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Synthesis of N-substituted Pyrrolin-2-ones

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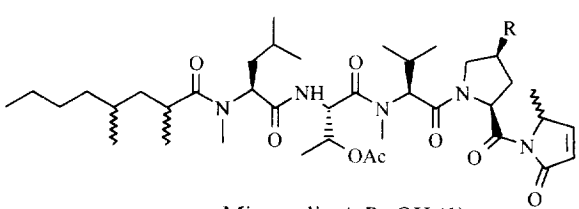
Abstract: During studies towards the synthesis of microcolin analogues, an unexpected dehydration was observed when 1-benzyloxycarbonyl-4-hydroxy-5-methylpyrrolidin-2-one was treated with di-*tert*-butyl dicarbonate in the presence of 4-dimethylaminopyridine. This reaction was used for the stereospecific synthesis of several N-protected pyrrolin-2-ones.

Several biologically active natural products have been reported to contain an unsaturated N-acylated pyrrolin-2-one unit which is assumed to be biosynthetically derived from amino acids. In most examples the N-acyl group is a peptide chain, often with unique amino acids. Some examples of compounds containing this lactam moiety are the dolastatins,[1] highly potent cytotoxic peptides bearing a C-terminal S-5-benzyl-4-methoxypyrrolin-2-one, which is likely to be derived from phenylalanine. Another set of examples are the immunosuppressive and cyctotoxic microcolins (**1**,**2**)[2] and the closely related cytotoxic majusculamides[3]. All these compounds possess the 5-methylpyrrolin-2-one moiety, which is asssumed to be derived from L-alanine. The double bond in the lactam moiety was reported to be mandatory for the immunosuppressive activity of the microcolins.[4]

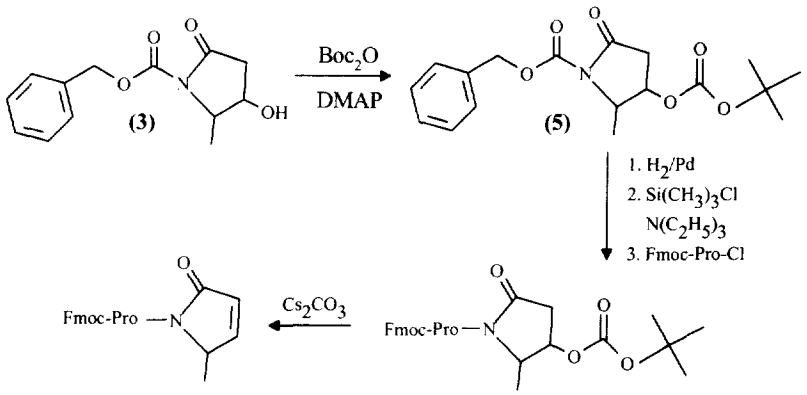
During the course of our studies towards the synthesis of microcolin analogues we were interested in a stereospecific synthesis of the pyrrolin-2-one unit.



Microcolin A:R=OH (**1**)
Microcolin B:R=H (**2**)

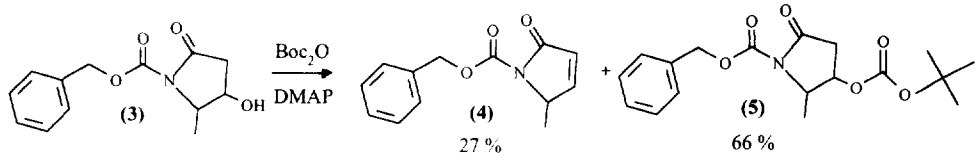
The condensation of N-protected amino acids and Meldrum's acid as described by Castro and coworkers[5] proved to be a very useful two step reaction leading to N-protected 4-hydroxypyrrolin-2-ones. When the double bond is reduced with sodium borohydride, N-protected 4-hydroxypyrrolidin-2-ones are obtained, which are suitable starting materials for dehydration to unsaturated lactams. In this context we became interested in the reaction reported by Schmidt and coworkers[6] who described the elimination of the *tert.* butyloxycarbonyloxy group in a pyrrolidinone with Cs_2CO_3 in methanol at room temperature.

Following the procedure described by Castro we synthesized (S)-N-benzyloxycarbonyl-4-hydroxy-5-methylpyrrolidin-2-one (**3**) from Z-L-alanine and Meldrum's acid followed by reduction with $NaBH_4$. Our plan was to protect the OH group in the 4-hydroxypyrrolidin-2-one with the Boc group using Boc_2O/DMAP and to cleave the Z-group via hydrogenolysis in the next step. The lactam should have been coupled with Fmoc-Pro chloride after silylation of the lactam nitrogen[7] as outlined in scheme 1. In a final step the elimination of the *tert.* butyloxycarbonyloxy group should have been performed with Cs_2CO_3 as described by Schmidt *et al.* to yield the protected N-prolyl-5-methyl-pyrrolin-2-one unit of microcolin B.



Scheme 1

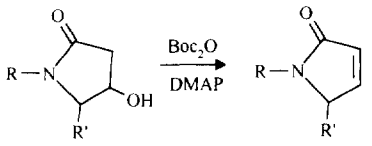
However, when (**3**) was treated with Boc_2O and DMAP, both the Boc-protected pyrrolidinone (**5**)[10] and the unsaturated 1-benzyloxycarbonyl-5-methylpyrrolin-2-one (**4**)[9] were obtained (scheme 2). The primary product of this reaction is probably (**5**) which then undergoes elimination under the influence of the base DMAP.



Scheme 2

The yield of **4** was conveniently raised to 62 % by increasing the lenght of reaction time.[8] To further investigate the use of this reaction, several N-substituted 4-hydroxypyrrolidinones were synthesized from Boc-L-Ala, Z-Gly or Octanoyl-L-Pro-L-Ala and Meldrum's acid according to the method described by Castro *et al.*[5] and then reacted with di-*tert*-butyl dicarbonate to yield the unsaturated lactams. The results of these reactions are given in table 1.

Table 1. Synthesis of N-acylated Pyrrolin-2-ones



compound	Yield %
4: R=Z, R'=methyl	62
6: R=Boc, R'=methyl[11]	46
7: R=Octanoyl-L-Pro, R'=methyl[12]	65
8: R=Z, R'=H[13]	51

Acknowledgement

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References and Notes

Abbreviations: Boc: tert-butoxycarbonyl-; Z: benzyloxycarbonyl-, DMAP: 4-Dimethylaminopyridine, Fmoc: Fluorenylmethoxycarbonyl, Boc_2O: di-*tert*-butyl dicarbonate.

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8. Procedure for the dehydration of 4-hydroxypyrrolidin-2-ones: 900 mg 1-carbobenzoxy-4-hydroxy-5-methylpyrrolidin-2-one (3.8 mMol) was dissolved in 50 mL anhydrous THF, 90 mg DMAP (0.8 mMol) and 1.6 g Boc_2O (7.8 mMol) were added and the mixture was stirred at room temperature for 48 hours. Afterwards the THF was distilled of under reduced pressure and the residue was redissolved in 75 mL ethyl actetate and extracted twice with 30 mL 1N HCl, twice with 30 mL saturated $KHCO_3$ and finally with 30 mL brine, dried over $MgSO_4$. After filtration the solvent was removed in vacuo and the crude product was purified by chromatography on silica gel using ethyl acetate/heptane 4:1 as solvent. 520 mg of the 1-carbobenzoxy-5-methylpyrrolin-2-one (**4**, 62.1 %) and 435 mg 1-carbobenzoxy-4-butyloxycarbonyloxy-5-methylpyrrolidin-2-one (**5**, 34.6 %) were obtained.

9. **4**: colorless oil; ^{1}H-NMR (TMS,$CDCl_3$): 1.42 (3H,d, J= 5.9 Hz, 5-Me); 4.65 (1H, dq, J= 6.8, 1.9, C-5), 5.08 (1H, d, J=11.7, benzyl-CH_2),), 5.18 (1H, d, J=11.7, benzyl-CH_2), 6.05 (1H, dd, J= 6.1, 1.6, C-3)., 7.10 (1H, dd, J=6.1, 2.1, C-4), 7.3-7.5 (5H, m, aromatic); ^{13}C-NMR (TMS,$CDCl_3$): 17.8, 58.2, 67.5, 125.2, 127.8, 128.0, 128.3, 135.1, 150.5, 152.4, 168.4; $[\alpha]_D^{20}$= -13.2 ° (c=1, $CHCl_3$).

10. **5**: colorless oil; ^{1}H-NMR (TMS,$CDCl_3$): 1.27 (3H, d, J=6.1 Hz, 5-Me); 1.48 (9H, s, Boc); 2.27(1H, dd, J=11.2, 4.6 Hz, C-3); 2.84 (1H, dd, J=11.2, 6.4 Hz, C-3); 4.55 (1H, qd, J= 6.7, 1.9, C-5); 5.12 (1H, ddd, 6.8, 6.4, 4.6 Hz, C-4); 5.18 (1H, d, J=11.7, benzyl-CH_2),), 5.28 (1H, d, J=11.7, benzyl-CH_2), 7.3-7.5 (5H, m, aromatic); ^{13}C-NMR(TMS,$CDCl_3$): 13.2, 13.9, 20.6, 27.3, 36.3, 55.7, 60.0, 67.8, 68.9, 82.9, 127.9, 128.1, 128.3, 134.8, 150.5, 152.2, 169.0;

11. **6**: colorless oil; ^{1}H-NMR (TMS,$CDCl_3$): 1.44 (3H,d, J= 6.5 Hz,); 1.57 (9H,s); 4.65 (1H, dq, J= 6.6, 1.7), 6.05 (1H, dd, J= 6.3, 1.5)., 7.10 (1H, dd, J=5.6, 1.8); ^{13}C-NMR (TMS,$CDCl_3$): 17.2, 27.4, 58.1, 82.9, 124.8, 149.6, 152.5, 170.5; $[\alpha]_D^{20}$= -9.6 ° (c=1, $CHCl_3$).

12. **7**: colorless oil; ^{1}H-NMR (TMS,$CDCl_3$): 0.85 (3H, t, J=6.4 Hz, C8-octanoic acid); 1.28 (10H, m, octanoic acid); 1.46 (3H, d, J=6.7, 5-Me); 1.65 (2H, m, C-2 octanoic acid); 1.97 (2 H, m, γ-Pro); 2.31 (2H, m, β-Pro); 3.67 (2H, m, δ-Pro); 4.76 (1H, dq, J=6.4, 1.6, C-5), 5.47 (1H, dd, J=8.8, 4.2, α-Pro), 6.05 (1H, dd, J=6.2, 1.4, C-3), 7.22 (1H, dd, J=5.6,1.8, C-4): ^{13}C-NMR (TMS,$CDCl_3$): 14.0, 17.2, 22.6, 24.6,24.8, 29.0, 29.1, 29.4, 31.7, 34.5, 47.7, 58.1, 59.7, 125.5, 153.7, 169.9, 171.6, 172.5; LRFABMS: 321.2; $[\alpha]_D^{20}$= -94.1 ° (c=1, $CHCl_3$).

13. **8**: colorless oil; ^{1}H-NMR (TMS,$CDCl_3$): 4.84 (1H, dd, J= 11.6, 1.9, C-5), 4.95 (1H, dd, J=11.6, 6.8, C-5), 5.09 (1H, J=11.7, benzyl-CH_2),), 5.18 (1H, d, J=11.7, benzyl-CH_2), 6.02 (1H, dd, J= 6.1, 1.6, C-3)., 7.25 (1H, dd, J=6.1, 2.1, C-4), 7.3-7.5 (5H, m, aromatic); ^{13}C-NMR (TMS,$CDCl_3$): 43.8, 58.2, 67.5, 125.2, 127.8, 128.0, 128.3, 135.1, 150.5, 152.4, 168.4.

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