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Synthesis and reactions of polymer-bound $Ph_3P{=}C{=}C{=}O$: a quick route to tenuazonic acid and other optically pure 5-substituted tetramates

Rainer Schobert,* Carsten Jagusch, Claire Melanophy and Gillian Mullen
Organic Chemistry Laboratory, University of Bayreuth, D-95440, Bayreuth, Germany.
E-mail: Rainer.Schobert@uni-bayreuth.de; Fax: +49 (0)921 552671

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Polystyrene-bound cumulated ylide Ph_3PCCO was prepared on a large scale in two steps. It reacts with Grignard compounds, amines and alcohols to give immobilized acyl, amide and ester ylides, respectively. Their Wittig reactions lead to alkenes free of phosphane oxide. Optically pure 5-substituted tetramates were obtained from reactions of resin-bound Ph_3PCCO with α-ammonium esters in one step. The mycotoxin (−)-tenuazonic acid was accordingly prepared in just three steps.

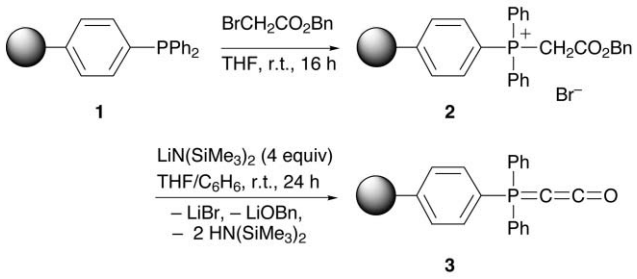
Introduction

Polymer-supported reagents offer numerous procedural and conceptual advantages over their soluble congeners, first and foremost the suitability for automation and parallelization.[1] Hence almost every useful class of reagents has been made available in an immobilized form. This includes various types of phosphorus ylides,[2] such as alkylides,[3–5] benzylides,[4–6] allylides,[7,8] methylide,[4,5] methoxycarbonylmethylide,[6] cyanomethylide,[5,9] and α-iodoalkylides.[5] However, cumulated P-ylides have not yet been attached to a solid support. $Ph_3P{=}C{=}C{=}O$, for instance, offers a multi-faceted chemistry of its own,[10] serving as a versatile C_2-building block for heterocycles in domino and multicomponent reactions with functionalized carbonyl compounds.[11] Through addition of alcohols,[12] amines,[13] and Grignard compounds[14] it also renders accessible the families of stabilized ester, amide, and acyl ylides. The employment of an immobilized variant of this ylide combines these features with the intrinsic advantages of solid-phase organic synthesis. This is demonstrated for the synthesis of 5-substituted tetramates from α-ammonium esters where the typical problems of base-induced racemization at C-5 and incomplete separation from byproduct Ph_3PO are overcome by the use of polystyrene-bound Ph_3PCCO.

Results and discussion

Synthesis of polystyrene-bound Ph_3PCCO

The preparation of the polystyrene-bound cumulated ylide **3** (Scheme 1) had to be modified when compared with that of free Ph_3PCCO,[10a] mainly due to problems related to swelling of the resin and removability of byproduct alkoxides. The most important alteration was the quantitative alkylation of the polystyrene-bound triphenylphosphane **1** (1.41 mmol g^{-1}) with benzyl bromoacetate instead of methyl bromoacetate to give the immobilized benzoxycarbonylmethylphosphonium bromide **2**. Salt **2** was then washed with dry benzene and finally converted to **3** by shaking with an excess of lithium bis(trimethylsilyl)amide in THF–benzene at room temperature for 24 h.[15] Unlike sodium or lithium methoxide which pertinaciously adhere to the resin, the byproduct lithium benzoxide, together with lithium bromide and hexamethyldisilazane, can be completely removed by filtration and repeated rinsing with THF, benzene and toluene. **3** was obtained as a yellow, pH-neutral, fairly air-stable resin. The ^{31}P MAS TOSS NMR[16a] (δ 4.97 ppm) and ATR-IR[16b] (ν = 2092 cm^{-1}) (Fig. 1) spectra of **3** clearly proved the absence both of starting salt **2** and its corresponding ester ylide which is an intermediate *en route* from **2** to **3**. Batches of **3** were occasionally contaminated with a little (<10%) immobilized phosphane oxide which does not interfere with the reactions of the cumulated ylide. From the yields of these reactions, from the spectra, and from the weight increase during its synthesis, an effective loading of >85% available for reactions was gauged for representative samples of **3**.



Scheme 1 Two-step synthesis of polystyrene-supported (triphenylphosphoranylidene)ketene **3**.

Synthesis of α,β-unsaturated esters, amides and ketones

Immobilized ylide **3** underwent the same reactions as Ph_3PCCO in solution under almost identical conditions with the bonus of ease of product purification, in particular the straightforward removal of resin-bound phosphane oxide as formed in Wittig alkenations. For example, the three-component reaction of **3** with an aldehyde (*e.g.* piperonal) and an alcohol (*e.g.* hexanol) or amine (*e.g.* piperidine) produced the *E*-α,β-unsaturated esters or amides **5**, respectively, as products of a domino addition–Wittig alkenation process. The intermediate ester or amide ylides **4** can be obtained in the absence of an aldehyde and may be used separately for olefinations or other ylide reactions. Immobilized acyl ylides **7** were readily accessible by Grignard reaction[14] of **3**. The ylide can be simply added in one portion to the Grignard solution. Wittig alkenation of **7** with aldehydes furnished the corresponding pure *E*-enones **8** (Scheme 2).

Synthesis of nonracemic 5-substituted tetramates

Ph_3PCCO is also known[11,17] to add and Wittig alkenate primary α-amino esters in a tandem fashion to give the corresponding tetramates, a class of compounds that has attracted considerable interest due to their often distinct biological activity.[18–20] However, in solution the reaction with Ph_3PCCO proceeds only slowly and N-substituted derivatives sometimes fail to react

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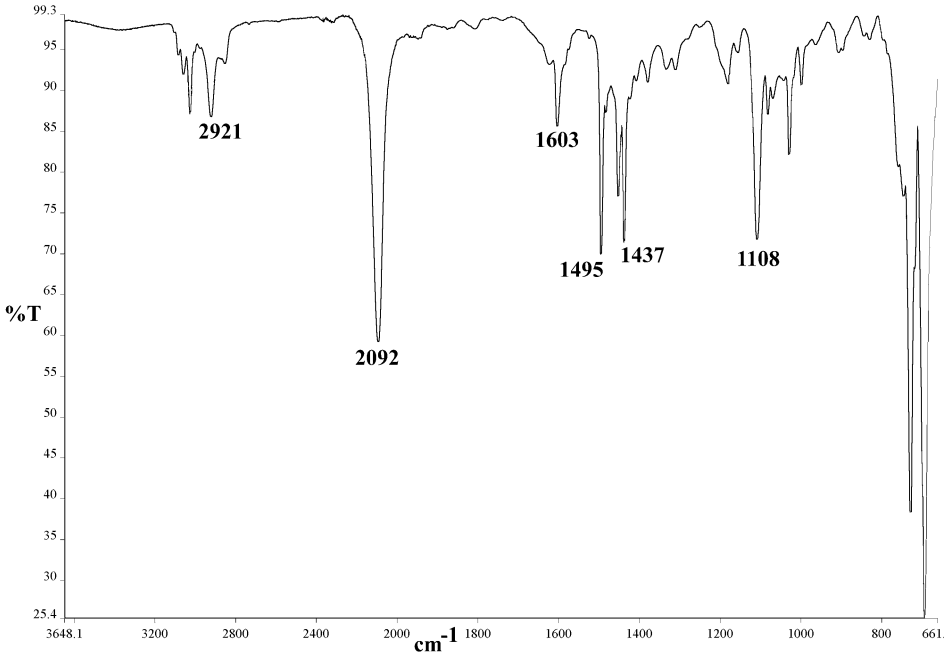
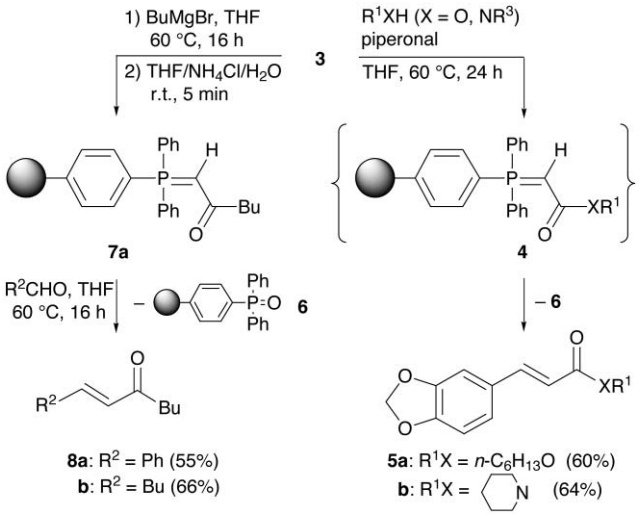
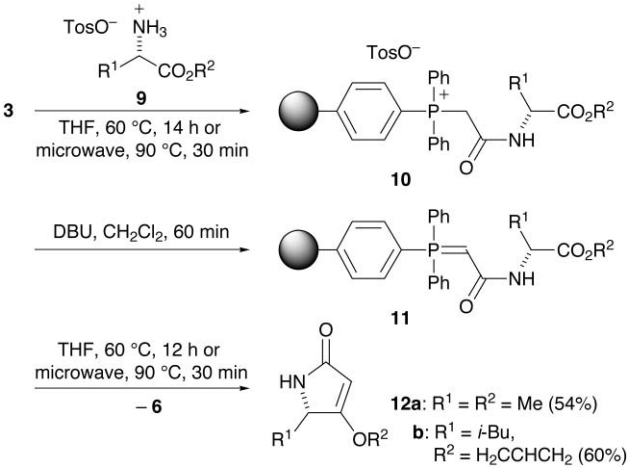


Fig. 1 IR spectrum of pulverized polystyrene-bound Ph_3PCCO **3**.



Scheme 2 Acyl ylides **4** and **7** from **3** and consecutive Wittig alkenation reactions to give *E*-α,β-unsaturated esters, amides, or ketones.

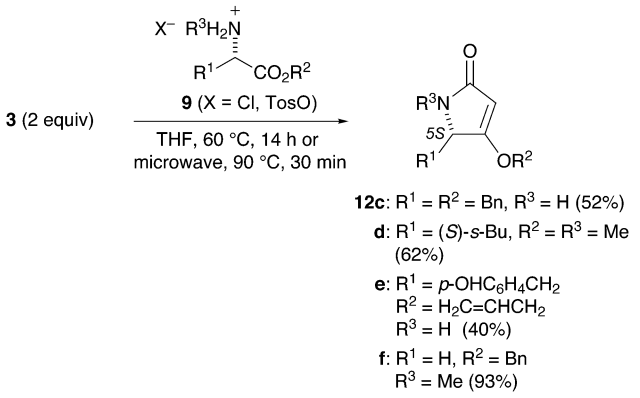
altogether. Hence it was gratifying to find both primary and secondary α-amino esters as well as their ammonium salts react with immobilized ylide **3** to give tetramates in decent yields and not contaminated with otherwise difficult to remove phosphane oxide. Ammonium salts, which are the customary form of storage of α-amino esters, generally reacted faster and their use also allowed a stepwise procedure with optional isolation and washing of the intermediates. For instance, ammonium tosylates **9** readily added onto **3**, either under thermal (THF, 60 °C, 14 h) or microwave (THF, max. 300 W, 90 °C, 30 min) conditions, quantitatively furnishing easy to purify phosphonium salts **10** (Scheme 3). Deprotonation of **10** with DBU at room temperature gave the conjugate amide ylides **11** which after rinsing were submitted to a thermal or microwave induced intramolecular Wittig alkenation to leave pure tetramates **12** in 50–60% overall yields. Optically pure chiral α-ammonium esters were converted with retention to enantiopure (>94% ee) tetramates (HPLC: CD-β-PM, Macherey-Nagel; comparison with baseline separated authentic racemic samples). This is a major advantage over reactions with Ph_3PCCO in solution which were frequently found to give racemic products due to adhering traces of alkoxides formed as byproducts in the generation of Ph_3PCCO from ester ylides.



Scheme 3 Consecutive addition and Wittig alkenation of α-ammonium esters **9** with **3** to give tetramates **12**.

With **3** being so readily available now, an excess of it can be used as the base in lieu of DBU, thus immobilizing both by-products (phosphane oxide and the counter anion of the ammonium salt) and yielding pure tetramates in a one-pot variant. This was demonstrated for the hydrogen chlorides or tosylates **9** which furnished optically pure tetramates **12** in yields ranging from 40% to 93% (Scheme 4). No 5-epimers were detectable by NMR, GC and HPLC, respectively. It is worthy of note that even relatively acidic hydroxy groups such as the one in tyrosine allyl ester tosylate **9e** need not be protected.

The twofold action of **3** as a base was not anticipated in the first place. The deprotonation of intermediate phosphonium salts of type **10** is slow and requires them to get in contact with another ylide group attached to the same resin which is only possible for sufficiently packed, coiled-up, or backfolded polymer strands. When THF was replaced by the less polar solvent benzene the yields of the respective product tetramates dropped sharply, *e.g.* from 52% to 5% for **12c**. Apparently, the solvent is crucial to the shape of the swollen resin and thus to the spatial distribution of the immobilized functional



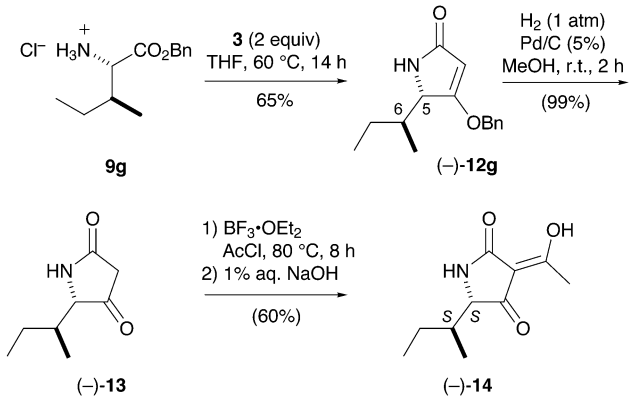
Scheme 4 One-pot synthesis of tetramates **12** from α-ammonium esters **9** and two equivalents of **3**.

groups. This interaction of individual ylide groups on the resin somewhat dashed our hopes to generate highly reactive spatially sequestered ketenylium cations *PS*-Ph_3P^+-CH=C=O by treating **3** with HBF_4 or other acids with non-nucleophilic counter anions. In solution and in the absence of a suitably nucleophilic anion, the cation Ph_3P^+-CH=C=O reacts rapidly with a second molecule of the starting ylide to give a preparatively useless protonated "dimer" with cyclobutane-1,3-dione structure.

Synthesis of tenuazonic acid

The above one-pot process is applicable to the synthesis of 3-unsubstituted tetramates. Tetramic acids (pyrrolidine-2,4-diones) bearing 3-allyl residues are also readily accessible from the corresponding allyl esters (**9**: R^2 = allyl) *via* a sequence extended by a terminal Claisen rearrangement step.[21] 3-Acyl residues which are so common in naturally occurring tetramates must be introduced by downstream acylation of tetramic acids with the appropriate acid chloride in the presence of boron trifluoride–diethyl etherate.[22,23] This is no less economical than the alternative Lacey–Dieckmann condensation of *N*-(β-ketoacyl)-α-amino esters which requires an initial *N*-acylation of the respective α-amino esters.[24–27] In addition, racemization still poses a problem when the cyclization is carried out under basic conditions.[28]

Scheme 5 depicts a straightforward three-step synthesis of optically pure tenuazonic acid (−)-**14**, a mycotoxin exhibiting a broad spectrum of biological activity.[29,30] It was first isolated in 1957 from the culture filtrates of *Alternaria tenuis* and later on also from other *Alternaria* and *Pyricularia* species.[31,32] L-Isoleucine benzyl ester chloride **9g**[33] was reacted with a twofold excess of ylide **3** in THF at 60 °C to give tetramate (−)-**12g**. The purity and in particular the absence of the (5*R*,6*S*)-epimer of **12g** was ascertained by GC and ^{1}H NMR [(5*S*,6*S*)-**12g**: δ 0.95 (6-CH_3), 4.08 (5-H); (5*R*,6*S*)-**12g**: δ 0.73 (6-CH_3), 4.15 (5-H)]. Debenzylation of **12g** by hydrogenolysis with 5% Pd on charcoal in dry methanol quantitatively furnished 5-*s*-butylpyrrolidine-2,4-dione (5*S*,6*S*)-**13** with properties identical to those reported earlier.[28] As anticipated, the enol tautomer of **13**, the 4-hydroxy-5-*s*-butyl-pyrrol-2(5*H*)-one, was not detectable in the NMR spectra. Acylation of (−)-**13** with an excess of acetyl chloride and boron trifluoride–diethyl etherate[23] and careful hydrolytic work-up[24] gave tenuazonic acid, (−)-(5*S*,6*S*)-3-acetyl-5-*s*-butylpyrrolidine-2,4-dione, **14** as a mixture of various tautomers[34] in 60% yield.



Scheme 5 Three-step synthesis of tenuazonic acid.

In conclusion we have established a large-scale synthesis of **3**, the first immobilized cumulated phosphorus ylide. It can be used as a precursor to resin-bound stabilized acyl, ester and amide ylides and as a C_2-building block in the stereoselective synthesis of heterocycles, *e.g.* of tetramates from α-ammonium esters. This approach complements the inverse protocol employing resin-bound amino- and hydroxy-substituted carbonyl derivatives with Ph_3PCCO in solution, as described previously.[35]

Experimental

Microwave irradiations were carried out in sealed vials inside a CEM Discover™ single-mode synthesizer (300 W). Melting points were recorded using a Gallenkamp apparatus and are uncorrected. Optical rotations were recorded at 589 nm using a Perkin-Elmer polarimeter 241 and 5 mL cuvettes (10 cm); [*a*] values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded of solids or neat films on a Perkin-Elmer Spectrum One FT-IR spectrophotometer equipped with an ATR sampling unit. Nuclear magnetic resonance (NMR) spectra were recorded under conditions as indicated using a Bruker Avance 300 spectrometer. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard for ^{1}H and ^{13}C nuclei and H_3PO_4 as external standard for ^{31}P; coupling constants (*J*) are given in Hz. Mass spectra were recorded using a Varian MAT 311A (EI). Analytical HPLC was performed on a Beckman system with programmable solvent module 126 and a diode array detector 168 equipped with a Nucleodex CD-β-PM column from Macherey-Nagel. Analytical GC was conducted using a Lipodex-E column (25 m, 0.25 mm) from Macherey-Nagel. Microanalyses were carried out with a Perkin-Elmer 2400 CHN elemental analyser. Flash chromatography was effected using Merck silica gel 60 (230–400 mesh). α-Ammonium ester chlorides and tosylates were prepared from the respective α-amino acids according to the method by Muramatsu and Arai,[36] triphenylphosphane polystyrene **1** (100–200 mesh, 1% divinylbenzene) was purchased from Rapp Polymere GmbH, Tübingen (Germany), all other starting compounds were purchased from Aldrich and used as such without further purification.

1 Immobilized (triphenylphosphoranylidene)ketene 3

Triphenylphosphane polystyrene **1** (10.0 g, 1.4 mmol g^{-1}, 14.1 mmol) in a fritted solid-phase reaction flask was treated with dry THF (40 mL) and shaken at room temperature for 1 h. A solution of benzyl bromoacetate (12.9 g, 56.4 mmol, 4 equiv.) in THF (40 mL) was added under argon and the mixture was shaken for 16 h. The resin was filtered and washed carefully with dry THF (3 × 30 mL), diethyl ether (2 × 30 mL), CH_2Cl_2 (3 × 30 mL) and benzene (2 × 30 mL). The light yellow resin **2** was dried under reduced pressure; conversion: 99% as to the weight increase; ν_{max}(ATR)/cm^{-1} 1721 and 1110. An aliquot of the obtained carbobenzyloxymethyltriphenylphosphonium bromide resin **2** (10.6 g, 10 mmol) was washed with dry benzene (100 mL) under exclusion of air and moisture and then treated first with THF–benzene (1 : 1, 40 mL) and then with lithium hexamethyldisilazanide (6.7 g, 40 mmol, 4 equiv.). The mixture was shaken at room temperature for 24 h and the yellow resin was finally filtered and washed with dry THF (3 × 250 mL), benzene (3 × 250 mL) and toluene (2 × 250 mL) and dried under reduced pressure to leave 8.2 g of bright yellow resin **3**

(98%); ν_{max}(ATR)/cm^{-1} 2092 and 1108; δ_P (TOSS; 203 MHz; $CDCl_3$; $H_3PO_{4\,ext}$) 4.97 ppm.

2 General procedure for the synthesis of (*E*)-α,β-unsaturated esters and amides 5

3 (830 mg, 1.0 mmol) was suspended in THF (6 mL) and treated with piperonal (75 mg, 0.5 mmol) and 0.5 mmol of the appropriate alcohol or amine, respectively. The mixture was shaken at 60 °C for 24 h with the exclusion of air and moisture. The resin was filtered and washed twice with THF (10 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained was purified by preparative TLC or column chromatography (silica gel).

Hexyl (*E*)-3′,4′-(methylenedioxy)cinnamate 5a. Yellow oil (82 mg, 60%) from hexanol (50 mg). R_f 0.48 (ethyl acetate–*n*-hexane, 1 : 12, v/v) (Found: C, 69.3; H, 7.5. $C_{16}H_{20}O_4$ requires C, 69.5; H, 7.3%); δ_H (270 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.0, Me), 1.20–1.34 (8 H, m, CH_2), 4.11 (2 H, t, *J* 6.6, CO_2CH_2), 5.93 (2 H, s, OCH_2O), 6.20 (1 H, d, *J* 16.1, =CHCO), 6.81–7.01 (3 H, m, ArH), 7.52 (1 H, d, *J* 16.1, *H*C=CHCO); δ_C (75 MHz; $CDCl_3$) 14.1 (Me), 22.6, 25.7, 28.8, 31.5 (CH_2), 77.6 (CO_2CH_2), 101.6 (OCH_2O), 106.6, 108.6 (ArC), 116.3 (*C*CO_2), 124.4, 128.9 (ArC), 144.3 (*C*=CCO_2), 148.4, 149.6 (ArC), 167.3 (CO_2).

(*E*)-1-[3′,4′-(Methylenedioxy)cinnamoyl]piperidine 5b. White solid (84 mg, 64%) from piperidine (42 mg), mp 84 °C (lit.,[37] 85–87 °C; lit.,[13] 83 °C). δ_H (300 MHz; $CDCl_3$) 1.59–1.72 (6 H, m), 3.74 (4 H, m), 5.98 (2 H, s), 6.74 (1 H, d, *J* 15.5), 6.77–7.03 (3 H, m), 7.56 (1 H, d, *J* 15.5).

3 General procedure for the synthesis of (*E*)-enones 8

3 (830 mg, 1.0 mmol) was added to a solution of butylmagnesium bromide (1.5 mmol) in THF (5 mL), freshly prepared from 1-bromobutane (210 mg) and magnesium turnings (40 mg). The mixture was shaken at 60 °C for 16 h or alternatively heated at 90 °C for 30 min in a microwave reactor. The resin was filtered, washed with THF and resuspended in THF (4 mL). Saturated aqueous NH_4Cl solution (4 mL) was added and the mixture was shaken at rt for 5 min. The resin of **7** thus obtained was washed with 2 × 10 mL each of H_2O, Et_2O, THF, CH_2Cl_2, and toluene, then dried on an oil pump and resuspended in THF (3 mL). The respective aldehyde (1 mmol) was added, the resulting mixture was shaken for 16 h while gently refluxing and finally filtered. Concentration of the filtrate and prep. TLC (silica gel) of the residue gave pure (*E*)-enone **8**.

(*E*)-1-Phenylhept-1-en-3-one 8a[38]. Colourless oil (100 mg, 55%) from benzaldehyde (105 mg), R_f 0.75 (diethyl ether–*n*-hexane, 1 : 1, v/v); ν_{max}(ATR)/cm^{-1} 3029, 2958, 1690, 1608; δ_H (300 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 7.3, Me), 1.30 (2 H, tq, *J* 7.5, 7.3, C*H*$_2$CH$_3$), 1.58 (2 H, tt, *J* 7.5, 7.3, C*H*$_2$Et), 2.58 (2 H, t, *J* 7.3, CH_2CO), 6.66 (1 H, d, *J* 16.2, =CHCO), 7.28–7.50 (5 H, m, ArH), 7.46 (1 H, d, *J* 16.2, HC=CCO); δ_C (75 MHz; $CDCl_3$) 13.8 (Me), 20.9, 22.4, 40.6 (CH_2), 126.2 (*C*CO), 128.8, 129.6, 130.3, 134.5 (ArC), 142.2 (*C*=CCO), 203.5 (CO).

(*E*)-Undec-6-en-5-one 8b[14]. Yellowish oil (110 mg, 66%) from pentanal (85 mg), R_f 0.76 (ethyl acetate–*n*-hexane, 1 : 4, v/v); ν_{max}(ATR)/cm^{-1} 2958, 1676, 1630; δ_H (300 MHz; $CDCl_3$) 0.85 (6 H, t, *J* 7.3, 2 × Me), 1.20–1.60 [8 H, m, 2 × $(CH_2)_2$], 2.10–2.22 (2 H, m, CH_2C=), 2.45 (2 H, t, *J* 7.0, CH_2CO), 6.00 (1 H, dt, *J* 15.85, 1.5, =CHCO), 6.75 (1 H, dt, *J* 15.85, 7.0, HC=CCO); δ_C (75 MHz; $CDCl_3$) 13.9 (Me), 14.2 (Me), 22.2, 22.4, 26.4, 30.2, 32.1, 39.8 (CH_2), 130.3 (*C*CO), 147.2 (*C*=CCO), 201.0 (CO).

4 General procedure for the three-step synthesis of tetramates 12

A sealed vial charged with **3** (830 mg, 1.0 mmol), THF (4 mL) and **9** (1.0 mmol) was placed in a CEM Discover™ microwave synthesizer and irradiated at 90 °C and 3.5 bar for 30 min. The resin-bound salt **10** was washed three times with 10 mL each of THF, toluene, CH_2Cl_2 and then dried under reduced pressure. It was resuspended in CH_2Cl_2 (4 mL) and treated with DBU (0.15 mL, 1.0 mmol). The resulting mixture was shaken for 60 min at rt. Washing of the resin with 2 × 10 mL each of CH_2Cl_2, THF, toluene and drying left polymer-bound ylide **11**. This was suspended in THF (4 mL) and irradiated with microwaves as described above. After filtration of the reaction mixture and washing of the resin with THF (20 mL), pure tetramates **12** were obtained upon concentration of the combined organic phases.

(5*S*)-4-Methoxy-5-methylpyrrolin-2-one 12a. Colourless solid (70 mg, 54%) from L-alanine methyl ester tosylate **9a** (275 mg), R_f 0.21 (ethyl acetate), mp 115 °C (lit.,[39] 112.5–117.3 °C), $[\alpha]_D^{25}$ +4.0 (*c* 0.5, MeOH) (lit.,[39] +4.5), ν_{max}(ATR)/cm^{-1} 3199 (br), 1658, 1615; δ_H (300 MHz; $CDCl_3$) 1.29 (3 H, d, *J* 6.7, 5-Me), 3.76 (3 H, s, OMe), 4.05 (1 H, q, *J* 6.7, 5-H), 4.96 (1 H, s, 3-H), 6.31 (1 H, br s, NH); δ_C (75 MHz; $CDCl_3$) 17.8 (5-Me), 53.7 (C-5), 58.3 (OMe), 92.8 (C-3), 174.2 (C-2), 179.4 (C-4).

(5*S*)-4-Allyloxy-5-*i*-butylpyrrolin-2-one 12b. Colourless solid (117 mg, 60%) from L-leucine allyl ester tosylate **9b** (315 mg), R_f 0.21 (ethyl acetate), mp 86 °C, $[\alpha]_D^{25}$ −20.4 (*c* 0.25, MeOH) (Found: C, 67.8; H, 8.9; N, 7.3. $C_{11}H_{17}NO_2$ requires C, 67.7; H, 8.8; N, 7.2%); ν_{max}(ATR)/cm^{-1} 3189 (br), 1666, 1610; δ_H (300 MHz; $CDCl_3$) 0.95 (6 H, d, *J* 6.4, CMe_2), 1.36–1.44 (1 H, m, C*H*Me$_2$), 1.67–1.75 (2 H, m, CH_2), 4.12 (1 H, dd, *J* 9.6, 3.5, 5-H), 4.48 (2 H, d, *J* 5.5, OCH_2), 5.05 (1 H, s, 3-H), 5.26 (1 H, dd, *J* 10.1, 1.4, H_2C=), 5.32 (1 H, dd, *J* 17.1, 1.4, H_2C=), 5.88–5.99 (1 H, m, =CH), 6.57 (1 H, br s, NH); δ_C (75 MHz; $CDCl_3$) 21.9 (Me), 22.8 (Me), 25.5 (*C*Me$_2$), 42.7 (CH_2), 56.9 (C-5), 72.2 (OCH_2), 93.2 (C-3), 119.7 (=CH_2), 130.8 (*C*=CH_2), 174.6 (C-2), 178.4 (C-4).

5 General procedure for the one-pot synthesis of tetramates 12

3 (1.66 g, 2.0 mmol) was suspended in THF (10 mL) and after 10 min swelling treated with the appropriate α-ammonium ester salt **9** (1.0 mmol). The mixture was either shaken at 60 °C for 14 h or irradiated in the microwave synthesizer at 90 °C for 30 min. After filtration and washing of the resin with 2 × 10 mL each of THF, CH_2Cl_2, and MeOH, the combined filtrates were evaporated under reduced pressure and the crude products were purified by column chromatography (silica gel).

(5*S*)-5-Benzyl-4-benzyloxypyrrolin-2-one 12c. Colourless viscous oil (145 mg, 52%) from L-phenylalanine benzyl ester tosylate **9c** (420 mg), R_f 0.35 (ethyl acetate), $[\alpha]_D^{25}$ −13.2 (*c* 0.7, MeOH) (Found: C, 77.3; H, 6.0; N, 4.9. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.1; N, 5.0%); ν_{max}(ATR)/cm^{-1} 3222 (br), 1681, 1617; δ_H (300 MHz; $CDCl_3$) 2.60 (1 H, dd, *J* 13.45, 8.9, CH_2), 3.14 (1 H, dd, *J* 13.45, 3.0, CH_2), 4.21 (1 H, m, 5-H), 4.89 (2 H, d, *J* 4.4, OCH_2), 4.98 (1 H, s, 3-H), 5.84 (1 H, br s, NH) 7.09–7.38 (10 H, m, ArH); δ_C (75 MHz; $CDCl_3$) 38.5 (CH_2), 58.7 (C-5), 73.2 (OCH_2), 95.1 (C-3), 126.9, 127.8, 128.6, 128.7 128.8, 129.1 (ArC), 134.6 (C-*ipso*), 136.4 (C-*ipso*), 172.5 (C-2), 176.0 (C-4).

(5*S*,6*S*)-5-*s*-Butyl-4-methoxy-1-methylpyrrolin-2-one 12d. Colourless oil (102 mg, 62%) from *N*-methyl-L-isoleucine methyl ester hydrogen chloride **9d** (195 mg), R_f 0.18 (ethyl acetate), $[\alpha]_D^{25}$ +10.5 (*c* 1.0, $CHCl_3$) (Found: C, 65.3; H, 9.2; N, 7.4. $C_{10}H_{17}NO_2$ requires C, 65.5; H, 9.35; N, 7.6%); ν_{max}(ATR)/cm^{-1} 1683, 1621; δ_H (300 MHz; $CDCl_3$) 0.67 (3 H, d, *J* 6.9, CHC*H*$_3$), 0.89 (3 H, t, *J* 7.4, CH_2CH_3), 1.27–1.52 (2 H, m, CH_2), 1.76–1.85 (1 H, m, C*H*Me), 2.79 (3 H, s, NCH_3), 3.67 (3 H, s, OCH_3), 3.76 (1 H, d, *J* 2.8, 5-H), 4.98 (1 H, s, 3-H); δ_C (75 MHz; $CDCl_3$) 12.3 (*C*H$_3$CH$_2$), 12.9 (*C*H$_3$CH), 25.2 (Me*C*H$_2$), 26.7 (NCH_3), 35.0 (Me*C*H), 57.7 (OCH_3), 65.7 (C-5), 94.8 (C-3), 171.9 (C-4), 175.3 (C-2); *m*/*z* (EI, 70 eV) 183 (M^+, 20%), 152 ($M^+ - OCH_3$, 5%), 126 (100%).

(5*S*)-4-Allyloxy-5-(*p*-hydroxybenzyl)pyrrolin-2-one 12e. Colourless oil (95 mg, 40%) from tyrosine allyl ester tosylate **9e** (410 mg), R_f 0.18 (ethyl acetate), $[\alpha]_D^{25}$ +2.4 (*c* 0.35, MeOH) (Found: C, 68.8; H, 6.45; N, 5.6. $C_{14}H_{15}NO_3$ requires C, 68.6; H, 6.2; N, 5.7%); ν_{max}(ATR)/cm^{-1} 3149 (br), 1651, 1610, 1592, 1516; δ_H (300 MHz; $CDCl_3$) 2.89 (1 H, dd, *J* 10.8, 2.9, 5-CH_2), 3.08 (1 H, dd, *J* 10.8, 2.9, 5-CH_2), 4.22 (1 H, m, 5-H), 4.40–4.50 (2 H, m, OCH_2), 4.94 (1 H, s, 3-H), 5.32 (1 H, dd, *J* 12.7, 0.9, =CH_2), 5.36 (1 H, dd, *J* 18.5, 0.9, =CH_2), 5.95 (1 H, m, =CH), 6.37 (1 H, br s, NH), 6.65 (2 H, d, *J* 7.7, ArH), 6.94 (2 H, d, *J* 7.7, ArH), 7.99 (1 H, s, OH); δ_C (75 MHz; $CDCl_3$) 37.2 (5-CH_2), 59.1 (C-5), 72.1 (OCH_2), 93.4 (C-3), 115.5 (ArC), 119.5 (=CH_2), 126.5, 130.9 (ArC), 132.7 (=CH), 156.8 (COH), 172.1 (C-2), 176.6 (C-4); *m*/*z* (EI, 70 eV) 245 (M^+, 18%), 139 (45%), 107 (100%).

4-Benzyloxy-1-methylpyrrolin-2-one 12f. Colourless solid (190 mg, 93%) from sarcosine benzyl ester tosylate **9f** (315 mg), R_f 0.23 (ethyl acetate), mp 84 °C (lit.,[40] 85 °C); ν_{max}(ATR)/cm^{-1} 3032, 1675, 1616; δ_H (300 MHz; $CDCl_3$) 2.89 (3 H, s, NCH_3), 3.81 (2 H, s, CH_2), 4.89 (2 H, s, OCH_2), 5.07 (1 H, s, 3-H), 7.37–7.40 (5 H, m, ArH); *m*/*z* (EI, 70 eV) 203 (M^+, 18%), 91 (100%).

6 Synthesis of tenuazonic acid (−)-14

(5*S*,6*S*)-4-Benzyloxy-5-*s*-butylpyrrolin-2-one 12g. According to the above general procedure (N° 5) **12g** (315 mg, 65%) was prepared as a colourless solid from L-isoleucine benzyl ester tosylate **9g**[33] (390 mg); R_f 0.32 (ethyl acetate), mp 140 °C, $[\alpha]_D^{25}$ −5.8 (*c* 0.4, MeOH) (Found: C, 73.6; H, 7.6; N, 5.5. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); ν_{max}(ATR)/cm^{-1} 3206 (br), 1682, 1615; δ_H (300 MHz; $CDCl_3$) 0.81 (3 H, t, *J* 7.35, CH_3CH$_2$), 0.95 (3 H, d, *J* 7.1, CH_3CH), 1.11–1.28 (2 H, m, MeCH_2), 1.79–1.83 (1 H, m, MeC*H*), 4.08 (1 H, d, *J* 3.2, 5-H), 4.92 (1 H, d, *J* 14.9, OC*H*H), 4.97 (1 H, d, *J* 14.9, OCH*H*), 5.07 (1 H, s, 3-H), 6.60 (1 H, br s, NH), 7.26–7.33 (5 H, m, ArH); δ_C (75 MHz; $CDCl_3$) 11.9 (*C*H$_3$CH$_2$), 15.7 (*C*H$_3$CH), 23.1 (Me*C*H$_2$), 36.4 (Me*C*H), 62.8 (C-5), 73.1 (OCH_2), 95.3 (C-3), 127.7, 128.65, 128.7 (ArC), 134.8 (C-*ipso*), 174.9 (C-2), 176.5 (C-4).

(5*S*,6*S*)-5-*s*-Butyl-pyrrolidine-2,4-dione 13. 12g (245 mg, 1.0 mmol) was dissolved in dry methanol (20 mL) and treated with 5% Pd on charcoal (25 mg). The reaction vessel was repeatedly evacuated and flushed with hydrogen gas and left to stir at room temperature for 2 h, pressurized with 1 atm of H_2. The resulting reaction mixture was filtered through a short plug of celite and the filtrate was concentrated on an oil pump to give analytically pure **13** (155 mg, 99%) as colourless crystals, mp 113 °C (lit.,[28] 115 °C; lit.,[32] 117.5–119 °C), $[\alpha]_D^{20}$ −38 (*c* 1.0, MeOH) [lit.,[28] −40 (*c* 1.0, MeOH)]; ν_{max}(ATR)/cm^{-1} 3302, 2969, 1767, 1675, 1616; δ_H (300 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.4, CH_3CH$_2$), 1.03 (3 H, d, *J* 7.0, CH_3CH), 1.20–1.45 (2 H, m, MeCH_2), 1.83–2.00 (1 H, m, C*H*Me), 3.00 (2 H, s, 3-H), 3.93 (1 H, d, *J* 3.9, 5-H), 7.12 (1 H, br s, NH); δ_C (75 MHz; $CDCl_3$) 11.6 (*C*H$_3$CH$_2$), 15.2 (*C*H$_3$CH), 24.3 (Me*C*H$_2$), 37.8 (Me*C*H), 41.6 (C-3), 68.9 (C-5), 171.8 (C-2), 207.3 (C-4).

Tenuazonic acid 14. 13 (155 mg, 1.0 mmol) was added to $BF_3 \times OEt_2$ (3.8 mL) while stirring, followed by the addition of acetyl chloride (212 µL, 2.9 mmol). The mixture was heated at 75 °C for 8 h, treated with another quantity of acetyl chloride (70 µL, 1.0 mmol) and finally heated for a further 2 h. After cooling to room temperature water (15 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic phases were extracted with ice-cold 1% aqueous NaOH (2 × 15 mL), the extracts were washed with chloroform (2 × 10 mL) and then carefully acidified to pH 4 with cold 1 M HCl. The mixture was extracted with chloroform (3 × 15 mL), the combined organic phases were dried over $MgSO_4$, filtered and concentrated on a rotary evaporator. The crude oily product was purified first by preparative TLC[41] (silica gel; MeOH–$CHCl_3$, 1 : 5) and then by "recrystallization" from petroleum ether (bp range 40–60 °C) to give beige gummy **14** (120 mg, 60%), $[\alpha]_D^{20}$ −128 (*c* 1.0, MeOH) {lit.,[31] $[\alpha]_D^{20}$ −132 (*c* 0.5, $CHCl_3$)}; ν_{max}(film)/cm^{-1} 3296, 1769, 1696, 1628; δ_H (300 MHz; CD_3OD) 0.90 (3 H, t, *J* 7, CH_3CH$_2$), 1.00 (3 H, d, *J* 7, CH_3CH), 1.20–1.45 (2 H, m, MeCH_2), 1.86 (1 H, m, MeC*H*), 2.43 (3 H, s, CH_3C=), 3.84 (1 H, d, *J* 3, 5-H); δ_C (75 MHz; CD_3OD) 12.2 (*C*H$_3$CH$_2$), 15.9 (*C*H$_3$CH), 20.3 (*C*H$_3$C=), 24.8 (CH$_3$*C*H$_2$), 38.2 (CH$_3$*C*H), 67.2 (C-5), 103.9 (C-3), 175.2 (C-2), 187.5 (C-1′), 199.2 (C-4).

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