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Total Synthesis of (+)-4-Deoxygigantecin

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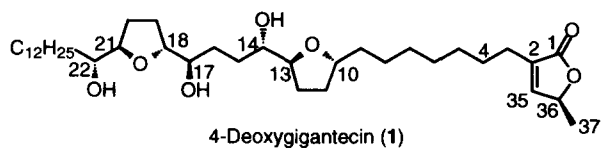
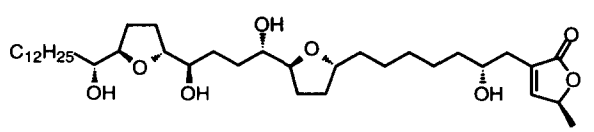
Abstract: (+)-4-Deoxygigantecin (**1**) was totally synthesized from enantiomerically pure (–)-muricatacin (**3**). Thus, **3** afforded the key intermediate **5** through a five-step reaction sequence, which was then converted to (+)-4-deoxygigantecin (**1**) *via* the formation of bis-tetrahydrofuran unit **11** and a coupling reaction with iodo lactone synthon **16**.

The Annonaceous acetogenins, which have been isolated from a number of plants of the *Annonaceae*, have attracted much attention in view of their biological activities such as cytotoxic, antitumor, antifeedant, antiparasitic pesticidal, and immnosuppressive activities.[1] Thus far, more than 230 compounds have been isolated since isolation of the first in 1982.[2] These compounds are characterized by one or more tetrahydrofuran rings, together with a terminal α, β-unsaturated γ-lactone part on a *C*-35 or *C*-37 carbon chain.[1] Although several total syntheses of these compounds including some adjacent bis-tetrahydrofuranic acetogenins have been reported,[3] non-adjacent bis-tetrahydrofuran type annonaceous acetogenins such as 4-deoxygigantecin have not been synthesized yet.

4-Deoxygigantecin (**1**) was isolated from the bark of *Goniothalamus giganteus* by J. L. McLaughlin *et al.*[4] in 1992. The absolute stereochemistry of natural 4-deoxygigantecin has not yet been reported. However, we assumed that the compound (**1**) possessed, except for a*C*-4 carbinol center, the same absolute configuration as that of gigantecin (**2**), whose absolute stereostructure had been established by an X-ray crystallographic analysis, on the basis of the very similar optical rotation values of **1** and **2**, as depicted in Fig. 1. Here we report a total synthesis of natural (+)-4-deoxygigantecin (**1**). This is the first example of the synthesis of a non-adjacent bis-tetrahydrofuran type annonaceous acetogenin.



4-Deoxygigantecin (**1**)

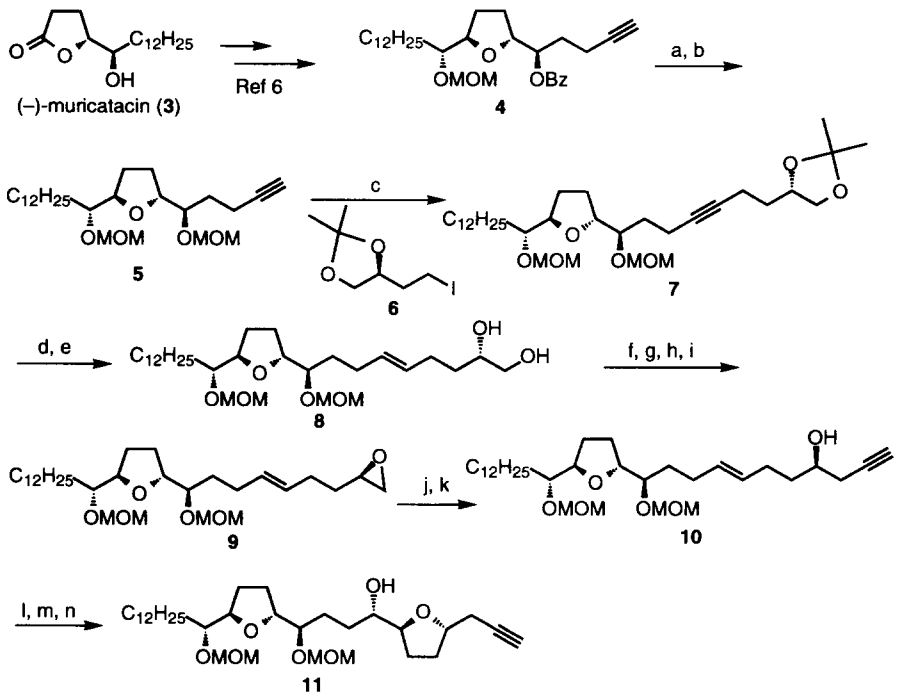


Gigantecin (**2**)

Fig. 1

The starting material was (–)-muricatacin (**3**), which had been reported earlier by us[5] and could be easily obtained in an enantiomerically pure form by recrystallization. The five-step sequence of reactions from **3**, that

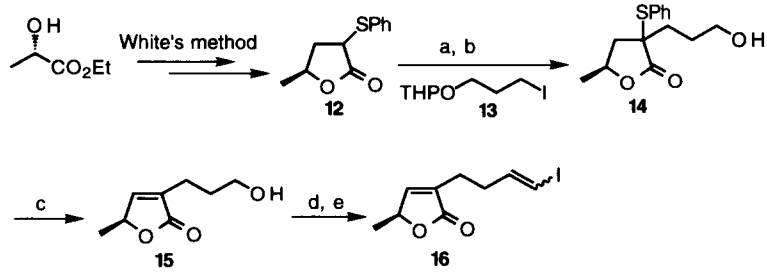
had been reported by us,[6] led to benzoate **4**. Hydrolysis of this ester and reprotection with MOM ether gave bis-MOM ether **5**, which was then converted to **7** by alkylating with iodide **6**[7] employing *n*-BuLi. Reduction of **7** with Na in liquid ammonia and subsequent removal of the acetonide group with 60% aqueous AcOH gave *E* olefinic diol **8** in high yield. Selective protection of the primary hydroxyl group of **8** as a TBS ether and successive treatment with $MsCl/Et_3N$, TBAF and 10% aqueous NaOH afforded the desired epoxide **9**. The coupling reaction of **9** with lithium trimethylsilylacetylide in the presence of $BF_3{\bullet}Et_2O$[8] and subsequent deprotection with TBAF gave **10** in excellent yield. Mesylate formation from **10** with $MsCl/Et_3N$ followed by the Sharpless asymmetric dihydroxylation[9] using AD mix α ,and subsequent cyclization with Triton B furnished the key bis-tetrahydrofuran ring-containing synthon **11**,[10] which was proved to have 92% de by ^{1}H-NMR analysis of the corresponding Mosher ester derivative (Scheme 1).



Scheme 1

Reagents and conditions: a) NaOH, MeOH, 91%. b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 96%. c) *n*-BuLi, THF-HMPA, 70%. d) Na/NH_3, *t*-BuOH, THF, 94%. e) 60% AcOH, 96%. f) TBSCl, Et_3N, DMAP, CH_2Cl_2, 95%. g) MsCl, Et_3N, CH_2Cl_2, 99%. h) TBAF, THF, 89%. i) 10% NaOH, THF, 87%. j) trimethylsilylacetylene, *n*-BuLi, $BF_3{\bullet}Et_2O$, THF, 96%. k) TBAF, THF, 89%. l) MsCl, Et_3N, CH_2Cl_2, 97%. m) AD mix α, *t*-BuOH-H_2O, 88% (92% de). n) Triton B, MeOH, 56%.

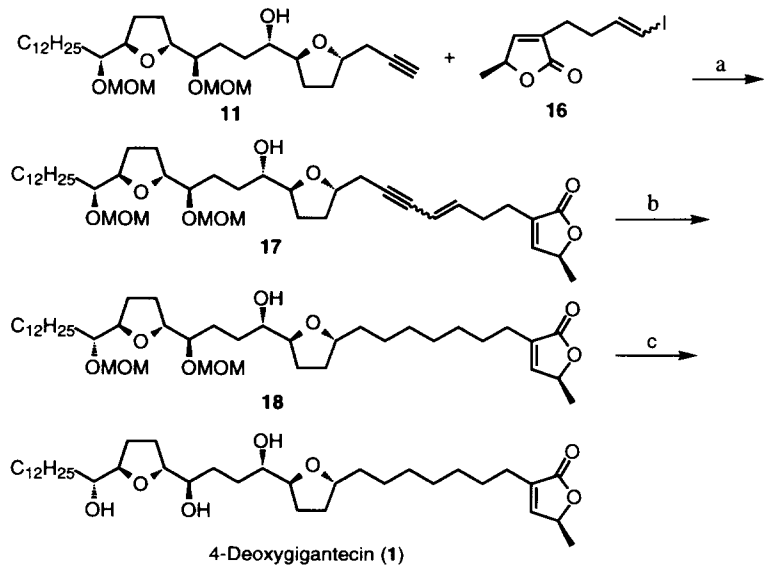
As shown in Scheme 2, the γ-lactone part **16** of **1** was constructed as follows. The substituted γ-lactone **12** was prepared by White's method[11], starting from (*S*)-(–)-ethyl lactate. Base-promoted alkylation of **12** with iodide **13**[12] and subsequent treatment with *p*-TsOH in MeOH gave alcohol **14**. Oxidation with *m*CPBA followed by thermal elimination afforded butenolide **15**. After oxidation of the hydroxyl group with Dess-Martin periodinane, treatment of the resulting aldehyde with CHI_3 in the presence of $CrCl_2$[13] afforded γ-lactone part **16** (*E*:*Z* = 8:1) (Scheme 2).



Scheme 2

Reagents and conditions: a) NaHMDS, THF-HMPA, 89%. b) *p*-TsOH, MeOH, 96%. c) i:*m*CPBA, CH_2Cl_2, ii: toluene, reflux, 85%. d) Dess-Martin periodinane, CH_2Cl_2, 95%. e) CHI_3, $CrCl_2$, THF, 85%.

As shown in Scheme 3, completion of the carbon skeleton to give the coupled product **17** was achieved by application of Hoye's method.[14] A Pd(0)-catalyzed cross coupling reaction of compound **11** with vinyl iodide **16** gave **17**. Finally, catalytic hydrogenation of **17** using Wilkinson's catalyst and subsequent deprotection of the MOM group with BF_3•Et_2O in the presence of dimethyl sulfide[15] gave (+)-4-deoxygigantecin (**1**)[16] in 95% overall yield. Its ^{1}H-NMR data were in good agreement with those recorded for natural **1** and the optical rotation value {$[\alpha]_D^{23}$ +16.0 (*c* 0.05, MeOH)}of the synthetic sample was also consistent with that of natural **1**{$[\alpha]_D$+15.5 (*c* 0.2, MeOH)}.



Scheme 3

Reagents and conditions: a) $Pd(PPh_3)_4$, Et_3N, CuI, benzene, 66%. b) $H_2/Rh(PPh_3)_3Cl$, benzene. c) BF_3•Et_2O, dimethylsulfide, 95% (2 steps).

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10. Data for **11**: $[\alpha]_D^{22}$ +17.2 (*c* 0.18, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3450, 3300, 2930, 2850, 1150, 1100, 1030, 920. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.88 (3H, t, *J*=6.7 Hz), 1.20~2.10 (35H, m), 1.97 (1H, t, *J*= 2.8 Hz), 2.33 (1H, ddd, *J*= 16.7, 6.8, 2.8 Hz), 2.44 (1H, ddd, *J*= 16.7, 5.0, 2.8 Hz), 3.39 (1H, m), 3.40 (6H, s), 3.52 (2H, m), 3.85 (1H, m), 3.95 (2H, m), 4.07 (1H, m), 4.65 (1H, d, *J*= 6.6 Hz), 4.66 (1H, d, *J*= 6.6 Hz), 4.83 (1H, d, *J*= 6.6 Hz), 4.85 (1H, d, *J*= 6.6 Hz). HRFABMS (M+Na^+): Calcd. for $C_{32}H_{58}O_7Na$; 577.4080 Found; 577.4091.
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16. Data for synthetic **1**: mp 105-107 °C. $[\alpha]_D^{23}$ +16.0 (*c* 0.05, MeOH){lit., mp 97-99 °C. $[\alpha]_D$ +15.5 (*c* 0.2, MeOH)}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 0.88 (3H, t, *J*=6.8 Hz), 1.40 (3H, d, *J*=6.9 Hz), 1.21~1.80 (42H, m), 1.99 (4H, m), 2.15 (1H, br. OH), 2.26 (2H, tt, *J*= 7.3, 1.5 Hz), 2.40 (1H, br. OH), 2.65 (1H, br. OH), 3.40~3.45 (3H, m), 3.80~3.89 (4H, m), 5.00 (1H, dq, *J*=6.8, 1.5 Hz), 6.99 (1H, d, *J*=1.5 Hz).

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