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A Concise Synthesis of Piperazine-2-Carboxylic Acids via β-lactam-Derived α-Amino Acid N-Carboxy Anhydrides.

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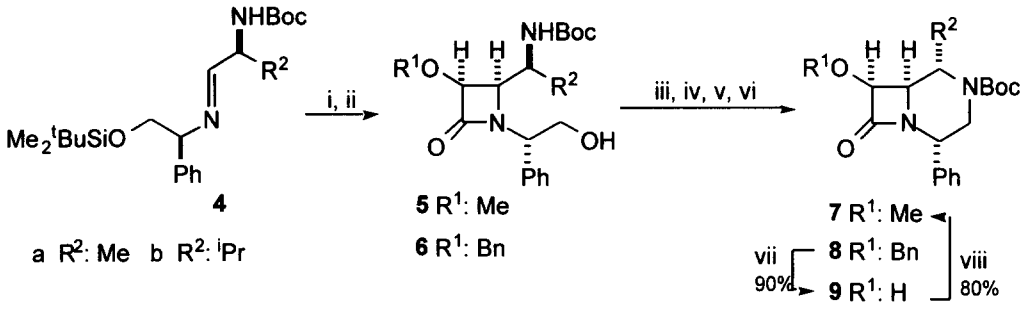
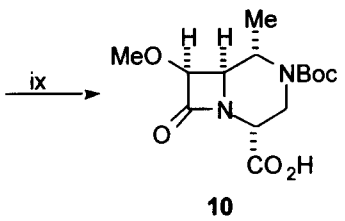
Abstract: A route to piperazine-fused 3-hydroxy β-lactams was accomplished via [2+2] cycloaddition of alkoxyketenes with imines derived from chiral α-amino aldehydes and chiral β-aminoalcohols. The resulting β-lactams on exposure to 0.55M NaOCl and a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) afforded α-amino acid N-carboxy anhydrides formally derived from piperazine-2-carboxylic acids. © 1997 Elsevier Science Ltd.

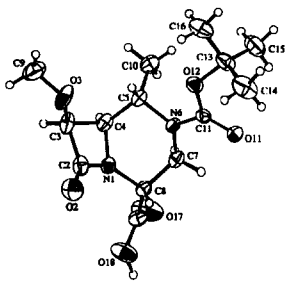
Despite the interest in 2-carboxypiperazines for the study and design of bioactive targets, there is a lack of methods for the asymmetric synthesis of substituted derivatives[1]. Whilst there are a few routes to both 5-alkyl- and 6-alkyl-piperazine-2-carboxylic acids[2], there does not exist, to our knowledge, a general methodology for the construction of 3,6-disubstituted piperazine-2-carboxylic acids. In concert with this latter aspect, all of the studies on the synthesis of 2-carboxypiperazines have dealt with the synthesis of the non-proteinogenic amino acid in its free form rather than the generation of simultaneously amino protected and carboxy- activated species. Therefore, still it would be of greater value if the synthesis of the α-amino acid could be directly combined with a peptide coupling reaction. Here we report a new approach to 2-carboxy-piperazines that fulfils this criterion and, at the same time, provides a new entry to the 2-iso-azacepham skeleton, thereby opening a way for the preparation of nuclear analogs of β-lactam antibiotics[3].

As Scheme 1 illustrates, the approach to the 2-iso-azacepham skeleton is based on the use of the phenyl group, as the latent carboxyl moiety[4], to prevent loss of homogeneus optical integrity during the cyclization step. Accordingly, upon treatment of methoxyketene, generated from methoxyacetyl chloride and triethylamine, with the readily available imine **4a**[5], we found we could prepare the β-lactam **5a** [m.p.: 105-106°C, $[\alpha]_D^{25}$= -131.1 (c= 1.0, CH_2Cl_2)] in 59% yield after desilylation of the resulting intermediate with TBAF. In a similar way, the reaction of benzyloxyacetyl chloride and triethylamine with imines **4a** and **4b** led to the corresponding adducts which, after desilylation, gave **6a** [m.p.: 131-132°C, $[\alpha]_D^{25}$= -152.2 (c= 1.0, CH_2Cl_2)] and **6b** [m.p.: 124-125°C, $[\alpha]_D^{25}$= -101.4 (c= 1.0, CH_2Cl_2)] in 65% and 50% yield, respectively. In each case, a single diastereomer was detected by ^{1}H-NMR (300 MHz) of the corresponding crude reaction

mixture and the relative cis-stereochemistry was primarily determined by the coupling constants between the C_3 and C_4 positions of the β-lactam ring ($J_{3,4}$≅5 Hz).





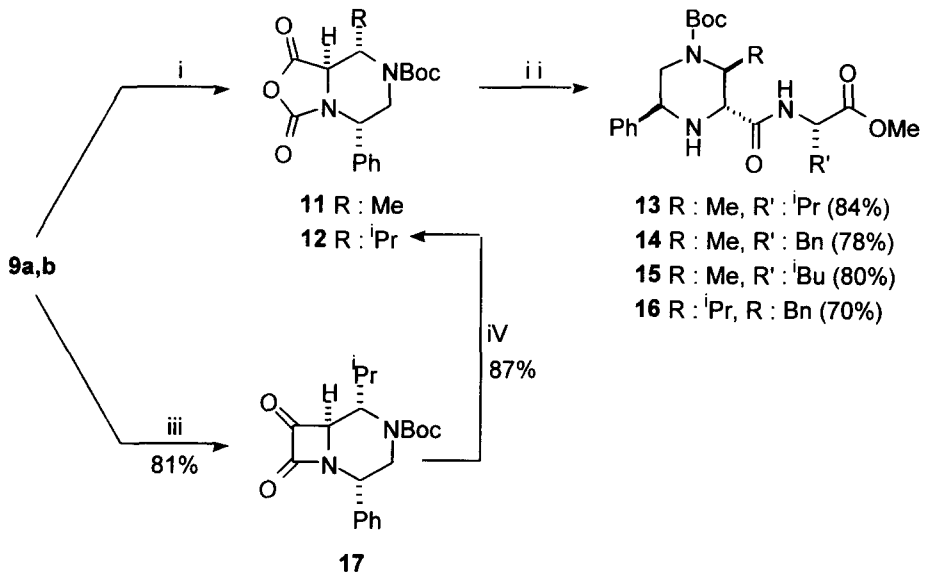


Crystal structure of **10**
(arbitrary numbering)

Scheme 1. *Reagents and conditions*: y, R^1OCH_2COCl, Et_3N, CH_2Cl_2, -15°C, r.t., 20h; ii, TBAF, THF, r.t., 2h; iii, MsCl, Et_3N, CH_2Cl_2, 0°C, 2h; iv, TFA, CH_2Cl_2, 0°C, 2h; v, Et_3N, CH_2Cl_2, r.t., 12h; vi, Boc_2O, CH_2Cl_2, r.t., 20h; vii, H_2 (1 atm.), Pd/C, MeOH, r.t., 20h; viii, NaH, THF/HMPTA then MeI, r.t., 3h; ix H_5IO_6, $Cl_3Ru{\cdot}nH_2O$ (catal.), $CH_3CN/CCl_4/H_2O$, r.t., 4h.

Conversion of both **5a** and **6a** into the corresponding **7a** [m.p.: 117-118°C, $[\alpha]_D^{25}$= +71.9 (c=1.0, CH_2Cl_2)] and **8a** [m.p.: 176-177°C, $[\alpha]_D^{25}$= +68.6 (c= 1.0, CH_2Cl_2)] was accomplished in 63% and 61% yield, respectively, by mesylation, N-Boc deprotection, cyclization and further N-Boc protection, as shown in Scheme 1. In a similar way, **6b** was converted into **8b** [m.p.: 167-169°C, $[\alpha]_D^{25}$= +48.4 (c= 1.0 CH_2Cl_2)] in 76% yield. Direct cyclization of the corresponding mesylate of **5a** also led to **7a**, but in substantially lower yield. Attempts to directly transform **5a** into **7a** by the use of the Mitsunobu reaction were completely unfruitful. Finally, transformation of the phenyl group to the carboxylic acid function was achieved smoothly by using the Sharpless procedure, but a better yield was obtained by using the procedure modified by Martin[6]. In this way, **10** [m.p.: 154-156°C, $[\alpha]_D^{25}$= +65.8 (c= 1.0, CH_2Cl_2)] was obtained in 90% yield, and its absolute configuration relative to the known chiral stereocenters was established by X-ray analysis[7]. Correlation of the stereochemical course of these cycloadditions was established by transformation of both **8a** and **8b** into the corresponding hydroxy derivatives **9a** [m.p.: 186-187°C, $[\alpha]_D^{25}$= +45.2 (c= 1.0, CH_2Cl_2)] and **9b** [m.p.: 148-150°C, $[\alpha]_D^{25}$= +24.8 (c= 1.0, CH_2Cl_2)]. Then, the α-hydroxy β-lactam **9a** was converted into the methoxy derivative **7a** which was identical to that obtained from **5a**[8].

The utility of this simple approach to piperazine-fused β-lactams is further shown by their cycloexpansion to piperazine-derived α-amino acid N-carboxy anhydrides (NCAs), thereby enabling direct coupling with α-amino acid esters. For example, compound **9a**, on treatment with NaOCl and a catalytic amount of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) in a phosphate buffer solution, according to our procedure[9], afforded, within about 2 min., the NCA **11** in almost quantitative yield. The subsequent coupling of **11** with (L)-ValOMe, (L)-PheOMe and (L)-LeuOMe provided the respective dipeptide products **13** [m.p.: 172-174°C, $[\alpha]_D^{25}$= +1.9 (c= 1.0, CH_2Cl_2)], **14** [m.p.: 192-194°C, $[\alpha]_D^{25}$= -2.6 (c= 1.0, CH_2Cl_2)] and **15** [m.p.: 162-164°C, $[\alpha]_D^{25}$= -5.0 (c= 1.0, CH_2Cl_2)] in good yields. Surprisingly, when mediated by TEMPO, conversion of **9b** into the NCA **12** repeatedly gave lower yields along with concomitant side products. In this instance, however, the alternative Baeyer-Villiger rearrangement of the α-keto β-lactam **17** [oil, $[\alpha]_D^{25}$= -8.8 (c= 1.0, CH_2Cl_2)] provided the best results, giving **12** in 70% yield, which on coupling with (L)-PheOMe led to the dipeptide **16** [m.p.: 147-148°C, $[\alpha]_D^{25}$= -12.8 (c= 1.0, CH_2Cl_2)] in 70 % yield.



Scheme 2. *Reagents and Conditions*: i, 0.55M NaOCl, TEMPO, CH_2Cl_2, KBr, $NaHCO_3$, KH_2PO_4-Na_2HPO_4 buffer, 0°C, 1 min.; ii, (L)-H_2N-CHR'-CO_2Me (1.2 eq.), CH_2Cl_2, r.t., 20h; iii, P_2O_5, DMSO, r.t., 12h; iv, mCPBA, CH_2Cl_2, -40°C, 1h.

From the results presented here, it is expected that more substituted piperazine-derived peptides could be made accessible by this approach without the necessity to initially prepare each individual piperazine-2-carboxylic acid.

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