trans-2,5-Disubstituted pyrrolidines: rapid stereocontrolled access from sulfones

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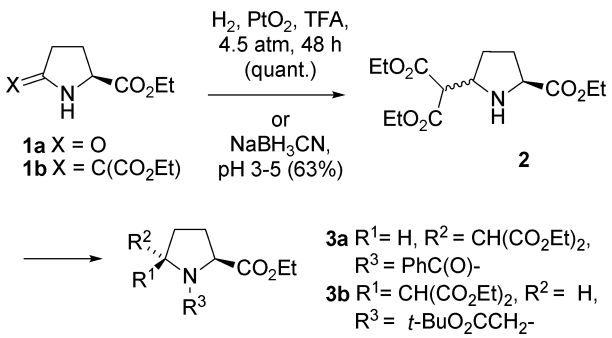
A direct and versatile route for the reliable synthesis of *trans*-2,5-disubstituted pyrrolidines from pyroglutamic acid is reported, which can be conducted at scale and without chromatographic purification of key intermediates.

2,5-Disubstituted pyrrolidines are of widespread occurrence amongst natural products and considerable importance in a variety of contexts, and much effort has been expended on the development of suitable synthetic methodology to access them,[1,2] and some recent developments expand the opportunities in that regard.[3–5] The synthesis of these compounds by elaboration of pyroglutamic acid **1a** has been achieved using a variety of approaches, but common difficulties have been operational complexity, scalability, generality, or control of diastereoselectivity.[6–12] The first report of diastereoselective access to *cis*- and *trans*-2,5-disubstituted pyrrolidines using pyroglutamate was made by Rapoport.[13] Subsequent to this, more general approaches, based upon nucleophilic additions to *N*-acyliminium species, also readily available from pyroglutamate, became available, but these principally gave access to mixtures of diastereomeric products,[11,14] although careful choice of conditions did enable high levels of *trans*-diastereocontrol; organocuprates[15] and the use of bicyclic systems[10] were found to be particularly useful in that regard. Other methods of attaining high *trans*-selectivity involve cyclisations of suitable substrates derived from pyroglutamate,[16–20] more recently by Pd(0)-mediated coupling[21] and sequential lithiation of *N*-Boc pyrrolidine.[22] *Cis*-selective synthesis of 2,5-disubstituted pyrrolidines is generally achieved by reduction of a suitable monosubstituted system,[4,6,8,9,23–26] but has also been reported to be possible by nucleophilic additions to *N*-acyliminium species; in this case, the diastereoselectivity was found to critically depend on the nature of the nitrogen protecting groups and the ring substituents.[27]

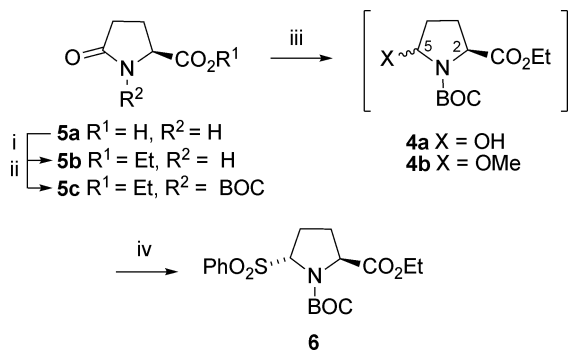
We recently reported that both *cis*- and *trans*-2,5-disubstituted pyrrolidines were available from pyroglutamic acid **1a**, by application of an Eschenmoser sulfide contraction[28] to give an enamine intermediate **1b**, followed by reduction (Scheme 1); depending on the nature of the R group, either *cis*- and *trans*-2,5-disubstituted pyrrolidines **3a** or **3b** could be accessed.[29,30] However, although an effective sequence, this methodological approach was limited by the difficulty of the reduction of the enamine **1b**, which typically required Adams catalyst and high pressure, and the formation of an activated β-aminoester moiety **2** that was particularly susceptible to retro-conjugate addition, leading to facile epimerisation



Scheme 1

at the newly introduced chiral centre. However, because of the potential simplicity of this overall approach, and the utility of the products, it was of interest to us to optimise this chemistry as far as possible. The difficulties appeared to derive from the order of the manipulations on pyroglutamic acid **1a**; for maximum effectiveness, the Eschenmoser sulfide contraction proceeds best with (doubly activated) bromomalonates, but this in turn generates a highly deactivated enamine product **1b** that is both difficult to reduce in the first instance, and then prone to epimerisation once reduced.

A much more common approach to 2,5-difunctionalised pyrrolidines in the literature is initial partial reduction of pyroglutamate to an intermediate lactol **4a**, followed by displacement with methanol to give aminal **4b** (Scheme 2).[14] Reaction of **4b** with organometallic nucleophiles yields 2,5-disubstituted pyrrolidines, but the stereocontrol is largely dependent on the



Scheme 2 *Reagents and conditions*: (i) 3 equiv. EtOH, cat. H_2SO_4, toluene, reflux, overnight, 94%; (ii) 1.1 equiv. Boc_2O, 0.1 equiv. DMAP, 1.5 equiv. Et_3N, DCM, rt, overnight, 97%; (iii) 1 equiv. $LiBEt_3H$, THF, −78 °C, 1 h, product not isolated; (iv) 1 equiv. $PhSO_2H$, 3 equiv. $CaCl_2$, DCM, rt, overnight, 57%.

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Table 1 Reaction of sulfone **6** with organometallic reagents according to Scheme 3

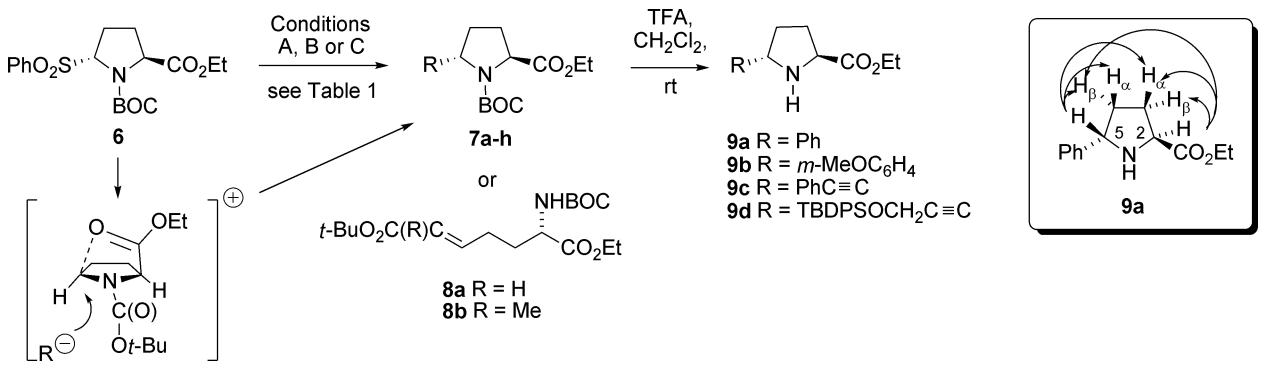
R	Conditions[a]	Product **7** or **8** (yield, %)	Product **9** (yield, %)
Ph-	A	**7a** (93)	**9a** (34)
m-$MeOC_6H_4$-	A	**7b** (72)	**9b** (68)
H_2C=CH-	A	**7c** (28)	—
H_2C=$CHCH_2$-	C	**7d** (39)	—
PhCH=CH-	A	**7e** (15)	—
PhC≡C-	A	**7f** (76)	**9c** (70, 68[b])
$MEMOCH_2C$≡C-	A	**7g** (68)	—
$TBDPSOCH_2C$≡C-	A	**7h** (76)	**9d** (45)
t-BuO_2CCH_2-	B	**8a** (39)	—
t-BuO_2CCH(Me)-	B	**8b** (38)	—

[a] Conditions A (RMgBr, $ZnBr_2$, rt, THF); B (RZnBr, reflux, overnight); C (RMgBr, $ZnCl_2$, rt, CH_2Cl_2, THF). [b] Direct conversion of **6** → **7f** → **8c** without isolation of intermediates.

nature of the nucleophile, the N-protecting group and other ring substituents.[27] An analogous reaction involving the partial reduction of succinimides and displacement of the resulting lactol with benzenesulfinic acid yields sulfonyl pyrrolidinones, which undergo selective nucleophilic displacement of the sulfone with Grignard reagents and zinc bromide.[38] This method is versatile, and applicable to a range of organometallic nucleophiles, but since the reaction appears to proceed through an S_N1-like mechanism, the diastereoselectivity is principally dependent on the substrate. It therefore seemed to us that a highly diastereoselective and general approach to 2,5-difunctionalised pyrrolidines could be achieved by applying this strategy to the pyroglutamate system.

Conversion of pyroglutamic acid **5a** to its ester **5b**, *N*-BOC protection to **5c** and reduction to the hemiaminal intermediate **4a** followed the literature protocol.[14] Displacement of the hydroxyl group with benzenesulfinic acid gave the crystalline product **6** in 57% yield (Scheme 2);[31] the presence of the BOC protection is essential for the stability of this compound. NOESY analysis did not give correlation between H-2 and H-5, as expected for a *trans*-relationship,[32] and this assignment was easily confirmed by single-crystal X-ray analysis.[33] Significantly, this four-step synthesis from commercially available pyroglutamic acid requires no chromatographic purification of intermediates, the product sulfone is readily purified by recrystallisation, and the sequence proceeds in 52% overall yield. The reaction has been successfully run on a thirty-gram scale.

An investigation of the displacement of the sulfone residue was then made; we found that displacement of the phenylsulfone residue was most readily achieved on a scale up to 1.5 mmol using a mixture of Grignard reagents† with zinc halide salts to give products **7a–h**, or less efficiently with Reformatsky reagents, to give aminoesters **8a**,**b** (Table 1).[31] This reaction was entirely chemoselective for the phenylsulfonyl residue, and the *trans*-2,5-disubstituted products were obtained exclusively after chromatography. Unfortunately these were not crystalline, and direct stereochemical assignment was therefore not possible, since NOESY analysis was not a reliable method, as discussed above. Removal of the BOC group from compounds **7a**, **7b**, **7f** and **7h** with TFA readily gave products **9a–d** and simultaneously permitted stereochemical assignment. NOE analysis of **9a** showed only a very weak direct enhancement of H-2 and H-5, irradiation of H-5 gave enhancements to all of H-4α, H-4β and H-3α, and irradiation of H-2 gave enhancements to all of H-3α, H-3β and H-4β; this is consistent with *trans*-2,5-stereochemistry, and by implication *trans*-2,5-stereochemistry of the BOC-protected pyrrolidine **7a** (Scheme 3).[34] The relative stereochemistry of the compounds **7b**, **7f** and **7h** were assigned in a similar manner. This *trans*-stereochemical outcome could be explained by initial elimination of the sulfone residue by assistance from the adjacent ester to generate an iminium ion, followed by subsequent nucleophilic attack which occurs *anti* to the C-2 ester substituent (Scheme 3); this nicely complements the route selective for the *cis*-isomer reported by Langlois.[8,9] Evidence for the straightforward formation of the required intermediate



Scheme 3

acyliminium ion (Scheme 3) comes from the X-ray analysis of **6**, in which the distance from the oxygen of the ester carbonyl to the C-5 carbon is only 3.30 Å, thereby facilitating neighbouring group participation.

This sequence can be operated without isolation of intermediates; thus, conversion of sulfone **6** to acetylene **7f** immediately followed by deprotection (TFA) gave a 68% yield of product **9c**.

A novel method providing exclusive access to *trans*-2,5-disubstituted pyrrolidines from pyroglutamic acid which can be operated at scale *via* a crystalline intermediate and with no chromatographic purification has been established. We anticipate that this approach will be of synthetic importance for the preparation of similarly substituted pyrrolidines in natural product systems.

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Notes and references

† Grignard reagents were chosen on the basis of their potential for side chain extension, but alkyl Grignard cases are equally satisfactory; octylmagnesium gave the corresponding product **7** in 65% yield.

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30 S. R. Hussaini and M. G. Moloney, *Tetrahedron Lett.*, 2004, **45**, 1125–1127.
31 **Preparation of 6**: Lactam **5c** (13.7 g, 53.4 mmol) in dry THF (550 ml) under N_2 was cooled to −78 °C, and lithium triethylborohydride solution (53.4 ml, 1.0 M in THF) slowly added such that the temperature was maintained below −65 °C. The mixture was left for 1 h and quenched by addition of sat. aq. $NaHCO_3$ solution (70 ml) followed by hydrogen peroxide (35% w/w) (27 ml). The mixture was allowed to warm to rt and stirred for 30 min. The solvent was removed *in vacuo* and the solid residue was extracted with DCM (3 × 200 ml) and the solution filtered. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give crude **4a** which was used immediately without further purification. Crude **4a**, benzenesulfinic acid (7.59 g, 53.4 mmol) and calcium chloride (17.8 g, 160 mmol) were suspended in DCM (690 ml) and stirred at rt under N_2 overnight. Water (345 ml) was added and the mixture was extracted with DCM (3 × 345 ml). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude product as a yellow solid. The solid was purified by recrystallisation from diethyl ether to give the product as a white crystalline solid (10.1 g, 49%). $[a]_D^{22} = -56.3$ (*c* 1.00, CH_2Cl_2); mp 122–124 °C (diethyl ether); δ_H (C_6D_6, 400 MHz) (2 rotamers) 1.00 (3H, 2 × t, *J* 7.1, OCH_2CH_3), 1.23 and 1.25 (3H and 6H, 2 × s, $C(CH_3)_3$), 1.58–1.70 (1H, m, C(3)H), 2.02–2.24 (1H, m, C(4)H), 2.53–2.95 (2H, m, C(3)H and C(4)H), 3.84–4.04 (2H, m, OCH_2), 4.45 and 4.67 (0.7H and 0.3H, 2 × d, *J* 9.1, C(2)H), 5.20 and 5.40 (0.3H and 0.7H, 2 × d, *J* 8.1, C(5)H), 7.00–7.16 (3H, m, ArH), 7.87–8.04 (2H, m, ArH); δ_C (C_6D_6, 100 MHz) (2 rotamers) 14.0, 14.1 (OCH_2CH_3), 24.8, 26.4 (C(3)), 27.7, 37.8 ($C(CH_3)_3$), 28.2, 29.7 (C(4)), 61.0 (OCH_2), 60.9, 61.1 (C(2)), 78.6, 79.1 (C(5)), 80.8, 81.3 ($C(CH_3)_3$), 127.8, 127.9, 128.0, 128.2, 128.8, 129.2, 129.8, 133.3, 133.5 (Ar(C)), 138.9 (q, Ar(C)), 152.9, 153.4 ($CO_2C(CH_3)_3$), 172.1, 172.3 ($CO_2CH_2CH_3$); *m/z* (EI) 789 (2M + Na^+, 75%), 442 (M + MeCN + NH_4^+, 100%), 406 (M + Na^+, 15%); HRMS (M + Na^+) calculated 406.1300, found 406.1309. **Preparation of pyrrolidine 7f**: Isopropylmagnesium chloride solution (1.3 ml, 2.0 M in diethyl ether) was added to a solution of phenylacetylene (0.29 ml, 2.58 mmol) in dry THF (5 ml) under N_2 at 0 °C so that the temperature did not exceed 25 °C. After, the addition was complete, the mixture was warmed to rt and left for 1 h. A solution of anhydrous zinc bromide (0.580 g, 2.58 mmol) in dry THF (5 ml) was added to the mixture and stirred for 30 min. A solution of sulfone **6** (0.494 g, 1.29 mmol) in dry THF (10 ml) was added to the mixture and the reaction was left overnight. The reaction was quenched by addition of sat. aq. NH_4Cl (15 ml) and water (15 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 25 ml). The combined organic layers were dried over brine (50 ml) and $MgSO_4$, and concentrated *in vacuo* to give the crude product. The product was purified by silica gel flash column chromatography [10 : 90 EtOAc–petrol (40–60)], which gave the pure product as a colourless liquid (0.34 g, 76%). $R_f = 0.54$ [40 : 60 EtOAc–petrol (40–60)]; $[a]_D^{22} = -151$ (*c* 0.50, CH_2Cl_2); δ_H ($CDCl_3$, 400 MHz) (2 rotamers) 1.23–1.30 (3H, m, OCH_2CH_3), 1.43 and 1.50 (4.5H and 4.5H, 2 × s, $C(CH_3)_3$), 2.00–2.10 (2H, m, C(3)H^a and C(4)H^b), 2.22–2.34 (1H, m, C(4)H^a), 2.43–2.60 (1H, m, C(3)H^b), 4.06–4.23 (2H, m, OCH_2CH_3), 4.34 and 4.44 (0.5H and 0.5H, 2 × d, *J* 8.8, C(2)H), 4.83 and 4.95 (0.5H and 0.5H, 2 × d, *J* 7.8, C(5)H), 7.24–7.43 (5H, m, ArH); δ_C ($CDCl_3$, 100 MHz) (2 rotamers) 14.1, 14.3 (OCH_2CH_3), 28.3, 28.4 ($C(CH_3)_3$), 28.6, 29.7 (C(3)), 31.3, 31.9 (C(4)), 49.3, 49.5 (C(5)), 58.7, 59.1 (C(2)), 61.0, 61.1 (OCH_2CH_3), 80.4 ($C(CH_3)_3$), 81.8, 82.0 (C(7)), 89.2, 89.4 (C(6)), 123.0 (q, Ar(C)), 128.0, 128.1, 128.3, 131.5, 131.8 (Ar(C)), 153.1, 153.8 ($CO_2C(CH_3)_3$), 172.5, 172.8 ($CO_2CH_2CH_3$); *m/z* (EI) 402 (M + MeCN + NH_4^+, 100%), 366 (M + Na^+, 2%); HRMS (M + H^+) calculated 344.1862, found 344.1859.
32 This lack of NOE enhancement is not an unequivocal demonstration of *trans*-2,5-disubstitution, since our own NOESY analysis of *cis*- and

trans-**4b** showed no enhancement between H-2 and H-5 in both cases. However, we have recently reported that stereochemical assignment in related systems can be more reliably achieved using a VT-NOESY protocol which eliminates complicating conformational effects, and in this case the *cis*-2,5-disubstituted pyrrolidines gave clear NOE(SY) enhancements between H-2 and H-5, but the *trans*-2,5-disubstituted pyrrolidines did not.[36] This assignment was confirmed by single crystal X-ray analysis in several cases.

33 Crystal data and data collection parameters for compound **6**: $C_{18}H_{25}NO_6S$, $M = 383.47$, monoclinic, $a = 10.6783(3)$, $b = 8.1891(2)$, $c = 11.1365(3)$ Å, $\beta = 98.9319(17)°$, $V = 962.03(4)$ Å^3, $T = 150$ K, space group $P2_1$, $Z = 2$, $D_x = 1.324$ Mg m^{-3}, $\mu = 0.201$ mm^{-1}, 9083 reflections measured, 4183 unique ($R_{int} = 0.039$). The final $wR(F^2)$ was 0.0340 (all data). The compound was crystallised from EtOAc. CCDC reference number 615009. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b611583g.

34 Our proton spectrum for *trans*-**9a** was identical to the spectroscopic data reported for *trans*-**9a**; data for *cis*-**9a** has also been reported.[15] These were assigned by reference to compounds previously reported in the literature (see ref. 37).

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