Diastereo- and Enantio-selective Synthesis of Dihydro- and Tetrahydro-pyrimidines. A New Strategy for the Asymmetric Synthesis of β-Amino Ketones and γ-Amino Alcohols

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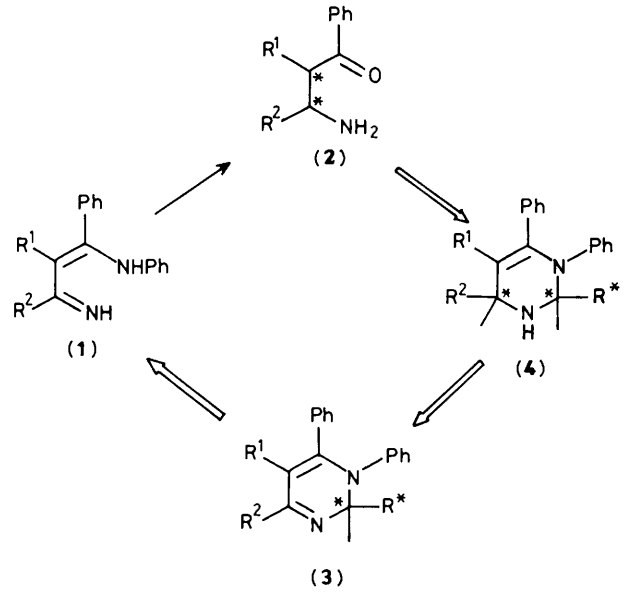
Chiral 1,2-dihydro- (**3**) and 1,2,3,6-tetrahydro-pyrimidines (**4**) have been synthesized by reaction of 3-aminoalk-2-enimines (**1**) with chiral aldehydes, the structure of (**4**) being confirmed by an *X*-ray crystal structure determination of a reduction product; a new strategy for the asymmetric synthesis of β-amino ketones (**2**) and γ-amino alcohols (**6**) with two or three chiral centres is described.

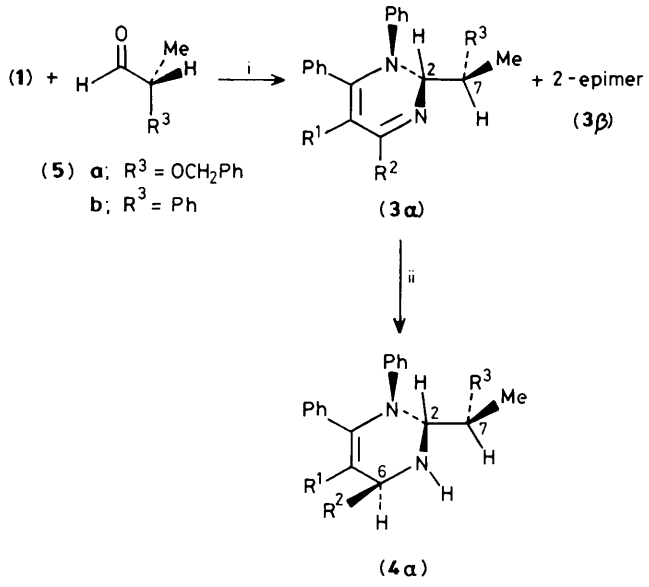
There has been much recent interest in the enantioselective synthesis of β-hydroxy carbonyl compounds, the aldol reaction using chiral enolates being employed in most instances.[1] In sharp contrast, methods leading to the analogous chiral *N*-unsubstituted-β-amino carbonyl compounds are, as far as we are aware, hitherto unknown. As a part of our investigation on the reactivity of the easily prepared 3-aminoalk-2-enimines (**1**),[2] we have recently reported the synthesis of β-amino ketones, γ-diamines, γ-amino alcohols, and γ-diols, by reduction of (**1**).[3] We have now focused our attention on their enantioselective preparation, and we report here the asymmetric synthesis of β-amino ketones (**2**) and γ-amino alcohols (**6**) with two or three chiral centres.

In our strategy the chiral 1,2-dihydropyrimidines (**3**)[4] are prepared for the first time from (**1**) and a chiral auxiliary; compounds (**3**) are then stereoselectively reduced to give the tetrahydropyrimidines (**4**). Finally, the heterocycle is cleaved by hydrolysis to liberate the chiral auxiliary and to yield the



Scheme 1

target compound (**2**) (Scheme 1). As chiral auxiliary we have chosen the α-alkoxy aldehyde (*S*)-(−)-2-benzyloxypropanal, (−)-(**5a**),[5] and have also used its racemate, (±)-(**5a**), and (±)-2-phenylpropanal, (±)-(**5b**), owing to their ready availability (see Scheme 2). Reaction at room temperature of (**1**) with the aldehydes (**5**) and $ZnCl_2$ [(**1**) : (**5**) : $ZnCl_2$, 1 : 1.1 : 1] in tetrahydrofuran (THF) for several hours afforded, after basic hydrolysis, a mixture of two diastereoisomeric dihydropyrimidines (**3α**) and (**3β**) [diastereomeric excess (d.e.) 88—97%]† in excellent yields (>91%) (Scheme 2). A single recrystallization gave (**3α**) free of any epimeric material.‡ The



For (**3**) and (**4**):
a;R^1 = Me, R^2 = R^3 = Ph
b;R^1 = Me, R^2 = *p*-MeC_6H_4, R^3 = Ph
c;R^1 = Me, R^2 = *p*-MeC_6H_4, R^3 = OCH_2Ph
d;R^1 = Me, R^2 = Ph, R^3 = OCH_2Ph
e;R^1 = Me, R^2 = cyclo-C_6H_{11}, R^3 = OCH_2Ph
f;R^1 = CH_2Ph, R^2 = *p*-MeC_6H_4, R^3 = OCH_2Ph
g;R^1 = CH_2=$CHCH_2$, R^2 = Ph, R^3 = OCH_2Ph

Scheme 2. *Reagents and conditions*: i, $ZnCl_2$, THF, 25 °C; ii, $NaBH_4$, MeOH, 25 °C, then H_2O/OH^-

assignment of the relative stereochemistry at C-2 and C-7 in the products (**3**) was based on ^1H n.m.r. data‡ and confirmed by *X*-ray crystallographic analysis of the reduction product (−)-(**4cα**) (see later).

Reduction of (**3α**) with $NaBH_4$/MeOH at 25 °C led, after basic hydrolysis, to single stereoisomers of the tetrahydropyrimidines (**4α**) (d.e. >99%)‡ in nearly quantitative yields (Scheme 2), ^1H n.m.r. spectra of the crude products showing no contamination with the C-6 epimer or other reduction products. The ^1H and ^{13}C n.m.r. spectra and nuclear Overhauser enhancement (n.O.e.) experiments for compounds (**4α**) did not reveal clearly the relative stereochemistry at C-2 and C-6, and so the *X*-ray crystal structure of the chiral compound (−)-(**4cα**) was determined (Figure 1).§ C-2 and C-6 are in the *anti*-configuration, and the absolute configuration is (−)-(2*R*,6*S*,7*S*).

The potential utility of this methodology is demonstrated in the enantioselective preparation of the β-amino ketones (**2**) and the pharmacological and synthetically important chiral γ-amino alcohols (**6**) (Scheme 3).[6] Thus, acidic hydrolysis of

† Diastereoisomeric ratio (d.r.) (^1H n.m.r., 250 MHz) for compounds (**3**): (**3aα/β**) 94/6; (**3bα/β**) 95/5; (**3cα/β**) >98/2; (**3dα/β**) >98/2; (**3eα/β**) 94/6; (**3fα/β**) >98/2; (**3gα/β**) 97/3. The diastereoisomeric ratio (**3α/β**) depended on the Lewis acid; other Lewis acids ($AlCl_3$, $BF_3{\cdot}Et_2O$, $TiCl_4$, or $MgBr_2$) gave less satisfactory stereoselectivities (d.e. 26—62%).

‡ Physical data for compounds (**3α**) and (**4α**): (±)-(2*SR*, 7*RS*)-(**3aα**), m.p. 211—213 °C; (±)-(2*SR*,7*RS*)-(**3bα**), m.p. 196—198 °C; (±)-(2*SR*,7*RS*)-(**3cα**), m.p. 136—138 °C; (−)-(2*S*,7*S*)-(**3cα**), m.p. 136—138 °C, $[\alpha]_D^{23}$ −734.7° (*c* 1.1, $CHCl_3$); (−)-(2*S*,7*S*)-(**3dα**), m.p. 70—72 °C, $[\alpha]_D^{23}$ −721.2° (*c* 1.1, $CHCl_3$); (−)-(2*S*,7*S*)-(**3fα**), m.p. 137—140 °C, $[\alpha]_D^{23}$ −533.0° (*c* 1.0, $CHCl_3$); (**3eα**) and (**3gα**), oils, not purified. (±)-(2*RS*,6*SR*,7*SR*)-(**4aα**), m.p. 165—167 °C; (±)-(2*RS*,6*SR*,7*SR*)-(**4bα**), m.p. 148—150 °C; (±)-(2*RS*,6*SR*,7*SR*)-(**4cα**), m.p. 114—116 °C; (−)-(2*R*,6*S*,7*S*)-(**4cα**), m.p. 114—116 °C, $[\alpha]_D^{23}$ −400.6° (*c* 1.1, $CHCl_3$); (−)-(2*R*,6*S*,7*S*)-(**4dα**), m.p. 148—151 °C, $[\alpha]_D^{23}$ −422.5° (*c* 1.2, $CHCl_3$); (−)-(2*R*,6*S*,7*S*)-(**4eα**), m.p. 160—162 °C, $[\alpha]_D^{23}$ −527.8° (*c* 1.0, $CHCl_3$); (−)-(2*R*,6*S*,7*S*)-(**4fα**), oil, $[\alpha]_D^{23}$ −154.3° (*c* 1.1, $CHCl_3$).

Spectral data for compounds (**2**)—(**4**), and (**6**) are in agreement with the proposed structures: *e.g.* (−)-(**3cα**): ^1H n.m.r. ($CDCl_3$) δ 1.55 (d, 3H, *J* 7.5 Hz), 1.95 (s, 3H), 2.35 (s, 3H), 3.90 (m, 1H), 4.50 (d, 1H, *J* 12.0 Hz), 4.80 (d, 1H, *J* 12.0 Hz), 5.60 (d, 1H, *J* 8.5 Hz), and 6.60—7.60 (m, 19H); (−)-(**4cα**): ^1H n.m.r. ($CDCl_3$) δ 1.50 (d, 3H, *J* 6.0 Hz), 1.55 (s, 3H), 1.90 (1H, br.s, NH), 2.35 (s, 3H), 4.20 (m, 1H), 4.30 (s, 1H), 4.50 (d, 1H, *J* 9.0 Hz), 4.75 (d, 1H, *J* 10.5 Hz), 4.85 (d, 1H, *J* 10.5 Hz), and 6.90—7.60 (m, 19H); (+)-(**2cα**): ^1H n.m.r. ($CDCl_3$) δ 0.94 (d, 3H, *J* 7.2 Hz), 1.64 (br.s, 2H), 2.35 (s, 3H), 3.72 (m, 1H, *J* 7.2 and 9.2 Hz), 4.28 (d, 1H, *J* 9.2 Hz), and 7.18—8.00 (m, 9H); (−)-(**6cα**): ^1H n.m.r. ($CDCl_3$) δ 0.75 (d, 3H, *J* 7.5 Hz), 2.08 (m, 1H), 2.33 (s, 3H), 3.16 (br.s, 1H), 4.05 (d, 1H, *J* 3.0 Hz), and 7.14—7.36 (m, 9H).

§ *Crystal data*: $C_{33}H_{34}N_2O$, M_r = 474.64, yellow hexagonal prisms, space group $P6_1$, *a* = 10.3474(1), *c* = 44.5122(24) Å, *U* = 4127.4(2), *Z* = 6, D_c = 1.146 g cm^{-3}; *F*(000) = 1524, μ = 4.98 cm^{-1}. 2341 Independent reflexions were measured with graphite-monochromated Cu-K_α radiation on a Philips PW1100 diffractometer (ω–2θ scans). 1960 Reflexions with $I > 3\sigma(I)$ were used in the solution (MULTAN) and refinement (least squares) to R = 0.040, R_w = 0.048. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1. Since the absolute configuration at C-7 is known (*S*), the absolute configuration at C-2 (*R*) and C-6 (*S*) is readily deduced.

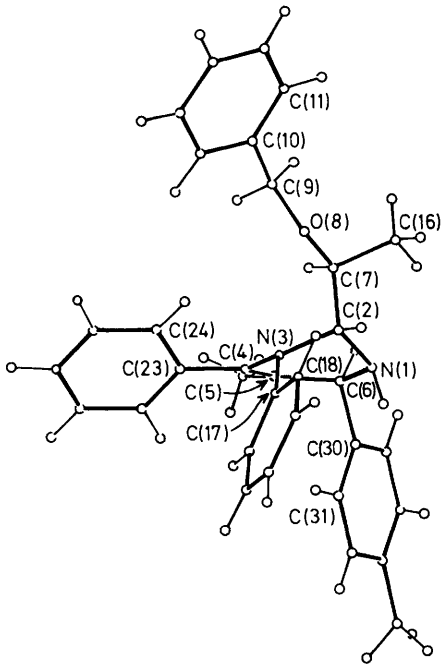
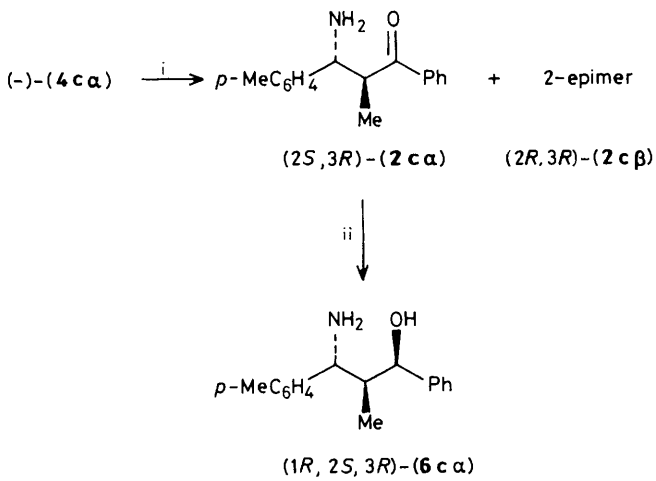


Figure 1. Molecular conformation of (−)-(**4cα**) showing the atomic labelling. Selected torsion angles (°): O(8)–C(7)–C(2)–N(3) +60.7(4), O(8)–C(7)–C(2)–N(1) −174.8(3), O(8)–C(7)–C(2)–H(2) −57(3); C(31)–C(30)–C(6)–C(5) −60.5(5), C(31)–C(30)–C(6)–N(1) +66.9(5), C(31)–C(30)–C(6)–H(6) −176(3); H(16a)–C(16)–C(7)–O(8) +179(4), H(16a)–C(16)–C(7)–C(2) +60(4), H(16a)–C(16)–C(7)–H(7) −61(5); C(2)–N(1)–C(6)–H(6) +97(3), C(2)–N(1)–C(6)–C(5) −22.4(5); C(4)–N(3)–C(2)–H(2) −172(3), C(4)–N(3)–C(2)–N(1) −54.5(4).



Scheme 3. *Reagents and conditions*: i, 1 M H_2SO_4, 1 h, 40 °C, −(−)-(**5a**), $-PhNH_2$; ii, $LiAlH_4$, Et_2O, 25 °C.

(−)-(**4cα**), followed by removal of the chiral auxiliary (−)-(**5a**), led to a diastereoisomeric mixture of (2*S*,3*R*)-(**2cα**) and (2*R*,3*R*)-(**2cβ**) (95% yield) in a ratio of 94 : 6 (Scheme 3). The chirality of the created stereogenic centre, C-6, in (**4α**) is not destroyed or modified, as expected, during the acid hydrolysis, whereas partial racemisation was observed during hydrolysis of (−)-(**5a**). The major diastereoisomer (+)-(**2cα**) was readily separated by stirring the mixture with n-hexane, filtration, and recrystallization (73% yield of isolated product); (+)-(**2cα**), m.p. 64—66 °C, $[\alpha]_D^{23}$ +108.6° (*c* 0.7, $CHCl_3$). The ^1H n.m.r. spectrum of the methoxy(trifluoromethyl)phenylacetyl derivative[7] showed the isomer (+)-(2*S*,3*R*)-(**2cα**) to be >99% enantiomerically pure.

Finally, reduction of (+)-(**2cα**) with $LiAlH_4/Et_2O$ at 25 °C led (92% yield) to the corresponding diastereoisomeric γ-amino-alcohols (1*R*,2*S*,3*R*)-(**6cα**) and (1*S*,2*S*,3*R*)-(**6cα′**) (d.e. 95%) (Scheme 3). (−)-(**6cα**) was easily separated and purified by recrystallization (n-hexane) (75% yield of isolated product); (−)-(**6cα**), m.p. 104—106 °C (lit.[3b] 106—107 °C, $[\alpha]_D^{23}$ −34.4° (*c* 0.6, $CHCl_3$).

In summary, we have provided an efficient and simple enantioselective synthesis of β-amino ketones and γ-amino alcohols of the types (**2**) and (**6**), and also report here the first examples of chiral 1,2-dihydro- and 1,2,3,6-tetrahydro-pyrimidines.

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