Enantioselective Total Synthesis of (–)-Chlorothricolide

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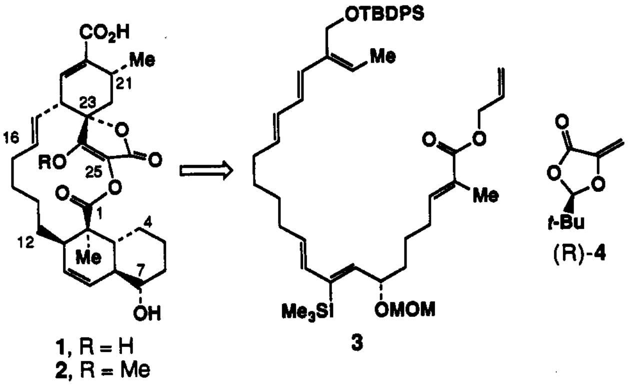
Chlorothricolide (**1**), the aglycon of the antibiotic chlorothricin,[1] is the simplest member of the spirotetronate class of natural products that includes the kijanimicins and tetrocarcins.[2] Although Yoshii and co-workers have synthesized racemic 24-*O*-methylchlorothricolide (**2**),[3a] chlorothricolide itself has remained an elusive target.[3,4] We therefore are pleased to report herein the first total synthesis of (–)-**1** by a route involving the tandem inter- and intramolecular Diels–Alder reaction of hexaenoate **3** and the chiral dienophile (*R*)-**4**.[5] This approach, which we believe is inherently more efficient than potential sequences involving the coupling of fully elaborated top and bottom half fragments, is feasible only by virtue of the high diastereofacial and exo selectivity of **4**.[4b,5] The *C*(9)-trimethylsilyl steric directing group of **3** also plays a key role by controlling the stereochemical course of the intramolecular Diels–Alder reaction leading to the bottom half octahydronaphthalene unit.[4a]

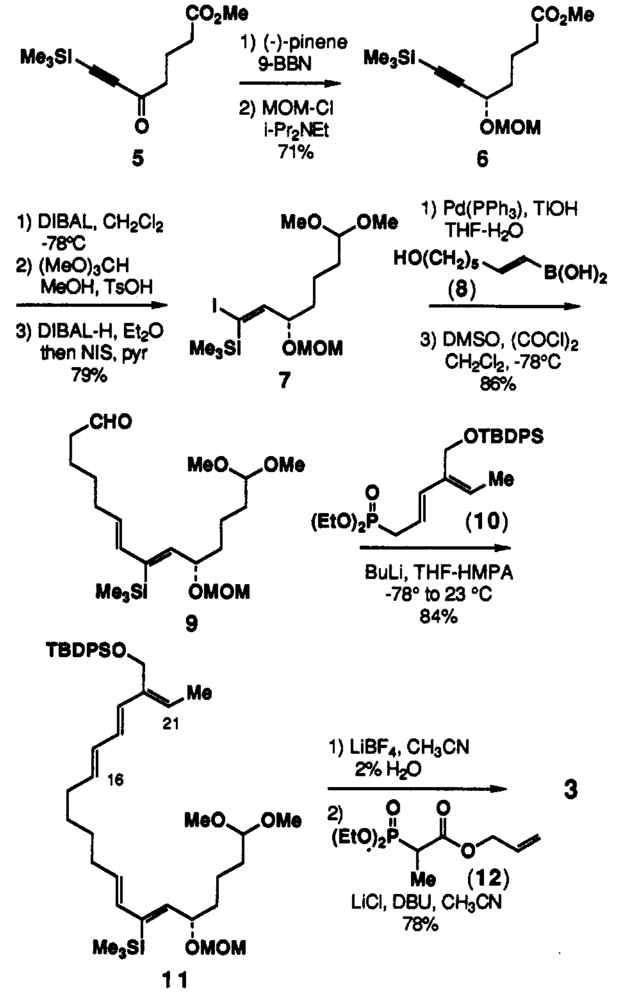


1, R = H
2, R = Me

3

(R)-**4**

Hexaenoate **3** was synthesized by a 10-step sequence from the known acetylenic ketone **5**.[6] Thus, asymmetric reduction of **5** with the chiral borane generated *in situ* from (–)-α-pinene and 9-BBN (neat)[7] and protection of the resulting alcohol (89–94% ee) as a MOM ether provided **6** in 71% yield overall. α-Iodo vinylsilane **7** was prepared in 79% yield by a three-step sequence involving partial DIBAL reduction of the carbomethoxyl group, protection of the aldehyde as a dimethyl acetal, and hydroalumination–iodination of the acetylenic silane using the conditions developed in our previous synthesis of racemic **6**.[4a] Suzuki cross coupling of **7** and 1.4 equiv of vinylboronic acid **8**[4b] using Kishi's modified conditions[8] followed by Swern oxidation of the primary alcohol then gave aldehyde **9** (86% yield).[9] The upper triene unit was then elaborated by treatment of **9** with the lithium anion of dienylic phosphonate **10** [a 5:1 mixture of C(20) (*Z*)- and (*E*)-olefin isomers],[10] giving **11**, also as a ca. 5:1 mixture of C(20)–C(21) olefin isomers, in 84% yield. The newly formed C(16)–C(17) olefin is trans in **11**. Finally, the C(1)–C(3) dienophile unit was introduced by deprotection of the dimethyl acetal ($LiBF_4$, wet CH_3CN)[11] and Horner–Wadsworth–Emmons reaction of the resulting aldehyde with β-keto phosphonate **12**,[10] thereby completing the synthesis of **3** (78% yield).



The tandem inter–intramolecular Diels–Alder reaction was performed by heating a mixture of **3** and (*R*)-**4** (2 equiv) in toluene (1 M in **3**) at 120 °C for 20 h. This provided the desired cycloadduct **13** in 40–45% yield along with 19% of a mixture of cycloadduct isomers[12] and 25–30% of the intramolecular Diels–

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(10) Syntheses of dienylic phosphonate **10** and β-keto phosphonate **12** are described in the supplementary material.

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(12) HPLC analysis of the reaction mixture revealed that four predominate double cycloadducts were produced in the ratio of 67:13:10:10 (average of several runs). This closely approximates the mixture that would be expected if the Diels–Alder reaction of **4** and the C(16)–C(21) triene proceeded with 93:7 selectivity (cf. ref 4b), and if the intramolecular Diels–Alder reaction of the C(1)–C(11) undecatrienoate proceeded with 72:19:9 selectivity (cf. ref 4a). The HPLC trace also contained several other minor bands that presumably account for minor diastereomeric products expected from the Diels–Alder reaction of (*R*)-**4** and *ent*-**3** (present at the ca. 3–5% level in **3**).

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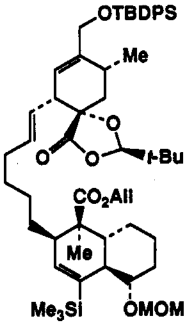
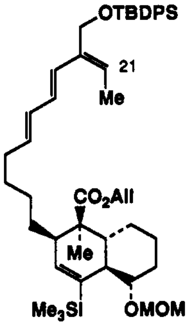
Alder adduct **14** with a C(16)–C(21) (*E*,*E*,*E*)-triene. Owing to the ease with which the C(20)–C(21) trisubstituted olefin isomerizes,[3a,4b] **14** was treated with an additional 2 equiv of (*R*)-**4** in $Cl_2C{=}CHCl$ at 125 °C for 28–36 h, which provided additional **13** (up to 58% from **14**; 55–59% total yield from **3** after one recycle).

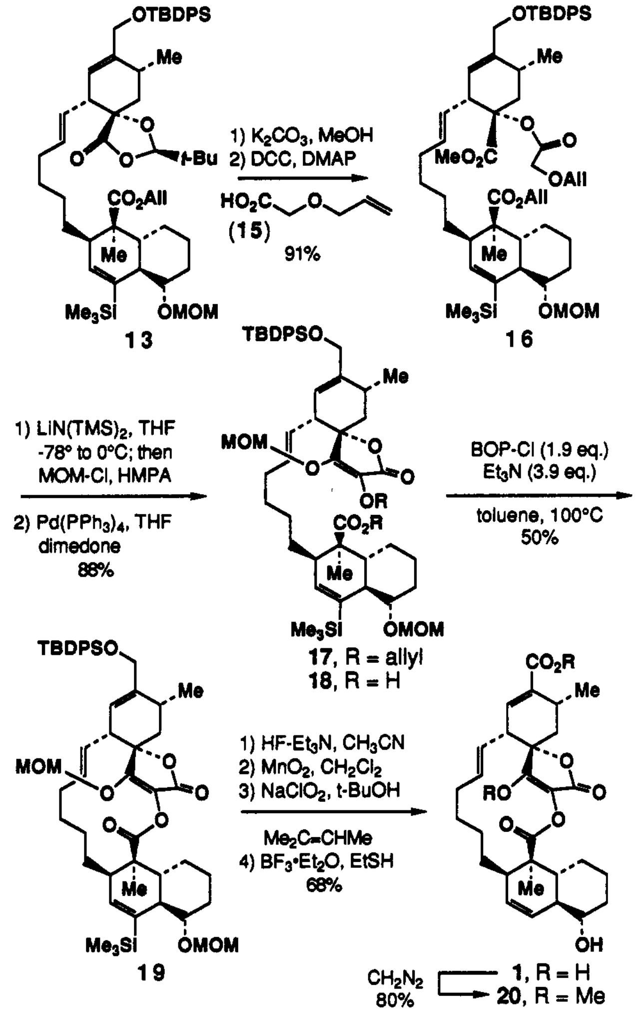


13



14

Methanolysis of **13** (K_2CO_3, MeOH) and then DCC-DMAP-mediated esterification of the resulting tertiary α-hydroxy ester with **15** (5 equiv) provided triester **16** in 91% yield. Dieckmann closure of the spiro tetronate was accomplished by treatment of **16** with $LiN(TMS)_2$ in THF at −78 °C, warming the solution of the enolate to 0 °C, and then addition of MOM-Cl and HMPA (1.8 equiv).[4b,13] The two allyl protecting groups then were removed from **17** by using $Pd(PPh_3)_4$ (0.05 equiv) and dimedone in THF, giving the seco acid **18** in 88% yield for the two steps.[14] Macrolactonization of **18** was accomplished by using BOP-Cl (1.9 equiv) and Et_3N (3.9 equiv) in toluene at 100 °C for 1 h.[15] Under these conditions, macrolactone **19** was obtained in 50% yield along with 31% of recovered **18** (72% based on recovered **18**). Finally, removal of the TBDPS ether (HF–Et_3N, CH_3CN), oxidation of the primary allylic alcohol to the carboxylic acid,[16] and simultaneous removal of the two MOM ethers and cleavage of the vinylsilane by using BF_3–Et_2O and EtSH provided synthetic chlorothricolide (**1**) ($[\alpha]^{25}_D$ −23° ($c = 0.2$, CH_2Cl_2)).[3c,4a,17] Because an authentic reference sample of **1** was unavailable, synthetic chlorothricolide was treated with CH_2N_2 to give dimethylchlorothricolide **20** ($[\alpha]^{25}_D$ −29.3° ($c = 0.95$, $CHCl_3$), mp 228.5–229 °C; lit.[1a] $[\alpha]^{20}_D$ −30° ($c = 1$, $CHCl_3$), lit.[1a] mp 230 °C), which proved identical in all respects (except optical rotation and melting point) with an authentic sample of racemic **20** kindly provided by Professor Yoshii.



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Supplementary Material Available: Experimental procedures and full characterization data for **1** and **6–20** (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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