A Novel Synthetic Method for Tetronic Acids from 1,3-Dioxin-4-ones *via* Intra- or Intermolecular Ketene Trapping[1)]

Masayuki SATO, Jun-ichi SAKAKI,* Kazuhisa TAKAYAMA, Satoshi KOBAYASHI, Miwako SUZUKI, and Chikara KANEKO*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan. *Received July 17, 1989*

Novel synthetic routes to tetronic acid and its derivatives from 6-substituted 1,3-dioxin-4-ones through cycloreversion to acylketenes followed by either intra- or intermolecular ketene trapping by a hydroxy function is described. While tetronic acid and its 5-substituted derivatives were synthesized directly from 6-(α-hydroxyalkyl)-1,3-dioxin-4-ones by intramolecular trapping, 3-acyltetronic acids were prepared by Dieckmann reaction of the β-keto esters obtained from the 6-substituted dioxinones and an appropriate α-hydroxy ester by intermolecular trapping.

Keywords tetronic acid derivative; 1,3-dioxin-4-one; intramolecular ketene trapping; (*S*)-carlosic acid; (*S*)-viridicatic acid; total synthesis; cycloreversion

Previously, we reported that 1,3-dioxin-4-ones (A), when heated in an aprotic solvent, underwent cycloreversion to acylketenes (B), which reacted either with nucleophiles to give β-keto acid derivatives (C) or with dipolarophiles to give six-membered heterocyclic compounds (D).[2)]

In this paper, we wish to report new applications of the transformation of A to C *via* B leading to new and efficient synthetic methods either by intramolecular ketene trapping to give directly tetronic acid and its 5-substituted derivatives (E) or by intermolecular ketene trapping with α-hydroxy esters [R′-CH(OH)CO_2R] giving appropriately functionalized β-keto esters (F), which are precursors of 3-acyltetronic acids (G).

Synthesis of Tetronic Acid and Its 5-Substituted Derivatives Though a large number of synthetic routes to tetronic acid **1a** (**1**: R = H) have been developed so far, none seems to be satisfactory. Originally, this acid (**1a**) was synthesized by decarboxylation of 3-carboxytetronic acid obtained by lactonization of diethyl bromoacetylmalonate.[3)] Since then, several routes to **1a** by using direct lactonization of ethyl acetoacetate having an appropriate leaving group (Cl,[4)] Br,[5)] or $OCOCH_3$[6)] at the 4-position have been elaborated as attractive alternatives. All of these methods, however, used an aqueous medium in the cyclization step and hence required a rather laborious work-up procedure in the extraction of the highly hydrophilic lactone (**1a**) from an aqueous mother liquor. In our previous study, we made two important observations (1 and 2) concerning the use of the dioxinones as alternatives of acylketenes. 1) Formyl acetates (in their free form), whose synthesis had not been attained previously, could be prepared readily by heating 5,6-unsubstituted dioxinone in an aprotic solvent containing a variety of alcohols, and most of them were found to be distillable under a reduced pressure.[7)] This success depended upon the fact that formylketene generation and its trapping can be carried out in one-pot in an aprotic solvent. 2) The fact that 6-(α-aminoalkyl)dioxinones when refluxed in an aprotic solvent gave tetramic acid and its derivatives indicates that the ketene trapping also proceeds intramolecularly.[8)]

Knowing these facts, we planned a novel synthesis of 3-

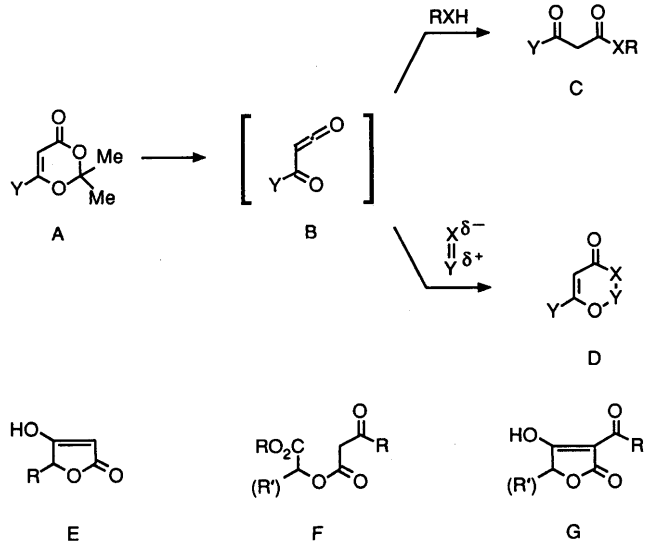

Chart 1

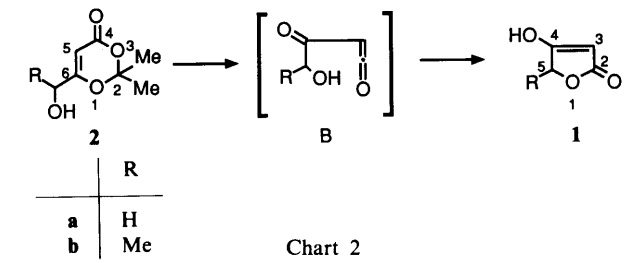

Chart 2

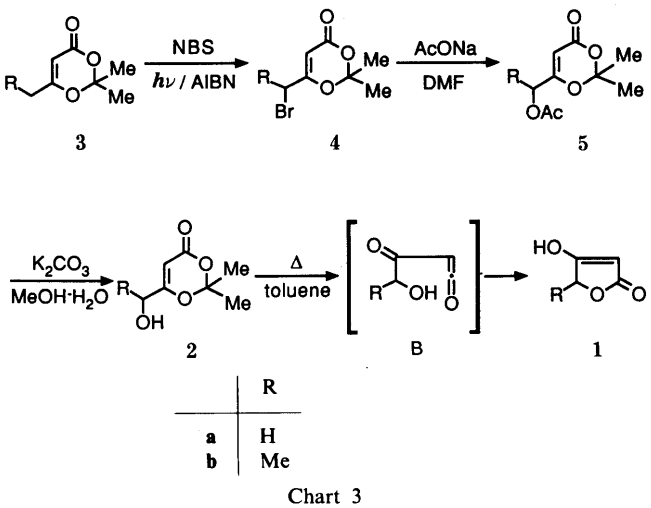

Chart 3

unsubstituted tetronic acids (**1**) from 6-(α-hydroxyalkyl)-dioxinones (**2**) by the use of intramolecular ketene trapping[9,10] according to Chart 2.

In order to synthesize tetronic acid itself (**1a**) according to this plan, the necessary starting alcohol (**2a**) was prepared as follows. Thus, 2,2,6-trimethyl-1,3-dioxin-4-one (**3a**: R=H) was brominated selectively at the 6-methyl group under irradiation (≥300 nm) with *N*-bromosuccinimide in carbon tetrachloride containing a catalytic amount of α,α′-azobisisobutyronitrile.

Though the bromomethyl derivative (**4a**) could be easily purified by silica gel column chromatography,[11] the crude bromide obtained after elimination of succinimide (insoluble in carbon tetrachloride) from the product was used directly in the subsequent reaction. Crude **4a** was treated with sodium acetate in dimethylformamide to give the acetoxyl derivative (**5a**) in 90% overall yield from **3a**. The 6-(α-hydroxymethyl) derivative (**2a**), obtained by hydrolysis of the acetate (**5a**), was then converted smoothly to the parent tetronic acid (**1a**) in *ca.* 80% yield. After thorough investigation to optimize the yield of **1a**, we have arrived at the following procedure as the best choice for this intramolecular ketene trapping. Thus, a solution of **2a** in toluene was added dropwise to refluxing toluene and after the addition was completed, the whole was further refluxed for several minutes. If a solution of **2a** in toluene was merely refluxed, the yield of **1a** became lower owing to undesired intermolecular ketene trapping (self-condensation of B) to give di- and/or polymeric products. It should be noted that **4a** was also synthesized from 4-bromoacetoacetic acid according to the general procedure elaborated already in our laboratories.[12]

In order to examine the scope of this methodology, we then applied this method to the synthesis of 5-substituted tetronic acids. Use of 6-ethyl-2,2-dimethyl-1,3-dioxin-4-one (**3b**), instead of **3a**, afforded the desired 5-methyl derivative (**1b**). The reaction sequence of this synthesis is essentially the same as the case of **1a**. Thus, bromination, acetoxylation, and hydrolysis afforded the 6-(α-hydroxyethyl)-dioxinone (**2b**). Refluxing of **2b** in toluene as in the case of **2a** then gave **1b** in almost quantitative yield (92%). The fact that tetronic acid (**1a**) and its 5-methyl derivative (**1b**) have been synthesized in high overall yields from the 6-methyl- and 6-ethyldioxinones indicates clearly that this intramolecular ketene trapping method has wide applicability for the synthesis of a variety of 5-substituted tetronic acid derivatives.

Synthesis of 3-Acyltetronic Acids from 6-Substituted 1,3-Dioxin-4-ones by Using Intermolecular Ketene Trapping as the Key Step Tetronomycin,[13] ICI 139603,[14] tetrocarcin,[15] and kijanimicin[16] are all recently isolated examples of biologically active natural products containing 3-acyltetronic acids [throughout this paper, we use the tautomeric structure (G) to represent the acyltetronic acids, though other tautomers (*e.g.* G′) are expected to be involved in the equilibrium[17]]. Such tetronic acids (G) have previously been found as mold metabolic products and coloring matters in lichens,[18] and a number of methods are available for the preparation of simple acyltetronic acid. These can be classified broadly into two types: i) acylation of 3-unsubstituted tetronic acids and ii) the Dieckmann-type cyclization of acetoacetates prepared from diketene and α-hydroxy ester.

Thus, as regards method i, Ley *et al.*[19] recently succeeded in direct acylation of 3-stannyltetronic acids. Though this method seems to be superior to the conversion of the *O*-acylated tetronic acids (H) by Fries-type rearrangement as originally disclosed by Bloomer *et al.*,[20] these routes (i) gave in general low yields of the products and suffered severe restriction as to the kind of acyl group.

Lacey, according to the methodology ii, synthesized 3-acetyltetronic acid (G) by alkali metal alkoxide-mediated Dieckmann-type cyclization of the acetoacetates (F) which were prepared from diketene and α-hydroxy ester (I).[21] Later, in order to avoid competitive alcoholysis of the acetoacetate moiety, Bloomer and Kappler suggested improvements involving the use of *tert*-butoxide and accomplished the synthesis of the mold metabolite (*S*)-carlosic acid (*vide infra*) by using *tert*-BuO$^-$–*tert*-BuOH at 0 °C.[20] Since higher temperature could not be used owing both to elimination of the acetoacetic acid moiety giving dimethyl fumarate (N) and to possible base-catalyzed epimerization of the chiral center, the yield was less than 40%.

Ley *et al.* recently developed a new methodolgy to synthesize carlosic acid and its higher homologues (M) starting from diketene (I).[22] Conceptually the route to the acyltetronic acids (*e.g.* M) requires only four operations: preparation of *S*-*tert*-butyl acetothioacetate (J) from di-

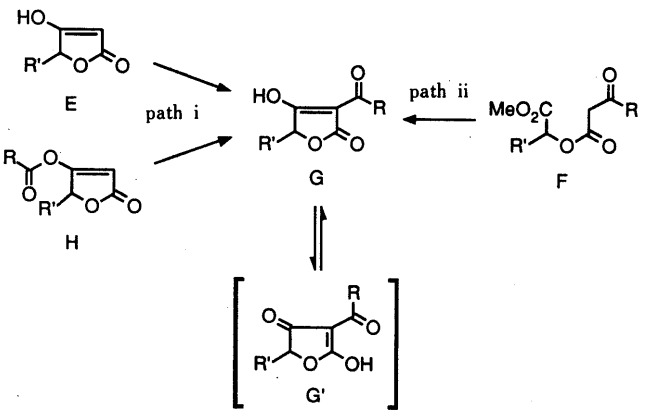

Chart 4

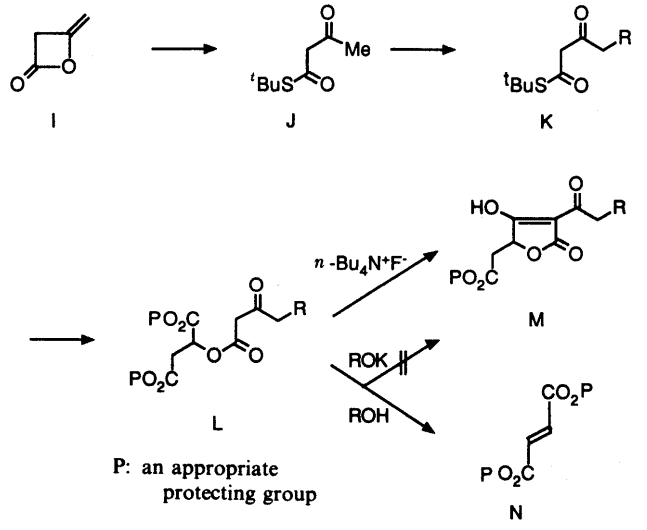

Chart 5

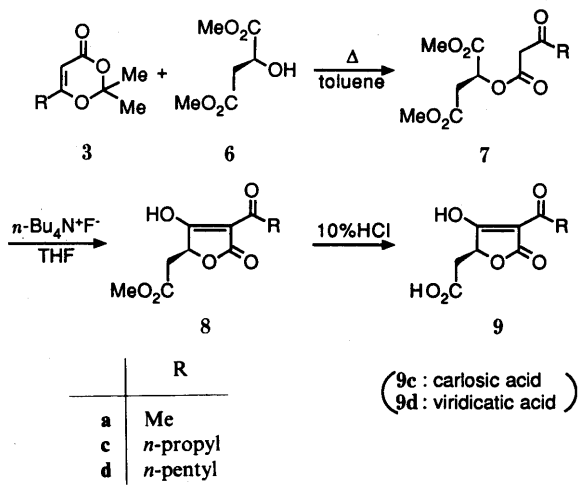

Chart 6

ketene (I), alkylation of the dianion to give K, transesterification with an α-hydroxy ester, and Dieckmann cyclization of the resulting product (L) by using tetrabutylammonium fluoride in tetrahydrofuran (THF).

The method not only affords 5-mono- and 5-unsubstituted 3-acyltetronic acids in good yields, which was not possible using the original Lacey protocol (Chart 5), but also is ideal for more complex situations where base epimerization of chiral centers could be a problem.

In order to improve Ley's method further, we have investigated a shorter and more efficient route to L (as a model for chiral α-hydroxy esters of β-keto acids) from the dioxinones utilizing the afore-mentioned intermolecular ketene trapping.

The starting 1,3-dioxin-4-ones (**3**) were prepared from readily available acyl Meldrum's acids[23] and acetone according to our general procedure.[12]

These dioxinones (**3**), when heated in boiling toluene containing (*S*)-dimethyl malate (**6**) [prepared in the usual manner from (*S*)-malic acid; purchased from Wako Junyaku Co., Ltd.], gave the corresponding β-keto esters (**7**) in quantitative yields. The resulted esters (**7**) were then treated with tetrabutylammonium fluoride in THF at room temperature to afford 3-acyltetronic acid methyl esters (**8**). Hydrolysis with hydrochloric acid under Ley's conditions[22] gave the free acids (**9**) in satisfactory yields. Complete preservation of the configuration of the initial (*S*)-malic acid ester was confirmed by determination of specific rotation values of (*S*)-carlosic acid (**9c**) and (*S*)-viridicatic acid (**9d**) thus obtained (see Experimental). It seems noteworthy that, though several syntheses of the former have been reported previously,[20,22] the synthesis of the latter in enantiomerically pure form has not yet been reported.[24]

Conclusions

The newly developed synthetic methods for tetronic acids from appropriate 6-substituted 1,3-dioxin-4-ones by novel ketene trapping are short and highly efficient. Thus, practical synthesis of tetronic acid and its 5-substituted derivatives was achieved by intramolecular trapping and that of 3-acyltetronic acids as enantiomerically pure materials by intermolecular trapping. Since the desired substituents can now be introduced readily into any position of the dioxinone skeleton[2] and their opening to acylketenes can be accomplished either thermally[25] or at room temperature by irradiation at 254 nm,[8] it is clear that the present methodology should find application in more complex syntheses of tetronic acid derivatives.

Experimental

All melting points were determined on a Yanagimoto micro-hot stage and are uncorrected. Optical rotations were measured with a JASCO DIP-340 digital polarimeter. Infrared (IR) spectra were measured on a JASCO A-102 spectrophotometer and proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL JNM-PMX 60 SI or JEOL JNM-GX 500 spectrometer with tetramethylsilane (TMS) as an internal standard, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublets of doublets; br, broad. Low- and high-resolution mass spectra (MS) were obtained on JEOL JMS-01SG-2 and JEOL JMS-DX-303 spectrometers, respectively. Wakogel (C-200) and Merck Kiesel-gel 60 F254 were employed for silica gel column and preparative thin layer chromatography (TLC), respectively. The ratios of solvent mixtures for chromatography are shown as volume/volume.

Preparation of 6-Alkyl-1,3-dioxin-4-ones (3) (a) Preparation of 1,3-Dioxin-4-ones (**3a**—**c**): These dioxinones were prepared according to our reported procedure.[12]

(b) 2,2-Dimethyl-6-pentyl-1,3-dioxin-4-one (**3d**): Hexanoyl chloride (2.96 g, 22 mmol) was added dropwise to a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (2.88 g, 20 mmol) and pyridine (3.48 g, 44 mmol) in CH_2Cl_2 (50 ml) at −5—−10 °C with stirring. After the addition was completed, the whole was stirred for 2 h at room temperature. This solution was washed with 5% HCl and water successively. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. A mixture of the resulting residue, acetone (0.58 g, 10 mmol), and toluene (20 ml) was refluxed for 1.5 h. The reaction mixture was concentrated *in vacuo* and the residue was distilled under reduced pressure to give **3d** (2.89 g, 73%) as an oil of bp 69—70 °C (0.01 mmHg). High-resolution MS *m/z* Calcd for $C_{11}H_{18}O_3$ (M^+): 198.1255. Found: 198.1263. IR ($CHCl_3$): 1720, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=5.2 Hz, Me), 0.90—1.90 [6H, m, $(CH_2)_3$], 1.67 (6H, s, C_2-Me_2), 2.22 (2H, t, J=7.2 Hz, CH_2C=C), 5.22 (1H, s, C_5-H).

6-Bromomethyl-2,2-dimethyl-1,3-dioxin-4-one (4a) Method i[26]: A mixture of **3a** (1.42 g, 10 mmol), *N*-bromosuccinimide (1.96 g, 11 mmol), α,α′-azobisisobutyronitrile (50 mg, 0.304 mmol) and carbon tetrachloride (50 ml) was irradiated externally with a RIKO 1 kW high-pressure mercury lamp equipped with a Pyrex filter for 45 min with vigorous stirring at room temperature. The reaction mixture was filtered and the filtrate was evaporated *in vacuo* to give almost pure **4a** as an oil, which was used for the next reaction without further purification. A portion of the oil was purified by silica gel column chromatography [hexane–AcOEt (10 : 1)] to give an analytical sample of **4a**. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (6H, s, Me_2), 3.88 (2H, s, CH_2Br), 5.51 (1H, s, CH=C).

Method ii[12]: Concentrated sulfuric acid (4.9 g, 0.05 mol) was added drowpise to a mixture of 4-bromoacetoacetic acid (88 g, 0.49 mol), acetone (58 g, 1 mol), and acetic anhydride (102 g, 1 mol) at below 5 °C with stirring. The whole was stirred for 30 min at the same temperature and then for 2 h at room temperature. The mixture was poured into 10% Na_2CO_3 (2 l) under ice-cooling and the resulting mixture was stirred for 1 h at room temperature and then extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give almost pure **4a**, which was used for the next reaction without further purification.

6-(1-Bromoethyl)-2,2-dimethyl-1,3-dioxin-4-one (4b) According to the procedure described for the synthesis of **4a** (method i), 6-ethyl-2,2-dimethyl-1,3-dioxin-4-one (**3b**) was brominated to give almost pure **4b**[26] as an oil, which was used for the next reaction without further purification. A portion of the oil was purified by silica gel column chromatography [hexane–AcOEt (10 : 1)] to give an analytical sample of **4b**. ^{1}H-NMR (CCl_4) δ: 1.72 (6H, s, Me_2), 1.85 (3H, d, J=7.0 Hz, MeCH), 4.50 (1H, q, J=7.0 Hz, MeCH), 5.49 (1H, s, C_5-H).

6-Acetoxymethyl-2,2-dimethyl-1,3-dioxin-4-one (5a) A mixture of **4a** (2.21 g, 10 mmol) and anhydrous NaOAc (1.64 g, 20 mmol) in *N*,*N*-dimethylformamide (DMF) (20 ml) was heated for 3 h at 70 °C. The reaction mixture was poured into ice-water and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography [hexane–AcOEt (5 : 1)] to give **5a** (1.80 g, 90%) as a colorless oil. High-resolution

MS *m/z* Calcd for $C_9H_{12}O_5$ (M^+): 200.0684. Found: 200.0676. IR ($CHCl_3$): 1730, 1650 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.69 (6H, s, C_2-Me_2), 2.12 (3H, s, Ac), 4.56 (2H, s, OCH_2), 5.36 (1H, br s, C_5-H).

6-(1-Acetoxyethyl)-2,2-dimethyl-1,3-dioxin-4-one (5b) Following the procedure given for the preparation of **5a**, **4b** (2.35 g, 10 mmol) was treated with anhydrous NaOAc (1.64 g, 20 mmol) to afford **5b** (1.11 g, 52%) as a colorless oil. High-resolution MS *m/z* Calcd for $C_{10}H_{14}O_5$ (M^+): 214.0800. Found: 214.0838. IR ($CHCl_3$): 1730, 1640 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.43 (3H, d, J=6.6 Hz, MeCH), 1.70 (6H, s, C_2-Me_2), 2.10 (3H, s, OAc), 5.27 (1H, q, J=6.6 Hz, OCH), 5.42 (1H, s, C_5-H).

6-Hydroxymethyl-2,2-dimethyl-1,3-dioxin-4-one (2a) A solution of K_2CO_3 (448 mg, 3 mmol) in water (5 ml) was added to a solution of **5a** (1.0 g, 5 mmol) in methanol (20 ml) under ice-cooling. The mixture was stirred for an additional 30 min at the same temperature. Methanol was removed under reduced pressure. The residue was acidified with 10% HCl and then extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography [hexane–AcOEt (3:1)] to give **2a** (567 mg, 72%) as a colorless oil. High-resolution MS *m/z* Calcd for $C_7H_{10}O_4$ (M^+): 158.0584. Found: 158.0603. IR ($CHCl_3$): 1725, 1645 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.70 (6H, s, C_2-Me_2), 2.50 (1H, br t, J=5.5 Hz, OH), 4.21 (2H, br d, J=5.5 Hz, OCH_2), 5.61 (1H, br s, C_5-H).

6-(1-Hydroxyethyl)-2,2-dimethyl-1,3-dioxin-4-one (2b) Following the procedure given for the preparation of **2a**, **5b** (560 mg, 2.62 mmol) was treated with K_2CO_3 (90.3 mg, 0.654 mmol) to give **2b** (340 mg, 75%) as a colorless oil. High-resolution MS *m/z* Calcd for $C_8H_{12}O_4$ (M^+): 172.0735. Found: 172.0747. IR ($CHCl_3$): 3450, 1725, 1635 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.41 (3H, d, J=6.6 Hz, MeCH), 1.71 (6H, s, C_2-Me_2), 2.75 (1H, br s, OH), 4.05—4.59 (1H, br, OCH), 5.57 (1H, s, C_5-H).

Tetronic Acid (1a) A solution of **2a** (158 mg, 1 mmol) in toluene (30 ml) was dropped into refluxing toluene (30 ml) over 10 min. The reaction mixture was refluxed for an additional 5 min. The solvent was evaporated off *in vacuo* and the residue was recrystallized from AcOEt to give **1a** (78 mg, 78%) as prisms of mp 141 °C (lit.[5] 140—141 °C).

5-Methyltetronic Acid (1b) Following the procedure given for the preparation of **1a**, **2b** (172 mg, 1 mmol) gave **1b** (105 mg, 92%), mp 121.5—122 °C (lit.[5] 121-122 °C).

(*S*)-1,2-Bis(methoxycarbonyl)ethyl 3-Oxobutanoate (7a) A solution of 2,2,6-trimethyl-1,3-dioxin-4-one (**3a**) (710 mg, 5 mmol) and (*S*)-dimethyl malate (**6**) (810 mg, 5 mmol) in toluene (20 ml) was refluxed for 1 h. The solvent was evaporated off *in vacuo*, and the residue was purified by silica gel column chromatography [hexane–AcOEt (7:1)] to give **7a** (1.2 g, 98%) as a colorless oil, $[\alpha]_D^{22}$ −18.8° (c=1.18, $CHCl_3$) [lit.[22] $[\alpha]_D^{26}$ −20.9° (c=1.16, $CHCl_3$)].

(*S*)-1,2-Bis(methoxycarbonyl)ethyl 3-Oxohexanoate (7c) Following the procedure given for the preparation of **7a**, 2,2-dimethy-6-propyl-1,3-dioxin-4-one (**3c**) (1.7 g, 10 mmol) and **6** (1.62 g, 10 mmol) afforded **7c** (2.54 g, 93%) as a colorless oil, $[\alpha]_D^{23}$ −14.6° (c=2.52, $CHCl_3$) [lit.[22] $[\alpha]_D^{28}$ −9.83° (c=10.71, $CHCl_3$)].

(*S*)-1,2-Bis(methoxycarbonyl)ethyl 3-Oxooctanoate (7d) Following the procedure given for the preparation of **7a**, 2,2-dimethyl-6-pentyl-1,3-dioxin-4-one (**3d**) (990 mg, 5 mmol) and **6** (810 mg, 5 mmol) afforded **7d** (1.22 g, 81%) as a colorless oil, $[\alpha]_D^{24}$ −13.2° (c=3.02, $CHCl_3$). High-resolution MS *m/z* Calcd for $C_{14}H_{22}O_7$ (M^+): 302.1364. Found: 302.1344. IR ($CHCl_3$): 1770, 1745, 1695, 1670, 1605 cm^{-1}. ^1H-NMR ($CDCl_3$) (keto form : enol form = *ca.* 7:1) δ: 0.90 (3H, t, J=5.2 Hz, Me), 1.06—1.90 (6H, m, $C_{5,6,7}$–CH_2), 2.58 (2H, t, J=7.0 Hz, C_4–CH_2), 2.93 (2H, d, J=6.2 Hz, C_2, –CH_2), 3.52 (2H × 7/8, s, C_2-CH_2), 3.74 (3H, s, CO_2Me), 3.79 (3H, s, CO_2Me), 5.11 (1H × 1/8, s, CH=C–OH), 5.56 (1H , t, J=6.2 Hz, C_1, –CH), 11.72 (1H × 1/8, s, OH).

Methyl (*S*)-4-Acetyl-2,5-dihydro-3-hydroxy-5-oxofuran-2-ylacetate (8a) Tetrabutylammonium fluoride 1 M solution in THF (2.61 ml, 2.61 mmol) was added to a solution of **7a** in THF (1 ml) at room temperature and the whole was stirred for 1 h. The reaction mixture was acidified with 50% HCl, diluted with water and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The crystalline residue was recrystallized from hexane to give **8a** (235 mg, 84%) as colorless needles, mp 84—85 °C, $[\alpha]_D^{20}$ −106.7° (c=1.10, $CHCl_3$) [lit.[22] mp 83—85 °C, $[\alpha]_D$ −102.9° (c=1.12, $CHCl_3$)].

Methyl (*S*)-2,5-Dihydro-3-hydroxy-5-oxo-4-(1-oxobutyl)furan-2-ylacetate (8c) Following the procedure given for the preparation of **8a**, compound **7c** (548 mg, 2 mmol) was treated with tetrabutylammonium fluoride 1 M solution in THF (4 ml, 4 mmol) to give **8c** (387 mg, 80%) as colorless needles (from hexane), mp 61 °C, $[\alpha]_D^{22}$ −102.2° (c=0.92, $CHCl_3$) [lit.[22] mp 58—60 °C, $[\alpha]_D$ −100.9° (c=0.96, $CHCl_3$)].

Methyl (*S*)-2,5-Dihydro-3-hydroxy-5-oxo-4-(1-oxohexyl)furan-2-ylacetate (8d) Following the procedure given for the preparation of **8a**, compound **7d** (700 mg, 2.32 mmol) was treated with tetrabutylammonium fluoride 1 M solution in THF (4.63 ml, 4.63 mmol) to give **8d** (452 mg, 72%) as colorless needles (from hexane), mp 65.5—66 °C, $[\alpha]_D^{19}$ −91.9° (c=1.13, $CHCl_3$). *Anal.* Calcd for $C_{13}H_{18}O_6$: C, 57.75; H, 6.72. Found: C, 57.45; H, 6.80. IR ($CHCl_3$):1770, 1745, 1695, 1670, 1605 cm^{-1}. 500 MHz ^1H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.02 Hz, Me), 1.30—1.43 [4H, m, $(CH_2)_2$], 1.67—1.77 (2H, m, CH_2), 2.83—3.07 (4H, m, CH_2CO, CH_2CO_2Me), 3.71 (3H × 1/2, s, CO_2Me), 3.72 (3H × 1/2, s, CO_2Me), 4.88 (1/2, dd, J=5.50, 4.27 Hz, OCH), 5.01 (1/2, dd, J=6.11, 4.27 Hz, OCH).

(*S*)-(−)-Carlosic Acid (9c) A mixture of **8c** (100 mg, 0.413 mmol) and 10% HCl (10 ml) was stirred for one week at room temperature. The resulting mixture was extracted with CH_2Cl_2 and the organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from benzene to give **9c** (53 mg, 56%) as colorless needles of mp 176.5—177.5 °C, $[\alpha]_D^{25}$ −133.9° (c=0.34, H_2O) [lit.[22] mp 165—166 °C, $[\alpha]_D$ −138° (c=0.28, H_2O)].

(*S*)-(−)-Viridicatic Acid (9d) Following the procedure given for the preparation of **9c**, **8d** (200 mg, 0.74 mmol) was treated with 10% HCl (20 ml) to give **9d** (114 mg, 61%) as colorless needles of mp 172—173 °C (from benzene), $[\alpha]_D^{26}$ −117.8° (c=0.27, H_2O) [lit.[24a] mp 174.5 °C, $[\alpha]_{5461}^{20}$ −105° (c=1, EtOH)]. *Anal.* Calcd for $C_{12}H_{16}O_6$: C, 56.23; H, 6.30. Found: C, 56.18; H, 6.21. IR ($CHCl_3$): 1770, 1740, 1725, 1696, 1605 cm^{-1}. 500 MHz ^1H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.02 Hz, Me), 1.30—1.41 [4H, m, $(CH_2)_2$], 1.67—1.75 (2H, m, CH_2), 2.83—3.11 (4H, m, CH_2CO, CH_2CO_2Me), 4.89 (1/2H, dd, J=6.72, 4.27 Hz, OCH), 5.02 (1/2H, dd, J=6.72, 4.27 Hz, OCH).

References and Notes

1) This paper forms part XXII of the series entitled "Synthesis of 1,3-dioxin-4-ones and their use in synthesis." Part XXI in this series, M. Sato, Y. Abe, C. Kaneko, T. Furuya, and N. Inukai, *Heterocycles*, in press.
2) Reviews: *a*) M. Sato, *Yakugaku Zasshi*, **108**, 805 (1988); *b*) *Idem*, *Yuki Gosei Kagaku Kyokai Shi*, **46**, 596 (1988); *c*) C. Kaneko, M. Sato, J. Sakaki, and Y. Abe, *J. Heterocycl. Chem.*, in press.
3) A. Ogata, Y. Nosaki, and K. Takagi, *J. Pharm. Soc. Jpn.*, **59**, 105 (1939); T. P. C. Mulholland, R. Foster, and D. B. Haydock, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 1225.
4) K. J. Boosen, U. S. Patent 3758515 [*Chem. Abstr.*, **79**, 126297*b* (1973)].
5) A. Svendsen and P. M. Boll, *Tetrahedron*, **29**, 4251 (1973).
6) T. Momose, N. Toyooka, and Y. Takeuchi, *Heterocycles*, **24**, 1429 (1986).
7) Originally, we used formylated Meldrum's acid as the equivalent of formylketene[a] but later found that the 5,6-unsubstituted dioxinones could also be used.[b,2] *a*) M. Sato, N. Yoneda, N. Katagiri, H. Watanabe, and C. Kaneko, *Synthesis*, **1986**, 672; *b*) M. Sato, N. Yoneda, and C. Kaneko, *Chem. Pharm. Bull.*, **34**, 4577 (1986).
8) M. Sato, H. Ogasawara, K. Takayama, and C. Kaneko, *Heterocycles*, **26**, 2611 (1987).
9) Quite recently, Winders *et al.* reported the synthesis of several lactones which served as synthons for eldanolide and leukotriene B_4. Though the method (photolysis of hydroxybicyclo[3.2.0]heptanones) for generation of the ketene species was different from our case, the intramolecular ketene trapping by an alcoholic hydroxyl group has been elegantly applied to their synthesis. H. G. Davis, S. M. Roberts, B. J. Wakefield, and J. A. Winders, *J. Chem. Soc., Chem. Commun.*, **1985**, 1166; S. Butt, H. G. Davies, M. J. Dawson, G. C. Lawrence, J. Leaver, S. M. Roberts, M. K. Turner, B. J. Wakefield, and J. A. Winders, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 903.
10) The formation of tetronic acids *via* ketenol species by an intramolecular cyclization was suggested previously by De Keukeleire *et al.* in dye-sensitized photo-oxidation of humulone and related compounds giving 3-acyltetronic acids. The yields of the products, however, were poor (0.5—8%). D. De Keukeleire, L. De Taeye, and M. Verzele, *Tetrahedron*, **32**, 2923 (1976).
11) So far, we have examined the same bromination of dioxinones having a methyl (or other alkyl) group at the 5- and/or 6-positions. It was found that while 6-bromomethyl and its higher homologues were quite stable, the corresponding 5-(α-bromoalkyl) derivatives in general were too unstable to be purified by column chromatography.
12) M. Sato, H. Ogasawara, K. Oi, and T. Kato, *Chem. Pharm. Bull.*, **31**, 1896 (1983). See also, M. Sato, C. Orii, J. Sakaki, and C. Kaneko, *J.*

Chem. Soc., Chem. Commun., **1989**, 1435.
13) C. Keller-Juslen, H. D. King, M. Kuhn, H. R. Loosli, W. Pache, T. J. Petcher, H. P. Weber, and A. von Wartburg, *J. Antibiot.*, **35**, 142 (1982).
14) D. H. Davies, E. W. Snape, P. J. Suter, T. J. King, and C. P. Falshaw, *J. Chem. Soc., Chem. Commun.*, **1981**, 1073.
15) N. Hirayama, M. Kasai, K. Shirahata, Y. Ohashi, and Y. Sasada, *Bull. Chem. Soc. Jpn.*, **55**, 2984 (1982); *idem*, *Tetrahedron Lett.*, **1980**, 2559.
16) A. K. Mallams, M. S. Puar, R. R. Rossman, A. K. McPhail, and R. D. Macfarlane, *J. Am. Chem. Soc.*, **103**, 3940 (1981).
17) S. Gelin, *Tetrahedron Lett.*, **21**, 4491 (1980) and references cited therein.
18) L. J. Haynes and J. R. Plimmer, *Quart. Rev.*, **13**, 292 (1959).
19) S. V. Ley and D. J. Wadsworth, *Tetrahedron Lett.*, **30**, 1001 (1989).
20) J. L. Bloomer and F. E. Kappler, *J. Org. Chem.*, **39**, 113 (1974); *idem*, *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1485.
21) R. N. Lacey, *J. Chem. Soc.*, **1954**, 832. See also, D. J. Ager and S. J. Mole, *Tetrahedron Lett.*, **29**, 4807 (1988).
22) P. M. Booth, C. M. J. Fox, and S. V. Ley, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 121; *idem*, *Tetrahedron Lett.*, **24**, 5143 (1983).
23) Y. Oikawa, K. Sugano, and O. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978).
24) Viridicatic acid (**9d**) is a metabolite obtained from the culture filtrate of a strain of *P. viridicatum* WESTLING G. A. 834.[a] This acid was synthesized in racemic form by Svendsen[b] and Gelin.[c] *a*) J. H. Birkinshaw and M. S. Samant, *J. Biochem.*, **74**, 369 (1960); *b*) A. Svendsen and P. M. Boll, *J. Org. Chem.*, **40**, 1927 (1975); *idem*, *Tetrahedron Lett.*, **33**, 2821 (1974); *c*) S. Gelin and P. Pollet, *C. R. Acad. Sci.*, **279**, 345 (1974).
25) The temperature required for the ring opening of 1,3-dioxin-4-ones to the ketene species is highly dependent upon the kinds and patterns of the substituents at the 2-, 5-, and/or 6-positions. J. Sakaki, S. Kobayashi, M. Sato, and C. Kaneko, *Chem. Pharm. Bull.*, **37**, 2952 (1989).
26) R. K. Boeckman, Jr. and A. J. Thomas, *J. Org. Chem.*, **47**, 2823 (1982).