Tetrahedron Vol 45, No 22, pp 6949 to 6962, 1989
Printed in Great Britain

0040-4020/89 $3.00 + 00

ASYMMETRIC ADDITION TO CHIRAL NAPHTHALENES 5. AN APPROACH TO THE CHLOROTHRICOLIDE SYSTEM

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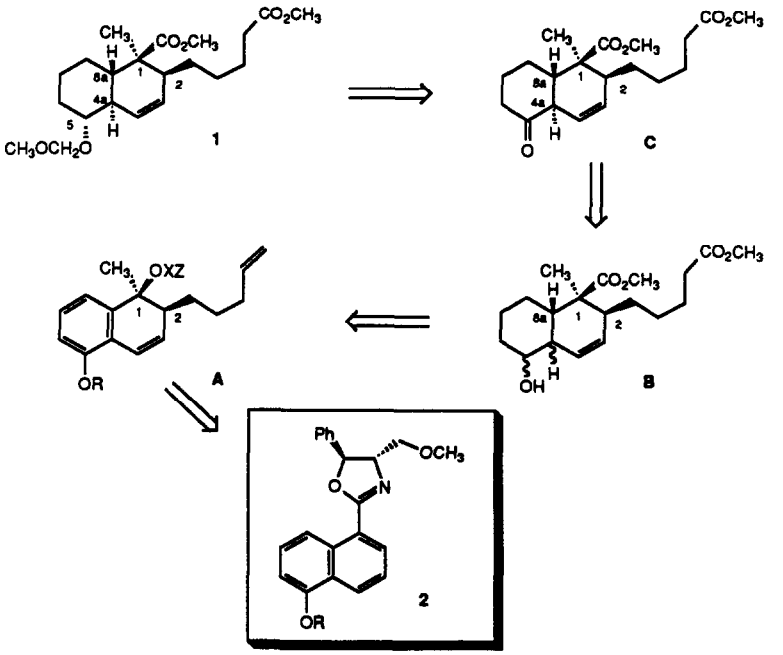
(*Received in USA* 19 *June* 1989)

Abstract—The asymmetric synthesis of several analogs of the so-called bottom half of chlorothricolide has been accomplished. The key reaction involves addition of a pentenyl lithium to the chiral naphthyl oxazoline **2** followed by methyl iodide quench to afford the quaternary tetralin system **3**. Further elaboration and Birch reduction gave the hexahydro- naphthalene **9** which was readily transformed into the bottom-half analogs **15**, **18**, **22**, and **24**. Unfortunately, none of these corresponded to the correct stereochemical configuration of the natural bottom half degradation product. Extensive NMR studies confirmed the stereochemistry of the products analogous to the latter and showed that the metal-ammonia reductions or the catalytic hydrogenation studies were inappropriate methods to reduce aromatic or dihydro analogs to the natural configuration.

In recent reports from this laboratory, asymmetric additions to chiral naphthalenes have been shown to possess considerable potential in reaching enantiomerically enriched di- and trisubstituted dihydronaphthalenes (< 95 % ee).[1,2] In addition, we have successfully applied this technique to the asymmetric total synthesis of podophyllotoxin,[3] phyltetralin,[1] and the AB ring of aklavinone.[4] Based on these results, we have attempted to extend this effort to other systems of current interest; namely that of the chlorothricin family and their degradation products.[5] This effort has been only partially successful but did provide a number of interesting results that we wish to relate here. Our major focus was to reach the "bottom-half" of the antibiotic chlorothricolide **1** which has been the subject of a number of extensive investigations by Ireland,[5,6] Roush,[7] Marshall,[8] and Snider.[9] The studies by these groups except that of Ireland involved intramolecular Diels-Alder strategies of suitably substituted trienes producing octahydronapththalenes containing the appropriate functionality and stereochemical characteristics. It was, therefore, of interest to us whether or not we could utilize the asymmetric addition to chiral naphthalenes as an alternative route to this octahydronaphthalene system. Furthermore, since there were no reports on any asymmetric syntheses[10] leading to the bottom half of chlorothricolide we felt this was a worthwhile venture.[11]

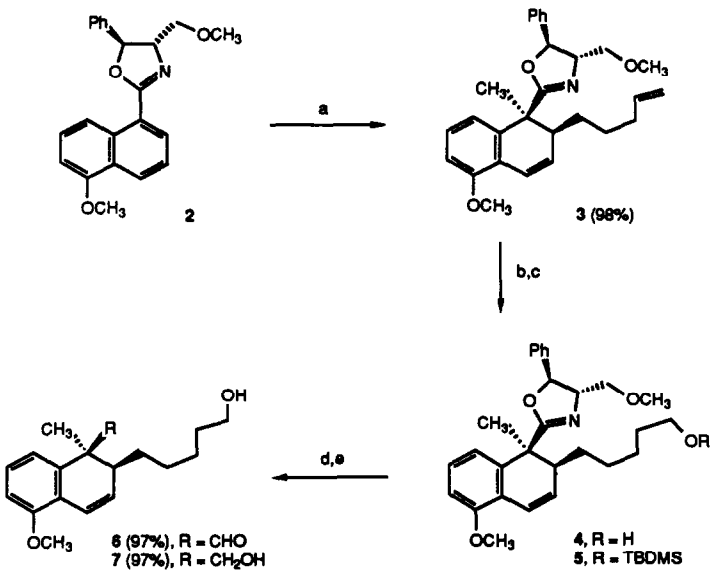
The retrosynthetic plan to reach our target is presented in Scheme 1. The employment of the appropriate naphthalene **2** containing the oxazoline as a chiral auxiliary should serve as the template upon which to introduce the several necessary stereocenters. Thus **A** will be the product of the now well established tandem addition[1] and this will be followed by introduction of the carboxyl functions and reduction of the remaining aromatic ring to **B**. Further manipulations to give the ketone **C** can be followed by reduction to the known bottom half of chlorothricolide **1**. This plan, however, contains some potentially serious problems; some of which we were unable to avoid

Scheme I



and these will be described in this report along with the successful aspects of this effort. The starting chiral naphthalene **2** was prepared as previously described.[4] Addition of 1-lithio-4-pentene, generated from 1-iodo-4-pentene and *t*-butyllithium, to the naphthyl oxazoline at -85° C with subsequent methyl iodide quenching gave the adduct **3** in 98 % yield and a 97:3 ratio of diastereoisomers (HPLC). Hydroboration with 9-BBN and oxidation furnished the carbinol **4** which was protected as the tert-butyldimethylsilyl ether **5.** Oxazoline removal was accomplished by utilization of the well precedented procedure[1] of quaternization (MeOTf), reduction ($NaBH_4$), and hydrolysis (oxalic acid) affording the hydroxy aldehyde **6.** *The overall yield of 6 from the naphthyl oxazoline 2 was greater than 85%.* It was noted that aldehyde **6** possessed a tendency to slowly undergo aromatization to the naphthalene with concurrent loss of the formyl group. Thus, both the formyl group and the styrene double bond were removed by successive treatment with sodium borohydride and lithium-liquid ammonia to producethe dihydro-diol **7.**

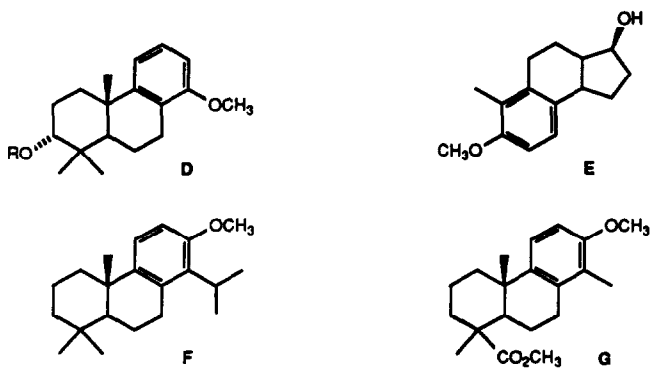
The next task was the Birch reduction of **7** and establishing the stereochemistry at the ring junctions, C-4a, C-8a, and the adjacent center at C-5. There are two possible reduction products (**8** and **9**), that may arise and each will have a major effect on the stereochemistry of the process. Hydrolytic cleavage of the enol ethers derived from the above would give rise to two β,γ-enones **10** and **11**. If **10** is formed we will be unable to control the stereochemistry at 8a if the proton entered from the α-face. On the other hand, if the Birch reduction leads to **9** then the enone **11** will be formed after hydrolysis and routes should be available to introduce the proton from the desired β-face. When the Birch reduction was attempted, it was surprising to find that the starting material was recovered unchanged. A variety of conditions were implemented and all failed to reduce the



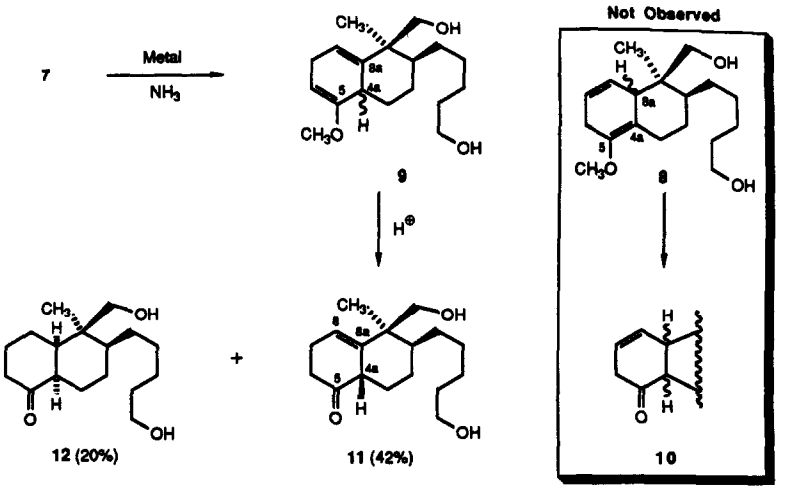
a. 1-lithio-4-pentene; CH_3I; b. 9-BBN; H_2O_2, NaOH; c. TBDMS-Cl, Et_3N;
d. MeOTf; $NaBH_4$; H^+/H_2O; e. $NaBH_4$; Li/NH_3

aromatic ring. A search of the literature revealed that anisole derivatives containing 1,2,3,-substitution patterns were poorly reduced, if at all, under Birch conditions.[12] In the case at hand, we have a 5-methoxytetralin, which Birch reported in 1946,[13] could not be reduced under sodium-ammonia conditions. Later, Wilds and Nelson, utilizing lithium-ammonia, reported improved yields for reduction of the parent tetralin [14]

There are a number of reports[12] describing failure to reduce the 1,2,3-substituted benzenes and success was ultimately achieved by incorporating massive quantities of lithium. Thus, **D** and **E** have been examined with respect to metal-ammonia reductions and were successfully reduced using 500-600 equivalents of lithium whereas **F** and **G** were reported to be completely resistant to reduction conditions.



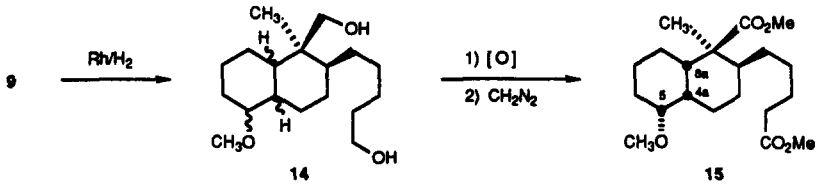
The successful reduction of **7** was ultimately accomplished using 40-60 equivalents of lithium wire added to a vigorously stirred solution made up of 0.5 mmol of **7** in ammonia-tetrahydrofuran-



ethanol (15:1:2). The reaction was conducted at -78° with rigorous exclusion of oxygen and as reported[12] the order of addition of the reagents is the single most important variable with regard to product distribution. Thus, when **7** was added to the metal ammonia mixture no reduction occurred. However, when the lithium was added to **7** in the ammonia-THF-ethanol solution, only **9** was obtained as a single regioisomer along with its dihydro derivative as seen from the ^{13}C NMR spectrum. Within the limits of NMR, HPLC, or TLC detection we could not identify any amount of regioisomer **8**. Chromatographic separation of **9** and its dihydro analog was not feasible due to rearomatization of **9** when in contact with air. Therefore, the mixture was treated with acid to furnish the two stable products,**11** and **12** in the ratio of 2.1:1. This mixture was readily separated by column chromatography and further evaluation of **11** by capillary gas chromatography showed a single diastereomer to be present. The position of the double bond in **11** was verified by NMR which showed a single vinylic signal at 5.81 ppm while the ^{13}C spectrum confirmed that only three sp^2 centers were present. The signal at 212.6 ppm was assigned to the carbonyl carbon and the signals at 142.6 and 121.5 ppm were assigned to the olefinic carbons. If **11** is correct it should show a tertiary (C-8) and a quaternary (C-8a) olefinic carbon. A DEPT experiment[15] was performed and showed that the olefinic carbon corresponding to the downfield signal was quaternary, and the other olefinic carbon with a signal at 121.5 ppm was tertiary thus excluding **10** as a possible product and precluding **8** as a product from the Birch reduction.

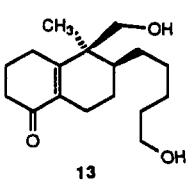
It was also necessary to determine the stereochemistry of the C-4a proton in **11**. Due to the propensity for isomerization of the double bond, epimerization of the 4a proton was not possible. In fact, treatment of **11** with a catalytic quantity of sodium methoxide gave the conjugated ketone **13** in quantitative yield.

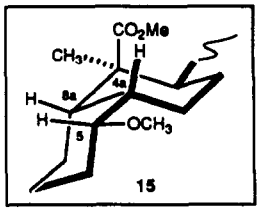
Since the Birch reduction gave only a single dihydrobenzene, we felt that direct hydrogenation of **9** might lead to a single perhydronaphthalene which could be correlated to previously known chlorothricolide degradation products. Hydrogenation of **9** with rhodium-on alumina gave the fully saturated intermediate **14** which was directly oxidized with Jones reagent and esterified with diazomethane furnishing the diester **15** as single diastereomer.

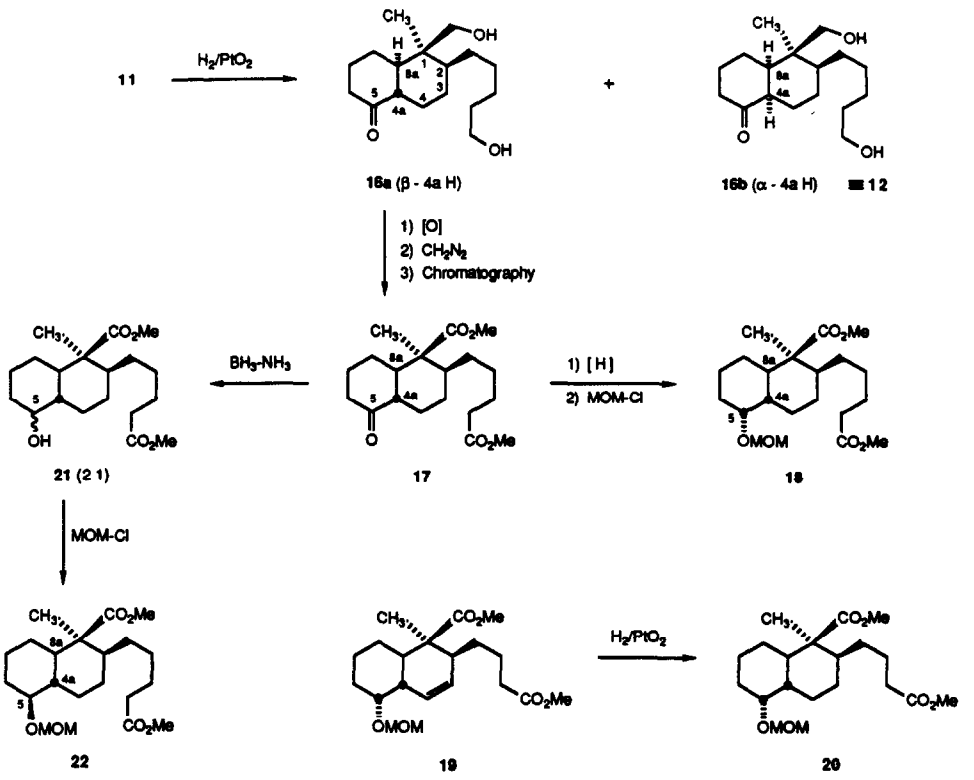


The task now at hand was to assess *via* NMR techniques, the stereochemistry at C-8a, C-4a, and C-5 in **15**. Furthermore, it should be possible to assign the stereochemistry at C-4a in unsaturated ketone **11** since it would be expected to be the same as C-4a in **15**. Selective irradiation of the C-5 proton in **15** at 3.13 ppm causes the adjacent C-4a proton at 2.02 to simplify and the converse treatment (irradiation at 2.02) showed similar behavior. From this, a coupling constant of 4.3Hz was obtained for C-5-C4a and indicates a *cis*-relationship for this region.[16] Based on this finding, it is reasonable to conclude that the C-5 proton occupies an axial site and the methoxyl group resides in the equatorial position. Since the absolute stereochemistry at C1 and C2 are known from earlier studies,[1] we may assign C-5 as 5R. The assignment of the C4a-C8a ring fusion was not as simple to assess since the signal for C-8 was buried within the complex spectral envelope between 1.0 and 2.0 ppm. However, HETCOR experiments[17] provided one tool necessary to assign the chemical shifts in the complex proton spectrum. This furnished unambiguous assignment of the C-8 proton multiplet. With this information in hand, a DQF-COSY[18] experiment was performed and showed that cross peaks were observed between H-5 and H-4a as well as between H-4a and H-8a. Analysis of the anti-phase doublets showed that $J_{4a,5}$ was no larger than 4Hz and that $J_{4a,8a}$ was approximately 6Hz, thus verifying that all three protons in **15** were *cis* to each other. Further proof was gathered for the overall relationship of these protons by qualitative homonuclear NOE difference spectroscopy. Thus, individual irradiation of either H-5, H-4a, or H-8a showed a large enhancement of the remaining neighboring protons as well as a modest enhancement of the C-1 methyl group.

With the stereochemistry of **15** on rather firm ground, we returned to the unconjugated ketone **11** which may, on hydrogenation, be reasonably expected to give the epimeric C-8a derivatives **16a** and **16b** and therefore provide access to the *trans* ring systems. Indeed, reduction of **11** gave the two epimers **16a-16b** in a 1.2:1 ratio. These were oxidized as the mixture to give **17** and **23** which were separated and characterized. Alternatively, **16a** and **16b** were separated and the former oxidized (Jones) and esterified solely to the di-ester **17** which was reduced with LS-Selectride[19] to a single alcohol. The latter was immediately transformed into the MOM ether **18**. This material was compared with a sample of the very closely related analog **20** (one less methylene group in the side chain) obtained from hydrogenation of **19**.[20] Both the proton



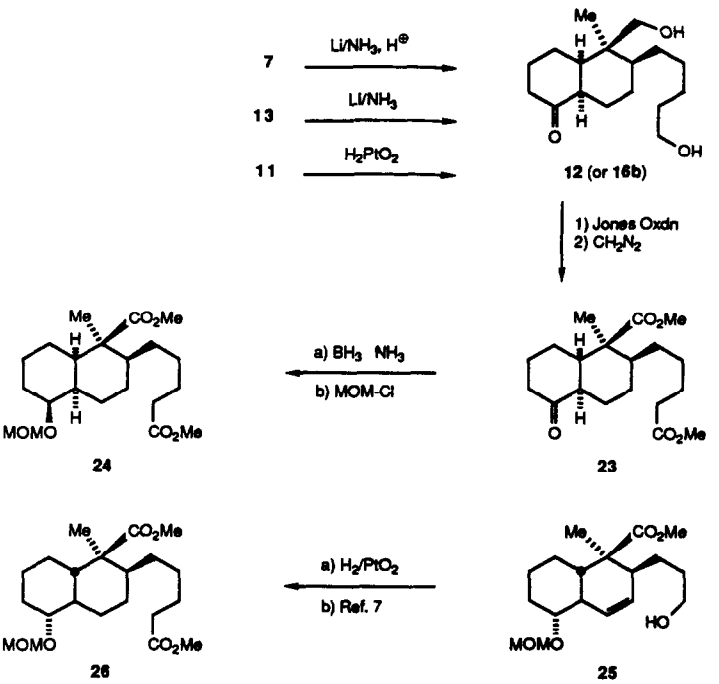




and carbon NMR spectra were virtually identical except for a slight difference in the methylene region. The other epimer **16b** was shown to be identical with the over-reduced Birch product **12** and therefore supported the fact that the 8aH was α-oriented in **12** or **16b**.

Although comparison of **18** and **20** was quite convincing, there still remained some room for further verification. In this regard, an additional analog **22** was prepared by borane reduction of ketone **16a** and produced the 5-hydroxy derivatives **21** as a 2:1 mixture of α, β-epimers. Chromatographic separation gave pure materials which were transformed into the MOM ethers **22** and **18**. Thus, the latter two derivatives differed only at C-5. Due to the complex nature of their respective proton NMR spectra, a DQF-COSY experiment was performed on **18** at 500 MHz.[21] Cross peak relationships were observed between 5-H and 4a-H and analysis of the antiphase doublets from a cross peak slice indicated a *trans*-relationship with $J_{4a,5}$ = 10Hz. Similarly, the cross peaks corresponding 4a-H and 8a-H showed $J_{4a,8a}$ = 10.5Hz. This data also confirmed the fact that **18** and **22** both possessed *trans*-ring fusions and differed only at C-5.

The results below show rather clearly that although the asymmetric addition to the chiral naphthalenes **2** was performed quite efficiently, the Birch reduction of the tetralin system **7** proceeded in an undesired fashion giving rise to epimeric analogs of the target **1**; namely **15**, and **18**, and **22**. There were other attempts to carry the tetralin **7** on to the bottom-half derivative **1**. Specifically, it was found that metal-NH_3 reduction the α,β-unsaturated ketone **13** gave the saturated ketone **12** (**16b**), a product which was identical to that also obtained from over-



reduction of **7** in the Birch process. It is noteworthy to again state that the catalytic hydrogenation of the β,γ-unsaturated ketone **11** also produced **16b** which was identical to **12**. Combination of the saturated ketones from all three above routes was followed by side chain oxidation to the diacid and subsequent diazomethane esterification. This furnished the diester ketone **23** as the sole product. Extended treatment with sodium methoxide in methanol left the starting ketone unchanged. Reduction of the keto group with borane-ammonia complex followed by derivatization of the resultant alcohol as the methoxymethyl ether gave the bottom half analog **24**.

For purposes of comparison, a sample of the trans-fused unsaturated ring system **25** was obtained[22] and was hydrogenated and then homologated to the ester **26** in racemic form. Proton NMR comparison of **26** with the bottom half analog **24** showed the two compounds to be completely different. Comparison of racemic **26** with the bottom half analogs **20** and **22** indicated only a few common spectral features. At this point it was necessary to determine the relative stereochemistry of the C-5, 4a, and 8a protons in **24** since this should also reflect the stereochemistry of the diester ketone **23**. DQF-COSY experiments conducted at 300 MHz did not provide sufficient resolution of the cross peaks corresponding to the H-5, 4a and H-4a, 8a active coupling interactions. The cross peak corresponding to the H-4a, 8a interaction was cluttered by overlapping AB multiplets arising from the C-8 and C-4 methylene protons causing poor separation of the anti-phase line pairs. The higher resolution DQF-COSY spectra of **24** obtained at 500 MHz provided sufficient signal separation so that the molecular geometry could be determined. Cross peak analysis indicated a *cis* coupling relationship for H-5 and 4a ($J_{5,4a}$ = 4.7 Hz) as well as a *cis* fused ring system ($J_{4a,8a}$ = 3.6 Hz). Since the analog **15** was also shown to be an all *cis* isomer, then **15** and **24** differ in the relation between the 5, 4a, and 8a protons and the fixed stereocenters

at C-1 and 2. In other words, **15** most likely has an absolute stereochemistry of S at C-4a and 8a (C-5 is R) while **24** is epimeric (R) at these centers.

In summary, although a number of tetralin systems were prepared, the routes taken *via* this asymmetric addition to naphthalenes did not allow entry into the specific chlorothricolide moiety.

Experimental Section[21]

1α-Methyl-1β-oxazolinyl-2β-(4-pentenyl)-3,4-dehydro-5-methoxy- tetralin 3. A flame dried flask was charged with 1-iodo-4-pentene (1.6 g, 8.5 mmol) and 8 mL of dry pentane followed by cooling to -85°C in a controlled temperature bath. *tert*- Butyllithium (9.5 mL, 16.2 mmol, 1.7 M in pentane) was added dropwise over a 5 min period and the resulting suspension was allowed to stir for 30 min. A solution consisting of the naphthyloxazoline **2**[4] (2.0 g, 5.7 mmol) in 50 mL of THF was added *via* cannula and the deep red solution was allowed to stir for 4 h at that temperature before quenching with an excess of iodomethane. The quenched reaction was warmed to ambient temperature, diluted with 20 mL of water, then the solvent evaporated. The resulting yellow slurry was taken up in CH_2Cl_2, washed with water, and the organic fraction was dried ($MgSO_4$) then concentrated to give 2.3 g of a crude oil. HPLC analysis of the product (Zorbax; hexane/THF 10%) showed it to contain 98% of the desired addition product in a diastereomeric ratio of 97:3: IR (film) 2970, 1645, 1570, 1470, 1260, 1050, 750 cm-1; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.35-7.19 (m, 5 H), 7.16 (t, 1 H, J = 7.7 Hz), 6.86 (dd, 1 H, J = 7.7, 1.0 Hz), 6.75 (dd, 1 H, J = 7.7, 1.5 Hz), 6.01 (dd, 1 H, J = 9.9, 4.7 Hz), 5.76-5.70 (m, 1 H); 5.27 (d, 1 H, J = 6.8 Hz), 4.98-4.87 (m, 1 H), 4.24-4.17 (m, 1 H), 3.82 (s, 3 H), 3.67 (dd, 1 H, J = 9.6, 4.1 Hz), 3.49-3.42 (m, apparent dd, 1 H), 3.39 (s, 3 H), 2.46-2.42 (br.s, 1 H), 2.01-1.25 (env., 6 H), 1.64 (s, 3 H).

1α-Methyl-1β-oxazolinyl-2β-(5-hydroxypentane)-3,4-dehydro-5-methoxytetralin 4. A solution of the crude tandem addition product **3** (1.0 g, 2.3 mmol) in THF (40 mL) was cooled to 0°C in an ice-water bath then treated with 9-BBN (6.8 mL, 3.4 mmol, 0.5 M in THF). The resulting solution was allowed to warm to ambient temperature and stir overnight and again cooled to 0°C and treated with 4 mL of 3 N NaOH followed by 4 mL of 30% aqueous H_2O_2. The reaction was allowed to stir for 30 min as it warmed to ambient temperature then the solvent was evaporated. The residue was taken up in $CHCl_3$ and washed with water. The organic fraction was dried ($MgSO_4$) to afford a crude oil. HPLC: Zorbax column, hexane/ethyl acetate 1:1, 2.0 ml/min flow rate. Major isomer: t_r = 11.56 min, 97%. Minor isomer: t_r = 16.43 min, 3%. The crude oil was then purified by column chromatography (20% EtOAc/hexanes) to yield 951 mg (92%) of **4** a colorless oil: $[\alpha]_D$ +159.37° (c 0.48, $CHCl_3$); IR (film) 3400, 2920, 1730, 1630, 1565, 690, 640 cm-1; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.36-7.18 (m, 5 H), 7.15 (t, 1 H, J = 7.7 Hz), 6.86 (dd, 1 H, J = 7.7, 1.0 Hz), 6.75 (dd, 1 H, J = 7.7, 1.5 Hz), 6.01 (dd, 1 H, J = 9.9, 4.7 Hz), 5.28 (d, 1 H, J = 6.8 Hz), 4.22-4.17 (m, 1 H), 3.79 (s, 3 H), 3.68-3.40 (m, 4 H), 3.37 (s, 3 H), 2.44-2.40 (br.s, 1 H), 2.27 (br.s, ex, 1 H), 1.64 (s, 3 H), 1.75-1.14 (env., 8 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 170.18, 154.87, 141.01, 139.52, 129.27, 128.43, 127.72, 125.62, 125.09, 122.08, 119.85, 119.59, 109.29, 83.07, 82.86, 74.40, 74.09, 62.57, 59.02, 55.54, 44.74, 43.54, 32.54, 31.17, 27.15, 26.44, 25.76.

1α-Methyl-1β-formyl-2β-(5-hydroxypentane)-3,4-dehydro-5-meth-oxytetralin 6. A solution consisting of the oxazoline-alcohol **4** (539.5 mg, 1.19 mmol) in dry CH_2Cl_2 (10 mL) was

treated with a catalytic amount of 4-dimethyl aminopyridine, followed by addition of *tert*-butyldimethylchlorosilane (217.2 mg, 1.44 mmol) and triethylamine (0.23 mL, 1.6 mmol). The resulting solution was allowed to stir overnight then quenched with water. After stirring for 20 min the organic fraction was dried ($MgSO_4$) and concentrated to give 631.2 mg (94%) of a colorless oil. The O-silyl oxazoline **5** (132 mg, 0.23 mmol) was taken up in 5 mL of dry CH_2Cl_2 and cleaved according to the general procedure[1] for oxazoline removal to give a crude oil. The product was purified by chromatography (hexane/EtOAc 1:1) to give 64.0 mg (97%) of **6** as a colorless oil: $[\alpha]_D$ +9.5° (c 1.47, $CHCl_3$); IR (film) 3320, 2920, 1700, 1560, 1450, 1250, 1030, 730 cm^{-1}, ^1H NMR (270 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 7.19 (t, 1 H, J = 8.0 Hz), 6.88 (dd, 1 H, J = 9.9, 1.6 Hz), 6.81 (d, 1 H, J = 8.0 Hz), 6.75 (d, 1 H, J = 8.0 Hz), 3.85 (s, 3 H), 3.61 (t, 2 H, J = 6.5 Hz), 2.53-2.39 (br.s, 1 H), 1.64-1.42 (env., 8 H), 1.37 (s, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 204.06,155.39, 136.77, 129.06, 128.63, 120.65, 118.85, 110.19, 77.21, 62.78, 55.64, 52.57, 42.59, 32.60, 29.95, 27.31, 25.78, 19.54.

1α-Methyl-1β-hydroxymethyl-2β-(5-hydroxypentyl)-5-methoxytetralin 7. A solution consisting of the formyl alcohol **6** (230 mg, 8,0 mmol) in 20 mL of dichloromethane containing 10% anhydrous ethanol was cooled to 0°C in an ice-water bath. The solution was then treated with $NaBH_4$ (57.4 mg, 1.6 mmol) and allowed to stir for 10 min. The reaction was quenched with 5 mL of saturated aqueous NH_4Cl solution, warmed to ambient temperature and diluted with 20 mL of water. The organic fraction was isolated and the aqueous portion was extracted with 2 x 10 mL of dichloromethane. The combined organic fractions were dried ($MgSO_4$) and concentrated to give a colorless oil. The crude oil was taken up in 2 mL of tetrahydrofuran and carefully added to a blue solution of distilled ammonia (30 mL) containing lithium wire (22.4 mg, 3.2 mmol). The solution was allowed to reflux (-33°C) for 20 min then quenched by careful addition of excess solid NH_4Cl. After the ammonia evaporated the residue was taken up in 10 mL water and extracted with 3 x 15 ml $CHCl_3$. The combined organic fractions were dried ($MgSO_4$) and concentrated and the crude oil purified by flash chromatography (hexane/EtOAc 1:1) to give 228 mg (97%) of **7** as a colorless oil: $[\alpha]_D$ +8.7° (c 2.9, $CHCl_3$); IR (film) 3345, 2940, 1580, 1460, 1260, 1050 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.16 (t, 1 H, J = 8.0 Hz), 6.96 (d, 1 H, J = 8.0 Hz), 6.69 (d, 1 H, J = 8.0 Hz), 3.77 (apparent dd, 2 H) on which is superimposed 3.81 (s, 3 H) and 3.63 (t, 2 H, J = 6.5 Hz), 2.84 (dt, 2 H, J = 17.8, 4.9 Hz), 2.48 (complex m, 2 H), 1.95-1.04 (complex m, 9 H) on which is superimposed 1.27 (s, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 157.28, 143.12, 127.21, 126.15, 119.12, 107.38, 69.38, 62.99, 55.33, 42.85, 42.16, 32.91, 29.59, 28.26, 26.15, 25.46, 23.24, 22.50. High resolution mass spectrum calcd for $C_{18}H_{28}O_3$: 292.2038. Found: 292.2031.

Preparation of Several Chlorothricolide Bottom Half Analogs Dissolving Metal Reduction of 7. A dry three necked flask equipped with a gas inlet, glass covered magnetic stir bar, and Dewar condenser was cooled to -78°C in a Dry Ice-acetone bath and charged with 35 mL of anhydrous ammonia. To this was added a solution consisting of tetralin **7** (142 mg, 0.49 mmol) in 2 mL of THF and 4 mL of anhydrous ethanol. While stirring vigorously, 0.5 cm lengths of lithium wire (Aldrich, 3.2 mm diameter, 0.01% sodium content) was added. A blue color slowly appeared. When the blue color faded another 0.5 mm piece of lithium wire was added. A typical reaction required the

addition of 4-5 lengths of wire (40-60 mmol) before the reaction mixture retained the blue color for at least 1 h (approx. 3-4 h total reaction time). Once the reaction was complete, the cloudy white suspension was treated with 500 mg of solid ammonium chloride and the solvent was allowed to evaporate over a period of several hours. The residue was dissolved in water and extracted with chloroform. The combined organic fractions were dried ($MgSO_4$) and concentrated to give 130 mg of a colorless oil. The crude product consisted of **9** as well as the enol ether of the over-reduction product. The product mixture was passed directly on to the hydrolysis step.

β-γ Unsaturated Ketone 11. The crude reduction product mixture from above (130 mg) was taken up in 20 mL of THF/water (4:1) and treated with 100 mg of oxalic acid-dihydrate. The resulting solution was allowed to stir at ambient temperature for 3 h and the solvent was removed by rotary evaporation. The resulting residue was dissolved in water and extracted with several portions of chloroform. The combined organic fractions were dried ($MgSO_4$) and concentrated to give a crude oil. Preparative layer chromatography of the crude oil, first in hexanes/ethyl acetate (1:1), then in methanol/chloroform (5%, eluted twice) gave 57.6 mg (42%) of the desired unsaturated ketone **11** as a colorless oil: $[\alpha]_D$ +78.1° (c 1.05, $CHCl_3$); IR (film) 3392, 2932, 2860, 1701, 1455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (br s, 1H), 3.77 (A of AB, d, 1H, J=10.6 Hz), 3.64 (t, 2H, J=6.4 Hz), 3.34 (B of AB, d, 1H, J=10.6 Hz), 2.82-2.77 (m, 1H), 2.48 (t, 2H, J=5.2 Hz) with overlapping multiplet at 2.53-2.40 (2H), 2.21-0.94 (env, 13H), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) DEPT experiment with multiplicity analysis[21] δ 212.63 (s), 142.64 (s), 121.59 (d), 63.19 (t), 62.84 (t), 47.31 (d), 46.45 (d), 45.03 (s), 36.91 (t), 32.65 (t), 30.55 (t), 30.40 (t), 28.40 (t), 27.09 (t), 25.88 (t), 25.36 (t), 20.55 (q). High resolution mass spectrum calcd for $C_{17}H_{28}O_3$: 280.2038. Found: 280. 2040.

The Saturated Ketone (12). Obtained from chromatography showed the following physical data: IR (film) 3392, 2938, 1694, 1450, 710 CM^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 (A of AB, d, 1H, J= 10.8 Hz), 3.64 (t, 2H, J= 6.6 Hz), 3.41 (B of AB, d, 1H, J= 10.8 Hz), 2.66 (dt, 1H, J= 4.5,12.8 Hz), 2.47 (m, 2H), 2.40 (m, 1H), 2.20 (broad DD, 1H, J= 1.8,14.6 Hz), 2.14-2.08 (m, 2H), 1.80-0.84 (env., 15H), 1.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.45; 64.41, 62.94, 49.51, 41.70, 40.35, 39.73, 37.54, 32.73, 29.75, 28.46, 27.88, 26.64, 25.27, 22.91, 22.66, 20.02.

α,β-Unsaturated Ketone 13. The β,γ-unsaturated ketone **11** was isomerized by treating its solution (85 mg, 0.3 mmol) in dry methanol (5 mL) with a catalytic amount of freshly prepared sodium methoxide and allowing the reaction to stir at ambient temperature overnight. The solvent was removed by rotary evaporation and the residue was partitioned between water (10 mL) and chloroform (25 mL). The organic fraction was collected and dried ($MgSO_4$). Concentration afforded 80 mg (94%) of **13** as a colorless oil: $[\alpha]_D$ -33.88° (c 0.018, $CHCl_3$); IR (film) 3412, 2931, 1644, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67-3.62 (m, 2H), 2.44-2.34 (m, 2H), 2.14-2.06 (m, 1H), 1.98-1.01 (complex env), 1.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.45, 159.29, 134.59, 66.06, 62.97, 42.44, 37.91, 32.74, 29.40, 27.80, 26.18, 26.65, 22.99, 22.67, 21.81. High resolution mass spectrum calcd for $C_{12}H_{28}O_3$: 280.2038. Found: 280.2034.

Bottom Half Analog 15. A degassed dichloromethane solution of the crude Birch reduction product **9** (50.0 mg) was placed in a Fisher-Porter hydrogenation bottle along with 7.0 mg

of 5% rhodium on alumina. The apparatus was flushed with hydrogen several times then pressurized to 50 psi. After stirring overnight, the reaction was vented and the resulting suspension filtered through a plug of Celite. Solvent removal furnished the reduced product as a colorless oil. The crude product was taken up in acetone (5 mL) and cooled to 0°C in an ice-water bath. An excess of 2.67M Jones reagent[23] was added and the reaction was allowed to stir for 5 h at 0°C before quenching with isopropanol (1 mL). The solvent was removed by rotary evaporation and the residue was partitioned between water (5 mL) and ethyl acetate (10 mL). The organic fraction was collected and the aqueous portion extracted with 2x10 mL of ethyl acetate. The combined organic fractions were dried ($MgSO_4$), filtered, and the solution was treated with an excess of diazomethane. After stirring for 30 min the solvent was removed to provide the crude diester which was purified by chromatography (plc, hexanes/EtOAc 9:1) to give 43 mg of the bottom half analog **15**: $[\alpha]_D$ +80.66° (c 0.030, $CHCl_3$); IR (film) 1725; 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.64 (s, 3H), 3.15 (dt, 1H, J= 4.6,11.3 Hz), 2.30 (t, 2H, J= 7.7 Hz); 2.05-2.01 (m, 1H), 1.93-0.85 (complex env.), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)[21] δ 177.40, 174.28, 81.74, 55.61, 51.45, 51.24, 49.64, 44.62, 41.17, 37.38, 34.13;,30.48, 28.62, 27.66, 25.97, 25.24, 24.08, 23.69, 19.92, 18.98. High resolution mass spectrum calcd for $C_{20}H_{34}O_5$: 354.2407. Found: 354.2422.

Diester Ketone 17. A solution of the β,γ-unsaturated ketone **11** (95 mg, 0.34 mmol) in dry, degassed dichloromethane (5 mL) was placed in a Fisher-Porter hydrogenation bottle under an argon atmosphere along with 10 mg of Adams catalyst (PtO_2, ~ 40 mesh). The reaction bottle was flushed five times with hydrogen then filled to a final pressure of 50 psi. After stirring for 16 h at ambient temperature the reaction was vented and filtered through a bed of Celite. The filtrate was concentrated and the crude oil, a mixture of **16a** and **16b** was taken up in acetone (20 mL), cooled to 0°C in an ice-water bath, and treated with an excess of Jones reagent.[23] After stirring for 5 h at 0°, the orange suspension was quenched by addition of isopropanol (1 mL) and warmed to ambient temperature. The solvent was removed by evaporation and the green residue was taken up in water (10 mL) and extracted with 3x20 mL of ethyl acetate. The combined organic fractions were dried ($MgSO_4$) and filtered. The filtrate was treated with an excess of diazomethane then concentrated to give 104 mg (91%) of the desired product as a mixture of isomers **17** and **23** by capillary GC analysis at 230°C (t_r major= 20.14 min; t_r minor= 22.41 min). Chromatography (plc, 20% hexanes/EtOAc) afforded 51.2 mg of **17** as a colorless oil: IR (film) 2940, 1730, 1708, 1425 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[21] δ 3.67 (s, 3H), 3.65 (s, 3H), 2.78 (dt, 2H, J= 2.8,11.4 Hz) which is lost upon deuterium exchange in the presence of NaOMe-MeOD, 2.82-2.75 (m, 4H); 2.37-2.01 (m, 3H), 1.78-1.70 (apparent dd, 1H), 1.66-0.70 (complex env.), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) DEPT experiment with multiplicity analysis[21] δ 212.87, 174.93, 174.10, 52.05 (d), 51.49 (q), 51.05 (q), 49.85, 45.95 (d), 42.96 (d), 41.96 (t) which is lost upon deuterium exchange in the presence of NaOMe-MeOD 33.98, 30.92, 28.17, 27.07, 26.82, 26.06, 25.91, 25.06, 24.72, 23.45.

Diester Ketone 23. Also isolated from the above chromatography was 40.0 mg of **23**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3 HO, 3.62 (s, 3 H), 2.50-2.34 (m, 3 h), 2.30 (dt, 2 H, J = 1.8, 5.5 Hz), 2.24 (broad dd, 1 H, J = 2.4, 15.0 Hz), 2.18-2.08 (m, 2 H), 1.78-1.10 (complex env.), 1.19 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.38, 176.23, 176.18, 51.47, 51.14, 48.56, 45.17, 40.48, 37.50,

34.04, 30.18, 28.29, 27.04, 25.18, 25.12, 25.08, 23.62, 19.74.

Bottom Half Analog 18. A tetrahydrofuran solution (5 mL) of **17** (4.9 mg, 0.014 mmol) was cooled to -78°C in a dry ice-acetone bath and treated with LS-Selectride® (1.0 M in THF, 14.5 μL; 0.014 mmol). The reaction was allowed to stir at that temperature for 3 h then was allowed to warm to ambient temperature. The solution was then treated with 3 N NaOH (1 mL) and 30% aqueous hydrogen peroxide (1 mL) and allowed to stir for 30 min. The mixture was then diluted with 20 mL of chloroform and washed with water (10 mL). The organic fraction was dried ($MgSO_4$) and concentrated to give exclusively 3.7 mg of the axial alcohol. The alcohol was taken up in dry dichloromethane (5 mL) and treated with chloromethyl methylether (25 μL, 0.033 mmol) followed by N,N-diisopropylethylamine (57.4 μL, 0.33 mmol). After stirring overnight, the reaction was diluted with chloroform (20 mL) and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and concentrated to give 4.0 mg (75%) of **18** as an oil. Chromatography (plc 20% EtOAc/hexanes) furnished **18** as a colorless oil with a GC retention time of 22.71 min. at 230°C: $[\alpha]_D$ +48.80° (c 0.019, $CHCl_3$); IR (film) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$,) δ 4.71 (A of AB, d, 1H, J= 6.7 Hz), 4.59 (B of AB, d, 1H J= 6.7 Hz), 3.65 (s, 3H), 3.64 (s, 3H); 3.60 (br d, 1H, J= 2.3 Hz), 3.38 (s, 3H), 2.28 (dt, 2H, J= 1.6,7.6 Hz), 2.20 (dd, 1H, J= 2.7,11.7 Hz), 1.92 (br d, 1H, J= 10 Hz), 1.76-0.85 (complex env), 1.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.48, 174.18, 95.60, 55.45, 51.44, 51.18, 49.33, 43.49, 41.28, 34.15, 34.01, 30.86, 29.68, 28.69, 27.63, 27.31, 24.92, 22.70, 22.54, 20.94, 18.52. High resolution mass spectrum calcd for $C_{21}H_{37}O_6$: 385.2591. Found: 385.2563.

Racemic Bottom Half Analog 20. A sample of racemic diacid[20] was taken up in dry ethyl acetate (5 mL) and treated with an excess of diazomethane, which furnished the diester **19** in quantitative yield (NMR). The diester was taken up in dry, degassed dichloromethane (2 mL) and was hydrogenated over Adams catalyst (PtO_2, -40 mesh) at 50 psi for 3 h. The reaction was vented and filtered through a bed of Celite. The filtrate was concentrated to give 3.0 mg of the bottom half analog **20** as a single isomer by GC analysis t_r = 22.51 min. at 230°C: IR (film) 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[21] δ 4.71 (A of AB, d, 1H, J= 6.7 Hz), 4.59 (B of AB, d, 1H J= 6.7 Hz), 3.65 (s, 3H), 3.63 (s, 3H), 3.60 (br d, 1H, J= 2.5 Hz), 3.38 (s, 3H), 2.26 (dt, 2H, J= 2.6,7.6 Hz), 2.19 (dd, 1H, J= 2.6,11.3 Hz), 1.93 (br d, 1H, J= 10.2 Hz), 1.75-0.83 (complex env), 1.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.38, 174.05, 95.60, 55.47, 51.44, 51.22, 49.32, 43.50, 41.25, 34.17, 34.09, 30.83, 29.69, 28.67, 27.63, 27.29, 22.66, 22.46, 20.93, 18.47.

Bottom Half Analog 22. A solution of the diester ketone **17** (17.6 mg, 0.052 mmol) in 6 mL of methanol-water (2:1) was cooled to 0°C in an ice-water bath. Borane-ammonia complex (3.0 mg, 0.097 mmol) was then added in one portion and the ice bath was removed. The reaction was allowed to stir for 30 min then quenched by addition of saturated ammonium chloride solution (1 mL). The solvent was removed by rotary evaporation and the residue extracted with 3x10 mL of chloroform. The combined organic fractions were dried ($MgSO_4$) and concentrated to give the crude alcohol as a 2:1 mixture of C-5 epimers. Chromatographic purification (plc, 3 elutions with 5% EtOAc/hexanes) furnished 10.2 mg of the desired alcohol (**21**). Derivatization as the methoxymethyl ether (chloromethyl methyl ether, 3.8 μL, 0.051 mmol; i-Pr_2NEt, 88 μL, in CH_2Cl_2) gave 11 2 mg

(56%) of the bottom half analog **22** as a colorless oil: $[\alpha]_D$ +32.5° (c 0.012, $CHCl_3$); IR (film) 3020, 2925, 1735, 1460, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)[21] δ 4.74 (A of AB, d, 1H, J= 6.8 Hz), 4.57 (B of AB, d, 1H, J= 6.8 Hz), 3.65 (s, 3H), 3.61 (s, 3H), 3.37 (s, 3H), 3.01 (dt, 1H, J= 4.2, 14.4 Hz), 2.28 (t, 2H, J= 7.2 Hz), 2.04 (m, 1H), 1.70-0.68 (complex env.), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.32, 174.16, 95.39, 81.37, 55.45, 51.46, 50.83, 49.60, 49.53, 46.03, 43.04; 34.03, 32.05, 31.02, 29.69, 27.57, 27.10, 26.68, 25.05, 23.96, 23.88. High resolution mass spectrum calcd $C_{21}H_{37}O_6$: 385.2591. Found: 385.2565.

Bottom Half Analog 24. A solution of the diester ketone **23** (6.0 mg, 0.018 mmol) in 6 mL of methanol-water (2:1) was cooled to 0°C in an ice-water bath. Borane-ammonia complex (1.0 mg, 0.032 mmol) was then added in one portion and the ice bath was removed. The reaction was allowed to stir for 30 min then quenched by addition of saturated ammonium chloride solution (1 mL). The solvent was removed by rotary evaporation and the residue extracted with 3 x 10 mL of chloroform. The combined organic fractions were dried ($MgSO_4$) and concentrated to give the crude alcohol as a single epimer. Derivatization as the methoxymethyl ether (chloromethyl methyl ether, 3.8 μL, 0.051 mmol; i-Pr_2NEt, 88 μL, in CH_2Cl_2) followed by chromatography (plc, 20% EtOAc/hexanes) gave 5.2 mg (75%) of the bottom half analog **24** as a colorless oil: $[\alpha]_D$ + 64.4° (c 0.050, $CHCl_3$); IR (film) 3010, 2925, 1735, 1650, 1460, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.64 (A of AB, d, 1 H = J = 6.7 Hz), 4.59 (B of AB, d, 1 H, J = 6.7 Hz), 3.68 (s, 3 H), 3.62 (s, 3 H), 3.56 (dt, 1 H, J = 3.1, 11.7 Hz), 3.33 (s, 3 H), 2.29 (dt, 2 H, J = 1.0, 6.0 Hz), 1.98-0.86 (complex env.), 1.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.23, 174.29, 94.42, 7.72, 55.20, 51.45, 51.25, 49.53, 44.68, 41.13, 38.45, 34.13, 30.45, 28.58, 27.61, 26.78, 25.23, 24.14, 23.63, 19.68, 19.31. High resolution mass spectrum calcd for $C_{21}H_{37}O_6$: 385.2591. Found: 385.2565.

Racemic Dihydro Bottom Half Analog 26. A sample (40 mg) of the *trans*-fused ring system, C-2 three carbon alcohol **25** supplied by Professor W. R. Roush was converted to the dihydro analog by hydrogenation over platinum oxide. The side chain was homologated by the exact procedure described by Rousch and Hall[7] for the chlorothricolide bottom half synthesis. This procedure furnished 38.2 mg of the racemic bottom half analog **26** as a colorless oil: IR (film) 3030, 1730, 1654, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (A of AB, d, 1 H, J = 6.8 Hz), 4.58 (B of AB, d, 2 H, J = 6.8 Hz), 3.66 (s, 3 H), 3.64 (s, 3 H), 3.38 (s, 3 H), 3.18 (apparent ddd, 1 H, J = 4.1, 9.9 Hz), 2.28 (t, 2 H, J = 7.5 Hz), 2.30-2.26 (broad dd, 1 H, J = 3.1, 11.9 Hz), 1.93-1.87 (broad dd, 1 H, J = 3.5, 13.1 Hz), 1.76-0.88 (complex env.), 1.21 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.19, 174.13, 95.44, 81.37, 55.53, 51.46, 51.28, 49.23, 43.01, 39.30, 33.98, 32.79, 28.18, 27.77, 27.31, 24.91, 23.85, 22.79, 22.40, 18.66.

NMR Details. NMR spectra were aquired on Brüker AC and AM spectrometers. Proton NMR spectra were obtained at 270, 300 and 500 MHz while carbon spectra were obtained with complete composite pulse proton decoupling at 75 and 125 MHz. Phase-sensitive ^1H-^1H and ^1H-$^{13}C\{^1H\}$ 2D correlated data were obtained by using TPPI and Brüker DISNMR software programs. The 2D experiments were performed on 5 mmolar samples prepared in 5 mm NMR tubes. For these experiments a π/2 shifted-sine-bell window function was applied to both domains and the data sets were zero-filled prior to Fourier transformation. The final spectral resolution in the 2D

heteronuclear experiments was 20 Hz/point along the ^1H (F_1) axis and 4 Hz/point doing the ^{13}C (F_2) axis. The final spectral resolution in the 2D homonuclear correlated experiments was 4.0 Hz/point along F_1 and 1.0 Hz/point along F_2. No data symmetrization was applied. ^1H-^1H coupling constants were measured by examining relevant slices of the DQF-COSY spectrum along F_2. Measured coupling less than 3 Hz in magnitude were subject to large errors and are reported cautiously.

Acknowledgment. Financial support for this work was provided by the National Institutes of Health. The authors are grateful to the Colorado State University Regional NMR Center funded by the National Science Foundation for access to the 500 MHz NMR instrument.

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