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A SECOND-GENERATION SYNTHESIS OF SCALEMIC 3,5,5-TRISUBSTITUTED PYRROLIN-4-ONES: INCORPORATION OF FUNCTIONALIZED AMINO ACID SIDE-CHAINS

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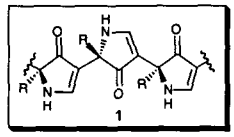
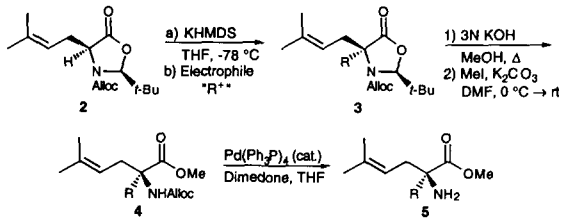
Abstract: To access mimics of peptidal β-strands (**1**), scalemic 3,5,5-trisubstituted pyrrolin-4-ones bearing the tyrosine, serine, and lysine side-chains have been generated via cyclization of metalated imino esters and deprotection. The functionalized imino esters were prepared by asymmetric alkylation of a common oxazolidinone precursor (**2**) derived from L-prenylglycine. © 1997 Elsevier Science Ltd.

We have previously reported the design and synthesis of mimics of peptidal β-strands based on the 3,5,5-trisubstituted pyrrolin-4-one motif (**1**).[1] In these studies the Seebach[2]/Karady[3] oxazolidinone methodology was utilized to convert leucine, valine, and phenylalanine to α,α-disubstituted amino ester building blocks. The respective alkyl and phenyl substituents readily tolerated the vigorous conditions used to elaborate the amino esters into pyrrolinones. Unfortunately, the reactivity of most amino acid side-chains has precluded the generalization of this approach.



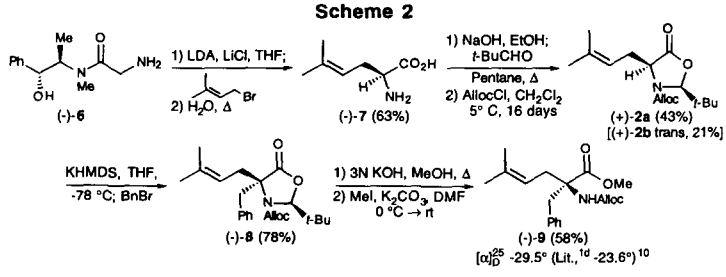
We envisioned that the stereoselective alkylation of a preformed common oxazolidinone **2** (Scheme 1), derived from L-prenylglycine, with suitably protected electrophiles[4] would lead to an effective synthesis of amino ester building blocks (i.e., **5**) incorporating functionalized side-chain precursors. In addition, this strategy should provide access to pyrrolinones with non-DNA-coded side-chains, affording important flexibility in peptidomimetic design.

Scheme 1



We immediately recognized that the need for decagram quantities of L-prenylglycine [(-)-**7**, Scheme 2] might present a significant obstacle, as nearly all of the numerous asymmetric constructions of α-amino acids[5] seemed unlikely to prove satisfactory. The most promising method appeared to be the asymmetric alkylation of pseudoephedrine glycinamide, recently devised by Myers and co-workers.[6] Indeed, alkylation of (*R,R*)-(-)-pseudoephedrine glycinamide [(-)-**6**] with prenyl bromide followed by hydrolysis of the pseudoephedrine auxiliary provided the requisite L-prenylglycine [(-)-**7**][7,8] (63% yield, 94% ee by HPLC; Scheme 2).[9]

Scheme 2

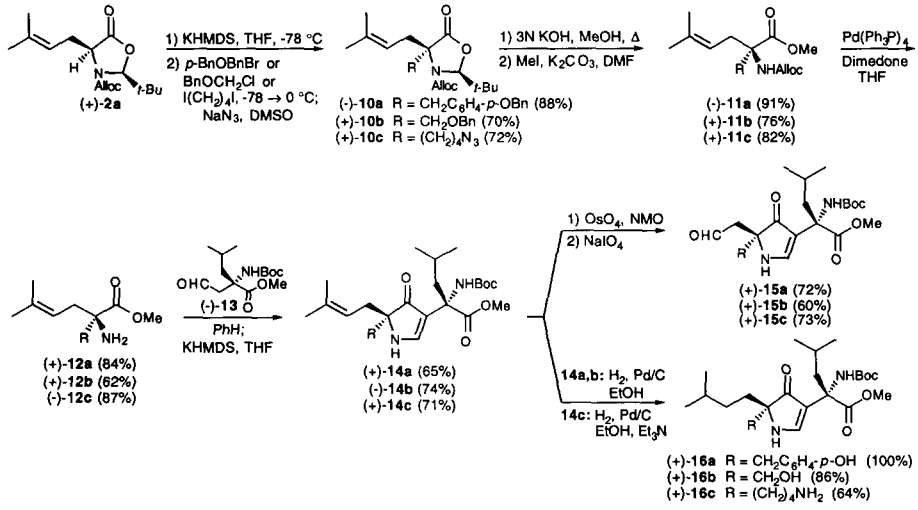


Following condensation of the sodium salt of L-prenylglycine [(-)-**7**] with pivalaldehyde via the Seebach protocol,[2a] treatment of the resultant imine

with allyl chloroformate[1b] induced cyclization to furnish the common oxazolidinone as a 2:1 mixture of cis [(+)-**2a**][7,8] and trans [(+)-**2b**][8] diastereomers (64% yield; Scheme 2); the pure cis isomer was obtained in 43% yield after silica gel chromatography. To test the utility of the oxazolidinone, we undertook the synthesis of (-)-**9**, the known[1b,1d] amino ester building block for pyrrolinones bearing the phenylalanine side-chain (Scheme 2). In the event, stereoselective alkylation of (+)-**2a** with benzyl bromide, basic hydrolysis of the alkylated oxazoldinone, and O-methylation of the resultant acid yielded the protected amino ester (-)-**9**,[8] identical in all respects with material derived from D-phenylalanine.[1d,10]

The successful preparation of (-)-**9** from oxazolidinone (+)-**2a** set the stage for the synthesis of heretofore inaccessable pyrrolinones containing the functionalized side-chains of the tyrosine,[11] serine, and lysine amino acids (Scheme 3). Here, careful selection of protecting groups was expected to be critical. In the interest of efficiency, we also sought to devise a strategy employing a standardized sequence of deprotection reactions. Protection of the tyrosine and serine hydroxyls as benzyl ethers and the use of an azide as precursor to the lysine side-chain amine would enable us to unmask all three side-chains via a straightforward single-step hydrogenation procedure.

Scheme 3



Accordingly, the common oxazolidinone (+)-**2a** was alkylated with *p*-benzyloxybenzyl bromide,[12] benzyloxymethyl chloride,[13] and 1,4-diiodobutane (5 equiv), respectively. In each case, alkylation proceeded with high diastereoselectivity (>95%); the unwanted diastereomers could not be detected by ^{1}H NMR. For the lysine mimetic, the intermediate primary iodide was treated with NaN_3 in DMSO to generate primary azide (+)-**10c** in high yield. Basic hydrolysis of the alkylated oxazolidinones **10a-c**[8] followed by O-methylation of the resultant acids then provided the protected amino esters **11a-c**.[8] Palladium-catalyzed removal of the Alloc protecting groups[14] gave amino esters **12a-c**,[7,8] which in turn were condensed with aldehyde building block (-)-**13**,[1d] derived from D-leucine. Cyclization of the corresponding imines with KHMDS (4 equiv) in THF afforded the protected pyrrolinones **14a-c**[7,8] in yields (65-74%) comparable to those obtained with chemically inert side-chains. A two-step oxidation (OsO_4 and NMO followed by $NaIO_4$) then produced aldehydes **15a-c**,[7,8] suitable for chain extension to polypyrrolinones. Alternatively, the side-chains in **14a-c** could be umasked via catalytic hydrogenolysis, which also reduced the terminal prenyl group to give **16a-c**.[7,8] The successful generation of the lysine aminobutyl moiety

unexpectedly required the inclusion of triethylamine, whereas deprotection of the tyrosine and serine side-chains proceeded cleanly and rapidly.

In summary, we have developed methodology that provides efficient access to pyrrolinones bearing both DNA-coded and uncoded amino acid side-chains. The successful strategy employs enantioselective alkylation of a common oxazolidinone with protected side-chain electrophiles, and has already furnished pyrrolinones mimicking tyrosine, serine, and lysine. Applications to the design and synthesis of side-chain functionalized peptidomimetics will be reported in due course.

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7. (+)-**2a**: colorless oil; $[\alpha]_D^{23}$ +46.8° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 2980 (m), 2910 (m), 1795 (s), 1720 (s), 1390 (m), 1335 (m), 1045 (m), 980 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 (m, 1 H), 5.51 (s, 1 H), 5.30 (m, 3 H), 4.62 (m, 2 H), 4.24 (dd, *J* = 8.0, 6.7 Hz, 1 H), 2.58 (m, 2 H), 1.72 (s, 3 H), 1.63 (s, 3 H), 0.97 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 155.8, 135.0, 131.8, 118.9, 118.5, 96.2, 67.0, 57.5, 37.0, 31.8, 29.7, 25.8, 25.0, 17.9; high resolution mass spectrum (CI, NH_3) *m/z* 296.1858 [$(M+H)^+$; calcd for $C_{16}H_{26}NO_4$: 296.1861]. Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74. Found: C, 64.96; H, 8.38; N, 4.74.

(-)-**7**: white solid; $[\alpha]_D^{23}$ -4.0° (*c* 1.03, 1 N aq HCl); IR (KBr) 3420 (w), 3300-2400 (s), 2110 (w), 1590 (s), 1520 (s), 1430 (s), 1400 (s), 1360 (m), 1320 (m), 1300 (m), 1150 (m) cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 5.04 (apparent t, *J* = 7.5 Hz, 1 H), 3.63 (m, 1 H), 2.50 (m, 2 H), 1.67 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (125 MHz, D_2O; DSS) δ 177.2, 141.6, 118.8, 57.4, 31.8, 27.7, 19.8; high resolution mass spectrum (CI, NH_3) *m/z* 144.1026 [$(M+H)^+$; calcd for $C_7H_{14}NO_2$: 144.1024].

(+)-**12a**: light yellow wax; $[\alpha]_D^{23}$ +4.0° (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3010 (m), 2960 (m), 2940 (m), 1735 (s), 1615 (m), 1510 (s), 1455 (m), 1230 (s), 1180 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 7.05 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 5.04 (apparent t, *J* = 7.6 Hz, 1 H), 5.01 (s, 2 H), 3.67 (s, 3 H), 3.11 (d, *J* = 13.4 Hz, 1 H), 2.72 (d, *J* = 13.4 Hz, 1 H), 2.56 (dd, *J* = 14.0, 6.7 Hz, 1 H), 2.33 (dd, *J* = 14.1, 8.5 Hz, 1 H), 1.70 (s, 3 H), 1.64 (s, 3 H), 1.61 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 157.9, 137.1, 136.3, 130.8, 128.8, 128.5, 127.9, 127.4, 118.0, 114.8, 70.0, 62.7, 51.8, 45.0, 38.6, 26.0, 18.1; high resolution mass spectrum (CI, NH_3) *m/z* 354.2076 [$(M+H)^+$; calcd for $C_{22}H_{28}NO_3$: 354.2069]. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.97. Found: C, 74.52; H, 7.72; N, 3.79.

(+)-**14a**: white foam; $[\alpha]_D^{23}$ +50.9° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 3320 (w), 3010 (m), 2980 (m), 1705 (s), 1510 (s), 1235 (s), 1170 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1 H), 7.32 (m, 5 H), 6.99 (d, *J* = 8.5 Hz, 2 H), 6.94 (s, 1 H), 6.81 (d, *J* = 8.6 Hz, 2 H), 5.31 (s, 1 H), 5.00 (s, 2 H), 4.97 (apparent t, *J* = 7.3 Hz, 1 H), 3.59 (s, 3 H), 2.87 (d, *J* = 13.8 Hz, 1 H), 2.75 (d, *J* = 13.8 Hz, 1 H), 2.34 (dd, *J* = 14.4, 7.4 Hz, 1 H), 2.26 (dd, *J* = 14.4, 7.3 Hz, 1 H), 2.17 (m, 1 H), 2.00 (m, 1 H), 1.64 (s, 3 H), 1.55 (m, 1 H), 1.54 (s, 3 H), 1.38 (s, 9 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 173.6, 161.8, 157.7, 154.4, 137.0, 136.1, 131.0, 128.6, 128.0, 127.4, 117.0, 114.4, 78.8, 71.1, 70.0, 59.8, 52.4, 42.4, 40.9, 34.6, 28.4, 25.8, 24.3, 24.2, 23.5, 18.0; high resolution mass spectrum (CI, NH_3) *m/z* 591.3451 [$(M+H)^+$; calcd for $C_{35}H_{47}N_2O_6$: 591.3434].

(+)-**15a**: colorless oil; $[\alpha]_D^{23}$ +115.4° (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 3010 (m), 2960 (m), 1710 (s), 1510 (s), 1490 (s), 1240 (s), 1175 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1 H), 7.93 (s, 1 H), 7.34 (m, 5 H), 6.99 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.6 Hz, 2 H), 6.44 (s, 1 H), 6.03 (s, 1 H), 5.00 (s, 2 H), 3.62 (s, 3 H), 2.89 (s, 2 H), 2.75 (d, *J* = 16.9 Hz, 1 H), 2.61 (d, *J* = 17.0 Hz, 1 H), 2.31 (m, 1 H), 1.83 (m, 1 H), 1.53 (sept, *J* = 6.5 Hz, 1 H), 1.36 (s, 9 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.79 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 199.2, 173.1, 162.3, 157.9, 154.0, 136.9, 131.0, 128.6, 128.0, 127.4, 126.9, 114.5, 112.3, 79.0, 70.0, 68.0, 58.9, 52.6, 48.7, 42.0, 40.6, 29.7, 28.3, 24.2, 24.0, 23.4; high resolution mass spectrum (CI, NH_3) *m/z* 565.2905 [$(M+H)^+$; calcd for $C_{32}H_{41}N_2O_7$: 565.2913].

(+)-**16a**: white glass; $[\alpha]_D^{23}$ +77.5° (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 3330 (m), 3010 (m), 2960 (s), 1705 (s), 1520 (s), 1495 (s), 1370 (m), 1240 (s), 1215 (s), 1175 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 6.92 (d, *J* = 8.1 Hz, 2 H), 6.71 (d, *J* = 8.2 Hz, 2 H), 6.41 (s, 1 H), 5.71 (s, 1 H), 3.63 (s, 3 H), 2.80 (d, *J* = 13.7 Hz, 1 H), 2.69 (d, *J* = 13.8 Hz, 1 H), 2.23 (m, 1 H), 1.95 (m, 1 H), 1.75 (m, 2 H), 1.51 (m, 3 H), 1.37 (s, 9 H), 0.96 (m, 2 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H), 0.76 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 173.7, 162.3, 155.1, 154.4, 131.1, 127.0, 115.1, 111.6, 79.0, 71.5, 59.6, 52.6, 42.3, 34.0, 31.5, 28.4, 28.2, 24.2, 23.5, 22.4; high resolution mass spectrum (CI, NH_3) *m/z* 503.3124 [$(M+H)^+$; calcd for $C_{28}H_{43}N_2O_6$: 503.3121].

8. All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 500-MHz ^1H NMR, and 125-MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. In addition, compounds **10a-c**, **11a**, **12a,c**, **15c**, **16b** gave satisfactory combustion analyses.
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