Registry No. (±)-**5**, 82977-33-1; (±)-**6**, 82933-10-6; **7**, 82933-11-7; **8**, 82933-12-8; **9**, 82933-13-9; **10**, 82933-14-0; **11**, 82933-15-1; (*S*)-**12**, 32233-43-5; (*S*)-**13**, 69985-24-6; (*S*)-**15**, 82933-16-2; **17**, 82933-17-3; (DL)-**18**, 82933-18-4; **19a**, 3440-28-6; **19b**, 2304-94-1; **19c**, 3303-84-2; **19d**, 3339-73-9; **20a**, 3878-55-5; **20b**, 2564-95-6; **20c**, 56269-39-7; **21a**, 27034-77-1; **21b**, 55150-34-0; **21c**, 82933-19-5; **22a**, 82933-20-8; **22b**, 54755-77-0; **22c**, 23159-09-3; (L)-**23**, 82933-21-9; (*S*)-**24**, 82933-22-0; $MeBF_3Li$, 82977-34-2; Me_2CuLi, 15681-48-8; $(Bu)_2CuLi$, 24406-16-4; Me_3CuLi_2, 61278-42-0; DPPA, 26386-88-9; (*S*)-*N'*-methyl-*N*^{2}-benzoylhomoserinamide, 82933-23-1.

Synthesis of the Bottom Half of Chlorothricolide

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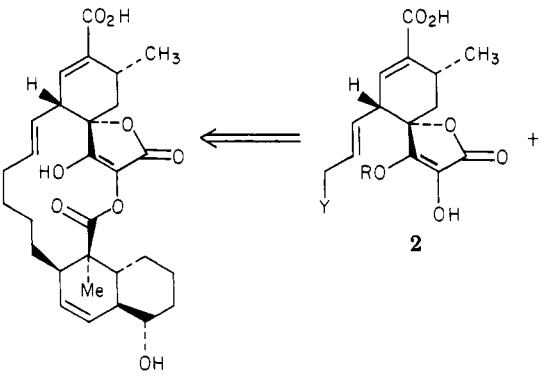
An efficient, stereoselective synthesis of lactone **5**, a synthetic equivalent of the bottom half of chlorothricolide (**1**) is described. The key steps of this synthesis are (i) the intramolecular Diels–Alder reaction of diene acetylene **13**, (ii) the dissolving metal reduction of unsaturated acid **34**, and (iii) the stereoselective alkylation of lactone enolate **44**. The overall yield of **5** is 15% for the 14-step sequence.

Introduction

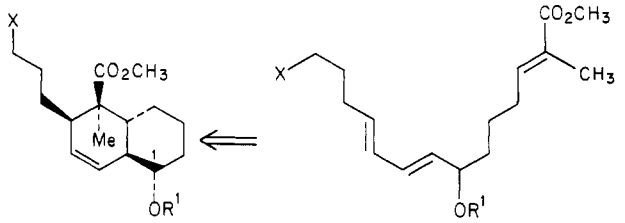
Chlorothricolide (**1**) is the aglycon of the antibiotic chlorothricin, which was isolated from *Streptomyces antibioticus* in 1969.[1] Chlorothricin is an inhibitor of pyruvate carboxylase and maleate dehydrogenase and is active against gram-positive bacteria.[2] Chlorothricolide methyl ester, produced by methanolysis of the natural product, retains some of the biological activity of chlorothricin itself.[3] Our original plan for the synthesis of **1** involved construction of the bottom half **3** by the intramolecular Diels–Alder reaction of **4**.[4] We recently reported a study of the intramolecular Diels–Alder reactions of a series of trienes in this structural series.[5] We found, however, that trienes of this type cyclize preferentially to cis- rather than trans-fused cycloadducts.[6] These results prompted us to explore a modified synthetic approach to the lower half of **1** (Scheme I).

We envisioned that hexahydronaphthalene **7**, a product of an intramolecular Diels–Alder reaction of diene acetylene **6**, might undergo a dissolving metal reduction to afford the desired trans-fused ring system **8**. Subsequent alkylation of this intermediate would afford the lower half **3** of chlorothricolide. Ideally, the two latter transformations would be accomplished in a single step via a reductive alkylation sequence.

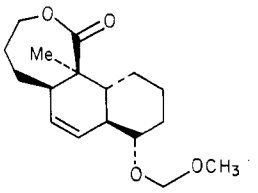
It seemed to us at the outset that the success of this plan would not be critically dependent on the protecting groups selected for **6** nor on the choice of the functionality present within the C-11 side chain. This assumption proved, however, to be incorrect, a conclusion which necessitated that two approaches to **3** be pursued. We describe herein



1 **2**



3 **4**



5

the results of these studies which culminated in an efficient, stereoselective synthesis of **3** (X = OH, R^1 = CH_2OCH_3) via lactone **5**.

Synthesis and Cyclizations of Diene Acetylenes 13 and 18. Condensation of 4-(benzyloxy)butyraldehyde **9**[8] with the lithium anion of 1-methoxybut-1-en-3-yne fol-

(1) (a) Keller-Schierlein, W.; Muntwyler, R.; Pache, W.; Zähner, H. *Helv. Chim. Acta* **1969**, *52*, 127. (b) Muntwyler, R.; Widmer, J.; Keller-Schierlein, W. *Ibid.* **1970**, *53*, 1544. (c) Muntwyler, R.; Keller-Schierlein, W. *Ibid.* **1972**, *55*, 2071. (d) Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Ibid.* **1972**, *55*, 2094.

(2) (a) Schindler, P. W.; Zähner, H. *Arch. Microbiol.* **1972**, *82*, 66; *Eur. J. Biochem.* **1973**, *39*, 591. (b) Pache, W.; Chapman, D. *Biochim. Biophys. Acta* **1972**, *255*, 348. (c) Schindler, P. W. *Eur. J. Biochem.* **1975**, *51*, 579.

(3) Schindler, P. W.; Scrutton, M. C. *Eur. J. Biochem.* **1975**, *55*, 543.

(4) Ireland and co-workers have recently reported their progress on the total synthesis of **1**: (a) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *J. Org. Chem.* **1981**, *46*, 4863. (b) Ireland, R. E.; Thompson, W. J. *Ibid.* **1979**, *44*, 3041. (c) Ireland, R. E.; Thompson, W. J. *Tetrahedron Lett.* **1079**, 4705. (d) Ireland, R. E.; Thompson, W. J.; Mandel, N. S.; Mandel, G. S. *J. Org. Chem.* **1979**, *44*, 3583.

(5) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.

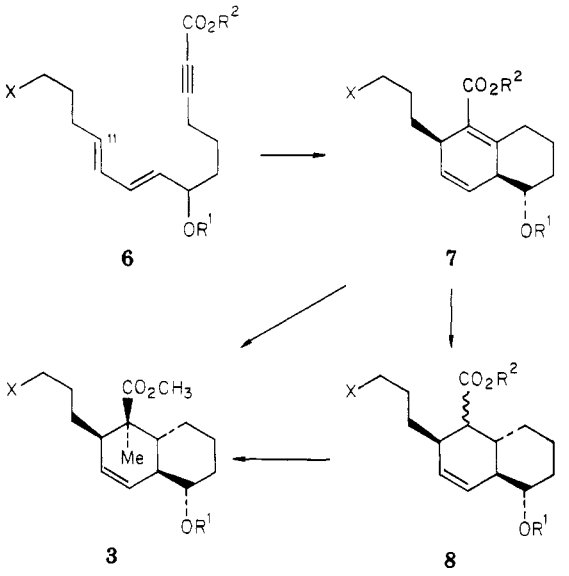
(6) The endo/exo selectivity observed in these cyclizations was virtually independent of dienophile stereochemistry, a result previously observed in the thermal cyclizations of trienes in the perhydroindene series.[7]

(7) (a) Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008. (b) Roush, W. R.; Ko, A. I.; Gillis, H. R. *Ibid.* **1980**, *45*, 4264. (c) White, J. D.; Sheldon, B. G. *Ibid.* **1981**, *46*, 2273. (d) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.

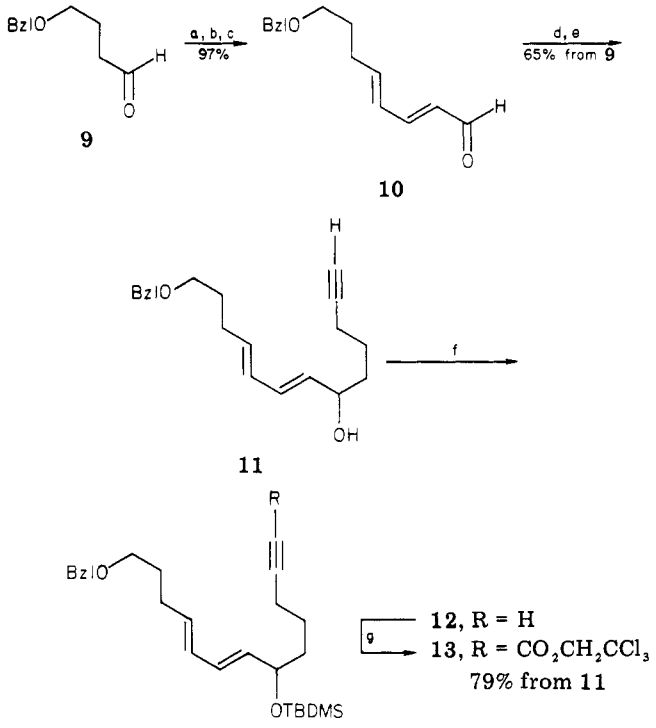
(8) Hurd, R. N.; Shah, D. H. *J. Org. Chem.* **1973**, *38*, 607. See also Wilson, C. L. *J. Chem. Soc.* **1945**, *87*, 45. Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1948**, *15*, 197.

0022-3263/82/1947-4611$01.25/0

Scheme I



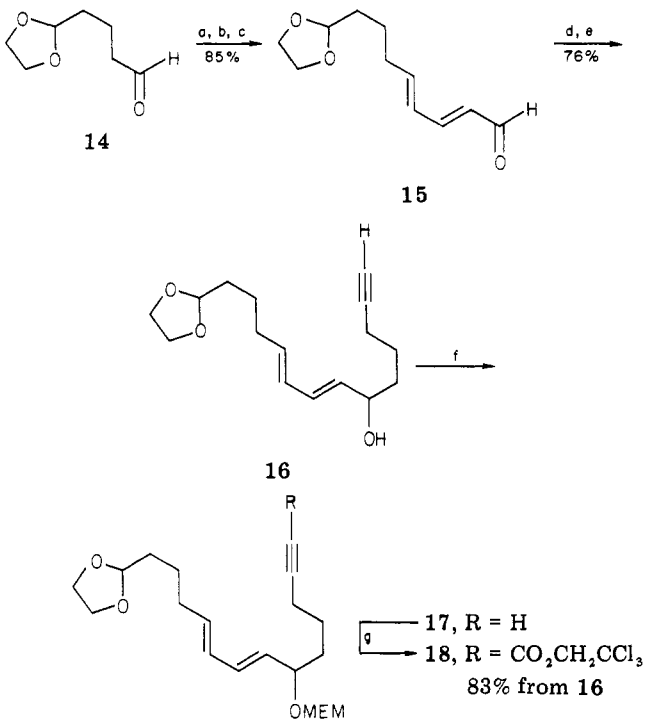
Scheme II[a]



[a] (a) LiC≡CCH=CHOCH$_3$ (1.2 equiv), THF, 0–23 °C, 2 h; then EtOH (0.7 equiv), 0 °C; (b) LiAlH$_4$ (3.4 equiv), THF, 0–23 °C, 2–5 h; (c) 1 N HCl, CH$_3$OH, 23 °C, 1 h; (d) BrMg(CH$_2$)$_3$C≡CSiMe$_3$ (1.5 equiv), THF, 0 °C; (e) KF, DMF, H$_2$O, 23 °C, 39 h; 65% yield from **9**; (f) *t*-BuMe$_2$SiCl; DMF, imidazole, 23 °C, 53 h; (g) *n*-BuLi (1.3 equiv), THF, −78 °C; then excess ClCO$_2$CH$_2$CCl$_3$, −78 → 0 °C.

lowed by sequential addition of EtOH, LiAlH$_4$, and aqueous 1 N HCl afforded[9] 97% of crude dienal **10** (Scheme II). The *E,E* stereochemistry of the newly formed double bonds was suggested by the similarity of the ^{1}H NMR spectrum of **10** to that of sorbaldehyde and related diene aldehydes.[10] The isomeric purity of crude dienal **10** was estimated to be at least 85% by integration

Scheme III[a]



[a] (a) LiC≡CCH=CHOCH$_3$ (1.1 equiv), THF, 0–23 °C, 2 h; then EtOH (0.6 equiv), 0 °C; (b) LiAlH$_4$ (3.1 equiv), THF, 0–23 °C, 2–5 h; (c) 1 N HCl, CH$_3$OH, 23 °C, 30 min; 85% from **14**; (d) BrMg(CH$_2$)$_3$C≡CSiMe$_3$ (1.5 equiv), THF, 0 °C; (e) KF, DMF, H$_2$O, 23 °C, 48 h; 76% yield from **15**; (f) MEMCl[15] (1.5 equiv), Et$_2$N-*i*-Pr (1.6 equiv), CH$_2$Cl$_2$, 23 °C, 12 h; (g) *n*-BuLi (1.6 equiv), THF, −78 °C; then excess ClCO$_2$CH$_2$CCl$_3$ −78 → 0 °C; 83% from **16**.

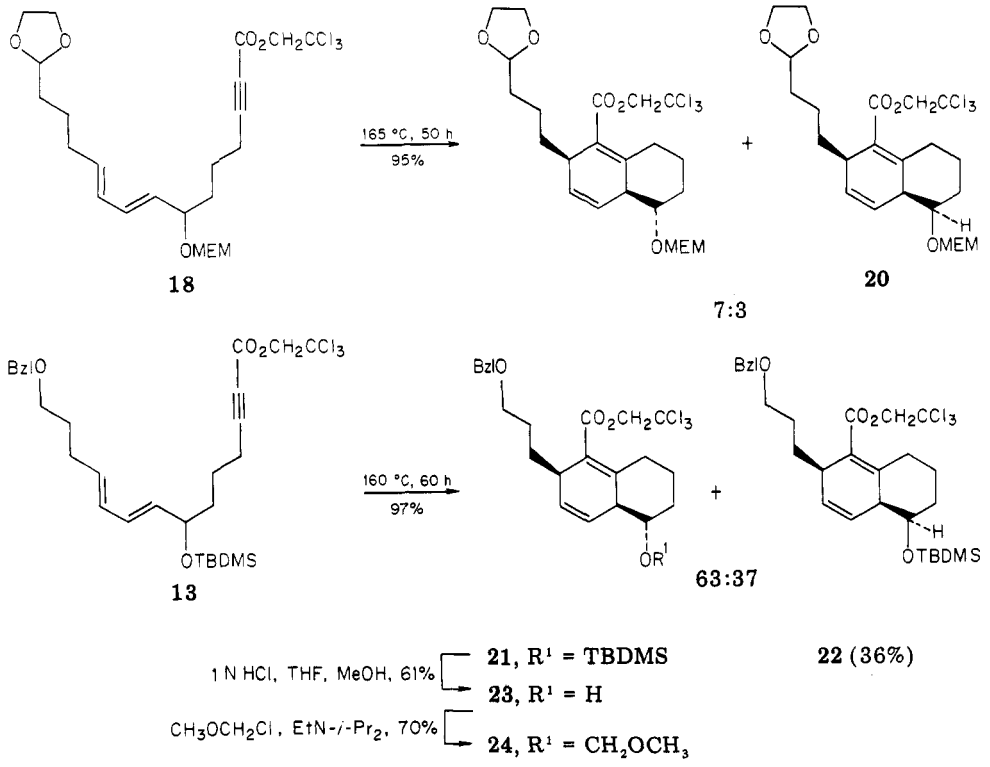
of the vinylic hydrogens in the high-field NMR spectrum. No effort, however, was made to remove the undesired isomers at this stage. Condensation of crude **10** with the Grignard reagent prepared from (5-bromo-1-pentynyl)-trimethylsilane[11] followed by desilylation[12] afforded diene alcohol **11** in 65% overall yield from **9**. Protection of the hydroxyl group of **11** as the *tert*-butyldimethylsilyl ether[13] gave **12** which, without purification, was converted to acetylenic ester **13** by sequential treatment with *n*-butyllithium and then excess trichloroethyl chloroformate. Silica gel chromatography was effective at this point in removing the undesired butadiene isomers. Thus, the overall yield of isomerically pure **13** from **11** was 79%.

An analogous sequence was used to prepare diene acetylene **18** (Scheme III) in 53% yield from **14**.[14] Cyclization of **18** in dilute toluene solution (165 °C, 50 h) proceeded smoothly to afford a 7:3 mixture of cycloadducts **19** and **20** in 95–98% yield (Scheme IV). Although the mixture of **19** and **20** could be separated by analytical TLC (two adjacent but well-resolved spots), preparative chromatography effected only partial separation of the two products. This mixture, therefore, was used in subsequent transformations without being separated.

The cyclization of **13** proceeded under conditions comparable to those used for **18** (0.2 M in toluene, 160 °C, 60 h) and afforded a 63:37 mixture of cycloadducts **21** and

(9) Marshall, P.; Whiting, M. C. *J. Chem. Soc.* **1956**, 4081.
(10) (a) Leraux, Y.; Vauthier, E. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1970**, *271*, 1333. (b) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390.
(11) Flahaut, J.; Miginiac, P. *Helv. Chim. Acta* **1978**, *61*, 2275. Courtois, G.; Masson, A.; Miginiac, P. *C. R. Hebd. Seances Acad. Sci., Ser. C.* **1978**, *286*, 265.
(12) Drouin, J.; Leyendecker, D.; Conia, J. M. *Tetrahedron* **1980**, *36*, 1203.
(13) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(14) Takizawa, K.; Yoshida, R. (Ajinomoto Co., Inc.) Japan Patent 24 698; *Chem. Abstr.* **1971**, *75*, P129790k.

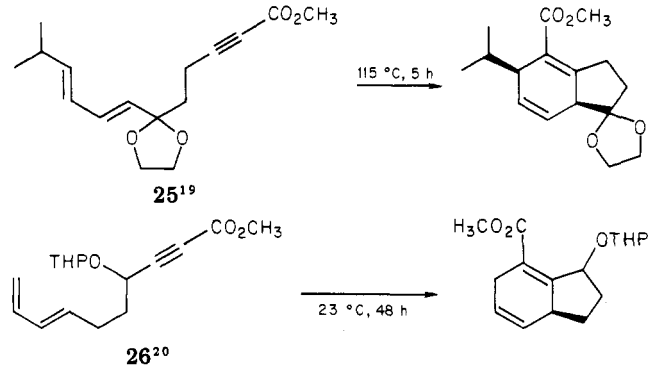
Scheme IV



22 in nearly quantitative yield. Again, separation of the two epimeric products proved to be exceedingly difficult. In this case, however, it was found that treatment of this mixture with 1 N HCl–CH_3OH–THF (1:7:5, v/v) resulted in *exclusive* deprotection of equatorial silyl ether **21** in the presence of its axial isomer **22**. The resulting mixture was easily separated by chromatographic methods which afforded **22** and **23** in 36% and 61% yields, respectively.[16] Alcohol **23** was then converted into its methoxymethyl ether derivative **24** in 70% yield.[17]

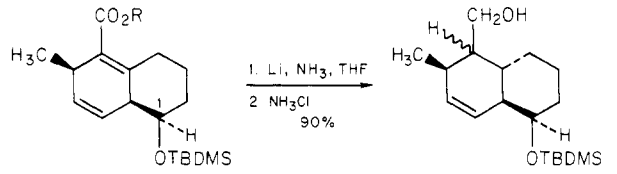
The stereochemistry of C-1 of cycloadducts **19**, **22**, and **23** was determined by ^1H NMR spectroscopy. The resonance for C-1 H of **19** appears at δ 3.28 as a doublet of triplets (J = 5, 10 Hz). The corresponding signal for **23** appears at δ 3.40 (dt, J = 4, 10 Hz). These data indicate that **19** and **23** possess equatorial alkoxyl groups. The axial nature of the silyloxy group in **22** was confirmed by the chemical shift and multiplicity of C-1 H (δ 4.08, br s).[18] The resonance for C-1 H of **20** could not, however, be assigned.

The level of stereoselection realized in the cyclizations of **13** and **18** is on the order of that obtained in the intramolecular cyclizations of trienes possessing diene allylic alkoxyl functions.[5,7a] The rates of cyclization, however, are much slower than the rates of diene acetylene cyclizations in the perhydroindene series. Whereas **25** and **26** cyclize via relatively strain-free transition states, **13** and **18** must cyclize through transition states in which the atoms bridging the diene and dienophile adopt a boatlike conformation.



Dissolving Metal Reduction and Alkylation Sequence. We were optimistic from the outset about the stereochemical outcome of the planned dissolving metal reduction sequence, for a wide variety of perhydronaphthalene derivatives are known to undergo dissolving metal reductions to afford, almost exclusively, trans-fused products.[21,22] Although unsaturated esters have served as substrates for dissolving metal reductions, overreduction to the saturated alcohol derivative is a frequent problem especially when excess metal is employed.[21,23] We encountered this problem in attempts to effect reduction of model ester **27**. Saturated alcohols were the major products of this reaction; the complexity of the ^1H NMR spectrum, however, prevented unambiguous assignment

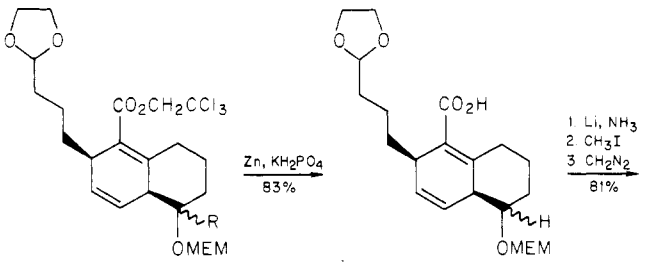
(15) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *809*.
(16) On one occasion the hydrolysis reaction was terminated short of completion, and a 6:1 mixture of **22**/**21** was recovered. This mixture was resubjected to the prescribed reaction conditions and, again, only the TBDMS ether of **21** was hydrolyzed. The selectivity of this reaction may prove to be generally useful in other contexts.
(17) (a) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827. (b) LaForge, F. B. *J. Am. Chem. Soc.* **1933**, *55*, 3040.
(18) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Elmsford, NY, 1972; pp 238–241 and references therein.
(19) Roush, W. R.; Gillis, H. R., unpublished results.
(20) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696.
(21) (a) For a tabulation of many examples, see Cain, D. *Org. React.* **1976**, *23*, 1. (b) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275. (c) Stork, G.; Darling, S. D. *J. Am. Chem. Soc.* **1964**, *86*, 1761.
(22) Several examples of dissolving metal reductions of hexahydronaphthalenes: (a) Grieco, P. A.; Ferrino, S.; Oguri, T. *J. Org. Chem.* **1979**, *44*, 2593. (b) Coates, R. M.; Shaw, J. E. *Ibid.* **1970**, *35*, 2597.
(23) (a) Arth, G. E.; Poos, G. I.; Lukes, R. M.; Robinson, F. M.; Johns, W. F.; Feurer, M.; Sarett, L. H. *J. Am. Chem. Soc.* **1954**, *76*, 1715. (b) Coates, A. M.; Shaw, J. E. *J. Org. Chem.* **1970**, *35*, 2601.



27, R = CH_3
28, R = H

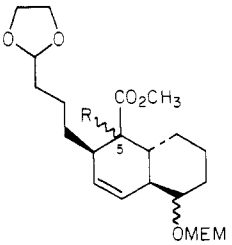
of stereochemistry. In contrast, overreduction is not generally observed in the dissolving metal reductions of α,β-unsaturated acids.[23b] Thus, it was clear at an early stage in the development of this synthetic scheme that an unsaturated acid would be required as the substrate for the dissolving metal reduction sequence. Under most circumstances, the unsaturated acid would be prepared by hydrolysis of the corresponding methyl ester; however, the sensitive nature of cyclohexadiene esters such as **27** precluded this approach. Attempts to obtain acid **28** from **27** by either alkaline hydrolysis or S_N2-type cleavage conditions (i.e., LiI, DMF)[24] were plagued by substrate aromatization with concomitant loss of the C-1-alkoxyl function. Clearly, the carboxyl function needed to be protected with a group which could be removed under mild, nonhydrolytic conditions. These considerations led to the selection of a trichloroethyl ester protecting group[25] for use in the sequences summarized in Schemes II, III, and IV.

Treatment of an unseparated mixture of cycloadducts **19** and **20** with zinc dust in THF containing 1 M KH_2PO_4 at 23 °C afforded acid **29**, a mixture of C-1 epimers in 83% yield.[26] Several conditions for reductive alkylation of **29** were examined (Li, NH_3, then CH_3I (−78 → 23 °C); Li, NH_3, THF, then addition of HMPT and $FeCl_3$ (to quench excess Li), removal of NH_3 by distillation and addition of CH_3I (−78 → 23 °C); Li, HMPT,[27] then CH_3I), but each attempt resulted in simple reduction with *no* alkylation. In all cases a mixture of products containing esters **30** and **31** was obtained.



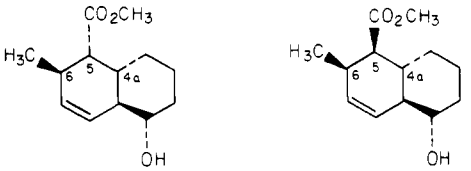
19, R = β-H
20, R = α-H

29



30, R = β-H
31, R = α-H

The stereochemistry depicted for the major product, **30** was assigned by comparison of the ^1H NMR spectroscopic data with that of stereochemically related ester **32**, the



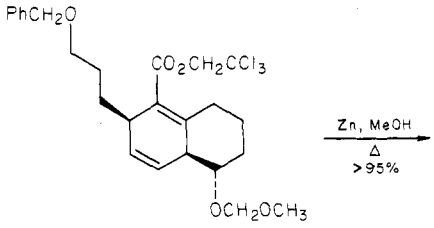
32 33

structure of which had been assigned previously by a combination of chemical and spectroscopic methods.[5] In particular, the diagnostic signal of C-5 H for **30** appears as a doublet, J = 3 Hz. The multiplicity of this signal is consistent only with structures in which an axial carbomethoxyl group is flanked by a pseudoxial alkyl group at C-6.[5] The stereochemistry of one of the minor products, **31**, was assigned by comparison with the NMR data for ester **33**. The ^1H NMR resonance for C-5 H of **31** appears as a doublet of doublets, J = 5, 10 Hz, which indicates that C-5 H occupies an axial position and is flanked by an axial C-4a H and a pseudoequatorial C-6 H.[5] The ratio of trans-fused products **30** and **31** was determined to be approximately 5:1 by integration of the ^1H NMR resonances for C-5 H of the two isomers.

Since it appeared that the one-step reductive alkylation was not going to be straightforward, we decided to execute this conversion in two separate steps. The crude mixture of acids obtained from the Li, NH_3 reduction of **29** was esterified with CH_2N_2 to afford a mixture of esters **30** and **31**, estimated to be approximately 5:1 by 250-MHz ^1H NMR, in 81% yield. Attempts to alkylate this mixture, however, with CH_3I under a variety of conditions (LDA, THF, −78 → 0 °C; LDA, THF, HMPT, −78 → 23 °C; $KN(Me_3Si)_2$,[28] THF, −78 °C; $KN(Me_3Si)_2$, THF, HMPT, −78 → 0 °C; KO-*t*-Bu, *t*-BuOH, THF, reflux; KH,[28] THF, reflux) afforded no detectable amounts of alkylated products (<5%). It was apparent from these results that **30** and **31** were recalcitrant with respect to alkylation, but the reasons for this unexpected behavior were not yet clear. Because we were working with a mixture of diastereomers, we could not rule out the possibility that impurities in these mixtures were responsible for our inability to effect this transformation. We therefore turned to an examination of cycloadduct **24** which was available in isomerically pure form by the sequence outlined in Schemes II and IV.

Cycloadduct **24** was deprotected by treatment with Zn dust in refluxing methanol to afford the highly viscous acid **34** in greater than 95% yield. Addition of a THF solution of acid **34** to a solution of excess lithium in anhydrous ammonia followed by addition of solid NH_4Cl at −78 °C[29] afforded, almost exclusively, a mixture of trans-fused hydroxy acids, **35** and **36**. The crude reaction product was treated with excess ethereal diazomethane and then with *tert*-butyldimethylsilyl chloride and imidazole in DMF[13] in order to protect the side-chain hydroxyl group. Careful chromatography of this mixture afforded *trans*-perhydronaphthalenes **37** and **38** in 71% and 15% yields, respectively, along with approximately 5% of products tentatively assigned cis-ring fusions. The assignment of stereochemistry to **37** and **38** was again based upon ^1H

(24) Dean, P. D. G. *J. Chem. Soc.* **1965**, 6655. For a review of related methods, see McMurray, J. *Org. React.* **1976**, *24*, 187.
(25) (a) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555. (b) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852.
(26) Just, G.; Grozinger, K. *Synthesis* **1976**, 457.
(27) Larchevêque, M. *Ann. Chim. (Paris)* **1970**, Ser. 14, *5*, 129.
(28) For the preparation of $KN(TMS)_2$, see Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.
(29) Watt, D. S.; McKenna, J. M.; Spencer, T. A. *J. Org. Chem.* **1967**, *32*, 2674. Quenching the reaction mixture with solid NH_4Cl at −78 °C provided the best conditions to prevent overreduction.



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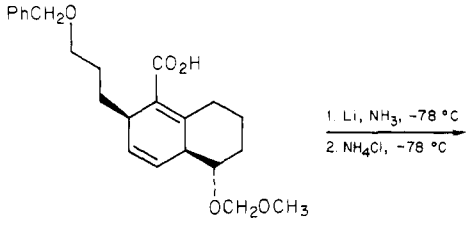
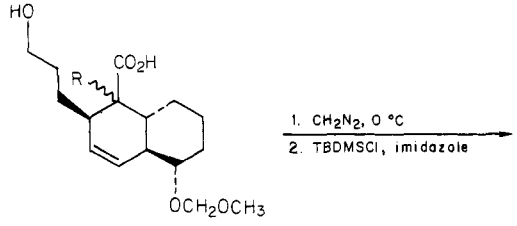
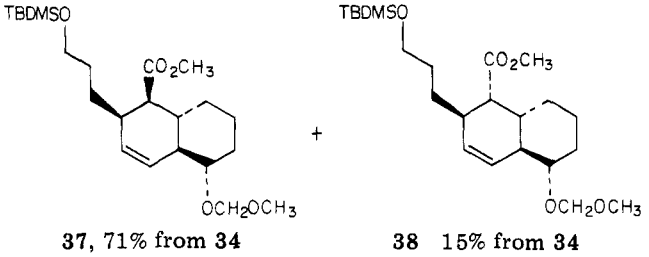


34

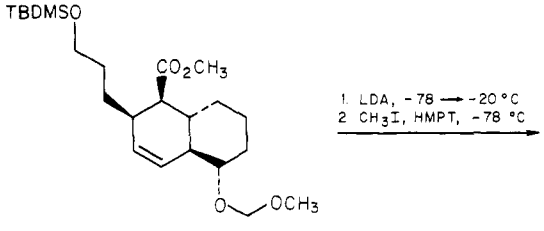


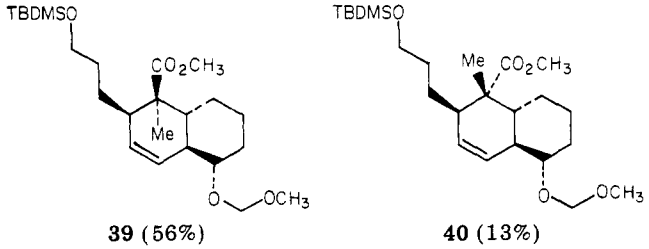
35, R = α-H
36, R = β-H



37, 71% from 34 38 15% from 34
plus 5% cis-fused products

NMR spectroscopy. The diagnostic resonance for C-5 H of the major product **37** appeared as a doublet of doublets, J = 7, 11 Hz. The corresponding resonance in minor product **38** appeared as a doublet, J = 3.3 Hz.



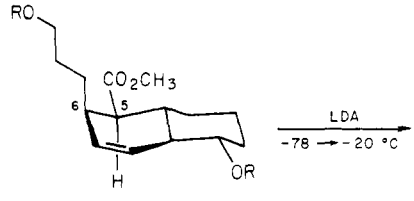


39 (56%) 40 (13%)

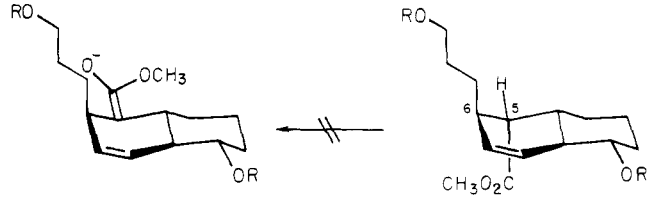
It is clear from these results that the stereoselectivity of the enolate protonation step in the workup of the dissolving metal reduction of **34** is completely reversed from that of the reduction of **29** (5:1 (**37**/**38**) from **34** vs. 1:5 (**31**/**30**) from **29**). *This change in selectivity, which initially we regarded as a curious result, proved ultimately to be crucial to the success of the synthetic scheme (vide infra).*

With pure **37** and **38** in hand, we next examined the alkylation reactions of these epimeric esters. Treatment of silyl ester **37** with lithium diisopropylamide in THF–HMPT at −78 °C with warming to −20 °C followed by addition of excess methyl iodide at −78 °C afforded a mixture of two methylated products, **39** and **40**, in 56% and 13% yield, respectively. That **39** was the desired product was suggested by the similarities of the ^{1}H NMR spectra of **39** and **41**,[4a] a degradation product of chlorothricin. This assignment was confirmed by the eventual synthesis of **41** from **39** (Scheme VI). Attempts to alkylate **38**, on the other hand, were unsuccessful. When **38** was subjected to conditions similar to those described above (enolate solution warmed to −5 °C instead of −20 °C), only traces (<5%) of alkylated products were obtained along with starting material and a considerable amount of decomposition products.

The behavior of **38** under these conditions parallels the behavior previously noted for the mixtures of **30** and **31**. In retrospect, we suspect that the failure to alkylate **38** (and **30**) is a consequence of the stereochemistry of C-5 H in these intermediates. In **37**, C-5 H occupies a relatively unhindered axial orientation, whereas C-5 H in **38** (and **30**), although equatorial, is hindered by the pseudoaxial alkyl chain at C-6. It is likely that the latter group inhibits the approach of bulky dialkylamide bases to C-5 H, thereby retarding the rate of deprotonation. Although deprotonation appeared to occur to some extent at −5 °C, the enolate decomposed under these conditions and only traces of alkylation products were obtained.



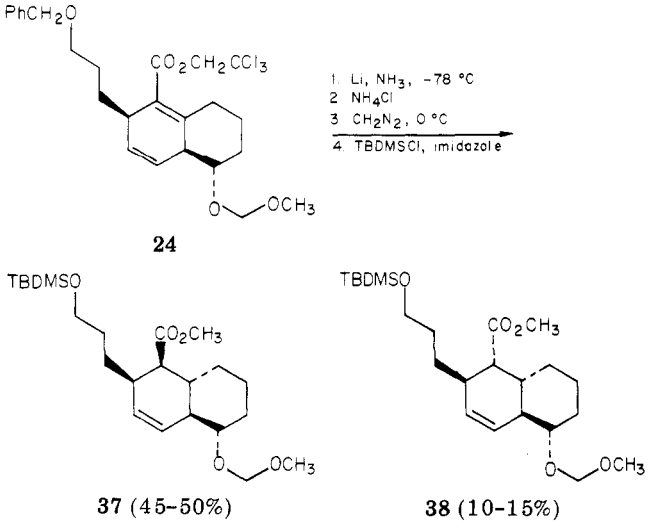
37



38

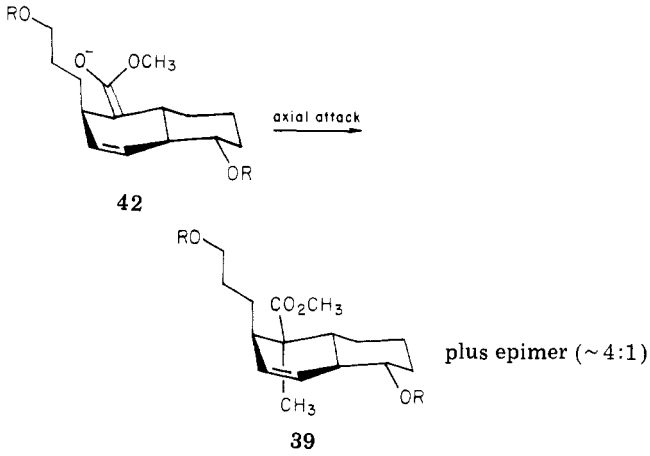
Our inability to alkylate **38** prompted us to investigate the dissolving metal reduction of **34** in detail in order to attempt to suppress the formation of **38**. Although the reaction temperature did not affect the ratio of **37**/**38**, the amount of cis-fused products was minimized by conducting the reaction at −78 °C (approximately 10% of cis-fused products were obtained at −33 °C, vs. approximately 5% at −78 °C). The use of sodium instead of lithium or addition of proton sources such as t-BuOH during the reduction were clearly detrimental since the ratio of **37**/**38** became nearly 1:1 under these conditions, and the amount of cis-fused products increased slightly. A variety of protonation conditions were examined with no dramatic changes in the ratio of products. It did, however, seem beneficial to conduct the protonation at −78 °C by the addition of solid NH_4Cl at this temperature.[29] All things considered, the conditions cited originally proved to give the most favorable ratio of **37**/**38**.

An interesting result which derives from this study is that trichloroethyl ester **24** can be used directly in the dissolving metal reduction without prior deprotection. Although the yield of **37** is only 45–50% compared to 67%



when the deprotection and reduction steps are conducted separately, it is noteworthy that two deprotection steps and a double bond reduction can be performed in a single synthetic operation.

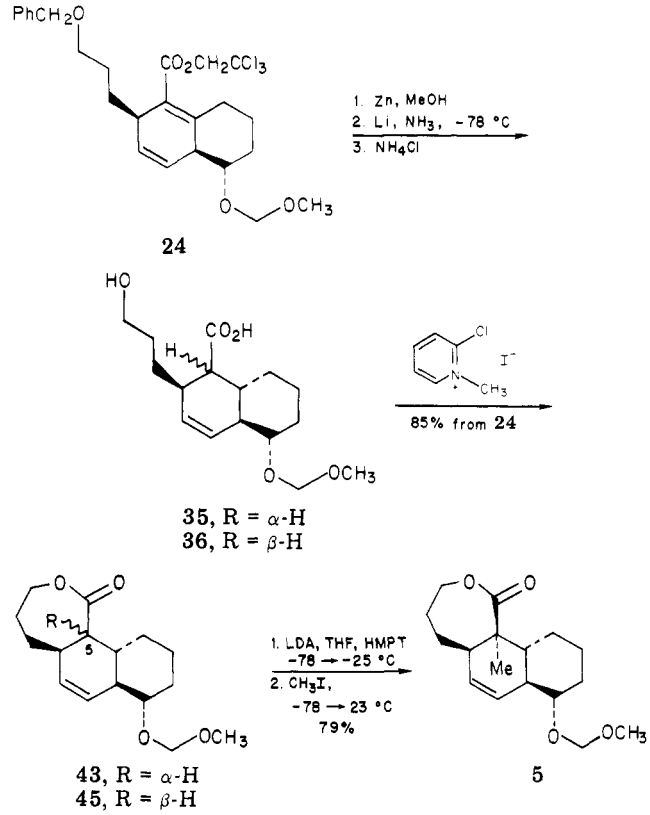
We next turned to the problem posed by the modest stereoselectivity (4:1) realized in the alkylation of **37**. That alkylation of the enolate of **37** had occurred preferentially by axial approach of methyl iodide was attributed to a steric interaction between the pseudoaxial C-6 side chain of enolate **42** and methyl iodide in the equatorial alkylation



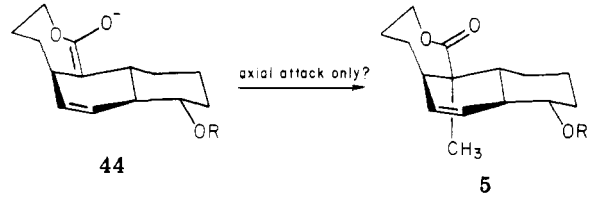
transition state. In the absence of such interactions one would expect the equatorial alkylation mode to predominate.[30]

It was anticipated that the selectivity of the alkylation step could be increased by using lactone **43** as a substrate. Assuming that the lactone enolate **44** retains the cyclohexene half-chair conformation adopted by **43**, one expects that the transition state for the equatorial alkylation should be substantially destabilized relative to the axial mode. As bonding begins to develop, the acyl carbon must

Scheme V



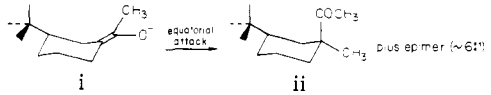
begin to move into an axial position. Substantial strain must develop for the product, if one were to form from this transition state, would contain a seven-membered ring diaxially fused to a six-membered ring.



The feasibility of this plan was quickly verified. Hydrolysis of **37** to the corresponding hydroxy acid **35** followed by treatment of **35** with 2-chloro-*N*-methylpyridinium iodide (Mukaiyama's salt)[31] afforded lactone **43** in 81% yield. Treatment of **43** with excess LDA in THF (−78 → −25 °C) followed by excess methyl iodide afforded the target lactone **5** *as the sole product of alkylation* in 75% yield. The stereochemistry of **5** was confirmed as described in a subsequent paragraph. The only problem which now remained was the development of a direct preparation of **5** from **24** (Scheme V).

The unseparated 5:1 mixture of hydroxy acids **35** and **36**, obtained from the dissolving metal reduction of **34**, was treated with 2-chloro-*N*-methylpyridinium iodide[31] in CH_2Cl_2 to give a 6:1 mixture of lactones **43** and **45** in 85% yield. Whereas hydroxy acid **35** can lactonize via a relatively strain-free transition state, **36** can not lactonize from its preferred conformation which is one in which the C-5 acyl and C-6 hydroxypropyl groups occupy axial and pseudoaxial orientations, respectively, on a half-chair cyclohexenyl ring (vide supra). Thus, **36** must adopt a half-boat (or twist-boat) conformation *prior* to lactonization. The barrier to conformational interconversion of

(30) House, H. O.; Bare, T. M. *J. Org. Chem.* **1968**, *33*, 943. See, for example, the case shown below.

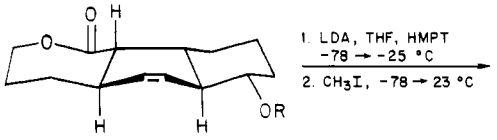


(31) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

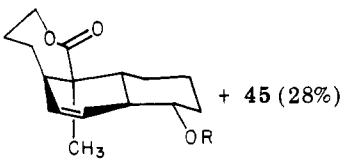
cyclohexenes is quite low, however, and so **36** lactonized readily.[32]

A sample of **45** was purified by chromatography and recrystallization of mixtures of **43** and **45**. The ^1H NMR data for C-5 H of **45** (t, J = 7.3 Hz) is consistent with a twist-boat conformation for the cyclohexenyl ring. The relatively unhindered nature of C-5 H in this ring system suggested that **45** might not be subject to the problems which plagued the attempts to alkylate **30** and **38** (vide supra).

Indeed, treatment of **45** with LDA and then CH_3I under the conditions successfully applied to **43** afforded lactone **5** in 31% yield; 28% of **45** was also recovered. Although the alkylation of **45** proceeded in somewhat lower yield than the alkylation of **43**, separation of these isomers prior to alkylation became unnecessary.



45



+ **45** (28%)

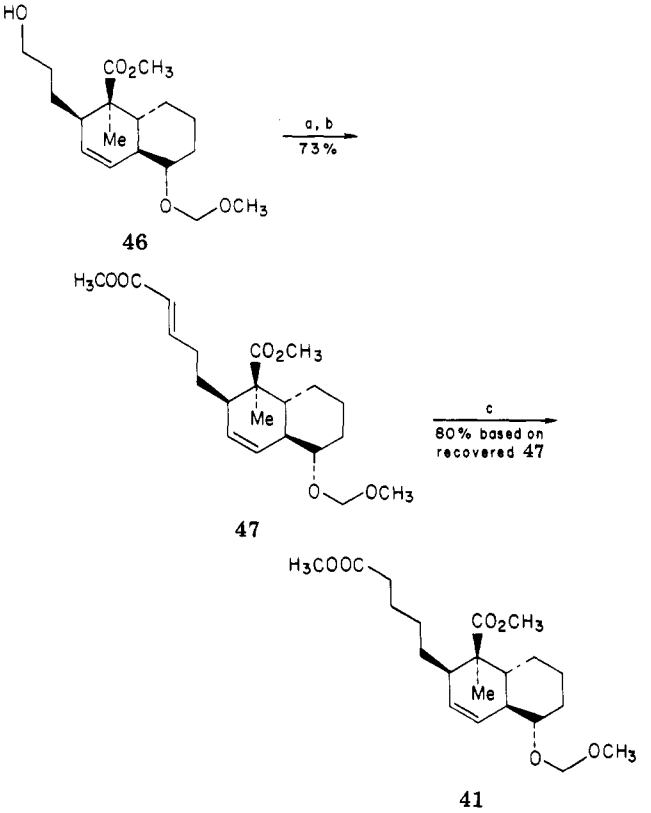
5 (31%)

The successful completion of the synthesis of **5** is summarized in Scheme V. Thus, lactonization of a mixture of **35** and **36** afforded a mixture of **43** and **45** (85% yield) which, without separation, was transformed into **5** in 79% yield. The overall yield of **5** from 4-(benzyloxy)butyraldehyde, **9**, was 15% for the 14-step sequence.

The stereochemistry of **5** was established unambiguously by correlation with a degradation product of natural chlorothricolide (Scheme VI). Thus, transesterification of **5** with sodium methoxide in methanol afforded hydroxy ester **46** in 86% yield. This compound was also prepared by desilylation of **39** (n-Bu_4NF, THF, 23 °C, 96% yield). Collins oxidation[33] of **46** afforded the expected aldehyde which was treated with (carbomethoxymethylene)triphenylphosphorane[34] to give unsaturated ester **47** in 73% yield (from **46**). Selective reduction of the less hindered double bond of **47** using Wilkinson's catalyst[35] afforded synthetic **41**[4a] which was identical in all respects with the exception of optical rotation to a naturally derived sample kindly provided by Professor R. E. Ireland.

Future Studies. Current research efforts include the development of methods to increase the stereoselection in the Diels–Alder reaction of **13**[36] and also the development

Scheme VI[a]



[a] (a) CrO_3, pyridine; (b) $(C_6H_5)_3P{=}CHCOOCH_3$, 23 °C (73% from **46**); (c) $[(C_6H_5)_3P]_3RhCl$ (0.2 equiv), H_2, C_6H_6, 23 °C, 6 h.

of an efficient, stereoselective synthesis of the top half of chlorothricolide. The results of these studies will be reported in due course.

Experimental Section

^1H NMR spectra were measured at 250- and 270-MHz on Bruker 250 and 270 instruments. Chemical shifts are reported in δ units relative to internal Me_4Si. Infrared spectra were measured on a Perkin-Elmer Model 283B infrared spectrophotometer and were calibrated with the 1601-cm^{-1} absorbtion of polystyrene. Mass spectra were measured at 70 eV on a Varian MAT 44 instrument. High-resolution mass spectra were provided by the Facility supported by NIH Grant RR0317 (principal investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources, and were obtained on a CEC 21-110B high-resolution mass spectrometer equipped with a PDP-1145 based computer system to process data recorded on photographic plates. Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ. Melting points were recorded on a Fisher-Johns hot stage melting point apparatus and are uncorrected.

All reactions were conducted in oven-dried (120 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use: ether, THF, and DME were distilled from sodium benzophenone ketyl; CH_2Cl_2 and Me_2SO were distilled from CaH_2; toluene was distilled from sodium metal. Preparative thin-layer chromatography (TLC) was performed with 20 × 20 cm plates coated with 0.5- and 2-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Unless indicated otherwise, compounds were eluted from the adsorbents with ether. Column chromatography was performed with activity 1 Woelm silica gel. Flash chromatography was performed as described by Still.[37] All chromatography solvents were distilled prior to use.

(*E*,*E*)-8-(Benzyloxy)-2,4-octadienal (10). A solution of 7.25 g of 1-methoxy-1-buten-3-yne (88.3 mmol) in 100 mL of dry THF

(32) Benard, M.; St.-Jaques, M. *Tetrahedron* **1973**, *29*, 2539 and references cited therein.

(33) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

(34) House, H. O.; Jones, V. K.; Frank, G. A. *J. Org. Chem.* **1964**, *29*, 3327.

(35) Young, J. F.; Osborn, J. A.; Jordine, F. H.; Wilkinson, G. *J. Chem. Soc., Chem. Commun.* **1965**, 131. For a review of this and other homogeneous hydrogenation catalysts, see Birch, A. J.; Williamson, D. H. *Org. React.* **1976**, *24*, 1.

(36) It is readily apparent that the minor cycladduct **22** could be converted into the bottom half of chlorothricolide (racemic!) by inversion of the stereocenter at C-1 at an appropriate stage. This option was not pursued, however, since this strategy can not be utilized in our planned synthesis of optically active lactone **5**. If the ultimate transfer of chirality in a synthesis of **5** originates in a synthesis of chiral **13**, it is clear that **22** is a useless byproduct: epimerization of C-1 of chiral **22** or of intermediates derivable therefrom would lead to the *enantiomers* of the intermediates derived from chiral **21**.

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

was cooled to −78 °C. To this solution was added dropwise over 20 min 42.0 mL of 2.4 M *n*-butyllithium in hexane. A white precipitate formed after ~75% of the butyllithium had been added, so an additional 20 mL of THF was added. This mixture was stirred at −78 °C for 40 min before being warmed to 0 °C (ice bath). At this point, the precipitate dissolved to form a dark-brown solution. To this solution was added a mixture of 12.3 g of 4-(benzyloxy)butyraldehyde[8] (**9**; 73.5 mmol) in 25 mL of THF. The ice bath was removed and the reaction mixture was allowed to warm to 23 °C over 2 h. The solution was cooled to 0 °C and was then treated sequentially with 3.11 mL of absolute ethanol (49.8 mmol) and a slurry of 2.33 g of $LiAlH_4$ (62.2 mmol) in 35 mL of THF. The reaction mixture was then allowed to warm to 23 °C. After being stirred for 2 h at 23 °C, the reaction mixture was cooled in an ice bath, and 2.3 mL of H_2O, 2.3 mL of 15% aqueous NaOH, and 6.9 mL of H_2O were added sequentially. This caused the formation of a tan precipitate, which was removed by vacuum filtration. To the filtrate was added 40 mL of 1 N HCl, 60 mL of H_2O, 20 mL of MeOH, and 100 mL of THF. This two-phase mixture was vigorously stirred for 45 min. This reaction mixture was then poured into a separatory funnel containing 400 mL of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with two 200-mL portions of ether. The combined organic extracts were dried over Na_2SO_4 and $NaHCO_3$, filtered, and concentrated in vacuo to give 16.4 g of crude diene aldehyde. This compound was routinely used in the next step without purification. A sample from a small-scale run was chromatographed to give diene aldehyde **10** in 74% yield: NMR ($CDCl_3$) δ 9.53 (d, J = 8 Hz, 1 H), 7.33 (m, 5 H), 7.06 (m, 1 H), 6.29 (m, 2 H), 6.06 (dd, J = 15.4, 8 Hz, =CHCHO), 4.50 (s, 2 H), 3.49 (t, J = 6.2 Hz, 2 H), 2.32 (m, 2 H, allylic CH_2), 1.78 (quint, J = 6.3 Hz, 2 H); IR (neat) 3025, 2735, 1675, 1630, 1595 cm^{-1}; mass spectrum, m/e 230 (parent ion); high-resolution mass spectrum calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1289. Diene aldehyde **10** was further characterized as the semicarbazone, which was recrystallized three times from 50% aqueous EtOH, mp 147.5–149 °C. Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 67.03; H, 7.11; N, 14.57.

(*E*,*E*)-1-(Benzyloxy)-8-hydroxy-4,6-tridecadien-12-yne (11). To a vigorously stirred mixture of 3.14 g of Mg turnings (129 mmol) in 170 mL of dry THF was added a small crystal of I_2. The mixture was heated to reflux and when the I_2 color dissipated a solution of 12.1 g of (5-bromo-1-pentyn-1-yl)trimethylsilane[11] (55.4 mmol) in 140 mL of dry THF was added dropwise. On this scale, the addition required 2 h. The mixture was refluxed for an additional 25 min after the addition was complete. The Grignard reagent was then cooled to 0 °C and a solution of 8.45 g of crude diene aldehyde **10** (36.7 mmol) in 20 mL of dry THF was added. The resulting solution was stirred for 30 min (0 → 23 °C) before being quenched with 1 mL of MeOH. The reaction mixture was poured through a glass wool plug into a separatory funnel containing 200 mL each of ether and saturated aqueous NH_4Cl. The ether layer was washed once with 200 mL of saturated aqueous NH_4Cl. The combined aqueous extracts were then washed with two 150-mL portions of ether. The combined ether extracts were concentrated in vacuo, dissolved in CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 14.1 g of a semiviscous oil. Another experiment, performed on a similar scale, yielded 13.7 g of crude product from 7.43 g of starting aldehyde **10**. These two samples were combined and taken on to the next step without further purification.

To a chilled solution (cold water bath) of 30.1 g of $KF{\cdot}2H_2O$ (320 mmol) in 100 mL of distilled H_2O and 200 mL of DMF was added a solution of 27.8 g of crude Grignard product in 200 mL of DMF.[12] Two phases separated, so an additional 200 mL of DMF was added. The resulting mixture was stirred vigorously at 23 °C. After being stirred for 39 h, the reaction mixture was poured into a separatory funnel containing 2.5 L of distilled H_2O and 1 L of 1:1 hexane–ether. The aqueous phase was washed with three 1-L portions of 1:1 hexane–ether. The combined organic layers were concentrated in vacuo, dissolved in CH_2Cl_2, filtered through a cotton plug, and concentrated in vacuo to give 23.2 g of crude alcohol **11**. The crude product was purified by chromatography on 645 g of silica gel, using 3:1 hexane–ether as eluant for fractions 1–41 and then 5:3 hexane–ether for the remaining fractions; 100-mL fractions were collected. Fractions 44–59 were combined and concentrated in vacuo to give 13.8 g of alcohol **11** (65% overall yield from **9**): NMR ($CDCl_3$) δ 7.31 (m, 5 H), 6.08 (m, 2 H, H_6 + H_5), 5.67 (dt, J = 14.3, 7 Hz, H_4), 5.55 (dd, J = 15.1, 7 Hz, H_7), 4.48 (s, 2 H), 4.13 (br q, J = 6.3 Hz, CH(OH)), 3.46 (t, J = 6.3 Hz, CH_2OBzl), 2.18 (m, 4 H), 1.94 (t, J = 1.6 Hz, H_{13}); IR (neat) 3400, 3280, 3015, 2107, 1675, 1658, 1635 cm^{-1}; mass spectrum, m/e 207 (M − C_7H_7); high-resolution mass spectrum calcd for $C_{13}H_{19}O_2$ 207.1385, found 207.1368. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.42; H, 8.71.

(*E*,*E*)-1-(Benzyloxy)-8-[(*tert*-butyldimethylsilyl)oxy]-4,6-tridecadien-12-yne (12). To a solution of 13.2 g of **11** (44.2 mmol) in 60 mL of dry DMF was added 10.8 g of *tert*-butyldimethylsilyl chloride (66.3 mmol) and 9.49 g of imidazole (140 mmol).[13] This solution was stirred for 53 h at 23 °C. The reaction mixture was poured into a separatory funnel containing 400 mL of H_2O and 400 mL of 4:1 hexane–ether. The aqueous layer was washed once with 400 mL of 4:1 hexane–ether and then with five 300-mL portions of 3:1 hexane–ether. The combined organic extracts were dried over Na_2SO_4 and Na_2CO_3, filtered and concentrated in vacuo to afford 18.4 g of crude **12**. This crude product was routinely taken directly to the next step without purification. A small sample (68 mg) was chromatographed on a 0.5-mm silica gel plate, using 6:1 hexane–ether as eluant, to afford 66.4 mg (98%) of **12**: NMR ($CDCl_3$) δ 7.32 (m, 5 H), 6.03 (m, 2 H), 5.60 (dt, J = 14.3, 7 Hz, H_4), 5.49 (dd, J = 14.3, 6.6 Hz, H_7), 4.48 (s, 2 H), 4.12 (m, 1 H, CH(OH)), 3.46 (t, J = 6.4 Hz, 2 H), 2.15 (m, 4 H), 1.92 (t, J = 1.6 Hz, H_{13}), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H); IR (neat) 3310, 3022, 2115, 1657 cm^{-1}; mass spectrum, m/e 412 (parent ion); high resolution mass spectrum calcd for $C_{26}H_{40}O_2Si$ 412.2798, found 412.2795.

2,2,2-Trichloroethyl (*E*,*E*)-14-(Benzyloxy)-7-[(*tert*-butyldimethylsilyl)oxy)]-8,10-tetradecadien-2-ynoate (13). A solution of 18.2 g of crude silyl ether **12** (43.8 mmol) in 250 mL of dry THF was cooled to −78 °C. To this solution was added 23.5 mL of a 2.4 M *n*-butyllithium solution in hexane (57.0 mmol) over 30 min. This solution was stirred at −78 °C for 30 min and then 12.1 mL of 2,2,2-trichloroethyl chloroformate (87.6 mmol) was added. After an additional 55 min at −78 °C, the solution was allowed to warm to 0 °C and then was quenched with 150 mL of saturated aqueous $NaHCO_3$. This two-phase mixture was stirred for 2 h at 23 °C and poured into a separatory funnel containing 200 mL of CH_2Cl_2 and 100 mL of H_2O. The aqueous layer was washed twice with 150 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 30.0 g of crude ester **13**. Purification of ester **13** was effected by chromatography on 600 g of silica gel, using 10:1 hexane–ether as eluant. Rechromatography of mixed fractions gave 20.0 g of pure **13** (79% from **11**): NMR ($CDCl_3$) δ 7.32 (m, 5 H), 6.03 (m, 2 H, H_9 + H_{10}), 5.63 (dt, J = 14.3, 7.2 Hz, H_{11}), 5.47 (dd, J = 14.7, 6.6 Hz, H_8), 4.78 (s, 2 H), 4.48 (s, 2 H), 4.14 (m, 1 H, CH(OH)), 3.46 (t, J = 6.4 Hz, 2 H), 2.37 (t, J = 6.3 Hz, 2 H), 2.16 (q, J = 7.3 Hz, 2 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H); IR (neat) 3025, 2240, 1728, 1658 cm^{-1}; mass spectrum, m/e 571 (M − CH_3); high-resolution mass spectrum calcd for $C_{29}H_{41}Cl_3O_4Si$ 586.1840, found 586.1839. Anal. Calcd for $C_{29}H_{41}Cl_3O_4Si$: C, 59.23; H, 7.03. Found: C, 59.28; H, 7.01.

Cyclization of 13. 2,2,2-Trichloroethyl 6β-[3-(Benzyloxy)prop-1-yl]-1α-hydroxy-1,2,3,4,6,8aα-hexahydronaphthalene-5-carboxylate (23) and 2,2,2-Trichloroethyl 6β-[3-(Benzyloxy)prop-1-yl]-1β-[(*tert*-butyldimethylsilyl)oxy]-1,2,3,4,6,8aα-hexahydronaphthalene-5-carboxylate (22). A solution of 10.0 g of ester **13** in 55 mL of dry toluene was added to a resealable Carius tube and was purged with dry Ar for 40 min. The tube was then sealed and heated in a 160 °C oil bath for 61 h. The cooled tube was opened and then all volatile components were removed in vacuo to give 9.83 g of a mixture of two epimeric silyl ethers, **21** and **22**. This mixture was dissolved in 66 mL of THF and 90 mL of MeOH. The resulting solution was purged with Ar, cooled to 10 °C, and then 13 mL of 1 N aqueous HCl was slowly added. The mixture was allowed to warm to 23 °C and was stirred vigorously for 10 h. In another run, 9.40 g of the crude mixture of **21** and **22** (15.8 mmol; obtained from a cyclization of 9.26 g of **13**) was treated in the same manner. These two reaction mixtures were combined and poured into a separatory funnel containing 400 mL of saturated aqueous $NaHCO_3$ and 200 mL of CH_2Cl_2. The aqueous layer was extracted

with three 200-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2CO_3 and concentrated in vacuo to give 19.4 g of a mixture of alcohol **23** and silyl ether **22**. This mixture was easily separated in a single chromatographic run with a Waters Prep 500 LC, using 4:1 hexane–ether as eluant. This afforded 9.81 g (61%) of **23** and 7.12 g of recovered **22** (36%). A small sample of **22** (289 mg) was purified by preparative TLC on a 1.5-mm silica gel plate, using 5% ether–hexane as eluant, affording 214 mg of pure **22**.

Data for **23**: NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.97 (ddd, J = 9.3, 3.7, 1.1 Hz, H_8), 5.75 (ddd, J = 9.3, 3.7, 1.1 Hz, H_7), 4.81 (d, J_{AB} = 12 Hz, 1 H), 4.67 (d, J_{AB} = 12 Hz, 1 H), 4.44 (s, 2 H), 3.40 (m, 4 H, H_{8a}, CH_2OBzl, CH(OH)), 3.08 (br d, J = 12.9 Hz, 1 H), 2.58 (m, H_5); IR (CCl_4) 3618, 3030, 1730, 1630 cm^{-1}; mass spectrum, m/e 454, 456 (M – H_2O). Anal. Calcd for $C_{23}H_{27}Cl_3O_4$: C, 58.30; H, 5.74; Cl, 22.45. Found: C, 58.25; H, 5.61; Cl, 21.97.

Data for **22**: NMR ($CDCl_3$) δ 7.29 (m, 5 H), 5.81 (ddd, J = 10.0, 3.7, 1.5 Hz, 1 H) 5.42 (ddd, J = 10.0, 3.0, 1.5 Hz, 1 H), 4.82 (d, J_{AB} = 12 Hz, 1 H), 4.69 (d, J_{AB} = 12 Hz, 1 H), 4.44 (s, 2 H, CH_2Ph), 4.08 (br s, H_1), 3.39 (t, J = 6.4 Hz, OCH_2), 3.18 (m, 2 H), 2.75 (m, 1 H), 0.81 (s, 9 H, t-Bu), 0.00 (s, 3 H), –0.02 (s, 3 H); IR (CCl_4) 3022, 1730, 1635 cm^{-1}; mass spectrum, m/e 529, 531 (M – t-Bu); high-resolution mass spectrum calcd for $C_{25}H_{32}{}^{35}Cl_3O_4Si$ (M – t-Bu) 529.1136, found 529.1153. Anal. Calcd for $C_{29}H_{41}Cl_3O_4Si$: C, 59.23; H, 7.03. Found: C, 59.25; H, 7.09.

2,2,2-Trichloroethyl 6β-[3-(Benzyloxy)prop-1-yl]-1α-[(methoxymethyl)oxy]-1,2,3,4,6,8aα-hexahydronaphthalene-5-carboxylate (24). To a stirred solution of 9.45 g of alcohol **23** (20.0 mmol), 11 mL of dry diisopropylethylamine (61.8 mmol), and 100 mL of dry CH_2Cl_2 was added 4.45 mL of chloromethyl methyl ether (58.6 mmol). This mixture was stirred at 23 °C for 15 h and was then poured into a separatory funnel containing 100 mL of ether and 100 mL of 0.3 N aqueous HCl. The organic layer was washed once with 100 mL of 0.3 N HCl. The combined aqueous extracts were washed with two 100-mL portions of ether. The combined organic extracts were dried over Na_2SO_4 and $NaHCO_3$, filtered, and concentrated in vacuo to give 8.57 g of crude **24** (83%). This material was purified by chromatography on a Waters Prep 500. In this manner, 6.25 g of pure **24** (60%) along with 1.17 g of mixed fractions containing **24** were obtained. Rechromatography of this mixture afforded an additional 1.03 g (10%) of **24**.

Data for **24**: NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.94 (ddd, J = 10.3, 3.3, 1.1 Hz, H_8), 5.71 (ddd, J = 10.3, 3.7, 1.1 Hz, H_7), 4.81 (d, J_{AB} = 12 Hz, 1 H), 4.71 (d, J_{AB} = 7 Hz, 1 H), 4.69 (d, J_{AB} = 12 Hz, 1 H, CH_2CCl_3), 4.61 (d, J_{AB} = 7 Hz, 1 H, OCH_2O), 4.44 (s, CH_2Ph), 3.38 (m, 5 H, CH_2OBzl, OCH_3), 3.25 (dt, J = 4.7, 10.3 Hz, H_1), 3.08 (br d, 1 H), 2.68 (m, H_6), 2.19 (m, 1 H), 1.89 (m, 1 H); IR (neat) 3033, 1730, 1638 cm^{-1}; mass spectrum, m/e 484, 486 (M – MeOH); high-resolution mass spectrum calcd for $C_{24}H_{27}{}^{35}Cl_3O_4$ (M – MeOH) 484.0975, found 484.0984. Anal. Calcd for $C_{25}H_{31}Cl_3O_5$: C, 57.98; H, 6.03; Cl, 20.54. Found: C, 58.25; H, 6.05; Cl, 21.22.

6β-[3-(Benzyloxy)prop-1-yl]-1α-[(methoxymethyl)oxy]-1,2,3,4,6,8aα-hexahydronaphthalene-5-carboxylic Acid (34). A solution of 2.81 g of ester **24** (5.42 mmol) in 80 mL of reagent grade MeOH was purged with a stream of dry N_2 for 25 min. To this stirred solution was added 3.79 g of Zn dust (58.0 mmol). The mixture was then heated to reflux for 2 h. The reaction mixture was cooled and filtered to remove the spent reagent. The filtrate was concentrated in vacuo to afford 3.09 g of crude acid **34**, which was purified by flash chromatography (40-mm column), using 1:1 ether–hexane containing 0.5% HOAc as eluant. This gave 2.01 g of highly viscous **34** (96%) and 0.12 g (4%) of a compound which was tentatively assigned the structure of the dichloroethyl ester analogue of **24**.

Data for **34**: NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.93 (dd, J = 10.3, 2.6 Hz, H_8), 5.73 (dd, J = 10.3, 2.7 Hz, H_7), 4.72 (d, J_{AB} = 6.5 Hz, 1 H), 4.62 (d, J_{AB} = 6.5 Hz, 1 H), 4.46 (s, CH_2Ph), 3.43 (t, J = 5 Hz, CH_2OBzl), 3.34 (s, OCH_3), 3.25 (m, 2 H), 2.67 (m, H_6), 2.17 (m, 1 H), 1.89 (m, 1 H); IR (CCl_4) 3032, 3400–2500, 1695, 1638 cm^{-1}; mass spectrum, m/e 386 (parent ion); high-resolution mass spectrum calcd for $C_{23}H_{30}O_5$ 386.2093, found 386.2106. Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.32; H, 7.59.

6β-(3-Hydroxyprop-1-yl)-1α-[(methoxymethyl)oxy]-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylic Acid (35) and 6β-(3-Hydroxyprop-1-yl)-1α-[(methoxymethyl)oxy]-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5α-carboxylic Acid (36). Several small pieces of sodium metal and several milligrams of $FeCl_3$ were added to a 1-L flame-dried flask fitted with a dry-ice condenser. Approximately 500 mL of NH_3 was condensed into this flask. Then approximately 400 mL of ammonia was distilled from the resulting $NaNH_2$ solution into a reaction vessel which contained 0.21 g of Li wire (30 mmol). The resulting deep-blue solution was then cooled to –75 °C, and a solution of 2.01 g of acid **34** (5.21 mmol) in 50 mL of dry THF was added dropwise. On this scale the addition required 30 min. Residual acid **34** was rinsed into the reaction mixture with an additional 25 mL of dry THF, which was added dropwise over a period of 10 min. After the addition was complete, the reaction mixture was stirred for 30 min at –75 °C. Then 125 mL of dry THF was added over a period of 10 min. To this vigorously stirred solution was added 4.7 g of NH_4Cl (88 mmol) in one portion. The blue color dissipated in ~90 s and the colorless mixture was allowed to warm to room temperature with removal of NH_3 by distillation. Saturated aqueous NH_4Cl (50 mL) was then added, followed by 100 mL of ether. The aqueous layer was acidified to pH 3 by the addition of 170 mL of 1 N HCl and 20 mL of 2 N HCl and was extracted with three additional 150-mL portions of ether. The combined ether extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 1.57 g (100%) of a semicrystalline mixture of acids **35**/**36** (~5:1). This mixture was routinely used in subsequent transformations without purification. A pure sample of the major product, acid **35**, was obtained by recrystallization of the above mixture from hexane–EtOAc: mp 148–149.5 °C; NMR ($CDCl_3$) δ 5.96 (d, J = 10.3 Hz, 1 H), 5.76 (ddd, J = 2.6, 4.4, 10.3 Hz), 4.79 (d, J_{AB} = 7 Hz, 1 H), 4.64 (d, J_{AB} = 7 Hz, 1 H), 3.62 (m, 2 H), 3.41 (s, 3 H), 3.20 (dt, J = 4.4, 10.3 Hz, H_1), 2.67 (dd, J = 6.0, 11.5 Hz, H_5), 2.48 (m, 1 H), 2.18 (m, 1 H), 2.02 (m, 1 H); IR ($CHCl_3$) 3500–2500 (br), 3040, 1708 cm^{-1}; mass spectrum, m/e 280 (M – H_2O); high-resolution mass spectrum calcd for $C_{16}H_{26}O_5$ 298.1780, found 298.1785. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.80; H, 8.89.

Acid **36** was not purified, but its presence was evident by inspection of the ^1H NMR spectrum of the mixture. Partial ^1H NMR data for **36** (obtained on the 5:1 mixture of **35**/**36**): δ 5.98 (d, J = 10 Hz, 1 H), 5.70 (m, 1 H), 2.55 (d, J = 3 Hz, 1 H, H_5).

Hydroxy acid **35** was also prepared in 68% yield by alkaline hydrolysis (1 N NaOH, CH_3OH, 90 °C; 0.1 N HCl workup) of **37**; 25% of the corresponding hydroxy methyl ester was also obtained.

Methyl 6β-[3-[(*tert*-Butyldimethylsilyl)oxy]prop-1-yl]-1α-[(methoxymethyl)oxy]-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (37) and Methyl 6β-[3-[(*tert*-Butyldimethylsilyl)oxy]prop-1-yl]-1α-[(methoxymethyl)oxy]-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5α-carboxylate (38). Method A. A solution of the crude mixture of hydroxy acids **35** and **36** (from the Li, NH_3 reduction of 60 mg of acid **34**, 0.16 mmol) in 3 mL of anhydrous ether was cooled to 0 °C. An ethereal solution of diazomethane was added dropwise until a yellow color persisted. After being stirred for an additional 5 min, the solution was purged with a stream of Ar to remove excess diazomethane. The solution was concentrated in vacuo to give a mixture of crude hydroxy esters. These compounds, without separation, were converted into the corresponding *tert*-butyldimethylsilyl ethers by treatment with 184 mg of *tert*-butyldimethylsilyl chloride (1.1 mmol) and 108 mg of imidazole (1.6 mmol) in 2 mL of dry DMF (23 °C, 48 h). The reaction mixture was then diluted with 10 mL of H_2O and extracted four times with 10 mL portions of 6:1 hexane–ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give 148 mg of crude silyl ethers **37** and **38**. These compounds were separated by preparative TLC on a 0.5-mm silica gel plate, using 6:1 hexane–ether as eluant, to afford 47 mg (71%) of pure silyl ester **37** and 11 mg (17%) of an 8:1 mixture of silyl ester **38** and a *cis*-fused product.

Data for **37**: NMR ($CDCl_3$) δ 5.91 (d, J = 10.3 Hz, H_8), 5.74 (ddd, J = 2.6, 4.4, 10.3 Hz, H_7), 4.75 (d, J_{AB} = 6.7 Hz, A of AB), 4.61 (d, J_{AB} = 6.7 Hz, B of AB), 3.64 (s, 3 H), 3.53 (m, 2 H), 3.37 (s, 3 H), 3.17 (dt, J = 4.4, 10.3 Hz, H_1), 2.61 (dd, J = 7, 11.4 Hz, H_5), 2.37 (m, H_6, $J_{5,6}$ = 7 Hz, $J_{6,7}$ = 4.4 Hz), 2.13 (m, $H_{2\beta}$, $J_{1,2\beta}$ = 4.4 Hz), 1.89 (br d, 1 H), 0.86 (s, 9 H), 0.01 (s, 6 H); IR (neat) 3025, 1736, 1652 cm^{-1}; mass spectrum, m/e (no parent observed),

369 (M − *t*-Bu); high-resolution mass spectrum calcd for $C_{23}H_{42}O_5Si$ 426.2802, found 426.2797.

Data for **38**: NMR ($CDCl_3$) δ 5.96 (d, J = 10.3 Hz, H_8), 5.67 (ddd, J = 2.5, 3.4, 10.3 Hz, H_7), 4.78 (d, J_{AB} = 7 Hz, A of AB), 4.64 (d, J_{AB} = 7 Hz, B of AB), 3.65 (s, 3 H), 3.62 (dt, J = 1.5, 6.6 Hz, 2 H), 3.40 (s, 3 H), 3.12 (dt, J = 4.5, 9.9 Hz, H_1), 2.51 (d, J = 3.3 Hz, H_5), 2.31 (m, H_6), 2.12 (m, 2 H), 0.89 (s, 9 H), 0.05 (s, 6 H); IR (neat) 3025, 1730, 1651 cm^{-1}; mass spectrum, m/e 396 (M − *t*-Bu).

Method B. This procedure illustrates the dissolving metal reduction of trichloroethyl ester **24**. A solution of 16 mg of lithium wire (2.3 mmol) and 12 mL of dry NH_3 at −78 °C was prepared according to the procedure described above for the preparation of **35** and **36**. To this solution was added dropwise a mixture of 130 mg of **24** (0.25 mmol) in 3 mL of dry THF over 4 min. The solution was stirred for 30 min at −78 °C and then an additional 5 mL of THF was added slowly. Solid NH_4Cl (0.5 g) was then added and the colorless mixture was allowed to warm to room temperature with removal of NH_3 by distillation. (In some experiments the excess Li was quenched by the addition of benzyl methyl ether at −78 °C in lieu of NH_4Cl. The experimental details were otherwise identical with those described here. The yield of pure **37** was 46% in one such experiment.) The reaction mixture was then worked up as described above for the preparation of **35** and **36**. The mixture of crude carboxylic acids was then transformed to **37** and **38**, using the procedure described in method A. Chromatography of the crude product as previously described afforded 45 mg (42%) of pure **37** and 21 mg (20%) of an approximate 5:1:1 mixture of **38**, **37**, and cis-fused products, respectively.

Methyl 6β-[3-[(*tert*-Butyldimethylsilyl)oxy]prop-1-yl]-1α-[(methoxymethyl)oxy]-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (39) and Methyl 6β-[3-[(*tert*-Butyldimethylsilyl)oxy]prop-1-yl]-1α-[(methoxymethyl)oxy]-5β-methyl-1,2,3,4aβ,5,6,8aα-octahydronaphthalene-5α-carboxylate (40). A solution of 0.07 mL of dry diisopropylamine (0.5 mmol) in 2 mL of THF was cooled to −78 °C under argon. To this solution was added 0.19 mL of 2.43 M *n*-BuLi (0.46 mmol) in hexane. The resulting solution was stirred for 30 min at −78 °C, after which a solution of 60 mg of silyl ether **37** (0.14 mmol) in 2 mL of THF was added in a dropwise manner over a period of 1 min. The resulting yellow solution was stirred at −78 °C for 20 min, warmed to −20 °C for 30 min, and then recooled to −78 °C. A solution of 0.1 mL of methyl iodide (1.6 mmol) in 0.8 mL of dry HMPT was added. The resulting solution was stirred at −78 °C for 90 min and then the mixture was allowed to warm to 15 °C over a period of 3 h. The mixture was stored overnight (11 h) at 0 °C and then was quenched by the addition of 0.3 mL of MeOH. The reaction mixture was partitioned between 10 mL of 0.1 N HCl and 10 mL of ether. The aqueous layer was extracted with two 10-mL portions of ether. The combined ether extracts were washed with 10 mL of saturated $Na_2S_2O_3$, dried over Na_2SO_4, and concentrated in vacuo to afford 183 mg of crude product. Purification of this material was effected by preparative TLC, using 10:1 hexane–ether as eluant. This afforded 35 mg of silyl ether **39** (56%), 8 mg of silyl ether **40** (13%), and 10 mg of an unidentified mixture of byproducts (15%).

Data for **39**: NMR ($CDCl_3$) δ 5.87 (d, J = 10.3 Hz, H_8), 5.69 (ddd, J = 2.2, 4.7, 10.3 Hz, H_7), 4.75 (d, J_{AB} = 7 Hz, A of AB), 4.63 (d, J_{AB} = 7 Hz, B of AB), 3.63 (s, 3 H), 3.53 (m, 2 H), 3.37 (s, 3 H), 3.22 (dt, J = 4.4, 10 Hz, H_1), 2.15 (m, 1 H), 1.14 (s, 3 H), 0.86 (s, 9 H), 0.01 (s, 6 H); IR (neat) 3033, 1727, 1656 cm^{-1}; mass spectrum, m/e 440 (parent ion). This compound was further characterized as the hydroxy acid **48** (see procedure for preparation of **5**). Thus, treatment of 11.2 mg of **39** with 1 N NaOH in THF (90 °C, 20 h) afforded 5.6 mg of **48** (68%) and 2 mg of hydroxy ester **46** (25%).

Data for **40**: NMR ($CDCl_3$) δ 5.82 (m, 2 H), 4.74 (d, J_{AB} = 6.8 Hz, A of AB), 4.00 (d, J_{AB} = 6.8 Hz, B of AB), 3.60 (m, 5 H), 3.36 (s, 3 H), 3.08 (dt, J = 4.4, 10.3 Hz, H_1), 2.52 (m, 1 H), 1.14 (s, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H); IR (CCl_4) 3030, 2948, 1729 cm^{-1}; mass spectrum, m/e 383 (parent − *t*-Bu); high-resolution mass spectrum calcd for $C_{24}H_{44}O_5Si$ 440.2958, found 440.2956.

6β-(3-Hydroxyprop-1-yl)-1α-[(methoxymethyl)oxy]-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylic Acid ϵ-Lactone (43) and 6β-(3-Hydroxyprop-1-yl)-1α-(methoxymethyl)oxy]-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5α-carboxylic Acid ϵ-Lactone (45). To a refluxing solution of 3.27 g of 2-chloro-1-methylpyridinium iodide[31] (12.8 mmol) in 800 mL of dry CH_2Cl_2 under Ar was added dropwise a solution of 1.43 g of a mixture of crude acids **35** and **36** (4.73 mmol), 6.3 mL of dry Et_3N (45.2 mmol), and 500 mL of dry CH_2Cl_2. On this scale the addition required 6 h. After the addition was complete the solution was refluxed for an additional 45 min. The reaction mixture was cooled and concentrated in vacuo to give a dark residue which was partitioned between 60 mL of ether and 60 mL of H_2O. The aqueous layer was washed with three 60-mL portions of ether. The combined ether layers were dried over Na_2SO_4 and concentrated in vacuo to give 1.56 g of crude product, purification of which was effected by flash chromatography (50 mm column) by using 3:2 hexane–ether as eluant. This afforded 1.12 g (84%) of a 6:1 mixture of **43**/**45**, 0.032 g (3%) of **43**, and 0.024 g (2%) of a 1:6 mixture of **43**/**45**. The latter mixture was recrystallized from hexane–EtOAc to afford a pure sample of **45**.

Pure **35** was transformed into lactone **43** in 81% yield using this procedure.

Data for **43**: NMR ($CDCl_3$) δ 5.90 (d, J = 9.9 Hz, 1 H), 5.62 (ddd, J = 9.9, 4.0, 2.6 Hz, 1 H), 4.76 (d, J_{AB} = 6.8 Hz, A of AB), 4.61 (d, J_{AB} = 6.8 Hz, B of AB), 4.20 (m, 2 H, lactone CH_2O), 3.37 (s, 3 H), 3.32 (dt, J = 5.5, 9.9 Hz, H_1), 3.08 (dd, J = 10.3, 6.7 Hz, H_5), 2.42 (m, 1 H), 2.15 (m, 1 H); IR (CCl_4) 3030, 2931, 1726, 1640 cm^{-1}; high-resolution mass spectrum calcd for $C_{16}H_{24}O_4$ 280.1675, found 280.1671.

Data for **45**: mp 96–98 °C; NMR ($CDCl_3$) δ 6.10 (ddd, J = 2, 3.4, 9.5 Hz, 1 H), 5.54 (dt, J = 9.5, 2.5 Hz, 1 H), 4.82 (d, J_{AB} = 6.7 Hz, A of AB), 4.54 (d, J_{AB} = 6.7 Hz, B of AB), 4.33 (m, 2 H), 3.41 (s, 3 H), 3.16 (dt, J = 4.4, 10.4 Hz, H_1), 2.87 (t, J = 7.4 Hz, H_5); IR (CCl_4) 3028, 2927, 1749 cm^{-1}; mass spectrum, m/e 218 (M − $HOCH_2OCH_3$).

6β-(3-Hydroxyprop-1-yl)-1α-[(methoxymethyl)oxy]-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylic Acid ϵ-Lactone (5). To a solution of 2.7 mL of dry diisopropylamine (19.3 mmol) in 85 mL of dry THF at −78 °C was added dropwise 7.2 mL of 2.43 M *n*-BuLi in hexane (17.5 mmol). This solution was stirred for 40 min at −78 °C and then a solution of 1.08 g of a 6:1 mixture of **43**/**45** (3.86 mmol) in 15 mL of dry THF and 20 mL of dry HMPT was added dropwise. On this scale the addition required 20 min. This solution was stirred for 15 min at −78 °C, warmed to −27 °C over 15 min, and then recooled to −78 °C. Iodomethane (3 mL) was then added. The resulting solution was stirred at −78 °C for 4 h and was then allowed to warm gradually to room temperature overnight (13 h). The reaction was quenched by addition of 0.5 mL of MeOH, and then the solution was poured into a separatory funnel containing 100 mL of 0.2 N HCl, 20 mL of H_2O, and 120 mL of ether. The aqueous layer was extracted with two additional 120-mL portions of ether. The combined ether layers were washed once with 100 mL of half-saturated $Na_2S_2O_3$, which was back-extracted with 75 mL of ether. The combined ether layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 2.91 g of crude product, which was purified by flash chromatography (50 mm column, 4:1 hexane–ether) to afford 0.901 g of lactone **5** (79%).

By use of this procedure pure **43** was converted into lactone **5** in 75% yield (1.5-mmol scale).

Data for **5**: NMR ($CDCl_3$) δ 5.87 (d, J = 10.3 Hz, 1 H), 5.55 (ddd, J = 2.2, 4.1, 10.3 Hz, 1 H), 4.75 (d, J_{AB} = 7 Hz, 1 H), 4.61 (d, J_{AB} = 7.0 Hz, 1 H), 4.37 (dd, J = 5.9, 10.3 Hz, 1 H), 3.76 (m, 1 H), 3.37 (s, 3 H), 3.19 (dt, J = 4.4, 10.1 Hz, H_1), 2.12 (m, 1 H), 1.10 (s, 3 H); IR (neat) 3022, 1733, 1648 cm^{-1}; high-resolution mass spectrum calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1851. Saponification of lactone **5** afforded the crystalline hydroxy acid **48**, which was fully characterized.

Data for **48**: mp 102–103 °C; NMR ($CDCl_3$) δ 5.92 (d, J = 10.4 Hz, 1 H), 5.72 (ddd, J = 2.2, 4.8, 10.4 Hz, 1 H), 4.79 (d, J_{AB} = 6.8 Hz, 1 H), 4.66 (d, J_{AB} 6.8 Hz, 1 H), 3.62 (m, 2 H), 3.48 (s, 3 H), 3.25 (dt, J = 4.4, 10 Hz, H_1), 2.18 (m, 1 H), 2.00 (m, 1 H), 1.20 (s, 3 H); IR (CCl_4) 3600–2400, 3038, 1695 cm^{-1}; high-resolution mass spectrum calcd for $C_{17}H_{28}O_5$ 312.1937, found 312.1940. Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.62; H, 8.84.

Alkylation of Lactone 45. A solution of 0.05 mL of dry diisopropylamine (0.36 mmol) in 1.5 mL of dry THF under Ar was cooled to −78 °C, and 0.13 mL of 2.43 M *n*-BuLi in hexane

(0.31 mmol) was added. The resulting solution was stirred for 40 min at −78 °C. A solution of 20 mg of lactone **45** (0.07 mmol) in 0.38 mL of dry HMPT and 1.0 mL of THF was added dropwise. This solution was stirred for 2 h at −78 °C, warmed to −25 °C for 30 min, and recooled to −78 °C. Iodomethane (0.06 mL, 1.0 mmol) was then added and the resulting solution was allowed to warm slowly to 23 °C overnight. The reaction was quenched with 0.2 mL of MeOH and partitioned between 10 mL of 0.15 N HCl and 10 mL of ether. The aqueous layer was washed twice with 10-mL portions of ether. The combined ether extracts were washed once with 10 mL of half-saturated $Na_2S_2O_3$, dried over Na_2SO_4, and concentrated in vacuo to give 31 mg of crude product. The mixture of products was separated by preparative TLC, using 4:1 hexane–ether as eluant, giving 6.5 mg of lactone **5** (31%) and 5.5 mg of recovered **45** (28%).

Methyl 6β-(3-Hydroxyprop-1-yl)-1α-[(methoxymethyl)oxy]-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (46). A solution of 171 mg of lactone **5** (0.58 mmol) in 5 mL of dry MeOH was added to a resealable Carius tube and purged with a stream of dry Ar for 10 min. To this solution was added 13 mg of NaOMe (0.24 mmol), and the resultant mixture was purged with Ar for an additional 5 min. The tube was then sealed and placed in a 100 °C oil bath for 23 h (temperature of the oil bath slowly increased to 105–110 °C). The reaction mixture was cooled, neutralized with 0.025 mL of HOAc, and then concentrated in vacuo to give crude ester **46**. The crude product was purified by preparative TLC (0.5-mm silica gel), using 1:1 hexane–ether containing 1% HOAc as eluant, giving 161 mg of ester **46** (86%): NMR ($CDCl_3$) δ 5.89 (d, J = 10.3 Hz, 1 H), 5.68 (ddd, J = 2.2, 4.8, 10.3 Hz, 1 H), 4.75 (d, J_{AB} = 6.6 Hz, 1 H), 4.63 (d, J_{AB} = 6.6 Hz, 1 H), 3.65 (s, 3 H), 3.58 (t, J = 6.6 Hz, 2 H), 3.38 (s, 3 H), 3.22 (dt, J = 4.4, 10 Hz, H_1), 2.15 (m, 1 H), 1.94 (m, 1 H), 1.15 (s, 3 H); IR (neat) 3425, 3022, 1726, 1655 cm^{-1}; high-resolution mass spectrum calcd for $C_{18}H_{30}O_5$ 326.2093, found 326.2104.

Methyl 1α-[(Methoxymethyl)oxy]-5α-methyl-6β-(3-oxoprop-1-yl)-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (49). A solution of 0.97 mL of dry pyridine (12.0 mmol) in 20 mL of dry CH_2Cl_2 was cooled to 0 °C. To this solution was added 599 mg of CrO_3 (5.99 mmol) followed by a solution of 155 mg of alcohol **46** (0.48 mmol) in 5 mL of dry CH_2Cl_2. After being stirred for 90 min at 0 °C, the solution was diluted with 25 mL of dry ether and was filtered through a short pad of Florisil. The black gummy residue in the reaction flask was washed with several 5-mL portions of dry ether which were also passed through the Florisil pad. The combined filtrates were concentrated in vacuo to give crude aldehyde **49**, which was purified by preparative TLC (0.5 mm silica gel plate), using 1:1 hexane–ether as eluant. This gave 120 mg of aldehyde **49** (78%): NMR ($CDCl_3$) δ 9.64 (t, J = 1.6 Hz, 1 H), 5.87 (d, J = 10.3 Hz, 1 H), 5.54 (ddd, J = 2.6, 5.2, 10.3 Hz, 1 H), 4.68 (d, J_{AB} = 6.8 Hz, 1 H), 4.55 (d, J_{AB} = 6.8 Hz, 1 H), 3.60 (s, 3 H), 3.30 (s, 3 H), 3.15 (dt, J = 4.5, 10 Hz, H_1), 2.37 (m, 2 H), 2.07 (m, 1 H), 1.91 (m, 1 H), 1.08 (s, 3 H); IR (CCl_4) 3035, 2720, 1727, 1655 cm^{-1}; high-resolution mass spectrum calcd for $C_{18}H_{28}O_5$ 324.1937, found 324.1966.

Methyl 6β-[4-(Methoxycarbonyl)-3-buten-1-yl]-1α-[(methoxymethyl)oxy]-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (47). To a stirred solution of 98.5 mg of aldehyde **49** (0.30 mmol) in 5 mL of dry CH_2Cl_2 was added 167 mg of (carbomethoxymethylene)triphenylphosphorane[34] (0.5 mmol). The resultant solution was stirred for 20.5 h at 23 °C and then was heated to reflux for 45 min. The reaction mixture was cooled and concentrated in vacuo to give the crude product, which was purified by preparative TLC (0.5-mm silica gel plate), using 2:1 hexane–ether as eluant. This gave 108 mg of unsaturated ester **47** (93%): NMR ($CDCl_3$) δ 6.84 (dt, J = 15.4, 6.8 Hz, 1 H), 5.88 (d, J = 10.3 Hz, 1 H), 5.75 (dt, J = 15.4, 1.5 Hz, 1 H), 5.60 (ddd, J = 2.6, 5.2, 10.3 Hz, 1 H), 4.70 (d, J_{AB} = 6.6 Hz, 1 H), 4.58 (d, J_{AB} = 6.6 Hz, 1 H), 3.65 (s, 3 H), 3.60 (s, 3 H), 3.33 (s, 3 H), 3.18 (dt, J = 4.2, 10.1 Hz, H_1), 1.09 (s, 3 H); IR (neat) 3031, 1736, 1721, 1656 cm^{-1}; high-resolution mass spectrum calcd for $C_{21}H_{32}O_6$ 380.2199, found 380.2194.

Methyl 6β-[4-(Methoxycarbonyl)but-1-yl]-1α-[(methoxymethyl)oxy]-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (41). A solution of 25 mg of tris(triphenylphosphine)chlororhodium[35] (0.027 mmol) in 5 mL of dry benzene was prepared in an Ar-flushed flask. The reaction vessel was then filled with H_2 via several vacuum/purge cycles. This solution was vigorously stirred and then a solution of 52 mg of unsaturated ester **47** in 1 mL of benzene was added. This solution was stirred for 6 h at 23 °C by which time a black precipitate had formed on the flask walls. The reaction was then immediately worked up by filtration and concentration in vacuo. The crude product was purified by preparative TLC (0.5-mm silica gel plate, 3:1 hexane–ether), giving 34 mg (65%) of a 4:1 mixture of starting ester **47** and product **41** and 8.1 mg of pure **41** (15%): NMR ($CDCl_3$) δ 5.87 (d, J = 10.3 Hz, 1 H), 5.67 (ddd, J = 2.2, 4.8, 10.3 Hz, 1 H), 4.75 (d, J_{AB} = 6.6 Hz, 1 H), 4.63 (d, J_{AB} = 6.6 Hz, 1 H), 3.64 (s, 3 H), 3.38 (s, 3 H), 3.21 (dt, J = 4, 10 Hz, H_1), 2.26 (t, J = 7.7 Hz, 2 H), 2.15 (m, 1 H), 1.91 (m, 1 H), 1.13 (s, 3 H); IR (neat) 3030, 1730, 1654 cm^{-1}; mass spectrum, m/e 351 (M − MeO); high-resolution mass spectrum calcd for $C_{21}H_{34}O_6$ 382.2355, found 382.2354.

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