Furans in Synthesis. 8.[1] Formal Total Syntheses of (±)- and (+)-Aphidicolin

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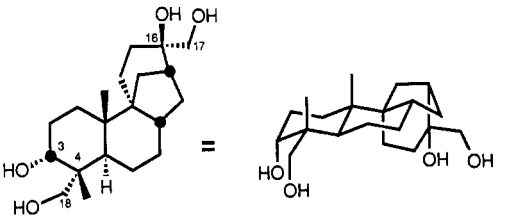
A concise formal total synthesis of (±)- and (+)-aphidicolin (1) via a furan-terminated–epoxide-initiated cationic cyclization is reported. Of particular interest is the observaton that (−)-epoxyfuran **19** suffers cyclization to afford (+)-**20** with *complete* transmission of asymmetry from the starting epoxide. Alcohols (±)- and (+)-**20** are then smoothly transformed to the McMurry intermediate diones (±)- and (−)-**3**. These sequences produce (±)-**3** and (−)-**3** in 13.9% and 10.7% yield, respectively, over 16 steps from geraniol.

Aphidicolin (1), a diterpene tetraol produced by the mold *Cephalosporium aphidicola* Petch,[3] has provoked wide interest in recent years owing to its striking biological activity and unusual tetracyclic structure. Aphidicolin shows marked activity against Herpes simplex Type I virus, both in vitro and in the rabbit eye.[4,5] In addition 1 is reported to possess considerable antitumor activity in the C6 mouse colon and B16 mouse melanosarcoma screens[6] and has been shown to inhibit the growth of leukemic T- and B-lymphocytes.[7] The development of 1 as an antitumor agent has been hampered by the poor water solubility of the parent compound; however, a recent report of enhanced antitumor activity associated with the more water-soluble aphidicolin glycinate ester HCl salt[8] might revive interest in 1 and its analogues as potential therapeutic agents. The potent activity of aphidicolin (1) is presumed to arise through its activity as a specific reversible inhibitor of DNA polymerase-α.[9]



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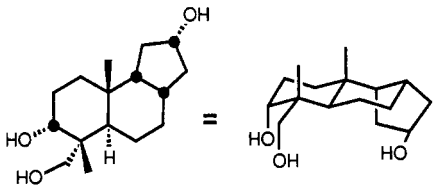

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These biological properties, together with the unusual tetracyclic structure of aphidicolin, have prompted numerous synthetic studies. These efforts have culminated in some seven total[10a–f] or formal total syntheses[10g] of racemic 1, and numerous approaches to the aphidicolane ring system.[11] Recently Holton[12] has capped these efforts with his report of the first enantioselective total synthesis of aphidicolin (1).

While these studies have indeed provided access to both racemic and optically pure 1 in relatively modest overall yields, it may not be necessary to construct the entire

(1) For part 7 in this series, see: Tanis, S. P.; Dixon, L. A. *Tetrahedron Lett.* **1987**, *28*, 2495.

(2) (a) Current address: Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106. (b) Current address: Department of Chemistry, University of California—Los Angeles, Los Angeles, CA.

(3) (a) Bundret, K. M.; Dalziel, W.; Hesp, B.; Jarvis, J. A. J.; Neidle, S. *J. Chem. Soc., Chem. Commun.* **1972**, 1027. (b) Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2841.

(4) Bucknall, R. A.; Moores, J.; Simms, R.; Hesp, B. *Antimicrob. Agents Chemother.* **1973**, *4*, 294.

(5) Ikegami, S.; Taguchi, T.; Ohashi, M.; Oguro, M.; Nagano, H.; Mano, Y. *Nature (London)* **1978**, *275*, 458.

(6) Douros, J.; Suffness, M. In *New Anticancer Drugs*; Carter, S. K., Sakurai, Y., Eds.; Springer-Verlag: Berlin, 1980; p 29.

(7) Pedrali-Noy, G.; Belvedere, M.; Crepaldi, T.; Focher, F.; Spedari, S. *Cancer Res.* **1982**, *42*, 3810.

(8) For a reference to the biological activity of aphidicolin glycinate ester hydrochloride (NSC-303812), see: O'Dwyer, P. J.; Moyer, J. D.; Suffness, M.; Plowman, J. *Proceedings* of the Seventy-Sixth Annual Meeting of the American Association for Cancer Research; May 22–25, 1985; Houston, TX; Abstract 1009.

(9) (a) Spadari, S.; Focher, F.; Sala, F.; Ciarrocchi, G.; Koch, G.; Falasch, A.; Pedrali-Noy, G. *Arnzeim-Forsch. Drug Res.* **1985**, *35*, 1108. (b) Ohashi, M.; Taguchi, T.; Ikegami, S. *Biochem. Biophys. Res. Commun.* **1978**, *82*, 1084. (c) For a recent review, see: Huberman, J. A. *Cell* **1981**, *23*, 647. (d) For another recent review, see: Spadari, S.; Sals, F.; Pedrali-Noy, G. *Trends Biochem. Soc.* **1982**, *7*, 29.

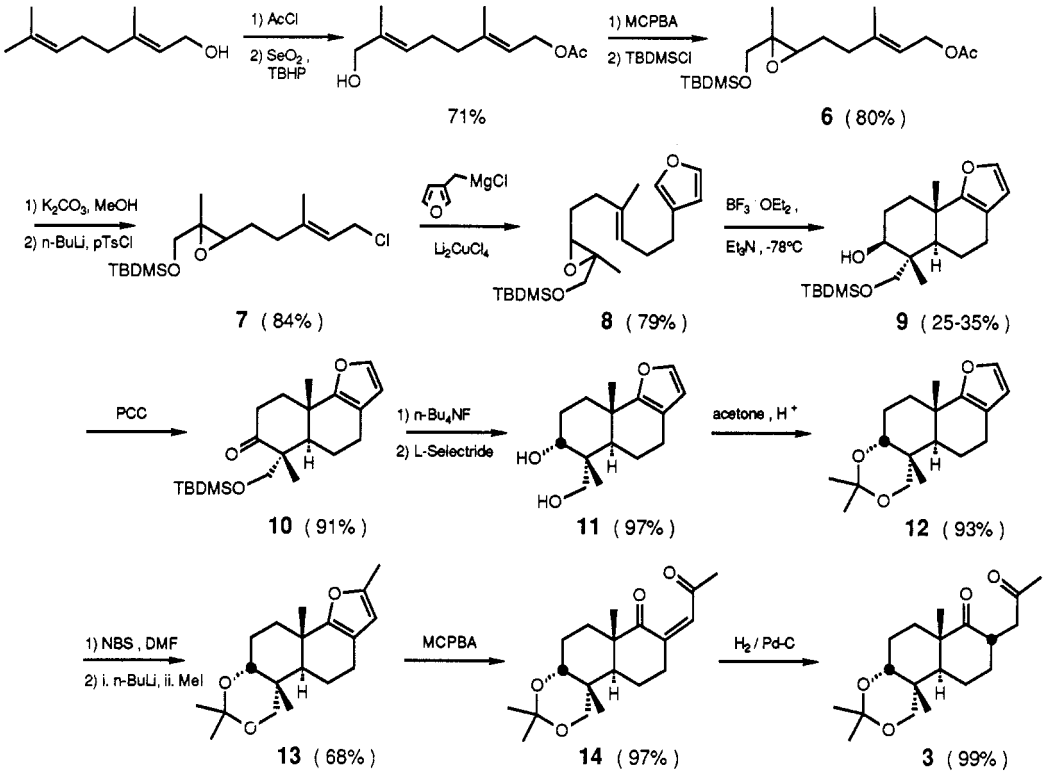
(10) (a) Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Am. Chem. Soc.* **1979**, *101*, 1328. (b) McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, G. H.; Johnson, M. A. *J. Am. Chem. Soc.* **1979**, *101*, 1330; *Tetrahedron* **1981**, *37*, Suppl. i, 319. (c) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742. (d) Ireland, R. E.; Godfrey, J. D.; Thiasrivongs, S. *J. Am. Chem. Soc.* **1981**, *103*, 2446. Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thiasrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001. (e) Van Tamelen, E. E.; Zawacky, S. R.; Russel, R. K.; Carlson, J. G. *J. Am. Chem. Soc.* **1983**, *105*, 142. Van Tamelen, E. E.; Zawacky, S. R. *Tetrahedron Lett.* **1985**, *26*, 2833. (f) Marini-Bettolo, R.; Tagliatesta, P.; Lupi, A.; Bravetti, D. *Helv. Chim. Acta* **1983**, *66*, 1922. (g) Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *Tetrahedron Lett.* **1985**, *26*, 6147.

(11) (a) Rizzo, C. J.; Smith, A. B. III *Tetrahedron Lett.* **1988**, *29*, 2793. (b) White, J. D.; Somers, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 4424. (c) Bell, V. L.; Giddings, P. J.; Holmes, A. B.; Mock, G. A.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1515. Bell, V. L.; Holmes, A. B.; Hsu, S.-Y.; Mock, G. A.; Raphael, R. A. *Ibid.* **1986**, 1507. (d) Koyama, H.; Okawara, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1985**, *26*, 2685. (e) Iwata, C.; Morie, T.; Maezaki, N.; Shimamura, H.; Tanaka, T.; Imanishi, T. *J. Chem. Soc., Chem. Commun.* **1984**, 930. (f) Kelly, R. B.; Sankar Lal, G.; Gowda, G.; Rej, R. N. *Can. J. Chem.* **1984**, *62*, 1930. (g) Pearson, A. J.; Heywood, G. C.; Chandler, M. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2631. (h) Cargill, R. L.; Bushey, D. F.; Dalton, J. R.; Prasad, R. S.; Dyer, R. D.; Bordner, J. *J. Org. Chem.* **1981**, *46*, 3389. (i) Kametani, T.; Honda, T.; Shiratori, Y.; Matsumoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1386. (j) Nicolaou, K. C.; Zipkin, R. E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 785.

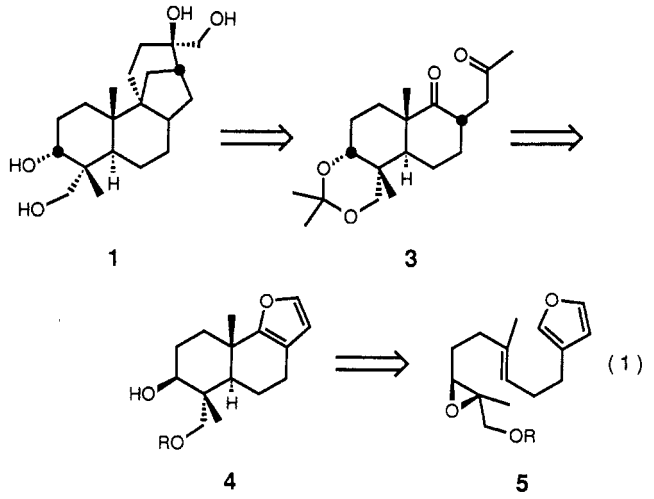
(12) Holton, R. A.; Kennedy, R. M.; Kim, H.-B.; Krafft, M. E. *J. Am. Chem. Soc.* **1987**, *109*, 1597.

0022-3263/88/1953-4929$01.50/0

Scheme I



aphidicolin molecule to retain significant biological activity. McMurry has examined the stereostructure of 1[13] and has noted that all four of aphidicolin's hydroxyl moieties very nearly touch the same flat surface. This observation, and the fact that the nonrigidly held C-17 and C-18 hydroxyl group are less crucial[13] to the maintenance of biological activity in vitro have led the McMurry group to examine the simpler triol 2. Triol 2 possesses two rigidly held hydroxyl groups at a distance of approximately 6 Å, approximating the relationship of the C-3 and C-16 OH groups in 1. McMurry reported that racemic 2 showed 45% of the activity of natural 1 in inhibiting in vitro DNA synthesis. Herein we report in full, concise formal total syntheses of (±)-[14,15] and (−)-1[15] via diketone 3 (eq 1), which has been previously prepared by McMurry[10b] and utilized in the preparation of (±)-2.[13]



(13) McMurry, J. E.; Webb, T. R. *J. Med. Chem.* **1984**, *27*, 1367.
(14) For our first generation synthesis of (±)-3, see: ref 10g.
(15) Presented at the 192nd National Meeting of the ACS, Anaheim, CA, 9/86; Abstract ORGN 47.

Results and Discussion

(a) First-Generation Synthesis of (±)-3. As part of a general program in furan chemistry and as a result of our interest in the utilization of the furyl moiety as a dianion equivalent in annulation sequences, we were interested in accomplishing formal total syntheses of (±)- and (+)-1 as outlined in eq 1. Such a study would exploit (1) a furan-terminated cationic cyclization[1,16] to establish rapidly the carbocyclic nucleus of 1 with the correct relative stereochemistry created at carbons 4, 5, and 10[17,18] and (2) a furan-to-dione conversion ultimately yielding McMurry's intermediate dione 3. The potential advantages of such a sequence are rapid construction of the carbocyclic nucleus and excellent stereochemical control at three of the five stereocenters present in the target dione 3. An additional consideration is the potential for the asymmetric synthesis of 3 from optically pure 5, the product of an asymmetric Sharpless[19] epoxidation.

These considerations caused us to select epoxide 5 as the crucial cyclization substrate for proposed formal total syntheses of (±)- and (+)-1. Our first-generation route to (±)-3, previously published,[10g] is described in Scheme I. In the planning stages for this sequence, we considered the nature of the C-8 OH protecting moiety present in the highly oxidized geranyl acetate side chain precursor 6. This group must survive conversion to chloride 7 and

(16) See: (a) Tanis, S. P.; Dixon, L. A.; Herrinton, P. M. *Tetrahedron Lett.* **1985**, *26*, 5347. (b) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 3988. (c) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572 and references cited therein.
(17) For citations relevant to the extensive body of work in the area of cationic polyene cyclizations, see: References 10c, 10e, 10g, 16c and Tanis, S. P.; Raggon, J. W. *J. Org. Chem.* **1987**, *52*, 819.
(18) Corey, (ref 10c) and Tanis (ref 10g) controlled the relative stereochemistry at carbons 4, 5, and 10 by this method of synthesis; however, van Tamelen controlled the orientation at carbons 3, 4, 5, and 10 in his elegant construction of 1 via cationic cyclization.
(19) (a) Stoichiometric asymmetric epoxidation: Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Catalytic asymmetric epoxidation: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

coupling of 7 with the Grignard reagent prepared from 3-(chloromethyl)furan[10g] and allow inversion of the C-3 OH in 9, via the 3-one, without suffering the retro-aldol loss of formaldehyde. This choice was made simpler by the observations of Trost,[10a] McMurry,[10b] and Corey,[10c] who demonstrated that control in the reduction of the C-3 one could be realized from the deprotected aldol and that the TBDMS protecting group survives cationic cyclization and can be removed *without* the loss of formaldehyde.

In the event, allylic hydroxylation of geranyl acetate (SeO_2, TBHP)[20] gave 8-hydroxygeranyl acetate (72%), which afforded the epoxide 6 after epoxidation (MCPBA, 85%) and protection (TBDMSCl, 95%).[21] Acetate 6 was converted to the corresponding allylic alcohol (K_2CO_3, MeOH, 99%) and then to chloride 7 (Scheme I, 84%) by the procedure of Stork.[22] Chloride 7 was smoothly coupled with (3-methylfuranyl)magnesium chloride in the presence of Li_2CuCl_4[10g,23] to yield the crucial cyclization substrate 8 (79%). With 8 in hand, we turned our attention to the furan-terminated–epoxide-initiated cyclization reaction.

During our earlier studies of furan-terminated–epoxide-initiated cyclizations,[16c] we had examined a variety of Lewis acids for their efficacy in promoting closure without significant byproduct formation. We had settled upon ZnI_2 and $Ti(OiPr)_3Cl$ as our "standard" Lewis acids in epoxide-initiated cyclizations, in fact these Lewis acids gave 62% and 65% yields, respectively, of 3β-hydroxypallescensin A,[16c] the 4α-CH_3 analogue of 9 from epoxydendrolasin. In the present case, exposure of the more highly oxygenated 8 to ZnI_2 and $Ti(OiPr)_3Cl$ provided highly variable yields (0–49%) of 9. After *considerable* experimentation we discovered that consistent 25–35% yields of 9 could be realized after treatment of 8 with $BF_3{\cdot}OEt_2$ (3 equiv) and Et_3N (1.5 equiv) in a hexane–methylene chloride–benzene (1:1:1) solvent mixture at −78 °C. Under these conditions the bulk of the reaction mixture consisted of acyclic ketones. While this solution is by no means ideal, it did provide sufficient material for the completion of the synthetic sequence.

As is outlined in Scheme I, the C-3, stereochemistry can be readily altered. Treatment of alcohol 9 with PCC[24] afforded 3-one 10 (91%), which was deprotected (*n*-Bu_4NF),[21] and the product aldol was immediately reduced with L-Selectride[10b,c,g,25] (Aldrich) to give diol 11 in 97% yield from ketone 10. Exposure of 11 to acetone and oxalic acid in methylene chloride containing $CaSO_4$ led to acetonide 12 in 93% yield.

With 12 in hand, we then examined the conversion of the furyl moiety to the requisite dione. Initially we attempted to introduce the necessary methyl at the unsubstituted furyl α-position by direct metallation (*n*-BuLi) followed by alkylation with CH_3I. Unfortunately all attempts to deprotonate furan 12 and/or capture the furanyl lithium intermediate with CH_3I or D_2O afforded no products of electrophile capture. Application of more forcing conditions, *s*-BuLi or *t*-BuLi with or without additives such as HMPA, TMEDA, DABCO, at temperatures ranging from −78 °C to room temperature, led to destruction of the acetonide moiety. Similarly the free diol, bis(MEM) ether, bis(TMS) ether, and bis(TBDMS) ether also resisted furan metalation. Though we do not yet understand the reasons for this difficulty, these observations are in good agreement with the similar difficulties noted by Heathcock[26] in the thiophene series during an approach to the *Securinega* alkaloids.

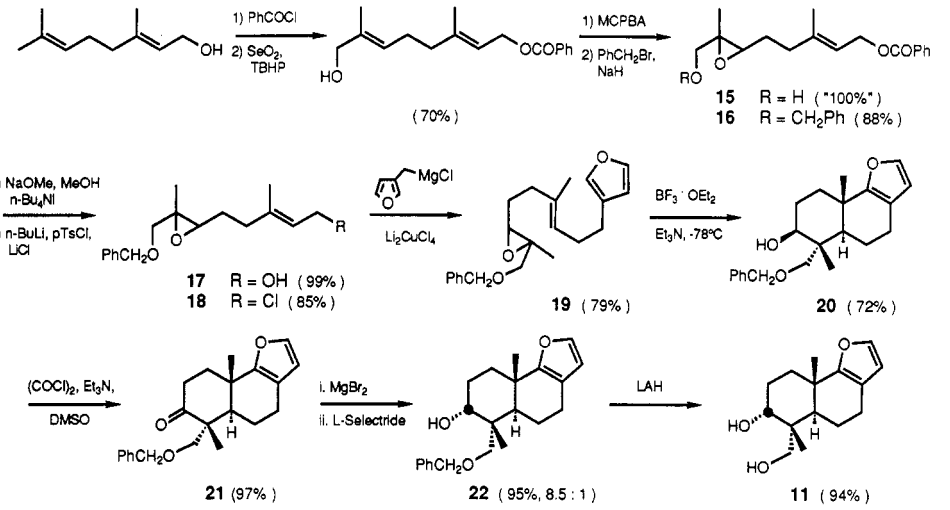
A solution to this problem was found in a selective and careful bromination of the furyl nucleus, followed by metal–halogen exchange and alkylation. Treatment of acetonide 12 with NBS, under the conditions of Mitchell[27] (DMF, 0 °C to room temperature), afforded an unstable bromide, which without purification was immediately subjected to metal–halogen exchange (*n*-BuLi, −78 °C) and alkylation (CH_3I) to yield the desired methylated furan 13 (68%) and 8% of unreacted 12. The mixture of 12 and 13 was oxidized with MCPBA[28] to give ene–dione 14 in 97% yield (based upon 13) and 8% of recovered 12. Ene–dione 14 was then hydrogenated to provide the McMurry intermediate (±)-3[10b] (97%). The identity of (±)-3 was secured after a comparison of spectral data with spectra kindly provided by Professor John E. McMurry. Although a formal total synthesis of (±)-aphidicolin (1) had been accomplished, the problems encountered in the crucial cyclization of epoxide 8 were unresolved. We viewed the 25–35% yields obtained with these "optimized" conditions and low overall yield (7.1%; 16 steps) as unacceptable for a planned synthesis of (+)-3.

(b) Second-Generation Synthesis of (±)-3. We assumed that the size and fragility of the silyl ether present in 8 were responsible for the low and variable yields of 9 that were obtained. This assumption was based upon a relatively 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 *tert*-butyldimethylsilyl ether was hindering the starting epoxide from assuming a productive conformation for cyclization, thus diverting quantities of material to the unproductive epoxide opening. The rationale for the choice of the TBDMS ether as the protecting group for the eventual C-4α CH_2OH was presented previously (vide supra); these considerations still hold. Any alternative masking function for this hydroxyl group must be smaller than the TBDMS ether currently employed and must be removable so as to allow the selective reduction of the C-3 one as described in Scheme I. We selected the relatively small and much more stable benzyl ether to block this hydroxyl moiety in our second-generation synthesis of (±)-3 (Scheme II).

Benzylation of 6,7-epoxy-8-hydroxygeranyl acetate ($PhCH_2Br$, NaH) afforded a poor 21% yield of the desired benzyl ether as a result of acetate scrambling. The more robust benzoate was prepared as outlined in Scheme II. Benzoylation of geraniol (PhCOCl, pyridine, DMAP, 99%) followed by catalytic allylic hydroxylation (SeO_2, TBHP, 71%) provided 8-hydroxygeranyl benzoate. Epoxidation (MCPBA) gave a quantitative crude yield of the desired epoxide 15. Without further purification epoxide 15 was converted to benzyl ether 16 with NaH and benzyl bromide in THF with added *n*-Bu_4NI (88%). In the absence of *n*-Bu_4NI, benzyl ether formation was sluggish, affording but 22% of 16 after 7 h at room temperature. With 16 in hand, we examined several benzoate saponification conditions such as: (a) NaOH, MeOH, room temperature; (b) NaOH, MeOH reflux; (c) NaOMe, MeOH, room temperature; (d) NaOMe, MeOH, reflux; (e) LiOH, THF, reflux; and (f) LiOH, aqueous THF, room temperature (14 days).

(20) Sharpless, K. B.; Umbreit, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
(21) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(22) Stork, G.; Grieco, P. A.; Gregson, M. *Org. Synth.* **1975**, *54*, 68.
(23) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.
(24) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(25) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
(26) Heathcock, C. H.; Jennings, R. A.; von Geldern, T. W. *J. Org. Chem.* **1983**, *48*, 3428.
(27) Mitchell, R. H.; Lai, Y. H.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733.
(28) (a) Williams, P. D.; LeGoff, E. *J. Org. Chem.* **1981**, *46*, 4143. (b) Williams, P. D.; LeGoff, E. *Tetrahedron Lett.* **1985**, *26*, 1367.

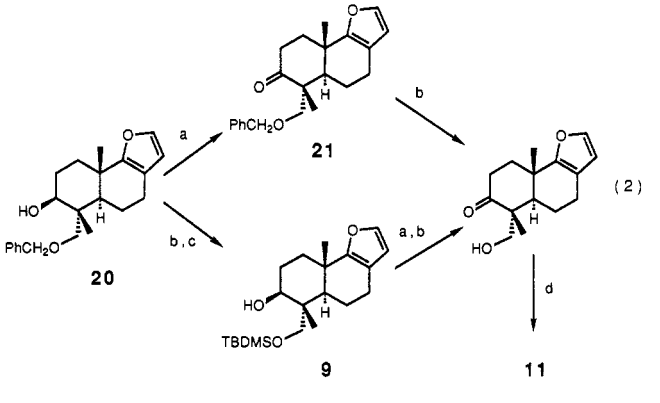
Scheme II



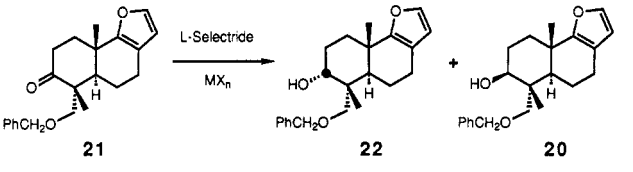
These sets of reaction conditions were not completely satisfactory, runs a–e afforded either no reaction (a, c) or decomposition (b, d, e). Run f did indeed afford the desired allylic alcohol **17** (91%); however, the 14-day reaction time was judged to be unacceptably long. The proper balance of reaction conditions and reaction time was realized upon the addition of n-Bu_4NI to run c; this mixture afforded alcohol **17** in 99% yield after only 12 h. Alcohol **17** was smoothly converted to chloride **18** (85%), which was coupled with 3-$ClMgCH_2$–furan (Li_2CuCl_4) to provide the crucial cyclization substrate **19** (79%).

Exposure of **19** to BF_3·OEt_2 (6 equiv) and Et_3N (3 equiv) in CH_2Cl_2–PhH–n-hexane (1:1:1, –78 °C) gave an excellent yield (72%) of tricyclic alcohol **20** and only a small amount (5%) of acyclic ketone. This result suggests 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 **19** between desired and undesired pathways. The vast improvement in yield and reproducibility of the furan-terminated cationic cyclization raised our hopes of accomplishing a formal total synthesis of (+)-1. However we must first demonstrate that the C-3 OH stereochemistry can be adjusted in the racemic series, an operation that was the cause of considerable concern.

Given that a 4α-CH_2OH 3-ketone such as **21** was thought to be the ultimate precursor of diol **11**, we examined two routes to that compound as outlined in eq 2. The more



direct top path was studied first. Alcohol **20** was smoothly oxidized via the Swern technique[29] to provide ketone **21** in 97% yield. The successful completion of the synthesis now required the cleavage of the benzyl-O bond, to the aldol adduct encountered in Scheme I, followed by L-Selectride reduction. We examined hydrogenolytic and dissolving metal deprotection of the benzyl ether moiety under a variety of reaction conditions, to no avail. We observed either no ether cleavage or deprotection with concomitant ketone reduction, which yielded a ca. 1:1 mixture of C-3 alcohols. A second, more conservative approach is presented as the lower path in eq 2. With C-3 already in the alcohol oxidation state, we were confident that benzyl ether removal could be effected affording a primary–secondary diol, which might be selectively silylated to give **9**. With **9** in hand the synthesis would be completed according to the protocol established in Scheme I. Again we examined a variety of hydrogenolytic and dissolving metal deprotection conditions only to discover that the benzyl ether moiety could not be removed without accompanying furan reduction.



Entry	MX_n	Ratio (22:20)	Yield
a	none	2.8 : 1	99%
b	ZnI_2OEt_2 (1.5 eq.)	1.2 : 1	93%
c	$MgBr_2OEt_2$ (1.5 eq.)	7.0 : 1	95%
d	$MgBr_2OEt_2$ (2.0 eq.)	8.5 : 1	95%
e	$Ti(OiPr)_3Cl$ (1.5 eq.)	4.0 : 1	96%
f	$Ti(OiPr)_4$ (1.5 eq.)	5.7 : 1	93%

Figure 1. Reduction selectivity of **21** with L-Selectride in the presence and absence of added metal salts.

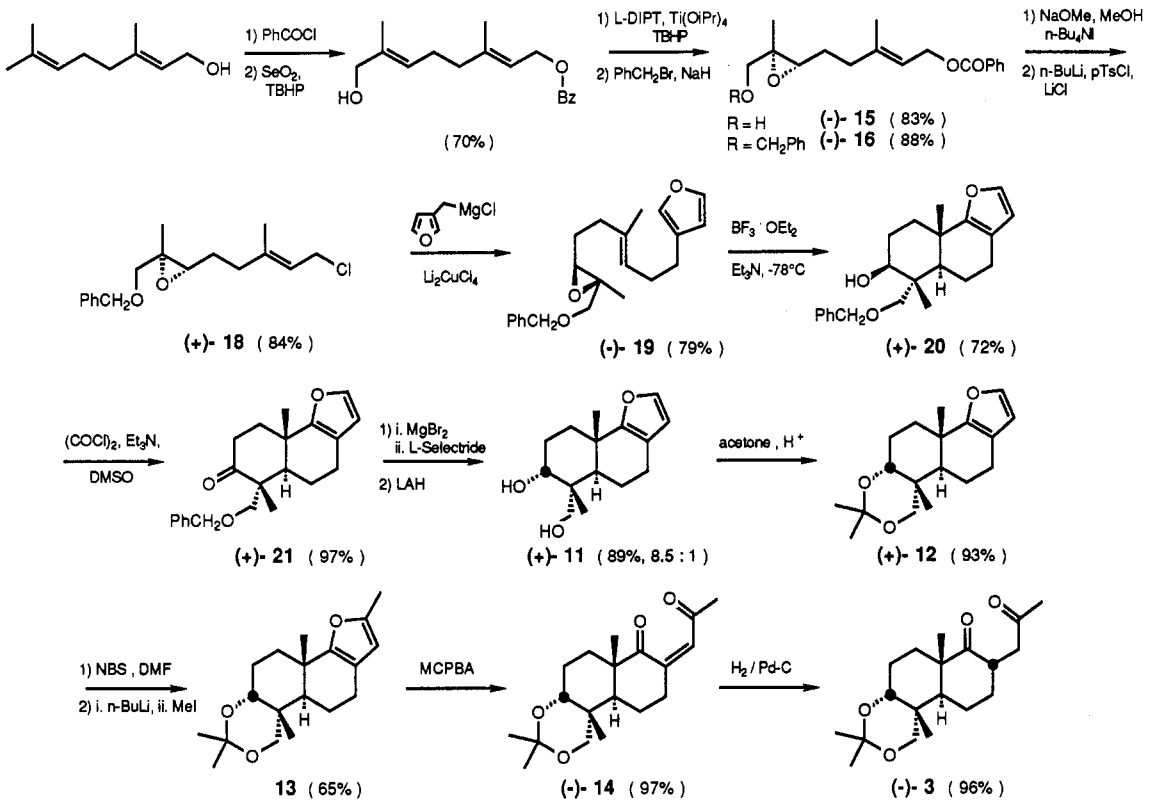
As we were unable to access the necessary diol thought to be a prerequisite for selectivity in the reduction of the 3-one, we initiated the study presented in Figure 1. We reasoned that should we be able to control the reduction of ketone **21** to yield selectively or exclusively monoprotected diol **22**, and we could then avail ourselves of the neighboring group assistance of the 3α-OH in benzyl ether cleavage, by analogy to the precedent established by Kutney.[30]

We examined the reduction of **21**, with L-Selectride in methylene chloride with and without added metal salts.

(29) Mancuso, A.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(30) Kutney, J. P.; Abduraham, N.; Gletsos, C.; LeQuesne, P.; Piers, E.; Vlattas, I. *J. Am. Chem. Soc.* **1970**, *92*, 1727.

Scheme III



We assumed that the proper choice of metal salt might conspire to provide a chelated intermediate, which could be selectively reduced.[31,32] Precomplexation of **21** with ZnI_2, $MgBr_2 \cdot OEt_2$, $Ti(OiPr)_3Cl$, or $Ti(OiPr)_4$ followed by the addition of L-Selectride (−78 °C, Figure 1) gave 3α:3β alcohols **22** and **20** in ratios ranging from 1.2:1 to 8.5:1. Our optimum conditions (Figure 1, entry d) employed 2 equiv of $MgBr_2 \cdot OEt_2$ and provided a very respectable 8.5:1 ratio of **22** and **20** in 95% combined yield.

With a supply of 3α-alcohol **22** secured, the second-generation synthesis of (±)-**3** was completed as presented in Scheme II. Treatment of **22** with $LiAlH_4$ in THF at room temperature (12 h) afforded exclusively diol **11** (mp 119–121 °C) in 94% yield after chromatography. The monoprotected 3β-diol **20**, when submitted to harsher $LiAlH_4$ cleavage conditions (THF, reflux, 8 days), yielded a ca. 1:1 mixture of diol and starting material. Diol **11** can be converted to dione–acetonide **3** as previously described (Scheme I), thus completing the second-generation synthesis of (±)-**3** in 16 steps and 13.9% overall yield from geraniol.

The Formal Total Synthesis of (+)-Aphidicolin. (c) The Synthesis of (−)-3. Having successfully overcome the cyclization and protecting group difficulties in the racemic series, we examined the route to (+)-**1** outlined in Scheme III. Our sole concern in this sequence was the transmission of chirality from the starting epoxy furan to the product tricyclic aphidicolin precursor **20**. Given the accepted chair–chair type folding of acyclic substrates in cationic cyclizations leading to the formation of six-membered rings[17] and our preparation of the proper relative stereochemistry in the racemic routes described above, we were confident of a successful outcome provided the secondary epoxide C–O bond is not compromised in the process. Our formal total synthesis of (+)-**1** is described in Scheme III.

Stoichiometric Sharpless asymmetric epoxidation[19a] of 8-hydroxygeranyl benzoate (1 equiv of L-DIPT, 1 equiv of $Ti(OiPr)_4$, 2 equiv of TBHP) afforded (−)-**15** [$[\alpha]_D$ −5.769° (c = 0.364, CH_2Cl_2)] in 71% yield. The optical purity of (−)-**15** was determined by examination of the ^1H NMR spectrum (250 MHz, $CDCl_3$) of (−)-**15** in the presence of $Eu(hfpc)_3$, as previously described by Sharpless for the corresponding acetate,[19a] and HPLC analyses of the Mosher ester (MTPA).[33] The optical purity of (−)-**15** was judged to be ≥95% ee when we were unable to detect the presence of the optical antipode of (−)-**15**. Alternatively, (−)-**15** could be prepared in 83% chemical yield (≥95% ee) via Sharpless' catalytic asymmetric epoxidation protocol.[19b] Benzyl ether formation (Scheme III) yielded (−)-**16** (88%). Benzoate saponification (99%) and chlorination as previously described furnished chloride (+)-**18** in 85% yield after chromatography. Allylic chloride (+)-**18** was smoothly coupled with furan-3-methylmagnesium chloride (Li_2CuCl_4) to provide the desired cyclization substrate (−)-**19** (79%).

Exposure of (−)-**19** to $BF_3 \cdot OEt_2$ (6 equiv) and Et_3N (3 equiv) in 1:1:1 PhH–CH_2Cl_2–*n*-hexane (−78 °C) gave (+)-**20** in 72% yield. Again, we examined the ^1H NMR spectrum (250 MHz, $CDCl_3$) of (+)-**20** in the presence of $Eu(hfpc)_3$ and converted (+)-**20** to the corresponding MTPA ester (^1H NMR and HPLC). We were unable to detect any trace

(31) For some recent examples of diastereoselective reductions of 3-alkoxy and 3-hydroxy ketones, see: (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. (b) Oishi, T. In *New* Synthetic *Methodology and Functionally Interesting Compounds*; Proceedings of the 3rd International Kyoto Conference on New Aspects of Organic Chemistry; Yoshida, Z.-i., Ed.; Elsevier: Amsterdam, 1986; pp 81–96 and references cited therein. (c) Narasaka, K.; Pai, F.-C. *Tetrahdron* **1984**, *40*, 2233.

(32) For some recent references describing metal coordination to β-RO-carbonyl compounds, see: (a) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. (b) Mead, K.; Macdonald, T. L. *J. Org. Chem.* **1985**, *50*, 422 and references cited therein.

(33) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

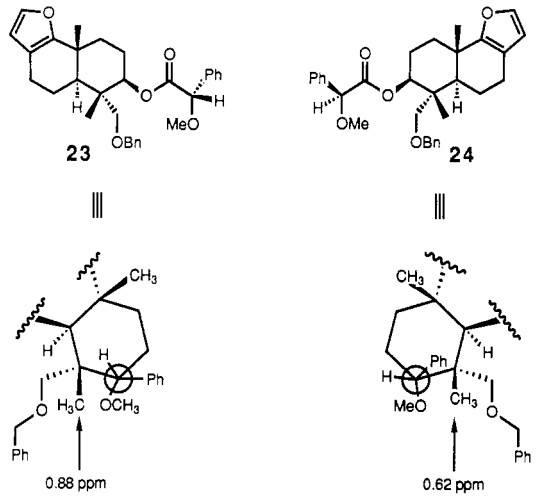


Figure 2. Extended Newman projections of **23** and **24**.

of an alternative enantiomer; therefore, we conclude that the cyclization of (−)-**19** to give (+)-**20** occurs with complete transmission of chirality. The remainder of the sequence was completed as described in Scheme III.

Swern oxidation[29] led to (+)-**21** (97%), which afforded (+)-**22** (85%) after reduction with L-Selectride in the presence of 2.0 equiv of $MgBr_2 \cdot OEt_2$. Benzyl ether cleavage ($LiAlH_4$, 94%) furnished (+)-diol **11**, which was immediately converted to acetonide (+)-**12** (93%). Bromination, metal–halogen exchange, alkylation, and oxidation of (+)-**12** (Scheme III) yielded ene–dione (−)-**14** in 63% overall yield from (+)-**12**. Hydrogenation of (−)-**14** as previously described afforded the target dione (−)-**3** (96%), thus completing our asymmetric synthesis of (−)-**3** in 16 steps and 10.7% overall yield from geraniol.

While we were indeed pleased at the outcome of this process we felt it necessary to demonstrate that (+)-**20** was produced with the absolute stereochemistry required and depicted in Scheme III. Toward that end we envisioned employing the exciton chirality technique of Nakanishi[34] to establish unequivocally the absolute configuration produced in the furan-terminated cationic cyclizatioin sequence. Unfortunately we were unable to prepare a bis(*p*-bromobenzoate) from diol (+)-**11**, nor did we succeed in synthesizing a bis(benzoate) from a diol derived from (+)-**20**. Having failed in our efforts to utilize the exciton chirality technique, we next investigated the *O*-methyl mandelate ester approach for the absolute configuration determination of secondary alcohols, recently elaborated upon by Trost.[35] In this model the ester is viewed in an extended Newman projection and one observes upfield shifts in the ^1H NMR spectrum for substrate sunstituents in close proximity to the mandelate phenyl moiety.

Therefore (±)-**20** was converted to a mixture of diastereomers **23** and **24** (Figure 2) with (*S*)-*O*-methyl mandelic acid, DCC, and DMAP in CH_2Cl_2 (84%). According to the Trost model one would predict that the diastereomer corresponding to the coupling of *O*-methyl mandelic acid with **23** (the enantiomer *not* expected to be produced from (−)-**19**) would exhibit a C-4-methyl resonance, which should not experience an upfield shift. Alternatively the diastereomer prepared from **24** should present a "shielded" methyl resonance. We observed two methyl signals from the mixture depicted in Figure 2 at δ 0.88 and 0.62, respectively. Therefore we anticipate observing a methyl signal for the *O*-methyl mandelate prepared from (+)-**20** at δ 0.62 ppm.

In the event, reaction of (+)-**20** with (*S*)-*O* methyl mandelic acid, DCC, and DMAP in CH_2Cl_2 afforded a single compound (83%) which exhibits a C-4β methyl signal at δ 0.62, thus confirming the absolute configuration of the material in hand as that expected and indicated in Scheme III. Further confirmation (not shown) of the absolute configuration produced via the cyclization of optically pure epoxyfuran (−)-**19** was obtained from a similar study employing alcohols (±)-**22** and (+)-**22**.

Conclusion

We have described formal total syntheses of (±)- and (+)-aphidicolin (**1**), which employ furan-terminated–epoxide-initiated cationic cyclizations to establish the correct relative and absolute stereochemistry at three of the five asymmetric centers in the target dione **3**. Our second generation approach affords (±)- and (−)-**3** in 16 steps and 13.9% and 10.7% yields, respectively (Schemes II and III). This represents a considerable improvement over our first-generation synthesis (Scheme I, 16 steps, 7.1%). The successful transmission of chirality from epoxyfuran (−)-**19** to the tricyclic (+)-**20** (≥95% ee) demonstrates the utility of such a cyclization sequence in asymmetric synthesis and is worthy of note. An application of this chemistry to the synthesis of optically pure **2** is under way and will be reported in due course.

Experimental Section

General Procedures. Tetrahydrofuran (THF), *n*-hexane, and benzene were dried by distillation under argon from sodium benzophenone ketyl; methylene chloride, pyridine, and triethylamine were dried by distillation under argon from calcium hydride; *N,N*-dimethylformamide (DMF) was dried by distillation at reduced pressure from phosphorus pentoxide; hexamethylphosphoramide (HMPA) and dimethyl sulfoxide (DMSO) were dried by distillation at reduced pressure from calcium hydride. Diethyl ether was purchased from Mallinkrodt, Inc., St. Louis, MO, and was used as received. Boron trifluoride etherate was purified by the addition of ca. 5% ether and distillation at reduced pressure from calcium hydride. *N*-Bromosuccinimide was purified by recrystallization from hot water and was dried in vacuo over phosphorus pentoxide. *p*-Toluenesulfonyl chloride was purified by recrystallization from petroleum ether and was dried in vacuo. *n*-Butyllithium in hexanes was purchased from Aldrich Chemical Co., Milwaukee, WI, and was titrated by the method of Watson and Eastham.[36] Petroleum ether refers to the 35–60 °C boiling point fraction petroleum benzin. All other reagents were used as received unless otherwise stated. All reactions were performed in oven (150 °C) dried glassware under argon with rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points are uncorrected. Infrared spectra were recorded either neat as a film on NaCl plates or as a solution in the solvent mentioned, with polystyrene as standard. Proton magnetic resonance spectra (^1H NMR) were recorded at 60 MHz, or 250 MHz as mentioned in deuteriochloroform, unless otherwise indicated. Chemical ionization (CI-MS) mass spectra were recorded utilizing methane as the carrier gas. Optical rotations were measured in the solvents indicated at 25 °C. Flash column chromatography was performed according to the procedure of Still[37] et. al. by using the Merck silica gel mentioned and eluted with the solvents mentioned. The column outer diameter (o.d.) is listed in millimeters.

8-Hydroxy-3,7-dimethyl-2,6-octadien-1-yl Benzoate. To selenium dioxide (0.30 g, 2.7 mmol) and salicylic acid (1.88 g, 13.6 mmol) in dry methylene chloride (50 mL), chilled in an ice–water bath, was added *tert*-butyl hydroperoxide (90%, 54.6 mL, 0.49

(34) See: Harada, N.; Nakanishi, K. In *Circular Dichroism Spectroscopy-Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983; and references cited therein.
(35) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370.
(36) Watson, S. L.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
(37) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *41*, 2923.

mol) in one portion.[20] To this mixture was added a solution of geranyl benzoate (32.84 g, 0.13 mol) in dry methylene chloride (50 mL) over 30 min. The resulting colorless solution was stirred for 24 h at room temperature, diluted with benzene (70 mL), and concentrated in vacuo. Ether (150 mL) was added to the residue; then the organic phase was separated, washed with 10% aqueous KOH (4 × 50 mL), and concentrated in vacuo to give a yellow liquid. The mixture was dissolved in cold (ice–water) acetic acid (30 mL), and dimethyl sulfide (33 mL) was added over 15 min while cooling in an ice–water bath. The cooling bath was removed after the addition was complete, and the mixture was stirred for 5 h at room temperature. The solution was then chilled in an ice–water bath, neutralized with 20% aqueous K_2CO_3, and cast into ether (300 mL). The organic phase was separated, washed with water (300 mL) and brine (300 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the crude product as a yellow liquid. The mixture was dissolved in ice–cold ethanol (100 mL, ice–water bath), and $NaBH_4$ (5 g, 0.13 mol) was added over 0.5 h. Stirring was continued for 10 min after the addition was complete, and the reaction was carefully quenched by the addition of 1 N aqueous HCl (250 mL). The solution was cast into water (300 mL) and extracted with ether (3 × 250 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, 50 mm o.d., hexane–ether (80:20)) by using the flash technique. Fractions 13–16 afforded 3.74 g (11%) of geranyl benzoate. Fractions 18–29 yielded 25.29 g (71%) of 8-hydroxygeranyl benzoate as a clear, colorless liquid: ^{1}H NMR (250 MHz) δ 8.00–8.05 (m, 2), 7.36–7.58 (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), 2.04–2.22 (m, 5), 1.75 (s, 3), 1.64 (s, 3); IR (neat) 3430 (br), 3030, 2930, 1715, 1600, 1585, 1450, 1385, 1315, 1275, 1105, 1070, 1025, 715 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 274 (M^+, 0.26), 257 (0.47), 206 (3.07), 189 (4.91), 152 (16.79), 134 (71.2), 119 (23.08), 105 (base). 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 ((±)-15). To a solution of 8-hydroxygeranyl benzoate (9.65 g, 35.19 mmol) in dry methylene chloride (130 mL), chilled in an ice–water bath, was added a solution of *m*-chloroperoxybenzoic acid (85%, 7.5 g, 36.95 mmol) in methylene chloride (110 mL) over 1 h. Stirring was continued for 0.5 h at 0 °C after the addition was complete, followed by 2 h at room temperature. The reaction mixture was then cast into ether (1 L) and saturated aqueous $NaHCO_3$ (1 L). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (1 L), water (1 L), and brine (1 L), dried (Na_2SO_4), and concentrated in vacuo to give 10.2 g (100% crude yield) of (±)-**15** as a colorless liquid, which was utilized without further purification: ^{1}H NMR (250 MHz) δ 7.97–8.05 (m, 2), 7.36–7.54 (m, 3), 5.48 (t, J = 7.3 Hz, 1), 4.81 (d, J = 7.3 Hz, 2), 3.52–3.65 (m, 2), 2.99 (t, J = 6.4 Hz, 1), 2.10–2.28 (m, 2), 1.75 (s, 3), 1.62–1.76 (m, 3), 1.25 (s, 3); IR (neat) 3440 (br), 3030, 2930, 1715, 1450, 1385, 1315, 1275, 1105, 1070, 1025, 715 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 290 (M^+, 0.05), 273 (0.29), 257 (0.16), 214 (0.32), 188 (4.17), 167 (1.51), 150 (2.21), 137 (1.83), 123 (3.04), 105 (base); exact mass calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1510.

(−)-6,7-Epoxy-8-hydroxygeranyl Benzoate ((−)-15). Stoichiometric Sharpless Epoxidation. To a solution of L-diisopropyl tartrate (6.87 g, 25 mmol) in dry methylene chloride (230 mL), cooled in a dry ice–CCl_4 bath, was added $Ti(OiPr)_4$ (7.25 g, 25.5 mmol). The solution was allowed to stir for 5 min and then 8-hydroxygeranyl benzoate (6.87 g, 25 mmol) in 40 mL of methylene chloride was added over a period of 30 min, followed immediately by the addition of *tert*-butyl hydroperoxide (TBHP, 3.5 M in toluene, 14.5 mL, 50 mmol). The resulting yellow solution was allowed to stir for 2 h at −23 °C and then was stored in a freezer (−20 °C) overnight. To the chilled (dry ice–CCl_4) reaction mixture was added 4.5 mL of Me_2S, and the mixture was stirred for an additional 40 min. The cold solution was slowly added to a vigorously stirred saturated aqueous NaF solution (550 mL) at room temperature and stirred for 10 min, and the aqueous layer was then saturated with NaCl. The gellike precipitated inorganic fluorides were removed by tedious filtration through pads of Celite. The organic phase was separated, the aqueous layer extracted with methylene chloride (3 × 200 mL), and the combined organic extracts were washed with water and 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, 50 mm o.d., hexane–ethyl acetate (50:50), 100-mL fractions) by using the flash technique. Fractions 30–45 afforded 5.16 g (71%) of (−)-**15** as a viscous, clear, colorless liquid: $[\alpha]_D$ −5.769° (*c* 0.364, CH_2Cl_2). Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.04; H, 7.85.

(−)-6,7-Epoxy-8-hydroxygeranyl Benzoate ((−)-15). Catalytic Sharpless Epoxidation. To 4.12 g of powdered, activated 3-Å molecular sieves, suspended in dry methylene chloride (200 mL), cooled to −10 °C internal, was added in order L-(+)-DIPT (1.29 g, 5.51 mmol), $Ti(OiPr)_4$ (1.05 g, 3.7 mmol), and TBHP (3.0 M in 2,2,4-trimethylpentane, 37.3 mL, 0.112 mol). After 10 min the mixture was cooled to −30 °C (internal), and a solution of 8-hydroxygeranyl benzoate (20.6 g, 75 mmol) in dry methylene chloride (50 mL) was added over 0.5 h. The resulting mixture was stirred for 3.5 h at −30 °C (internal), warmed to −15 °C (internal), and treated with a solution of triethanolamine in methylene chloride (1.0 M, 7.4 mL, 7.4 mmol). The solution was stirred for 0.5 h then filtered through a pad of ca. 1.5 cm of flash mesh (230–400 mesh) silica gel covered with Celite. The filter cake was rinsed with ether (1.2 L), and the combined filtrates were dried (Na_2SO_4). Concentration in vacuo finished the crude product as a clear, pale yellow, viscous liquid, which provided (−)-**15** (18.06 g, 83%) after chromatography on a column of silica gel as described above.

(±)-6,7-Epoxy-8-(benzyloxy)geranyl Benzoate ((±)-16). To a solution of crude (±)-**15** (10.2 g, 35.19 mmol) in dry THF (200 mL) was added NaH (1.86 g, 38.66 mmol, 50% in oil, washed with dry hexane (2×)) in one portion. The mixture was allowed to stir for 20 min at room temperature, and benzyl bromide (4.6 mL, 38.66 mmol) was added followed immediately by *n*-Bu_4NI (5.19 g, 14.05 mmol). The resulting mixture was allowed to stir for 5 h at room temperature, the solvent was removed in vacuo, and the reaction was quenched by the addition of saturated aqueous ammonium chloride (300 mL). The mixture was cast into ether (200 mL), the organic phase was separated, and the aqueous layer was extracted with ether (2 × 300 mL). The combined organic extracts were washed with water and brine (500 mL each), dried (Na_2SO_4), and concentrated in vacuo to provide the crude product as a yellow liquid. The mixture was purified by chromatography on a column of silica gel (230–400 mesh, 120 g, 50 mm o.d., hexane–ethyl acetate (90:10), 75-mL fractions) by use of the flash technique. Fraction 20–38 provided 11.89 g (89%) of (±)-**16** as a pale yellow liquid: ^{1}H NMR (250 MHz) δ 7.93–8.01 (m, 2), 7.33–7.51 (m, 3), 7.22–7.31 (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), 2.17–2.35 (m, 2), 1.88 (s, 3), 1.66–1.88 (m, 2), 1.36 (s, 3); EI-MS (70 eV), m/z (relative intensity) 289 (0.5), 273 (3.65), 257 (0.66), 214 (0.92), 189 (2.93), 174 (1.45), 167 (3.36), 137 (4.46), 121 (2.51), 105 (base); IR ($CHCl_3$) 2965, 2930, 2857, 1717, 1497, 1451, 1382, 1365, 1337, 1272, 1176, 1108, 1099, 1070, 1027, 1002, 968, 938, 738, 714 cm^{-1}. Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.49; H, 7.77.

(−)-6,7-Epoxy-8-(benzyloxy)geranyl Benzoate ((−)-16). According to the procedure described for the preparation of (±)-**16**, 4.0 g (13.8 mmol) of (−)-**15**, benzyl bromide (1.8 mL, 15.1 mmol), NaH (0.7 g, 14.5 mmol, 50% in oil, washed with hexane (2×), and *n*-Bu_4NI (2.0 g, 5.4 mmol) furnished 4.61 g, 88%, of (−)-**16** as a clear, colorless liquid after chromatography on a column of silica gel: $[\alpha]_D$ −3.0° (*c* 0.230, CH_2Cl_2); exact mass calcd for $C_{24}H_{28}O_4$ 380.1987, found 380.1980.

(±)-6,7-Epoxy-8-(benzyloxy)geranyl Alcohol ((±)-17). A mixture of (±)-**16** (7.51 g, 19.76 mmol), sodium methoxide (32.0 g, 0.59 mol), and *n*-Bu_4NI (8.76 g, 23.71 mmol) in methanol (475 mL) was allowed to stir for 12 h at room temperature. Then ca. 75% of the solvent was removed in vacuo, and 300 mL of H_2O was added. The mixture was extracted with ether (2 × 200 mL), and the combined organic extracts were washed with water (400 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. The crude product was purified by chromatography on a column of silica gel (60–230 mesh, 100 g, 50 mm o.d., hexane–ether (50:50), 50-mL fractions) by using the flash technique. Fractions 16–32 were combined to give 5.40 g, 99%, of (±)-**17** as

a clear, colorless, viscous liquid: ^{1}H NMR (250 MHz) δ 7.20–7.34 (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), 2.16–2.27 (m, 2), 1.67–1.79 (m, 3), 1.72 (s, 3), 1.35 (s, 3); IR (neat) 3420 (br), 3030, 2920, 2860, 1670, 1450, 1380, 1195, 1000, 740, 700 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 74.04; H, 9.15.

(–)-6,7-Epoxy-8-(benzyloxy)geranyl Alcohol ((–)-17). According to the procedure for the preparation of (±)-**17**, 2.45 g (6.4 mmol) of (–)-**16**, NaOMe (10.5 g, 0.19 mol), and n-Bu_4NI (2.9 g, 7.8 mmol) in methanol (120 mL) led to 1.76 g, 99%, of (–)-**17** as a clear, colorless, viscous liquid after chromatography on a column of silica gel: $[\alpha]_D$ –6.132° (c 0.424, MeOH); exact mass calcd for $M^+ - OH$ $C_{17}H_{23}O_2$ 259.1698, found 259.1694.

(±)-6,7-Epoxy-8-(benzyloxy)geranyl Chloride ((±)-18). To a solution of (±)-**17** (2.10 g, 7.61 mmol) 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 mmol) over 10 min. The resulting mixture was stirred for 10 min at 0 °C; and then pTsCl (1.45 g, 7.61 mmol) in dry ether (5 mL) was added in one portion followed by anhydrous lithium chloride (0.64 g, 15.2 mmol). The solution was allowed to stir for 1 h at 0 °C and for 2 h at room temperature and then was cast into saturated aqueous $NaHCO_3$ (200 mL) and ether (300 mL). The organic phase was separated, washed with water (2 × 200 mL) and 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, 30 mm o.d., hexane–ether (50:50), 25-mL fractions) to provide 1.90 g, 85%, of (±)-**18** as a clear, colorless, viscous liquid: ^{1}H NMR (250 MHz) δ 7.24–7.42 (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), 2.09–2.28 (m, 2), 1.72 (s, 3), 1.61–1.73 (m, 2), 1.31 (s, 3); IR (neat) 3020, 2920, 1665, 1455, 1385, 1255, 1095, 740, 700 cm^{-1}; CI-MS (7 eV), m/z (relative intensity) 295 (M^+ + 1, 0.7), 169 (11.4), 151 (17.9), 111 (base), 91 (65.2). Anal. Calcd for $C_{17}H_{23}ClO_2$: C, 69.26; H, 7.86; Cl, 12.03. Found: C, 68.71; H, 7.74; Cl, 12.33.

(+)-6,7-Epoxy-8-(benzyloxy)geranyl Chloride ((+)-18). According to the procedure described for the preparation of (±)-**18**, 1.22 g (4.4 mmol) of (–)-**17**, n-BuLi (2.43 M in hexane, 2 mL, 4.86 mmol), HMPA (3.5 mL), pTsCl (1.0 g, 5.2 mmol), and LiCl (0.37 g, 8.8 mmol) furnished 1.11 g, 85%, of (+)-**18** as a clear, colorless liquid after chromatography on a column of silica gel: $[\alpha]_D$ +2.179° (c 0.78, CH_2Cl_2).

(±)-1-(3-Furyl)-7,8-epoxy-9-(benzyloxy)non-3-ene ((±)-19). To 7.1 mmol of (3-methylfuranyl)magnesium chloride[10g] in dry THF (10 mL), chilled in an ice–water bath, was added (±)-**18** (1.9 g, 6.5 mmol) in dry THF (10 mL) followed immediately by Li_2CuCl_4[10g,23] (0.1M in THF, 0.65 mL, 0.065 mmol). The mixture was allowed to stir for 0.5 h and then was cast into saturated aqueous NH_4Cl (150 mL) and ether (150 mL). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), and dried (Na_2SO_4). Concentration in vacuo provided the crude product, which was purified by chromatography on a column of silica gel (230–400 mesh, 100 g, 50 mm o.d., hexane–ether (90:10), 50-mL fractions) by using the flash technique. Fractions 29–33 afforded 1.73 g, 79%, of (±)-**19** as a sweet-smelling, colorless, viscous liquid: ^{1}H NMR (250 MHz) δ 7.24–7.41 (m, 6), 7.18 (br s, 1), 6.25 (br s, 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), 2.38–2.47 (m, 2), 2.04–2.29 (m, 4), 1.56–1.69 (m, 2), 1.59 (s, 3), 1.32 (s, 3); IR (neat) 3020, 2920, 1500, 1450, 1380, 1105, 1025, 875, 735, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 340 (M^+, 0.3), 173 (15.0), 91 (base), 81 (30.0); exact mass calcd for $C_{22}H_{28}O_3$ 354.2195, found 354.2022.

(–)-1-(3-Furyl)-7,8-epoxy-9-(benzyloxy)non-3-ene ((–)-19). According to the procedure described for the preparation of (±)-**19**, 0.42 g (1.43 mmol) of (+)-**18**, 3-$ClMgCH_2$–furan (1.7 mmol), and Li_2CuCl_4 (0.1 M in THF, 0.143 mL, 0.0143 mmol) gave 0.384 g, 79%, of (–)-**19** after chromatography on a column of silica gel: $[\alpha]_D$ –2.168° (c 0.764, CH_2Cl_2); exact mass calcd for $C_{22}H_{28}O_3$ 340.2038, found 340.2033.

(±)-(5aα,6α,7β,9aβ)-6-[(Benzyloxy)methyl]-4,5,5a,6,7,8,-9,9a-octahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-ol ((±)-20). To a solution of (±)-**19** (0.11 g, 0.32 mmol) in dry methylene chloride (3 mL), benzene (3 mL), and hexane (3 mL), was added Et_3N (0.14 mL, 1 mmol). The mixture was cooled in a dry ice–i-PrOH bath, and a solution of BF_3·OEt_2 (0.24 mL, 1.95 mmol) in methylene chloride (7 mL) was added over a period of 2 h. The resulting yellow solution was allowed to stir for 45 min at –78 °C and then was cast into ether (150 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic phase was separated, washed with 0.1 N HCl (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the crude product as a pale yellow viscous oil. The crude mixture was purified by chromatography on a column of silica gel (230–400 mesh, 50 g, 40 mm o.d., hexane–ether (80:20), 25-mL fractions) by use of the flash technique. Fractions 24–36 provided 79 mg, 72%, of (±)-**20** as a white solid: mp 92–93 °C; ^{1}H NMR (250 MHz) 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 = 10.0, 5.0 Hz, 1), 3.51 (d J = 8.8 Hz, 1), 3.30 (d, J = 8.8 Hz, 1), 2.13–2.55 (m, 2), 1.49–1.90 (m, 8), 1.27 (s, 3); 1.06 (s, 3); IR ($CHCl_3$) 3440 (br), 3030, 2930, 1505, 1455, 1375, 1075, 1025, 735, 695 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 340 (M^+, 18.0), 201 (21.1), 173 (24.9), 159 (22.7), 91 (base); exact mass calcd for $C_{22}H_{28}O_3$ 340.2038, found 340.2031.

(+)-(5aα,6a,7β,9aβ)-6-[(Benzyloxy)methyl]-4,5,5a,6,7,8,-9,9a-octahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-ol ((+)-20). According to the procedure described for the preparation of (±)-**20**, 0.26 g (0.76 mmol) of (–)-**19** was cyclized with BF_3·OEt_2 (0.57 mL, 4.56 mmol, in 17 mL of CH_2Cl_2) and Et_3N (0.32 mL, 2.28 mmol) in hexane–benzene–methylene chloride (21 mL, 1:1:1) to furnish 0.36 g, 72%, of (+)-**20** as white solid: mp 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.

(±)-(5aα,6α,9aβ)-6-[(Benzyloxy)methyl]-4,5,5a,6,9,9a-hexahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-one ((±)-21). To a solution of oxalyl chloride (51 μL, 0.58 mmol) in dry THF (2 mL), cooled in a dry ice–i-PrOH bath, was added DMSO (43 μL, 0.6 mmol). The solution was warmed to –35 °C (3 min) and then chilled again in a dry ice–i-PrOH bath. To the resulting greenish-yellow solution was added (±)-**20** (0.19 g, 0.56 mmol) in THF (2 mL) over 5 min. The solution was warmed to –35 °C (15 min) and then chilled to –50 °C (internal), and Et_3N (0.4 mL, 2.85 mmol) was added in one portion. The mixture was then warmed to room temperature, stirred for 1 h, and cast into ether (50 mL) and water (30 mL). The aqueous phase was extracted with ether (2 × 50 mL), and the combined organic extracts were washed with 0.1 N HCl (150 mL) and brine (150 mL) and dried (Na_2SO_4). Concentration in vacuo gave the crude product as a white solid, which was purified by chromatography on a column of silica gel (230–400 mesh, 30 g, 30 mm o.d., hexane–ether (80:20), 10-mL fractions) using the flash technique. Fractions 11–14 provided 0.183 g, 97%, of (±)-**21** as a white solid: mp 82–84 °C; ^{1}H NMR (250 MHz) δ 7.19–7.34 (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), 2.22–2.68 (m, 6), 1.89–2.03 (m, 1), 1.53–1.66 (m, 2), 1.19 (s, 3), 0.98 (s, 3); IR ($CHCl_3$) 3030, 2950, 2850, 1700, 1500, 1450, 1375, 1230, 1105, 1030, 735, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 338 (M^+, 4.0), 232 (8.6), 217 (10.5), 149 (8.9), 105 (8.5), 91 (base); exact mass calcd for $C_{22}H_{26}O_3$ 338.1882, found 338.1892.

(+)-(5aα,6α,9aβ)-6-[(Benzyloxy)methyl]-4,5,5a,6,9,9a-hexahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-one ((+)-21). According to the procedure described for the preparation of (±)-**21**, 0.56 g (1.65 mmol) of (+)-**20** was oxidized with oxalyl chloride (0.15 mL, 1.71 mmol), DMSO (0.127 mL, 1.77 mmol), and Et_3N (1.17 mL, 8.4 mmol) in THF (12 mL) to yield 0.527 g, 95%, of (+)-**21** as a white solid: mp 72–73 °C; $[\alpha]_D$ +75.2° (c 0.125, MeOH); exact mass calcd for $C_{22}H_{26}O_3$ 338.1882, found 338.1873.

(±)-(5aα,6α,7α,9aβ)-6-[(Benzyloxy)methyl]-4,5,5a,6,7,8,-9,9a-octahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-ol ((±)-22). To a solution of (±)-**21** (0.1 g, 0.3 mmol) in dry methylene chloride (25 mL), chilled to –10 °C (internal) in an ice–salt bath, was added $MgBr_2$·OEt_2 (0.153 g, 0.6 mmol) in one portion. The mixture was allowed to stir for 5 min and then was cooled in a dry ice–i-PrOH bath, and L-Selectride (1 M in THF, 0.9 mL, 0.9 mmol) was added over 5 min. The reaction mixture was allowed to stir for 0.5 h at –78 °C and was then warmed slowly to room temperature over 1.5 h. The reaction was quenched by

carefully adding MeOH (4 mL), followed by 20% aqueous NaOH (6 mL) and 30% H_2O_2 (12 mL). The mixture was stirred for 1.5 h 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), and dried (Na_2SO_4). Concentration in vacuo afforded the crude alcohol as a viscous pale yellow oil, which was purified by chromatography on a column of silica gel (230–400 mesh, 50 g, 40 mm o.d., hexane–ether (90:10), 25-mL fractions) by use of the flash technique. Fractions 30–48 gave 85 mg (85%) of (±)-**22** as a clear colorless oil: ^1H NMR (250 MHz) 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), 2.29–2.49 (m, 2), 1.51–2.01 (m, 8), 1.25 (s, 3), 0.87 (s, 3); IR ($CHCl_3$) 3480 (br), 3030, 2930, 1505, 1455, 1065, 730, 695 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 340 (M^+, 1.4), 217 (17.0), 149 (36.3), 122 (13.8), 91 (base); exact mass calcd for $C_{22}H_{28}O_3$ 340.2038, found 340.2036. Fractions 52–56 provided 10 mg, 10%, of (±)-**20**.

(+)-(5aα,6α,7α,9aβ)-6-[(Benzyloxy)methyl]-4,5,5a,6,7,8,-9,9a-octahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-ol ((+)-22). According to the procedure described for the preparation of (±)-**22**, 0.53 g (1.57 mmol) of (+)-**21** was reduced with L-Selectride (1.0 M in THF, 6.4 mL, 6.4 mmol) and $MgBr_2{\cdot}OEt_2$ (0.81 g, 3.13 mmol) in methylene chloride (130 mL) to give 0.454 g, 85%, of (+)-**22** as a clear colorless oil: $[\alpha]_D$ +53.64° (c 0.11, MeOH); exact mass calcd for $C_{22}H_{28}O_3$ 340.2038, found 340.2034. Also isolated was 53 mg, 10%, of (+)-**20**.

(±)-(5aα,6α,7α,9aβ)-6-(Hydroxymethyl)-4,5,5a,6,7,8,9,9a-octahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-ol ((±)-11). To $LiAlH_4$ (25 mg, 0.66 mmol) in dry THF (5 mL) was added (±)-**22** (15 mg, 0.05 mmol) in THF (5 mL) over 10 min. The mixture was allowed to stir for 11 h at room temperature and then 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), and dried (Na_2SO_4). Concentration provided the crude diol as a pale yellow solid, which was purified by chromatography on a column of silica gel (230–400 mesh, 10 g, 10 mm o.d., hexane–ether (35:65), 5-mL fractions) by use of the flash technique. Fractions 12–16 furnished 10.4 mg, 94%, of (±)-**11** as a white solid: mp 119–121 °C; ^1H NMR (250 MHz) 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), 3.48 (d, J = 12.5 Hz, 1), 2.27–2.54 (m, 2), 1.54–1.96 (m, 9), 1.26 (s, 3), 0.83 (s, 3); IR ($CHCl_3$) 3350, 2950, 1505, 1480, 1455, 1385, 1270, 1210, 1165, 1135, 1055, 1000, 890, 745 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 250 (M^+, 31.6), 235 (21.5), 217 (base), 199 (19.3), 159 (22.3), 91 (36.4); exact mass calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1558.

(+)-(5aα,6α,7α,9aβ)-6-(Hydroxymethyl)-4,5,5a,6,7,8,9,9a-octahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-ol ((+)-11). According to the procedure for the preparation of (±)-**11**, 0.40 g (1.18 mmol) of (+)-**22** was debenzylated with $LiAlH_4$ (0.45 g, 11.9 mmol) in THF (100 mL) to give 0.276 g, 94%, of (+)-**11** as a white solid: mp 138–140 °C; $[\alpha]_D$ +43.75° (c 0.16, MeOH); exact mass calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1573.

(+)-(4aα,4bβ,9bα,11aα)-4a,4b,5,6,9b,10,11,11a-Octahydro-2,2,4a,9b-tetramethyl-4*H*-furo[2′,3′:5,6]naphtho[2,1-*d*]-1,3-dioxane ((+)-12). To a solution of diol (+)-**11** (0.25 g, 1 mmol) in dry methylene chloride (30 mL) was added dry acetone (2 mL), oxalic acid (several crystals), and anhydrous $CaSO_4$ (1.0 g, 4.77 mmol). The mixture was stirred overnight at room temperature, and the solution was then diluted with ether (150 mL), washed with saturated aqueous $NaHCO_3$ (2 × 150 mL), and dried (Na_2SO_4). Concentration in vacuo gave the crude acetonide as a pale yellow solid, which was purified by chromatography on a column of silica gel (60–230 mesh, 30 g, 30 mm o.d., hexane–ether (88:12), 10-mL fractions) by using the flash technique. Fractions 9–12 yielded 0.27 g, 93%, of (+)-**12** as a white solid: mp 165–167 °C; ^1H NMR (250 MHz, acetone-d_6) 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), 2.30–2.55 (m, 2), 1.50–2.11 (m, 7), 1.43 (s, 3), 1.28 (s, 3), 1.21 (s, 3), 0.82 (s, 3); IR (KBr) 3010, 2970, 2890, 1505, 1480, 1380, 1205, 1165, 1095, 1010, 860, 765 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 290 (M^+, 41.5), 275 (25.8), 232 (4.5), 217 (base), 149 (47.6); $[\alpha]_D$ +22.60° (c 0.77, CH_2Cl_2); exact mass calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1868.

(±)-(4aα,4bβ,9bα,11aα)-4a,4b,5,6,9b,10,11,11a-Octahydro-2,2,4a,9b-tetramethyl-4*H*-furo[2′,3′:5,6]naphtho[2,1-*d*]-1,3-dioxane ((±)-12). According to the procedure described for the preparation of (+)-**12**; 0.25 g (1.0 mmol) of diol (±)-**11** was treated with acetone (2 mL) and oxalic acid (several crystals) in dry methylene chloride (30 mL) to give 0.269 g (93%) of (±)-**12** as a white solid: mp 137–139 °C; exact mass calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1874.

(4aα,4bβ,9aα,11aα)-8-Bromo-4a,4b,5,6,9b,10,11,11a-octahydro-2,2,4a,9b-tetramethyl-4*H*-furo[2′,3′:5,6]naphtho[2,1-*d*]-1,3-dioxane. To a solution of (+)-**12** (0.15 g, 0.52 mmol) in dry DMF (20 mL), cooled in an ice–water bath, was added NBS (0.112 g, 0.57 mmol) in DMF (8 mL) over 10 min. Stirring was continued for 20 min at 0 °C, followed by 1 h at room temperature. The mixture was then diluted with water (200 mL), and cast into ether (100 mL) and pentane (100 mL). The organic phase was separated, washed with water (200 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo to give an unstable bromide (0.169 g, 88%), which was utilized without further purification: ^1H NMR (250 MHz) 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), 2.34–2.49 (m, 2), 1.48–1.98 (m, 7), 1.42 (s, 3), 1.36 (s, 3), 1.22 (s, 3), 0.79 (s, 3); EI-MS (70 eV), m/z (relative intensity) 370 (M^+, 2.0), 368 (M^+, 2.0), 297 (11.3), 295 (11.4), 205 (17.9), 149 (99.7), 91 (28.2), 43 (base).

(4aα,4bβ,9aα,11aα)-8-Bromo-4a,4b,5,6,9b,10,11,11a-octahydro-2,2,4a,9b-tetramethyl-4*H*-furo[2′,3′:5,6]naphtho[2,1-*d*]-1,3-dioxane. According for the precedure described for the bromination of (+)-**12**, treatment of (±)-**12** (80 mg, 0.28 mmol) with NBS (60 mg, 0.3 mmol) in dry DMF (3 mL) afforded 90 mg (88%) of the related (±)-bromide.

(4aα,4bβ,9aα,11aα)-4a,4b,5,6,9b,10,11,11a-Octahydro-2,2,4a,8,9b-pentamethyl-4*H*-furo[2′,3′:5,6]naphtho[2,1-*d*]-1,3-dioxane (13). To a solution of the crude bromide prepared from (+)-**12** (0.169 g, 0.46 mmol) in dry ether (20 mL) cooled in a dry ice–*i*-PrOH bath was added *n*-BuLi (2.43 M in hexanes, 0.3 mL, 0.73 mmol) over 2 min. The mixture was allowed to stir for 30 min at −78 °C, and MeI (0.13 mL, 1.5 mmol) was added in one portion to the resulting bright yellow solution. The mixture was allowed to slowly warm to room temperature over 1 h and then was stirred for 4 h at room temperature. The solution was diluted with water (100 mL) and ether (100 mL), and the organic phase was separated, washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the crude methylated furan as a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 40 mm o.d., hexane–ether (95:5), 20-mL fractions) by using the flash technique. Fractions 16–24 afforded 0.116 g of a ca. 88:12 mixture of **13** (65%) and (+)-**12** (9%). Spectral data attributed to **13**: ^1H NMR (250 MHz) 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), 2.35–2.50 (m, 2), 1.42–1.97 (m, 7), 2.21 (s, 3), 1.40 (s, 3), 1.33 (s, 3), 1.18 (s, 3), 0.77 (s, 3); EI-MS (70 eV), m/z (relative intensity) 304 (M^+, 5.0), 289 (3.8), 231 (30.4), 43 (base).

(4aα,4bβ,9aα,11aα)-4a,4b,5,6,9b,10,11,11a-Octahydro-2,2,4a,8,9b-pentamethyl-4*H*-furo[2′,3′:5,6]naphtho[2,1-*d*]-1,3-dioxane (13). According to the procedure described for the methylation of the bromofuran prepared from (+)-**12**, treatment of the bromide prepared from (±)-**12** (90 mg, 0.246 mmol) was treated with *n*-BuLi (2.5 M, 0.1 mL, 0.25 mmol) and MeI (0.32 mmol) to give 63 mg of a ca. 89:11 mixture of (±)-**13** (68%) and (±)-**12** (8%).

(−)-(4aα,6aα,8β,10β,10bα)-Decahydro-3,3,6a,10b-tetramethyl-8-(2-oxopropylene)-6*H*-naphtho[2,1-*d*][1,3]dioxan-7-one ((−)-14). To a solution of the mixture of (+)-**12** and **13** prepared above (0.116 g, ca. 0.34 mmol of **13**) in dry methylene chloride (20 mL), cooled in an ice–water bath, was added MCPBA (85%, 70 mg, 0.34 mmol) in one portion. Stirring was continued for 1 h at 0 °C and then for 7 h at room temperature. The mixture was cast into ether (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The organic phase was separated, washed with water (100 mL) and brine (100 mL), and dried (Na_2SO_4). Concentration in vacuo furnished the crude ene–dione as a yellow solid, which was purified by chromatography on a column of silica gel (230–400 mesh, 30 g, 30 mm o.d., hexane–ether (50:50), 20-mL fractions) by use of the flash technique. Fractions 13–15 gave 0.104 g (97%) of (−)-**14** as a waxy solid, which was immediately utilized in the

next reaction: $[\alpha]_D$ −95.08° (c 0.061, MeOH); ^{1}H NMR (250 MHz) 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), 2.15–2.65 (m, 3), 1.56–1.91 (m, 6), 2.18 (s, 3), 1.39 (s, 3), 1.35 (s, 3), 1.23 (s, 3), 0.80 (s, 3); IR ($CHCl_3$) 2940, 2850, 1690, 1625, 1455, 1384, 1195, 1095, 1000, 915, 855, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 320 (M^+, 0.3), 204 (30.0), 149 (base), 134 (54.2); exact mass calcd for $C_{19}H_{28}O_4$ 320.1987, found 320.1984.

(±)-(4aα,6aα,8β,10β,10bα)-Decahydro-3,3,6a,10b-tetramethyl-8-(2-oxopropylene)-6*H*-naphtho[2,1-*d*][1,3]dioxan-7-one ((±)-14). According to the procedure described for the preparation of (−)-**14**, treatment of a mixture of (±)-**12** and (±)-**13** (ca. 114 mg, 0.38 mmol of (±)-**13**) with MCPBA (85%, 78 mg, 0.38 mmol) in CH_2Cl_2 (6 mL) furnished 116 mg (97%) of (±)-**14** as a waxy solid: exact mass calcd for $C_{19}H_{28}O_4$ 320.1987, found 320.1990.

(−)-(4aα,6aα,8β,10β,10bα)-Decahydro-3,3,6a,10b-tetramethyl-8-(2-oxopropyl)-7*H*-naphtho[2,1-*d*][1,3]dioxan-7-one ((−)-3). To a solution of (−)-**14** (30 mg, 0.1 mmol) in EtOAc (10 mL) was added Pd/C (10%, 10 mg). The resulting mixture was hydrogenated under 1 atm of H_2 until 3 mL of H_2 (1.35 equiv) had been absorbed. The catalyst was removed by filtration through a pad of Celite, the filter pad was rinsed with EtOAc (25 mL), and the combined filtrates were concentrated in vacuo to yield the crude diones, which were dissolved in MeOH (20 mL) and treated with K_2CO_3 (0.5 g, 3.6 mmol). The mixture was stirred for 5 h at room temperature and then filtered through a pad of silica gel. The filter cake was rinsed with MeOH (25 mL), and the combined filtrates were concentrated in vacuo to give a pale yellow solid, which was purified by chromatography on a column of silica gel (230–400 mesh, 10 g, 10 mm o.d., hexane–ether (80:20), 10-mL fractions) by using the flash technique. Fractions 7–9 gave 29 mg, 96%, of (−)-**3** as a white solid: mp 117–119 °C; $[\alpha]_D$ −44.0° (c 0.025, MeOH); ^{1}H NMR (250 MHz) 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 = 17.5, 8.4 Hz, 1), 1.94–2.23 (m, 5), 2.18 (s, 3), 1.52–1.88 (m, 6), 1.37 (s, 3), 1.32 (s, 3), 1.19 (s, 3), 0.79 (s, 3); IR ($CHCl_3$) 2930, 2870, 1705, 1455, 1375, 1255, 1235, 1195, 1160, 1090, 1000, 855 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 323 (M^+ + 1, 1.2), 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); exact mass calcd for $C_{19}H_{30}O_4$ 322.2144, found 322.2139.

(±)-(4aα,6aα,8β,10β,10bα)-Decahydro-3,3,6a,10b-tetramethyl-8-(2-oxopropyl)-7*H*-naphtho[2,1-*d*][1,3]dioxan-7-one ((±)-3). According to the procedure described for the preparation of (±)-**3**, treatment of (±)-**14** (50 mg, 0.16 mmol) and 10% Pd/C (10 mg) in EtOAc (20 mL) with H_2 (1 atm) gave (±)-**3** (50 mg, 99%) as a white solid: mp 104–105 °C (lit.[10b] mp 104–105 °C); exact mass calcd for $C_{19}H_{30}O_4$ 322.2144, found 322.2146; physical constants and spectral data for (±)-**3** were compared with literature values[10b] and ^{1}H NMR, IR, and EI-MS values for authentic (±)-**3** provided by Professor J. E. McMurry.

(5aα,6aα,7β,9aβ)-6-[(Benzyloxy)methyl]-4,5,5a,6,7,8,9,9a-octahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-ol (*S*)-*O*-Methylmandelate Esters (23 and 24). To a solution of (±)-**20** (10 mg, 0.03 mmol) in CH_2Cl_2 (25 mL) was added (*S*)-*O*-methylmandelic acid (5 mg, 0.03 mmol), 1,3-dicyclohexylcarbodiimide (6 mg, 0.03 mmol), and a few crystals of DMAP. The resulting solution was allowed to stir at room temperature for 24 h, was diluted with ether (50 mL), and was cast into 1 N aqueous HCl (75 mL). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (75 mL) and brine (75 mL), and dried (Na_2SO_4). Concentration in vacuo provided the crude mixture of **23** and **24**, which was filtered through silica gel (5 g, eluted with ether) to give **23** and **24** as a viscous, clear colorless oil (12.1 mg, 84%). Data attributed to **23**: ^{1}H NMR (250 MHz) δ 7.22–7.48 (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), 2.30–2.39 (m, 2), 2.15 (d, J = 9.8 Hz, 1), 2.10 (dt, J = 3.2, 12.5 Hz, 1), 1.40–1.97 (m, 6), 1.21 (s, 3), 0.88 (s, 3). Data attributed to **24**: ^{1}H NMR (250 MHz) δ 7.26–7.48 (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), 2.30–2.40 (m, 2), 2.16 (d, J = 9.8 Hz, 1), 2.11 (dt, J = 3.2, 12.5 Hz, 1), 1.39–2.01 (m, 6), 1.18 (s, 3), 0.62 (s, 3).

(5aα,6aα,7β,9aβ)-6-[(Benzyloxy)methyl]-4,5,5a,6,7,8,9,9a-octahydro-6,9a-dimethylnaphtho[1,2-*b*]furan-7-ol (*S*)-*O*-Methylmandelate Ester (24). According to the procedure described for the preparation of the mixture of **23** and **24**, 10 mg (0.03 mmol) of (+)-**20** was treated with (*S*)-*O*-methylmandelic acid (5 mg, 0.03 mmol), 1,3-dicyclohexylcarbodiimide (6 mg, 0.03 mmol), and DMAP (a few crystals) in CH_2Cl_2 (25 mL) to furnish 12 mg (83%) of **24** as a clear, colorless viscous oil.

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Registry No. (+)-**1**, 38966-21-1; (±)-**1**, 69926-98-3; (−)-**3**, 116257-22-8; (±)-**3**, 116179-42-1; (±)-**6**, 116179-44-3; (±)-**6** (deacetyl deriv), 116179-43-2; (±)-**7**, 116179-45-4; (±)-**8**, 116181-11-4; (±)-**9**, 105986-15-0; (±)-**10**, 105986-16-1; (±)-**10** (desilyl deriv), 105986-17-2; (+)-**11**, 116179-46-5; (±)-**11**, 105986-18-3; (+)-**12**, 116179-47-6; (±)-**12**, 105986-19-4; **12** (8-bromide), 116179-58-9; (±)-**12** (8-bromide), 116078-13-8; **13**, 116179-48-7; (±)-**13**, 105986-20-7; (−)-**14**, 116179-49-8; (±)-**14**, 105986-21-8; (−)-**15**, 116179-50-1; (±)-**15**, 116078-03-6; (−)-**16**, 116179-51-2; (±)-**16**, 116078-04-7; (−)-**17**, 116179-52-3; (±)-**17**, 116078-05-8; (+)-**18**, 116179-53-4; (±)-**18**, 116078-06-9; (−)-**19**, 116179-54-5; (±)-**19**, 116078-07-0; (+)-**20**, 116179-55-6; (±)-**20**, 116078-08-1; (+)-**21**, 116179-56-7; (±)-**21**, 116078-09-2; **22**, 116179-57-8; (±)-**22**, 116078-10-5; **23**, 116078-11-6; **24**, 116078-12-7; geraniol, 106-24-1; geranyl acetate, 105-87-3; 8-hydroxygeranyl acetate, 37905-03-6; geranyl benzoate, 94-48-4; 8-hydroxygeranyl benzoate, 88218-65-9; (3-furyl)methylmagnesium chloride, 85757-86-4.