4-tert-Butoxy-1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene. A New Diene and its Application to the Synthesis of γ-Alkyldenetetronic Acids

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A new approach to γ-alkylidenetetronic acids is reported which is based on Me\textsubscript{3}SiOTf-catalyzed [3 + 2] cyclization of 4-tert-butoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with oxalyl chloride, orthogonal protection of the α-hydroxy group by benzylation and subsequent deprotection of the β-hydroxy group.

Key words: Butenolides, Cyclizations, O-Heterocycles, Oxalic Acid, Silyl Enol Ethers

Introduction

γ-Alkyldenetetronic acids occur in a number of pharmacologically relevant natural products, such as pulvinic acids [1 – 10]. These heterocycles have also been used as building blocks during the synthesis of natural products [11, 12]. γ-Alkyldenetetronic acids are available, for example, from ascorbic acid. However, the scope of this approach is limited by the fact that derivatives containing substituents located at the exocyclic double bond or at the butenolide moiety are not available [13]. An additional problem arises from the requirement to regioselectively protect the two hydroxy groups [14, 15]. Some years ago, we reported [16, 17] the synthesis of γ-alkyldenebutenolides by [3 + 2] cyclization of 1,3-bis-silyl enol ethers – electroneutral 1,3-dicarbonyl dianion equivalents [18] – with oxalyl chloride. Herein, we wish to report the application of this method to the synthesis of γ-alkyldenetetronic acids based on the synthesis of what is, to the best of our knowledge, the first tert-butoxy substituted 1,3-bis-silyl enol ether.

Results and Discussion

We reported earlier the synthesis of β-methoxy- and β-benzyloxy-γ-alkyldenebutenolides 5\textsubscript{a} and 5\textsubscript{c} from alkyl 4-chloroacetoacetates 1\textsubscript{a}, b [19]. In the present study we report, for the first time, the synthesis of β-ethoxy- and β-(tert-butoxy)-γ-alkyldenebutenolides 5\textsubscript{b} and 5\textsubscript{d} (Scheme 1, Table 1): the reaction of ethyl 4-chloroacetoacetate (1\textsubscript{b}) with EtOH and tBuOH, in the presence of NaH, afforded, in analogy to the known synthesis of 2\textsubscript{c}, the ethyl 4-alkoxyacetoacetates 2\textsubscript{b} and 2\textsubscript{d}, respectively. The latter were transformed, according to a known procedure [20, 21], into the novel 1,3-bis-silyl enol ethers 4\textsubscript{b}, d [20, 21]. The Me\textsubscript{3}SiOTf-catalyzed cyclization of 4\textsubscript{b}, d with oxalyl chloride afforded the Z-configured butenolides 5\textsubscript{b}, d.

We have previously reported the synthesis of γ-alkyldenebutenolide 6, containing two orthogonal protective groups, by [3 + 2] cyclization and subsequent protection of the free hydroxy group with benzoyl chloride (Scheme 2). The deprotection of the benzyl group by hydrogenation afforded, as reported earlier, the desired γ-alkyldenebutenolide 7. However, the reaction is difficult to carry out, since the exocyclic double bond was, to some extent, hydrogenated to give the γ-lactone 8. The product ratio strongly depended on the reaction conditions and, thus, tlc control was mandatory; unfortunately, the separation of 7 from 8 proved to be difficult. In addition, all attempts to remove the benzyl group of 7 (e. g. by K\textsubscript{2}CO\textsubscript{3}/MeOH) resulted in decomposition, due to attack of the methanolate onto the exocyclic double bond and cleavage of the butenolide moiety.
A solution of this problem was developed based on the use of the tert-butyl protective group. The benzylation of butenolide 5d afforded γ-alkyldienobutenolide 9 containing the orthogonal benzyl and tert-butyl protective groups (Scheme 3). Treatment of 9 with TFA resulted in selective cleavage of the tert-butyl ether to give the desired γ-alkyldienetetronic acid 10. The synthesis of 10 proved to be reliable and easy to carry out. Compound 10 represents an important building block for further transformations. Treatment of 5d with triflic anhydride resulted in cleavage of the tert-butyl ether and formation of triflate 11. While Suzuki reactions of the triflate of 5a and 5c were successful [22, 23], the corresponding reactions of 1, containing an unprotected hydroxyl group, failed.

In conclusion, we have reported the synthesis of γ-alkyldienetetronic acids by Me3SiOTf-catalyzed cyclization of a 4-tert-butoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with oxalyl chloride, orthogonal protection of the α-hydroxy group and subsequent deprotection of the β-hydroxy group.

**Experimental Section**

**General comments**

All solvents were dried by standard methods, and all reactions were carried out under an inert atmosphere. For 1H and 13C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron impact ionization (EI, 70 eV), chemical ionization (CI, CH3O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

**Procedure for the synthesis of 2**

To a benzene suspension of NaH was slowly added the corresponding alcohol within 30 min. After stirring for 1 h, methyl 4-chloroacetoacetate (1a) or ethyl 4-chloroacetoacetate (1b) was added slowly by syringe, and the solution was allowed to stir for 8–12 h. An aqueous solution of HCl (10%, 200 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH2Cl2 (3 × 100 mL). The combined organic layers were dried (Na2SO4) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, n-hexane-EtOAc = 20 : 1) to give 2.

**Ethyl 4-ethoxy-3-oxobutanoate (2b)**

Starting with ethanol (260.0 mmol, 15.2 mL), ethyl 4-chloroacetoacetate (145.0 mmol, 19.7 mL) and NaH (330.0 mmol, 8.00 g) in benzene (200 mL), 2b was isolated as a yellow oil (15.0 g, 60%). – 1H NMR (300 MHz, CDCl3): δ = 1.26 (t, J = 7.2 Hz, 3 H, OCH2CH3), 1.31 (t, J = 7.2 Hz, 3 H, OCH2CH3), 3.52 (s, 2 H, CH2), 3.57 (q, J = 7.2 Hz, 2 H, CH2OCH2CH3), 4.11 (s, 2 H, OCH2CO), 4.23 (q, J = 7.2 Hz, 2 H, OCH2CH3).

**Ethyl 4-(tert-butoxy)-3-oxobutanoate (2d)**

Starting with tert-butanol (135.0 mmol, 9.9 g), ethyl 4-chloroacetoacetate (75.0 mmol, 10.2 mL) and NaN (172.0 mmol, 4.14 g) in benzene (140 mL), 2d was isolated as a yellow oil (6.80 g, 49%). – 1H NMR (300 MHz, CDCl3): δ = 1.22 (s, 9 H, CH3, tBu), 1.28 (t, J = 7.2 Hz, 3 H, OCH2CH3), 3.54 (s, 2 H, CH2), 4.01 (s, 2 H, tBuOCH2), 4.20 (q, J = 7.2 Hz, 2 H, OCH2CH3). – 13C NMR (75 MHz, CDCl3): δ = 14.2 (CH3), 27.3 (CH3, tBu), 46.3, 61.3, 68.1 (CH2), 74.3 (C), 167.5, 203.6 (CO), – MS (EI, 70 eV): m/z (%): 203 (1) [M]+, 157 (3), 114 (15), 87 (12), 57 (100), 41 (30), 20 (29). – IR (KBr, cm−1): v = 2978 (s), 2361 (m), 1746 (s), 1726 (s), 1657 (m), 1527 (m), 1452 (m), 1369 (s), 1232 (s), 1195 (s), 1103 (s), 1036 (m). – UV/Vis (CH3CN, nm): λmax(log ε) = 244.8 (2.56).

**General procedure for the synthesis of silyl enol ethers 3**

To a benzene solution of β-ketoester 2 (1.0 equiv.) was added NEt3 (1.5 equiv.). After stirring for 1 h at 20°C, Me3SiCl (1.5 equiv.) was added dropwise at 20°C. After stirring for 48 h, precipitated salts were filtered, and the filtrate was concentrated in vacuo to give the silyl enol ether 3. Due to the unstable nature of the products, only 1H NMR spectra were recorded. The synthesis of 3a and 3c has been previously reported [19].

**Table 1. Synthesis of γ-alkyldienobutenolides.**

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(a) Yields of isolated products; (b) ref. [19]; (c) chemical shift (1H NMR, CDCl3) of the proton located at the exocyclic double bond.
Scheme 1. Synthesis of butenolides 5a-d; i: 1) R^1OH, NaH, C_2H_5OH, 20 °C, 1 h; 2) 20 °C, 12 h; ii: Me_3SiCl, NEt_3, C_2H_5OH, 20 °C, 48 h; iii: 1) LDA, THF, –78 °C, 1 h; 2) Me_3SiCl, 20 °C, –78 → 20 °C; iv: oxalyl chloride (1.2 equiv.), Me_3SiOTf (0.5 equiv.), CH_2Cl_2, –78 → 20 °C, 12 h.

1,4-Diethoxy-3-(trimethylsilyloxy)but-2-ene (3b)

Starting with 2b (79.1 mmol, 13.78 g) in benzene (300 mL), NEt_3 (118.7 mmol, 16.68 mL) and Me_3SiCl (118.7 mmol, 15.0 mL), 3b was isolated as a yellow oil (19.5 g, 93 %, E/Z = 1:1). 1H NMR (300 MHz, CDCl_3): δ = 0.15 (s, 9 H, CH_3 of TMS), 1.07 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.14 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 3.37 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 3.67 (s, 2 H, OCH_2CO), 3.99 (E/Z, q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.40, 5.27 (E/Z, s, 1 H, CH).

1-Ethoxy-4-tert-butoxy-3-(trimethylsilyloxy)but-2-ene (3d)

Starting with 2d (32.5 mmol, 6.50 g) in benzene (100 mL), NEt_3 (48.7 mmol, 6.75 mL) and Me_3SiCl (48.7 mmol, 6.15 g), 3d was isolated as yellow oil (7.52 g, 84 %). 1H NMR (300 MHz, CDCl_3): δ = 0.21 (s, 9 H, CH_3 of TMS), 1.16 (s, 9 H, CH_2, 8Bu), 1.21 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 3.69 (s, 2 H, OCH_2CO), 4.04 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 5.40 (s, 1 H, CH).

General procedure for the synthesis of 1,3-bis-silyl enol ethers 4

A THF solution of LDA was prepared by addition of nBuLi (1.5 equiv., 2.5 m or 15 % solution in hexanes) to a THF solution of diisopropylamine (1.5 equiv.) at 0 °C and subsequent stirring for 20 min. To this solution was added a THF solution of 3 (1.0 equiv.) at –78 °C. After stirring for 1 h at –78 °C, Me_3SiCl (1.5 equiv.) was added. The
temperature of the solution was allowed to rise to ambient temperature during 2 h, and the solution was stirred for 1 h at 20 °C. The solvent was removed in vacuo, and n-hexane was added to the residue. The precipitated lithium chloride was removed by filtration under inert conditions, and the solvent of the filtrate was removed in vacuo to give 4. The product was stored at −20 °C and used without further purification. Due to the unstable nature of the products, only 1H NMR spectra were recorded (except for 4d which proved to be relatively stable). The synthesis of 4a and 4e has been previously reported [19].

1,4-Diethoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (4b)

Starting with diisopropylamine (105.0 mmol, 14.76 mL), nBuLi (15% in n-hexane, 105.0 mmol, 65.63 mL) in 200 mL of THF, 3b (70.0 mmol, 17.20 g) and Me3SiCl (105.0 mmol, 13.26 mL, 4b) was isolated as a yellow oil (18.50 g, 83%). – 1H NMR (300 MHz, CDCl3): δ = 0.13 (s, 9 H, CH2 of TMS), 0.25 (s, 9 H, CH2 of TMS), 1.14 (t, J = 7.2 Hz, 3 H, OCH2CH3), 1.25 (t, J = 7.0 Hz, 3 H, OCH2(CH2)3), 3.59 (q, J = 7.1 Hz, OCH2CH3), 4.07 (q, J = 7.2 Hz, 2 H, OCH2CH3), 4.80 (s, 1 H, CH), 5.42 (s, 1 H, CH).

1-Ethoxy-4-((tert-butoxy)-1,3-bis(trimethylsilyloxy)buta-1,3-diene (4d)

Starting with diisopropylamine (35.6 mmol, 5.0 mL), nBuLi (15% in n-hexane, 35.6 mmol, 22.26 mL) in 100 mL of THF, 3d (23.7 mmol, 6.51 g) and Me3SiCl (35.6 mmol, 4.50 mL, 4d) was isolated as a yellow oil (7.52 g, 92%). – 1H NMR (300 MHz, CDCl3): δ = 0.18 (s, 9 H, CH2 of TMS), 0.27 (s, 9 H, CH2 of TMS), 1.21 (t, J = 7.2 Hz, 3 H, OCH2CH3), 1.27 (s, 9 H, CH2 (tBu), 3.79, 4.03 (E/Z, q, J = 7.1 Hz, OCH2CH3), 4.52, 5.41 (E/Z, s, 1 H, CH), 5.64, 5.77 (E/Z, s, 1 H, CH). – IR (KBr, cm−1): ν = 2976 (s), 1670 (m), 1610 (s), 1567 (m), 1250 (s), 1193 (m), 1136 (s), 1075 (m), 847 (s), UV/Vis (CH2CN, nm): λmax (log ε) = 205.9 (3.61), 293.0 (2.93). – MS (EI, 70 eV): m/z (%) = 346 (7) [M]+, 289 (28), 243 (29), 171 (59), 147 (52), 74 (100), 57 (56), 28 (57). – Anal. for C12H12O2Si2 (346.45): calcd. C 55.47, H 9.89; found C 55.07, H 9.27.

Procedure for the synthesis of butenolides 5a–d

To a CH2Cl2 solution of Me3SiOTf (0.5 equiv.) was added a CH2Cl2 solution of 4 (1.0 equiv.) at −78 °C. Subsequently, oxalyl chloride (1.2 equiv.) was added at −78 °C. The temperature of the solution was allowed to rise to 20 °C over 12 h. A 4:1 mixture of a saturated solution of brine and of hydrochloric acid (10%) was added. The organic layer was separated, and the aqueous layer was repeatedly extracted with CH2Cl2. The combined organic layers were dried (Na2SO4) and filtered. The solvent of the filtrate was removed in vacuo, and the residue was purified by column chromatography (silica gel, n-hexane-EtOAc). The synthesis of 5a and 5e has been previously reported [19].

(ZZ)-Ethyl 2-(3-ethoxy-4-hydroxy-5-oxofuran-2(5H)-ylidene)acetate (5b)

Starting with 4b (12.0 mmol, 3.82 g) in 240 mL of CH2Cl2, oxalyl chloride (14.4 mmol, 1.83 g) and Me3SiOTf (6.0 mmol, 1.330 g, 5b) was isolated by column chromatography (n-hexane-EtOAc = 5 : 1) as a yellow solid (1.25 g, 46%), m. p. = 103 °C. – 1H NMR (300 MHz, CDCl3): δ = 1.31 (t, J = 7.1 Hz, 3 H, OCH2CH3), 1.40 (t, J = 7.1 Hz, 3 H, OCH2CH3), 4.26 (q, J = 7.0 Hz, 2 H, OCH2CH3), 4.54 (q, J = 7.0 Hz, 2 H, OCH2CH3), 5.61 (s, 1 H, CH). – 13C NMR (75 MHz, CDCl3): δ = 14.4, 15.5 (CH3), 61.2, 68.3 (CH2), 96.6 (CH), 122.9, 141.4, 151.8, 163.7, 165.9 (C). – MS (EI, 70 eV): m/z (%) = 228 (24) [M]+, 200 (9), 183 (38), 154 (100), 127 (19), 98 (30), 70 (27), 29 (89). – IR (KBr, cm−1): ν = 3231 (br, s), 2985 (m), 1708 (s), 1686 (s), 1565 (s), 1376 (s), 1344 (s), 1318 (s), 1196 (s), 1120 (s), 1035 (s), 995 (m), 837 (m), 755 (m). – UV/Vis (CH2CN, nm): λmax (log ε) = 215.8 (3.74), 259.0 (3.95), 309.9 (3.79). – Anal. for C7H12O2: calcd. C 52.64, H 5.30; found C 52.43, H 6.12.

(ZZ)-Ethyl 2-(3-tert-butoxy-4-hydroxy-5-oxofuran-2(5H)-ylidene)acetate (5d)

Starting with 4d (10.0 mmol, 3.46 g) in 200 mL of CH2Cl2, oxalyl chloride (12.0 mmol, 1.52 g) and Me3SiOTf (5.0 mmol, 1.11 g, 5d) was isolated by column chromatography (n-hexane-EtOAc = 5 : 1) as a yellow solid (1.20 g, 47%). – 1H NMR (300 MHz, CDCl3): δ = 1.32 (t, J = 7.1 Hz, 3 H, OCH2CH3), 1.51 (s, 9 H, CH2 (tBu), 4.26 (q, J = 7.0 Hz, 2 H, OCH2CH3), 5.30 (s, 1 H, OH), 5.63 (s, 1 H, CH). – 13C NMR (75 MHz, CDCl3): δ = 14.4 (CH3), 26.63 (CH2, tBu), 61.4 (CH2), 70.8, (C), 95.7 (CH), 123.6, 138.2, 163.8, 165.8, 167.6 (C). – MS (EI, 70 eV): m/z (%) = 257 (1) [M]+, 200 (20), 144 (21), 116 (24), 99 (19), 70 (20), 57 (100), 41 (45), 29 (57). – IR (KBr, cm−1): ν = 3352 (s), 2986 (m), 1768 (s), 1678 (s), 1382 (s), 1285 (s), 1171 (s), 1126 (s), 846 (m), 753 (m). – UV/Vis (CH2CN, nm): λmax (log ε) = 213.1 (3.77), 260.7 (3.89), 404.9 (2.83). – Anal. for C13H16O2: calcd.: C 56.24, H 6.29; found C 56.43, H 7.08.

(ZZ)-Ethyl 2-(3-tert-butoxy-4-benzzyloxy-5-oxofuran-2(5H)-ylidene)acetate (5f)

To a solution of 5d (0.357 g, 1.4 mmol) in 6 mL of THF was added DEAD (0.293 g, 1.7 mmol, dissolved in 2 mL of THF), benzylic alcohol (0.184 g, 1.7 mmol) and PPh3 (0.446 g, 1.7 mmol, dissolved in 2 mL of THF). The mixture was stirred at 20 °C for 12 h. The solvent (THF) was evaporated.
in vacuo. The residue was purified by column chromatography (silica gel; n-hexane-ethyl acetate = 25 : 1) to give 9 as a colorless oil (0.205 mg, 45%). – 1H NMR (300 MHz, CDCl3): δ = 1.32 (q, J = 7.1 Hz, 3H, CH2CH3), 1.43 (s, 9H, CH2t-Bu), 4.24 (q, J = 7.1 Hz, 2H, OCH2CH3), 5.29 (s, 1H, CH). – 13C NMR (75 MHz, CDCl3): δ = 14.2 (CH3), 28.7 (CH2t-Bu), 60.8, 73.1 (CH3), 73.8 (CH), 126.1 (CH), 128.6 (2CH, Ph), 128.7 (2CH, Ph), 135.5, 147.7, 153.3, 163.5, 163.8 (C). – MS (EI, 70 eV): m/z (%) = 336 (1) [M]+, 290 (10), 114 (10), 91 (100), 57 (18), 29 (7). – IR (KBr, cm−1): ν = 2982 (s), 1786 (s), 1723 (s), 1706 (s), 1693 (s), 1460 (m), 1393 (s), 1278 (s), 1181 (s), 1098 (s), 1036 (s), 843 (m), 751 (m). – UV/Vis: λmax (log ε) = 205.3 (4.20), 263.8 (4.13).

(ZZ)-Ethyl 2-(4-benzoxyl)-3-hydroxy-5-oxofuran-2(5H)-ylideneacetate (10)

To a CH2Cl2 solution (1.5 mL) of 9 (0.010 g, 0.343 mmol) was added trifluoroacetic acid (0.395 g, 3.43 mmol). The reaction mixture was stirred for 36 h at 20 °C. The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel; n-hexane-EtOAc = 20 : 1) to give 10 as a colorless oil (0.062 g, 62%). – 1H NMR (300 MHz, CDCl3): δ = 1.29 (t, J = 7.1 Hz, 3H, OCH2CH3), 4.33 (q, J = 7.1 Hz, 2H, OCH2CH3), 5.30 (s, 2H, CH2t-Bu), 5.54 (s, 1H, CH), 7.35 – 7.37 (m, 5H, Ar). – 13C NMR (75 MHz, CDCl3): δ = 14.2 (CH3), 60.8, 73.9 (CH3), 96.1 (CH), 123.8 (C), 128.7 (2CH, Ph), 128.8 (CH, Ph), 128.9 (2CH, Ph), 135.4, 147.7, 150.9, 163.2, 163.5 (C). – MS (EI, 70 eV): m/z (%) = 323 (9) [M]+, 287 (35), 199 (49), 154 (19), 114 (189, 70 (100), 29 (30). – IR (KBr, cm−1): ν = 3435 (br, m), 2992 (w), 1672 (s), 1653 (s), 1433 (s), 1243 (s), 1220 (s), 1031 (s), 645 (m). – UV/Vis: λmax (log ε) = 204.3 (4.02), 261.8 (4.02).

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