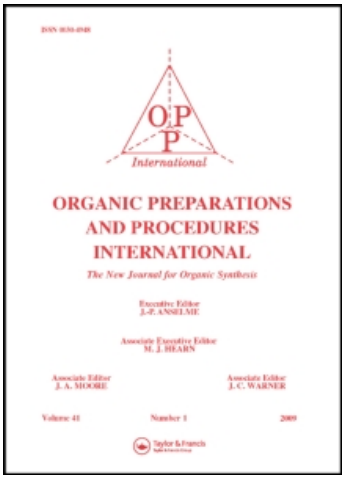

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EFFICIENT PREPARATION OF THE CHIRAL AUXILIARIES *SAMP* AND *RAMP*. *N*-AMINATION *via* HOFMANN DEGRADATION

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In view of the often different biological activity of enantiomers, the synthesis of chiral compounds of high enantiomeric purity is of considerable significance. In this context, the SAMP-/RAMP-hydrazone method[1] has been used very successfully in the enantioselective synthesis of a variety of important compounds such as carbonyl compounds and amines.

The procedure insolves transformation of carbonyl compounds to the corresponding SAMP- or RAMP-hydrazones followed by metalation, trapping of the intermediate chiral azaenolates with various electrophiles, and either hydrazone cleavage (carbonyl compounds) or hydrazone reduction/N-N bond cleavage (amines). As is demonstrated in FIG.1, α-substituted aldehydes[1-4], α-substituted cyclic[3a] and acyclic ketones[5-7], β-substituted δ-ketoesters[8], as well as β-substituted primary amines[9] are obtained in good overall chemical yields and excellent enantiomeric excesses (ee). Successful applications of the SAMP/RAMP-hydrazone method in natural product synthesis have recently been reported by Nicolaou *et al.* (ionophore antibiotic X-14547A, indanomycin)[10], Pennanen (eremophilenolide)[11], Enders *et al.* (ant alarm pheromone[5], defensive substance of

"daddy longlegs"[7]), Mori *et al.* (Serricornin)[12], and Bestmann *et al.* (pheromone analogues)[13]. Finally, it should be mentioned that the title chiral auxiliaries may also be used in the resolution of aldehydes[1] and ketones[14].

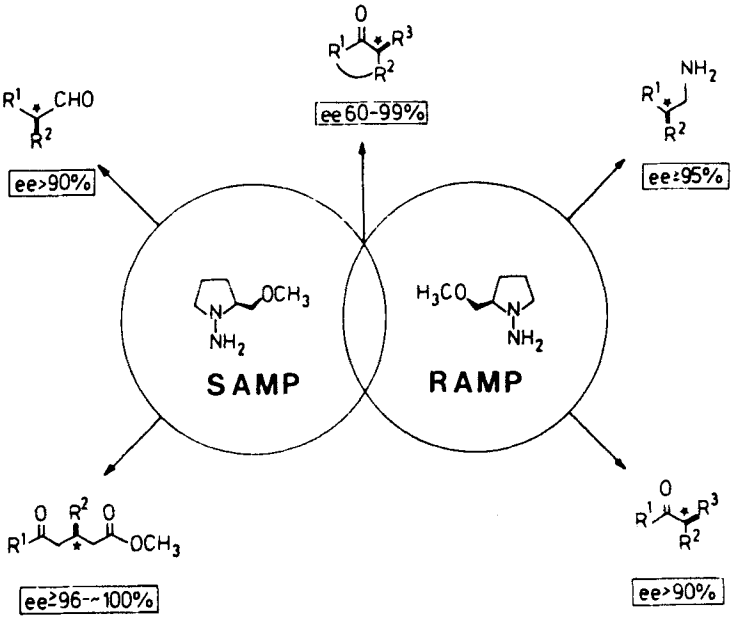

Fig. 1
Synthetic Scope of the SAMP/RAMP Hydrazone Method
(New C-C Bonds printed in Bold)

Our previously reported synthesis of SAMP and RAMP[3] involved the hazardous, potentially carcinogenic nitrosamines as intermediates. It was therefore desirable to devise a safe and efficient alternative route to these chiral auxiliaries.

As is shown in FIG.2, the new procedure involves an N-amination *via* a Hofmann degradation and an optimization of the previously reported synthesis of (S)-2-methoxymethyl-pyrrolidine[15]. Thus, SAMP is obtained from (S)-proline in six steps and an overall yield of 57%.

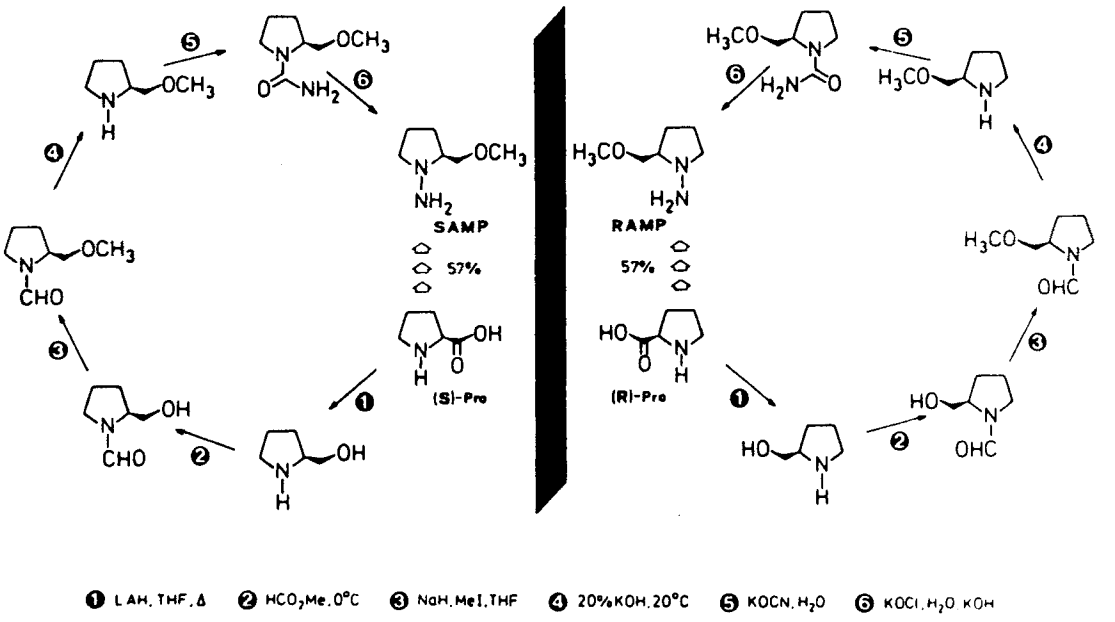

Fig. 2
"Nitrosamine-free" Route to SAMP/RAMP via Hofmann Degradation

EXPERIMENTAL SECTION

1 (S)-(+)-2-Hydroxymethyl-pyrrolidine (I).- A 4 L, three-necked flask, was fitted with a heating mantle, mechanical stirrer, and reflux condenser with drying tube, was charged with 2.5 L of anhydrous THF and 60 g (1.6 mol) of $LiAlH_4$. The mixture was heated to reflux and then 115.1 g (1 mol) of powdered (S)-proline were added in small portions so as to maintain reflux. After the addition (which required approximately 45 min.) was complete, the reaction mixture was maintained under reflux for 1 hr, after which a solution of 28 g KOH in 112 ml H_2O was added cautiously. The resulting slurry may temporarily become difficult to stir. To complete the hydrolysis, the mixture was refluxed for additional 15 min. The colorless salts

were removed by suction filtration (large Büchner funnel) and then again refluxed with 1.5 L THF in order to extract all of the prolinol (I). The combined solutions were concentrated *in vacuo* so that the temperature of the heating bath did not exceed 30°. The crude product (I) (115-125 g, ~100%) was sufficiently pure to be used in the next step. Lit.data[3a]: bp. 79-82°/3 Torr, $[\alpha]_D^{20}$= +31.6° (c=1.0, benzene), $[\alpha]_D^{20}$= +3.76° (neat); IR(film): 3000-3500 (OH,NH), 2960,2870(CH), 1455-1045 cm^{-1}; ^{1}H-NMR($CDCl_3$/TMS):δ 1.7(m, 4H, CH_2), 2.95 (m, 2H,CH_2N), 3.15-3.75(m, 3H, CH, CH_2O), 4.55 (s, 2H, OH, NH) ppm.

2 (S)-(-)-1-Formyl-2-hydroxymethyl-pyrrolidine (II).- Crude (I) was cooled to 0°, 80 ml (1.3 mol) methyl formate were added dropwise and the reaction mixture was allowed to stir at 0° for additional 30 min. Excess methyl formate was stripped off at 30°, the resulting oil was taken up in 600 ml CH_2Cl_2, dried twice (Na_2SO_4) and concentrated. Remaining traces of the solvent were removed under vacuum (20°,1 Torr;2hrs) to yield approximately 130 g (~100%)II. Lit data [15]: bp. 122°/ 0.5 Torr, $[\alpha]_D^{20}$= -18° (c=2, benzene); IR(film): 3380, 2940, 2870, 1650, 1420, 1385 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS):δ 1.6-2.2 (m, 4H, $2CH_2$), 3.1-4.4 (m, 5H, CHN, CH_2N, CH_2O), 4.87 (s, 1H, OH), 8.17, 8.21 (s, 1H, CHO) ppm.

3 (S)-(-)-1-Formyl-2-methoxymethyl-pyrrolidine (III).- A magnetically stirred solution of crude (II) in 1.5 L of anhydrous THF under argon was cooled (Dry Ice/aceton) to -50° to -60° (internal temperature). The cooling bath was removed and 28.8 g (1.2 mol) NaH were added, followed by 81 ml (1.3 mol) methyl iodide all at once. The flask was flushed with argon

and the mixture was allowed to come to room temperature. Hydrogen evolved and a solid precipiated, making it difficult to stir. At approximately 0^{o}, the precipitate dissolved and again a stream of hydrogen was evolved. After refluxing for 15 min, the solution was hydrolyzed by adding 90 ml 6N HCl. Evaporation of the THF afforded a dark residue (III in aqueous HCl), which was used without further purification. Lit.data[15]: bp. 67^{o}/ 0.25 Torr, $[\alpha]_D^{20} = -43.5^{o}$ (c=2, benzene); IR(film): 2980, 2930, 2880, 2830, 1665, 1445, 1390, 1380, 1110 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.47-2.2 (m, 4H, $2CH_2$), 3.27 (s, 3H, CH_3O), 3.0-4.2 (m, 5H, CHN, CH_2N, CH_2O), 8.3, 8.34 (s, 1H, CHO) ppm.

4 (S)-(+)-2-Methoxymethyl-pyrrolidine (IV).- A solution of 180 g KOH in 720 ml water was added to crude (III) and the resulting mixture was stirred under argon at room temperature overnight. After saturation with 500 g K_2CO_3, the precipitated potassium salts were collected by suction and the filtrate was extracted three times with ether. *At this point, the chiral pyrrolidine (IV) is quite pure and can easily be purified after the usual work up by distillation with a 15 cm Vigreux column, bp. 62°/40 Torr.* Lit.data[15]: $[\alpha]_D^{20} = +3^{o}$ (c=2, benzene); IR (film): 3300, 2950, 2860, 2820, 1450, 1375, 1100 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.5-2.33 (m, 4H, $2CH_2$), 2.68 (s, 1H, NH), 3.33 (s, 3H, CH_3O), 2.6-3.5 (m, 5H, CH_2O, CHN, CH_2N) ppm. The ethereal layer was acidified with 100 ml 12N HCl at 0^{o}, extracted twice with 100 ml water respectively, to yield an aqueous solution of the amine hydrochloride. The combined aqueous solutions were adjusted to pH 3 (pH meter) with a concentrated solution of KOH in water.

5 (S)-(-)-1-carbamoyl-2-methoxymethyl-pyrrolidine (V).- The aqueous solution of the amine hydrochloride (IV) was treated in one portion with 80 g (1 mol) KOCN dissolved in 140 ml water at 15°. The homogeneous solution should be stirred for a minimum of 12 hrs at room temperature and was used without further purification.

The chiral urea (V) may be isolated at this point by extraction with $CHCl_3$ and usual work-up and is obtained as colorless crystals, mp. 60.5-61.5° (i-PrOH/Et_2O); $[\alpha]_D^{20} = -6.67°$ (c=2, EtOH); IR(KBr): 3200-3500 (NH_2), 2950, 2900, 2850, 1670 (CO), 1470, 1360, 1210, 980, 780 cm^{-1}; ^{1}H-NMR ($CDCl_3$/TMS): δ 1.9 (m, 4H, CH_2), 3.2-3.7 (m, 4H, CH_2O, CH_2N), 3.4 (s, 3H, OCH_3), 4.0 (m, 1H, NCH), 5.2 (br. s, 2H, NH_2) ppm; ^{13}C-NMR ($CDCl_3$/TMS): δ 159.6 (CO), 76.7 (CH_2O), 59.1 (CH_3O), 57.4 (NCH), 46.8 (CH_2N), 29.1 (CH_2), 23.8 (CH_2) ppm; mass spectrum (70 eV) m/e (rel. intensity): M^+ 158.1053 (calcd. 158.1055), 126.1 (5.8), 114.1 (2.2), 113.1 (41.1), 82.1 (2.3), 71.1 (4.5), 70.1 (100.0), 68.0 (6.5), 55.1 (2.6), 45.0 (6.8), 44.0 (3.2), 43.1 (11.2), 42.0 (2.6), 41.0 (7.7), 39.0 (3.3);

Anal.Calcd. for $C_7H_{14}N_2O_2$: C, 53.15 ; H 8.92 ; N 17.71

Found : C 52.88 ; H 8.91 ; N 17.51

Preparation of the KOCl Solution.- An aqueous KOCl solution was prepared by a modification of a published procedure[16]. In a separatory funnel, 200 g HTH[16] [≙ 65% Ca $(OCl)_2$] and 600 ml water were vigorously shaken and then a solution of 40 g KOH and 140 g K_2CO_3 in 250 ml water was added. Shaking was continued and the salts were collected by suction through a large Büchner funnel, pressed dry to afford a yellow, con-

centrated solution of KOCl. Varying concentrations (determined iodometrically) ranging from 1.8 to 2.2 mol/l KOCl were obtained. A minimum concentration of 1.6 mol/l KOCl is essential.

6 (S)-(-)-1-Amino-2-methoxymethyl-pyrrolidine (SAMP).- The reaction mixture containing the crude urea (V) was cooled to -5° (ice/salt bath), and a precooled (-5°) solution of 168 g KOH in 150 ml water was introduced, followed at once by 685 ml (1.3 mol) of an 1.9N aqueous KOCl solution (-5°), prepared as described above. Alternatively, a NaOCl solution may be employed (lower yield). The reaction became exothermic and the temperature rose to 40°, higher temperatures should be avoided. Cooling was continued until the mixture reached room temperature, after which the cooling bath was removed and stirring was continued for at least 12 hrs. Excess hypochloride was destroyed with about 20 g sodium sulfite. Acidification with 12N HCl (~350 ml) to pH 2 under ice cooling caused vigorous evolution of carbon dioxide. Stirring was continued for 15 min at room temperature and the solution was then made alkaline by adding a 50% aqueous KOH solution (~100ml). The mixture was saturated with 500 g K_2CO_3 and filtered by suction. The salts were washed twice with 300 ml ethanol, respectively, and the aqueous solution was extracted with $CHCl_3$/EtOH (1:1), once with 800 ml and twice with 400 ml [Note that the organic layer is the upper layer]. Addition of the solvents caused salt precipitation. In order to obtain a better phase separation, the salts should be removed by suction. The organic layers were collected, concentrated *in vacuo* (max. 30° bath temperature) and the resulting oil was taken up in 500 ml

$CHCl_3$. Drying (Na_2SO_4) and evaporation of the solvents yielded 80-90 g (61-69%) of a dark oil, which was destilled through a 40 cm Vigreux column. To avoid loss of substance, ice cooling of the receiver is necessary. The forerun (~ 1 ml) contained (IV) and SAMP distilled as a colorless liquid at 42°/1.8 Torr (bath temperature 80°). 75 g [57.6% based on (S)-proline], $[\alpha]_D^{20}$= -79.6°(neat); IR(film): 3360 (NH_2), 3150, 2980, 2880, 2820, 1610, 1465, 1200, 1120, 960, 920 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$/TMS): δ1.4-2.1 (m, 4H, CH_2), 2.1-2.6 (m, 2H, CH_2N), 3.1 (m, 3H, NH_2, NCH), 3.3 (s, 3H, OCH_3), 3.4(m, 2H, CH_2O)ppm; mass spectrum (70 eV) m/e (rel. intensity): M^+ 130.1100 (6.7%) (calcd. 130.1106); 97.07 (3.9); 86.07 (8.9); 85.07 (100.0); 83.06 (4.1); 71.06 (16.3); 68.05 (31.3); 57.04 (5.6); 56.05 (4.6); 45.03 (10.7); 43.03 (12.1); 42.04 (3.4); 41.04 (28.9); 39.02 (5.5).

The optical antipode RAMP was prepared in the same way, starting from (R)-proline, $[\alpha]_D^{20}$= +79.8°(neat).

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