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Amino analogs of actic acids—synthesis and lactamization

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Dedicated to Professor Roland Mayer on the occasion of his 75th birthday

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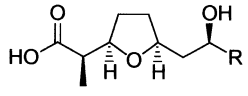
Abstract—Novel THF-amino acids were efficiently synthesized from actic acid methyl esters. The conformational restriction imposed by the 2,5-*cis* disubstituted tetrahydrofuran moiety is apparent from their facile cyclization to give medium-sized lactams. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Tetrahydrofuran containing amino acids combine the cation complexing ability of ethers with the synthetic potential offered by amino acids.[1] These designed structures have proven to be interesting building blocks for peptidomimetics and have recently been used successfully for the construction of artificial ion channels.[2] Moreover, replacement of the hydroxyl function in naturally occurring hydroxy acids by an amino group and incorporation of the resultant unnatural amino acids into β- or γ-peptides has led to highly bioactive peptide mimics.[3] Inspired by this work, we studied the conversion of actic acids such as nonactic acid **1a**,[4] the monomeric subunit of the macrotetrolide antibiotic nonactin,[5] as well as of the propyl substituted compound **1b**,[6] a precursor for both hydroxy acid fragments of the macrodiolide antibiotic pamamycin-607,[7] into their amino analogs with overall retention of relative configuration (Fig. 1). Here we describe a convenient protocol for this transformation, as well as the smooth lactamization of the resultant novel THF-amino acids.



1; **a**: R = Me, **b**: R = Pr

Figure 1. Actic acids **1a** (nonactic acid) and **1b**.

2. Results and discussion

2.1. Synthesis of THF-amino acids 6

The methyl esters **2** of acids **1** are readily available in only six steps from furan by our highly diastereoselective and general sultone route.[4,6a,8] While these esters can be easily prepared in enantiomerically pure form either by departing from an enantiopure epoxide[6a] or by application of a facile resolution technique,[9] we first used racemic **2a**,**b** for our purposes (Scheme 1).

Attempted tosylation of **2b** with inversion of configuration using zinc tosylate[10] under Mitsunobu conditions failed. However, treatment of **2a**,**b** with triphenylphosphine dibromide[11] cleanly effected the desired S_N2 substitution to give the bromides **3**. A second inversion of configuration during azide displacement[12] then provided the azido esters **4** as single diastereomers in high yields. In order to aid product isolation, esters **4** were first hydrolyzed without epimerization at C(2) to give the relatively unpolar azido acids **5**, purification of which by flash chromatography was facile. In case of azido acid **5b**, suitable crystals were obtained that allowed an unambiguous determination of its relative configuration by X-ray diffraction analysis (Fig. 2).[13] Finally, reductive release[14] of the amino group provided the target compounds **6**.

Having established suitable conditions for the conversion of racemic actic acid methyl esters **2** into racemic amino acids **6**, we applied this double inversion procedure to the preparation of enantiomerically pure building blocks ready for peptide coupling. As exemplified in Scheme 2 for (2*R*,3*R*,6*S*,8*S*) methyl nonactate ((−)-**2a**),[9] hydrogenation[14] of azido ester (+)-**4a** afforded amino ester (−)-**7a** in excellent yield. Likewise, the *N*-protected amino acid

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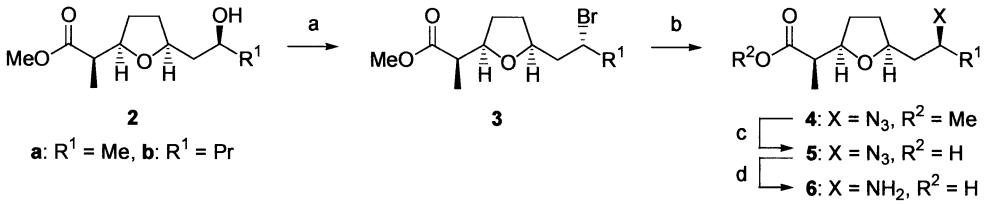


Scheme 1. Preparation of amino acids **6a** and **6b**: (a) $Ph_3P{\cdot}Br_2$, CH_2Cl_2, toluene, 0°C to rt, 83% **3a**, 75% **3b**; (b) NaN_3, DMF, 60°C, 98% **4a**, 97% **4b**; (c) 2N NaOH, MeOH, rt, 92% **5a**, 90% **5b**; (d) H_2, 10% Pd/C, MeOH, rt, 83% **6a**, 79% **6b**.

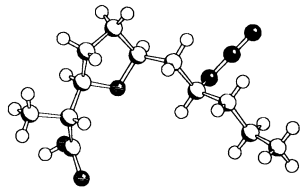
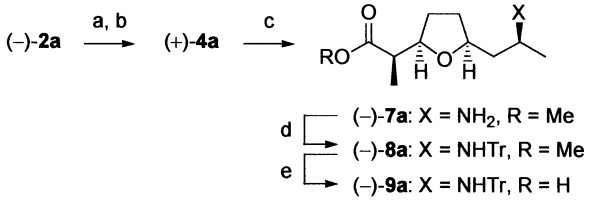


Figure 2. Crystal structure of azido acid **5b**.[13]

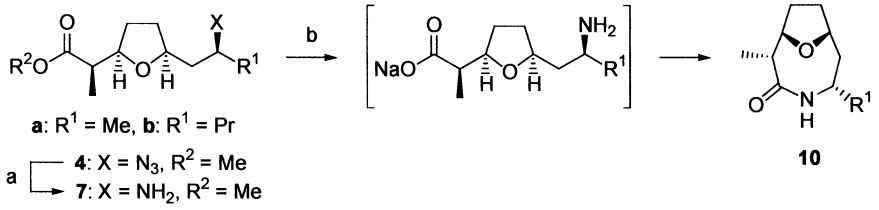


Scheme 2. Preparation of partially protected, enantiomerically pure building blocks (−)-**7a** and (−)-**9a**: (a,b) see Scheme 1; (c) H_2, 10% Pd/C, MeOH, rt, 98%; (d) Ph_3CCl, Et_3N, CH_2Cl_2, rt, 96%; (e) KOH, THF, MeOH, rt, 84%.

the resultant sodium carboxylates, treatment with DPPA induced a smooth ring closure to give the lactams **10**.[16b] Application of high dilution conditions[6d] was not required in this case, which clearly underlines the conformational restriction caused by the cyclic ether. In contrast to the corresponding lactonization of acids **1a**,**b**, no epimerization was observed during the formation of **10a**,**b**, the relative configuration of which was unequivocally established by single crystal X-ray analyses (Figs. 3 and 4).

3. Conclusion

In summary, the novel THF-amino acids **6** and partially protected derivatives suitable for peptide coupling were efficiently synthesized from actic acid methyl esters **2**. Utilization of these conformationally constrained building blocks for peptidomimetics and ion transport systems is currently under investigation in our laboratories and will be reported in due course.



Scheme 3. Preparation of lactams **10a** and **10b**: (a) H_2, 10% Pd/C, MeOH, rt, 98% **7a**, 96% **7b**; (b) (i) 2N NaOH, MeOH, rt, (ii) $N_3PO(OPh)_2$, Et_3N, DMF, 0°C to rt, 53% **10a**, 61% **10b**.

(−)-**9a** was efficiently secured by *N*-tritylation of (−)-**7a** followed by mild ester hydrolysis.

2.2. Lactamization of THF-amino acids 6

We recently reported the lactonization of hydroxy acids **1a**,**b** under Yamaguchi conditions.[6d] Formation of the corresponding medium-sized lactones was accompanied by extensive epimerization at C(2). With amino acids **6a**,**b** at hand, it was tempting to see as to whether the conformational constraint imposed by the 2,5-*cis* disubstituted tetrahydrofuran moiety would also facilitate lactamization. Among the various methods used for the synthesis of medium-ring lactams by amide bond formation,[15] we chose carboxyl activation by diphenylphosphoryl azide (DPPA) (Scheme 3).[16]

To this end, the racemic azides **4a**,**b** were hydrogenated to give the amino esters **7**. After saponification and drying of

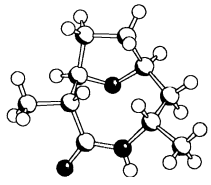


Figure 3. Crystal structure of lactam **10a**.[13]

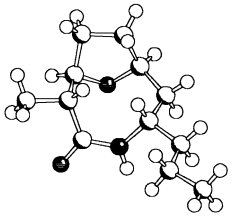


Figure 4. Crystal structure of lactam **10b**.[13]

4. Experimental

4.1. General experimental information

All reactions requiring exclusion of moisture were run under argon using flame-dried glassware. Solvents were dried by distillation from potassium (THF) or else CaH_2. Flash chromatography was performed on Merck silica gel 60 (40–63 μm). Capillary GC analyses were performed with a Shimadzu GC-14A or GC-14B, a Shimadzu C-R6A integrator, and a HP 5 column (25 m length, 0.25 mm i.d., 0.25 μm film). Melting points were determined on a Kofler microscope desk. Optical rotations were measured with a Perkin–Elmer 241 and a Perkin–Elmer 341 polarimeter. FT-IR spectra were obtained on a Nicolet 205; w=weak, s=strong, m=medium, br=broad. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker ASP-300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz) and a Bruker DRX-500 (^{1}H: 500 MHz, ^{13}C: 126 MHz); br=broad. ^{13}C multiplicities were determined using DEPT pulse sequences. Mass spectra (GC/MS, 70 eV) were recorded with a Hewlett Packard 5972 detector coupled with a Hewlett Packard 5890 GC. Mass spectra (ESI) were obtained with a Bruker Esquire-LC. Mass spectra (EI, 70 eV) and high resolution mass spectra (HR-EI, 70 eV and HR-CI) were obtained with a Finnigan MAT 95. Microanalyses were performed by the analytical laboratory of the Institut für Organische Chemie, Technische Universität Dresden.

4.2. Preparation of bromides 3

A solution of methyl nonactate (**2a**) (2.20 g, 10.2 mmol) in anhydrous dichloromethane (15 mL) was added dropwise by syringe to a suspension of triphenylphosphine dibromide (4.77 g, 11.3 mmol) in dry toluene (25 mL) cooled to 0°C. After stirring for 3.5 h at room temperature, the reaction mixture was filtered through a plug of silica and eluted with ether. The solvent was removed in vacuo, and the residue was purified by flash chromatography (dichloromethane/ether 40:1) to give the bromide **3a** (2.35 g, 83%). Similarly, **3b** (944 mg, 75%) was obtained from **2b** (1.00 g, 4.09 mmol).

4.2.1. Bromide 3a. Colorless oil; R_f 0.46 (dichloromethane/ether 40:1); IR (neat): 2976 (s), 2949 (s), 1740 (s, C=O), 1460 (m), 1435 (m), 1378 (m), 1262 (m), 1200 (s), 1161 (m), 1081 (s), 1061 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.09 (d, J=7.2 Hz, 3H), 1.45–1.50 (m, 1H), 1.57–1.63 (m, 1H), 1.70 (d, J=6.7 Hz, 3H), 1.83–1.88 (m, 1H), 1.93–2.04 (m, 2H), 2.17–2.22 (m, 1H), 2.49 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 3.68 (s, 3H), 3.98–4.02 (m, 2H), 4.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 13.43 (q), 25.95 (q), 28.35 (t), 30.71 (t), 45.33 (d), 47.19 (t), 47.44 (d), 51.62 (q), 77.23 (d), 80.58 (d), 175.22 (s); MS (GC/MS, 70 eV) m/z (relative intensity): 249 (0.1) [M^+-OCH_3], 247 (0.1) [M^+-OCH_3], 199 (0.9) [M^+-Br], 193 (20) [$M^+-CH_3CHCO_2CH_3$], 191 (22) [$M^+-CH_3CHCO_2CH_3$], 157 (31) [$M^+-C_3H_6Br$], 125 (33) [$M^+-C_3H_6Br-CH_3OH$], 41 (100); Anal. calcd for $C_{11}H_{19}BrO_3$: C, 47.33; H, 6.86. Found C, 47.23; H, 6.84.

Bromide (−)-**3a** obtained from (−)-**2a**: $[\alpha]_D^{25}=-55.7$ (c 1.29, $CHCl_3$).

4.2.2. Bromide 3b. Colorless oil; R_f 0.47 (dichloromethane/ether 40:1); IR (neat): 2960 (s), 2912 (m), 2876 (m), 1740 (s, C=O), 1461 (m), 1434 (m), 1378 (w), 1353 (w), 1340 (w), 1260 (m), 1199 (s), 1164 (m), 1087 (m), 1065 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.90 (t, J=7.4 Hz, 3H), 1.10 (d, J=7.0 Hz, 3H), 1.38–1.65 (m, 4H), 1.73–1.85 (m, 2H), 1.87–1.93 (ddd, J=6.2, 6.2, 14.3 Hz, 1H), 1.94–2.06 (m, 2H), 2.18–2.40 (ddd, J=7.3, 7.3, 14.2 Hz, 1H), 2.50 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 3.68 (s, 3H), 3.98–4.03 (m, 1H), 4.04–4.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 13.38 (q), 13.44 (q), 20.67 (t), 28.39 (t), 30.66 (t), 40.58 (t), 45.22 (t), 45.37 (d), 51.64 (q), 54.17 (d), 77.33 (d), 80.54 (d), 175.26 (s); MS (GC/MS, 70 eV) m/z (relative intensity): 277 (2) [M^+-OCH_3], 275 (2) [M^+-OCH_3], 227 (6) [M^+-Br], 221 (31) [$M^+-CH_3CHCO_2CH_3$], 219 (32) [$M^+-CH_3CHCO_2CH_3$], 157 (100) [$M^+-C_5H_{10}Br$], 125 (80) [$M^+-C_5H_{10}Br-CH_3OH$], 43 (39) [$C_3H_7^+$]; Anal. calcd for $C_{13}H_{23}BrO_3$: C, 50.82; H, 7.55; Br 26.01. Found C, 51.08; H, 7.67; Br, 26.16.

4.3. Preparation of azido esters 4

Sodium azide (820 mg, 12.6 mmol) was added at 60°C to a solution of bromide **3a** (2.35 g, 8.42 mmol) in dry DMF (100 mL), and stirring was continued at this temperature for 2 h. The mixture was allowed to cool to room temperature, and the solvent was removed in vacuo. Purification of the crude product by flash chromatography (dichloromethane/ether 40:1 for **3a**, pentane/ethyl acetate 10:1 for **3b**) gave azido ester **4a** (1.99 g, 98%). Similarly, **4b** (2.00 g, 97%) was obtained from **3b** (2.36 g, 7.68 mmol).

4.3.1. Azido ester 4a. Colorless oil; R_f 0.44 (dichloromethane/ether 40:1); IR (neat): 2973 (s), 2950 (s), 2880 (m), 2101 (s, N_3), 1741 (s, C=O), 1461 (m), 1436 (m), 1378 (m), 1256 (s), 1199 (s), 1164 (m), 1093 (m), 1059 (s); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (d, J=7.0 Hz, 3H), 1.24 (d, J=6.5 Hz, 3H), 1.43–1.49 (m, 1H), 1.53–1.69 (m, 3H), 1.91–2.02 (m, 2H), 2.47 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 3.58–3.64 (m, 1H), 3.68 (s, 3H), 3.97–4.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.40 (q), 20.15 (q), 28.53 (t), 31.26 (t), 42.93 (t), 45.53 (d), 51.62 (q), 55.73 (d), 76.31 (d), 80.58 (d), 175.20 (s); MS (GC/MS, 70 eV) m/z (relative intensity): 198 (0.4) [M^+-HN_3], 182 (8) [$M^+-CO_2CH_3$], 157 (26) [$M^+-C_3H_6N_3$], 154 (13) [$M^+-CH_3CHCO_2CH_3$], 88 (85) [$C_4H_8O_2^+$], 55 (100); Anal. calcd for $C_{11}H_{19}N_3O_3$: C, 54.76; H, 7.94; N, 17.42. Found C, 54.87; H, 8.00; N, 17.71.

Azido ester (+)-**4a** obtained from (−)-**3a**: $[\alpha]_D^{25}=+52.3$ (c 1.44, $CHCl_3$).

4.3.2. Azido ester 4b. Colorless oil; R_f 0.24 (pentane/ethyl acetate 10:1); IR (neat): 2960 (s), 2941 (s), 2876 (s), 2102 (s, N_3), 1741 (s, C=O), 1462 (m), 1436 (m), 1378 (m), 1360 (m), 1341 (m), 1261 (s), 1198 (s), 1163 (m), 1119 (m), 1089 (m), 1066 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.92 (t, J=7.1 Hz, 3H), 1.10 (d, J=7.0 Hz, 3H), 1.34–1.64 (m, 8H), 1.94–2.06 (m, 2H), 2.40 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 3.44–3.50 (m, 1H), 3.68 (s, 3H), 3.97–4.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 13.37 (q), 13.81 (q), 19.23 (t), 28.57 (t), 31.31 (t), 37.31 (t), 41.16 (t), 45.59 (d), 51.61 (q), 60.35 (d), 76.34 (d), 80.54 (d), 175.20 (s); MS (GC/MS,

70 eV) *m/z* (relative intensity): 241 (0.5) [M^+-N_2], 226 (4) [$M^+-C_3H_7$ or M^+-HN_3], 210 (10) [$M^+-CO_2CH_3$], 198 (23) [$M^+-C_3H_7-N_2$], 182 (5) [$M^+-CH_3CHCO_2CH_3$], 171 (6) [$M^+-C_4H_8N_3$], 157 (39) [$M^+-C_5H_{10}N_3$], 112 (34) [$C_5H_{10}N_3^+$], 88 (77) [$C_4H_8O_2^+$], 43 (65) [$C_3H_7^+$], 41 (100); Anal. calcd for $C_{13}H_{23}N_3O_3$: C, 57.97; H, 8.61; N, 15.60. Found C, 58.00; H, 8.68; N, 15.48.

4.4. Preparation of azido acids 5

To a solution of azido ester **4a** (1.21 g, 5.0 mmol) in MeOH (20 mL) was added 2N NaOH (20 mL, 40.0 mmol) at room temperature, and the mixture was stirred vigorously for 10 h. The mixture was acidified to pH 1 with 2N HCl, extracted with ethyl acetate (4×15 mL), and the combined organic layers were dried over $MgSO_4$. Concentration in vacuo and purification of the residue by flash chromatography (dichloromethane/ether 4:1) gave azido acid **5a** (1.04 g, 92%). Similarly, **5b** (861 mg, 90%) was obtained from **4b** (1.01 g, 3.75 mmol).

4.4.1. Azido acid 5a. Colorless oil; R_f 0.27–0.54 (dichloromethane/ether 1:1); IR (neat): 3500–2500 (br, m, OH), 2966 (s), 2945 (s), 2109 (s, N_3), 1715 (s, C=O), 1455 (s), 1419 (s), 1377 (s), 1251 (s), 1089 (s), 1061 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.17 (d, J=7.1 Hz, 3H), 1.29 (d, J=6.5 Hz, 3H), 1.42–1.72 (m, 4H), 1.97–2.11 (m, 2H), 2.51 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 3.61–3.72 (m, 1H), 4.01–4.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.30 (q), 20.04 (q), 28.71 (t), 31.16 (t), 42.85 (t), 45.26 (d), 55.54 (d), 76.62 (d), 80.35 (d), 179.63 (s); MS (GC/MS, 70 eV) *m/z* (relative intensity): 184 (3) [M^+-HN_3], 154 (13) [$M^+-CH_3CHCO_2H$], 143 (17) [$M^+-C_3H_6N_3$], 125 (40) [$M^+-C_3H_6N_3-H_2O$], 84 (23) [$C_3H_6N_3^+$], 70 (24) [$C_2H_4N_3^+$], 42 (100); Anal. calcd for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54; N, 18.49. Found C, 53.11; H, 7.66; N, 18.55.

4.4.2. Azido acid 5b. White needles; R_f 0.30–0.48 (dichloromethane/ether 4:1); mp 34–39°C; IR (KBr): 3029 (br, m, OH), 2962 (s), 2939 (s), 2876 (s), 2102 (s, N_3), 1737 (s, C=O), 1712 (s, C=O), 1465 (m), 1276 (s), 1259 (s), 1228 (s), 1066 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.93 (t, J=7.1 Hz, 3H), 1.15 (d, J=7.0 Hz, 3H), 1.37–1.68 (m, 8H), 2.00–2.08 (m, 2H), 2.51 (dq, J_d=7.5 Hz, J_q=7.5 Hz, 1H), 3.47–3.50 (m, 1H), 4.01–4.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 13.92 (q), 13.82 (q), 19.19 (t), 28.81 (t), 31.21 (t), 37.13 (t), 41.04 (t), 45.22 (d), 60.18 (d), 76.75 (d), 80.30 (d), 179.32 (s); MS (GC/MS, 70 eV) *m/z* (relative intensity): 212 (1) [$M^+-C_3H_7$ or M^+-HN_3], 184 (11) [$M^+-C_3H_7-N_2$], 143 (28) [$M^+-C_5H_{10}N_3$], 125 (57) [$M^+-C_5H_{10}N_3-H_2O$], 112 (22) [$C_5H_{10}N_3^+$], 98 (13) [$C_4H_8N_3^+$], 69 (72) [$C_5H_9^+$], 43 (97) [$C_3H_7^+$], 41 (100); Anal. calcd for $C_{12}H_{21}N_3O_3$: C, 56.45; H, 8.29; N, 16.46. Found C, 56.57; H, 8.57; N, 16.80.

4.5. Preparation of amino acids 6

To a solution of azido acid **5a** (210 mg, 0.93 mmol) in dry MeOH (30 mL) was added 10% Pd/C (30 mg) at ambient temperature. After purging the suspension with hydrogen (5 min), stirring was continued for 10 h (**5a**) or 1 h (**5b**) under a hydrogen atmosphere of 10 bar (**5a**) or 1.5 bar (**5b**). The catalyst was removed by filtration through a glass-filter funnel G5, and the filtrate was evaporated in vacuo to give the amino acid **6a** (156 mg, 83%). Similarly, **6b** (253 mg, 79%) was obtained from **5b** (356 mg, 1.39 mmol) after purification by flash chromatography (methanol).

4.5.1. Amino acid 6a. Colorless solid; mp 185–188°C (decomposition); IR (KBr): 3200–2500 (br, s, OH), 2970 (s), 2918 (s), 2877 (s), 2568 (m), 2224 (m), 1629 (s, C=O), 1552 (s), 1547 (s), 1460 (m), 1406 (s), 1362 (m), 1103 (m), 1074 (m), 1060 (m) cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): δ 1.10 (d, J=7.0 Hz, 3H), 1.32 (d, J=6.8 Hz, 3H), 1.56–2.07 (m, 6H), 2.23 (dq, J_d=7.0 Hz, J_q=7.0 Hz, 1H), 3.48–3.58 (m, 1H), 3.86–3.93 (m, 1H), 4.06–4.11 (m, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 16.50 (q), 19.58 (q), 30.82 (t), 32.06 (t), 39.76 (t), 47.20 (d), 50.65 (d), 77.50 (d), 84.78 (d), 184.28 (s); MS (ESI) *m/z*: 224.1 [M+Na^+], 202.1 [M+H^+], 184 [M+H^+-H_2O]; Anal. calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found C, 59.56; H, 9.87; N, 6.95.

4.5.2. Amino acid 6b. White needles; R_f 0.44 (methanol); mp 249°C (decomposition); IR (KBr): 3419 (m), 2963 (s), 2936 (s), 2874 (s), 2364 (m), 2146 (w), 1567 (s, C=O), 1461 (m), 1402 (s), 1365 (m), 1287 (w), 1090 (w), 1062 (m) cm^{-1}; ^1H NMR (CD_3OD, 500 MHz): δ 1.05 (t, J=7.3 Hz, 3H), 1.17 (d, J=7.1 Hz, 3H), 1.45–1.53 (m, 2H), 1.64–1.80 (m, 4H), 1.90 (ddd, J=3.4, 7.2, 15.3 Hz, 1H), 1.98 (ddd, J=2.9, 7.9, 15.3 Hz, 1H), 2.02–2.12 (m, 2H), 2.36 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 3.43 (ddd, J=2.9, 7.1, 7.1 Hz, 1H), 3.96 (ddd, J=7.2, 7.2, 7.2 Hz, 1H), 4.12–4.17 (m, 1H); ^{13}C NMR (CD_3OD, 126 MHz): δ 14.87 (q), 16.56 (q), 20.60 (t), 30.82 (t), 32.17 (t), 36.37 (t), 37.49 (t), 50.88 (d), 51.14 (d), 77.46 (d), 84.89 (d), 184.48 (s); MS (EI, 70 eV) *m/z* (relative intensity): 186 (31) [$M^+-C_3H_7$], 157 (1) [$M^+-C_4H_8NH_2$], 143 (42) [$M^+-C_5H_{10}NH_2$], 86 (4) [$C_5H_{10}NH_2^+$], 72 (100) [$C_4H_8NH_2^+$]; HRMS (EI, 70 eV) Calcd for $C_{12}H_{23}NO_3$ [M^+]: 229.168. Found: 229.164.

4.6. Preparation of amino esters 7

To a solution of azido ester **4a** (1.61 g, 6.67 mmol) in MeOH (40 mL) was added 10% Pd/C (160 mg) at ambient temperature. After purging the suspension with hydrogen (5 min), stirring was continued for 12 h (**4a**) or 24 h (**4b**) under a hydrogen atmosphere of 10 bar (**4a**) or 1.5 bar (**4b**). The catalyst was removed by filtration through a glass filter funnel G5, and the filtrate was evaporated in vacuo to give the amino ester **7a** (1.40 g, 98%). Similarly, **7b** (447 mg, 96%) was obtained from **4b** (515 mg, 1.91 mmol).

4.6.1. Amino ester 7a. Colorless oil; IR (neat): 3311 (w, NH), 3302 (w, NH), 2955 (s), 2877 (s), 1740 (s, C=O), 1596 (w), 1460 (m), 1436 (m), 1377 (m), 1263 (m), 1199 (s), 1164 (s), 1085 (s), 1063 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.07 (d, J=6.4 Hz, 3H), 1.10 (d, J=7.0 Hz, 3H), 1.39–1.63 (m, 6H), 1.89–2.03 (m, 2H), 2.51 (dq, J_d=7.0 Hz, J_q=7.0 Hz, 1H), 3.01–3.12 (m, 1H), 3.67 (s, 3H), 3.92–4.02 (m, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.40 (q), 24.31 (q), 28.52 (t), 31.32 (t), 44.34 (d), 45.42 (d), 45.61 (t), 51.59 (q), 76.91 (d), 80.53 (d), 175.38 (s); MS (ESI) *m/z*: 238 [M+Na^+], 216 [M^++H^+]; Anal. calcd for

$C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found C, 61.77; H, 9.50; N, 6.38.

Amino ester (−)-**7a** obtained from (+)-**4a**: $[\alpha]_D^{25}=-14.5$ (*c* 1.25, $CHCl_3$).

4.6.2. Amino ester 7b. Colorless oil; R_f 0.50 (methanol); IR (neat): 2956 (s), 2935 (s), 2874 (m), 1740 (s, C=O), 1575 (w), 1573 (w), 1462 (m), 1436 (m), 1378 (m), 1340 (w), 1265 (w), 1199 (m), 1164 (m), 1087 (w), 1062 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.89 (t, *J*=6.7 Hz, 3H), 1.09 (d, *J*=7.0 Hz, 3H), 1.20–1.42 (m, 5H), 1.43–1.65 (m, 5H), 1.90–2.00 (m, 2H), 2.50 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 2.86–2.91 (m, 1H), 3.66 (s, 3H), 3.96–4.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 13.34 (q), 14.11 (q), 19.21 (t), 28.52 (t), 31.43 (t), 40.61 (t), 43.73 (t), 45.42 (d), 48.14 (d), 51.57 (q), 76.82 (d), 80.49 (d), 175.39 (s); MS (GC/MS, 70 eV) *m/z* (relative intensity): 212 (6) [M^+-OCH_3], 200 (27) [$M^+-C_3H_7$], 157 (54) [$M^+-C_5H_{10}NH_2$)], 86 (5) [$C_5H_{10}NH_2^+$], 72 (100) [$C_4H_8NH_2^+$], 43 (19) [$C_3H_7^+$]; HRMS (CI) Calcd for $C_{13}H_{26}NO_3$ [$M+H^+$]: 244.1913. Found: 244.1903.

4.7. Preparation of *N*-trityl ester (−)-8a

To a solution of amino ester (−)-**7a** (1.18 g, 5.48 mmol) and triethylamine (1.21 g, 12.0 mmol) in anhydrous dichloromethane (30 mL) cooled to 0°C was added a solution of trityl chloride (1.65 g, 5.92 mmol) in dichloromethane (15 mL). The mixture was stirred for 6 h at room temperature and diluted with ether (100 mL). The organic layer was washed with 5% aqueous citric acid (50 mL) and saturated aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (dichloromethane/pentane/ether 10:10:1 containing 0.5% triethylamine) afforded *N*-trityl ester (−)-**8a** (2.40 g, 96%) as a colorless oil. R_f 0.28 (dichloromethane/pentane/ether 5:5:1); $[\alpha]_D^{25}=-6.51$ (*c* 2.09, $CHCl_3$); IR (neat): 3330 (w, NH), 3085 (w), 3031 (m), 2972 (s), 2873 (s), 1740 (s, C=O), 1696 (m), 1489 (s), 1457 (s), 1448 (s), 1376 (m), 1259 (m), 1201 (s), 1164 (s), 1067 (s), 901 (m), 775 (m), 746 (m), 708 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.82 (d, *J*=6.4 Hz, 3H), 1.05 (d, *J*=7.0 Hz, 3H), 1.09–1.15 (m, 3H), 1.36–1.47 (m, 1H), 1.63–1.86 (m, 2H), 1.90 (br s, 1H), 2.43 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 2.55–2.62 (m, 1H), 3.54 (s, 3H), 3.69–3.78 (m, 1H), 3.92 (m, 1H), 7.13–7.18 (m, 3H), 7.22–7.27 (m, 6H), 7.53–7.57 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.38 (q), 22.62 (q), 28.07 (t), 31.10 (t), 43.71 (t), 45.13 (d), 47.04 (d), 51.51 (q), 71.46 (s), 77.21 (d), 80.30 (d), 126.05 (d), 127.65 (d), 128.91 (d), 147.27 (s), 175.37 (s); MS (ESI) *m/z*: 480.2 [$M+Na^+$], 458.1 [$M+H^+$], 243.1 [Tr^+]; Anal. calcd for $C_{30}H_{35}NO_3$: C, 78.74; H, 7.71; N, 3.06. Found C, 78.51; H, 7.97; N, 3.18.

4.8. Preparation of *N*-trityl acid (−)-9a

To a solution of *N*-trityl ester (−)-**8a** (1.11 g, 2.43 mmol) in THF (10.5 mL)/MeOH (3.5 mL) was added 5N KOH (3.5 mL, 17.5 mmol) at room temperature. After stirring the mixture for 15 h at ambient temperature, it was acidified to pH 5 with 5% citric acid and extracted with ether (3×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (dichloromethane/ether 5:1) yielded *N*-trityl acid (−)-**9a** (900 mg, 84%) as a colorless foamy solid. R_f 0.15 (dichloromethane/ether 5:1); mp 53–55°C; $[\alpha]_D^{25}=-3.16$ (*c* 1.05, $CHCl_3$); IR (KBr): 3600–2500 (br, m, OH), 3337 (w, NH), 3057 (m), 2971 (s), 2876 (m), 1710 (s, C=O), 1490 (m), 1448 (m), 1208 (m), 1095 (m), 1056 (m), 771 (m), 747 (m), 707 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.84 (d, *J*=6.4 Hz, 3H), 1.10 (d, *J*=7.1 Hz, 3H), 1.12–1.25 (m, 3H), 1.41–1.48 (m, 1H), 1.70–1.76 (m, 1H), 1.84–1.91 (m, 1H), 2.40 (dq, J_d=7.1 Hz, J_q=7.1 Hz, 1H), 2.57–2.61 (m, 1H), 3.81 (m, 1H), 3.89 (m, 1H), 7.15–7.18 (m, 3H), 7.23–7.27 (m, 6H), 7.54–7.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 13.38 (q), 22.61 (q), 28.75 (t), 30.71 (t), 43.77 (t), 44.63 (d), 46.92 (d), 71.44 (s), 78.01 (d), 80.08 (d), 126.15 (d), 127.69 (d), 128.86 (d), 147.09 (s), 177.60 (s); MS (ESI) *m/z*: 466.2 [$M+Na^+$], 444.0 [$M+H^+$], 243.1 [Tr^+]; Anal. calcd for $C_{29}H_{33}NO_3$: C, 78.52; H, 7.50; N, 3.16. Found C, 78.69; H, 7.75; N, 3.19.

4.9. Preparation of lactams 10

To a solution of amino ester **7a** (302 mg, 1.40 mmol) in MeOH (5 mL) was added 2N NaOH (0.70 mL, 1.40 mmol) at ambient temperature, and stirring was continued for further 3 d. The solvent was evaporated at reduced pressure, and the residue was dried in vacuo over phosphorous pentoxide for 3 d. The resultant amino acid sodium salt was dissolved in dry DMF (300 mL), and diphenylphosphoryl azide (389 μL, 1.80 mmol) and anhydrous triethylamine (297 μL, 2.00 mmol) were subsequently added at 0°C. While stirring was continued, the reaction mixture was allowed to warm to room temperature overnight. The solvents were evaporated in vacuo, and the residue was purified by flash chromatography (dichloromethane/methanol 20:1) to give the lactam **10a** (136 mg, 53%). Similarly, **10b** (184 mg, 61%) was obtained from **7b** (346 mg, 1.42 mmol).

4.9.1. Lactam 10a. Colorless solid; R_f 0.25 (dichloromethane/methanol 20:1); mp 177–180°C; IR (KBr): 3214 (s, NH), 3087 (m, NH), 2969 (s), 2932 (s), 2916 (s), 2891 (m), 1660 (s, C=O), 1464 (m), 1451 (m), 1423 (s), 1384 (w), 1371 (m), 1338 (m), 1301 (s), 1178 (m), 1100 (m), 1029 (s), 817 (m), 738 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.09 (d, *J*=6.5 Hz, 3H), 1.20 (d, *J*=6.5 Hz, 3H), 1.47 (d, *J*=14.5 Hz, 1H), 1.85–1.96 (m, 3H), 1.98–2.14 (m, 2H), 2.52 (dq, J_d=9.1 Hz, J_q=6.5 Hz, 1H), 3.86 (dd, *J*=6.0, 9.2 Hz, 1H), 3.90–3.95 (m, 1H), 4.44–4.48 (m, 1H), 5.21 (d, *J*=7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 13.40 (q), 22.81 (q), 26.95 (t), 32.80 (t), 41.52 (d), 42.18 (t), 43.87 (d), 76.67 (d), 82.59 (d), 175.16 (s); MS (GC/MS, 70 eV) *m/z* (relative intensity): 183 (47) [M^+], 168 (5) [M^+-CH_3], 44 (100); Anal. calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found C, 65.94; H, 9.77; N, 7.70.

4.9.2. Lactam 10b. White needles; R_f 0.22 (dichloromethane/methanol 20:1); mp 110–112°C; IR (KBr): 3299 (m, NH), 3207 (s, NH), 3086 (s), 2962 (s), 2927 (s), 2905 (s), 2872 (s), 1662 (s, C=O), 1465 (m), 1457 (m), 1442 (m), 1423 (s), 1376 (m), 1340 (m), 1309 (m), 1294 (s), 1160 (m), 1109 (m), 1090 (s), 1040 (m), 980 (m), 817 (m) cm^{-1}; ^1H

NMR ($CDCl_3$, 500 MHz): δ 0.91 (t, J=6.9 Hz, 3H), 1.10 (d, J=6.4 Hz, 3H), 1.33–1.50 (m, 5H), 1.83–1.95 (m, 3H), 1.99–2.14 (m, 2H), 2.51 (dq, J_d=8.7 Hz, J_q=6.5 Hz, 1H), 3.70–3.76 (m, 1H), 3.87 (dd, J=6.0, 9.0 Hz, 1H), 4.46–4.51 (m, 1H), 5.17 (d, J=7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 13.45 (q), 13.74 (q), 19.17 (t), 26.95 (t), 32.83 (t), 38.70 (t), 40.56 (t), 41.52 (d), 48.02 (d), 76.75 (d), 82.62 (d), 175.25 (s); MS (GC/MS, 70 eV) *m/z* (relative intensity): 211 (32) [M^+], 196 (1) [M^+-CH_3], 168 (24) [$M^+-C_3H_7$], 72 (100), 43 (26) [$C_3H_7^+$]; Anal. calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found C, 67.99; H, 10.36; N, 6.53.

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References

1. For a recent review, see: Koert, U. *J. Prakt. Chem.* **2000**, *342*, 325–333.
2. Schrey, A.; Vescovi, A.; Knoll, A.; Rickert, C.; Koert, U. *Angew. Chem.* **2000**, *112*, 928–931; *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 900–902.
3. Seebach, D.; Albert, M.; Arvidsson, P. I.; Rüping, M.; Schreiber, J. V. *Chimia* **2001**, *55*, 345–353.
4. (a) Metz, P.; Meiners, U.; Cramer, E.; Fröhlich, R.; Wibbeling, B. *Chem. Commun.* **1996**, 431–432. (b) Meiners, U.; Cramer, E.; Fröhlich, R.; Wibbeling, B.; Metz, P. *Eur. J. Org. Chem.* **1998**, 2073–2078.
5. For reviews, see: (a) Keller-Schierlein, W.; Gerlach, H. *Fortschr. Chem. Org. Naturst.* **1968**, *26*, 161–189. (b) Nawata, Y.; Ando, K.; Iitaka, Y. *Met. Ions Biol. Syst.* **1985**, *19*, 207–227. (c) Zizka, Z. *Folia Microbiol.* **1998**, *43*, 7–14.
6. (a) Bernsmann, H.; Hungerhoff, B.; Fechner, R.; Fröhlich, R.; Metz, P. *Tetrahedron Lett.* **2000**, *41*, 1721–1724. (b) Bernsmann, H.; Fröhlich, R.; Metz, P. *Tetrahedron Lett.* **2000**, *41*, 4347–4351. (c) Bernsmann, H.; Gruner, M.; Metz, P. *Tetrahedron Lett.* **2000**, *41*, 7629–7633. (d) Bernsmann, H.; Gruner, M.; Fröhlich, R.; Metz, P. *Tetrahedron Lett.* **2001**, *42*, 5377–5380. (e) Wang, Y.; Bernsmann, H.; Gruner, M.; Metz, P. *Tetrahedron Lett.* **2001**, *42*, 7801–7804.
7. For reviews, see: (a) Pogell, B. M. *Cell Mol. Biol.* **1998**, *44*, 461–463. (b) Natsume, M. *Recent Res. Dev. Agric. Biol. Chem.* **1999**, *3*, 11–22.
8. For a recent review on sultones, see: Metz, P. *J. Prakt. Chem.* **1998**, *340*, 1–10.
9. Wang, Y.; Metz, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3995–3999.
10. (a) Galynker, I.; Still, W. C. *Tetrahedron Lett.* **1982**, *23*, 4461–4464. (b) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A. *J. Org. Chem.* **1992**, *57*, 3631–3636.
11. (a) Horner, L.; Oediger, H.; Hoffmann, H. *Liebigs Ann. Chem.* **1959**, *626*, 26–34. (b) Castro, B. R. *Org. React.* **1983**, *29*, 1–162.
12. (a) Biffin, M. E. C.; Miller, J.; Paul, D. B. In *The Chemistry of the Azide Group*, Patai, S., Ed.; Interscience: London, 1971; pp 57–190. (b) Scriven, E.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368. (c) Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry* **1995**, *6*, 469–498.
13. Crystal data for **5b**: $C_{12}H_{21}N_3O_3$, M=255.32, monoclinic, space group $P2_1/c$ (No. 14), a=5.371(1), b=20.654(3), c=12.688(2) Å, β=100.81(1)°, V=1382.5(4) Å^3, Z=4, D_c=1.227 g cm^{-3}, μ=7.30 cm^{-1}, empirical absorption correction via Ψ-scan data ($0.839 \le T \le 0.931$), $F(000)$=552, colorless crystal with dimensions 0.25×0.10×0.10 mm^3, λ=1.54178 Å, T=223(2) K, θ-range 4.14–74.26°, index ranges $0 \le h \le 6$, $-25 \le k \le 0$, $-15 \le l \le 15$, 3122 reflections collected, 2819 independent [R_{int}=0.035], 1651 observed [$I>2\sigma(I)$], full matrix least-squares refinement on F^2, 166 parameters, GOF on F^2 1.000, final R indices [$I>2\sigma(I)$] R=0.052 and wR^2=0.132, largest difference peak and hole 0.34 and −0.36 eÅ^{-3}, hydrogen atoms calculated and refined as riding atoms. Crystal data for **10a**: $C_{10}H_{17}NO_2$, M=183.25, monoclinic, space group $P2_1/c$ (No. 14), a=8.650(4), b=12.738(4), c=9.774(2) Å, β=114.04(3)°, V=983.5(6) Å^3, Z=4, D_c=1.238 g cm^{-3}, μ=6.88 cm^{-1}, empirical absorption correction via Ψ-scan data ($0.875 \le T \le 0.966$), $F(000)$=400, colorless crystal with dimensions 0.20×0.20×0.05 mm^3, λ=1.54178 Å, T=223(2) K, θ-range 5.60–74.35°, index ranges $-9 \le h \le 10$, $-15 \le k \le 0$, $-12 \le l \le 0$, 2117 reflections collected, 1998 independent [R_{int}=0.031], 1269 observed [$I>2\sigma(I)$], full matrix least-squares refinement on F^2, 124 parameters, GOF on F^2 1.014, final R indices [$I>2\sigma(I)$] R=0.052 and wR^2=0.128, largest difference peak and hole 0.28 and −0.23 eÅ^{-3}, hydrogen atoms calculated and refined as riding atoms. Crystal data for **10b**: $C_{12}H_{21}NO_2$, M=211.30, orthorhombic, space group $Pbca$ (No. 61), a=9.737(3), b=21.204(1), c=23.917(1) Å, V=4939.0(16) Å^3, Z=16, D_c=1.137 g cm^{-3}, μ=6.07 cm^{-1}, empirical absorption correction via Ψ-scan data ($0.751 \le T \le 0.915$), $F(000)$=1856, colorless crystal with dimensions 0.50×0.25×0.15 mm^3, λ=1.54178 Å, T=223(2) K, θ-range 3.70–74.22°, index ranges $0 \le h \le 12$, $0 \le k \le 26$, $-29 \le l \le 0$, 5021 reflections collected, 5021 independent [R_{int}=0.000], 3781 observed [$I>2\sigma(I)$], full matrix least-squares refinement on F^2, 282 parameters, GOF on F^2 1.025, final R indices [$I>2\sigma(I)$] R=0.046 and wR^2=0.128, largest difference peak and hole 0.22 and −0.22 eÅ^{-3}, hydrogen atoms calculated and refined as riding atoms, two independent molecules in the asymmetric unit, bridged by hydrogen bonds. Data sets were collected with an Enraf-Nonius CAD4 diffractometer. Programs used: data collection EXPRESS (Nonius B.V., 1994), data reduction MolEN (Fair, K. Enraf-Nonius B.V., 1990), structure solution SHELXS-97 (Sheldrick, G. M. *Acta Crystallogr. A*, **1990**, *A46*, 467–473), structure refinement SHELXL-97 (Sheldrick, G. M., Universität Göttingen, 1997), graphics SCHAKAL 99 (Keller, E. Universität Freiburg, 1999). Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbers CCDC 176898 (**5b**), CCDC 176899 (**10a**), CCDC 176900 (**10b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
14. (a) Sheradsky, T. In *The Chemistry of the Azide Group*, Patai, S., Ed.; Interscience: London, 1971; pp 331–395.

(b). Wessjohann, L.; Krass, N.; Yu, D.; de Meijere, A. *Chem. Ber.* **1992**, *125*, 867–882.
15. For a recent review, see: Nubbemeyer, U. *Topics in Current Chemistry*; Metz, P., Ed.; Springer: Berlin, 2001; Vol. 216, pp 125–196.
16. (a) Shioiri, T.; Ninomiya, K.; Yamada, S.-i. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205. (b) de Laszlo, S. E.; Ley, S. V.; Porter, R. A. *J. Chem. Soc., Chem. Commun.* **1986**, 344–346.