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METHYL α-ACYLOXY-γ-METHYLENE-β-TETRONATE. PREPARATION AND USE AS A BUILDING BLOCK FOR THE SYNTHESIS OF THE SPIROTETRONIC ACID STRUCTURE OF CHLOROTHRICOLIDE

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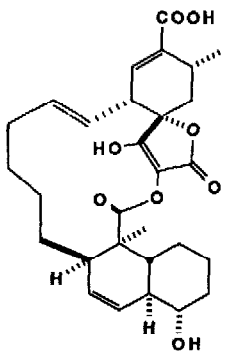
Abstract: The Diels-Alder reaction of the title compound **4** and octatrienol **10**, which were prepared from 4-methoxy-5-methylene-2(5H)-furanone and furfuryl alcohol or D-glyceraldehyde, respectively, produced in high yield a mixture of stereo- and regio-isomeric spirotetronates: **14**, **15**, and **16** in about 65:25:10 ratio. The exo-mode adduct **15** (R= 2,4-difluorophenyl) was transformed into carboxylic acid **19**, the tetronic acid subunit of chlorothricolide (**1**), and also to **21** which can be utilized in the synthesis of **1**.

Chlorithricolide (**1**), the aglycone of the antibiotic chlorothricin reported in 1969,[1] has been the molecule of synthetic endeavors in several laboratories.[2,3] Of the two bridging subunits in the macrolide structure, a hydronaphthalene and a spirotetronic acid, great advance has been made in the stereoselective synthesis of the former fragment (bottom-half),[2,3] whereas synthesis of the functionalized spiro-α-hydroxytetronic acid (top-half) has remained unachieved.[2,4]



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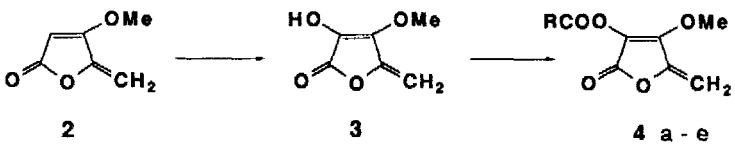
We describe here an easy access to the top-half structure of **1** via Diels-Alder reaction of α-acyloxy-γ-methylene-β-tetronate (**4**) with an appropriate triene **10**.[5]

The dienophile (**4**) was prepared from (γ-methylene)tetronate (**2**)[5] as shown in Scheme 1: (1) lithiation of **2** with $LiN(i\text{-}Pr)_2$ in THF at -90 °C followed by sequential treatment with $B(OMe)_3$ and H_2O_2[6] (ca. 50% yield of **3**), and (2) O-acylation of **3** by conventional manners.[7]

Scheme 1.

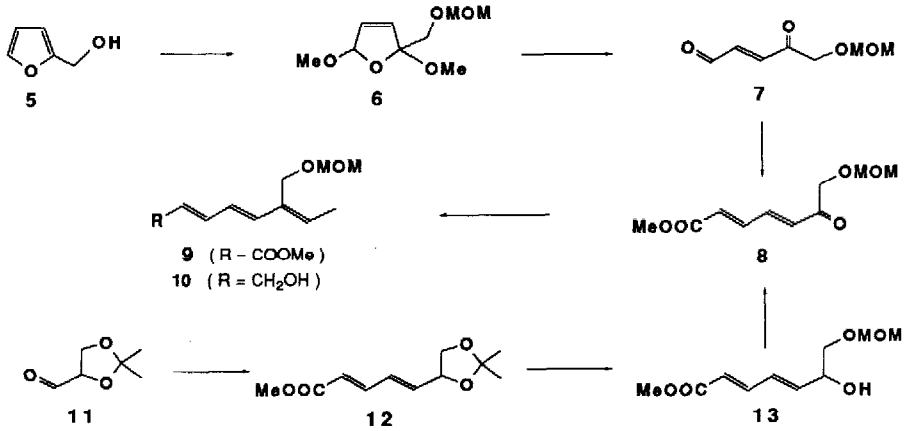


2 **3** **4 a - e**

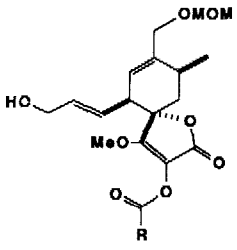
	R	mp (°C)	yield (%)
a	Me	76-7	84
b	Me_3C	61-3	84
c	C_6H_5	136-8	79
d	$2,4\text{-}F_2C_6H_3$	120-2	78
e	$2,4\text{-}Cl_2C_6H_3$	118-20	83

Triene **10** was prepared by using furfuryl alcohol (**5**) as the starting material (Scheme 2). Oxidative methoxylation[8] of **5** (Br_2, MeOH, Et_2O) followed by O-methoxymethylation produced dihydrofuran **6** (73% overall yield), which upon treatment with a cation exchange resin (Dowex 50x) in aqueous acetone afforded 3-oxo-2(E)-pentenal **7**. The crude aldehyde (bp 80 °C/0.2 torr) was allowed to react with Ph_3P=CHCOOMe in benzene at room temperature to give keto-ester **8**, mp 40-41 °C, in 25-30% yield from dihydrofuran **6**. Wittig olefination of **8** with Ph_3P=CHMe (phosphonium iodie + n-BuLi) in THF at -78 to 25 °C afforded trienoate **9** (85-90% diastereomeric purity) in 71% yield, which was then reduced with i-Bu_2AlH to give the requisite trienol **10** (92% yield). Alternatively, the intermediate **8** was prepared from D-glyceraldehyde (**11**) in 4 steps: (1) Wittig-Horner reaction with $(EtO)_2P(O)CH_2CH$=CHCOOMe/NaH (57% yield of **12**), (2) deacetalization (TsOH, H_2O-MeCN), (3) O-methoxymethylation (40% yield from **12**), and (4) Swern oxidation[9] of **13** (76% yield).

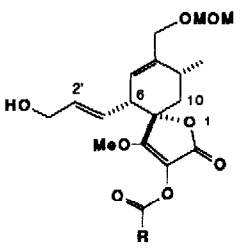
Scheme 2.



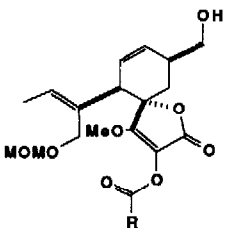
The Diels-Alder reaction of **10** with **4a-e** proceeded in high yields but produced three isomeric adducts: **14**, **15**, and **16** in the ratios shown in Table 1.[10,11] The major product in all cases was not unexpectedly[5] the undesired stereoisomer **14** arising from an endo-mode addition, and the yield of the desired diastereomer **15** is not high (ca. 23%). Nonetheless, we believe that this synthetic approach to the top-half of **1** is attractive since the Diels-Alder reaction partners are readily accessible.



14 a - e



15 a - e



16 a - e

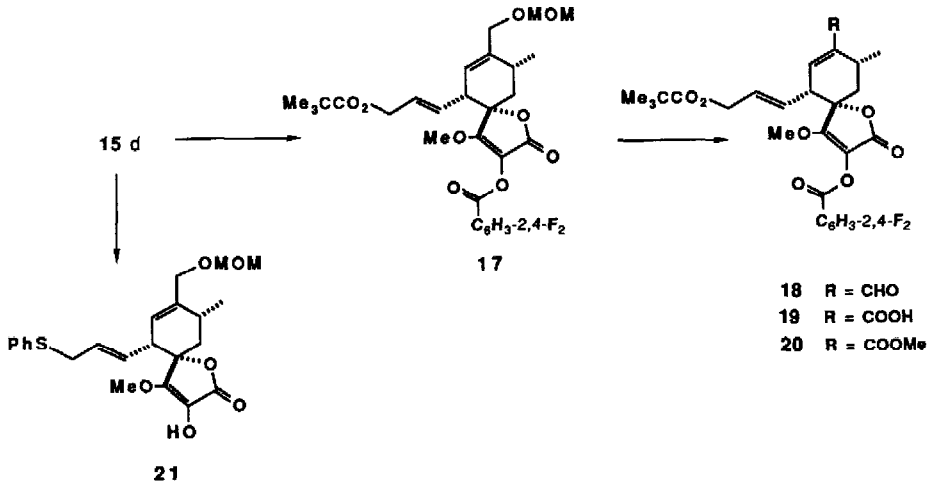
Table 1. Diels-Alder Reaction[a] of **4** and **10**.[b]

dienophile[c]	combined yield[d] (%)	ratio[e] of **14**, **15**, and **16**	yield of **15** (%)
4a	57 (70)[f]	67 : 23 : 10	16
4b	67 (96)[f]	65 : 24 : 11	23
4c	66 (76)[f]	68 : 23 : 9	17
4d	78 (98)[g]	66 : 23 : 11	22.5
4e	79 (100)[f]	61 : 24 : 15	24

[a] With chlorobenzene solvent in the presence of 4,4'-thiobis(2-t-butyl-6-methylphenol). [b] A ca. 6:1 mixture of **10** and its 6(E) isomer was employed. [c] 1.5 Equiv. of **4** was used. [d] Numbers in parenthesis are the yields based on recovered triene. [e] Ratios were estimated by 270 MHz ^{1}H-NMR spectroscopy. [f] 170-175 °C for 6 h. [g] 140-143 °C for 10 h.

With a short-step entry to the top-half structure of **1** established, we pursued conversion of the MOM-protected allyl alcohol group in **15** into carboxylic acid, the synthetic operation required in the total synthesis of **1** after construction of the macrolide nucleus. Thus, O-trimethylacetate (**17**) of **15d** (Scheme 3) was first subjected to removal of the MOM group by heating with $LiBF_4$ in wet acetonitrile[12]. The resulting free alcohol (78%) was oxidized with PDC[13] to give the corresponding aldehyde **18**, which on treatment with $NaClO_2$ in the presence of 2-methyl-2-butene[14] afforded the carboxylic acid **19**. The structure of **19** was confirmed by leading it to the methyl ester **20** with diazomethane (48% overall yield from **17**)[15]. In addition, compound **15d** could be readily transformed into **21** by phenylsulfenylation of the allylic hydroxyl group (PhSSPh, n-Bu_3P, pyridine)[16] followed by hydrolysis of the benzoate group (LiOH, MeOH). Esterification of **21** with an appropriate bottom-half carboxylic acid and subsequent macrocyclization are in progress.

Scheme 3.



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5. For utilization of the α-unsubstituted compound **2** in the synthesis of the top-half of kijanolide, an analogue of chlorithricolide (**1**) having a 13-membered ketone nucleus, see K. Takeda, S. Yano, M. Sato, and E. Yoshii, J. Org. Chem., **52**, 4135(1987).
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7. The acylation was carried out in CH_2Cl_2 solvent at room temperature using the following reagents: **4a** Ac_2O/Et_3N; **4b** pivaloyl chloride/Et_3N/4-dimethylaminopyridine (DMAP); **4c-e** carboxylic acid/Et_3N/N,N'-dicyclohexylcarbodiimide/DMAP.
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10. Silica gel chromatography of the product mixture provided **14**, and a mixture of **15** and **16** from which **15** was isolated after O-acylation or O-silylation. The regioisomer **16** could not be obtained in a pure state due to contamination of presumably its diastereomer.
11. The stereochemistries of the Diels-Alder adducts as depicted were assigned on the basis of ^{1}H-NMR spectral analysis (270 MHz, $CDCl_3$). Characteristic difference between **14** and **15** is observed in the chemical shifts and coupling constants of the C(6) methine and C(10) methylene protons on the cyclohexane ring.[5] Spectral data for the representative compounds are given below.
Compound 14d (R=2,4-difluorophenyl) [R_f 0.29, hexane-AcOEt = 1:2]:^{1}H-NMR δ 1.14 (d, J = 7.1 Hz, 3H, Me-9), 1.59 (br, 1H, OH), 1.82 (dd, J = 13.9, 10.3, 1H, H-10), 1.96 (ddd, J = 13.9, 4.9, 1.5 Hz, 1H, H-10), 2.67 (br m, 1H, H-9), 3.01 (br dd, J = ca. 8 Hz, 1H, H-6), 3.39 (s, 3H, OMe), 4.0 (d, J = ca. 12 Hz, 1H, CHH-8, overlapped with 4.03 singlet), 4.03 (s, 3H, OMe), 4.13 (br m, 3H, CH_2-3' and CHH-8), 4.61 and 4.67 (each d, J = 6.6, 1H, OCH_2OMe), 5.58 (br s, 1H, H-7), 5.59 (ddt, J = 15.4, 8.2, ca. 1 Hz, 1H, H-1'), 5.72 (dt, J = 15.4, 5.0 Hz, 1H, H-2'), 6.90-7.04 and 8.07-8.15 (m, ArH). IR (neat): 3450, 1760, 1680 cm^{-1}. Mass spectrum (EI) m/z: 480 (M^+), 419, 418, 338, 141 (base peak).
Compound 17 [R_f 0.35, hexane-AcOEt = 3:2]: ^{1}H-NMR δ 1.27 (d, J = 7.3 Hz, Me-9), 1.81 (dd, J = 14.2, 1.3 Hz, H-10), 2.32 (dd, J = 14.2, 7.3 Hz, H-10), 2.65 (m, H-9), 3.29 (dm, J = ca. 7.5 Hz, H-6), 3.39 (s, OMe), 4.01 (d, J = 12.1 Hz, CHH-8), 4.08 (s, OMe), 4.16 (br d, J = 12.1 Hz, CHH-8), 4.54 (t, J = 5.3 Hz, 2H, H-3'), 4.63 and 4.66 (each d, J = 6.6 Hz, OCH_2OMe), 5.55 (br s, H-7), 5.63 (dd, J = 15.4, 7.5 Hz, H-1'), 5.71 (dt, J = 15.4, 5.3 Hz, H-2'), 7.04-6.89 and 8.14-8.06 (m, ArH). IR (neat): 1775, 1765, 1725, 1690 cm^{-1}. Mass spectrum (EI) m/z: 564.2149 (M^+, calcd 564.2169), 503 (M^+ - $MeOCH_2O$), 141 (base peak, difluorobenzoyl).
O-Trimethylacetate of 16d (R= 2,4-difluorophenyl) [R_f 0.38, hexane-AcOEt = 3:2]: ^{1}H-NMR (C_6D_6) δ 1.15 (s, t-Bu), 1.40 (dd, J = 13.4, 5.9 Hz, H-10), 1.62 (d, J = 7.1 Hz, =CHMe), 1.83 (dd, J = 13.4, 11.4 Hz, H-10), 2.63 (m, H-9), 3.23 (s, OMe), 3.31 (br s, H-6), 3.79 (dd, J = 10.9, 5.8 Hz, CHH-9), 3.83 (d, J = 11 Hz, OCHHC=), 3.98 (dd, J = 10.9, 5 Hz, CHH-9), 4.29 (d, J = 11 Hz, OCHHC=), 4.53 (d, J = 6.4 Hz, OCHHO), 4.57 (d, J = 6.4 Hz, OCHHO), 5.53 (ddd, J = 10.5, 4.4, 2.7 Hz, H-8), 5.60 (q, J = 7.1 Hz, =CHMe), 5.67 (br d, J = 10.5 Hz, H-7), 6.2-6.3 and 7.65-7.75 (m, ArH). IR (neat): 1775, 1725, 1685 cm^{-1}. Mass spectrum (EI) m/z: 565 (M^+ + 1), 520, 141 (base peak).
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15. Spectral data of **20**: ^{1}H-NMR (270 MHz,$CDCl_3$) δ 1.21 (s, t-Bu), 1.31 (d, J = 7.3 Hz, Me-9), 1.87 (dd, J = 14.2, 1.2 Hz, 1H, H-10), 2.30 (dd, J = 14.2, 7.2 Hz, 1H, H-10), 3.00 (m, 1H, H-9), 3.36 (dt, J = 8.2, 2.3 Hz, H-6), 3.78 (s, COOMe), 4.09 (s, MeO-4), 4.56 (dd, J = 13, 5.5 Hz, 1H, H-3'), 4.62 (dd, J = 13, 5 Hz, 1H, H-3'), 5.64 (dd, J = 15.5, 8.2 Hz, H-1'), 5.77 (dt, J = 15.5, 5 Hz, H-2'), 6.90-7.04 and 8.06-8.14 (m ArH). IR (neat): 1775, 1720, 1695, 1615 cm^{-1}. Mass spectrum (EI) m/e: 548 (M^+), 517, 266.
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