

Stereoselective synthesis of 2,4,5-trisubstituted piperidines by carbonyl ene and Prins cyclisations

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Cyclisation of aldehydes **3a–e** catalysed by concentrated hydrochloric acid affords predominantly the all *cis* 2,4,5-trisubstituted piperidines **4a–e** when the 2-substituent is small, while catalysis by MeAlCl₂ in refluxing chloroform gives the *trans* piperidines **5a–e** with diastereomeric ratios of up to 99 : 1.

Piperidines are widely distributed throughout Nature¹ and are an important scaffold for drug discovery,² forming the core of many pharmaceuticals. Methods for their stereocontrolled synthesis are of continuing interest, driven by the wide variety of functionality and substitution patterns present in piperidine targets.³

Intramolecular carbonyl ene reactions present an attractive method for ring closure, leading to the formation of two contiguous stereocentres with an often high degree of stereocontrol.⁴ We recently published a route to 3,4-disubstituted piperidines which had a carbonyl ene reaction as the key ring-closing step.⁵ The Brønsted acid-catalysed reaction at low temperatures strongly favoured a *cis* relationship between the two new stereocentres, while the Lewis acid-catalysed reaction at elevated temperatures gave the corresponding *trans* product.

We now describe our efforts towards extending this approach to the synthesis of 2,4,5-trisubstituted piperidines, using cyclisation precursors derived from α -amino alcohols. Such trisubstituted piperidines are of particular interest as they form the core of a number of important natural products, including the pseudodistomin family of anti-tumour compounds. These were isolated by Kobayashi⁶ from a marine tunicate, and have recently been the focus of synthetic attention.⁷

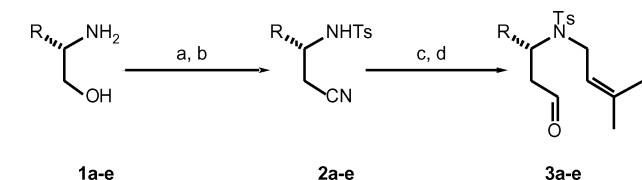
The cyclisation precursors were readily synthesised from commercially available α -amino alcohols *via* a procedure involving a one-carbon homologation by cyanide, Scheme 1. Bis tosylation of the α -amino alcohols **1a–e** followed by displacement of the *O*-tosyl group by sodium cyanide in DMF proceeded smoothly

and in good yield to afford the *N*-tosyl- β -amino nitriles **2a–e**. These were alkylated with prenyl bromide before being reduced by Dibal-H to the β -amino aldehyde cyclisation precursors **3a–e** in excellent overall yield. The β -amino aldehydes could be readily chromatographed and were unchanged on storing for several weeks at $-20\text{ }^{\circ}\text{C}$.

Cyclisation of **3a–e** was first studied using our optimised Brønsted acid conditions† of three equivalents of concentrated hydrochloric acid in CH₂Cl₂ at $-78\text{ }^{\circ}\text{C}$.⁵ In our earlier work, these conditions were found to favour formation of the kinetic product, in which there is a *cis* relationship between the hydroxyl and isopropenyl substituents. The results are summarised in Table 1.

In all cases, of the four possible stereoisomers, only two, piperidines **4** and **5**, were observed, in excellent combined yields. In the case of β -amino aldehydes with sterically undemanding 2-substituents, entries 1–3, the diastereoselectivity was moderate to good, although it decreased markedly in the case of **3d** and **3e** with very bulky 2-substituents. Traces (typically <5%) of chloride side-products were often isolated, arising from the addition of HCl across the double bond in **4** or **5**. These were generally separable by chromatography, but could also be converted back to the alkenes **4** and **5** by stirring with aqueous ammonia in THF.

The major diastereomer was confirmed as the all *cis* piperidine **4** by single crystal X-ray analysis of **4c**, Fig. 1.‡ Formation of this product can be rationalised by considering two factors. Firstly, there is a strong preference for the 2-substituent to adopt an axial disposition in the chair-like transition state, thus avoiding the pseudo A^{1,3} strain with the sulfonamide; this stereochemical preference in *N*-acyl and *N*-sulfonamido piperidines has been shown to be pronounced in a number of cases.⁹ The second factor



Scheme 1 Synthesis of cyclisation precursors. (a) TsCl, pyridine, CH₂Cl₂, 25 °C, 68–85%; (b) NaCN, DMF, 25 °C, 70–90%; (c) BrCH₂CH=C(CH₃)₂, Cs₂CO₃, CH₃CN, 25 °C, 82–98%; (d) Dibal-H, CH₂Cl₂, $-78\text{ }^{\circ}\text{C}$, 83–97%.

Table 1 Cyclisations of **3a–e** with HCl

Entry	Aldehyde	R	4 : 5 ^a	Yield (%) ^b
1	3a	Me	78 : 22	70 (22)
2	3b	Bn	94 : 6	70 (3)
3	3c	ⁱ Pr	80 : 20	75 (19)
4	3d	^t Bu	47 : 53	42 (37)
5	3e	Ph	54 : 46	53 (40)

^a Ratio determined by ¹H NMR of crude reaction mixtures. ^b Isolated yields of major (minor in parentheses) isomers following chromatography.

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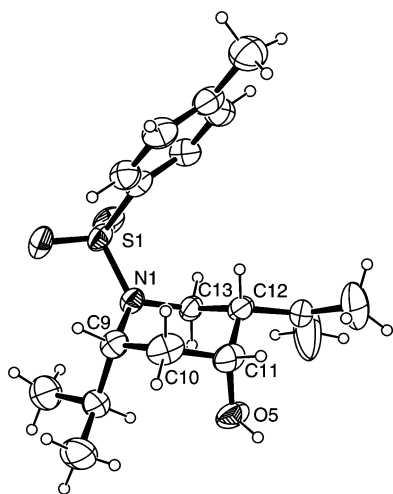


Fig. 1 ORTEP[®] representation of **4c**; ellipsoids drawn at the 30% probability level.

is the kinetic preference for the ene component and the aldehyde to adopt a *cis* relationship in the cyclisation transition state, as observed in our earlier work.⁵ This *cis* relationship is achieved with the aldehyde lying in an axial position in the TS, and the more bulky ene component lying equatorial, Fig. 2. More bulky 2-substituents lead to a lowering of the diastereoselectivity as a result of increased 1,3-diaxial interactions with the aldehyde, forcing the aldehyde into an equatorial position to give **5**.

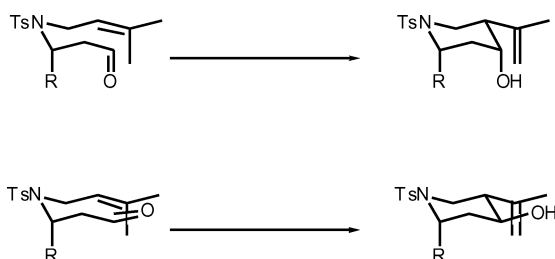


Fig. 2 Conformations leading to major and minor isomers in the Brønsted acid-catalysed reactions.

Turning to the Lewis acid-catalysed reaction, aldehydes **3a–e** were treated with one equivalent of methyl aluminium dichloride, which had been found to be the optimal Lewis acid in our earlier studies.⁵ As in the Brønsted acid-catalysed reactions, only two of the four possible diastereomers were observed (Table 2). The

Table 2 Cyclisations with methyl aluminium dichloride^a

Entry	Aldehyde	R	Temperature	4 : 5 ^b	Yield (%) ^c
1	3a	Me	23	12 : 88	76 (5)
2	3a	Me	40	7 : 93	60 (4)
3	3a	Me	60	4 : 96	71 (4)
4	3b	Bn	23	10 : 90	61 (10)
5	3b	Bn	40	5 : 95	64 (5)
6	3c	ⁱ Pr	40	2 : 98	82 (2)
7	3d	^t Bu	60	1 : 99	88 (1)
8	3e	Ph	60	2 : 98	80 (2)

^a All reactions were performed using 1 equivalent of MeAlCl₂. ^b Ratio determined by ¹H NMR or HPLC of crude reaction mixtures. ^c Isolated yields of major (minor) isomers following chromatography.

stereoselectivities ranged from good to excellent, with the major diastereomer identified as **5** from a combination of NOE data and ¹H NMR coupling constants. Further confirmation came from single crystal X-ray analysis of **5a**, Fig. 3.§

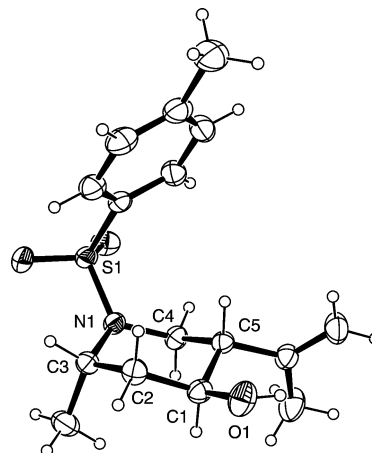


Fig. 3 ORTEP representation of **5a**; ellipsoids drawn at 30% probability level.

Under the equilibrating Lewis acidic conditions the thermodynamic product is favoured, in which the 4- and 5-substituents are equatorial, and the 2-substituent is axial to avoid the pseudo A^{1,3} strain with the sulfonamide. The increased 1,3-diaxial interactions present in the TS leading to **4** results in the equilibration to the thermodynamic product (Fig. 4) being facile even at room temperature, but improved ratios were obtained on heating at 40 or 60 °C (see, for example, entries 1–3).

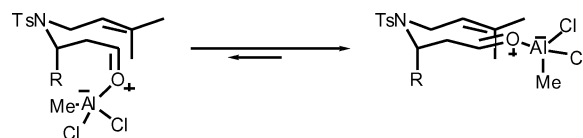


Fig. 4 Increased 1,3-diaxial interactions in Lewis acid-catalysed reaction favours the equatorial aldehyde.

Removal of the tosyl protecting group from a representative range piperidines was readily effected by stirring with sodium naphthalenide¹⁰ for 5 min at –78 °C, Table 3. The crude yields of

Table 3 Tosyl removal

4 or 5		6 or 7		
Entry	Tosyl piperidine	R	Product	Yield (%)
1	4a	Me	6a	54
2	5a	Me	7a	52
3	4b	Bn	6b	61
4	5b	Bn	7b	87
5	5c	ⁱ Pr	7c	90
6	5d	^t Bu	7d	99
7	5e	Ph	7e	67

essentially pure piperidines were near quantitative in most cases, although compounds **4a** and **5a** in particular were difficult to handle and chromatograph due to their significant polarity and water solubility.

In summary, we have discovered a highly diastereoselective synthesis of 2,4,5-trisubstituted piperidines from simple acyclic precursors, which should have application to the synthesis of more complex molecules.

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Notes and references

† Brønsted acid-catalysed cyclisation procedure. Preparation of (2*S**, 4*R**, 5*S**)-2-methyl-5-*iso*-propenyl-1-(*p*-toluenesulfonyl)piperidin-4-ol **4a**. Concentrated HCl (37%, 85 μ L) was added to a solution of aldehyde **3a** (0.102 g, 0.33 mmol) in dichloromethane (10 mL) at -78°C . The solution was stirred at -78°C overnight, after which it was quenched by addition of water (10 mL). The aqueous phase was then extracted with dichloromethane (4×10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo* to leave a colourless oil, which was purified by flash column chromatography (silica; ethyl acetate–hexane, 2 : 3, $R_f = 0.41$) to afford the piperidine **4a** (0.07 g, 70%) as a colourless thick oil. $[a]_D^{25} -3.6$ (c 0.5 in CHCl_3); ($\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3525 (O–H), 2923 (C–H), 1644 (C=C aliphatic), 1598 (C=C aromatic), 1494 (C=C aromatic), 1451 (C=C aromatic), 1383 (C–H), 1336 (SO_2), 1305 (C–H), 1153 (SO_2), 1088 (C–O); δ_{H} (300 MHz, CDCl_3) 1.21 (3H, d, J 7.0), 1.63–1.67 (2H, envelope), 1.73 (3H, s), 1.80–1.82 (1H, m), 2.12 (1H, broad d, J 11.8), 2.40 (3H, s), 3.30 (1H, t, J 12.7), 3.62 (1H, dd, J 4.1, J 13.2), 3.99 (1H, d, J 2.6), 4.17–4.22 (1H, m), 4.69 (1H, s), 5.00 (1H, s), 7.27 (2H, d, J 8.1), 7.69 (2H, d, J 8.1); δ_{C} (75 MHz, CDCl_3) 18.9, 21.5, 22.8, 35.7, 37.6, 46.5, 47.4, 64.6, 112.3, 127.0, 129.7, 138.4, 143.0, 144.1; m/z (ES^+) 332 (100%, $[\text{M} + \text{Na}]^+$) [HRMS Found: ($\text{M} + \text{Na})^+$ 332.1297. $\text{C}_{16}\text{H}_{23}\text{NNaO}_3\text{S}$ requires M , 332.1296]. Lewis acid-catalysed cyclisation procedure. Preparation of (2*R*, 4*S*, 5*S*)-2-*tert*-butyl-5-*iso*-propenyl-1-(*p*-toluenesulfonyl)piperidin-4-ol **5d**. Methyl aluminium dichloride (1 M solution in hexane, 480 μ L, 0.48 mmol) was added to a solution of the aldehyde **3d** (0.168 g, 0.48 mmol) in chloroform (20 mL). The solution was stirred overnight at 60°C , after which it was quenched by addition of water (20 mL). The aqueous phase was then extracted with dichloromethane (4×20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO_4 and concentrated *in vacuo* to leave a colourless oil, that was purified by flash column chromatography (silica; ethyl acetate–petroleum ether, 1 : 2, $R_f = 0.22$) to afford piperidine **5d** as a colourless oil (0.147 g, 88%). $[a]_D^{19} -6.0$ (c 0.3 in CHCl_3); (Found: C, 64.8; H, 8.1; N, 3.8. $\text{C}_{19}\text{H}_{29}\text{NO}_3\text{S}$ requires C, 64.9; H, 8.3; N, 4.0%); ($\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3498 (O–H), 2964 (C–H), 1646 (C=C aliphatic), 1598 (C=C aromatic), 1401, 1367 (C–H), 1336 (SO_2), 1084 (C–O); δ_{H} (300 MHz, CDCl_3) 1.05 (9H, s), 1.16–1.27 (1H, m), 1.30–1.38 (1H, m), 1.60 (3H, s), 1.71 (1H, s), 2.13 (1H, dd, J 4.4, J 14.0), 2.42 (3H, s), 3.04 (1H, dd, J 12.3, J 15.4), 3.79 (1H, dd, J 3.7, J 15.4), 3.91 (1H, dt, J 4.7, J 11.0), 3.99 (1H, d, J 8.1), 4.64 (1H, s), 4.89 (1H, s), 7.30 (2H, d, J 8.1), 7.73 (2H, d, J 8.1); δ_{C} (75 MHz, CDCl_3) 20.3, 21.6, 29.5, 31.7, 36.9, 46.2, 49.9, 61.4, 66.5, 113.9, 127.2, 129.9, 138.4, 142.6, 143.4; m/z (ES^+) 374 (100%, $[\text{M} + \text{Na}]^+$) [HRMS Found: ($\text{M} + \text{Na})^+$ 374.1768. $\text{C}_{19}\text{H}_{29}\text{NNaO}_3\text{S}$ requires M , 374.1766]. Tosyl group removal procedure. Preparation of (2*S*, 4*S*, 5*S*)-2-benzyl-5-*iso*-propenylpiperidin-4-ol **7b**. To a solution of **5b** (0.099 g, 0.26 mmol) in tetrahydrofuran (1.5 mL) under nitrogen was added at

-78°C a freshly prepared solution of sodium naphthalenide (1.2 mL of a 1 M solution in tetrahydrofuran, 4.6 eq). After 5 min the reaction was quenched with methanol (0.4 mL), warmed up to room temperature, diluted with water (5 mL) and acidified to pH 1 with aqueous HCl (2 M). The aqueous phase was washed with diethyl ether (3×10 mL), basified to pH 9 with aqueous NaOH (2 M) and extracted with ethyl acetate (4×10 mL). The combined organic phases were washed with brine (10 mL), dried over MgSO_4 and concentrated *in vacuo* to afford piperidine **7b** (0.052 g, 87%) as colourless crystals. Mp 119°C ; $[a]_D^{23} -49$ (c 0.98 in CHCl_3); ($\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}$ 3306 (O–H, N–H), 2917 (C–H), 1641 (C=C aliphatic), 1602 (C=C aromatic), 1493 (C=C aromatic), 1455 (C=C aromatic), 1090 (C–O); δ_{H} (300 MHz, CDCl_3) 1.63 (1H, ddd, J 5.1, J 9.9, J 12.9), 1.79 (3H, s), 1.91 (1H, broad s), 1.97 (1H, dt, J 3.7, J 12.9), 2.07–2.15 (1H, m), 2.72 (1H, dd, J 6.4, J 13.4), 2.87–2.94 (3H, envelope), 3.33–3.40 (1H, m), 3.99 (1H, dt, J 4.1, J 9.4), 4.94 (1H, s), 4.98 (1H, s), 7.16–7.33 (5H, m); δ_{C} (75 MHz, CDCl_3) 21.2, 37.0, 38.8, 43.7, 53.4, 54.4, 66.4, 113.3, 126.4, 128.7, 129.1, 139.6, 144.4; m/z (ES^+) 232 (65%, $[\text{M} + \text{H}]^+$), 214.1 (100, $[\text{M} - \text{OH}]^+$) [HRMS Found: ($\text{M} + \text{H})^+$ 232.1700. $\text{C}_{15}\text{H}_{22}\text{NO}$ requires M , 232.1701].

‡ Crystal data for **4c**. $\text{C}_{18}\text{H}_{27}\text{NO}_3\text{S}$, $M = 337.47$, monoclinic, $a = 8.4757(1)$, $b = 19.2080(3)$, $c = 11.8021(2)$ Å, $U = 1902.87(5)$ Å³, $T = 296$ K, space group $P2_1$, $Z = 4$, $\mu(\text{Cu K}\alpha) = 1.617$ mm^{−1}, 5917 reflections measured, 5423 unique ($R_{\text{int}} = 0.0374$) which were used in all calculations. The final $wR(F_2)$ was 0.1035 (all data). Crystal data for **4a**. $\text{C}_{16}\text{H}_{23}\text{NO}_3\text{S}$, $M = 309.41$, monoclinic, $a = 22.4722(3)$, $b = 7.8727(1)$, $c = 19.9610(2)$ Å, $U = 3270.17(7)$ Å³, $T = 296$ K, space group $C2/c$, $Z = 8$, $\mu(\text{Cu K}\alpha) = 1.837$ mm^{−1}, 2943 reflections measured, 2689 unique ($R_{\text{int}} = 0.0392$) which were used in all calculations. The final $wR(F_2)$ was 0.1150 (all data). CCDC reference number 288320. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515547a

§ CCDC reference number 288321. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515547a

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