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New Approach to Chiral 5,5-Disubstituted Tetronic Acids. Enantioselective Synthesis of (-)-Vertinolide.

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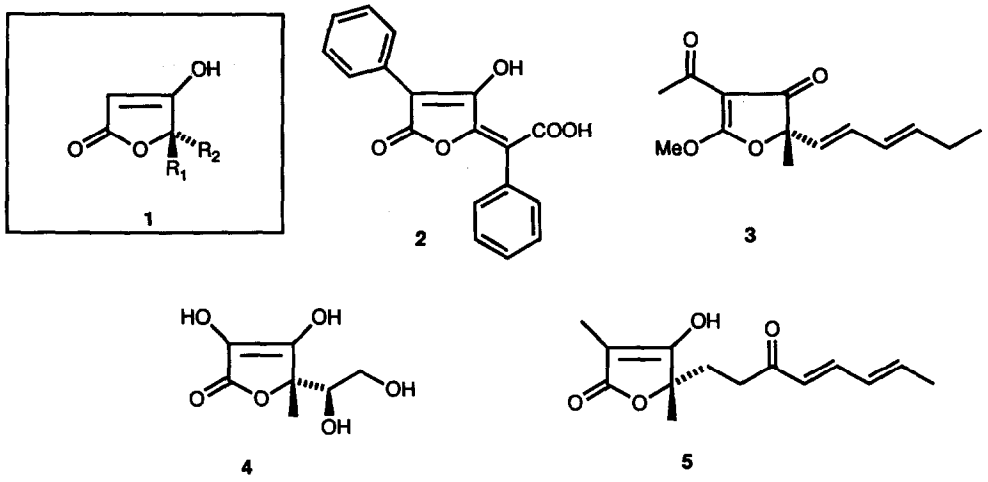
Key words: *Tetronic acid; Asymmetric Michael addition; Chiral imines; 4,5-Dihydrofuran-3-one, Vertinolide.*

Abstract: *A general protocol for enantioselective construction of tetronic acids bearing a stereogenic center at C-5 is described. The readily available Michael adduct* ***12****, obtained by addition of methyl acrylate to imine* ***10*** *derived from 2-methyl-4,5-dihydrofuran-3 one* ***8****, and (R)-1-phenylethylamine* ***9****, was transformed into tetronic acid* ***21*** *by a five step sequence. Silylation and saponification of pivotal intermediate* ***19*** *gave acid* ***14a****. Methylation at C-3 followed by derivatization of the propionic side chain of* ***25a*** *as N-methoxy-N-methyl propionamide and unmasking of the tetronic nucleus as described for* ***19*** *gave compound* ***27****. Addition of 1-lithiopentyne to* ***27*** *produced ynone* ***28*** *whose palladium acetate induced isomerization gave (-)-vertinolide* ***5*** *a fungal metabolite.*

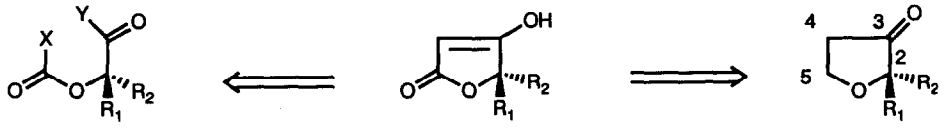
INTRODUCTION

A large variety of metabolites produced by moulds and fungi are covered by the generic name "mycotoxin". Among them,4-hydroxy-butenolides (tetronic acids) **1** are commonly encountered as yellow pigments of lichens and as metabolites of numerous strains of higher fungi.[1] The anti-inflammatory agent vulpinic acid **2**,[2] antibiotic aspertetronin **3**[3] and vitamin C **4**[4] exemplify simple tetronic acid derivatives, although the subunit can also be found in highly complex structures like antitumor agents,tetrocarcine and kijamicine.[5] The broad scope of biological properties displayed by tetronic acids has triggered considerable interest in their synthesis.[6] A fully substituted tetronic nucleus is present in vertinolide **5** a mycotoxin isolated from *Verticillium intertextum*. Structural elucidation of vertinolide, including X-ray analysis, appeared in 1982.[7] Two total syntheses have since confirmed the original assignment and unambiguously established the 5-(*S*) absolute configuration.[8] New methods to prepare such moieties are highly desirable, considering their frequent occurrence in biologically active compounds. We now report on a general pathway for producing chiral tetronic acids as well as an enantioselective synthesis of (-)-vertinolide **5**.



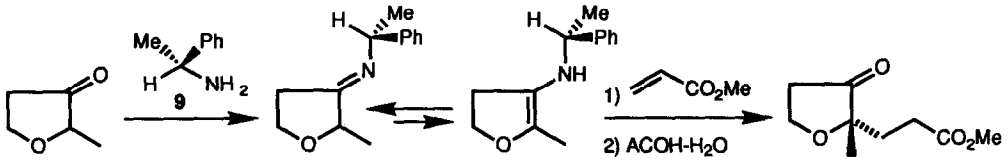
RESULTS AND DISCUSSION

To date the most common pathway for synthesizing γ,γ-disubstituted tetronic acid derivatives in their optically active form has been the ring closure of various acyclic precursors of type **6** derived from tertiary alcohols bearing a previously controlled stereogenic center.[6b] An unexplored possibility of preparing these heterocycles would involve oxidation of the C-5 carbon atom of a 2,2-dialkyl-4,5-dihydrofuran-3-one **7**.

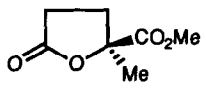


The efficiency of such a strategy relies on the ability to prepare compounds **7** enantioselectively .In this respect we have recently reported that 4,5-dihydrofuran-3-one of type **7** (R_1 = alkyl, R_2= $CH_2CH_2CO_2Me$) can easily be obtained with high optical purity [9] by the asymmetric Michael addition of enamine **11**,the transient tautomeric form of imine **10**,to electron deficient olefins. This process that enabled us to prepare substituted furanones and butenolides is, in fact, an extended application of a very general deracemizing alkylation widely used to build sterogenic quaternary carbon centers [10]. Several applications in the steroid, terpene and alkaloid fields have already revealed the great synthetic potential of the asymmetric process we have disclosed [11]. Thus reaction of methyl acrylate with imine **10**, derived from 2-methyl-4,5-dihydrofuran-3-one **8**[12] and optically pure *R*(+)-1-phenylethylamine ($[\alpha]_D^{20}$ + 40.7° (neat))[13] **9** led, after hydrolytic work up, to adduct **12** with a 78% yield on multigram scale (E.e. 95%, estimated from the ^1H NMR spectrum run in the presence of the chiral lanthanide shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III)). The alkylation took place exclusively on the more substituted α- side of the imine as usually observed in related Michael processes involving chiral imines.[10,11] However, the high regioselectivity observed is noteworthy since the "normal"enolization direction of 4,5-dihydrofuran-3-one

derivatives is away from the cyclic oxygen atom.[14] The 2(*S*) absolute configuration of keto ester **12** has been previously secured by chemical correlation with the known (*S*)-(-) lactone **13**.[9] This assignment is in agreement with an addition predominantly on the *si*-π face of the enamine **11**, namely the face opposite the phenyl ring of the amine moiety in the energetically preferred conformation of the imine, the C-H bond nearly eclipsing the dihydrofuran ring.[10b,c]



8 **10** **11** **12**



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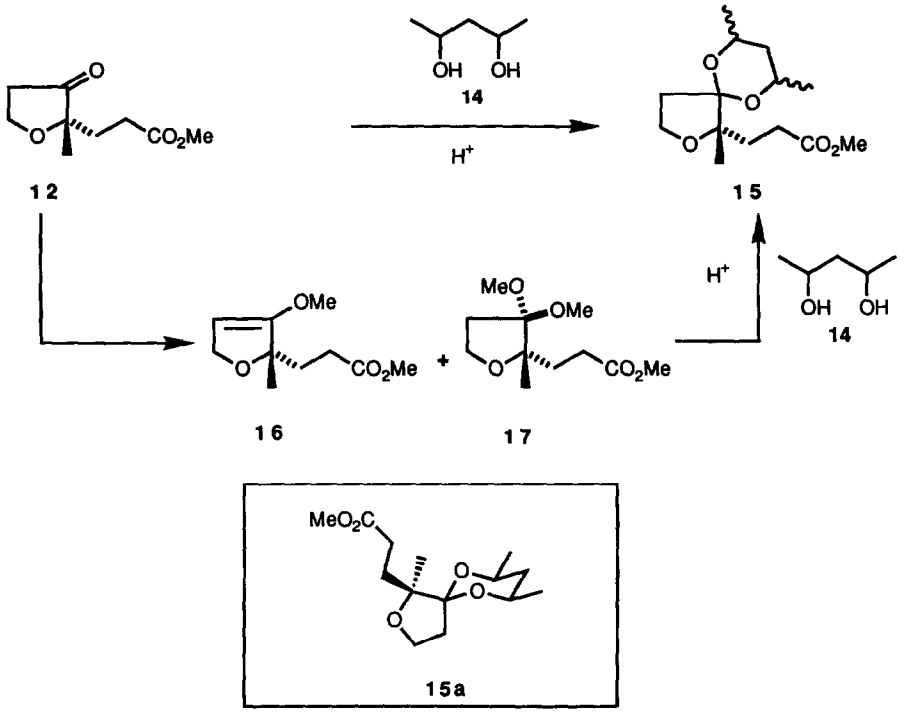
The fully enolized nature of tetronic acids precludes oxidation at C-5 without prior protection of the ketonic carbonyl group.[15] This protecting group must fulfill two requirements: it should survive RuO_4 oxidation and furthermore be removable in mild operating conditions. The aqueous media, even buffered, of the catalytic ruthenium tetroxide oxidation precluded use of simple alkyl ketals,moreover both alkyl ketals and 1,3 dioxolanes led during the hydrolysis to very stable O-alkyl tetronates which required strongly acidic conditions[18a,b] or highly nucleophilic reagents[6b] to regenerate free tetronic acids. Preliminary experiments have revealed that our tetronate derivatives bearing a propionate side chain did not survive in these conditions. 2,4-Pentanediol **14** (as a meso,dl mixture) turned out to be a suitable candidate to solve the two aformentioned problems. Ketalization of keto ester **12** by diols **14** (cat TsOH, refluxing toluene,Dean-Stark trap,120 h) yielded 65% of ketal **15** as a 88/7/5 mixture of isomers. Interestingly, a significant degree of discrimination between the three components of the commercial diols **14** took place,leading mainly to the ketal **15a**, the sole isomer exhibiting no 1,3 diaxial interaction. Alternatively,a simple two-step procedure allowed us to bypass the sluggish direct ketalization. Dihydrofuranone **12** was first treated with trimethylorthoformate and Montmorillonite K10 [16] (20°C,12 h), to give a nearly equimolar mixture of enol ether **16** and dimethyl ketal **17**. This crude mixture upon treatment with an excess of pentanediols **14** (refluxing benzene,TsOH,1 h) gave ketal **15** (75 % yield) as a mixture of diastereoisomers.

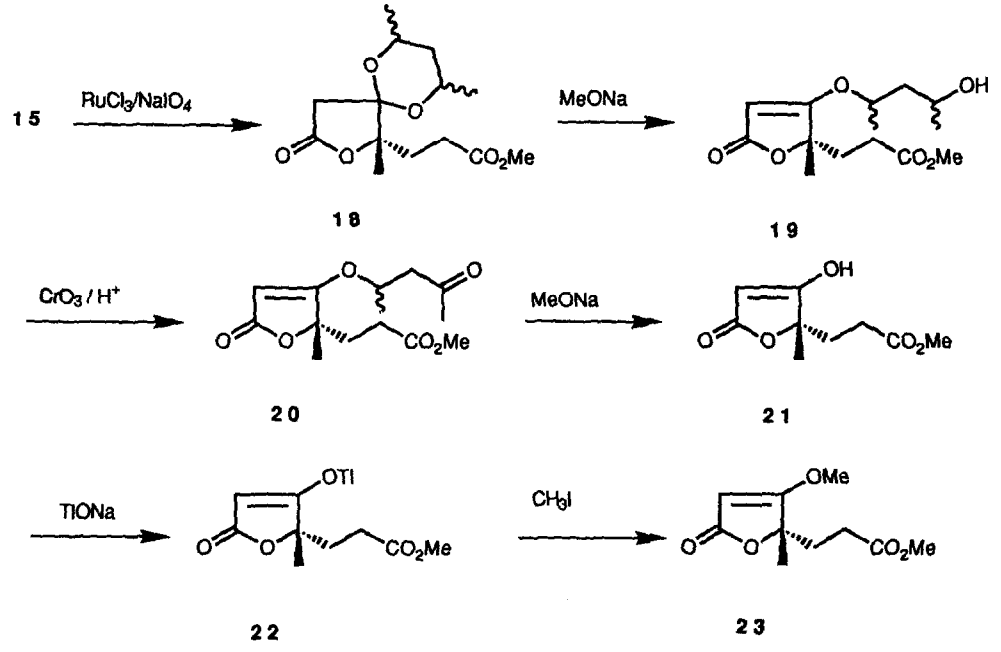
Exposure of compound **15** to ruthenium tetroxide according to Sharpless conditions[17] (3 mol % of $RuCl_3.3H_2O$, $NaIO_4$, $H_2O/CCl_4/CH_3CN$, 24 h, 20°C), resulted in smooth conversion into butyrolactone **18** (84 % yield). Acidic hydrolysis of the ketal group of compoud **18** leading to a complex mixture,the ketal ring was opened by base induced elimination to give rise to the O-alkyl tetronate derivative **19** (80 % yield), along with some starting material. Careful examination of the ^1H and ^{13}C NMR spectra revealed that **19** was a mixture of several isomers,the two main components, in a 1:1 ratio, arising from the abstraction of the two possible hydrogens at C-3, on the lactone derived from ketal **15a**.



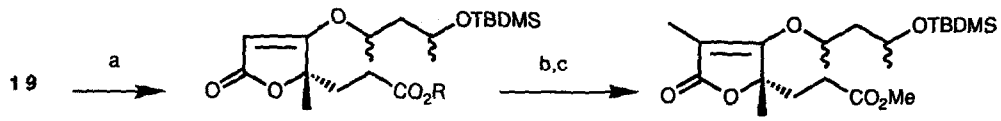
Reasoning that the tetronate anion should be a good leaving group (for tetronic acid : pKa = 3.8[1a]) we then explored the regeneration of this moiety by a ß-elimination reaction.[19] For this purpose, Jones oxidation of the alcohol function of butenolide **19** led to ketone **20**. The latter derivative was then treated with sodium methoxide (MeOH, 20°C, 1h) to afford, after acidic work-up,the desired tetronic acid **21** in 65 % overall yield from lactone **18**. By comparison with the usual conditions of deprotection of O-alkyltetronate derivatives, our operating conditions were very mild, thus emphasizing the usefulness of the aforementioned protecting group [19] to mask the tetronic acid nucleus in the presence of sensitive functional groups.

Completion of the vertinolide synthesis from a protected 4-hydroxy butenolide system like **19** then required methylation at C-3 and homologation of the propionate side chain. We chose to postpone introduction of the highly sensitive dienone appendage until the final stage of the synthesis. C-Alkylation of strongly acidic ß-dicarbonyl compounds remains a problematic task.Thus reaction of the thallium salt [20] **22** derived from **21** (TlOEt, O°C, benzene) with methyl iodide (reflux, 1 h) led only to O-methyl tetronate **23**.Studies by Pattenden and Schmidt [21]have shown that alkylation of O-alkyl tetronate derivatives by using LDA as a base is highly regioselective, leading to C-3 substituted products. In order to adapt such a process to our synthesis, alcohol **19** was first protected as tert-butyldimethylsiloxy ether giving ester **24b**.The ester function was then saponified to provide the corresponding acid **24a**. Addition of a THF solution of this acid to an excess of LDA (-78°C, 30 min.), followed by methyl iodide exclusively produced the desired C-3 methylated tetronate derivative **25a** in 75 % yield. Activation of the carboxyl group on the propionic acid side chain was then completed by using the Weinreb-Nahm procedure.[22] After cleavage of the tert-

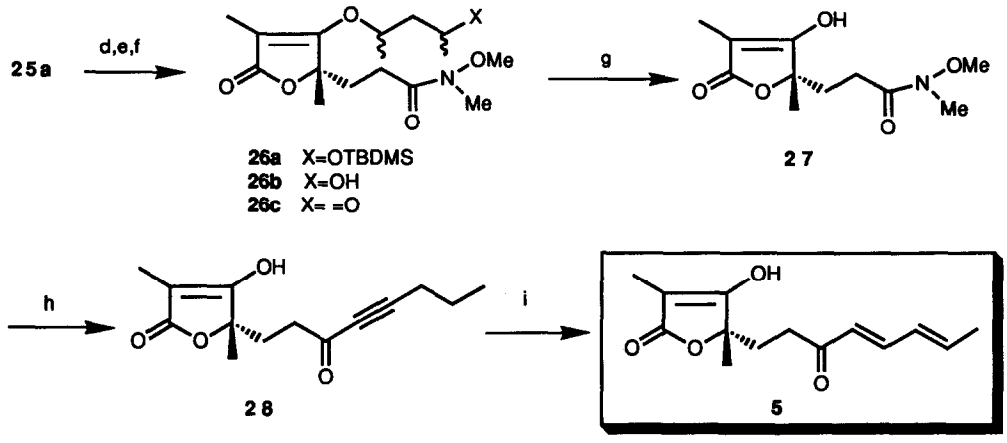
butyldimethylsiloxy group, the pentanediol protecting moiety of **26b** was removed, analogously to the conversion [**19** → **21**], by an oxidation, ß-elimination sequence, giving tetronic acid **27** in 66 % overall yield from acid **25a**.



Since preparation of *E,E*-1-lithio-pentadiene is quite lenghthly [23], we chose a more convenient way to build the dienone side chain, namely the palladium-catalyzed isomerisation of ynones to conjugated dienones introduced by Trost [24].For this purpose, addition of excess 1-lithio-pentyne to N-methoxy-N-methyl-amide **27** led to ynone **28** (76 % yield). Heating a toluene solution (100°C, 1h) of **28** with a catalytic amount of palladium acetate gave a 65 % yield of vertinolide **5**. Crystallization from acetone-ether gave an analytical sample of (*S*)-(-)-**5**, as small white plates, whose physical and spectral properties matched those of natural vertinolide.[7]



a:TBDMSCl/Et_3N/DMAP/DMF, b:NaOH 1N-MeOH, c: LDA ,30 min. -78°C THF then CH_3I



d: MeONHMe.HCl , DCC/DMAP/Et_3N/CH_2Cl_2/20°C12h , e: nBu_4NF 1M,THF 1h 20°C, f : Jones' reagent / acetone 0°C, g: MeONa 1.1 eq MeOH /1h 20°C h: 1-Lithiopentyne THF -30°C , i: $Pd(OAc)_2$/ $P(Ph)_3$/Toluene, 100°C, 1h.

CONCLUSION

In this paper we have shown that chiral 2,2-disubstituted-4,5-dihydrofuran-3-one are suitable precursors of 5,5-disubstituted tetronic acids. This strategy has been sucessfully used to prepare (-)-vertinolide **5** in 12 steps with an overall yield of 11.5 % from the keto ester **12**. We believe this method has considerable potential in the synthesis of complex natural products incorporating the tetronic acid moiety.

EXPERIMENTAL

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were obtained as a neat film between salt plates or KBr pellets,.and were recorded on a Perkin Elmer 298 or a Nicolet FT IR 205 spectrometer. Only significant absorptions are listed. Optical rotations were measured on a Schmidt & Haensch Polartronic I polarimeter in a 1-dm cell. ^1H NMR spectra were recorded on a Bruker AM 250 (250 MHz) instrument. ^{13}C NMR spectra were recorded on a 20 MHz or a 62.9 MHz instrument, and the multiplicities were determined using DEPT sequence. $CDCl_3$ with tetramethylsilane (TMS) as internal standard was used as NMR solvent unless otherwise noted. Mass specra analyses were recorded by electron impact at 70 eV on a JEOL-JMS-AX500. All liquid chromatography separations were performed using Merck SiO_2 60. Thin-layer chromatography analyses were performed on Merck SiO_2 60 F 254 precoated plates.Ether and tetrahydrofuran (THF) were distilled from Na-bezophenone ketyl. Methanol was dried over magnesium and distilled. Diisopropylamine, CH_2Cl_2 and DMF were distilled from calcium hydride, in an nitrogen atmosphere. Small scale distillations were performed with a cold finger apparatus. The boiling points refer to oil bath temperatures. Materials were obtained from commercial suppliers and used without further purification,unless otherwise noted.

(2*S*)-2-Methyl-4,5-dihydro-2(H) furan-3-one-2-propionic acid methyl ester 12. To a mixture of 48 g of 5Å molecular sieves and 12 g of silica-alumina catalyst [25] (activated by heating for a few minutes at 0.05 torr with a burner)was added optically pure (*R*)-(+)-1-phenylethylamine **9**[13] (21 g,0.17 mol) in 100 mL of cyclohexane followed by 2-methyl-4,5-dihydro-3-furanone **8** (15g, 0.15 mol) in 20 mL of cyclohexane. The suspension was stirred vigorously at 20°C for 18 h. The reaction mixture was then filtered and the solid residue was repeatedly washed with anhyd. ether. The organic filtrate was concentrated under reduced pressure.(0.05 torr, 40°C).To the viscous crude imine **10** obtained was added freshly distilled methyl acrylate (26 g, 0.3 mol) and hydroquinone (0.05 g). The stirred mixture was heated at 65°C for 4 days. After cooling to 20°C, 20% aqueous acetic acid (100 mL) and THF (300 mL) were added, and the

mixture was stirred for 3 h. The solvents were removed under reduced pressure then 1 N hydrochloric acid (100 mL) was added.The mixture was extracted with ether and the collected organic phases were dried over magnesium sulfate and concentrated.Chromatography (80:20 hexane/ethyl acetate) gave keto ester **12** (22 g,78 %). Distillation afforded an analytical sample: bp 90-95°C (0.05 mm Hg); $[\alpha]_D^{20}$ - 49 (c=11, EtOH) ; IR (film, cm^{-1}) 1750, 1730, 1440; ^1H NMR δ 4.17 (dt, 1H, J=9.5 Hz, J=7.4 Hz), 4.11 (dt, 1H, J=9.5 Hz, J=7.4Hz), 3.66 (s, 3H), 2.55 (t, 2H, J=7.4 Hz), 2.40 (ddd, 1H, J=15.9 Hz, J=8.8 Hz, J=7.1 Hz), 2.29 (ddd,1H, J=15.9 Hz, J=8.8 Hz, J=6.2 Hz), 1.95 (m,2H), 1.18 (s,3H); ^{13}C NMR (20 MHz) δ 216.9(C), 173.5(C), 80.5(C), 61.7(CH_2), 51.7(CH_3), 36.3(CH_2), 30.8(CH_2), 28.6(CH_2), 20.3(CH_3). Anal. Calcd.for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found : C, 57.84; H, 7.50%.

2,4,7,-Trimethyl-1,5,8 trioxaspiro[4,5]decane-7-propanoic acid methyl ester 15 To a solution of keto ester 12 (8.2 g,44 mmol) in anhyd. methanol (4mL) were added methyl orthoformate (40 mL) and Montmorillonite K 10 (40 g). The thick suspension was stirred for 24 hours. The mixture was filtered and the grey solid residue repeatedly washed with anhyd. ether. The filtrate was concentrated in vacuo and dissolved in 200 mL of dry benzene. Anhydrous 2,4 pentanediol **14** (10 g, 96 mmol) and TsOH (0.5g) were added to the stirred solution.The reaction mixture was refluxed for to 2h in an appartus equipped with a Dean-Stark trap, filled with 4 Å molecular sieves .After cooling to 20°C, ether (200 mL) was added,and the mixture was washed with saturated aqueous sodium bicarbonate,dried over $MgSO_4$ and concentrated.The residue was chromatographed (20:80 ethyl acetate / hexane) to give **15** (9.0 g, 75 %) as a mixture of diastereoisomers, bp. 100°C (0.05 torr); IR (film, cm^{-1}) 1740, 1440. Only the major isomer **15a** is described. ^1H NMR δ 3.75 (m, 4H), 3.54 (s, 3H), 2.32(m, 2H), 2.13(m, 2H), 1.79(m, 2H), 1.41(dt, 1H, J=13.0 Hz, J=2.4 Hz), 1.10(m, 1H), 1.06(d, 6H, J=6.1 Hz), 1.01(s, 3H); ^{13}C NMR (62.9 MHz) δ 174.5(C), 106.9(C), 83.75(C), 67.2(CH), 67.0(CH), 63.4(CH_2), 51.0(CH_3), 40.4(CH_2), 30.2(CH_2), 30.1(CH_2), 28.8(CH_2), 21.65(CH_3), 21.6(CH_3), 19.1(CH_3). Anal. Calcd. for $C_{14}H_{24}O_5$: C, 61.74 ; H, 8.88. Found : C, 61.63 ; H, 8.65%.

9-Oxo-2,4,7-trimethyl-1,5,8-trioxaspiro[4,5]decane-7-propanoic acid methyl ester 18. To a stirred solution of the ketal **15** (7.3 g, 26.8 mmol) in acetonitrile (90 mL) and carbon tetrachloride (90 mL)was added ruthenium trichloride hydrate (0.21 g, 0.8 mmol). After 10 min., a solution of sodium metaperiodate (25 g, 116 mmol) in water (140 mL) was added dropwise. The yellow mixture was vigorously stirred for 24 h. The mixture was filtered through Celite. Saturated aqueous NaCl was then added, the mixture was extracted with CH_2Cl_2 and the collected organic phases were dried and concentated under reduced pressure. The residue was chromatographed (30:70, ethyl acetate / hexane) to give **18** as a mixture of diastereoisomers.(6.45 g, 84 %). IR (film, cm^{-1}) 1780, 1735, 1440. Only the main isomer is described ^1H NMR δ 3.79 (ddq, 2H, J=11.7 Hz, J=2.5 Hz, J=6.1 Hz), 3.66 (s, 3H), 2.94 (d, 1H, J=17.1 Hz), 2.81 (d, 1H, J=17.1Hz), 2.48 (m, 2H), 2.09 (m, 2H), 1.55 (dt, 1H, J=13 Hz, J=2.5Hz), 1.32 (s, 3H), 1.22(m, 1H), 1.17 (d, 3H, J=6.1Hz), 1.16 (d, 3H, J=6.1Hz).^{13}C NMR (62.9 MHz), δ 173.6(C), 172.2(C), 103.0(C), 89.5(C), 68.3(CH), 67.8(CH), 51.5(CH_3), 40.0(CH_2), 35.5(CH_2), 29.7(CH_2), 28.8(CH_2), 21.5(CH_3), 21.4(CH_3), 19.3(CH_3). Anal. Calcd.for $C_{14}H_{22}O_6$: C, 58.73; H,7.74. Found: C, 58.96; H, 7.86%.

4-(3-Hydroxy-1-methylbutoxy)-5-(2-carbomethoxyethyl)-5-methyl-2(5H)-furanone 19 To a stirred solution of sodium methoxide (from 50 mL of anhydr methanol and 0.2g of sodium) lactone **18** (2.78 g,9.7 mmol) in methanol (20 mL) was added. The mixture was refluxed for 15 h. After cooling to 0°C, acetic acid (0.6 mL, 10 mmol) was added and the mixture evaporated to dryness. The residue was chromatographed (50:50 ethyl acetate / hexane) to provide 2.3 g (80 %) of butenolide **19** as an unseparable mixture of stereoisomers. IR (film, cm^{-1}) 3400, 1760-1735 broad, 1630.^1H NMR (90 MHz) δ 5.10 (s, 1H), 4.50 (m, 1H), 3.90 (m, 1H), 3.70(s, 3H), 2.90(m, 1H), 2.5-1.5 (m, 6H), 1.43(s, 3H), 1.41(d, 3H, J=6Hz), 1.25(d, 3H, J=6Hz).This compound was used directly in the next step without purification and was fully characterized as tert-butyldimethylsilyl ether **24b** (*vide infra*)

(5*S*)-4-Hydroxy-5-methyl-5-(2-carbomethoxyethyl)-2(5H)-furanone 21. To a stirred solution of alcohol **19** (420 mg, 1.46mmol) in acetone (10 mL) at 0°C, was added dropwise a solution of Jones' reagent until a persistent red color remained. The reaction mixture was stirred for an additional 10 min. and any excess of Jones' reagent was destroyed by adding a few drops of isopropyl alcohol. Saturated aqueous $NaHCO_3$ was then added.and the mixture was extracted with ethyl acetate and the collected organic phases were dried and concentated under reduced pressure. The residue was chromatographed (50:50, ethyl acetate / hexane) to give 390 mg (94 %) of ketone **20** as a yellow oil .This compound was used directly in the next step without further purification. To a stirred solution of sodium methoxide in methanol (from anhyd. methanol (10 mL) and 46 mg (2mmol) of sodium) a solution of ketone **20** (390 mg, 1.37 mmol) in methanol (5 mL) was added. After stirring for 1 h at 20°C, the mixture was acidified to pH 2 with 1N HCl, and concentrated under reduced pressure. The residue was taken into CH_2Cl_2, filtered through Celite, and the filtrate dried over $MgSO_4$. Concentration and chromatography (2:1 chloroform / ethanol) gave tetronic acid

21 as an amorphous solid (210 mg 77 %).$[\alpha]_D^{20}$ -17 (c=0.96, EtOH).IR (KBr, cm^{-1}), 3450, 3100, 2500, 1725, 1685, 1635, 1560, 1470. ^1H NMR (DMSO d_6) δ 4.0(broad s, 1H), 3.55 (s, 3H), 2.5(m, 2H), 1.83 (m, 2H) 1.21(s, 3H). ^{13}C NMR (62.9 MHz, DMSO d_6), δ 192.1(C), 175.7(C), 173.0(C), 82.7(C), 79.4(CH), 51.1(CH_3), 31.6(CH_2), 28.0(CH_2), 23.2(CH_3).Methylation of **21** with ethereal diazomethane gave a sample of O-methyl-tetronic acid derivative suitable for elemental analysis. Anal. Calcd.for $C_{10}H_{14}O_5$: C,56.07; H,6.59. Found: C,56.09; H, 6.93.

4-(1-Methyl-3-[[tert-butyldimethylsilyl]oxy]-5-methyl-2-(5H)-furanone-5-propionic acid methyl ester 24b To a solution of alcohol **19** (2.3 g, 8.04 mmol) in dry DMF (20 mL) was added dropwise 1.43 mL (10 mmol) of triethylamine followed by a solution of 4-dimethylaminopyridine (0.09 g,0.8 mmol) and tert-butyldimethylchlorosilane (2.61 g,9.5 mmol) in 10 mL of DMF. The reaction mixture was stirred for 6h at 20°C and saturated ammonium chloride was then added..The mixture was extracted with ether and the collected organic phases were dried and concentated under reduced pressure. The residue was chromatographed (50:50, ethyl acetate / hexane) to afford 3.05 g (95 %) of butenolide **24b** as a mixture of stereoisomers. IR (film, cm^{-1})1765, 1740, 1630. Only the two main isomers are described.^1H NMR δ 4.95 and 4.96(2s,1H), 4.35(m, 1H), 3.86(m, 1H), 3.63(s, 3H), 2.40-1.87(m, 5H), 1.55(m, 1H), 1.42(2s, 3H), 1.32(d, 3H, J=6.1 Hz), 1.14 and 1.16(2d, 3H, J=6.1 Hz), 0.85(s, 9H), 0.04(s, 3H), 0.02(s, 3H). ^{13}C NMR (62.9 MHz), δ 181.9(C), 172.8(C), 171.5(C), 88.0(CH), 83.2(C), 77.7(CH), 65.3(CH), 51.6(CH_3), 45.0(CH_2), 31.6(CH_2), 28.0(CH_2) 25.7(3 CH_3), 23.8(CH_3), 23.2(CH_3), 19.0(CH_3), 17.9(C), -4.3(2 CH_3). Anal. Calcd.for $C_{20}H_{36}O_6Si$: C, 59.96; H, 9.06; Si, 7.01. Found : C, 59.97; H, 8.95 ; Si, 6.53%.

(5*S*)-4-(1-Methyl-3-[[tert-butyldimethylsilyl]oxy]butoxy)-3,5-dimethyl-2(5H)-furanone -5 propanoic acid 25a. 20 mL of 1N NaOH was added to a solution of methyl ester **24b** (3.8 g, 9.5 mmol) in THF (40 mL) and methanol.(5 mL). After stiring for 2 h at 20°C,the mixture was cooled at 0°C and 1N HCl was added dropwise to pH 2.The mixture was extracted with CH_2Cl_2 and the collected organic phases were dried and concentated under reduced pressure.The yellow residue was dried by standing over P_2O_5 at 0.1 torr for two days,to give 3.85 g (95 %) of crude acid **24a** .

To a stirred solution of diisopropylamine(1.55 g,15.3 mmol) in 20 mL of THF at -20°C,was added dropwise a 2.5 M solution of n-butyllithium in hexane (5.6 mL, 14 mmol). The mixture was stirred for 15 min. at -20°C and cooled to -78°C. Acid **24a** (1.65 g, 4.27 mmol) in THF (10 mL) was subsequently added slowly by syringe, and the resulting mixture stirred for 1 h at -78°C. Methyl iodide (1.9 g, 15.5 mmol) was then added and the reaction mixture warmed up to 0°C over a 2h.period. The mixture was acidified to pH 2 with 1N HCl solution.After extraction with CH_2Cl_2 the collected organic phases were dried and concentated under reduced pressure.Chromatography (50:50, ethyl acetate / hexane) gave 1.24 g (74 %) of acid **25a.** For characterization purposes this acid was converted into methyl ester **25b** by using ethereal diazomethane.IR (film, cm^{-1}) 1757, 1745, 1664.Only the two major isomers are described.^1H NMR δ 4.83(m, 1H), 3.86(m, 1H), 3.56(s, 3H), 2.2-1.2(m, 6H), 1.85 and 1.84(2s, 3H), 1.30(s, 3H), 1.26 and 1.24(2d, 3H, J=6.1 Hz), 1.09 and 1.08(2d, 3H, J=6.1 Hz), 0.78(s, 9H), -0.02 and -0.03 (2s, 6H). ^{13}C NMR (62.9 MHz), δ 173.6(C), 173.2(C), 172.7(C), 95.1 and 94.9(C), 74.4(CH), 65.3(CH), 51.4(CH_3), 45.8 and 45.7(CH_2), 31.6(CH_2), 27.9(CH_2), 25.5 (3 CH_3), 23.8 (CH_3), 23.2 and 23.1(CH_3), 20.4 and 20.1(CH_3), 17.7(C), 8.6(CH_3), -4.5(CH_3), -5.0 (CH_3). Anal. Calcd.for $C_{21}H_{38}O_6Si$: C, 60.83; H, 9.23. Found: C, 60.98; H, 9.41

4-(1-Methyl-3-hydroxy-butoxy)-3,5,N-trimethyl-2(5H)-furanone-5-N-methoxy-propanamide 26b To a solution of N,O-dimethylhydroxylamine hydrochloride (1.7 g, 4.25 mmol) in CH_2Cl_2 (15 mL) were added 1.1 g (5 mmol) of dicyclohexylcarbodiimide, 20 mg (0.16 mmol) of N,N-dimethylaminopyridine and 1.7 g (4.25 mmol) of acid **25a** in 5 mL of CH_2Cl_2 After stirring for 5 min.triethylamine (0.6 g, 6mmol) was added and the reaction mixture was stirred for 2 h at 20°C.Ether (100 mL) was then added and the resulting suspension was filtered through Celite. The filtrate was sequentially washed with 1N HCl (20 mL), water (20 mL), and brine (20 mL). The organic phases were dried over MgSO4 and concentrated to give 1.56 g (83 %) of amide **26a**.This product was directly used in the next step without further purification.

To a stirred solution of amide **26a** (1.56 g,3.52 mmol) in anhyd. THF (3 mL) a 1 M solution of tetra-n-butylammonium fluoride in THF (9 mL) was added dropwise. After stirring for 2 h at 20°C, aqueous ammonium chloride was added.The mixture was extracted with CH_2Cl_2 and the collected organic phases were dried and concentated under reduced pressure.Chromatography (99:1 ethyl acetate /methanol) afforded 1.01 g (87 %) of alcohol **26b** as a mixture of diastereoisomers.IR (film, cm^{-1}) 3450, 1755, 1740, 1670, 1600. Only the two major isomers are described ^1H NMR δ 4.95(m, 1H), 3.93(m, 1H), 3.63(s, 3H), 3.13(s, 3H), 2.5-1.9(m, 5H), 1.91 and 1.93(2s, 3H), 1.62(m, 1H),1.38(s, 3H), 1.33 and 1.35 (2d, 3H, J=5.8 Hz), 1.22 and 1.21(2d, 3H, J=6.2 Hz).^{13}C NMR (62.9 MHz), δ 174.4(C), 173.9(C), 173.2(broad ,C), 95.0(C), 82.2(C), 75.4 and 75.0(1 CH), 65.2 and 64.9(1 CH), 61.2(CH_3), 45.5 and 45.1(1 CH_2),

32.16(broad,CH_3), 31.4 and 31.2(1 CH_2), 25.7(CH_2), 24.2(CH_3), 23.5 and 23.2(1 CH_3), 20.6 and 20.5 (1 CH_3), 8.7(CH_3).Anal. Calcd.for $C_{16}H_{27}O_6N$: C, 58.33; H, 8.26; N, 4.25. Found: C, 58.39; H, 8.40; N, 4.47.

4-(1-Methyl-3-oxo-butoxy)-3,5,N-trimethyl-2(5H)-furanone-5-N-methoxy-propanamide 26c. To a stirred solution of the alcohol **26b** (420 mg, 1.27 mmol) in acetone (20 mL), a solution of Jones' reagent was added at 0°C until a persistent red color remained. The reaction mixture was stirred for an additional 10 min, and isopropyl alcohol was added to destroy the excess of Jones' reagent. Saturated aqueous $NaHCO_3$ was added.The mixture was extracted with CH_2Cl_2 and the collected organic phases were dried and concentated under reduced pressure.Chromatography (99:1, ethyl acetate / methanol) yielded 387 mg (92 %) of ketone **26c** as a mixture of diastereoisomers.IR (film, cm^{-1}) 1749, 1717, 1662, 1391. Only the two major isomers are described. ^1H NMR δ 5,26(m,1H), 3.68 and 3.66 (2s, 3H), 3.16(s, 3H), 2.93(ddd, 1H, J=17.6 Hz, J=7.5 Hz, J=3.6 Hz), 2.66(ddd, 1H, J=17.6 Hz, J=4.6 Hz, J=5.0 Hz), 2.5-1.9 (m, 4H), 2.20 and 2.18(2s, 3H), 1.98 and 1.96 (2s, 3H), 1.40(m, 3H).^{13}C NMR (20 MHz), δ 205.1 and 204.8 (C), 174.3 and 174.2(C), 173.8 and 173.7(C), 173.3 (broad,C), 95.5 and 95.4(C), 82.4 and 82.3(C), 72.8 and 77.3(CH), 61.3(CH_3), 49.7 (CH_2), 32.5(broad,CH_3), 31.6 and 31.3(CH_2), 30.9(CH_3), 25.9 and 25.7(CH_2), 23.8 and 23.4(CH_3), 20.8 and 20.6(CH_3), 8.8(CH_3) .Anal. Calcd.for $C_{16}H_{25}O_6N$: C, 58.70; H, 7.70; N, 4.27..Found : C, 59.24; H, 7.90; N, 4.46.

(5*S*)-4-hydroxy-3,5,N-trimethyl-2(5H)-furanone-N-methoxypropanamide 27. To a stirred solution of ketone **26c** (287 mg, 0.87 mmol) in dry methanol(10 mL) was added a solution of sodium methoxide in methanol (from 40 mg of sodium (1.7 mmol) and 5mL of methanol) After stirring for 1h at 20°C, the mixture was acidified to pH 2 with 1 N HCl and evaporated to dryness. The residue was taken up in CH_2Cl_2, filtered through Celite, and the filtrate dried over MgSO4. Concentration gave a quantitative yield of crude tetronic acid **27**.$[\alpha]_D^{20}$ +11° (c=1.6, EtOH).IR (film, cm^{-1}) 3600-2400 broad, 1755, 1650 broad.^1H NMR(CD_3OD) δ 4.9 (broad s,OH), 3.89 and 3.68 (2s in 1 : 5 ratio, splitting induced by amide resonance, 3H), 3.16 and 2.98 (2s in 1 : 5 ratio, 3H), 2.4-2.0(m, 4H), 1.67(s, 3H), 1.45(s, 3H). ^{13}C NMR (20MHz, CD_3OD), δ 178.5(C), 176.7 and175.9(C), 174.6 (broad,C), 96.6(C), 83.9 and 83.7(C), 61.9 and 61.7(CH_3), 32.5(broad,CH_3), 32.2(CH_2), 28.9 and 26.7(CH_2), 23.4(CH_3), 6.0(CH_3). MS : m/z(rel.intensity): 243(1), 235(1), 212(1), 183(30), 165(9), 99(100), 83(10), 61(62), 43(58).No satisfactory combustion analysis could be obtained for this highly polar oil.

(5*S*)-4-hydroxy-3,5-dimethyl-5(-3-oxo-octyn-4-yl)-2-(5H)-furanone 28.To a solution of 1-pentyne (0.36 g, 5.3 mmol) in anhyd. THF (2 mL) cooled at -78°C, was added a 2.5 M solution of n-butyllithium in hexane (2 mL, 5 mmol). The reaction mixture was stirred for 15 min. at -20°C and cooled to -78°C. A solution of amide **27** (2.55 mg, 1.05 mmol) in 5 mL of THF was added dropwise by syringe and the resulting mixture warmed to -20°C, over a 30 min. period. After 15min. at -20°C, the reaction mixture was recooled to -78°C and quenched by addition of 1 N HCl (6 mL).The mixture was extracted with CH_2Cl_2 and the collected organic phases were dried and concentated under reduced pressure.Chromatography (75:25 ethyl acetate /methanol) yielded 196 mg (76 %) of ynone **28**. $[\alpha]_D^{20}$ +14.5 (c=2.4, $CHCl_3$);.IR (film, cm^{-1}) 2600-2400, 2205, 1750, 1720, 1670, 1640, 1450. ^1H NMR δ 11.0(broad s, 1H), 3.50(m, 2H), 3.33(t, 2H, J=7 Hz), 3.16(m, 2H), 2.73(s, 3H), 2.58(tq, 2H, J=7 Hz, J=7.3 Hz), 1.99(t, 3H, J=7.3 Hz).^{13}C NMR (20 MHz), δ 186.7(C), 177.7(C), 176.4(C), 96.1(C), 95.8(C), 85.1(C), 80.5(C), 39.2(CH_2), 30.1(CH_2), 22.9(CH_3), 21.0(CH_2), 20.7(CH_2), 13.2(CH_3), 5.9(CH_3).Anal. Calcd.for $C_{14}H_{18}O_4$: C, 67.18; H, 7.24. Found: C, 67.26; H, 7.11.

(*S*)-(-)-Vertinolide 5. To a solution of ynone **22** (310 mg, 1.2 mmol) in anhyd. toluene (20 mL) was added 115 mg (0.43 mmol) of triphenylphosphine and 14 mg (0.06 mmol) of palladium acetate. Argon was bubbled in the stirred solution for 15 min. The reaction mixture was then heated at 100°C for 1 h. After cooling, the organic solution was extracted three times with aqueous sodium bicarbonate (20 mL). The aqueous phase was acidified with 1 N HCl to pH 2 and saturated with sodium chloride. The mixture was extracted with CH_2Cl_2 and the collected organic phases were dried and concentated under reduced pressure.Chromatography over silica gel (94:6, chloroform/ethanol) yielded 200 mg (65 %) of vertinolide **5** , crystallization from ethyl acetate-ether gave small white plates: mp 146-149°C dec. $[\alpha]_D^{20}$ -23 (c=0.1, $CHCl_3$) (lit [7] mp 149°C dec.; $[\alpha]_D^{20}$ -25 (c=0.05, $CHCl_3$)). HRMS. Calcd. for $C_{14}H_{18}O_4$:250.1205. Found :250.1197. The IR, ^1H NMR, ^{13}C NMR and MS spectra were in agreement with the literature data reported for natural (S)-(-)-vertinolide .[7,8]

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