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ENANTIOSELECTIVE SYNTHESIS OF THE BOTTOM-HALF OF CHLOROTHRICOLIDE

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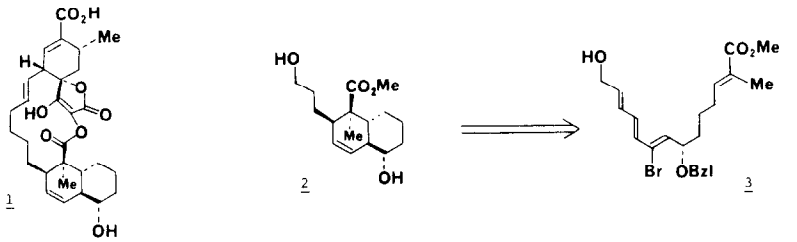
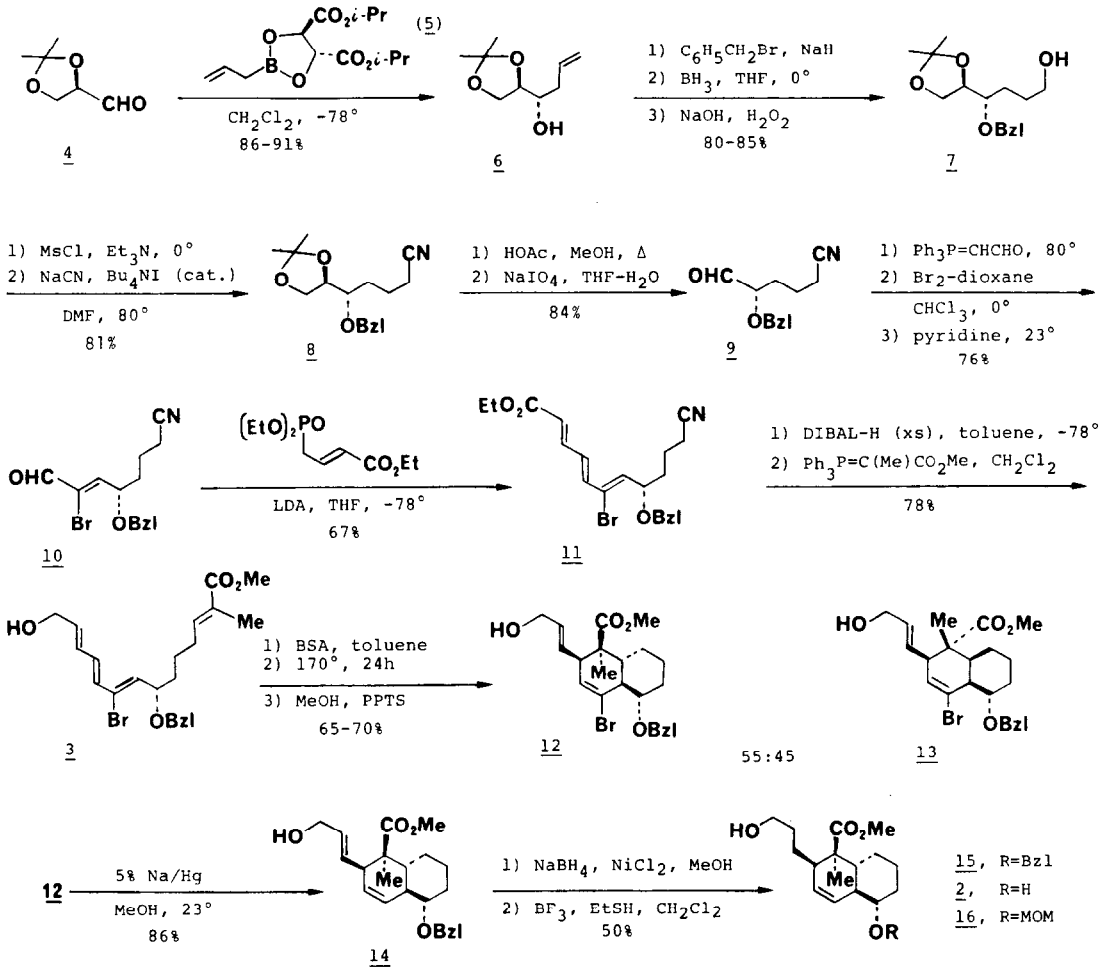
Abstract. The first enantioselective synthesis of a chlorothricolide intermediate is described. The synthesis features the intramolecular Diels-Alder reaction of tetraene 3.

Chlorothricolide (1), the aglycone of the antibiotic chlorothricin,[2] is the object of synthetic endeavors in several laboratories.[3,4] In continuation of our earlier efforts[3a] we now report the first enantioselective synthesis of a chlorothricolide intermediate (2) by a route featuring the intramolecular Diels-Alder reaction of 3.



Treatment of D-glyceraldehyde acetonide (4) with 1.2 equiv. of the chiral allylic boronate 5 prepared from (+)-DIPT[5] in CH_2Cl_2 (0.2 M) at -78° until complete (typically 24-48 h) afforded 96:4 mixture of erythro and threo isomers of 6 in 86-91% yield.[6] This mixture was benzylated ($C_6H_5CH_2Br$, NaH, 3:1 THF-DMF, reflux), separated chromatographically, and then the erythro isomer was treated with 1.0 equiv. of BH_3 in THF at 0°C (3 M NaOH, 30% H_2O_2 workup) to afford primary alcohol 7 ($[\alpha]_D^{23}$ + 16.2° (c=2.1, $CHCl_3$)) in ca. 85% overall yield.[7] Chain elongation via cyanide displacement (1.5 equiv. NaCN, cat. Bu_4NI, DMF, 80°) of the corresponding mesylate proceeded smoothly to afford 8 (81%; $[\alpha]_D^{23}$ + 51.3° (c=1.5, $CHCl_3$)) which upon acidic methanolysis (50% HOAc-MeOH, reflux) and periodate cleavage provided 84% of aldehyde 9 ($[\alpha]_D^{23}$ - 77.8° (c=2.0, $CHCl_3$)). Condensation of 9 with 1.2 equiv. of Ph_3P=CHCHO in C_6H_6 at 80°C afforded a 10:1 mixture of (E)- and (Z)-unsaturated aldehydes, which, without separation, was treated sequentially with 1.2 equiv. of bromine-dioxane complex at 0°C in $CHCl_3$ followed by excess pyridine to effect dehydrobromination (76% yield of 10 for the three steps). This intermediate, which was essentially one isomer (>95%), was elaborated to triene ester 11 ($[\alpha]_D^{23}$ - 58.6° (c=1.6, $CHCl_3$)) by exposure to 2.5 equiv. of the lithium anion of trimethyl 4-phosphonocrotonate in THF (-78° → 23°, 67% yield). Finally, reduction of 11 with

Scheme I

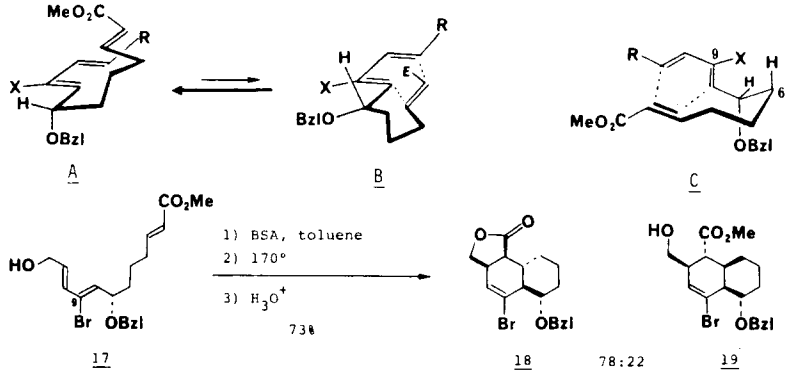


a large excess DIBAL-H (10 equiv.) in toluene at -78° followed by a mildly acidic aqueous workup and then treatment with $Ph_3P{=}C(Me)CO_2Me$ in CH_2Cl_2 at room temperature afforded the key Diels-Alder substrate 3 ($[\alpha]_D^{23}$ - 30.3° (c=1.8, $CHCl_3$)) in 78% yield.

A 0.5 M solution of 3 in toluene was treated with 2 equiv. of BSA at 23° for 1-2 h and then was heated at 170° for 24-30 h (sealed tube).[3a] The crude product was partially purified by filtration through Florisil and then was deprotected by brief exposure to catalytic pyridinium p-toluene sulfonate (PPTS) in MeOH. Separation of the resulting product mixture by silica gel chromatography afforded pure 12 ($[\alpha]_D^{23}$ - 120° (c=1.4, $CHCl_3$)) in 36-39% yield along with 30-31% of 13 ($[\alpha]_D^{23}$ - 170° (c=1.95, $CHCl_3$)). Exposure of 12 to excess 5% Na/Hg in MeOH (24 h, 23°C) afforded diene 14 (86%; $[\alpha]_D^{23}$ - 104° (c=1.02, $CHCl_3$)), the allylic alcohol functionality of which was reduced with moderate selectivity by treatment with $NiCl{\cdot}6H_2O$

(1 equiv.) and $NaBH_4$ (10 equiv.) in MeOH (0° → 23°, 1.5 h).[8] Finally, deprotection of 15 by using the methodology described by Fujita[9] completed the synthesis of 2 ($[\alpha]_D^{23}$ - 87° (c=0.44, $CHCl_3$)).[10] The optical purity (≥98%) of this compound was established by comparison of the bis-MPTA derivative[11] with that prepared from a sample of racemic 2 obtained by deprotection ($BF_3 \cdot Et_2O$, PhSH, CH_2Cl_2, 95% yield)[12] of 16.[3a] Since the stereochemistry of 6 has been firmly established,[6] it follows that the absolute configuration of tetraene 3 is (S) and that (-)-2 is of the same enantiomeric series as the natural product.

This synthesis overlaps with studies ongoing in our laboratory on the development of new methodology for achieving stereochemical control in intramolecular Diels-Alder reactions. We reasoned that introduction of selectively removable steric directing groups[13] at C.9 (see 17) would enhance the magnitude of allylic interactions involving the C.7-alkoxyl group and lead to increased asymmetric induction relative to cases when X=H (compare transition states A and B).[3a] Second, non-hydrogen C.9 substituents were expected to destabilize exo transition state C (only one of the two possible diastereomeric arrangements is shown) relative to A owing to interactions between the axial hydrogen at C.6.[14] Although the bromine substituent nicely satisfies the first of these objectives,[15,16] the increased selectivity[15] for trans-fused endo cycloadducts such as 12 from 11, or 18 from 17, is not as great as we hope ultimately to achieve Consequently, additional studies are in progress to introduce more sterically demanding directing groups (e.g., $-SiR_3$). Reports on these efforts and studies directed towards the synthesis of the top half of 1 will appear in due course.



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7. All new compounds (2, 3, 7-19) were fully characterized spectroscopically (NMR, IR, mass spectrum) and each gave a correct combustion analysis (C,H) or high resolution mass determination.

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10. Partial data for 2: NMR (250 MHz, $CDCl_3$) δ 5.96 (d, J=10.3 Hz, 1 H), 5.72 (ddd, J=10.3, 4.9, 1.6 Hz, 1 H), 3.65 (s, 3 H), 3.58 (t, J=6.5 Hz, 2 H), 3.33 (br dt, J=4, 9.4 Hz, 1 H), 2.07-1.92 (m, 2 H), 1.15 (s, 3 H); IR ($CHCl_3$) 3600, 3460, 1720, 1250, 1130, 1020; high resolution mass spectrum, calcd for $C_{16}H_{26}O_4$, 282.1831, found 282.1850 (±0.0006).

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13. Professor R.K. Boeckman of the University of Rochester has performed independent studies in this area. We thank Professor Boeckman for several discussions on this topic and for the exchange of manuscripts prior to publication.

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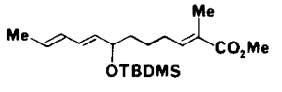
15. In earlier studies we have shown that the cyclization of triene i affords a 15:13:23:49 mixture of diastereomers of which the two major isomers possess cis ring fusions (see ref. 3a).



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16. In all cases examined thus far the level of asymmetric induction is ≥7:1. Only two cycloadducts, 12 and 13, were detected in the cyclization of 6; cycloadducts 18 and 19 were obtained as 7:1 mixtures of alkoxyl epimers.

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