Novel Synthesis of Optically Active Morpholines

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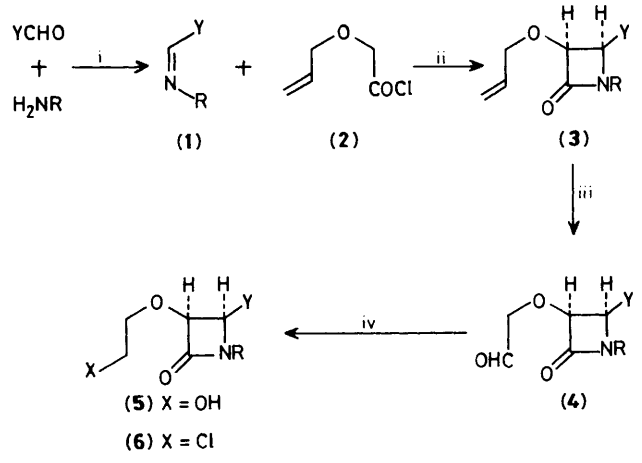
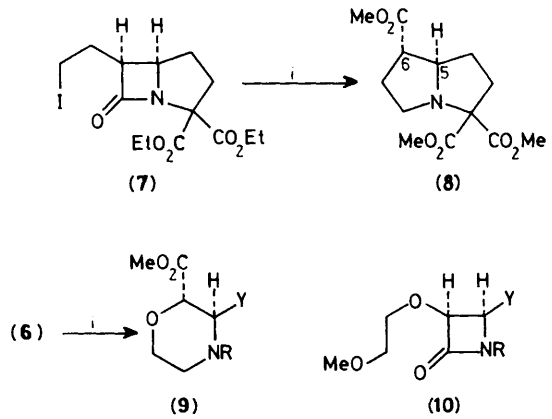
Morpholines have been synthesized by an efficient molecular rearrangement of appropriate derivatives of α-hydroxy- β-lactams including optically active β-lactams prepared from homochiral Schiff bases.

In the course of our studies on the use of β-lactams as synthons[2] for various heterocycles[3] we have been interested in pharmacologically active morpholines[1]† some of which can be considered as bioisosteres (4-oxa-analogues) of piperidine alkaloids.[4] We describe here a stereospecific pathway to members of this family substituted with versatile functional groups.

The well known acid chloride–imine cycloaddition approach for β-lactam synthesis[5] was employed for the preparation of *cis* 3-allyloxy-2-azetidinone (**3**) (Scheme 1). Ozonization with reductive work up led readily to an aldehyde (**4**) which was reduced with sodium borohydride to the corresponding alcohol (**5**) in about 80% yield without β-lactam cleavage. The primary alcohol (**5**) so obtained was converted without purification to a chloro compound (**6**) by treatment with thionyl chloride.



Scheme 1. *Reagents*; i, molecular sieve, CH_2Cl_2; ii, NEt_3, CH_2Cl_2; iii, O_3, then Me_2S, CH_2Cl_2; iv, (a) $NaBH_4$, EtOH; (b) $SOCl_2$, PhH.



Scheme 2. *Reagents*: i, NaCN, MeOH.

Hoeschst scientists[6] have reported the rearrangement of suitably substituted carbapenam (**7**) to a pyrrolizidine (**8**) and noted that the configuration at C(5) and C(6) remains unaltered (Scheme 2). Following their method, (**6**) was refluxed in methanol solution with sodium cyanide, when a morpholine derivative (**9**)‡ was obtained in about 60% yield. The isomeric β-lactam structure (**10**) was inadmissible on the basis of spectral data.‡

In previous publications,[7] we have reported extensions of a strategy§ for the enantiospecific synthesis of 3,4-disubstituted-2-azetidinones. Employing a variation of this approach, optically pure¶ *cis* 3-allyloxy-2-azetidinone (**13**) was prepared starting with a Schiff base (**12**) derived from D-glyceraldehyde acetonide (**11**) (Scheme 3). The absolute configuration of (**13**) was established to be 3*R*, 4*S* by chemical correlation to known compounds.[1a]

Ozonization of (**13**), reduction to a primary alcohol (**15**) and tosylation led to (**16**), which was converted to the iodo compound (**17**). Upon treatment with sodium cyanide in methanol, rearrangement of (**17**) to a morpholine derivative (**18**)‡ was achieved in good yield. The expected *trans* stereochemistry at C(2) and C(3) was confirmed by ^1H n.m.r. spectroscopic data.

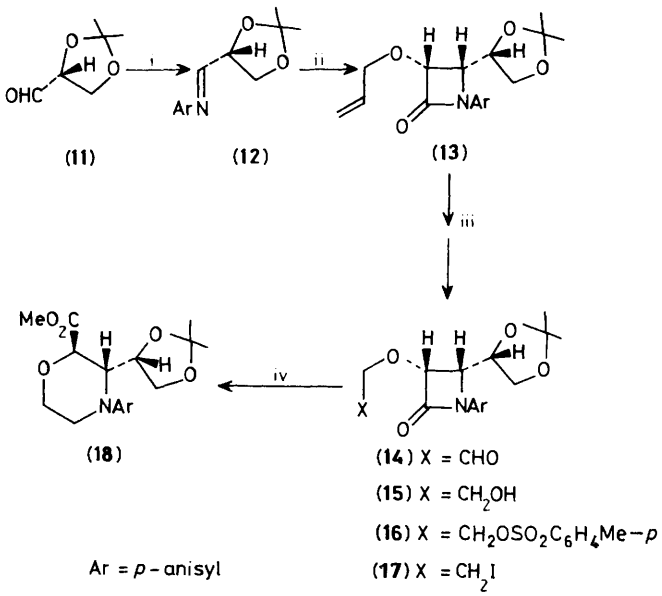
† For example, phenmetrazine, (+)-3-methyl-2-phenylmorpholine, and phendimetrazine, (+)-3,4-dimethyl-2-phenylmorpholine, are in clinical use.

‡ All new compounds exhibited satisfactory spectral and analytical data. For example, the morpholine compound (**9a**): oil, i.r. (neat) 1740 cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 7.3 (m, 5H), 6.95 (d, *J* 9 Hz, 2H), 6.85 (d, *J* 9 Hz, 2H), 4.5 (d, *J* 7.3 Hz, 1H), 4.3 (d, *J* 7.3 Hz, 1H), 4.1 (m, 2H), 3.7 (s, 3H), 3.5 (s, 3H), 3.1 (m, 2H), ^{13}C n.m.r. ($CDCl_3$) δ 167.13, 160.47, 141.23, 130.03, 129.64, 129.50, 129.06, 123.59, 115.05, 78.02, 71.64, 64.16, 57.00, 55.54, 52.56, chemical ionization mass spectrum (NH_3) *m/z* 328 $(M + 1)^+$. The formation of the displacement product (**10a**) from the reaction of (**6a**) with sodium cyanide in methanol was ruled out since the product formed a HCl salt. Also, in the ^1H n.m.r. spectrum of the reaction product a downfield shift of signals consistent with the structure (**9a**) was observed when a drop of trifluoroacetic acid was added.

The optically active morpholine compound (**18**): oil $[\alpha]_D^{26}$ −35.3° (*c* 0.18 MeOH), i.r. (neat) 1745 cm^{-1}, ^1H n.m.r. ($CDCl_3$) δ 6.95 (d, *J* 9 Hz, 2H), 6.80 (d, *J* 9 Hz, 2H), 4.4 (d, *J* 8.1 Hz, 1H), 4.25—3.70 (m, 6H), 3.90 (s, 3H), 3.80 (s, 3H) 3.35—3.05 (m, 2H), 1.35 (s, 3H), 1.20 (s, 3H), chemical ionization mass spectrum (NH_3) *m/z* 352 $(M + 1)^+$.

§ Independent work from two laboratories[7,10] has led to the synthesis of optically active *cis* α-amino-β-lactams *via* cycloaddition to Schiff bases derived from homochiral aldehydes.

¶ The optical purity of the *cis* 1-(*p*-anisyl)-3-allyloxy-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-azetidinone (**13**) was established by comparing the effect of a chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato] europium (III) [Eu(hfc)$_3$], on the ^1H and ^{13}C n.m.r. spectra of (**13**) and its racemic version prepared from (±)-glyceraldehyde acetonide.



Scheme 3. *Reagents*: i, molecular sieve, CH_2Cl_2; ii, CH_2=$CHCH_2OCH_2COCl$, NEt_3, CH_2Cl_2; iii, (a) O_3, then Me_2S, CH_2Cl_2; (b) $NaBH_4$, EtOH; (c) *p*-$MeC_6H_4SO_2Cl$, NEt_3, 4-dimethylaminopyridine (cat.), CH_2Cl_2; (d) NaI, Me_2CO; iv, NaCN, MeOH.

We have devised stereospecific methods for changing the configuration of optically active β-lactams.[8] The application of such methods would permit the preparation of the *cis* isomer of (**18**) and/or a change in the absolute configuration. Also, by using diverse sugar derivatives as the starting aldehyde in place of (**11**) in Scheme 3, we have altered the absolute configuration of the β-lactams prepared and provided a variety of functional groups at C(4) of 2-azetidinones.[9] The application of these strategies leading to oxa-analogues of naturally occurring piperidine alkaloids and their unnatural (antipodal) versions will be reported in the future.

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