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A synthetic approach to 5/5/6-polycyclic tetramate macrolactams of the discodermide type

Kevin Bodenschatz, Julia Stöckl, Markus Winterer, Rainer Schobert*

Department of Chemistry, University Bayreuth, Universitaetsstr. 30, D-95440, Bayreuth, Germany

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ABSTRACT

A flexible synthetic route to the 16-membered tetramate-embedding macrocyclic scaffold present in various polycyclic tetramate macrolactams (PTMs) was developed which differs from the seminal synthesis of ikarugamycin by Boeckman Jr. in protecting groups and the order of connections. We also devised a short approach to various stereoisomers of the 5/5/6-tricarbocyclic motif found in discodermide and other PTMs, starting from the Weiss' diketone.

1. Introduction

Polycyclic tetramate macrolactams (PTMs) are structurally complex bacterial metabolites featuring a 3-acyltetramic acid which is embedded in an oligo-unsaturated macrocyclic lactam via attachment to C-3 and C-5 [1]. The macrocycle is annulated by specific sets of carbocycles, e.g. a 5/5-bicycle as in cylindramide (**1**) [2,3], a 5/6/5-tricycle as in ikarugamycin (**2**) [4,5], or a 5/5/6-tricycle as in pactamide A (**3**) [6], discodermide (**4**) [7], xanthobaccin A (**5**) [8] and HSAF (**6**) [9] (Fig. 1). While their frequent antiprotozoal, antibacterial, antifungal and antitumoral activities stimulated the large-scale production of certain PTMs via fermentation, synthetic approaches remained comparatively rare.

Herein we report a study of synthetically less well explored 5/5/6-type PTMs that share the same macrolactam scaffold, such as compounds **3**–**6** depicted in Fig. 1. The emphasis was on a quick access to the 16-membered ring and on maximum flexibility concerning the stereochemistry in the tricarbocycle. The macrocycle was to be built up around a 1,2-disubstituted cyclohexane as a surrogate for the 5/5/6-tricycle leading to the simplified model compound **7**. The tricarbocycle was to be prepared from a common *cis*-configured bicyclo[3.3.0]octane precursor **8** which could be converted by stereoselective Robinson annulations and hydrogenations to tricycles **9** with the H-atoms between B and C rings adopting any of the possible relative configurations reflecting those found in natural PTMs of general type **10** (Scheme 1).

2. Results and discussion

2.1. PTM-model compound 7

Retrosynthetically, we divided PTM-model **7** in three building blocks: a *trans*-1,2-disubstitituted cyclohexane **11**, bearing a *Z*-enoic acid and a dioxolane as a masked aldehyde, an ornithine-derived aminoester **12**, and phosphonate **13** (Scheme 1).

For the synthesis of racemic compound **11**, cyclohexanone **16** was α-allylated with allyl bromide and sodium amide in Et_2O to give ketone **17** in 54% yield [10]. 2-Allylcyclohexanone **17** was submitted to a Wittig olefination with methoxymethylidene triphenylphosphorane obtained by deprotonation of phosphonium salt **15**, which is readily available by reaction of dimethoxymethane **14** with PPh_3 [11]. The resulting 4:1 *E*/*Z*-mixture of enol ethers **18** was hydrolysed to afford, upon base-catalysed equilibration, a 5:1 mixture of racemic *trans*- and *cis*-aldehydes **19**. The latter was protected to give a 4:1 mixture of racemic *trans*- and *cis*-dioxolanes (±)-**20**. The double bond of (±)-**20** was dihydroxylated with potassium osmate (VI) dihydrate to give diols **21** which were submitted to a Criegee cleavage affording the monoprotected racemic aldehyde (±)-**22** as a 4:1 mixture of *trans*- and *cis*-isomers. A Horner-Wadsworth-Emmons (HWE) reaction of aldehyde (±)-**22** with Ando's phosphonate **25** furnished *Z*-enoate (±)-**23** in 92% yield. Phosphonate **25** was readily accessible from methyl

* Corresponding author.
E-mail address: rainer.schobert@uni-bayreuth.de (R. Schobert).

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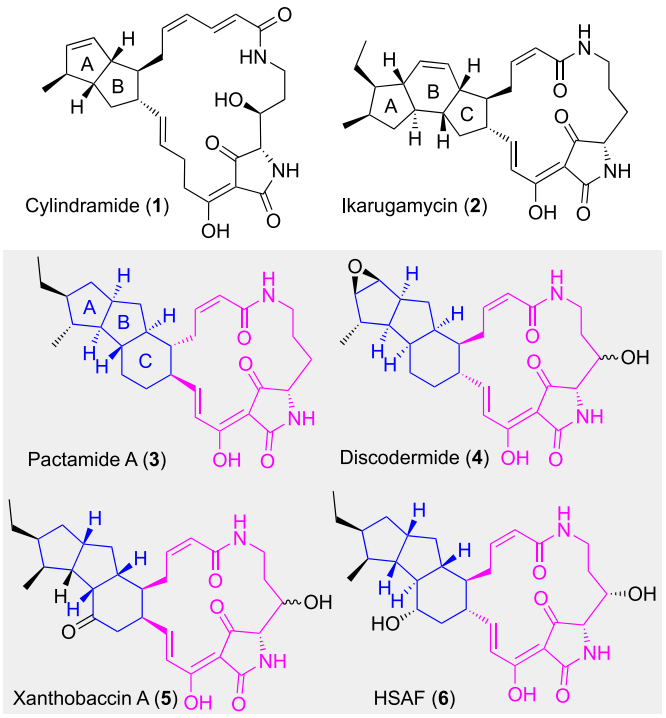
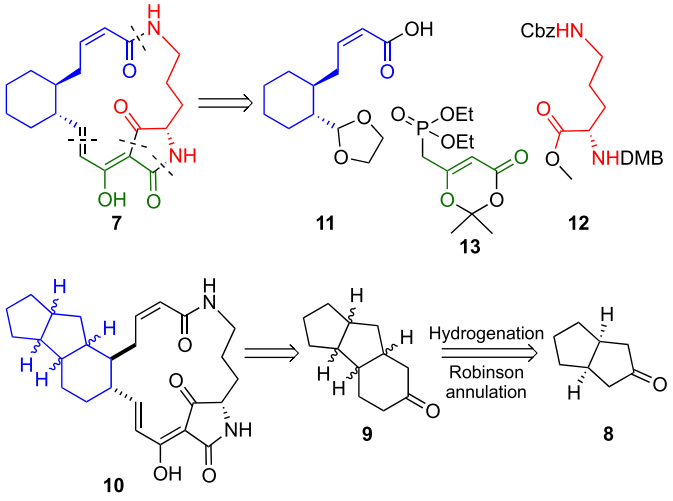


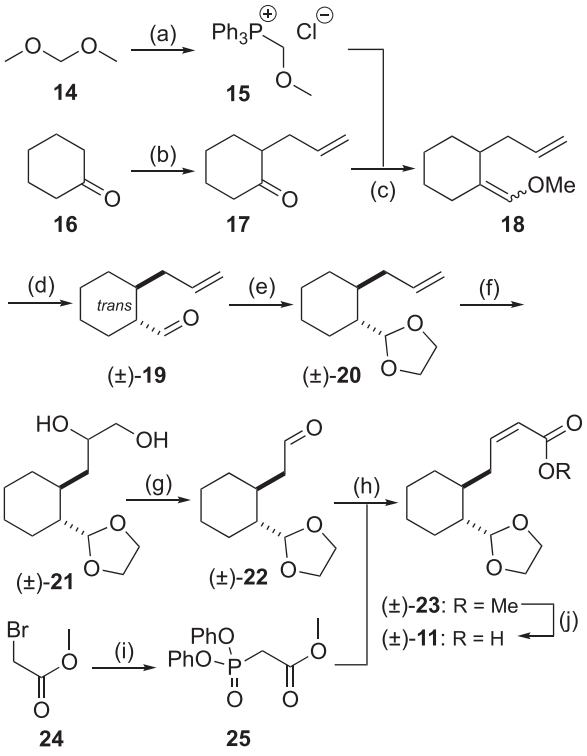
Fig. 1. Structures of typical PTMs with **3**–**6** sharing the same 5/5/6-tricarbocyclic and macroheterocyclic rings.



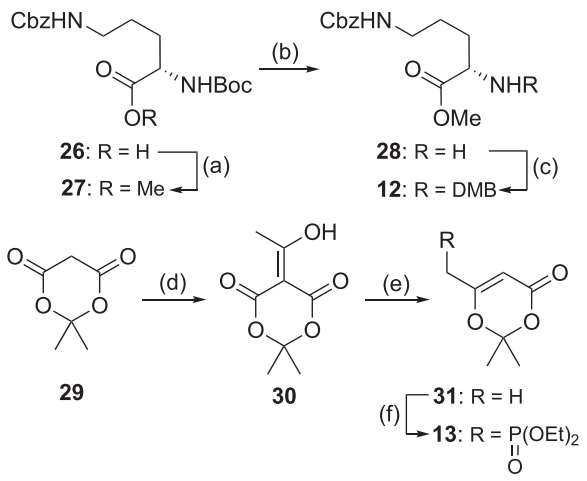
Scheme 1. Retrosynthetic approaches to PTM-model **7** (top) and tricarbocycles **9** as occurring in PTMs **10** (bottom).

bromoacetate **24** and diphenylphosphite [12]. Alkaline hydrolysis of ester **23** afforded building block (±)-**11** in an overall yield of 36% over nine steps (Scheme 2).

The second building block, N^{α}-DMB-N^{δ}-Cbz-L-ornithine-OMe **12**, was prepared from commercially available N^{α}-Boc-N^{δ}-Cbz-L-ornithine-OH **26** which was first esterified with iodomethane in DMF [13]. The Boc-protecting group of the resulting methyl ester **27** was removed under acidic conditions and replaced with a DMB group by reaction with 2,4-dimethoxybenzaldehyde and $NaBH_3CN$ to afford N^{α}-DMB-N^{δ}-Cbz-L-ornithine-OMe **12** with an overall yield of 45% in three steps (Scheme 3, top) [14]. The switch from Boc to DMB as an N^{α}-protecting group was necessary due to the former

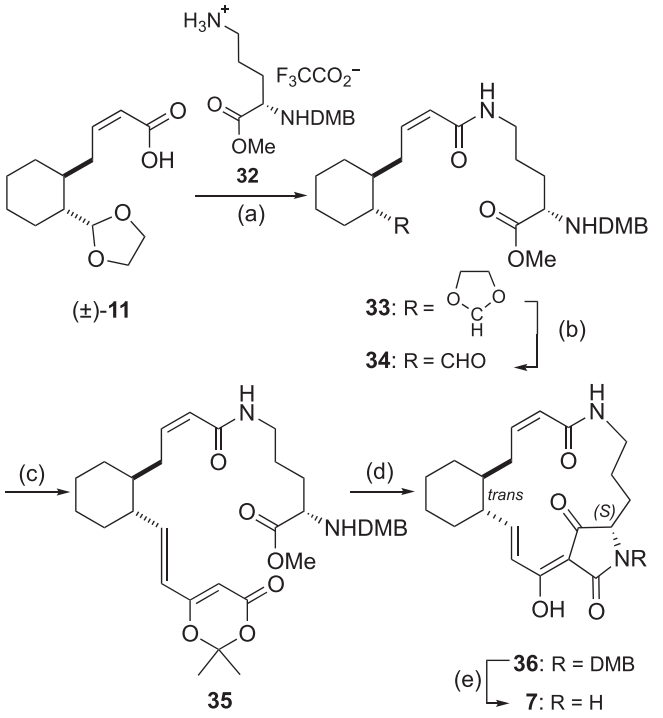


Scheme 2. Synthesis of difunctionalised cyclohexane (±)-**11**. *Reagents and conditions*: (a) PPh_3, AcCl, MeOH, 65 °C, 3 h, 94%; (b) $NaNH_2$, allyl bromide, Et_2O, 35 °C, 3 h, 54%; (c) $NaNH_2$, HMDS, THF, 65 °C, 3 h, 95%; (d) 1. THF:5% HCl (4:1), 66 °C, 30 min; 2. MeOH:5% KOH (1:1), 65 °C, 3 h, 99% (2 steps); (e) $(CH_2OH)_2$, PPTS, benzene, 80 °C, 18 h, 93%; (f) $K_2OsO_4 \cdot 2H_2O$, NMO, acetone, 0 °C, 16 h, 96%; (g) $Pb(OAc)_4$, CH_2Cl_2, r.t., 2 h, 94%; (h) NaH, THF, −78 °C, 2 h, 92%; (i) $(PhO)_2P(O)H$, NEt_3, CH_2Cl_2, 0 °C, 1h, 43%; (j) 1 M KOH, MeOH, 50 °C, 24 h, 85%.



Scheme 3. Synthesis of building blocks **12** and **13**. *Reagents and conditions*: (a) Cs_2CO_3, MeI, DMF, 24 h, quant.; (b) TFA, CH_2Cl_2, r.t., 1 h, 75%; (c) DMB, $NaBH_3CN$, MeOH, r.t., 72 h, 60%; (d) AcCl, pyridine, CH_2Cl_2, 0 °C, 2 h, 75%; (e) toluene, acetone, 111 °C, 2 h, 80%; (f) DIPA, *n*BuLi, $(EtO)_2POCl$, THF, −78 °C, 40 min, 30%.

leading to difficulties with the amidation of carboxylic acid **11**. The third building block, dioxinone phosphonate **13** was readily accessible via a short 3-step reaction sequence with an overall yield of 18% [15]. Meldrum's acid **29** was acylated with acetyl chloride to give tris-β-carbonyl compound **30**, which upon heating underwent a rearrangement–decarboxylation reaction affording dioxinone **31**. This was converted to dioxinone phosphonate **13** with



Scheme 4. Assembly of PTM-model **7**. *Reagents and conditions:* (a) DIPEA, HBTU, DMF, 0 °C, 24 h, 40%; (b) I_2, acetone, r.t., 2 h, 59%; (c) **13**, *n*BuLi, HMPA, DIPA, THF, −78 °C, 1 h, 64%; (d) 1. toluene, 111 °C, 2 h; 2. KO*t*Bu, *t*BuOH, r.t., 20 min, 53%; (e) TFA, CH_2Cl_2, r.t., 18 h, 50%.

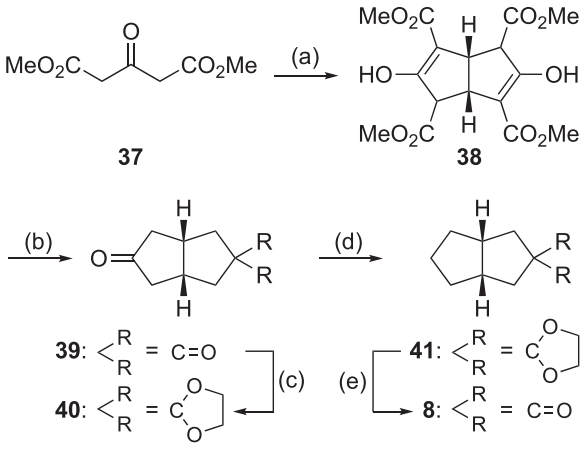
chlorodiethylphosphite in THF under basic conditions (Scheme 3, bottom).

The following assembly of the three building blocks **11**, **12**, and **13** to afford PTM-model **7** is reminiscent of Boeckman's approach to ikarugamycin (**2**) [5a], yet differs in the protecting groups used and in the order in which the key functional groups are established (cf. Supporting Information for a side-by-side comparison).

Z-enoic acid (±)-**11** was coupled with ammonium trifluoroacetate **32**, obtained by hydrogenolytical cleavage of the Cbz group of aminoester **12** in the presence of TFA. The resulting amide **33** was treated with iodine to liberate aldehyde **34** which was submitted to an *E*-selective HWE olefination by the phosphonate anion generated from phosphonate **13** with lithium diisopropylamide. The product **35** was heated at reflux in toluene to undergo a ring-closing intramolecular *N*-β-ketoacylation of the electron-rich DMB-substituted amino group. The resulting macrocyclic β-ketoamide was not purified but treated with two equivalents of KO*t*Bu at room temperature for 20 min right away to initiate a Dieckmann condensation affording DMB-protected tetramic acid **36** in 53% over two steps. The latter was deprotected under acidic conditions to leave the PTM-model compound **7** (Scheme 4).

2.2. 5/5/6-Tricarbocyclic scaffolds

Ketone **8**, used as a starting compound for the synthesis of 5/5/6-tricarbocycles with flexible connectivity between B and C rings, was prepared from Weiss' diketone **39** which was synthesised according to lit [16]. via two aldol additions between dimethyl 3-oxopentanedioate **37** and glyoxal, followed by Michael reactions affording bisenol **38** which was subjected to acidic hydrolysis for removal of the ester groups. Monoketone **8** was then obtained analogously to lit [17]. in 11% yield by first protecting one carbonyl



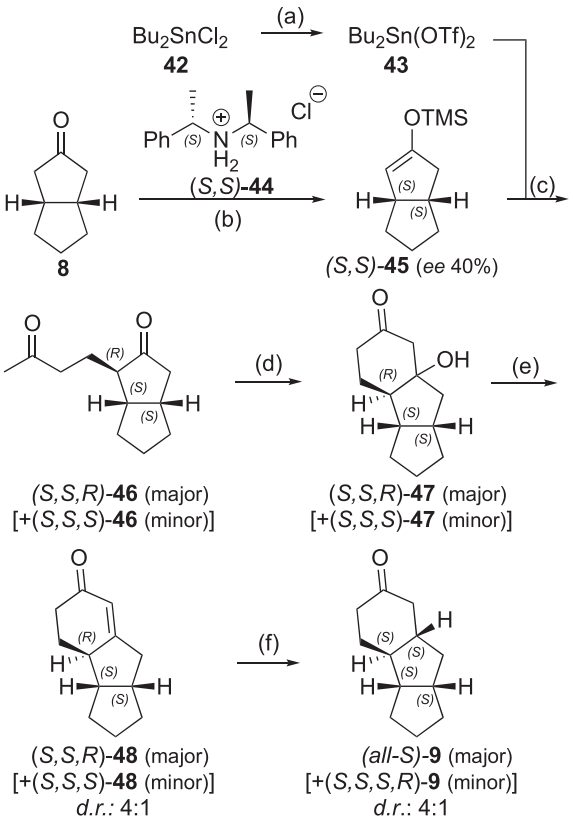
Scheme 5. Synthesis of monoketone **8** via Weiss' diketone **39**. *Reagents and conditions:* (a) 1. NaOH, glyoxal, MeOH, 0 °C => 65 °C, 18 h; 2. 1 M HCl, $H_2O/CHCl_3$, r.t., 30 min, 44%; (b) 1 M HCl, AcOH, 100 °C, 2.5 h, 64%; (c) *p*TosOH, $(CH_2OH)_2$, toluene, 111 °C, 18 h, 67%; (d) NaOH, $N_2H_4 \cdot H_2O$, DEG, 200 °C, 18 h, 60%; (e) *p*TosOH, acetone, 56 °C, 3 h, quant.

function of **39** to give ketal **40**, reducing the remaining ketone under Wolff-Kishner conditions to afford **41**, and then removing the protecting group (Scheme 5).

For the attachment of the C ring, ketone **8** was treated with *n*BuLi/HMPA in the presence of ammonium salt (*S,S*)-**44** to selectively abstract one of the α-protons. Quenching of the resulting lithium enolate with TMSCl gave silyl enol ether (*S,S*)-**45** with an *ee* of 40% as determined by a literature method [18] (cf. Supp. information). A screening of other chiral bases, potentially yielding a higher *ee*, was not performed at this point. For a mere proof of the synthetic concept, the mixture of enantiomers of enol ether **45** was used henceforth. It was α-alkylated with methyl vinyl ketone and catalytic amounts of $Bu_2Sn(OTf)_2$ **43** to give predominantly ketone (*S,S,R*)-**46** and a minor amount of diastereomer (*S,S,S*)-**46** as an inseparable mixture. Isomeric reaction products originating from the minor enantiomer (*R,R*)-**45** were not separated and are not shown in Scheme 6. The ketones **46** were cyclised under basic conditions to afford a mixture of tertiary alcohols **47** [19]. Elimination of water with catalytic amounts of *p*TosOH gave enones **48** which were separated by column chromatography to leave the individual diastereomers (*S,S,R*)-**48** and (*S,S,S*)-**48** in a ratio of 4:1, and both in mixture with their minor enantiomers stemming from (*R,R*)-**45**. The major isomer (*S,S,R*)-**48** was hydrogenated with Pd/C under a H_2 atmosphere to afford 5/5/6-tricarbocycles **9** as an inseparable 4:1-mixture of (*S,S,S,S*)- and (*S,S,S,R*)-diastereoisomers. All reactions were also run with ammonium salt (*R,R*)-**44** to afford analogous results and products enantiomeric to those obtained with (*S,S*)-**45**. With a more enantioselective chiral base for the synthesis of enol ether **45** and a more diastereoselective catalyst for the hydrogenation of the olefins **48**, all possible stereoisomers of the 5/5/6-tricyclic ketones **9** with *cis*-connected A and B rings should in principle be accessible on this route.

3. Conclusion

Our synthetic route to model compound **7** in 15 steps should be applicable to the tetramate macrolactam scaffold present in PTMs such as those shown in Fig. 1. It is flexible enough to accommodate additional residues on the perimeter by starting from the respective amino acid, e.g. hydroxyornithine in the case of PTMs **4**–**6**. The latter also share the same 5/5/6-tricarbocyclic scaffold which we found accessible in all relevant configurations via a route starting from the Weiss' monoketone **8**. Key steps of this route, such as the



Scheme 6. Synthesis of 5/5/6-tricarbocycles **9**. *Reagents and conditions*: (a) AgOTf, EtOH, r.t., 2 h, 70%; (b) HMPA, 2eq. *n*BuLi, TMSCl, THF, −40 °C, 48 h, 55% (82% based on recovered s.m.); (c) $Bu_2Sn(OTf)_2$, methyl vinyl ketone, CH_2Cl_2, -78 °C, 5 h, 17% (55% b.r.s.m.); (d) KOH, EtOH, Et_2O, 0 °C, 2 h, 80%; (e) *p*TosOH, benzene, 80 °C, 3 h, 55%; (f) 10% Pd/C, H_2, EtOAc, r.t., 2 h, 75%.

enantioselective deprotonation of **8** and the stereoselective hydrogenation of tricyclic enone **48**, still require an optimisation, though. It also remains to be clarified at which stage substituents on the tricarbocycle such as the vicinal methyl-ethyl residues of **3**, **5** or **6** and the epoxide of **4** were to be introduced.

4. Experimental

4.1. General

Melting points (uncorrected): Büchi melting point apparatus M-565. IR: Perkin-Elmer Spectrum 100 FT-IR spectrophotometer with ATR sampling unit. NMR: ^1H and ^{13}C NMR spectra were recorded on Bruker DRX 500 and Avance 300 spectrometers; chemical shifts are given in parts per million (δ) using the residual solvent peak as an internal standard. Mass spectra: Finnigan MAT 8500 (EI, 70 eV). HRMS: UPLC/Orbitrap MS system in ESI mode. Optical rotations: Perkin-Elmer Polarimeter 241 ($\lambda = 589$ nm); $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. For column chromatography Merck silica gel 60 (230–400 mesh) was used. Analytial TLC was carried out using Merck silica gel 60 F_{254s} foil plates. Analytical HPLC was performed on a Beckman System Gold Programmable Solvent Module 126 using Phenomenex Kinetex® C-18-HPLC column, length 250 × 4.6 mm, pore size 100 Å, particle size 5 μm; detection by a Beckman Instruments Diode Array Detection Module 168. Starting compounds were bought from the usual sources and used without further purification.

4.2. Syntheses and characterisation

4.2.1. 2-Allylcyclohexan-1-one (**17**) [10].

A solution of cyclohexanone (10.00 g, 102 mmol, 1.00 equiv) and $NaNH_2$ (4.18 g, 102 mmol, 1.00 equiv) in 60 mL Et_2O was stirred at reflux for 3 h. The reaction mixture was then slowly treated with a solution of allyl bromide (12.34 g, 102 mmol, 1.00 equiv) in 40 mL Et_2O at ambient temperature and was stirred for additional 20 h. Water was added to dissolve the NaBr. The aqueous layer was extracted with Et_2O and the combined organic phases were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo*. The remainder was purified by fractionated distillation to leave the title compound as a colorless oil (7.42 g, 54%) of b.p. 75 °C at 15 mbar (lit [10]. 90–92 °C at 17 mm); ν_{max} 3075, 2933, 2862, 1707, 1640, 1449, 1431, 1362, 1339, 1313, 1228, 1197, 1125, 1063, 995, 910, 884, 818, 761, 728, 634, 566 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.22–1.40 (1H, m, H-5), 1.52–1.72 (2H, m, H-3/7), 1.75–1.87 (1H, m, H-7), 1.87–2.15 (3H, m, H-3/4/5), 2.20–2.41 (3H, m, H-2/6), 2.42–2.55 (1H, m, H-4), 4.91–5.03 (2H, m, H-9), 5.65–5.80 (1H, m, H-8); δ_C (75 MHz, $CDCl_3$) 25.0 (C-7), 28.0 (C-3), 33.4 (C-5), 33.8 (C-4), 42.1 (C-6), 50.3 (C-2), 116.2 (C-9), 136.5 (C-8), 212.4 (C-1).

4.2.2. (Methoxymethyl)triphenylphosphonium chloride (**15**)

A solution of dimethoxymethane **14** (8.00 mL, 90 mmol, 2.60 equiv) and PPh_3 (8.90 g, 34 mmol, 1.00 equiv) in 0.11 mL MeOH was slowly treated with acetyl chloride (3.00 mL, 84 mmol, 2.50 equiv) and was subsequently stirred at reflux for 3 h. The reaction mixture was then cooled to 0 °C and treated with 6.00 mL acetone. After letting it stand for 1 h at 0 °C the solids were filtered off and washed with hexane and Et_2O. The volatiles were removed *in vacuo* to leave the title compound as a white solid (11.0 g, 94%) of m.p. 193–196 °C; ν_{max} 3045, 2991, 2958, 2861, 2833, 1586, 1486, 1465, 1433, 1332, 1317, 1187, 1162, 1114, 1101, 1064, 1028, 1012, 996, 958, 900, 881, 851, 801, 753, 719, 688, 614, 572 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.56 (3H, s, H-2), 5.68 (2H, d, J_{PH} 4.0 Hz, H-1), 7.54–7.60 (6H, m, Ar-H_{meta}), 7.63–7.72 (9H, m, Ar-$H_{ortho/para}$); δ_C (125 MHz, $CDCl_3$) 62.5 (d, J_{PC} 12.5 Hz, C-2), 65.8 (d, J_{PC} 68.3 Hz, C-1), 116.4 (d, J_{PC} 86.2 Hz, C_{ipso}), 130.3 (d, J_{PC} 12.7 Hz, C_{meta}), 133.9 (d, J_{PC} 9.8 Hz, C_{para}), 135.2 (d, J_{PC} 2.9 Hz, C_{ortho}).

4.2.3. 1-Allyl-2-(methoxymethylene)cyclohexane (**18**)[11]

A solution of $NaNH_2$ (1.05 g, 27 mmol, 1.30 equiv) in 80 mL THF was treated with HMDS (5.70 mL, 27 mmol, 1.30 equiv) and was subsequently stirred at reflux for 3 h. The reaction mixture was then cooled to 0 °C and treated with **17** (8.06 g, 23 mmol, 1.10 equiv) and 15 (2.90 g, 21 mmol, 1.00 equiv). After 30 min the ice-bath was removed, and the solution stirred for 20 h at ambient temperature. Saturated $NH_4Cl_{(aq)}$ was added and the aqueous layer was extracted with Et_2O. The combined organic phases were then washed with brine and dried over Na_2SO_4 and the volatiles removed *in vacuo*. After most of the Ph_3PO was removed via crystallization the remainder was purified by column chromatography (Et_2O/hexane 1:40) to afford the title compound as a colorless oil (3.31 g, 95%); ν_{max} 3075, 2926, 2852, 1681, 1640, 1447, 1435, 1377, 1234, 1212, 1199, 1126, 1105, 1062, 1027, 993, 908, 836, 743, 696, 662, 620, 594, 575 cm^{-1}; 4:1 *E*/*Z*-mixture; Major isomer: δ_H (300 MHz, $CDCl_3$) 1.27–1.74 (6H, m, H-3/5/6), 1.92–2.37 (5H, m, H-2/4/7), 3.53 (3H, s, H-11), 4.94–5.06 (2H, m, H-9), 5.67–5.84 (2H, m, H-8/10); δ_C (75 MHz, $CDCl_3$) 23.7/23.9/27.4 (C-4/5/6), 33.1 (C-3), 36.8 (C-7), 39.2 (C-2), 59.4 (C-11), 115.3 (C-9), 120.8 (C-1), 138.0 (C-8), 139.3 (C-10); Minor isomer: δ_H (300 MHz, $CDCl_3$) 1.27–1.74 (6H, m, H-3/5/6), 1.92–2.37 (5H, m, H-2/4/7), 3.50 (3H, s, H-11), 4.94–5.06 (2H, m, H-9), 5.67–5.84 (2H, m, H-8/10); δ_C (75 MHz, $CDCl_3$) 21.5/26.8/28.5 (C-4/5/6), 30.4 (C-3), 32.9 (C-7), 36.0 (C-2), 59.3 (C-11), 114.8 (C-9), 120.2 (C-1), 138.2 (C-8), 139.7 (C-10).

*4.2.4. 2-Allylcyclohexane-1-carbaldehyde (±)-(**19**)[11]*

A solution of **18** (4.70 g, 28.27 mmol, 1.00 equiv) in 500 mL THF:5% aqueous HCl (4:1) was stirred at reflux for 30 min. The reaction mixture was neutralized with saturated $NaHCO_{3\ (aq)}$. The aqueous layer was extracted with Et_2O and the combined organic phases were washed with brine. The solution was dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The remainder was taken up in MeOH and treated with 110 mL 5% KOH solution. Then the reaction mixture was stirred at reflux for 3 h. The aqueous layer was extracted with Et_2O. The combined organic phases were washed with saturated $NH_4Cl_{\ (aq)}$ and brine and were dried over Na_2SO_4. The volatiles were removed *in vacuo* and the remainder was purified by column chromatography (hexane/Et_2O 40:1) to leave the title compound as a colorless oil (4.26 g, 99%); ν_{max} 3077, 2978, 2926, 2855, 2705, 1722, 1640, 1448, 996, 912, 697, 650, 556 cm^{-1}; 5:1 *trans*/*cis*-mixture; Major isomer: δ_H (300 MHz, $CDCl_3$) 0.85–1.02 (1H, m, H-6), 1.06–1.34 (3H, m, H-3/4/5), 1.56–1.79 (5H, m, H-2/3/4/5/6), 1.79–2.15 (3H, m, H-1/7), 4.85–4.98 (2H, m, H-9), 5.57–5.74 (1H, m, H-8), 9.49 (1H, d, J_{HH} 3.5 Hz, H-10); δ_C (75 MHz, $CDCl_3$) 24.7/25.0/25.9 (C-3/4/5), 30.3 (C-6), 36.3 (C-2), 38.8 (C-7), 54.8 (C-1), 116.7 (C-9), 135.9 (C-8), 204.8 (C-10); Minor isomer: δ_H (300 MHz, $CDCl_3$) 0.86–2.15 (5H, m, H-2/3/4/5/6/7), 2.36–2.45 (1H, m, H-1), 4.85–4.98 (2H, m, H-9), 5.57–5.74 (1H, m, H-8), 9.70 (1H, m, H-10); δ_C (75 MHz, $CDCl_3$) 23.6/23.7/24.2 (C-3/4/5), 29.0 (C-6), 35.7 (C-2), 37.0 (C-7), 51.4 (C-1), 116.3 (C-9), 136.9 (C-8), 205.1 (C-10).

*4.2.5. 2-(2-Allylcyclohexyl)-1,3-dioxolane (±)-(**20**)[11]*

A solution of **19** (4.04 g, 26.51 mmol, 1.00 equiv) in 75 mL ethylene glycol and 120 mL benzene was treated with PPTS (660 mg, 2.65 mmol, 0.10 equiv) and was subsequently stirred at reflux with a Dean-Stark-apparatus for 18 h. Saturated $NaHCO_{3\ (aq)}$ and water were added and the aqueous layer was extracted with benzene. The combined organic phases were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by column chromatography (hexane/Et_2O 50:1) to give the title compound as a colorless oil (4.83 g, 93%); ν_{max} 3077, 2973, 2922, 2882, 2855, 1640, 1450, 1402, 1356, 1322, 1302, 1241, 1210, 1157, 1143, 1119, 1068, 1056, 1036, 987, 944, 908, 878, 824, 786, 713, 680, 648, 571, 558 cm^{-1}; 4:1 *trans*/*cis*-mixture; Major isomer: δ_H (500 MHz, $CDCl_3$) 0.91–1.03 (1H, m, H-3), 1.07–1.20 (3H, m, H-4/5/6), 1.39–1.48 (2H, m, H-1/2), 1.57–1.79 (4H, m, H-3/4/5/6), 1.86–2.37 (2H, m, H-7), 3.72–3.92 (4H, m, H-11/12), 4.89–5.00 (3H, m, H-9/10), 5.66–5.80 (1H, m, H-8); δ_C (125 MHz, $CDCl_3$) 24.6/25.5/25.8 (C-4/5/6), 31.7 (C-3), 37.8 (C-2), 37.9 (C-7), 44.1 (C-1), 64.9/65.0 (C-11/12), 104.9 (C-10), 115.9 (C-9), 137.0 (C-8); Minor isomer: δ_H (500 MHz, $CDCl_3$) 0.91–1.03 (1H, m, H-3), 1.07–1.20 (3H, m, H-4/5/6), 1.39–1.48 (2H, m, H-1/2), 1.57–1.79 (4H, m, H-3/4/5/6), 1.86–2.37 (2H, m, H-7), 3.72–3.92 (4H, m, H-11/12), 4.68 (1H, d, J_{HH} 6.6 Hz, H-10), 4.89–5.00 (2H, m, H-9), 5.66–5.80 (1H, m, H-8); δ_C (125 MHz, $CDCl_3$) 21.0/23.2/25.3 (C-4/5/6), 28.4 (C-3), 31.8 (C-7), 34.8 (C-2), 44.2 (C-1), 64.6/64.7 (C-11/12), 105.9 (C-10), 115.3 (C-9), 138.2 (C-8).

*4.2.6. 2-((1,3-Dioxolan-2-yl)cyclohexyl)acetaldehyde (±)-(**22**)*

A solution of **20** (3.44 g, 17.5 mmol, 1.00 equiv) in 30 mL acetone was treated with a solution of $K_2OsO_4 \cdot H_2O$ (130 mg, 0.35 mmol, 0.02 equiv) in 30 mL H_2O at 0 °C. Subsequently, 6.00 mL NMO (50% in water) was added and stirred for 16 h at ambient temperature. Acetone was removed *in vacuo* and the remainder treated with 15 mL EtOAc and a solution of Na_2SO_3 (15.4 g, 0.12 mol, 7.00 equiv) in 50 mL water. After stirring for 2 h at ambient temperature the aqueous layer was extracted with EtOAc. The combined organic phases where washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo*. The remainder was quickly purified by column chromatography (hexane/acetone 2:1 to 1:1) to leave diol **21** as a colorless oil (3.86 g, 96%) prone to decomposition; A solution of diol **21** (3.86 g, 16.73 mmol, 1.00 eq) in 50 mL CH_2Cl_2 was treated with freshly recrystallized $Pb(OAc)_4$ (9.64 g, 21.75 mmol, 1.30 eq) and stirred for 2 h at ambient temperature. The volatiles were removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 4:1) to afford the title compound as a colorless oil (3.12 g, 94%). ν_{max} 2923, 2856, 2719, 1721, 1449, 1402, 1353, 1282, 1254, 1219, 1160, 1122, 1092, 1054, 1035, 974, 948, 925, 878, 868, 847, 802, 732, 649, 624, 596, 585, 571, 560 cm^{-1}; 4:1 *trans*/*cis*-mixture; Major isomer: δ_H (500 MHz, $CDCl_3$) 1.03–1.25 (4H, m, H-3/4/5/6), 1.39–1.48 (1H, m, H-1), 1.59–1.85 (4H, m, H-3/4/5/6), 1.90–2.01 (1H, m, H-2), 2.20 (1H, ddd, J_{HH} 16.7, 6.9, 2.3 Hz, H-7), 2.73 (1H, ddd, J_{HH} 16.6, 5.2, 1.8 Hz, H-7), 3.70–3.92 (4H, m, H-10/11), 4.66 (1H, d, J_{HH} 4.6 Hz, H-9), 9.66–9.69 (1H, t, J_{HH} 2.1 Hz, H-8); δ_C (125 MHz, $CDCl_3$) 25.4/25.9/26.6 (C-3/4/5), 33.6 (C-2), 33.6 (C-3), 45.1 (C-1), 49.0 (C-7), 64.4/64.9 (C-10/11), 105.9 (C-9), 203.2 (C-8); Minor isomer: δ_H (500 MHz, $CDCl_3$) 1.00–2.00 (9H, m, H-2/3/4/5/6), 2.09 (1H, ddd, J_{HH} 15.9, 5.4, 1.6, H-7), 2.33 (1H, ddd, J_{HH} 16.4, 8.2, 2.6, H-1), 2.44 (1H, ddd, J_{HH} 15.9, 7.7, 3.8, H-7), 3.70–3.92 (4H, m, H-10/11), 4.61 (1H, d, J_{HH} 5.9 Hz, H-9), 9.61 (1H, dd, J_{HH} 3.8, 1.7 Hz, H-8); δ_C (125 MHz, $CDCl_3$) 23.8/25.0/30.6 (C-3/4/5), 34.6 (C-3), 35.4 (C-2), 40.5 (C-1), 44.5 (C-7), 64.1/64.8 (C-10/11), 105.6 (C-9), 202.0 (C-8);

*4.2.7. Methyl 2-(diphenoxyphosphoryl)acetate (**25**)[12]*

A solution of diphenylphosphite (17.23 mL, 90 mmol, 1.00 equiv) in 90 mL CH_2Cl_2 was treated with methyl bromoacetate (8.52 mL, 90 mmol, 1.00 equiv) and NEt_3 (17.50 mL, 126 mmol, 1.40 equiv) at 0 °C and was stirred for 15 min. After that the reaction mixture was stirred for 1 h at ambient temperature. Water was added and the layers were separated. The aqueous phase was extracted with EtOAc/hexane 3:1. The combined organic phases were washed with water and brine and were dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 2:1) to afford the title compound as a colorless oil (11.91 g, 43%); ν_{max} 1739, 1590, 1488, 1456, 1436, 1397, 1280, 1208, 1183, 1161, 1116, 1071, 1025, 1008, 927, 832, 812, 760, 688, 619, 561, 555 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.28 (2H, d, J_{PH} 21.6 Hz, H-1), 3.72 (3H, s, H-3), 7.14–7.19 (2H, m, Ar-H_{para}), 7.21–7.25 (4H, m, Ar-H_{ortho}), 7.29–7.34 (4H, m, Ar-H_{meta}); δ_C (125 MHz, $CDCl_3$) 33.6 (d, J_{PH} 137.2 Hz, C-1), 52.6 (C-3), 120.4 (d, J_{PC} 4.5 Hz, Ar-CH_{ortho}), 125.4 (Ar-CH_{para}), 129.7 (Ar-CH_{meta}), 149.7 (d, J_{PC} 8.2 Hz, Ar-C_q), 165.0 (d, J_{PC} 6.5 Hz, C-2); HRMS: *m*/*z* calcd for [M + H, $C_{15}H_{16}O_5P^+$]: 307.07299; found: 307.07203.

*4.2.8. Methyl 4-((2-(1,3-dioxolan-2-yl)cyclohexyl)but-(2Z)-enoate (±)-(**23**)*

A solution of **25** (1.83 g, 6.00 mmol, 1.00 equiv) in 100 mL THF was treated with NaH (60% in paraffin, 330 mg, 8.40 mmol, 1.40 equiv) at − 78 °C. After 25 min, a solution of (±)-**22** (1.29 g, 6.60 mmol, 1.10 equiv) in 50 mL THF was added slowly. The reaction mixture was stirred for 2 h at − 78 °C and subsequently 2.5 h at ambient temperature. Saturated $NH_4Cl_{\ (aq)}$ was added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 4:1) to leave the title compound as a colorless oil (1.40 g, 92%); ν_{max} 3417, 2924, 2882, 2855, 1721, 1645, 1606, 1595, 1502, 1472, 1438, 1408, 1357, 1268, 1202, 1170, 1123, 1071, 1034, 996, 980, 945, 878, 850, 827, 814, 755, 734, 692, 610, 577, 569 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.09–1.25 (3H, m, H-3/4/5), 1.44–1.60 (2H, m, H-1/2), 1.60 (5H, m, H-3/4/5/6), 2.69–2.87 (2H, m, H-7), 3.68 (3H, s, H-11), 3.77–3.95 (4H, m, H-13/14), 4.94 (1H, d, J_{HH} 3.1 Hz, H-12), 5.79 (1H, dt, J_{HH} 11.6, 1.8 Hz, H-9), 6.25 (1H, ddd, J_{HH} 11.6, 8.3, 6.6 Hz, H-8); δ_C (125 MHz,

$CDCl_3$) 24.9/25.5/25.8 (C-3/4/5), 32.1 (C-6), 33.0 (C-7), 38.4 (C-2), 44.5 (C-12), 51.1 (C-11), 64.9/65.1 (C-13/14), 105.1 (C-12), 120.0 (C-9), 149.9 (C-8), 167.1 (C-10).

4.2.9. 4-((2-(1,3-Dioxolan-2-yl)cyclohexyl)but-(2Z)-enoic acid (±)-*11*

A solution of (±)-**23** (781 mg, 3.07 mmol, 1.00 equiv) in 35 mL MeOH was treated with 1 M KOH (22 mL) and stirred at 50 °C for 24 h. The volatiles were removed *in vacuo* and the remainder was washed with Et_2O. The aqueous layer was acidified with 1 M HCl and extracted with Et_2O. The combined organic phases were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by column chromatography (hexane/Et_2O 40:1 => EtOAc/hexane 2:1 + 5% MeOH) to leave the title compound as a colorless oil (627 mg, 85%); ν_{max} 2926, 2856, 1722, 1692, 1638, 1447, 1295, 1235, 1191, 1156, 1121, 1071, 1035, 980, 944, 908, 878, 831, 728, 648, 559 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.98–1.34 (4H, m, H-3/4/5/6), 1.34–1.90 (6H, m, H-1/2/3/4/5/6), 2.51–3.10 (2H, m, H-7), 3.77–3.98 (4H, m, H-12/13), 4.93 (1H, d, J_{HH} 3.0 Hz, H-11), 5.81 (1H, d, J_{HH} 12.0 Hz H-9), 6.30–6.43 (1H, m, H-8), 7.82 (1H, br.s, COOH); δ_C (125 MHz, $CDCl_3$) 25.1/25.5/25.9 (C-4/5/6), 32.3 (C-3), 33.4 (C-7), 38.5 (C-2), 44.5 (C-1), 64.9/65.1 (C-12/13), 105.2 (C-11), 119.8 (C-9), 152.5 (C-8), 172.0 (C-10).

4.2.10. 5-(1-Hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (*30*)[15]

A solution of Meldrum's acid (10.80 g, 75 mmol, 1.00 equiv) and pyridine (12.00 g, 150 mmol, 2.00 equiv) in 50 mL CH_2Cl_2 was treated with a solution of acetyl chloride (6.28 g, 80 mmol, 1.07 equiv) in 20 mL CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and another 1 h at ambient temperature. 2 M HCl was added and the layers were separated. The combined organic layers were washed with brine and were dried over Na_2SO_4. The volatiles were removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 3:1) to give the title compound as a yellow solid (10.50 g, 75%); ν_{max} 2986, 1724, 1659, 1546, 1531, 1437, 1395, 1366, 1333, 1322, 1284, 1262, 1201, 1151, 1099, 1065, 1021, 995, 938, 922, 890, 794, 733, 703, 679, 643, 587, 561 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.64 (6H, s, H-7/8), 2.58 (3H, s, H-10), 15.02 (1H, s, OH); δ_C (125 MHz, $CDCl_3$) 23.4 (C-10), 26.7 (C-7/8), 91.8 (C-5), 104.8 (C-2), 160.3/170.1 (C-4/6), 194.5 (C-9).

4.2.11. 2,2,6-Trimethyl-4H-1,3-dioxin-4-one (*31*)[15]

A solution of **30** (9.00 g, 48.34 mmol, 1.00 equiv) in 50 mL toluene and 4 mL acetone was stirred at reflux for 2 h. Subsequently the volatiles were removed *in vacuo*. The remainder was purified by fractionated distillation to afford the title compound as a yellow oil (5.49 g, 80%) of b.p. 80 °C at 11 mbar; ν_{max} 3105, 3000, 2948, 1718, 1636, 1558, 1463, 1438, 1390, 1378, 1354, 1310, 1271, 1252, 1201, 1186, 1145, 1117, 1092, 1030, 1005, 960, 932, 900, 856, 803, 745, 707, 628, 567 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.56 (6H, s, H-8/9), 1.87 (3H, s, H-7), 5.11 (1H, s, H-5); δ_C (125 MHz, $CDCl_3$) 19.8 (C-7), 24.8 (C-8/9), 93.6 (C-5), 106.2 (C-2), 161.0 (C-4), 168.7 (C-6).

4.2.12. Diethyl ((2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)methyl)-phosphonate (*13*)[15]

A solution of diisopropylamine (0.52 mL, 3.68 mmol, 1.40 equiv) in 3 mL THF was slowly treated with *n*BuLi (2 M in hexane, 1.48 mL, 3.68 mmol, 1.40 equiv) at 0 °C. After 30 min **31** (374 mg, 2.63 mmol, 1.00 equiv) was added at −78 °C. After 40 min, chlorodiethylphosphite (0.55 mL, 3.68 mmol, 1.40 equiv) was added and the reaction mixture was allowed to warm up to ambient temperature. Half saturated NaCl $_{(aq)}$ was added and the aqueous layer was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The remainder was treated with 1 mL H_2O_2 in 10 mL CH_2Cl_2 and stirred for 1h at ambient temperature. Brine was added and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by column chromatography (EtOAc) to furnish the title compound as a yellow oil (219 mg, 30%); ν_{max} 2917, 2850, 1738, 1635, 1468, 1374, 1239, 1165, 1099, 1020, 970, 904, 883, 865, 802, 719, 610, 559 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.31 (6H, t, J_{HH} 7.1 Hz, H-11/13), 1.67 (6H, s, H-7/8), 2.77 (2H, d, J_{PH} 22.1 Hz, H-9), 4.08–4.16 (4H, dq, J_{HH} 8.1, 7.1 Hz, H-10/12), 5.36 (1H, d, J_{HH} 3.6 Hz, H-5); δ_C (125 MHz, $CDCl_3$) 16.4 (d, J_{PC} 6.3 Hz, C-11/13), 25.0 (C-7/8), 32.4 (d, J_{PC} 137.2 Hz, C-9), 62.8 (d, J_{PC} 6.7 Hz, C-10/12), 96.2 (d, J_{PC} 8.2 Hz, C-5), 107.2 (C-2), 160.7 (d, J_{PC} 2.7 Hz, C-4), 163.1 (d, J_{PC} 10.0 Hz, C-6).

4.2.13. Methyl (S)-5-(((benzyloxy)carbonyl)amino)-2-((tert-butoxycarbonyl)amino)-pentanoate (*27*)[13]

A solution of Boc-Orn(Z)-OH (4.00 g, 10.92 mmol, 1.00 equiv) in 40 mL DMF was treated with Cs_2CO_3 (5.34 g, 16.38 mmol, 1.50 equiv) and MeI (0.83 mL, 13.21 mmol, 1.21 equiv) and was stirred at ambient temperature for 24 h. Subsequently, water was added, and the aqueous layer was extracted with EtOAc. The combined organic phases were washed with 10% $Na_2S_2O_5$, $NaHCO_{3\ (aq)}$ and brine, respectively. The solution was then dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by column chromatography (EtOAc/hexane 4:1) to leave the title compound as a colorless oil (4.15 g, quant.); ν_{max} 3340, 3065, 3034, 2976, 2953, 2872, 1693, 1516, 1454, 1440, 1392, 1366, 1245, 1216, 1158, 1081, 1046, 1023, 912, 865, 776, 734, 697, 593, 573, 557 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.43 (9H, s, H-9), 1.45–1.88 (4H, m, H-2/3), 3.20 (2H, q, J_{HH} 6.4 Hz, H-1), 3.72 (3H, s, H-6), 4.24–4.34 (1H, m, H-4), 4.88–4.97 (1H, m, N*H*), 5.08 (2H, s, H-11), 5.09–5.15 (1H, m, N*H*), 7.28–7.37 (5H, m, H-13/14/15); δ_C (75 MHz, $CDCl_3$) 26.0 (C-2), 28.3 (C-9), 29.9 (C-3), 40.5 (C-1), 52.2 (C-6), 53.1 (C-4), 66.5 (C-11), 79.9 (C-8), 128.0 (C-13/15), 128.5 (C-14), 136.7 (C-12), 155.4 (C-10), 156.5 (C-7), 173.1 (C-5).

4.2.14. Methyl (S)-2-amino-5-(((benzyloxy)carbonyl)amino) pentanoate (*28*)

A solution of **27** (1.00 g, 2.63 mmol, 1.00 equiv) in 10 mL CH_2Cl_2 was treated with 10 mL TFA and stirred for 1 h at ambient temperature. The volatiles were removed *in vacuo* and the remainder was repeatedly co-evaporated with toluene. Purification by column chromatography (hexane/EtOAc 1:4 => EtOAc) afforded the title compound as a yellow oil (555 mg, 75%); ν_{max} 3334, 2951, 2483, 1699, 1587, 1531, 1498, 1452, 1427, 1359, 1245, 1211, 1176, 1145, 1081, 1002, 913, 822, 774, 733, 697, 647, 608, 575, 561 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.40–1.72 (4H, m, H-4/5), 2.99–3.16 (2H, m, H-6), 3.28–3.39 (1H, m, H-3), 3.60 (3H, s, H-1), 4.99 (2H, s, H-8), 5.03 (1H, s, N*H*), 5.38 (1H, m, N*H*), 7.15–7.32 (5H, m, H-10/11/12/13/14); δ_C (125 MHz, $CDCl_3$) 26.1 (C-5), 31.7 (C-4), 40.4 (C-6), 51.9 (C-3), 53.7 (C-1), 66.4 (C-8), 127.9 (C-10/14), 128.0 (C-12), 128.4 (C-11/13), 136.6 (C-9), 156.4 (C-7), 176.1 (C-2).

4.2.15. Methyl (S)-5-(((benzyloxy)carbonyl)amino)-2-((2,4-dimethoxybenzyl)amino)-pentanoate (*12*)[14]

A solution of **28** (555 mg, 1.98 mmol, 1.00 equiv) in 20 mL MeOH was treated with 2,4-dimethoxybenzaldehyde (658 mg, 3.96 mmol, 2.00 equiv) and $NaBH_3CN$ (311 mg, 4.95 mmol, 2.50 equiv) and was stirred at ambient temperature for 24 h. Saturated $NaHCO_{3\ (aq)}$ was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 1:2 + 5% MeOH) to afford the title compound as a colorless oil (512 mg, 60%); ν_{max} 3345, 2948, 2836,

1716, 1612, 1588, 1506, 1455, 1439, 1419, 1371, 1334, 1288, 1247, 1206, 1155, 1131, 1034, 934, 920, 832, 776, 736, 697, 635, 606, 583, 573, 552 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.42–1.71 (4H, m, H-2/3), 3.13 (2H, q, J_{HH} 6.4 Hz, H-1), 3.22 (1H, t, J_{HH} 6.4 Hz, H-4), 3.60 (3H, s, H-6), 3.62 (2H, d, J_{HH} 13.0 Hz, H-7), 3.66 (2H, d, J_{HH} 13.0 Hz, H-7), 3.74 (3H, s, H-14/15), 3.74 (3H, s, H-14/15), 5.05 (2H, s, H-17), 5.57 (1H, s, N*H*), 6.35–6.42 (2H, m, H-10/12), 7.09 (1H, d, J_{HH} 8.1 Hz, H-13), 7.25–7.35 (5H, m, H-19/20/21/22/23); δ_C (125 MHz, $CDCl_3$) 26.1 (C-2), 30.4 (C-3), 40.5 (C-1), 46.9 (C-6), 51.4 (C-6), 55.0 (C-14/15), 60.2 (C-4), 66.2 (C-17), 98.2 (C-10), 103.5 (C-12), 119.9 (C-8), 127.8 (C-19/23), 127.8 (C-20/22), 128.2 (C-21), 130.2 (C-13), 136.6 (C-18), 156.3 (C-16), 158.4 (C-9), 160.0 (C-11), 175.4 (C-5).

4.2.16. Methyl (S)-5-((Z)-4-(2-(1,3-dioxolan-2-yl)cyclohexyl)but-2-enamido)-2-((2,4-dimethoxybenzyl)amino)pentanoate (**33**)

A solution of **12** (1.93 g, 4.49 mmol, 1.00 equiv) in 20 mL EtOAc was treated with 10 wt-% Pd/C and TFA (0.40 mL, 5.39 mmol, 1.20 eq) and stirred in an H_2-atmosphere at ambient temperature for 2 h. The reaction mixture was filtered over celite and the volatiles were removed *in vacuo*. The crude product salt **32** was immediately used without further purification. A solution of (±)-**11** (920 mg, 3.83 mmol, 1.00 equiv) in 35 mL DMF was treated with DIPEA (1.30 mL, 7.66 mmol, 2.00 eq) and HBTU (1.63 g, 4.21 mmol, 1.10 equiv) at 0 °C and was stirred for 20 min. Crude **32** (1.57 g, 3.83 mmol, 1.00 equiv) was added and the solution was stirred at ambient temperature for 24 h. Saturated $NH_4Cl_{(aq)}$ was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by column chromatography (CH_2Cl_2/MeOH 20:1) to afford the product mixture of two diastereomers as an orange resin (700 mg, 40%); ν_{max} 3423, 2927, 2856, 1739, 1656, 1614, 1588, 1532, 1509, 1454, 1440, 1375, 1332, 1291, 1260, 1242, 1208, 1158, 1136, 1121, 1071, 1031, 978, 940, 837, 738, 698, 637, 585, 573, 557 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.94–2.00 (12H, m, H-5/6/7/8/15/16), 1.37–1.50 (2H, m, H-4/9), 2.62–2.80 (2H, m, H-10), 3.14–3.28 (2H, m, H-14), 3.54–3.61 (1H, m, H17), 3.70 (3H, s, H-19), 3.77/3.83 (6H, s, H-27/28), 3.77–3.93 (4H, m, H-1/2), 3.86–4.02 (2H, m, H-20), 4.92 (1H, t, J_{HH} 2.71 Hz, H-3), 5.42 (1H, s, N*H*), 5.70 (1H, d, J_{HH} 11.5 Hz, H-12), 5.91–6.00 (1H, m, H-11), 6.38–6.45 (2H, m, H-23/25), 6.52–6.58 (1H, m, N*H*), 7.12–7.20 (1H, m, H-26); δ_C (125 MHz, $CDCl_3$) 24.7/25.5/25.8/28.6/32.1/32.6 (C-5/6/7/8/15/16), 32.6 (10), 38.3 (C-14), 38.4 (C-9), 44.5 (C-4), 47.6 (C-20), 52.9 (C-19), 55.5/55.6 (C-27/28), 59.6 (C-17), 64.9/65.1 (C-1/2), 98.5 (C-23), 104.6 (C-3), 104.9 (C-25), 113.7/113.8 (C-21), 122.7/122.8 (C-12), 132.2 (C-26), 144.7/144.8 (C-11), 159.0 (C-22), 161.8/161.9 (C-24), 167.6 (C-13), 171.8 (C-18); HRMS: *m*/*z* calcd for [M + H, $C_{28}H_{43}N_2O_7^+$]: 519.30648; found: 519.30542.

4.2.17. Methyl (S)-2-((2,4-dimethoxybenzyl)amino)-5-((Z)-4-(2-formylcyclohexyl)-but-2-enamido)pentanoate (**34**)

A solution of **33** (106 mg, 0.20 mmol, 1.00 equiv) in 10 mL acetone was treated with I_2 (43 mg, 0.17 mmol, 0.83 equiv) and stirred at ambient temperature for 2 h. 5% $Na_2S_2O_3$ was added and the aqueous layer extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and then dried over Na_2SO_4. The volatiles were removed *in vacuo* to give the product diastereomers as a yellow oil (57 mg, 59%); ν_{max} 3421, 2930, 2855, 1746, 1717, 1655, 1615, 1589, 1533, 1511, 1440, 1368, 1329, 1293, 1268, 1245, 1209, 1160, 1136, 1121, 1029, 979, 937, 832, 736, 701, 556 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.86–2.08 (16H, m, H-2/3/4/5/6/7/13/14), 2.48–2.65 (2H, m, H-8), 3.01–3.27 (2H, m, H-12), 3.70 (3H, s, H-17), 3.73/3.80 (6H, s, H-25/26), 3.77–3.82 (1H, m, H-15), 4.14/4.24 (2H, d, J_{HH} 12.9 Hz, H-18), 5.80–5.93 (2H, m, H-9/10), 6.34–6.44 (2H, m, H-21/23), 7.02–7.08 (1H, m, N*H*), 7.30 (1H, d, J_{HH} 8.4 Hz, H-24), 9.48 (1H, d, J_{HH} 3.6 Hz, H-1); δ_C (125 MHz, $CDCl_3$) 24.6/24.7/25.1/26.1/27.0 (C-4/5/6/13/14), 30.3 (C-7), 30.3/30.5 (C-8), 33.3 (C-3), 36.9 (C-2), 37.8 (C-12), 46.7 (C-18), 53.4 (C-17), 55.5/55.6 (C-25/26), 58.4 (C-15), 98.4 (C-21), 105.0 (C-23), 109.8 (C-19), 123.7/123.8 (C-10), 133.4 (C-24), 142.9/143.0 (C-9), 159.2 (C-20), 162.7 (C-22), 167.3 (C-11), 169.0 (C-16), 206.0 (C-1); HRMS: *m*/*z* calcd for [M + H, $C_{26}H_{39}N_2O_6^+$]: 475.28026; found: 475.27935.

4.2.18. Methyl (S)-2-((2,4-dimethoxybenzyl)amino)-5-((Z)-4-((2-((E)-2-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)vinyl)cyclohexyl) but-2-enamido)pentanoate (**35**)

Compound **35** was synthesized analogously to a literature protocol [15a]. A solution of diisopropylamine (0.02 mL, 0.14 mmol, 1.05 eq) in 1.00 mL THF was treated with *n*BuLi (2.5 M in hexane, 0.14 mmol, 1.05 eq) at 0 °C. After 30 min a solution of **13** (36 mg, 0.13 mmol, 1.00 eq) in 1 mL THF was added at −78 °C. The reaction mixture was allowed to warm up to 0 °C and was stirred for 15 min at that temperature. HMPA (0.04 mL, 0.23 mmol, 1.77 eq) was added at −78 °C and the reaction mixture was stirred for 30 min. Then a solution of **34** (60 mg, 0.13 mmol, 1.00 equiv) in 1 mL THF was added dropwise. The temperature was raised to 0 °C and the reaction mixture was stirred for an additional hour. Saturated $NH_4Cl_{(aq)}$ was added and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the remainder purified by column chromatography (CH_2Cl_2/MeOH 20:1) to give a product mixture of two diastereoisomers as a yellow oil (50 mg, 64%); ν_{max} 3320, 2999, 2924, 2853, 1722, 1649, 1614, 1588, 1534, 1506, 1456, 1389, 1374, 1273, 1249, 1205, 1156, 1135, 1018, 974, 935, 903, 859, 833, 800, 731, 697, 674, 639, 608, 591, 568 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.12–1.97 (14H, m, H-1/2/3/4/5/6/12/13), 1.69 (6H, s, H-32/33), 2.40–2.73 (2H, m, H-7), 3.19–3.28 (3H, m, H-11/14), 3.60–3.70 (2H, m, H-17), 3.64 (3H, s, H-16), 3.78/3.79 (6H, s, H-24/25), 5.21 (1H, s, H-29), 5.58 (1H, d, J_{HH} 11.6 Hz, H-9), 5.81–5.90 (1H, m, H-26), 5.87 (1H, d, J_{HH} 15.6 Hz, H-27) 6.30–6.44 (3H, m, H-8/20/22), 7.09 (1H, d, J_{HH} 8.1 Hz, H-23); δ_C (125 MHz, $CDCl_3$) δ 25.1/25.2 (C-32/33), 25.7/25.9/31.0/31.5/32.9/33.9 (C-2/3/4/5/7/12/13), 39.0 (C-11), 42.2 (C-6), 47.4 (C-1), 47.5 (C-17), 51.9 (C-16), 55.4/55.5 (C-24/25), 60.6 (C-14), 93.4 (C-29), 98.6 (C-20), 103.9 (C-22), 106.4 (C-18), 119.9 (C-31), 122.4 (C-27), 123.4 (C-9), 130.7 (C-23), 144.0 (C-26), 146.8 (C-8), 158.8 (C-19), 160.5 (C-21), 162.3 (C-30), 163.6 (C-10), 166.5 (C-28), 175.5 (C-15); HRMS: *m*/*z* calcd for [M + H, $C_{33}H_{47}N_2O_8^+$]: 599.33269; found: 599.33141.

4.2.19. Protected PTM-model **36**

Compound **36** was synthesized analogously to a literature protocol [5a]. A solution of **35** (24 mg, 0.04 mmol, 1.00 eq) in 50 mL toluene was added dropwise to 100 mL of toluene stirred at reflux. After being stirred for 2 h the volatiles were removed *in vacuo* to leave the intermediate β-ketoamide which was taken up in 2 mL *t*BuOH and treated with KO*t*Bu (8 mg, 0.07 mmol, 2.00 eq). After stirring for 20 min at ambient temperature, 5% citric acid was added and the aqueous layer was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and the volatiles removed *in vacuo* to afford the product mixture of two diastereomers an orange oil (11 mg, 53% 2 steps); ν_{max} 3314, 2921, 2852, 1705, 1640, 1612, 1583, 1508, 1455, 1363, 1290, 1263, 1237, 1208, 1185, 1157, 1130, 1116, 1033, 988, 941, 919, 830, 817, 786, 731, 698, 677, 640, 619, 599, 582 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.64–2.47 (18H, m, H-1/2/3/4/5/6/7/11/12/13), 3.59–3.70 (1H, m, H-14), 3.79 (6H, s, H-23/24), 4.15 (1H, d, J_{HH} 14.8 Hz, H-16), 4.90 (1H, t, J_{HH} 14.8 Hz, H-16), 5.70–5.81 (2H, m, H-9/26), 6.04–6.12 (1H, m, H-25), 6.41–6.47 (2H, m, H-19/21), 6.70 (1H, dd, J_{HH} 15.5, 10.5 Hz, H-8), 7.20 (1H, d, J_{HH} 8.2 Hz, H-22); δ_C (125 MHz, $CDCl_3$) 24.2/25.4/26.4/26.7/30.2/33.0/33.5 (C-2/3/4/5/7/12/13), 37.8/37.9 (C-11), 38.8/38.9 (C-16), 38.95/39.1 (C-6),

45.6/46.6 (C-1), 55.6 (C-23/24), 64.5/64.6 (C-14), 98.6 (C-19), 101.0/101.1 (C-28), 104.5 (C-21), 116.6 (C-17), 121.7/121.8 (C-9), 123.6 (C-26), 131.4/131.5 (C-22), 142.0/143.1 (C-25), 152.4 (C-8), 158.5 (C-18), 160.9 (C-20), 166.5 (C-10), 166.9 (C-15), 173.6/173.9 (C-29), 195.5/195.9 (C-27); HRMS: *m/z* calcd for [M + H, $C_{29}H_{37}N_2O_6^+$]: 509.26461; found: 509.26483.

4.2.20. PTM-model **7**

Compound **7** was synthesized analogously to a literature protocol [5a]. A solution of **36** (8 mg, 0.02 mmol, 1.00 equiv) in 1 mL CH_2Cl_2 was treated with 1 mL TFA and stirred at ambient temperature for 18 h. The volatiles were removed *in vacuo* and the remainder was repeatedly co-evaporated with toluene to leave a crude orange oil (4 mg, 50%). Purification by reverse phase column chromatography afforded the product mixtures of two diastereomers as an orange oil; ν_{max} 3299, 2923, 2853, 1780, 1702, 1645, 1610, 1582, 1508, 1437, 1365, 1294, 1262, 1203, 1173, 1135, 1117, 1034, 988, 943, 909, 855, 817, 799, 761, 729, 705, 672, 644, 629, 606, 596, 583, 574, 567 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.80–2.36 (16H, m, H-9/10/11/12/13/14/15/20/21), 3.46–3.71 (2H, m, H-19), 3.74–3.94 (1H, m, H-5), 5.73–5.98 (2H, m, H-17/N*H*), 6.06–6.15 (1H, m, H-16), 6.76 (1H, dd, J_{HH} 15.5, 10.4 Hz, H-8), 7.11 (1H, d, J_{HH} 15.5 Hz, H-7); δ_C (125 MHz, $CDCl_3$) 21.1/25.3/26.4/29.8/30.2/32.0/33.0 (C-10/11/12/13/15/20/21), 38.9 (C-19), 39.2 (C-14), 46.8 (C-9), 61.5 (C-5), 100.5 (C-3), 121.6 (C-17), 123.6 (C-7), 142.1 (C-8), 153.5 (C-16), 166.6 (C-18), 174.6 (C-2), 176.0 (C-4), 196.2 (C-6); HRMS: *m/z* calcd for [M + H, $C_{20}H_{27}N_2O_4^+$]: 359.19653; found: 359.19659.

4.2.21. Tetramethyl 2,5-dihydroxy-1,3a,4,6a-tetrahydropentalene-1,3,4,6-tetracarboxylate (**38**)[16]

A solution of NaOH (3.20 g, 80 mmol, 1.81 equiv) in MeOH was slowly treated with dimethyl-1,3-acetonedicarboxylate (11.32 mL, 78.50 mmol, 1.77 eq) at 0 °C. The reaction mixture was stirred at reflux until the white solid was completely dissolved. Then glyoxal (50% in water, 6.11 mL, 44.30 mmol, 1.00 equiv) was added dropwise in a manner that the internal temperature remained at 65 °C. After that the mixture was stirred at ambient temperature for 18 h. The solid was filtered off and washed with MeOH. The volatiles were removed *in vacuo* to leave the disodium salt as a yellow solid (9.10 g, 50%). A solution of the disodium salt (9.10 g, 21.98 mmol, 1.00 equiv) in 50 mL $CHCl_3$ and 40 mL H_2O was treated with HCl (1 M, 50 mL, 50 mmol, 2.27 equiv) and stirred at ambient temperature for 30 min. The aqueous and organic layers were separated, and the former extracted with $CHCl_3$. The combined organic phases were washed with brine and subsequently dried over Na_2SO_4. The volatiles were removed *in vacuo*. The remainder was purified by recrystallisation to afford the title compound as a white solid (7.10 g, 87%); ν_{max} 3004, 2957, 1735, 1669, 1632, 1445, 1437, 1373, 1326, 1242, 1195, 1151, 1051, 1023, 987, 960, 935, 842, 788, 761, 733, 702, 590, 561 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.62 (2H, t, J_{HH} 2.5 Hz, H-3/6), 3.75 (6H, s, H-8/13), 3.77 (6H, s, H-11/16), 3.84 (2H, t, J_{HH} 2.5 Hz, H-3a/6a), 10.31 (2H, s, OH); δ_C (125 MHz, $CDCl_3$) 43.9 (C-3/6), 51.8/52.8/55.4 (C-8/11/14/17), 104.0 (C-1/4), 169.3 (C-7/13), 170.8 (C-10/16), 171.0 (C-2/5).

4.2.22. Tetrahydropentalene-2,5(1H,3H)-dione (**39**) [16]

A solution of **38** (7.10 g, 19.20 mmol, 1.00 equiv) in 41.6 mL 1 M HCl and 4.5 mL glacial acetic acid was stirred at reflux for 2.5 h. The layers were saparated and the aqueous phase was extracted with $CHCl_3$. The combined organic phases were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was repeatedly co-evaporated with toluene. Saturated $NaHCO_{3\ (aq)}$ was added and the aqueous layer was extracted with $CHCl_3$. The combined organic phases were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by recrystallisation to leave the title compound as pale-yellow crystals (1.70 g, 64%) of m.p. 85 °C (lit [16] 84–85 °C); ν_{max} 3445, 2956, 2917, 2898, 1721, 1628, 1592, 1490, 1437, 1401, 1341, 1293, 1256, 1234, 1208, 1179, 1146, 1114, 1046, 955, 941, 915, 834, 792, 729, 692, 661, 613, 571, 562 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.12 (4H, dd, J_{HH} 19.6, 5.3 Hz, H-1/3/4/6), 2.55 (4H, dd, J_{HH} 19.6, 8.7 Hz, H-1/3/4/6), 2.97–3.07 (2H, m, H-7/8); δ_C (125 MHz, $CDCl_3$) 36.3 (3a/6a), 43.4 (1/3/4/6), 218.0 (2/5).

4.2.23. Tetrahydro-1H-spiro[pentalene-2,2'-[1,3]dioxolan]-5(3H)-one (**40**)

Compound **40** was synthesized analogously to a literature protocol [17]. A solution of **39** (24.20 g, 175 mmol, 1.00 equiv) in 500 mL toluene was treated with *p*-TosOH·H_2O (3.29 g, 17.5 mmol, 0.10 equiv) and ethylene glycol (8.23 mL, 158 mmol, 0.90 equiv) which was added in 4 portions over 8 h. Subsequently the reaction mixture was stirring at reflux for an additional 16 h with a Dean-Stark-apparatus. The reaction mixture was washed with 1 M NaOH and brine. The combined organic phases were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 9:1 => 7:3). The starting material (4.13 g, 19%) and the double-protected by-product (6.31 g, 18%) could be removed to afford the title compound as a colorless oil (18.96 g, 67%); ν_{max} 2958, 2887, 1735, 1591, 1490, 1434, 1404, 1343, 1326, 1291, 1277, 1244, 1209, 1185, 1161, 1113, 1048, 1018, 983, 945, 895, 842, 796, 768, 730, 691, 648, 616, 584, 568 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.61 (2H, dd, J_{HH} 13.8, 4.1 Hz, H-1/3), 2.02–2.12 (4H, m, H-1/3/4/6), 2.36 (2H, dd, J_{HH} 19.4, 8.1 Hz, H-4/6), 2.66–2.77 (2H, m, H-3a/6a), 3.78 (4H, s, H-7/8); δ_C (125 MHz, $CDCl_3$) 37.0 (C-3a/6a), 41.4 (C-1/3), 44.2 (C-4/6), 63.9 (C-7/8), 64.6 (C-7/8), 118.6 (C-2), C-5 outside range.

4.2.24. Hexahydro-1H-spiro[pentalene-2,2'-[1,3]dioxolane] (**41**)

Compound **41** was synthesized analogously to a literature protocol [17]. A solution of **40** (180 mg, 0.99 mmol, 1.00 equiv) in 20 mL diethylene glycol was treated with NaOH (292 mg, 7.30 mmol, 7.37 equiv) and hydrazine hydrate (0.48 mL, 9.90 mmol, 10.00 equiv) and stirred first at 136 °C for 2 h, then at 200 °C for 18 h with a Dean-Stark-apparatus on the flask. Water was added and the aqueous layer extracted with Et_2O. The combined organic layers were washed with brine and subsequently dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 9:1) to give the title compound as a colorless oil (100 mg, 60%); ν_{max} 2940, 2864, 1470, 1449, 1431, 1331, 1302, 1277, 1241, 1203, 1124, 1100, 1025, 992, 978, 945, 903, 886, 847, 795, 724, 715, 681, 605, 571 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.33–1.41 (2H, m, H-4/6), 1.42–1.56 (3H, m, H-1/3/5), 1.58–1.69 (3H, m, H-4/5/6), 1.92–1.99 (2H, m, H-1/3), 2.44–2.53 (2H, m, H-3a/6a), 3.84–3.91 (4H, m, H-7/8); δ_C (125 MHz, $CDCl_3$) 25.6 (C-5), 33.6 (C-4/6), 40.0 (C-3a/6a), 41.9 (C-1/3), 64.0/64.7 (C-7/8), 118.9 (C-2).

4.2.25. Hexahydropentalen-2(1H)-one (**8**)

Compound **8** was synthesized analogously to a literature protocol [17]. A solution of **41** (180 mg, 1.07 mmol, 1.00 eq) in 5 mL acetone was treated with *p*TosOH·H_2O (20 mg, 0.11 mmol, 0.10 equiv) and stirred at reflux for 3 h. The volatiles were removed *in vacuo* and the remainder purified by column chromatography (hexane/EtOAc 3:1) to give the title compound as a yellow oil (133 mg, quant.); ν_{max} 2946, 2866, 1735, 1470, 1450, 1404, 1310, 1279, 1241, 1163, 1041, 945, 913, 898, 800, 659, 605, 578, 555 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.30–1.38 (2H, m, H-4/6), 1.52–1.62 (1H, m, H-5), 1.64–1.74 (1H, m, H-5), 1.84–1.92 (2H, m, H-4/6), 1.95 (2H, dd, J_{HH} 19.2, 4.1 Hz, H-1/3), 2.37–2.45 (2H, m, H-1/3), 2.59–2.69 (2H, m, H-3a/6a); δ_C (125 MHz, $CDCl_3$) 25.5 (C-5), 33.4 (C-4/6), 39.6 (C-3a/6a), 44.7 (C-1/3), C-2 outside measuring range; HRMS: *m/z* calcd for

[M + H, $C_8H_{13}O^+$]: 125.09609; found: 125.09613.

*4.2.26. 1,3a,4,5,6,6a-Hexahydropentalen-2-yl)oxy)trimethylsilanes (S,S)-**45** and (R,R)-**45***

Compound **45** was synthesized analogously to a literature protocol [18]. A solution of either chiral ammonium salt (*S,S*)-**44** or (*R,R*)-**44** (654 mg, 2.50 mmol, 1.00 equiv) in 10 mL THF was treated with *n*BuLi (2.5 M in hexane, 2.00 mL, 5.00 mmol, 2.00 equiv) and HMPA (0.88 mL, 5.00 mmol, 2.00 equiv) at −78 °C and then stirred for 1 h at ambient temperature. TMSCl (1.30 mL, 12.75 mmol, 5.10 equiv) and **8** (250 mg, 2.00 mmol, 0.80 equiv) were slowly added at −78 °C. The reaction mixture was stirred for 48 h at −40 °C, NEt_3 and saturated $NaHCO_{3\ (aq)}$ were added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with saturated $NH_4Cl_{\ (aq)}$ and saturated $NaHCO_{3\ (aq)}$ and subsequently dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 9:1) to afford the respective product enantiomer of **45** with an *ee* of 40% as a yellow oil (215 mg, 55% (82% b.r.s.m.)); ν_{max} 3060, 2944, 2907, 2862, 1645, 1468, 1447, 1414, 1343, 1323, 1298, 1282, 1251, 1220, 1190, 1167, 1146, 1122, 1098, 1027, 989, 974, 926, 898, 868, 839, 787, 751, 690, 626, 586 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.18 (9H, s, H-7/8/9), 1.29–1.40 (2H, m, H-3/6), 1.40–1.49 (1H, m, H-5), 1.49–1.63 (2H, m, H-3/5), 1.63–1.74 (1H, m, H-6), 1.88–1.94 (1H, m, H-4), 2.53–2.61 (2H, m, H-3a/4), 3.00–3.09 (1H, m, H-6a), 4.48 (1H, m, H-1); δ_C (125 MHz, $CDCl_3$) 0.1 (C-7/8/9), 25.2 (C-5), 33.5 (C-3), 35.8 (C-6), 38.2 (C-3a), 42.0 (C-4), 46.5 (C-6a), 107.5 (C-1), 153.3 (C-2).

*4.2.27. 1-(3-Oxobutyl)hexahydropentalen-2(1H)-ones (S,S,R)-**46** and (R,R,S)-**46***

Compound **46** was synthesized analogously to a literature protocol [19]. A solution of either (*S,S*)-**45** or (*R,R*)-**45** (105 mg, 0.53 mmol, 1.00 equiv) in 5 mL CH_2Cl_2 was treated with methyl vinyl ketone (0.06 mL, 0.70 mmol, 1.30 equiv) and $Bu_2Sn(OTf)_2$ 43 (16 mg, 0.03 mmol, 0.05 equiv) at −78 °C and then stirred first at −78 °C for 1 h and then for 4 h at ambient temperature. Saturated $NaHCO_{3\ (aq)}$ was added and the aqueous layer extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and the volatiles removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 1:1) to afford inseparable diastereomeric mixtures of either alkylated ketones (*S,S,R*)-**46** and (*S,S,S*)-**46** or of alkylated ketones (*R,R,S*)-**46** and (*R,R,R*)-**46**, as a yellow oil (17 mg, 17%, 55% b.r.s.m.); ν_{max} 3418, 2929, 2861, 1730, 1716, 1449, 1409, 1365, 1306, 1282, 1226, 1166, 1101, 1074, 1042, 1018, 973, 900, 841, 806, 724. ^{1}H NMR (500 MHz, $CDCl_3$) 1.33–1.37 (1H, m, H-6), 1.48–1.54 (1H, m, H-4), 1.64–1.68 (1H, m, H-5), 1.68–1.73 (1H, m, H-7), 1.73–1.79 (1H, m, H-5), 1.81–1.86 (1H, m, H-7), 1.86–1.91 (1H, m, H-3), 1.91–1.97 (2H, m, H-4/6), 2.08–2.17 (4H, m, H-1/10), 2.26–2.31 (1H, m, H-3a), 2.44–2.51 (1H, m, H-1), 2.53–2.65 (3H, m, H-6a/8). δ_C (125 MHz, $CDCl_3$) 24.3 (C-7), 25.8 (C-5), 30.1 (C-10), 32.9 (C-4), 33.7 (C-6), 37.6 (C-6a), 41.1 (C-8), 44.1 (C-1), 46.6 (C-3a), 53.3 (C-3), 208.7 (C-9), C-2 outside range.

*4.2.28. 7a-Hydroxydecahydrocyclopenta[a]inden-6(1H)-one (S,S,R)-**47** and (R,R,S)-**47***

Compound **47** was synthesized analogously to a literature protocol [19]. A solution of either (*S,S,R*)-**46** or (*R,R,S*)-**46** (5 mg, 0.03 mmol, 1.00 equiv) in 0.4 mL Et_2O was treated with a solution of KOH (0.65 mg, 0.01 mmol, 0.40 equiv) in 0.2 mL EtOH at 0 °C and stirred for 2 h at ambient temperature. Water was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and subsequently dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 1:1) to afford either the alcohols (*S,S,R*)-**47** or the alcohols (*R,R,S*)-**47**, each as a white solid (4 mg, 80%); ν_{max} 3359, 2966, 2938, 2900, 2871, 2859, 1705, 1466, 1451, 1440, 1430, 1408, 1348, 1329, 1306, 1291, 1271, 1247, 1213, 1184, 1141, 1104, 1040, 1013, 990, 966, 936, 893, 852, 802, 758 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.31–1.37 (1H, dd, J_{HH} 12.5, 8.5 Hz, H-4), 1.37–1.47 (2H, m, H-3/10), 1.47–1.62 (5H, m, H-1/3/6/10), 1.79–1.88 (1H, m, H-1), 1.88–1.96 (1H, dd, J_{HH} 12.6, 8.2 Hz, H-4), 2.00–2.09 (1H, m, H-1), 2.12–2.19 (1H, m, H-9), 2.22 (1H, d, J_{HH} 14.3 Hz, H-7), 2.32–2.43 (3H, m, H-3a/6a/9), 2.46–2.52 (1H, d, J_{HH} 14.3 Hz, H-7), 3.09 (1H, s, OH); δ_C (125 MHz, $CDCl_3$) 24.1 (C-1), 24.8 (C-2), 32.1 (C-10), 33.3 (C-3), 36.1 (C-9), 38.6 (C-3a), 43.4 (C-6a), 47.7 (C-4), 49.3 (C-6), 49.6 (C-7), 84.2 (C-5), 212.5 (C-8); HRMS: *m/z* calcd for [M + H, $C_{12}H_{19}O_2^+$]: 195.13796 found 195.13830.

*4.2.29. 2,3,3a,3b,4,5,8,8a-Octahydrocyclopenta[a]inden-6(1H)-one (S,S,R)-**48** and (R,R,S)-**48***

A solution of either (*S,S,R*)-**47** or (*R,R,S*)-**47** (265 mg, 1.36 mmol, 1.00 equiv) in 20 mL benzene was treated with *p*TosOH·H_2O (273 mg, 1.36 mmol, 1.00 equiv) and stirred at reflux for 3 h. Et_2O and saturated $NaHCO_{3\ (aq)}$ was added and the layers were separated. The combined organic phases were washed with brine and subsequently dried over Na_2SO_4 and the volatiles were removed *in vacuo*. The remainder was purified by column chromatography (hexane/EtOAc 1:1) to give the enone (*S,S,R*)-**48** or (*R,R,S*)-**48** as yellow oils (94 mg, 39%), separated from their minor diastereoisomers (*S,S,S*)-**48** or (*R,R,R*)-**48**, also as yellow oils (39 mg, 16%); (*R,R,S*)-**48** (40% *ee*): [α] $[20]_D$ −14.0 (c 1.52, $CHCl_3$), (*S,S,R*)-48 (40% *ee*): [α] $[20]_D$ + 11.0 (c 0.34, $CHCl_3$); ν_{max} 3303, 2939, 2862, 1665, 1467, 1450, 1421, 1358, 1319, 1295, 1266, 1248, 1225, 1188, 1150, 1121, 1040, 1008, 965, 944, 919, 866, 797, 756, 692, 639, 609.

Major isomers (*S,S,R*)-**48** or (*R,R,S*)-**48**: δ_H (500 MHz, $CDCl_3$) 1.37–1.44 (1H, m, H-1), 1.54–1.63 (2H, m, H-3/10), 1.63–1.78 (4H, m, H-1/2/3), 2.10–2.17 (1H, m, H-6a), 2.19–2.30 (4H, m, H-4/6/9/10), 2.39–2.45 (1H, m, H-9), 2.53–2.62 (1H, m, H-3a), 2.67–2.76 (1H, dd, J_{HH} 8.7, 17.8 Hz, H-4), 5.79 (1H, s, H-7); δ_C (125 MHz, $CDCl_3$) 25.7 (C-2), 29.6 (C-10), 32.1 (C-3), 33.9 (C-1), 37.6 (C-9), 39.5 (C-4), 41.7 (C-3a), 47.6 (C-6), 50.3 (C-6a), 121.3 (C-7), 176.2 (C-5), 200.2 (C-8);

Minor isomers (*S,S,S*)-**48** or (*R,R,R*)-**48**: δ_H (500 MHz, $CDCl_3$) 1.10–1.17 (m, 1H, H-1), 1.28–1.36 (m, 1H, H-3), 1.43–1.52 (m, 1H, H-2), 1.52–1.60 (m, 1H, H-1), 1.60–1.69 (m, 1H, H-2), 1.69–1.78 (m, 1H, H-10), 1.90–1.98 (m, 1H, H-3), 2.00–2.08 (m, 1H, H-10), 2.08–2.18 (m, 1H, H-4), 2.24–2.34 (m, 1H, H-9), 2.39–2.47 (m, 1H, H-9), 2.51–2.59 (m, 1H, H-6a), 2.59–2.67 (m, 1H, H-3a), 2.78–2.90 (m, 2H, H-4/6), 5.88 (m, 1H, H-7); δ_C (125 MHz, $CDCl_3$) 25.8 (C10), 26.1 (C2), 27.7 (C1), 33.6 (C3), 37.4 (C9), 39.9 (C4), 41.3 (C3a), 44.8 (C6), 47.9 (C6a), 123.0 (C7), 175.5 (C5), 200.3 (C8);

HRMS: *m/z* calcd for [M + H, $C_{12}H_{17}O^+$]: 177.12739; found: 177.12768.

*4.2.30. Decahydrocyclopenta[a]inden-6(1H)-one (all-S)-**9** and (all-R)-**9***

A solution of either (*S,S,R*)-**48** or (*R,R,S*)-**48** (20 mg, 0.12 mmol, 1.00 equiv) in 5 mL EtOAc was treated with 10% Pd/C (10 mg, 0.01 mmol, 0.08 equiv) and was stirred for 2 h under a H_2-atmosphere at ambient temperature. The solids were filtered off over celite and the volatiles removed *in vacuo* to leave the target tricyclic ketones as an inseparable 4:1 mixtures of either (*all-S*)-**9**/(*S,S,S,R*)-**9** or of (*all-R*)-**9**/(*R,R,R,S*)-**9** (yellow oils in either case, 16 mg, 75%); ν_{max} 3420, 2933, 2860, 1710, 1467, 1451, 1422, 1362, 1345, 1314, 1276, 1261, 1236, 1190, 1171, 1138, 1097, 1076, 1030, 959, 941, 914, 903, 882, 841, 804, 732, 672, 647 cm^{-1}; 4:1 mixture of **9a/9b**;

Major isomers (*all-S*)-**9** or (*all-R*)-**9**: δ_H (500 MHz, $CDCl_3$) 1.20–1.34 (2H, m, H-1/3), 1.34–1.42 (1H, m, H-4), 1.42–1.51 (1H, m, H-2), 1.51–1.61 (1H, m, H-2), 1.61–1.70 (1H, m, H-4), 1.70–1.87 (4H,

m, H-1/3/6/10), 1.91–2.05 (1H, m, H-10), 2.20–2.29 (2H, m, H-7/9), 2.29–2.42 (3H, m, H-6a/7/9), 2.42–2.51 (1H, m, H-5), 2.51–2.63 (1H, m, H-3a); δ_C (125 MHz, $CDCl_3$) 26.4 (C-2), 28.5 (C-10), 33.3 (C-1/3), 34.5 (C-1/3), 38.7 (C-4), 38.8 (C-7/9), 41.4 (C-5), 41.5 (C-3a), 43.1 (C-7/9), 44.8 (C-6), 47.5 (C-6a), 213.7 (C-8);

Minor isomeres (*S,S,S,R*)-**9** or (*R,R,R,S*)-**9**: δ_H 0.81–0.87 (1H, m, H-4), 1.15–1.21 (1H, m, H-6a), 1.21–1.27 (1H, m, H-10), 1.35–1.43 (2H, m, 1/3/10), 1.44–1.63 (5H, m, H-1/2/3/3a), 1.97–2.06 (2H, m, H-4/6), 2.06–2.16 (2H, m, 7/9/10), 2.22–2.30 (1H, m, H-7/9), 2.35–2.41 (1H, m, H-7/9), 2.45–2.55 (2H, m, H-5/7/9); δ_C 25.3 (C-2), 29.6 (C-10), 31.3 (C-1/3), 33.4 (C-1/3), 40.4 (C-4), 41.3 (C-7/9), 43.3 (C-5), 47.0 (C-3a), 47.5 (C-7/9), 47.8 (C-6), 51.0 (C-6a), 212.4 (C-8);

HRMS: *m/z* calcd for [M + H, $C_{12}H_{19}O^+$]: 179.14304; found: 179.14321.

*4.2.31. Dibutylstannanediyl bis(trifluoromethanesulfonate) (**43**)*[20]

A solution of Bu_2SnCl_2 (75 mg, 0.25 mmol, 1.00 equiv) in 2.5 mL EtOH *p.a.* was treated with silver triflate (130 mg, 0.51 mmol, 2.06 equiv) and was stirred for 2 h at ambient temperature. The solids were filtered off and the volatiles removed *in vacuo* to afford the title compound as a grey solid (96 mg, 70%); ν_{max} 3335, 3216, 2969, 2938, 2878, 1645, 1467, 1421, 1384, 1276, 1231, 1212, 1187, 1089, 1016, 973, 889, 862, 771, 693 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.37 (6H, t, J_{HH} 7.1 Hz, H-1/8), 1.41 (4H, sx, J_{HH} 7.4 Hz, H-2/7), 1.73–1.81 (4H, m, H-3/6), 2.05–2.12 (4H, m, H-4/5); δ_C (125 MHz, $CDCl_3$) 13.3 (C-1/8), 25.8 (C-2/7), 26.4 (C-3/4/5/6), 119.3 (q, J_{CF} 316.6 Hz, CF_3).

Supplementary data

Supplementary data associated with this article NMR spectra can be found in the online version, at https://doi.org/10.1016/j.tet.2021.132113.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132113.

References

[1] a) J.A.V. Blodgett, D.-C. Oh, S. Cao, C.R. Currie, R. Kolter, J. Clardy, Common biosynthetic origins for polycyclic tetramate macrolactams from phylogenetically diverse bacteria, Proc. Natl. Acad. Sci. U.S.A. 107 (2010) 11692–11697;
b) M. Jiang, S. Chen, J. Li, L. Liu, The biological and chemical diversity of tetramic acid compounds from marine-derived microorganisms, Mar. Drugs 18 (2020) 114.

[2] S. Kanazawa, N. Fusetani, S. Matsunaga, Cylindramide: cytotoxic tetramic acid lactam from the marine sponge Halichondria cylindrata Tanita & Hoshino, Tetrahedron Lett. 34 (1993) 1065–1068.

[3] a) N. Cramer, M. Buchweitz, S. Laschat, W. Frey, A. Baro, D. Mathieu, C. Richter, H. Schwalbe, Total synthesis and NMR investigations of cylindramide, Chem. Eur J. 12 (2006) 2488–2503;
b) A.C. Hart, A.J. Phillips, Total synthesis of (+)-cylindramide A, J. Am. Chem. Soc. 128 (2006) 1094–1095.

[4] K. Jomon, Y. Kuroda, M. Ajisaka, H. Sakai, A new antibiotic, Ikarugamycin. *J. Antibiot.* 25 (1972) 271–280.

[5] a) R.K. Boeckman Jr., C.H. Weidner, R.B. Perni, J.J. Napier, An enantioselective and highly convergent synthesis of (+)-ikarugamycin, J. Am. Chem. Soc. 111 (1989) 8036–8037;
b) L.A. Paquette, D. Macdonald, L.G. Anderson, J. Wright, A triply convergent enantioselective total synthesis of (+)-ikarugamycin, J. Am. Chem. Soc. 111 (1989) 8037–8039;
c) W.R. Roush, C.K. Wada, Application of η^4-diene iron tricarbonyl complexes in acyclic stereocontrol: asymmetric synthesis of the as-indacene unit of ikarugamycin (a formal total synthesis), J. Am. Chem. Soc. 116 (1994) 2151–2152;
d) C. Greunke, A. Glöckle, J. Antosch, T.A.M. Gulder, Biocatalytic total synthesis of ikarugamycin, Angew. Chem. Int. Ed. 56 (2017) 4351–4355.

[6] S. Saha, W. Zhang, G. Zhang, Y. Zhu, Y. Chen, W. Liu, C. Yuan, Q. Zhang, H. Zhang, L. Zhang, W. Zhang, C. Zhang, Activation and characterization of a cryptic gene cluster reveals a cyclization cascade for polycyclic tetramate macrolactams, Chem. Sci. 8 (2017) 1607–1612.

[7] S.P. Gunasekera, M. Gunasekera, P. McCarthy Discodermide, A new bioactive macrocyclic lactam from the marine sponge *Discodermia dissoluta*, J. Org. Chem. 56 (1991) 4830–4833.

[8] Y. Hashidoko, T. Nakayama, Y. Homma, S. Tahara, Structure elucidation of xanthobaccin A, a new antibiotic produced from *Stenotrophomonasp.* Strain SB-K88, Tetrahedron Lett. 40 (1999) 2957–2960.

[9] a) P.R. Graupner, S. Thornburgh, J.T. Mathieson, E.L. Chapin, G.M. Kemmitt, J.M. Brown, C. E. Snipes Dihydromaltophilin, A novel fungicidal tetramic acid containing metabolite from *Streptomyces* sp, J. Antibiot. 50 (1997) 1014–1019;
b) F. Yu, K. Zaleta-Rivera, X. Zhu, J. Huffman, J.C. Millet, S.D. Harris, G. Yuen, X.-C. Li, L. Du, Structure and biosynthesis of heat-stable antifungal factor (HSAF), a broad-spectrum antimycotic with a novel mode of action, Antimicrob. Agents Chemother. 51 (2007) 64–72;
c) Y. Ding, Z. Li, Y. Li, C. Lu, H. Wang, Y. Shen, L. Du, HSAF-induced antifungal effects in Candida albicans through ROS-mediated apoptosis, RSC Adv. 6 (2016) 30895–30904.

[10] C.A. Vanderwerf, 2-Allylcyclohexanone, Org. Synth. 28 (1948) 8–10.

[11] C. Kuroda, S. Shimizu, J.Y. Satoh, A short-step synthesis of 14,15-dinoreudesmanolides using intramolecular cyclization of an allylsilane, Chem. Soc. Perkin Trans. 1 (1990) 519–524.

[12] a) K. Ando, Practical synthesis of Z-unsaturated esters by using a new Horner-Emmons reagent, ethyl diphenylphosphonoacetate, Tetrahedron Lett. 36 (1995) 4105–4108. K. Ando. Convenient preparations of (diphenylphosphono)acetic acid esters and the comparison of the Z-selectivities of their Horner–Wadsworth–Emmons reaction with aldehydes depending on the ester moiety, J. Org. Chem. 1999, 64, 8406-8408.

[13] P. Kumar, D.R. Jain, C^{γ}-Aminopropylene peptide nucleic acid (amp-PNA): chiral cationic PNAs with superior PNA:DNA/RNA duplex stability and cellular uptake, Tetrahedron 71 (2015) 3378–3384.

[14] D. Nunez-Villanueva, M.A. Bonache, L. Infantes, T. Garcia-Lopez, M. Martin-Martinez, R. Gonzales-Muniz, Quaternary α,α-2-oxoazepane α-amino acids: synthesis from ornithine-derived β-lactams and incorporation into model dipeptides, J. Org. Chem. 76 (2011) 6592–6603.

[15] a) J.H. Sahner, H. Sucipto, S.C. Wenzel, M. Groh, R.W. Hartmann, R. Müller, Advanced mutasynthesis studies on the natural α-pyrone antibiotic myxopyronin from *Myxococcus fulvus*, Chembiochem 16 (2015) 946–953;
b) R.K. Boeckman Jr., T.M. Kamenecka, S.G. Nelson, J.R. Pruitt, T.E. Barta, C-phosphorylation of enolates: an alternate route to complex carbonyl-activated phosphonates, Tetrahedron Lett. 23 (1991) 2581–2584.

[16] S.H. Bertz, G. Rihs, R.B. Woodward, Reaction of dimethyl sodio-3-ketoglutarate with glyoxal and substituted glyoxals: first expeditious preparation of bicyclo[3.3.0]octane-3,7-dione; synthesis and crystal structure of 5,7-dihydroxy-4-methoxycarbonyl-3-phenyl-1-indanone, Tetrahedron 38 (1982) 63–70.

[17] H. Torres-Gómez, K. Lehmkuhl, B. Frehland, C. Daniliuc, D. Schepmann, C. Ehrhardt, B. Wünsch, Stereoselective synthesis and pharmacological evaluation of [4.3.3]propellan-8-amines as analogs of adamantanamines, Bioorg. Med. Chem. 23 (2015) 4277–4285.

[18] R.P.C. Cousins, N.S. Simpkins, Chiral products via asymmetric deprotonation of 4-tert-butylcyclohexanone using chiral lithium amide bases, Tetrahedron Lett. 30 (1989) 7241–7244.

[19] T. Sato, Y. Wakahara, J. Otera, H. Nozaki, Organotin triflate as practical catalyst for Michael addition of enol silyl ethers, Tetrahedron 47 (1991) 9773–9782.

[20] C.A. Obafemi, J.A. Obaleye, M.S. Akanni, Organotin compounds. I. The synthesis of some dibutyltin and dibenzyltin azides and sulfonates, Synth. React. Inorg. Met. Org. Chem. 16 (1986) 777–793.