α-Carboxy-β-Lactones from Photoinduced Ring Contraction of 3-Diazodihydrofuran-2,4-diones

Julia Beneke, Rainer Schobert*

Lehrstuhl für Organische Chemie, Universität Bayreuth, Universitätsstraße 30, 95440 Bayreuth, Germany
Fax +49(921)552671; E-mail: Rainer.Schobert@uni-bayreuth.de

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Abstract: β-Lactones were prepared by irradiation of 3-diazodihydrofuran-2,4-diones via Wolff rearrangement proceeding with retention of the configuration of the migrating carbon atom. In the presence of alcohols or thiols, but not amines, the corresponding 3-(alkoxycarbonyl)- or 3-[(alkylsulfanyl)carbonyl]-β-lactones were obtained. 5-Alkyl-3-diazodihydrofuran-2,4-diones gave exclusively *trans*-3,4-disubstituted β-lactones.

Key words: tetronic acids, β-lactones, ring contraction, rearrangement, diazo compounds

β-Lactones are prepared in numerous ways.[1] The oxetan-2-one ring is a versatile synthetic building block[2] and it also represents the structural core of many bioactive natural products,[3,4] which are thought to act mainly by acylating nucleophilic amino acid residues in the active site of enzymes.[5] Two examples are the *Cephalosporum* metabolite 1233A[6] that inhibits a key enzyme in the biosynthesis of cholesterol and the anti-obesity drug lipstatin, an inhibitor of pancreatic lipase[7] (Figure 1).

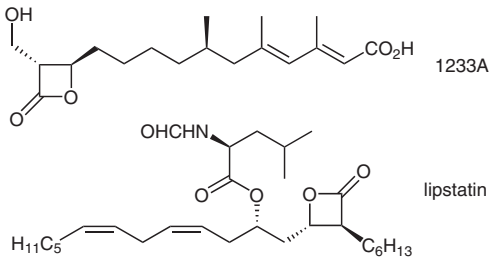
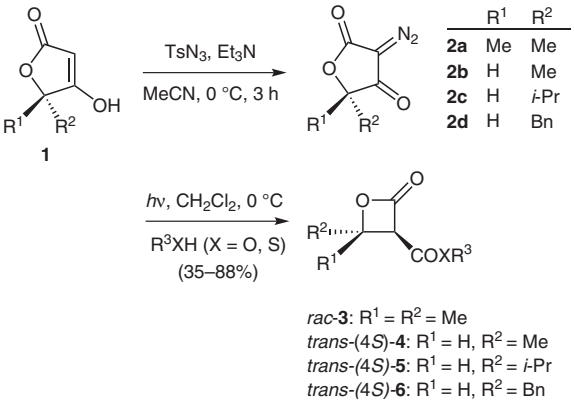


Figure 1 Natural enzyme inhibiting 3,4-disubstituted β-lactones

In 1974, Stork et al. reported the synthesis of β-lactams via photochemically induced Wolff rearrangement of 3-diazopyrrolidine-2,4-diones in the presence of ketene-trapping alcohols or amines. The resulting 3,4-disubstituted β-lactams were predominantly *trans* configured. The *cis* isomers which are more prominent in bioactive β-lactams were not accessible in this way. The migration of the N-neighboring carbon atom took place with configurational retention.[8]

Since most bioactive β-lactones are *trans* 3,4-disubstituted, we now investigated photoreactions of four exemplary 3-diazodihydrofuran-2,4-diones **2**. These were prepared by diazo transfer to tetronic acids **1** according to the Regitz protocol.[9] The tetronic acids **1** were obtained from domino addition–Wittig cyclization of the respective α-hydroxy esters with the ylide Ph_3PCCO.[10] The photolysis (150-W Hg lamp) of the diazo compounds **2** in the presence of alcohols or thiols gave racemic β-lactones **3** or *trans*-(4*S*)-β-lactones **4**–**6**, respectively (Scheme 1, Table 1).



	R^1	R^2
2a	Me	Me
2b	H	Me
2c	H	*i*-Pr
2d	H	Bn

Scheme 1

The *trans* assignment of H3 and H4 of β-lactones **4**–**6** is based on their typical ^{1}H NMR coupling constants $J = 4.3$ Hz. They were obtained as pure enantiomers with the *S* configuration at C4 retained as proven by GC on a chiral Lipodex column. This is in keeping with Stork's findings for β-lactams. The 4,4-dimethyl products **3** were racemates.

The nature of the solvent and the amount of alcohol added were decisive for the yield of product lactones. Photolysis reactions gave lower yields when run in ethers (Et_2O, THF) rather than dichloromethane. Low yields were also found upon photolysis of **2** in dichloromethane in the presence of an excess of alcohol due to formation of diesters such as **7** via ring opening and subsequent dehydration (Scheme 2).

Attempts at trapping the ketene intermediate by a built-in alcohol as in the 5-(hydroxyalkyl) derivatives **8** (X = O; n = 1, 2) failed and decomposition products rather than bislactones were isolated. In contrast, an analogous bicyclic lactam **9** was obtained from the corresponding 3-diazotetramic acid **8a** (X = NBoc; n = 1) under identical conditions (Scheme 3).

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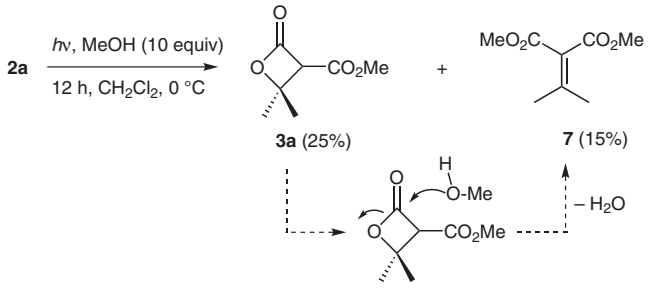
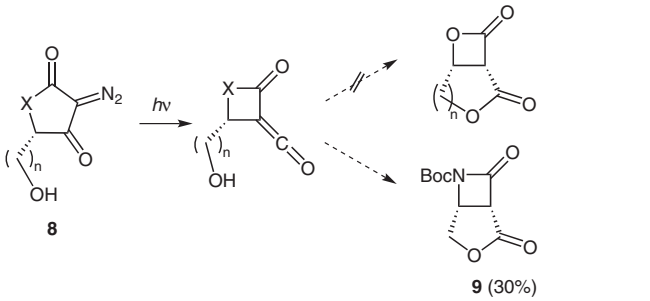
Table 1 β-Lactones **3**–**6** from 3-Diazodihydrofuran-2,4-diones **2**

3–6	XR^3	Yield (%)
3a	OMe	35
3b	$O(CH_2)_3Ph$	41
3c	O*t*-Bu	60
3d	$O(CH_2)_9Me$	37
3e	S*t*-Bu	53
3f	SPr	88
4a	OMe	38
4b	$O(CH_2)_3Ph$	41
4c	O*t*-Bu	60
4d	$O(CH_2)_9Me$	37
4e	S*t*-Bu	50
4f	SPr	50
5a	S*t*-Bu	60
5b	$O(CH_2)_3Ph$	37
6a	S*t*-Bu	50
6b	$O(CH_2)_3Ph$	40



Scheme 2



Scheme 3

Remarkably, the irradiation of mixtures of diazoketones **2** with ammonia, primary amines, or hydrazines led only to decomposition. This is in stark contrast to Stork's 3-diazopyrrolidine-2,4-diones which when irradiated in the presence of these N-nucleophiles afforded 3-carboxamide-β-lactams. C-Nucleophiles such as malonates, Meldrum's acid, or *N*-methylindole did not give defined products, either, upon irradiation with **2**. It should be noted that no reaction at all took place in the dark between **2** and all types of O-, S-, N-, or C-nucleophiles. We also tried to initiate the Wolff rearrangement of **2** with silver benzoate in the presence of alcohols or thiols; no reaction was observed. However, this is not unusual for α-diazoketones lacking α-protons.[11]

In conclusion, the irradiation of 3-diazodihydrofuran-2,4-diones in the presence of alcohols or thiols is an expeditious method for the synthesis of *trans*-3,4-disubstituted β-lactones in two steps from 5-monosubstituted tetronic acids.

IR: Perkin-Elmer Spectrum One FT-IR/ATR. NMR: Bruker Avance 300, with TMS as internal standard. Mass spectra: Perkin-Elmer MAT 8500 (EI, 70 eV). Optical rotation: Perkin-Elmer Polarimeter 241 at 589 nm. Microanalyses: Perkin-Elmer 2400 CHN elemental analyzer. GC: chiral Lipodex E column, Macherey-Nagel. Column chromatography: Merck silica gel 60 (230–400 mesh); R_f obtained in cyclohexane–EtOAc (3:1). **1a**[10,12] and **1b**–**d**[10,13] were prepared according to literature procedures (see the Supporting Information).

β-Lactones 3–6; General Procedure

A solution of diazo compound **2** and alcohol or thiol (1.2 equiv) in anhyd CH_2Cl_2 was irradiated at 0 °C with a 150-W medium pressure Hg lamp until the disappearance of the IR band at 2140 cm^{-1}. The solvent was evaporated and the crude product was purified by column chromatography (cyclohexane–EtOAc, 4:1).

Selected examples of β-lactones **3**–**6** (details of the remaining compounds are given in the Supporting Information):

(±)-3-(*tert*-Butoxycarbonyl)-4,4-dimethyloxetan-2-one (3c)

Using **2a** (233 mg, 1.5 mmol) gave **3c** as a colorless oil (180 mg, 60%); R_f = 0.33.

IR (ATR): 1829, 1726 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.37 (s, 9 H, CH_3), 1.53 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 4.03 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 22.5, 27.4, 27.7, 63.7, 79.0, 83.2, 163.1, 163.3.

MS: *m*/*z* (%) = 127 (4, $[C_6H_7O_3^+]$), 101 (23), 100 (34), 83 (61), 58 (199), 42 (36).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.85; H, 8.02.

(±)-3-(Decyloxycarbonyl)-4,4-dimethyloxetan-2-one (3d)

Using **2a** (233 mg, 1.5 mmol) gave **3d** as a colorless oil (160 mg, 37%); R_f = 0.43.

IR (ATR): 1832, 1735 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.81 (t, *J* = 6.9 Hz, 3 H, CH_3), 1.13–1.34 (m, 14 H, CH_2), 1.55 (s, 3 H, CH_3), 1.56–1.63 (m, 2 H, CH_2), 1.64 (s, 3 H, CH_3), 4.07–4.17 (m, 2 H, CH_2), 4.15 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 13.9, 22.5, 22.7, 25.6, 27.4, 28.3, 29.0, 29.1, 29.3, 29.5, 31.7, 62.9, 66.0, 79.0, 162.7, 164.2.

MS: *m*/*z* (%) = 240 (19, $[M^+ - CO_2]$), 185 (2), 157 (2), 145 (29), 127 (41), 111 (12), 101 (100), 83 (97), 69 (39), 56 (70).

Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.42; H, 9.77.

(±)-3-[(*tert*-Butylsulfanyl)carbonyl]-4,4-dimethyloxetan-2-one (3e)
Using **2a** (233 mg, 1.5 mmol) gave **3e** as a colorless oil (173 mg, 53%); R_f = 0.43.

IR (ATR): 1819, 1666 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.40 (s, 9 H, CH_3), 1.50 (s, 3 H, CH_3), 1.59 (s, 3 H, CH_3), 4.20 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 21.8, 27.4, 29.3, 49.6, 69.6, 79.8, 162.9, 198.7.

MS: *m*/*z* (%) = 172 (2, [$M^+ - CO_2$]), 117 (5), 115 (24), 90 (5), 84 (37), 83 (20), 57 (65), 55 (100).

Anal. Calcd for $C_{10}H_{16}SO_3$: C, 55.53; H, 7.46. Found: C, 55.42; H, 7.35.

(3*S*,4*S*)-3-(*tert*-Butoxycarbonyl)-4-methyloxetan-2-one (4c)
Using **2b** (210 mg, 1.5 mmol) gave **4c** as a colorless oil (166 mg, 60%); R_f = 0.35; $[\alpha]_D^{25}$ –49 (*c* 1.0, $CHCl_3$).

IR (ATR): 1823, 1725 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9 H, CH_3), 1.56 (d, *J* = 6.2 Hz, 3 H, CH_3), 3.96 (d, *J* = 4.2 Hz, 1 H, CH), 4.85 (dq, *J* = 4.2, 6.2 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 19.6, 27.8, 62.7, 71.2, 83.5, 162.9, 163.2.

MS: *m*/*z* (%) = 131 (3), 103 (11), 87 (23), 69 (76), 58 (100).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.78; H, 7.56.

(3*S*,4*S*)-3-[(*tert*-Butylsulfanyl)carbonyl]-4-methyloxetan-2-one (4e)
Using **2b** (210 mg, 1.5 mmol) gave **4e** as a colorless oil (153 mg, 50%); R_f = 0.44; $[\alpha]_D^{25}$ –45 (*c* 1.0, $CHCl_3$).

IR (ATR): 1823, 1666 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 9 H, CH_3), 1.54 (d, *J* = 6.2 Hz, 3 H, CH_3), 4.17 (d, *J* = 4.2 Hz, 1 H, CH), 4.89 (dq, *J* = 4.2, 6.2 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 19.5, 29.5, 49.8, 69.1, 70.8, 162.8, 189.1.

MS: *m*/*z* (%) = 158 (12, [$M^+ - CO_2$]), 102 (14), 69 (100), 57 (40).

Anal. Calcd for $C_9H_{14}SO_3$: C, 53.44; H, 6.98. Found: C, 53.51; H, 7.02.

(3*S*,4*S*)-4-Methyl-3-[(propylsulfanyl)carbonyl]oxetan-2-one (4f)
Using **2b** (210 mg, 1.5 mmol) gave **4f** as a colorless oil (142 mg, 50%); R_f = 0.38; $[\alpha]_D^{25}$ –59 (*c* 1.0, $CHCl_3$).

IR (ATR): 1823, 1669 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.58 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.69 (qt, *J* = 7.2, 7.3 Hz, 2 H, CH_2), 2.92 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.27 (d, *J* = 4.3 Hz, 1 H, CH), 4.94 (dq, *J* = 4.3, 6.2 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): 13.1, 19.6, 22.4, 31.3, 68.8, 71.0, 162.6, 189.1.

MS: *m*/*z* (%) = 144 (11, [$M^+ - CO_2$]), 69 (100).

Anal. Calcd for $C_8H_{12}SO_3$: C, 51.04; H, 6.43. Found: C, 51.32; H, 6.57.

(3*S*,4*S*)-3-[(*tert*-Butylsulfanyl)carbonyl]-4-isopropyloxetan-2-one (5a)
Using **2c** (252 mg, 1.5 mmol) gave **5a** as a colorless oil (208 mg, 60%); R_f = 0.41; $[\alpha]_D^{25}$ –50 (*c* 1.0, $CHCl_3$).

IR (ATR): 1829, 1667 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.92 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.43 (s, 9 H, CH_3), 1.86–1.99 (m, 1 H, CH), 4.18 (d, *J* = 4.3 Hz, 1 H, CH), 4.40 (dd, *J* = 4.3, 8.2 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 16.6, 17.4, 29.5, 31.7, 49.8, 65.9, 78.6, 163.0, 189.4.

MS: *m*/*z* (%) = 186 (2, [$M^+ - CO_2$]), 143 (5), 130 (8), 97 (100), 69 (12), 57 (28).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{19}O_3S$: 231.1055; found: 231.1053.

(3*S*,4*S*)-4-Benzyl-3-[(*tert*-butylsulfanyl)carbonyl]oxetan-2-one (6a)
Using **2d** (117 mg, 0.5 mmol) gave **6a** gave as a pale yellow solid (70 mg, 50%); mp 66 °C; R_f = 0.26; $[\alpha]_D^{25}$ –78 (*c* 1.0, $CHCl_3$).

IR (ATR): 1824, 1662 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9 H, CH_3), 3.15 (d, *J* = 6.0, 2 H, CH_2), 4.22 (d, *J* = 4.3 Hz, 1 H, CH), 4.99–5.07 (m, 1 H, CH), 7.15–7.37 (m, 5 H, CH).

^{13}C NMR ($CDCl_3$): δ = 29.5, 39.0, 49.9, 67.0, 73.5, 127.4, 128.8, 129.2, 134.0, 162.6, 189.0.

MS: *m*/*z* (%) = 178 (12), 145 (100), 127 (38), 117 (37), 91 (34), 57 (42).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}OS$: 279.1055; found: 279.1059.

(1*R*,5*R*)-6-(*tert*-Butoxycarbonyl)-3-oxa-6-azabicyclo[3.2.0]heptane-2,7-dione (9)
Analogously to the synthesis of compounds **3**–**6**, β-lactam **9** (16 mg, 30%) was obtained as a colorless oil from **8a** (X = NBoc, n = 1) (64 mg, 0.25 mmol); R_f = 0.23; $[\alpha]_D^{26}$ +3.3 (*c* 1.0, $CHCl_3$).

IR (ATR): 1815, 1764, 1723 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.54 (s, 9 H, CH_3), 4.06 (d, *J* = 4.7 Hz, 1 H, CH), 4.46 (dd, *J* = 4.8, 11.4 Hz, 1 H, C*H*^{a}H), 4.71 (d, *J* = 11.4 Hz, 1 H, CH*H*^{b}), 4.77 (dd, *J* = 4.8, 4.7 Hz, 1 H, CH).

^{13}C NMR ($CDCl_3$): δ = 28.0, 52.2, 54.6, 69.8, 85.3, 147.2, 155.5, 167.3.

MS: *m*/*z* (%) = 154 (21, [M^+ – O*t*-Bu]), 127 (1, [M^+ – Boc]), 110 (3), 84 (22), 70 (15), 57 (100).

HRMS: *m*/*z* [2 M + Na]$^+$ calcd for $C_{20}H_{26}N_2NaO_{10}$: 477.1486; found: 477.1481.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are experimental details and data for compounds **2**–**8**.

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