Tetrahedron 68 (2012) 697–704

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Influence of steric parameters on the synthesis of tetramates from α-amino-β-alkoxy-esters and Ph_3PCCO

Inga Loke [a], Natja Park [a], Karl Kempf [b], Carsten Jagusch [b], Rainer Schobert [b,*], Sabine Laschat [a,*]

[a] Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany
[b] Lehrstuhl für Organische Chemie, Universität Bayreuth, Universitätsstr. 30, D-95440 Bayreuth, Germany

ARTICLE INFO

Article history:
Received 9 September 2011
Received in revised form 25 October 2011
Accepted 27 October 2011
Available online 4 November 2011

Keywords:
Amino acids
Tetramic acids
Phosphorus ylides
Wittig olefination

ABSTRACT

α-Aminoesters react with Ph_3PCCO in a domino addition–Wittig cyclization sequence affording enantiomerically pure tetramates. In the case of β-oxo functionalized α-aminoesters, e.g., esters of serine, threonine or β-hydroxyornithine the yields of this reaction depend heavily on the bulkiness of the β-OR group and on the configuration of β-carbon atom C-3. Smaller residues and 2*R*/3*R*-configured amino-esters give better yields. The alkoxycarbonyl group of the ester moiety and the residue on the N-atom are less important. These findings can be accounted for by assuming an early puckered transition state for the intramolecular ring-closing Wittig reaction. The addition of sub-stoichiometric amounts of benzoic acid or *N*-hydroxysuccinimide (for acid-sensitive compounds) is advantageous in some cases as it accelerates the formation of the intermediate amide ylides.

1. Introduction

Tetramic acids, i.e., pyrrolidine-2,4-diones **1** are frequently found in natural products of both terrestrial and marine origin and are often associated with antibiotic, anthelminthic, cytotoxic or other sorts of biological activities. This and their challenging structures and chemistry have spawned a steadily increasing number of synthetic and biological studies over the last decade.[1] Fig. 1 depicts a few naturally occurring bioactive 3-acyltetramic acids: the marine sponge-bacteria metabolite melophlin A (**2**),[2] reutericyclin (**3**) produced by *Lactobacillus reuteri*,[3] the fungal herbicides macrocidin A (**4a**) and B (**4b**)[4] and the sponge-derived cylindramide **5**.[5] Recently, the pivotal role of tetramic acids derived from 3-oxo-*N*-acylhomoserines such as **6** for bacterial quorum sensing was uncovered and might be exploited for the development of conceptually novel antibiotics.[6]

Several routes are known for the synthesis of tetramic acids. Early protocols were developed by Lacey[7a] who cyclized under basic Dieckmann conditions *N*-(β-ketoacetyl)-α-amino esters as obtained from α-amino acids and diketene, and by Jouin et al.[7b] who gained tetramic acids or directly 3-acyltetramic acids from reaction of amino acids with Meldrum's acid. More recent approaches to enantiopure tetramic acids include the Ugi–Dieckmann reaction of isocyanides,[8] the Dieckmann cyclization of *N*-acyloxazolidines,[9] the domino amide formation/Dieckmann condensation,[10] the palladium-catalyzed α-arylation of pre-formed tetramic acids,[11] the transannular rearrangement of diketopiperazines,[12] the condensation of amino acid

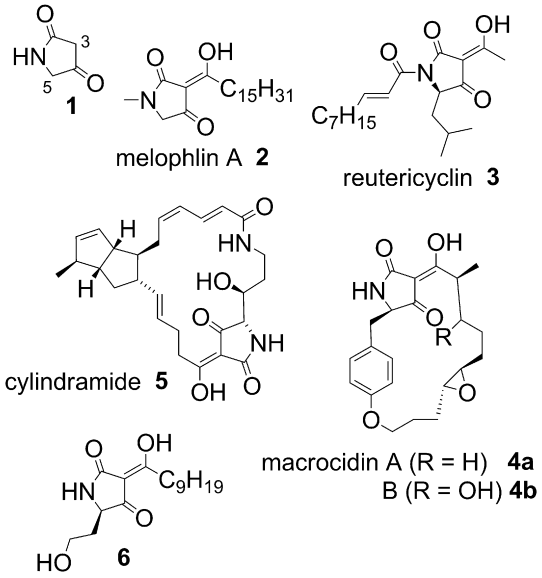


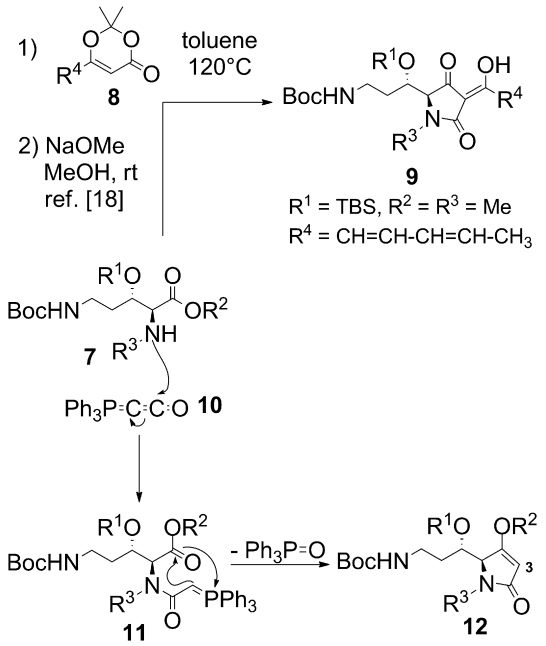
Fig. 1. Tetramic acid natural products.

* Corresponding authors. Tel.: +49 921 552680; fax: +49 921 552671 (R.S.); tel.: +49 711 685 64565; fax: +49 711 685 64285 (S.L.); e-mail addresses: rainer.schobert@uni-bayreuth.de(R. Schobert), sabine.laschat@oc.uni-stuttgart.de (S. Laschat).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.10.099

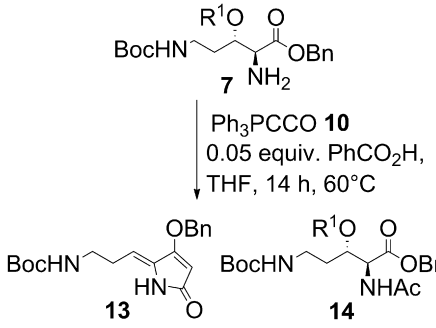
derivatives with malonates[13] or diketene[14] followed by Dieckmann condensation and the ring expansion of 2-azetidinone-tethered allenols.[15] More pertinent to the target compounds of the current paper are studies towards Dysidin, which also encompass an access to 5-(1-alkoxy)alkyltetramic acids.[16] Also, Hunter and Thomson reported the preparation of 5-(α-hydroxyalkyl)tetramic acids using a trimethylsilyl mediated aldol reaction of pyrrolinone with an aldehyde.[17] Finally, Yoda et al.[18] disclosed a synthetic route to such systems by condensation of threonine derivatives with Meldrum's acid.

Based on our previous experience with the efficient synthesis of tetramates from α-aminoesters and the cumulated phosphorus ylide triphenylphosphoranylideneketene, Ph_3PCCO **10**,[3e,19–21] we planned to extend this methodology to tetramic acids derived from β-hydroxyornithine, which are subunits of naturally occurring macrocyclic lactams such as cylindramide **5** or aburatubolactam.[22] So far, 3-acyl-5-(1-alkoxy)alkyltetramic acids have been built up mostly by the Lacey–Dieckmann condensation utilizing α-aminoesters and Meldrum's acid as exemplified for compound **9** (Scheme 1). We expected the reaction of β-oxo functionalized α-aminoesters **7** with ylide **10** to give the corresponding tetramates **12** by the usual domino sequence of amine addition to the C=C bond of **10** followed by an intramolecular Wittig olefination of the intermediate amide ylide **11**. The tetramates can be converted to the tetramic acids, which, in turn, are amenable to acylation at C-3 by any of the established methods.



Scheme 1.

In preliminary experiments *O*-TBS protected 3-hydroxyornithine benzyl ester **7a** was treated with **10** in the presence of 0.05 equiv of benzoic acid in THF (Scheme 2). The addition of benzoic acid had been previously found to accelerate the first step of the domino process, the addition of the amino group onto the C=C bond of ylide **10**.[3e] However, in the case of **7a** no product tetramate **12a** was formed. Instead, the *N*-acetylated hydroxyornithine ester **14a** could be isolated in 29% after column chromatography, presumably arising from hydrolysis of the intermediate amide ylide **11**. When the *O*-TIPS- and *O*-TES protected hydroxyornithinates **7b** and **7c** were reacted under similar conditions, the amount of *N*-acetamide **14b** and **14c** dropped to 6% and 7%, respectively, and 25% or 24% of the dehydration product **13** were obtained. These findings demonstrate a distinct influence of the protecting group on the β-oxygen atom on the readiness of the cyclising olefination step and thus on the likelihood of competing processes such as elimination of the corresponding silanol to give 5-*exo*-alkylidenetetramates, or even hydrolysis of the intermediate amide ylides **11**. Therefore, we investigated the β-substituent effect in cyclizations of various amino esters with ylide **10** in more detail.

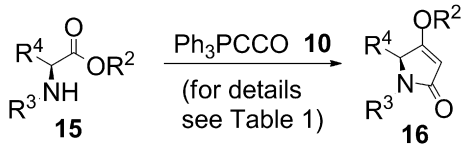


7	R^1	13 Yield [%]	14	Yield [%]
a	TBS	0	**a**	29
b	TIPS	25	**b**	6
c	TES	24	**c**	7

Scheme 2.

2. Results and discussion

α-Aminoesters **15** with residues of varying bulkiness on the carboxylate (R^2), the N-atom (R^3) and the α-C-atom (R^4), were reacted with ylide **10** under different conditions. Variations in R^4 comprised β-alkoxy- and β-silyloxy substituted ones (Scheme 3, Table 1). For comparison entries 1–5 and 8,9 were taken from literature and included.[3e,20] The glycine and alanine esters **15a–d** afforded the respective tetramates **16a–d** in good to excellent yields (entries 1–4), regardless of reaction conditions and of the bulkiness of the residues R^2 (Me, *t*-Bu or Bn) and R^3 (H or Me). In contrast, α-aminoesters **15e–i** with sterically encumbered β-carbon atoms prepared from leucine, isoleucine, valine, phenylalanine or tyrosine esters when reacted with **10** gave the corresponding tetramates **16e–i** in merely moderate to fair yields (entries 5–9). The analogous reactions of benzyl β-*t*-BuO- and β-*O*-silyl-substituted serinates furnished the product tetramates **16j–m** in yields ranging from 15% to ca. 50% with the *O*-*t*-Bu-protected benzyl ester **15j** giving the best result (entries 10–13). In the case of the benzyl serinate **15m** O-protected with an acid labile TES group, the reaction with ylide **10** in THF in the presence of 0.2 equiv benzoic acid (method A) afforded only 15% of product **16m** alongside 22% of the corresponding elimination product **16x**, benzyl 5-methylidenetetramate and 2% of the starting amino ester, while 28% of **16m** alongside 41% of elimination product **16x** and 7% of the amino ester were obtained in toluene in the absence of benzoic acid (entry 14, method C). However, for less sensitive O-protecting groups the addition of benzoic acid is advisable since accelerating the amide ylide formation and thus the overall reaction. Alongside the desired tetramates and the corresponding elimination products no other products could be isolated.

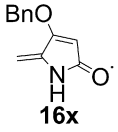


Scheme 3.

Table 1
Conversion of α-aminoesters **15** to tetramates **16**[a]

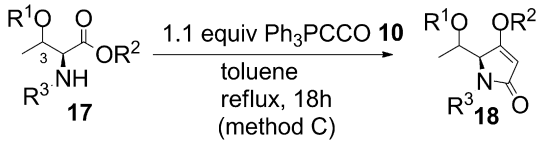
Entry	15	R^2	R^3	R^4	Method	16	Yield (%)
1	**a**	Bn	H	H	A	**a**	83[b]
2	**b**	*t*-Bu	Me	H	B	**b**	92[b]
3	**c**	Me	H	Me	B	**c**	84[b]
4	**d**	*t*-Bu	Me	Me	B	**d**	96[b]
5	**e**	Bn	H	*i*-Bu	C	**e**	45[b]
6	**f**	Bn	H	*i*-Pr	A	**f**	45
7	**g**	Me	Me	*s*-Bu	A	**g**	60
8	**h**	Bn	H	Bn	A	**h**	52[b]
9	**i**	allyl	H	4-HO-$C_6H_4CH_2$	A	**i**	40[b]
10	**j**	Bn	H	CH_2O*t*-Bu	A	**j**	47
11	**k**	Bn	H	CH_2OTIPS	A	**k**	38
12	**l**	Bn	H	CH_2OTBS	A	**l**	20
13	**m**	Bn	H	CH_2OTES	A	**m**	15[c]
14	**m**	Bn	H	CH_2OTES	C	**m**	28[c]

[a] Reaction conditions: method A: 1.1 equiv **10**, 0.2 equiv $PhCO_2H$, THF, reflux, 18 h; method B: 1.0 equiv **10**, 0.2 equiv $PhCO_2H$, toluene, reflux, 18 h; method C: 1.1 equiv **10**, toluene, reflux, 18 h.
[b] Data are taken from Ref. 3e,20.
[c] Alongside elimination product **16x**



16x

Next, a series of threonine derivatives **17** was submitted to the domino addition–Wittig cyclization reaction with ylide **10** under the optimised conditions of method C to give the *O*-protected tetramates **18** (Scheme 4, Table 2). Whereas benzyl β-*t*-BuO threoninate **17a** afforded 59% of **18a**, the yield decreased to 34% for the β-*O*-benzyl threoninates **17b**. The similarity of the yields of **18b** and **18c** shows that the size of the residue R^2 is less important. For the benzyl β-OTIPS threoninate **17d** employing a slight excess of **10**, tetramate **18d** was obtained in 46% yield.

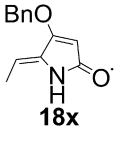


Scheme 4.

Table 2
Conversion of threonine esters **17** to *O*-protected tetramates **18**[a]

Entry	17	Configuration at C-3	R^1	R^2	R^3	Method	18	Yield (%)
1	**a**	(*R*)	*t*-Bu	Bn	H	C	**a**	59
2	**b**	(*R*)	Bn	Bn	H	C	**b**	34
3	**c**	(*R*)	Bn	Me	Me	C	**c**	38
4	**d**	(*R*)	TIPS	Bn	H	C	**d**	46[b]
5	**e**	(*R*)	TIPS	Bn	Me	C	**e**	55
6	**f**	(*R*)	TES	Bn	H	C	**f**	39
7	**g**	(*R*)	Me	Bn	H	C	**g**	82
8	**h**	(*S*)	Me	Bn	H	C	**h**	8
9	**i**	(*S*)	TIPS	Bn	H	C	**i**	17
10	**j**	(*S*)	TES	Bn	H	C	**j**	13

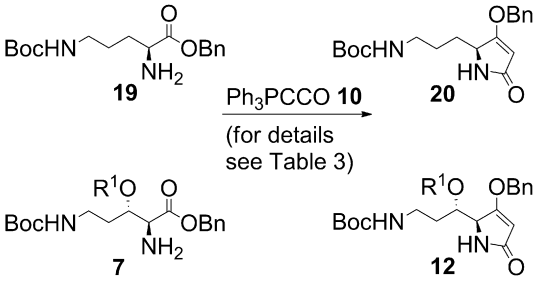
[a] Reaction conditions: method C: 1.1 equiv **10**, toluene, reflux, 18 h.
[b] Alongside elimination product **18x**



18x

Further experiments showed that the addition of benzoic acid led to elimination only upon heating in toluene but not in THF, yet did not increase the yields. In case of β-OTIPS threoninate an increase in yield of **18d** to 63% with virtually complete consumption of starting ester **17d** was achieved when 0.1 equiv of *N*-hydroxysuccinimide (NHS) was added and the reaction was carried out in refluxing toluene. In contrast, the same reaction with 0.3 equiv of NHS and 0.1 equiv of *N*,*N*-dimethylaminopyridine added afforded 50% of **18d** aside 33% of residual **17d**. For residues R^1 other than TIPS the addition of NHS failed to produce higher yields of the corresponding tetramates. Interestingly, the addition of up to 0.3 equiv of HOBt, also customarily used to generate 'active esters', gave mainly elimination product **18x** and very little tetramate **18d** when reacted in toluene, presumably due to the reluctance of the 'active ester ylide' formed by reaction of ylide **10** with HOBt to react with the aminoester **17d**. When set in THF and with 0.3 equiv of HOBt added, the reaction afforded 44% of the desired product **18d** as well as 46% of residual **17d**. The presence of a methyl group at the N-atom as in **17e** (entry 5) makes little difference in terms of yields and reactivity, nor does exchanging the TIPS for a TES group as in **17f** (entry 6). While the threoninate **17g** bearing a small β-methoxy group, which is also a poor leaving group gave rise to 82% of product tetramate **18g**, the corresponding 3*S*-diastereoisomer ('*allo*-threoninate') **17h** gave a miserable 8% of tetramate **18h**. Interestingly, a similar discrepancy was found for the yields of the 3*R*- and 3*S*-configured benzyl tetramates bearing bigger TIPS- or TES-residues R^1, i.e., for the couples **18d**/**i** and **18f**/**j**. As a rule, the 3*S*-configured isomers having the substituents at C-2/C-3 in *anti*-configuration gave distinctly lower yields.

Finally, ornithine derivative **19** and ylide **10** were reacted under standard conditions (methods B or C) to leave the tetramate **20** in 77% and 63% yield, respectively. This shows that the length of the side chain at C-3 is not crucial (Scheme 5, Table 3, entries 1 and 2). Based on these results, β-hydroxy ornithinates **7** were once more reacted with **10** (Scheme 5, Table 3, entries 3–5). As expected, in the absence of benzoic acid (method C) the tetramates **12b**–**d** were obtained in yields ranging from 13% to 27% and no elimination product was formed. This confirms that a bulky β-group in the α-aminoester is detrimental to the yield of the corresponding product tetramate especially for an *anti*-configuration of C-2/C-3 and large groups R^1 such as benzyl, e.g., in **7d**.



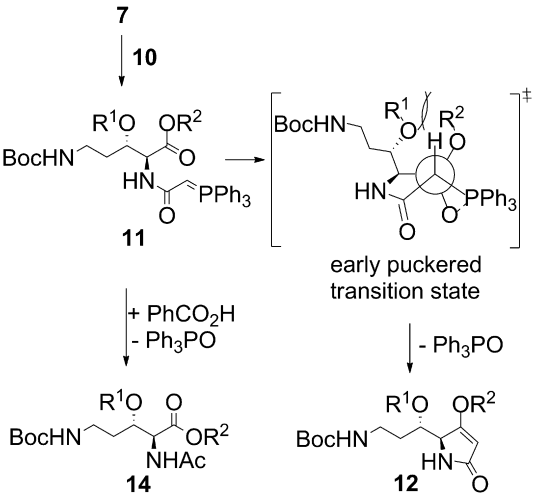
Scheme 5.

Table 3
Tetramates **20** and **12** from ornithine esters **19** and **7**[a]

Entry	Ester	R^1	Method	Tetramate	Yield (%)
1	**19**	—	C	**20**	63
2	**19**	—	B	**20**	77
3	**7b**[b]	TIPS	C	**12b**[b]	27
4	**7c**	TES	C	**12c**	19
5	**7d**	Bn	C	**12d**	13[c]

[a] Reaction conditions: method B: 1.0 equiv **10**, 0.2 equiv $PhCO_2H$, toluene, reflux, 18 h; method C: 1.1 equiv **10**, toluene, reflux, 18 h.
[b] A diastereomeric mixture of 2:1.
[c] In addition 17% of the *N*-acetamide **14d** was isolated.

The above results suggest that the intramolecular Wittig olefination of the intermediate amide ylide **11** proceeds via an early, puckered, reactant-like transition state in which the repulsion between the PPh_3 group and the largest residue on the carbonyl carbon atom, i.e., C-2, is decisive for the geometry.[23] In this case, the residues OR^1 and OR^2 get close to each other and the rotatability around the C2–C3 bond is restricted. Such a sterically congested transition state should occur whenever C-3 bears a bulky group OR^1 and is *S*-configured (Scheme 6). It should thus lead to low yields of product tetramates **12**. This mechanistic rationale also rules out the involvement of stabilising hydrogen bridges C2–N–H–OR^1 between the alkoxy residue OR^1 and the amide nitrogen. This is in line with the finding that otherwise identical tetramates differing only in N–Me versus N–H substitution such as **18b**/**c** or **18d**/**e** (Table 2) were obtained in similar yields.



Scheme 6.

The mechanism also explains the conservation of the stereogenic centres at C-2/C-3 as ascertained by NMR spectroscopy. Since no more than one stereoisomer were observed and a simultaneous inversion of both centres C-2 and C-3 can be excluded the reaction is assumed to proceed stereoselectively.

3. Conclusion

We have studied the domino addition–Wittig cyclization reaction between the cumulated phosphorus ylide Ph_3PCCO (**10**) and a series of α-aminoesters with different substituents in the β-position. Sterically bulky or large alkoxy or silyloxy residues at the β-carbon atom C-3 give rise to relatively low chemical yields, especially if C-3 is *S*-configured. Smaller residues give fair to good yields. The ester alkoxycarbonyl group and the residue on the N-atom are of little influence. We assume an early, puckered, reactant-like transition state for the intramolecular ring-closing Wittig reaction step. In this case the repulsion between the large groups PPh_3 and C-2 is decisive for the transition state geometry. Although the customary addition of benzoic acid to the reaction of ylide **10** with aminoesters accelerates the initial addition step leading to the respective intermediate amide ylides, it can be replaced in some cases by *N*-hydroxysuccinimide. This allows the use of 'small' acid-sensitive protecting groups such as OTIPS at C-3 of the starting α-aminoesters. Their reaction with ylide **10** gives rise to good yields of the respective enantiomerically pure tetramates. These empirical rules should now enable us to employ this tetramate synthesis for the construction of more complex macrocyclic derivatives of the cylindramide type.

4. Experimental

4.1. General

Melting points (uncorrected) were determined on a Büchi 510 melting point apparatus. Optical rotations were determined with a Perkin–Elmer 241 LC polarimeter. IR spectra: Bruker Vektor 22 FT-IR spectrometer/PerkinElmer Spectrum 100 ATR. Mass spectra: Finnigan MAT 95, Varian MAT 711 and Bruker Daltonics micrOTOF_Q spectrometers. NMR spectra: Bruker ARX 300 and Bruker ARX 500 spectrometers. The spectra were recorded with TMS as an internal standard. ^{13}C NMR multiplicities were determined by DEPT135 experiments. Signals with * denote the minor diastereomer. Assignments were done by using ^1H–^1H-COSY, ^1H–^{13}C-correlation and NOESY experiments. Column chromatography: Fluka silica gel 60 (40–63 μm). All syntheses were performed under nitrogen or argon using standard Schlenk technique.

4.2. Synthesis and characterization

4.2.1. General procedure. The α-aminoester was dissolved in the indicated solvent and the additives (Ph_3PCCO **10**, $PhCO_2H$) were added. The solution was stirred under the given conditions. After cooling to rt the solvent was evaporated and the crude product was purified.

*4.2.2. tert-Butyl ((S)-3-((S)-3-(benzyloxy)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-3-((triisopropylsilyl)oxy)propyl)carbamate (**12b**).* From **7b** [18.0 mg, 36.8 μmol, diastereomeric mixture of 2:1 (see Supplementary data)]; solvent: toluene (3 mL), additives: Ph_3PCCO **10** (1.1 equiv); conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **12b** (5.00 mg, 9.91 μmol, 27%) with a diastereomeric ratio of 2:1. R_f=0.70 (EtOAc). $[\alpha]_D^{20}$=−34.7 (*c* 1.00, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ=0.95–1.11 [m, 42H, $CH(CH_3)_2$, $CH(CH_3)_2^*$], 1.42 [s, 18H, $C(CH_3)_3$, $C(CH_3)_3^*$], 1.52–1.61 (m, 4H, 2′-H, 2′-H*), 3.06–3.26 (m, 4H, 3′-H, 3′-H*), 4.15–4.20 (m, 1H, 1′-H), 4.24–4.28 (m, 1H, 1′-H*), 4.30 (d, *J*=3.2 Hz, 1H, 5-H), 4.36 (d, *J*=3.2 Hz, 1H, 5-H*), 4.52 (br, NH, NH*), 4.93–5.03 (m, 4H, CH_2Ph, CH_2Ph^*), 5.106 (s, 1H, 3-H), 5.114 (s, 1H, 3-H*), 5.55 (s, 1H, 1-H), 5.56 (s, 1H, 1-H*), 7.32–7.44 (m, 10H, Ar, Ar*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.6, 12.8 [$CH(CH_3)_2$, $CH(CH_3)_2^*$], 17.71, 17.74, 18.1 [$CH(CH_3)_2$, $CH(CH_3)_2^*$], 28.4 [$C(CH_3)_3$, $C(CH_3)_3^*$], 30.6 (C-2′, C-2′*), 37.7 (C-3′, C-3′*), 62.8 (C-5), 62.9 (C-5*), 70.5 (C-1′, C-1′*), 73.4 (CH_2Ph, CH_2Ph^*), 79.1 [$C(CH_3)_3$, $C(CH_3)_3^*$], 96.31 (C-3), 96.33 (C-3*), 127.92, 127.94, 128.8, 128.9 (*o*-C, *m*-C, *p*-C, *o*-C*, *m*-C*, *p*-C*), 134.5 (*i*-C, *i*-C*), 155.7 (NHCOO, NHCOO*), 173.4 (C-4, C-4*), 174.0 (C-2, C-2*) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3270, 2927, 2866, 1690, 1620, 1500, 1456, 1365, 1337, 1250, 1173, 1104, 1012, 882, 806, 738, 697. MS (ESI): *m*/*z*=541.3 $[M+Na]^+$, 519.3 $[M+H]^+$, 463.3 $[M+H-C_4H_9]^+$, 419.3 $[M+H-C_5H_9O_2]^+$, 395.7, 360.9, 285.2, 245.1, 176.3, 154.4. HRMS (ESI): calcd for $C_{28}H_{47}N_2O_5Si^+$ 519.3249, found 519.3260 $[M+H]^+$.

*4.2.3. tert-Butyl ((S)-3-((S)-3-(benzyloxy)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-3-((triethylsilyl)oxy)propyl)carbamate (**12c**).* From **7c** (46.0 mg, 102 μmol); solvent: toluene (8 mL); additives: Ph_3PCCO **10** (1.1 equiv); conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **12c** (10.1 mg, 19.0 μmol, 19%). R_f=0.47 (EtOAc). $[\alpha]_D^{20}$=−13.7 (*c* 1.00, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ=0.66 (q, *J*=7.9 Hz, 6H, CH_2CH_3), 0.96 (t, *J*=7.9 Hz, 9H, CH_2CH_3), 1.33–1.41 (m, 1H, 2′-H_a), 1.43 [s, 9H, $C(CH_3)_3$], 1.52–1.63 (m, 1H, 2′-H_b), 3.05–3.14 (m, 1H, 3′-H_a), 3.15–3.25 (m, 1H, 3′-H_b), 4.07–4.11 (m, 1H, 1′-H), 4.24 (d, *J*=3.2 Hz, 1H, 5-H), 4.58 (br, 1H, NH), 4.93–5.02 (m, 2H, CH_2Ph), 5.10 (s, 1H, 3-H), 5.66 (s, 1H, 1-H), 7.33–7.43 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=4.8 (CH_2CH_3), 6.8 (CH_2CH_3), 28.4 [$C(CH_3)_3$], 30.1 (C-2′), 37.7 (C-3′),

62.7 (C-5), 70.4 (C-1′), 73.4 (*C*H$_2$Ph), 79.1 [*C*(CH$_3$)$_3$], 96.3 (C-3), 128.5, 128.6 (*o*-C, *m*-C), 128.8 (*p*-C), 134.5 (*i*-C), 155.8 (NHCOO), 173.4 (C-4), 174.1 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3264, 2956, 2876, 1687, 1620, 1526, 1437, 1365, 1335, 1249, 1179, 1118, 1000, 807, 720, 694. MS (ESI): *m*/*z*=477.3 [M+H]$^+$, 453.3, 421.2, 279.1, 245.1. HRMS (ESI): calcd for $C_{25}H_{41}N_2O_5Si^+$ 477.2779, found 477.2792 [M+H]$^+$.

*4.2.4. tert-Butyl ((S)-3-(benzyloxy)-3-((S)-3-(benzyloxy)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)propyl)carbamate (**12d**).* From **7d** (71.0 mg, 166 μmol); solvent: toluene (10 mL); additives: Ph$_3$PCCO **10** (1.1 equiv); conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **12d** (10.0 mg, 22.0 μmol, 13%) and the byproduct **14d** (13.0 mg, 28.0 μmol, 17%). R_f=0.39 (EtOAc). $[\alpha]_D^{20}$=−51.2 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.34–1.40 (m, 1H, 2′-H$_a$), 1.41 [s, 9H, C(CH$_3$)$_3$], 1.60–1.69 (m, 1H, 2′-H$_b$), 3.09–3.26 (m, 2H, 3′-H), 3.82 (ddd, *J*=9.9, 2.9, 2.9 Hz, 1′-H), 4.49 (d, *J*=2.9 Hz, 1H, 5-H), 4.52–4.66 (m, 2H, OCH$_2$Ph), 4.93–5.01 (m, 2H, COOCH$_2$Ph), 5.12 (s, 1H, 3-H), 5.72 (s, 1H, 1-H), 7.29–7.43 (m, 10H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=28.3 (C-2′), 28.4 [C(*C*H$_3$)$_3$], 37.5 (C-3′), 58.9 (C-5), 72.2 (OCH$_2$Ph), 73.5 (COO*C*H$_2$Ph), 76.7 (C-1′), 79.1 [*C*(CH$_3$)$_3$], 96.3 (C-3), 128.0, 128.1, 128.2 (*o*-C, *m*-C, *p*-C COOCH$_2$*Ph*), 128.7, 128.85, 128.93 (*o*-C, *m*-C, *p*-C OCH$_2$*Ph*), 134.4 (*i*-C COOCH$_2$*Ph*), 137.5 (*i*-C OCH$_2$*Ph*), 155.9 (NHCOO), 173.3 (C-4), 174.0 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3280, 2929, 1965, 1682, 1617, 1499, 1455, 1365, 1335, 1251, 1168, 1097, 976, 911, 807, 733, 697. MS (ESI): *m*/*z*=453.0 [M+H]$^+$, 245.1, 228.1, 216.1, 129.4, 91.1 [C$_7$H$_7$]$^+$. HRMS (ESI): calcd for $C_{26}H_{32}N_2O_5Na^+$ 475.2203, found 475.2218 [M+Na]$^+$.

*4.2.5. (Z)-tert-Butyl 2-(3-(benzyloxy)-5-oxo-1H-pyrrol-2(5H)ylidene) ethylcarbamate (**13**).* From **7b** (90.0 mg, 0.18 mmol); solvent: THF (1.5 mL), additives: Ph$_3$PCCO **10** (1.0 equiv), PhCO$_2$H (0.02 equiv), conditions: 60 °C for 18 h; purification: flash chromatography (hexane/EtOAc 1:4). Products: **13** (15.6 mg, 45.0 μmol, 25%) and **14b** (6.00 mg, 10.9 μmol, 6%).

From **7c** (90.0 mg, 0.20 mmol); solvent: THF (1.5 mL), additives: Ph$_3$PCCO **10** (1.0 equiv), PhCO$_2$H (0.02 equiv), conditions: 60 °C for 18 h, purification: flash chromatography (hexane/EtOAc 1:3). Products: crude **13** (16.6 mg, 48.0 μmol, 24%) and **14c** (7.00 mg, 14.0 μmol, 7%). R_f=0.62 (hexane/EtOAc 4:1, UV). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.43 [s, 9H, C(CH$_3$)$_3$], 2.35–2.46 (m, 2H, 2′-H), 3.22–3.29 (m, 2H, 3′-H), 4.89 (br, 1H, NH), 5.01 (s, 2H, C*H*$_2$Ph), 5.18 (s, 1H, 3-H), 5.47 (t, *J*=8.3 Hz, 1H, 1′-H), 7.24 (br, 1H, NH), 7.34–7.42 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=28.4 [C(*C*H$_3$)$_3$], 28.7 (C-2′), 39.7 (C-3′), 73.4 (*C*H$_2$Ph), 79.2 [*C*(CH$_3$)$_3$], 94.6 (C-3), 106.6 (C-1′), 128.4, 128.6, 128.7 (*o*-C, *m*-C, *p*-C), 134.8 (*i*-C), 156.1 (C-4), 164.7 (C-5), 168.7 (NHCOO), 171.9 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3353, 2939, 2927, 2361, 1678, 1596, 1509, 1455, 1366, 1250, 1214, 1166, 983, 750, 697, 667. MS (ESI): *m*/*z*=711.3 [2M+Na]$^+$, 689.4 [2M+H]$^+$, 367.2 [M+Na]$^+$, 345.2 [M+H]$^+$, 307.1, 263.2.

*4.2.6. (2S,3S)-Benzyl 2-acetamido-5-(tert-butoxycarbonylamino)-3-[tert-butyl(dimethyl)silyloxy]pentanoate (**14a**).* From **7a** (45.0 mg, 0.10 mmol); solvent: THF (0.35 mL), additives: Ph$_3$PCCO **10** (1.0 equiv), PhCO$_2$H (0.02 equiv), conditions: 60 °C for 14 h, purification: flash chromatography (hexane/EtOAc 1:1). Product: **14a** (13.0 mg, 30.0 μmol, 29%). R_f=0.65 (hexane/EtOAc 1:1, UV). $[\alpha]_D^{20}$=−4.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.10 [s, 3H, Si(CH$_3$)$_2$], 0.11 [s, 3H, Si(CH$_3$)$_2$], 0.81 [s, 9H, SiC(CH$_3$)$_3$], 1.41 [s, 9H, C(CH$_3$)$_3$], 1.72–1.83 (m, 2H, 4-H), 2.10 (s, 3H, COCH$_3$), 3.06–3.14 (m, 1H, 5-H$_a$), 3.21–3.30 (m, 1H, 5-H$_b$), 3.95–4.02 (m, 1H, 3-H), 4.61 (dd, *J*=7.6, 2.3 Hz, 1H, 2-H), 4.87 (br, 1H, N*H*), 5.16 (d, *J*=11.9 Hz, 1H, C*H*$_2$Ph), 5.18 (d, *J*=11.9 Hz, 1H, C*H*$_2$Ph), 7.33–7.38 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=−4.7 [Si(CH$_3$)$_2$], −4.6 [Si(CH$_3$)$_2$], 17.9 [Si*C*(CH$_3$)$_3$], 23.2 (CO*C*H$_3$), 25.7 [SiC(*C*H$_3$)$_3$], 28.4 [C(*C*H$_3$)$_3$], 34.4 (C-4), 37.4 (C-5), 56.8 (C-2), 67.4 (*C*H$_2$Ph), 72.4 (C-3), 79.1 [*C*(CH$_3$)$_3$], 128.4, 128.5, 128.7 (*o*-C, *m*-C, *p*-C), 135.1 (*i*-C), 155.9 (NH*C*OO), 169.5 (C-1), 169.7 (*C*OCH$_3$) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3327, 2997, 2938, 2928, 2361, 1757, 1715, 1667, 1514, 1388, 1366, 1251, 1214, 1172, 1082, 1003, 837, 748, 698, 668, 533. MS (ESI): *m*/*z*=517.3 [M+Na]$^+$, 495.3 [M+H]$^+$, 403.2, 381.2, 325.1, 307.3, 281.1. HRMS (ESI, [MH]$^+$) calcd for $C_{25}H_{42}N_2O_6Si^+$ 495.2885, found 495.2879.

*4.2.7. (2S,3S)-Benzyl 2-acetamido-5-(tert-butoxycarbonylamino)-3-[triisopropylsilyloxy]pentanoate (**14b**).* R_f=0.79 (hexane/EtOAc 1:1, UV). $[\alpha]_D^{20}$=−5.8 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98–1.06 {m, 21H, Si[CH(CH$_3$)$_2$]$_3$}, 1.43 [s, 9H, C(CH$_3$)$_3$], 1.72–1.83 (m, 1H, 4-H$_a$), 1.85–1.97 (m, 1H, 4-H$_b$), 2.05 (s, 3H, COCH$_3$), 3.05–3.15 (m, 1H, 5-H$_a$), 3.34–3.46 (m, 1H, 5-H$_b$), 4.16–4.22 (m, 1H, 3-H), 4.64 (d, *J*=7.6 Hz, 1H, 2-H), 5.16 (d, *J*=11.9 Hz, 1H, C*H*$_2$Ph), 5.18 (d, *J*=11.9 Hz, 1H, C*H*$_2$Ph), 5.29 (br, 1H, N*H*), 6.64 (br, 1H, N*H*), 7.33–7.38 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.2 {Si[*C*H(CH$_3$)$_2$]$_3$}, 17.7 {Si[CH(*C*H$_3$)$_2$]$_3$}, 23.1 (CO*C*H$_3$), 28.4 [C(*C*H$_3$)$_3$], 31.9 {Si[CH(CH$_3$)$_2$]$_3$}, 34.7 (C-4), 37.2 (C-5), 65.4 (C-2), 67.4 (*C*H$_2$Ph), 73.0 (C-3), 79.0 [*C*(CH$_3$)$_3$], 128.4, 128.5, 128.7 (*o*-C, *m*-C, *p*-C), 135.1 (*i*-C), 156.0 (NH*C*OO), 169.4 (C-1), 169.9 (*C*OCH$_3$) ppm. FT-IR (ATR): ν_{max}/cm^{-1}=3327, 2997, 2938, 2927, 2362, 1678, 1596, 1509, 1455, 1366, 1250, 1214, 1166, 983, 750, 698, 667. MS (ESI): *m*/*z*=559.3 [M+Na]$^+$, 503.3, 459.3, 351.2, 285.1. HRMS (ESI, [MNa]$^+$): calcd for $C_{28}H_{48}N_2O_6SiNa^+$ 559.3174, found 559.3171.

*4.2.8. (2S,3S)-Benzyl 2-acetamido-5-(tert-butoxycarbonylamino)-3-[triethylsilyloxy]pentanoate (**14c**).* R_f=0.76 (hexane/EtOAc 1:1, UV). $[\alpha]_D^{20}$=−5.2 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.52–0.67 [m, 6H, Si(C*H*$_2$CH$_3$)$_3$], 0.83–0.99 [m, 9H, Si(CH$_2$C*H*$_3$)$_3$], 1.41 [s, 9H, C(CH$_3$)$_3$], 1.69–1.85 (m, 2H, 4-H), 2.00 (s, 3H, COCH$_3$), 3.03–3.19 (m, 1H, 5-H$_a$), 3.21–3.32 (m, 1H, 5-H$_b$), 4.00–4.13 (m, 1H, 3-H), 4.62 (dd, *J*=7.1, 2.3 Hz, 1H, 2-H), 4.93 (br, 1H, N*H*), 5.16 (d, *J*=11.9 Hz, 1H, C*H*$_2$Ph), 5.18 (d, *J*=11.9 Hz, 1H, C*H*$_2$Ph), 7.31–7.39 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=4.1 (SiCH$_2$CH$_3$), 5.2 (SiCH$_2$CH$_3$), 23.2 (COCH$_3$), 28.4 [C(*C*H$_3$)$_3$], 34.4 (C-4), 37.4 (C-5), 65.3 (C-2), 67.4 (CH$_2$Ph), 72.9 (C-3), 79.1 [*C*(CH$_3$)$_3$], 128.4, 128.5, 128.7 (*o*-C, *m*-C, *p*-C), 135.1 (*i*-C), 155.9 (NH*C*OO), 169.5 (C-1), 169.7 (*C*OCH$_3$) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3347, 2923, 2853, 2362, 1694, 1513, 1455, 1366, 1251, 1214, 1170, 745, 696. MS (ESI): *m*/*z*=517.3 [M+Na]$^+$, 495.3 [M+H]$^+$, 411.2, 279.1, 204.1. HRMS (ESI, [MNa]$^+$): calcd for $C_{25}H_{42}N_2O_6SiNa^+$ 517.2704, found 517.2708.

*4.2.9. (2S,3S)-Benzyl 2-acetamido-3-(benzyloxy)-5-((tert-butoxycarbonyl)amino)pentanoate (**14d**).* R_f=0.72 (EtOAc). $[\alpha]_D^{20}$=−2.00 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.43 [s, 9H, C(CH$_3$)$_3$], 1.52–1.68 (m, 1H, 4-H$_a$), 1.68–1.82 (m, 1H, 4-H$_b$), 1.97 (s, 3H, CH$_3$), 3.05–3.30 (m, 2H, 5-H), 3.76–3.84 (m, 1H, 3-H), 4.47–4.63 (m, 2H, OCH$_2$Ph), 4.67 (br, 1H, NHCOO), 4.93–5.04 (m, 1H, 2-H), 5.09–5.28 (m, 2H, COOCH$_2$Ph), 6.17 (d, *J*=7.1 Hz, CONH), 7.28–7.41 (m, 10H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=23.2 (CH$_3$), 28.4 [C(*C*H$_3$)$_3$], 30.9 (C-4), 37.5 (C-5), 54.2 (C-3), 67.5 (COO*C*H$_2$Ph), 72.1 (OCH$_2$Ph), 77.5 (C-2), 79.2 [*C*(CH$_3$)$_3$], 128.1, 128.5, 128.57, 128.6, 128.7 (*o*-C, *m*-C, *p*-C), 135.1 (*i*-C COOCH$_2$Ph), 137.6 (*i*-C OCH$_2$Ph), 159.2 (NHCOO), 169.99 (C-1), 170.02 (NHCO) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3312, 2976, 1966, 1667, 1506, 1455, 1366, 1250, 1168, 1101, 1056, 909, 804, 728, 696. MS (ESI): *m*/*z*=471.0 [M+H]$^+$, 415.2, 371.2, 353.2, 307.1, 263.1, 245.1, 204.1, 186.1, 155.1, 113.1, 91.1 [C$_7$H$_7$]$^+$. HRMS (ESI): calcd for $C_{26}H_{34}N_2O_6Na^+$ 493.2309, found 493.2315 [M+Na]$^+$.

*4.2.10. (5S)-4-(Benzyloxy)-5-isopropyl-1H-pyrrol-2(5H)-one (**16f**).* From **15f** (190 mg, 0.50 mmol); solvent: THF (1.5 mL), additives: Ph$_3$PCCO **10** (1.1 equiv), PhCO$_2$H (0.2 equiv), conditions: reflux for 18 h, purification: flash chromatography (hexane/EtOAc 1:1). Product: **16f** (52.0 mg, 0.23 mmol, 45%). R_f=0.26 (EtOAc). $[\alpha]_D^{25}$=−7.15 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.73 (d, *J*=6.9 Hz, 3H, CHC*H*$_3$), 0.96 (d, *J*=6.9 Hz, 3H, CHC*H*$_3$), 2.04–2.09 [m,

1H, C*H*(CH_3)$_2$], 3.98 (d, *J*=3.3 Hz, 1H, 5-H), 4.86 (d, *J*=11.2 Hz, 1H, CH_2Ph), 4.91 (d, *J*=11.2 Hz, 1H, CH_2Ph), 5.03 (s, 1H, 3-H), 6.67 (br, 1H, NH), 7.2–7.34 (m, 5H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=15.2 (CH*C*H_3), 19.5 (CH*C*H_3), 29.4 [*C*H(CH_3)$_2$], 62.9 (C-5), 73.1 (CH_2Ph), 95.4 (C-3), 127.8, 128.2, 128.8 (*o*-C, *m*-C, *p*-C), 134.9 (*i*-C), 171.6 (C-2), 176.3 (C-4) ppm. IR (ATR): ν_{max}/cm^{-1}=3186, 3068, 2963, 2933, 2875, 1666, 1616, 1499, 1464, 1455, 1401, 1385, 1370, 1333, 1306, 1223, 1207, 1135, 1103, 1081, 1039, 1004, 970, 952, 913, 846, 805, 760, 742, 695, 665. MS (EI, 70 eV): *m*/*z* (%)=231 [M$^+$] (10), 189 (26), 140 (7), 132 (8), 91 (100). HRMS: calcd for $C_{14}H_{17}NO_2^+$ 231.12593, found 231.12597 [M]$^+$.

*4.2.11. (5S,6S)-5-s-Butyl-4-methoxy-1-methyl-1H-pyrrol-2(5H)-one (**16g**).* From **15g** (196 mg, 1.00 mmol); solvent: THF (1.5 mL), additives: Ph_3PCO **10** (1.1 equiv), $PhCO_2H$ (0.2 equiv), conditions: reflux for 18 h, purification: flash chromatography (hexane/EtOAc 1:1). Product: **16g** (99.0 mg, 0.60 mmol, 60%). R_f=0.18 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.67 (d, *J*=6.9 Hz, 3H, CH*C*H_3), 0.89 (t, *J*=7.4 Hz, 3H, CH_2*C*H_3), 1.27–1.52 (m, 2H, CH_2), 1.76–1.85 (m, 1H, *C*HCH$_3$), 2.79 (s, 3H, NCH$_3$), 3.67 (s, 3H, OCH$_3$), 3.76 (d, *J*=2.7 Hz, 1H, 5-H), 4.98 (s, 1H, 3-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.3 (CH_2*C*H_3), 12.9 (CH*C*H_3), 25.2 (*C*H_2CH$_3$), 26.7 (NCH$_3$), 35.0 (*C*HCH$_3$), 57.7 (OCH$_3$), 65.7 (C-5), 94.8 (C-3), 171.9 (C-2), 175.3 (C-4) ppm. IR (ATR): ν_{max}/cm^{-1}=2964, 2936, 2875, 1683, 1621, 1457, 1423, 1380, 1362, 1336, 1231, 1174, 1136, 1066, 1016, 990, 939, 905, 802, 713, 688. MS (EI, 70 eV): *m*/*z* (%)=183 [M$^+$] (20), 152 (5), 126 (100), 112 (10), 98 (5), 85 (5), 42 (5). HRMS: calcd for $C_{10}H_{17}NO_2^+$ 183.12593, found 183.12588 [M]$^+$.

*4.2.12. 4-(Benzyloxy)-5-((S)-(tert-butoxy)methyl)-1H-pyrrol-2(5H)-one (**16j**).* From **15j** (251 mg, 1.00 mmol); solvent: toluene (8 mL), additives: Ph_3PCO **10** (1.1 equiv), conditions: reflux for 18 h, purification: flash chromatography (EtOAc). Product: **16j** (130 mg, 0.47 mmol, 47%). R_f=0.25 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.13 [s, 9H, C(CH$_3$)$_3$], 3.20 (t, *J*=9.1 Hz, 1H, 5-H), 3.72 (dd, *J*=9.1, 3.6 Hz, 1H, 1′-H$_a$), 4.17 (dd, *J*=9.1, 3.6 Hz, 1H, 1′-H$_b$), 4.89 (d, *J*=11.8 Hz, 1H, CH_2Ph$_a$), 4.92 (d, *J*=11.8 Hz, 1H, CH_2Ph$_b$), 5.07 (d, *J*=1.1 Hz, 1H, 3-H), 6.20 (br, 1H, NH), 7.29–7.35 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=27.2 [C(*C*H$_3$)$_3$], 58.3 (C-5), 63.0 (C-1′), 72.9 (*C*H$_2$Ph), 73.4 [*C*(CH$_3$)$_3$], 95.5 (C-3), 127.6 (*o*-C), 128.2 (*m*-C), 128.5 (*p*-C), 134.5 (*i*-C), 173.7 (C-4), 173.9 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3215, 2974, 1687, 1619, 1498, 1455, 1437, 1363, 1331, 1190, 1118, 1102, 1079, 1025, 996, 972, 913, 866, 807, 746, 719, 694. MS (EI): *m*/*z*=260 [M−CH$_3$]$^+$, 219 [MH−C$_4$H$_9$]$^+$, 201 [M−C$_4$H$_{10}$O]$^+$, 189 [MH−C$_4$H$_9$]$^+$. HRMS: calcd for $C_{16}H_{22}NO_3^+$ 276.1594, found 276.1605 [M+H]$^+$.

*4.2.13. 4-(Benzyloxy)-5-((triisopropylsilyloxy)methyl)-1H-pyrrol-2(5H)-one (**16k**).* From **15k** (112 mg, 0.32 mmol); solvent: THF (2 mL), additives: Ph_3PCO **10** (1.1 equiv), $PhCO_2H$ (0.2 equiv), conditions: reflux for 18 h, purification: HPLC (hexane/EtOAc 2:1→0:1). Product: **16k** (46.0 mg, 122 μmol, 38%). R_f=51.56 min (HPLC). $[\alpha]_D^{20}$=−51.2 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.00–1.08 {m, 21H, Si[C*H*(CH$_3$)$_2$]$_3$, Si[CH(C*H*$_3$)$_2$]$_3$}, 3.66 (dd, *J*=9.8, 8.1 Hz, 1H, 1′-H$_a$), 4.06 (dd, *J*=9.8, 3.4 Hz, 1H, 1′-H$_b$), 4.21 (ddd, *J*=8.1, 3.4, 0.8 Hz, 1H, 5-H), 4.91–5.01 (m, 2H, CH_2Ph), 5.12 (d, *J*=0.8 Hz, 1H, 3-H), 5.72 (br, 1H, NH), 7.32–7.44 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=11.9 {Si[*C*H(CH$_3$)$_2$]$_3$}, 17.9 {Si[CH(*C*H$_3$)$_2$]$_3$}, 60.1 (C-5), 64.5 (C-1′), 73.3 (*C*H$_2$Ph), 95.8 (C-3), 127.9 (*o*-C), 128.76 (*m*-C), 128.79 (*p*-C), 134.6 (*i*-C), 173.9 (C-4), 174.0 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3359, 3057, 2921, 2852, 2360, 2341, 1634, 1437, 1193, 1119, 1070, 997, 754, 720, 694, 669. MS (ESI): *m*/*z*=376.2 [M+H]$^+$, 322.2, 254.1, 202.1, 163.1, 145.1, 91.1 [C$_7$H$_7$]$^+$. HRMS (ESI): calcd for $C_{21}H_{33}NO_3SiNa^+$ 398.2122, found 398.2123 [M+Na]$^+$.

*4.2.14. (S)-4-(Benzyloxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-1H-pyrrol-2(5H)-one (**16l**).* From **15l** (227 mg, 0.73 mmol); solvent: THF (3 mL), additives: Ph_3PCO **10** (1.1 equiv), $PhCO_2H$ (0.2 equiv), conditions: reflux for 18 h, purification: HPLC (hexane/EtOAc 2:1→0:1). Product: **16l** (49.0 mg, 147 μmol, 20%). R_f=14.32 min (GC–MS). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.05 [s, 6H, Si(CH$_3$)$_2$], 0.88 [s, 9H, SiC(CH$_3$)$_3$], 3.55 (dd, *J*=10.1, 8.2 Hz, 1H, 1′-H$_a$), 3.98 (dd, *J*=10.1, 3.5 Hz, 1H, 1′-H$_b$), 4.19 (ddd, *J*=8.2, 3.5, 0.9 Hz, 1H, 5-H), 4.93–5.00 (m, 2H, CH_2Ph), 5.12 (d, *J*=0.9 Hz, 1H, 3-H), 5.69 (br, 1H, NH), 7.33–7.43 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=−5.5, −5.4 [Si(CH$_3$)$_2$], 18.2 [SiC(CH$_3$)$_3$], 25.8 [SiC(*C*H$_3$)$_3$], 59.9 (C-5), 64.1 (C-1′), 73.3 (*C*H$_2$Ph), 95.8 (C-3), 127.9 (*o*-C), 128.77 (*m*-C), 128.81 (*p*-C), 134.6 (*i*-C), 173.9 (C-4), 174.0 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3219, 2952, 2928, 2884, 2856, 2364, 1689, 1624, 1499, 1463, 1388, 1336, 1256, 1220, 1201, 1125, 1030, 973, 900, 837, 808, 778, 738, 697. MS (ESI): *m*/*z*=334.2 [M+H]$^+$, 301.1, 297.1, 240.1, 202.1, 91.1 [C$_7$H$_7$]$^+$. HRMS (ESI): calcd for $C_{18}H_{27}NO_3SiNa^+$ 356.1652, found 356.1652 [M+Na]$^+$.

*4.2.15. 4-(Benzyloxy)-5-((S)-(triethylsilyloxy)methyl)-1H-pyrrol-2(5H)-one (**16m**).* From **15m** (0.77 g, 0.25 mmol); solvent: toluene (5 mL), additives: Ph_3PCO **10** (1.1 equiv), conditions: reflux for 18 h, purification: HPLC (EtOAc). Product: **16m** (23.0 mg, 0.07 mmol, 28%) and **16x** (0.10 mmol, 20.6 mg, 41%). R_f=0.44 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.57 (q, *J*=8.2 Hz, 6H, Si*C*H_2), 0.92 (t, *J*=8.2 Hz, 9H, SiCH$_2$*C*H_3), 3.50 (dd, *J*=10.4, 8.3 Hz, 1H, 1′-H$_a$), 3.96 (dd, *J*=10.4, 3.6 Hz, 1H, 1′-H$_b$), 4.17 (dd, *J*=8.3, 3.6 Hz, 1H, 5-H), 4.92 (d, *J*=11.7 Hz, 1H, CH_2Ph$_a$), 4.96 (d, *J*=11.7 Hz, 1H, CH_2Ph$_b$), 5.08 (d, *J*=1.2 Hz, 1H, 3-H), 5.68 (br, 1H, NH), 7.30–7.39 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=4.2 (Si*C*H$_2$), 6.6 (SiCH$_2$*C*H$_3$), 59.9 (C-5), 64.0 (C-1′), 73.2 (*C*H$_2$Ph), 95.8 (C-3), 127.8 (*o*-C), 128.5 (*m*-C), 128.7 (*p*-C), 134.6 (*i*-C), 173.77 (C-4), 173.84 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3211, 2953, 2911, 2875, 1687, 1622, 1498, 1456, 1437, 1377, 1334, 1294, 1221, 1198, 1117, 1003, 970, 895, 845, 798, 721, 694. MS (ESI): *m*/*z*=304 [M−Et]$^+$, 261, 212, 201, 117, 115, 103, 91, 75, 65.

*4.2.16. 4-(Benzyloxy)-5-methylene-1H-pyrrol-2(5H)-one (**16x**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.82 (t, *J*=1.5 Hz, 1H, 3-H), 5.03 (s, 2H, CH_2Ph), 5.06 (d, *J*=1.5 Hz, 1H, =CH$_{2a}$), 5.20 (t, *J*=1.4 Hz, 1H, =CH$_{2b}$), 7.33–7.42 (m, 5H, Ar), 8.06 (br, 1H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=72.9 (CH_2Ph), 92.5 (=CH_2), 94.6 (C-3), 127.7, 128.66, 128.70, (*o*-C, *m*-C, *p*-C), 134.7 (*i*-C), 139.4 (C-5), 164.7 (C-4), 171.8 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3089, 3036, 3013, 1731, 1661, 1604, 1497, 1453, 1402, 1355, 1304, 1227, 1196, 1012, 982, 946, 915, 876, 842, 822, 738, 710, 694, 655. MS (EI, 70 eV): *m*/*z*=201 [M]$^+$, 173, 158, 91 [Bn]$^+$, 65.

*4.2.17. (S)-4-(Benzyloxy)-5-((R)-1-(tert-butyloxy)ethyl)-1H-pyrrol-2(5H)-one (**18a**).* From **17a** (0.77 g, 0.25 mmol); solvent: toluene (5 mL), additives: Ph_3PCO **10** (1.1 equiv), conditions: reflux for 18 h, purification: HPLC (EtOAc). Product: **18a** (43.0 mg, 0.15 mmol, 59%). R_f=0.16 (EtOAc). $[\alpha]_D^{20}$=+7.9 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.15 [s, 9H, C(CH$_3$)$_3$], 1.26 (d, *J*=6.0 Hz, 3H, 2′-H), 3.71 (q, *J*=6.3 Hz, 1H, 1′-H), 3.89 (d, *J*=6.0 Hz, 1H, 5-H), 4.92 (s, 2H, CH_2Ph), 5.10 (d, *J*=1.9 Hz, 1H, 3-H), 6.06 (br, 1H, NH), 7.27–7.49 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.0 (C-2′), 28.5 [C(*C*H$_3$)$_3$], 63.2 (C-1′), 68.0 (C-5), 73.1 (CH_2Ph), 95.7 (C-3), 127.7, 128.6, 128.7 (*o*-C, *m*-C, *p*-C), 134.7 (*i*-C), 173.8 (C-4), 174.6 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3239, 2974, 1683, 1619, 1499, 1455, 1437, 1366, 1331, 1257, 1221, 1189, 1118, 1082, 1027, 978, 913, 849, 806, 746, 720, 693. MS (EI): *m*/*z*=276, 259, 216 [M−C$_4$H$_9$O]$^+$, 199 [MH−C$_7$H$_7$]$^+$, 189, 122, 101.91 [C$_7$H$_7$]$^+$, 57. HRMS: calcd for $C_{17}H_{24}NO_3^+$ 290.1751, found 290.1760 [M+H]$^+$.

*4.2.18. (S)-4-(Benzyloxy)-5-((R)-1-(benzyloxy)ethyl)-1H-pyrrol-2(5H)-one (**18b**).* From **17b** (80.8 mg, 0.25 mmol), solvent: toluene (5 mL), additives: Ph_3PCO **10** (1.3 equiv), conditions: reflux for 18 h, purification: HPLC (EtOAc). Product: **18b** (27.0 mg, 0.08 mmol, 34%). R_f=0.17 (EtOAc). $[\alpha]_D^{20}$=−17.1 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.34 (d, *J*=6.2 Hz, 3H, 2′-H), 3.67 (dq, *J*=6.2, 6.2 Hz, 1H, 1′-

H), 4.05 (d, J=6.2 Hz, 1H, 5-H), 4.43 (d, J=11.5 Hz, 1H, OCH_2Ph$_a$), 4.61 (d, J=11.5 Hz, 1H, OCH_2Ph$_b$), 4.95 (d, J=11.8 Hz, 1H, COOCH_2Ph$_a$), 4.95 (d, J=11.8 Hz, 1H, COOCH_2Ph$_b$), 5.15 (d, J=1.1 Hz, 1H, 3-H), 6.24 (br, 1H, NH), 7.21–7.40 (m, 10H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=16.7 (C-2′), 62.4 (C-1′), 71.0 (OCH_2Ph), 73.2 (COOCH_2Ph), 75.1 (C-5), 96.0 (C-3), 127.6, 127.7, 128.4, 128.5, 128.6, 128.7 (*o*-C, *m*-C, *p*-C), 134.7, 137.9 (*i*-C), 173.9 (C-4), 174.2 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3209, 3061, 2871, 1681, 1616, 1497, 1454, 1437, 1377, 1336, 1269, 1220, 1202, 1118, 1092, 1026, 997, 956, 914, 805, 737, 720, 694. MS (EI): m/z=324 [MH$^+$], 279, 251, 217, 188, 160, 135, 120, 91 [C_7H_7]$^+$.

*4.2.19. (S)-5-((R)-1-(Benzyloxy)ethyl)-4-methoxy-1-methyl-1H-pyrrol-2(5H)-one (**18c**).* From **17c** (0.65 g, 2.70 mmol); solvent: toluene (8 mL), additives: Ph_3PCCO **10** (1.1 equiv), conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **18c** (0.27 g, 1.00 mmol, 38%). R_f=0.25 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.96 (d, J=6.3 Hz, 3H, CHCH_3, 7-H), 2.92 (s, 3H, NCH_3, 9-H), 3.66 (s, 3H, OCH_3, 8-H), 3.88 (dq, J=6.3 Hz, J=2.2 Hz, 1H, CHCH$_3$, 6-H), 4.09 (d, J=2.2 Hz, 1H, CHNH, 5-H), 4.48 (d, J=12.0 Hz, 1H, CH_2Ph, 10-H), 4.55 (d, J=12.0 Hz, 1H, CH_2Ph, 10-H), 4.99 (d, J=0.7 Hz, 1H, CH, 3-H), 7.17–7.29 (m, 5H, Ar) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=12.7 (C-7), 28.2 (C-9), 58.0 (C-8), 64.8 (C-5), 70.8 (C-10), 74.5 (C-6), 94.7 (C-3), 127.1, 127.4, 128.2 (*o*-C, *m*-C, *p*-C), 137.9 (*i*-C), 172.2 (C-4), 174.2 (C-2) ppm. FTIR (ATR): ν_{max} (cm^{-1})=2936, 2341, 1679, 1623, 1496, 1483, 1453, 1436, 1380, 1349, 1231, 1196, 1100, 1027, 997, 950, 887, 802, 745, 719, 693. MS (EI, 70 eV); m/z (%): 164 (12), 126 (20) [M$^+$–(CH$_3$(CH)OBn)], 120 (19), 91 (100) [Bn$^+$].

*4.2.20. (S)-4-(Benzyloxy)-5-((R)-1-((triisopropylsilyl)oxy)ethyl)-1H-pyrrol-2(5H)-one (**18d**).* From **17d** (97.2 mg, 0.25 mmol); solvent: toluene (5 mL), additives: Ph_3PCCO **10** (1.1 equiv), conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **18d** (45.0 mg, 0.12 mmol, 46%). R_f=0.45 (EtOAc). $[\alpha]_D^{20}$=+12.7 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98–1.03 [m, 21H, CH(CH_3)$_2$], 1.29 (d, J=6.0 Hz, 3H, 2′-H), 3.95 (d, J=4.6 Hz, 1H, 5-H), 4.18 (dq, J=6.0, 4.6 Hz, 1H, 1′-H), 4.92 (s, 2H, CH_2Ph), 5.11 (dd, J=1.6, 0.5 Hz, 1H, 3-H), 6.26 (br, 1H, NH), 7.30–7.36 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.5 [CH(CH$_3$)$_2$], 17.9 [CH(CH_3)$_2$], 20.9 (C-2′), 64.0 (C-1′), 68.4 (C-5), 73.0 (CH_2Ph), 98.8 (C-3), 127.8, 128.4, 128.5 (*o*-C, *m*-C, *p*-C), 134.6 (*i*-C), 174.3 (C-4), 174.5 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3213, 2942, 2866, 1967, 1686, 1620, 1463, 1338, 1261, 1202, 1099, 1008, 952, 882, 803, 735, 696, 678. MS (ESI): m/z=390.2 [M+H]$^+$, 346.2 [M–C_3H_7]$^+$, 201.2, 177.1, 159.1, 131.1, 91.0 [C_7H_7]$^+$. HRMS (ESI): calcd for $C_{22}H_{36}NO_3Si^+$ 390.2459, found 390.2453 [M+H]$^+$.

*4.2.21. (S)-4-(Benzyloxy)-1-methyl-5-((R)-1-((triisopropylsilyl)oxy)ethyl)-1H-pyrrol-2(5H)-one (**18e**).* From **17e** (565 mg, 1.50 mmol); solvent: toluene (10 mL); additives: Ph_3PCCO **10** (1.1 equiv), conditions: reflux for 18 h; purification: flash chromatography (cyclohexane /EtOAc 1:1). Product: **18e** (330 mg, 0.82 mmol, 55%). R_f=0.27 (cyclohexane/ EtOAc 1:1). $[\alpha]_D^{20}$=+45.5 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93–1.02 {m, 21H, Si[CH(CH_3)$_2$]$_3$}, 1.09 (d, J=6.3 Hz, 3H, 2′-H), 2.87 (s, 3H, NMe), 3.86 (d, J=3.0 Hz, 1H, 5-H), 4.32 (qd, J=6.3, 3.0 Hz, 1H, 1′-H), 4.87 (d, J=11.8 Hz, 1H, CH_2Ph_a) 4.87 (d, J=11.8 Hz, 1H, CH_2Ph_b), 5.09 (s, 1H, 3-H) 7.25–7.33 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.1 [SiCH(CH$_3$)$_2$], 17.8 [SiCH(CH_3)$_2$], 18.3 (C-2′), 27.5 (NMe), 66.4 (C-1′), 67.4 (C-5), 72.5 (CH_2Ph), 95.6 (C-3), 127.6, 128.2, 128.4 (*o*-C, *m*-C, *p*-C), 134.8 (*i*-C), 171.9 (C-4), 173.3 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=2942, 2865, 1689, 1620, 1499, 1462, 1422, 1377, 1351, 1308, 1225, 1200, 1141, 1114, 1071, 989, 916, 881, 846, 802, 755, 737, 716, 676. MS (EI): m/z=403 [M]$^+$, 359 [M–C_3H_7]$^+$, 268, 226, 203, 201, 157, 115, 91 [C_7H_7]$^+$. HRMS: calcd for $C_{23}H_{37}NO_3Si^+$ 404.2615, found 404.2626 [M+H]$^+$.

*4.2.22. (S)-4-(Benzyloxy)-5-((R)-1-((triethylsilyl)oxy)ethyl)-1H-pyrrol-2(5H)-one (**18f**).* From **17f** (86.9 mg, 0.25 mmol); solvent: toluene (5 mL); additives: Ph_3PCCO **10** (1.1 equiv); conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **18f** (35.0 mg, 0.10 mmol, 39%). R_f=0.30 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.56 (q, J=7.7 Hz, 6H, SiCH_2), 0.92 (t, J=7.7 Hz, 9H, SiCH$_2$CH_3), 1.28 (d, J=5.8 Hz, 3H, 2′-H), 3.81–4.01 (m, 2H, 1′-H, 5-H), 4.94 (s, 2H, CH_2Ph), 5.11 (d, J=1.6 Hz, 1H, 3-H), 5.79 (br, 1H, NH), 7.27–7.41 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=4.9 (SiCH_2), 6.8 (SiCH_2CH$_3$), 21.3 (C-2′), 59.9 (C-5), 64.0 (C-1′), 73.2 (CH_2Ph), 95.8 (C-3), 127.8, 128.5, 128.7 (*o*-C, *m*-C, *p*-C), 134.6 (*i*-C), 173.77 (C-4), 173.84 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3216, 3062, 2953, 2875, 1685, 1619, 1499, 1456, 1437, 1376, 1335, 1308, 1220, 1198, 1142, 1118, 1095, 1003, 975, 950, 913, 881, 844, 805, 784, 719, 694. MS: m/z=318 [M–Et]$^+$, 303, 215, 189, 159, 131, 115, 103 [Et$_2$SiOH]$^+$, 91[C_7H_7]$^+$.

*4.2.23. (S)-4-(Benzyloxy)-5-((R)-1-(methoxy)ethyl)-1H-pyrrol-2(5H)-one (**18g**).* From **17g** (448 mg, 1.82 mmol); solvent: toluene (8 mL); additives: Ph_3PCCO **10** (1.1 equiv); conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **18g** (365 mg, 1.48 mmol, 82%). R_f=0.14 (EtOAc). $[\alpha]_D^{20}$=–2.4 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.17 (d, J=6.3 Hz, 3H, 2′-H), 3.22 (s, 3H, OMe), 3.38 (qd, J=6.3, 5.6 Hz, 1H, 1′-H), 3.92 (d, J=5.6 Hz, 1H, 5-H), 4.87 (s, 2H, CH_2Ph), 5.04 (d, J=1.1 Hz, 1H, 3-H), 7.05 (s, 1H, NH), 7.20–7.29 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.6 (C-2′), 56.5 (C-1′), 62.2 (C-5), 72.9 (CH_2Ph), 76.4 (OCH_3), 95.7 (C-3), 127.4, 128.3, 128.4 (*o*-C, *m*-C, *p*-C), 134.6 (*i*-C), 174.2 (C-4), 174.3 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3204, 3067, 2983, 2936, 2883, 2827, 1677, 1610, 1498, 1454, 1397, 1334, 1222, 1204, 1159, 1142, 1091, 1044, 1013, 996, 963, 913, 884, 848, 803, 755, 740, 699, 670. HRMS: calcd for $C_{14}H_{18}NO_3^+$ 248.1281, found 248.1269 [M+H]$^+$.

*4.2.24. (S)-4-(Benzyloxy)-5-((S)-1-(methoxy)ethyl)-1H-pyrrol-2(5H)-one (**18h**).* From **17h** (62.0 mg, 0.25 mmol); solvent: toluene (8 mL); additives: Ph_3PCCO **10** (1.1 equiv); conditions: reflux for 18 h; purification: flash chromatography (MeOH in EtOAc 0–10%). Product: **18h** (5.00 mg, 0.02 mmol, 8%). R_f=0.15 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.99 (d, J=6.0 Hz, 3H, 2′-H), 3.38 (s, 3H, OMe), 3.72 (qd, J=6.0, 3.2 Hz, 1H, 1′-H), 4.45 (d, J=3.2 Hz, 1H, 5-H), 4.94 (d, J=11.6 Hz, 1H, CH_2Ph_a), 5.01 (d, J=11.4 Hz, 1H, CH_2Ph_b), 5.14 (d, J=1.7 Hz, 1H, 3-H), 5.66 (br, 1H, NH), 7.33–7.42 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=11.9 (C-2′), 56.7 (C-1′), 59.9 (C-5), 73.3 (CH_2Ph), 75.9 (OCH_3), 96.1 (C-3), 127.7, 128.4, 128.8 (*o*-C, *m*-C, *p*-C), 134.5 (*i*-C), 173.9 (C-4), 174.2 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3211, 2974, 2933, 2222, 1684, 1616, 1499, 1455, 1437, 1389, 1331, 1220, 1193, 1119, 1076, 975, 954, 913, 888, 848, 806, 782, 721, 695. HRMS: calcd for $C_{14}H_{18}NO_3^+$ 248.1281, found 248.1297 [M+H]$^+$.

*4.2.25. (S)-4-(Benzyloxy)-5-((S)-1-((triisopropylsilyl)oxy)ethyl)-1H-pyrrol-2(5H)-one (**18i**).* From **17i** (97.2 mg, 0.25 mmol); solvent: toluene (5 mL); additives: Ph_3PCCO **10** (1.1 equiv), conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **18i** (25.0 mg, 0.06 mmol, 26%). R_f=0.46 (EtOAc). $[\alpha]_D^{20}$=–35.6 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.97 (d, J=6.5 Hz, 3H, 2′-H), 1.01–1.05 [m, 21H, SiCH(CH_3)$_2$], 4.25–4.34 (m, 2H, 5-H, 1′-H), 4.90 (d, J=11.9 Hz, 1H, CH_2Ph$_a$), 4.97 (d, J=11.9 Hz, 1H, CH_2Ph$_b$), 5.07 (d, J=1.3 Hz, 1H, 3-H), 5.53 (br, 1H, NH), 7.30–7.39 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=12.2 [SiCH(CH$_3$)$_2$], 16.0 (*C*-2′), 18.0 [SiCH(CH_3)$_2$], 63.2 (C-5), 67.9 (C-1′), 73.2 (CH_2Ph), 96.1 (C-3), 127.7, 128.7 (*o*-C, *m*-C, *p*-C), 134.6 (*i*-C), 173.7 (C-4), 174.2 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3216, 2942, 2865, 1689, 1620, 1498, 1462, 1383, 1353, 1332, 1199, 1143, 1103, 1068, 1030, 984, 942, 915, 881, 857, 807, 744, 678. MS (EI): m/z=346 [M–C_3H_7]$^+$, 302, 255, 201, 157, 115, 91 [C_7H_7]$^+$. HRMS: calcd for $C_{22}H_{36}NO_3Si^+$ 390.2459, found 390.2470 [M+H]$^+$.

*4.2.26. (S)-4-(Benzyloxy)-5-((S)-1-((triethylsilyl)oxy)ethyl)-1H-pyrrol-2(5H)-one (**18j**).* From **17j** (86.9 mg, 0.25 mmol); solvent:

toluene (5 mL); additives: Ph_3PCCO **10** (1.1 equiv); conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **18j** (11.0 mg, 0.03 mmol, 13%). R_f=0.34 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.59 (q, J=8.2 Hz, 6H, $SiCH_2$), 0.97 (d, J=6.0 Hz, 3H, 2′-H), 0.94 (t, J=8.2 Hz, 9H, $SiCH_2CH_3$), 4.08–4.32 (m, 2H, 1′-H, 5-H), 4.92 (d, J=11.7 Hz, 1H, CH_2Ph_a), 4.99 (d, J=11.7 Hz, 1H, CH_2Ph_b), 5.09 (dd, J=1.9, 0.5 Hz, 1H, 3-H), 5.55 (br, 1H, NH), 7.29–7.51 (m, 5H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=4.7 ($SiCH_2$), 6.7 ($SiCH_2CH_3$), 16.1 (C-2′), 63.1 (C-5), 67.6 (C-1′), 73.2 (CH_2Ph), 96.1 (C-3), 127.8, 128.5, 128.8 (*o*-C, *m*-C, *p*-C), 134.7 (*i*-C), 173.8 (C-4), 174.1 (C-2) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3212, 2954, 2876, 1687, 1618, 1498, 1456, 1381, 1333, 1220, 1199, 1142, 1099, 1063, 986, 942, 912, 857, 806, 783, 726, 695. MS (EI): m/z=318 $[M-Et]^+$, 303, 215, 189, 159, 131, 115, 103 $[Et_2SiOH]^+$, 91$[C_7H_7]^+$.

*4.2.27. (5Z)-4-(Benzyloxy)-5-ethylidene-1H-pyrrol-2(5H)-one (**18x**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.86 (d, J=7.3 Hz, 3H, CH_3), 5.01 (s, 2H, CH_2Ph), 5.16 (d, J=1.6 Hz, 1H, 3-H), 5.55 (q, J=7.3 Hz, 1H, $CHCH_3$), 7.30–7.44 (m, 5H, Ar), 8.54 (br, 1H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=12.1 ($CHCH_3$), 72.6 (CH_2Ph), 93.6 (C-3), 106.0 ($CHCH_3$), 127.6, 128.5, 128.6, (*o*-C, *m*-C, *p*-C), 134.2 (C-5), 134.9 (*i*-C), 164.6 (C-2), 172.5 (C-4) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3166, 3099, 3038, 2921, 1663, 1590, 1582, 1498, 1452, 1409, 1336, 1319, 1271, 1232, 1216, 1207, 1152, 1085, 1015, 976, 955, 915, 860, 802, 741, 699, 676. MS (EI, 70 eV): m/z=215 $[M]^+$, 200 $[M-CH_3]^+$, 172, 132, 124 $[M-Bn]^+$, 91 $[Bn]^+$, 65, 54.

*4.2.28. (S)-tert-Butyl-(3-(3-(benzyloxy)-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)propyl)carbamate (**20**). Method B*: from **19** (65.0 mg, 0.18 mmol); solvent: toluene (3 mL); additives: Ph_3PCCO **10** (1.0 equiv), $PhCO_2H$ (0.2 equiv); conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **20** (34.0 mg, 98.0 μmol, 77%). *Method C*: starting material: **19** (50.0 mg, 0.16 mmol); solvent: toluene (5 mL); additives: Ph_3PCCO **10** (1.1 equiv); conditions: reflux for 18 h; purification: flash chromatography (EtOAc). Product: **20** (34.0 mg, 98.0 μmol, 63%). R_f=0.3 (EtOAc). $[\alpha]_D^{20}$=−11.1 (*c* 1.00, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.43 [s, 9H, $C(CH_3)_3$], 1.47–1.62 (m, 3H, 2′-H, 1′-H_a), 1.82–1.91 (m, 1H, 1′-H_b), 3.06–3.19 (m, 2H, 3′-H), 4.09–4.15 (m, 1H, 5-H), 4.67 (br, 1H, NH), 4.93–5.01 (m, 2H, CH_2Ph), 5.08 (s, 1H, 3-H), 6.76 (br, 1H, 1-H), 7.33–7.42 (m, 5H, Ar) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=25.6 (C-2′), 28.4 [$C(CH_3)_3$], 29.0 (C-1′), 40.1 (C-3′), 57.4 (C-5), 73.2 (CH_2Ph), 79.2 [$C(CH_3)_3$], 94.8 (C-3), 127.8, 128.5, 128.6 (*o*-C, *m*-C, *p*-C), 134.7 (*i*-C), 156.0 (NHCOO), 174.6 (C-2), 176.7 (C-4) ppm. FTIR (ATR): ν_{max}/cm^{-1}=3280, 2932, 1966, 1674, 1615, 1515, 1454, 1335, 1250, 1166, 977, 913, 807, 730. HRMS (ESI): calcd for $C_{19}H_{26}N_2O_4Na^+$ 369.1785, found 369.1790 $[M+Na]^+$. MS (ESI): m/z=347.2 $[M+H]^+$, 291.1, 247.1, 230.1, 140.1, 91.1 $[C_7H_7]^+$.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft (grants Scho 402/9-2 and La 907/8-2), the Ministerium für Wissenschaft, Forschung und Kunst des Landes Baden-Württemberg (Landesgraduierten fellowship for N.P.), F. Hoffmann-La Roche AG, Basel (internship for I.L.) and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.10.099.

References and notes

1. Reviews: (a) Athanasellis, O. I.-M. G.; Markopoulos, J. *Bioinorg. Chem. Appl.* **2010**, 1–11; (b) Schobert, R.; Schlenk, A. *Bioorg. Med. Chem.* **2008**, *16*, 4203–4221; (c) Edwards, P. *Drug Discovery Today* **2007**, *12*, 345–346; (d) Royles, B. J. L. *Chem. Rev.* **1995**, *95*, 1981–2001; (e) Henning, H.-G.; Gelbin, A. *Adv. Heterocycl. Chem.* **1993**, *57*, 139–185.
2. (a) Biersack, B.; Diestel, R.; Jagusch, C.; Sasse, F.; Schobert, R. *J. Inorg. Biochem.* **2009**, *103*, 72–76; (b) Knoth, T.; Warburg, K.; Katzka, C.; Rai, A.; Wolf, A.; Brockmeyer, A.; Janning, O.; Reubold, T. F.; Eschenburg, S.; Manstein, D. J.; Hübel, K.; Kaiser, M.; Waldmann, H. *Angew. Chem.* **2009**, *121*, 7376–7381; *Angew. Chem. Int. Ed.* **2009**, *48*, 7240–7245; (c) Biersack, B.; Diestel, R.; Jagusch, C.; Rapp, G.; Sasse, G.; Schobert, R. *Chem. Biodiv.* **2008**, *5*, 2423–2430; (d) Schobert, R.; Jagusch, C. *Tetrahedron* **2005**, *61*, 2301–2307; (e) Aoki, S.; Higuchi, K.; Ye, Y.; Satari, R.; Kobayashi, M. *Tetrahedron* **2000**, *56*, 1833–1836.
3. (a) Boehme, R.; Jung, G.; Bretmaier, E. *Helv. Chim. Acta* **2005**, *88*, 2837–2841; (b) Marquardt, U.; Schmid, D.; Jung, G. *Synlett* **2000**, 1131–1132; (c) Holtzel, A.; Gänzle, M. G.; Nicholson, G. J.; Hamer, W. P.; Jung, G. *Angew. Chem.* **2000**, *39*, 2766–2768; *Angew. Chem. Int. Ed.* **2000**, *39*, 2766–2768; (d) Gänzle, M. G.; Höltzel, A.; Walter, J.; Jung, G.; Hammer, W. P. *Appl. Environ. Microbiol.* **2000**, *66*, 4325–4333; (e) Schobert, R.; Dietrich, M.; Mullen, G.; Urbina-Gonzalez, J.-M. *Synthesis* **2006**, *22*, 3902–3914.
4. (a) Yoshinari, T.; Ohmori, K.; Schrenz, M. G.; Pfaltz, A.; Suzuki, K. *Angew. Chem.* **2010**, *122*, 893–897; *Angew. Chem., Int. Ed.* **2010**, *49*, 881–885; (b) Barnickel, B.; Schobert, R. *J. Org. Chem.* **2010**, *75*, 6716–6719; (c) Ramane, C. V.; Mondal, M. A.; Puranik, V. G.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 4061–4064; (d) Graupner, P. R.; Carr, A.; Clancy, E.; Gilbert, J.; Bailey, K. L.; Derby, J. A.; Gerwick, B. C. *J. Nat. Prod.* **2003**, *66*, 1558–1561.
5. (a) Cramer, N.; Helbig, S.; Baro, A.; Laschat, S.; Diestel, R.; Sasse, F.; Mathieu, D.; Richter, C.; Kummerlöwe, G.; Luy, B.; Schwalbe, H. *ChemBioChem* **2008**, *9*, 2474–2486; (b) Cramer, N.; Buchweiz, M.; Laschat, S.; Frey, W.; Baro, A.; Mathieu, D.; Richter, C.; Schwalbe, H. *Chem.—Eur. J.* **2006**, *12*, 2488–2503; (c) Hart, A. C.; Philipps, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 1094–1095; (d) Cramer, N.; Laschat, S.; Baro, A.; Schwalbe, H.; Richter, C. *Angew. Chem.* **2005**, *117*, 831–833; *Angew. Chem., Int. Ed.* **2005**, *44*, 820–822; (e) Kanazawa, S.; Fusetani, N.; Matsunaga, S. *Tetrahedron Lett.* **1993**, *34*, 1065–1068.
6. (a) Kaparis, P. B.; Hall, E.; Ramstedt, M.; Galloway, W. R. J. D.; Welch, M.; Spring, D. R. *Chem. Commun.* **2009**, 538–540; (b) Lowery, C. A.; Park, J.; Gloeckner, C.; Meijler, M. M.; Mueller, R. S.; Boskoff, H. I.; Ulrich, R. L.; Barry, C. E.; Bartlett, D. E.; Kravchenko, V. V.; Kaufmann, G. F.; Janda, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 14473–14479; (c) Gerke, G. D.; O'Neill, J. C.; Miller, D. M.; Wezeman, R. J.; Mattmann, M. E.; Lin, Q.; Blackwell, H. E. *ChemBioChem* **2008**, *9*, 389–400; (d) Hodgkinson, J. T.; Welch, M.; Spring, D. R. *ACS Chem. Biol.* **2007**, *2*, 715–717; (e) Kaufmann, G. F.; Sartorio, R.; Lee, S.-H.; Rogers, C. J.; Meijler, M. M.; Moss, J. A.; Clapham, B.; Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 309–314.
7. (a) Lacey, R. N. *J. Chem. Soc.* **1954**, 850–854; (b) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1177–1182.
8. Spatz, J. H.; Welsch, S. J.; Duhaut, D.-E.; Jäger, N.; Bournier, T.; Fredrick, M.; Allmendinger, L.; Ross, G.; Kolb, J.; Burdack, C.; Umkehrer, M. *Tetrahedron Lett.* **2009**, *50*, 1705–1707.
9. Anwar, M.; Maloney, M. G. *Tetrahedron Lett.* **2007**, *48*, 7259–7262.
10. Mallinger, A.; Nadal, B.; Chopin, N.; LeGall, T. *Eur. J. Org. Chem.* **2010**, 1142–1148.
11. Storgaard, M.; Zaragoza Dörwald, F.; Peschke, B.; Tanner, D. *J. Org. Chem.* **2009**, *74*, 5032–5040.
12. Farran, D.; Parrot, I.; Martinez, J.; Dewynter, G. *Angew. Chem.* **2007**, *119*, 7632–7634; *Angew. Chem., Int. Ed.* **2007**, *46*, 7488–7489.
13. (a) Matiadis, D.; Igglesi-Markopoulou, O. *Eur. J. Org. Chem.* **2010**, 5989–5995; (b) Prousis, K. C.; Markopoulos, J.; McKee, V.; Igglessi-Markopoulou, O. *Tetrahedron* **2010**, *66*, 3944–3950.
14. Riache, N.; Bailly, C.; Deville, A.; Dubost, L.; Nay, B. *Eur. J. Org. Chem.* **2010**, 5402–5408.
15. Alcaide, B.; Almendros, P.; Luna, A.; Torres, M. R. *Adv. Synth. Catal.* **2010**, *352*, 621–626.
16. (a) Hofheinz, W.; Oberhänsli, W. E. *Helv. Chim. Acta* **1977**, *60*, 660–669; (b) Williard, P. G.; De Laszlo, S. E. *J. Org. Chem.* **1984**, *49*, 3489–3493; (c) Köhler, H.; Gerlach, H. *Helv. Chim. Acta* **1984**, *67*, 1783–1792; (d) Jones, R. C. F.; Bates, A. D. *Tetrahedron Lett.* **1986**, *27*, 5285–5288.
17. (a) Hunter, R.; Rees-Jones, S. C. M.; Su, H. *Tetrahedron Lett.* **2007**, *48*, 2819–2822; (b) Clift, M. D.; Thomson, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 14579–14583.
18. Sengoku, T.; Wierzejska, J.; Takahashi, M.; Yoda, H. *Synlett* **2010**, 2944–2946.
19. (a) Bestmann, H. J.; Kellermann, W. *Synthesis* **1994**, 1257–1261; (b) Bestmann, H. J.; Schmidt, M.; Schobert, R. *Synthesis* **1988**, 49–53; (c) Bestmann, H. J.; Schobert, R. *Angew. Chem.* **1985**, *97*, 783–784; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 791–792; (d) Bestmann, H. J.; Sandmeier, D. *Angew. Chem.* **1975**, *87*, 630; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 634.
20. (a) Schobert, R.; Jagusch, C. *Tetrahedron* **2005**, *61*, 2301–2307; (b) Schobert, R.; Jagusch, C.; Melanophy, C.; Mullen, G. *Org. Biomol. Chem.* **2004**, *2*, 3524–3529.
21. Barnickel, B.; Bayliffe, F.; Diestel, R.; Kempf, K.; Laschat, S.; Pachali, S.; Sasse, F.; Schlenk, A.; Schobert, R. *Chem. Biodiv.* **2010**, *7*, 2830–2845.
22. (a) Henderson, J.; Phillips, A. *Angew. Chem.* **2008**, *120*, 8627–8629; *Angew. Chem., Int. Ed.* **2008**, *47*, 8499–8501; (b) Bae, M. A.; Yamada, K.; Ijuin, Y.; Tsuji, T.; Yazawa, K.; Tomono, Y.; Uemura, D. *Heterocycl. Commun.* **1996**, *2*, 315–318.
23. Vedejs, E.; Marth, C. F. *J. Am. Chem. Soc.* **1988**, *110*, 3948–3958.