NBS (0.256 g, 1.3 mmole, in 3 ml DMF). The crude bromide **90** was submitted to lithium-halogen exchange by nBuLi (2.5 M in hexane, 0.57 ml, 1.43 mmole, -78°C) and quenched with MeI (0.1 ml, 1.61 mmole) to afford **94** in 55% overall yield from **89** with 0.053 g, 14%, of recovered starting material, **89**, after purification by chromatography on silica gel. TLC

(Merck, UV-vanillin, ether:hexane 1:1) R_f=0.4.

<u>^{1}H NMR</u> (60 MHz, CCl_4): δ= 5.52 (s, 1), 4.75 (d, J= 7.0 Hz, 1), 4.55 (d, J= 7.0 Hz, 1), 3.73-3.38 (m, 4), 3.30 (s, 3), 2.53-2.10 (m, 3), 2.17 (s, 3), 2.00-1.26 (m, 6), 1.17 (s, 3), 1.00 (s, 3), 0.83 (s, 3)

Octahydro-6-(methoxyethoxymethoxy)-5,5,8a-trimethyl-(2-oxopropylene)-(4aβ,6β,8aα)-1-naphthalenone 95

According to the general procedure for preparation of 99, a mixture of **94** (0.22 g, 0.65 mmole) and **89** (0.053 g, 0.16 mmole) was treated with m-chloroperoxybenzoic acid (0.135 g, 85%, 0.65 mmole) to provide desired **95**, 0.219 g, in 95% yield and recovered the unreacted **89**, 0.05 g, after purification by chromatography on silica gel, TLC (Merck, UV-vanillin, ether:hexane 5:1) R_f=0.21 for **95**.

<u>^{1}H NMR</u> (250 MHz, $CDCl_3$): δ= 5.83 (d, J=1.9 Hz, 1), 4.74 (d, J=8.4 Hz, 1), 4.62 (d, J=8.4 Hz, 1), 3.69-3.62 (m, 2), 3.48 (t, J=4.2 Hz, 2), 3.30 (s, 3), 3.05 (dd, J=4.2, 12.5 Hz, 1), 2.60-2.20 (m, 2), 2.09 (s, 3), 1.88-1.45 (m, 7), 1.15 (s, 3), 0.94 (s, 3), 0.84 (s, 3)

<u>EI-MS</u>: (70 eV) 352 (M^+, 0.8), 246 (5.6), 136 (16.5), 121 (5.6), 89 (78.1), 59 (base)

<u>IR</u>: (Neat) 2940, 2880, 1700, 1630, 1455, 1365, 1050, 930, 730 cm^{-1}

Octahydro-6-(methoxyethoxymethoxy)-5,5,8a-trimethyl-(2-oxopropyl)-(2β,4aβ,6β,8aα)-1(2H)-naphthalenone 96

According to the general procedure for preparation of **18**, **95** (43 mg, 0.12 mmole , in 10 ml EtOAc) was hydrogenated to afford **96**, 43 mg, in 99% yield as a colorless viscous liquid after purification by chromatography on silica gel, TLC (Merck, UV-vanillin, ether:hexane 5:1) R_f=0.26.

^{1}<u>H NMR</u> (250 MHz, $CDCl_3$): δ= 4.79 (d, J=6.5 Hz, 1), 4.66 (d, J=6.5 Hz, 1), 3.71-3.65 (m, 2), 3.52-3.48 (m, 2), 3.33 (s, 3), 3.09 (dd, J=4.2, 11.2 Hz, 1), 2.81 (dd, J=6.5, 16.4 Hz, 1), 2.15 (s, 3), 2.23-1.98 (m, 5), 1.93-1.42 (m, 6), 1.03 (s, 3), 0.93 (s, 3), 0.85 (s, 3)

8-Bromo-4a,4b,5,6,9b,10,11,11a-octahydro-2,2,4a,9b-tetramethyl-(4aα,4bβ,9aα,11aα)-4H-furo[2',3':5,6] naphtho[2,1-d]-1,3-dioxin (±)-97

To a solution of acetonide (±)-**86** (80 mg, 0.28 mmole) in dry DMF (10 ml) was added a solution of NBS (60 mg, 0.3 mmole) in dry DMF (4 ml) over 10 minutes at 0°C. Stirring was continued for 20 minutes at 0°C and then 50 minutes at room temperature. The resulting pale yellow solution was diluted with water (100 ml), and then cast into ether (50 ml) and pentane (50 ml). The organic phase was separated; washed with water (100 ml), brine (100 ml); dried ($MgSO_4$); and concentrated <u>in vacuo</u> to provide 90 mg, 88%, of crude bromide as a pale yellow solid which was readily transformed into the methylated adduct without further purification. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 35 g, 9:1 hexane:ether), TLC (Merck, UV-vanillin, ether:hexane 1:9) R_f=0.21, with some decomposition to provide 40 mg, 40%, of pure bromide (±)-97 as a white solid for spectral data.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 6.04 (s, 1), 3.74 (m, 1), 3.70 (d, J=12.8 Hz, 1), 3.34 (d, J=12.8 Hz, 1), 2.49-2.34 (m, 2), 1.98-1.48 (m, 7H), 1.42 (s, 3), 1.36 (s, 3), 1.22 (s, 3), 0.79 (s, 3)

EI-MS (70 eV): 370, 368 (M^+, 2.0), 297, 295 (11.3, 11.4), 205 (17.9), 149 (99.7), 91 (28.2), 43 (base)

4a,4b,5,6,9b,10,11,11a-Octahydro-2,2,4a,8,9b-pentamethyl-(4aα,4bβ,9aα,11aα)-4H-furo[2',3':5,6]naphtho[2,1-d]-1,3-dioxin (±)-98

To a solution of crude bromide (±)-97 (90 mg, 0.24 mmole) in dry ether (10 ml) cooled in a dry ice-acetone bath was added n-BuLi (2.5 M in hexane, 0.1 ml, 0.25 mmole) via syringe and stirred for 30 minutes at -78°C. To the resulting bright yellow solution was added methyl iodide (0.02 ml, 0.32 mmole). The mixture was allowed to slowly warm to room temperature over 1 hour and then stirred for 4 hours at room temperature. Then, this reaction mixture was diluted with water (50 ml) and ether (50 ml). The organic phase was separated; washed by brine (50 ml); dried (Na_2SO_4) and concentrated in vacuo to give a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 20 g, 20:1 hexane:ether) using flash technique. Fractions 20 to 24 afforded , TLC (Merck, UV-vanillin, ether:hexane 1:9) R_f=0.26, 57 mg, 68%, of methylated product (±)-**98** and 6 mg, 8%, of starting acetonide (±)-**86** as a mixture. This mixture can be readily separated at next step.

^{1}<u>H NMR</u> (250 MHz, $CDCl_3$): δ= 5.70 (s, 1), 3.72 (t, J=3.0 Hz, 1), 3.70 (d, J=12.3 Hz, 1), 3.32 (d, J=12.3 Hz, 1), 2.50-2.35 (m, 2), 1.97-1.42 (m, 7), 2.21 (s, 3), 1.40 (s, 3), 1.33 (s, 3), 1.18 (s, 3), 0.77 (s, 3)

<u>EI-MS</u>: (70 eV) 304 (M^+, 5.0), 289 (3.8), 231 (30.4), 43 (base).

Decahydro-3,3,6a,10b-tetramethyl-8-(2-oxopropylene)-(4aα,6aα, 8β,10β,10bα)-6H-naphtho[2,1-d][1,3]dioxin-7-one (±)-**99**

To a solution of the mixture (114 mg, 0.38 mmole, of methylated acetonide (±)-**98** and 12 mg, 0.04 mmole, of acetonide (±)-**86**) in dry methylene chloride (6 ml) chilled in an ice-water bath was added m-chloroperoxy benzoic acid (76 mg, 85%, 0.38 mmole) in one portion. Stirring was continued for 1 hour at 0°C and then 7 hours at room temperature. The reaction mixture was then diluted with ether (60 ml), aqueous $NaHCO_3$ (60 ml), water (50 ml), brine (50 ml), dried (Na_2SO_4) and concentrated <u>in vacuo</u> to give a yellow solid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 30 g, 1:1 hexane:ether) using flash technique. Fractions 13 to 14 afforded , TLC (Merck, UV-vanillin, ether:hexane 5:1) R_f=0.2, 116 mg, 97%, of (±)-**99** as a white solid and recoverd 12 mg of starting acetonide (±)-

86.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 5.99 (d, J=1.9 Hz, 1), 3.67 (t, J=2.9 Hz, 1), 3.60 (d, J=12.4 Hz, 1), 3.31 (d, J=12.4 Hz, 1), 2.65-2.15 (m, 3), 1.91-1.56 (m, 6), 2.18 (s, 3), 1.39 (s, 3), 1.35 (s, 3), 1.23 (s, 3), 0.80 (s, 3)

EI-MS (70 eV): 320 (M^+, 0.3), 204 (30.0), 149 (base), 134 (54.2)

IR (Neat): 2940, 2850, 1690, 1625, 1455, 1385, 1195, 1095, 1000, 915, 855, 730 cm^{-1}

(-)-**99**

According to the procedure outlined for bromination of (±)-**86**, (+)-**86** (150 mg, 0.52 mmole) was brominated with NBS (112 mg, 0.57 mmole) in 3 ml of DMF to give crude chiral bromide which was utilized without further purification. The chiral bromide **97** was metallated by n-BuLi (0.3 ml, 2.43 M in hexane, 0.73 mmole) and quenched with MeI (0.13 ml, 1.5 mmole) in 20 ml of dry ether at -78°C to provide 102 mg, 65%, of chiral **98** and 13.5 mg, 9%, of (+)-**86** as a mixture which was oxidized with MCPBA (70 mg, 85%, 0.34 mmole) in 30 ml of CH_2Cl_2 to give 104 mg, 97%, of (-)-**99**.

$[\alpha]_D$= -95.08 (c: 0.061, MeOH)

Decahydro-3,3,6a,10b-tetramethyl-8-(2-oxopropyl)-(4aα,6aα, 8β,10β,10bα)-7H-naphtho[2,1-d][1,3]dioxin-7-one (±)-18

A solution of conjugated dione (±)-**99** (50 mg, 0.16 mmole) and Pd-C (10%, 0.01 g) in ethyl acetate (20 ml) was hydrogenated under H_2 (1 atm) for 7 hours at room temperature. The catalyst was then filtered off and rinsed with ether (10 ml). The solution was concentrated _in vacuo_ and MeOH (20 ml) was added followed by K_2CO_3 (0.5 g). The resulting suspension was stirred for 5 hours at room temperature. The solution was filtered through a pad of silica gel and concentrated to give a pale yellow solid. The crude product was purified by a column of silica gel (230-400 mesh, 10 g, 4:1 hexane:ether), TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.13, to provide 50 mg, 99%, of (±)-**18** as a white solid. m.p.=104-105°C.

<u>^{1}H NMR</u> (250 MHz, $CDCl_3$): δ= 3.63 (t, J=2.7 Hz, 1), 3.58 (d, J=12.5 Hz, 1),3.26 (d, J=12.5 Hz, 1), 2.93 (dd, J=8.4, 17.5 Hz, 1), 2.23-1.94 (m, 5), 2.18 (s, 3), 1.37 (s, 3), 1.32 (s, 3), 1.88-1.52 (m, 6), 1.19 (s, 3), 0.79 (s, 3)

<u>^{13}C NMR</u> (250 MHz, $CDCl_3$): δ= 214.36, 207.74, 98.22, 72.65, 67,96, 47.92, 43.49, 41.73, 41.41, 35.88, 32.84, 30.57, 29.39, 26.04, 23.25, 20.23, 18.93 (2), 17.54

<u>EI-MS</u>: (70 eV) 323 (M^++1), 307 (8.2), 171 (9.3), 158 (5.3), 119 (6.0), 107 (8.1), 105 (6.1), 93 (10.0), 86 (19.8), 84 (33.8), 43 (base) <u>IR</u>: (neat) 2930, 2870, 1705, 1455, 1375, 1255, 1235, 1195, 1160, 1090, 1000, 855 cm^{-1}.

(-)-**18**

According to the procedure for the hydrogenation of (±)-**99**, (-)-**99** (30 mg, 0.1 mmole) was hydrogenated (1 atm. H_2, Pd-C) in 10 ml of ethylacetate to provide 29 mg, 96%, of (-)-

18.

$[\alpha]_D$= -44.0 (c: 0.025; MeOH).

6,7-Epoxy-8-benzyloxygeranyl alcohol 101

To a solution of **100** (4.3 g, 18.9 mmole) and benzyl bromide (3.87 g, 22.6 mmole) in dry THF (100 ml) chilled in an ice-water bath was added NaH (1 g, 20.8 mmole, 50% in oil, washed with dry hexane twice) in one portion. The resulting suspension was stirred at 0°C for 1 hour and room temperature for 2 hours, then quenched with saturated aqueous NH_4Cl (100 ml) and cast into ether (200 ml). The organic phase was separated; washed with water (100 ml), brine (100 ml); dried (Na_2SO_4); and concentrated in vacuo to afford yellow liquid. The crude mixture was separated by chromatography on a column of silica gel (230-400 mesh, 30 g, 1:1 hexane:ether) to provide a mixture of **101** 1.405 g, 21%, TLC (Merck, UV-vanillin, ether:hexane 3:1) R_f=0.18.

^{1}H NMR of **101** (60 MHz, $CDCl_3$): δ= 7.30 (s, 5), 5.42 (t, J=7.0 Hz, 1), 4.53 (s, 2), 4.10 (d, J=7.0 Hz, 2), 3.43 (s, 2), 2.83 (t, J=6.0 Hz, 1), 2.45-2.00 (m, 2), 1.88-1.66 (m, 3), 1.66 (s, 3), 1.33 (s, 3)

8-Hydroxygeranyl-benzoate 102

To selenium dioxide (0.30 g, 2.7 mmole) and salicylic acid (1.88 g, 13.6 mmole) in dry methylene chloride (50 ml), chilled in an ice-water bath under argon was added t-butyl hydroperoxide (90%, 54.6 ml, 0.49 mole) in one portion. To this mixture was added a solution of geranyl benzoate (32.85 g, 0.13 mole) in methylene chloride (50 ml) over 30 minutes. The resulting colorless solution was stirred for 24 hours at room temperature, then was diluted with benzene (70 ml) and concentrated _in_ _vacuo_. Ether (150 ml) was added to the residue; the organic phase was separated; washed with 10% KOH (4x50 ml) and concentrated _in_ _vacuo_ to provide a yellow liquid. The reaction mixture was dissoved in cold (ice-water) acetic acid (30 ml) and dimethyl sulfide (33 ml) was added slowly at 0°C and the resulting solution was stirred for 5 hours at room temperature. The solution was then chilled in an ice-water bath and neutralized with 20% aqueous K_2CO_3 and was then cast into ether (300 ml). The combined organic phase was washed with water (300 ml), brine (300 ml); dried (Na_2SO_4); and concentrated _in_ _vacuo_ to provide a yellow liquid. The crude product was dissoved in EtOH (100 ml), cooled in an ice-water bath and $NaBH_4$ (5 g, 0.13 mole) was added slowly. Stirring was continued for 10 minutes and reaction was quenched by carefully addition of 1N aqueous HCl (250 ml).The mixture was cast into water (300 ml), extracted with Et_2O (3x250 ml), and the combined organic extracts were washed with brine (800 ml), dried (Na_2SO_4) and concentrated _in_ _vacuo_ to give a colorless liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 120 g, 50mm o.d., 4:1 hexane:ether) using flash technique. Fractions 13 to 16 afforded 3.74 g, 11%, of starting material, TLC (Merck, UV-vanillin, ether:hexane 1:1)

R_f=0.67 and fractions 18 to 29 afforded 22.34 g, 64% (71% based on the recovery of starting material) of 8-hydroxy geranyl benzoate **102**, R_f=0.2, as a colorless liquid.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 8.05-8.00 (m, 2), 7.58-7.36 (m, 3), 5.45 (t, J=6.5 Hz, 1), 5.38 (t, J=6.5 Hz, 1), 4.82 (d, J=6.5 Hz, 2), 3.95 (s, 2), 3.95 (s, 2), 2.22-2.04 (m, 5), 1.75 (s, 3), 1.64 (s, 3).

CI-MS (7 eV): 275 (M^++1, 6.7), 274 (M^+, 0.5), 257 (35.5), 153 (32.8), 135 (base), 107 (17.7)

IR (Neat): 3430 (br.), 3030, 2930, 1715, 1600, 1585, 1450, 1385, 1315, 1275, 1105, 1070, 1025, 715 cm^{-1}

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.4; H, 8.08. Found: C, 74.41; H, 8.27.

(±)-6,7-Epoxy-8-hydroxygeranyl benzoate (±)-103

To a solution of 8-hydroxy geranyl benzoate **102** (9.65 g, 35.19 mmole) in dry methylene chloride (130 ml) chilled in an ice-water bath was added a solution of m-chloroperoxybenzoic acid (7.5 g, 85% purity, 36.95 mmole) in methylene chloride (110 ml) over a period of 1 hour. Stirring was continued for another 0.5 hour at 0°C and then 2 hours at room temperature. The reaction mixture was then cast into ether (300 ml) and saturated aqueous $NaHCO_3$ (300 ml). The organic phase was separated; washed with aqueous $NaHCO_3$ (300 ml), water (300 ml), brine (300 ml); dried ($MgSO_4$); and concentrated in vacuo to give 10.2 g, 100% crude yield, of 6,7-Epoxy-8-hydroxygeranyl benzoate **103** as a colorless liquid which was utilized without further purification.

<u>^{1}H NMR</u> (250 MHz, $CDCl_3$): δ= 8.05-7.97 (m, 2), 7.54-7.36 (m, 3), 5.48 (t, J=7.3 Hz, 1), 4.81 (d, J=7.3 Hz, 2), 3.65-3.52 (m, 2), 2.99 (t, J=6.4 Hz, 1), 2.28-2.10 (m, 2), 1.75 (s, 3), 1.76-1.62 (m, 3), 1.25 (s, 3)

<u>CI-MS</u>: (7 eV) 291 (M^{+1}, 0.4), 205 (11.9), 169 (46.5), 151 (48.1), 111 (base)

<u>IR</u> (neat): 3440 (br.), 3030, 2930, 1715, 1450, 1385, 1315, 1275, 1105, 1070, 1025, 715 cm^{-1}

(-)-6,7-Epoxy-8-hydroxygeranyl benzoate (-)-103

To a solution of L-diisopropyltartrate (5.87 g, 25 mmole) in dry methylene chloride (230 ml) cooled in a dry ice-CCl_4 bath was added $Ti(OiPr)_4$ (7.82 ml, 26.3 mmole). The solution was allowed to stir for 5 minutes then 6.87 g (25 mmole) of 8-hydroxygeranyl benzoate in 40 ml of CH_2Cl_2 was added over a period of 30 minutes followed immediately by the addition of TBHP (3.5 M in toluene, 14.5 ml, 50 mmole). The resulting yellow solution was stirred for 2 hours at -23°C and then was stored in a freezer overnight. To the chilled (dry ice-CCl_4) reaction mixture was added 4.5 ml of Me_2S and the solution was stirred for 40 minutes at -20°C; then the cold reaction mixture was added slowly to a vigorously stirred saturated aqueous NaF solution (550 ml) at room temperature. The solution was stirred for 10 minutes; the aqueous layer was saturated with NaCl; and the gel-like precititated inorganic fluorides were removed by filtration through a pad of celite.

The organic phase were separated; the aqueous layer was extracted with CH_2Cl_2 (3x200 ml) and the combined organic extracts were washed with water, brine (600 ml each); and dried (Na_2SO_4). The crude product was purified by chromatography on a column of silica gel (60-240 mesh, 200 g, 1:1 hexane:ethyl acetate) using flash technique. Fractions 30 to 45 afforded 5.16 g, 71%, of (-)-**103** as a viscous colorless liquid.

$[\alpha]_D$= -5.769 (c: 0.364, CH_2Cl_2)

(±)-6,7-Epoxy-8-benzyloxygeranyl benzoate (±)-104

To a solution of crude (±)-6,7-epoxy-8-hydroxygeranyl benzoate **103** (10.2 g, 35.19 mmole) in dry THF (200 ml) was added NaH (1.86 g, 38.66 mmole, 50% in oil, washed with dry hexane (2X)) in one portion. The mixture was stirred for 20 minutes at room temperature under argon. To the resulting dark brown solution was added benzyl bromide (4.6 ml, 38.66 mmole) in one portion, followed immediately by tetrabutyl ammonium iodide (5.19 g, 14.05 mmole); the resulting mixture was allowed to stir for 5 hours at room temperature. Solvent was removed in vacuo and the reaction was quenched by carefully addition of saturated aqueous NH_4Cl (300 ml). The solution was cast into ether (200 ml); the organic phase was separated and the aqueous layer was extracted with ether (2X300 ml). The combined organic extracts were washed with water, brine (500 ml each); and dried (Na_2SO_4); and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 120 g, 50 mm o.d., 9:1 hexane:ethyl acetate) using flash technique. Fractions 20 to 38 afforded 11.89 g, 89%, of **104** as a pale yellow liquid, TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.41.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 8.01-7.93 (m, 2), 7.51-7.33 (m, 3), 7.31-7.22 (m, 5), 5.50 (t, J=8.0 Hz, 1), 4.82 (d, J=8.0 Hz, 2), 4.54 (d, J=12.2 Hz, 1), 4.48 (d, J=12.2 Hz, 1), 3.51 (d, J=10.3 Hz, 1), 3.44 (d, J=10.3 Hz, 1), 2.88 (t, J=6.2 Hz, 1), 2.35-2.17 (m, 2), 1.88 (s, 3), 1.88-1.66 (m, 2), 1.36 (s, 3)

Chiral 104

According to the procedure of preparation of (±)-**104**, (-)-**103** (4 g, 13.8 mmole) was benzylated by benzylbromide (1.8 ml, 15.1 mmole), NaH (0.7 g, 14.5 mmole, 50% in oil) and Bu_4NF (2 g, 5.4 mmole) in 200 ml of THF to provide 4.61 g, 88%, of chiral **104**.

(±)-6,7-Epoxy-8-benzyloxygeranyl alcohol (±)-105

A mixture of **104** (7.51 g, 19.76 mmole), sodium methoxide (32 g, 0.59 mole) and tetrabutyl ammonium iodide (8.76 g, 23.71 mmole) in MeOH (475 ml) was stirred for 12 hours at room temperature. Then, MeOH was removed in vacuo and water (80 ml) was added. The solution was extracted with ether (2x200 ml), water (400 ml); dried (Na_2SO_4); and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 100 g, 1:1 hexane:ether) using flash technique. Fractions 16 to 32 afforded 5.4 g, 99%. of **105** as a pale colorless liquid. TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.09.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 7.34-7.20 (m, 5), 5.42 (t, J=8.0 Hz, 1), 4.55 (d, J=12.1 Hz, 1), 4.49 (d, J=12.1 Hz, 2), 4.13 (d, J=8.0 Hz, 2), 3.47 (s, 2), 2.87 (t, J=6.5 Hz, 1), 2.27-2.16 (m, 2), 1.79-1.67 (m, 3), 1.72 (s, 3), 1.35 (s, 3)

CI-MS (7 eV): 277 (M^++1, 1.2), 259 (31.0), 151 (19.0), 111 (base), 91 (72.2)

IR (Neat): 3420 (br.), 3030, 2920, 2860, 1670, 1450, 1380, 1195, 1000, 740, 700 cm^{-1}

(-)-6,7-Epoxy-8-benzyloxygeranyl alcohol (-)-105

According to the procedure of preparation of (±)-**105**, the chiral **104** (2.45 g, 6.4 mmole) was treated with MeONa (10.5 g, 0.19 mole) and Bu_4NF (2.9 g, 7.8 mmole) in 120 ml of MeOH to provide 1.76 g, 99% of (-)-**105**.

$[\alpha]_D$= -6.132 (c: 0.424, MeOH)

M^+-OH cald. for $C_{17}H_{23}O_2$ 259.1698, M^+-OH found 259.1694

(±)-6,7-Epoxy-8-benzyloxygeranyl chloride (±)-106

To a solution of (±)-**105** (2.1 g, 7.61 mmole) in dry ether (18 ml) and HMPA (6 ml) chilled in an ice-water bath was added n-BuLi (2.4 M in hexane, 3.2 ml, 7.61 mmole) over 10 minutes. The resulting mixture was stirred for 10 minutes at

0°C; then p-toluenesulfonyl chloride (1.45 g, 7.61 mmole) in dry ether (5 ml) was added in one portion followed by anhydrous lithium chloride (0.64 g, 15.2 mmole). The resulting mixture was allowed to stirr for 1 hour at 0°C and 2 hours at room temperature; then was cast into saturated aqueous $NaHCO_3$ (200 ml) and ether (300 ml). The organic phase was washed with water (2x200 ml), brine (200 ml); dried (Na_2SO_4); and concentrated *in vacuo* to give a yellow liquid. The crude product was purified by chromatography on a column of silica gel (60-230 mesh, 50 g, 1:1 hexane:ether), TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.73, to provide 1.9 g, 85%, of **106** as a colorless liquid.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 7.42-7.24 (m, 5), 5.47 (t, J=6.7 Hz, 1), 4.56 (d, J=12.2 Hz, 1), 4.50 (d, J=12.2 Hz, 1), 4.06 (d, J=7.9 Hz, 2), 3.50 (d, J=11.2 Hz, 1), 3.42 (d, J=11.2 Hz, 1), 2.83 (t, J=6.4 Hz, 1), 2.28-2.09 (m, 2), 1.72 (s, 3), 1.73-1.61 (m, 2), 1.31 (s, 3)

CI-MS (7 eV): 295 (M^+, 0.7), 169 (11.4), 151 (17.9), 111 (base), 91 (65.2)

IR (Neat): 3020, 2920, 1665, 1455, 1385, 1255, 1095, 740, 700 cm^{-1}

(+)-6,7-Epoxy-8-benzyloxygeranyl chloride (+)-106

According to the procedure for chlorination of (±)-**105**, (-)-**105** (1.22 g, 4.4 mmole) was treated with nBuLi (2 ml, 2.43 M in hexane, 4.86 mmole) and HMPA (3.5 ml) in 60 ml of ether; followed by p-TsCl (1 g, 5.2 mmole) and LiCl (0.37 g, 8.8 mmole) to give 1.11 g, 85%, of (+)-106.

$[\alpha]_D = +2.179$ (c: 0.78, CH_2Cl_2)

(±)-1-(3-Furyl)-7,8-epoxy-9-benzyloxy non-3-ene (±)-107

In the usual procedure[22], 3-chloromethylfuran (0.83 g, 7.1 mmole) in 10 ml of THF was converted to the corresponding Grignard reagent and coupled with (±)-6,7-epoxy-8-benzyloxygeranyl chloride **106** (1.9 g, 6.5 mmole). Purification by chromatgraphy on a column of silica gel (240-400 mesh, 100 g, 9:1 hexane:ether) using flash technique afforded 1.73 g, 79%, of (±)-**107** as a colorless viscous liquid, TLC (Merck, UV-vanillin, ether:hexane 1:4) R_f=0.34.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 7.41-7.24 (m, 6), 7.18 (m, 1), 6.25 (m, 1), 5.19 (t, J=7.5 Hz, 1), 4.57 (d, J=12.1 Hz, 1), 4.51 (d, J=12.1 Hz, 1), 3.48 (d, J=11.0 Hz, 1), 3.40 (d, J=11.0 Hz, 1), 2.82 (t, J=6.4 Hz, 1), 2.47-2.38 (m, 2), 2.29-2.04 (m, 4), 1.69-1.56 (m, 2), 1.59 (s, 3), 1.32 (s, 3)

EI-MS (70 eV): 340 (M^+, 0.3), 173 (15.0), 91 (base), 81 (30.0)

IR (Neat): 3020, 2920, 1500, 1450, 1380, 1105, 1025, 875, 735, 700 cm^{-1}

(-)-1-(3-Furyl)-7,8-epoxy-9-benzyloxy non-3-ene (-)-107

According to the procedure for the preparation of (±)-107, (+)-**106** (0.42 g, 1.43 mmole) was coupled with 3-furfurylMgCl (0.2 g, 1.7 mmole, of furfurylchloride and 0.08 g of Mg) and Li_2CuCl_4 in 20 ml of THF to give 0.364 g, 75%, of (-)-**107**.

$[\alpha]_D$= -2.168 (c: 0.764, CH_2Cl_2)

M^+ cald. for $C_{22}H_{28}O_3$ 340.20386, M^+ found 340.2033

6-Benzyloxymethylene-4,5,5a,6,7,8,9,9a-octahydro-6,9a-dimethyl-(5aα,6α,7β,9aβ)-(±)-naphtho[1,2-b]furan-7-ol (±)-108

To a solution of (±)-**107** (0.11 g, 0.32 mmole) in dry methylene chloride (3 ml), benzene (3 ml) and hexane (3 ml) was added triethylamine (0.14 ml, 1 mmole). The solution was cooled in a dry ice-acetone bath and a solution of boron trifluoride etherate (0.24 ml, 1.95 mmole) in methylene chloride (7 ml) was added very slowly over a period of 2 hours. The resulting yellow solution was stirred for 45 minutes at -78°C. The reaction mixture was cast into ether (150 ml) and aqueous $NaHCO_3$ (100 ml). The organic phase was separated; washed with 0.1 N HCl (100 ml), brine (100 ml); dried (Na_2SO_4); and concentrated <u>in vacuo</u>. The crude product was purified by chromatography on a column of silica gel (240-400 mesh, 50 g, 4:1 hexane:ether) using the flash technique. Fractions 13 to 16 afforded 5.5 mg, 5%, TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.45, of uncyclized ketone **109** and 79 mg, 72%, of cyclized product (±)-**108** as a white solid, R_f=0.22. m.p.=92-93°C.

<u>^{1}H NMR</u> (250 MHz, $CDCl_3$): δ= 7.26 (m, 5), 7.14 (d, J=2.0 Hz, 1), 6.08 (d, J=2.0 Hz, 1), 4.52 (s, 2), 3.74 (dd, J=5.0, 10.0 Hz, 1), 3.61 (d, J=8.8 Hz, 1), 3.30 (d, J=8.8 Hz, 1), 2.55-

2.13 (m, 2), 1.90-1.49 (m, 8), 1.27 (s, 3), 1.06 (s, 3).

<u>EI-MS</u> (70 eV): 340 (M^+, 18.0), 201 (21.1), 173 (24.9), 159 (22.7), 91 (base)

<u>IR</u> (Neat): 3440 (br.), 3030, 2930, 1505, 1455, 1375, 1075, 1025, 735, 695 cm^{-1}

(+)-108

According to the procedure for the preparation of (±)-**108**, (-)-**107** (0.26 g, 0.76 mmole) was cyclized with BF_3-OEt_2 (0.57 ml, 4.56 mmole, in 17 ml CH_2Cl_2) and Et_3N (0.32 ml, 2.28 mmole) in hexane, benzene, CH_2Cl_2 (7 ml each) to afford 0.36 g, 72%, of (+)-**108**. p.m.=84-85°C.

$[\alpha]_D$= +46.813 (c: 0.455, MeOH)

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.28. Found: C, 77.51; H, 8.31.

Benzyloxymethylene-4,5,5a,6,9,9a-hexahydro-6-6,9a-dimethyl-(5aα,6α,9aβ)-(±)-naphtho[1,2-b]furan-7(8H)-one (±)-111

To a solution of oxalyl chloride (51 ul, 0.58 mmole) in dry THF (2 ml) cooled in a dry ice-acetone bath was added DMSO (43 ul, 0.6 mmole). The solution was warmed to -35°C for 3 minutes. The resulting greenish yellow solution was cooled in a dry ice-acetone bath and then a solution of β-OH benzylether **108** (0.19 g, 0.56 mmole) in THF (2 ml) was added over 5 minutes. The solution was warmed to -35°C for 15 minutes, cooled back to -50°C and triethylamine (0.4 ml) was added. The resulting cloudy solution was warmed to room temperature and stirred for 1 hour. The reaction mixture was diluted with ether (50 ml) and water (30 ml). Aqueous layer was furthered extracted with ether (2x50 ml). The combined organic extracts were washed with 0.1 N HCl (50 ml), brine (50 ml); and dried (Na_2SO_4). Removal of solvent followed by chromatography on a column of silica gel (240-400 mesh, 30 g, 4:1 hexane:ether) using the flash technique afforded 0.183 g, 97%, of keto benzylether (±)-**111** as a white solid, TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.5.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 7.34-7.19 (m, 6), 6.14 (d, J=1.7 Hz, 1), 4.50 (d, J=12.4 Hz, 1), 4.36 (d, J=12.4 Hz, 1), 3.48 (d, J=8.4 Hz, 1), 3.29 (d, J=8.4 Hz, 1), 2.68-2.22 (m, 6), 2.03-1.89 (m, 1), 1.66-1.53 (m, 2), 1.19 (s, 3), 0.98 (s, 3)

EI-MS (70 eV): 338(M^+, 4.0), 232 (8.6), 217 (10.5), 149 (8.9), 105 (8.5), 91 (base)

IR (Neat): 3030, 2950, 2850, 1700, 1500, 1450, 1375, 1230, 1105, 1030, 735, 700 cm^{-1}

(+)-**111**

According to the procedure of preparation of (±)-**111**, (+)-**108** (70 mg, 20.6 mmole) was oxidized with oxalyl chloride (0.05 ml), DMSO (0.05 ml) and Et_3N (0.4 ml) in 5 ml of THF to provide 66 mg, 95%, of (+)-**111**.

$[\alpha]_D$= +75.2 (c: 0.125, MeOH)

General Procedure for the Reduction by L-selectride and Salt:

Preparation of benzyloxymethylene-4,5,5a,6,7,8,9,9a-octahydro-6-6,9a-dimethyl-(5aα,6α,7α,9aβ)-(±)-naphtho[1,2-b] furan-7-ol (±)-113

To a solution of keto benzyl ether (±)-111 (100 mg, 0.3 mmole) in dry methylene chloride (25 ml) chilled to -10°C (ice-salt) was added $MgBr_2$-Et_2O (153 mg, 0.6 mmole) in one portion and stirred for 1 minute at -10°C. The result suspension was then cooled in a dry ice-acetone bath and added L-selectride (1 M in THF, 0.9 ml, 0.9 mmole) over a period of 5 minutes. The reaction mixture was stirred for 0.5 hour at -78°C and warmed to room temperature slowly over 1 hour. Stirring was continued at room temperature for 20 minutes. The reaction was quenched by carefully adding methanol (4 ml), followed by 20% aqueous NaOH (6 ml) and 30% aqueous H_2O_2 (12 ml). The solution was stirred at room temperature for 1.5 hours and then diluted with ether (100 ml), washed with water (100 ml), saturated aqueous NH_4Cl (100 ml) and saturated aqueous $NaHCO_3$ (100 ml). The organic phase was dried (Na_2SO_4) and removal of solvent _in vacuo_ followed with purification by chromatography on a column of silica gel (240-400 mesh, 50 g, 9:1 hexane:ether) using flash technique. Fractions 30 to 48 afforded 85 mg, 85%, of desired α-OH benzyl ether (±)-113, TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.31 and fractions 52 to 56 afforded 10 mg, 10%, of β-OH benzyl ether (±)-108 which was resubmitted to Swern oxidation, R_f=0.22.

^{1}<u>H NMR</u> (250 MHz, $CDCl_3$): δ= 7.25 (m, 5), 7.14 (d, J=2.0 Hz, 1), 6.07 (d, J=2.0 Hz, 1), 4.57 (d, J=12.7 Hz, 1), 4.41 (d, J=12.7 Hz, 1), 3.77 (m, 1), 3.54 (d, J=8.5 Hz, 1), 3.31 (d, J=8.5 Hz, 1), 2.49-2.29 (m, 2), 2.01-1.51 (m, 8), 1.25 (s, 3), 0.87 (s, 3)

EI-MS (70 eV): 340 (M^+, 1.4), 217 (17.0), 149 (36.3), 122 (13.8), 91 (base)

IR (Neat): 3480(br.), 3030, 2930, 1505, 1455, 1065, 730, 695 cm^{-1}

(+)-**113**

According to the procedure of preparation of (±)-**113**, (+)-**111** (530 mg, 1.57 mmole) was reduced with L-selectride (6.4 ml, 1 M in THF, 6.4 mmole) and $MgBr_2$-OEt_2 (810 mg, 3.13 mmole) in 130 ml of CH_2Cl_2 to give 496 mg, 93%, of a mixture of (+)-**108** and (+)-**113** (8.5:1).

$[\alpha]_D$=+53.64 (c: 0.11, MeOH)

4,5,5a,6,7,8,9,9a-Octahydro-6-hydroxymethylene-6,9a-dimethyl-(5aα,6α,7β,9aβ)-(±)-naphtho[1,2-b]furan-7-ol (±)-110

According to the general procedure outlined for the preparation of (±)-**85**, (±)-**108** was converted to (±)-**110** in 50% yield with 42% recovered starting material after purification by chromatography on silica gel.

^{1}H NMR of **110** (60 MHz, $CDCl_3$): δ= 7.12 (d, J=2.0 Hz, 1), 6.05 (d, J=2.0 Hz, 1), 3.90-3.20 (m, 3), 2.60-2.10 (m, 2), 2.00-1.40 (m, 9), 1.20 (s, 3), 0.95 (s, 3)

General Procedure for the Reductive Debenzylation: Preparation of 4,5,5a,6,7,8,9,9a-octahydro-6-hydroxy methylene-6,9a-dimethyl-(5aα,6α,7α,9aβ)-(±)-naphtho[1,2-b] furan-7-ol (±)-85

To a solution of lithium aluminum hydride (25 mg, 0.66 mmole) in dry THF (5 ml) was added a solution of benzyl ether (±)-113 (15 mg, 0.04 mmole) in THF (5 ml) over 10 minutes and stirred for 11 hours at room temperature. The reaction mixture was carefully quenched with 20% aqueous NaOH (30 ml) and cast into ether (50 ml). The organic phase was separated; washed with saturated aqueous NH_4Cl (50 ml), water (50 ml), brine (50 ml); dried (Na_2SO_4) and concentrated *in vacuo* to provide a yellow solid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 8 g, 1:2 hexane:ether), TLC (Merck, UV-vanillin, ether:hexane 5:1) R_f=0.18, to provide 10.4 mg, 94%, of (±)-85 as a white solid. m.p.=119-121°C.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 7.13 (d, J=2.0 Hz, 1), 6.09 (d, J=2.0 Hz, 1), 3.79 (t, J=3.0 Hz, 1), 3.59 (d, J=12.5 Hz, 1), 3.48 (d, J=12.5 Hz, 1), 2.54-2.27 (m, 2), 1.96-1.54 (m, 9), 1.26 (s, 3), 0.83 (s, 3).

EI-MS (70 eV): 250 (M^+, 31.6), 235 (21.47), 217 (base), 199 (19.3), 159 (22.3), 91 (36.4)

IR (neat): 3350, 2950, 1505, 1480, 1455, 1385, 1270, 1210, 1165, 1135, 1055, 1000, 890, 745 cm^{-1}

(+)-85

According to the procedure of preparation of (±)-**85**, (+)-**113** (400 mg, 1.18 mmole) was debenzylated by LAH (0.45 g) in 100 ml of THF to give 276 mg, 94%, of (+)-**85**. m.p.=138-140°C

$[\alpha]_D$= +43.75 (c: 0.16, MeOH).

4a,4b,5,6,9b,10,11,11a-Octahydro-2,2,4a,9b-tetramethyl-(4aα,4bβ,9bα,11aα)-4H-furo[2',3':5,6]naphtho[2,1-d]-1,3-dioxin (±)-86

To a solution of diol (±)-**85** (250 mg, 1.0 mmole) in dry methylene chloride (30 ml) and dry acetone (2 ml) was added oxalic acid (few crystals) and anhydrous $CaSO_4$ (1 g, 4.77 mmole). The mixture was stirred overnight at room temperature. The solution was diluted with ether (30 ml), washed with aqueous $NaHCO_3$ (2x30 ml) and dried (Na_2SO_4). Removal of solvent followed with purification by chromatography on a column of silica gel (60-230 mesh, 8 g, 8:1 hexane:ether) using flash technique. Fractions 6 to 9 afforded 270 mg, 93%, of acetonide (±)-**86** as a white solid, TLC (Merck, UV-vanillin, ether:hexane 1:9) R_f=0.27. m.p.=137-139°C.

<u>^{1}H NMR</u> (250 MHz, d_6-acetone): δ= 7.26 (d, J=2.0 Hz, 1), 6.15 (d, J=2.0 Hz, 1), 3.78 (t, J=3.0 Hz, 1), 3.70 (d, J=12.0 Hz, 1), 3.37 (d, J=12.0 Hz, 1), 2.55-2.30 (m, 2), 2.11-1.50 (m, 7), 1.43 (s, 3), 1.28 (s, 3), 1.21 (s, 3), 0.82 (s, 3).

<u>EI-MS</u> (70 eV): 290 (M^+, 41.5), 275 (25.8), 232 (4.5), 217

(base), 149 (47.6)

IR (KBr): 3010, 2970, 2890, 1505, 1480, 1380, 1205, 1165, 1095, 1010, 860, 765 cm^{-1}

(+)-**86**

According to the procedure of preparation of (±)-**86**, (+)-**85** (250 mg, 1 mmole) was treated with acetone (2 ml), oxalic acid (few crystals) and $CaSO_4$ (1 g) in 30 ml of CH_2Cl_2 to give 270 mg, 93%, of (+)-**86**.

$[\alpha]_D$= +22.60 (c: 0.77, CH_2Cl_2)

6,7-Epoxy-8-acetyloxygeranyl benzoate 114

To a solution of (-)-**103** (50 mg, 0.17 mmole) in a mixture of dry methylene chloride (20 ml) and pyridine (0.5 ml, 6.2 mmole) chilled in an ice-water bath was added a solution of acetic anhydride (20 mg, 0.19 mmole) in methylene chloride (15 ml) slowly. The mixture was stirred overnight at room temperature. The resulting solution was cast into water (40 ml) and ether (50 ml). The organic phase was separated; washed with 5% HCl (3x40 ml), aqueous $NaHCO_3$ (40 ml), water (40 ml), brine (40 ml); dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (60-240 mesh, 20 g, 4:1 hexane:ether) using flash technique. Fractions 6 to 8 afforded **114** ,53 mg, (93%). TLC (Merck, UV-vanillin, ether:hexane 5:1) R_f=0.55.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 7.98-7.92 (m, 2), 7.50-7.30 (m, 3), 5.48 (t, J=7.4 Hz, 1), 4.82 (d, J=8.5 Hz, 2), 4.13 (d, J=11.7 Hz, 1), 3.92 (d, J=11.7 Hz, 1), 2.89 (t, J=6.4 Hz, 1), 2.36-2.17 (m, 2), 2.10 (s, 3), 1.83-1.63 (m, 2), 1.82 (s, 3), 1.35 (s, 3).

MTPA ester 115

A solution of (-)-α-Methoxy-α-(trifluoromethyl)phenyl acetic acid (60 mg, 0.26 mmole) and $SOCl_2$ (20 ml) was refluxed for 45 hours. The excess $SOCl_2$ was removed in vacuo and diluted with dry methylene chloride (5 ml). To this crude MTPACl solution was added a solution of (-)-**103** (50 mg, 0.17 mmole) in methylene chloride (10 ml), followed by pyridine (5 ml) and DMAP (5 mg). The reaction mixture was refluxed for 1.5 hours and quenched with 1 N HCl (50 ml) and cast into ether (50 ml). The organic phase was separated; washed with saturated aqueous $NaHCO_3$ (50 ml), water (50 ml), brine (50 ml); dried ($MgSO_4$) and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 10 g, 4:1 hexane:ether) using flash technique. Fractions 9 to 11 afforded **115**, 18 mg, in 20% yield, TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.35 and 20 mg of starting material was recovered.

^{1}H NMR (250 MHz, $CDCl_3$): δ= 8.02-7.74 (m, 2), 7.56-7.35 (m, 3), 5.49 (t, J=7.4 Hz, 1), 4.84 (d, J=8.5 Hz, 2), 4.39 (d, J=11.7 Hz, 1), 4.25 (d, J=11.7 Hz, 1), 3.59 (q, J=1.4 Hz, 3), 2.93 (t, J=6.4 Hz, 1), 2.36-2.10 (m, 2), 1.87-1.47 (m, 2), 1.82 (s, 3), 1.36 (s, 3)

Monobromobenzoate 116

According to the general procedure outlined for the preparation of MTPA ester **115**, (+)-**110** was converted to **116** in 85% yield after purification by chromatography on silica gel, TLC (Merck, UV-vanillin, ether:hexane 1:1) R_f=0.55.

^{1}<u>H NMR</u> (250 MHz, $CDCl_3$): δ= 7.90-7.77 (m, 2), 7.67-7.44(m, 2), 7.13 (d, J=2.0 Hz, 1), 6.09 (d, J=2.0 Hz, 1), 4.40 (d, J=10.0 Hz, 1), 4.25 (d, J=10.0 Hz, 1), 3.81 (m, 1), 2.63-2.30 (m, 2), 2.10-1.53 (m, 8), 1.31 (s, 3), 1.13 (s, 3)

General Procedure for the Preparation of (S)-O-Methylmandelate ester: Preparation of **119**

A few crystals of DMAP was added all at once to a colorless solution of (+)-**108** (10 mg, 0.03 mmole), (S)-O-methylmandelic acid (5 mg, 0.03 mmole) and 1,3 dicyclohexyl carbodiimide (6 mg, 0.03 mmole) in 25 ml of methylene chloride. After 24 hours, the reaction mixture was diluted with ether (25 ml) and washed with 1 N aqueous HCl (20 ml), saturated aqueous $NaHCO_3$ (20 ml), brine (20 ml), dried ($MgSO_4$) and concentrated <u>in vacuo</u> to provide a viscous liquid. The crude product was purified by chromatography on a column of silica gel (230-400 mesh, 5 g, 4:1 hexane:ether) to afford 12 mg, 83% ($\geq$95% de), of **119**.

^{1}<u>H NMR</u> of **118** (250 MHz, $CDCl_3$): δ= 7.48-7.22 (m, 10), 7.16

(d, J=1.8 Hz, 1), 6.08 (d, J=1.8 Hz, 1), 5.09 (dd, J=5.0, 11.7 Hz, 1), 4.73 (s, 1), 4.10 (d, J=12.2 Hz, 1), 3.85 (d, J=12.2 Hz, 1), 3.41 (s, 3), 2.86 (d, J=9.8 Hz, 1), 2.39-2.30 (m, 2), 2.15 (d, J=9.8 Hz, 1), 2.10 (dt, J=3.2, 12.5 Hz, 1), 1.97-1.40 (m, 6), 1.21 (s, 3), 0.88 (s, 3)

^{1}H NMR of **119** (250 MHz, $CDCl_3$): δ= 7.48-7.26 (m, 10), 7.16 (d, J=1.8 Hz, 1), 6.08 (d, J=1.8 Hz, 1), 5.09 (dd, J=5.0, 11.7 Hz, 1), 4.73 (s, 1), 4.11 (d, J=12.2 Hz, 1), 3.85 (d, J=12.2 Hz, 1), 3.41 (s, 3), 2.86 (d, J=9.8 Hz, 1), 2.40-2.30 (m, 2), 2.16 (d, J=9.8 Hz, 1), 2.11 (dt, J=3.2, 12.5 Hz, 1), 2.01-1.39 (m, 6), 1.18 (s, 3), 0.62 (s, 3)

^{1}H NMR of **120** (250 MHz, $CDCl_3$): δ= 7.49-7.20 (m, 10), 7.07 (m, 1), 6.16 (d, J=1.8 Hz, 1), 5.06 (t, J=1.5 Hz, 1), 4.69 (s, 1), 3.65 (s, 2), 3.34 (s, 3), 2.97 (d, J=7.9 Hz, 1), 2.68 (d, J=7.9 Hz, 1), 2.60-2.36 (m, 2), 2.08-1.57 (m, 6), 1.21 (s, 3), 1.00 (s, 3)

^{1}H NMR of **121** (250 MHz, $CDCl_3$): δ= 7.49-7.20 (m, 10), 7.10 (d, J=1.8 Hz, 1), 6.14 (d, J=1.8 Hz, 1), 5.02 (t, J=1.5 Hz, 1), 4.58 (s, 1), 4.26 (d, J=12.2 Hz, 1), 4.19 (d, J=12.2 Hz, 1), 3.30 (s, 3), 3.26 (d, J=8.6 Hz, 1), 3.16 (d, J=8.6 Hz, 1), 2.60-2.36 (m, 2), 2.08-1.57 (m, 6), 1.15 (s, 3), 1.01 (s, 3)

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