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AN EFFECTIVE SYNTHESIS OF SCALEMIC 3,5,5-TRISUBSTITUTED PYRROLIN-4-ONES

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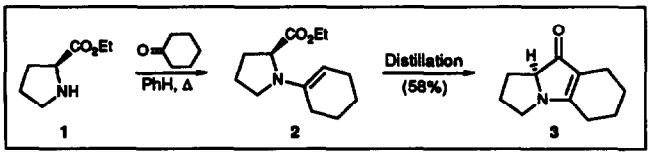
Summary: A new two-step method employs the intramolecular cyclization of metalated imino esters for the construction of scalemic 3,5,5-trisubstituted pyrrolin-4-ones (4). The imino esters in turn derive from α-disubstituted amino acids, the latter readily available via a new protocol exploiting the enantioretentive alkylation of oxazolidinones.

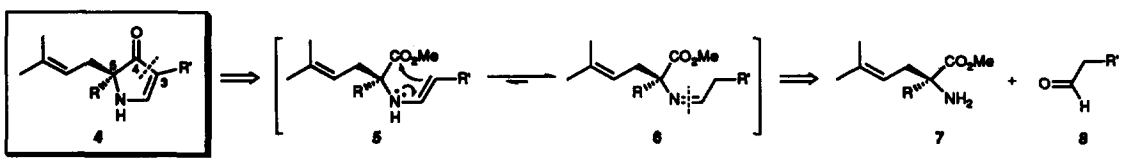
In our research program directed toward the design and synthesis of novel peptidomimetics, we required an efficient method for the preparation of scalemic 3,5,5-trisubstituted pyrrolin-4-ones (4). Whereas many procedures are available for the formation of racemic pyrrolinones,[1] only one affords chiral material. Hiroi et al. discovered that enamine 2, the condensation product of L-proline ethyl ester (1) with cyclohexanone, cyclizes upon distillation to generate the tricyclic pyrrolinone 3 in 58% yield (Scheme I).[2]

Scheme I



Retrosynthetic disconnection of 4 in a similar fashion leads to amine 7 and aldehyde 8 (Scheme II). Reaction of primary amine 7 with 8 would presumably give imine 6[3] rather than the corresponding enamine. Nonetheless, we reasoned that thermolysis of the imine might induce tautomerization to enamine 5; subsequent cyclization would then furnish 4. A second approach would entail alkylation or acylation of the imine nitrogen in 6, providing an enamine which would be expected to cyclize upon heating. Alternatively, a secondary amine could be prepared from 7 prior to condensation with 8. To test these possibilities, we required an effective preparation of scalemic amino esters such as 7.

Scheme II

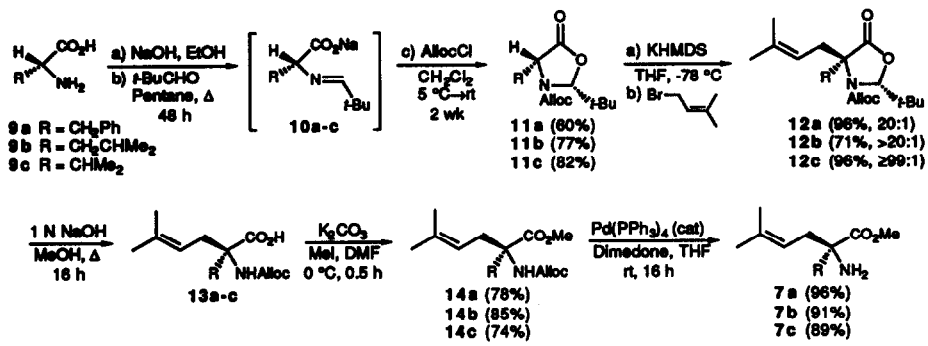


Two published methods for the synthesis of α-alkylated amino acids employ enantioretentive alkylation of *cis*-oxazolidinones. The Merck group[4] utilized oxazolidinones prepared from Cbz-protected amino acids and aromatic aldehydes, while Seebach[5] formed similar heterocycles by N-acylation of Schiff bases derived from pivaldehyde and amino acid sodium salts. In our hands, the water solubility of the resultant α-alkyl amino acids proved to be inconvenient for large-scale work. Moreover, the nitrogen protecting groups employed previously

were incompatible with the proposed pyrrolinone synthesis. We therefore sought a modification that would directly furnish the required amino esters.

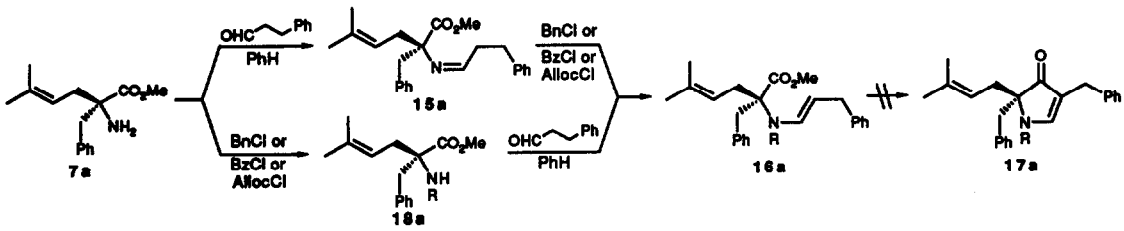
Our construction of α-alkylated amino esters **7a-c** begins with formation of the pivaldehyde imines of D-phenylalanine (**9a**), D-leucine (**9b**), and D-valine (**9c**) via the Seebach protocol (Scheme III). Treatment of the imines (**10a-c**) with allyl chloroformate[6] (rather than benzoyl chloride as employed by Seebach) induced cyclization to furnish *cis*-oxazolidinones **11a-c**.[7] Interestingly, exposure to Boc anhydride did not produce the corresponding oxazolidinone. Enantioretentive alkylation as described by Seebach (i.e., KHMDS, prenyl bromide, THF, -78 °C) then afforded the oxazolidinones **12a-c**[7] with >95% diastereoselectivity. Hydrolysis to the Alloc-protected amino acids (**13a-c**) was then achieved via the Merck procedure (1 N NaOH, MeOH, reflux, 16 h), and the resultant acids were immediately methylated [K_2CO_3 (2.5 equiv), MeI (2 equiv), DMF, 0.5 h] to furnish esters **14a-c**.[7] The Alloc protecting group could be removed in the presence of the prenyl group with catalytic $Pd(PPh_3)_4$ and dimedone (5 equiv),[8] providing the desired α-alkyl amino esters **7a-c**[7] after Kugelrohr distillation. This sequence is both efficient (42-52% yields for the 6-step sequence) and amenable to large-scale production (ca. 100 g).

Scheme III



These results set the stage for evaluation of the proposed pyrrolinone synthesis. Amino ester **7a** was condensed with hydrocinnamaldehyde (1.1 equiv) by *in-vacuo* concentration of a benzene or toluene solution of the compounds at ambient temperature; ^1H NMR analysis verified the formation of imine **15a** (Scheme IV). Unfortunately, attempted cyclization of **15a** by heating in benzene solution (ca. 80 °C) or neat invariably led to recovery of the starting material or decomposition. We found no evidence for enamine formation under these conditions. Neither alkylation of **15a** with BnCl nor acylation with BzCl or AllocCl proved successful.

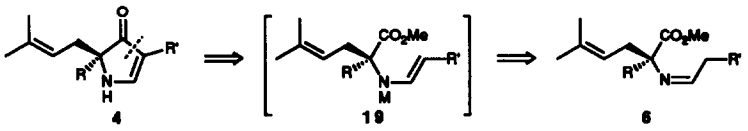
Scheme IV



Moreover, attempted alkylation and acylation of **7a** followed by *in situ* preparation of the enamine and thermolysis likewise failed to provide the pyrrolinone.

We next sought to develop a new method, exploiting the cyclization of metallo imines **19** to furnish the desired pyrrolinones **4** (Scheme V). We recognized that most carbon-carbon bond forming reactions of metalated imines involve alkylation.[9] Indeed, at the outset of this work, only a single intermolecular acylation of a lithiated acyclic imine had been reported;[10] Bartoli et al.[11] recently expanded upon that precedent. Our investigation of the intramolecular acylation of imines also proved productive.

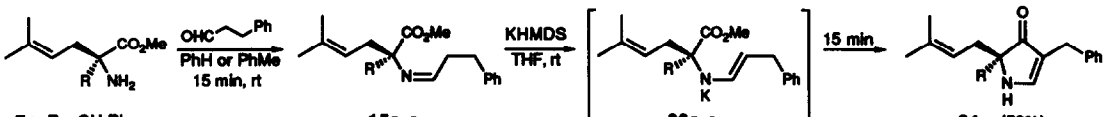
Scheme V



4 **19** **6**

Imine **15a** was generated from **7a** *(vide supra)* and used without purification. Metalation with KHMDS (THF, rt) then furnished metallo imine **20a** (Scheme VI). Upon stirring at room temperature for 15 min, TLC analysis (20% EtOAc/hexanes) revealed the formation of the desired pyrrolinone **21a**,[7] isolable in 59% yield overall from **7a**. Similar treatment of the imines derived from amines **7b** and **7c** led to heterocycles **21b** and **21c**. The use of LDA for metalation afforded lower yields of the pyrrolinones.

Scheme VI



7a R = CH_2Ph
7b R = CH_2CHMe_2
7c R = $CHMe_2$

15a-c **20a-c**

21a (59%)
21b (64%)
21c (60%)

A typical experimental procedure follows: To a solution of amino ester **7b** (500 mg, 2.34 mmol) in benzene (9.4 mL) was added hydrocinnamaldehyde (0.34 mL, 346 mg, 2.57 mmol). The mixture was allowed to stand for 15 min at room temperature, becoming turbid as water was generated; the solvent was then evaporated *in vacuo*. The oily concentrate was dried azeotropically with four 9-mL portions of benzene and placed under vacuum for 45 minutes. The crude imine was then dissolved in THF (23 mL) and treated with potassium bis(trimethylsilyl)amide (KHMDS; 0.5 M in toluene, 11.7 mL, 5.85 mmol). As the resultant solution was stirred for 15 min, the color changed from green to rusty red. The reaction was then quenched by addition of 10% aqueous sodium bisulfate solution (25 mL) and the biphasic mixture extracted with ethyl acetate (3 x 25 mL). The organic phases were combined, washed with saturated aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. Concentration *in vacuo* afforded a solid, which upon crystallization from hexane furnished 450 mg (64%) of **21b**.[12]

In summary, we have developed an efficient, new approach for the construction of scalemic 3,5,5-trisubstituted pyrrolin-4-ones. The successful strategy employs a new protocol for the generation of α-substituted amino esters via enantioretentive alkylation of oxazolidinones. Application of this methodology to the design and synthesis of non-peptide peptidomimetics will be reported in due course.

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7. All new compounds gave satisfactory IR, 500-MHz ^{1}H NMR, and 125-MHz ^{13}C NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry.

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12. **21a:** white solid; mp 140.5-142.5 °C (hexanes/ethyl acetate); $[\alpha]_D^{20}$ +22.0° (*c* 1.43, $CHCl_3$); IR ($CHCl_3$) 3470 (m), 2990 (m), 1660 (s), 1580 (s), 1490 (w), 1450 (m), 1420 (m), 1145 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 3.7 Hz, 1 H), 7.22-6.90 (m, 10 H), 5.34 (d, *J* = 2.9 Hz, 1 H), 5.00 (m, 1 H), 3.35 (s, 2 H), 3.00 (d, *J* = 13.4 Hz, 1 H), 2.86 (d, *J* = 13.4 Hz, 1 H), 2.44 (dd, *J* = 14.5, 7.2 Hz, 1 H), 2.36 (dd, *J* = 14.5, 7.5 Hz, 1 H), 1.66 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 161.5, 140.7, 135.8, 135.6, 130.0 (2 C), 128.3 (2 C), 128.2 (2 C), 127.9 (2 C), 126.6, 125.6, 117.4, 113.7, 70.4, 42.1, 34.9, 28.1, 25.8, 18.1; high-resolution mass spectrum (CI, NH_3) *m/z* 332.2034 [$(M+H)^+$; calcd for $C_{23}H_{26}NO$: 332.2014].

21b: yellow solid; mp 82-83 °C (hexanes); $[\alpha]_D^{20}$ -64.4° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3440 (m), 2975 (m), 1655 (s), 1580 (s), 1490 (w), 1450 (m), 1415 (m), 1150 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.0 Hz, 1 H), 7.28-7.15 (m, 5 H), 5.02 (br s, 1 H), 4.99-4.95 (m, 1 H), 3.49 (apparent q, *J* = 15.8 Hz, 2 H), 2.28 (apparent d, *J* = 7.9 Hz, 2 H), 1.69-1.54 (m, 3 H), 1.66 (s, 3 H), 1.58 (s, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 161.2, 140.9, 135.4, 128.5 (2 C), 128.3 (2 C), 125.8, 117.7, 113.5, 70.4, 44.6, 36.4, 28.4, 25.8, 24.5, 24.3, 23.8, 18.0; high-resolution mass spectrum (CI, NH_3) *m/z* 297.2074 [M^+; calcd for $C_{20}H_{27}NO$: 297.2093].

21c: yellow solid; mp 96-97 °C (hexanes/ethyl acetate); $[\alpha]_D^{20}$ -22.5° (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) 3450 (m), 2980 (m), 1655 (s), 1590 (s), 1495 (w), 1450 (m), 1160 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 3.3 Hz, 1 H), 7.26-7.14 (m, 5 H), 4.97 (br s, 1 H), 4.93-4.89 (m, 1 H), 3.50 (d, *J* = 15.8 Hz, 1 H), 3.40 (d, *J* = 15.8 Hz, 1 H), 2.44 (dd, *J* = 14.5, 7.9 Hz, 1 H), 2.36 (dd, *J* = 14.5, 7.9 Hz, 1 H), 2.00 (hept, *J* = 6.6 Hz, 1 H), 1.61 (s, 3 H), 1.57 (s, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 162.2, 141.1, 134.6, 128.4 (2 C), 128.2 (2 C), 125.7, 117.5, 114.4, 72.8, 33.5, 28.2, 25.8, 18.0, 17.1, 16.5; high-resolution mass spectrum (CI, NH_3) *m/z* 283.1948 [M^+; calcd for $C_{19}H_{25}NO$: 283.1936].

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