A New, General Entry to 3,5-Unsubstituted 4-*O*-Alkyl Tetramates

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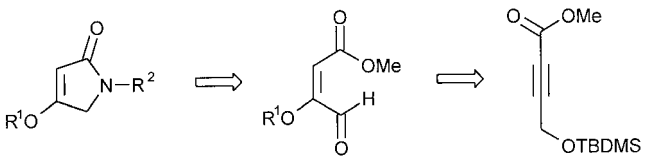
Dedicated to Prof. Dr. Gotthard Wurm on the occasion of his 65th birthday

Abstract: A variety of 3,5-unsubstituted 4-*O*-benzyl tetramates **10** was prepared in good overall yield from methyl (*E*)-3-benzyloxy-4-oxobut-2-enoate **7** by a reductive amination–lactamization sequence. An efficient approach to this building block as well as to various 3-alkoxy analogues is presented.

Key words: tetramic acids, enols, conjugate additions, aminations, lactams

Enol ethers of 3,5-unsubstituted tetramic acids [4-alkoxypyrrol-2(5*H*)-ones] **1** are versatile building blocks for the synthesis of a wide variety of natural products and analogues thereof,[1] a number of which exhibit interesting biological activities, including potent antibacterial and immunosupressive properties. Unlike their oxygen analogue, tetronic acid, 3,5-unsubstituted tetramic acids (pyrrolidine-2,4-diones) are generally unsuitable starting materials for the preparation of the corresponding enol ethers,[2] since they are prone to self-condensations under the requisite reaction conditions.[3,4] Thus they are usually prepared by reaction of alkyl (*E*)-4-bromo-3-alkoxybut-2-enoates or the respective 4-chloro analogues with ammonia or primary amines in moderate to good yields.[5] The former building blocks are readily available by bromination of alkyl acetoacetate derivative alkyl 3-alkoxybut-2-enoates with *N*-bromosuccinimide or by acid-catalyzed enol ether formation from alkyl 4-chloroacetoacetates. These approaches, however, are essentially restricted to the formation of 4-*O*-methyl and 4-*O*-ethyl derivatives. Other 4-*O*-alkyl tetramates, e.g. 4-benzyloxypyrrol-2(5*H*)-one have to be prepared indirectly.[6] Thus heating of commercially available 4-methoxypyrrol-2(5*H*)-one with an excess of benzyl alcohol in the presence of strong acid afforded the corresponding 4-*O*-benzyl tetramate in satisfactory yield. Quite naturally, this method is incompatible with acid-sensitive alcohols and tetramates. We now report a new, general entry to 3,5-unsubstituted 4-*O*-alkyl tetramates, which offers high flexibility in the choice of substituents both at O-4 and N-1.

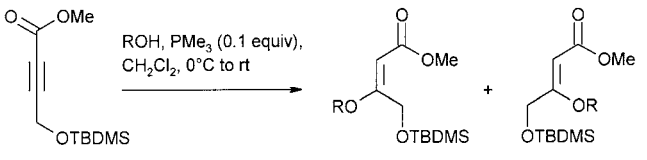
Tetramates **1** were envisioned to arise from two key transformations: (a), the conjugate addition of alcohols to the known butynoate **3**,[7] followed by deprotection and subsequent oxidation of the allylic hydroxyl group to give aldehyde **2**; and (b), reductive amination of this building block followed by lactamization (Scheme 1).



1 2 3

Scheme 1

According to the method of Inanaga and co-workers,[8] a variety of alcohols was added to butynoate **3**, using trimethylphosphine as a nucleophilic catalyst to give enol ethers **4** and **5** in good overall yields (Scheme 2; Table 1). To attain such high yields, however, the order of addition of the reagents is quite critical, since **3** rapidly undergoes self-condensation in the presence of the trialkylphosphine catalyst. Accordingly, the best yields of enol ethers were accomplished by slow addition of **3** to a mixture of the respective alcohol (1.1–3.0 equiv) and trimethylphosphine (10 mol%) in dichloromethane at 0 °C. In the case of primary alcohols, the desired *E*-configurated enol ethers **4** were obtained almost exclusively (*E*:*Z* ≥ 97:3) (Table 1, entries 1–5). However, even with a secondary alcohol bearing bulky substituents, only slightly higher amounts of the respective *Z*-isomer **5** arose (Table 1, entry 7). The double-bond geometry in *E*/*Z*-isomers **4** and **5** was determined on the basis of NOE experiments. Thus irradiation of H-4, in the case of *Z*-isomers **5**, gave rise to significant NOE's for H-2.



3 4 5

Scheme 2

In the course of our further studies we focused on the synthesis of 4-*O*-benzyl tetramates **10**. As depicted in Scheme 3, the appropriate key intermediate **7** was readily obtained from **4c** in an efficient two-step sequence. Deprotection of the hydroxy group was achieved under mild conditions by treatment with HF–pyridine[9] (Olah´s

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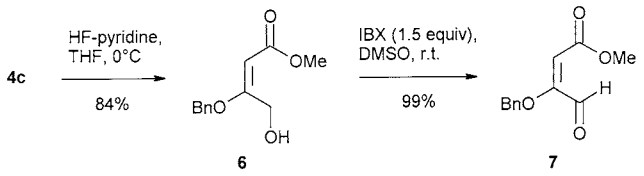
Table 1 Conjugate Additions of Various Alcohols to Butynoate **3**

Entry	R =	Product	Yield [a] (%)	Ratio [b] **4**:**5**
1	Me	**4a**	80	98:2
2	$TMSCH_2CH_2$	**4b**	85	99:1
3	Bn	**4c**	90	97:3
4	*p*-$MeOC_6H_4CH_2$	**4d**	69	97:3
5	CH_2=$CHCH_2$	**4e**	81	97:3
6	*i*-Pr	**4f**	75	96:4
7	(1*R*)-menthyl	**4g**	78	95:5

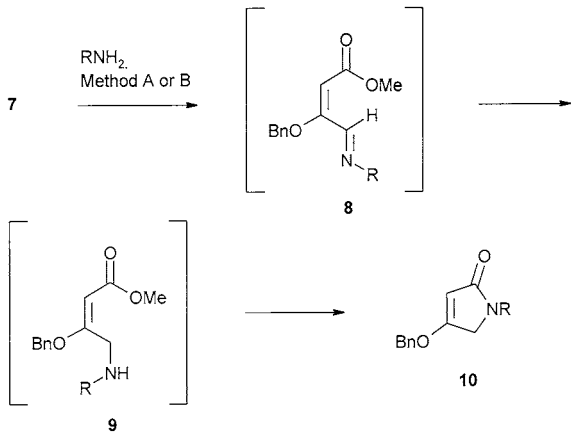
[a] Yield of isolated, purified product **4**.
[b] Ratio **4**:**5** determined by ^{1}H NMR (500 MHz) of the crude products.

reagent) in THF at 0 °C or alternatively with HF (1.0 equiv) in acetonitrile at the same temperature to give γ-hydroxy ester **6** in 84% and 80% yield, respectively. Under the latter conditions, however, we also obtained small amounts of 4-benzyloxyfuran-2(5*H*)-one, due to lactonization of the γ-hydroxy ester. The subsequent oxidation of alcohol **6** was accomplished with 2-iodoxybenzoic acid (IBX)[10] in DMSO at r.t. to afford aldehyde **7** in excellent yield (99%).



Scheme 3

Finally key building block **7** was converted into a series of 4-*O*-benzyl tetramates **10** by a reductive amination–lactamization sequence (Scheme 4, Table 2).[11]



Scheme 4

Table 2 Consecutive Reductive Amination–lactamization of Aldehyde **7** with Various Primary Amines

Entry	R =	Method [a]	Product	Yield [b] (%)
1	Me	A[c]	**10a**	84
2	$HC{\equiv}CCH_2$	A	**10b**	48
3	Bn	A	**10c**	73
4	(*S*)-PhCH(Me)	B	**10d**	74
5	(±)-CH(*i*-Pr)COOMe	B[c]	**10e**	65
6	*t*-Bu	B	**10f**	66
7	Ph	B[d]	**10g**	53

[a] Method A: (i), amine (1.5 equiv), MS 3 Å, THF, r.t., 24–40 h; (ii), $NaBH_4$ (1.3 equiv), MeOH, 45 °C, 24 h. Method B: (i), amine (1.5 equiv), MS 3 Å, THF, r.t., 24–40 h; (ii), $NaBH_4$ (1.3 equiv), MeOH, 45 °C, 24 h; (iii), toluene–HOAc = 10:1, Δ, 1.5 h.
[b] Yield of isolated, purified product **10**.
[c] The respective hydrochlorimide (1.5 equiv) together with *i*-Pr_2NEt (2 equiv) was used instead of the free amine.
[d] HOAc (1.0 equiv) was added to catalyze the formation of the imine.

The reductive aminations were best accomplished in a stepwise manner involving preformation of the intermediate imines **8** followed by reduction.[12] Initially the imines **8** were generated almost quantitatively by reaction of aldehyde **7** with the respective amines (1.5 equiv) in the presence of a dehydrating agent [molecular sieves (MS) 3 Å, THF, r.t., 24–40 h]. In the case of volatile or unstable amines the respective hydrochlorides (1.5 equiv) were used by adding *N*,*N*-diisopropylethylamine (2.0 equiv). As determined by ^{1}H NMR, the crude imines **8** were sufficiently pure (> 95%) for the subsequent reactions and employed as such. The reductions were carried out by treatment of the imines **8** with sodium borohydride (1.3 equiv) in methanol at 45 °C for 24 hours.[13] In case of unhindered aliphatic amino residues, spontaneous cyclisation of the intermediate γ-amino esters **9** occurred, to give the corresponding 4-*O*-benzyl tetramates **10** directly in satisfactory to good overall yields (Table 2, entries 1–3). On the other hand, with aromatic or bulky aliphatic residues present, mainly the respective γ-amino esters **9** were obtained, even after prolonged heating at 45 °C, in addition to minor amounts of the desired tetramates **10**. Nevertheless these lactamizations could be driven to completion by heating the crude reduction products in a 10:1 mixture of toluene and glacial acetic acid for 1.5 hours (Table 2, entries 4–7).

In conclusion we have developed a general approach to 3,5-unsubstituted 4-*O*-alkyl tetramates starting from readily available butynoate **3**, which offers high flexibility in the choice of substituents both at O-4 and N-1.

Unless otherwise noted, reactions were carried out in oven-dried glassware under an atmosphere of dry N_2. All reagents were used as commercially available. CH_2Cl_2 was distilled from CaH_2 and THF from sodium metal immediately before use. Flash chromatography:

silica gel (Merck 60, 0.040–0.063 mm). Mp (uncorrected values): Electrothermal 9100 (Electrothermal). Optical rotations: Polarimeter 241 (Perkin Elmer). ^{1}H NMR spectra: Eclipse 500 FTNMR spectrometer (Jeol), 500 MHz, chemical shifts (δ) are reported in ppm, TMS as internal standard. IR spectra: FT-IR spectrometer FT/IR-410 (Jasco). Mass spectra: 5989 Mass spectrometer with 59980 B particle beam LC/MS interface (Hewlett Packard); API 2000 (Applied Biosystems). High resolution mass spectrometry: MStation 700 (Jeol). Elemental analysis: CHN Rapid (Heraeus).

Conjugate Addition of Alcohols to Butynoate 3; General Procedure

A solution of butynoate **3** (228 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of the alcohol (3.0 mmol) and PMe_3 (100 μL, 1.0 M in THF, 0.1 mmol) in CH_2Cl_2 (5 mL) at 0 °C by means of a syringe. Then the reaction mixture was allowed to warm to r.t. and stirred overnight, before it was concentrated under reduced pressure. The crude product (mixture of *E*/*Z*-isomers) was purified by flash chromatography.

Methyl (*E*)-4-(*tert*-Butyldimethylsilanyloxy)-3-methoxybut-2-enoate (4a) and Methyl (*Z*)-4-(*tert*-Butyldimethylsilanyloxy)-3-methoxybut-2-enoate (5a)

Prepared according to the general procedure from **3** (183 mg, 0.8 mmol) and MeOH (97 μL, 2.4 mmol). Purified by flash chromatography (hexane–CH_2Cl_2–Et_2O, 90:5:5) to give **4a** (167 mg, 80%) and **5a** (4 mg, 2%) as colorless oils.

4a: IR (film): 3008, 1715, 1632 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.09 (s, 6 H, $SiCH_3$), 0.91 [s, 9 H, $(CH_3)_3C$], 3.68 (2 × s, 6 H, 2 × OCH_3), 4.83 (s, 2 H, CH_2OSi), 5.02 (s, 1 H, C=CH).

MS (CI, CH_4): *m*/*z* (%) = 261 (58) [M + H$^+$] 107 (100).

Anal. Calcd for $C_{12}H_{24}O_4Si$ (260.4): C, 55.35; H, 9.20. Found: C, 55.35; H, 9.29.

5a: ^{1}H NMR ($CDCl_3$): δ = 0.10 (s, 6 H, $SiCH_3$), 0.92 [s, 9 H, $(CH_3)_3C$], 3.68 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.19 (d, 2 H, *J* = 0.9 Hz, CH_2OSi), 5.24 (t, 1 H, *J* = 0.9 Hz, C=CH).

Methyl (*E*)-4-(*tert*-Butyldimethylsilanyloxy)-3-(2-trimethylsilanylethoxy)but-2-enoate (4b) and Methyl (*Z*)-4-(*tert*-Butyldimethylsilanyloxy)-3-(2-trimethylsilanylethoxy)but-2-enoate (5b)

Prepared according to the general procedure from **3** (686 mg, 3.0 mmol) and 2-(trimethylsilyl)ethanol (1.29 mL, 9.0 mmol). Purified by flash chromatography (hexane–CH_2Cl_2–Et_2O, 95:2.5:2.5) to give **4b** (882 mg, 85%) and **5b** (2.2 mg, 0.2%) as colorless oils.

4b: IR (film): 3010, 1716, 1628 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.06 (s, 9 H, $SiCH_3$), 0.09 (s, 6 H, $SiCH_3$), 0.91 [s, 9 H, $(CH_3)_3C$], 1.10 (m, 2 H, CH_2CH_2Si), 3.67 (s, 3 H, OCH_3), 3.88 (m, 2 H, CH_2CH_2Si), 4.80 (br d, 2 H, *J* ≈ 0.5 Hz, CH_2OSi), 4.97 (br t, 1 H, *J* ≈ 0.5 Hz, C=CH).

MS (CI, CH_4): *m*/*z* (%) = 347 (20) [M + H$^+$] 303 (100).

Anal. Calcd for $C_{16}H_{34}O_4Si_2$ (346.6): C, 55.44; H, 9.89. Found: C, 55.56; H, 9.71.

5b: ^{1}H NMR ($CDCl_3$): δ = 0.04 (s, 9 H, $SiCH_3$), 0.09 (s, 6 H, $SiCH_3$), 0.91 [s, 9 H, $(CH_3)_3C$], 1.10 (m, 2 H, CH_2CH_2Si), 3.67 (s, 3 H, OCH_3), 4.14 (d, 2 H, *J* = 1.0 Hz, CH_2OSi), 4.26 (m, 2 H, CH_2CH_2Si), 5.27 (t, 1 H, *J* = 1.0 Hz, C=CH).

Methyl *(E)*-3-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)but-2-enoate (4c) and Methyl *(Z)*-3-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)but-2-enoate (5c)

Prepared according to the general procedure from **3** (2.28 g, 10.0 mmol) and benzyl alcohol (1.14 mL, 11.0 mmol). Purified by flash chromatography (hexane–CH_2Cl_2–Et_2O, 90:5:5) to give **4c** (3.03 g, 90%) and **5c** (106 mg, 3%) as colorless oils.

4c: IR (film): 3093, 3065, 3034, 1714, 1630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.05 (s, 6 H, $SiCH_3$), 0.88 [s, 9 H, $(CH_3)_3C$], 3.67 (s, 3 H, OCH_3), 4.87 (s, 2 H, CH_2OSi), 4.88 (s, 2 H, CH_2Ph), 5.12 (s, 1 H, C=CH), 7.31–7.38 (m, 5 H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = –5.28 ($SiCH_3$), 18.39 [$(CH_3)_3C$], 25.88 [$(CH_3)_3C$], 50.99 (OCH_3), 60.57 (C-4), 70.32 (CH_2Ph), 91.99 (C-2), 127.61–128.23, 135.35 (C_6H_5), 167.36 (C-1), 171.97 (C-3).

MS (CI, CH_4): *m*/*z* (%) = 337 (80) [M + H$^+$] 279 (100).

Anal. Calcd for $C_{18}H_{28}O_4Si$ (336.5): C, 64.25; H, 8.39. Found: C, 64.38; H, 8.30.

5c: ^{1}H NMR ($CDCl_3$): δ = 0.06 (s, 6 H, $SiCH_3$), 0.90 [s, 9 H, $(CH_3)_3C$], 3.71 (s, 3 H, OCH_3), 4.14 (d, 2 H, *J* = 1.1 Hz, CH_2OSi), 5.25 (s, 2 H, CH_2Ph), 5.38 (t, 1 H, *J* = 1.1 Hz, C=CH), 7.29–7.42 (m, 5 H, H_{arom}).

Methyl (*E*)-4-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)but-2-enoate (4d) and Methyl (*Z*)-4-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)but-2-enoate (5d)

Prepared according to the general procedure from **3** (183 mg, 0.8 mmol) and 4-methoxybenzyl alcohol (298 μL, 2.4 mmol). Purified by flash chromatography (hexane–CH_2Cl_2–Et_2O, 8:1:1) to give **4d** (202 mg, 69%) and **5d** (12 mg, 3%) as colorless oils.

4d: IR (film): 2998, 1714, 1628 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.03 (s, 6 H, $SiCH_3$), 0.87 [s, 9 H, $(CH_3)_3C$], 3.67 (s, 3 H, $COOCH_3$), 3.81 (s, 3 H, OCH_3), 4.80 (s, 2 H, $CH_2C_6H_4OCH_3$), 4.85 (s, 2 H, CH_2OSi), 5.12 (s, 1 H, C=CH), 6.87–6.91 (m, 2 H, H_{arom}), 7.28–7.32 (m, 2 H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = –5.28 ($SiCH_3$), 18.40 [$(CH_3)_3C$], 25.83 [$(CH_3)_3C$], 50.97 ($COOCH_3$), 55.29 (OCH_3), 60.63 (C-4), 70.21 ($CH_2C_6H_4OMe$), 91.76 (C-2), 113.92, 127.40, 129.41, 159.65 ($C_6H_4OCH_3$), 167.43 (C-1), 172.10 (C-3).

MS (CI, CH_4): *m*/*z* (%) = 367 (48) [M + H$^+$] 121 (100).

Anal. Calcd for $C_{19}H_{30}O_5Si$ (366.5): C, 62.26; H, 8.25. Found: C, 62.01; H, 8.53.

5d: ^{1}H NMR ($CDCl_3$): δ = 0.06 (s, 6 H, $SiCH_3$), 0.90 [s, 9 H, $(CH_3)_3C$], 3.71 (s, 3 H, $COOCH_3$), 3.81 (s, 3 H, OCH_3), 4.12 (d, 2 H, *J* = 1.0 Hz, CH_2OSi), 5.18 (s, 2 H, $CH_2C_6H_4OCH_3$), 5.38 (t, 1 H, *J* = 1.0 Hz, C = CH), 6.87–6.91 (m, 2 H, H_{arom}), 7.26–7.34 (m, 2 H, H_{arom}).

Methyl (*E*)-3-Allyloxy-4-(*tert*-butyldimethylsilanyloxy)but-2-enoate (4e) and (*Z*)-3-Allyloxy-4-(*tert*-butyldimethylsilanyloxy)but-2-enoate (5e)

Prepared according to the general procedure from **3** (183 mg, 0.8 mmol) and allyl alcohol (164 μL, 2.4 mmol). Purified by flash chromatography (hexane–CH_2Cl_2–Et_2O, 90:5:5) to give **4e** (188 mg, 82%) and **5e** (6 mg, 3%) as colorless oils.

4e: IR (KBr): 3089, 3019, 1715, 1630 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.09 (s, 6 H, $SiCH_3$), 0.90 [s, 9 H, $(CH_3)_3C$], 3.67 (s, 3 H, OCH_3), 4.36 (dt, 2 H, *J* = 1.5, 5.5 Hz, $CH_2CH=CH_2$), 4.84 (s, 2 H, CH_2OSi), 5.02 (s, 1 H, C=CH), 5.29 (ddd, 1 H, *J* = 1.5, 3.0, 10.6 Hz, $CH_2CH=CH_2$), 5.39 (ddd, 1 H, *J* = 1.5, 3.0, 17.3 Hz, $CH_2CH=CH_2$), 5.97 (ddt, 1 H, *J* = 5.5, 10.6, 17.3 Hz, $CH_2CH=CH_2$).

^{13}C NMR ($CDCl_3$): δ = –5.25 ($SiCH_3$), 18.42 [$(CH_3)_3C$], 25.85 [$(CH_3)_3C$], 50.95 (OCH_3), 60.61 (C-4), 69.16 ($CH_2CH=CH_2$), 91.53 (C-2), 118.40 ($CH_2CH=CH_2$), 131.62 ($CH_2CH=CH_2$), 167.37 (C-1), 171.88 (C-3).

MS (CI, CH_4): *m*/*z* (%) = 287 (85) [M + H$^+$] 255 (100).

HRMS: *m*/*z* Calcd for $C_{14}H_{26}O_4Si$ (M^+): 286.1600. Found: 286.1600.

5e: ^{1}H NMR ($CDCl_3$): δ = 0.09 (s, 6 H, $SiCH_3$), 0.91 [s, 9 H, $(CH_3)_3C$], 3.69 (s, 3 H, OCH_3), 4.17 (d, 2 H, *J* = 1.0 Hz, CH_2OSi), 4.70 (dt, 2 H, *J* = 1.5, 5.3 Hz, $CH_2CH{=}CH_2$), 5.24 (ddd, 1 H, *J* = 1.5, 3.1, 10.6 Hz, $CH_2CH{=}CH_2$), 5.33 (t, 1 H, *J* = 1.0 Hz, C=CH), 5.40 (ddd, 1 H, *J* = 1.5, 3.1, 17.2 Hz, $CH_2CH{=}CH_2$), 5.96 (ddt, 1 H, *J* = 5.3, 10.6, 17.2 Hz, $CH_2CH{=}CH_2$).

Methyl (*E*)-4-(*tert*-Butyldimethylsilanyloxy)-3-isopropoxybut-2-enoate (4f) and Methyl (*Z*)-4-(*tert*-Butyldimethylsilanyloxy)-3-isopropoxybut-2-enoate (5f)

Prepared according to the general procedure from **3** (183 mg, 0.8 mmol) and *i*-PrOH (184 μL, 2.4 mmol). Purified by flash chromatography (hexane–CH_2Cl_2–Et_2O, 90:5:5) to give **4f** (173 mg, 75%) and **5f** (7 mg, 3%) as colorless oils.

4f: IR (film): 1716, 1624 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.08 (s, 6 H, $SiCH_3$), 0.93 [s, 9 H, $(CH_3)_3C$], 1.31 [d, 6 H, *J* = 6.1 Hz, $CH(CH_3)_2$], 3.66 (s, 3 H, OCH_3), 4.40 [sept, 1 H, *J* = 6.1 Hz, $CH(CH_3)_2$], 4.80 (br s, 2 H, CH_2OSi), 4.98 (br s, 1 H, C=CH).

MS (CI, CH_4): *m*/*z* (%) = 289 (24) [M + H^+] 257 (100).

Anal. Calcd for $C_{14}H_{28}O_4Si$ (288.5): C, 58.29; H, 9.78. Found: C, 58.39; H, 9.61.

5f: ^{1}H NMR ($CDCl_3$): δ = 0.09 (s, 6 H, $SiCH_3$), 0.92 [s, 9 H, $(CH_3)_3C$], 1.29 [d, 6 H, *J* = 6.1 Hz, $CH(CH_3)_2$], 3.68 (s, 3 H, OCH_3), 4.11 (d, 2 H, *J* = 1.1 Hz, CH_2OSi), 4.81 [sept, 1 H, *J* = 6.1 Hz, $CH(CH_3)_2$], 5.39 (t, 1 H, *J* = 1.1 Hz, C=CH).

Methyl (*E*)-4-(*tert*-Butyldimethylsilanyloxy)-3-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]but-2-enoate (4g) and Methyl (*Z*)-4-(*tert*-Butyldimethylsilanyloxy)-3-[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy]but-2-enoate (5g)

Prepared according to the general procedure from **3** (228 mg, 1.0 mmol) and (–)-menthol (469 mg, 3.0 mmol). Purified by flash chromatography (hexane–CH_2Cl_2–Et_2O, 90:5:5) to give **4g** (299 mg, 78%) and **5g** (11 mg, 3%) as colorless oils.

4g: $[\alpha]_D^{20}$ –107° (*c* = 1.08, CH_2Cl_2).

IR (film): 3089, 3018, 1715, 1623 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.72 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 0.86–1.10 (m, 3 H, CH and CH_2), 0.88 [d, 3 H, *J* = 7.1 Hz, $CH(CH_3)_2$], 0.90 [s, 9 H, $(CH_3)_3C$], 0.92 [d, 3 H, *J* = 6.6 Hz, $CH(CH_3)_2$], 1.37–1.50 [m, 2 H, CH and $CH(CH_3)_2$], 1.66–1.74 (m, 2 H, CH_2), 2.09–2.19 (m, 2 H, CH_2 and $CHCH_3$), 3.67 (s, 3 H, OCH_3), 3.92 [dt, 1 H, *J* = 4.1, 10.6 Hz, OCH], 4.60 (d, 1 H, *J* = 13.7 Hz, CH_2OSi), 4.99 (d, 1 H, *J* = 13.7 Hz, CH_2OSi), 5.02 (br s, 1 H, C=CH).

MS (CI, CH_4): *m*/*z* (%) = 385 (100) [M + H^+].

Anal. Calcd for $C_{21}H_{40}O_4Si$ (384.6): C, 65.58; H, 10.48. Found: C, 65.53; H, 10.76.

5g: ^{1}H NMR ($CDCl_3$): δ = 0.10 (s, 6 H, $SiCH_3$), 0.81 (d, 3 H, *J* = 7.0 Hz, $CHCH_3$), 0.86–1.13 (m, 3 H, CH and CH_2), 0.91 [d, 3 H, *J* = 6.4 Hz, $CH(CH_3)_2$], 0.92 [s, 9 H, $(CH_3)_3C$], 0.92 [d, 3 H, *J* = 6.9 Hz, $CH(CH_3)_2$], 1.35–1.49 [m, 2 H, CH and $CH(CH_3)_2$], 1.63–1.71 (m, 2 H, CH_2), 2.00–2.18 (m, 2 H, CH_2 and $CHCH_3$), 3.66 (s, 3 H, OCH_3), 4.10 (dd, 1 H, *J* = 0.8, 15.7 Hz, CH_2OSi), 4.17 (dd, 1 H, *J* = 0.8, 15.7 Hz, CH_2OSi), 4.36 [dt, 1 H, *J* = 4.2, 10.4 Hz, OCH], 5.27 (t, 1 H, *J* = 0.8 Hz, C=CH).

Methyl (*E*)-3-Benzyloxy-4-hydroxybut-2-enoate (6)

HF–pyridine complex (Olah's reagent) (10.0 mL, ca. 70% HF) was added dropwise to a solution of **4c** (2.82 g, 8.38 mmol) in THF (168 mL) at 0 °C and stirred for 3.5 h. Sat. aq $NaHCO_3$ (300 mL) was added, the pH value was adjusted to 8.0 with $NaHCO_3$, and the mixture was extracted with Et_2O (4 × 300 mL). The combined organic layers were washed with 10% aq KH_2PO_4 (3×100 mL) and H_2O (2 × 100 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (pentane–acetone, 9:1) to give **6** (1.56 g, 84%) as a colorless oil.

IR (film): 3447, 1709, 1688 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.73 (s, 3 H, OCH_3), 4.30 (t, 1 H, *J* = 7.4 Hz, OH), 4.45 (d, 2 H, *J* = 7.4 Hz, CH_2OH), 4.85 (s, 2 H, CH_2Ph), 5.25 (s, 1 H, C = CH), 7.34–7.42 (m, 5 H, H_{arom}).

MS (CI, CH_4): *m*/*z* (%) = 223 (20) [M + H^+], 191 (100).

Anal. Calcd for $C_{12}H_{14}O_4$ (222.2): C, 64.85; H, 6.35. Found: C, 65.18; H, 6.24.

Methyl *(E)*-3-Benzyloxy-4-oxobut-2-enoate (7)

A solution of 2-iodoxybenzoic acid (924 mg, 3.3 mmol) in DMSO (3.3 mL) was added to the alcohol **6** (490 mg, 2.2 mmol) and the mixture was stirred for 2 h at r.t. The resulting suspension was diluted with Et_2O (5 mL), applied on a silica gel column (ca. 500 mL) and eluted with pentane–Et_2O (70:30) to give **7**.

Yield: 481 mg (99%); colorless crystals; mp 83 °C.

IR (film): 3072, 3034, 1713, 1694, 1627 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.77 (s, 3 H, OCH_3), 4.95 (s, 2 H, CH_2Ph), 5.84 (s, 1 H, C=CH), 7.33–7.42 (m, 5 H, H_{arom}), 10.50 (s, 1 H, CHO).

MS (CI, CH_4): *m*/*z* (%) = 221 (100) [M + H^+].

Anal. Calcd for $C_{12}H_{12}O_4$ (220.2): C, 65.45; H, 5.49. Found: C, 65.76; H, 5.46.

Preparation of 4-*O*-Benzyl Tetramates; General Procedures

Method A: The respective amine (1.5 mmol) was added to a mixture of **7** (220 mg, 1.0 mmol) and molecular sieves (MS) 3 Å (ca. 1 g) in THF (10 mL). After stirring for 24–40 h at r.t. the MS were filtered off and the filtrate was evaporated under reduced pressure to give the corresponding imine in almost quantitative yield. This crude product was sufficiently pure for the subsequent reduction with $NaBH_4$. To a solution of the imine in MeOH (20 mL), $NaBH_4$ (49 mg, 1.3 mmol) was added at r.t. Then the mixture was stirred for 24 h at 45 °C. After cooling to r.t., sat. aq $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography.

Method B: As described above with the exception of refluxing the crude reduction product in a mixture of toluene (10 mL) and HOAc (1 mL) for 1.5 h. After cooling to r.t., the solvents were evaporated under reduced pressure and the residue was purified by flash chromatography.

4-Benzyloxy-1-methylpyrrol-2(5*H*)-one (10a)

Prepared according to Method A from **7** (110 mg, 0.5 mmol). However, instead of the free amine, methylamine hydrochloride (51 mg, 0.75 mmol) together with *i*-Pr_2NEt (166 μL, 1.0 mmol) was employed. Purified by flash chromatography (EtOAc–CH_2Cl_2–MeOH, 80:16:4) to give **10a**.

Yield: 85 mg (84%); colorless crystals; mp 85 °C.

IR (film): 3091, 3034, 1682, 1621, 1585 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.95 (s, 3 H, NCH_3), 3.87 (s, 2 H, CH_2), 4.96 (s, 2 H, CH_2Ph), 5.13 (s, 1 H, C=CH), 7.36–7.39 (m, 5 H, H_{arom}).

MS (CI, CH_4): *m*/*z* (%) = 204 (100) [M + H^+].

Anal. Calcd for $C_{12}H_{13}NO_2$ (203.2): C, 70.92; H, 6.45; N, 6.89. Found: C, 70.79; H, 6.49; N, 6.86.

4-Benzyloxy-1-prop-2-ynylpyrrol-2(5*H*)-one (10b)
Prepared according to Method A from **7** (110 mg, 0.5 mmol) and propargylamine (51 μL, 0.75 mmol). Purified by flash chromatography (hexane–EtOAc, 40:60) to give **10b**.

Yield: 55 mg (48%); colorless crystals; mp 58 °C.

IR (film): 3286, 3099, 3035, 2119, 1682, 1620, 1453 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.24 (t, 1 H, *J* = 2.5 Hz, HC≡C), 4.01 (s, 2 H, CH_2), 4.23 (d, 2 H, *J* = 2.5 Hz, C*H*$_2$C≡CH), 4.99 (s, 2 H, CH_2Ph), 5.14 (s, 1 H, C=CH), 7.35–7.45 (m, 5 H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 30.88 (*C*H_2C≡CH), 49.90 (C-5), 72.25 (CH_2C≡*C*H), 73.20 (*C*H_2Ph), 77.34 (CH_2*C*≡CH), 95.08 (C-3), 127.99, 128.79, 128.84, 134.56, (C_6H_5), 171.59 (C-2), 172.42 (C-4).

MS (CI, CH_4): *m*/*z* (%) = 228 (100) [M + H^+].

Anal. Calcd for $C_{14}H_{13}NO_2$ (227.3): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.71; H, 5.77; N, 6.14.

1-Benzyl-4-benzyloxypyrrol-2(5*H*)-one (10c)
Prepared according to Method A from **7** (44 mg, 0.2 mmol) and benzylamine (33 μL, 0.3 mmol). Purified by flash chromatography (hexane–EtOAc, 50:50) to give **10c**.

Yield: 38 mg (73%); colorless crystals; mp 97 °C.

IR (film): 3031, 1666, 1623 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.78 (s, 2 H, CH_2), 4.58 (s, 2 H, NCH_2Ph), 4.95 (s, 2 H, OCH_2Ph), 5.18 (s, 1 H, C=CH), 7.24–7.37 (m, 10 H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 45.41 (N*C*H_2Ph), 50.17 (C-5), 73.07 (O*C*H_2Ph), 95.32 (C-3), 127.48, 127.94, 128.75, 134.70, 137.42 (C_6H_5), 172.00 (C-2 and C-4).

MS (CI, CH_4): *m*/*z* (%) = 280 (100) [M + H^+].

Anal. Calcd for $C_{18}H_{17}NO_2$ (279.3): C, 77.40; H, 6.13; N, 5.01. Found: C, 77.12; H, 6.11; N, 4.94.

(*S*)-4-Benzyloxy-1-(1-phenylethyl)pyrrol-2(5*H*)-one (10d)
Prepared according to Method B from **7** (220 mg, 1.0 mmol) and (*S*)-(–)-1-phenylethylamine (192 μL, 1.5 mmol). Purified by flash chromatography (hexane–EtOAc, 80:20 + 3% Me_2NEt) to give **10d**.

Yield: 217 mg (74%); colorless crystals; mp 84 °C; $[\alpha]_D^{20}$ – 40.3 (*c* 1.17, CH_2Cl_2).

IR (film): 3061, 3032, 1678, 1626 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.57 (d, 3 H, *J* = 7.3 Hz, CHC*H*$_3$), 3.53 (d, 1 H, *J* = 17.6 Hz, CH_2), 3.83 (d, 1 H, *J* = 17.6 Hz, CH_2), 4.93 (s, 2 H, OCH_2Ph), 5.15 (s, 1 H, C=CH), 5.59 (q, 1 H, *J* = 7.3 Hz, CHC*H*$_3$), 7.24–7.40 (m, 10 H, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 17.51 (CH_3), 46.59 (C-5) 48.14 (*C*HCH_3), 73.11 (*C*H_2Ph), 95.41 (C-3), 127.06–128.81, 134.78, 141.12 (2 × C_6H_5), 171.68 (C-2), 172.15 (C-4).

MS (CI, CH_4): *m*/*z* (%) = 294 (100) [M + H^+].

Anal. Calcd for $C_{19}H_{19}NO_2$ (293.4): C, 77.79; H, 6.53; N, 4.77. Found: C, 77.69; H, 6.51; N, 4.75.

(*RS*)-Methyl 2-(4-Benzyloxypyrrol-2(5*H*)-on-1-yl)-3-methylbutanoate (10e)
Prepared according to Method B from **7** (110 mg, 0.5 mmol). However, instead of the free amine, DL-valine methyl ester hydrochloride (126 mg, 0.75 mmol) together with *i*-Pr_2NEt (166 μl, 1.0 mmol) was employed. Purified by flash chromatography (hexane–EtOAc, 70:30 + 3% Me_2NEt) to give **10e**.

Yield: 96 mg (65%); colorless crystals; mp 75–78 °C.

IR (film): 3096, 1733, 1666, 1614 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.92 [d, 3 H, *J* = 6.7 Hz, CH(C*H*$_3$)$_2$], 0.98 [d, 3 H, *J* = 6.7 Hz, CH(C*H*$_3$)$_2$], 2.16 [m, 1 H, C*H*(CH$_3$)$_2$], 3.71 (s, 3 H, OCH_3), 3.93 (d, 1 H, *J* = 17.2 Hz, NCH_2), 4.29 (d, 1 H, *J* = 17.2 Hz, NCH_2), 4.60 (d, 1 H, *J* = 9.6 Hz, C*H*$COOCH_3$), (4.98 (s, 2 H, CH_2Ph), 5.16 (s, 1 H, C=CH), 7.36–7.42 (m, 5 H, H_{arom}).

MS (CI, CH_4): *m*/*z* (%) = 304 (100) [M + H^+].

Anal. Calcd for $C_{17}H_{21}NO_4$ (303.4): C, 67.31; H, 6.98; N, 4.62. Found: C, 67.21; H, 6.87; N, 4.53.

4-Benzyloxy-1-*tert*-butylpyrrol-2(5*H*)-one (10f)
Prepared according to Method B from **7** (110 mg, 0.5 mmol) and *tert*-butylamine (80 μL, 0.75 mmol). Purified by flash chromatography (hexane–EtOAc, 70:30 + 3% Me_2NEt) to give **10f**.

Yield: 81 mg (66%); colorless crystals; mp 51 °C.

IR (film): 3033, 1677, 1633 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.42 [s, 9 H, C(CH$_3$)$_3$], 3.92 (s, 2 H, CH_2), 4.92 (s, 2 H, CH_2Ph), 5.07 (s, 1 H, C=CH), 7.33–7.41 (m, 5 H, H_{arom}).

MS (CI, CH_4): *m*/*z* (%) = 246 (100) [M + H^+].

Anal. Calcd for $C_{15}H_{19}NO_2$ (245.3): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.20; H, 7.55; N, 5.59.

4-Benzyloxy-1-phenylpyrrol-2(5*H*)-one (10g)
Prepared according to Method B from **7** (110 mg, 0.5 mmol) and aniline (68 μL, 0.75 mmol). HOAc (43 μL, 0.75 mmol) was added to the aromatic amine. Purified by flash chromatography (hexane–EtOAc, 80:20 + 3% Me_2NEt) to give **10g**.

Yield: 72 mg (69%); colorless crystals; mp 58 °C.

IR (film): 3109, 3063, 3033, 1676, 1629, 1600, 1503, 1451 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.34 (s, 2 H, CH_2), 5.05 (s, 2 H, CH_2Ph), 5.27 (s, 1 H, C=CH), 7.06–7.65 (m, 10 H, H_{arom}).

MS (CI, CH_4): *m*/*z* (%) = 266 (100) [M + H^+].

Anal. Calcd for $C_{17}H_{15}NO_2$ (265.3): C, 76.96; H, 5.70; N, 5.28. Found: C, 76.65; H, 5.66; N, 5.17.

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References and Notes

(1) (a) For a review covering tetramic acid based natural products, see: Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981. (b) Jones, R. C. F.; Bates, A. D. *Tetrahedron Lett.* **1986**, *27*, 5285. (c) James, G. D.; Mills, S. D.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2581. (d) D´Allesio, R.; Bargiotti, A.; Carlini, O.; Colotta, F.; Ferrari, M.; Gnocchi, P.; Isetta, A.; Mongelli, N.; Motta, P.; Rossi, A.; Tibolla, M.; Vanotti, E. *J. Med. Chem.* **2000**, *43*, 2557. (e) Zarantonello, P.; Leslie, C. P.; Ferritto, R.; Kazmierski, W. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 561.
(2) 4-Methoxypyrrol-2(5*H*)-one was prepared from pyrrolidine-2,4-dione[3a] in moderate yield by methylation with diazomethane: Inami, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 352.
(3) (a) Mulholland, T. P. C.; Foster, R.; Haydock, D. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2121. (b) Van der Baan, J. L.; Barnick, J. W. F. K.; Bickelhaupt, F. *Tetrahedron* **1978**, *34*, 223.

(4) For the synthesis of 4-*O*-alkyl tetronates starting from tetronic acids, see: Schobert, R.; Siegfried, S. *Synlett* **2000**, 686; and references cited therein.
(5) (a) Kochhar, K. S.; Carson, H. J.; Clouser, K. A.; Elling, J. W.; Gramens, L. A.; Parry, J. L.; Sherman, H. L.; Braat, K.; Pinnick, H. W. *Tetrahedron Lett.* **1984**, *25*, 1871. (b) Duc, L.; McGarrity, J. F.; Meul, T.; Warm, A. *Synthesis* **1992**, 391.
(6) Meul, T. Eur. Pat. Appl. EP 252363, **1988**; *Chem. Abstr.* **1988**, *108*, 186563.
(7) (a) Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *Tetrahedron Lett.* **1988**, *29*, 1489. (b) Schlessinger, R. H.; Pettus, T. R. R. *J. Org. Chem.* **1994**, *59*, 3246.
(8) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241.
(9) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.
(10) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.
(11) For tandem reductive amination-lactamizations, see: Abdel-Magid, A. F.; Harris, B. D.; Maryanoff, C. A. *Synlett* **1994**, 81; and references cited therein.
(12) Direct reductive aminations of aldehyde **7** with sodium cyanoborohydride according to Borch and co-workers involving in situ generated imines gave only small amounts (< 20%) of the desired tetramates **10** in addition to 4-benzyloxyfuran-2(5*H*)-one and a series of unidentified side-products, see: Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(13) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.