Synthesis of γ-Unsubstituted α-Acyl-β-tetronic Acids from Aldehydes

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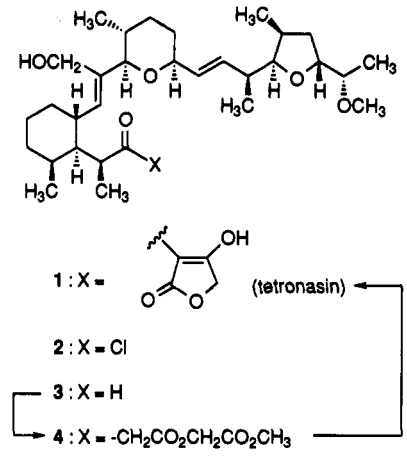
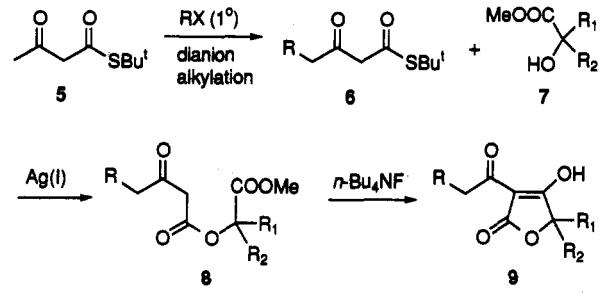
As a part of our studies directed toward the total synthesis of tetronasin (1),[1] an acyltetronic acid polyether antibiotic,[2] we needed an efficient method for the preparation of γ-*unsubstituted* α-acyl-β-tetronic acids that can be utilized at a final stage of the synthesis.[3,4] Several years ago, we reported a new technique for α-acylation of β-tetronic acids (γ-unsubstituted and -substituted) that involves O to C migration of *O*-acylates which is induced by DMAP in CH_2Cl_2 solvent at room temperature.[5] This advanced version of classical Friedel–Crafts acylation[6] can be carried out under exceptionally mild conditions, but unfortunately it has been found that there is a limitation in which sterically hindered *O*-acylates (e.g. *O*-trimethylacetate) strongly resist to the base-induced acyl migration. More recently, Ley and Wadsworth[7] introduced a palladium-catalyzed acylation of *O*-methyl-protected α-(tributylstannyl)tetronic acid in the course of studies aimed at total synthesis of 1, but application of this method to sterically hindered acid chlorides such as 2 has not been recorded.

In the meantime, Ley and co-workers[8] reported a new three-step entry to γ-substituted acyltetronic acids 9: γ-alkylation of *S-tert*-butyl acetothioacetate (5) with primary alkyl halide; transesterification of the homologated acetothioacetate 6 with α-hydroxy ester 7; TBAF-mediated Dieckman cyclization of the resulting diester 8. This methodology, however, is apparently intolerable for the synthesis of 1 which has a bulky α-branched acyl residue, since the keto ester intermediate 4 should not be accessible via a γ,γ-dialkylation of 5. In this context, we planned to prepare 4 by a Lewis acid catalyzed reaction of aldehyde 3 with (diazoacetoxy)acetic ester 11 according to Roskamp's β-keto ester synthesis from aldehyde and



ethyl diazoacetate.[9] After an extensive model study on the proposed transformation, we were able to obtain 4 in high yield, which was cyclized to 1 (74% overall yield), achieving the first total synthesis of tetronasin sodium.[1] This paper describes the results of model studies on the two-step synthesis of γ-unsubstituted α-acyltetronic acids from aldehydes.



Methyl (diazoacetoxy)acetate (11) was prepared from methyl glycolate (10) by two conventional routes as illustrated in Scheme 1.[10] Reaction of 11 with some representative aldehydes was first attempted according to the protocol ($SnCl_2$ catalysis) of Holmquist and Roskampf.[9] As shown in Table 1, reactions of primary and secondary aldehydes (**14a-d**) with 11 in the presence of $SnCl_2$ in dichloromethane at room temperature afforded the desired β-keto esters **15a-d** in good to high yields. On the other hand, reactions of tertiary aldehydes (**14e-g**) proved quite sluggish, resulting in poor yields of the corresponding keto esters even after prolonged reaction and/or with excess amounts of the Sn(II) catalyst. Toward this end, we have made a brief survey of Lewis acid catalysts and have found that $ZrCl_4$ and $TiCl_4$ are quite effective in the C–H insertion reaction to sterically hindered aldehydes (Scheme 2). Thus, reactions of 11 in CH_2Cl_2 with trimethylacetaldehyde (**14e**) and 1-methyl-1-cyclohexanecarboxaldehyde (**14f**) proceeded rapidly at 0 °C and were completed within 0.5 h to give the corresponding keto esters **15e** and **15f**, respectively, in more than 72% isolated yields (Table 1). 2,2-Diphenylpropanal (**14g**) also afforded a good yield of **15g**, although the reaction proved to be somewhat slower. The heterogeneous reaction with $ZrCl_4$ in dichloromethane solvent can be made homoge-

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(3) Reviews on the chemistry and synthesis of tetronic acids: (a) Haynes, L. J.; Plimer, J. R. *Quart. Rev.* **1960**, *14*, 292. (b) Pattenden, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 133.
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Scheme 1

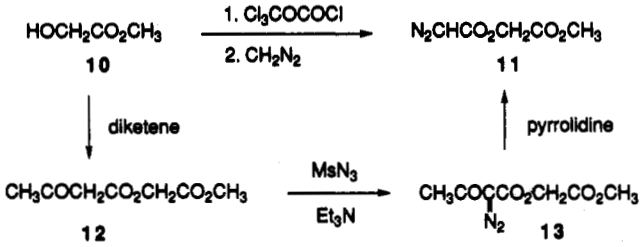
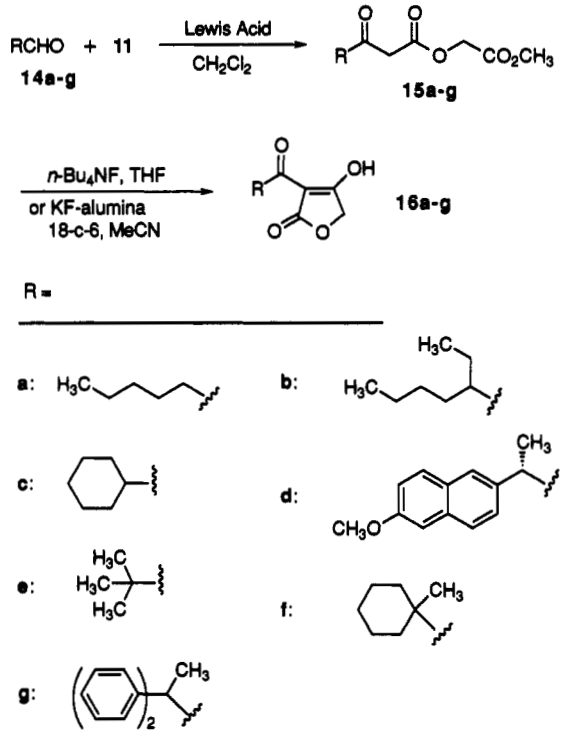


Table 1. Lewis Acid Catalyzed Reaction of Aldehydes with Diazo Ester 11 in Dichloromethane

RCHO	catalyst (equiv)	11 (equiv)	temp (h)	product[a] (%)
14a	$SnCl_2$ (0.2)	1.2	rt (0.5)	**15a** (77)
14b	$SnCl_2$ (0.2)	1.2	rt (10)	**15b** (72)
14c	$SnCl_2$ (0.2)	1.2	rt (2)	**15c** (78)
14d	$SnCl_2$ (0.2)	1.2	rt (5)	**15d** (88)
14e	$SnCl_2$ (0.2)	1.2	rt (10)	**15e** (29)
14e	$TiCl_4$ (1.0)	3.0	0 °C (0.5)	**15e** (75)
14e	$ZrCl_4$ (1.0)	3.0	0 °C (0.5)	**15e** (73)
14e	$ZrCl_4$·$(THF)_2$ (1.0)	3.0	0 °C (0.5)	**15e** (72)
14f	$SnCl_2$ (1.0)	1.5	rt (19)	**15f** (38)
14f	$TiCl_4$ (1.0)	3.0	0 °C (0.5)	**15f** (79)
14f	$ZrCl_4$·$(THF)_2$ (1.0)	3.0	0 °C (0.5)	**15f** (84)
14g	$ZrCl_4$ (1.0)	3.0	0 °C (1)	**15g** (65)

[a] All products were obtained as colorless oils after chromatographic purification.

Scheme 2



neous by using its THF complex, $ZrCl_4$·$(THF)_2$,[11] giving similar yields. The $ZrCl_4$ catalysis method has been successfuly applied to the transformation of **3** into **4** (80% yield). It should be noted that for obtaining high yields it is necessary to use an excess amount of the diazoacetate **11** since there is a loss of **11** due to a side reaction producing $ClCH_2COOCH_2COOCH_3$.

Dieckmann cyclization of β-keto esters **15** was effected by treatment with 2 equiv of TBAF in THF at room temperature[8,12] to afford the acyltetronic acids **16** in modest to good yields (Table 2). The rate of the cyclization reaction was not unexpectedly sensitive to bulkiness at the α-position of the R group, and the tertiary acyl substrates **15e-g** required much longer reaction times than the less hindered ones, **15a-d**. A low yield of **16g** (52%) is largely responsible to a degradation of **15g** to 3,3-diphenyl-2-butanone (38%) under the basic conditions. Potassium fluoride on basic alumina[13] can also be used in combination with 18-crown-6 ether in MeCN. Although the cyclization reactions with the KF reagent were quite slow, there were obtained better yields than with TBAF in the reactions with α-primary and -secondary acyl esters (**15a,c**). Use of tetra-*n*-propylammonium hydroxide[14] resulted in poor yields of tetronic acids owing to competitive hydrolysis of the starting keto esters.

Table 2. γ-Unsubstituted Tetronic Acids

tetronic acid	mp (bp/Torr), °C	% yield	method[a] (time, h)
16a	71–72[b]	73	A (7.5)
		84	B (70)
16b	(73/0.4)	78	A (7)
16c	113–114	72	A (7)
		86	B (44)
16d	135–136	69	A (21)
16e	(70/0.03)	61	A (35)
16f	68–69	61	A (26)
		53 (88)[c]	B (88)
16g	147–148	52	A (90)

[a] Method A: TBAF in THF at rt. Method B: KF·Al_2O_3/18-crown-6 in MeCN at rt. [b] Lit.[3] mp 70–72 °C. [c] The yield based on recovered keto ester **15f**.

In conclusion, we have developed a highly efficient route from aldehydes to γ-unsubstituted α-acyltetronic acids which are otherwise difficult to prepare. The two-step methodology should be quite useful for complex molecules possessing the tetronic acid subunit as demonstrated in the synthesis of tetronasin (**1**).

Experimental Section

Methyl (Diazoacetoxy)acetate (11). (a) A solution of **10** (1.0 g, 11 mmol) in dry benzene (7 mL) was stirred and cooled at 0 °C, and charcoal powder (4 mg) and trichloromethyl chloroformate (1.7 mL, 26 mmol) were added. After dropwise addition of dry pyridine (1.0 mL, 13 mmol) over 3 min (a vigorous gas evolution), the reaction mixture was stirred at 15 °C for 1 h. The mixture was suction-filtered through a layer of Celite after addition of dry ether (10 mL), and the layer was washed with dry ether (40 mL × 2). The combined filtrates were concentrated at a reduced pressure. The residue was dissolved in ether (10 mL), and the solution was treated with ethereal diazomethane [generated from *N*-nitrosomethylurea (15 g) and 50% KOH (45 mL) in ether (150 mL)] for 2 h. Excess diazomethane was purged out by passing nitrogen gas through the solution, and the ether solution was concentrated. The residue (2.7 g) was subjected to flash chromatography (silica gel 50 g, 19:1 benzene/AcOEt) to give **11** (0.89 g, 51%) as a pale yellow oil (Rf = 0.33, 2:1 hexane/AcOEt): IR (neat) 2120, 1762, 1700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 3.82 (3H, s), 4.73 (2H, s,), 4.93 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 52.47, 60.80, 168.53 (the methine carbon adjacent to N_2 could not be detected).

(b) Freshly distilled diketene (5.8 mL, 75.8 mmol) was added to a solution of **10** (4.55 g, 50.6 mmol) in THF (100 mL), and after addition of triethylamine (0.8 mL), the solution was stirred at room temperature for 20 h. It was concentrated at a reduced pressure, and the residue was subjected to flash chromatography (silica gel 350 g, hexane/AcOEt = 1:1) to give **12** (8.14 g, 93%) as a pale yellow oil: Rf = 0.38 (hexane/AcOEt = 1:1); IR (neat)

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1752, 1719 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.30 (3H, s), 3.53 (2H, s), 3.77 (3H, s), 4.67 (2H, s). To a solution of **12** (5.12 g, 29.4 mmol) in THF (80 mL) were added mesyl azide (4.22 g, 34.9 mmol) and triethylamine (6 mL, 43 mmol) by using THF (10 mL) for the transfer, and the mixture was stirred at room temperature for 6 h. Pyrrolidine (4.9 mL 59 mmol) was then added, and stirring at room temperature was continued for 24 h. The solution was concentrated under reduced pressure, and the residue was subjected to flash chromatography (silica gel 460 g, benzene/AcOEt = 15:1) to give **11** (1.69 g, 36%).

Methyl [(1-Methyl-1-cyclohexanecarbonyl)acetoxy]acetate (15f) (General Procedure for the Transformation of 14 to 15). To a stirred and cooled (−10 °C) solution of $ZrCl_4$·$(THF)_2$ (0.31 M in CH_2Cl_2, 3.2 mL) were added **14f** (132 mg, 1.05 mmol) and **11** (497 mg, 3.14 mmol) via a cannula, each as a CH_2Cl_2 solution (1 mL) (a vigorous gas evolution). After the mixture was stirred at 0 °C for 0.5 h, the reaction was quenched by addition of saturated brine (0.5 mL). The organic phase was successively washed with saturated $NaHCO_3$ (1 mL) and brine (1 mL × 2), dried on $MgSO_4$, and concentrated. The residue was subjected to flash chromatography (silica gel 50 g, hexane/AcOEt = 4:1) to give, in order of elution, **15f** (227 mg, 84%) as a colorless oil, $ClCH_2COOCH_2COOCH_3$ (216 mg), and recovered **11** (100 mg). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.78. Found: C, 60.80; H, 7.55.

4-Hydroxy-3-(1-methyl-1-cyclohexanecarbonyl)furan-2-(5*H*)-one (16f) (Cyclization with TBAF). To a solution of **15f** (253 mg, 1.03 mmol) in THF (2 mL) under N_2 was added TBAF (1 M in THF, 2.1 mL), and the mixture was stirred at room temperature. The reaction was monitored by silica gel TLC with the solvent system of AcOEt/$CHCl_3$/MeOH/AcOH = 20:10:9:1. After 26 h, the solution was diluted with AcOEt (6 mL), and 10% HCl (1 mL) was added at 0 °C. The whole was extracted with AcOEt (10 mL × 3) after being saturated with NaCl, dried, and concentrated. The residue was subjected to flash chromatography (silica gel 17 g, AcOEt/MeOH = 9:1) to give the crude tetronic acid (191 mg). This material was purified by partitioning between AcOEt (20 mL) and 10% HCl (2 mL) to obtain **16f** as a white solid (140 mg, 61%), which was crystallized from hexane, mp 68–69 °C (colorles plates). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.36.

4-Hydroxy-3-pentanoylfuran-2(5*H*)-one (16a) (Cyclization with KF–Alumina). To a solution of **15a** (211 mg, 0.92 mmol) in dry MeCN under N_2 were added 18-crown-6 ether (243 mg, 0.92 mmol) and 37% KF on basic alumina (Woelm) (288 mg), and the suspension was stirred at room temperature. After 70 h when **15a** was not detected by TLC analysis, the mixture was suction-filtered through a layer of Celite. The filtrate and MeCN washings were combined and concentrated. The residue was dissolved in AcOEt (20 mL), and the solution was washed with a mixture of saturated brine (1 mL) and 10% HCl (1 mL), dried on Na_2SO_4, and concentrated. The residual pale yellow solid (crude tetronic acid, 190 mg) was recrystallized from *i*-Pr_2O to give **16a** (145 mg, 80%) as colorless leaflets, mp 71–72 °C. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.54; H, 7.04

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Supplementary Material Available: Combustion analytical and spectral data and copies of ^1H NMR spectra of compounds **15a-g** and **16a-g** (18 pages). This material is contained in 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.